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C07D 235/16 (2006.01) ***C07D 319/20*** (2006.01)
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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CUTSHALL, Neil, S.** [US/US]; 3817 165th Avenue Southeast, Snohomish, WA 98290 (US). **GAGE, Jennifer, Lynn** [US/US]; 15318 62nd Place Northeast, Kenmore, WA 98028 (US).

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, 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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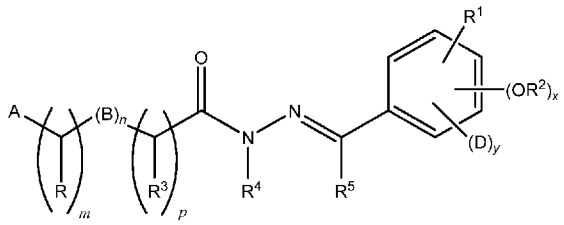
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

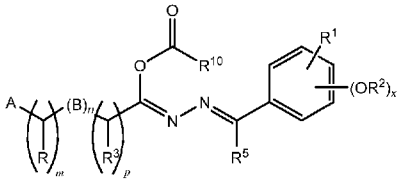
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

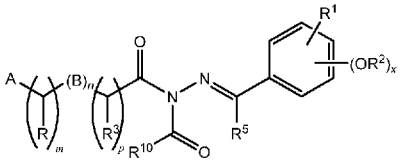
(54) **Title**: PDE10 INHIBITORS AND RELATED COMPOSITIONS AND METHODS



(I)



(II-A)



(II-B)

(57) **Abstract**: Compounds that inhibit PDE10 are disclosed that have utility in the treatment of a variety of conditions, including (but not limited to) psychotic, anxiety, movement disorders and/or neurological disorders such as Parkinson's disease, Huntington's diseases, Alzheimer's disease, encephalitis, phobias, epilepsy, aphasia, Bell's palsy, cerebral palsy, sleep disorders, pain, Tourette syndrome, schizophrenia, delusional disorders, drug-induced psychosis and panic and obsessive-compulsive disorders. The compounds have one of the following general structures: wherein *m, n, p, x, y,* R, R^1, R^2, R^3, R^4, R^5, R^{10}, A, B and D, are as defined herein, including pharmaceutically acceptable salts, stereoisomers, solvates or prodrugs thereof. Also disclosed are compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier, as well as methods relating to the use thereof for inhibiting PDE10 in a warm-blooded animal in need of the same.

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/42 C07D213/70 C07D213/78 C07D215/36 C07D235/02
C07D235/16 C07D235/28 C07D239/10 C07D239/93 C07D241/24
C07D249/12 C07D263/58 C07D307/68 C07D319/20 C07D495/04

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 A61K A61P

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, BEILSTEIN Data, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008/064342 A (OMEROS CORP [US]; CUTSHALL NEIL S [US]; JOHNSTON DEREK [GB]; UROGDI LA) 29 May 2008 (2008-05-29) claims 1-14,23	1,6,14, 15,18-23
A	WO 2007/047394 A (EPIX DELAWARE INC [US]; FICHMAN MERAV [IL]; CHEN DONGLI [US]; PENLAND) 26 April 2007 (2007-04-26) claims 1,9 page 42; examples 15,16	1,6,14, 15,18-23
X	WO 2006/127396 A (ACADIA PHARM INC [US]; BURSTEIN ETHAN [US]; KNAPP ANNE EEG [DK]) 30 November 2006 (2006-11-30) claims 1,5,11,15,20 page 9; compound 24 paragraphs [0107] - [0121]	1,6,14, 15,18-21

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

[X] 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

"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

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2009	20/05/2010

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, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRAGA ALINE G M ET AL: "Synthesis and pharmacological evaluation of novel heterotricyclic acylhydrazone derivatives, designed as PAF antagonists" EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 11, no. 4, October 2000 (2000-10), pages 285-290, XP002545200 ISSN: 0928-0987 page 286; compound 7E	1,6,14, 15
X	DIAS L R ET AL: "Synthesis and analgesic properties of 5-acyl-arylhydrazone 1-H pyrazolo [3,4-b] pyridine derivatives." PHARMACEUTICA ACTA HELVETIAE DEC 1994, vol. 69, no. 3, December 1994 (1994-12), pages 163-169, XP002545201 ISSN: 0031-6865 page 164; compound 1D	1,6,14, 15
X	DE NARDO M: "Fusaric acid derivatives and analogues as possible antihypertensive drugs. Note II." IL FARMACO; EDIZIONE SCIENTIFICA APR 1981, vol. 36, no. 4, April 1981 (1981-04), pages 269-273, XP008111569 ISSN: 0430-0920 page 271; compounds II,XI	1,6,14, 15
X	BERNARDINO ALICE M R ET AL: "Synthesis and leishmanicidal activities of 1-(4-X-phenyl)-N '-[(4-Y-phenyl)methylene]-1H-pyrazole-4-carbohydrazides" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 1, January 2006 (2006-01), pages 80-87, XP002545202 ISSN: 0223-5234 page 82; compounds 3, 21	1,6,14, 15
X	HANNA M LESLIE ET AL: "Mechanistic differences between in vitro assays for hydrazone-based small molecule inhibitors of anthrax lethal factor" BIOORGANIC CHEMISTRY, vol. 35, no. 1, February 2007 (2007-02), pages 50-58, XP002545203 ISSN: 0045-2068 compounds 6D, 6E, 6I	1,6,14, 15

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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	SOUZA MARCUS V N DE ET AL: "4-Cyanobenzaldehyde isonicotinoylhydrazone monohydrate: a three-dimensional hydrogen-bonded framework structure." ACTA CRYSTALLOGRAPHICA. SECTION C, CRYSTAL STRUCTURE COMMUNICATIONS MAR 2007, vol. 63, no. Pt 3, March 2007 (2007-03), pages o166-o168, XP002545204 ISSN: 0108-2701 page 0166; compound I	1,6,14, 15
X	DA SILVA LOURENCO MARIA CRISTINA ET AL: "Synthesis and anti-mycobacterial activity of (E)-N '-(monosubstituted-benzylidene)isonicotino hydrazide derivatives" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 6, June 2008 (2008-06), pages 1344-1347, XP002545205 ISSN: 0223-5234 available online: 2 September 2007 pages 2K,2L,2M	1,6,14, 15
P,X	SINK ROMAN ET AL: "Synthesis and biological evaluation of N-acylhydrazones as inhibitors of MurC and MurD ligases." CHEMMEDCHEM SEP 2008, vol. 3, no. 9, September 2008 (2008-09), pages 1362-1370, XP002545206 ISSN: 1860-7187 page 1364; compound 16	1,6,14, 15
X	US 2002/091148 A1 (BAMAUNG NWE Y [US] ET AL) 11 July 2002 (2002-07-11) claims 1,40 examples 10,32-35,51,52d,62,72,126	1,6,14, 15,18
X	LIMA P C ET AL: "Synthesis and analgesic activity of novel N-acylarylhydrazones and isosters, derived from natural safrole#" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 35, no. 2, 1 February 2000 (2000-02-01), pages 187-203, XP004330413 ISSN: 0223-5234 page 188; figure 1; compounds 5G,6G page 190; figure 2; compound 9G page 202, paragraph 4.2	1,6,14, 15,18, 20,21

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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	RIBEIRO IZABELLA G ET AL: "Synthesis and antinociceptive properties of new structurally planned imidazo(1,2-a)pyridine 3-acylarylhydrazone derivatives" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 3, March 1998 (1998-03), pages 225-235, XP002545207 ISSN: 0223-5234 page 228; compound 2F paragraph [4.2.2]	1,6,14, 15,18, 20,21
X	JP 64 002058 A (CANON KK) 6 January 1989 (1989-01-06) page 7; compound 4A	1,6,14, 15
X	EP 0 259 099 A (MITSUI TOATSU CHEMICALS [JP]) 9 March 1988 (1988-03-09) page 13; compound 36	1,6,14, 15
X	MASANORI OZAKI, KAZUHIRO DAIDO, KATSUMI YOSHINO, MINEO NAKAGAWA, TAKAHASHI SUZUKI: "Nonlinear Optical Properties of Carbohydrazano-Pyrazole Derivatives with Excellent Transparency" JAPANESE JOURNAL OF APPLIED PHYSICS PART 2, vol. 31, no. 8A, 1 August 1992 (1992-08-01), pages 1068-1070, XP008111575 table 1; compound 8	1,6,14, 15
X	AN, YUE; ZHOU, GUAGHUA; MOU, PINGPING; ZHOU XIAOXIA; XING, YONGHENG, HU JIEHAN: "Synthesis and Characterisation of 5-(4-methoxyphenyl)-1H-pyrazole acyl hydrazones" JOURNAL OF LIAONING NORMAL UNIVERSITY (NATURAL SCIENCE EDITION), vol. 31, no. 1, March 2008 (2008-03), pages 78-81, XP008111597 page 78; compound 4C	1,6,14, 15
X	MASANORI OZAKI, KAZUHIRO DAIDO, KATSUMI YOSHINO, MINEO NAKAGAWA, TAKASHI SUZUKI: "Second-order Nonlinear Optical Properties in Hydrazone Derivatives" TECHNOLOGY REPORTS OF THE OSAKA UNIVERSITY, vol. 42, no. 2109, October 1992 (1992-10), pages 285-290, XP008111755 page 286; compound 8	1,6,14, 15

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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	SATO DAISY NAKAMURA ET AL: "Minimal inhibitory concentration and minimal bactericidal concentration determination of isonicotinic acid derivatives against Mycobacterium tuberculosis" REVISTA DO INSTITUTO ADOLFO LUTZ, vol. 58, no. 1, 1999, pages 25-31, XP008111797 ISSN: 0073-9855 page 27; compound 7 _____	1,6,14, 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/044556

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.: 16,17
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 all searchable 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.:

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.:
see annex

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

Continuation of Box II.2

Claims Nos.: 16,17

Since the meaning of the definition for R10 is defined neither in the corresponding claims nor in the description, no meaningful could be carried out for claims 16 and 17.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: claim 6 (full); 1, 14, 15, 18-23 (part)

compounds I where m, n and p are all 0

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2. claims: claims 2, 3, 5 (full); 1, 14, 15, 18-23 (part)

compounds I where m = 1, or where m = 0, n = 0 and p = 1

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3. claims: claims 4, 7-13 (full); 1, 14, 15, 18-23 (part)

compounds I where m = 0, n and p are both 1

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4. claims: claims 1, 14, 15, 18-23 (part)

compounds I where m = 0, n = 1 and p = 0

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5. claims: claims 24-41 (full)

compounds II (II-A and II-B)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/044556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008064342 A	29-05-2008	EP 2083819 A2	05-08-2009
WO 2007047394 A	26-04-2007	AR 061399 A1	27-08-2008
WO 2006127396 A	30-11-2006	US 2007123508 A1	31-05-2007
US 2002091148 A1	11-07-2002	NONE	
JP 64002058 A	06-01-1989	JP 2083715 C	23-08-1996
		JP 7117759 B	18-12-1995
EP 0259099 A	09-03-1988	DE 3787780 D1	18-11-1993
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		JP 1820334 C	27-01-1994
		JP 5029106 B	28-04-1993
		JP 63060455 A	16-03-1988
		US 4808507 A	28-02-1989