

380 380

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

División de Nuevas Creaciones

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-077652- -00005-0000

Fecha: 2008-06-06 13:28:25 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

REF. SOLICITUD DE PATENTE DE INVENCION

Trámite: PCT – FASE NACIONAL

**Invención: COMPUESTOS DE TETRAZOL Y SU USO COMO ANTAGONISTAS DEL
RECEPTOR DE GLUTAMATO METABOTRÓPICO**

Expediente: 06-077.652

Asunto: SOLICITUD DE EXAMEN DE PATENTABILIDAD

MAURICIO PATIÑO BONNET, mayor de edad, vecino de esta ciudad, identificado como aparece al pie de mi firma, portador de la tarjeta profesional número 73.583 del Consejo Superior de la Judicatura, actuando como apoderado dentro de la solicitud de la referencia y en cumplimiento de la exigencia del Artículo 44 de la Decisión 486 de 2000 de la Comunidad Andina, comedidamente y estando dentro del término de seis (6) meses previsto para el efecto, por medio del presente memorial acudo a la División de Nuevas Creaciones de la Superintendencia de Industria y Comercio con el fin de **SOLICITAR SE PROCEDA A LA REALIZACIÓN DEL EXAMEN DE PATENTABILIDAD** correspondiente a la solicitud de patente de invención PCT, en fase nacional, que se tramita bajo el expediente No. 06-077.652 y cuyo objeto se denomina **“COMPUESTOS DE TETRAZOL Y SU USO COMO ANTAGONISTAS DEL RECEPTOR DE GLUTAMATO METABOTRÓPICO”**, la cual fue publicada en la Gaceta de la Propiedad Industrial No. 587 del 31 de Enero de 2008, con Número de Publicación 1240.

De conformidad con la Resolución 44372 de Diciembre 26 de 2007 de la Superintendencia de Industria y Comercio, adjunto a la presente solicitud allego al expediente los Recibos Oficiales de Pago de Tasas No. 08-42.938 del 29 de Mayo 2008 y 08-44,070 del 4 de Junio de 2008, por valor de **CUATROCIENTOS VEINTE MIL PESOS (\$420.000) M/CTE.**

De la señora Jefe de la División de Nuevas Creaciones,

MAURICIO PATIÑO BONNET

C.C. 11.342.699 de Zipaquirá

T.P. 73583 del C.S. de la J.

N/Ref: 58616

381 381

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-077652- -00005-0000

Fecha: 2008-06-06 13:28:25 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

CERTIFICACION DE EXCEDENTE : 08 - 44,070
FECHA : JUNIO 4 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PRIETO & CARRIZOSA S.A	CONSIGNACION	BANCO DE BOGOTA	062754387	47051	03/06/2008	16,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	16,000.00
		99 OTROS SERVICIOS ADMINISTRATIVOS	16,000.00
		TOTAL :	\$ 16,000.00

DIEZ Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 April 2003 (10.04.2003)

PCT

(10) International Publication Number
WO 03/029210 A2

- (51) International Patent Classification⁷: **C07D**
- (21) International Application Number: **PCT/US02/31294**
- (22) International Filing Date: 1 October 2002 (01.10.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/327,132 4 October 2001 (04.10.2001) US
- (71) Applicant (for all designated States except US): **MERCK & CO. INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **COSFORD, Nicholas, D.** [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ROPPE, Jeffrey** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **CHEN, Chixu** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SMITH, Nicholas** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **REGER, Thomas** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (74) Common Representative: **MERCK & CO. INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

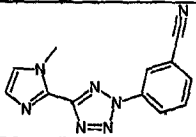
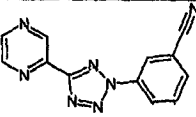
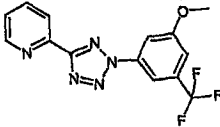
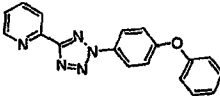
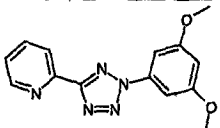
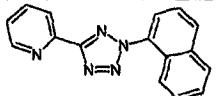
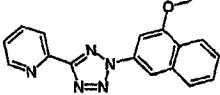
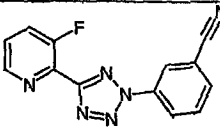
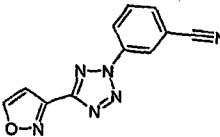
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/029210 A2

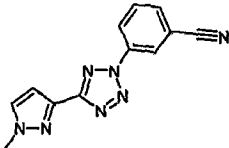
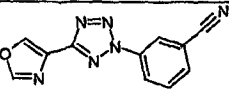
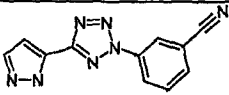
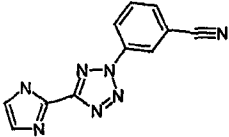
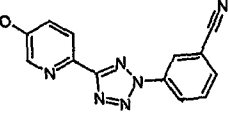
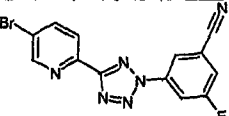
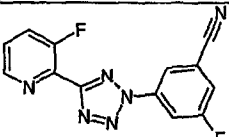
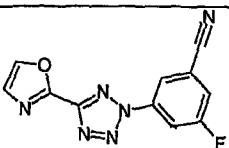
(54) Title: HETEROARYL SUBSTITUTED TETRAZOLE MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5

(57) Abstract: Tetrazole compounds substituted directly, or by a bridge, with a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl, are mGluR5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, and panic, as well as in the treatment of pain and other diseases.

385 205

EXAMPLE	Structure	¹ H NMR	MS (ESI)
48		8.58-8.59 (m, 1H), 8.51-8.55 (m, 1H), 7.81-7.84 (d, 1H), 7.72-7.77 (dd, 1H), 7.28 (s, 1H), 7.13 (s, 1H), 4.19 (s, 3H).	MS 252.1 (M ⁺ +H).
49		9.55-9.57 (s, 1H), 8.81-8.87 (m, 2H), 8.67 (s, 1H), 8.57-8.62 (m, 1H), 7.94- 7.97 (d, 1H), 7.84-7.91 (dd, 1H).	MS 250.1 (M ⁺ +H).
50		8.85-8.87 (d, 1H), 8.36-8.39 (d, 1H), 8.16 (s, 1H), 8.00-8.01 (t, 1H), 7.90-7.96 (t, 1H), 7.45-7.49 (m, 1H), 7.29 (s, 1H).	MS 322.0 (M ⁺ +H).
51		8.83-8.85 (d, 1H), 8.33-8.36 (d, 1H), 8.20-8.23 (d, 2H), 7.87-7.93 (t, 1H), 7.39-7.46 (m, 3H), 7.08-7.23 (m, 5H).	MS 316.1 (M ⁺ +H).
52		(HCl salt in CD ₃ OD) 8.95-9.05 (br, 1H), 8.84-8.87 (d, 1H), 8.76-8.80 (t, 1H), 8.19-8.25 (t, 1H), 7.40-7.41 (d, 2H), 6.74-6.76 (t, 1H), 3.92 (s, 6H).	MS 284.6 (M ⁺ +H).
53		8.85-8.87 (d, 1H), 8.37-8.40 (d, 1H), 8.07-8.11 (m, 2H), 7.90-8.00 (m, 3H), 7.59-7.67 (m, 3H), 7.43-7.48 (m, 1H).	MS 274.6 (M ⁺ +H).
54		ND	MS 304.6 (M ⁺ +H).
55		8.71 - 8.72 (m, 1H), 8.66 (m, 1H), 8.51 - 8.54 (m, 1H), 8.15 - 8.16 (m, 1H), 8.06 - 8.10 (m, 1H), 7.94 (dd, 1H), 7.77 - 7.80 (m, 1H).	MS 267.4 (M ⁺ +H).
56		9.32 (d, 1H), 8.65 - 8.67 (m, 1H), 8.50 - 8.52 (m, 1H), 8.14 - 8.15 (m, 1H), 7.91 (d, 1H), 7.32 (d, 1H).	MS 239.1 (M ⁺ +H).

386486

EXAMPLE	Structure	¹ H NMR	MS (ESI)
57		8.59 – 8.60 (m, 1H), 8.45 – 8.48 (m, 1H), 8.08 – 8.10 (m, 1H), 7.94 (d, 1H), 7.87 (dd, 1H), 6.91 (d, 1H), 3.98, (s, 3H).	MS 252.1 (M ⁺ +H).
58		8.80 (d, 1H), 8.63 – 8.64 (m, 1H), 8.55 – 8.57 (m, 1H), 8.51 (d, 1H), 7.97 – 7.99 (m, 1H), 7.87 (dd, 1H).	MS 239.0 (M ⁺ +H).
59		8.61 (m, 1H), 8.44 – 8.50 (m, 1H), 8.11 – 8.12 (m, 1H), 8.00 (m, 1H), 7.91 (dd, 1H), 6.96 (m, 1H).	MS 238.0 (M ⁺ +H).
60		8.68 – 8.69 (m, 1H), 8.60 – 8.62 (m, 1H), 8.06 – 8.09 (m, 1H), 7.94 (dd, 1H), 7.87 (s, 2H).	MS 238.0 (M ⁺ +H).
61		10.51 (s, 1H), 8.66 (m, 1H), 8.50 – 8.52 (m, 1H), 8.27 – 8.28 (m, 1H), 8.12 – 8.14 (m, 1H), 7.93 (dd, 1H), 7.47 – 7.53 (m, 2H).	MS 265.1 (M ⁺ +H).
62		8.96 (m, 1H), 8.57 (m, 1H), 8.45 – 8.47 (m, 1H), 8.36 – 8.38 (m, 1H), 8.21 – 8.24 (m, 2H).	MS 345.2 (M ⁺ +H).
63		8.71 – 8.73 (m, 1H), 8.56 (m, 1H), 8.45 – 8.47 (m, 1H), 8.22 – 8.25 (m, 1H), 8.07 – 8.10 (m, 1H), 7.77 – 7.81 (m, 1H).	MS 285.0 (M ⁺ +H).
64		8.45 (m, 1H), 8.27 – 8.36 (m, 1H), 7.98 (s, 1H), 7.58 – 7.60 (m, 1H), 7.49 (m, 1H).	MS 257.0 (M ⁺ +H).

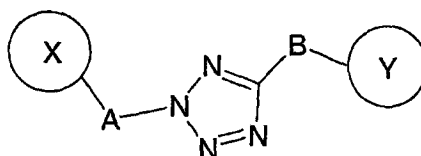
387
20x

EXAMPLE	Structure	¹ H NMR	MS (ESI)
65		8.91 (m, 1H), 8.74 (m, 1H), 8.38 – 8.40 (m, 1H), 8.09 (dd, 1H), 8.04 – 8.07 (m, 2H), 7.91 (s, 2H), 7.41 – 7.43 (m, 1H)	MS 324.3 (M ⁺ +H).
66		8.51 (m, 1H), 8.40 – 8.42 (m, 1H), 8.23 – 8.25 (m, 1H), 7.23 (m, 1H), 2.30 (s, 3H).	MS 270.5 (M ⁺ +H).
67		8.61 (d, 1H), 8.53 – 8.54 (m, 1H), 7.85 – 7.87 (m, 1H), 7.75 – 7.78 (m, 1H), 7.60 (d, 1H), 7.54 (dd, 1H), 7.33 – 7.36 (m, 1H).	MS 325.1 (M ⁺ +H).
68		9.09 (d, 2H), 8.67 – 8.68 (m, 1H), 8.53 – 8.62 (m, 1H), 7.90 – 7.92 (m, 1H), 7.86 – 7.88 (m, 1H), 7.72 (t, 1H), 7.61 – 7.66 (m, 2H), 7.39 – 7.42 (m, 1H).	MS 336.3 (M ⁺ +H).
69		8.65 (d, 1H), 8.56 – 8.57 (m, 1H), 7.97 (d, 1H), 7.83 – 7.87 (m, 2H), 7.60 – 7.64 (m, 2H), 7.34 – 7.36 (m, 1H), 6.93 (d, 1H).	MS 324.0 (M ⁺ +H).
70		8.70 (d, 1H), 8.58 – 8.60 (m, 1H), 7.94 (d, 1H), 7.90 – 7.92 (m, 1H), 7.86 – 7.88 (m, 1H), 7.68 (dd, 1H), 7.64 (m, 1H), 7.36 – 7.38 (m, 1H), 6.90 (d, 1H), 4.02 (s, 3H).	MS 338.3 (M ⁺ +H).
71		8.51 (s, 1H), 8.40 – 8.43 (m, 1H), 8.13 – 8.19 (m, 1H), 7.96 (d, 1H), 6.94 (d, 1H), 4.00 (s, 3H).	MS 270.3 (M ⁺ +H).
72		8.9-8.85 (br, 1H), 8.57-8.56 (m, 2H), 8.41-8.37 (m, 1H), 8.30-8.27 (m, 4H), 7.9 (dd, 1H), 7.87 (br, 1H), 7.57 (d, 2H).	MS 315.98 (M ⁺ +H).

328
588

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



5

(I)

or a pharmaceutically acceptable salt thereof, wherein

X and Y each independently is aryl or heteroaryl wherein at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively;

10

X is optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) groups;

20

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

25

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

389
329

A is -C₀-4alkyl, -C₀-2alkyl-SO-C₀-2alkyl-, -C₀-2alkyl-SO₂-C₀-2alkyl-, -C₀-2alkyl-CO-C₀-2alkyl-, -C₀-2alkyl-NR⁹CO-C₀-2alkyl-, -C₀-2alkyl-NR⁹SO₂-C₀-2alkyl- or -heteroC₀-4alkyl;

- Y is optionally substituted with 1-7 independent halogen, -CN, NO₂,
 5 -C₁-6alkyl, -C₁-6alkenyl, -C₁-6alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷,
 -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸,
 -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or -
 C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to form
 10 cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5
 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -
 O(aryl), -O(heteroaryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), or
 -N(C₀-6alkyl)(aryl) groups;

- R⁵, R⁶, and R⁷ each independently is -C₀-6alkyl, -C₃-7cycloalkyl,
 15 heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent
 halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -
 O(heteroaryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-
 6alkyl)(aryl) substituents;

- R⁸ is -C₁-6alkyl, -C₃-7cycloalkyl, heteroaryl, or aryl; optionally
 20 substituted with 1-5 independent halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-
 7cycloalkyl), -O(aryl), -O(heteroaryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-
 7cycloalkyl), -N(C₀-6alkyl)(aryl) substituents;

- B is -C₀-4alkyl, -C₀-2alkyl-SO-C₀-2alkyl-, -C₀-2alkyl-SO₂-C₀-
 2alkyl-, -C₀-2alkyl-CO-C₀-2alkyl-, -C₀-2alkyl-NR¹⁰CO-C₀-2alkyl-, -C₀-2alkyl-
 25 NR¹⁰SO₂-C₀-2alkyl- or -heteroC₀-4alkyl;

- R⁹ and R¹⁰ each independently is -C₀-6alkyl, -C₃-7cycloalkyl,
 heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent
 halogen, -CN, -C₁-6alkyl, -O(C₀-6alkyl), -O(C₃-7cycloalkyl), -O(aryl), -
 O(heteroaryl), -N(C₀-6alkyl)(C₀-6alkyl), -N(C₀-6alkyl)(C₃-7cycloalkyl), -N(C₀-
 30 6alkyl)(aryl) substituents; and

any N may be an N-oxide.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/077918 A1

(51) International Patent Classification⁷: A61K 31/4439,
C07D 401/12

Brian, W. [CA/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

(21) International Application Number: PCT/US03/07074

(74) Common Representative: MERCK & CO., INC.; 126
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(22) International Filing Date: 7 March 2003 (07.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/363,456 12 March 2002 (12.03.2002) US

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

(71) Applicant (*for all designated States except US*): MERCK
& CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

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

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): SMITH, Nicholas,
D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). COSFORD, Nicholas, D. P. [GB/US];
126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
REGER, Thomas, R. [US/US]; 126 East Lincoln Ave-
nue, Rahway, NJ 07065-0907 (US). ROPPE, Jeffrey,
R. [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). POON, Steven, F. [US/US]; 126 East
Lincoln Avenue, Rahway, NJ 07065-0907 (US). HUANG,
Dehua [CN/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). CHEN, Chixu [US/US]; 126 East Lin-
coln Avenue, Rahway, NJ 07065-0907 (US). EASTMAN,

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

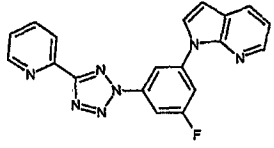
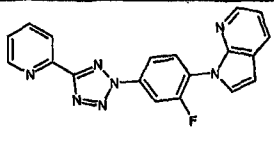
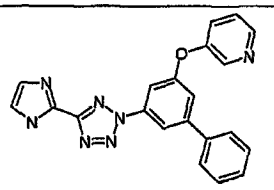
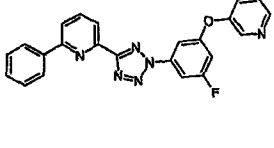
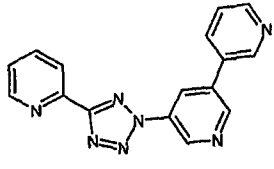
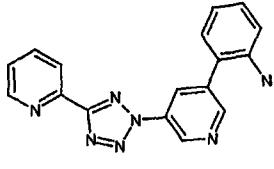
(54) Title: DI-ARYL SUBSTITUTED TETRAZOLE MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5

(57) Abstract: Tetrazole compounds substituted directly, or by a bridge, with i) a heteroaryl moiety containing N adjacent to the point of connection of the heteroaryl and ii) another heteroaryl or aryl ring; with at least one of the rings being further substituted with another ring, are mGluR5 modulators useful in the treatment of psychiatric and mood disorders such as, for example, schizophrenia, anxiety, depression, panic, and bipolar disorder, as well as in the treatment of pain, Parkinson's disease, cognitive dysfunction, epilepsy, circadian rhythm disorders, drug addiction, drug abuse, drug withdrawal, obesity and other diseases.

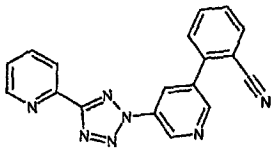
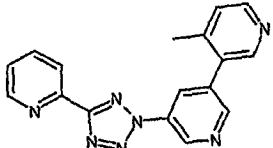
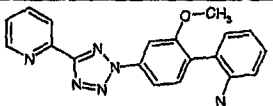
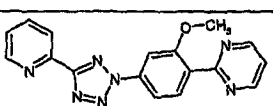
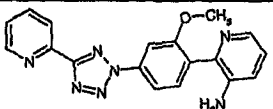
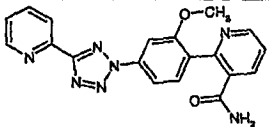
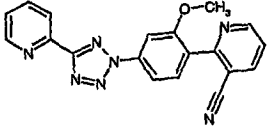
WO 03/077918 A1

390306
D2

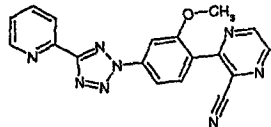
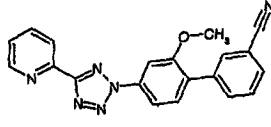
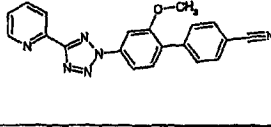
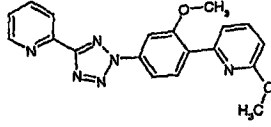
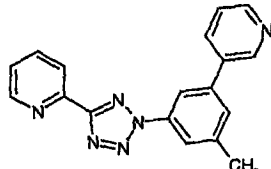
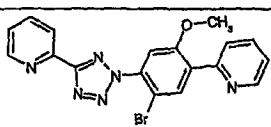
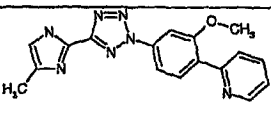
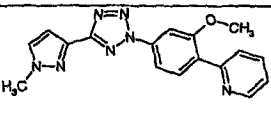
391
201

EXAMPLE	Structure	¹ H NMR	MS (ESI)
		(ddd, 1H), 7.29 (dd, 1H), 6.83 (d, 1H)	
47.		8.98 (br s, 1H), 8.83 (d, 1H), 8.45 (dd, 1H), 8.32 (d, 1H), 8.26 (dt, 1H), 8.26 (d, 1H), 8.16 (dd, 1H), 8.10 (dt, 1H), 8.01 (dt, 1H), 7.64 (ddd, 1H), 7.32 (dd, 1H), 6.86 (d, 1H)	MS 358 (M+H) ⁺
48.		8.84 (d, 1H), 8.35 (dd, 1H), 8.32 (s, 1H), 8.31 (dd, 1H), 8.23 (dd, 1H), 8.15 (dd, 1H), 8.14 – 8.08 (m, 2H), 7.87 (dd, 1H), 7.64 (ddd, 1H), 7.27 (dd, 1H), 6.83 (d, 1H)	MS 358 (M+H) ⁺
49.		8.60 (s, 1H), 8.52-8.51 (d, 1H), 8.364-8.358 (t, 1H), 7.923-7.919 (t, 1H), 7.88-7.786 (m, 1H), 7.77-7.72 (m, 4H), 7.697-7.658 (m, 2H), 7.56-7.53 (m, 2H), 7.50-7.47 (m, 1H).	MS 410.97 (M ⁺ +H).
50.		8.85 (s, 1H), 8.68-8.67 (d, 1H), 8.33-8.31 (dd, 1H), 8.27-8.55 (d, 1H), 8.17-78.00 (m, 7H), 7.54-7.46 (m, 3H), 7.31-7.30 (m, 1H).	MS 382.41 (M ⁺ +H).
51.		9.60 (d, 1H), 9.01 (d, 1H), 8.99 (d, 1H), 8.87 (d, 1H), 8.78 (m, 1H), 8.75 (d, 1H), 8.39 (d, 1H), 8.02 (d, 1H), 7.94 (dd, 1H), 7.50 (m, 2H).	MS 302.2 (M ⁺ +H).
52.		9.51 (d, 1H), 8.90 (d, 1H), 8.85 (d, 1H), 8.70 (dd, 1H), 8.36 (d, 1H), 7.92 (dd, 1H), 7.46 (m, 1H), 7.25 (dd, 1H), 7.19 (d, 1H), 6.91 (dd, 1H), 6.84 (d, 1H), 3.89 (s, 2H).	MS 316.5 (M ⁺ +H).

3923⁰²

EXAMPLE	Structure	¹ H NMR	MS (ESI)
53.		9.66 (d, 1H), 8.97 (s, 1H), 8.86 (d, 1H), 8.79 (m, 1H), 8.38 (d, 1H), 7.94 (dd, 1H), 7.87 (d, 1H), 7.78 (dd, 1H), 7.63 (m, 2H), 7.47 (m, 1H).	MS 326.4 (M ⁺ +H).
54.		9.51 (d, 1H), 8.79 (d, 1H), 8.74 (d, 1H), 8.68 (m, 1H), 8.49 (m, 2H), 8.36 (d, 1H), 8.03 (dd, 1H), 7.58 (m, 1H), 7.40 (d, 1H), 2.42 (s, 3H).	MS 316.0 (M ⁺ +H).
55.		9.06 (d, 1H), 9.00 (d, 1H), 8.79 (dd, 1H), 8.23 (dd, 1H), 8.09 (m, 2H), 7.70 (d, 1H), 7.64 (m, 2H), 7.58 (m, 1H), 7.53 (m, 1H), 4.07 (s, 3H).	MS 345.3 (M ⁺ +H).
56.		9.25 (d, 2H), 8.94 (s, broad, 1H), 8.70 (s, broad, 1H), 8.49 (m, 2H), 8.18 (s, 1H), 8.13 (d, 1H), 7.97 (s, broad, 1H), 7.91 (dd, 1H), 4.23 (s, 3H).	MS 331.9 (M ⁺ +H).
57.		ND	MS 346.3 (M ⁺ +H).
58.		9.06 (m, 2H), 8.81-8.92 (m, 3H), 8.25 (m, 2H), 8.16 (d, 1H), 8.14 (s, 1H), 7.93 (d, 1H), 4.07 (s, 3H).	MS 374.3 (M ⁺ +H).
59.		8.86-8.92 (m, 2H), 8.39 (d, 1H), 7.91-8.08 (m, 4H), 7.69 (d, 1H), 7.43-7.51 (m, 2H), 4.05 (s, 3H).	MS 356.4 (M ⁺ +H).

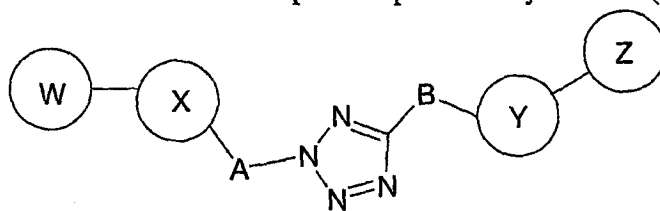
393-203

EXAMPLE	Structure	¹ H NMR	MS (ESI)
60.		8.89 (m, 2H), 8.69 (d, 1H), 8.39 (d, 1H), 8.11 (d, 1H), 8.02 (d, 1H), 7.94 (dd, 1H), 7.73 (d, 1H), 7.48 (m, 1H), 4.08 (s, 3H).	MS 357.3 (M ⁺ +H).
61.		8.90 (d, 1H), 8.39 (d, 1H), 7.89-8.00 (m, 4H), 7.79 (d, 1H), 7.66 (d, 1H), 7.56 (m, 1H), 7.49 (m, 2H), 3.96 (s, 3H).	MS 355.3 (M ⁺ +H).
62.		8.88 (d, 1H), 8.38 (d, 1H), 8.00 (d, 1H), 7.92 (m, 2H), 7.73 (d, 2H), 7.69 (d, 2H), 7.49 (m, 2H), 3.98 (s, 3H).	MS 355.3 (M ⁺ +H).
63.		9.02 (d, 1H), 8.37 (d, 1H), 8.21 (d, 1H), 7.99 (d, 1H), 7.91 (m, 2H), 7.63 (m, 2H), 7.46 (m, 1H), 6.72 (m, 1H), 4.04 (s, 3H), 4.03 (s, 3H).	MS 361.1 (M ⁺ +H).
64.		8.95 (d, 1H), 8.88 (d, 1H), 8.68 (m, 1H), 8.41 (d, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 8.01 (m, 1H), 7.95 (m, 1H), 7.56 (s, 1H), 7.45 (m, 2H), 2.59 (s, 3H).	MS 315.4 (M ⁺ +H).
65.		8.88 (d, 1H), 8.78 (d, 1H), 8.41 (d, 1H), 8.32 (s, 1H), 7.96 (m, 2H), 7.82 (m, 1H), 7.50 (m, 1H), 7.34 (m, 2H), 3.95 (s, 3H).	MS 411.0 (M ⁺ +H+2).
66.		8.92-8.94 (m, 1H), 8.77-8.79 (m, 1H), 8.38-8.40 (m, 1H), 8.11-8.16 (m, 3H), 8.02-8.04 (m, 1H), 7.62 (s, 1H).	MS 334.3 (M ⁺ +H).
67.		8.8 (d, 1H), 8.18-8.20 (m, 1H), 8.09-8.10 (m, 1H), 8.05 (d, 1H), 7.97 (d, 1H), 7.92 (m, 1H), 7.90 (s, 1H).	MS 334.2 (M ⁺ +H).

3943^{aa}

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

X and Y each independently is aryl or heteroaryl wherein at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively;

X is optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or -N(C₀₋₆alkyl)(aryl) groups;

R¹, R², and R³ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁴ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

A is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-, -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR⁹SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

398²as

W is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³,
 5 -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴,
 -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or
 -C(=NOR¹)R² substituents;

Y is optionally substituted with 1-7 independent halogen, -CN, NO₂,
 -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷,
 -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸,
 10 -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or
 -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to
 form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl
 substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further
 substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇
 15 7cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or
 -N(C₀₋₆alkyl)(aryl) groups;

R⁵, R⁶, and R⁷ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl,
 heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent
 halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆
 20 6alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

R⁸ is -C₁₋₆alkyl, -C₃₋₇cycloalkyl, heteroaryl, or aryl; optionally
 substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇
 7cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl),
 -N(C₀₋₆alkyl)(aryl) substituents;

25 B is -C₀₋₄alkyl, -C₀₋₂alkyl-SO-C₀₋₂alkyl-, -C₀₋₂alkyl-SO₂-C₀₋₂alkyl-,
 -C₀₋₂alkyl-CO-C₀₋₂alkyl-, -C₀₋₂alkyl-NR¹⁰CO-C₀₋₂alkyl-, -C₀₋₂alkyl-
 NR¹⁰SO₂-C₀₋₂alkyl- or -heteroC₀₋₄alkyl;

R⁹ and R¹⁰ each independently is -C₀₋₆alkyl, -C₃₋₇cycloalkyl,
 heteroaryl, or aryl; any of which is optionally substituted with 1-5 independent
 30 halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆
 6alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), -N(C₀₋₆alkyl)(aryl) substituents;

Z is -C₃₋₇cycloalkyl, -heteroC₃₋₇cycloalkyl, -C₀₋₆alkylaryl, or -C₀₋₆alkylheteroaryl optionally substituted with 1-7 independent halogen, -CN, NO₂, -C₁₋

396.
300

6alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R², -C(=NR¹)NR²R³,
 -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴, -NR¹CONR²R³, -SR⁴,
 -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R², -C(=NR¹)R², or
 -C(=NOR¹)R² substituents;

- 5 one of W and Z is optionally absent; and
 any N may be an N-oxide.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein

- 10 X is 2-pyridyl optionally substituted with 1-4 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR¹, -NR¹R²,
 -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -NR¹COR², -NR¹CO₂R², -NR¹SO₂R⁴,
 -NR¹CONR²R³, -SR⁴, -SOR⁴, -SO₂R⁴, -SO₂NR¹R², -COR¹, -CO₂R¹, -CONR¹R²,
 15 -C(=NR¹)R², or -C(=NOR¹)R² substituents, wherein optionally two substituents are
 combined to form a cycloalkyl or heterocycloalkyl ring fused to X; wherein the -C₁₋₆alkyl substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further
 substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or
 -N(C₀₋₆alkyl)(aryl) groups.

20

3. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein

- Y is phenyl optionally substituted with 1-5 independent halogen, -CN, NO₂, -C₁₋₆alkyl, -C₁₋₆alkenyl, -C₁₋₆alkynyl, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷,
 25 -N(=NR⁵)NR⁶R⁷, -NR⁵COR⁶, -NR⁵CO₂R⁶, -NR⁵SO₂R⁸, -NR⁵CONR⁶R⁷, -SR⁸,
 -SOR⁸, -SO₂R⁸, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, -C(=NR⁵)R⁶, or
 -C(=NOR⁵)R⁶ substituents, wherein optionally two substituents are combined to
 form a cycloalkyl or heterocycloalkyl ring fused to Y; wherein the -C₁₋₆alkyl
 substituent, cycloalkyl ring, or heterocycloalkyl ring each optionally is further
 30 substituted with 1-5 independent halogen, -CN, -C₁₋₆alkyl, -O(C₀₋₆alkyl), -O(C₃₋₇cycloalkyl), -O(aryl), -N(C₀₋₆alkyl)(C₀₋₆alkyl), -N(C₀₋₆alkyl)(C₃₋₇cycloalkyl), or
 -N(C₀₋₆alkyl)(aryl) groups..

United States Patent [19]

Carson et al.

[11] Patent Number: 4,663,332

[45] Date of Patent: May 5, 1987

D3-3a2
397

[54] 5-SUBSTITUTED N-ALKYLATED TETRAZOLES

[75] Inventors: Matthew Carson, Nutley; Ronald A. LeMahieu, North Caldwell, both of N.J.

[73] Assignee: Hoffman-La Roche Inc., Nutley, N.J.

[21] Appl. No.: 786,386

[22] Filed: Oct. 10, 1985

[51] Int. Cl.⁴ C07D 401/06; A61K 31/44

[52] U.S. Cl. 514/340; 546/276;
548/252; 514/381

[58] Field of Search 546/276; 514/340

[56] References Cited

U.S. PATENT DOCUMENTS

4,105,852 8/1978 Hassall et al. 546/276

FOREIGN PATENT DOCUMENTS

0108592 5/1984 European Pat. Off. .

0110541 6/1984 European Pat. Off. .

OTHER PUBLICATIONS

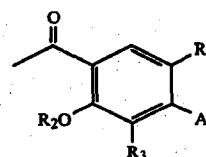
The Journal of Pharmacology and Experimental Therapeutics, vol. 233, No. 1 (1985).
Naunyn-Schmiedeberg's Arch. Pharmacol. (1986) 333; 70-77.

Primary Examiner—Jane T. Fan

Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; Matthew Boxer

[57] ABSTRACT

Compounds of the formula



wherein R₁, R₂, R₃, and A are as described herein, are set forth.

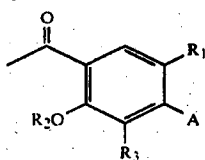
These compounds are useful as anti-allergic agents and agents for the treatment of cardiovascular diseases.

23 Claims, No Drawings

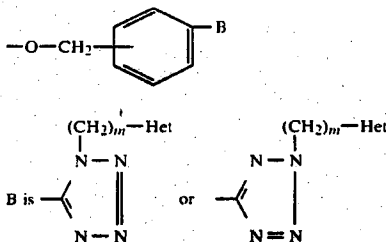
5-SUBSTITUTED N-ALKYLATED TETRAZOLES

BRIEF SUMMARY OF THE INVENTION

The invention relates to compounds of the formula



wherein R_1 is hydrogen or halogen; R_2 is hydrogen or C_2-C_4 alkanoyl; R_3 is hydrogen or C_1-C_6 alkyl; A is $-O-(CH_2)_n-B$ or,

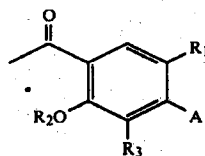


Het is a 5- or 6-membered heterocycle, containing one or two nitrogens and optionally mono-substituted by C_1-C_6 alkyl; n is an integer from 3 to 8; and m is an integer from 1 to 6; or pharmaceutically acceptable acid addition salts thereof. The compounds of formula I are useful as anti-allergic agents and agents for the treatment of cardiovascular diseases.

DETAILED DESCRIPTION OF THE INVENTION

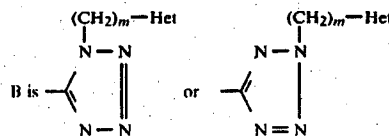
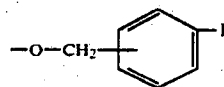
As used herein, the term "alkyl" denotes straight or branched chain alkyl of up to 12 carbon atoms, or the number of carbon atoms otherwise designated. Thus C_1-C_6 alkyl denotes a straight or branched chain alkyl of up to six carbon atoms. The term "alkyl" includes, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "alkanoyl" denotes a straight or branched chain alkanoyl of one to six carbon atoms, or the number of carbon atoms otherwise designated. The term "alkanoyl" includes, for example, acetyl, propionyl, iso-butyryl and the like. As used herein the term "halogen" denotes chlorine, bromine, iodine and fluorine.

The invention relates to compounds of the formula



wherein R_1 is hydrogen or halogen; R_2 is hydrogen or C_2-C_4 alkanoyl;

R_3 is hydrogen or C_1-C_6 alkyl; A is $-O-(CH_2)_n-B$, or

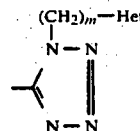


Het is a 5- or 6-membered heterocycle, containing one or two nitrogens and optionally monosubstituted by C_1-C_6 alkyl, preferably 3-pyridyl, 4-pyridyl or 1-imidazolyl;

n is an integer from 3 to 8; and m is an integer from 1 to 6; or a pharmaceutically acceptable acid addition salt thereof.

Preferred compounds of formula I are those wherein R_1 is chlorine; R_2 is hydrogen; R_3 is propyl; A is $-O-(CH_2)_n-B$;

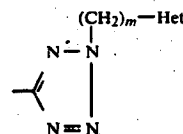
B is



Het is 3-pyridyl, n is an integer from 3 to 5 and m is an integer from 1 to 4.

Other preferred compounds of formula I are those wherein R_1 is hydrogen; R_2 is hydrogen; R_3 is propyl; A is $-O-(CH_2)_n-B$;

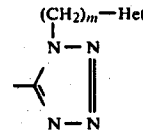
B is



Het is 3-pyridyl, n is an integer from 3 to 5, and m is an integer from 1 to 4, or preferably from 3 to 4.

Still other preferred compounds of formula I are those wherein R_1 is hydrogen; R_2 is hydrogen; R_3 is propyl; A is $-O-(CH_2)_n-B$;

B is



Het is 3-pyridyl, n is an integer from 3 to 5; and m is an integer from 1 to 4, preferably from 3 to 4.

Exemplary compounds of formula I are:

1-[2-hydroxy-3-propyl-4-[4-[1-[3-(1H-imidazol-1-yl)propyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone;

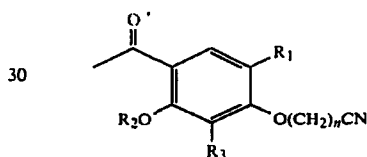
3

- 1-[2-hydroxy-3-propyl-4-[4-[2-[3-(1H-imidazol-1-yl)propyl-2H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[3-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[3-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[3-[2-(1H-imidazol-1-yl)propyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[5-chloro-2-hydroxy-3-propyl-4-[5-[1-[4-(3-pyridinyl)butyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-acetoxy-3-propyl-4-[5-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]propoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[1-[4-(3-pyridinyl)butyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[1-[4-(3-pyridinyl)butyl]-1H-tetrazol-5-yl]propoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[2-[4-(3-pyridinyl)butyl]-2H-tetrazol-5-yl]propoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[2-(3-pyridinyl)methyl]-2H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[1-[2-(3-pyridinyl)ethyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[2-[2-(3-pyridinyl)ethyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone; and
 1-[2-hydroxy-3-propyl-4-[4-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone.
 1-[2-hydroxy-3-propyl-4-[5-[1-[2-(3-pyridinyl)ethyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[1-[1-(3-pyridinyl)methyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[1-[4-(3-pyridinyl)butyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[1-[2-(3-pyridinyl)ethyl]-1H-tetrazol-5-yl]propoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[1-[1-(3-pyridinyl)methyl]-1H-tetrazol-5-yl]propoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[1-[5-(3-pyridinyl)pentyl]-1H-tetrazol-5-yl]propoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[2-[2-(3-pyridinyl)ethyl]-2H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[2-[1-(3-pyridinyl)methyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[4-[2-[4-(3-pyridinyl)butyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[1-[3-(1H-imidazol-1-yl)propyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[2-[3-(1H-imidazol-1-yl)propyl]-2H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[2-[2-(1H-imidazol-1-yl)ethyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[4-[2-(1H-imidazol-1-yl)butyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[3-[1-[2-(3-pyridinyl)ethyl]-1H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;

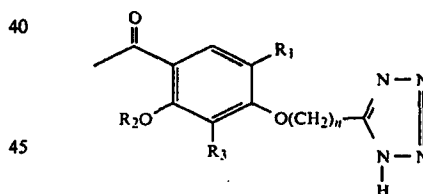
4

- 1-[2-hydroxy-3-propyl-4-[[3-[1-[4-(3-pyridinyl)butyl]-1H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[3-[2-[2-(3-pyridinyl)ethyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[[3-[2-[4-(3-pyridinyl)butyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[5-chloro-2-hydroxy-3-propyl-4-[[3-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[2-[4-(3-pyridinyl)butyl]-2H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[5-[1-[4-(3-pyridinyl)butyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone;
 1-[2-hydroxy-3-propyl-4-[3-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]propoxy]phenyl]ethanone; and
 1-[2-hydroxy-3-propyl-4-[5-[1-(3-pyridinyl)methyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone.
 Most preferred compounds of formula I are;
 1-[2-hydroxy-3-propyl-4-[5-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone; and
 1-[2-hydroxy-3-propyl-4-[4-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone.
 The preparation of the compounds of formula I is exemplified as hereinafter described.

A compound of the formula



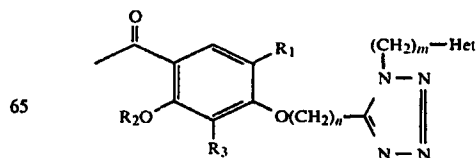
- wherein R_1 , R_2 , R_3 and n are as previously described, is reacted with sodium azide and ammonium chloride to yield a tetrazole of the formula



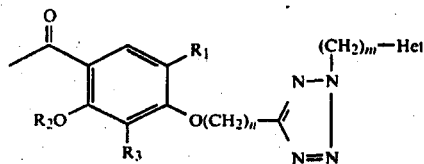
- wherein R_1 , R_2 , R_3 , and n are as previously described. Compounds of formula II are known compounds or can be prepared according to known methods.

The reaction is run with an excess of sodium azide, in a polar, aprotic solvent such as anhydrous dimethylacetamide, or, more preferably, anhydrous dimethylformamide, at a temperature in a range from about 80° to about 120°. The product is recovered by usual means, such as crystallization.

A compound of formula III is converted to the N-1 and N-2 isomers of formulas Ia and Ib respectively



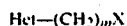
and



Ib

5

wherein R_1 , R_2 , R_3 , n , m , and Het are as previously described, by reaction with a compound of formula



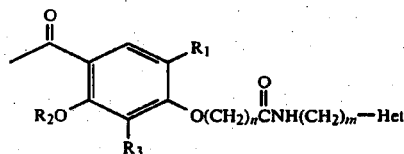
IV

wherein m , X and Het are as previously described. Compounds of formula IV are known compounds or can be prepared according to known methods. The reaction is carried out in a polar, aprotic solvent such as anhydrous methyl ethyl ketone, anhydrous acetone, anhydrous dimethylformamide, or most preferably a mixture of anhydrous acetone and anhydrous dimethylformamide. The reaction is conducted at elevated temperatures, up to the reflux temperature of the particular solvent system used. When anhydrous dimethylformamide is used the reaction is conducted at a temperature from about 50° to about 120° . The reaction is conducted in the presence of a base such as an alkali metal carbonate, like lithium carbonate, sodium carbonate, or more preferably potassium carbonate; a lower alkyl tertiary amine such as tripropylamine, tributylamine, or more preferably triethylamine or tributylstannoxide. Separation of compounds of formula Ia and Ib can be carried out by known chromatographic techniques such as column chromatography or high pressure liquid chromatography.

A compound of Ia or Ib, wherein R_2 is hydrogen can be converted to a corresponding compound of Ia or Ib wherein R_2 is alkanoyl, by reaction with an alkanoyl anhydride, at elevated temperature, in the presence of an organic base. For example, compounds of formula Ia or Ib wherein R_2 is acetyl can be prepared by reacting a compound of formula Ia or Ib with acetic anhydride, in pyridine, at a temperature of from about 50° to about 100° .

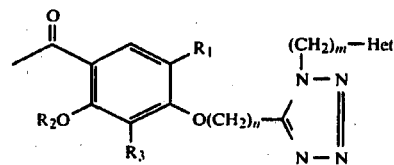
Compounds of formula Ia and Ib are encompassed by compounds of formula I.

The compounds of formula Ia can also be prepared by reacting an amide of the formula



V

wherein R_1 , R_2 , R_3 , n , m , and Het are as previously described, first with phosphorous pentachloride and then with an excess of hydrazoic acid to obtain,

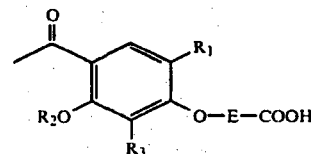


Ia

wherein R_1 , R_2 , R_3 , n , m and Het are as previously described.

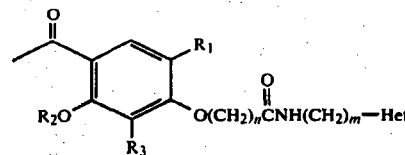
The reaction is carried out in an anhydrous halo alkane solvent such as anhydrous chloroform. There is added an excess of hydrazoic acid. The temperature of the reaction is from about 0° to about 30° during addition of the phosphorous pentachloride and from 30° up to the reflux temperature of the solvent system used afterwards.

The amide of formula V can be obtained as follows: an acid of the formula



VIa

wherein R_1 , R_2 , and R_3 are as described above and E is $-(CH_2)_n-$ can be converted to an amide of the formula



V

wherein R_1 , R_2 , R_3 , n , m and Het are as described above.

The conversion of an acid of formula VIa to the desired intermediate of formula V is carried out as follows. A compound of formula VIa is converted to an intermediate acid azide by reaction with diphenylphosphoryl azide in an anhydrous polar solvent, such as, dimethylformamide, at a temperature in the range of from about 0° to about $25^\circ C.$, preferably at about $5^\circ C.$, and in the presence of an organic base, such as, a trialkylamine, for example, triethylamine. The reaction mixture containing the acid azide is then treated with an amine of formula



VII

wherein m and Het are as described above, which are known compounds, at a temperature in the range of from about 0° to about $25^\circ C.$, to give the corresponding intermediate of formula V which can be separated by known procedures, for example, crystallization, chromatography and the like.

Alternatively, a compound of formula

mL of pyridine was stirred and heated at 80° for 18 hr. The solvent was removed in vacuo and the residual oil was purified by chromatography on silica gel. Elution with methylene chloride (90):95% methanol (10):concentrated ammonium hydroxide (0.05) gave a solid which was recrystallized from methylene chloride-ether to give 87 mg, mp 94°-96°, of 1-[2-acetoxy-3-propyl-4-[5-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]pentyloxy]phenyl]ethanone.

Analysis. Calculated for $C_{27}H_{35}N_5O_4$: C, 65.70; H, 7.15; N, 14.19. Found: C, 65.33; H, 7.09; N, 13.92.

EXAMPLE 11

1-[2-Hydroxy-3-propyl-4-[4-[1-[3-(1H-imidazol-1-yl)propyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone and

1-[2-Hydroxy-3-propyl-4-[4-[2-[3-(1H-imidazol-1-yl)propyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone

A mixture of 2.00 g 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]ethanone, 1.69 g 3-bromopropyl-1H-imidazol-1-yl hydrobromide, 2.65 mL triethylamine, 20 mL anhydrous acetone and 20 mL anhydrous dimethylformamide was stirred and refluxed for 42 hr. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residual oil was dissolved in ethyl acetate and washed with sodium bicarbonate solution and with saturated sodium chloride solution. The dried (potassium carbonate) extract was concentrated in vacuo to an oil which was purified by high pressure liquid chromatography. Elution with triethyl amine (3):methanol (5):ethyl acetate (92) separated 1-[2-hydroxy-3-propyl-4-[4-[1-[3-(1H-imidazol-1-yl)propyl]-1H-tetrazol-5-yl]butoxy]phenyl]ethanone, which is the N-1 isomer, and 1-[2-hydroxy-3-propyl-4-[4-[2-[3-(1H-imidazol-1-yl)propyl]-2H-tetrazol-5-yl]butoxy]phenyl]ethanone, which is the N-2 isomer.

The N-1 isomer, was recrystallized from methylene chloride-ether to give 0.37 g, mp 72°-75°.

Analysis. Calculated for $C_{22}H_{30}N_6O_3$: C, 61.95; H, 7.09; N, 19.70. Found: C, 61.83; H, 7.21; N, 19.88.

The N-2 isomer, was isolated as an oil, 1.40 g.

Analysis. Calculated for $C_{22}H_{30}N_6O_3$: C, 61.95; H, 7.09; N, 19.70. Found: C, 61.65; H, 7.22; N, 19.69.

EXAMPLE 12

3-[4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]benzonitrile

A mixture of 5.94 g 1-(2,4-dihydroxy-3-propylphenyl)ethanone, 6.00 g 3-cyanobenzyl bromide and 6.40 g potassium carbonate in 150 mL anhydrous acetone was stirred and refluxed for 4 hr. The reaction mixture was filtered and the filtrate was concentrated in vacuo to give a solid which was recrystallized from methylene chloride-ether to give 8.35 g, mp 115°-117°, 3-[4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzonitrile.

Analysis. Calculated for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.66; H, 6.22; N, 4.62.

EXAMPLE 13

1-[2-Hydroxy-3-propyl-4-[[3-(1H-tetrazol-5-yl)phenyl]methoxy]phenyl]ethanone

A mixture of 8.25 g 3-[(4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzonitrile, 5.20 g sodium azide and 4.30 g ammonium chloride in 125 mL anhydrous dimethylformamide was stirred and heated at 120° for 6 hr. The solvent was removed in vacuo and the residue

was treated with 250 mL water and acidified with 10 mL 6N hydrochloric acid. The resulting solid was recrystallized from ethanol-water to give 7.78 g, mp 194°-195° of 1-[2-hydroxy-3-propyl-4-[[3-(1H-tetrazol-5-yl)phenyl]methoxy]phenyl]ethanone.

Analysis. Calculated for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.60; H, 5.72; N, 16.17.

EXAMPLE 14

1-[2-Hydroxy-3-propyl-4-[[3-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone and 1-[2-Hydroxy-3-propyl-4-[[3-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone

A mixture of 1.00 g 1-[2-hydroxy-3-propyl-4-[[3-(1H-tetrazol-5-yl)phenyl]methoxy]phenyl]ethanone, 0.80 g 3-(3-bromopropyl)pyridine hydrobromide and 1.20 mL triethylamine (8.52 mmol in 10 mL anhydrous acetone and 10 mL anhydrous dimethylformamide) was stirred and refluxed for 6 hr. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residual oil was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and with saturated sodium chloride solution. The dried (magnesium sulfate) extract was concentrated in vacuo to an oil which was purified by high pressure liquid chromatography. Elution with triethyl amine (1.5):ethyl acetate (98.5) separated 1-[2-hydroxy-3-propyl-4-[[3-[1-[3-(3-pyridinyl)propyl]-1H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone, which is the N-1 isomer, and 1-[2-hydroxy-3-propyl-4-[[3-[2-[3-(3-pyridinyl)propyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone, which is the N-2 isomer.

The N-1 isomer, was recrystallized from ether to give 23 mg, mp 58°-61°.

The N-2 isomer, was recrystallized from ether-hexane to give 0.86 g, mp 82°-83°.

Analysis. Calculated for $C_{27}H_{29}N_5O_3$: C, 68.77; H, 6.20; N, 14.85. Found: C, 68.64; H, 6.45; N, 14.97.

EXAMPLE 15

1-[2-Hydroxy-3-propyl-4-[[3-[2-(1H-imidazol-1-yl)propyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone

A mixture of 1.00 g 1-[2-hydroxy-3-propyl-4-[[3-(1H-tetrazol-1-yl)phenyl]methoxy]phenyl]ethanone, 0.77 g 3-bromopropyl-1H-imidazol-1-yl hydrobromide and 1.20 mL triethylamine in 10 mL anhydrous acetone and 10 mL anhydrous dimethylformamide was stirred and refluxed for 10 hr. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residual oil was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and with saturated sodium chloride solution. The dried potassium carbonate extract was concentrated in vacuo to an oil which was purified by high pressure liquid chromatography. Elution with triethylamine (3):methanol (7.5):ethyl acetate (89.5) gave 0.77 g of 1-[2-hydroxy-3-propyl-4-[[3-[2-(1H-imidazol-1-yl)propyl]-2H-tetrazol-5-yl]phenyl]methoxy]phenyl]ethanone, mp 88°-91°.

Analysis. Calculated for $C_{25}H_{28}N_6O_3$: C, 65.20; H, 6.13; N, 18.25. Found: C, 64.99; H, 6.16; N, 18.10.

402 402

402

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

2020
Bogotá, D.C., 12/02/2010

Abogado
Mauricio Patiño Bonnet
(Apoderado)

ASUNTO	Radicación	06 77652
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	2213
	Folios	009

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐

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

- | | | |
|------|--------------------------|---|
| 1.1. | <u>Descripción:</u> | Folios: 152 a 291 |
| 1.2. | <u>Reivindicaciones:</u> | Folios: 292 a 308 |
| 1.3. | <u>Datos PCT:</u> | Solicitud Internacional: PCT/US05/005217
Capítulo II
Fecha Sol. Internacional: 17/02/2005
Publicación. Internacional: WO05/080356
Fecha Pub. Internacional: 01/09/2005
Fecha Inicio Fase Nacional: 18/09/2006
Fecha Sol. Nacional: 08/08/2006 |
| 1.4. | <u>Prioridad:</u> | US60/545,291 de 18/02/2004 |

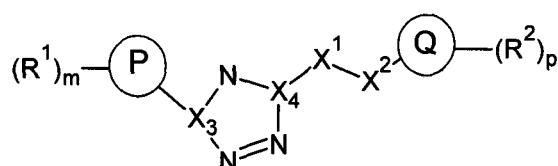
2. Objeto de la invención

Título de la solicitud

Compuestos de tetrazol y su uso como antagonistas del receptor de glutamato metabotrópico

Reivindicaciones

Reivindicaciones 1 a 17: Se reivindican compuestos de fórmula (I):



Reivindicaciones 18 y 19: Se reivindican las formulaciones farmacéuticas que comprenden el principio activo de fórmula (I) en asociación con uno o más diluyentes para uso farmacéutico.

Reivindicaciones 20 a 22: Se reivindican los compuestos para ser usados en terapia y el uso de los compuestos para la fabricación de un medicamento.

Reivindicaciones 23 a 28: Se reivindica un método de tratamiento de trastornos mediados por mGluR5 que comprende administrar a un mamífero, incluyendo el humano una cantidad eficaz en términos terapéuticos de los compuestos.

Sustento Descriptivo

La Descripción hace referencia a una nueva clase de compuestos y sus formulaciones farmacéuticas que son capaces de antagonizar la actividad del receptor de glutamato metabotrópico.

Los receptores de glutamato metabotrópicos (mGluR) se encuentran acoplados a proteína G y activan numerosos sistemas de mensajeros secundarios intracelulares después de la unión del glutamato.

La activación de este sistema genera respuestas como la activación de la fosfolipasa C, incremento en la hidrólisis de fosfoinositol (PI), liberación de calcio intracelular, activación de la fosfolipasa D, activación o inhibición de la adenilo ciclasa, incremento o disminución en la formación de adenosina monofosfato cíclico (AMPc), activación de la guanililo ciclasa, incremento en la formación de guanosina monofosfato cíclico (GMPc), activación de la fosfolipasa A₂, incremento en la liberación de ácido araquidónico e incremento o disminución en la actividad de los canales iónicos activados por voltaje y ligandos.

Se sabe además, que los receptores de glutamato metabotrópicos cumplen funciones en diversos procesos fisiopatológicos que incluyen accidente cerebrovascular, trauma cefálico, lesiones anóxicas e isquémicas, hipoglucemia, epilepsia, trastornos neurodegenerativos como Enfermedad de Alzheimer, trastornos psiquiátricos y dolor y se cree que una gran parte de la patología en estas afecciones se debe a una excitación excesiva inducida por glutamato de las neuronas del SNC.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K** ³¹/₄₉₆ // ³¹/₄₁ // ³¹/₄₄₃₉ de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

Teniendo en cuenta el contenido y alcance de la materia reivindicada esta Superintendencia se permite señalar lo siguiente:

- Las cláusulas 1 a 16 definen las características de la estructura Markush de la fórmula (I) e incluyen términos que evocan géneros funcionales y no permiten una interpretación inequívoca del grado de complejidad que presenta la fórmula una vez se producen las sustituciones sobre la misma. Es el caso de las expresiones y definiciones que forman parte de las opciones contempladas para el caso de los radicales: P, R¹, R³, R⁴, Q, R², A R⁵ y R⁶ a continuación relacionadas:
 - Grupo arilo o heteroarilo
 - Anillo de 5 ó 6 miembros que contiene uno o más átomos seleccionados en forma independiente entre el grupo formado por C, N, O y S
 - Anillo heterocíclico de 4, 5, 6 ó 7 miembros que contiene uno o más heteroátomos seleccionados entre N, O, S y está fusionado a un anillo de triazol
 - Anillo de 5 ó 6 miembros que contiene uno o más átomos seleccionados en forma independiente entre el grupo formado por C, N, O y S y dicho anillo opcionalmente puede fusionarse con un anillo de 5 ó 6 miembros que contiene uno o más átomos seleccionados en forma independiente entre el grupo formado por C, N y O y en donde dicho anillo y anillo fusionado pueden sustituirse con uno o más A.

Al respecto es preciso requerir al señor solicitante en los términos del presente examen técnico para que identifique claramente cuáles son las especies químicas y funcionales que sustituyen la estructura Markush y que se encuentran contempladas dentro de los géneros antes indicados, lo anterior, atendiendo las normas por la IUPAC para la denominación de compuestos orgánicos¹ y las modalidades particulares de la invención que se presentan en la cláusula 17.

¹ ARYL GROUPS:

Groups derived from arenes by removal of a hydrogen atom from a ring carbon atom. NOC Rule A-13.5. Groups similarly derived from heteroarenes are sometimes subsumed in this definition (see heteroaryl groups). E.g. o-tolyl.

ARENES:

Monocyclic and polycyclic aromatic hydrocarbons. NOC Rule A-12.4. (See aromatic compounds).

AROMATIC COMPOUNDS:

Historically, the term "aromatic" originally referred to the smell of selected compounds that later were found to contain benzene or fused benzene rings in the structure. In a structural sense, it designates compounds that, in accordance with the theory of Hückel, have a cyclic, delocalized (4n+2) pi-electron system. This includes arenes and their substitution products. E.g. benzene, naphthalene, toluene. The term has been generalized to include aromatic heterocyclic structures, such as thiophene and pyridine, but it is more precise to call compounds of the latter type heteroaromatic. See also arenes, heteroarenes. GTPC (aromatic).

HETEROARENES:

Heterocyclic compounds formally derived from arenes by replacement of one or more methine (-C=) and/or vinylene (-CH=CH-) groups by trivalent or divalent heteroatoms, respectively, in such a way as to maintain the continuous -electron system characteristic of aromatic systems and a number of out-of-plane -electrons corresponding to the Hückel rule (4n + 2); an alternative term is hetarenes. Comprehensive Heterocyclic Chemistry, Vol. 1, Ed. O. Meth-Cohn, Pergamon, 1984, p. 3.

HETEROARYL GROUPS:

The class of heterocyclyl groups derived from heteroarenes by removal of a hydrogen atom from any ring atom; an alternative term is hetaryl. E.g. 2-pyridyl (pyridin-2-yl), indol-1-yl.

HETEROCYCLYL GROUPS:

Univalent groups formed by removing a hydrogen atom from any ring atom of a heterocyclic compound. E.g. 4-pyridyl, pyrrolidin-1-yl, pyrrolidin-2-yl.

CYCLOALKYL GROUPS:

Univalent groups derived from cycloalkanes by removal of a hydrogen atom from a ring carbon atom.

4. Excepción a la patentabilidad (artículo 20 D. 486 literal a)-d))

Las cláusulas 23 a 28 de los folios 307 y 308 hacen referencia a un método que comprende la administración de una cantidad eficaz de un compuesto de fórmula (I).

Al respecto es preciso señalar que el artículo 20 literal d) de la Decisión 486 contempla la excepción a la patentabilidad para los métodos de tratamiento humano y animal, razón por la cual, el contenido de la presente solicitud no constituye un objeto patentable conforme a la disposición legal.

Por lo que mediante el presente concepto técnico se le comunica al señor solicitante que en tratándose de un método como el reivindicado, esta Dependencia se encuentra impedida en virtud de la ley, para realizar estudio de patentabilidad en razón a la excepción señalada.

5. Reivindicaciones relativas a un uso (artículos 14 D. 486)

Las cláusulas 21 y 22 hacen referencia al uso de de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento de trastornos mediados por mGluR5, es decir, de esta manera la solicitud incorpora una categoría de invención que no ha sido contemplada por el ordenamiento jurídico andino.

La Decisión 486 define de manera taxativa el grupo de invenciones susceptibles de protección a través del privilegio de patente y precisa que sólo los productos y procedimientos de los diversos campos tecnológicos pueden ser objeto del derecho de exclusividad, situación por la cual, resulta procedente requerir al señor solicitante en los términos del presente examen técnico para que elimine del alcance de su invención las cláusulas en comento.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 18/02/2004, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	WO03029210	"Heteroaryl substituted tetrazole modulators of metabotropic glutamate receptor-5"	10/04/2003
D2	WO03077918	"Di-aryl substituted tetrazole modulators of metabotropic glutamate receptor-5"	25/09/2003
D3	US4663332	"5-substituted N-alkylated tetrazoles"	05/05/1987

Anterioridades D1 a D3 en los folios 384 a 400.

7. Análisis de patentabilidad (artículo 14 D. 486)

URL: <http://www.chem.qmul.ac.uk/iupac/class/rings.html#12>.

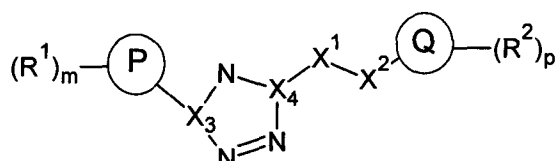
Glossary of class names of organic compounds and reactive intermediates based on structure (IUPAC Recommendations 1994). Miscellaneous.

7.1 Novedad (artículo 16 D. 486)

La novedad del objeto se evaluó mediante el análisis de identidad técnica entre los elementos característicos de la fórmula (I) y las anticipaciones cercanas a la invención.

• **Se reivindica:**

Un compuesto según la fórmula (I):



Para el cual:

X_3 y X_4 se elige entre N y C

P se elige entre arilo y heteroarilo

si $m=1$ entonces R^1 se une a P a través de un átomo de carbono en el anillo P en una meta-posición del anillo P respecto del punto de unión de P a X_3 .

y si $m=2$ entonces R^1 se une a P por medio de un átomo de carbono en el anillo P en las posiciones 2 y 5 del anillo P.

R^1 se elige entre: hidroxilo, halo, nitro, alquilo C_{1-6} halo, Oalquil C_{1-6} halo, entre otros.

X^1 se elige entre: alquilo C_{2-3} , alquenoilo C_{2-3} , NR^3 , O, S, CR^3R^4 , SO, SO_2

X^2 se selecciona entre un enlace, CR^3R^4 , O, S, NR^3 , SO, SO_2

R^3 y R^4 se seleccionan independientemente entre hidrógeno, hidroxilo, alquilo C_{1-6} , oxo, $=NR^5$, $=NOR^5$

Q es triazol, piperazina e imidazol, o bien Q es cualquier otro anillo heterociclo de 4, 5, 6 ó 7 miembros que contiene uno o más heteroátomos elegidos entre N, O, S y está fusionado a un anillo de triazol.

R^2 se selecciona entre hidroxilo, alquil C_{0-6} ciano, $=NR^5$, $=O$, $=NOR^5$, entre otros.

A se selecciona entre hidrógeno, hidroxilo, halo, nitro, oxo, alquil C_{0-6} -ciano, alquil C_{1-6} ciano, entre otros.

R^5 y R^6 se seleccionan entre H, alquilo C_{1-6} , cicloalquilo C_{3-7} y arilo.

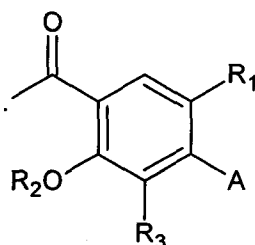
m se selecciona entre 1 ó 2

p se selecciona entre 0, 1, 2, 3 ó 4

Y en particular, las siguientes especies químicas:

Anterioridad D3:

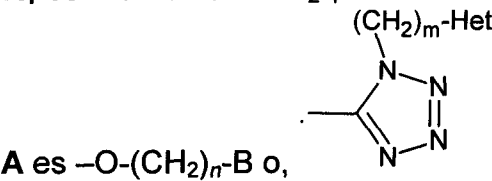
La publicación D3 revela estructuras que presentan el siguiente núcleo:



Donde:

207

R₁ es -H o alcanoil C₂₋₄
(CH₂)_m-Het



Het es un heterociclo de 5 ó 6 miembros que contiene uno o dos nitrógenos como heteroátomos que se encuentra opcionalmente sustituido por un grupo alquilo C₁₋₆

R₂ es -H

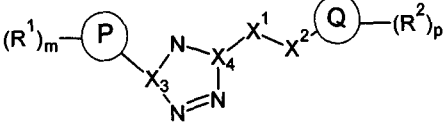
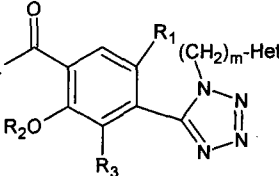
R₃ es -H o propilo

Y el antecedente hace referencia a los compuestos químicos:

1-[2-hidroxi-3-propil-4-[[3-[2-(1H-imidazol-1-il)propil]2H-tetrazol-5-il]fenil]metoxi]fenil]etanona

1-[5-cloro-2-hidroxi-3-propil-4-[[3-[1-[3-(3-piridinil)propil]-1H-tetrazol-5-il]fenil]metoxi]-fenil]etanona

Tabla 1. Comparación técnica

Materia Reivindicada	Antecedente D3 (US4663332)
	
P es arilo	R ₂ es H
R ¹ es (CO)R ⁵ donde R ⁵ es -H, alquilo C ₁₋₆ , O-alquilo C ₁₋₆ , -OH	R ₁ es -H, halo
m es 2	R ₃ es -H o alquilo C ₁₋₆
X ₃ y X ₄ se eligen entre N y C	m es un número elegido entre 1 a 6
X ¹ es alquilo C ₂₋₃	Het es un heterociclo de 5 ó 6 miembros
X ² es un enlace	
Q es triazol, piperazina e imidazol o bien cualquier otro anillo heterocíclico de 4, 5, 6 ó 7 miembros con uno o más heteroátomos elegidos entre N, O y S	
R ² es halo, hidroxi, alquil C ₀₋₆ -ciano, alquilo C ₁₋₆	
p es 0, 1, 2, 3 ó 4	

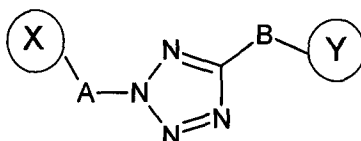
Así, al efectuar la comparación técnica entre los elementos característicos que definen los compuestos de la invención y aquellos que revela el estado del arte en la publicación D3 fue posible concluir que existe identidad técnica entre ellos, por lo ésta Superintendencia se permite comunicar al señor solicitante que la materia reivindicada carece de novedad y por consiguiente incumple con las disposiciones normativas del artículo 16 de la Decisión 486.

7.2 Nivel Inventivo (artículo 18 D. 486)

- El estado del arte previo a la invención presenta los siguientes documentos:

Anterioridad D1:

La publicación D1 revela estructuras que presentan el siguiente núcleo:



X y Y son elegidos entre arilo o heteroarilo donde al menos uno de X y Y es heteroarilo con B adyacente a la posición de enlace con A o B respectivamente.

A es alquilo C₀₋₄, alquilo C₀₋₂-SO-alquilo C₀₋₂, alquilo C₀₋₂-SO₂-alquilo C₀₋₂, alquilo C₀₋₂-CO-alquilo C₀₋₂, alquilo C₀₋₂-NR⁹CO-alquilo C₀₋₂, alquilo C₀₋₂-NR⁹SO₂-alquilo C₀₋₂ o hetero-alquilo C₀₋₄.

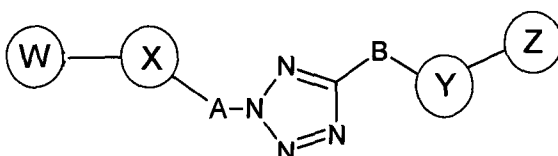
B es alquilo C₀₋₄, alquilo C₀₋₂-SO-alquilo C₀₋₂, alquilo C₀₋₂-SO₂-alquilo C₀₋₂, alquilo C₀₋₂-CO-alquilo C₀₋₂, alquilo C₀₋₂-NR¹⁰CO-alquilo C₀₋₂, alquilo C₀₋₂-NR¹⁰SO₂-alquilo C₀₋₂ o hetero-alquilo C₀₋₄.

X se encuentra opcionalmente sustituido por halógeno, CN, NO₂, alquilo C₁₋₆, alquenilo C₁₋₆, alquinilo C₁₋₆, -OR¹, -NR¹R², -C(=NR¹)NR²R³, -N(=NR¹)NR²R³, -COR¹, -CO₂R¹, -CONR¹R², C(=NOR¹)R².

Y se encuentra opcionalmente sustituido por halógeno, CN, NO₂, alquilo C₁₋₆, alquenilo C₁₋₆, alquinilo C₁₋₆, -OR⁵, -NR⁵R⁶, -C(=NR⁵)NR⁶R⁷, -SO₂NR⁵R⁶, -COR⁵, -CO₂R⁵, -CONR⁵R⁶, C(=NR⁵)R⁶.

Anterioridad D2:

La publicación D2 revela estructuras que presentan el siguiente núcleo:



X y Y son cada uno independientemente elegidos entre arilo y heteroarilo cuando al menos uno de X y Y son heteroarilo con el átomo de N adyacente a la posición de enlace a A o B respectivamente.

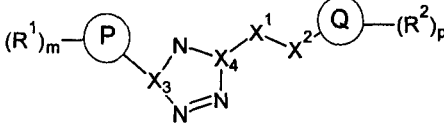
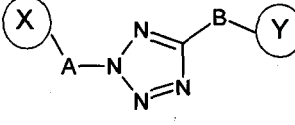
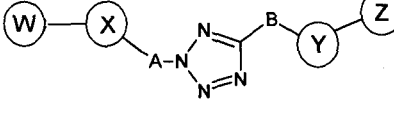
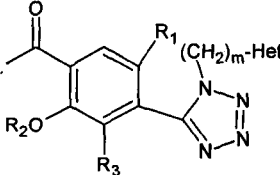
A es alquilo C₀₋₄, alquilo C₀₋₂-SO-alquilo C₀₋₂, alquilo C₀₋₂-SO₂-alquilo C₀₋₂, alquilo C₀₋₂-CO-alquilo C₀₋₂, alquilo C₀₋₂-NR⁹CO-alquilo C₀₋₂, alquilo C₀₋₂-NR⁹SO₂-alquilo C₀₋₂ o hetero-alquilo C₀₋₄.

B es alquilo C₀₋₄, alquilo C₀₋₂-SO-alquilo C₀₋₂, alquilo C₀₋₂-SO₂-alquilo C₀₋₂, alquilo C₀₋₂-CO-alquilo C₀₋₂, alquilo C₀₋₂-NR¹⁰CO-alquilo C₀₋₂, alquilo C₀₋₂-NR¹⁰SO₂-alquilo C₀₋₂ o hetero-alquilo C₀₋₄.

W es cicloalquilo C₃₋₇, heterocicloalquilo C₃₋₇, aril-alquilo C₀₋₆, heteroaril-alquilo C₀₋₆.

Z es cicloalquilo C₃₋₇, heterocicloalquilo C₃₋₇, aril-alquilo C₀₋₆, alquil C₀₋₆-heteroarilo

Tabla 2. Comparación técnica

Materia Reivindicada	Antecedente D1 (WO03029210)	Antecedente D2 (WO03077918)	Antecedente D3 (US4663332)
			

Análisis de Diferencias Técnicas:

Al comparar los elementos característicos de los compuestos reivindicados junto a las enseñanzas reveladas por el estado del arte fue posible concluir que existen las siguientes diferencias técnicas:

Con respecto a **D1** las diferencias estriban en que los grupos heterociclos P y Q de la materia reivindicada presentan sustituciones adicionales tipo (R¹)_m y (R²)_p, mientras que en el caso de **D1** no se precisa la posición de los sustituyentes.

Con respecto a **D2** las diferencias estriban en que para los grupos W y Z equivalentes a R¹ y R² de la materia reivindicada no se especifica la posición que ocupan sobre los anillos X y Y.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con la memoria descriptiva de la solicitud existía la necesidad de diseñar y desarrollar nuevos agonistas y antagonistas del receptor de glutamato (mGluR) con gran selectividad.

Al respecto es preciso señalar que el estado del arte más cercano a la invención indica que los derivados heterocíclicos de tetrazol comparten actividad como moduladores del receptor metabotrópico de glutamato, por lo que la alternativa farmacoterapéutica que presenta el señor solicitante mediante el pliego reivindicatorio de los folios 292 a 308 no aporta ningún efecto inesperado frente a las enseñanzas de las publicaciones **D1** o **D2**, las que combinadas con **D1** anticipan todos los elementos característicos de la materia reivindicada.

Por las razones expuestas anteriormente esta dependencia encuentra que la materia reivindicada carece de altura inventiva, y por tal razón no cumple con las disposiciones normativas señaladas por el artículo 18 de la Decisión comunitaria 486.

8. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO03029210	1 a 28	Nivel Inventivo
D2	WO03077918	1 a 28	Nivel Inventivo
D3	US4663332	1 a 28	Novedad

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.

ÁLIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

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

CONCEPTO TÉCNICO No. 718	EXAMINADOR TÉCNICO Código No. 202044
--------------------------	---