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

Ref: Expediente No. 02.103.708
Solicitud de patente de invención titulada:
"ANTAGONISTAS RECEPTORES DE ADENOSINA A2A."
Solicitante: SCHERING CORPORATION.

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, según consta en el poder adjunto, 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 $177.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.
Igualmente ratifico toda actuación realizada en el presente expediente por el Dr. Alvaro Correa-Ordoñez.

Atentamente,

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

Anexo: Recibo por $177.000 pesos
Poder

FTT/P1002/000040-040628

149

NIT : 800174099-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02103708 00000003 Folios: 6
Fecha (AMD): 2004-07-14 08:44:51
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 55,073
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	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	177,000.00
		TOTAL: $	177,000.00

SON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

150

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
   - Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguertie La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey 8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el Poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

COMO NOTARIO ONCE DE ESTE CÍRCULO DAGO CONSTAR QUE ESTA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

05 MAY 2003

BOGOTÁ, D.C. - COLOMBIA

ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

151

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

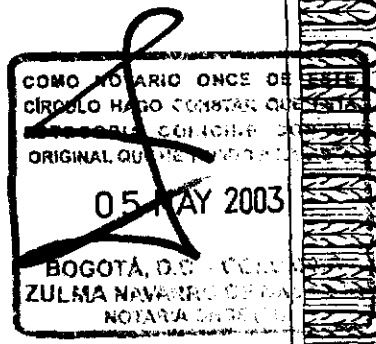
6. THE 29TH DAY OF AUGUST 2003

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:

10. SIGNATURE



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Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **02-103708**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION - PCT** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **538**, DE FECHA **31** DE **MARZO** DE **2004**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **01** DE **JULIO** DE **2004**.

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** ____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C. 31 de enero de 2007

Apoderado: Carlos Reinaldo Olarte Oficio: 1994

REFERENCIA: **Radicación N° 02-103708**
Trámite **002**
Evento **001**
Actuación **430**
Folios

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

1. DEL ARTÍCULO 46

Artículo 46. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina:
a) copia de la solicitud extranjera;
b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera;
c) copia de la patente u otro título de protección que se hubiese concedido con base en esa solicitud extranjera;
d) copia de cualquier resolución o fallo por el cual se hubiese rechazado o

denegado la solicitud extranjera; o

e) copia de cualquier resolución o fallo por el cual se hubiese anulado o invalidado la patente u otro título de protección concedido con base en la solicitud extranjera.

Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente.

2. DE LA SOLICITUD PCT

El solicitante presentó una solicitud de patente PCT/SE01/016954 que ahora esta en fase nacional y fue publicada el 06/12/2001; WO01/92264. Dicha solicitud le fue realizado su examen preliminar internacional, al respecto de lo cual existen documentos relativos a la patentabilidad.

3. DE LA SOLICITUD DE LA OFICINA

A efectos del examen de patentabilidad y como requerimiento de esta oficina, el solicitante deberá proporcionar, en un plazo que no excederá de 3 meses, los siguientes documentos relativos a la solicitud extranjera correspondiente a la misma invención que se examina y tales documentos son los que a continuación se enumeran:

1- JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 5, 1; fecha de publicación: March 1996 (1996-03-01), pages 1164-71; Autor: P. G. BARALDI ET. AL.: Titulo: "PyrazoloÄ4,3-eÜ-1,2,4-triazoloÄ1,5-cÜpyrimidine Derivatives. Potent and Selective A2A Adenosine Antagonists."

En cumplimiento del artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe proporcionar éstos documentos, en un plazo que no excederá de tres meses, a partir a partir de la fecha de la notificación de la presente comunicación. Si el solicitante no presentara los documentos requeridos dentro del plazo señalado, la oficina nacional competente denegará la patente.

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DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, DC, viernes 02 de febrero de 2007

Apoderado: Carlos Reinaldo Olarte Oficio: 0001991

REFERENCIA: Radicación No. 02-103708
Tramite 002
Evento 001
Actuación 430
Folios

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

Documentos estudiados:

- Capítulo descriptivo; folios 86 a 165;
- capítulo reivindicatorio folios 166 a 175;
-Solicitud PCT/US01/16954, en fase nacional.
-solicitud del examen de patentabilidad, folios 148 y 149.

Objeto de invención:

El objeto de la solicitud se refiere 7-(alquilsustituido-aril)-2-(heteroarilsustituido)-7H-pirazolo[4,3-e][1,2,4]triazolo[1,5-c]pirimidin-5-amina .

Clasificación Internacional de Patentes: C07D487/14; A61K 31/505

Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la*

descripción".

-En la reivindicación 2, no es claro donde dice R es R^1-furanilo, entonces, R^1 para esta reivindicación no esta definido.

-En la reivindicación 3 no esta establecido el significado de Q, m, n y R^4.

-La reivindicación 5, no es clara se coloco dependiente de si misma.

-La reivindicación 6 no es clara, en esta reivindicación no esta definido el significado de R^5 y R^6.

Reivindicaciones de uso

La reivindicación 10 reclama el uso, y de acuerdo con la legislación colombiana el uso reclamado no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina"... Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología..."; AQUÍ NO se hace alusión al uso.

Continuando con la última parte del Artículo 14"... (Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial." El hecho que se diga que el producto o el procedimiento tengan aplicación industrial no quiere decir que la aplicación industrial sea susceptible de patente.

Así mismo, citando **completamente** el artículo 19 este reza: " Se considerará que una **invención** *(léase producto o procedimiento)* es susceptible de aplicación industrial *(una característica de la invención)* cuando su objeto puede ser producido o utilizado en cualquier clase de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios." Esta diciendo que una invención, producto o procedimiento, debe servir para algo. En ningún momento se dice que un uso pueda ser protegido como patente.

El artículo 16 dice: " Los productos o procedimientos *(o sea, los inventos, nótese que nunca se refieren a nada diferente)* ya patentados comprendidos en el estado de la técnica de conformidad con el Artículo 21 de la presente Decisión, no serán objeto de nueva patente por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial." Nunca se refieren a una protección para el uso, como erróneamente se podría interpretar. Se trata de no conceder nueva patente a un invento (exclusivamente productos o procedimientos) al que se le ha encontrado

D1

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 487/14, A61K 31/495 // (C07D 487/14, 239:00, 249:00, 249:00) (C07D 487/14, 231:00, 239:00, 249:00) — A1

(11) International Publication Number: **WO 95/01356**

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(21) International Application Number: PCT/EP94/02031

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MI93A001396 29 June 1993 (29.06.93) IT

(71) Applicant (*for all designated States except US*): SCHERING-PLOUGH S.p.A. [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BARALDI, Pier, Giovanni [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). ZAPPATERRA, Laura [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). ONGINI, Ennio [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

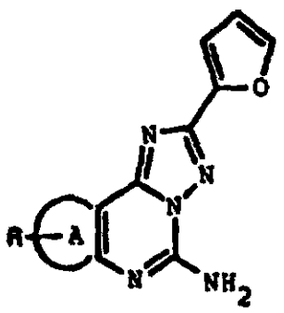
(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_2 RECEPTOR

(57) Abstract

The compounds of formula (I) wherein R and A have the meanings given in the specification, are endowed with selective A_2 adenosine receptor antagonistic activity.



(I)

1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_2 RECEPTOR

The present invention relates to compounds having antagonistic activity on adenosine A_2 receptor.

Adenosine is known to modulate a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a diphasic action, inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97).

A number of studies showed adenosine actions are mediated by two subtypes of receptors which are located on the cell membrane: an high-affinity one, inhibiting the activity of the enzyme adenylate cyclase (A_1 receptor), and a low-affinity one, stimulating the activity of the same enzyme (A_2 receptor) (J. Med. Chem. 1982, 25, 197-207. Physiol. Rev. 1990, 70(3), 761-845. J. Med. Chem. 1992, 35, 407-422).

Intense research efforts have made it possible to identify and develop analogs to adenosine able to interact as agonists with the A_1 and A_2 receptor. As far as the antagonists are concerned, it is known that some

compounds with a xanthine structure are selective antagonists for the A_1 receptor.

(J. Med. Chem., 1992, 25, 407-422). New compounds of pharmacological interest which possess an high antagonistic action for the A_2 receptor have not yet been found.

The knowledge available on the physiological role of adenosine and its involvement in some pathological processes suggests that selective antagonists for the A_2 receptor can be of pharmacological interest. At the level of the central nervous system, antagonistic A_2 compounds should stimulate various cerebral functions and so possess antidepressive and stimulating properties for the cognitive functions. Moreover, numerous data show that the A_2 receptors are present in high density in the basal ganglia of which the importance in the control of movement is known. Hence the hypothesis that A_2 antagonists can improve motor-deficiency due to neurodegenerative processes at the level of important cerebral nuclei. It follows that A_2 receptor antagonists could be useful in the treatment of neurodegenerative pathologies. Amongst these are included Parkinson's disease, senile dementia as in Alzheimer's disease and psychosis of an organic origin (Drug Dev. Res., 1993, 28, 381-385).

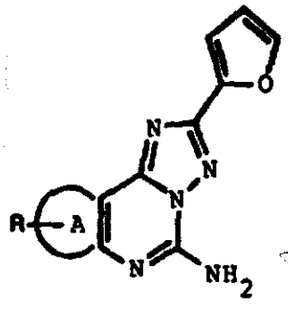
At a peripheric level, A_2 receptor antagonists could stimulate the respiratory functions and therefore have a therapeutic effect in the treatment of bronchospasm and more generally asthma. Moreover, with regard to the effects at a cardiovascular or renal level, an advantageous activity on renal flow can be envisaged

and therefore the possibility of the treatment of renal insufficiency and of various cardiovascular disturbances.

Some reference compounds interacting with A_2 receptor, even though in a not selective way, are known.

5-Amino-9-chloro-2(2-furyl)1,2,4-triazolo[1,5-c]quinazoline, named CGS 15943 (J. Med. Chem., 1988, 31, 1014-1020) and 4-amino-8-chloro-1-phenyl(1,2,4)-triazolo(4,3-a)quinoxaline, named CP 66,713 (J. Med. Chem., 1990, 33, 2240-2254) are compounds having a good affinity for A_2 receptor, but also active on A_1 receptor. Only recently, xanthine derivatives have been found, e.g. (E)-1,3-dialkyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthines (J. Med. Chem., 1992, 35, 2342-2345), which seem to have a selective antagonistic activity on A_2 receptors. However, the pharmacological profile thereof is unknown.

The compounds of the invention have the following general formula I:



I

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl, C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with

one or more halogen atoms, hydroxy groups, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$; aryl optionally substituted with halogen atoms, C_1-C_4 alkoxy groups, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxyamido; C_7-C_{10} aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula $-(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer from 1 to 5;

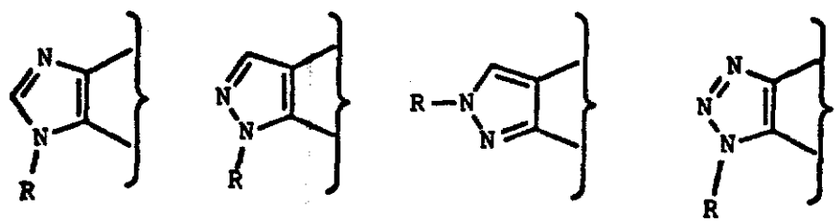
R_1, R_2 which are the same or different, are hydrogen, C_1-C_5 alkyl, C_7-C_{10} aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms such as N, O, S and n is an integer from 2 to 5, with the proviso that, when A is a pyrazole or imidazole, R is different from fluorobenzyl.

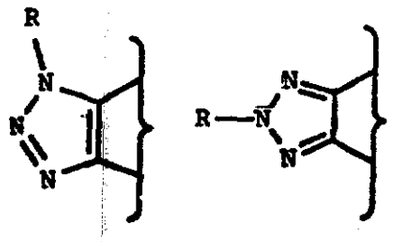
The disclaimed compounds are disclosed in Eur. J. Med. Chem., 1993, 28, 569-576,

The invention also comprises the pharmaceutically acceptable salts of the compounds of general formula I.

The possible meanings of A can be represented by the following structural formulae:

5





In compounds of formula I, examples of C_1-C_8 alkyl groups comprise preferably methyl, butyl and isopentyl.

Examples of C_3-C_7 cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl.

Examples of C_1-C_5 alkyl groups substituted with C_3-C_7 cycloalkyl groups are cyclohexylmethyl, cyclopentylmethyl, 2-cyclopentylethyl.

Examples of substituted C_1-C_5 alkyl groups comprise 2-hydroxyethyl, 2-methoxyethyl, trifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 3-aminopropyl, 2-(4-methyl-1-piperazine)ethyl, 2-(4-morpholinyl)ethyl, 2-aminocarbonylethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl. Aryl is preferably phenyl, optionally substituted with chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups. Examples of 5-6 membered heterocyclic groups containing N, O, S comprise piperazinyl, morpholinyl, thiazolyl, pyrazolyl, pyridyl, furyl, thienyl, pirrolyl, triazolyl, tetrazolyl. Examples of C_7-C_{10} aralkyl groups comprise benzyl or phenetyl optionally substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

Preferably, R is hydrogen, C_1-C_8 alkyl, aryl or C_7-C_{10} aralkyl optionally substituted, preferably with halogen atoms.

Particularly preferred compounds I are those in which R is a phenetyl group in which the phenyl ring may optionally be substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

The compounds of general formula I have advantageous biochemical and functional properties related to their antagonistic action on the A_2 adenosine receptor, compared with the reference compounds CGS 15943 and (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-pyrazolo [4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine), disclosed in Eur. J. Med. Chem., 1993, 28, 569-576 and hereinafter referred to as 8FB-PTP. The effects of the disclosed A_2 receptor antagonists may be demonstrated in one or more of the following standard in vitro and/or in vivo tests.

IN VITRO TESTS

Receptor binding

This test involves the ability of adenosine antagonists to displace radiolabeled agonists from A_1 and A_2 adenosine binding sites in membrane preparations from rat brain.

The rat cerebral tissue (whole brain and striatum) was from male Sprague-Dawley rats weighing 150-200 g. A_1 and A_2 receptor binding assays were performed according to Bruns et al. (Proc. Natl. Acad Sci. U.S.A., 1980, 77, 5547-5551) and Jarvis et al. (J.

Pharmacol. Exp. Ther., 1989, 251, 888-893), using [3H]N6-cyclohexyladenosine ([3H]CHA) and [3H]2-[p-(2-carboxy ethyl)-phenetylamino]-5'-N-ethylcarboxamido-adenosine ([3H]CGS 21680) as radioligands, respectively.

The test compounds were dissolved in dimethylsulphoxide (DMSO) and then diluted with assay buffer to give the test solutions. The final concentration of DMSO did not exceed 1% by volume, at which level it did not affect radio ligand binding to the membrane receptor.

The selectivity for A_2 receptors was evaluated by comparing the affinities of each compound for A_1 and A_2 receptors. A marked relationship between binding affinities and physiological effects modulated by adenosine receptors has been demonstrated elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348,108-112).

The disclosed compounds, described in formula I, have marked A_2 receptor affinity with Ki values ranging from 1 nM to 100 nM (Table). Moreover, some compounds show A_2 versus A_1 selectivity higher than that of the reference compounds CGS 15943 and 8FB-PTP. In particular, compound 341 has a selectivity for A_2 versus A_1 receptors of about 50-fold.

Rat aorta and bovine coronary artery

The A_2 adenosine antagonistic activity of these compounds was investigated by evaluating their ability to counteract vasodilation induced by adenosine agonists in vascular tissues, such as rat aorta and bovine coronary arteries, after precontraction with 3μM

of prostaglandin F2α . The method used to test adenosine agonists is described elsewhere (Conti et al.,Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112). Cumulative dose-response curves were constructed, using increasing concentration of NECA (1 nM-10 uM), in the absence or presence of the antagonist.

Many of the test compounds, at concentrations ranging from 0.03 to 1µM, were able to shift to the right the dose-response curves of the agonist in a concentration-dependent manner.

Rat atria

The ability of the disclosed compounds to antagonize the negative chronotropic effect induced by A_1 receptor agonists was tested on isolated rat atria, whose beating rate is known to be modulated by A_1 adenosine receptors. The method used to test adenosine agonists is described elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112). The decrease in atrial rate evoked by cumulative addition of the A_1 selective agonist, 2-chloro-$_N$6-cyclopentyladenosine (CCPA) was measured. The dose-response curves of the agonist was then repeated in the presence of the antagonist. The receptor selectivity of test compounds can be evaluated by comparing the activities of each compound in antagonizing either A_2 (vasodilation)- or A_1 (heart rate)-mediated responses.

Some of the disclosed compounds were found to have little or no effects on the A_1-mediated response in isolated rat atria. Inparticular, compound 341 is ineffective in this functional model, thus confirming

its A_2 versus A_1 selectivity observed from binding studies.

IN VIVO TESTS

Behavioral effects

The behavioral response to treatment with different doses (ranging from 1 to 100 mg/Kg) of the test compounds administered parenterally were evaluated in Swiss mice using the classic "Irwin test" (Irwin, Psychopharmacologia, 1968 13, 222-257). Behavior, autonomic and neurological functions of the animals were assessed through 36 different parameters evaluated during observation sessions at 1, 2, 4 and 6 h after drug administration. The animals were observed until 24 h after administration for checking mortality.

The test compounds produced no mortality and only tended to stimulate central nervous system activity.

Hemodynamic tests

In adult male spontaneously hypertensive rats, some of the disclosed compounds were administered parenterally at increasing doses (1-30 mg/Kg) and their ability in antagonizing the bradycardic and hypotensive effects induced by A_1 and A_2 adenosine receptor agonists, respectively, was measured. Systolic blood pressure and heart rate were measured in conscious animals by the tail-cuff method as described elsewhere (Monopoli et al., Arch. Int. Pharmacodyn. Ther., 1987, 286, 246-254).

The test compounds antagonize hypotension induced by A_2 agonists with a potency similar or higher than that of the reference compounds CGS 15943 and 8FB-PTP, whereas some of them antagonize the

A_1-mediated responses slightly and only at higher doses.

TABLE - BIOLOGICAL ACTIVITY OF A SERIES OF NEW A2 ADENOSINE RECEPTOR ANTAGONISTS

Compound N°	Binding[a] Ki (nM) A_1	Ki (nM) A_2	Selectivity A_1/A_2
DCPCX	1.5	727	0.002
CGS 15943	6.4	1.2	5.3
8FB-PTP	3.3	1.2	2.8
N° 292	237	9.0	26.3
N° 294	31.2	2.4	13.0
N° SP 319	120	12.6	9.5
N° SP 320	5.8	1.9	3.1
N° SP 340	61.5	13.8	4.4
N° SP 341	123	2.4	51.3
N° SP 363	18.6	2.6	7.2
N° SP 375	4.7	1.5	3.2
N° SP 376	42.6	7.1	6.0

[a]Inhibition of [^{3}H]CHA binding (A_1) in rat whole brain homogenates or [^{3}H]CGS 21680 binding (A_2) in rat striatal homogenates.

- **DPCPX** (8-cyclopentyl-1,3-dipropylxanthine) is a standard A_1 selective antagonist (Bruns et al., Naunyn-Schmied. Arch. Pharmacol., 1987, 335, 59-63).
- **CGS 15943** (5-amino-9-chloro-2-(2-furyl)1,2,4-triazolo[1,5-c]quinazoline is a reference slightly selective A2 antagonist (Francis et al., 1988, J.

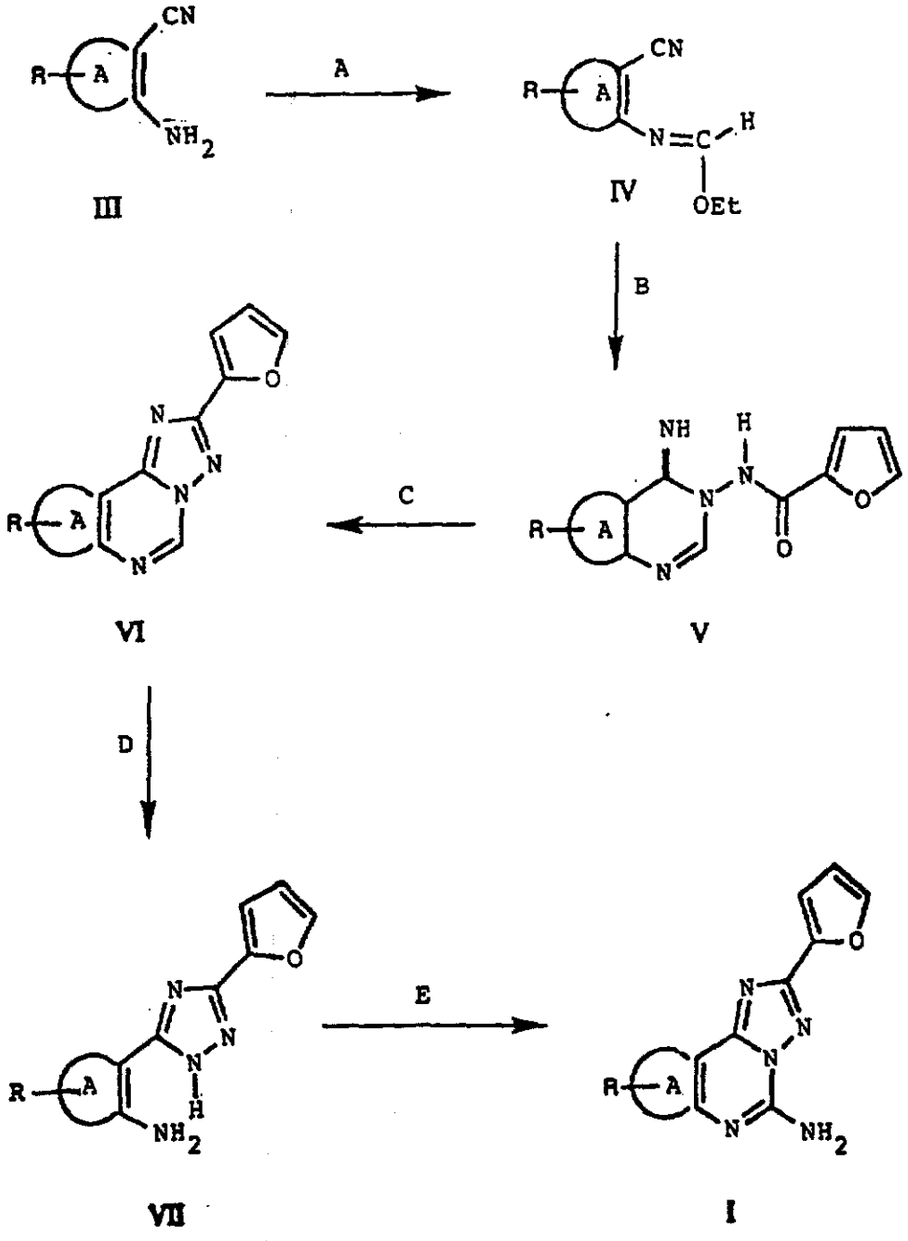
Med. Chem., 31, 1014-1020).

- 8FB-PTP (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-pyrazolo[4,3-4e]-1,2,4-triazolo[1,5-c]pyrimidine) is a reference slightly selective A2 antagonist (Gatta et al., Eur. J. Med. Chem., 1993, 28, 569-576).

For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical compositions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII ed. The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0,01 to 10 mg/kg body weight, preferably from 0,1 to 1 mg/kg, optionally subdivided in more administrations. Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (cerotti) and the like.

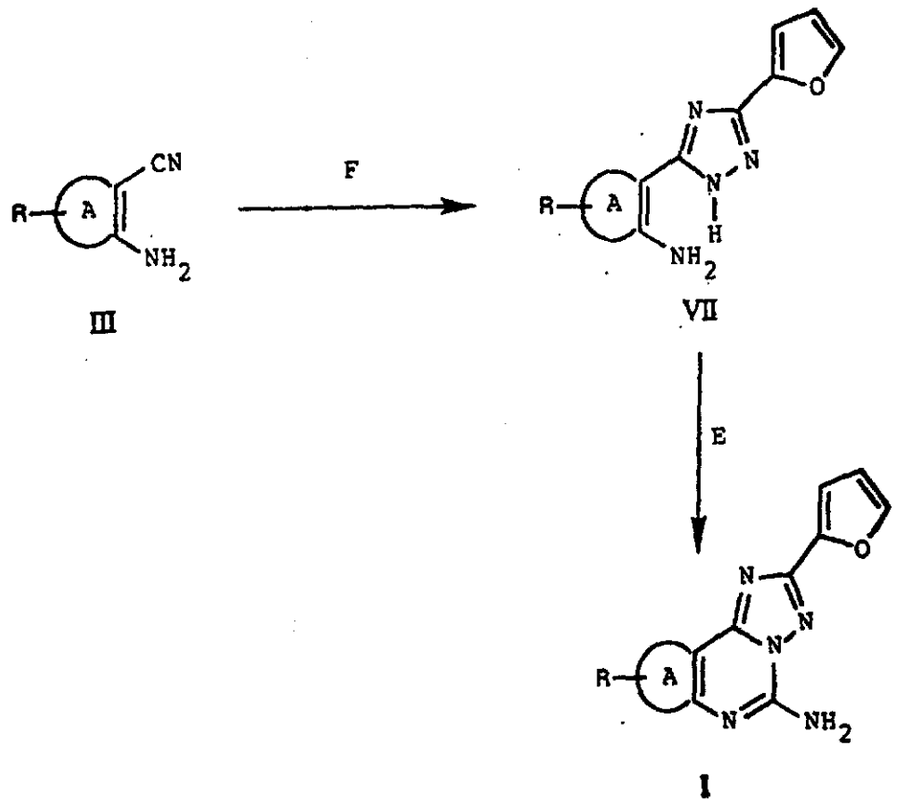
The compounds of the invention were prepared according to the synthetic schemes reported below.

Scheme I



Reagents: A) triethyl orthoformate; B) 2-furoic acid hydrazide, 2-methoxyethanol; C) PhOPh, 260°C; D) 10% HCl, under reflux; E) cyanamide, pTsOH, N-methylpyrrolidone

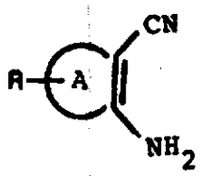
Scheme II



Reagents: F) furoic acid hydrazide, diphenylether; E) cyanamide, pTsOH, N-methylpyrrolidone.

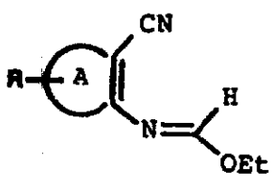
The compounds of formula I of the invention can be prepared through either an indirect route described in Scheme I or a direct route described in Scheme II.

Suitable starting materials for both schemes are the heterocyclic ortho-amino nitriles of formula III, generally prepared according to synthetic procedures known in literature and reported in the book by E.C.Taylor and A.McKillop (vol. 7 of the series Advances in Organic Chemistry, Ed. Interscience, 1970).



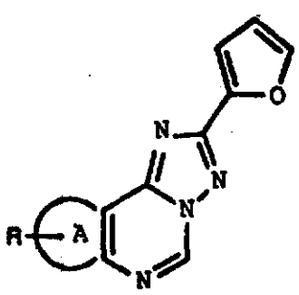
III

Ortho-amino nitriles III are transformed into the corresponding imidates of formula IV by reaction with an ethyl orthoformate excess at the reflux temperature for 8-10h. The reaction, after evaporation of the ethyl orthoformate, leads to the substantially pure corresponding imidates IV in a high yield as evidenced by the IR and ^1H NMR analysis on the crude reaction products.



IV

The imidates of formula IV are then subjected to a sequence of two reactions allowing to obtain the tricyclic structures of formula VI in a high yield.

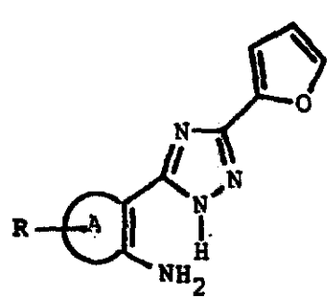


VI

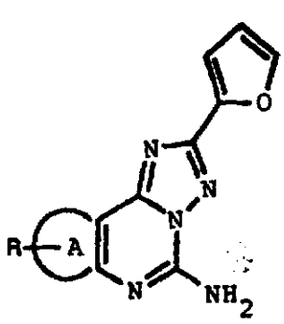
The reaction sequence comprises: a) reaction with 2-furoic acid hydrazide in a 2-methoxyethanol solution at the reflux temperature for 8-10h, to obtain the intermediates compounds of formula V; b) thermal cyclization of the latter to corresponding compounds of for-

mula VI, by heating in diphenyl ether at the temperature of 260°C for 0.5-1h.

The tricyclic compounds VI are then hydrolyzed with 10% HCl at the reflux temperature for 1-3h to give triazoles VII, which are finally cyclized to desired compounds I with cyanamide in N-methyl pyrrolidone at the reflux temperature and in the presence of para-toluenesulfonic acid (Scheme I).



VII

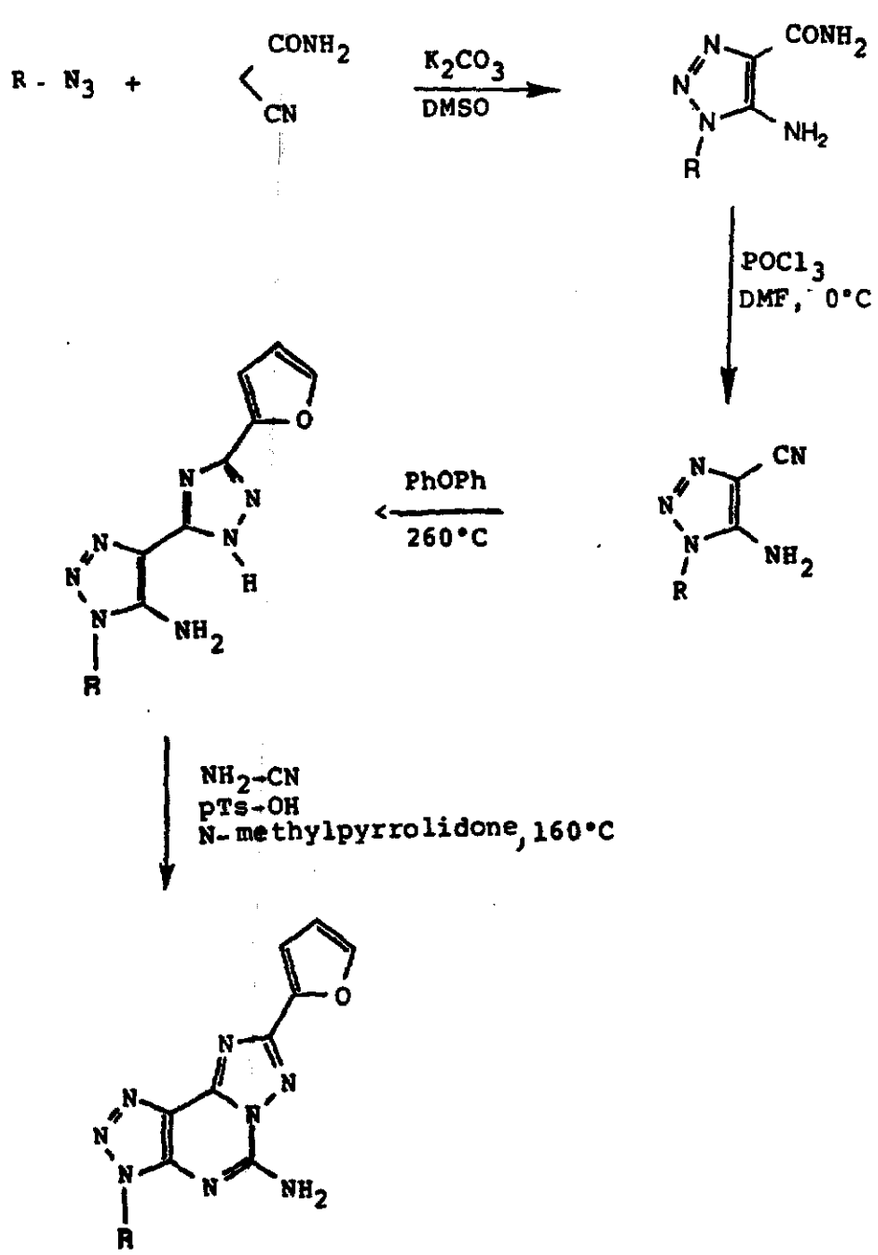


I

In some cases, triazoles VII can be obtained directly heating in diphenyl ether ortho-amino nitriles III with 2-furoic acid hydrazide. Triazoles VII are then cyclized as described above (Scheme II). In the following schemes III, IV and V, the synthesis of the compounds I in which A is a triazole ring is reported in more detail.

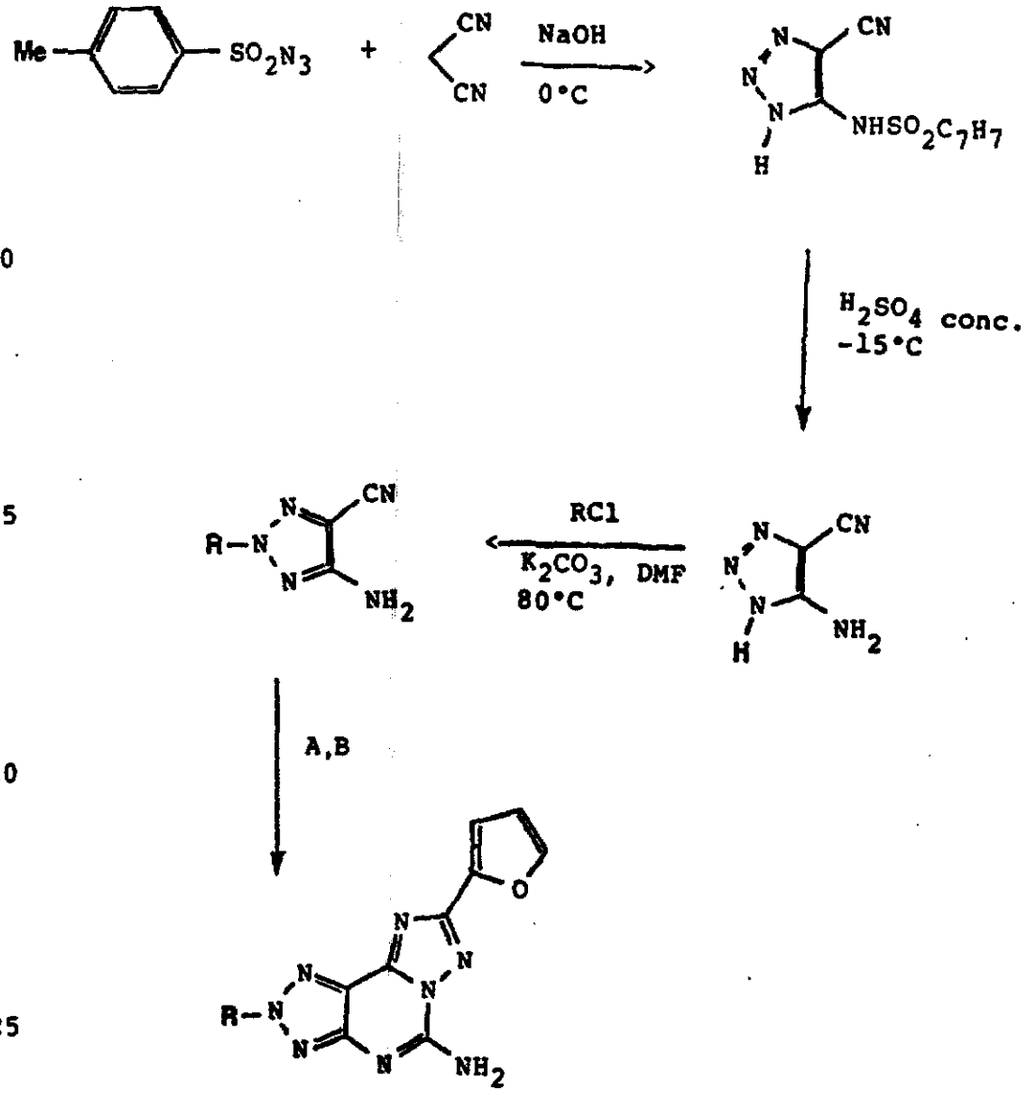
Scheme III

Synthesis of 5-amino-7-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



Scheme IV

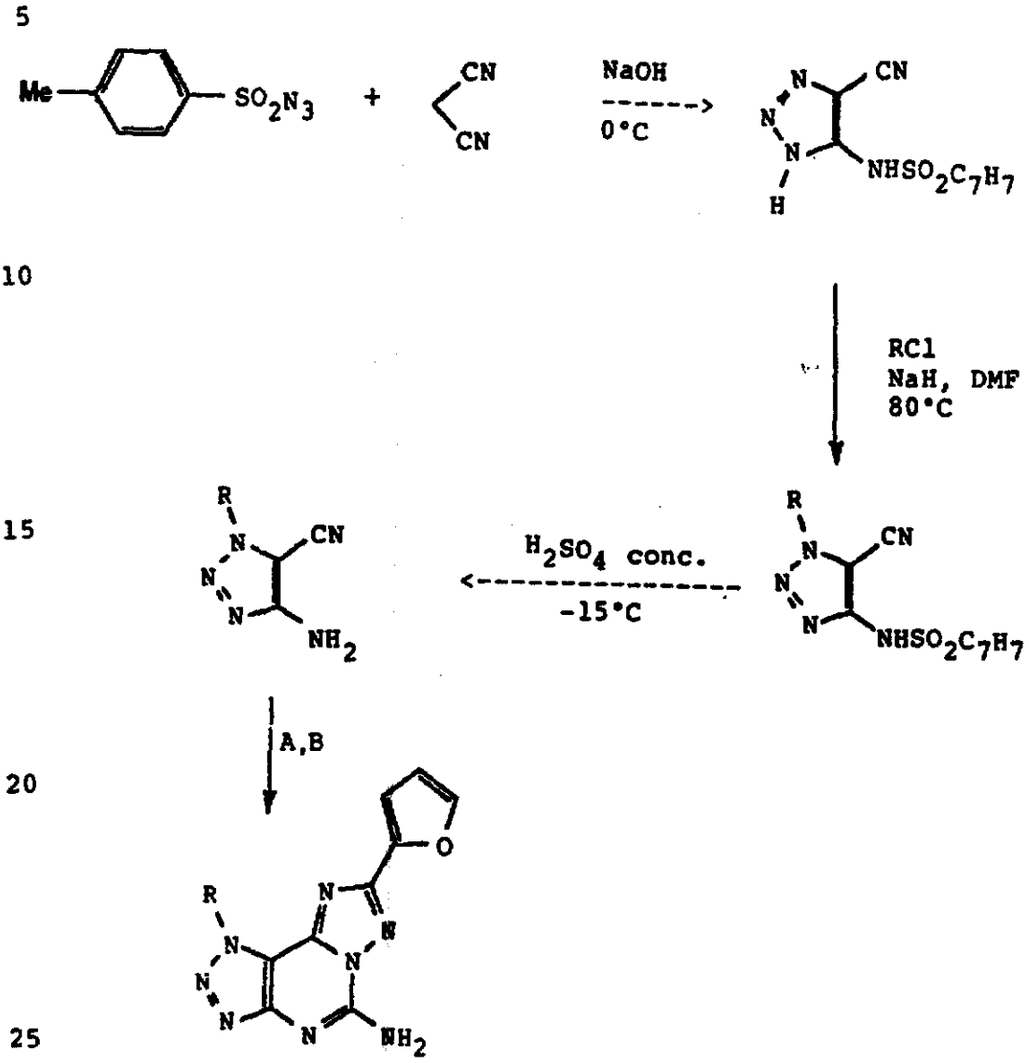
Synthesis of 5-amino-8-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



Reagents: A) furoic acid hydrazide, PhOPh, 260°C, B) NH_2CN, pTsOH, N-methylpyrrolidone.

Scheme V

Synthesis of 5-amino-9-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



Reagents: A) furoic acid hydrazide, PhOPh, 260°C, B) NH_2CN, pTsOH, N-methylpyrrolidone.

The following examples illustrate the invention in more detail.

Example 1

According to the procedures described in J. Org. Chem. 1956, 21, 1240; J. Am. Chem. Soc. 1956, 78, 784 and the references herein cited, the following compounds are prepared, starting from commercially available ethoxy-methylene malondinitrile and N1-substituted hydrazines, which also are mainly commercially available:

1-methyl-4-cyano-5-aminopyrazole
1-n-butyl-4-cyano-5-aminopyrazole
1-isopentyl-4-cyano-5-aminopyrazole
1-(2-cyclopentyl)ethyl-4-cyano-5-aminopyrazole
1-hydroxyethyl-4-cyano-5-aminopyrazole
1-phenyl-4-cyano-5-aminopyrazole
1-tert-butyl-4-cyano-5-aminopyrazole
1-phenylethyl-4-cyano-5-aminopyrazole
1-(2-chlorophenyl)-4-cyano-5-aminopyrazole.

Example 2

Starting from 4-cyano-5-aminopyrazole, prepared according the procedure reported in Chem. Pharm. Bull. 1970, 18, 2353 or in J. Heterocyclic Chem. 1979, 16, 1113, 1-substituted 4-cyano-3-aminopyrazoles can be prepared by direct alkylation with the corresponding alkyl halide in dimethylformamide at 80°C for 1-2h in the presence of anhydrous potassium carbonate. From the reaction mixture, containing the two N_1 and N_2 alkylated position isomers in an about 1:2 ratio, the N_2 isomer can be isolated by a single crystallization or column chromatography on silica gel eluting with

ethyl acetate and petroleum ether mixtures. Using said procedures, the following compounds were prepared:

1-methyl-4-cyano-3-aminopyrazole

1-butyl-4-cyano-3-aminopyrazole

1-benzyl-4-cyano-3-aminopyrazole

1-isopentyl-4-cyano-3-aminopyrazole

1-phenylethyl-4-cyano-3-aminopyrazole

Example 3

a) A suspension of anhydrous potassium carbonate (30 mmols) in DMF (50 ml) is added with 3-amino-4-cyano-pyrazole (20 mmols), heating to a temperature of 80°C for 30 minutes. The suspension is added with phenethyl bromide (25 mmols) and is heated to 80°C for 2h. After cooling to room temperature, the mixture is evaporated to dryness under vacuum and the resulting residue is taken up with distilled water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts are dried over anhydrous sodium sulfate and evaporated to dryness under vacuum.

The resulting residue consists of a 1:3 mixture of 1-phenylethyl-4-cyano-5-aminopyrazole (20%) and of 1-phenylethyl-4-cyano-3-aminopyrazole (60%) which may be used as such in Example 4 or chromatographed on silica gel column eluting with an ethyl acetate/hexane mixture to give:

1-phenylethyl-4-cyano-5-aminopyrazole m.p. 172-173°C; (20%);

^{1}H-NMR (DMSO-d_6): 3.04 (t, 2H); 4.12 (t, 2H); 5.85 (sb, 2H); 7.21-7.30 (m, 5H); 7.41 (s, 1H); e 1-β-phenylethyl-4-cyano-3-aminopyrazole m.p. 98-100°C (60%); ^{1}H-NMR ($CDCl_3$): 3.07 (t, 2H); 4.10 (t, 2H); 4.23

(sb, 2H); 7.17 (s, 1H); 7.00-7.28 (m, 5H).

b) A solution of 1-ß-phenylethyl-4-cyano-5-aminopyrazole (20 mmol)in triethylorthoformiate (40 ml) is refluxed under nitrogen for 8 h.

The excess orthoformiate is evaporated to dryness under vacuum and the residual yellow oil is dissolved in ethyl ether and percolated onto silica gel to give the corresponding iminoether (87% yield). The residue obtained after orthoformiate evaporation is practically pure and is directly used in the following step. A solution of the iminoether (20 mmol) and of 2-furoic acid hydrazide (2.5 g, 22 mmol) in 2-methoxyethanol (50 ml) is refluxed for 5-10 h. After cooling, the solution is evaporated to dryness to give an oily residue which is subjected to thermal cyclization in diphenylether (50 ml) using a Dean-Stark apparatus so as to azestropically remove water formed during the reaction. After 1.5 h, the reaction is checked in TLC (ethyl acetate:petroleum ether 2:1) and when the starting compound is completely absent, the mixture is cooled and added with hexane. The resulting precipitate is filtered and crystallized to give 7-(ß-phenylethyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazole[1,5-c]pyrimidine m.p. 174-175°C (20%) 1H-NMR (DMSO-d_6):3.23 (t,2H); 4.74 (t, 2H); 6.75 (s, 1H); 7.14-7.17 (m, 5H); 7.28 (s, 1H); 7.98 (s, 1H); 8.53 (s, 1H); 9.56 (s, 1H).

In a similar way, starting from 1-ß-phenylethyl-4-cyano-3-aminopyrazole, 8-(ß-phenylethyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazole[1,5-c]pyrimidine m.p. 268-270°C (60%) 1H-NMR (DMSO-d_6): 3.32 (t, 2H); 4.72 (t, 2H); 6.73 (s, 1H), 7.23 (m, 5H); 7.95 (s, 1H); 8.8

(s, 1H); 9.41 (s, 1H) is obtained.

c) A suspension of a compound VI of step b) (10 mmol) in 10% HCl (5.0 ml) is refluxed under stirring for 3 h. After cooling, the solution is alkalinized with concentrated ammonium hydroxide at 0°C and the resulting precipitate is filtered or extracted with ethyl acetate (3 x 100 ml), dried and evaporated to dryness under vacuum, to give the corresponding 1-(ß-phenylethyl)-4-[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-pyrazole m.p. 175-176°C; ^{1}H-NMR (DMSO-d_6):3.15 (t, 2H); 4.48 (t, 2H); 5.78 (s, 1H), 6.37 (s, 1H); 6.68 (s, 1H); 7.1 (s, 1H); 7.27-7.28 (m, 5H); 7.82 (s, 1H); 14.51 (sb, 2H): in a similar way 1-(ß-phenylethyl)-4-[3(2-furyl)-1,2,4-triazol-5-yl]-3-aminopyrazole (m.p. 205-206°C); 1H-NMR (DMSO-d_6): 3.12 (t, 2H); 4.46 (t, 2H); 5.75 (s, 1H); 14.41 (sb, 2H) is obtained.

d) Cyanamide (60 mmol) is added to a suspension of an amine of formula VII prepared in step c) (10 mmol) in N-methylpyrrolidone (40 ml) followed by p-toluensulfonic acid (15 mmol).

The mixture is heated to 160°C under stirring. After 4 h a second portion of cyanamide (60 mmol) is added and heating is continued overnight. The mixture is then treated with hot water (200 ml) and the precipitate is filtered, washed with water and crystallized from ethanol to give the corresponding 5-amino-7-(ß-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazo-le[1,5-c]pyrimidine m.p. 225-226°C 1H-NMR (DMSO-d_6): 3.21 (t, 2H); 4.51 (t, 2H); 6.65 (s, 1H); 7.1-7.44 (m, 5H, arom and 1H); 7.78 (s, 1H); 7.89 (sb, 2H); 8.07 (s, 1H) (Compound 341): in a similar way 5-amino-8-(ß-

phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazole[1,5-c]pyrimidine m.p. 212-213°C 1H-NMR (DMSO-d_6): 3.21 (t, 2H); 4.53 (t, 2H); 6.7 (s, 1H); 7.1-7.4 (m, 5H, arom and 1H); 7.65 (sb, 2H); 7.93 (s, 1H); 8.45 (s, 1H) (Compound 375) is obtained.

Example 4

A suspension of potassium carbonate (0.23 mole) in DMSO (70 ml) is added subsequently with cyanoacetamide (70 mmols) and p-fluorobenzylazide (54.5 mmols). The resulting solution is stirred at room temperature for 1h and then poured into a large volume of water (1.5 l). The separated solid is filtered, washed with water and dried in oven at 70°C to give 1(p-fluorobenzyl)-4-carboxamido-5-amino-1,2,3-triazole (96% yield).
M.p.: 198-199°C; ^{1}H NMR (DMSO-d_6): 7.5-7.1 (m,6H); 6.4 (s,2H); 5.4 (s,2H).

An amide suspension (0.005 mole), stirred and cooled to 0°C, in DMF (5 ml) is added with phosphorous oxychloride (0.01 mole). The resulting solution is stirred for 5 minutes at 0°C, 10 minutes at 25°C and 15 minutes at 80°C. After cooling to room temperature, 5 ml of N HCl are added and the mixture is refluxed for 5 minutes. 1(p-Fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole separates from the cooled solution (90% yield).
M.p. 185-186°C; ^{1}H NMR (DMSO-d_6): 7.3-7.0 (m,6H); 5.5 (s,2H); IR (KBr) : 3400, 3220, 2220, 1655 cm-1.

Analogously, the following compounds were prepared:

1- or 2-benzyl-4-cyano-5-amino-1,2,3-triazole
1- or 2-(o-fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole
1- or 2-(p-fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole

1- or 2-butyl-4-cyano-5-amino-1,2,3-triazole

1- or 2-isopentyl-4-cyano-5-amino-1,2,3-triazole

1- or 2-(2-methoxyethyl)-4-cyano-5-amino-1,2,3-triazole

1- or 2-heptyl-4-cyano-5-amino-1,2,3-triazole

1- or 2-octyl-4-cyano-5-amino-1,2,3-triazole.

Example 5

The preparation of ethoxymethyleneamino heterocycles of formula IV is performed refluxing the respective ortho-aminonitrile with ethyl orthoformate. By way of example, the preparation of 4-cyano-5-(ethoxymethyleneamino)-1-butylpyrazole is reported.

A solution of 4-cyano-5-amino-1-butylpyrazole (20 mmols) in triethyl orthoformate (40 ml) is heated to the reflux temperature under nitrogen atmosphere for 8h. The orthoformate excess is evaporated to dryness under vacuum and the residual yellow oil is dissolved in ethyl ether and eluted through silica gel to give the pure compound (87% yield). In many cases, the residue obtained after evaporation of the orthoformate is substantially pure and is used as such in the subsequent step.

IR (nujol): 3140, 2240, 1640 cm-1; ^{1}H NMR ($CDCl_3$): 8.4 (s,1H); 7.9 (s,1H); 4.5 (t,2H); 4.3 (q,2H); 1.8 (m,2H); 1.5 (m,2H); 1.4 (t,3H); 0.9 (t,3H).

Example 6

A solution of the ethoxymethyleneamino heterocycle (20 mmols) and 2-furoic acid hydrazide (2.5 g, 22 mmols) in 2-methoxyethanol (50 ml) is refluxed for 5-10h. After cooling, the solution is evaporated to dryness to obtain a residual oil which is subjected to thermal cyclization in diphenyl ether (50 ml) using a

round-bottom flask fitted with a Dean-Stark apparatus, to remove azeotropically the water formed during the reaction. After varying times (3-5h) the reaction is checked by TLC (2:1 ethyl acetate:petroleum ether) and when the whole starting product has disappeared, the mixture is cooled and added with hexane. The resulting precipitate is filtered and crystallized from the suitable solvent. In some cases, from the solution a viscous oil separates which is decanted and subsequently extracted. The oily residue is then chromatographed on silica gel, eluting with ethyl acetate/petroleum ether mixtures, to give the tricyclic compound VI.

By way of examples, the analytical and spectroscopical characteristics of some compounds prepared by these procedures are reported:

7-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^{1}H NMR (DMSO-d_6): 9.6 (s,1H); 8.6 (s,1H); 8.0 (m,1H); 7.4 (m,1H); 6.7 (m,1H); 4.5 (t,2H); 1.9 (m,2H); 1.3 (m,2H); 0.9 (t,3H).

8-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^{1}H NMR (DMSO-d_6): 9.4 (s,1H); 8.9 (s,1H); 8.0 (m,1H); 7.3 (m,1H); 6.2 (m,1H); 4.5 (t,2H); 1.9 (m,2H); 1.3 (m,2H); 0.9 (m,3H). In the 2D-NMR (NOESY) spectrum, the N-CH2 signal resonating at 4.5 shows cross peaks with the C9-H signal resonating at 8.9.

7-isopentyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^{1}H NMR ($CDCl_3$) : 9.1 (s,1H); 8.8 (s,1H); 7.7 (m,1H); 7.3 (m,1H); 6.6 (m,1H); 4.6 (t,2H); 1.18-1.7 (m,3H);

1.0 (d,6H).

8-isopentyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

9.1 (s,1H); 8.8 (s,1H); 7.7 (m,1H); 7.3 (m,1H); 6.6 (m,1H); 4.6 (t,2H); 1.9-1.5 (m,3H); 1.0 (d,6H).

Following this procedure, the following compounds were prepared:

7-methyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

8-methyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-chlorophenyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-phenylethyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-tert-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-cyclopentyl)ethyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

8-benzyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-benzyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-butyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-isopentyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-methoxy)ethyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-heptyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-octyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-benzyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-butyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-isopentyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-hexyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-heptyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-octyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

9-benzyl-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

9-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

9-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

Example 7

The compounds of formula VII were prepared according to two methods:

a) by hydrolysis of compounds of formula VI with diluted hydrochloric acid;

b) by thermal cyclization of heterocyclic ortho-amino-nitriles of formula III with 2-furoic acid hydrazide in diphenyl ether at a temperature of 260°C .

A) a suspension of the tricyclic compound VI (10 mmols) in 10% HCl (50 ml) is heated to the reflux temperature under stirring for 3h. After cooling, the mixture is alkalinized with concentrated ammonium hydroxide at 0°C and the resulting precipitate is recovered by filtration or extracted with ethyl acetate (3 x 100 ml), dried and evaporated to dryness under vacuum.

The residue is purified by either crystallization from the suitable solvents or chromatographed over a silica gel column eluting with ethyl acetate and petroleum ether.

1-t-butyl-4-[3(2-furyl)-1,2,4-triazol-5-yl]-4-amino-pyrazole

^1H NMR ($CDCl_3$): 13.9 (sb,1H); 7.8 (s,1H); 7.7 (s,1H); 6.9 (m,1H); 6.6 (s,1H); 6.1 (s,2H); 1.6 (s,9H).

B) A suspension of the heterocyclic ortho-amino-nitriles (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the starting compound has disappeared (TLC, 1-2h). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum ether.

1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-

amino-1,2,3-triazole: ^{1}H NMR (DMSO-d_6): 14.5 (s,1H); 7.8 (s,1H); 7.4-7.1 (m,5H); 6.6 (s,1H); 6.5 (s,2H); 5.5 (s,2H).

Example 8

A suspension of the amines of formula VII (10 mmols) in N-methyl-pyrrolidone (40 ml) is added with cyanamide (60 mmols) followed by p-toluenesulfonic acid (15 mmols). The mixture is heated to 160°C with magnetic stirring. After 4h, a second portion of cyanamide (60 mmols) is added and heating is continued overnight. The mixture is then treated with hot water (200 ml) and the precipitated solid is filtered, washed with water and crystallized from ethanol. If no precipitations take place, the solution is extracted with ethyl acetate (4 x 100 ml), the extracts are washed with brine (2 x 50 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate.

In the following, the analytical and spectroscopical data of some compounds prepared by this procedure are reported:

5-amino-7-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (Compound 292).

M.p. 157-158°C; ^{1}H NMR (DMSO-d_6) : 8.1 (s,1H); 8.0 (s,2H); 7.9 (m,1H); 7.2 (m,1H); 6.7 (m,1H); 4.2 (t,2H); 1.9 (m,2H); 1.5 (m,2H); 0.9 (t,3H).

5-amino-8-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (Compound 294).

M.p. 183-185°C; ^{1}H NMR (DMSO-d_6): 8.6 (s,1H); 8.0 (s,1H); 7.6 (s,2H); 7.2 (m,1H); 6.7 (m,1H); 4.2 (t,2H); 1.8 (m,2H); 1.2 (m,2H); 0.9 (t,3H).

5-amino-7-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine.

M.p. 295-297°C; ^1H NMR (DMSO-d_6): 8.5 (s,2H); 8.0 (s,1H); 7.3 (m,6H); 6.7 (m,1H); 5.7 (s,2H).

5-amino-7-o-fluoro-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine

M.p. 310-312°C; ^1H NMR (DMSO-d_6): 8.5 (s,2H); 8.0 (s,1H); 7.3 (m,5H); 6.8 (s,1H); 5.75 (s,2H).

5-amino-7-methyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 210-213°C

5-amino-7-tert-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 238-240°C

5-amino-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 248-250°C

5-amino-7-(2-hydroxyethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 258-260°C

5-amino-7-phenyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 295-297°C

5-amino-7-isopentyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 208-210°C (Compound 319).

5-amino-8-isopentyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 200-203°C (Compound 320).

5-amino-7-phenethyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 225°C (Compound 341).

5-amino-7ß-benzyloxyethyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine.

5-amino-7-[ß-(4-isobutylphenethyl)]-2-(2-furyl)-pyrazole[4,3-e]-1,2,4-triazole[1,5-c]pyrimidine m.p. 207-210°C.

Example 9

A suspension of sodium azide (0.23 mole, 15 g) and p-fluorobenzyl chloride (0.15 mole, 18.8 ml) in absolute ethanol (45 ml) is stirred and heated to reflux overnight. After cooling, the suspension is poured into water (200 ml) and from the solution an oil separates which is extracted with ethyl acetate (3 x 100 ml), dried over sodium sulfate and evaporated under vacuum with a bath temperature below 35°C. The residue (20 g, 90%) is used directly in the subsequent step, after IR checking for the presence of the characteristic band of the azido group at 2140 cm^{-1}.

Analogously, starting from ß-phenylethanol tosylate in DMF, the 1-ß-phenethylazide is obtained.

Example 10

p-Fluorobenzylazide (15.1 g, 0.1 mole) and cyanacetamide (10.8 g, 0.13 moles) are added in this order to a suspension of powdered potassium carbonate (57.5 g, 0.42 mole) in dimethylsulfoxide (150 ml).

The mixture is stirred at room temperature for 1h. The mixture is poured into 3 l of water and the solid which separates is filtered and washed thoroughly with water to give 22.47 g (96%) of 1-p-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole.

M.p.: 198-199°C; ^1H NMR (DMSO-d_6): 7.5-7.1 (m,6H); 6.4 (s,2H); 5.4 (s,2H).

Analogously, 2-fluoro-6-chlorobenzyl-4-carbossamide-5-amino 1,2,3-triazole; m.p. 230-231°C; ^1H-NMR (DMSO-d_6): 5.40 (s, 2H); 6.52 (sb, 2H); 7.12-7.45 (m, 5H).

3-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole; m.p. 211-211°C ^1H-NMR (DMSO-d_6): 5.46 (s, 2H); 6.47

(sb, 2H); 7.00-7.52 (m, 6H).

2-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole; m.p. 195-197°C.

1-(β-phenylethyl)-4-carboxamido-5-amino-1,2,3-triazole; m.p. 181-183°C; ^{1}H-NMR (DMSO-d_6): 3.04 (t, 2H); 4.35 (t, 2H); 6.30 (sb, 2H); 7.20-7.47 (m, 7H) are obtained.

Example 11

A suspension of 1-p-fluorobenzyl-4-carboxamido-5-amino-1,2,3-triazole (23.4 g, 0.1 mole) in DMF (100 ml), magnetically stirred at 0°C, is added with 20.8 ml (0.2 mole) of $POCl_3$. The solution is stirred for 5' at 0°C, 10' at room temperature and finally 15' at 80°C. After cooling, N HCl (100 ml) is added thereto and the resulting solution is refluxed for 5'; upon cooling 1-p-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole (18.54 g, 90%) precipitates. M.p. 185-186°C; ^{1}H NMR (DMSO-d_6): 7.3-7.0 (m,6H); 5.5 (s,2H); IR (KBr): 3400, 3220, 2220, 1655 cm-1.

Analogously, the following compounds are obtained:

2-fluoro-6-chlorobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p. 181-185°C ^{1}H-NMR (DMSO-d_6): 5.40 (s, 2H); 7.26-7.50 (m, 5H).

3-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p. 195-197°C ^{1}H-NMR (DMSO-d_6): 5.44 (s, 2H); 7.00-7.43 (m, 6H).

2-flurobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p.: 195-197°C.

1-(β-phenylethyl)-4-cyano-5-amino-1,2,3-triazole; m.p. 149-150°C ^{1}H-NMR (DMSO-d_6): 3.04 (t, 2H), 4.36 (t, 2H); 7.03 (sb, 2H); 7.23-7.28 (m, 5H).

take place, the solution is extracted with ethyl acetate (4 x 10 ml), the extracts are washed with brine (2 x 5 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate to give 105 mg (30% yield) of 5-amino-7-p-fluoro-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine M.p.: 266-268°C; ^{1}H NMR (DMSO-d_6) : 8.5 (sb, 2H); 7.95 (s, 1H); 7.4-7.1 (m, 6H); 6.7 (s, 1H); 5.7 (s, 2H) (Compound 340).

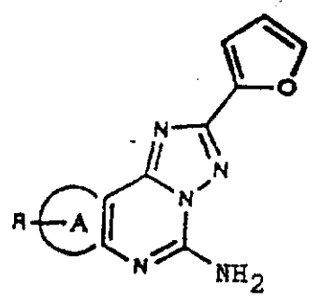
Analogously, were obtained:
5-amino-7-o-fluorobenzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p. 310°C.
5-amino-7-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine; m.p. 295-7°C.
5-amino-7-(2-fluoro-6-chlorobenzyl)-2-(2-furyl)-1,2,3-triazolo5,4-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p. 218-220°C; ^{1}H-NMR (DMSO-d_6): 8.51 (sb, 2H); 7.98 (s, 1H); 7.55-7.28 (m, 4H); 6.77 (m, 1H); 5.73 (s, 2H).
5-amino-7-(m-fluorobenzyl)-2-(2-furyl)1,2,3-triazolo[5,4-e] 1,2,4-triazolo[1,5-c]pyrimidine; m.p. 280-283°C; ^{1}H-NMR (DMSO-d_6): 8.45 (sb, 2H); 7.98 (s, 1H); 7.4-7.1 (m, 5H); 6.76 (s, 1H); 5.75 (s, 2H).
5-amino-7-(ß-phenylethyl)-2-(2-furyl)-1,2,3-triazolo[5,4-e] 1,2,4-triazolo[1,5-c]pyrimidine; m.p. 269-271°C; ^{1}H-NMR (DMSO-d_6): 8.4 (sb, 2H); 7.98 (s, 1H); 7.3-7.15 (m, 6H); 6.8 (s, 1H); 4.71 (t, 2H); 3.31 (t, 2H) (Compound 376) are obtained.

Example 14

A suspension of anhydrous potassium carbonate (30 mmols) in anhydrous DMF (50 ml) is added with 5-amino-

THE USE OF 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES FOR THE PREPARATION OF MEDICAMENTS USEFUL FOR THE TREATMENT OF CEREBROVASCULAR DISTURBANCES

The present invention relates to the use of 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues of formula (I)



(I)

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl, C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with 1-3 halogen atoms, hydroxy, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$, wherein R_1 and R_2, which can be the same or different, are hydrogen, C_1-C_5 alkyl, C_7-C_{10} aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms selected from N, O, S; aryl optionally substituted with halogen atoms, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxyamido groups; C_7-C_{10} aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a

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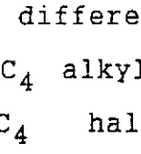
group of formula -$(CH_2)_n$-  wherein R_3 and R_4 which can be the same or different, are H, OH, halogen atoms, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy or carboxyamido groups; moreover the OH group, together with one of R_3 or R_4, or R_3 and R_4 together, can form the methylenedioxy group -O-CH_2-O-, n is an integer of 0 to 4; a group of formula -$(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer of 1 to 5;

or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cerebrovascular disorders, i.e. in all those brain injuries caused by either impairments of the cerebral circulation or trauma, following deprivation of oxygen and of those nutritional substances which the area vascularized by the vessels involved in the pathological condition is subjected to Stroke, cerebral infarction and brain trauma are among the most severe conditions which can be treated with the medicaments here described.

The compounds of formula (I) are selective antagonists of adenosine A_{2A} receptors.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system,

adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97; Williams M., Adenosine and Adenosine receptors. The Humana Press, 1990).

A number of studies showed adenosine actions are mediated by four subtypes of receptors which are located on the cell membrane: two high-affinity ones, inhibiting the activity of the enzyme adenylate cyclase (A_1 and A_3 receptors), and two low-affinity ones, stimulating the activity of the same enzyme (A_{2A} and A_{2B} receptors) (J. Med. Chem. 1982, 25, 197-207; Physiol. Rev. 1990, 70, 761-845; J. Med. Chem. 1992, 35, 407-422; Pharmacol. Rev. 1994, 46, 143-156).

Intense research efforts have made it possible to identify and develop analogs of adenosine which are able to interact as selective agonists for the four receptors, including the A_{2A} receptor type (Pharmacol. Rev., 1994, 46, 143-156).

Other studies allowed to develop heterocyclic compounds capable of antagonizing some receptor types. The xanthine compounds, for example, antagonize both A_1 and A_{2A} receptors (J. Med. Chem., 1992, 35, 407-422).

As far as the A_{2A} receptor antagonists are concerned, the compounds of general formula (I), which are known to exert a selective action on said receptors,

as well as the process for the preparation thereof, are disclosed in WO 9501356 and WO 9705138 applications. A number of different possible uses of the compounds of formula (I) are cited in said applications, but in no cases a specific use in the treatment of cerebrovascular disorders is described.

Now it has surprisingly been found that compounds of general formula (I) are capable of reducing by more than 40% the total volume of cerebral infarction in animal models in which a focal cerebral ischemia has been induced.

Particularly, the study was carried out on animals (rats) subjected to occlusion of the median cerebral artery (MCA), by electrocauterization and subsequent determination of the cerebral infarction total volume by means of histologic analysis of the brain preparations (Surg. Neurol. 1985, 24:47-51).

Said models are considered relevant to cerebrovascular pathologies in humans.

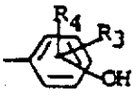
Although other heterocyclic compounds (CGS 15943 and CP66713, respectively; Life Sciences, 55, 61-65, 1994 and Brain Research 705, 79-84, 1995) are known to act favourably in cerebral ischemia animal models, nevertheless such compounds act as non-selective antagonists of the A_{2A} receptors, in that they also block other adenosine receptor subtypes thus causing undesired side-effects.

On the contrary, the compounds of formula (I) showed a high affinity for A_{2A} receptors and a remarkable selectivity compared with the other receptors subtypes, having, for instance, a A_{2A} receptor affinity

up to 800-fold higher than the affinity to A_1 receptors, therefore being safer and more suitable even for a long-term treatment of disturbances due to cerebrovascular pathologies.

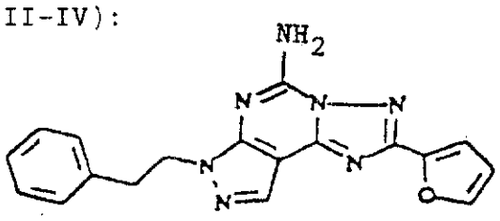
Particularly effective and therefore preferred are those compounds of formula (I) wherein:

A is pyrazole, imidazole or triazole;

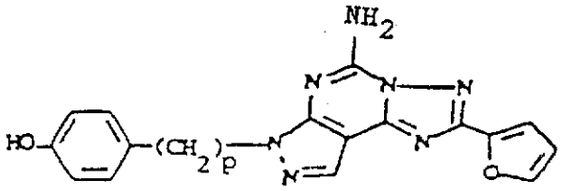
R is C_7-C_{10} aralkyl or the group $-(CH_2)_n$-  wherein

R_3 and R_4, which can be the same or different, are hydrogen, OH, halogen, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, carboxy or carboxyamido; moreover the OH group, together with one of R_3 or R_4, or R_3 and R_4 together, can form the methylenedioxy group $-O-CH_2-O-$; n is an integer of 0 to 4,

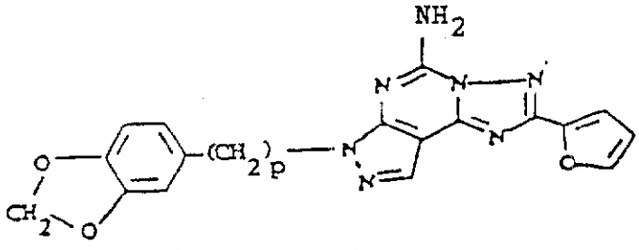
most preferred are the compounds having the following formulae (II-IV):



(II)



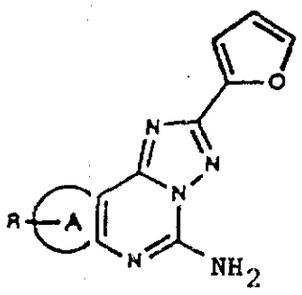
(III)



(IV)

CLAIMS

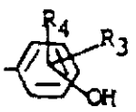
1. The use of the compounds of formula I:



(I)

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl, C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with 1-3 halogen atoms, hydroxy, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$, wherein R_1 and R_2, which can be the same or different, are hydrogen, C_1-C_5 alkyl, C_7-C_{10} aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms selected from N, O, S; aryl optionally substituted with halogen atoms, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxyamido groups; C_7-C_{10} aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula $-(CH_2)_n$  wherein R_3 e R_4 which can be the same or different, are H, OH, halogen

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United States Patent [19]

Baraldi et al.

[11] **Patent Number: 5,935,964**

[45] **Date of Patent: Aug. 10, 1999**

[54] **1,2,4-TRIAZOLO[1,5-C] PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_{2A} RECEPTOR**

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[58] **Field of Search** 544/251; 514/267

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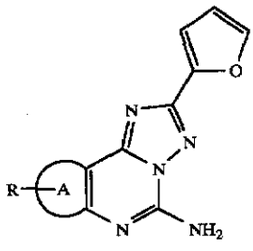
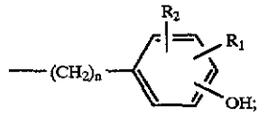
[57] **ABSTRACT**

Disclosed are adenosine A_{2a} receptor antagonists of the formula



wherein A is pyrazole, imidazole or triazole ring;

R is



R_1 and R_2 are independently H, OH, halogen, alkoxy, alkyl, nitro, amino, CN, haloalkyl, haloalkoxy, carboxy or carboxamido; or the OH group together with one of R_1 or R_2, or R_1 and R_2 together, form a methylenedioxy group;

and n is 0–4;

said compounds are useful in the treatment of cardiovascular, central nervous system, and respiratory diseases.

9 Claims, No Drawings

1,2,4-TRIAZOLO[1,5-C] PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_{2A} RECEPTOR

The present invention relates to compounds having antagonistic activity on adenosine A_{2a} receptors.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T. W. Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291–429; Progress Cardiovasc. Dis. 1989, 32, 73–97; Williams M., Adenosine and Adenosine receptors. The Humana Press, 1990).

Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins.

Biochemical and pharmacological studies, together with the recent acquirements in the molecular biology field, have up to now allowed to identify at least 4 different adenosine receptors: A_1, A_{2a}, A_{2b}, ed A_3 (Pharmacol. Rev., 1994, 46, 143–156).

Intense research efforts have made it possible to identify and develop analogs to adenosine able to interact as agonists with the A_1, A_{2a} and A_3 receptors (Pharmacol. Rev., 1994, 46, 143–156).

The knowledge available on the physiological role of adenosine and its involvement in some pathological processes suggests that selective antagonists for the A_{2a} receptor can be of pharmacological interest. At the level of the central nervous system, antagonistic A_{2a} compounds could have antidepressive properties and stimulate the cognitive functions. Moreover, numerous data show that the A_{2a} receptors are present in high density in the basal ganglia of which the importance in the control of movement is known. Hence, the hypothesis that A_{2a} antagonists can improve motor-impairment due to neurodegenerative processes. Amongst these are included Parkinson's disease, senile dementia as in Alzheimer's disease and psychosis of organic origin (Drug Dev. Res., 1993, 28, 381–385).

At a peripheral level, A_{2a} receptor antagonists could stimulate the respiratory functions and therefore have a therapeutic effect in the treatment of bronchospasm and, more generally, asthma. Moreover, with regard to the effects at a cardiovascular or renal level, an advantageous activity on renal flow can be envisaged and therefore the possibility of the treatment of renal insufficiency and of various cardiovascular disturbances.

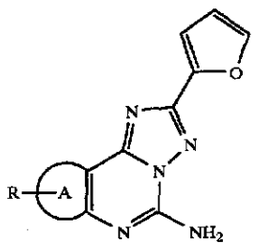
Whilst some xanthine-structure have been known to be A_1 receptor selective antagonists (J Med. Chem., 1992, 35, 407–422), only recently novel xanthine (J. Med. Chem, 1993, 36, 3731–3733) and non-xanthine (PCT WO 9501356, published on Dec. 1, 1995, corresponding to Italian Patent application MI93A001396) Bioorg. Med. Chem. Lett, 1994, 4, 2539–2544) have been found to have high A_{2a} affinity and moderate A_{2a} vs A_1 selectivity (about 50-fold).

The compounds disclosed in WO 9501356 are 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues, on the heterocyclic ring of which is present, inter alia, an aryl group, particularly phenyl or phenylalkyl, optionally substituted with halogen atoms, C_{1-C4} alkoxy, C_1–C_4 alkyl, nitro, amino, cyano, C_1–C_4 haloalkyl, C_1–C_4 haloalkoxy, carboxy, carboxamido groups.

Moreover, it has surprisingly been found that the presence of at least one hydroxyl on the phenyl ring gives the compounds disclosed in WO9501356 an increased A_{2a} selectivity.

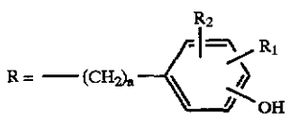
Therefore, the present invention relates to compounds of general formula I:

I



wherein:

A is a pyrazole, imidazole or triazole ring



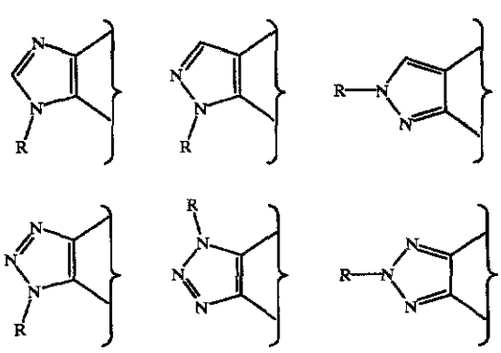
wherein

R_1 and R_2, which are the same or different, are H, OH, halogen, C_1–C_4 alkoxy, C_1–C_4 alkyl, nitro, amino, cyano, C_1–C_4 haloalkyl, C_1–C_4 haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of R_1 or R_2, or R_1 and R_2, can form the methylenedioxy group —O—CH_2—O—;

n is an integer from 0 to 4.

The invention also comprises the pharmaceutically acceptable salts of the compounds of general formula I.

The possible meanings of A can be represented by the following structural formulae:



Examples of C_1–C_4 alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and isobutyl.

Examples of C_1–C_4 alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy.

Halogen atoms are fluorine, chlorine, bromine, iodine.

Examples of C_1–C_4 groups haloalkyl are trifluoromethyl, 2-fluoroethyl, 2-chloroethyl.

Examples of C_1–C_4 haloalkoxy groups are trifluoromethoxy chloromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy.

Preferred compounds of formula I are those wherein A is pyrazolo[4,3-e] or 1,2,3-triazolo[5,4-e].

Particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n ranges from 1 to 4 included, preferably 2 or 3, the OH group on the phenyl ring is at the para position and R_1 and R_2 are hydrogen.

A second group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 3, preferably 1 or 2, the OH group on the phenyl ring is at the meta position and R_1 and R_2 are hydrogen.

A third group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R_1 is methoxy, preferably at the meta position, R_2 is hydrogen.

A fourth group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R_1 is hydroxy, preferably at the meta position, R_2 is hydrogen.

A fifth group of particularly preferred compounds of formula I are those wherein A is 1,2,3-triazolo[5,4 -e], n is from 1 to 4, preferably 2 or 3, and the OH group on the phenyl ring can be at all the possible positions.

Particularly preferred are the following compounds:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyriidine;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine; m.p 210–211° C.;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-dihydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

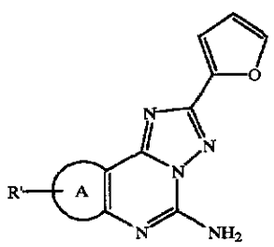
The compounds according to the present invention are prepared with known processes, in particular they are according to the processes described in WO Application 9501356.

Since in all the intermediates for the synthesis of the compounds of Formula I at least one OH group is present on the phenyl ring, to protect the OH group(s), during the various synthetic steps. The final compounds of formula I are thus obtained by deprotecting the phenyl OH group(s) once the complete structure has been obtained. Protection methods are conventionally known, for example as described in T. W. Greene, P. G. M. Woots, Protective Groups in Organic Synthesis, J. Wiley. N.Y. 1991, 2nd Edition.

A preferred protection method is the benzylation and following debenzylation on Pd/C in tetrahydrofuran. Alternatively, the protection method involves the use of the allyl group or, when two adjacent hydroxy groups are present, the methylendioxy group.

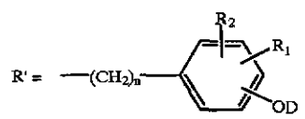
Therefore, another object of the present invention is a process for the preparation of compounds of formula (I), as reported above, which comprises the deprotection of the phenyl hydroxy groups of the compounds of formula (Ia)

(Ia)



wherein:

A is as defined in formula (I);



wherein D is a suitable protective group, preferably benzyl or allyl (or —CH_2— as protective group of two adjacent hydroxyl groups), R_1 and R_2, which are the same or different, are hydrogen, OD, wherein D is as defined above, a halogen atom, C_1–C_4 alkyl, nitro, amino, cyano, C_1–C_4 halogen alkoxy, carboxy, carboxamido group; n is as above defined.

The process according to the present invention also comprises the optional transformation of the obtained compound into a pharmaceutically acceptable salt.

BIOLOGICAL ACTIVITY

The pharmacological properties of the disclosed compounds were studied in the most sensitive and suitable experimental models both in vitro and in vivo.

The compounds of general formula I have advantageous properties of selectivity for the A_{2a} receptor compared with those described in the above cited WO 9501356.

Adenosine A_{2a} receptor affinity was tested by means of receptor binding techniques on bovine and rat (Sprague-Dawley strain), cerebellar corpus striatum, which is a tissue rich in A_{2a} receptors. Compound ^{3}H-CGS 21680 (J. Pharm. Exp. Ther. 1989, 251, 888–893) was used as the radioligand. The A_1 receptor affinity was tested with receptor binding techniques on bovine and rat (Sprague-Dawley strain), cerebellar cortex membranes, which is a tissue rich in A_1 receptors. ^{3}H-Cyclohexyl-adenosine, ^{3}H-CHA (Proc. Natl. Acad. Sci.—USA—1980, 77, 5547–5551) was used as the radioligand. The selectivity for the A_{2a} receptor was evaluated from the comparison between the affinities for the A_1 or A_{2a} receptor shown by each compound. A number of experimental data support the evidence that a marked relationship exists between the affinity found with binding techniques in brain tissues and the physiological effects modulated by adenosine receptors.

A_{2a} receptors are mainly present in the vascular system and the stimulation thereof causes vasodilation. Therefore, the A_{2a} antagonistic activity of these molecules has been studied by evaluating the capability of inhibiting vasodilation induced by adenosine agonists in vascular tissues such as rat aorta and bovine or porcine coronary arteries.

These compounds were unable to antagonize negative chronotropic effects induced by A_1 receptor agonists when tested on isolated rat atria (Br. J. Pharmacol., 1983, 78, 207–212).

Another test to evaluate the antagonistic activity of the new compounds is the study of platelet aggregation. In fact, adenosine or the analogues thereof are known to inhibit platelet aggregation induced by different aggregatory agents, among which ADP. Therefore, the capability of the novel compounds of antagonizing the inhibitory effect induced by NECA or CGS 21680 agonists was tested using rabbit platelets.

This test is particularly important as only the A_{2a} receptor is present on platelet cell membranes.

The in vivo activity was evaluated in Swiss mice and spontaneously hypertensive rats (SHR). The behavioural response to a treatment with different doses of the tested compounds administered parenterally was evaluated in the mice. In the SHR rats, the tested compounds were administered parenterally at increasing doses and the capability thereof of antagonizing the bradycardic and hypotensive effects induced by A_1 and A_{2a} receptor agonists, respectively, was measured.

A number of the compounds of formula I showed a marked A_{2a} affinity with Ki ranging from 1 to 10 nM. The A_{2a} selectivity for some compounds is 200–800fold, which is markedly higher than that of the compounds known up to now.

In the platelet aggregation test, said compounds proved to effectively block the antiaggregatory effects induced by A_{2a} agonists, with pA_2 values ranging from 8 to 10.

The compounds of the invention antagonize in a variety of vascular districts, with a similar potency, vasodilatation mediated by A_{2a} receptors, whereas they are not able of blocking the negative chronotropic effect induced by A_1 agonists in rat isolated atria. In the in vivo models, the tested compounds showed a poor stimulating activity on central nervous system, they antagonized the hypotension induced by A_{2a} agonists without changing significantly the heart rate. The compounds turned out to be active at doses from 0.001 to 3 mg/kg intraperitoneally.

For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical compositions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII ed. Said compositions are comprised within the scope of the present invention.

The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0.01 to 10 mg/kg body weight, preferably from 0.1 to 1 mg/kg, optionally subdivided in more administrations. Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (patches) and the like.

The following examples further illustrate the invention.

EXAMPLE 1

5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine

A solution of 5-amino-7-[β-(4-benzyloxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine (1.5 g; 0.003 moles) in THF (20 ml) is added with $HCOONH_4$ (0.81 g, 0.012 moles) and 10% C-Pd (0.3 g) and refluxed for 2 hours. When the reaction is complete, the catalyst is filtered off and the supernatant is concentrated. The residue is chromatographed (AcOEt) to give 0.44 (41%) of the desired compound, which is a white solid, m.p. 265 (dec.). IR (KBr) cm^{-1}: 3500–3100. 1650. 1610. 1525, 1435; ^{1}H NMR (DMSO) δ: 3.04, (t, 2H, J=8 Hz); 4.41 (t, 2H, J=8 Hz); 6.60 (d, 2H, J=8 Hz); 6.73–6.74 (m, 1H); 6.93 (d, 2H, J=8); 7.22 (d, 1H, J=4 Hz); 7.94 (s, 1H); 8.07 (bs, 2H); 8.16 (s, 1H), 9.22 (s, 1H).

EXAMPLE 2

0.25 ml of an 1M BCl_3 solution in CH_2Cl_2 were added at 0° C. to a solution of 50 mg (0.12 mmol) of 5-amino-7[β-(3,4-methylenedioxy)phenylethyl]-2-(2-furyl)-pyrazole-[4,3-e]-1,2,4-triazole-[1,5-c]-pyrimidine.

The mixture was left at 4° C. for 5 h. 1 ml of methanol was added and the solvent was evaporated, to give 33 mg of the corresponding 3,4-dihydroxy derivative (m.p. 272° dec.).

EXAMPLE 3

Following the same procedures of Example 1 or 2, starting from the suitable benzyloxy- or methylendioxy-substituted precursors, the following compounds were obtained:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p 189–191° C.;

5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine, m.p.>280° C.;

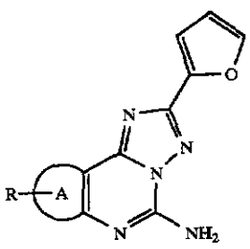
5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[γ-(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine; m.p.204–206° C.;
5-amino-7-[γ-(3,4-methylendioxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine; m.p 210–211° C.;
5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[β-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine.

We claim:

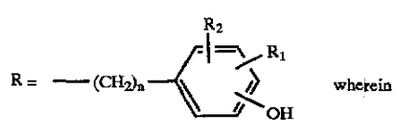
1. Compounds of general formula (I)



I

wherein:

A is a pyrazole, imidazole or triazole ring



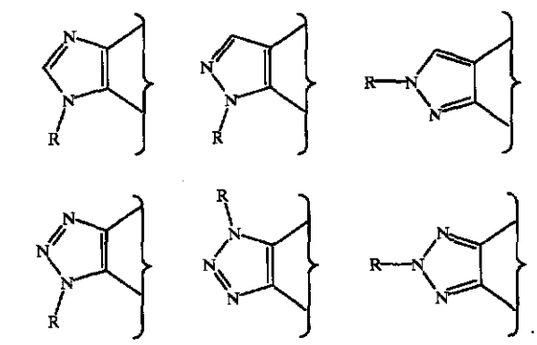
wherein

R_1 and R_2, which are the same or different, are H, OH, halogen, C_1–C_4 alkoxy, C_1–C_4 alkyl, nitro, amino, cyano, C_1–C_4 haloalkyl, C_1–C_4 haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of R_1 or R_2, or R_1 and R_2, can form the methylenedioxy group —O—CH_2—O—;

n is an integer from 0 to 4,

or the pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein A is a group selected from



3. Compounds according to claim 1, wherein A is pyrazolo, n is from 1 to 4, the OH group on the phenyl ring is at the para position and R_1 and R_2 are hydrogen.

4. Compounds according to claim 1, wherein A is pyrazolo, n is from 1 to 4, the OH group on the phenyl ring is at the meta position and R_1 and R_2 are hydrogen.

5. Compounds according to claim 1, wherein A is pyrazolo, n is from 1 to 4, the OH group on the phenyl ring is at the para position, R_1 is methoxy, preferably at the meta position, R_2 is hydrogen.

6. Compounds according to claim 1, wherein A is pyrazolo, n is from 1 to 4, the OH group on the phenyl ring is at the para position, R_1 is hydroxy, preferably at the meta position, R_2 is hydrogen.

7. Compounds according to claim 1, wherein A is 1,2,3-triazolo, n is from 1 to 4, and the OH group on the phenyl ring can be at all the possible positions.

8. A compound according to claim 1, selected from the group consisting of:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(3,4-methylendioxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine; m.p 210–211° C.;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine.

9. Pharmaceutical compositions containing as the active ingredient a therapeutically effective amount of a compound of the claim **1** in admixture with conventional carriers and excipients.

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