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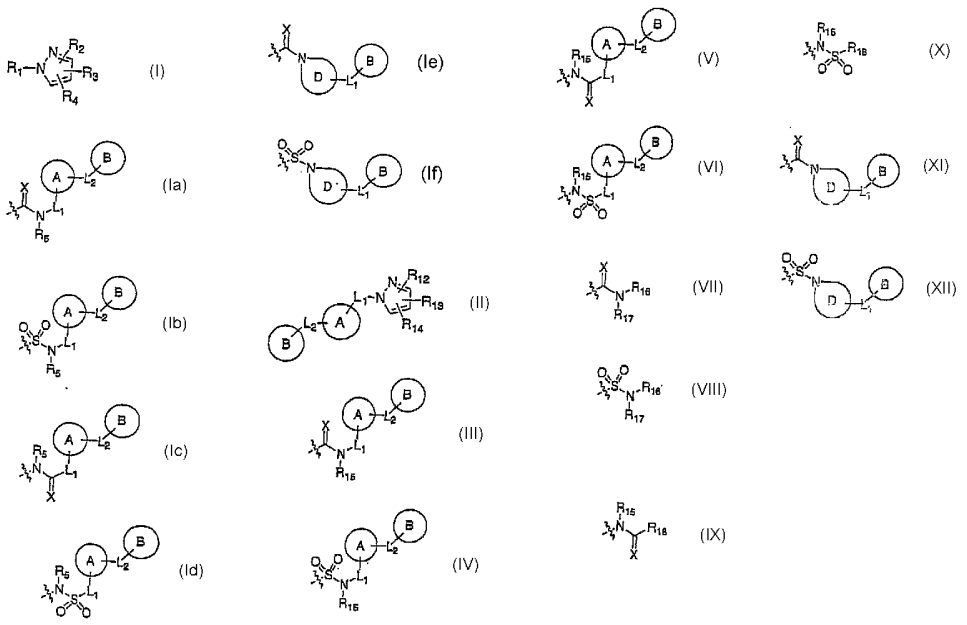
(54) Title: PYRAZOLE-AMIDES AND SULFONAMIDES AS SODIUM CHANNEL MODULATORS



(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, wherein R_1 is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocycle, heterocyclealkyl, heteroaryl, or heteroarylalkyl; R_4 is formula (Ia), formula (Ib), formula (Ic), formula (Id), formula (Ie) or formula (If); or formula (II), or a pharmaceutically acceptable salt, amide, ester or prodrug thereof, wherein R_{14} is formula (III), formula (IV), formula (V), formula (VI), formula (VII), formula (VIII), formula (IX), formula (X), formula (XI), or formula (XII); modulate PN3 in mammals and are useful in treating pain in mammals.

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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/14 A61K31/415 C07D231/20 C07D231/22 C07D231/24
C07D401/04 C07D401/12

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 A61K

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, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/57024 A (SELWOOD DAVID ; UNIV LONDON (GB); WISHART GRANT (GB); KLING MARCEL (GB) 9 August 2001 (2001-08-09) page 71; claim 1 page 38, line 14 -----	1,8,12
X	WO 98/28269 A (DU PONT MERCK PHARMA) 2 July 1998 (1998-07-02) page 397 - page 492; claim 1 pages 287-291; table 1b, the compounds of the examples 65, 75, 109, and 169-173 pages 90-106; examples 10D, 13A, 14D, 15E, 18B, and the corresponding 1-(cyanophenyl)-pyrazole derivatives (intermediates) of the examples 27-32, 34-38, 41-43, etc. ----- -/--	1,8,12

[X] Further documents are listed in the continuation of box C.

[X] 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

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2004	**08.02.2005**

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

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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.
X	WO 98/57937 A (DU PONT MERCK PHARMA) 23 December 1998 (1998-12-23) page 232 - page 239; claim 1 pages 191-196; table 1, the compounds of the examples 1-11, 15, 38-41, 47, 49, 50, 57, 61, 63, 64, 74, 75, 97, 101, 103-108, 154-157, 164-166, 169, and 170	1,8,12
X	WO 99/32454 A (DU PONT PHARM CO) 1 July 1999 (1999-07-01) page 203 - page 208; claim 1 page 107 - page 111; examples 37,38 page 114, line 25 - line 37 page 115, line 33 - page 116, line 6	1,8,12
X	WO 00/69849 A (ORTHO MCNEIL PHARM INC) 23 November 2000 (2000-11-23) page 44 - page 46; claim 1 pages 44-46; the table, the compounds no. 15, 54, 56, and 111	1,8,12
X	PINTO, DONALD J. P. ET AL: "Discovery of 1-[3-(Aminomethyl)phenyl]-N-[3-fluoro-2'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (DPC423), a Highly Potent, Selective, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa" JOURNAL OF MEDICINAL CHEMISTRY , 44(4), 566-578 CODEN: JMCMAR; ISSN: 0022-2623, 2001, XP002302828 page 567; Scheme 1, the compound 5 page 567; Scheme 2, the compound 8b page 568; Scheme 3, the compound 13a page 569; Scheme 5, the compounds 8 and 13	1,8,12
X	WO 01/19798 A (COR THERAPEUTICS INC) 22 March 2001 (2001-03-22) page 255 - page 261; claim 1 page 236 - page 238; examples 120,121,and,123	1,8,12

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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.
X	MUTLIB, ABDUL E. ET AL: "P450-mediated metabolism of 1-[3-(aminomethyl)phenyl]-N-[3-fluoro-2'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole- 5-carboxamide (DPC 423) and its analogs to aldoximes. Characterization of glutathione conjugates of postulated intermediates derived from aldoximes" CHEMICAL RESEARCH IN TOXICOLOGY , 15(1), 63-75 CODEN: CRTOEC; ISSN: 0893-228X, 2002, XP002302829 page 64; Figure 3, the compounds M12 and M18 page 65; Scheme 1, the compound M1 page 73; Scheme 3, the compound M2 -----	1,8,12
X	KORDIK, C. P. ET AL: "Pyrazolecarboxamide human neuropeptide Y5 receptor ligands with in vivo antifeedant activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 11(17), 2287-2290 CODEN: BMCLE8; ISSN: 0960-894X, 2001, XP002302830 page 2288; Table 2, the compound 18 -----	1,8,12
X	US 6 339 099 B1 (LAM PATRICK Y ET AL) 15 January 2002 (2002-01-15) column 39; Scheme 7, the N-(3-cyano-4-fluorophenyl) substituted heterocycle column 101, line 15 - line 37 column 124, line 34 - line 53 column 126, line 8 - line 27 column 128, line 37 - line 54 column 103, line 19 - line 31 -----	1,8,12
P,X	WO 03/037274 A (GROSS MICHAEL FRANCIS ; ICAGEN INC (US); ATKINSON ROBERT NELSON (US)) 8 May 2003 (2003-05-08) page 117 - page 118; claim 1 page 47; the compound 122 page 48; the compounds 130 and 138 page 72; the compounds 510 and 515 page 3, line 22 - line 26 ----- -/--	1,8,12

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LAM, PATRICK Y. S. ET AL: "Structure-based design of novel guanidine/benzamidine mimics: potent and orally bioavailable factor Xa inhibitors as novel anticoagulants" JOURNAL OF MEDICINAL CHEMISTRY , 46(21), 4405-4418 CODEN: JMCMAR; ISSN: 0022-2623, 9 October 2003 (2003-10-09), XP002302831 page 4407; Scheme 1, the compounds 14a-14c and 14e-14i page 4408; Table 1, the compounds 15b-d page 4409; Table 2, the compounds 22a-e and g --- PRUITT, JAMES R. ET AL: "Discovery of 1-(2-Aminomethylphenyl)-3-trifluoromethyl-N-[3-fluoro-2'-(aminosulfonyl)[1,1'-biphenyl)]-4-yl]-1H-pyrazole-5-carboxamide (DPC602), a Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor" JOURNAL OF MEDICINAL CHEMISTRY , 46(25), 5298-5315 CODEN: JMCMAR; ISSN: 0022-2623, 4 December 2003 (2003-12-04), XP002302832 page 5299; Scheme, the compounds 5a-d, 6a-d, and 7a-c page 5299; Scheme 2, the compounds 12a, c and d, and 13a and e page 5303; Scheme 7, the compounds 43 and 44 page 5312; column 2, last paragraph, the free acid of 43 ---	1,8,12 1,8,12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/013530

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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 III Observations where unity of invention is lacking (Continuation of item 3 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, 8 and 12 (all partly)

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, 8 and 12 (all partly)

the compounds of the present general formulae (I) and (II) wherein R4 / R14 are -C(=X)-N(R5)-L1-A-L2-B and -C(=X)-N(R15)-L1-A-L2-B wherein A is aryl and B is aryl, cycloalkyl, heteroaryl or heterocycle;

---

2. claims: 1, 8 and 12 (all partly)

the compounds of the present general formulae (I) and (II) wherein R4 / R14 are -C(=X)-N(R5)-L1-A-L2-B and -C(=X)-N(R15)-L1-A-L2-B wherein A is heteroaryl and B is aryl, cycloalkyl, heteroaryl or heterocycle;

---

3. claims: 1 (partly), 8 (partly), 9-11, and 12 (partly)

the compounds of the present general formulae (I) and (II) wherein R4 / R14 are -C(=X)-N(R5)-L1-A-L2-B and -C(=X)-N(R15)-L1-A-L2-B wherein A is selected from cycloalkyl and heterocycle and B is aryl, cycloalkyl, heteroaryl or heterocycle;

---

4. claim: 1 and 12 (both partly)

the compounds of the present general formulae (I) and (II) wherein R4 / R14 are -S(O)2-N(R5)-L1-A-L2-B, -S(O)2-ND-L1-B, -S(O)2-N(R15)-L1-A-L2-B, and -S(O)2-N(R16)(R17);

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5. claim: 1 and 12 (both partly)

the compounds of the present general formulae (I) and (II) wherein R4 / R14 are -N(R5)-C(=X)-L1-A-L2-B, -N(R5)-SO2-L1-A-L2-B, -N(R15)-C(=X)-L1-A-L2-B, -N(R15)-SO2-L1-A-L2-B, -N(R15)-C(=X)-R18, and -N(R15)-SO2-R18;

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6. claims: 1 (partly), 2-7, and 12 (partly)

the compounds of the present general formulae (I) and (II) wherein R4 / R14 are -C(=X)-ND-L1-B;

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7. claim: 12 and 18 (both partly)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the compounds of the present general formula (II) (claim 12) wherein R14 is
-C(=X)-N(R16)(R17) or -C(=X)-N(R15)-L1-A-L2-B (wherein B is absent), and wherein the ring A (which is attached to the 1-position of the pyrazole) is aryl;

---

8. claims: 12 (partly), 13-17, and 18 (partly)

the compounds of the present general formula (II) (claim 12) wherein R14 is
-C(=X)-N(R16)(R17) or -C(=X)-N(R15)-L1-A-L2-B (wherein B is absent), and wherein the ring A (which is attached to the 1-position of the pyrazole) is selected from cycloalkyl and heterocycle;

---

9. claim: 12 and 18 (both partly)

the compounds of the present general formula (II) (claim 12) wherein R14 is
-C(=X)-N(R16)(R17) or -C(=X)-N(R15)-L1-A-L2-B (wherein B is absent), and wherein the ring A (which is attached to the 1-position of the pyrazole) is heteroaryl;

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]2004/013530

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International Application No
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