OLARTERAISBECK
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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN 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.

RESPUESTA AL OFICIO No. 1996 NOTIFICADO POR FIJACIÓN EN LISTA No. 44, DE FECHA 09 DE FEBRERO DE 2007.
(REQUERIMIENTO ARTÍCULO 46)

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de en mi carácter de apoderado sustituto de la sociedad solicitante, como consta en la sustitución de poder adjunta, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486:

1. Presento copia completa del siguiente documento exigido por el Examinador en el examen de búsqueda de anterioridades, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

P. G. BARALDI ET. AL.:
"Pyrazolo'4,3-e!-1,2,4-triazolo'1,5-c!pyrimidine Derivatives. Potent and Selective A2A Adenosine Antagonists."
JOURNAL OF MEDICINAL CHEMISTRY,
vol. 39, no. 5, 1 March 1996 (1996-03-01),
pages 1164-71, XP002180962

Atentamente,

J. IAN RAISBECK
C.C. 79'376.996 de Bogotá D.C.
T.P. 135.799 del C. S. de la J.

Anexo:
- Artículo mencionado.
- Sustitución de poder.

238

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **J. IAN RAISBECK LLINAS**, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.

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Pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine Derivatives: Potent and Selective A_{2A} Adenosine Antagonists

XP-002180962 PD: 01-03-1996 (8) P: 1164-71

Pier Giovanni Baraldi,*,[‡] Barbara Cacciari,[‡] Giampiero Spalluto,[‡] Maria José Pineda de las Infantas y Villatoro,[‡] Cristina Zocchi,[§] Silvio Dionisotti,[‡] and Ennio Ongini[§]

Dipartimento di Scienze Farmaceutiche, Università degli Studi di Ferrara, Via Fossato di Mortara 17-19, 44100 Ferrara, Italy, and Centro Ricerche Schering-Plough, Parco Scientifico San Raffaele, Via Olgettina 58, 20132 Milano, Italy

Received October 10, 1995[⊗]

A series of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine derivatives (**10a−o,q,r**), bearing alkyl and aralkyl chains on positions 7 and 8, were synthesized in the attempt to obtain potent and selective antagonists for the A_{2A} adenosine receptor subtype. The compounds were tested in binding and functional assays to evaluate their potency for the A_{2A} compared with the A_1 adenosine receptor subtype. In binding studies in rat brain membranes, most of the compounds showed affinity for A_{2A} receptors in the low nanomolar range with a different degree of A_{2A} versus A_1 selectivity. Comparison of N^7 (**10a−d,h−o**)- and N^8 (**10e−g**)-substituted pyrazolo derivatives indicates that N^7 substitution decreases the A_1 affinity with the concomitant increase of A_{2A} selectivity. Specifically, the introduction of a 3-phenylpropyl group at pyrazolo nitrogen in position 7 (**10l**) increased significantly the A_{2A} selectivity, being 210-fold, while the A_{2A} receptor affinity remained high (K_i = 2.4 nM). With regards to the affinity for A_{2A} receptors, also the compound **10n**, bearing in the 7-position a β-morpholin-4-ylethyl group, deserves attention (K_i = 5.6 nM) even though the A_{2A} selectivity (84-fold) was not as high as that of **10l**. Conversely, the compound **10m** (N^7-4-phenylbutyl derivative) showed a remarkable selectivity (A_1/A_{2A} ratio = 129) associated with lower A_{2A} affinity (K_i = 21 nM). In functional studies, most of the compounds examined reversed 5′-(*N*-ethylcarbamoyl)adenosine-induced inhibition of rabbit platelet aggregation inhibition which is a biological response mediated by the A_{2A} receptor subtype. The compounds are potent and selective A_{2A} antagonists which can be useful to elucidate the pathophysiological role of this adenosine receptor subtype. These compounds deserve to be further developed to assess their potential for treatment of neurodegenerative disorders such as Parkinson's disease.

Introduction

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors which have been classified as A_1, A_{2A}, A_{2B}, and A_3 adenosine receptor subtypes.[1,2] Efforts made in medicinal chemistry over the last 2 decades have led to the discovery of a series of adenosine analogs which possess specific agonist properties at A_1, A_{2A}, or A_3 receptors.[3,4] As for adenosine receptor antagonists, a large number of xanthine derivatives have been synthesized in the attempts to improve both receptor subtype affinity and selectivity of the natural compounds caffeine and theophylline.[3] Combined substitution at the 1-, 3-, and 8-positions of the xanthine moiety led to potent and selective A_1 receptor antagonists. For example, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX)[5] is currently used as a reference compound.

A series of 8-styrylxanthines have been also found to have high affinity and selectivity at A_{2A} receptors.[6,7] Two of these compounds, namely, 7-methyl-8-(3,4-dimethoxystyryl)xanthine (KF 17837)[6] and 8-(3-chlorostyryl)-caffeine (CSC),[7] have been further investigated and found to possess antagonist properties in both *in vitro*[8,9] and *in vivo* studies.[9−11] However, these compounds undergo rapid photoisomerization when diluted and exposed to natural light,[12] and this may limit their use as pharmacological tools.

Non-xanthine heterocyclic compounds, including 5-amino-9-chloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline (CGS 15943, **1**)[13] and 4-amino-8-chloro-1-phenyl-[1,2,4]triazolo[4,3-*a*]quinoxaline (CP 66,713),[14] also have high affinity for A_{2A} receptors, but they are unselective, being potent at A_1 receptors as well. Recently, a series of CGS 15943 derivatives, in which the *m*-chlorophenyl group was replaced by a heterocycle ring, such as pyrazole or imidazole, have been described to retain high affinity for adenosine receptors.[15] One of them, 5-amino-8-(4-fluorobenzyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8FB-PTP, **2a**), has high affinity at A_{2A} receptors and shows competitive A_{2A} antagonist properties in *in vitro* functional studies, but its selectivity versus A_1 receptor is still low.[16] Conversely, the corresponding N^7 derivative 5-amino-7-(4-fluorobenzyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (7FB-PTP, **2b**) showed a decrease in the affinity at both receptor subtypes, but it was associated with a concomitant increase of A_{2A} versus A_1 selectivity.[15]

With the aim to enhance the A_{2A} selectivity, we have further investigated the lead compounds **2a,b**. In our previous study[17] the importance of the hydrophobic, electronic, and steric parameters of substituents at the

* To whom correspondence should be addressed at Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17-19, 44100 Ferrara, Italy. Tel: +39-(0)532-291293. Fax: +39-(0)-532-291296.

‡ Università degli Studi di Ferrara.

§ Centro Ricerche Schering-Plough.

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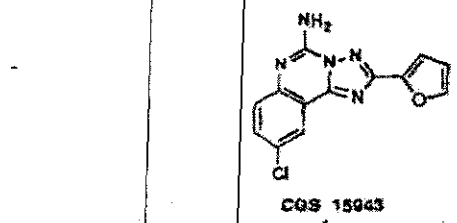
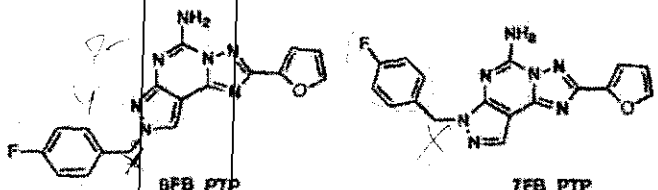


CGS 15943
1

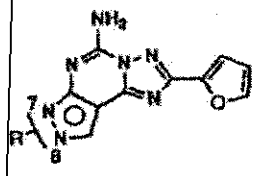


8FB PTP
2a

7FB PTP
2b

pyrazole N^7 or N^8 nitrogens (compounds **10a–c,e–h**) had been evaluated, according to the Topliss operational scheme for aliphatic substituents.[18] The derivatives bearing a substituent in the 7-position showed a better A_{2A} selectivity than the corresponding N^8 derivatives having the same substituent. One of them, namely, SCH 58261 (**10c**), was shown to have high affinity and good selectivity for the A_{2A} receptor subtype and to also possess competitive A_{2A} antagonist properties in *in vitro* functional studies.[19]

On the basis of these interesting results, we have synthesized N^7 derivatives in order to better evaluate the Topliss operational scheme for aliphatic substituents (**10i,k,q**). Moreover, we focused our studies on the lead compound **10c**, designing the following structural modifications: (i) introduction of different spacers between N^7 nitrogen and phenyl ring (**10l,m,o**) in order to optimize the length spacer, (ii) increase of the lipophilic nature of the substituent at the N^7 position (**10d**), an essential condition for the interaction with A_{2A} receptors,[17] and (iii) increase of the water solubility (**10d,j,n,r**) of this series of chemical structures.



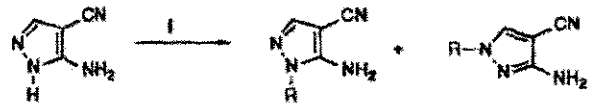
10a–o,q

Chemistry

The preparation of the compounds **10a–o** was performed following the general synthetic strategy depicted in Schemes 1–5. Alkylation of 5-amino-4-cyanopyrazole (**3**) with the appropriate alkyl halide in DMF in the presence of anhydrous potassium carbonate led to an ca. 1:1 mixture of N^1 isomers **4a–d** and N^2 isomers **4e–g**, separable by crystallization or column chromatography (Scheme 1).

In order to improve and facilitate the synthesis of the N^7-substituted derivatives, we decided to synthesize the pyrazole ring using the appropriate hydrazine. This pathway afforded only the N^1 isomer and allowed us to avoid tedious purification procedures. Pyrazoles **4h–n** were prepared by reacting (ethoxymethylene)malononitrile with the appropriate hydrazines[20,21] following a well-known procedure[22] (Scheme 2).

Scheme 1[a]

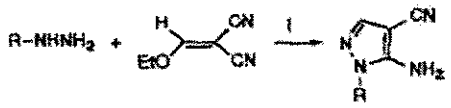


3 4a-d 4e-g

a) R = n-butyl; b) R = isopentyl; c) R = β-phenylethyl; d) R = β[(4-isobutyl)phenyl]ethyl; e) R = *n*-butyl f) R = isopentyl ; g) R = β-phenylethyl;

[a] Reagents: (i) RX, K_2CO_3, EtOH, reflux.

Scheme 2[a]

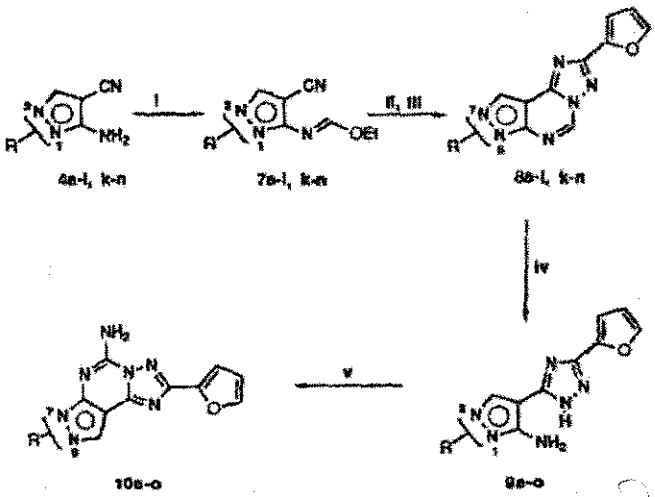


5 6 4h-n

h) R = methyl; i) R = phenyl; j) R = β-hydroxyethyl; k) R = t-butyl; l) R = 3-phenylpropyl ; m) R = 4-phenylbutyl; n) R = β-(morpholin-4-yl)ethyl

[a] Reagents: (i) EtOH, reflux.

Scheme 3[a]



4a-i, k-n 7a-i, k-n 8a-i, k-n

10a-o 9a-o

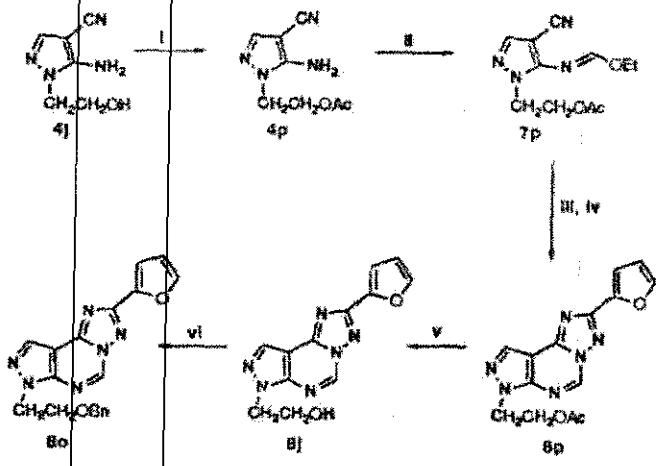
a) R = N^1-n-butyl; b) R = N^1-isopentyl; c) R = N^1-β-phenylethyl; d) R = N^1-β[(4-isobutyl)phenyl]ethyl; e) R = N^2-n-butyl; f) R = N^2-isopentyl; g) R = N^2-β-phenylethyl ; h) R = N^1-methyl; i) R = N^1-phenyl; j) R = N^1-β-hydroxyethyl; k) R = N^1-t-butyl; l) R = N^1-3-phenylpropyl; m) R = N^1-4-phenylbutyl; n) R = N^1-β-(morpholin-4-yl)ethyl; o) R = N^1-β-benzyloxyethyl

[a] For tricyclic compounds 10a-o: N^1=N^7 and N^2=N^8

[a] Reagents: (i) $HC(OEt)_3$, reflux; (ii) furoic hydrazide, $MeO(CH_2)_2OH$; (iii) Ph_2O, 260 °C; (iv) 10% HCl, reflux; (v) NH_2CN, 1-methyl-2-pyrrolidone, pTsOH, 140 °C.

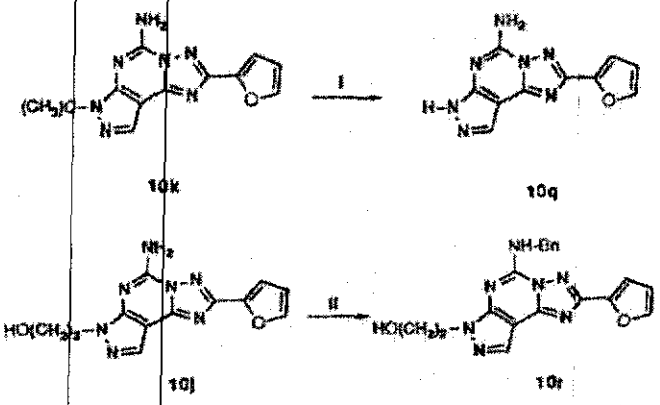
The designed compounds **10a–o** were synthesized according to Gatta et al.[15] for the synthesis of pyrazolo[4,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines (Scheme 3). Following the general strategy, the first step involved transformation of pyrazoles **4a–i,k–n** to the corresponding imidates **7a–i,k–n** by refluxing in triethyl orthoformate. This conversion was not possible for **4j** because the hydroxy group prevented a clean reaction. Therefore in order to achieve an improvement in the overall yield, we converted the pyrazole **4j** into the corresponding acetyl derivative **4p** (Scheme 4). Imidates **7a–i,k–n** were reacted with 2-furoic acid hydrazide in refluxing 2-methoxyethanol to provide the pyrazolo[3,4-*d*]pyrimidine intermediates. The latter compounds were converted through a thermally induced

Scheme 4[a]



[a] Reagents: (i) Ac_2O, Py, room temperature; (ii) $HC(OEt)_3$, reflux; (iii) furoic hydrazide, $MeO(CH_2)_2OH$; (iv) Ph_2O, 260 °C; (v) NH_3, MeOH, room temperature; (vi) NaH, BnBr, DMF.

Scheme 5[a]



[a] Reagents: (i) HCO_2H, reflux; (ii) NaH, BnBr, room temperature.

cyclization in diphenyl ether to the derivatives **8a–i,k–n** in good overall yield.

The cyanoaminopyrazole **4p** underwent the same reactions with triethyl orthoformate to afford imidate **7p** and subsequently the tricyclic compound **8p**. The latter was deprotected with methanolic ammonia to give **8j** which was converted to **8o** by benzylation in the presence of sodium hydride (Scheme 3). Benzylation was performed on β-hydroxyethyl derivative **8j** instead of the pyrazole **4j** because direct reaction on **4j** with benzyl bromide afforded only the benzylamino derivative. Treatment of **8a–o** with dilute hydrochloric acid at reflux temperature induced pyrimidine ring opening to furnish the 5-amino-4-(1*H*-1,2,4-triazol-5-yl)pyrazoles **9a–o** in good yield.

These derivatives were converted into the final compounds **10a–o** by reaction with an excess of cyanamide in 1-methyl-2-pyrrolidone at 140 °C. Compound **10k** was transformed into **10q** by refluxing in formic acid, as previously described for the N-di-*tert*-butylation of pyrazole intermediates.[23] In an attempt to prepare directly the benzyloxy derivative **10o**, alkylation of **10j** with benzyl bromide in the presence of sodium hydride at room temperature afforded *N*-benzyl derivative **10r**, as the only product (Scheme 5).

Results and Discussion

The results show that many of the tested compounds have affinity at A_{2A} receptors in the low nanomolar range with different degree of selectivity (Table 1). Most of the compounds examined were able to reverse the platelet aggregation inhibition induced by *N*-ethyl-1′-deoxy-1′-(6-amino-9*H*-purin-9-yl)-β-D-ribofuranuronamide (NECA) with potency similar to (**10a–c,g,h,j,q**) or higher than (i.e., **10e,f,l,n**) that of the reference compound CGS 15943 (Table 1).

The study shows that N^7 substitution (**10a–d,h–o**) on the pyrazole ring retains high affinity at A_{2A} receptors. On the contrary, either substitution at N^8 (**10e–g**) or no substitution (**10q**) led to compounds with a good affinity for adenosine receptors but with very low selectivity. Specifically, the introduction of the phenylethyl group at the pyrazole nitrogen in position 7, **10c**, increased significantly A_{2A} selectivity, being about 50- or 100-fold in rat or bovine striatal membranes, respectively.[18] On this basis, further studies were undertaken to investigate the pharmacological characteristics of **10c** as a new prototypic A_{2A} antagonist. The results of *in vitro* functional studies carried out in various models indicate that **10c** is a competitive antagonist for the A_{2A} receptor subtype and has little or no interaction with A_1, A_{2B}, and A_3 receptors.[18] Encouraged by these results, we continued the investigation on the influence of substituents in N^7. For compound **10r**, where the amino group was protected as benzyl derivative, the A_{2A} receptor affinity is low (K_i = 166 nM). This confirms that a free amino group is necessary for an efficient receptor interaction. Introduction of an oxygen atom in the substituent chain (**10o**) reduced dramatically the A_{2A} receptor affinity (K_i > 1000 nM) and did not improve water solubility, the latter being a limitation for **10c** and other xanthine and non-xanthine adenosine antagonists.[3] It is likely that the presence of an oxygen atom hinders a correct ligand–receptor interaction. At this time, this problem is under investigation by molecular modeling studies. Instead, replacement of the oxygen atom with a methylene group led to interesting data. For example, A_{2A} affinity of **10m** remained in the nanomolar range (K_i = 21 nM), but A_{2A} selectivity significantly increased when compared with **10c** (129- versus 53-fold). Further shortening of the chain using 3-phenylpropyl, **10l**, led to a compound having higher affinity (K_i = 2.4 nM) and a very good selectivity (A_1/A_{2A} ratio of 210). Thus, it seems that a spacer between the pyrazole and aromatic moiety is necessary to achieve high A_{2A} selectivity, the optimal length being from two to four carbon atoms (**10c,d,l–m**). These data provide support to the concept that the lipophilic nature of the substituent can be important for the interaction with A_{2A} receptors. This is confirmed by the results obtained with (4-isobutylphenyl)ethyl derivative **10d** which has good affinity (K_i = 22 nM) and selectivity (A_1/A_{2A} ratio of >136). In analogy to the compound synthesized at Zeneca, 2-(2-furyl)-5-[(2-morpholinoethyl)amino][1,2,4]-triazolo[1,5-*a*][1,3,5]triazin-7-amine (pIC_{50} value at A_{2A} receptors of 7.6),[24] the introduction of a morpholinoethyl group in the N^7 position led to a compound with an increased affinity (K_i = 5.6 nM) and high A_{2A} selectivity, although lower (84-fold) than **10l**. Very recently, another heterocycle compound, the 4-[2-[[7-amino-2-(2-furyl)[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-5-yl]amino]ethyl]-phenol (ZM 241385), has been reported to be a potent (pIC_{50} = 9.5) and selective A_{2A} antagonist.[25] However, the lack of binding data carried out according to

6.6 (m, 1H), 7.3 (m, 1H), 7.7 (m, 1H), 8.8 (s, 1H), 9.1 (s, 1H). Anal. ($C_{15}H_{16}N_6O$) C, H, N.

8-(β-Phenylethyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8g): yield 60%; mp 268–270 °C (EtOAc–light petroleum); IR (KBr) 1660, 1510, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.32 (t, 2H, J = 6.7), 4.72 (t, 2H, J = 6.7), 6.73 (s, 1H), 7.23 (m, 5H), 7.95 (s, 1H), 8.8 (s, 1H), 9.41 (s, 1H). Anal. ($C_{18}H_{14}N_6O$) C, H, N.

7-(β-Hydroxyethyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8j). This product can also be obtained starting from compound **8p** with the following procedures. To a saturated methanolic solution of ammonia (15 mL) was added at 0 °C compound **8p** (0.5 g, 1.6 mmol). The resulting mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residue was purified by chromatography (EtOAc/light petroleum, 1:1) to afford the product as a pale yellow solid (0.3 g, 70%): mp 216–217 °C dec; IR (KBr) 3500–3100, 1645, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.89 (m, 2H), 4.94 (bs, 1H), 6.75 (m, 1H), 7.30 (d, 1H, J = 3.4), 7.98 (s, 1H), 8.53 (s, 1H), 9.62 (s, 1H). Anal. ($C_{12}H_{10}N_6O_2$) C, H, N.

7-*tert*-Butyl-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine (8k): yield 63%, pale yellow solid; mp 162–163 °C (EtOAc); IR (KBr) 1645, 1520, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (s, 9H), 6.62 (m, 1H), 7.28 (d, 1H, J = 4.2), 7.65 (d, 1H, J = 1.2), 8.35 (s, 1H), 9.09 (s, 1H). Anal. ($C_{14}H_{14}N_6O$) C, H, N.

7-(3-Phenylpropyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8l): yield 68%, pale yellow solid; mp 155 °C (EtOAc); IR (KBr) 1650, 1520, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3–2.5 (m, 2H), 2.68 (t, 2H, J = 8), 4.58 (t, 2H, J = 8), 6.61 (m, 1H), 7.16–7.29 (m, 6H), 7.65 (s, 1H), 8.38 (s, 1H), 9.1 (s, 1H). Anal. ($C_{19}H_{16}N_6O$) C, H, N.

7-(4-Phenylbutyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8m): yield 65%, pale yellow solid; mp 156–158 °C (EtOAc); IR (KBr) 1660, 1520, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64–1.68 (m, 2H), 1.99–2.07 (m, 2H), 2.66 (t, 2H, J = 8), 4.56 (t, 2H, J = 8), 6.58–6.61 (m, 1H), 7.11–7.29 (m, 6H), 7.64 (s, 1H), 8.38 (s, 1H), 9.09 (s, 1H). Anal. ($C_{20}H_{18}N_6O$) C, H, N.

7-(β-Morpholin-4-ylethyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8n): yield 67%, yellow solid; mp 202–203 °C (EtOAc); IR (KBr) 1660, 1510, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (t, 4H, J = 4), 2.94 (t, 2H, J = 6), 3.6 (t, 4H, J = 4), 4.66 (t, 2H, J = 6), 6.60 (bs, 1H), 7.27 (d, 1H, J = 4), 7.65 (s, 1H), 8.37 (s, 1H), 9.11 (s, 1H). Anal. ($C_{16}H_{17}N_7O_2$) C, H, N.

7-[β-(Benzyloxy)ethyl]-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8o). To a suspension of NaH (38 mg, 80% in oil, 1.2 equiv) in dry DMF (20 mL) at 0 °C was added **8j** (0.3 g, 1.1 mmol), and the mixture was allowed to warm at room temperature. When the solution was clear, it was cooled at 0 °C again, benzyl bromide (0.2 mL, 1.2 equiv) was added, and the solution was stirred at room temperature for 18 h. Then the solvent was removed, and the crude oily compound **8o** was used for the next step without any further purifications. An analytical sample was purified by flash chromatography (AcOEt): IR (neat) 1660, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.48 (m, 2H), 4.59 (m, 2H), 5.61 (s, 2H), 6.71 (m, 1H), 7.05 (d, 1H, J = 3.5), 7.23 (s, 1H), 7.15–7.48 (m, 5H), 7.9 (s, 1H), 8.5 (s, 1H). Anal. ($C_{19}H_{16}N_6O_2$) C, H, N.

7-[β-(Acetyloxy)ethyl]-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (8p): yield 76%, yellow solid; mp 174–176 °C dec (EtOAc–light petroleum); IR (KBr) 1735, 1645, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H), 4.60 (t, 2H, J = 5.3), 4.80 (t, 2H, J = 5.3), 6.62 (m, 1H), 7.29 (d, 1H, J = 4.3), 7.66 (d, 1H, J = 1.1), 8.41 (s, 1H), 9.12 (s, 1H). Anal. ($C_{14}H_{12}N_6O_3$) C, H, N.

General Procedures for the Preparation of N-Substituted-4-[3-(2-furyl)-1,2,4-triazol-5-yl]-5-aminopyrazoles 9a–c,h–o and N-Substituted-4-[3-(2-furyl)-1,2,4-triazol-5-yl]-3-aminopyrazoles 9d–g. A solution of the mixture of **8a–o** (10 mmol) in aqueous 10% HCl (50 mL) was refluxed for 3 h. Then the solution was cooled and basified with concentrated ammonium hydroxide at 0 °C. The compounds were extracted with EtOAc (3 × 20 mL); the organic layers were dried with Na_2SO_4 and evaporated under vacuum. The residue was purified by chromatography (EtOAc/light petroleum, 2:1) to afford the desired compound as a solid. The following spectral data are reported as examples.

5-Amino-1-(β-phenylethyl)-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9c): yield 75%, yellow solid; mp 175–176 °C (EtOH); IR (KBr) 3350–3150, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.15 (t, 2H, J = 6.5), 4.48 (t, 2H, J = 6.5), 5.78 (s, 1H), 6.37 (s, 1H), 7.1 (s, 1H), 7.27–7.28 (m, 5H), 7.82 (s, 1H), 14.51 (bs, 2H). Anal. ($C_{17}H_{16}N_6O$) C, H, N.

3-Amino-1-(β-phenylethyl)-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9g): yield 80%, yellow solid; mp 205–206 °C (EtOH); IR (KBr) 3350–3150, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.12 (t, 2H, J = 6.5), 4.46 (t, 2H, J = 6.5), 5.75(s, 1H), 6.34 (s, 1H), 6.63 (s, 1H), 7.01 (s, 1H), 7.21–7.27 (m, 5H), 7.79 (s, 1H), 14.41 (bs, 2H). Anal. ($C_{17}H_{16}N_6O$) C, H, N.

5-Amino-1-methyl-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9h): yield 68%, yellow solid; mp 130–131 °C (EtOAc–light petroleum); IR (KBr) 3280–3150, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.60 (s, 3H), 6.16 (bs, 2H), 6.62 (s, 1H), 6.96 (s, 1H), 7.63 (s, 1H), 7.77 (s, 1H), 13.81 (bs, 1H). Anal. ($C_{10}H_{10}N_6O$) C, H, N.

5-Amino-1-phenyl-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9i): yield 70%, yellow solid; mp 185–186 °C (EtOAc); IR (KBr) 3200–3100, 1640, 1470 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.60 (bs, 2H), 6.65 (m, 1H), 6.70 (bs, 1H), 7.20 (d, 1H, J = 3.4), 7.4–7.6 (m, 5H), 7.78 (s, 1H), 7.9 (bs, 1H). Anal. ($C_{15}H_{12}N_6O$) C, H, N.

5-Amino-1-(β-hydroxyethyl)-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9j): yield 78%, yellow solid; mp 218–220 °C (EtOAc); IR (KBr) 3480–3100, 1630, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.20 (bs, 1H), 3.80 (t, 2H, J = 5.3), 4.07 (t, 2H, J = 5.3), 5.99 (bs, 2H), 6.54 (m, 1H), 6.93 (d, 1H, J = 4.2), 7.61 (d, 1H, J = 1.2), 7.72 (s, 1H), 13.6 (bs, 1H). Anal. ($C_{11}H_{12}N_6O_2$) C, H, N.

5-Amino-1-*tert*-butyl-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9k): yield 75%, yellow solid; mp 148–150 °C (MeOH); IR (KBr) 3160, 1600, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (m, 9H), 6.1 (s, 1H), 6.6 (s, 1H), 6.9 (m, 1H), 7.7 (s, 1H), 7.8 (s, 1H), 13.9 (bs, 1H). Anal. ($C_{13}H_{16}N_6O$) C, H, N.

5-Amino-1-(3-phenylpropyl)-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9l): yield 78%, pale yellow solid; mp 138–140 °C (EtOH); IR (KBr) 3150, 1610, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04–2.15 (m, 2H), 2.59 (t, 2H, J = 8), 3.89 (t, 2H, J = 8), 5.13 (bs, 2H), 6.44 (bs, 1H), 6.93 (d, 1H, J = 2), 7.09–7.26 (m, 5H), 7.42 (s, 1H), 7.73 (s, 1H), 13.9 (bs, 1H). Anal. ($C_{18}H_{18}N_6O$) C, H, N.

5-Amino-1-(4-phenylbutyl)-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9m): yield 82%, pale yellow oil; IR (neat) 3140, 1600, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.8 (m, 2H), 1.81–2.0 (m, 2H), 2.64 (t, 2H, J = 7), 3.95 (t, 2H, J = 7), 5.1 (bs, 2H), 6.55 (d, 1H, J = 2), 7.21–7.26 (m, 6H), 7.49 (s, 1H), 7.74 (s, 1H), 9.06 (bs, 1H). Anal. ($C_{19}H_{20}N_6O$) C, H, N.

5-Amino-1-(β-morpholin-4-ylethyl)-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9n): yield 76%, dark yellow oil; IR (neat) 3150, 1620, 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (t, 4H, J = 4), 2.70–2.75 (m, 2H), 3.71 (t, 4H, J = 4), 4.08–4.17 (m, 2H), 6.33 (bs, 2H), 6.49 (dd, 1H, J = 2, 4), 6.99 (d, 2H, J = 4), 7.43 (s, 1H), 7.49 (d, 1H, J = 2), 7.7 (bs, 1H). Anal. ($C_{15}H_{19}N_7O_2$) C, H, N.

5-Amino-1-[β-(benzyloxy)ethyl]-4-[3-(2-furyl)-1,2,4-triazol-5-yl]pyrazole (9o): yield 70%, yellow solid; mp 167–168 °C (EtOAc); IR (KBr) 3350–3150, 1625, 1500 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (t, 2H, J = 5.3), 4.00 (t, 2H, J = 5.3), 5.02 (m, 2H), 5.62 (s, 2H), 6.43 (bs, 1H), 6.63 (m, 1H), 7.03 (d, 1H, J = 4.2), 7.15–7.35 (m, 6H), 7.8 (s, 1H). Anal. ($C_{18}H_{18}N_6O_2$) C, H, N.

General Procedures for the Preparation of 5-Amino-7(or 8)-substituted-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines 10a–o. To a solution of pyrazole derivatives **9a–o** (10 mmol) in *N*-methylpyrrolidone (40 mL) were added cyanamide (0.42 g, 60 mmol) and *p*-toluenesulfonic acid (2.85 g, 15 mmol), and the mixture was heated at 160 °C for 4 h. Then cyanamide (0.42 g, 60 mmol) was added again, and the solution was heated overnight. Then the solution was diluted with EtOAc (80 mL), and the precipitate (excess of

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

Radicación No.02-103708
Clasificación Internacional de Patentes: C07D 473/14, A61K31/505
Concepto Técnico No.

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

☒Capitulo descriptivo, folios 86 a 165;
☒Capitulo reivindicatorio modificado en fase nacional, folios 176 a 185;
☒Solicitud P.C.T/US01/16954, Fase nacional;
☒Solicitud del examen de patentabilidad, folios 148 y 149;
☒Examen de patentabilidad, folios 155 a 216;
☒Respuesta técnica, folios 217 a 246.

Objeto de la invención:

El titulo de la invención es "ANTAGONISTAS DE RECEPTORES DE ADENOSINA A_{2A}".
El objeto de la presente solicitud se refiere a derivados 2-(2-furil)-7H-pirazolo[4,3-e][1,2,4]triazolo[1,5-c]pirimidina.

Evaluación de los requisitos de patentabilidad:

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

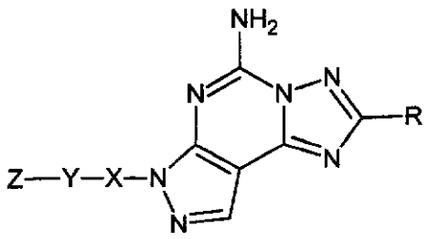
En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio en las reivindicaciones 1 a 14 folios 227 y 236, consultada la fuente de información con que cuenta este despacho, se encontró un documentos que son

directamente relacionado con la materia reclamada en la presente solicitud, WO9501356, WO9852568, US5935964, Journal of Medicine 1996, 39.11 .

Evaluación de la novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina dispone que: "*Una invención se considerará nueva cuando no está comprendida en el estado de la técnica*".

En la solicitud en estudio se reclaman compuestos de formula I:



-En el estado de la técnica más cercano las publicaciones referidas arriba se diferencian en el sustituyente Y-Z de la solicitud que es un heterociclo con N como heteroatomo-con sustitución Z, de la presente solicitud, y las anterioridades no comprenden esa sustitución Y-Z, por lo tanto la presente solicitud en estudio es nueva.

Evaluación del Nivel Inventivo:

El art. 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*"

Los compuestos de la solicitud de fórmula I de la solicitud en estudio que se diferencian en el sustituyente de la posición 7 de los anillos 2-(2-furil)-7H-pirazolo[4,3-e][1,2,4]triazolo[1,5-c]pirimidina, mientras que en la anterioridad es no existe el sustituyente alquil C2-C6-N-heteciclil-sustituido, por lo tanto los compuestos reclamados en la solicitud en estudio son diferentes y para una persona del nivel medio no le es posible derivar la invención del estado de la técnica, tomando compuestos análogos y conocidos que pudiesen tener el mismo efecto terapéutico, por lo tanto la oficina considera que la invención tiene nivel inventivo, cumpliendo con el requisito del art. 16.

Evaluación de la Aplicación Industrial:

El art. 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto puede ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria, la referida a cualquier actividad productiva, incluidos los servicios.*"

Los compuestos de la presente solicitud son susceptibles de síntesis con el sustituyente de la posición 7, alquil C2-C6-N-hetecifclil-sustituido del anillo 2-(2-furil)-7H-pirazolo[4,3-e][1,2,4]triazolo[1,5-c]pirimidina, en las cantidades requeridas por la industria farmacéutica, para producir medicamentos, por lo tanto se considera que tiene aplicación industrial.

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Conceder** el privilegio solicitado para las 1 a 14 folios 227 a 236.

Bogotá, D. C., 23 de agosto de 2007.

CONCEPTO TÉCNICO No. 1540	**JEFE DE DIVISIÓN NUEVAS CREACIONES**	**EXAMINADOR TÉCNICO** Código No. 202012

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACION: **2-103708** EDICTO No. **19788**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **32367** de **28-SEP-2007**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Otorgar el privilegio de patente de invención a la solicitud que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), para la creación denominada:

" ANTAGONISTAS RECEPTORES DE ADENOSINA A2A "

Clasificación IPC: C 07 D 473/14, A 61 K 31/505.

Reivindicación(es): 1 a 14 **Folio(s):** 227 a 236.

Titular(es): SCHERING CORPORATION.

Domicilio(s): Kenilworth, New Jersey, Estados Unidos de América.

Inventor(es): Bernard R. Neustadt, Neil A. Lindo, William J. Greenlee, Deen Tulshian, Lisa S. Silverman, Yan Xia, Craig D. Boyle y Samuel Chacklamannil.

Prioridad N°: 60/207,143 **Fecha:** 26 de mayo del 2000 **País:** US.

Solicitud Internacional N°: PCT/US 01/16954 **Fecha:** 24 de mayo del 2001.

Vigente desde: 24 de mayo del 2001 **Hasta:** 24 de mayo del 2021

ARTICULO SEGUNDO: El titular tendrá los derechos y las obligaciones establecidos en la Decisión 486 de la Comisión de la Comunidad Andina y su privilegio caducará en las condiciones prescritas por las disposiciones legales vigentes sobre propiedad industrial.

ARTICULO TERCERO: Entregar al titular copia auténtica de esta resolución y el certificado de patente, previas las anotaciones en los libros de registro.

ARTICULO CUARTO: Notificar el contenido de la presente resolución al doctor Ian Raisbeck Llinas, o a quien haga sus veces, en su calidad de apoderado de Schering Corporation., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio, del cual podrá hacer uso al momento de la notificación personal o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 28 SET. 2007

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaria General Ad-Hoc **17-OCT-2007** Este edicto se desfija hoy **30-OCT-2007** a las 4:30 p.m.
Secretaria General Ad-Hoc