

Doctor

José Luis Salazar

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SUPERINTENDENCIA DE INDUSTRIA

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-131169-00008-0000

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Solicitud de Patente de Invención titulada: "Compuestos de quinuclidina como ligandos del receptor nicotínico de acetilcolina ALFA-7"

Solicitante: Bristol-Myers Squibb Company

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 442
DEL 23 DE OCTUBRE DE 2012, OFICIO NO. 18634 (EXAMEN DE FONDO)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término de prórroga solicitado en mi memorial 10-131169-00007-0000 de fecha 18 de enero de 2013:

1. Objeciones del Examinador**1.1 Nivel Inventivo**

Su Despacho establece que los documentos D1¹ (ES2137926) y D2² (Curr. Med. Chem.-Central Nervous System Agents, 2005, 5, 171-184) afectan el nivel inventivo de las reivindicaciones 1 a 12 de la presente solicitud de patente.

¹ Compuestos espiro heterocíclicos puenteados y no puenteados

² $\alpha 7$ Nicotinic Receptor Agonists as Potential Therapeutic Drugs for Schizophrenia

En forma resumida, el examinador establece que:

"... una persona del oficio normalmente versada en la materia, estaría motivada o tendría suficientemente expectativa de éxito modificar el sustituyente en la posición 2 del anillo espiro (1,3-oxazolin-5,3")quinuclidina de los compuestos del documento D1 para obtener nuevos agonistas en $\alpha 7$ nAChR alternativos empleando el grupo 2-amino-oxazolin-5,3' como grupo espaciador e introduciendo un anillo arilo o heteroarilo para así obtener agonista en $\alpha 7$ nAChR como lo sugiere el documento D2 para así llegar al objeto de la reivindicación 1. Por lo cual, la reivindicación 1 se considera obvia.

Puesto que las reivindicaciones dependientes 2-12 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas".

2. Argumentos a favor de la patentabilidad de la solicitud

2.1 Novedad

Su Despacho reconoce la novedad de la presente invención. Por lo tanto, el requisito a sustentar es el nivel inventivo.

2.2 Nivel inventivo

El nivel inventivo de una solicitud se encuentra definido en el Artículo 18 de la Decisión 486 y se establece cuando *"si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*.

Contrario a lo que plantea el Examinador, el documento del arte previo citado no afecta el nivel inventivo de la presente solicitud por cuanto no es posible derivar la presente invención a partir de las enseñanzas presentadas en los documentos D1 (ES 2137926) y D2 (Curr. Med. Chem.-Central Nervous System Agents, 2005, 5, 171-184).

El documento D1 revela compuestos con actividad biológica para los receptores muscarínicos y no para los receptores ácido nicotínico $\alpha 7$. D1 no sugiere adicionar grupos

aromáticos a la parte 2-amino del anillo oxazolina y cualquier sugerencia conduciría a otros compuestos con actividad muscarínica.

El documento D2 es una publicación que discute compuestos de quinuclidina con actividad en ácido nicotínico α 7. Aunque se revela la oxazolinona AR-R17779, el documento no sugiere la conversión de la oxazolinona a la parte o fracción de 2-aminooxazolina o cualquier otra parte o fracción similar.

Por el contrario, dicha publicación sugiere que el anillo de oxazolinona no es necesario y que la fracción de quinuclidina por sí sola pueda tener cualquier espaciador incluyendo espaciadores acíclicos o lineales a la porción aromática. El trabajo propio de los autores conduce a tales espaciadores acíclicos. Por lo tanto, el documento D2 no le sugiere a la persona medianamente experta en la técnica, la conversión de oxazolinona en 2-aminooxazolina.

Teniendo en cuenta que el documento D1 se relaciona con compuestos con actividad muscarínica, no hay sugerencia que condujera a la persona del oficio normalmente versada en la materia buscar por sustituciones moleculares para aplicar las enseñanzas del documento D2 que conduzca a los compuestos selectivos de α 7. Así mismo, la persona del oficio normalmente versada en la materia técnica de la lectura del documento D2 no le sugiere el emplear la fracción 2-aminooxazolina del documento D1 como un espaciador ya que el cambio remueve la actividad del ácido nicotínico α 7 y promueve la actividad muscarínica.

De lo anteriormente expuesto, es claro que los inventores de la solicitud en estudio no han hecho compuestos de ninguno de los compuestos revelados en D1 y D2, y por lo tanto, a partir de dichos documentos no se sugiere ni se enseña de manera obvia a una persona del oficio normalmente versada en la materia técnica los compuestos de quinuclidina como ligandos del receptor nicotínico de acetilcolina alfa-7 reclamados por la presente invención.

Su Despacho podrá notar que el examen preliminar internacional es favorable para para la presente invención, es decir, la oficina de patentes europea encargada de la búsqueda internacional encontró que la presente solicitud es novedosa inventiva y tiene aplicación

industrial. Así mismo, como se menciona adelante las oficinas estadounidense y mexicana de patentes han otorgado patente a la presente invención.

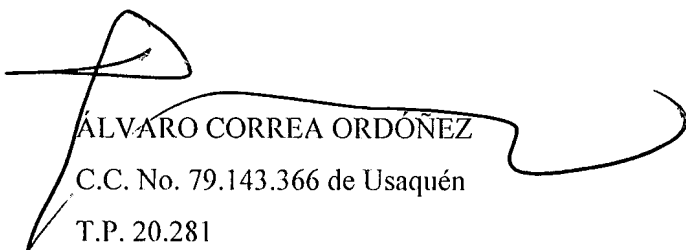
En este orden de ideas, tenemos que la invención propuesta por el solicitante no solamente es novedosa como ya lo ha reconocido su Despacho sino que también tiene altura inventiva y de esta manera es susceptible de ostentar el título de patente de invención.

3. Solicitudes concedidas en otros países para esta misma invención.

A manera informativa, pongo en conocimiento del Examinador que las patentes US 7,863,291 y MX 295935 equivalentes a la presente solicitud colombiana han sido otorgadas. Aún cuando entiendo que estas decisiones de ninguna manera obligan al Despacho para decidir de igual forma, considero que por tratarse de una pregunta fáctica la determinación de la existencia de novedad, nivel inventivo y aplicación industrial, las decisiones de otras oficinas de patentes constituyen un antecedente persuasivo en la materia.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos: - Copia de la Patente US 7,863,291.
 - Copia del Examen Preliminar Internacional



US007863291B2

(12) **United States Patent**
Cook, II et al.

(10) Patent No.: **US 7,863,291 B2**
(45) Date of Patent: **Jan. 4, 2011**

(54) **QUINUCLIDINE COMPOUNDS AS ALPHA-7
NICOTINIC ACETYLCHOLINE RECEPTOR
LIGANDS**

2007/0004715 A1 1/2007 Huang et al.

FOREIGN PATENT DOCUMENTS

EP	0 337 547	10/1989
EP	0 452 101	10/1991
WO	WO 96/06098	2/1996
WO	WO 03/092580	11/2003
WO	WO 2005/005435	1/2005
WO	WO 2006/065209	6/2006
WO	WO 2008/000469	1/2008

OTHER PUBLICATIONS

Swain, C.J. et al., "Novel 5-HT₃ Antagonists: Indol-3-ylspiro(azabicycloalkane-3,5'(4'H)-oxazoles)", *Journal of Medicinal Chemistry*, vol. 35, No. 6, pp. 1019-1031 (1992).
Tatsumi, R. et al., "(R)-3'-(3-Methylbenzo[b]thiophen-5-yl)spiro[1-azabicyclo[2,2,2]octane-3,5'-oxazolidin]-2'-one, a Novel and Potent $\alpha 7$ Nicotinic Acetylcholine Receptor Partial Agonist Displays Cognitive Enhancing Properties", *Journal of Medicinal Chemistry*, vol. 49, No. 14, pp. 4374-4383 (2006).

Primary Examiner—James O Wilson

Assistant Examiner—Douglas M Willis

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(75) *Inventors*: James H. Cook, II, East Hampton, CT (US); Ivar M. McDonald, East Haddam, CT (US); Dalton King, Hamden, CT (US); Richard E. Olson, Orange, CT (US); Nenghui Wang, Guilford, CT (US); Christiana I. Iwuagwu, Hamden, CT (US); F. Christopher Zusi, Hamden, CT (US); John E. Macor, Guilford, CT (US)

(73) *Assignee*: Bristol-Myers Squibb Company, Princeton, NJ (US)

(*) *Notice*: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) *Appl. No.*: 12/423,299

(22) *Filed*: Apr. 14, 2009

(65) **Prior Publication Data**
US 2009/0270405 A1 Oct. 29, 2009

Related U.S. Application Data

(60) Provisional application No. 61/047,211, filed on Apr. 23, 2008.

(51) **Int. Cl.**
A01N 43/90 (2006.01)

(52) **U.S. Cl.** 514/305; 544/322; 544/356;
546/133; 546/143; 546/268.1; 548/216

(58) **Field of Classification Search** 514/305;
544/322, 356; 546/133, 143, 268.1; 548/216
See application file for complete search history.

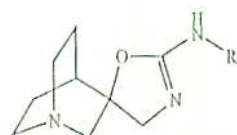
(56) **References Cited**

U.S. PATENT DOCUMENTS

5,053,412 A 10/1991 Fisher et al.

(57) **ABSTRACT**

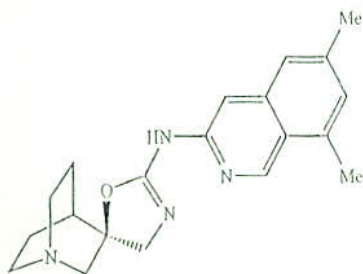
The disclosure provides compounds of formula 1, including their salts, as well as compositions and methods of using the compounds. The compounds are ligands for the nicotinic $\alpha 7$ receptor and may be useful for the treatment of various disorders of the central nervous system, especially affective and neurodegenerative disorders.



14 Claims, No Drawings

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Step C: (2R)—N-(6,8-Dimethyl-3-isoquinolinyl)-4'H-spiro[4-azabicyclo[2.2.2]octane-2,5'-[1,3]oxazol]-2'-amine

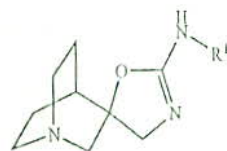


To (S)-3-(aminomethyl)quinuclidin-3-ol dihydrochloride (99 mg, 0.43 mmol) in N,N-dimethylformamide (1.4 mL) was added triethylamine (0.18 mL, 1.3 mmol) and 3-isothiocyanato-6,8-dimethylisoquinoline (93 mg, 0.43 mmol). The suspension was placed into a preheated oil-bath and stirred at 70° C. for 2 h and 30 min. N,N'-Diisopropylcarbodiimide (0.27 mL, 1.7 mmol) was then added and the mixture was stirred at 85° C. for 16 h. The mixture was concentrated and purified by silica gel chromatography (0-40% [9:1 methanol: ammonium hydroxide] in chloroform) followed by purification by reverse phase preparative HPLC (0-40% [0.1% TFA]-methanol-water) to afford (2R)—N-(6,8-dimethyl-3-isoquinolinyl)-4'H-spiro[4-azabicyclo[2.2.2]octane-2,5'-[1,3]oxazol]-2'-amine as the trifluoroacetic acid salt (24 mg, 0.053 mmol, 12% yield) as a white solid. ¹H NMR (400 MHz, MeOD) δ ppm 9.29 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 4.38 (d, J=11.04 Hz, 1H), 4.17 (d, J=11.04 Hz, 1H), 3.94-4.10 (m, 1H), 3.86 (dd, J=15.06, 2.26 Hz, 1H), 3.51-3.67 (m, 1H), 3.37-3.51 (m, 3H), 2.77 (s, 3H), 2.73 (d, J=3.51 Hz, 1H), 2.48-2.57 (m, 3H), 2.30-2.46 (m, 1H), 1.94-2.28 (m, 3H). MS (LC/MS) R.T.=0.90; [M+H]⁺=337.38.

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

The invention claimed is:

1. A compound of formula I, or a stereoisomer thereof,



wherein

R¹ is selected from the group consisting of isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, naphthyridinyl, indazolyl, indolyl, 2-indolonyl, benzisoxazolyl, benzoisothiazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, furopyridinyl, thienopyridinyl, thienopyrimidinyl, isothiazolopyridinyl, thiazolopyridinyl, thiazolopyrimidinyl, thiazolopyrazinyl, thiazolopyrimidinyl, thiazolopyridinyl,

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triazolopyrazinyl, pyrrolotriazinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, 7,8-dihydroquinazolin-5(6H)-onyl, and tetrahydrobenzothiazolyl, and is substituted with 0-3 substituents independently selected from the group consisting of C₁₋₄alkyl, C₃₋₇cycloalkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄haloalkoxy, C₃₋₇cycloalkoxy, C₁₋₄alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C₁₋₄alkylsulfonyl, NR²R³, pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C₁₋₄alkylamido, CONR²R³, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄haloalkyl, C₁₋₄haloalkoxy, and NR²R³;

R² is hydrogen, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, or C₁₋₄aminoalkyl;

R³ is hydrogen, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, or C₁₋₄aminoalkyl;

or R₂ and R₃ taken together with the nitrogen atom to which they are attached is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, N-(C₁₋₄alkyl)piperazinyl, morpholinyl, or homopiperidinyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 where R¹ is selected from the group consisting of dimethylisoxazolyl, (methyl)(phenyl)isoxazolyl, methylpyrazolyl, dimethylpyrazolyl, thienylpyrazolyl, methoxyphenylpyrazolyl, thiazolyl, bromothiazolyl, cyanothiazolyl, methylthiazolyl, dimethylthiazolyl, (methyl)(phenyl)thiazolyl, isopropylthiazolyl, butylthiazolyl, benzylthiazolyl, methoxyphenylmethylthiazolyl, phenylthiazolyl, chlorophenylthiazolyl, methoxyphenylthiazolyl, (methoxyphenyl)(methyl)thiazolyl, pyridinylthiazolyl, (phenyl)(methyl)imidazolyl, methylloxadiazolyl, ethyloxadiazolyl, methylthiadiazolyl, fluorophenylthiadiazolyl, furylthiadiazolyl, (dimethylcarboxamido)(methyl)thiazolyl, pyrrolidinoylthiazolyl, phenyltriazolyl, pyridinyl, bromopyridinyl, chloropyridinyl, (chloro)(fluoro)pyridinyl, (chloro)(methyl)pyridinyl, dichloropyridinyl, fluoropyridinyl, cyanopyridinyl, (cyano)(methyl)pyridinyl, (cyano)(dimethyl)pyridinyl, methoxypyridinyl, (methylpyrrolidinyl)pyridinyl, phenylpyridinyl, methoxypyridinylpyridinyl, pyridazinyl, bromopyridazinyl, chloropyridazinyl, methylpyridazinyl, methoxypyridazinyl, methylthiopyridazinyl, pyrrolidinylpyridazinyl, pyrrolidinonylpyridazinyl, phenylpyridazinyl, pyridinylpyridazinyl, methoxypyridinylpyridazinyl, pyrimidinyl, (bromo)(isopropyl)pyrimidinyl, (bromo)(dimethyl)pyrimidinyl, (bromo)(cyclopropyl)pyrimidinyl, (bromo)(methoxy)pyrimidinyl, (bromo)(phenyl)pyrimidinyl, (bromo)(pyridinyl)pyrimidinyl, chloropyrimidinyl, (chloro)(dimethyl)pyrimidinyl, (methyl)(methoxy)pyrimidinyl, methylpyrimidinyl, ethylpyrimidinyl, (methyl)(phenyl)pyrimidinyl, dimethylpyrimidinyl, butylpyrimidinyl, isopropylpyrimidinyl, cyclopropylpyrimidinyl, methoxypyrimidinyl, dimethoxypyrimidinyl, isopropoxypyrimidinyl, cyclopentoxypyrimidinyl, difluoromethoxypyrimidinyl, trifluoroethoxypyrimidinyl, phenoxy pyrimidinyl, methylthiopyrimidinyl, phenylpyrimidinyl, chlorophenylpyrimidinyl, methylphenylpyrimidinyl, methoxyphenylpyrimidinyl, (phenyl)(triazolyl)pyrimidinyl, pyridinylpyrimidinyl, methoxypyridinylpyrimidinyl, methoxypyrimidinylpyrimidinyl, naphthylpyrimidinyl, pyrazinyl, bromopyrazinyl, (bromo)(methoxy)pyrazinyl, chloropyrazinyl, methylpyrazinyl, dimethylpyrazinyl, butylpyrazinyl, cyanopyrazinyl, methoxypyrazinyl, isopropoxypyrazinyl, trifluoromethylpyrazinyl, phenylpyrazinyl, and dimethyltriazinyl;

or a pharmaceutically acceptable salt thereof.

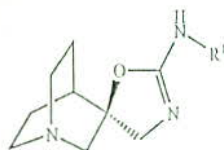
3. A compound of claim 1 where R^1 is selected from the group consisting of dimethylpyridinoisoxazolyl, benzoxazolyl, chlorobenzoxazolyl, fluorophenylbenzoxazolyl, ethylphenylbenzoxazolyl, dimethylaminophenylbenzoxazolyl, pyridinylbenzoxazolyl, benzothiazolyl, acetamidobenzothiazolyl, bromobenzothiazolyl, chlorobenzothiazolyl, (chloro)(methyl)benzothiazolyl, (chloro)(methoxy)benzothiazolyl, fluorobenzothiazolyl, difluorobenzothiazolyl, cyanobenzothiazolyl, methylbenzothiazolyl, dimethylbenzothiazolyl, (methyl)(methoxy)benzothiazolyl, ethylbenzothiazolyl, trifluoromethylbenzothiazolyl, hydroxybenzothiazolyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, isopropoxybenzothiazolyl, trifluoromethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, dimethoxybenzothiazolyl, morpholinylbenzothiazolyl, pyrrolidinylbenzothiazolyl, methylsulfonylbenzothiazolyl, chlorothiazolopyridinyl, dimethylthiazolopyridinyl, benzyloxythiazolopyridinyl, difluoromethoxythiazolopyridinyl, benzotriazolyl, indolonyl, indazolyl, bromoindazolyl, chloroindazolyl, fluoroindazolyl, (methyl)(methoxy)indazolyl, methoxyindazolyl, trifluoromethylindazolyl, trifluoromethoxyindazolyl, difluoromethoxyindazolyl, benzimidazolyl, fluorobenzimidazolyl, methylbenzimidazolyl, (methyl)(methoxy)benzimidazolyl, methoxybenzimidazolyl, tetrahydrobenzothiazolyl, furopyridinyl, dimethylfuropyrimidinyl, thienopyrimidinyl, isopropylthienopyrimidinyl, dimethylthienopyrimidinyl, chlorotriazolopyridinyl, methyltriazolopyridinyl, trifluoromethyltriazolopyridinyl, methoxytriazolopyridinyl, triazolopyrazinyl, bromopyrrolotriazinyl, dimethylaminothiazolopyrimidinyl, thiazolopyrazinyl, bromothiazolopyrazinyl, methoxythiazolopyrazinyl, methylthiothiazolopyrazinyl, methoxythiazolopyrimidinyl, (methyl)(methoxy)thiazolopyrimidinyl, quinolonyl, bromoquinolonyl, fluoroquinolonyl, methylquinolonyl, (methyl)(methoxy)quinolonyl, isoquinolonyl, bromoisoquinolonyl, dichloroisoquinolonyl, methylisoquinolonyl, dimethylisoquinolonyl, quinoxalonyl, chloroquinoxalonyl, methylquinoxalonyl, methoxyquinoxalonyl, quinazolonyl, bromoquinazolonyl, naphthylridinyl, 5,6-dihydrobenzo [h] quinazolonyl, 5 H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5 H-cyclopenta [d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolonyl, and 7,8-dihydroquinazolin-5(6H)-onyl;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 where R^1 is selected from the group consisting of phenylthiazolyl, (chloro)(methyl)pyridinyl, (bromo)(phenyl)pyrimidinyl, methoxypyrimidinyl, difluoromethoxypyrimidinyl, difluoroethoxypyrimidinyl, cyclopentoxypyrimidinyl, (methylphenyl)pyrimidinyl, (methoxyphenyl)pyrimidinyl, bromopyrazinyl, chloropyrazinyl, methylthiopyrazinyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, thiazolopyridinonyl, trifluoromethylindazolyl, benzimidazolyl, isoquinolonyl, and quinazolonyl;

or a pharmaceutically acceptable salt thereof.

5. The stereoisomer of claim 1 according to Formula Ia;



or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5 where R^1 is selected from the group consisting of dimethylisoxazolyl, (methyl)(phenyl)isoxazolyl, methylpyrazolyl, dimethylpyrazolyl, thienylpyrazolyl, methoxyphenylpyrazolyl, thiazolyl, bromothiazolyl, cyanothiazolyl, methylthiazolyl, dimethylthiazolyl, (methyl)(phenyl)thiazolyl, isopropylthiazolyl, butylthiazolyl, benzylthiazolyl, methoxyphenylmethylthiazolyl, phenylthiazolyl, chlorophenylthiazolyl, methoxyphenylthiazolyl, (methoxyphenyl)(methyl)thiazolyl, pyridinylthiazolyl, (phenyl)(methyl)imidazolyl, methyloxadiazolyl, ethyloxadiazolyl, methylthiadiazolyl, fluorophenylthiadiazolyl, furylthiadiazolyl, (dimethylcarboxamido)(methyl)thiazolyl, pyrrolidinonylthiazolyl, phenyltriazolyl, pyridinyl, bromopyridinyl, chloropyridinyl, (chloro)(fluoro)pyridinyl, (chloro)(methyl)pyridinyl, dichloropyridinyl, fluoropyridinyl, cyanopyridinyl, (cyano)(methyl)pyridinyl, (cyano)(dimethyl)pyridinyl, methoxypyridinyl, (methylpyrrolidinyl)pyridinyl, phenylpyridinyl, methoxypyridinylpyridinyl, pyridazinyl, bromopyridazinyl, chloropyridazinyl, methylpyridazinyl, methoxypyridazinyl, methylthiopyridazinyl, pyrrolidinylpyridazinyl, pyrrolidinonylpyridazinyl, phenylpyridazinyl, pyridinylpyridazinyl, methoxypyridinylpyridazinyl, pyrimidinyl, (bromo)(isopropyl)pyrimidinyl (bromo)(dimethyl)pyrimidinyl, (bromo)(cyclopropyl)pyrimidinyl, (bromo)(methoxy)pyrimidinyl, (bromo)(phenyl)pyrimidinyl, (bromo)(pyridinyl)pyrimidinyl, chloropyrimidinyl, (chloro)(dimethyl)pyrimidinyl, (methyl)(methoxy)pyrimidinyl, methylpyrimidinyl, ethylpyrimidinyl, (methyl)(phenyl)pyrimidinyl, dimethylpyrimidinyl, butylpyrimidinyl, isopropylpyrimidinyl, cyclopropylpyrimidinyl, methoxypyrimidinyl, dimethoxypyrimidinyl, isopropoxypyrimidinyl, cyclopentoxypyrimidinyl, difluoromethoxypyrimidinyl, trifluoroethoxypyrimidinyl, phenoxypyrimidinyl, methylthiopyrimidinyl, phenylpyrimidinyl, chlorophenylpyrimidinyl, methylphenylpyrimidinyl, methoxyphenylpyrimidinyl, (phenyl)(triazolyl)pyrimidinyl, pyridinylpyrimidinyl, methoxypyridinylpyrimidinyl, methoxypyrimidinylpyrimidinyl, naphthylpyrimidinyl, pyrazinyl, bromopyrazinyl, (bromo)(methoxy)pyrazinyl, chloropyrazinyl, methylpyrazinyl, dimethylpyrazinyl, butylpyrazinyl, cyanopyrazinyl, methoxypyrazinyl, isopropoxypyrazinyl, trifluoromethylpyrazinyl, phenylpyrazinyl, and dimethyltriazinyl;

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 5 where R^1 is selected from the group consisting of dimethylpyridinoisoxazolyl, benzoxazolyl, chlorobenzoxazolyl, fluorophenylbenzoxazolyl, ethylphenylbenzoxazolyl, dimethylaminophenylbenzoxazolyl, pyridinylbenzoxazolyl, benzothiazolyl, acetamidobenzothiazolyl, bromobenzothiazolyl, chlorobenzothiazolyl, (chloro)(methyl)benzothiazolyl, (chloro)(methoxy)benzothiazolyl, fluorobenzothiazolyl, difluorobenzothiazolyl, cyanobenzothiazolyl, methylbenzothiazolyl, dimethylbenzothiazolyl, (methyl)(methoxy)benzothiazolyl, ethylbenzothiazolyl, trifluoromethylbenzothiazolyl, hydroxybenzothiazolyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, isopropoxybenzothiazolyl, trifluoromethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, dimethoxybenzothiazolyl, morpholinylbenzothiazolyl, pyrrolidinylbenzothiazolyl, methylsulfonylbenzothiazolyl, chlorothiazolopyridinyl, dimethylthiazolopyridinyl, benzyloxythiazolopyridinyl, difluoromethoxythiazolopyridinyl, benzotriazolyl, indolonyl, indazolyl, bromoindazolyl, chloroindazolyl, fluoroindazolyl, (methyl)(methoxy)indazolyl, methoxyindazolyl, trifluoromethylindazolyl, trifluoromethoxyindazolyl, difluoromethoxyindazolyl, benzimidazolyl, fluorobenzimidazolyl, methylbenzimidazolyl, (methyl)(methoxy)benzimidazolyl,

methoxybenzimidazolyl, tetrahydrobenzothiazolyl, furopyridinyl, dimethylfuoropyrimidinyl, thienopyrimidinyl, isopropylthienopyrimidinyl, dimethylthienopyrimidinyl, chlorotriazolopyridinyl, methyltriazolopyridinyl, trifluoromethyltriazolopyridinyl, methoxytriazolopyridinyl, triazolopyrazinyl, bromopyrrolotriazinyl, dimethylaminothiazolopyrimidinyl, thiazolopyrazinyl, bromothiazolopyrazinyl, methoxythiazolopyrazinyl, methylthiothiazolopyrazinyl, methoxythiazolopyrimidinyl, (methyl)(methoxy)thiazolopyrimidinyl, quinolinyl, bromoquinolinyl, fluoroquinolinyl, methylquinolinyl, (methyl)(methoxy)quinolinyl, isoquinolinyl, bromoisoquinolinyl, dichloroisoquinolinyl, methylisoquinolinyl, dimethylisoquinolinyl, quinoxalinyl, chloroquinoxalinyl, methylquinoxalinyl, methoxyquinoxalinyl, quinazolinyl, bromoquinazolinyl, naphthylidinyl, 5,6-dihydrobenzo [h]quinazolinyl, 5H-chromeno[4,3-d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta [d]pyrimidinyl, 5,6,7,8-tetrahydroquinazolinyl, and 7,8-dihydroquinazolin-5(6H)-onyl;

or a pharmaceutically acceptable salt thereof.

8. A compound of claim 5 where R^1 is selected from the group consisting of phenylthiazolyl, (chloro)(methyl)pyridinyl, (bromo)(phenyl)pyrimidinyl, methoxypyrimidinyl, difluoromethoxypyrimidinyl, difluoroethoxypyrimidinyl, cyclopentoxypyrimidinyl, (methylphenyl)pyrimidinyl, (methoxyphenyl)pyrimidinyl, bromopyrazinyl, chloropyrazinyl, methylthiopyrazinyl, methoxybenzothiazolyl, ethoxybenzothiazolyl, difluoromethoxybenzothiazolyl, thiazolopyridinonyl, trifluoromethylindazolyl, benzimidazolyl, isoquinolinyl, and quinazolinyl;

or a pharmaceutically acceptable salt thereof.

9. A compound of claim 5 where R^1 is selected from the group consisting of thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzothiazolyl, thiazolopyridinyl, indazolyl, benzimidazolyl, isoquinolinyl, and quinazolinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4} alkylsulfonyl, NR^2R^3 , pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4} alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and NR^2R^3 ;

or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9 where R^1 is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, thiazolopyridinyl, and isoquinolinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4} alkylsulfonyl, NR^2R^3 , pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4} alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and NR^2R^3 ;

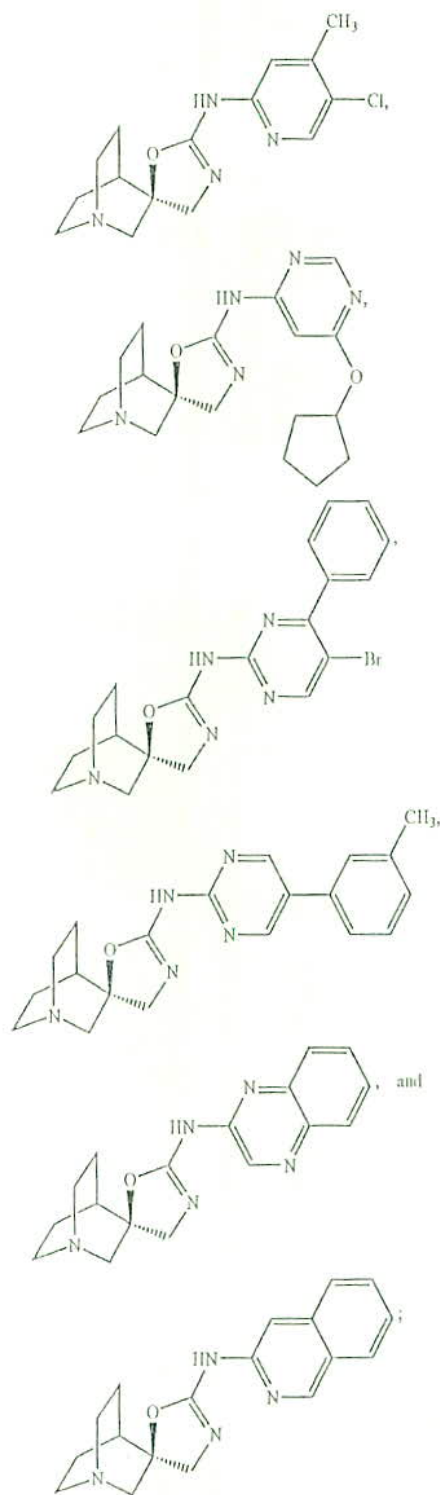
or a pharmaceutically acceptable salt thereof.

11. A compound of claim 10 where R^1 is selected from the group consisting of pyridinyl and isoquinolinyl, and is substituted with 0-3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkylthio, phenoxy, benzyloxy, halo, hydroxy, cyano, C_{1-4} alkylsulfo-

nyl, NR^2R^3 , pyrrolidinonyl, methylenedioxy, furyl, thienyl, triazolyl, pyrimidinyl, naphthyl, C_{1-4} alkylamido, $CONR^2R^3$, pyridyl, phenyl, and benzyl, and where pyridyl, phenyl and benzyl are substituted with 0-2 substituents independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and NR^2R^3 ;

or a pharmaceutically acceptable salt thereof.

12. A compound selected from the group consisting of



or a pharmaceutically acceptable salt thereof.

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13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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14. A method for the treatment of schizophrenia or Alzheimer's Disease which comprises administering to a patient a therapeutically effective amount of a compound of claim 1.

* * * * *

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 11163 PCT	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2009/041076	International filing date (day/month/year) 20 April 2009 (20.04.2009)	Priority date (day/month/year) 23 April 2008 (23.04.2008)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant BRISTOL-MYERS SQUIBB COMPANY			

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).		
2.	This REPORT consists of a total of 7 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.		
3.	This report contains indications relating to the following items:		
☒	Box No. I	Basis of the report	
☐	Box No. II	Priority	
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	
☐	Box No. IV	Lack of unity of invention	
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement	
☐	Box No. VI	Certain documents cited	
☒	Box No. VII	Certain defects in the international application	
☐	Box No. VIII	Certain observations on the international application	
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).		

		Date of issuance of this report 26 October 2010 (26.10.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland		Authorized officer Nora Lindner
Facsimile No. +41 22 338 82 70		e-mail: pt11.pct@wipo.int

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited documents

- D1: EP-A-0 337 547 (MERCK SHARP & DOHME [GB]) 18 October 1989 (1989-10-18) cited in the application
- D2: EP-A-0 452 101 (ISRAEL INST BIOLOG RES [IL]) 16 October 1991 (1991-10-16) cited in the application
- D3: SWAIN C J: "Novel 5-HT₃ Antagonists: Indol-3-ylspiro(azabicycloalkane-3,5'(4'H)-oxazoles)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 35, 1 January 1992 (1992-01-01), pages 1019-1031, XP002095203 ISSN: 0022-2623 cited in the application
- D4: WO 2005/005435 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; CHANG HUI-FANG [US]; PHI) 20 January 2005 (2005-01-20)
- D5: WO 2006/065209 A (ASTRAZENECA AB [SE]; CHAPDELAINE MARC [US]; CHANG HUI-FANG [US]; HERZO) 22 June 2006 (2006-06-22)
- D6: WO 96/06098 A (ASTRA AB [SE]; BALESTRA MICHAEL [US]; GORDON JOHN CHARLES [US]; GRIFFI) 29 February 1996 (1996-02-29)
- D7: US 2007/004715 A1 (HUANG YIFANG [US] ET AL) 4 January 2007 (2007-01-04) cited in the application
- D8: R. TATSUMI ET AL.: "(R)-3'-(3-Methylbenzo(b)thiophen-5-yl)-spiro(1-azabicyclo(2,2,2)octane-3,5'-oxazolidin)-2'-one, a Novel and Potent α 7 Nicotinic Acetylcholine Receptor Partial Agonist Displays Cognitive Enhancing Properties" JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 14, 2006, pages 4374-4383, XP002538696

The indicated designations will be adhered to throughout the examination procedure.

2. Rule 39.1(iv) / 67.1(iv) PCT

Claim 14 relates to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can depend on the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment

been solved in a non-obvious way.

Consequently, inventive step is to be acknowledged for the subject-matter of claims 1-14.

Re Item VII

Certain defects in the international application

The document WO 2004/000469, cited on page 4 of the description, deals with "Hoses" (classification: B05B 7/24). So the number is probably wrong.