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(54) Title: METHODS OF SYNTHESIS FOR 9-SUBSTITUTED HYPOXANTHINE DERIVATIVES

(57) Abstract: An improved method of synthesis of a 9-substituted hypoxanthine derivative comprises the steps of: (1) reacting aminocyanacetamide with triethyl orthoformate to form an imidoester derivative of aminocyanacetamide; (2) forming a compound having a reactive amino group on a hydrocarbyl moiety, the hydrocarbyl moiety being linked through an amide group to a physiologically active moiety or an esterified derivative of a physiologically active moiety including therein an esterified benzoyl group; (3) reacting the imidoester with the compound having the reactive amino group on the hydrocarbyl moiety to form a derivative of 5-aminoimidazole-4-carboxamide substituted at the 1-position with a hydrocarbyl moiety linked through an amide group to a physiologically active moiety including therein an optionally esterified benzoyl group; (4) forming the six-membered heterocyclic ring of the purine moiety of the hypoxanthine by reacting the derivative of 5-aminoimidazole-4-carboxamide formed in step (3) with triethyl orthoformate to form a 9-substituted hypoxanthine compound substituted at the 9-position with a hydrocarbyl moiety linked through an amide group to a physiologically active moiety including therein an optionally esterified benzoyl group; and (5) hydrolyzing the ester of the optionally esterified group if present.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D233/88 C07D473/30 A61K31/522 A61P25/28

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)

IPC 7 C07D

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)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 091 432 A (GLASKY ALVIN J) 25 February 1992 (1992-02-25) cited in the application column 1, line 15 - line 16 column 4, line 51 - line 52 examples 1,2,36-39 -----	1-27



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5091432	A	25-02-1992	AT 154880 T 15-07-1997
		AU 7678191 A	21-10-1991
		CA 2079342 A1	29-09-1991
		CS 9100859 A3	19-02-1992
		DE 69126701 D1	07-08-1997
		DE 69126701 T2	04-12-1997
		DK 522082 T3	21-07-1997
		EP 0522082 A1	13-01-1993
		ES 2104700 T3	16-10-1997
		GR 3024904 T3	30-01-1998
		IE 910994 A1	09-10-1991
		IL 97638 A	12-03-1999
		JP 3198335 B2	13-08-2001
		JP 5508390 T	25-11-1993
		NZ 237574 A	27-09-1993
		WO 9114434 A1	03-10-1991