

05-43407

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Señor

SUPERINTENDENTE DE INDUSTRIA Y C

DIVISION DE NUEVAS CREACIONES

E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-043407- -00003-0000

Fecha: 2007-09-11 15:55:54 Dep. 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

Re: P1.-CYTOKINETICS, INC. Y SMITHKLINE BEECHAM
CORPORATION.-Solicitud de Patente de Invención en Fase
Nacional PCT para "CIERTOS TRIAZOLES SUBSTITUIDOS
Y COMPOSICIONES PARA INHIBIR LA KSP".-Clase
C07D 249/12.-Expediente número 05-043.407.-

1. Me refiero a mi memorial de 12 de Julio de 2005.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **574** de 30 de Marzo de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo **II**.
4. Anexo me permito acompañar recibo número 07-72.508, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-043407- -00003-0000

Fecha: 2007-09-11 15:55:54 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 72,508
FECHA : SEPTIEMBRE 10 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LLOREDA & CIA. S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	47999525	10/09/2007	1,010,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	202,000.00
	TOTAL :	\$ 202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 800178089-3

FECHA : SEPTIEMBRE 10 DE 2003
RECIBO OFICIAL DE CITA : 07 - 75,503

***** CONSIGNACION VENTA

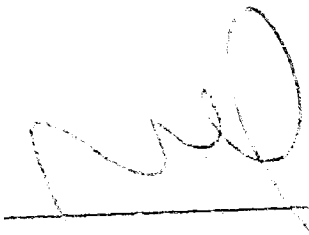
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	RCI. PAGO	FECHA PGO	VAL. PAGO
ALFONSO S CIA. S.A.	CONSIGNACION	BANCO POPULAR	020-00110-6	ALFONSO S	10/09/2003	1,010,000.00

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

CANT. ENTREGADO	CONCEPTO	TOTAL CONCEPTO

1 8008-01-01 SOLICITUDES
114 PTC CAP-II EXAMEN DE PATENTABILIDAD
TOTAL :
203,000.00
203,000.00

BOLETIN 003 MIL PEROS



RECEBIBLE :

RECIBO DE CASH APURADO AL EXPEDIENTE N°.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-43407

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **574** DE

FECHA **30 DE MARZO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **03 DE JULIO DE 2007**

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 _____

NO X

D-1 773 193



US005250558A

United States Patent [19]

Chakravarty et al.

[11] Patent Number: 5,250,558

[45] Date of Patent: Oct. 5, 1993

[54] SUBSTITUTED TRIAZOLINONES, TRIAZOLINETHIONES, AND TRIAZOLINIMINES AS NEUROTENSIN ANTAGONISTS USED TO TREAT PSYCHOSIS

[75] Inventors: Prasun K. Chakravarty, Edison, N.J.; Richard W. Ransom, New Britian, Pa.

[73] Assignee: Merck & Co., Inc., Rahway, N.J.

[21] Appl. No.: 826,704

[22] Filed: Jan. 28, 1992

[51] Int. Cl.⁵ A61K 31/41; A61K 31/34; A61K 31/40; A61K 31/445

[52] U.S. Cl. 514/383; 514/384; 514/315; 514/336; 514/343; 514/461; 514/465; 514/408; 514/427; 514/329; 514/330

[58] Field of Search 514/381, 382, 383, 384, 514/408

[56] References Cited

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4,439,359 3/1984 Holly et al. 260/112.50 R
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5,137,902 8/1992 Carini 514/381
5,137,906 8/1992 Chiu et al. 514/381

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452926 10/1991 European Pat. Off. .
0477049A1 3/1992 France .

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deQuidt et al, "Neutrotensin facilitates dopamine release in vitro from rat striatal slices", Brain Research, 274, (1983), 376-380.

Shi et al, "Roles of Intracellular cAMP and Protein Kinase A in the Actions of Dopamine ...", J. of Neuroscience, Jun. 1992, 12(6): 2433-2438.

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(List continued on next page.)

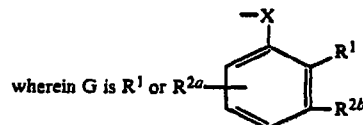
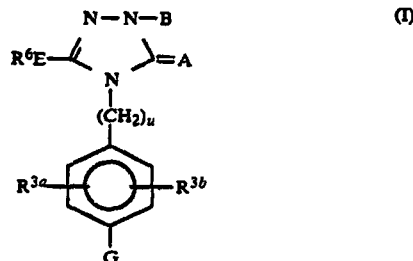
Primary Examiner—Frederick E. Waddell

Assistant Examiner—T. I. Criares

Attorney, Agent, or Firm—Valerie J. Camara; William H. Nicholson; Joseph F. DiPrima

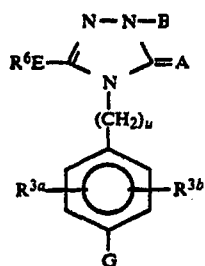
[57] ABSTRACT

Substituted triazolinone, triazolinethione, and triazolinimine compounds of formula (I) are as neurotensin II antagonists. These compounds have the general formula:

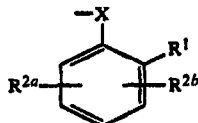


7 Claims, No Drawings

43



or a pharmaceutically acceptable salt thereof, wherein:
G is R¹ or



R¹ is

- (a) —NHSO₂R²³,
- (b) —NHSO₂NHCOR²³,
- (c) —NHCONHSO₂R²³,
- (d) —SO₂NHR²³,
- (e) —SO₂—NHCOR²³,
- (f) —SO₂NHCOR²³R²⁴,
- (g) —SO₂NHCOOR²³,
- (h) —SO₂NHOR²³,
- (i) —CH₂SO₂NHCOR²³,
- (j) —CH₂SO₂NHCONHR²³, or
- (k) —CO₂H;

R^{2a} and R^{2b} are each independently:

- (a) hydrogen,
- (b) —Cl, —Br, —I, or —F
- (c) —CF₃,
- (d) C₁–C₄-alkyl, or
- (e) C₁–C₄-alkoxy;

R^{3a} is

- (a) —H,
- (b) —Cl, —Br, —I, or —F
- (c) C₁–C₆-alkyl,
- (d) C₁–C₆-alkoxy, or
- (e) C₁–C₆-alkoxy-C₁–C₄-alkyl;

R^{3b} is

- (a) —H,
- (b) —Cl, —Br, —I, or —F,
- (c) C₁–C₆-alkyl,
- (d) C₁–C₃-alkylcarbonyloxy,
- (e) C₃–C₆-cycloalkyl
- (f) C₁–C₆-alkoxy, or
- (g) CF₃;

R⁴ is H, C₁–C₆-alkyl, —CH₂-aryl or aryl wherein aryl is phenyl or naphthyl unsubstituted or substituted with one or two substituents selected from the group consisting of: —Cl, —Br, —I, —F, C₁–C₄-alkyl, C₁–C₄-alkoxy, NO₂, CF₃, C₁–C₄-alkylthio, 60 —OH, —NH₂, —CO₂H, —CO₂—C₁–C₄-alkyl, —CN and —NHCOR⁹;

R⁵ is H or —CH(R⁴)—O—CO—R^{4a}, wherein R^{4a} is C₁–C₆-alkyl, aryl or —CH₂-aryl;

E is a single bond, —NR¹³(CH₂)_s—, —S(O)_x(CH₂)_s—, where x is 0 to 2 and s is 0 to 5, —CH(OH)—, —O(CH₂)_s—, —CO—;

R⁶ is

44

- (a) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F, —O—C₁–C₄-alkyl, C₁–C₄-alkyl, —NO₂, —CF₃, —SO₂NR⁹R¹⁰, —S—C₁–C₄-alkyl, —OH, —NH₂, C₃–C₇-cycloalkyl, and C₃–C₁₀-alkenyl;
- (b) C₁–C₆-alkyl, C₂–C₆-alkenyl or C₂–C₆-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of: aryl, C₃–C₇-cyclo-alkyl, Cl, Br, I, F, —OH, —O—C₁–C₄-alkyl, —NH₂, —NH(C₁–C₄-alkyl), —N(C₁–C₄-alkyl)₂, —N-H—SO₂R⁴, —COOR⁴, —SO₂NHR⁹, and —S—C₁–C₄-alkyl;
- (c) mono-, di-, tri- or polyfluoro-C₁–C₃-alkyl;
- (d) C₃–C₇-cycloalkyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁–C₄-alkyl, O—C₁–C₄-alkyl, S—C₁–C₄-alkyl, OH, perfluoro-C₁–C₄-alkyl, Cl, Br, F, and I; or
- (e) C₃–C₇-cycloalkyl-C₁–C₃-alkyl, wherein the cycloalkyl is unsubstituted or substituted as in (e) above;

A is =O, =S or =NR²¹;

B is

- (a) H provided A is not NR²¹;
- (b) C₁–C₁₀-alkyl;
- (c) substituted C₁–C₁₀-alkyl in which one or more substituent(s) is selected from the group consisting of:
 - (1) I, Br, Cl, or F,
 - (2) hydroxy,
 - (3) C₁–C₁₀-alkoxy,
 - (4) C₁–C₃-alkoxycarbonyl,
 - (5) C₁–C₄-alkylcarbonyloxy,
 - (6) C₃–C₈-cycloalkyl,
 - (7) phenyl, naphthyl or biphenyl,
 - (8) substituted phenyl, naphthyl or biphenyl in which the substituents are V₁, V₂, V₃, V₄ and V₅,
 - (9) C₁–C₁₀-alkyl-S(O)_p in which p is 0 to 2,
 - (10) C₃–C₈-cycloalkyl-S(O)_p,
 - (11) phenyl-S(O)_p,
 - (12) substituted phenyl-S(O)_p in which the substituents are V₁–V₅,
 - (13) oxo,
 - (14) carboxy,
 - (15) NR⁹R⁹,
 - (16) C₁–C₃-alkylaminocarbonyl,
 - (17) di(C₁–C₃-alkyl)aminocarbonyl,
 - (18) cyano,
 - (19) —OCONR²¹R²²,
 - (20) —NR²¹COR²²,
 - (21) —NR²¹CO₂R²², or
 - (22) —NR²¹CONR²¹R²²;

(d) C₂–C₁₀-alkenyl,

(e) C₂–C₁₀-alkynyl,

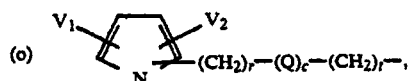
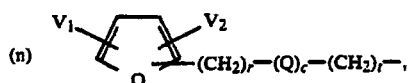
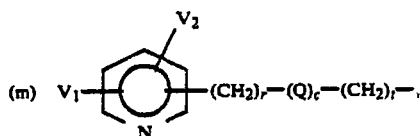
(f) C₃–C₈-cycloalkyl,

(g) substituted C₃–C₈-cycloalkyl or substituted C₃–C₈-cycloalkyl-C₁–C₄-alkyl having one or more substituents selected from the group consisting of:

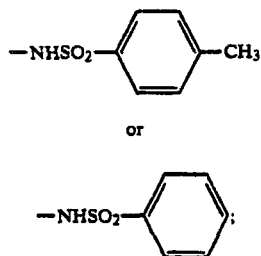
- (1) Cl, Br, F, or I,
- (2) hydroxy,
- (3) C₁–C₆-alkyl,
- (4) C₁–C₆-alkoxy,
- (5) C₁–C₄-alkylcarbonyloxy,
- (6) C₁–C₅-alkoxycarbonyl,

175
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- (7) carboxy,
 (8) oxo,
 (9) C₁-C₅-alkylaminocarbonyl,
 (10) di(C₁-C₅-alkyl)aminocarbonyl,
 (11) C₁-C₄-alkylcarbonyl,
 (12) phenyl, naphthyl or biphenyl,
 (13) substituted phenyl, naphthyl or biphenyl in which the substituents are V₁, V₂, V₃, V₄ and V₅,
 (14) —NR²¹COR²²,
 (15) —NR²¹CO₂R²²,
 (16) —OCONR²¹R²², and
 (17) —CN;
 (h) phenyl, naphthyl or biphenyl,
 (i) substituted phenyl, naphthyl or biphenyl in which the substituents are V₁, V₂, V₃, V₄ and V₅,
 (j) phenyl—(CH₂)_r—(Q)_c—(CH₂)_r—,
 (k) substituted phenyl—(CH₂)_r—(Q)_c—(CH₂)_r— in which the phenyl group is substituted with V₁, V₂, V₃, V₄ and V₅,



- R⁹ is H, C₁-C₃-alkyl, aryl or —CH₂-aryl;
 R¹⁰ is H, C₁-C₄-alkyl, or
 R⁹ and R¹⁰ together can be —(CH₂)_m— where m is 3-6;
 R¹¹ is H, C₁-C₆-alkyl, C₂-C₄-alkenyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, or —CH₂-C₆H₄R²⁰;
 R¹² is —CN, —NO₂ or —CO₂R⁴;
 R¹³ is H, C₂-C₄-alkanoyl, C₁-C₆-alkyl, allyl, C₃-C₆-cycloalkyl, phenyl or benzyl;
 R¹⁴ is H, C₁-C₈-alkyl, C₁-C₈-perfluoroalkyl, C₃-C₆-cycloalkyl, phenyl or benzyl;
 R¹⁵ is H, C₁-C₆-alkyl, hydroxy;
 R¹⁶ is H, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, phenyl or benzyl;
 R¹⁷ is —NR⁹R¹⁰, —OR¹⁰, —NHCONH₂, —NHCSNH₂, —NHSO₂CF₃,



- R¹⁸ and R¹⁹ are independently C₁-C₄-alkyl or taken together are —(CH₂)_q— where q is 2 or 3;
 R²⁰ is H, —NO₂, —NH₂, —OH or —OCH₃;

- R²¹ is
 (a) H,
 (b) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of: Cl, Br, I, F, —O—C₁-C₄-alkyl, C₁-C₄-alkyl, —NO₂, —CF₃, —SO₂NR⁹R¹⁰, —S—C₁-C₄-alkyl, —OH, —NH₂, —COOR⁴, C₃-C₇-cycloalkyl and C₃-C₁₀-alkenyl;
 (c) C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C₃-C₇-cycloalkyl, Cl, Br, I, F, —OH, —O—C₁-C₄-alkyl, —NH₂, —NH(C₁-C₄-alkyl), —N(C₁-C₄-alkyl)₂, —N—H—SO₂R⁴, —COOR⁴, —SO₂NHR⁹, and —S—C₁-C₄-alkyl;
 (d) C₃-C₇-cycloalkyl, unsubstituted or substituted with one or more substituents selected from the group consisting of: C₁-C₄-alkyl, —O—C₁-C₄-alkyl, —S—C₁-C₄-alkyl, —OH, —COOR⁴, C₁-C₄-perfluoroalkyl, Cl, Br, F, and I, or
 (e) (C₁-C₄)-perfluoroalkyl;
 R²² is R²¹ excluding H;
 R²³ is
 (a) aryl,
 (b) heteroaryl, wherein heteroaryl is defined as pyridine and which can be unsubstituted, mono-substituted or disubstituted with substituents selected from the group consisting of —OH, —SH, C₁-C₄-alkyl, C₁-C₄-alkoxy, —CF₃, Cl, Br, F, I, —NO₂, —CO₂H, —CO₂-C₁-C₄-alkyl, —NH₂, —NH(C₁-C₄-alkyl) and —N(C₁-C₄-alkyl)₂;
 (c) C₃-C₇-cycloalkyl optionally substituted with one or more substituents selected from the group consisting of C₁-C₄-alkyl, —O—C₁-C₄-alkyl, —S—C₁-C₄-alkyl, —OH, —COOR⁴, perfluoro-C₁-C₄-alkyl, Cl, Br, F, and I;
 (d) C₁-C₈-alkyl unsubstituted or substituted with one or two substituents selected from the group consisting of: aryl, heteroaryl, —OH, —SH, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, —O(C₁-C₄-alkyl), S(C₁-C₄-alkyl), —C₃-C₈-cycloalkyl, —CF₃, Cl, Br, F, I, —NO₂, —CO₂H, —CO₂-C₁-C₄-alkyl, —PO₃H, —PO(OH)(O—C₁-C₄-alkyl), —PO(OR⁴)(R⁹), —NH₂, —NH(C₁-C₄-alkyl), —N(C₁-C₄-alkyl)₂, —NH-aryl, —N(aryl)₂, —N(CH₂CH₂)₂L, —NR⁴COR²², —CONR⁴R²², —OCONR⁴R²², SO₂NR⁴R²², —NR⁴SO₂R²²,
 (e) polyfluoro-C₁-C₄-alkyl;
 (f) —NR²¹R²¹, or
 (g) —N(CH₂CH₂)₂L;
 X is
 (a) a single bond,
 (b) —CO—,
 (c) —O—,
 (d) —S—,

