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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-053905- -00001-0000

Fecha: 2008-06-12 16:29:46 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 538 PETICION Folios: 2

Señora Jefe de la  
**DIVISION DE NUEVAS CREACIONES**  
Superintendencia de Industria y Comercio  
E. S. D.

Trámite : 011  
Evento : 378  
Actuación : 538

Referencia : Expediente No. 07053905  
Asunto : Solicitud de patente para **CLORHIDRATO DIHIDRATO DE  
(S)-(-)-1-(4-FLUOROISOQUINOLIN -5-IL)SULFONIL-2-  
METIL-1,4-HOMOPIPERAZINA**  
Solicitante : **KOWA CO., LTD. AND D. WESTERN THERAPEUTICS  
INSTITUTE, INC.**  
Clase : A61K 031/551, A61P 009/010, C07D 401/012, C07D 401/12  
Publicada en : La Gaceta No. 583 del 18 de diciembre de 2007  
Fecha de Solicitud : 29 de mayo de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$ 420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

**EMILIO FERRERO**  
T.P.A. No. 31.929

✓ COLO-15943-841-001-5  
SDCIAMGID-128013WPC15943  
No. M-2008-128013SDC

101

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-053905- -00001-0000

Fecha: 2008-08-12 16:29:48 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 46,066  
FECHA : JUNIO 9 DE 2008

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE       | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-------------------|--------------|-----------------|-----------|----------|------------|---------------|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 2678328  | 09/06/2008 | 89,445,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| RENTISTICO                | CONCEPTO                             | TOTAL CONCEPTO |
|---------------------------|--------------------------------------|----------------|
| 1 50005-01-01 SOLICITUDES | 85 EXAMEN DE PATENTABILIDAD DE INVEN | 420,000.00     |
|                           | TOTAL :                              | \$ 420,000.00  |

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Bo 15943-841-001-5

**DIVISIÓN DE NUEVAS CREACIONES**

**RADICACIÓN EXPEDIENTE No. 07-53905**

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

**FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 583 DE**

**FECHA 18 DE DICIEMBRE DE 2007 EL TÉRMINO HÁBIL SEÑALADO POR LA**

**LEY EXPIRA EL 14 DE MARZO DE 2008**

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

**SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.**

SI \_\_\_\_\_

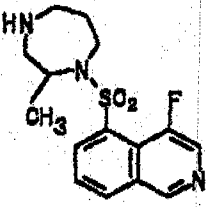
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PCT

世界知的所有権機関  
国際事務局

特許協力条約に基づいて公開された国際出願

DL  
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                        |                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| (51) 国際特許分類6<br>C07D 401/12, A61K 31/55                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | A1                                                                                                                                                                                                                                                                                                     | (11) 国際公開番号<br>WO99/20620<br><br>(43) 国際公開日<br>1999年4月29日 (29.04.99) |
| (21) 国際出願番号<br>PCT/JP98/04781<br><br>(22) 国際出願日<br>1998年10月22日 (22.10.98)<br><br>(30) 優先権データ<br>特願平9/289688<br>1997年10月22日 (22.10.97) JP<br><br>(71) 出願人 (米国を除くすべての指定国について)<br>日本新薬株式会社(NIPPON SHINYAKU CO., LTD.)[JP/JP]<br>〒601-8550 京都府京都市南区吉祥院西ノ庄門口町14番地<br>Kyoto, (JP)<br>(71) 出願人 ; および<br>(72) 発明者<br>日高弘義(HIDAKA, Hiroyoshi)[JP/JP]<br>〒468-0063 愛知県名古屋市中天白区音聞山607番地 Aichi, (JP)<br>(72) 発明者 ; および<br>(75) 発明者 / 出願人 (米国についてのみ)<br>松浦 明(MATSUURA, Akira)[JP/JP]<br>〒300-1236 茨城県牛久市田宮町391-114 Ibaraki, (JP)                                                                                                                                                                             | (81) 指定国 AT, AU, BG, BR, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, ID, IL, JP, KR, LK, LU, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, UA, US, VN, YU, ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br>添付公開書類<br>国際調査報告書 |                                                                      |
| (54) Title: ISOQUINOLINE DERIVATIVE AND DRUG<br><br>(54) 発明の名称 イソキノリン誘導体及び医薬<br><br><div style="text-align: center;">  <p>(I)</p> </div><br>(57) Abstract<br>The isoquinoline derivative represented by formula (I), pharmaceutically acceptable salts thereof, and pharmaceutical compositions containing either of them as the active ingredient. The compound (I) is useful as a preventive or remedy for cerebrovascular accident and is particularly excellent as a depressor for cerebrovascular contraction. It is also useful as a preventive or remedy for diseases accompanied by ischemic lesion. |                                                                                                                                                                                                                                                                                                        |                                                                      |

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WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/JP2005/021844

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                      |      |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----|
| Box No. V                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |      |     |
| 1. Statement                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                      |      |     |
| Novelty (N)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Claims                                                                                                                                                               | 1-7  | YES |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Claims                                                                                                                                                               | 8-11 | NO  |
| Inventive step (IS)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Claims                                                                                                                                                               | 1-7  | YES |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Claims                                                                                                                                                               | 8-11 | NO  |
| Industrial applicability (IA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Claims                                                                                                                                                               | 1-11 | YES |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Claims                                                                                                                                                               |      | NO  |
| 2. Citations and explanations:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                      |      |     |
| <p>Document 1: WO, 1999-020620, A1 (Nippon Shinyaku Co., Ltd.), 29 April, 1999 (29.04.99)</p> <p>Document 2: WO, 1997-002260, A1 (Asahi Chemical Industry Co., Ltd.), 23 January, 1997 (23.01.97)</p> <p>Document 3: JP, 9-12573, A2 (Asahi Chemical Industry Co., Ltd.), 14 January, 1997 (14.01.97)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                      |      |     |
| <p>Claims 8-11</p> <p>Document 1 describes pharmaceutical compositions for treatment of cerebrovascular accident which contains (S)-(-)-1-(4-fluoroisoquinolin-5-yl) sulfonyl-2-methyl-1,4-homopiperazine hydrochloride. It also describes that a liquid diluent is used as a carrier (1<sup>st</sup> and 2<sup>nd</sup> lines from the bottom, page 8) and that said composition can be made into an aqueous injection (preparation example 1).</p> <p>On the other hand, according to the description "when preparing an orally administered medicine, ... can be made into solution, syrup, elixir, oily or aqueous suspension, etc." ([0028] of the specification) or "when preparing injection or eye drops" ([0030]), it is considered that the pharmaceutical compositions in claims 8-11 of the present application also include those in liquid condition.</p> <p>Since hydrate dissolves when the pharmaceutical compositions in claims 8-11 are in liquid condition, it is impossible to distinguish them from the pharmaceutical compositions described in document 1. Therefore, the subject matters of claims 8-11 do not appear to be novel or to involve an inventive step in view of document 1.</p> |                                                                                                                                                                      |      |     |
| <p>Claims 1-7</p> <p>Though (S)-(-)-1-(4-fluoroisoquinolin-5-yl) sulfonyl-2-methyl-1,4-homopiperazine hydrochloride is described in document 1, there is no description or suggestion about dihydrate in the document.</p> <p>Though a hydrate of 1-(5-isoquinolinsulfonyl)homopiperazine hydrochloride, which is similar in structure to (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine, is described in documents 2 and 3, there is no description or suggestion in them about a dihydrate of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine.</p> <p>So, the subject matters of claims 1-7 appear to be novel and to involve an inventive step in view of documents 1-3.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                      |      |     |



US006153608A

**United States Patent** [19]**Hidaka et al.**[11] **Patent Number:** **6,153,608**[45] **Date of Patent:** **Nov. 28, 2000****[54] ISOQUINOLINE DERIVATIVES AND DRUGS**[75] **Inventors:** Hiroyoshi Hidaka, Nagoya; Akira Matsuura, Shiga-gun; Takushi Matsuzaki, Nagaokakyo, all of Japan[73] **Assignee:** Nippon Shinyaku Co., Ltd., Kyoto, Japan[21] **Appl. No.:** 09/117,433[22] **PCT Filed:** Jan. 31, 1997[86] **PCT No.:** PCT/JP97/00240

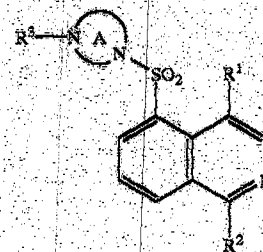
§ 371 Date: Jul. 29, 1998

§ 102(e) Date: Jul. 29, 1998

[87] **PCT Pub. No.:** WO97/28130**PCT Pub. Date:** Aug. 7, 1997**[30] Foreign Application Priority Data**Feb. 2, 1996 [JP] Japan ..... 8-017946  
Oct. 18, 1996 [JP] Japan ..... 8-275886[51] **Int. Cl.<sup>7</sup>** ..... A61K 31/55; A61K 31/495;  
C07D 245/00; C07D 491/00; C07D 401/00;  
C07D 239/00; C07D 487/00; C07D 239/70;  
C07D 239/02[52] **U.S. Cl.** ..... 514/218; 514/218; 514/221;  
514/247; 514/248; 514/249; 514/253.05;  
514/258; 514/307; 540/470; 540/472; 540/556;  
540/575; 540/577; 540/579; 540/597; 544/235;  
544/238; 544/242; 544/253; 544/282; 544/316;  
544/319; 544/349; 544/351; 544/363[58] **Field of Search** ..... 540/470, 472,  
540/556, 575, 577, 579, 597; 544/235,  
238, 242, 253, 282, 316, 319, 349, 351,  
363; 546/146, 139, 141, 142; 514/218,  
221, 247, 248, 249, 254, 258, 307, 253,  
253.05**[56] References Cited****U.S. PATENT DOCUMENTS**4,456,757 6/1984 Hidaka et al. .... 546/139  
4,634,770 1/1987 Hidaka et al. .... 546/145  
4,678,783 7/1987 Hidaka et al. .... 514/218**Primary Examiner**—Mukund J. Shah**Assistant Examiner**—Ben Schroeder**[57] ABSTRACT**

The invention relates to a compound of the following general formula [I] or a medicinally acceptable salt thereof, or a solvate thereof.

[I]



wherein  $R^1$  represents alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, or halogen;  $R^2$  represents hydrogen, hydroxy, or halogen;  $R^3$  represents hydrogen, alkyl, or amidino; Ring A represents a 5- to 11-membered cyclic amino group which may be substituted, which cyclic amino group may be bridged between two carbon atoms in optional positions. The compound of this invention is useful for the prevention or treatment of cerebral tissue impairment due to the vasospasm following cerebral hemorrhage.

**16 Claims, No Drawings**

# ISOQUINOLINE DERIVATIVES AND DRUGS

## TECHNICAL FIELD

The present invention relates to an isoquinoline derivative having cerebral vasospasm-inhibiting activity and, thus, finding application as a medicine.

## BACKGROUND ART

Cerebrovascular disease can be groupified into a hemorrhagic group and an ischemic group. The hemorrhagic group typically comprises subarachnoid hemorrhage arising from aneurysmal rupture, hypertensive cerebral hemorrhage, and head trauma. Subarachnoid hemorrhage entails a delayed vasospasm of the major cerebral arteries and may lead to vascular constriction disorders and sometimes to death. The ischemic group is represented by cerebral infarction and transient ischemic attack (TIA). The vascular disorder and neuronal injury caused by infarction or hemorrhage may lead to dyskinesia such as numbness or motor paralysis of the limbs and neurologic and mental dysfunctions in the acute through chronic stage, with disturbance of consciousness and death ensuing in severe cases.

For the treatment of such cerebrovascular diseases, anti-thrombotics and enhancers of cerebral circulation and metabolism have been used to this day. However, few drugs are available which inhibit this fatal cerebral vasospasm or the neuronal injury leading to dementia and there exists a pressing need for an effective therapeutic agent.

By way of illustration, as subarachnoid hemorrhage takes place, narrowing of the vascular lumen persisting for several weeks is induced in the major cerebral arteries in 4-5 days following the bleeding event. This phenomenon is known as cerebral vasospasm and once the ultimate ischemia triggers the onset of neurological symptoms, the functional prognosis and, at times, even the vital prognosis of the case are seriously influenced.

As the therapeutic drug for cerebral vasospasm subsequent to subarachnoid hemorrhage, fasudil [hexahydro-1-(5-isoquinolylsulfonyl)-1H-1,4-diazepine] hydrochloride is the only drug that is used clinically today (Japanese Kokai Tokkyo Koho S61-227581).

Aside from the above drug, it is known that compounds having an isoquinoline ring substituted by cyclic aminosulfonyl in its 5-position are useful as cerebrovascular drugs (vasodilators, enhancers of cerebral circulation and metabolism, antitanginal drugs, prophylactic and therapeutic drugs for cerebrovascular or cardiovascular thrombosis, and prophylactic and therapeutic drugs for hypertension) [Japanese Kokai Tokkyo Koho S57-156463, S58-121279, and S61-227581].

Not known, however, is a compound such that its isoquinoline skeleton has been substituted by a cyclic aminosulfonyl group in its 5-position and further substituted in its 4-position.

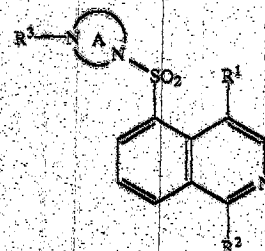
## DISCLOSURE OF THE INVENTION

The object of the invention is to provide a compound which is structurally novel, only sparingly toxic, and superior to any known drug as a prophylactic or therapeutic drug for cerebrovascular diseases, particularly as a cerebral vasospasm inhibitor.

To accomplish the above object, the inventors of the present invention synthesized and screened a large number of structurally new compounds and found that a compound of the following general formula [I] has very satisfactory

cerebral vasospasm-reversing activity. The present invention has been developed on the basis of the above finding.

The present invention, therefore, is concerned with a compound of the following general formula [I] or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a medicinal composition comprising it as an active ingredient.



wherein  $R^1$  represents alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, or halogen;

$R^2$  represents hydrogen, hydroxy, or halogen;

$R^3$  represents hydrogen, alkyl, or amidino;

Ring A represents a 5 to 11-membered cyclic amino group which maybe substituted, which cyclic amino group may be bridged between two carbon atoms in optional positions.

In chemical structure, the compound of the invention is characterized in that the 4-position of an isoquinoline skeleton is substituted by a substituent selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, and halogen.

The present invention is now described in detail.

The "alkyl" in the context of the present invention includes straight-chain or branched alkyl groups of 1-6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, and isohexyl. Among them, alkyl groups of 1 to 4 carbon atoms are preferred and methyl is particularly preferred.

The "alkenyl" includes straight-chain or branched alkenyl groups of 2 to 6 carbon atoms, such as vinyl, allyl, isopropenyl, methallyl, 2-butenyl, and 3-butenyl. Among them, alkenyl groups of 2 to 4 carbon atoms are preferred.

The "alkynyl" includes straight-chain or branched alkynyl groups of 2 to 6 carbon atoms, such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, and 3-butyne. Among them, alkynyl groups of 2 to 4 carbon atoms are preferred.

The "alkoxy" includes straight-chain or branched alkoxy groups of 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, and tert-butoxy.

The "halogen" includes chlorine, fluorine, bromine, and iodine.

Ring A includes saturated 5 to 11-membered monocyclic or bridged heterocyclic groups each containing 2 nitrogen atoms as ring-constituent hetero atoms. Thus, for example, imidazolidyl, piperazino, hexahydro-1H-1,4-diazepin-1-yl, 1,5-diazacyclooctan-1-yl, 3,6-diazabicyclo[3.2.2]nonan-3-yl, 3,6-diazabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, and 2,5-diazabicyclo[2.2.2]octan-2-yl can be mentioned. This Ring A may be substituted by 1-4 same or different substituent(s) selected from the group consisting of alkyl, halogen, phenyl, and aminoalkyl on its carbon atom or atoms.

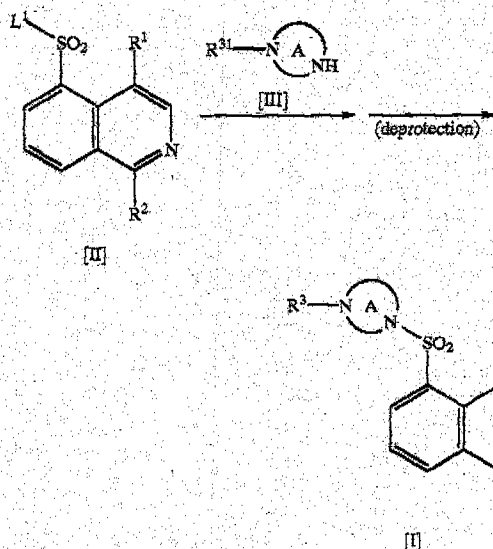
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$R^1$  is preferably  $C_{1-4}$  alkyl, particularly methyl.  $R^2$  is preferably hydrogen.  $R^3$  is preferably hydrogen. Ring A is preferably a hexahydro-1H-1,4-diazepin-1-yl, particularly 2- or 7-methyl-hexahydro-1H-1,4-diazepin-1-yl.

The salt of compound [I] according to the invention includes salts with inorganic acids such as sulfuric acid, nitric acid, phosphoric acid, hydrofluoric acid and hydrobromic acid, and salts with organic acids such as acetic acid, tartaric acid, lactic acid, citric acid, fumaric acid, maleic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid and camphorsulfonic acid.

The compound [I] of the invention can be produced by, for example, the following procedure.

Process 1



(wherein  $R^1$ ,  $R^2$ ,  $R^3$ , and Ring A are respectively as defined hereinbefore;  $R^{31}$  means  $R^3$  or represents a protective group;  $L^1$  represents a leaving group)

The leaving group  $L^1$  includes residues of the reactive derivatives of sulfonic acid to be mentioned hereinafter. The protective group  $R^{31}$  includes acyl such as formyl, acetyl or benzoyl; aralkyloxycarbonyl such as benzyloxycarbonyl; alkoxycarbonyl such as tert-butyloxycarbonyl; and aralkyl such as benzyl.

An amine of general formula [III] is reacted with a sulfonic acid of general formula [II] or a reactive derivative thereof in a suitable solvent and, where necessary, the protective group is removed to provide compound [I]. The reaction solvent may be any solvent that does not interfere with the reaction, thus including ethers such as tetrahydrofuran, dioxane and diethyl ether; hydrocarbons such as benzene and toluene; halogenated hydrocarbons such as methylene chloride and chloroform; aprotic solvents such as N,N-dimethylformamide and N,N-dimethylacetamide; pyridine, acetonitrile, etc.; and mixtures of such solvents. The reactive derivative of sulfonic acid includes sulfonic acid halides (e.g. sulfonyl chloride and sulfonyl bromide), sulfonic anhydride, and N-sulfonylimidazolidine, among others. Particularly preferred is a sulfonyl halide.

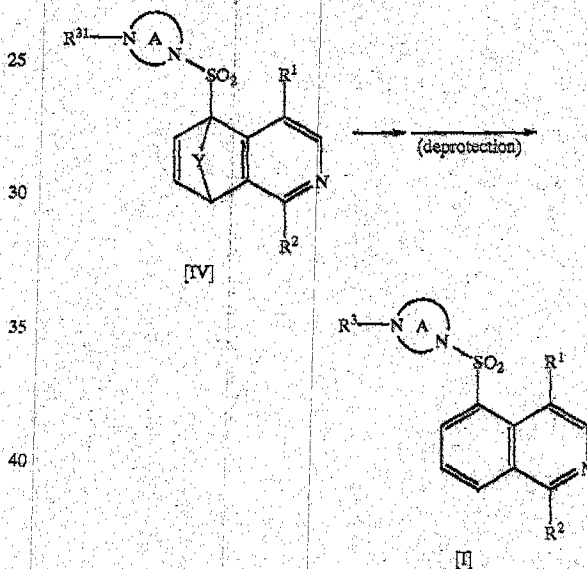
This reaction is preferably conducted in the presence of a base. The base includes various alkalis such as alkali metal hydrogencarbonates (e.g. sodium hydrogencarbonate), alkali metal carbonates (e.g. potassium carbonate), and alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide) and organic tertiary amines such as triethy-

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lamine and triethylenediamine. When a basic solvent such as pyridine is used as the reaction solvent, said base need not be used. Therefore, a solvent of this kind can be used with advantage.

This reaction usually proceeds at room temperature but may optionally be conducted under cooling or heating, for example at  $-78$ – $150^\circ\text{C}$ ., preferably  $0$ – $120^\circ\text{C}$ . When a base is used, the amount of the reactive derivative [II] relative to amine [III] is preferably 1–10 molar equivalents and more preferably 1–3 molar equivalents. The amount of the base relative to amine [III] is preferably 1–10 molar equivalents and more preferably 1–3 equivalents. When the base is not used, the amount of said or reactive derivative [II] relative to amine [III] is equimolar or less and preferably in the range of 0.5–0.1 molar equivalents. The reaction time is dependent on the species of starting compounds and solvent used, reaction temperature, and other conditions but is generally 5 minutes to 70 hours. Where necessary, the protective group is removed by a per se known procedure after completion of the reaction.

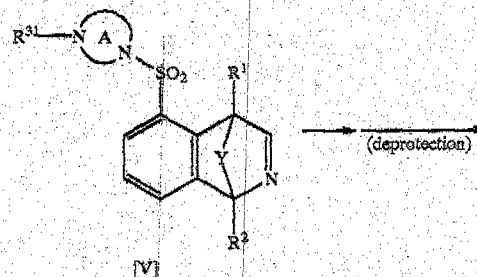
Process 2



(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{31}$ , and Ring A are respectively as defined hereinbefore; Y represents oxygen, sulfur, or  $\text{SO}_2$ ).

A compound of general formula [IV] is treated with an acid or heated for aromatization and, where necessary, the protective group is removed to provide compound [I]. This reaction can be carried out by a known method (J. Chem. Soc. C., 1971, 1227).

Process 3



amines such as triethylamine and triethylenediamine. This reaction is carried out using the same reaction solvent under the same conditions as mentioned for Process 1.

Compound [Ib] can also be obtained by subjecting compound [VIIId] to intramolecular dehydration reaction using triphenylphosphine and diethyl azodicarboxylate and removing the protective group.

The compound of formula [I] wherein  $R^1$  is alkenyl or  $C_{3-6}$  alkyl can also be produced by reducing the compound [Ic] (formula [I] in which  $R^1$  is alkynyl) prepared by any of the above-described processes. For example, the compound [I] wherein  $R^1$  is alkenyl can be obtained by subjecting compound [Ic] to catalytic reduction in a solvent such as methanol, ethanol, ethyl acetate, or quinoline in the presence of palladium/barium carbonate, palladium/calcium carbonate, or Rindlar catalyst at atmospheric temperature and pressure. The compound in which  $R^1$  is alkyl can be obtained by subjecting the compound in which  $R^1$  is alkynyl or alkenyl to catalytic reduction with the aid of a catalyst such as platinum, platinum oxide, palladium-on-carbon, or Raney nickel in a solvent such as methanol, ethanol, or acetic acid at atmospheric temperature and pressure or optionally at elevated temperature and pressure.

The compound of formula [I] in which  $R^1$  is alkyl and  $R^2$  is hydroxy or halogen can also be produced by oxidizing the compound [Id] (formula [I] in which  $R^1$  is alkyl and  $R^2$  is hydrogen) obtained by any of the above-described processes. Thus, the compound in which  $R^2$  is hydroxy can be obtained by heating compound [Id] together with an oxidizing agent such as hydrogen peroxide, a peracid, or tert-butyl peroxide in a solvent such as acetic acid, methylene chloride, or chloroform to give isoquinoline N-oxide and hydrolyzing the same with acetic anhydride under heating. Furthermore, by heating said isoquinoline N-oxide together with phosphorus oxychloride or phosphorus tribromide, the compound in which  $R^2$  is halogen can be provided.

The compound [I] having a substituent on the nitrogen atom of Ring A, i.e. compound [Ie] ( $R^3$  in formula [I] represents alkyl or amidino), can also be produced by introducing a substituent group into the compound [If] ( $R^3$  in formula [I] represents hydrogen) obtained by any of the processes described hereinbefore. For example, the compound having alkyl for  $R^3$  can be obtained by reacting compound [If] with an alkylating agent in the presence of a base. The compound having amidino for  $R^3$  can be obtained by reacting compound [If] with an isourea derivative in the presence of a base. The base which can be used here includes various alkalis such as sodium hydrogencarbonate, potassium carbonate, sodium hydroxide and potassium hydroxide, and organic tertiary amines such as triethylamine and so forth. The reaction solvent which can be used includes but is not limited to ethanol, methanol, benzene, toluene, N,N-dimethylformamide, and dimethyl sulfoxide. Thus, the compound in which  $R^3$  is amidino can be produced by reacting compound [If] with S-methylisothiourea or O-methylisourea in a solvent (e.g. tetrahydrofuran, ethanol, or methanol) at room temperature or under heating.

In the above production processes, hydroxyl and amino groups can be protected, whenever necessary, with suitable known protective groups and, after completion of the contemplated reaction, deprotected by per se known procedures such as acid treatment, alkali treatment, and catalytic reduction. The amino-protecting group that can be used includes but is not limited to benzyl, benzyloxycarbonyl, and trifluoroacetyl. The hydroxy-protecting group that can be used includes but is not limited to methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl, tetra-

hydropyranyl, tert-butyl, benzyl, trimethylsilyl, and tert-butyldimethylsilyl. When the hydroxyl group is protected with benzyl, the catalytic reduction results in simultaneous debenzoylation to regenerate a free hydroxyl group.

The starting compound [II] can be prepared by the procedure described in Reference Example 1.

The starting compound [III] can be purchased from a commercial source or prepared by the procedure described in Reference Example 2.

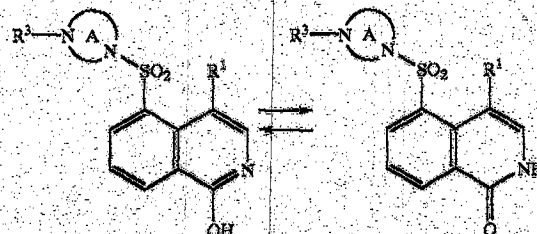
The starting compounds [IV] and [V] can be prepared by the method described in J. Chem. Soc. C., 1971, 1227.

The starting compounds [VI] and [VII] can be prepared in accordance with the procedures described in Acta. Chemica. Scand., 1991, 45, 621.

The starting compounds [IX] and [XI] can be purchased from commercial sources.

The starting compounds [XII] and [XIII] can also be purchased from commercial sources.

While compound [I] wherein  $R^2$  represents hydroxy may exist in the following tautomeric forms, both isomers fall within the scope of the invention.



Some species of the compound [I] of the invention have asymmetric carbon atoms and, as such, each may occur as optical isomers. Such respective isomers and mixtures thereof also fall within the scope of the invention. Usually, a racemic modification is produced. While the racemic modification as such is pharmacologically active, each racemic modification may optionally be resolved into the component isomers. Such a mixture of isomers can be fractionated into the respective isomers by known optical resolution techniques, for example the technique which comprises reacting the racemic modification with an optically active carboxylic acid (e.g. (+) or (-)-tartaric acid or (+) or (-)-malic acid) or sulfonic acid (e.g. (+)-camphorsulfonic acid) to provide a salt and isolating the salt by fractional crystallization or the technique which comprises using a chiral column. Optical isomers can be also obtained by using the optically active form of starting compound [III], [IV], [V], [VI], [VII], [XII], [XIII], or [Ia] (S-configuration or R-configuration).

The salt of compound [I] of the present invention can be provided by a per se known method. For example, the hydrochloride of compound [I] can be prepared by dissolving compound [I] in a solution of hydrogen chloride in alcohol or ethyl ether.

Recrystallizing compound [I] or a salt thereof from a suitable solvent (inclusive of water) may give rise to the corresponding solvate (inclusive of hydrate). Such solvates also fall within the scope of the invention. For example, the hydrate of compound [I] according to the invention may form upon recrystallization of compound [I] from an aqueous alcohol.

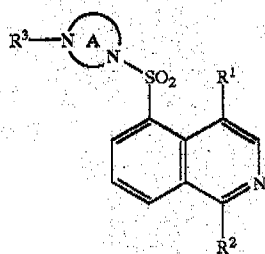
The compound of the invention may show polymorphism. Such polymorphs all fall within the scope of the invention.

The compound of the invention as produced in the above manner can be isolated and purified, in the form of a free

vasospasm-reversing activity in much lower dose. Moreover, the duration of action of the compound of the invention was also considerably longer. Those findings suggest the usefulness of the compound of the invention in the prevention and treatment of cerebrovascular diseases, particularly brain tissue impairments due to the cerebral vasospasm subsequent to cerebral hemorrhage. Furthermore, the compound of the invention has cerebral vasodilating activity and protectant activity against ischemic neuronal death, thus being useful for the management of sequelae of cerebral hemorrhage, cerebral infarction, transient cerebral ischemic attack, or head trauma.

What is claimed is:

1. A compound of formula [I],



where

R<sup>1</sup> is alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, or halogen;

R<sup>2</sup> is hydrogen, hydroxy, or halogen;

R<sup>3</sup> is hydrogen, alkyl, or amidino; and

Ring A is a 5 to 11-membered cyclic amino group which may be bridged between two carbon atoms in optional positions and which may be substituted, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. The compound according to claim 1, wherein R<sup>1</sup> is alkyl.

3. The compound according to claim 2, wherein the alkyl is straight-chain or branched of 1-6 carbon atoms.

4. The compound according to claim 3, wherein the alkyl includes 1-4 carbon atoms.

5. The compound according to claim 3, wherein the alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, and isohexyl.

6. The compound according to claim 5, wherein the alkyl is methyl.

7. The compound according to claim 1, wherein R<sup>2</sup> is hydrogen.

8. The compound according to claim 1, wherein R<sup>3</sup> is hydrogen.

9. The compound according to claim 1, wherein ring A is hexahydro-1H-1,4-diazepin-1-yl, the ring carbon atom or atoms of which may be substituted by an alkyl moiety.

10. The compound according to claim 9, wherein ring A is selected from the group consisting of 2-methyl-hexahydro-1H-1,4-diazepinyl or 7-methyl-hexahydro-1H-1,4-diazepinyl.

11. The compound according to claim 1, wherein the compound is selected from the group consisting of hexahydro-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine dihydrochloride, (S)-(+)-hexahydro-2-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride, hexahydro-7-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine dihydrochloride, hexahydro-5-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine dihydrochloride, hexahydro-2-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride, (R)-(-)-hexahydro-2-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride and (R)-(+)-hexahydro-5-methyl-1-[(4-methyl-5-isoquinolinyl)sulfonyl]-1H-1,4-diazepine hydrochloride.

12. A pharmaceutical composition useful for treating cerebrovascular disease comprising a therapeutically effective amount of the compound of claim 1, in combination with a pharmaceutically acceptable carrier or diluent.

13. A method of reducing the risk of cerebral vasospasm following a subarachnoid hemorrhage in a subject at risk, comprising administering to the subject the compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent in an amount effective to reduce the risk of cerebral vasospasm in the subject.

14. A method of treating a subject suffering from a cerebrovascular disease, comprising administering to the subject the compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent in an amount sufficient to treat the subject.

15. A method of inhibiting or preventing cerebral vasospasm following a subarachnoid hemorrhage in a subject at risk, comprising administering to the subject the compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent in an amount sufficient to inhibit or prevent the cerebral vasospasm in the subject.

16. A method for increasing cerebral blood-flow volume in a subject comprising administering to the subject the compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent in an amount sufficient to increase cerebral blood flow in the subject.

\* \* \* \* \*

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

2020  
Bogotá, D.C.,

Abogado  
**EMILIO FERRERO**  
Apoderado

|               |            |           |
|---------------|------------|-----------|
| <b>ASUNTO</b> | Radicación | 07-053905 |
|               | Trámite    | 002       |
|               | Evento     | 001       |
|               | Actuación  | 430       |
|               | Oficio     |           |
|               | Folios     | 08        |

**14793**

|                         |                                     |                               |                                                                      |
|-------------------------|-------------------------------------|-------------------------------|----------------------------------------------------------------------|
| Patente de Invención    | <input checked="" type="checkbox"/> | Patente de Modelo de Utilidad | <input type="checkbox"/>                                             |
| Vía Nacional            | <input type="checkbox"/>            |                               |                                                                      |
| Vía PCT (fase nacional) | <input checked="" type="checkbox"/> | Cap. I                        | <input checked="" type="checkbox"/> Cap. II <input type="checkbox"/> |

No. Sol. Internacional      PCT/JP2005/021844  
Fecha de Presentación Internal.      29 de noviembre de 2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

**1. Documentos estudiados**

|                          |                                                                       |
|--------------------------|-----------------------------------------------------------------------|
| <u>Descripción:</u>      | Folios: <u>63</u> a <u>84</u> y <u>87</u> como se radicó inicialmente |
| <u>Reivindicaciones:</u> | Folios <u>84</u> a <u>86</u> como se radicó inicialmente              |
| <u>Dibujos:</u>          | Folios <u>88</u> a <u>95</u> como se radicó inicialmente              |
| <u>Prioridad:</u>        | Folios: <u>1</u><br>29/11/2004, JP, 2004-344271                       |

**2. Análisis de la Prioridad**

La fecha de prioridad del 29 de noviembre de 2004 y su correspondiente documento, corresponden con la materia solicitada de protección.

**3. Objeto de la invención**

Título de la solicitud: Clorhidrato dihidrato de (S)-(-)-1-(4-fluoroisoquinolin-5-il)sulfonil-2-metil-1,4-homopiperazina

El problema planteado en esta solicitud es la necesidad de obtener un compuesto cristalino del compuesto clorhidrato dihidrato de (S)-(-)-1-(4-fluoroisoquinolin-5-il)sulfonil-2-metil-1,4-homopiperazina más estable en comparación con la forma anhidra ya existente.

Para solucionar este problema técnico la solicitud en estudio, el solicitante proporciona el compuesto clorhidrato dihidrato de (S)-(-)-1-(4-fluoroisoquinolin-5-il)sulfonil-2-metil-1,4-homopiperazina

IPC: C07D 401/12

**4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d))**

Las reivindicación 12, se refiere a un método de tratamiento, el cual no es patentable de acuerdo a los artículos mencionados de la normatividad vigente.

**5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)**

Las reivindicación 11, se refiere al uso del compuesto, los cuales no son patentables de acuerdo a los artículos mencionados de la normatividad vigente.

**6. Determinación del Estado de la Técnica**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de la publicación en fase internacional: 29 de noviembre de 2004

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 29/11/2004 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

| Nº | Documento    | Título                             | Fecha de publicación |
|----|--------------|------------------------------------|----------------------|
| D1 | WO 99/20620  | Isoquinoline derivative and drug   | 29/04/1999           |
| D2 | US 6,153,608 | Isoquinoline derivatives and drugs | 28/11/2000           |

**D1** enseña el compuesto derivado de fórmula I y sus sales farmacéuticamente aceptables, útiles en las enfermedades cerebrovasculares

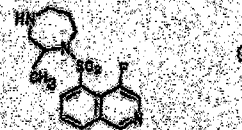
**D2** enseña previamente compuestos de fórmula I, sus sales y solvatos útiles en el tratamiento o prevención del deterioro de los tejidos cerebrales debido al vasoespismo después de una hemorragia cerebral.

**7. Análisis de patentabilidad (artículo 14 D486)****Nivel Inventivo (artículo 18 D486)**

La reivindicación 1 consiste en:

Clorhidrato dihidrato de (S)-(-)-1-(4-fluoroisoquinolin-5-il)sulfonil-2-metil-1,4-homopiperazina. (En adelante compuesto I)

El Estado de la Técnica más cercano es **D1**, que da a conocer el compuesto y las composiciones del clorhidrato de (S)-(-)-1-(4-fluoroisoquinolin-5-il)sulfonil-2-metil-1,4-homopiperazina. (Ver resumen) (Ver Folio 104, Informe escrito de la Oficina de Búsqueda Internacional)



El compuesto objeto de esta solicitud se diferencia del compuesto de **D1**, en que es dihidrato.

El hecho de incluir esta molécula de agua en el compuesto que se daba a conocer en **D1**, causa que se obtenga un compuesto cristalino más estable en comparación con la forma anhidra ya existente (Ver Folio 65, [009])

El Problema Técnico Objetivo era obtener un compuesto cristalino más estable en comparación con la forma anhidra ya existente.

D2 describe una manera de solucionar el problema técnico, mediante los compuestos derivados del isoquinolinas de fórmula I, los cuales son actúan en la prevención de enfermedades con daño cerebral. En D2 se encuentran sugeridos los compuestos de la solicitud presentada (cuando R<sup>1</sup> es halógeno, R<sup>2</sup> es hidrógeno, R<sup>3</sup> es hidrógeno, y el anillo representa un ciclo de 5-11 miembros el cual puede estar sustituido por alquilo (Ver resumen, columna 2, columna 3, líneas 1-4)), los cuales pueden encontrarse en la forma de sal clorhidrato (Ver columna 3, línea 6) y en forma isomérica. (Ver columna 10, líneas 33-36)

D2 además enseña que los compuestos pueden ser recristalizados o su sal de un adecuado solvente (inclusive agua) que puede guiar al correspondiente solvato (inclusive de hidrato) (Ver columna 10, líneas 57-63) y además divulga que los compuestos presentan polimorfismo. (Ver columna 10, línea 64)

La diferencia presentada, no parece concederle un efecto técnico inesperado al compuesto, puesto que D2 ya enseñaba que dichos compuestos se podían obtener en su forma hidrato y que presentan polimorfismo. Por lo tanto el experto medio de acuerdo con su trabajo rutinario los obtendría de forma fácil, y sin emplear actividad inventiva en forma clorhidrato y dihidrato.

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de obtener "un compuesto cristalino más estable del compuesto I en comparación con la forma anhidra ya existente", emplearía la sal clorhidrato con su correspondiente hidrato, mediante procesos de solvatación como lo revela D2 en el compuesto de D1. Por tanto, la reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2-10, no menciona alguna característica que haga inventivos a los compuestos de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

### 8. Conclusión:

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

| N° | Documento N° | Reivindicaciones afectadas | Requisito que afecta |
|----|--------------|----------------------------|----------------------|
| D1 | WO 99/20620  | 2-10                       | Nivel Inventivo      |
| D2 | US 6,153,608 | 2-10                       | Nivel Inventivo      |

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

**ALIX CARMENZA CÉSPEDES DE VERGEL**

Directora de Nuevas Creaciones (C)

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

12 NOV. 2010

CONCEPTO TÉCNICO No. 03345

EXAMINADOR TÉCNICO

Código No. 202070

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

2020  
Bogotá, D.C.

Abogado  
**EMILIO FERRERO**  
Apoderado

|               |            |              |
|---------------|------------|--------------|
| <b>ASUNTO</b> | Radicación | 07-053905    |
|               | Trámite    | 002          |
|               | Evento     | 001          |
|               | Actuación  | 430          |
|               | Oficio     | <b>14794</b> |
|               | Folios     | 01           |

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

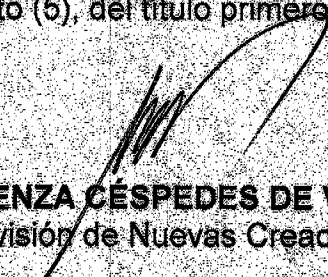
**1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN**

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- WO 99/20620-Isoquinoline derivative and drug (En idioma inglés)

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.

  
**ALIX CARMENZA CÉSPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones

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

**12 NOV. 2010**

**CONCEPTO TÉCNICO No. 03345**

**EXAMINADOR TÉCNICO**  
Código No. 202070