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Señores
SUPERINTENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00020442 00000001 Folios: 2
Fecha (AMD): 2004-07-14 08:41:06
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No. 00.020.442
Solicitud de patente de invención titulada:
"MEJORA EN LA DISPERSION DE QT Y EN LA VARIABILIDAD DE LA FRECUENCIA CARDIACA CON ANTAGONISTAS DE CRF PARA PREVENIR MUERTE SUBITA."
Solicitante: PFIZER PRODUCTS INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTICULO 44 DE LA DECISION 486, GACETA No. 538

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de $353.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo:Recibo por $353.000 pesos
FTT/P2000/000036 040624

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00020442 00000001 Folios: 2
Fecha (AMD): 2004-07-14 08:41:06
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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 55,084
FECHA : JULIO 12 DE 2004

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	23286882	12/07/2004	9,344,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	353,000.00
			TOTAL : $	353,000.00

SON: TRESCIENTOS CINCUENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/04, 239/52, 239/48, 239/50, 473/34, 213/69, A61K 31/44, 31/505, C07D 213/70, 213/74, 405/12

A1

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08/255,514 8 June 1994 (08.06.94) US

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(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

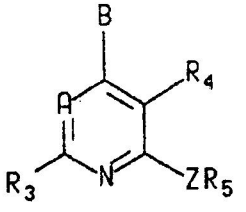
(81) Designated States: AU, CA, CN, CZ, FI, HU, JP, KR, MX, NO, NZ, PL, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
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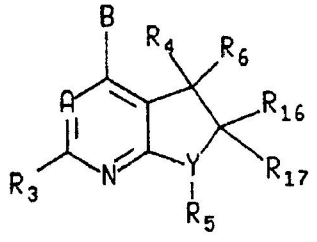
(54) Title: CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

(57) Abstract

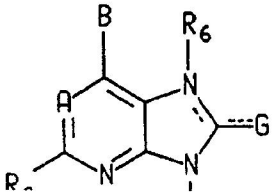
Corticotropin-releasing factor (CRF) antagonists having formulae (I), (II) or (III) wherein the dashed lines, A, B, Y, Z, G, R_3, R_4, R_5, R_6, R_{16} and R_{17} are as defined in the description, and processes for preparing them. These compounds and their pharmaceutically acceptable salts are useful in the treatment of CNS and stress-related disorders.



(I)



(II)



(III)

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;

[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine; or

6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one;

or a pharmaceutically acceptable salt of one of the above compounds.

13. A pharmaceutical composition for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

14. A method for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders

such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; and hypoglycemia in a mammal, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder.

15. A compound of the formula

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 471/04, A61K 31/435 // (C07D 471/04, 221:00, 209:00) (C07D 471/04, 231:00, 221:00)

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(60) Parent Application or Grant
(63) Related by Continuation
US 08/260,055 (CON)
Filed on 16 June 1994 (16.06.94)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

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(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

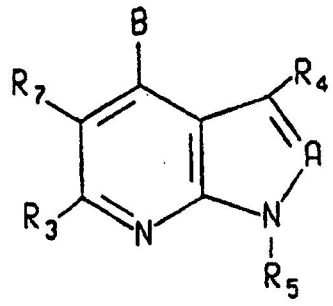
(81) Designated States: AU, CA, CN, CZ, FI, HU, JP, KR, MX, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PYRAZOLO AND PYRROLOPYRIDINES

(57) Abstract

This invention relates to compounds of formula (I), wherein A is N or -CT_6; B is -NR_1R_2, -$CR_1R_2R_{11}$, - $C(=CR_2R_{12})R_1$, -$NHCHR_1R_2$, -$OCHR_1R_2$, -$SCHR_1R_2$, -CHR_2OR_{12}, -CHR_2SR_{12}, -$C(S)R_1$ or -$C(O)R_1$. The compounds show corticotropin-releasing factor (CRF) antagonist activity. CFR antagonists are believed to be effective in the treatment of a wide range of stress-related illnesses, such as depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppressin, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, hemmorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction and infertility.



(I)

10. A compound according to claim 1, wherein R_5 is phenyl substituted with two or three substituents independently selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may be substituted by one of hydroxy, C_1-C_4 alkoxy and fluoro and may optionally contain one carbon-carbon double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, COO(C_1-C_2 alkyl) and -C(O)(C_1-C_4 alkyl).

11. A compound according to claim 1, wherein said compound is

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;

[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;

4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;

(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;

4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;

4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine; or

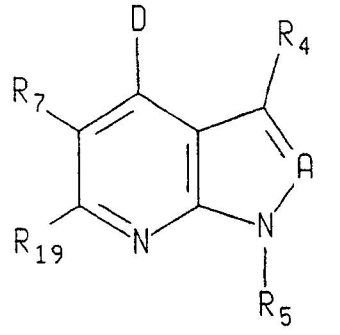
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine; or a pharmaceutically acceptable salt of one of the foregoing compounds.

12. A pharmaceutical composition for the treatment of: (a) a disorder the treatment of which is effected or facilitated by antagonizing CRF; or (b) a disorder selected from inflammatory disorders; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception; mood disorders; depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurogenerative diseases; Alzheimer's disease; Parkinson's disease; Huntington's disease; gastrointestinal diseases; eating disorders; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head

epilepsy; stroke; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; and hypoglycemia in a mammal, comprising an amount of a compound according to claim 1 that is effective in the treatment of said disorder, and a pharmaceutically acceptable carrier.

13. A method for the treatment of: (a) a disorder the treatment of which is effected or facilitated by antagonizing CRF; or (b) a disorder selected from inflammatory disorders; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception; mood disorders; depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; gastrointestinal diseases; eating disorders; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage excitotoxic neuronal damage; epilepsy; stroke; stress induced immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; and hypoglycemia in a mammal, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1 that is effective in treating such disorder.

14. A compound of the formula



II

wherein A is N or -CR_6;

D is chloro, hydroxy or cyano;

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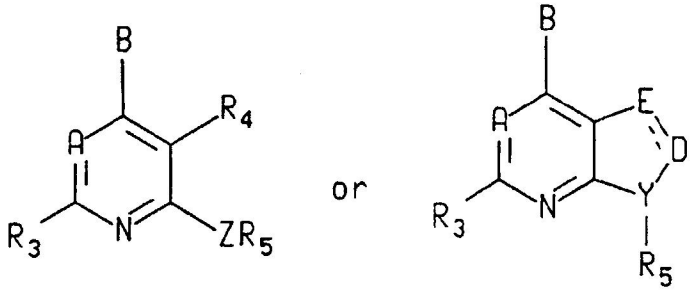
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(54) New uses for corticotropin releasing factor (CRF) antagonists

(57) A method of treating, preventing or inhibiting a disorder selected from the group consisting of cardiovascular or heart related diseases such as stroke, hypertension, tachycardia, and congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, and colonic hypersensitivity associated with psychopathological disturbance and stress, comprising administering to a mammal, including a human, in need of such treatment a therapeutically effective amount of a compound of the formula



I II

or a pharmaceutically acceptable salt thereof, wherein A, B, D, E, Y, Z, R_3, R_4, and R_5 are as defined herein.

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the compounds of formula I are prepared by one or more of the synthetic methods referred to in PCT international application number PCT/IB95/00439, referred to above.

Pharmaceutically acceptable salts of the compounds of formulas I and II include salts of acidic or basic groups. For example, pharmaceutically acceptable salts include sodium, calcium and potassium salts of acidic groups, such as when the R_{10} substituent is carboxy. Such salts are generally prepared by combining a compound of formula I or II with one molar equivalent of NaOH or KOH in a suitable solvent. Pharmaceutically acceptable acid addition salts of basic groups, such as amino groups, are formed by reacting the base form of a compound of formula I or II with an appropriate acid. Pharmaceutically acceptable salts of basic groups include hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), at least one molar equivalent and usually a molar excess of the acid is employed. However, when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration or addition of a non-solvent.

In the method of the invention, the compounds of formulas I and II, and their pharmaceutically acceptable salts, can be administered alone or in combination with pharmaceutically acceptable carriers, in ether single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the active compounds and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type can also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof. Oral administration is generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, another route of administration such as suppositories, parenteral (i.m., i.v.), or topical administration will be appropriate.

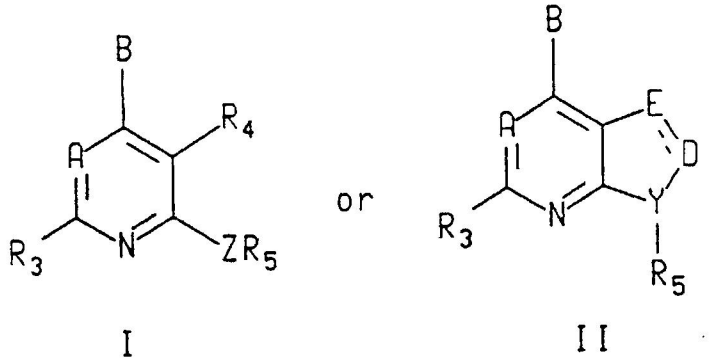
For parenteral administration, solutions of the active compound in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution can be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

In the method of the invention, the effective dosage for the compounds of formulas I and II, and their pharmaceutically acceptable salts, depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. In general, the daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. The daily dosage may be given in a single dose or up to three divided doses. In the prevention of premature birth, the dosage should be administered daily after high levels of corticotropin-releasing hormone have been detected early in pregnancy and then discontinued just prior to the end of the term for normal pregnancy.

The methods for testing the compounds of formulas I and II, and their pharmaceutically acceptable salts, for CRF antagonist activity are as described in Endocrinology, 116, 1653-1659 (1985) and Peptides 10, 179-188 (1989) which determine the binding affinity of a test compound for a CRF receptor. The binding affinities for the active compounds, expressed as IC_{50} values, generally range from about 0.2 nanomolar to about 10 micromolar.

Claims

1. The use of a compound of the formula



I or II

or a pharmaceutically acceptable salt thereof, wherein

the dashed line represents an optional double bond;

A is $-CR_7$ or N;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_1R_{12})R_2$, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SCR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;

D is: (i) N or $-CR_{10}$ when a double bond connects E and D and E is $-CR_4$; (ii) $-CR_{10}$ when a double bond connects E and D and E is N; or (iii) $-CR_8R_9$, $-CHR_{10}$, -C=O, -C=S, -C=NH, or $-C=NCH_3$ when a single bond connects E and D;

E is $-CR_4$ or N when a double bond connects E and D, and E is $-CR_4R_6$ or $-NR_6$ when a single bond connects E and D;

Y is N or -CH;

Z is NH, O, S, $-N(C_1-C_2$ alkyl) or $-CR_{12}R_{13}$, wherein R_{12} and R_{13} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{12} and R_{13} is cyano and the other is hydrogen or methyl;

R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with one or two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, $-O-CO-(C_1-C_4$ alkyl), $-O-CO-NH(C_1-C_4$ alkyl), $-O-CO-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_2$ alkyl)$(C_1-C_4$ alkyl), $-S(C_1-C_4$ alkyl), $-N(C_1-C_4$alkyl)$CO(C_1-C_4$alkyl), $-NHCO(C_1-C_4$alkyl), $-CO_2(C_1-C_4$alkyl), $-CONH(C_1-C_4$ alkyl), $-CON(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $(C_1-C_4$ alkyl)sulfinyl, $(C_1-C_4$ alkyl)sulfonyl, and $(C_1-C_4$ alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy and the C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;

R_2 is C_1-C_6 alkyl, aryl or (aryl)C_1-C_4 alkyl wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by $-NR_{14}$ wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, $-O-CO-(C_1-C_4$ alkyl), $-O-CO-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-CO_2(C_1-C_4$ alkyl), $(C_1-C_4$ alkyl)sulfanyl, $(C_1-C_4$ alkyl)sulfinyl, and $(C_1-C_4$ alkyl)sulfonyl, and wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;

or R^1 and R^2 of said $-NR_1R_2$ and said $-CR_1R_2R_{11}$ are taken together to form a saturated 5 to 8 member ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by an oxygen or sulfur atom;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$(C_1-C_2$ alkyl), $-CH_2OH$, $-CH_2OCH_3$, $-O(C_1-C_4$ alkyl), $(C_1-C_4$ alkyl)sulfanyl, $(C_1-C_4$ alkyl)sulfonyl, or $(C_1-C_4$ alkyl)sulfinyl, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, $-NH(C_1-C_2$ alkyl), $-N(C_1-C_2)_2$, $-NHCOCH_3$, fluoro, chloro and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2CF_3$, CF_3, amino, nitro, $-NH(C_1-C_4$ alkyl), $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $(C_1-C_4$ alkyl)sulfanyl, $(C_1-C_4$ alkyl)sulfinyl, $(C_1-C_4$ alkyl)sulfonyl, cyano, hydroxy, $-CO(C_1-C_4$

alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy and the C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfany, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, wherein said cycloalkyl and bicycloalkyl optionally contain one or two of O, S or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each of the above R_5 groups is optionally substituted by from one to three substituents independenly selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, - NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2 -$NHSO_2$(C_1-C_4 alkyl), - S(C_1-C_4 alkyl), and -SO_2(C_1C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy or fluoro group;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1-C_4 alkoxy, -CO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy;

or R_8 and R_9 together form an oxo (=O) group;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro; and,

R_{11} is hydrogen, hydroxy, fluoro, or methoxy; for the preparation of a medicament for treating a disorder selected from the group consisting of cardiovascular or heart related diseases including hypertension, tachycardia, and congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, and colonic hypersensitivity associated with psychopathological disturbance and stress.

2. The use of claim 1 wherein B is -NR_1R_2, -$NHCHR_1R_2$, -$CR_1R_2R_{11}$, -$SCHR_1R_2$ or -$OCHR_1R_2$; R_1 is C_1C_6 alkyl which is optionally substituted with a single hydroxy, fluoro or C_1-C_2 alkoxy group and optionally contains one carbon-carbon double or triple bond; R_2 is benzyl or C_1-C_6 alkyl which optionally contains one carbon-carbon double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl are optionally substituted with fluoro, C_1-C_2 alkyl, or C_1-C_2 alkoxy; and R_{11} is hydrogen or fluoro.

3. The use of claim 1 wherein R_2 is (aryl)C_1-C_4 alkyl in which said aryl moiety is phenyl, thienyl, benzofuranyl, furanyl, benzothienyl, thiazolyl, pyridyl or benzothiazolyl.

4. The use of claim 1 wherein B is NR_1R_2 or CHR_1R_2 in which R_1 and R_2 are taken together with N or CH to form a 5- or 6-membered ring optionally having sulfur, oxygen, or, where B is NR_1R_2, one more nitrogen in said ring.

5. The use of claim 1 wherein B is -$NHCHR_1R_2$ or -$OCHR_1R_2$, wherein the CHR_1R_2 moiety is a 5- or 6-membered ring which optionally contains one oxygen or sulfur.

6. The use of claim 6 wherein B is tetrahydrofuranyl, tetrahydrothiafuranyl or cyclopentanyl.

7. The use of claim 6 wherein B is tetrahydrofuranyl, tetrahydrothienyl or thiazolidinyl.

8. The use of claim 1 wherein R_3 is methyl, chloro, or methoxy; R_4 is methyl, -CH_2OH, cyano, trifluoromethoxy, methoxy, trifluoromethyl, chloro, -CO_2CH_3, -CH_2OCH_3, -CH_2Cl, -CH_2F, amino or nitro; R_6 is hydrogen, methylsulfinyl, methylsulfanyl, methylsulfonyl, methyl or ethyl; and R_5 is phenyl or pyridyl wherein said phenyl or pyridyl is substituted by two or three substituents independently selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl,(C_1-C_2 alkoxy)C_1-C_4 alkyl, C_1-C_3 hydroxyalkyl, hydroxy, formyl, -CO_2(C_1-C_2 alkyl), (amino)C_1-C_2

alkyl, -CO(C_1-C_4 alkyl) , and C_1-C_6 alkyl, wherein said C_1-C_6 alkyl and said C_1-C_4 alkyl are optionally substituted by a single hydroxy, C_1-C_2 alkoxy or fluoro group and optionally contains one carbon-carbon double or triple bond.

9. The use of claim 1 wherein the compound of formula I or II is selected from the group consisting of:

4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine;
2-(4-bromo-2,6-dimethyl-phenoxy)4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine;
2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;
[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl] (1-ethyl-propyl)-amine;
butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;
butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester;
[3,6-dimethyl-[2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;
1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;
3,6-dimethyl-2-(2,4,6-kimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;
[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-(1-ethyl-propyl)-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo [2,3-d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pydmidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-amine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethylpropyl)-amine;
N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethylphenyl)-pyrimidine-4,5-diamine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
6-(ethyl-propyl-amino)-2,7-dimethyl-9(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one, and pharmaceutically acceptable salts of the foregoing compounds.

10. The use of claim 1 wherein said compound is a compound of formula II in which E and D are connected by a double bond, E is $-CR_4$, D is $-CR_{10}$ or N, Y is N, and A is $-CR_7$.

11. The use of claim 10 wherein said compound is selected from the group consisting of:

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;
3,6-dimethyl-4-(tetrahydrofuran-3-yloxy)-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(214,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;

(1-ethylpropyl)-[3,5,6-trimethyl-1(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo [2,3-b]pyridine;
4-(1 -ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine, and pharmaceutically acceptable salts of the foregoing compounds.

12. The method of claim 1 wherein said compound is a compound of formula II in which E and D are connected by a double bond, E is $-CR_4$, and D, Y and A are N.

13. The use of claim 12 wherein said compound is selected from the group consisting of:

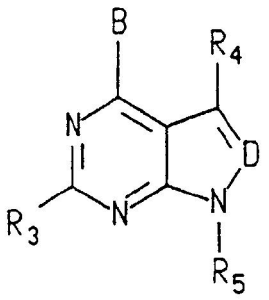
3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}propan-1-ol;
diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1 H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;
dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;
butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d] pyrimidin-4-yl]-amine;
4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d] pyrimidine;
2-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine]-butan-1-ol;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo-[3,4-d] pyrimidin-4-yl]-(1-methylpropyl)amine;
4-(1 -methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine, and pharmaceutically acceptable salts of the foregoing compounds.

14. The use of claim 1 wherein said compound is a compound of formula II in which E and D are connected by a double bond, E is $-CR_4$, D is $-CR_{10}$, and Y and A are N.

15. The use of claim 14 wherein said compound is selected from the group consisting of:

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo [2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;
2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-(S)-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-methoxymethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine;
[7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-(1-methoxymethyl-propyl)-amine;
2-[7-(2-bromo-4,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(4-ethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo [2,3-d] pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(2-ethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(2-fluoromethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol, and pharmaceutically acceptable salts of the foregoing compounds.

16. The use of a compound of the formula



III

or a pharmaceutically acceptable salt thereof, wherein

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_1R_{12})R_2$, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SOR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;

D is N or $-CR_{10}$;

R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with one or two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO(C_1C_4 alkyl), -NHCO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, and (C_1-C_4 alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy and the C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;

R_2 is C_1-C_6 alkyl, aryl or (aryl)C_1-C_4 alkyl wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_8 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by $-NR_{14}$ wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, and (C_1-C_4 alkyl)sulfonyl, and wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;

or R^1 and R^2 of said $-NR_1R_2$ and said $-CR_1R_2R_{11}$ are taken together to form a saturated 5 to 8 member ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by an oxygen or sulfur atom;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-CH_2OH$, $-CH_2OCH_3$, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4alkyl)sulfonyl, or (C_1-C_4 alkyl)sulfinyl, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2)$_2$, $-NHCOCH_3$, fluoro, chloro and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, $-CH_2OCH_3$, $CH_2OCH_2CH_3$ $-CH_2CH_2OCH_3$, $-CH_2CF_3$, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, $-NHCOCH_3$, $-NHCONHCH_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy and the C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfanyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl,

pyridinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, wherein said cycloalkyl and bicycloalkyl optionally contain one or two of O, S or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each of the above R_5 groups is optionally substituted by from one to three substituents independenly selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_4 alkyl), wherein n is O, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro; and,

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

for the preparation of a medicament for treating patients who have suffered a stroke.

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2005-03-31
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Febrero 25 de 2005

Doctor
CARLOS R. OLARTE

ASUNTO	Radicación No.	00 020 442
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	12431
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 47 a 56 y el nuevo capítulo reivindicatorio de los folios 57 a 65 de la solicitud en estudio.

2. Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 a 10 se refieren a un método preventivo que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II).

El problema planteado en esta solicitud es la necesidad de proporcionar un método de tratamiento para reducir la incidencia de muerte súbita en pacientes que sufren insuficiencia cardiaca.

Para resolver este problema técnico la solicitud en estudio proporciona un método preventivo que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II).

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/395.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 127 659 de abril 2 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: "*No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*"

Las reivindicaciones 1 a 10 se refieren a un método preventivo que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II).

Los métodos terapéuticos "no solo implican la curación de enfermedades o mal funcionamiento del cuerpo, sino que también incluyen los tratamientos profilácticos o preventivos". Así que, el método que consiste en administrar un compuesto terapéuticamente activo, de las reivindicaciones 1 a 10, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el método que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II), de las reivindicaciones 1 a 10, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "*El estado de la técnica comprenderá todo lo que haya sido accesible al publico por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el articulo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es abril 2 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	WO 95 33750	Antagonistas del Factor de Liberación de Corticotropina	Dic 14, 1995
D2	WO 95 34563	Pirazolo y pirrolopiridinas	Dic 21, 1995
D3	EP 0 773 023	Nuevos Usos de Antagonistas del Factor de Liberación de Corticotropina (CRF)	May 14, 1997

4. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*".

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad

El Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40".

Las reivindicaciones 1 a 10 se refieren a un método preventivo que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II).

D1 enseña un método de tratamiento que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II).

D2 enseña un método de tratamiento que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmula II).

D3 enseña un método de tratamiento que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II).

Se observa que el método que consiste en administrar un compuesto terapéuticamente activo (Antagonista del Factor de Liberación de Corticotropina de fórmulas I y II) solicitado en las reivindicaciones 1 a 10, se enseñaba en las anterioridades D1, D2 y D3, por lo cual no puede ser considerado nuevo.

5. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 95 33750	1 a 10	Novedad
D2	WO 95 34563	1 a 10	Novedad
D3	EP 0 773 023	1 a 10	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 la 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 Unica No. 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 31 MAR. 2005

CONCEPTO TÉCNICO No. 301	EXAMINADOR TÉCNICO Código 202007

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-20442** EDICTO No. **10061**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **17961** de **27-JUL-2005**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "MEJORA EN LA DISPERSION DE QT Y EN LA VARIABILIDAD DE LA FRECUENCIA CARDIACA CON ANTAGONISTAS DE CRIF PARA PREVENIR MUERTE SUBITA".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos R. Olarte, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 27 JUL. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIME RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **19-AGO-2005** Este edicto se desfija hoy **01-SEP-2005** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. **10061**