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(72) ONGINI, ENNIO, IT
(72) ADAMI, MARINA, IT
(72) BERTORELLI, ROSALIA, IT
(71) SCHERING-PLOUGH S.P.A., IT

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(54) **UTILISATION D'ANALOGUES HETEROCYCLIQUES DE 1,2,4-TRIAZOLO[1,5-C]PYRIMIDINE POUR LA PREPARATION DE MEDICAMENTS S'UTILISANT DANS LE TRAITEMENT D'ACCIDENTS VASCULAIRES CEREBRAUX**

(54) **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**

(57) L'invention concerne l'utilisation d'analogues hétérocycliques de 1,2,4-triazolo[1,5-c]pyrimidine pour la préparation de médicaments s'utilisant dans le traitement d'accidents vasculaires cérébraux, tels que l'ictus, le traumatisme cérébral, l'infarctus cérébral et leurs séquelles neurologiques.

(57) The present invention relates to the use of 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues for the preparation of medicaments for the treatment of cerebrovascular disorders, such as stroke, brain trauma, cerebral infarction and their neurological sequelae.

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(71) **Applicant:** SCHERING–PLOUGH S.P.A. [IT/IT]; Via Ripamonti, 90, I–20141 Milano (IT).

(72) **Inventors:** ONGINI, Ennio; Residenza Sorgente, Milano 2, I–20090 Segrate (IT). ADAMI, Marina; Via Ferrandina, 12/A, I–20097 S. Donato Milanese (IT). BERTORELLI, Rosalia; Via Felice Romani, 3/A, I–20125 Milano (IT).

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

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(54) **Title:** 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

(57) **Abstract**

The present invention relates to the use of 1,2,4–triazolo[1,5–c]pyrimidine heterocyclic analogues for the preparation of medicaments for the treatment of cerebrovascular disorders, such as stroke, brain trauma, cerebral infarction and their neurological sequelae.

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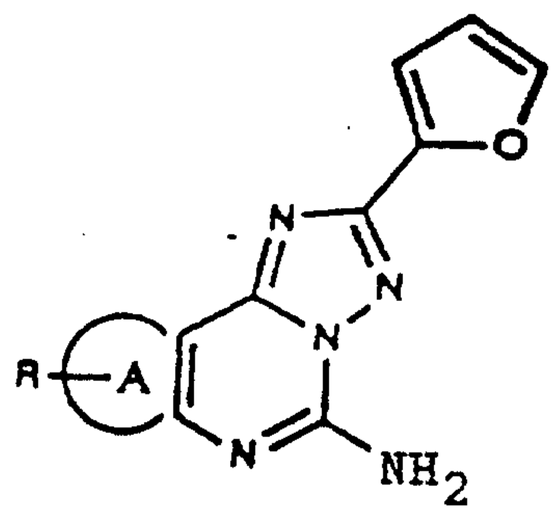
THE USE OF 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES FOR THE PREPARATION OF MEDICAMENTS USEFUL FOR THE TREATMENT OF CEREBROVASCULAR DISTURBANCES

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

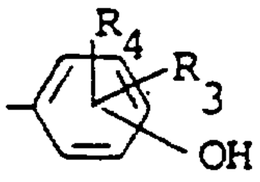


(I)

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

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.

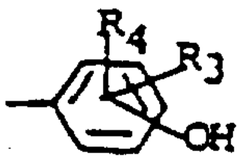
Although other heterocyclic compounds (CGS 15943 and CP66713, respectively; Life Sciences, 55, 61-65, 1994 and Brain Research 705, 79-84, 1995) are known to act favourably in cerebral ischemia animal models, nevertheless such compounds act as non-selective antagonists of the A_{2A} receptors, in that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

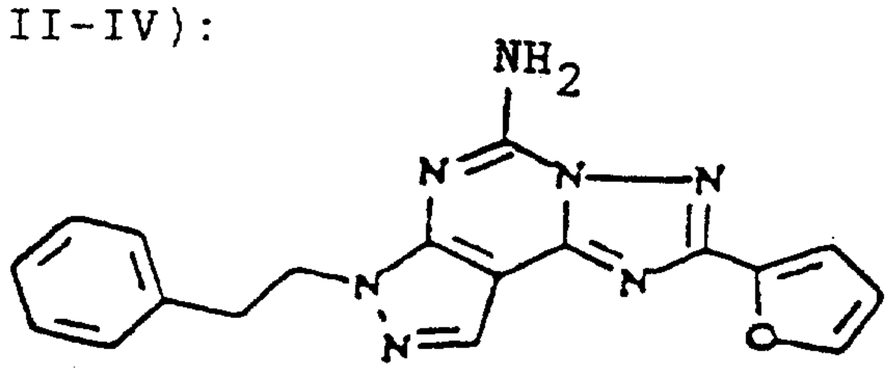
Particularly effective and therefore preferred are those compounds of formula (I) wherein:

A is pyrazole, imidazole or triazole;

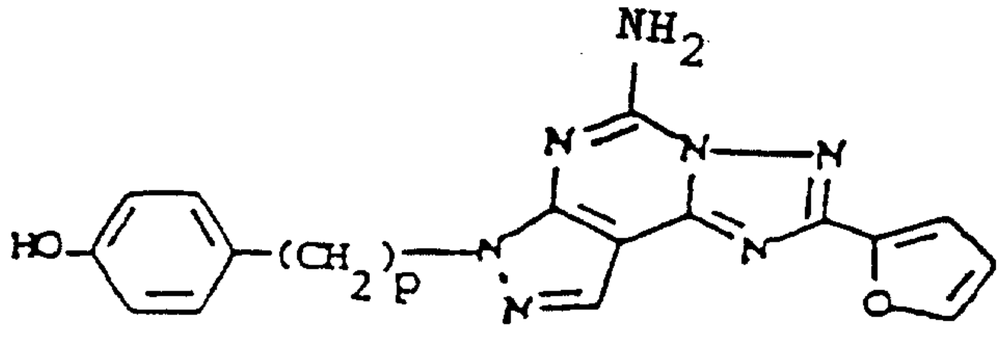
R is C_7-C_{10} aralkyl or the group $-(CH_2)_n$-  wherein

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,

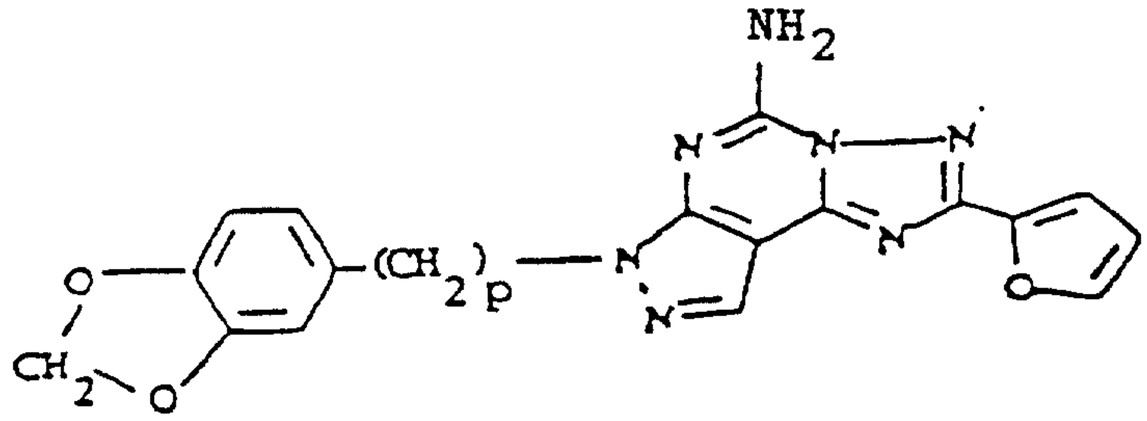
most preferred are the compounds having the following formulae (II-IV):



(II)



(III)



(IV)

wherein p = 2 or 3.

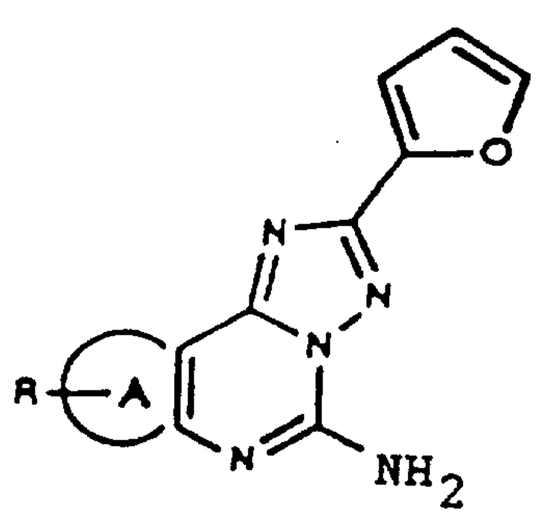
For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical compositions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, 17th ed., 1985.

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 1 mg/kg body weight.

Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (plasters) and the like.

CLAIMS

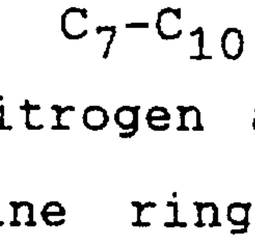
1. The use of the compounds of formula I:



(I)

in which:

A is a pyrazole, imidazole or triazole ring;

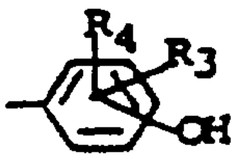
R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl, C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with 1-3 halogen atoms, hydroxy, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$, wherein R_1 and R_2, which can be the same or different, are hydrogen, C_1-C_5 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

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;

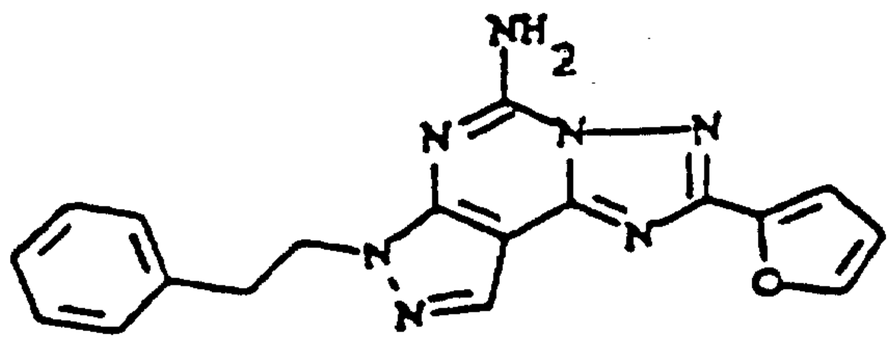
or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cerebrovascular disorders, such as stroke, cerebral infarction and brain trauma.

2. The use according to claim 1 of the compounds in which:

A is pyrazole, imidazole or triazole;

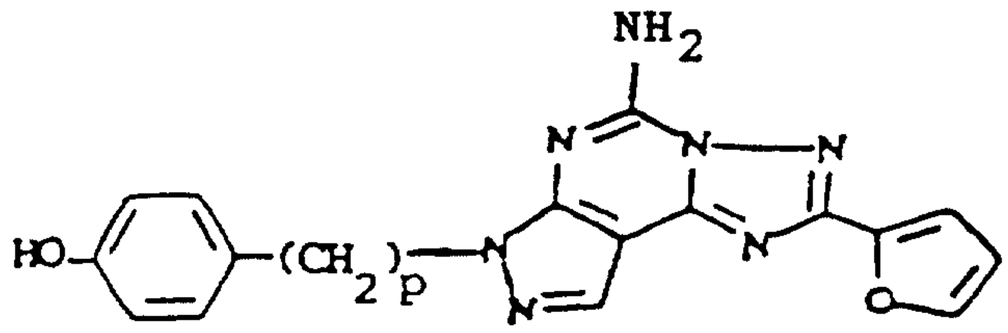
R is C_7-C_{10} aralkyl or the group -$(CH_2)_n$  wherein R_3 and R_4, which can be the same or different, are hydrogen, OH, halogen, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkoxy, C_1-C_4 haloalkyl, carboxy or carboxyamido; moreover the OH group, together with one of R_3 or 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.

3. The use according to claim 2 of the compound of formula (II)



(II)

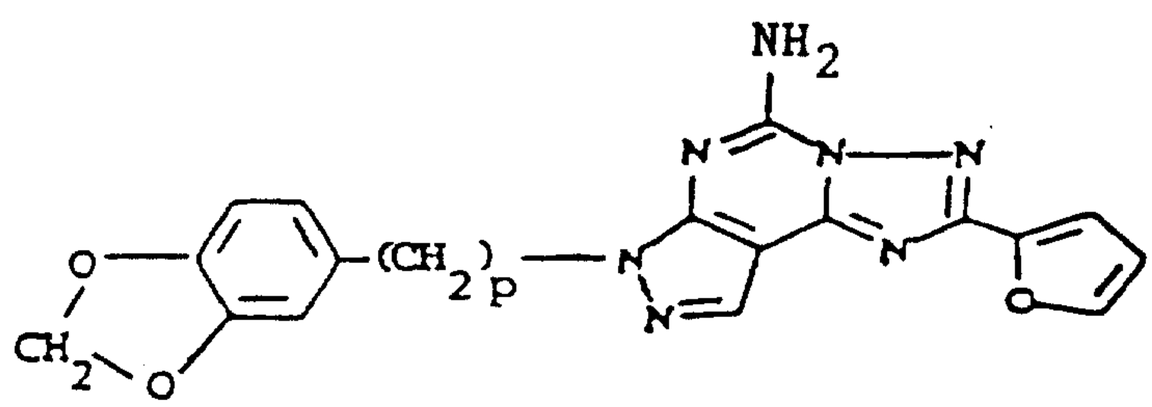
4. The use according to claim 2 of the compounds of formula (III)



(III)

wherein p = 2 or 3.

5. The use according to claim 2 of the compounds of formula (IV)



(IV)

wherein p = 2 or 3.