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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: SUBSTITUTION DERIVATIVES OF N⁶-BENZYLADENOSINE, METHODS OF THEIR PREPARATION, THEIR
USE FOR PREPARATION OF DRUGS, COSMETIC PREPARATIONS AND GROWTH REGULATORS, PHARMACEUTICAL
PREPARATIONS, COSMETIC PREPARATIONS AND GROWTH REGULATORS CONTAINING THESE COMPOUNDS

(57) Abstract: The invention concerns novel substitution derivatives of N⁶-benzyladenosine having anticancer, mitotic, immuno-
suppressive and antisenescent properties for plant, animal and human cells. This invention also relates to the methods of preparation
of these N⁶-benzyladenosine derivatives and their use as drugs, cosmetic preparations and growth regulators comprising these deriva-
tives as active compound and use of these derivatives for preparation of pharmaceutical compositions, in biotechnological processes,
in cosmetics and in agriculture.



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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 781 273 A (FAULAND E ET AL) 25 December 1973 (1973-12-25) N6-benzyladenosine the whole document	1-4,7,9, 14
A	DUTTA S P ET AL: "SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME N-(NITRO-AMINOBENZYL) ADENOSINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 18, no. 8, 1 August 1975 (1975-08-01), pages 780-783, XP000653225 ISSN: 0022-2623 compounds 2-4,6-9,11 the whole document	1-5,7,9, 12
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CZ 03/00078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRESSI J C ET AL: "ADENOSINE ANALOGUES AS INHIBITORS OF TRYPANOSOMA BRUCEI PHOSPHOGLYCERATE KINASE: ELUCIDATION OF A NOVEL BINDING MODE FOR A 2-AMINO-N6-SUBSTITUTED ADENOSINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 22, 2000, pages 4135-4150, XP000999137 ISSN: 0022-2623 compounds 27a,b the whole document	1-4,7,9, 14
X	----- M.H. FLEYSHER ET AL.: "Synthesis and biological activity of some new N6-substituted purine nucleosides" J. MED. CHEM., vol. 12, 1969, pages 1056-1061, XP002280031 N6-benzyladenosine the whole document	1-5,7,9, 12
X	----- US 3 551 409 A (DIETMANN KARL ET AL) 29 December 1970 (1970-12-29) examples 6 and 55 the whole document	1-4,7,9, 14
X	----- EP 0 540 854 A (SANSHO SEIYAKU KK) 12 May 1993 (1993-05-12) page 10, N6-benzyladenosine the whole document	1-3,6
X	----- WANNER M J ET AL: "2-Nitro analogues of adenosine and 1-deazaadenosine: synthesis and binding studies at the adenosine A1, A2A and A3 receptor subtypes" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 18, September 2000 (2000-09), pages 2141-2144, XP004208330 ISSN: 0960-894X compound 9d the whole document	1-4,7,9, 14
X	----- TRIVEDI B K ET AL: "C2N6-DISUBSTITUTED ADENOSINES: SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 32, 1989, pages 1667-1673, XP002053657 ISSN: 0022-2623 compounds 52 and 53 the whole document ----- -/--	1-4,7,9

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CZ 03/00078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>K. MAGYAR-TABORI ET AL.: "High in vitro shoot proliferation in the apple cultivar jonagold induced by benzyladenine analogues"</p> <p>ACTA AGRONOMICA HUNGARICA, vol. 50, 2002, pages 191-195, XP008030626</p> <p>N6-benzyladenosine</p> <p>the whole document</p> <p>-----</p>	<p>1-5,7, 10,12,13</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CZ 03/00078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where R1 is hydrogen, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto.

2. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is hydroxyl, alkoxy, acyloxy or carbylalkoxy, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto.

3. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is halogen, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

4. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is amino, hydrazo, nitro, amido, acylamino, alkylamino or dialkylamino, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

5. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is mercapto, methylmercapto or alkylmercapto, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

6. claims: 1-14 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is carboxyl, cyano or carbamoyl alkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

7. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is sulpho or sulphamido, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

8. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is cycloalkyl, substituted cycloalkyl or cycloalkylalkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

9. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is substituted alkyl or arylalkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

10. claims: 1-14 (in part)

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is heteroalkyl, heteroarylalkyl or cycloheteroalkyl alkyl, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

11. claims: 1-14 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Substitution derivatives of N6-benzyladenosine of the general formula I of claim 1 where at least one of R1 is R1'-X with R1' and X as defined in claim 1, methods, pharmaceuticals, cosmetics, growth regulators and uses pertaining thereto inasfar as this subject does not fall within one of the earlier subjects.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CZ 03/00078

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3781273	A	25-12-1973	DE 2007273 A1	26-08-1971
			AT 313483 B	25-02-1974
			AT 306251 B	10-04-1973
			CA 953714 A1	27-08-1974
			CH 549596 A	31-05-1974
			CH 549600 A	31-05-1974
			DK 123357 B	12-06-1972
			ES 388194 A1	01-05-1973
			FR 2081524 A5	03-12-1971
			GB 1279946 A	28-06-1972
			HU 162739 B	28-04-1973
			JP 51016440 B	24-05-1976
			NL 7102026 A	20-08-1971
			SU 399134 A3	27-09-1973
			ZA 7101030 A	24-11-1971

US 3551409	A	29-12-1970	AT 272529 B	10-07-1969
			AT 272528 B	10-07-1969
			CH 538485 A	15-08-1973
			CH 495364 A	31-08-1970
			DE 1670175 A1	05-11-1970
			FI 49622 B	30-04-1975
			FR 1558462 A	28-02-1969
			GB 1143150 A	19-02-1969
			NL 6717061 A	24-06-1968
			SE 323384 B	04-05-1970

EP 0540854	A	12-05-1993	JP 2636118 B2	30-07-1997
			JP 5320028 A	03-12-1993
			AT 162394 T	15-02-1998
			AU 659861 B2	01-06-1995
			AU 2281792 A	11-03-1993
			CA 2077850 A1	11-03-1993
			DE 69224145 D1	26-02-1998
			DE 69224145 T2	27-08-1998
			DK 540854 T3	11-05-1998
			EP 0540854 A2	12-05-1993
			ES 2114900 T3	16-06-1998
			FI 924034 A	11-03-1993
			GR 3026675 T3	31-07-1998
			HK 1007379 A1	09-04-1999
			KR 238355 B1	01-02-2000
			NO 923503 A	11-03-1993
			NZ 244259 A	26-01-1996
			US 5656264 A	12-08-1997
