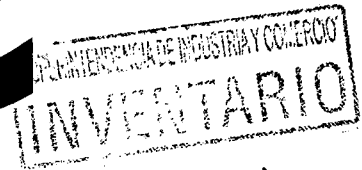


SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



Organizacion CSA Ltda



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

DYN
NOV

SOLICITUD **PCT**
PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

07-117133

54. TITULO COMPUESTOS MULTI-CÍCLICOS Y MÉTODOS DE EMPLEO DE LOS MISMOS

51. CLASIFICACION INTERNACIONAL A61K31/506 // A61K31/496
A61K31/551 // A61P25/28

71. SOLICITANTE LEXICON GENETICS INCORPORATED

DOMICILIO THE WOODLANDS, TX, ESTADOS UNIDOS DE AMÉRICA

74. APODERADO JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C. 06/11/2007

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PETITORIO

AS: 105.375



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-117133- -00000-0000

Fecha: 2007-11-06 16:36:17 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 186

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☒ Capítulo I.

☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **LEXICON GENETICS INCORPORATED**

Dirección: 8800 Technology Forest Place, The Woodlands, Texas 77381, Estados Unidos de América.

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono:

Fax:

E-mail

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3 REPRESENTANTE O APODERADO

Nombre: **JUAN PABLO CADENA SARMIENTO**

Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia.

Teléfono: 744-2200

Fax: 742-2200

E-mail:

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 80.410.337 TP 57492

4 INVENTOR (ES) (72)

Nombre: **Joseph BARBOSA, Li DONG, Cynthia Ann FINK, Jiancheng WANG, G. Gregory ZIPP.**

Dirección: 2 Big Top Drive, Lambertville, NJ 08530, US; 11 Pagoda Court, Lawrenceville, NJ 08648, US; 1 Kensington Court, Lebanon, NJ 08833, US; 5707 Fox Run Drive, Plainsboro, NJ 08536, US; 31 Kettering Court, Robbinsville, NJ 08691, US (Respectivamente).

Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente).

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6 Título (54): COMPUESTOS MULTI-CÍCLICOS Y MÉTODOS DE EMPLEO DE LOS MISMOS

7 Clasificación Internacional (51): A61K31/506 // A61K31/496 // A61K31/551 // A61P25/28

8 Prioridad

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US

13-05-2005

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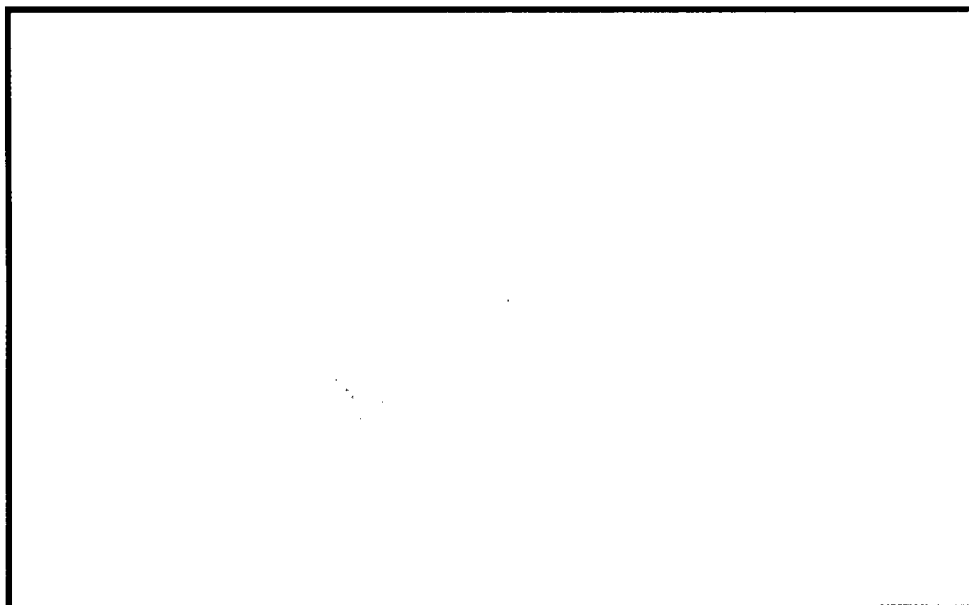
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 482.000.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción 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 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Tarjeta de Propietarios
Documentos PCT

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA: 

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act. 411 PRESENTACION Folios: 186

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	59040581	10/09/2007	2,430,000.00
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	62762483	10/09/2007	32,280,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE ☒ PCT/US2006/018682 MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL ☐

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES LEXICON GENETICS INCORPORATED

DOMICILIO THE WOODLANDS, TX, ESTADOS UNIDOS DE AMERICA.

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO COMPUESTOS MULTI-CÍCLICOS Y MÉTODOS DE EMPLEO DE LOS MISMOS

CLASIFICACION _____

EXPEDIENTE No. _____ FECHA DE SOLICITUD _____ ROLLO MICROFILM _____

CERTIFICADO No. _____ FECHA DE CONCESION _____ VIGENCIA DESDE _____ HASTA _____

PRORROGA _____ CAMBIO DE NOMBRE _____

TRASPASO A _____

INVENTOR (ES) JOSEPH BARBOSA, L-I DONG, CYNTHIA ANN FINK, JIANCHENG WANG, G- GREGORY ZIPP.

OTROS _____

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C07D 239/42 (2006.01) C07D 451/02 (2006.01)
C07D 401/12 (2006.01) C07D 487/08 (2006.01)
C07D 401/04 (2006.01) A61P 25/28 (2006.01)

(74) Agents: ISHIMOTO, Lance K. et al.; LEXICON GENETICS INCORPORATED, 8800 Technology Forest Place, The Woodlands, Texas 77381 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(71) Applicant (for all designated States except US): LEXICON GENETICS INCORPORATED [US/US]; 8800 Technology Forest Place, The Woodlands, Texas 77381 (US).

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BARBOSA, Joseph [US/US]; 2 Big Top Drive, Lambertville, NJ 08530 (US). DONG, Li [CN/US]; 11 Pagoda Court, Lawrenceville, NJ 08648 (US). FINK, Cynthia Ann [US/US]; 1 Kensington Court, Lebanon, NJ 08833 (US). WANG, Jiancheng [CN/US]; 5707 Fox Run Drive, Plainsboro, NJ 08536 (US). ZIPP, G. Gregory [US/US]; 31 Kettering Court, Robbinsville, NJ 08691 (US).

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

(54) Title: MULTICYCLIC COMPOUNDS AND METHODS OF THEIR USE

(57) Abstract: This invention relates to multicyclic compounds, pharmaceutical compositions comprising them, and methods of their use in, for example, the treatment of cognitive disorders.



WO 2006/124748 A3

MULTICYCLIC COMPOUNDS AND METHODS OF THEIR USE

This application claim priority to U.S. provisional application no. 60/680,501, filed May 13, 2005.

1. FIELD OF THE INVENTION

5 This invention relates to multicyclic compounds, pharmaceutical compositions comprising them, and methods of their use.

2. BACKGROUND OF THE INVENTION

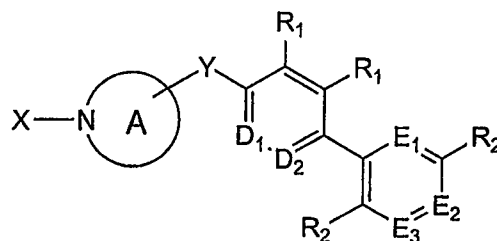
The amino acid L-proline reportedly plays a role in regulating synaptic transmission in the mammalian brain. *See, e.g., Crump et al., Molecular and Cellular*
10 *Neuroscience*, 13: 25-29 (1999). For example, a synaptosomal bisynthetic pathway of L-proline from ornithine has been reported, and high affinity Na⁺-dependent synaptosomal uptake of L-proline has been observed. Yoneda *et al., Brain Res.*, 239: 479-488 (1982); Balcar *et al., Brain Res.*, 102: 143-151 (1976).

In general, neurotransmitter systems typically have mechanisms that inactivate
15 signaling, many of which work through the action of a Na⁺-dependent transporter. In this case, a Na⁺-dependent transporter for proline has been described, and the molecular entity cloned (SLC6A7 in humans). *See, e.g., U.S. patent nos. 5,580,775 and 5,759,788.* But the transporter's specific role remains unknown. For example, the human Na⁺-dependent proline transporter is generally localized to synaptic terminals, which is consistent with a
20 role in neurotransmitter signaling. But no high-affinity receptor has been found for proline, suggesting that it is a neuromodulator rather than a neurotransmitter. Shafqat S., *et al., Molecular Pharmacology* 48:219-229 (1995).

The fact that the Na⁺-dependent proline transporter is expressed in the dorsal root ganglion has led some to suggest that it may be involved in nociception, and that
25 compounds which inhibit the transporter may be used to treat pain. *See, e.g., U.S. Patent Application No. 20030152970A1.* But this suggestion is not supported by experimental data.

3. SUMMARY OF THE INVENTION

This invention encompasses multicyclic compounds, pharmaceutical compositions comprising them, and methods of their use. One embodiment of the invention encompasses a compound of formula I:



(I)

and pharmaceutically acceptable salts and solvates thereof, wherein: A is an optionally substituted non-aromatic heterocycle; each of D₁ and D₂ is independently N or CR₁; each of E₁, E₂ and E₃ is independently N or CR₂; X is optionally substituted heteroaryl; Y is O, C(O), CH(OH), or CH₂; each R₁ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A; each R₂ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A; each R_A is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and each R_B is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle.

Preferred compounds inhibit the proline transporter, and particular compounds do so without substantially affecting the dopamine or glycine transporters.

Another embodiment of the invention encompasses pharmaceutical compositions of the various compounds described herein.

Another embodiment encompasses methods of improving cognitive performance, and of treating, managing and/or preventing various diseases and disorders, using compounds of the invention.

4. BRIEF DESCRIPTION OF THE FIGURES

Certain aspects of the invention may be understood with reference to the attached figures.

Figure 1 shows differences between wildtype and SLC6A7-knockout mice in a conditioned response test.

Figure 2 shows the effect of a compound of the invention administered to mice prior to the learning phase of a conditioned response test.

Figure 3 shows the effect of a compound of the invention administered to mice prior to a context test.

5. DETAILED DESCRIPTION OF THE INVENTION

This invention is based, in part, on the discovery that the proline transporter encoded by the human gene at map location 5q31-q32 (SLC6A7 gene; GENBANK accession no. NM_014228) can be a potent modulator of mental performance in mammals. In particular, it has been found that genetically engineered mice that do not express a functional product of the murine ortholog of the SLC6A7 gene display significantly increased cognitive function, attention span, learning, and memory relative to control animals. It is believed that this is the first report of experimental data tying inhibition of the proline transporter to a beneficial pharmacological effect.

In view of this discovery, the protein product associated with the SLC6A7 coding region was used to discover compounds that may improve cognitive performance and may be useful in the treatment, prevention and/or management of diseases and disorders such as Alzheimer's disease, autism, cognitive disorders, dementia, learning disorders, and short- and long-term memory loss.

5.1. Definitions

Unless otherwise indicated, the term "alkenyl" means a straight chain, branched and/or cyclic hydrocarbon having from 2 to 20 (e.g., 2 to 10 or 2 to 6) carbon atoms, and including at least one carbon-carbon double bond. Representative alkenyl moieties include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl and 3-decenyl.

Unless otherwise indicated, the term "alkyl" means a straight chain, branched and/or cyclic ("cycloalkyl") hydrocarbon having from 1 to 20 (e.g., 1 to 10 or 1 to 4) carbon atoms. Alkyl moieties having from 1 to 4 carbons are referred to as "lower alkyl." Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl and dodecyl. Cycloalkyl moieties may be monocyclic or

multicyclic, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and adamantyl. Additional examples of alkyl moieties have linear, branched and/or cyclic portions (e.g., 1-ethyl-4-methyl-cyclohexyl). The term "alkyl" includes saturated hydrocarbons as well as alkenyl and alkynyl moieties.

5 Unless otherwise indicated, the term "alkylaryl" or "alkyl-aryl" means an alkyl moiety bound to an aryl moiety.

Unless otherwise indicated, the term "alkylheteroaryl" or "alkyl-heteroaryl" means an alkyl moiety bound to a heteroaryl moiety.

10 Unless otherwise indicated, the term "alkylheterocycle" or "alkyl-heterocycle" means an alkyl moiety bound to a heterocycle moiety.

Unless otherwise indicated, the term "alkynyl" means a straight chain, branched or cyclic hydrocarbon having from 2 to 20 (e.g., 2 to 6) carbon atoms, and including at least one carbon-carbon triple bond. Representative alkynyl moieties include acetylenyl, propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-methyl-1-butylnyl, 4-pentylnyl, 15 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonylnyl, 2-nonylnyl, 8-nonylnyl, 1-decynyl, 2-decynyl and 9-decynyl.

Unless otherwise indicated, the term "alkoxy" means an -O-alkyl group. Examples of alkoxy groups include, but are not limited to, -OCH₃, -OCH₂CH₃, 20 -O(CH₂)₂CH₃, -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, and -O(CH₂)₅CH₃.

Unless otherwise indicated, the term "aryl" means an aromatic ring or an aromatic or partially aromatic ring system composed of carbon and hydrogen atoms. An aryl moiety may comprise multiple rings bound or fused together. Examples of aryl moieties include anthracenyl, azulenyl, biphenyl, fluorenyl, indan, indenyl, naphthyl, 25 phenanthrenyl, phenyl, 1,2,3,4-tetrahydro-naphthalene, and tolyl.

Unless otherwise indicated, the term "arylalkyl" or "aryl-alkyl" means an aryl moiety bound to an alkyl moiety.

Unless otherwise indicated, the term "DTIC₅₀" means an IC₅₀ against human recombinant dopamine transporter as determined using the assay described in the 30 Examples, below.

Unless otherwise indicated, the term "GTIC₅₀" means an IC₅₀ for human recombinant glycine transporter as determined using the assay described in the Examples, below.

Unless otherwise indicated, the terms "halogen" and "halo" encompass fluorine, chlorine, bromine, and iodine.

Unless otherwise indicated, the term "heteroalkyl" refers to an alkyl moiety (*e.g.*, linear, branched or cyclic) in which at least one of its carbon atoms has been replaced
5 with a heteroatom (*e.g.*, N, O or S).

Unless otherwise indicated, the term "heteroaryl" means an aryl moiety wherein at least one of its carbon atoms has been replaced with a heteroatom (*e.g.*, N, O or S). Examples include acridinyl, benzimidazolyl, benzofuranyl, benzoisothiazolyl, benzoisoxazolyl, benzoquinazolinyl, benzothiazolyl, benzoxazolyl, furyl, imidazolyl,
10 indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phthalazinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, tetrazolyl, thiazolyl, and triazinyl.

Unless otherwise indicated, the term "heteroarylalkyl" or "heteroaryl-alkyl" means a heteroaryl moiety bound to an alkyl moiety.

Unless otherwise indicated, the term "heterocycle" refers to an aromatic, partially aromatic or non-aromatic monocyclic or polycyclic ring or ring system comprised of carbon, hydrogen and at least one heteroatom (*e.g.*, N, O or S). A heterocycle may comprise multiple (*i.e.*, two or more) rings fused or bound together. Heterocycles include heteroaryls. Examples include benzo[1,3]dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl,
20 cinnolyl, furanyl, hydantoinyl, morpholinyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyrrolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and valerolactamyl.

Unless otherwise indicated, the term "heterocyclealkyl" or "heterocycle-alkyl" refers to a heterocycle moiety bound to an alkyl moiety.

Unless otherwise indicated, the term "heterocycloalkyl" refers to a non-aromatic heterocycle.

Unless otherwise indicated, the term "heterocycloalkylalkyl" or "heterocycloalkyl-alkyl" refers to a heterocycloalkyl moiety bound to an alkyl moiety.

Unless otherwise indicated, the terms "manage," "managing" and "management"
30 encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms

encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

Unless otherwise indicated, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including

5 inorganic acids and bases and organic acids and bases. Suitable pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

10 Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic,

15 salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art. *See, e.g., Remington's Pharmaceutical Sciences* (18th ed., Mack Publishing, Easton PA: 1990) and *Remington: The Science and*

20 *Practice of Pharmacy* (19th ed., Mack Publishing, Easton PA: 1995).

Unless otherwise indicated, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity of the disease or disorder. In other words, the terms encompass prophylaxis.

25 Unless otherwise indicated, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease or condition, or one or more symptoms associated with the disease or condition, or to prevent its recurrence. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of

30 the disease or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

12

Unless otherwise indicated, the term "PTIC₅₀" means an IC₅₀ for human recombinant Na⁺-dependent proline transporter as determined using the assay described in the Examples, below.

Unless otherwise indicated, the term "specific proline transporter inhibitor" means a compound that has a PTIC₅₀ of less than about 200 nM.

Unless otherwise indicated, the term "substituted," when used to describe a chemical structure or moiety, refers to a derivative of that structure or moiety wherein one or more of its hydrogen atoms is substituted with a chemical moiety or functional group such as, but not limited to, alcohol, aldehyde, alkoxy, alkanoyloxy, alkoxycarbonyl, alkenyl, alkyl (*e.g.*, methyl, ethyl, propyl, *t*-butyl), alkynyl, alkylcarbonyloxy (-OC(O)alkyl), amide (-C(O)NH-alkyl- or -alkylNHC(O)alkyl), amidinyl (-C(NH)NH-alkyl or -C(NR)NH₂), amine (primary, secondary and tertiary such as alkylamino, arylamino, arylalkylamino), aroyl, aryl, aryloxy, azo, carbamoyl (-NHC(O)O-alkyl- or -OC(O)NH-alkyl), carbamyl (*e.g.*, CONH₂, CONH-alkyl, CONH-aryl, and CONH-arylalkyl), carbonyl, carboxyl, carboxylic acid, carboxylic acid anhydride, carboxylic acid chloride, cyano, ester, epoxide, ether (*e.g.*, methoxy, ethoxy), guanidino, halo, haloalkyl (*e.g.*, -CCl₃, -CF₃, -C(CF₃)₃), heteroalkyl, hemiacetal, imine (primary and secondary), isocyanate, isothiocyanate, ketone, nitrile, nitro, oxo, phosphodiester, sulfide, sulfonamido (*e.g.*, SO₂NH₂), sulfone, sulfonyl (including alkylsulfonyl, arylsulfonyl and arylalkylsulfonyl), sulfoxide, thiol (*e.g.*, sulfhydryl, thioether) and urea (-NHCONH-alkyl-).

Unless otherwise indicated, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

Unless otherwise indicated, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a patient is suffering from the specified disease or

disorder, which reduces the severity of the disease or disorder or one or more of its symptoms, or retards or slows the progression of the disease or disorder.

Unless otherwise indicated, the term "include" has the same meaning as "include, but are not limited to," and the term "includes" has the same meaning as "includes, but is not limited to." Similarly, the term "such as" has the same meaning as the term "such as, but not limited to."

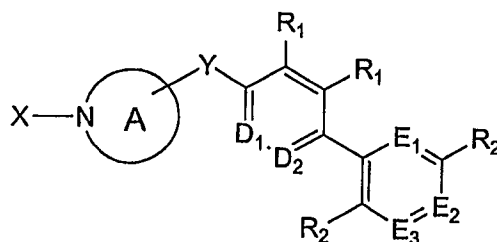
Unless otherwise indicated, one or more adjectives immediately preceding a series of nouns is to be construed as applying to each of the nouns. For example, the phrase "optionally substituted alky, aryl, or heteroaryl" has the same meaning as "optionally substituted alky, optionally substituted aryl, or optionally substituted heteroaryl."

It should be noted that a chemical moiety that forms part of a larger compound may be described herein using a name commonly accorded it when it exists as a single molecule or a name commonly accorded its radical. For example, the terms "pyridine" and "pyridyl" are accorded the same meaning when used to describe a moiety attached to other chemical moieties. Thus, the two phrases "XOH, wherein X is pyridyl" and "XOH, wherein X is pyridine" are accorded the same meaning, and encompass the compounds pyridin-2-ol, pyridin-3-ol and pyridin-4-ol.

It should also be noted that any atom shown in a drawing with unsatisfied valences is assumed to be attached to enough hydrogen atoms to satisfy the valences. In addition, chemical bonds depicted with one solid line parallel to one dashed line encompass both single and double (*e.g.*, aromatic) bonds, if valences permit. Structures that represent compounds with one or more chiral centers, but which do not indicate stereochemistry (*e.g.*, with bolded or dashed lines), encompasses pure stereoisomers and mixtures (*e.g.*, racemic mixtures) thereof. Similarly, names of compounds having one or more chiral centers that do not specify the stereochemistry of those centers encompass pure stereoisomers and mixtures thereof.

5.2. Compounds of the Invention

This invention encompasses compounds of formula I:

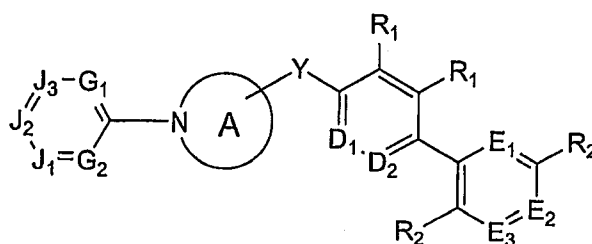


14

(I)

- and pharmaceutically acceptable salts and solvates thereof, wherein: A is an optionally substituted non-aromatic heterocycle; each of D₁ and D₂ is independently N or CR₁; each of E₁, E₂ and E₃ is independently N or CR₂; X is optionally substituted heteroaryl; Y is O, C(O), CH(OH), or CH₂; each R₁ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A; each R₂ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A; each R_A is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and each R_B is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle.

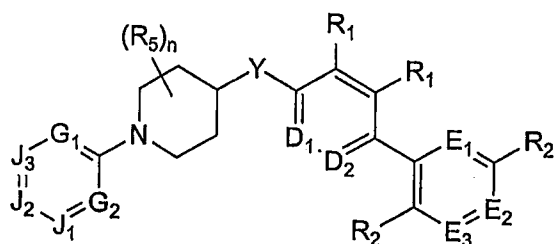
One embodiment of the invention encompasses compounds of formula IA:



(IA)

- and pharmaceutically acceptable salts and solvates thereof.

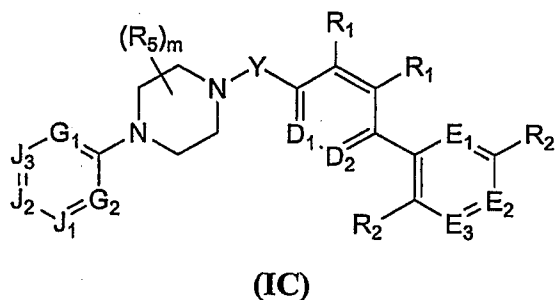
Another encompasses compounds of formula IB:



(IB)

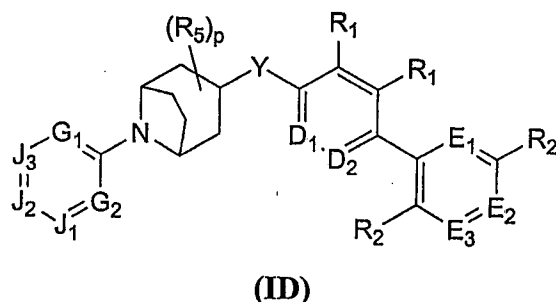
- and pharmaceutically acceptable salts and solvates thereof, wherein: each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and n is 0-5.

Another encompasses compounds of formula **IC**:



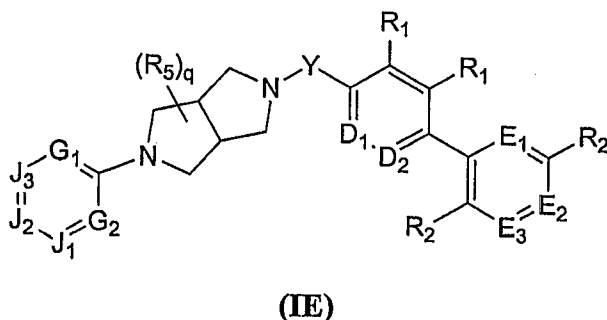
and pharmaceutically acceptable salts and solvates thereof, wherein: Y is O, C(O) or CH₂; each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and m is 0-4.

Another encompasses compounds of formula **ID**:



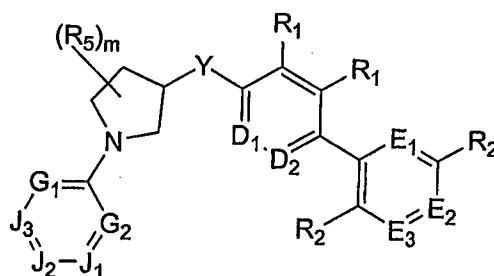
and pharmaceutically acceptable salts and solvates thereof, wherein: each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and p is 0-7.

Another encompasses compounds of formula **IE**:



and pharmaceutically acceptable salts and solvates thereof, wherein: Y is O, C(O) or CH₂; each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and q is 0-6.

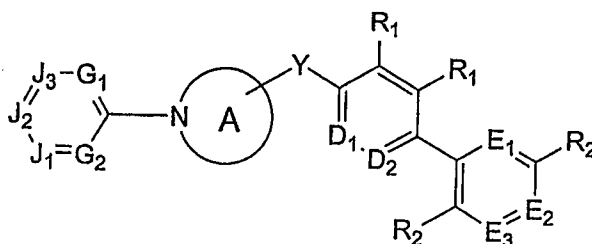
Another encompasses compounds of formula IF:



(IF)

and pharmaceutically acceptable salts and solvates thereof, wherein: each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and m is 0-4.

Another encompasses compounds of formula II:

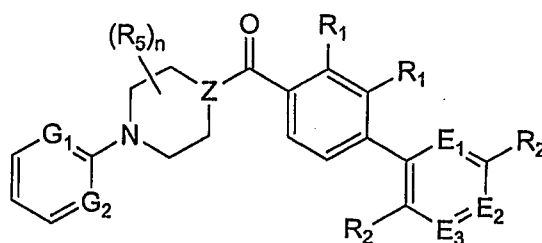


(II)

and pharmaceutically acceptable salts and solvates thereof, wherein: A is an optionally substituted non-aromatic heterocycle; each of D₁ and D₂ is independently N or CR₁; each of E₁, E₂ and E₃ is independently N or CR₂; each of G₁ and G₂ are independently N or CR₃; each of J₁, J₂ and J₃ are independently N or CR₄; Y is O, C(O), CH(OH), or CH₂; each R₁ is independently hydrogen, halogen, or (C₁₋₁₀)alkyl; each R₂ is independently halogen, cyano, R_{2A}, OR_{2A}, or SO₂R_{2A}; each R_{2A} is independently hydrogen or

(C₁₋₁₀)alkyl optionally substituted with one or more halogens; each R₃ is independently hydrogen, cyano, or (C₁₋₁₀)alkyl optionally substituted with one or more halogens; and each R₄ is independently hydrogen, cyano, or (C₁₋₁₀)alkyl optionally substituted with one or more halogens.

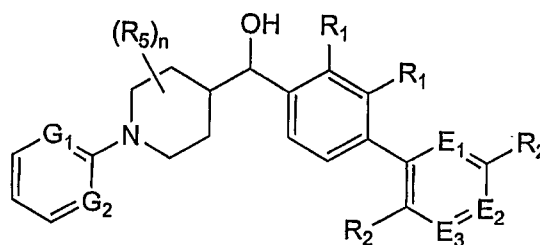
5 Another encompasses compounds of formula **IIA**:



(IIA)

and pharmaceutically acceptable salts and solvates thereof, wherein: Z is CR₅ or N; each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}),
 10 N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and n is 0-5 if Z is CR₅, or 0-4 if Z is N.

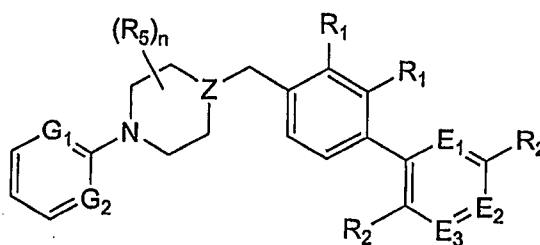
15 Another encompasses compounds of formula **IIB**:



(IIB)

and pharmaceutically acceptable salts and solvates thereof.

Another encompasses compounds of formula **IIC**:



(IIC)

and pharmaceutically acceptable salts and solvates thereof, wherein: Z is CR₅ or N; each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A}; each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; each
5 R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and n is 0-5 if Z is CR₅, or 0-4 if Z is N.

In one embodiment of the invention encompassed by formula II (and IIA-C, as appropriate), at least one of G₁, G₂, J₁, J₂ or J₃ is N. In another, at least one of J₁, J₂ and J₃
10 is CR₄. In another, if Y is C(O), A is piperazine, all of G₁, G₂, J₁, J₃, D₁, D₂, E₁, and E₃ are CH, and all of R₁ are hydrogen, then none of R₂ are lower alkyl. In another, if Y is C(O), A is piperazine, D₂ and E₁ are both N, and all of R₁ and R₂ are hydrogen, then R₄ is not cyano. In another, if Y is O, A is pyrrolidine, all of G₁, G₂, J₁, J₃, D₁, D₂, E₁, E₂, and E₃ are CH, and all of R₁ are hydrogen, then at least one R₂ is not hydrogen. In another, if
15 Y is CH₂, A is piperazine, all of G₂, J₁, J₂, J₃, D₁, and D₂ are CH, all of E₁, E₂ and E₃ are CR₂, and all of R₁ are hydrogen, at least one R₂ is not hydrogen. In another, if Y is C(O) or CH₂, A is piperazine, at least one of G₁ and G₂ is N, all of J₁, J₂, J₃, D₁, D₂, E₁, E₂ and E₃ are CH, and all of R₁ are hydrogen, then at least one R₂ is not hydrogen.

Various other embodiments of the invention, which pertain to each of the above
20 formulae (e.g., I, IA-F, II and IIA-C) when appropriate (when the particular formula contains the moiety referred to), are as follows.

In one, A is optionally substituted non-aromatic heterocycle containing no more than two nitrogen atoms (*i.e.*, the heterocycle, which contains no more than two nitrogen atoms, is optionally substituted).

25 In another, A is monocyclic. In another, A is bicyclic. In another, A is unsubstituted. In another, A is optionally substituted pyrrolidine, piperidine, piperazine, hexahydropyrimidine, 1,2,3,6-tetrahydropyridine, octahydrocyclopenta[c]pyrrole, or octahydropyrrolo[3,4-c]pyrrole.

30 In another, one of D₁ and D₂ is N. In another, both D₁ and D₂ are N. In another, both D₁ and D₂ are CR₁.

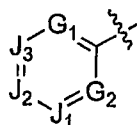
In another, one of E₁, E₂ and E₃ is N. In another, two of E₁, E₂ and E₃ are N. In another, all of E₁, E₂ and E₃ are N. In another, all of E₁, E₂ and E₃ are independently CR₂.

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In another, R_1 is hydrogen, halogen, or optionally substituted alkyl. In another, R_1 is OR_A and, for example, R_A is hydrogen or optionally substituted alkyl.

In another, R_2 is hydrogen, halogen, or optionally substituted alkyl. In another, R_2 is OR_A and, for example, R_A is hydrogen or optionally substituted alkyl.

5 In another, X is an optionally substituted 5-, 6-, 9- or 10-membered heteroaryl. In another, X is optionally substituted 5- or 6-membered heteroaryl. In another, X is of the formula:



10 wherein: each of G_1 and G_2 are independently N or CR_3 ; each of J_1 , J_2 and J_3 are independently N or CR_4 ; each R_3 is independently hydrogen, halogen, cyano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, or SO_2R_A ; and each R_4 is independently hydrogen, halogen, cyano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, or SO_2R_A ; provided that at least one of J_1 , J_2 and J_3 is CR_4 .

15 In another, one of G_1 and G_2 is N. In another, both G_1 and G_2 are N. In another, both G_1 and G_2 are CR_3 .

In another, one of J_1 , J_2 and J_3 is N. In another, two of J_1 , J_2 and J_3 are N. In another, all of J_1 , J_2 and J_3 are independently CR_4 .

In another, R_3 is hydrogen, halogen, or optionally substituted alkyl. In another, R_3 is OR_A and, for example, R_A is hydrogen or optionally substituted alkyl.

20 In another, R_4 is hydrogen, halogen, or optionally substituted alkyl. In another, R_4 is OR_A and, for example, R_A is hydrogen or optionally substituted alkyl.

In another, Y is $C(O)$. In another, Y is $CH(OH)$. In another, Y is CH_2 .

Examples of specific compounds include:

- (1-(pyrimidin-2-yl)piperidin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanol;
 25 (4'-chlorobiphenyl-4-yl)(2,6-dimethyl-4-(pyridin-2-yl)piperazin-1-yl)methanone;
 (3'-chloro-3-methoxybiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
 (4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
 (3-fluoro-4'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (4'-chlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 30 (2'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (4-(benzo[d]oxazol-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
 biphenyl-4-yl(4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)methanone;

- (S)-(2-benzyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(6-p-tolylpyridin-3-yl)methanone;
- 5 (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
- (6-(4-chlorophenyl)pyridin-3-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(6-(4-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
- 10 (5-(4-chlorophenyl)isoxazol-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(1-(pyridin-2-yl)piperidin-4-yl)methanone;
- biphenyl-4-yl(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)methanone;
- (8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 15 biphenyl-4-yl(1-(pyrimidin-2-yl)azetidin-3-yl)methanone;
- (6-(4-chloro-3-(trifluoromethyl)phenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (6-(4-chloro-3-methylphenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 20 (4'-chlorobiphenyl-4-yl)(1-(pyridin-2-yl)piperidin-4-yl)methanone;
- (2-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3,4'-dimethylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (5-(3-chlorophenyl)pyridin-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (4-(pyrimidin-2-yl)piperazin-1-yl)(5-p-tolylpyridin-2-yl)methanone;
- 25 (4-(pyridin-2-yl)piperazin-1-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (1-(pyrimidin-2-yl)piperidin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (3-fluoro-3'-(trifluoromethyl)biphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (4-(pyrimidin-2-yl)piperazin-1-yl)(3'-(trifluoromethoxy)biphenyl-4-yl)methanone;
- (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 30 biphenyl-4-yl(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (1-phenyl-5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;

- biphenyl-4-yl(4-(thiazol-2-yl)piperazin-1-yl)methanone;
 (4-(4-chlorophenyl)cyclohexyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 4'-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)biphenyl-3-carbonitrile;
 (4'-(methylsulfonyl)biphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 5 2-(4-((3'-chlorobiphenyl-4-yl)(hydroxy)methyl)piperidin-1-yl)pyrimidin-5-ol;
 (4-(pyridin-3-yl)phenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (3'-chloro-3-hydroxybiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
 1-(4'-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)biphenyl-3-yl)ethanone;
 (2',4'-difluoro-3-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 10 (5-phenyl-1H-pyrrol-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (6-(4-chlorophenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (5'-chloro-2'-fluorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanone;
 2-(4-(biphenylcarbonyl)piperazin-1-yl)nicotinonitrile;
 15 2-(4-(biphenyl-4-yloxy)piperidin-1-yl)pyrimidine;
 (2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl)(1-(pyrimidin-2-yl)pyrrolidin-3-yl)methanone;
 (4-(4-methylthiophen-2-yl)phenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
 (4'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 20 (2-fluoro-4'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 biphenyl-4-yl(3-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl)(4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
 biphenyl-4-yl(4-(5-methylpyridin-2-yl)piperazin-1-yl)methanone;
 25 biphenyl-4-yl(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (1-(pyridin-2-yl)piperidin-4-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
 (6-(3-chlorophenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (4-(pyrimidin-2-yl)piperazin-1-yl)(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
 (4-(pyrimidin-2-yl)piperazin-1-yl)(6-p-tolylpyridin-3-yl)methanone;
 30 (4'-chloro-3'-(trifluoromethyl)biphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
 (4-(2-chloropyridin-4-yl)phenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (2',4'-difluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (6-(2,4-difluorophenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;

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2

- (3',5'-dichlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
2-(4-(biphenyl-4-ylmethyl)piperazin-1-yl)pyrimidine;
(4'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
(6-(3-chlorophenyl)pyridin-3-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-
5 2(1H)-yl)methanone;
(1-(pyridin-2-yl)piperidin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
(2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(5-methylpyridin-2-yl)piperazin-1-yl)methanone;
10 1-(biphenylcarbonyl)-4-(pyrimidin-2-yl)piperazin-2-one;
biphenyl-4-yl(1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanone;
(3'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
biphenyl-4-yl(1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanol;
(3'-chlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
15 (4-(pyrimidin-2-yl)piperazin-1-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
(3'-chlorobiphenyl-4-yl)(1-(5-hydroxypyrimidin-2-yl)piperidin-4-yl)methanone;
(4'-ethylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(4-methylpyrimidin-2-yl)piperazin-1-yl)methanone;
(6-(2,4-difluorophenyl)pyridin-3-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-
20 2(1H)-yl)methanone;
(4'-chlorobiphenyl-4-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone;
(5-methyl-1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
biphenyl-4-yl(4-(5-ethylpyrimidin-2-yl)piperazin-1-yl)methanone;
25 (4-(pyridin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
(4-(pyridin-2-yl)phenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(pyrazin-2-yl)piperazin-1-yl)methanone;
(4'-methoxybiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(6-methylpyridazin-3-yl)piperazin-1-yl)methanone;
30 4'-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)biphenyl-4-carbonitrile;
(2,6-dimethyl-4-(pyridin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
(5-phenylthiophen-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;

- (6-(5-methylthiophen-2-yl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(pyridin-4-yl)piperazin-1-yl)methanone;
(R)-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 5 biphenyl-4-yl((2S,5S)-2,5-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(3'-chlorobiphenyl-4-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone;
(4-(pyrimidin-2-yl)piperazin-1-yl)(2'-(trifluoromethyl)biphenyl-4-yl)methanone;
(S)-(4'-chlorobiphenyl-4-yl)(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(5'-chloro-2'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 10 (4-(5-methylthiophen-2-yl)phenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
biphenyl-4-yl(4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)methanone;
(S)-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
(S)-(2-benzyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-chlorobiphenyl-4-yl)methanone;
- 15 biphenyl-4-yl(4-(pyridazin-3-yl)piperazin-1-yl)methanone;
(6-(4-methylthiophen-2-yl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
1-(2',4'-difluorobiphenylcarbonyl)-4-(pyrimidin-2-yl)piperazine-2-carbonitrile;
(4'-chlorobiphenyl-4-yl)((2S,5S)-2,5-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 20 biphenyl-4-yl(2-tert-butyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(S)-biphenyl-4-yl(2-isopropyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(2,6-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(3'-chloro-2'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4-(pyrimidin-2-yl)piperazin-1-yl)(6-(4-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
- 25 (4'-chloro-3'-methylbiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
(3'-chloro-2'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(2,6-dimethyl-4-(pyridin-2-yl)piperazin-1-yl)(4'-methylbiphenyl-4-yl)methanone;
3'-chloro-4-(1-(pyrimidin-2-yl)piperidine-4-carbonyl)biphenyl-3-yl acetate;
biphenyl-4-yl(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)methanone;
- 30 1-(biphenyl-4-ylmethyl)-4-(pyrimidin-2-yl)piperazin-2-one;
(3',4'-dichlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(3'-chlorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanol;
(S)-biphenyl-4-yl(2-isobutyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;

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- (3'-chlorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanone;
(S)-(4'-chlorobiphenyl-4-yl)(2-isopropyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4'-methylbiphenyl-4-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone;
(S)-(2-isopropyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
5 (3'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanol;
(S)-(2-isobutyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
(S)-(4'-chlorobiphenyl-4-yl)(2-isobutyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
10 (3'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)pyrrolidin-3-yl)methanone;
(2',4'-difluorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanone;
4'-(4-(pyridin-2-yl)piperazine-1-carbonyl)biphenyl-4-carbonitrile;
(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
15 methyl 1-(5'-chloro-2'-fluorobiphenylcarbonyl)-4-(pyrimidin-2-yl)piperazine-2-carboxylate;
(4-(benzo[d]oxazol-2-yl)piperazin-1-yl)(4'-chlorobiphenyl-4-yl)methanone;
(3'-chlorobiphenyl-4-yl)(4-(thiazol-2-yl)piperazin-1-yl)methanone;
(4-(5-chlorothiophen-2-yl)phenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
20 1-(5'-chloro-2'-fluorobiphenylcarbonyl)-4-(pyrimidin-2-yl)piperazine-2-carbonitrile;
(4-phenylthiophen-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(pyrimidin-2-yl)-3,4-dihydroquinoxalin-1(2H)-yl)methanone;
(5'-chloro-2'-fluorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanol;
25 (5-phenylfuran-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4'-chlorobiphenyl-4-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
4-(4'-chlorobiphenyl-4-yl)-1-(pyrimidin-2-yl)piperidin-4-ol;
(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
30 biphenyl-4-yl(5-(pyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
(3'-chlorobiphenyl-4-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;

- biphenyl-4-yl((2S,5S)-2,5-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
1-((3'-chlorobiphenyl-4-yl)methyl)-N,N-dimethyl-4-(pyrimidin-2-yl)piperazine-2-
carboxamide;
(2',4'-difluorobiphenyl-4-yl)(3-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
5 (4-(benzo[d]thiazol-2-yl)piperazin-1-yl)(biphenyl-4-yl)methanone;
biphenyl-4-yl(4-(quinolin-2-yl)piperazin-1-yl)methanone;
4-(biphenyl-4-yl)-1-(pyrimidin-2-yl)piperidin-4-ol;
4'-chloro-N-methyl-N-(2-(methyl(pyrimidin-2-yl)amino)ethyl)biphenyl-4-carboxamide;
and
10 2-(biphenyl-4-yl)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethanone.

Preferred compounds of the invention are specific proline transporter inhibitors. Particular specific proline transporter inhibitors have a PTIC₅₀ of less than about 150, 125, 100, 75, 50 or 25 nM.

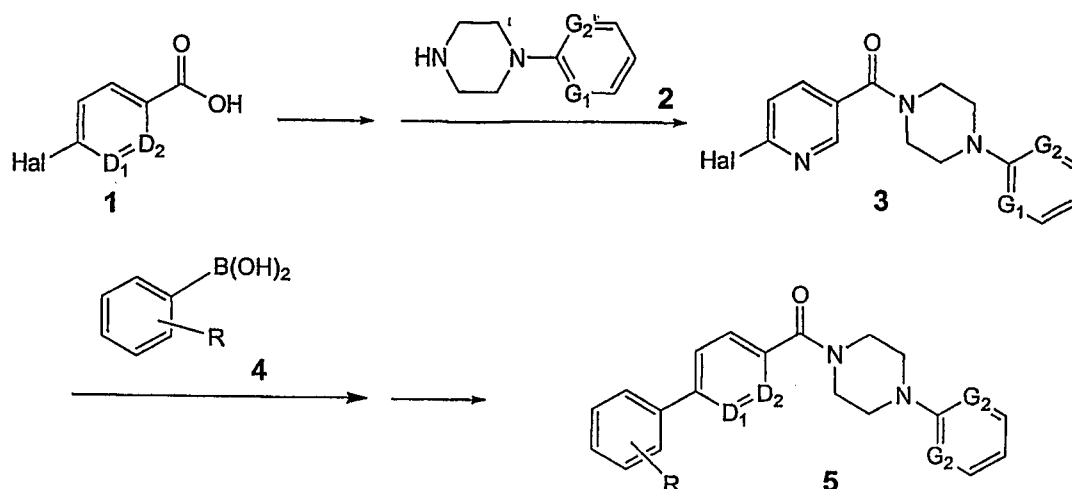
- Some compounds inhibit the murine Na⁺-dependent proline transporter, as
15 determined by the method described in the Examples below, with an IC₅₀ of less than about 150, 125, 100, 75, 50 or 25 nM.

- Some compounds do not significantly inhibit the dopamine transporter. For example, some specific proline transporter inhibitors inhibit the dopamine transporter with an IC₅₀ of greater than about 0.5, 1, 2.5, 5, or 10 μM as determined using the assay
20 described in the Examples below.

Some compounds do not significantly inhibit the glycine transporter. For example, some specific proline transporter inhibitors inhibit the glycine transporter with an IC₅₀ of greater than about 0.5, 1, 2.5, 5, or 10 μM as determined using the assay described in the Examples below.

25 5.3. Preparation of Compounds

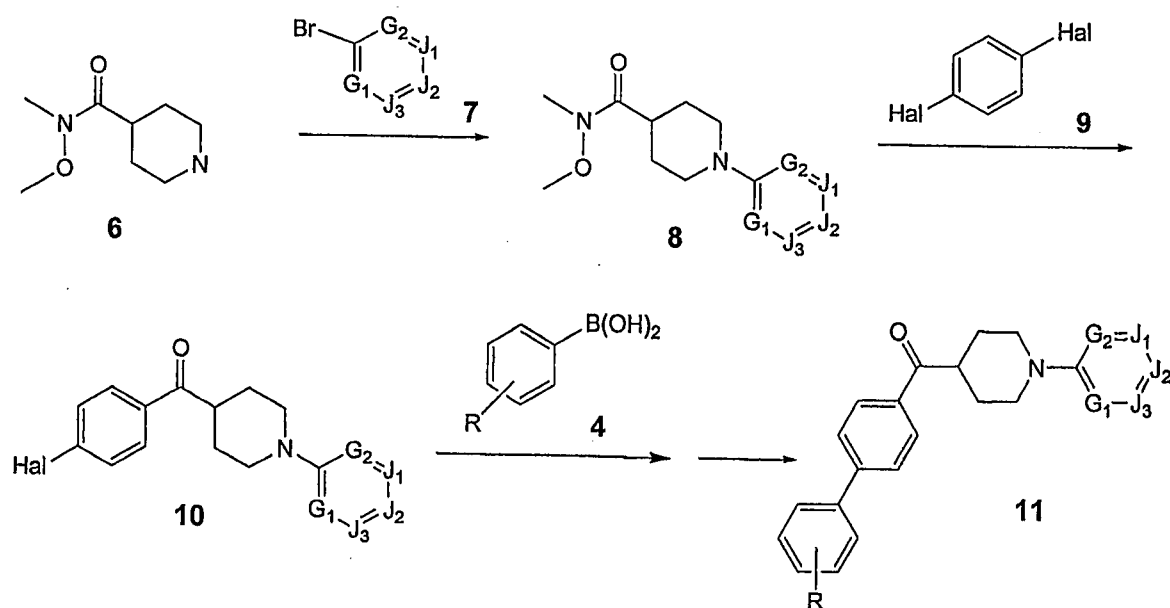
Compounds of the invention may be obtained or prepared using synthetic methods known in the art, as well as those described herein. For example, various piperazine-based compounds can be prepared according to the general approach shown in Scheme I:



Scheme I

In this approach, a compound of formula 1 (D₁ and D₂ are defined herein) is contacted with a compound of formula 2 (G₁ and G₂ are defined herein) under suitable conditions to provide a compound of formula 3. Suitable conditions include, for example, EDCI, HOBT, and Hunig's base in DMF. Compound 3 is then contacted with compound 4 under suitable conditions to provide a compound of formula 5. Suitable conditions include, for example, Pd(Ph₃P)₄, K₃PO₄, DME, water and heat.

Various piperidine-based compounds can be prepared according to the general approach shown below in Scheme II:



Scheme II

In this approach, a compound of formula 6 (e.g., as a TFA salt) is contacted with a compound of formula 7 (G₁, G₂, J₁, J₂ and J₃ are defined herein) under suitable conditions

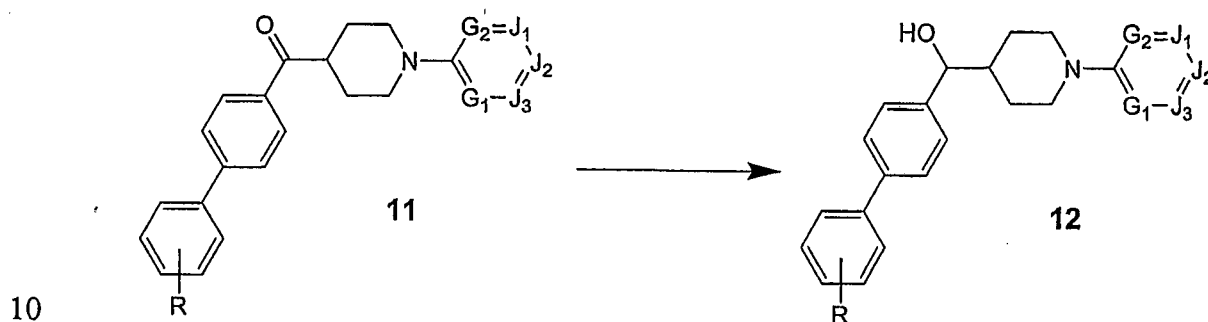
to provide compound 8. Suitable conditions include, for example, TEA and heat.

Compound 8 is then contacted with compound 9 under suitable conditions to provide compound 10. Here, suitable conditions include, for example, *n*-BuLi in THF.

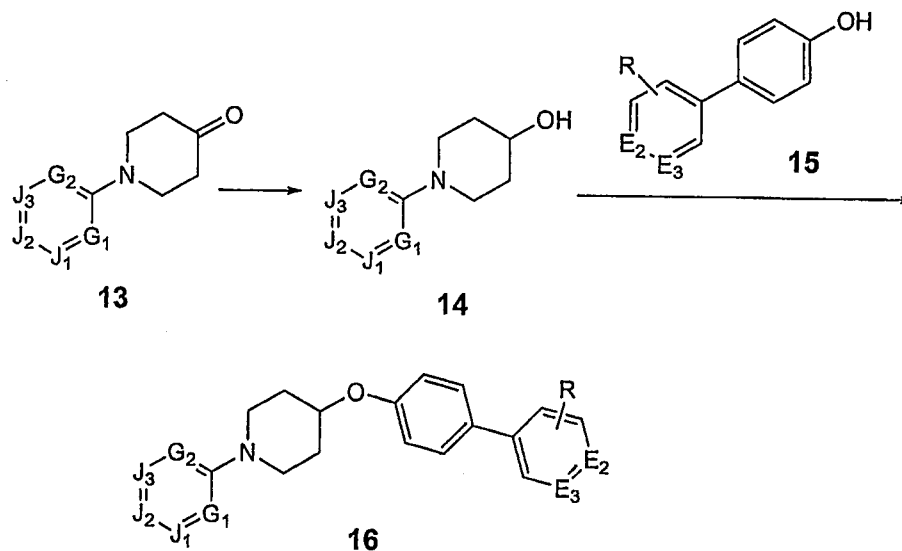
Compound 10 is then contacted with a compound of formula 4 to provide the final

- 5 compound, 11. Here, suitable conditions include, for example, $\text{Pd}(\text{Ph}_3\text{P})_4$, K_3PO_4 , DME, water and heat.

If desired, compounds of formula 11 can be reduced under suitable conditions (*e.g.*, sodium borohydride) to provide compounds of formula 12, as shown below in Scheme III:

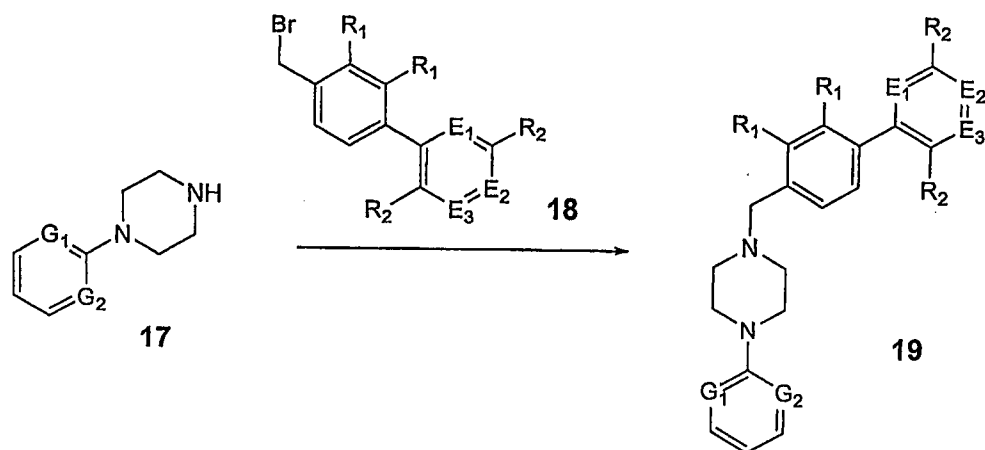


Compounds containing an ether link can be prepared by routes such as that shown in Scheme IV:



15 In this approach, a compound of formula 13 is reduced (*e.g.*, with sodium borohydride) to provide compound 14, which is then coupled under suitable reaction conditions with a compound of formula 15 to provide compound 16. Suitable reaction conditions include, for example, PPh_3 and DEAD in THF.

Compounds containing a methylene link can be prepared by routes such as that shown in Scheme V:



- 5 In this approach, a compound of formula 17 is contacted with compound 18 under suitable reaction conditions to provide compound 19. Suitable reaction conditions include, for example, potassium carbonate in DMF.

Some specific reaction conditions that can be used in the various synthetic schemes shown above are provided in the Examples, below.

10 5.4. Methods of Treatment

- One embodiment of this invention encompasses a method of inhibiting a proline transporter, which comprises contacting a proline transporter (*in vitro* or *in vivo*) with a sufficient amount of a compound of the invention. Preferred proline transporters are encoded by the human gene SLC6A7, the murine ortholog thereof, or a nucleic acid molecule that encodes a proline transporter and that hybridizes under standard conditions to the full length of either.

- Another embodiment encompasses a method of improving the cognitive performance of a human patient, which comprises administering to the patient an effective amount of a compound of the invention. Examples of improved cognitive performance include enhanced learning (*e.g.*, learning more quickly), improved comprehension, improved reasoning, and improved short- and/or long-term memory.

- Another embodiment encompasses a method of treating, managing or preventing a disease or disorder in a human patient, which comprises administering to the patient a therapeutically or prophylactically effective amount of a compound of the invention. Examples of diseases and disorders include Alzheimer's disease, autism, cognitive

disorders (e.g., difficulty in thinking, reasoning, or problem solving), dementia, learning disorders (e.g., dyslexia, dyscalculia, dysgraphia, dysphasia, dysnomia), and short- and long-term memory loss. Additional disorders include adverse sequelae of brain damage caused by, for example, oxygen starvation, traumatic injury or stroke.

5 **5.5. Pharmaceutical Compositions**

This invention encompasses pharmaceutical compositions and dosage forms comprising compounds of the invention as their active ingredients. Pharmaceutical compositions and dosage forms of this invention may optionally contain one or more pharmaceutically acceptable carriers or excipients. Certain pharmaceutical compositions are single unit dosage forms suitable for oral, topical, mucosal (e.g., nasal, pulmonary, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The formulation should suit the mode of administration. For example, oral administration may require enteric coatings to protect the active ingredient from degradation within the gastrointestinal tract. In another example, the active ingredient may be administered in a liposomal formulation to shield it from degradative enzymes, facilitate transport in circulatory system, and/or effect delivery across cell membranes to intracellular sites.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These

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and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

6. EXAMPLES

5 6.1. SLC6A7-Deficient Mice

To determine the effect of inhibiting the Na⁺-dependent proline transporter, mice homozygous for a genetically engineered mutation in the murine ortholog of the human SLC6A7 gene ("knockout" or "KO" mice) were generated using correspondingly mutated ES cell clones from the OMNIBANK collection of mutated murine ES cell clones (*see* 10 *generally* U.S. Patent No. 6,080,576).

Mice that were heterozygous, homozygous, or wildtype for the mutated allele were produced by breeding heterozygous animals capable of germline transmission of the mutant allele. The mutated allele assorted according to standard Mendelian genetics. The mice were subjected to a battery of medical and behavioral tests, including those 15 described below.

6.1.1. Trace Conditioning

Trace aversive conditioning measures a form of classical conditioning with temporal separation between the end of a conditioned stimulus (CS) (in this case an 80 db tone) and the onset of an unconditioned stimulus (US) (in this case a 0.7 mA electric 20 current) that are separated by a temporal "trace" (approximately 30 seconds). This assay measures higher-order learning (usually associated with hippocampal function or the cortex) by determining how rapidly the test subjects learn to associate the US with CS. The test animals are scored by calculating the percent freezing time as determined by comparing the difference between percent freezing post-CS and the percent freezing pre- 25 CS.

As shown in Figure 1, both male and female animals that were homozygous for the mutation in the murine ortholog of the SLC6A7 gene displayed significantly higher freezing percentages (approximately 50 percent for an average of 16 test animals) as compared to their wildtype control counterparts (approximately 30 percent for an average 30 of 16 control animals). These results indicate that homozygous mutant animals perform significantly better in this well established test for cognitive performance.

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6.1.2. Water Maze

The Morris water maze used a circular pool 2 meters in diameter and 40 cm in depth. See, e.g., Morris, 1984, *J. Neurosci. Methods* 11:47-60, Guillou *et al.*, 1999, *J. Neurosci.* 19:6183-90. The pool was filled to a depth of 30 cm with water at a
5 temperature of 24–26°C, made opaque by the addition of non-toxic water-based paint. The “escape” platform was about 30 cm high with a plastic disc 18 cm in diameter on top. The platform was placed about 0.5 cm below the water surface. The mouse was released into the pool facing the wall from one of 4 start positions labeled as N (North), S (South), W (West) or E (East). A videotracking system comprising the camera and the
10 WaterMaze image software (Actimetrics, Inc.) divided the pool into 4 equal quadrants designated as SE, SW, NE, and NW. The software calculates the latency to reach platform, distance to the platform, time spent in each quadrant, swimming speed, and other parameters.

Each trial lasted until the mouse climbed onto the platform or 90 seconds had
15 elapsed. If the mouse did not reach the platform in 90 seconds, the experimenter took it out of the water and gently placed it on the platform. At the end of each trial the mouse remained on the platform for further 20 seconds. There were 4 trials with platform per day with 8-12 min inter-trial intervals. During the inter-trial interval the mouse was kept in a clean cage under a heat lamp.

20 Typically one of two basic protocols were used: the first includes visible and hidden platform phases, and the second only uses a hidden platform phase; both protocols end with a 2 day reversal phase.

The visible phase generally precedes the hidden platform phase. In the visible phase, the pool was surrounded with white curtains in order to hide all external-maze
25 cues/references. During this phase, the platform was made visible with a metal cylinder 8 cm h x 3 cm, which was put on the platform. The start position was the same on each trial, while platform location was randomly changed during the trials. This phase lasted for approximately 3 days.

In the hidden platform phase, the platform was no longer marked and the curtains
30 were removed. A variety of extra-maze cues were optionally placed around the pool. Here the start position was changed every trial, while the platform remained in the same location. This phase typically lasted about 7 days.

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Probe trials were run before the training trials on day 1 and 5 of the hidden phase, and on day 1 of the visible phase, and also after the last trial on day 3 of the visible phase. During the probe trial, the platform was removed from the pool and the mouse was placed in the pool facing the wall in the quadrant opposite from the platform quadrant. The mouse swam for 60 sec and the percentage of time spent in each quadrant was recorded.

In the reversal phase, on each of 2 days, 5 trials were run. During the first trial the platform location was the same as it was in the hidden phase. In the next four trials, the platform was moved to the opposite quadrant. On the following day the platform was there on first trial and then again moved to the left or right adjoining quadrant for the last 4 trials. The start position was always kept opposite to the platform location.

When the above methods were used with SLC6A7 KO mice ($n=12$) and WT ($n=7$) controls, mice were first subjected to the visible platform task. Repeated measures (RM) and analysis of variance (ANOVA) were used to analyze genotype effect on the latency to reach platform over 11 trials.

The trial effect was $F(10, 170) = 8.57, p < 0.001$; the Genotype effect: $F(1, 17) = 0.65, p < 0.43$, interaction Genotype x Trial: $F(10, 170) = 0.42, p < 0.93$. Initially, there was no difference between WT and KO subjects, but a significant decrease in the latency over trials was observed.

When the trials progressed to the hidden platform task, RM ANOVA revealed a significant effect of the trials on the latency to reach platform: $F(19, 323) = 7.2, p < 0.001$. There was also a significant effect of genotype on same parameter: $F(1, 17) = 8.0, p < 0.012$; interaction Genotype x Trials was $F(19, 323) = 1.16, p < 0.29$. Overall, KO subjects had significantly shorter latencies to platform. No significant difference in swimming speed was detected so faster swimming did not account for the faster performance by the KO animals.

During the reversal phase, RM ANOVA was run on 4 trials with the platform switched to another quadrant on each of two days. On both days of reversal phase effect of trials was significant: $F_s(3, 51) > 6.4, p < 0.001$ indicating that both genotypes relearn well. However, there was no significant difference between them on each day of reversal: $F_s(1, 17) < 0.75, p_s > 0.39$, although KO mice did tend to reach the platform faster.

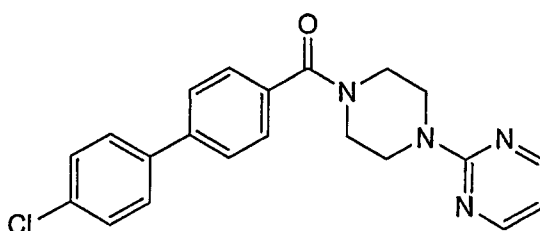
During probe trials, the percent of time spent in each quadrant was compared with 25% chance for WT and KO mice by non-parametric Mann-Whitney test. The first two probe trials run before hidden phase the percent time was not different from chance in

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each quadrant for both genotypes. In the third probe trial run on the fifth day of hidden phase, the platform quadrant time was significantly different from chance for WT [$p < 0.05$] and KO mice [$p < 0.001$]; and the opposite quadrant time was significantly different for KO mice [$p < 0.001$].

- 5 The above data indicate that KO mice learned the hidden platform task more quickly than WT animals. The data further establish that the observed difference cannot be explained by differences in visual abilities or swimming speed between genotypes.

6.2. Preparation of (4-Pyrimidin-2-yl-piperazin-1-yl)-[4-(4-chloromethylphenyl)phenyl]-methanone



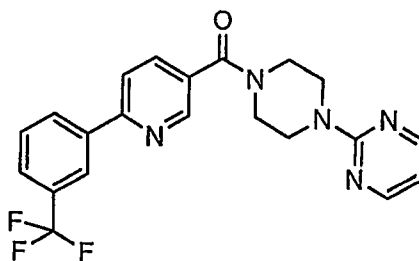
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To a solution of 4'-chloro-biphenyl-4-carboxylic acid (0.1 g, 0.43 mmol) and 1-(2-pyrimidyl)-piperazine (0.07 g, 0.43 mmol) in methylene chloride (3 ml), was added EDCI (0.098 g, 0.43 mmol) and HOAt (0.07 g, 0.43 mmol) triethylamine (0.07 ml, 0.52 mmol). The mixture was stirred for 16 hours and then washed with brine. The layers were separated, and the organic phase was dried over magnesium sulfate and concentrated. The resulting oil was purified by flash chromatography, and a white solid (0.11g) was collected. Spectral data was consistent with structure. MS (M+1) = 379. HPLC (> 95 %). ¹H NMR (CDCl₃) 8.35 (d, 2H), 7.55 (m, 8H), 6.58 (t, 1H), 3.80 (bm, 8H).

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6.3. Preparation of (4-Pyrimidin-2-yl-piperazin-1-yl)-[6-(3-trifluoromethyl-phenyl)pyridin-3-yl]-methanone



The title compound was prepared from (6-chloro-pyridin-3-yl)-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone as described below.

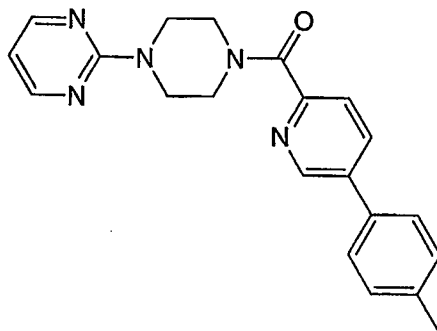
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(6-Chloro-pyridin-3-yl)-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone: To a solution of chloronicotinic acid (2.51 g, 15.9 mmol) in DMF (64 ml), EDCI (4.57 g, 23.9 mmol) and HOBt (3.23 g, 23.9 mmol) were added. Hunig's base (19.3 ml, 111 mmol) was added and the reaction was allowed to stir for 5 minutes. After this induction period, piperazine (4.52 g, 19.1 mmol) was added and the reaction stirred at room temperature. After stirring for 72 hours, the reaction was diluted with ethyl acetate and water. The layers were separated, and the aqueous portion was extracted twice more with ethyl acetate. The combined organic layers were washed with water three times and once with brine, dried over MgSO_4 , filtered, and concentrated. The crude product was purified by silica gel chromatography using 20-25% acetone/hexanes, yielding the product (2.05 g, 42%) as a tan solid: ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, $J=1.8$ Hz, 1H), 8.34 (d, $J=4.7$ Hz, 2H), 7.77 (dd, $J=8.2, 2.4$ Hz, 1H), 7.43 (d, $J=8.1$ Hz, 1H), 6.57 (t, $J=4.8$ Hz, 1H), 3.89 (bs, 6H), 3.52 (bs, 2H); m/z calcd. for $\text{C}_{14}\text{H}_{14}\text{ClN}_5\text{O}$: 303.08 found: $(\text{M}+\text{H})^+$ 304.1; HPLC retention time = 1.822 min (gradient of solvent B – 0 to 100%; wavelength 254 nm), purity = 100%.

(4-Pyrimidin-2-yl-piperazin-1-yl)-[6-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-ethanone: In a microwave reaction vessel, (6-chloro-pyridin-3-yl)-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone (1.12 g, 3.69 mmol) was taken up in DME (15 ml). To this solution, boronic acid (1.36 g, 7.38 mmol), potassium phosphate (2.35 g, 11.1 mmol) and water (5 ml) were added. This mixture was then degassed using nitrogen, and the tetrakis triphenylphosphine palladium (0.426 g, 0.369 mmol) was added and the vessel sealed. The reaction was heated in the microwave at 160°C for 5 minutes. After the reaction was complete, 1 N NaOH solution was added, and extraction twice with CH_2Cl_2 followed. The combined organic portions were washed with brine, dried, filtered, and concentrated. The crude product was purified by silica gel chromatography using 10-25% acetone in hexanes, yielding the final product (1.29 g, 85%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.80 (d, $J=1.3$ Hz, 1H), 8.34 (d, $J=4.8$ Hz, 2H), 8.32 (s, 1H), 8.22 (d, $J=7.8$ Hz, 1H), 7.93 (dd, $J=8.1, 2.2$ Hz, 1H), 7.87 (d, $J=8.1$ Hz, 1H), 7.72 (d, $J=7.7$ Hz, 1H), 7.63 (t, $J=7.8$ Hz, 1H), 6.57 (t, $J=4.7$ Hz, 1H), 3.91 (bs, 6H), 3.60 (bs, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.81, 161.42, 157.80, 156.93, 148.18, 139.06, 136.46, 131.52, 131.20, 130.26, 130.17, 129.39, 126.20, 126.16, 126.13, 125.36, 123.99, 123.95, 123.92, 123.88, 122.65, 120.27, 110.69; m/z calcd. for $\text{C}_{21}\text{H}_{18}\text{F}_3\text{N}_5\text{O}$: 413.15 found: $(\text{M}+\text{H})^+$ 414.05;

HPLC retention time = 3.233 min (gradient of solvent B – 0 to 100%; wavelength 254 nm); purity = 100%; mp = 124-126°C.

6.4. Preparation of (4-Pyrimidin-2-yl-piperazin-1-yl)-(5-p-tolyl-pyridin-2-yl)-methanone



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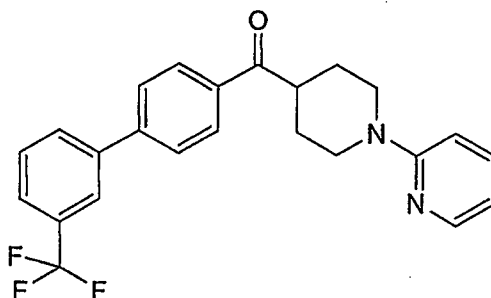
To a solution of 5-bromo-2-iodopyridine (100 mg, 0.35 mmol, Song *et al.*, *Org. Lett.*, 6: 4905-4907 (2004)) in THF (1 ml) was added isopropyl magnesium chloride (2 M in THF, 0.185 ml) at 0°C. After being stirred for 45 minutes, a solution of 1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-carboxylic acid methoxy-methyl amide (61 mg, 0.245 mmol) was added. The mixture was stirred at room temperature for another 1.5 hours and quenched with addition of water (15 ml) and EtOAc (50 ml). The aqueous phase was further extracted with EtOAc (20 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (3% MeOH/CH₂Cl₂) to give (5-bromo-pyridin-2-yl)-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone (25 mg, 25% for two steps) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.75 (m, 1 H), 8.31 (d, *J* = 6.4 Hz, 2 H), 7.98 (m, 2 H), 6.47 (t, *J* = 6.4 Hz, 1 H), 4.84 (m, 2 H), 4.09 (m, 1 H), 3.11 (m, 2 H), 1.74 (m, 2 H), 1.66 (m, 2 H); MS calc'd. for C₁₄H₁₅BrN₅O [M+H]⁺: 349; Found: 349.

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Following the general procedures for the Suzuki reactions, the title compound was obtained in 69% yield as an off-white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.92 (m, 1 H), 8.33 (d, *J* = 6.4 Hz, 2 H), 8.05 (m, 1 H), 7.54 (m, 1 H), 6.48 (t, *J* = 6.4 Hz, 1 H), 4.85 (m, 2 H), 4.22 (m, 1 H), 3.12 (m, 2 H), 2.44 (s, 3 H), 2.02 (m, 2 H), 1.75 (m, 2 H); MS calc'd. for C₂₁H₂₂N₅O [M+H]⁺: 359; Found: 359.

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6.5. Preparation of (3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-(3'-trifluoromethyl-biphenyl-4-yl)-methanone



The title compound was prepared from (4-bromo-phenyl)-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-methanone as described below.

3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methoxy-methyl-amide: In a sealed tube, Weinreb amide (0.5515 g, 1.927 mmol) was taken up in absolute ethanol (10 ml) and 2-bromopyridine (0.19 ml, 1.927 mmol) and triethylamine (0.81 ml, 5.781 mmol) were added. The tube was sealed and heated at 150°C for at least 48 hours. The reaction was then diluted with CH₂Cl₂, washed with water and brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography using 10-20% acetone in hexanes, yielding the product (0.1375 g, 29%) as a brown oil: ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J*=4.9, 1.2 Hz, 1H), 7.46 (m, 1H), 6.66 (d, *J*=8.6 Hz, 1H), 6.58 (m, 1H), 4.35 (dt, *J*=13.0, 2.9 Hz, 2H), 3.74 (s, 3H), 3.20 (s, 3H), 2.91 (m, 3H), 1.83 (m, 4H); *m/z* calcd. for C₁₃H₁₉N₃O₂: 249.15 found: (M+H)⁺ 250.05; HPLC retention time = 1.533 min (wavelength 220 nm), purity = 98.4%.

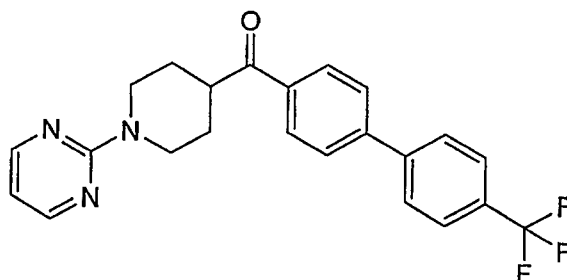
(4-Bromo-phenyl)-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-methanone: A solution of 1,4-dibromobenzene (0.223 g, 0.944 mmol) in anhydrous THF (3.0 ml) was cooled to -78°C. To the cooled solution, *n*-butyllithium (1.6 M in hexanes, 0.47 ml, 0.746 mmol) was added dropwise, and the reaction stirred at -78°C for 45 minutes. A solution of the 3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid methoxy-methyl-amide (0.124 g, 0.497 mmol) in anhydrous THF (3.0 ml) was then added dropwise to the reaction. The reaction stirred at -78°C for 3 hours and at 0°C until complete. The reaction was quenched at 0°C by the addition of 1 N HCl (5 ml) and saturated NaHCO₃ (7.5 ml). The mixture was extracted with ethyl acetate, washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography using 3-10% acetone in hexanes, yielding the product (0.1220 g, 71%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 8.16 (dd, *J*=4.9, 1.2 Hz, 1H),

7.81 (m, 2H), 7.61 (m, 2H), 7.46 (m, 1H), 6.67 (d, $J=8.7$ Hz, 1H), 6.59 (dd, $J=6.7, 5.1$ Hz, 1H), 4.33 (dt, $J=13.1, 3.1$ Hz, 2H), 3.42 (m, 1H), 3.14 (m, 2H), 1.93 (d, $J=13.2, 2.2$ Hz, 2H), 1.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) 201.20, 159.20, 147.87, 137.53, 134.57, 132.28, 129.80, 128.20, 113.09, 107.34, 45.01, 43.76, 28.01; m/z calcd. for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}$:

5 344.05 found: $(\text{M}+\text{H})^+$ 347.1; HPLC retention time = 3.205 min (wavelength 254 nm), purity = 100%.

(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-4-yl)-(3'-trifluoromethyl-biphenyl-4-yl)-methanone: In a vial, (4-bromo-phenyl)-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-methanone (0.0634 g, 0.184 mmol) was taken up in DME (1.5 ml). To this solution, 10 boronic acid (0.0846 g, 0.460 mmol), potassium phosphate (0.117 g, 0.551 mmol) and water (0.4 ml) were added. This mixture was then degassed using nitrogen. The tetrakis triphenylphosphine palladium (0.0213 g, 0.0184 mmol) was added, and the vial sealed. The reaction was then heated at 80°C for 18 hours. After completion, 1 N NaOH solution was added and extraction twice with CH_2Cl_2 followed. The combined organic portions 15 were washed with brine, dried, filtered, and concentrated. The crude product was purified by silica gel chromatography using 5-10% acetone in hexanes yielding the final product (0.042 g, 56%) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 8.19 (dd, $J=4.9, 1.2$ Hz, 1H), 8.08 (d, $J=8.5$ Hz, 2H), 7.87 (s, 1H), 7.81 (d, $J=7.5$ Hz, 1H), 7.72 (d, $J=8.5$ Hz, 2H), 7.63 (m, 2H), 7.48 (m, 1H), 6.71 (d, $J=8.6$ Hz, 1H), 6.62 (dd, $J=6.8, 5.2$ Hz, 1H), 4.34 (dt, 20 $J=13.1, 3.0$ Hz, 2H), 3.54 (m, 1H), 3.06 (m, 2H), 2.01 (dd, $J=13.1, 2.5$ Hz, 2H), 1.92 (dd, $J=11.3, 4.0$ Hz, 1H), 1.84 (m, 1H); m/z calcd. for $\text{C}_{24}\text{H}_{21}\text{F}_3\text{N}_2\text{O}$: 410.16 found: $(\text{M}+\text{H})^+$ 411.05; HPLC retention time = 3.313 min (wavelength 254 nm), purity = 96.9%.

6.6. Preparation of (1-(Pyrimidin-2-yl)piperidin-4-yl)(4-4-trifluoromethylphenyl)-phenylmethanone



The title compound was prepared from (4-bromophenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone as described below.

N-methoxy-N-methylpiperidine-4-carboxamide: A mixture of N-tert-butoxycarbonyl isonipecotic acid (1.50 g, 6.54 mmol, 1 eq), 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (1.88 g, 9.81 mmol, 1.5 eq), 1-hydroxybenzotriazole (1.33 g, 9.81 mmol, 1.5 eq), and N,N-dimethylformamide (26 ml) was treated with N,N-diisopropylethylamine (4.60 ml, 26.2 mmol, 4 eq). The resultant yellow solution was stirred at room temperature for 5 minutes, and then N,O-dimethylhydroxylamine hydrochloride (766 mg, 7.85 mmol, 1.2 eq) was added, and stirring continued for 92 hours. The reaction mixture was diluted with 100 ml of ethyl acetate and washed sequentially with 1 N aq. NaOH, 1 N aq. HCl and brine. The organic phase was dried over Na₂SO₄ and concentrated to give an oil which was used with no further purification.

This oil was dissolved in 1:2 trifluoroacetic acid/dichloromethane (9 ml), and the reaction mixture was stirred at ambient temperature for 17 hours and then concentrated. Ether (30 ml) was added and the white solid which formed was collected by filtration, washed with ether and dried to afford 1.50 g (80% yield, 2 steps) of analytically pure product: 400 MHz ¹H NMR (d₆-DMSO): 8.55 (br s, 1 H), 8.25 (br s, 1 H), 3.69 (s, 3 H), 3.31 (m, 2 H), 3.10 (s, 3 H), 2.98 (m, 3 H), 1.65-1.84 (m, 4 H).

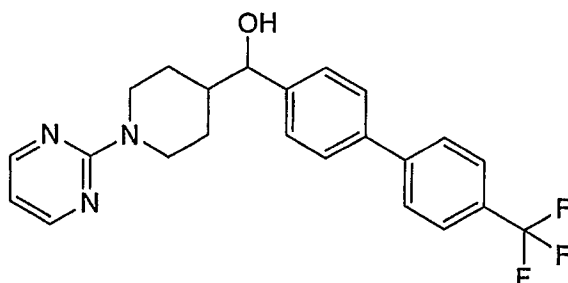
N-methoxy-N-methyl-1-(pyrimidin-2-yl)piperidine-4-carboxamide: A mixture of N-methoxy-N-methylpiperidine-4-carboxamide (1.50 g, 5.25 mmol, 1 eq), 2-chloropyrimidine (634 mg, 5.25 mmol, 1 eq), triethylamine (2.20 ml, 15.8 mmol, 3 eq), and ethanol (21 ml) was heated at 100°C in a sealed tube for 19 hours. The reaction mixture was allowed to cool to room temperature and then concentrated. The residue was dissolved in dichloromethane, washed with water and brine, dried over Na₂SO₄, and concentrated. Column chromatography (silica gel, 50% → 60% ethyl acetate/hexanes) gave 1.28 g (97% yield) of the product as a colorless oil: HPLC: 100% pure at 1.905 min

(YMC-Pack ODS-A 4.6 x 33 mm column, 0% → 100% solvent B over 4 min, 3 ml/min, 220 nm); LCMS (M+H)⁺ = 251.05; 400 MHz ¹H NMR (CDCl₃) 8.29 (d, J = 4.7 Hz, 2 H), 6.45 (t, J = 4.7 Hz, 1 H), 4.80 (m, 2 H), 3.73 (s, 3 H), 3.19 (s, 3 H), 2.95 (m, 3 H), 1.70-1.84 (m, 4 H).

5 (4-Bromophenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone: A solution of 1,4-dibromobenzene (2.29 g, 9.72 mmol, 1.9 eq) in THF (20 ml) under N₂ was cooled to -78°C, and n-butyllithium (1.6 M in hexanes, 4.8 ml, 7.67 mmol, 1.5 eq) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, and a solution of N-methoxy-N-methyl-1-(pyrimidin-2-yl)piperidine-4-carboxamide (1.28 g, 5.11 mmol, 1
10 eq) in THF (5 ml) was added dropwise via a cannula. After 3 hours at -78°C, the reaction mixture was warmed to 0°C, stirred for 1 hour, and then quenched with 1 N aq. HCl (10 ml). The mixture was diluted with 150 ml of ethyl acetate, washed sequentially with saturated aq. NaHCO₃ and brine (75 ml each), and the organic phase was dried over Na₂SO₄ and concentrated. Column chromatography (silica gel, CH₂Cl₂ → 3.5% ethyl
15 acetate/ CH₂Cl₂) afforded 1.47 g (83% yield) of the product as a pale yellow solid: HPLC: 99% pure at 3.748 min (YMC-Pack ODS-A 4.6 x 33 mm column, 0% → 100% solvent B over 4 min, 3 ml/min, 220 nm); LCMS (M+H)⁺ = 345.90; 400 MHz ¹H NMR (CDCl₃) 8.31 (d, J = 4.7 Hz, 2 H), 7.83 (d, J = 8.5 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 2 H), 6.48 (t, J = 4.7 Hz, 1 H), 4.81 (m, 2 H), 3.49 (m, 1 H), 3.08 (m, 2 H), 1.72-1.95 (m, 4 H).

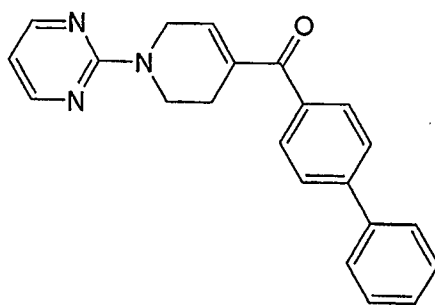
20 (1-(Pyrimidin-2-yl)piperidin-4-yl)(4-(4-trifluoromethylphenyl)-phenyl)methanone: A mixture of (4-bromophenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone (66 mg, 0.19 mmol, 1 eq), 4-trifluoromethylphenylboronic acid (91 mg, 0.47 mmol, 2.5 eq), potassium phosphate (122 mg, 0.57 mmol, 3 eq), and Pd(PPh₃)₄ (22 mg, 0.019 mmol, 0.1 eq) in 3:1 DME/water (2 ml) was heated at 80°C under N₂ for 16 hours. The reaction mixture was
25 cooled to room temperature, poured into 1 N NaOH, and extracted twice with dichloromethane. The combined organic layers were dried over Na₂SO₄ and concentrated. Column chromatography (silica gel, 25% ethyl acetate/hexanes) afforded 58 mg (73% yield) of the final product as a white solid: HPLC: 97% pure at 4.523 min (YMC-Pack ODS-A 4.6 x 33 mm column, 0% → 100% solvent B over 4 min, 3 ml/min,
30 220 nm); LCMS (M+H)⁺ = 412.20; 300 MHz ¹H NMR (CDCl₃) 8.32 (d, J = 4.7 Hz, 2 H), 8.08 (d, J = 8.4 Hz, 2 H), 7.70-7.74 (m, 6 H), 6.48 (t, J = 4.7 Hz, 1 H), 4.83 (m, 2 H), 3.58 (m, 1 H), 3.12 (m, 2 H), 1.75-2.01 (m, 4 H).

6.7. Preparation of (1-(Pyrimidin-2-yl)piperidin-4-yl)(4-4-trifluoromethylphenyl)-phenyl)methanol



Sodium borohydride (3.0 mg, 0.080 mmol, 1.5 eq) was added to a solution of (1-(pyrimidin-2-yl)piperidin-4-yl)(4-4-trifluoromethylphenyl)phenyl)methanone (22 mg, 0.053 mmol, 1 eq) in 1:1 methanol/dichloromethane. The reaction mixture was stirred at room temperature for 1 hour and then slowly quenched with saturated aq. NaHCO₃. The biphasic mixture was extracted twice with dichloromethane, and the combined organic layers were dried over Na₂SO₄ and concentrated. Preparative TLC (500 μm silica gel, 33% ethyl acetate/hexanes) gave 17 mg (77% yield) of the product as a white solid: HPLC: 100% pure at 4.285 min (YMC-Pack ODS-A 4.6 x 33 mm column, 0% → 100% solvent B over 4 min, 3 ml/min, 220 nm); LCMS (M+H)⁺ = 414.10; 300 MHz ¹H NMR (CDCl₃) 8.27 (d, J = 4.7 Hz, 2 H), 7.69 (s, 4 H), 7.59 (d, J = 8.3 Hz, 2 H), 7.42 (d, J = 8.2 Hz, 2 H), 6.43 (t, J = 4.7 Hz, 1 H), 4.71-4.87 (m, 2 H), 4.48 (m, 1 H), 2.72-2.89 (m, 2 H), 1.88-2.11 (m, 3 H), 1.19-1.49 (m, 3 H).

6.8. Preparation of Biphenyl-4-yl-(1-pyrimidin-2-yl-1,2,3,6-tetrahydropyridin-4-yl)-methanone



To a solution of 2-chloropyrimidine (300 mg, 2.619 mmol) in dioxane (5 ml), was added piperidin-4-one hydrochloride monohydrate (402.3 mg, 2.619 mmol) at room temperature. The mixture was heated at 80°C overnight and concentrated under reduced pressure. The residue was treated with EtOAc (30 ml) and saturated NaHCO₃ (10 ml). After separation of the layers, the aqueous phase was extracted with EtOAc (2 x 10 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO₄), filtered,

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and concentrated under reduced pressure to furnish a crude product. This material was purified by column chromatography (40% EtOAc/hexanes) to give 1-pyrimidin-2-yl-piperidin-4-one (320 mg, 53%) as an off-white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 8.38 (d, $J = 6.4$ Hz, 2 H), 6.61 (t, $J = 6.4$ Hz, 9 H), 4.16 (t, $J = 5.6$ Hz, 2 H), 2.53 (t, $J = 5.6$ Hz, 2 H).

To a solution of LDA (prepared from diisopropylamine (167.4 mg, 1.658 mmol) and *n*-BuLi (2.5 M in hexanes, 0.663 ml, 1.658 mmol) at -78°C , was added a solution of the above 1-pyrimidin-2-yl-piperidin-4-one (320 mg, 1.382 mmol). The mixture was stirred at the same temperature for 1 hour, followed by the addition of PhNTf_2 (543.1 mg, 1.52 mmol). The reaction mixture was warmed up to room temperature and stirred for 3 hours before it was quenched with the addition of saturated ammonium chloride (15 ml) and EtOAc (40 ml). After separation of the layers, the aqueous phase was extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO_4), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (20% EtOAc/hexanes) to give the corresponding triflate (210.7 mg, 49%) as a white solid as long with recovered starting material (142.9 mg): ^1H NMR (CDCl_3 , 400 MHz) δ 8.37 (d, $J = 6.4$ Hz, 2 H), 6.59 (t, $J = 6.4$ Hz, 1 H), 5.91 (m, 1 H), 4.41 (m, 2 H), 4.11 (t, $J = 5.6$ Hz, 2 H), 2.55 (m, 2 H); MS calc'd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 310; Found: 310.

To a solution of the above triflate (210.7 mg, 0.682 mmol) in methanol (10 ml), was added $\text{Pd}(\text{OAc})_2$ (10.7 mg, 0.047 mmol), PPh_3 (31.3 mg, 0.119 mmol) and diisopropyl ethylamine (352.6 mg, 2.728 mmol) at room temperature. Carbon monoxide was bubbled through the solution for 4 hours before the mixture was concentrated under reduced pressure. The residue was treated with EtOAc (30 ml) and water (10 ml). The aqueous phase was further extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO_4), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (30% EtOAc/hexanes) to give 1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-carboxylic acid methyl ester (73.8 mg, 50%) as white crystals: ^1H NMR (CDCl_3 , 400 MHz) δ 8.37 (d, $J = 6.4$ Hz, 2 H), 7.04 (m, 1 H), 6.54 (t, $J = 6.4$ Hz, 1 H), 4.41 (m, 2 H), 3.98 (t, $J = 5.6$ Hz, 2 H), 3.79 (s, 3 H), 2.52 (m, 2 H).

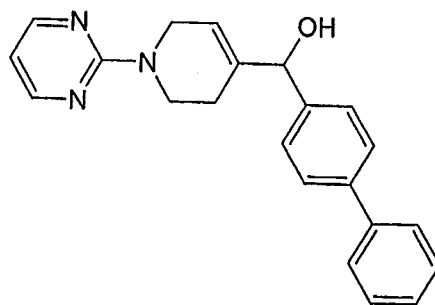
To a suspension of 1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-carboxylic acid methyl ester (73.8 mg, 0.337 mmol) and *N*-methyl-*O*-methyl hydroxylamine

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hydrochloride (51.0 mg, 0.552 mmol) in THF (3 ml), was added isopropyl magnesiumchloride (2.0 M in THF, 0.505 ml) at -20°C over 15 minute-period. The mixture was stirred at -10°C for another 30 minutes before it was quenched with the addition of saturated ammonium chloride (10 ml). The mixture was extracted with
5 EtOAc (2 × 15 ml). The combined organic layers were washed with brine (15 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (4% MeOH/CH₂Cl₂) to give 1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-carboxylic acid methoxy-methyl amide (48 mg, 58%) as white crystals: ¹H NMR (CDCl₃, 400 MHz) δ 8.35 (d, *J* = 6.4 Hz, 2 H), 6.53
10 (t, *J* = 6.4 Hz, 1 H), 6.43 (m, 1 H), 4.35 (m, 2 H), 3.99 (t, *J* = 5.6 Hz, 2 H), 3.66 (s, 3 H), 3.27 (s, 3 H), 2.55 (m, 2 H).

To a solution of 1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-carboxylic acid methoxy-methyl amide (48 mg, 0.196 mmol) in THF (1 ml), was added 1-biphenyl-4-yl magnesium bromide (0.5 M in THF) at 0°C. The mixture was stirred at this temperature
15 for 1 hour and quenched with addition of water (5 ml) and EtOAc (20 ml). The aqueous phase was further extracted with EtOAc (2 × 8 ml). The combined organic layers were washed with brine (5 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (4% MeOH/CH₂Cl₂) to give the title compound (20 mg, 30%) as an off-
20 white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.38 (d, *J* = 6.4 Hz, 2 H), 7.82-7.42 (m, 9 H), 6.70 (m, 1 H), 6.58 (t, *J* = 6.4 Hz, 1 H), 4.51 (m, 2 H), 4.13 (t, *J* = 5.6 Hz, 2 H), 2.72 (m, 2 H); MS calc'd for C₂₂H₂₀N₃O [M+H]⁺: 342; Found: 342.

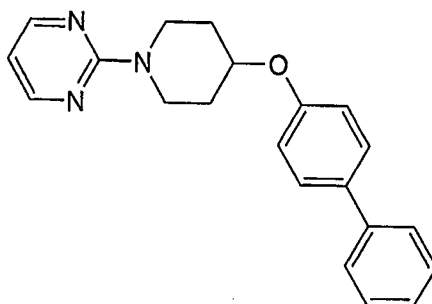
6.9. Preparation of Biphenyl-4-yl-(1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-yl)-methanol



To a solution of biphenyl-4-yl-(1-pyrimidin-2-yl-1,2,3,6-tetrahydro-pyridin-4-yl)-methanone (12.2 mg, 0.0355mmol) in methanol (0.5 ml), was added CeCl₃ heptahydate (13.2 mg, 0.0355 mmol) and sodium borohydride (1.5 mg, 0.0355 mmol) at room

temperature. The mixture was stirred for 1 hour and diluted with EtOAc (10 ml). The mixture was washed with water (5 ml), brine (5 ml), dried (MgSO_4), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (6% MeOH/ CH_2Cl_2) to give the title compound (12 mg, 98%) as a white gel: ^1H NMR (CDCl_3 , 400 MHz) δ 8.36 (d, $J = 6.4$ Hz, 2 H), 7.62-7.37 (m, 9 H), 6.46 (t, $J = 6.4$ Hz, 1 H), 6.02 (m, 1 H), 5.24 (m, 1 H), 4.31 (m, 2 H), 3.96 (m, 1 H), 3.83 (m, 1 H), 2.14 (m, 2 H); MS calc'd for $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 344; Found: 344.

6.10. Preparation of 2-[4-(Biphenyl-4-yloxy)-piperidin-1-yl]-pyrimidine



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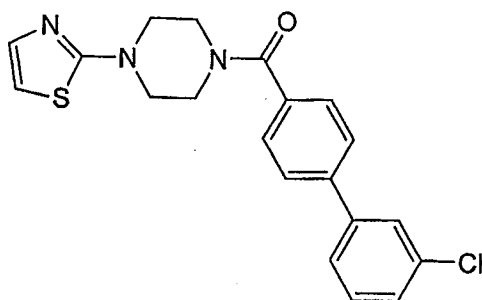
To a solution of 1-pyrimidin-2-yl-piperidin-4-one (50 mg, 0.282 mmol) in methanol (0.8 ml), was added sodium borohydride (12.0 mg, 0.282 mmol) at room temperature. After being stirred for 10 minutes, the mixture was treated with EtOAc (10 ml) and water (3 ml). The organic layer was washed with brine (2 ml), dried (MgSO_4), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (20% EtOAc/hexanes) to give the corresponding alcohol (51 mg, 100%) as a white solid.

To a mixture of the above alcohol (50 mg, 0.279 mmol), PPh_3 (109.6 mg, 0.418 mmol) and biphenyl-4-ol (57.0 mg, 0.335 mmol) in THF (3 ml), was added DEAD (40% in toluene, 0.152 ml, 0.335 mmol) at 0°C . After being stirred overnight, the mixture was treated with EtOAc (15 ml) and water (5 ml). The aqueous phase was extracted with EtOAc (2×5 ml). The combined organic layers were washed with brine (5 ml), dried (MgSO_4), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (15% EtOAc/hexanes) to give the title compound (81 mg, 88%) as white crystals: ^1H NMR (CDCl_3 , 400 MHz) δ 8.38 (d, $J = 6.4$ Hz, 2 H), 7.59-7.04 (m, 9 H), 6.61 (t, $J = 6.4$ Hz, 1 H), 4.62 (m, 1 H), 4.21 (m, 2 H), 3.68 (m, 2 H), 2.14 (m, 2 H), 1.83 (m, 2 H); MS calc'd for $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 332; Found: 332.

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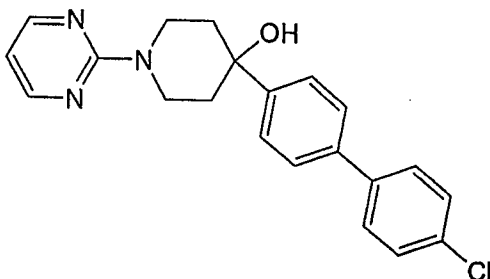
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6.11. Preparation of (3'-Chloro-biphenyl-4-yl)-(4-thiazol-2-yl-piperazin-1-yl)-methanone



To a solution of 1-(thiazol-2-yl)piperazine (ca. 0.915 mmol, prepared from 150
5 mg 2-bromothiazole according to the methods described in Astles *et al.*, *J. Med. Chem.*,
39: 1423-1432 (1996)), 3'-chloro-biphenyl-4-carboxylic acid (212.9 mg, 0.915 mmol) in
CH₂Cl₂ (4 ml), was added EDC (209.7 mg, 1.098 mmol) and HOBt (148.2 mg, 1.098
mmol). After being stirred overnight, the mixture was treated with EtOAc (50 ml) and
water (15 ml). The organic phase was washed with brine (5 ml), dried (MgSO₄), filtered,
10 and concentrated under reduced pressure to furnish the crude product. This material was
purified by column chromatography (20% acetone/hexanes) to give the title compound
(225 mg, 64% for two steps) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 7.64-7.23
(m, 9 H), 6.65 (t, *J* = 3.6 Hz, 1 H), 4.92 (m, br, 2 H), 3.57 (m, br, 6 H), 3.68 (m, 2 H),
2.14 (m, 2 H), 1.83 (m, 2 H); MS calc'd for C₂₀H₁₉ClN₃OS [M+H]⁺: 384; Found: 384.

15 6.12. Preparation of 4-(4'-Chloro-biphenyl-4-yl)-1-pyrimidin-2-yl-piperidin-4-ol

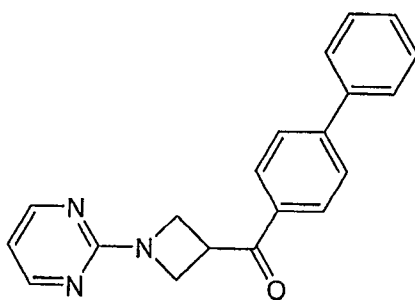


To a solution of 1,4-dibromobenzene (213.3 mg, 0.904 mmol) in THF (4 ml), was
added *n*-BuLi (2.5 M in hexanes, 0.362 ml, 0.904 mmol) at -78°C. After being stirred for
20 30 minutes at the same temperature, a solution of 1-pyrimidin-2-yl-piperidin-4-one (80
mg, 0.452 mmol) in THF (3 ml) was added. The mixture was allowed to warm to room
temperature and stirred for 1 hour. The reaction was quenched with addition of water (10
ml) and EtOAc (50 ml). The organic layer was washed with brine (5 ml), dried (MgSO₄),
filtered, and concentrated under reduced pressure to furnish the crude product. This

material was purified by column chromatography (40% EtOAc/hexanes) to give 4-(4-Bromo-phenyl)-1-pyrimidin-2-yl-piperidin-4-ol as a colorless oil (140 mg, 93%): ¹H NMR (CDCl₃, 400 MHz) δ 8.33 (d, *J* = 6.4 Hz, 2 H), 7.47 (d, *J* = 12.0 Hz, 2 H), 7.41 (d, *J* = 12.0 Hz, 2 H), 6.49 (t, *J* = 6.4 Hz, 1 H), 4.72 (m, 2 H), 3.40 (m, 2 H), 2.05 (m, 2 H), 1.78 (m, 2 H); MS calc'd for C₁₅H₁₇BrN₃O [M+H]⁺: 335; Found: 335.

Following the general procedures for the Suzuki reactions, the title compound was prepared in 61% yield as a colorless glass: ¹H NMR (CDCl₃, 400 MHz) δ 8.35 (d, *J* = 6.4 Hz, 2 H), 7.59-7.37 (m, 8 H), 6.50 (t, *J* = 6.4 Hz, 1 H), 4.73 (m, 2 H), 3.46 (t, *J* = 12.4 Hz, 2 H), 2.15 (m, 2 H), 1.88 (m, 2 H); MS calc'd for C₂₁H₂₁ClN₃O [M+H]⁺: 366; Found: 366.

6.13. Preparation of Biphenyl-4-yl-(1-pyrimidin-2-yl-azetidin-3-yl)-methanone



To a stirred solution of 3-azetidine carboxylic acid methyl ester hydrochloride (150 mg, 0.99 mmol) and 2-chloropyrimidine (113.4 mg, 0.99 mmol) in methanol, was added TEA (200 mg, 1.98 mmol) at room temperature. The mixture was stirred at 50°C for 5 hours and concentrated under reduced pressure. The residue was suspended in EtOAc (50 ml) and washed with water (15 ml), brine (5 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (40% EtOAc/hexanes) to give 1-pyrimidin-2-yl-azetidine-3-carboxylic acid methyl ester as a light yellow solid (137.3 mg, 72%): ¹H NMR (CDCl₃, 400 MHz) δ 8.37 (d, *J* = 6.4 Hz, 2 H), 6.58 (t, *J* = 6.4 Hz, 1 H), 4.30 (m, 4 H), 3.77 (s, 3 H), 3.56 (m, 1 H).

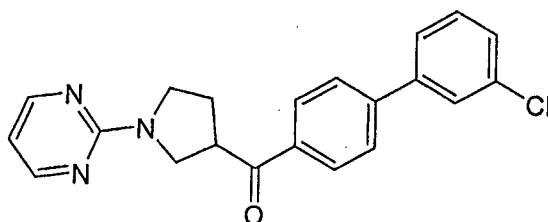
To a suspension of the above ester (137.3 mg, 0.711 mmol) and *N*-methyl-*O*-methyl hydroxylamine hydrochloride (127.6 mg, 1.103 mmol) in THF (5 ml), was added *iso*-propyl magnesium chloride (2.0 M in THF, 1.067 ml, 2.133 mmol) at -20°C during 15 minutes. The mixture was stirred at -10°C for another 30 minutes before it was quenched with the addition of saturated ammonium chloride (10 ml). The mixture was extracted

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with EtOAc (2 × 15 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (4% MeOH/CH₂Cl₂) to give 1-pyrimidin-2-yl-azetidine-3-carboxylic acid methoxy-methyl-amide (385.9 mg, 98%) as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.32 (d, *J* = 6.4 Hz, 2 H), 6.55 (t, *J* = 6.4 Hz, 1 H), 4.34 (m, 4 H), 3.88 (m, 1 H), 3.70 (s, 3 H), 3.23 (s, 3 H).

To a solution of the above amide (50 mg, 0.225 mmol) in THF (1 ml), was added 4-biphenyl magnesiumchloride (0.5 M in THF, 0.9 ml, 0.45 mmol) at -78°C. The mixture was slowly warmed up to room temperature and stirred for 2 hours before quenched with addition of water (10 ml) and EtOAc (30 ml). The organic layer was separated and washed with brine (5 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (3% MeOH/CH₂Cl₂) to furnish the title compound (21 mg, 30%) as white crystals: ¹H NMR (CDCl₃, 400 MHz) δ 8.33 (d, *J* = 6.4 Hz, 2 H), 7.98-7.43 (m, 9 H), 6.58 (t, *J* = 6.4 Hz, 1 H), 4.45 (m, 4 H), 4.38 (m, 1 H); MS Calc'd for C₂₀H₁₈N₃O [M+H]⁺: 316; Found: 316.

6.14. Preparation of (3'-Chloro-biphenyl-4-yl)-(1-pyrimidin-2-yl-pyrrolidin-3-yl)-methanone



To a solution of *N*-Boc-β-proline (400 mg, 1.858 mmol), EDC (425.9 mg, 2.23 mmol) and HOBt (326.1 mg, 2.415 mmol) in methylene chloride (8 ml), was added *N*-methyl-*O*-methyl hydroxylamine hydrochloride (217.5 mg, 2.23 mmol) and TEA (281.5 mg, 2.787 mmol) at 0°C. After stirring overnight, the mixture was treated with EtOAc (80 ml) and water (15 ml). The organic phase was washed with brine (15 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product.

To a solution of the above crude ester in methylene chloride (4 ml), was added dropwise TFA (4 ml) at room temperature. The mixture was stirred for 40 minutes and concentrated under reduced pressure to generate the crude product as the TFA salt.

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K

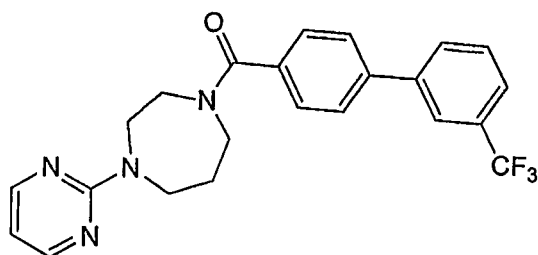
To a mixture of the above product and 2-chloropyrimidine (212.8 mg, 1.858 mmol) in dioxane (7 ml) was added TEA (563 mg, 5.574 mmol). The mixture was heated at 80°C for 4 hours, and was concentrated under reduced pressure. The residue was treated with water (20 ml) and EtOAc (60 ml). After separation of the layers, the aqueous phase was further extracted with EtOAc (20 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (40% acetone/hexanes) to furnish 1-pyrimidin-2-yl-pyrrolidine-3-carboxylic acid methoxy-methyl-amide (203.8 mg, 47% for three steps) as an off-white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.34 (d, *J* = 6.4 Hz, 2 H), 6.50 (t, *J* = 6.4 Hz, 1 H), 3.94 (m, 1 H), 3.82 (m, 1 H), 3.75 (s, 3 H), 3.70 (m, 1 H), 3.65 (m, 1 H), 3.63 (m, 1 H), 3.23 (s, 3 H), 2.33 (m, 3 H), 2.23 (m, 1 H).

To a solution of 1,4-dibromobenzene (407.5 mg, 1.727 mmol) in THF (6 ml) was added *n*-BuLi (2.5 M in hexanes, 0.691 ml, 1.727 mmol) at -78°C. The mixture was stirred at the temperature for 30 minutes before the addition of a solution of the above amide (203.8 mg, 0.8636 mmol) in THF (4 ml). After stirring at -78°C for 30 minutes, the mixture was warmed to room temperature for 1 hour. EtOAc (40 ml) and water (15 ml) was added to the reaction, followed by separation of the layers. The aqueous phase was extracted with EtOAc (15 ml). The combined organic layers were washed with brine (10 ml), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (40% acetone/hexanes) to furnish (4-bromo-phenyl)-(1-pyrimidin-2-yl-pyrrolidin-3-yl)-methanone (182.2 mg, 64%) as an off-white solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.32 (d, *J* = 6.4 Hz, 2 H), 7.87 (d, *J* = 12.0 Hz, 2 H), 7.63 (d, *J* = 12.0 Hz, 2 H), 6.51 (t, *J* = 6.4 Hz, 1 H), 4.07 (m, 1 H), 3.98 (m, 1 H), 3.86 (m, 1 H), 3.74 (m, 2 H), 2.38 (m, 2 H).

Following the general procedures for the Suzuki reactions, the title compound was prepared in 63% as a pale yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 8.38 (d, *J* = 6.4 Hz, 2 H), 8.11-7.42 (m, 8 H), 6.53 (t, *J* = 6.4 Hz, 1 H), 4.19 (m, 1 H), 4.04 (m, 1 H), 3.84 (m, 1 H), 3.77 (m, 2 H), 2.42 (m, 1 H), 2.38 (m, 1 H); MS Calc'd for C₂₁H₁₉ClN₃O [M+H]⁺: 364; Found: 364.

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6.15. Preparation of (4-Pyrimidin-2-yl-homopiperazin-1-yl)-[4-(3-trifluoromethylphenyl-phenyl)-methanone



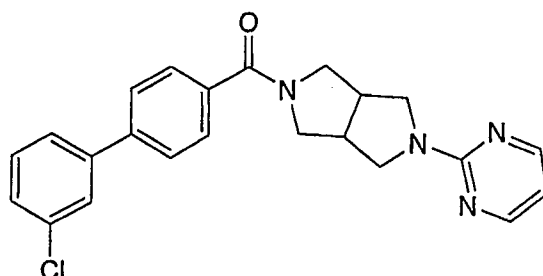
5 The title compound was prepared from 1-(2-pyrimidyl)-homopiperazine as described below.

1-(2-Pyrimidyl)-homopiperazine: To a solution of homopiperazine (3.5 g, 35 mmol) in ethanol (100 ml) at 40°C, was added portionwise 2-chloropyrimidine (2.0 g, 17.5 mmol). The mixture was stirred for 1 hour then concentrated *in vacuo*. The residue was dissolved in methylene chloride (75 ml) and washed with a saturated solution of sodium bicarbonate and brine. Layers were separated, and the organic layer was dried over magnesium sulfate and concentrated. The resulting residue was purified by flash chromatography and a semi-solid (1.0 g) was collected and used as is.

(4-Pyrimidin-2-yl-homopiperazin-1-yl)-[4-(3-trifluoromethylphenylphenyl)-methanone: To a solution of 3'-trifluoromethyl-biphenyl-4-carboxylic acid (0.38 g, 1.41 mmol) and 1-(2-pyrimidyl)-homopiperazine (0.25 g, 1.41 mmol) in methylene chloride (20 ml), was added EDCI (0.27 g, 1.41 mmol) and HOAt (0.19 g, 1.41 mmol) triethylamine (0.20 ml, 1.41 mmol). The mixture was stirred for 16 hours and then washed with brine. The layers were separated, and the organic phase was dried over magnesium sulfate and concentrated. The resulting oil was purified by flash chromatography and a clear oil was collected. The oil was dissolved in a minimal amount of t-butylmethylether, and crystals were formed collected (0.20 g). Spectral data was consistent with structure. MS (M+1) = 427. HPLC (> 95 %). ¹H NMR (CDCl₃) 8.35 (m, 2H), 7.55 (m, 8H), 6.58 (t, 1H), 3.87 (bm, 8H), 1.92 (m, 2H).

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6.16. Preparation of (3'-Chloro-biphenyl-4-yl)-(5-pyrimidin-2-yl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-methanone



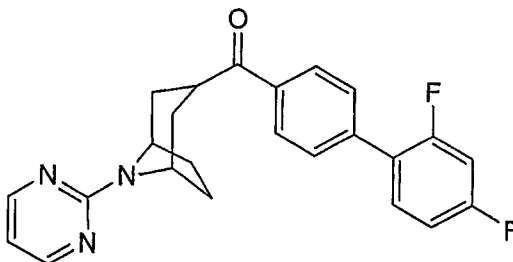
The title compound was prepared from 5-pyrimidin-2-yl-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester as described below.

5-Pyrimidin-2-yl-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester: A solution of hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester (1.0 g, 4.7 mmol), 2-chloropyrimidine (0.54 g, 4.7 mmol), triethylamine (2 ml, 14 mmol) and ethyl alcohol (25 ml) was maintained at reflux for 4 hours. The solution was then cooled to room temperature and concentrated to afford a solid residue that was dissolved in dichloromethane (CH_2Cl_2), which was washed sequentially with sat. aq. sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated to afford 0.82 g (60 %) of the product as an orange solid: ^1H NMR (400 MHz, CDCl_3): δ 8.34 (d, $J = 4.8$ Hz, 2H), 6.53 (t, $J = 4.8$ Hz, 1 H), 3.86-3.79 (m, 2H), 3.72-3.62 (m, 2H), 3.57-3.50 (m, 2H), 3.41-3.33 (m, 1H), 3.33-3.26 (m, 1H), 3.05-2.96 (m, 2H), 1.47 (s, 9H); LRMS m/z 291 ($\text{M} + \text{H}$) $^+$.

(3'-Chloro-biphenyl-4-yl)-(5-pyrimidin-2-yl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-methanone: A solution of 5-pyrimidin-2-yl-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester (0.70 g, 2.4 mmol) and CH_2Cl_2 (20 ml) was treated with trifluoroacetic acid (TFA, 10 ml) and maintained at room temperature for 3 hours. The resulting solution was concentrated, and the residue was dissolved in CH_2Cl_2 (5 ml) and added to a solution of 3'-chloro-biphenyl-4-yl-carboxylic acid (0.62 g, 2.6 mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (HATU, 1.0 g, 2.6 mmol), diisopropylethylamine (1.5 ml, 8 mmol), and CH_2Cl_2 (20 ml). The resulting solution was maintained at room temperature for 2 hours, diluted with EtOAc, washed with sat. aq. NaHCO_3 and brine, dried (MgSO_4), filtered, and concentrated. The solid residue was recrystallized from methyl alcohol to afford the final product as white needles: ^1H NMR (CD_3OD): δ 8.32 (d, $J = 4.8$ Hz, 2H), 7.71 (d, $J = 8.5$ Hz, 2 H), 7.67 (s, 1H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.60-7.50 (m, 1H), 7.45 (t, $J = 7.9$ Hz, 1H), 7.40-7.37 (m,

1H), 6.63 (t, $J = 4.8$ Hz, 1H), 3.96 (dd, $J = 7.8, 12.8$ Hz, 1H), 3.86 (ddd, $J = 3.0, 7.2, 10.6$ Hz, 2H), 3.76 (dd, $J = 7.5, 11.6$ Hz, 1H), 3.65-3.58 (m, 2H), 3.51 (dd, $J = 5.1, 11.3$ Hz, 1H), 3.43 (dd, $J = 4.7, 11.7$ Hz, 1H), 3.21-3.07 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ 171.8, 161.4, 159.1, 143.5, 142.9, 137.0, 136.0, 131.6, 129.0, 128.2, 128.1, 126.6, 110.9, 54.5, 51.9, 51.7, 51.1, 43.9, 42.0; LRMS m/z 405 ($\text{M} + \text{H}$) $^+$; Anal. calcd for $\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}$: C, 68.23; H, 5.23; N, 13.84. Found: C, 68.01; H, 5.23; N, 13.60.

6.17. Preparation of (2',4'-Difluoro-biphenyl-4-yl)-(8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanone



10 The title compound was prepared as follows.

8-Pyrimidin-2-yl-8-aza-bicyclo[3.2.1]octan-3-one: A solution of 8-aza-bicyclo[3.2.1]octan-3-one hydrochloric acid (5.0g, 30.9mmol), 2-chloro-pyrimidine (4.95g, 43.2mmol), NaHCO_3 (7.78g, 92.7mmol) and isopropanol (200ml) was maintained at reflux over weekend. The resulting reaction mixture was concentrated and purified by ISCO to afford 8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]octan-3-one (4.0g, 52.9%) as a white solid : MS ($\text{M} + 1$) = 204. ^1H NMR (MeOH) 8.36 (d, $J = 12$ Hz 2H), 6.75 (m, 1H), 4.97 (m, 2H), 2.75 (d, $J = 12$ Hz, 1H), 2.71 (d, $J = 12$ Hz, 1H), 2.32 (d, $J = 50$ Hz, 2H), 2.22 (m, 2H), 1.87 (m, 2H).

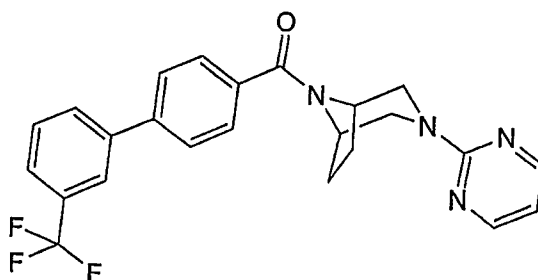
20 3-[(4-Bromo-phenyl)-methoxy-methylene]-8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]octane: To a solution of [(4-bromo-phenyl)-methoxy-methyl]-phosphonic acid diethyl ester (4.58g, 13.5mmol) in 1,2-dimethoxy-ethane (60ml), was added NaH (540mg, 13.5mmol, 60% in mineral oil) in one portion. The mixture was stirred at 50°C for 1.5 hrs before it was added by 8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]octan-3-one (2.0g, 9.85mmol) in 1,2-dimethoxy-ethane (5ml). The mixture was stirred at 50°C over the weekend. The resulting mixture was concentrated down and purified by ISCO to afford 3-[(4-bromo-phenyl)-methoxy-methylene]-8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]octane (600mg, 30%). The white solid product was used as it was. MS ($\text{M} + 1$) = 386.

(4-Bromo-phenyl)-(8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanone: A solution of 3-[(4-bromo-phenyl)-methoxy-methylene]-8-pyrimidin-2-yl-8-aza-

bicyclo[3.2.1]octane (2.44g, 6.32mmol), aqueous HCl (10.5ml, 6N) and THF (50ml) was stirred at room temperature overnight. The mixture was added by saturated aq. NaHCO₃ until bubbling was gone. The mixture was diluted with ethyl acetate and the organic phase was dried over MgSO₄ and concentrated. ISCO was used to do purification and (4-bromo-phenyl)-(8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanone was obtained as white solid (2.16g, 92%). MS (M+1) = 374. ¹H NMR (CDCl₃) 8.33 (d, *J* = 12 Hz 2H), 7.84 (d, *J* = 13 Hz 2H), 7.62 (d, *J* = 13 Hz 2H), 6.51 (t, *J* = 12 Hz 1H), 4.87 (m, 2H), 3.90 (m, 1H), 2.23 (m, 2H), 2.08 (m, 2H), 1.97 (m, 2H), 1.72 (m, 2H).

(2',4'-Difluoro-biphenyl-4-yl)-(8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanone: A solution of (4-bromo-phenyl)-(8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanone (250mg, 0.92mmol), 2,4-di-fluoro-phenylboronic acid (290mg, 1.84mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (67mg, 0.092mmol), K₃PO₄ (390mg, 1.84mmol), 2-dimethoxyethane (5ml) and water (1.6ml) was stirred at 80°C for one hour. The reaction mixture was diluted with ethyl acetate and 1N NaOH solution. The organic layer was dried by MgSO₄ and concentrated. ISCO was used for purification, and the product was obtained as a white solid (2',4'-difluoro-biphenyl-4-yl)-(8-pyrimidin-2-yl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanone (69.6mg, 19%). MS (M+1) = 406. ¹H NMR (CDCl₃) 8.34 (d, *J* = 12 Hz 2H), 8.00 (d, *J* = 21 Hz 2H), 7.62 (dd, *J* = 19Hz, 4Hz, 2H), 7.45 (m, 1H), 6.99 (m, 2H), 6.52 (t, *J* = 12 Hz, 1H), 4.90 (m, 2H), 4.00 (m, 1H), 2.25 (m, 2H), 2.12 (m, 2H), 2.02 (m, 2H), 1.78 (m, 2H).

6.18. Preparation of (3-(Pyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone



The title compound was prepared as follows.

3-Pyrimidin-2-yl-3,8-diaza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester: A solution of 3,8-diaza-bicyclo[3,2,1]octane-8-carboxylic acid tert-butyl ester (50 mg, 0.24 mmol), 2-chloropyrimidine (27 mg, 0.24 mmol), triethylamine (0.1 ml, 0.72 mmol) and

25

THF (2.5 ml) was heated at 180°C for 10 minutes. The solution was concentrated to afford a solid residue that was dissolved in dichloromethane, which was washed sequentially with sat. aq. sodium bicarbonate and brine, dried (Na₂SO₄), filtered, and concentrated to afford 50 mg (71 %) of the product as a brown solid: ¹H NMR (400 MHz, CDCl₃): δ 8.30 (d, *J* = 12.0 Hz, 2H), 6.52 (t, *J* = 12.0 Hz, 1 H), 4.38-4.29 (m, 4H), 3.13 (sb, 2H), 2.42 (m, 2H), 1.69 (q, *J* = 18.0 Hz, 2H), 1.49 (s, 9H); MS (M+1) = 291.

(3'-tert-Butyl-biphenyl-4-yl)-(3-pyrimidin-2-yl-3,8-diaza-bicyclo[3.2.1]oct-8-yl)-methanone: A solution of 3-pyrimidin-2-yl-3,8-diaza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (64 mg, 0.22 mmol) in HCl/dioxane was stirred for 5 hours at room temperature. The resulting solution was concentrated, and the residue was dissolved in CH₂Cl₂ (5 mL) and added to a solution of 3'-trifluoromethyl-biphenyl-4-carboxylic acid (117 mg, 0.44 mmol), EDC (85 mg, 0.44 mmol), HOBt (60 mg, 0.44 mol) and TEA (0.1 mL, 0.71mmol). After stirring overnight, the mixture was treated with EtOAc (50 mL) and water (15 mL). The organic phase was washed with brine (5 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure to furnish the crude product. This material was purified by column chromatography (30% EtOAc/hexanes) to give the title compound 14.2 mg, (32%) as a white solid: ¹H NMR (DMSO): δ 8.35 (d, *J* = 12 Hz, 2H), 7.79-7.76 (m, 3 H), 7.68 (dt, *J* = 20, 3 Hz, 1H), 7.63 (d, *J* = 21 Hz, 2H), 7.52-7.43 (m, 2H), 6.62 (t, *J* = 12 Hz, 1H), 4.77 (bs, 1H), 4.41 (d, *J* = 64 Hz, 2H), 4.17 (bs, 1H), 3.14 (bs, 2H), 2.48 (qt, *J* = 5 Hz, 1 H), 1.86 (t, *J* = 9 Hz, 2H), 1.60 (d, *J* = 24 Hz, 1H); MS (M+1) = 439.

6.19. Human Proline Transporter Assay

The ability of compounds to inhibit the proline transporter was determined as follows. A human SLC6A7 cDNA was cloned into a pcDNA3.1 vector and transfected into COS-1 cells. A cell clone stably expressing proline transporter was selected for the assay.

Transfected cells were seeded at 15,000 cells per well in a 384 well plate and grown overnight. The cells were then washed with Krebs-Ringer's-HEPES-Tris (KRHT) buffer, pH 7.4, containing 120 mM NaCl, 4.7 mM KCl, 2.2 mM CaCl, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 10 mM HEPES and 5 mM Tris. The cells were then incubated with 50 µl of KRHT buffer containing 45 nM ³H-Proline for 20 minutes at room temperature. Radiolabeled proline uptake was terminated by removing the radiolabeled proline and washing the cells rapidly three times with 100 µl of ice-cold KRHT buffer. Scintillation

fluid (50 μ l) was added per well, and the amount of tritiated proline present was determined using a Packard TopCount Scintillation counter.

Nonspecific uptake was determined by measuring of 3 H-proline uptake in the presence of 2 mM cold proline.

- 5 The IC_{50} of a compound was determined by measuring inhibition of four separate samples at ten concentrations, typically beginning with 10 μ M followed by nine three-fold dilutions (*i.e.*, 10, 3.3, 1.1, 0.37, 0.12, 0.41, 0.014, 0.0046, 0.0015, and 0 μ M). Percent inhibitions were calculated against the control. The IC_{50} of a compound was determined using the ten data points, each of which was an average of the four
- 10 corresponding measurements.

6.20. Murine Proline Transporter Assay

Forebrain tissue was dissected from a wild type mouse and homogenized in 7 ml ice-cold homogenization buffer: 0.32 M sucrose, 1mM $NaHCO_3$, protease inhibitor cocktail (Roche).

- 15 The brain homogenates were centrifuged at 1000xg for 10 min to remove nuclei. Supernatant was collected and re-centrifuged at 20000xg for 20 min to pellet crude synaptosomes. The synaptosomes were resuspended in ice-cold assay buffer: 122 mM NaCl, 3.1 mM KCl, 25 mM HEPES, 0.4 mM KH_2PO_4 , 1.2 mM $MgSO_4$, 1.3 mM $CaCl_2$, 10 mM dextrose at pH 7.4. Resuspended synaptosomes were centrifuged again at
- 20 20000xg for 20 minutes, and pelleted synaptosomes were resuspended in assay buffer. Protein concentration was measured by DC protein assay kit (BioRad).

- Proline transport assay was performed in 100 μ l reaction mix consisting of 10 μ g synaptosomes, 1 μ Ci/0.24 μ M [H^3]-proline in assay buffer for a time between 0 to 20 minutes at room temperature. The reaction was terminated by rapid filtration through
- 25 GF/B filter plate (Millipore) followed by three rapid washes in 200 μ l ice-cold assay buffer. Fifty microliters of Microscint-20 was added to each reaction and incubated for 2 hours. The [H^3]-proline transport was determined by radioactivity counting.

- To determine proline transport inhibition by compounds, compounds were incubated with the reaction mixture at concentrations ranging from 0 to 10 μ M (11 points,
- 30 beginning at 10 μ M; 3-fold dilutions; 4 replicates averaged to provide one point). The baseline activity, or nonspecific activity, was measured in the presence of 0.3 mM GGFL (Enkephalin, Sigma) in the reaction. The nonspecific activity was also measured in

52

synaptosomes of SLC6A7 knockout mice. The nonspecific activities measured by the two methods were found to be identical.

6.21. Human Dopamine Transporter Assay

5 The ability of compounds to inhibit the dopamine transporter was determined as follows. A human DAT cDNA (NM_001044) was cloned into a pcDNA3.1 vector and transfected into COS-1 cells. The resulting cell lines that stably express the dopamine transporter were used for further experimentation.

10 Transfected cells were seeded at 15,000 cells per well in a 384 well plate and grown overnight. The cells were then washed with Krebs-Ringer's-HEPES-Tris (KRHT) buffer, pH 7.4, containing 125 mM NaCl, 4.8 mM KCl, 1.3 mM CaCl₂, 1.2 mM MgSO₄, 10 mM D-glucose, 25 mM HEPES, 1 mM sodium ascorbate and 1.2 mM KH₂PO₄. The cells were then incubated with 50 µl of KRHT buffer containing 1 µM ³H-Dopamine for 10 minutes at room temperature. Radiolabeled dopamine uptake was terminated by removing the radiolabeled dopamine and washing the cells rapidly three times with 100 µl
15 of ice-cold KRHT buffer. Scintillation fluid (50 µl) was added per well and the amount of tritiated dopamine present was determined using a Packard TopCount Scintillation counter.

Nonspecific uptake was determined by measuring of ³H-dopamine uptake in the presence of 250 µM benztropine. The IC₅₀ of a compound was determined by measuring
20 inhibition of four separate samples at ten concentrations, typically beginning with 10 µM followed by nine three-fold dilutions (*i.e.*, 10, 3.3, 1.1, 0.37, 0.12, 0.41, 0.014, 0.0046, 0.0015, and 0 µM). Percent inhibitions were calculated against the control. The percentage inhibitions were calculated against the control, and the average of the quadruplicates was used for IC₅₀ calculation.

25 6.22. Human Glycine Transporter Assay

The ability of compounds to inhibit the glycine transporter was determined as follows. A human glycine transporter cDNA (NM_006934) was cloned into a pcDNA3.1 vector and transfected into COS-1 cells. The resulting cell lines that stably express the glycine transporter were used for further experimentation.

30 Transfected cells were seeded at 15,000 cells per well in a 384 well plate and grown overnight. The cells were then washed with Krebs-Ringer's-HEPES-Tris (KRHT) buffer, pH 7.4, containing 120 mM NaCl, 4.7 mM KCl, 2.2 mM CaCl₂, 1.2 mM MgSO₄,

1.2 mM KH₂PO₄, 10 mM HEPES and 5 mM Tris. The cells were then incubated with 50 µl of KRHT buffer containing 166 nM ³H-glycine for 10 minutes at room temperature. Radiolabeled glycine uptake was terminated by removing the radiolabeled glycine and washing the cells rapidly three times with 100 µl of ice-cold KRHT buffer. Scintillation fluid (50 µl) was added per well and the amount of tritiated glycine present was determined using a Packard TopCount Scintillation counter.

Nonspecific uptake was determined by measuring ³H-glycine uptake in the presence of 2 mM cold glycine. The IC₅₀ of a compound was determined by measuring inhibition of four separate samples at ten concentrations, typically beginning with 10 µM followed by nine three-fold dilutions (*i.e.*, 10, 3.3, 1.1, 0.37, 0.12, 0.41, 0.014, 0.0046, 0.0015, and 0 µM). Percent inhibitions were calculated against the control. The percentage inhibitions were calculated against the control, and the average of the quadruplicates was used for IC₅₀ calculation.

6.23. Calculating IC₅₀ Values

The IC₅₀ of a compound with regard to a given target is determined by fitting the relevant data, using the Levenburg Marquardt algorithm, to the equation:

$$y = A + ((B-A)/(1+((C/x)^D)))$$

wherein A is the minimum y value; B is the maximum y value; C is the IC₅₀; and D is the slope. The calculation of the IC₅₀ is performed using XLFit4 software (ID Business Solutions Inc., Bridgewater, NJ 08807) for Microsoft Excel (the above equation is model 205 of that software).

6.24. Pharmacological Effects

A compound having a PTIC₅₀ of less than 100 nM was administered to male C57B/6 albino mice subjected to a contextual fear conditioning program using a trace conditioning protocol. The compound was administered at doses ranging from 50-200 mg/kg, and was found to recapitulate phenotypes observed in SLC6A7 KO mice in a dose-dependent manner.

In the protocol, compound was administered p.o., two hours prior to training (Day 1) and again two hours prior to testing the next day (Day 2). Generally, 10-14 mice/group were tested in each study. The two hour pretreatment interval was chosen based on PK results to achieve of peak plasma and brain tissue levels.

5 In the trace conditioning experiments, no significant effect was observed in mice dosed at 50 mg/kg, p.o., although a numerical enhancement was seen. But at doses of 100 and 200 mg/kg, p.o., significant increases in performance were observed both during training (Day 1) and testing (Day 2). As shown in Figure 2, the compound enhanced performance during training as well as during memory testing, indicating that its effects are not changed upon repeated administration. And as shown in Figure 3, when administered prior to the recall test but not prior to training, the compound enhanced the conditioned response.

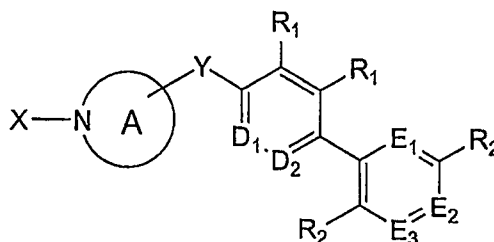
10 In order to gauge whether the compound's effect changed following repeated dosing, it was administered for three days b.i.d. prior to the training day, as well as b.i.d. on the training day and prior to the test. As in the acute studies, the compound was administered two hours prior to the training session and two hours prior to the test session. Based on separate PK studies, this administration regimen was expected to provide blood levels of the compound throughout the study. Results similar to those
15 shown in Figures 2 and 3 were observed, suggesting that the compound can enhance both learning and memory/recall.

The compound did not increase freezing by itself in naïve mice, as assessed in an open-field in the conditioning training apparatus, nor in mice given specific conditioning training and then placed in a novel open-field. Therefore, its effects appear to be specific
20 to the learned response, and not due to non-specific enhancement of freezing behavior.

27
5CLAIMS

What is claimed is:

1. A specific proline transporter inhibitor of formula I:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is an optionally substituted non-aromatic heterocycle;

each of D₁ and D₂ is independently N or CR₁;

each of E₁, E₂ and E₃ is independently N or CR₂;

X is optionally substituted heteroaryl;

Y is O, C(O), CH(OH), or CH₂;

each R₁ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;

each R₂ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;

each R_A is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

each R_B is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle.

2. The specific proline transporter inhibitor of claim 1, which has a PTIC₅₀ of less than about 150 nM.

3. The specific proline transporter inhibitor of claim 2, which has a PTIC₅₀ of less than about 100 nM.

4. The specific proline transporter inhibitor of claim 3, which has a PTIC₅₀ of less than about 50 nM.

5. The specific proline transporter inhibitor of claim 1, which has a DTIC₅₀ of greater than about 1 μM.

8

6. The specific proline transporter inhibitor of claim 5, which has a $GTIC_{50}$ of greater than about 1 μM .

7. The specific proline transporter inhibitor of claim 1, wherein A is monocyclic.

5 8. The specific proline transporter inhibitor of claim 1, wherein A is bicyclic.

9. The specific proline transporter inhibitor of claim 1, wherein A is unsubstituted.

10 10. The specific proline transporter inhibitor of claim 1, wherein A is optionally substituted pyrrolidine, piperidine, piperazine, hexahydropyrimidine, 1,2,3,6-tetrahydropyridine, octahydrocyclopenta[c]pyrrole, or octahydropyrrolo[3,4-c]pyrrole.

11. The specific proline transporter inhibitor of claim 1, wherein one of D_1 and D_2 is N.

12. The specific proline transporter inhibitor of claim 1, wherein both D_1 and D_2 are N.

15 13. The specific proline transporter inhibitor of claim 1, wherein both D_1 and D_2 are CR_1 .

14. The specific proline transporter inhibitor of claim 1, wherein one of E_1 , E_2 and E_3 is N.

20 15. The specific proline transporter inhibitor of claim 1, wherein two of E_1 , E_2 and E_3 are N.

16. The specific proline transporter inhibitor of claim 1, wherein all of E_1 , E_2 and E_3 are N.

17. The specific proline transporter inhibitor of claim 1, wherein all of E_1 , E_2 and E_3 are independently CR_2 .

25 18. The specific proline transporter inhibitor of claim 1, wherein R_1 is hydrogen, halogen, or optionally substituted alkyl.

19. The specific proline transporter inhibitor of claim 1, wherein R_1 is OR_A .

20. The specific proline transporter inhibitor of claim 19, wherein R_A is hydrogen or optionally substituted alkyl.

5

21. The specific proline transporter inhibitor of claim 1, wherein R_2 is hydrogen, halogen, or optionally substituted alkyl.

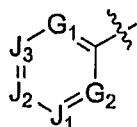
22. The specific proline transporter inhibitor of claim 1, wherein R_2 is OR_A .

23. The specific proline transporter inhibitor of claim 21, wherein R_A is
5 hydrogen or optionally substituted alkyl.

24. The specific proline transporter inhibitor of claim 1, wherein X is an optionally substituted 5-, 6-, 9- or 10-membered heteroaryl.

25. The specific proline transporter inhibitor of claim 24, wherein X is optionally substituted 5- or 6-membered heteroaryl.

10 26. The specific proline transporter inhibitor of claim 25, wherein X is of the formula:



wherein:

each of G_1 and G_2 are independently N or CR_3 ;

15 each of J_1 , J_2 and J_3 are independently N or CR_4 ;

each R_3 is independently hydrogen, halogen, cyano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, or SO_2R_A ; and

each R_4 is independently hydrogen, halogen, cyano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, or SO_2R_A ;

20 provided that at least one of J_1 , J_2 and J_3 is CR_4 .

27. The specific proline transporter inhibitor of claim 25, wherein one of G_1 and G_2 is N.

28. The specific proline transporter inhibitor of claim 25, wherein both G_1 and G_2 are N.

25 29. The specific proline transporter inhibitor of claim 25, wherein both G_1 and G_2 are CR_3 .

30. The specific proline transporter inhibitor of claim 25, wherein one of J_1 , J_2 and J_3 is N.

06

31. The specific proline transporter inhibitor of claim 25, wherein two of J_1 , J_2 and J_3 are N.

32. The specific proline transporter inhibitor of claim 25, wherein all of J_1 , J_2 and J_3 are independently CR_4 .

5 33. The specific proline transporter inhibitor of claim 25, wherein R_3 is hydrogen, halogen, or optionally substituted alkyl.

34. The specific proline transporter inhibitor of claim 25, wherein R_3 is OR_A .

35. The specific proline transporter inhibitor of claim 34, wherein R_A is hydrogen or optionally substituted alkyl.

10 36. The specific proline transporter inhibitor of claim 25, wherein R_4 is hydrogen, halogen, or optionally substituted alkyl.

37. The specific proline transporter inhibitor of claim 25, wherein R_4 is OR_A .

38. The specific proline transporter inhibitor of claim 37, wherein R_A is hydrogen or optionally substituted alkyl.

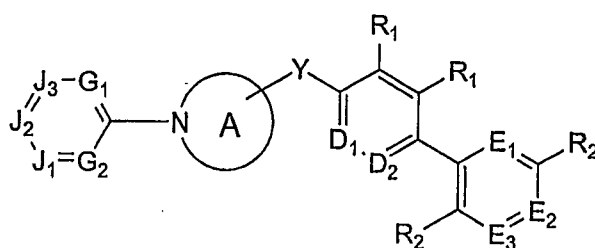
15 39. The specific proline transport inhibitor of claim 1, wherein Y is $C(O)$.

40. The specific proline transport inhibitor of claim 1, wherein Y is $CH(OH)$.

41. The specific proline transport inhibitor of claim 1, wherein Y is CH_2 .

42. The specific proline transport inhibitor of claim 25, which is of formula

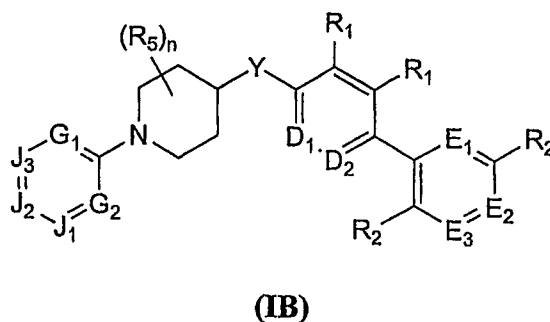
IA:



(IA)

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43. The specific proline transport inhibitor of claim 25, which is of formula
IB:



5 wherein:

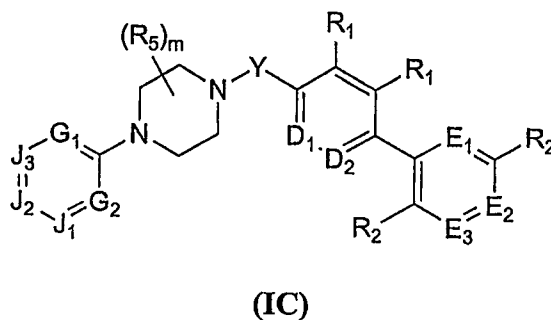
each R_5 is independently halogen, cyano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, or SO_2R_{5A} ;

each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

10 each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

n is 0-5.

44. The specific proline transport inhibitor of claim 25, which is of formula
IC:



15 wherein:

Y is O, $C(O)$ or CH_2 ;

20 each R_5 is independently halogen, cyano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, or SO_2R_{5A} ;

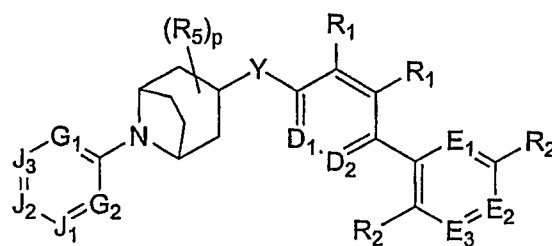
each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

25 m is 0-4.

62

45. The specific proline transport inhibitor of claim 25, which is of formula
ID:



(ID)

5 wherein:

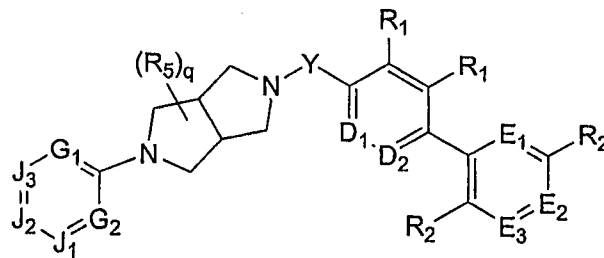
each R_5 is independently halogen, cyano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, or SO_2R_{5A} ;

each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

10 each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

p is 0-7.

46. The specific proline transport inhibitor of claim 25, which is of formula
IE:



(IE)

wherein:

Y is O, $C(O)$ or CH_2 ;

each R_5 is independently halogen, cyano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, or SO_2R_{5A} ;

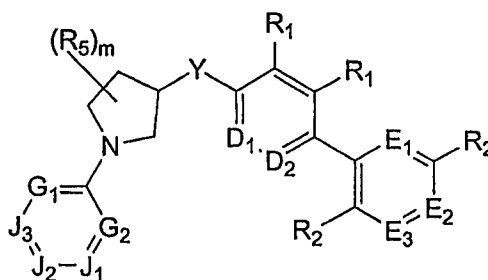
20 each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

3
6

q is 0-6.

47. The specific proline transport inhibitor of claim 25, which is of formula IF:



5

(IF)

wherein:

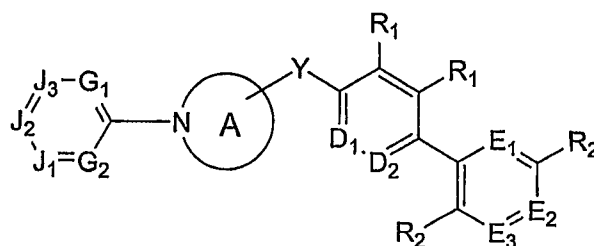
each R_5 is independently halogen, cyano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, or SO_2R_{5A} ;

each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

m is 0-4.

48. A compound of formula II:



15

(II)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is an optionally substituted non-aromatic heterocycle containing no more than two nitrogen atoms;

each of D_1 and D_2 is independently N or CR_1 ;

each of E_1 , E_2 and E_3 is independently N or CR_2 ;

each of G_1 and G_2 are independently N or CR_3 ;

each of J_1 , J_2 and J_3 are independently N or CR_4 ;

4
6

Y is O, C(O), CH(OH), or CH₂;

each R₁ is independently hydrogen, halogen, or (C₁₋₁₀)alkyl;

each R₂ is independently halogen, cyano, R_{2A}, OR_{2A}, or SO₂R_{2A};

5 each R_{2A} is independently hydrogen or (C₁₋₁₀)alkyl optionally substituted with one or more halogens;

each R₃ is independently hydrogen, cyano, or (C₁₋₁₀)alkyl optionally substituted with one or more halogens; and

each R₄ is independently hydrogen, cyano, or (C₁₋₁₀)alkyl optionally substituted with one or more halogens;

10 with the provisos that: 1) at least one of G₁, G₂, J₁, J₂ or J₃ is N; 2) at least one of J₁, J₂ and J₃ is CR₄; 3) if Y is C(O), A is piperazine, all of G₁, G₂, J₁, J₃, D₁, D₂, E₁, and E₃ are CH, and all of R₁ are hydrogen, then none of R₂ are lower alkyl; 4) if Y is C(O), A is piperazine, D₂ and E₁ are both N, and all of R₁ and R₂ are hydrogen, then R₄ is not cyano; 5) if Y is O, A is pyrrolidine, all of G₁, G₂, J₁, J₃, D₁, D₂, E₁, E₂, and E₃ are CH, and all of
15 R₁ are hydrogen, then at least one R₂ is not hydrogen; 6) if Y is CH₂, A is piperazine, all of G₂, J₁, J₂, J₃, D₁, and D₂ are CH, all of E₁, E₂ and E₃ are CR₂, and all of R₁ are hydrogen, at least one R₂ is not hydrogen; and 7) if Y is C(O) or CH₂, A is piperazine, at least one of G₁ and G₂ is N, all of J₁, J₂, J₃, D₁, D₂, E₁, E₂ and E₃ are CH, and all of R₁ are hydrogen, then at least one R₂ is not hydrogen.

20 49. The compound of claim 48, which has an PTIC₅₀ of less than about 200 nM.

50. The compound of claim 49, which has an DTIC₅₀ of greater than about 1 μM.

25 51. The compound of claim 50, which has an GTIC₅₀ of greater than about 1 μM.

52. The compound of claim 48, wherein A is monocyclic.

53. The compound of claim 48, wherein A is bicyclic.

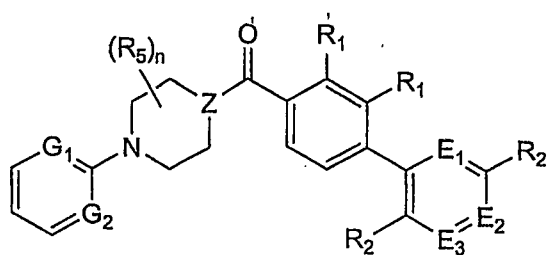
54. The compound of claim 48, wherein A is unsubstituted.

30 55. The compound of claim 48, wherein A is optionally substituted pyrrolidine, piperidine, piperazine, hexahydropyrimidine, 1,2,3,6-tetrahydropyridine, octahydrocyclopenta[c]pyrrole, or octahydropyrrolo[3,4-c]pyrrole.

15

56. The compound of claim 48, wherein one of D_1 and D_2 is N.
57. The compound of claim 48, wherein both D_1 and D_2 are N.
58. The compound of claim 48, wherein both D_1 and D_2 are CR_1 .
59. The compound of claim 48, wherein one of E_1 , E_2 and E_3 is N.
- 5 60. The compound of claim 48, wherein two of E_1 , E_2 and E_3 are N.
61. The compound of claim 48, wherein all of E_1 , E_2 and E_3 are N.
62. The compound of claim 48, wherein all of E_1 , E_2 and E_3 are CR_2 .
63. The compound of claim 48, wherein R_1 is hydrogen.
64. The compound of claim 48, wherein R_2 is halogen.
- 10 65. The compound of claim 48, wherein R_2 is OR_A .
66. The compound of claim 65, wherein R_A is hydrogen or optionally substituted alkyl.
67. The compound of claim 48, wherein one of G_1 and G_2 is N.
68. The compound of claim 48, wherein both G_1 and G_2 are N.
- 15 69. The compound of claim 48, wherein both G_1 and G_2 are CR_3 .
70. The compound of claim 48, wherein one of J_1 , J_2 and J_3 is N.
71. The compound of claim 48, wherein two of J_1 , J_2 and J_3 are N.
72. The compound of claim 48, wherein all of J_1 , J_2 and J_3 are CR_4 .
73. The compound of claim 48, wherein R_3 is hydrogen, halogen, or optionally substituted alkyl.
- 20 74. The compound of claim 48, wherein R_4 is hydrogen, halogen, or optionally substituted alkyl.
75. The compound of claim 48, wherein Y is $C(O)$.
76. The compound of claim 48, wherein Y is $CH(OH)$.
- 25 77. The compound of claim 48, wherein Y is CH_2 .
78. The compound of claim 48, which is of formula **IIA**:

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(IIA)

wherein:

Z is CR₅ or N;

5 each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A};

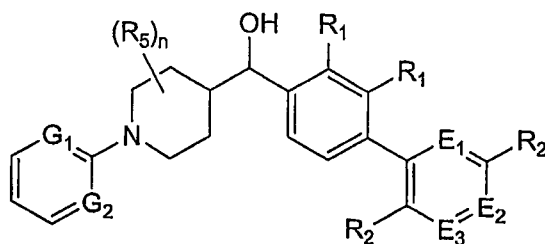
each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, 10 alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

n is 0-5 if Z is CR₅, or 0-4 if Z is N.

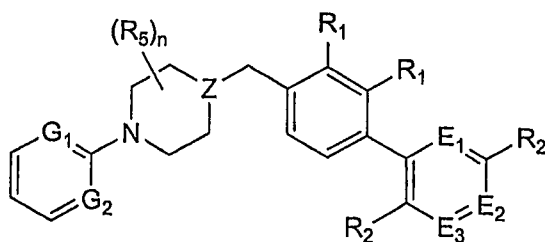
79. The compound of claim 78, wherein Z is CH, G₁ is N, and at least one R₂ is not hydrogen.

80. The compound of claim 48, which is of formula **IIB**:



(IIB)

81. The compound of claim 48, which is of formula **IIC**:



(IIC)

20 wherein:

Z is CR₅ or N;

each R₅ is independently halogen, cyano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), or SO₂R_{5A};

each R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle;

each R_{5B} is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

n is 0-5 if Z is CR₅, or 0-4 if Z is N.

82. The compound of claim 82, wherein Z is CH, G₁ is N, and at least one R₂ is not hydrogen.

83. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is:

- (1-(pyrimidin-2-yl)piperidin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanol;
 (4'-chlorobiphenyl-4-yl)(2,6-dimethyl-4-(pyridin-2-yl)piperazin-1-yl)methanone;
 15 (3'-chloro-3-methoxybiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
 (4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
 (3-fluoro-4'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (4'-chlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (2'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 20 (4-(benzo[d]oxazol-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
 biphenyl-4-yl(4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)methanone;
 (S)-(2-benzyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
 (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(6-p-tolylpyridin-3-yl)methanone;
 25 (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
 (6-(4-chlorophenyl)pyridin-3-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
 30 (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(6-(4-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
 (5-(4-chlorophenyl)isoxazol-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
 (3'-chlorobiphenyl-4-yl)(1-(pyridin-2-yl)piperidin-4-yl)methanone;

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- biphenyl-4-yl(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)methanone;
(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
biphenyl-4-yl(1-(pyrimidin-2-yl)azetidin-3-yl)methanone;
- 5 (6-(4-chloro-3-(trifluoromethyl)phenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(6-(4-chloro-3-methylphenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4'-chlorobiphenyl-4-yl)(1-(pyridin-2-yl)piperidin-4-yl)methanone;
(2-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 10 (3,4'-dimethylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(5-(3-chlorophenyl)pyridin-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4-(pyrimidin-2-yl)piperazin-1-yl)(5-p-tolylpyridin-2-yl)methanone;
(4-(pyridin-2-yl)piperazin-1-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
(1-(pyrimidin-2-yl)piperidin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 15 (3-fluoro-3'-(trifluoromethyl)biphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4-(pyrimidin-2-yl)piperazin-1-yl)(3'-(trifluoromethoxy)biphenyl-4-yl)methanone;
(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
biphenyl-4-yl(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- 20 (1-phenyl-5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
biphenyl-4-yl(4-(thiazol-2-yl)piperazin-1-yl)methanone;
(4-(4-chlorophenyl)cyclohexyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
4'-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)biphenyl-3-carbonitrile;
- 25 (4'-(methylsulfonyl)biphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
2-(4-((3'-chlorobiphenyl-4-yl)(hydroxy)methyl)piperidin-1-yl)pyrimidin-5-ol;
(4-(pyridin-3-yl)phenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(3'-chloro-3-hydroxybiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
1-(4'-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)biphenyl-3-yl)ethanone;
- 30 (2',4'-difluoro-3-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(5-phenyl-1H-pyrrol-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(6-(4-chlorophenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;

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- (5'-chloro-2'-fluorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanone;
- 2-(4-(biphenylcarbonyl)piperazin-1-yl)nicotinonitrile;
- 2-(4-(biphenyl-4-yloxy)piperidin-1-yl)pyrimidine;
- 5 (2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl)(1-(pyrimidin-2-yl)pyrrolidin-3-yl)methanone;
- (4-(4-methylthiophen-2-yl)phenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- (4'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (2-fluoro-4'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 10 biphenyl-4-yl(3-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl)(4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- biphenyl-4-yl(4-(5-methylpyridin-2-yl)piperazin-1-yl)methanone;
- biphenyl-4-yl(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 15 (1-(pyridin-2-yl)piperidin-4-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (6-(3-chlorophenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (4-(pyrimidin-2-yl)piperazin-1-yl)(6-(3-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
- (4-(pyrimidin-2-yl)piperazin-1-yl)(6-p-tolylpyridin-3-yl)methanone;
- (4'-chloro-3'-(trifluoromethyl)biphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- 20 (4-(2-chloropyridin-4-yl)phenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (2',4'-difluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (6-(2,4-difluorophenyl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3',5'-dichlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 2-(4-(biphenyl-4-ylmethyl)piperazin-1-yl)pyrimidine;
- 25 (4'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- (6-(3-chlorophenyl)pyridin-3-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (1-(pyridin-2-yl)piperidin-4-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (2'-fluoro-5'-(trifluoromethyl)biphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 30 (4'-methylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- biphenyl-4-yl(4-(5-methylpyridin-2-yl)piperazin-1-yl)methanone;
- 1-(biphenylcarbonyl)-4-(pyrimidin-2-yl)piperazin-2-one;
- biphenyl-4-yl(1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanone;

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- (3'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
biphenyl-4-yl(1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanol;
(3'-chlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4-(pyrimidin-2-yl)piperazin-1-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
5 (3'-chlorobiphenyl-4-yl)(1-(5-hydroxypyrimidin-2-yl)piperidin-4-yl)methanone;
(4'-ethylbiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(4-methylpyrimidin-2-yl)piperazin-1-yl)methanone;
(6-(2,4-difluorophenyl)pyridin-3-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-
2(1H)-yl)methanone;
10 (4'-chlorobiphenyl-4-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone;
(5-methyl-1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)(4'-
(trifluoromethyl)biphenyl-4-yl)methanone;
biphenyl-4-yl(4-(5-ethylpyrimidin-2-yl)piperazin-1-yl)methanone;
(4-(pyridin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
15 (4-(pyridin-2-yl)phenyl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(pyrazin-2-yl)piperazin-1-yl)methanone;
(4'-methoxybiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(6-methylpyridazin-3-yl)piperazin-1-yl)methanone;
4'-(4-(pyrimidin-2-yl)piperazine-1-carbonyl)biphenyl-4-carbonitrile;
20 (2,6-dimethyl-4-(pyridin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-
yl)methanone;
(5-phenylthiophen-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(6-(5-methylthiophen-2-yl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
biphenyl-4-yl(4-(pyridin-4-yl)piperazin-1-yl)methanone;
25 (R)-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-
yl)methanone;
biphenyl-4-yl((2S,5S)-2,5-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(3'-chlorobiphenyl-4-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone;
(4-(pyrimidin-2-yl)piperazin-1-yl)(2'-(trifluoromethyl)biphenyl-4-yl)methanone;
30 (S)-(4'-chlorobiphenyl-4-yl)(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(5'-chloro-2'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
(4-(5-methylthiophen-2-yl)phenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
biphenyl-4-yl(4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)methanone;

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- (S)-(2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (S)-(2-benzyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-chlorobiphenyl-4-yl)methanone;
- biphenyl-4-yl(4-(pyridazin-3-yl)piperazin-1-yl)methanone;
- 5 (6-(4-methylthiophen-2-yl)pyridin-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 1-(2',4'-difluorobiphenylcarbonyl)-4-(pyrimidin-2-yl)piperazine-2-carbonitrile;
- (4'-chlorobiphenyl-4-yl)((2S,5S)-2,5-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- biphenyl-4-yl(2-tert-butyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 10 (S)-biphenyl-4-yl(2-isopropyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- biphenyl-4-yl(2,6-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3'-chloro-2'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (4-(pyrimidin-2-yl)piperazin-1-yl)(6-(4-(trifluoromethyl)phenyl)pyridin-3-yl)methanone;
- (4'-chloro-3'-methylbiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- 15 (3'-chloro-2'-fluorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (2,6-dimethyl-4-(pyridin-2-yl)piperazin-1-yl)(4'-methylbiphenyl-4-yl)methanone;
- 3'-chloro-4-(1-(pyrimidin-2-yl)piperidine-4-carbonyl)biphenyl-3-yl acetate;
- biphenyl-4-yl(2-methyl-4-(pyridin-2-yl)piperazin-1-yl)methanone;
- 1-(biphenyl-4-ylmethyl)-4-(pyrimidin-2-yl)piperazin-2-one;
- 20 (3',4'-dichlorobiphenyl-4-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanol;
- (S)-biphenyl-4-yl(2-isobutyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanone;
- (S)-(4'-chlorobiphenyl-4-yl)(2-isopropyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 25 (4'-methylbiphenyl-4-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone;
- (S)-(2-isopropyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanol;
- (S)-(2-isobutyl-4-(pyrimidin-2-yl)piperazin-1-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 30 (S)-(4'-chlorobiphenyl-4-yl)(2-isobutyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(1-(pyrimidin-2-yl)pyrrolidin-3-yl)methanone;

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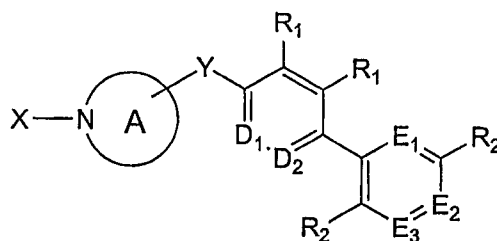
- (2',4'-difluorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanone;
- 4'-(4-(pyridin-2-yl)piperazine-1-carbonyl)biphenyl-4-carbonitrile;
- (4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)(3'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 5 methyl 1-(5'-chloro-2'-fluorobiphenylcarbonyl)-4-(pyrimidin-2-yl)piperazine-2-carboxylate;
- (4-(benzo[d]oxazol-2-yl)piperazin-1-yl)(4'-chlorobiphenyl-4-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(4-(thiazol-2-yl)piperazin-1-yl)methanone;
- (4-(5-chlorothiophen-2-yl)phenyl)(1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- 10 1-(5'-chloro-2'-fluorobiphenylcarbonyl)-4-(pyrimidin-2-yl)piperazine-2-carbonitrile;
- (4-phenylthiophen-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- biphenyl-4-yl(4-(pyrimidin-2-yl)-3,4-dihydroquinoxalin-1(2H)-yl)methanone;
- (5'-chloro-2'-fluorobiphenyl-4-yl)(8-(pyrimidin-2-yl)-8-azabicyclo[3.2.1]octan-3-yl)methanol;
- 15 (5-phenylfuran-2-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- (4'-chlorobiphenyl-4-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- 4-(4'-chlorobiphenyl-4-yl)-1-(pyrimidin-2-yl)piperidin-4-ol;
- (5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(4'-(trifluoromethyl)biphenyl-4-yl)methanone;
- 20 biphenyl-4-yl(5-(pyridin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (3'-chlorobiphenyl-4-yl)(5-(pyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- biphenyl-4-yl((2S,5S)-2,5-dimethyl-4-(pyrimidin-2-yl)piperazin-1-yl)methanone;
- 25 1-((3'-chlorobiphenyl-4-yl)methyl)-N,N-dimethyl-4-(pyrimidin-2-yl)piperazine-2-carboxamide;
- (2',4'-difluorobiphenyl-4-yl)(3-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)methanone;
- (4-(benzo[d]thiazol-2-yl)piperazin-1-yl)(biphenyl-4-yl)methanone;
- biphenyl-4-yl(4-(quinolin-2-yl)piperazin-1-yl)methanone;
- 30 4-(biphenyl-4-yl)-1-(pyrimidin-2-yl)piperidin-4-ol;
- 4'-chloro-N-methyl-N-(2-(methyl(pyrimidin-2-yl)amino)ethyl)biphenyl-4-carboxamide;
- or
- 2-(biphenyl-4-yl)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethanone.

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84. A pharmaceutical composition comprising a compound of claim 1 or 48 and a pharmaceutically acceptable excipient.

85. A single unit dosage form comprising the pharmaceutical composition of claim 84.

5 86. A method of inhibiting a proline transporter, which comprises contacting a proline transporter with sufficient amount of a compound of formula I:



(I)

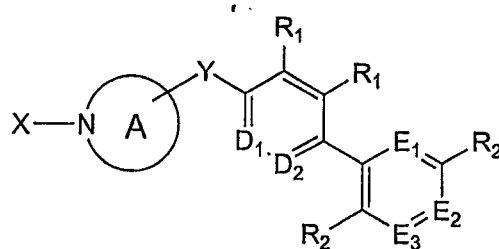
or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 10 A is an optionally substituted non-aromatic heterocycle;
 each of D₁ and D₂ is independently N or CR₁;
 each of E₁, E₂ and E₃ is independently N or CR₂;
 X is optionally substituted heteroaryl;
 Y is O, C(O), CH(OH), or CH₂;
- 15 each R₁ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;
 each R₂ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;
 each R_A is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and
- 20 each R_B is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle.

87. The method of claim 86, wherein the proline transporter is encoded by the human gene SLC6A7.

25 88. A method of improving the cognitive performance of a human patient, which comprises administering to the patient an effective amount of a compound of formula I:

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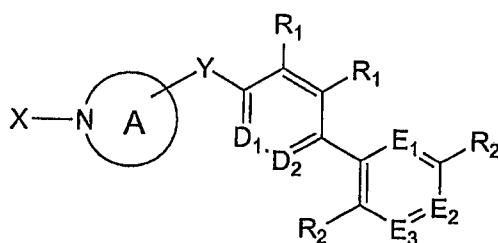
(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

- A is an optionally substituted non-aromatic heterocycle;
- 5 each of D₁ and D₂ is independently N or CR₁;
- each of E₁, E₂ and E₃ is independently N or CR₂;
- X is optionally substituted heteroaryl;
- Y is O, C(O), CH(OH), or CH₂;
- each R₁ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A,
- 10 C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;
- each R₂ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A,
- C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;
- each R_A is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl,
- alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and
- 15 each R_B is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl,
- alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle.

89. The method of claim 88, wherein the cognitive performance is rapidity of learning, comprehension, reasoning, or memory.

90. A method of treating, managing or preventing a disease or disorder in a
- 20 human patient, which comprises administering to the patient an effective amount of a compound of formula I:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 25 A is an optionally substituted non-aromatic heterocycle;
- each of D₁ and D₂ is independently N or CR₁;

25

each of E₁, E₂ and E₃ is independently N or CR₂;

X is optionally substituted heteroaryl;

Y is O, C(O), CH(OH), or CH₂;

each R₁ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A,

5 C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;

each R₂ is independently hydrogen, halogen, cyano, R_A, OR_A, C(O)R_A, C(O)OR_A,

C(O)N(R_AR_B), N(R_AR_B), or SO₂R_A;

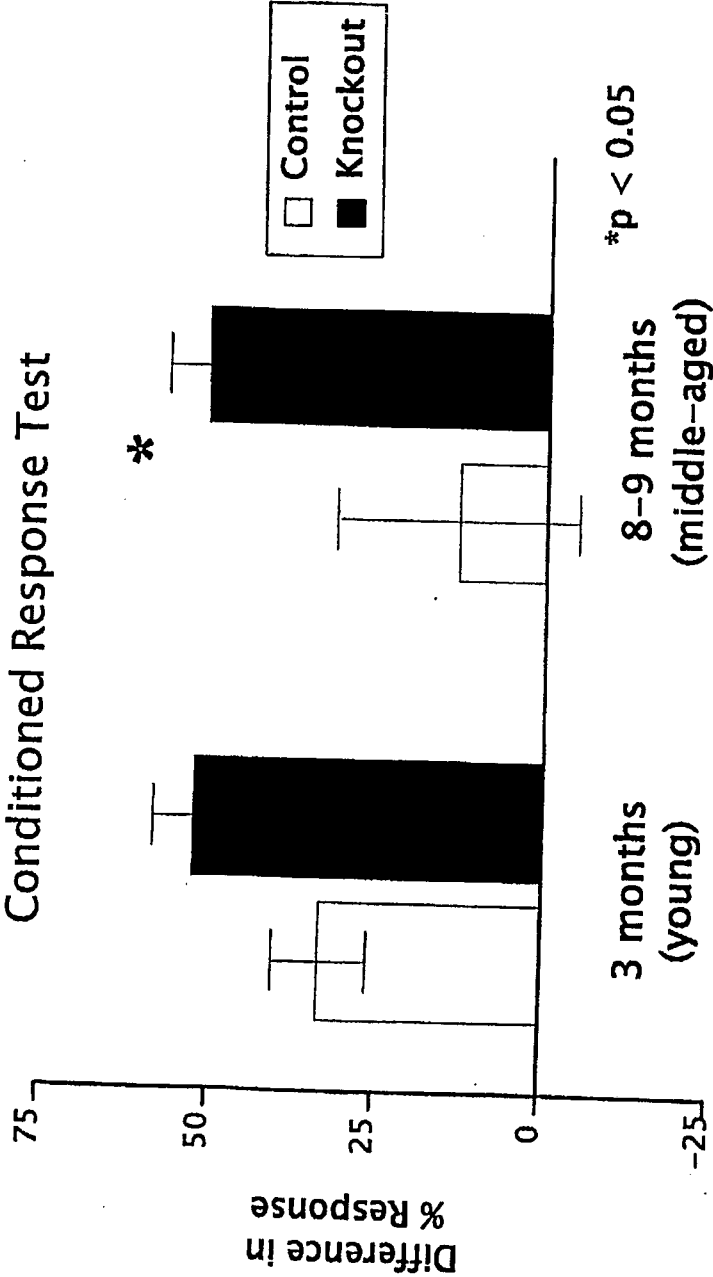
each R_A is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle; and

10 each R_B is independently hydrogen or optionally substituted alkyl, aryl, arylalkyl, alkylaryl, heterocycle, heterocycle-alkyl, or alkyl-heterocycle.

91. The method of claim 90, wherein the disease or disorder is Alzheimer's disease, autism, a cognitive disorder, dementia, a learning disorder, or memory loss.

92. The method of claim 91, wherein the learning disorder is dyslexia,
15 dyscalculia, dysgraphia, dysphasia, or dysnomia.

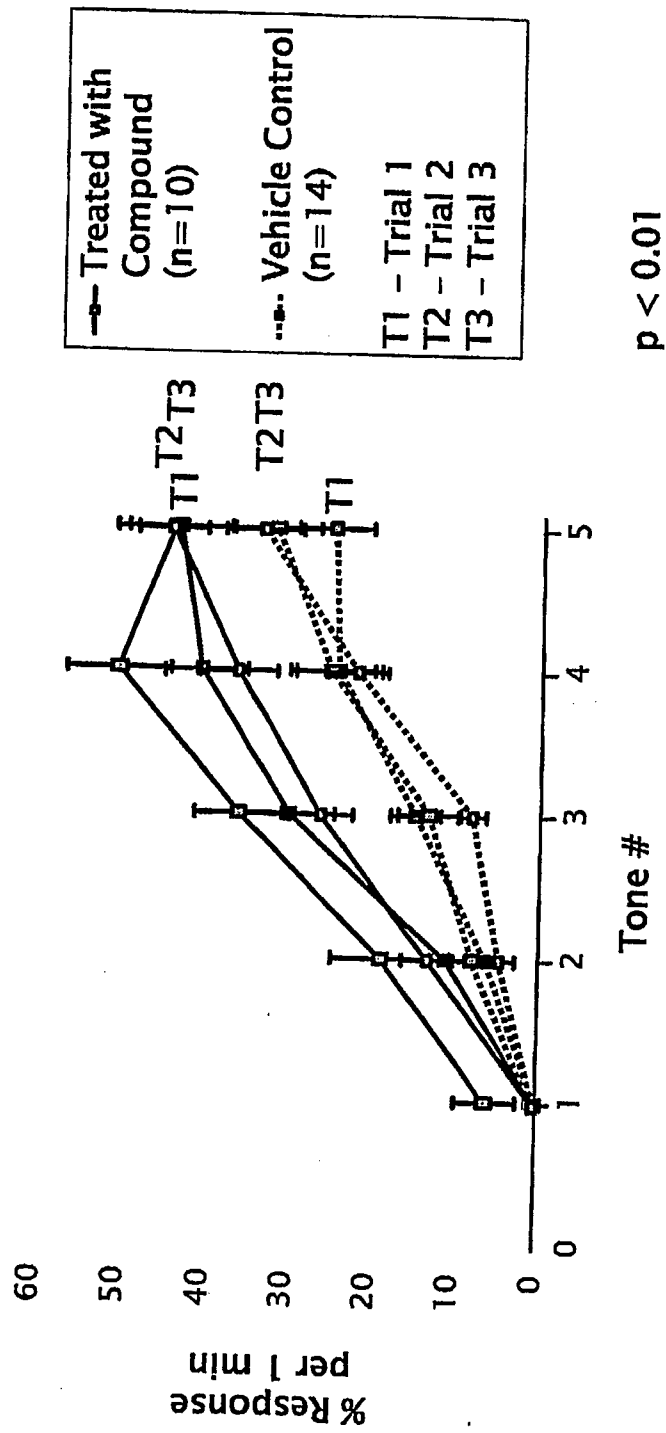
Figure 1



77

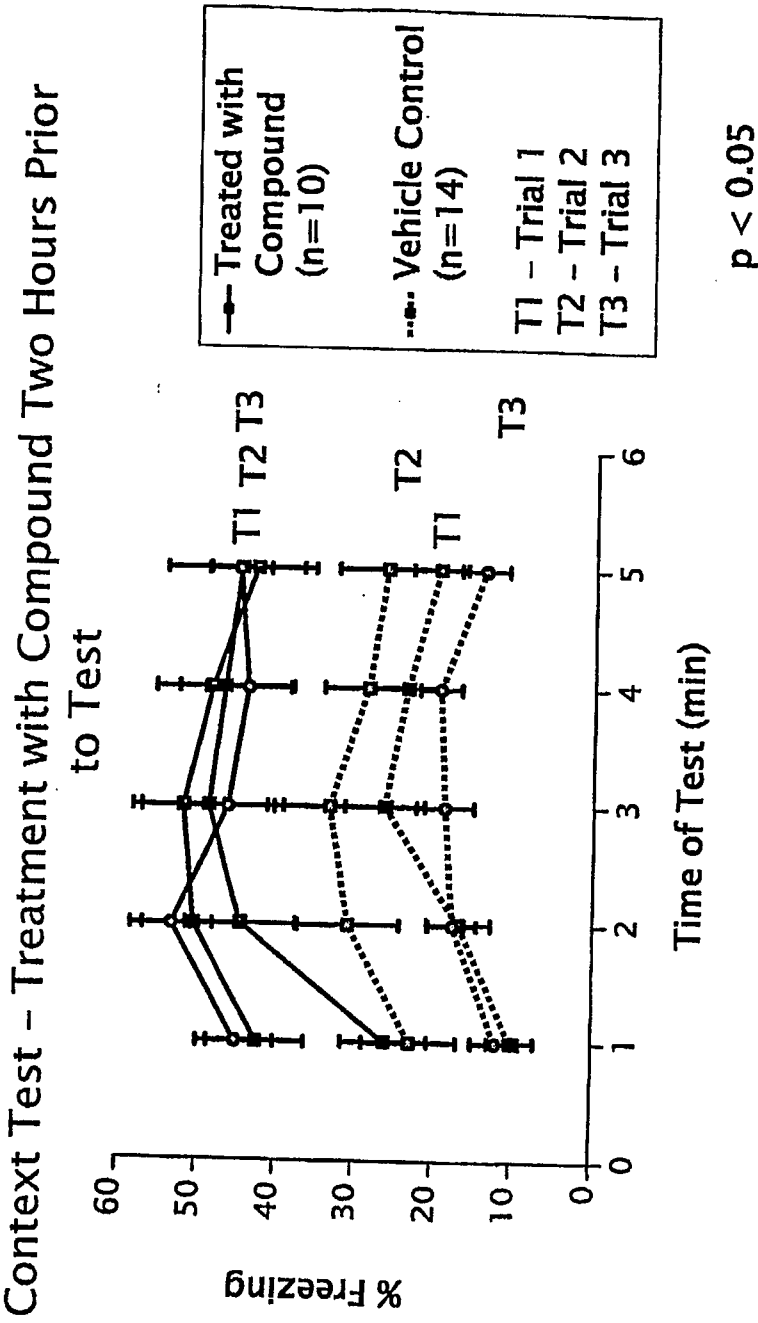
Figure 2

Learning Phase of Conditioned Response Test in Mice



78

Figure 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/018682

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/506 A61K31/496 A61K31/551 C07D239/42 C07D401/12
C07D401/04 C07D277/42 C07D403/04 C07D487/04 C07D451/02
C07D487/08 A61P25/28

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

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, BIOSIS, EMBASE, WPI Data, 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.
X	GB 2 263 636 A (MERCK & CO INC [US]) 4 August 1993 (1993-08-04) page 41; compound 34 ----- -/--	1-7, 13, 17, 18, 24-27, 33, 36, 41, 42, 84-92

☒ 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

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"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

22 November 2006

Date of mailing of the international search report

06/12/2006

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

Steendijk, Martin

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/018682

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/018682

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/018682

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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A61K 31/551 (2006.01) C07D 487/04 (2006.01)
C07D 239/42 (2006.01) C07D 451/02 (2006.01)
C07D 401/12 (2006.01) C07D 487/08 (2006.01)
C07D 401/04 (2006.01) A61P 25/28 (2006.01)

(74) Agente: ISHIMOTO, Lance K.; LEXICON GENETICS
INCORPORATED, 8800 Technology Forest Place, The
Woodlands, Texas 77381 (US).

(81) Países designados (a menos que se indique lo
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AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW,
BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK,
MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
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(71) Solicitante (para todos los países destinatarios con
excepción de US): LEXICON GENETICS
INCORPORATED [US/US]; 8800 Technology Forest
Place, The Woodlands, Texas 77381 (US).

(84) Países designados (a menos que se indique lo
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ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL,
SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY,
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LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR),
OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG).

Publicado:

— con informe internacional de búsqueda

(72) Inventores, e

(75) Inventores/Solicitantes (para US únicamente):

BARBOSA, Joseph [US/US]; 2 Big Top Drive,
Lambertville, NJ 08530 (US). DONG, Li [CN/US]; 11
Pagoda Court, Lawrenceville, NJ 08648 (US). FINK,
Cynthia Ann [US/US]; 1 Kensington Court, Lebanon, NJ
08833 (US). WANG, Jiancheng [CN/US]; 5707 Fox Run
Drive, Plainsboro, NJ 08536 (US). ZIPP, G. Gregory
[US/US]; 31 Kettering Court, Robbinsville, NJ 08691
(US).

(88) Fecha de publicación del informe de búsqueda
internacional:

1 de marzo de 2007

Para códigos de dos letras y otras abreviaturas, remítase a
las "Notas Guía sobre Códigos y Abreviaturas" que aparece
al comienzo de cada edición regular del Boletín Oficial PCT.

(54) Título: COMPUESTOS MULTICÍCLICOS Y MÉTODOS DE EMPLEO DE LOS MISMOS

(57) Extracto: Esta invención se refiere a compuestos multi-cíclicos, composiciones farmacéuticas que los
comprenden y métodos de empleo de los mismos, por ejemplo, en el tratamiento de trastornos cognitivos.

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COMPUESTOS MULTI-CÍCLICOS Y MÉTODOS DE EMPLEO DE LOS MISMOS

Esta solicitud reivindica prioridad a la solicitud provisional U.S. No. 60/680,501, presentada el 13 de mayo de 2005.

1. CAMPO DE LA INVENCION

Esta invención se refiere a compuestos multi-cíclicos, composiciones farmacéuticas que los comprenden y métodos de empleo de los mismos.

2. ANTECEDENTES DE LA INVENCION

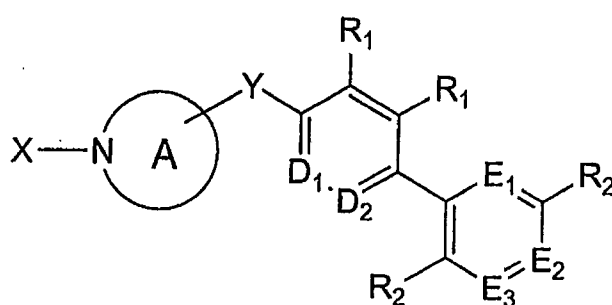
Supuestamente, el aminoácido L-prolina juega un papel en regular la transmisión sináptica en el cerebro mamífero. Véase, por ejemplo, Crump *et al.*, *Molecular and Cellular Neuroscience*, 13: 25-29 (1999). Por ejemplo, se ha divulgado una vía bi-sintética sinaptosómica de L-prolina a partir de ornitina, y se ha observado una absorción sinaptosómica, dependiente de Na^+ con afinidad elevada, de L-prolina. Yoneda *et al.*, *Brain Res.*, 239: 479-488 (1982); Balcar *et al.*, *Brain Res.*, 102: 143-151 (1976).

En general, los sistemas neurotransmisores poseen típicamente mecanismos que inactivan la señalización, muchos de los cuales funcionan gracias a la acción de un transportador dependiente de Na^+ . En este caso, se ha descrito un transportador dependiente de Na^+ para prolina, y la entidad molecular clonada (SLC6A7 en humanos). Véase, por ejemplo, Patentes de los Estados Unidos No. 5,580,775 y 5,759,788. Pero el papel específico de transportador sigue siendo desconocido. Por ejemplo, el transportador humano de prolina Na^+ -dependiente se localiza generalmente en las terminales sinápticas, lo cual es consistente con un papel en la señalización de neurotransmisores. Sin embargo, no se ha encontrado un receptor de alta afinidad para prolina, sugiriendo que es un neuromodulador antes que un neurotransmisor. Shafqat S., *et al.*, *Molecular Pharmacology* 48:219-229 (1995).

El hecho que el transportador de prolina Na^+ -dependiente, se exprese en el ganglio de la raíz dorsal ha llevado a algunos a sugerir que puede estar implicado en la nocicepción, y que compuestos que inhiben el transportador pueden emplearse para tratar el dolor. Véase, por ejemplo, Solicitud de Patente de los Estados Unidos No. 20030152970A1. No obstante, esta sugerencia no está sustentada por datos experimentales.

3. SUMARIO DE LA INVENCION

Esta invención abarca compuestos multi-cíclicos, composiciones farmacéuticas que los comprenden, y métodos de empleo de los mismos. Una incorporación de la invención comprende un compuesto de la fórmula I:



(I)

y sus sales y solvatos farmacéuticamente aceptables, en donde: A es un heterociclo no aromático, opcionalmente sustituido; cada uno de D_1 y D_2 es independientemente N o CR_1 ; cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ; X es heteroarilo opcionalmente sustituido; Y es O, $\text{C}(\text{O})$, $\text{CH}(\text{OH})$, o CH_2 ; cada R_1 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $\text{C}(\text{O})\text{R}_\text{A}$, $\text{C}(\text{O})\text{OR}_\text{A}$, $\text{C}(\text{O})\text{N}(\text{R}_\text{A}\text{R}_\text{B})$, $\text{N}(\text{R}_\text{A}\text{R}_\text{B})$, o $\text{SO}_2\text{R}_\text{A}$; cada R_2 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $\text{C}(\text{O})\text{R}_\text{A}$, $\text{C}(\text{O})\text{OR}_\text{A}$, $\text{C}(\text{O})\text{N}(\text{R}_\text{A}\text{R}_\text{B})$, $\text{N}(\text{R}_\text{A}\text{R}_\text{B})$, o $\text{SO}_2\text{R}_\text{A}$; cada R_A es independientemente hidrógeno o alquilo opcionalmente sustituido, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo; y cada R_B es independientemente hidrógeno o alquilo opcionalmente sustituido, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo.

b

Compuestos preferidos inhiben el transportador de prolina, y compuestos particulares actúan en esa forma sin afectar sustancialmente los transportadores dopamina o glicina.

Otra incorporación de la invención comprende composiciones farmacéuticas de los varios compuestos descritos en esta solicitud.

Otra incorporación comprende métodos de mejorar el desempeño cognitivo, y de tratar, controlar y/o prevenir varias enfermedades y trastornos, utilizando compuestos de la invención.

4. BREVE DESCRIPCIÓN DE LAS FIGURAS

Ciertos aspectos de la invención pueden entenderse con referencia a las figuras adjuntas.

Figura 1 muestra diferencias entre ratones silvestres y ratones con el gen SLC6A7 inactivado en una prueba de respuesta condicionada.

Figura 2 muestra el efecto de un compuesto de la invención administrado a ratones antes de la fase de aprendizaje de una prueba de respuesta condicionada.

Figura 3 muestra el efecto de un compuesto de la invención administrado a ratones antes de una prueba de contexto.

5. DESCRIPCIÓN DETALLADA DE LA INVENCION

En parte, esta invención se basa en el descubrimiento que el transportador de prolina codificado por el gen humano en el sitio del mapa 5q31-q32 (gen SLC6A7; No. de acceso al GENBANK NM_014228) puede ser un potente modulador del desempeño mental en humanos. En particular, se ha descubierto que ratones genéticamente modificados, que no expresan un producto funcional del ortólogo murino del gen SLC6A7, despliegan una función cognitiva, alcance de atención, aprendizaje, y memoria significativamente aumentados, en relación con animales de control. Se cree que éste es el primer informe de datos experimentales que asocian la inhibición del transportador de prolina a un efecto farmacológico benéfico.

A
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En vista de este descubrimiento, el producto proteínico asociado con la región codificante SLC6A7 se usó para descubrir compuestos que puedan mejorar el desempeño cognitivo y puedan ser útiles en el tratamiento, prevención y/o control de enfermedades y trastornos tales como la enfermedad de Alzheimer, autismo, trastornos cognitivos, demencia, trastornos de aprendizaje, y pérdida de la memoria a corto y largo plazo.

5.1. Definiciones

A menos que se indique lo contrario, el término "alquenilo" significa un hidrocarburo de cadena recta, ramificada y/o cíclico que tiene desde 2 a 20 (*por ejemplo*, 2 a 10 ó 2 a 6) átomos de carbono, y que incluye por lo menos un doble enlace carbono-carbono. Fracciones alquenilo representativas incluyen vinilo, alilo, 1-butenilo, 2-butenilo, isobutilenilo, 1-pentenilo, 2-pentenilo, 3-metil-1-butenilo, 2-metil-2-butenilo, 2,3-dimetil-2-butenilo, 1-hexenilo, 2-hexenilo, 3-hexenilo, 1-heptenilo, 2-heptenilo, 3-heptenilo, 1-octenilo, 2-octenilo, 3-octenilo, 1-nonenilo, 2-nonenilo, 3-nonenilo, 1-decenilo, 2-decenilo y 3-decenilo.

A menos que se indique lo contrario, el término "alquilo" significa un hidrocarburo de cadena recta, ramificada y/o cíclico ("cicloalquilo") que tiene desde 1 a 20 (*por ejemplo*, 1 a 10 ó 1 a 4) átomos de carbono. Fracciones alquilo que tienen desde 1 a 4 carbonos se denominan "alquilo inferior." Ejemplos de grupos alquilo incluyen metilo, etilo, propilo, isopropilo, n-butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo, nonilo, decilo, undecilo y dodecilo. Fracciones cicloalquilo pueden ser monocíclicas o multicíclicas, y los ejemplos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y adamantilo. Ejemplos adicionales de fracciones alquilo tienen porciones lineales, ramificadas y/o cíclicas (*por ejemplo*, 1-etil-4-metil-ciclohexilo). El término "alquilo" incluye hidrocarburos saturados, así como fracciones alquenilo y alquinilo. A menos que se indique lo contrario, el término "alquilarilo" o "alquil-arilo" significa una fracción alquilo unida a una fracción arilo.

A menos que se indique lo contrario, el término "alquilheteroarilo" o "alquil-heteroarilo" significa una fracción alquilo unida a una fracción heteroarilo.

A menos que se indique lo contrario, el término "alquilheterociclo" o "alquil-heterociclo" significa una fracción alquilo unida a una fracción heterociclo.

A menos que se indique lo contrario, el término "alquinilo" significa un hidrocarburo de cadena recta, ramificada o cíclica que tiene desde 2 a 20 (*por ejemplo*, 2 a 6) átomos de carbono, y que incluye por lo menos un enlace triple carbono-carbono. Fracciones alquinilo representativas incluyen acetilenilo, propinilo, 1-butinilo, 2-butinilo, 1-pentinilo, 2-pentinilo, 3-metil-1-butinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 5-hexinilo, 1-heptinilo, 2-heptinilo, 6-heptinilo, 1-octinilo, 2-octinilo, 7-octinilo, 1-noninilo, 2-noninilo, 8-noninilo, 1-decinilo, 2-decinilo y 9-decinilo.

A menos que se indique lo contrario, el término "alcoxi" significa un grupo -O-alquilo. Ejemplos de grupos alcoxi incluyen, pero no se limitan a, -OCH₃, -OCH₂CH₃, -O(CH₂)₂CH₃, -O(CH₂)₃CH₃, -O(CH₂)₄CH₃, y -O(CH₂)₅CH₃.

A menos que se indique lo contrario, el término "arilo" significa un anillo aromático o un sistema de anillo aromático o parcialmente aromático compuesto de átomos de carbono e hidrógeno. Una fracción arilo puede comprender múltiples anillos unidos o fusionados entre sí. Ejemplos de fracciones arilo incluyen antracenilo, azulenilo, bifenilo, fluorenilo, indano, indenilo, naftilo, fenantrenilo, fenilo, 1,2,3,4-tetrahidro-naftaleno, y tolilo.

A menos que se indique lo contrario, el término "arilalquilo" o "aril-alquilo" significa una fracción arilo unida a una fracción alquilo.

A menos que se indique lo contrario, el término "DTIC₅₀" significa una IC₅₀ contra transportador humano de dopamina recombinante como se determina usando el análisis descrito en los Ejemplos, más adelante.

A menos que se indique lo contrario, el término "GTIC₅₀" significa una IC₅₀ para el transportador humano de glicina recombinante como se determina usando el análisis descrito en los Ejemplos, más adelante.

A menos que se indique lo contrario, los términos "halógeno" y "halo" abarcan flúor, cloro, bromo, y yodo.

A menos que se indique lo contrario, el término "heteroalquilo" se refiere a una fracción alquilo (*por ejemplo*, lineal, ramificada o cíclica) en la cual por lo menos uno de sus átomos de carbono se ha reemplazado con un heteroátomo (*por ejemplo*, N, O o S).

A menos que se indique lo contrario, el término "heteroarilo" significa una fracción arilo en donde por lo menos uno de sus átomos de carbono se ha reemplazado con un heteroátomo (*por ejemplo*, N, O o S). Ejemplos incluyen acridinilo, benzimidazolilo, benzofuranilo, benzoisotiazolilo, benzoisoxazolilo, benzoquinazolinilo, benzotiazolilo, benzoxazolilo, furilo, imidazolilo, indolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, ftalazinilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirimidilo, pirrolilo, quinazolinilo, quinolinilo, tetrazolilo, tiazolilo, y triazinilo.

A menos que se indique lo contrario, el término "heteroarilalquilo" o "heteroaril-alquilo" significa una fracción heteroarilo unida a una fracción alquilo.

A menos que se indique lo contrario, el término "heterociclo" se refiere a un anillo, o sistema de anillo monocíclico o policíclico, aromático, parcialmente aromático o no aromático, compuesto por carbono, hidrógeno y por lo menos un heteroátomo (*por ejemplo*, N, O o S). Un heterociclo puede comprender múltiples anillos (es decir, dos o más) fusionados o unidos entre sí. Heterociclos incluyen heteroarilos. Ejemplos incluyen benzo[1,3]dioxolilo, 2,3-dihidro-benzo[1,4]dioxinilo, cinnolinilo, furanilo, hidantoinilo, morfolinilo, oxetanilo, oxiranilo, piperazinilo, piperidinilo, pirrolidinonilo, pirrolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo y valerolactamilo.

A menos que se indique lo contrario, el término "heterocicloalquilo" o "heterociclo-alquilo" se refiere a una fracción heterociclo unida a una fracción alquilo.

A menos que se indique lo contrario, el término "heterocicloalquilo" se refiera a un heterociclo no aromático.

A menos que se indique lo contrario, el término "heterocicloalquilalquilo" o "heterocicloalquil-alquilo" se refiere a una fracción heterocicloalquilo unida a una fracción alquilo.

A menos que se indique lo contrario, los términos "controlar," "controlando" y "control" abarcan prevenir la recurrencia de la enfermedad o trastorno especificados en un paciente que ya ha sufrido de la enfermedad o trastorno, y/o alargar el tiempo en que un paciente que ha sufrido de la enfermedad o trastorno permanece en remisión. Los términos abarcan modular el umbral, evolución y/o duración de la enfermedad o trastorno, o modificar la forma en que un paciente responde a la enfermedad o trastorno.

A menos que se indique lo contrario, el término "sales farmacéuticamente aceptables" se refiere a sales preparadas de ácidos no tóxicos, farmacéuticamente aceptables, o bases, incluidos ácidos inorgánicos y bases. Sales apropiadas de adición de ácido, farmacéuticamente aceptables incluyen, pero no se limitan a, sales metálicas preparadas de aluminio, calcio, litio, magnesio, potasio, sodio y zinc, o sales orgánicas preparadas de lisina, N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina (N-metilglucamina) y procaína. Ácidos no tóxicos apropiados incluyen, pero no se limitan a, ácidos orgánicos e inorgánicos tales como ácido acético, algínico, antranílico, bencenosulfónico, benzoico, naftalenosulfónico, cítrico, etenosulfónico, fórmico, fumárico, furoico, galacturónico, glucónico, glucurónico, glutámico, glicólico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, málico, mandélico, metanosulfónico, mícico, nítrico, pamoico, pantoténico, fenilacético, fosfórico, propiónico, salicílico, esteárico, succínico, sulfanílico, sulfúrico, tartárico, y ácido p-toluenosulfónico. Ácidos no tóxicos específicos incluyen ácidos clorhídrico, bromhídrico, fosfórico, sulfúrico, y metanosulfónicos. Ejemplos de sales específicas incluyen por lo tanto sales clorhidrato y mesilato. Otras sales son bien conocidas en el arte. Véase, por ejemplo,

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Remington's Pharmaceutical Sciences (18th ed., Mack Publishing, Easton PA: 1990) y *Remington: The Science and Practice of Pharmacy* (19th ed., Mack Publishing, Easton PA: 1995).

A menos que se indique lo contrario, los términos "prevenir," "previniendo" y "prevención" contemplan una acción que ocurre antes que un paciente empiece a sufrir de la enfermedad o trastorno especificados, acción que inhibe o reduce la severidad de la enfermedad o trastorno. En otras palabras, los términos abarcan profilaxis.

A menos que se indique lo contrario, una "cantidad profilácticamente efectiva" de un compuesto es una cantidad suficiente para prevenir una enfermedad o afección, o uno o más síntomas asociados con la enfermedad o afección, o para prevenir su recurrencia. Una cantidad profilácticamente efectiva de un compuesto significa una cantidad de agente terapéutico, solo o en combinación con otros agentes, que ofrece un beneficio profiláctico en la prevención de la enfermedad o afección. El término "cantidad profilácticamente efectiva" puede comprender una cantidad que mejora la profilaxis general o incrementa la eficacia profiláctica de otro agente profiláctico.

A menos que se indique lo contrario, el término "PTIC₅₀" significa una IC₅₀ para el transportador humano de prolina Na⁺-dependiente como se determina utilizando el análisis descrito en los Ejemplos, más adelante.

A menos que se indique lo contrario, el término "inhibidor específico de transportador de prolina" significa un compuesto que tiene una PTIC₅₀ de menos de alrededor de 200 nM.

A menos que se indique lo contrario, el término "sustituido," cuando se emplea para describir una estructura química o fracción, se refiere a un derivado de esa estructura o fracción en donde uno o más de sus átomos de hidrógeno se sustituye con una fracción química o grupo funcional tales como, pero sin limitarse a, alcohol, aldehído, alcoxi, alcanoiloxi, alcoxicarbonilo, alquenilo, alquilo (*por ejemplo*, metilo, etilo, propilo, t-butilo), alquinilo, alquilcarboniloxi (-OC(O)alquilo), amida (-C(O)NH-alquil- o -alquilNHC(O)alquilo), amidinilo (-C(NH)NH-alquil- o -

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C(NR)NH₂), amina (primaria, secundaria y terciaria tal como alquilamino, arilamino, arilalquilamino), aroilo, arilo, ariloxi, azo, carbamoil (-NHC(O)O-alkil- o -OC(O)NH-alkilo), carbamilo (*por ejemplo*, CONH₂, CONH-alkilo, CONH-arilo, y CONH-arilalquilo), carbonilo, carboxilo, ácido carboxílico, anhídrido de ácido carboxílico, cloruro de ácido carboxílico, ciano, éster, epóxido, éter (*por ejemplo*, metoxi, etoxi), guanidino, halo, haloalkilo (*por ejemplo*, -CCl₃, -CF₃, -C(CF₃)₃), heteroalkilo, hemiacetal, imina (primaria y secundaria), isocianato, isotiocianato, cetona, nitrilo, nitro, oxo, fosfodiéster, sulfuro, sulfonamido (*por ejemplo*, SO₂NH₂), sulfona, sulfonilo (incluidos alkilsulfonilo, arilsulfonilo y arilalkilsulfonilo), sulfóxido, tiol (*por ejemplo*, sulfhidrilo, tioéter) y urea (-NHCONH-alkil-).

A menos que se indique lo contrario, una "cantidad terapéuticamente efectiva" de un compuesto es una cantidad suficiente para proporcionar un beneficio terapéutico en el tratamiento o control de una enfermedad o afección, o para retrasar o minimizar uno o más síntomas asociados con la enfermedad o afección. Una cantidad terapéuticamente efectiva de un compuesto significa una cantidad de agente terapéutico, solo o en combinación con otras terapias, que brinda un beneficio terapéutico en el tratamiento o control de la enfermedad o afección. El término "cantidad terapéuticamente efectiva" puede comprender una cantidad que mejora la terapia general, reduce o evita los síntomas o causas de una enfermedad o afección, o aumenta la eficacia terapéutica de otro agente terapéutico.

A menos que se indique lo contrario, el términos "tratar," "tratando" y "tratamiento" contemplan una acción que ocurre mientras un paciente está sufriendo de una enfermedad o trastorno específicos, acción que reduce la severidad de la enfermedad o trastorno o uno o más de sus síntomas, o retarda o desacelera la evolución de la enfermedad o trastorno.

A menos que se indique lo contrario, el término "incluir" tiene el mismo significado de "incluyen, pero no se limitan a," y el término "incluye" tiene el mismo significado que "incluye, pero no se limita a."

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Análogamente, el término "tal como" tiene el mismo significado que el término "tal como, pero no limitado a."

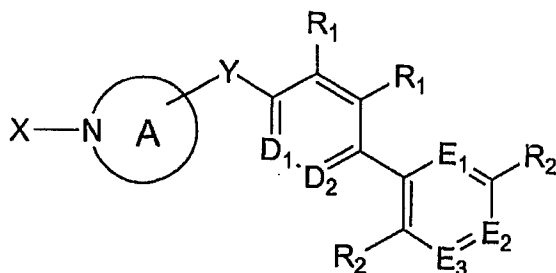
A menos que se indique lo contrario, uno o más adjetivos que preceden inmediatamente a una serie de sustantivos tiene que interpretarse como aplicándose a cada uno de los sustantivos. Por ejemplo, la expresión "alquilo, arilo, o heteroarilo opcionalmente sustituidos" tiene el mismo significado que "alquilo opcionalmente sustituido, arilo opcionalmente sustituido, o heteroarilo opcionalmente sustituido."

Debe observarse que una fracción química, que forma parte de un compuesto mayor, puede describirse en esta solicitud usando un nombre comúnmente asignado cuando existe como una molécula única o un nombre comúnmente asignado a su radical. Por ejemplo, a los términos "piridina" y "piridilo" se les asigna el mismo significado cuando se utilizan para describir una fracción unida a otras fracciones químicas. En consecuencia, a las dos expresiones "XOH, en donde X es piridilo" y "XOH, en donde X es piridina" se les asigna el mismo significado, y abarcan los compuestos piridin-2-ol, piridin-3-ol y piridin-4-ol.

Debe observarse igualmente que se asume que cualquier átomo mostrado en un dibujo con valencias no satisfechas se une a suficientes átomos de hidrógeno para satisfacer las valencias. Adicionalmente, los enlaces químicos representados con una línea gruesa, paralela a una línea punteada abarcan enlaces simples y dobles (*por ejemplo*, aromáticos), si las valencias lo permiten. Estructuras que representan compuestos con uno o más centros quirales, pero que no indican estereoquímica (*por ejemplo*, con líneas punteadas o resaltadas), abarcan estereoisómeros puros y sus mezclas (*por ejemplo*, mezclas racémicas). Análogamente, nombres de compuestos que tienen uno o más centros quirales que no especifican la estereoquímica de esos centros abarcan estereoisómeros puros y sus mezclas.

5.2. Compuestos de la invención

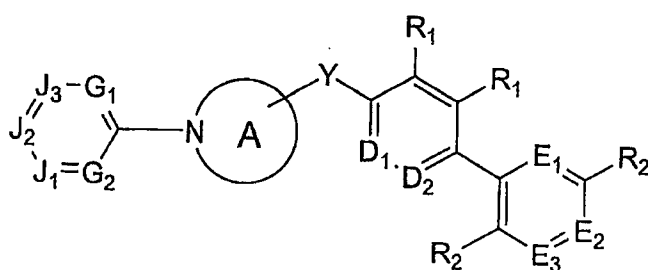
Esta invención abarca compuestos de fórmula I:



(I)

y sus sales y solvatos farmacéuticamente aceptables, en donde: A es un heterociclo no aromático, opcionalmente sustituido; cada uno de D_1 y D_2 es independientemente N o CR_1 ; cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ; X es heteroarilo opcionalmente sustituido; Y es O, C(O), CH(OH), o CH_2 ; cada R_1 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , C(O) R_A , C(O) OR_A , C(O) $N(R_A R_B)$, $N(R_A R_B)$, o $SO_2 R_A$; cada R_2 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , C(O) R_A , C(O) OR_A , C(O) $N(R_A R_B)$, $N(R_A R_B)$, o $SO_2 R_A$; cada R_A es independientemente hidrógeno o alquilo opcionalmente sustituido, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo; y cada R_B es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos.

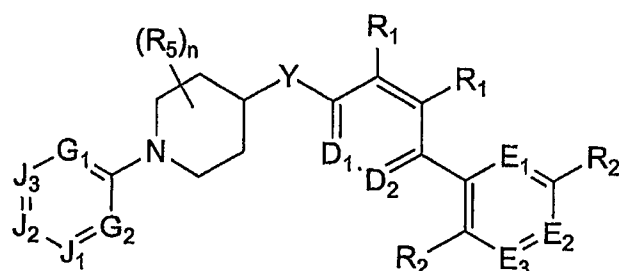
Una incorporación de la invención abarca compuestos de fórmula IA:



(IA)

y sus sales y solvatos farmacéuticamente aceptables.

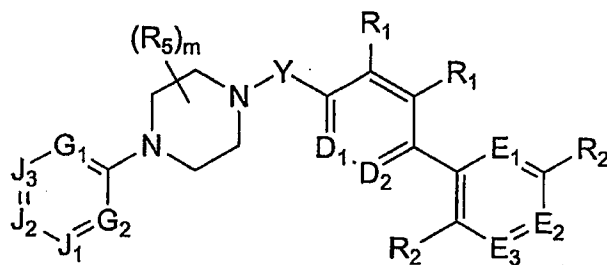
Otra incorporación abarca compuestos de fórmula IB:



(IB)

y sus sales y solvatos farmacéuticamente aceptables, en donde: cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y n es 0-5.

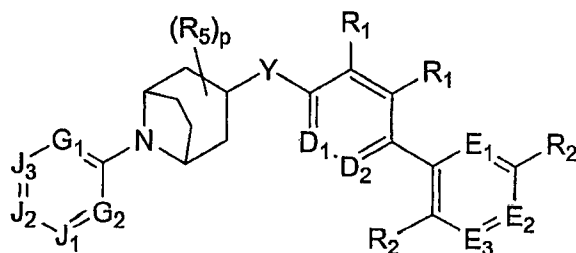
Otra incorporación abarca compuestos de fórmula IC:



(IC)

y sus sales y solvatos farmacéuticamente aceptables, en donde: Y es O, $C(O)$ o CH_2 ; cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y m es 0-4.

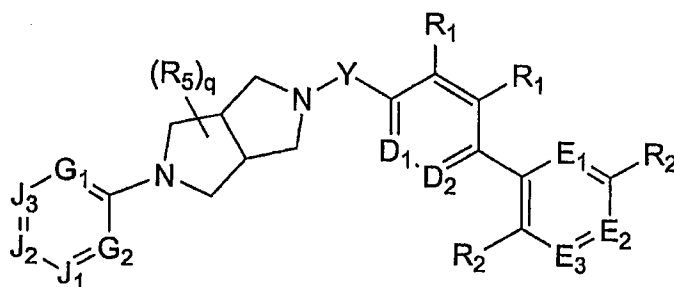
Otra incorporación abarca compuestos de fórmula ID:



(ID)

y sus sales y solvatos farmacéuticamente aceptables, en donde: cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y p es 0-7.

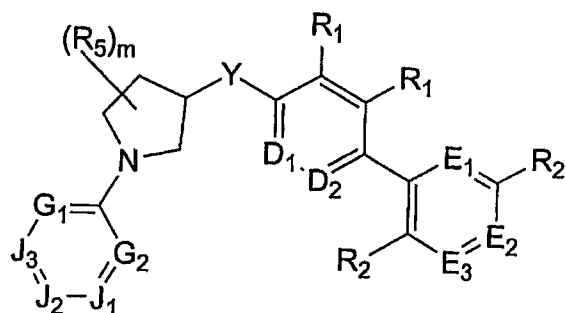
Otra incorporación abarca compuestos de fórmula **IE**:



(IE)

y sus sales y solvatos farmacéuticamente aceptables, en donde: Y es O, $C(O)$ o CH_2 ; cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y q es 0-6.

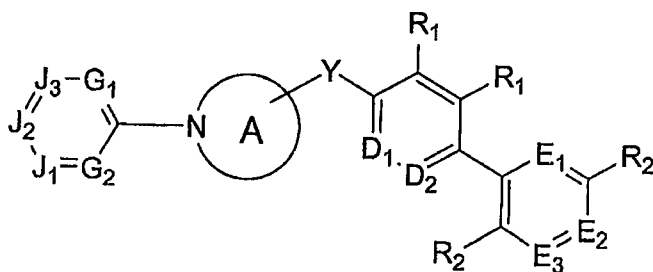
Otra incorporación abarca compuestos de fórmula **IF**:



(IF)

y sus sales y solvatos farmacéuticamente aceptables, en donde: cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y m es 0-4.

Otra incorporación abarca compuestos de fórmula II:



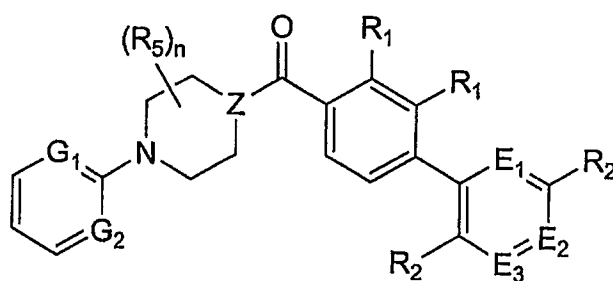
(II)

y sus sales y solvatos farmacéuticamente aceptables, en donde: A es un heterociclo no aromático, opcionalmente sustituido; cada uno de D_1 y D_2 es independientemente N o CR_1 ; cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ; cada uno de G_1 y G_2 son independientemente N o CR_3 ; cada uno de J_1 , J_2 y J_3 son independientemente N o CR_4 ; Y es O, $C(O)$, $CH(OH)$, o CH_2 ; cada R_1 es independientemente hidrógeno, halógeno, o (C_{1-10}) alquilo; cada R_2 es independientemente halógeno, ciano, R_{2A} , OR_{2A} , o SO_2R_{2A} ; cada R_{2A} es independientemente hidrógeno o (C_{1-10}) alquilo sustituido opcionalmente con uno o más halógenos; cada R_3 es independientemente hidrógeno, ciano, o (C_{1-10}) alquilo sustituido

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opcionalmente con uno o más halógenos; y cada R_4 es independientemente hidrógeno, ciano, o (C_{1-10}) alquilo sustituido opcionalmente con uno o más halógenos.

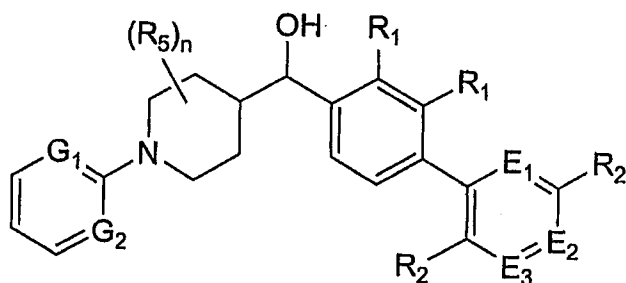
Otra incorporación abarca compuestos de fórmula **IIA**:



(IIA)

y sus sales y solvatos farmacéuticamente aceptables, en donde: Z es CR_5 o N; cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y n es 0-5 si Z es CR_5 , o 0-4 si Z es N.

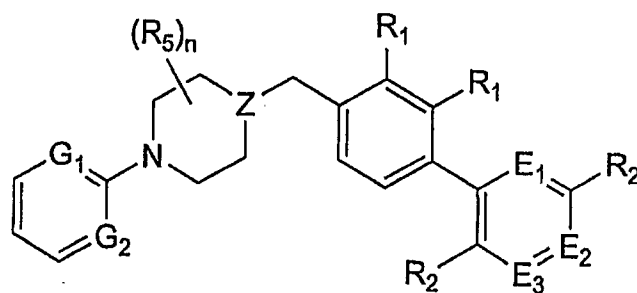
Otra incorporación abarca compuestos de fórmula **IIB**:



(IIB)

y sus sales y solvatos farmacéuticamente aceptables.

Otra incorporación abarca compuestos de fórmula **IIC**:



(IIC)

y sus sales y solvatos farmacéuticamente aceptables, en donde: Z es CR₅ o N; cada R₅ es independientemente halógeno, ciano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), o SO₂R_{5A}; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y n es 0-5 si Z es CR₅, o 0-4 si Z es N.

En una incorporación de la invención abarcada por fórmula II (y IIA-C, según lo apropiado), por lo menos uno de G₁, G₂, J₁, J₂ ó J₃ es N. En otra, por lo menos uno de J₁, J₂ y J₃ es CR₄. En otra, si Y es C(O), A es piperazina, todos los G₁, G₂, J₁, J₃, D₁, D₂, E₁, y E₃ son CH, y todos los R₁ son hidrógeno, entonces ninguno de R₂ son alquilo inferior. En otra, si Y es C(O), A es piperazina, D₂ y E₁ son ambos N, y todos los R₁ y R₂ son hidrógeno, entonces R₄ no es ciano. En otra, si Y es O, A es pirrolidina, todos los G₁, G₂, J₁, J₃, D₁, D₂, E₁, E₂, y E₃ son CH, y todos los R₁ son hidrógeno, entonces por lo menos un R₂ no es hidrógeno. En otra, si Y es CH₂, A es piperazina, todos los G₂, J₁, J₂, J₃, D₁, y D₂ son CH, todos los E₁, E₂ y E₃ son CR₂, y todos los R₁ son hidrógeno, por lo menos un R₂ no es hidrógeno. En otra, si Y es C(O) o CH₂, A es piperazina, por lo menos uno de G₁ y G₂ es N, todos los J₁, J₂, J₃, D₁, D₂, E₁, E₂ y E₃ son CH, y todos los R₁ son hidrógeno, entonces por lo menos un R₂ no es hidrógeno.

Varias otras incorporaciones de la invención, que pertenecen a cada una de las fórmulas anteriores (*por ejemplo*, I, IA-F, II y IIA-C), según lo

apropiado (cuando la fórmula particular contiene la fracción aludida), son como sigue.

En una, A es un heterociclo no aromático, opcionalmente sustituido, que contiene no más de dos átomos de nitrógeno (*es decir*, el heterociclo, que contiene no más de dos átomos de nitrógeno, es opcionalmente sustituido).

En otra, A es monocíclico. En otra, A es bicíclico. En otra, A es no sustituido. En otra, A es pirrolidina, piperidina, piperazina, hexahidropirimidina, 1,2,3,6-tetrahidropiridina, octahidrociclopenta[c]pirrol, u octahidropirrol[3,4-c]pirrol opcionalmente sustituidos.

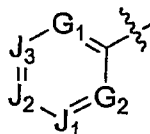
En otra, uno de D₁ y D₂ es N. En otra, ambos D₁ y D₂ son N. En otra, ambos D₁ y D₂ son CR₁.

En otra, uno de E₁, E₂ y E₃ es N. En otra, dos de E₁, E₂ y E₃ son N. En otra, todos los E₁, E₂ y E₃ son N. En otra, todos los E₁, E₂ y E₃ son independientemente CR₂.

En otra, R₁ es hidrógeno, halógeno, o alquilo opcionalmente sustituido. En otra, R₁ es OR_A y, por ejemplo, R_A es hidrógeno o alquilo opcionalmente sustituido.

En otra, R₂ es hidrógeno, halógeno, o alquilo opcionalmente sustituido. En otra, R₂ es OR_A y, por ejemplo, R_A es hidrógeno o alquilo opcionalmente sustituido.

En otra, X es un heteroarilo de 5, 6, 9 ó 10 miembros, opcionalmente sustituido. En otra, X es un heteroarilo de 5 ó 6 miembros opcionalmente sustituido. En otra, X es de la fórmula:



en donde: cada uno de G₁ y G₂ son independientemente N o CR₃; cada uno de J₁, J₂ y J₃ son independientemente N o CR₄; cada R₃ es independientemente hidrógeno, halógeno, ciano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), o SO₂R_A; y cada R₄ es independientemente hidrógeno, halógeno, ciano, R_A, OR_A, C(O)R_A,

$C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ; siempre que por lo menos uno de J_1 , J_2 y J_3 sea CR_4 .

En otra, uno de G_1 y G_2 es N. En otra, ambos G_1 y G_2 son N. En otra, ambos G_1 y G_2 son CR_3 .

En otra, uno de J_1 , J_2 y J_3 es N. En otra, dos de J_1 , J_2 y J_3 son N. En otra, todos los J_1 , J_2 y J_3 son independientemente CR_4 .

En otra, R_3 es hidrógeno, halógeno, o alquilo opcionalmente sustituido. En otra, R_3 es OR_A y, por ejemplo, R_A es hidrógeno o alquilo opcionalmente sustituido.

En otra, R_4 es hidrógeno, halógeno, o alquilo opcionalmente sustituido. En otra, R_4 es OR_A y, por ejemplo, R_A es hidrógeno o alquilo opcionalmente sustituido.

En otra, Y es C(O). En otra, Y es CH(OH). En otra, Y es CH_2 .

Ejemplos de compuestos específicos incluyen:

(1-(pirimidin-2-il)piperidin-4-il)(4'-(trifluorometil)bifenil-4-il)metanol;
(4'-clorobifenil-4-il)(2,6-dimetil-4-(piridin-2-il)piperazin-1-il)metanona;
(3'-cloro-3-metoxibifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(3-fluoro-4'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4'-clorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(2'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(benzo[d]oxazol-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
bifenil-4-il(4-(4-(trifluorometil)pirimidin-2-il)piperazin-1-il)metanona;
(S)-(2-bencil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(6-p-tolilpiridin-3-il)metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(6-(3-(trifluorometil)fenil)piridin-3-il)metanona;
(6-(4-clorofenil)piridin-3-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)metanona;

(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(6-(4-(trifluorometil)fenil)piridin-3-il)metanona;
(5-(4-clorofenil)isoxazol-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(1-(piridin-2-il)piperidin-4-il)metanona;
bifenil-4-il(4-(pirimidin-2-il)-1,4-diazepan-1-il)metanona;
(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)(4'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il(1-(pirimidin-2-il)azetidín-3-il)metanona;
(6-(4-cloro-3-(trifluorometil)fenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(4-cloro-3-metilfenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4'-clorobifenil-4-il)(1-(piridin-2-il)piperidin-4-il)metanona;
(2-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3,4'-dimetilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(5-(3-clorofenil)piridin-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(5-p-tolilpiridin-2-il)metanona;
(4-(piridin-2-il)piperazin-1-il)(3'-(trifluorometil)bifenil-4-il)metanona;
(1-(pirimidin-2-il)piperidin-4-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(3-fluoro-3'-(trifluorometil)bifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(3'-(trifluorometoxi)bifenil-4-il)metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(3'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)metanona;
(1-fenil-5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(4'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il(4-(tiazol-2-il)piperazin-1-il)metanona;
(4-(4-clorofenil)ciclohexil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
4'-(4-(pirimidin-2-il)piperazin-1-carbonil)bifenil-3-carbonitrilo;
(4'-(metilsulfonil)bifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;

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2-(4-((3'-clorobifenil-4-il)(hidroxi)metil)piperidin-1-il)pirimidin-5-ol;
(4-(piridin-3-il)fenil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-cloro-3-hidroxibifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
1-(4'-(4-(pirimidin-2-il)piperazin-1-carbonil)bifenil-3-il)etanona;
(2',4'-difluoro-3-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;
(5-fenil-1H-pirrol-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(4-clorofenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(5'-cloro-2'-fluorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)metanona;
2-(4-(bifenilcarbonil)piperazin-1-il)nicotinonitrilo;
2-(4-(bifenil-4-iloxi)piperidin-1-il)pirimidina;
(2'-fluoro-5'-(trifluorometil)bifenil-4-il)(1-(pirimidin-2-il)pirrolidin-3-il)
metanona;
(4-(4-metiltiofen-2-il)fenil)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(4'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(2-fluoro-4'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(3-metil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(2'-fluoro-5'-(trifluorometil)bifenil-4-il)(4-metil-1-(pirimidin-2-il) piperidin-4-il)metanona;
bifenil-4-il(4-(5-metilpiridin-2-il)piperazin-1-il)metanona;
bifenil-4-il(2-metil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(1-(piridin-2-il)piperidin-4-il)(3'-(trifluorometil)bifenil-4-il)metanona;
(6-(3-clorofenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(6-(3-(trifluorometil)fenil)piridin-3-il)
metanona;
(4-(pirimidin-2-il)piperazin-1-il)(6-p-tolilpiridin-3-il)metanona;
(4'-cloro-3'-(trifluorometil)bifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)
metanona;
(4-(2-cloropiridin-4-il)fenil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(2',4'-difluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(2,4-difluorofenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;

(3',5'-diclorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
2-(4-(bifenil-4-ilmetil)piperazin-1-il)pirimidina;
(4'-clorobifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(6-(3-clorofenil)piridin-3-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-
2(1H)-il)metanona;
(1-(piridin-2-il)piperidin-4-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(2'-fluoro-5'-(trifluorometil)bifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;
(4'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(5-metilpiridin-2-il)piperazin-1-il)metanona;
1-(bifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-ona;
bifenil-4-il(1-(pirimidin-2-il)-1,2,3,6-tetrahidropiridin-4-il)metanona;
(3'-clorobifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
bifenil-4-il(1-(pirimidin-2-il)-1,2,3,6-tetrahidropiridin-4-il)metanol;
(3'-clorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(3'-(trifluorometil)bifenil-4-il)metanona;
(3'-clorobifenil-4-il)(1-(5-hidroxi pirimidin-2-il)piperidin-4-il)metanona;
(4'-etilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(4-metilpirimidin-2-il)piperazin-1-il)metanona;
(6-(2,4-difluorofenil)piridin-3-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]
pirrol-2(1H)-il)metanona;
(4'-clorobifenil-4-il)(4-(piridin-2-il)piperazin-1-il)metanona;
(5-metil-1-(pirimidin-2-il)-1,2,3,6-tetrahidropiridin-4-il)(4'-(trifluorometil)
bifenil-4-il)metanona;
bifenil-4-il(4-(5-etilpirimidin-2-il)piperazin-1-il)metanona;
(4-(piridin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(4-(piridin-2-il)fenil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(pirazin-2-il)piperazin-1-il)metanona;
(4'-metoxibifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(6-metilpiridazin-3-il)piperazin-1-il)metanona;
4'-(4-(pirimidin-2-il)piperazin-1-carbonil)bifenil-4-carbonitrilo;

(2,6-dimetil-4-(piridin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(5-feniltiofen-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(5-metiltiofen-2-il)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(piridin-4-il)piperazin-1-il)metanona;
(R)-(2-metil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il((2S,5S)-2,5-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(4-(piridin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(2'-(trifluorometil)bifenil-4-il)metanona;
(S)-(4'-clorobifenil-4-il)(2-metil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(5'-cloro-2'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(5-metiltiofen-2-il)fenil)(1-(pirimidin-2-il)piperidin-4-il)metanona;
bifenil-4-il(4-(4,6-dimetilpirimidin-2-il)piperazin-1-il)metanona;
(S)-(2-metil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(S)-(2-bencil-4-(pirimidin-2-il)piperazin-1-il)(4'-clorobifenil-4-il)metanona;
bifenil-4-il(4-(piridazin-3-il)piperazin-1-il)metanona;
(6-(4-metiltiofen-2-il)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
1-(2',4'-difluorobifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-carbonitrilo;
(4'-clorobifenil-4-il)((2S,5S)-2,5-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(2-*terc*-butil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(S)-bifenil-4-il(2-isopropil-4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(2,6-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-cloro-2'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(6-(4-(trifluorometil)fenil)piridin-3-il)metanona;
(4'-cloro-3'-metilbifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(3'-cloro-2'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;

(2,6-dimetil-4-(piridin-2-il)piperazin-1-il)(4'-metilbifenil-4-il)metanona;
3'-cloro-4-(1-(pirimidin-2-il)piperidine-4-carbonil)bifenil-3-il acetato;
bifenil-4-il(2-metil-4-(piridin-2-il)piperazin-1-il)metanona;
1-(bifenil-4-ilmetil)-4-(pirimidin-2-il)piperazin-2-ona;
(3',4'-diclorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)
metanol;
(S)-bifenil-4-il(2-isobutil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)
metanona;
(S)-(4'-clorobifenil-4-il)(2-isopropil-4-(pirimidin-2-il)piperazin-1-il)
metanona;
(4'-metilbifenil-4-il)(4-(piridin-2-il)piperazin-1-il)metanona;
(S)-(2-isopropil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-
il)metanona;
(3'-clorobifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanol;
(S)-(2-isobutil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-
il)metanona;
(S)-(4'-clorobifenil-4-il)(2-isobutil-4-(pirimidin-2-il)piperazin-1-il)
metanona;
(3'-clorobifenil-4-il)(1-(pirimidin-2-il)pirrolidin-3-il)metanona;
(2',4'-difluorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)
metanona;
4'-(4-(piridin-2-il)piperazin-1-carbonil)bifenil-4-carbonitrilo;
(4-(pirimidin-2-il)-1,4-diazepan-1-il)(3'-(trifluorometil)bifenil-4-il)
metanona;
metil 1-(5'-cloro-2'-fluorobifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-
carboxilato;
(4-(benzo[d]oxazol-2-il)piperazin-1-il)(4'-clorobifenil-4-il)metanona;
(3'-clorobifenil-4-il)(4-(tiazol-2-il)piperazin-1-il)metanona;
(4-(5-clorotiofen-2-il)fenil)(1-(pirimidin-2-il)piperidin-4-il)metanona;

1-(5'-cloro-2'-fluorobifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-carbonitrilo;
(4-feniltiofen-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(pirimidin-2-il)-3,4-dihidroquinoxalin-1(2H)-il)metanona;
(5'-cloro-2'-fluorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)metanol;
(5-fenilfuran-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4'-clorobifenil-4-il)(5-(pirimidin-2-il)hexahidropirrol[3,4-c]pirrol-2(1H)-il)metanona;
4-(4'-clorobifenil-4-il)-1-(pirimidin-2-il)piperidin-4-ol;
(5-(pirimidin-2-il)hexahidropirrol[3,4-c]pirrol-2(1H)-il)(4'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il(5-(piridin-2-il)hexahidropirrol[3,4-c]pirrol-2(1H)-il)metanona;
(3'-clorobifenil-4-il)(5-pirimidin-2-il)hexahidropirrol[3,4-c]pirrol-2(1H)-il)metanona;
bifenil-4-il((2S,5S)-2,5-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;
1-((3'-clorobifenil-4-il)metil)-N,N-dimetil-4-(pirimidin-2-il)piperazin-2-carboxamida;
(2',4'-difluorobifenil-4-il)(3-metil-1-(pirimidin-2-il)piperidin-4-il)metanona;
(4-(benzo[d]tiazol-2-il)piperazin-1-il)(bifenil-4-il)metanona;
bifenil-4-il(4-(quinolin-2-il)piperazin-1-il)metanona;
4-(bifenil-4-il)-1-(pirimidin-2-il)piperidin-4-ol;
4'-cloro-N-metil-N-(2-(metil(pirimidin-2-il)amino)etil)bifenil-4-carboxamida; y
2-(bifenil-4-il)-1-(4-(pirimidin-2-il)piperazin-1-il)etanona.

Compuestos preferidos de la invención son inhibidores específicos del transportador de prolina. Inhibidores específicos particulares de transportador de prolina tienen una $PTIC_{50}$ de menos de alrededor de 150, 125, 100, 75, 50 ó 25 nM.

Algunos compuestos inhiben el transportador murino de prolina Na^{+} -dependiente, como se determina por el método descrito en los Ejemplos,

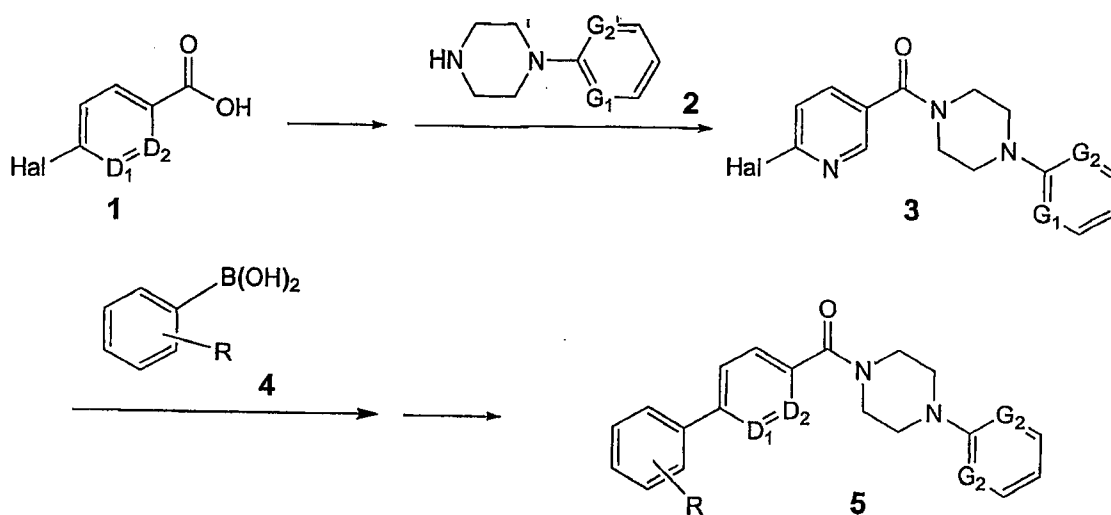
más adelante, con una IC_{50} de menos de alrededor de 150, 125, 100, 75, 50 ó 25 nM.

Algunos compuestos no inhiben significativamente el transportador de dopamina. Por ejemplo, algunos inhibidores específicos del transportador de prolina inhiben el transportador de dopamina con una IC_{50} superior a alrededor de 0.5, 1, 2.5, 5, ó 10 μ M como se determina utilizando el análisis descrito en los Ejemplos, más adelante.

Algunos compuestos no inhiben significativamente el transportador de glicina. Por ejemplo, algunos inhibidores específicos del transportador de prolina inhiben el transportador de glicina con una IC_{50} superior a alrededor de 0.5, 1, 2.5, 5, ó 10 μ M como se determina utilizando el análisis descrito en los Ejemplos, más adelante.

5.3. Preparación de Compuestos

Compuestos de la invención pueden obtenerse o prepararse utilizando métodos sintéticos conocidos en el arte, así como los descritos en esta solicitud. Por ejemplo, varios compuestos a base de piperazina pueden prepararse de acuerdo con el método general mostrado en Esquema I:

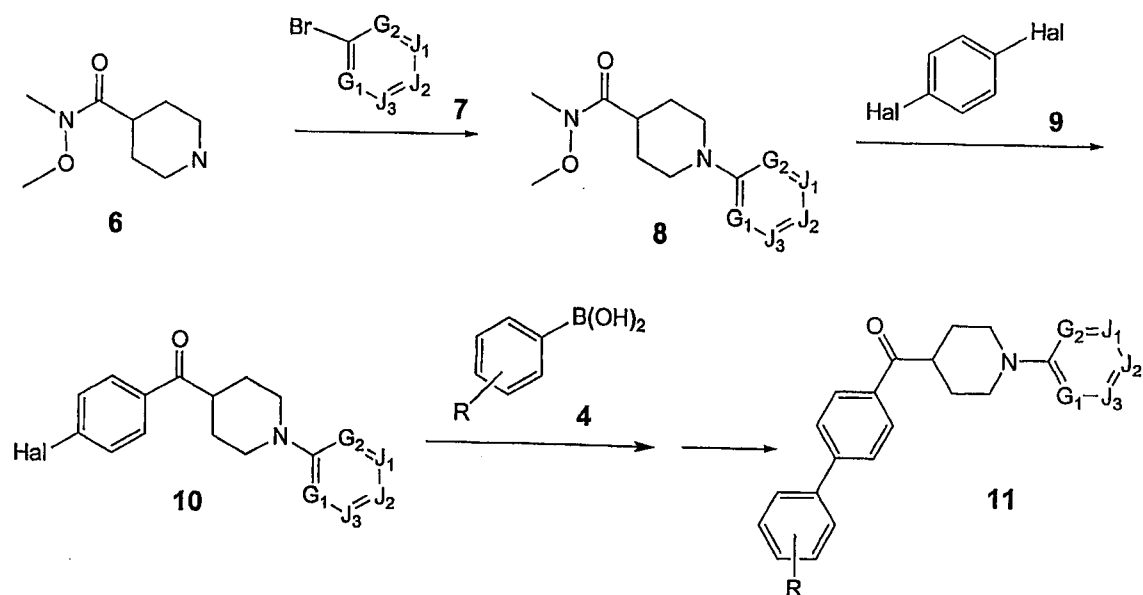


Esquema I

En este método, un compuesto de la fórmula 1 (D₁ y D₂ se definen en esta solicitud) se pone en contacto con un compuesto de la fórmula 2 (G₁ y G₂ se definen en esta solicitud) bajo condiciones apropiadas para proporcionar un compuesto de la fórmula 3. Condiciones apropiadas incluyen, por ejemplo,

EDCl, HOBt, y base de Hunig en DMF. El compuesto 3 se pone entonces en contacto con compuesto 4 bajo condiciones apropiadas para proporcionar un compuesto de la fórmula 5. Condiciones apropiadas incluyen, por ejemplo, $\text{Pd}(\text{Ph}_3\text{P})_4$, K_3PO_4 , DME, agua y calor.

Varios compuestos a base de piperidina pueden prepararse de acuerdo con el método general mostrado a continuación en Esquema II:

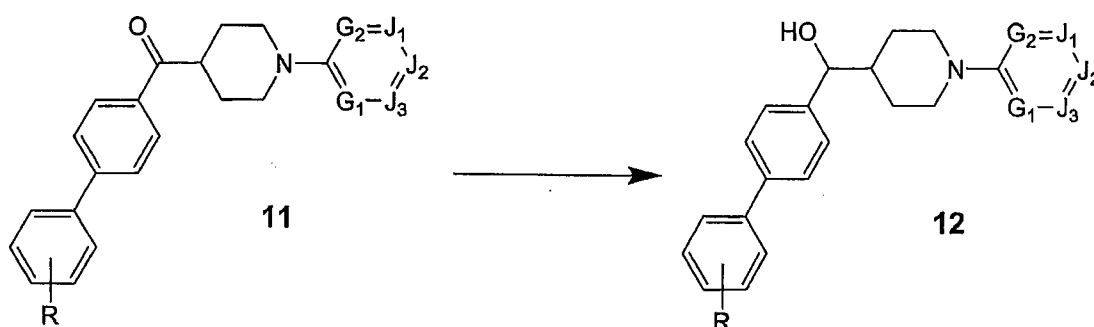


Esquema II

En este método, un compuesto de la fórmula 6 (*por ejemplo*, como una sal TFA) se pone en contacto con un compuesto de la fórmula 7 (G_1 , G_2 , J_1 , J_2 y J_3 se definen en esta solicitud) bajo condiciones apropiadas para proporcionar un compuesto 8. Condiciones apropiadas incluyen, por ejemplo, TEA y calor. El compuesto 8 se pone entonces en contacto con un compuesto 9 bajo condiciones apropiadas para proporcionar un compuesto 10. En esta solicitud, condiciones apropiadas incluyen, por ejemplo, $n\text{-BuLi}$ en THF. El compuesto 10 se pone entonces en contacto con un compuesto de la fórmula 4 para proporcionar el compuesto final, 11. En esta solicitud, condiciones apropiadas incluyen, por ejemplo, $\text{Pd}(\text{Ph}_3\text{P})_4$, K_3PO_4 , DME, agua y calor.

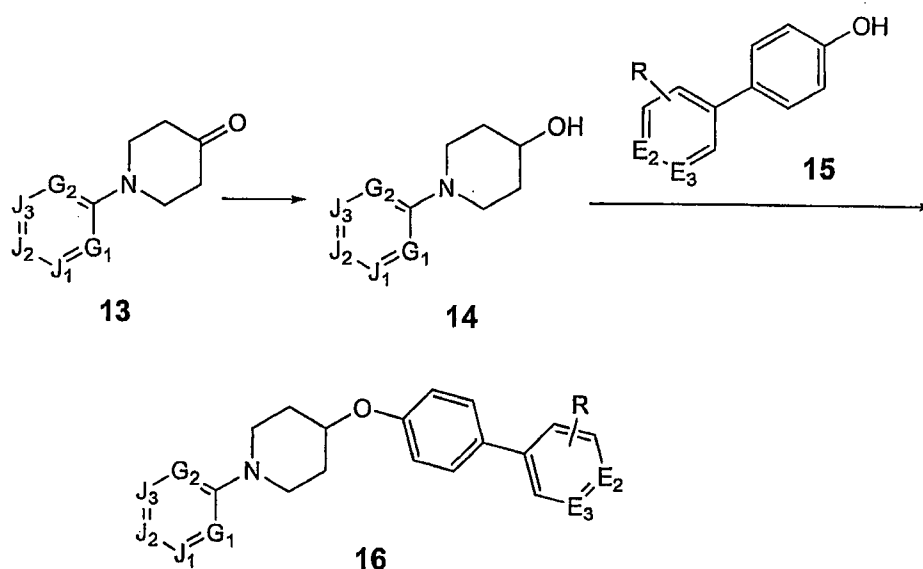
Si se desea, los compuestos de fórmula 11 pueden reducirse bajo condiciones apropiadas (*por ejemplo*, borohidruro de sodio) para

proporcionar compuestos de fórmula 12, como se muestra más adelante en el Esquema III:



Esquema III

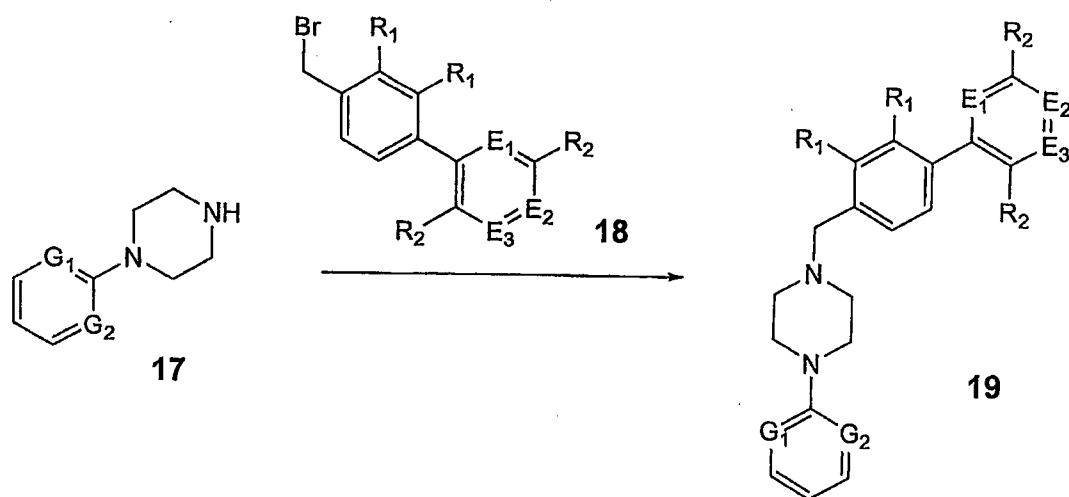
Los compuestos que contienen un enlace éter pueden prepararse por rutas tales como las ilustradas en el Esquema IV:



Esquema IV

En este método, un compuesto de la fórmula 13 se reduce (*por ejemplo*, con borohidruro de sodio) para proporcionar el compuesto 14, que se acopla entonces bajo condiciones apropiadas de reacción con un compuesto de la fórmula 15 para proporcionar el compuesto 16. Condiciones apropiadas de reacción incluyen, *por ejemplo*, PPh₃ y DEAD en THF.

Los compuestos que contienen un enlace metileno pueden prepararse por rutas tales como las ilustradas en el Esquema V:



Esquema V

En este método, un compuesto de la fórmula 17 se pone en contacto con el compuesto 18 bajo condiciones apropiadas de reacción para proporcionar el compuesto 19. Condiciones apropiadas de reacción incluyen, por ejemplo, carbonato de potasio en DMF.

Algunas condiciones específicas de reacción que pueden emplearse en los distintos esquemas sintéticos ilustrados anteriormente se proveen en los Ejemplos, más adelante.

5.4. Métodos de Tratamiento

Una incorporación de esta invención comprende un método de inhibir un transportador de prolina, método que incluye poner en contacto un transportador de prolina (*in vitro* o *in vivo*) con una cantidad suficiente de un compuesto de la invención. Transportadores preferidos de prolina son codificados por el gen humano SLC6A7, su ortólogo murino, o un ácido nucleico que codifica un transportador de prolina y que se hibrida bajo condiciones estándar a la longitud continua de cualquiera de los dos.

Otra incorporación comprende un método de mejorar el desempeño cognitivo de un paciente humano, método que comprende administrar al paciente una cantidad efectiva de un compuesto de la invención. Ejemplos de desempeño cognitivo mejorado incluyen aprendizaje incrementado (*por ejemplo*, aprender más rápidamente), mejor comprensión, razonamiento mejorado, y mejor memoria a corto y/o largo plazo.

Otra incorporación comprende un método de tratar, controlar o prevenir una enfermedad o trastorno en un paciente humano, método que incluye administrar a un paciente una cantidad terapéutica o profilácticamente efectiva de un compuesto de la invención. Ejemplos de enfermedades y trastornos incluyen enfermedad de Alzheimer, autismo, trastornos cognitivos (*por ejemplo*, dificultades en pensar, razonamiento, o resolución de problemas), demencia, trastornos de aprendizaje (*por ejemplo*, dislexia, acalculia, disgrafía, disfasia, disnomia), y pérdida de la memoria de corto y largo plazo. Trastornos adicionales incluyen secuelas adversas de lesión cerebral causada por, *por ejemplo*, supresión de oxígeno, lesión traumática o apoplejía.

5.5. Composiciones Farmacéuticas

Esta invención comprende composiciones farmacéuticas y formas farmacéuticas que comprenden compuestos de la invención como sus ingredientes activos. Composiciones y formas farmacéuticas de esta invención pueden contener opcionalmente uno o más sustancias portadoras o excipientes farmacéuticamente aceptables. Ciertas composiciones farmacéuticas son formas farmacéuticas unitarias apropiadas para administración oral, tópica, mucosal (*por ejemplo*, nasal, pulmonar, sublingual, vaginal, bucal, o rectal), parenteral (*por ejemplo*, subcutánea, intravenosa, inyección intravenosa rápida, intramuscular, o intraarterial), o transdérmica a un paciente. Ejemplos de formas farmacéuticas incluyen, pero no se limitan a: tabletas; comprimidos oblongos; cápsulas, tales como cápsulas de gelatina blandas elásticas; sellos/cápsulas amiláceas; trociscos; pastillas o tabletas para chupar; dispersiones; supositorios; ungüentos; cataplasmas (emplastos); pastas; polvos; apósitos; cremas; fomentos; soluciones; parches; aerosoles (*por ejemplo*, atomizadores nasales o inhaladores); geles; formas farmacéuticas líquidas apropiadas para administración oral o mucosal a un paciente, incluidas suspensiones (*por ejemplo*, suspensiones líquidas acuosas y no acuosas, emulsiones de aceite en agua, o emulsiones líquidas de agua en aceite), soluciones, y elixires;

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formas farmacéuticas líquidas apropiadas para administración parenteral a un paciente; y sólidos esterilizados (*por ejemplo*, sólidos cristalinos o amorfos) que pueden reconstituirse para proporcionar formas farmacéuticas líquidas apropiadas para administración parenteral a un paciente.

La formulación debe adaptarse al modo de administración. Por ejemplo, la administración oral puede requerir cubiertas gastrorresistentes para proteger el ingrediente activo de la degradación en el tubo digestivo. En otro ejemplo, el ingrediente activo puede administrarse en una formulación liposómica para blindarla contra enzimas degradadoras, facilitar el transporte en el sistema circulatorio, y/o efectuar la aplicación a través de las membranas celulares a sitios intracelulares.

La composición, forma, y tipo de las formas farmacéuticas de la invención variarán típicamente dependiendo de su uso. Por ejemplo, una forma farmacéutica empleada en el tratamiento inmediato ("*the acute treatment*") de una enfermedad puede contener cantidades mayores de uno o más de los ingredientes activos, contenidos en ella, que una forma farmacéutica utilizada en el tratamiento crónico de la misma enfermedad. Análogamente, una forma farmacéutica parenteral puede contener cantidades menores de uno o más de los ingredientes activos, contenidos en ella, que una forma farmacéutica oral utilizada para tratar la misma enfermedad. Éstas y otras modalidades, en las cuales variarán entre sí las formas farmacéuticas específicas abarcadas por esta invención, serán fácilmente evidentes a los expertos en el arte. Véase, *por ejemplo*, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

6. EJEMPLOS

6.1. Ratones Deficientes en SLC6A7

Para determinar el efecto de inhibir el transportador de prolina Na^+ -dependiente, se generaron usando ratones homocigóticos para una mutación genéticamente modificada en el ortólogo murino del gen SLC6A7 humano (ratones "knockout" o "KO") usando clones de células ES

correspondientemente mutadas de la colección OMNIBANK de clones de células ES murinas mutadas (*véase generalmente* Patente de los Estados Unidos No. 6,080,576).

Se produjeron ratones que eran heterocigóticos, homocigóticos, o silvestres para el alelo mutado, apareando animales heterocigóticos capaces de transmisión de línea germinal del alelo mutante. El alelo mutante se clasificó de acuerdo con la genética mendeliana estándar. Los ratones se sometieron a una batería de pruebas médicas y conductuales, incluidas las descritas a continuación.

6.1.1. Condicionamiento de Huella

El condicionamiento aversivo de huella mide una forma de condicionamiento clásico con una separación temporal entre el final de un estímulo condicionado (CS) (en este caso un tono de 80 db) y la iniciación de un estímulo incondicionado (US) (en este caso una corriente eléctrica de 0.7 mA) que se separan por una "huella" temporal (aproximadamente 30 segundos). Este estudio mide el aprendizaje de orden más elevado (usualmente asociado con la función del hipocampo o la corteza cerebral) determinando con qué rapidez los sujetos de prueba aprenden a asociar el US con el CS. Los animales de prueba se califican calculando el tiempo de inmovilidad porcentual determinado comparando la diferencia entre el pos-CS de inmovilidad porcentual y el pre-CS de inmovilidad porcentual.

Como se muestra en la Figura 1, los animales machos y hembras que eran homocigóticos para la mutación en el ortólogo murino del gen SLC6A7 exhibieron porcentajes de inmovilidad significativamente mayores (aproximadamente 50 por ciento para un promedio de 16 animales de prueba), comparados con sus contrapartes de control silvestres (aproximadamente 30 por ciento para un promedio de 16 animales de control). Estos resultados indican que los animales mutantes homocigóticos se desempeñan significativamente mejor en esta prueba bien establecida de desempeño cognitivo.

6.1.2. Laberinto de Agua

El laberinto de agua Morris utilizó un estanque circular de 2 metros de diámetro y 40 cm de profundidad. Véase, por ejemplo, Morris, 1984, *J. Neurosci. Methods* 11:47-60, Guillou *et al.*, 1999, *J. Neurosci.* 19:6183-90. El estanque se llenó a una profundidad de 30 cm con agua a una temperatura de 24-26°C, opacada por la adición de una pintura no tóxica a base de agua. La plataforma de "escape" tenía alrededor de 30 cm de altura con un disco de plástico de 18 cm de diámetro en la parte superior. La plataforma se puso alrededor de 0.5 cm debajo de la superficie del agua. Se echó al ratón en el estanque frente a la pared desde una de las 4 posiciones de partida marcadas como N (norte), S (sur), W (occidente) o E (oriente). Un sistema de análisis de vídeo que comprendía la cámara y software de imagen WaterMaze (Actimetrics, Inc.) dividía el estanque en 4 cuadrantes iguales designados como SE, SW, NE, y NW. El software calcula el tiempo de latencia para alcanzar la plataforma, la distancia a la plataforma, el tiempo gastado en cada cuadrante, la velocidad de nado, y otras variables.

Cada experimento duraba hasta que el ratón se encaramaba a la plataforma o habían transcurrido 90 segundos. Si el ratón no alcanzaba la plataforma en 90 segundos, el experimentador lo sacaba del agua y suavemente lo ponía sobre la plataforma. Al final de cada ensayo el ratón permanecía en la plataforma durante 20 segundos más. Se realizaron 4 experimentos con plataforma por día con intervalos entre-experimentos de 8-12 minutos. Durante el intervalo entre-experimentos el ratón se mantuvo en una jaula limpia bajo una lámpara de calor.

Típicamente se utilizó uno de los dos protocolos básicos: el primero incluye fases visibles y ocultas de la plataforma, y el segundo sólo emplea una fase oculta de la plataforma; ambos protocolos finalizan con una fase inversa de 2 días.

La fase visible precede por lo general a la fase oculta de la plataforma. En la fase visible, el estanque estuvo rodeado con cortinas blancas con el fin de ocultar todas las pistas/referencias externas al laberinto. Durante esta fase, la plataforma se hizo visible con un cilindro

metálico 8 cm h x 3 cm, que se puso sobre la plataforma. La posición de partida fue la misma en cada experimento, mientras que la ubicación de la plataforma se cambió aleatoriamente durante los experimentos. Esta fase duró aproximadamente 3 días.

En la fase oculta de la plataforma, la plataforma ya no se marcaba y las cortinas se retiraron. Una variedad de pistas extra-laberinto se colocaron opcionalmente alrededor del estanque. En este caso la posición de partida cambió en cada ensayo, mientras que la plataforma permanecía en el mismo sitio. Por lo general, esta fase duraba alrededor de 7 días.

Se realizaron experimentos de prueba antes de los ensayos de adiestramiento el día 1 y 5 de la fase oculta, y el día 1 de la fase visible, y asimismo después del último experimento el día 3 de la fase visible. Durante el experimento de prueba, la plataforma se retiró del estanque, y el ratón se puso en el estanque de cara a la pared en el cuadrante opuesto al cuadrante de la plataforma. El ratón nadó durante 60 segundos y se registró el porcentaje de tiempo gastado en cada cuadrante.

En la fase inversa, se llevaron a cabo 5 experimentos en cada uno de 2 días. Durante el primer ensayo la ubicación de la plataforma era la misma que en la fase oculta. En los siguientes 4 experimentos, la plataforma se trasladó al cuadrante opuesto. El día siguiente la plataforma estaba en el sitio del primer experimento y luego se desplazó nuevamente al cuadrante izquierdo o derecho adyacente para los últimos 4 ensayos. La posición de partida se mantuvo siempre opuesta a la ubicación de la plataforma.

Cuando se emplearon los métodos anteriores con ratones KO SLC6A7 KO (n=12) y controles WT (n=7), los ratones se sometieron primero a la tarea de la plataforma visible. Se utilizaron mediciones repetidas (RM) y análisis de varianza (ANOVA) para analizar el efecto del genotipo sobre el tiempo de latencia en alcanzar la plataforma durante 11 experimentos.

El efecto del experimento fue $F(10, 170) = 8.57, p < 0.001$; el efecto del genotipo: $F(1, 17) = 0.65, p < 0.43$, interacción genotipo x experimento: $F(10, 170) = 0.42, p < 0.93$. Inicialmente, no hubo diferencia entre sujetos

WT y KO, pero sí se observó una disminución significativa en el tiempo de latencia durante los experimentos.

Cuando los experimentos avanzaron a la tarea de la plataforma oculta, RM ANOVA reveló un efecto significativo de los experimentos sobre el tiempo de latencia en alcanzar la plataforma: $F(19, 323) = 7.2, p < 0.001$. Hubo asimismo un efecto significativo del genotipo sobre el mismo parámetro: $F(1, 17) = 8.0, p < 0.012$; interacción genotipo x experimentos fue $F(19, 323) = 1.16, p < 0.29$. En general, los sujetos KO tuvieron tiempos de latencia significativamente más cortos en alcanzar la plataforma. No se detectó una diferencia significativa en la velocidad de nado, de modo que un nado más rápido no se tuvo en cuenta para el desempeño más rápido por los animales KO.

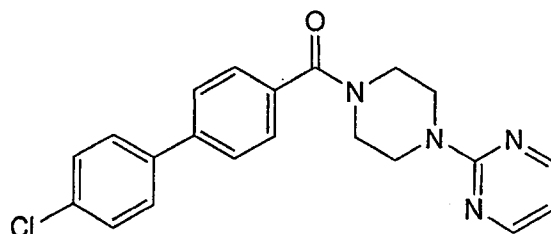
Durante la fase inversa, RM ANOVA se efectuó en 4 experimentos con la plataforma desplazada a otro cuadrante en cada uno de dos días. En los dos días de la fase inversa el efecto de los experimentos fue significativo: $F_s(3, 51) > 6.4, p < 0.001$ indicando que ambos genotipos vuelven a aprender bien. No obstante, no hubo una diferencia significativa entre ellos en cada día del cambio de papeles: $F_s(1, 17) < 0.75, ps > 0.39$, aunque los ratones KO no tendieron a alcanzar la plataforma más rápido.

Durante los experimentos de prueba, el porcentaje de tiempo gastado en cada cuadrante se comparó con el 25% de oportunidad para los ratones WT y KO mediante la prueba no paramétrica de Mann-Whitney. En los primeros dos experimentos de prueba realizados antes de la fase oculta el tiempo porcentual no fue diferente de la oportunidad en cada cuadrante para ambos genotipos. En el tercer ciclo de experimentos de prueba el día quinto de la fase oculta, el tiempo en el cuadrante de la plataforma fue significativamente diferente del cambio para los ratones WT [$p < 0.05$] y KO [$p < 0.001$]; y el tiempo en el cuadrante opuesto fue significativamente diferente para los ratones KO [$p < 0.001$].

Los datos anteriores indican que los ratones KO aprendieron la tarea de la plataforma oculta más rápidamente que los animales WT. Además, los datos establecen que la diferencia observada no puede explicarse por

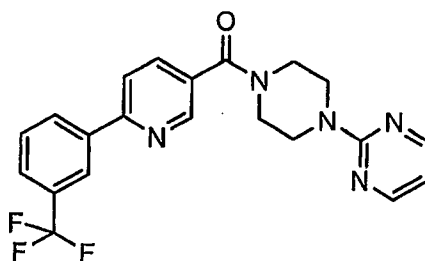
diferencias en las capacidades visuales o la velocidad de nado entre los genotipos.

6.2. Preparación de (4-Pirimidin-2-il-piperazin-1-il)-[4-(4-clorometilfenilfenil)]-metanona



A una solución de ácido 4'-cloro-bifenil-4-carboxílico (0.1 g, 0.43 mmol) y 1-(2-pirimidil)-piperazina (0.07 g, 0.43 mmol) en cloruro de metileno (3 ml), se agregó EDCI (0.098 g, 0.43 mmol) y HOAt (0.07 g, 0.43 mmol) trietilamina (0.07 ml, 0.52 mmol). La mezcla se agitó durante 16 horas y luego se lavó con salmuera. Las capas se separaron, y la fase orgánica se secó sobre sulfato de magnesio y se concentró. El aceite resultante se purificó mediante cromatografía instantánea, y se recogió un sólido blanco (0.11g). Los datos de espectro fueron consistentes con la estructura. MS (M+1) = 379. HPLC (> 95 %). ¹H NMR (CDCl₃) 8.35 (d, 2H), 7.55 (m, 8H), 6.58 (t, 1H), 3.80 (bm, 8H).

6.3. Preparación de (4-Pirimidin-2-il-piperazin-1-il)-[6-(3-trifluorometil-fenil)-piridin-3-il]-metanona



El compuesto del título se preparó de (6-cloro-piridin-3-il)-(4-pirimidin-2-il-piperazin-1-il)-metanona como se describe más adelante.

(6-Cloro-piridin-3-il)-(4-pirimidin-2-il-piperazin-1-il)-metanona: A una solución de ácido cloronicotínico (2.51 g, 15.9 mmol) en DMF (64 ml) se agregaron EDCI (4.57 g, 23.9 mmol) y HOBt (3.23 g, 23.9 mmol). Se

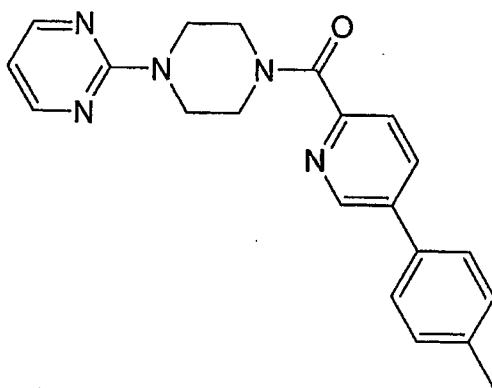
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agregó base de Hunig (19.3 ml, 111 mmol) y la reacción se dejó agitar durante 5 minutos. Luego de este período de inducción, se agregó piperazina (4.52 g, 19.1 mmol) y la reacción se agitó a temperatura de la sala. Luego de agitar durante 72 horas, la reacción se diluyó con acetato de etilo y agua. Las capas se separaron, y la porción acuosa se extrajo dos veces más con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua tres veces y una vez con salmuera, se secaron sobre MgSO_4 , se filtraron, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice usando 20-25% acetona/hexanos, lo cual proporcionó el producto (2.05 g, 42%) como un sólido marrón claro: ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, $J=1.8$ Hz, 1H), 8.34 (d, $J=4.7$ Hz, 2H), 7.77 (dd, $J=8.2, 2.4$ Hz, 1H), 7.43 (d, $J=8.1$ Hz, 1H), 6.57 (t, $J=4.8$ Hz, 1H), 3.89 (bs, 6H), 3.52 (bs, 2H); m/z calculado para $\text{C}_{14}\text{H}_{14}\text{ClN}_5\text{O}$: 303.08 hallado: $(\text{M}+\text{H})^+$ 304.1; tiempo de retención HPLC = 1,822 minutos (gradiente de solvente B - 0 a 100%; longitud de onda 254 nm), pureza = 100%.

(4-Pirimidin-2-il-piperazin-1-il)-[6-(3-trifluorometil-fenil)-piridin-3-il]-etanona: En un recipiente de reacción de microondas, (6-cloro-piridin-3-il)-(4-pirimidin-2-il-piperazin-1-il)-metanona (1.12 g, 3.69 mmol) se tomó en DME (15 ml). A esta solución, se agregaron ácido bórico (1.36 g, 7.38 mmol), fosfato de potasio (2.35 g, 11.1 mmol) y agua (5 ml). Esta mezcla se desgasificó entonces utilizando nitrógeno, y se agregó el tetrakis trifenilfosfina paladio (0.426 g, 0.369 mmol) y el recipiente se selló. La reacción se calentó en el microondas a 160°C durante 5 minutos. Una vez completa la reacción, se agregó una solución 1 N de NaOH, a la que siguió extracción dos veces con CH_2Cl_2 . Las porciones orgánicas combinadas se lavaron con salmuera, se secaron, se filtraron, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice usando 10-25% acetona en hexanos, lo cual proporcionó el producto final (1.29 g, 85%) como un sólido blanco: ^1H NMR (400 MHz, CDCl_3) δ 8.80 (d, $J=1.3$ Hz, 1H), 8.34 (d, $J=4.8$ Hz, 2H), 8.32 (s, 1H), 8.22 (d, $J=7.8$ Hz, 1H), 7.93 (dd, $J=8.1, 2.2$ Hz, 1H), 7.87 (d, $J=8.1$ Hz, 1H), 7.72 (d, $J=7.7$ Hz, 1H),

7.63 (t, $J=7.8$ Hz, 1H), 6.57 (t, $J=4.7$ Hz, 1H), 3.91 (bs, 6H), 3.60 (bs, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.81, 161.42, 157.80, 156.93, 148.18, 139.06, 136.46, 131.52, 131.20, 130.26, 130.17, 129.39, 126.20, 126.16, 126.13, 125.36, 123.99, 123.95, 123.92, 123.88, 122.65, 120.27, 110.69; m/z calculado para $\text{C}_{21}\text{H}_{18}\text{F}_3\text{N}_5\text{O}$: 413.15 hallado: $(\text{M}+\text{H})^+$ 414.05; tiempo de retención HPLC = 3,233 minutos (gradiente de disolvente B - 0 a 100%; longitud de onda 254 nm); pureza = 100%; mp = 124-126°C.

6.4. Preparación de (4-Pirimidin-2-il-piperazin-1-il)-(5-p-tolil-piridin-2-il)-metanona

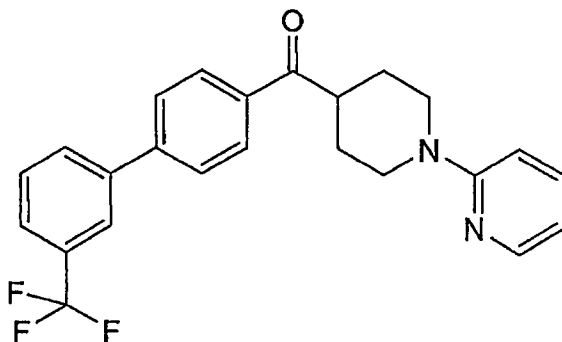


A una solución de 5-bromo-2-yodopiridina (100 mg, 0.35 mmol, Song *et al.*, *Org. Lett.*, 6: 4905-4907 (2004)) en THF (1 ml) se agregó cloruro de isopropil magnesio (2 M en THF, 0.185 ml) a 0°C. Luego de agitarse durante 45 minutos, se agregó una solución de metoxi-metilamida de ácido 1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-carboxílico (61 mg, 0.245 mmol). La mezcla se agitó a temperatura de la sala durante otras 1.5 horas y se extinguió con la adición de agua (15 ml) y EtOAc (50 ml). La fase acuosa se extrajo posteriormente con EtOAc (20 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (3% MeOH/ CH_2Cl_2) para producir (5-bromo-piridin-2-il)-(4-pirimidin-2-il-piperazin-1-il)-metanona (25 mg, 25% para dos pasos) como un sólido blanco: ^1H NMR (CDCl_3 , 400 MHz) δ 8.75 (m, 1 H), 8.31 (d, $J=6.4$ Hz, 2 H), 7.98 (m, 2 H), 6.47 (t, $J=6.4$ Hz, 1 H), 4.84

(m, 2 H), 4.09 (m, 1 H), 3.11 (m, 2 H), 1.74 (m, 2 H), 1.66 (m, 2 H); MS calculado para $C_{14}H_{15}BrN_5O$ $[M+H]^+$: 349; hallado: 349.

Siguiendo los procedimientos generales para las reacciones de Suzuki, se obtuvo el compuesto del título en 69% de rendimiento como un sólido blancuzco: 1H NMR ($CDCl_3$, 400 MHz) δ 8.92 (m, 1 H), 8.33 (d, $J=6.4$ Hz, 2 H), 8.05 (m, 1 H), 7.54 (m, 1 H), 6.48 (t, $J=6.4$ Hz, 1 H), 4.85 (m, 2 H), 4.22 (m, 1 H), 3.12 (m, 2 H), 2.44 (s, 3 H), 2.02 (m, 2 H), 1.75 (m, 2 H); MS calculado para $C_{21}H_{22}N_5O$ $[M+H]^+$: 359; hallado: 359.

6.5. Preparación de (3,4,5,6-Tetrahidro-2H-[1,2']bipiridinil-4-il)-(3'-trifluorometil-bifenil-4-il)-metanona



El compuesto del título se preparó de (4-bromo-fenil)-(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-4-il)-metanona como se describe a continuación.

Metoxi-metil amida de ácido 3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-4-carboxílico: En un tubo sellado, amida de Weinreb (0.5515 g, 1.927 mmol) se tomó en etanol absoluto (10 ml) y se agregaron 2-bromopiridina (0.19 ml, 1.927 mmol) y trietilamina (0.81 ml, 5.781 mmol). El tubo se selló y se calentó a 150°C durante por lo menos 48 horas. La reacción se diluyó entonces con CH_2Cl_2 , se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice usando 10-20% acetona en hexanos, lo cual proporcionó el producto (0.1375 g, 29%) como un aceite marrón: 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, $J=4.9, 1.2$ Hz, 1H), 7.46 (m, 1H), 6.66 (d, $J=8.6$ Hz, 1H), 6.58 (m, 1H), 4.35 (dt, $J=13.0, 2.9$ Hz, 2H), 3.74 (s, 3H), 3.20 (s, 3H), 2.91 (m, 3H), 1.83 (m, 4H); m/z calculado para $C_{13}H_{19}N_3O_2$: 249.15

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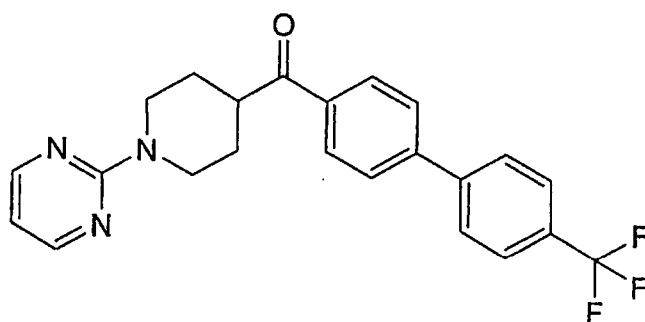
hallado: $(M+H)^+$ 250.05; Tiempo de retención HPLC = 1,533 min (longitud de onda 220 nm), pureza = 98.4%.

(4-Bromo-fenil)-(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-4-il)-metanona: Una solución de 1,4-dibromobenceno (0.223 g, 0.944 mmol) en THF (3.0 ml) anhidro se enfrió a -78°C . A la solución enfriada, se agregó gota a gota n-butil litio (1.6 M en hexanos, 0.47 ml, 0.746 mmol), y la reacción se agitó a -78°C durante 45 minutos. Una solución de la metoximetilamida de ácido 3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-4-carboxílico (0.124 g, 0.497 mmol) en THF anhidro (3.0 ml) se agregó entonces gota a gota a la reacción. La reacción se agitó a -78°C durante 3 horas y a 0°C hasta que se completó. La reacción se extinguió a 0°C mediante la adición de 1 N HCl (5 ml) y NaHCO_3 saturado (7.5 ml). La mezcla se extrajo con acetato de etilo, se lavó con salmuera, se secó sobre MgSO_4 , se filtró, y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice usando 3-10% acetona en hexanos, lo cual proporcionó el producto (0.1220 g, 71%) como un aceite incoloro: ^1H NMR (400 MHz, CDCl_3) δ 8.16 (dd, $J=4.9, 1.2$ Hz, 1H), 7.81 (m, 2H), 7.61 (m, 2H), 7.46 (m, 1H), 6.67 (d, $J=8.7$ Hz, 1H), 6.59 (dd, $J=6.7, 5.1$ Hz, 1H), 4.33 (dt, $J=13.1, 3.1$ Hz, 2H), 3.42 (m, 1H), 3.14 (m, 2H), 1.93 (d, $J=13.2, 2.2$ Hz, 2H), 1.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) 201.20, 159.20, 147.87, 137.53, 134.57, 132.28, 129.80, 128.20, 113.09, 107.34, 45.01, 43.76, 28.01; m/z calculado para $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}$: 344.05 hallado: $(M+H)^+$ 347.1; tiempo de retención HPLC = 3,205 minutos (longitud de onda 254 nm), pureza = 100%.

(3,4,5,6-Tetrahidro-2H-[1,2']bipiridinil-4-il)-(3'-trifluorometil-bifenil-4-il)-metanona: En un frasco, (4-bromo-fenil)-(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-4-il)-metanona (0.0634 g, 0.184 mmol) se tomó en DME (1.5 ml). A esta solución, se agregaron ácido bórico (0.0846 g, 0.460 mmol), pfosfato de potasio (0.117 g, 0.551 mmol) y agua (0.4 ml). Esta mezcla se desgasificó entonces usando nitrógeno. Se agregó tetrakis trifenilfosfina paladio (0.0213 g, 0.0184 mmol), y se selló el frasco. La reacción se calentó luego a 80°C durante 18 horas. Luego de la consumación, se agregó una solución 1 N de NaOH y siguió luego la

extracción dos veces con CH_2Cl_2 . Las porciones orgánicas combinadas se lavaron con salmuera, se secaron, se filtraron, y se concentraron. El producto crudo se purificó mediante cromatografía en gel de sílice usando 5-10% acetona en hexanos, lo cual proporcionó el producto final (0.042 g, 56%) como un sólido blanco: ^1H NMR (300 MHz, CDCl_3) δ 8.19 (dd, $J=4.9, 1.2$ Hz, 1H), 8.08 (d, $J=8.5$ Hz, 2H), 7.87 (s, 1H), 7.81 (d, $J=7.5$ Hz, 1H), 7.72 (d, $J=8.5$ Hz, 2H), 7.63 (m, 2H), 7.48 (m, 1H), 6.71 (d, $J=8.6$ Hz, 1H), 6.62 (dd, $J=6.8, 5.2$ Hz, 1H), 4.34 (dt, $J=13.1, 3.0$ Hz, 2H), 3.54 (m, 1H), 3.06 (m, 2H), 2.01 (dd, $J=13.1, 2.5$ Hz, 2H), 1.92 (dd, $J=11.3, 4.0$ Hz, 1H), 1.84 (m, 1H); m/z calculado para $\text{C}_{24}\text{H}_{21}\text{F}_3\text{N}_2\text{O}$: 410.16 hallado: $(\text{M}+\text{H})^+$ 411.05; tiempo de retención HPLC = 3,313 minutos (longitud de onda 254 nm), pureza = 96.9%.

6.6. Preparación de (1-(Pirimidin-2-il)piperidin-4-il)(4-4-trifluorometilfenil)-fenil)metanona



El compuesto del título se preparó de (4-bromofenil)(1-(pirimidin-2-il)piperidin-4-il)metanona como se describe a continuación.

N-metoxi-N-metilpiperidin-4-carboxamida: Una mezcla de ácido N-*tert*-butoxicarbonil isonipecótico (1.50 g, 6.54 mmol, 1 equivalente), clorhidrato de 1-(3-dimetilaminopropil)3-etilcarbodiimida (1.88 g, 9.81 mmol, 1.5 eq), 1-hidroxibenzotriazol (1.33 g, 9.81 mmol, 1.5 eq), y N,N-dimetilformamida (26 ml) se trató con N,N-diisopropiletilamina (4.60 ml, 26.2 mmol, 4 eq). La solución amarilla resultante se agitó a temperatura de la sala durante 5 minutos, y luego se agregó clorhidrato de N,O-dimetilhidroxilamina (766 mg, 7.85 mmol, 1.2 equivalentes), y se continuó la agitación durante 92 horas. La mezcla de reacción se diluyó

con 100 ml de acetato de etilo y se lavó consecutivamente con 1 N de NaOH acuoso, 1 N de HCl acuoso y salmuera. La fase orgánica se secó sobre Na₂SO₄ y se concentró para producir un aceite, el cual se usó sin purificación posterior. Este aceite se disolvió en 1:2 ácido trifluoroacético/diclorometano (9 ml), y la mezcla de reacción se agitó a temperatura ambiente durante 17 horas y luego se concentró. Se agregó éter (30 ml) y el sólido blanco que se formó se recogió mediante filtración, se lavó con éter y se secó para proporcionar 1.50 g (80% de rendimiento, 2 pasos) de producto analíticamente puro: 400 MHz ¹H NMR (d₆-DMSO): 8.55 (br s, 1 H), 8.25 (br s, 1 H), 3.69 (s, 3 H), 3.31 (m, 2 H), 3.10 (s, 3 H), 2.98 (m, 3 H), 1.65-1.84 (m, 4 H).

N-metoxi-N-metil-1-(pirimidin-2-il)piperadin-4-carboxamida: Una mezcla de N-metoxi-N-metilpiperidin-4-carboxamida (1.50 g, 5.25 mmol, 1 equivalente), 2-cloropirimidina (634 mg, 5.25 mmol, 1 equivalente), trietilamina (2.20 ml, 15.8 mmol, 3 equivalentes), y etanol (21 ml) se calentó a 100°C en un tubo sellado durante 19 horas. La mezcla de reacción se dejó enfriar a temperatura de la sala y luego se concentró. El residuo se disolvió en diclorometano, se lavó con agua y salmuera, se secó sobre Na₂SO₄, y se concentró. Cromatografía en columna (gel de sílice, 50% → 60% acetato de etilo/hexanos) proporcionó 1.28 g (97% de rendimiento) del producto como un aceite incoloro: HPLC: 100% puro a 1,905 minutos (columna YMC-Pack ODS-A 4.6 x 33 mm, 0% → 100% disolvente B durante 4 minutos, 3 ml/min, 220 nm); LCMS (M+H)⁺ = 251.05; 400 MHz ¹H NMR (CDCl₃) 8.29 (d, J = 4.7 Hz, 2 H), 6.45 (t, J = 4.7 Hz, 1 H), 4.80 (m, 2 H), 3.73 (s, 3 H), 3.19 (s, 3 H), 2.95 (m, 3 H), 1.70- 1.84 (m, 4 H).

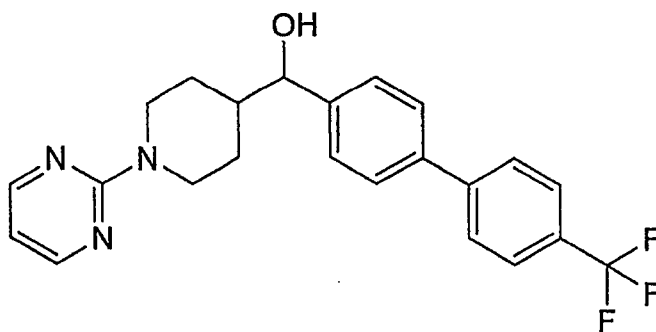
(4-Bromofenil)(1-(pirimidin-2-il)piperidin-4-il)metanona: Una solución de 1,4-dibromobenceno (2.29 g, 9.72 mmol, 1.9 equivalentes) en THF (20 ml) bajo N₂ se enfrió a - 78°C, y se agregó gota a gota n-butil litio (1.6 M en hexanos, 4.8 ml, 7.67 mmol, 1.5 equivalentes). La mezcla de reacción se agitó a -78°C durante 40 minutos, y una solución de N- metoxi-N-metil-1-(pirimidin-2-il)piperadin-4-carboxamida (1.28 g, 5.11 mmol, 1 equivalente) en THF (5 ml) se agregó gota a gota a través de una cánula.

Pasadas 3 horas a -78°C , la mezcla de reacción se calentó a 0°C , se agitó durante 1 hora, y luego se extinguió con 1 N de HCl acuoso (10 ml). La mezcla se diluyó con 150 ml de acetato de etilo, se lavó consecutivamente con NaHCO_3 acuoso saturado y salmuera (75 ml cada uno), y la fase orgánica se secó sobre Na_2SO_4 y se concentró. Cromatografía en columna (gel de sílice, $\text{CH}_2\text{Cl}_2 \rightarrow 3.5\%$ acetato de etilo/ CH_2Cl_2) proporcionó 1.47 g (83% de rendimiento) del producto como un sólido amarillo pálido: HPLC: 99% puro a 3,748 minutos (columna YMC-Pack ODS-A 4.6 x 33 mm, 0% $\rightarrow$ 100% disolvente B durante 4 minutos, 3 ml/minuto, 220 nm); LCMS $(\text{M}+\text{H})^+ = 345.90$; 400 MHz ^1H NMR (CDCl_3) 8.31 (d, $J = 4.7$ Hz, 2 H), 7.83 (d, $J = 8.5$ Hz, 2 H), 7.63 (d, $J = 8.5$ Hz, 2 H), 6.48 (t, $J = 4.7$ Hz, 1 H), 4.81 (m, 2 H), 3.49 (m, 1 H), 3.08 (m, 2 H), 1.72-1.95 (m, 4 H).

(1-(Pirimidin-2-il)piperidin-4-il)(4-4-trifluorometilfenil)-fenil

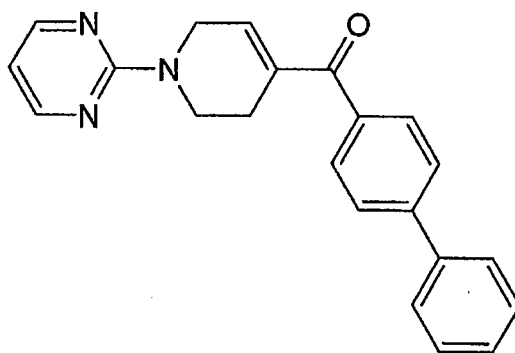
metanona: Una mezcla de (4-bromofenil)(1-(pirimidin-2-il)piperidin-4-il)metanona (66 mg, 0.19 mmol, 1 equivalente), ácido 4-trifluorometilfenilbórico (91 mg, 0.47 mmol, 2.5 equivalentes), fosfato de potasio (122 mg, 0.57 mmol, 3 equivalentes), y $\text{Pd}(\text{PPh}_3)_4$ (22 mg, 0.019 mmol, 0.1 equivalente) en 3:1 DME/agua (2 ml) se calentó a 80°C bajo N_2 durante 16 horas. La mezcla de reacción se enfrió a temperatura de la sala, se vertió en 1 N NaOH, y se extrajo dos veces con diclorometano. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron. Cromatografía en columna (gel de sílice, 25% acetato de etilo/hexanos) proporcionó 58 mg (73% de rendimiento) del producto final como un sólido blanco: HPLC: 97% puro a 4,523 minutos (columna YMC-Pack ODS-A 4.6 x 33 mm, 0% $\rightarrow$ 100% disolvente B durante 4 minutos, 3 ml/minuto, 220 nm); LCMS $(\text{M}+\text{H})^+ = 412.20$; 300 MHz ^1H NMR (CDCl_3) 8.32 (d, $J = 4.7$ Hz, 2 H), 8.08 (d, $J = 8.4$ Hz, 2 H), 7.70-7.74 (m, 6 H), 6.48 (t, $J = 4.7$ Hz, 1 H), 4.83 (m, 2 H), 3.58 (m, 1 H), 3.12 (m, 2 H), 1.75-2.01 (m, 4 H).

6.7. Preparación de (1-(Pirimidin-2-il)piperidin-4-il)(4-4-trifluorometilfenil)-fenil)metanol



Borohidruro de sodio (3.0 mg, 0.080 mmol, 1.5 equivalentes) se agregó a una solución de (1-(pirimidin-2-il)piperidin-4-il)(4-4-trifluorometilfenil)fenil)metanona (22 mg, 0.053 mmol, 1 equivalente) en 1:1 metanol/diclorometano. La mezcla de reacción se agitó a temperatura de la sala durante 1 hora y luego se extinguió lentamente con NaHCO_3 acuoso saturado. La mezcla bifásica se extrajo dos veces con diclorometano, y las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron. TLC preparativa (500 μm gel de sílice, 33% acetato de etilo/hexanos) proporcionó 17 mg (77% de rendimiento) del producto como un sólido blanco: HPLC: 100% puro a 4,285 minutos (columna YMC-Pack ODS-A 4.6 x 33 mm, 0% $\rightarrow$ 100% disolvente B durante 4 minutos, 3 ml/minuto, 220 nm); LCMS $(\text{M}+\text{H})^+ = 414.10$; 300 MHz ^1H NMR (CDCl_3) 8.27 (d, $J = 4.7$ Hz, 2 H), 7.69 (s, 4 H), 7.59 (d, $J = 8.3$ Hz, 2 H), 7.42 (d, $J = 8.2$ Hz, 2 H), 6.43 (t, $J = 4.7$ Hz, 1 H), 4.71-4.87 (m, 2 H), 4.48 (m, 1 H), 2.72-2.89 (m, 2 H), 1.88-2.11 (m, 3 H), 1.19-1.49 (m, 3 H).

6.8. Preparación de Bifenil-4-il-(1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-il)-metanona



A una solución de 2-cloropirimidina (300 mg, 2.619 mmol) en dioxano (5 ml), se agregó monohidrato de clorhidrato de piperidin-4-ona

(402.3 mg, 2.619 mmol) a temperatura de la sala. La mezcla se calentó a 80°C de un día para otro y se concentró bajo presión reducida. El residuo se trató con EtOAc (30 ml) y NaHCO₃ saturado (10 ml). Luego de la separación de las capas, la fase acuosa se extrajo con EtOAc (2 x 10 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (MgSO₄), se filtraron, y se concentraron bajo presión reducida para proporcionar un producto crudo. Este material se purificó mediante cromatografía en columna (40% EtOAc/hexanos) para producir 1-pirimidin-2-il-piperidin-4-ona (320 mg, 53%) como un sólido blancuzco: ¹H NMR (CDCl₃, 400 MHz) δ 8.38 (d, *J*= 6.4 Hz, 2 H), 6.61 (t, *J*= 6.4 Hz, 9 H), 4.16 (t, *J*= 5.6 Hz, 2 H), 2.53 (t, *J*= 5.6 Hz, 2 H).

A una solución de LDA (preparado de diisopropilamina (167.4 mg, 1.658 mmol) y *n*-BuLi (2.5 M en hexanos, 0.663 ml, 1.658 mmol) a -78°C, se agregó una solución de la 1-pirimidin-2-il-piperidin-4-ona de más arriba (320 mg, 1.382 mmol). La mezcla se agitó a la misma temperatura durante 1 hora, seguida por la adición de PhNTf₂ (543.1 mg, 1.52 mmol). La mezcla de reacción se calentó hasta temperatura de la sala y se agitó durante 3 horas antes de extinguirla con la adición de cloruro de amonio saturado (15 ml) y EtOAc (40 ml). Luego de la separación de las capas, la fase acuosa se extrajo con EtOAc (2 x 10 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (MgSO₄), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (20% EtOAc/hexanos) para producir el triflato correspondiente (210.7 mg, 49%) como un sólido blanco junto con el material de partida recuperado (142.9 mg): ¹H NMR (CDCl₃, 400 MHz) δ 8.37 (d, *J*= 6.4 Hz, 2 H), 6.59 (t, *J*= 6.4 Hz, 1 H), 5.91 (m, 1 H), 4.41 (m, 2 H), 4.11 (t, *J*= 5.6 Hz, 2 H), 2.55 (m, 2 H); MS calculado para C₁₀H₁₁F₃N₃O₃S [M+H]⁺: 310; hallado: 310.

A una solución del triflato anterior (210.7 mg, 0.682 mmol) en metanol (10 ml), se agregó Pd(OAc)₂ (10.7 mg, 0.047 mmol), PPh₃ (31.3 mg, 0.119 mmol) y diisopropiletilamina (352.6 mg, 2.728 mmol) a temperatura de la sala. Se hizo burbujear monóxido de carbono a través de

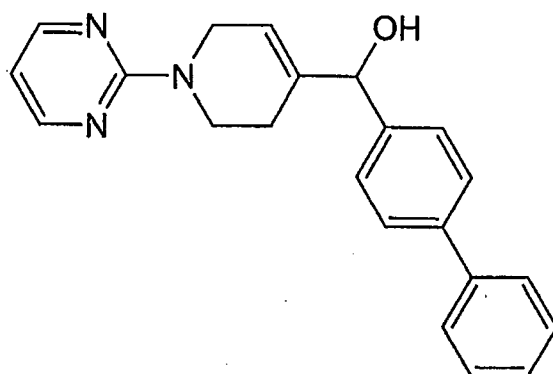
la solución durante 4 horas antes de concentrar la mezcla bajo presión reducida. El residuo se trató con EtOAc (30 ml) y agua (10 ml). La fase acuosa se extrajo posteriormente con EtOAc (2 x 10 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (30% EtOAc/hexanos) para producir éster metílico de ácido 1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-carboxílico (73.8 mg, 50%) como cristales blancos: ^1H NMR (CDCl_3 , 400 MHz) δ 8.37 (d, $J= 6.4$ Hz, 2 H), 7.04 (m, 1 H), 6.54 (t, $J= 6.4$ Hz, 1 H), 4.41 (m, 2 H), 3.98 (t, $J= 5.6$ Hz, 2 H), 3.79 (s, 3 H), 2.52 (m, 2 H).

A una suspensión de éster metílico de ácido 1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-carboxílico (73.8 mg, 0.337 mmol) y clorhidrato de *N*-metil-*O*-metil hidroxilamina (51.0 mg, 0.552 mmol) en THF (3 ml), se agregó cloruro de isopropil magnesio (2.0 M en THF, 0.505 ml) a -20°C durante un período de 15 minutos. La mezcla se agitó a -10°C durante otros 30 minutos antes de extinguirla con la adición de cloruro de amonio saturado (10 ml). La mezcla se extrajo con EtOAc (2 x 15 ml). Las capas orgánicas combinadas se lavaron con salmuera (15 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (4% MeOH/ CH_2Cl_2) para producir metoxi-metilamida de ácido 1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-carboxílico (48 mg, 58%) como cristales blancos: ^1H NMR (CDCl_3 , 400 MHz) δ 8.35 (d, $J= 6.4$ Hz, 2 H), 6.53 (t, $J= 6.4$ Hz, 1 H), 6.43 (m, 1 H), 4.35 (m, 2 H), 3.99 (t, $J= 5.6$ Hz, 2 H), 3.66 (s, 3 H), 3.27 (s, 3 H), 2.55 (m, 2 H).

A una solución de metoxi-metilamida de ácido 1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-carboxílico (48 mg, 0.196 mmol) en THF (1 ml), se agregó bromuro de 1-bifenil-4-il magnesio (0.5 M en THF) a 0°C . La mezcla se agitó a esta temperatura durante 1 hora y se extinguió con la adición de agua (5 ml) y EtOAc (20 ml). La fase acuosa se extrajo

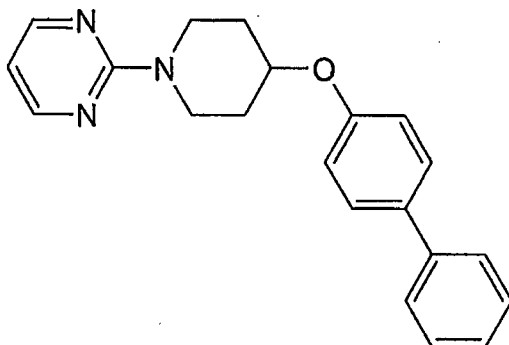
posteriormente con EtOAc (2 x 8 ml). Las capas orgánicas combinadas se lavaron con salmuera (5 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (4% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) para producir el compuesto del título (20 mg, 30%) como un sólido blancuzco: ^1H NMR (CDCl_3 , 400 MHz) δ 8.38 (d, J = 6.4 Hz, 2 H), 7.82-7.42 (m, 9 H), 6.70 (m, 1 H), 6.58 (t, J = 6.4 Hz, 1 H), 4.51 (m, 2 H), 4.13 (t, J = 5.6 Hz, 2 H), 2.72 (m, 2 H); MS calculado para $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 342; Hallado: 342.

6.9. Preparación de Bifenil-4-il-(1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-il)-metanol



A una solución de bifenil-4-il-(1-pirimidin-2-il-1,2,3,6-tetrahidro-piridin-4-il)-metanona (12.2 mg, 0.0355mmol) en metanol (0.5 ml), se agregó CeCl_3 heptahidrato (13.2 mg, 0.0355 mmol) y borohidruro de sodio (1.5 mg, 0.0355 mmol) a temperatura de la sala. La mezcla se agitó durante 1 hora y se diluyó con EtOAc (10 ml). La mezcla se lavó con agua (5 ml), salmuera (5 ml), se secó (MgSO_4), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (6% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) para producir el compuesto del título (12 mg, 98%) como un gel blanco: ^1H NMR (CDCl_3 , 400 MHz) δ 8.36 (d, J = 6.4 Hz, 2 H), 7.62- 7.37 (m, 9 H), 6.46 (t, J = 6.4 Hz, 1 H), 6.02 (m, 1 H), 5.24 (m, 1 H), 4.31 (m, 2 H), 3.96 (m, 1 H), 3.83 (m, 1 H), 2.14 (m, 2 H); MS calculado para $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 344; hallado: 344.

6.10. Preparación de 2-[4-(Bifenil-4-iloxi)-piperidin-1-il]-pirimidina

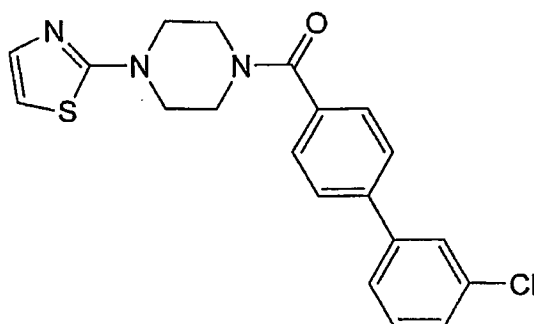


A una solución de 1-pirimidin-2-il-piperidin-4-ona (50 mg, 0.282 mmol) en metanol (0.8 ml), se agregó borohidruro de sodio (12.0 mg, 0.282 mmol) a temperatura de la sala. Luego de agitar durante 10 minutos, la mezcla se trató con EtOAc (10 ml) y agua (3 ml). La capa orgánica se lavó con salmuera (2 ml), se secó (MgSO_4), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (20% EtOAc/hexanos) para producir el alcohol correspondiente (51 mg, 100%) como un sólido blanco.

A una mezcla del alcohol anterior (50 mg, 0.279 mmol), PPh_3 (109.6 mg, 0.418 mmol) y bifenil-4-ol (57.0 mg, 0.335 mmol) en THF (3 ml), se agregó DEAD (40% en tolueno, 0.152 ml, 0.335 mmol) a 0°C . Luego de agitar de un día para otro, la mezcla se trató con EtOAc (15 ml) y agua (5 ml). La fase acuosa se extrajo con EtOAc (2 x 5 ml). Las capas orgánicas combinadas se lavaron con salmuera (5 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (15% EtOAc/hexanos) para producir el compuesto del título (81 mg, 88%) como cristales blancos: ^1H NMR (CDCl_3 , 400 MHz) δ 8.38 (d, J = 6.4 Hz, 2 H), 7.59-7.04 (m, 9 H), 6.61 (t, J = 6.4 Hz, 1 H), 4.62 (m, 1 H), 4.21 (m, 2 H), 3.68 (m, 2 H), 2.14 (m, 2 H), 1.83 (m, 2 H); MS calculado para $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 332; hallado: 332.

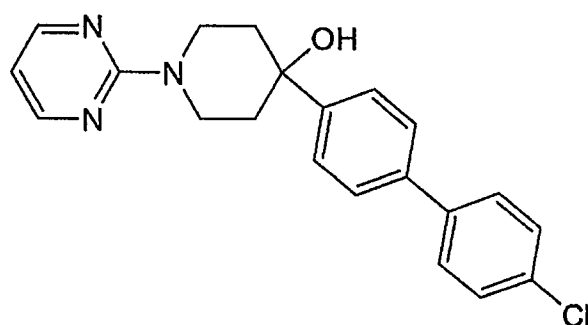


6.11. Preparación de (3'-Cloro-bifenil-4-il)-(4-tiazol-2-il-piperazin-1-il)-metanona



A una solución de 1-(tiazol-2-il)piperazina (aprox. 0.915 mmol, preparada de 150 mg 2-bromotiazol de acuerdo con los métodos descritos en Astles *et al.*, *J. Med. Chem.*, 39: 1423-1432 (1996)), ácido 3'-cloro-bifenil-4-carboxílico (212.9 mg, 0.915 mmol) en CH₂Cl₂ (4 ml), se agregó EDC (209.7 mg, 1.098 mmol) y HOBT (148.2 mg, 1.098 mmol). Luego de agitarse durante la noche, la mezcla se trató con EtOAc (50 ml) y agua (15 ml). La fase orgánica se lavó con salmuera (5 ml), se secó (MgSO₄), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (20% acetona/hexanos) para producir el compuesto del título (225 mg, 64% para dos pasos) como un sólido blanco: ¹H NMR (CDCl₃, 400 MHz) δ 7.64-7.23 (m, 9 H), 6.65 (t, *J* = 3.6 Hz, 1 H), 4.92 (m, br, 2 H), 3.57 (m, br, 6 H), 3.68 (m, 2 H), 2.14 (m, 2 H), 1.83 (m, 2 H); MS calculado para C₂₀H₁₉ClN₃OS [M+H]⁺: 384; hallado: 384.

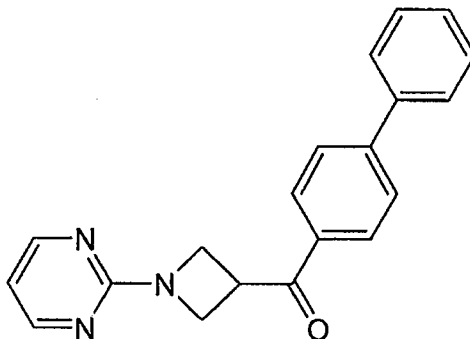
6.12. Preparación de 4-(4'-Cloro-pifenil-4-il)-1-pirimidin-2-il-piperidin-4-ol



A una solución de 1,4-dibromobenceno (213.3 mg, 0.904 mmol) en THF (4 ml), se agregó *n*-BuLi (2.5 M en hexanos, 0.362 ml, 0.904 mmol) a -78°C. Luego de agitar durante 30 minutos a la misma temperatura, se agregó una solución de 1-pirimidin-2-il-piperidin-4-ona (80 mg, 0.452 mmol) en THF (3 ml). La mezcla se dejó calentar a temperatura de la sala y se agitó durante 1 hora. La reacción se extinguió con adición de agua (10 ml) y EtOAc (50 ml). La capa orgánica se lavó con salmuera (5 ml), se secó (MgSO₄), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (40% EtOAc/hexanos) para producir 4-(4-bromo-fenil)-1-pirimidin-2-il-piperidin-4-ol como un aceite incoloro (140 mg, 93%): ¹H NMR (CDCl₃, 400 MHz) δ 8.33 (d, *J*= 6.4 Hz, 2 H), 7.47 (d, *J*= 12.0 Hz, 2 H), 7.41 (d, *J*= 12.0 Hz, 2 H), 6.49 (t, *J*= 6.4 Hz, 1 H), 4.72 (m, 2 H), 3.40 (m, 2 H), 2.05 (m, 2 H), 1.78 (m, 2 H); MS calculado para C₁₅H₁₇BrN₃O [M+H]⁺: 335; hallado: 335.

Siguiendo los procedimientos generales para las reacciones de Suzuki, el compuesto del título se preparó en 61% de rendimiento como un vidrio incoloro: ¹H NMR (CDCl₃, 400 MHz) δ 8.35 (d, *J*= 6.4 Hz, 2 H), 7.59-7.37 (m, 8 H), 6.50 (t, *J*= 6.4 Hz, 1 H), 4.73 (m, 2 H), 3.46 (t, *J*= 12.4 Hz, 2 H), 2.15 (m, 2 H), 1.88 (m, 2 H); MS calculado para C₂₁H₂₁ClN₃O [M+H]⁺: 366; hallado: 366.

6.13. Preparación de Bifenil-4-il-(1-pirimidin-2-il-azetidín-3-il)-metanona



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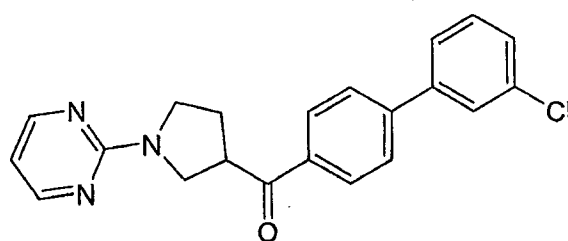
A una solución agitada de clorhidrato de éster metílico de ácido 3-azetidin-carboxílico (150 mg, 0.99 mmol) y 2-cloropirimidina (113.4 mg, 0.99 mmol) en metanol, se agregó TEA (200 mg, 1.98 mmol) a temperatura de la sala. La mezcla se agitó a 50°C durante 5 horas y se concentró bajo presión reducida. El residuo se suspendió en EtOAc (50 ml) y se lavó con agua (15 ml), salmuera (5 ml), se secó (MgSO₄), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (40% EtOAc/hexanos) para producir éster metílico de ácido 1-pirimidin-2-il-azetidin-3-carboxílico como un sólido amarillo claro (137.3 mg, 72%): ¹H NMR (CDCl₃, 400 MHz) δ 8.37 (d, *J* = 6.4 Hz, 2 H), 6.58 (t, *J* = 6.4 Hz, 1 H), 4.30 (m, 4 H), 3.77 (s, 3 H), 3.56 (m, 1 H).

A una suspensión del éster anterior (137.3 mg, 0.711 mmol) y clorhidrato de *N*-metil-*O*-metil hidroxilamina (127.6 mg, 1.103 mmol) en THF (5 ml), se agregó cloruro de *iso*-propil magnesio (2.0 M en THF, 1.067 ml, 2.133 mmol) a -20°C durante 15 minutos. La mezcla se agitó a -10°C durante otros 30 minutos antes de extinguirla con la adición de cloruro de amonio saturado (10 ml). La mezcla se extrajo con EtOAc (2 x 15 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (MgSO₄), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (4% MeOH/CH₂Cl₂) para producir metoxi-metil-amida de ácido 1-pirimidin-2-il-azetidin-3-carboxílico (385.9 mg, 98%) como un sólido blanco: ¹H NMR (CDCl₃, 400 MHz) δ 8.32 (d, *J* = 6.4 Hz, 2 H), 6.55 (t, *J* = 6.4 Hz, 1 H), 4.34 (m, 4 H), 3.88 (m, 1 H), 3.70 (s, 3 H), 3.23 (s, 3 H).

A una solución de la amida anterior (50 mg, 0.225 mmol) en THF (1 ml), se agregó cloruro de 4-bifenil magnesio (0.5 M en THF, 0.9 ml, 0.45 mmol) a -78°C. La mezcla se calentó lentamente a temperatura de la sala y se agitó durante 2 horas antes de extinguirla con la adición de agua (10 ml) y EtOAc (30 ml). La capa orgánica se separó y se lavó con salmuera (5 ml), se secó (MgSO₄), se filtró, y se concentró bajo presión reducida para

proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (3% MeOH/CH₂Cl₂) para proporcionar el compuesto del título (21 mg, 30%) como cristales blancos: ¹H NMR (CDCl₃, 400 MHz) δ 8.33 (d, *J* = 6.4 Hz, 2 H), 7.98-7.43 (m, 9 H), 6.58 (t, *J* = 6.4 Hz, 1 H), 4.45 (m, 4 H), 4.38 (m, 1 H); MS calculado para C₂₀H₁₈N₃O [M+H]⁺: 316; hallado: 316.

6.14. Preparación de (3'-Cloro-bifenil-4-il)-(1-pirimidin-2-il-pirrolidin-3-il)-metanona



A una solución de *N*-Boc-β-prolina (400 mg, 1.858 mmol), EDC (425.9 mg, 2.23 mmol) y HOBT (326.1 mg, 2.415 mmol) en cloruro de metileno (8 ml), se agregó clorhidrato de *N*-metil-*O*-metil hidroxilamina (217.5 mg, 2.23 mmol) y TEA (281.5 mg, 2.787 mmol) a 0°C. Luego de agitar de un día para otro, la mezcla se trató con EtOAc (80 ml) y agua (15 ml). La fase orgánica se lavó con salmuera (15 ml), se secó (MgSO₄), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo.

A una solución del éster crudo anterior en cloruro de metileno (4 ml), se agregó gota a gota TFA (4 ml) a temperatura de la sala. La mezcla se agitó durante 40 minutos y se concentró bajo presión reducida para generar el producto crudo como la sal TFA.

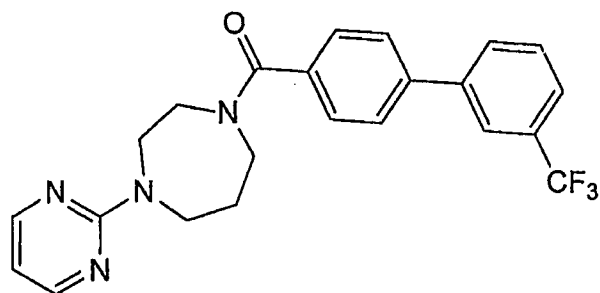
A una mezcla del producto anterior y 2-cloropirimidina (212.8 mg, 1.858 mmol) en dioxano (7 ml) se agregó TEA (563 mg, 5.574 mmol). La mezcla se calentó a 80°C durante 4 horas, y se concentró bajo presión reducida. El residuo se trató con agua (20 ml) y EtOAc (60 ml). Luego de la separación de las capas, la fase acuosa se extrajo posteriormente con EtOAc (20 ml). Las capas orgánicas combinadas se lavaron con salmuera

(10 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (40% acetona/hexanos) para proporcionar metoxi-metil-amida de ácido 1-pirimidin-2-il-pirrolidin-3-carboxílico (203.8 mg, 47% para tres pasos) como un sólido blancuzco: ^1H NMR (CDCl_3 , 400 MHz) δ 8.34 (d, J = 6.4 Hz, 2 H), 6.50 (t, J = 6.4 Hz, 1 H), 3.94 (m, 1 H), 3.82 (m, 1 H), 3.75 (s, 3 H), 3.70 (m, 1 H), 3.65 (m, 1 H), 3.63 (m, 1 H), 3.23 (s, 3 H), 2.33 (m, 3 H), 2.23 (m, 1 H).

A una solución de 1,4-dibromobenceno (407.5 mg, 1.727 mmol) en THF (6 ml) se agregó *n*-BuLi (2.5 M en hexanos, 0.691 ml, 1.727 mmol) a -78°C . La mezcla se agitó a la misma temperatura durante 30 minutos antes de la adición de una solución de la amida anterior (203.8 mg, 0.8636 mmol) en THF (4 ml). Luego de agitar a -78°C durante 30 minutos, la mezcla se calentó a temperatura de la sala durante 1 hora. Se agregaron EtOAc (40 ml) y agua (15 ml) a la reacción, seguidos por la separación de las capas. La fase acuosa se extrajo con EtOAc (15 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (MgSO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (40% acetona/hexanos) para proporcionar (4-bromo-fenil)-(1-pirimidin-2-il-pirrolidin-3-il)-metanona (182.2 mg, 64%) como un sólido blancuzco: ^1H NMR (CDCl_3 , 400 MHz) δ 8.32 (d, J = 6.4 Hz, 2 H), 7.87 (d, J = 12.0 Hz, 2 H), 7.63 (d, J = 12.0 Hz, 2 H), 6.51 (t, J = 6.4 Hz, 1 H), 4.07 (m, 1 H), 3.98 (m, 1 H), 3.86 (m, 1 H), 3.74 (m, 2 H), 2.38 (m, 2 H).

Siguiendo los procedimientos generales para las reacciones de Suzuki, el compuesto del título se preparó en 63% como un sólido amarillo pálido: ^1H NMR (CDCl_3 , 400 MHz) δ 8.38 (d, J = 6.4 Hz, 2 H), 8.11-7.42 (m, 8 H), 6.53 (t, J = 6.4 Hz, 1 H), 4.19 (m, 1 H), 4.04 (m, 1 H), 3.84 (m, 1 H), 3.77 (m, 2 H), 2.42 (m, 1 H), 2.38 (m, 1 H); MS calculado para $\text{C}_{21}\text{H}_{19}\text{ClN}_3\text{O}$ $[\text{M}+\text{H}]^+$: 364; hallado: 364.

6.15. Preparación de (4-Pirimidin-2-il-homopiperazin-1-il)-[4-(3-trifluorometilfenil-fenil)]-metanona



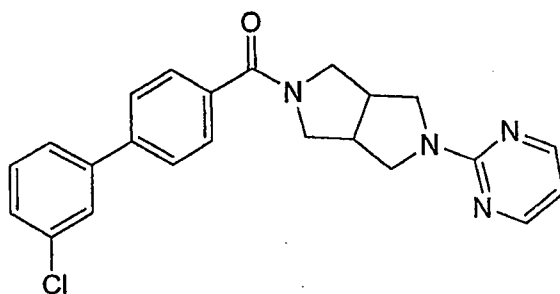
El compuesto del título se preparó de 1-(2-pirimidil)-homopiperazina como se describe a continuación.

1-(2-Pirimidil)-homopiperazina: A una solución de homopiperazina (3.5 g, 35 mmol) en etanol (100 ml) a 40°C, se agregó en porciones 2-cloropirimidina (2.0 g, 17.5 mmol). La mezcla se agitó durante 1 hora, luego se concentró *in vacuo*. El residuo se disolvió en cloruro de metileno (75 ml) y se lavó con una solución saturada de bicarbonato de sodio salmuera. Se separaron las capas, y la capa orgánica se secó sobre sulfato de magnesio y se concentró. El residuo resultante se purificó mediante cromatografía instantánea y se recogió un semisólido (1.0 g), el cual se utilizó tal como estaba.

(4-Pirimidin-2-il-homopiperazin-1-il)-[4-(3-trifluorometilfenilfenil)]-metanona: A una solución de ácido 3'-trifluorometil-bifenil-4-carboxílico (0.38 g, 1.41 mmol) y 1-(2-pirimidil)-homopiperazina (0.25 g, 1.41 mmol) en cloruro de metileno (20 ml), se agregó EDCI (0.27 g, 1.41 mmol) y HOAt (0.19 g, 1.41 mmol) trietilamina (0.20 ml, 1.41 mmol). La mezcla se agitó durante 16 horas y luego se lavó con salmuera. Las capas se separaron, y la fase orgánica se secó sobre sulfato de magnesio y se concentró. El aceite resultante se purificó mediante cromatografía instantánea y se recogió un aceite claro. El aceite se disolvió en una cantidad mínima de t-butilmetiléter, y se recogieron los cristales formados (0.20 g). Los datos de espectro fueron consistentes con la estructura. MS (M+1) = 427. HPLC (> 95 %). ¹H NMR (CDCl₃) 8.35 (m, 2H), 7.55 (m, 8H), 6.58 (t, 1H), 3.87 (bm, 8H), 1.92 (m, 2H).

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6.16. Preparación de (3'-Cloro-bifenil-4-il)-5-pirimidin-2-il-hexahidro-pirrol[3,4-c]pirrol-2-il)-metanona



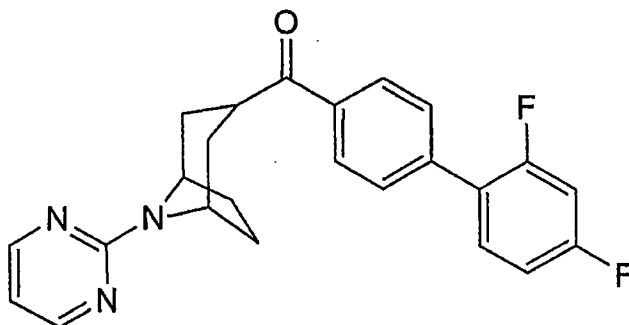
El compuesto del título se preparó de ácido 5-pirimidin-2-il-hexahidro-pirrol[3,4-c]pirrol-2-carboxílico y *terc*-butil éster como se describe a continuación.

terc-Butil éster de ácido 5-pirimidin-2-il-hexahidro-pirrol[3,4-c]pirrol-2-carboxílico: Una solución de *terc*-butil éster de ácido hexahidro-pirrol[3,4-c]pirrol-2-carboxílico (1.0 g, 4.7 mmol), 2-cloropirimidina (0.54 g, 4.7 mmol), trietilamina (2 ml, 14 mmol) y alcohol etílico (25 ml) se mantuvo a reflujo durante 4 horas. En seguida la solución se enfrió a temperatura de la sala y se concentró para proporcionar un residuo sólido que se disolvió en diclorometano (CH₂Cl₂), el cual se lavó consecutivamente con bicarbonato de sodio acuoso saturado y salmuera, se secó (Na₂SO₄), se filtró, y se concentró para proporcionar 0.82 g (60 %) del producto como un sólido anaranjado: ¹H NMR (400 MHz, CDCl₃): δ 8.34 (d, *J*= 4.8 Hz, 2H), 6.53 (t, *J*= 4.8 Hz, 1 H), 3.86-3.79 (m, 2H), 3.72-3.62 (m, 2H), 3.57-3.50 (m, 2H), 3.41-3.33 (m, 1H), 3.33-3.26 (m, 1H), 3.05-2.96 (m, 2H), 1.47 (s, 9H); LRMS *m/z* 291 (M + H)⁺.

(3'-Cloro-bifenil-4-il)-(5-pirimidin-2-il-hexahidro-pirrol[3,4-c]pirrol-2-il)-metanona: Una solución de *terc*-butil éster de ácido 5-pirimidin-2-il-hexahidro-pirrol[3,4-c]pirrol-2-carboxílico (0.70 g, 2.4 mmol) y CH₂Cl₂ (20 ml) se trató con ácido trifluoroacético (TFA, 10 ml) y se mantuvo a temperatura de la sala durante 3 horas. La solución resultante se concentró, y el residuo se disolvió en CH₂Cl₂ (5 ml) y se agregó a una solución de ácido 3'-cloro-bifenil-4-il-carboxílico (0.62 g, 2.6 mmol), *O*-(7-hexafluorofosfato de azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio

(HATU, 1.0 g, 2.6 mmol), diisopropiletilamina (1.5 ml, 8 mmol), y CH_2Cl_2 (20 ml). La solución resultante se mantuvo a temperatura de la sala durante 2 horas, se diluyó con EtOAc, se lavó con NaHCO_3 acuoso saturado y salmuera, se secó (MgSO_4), se filtró, y se concentró. El residuo sólido se recrystalizó de alcohol metílico para proporcionar el producto final como agujas blancas: ^1H NMR (CD_3OD): δ 8.32 (d, J = 4.8 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2 H), 7.67 (s, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.60-7.50 (m, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.40-7.37 (m, 1H), 6.63 (t, J = 4.8 Hz, 1H), 3.96 (dd, J = 7.8, 12.8 Hz, 1H), 3.86 (ddd, J = 3.0, 7.2, 10.6 Hz, 2H), 3.76 (dd, J = 7.5, 11.6 Hz, 1 H), 3.65-3.58 (m, 2H), 3.51 (dd, J = 5.1, 11.3 Hz, 1H), 3.43 (dd, J = 4.7, 11.7 Hz, 1H), 3.21-3.07 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ 171.8, 161.4, 159.1, 143.5, 142.9, 137.0, 136.0, 131.6, 129.0, 128.2, 128.1, 126.6, 110.9, 54.5, 51.9, 51.7, 51.1, 43.9, 42.0; LRMS m/z 405 ($\text{M} + \text{H}$) $^+$; análisis calculado para $\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}$: C, 68.23; H, 5.23; N, 13.84. Hallado: C, 68.01; H, 5.23; N, 13.60.

6.17. Preparación de (2',4'-Difluoro-bifenil-4-il)-(8-pirimidin-2-il-8-aza-biciclo [3.2.1]oct-3-il)-metanona



El compuesto del título se preparó en la siguiente forma.

8-Pirimidin-2-il-8-aza-biciclo[3.2.1]octan-3-ona: Una solución de ácido clorhídrico de 8-aza-biciclo[3.2.1]octan-3-ona (5.0g, 30.9mmol), 2-cloro-pirimidina (4.95g, 43.2mmol), NaHCO_3 (7.78g, 92.7mmol) e isopropanol (200ml) se mantuvo a reflujo durante el fin de semana. La mezcla de reacción resultante se concentró y se purificó mediante ISCO para proporcionar 8-pirimidin-2-il-8-aza-biciclo[3.2.1]octan-3-ona (4.0g, 52.9%) como un sólido blanco : MS ($\text{M}+1$) = 204. ^1H NMR (MeOH) 8.36

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(d, $J=12$ Hz 2H), 6.75 (m, 1H), 4.97 (m, 2H), 2.75 (d, $J=12$ Hz, 1H), 2.71 (d, $J=12$ Hz, 1H), 2.32 (d, $J=50$ Hz, 2H), 2.22 (m, 2H), 1.87 (m, 2H).

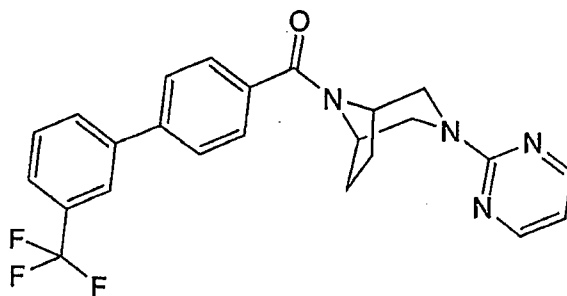
3-[(4-Bromo-fenil)-metoxi-metilene]-8-pirimidin-2-il-8-aza-biciclo [3.2.1]octano: A una solución de dietil éster de ácido [(4-bromo-fenil)-metoxi-metil]-fosfórico (4.58g, 13.5mmol) en 1,2-dimetoxi-etano (60ml), se agregó NaH (540mg, 13.5mmol, 60% en aceite mineral) en una porción. La mezcla se agitó a 50°C durante 1.5 horas antes de agregar 8-pirimidin-2-il-8-aza-biciclo[3.2.1]octan-3-ona (2.0g, 9.85mmol) en 1,2-dimetoxi-etano (5ml). La mezcla se agitó a 50°C durante el fin de semana. La mezcla resultante se concentró y se purificó mediante ISCO para proporcionar 3-[(4-bromo-fenil)-metoxi-metilen]-8-pirimidin-2-il-8-aza-biciclo[3.2.1]octano (600mg, 30%). El producto sólido blanco se utilizó tal como estaba. MS ($M+1$) = 386.

(4-Bromo-fenil)-(8-pirimidin-2-il-8-aza-biciclo[3.2.1]oct-3-il)-metanona: Una solución de 3-[(4-bromo-fenil)-metoxi-metilen]-8-pirimidin-2-il-8-aza-biciclo[3.2.1]octano (2.44g, 6.32mmol), HCl acuoso (10.5ml, 6N) y THF (50ml) se agitó a temperatura de la sala de un día para otro. A la mezcla se agregó NaHCO₃ acuoso saturado hasta que cesó el burbujeo. La mezcla se diluyó con acetato de etilo, y la fase orgánica se secó sobre MgSO₄ y se concentró. Se utilizó ISCO para realizar la purificación y se obtuvo (4-bromo-fenil)-(8-pirimidin-2-il-8-aza-biciclo [3.2.1]oct-3-il)-metanona como un sólido blanco (2.16g, 92%). MS ($M+1$) = 374. ¹H NMR (CDCl₃) 8.33 (d, $J=12$ Hz, 2H), 7.84 (d, $J=13$ Hz 2H), 7.62 (d, $J=13$ Hz 2H), 6.51 (t, $J=12$ Hz 1H), 4.87 (m, 2H), 3.90 (m, 1H), 2.23 (m, 2H), 2.08 (m, 2H), 1.97 (m, 2H), 1.72 (m, 2H).

(2',4'-Difluoro-bifenil-4-il)-(8-pirimidin-2-il-8-aza-biciclo[3.2.1]oct-3-il)-metanona: Una solución de (4-bromo-fenil)-(8-pirimidin-2-il-8-aza-biciclo[3.2.1]oct-3-il)-metanona (250mg, 0.92mmol), ácido 2,4-di-fluorofenilbórico (290mg, 1.84mmol), [1,1'-bis(difenilfosfino) ferroceno]dicloro paladio (II), complejo con diclorometano (1:1) (67mg, 0.092mmol), K₃PO₄ (390mg, 1.84mmol), 2-dimetoxi-etano (5ml) y agua (1.6ml) se agitó a 80°C durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo y una

solución 1N de NaOH. La capa orgánica se secó con MgSO_4 y se concentró. Se utilizó ISCO para purificación, y se obtuvo el producto como un sólido blanco (2',4'-difluoro-bifenil-4-il)-(8-pirimidin-2-il-8-aza-biciclo[3.2.1]oct-3-il)-metanona (69.6mg, 19%). MS (M+1) = 406. ^1H NMR (CDCl_3) 8.34 (d, $J=12$ Hz 2H), 8.00 (d, $J=21$ Hz 2H), 7.62 (dd, $J=19$ Hz, 4Hz, 2H), 7.45 (m, 1H), 6.99 (m, 2H), 6.52 (t, $J=12$ Hz, 1H), 4.90 (m, 2H), 4.00 (m, 1H), 2.25 (m, 2H), 2.12 (m, 2H), 2.02 (m, 2H), 1.78 (m, 2H).

6.18. Preparación de (3-(Pirimidin-2-il)-3,8-diazabicyclo[3.2.1]octan-8-il)(3'-(trifluorometil)bifenil-4-il)metanona



El compuesto del título se preparó en la siguiente forma.

tert-Butil éster de ácido 3-pirimidin-2-il-3,8-diazabicyclo[3.2.1]octan-8-carboxílico: Una solución de *tert*-butil éster de ácido 3,8-diaza-biciclo[3,2,1]octan-8-carboxílico (50 mg, 0.24 mmol), 2-cloropirimidina (27 mg, 0.24 mmol), trietilamina (0.1 ml, 0.72 mmol) y THF (2.5 ml) se calentó a 180°C durante 10 minutos. La solución se concentró para proporcionar un residuo sólido que se disolvió en diclorometano, el cual se lavó consecutivamente con bicarbonato de sodio acuoso saturado y salmuera, se secó (Na_2SO_4), se filtró, y se concentró para proporcionar 50 mg (71 %) del producto como un sólido marrón: ^1H NMR (400 MHz, CDCl_3): δ 8.30 (d, $J=12.0$ Hz, 2H), 6.52 (t, $J=12.0$ Hz, 1 H), 4.38-4.29 (m, 4H), 3.13 (sb, 2H), 2.42 (m, 2H), 1.69 (q, $J=18.0$ Hz, 2H), 1.49 (s, 9H); MS (M+1) = 291.

(3'-*tert*-Butil-bifenil-4-il)-(3-pirimidin-2-il-3,8-diaza-biciclo[3.2.1]oct-8-il)-metanona: Una solución de *tert*-butil éster de ácido 3-pirimidin-2-

il-3,8-diaza-biciclo[3.2.1]octan-8-carboxílico (64 mg, 0.22 mmol) en HCl/dioxano se agitó durante 5 horas a temperatura de la sala. La solución resultante se concentró, y el residuo se disolvió en CH_2Cl_2 (5 mL) y se agregó a una solución de ácido 3'-trifluorometil-bifenil-4-carboxílico (117 mg, 0.44 mmol), EDC (85 mg, 0.44 mmol), HOBt (60 mg, 0.44 mol) y TEA (0.1 mL, 0.71 mmol). Luego de agitar de un día para otro, la mezcla se trató con EtOAc (50 mL) y agua (15 mL). La fase orgánica se lavó con salmuera (5 mL), se secó (MgSO_4), se filtró, y se concentró bajo presión reducida para proporcionar el producto crudo. Este material se purificó mediante cromatografía en columna (30% EtOAc/hexanos) para producir el compuesto del título 14.2 mg, (32%) como un sólido blanco: ^1H NMR (DMSO): δ 8.35 (d, $J=12$ Hz, 2H), 7.79-7.76 (m, 3 H), 7.68 (dt, $J=20$, 3 Hz, 1H), 7.63 (d, $J=21$ Hz, 2H), 7.52-7.43 (m, 2H), 6.62 (t, $J=12$ Hz, 1H), 4.77 (bs, 1H), 4.41 (d, $J=64$ Hz, 2H), 4.17 (bs, 1H), 3.14 (bs, 2H), 2.48 (qt, $J=5$ Hz, 1 H), 1.86 (t, $J=9$ Hz, 2H), 1.60 (d, $J=24$ Hz, 1H); MS ($M+1$) = 439.

6.19. Análisis del Transportador Humano de Prolina

Se determinó la capacidad de los compuestos de inhibir el transportador de prolina en la siguiente forma. Un ADNc de SLC6A7 se clonó en un vector pcDNA3.1 y se transfectó en células COS-1. Para el análisis de selección un clon de célula que expresa en forma estable el transportador de prolina.

Las células transfectadas se sembraron a 15.000 células por pocillo en una placa de 384 pocillos y se cultivaron de un día para otro. A continuación las células se lavaron con amortiguador Krebs-Ringer's-HEPES-Tris (KRHT), pH 7.4, que contenía 120 mM NaCl, 4.7 mM KCl, 2.2 mM CaCl_2 , 1.2 mM MgSO_4 , 1.2 mM KH_2PO_4 , 10 mM HEPES y 5 mM Tris. Las células se incubaron entonces con 50 μL de amortiguador KRHT que contenía 45 nM ^3H -prolina durante 20 minutos a temperatura de la sala. Se terminó la absorción de prolina radiomarcada retirando la prolina radiomarcada y lavando las células rápidamente tres veces con 100 μL de

amortiguador KRHT helado. Se agregó fluido de centelleo (50 μ l) por pocillo, y se determinó la cantidad de prolina tritiada presente usando un contador de centelleo Packard TopCount.

Se determinó la absorción no específica midiendo la absorción de ^3H -prolina en la presencia de 2 mM de prolina fría.

Se determinó la IC_{50} de un compuesto midiendo la inhibición de cuatro muestras separadas en 10 concentraciones, comenzando típicamente con 10 μM , seguidas por 9 diluciones triples (*es decir*, 10, 3.3, 1.1, 0.37, 0.12, 0.41, 0.014, 0.0046, 0.0015, y 0 μM). Se calcularon las inhibiciones porcentuales contra el control. La IC_{50} de un compuesto se determinó usando los 10 puntos de datos, cada uno de los cuales era un promedio de las cuatro mediciones correspondientes.

6.20. Análisis del Transportador Murino de Prolina

Tejido del cerebro anterior se diseccionó de un ratón silvestre y se homogeneizó en 7 ml de amortiguador de homogeneización helado: 0.32 M sacarosa, 1mM NaHCO_3 , mezcla de inhibidor de proteasa (Roche).

Los homogenados de cerebro se centrifugaron a 1000xg durante 10 minutos para retirar los núcleos. Se recolectó el sobrenadante y se re-centrifugó a 20000xg durante 20 minutos para granular los sinaptosomas crudos. Los sinaptosomas se re-suspendieron en amortiguador de análisis helado: 122 mM NaCl, 3.1 mM KCl, 25 mM HEPES, 0.4 mM KH_2PO_4 , 1.2 mM MgSO_4 , 1.3 mM CaCl_2 , 10 mM dextrosa a pH 7.4. Los sinaptosomas re-suspendidos se centrifugaron nuevamente a 20000xg durante 20 minutos, y los sinaptosomas granulados se re-suspendieron en amortiguador de análisis. La concentración de proteína se midió con el kit de análisis de proteína DC (BioRad).

Se realizó análisis de transporte de prolina en 100 μ l de mezcla de reacción que consistía de 10 μ g de sinaptosomas, 1 μCi /0.24 μM [^3H]-prolina en amortiguador de análisis durante un tiempo entre 0 a 20 minutos a temperatura de la sala. La reacción se terminó mediante filtración rápida a través de una placa de filtración GF/B (Millipore), seguida por tres rápidos

lavados en amortiguador de análisis helado 200ul. Se agregaron cincuenta microlitros de Microscint-20 a cada reacción y se incubaron durante 2 horas. El transporte de $[H^3]$ -prolina se determinó mediante conteo de radioactividad.

Para determinar la inhibición del transporte de prolina por los compuestos, los compuestos se incubaron con la mezcla de reacción en concentraciones que variaban de 0 a 10 μM (11 puntos, comenzando con 10 μM ; diluciones triples; 4 réplicas se promediaron para proporcionar un punto). La actividad de comparación, o actividad no específica, se midió en la presencia de 0.3 mM GGFL (Enkephalin, Sigma) en la reacción. Se cuantificó asimismo la actividad no específica en sinaptosomas de ratones con el gen SLC6A7 inactivado. Se descubrió que las actividades no específicas medidas por los dos métodos eran idénticas.

6.21. Análisis del Transportador Humano de Dopamina

Se determinó la capacidad de los compuestos de inhibir el transportador de dopamina en la siguiente forma. Un cADN DAT humano (NM_001044) se clonó en un vector pcDNA3.1 y se transfectó en células COS-1. Las líneas de células resultantes que expresan en forma estable el transportador de dopamina se utilizaron para experimentación posterior.

Células transfectadas se sembraron a 15.000 células por pocillo en una placa de 384 pocillos y se cultivaron de un día para otro. Las células se lavaron entonces con amortiguador Krebs-Ringer's-HEPES-Tris (KRHT), pH 7.4, que contenía 125 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$ 10 mM D-glucosa, 25 mM HEPES, 1 mM de ascorbato de sodio y 1.2 mM KH_2PO_4 . En seguida las células se incubaron con 50 μl de amortiguador KRHT que contenía 1 μM 3H -dopamina durante 10 minutos a temperatura de la sala. Se terminó la absorción de dopamina radiomarcada retirando la dopamina radiomarcada y lavando las células rápidamente tres veces con 100 μl de amortiguador KRHT helado. Se agregó fluido de centelleo (50 μl) por pocillo, y se determinó la cantidad de dopamina tritiada presente usando un contador de centelleo Packard TopCount.

La absorción no específica se determinó midiendo la absorción de ^3H -dopamina en la presencia de 250 μM de benzotropina. La IC_{50} de un compuesto se determinó cuantificando la inhibición de cuatro muestras separadas en 10 concentraciones, comenzando típicamente con 10 μM , seguidas por 9 diluciones triples (*es decir*, 10, 3.3, 1.1, 0.37, 0.12, 0.41, 0.014, 0.0046, 0.0015, y 0 μM). Se calcularon las inhibiciones porcentuales contra el control, y el promedio de los cuadruplicados se utilizó para el cálculo de la IC_{50} .

6.22. Análisis de Transportador Humano de Glicina

Se determinó la capacidad de los compuestos de inhibir el transportador de glicina en la siguiente forma. Un cADN de transportador humano de glicina (NM_006934) se clonó en un vector pcDNA3.1 y se transfectó en células COS-1. Las líneas de células resultantes que expresan en forma estable el transportador de dopamina se utilizaron para experimentación posterior.

Células transfectadas se sembraron a 15.000 células por pocillo en una placa de 384 pocillos y se cultivaron de un día para otro. Las células se lavaron entonces con amortiguador Krebs-Ringer's-HEPES-Tris (KRHT) buffer, pH 7.4, que contenía 120 mM NaCl, 4.7 mM KCl, 2.2 mM CaCl_2 , 1.2 mM MgSO_4 , 1.2 mM KH_2PO_4 , 10 mM HEPES y 5 ml Tris. En seguida las células se incubaron con 50 μl de amortiguador KRHT que contenía 166 μM ^3H -glicina durante 10 minutos a temperatura de la sala. Se terminó la absorción de glicina radiomarcada retirando la glicina radiomarcada y lavando las células rápidamente tres veces con 100 μl de amortiguador KRHT helado. Se agregó fluido de centelleo (50 μl) por pocillo, y se determinó la cantidad de glicina tritiada presente usando un contador de centelleo Packard TopCount.

La absorción no específica se determinó midiendo la absorción de ^3H -glicina en la presencia de 2 μM de glicina fría. La IC_{50} de un compuesto se determinó cuantificando la inhibición de cuatro muestras separadas en 10 concentraciones, comenzando típicamente con 10 μM , seguidas por 9

diluciones triples (*es decir*, 10, 3.3, 1.1, 0.37, 0.12, 0.41, 0.014, 0.0046, 0.0015, y 0 μ M). Se calcularon las inhibiciones porcentuales contra el control, y el promedio de los cuadruplicados se utilizó para el cálculo de la IC₅₀.

6.23. Cálculo de Valores IC₅₀

La IC₅₀ de un compuesto con respecto a una diana dada se determina ajustando los datos relevantes, usando el algoritmo de Levenburg Marquardt a la ecuación:

$$y = A + ((B-A)/(1+((C/x)^D)))$$

en donde A es el valor mínimo de y; B es el valor máximo de y; C es la IC₅₀; y D es la pendiente. El cálculo de la IC₅₀ se realiza usando software XLFit4 (ID Business Solutions Inc., Bridgeagua, NJ 08807) para Microsoft Excel (la ecuación anterior es el modelo 205 de ese software).

6.24. Efectos Farmacológicos

Un compuesto con una PTIC₅₀ inferior a 100 nM se administró a ratones albinos machos C57B/6 sometidos a un programa contextual de condicionamiento al miedo usando un protocolo de condicionamiento de huella. El compuesto se administró a dosis que variaban de 50-200 mg/kg, y se descubrió que recapitulaba los fenotipos observados en los ratones KO SLC6A7 KO en una manera dependiente de la dosis.

En el protocolo, el compuesto se administró p.o., dos horas antes del adiestramiento (día 1) y de nuevo dos horas antes de los experimentos el día siguiente (día 2). Generalmente, se examinaron 10-14 ratones/grupo en cada estudio. El intervalo de pretratamiento de 2 horas se seleccionó basándose en resultados PK para lograr niveles picos en el plasma y en el tejido cerebral.

En los experimentos de condicionamiento de huella, no se observó un efecto significativo en ratones medicados con 50 mg/kg, p.o., aunque se apreció una mejoría numérica. Sin embargo, con dosis de 100 y 200 mg/kg, p.o., se observaron aumentos significativos en el desempeño tanto durante

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el adiestramiento (día 1) como durante los experimentos (día 2). Como se ilustra en Figura 2, el compuesto mejoró el desempeño durante el adiestramiento, así como durante las pruebas de memoria, indicando que sus efectos no varían con administración repetida. Y como se muestra en Figura 3, cuando se administra antes de la prueba de memoria, mas no antes del adiestramiento, el compuesto mejoró la respuesta condicionada.

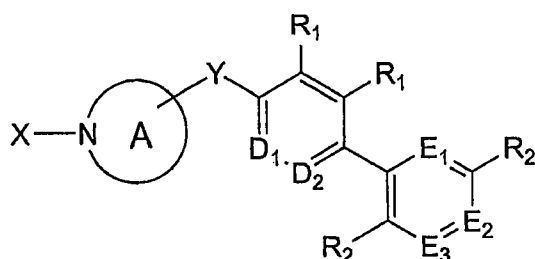
Con el fin de evaluar si el efecto del compuesto cambiaba luego de una dosificación repetida, éste se administró durante tres días b.i.d. antes del día de adiestramiento, así como b.i.d. el día del adiestramiento y antes de la prueba. Al igual que en los estudios inmediatos ("*the acute studies*"), el compuesto se administró dos horas antes de la sesión de adiestramiento y dos horas antes de la sesión de prueba. Basándose en estudios PK separados, se esperaba que este régimen de administración proporcionara niveles sanguíneos del compuesto de principio a fin del estudio. Se observaron resultados similares a los ilustrados en las Figuras 2 y 3, sugiriendo que el compuesto puede mejorar tanto el aprendizaje como la memoria/recordación.

En sí mismo, el compuesto no aumentó la inmovilización en ratones sin tratamiento previo, como se evaluó en un campo abierto en el aparato de adiestramiento de condicionamiento, ni en ratones a los que se impartió adiestramiento de condicionamiento específico y luego se pusieron en un terreno abierto novedoso ("*a novel open-field*"). Por consiguiente, sus efectos parecen ser específicos a la respuesta aprendida, y no debidos a una mejora no específica del comportamiento de inmovilización.

REIVINDICACIONES

Lo que se reivindica es:

1. Un inhibidor específico del transportador de prolina de fórmula I:



(I)

o su sal o solvato farmacéuticamente aceptables, en donde:

- A es un heterociclo no aromático, opcionalmente sustituido;
- cada uno de D₁ y D₂ es independientemente N o CR₁;
- cada uno de E₁, E₂ y E₃ es independientemente N o CR₂;
- X es heteroarilo opcionalmente sustituido;
- Y es O, C(O), CH(OH), o CH₂;
- cada R₁ es independientemente hidrógeno, halógeno, ciano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), o SO₂R_A;
- cada R₂ es independientemente hidrógeno, halógeno, ciano, R_A, OR_A, C(O)R_A, C(O)OR_A, C(O)N(R_AR_B), N(R_AR_B), o SO₂R_A;
- cada R_A es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y
- cada R_B es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos.

2. El inhibidor específico del transportador de prolina de la reivindicación 1, que tiene una PTIC₅₀ de menos de alrededor de 150 nM.

D
N

3. El inhibidor específico del transportador de prolina de la reivindicación 2, que tiene una $PTIC_{50}$ de menos de alrededor de 100 nM.
4. El inhibidor específico del transportador de prolina de la reivindicación 3, que tiene una $PTIC_{50}$ de menos de alrededor de 50 nM.
5. El inhibidor específico del transportador de prolina de la reivindicación 1, que tiene una $DTIC_{50}$ superior a alrededor de 1 μ M.
6. El inhibidor específico del transportador de prolina de la reivindicación 5, que tiene una $GTIC_{50}$ superior a alrededor de 1 μ M.
7. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde A es monocíclico.
8. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde A es bicíclico.
9. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde A es no sustituido.
10. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde A es pirrolidina, piperidina, piperazina, hexahidropirimidina, 1,2,3,6-tetrahidropiridina, octahidrociclopenta[c]pirrol, u octahidropirrol[3,4-c]pirrol opcionalmente sustituidos.
11. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde uno de D_1 y D_2 es N.
12. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde ambos D_1 y D_2 son N.

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13. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde ambos D_1 y D_2 son CR_1 .

14. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde uno de E_1 , E_2 y E_3 es N.

15. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde dos de E_1 , E_2 y E_3 son N.

16. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde todos los E_1 , E_2 y E_3 son N.

17. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde todos los E_1 , E_2 y E_3 son independientemente CR_2 .

18. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde R_1 es hidrógeno, halógeno, o alquilo opcionalmente sustituido.

19. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde R_1 es OR_A .

20. El inhibidor específico del transportador de prolina de la reivindicación 19, en donde R_A es hidrógeno o alquilo opcionalmente sustituido.

21. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde R_2 es hidrógeno, halógeno, o alquilo opcionalmente sustituido.

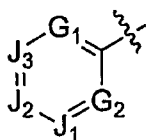
22. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde R_2 es OR_A .

23. El inhibidor específico del transportador de prolina de la reivindicación 21, en donde R_A es hidrógeno o alquilo opcionalmente sustituido.

24. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde X es un heteroarilo de 5, 6, 9 ó 10 miembros, opcionalmente sustituido.

25. El inhibidor específico del transportador de prolina de la reivindicación 24, en donde X es un heteroarilo de 5 ó 6 miembros, opcionalmente sustituido.

26. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde X es de la fórmula:



en donde:

cada uno de G_1 y G_2 son independientemente N o CR_3 ;

cada uno de J_1 , J_2 y J_3 son independientemente N o CR_4 ;

cada R_3 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ; y cada R_4 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ;

siempre que por lo menos uno de J_1 , J_2 y J_3 sea CR_4 .

27. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde uno de G_1 y G_2 es N.

28. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde ambos G_1 y G_2 son N.

29. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde ambos G_1 y G_2 son CR_3 .

30. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde uno de J_1 , J_2 y J_3 es N.

31. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde dos de J_1 , J_2 y J_3 son N.

32. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde todos los J_1 , J_2 y J_3 son independientemente CR_4 .

33. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde R_3 es hidrógeno, halógeno, o alquilo opcionalmente sustituido.

34. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde R_3 es OR_A .

35. El inhibidor específico del transportador de prolina de la reivindicación 34, en donde R_A es hidrógeno o alquilo opcionalmente sustituido.

36. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde R_4 es hidrógeno, halógeno, o alquilo opcionalmente sustituido.

37. El inhibidor específico del transportador de prolina de la reivindicación 25, en donde R_4 es OR_A .

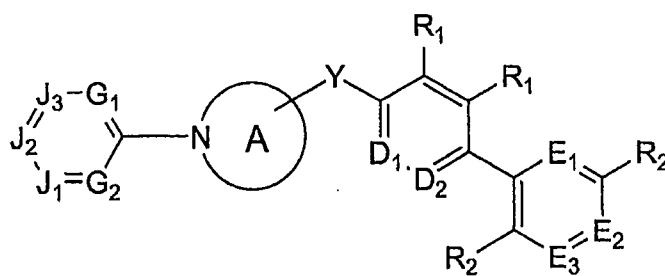
38. El inhibidor específico del transportador de prolina de la reivindicación 37, en donde R_A es hidrógeno o alquilo opcionalmente sustituido.

39. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde Y es $C(O)$.

40. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde Y es $CH(OH)$.

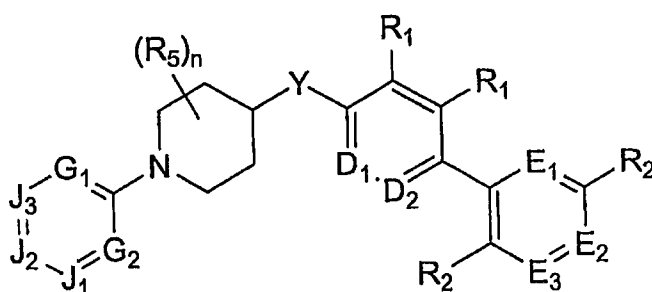
41. El inhibidor específico del transportador de prolina de la reivindicación 1, en donde Y es CH_2 .

42. El inhibidor específico del transportador de prolina de la reivindicación 25, que es de la fórmula **IA**:



(IA)

43. El inhibidor específico del transportador de prolina de la reivindicación 25, que es de la fórmula **IB**:



(IB)

en donde:

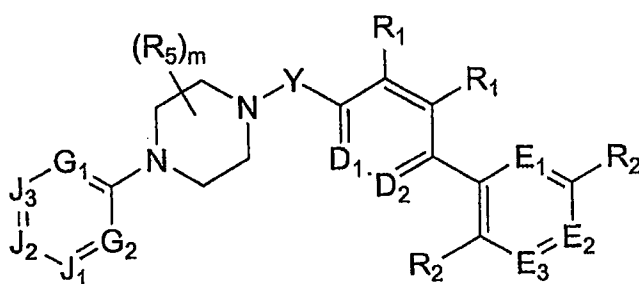
cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ;

cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos;

cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

n es 0-5.

44. El inhibidor específico del transportador de prolina de la reivindicación 25, que es de la fórmula IC:



(IC)

en donde:

Y es O , $C(O)$ o CH_2 ;

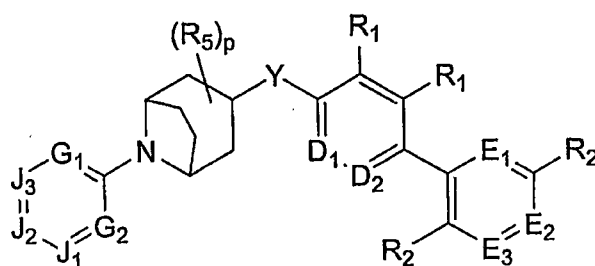
cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ;

cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos;

cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

m es 0-4.

45. El inhibidor específico del transportador de prolina de la reivindicación 25, que es de la fórmula **ID**:

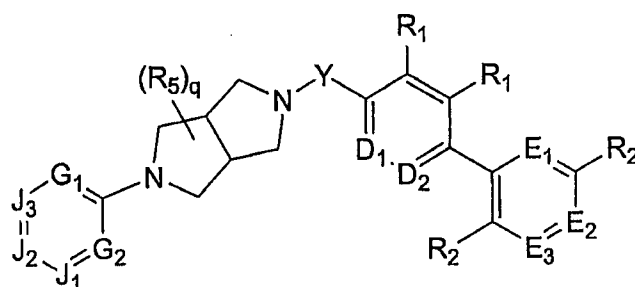


(ID)

en donde:

cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}R_{5B})$, o SO_2R_{5A} ; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y p es 0-7.

46. El inhibidor específico del transportador de prolina de la reivindicación 25, que es de la fórmula **IE**:



(IE)

en donde:

Y es O, C(O) o CH₂;

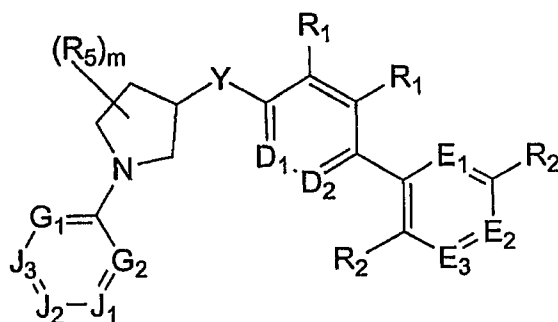
cada R₅ es independientemente halógeno, ciano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), o SO₂R_{5A};

cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos;

cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

q es 0-6.

47. El inhibidor específico del transportador de prolina de la reivindicación 25, que es de la fórmula IF:



(IF)

en donde:

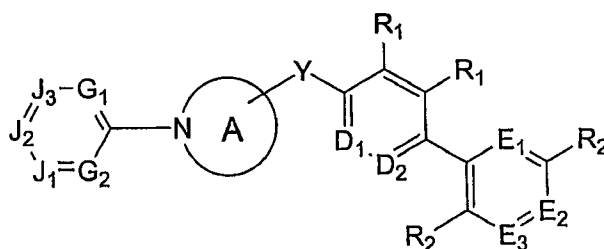
cada R₅ es independientemente halógeno, ciano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), o SO₂R_{5A}; cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente

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sustituidos; cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

m es 0-4.

48. Un compuesto de la fórmula II:



(II)

o su sal o solvato farmacéuticamente aceptables, en donde:

A es un heterociclo no aromático, opcionalmente sustituido que contiene no más de dos átomos de nitrógeno;

cada uno de D_1 y D_2 es independientemente N o CR_1 ;

cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ;

cada uno de G_1 y G_2 son independientemente N o CR_3 ;

cada uno de J_1 , J_2 y J_3 son independientemente N o CR_4 ;

Y es O, C(O), CH(OH), o CH_2 ; cada R_1 es independientemente hidrógeno, halógeno, o (C_{1-10}) alquilo;

cada R_2 es independientemente halógeno, ciano, R_2A , OR_{2A} , o SO_2R_{2A} ;

cada R_{2A} es independientemente hidrógeno o (C_{1-10}) alquilo sustituido opcionalmente con uno o más halógenos;

cada R_3 es independientemente hidrógeno, ciano, o (C_{1-10}) alquilo sustituido opcionalmente con uno o más halógenos; y

cada R_4 es independientemente hidrógeno, ciano, o (C_{1-10}) alquilo sustituido opcionalmente con uno o más halógenos;

con las condiciones que: 1) por lo menos uno de G_1 , G_2 , J_1 , J_2 ó J_3 es N; 2) por lo menos uno de J_1 , J_2 y J_3 es CR_4 ; 3) si Y es C(O), A es piperazina, todos los G_1 , G_2 , J_1 , J_3 , D_1 , D_2 , E_1 , y E_3 son CH, y todos los R_1

son hidrógeno, entonces ninguno de R_2 son alquilo inferior; 4) si Y es C(O), A es piperazina, D_2 y E_1 son ambos N, y todos los R_1 y R_2 son hidrógeno, entonces R_4 no es ciano; 5) si Y es O, A es pirrolidina, todos los G_1 , G_2 , J_1 , J_3 , D_1 , D_2 , E_1 , E_2 , y E_3 son CH, y todos los R_1 son hidrógeno, entonces por lo menos un R_2 no es hidrógeno; 6) si Y es CH_2 , A es piperazina, todos los G_2 , J_1 , J_2 , J_3 , D_1 , y D_2 son CH, todos los E_1 , E_2 y E_3 son CR_2 , y todos los R_1 son hidrógeno, por lo menos un R_2 no es hidrógeno; y 7) si Y es C(O) o CH_2 , A es piperazina, por lo menos uno de G_1 y G_2 es N, todos los J_1 , J_2 , J_3 , D_1 , D_2 , E_1 , E_2 y E_3 son CH, y todos los R_1 son hidrógeno, entonces por lo menos un R_2 no es hidrógeno.

49. El compuesto de la reivindicación 48, que tiene una $PTIC_{50}$ de menos de alrededor de 200 nM.

50. El compuesto de la reivindicación 49, que tiene una $DTIC_{50}$ superior a alrededor de 1 μ M.

51. El compuesto de la reivindicación 50, que tiene una $GTIC_{50}$ superior a alrededor de 1 μ M.

52. El compuesto de la reivindicación 48, en donde A es monocíclico.

53. El compuesto de la reivindicación 48, en donde A es bicíclico.

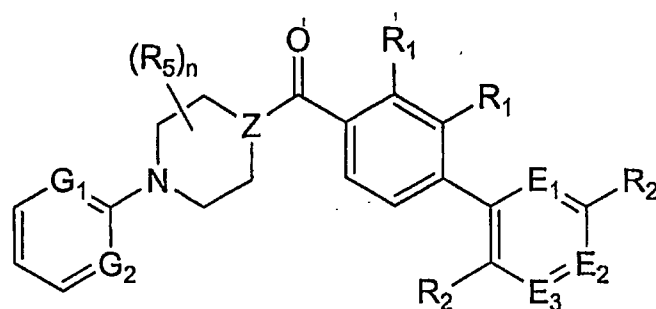
54. El compuesto de la reivindicación 48, en donde A es no sustituido.

55. El compuesto de la reivindicación 48, en donde A es pirrolidina, piperidina, piperazina, hexahidropirimidina, 1,2,3,6-tetrahidropiridina, octahidrociclopenta[c]pirrol, u octahidropirrolo[3,4-c]pirrol opcionalmente sustituidos.

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56. El compuesto de la reivindicación 48, en donde uno de D_1 y D_2 es N.
57. El compuesto de la reivindicación 48, en donde ambos D_1 y D_2 son N.
58. El compuesto de la reivindicación 48, en donde los dos D_1 y D_2 son CR_1 .
59. El compuesto de la reivindicación 48, en donde uno de E_1 , E_2 y E_3 es N.
60. El compuesto de la reivindicación 48, en donde dos de E_1 , E_2 y E_3 son N.
61. El compuesto de la reivindicación 48, en donde todos los E_1 , E_2 y E_3 son N.
62. El compuesto de la reivindicación 48, en donde todos los E_1 , E_2 y E_3 son CR_2 .
63. El compuesto de la reivindicación 48, en donde R_1 es hidrógeno.
64. El compuesto de la reivindicación 48, en donde R_2 es halógeno.
65. El compuesto de la reivindicación 48, en donde R_2 es OR_A .
66. El compuesto de la reivindicación 65, en donde R_A es hidrógeno o alquilo opcionalmente sustituido.

67. El compuesto de la reivindicación 48, en donde uno de G_1 y G_2 es N.
68. El compuesto de la reivindicación 48, en donde ambos G_1 y G_2 son N.
69. El compuesto de la reivindicación 48, en donde ambos G_1 y G_2 son CR_3 .
70. El compuesto de la reivindicación 48, en donde uno de J_1 , J_2 y J_3 es N.
71. El compuesto de la reivindicación 48, en donde dos de J_1 , J_2 y J_3 son N.
72. El compuesto de la reivindicación 48, en donde todos los J_1 , J_2 y J_3 son CR_4 .
73. El compuesto de la reivindicación 48, en donde R_3 es hidrógeno, halógeno, o alquilo opcionalmente sustituido.
74. El compuesto de la reivindicación 48, en donde R_4 es hidrógeno, halógeno, o alquilo opcionalmente sustituido.
75. El compuesto de la reivindicación 48, en donde Y es C(O).
76. El compuesto de la reivindicación 48, en donde Y es CH(OH).
77. El compuesto de la reivindicación 48, en donde Y es CH_2 .
78. El compuesto de la reivindicación 48, que es de la fórmula **IIA**:



(IIA)

en donde:

Z es CR₅ o N;

cada R₅ es independientemente halógeno, ciano, R_{5A}, OR_{5A}, C(O)R_{5A}, C(O)OR_{5A}, C(O)N(R_{5A}R_{5B}), N(R_{5A}R_{5B}), o SO₂R_{5A};

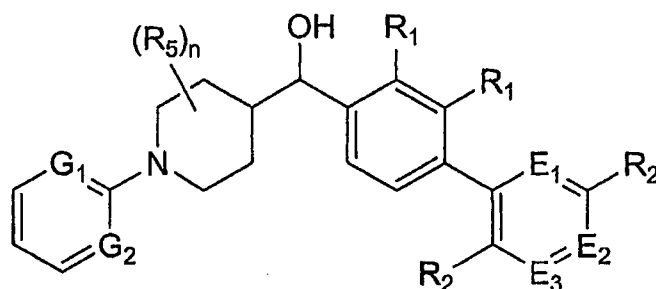
cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos;

cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

n es 0-5 si Z es CR₅, ó 0-4 si Z es N.

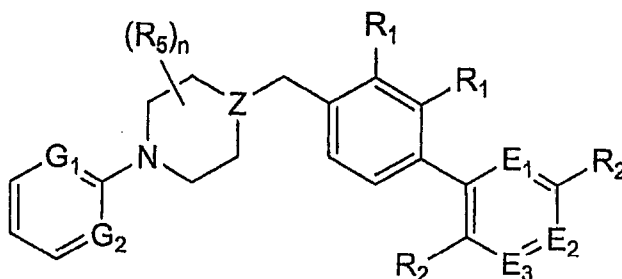
79. El compuesto de la reivindicación 78, en donde Z es CH, G₁ es N, y por lo menos un R₂ no es hidrógeno.

80. El compuesto de la reivindicación 48, que es de la fórmula **IIB**:



(IIB)

81. El compuesto de la reivindicación 48, que es de la fórmula **IIC**:



(IIC)

en donde:

Z es CR_5 ó N;

cada R_5 es independientemente halógeno, ciano, R_{5A} , OR_{5A} , $C(O)R_{5A}$, $C(O)OR_{5A}$, $C(O)N(R_{5A}R_{5B})$, $N(R_{5A}RSB)$, o SO_2R_{5A} ;

cada R_{5A} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos;

cada R_{5B} es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

n es 0-5 si Z es CR_5 , ó 0-4 si Z es N.

82. El compuesto de la reivindicación 82, en donde Z es CH, G_1 es N, y por lo menos un R_2 no es hidrógeno.

83. Un compuesto o su sal farmacéuticamente aceptable, en donde el compuesto es:

(1-(pirimidin-2-il)piperidin-4-il)(4'-(trifluorometil)bifenil-4-il) metanol;
 (4'-clorobifenil-4-il)(2,6-dimetil-4-(piridin-2-il)piperazin-1-il)metanona;
 (3'-cloro-3-metoxibifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
 (4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
 (3-fluoro-4'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
 (4'-clorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
 (2'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;

(4-(benzo[d]oxazol-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
bifenil-4-il(4-(4-(trifluorometil)pirimidin-2-il)piperazin-1-il)metanona;
(S)-(2-bencil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(6-p-tolilpiridin-3-
il)metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(6-(3-
(trifluorometil)fenil)piridin-3-il)metanona;
(6-(4-clorofenil)piridin-3-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-
2(1H)-il)metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(6-(4-
(trifluorometil)fenil)piridin-3-il)metanona;
(5-(4-clorofenil)isoxazol-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(1-(piridin-2-il)piperidin-4-il)metanona;
bifenil-4-il(4-(pirimidin-2-il)-1,4-diazepan-1-il)metanona;
(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)(4'-(trifluorometil)bifenil-4-
il)metanona;
bifenil-4-il(1-(pirimidin-2-il)azetidin-3-il)metanona;
(6-(4-cloro-3-(trifluorometil)fenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-
1-il)metanona;
(6-(4-cloro-3-metilfenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;
(4'-clorobifenil-4-il)(1-(piridin-2-il)piperidin-4-il)metanona;
(2-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3,4'-dimetilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(5-(3-clorofenil)piridin-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(5-p-tolilpiridin-2-il)metanona;
(4-(piridin-2-il)piperazin-1-il)(3'-(trifluorometil)bifenil-4-il)metanona;
(1-(pirimidin-2-il)piperidin-4-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(3-fluoro-3'-(trifluorometil)bifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;

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(4-(pirimidin-2-il)piperazin-1-il)(3'-(trifluorometoxi)bifenil-4-il)metanona;
(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(3'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)metanona;
(1-fenil-5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(4'-(trifluorometil)bifenil-4-il)metanona;
bifenil-4-il(4-(tiazol-2-il)piperazin-1-il)metanona;
(4-(4-clorofenil)ciclohexil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
4'-(4-(pirimidin-2-il)piperazin-1-carbonil)bifenil-3-carbonitrilo;
(4'-(metilsulfonil)bifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
2-(4-((3'-clorobifenil-4-il)(hidroxi)metil)piperidin-1-il)pirimidin-5-ol;
(4-(piridin-3-il)fenil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-cloro-3-hidroxibifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
1-(4'-(4-(pirimidin-2-il)piperazin-1-carbonil)bifenil-3-il)etanona;
(2',4'-difluoro-3-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(5-fenil-1H-pirrol-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(4-clorofenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(5'-cloro-2'-fluorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)metanona;
2-(4-(bifenilcarbonil)piperazin-1-il)nicotinonitrilo;
2-(4-(bifenil-4-iloxi)piperidin-1-il)pirimidina;
(2'-fluoro-5'-(trifluorometil)bifenil-4-il)(1-(pirimidin-2-il)pirrolidin-3-il)metanona;
(4-(4-metiltiofen-2-il)fenil)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(4'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(2'-fluoro-4'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(3-metil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(2'-fluoro-5'-(trifluorometil)bifenil-4-il)(4-metil-1-(pirimidin-2-il)piperidin-4-il)metanona;
bifenil-4-il(4-(5-metilpiridin-2-il)piperazin-1-il)metanona;

bifenil-4-il(2-metil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(1-(piridin-2-il)piperidin-4-il)(3'-(trifluorometil)bifenil-4-il)metanona;
(6-(3-clorofenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(6-(3-(trifluorometil)fenil)piridin-3-il)
metanona;
(4-(pirimidin-2-il)piperazin-1-il)(6-p-tolilpiridin-3-il)metanona;
(4'-cloro-3'-(trifluorometil)bifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)
metanona;
(4-(2-cloropiridin-4-il)fenil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(2',4'-difluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(2,4-difluorofenil)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3',5'-diclorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
2-(4-(bifenil-4-ilmetil)piperazin-1-il)pirimidina;
(4'-clorobifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(6-(3-clorofenil)piridin-3-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-
2(1H)-il)metanona;
(1-(piridin-2-il)piperidin-4-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(2'-fluoro-5'-(trifluorometil)bifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;
(4'-metilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(5-metilpiridin-2-il)piperazin-1-il)metanona;
1-(bifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-ona;
bifenil-4-il(1-(pirimidin-2-il)-1,2,3,6-tetrahidropiridin-4-il)metanona;
(3'-clorobifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
bifenil-4-il(1-(pirimidin-2-il)-1,2,3,6-tetrahidropiridin-4-il)metanol;
(3'-clorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(3'-(trifluorometil)bifenil-4-il)metanona;
(3'-clorobifenil-4-il)(1-(5-hidroxipirimidin-2-il)piperidin-4-il)metanona;
(4'-etilbifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(4-metilpirimidin-2-il)piperazin-1-il)metanona;
(6-(2,4-difluorofenil)piridin-3-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]
pirrol-2(1H)-il)metanona;

(4'-clorobifenil-4-il)(4-(piridin-2-il)piperazin-1-il)metanona;
(5-metil-1-(pirimidin-2-il)-1,2,3,6-tetrahidropiridin-4-il)(4'-(trifluorometil)
bifenil-4-il)metanona;
bifenil-4-il(4-(5-etilpirimidin-2-il)piperazin-1-il)metanona;
(4-(piridin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)metanona;
(4-(piridin-2-il)fenil)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(pirazin-2-il)piperazin-1-il)metanona;
(4'-metoxibifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(4-(6-metilpiridazin-3-il)piperazin-1-il)metanona;
4'-(4-(pirimidin-2-il)piperazin-1-carbonil)bifenil-4-carbonitrilo;
(2,6-dimetil-4-(piridin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
(5-feniltiofen-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(6-(5-metiltiofen-2-il)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;
bifenil-4-il(4-(piridin-4-il)piperazin-1-il)metanona;
(R)-(2-metil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
bifenil-4-il((2S,5S)-2,5-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(4-(piridin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(2'-(trifluorometil)bifenil-4-il)metanona;
(S)-(4'-clorobifenil-4-il)(2-metil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(5'-cloro-2'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(5-metiltiofen-2-il)fenil)(1-(pirimidin-2-il)piperidin-4-il)metanona;
bifenil-4-il(4-(4,6-dimetilpirimidin-2-il)piperazin-1-il)metanona;
(S)-(2-metil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-il)
metanona;
(S)-(2-bencil-4-(pirimidin-2-il)piperazin-1-il)(4'-clorobifenil-4-il)metanona;
bifenil-4-il(4-(piridazin-3-il)piperazin-1-il)metanona;
(6-(4-metiltiofen-2-il)piridin-3-il)(4-(pirimidin-2-il)piperazin-1-il)
metanona;
1-(2',4'-difluorobifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-carbonitrilo;

(4'-clorobifenil-4-il)((2S,5S)-2,5-dimetil-4-(pirimidin-2-il)piperazin-1-il)
metanona;
bifenil-4-il(2-tert-butil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(S)-bifenil-4-il(2-isopropil-4-(pirimidin-2-il)piperazin-1-il)metanona;
bifenil-4-il(2,6-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-cloro-2'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(4-(pirimidin-2-il)piperazin-1-il)(6-(4-(trifluorometil)fenil)piridin-3-il)
metanona;
(4'-cloro-3'-metilbifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanona;
(3'-cloro-2'-fluorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(2,6-dimetil-4-(piridin-2-il)piperazin-1-il)(4'-metilbifenil-4-il)metanona;
3'-cloro-4-(1-(pirimidin-2-il)piperidine-4-carbonil)bifenil-3-il acetato;
bifenil-4-il(2-metil-4-(piridin-2-il)piperazin-1-il)metanona;
1-(bifenil-4-ilmetil)-4-(pirimidin-2-il)piperazin-2-ona;
(3',4'-diclorobifenil-4-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)
metanol;
(S)-bifenil-4-il(2-isobutil-4-(pirimidin-2-il)piperazin-1-il)metanona;
(3'-clorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)
metanona;
(S)-(4'-clorobifenil-4-il)(2-isopropil-4-(pirimidin-2-il)piperazin-1-il)
metanona;
(4'-metilbifenil-4-il)(4-(piridin-2-il)piperazin-1-il)metanona;
(S)-(2-isopropil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-
il)metanona;
(3'-clorobifenil-4-il)(1-(pirimidin-2-il)piperidin-4-il)metanol;
(S)-(2-isobutil-4-(pirimidin-2-il)piperazin-1-il)(4'-(trifluorometil)bifenil-4-
il)metanona;
(S)-(4'-clorobifenil-4-il)(2-isobutil-4-(pirimidin-2-il)piperazin-1-il)
metanona;
(3'-clorobifenil-4-il)(1-(pirimidin-2-il)pirrolidin-3-il)metanona;

(2',4'-difluorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il) metanona;

4'-(4-(piridin-2-il)piperazin-1-carbonil)bifenil-4-carbonitrilo;

(4-(pirimidin-2-il)-1,4-diazepan-1-il)(3'-(trifluorometil)bifenil-4-il) metanona;

metil 1-(5'-cloro-2'-fluorobifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-carboxilato;

(4-(benzo[d]oxazol-2-il)piperazin-1-il)(4'-clorobifenil-4-il)metanona;

(3'-clorobifenil-4-il)(4-(tiazol-2-il)piperazin-1-il)metanona;

(4-(5-clorotiofen-2-il)fenil)(1-(pirimidin-2-il)piperidin-4-il)metanona;

1-(5'-cloro-2'-fluorobifenilcarbonil)-4-(pirimidin-2-il)piperazin-2-carbonitrilo;

(4-feniltiofen-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;

bifenil-4-il(4-(pirimidin-2-il)-3,4-dihidroquinoxalin-1(2H)-il)metanona;

(5'-cloro-2'-fluorobifenil-4-il)(8-(pirimidin-2-il)-8-azabicciclo[3.2.1]octan-3-il)metanol;

(5-fenilfuran-2-il)(4-(pirimidin-2-il)piperazin-1-il)metanona;

(4'-clorobifenil-4-il)(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)metanona;

4-(4'-clorobifenil-4-il)-1-(pirimidin-2-il)piperidin-4-ol;

(5-(pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)(4'-(trifluorometil)bifenil-4-il)metanona;

bifenil-4-il(5-(piridin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)metanona;

(3'-clorobifenil-4-il)(5-pirimidin-2-il)hexahidropirrolo[3,4-c]pirrol-2(1H)-il)metanona;

bifenil-4-il((2S,5S)-2,5-dimetil-4-(pirimidin-2-il)piperazin-1-il)metanona;

1-((3'-clorobifenil-4-il)metil)-N,N-dimetil-4-(pirimidin-2-il)piperazin-2-carboxamida;

(2',4'-difluorobifenil-4-il)(3-metil-1-(pirimidin-2-il)piperidin-4-il)metanona;

(4-(benzo[d]tiazol-2-il)piperazin-1-il)(bifenil-4-il)metanona;

bifenil-4-il(4-(quinolin-2-il)piperazin-1-il)metanona;

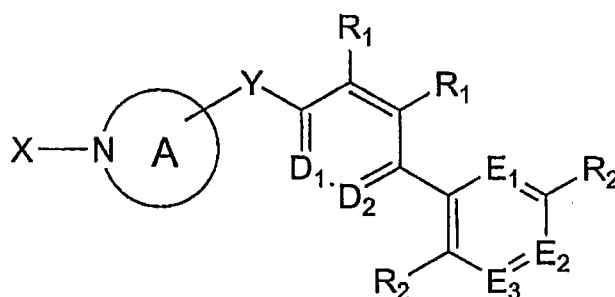
4-(bifenil-4-il)-1-(pirimidin-2-il)piperidin-4-ol;

4'-cloro-N-metil-N-(2-(metil(pirimidin-2-il)amino)etil)bifenil-4-carboxamida; o
2-(bifenil-4-il)-1-(4-(pirimidin-2-il)piperazin-1-il)etanona.

84. Una composición farmacéutica que comprende un compuesto de la reivindicación 1 ó 48 y un excipiente farmacéuticamente aceptable.

85. Una forma farmacéutica unitaria única que comprende la composición farmacéutica de la reivindicación 84.

86. Un método de inhibir un transportador de prolina, que comprende poner en contacto un transportador de prolina con una cantidad suficiente de un compuesto de la fórmula I:



(I)

o su sal o solvato farmacéuticamente aceptables, en donde:

A es un heterociclo no aromático, opcionalmente sustituido;

cada uno de D_1 y D_2 es independientemente N o CR_1 ;

cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ;

X es heteroarilo opcionalmente sustituido;

Y es O, C(O), CH(OH), o CH_2 ;

cada R_1 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ;

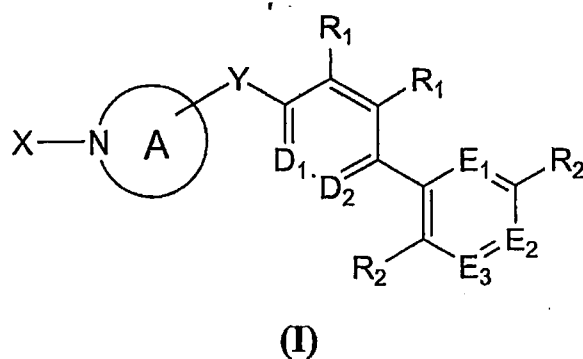
cada R_2 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ;

cada R_A es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

cada R_B es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos.

87. El método de la reivindicación 86, en donde el transportador de prolina es codificado por el gen humano SLC6A7.

88. Un método de mejorar el desempeño cognitivo de un paciente humano, que comprende administrar al paciente una cantidad efectiva de un compuesto de la fórmula I:



o su sal o solvato farmacéuticamente aceptables, en donde:

A es un heterociclo no aromático, opcionalmente sustituido;

cada uno de D_1 y D_2 es independientemente N o CR_1 ;

cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ;

X es heteroarilo opcionalmente sustituido;

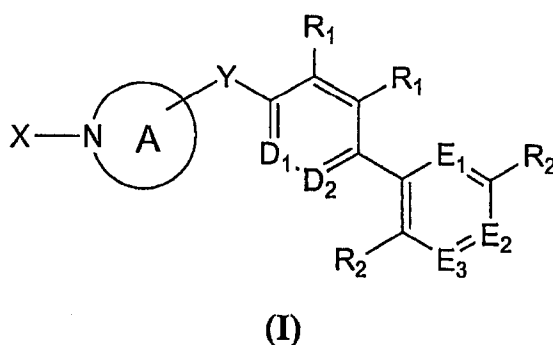
Y es O, C(O), CH(OH), o CH_2 ;

cada R_1 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ; cada R_2 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ; cada R_A es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente

sustituidos; y cada R_B es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos.

89. El método de la reivindicación 88, en donde el desempeño cognitivo es rapidez de aprendizaje, comprensión, razonamiento, o memoria.

90. Un método de tratar, controlar o prevenir una enfermedad o trastorno en un paciente humano, método que comprende administrar al paciente una cantidad efectiva de un compuesto de la fórmula I:



o su sal o solvato farmacéuticamente aceptables, en donde:

A es un heterociclo no aromático, opcionalmente sustituido;

cada uno de D_1 y D_2 es independientemente N o CR_1 ;

cada uno de E_1 , E_2 y E_3 es independientemente N o CR_2 ;

X es heteroarilo opcionalmente sustituido;

Y es O, C(O), CH(OH), o CH_2 ;

cada R_1 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ;

cada R_2 es independientemente hidrógeno, halógeno, ciano, R_A , OR_A , $C(O)R_A$, $C(O)OR_A$, $C(O)N(R_AR_B)$, $N(R_AR_B)$, o SO_2R_A ;

cada R_A es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos; y

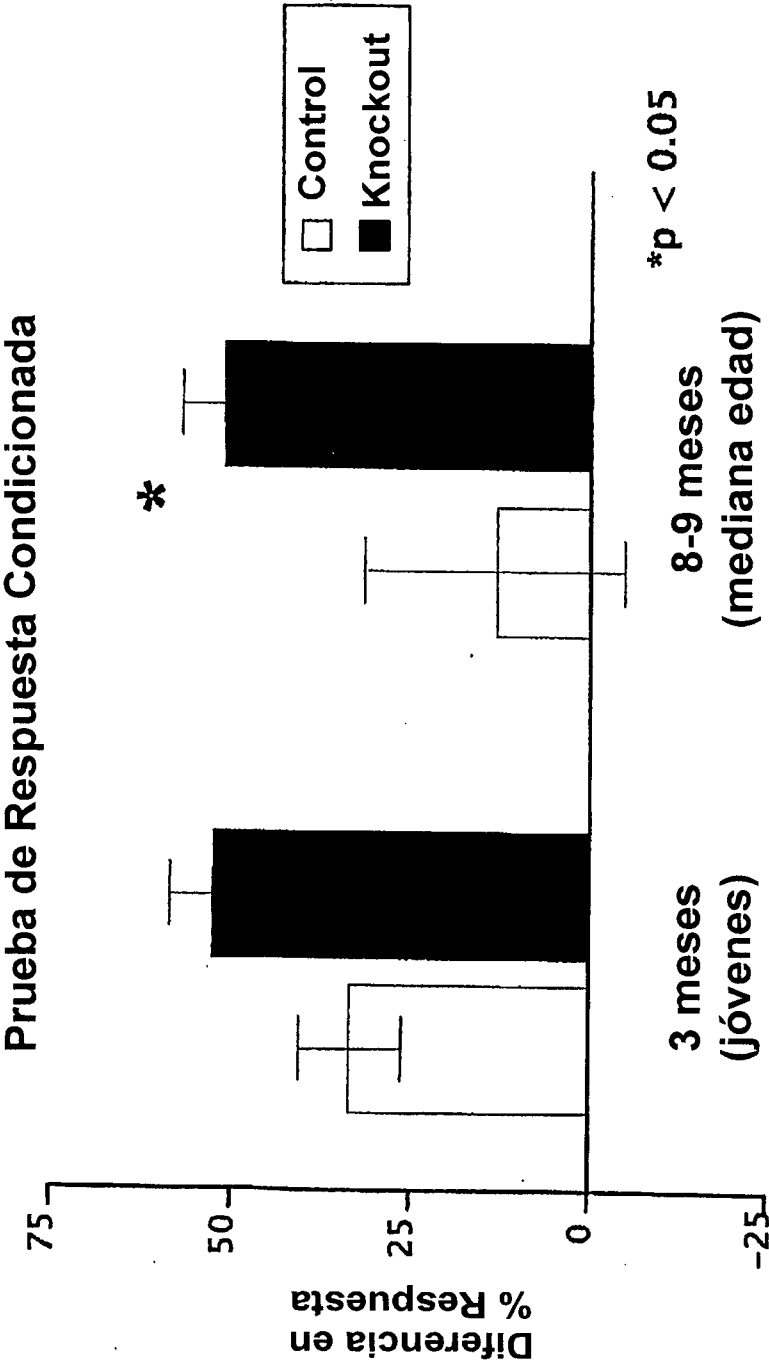
cada R_B es independientemente hidrógeno o alquilo, arilo, arilalquilo, alquilarilo, heterociclo, heterociclo-alquilo, o alquil-heterociclo opcionalmente sustituidos.

91. El método de la reivindicación 90, en donde la enfermedad o trastorno es enfermedad de Alzheimer, autismo, un trastorno cognitivo, demencia, un trastorno de aprendizaje, o pérdida de la memoria.

92. El método de la reivindicación 91, en donde el trastorno de aprendizaje es dislexia, acalculia, disgrafía, disfasia, o disnomia.

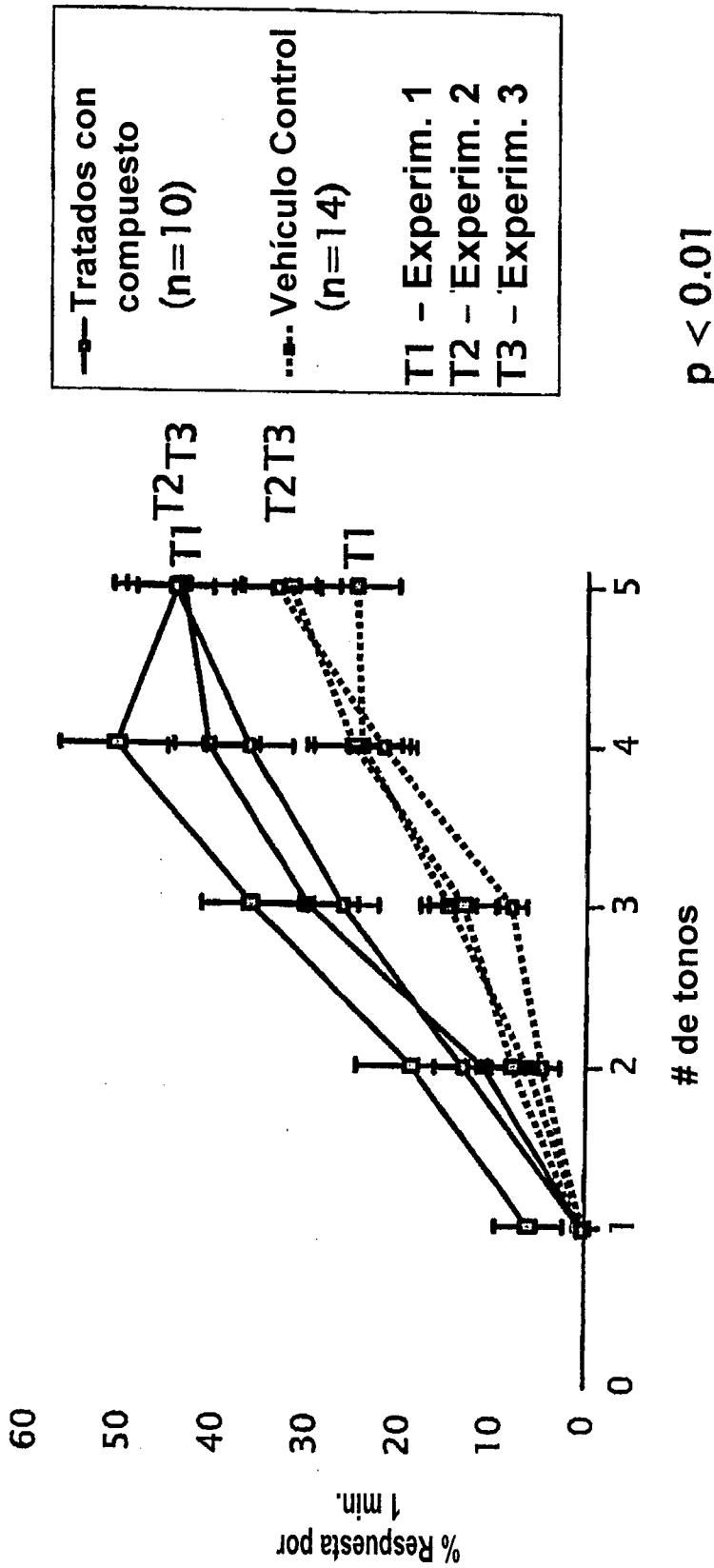
174

Figura 1



175

Figura 2
Fase de Aprendizaje de la Prueba de Respuesta Condicionada en Ratones

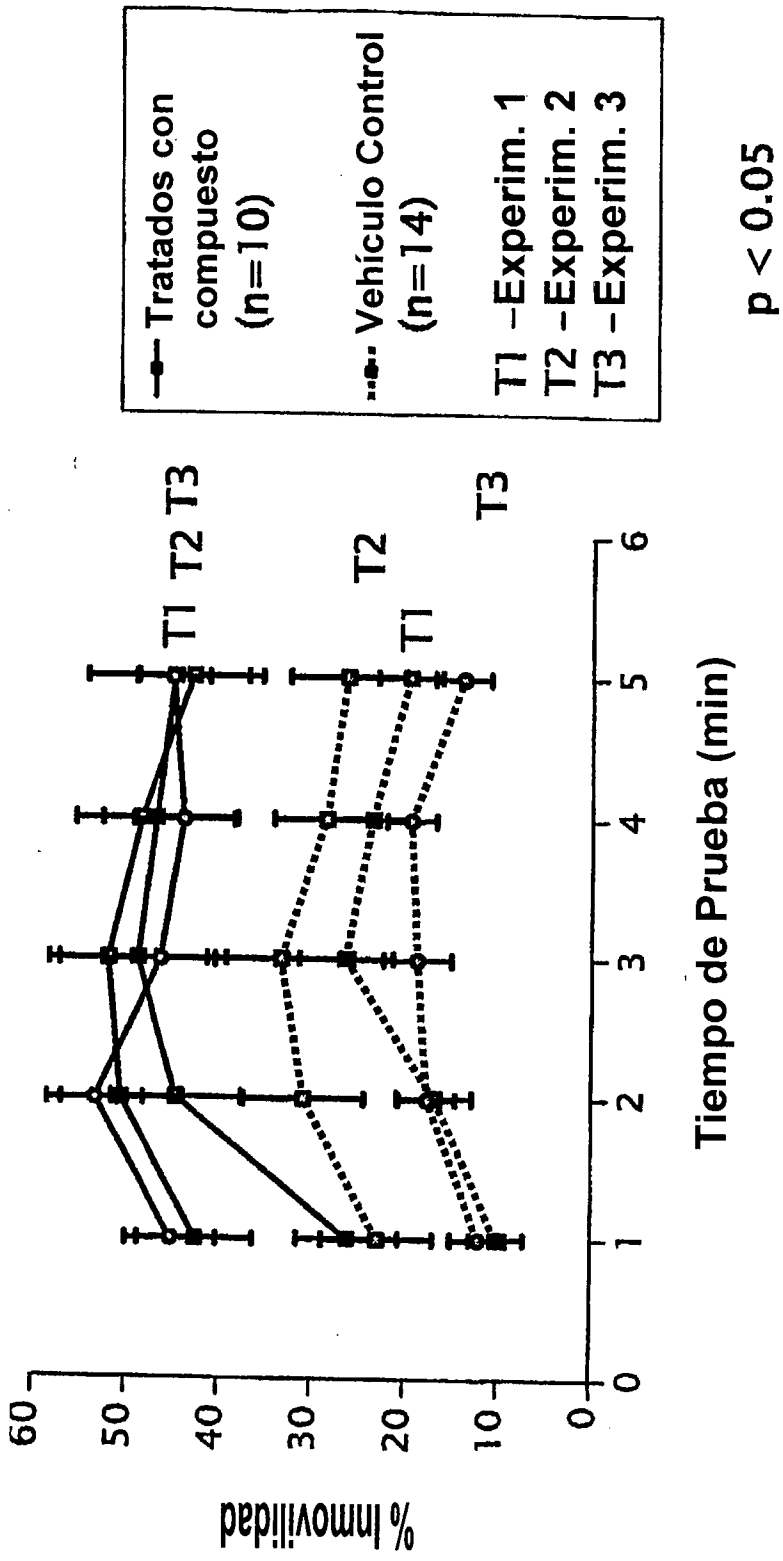


176

Figura 3

Prueba de Contexto – Tratamiento con Compuesto dos

Horas antes de la Prueba



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 November 2006 (23.11.2006)

PCT

(10) International Publication Number
WO 2006/124748 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2006/018682

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(26) Publication Language: English

(30) Priority Data:
60/680,501 13 May 2005 (13.05.2005) US

(71) Applicant (for all designated States except US): LEX-
ICON GENETICS INCORPORATED [US/US]; 8800
Technology Forest Place, The Woodlands, Texas 77381
(US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BARBOSA, Joseph
[US/US]; 2 Big Top Drive, Lambertville, NJ 08530 (US).
DONG, Li [CN/US]; 11 Pagoda Court, Lawrenceville, NJ
08648 (US). FINK, Cynthia Ann [US/US]; 1 Kensington
Court, Lebanon, NJ 08833 (US). WANG, Jiancheng
[CN/US]; 5707 Fox Run Drive, Plainsboro, NJ 08536
(US). ZIPP, G. Gregory [US/US]; 31 Kettering Court,
Robbinsville, NJ 08691 (US).

(74) Agents: ISHIMOTO, Lance K. et al.; LEXICON GE-
NETICS INCORPORATED, 8800 Technology Forest
Place, The Woodlands, Texas 77381 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,
SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

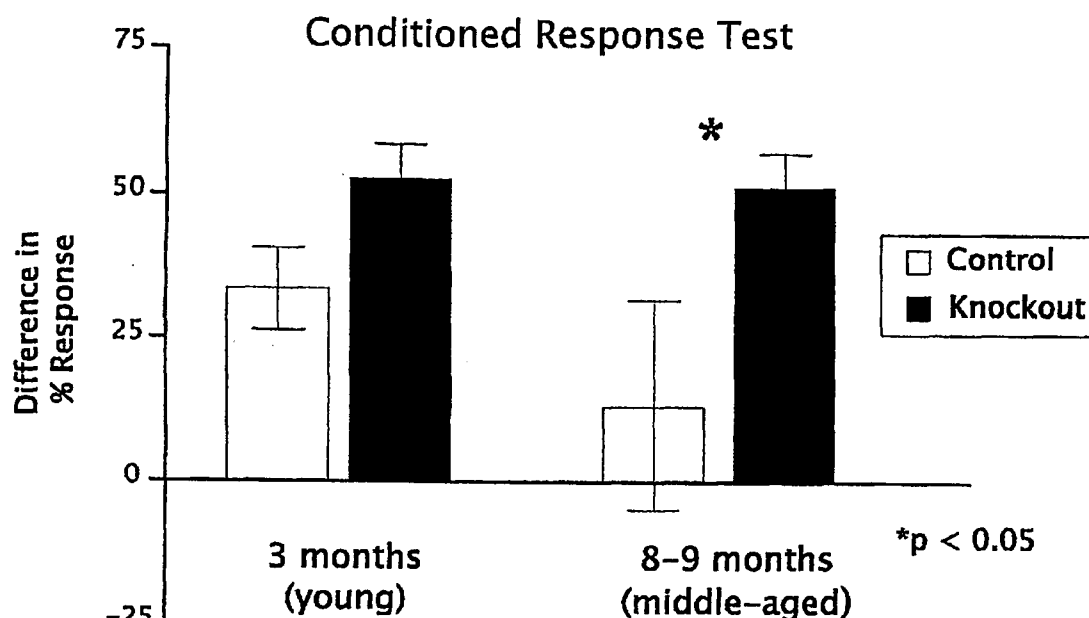
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

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

(54) Title: MULTICYCLIC COMPOUNDS AND METHODS OF THEIR USE



(57) Abstract: This invention relates to multicyclic compounds, pharmaceutical compositions comprising them, and methods of their use in, for example, the treatment of cognitive disorders.

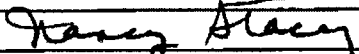
171

I. Certification under 37 CFR 1.10 (if applicable)

EV 220679790 US
Express Mail mailing number

August 1, 2006
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail to Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents,


Signature of person mailing correspondence

Nancy Stacey
Typed or printed name of person mailing correspondence

II. () New International Application

TITLE	Multicyclic Compounds and Methods of Their Use
-------	--

Earliest priority date (Day/Month/Year)
13 May 2005

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied: (Note: check as many boxes as apply):

- A. () The invention disclosed was **not** made in the United States.
- B. () There is no prior U.S. application relating to this invention.
- C. () The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)

application no.		filed on	
application no.		filed on	

- D. () The present international application (X) contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C above. The additional subject matter is found on pages (throughout the application) and (X) **DOES NOT ALTER** () **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. () A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed:

- A. () A Request for An Extension of Time to File a Response
- B. () A Power of Attorney (General or Regular) - copy general
- C. (X) Replacement pages:

pages		of the request (PCT/RO/101)	pages	1/3, 2/3, 3/3	of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. () Submission of Priority Documents

Priority document		Priority document	
-------------------	--	-------------------	--

- E. () Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. () A Request for Rectification under PCT Rule 91 () A petition () A Sequence Listing Diskette

V. (X) Other (please identify): return postcard; Amendment under PCT Article 34

The person
signing
this
form is the:

() Applicant	Max Bachrach
(X) Attorney/Agent (Reg. No.) 45,479	Typed name of signer
() Common Representative	
	Signature

PATENT COOPERATION TREATY

Application of: LEXICON GENETICS INCORPORATED

Application No.: PCT/US2006/018682

Authorized Officer: S. Barnes

Filed: May 12, 2006

Attorney Docket No.: LEX-0716-PCT

For: Multicyclic Compounds and Methods of
Their Use

AMENDMENT UNDER PCT ARTICLE 34

Mail Stop PCT
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant respectfully requests that the drawings of the above-identified international application be replaced with the enclosed substitute drawings. Unlike the originally submitted drawings, the enclosed drawings are consecutively numbered. No new matter has been added.

If any fees are due for the entry of this paper or to avoid abandonment of this application, please charge such fees to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Respectfully submitted,

Date: August 1, 2006


Max Bachrach 45,479
(Reg. No.)
Lexicon Genetics Incorporated
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3000

Customer Number 24231

Enclosures

LEX-0716-PCT

Figure 1

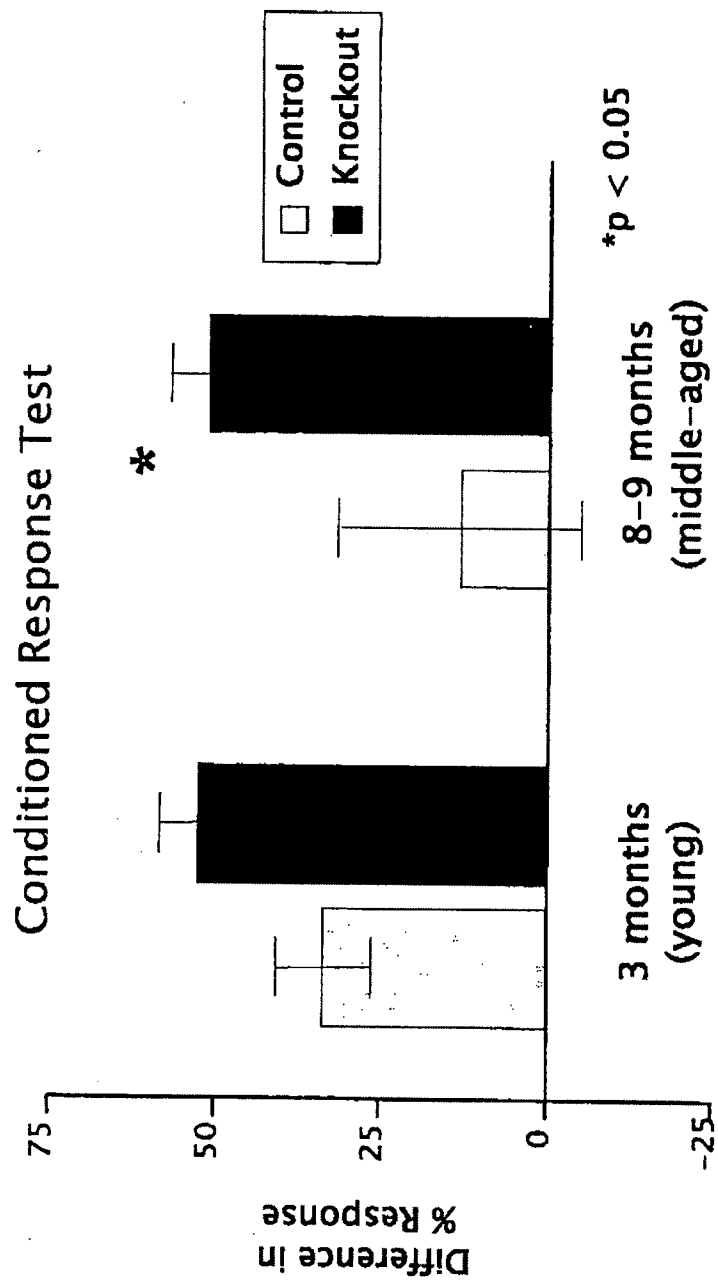


Figure 2

Learning Phase of Conditioned Response Test in Mice

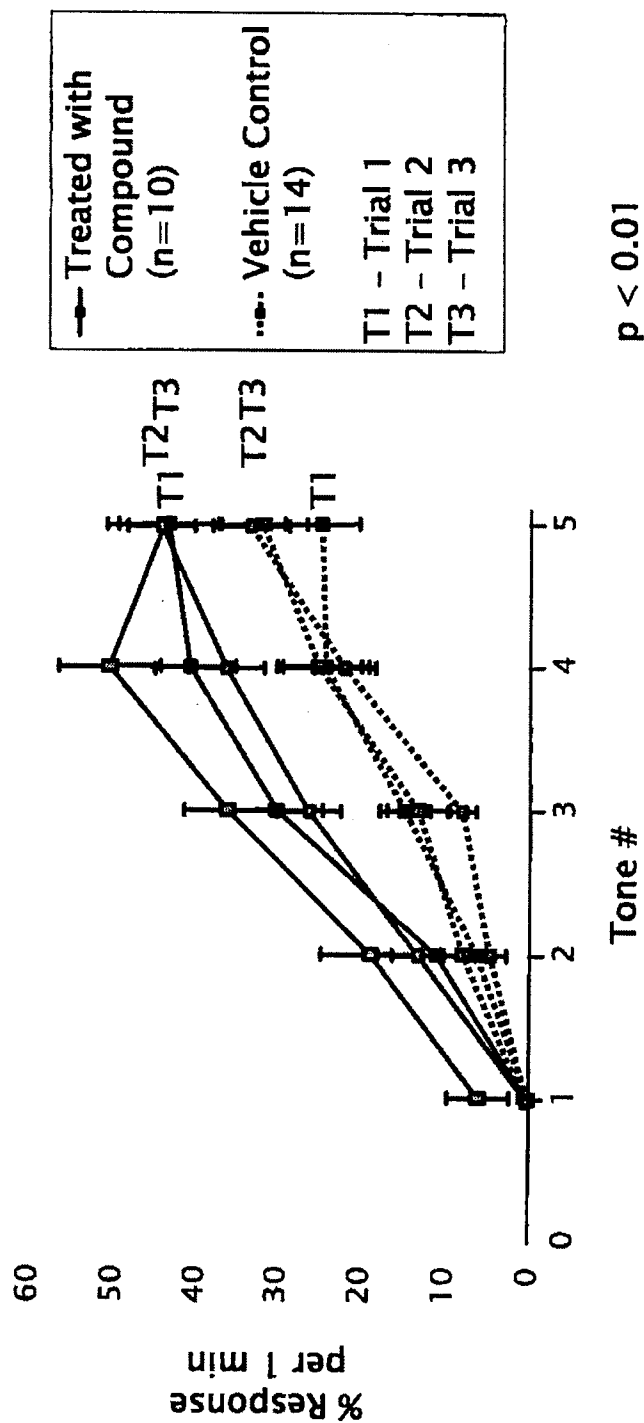
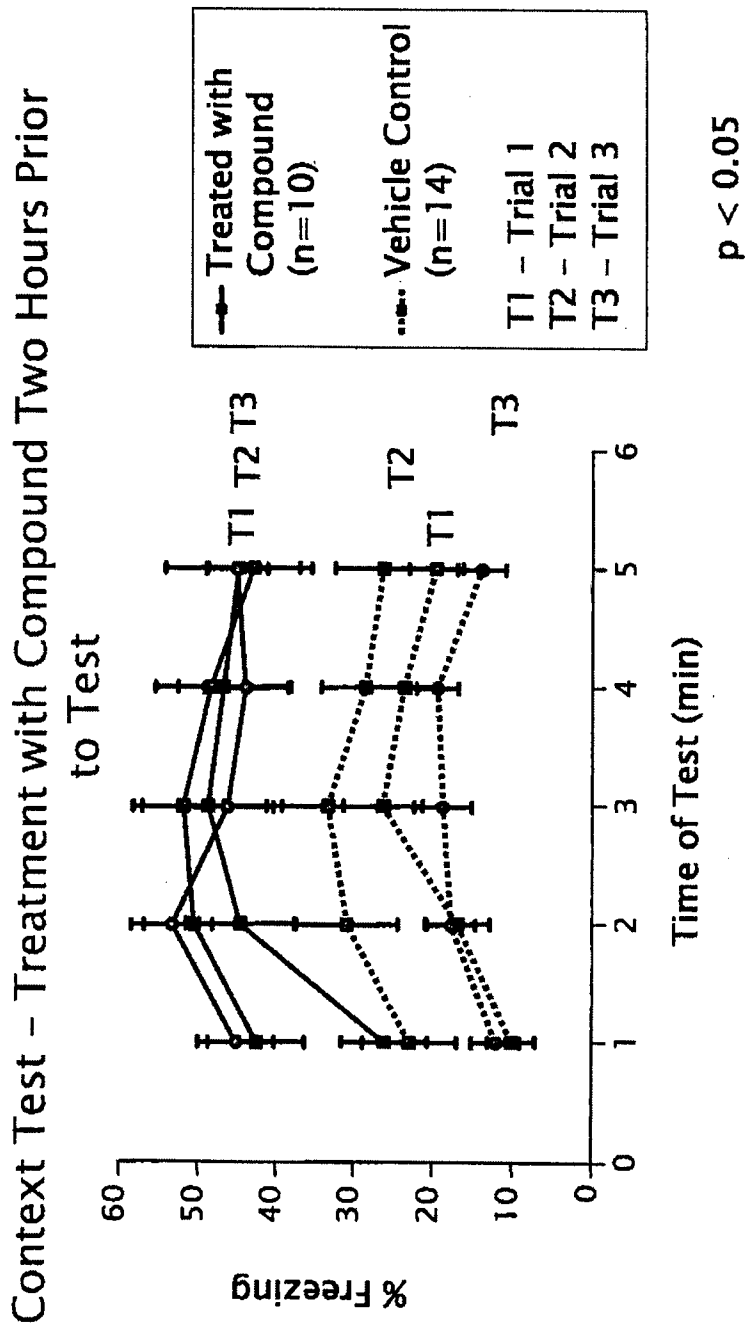


Figure 3



From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

ISHIMOTO, Lance K.
LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, Texas 77381
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
22 September 2006 (22.09.2006)

Applicant's or agent's file reference
LEX-0716-PCT

International application No.
PCT/US2006/018682

IMPORTANT NOTIFICATION

International filing date (day/month/year)
12 May 2006 (12.05.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address SCHMIDT, James M. 2026 Copperwood Park Lane Spring, TX 77386	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

The applicant and inventor identified in Box 1 should be deleted from the records

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Laskowski Marek
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 71 30
	Telephone No. +41 22 338 81 52

TRANSMITTAL LETTER TO THE
UNITED STATES RECEIVING OFFICE

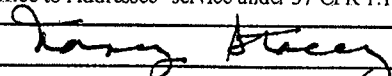
Date	August 23, 2006
International Application	PCT/US2006/018682
Attorney Docket No.	LEX-0716-PCT

I. Certification under 37 CFR 1.10 (if applicable)

EV 766804767 US
Express Mail mailing number

August 23, 2006
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail to Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents,


Signature of person mailing correspondence

Nancy Stacey
Typed or printed name of person mailing correspondence

II. () New International Application

TITLE	MULTICYCLIC COMPOUNDS AND METHODS OF THEIR USE
-------	--

Earliest priority date (Day/Month/Year)
13/05/2005

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied: (Note: check as many boxes as apply):

- A. () The invention disclosed was not made in the United States.
- B. () There is no prior U.S. application relating to this invention.
- C. () The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)

application no.		filed on	
application no.		filed on	

- D. () The present international application () contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C above. The additional subject matter is found on pages (throughout the application) and () **DOES NOT ALTER () MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. () A Response to an Invitation from the RO/US. The following document(s) is(are) enclosed:

- A. () A Request for An Extension of Time to File a Response
- B. () A Power of Attorney (General or Regular) - copy general
- C. () Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. () Submission of Priority Documents

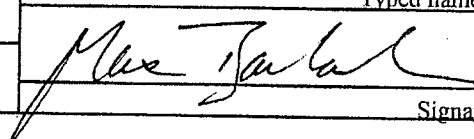
Priority document		Priority document	
-------------------	--	-------------------	--

- E. () Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. () A Request for Rectification under PCT Rule 91 () A petition () A Sequence Listing Diskette

- V. (X) Other (please identify): Amendment Under PCT Rule 92bis, General Power of Attorney (Schmidt); return postcard

The person
signing
this
form is the:

() Applicant	Max Bachrach
(X) Attorney/Agent (Reg. No.) 45,479	Typed name of signer
() Common Representative	
	Signature

PATENT COOPERATION TREATY

Application of: LEXICON GENETICS INCORPORATED

Application No.: PCT/US2006/018682

Attorney Docket No.: LEX-0716-PCT

Filed: May 12, 2006

For: Multicyclic Compounds and Methods of
Their Use

AMENDMENT UNDER PCT RULE 92bis

Mail Stop PCT
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

The list of inventors (identified as applicants and inventors for the U.S. only) submitted in the PCT Request for the above-identified international application incorrectly identified James M. Schmidt as an inventor (applicant/inventor in the U.S. only). James M. Schmidt is not an inventor of the invention(s) described and claimed in the application.

Please remove James M. Schmidt from the applicants/inventors identified in the above-identified international application. A copy of a General Power of Attorney executed by Mr. Schmidt is attached.

Respectfully submitted,

Date: August 23, 2006

 45,479
Max Bachrach (Reg. No.)
Lexicon Genetics Incorporated
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3000

Customer Number 24231

Attachment

LEX-0716-PCT

181

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s) :

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

James M. Schmidt
2026 Cooperwood Park Lane
Spring, TX 77386

hereby appoint(s) the following person 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.)

ISHIMOTO, Lance K. (Reg. No. 41,866);
BACHRACH, Max (Reg. No. 45,479);
SEFERIAN, Peter G. (Reg. No. 40,162); and
HIBLER, David W. (Reg. No. 41,071)

all of whom have the same address: LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, Texas 77381
United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

United States Patent and Trademark Office

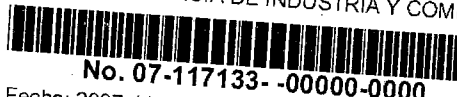
and to make or receive payments on behalf of the undersigned. _____ as receiving Office

Signature(s) (where there are several persons, each of them must sign; 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 this power):

Date:

18 August 2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-117133-00000-0000

Fecha: 2007-11-06 16:36:17 Dep. 2020 NUECREACIONE
Tra. 11. PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 186



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS

PCT

ISION A TRAMITE

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 ☐

Chudia M. Nova 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