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(72) Inventors; and

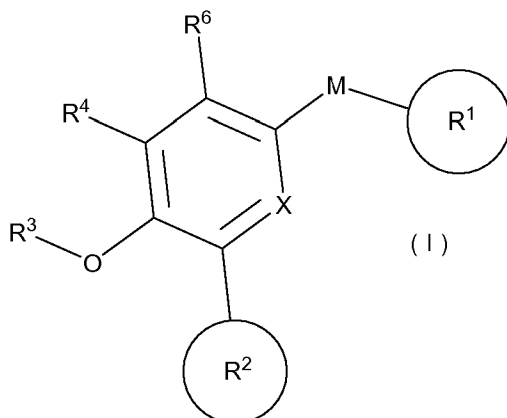
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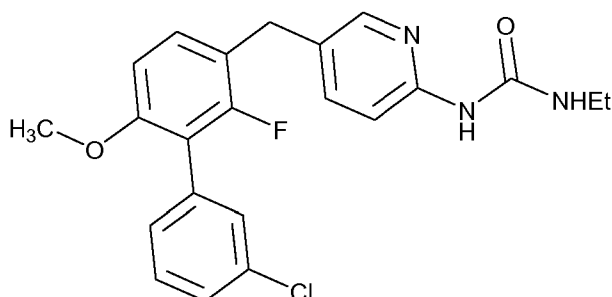
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[Continued on next page]

(54) Title: BIARYL PDE4 INHIBITORS FOR TREATING INFLAMMATION



(57) Abstract: The present invention relates to a genus of biaryl compounds containing at least one further ring. The compounds are PDE4 inhibitors useful for the treatment and prevention of stroke, myocardial infarct and cardiovascular inflammatory diseases and disorders. The compounds have general formula I: (formula should be inserted here). A particular embodiment is (a second formula should be inserted here)





EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, 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

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A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D207/16 C07D213/64 C07D213/79 C07D231/12 C07D239/42
C07D401/06 C07D471/04 C07D473/18 C07D473/40 C07D285/135
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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)

C07D A61P 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, WPI Data

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X	WO 02/072009 A (MAXIA PHARMACEUTICALS INC [US]) 19 September 2002 (2002-09-19) claims 23,25; examples 8-13,16,21,24,52 ----- -/--	1,3,4, 17,18, 30,35,46

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *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
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- * & * document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/

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X	WO 2006/066978 A (GALDERMA RES & DEV [FR]; BIADATTI THIBAUD [FR]; DUMAIS LAURENCE [FR];) 29 June 2006 (2006-06-29) page 15, line 21 - line 25; examples 1-54 -----	1,3-5,8, 9,12,13, 15,17, 23,24, 30, 34-36, 45-47,54
X	WO 2006/083477 A (SYNTA PHARMACEUTICALS CORP [US]; SUN LIJUN [US]; CHEN SHOUJUN [US]; XI) 10 August 2006 (2006-08-10) claim 110; examples 25,27,47,50-52 -----	1,3,6, 12,13, 17,19, 30,34, 36,41, 42,45, 51,54
X	WO 2005/047270 A (MERCK & CO INC [US]; PARK MIN K [US]; CHAKRAVARTY PRASUN K [US]; ZHOU) 26 May 2005 (2005-05-26) claims 45,61; example 9 -----	1,3,6, 12,17, 30,34, 45,54
X	WO 2004/084824 A (MERCK & CO INC [US]; CHAKRAVARTY PRASUN K [US]; FISHER MICHAEL H [US];) 7 October 2004 (2004-10-07) claim 55; examples 215,216 -----	1,3,4,6, 10,12, 15,17, 30,34, 45,54
X	WO 2004/092140 A (MERCK & CO INC [US]; CHAKRAVARTY PRASUN K [US]; FISHER MICHAEL H [US];) 28 October 2004 (2004-10-28) claim 41; examples 223-225,277-279 -----	1,3,4,6, 10,12, 15,17, 30,34, 45,54
X	WO 2007/079186 A (MERCK & CO INC [US]; ALI AMJAD [US]; LU ZHIJIAN [US]; SINCLAIR PETER J) 12 July 2007 (2007-07-12) page 23, line 1; examples 2-20 ----- -/--	1,3-5, 12,17, 30,34, 45,54

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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	EP 0 675 118 A (EISAI CO LTD [JP]) 4 October 1995 (1995-10-04) page 3, line 9; claims 1,3; examples 57,61,62,79 -----	1,3,4,6, 12,17, 30,37, 40,50,54
X	WO 2004/093799 A (SQUIBB BRISTOL MYERS CO [US]; RYONO DENNIS E [US]; HANGELAND JON J [US]) 4 November 2004 (2004-11-04) claims 1,2,9; examples 102-139,164,166a-c,168a-c -----	1,30,35, 41,51,54
X	WO 03/094845 A (SQUIBB BRISTOL MYERS CO [US]; ZHANG MINSHENG [US]; HANGELAND JON [US];) 20 November 2003 (2003-11-20) claim 17; examples 19,20,28-32,123-127,227,231,232,236,247 -----	1,30,41, 51,54
X	WO 2005/051298 A (METABASIS THERAPEUTICS INC [US]; ERION MARK D [US]; JIANG HONGJIAN [US]) 9 June 2005 (2005-06-09) page 370; compounds 7-1 page 58, line 11 - line 12 -----	1,4,29, 30,33, 35,41, 46,51,54
X	SRINIVASARAO ARULANANDA BABU, MAKOTO YASUDA, AND AKIO BABA: "In(III)-Mediated Chemoselective Dehydrogenative Interaction of ClMe ₂ SiH with Carboxylic Acids: Direct Chemo- and Regioselective Friedel-Crafts Acylation of Aromatic Ethers" ORGANIC LETTERS, vol. 9, no. 3, 12 January 2007 (2007-01-12), pages 405-408, XP002517831 table 3; compound 4B -----	1,4
X	R. FUSCO, AND F. SANNICOLA: "Rearrangement of arylhydrazones of aromatic and arylaliphatic carbonyl compounds to biphenyl derivatives. 3" JOURNAL OF ORGANIC CHEMISTRY, vol. 46, no. 1, 1981, pages 83-89, XP002517830 compounds 9A, 9B, 11A -----	1,4,14
X	NG. PH. BUU-HOI, AND MICHEL. SY: "The Pfitzinger Reaction with Ketones Derived from o-Hydroxydiphenyl" JOURNAL OF ORGANIC CHEMISTRY, vol. 21, no. 1, 1956, pages 136-138, XP002517829 compounds V, XI -----	1,4

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INTERNATIONAL SEARCH REPORT

 International application No
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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	S. YOGI, K. HOKAMA, S. TAKAYOSHI, O. TSUGE: "Synthesis of Imido-Substituted 3,8-Diphenyl-1,2-diazacycloocta-2,4,6,8-tetraenes and their Thermolysis" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 60, February 1987 (1987-02), pages 731-735, XP002517828 page 732; compound 15	1,2,4
X	WO 99/31062 A (SHIONOGI & CO [JP]; ADACHI MAKOTO [JP]; SASATANI TAKASHI [JP]; CHOMEI) 24 June 1999 (1999-06-24) page 110; compounds 2-10, 2-13	1,2,4, 13,30, 37,42, 48,49, 52,54
P,X	WO 2008/001959 A (SANWA KAGAKU KENKYUSHO CO [JP]; ASANO YUKIYASU [JP]; MAEDA KOJI [JP];) 3 January 2008 (2008-01-03) pages 80,114; tables 19,35; compounds 137,97-99	1,4,14, 29,30, 35,37, 41,42, 46,48, 49,51, 52,54
X	WO 96/16058 A (NEUROGEN CORP [US]; YUAN JUN [US]; THURKAUF ANDREW [US]) 30 May 1996 (1996-05-30) page 7, lines 8,9; example II	1,4,29, 30,37, 40,42, 48,50,54
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X	EP 1 227 086 A (TAKEDA CHEMICAL INDUSTRIES LTD [JP] TAKEDA PHARMACEUTICAL [JP]) 31 July 2002 (2002-07-31) Therapeutic use: see column 1, line 46 - column 2, line 24 page 56, line 56 - page 57, line 2; claim 11; examples 11,24,35	4,29,33, 40

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. 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 No. 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 allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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.:
1-26 (in part), 27-28, 29-54 (in part)
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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ 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: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "bond", pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

2. claims: 1-26 (in part), 27-28, 29-54 (in part)

Compounds of formula (I), where the variable "M" takes the value "-CR2OR21-", "-CR2O(OH)-" and "-C(O)-", pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

3. claims: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "-O-", pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

4. claims: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "-NR22-", pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

5. claims: 1-26, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "-S(O)n", with n=0-2, pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

6. claims: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "-CR2OR21-CR2OR21-", "-CR2O=CR21-", "-C(O)-CR2OR21-" and "-CR2OR21-C(O)-", pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "-CR₂OR₂1-O-", "CR₂OR₂1-NR₂2-", and "-CR₂OR₂1-S(O)n-", with n=0-2,, pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

8. claims: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "-OCR₂OR₂1-", "-NR₂2-CR₂OR₂1-" and "-S(O)n-CR₂OR₂1-", with n=0-2, pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

9. claims: 1-25, 29-54 (all in part)

Compounds of formula (I), where the variable "M" takes the value "spirocyclic carbon which is ring member of ring A", pharmaceutical composition with such compounds and their use for the treatment of diseases such as cancer, stroke, bone diseases/osteoporosis, asthma, COPD, anxiety.

INTERNATIONAL SEARCH REPORT

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