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(54) Title: PROCESS FOR THE SYNTHESIS OF 4-DIFLUOROMETHOXY-8-NITRO-1-FORMYL DIBENZO[B,D]FURAN-AN INTERMEDIATE FOR PDE IV INHIBITORS

(57) Abstract: The present invention relates to a process for preparing 4-difluoromethoxy-8-nitro-1-formyl dibenzo[b,d]furan, which is useful as an intermediate for preparing compounds with PDE4 inhibitory activity. The invention further provides a process for preparing a PDE4 inhibitor, such as oglemilast.



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INTERNATIONAL SEARCH REPORT

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A, CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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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, 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
A	WO 2004/037805 A (GLENMARK PHARMACEUTICALS LTD [IN]; BALASUBRAMANIAN GOPALAN [IN]; GHARA) 6 May 2004 (2004-05-06) Abstract; claims 1, 53-62; pages 51-52: intermediates 17-19 (= present compounds 3-6); pages 63-64: intermediates 47-50 (intermediate 50 = present compound 8). -----	1-18
A	WO 2004/089940 A (GLENMARK PHARMACEUTICALS LTD [IN]; GOPALAN BALASUBRAMANIAN [IN]; GHARA) 21 October 2004 (2004-10-21) cited in the application Abstract; claims 1, 80-82; pages 48-52: intermediate 1, steps 3-6 (step 6 product = present compound 8). ----- -/-	1-18



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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.
A	WO 2006/011024 A (GLENMARK PHARMACEUTICALS LTD [IN]; BALASUBRAMANIAN GOPALAN [IN]; GHARA) 2 February 2006 (2006-02-02) Claim 1; page 39: intermediate 1; page 41: intermediate 5; page 42: intermediate 6; page 45: intermediate 13. -----	1-18
A	WO 2006/040652 A (GLENMARK PHARMACEUTICALS S A [CH]; GOPALAN BALASUBRAMANIAN [IN]; GHARA) 20 April 2006 (2006-04-20) cited in the application Abstract; pages 16-17, schemes 1, IA; page 19, scheme II; page 23, scheme III; pages 29-30, example 6, method A; claims. -----	1-18
A	KEMP, D. S.; GALAKATOS, N. G.: "Peptide Synthesis by Prior Thiol Capture" J. ORG. CHEM., vol. 51, 1986, pages 1821-1829, XP002480480 Page 1822, scheme II; page 1826, preparation of 4-hydroxydibenzofuran (6) and 4-methoxydibenzofuran (7). -----	1-18
A	OLIVEIRA, A. M. A. G. ET AL.: "Synthesis of Psoralen Analogues Based on Dibenzofuran" HELV. CHIM. ACTA, vol. 86, 2003, pages 2900-2907, XP002480481 Page 2901, scheme 2; page 2902, scheme 3; pages 2904-2905, preparation of (3a) and (4a), -----	1-18
A	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY,, FRANKFURT-MAIN, DE; XP002480482 Database accession no. 104215 (Reaction ID) abstract & DEWAR; URCH: J. CHEM. SOC, 1957, page 345, -----	1-18
A	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002480483 Database accession no. 290633 (Reaction ID) abstract & SLOTTA; SOREMB: CHEM. BER., vol. 68, 1935, pages 2059-2063, ----- -/--	1-18

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002480484 Database accession no. 41000 (Reaction ID) abstract & RAO ET AL.: J. CHEM. SOC, vol. 127, 1925, page 557, -----	-1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IB2007/003698

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
wo 2004037805	A	06-05-2004	AT 380185 T 15-12-2007
			AU 2003269317 AI 13-05-2004
			BR 0314721 A 02-08-2005
			CA 2503015 AI 06-05-2004
			CN 1729181 A 01-02-2006
			EP 1554262 AI 20-07-2005
			ES 2298552 T3 16-05-2008
			JP 2006506379 T 23-02-2006
			KR 20050065624 A 29-06-2005
			MX PA05004432 A 23-11-2005
			US 2006178418 AI 10-08-2006
			ZA 200502969 A 22-02-2006
wo 2004089940	A	21-10-2004	AU 2004228453 AI 21-10-2004
			BR PI0409747 A 09-05-2006
			CA 2522023 AI 21-10-2004
			EP 1620429 AI 01-02-2006
			HR 20050944 A2 28-02-2006
			IS 8123 A 10-11-2005
			JP 2006522789 T 05-10-2006
			KR 20060017494 A 23-02-2006
			MA 27801 AI 01-03-2006
			MX PA05010948 A 31-05-2006
			NZ 542882 A 26-10-2007
wo 2006011024	A	02-02-2006	NONE
wo 2006040652	A	20-04-2006	AR 051933 AI 21-02-2007
			AU 2005293293 AI 20-04-2006
			CA 2583497 AI 20-04-2006
			EP 1799632 A2 27-06-2007