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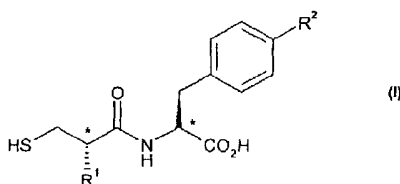
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ning of each regular issue of the PCT Gazette.

(54) Title: 4-PYRAZOL-PHENYLALANINE DERIVATIVES AS ACE-NEP INHIBITORS



(57) Abstract: The invention relates to compounds of formula (I) wherein R¹ represents benzyl; R² represents pyrazole; or a phar-
maceutically acceptable derivative thereof. The invention also relates to pharmaceutical compositions containing compounds of
formula (I) and to the use of compounds of formula (I) in medicine, particularly in the amelioration of a clinical condition for which
a ACE and/or NEP inhibitor is indicated.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/04 A61K31/415

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, PAJ, INSPEC, 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.
E	WO 03 068725 A (WHITEHEAD ANDREW JONATHAN ; HAYES DOUGLAS (GB); GLAXO GROUP LTD (GB)) 21 August 2003 (2003-08-21) page 4, line 14 -page 5, line 2; claims 1,2,9-11; example 3 ---	1-8
Y	WO 97 24342 A (ZAMBON SPA ; PELLACINI FRANCO (IT); FANTUCCI MARIO (IT); NORCINI GA) 10 July 1997 (1997-07-10) cited in the application page 2, line 24 -page 4, line 2 page 6, line 13 -page 7, line 30 claims 1-10; example 16 --- -/--	1-7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCHRÖDER E ET AL: "Arzneimittelchemie passage" ARZNEIMITTELCHEMIE GRUNDLAGEN NERVEN, MUSKELN UND GEWEBE, XX, XX, 1976, pages 30-33, XP002186820 page 33; table 8 -----	1-7

INTERNATIONAL SEARCH REPORT

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03068725	A	21-08-2003	WO 03068725 A2	21-08-2003
WO 9724342	A	10-07-1997	IT MI952773 A1	30-06-1997
			AU 713156 B2	25-11-1999
			AU 1301897 A	28-07-1997
			BG 63942 B1	31-07-2003
			BG 102553 A	30-04-1999
			BR 9612373 A	13-07-1999
			CA 2241414 A1	10-07-1997
			CN 1206411 A ,B	27-01-1999
			CZ 9802046 A3	11-11-1998
			EA 991 B1	28-08-2000
			EE 9800192 A	15-12-1998
			WO 9724342 A1	10-07-1997
			EP 0877740 A1	18-11-1998
			HK 1018008 A1	26-04-2002
			IL 124915 A	31-10-2001
			JP 2000502687 T	07-03-2000
			NO 982977 A	27-08-1998
			NZ 325785 A	29-09-1999
			PL 327580 A1	21-12-1998
			SK 88998 A3	02-12-1998
			TR 9801229 T2	21-09-1998
			ZA 9610891 A	27-06-1997