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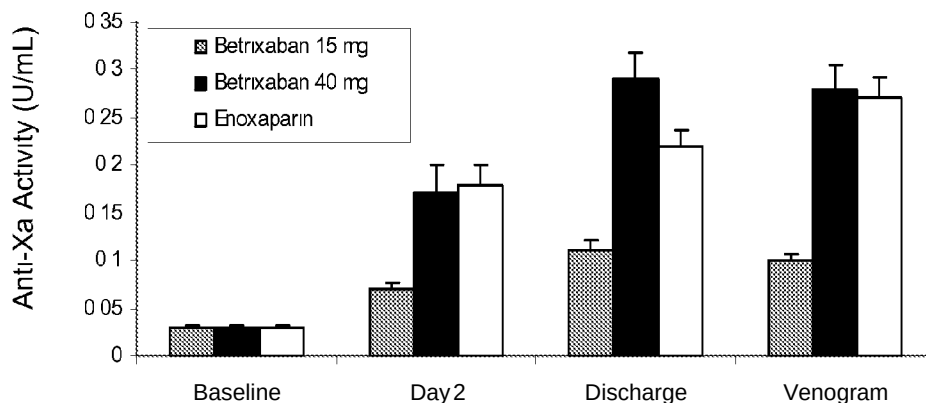
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[Continued on next page]

(54) Title: UNIT DOSE FORMULATIONS AND METHODS OF TREATING THROMBOSIS WITH AN ORAL FACTOR XA
INHIBITOR



(57) Abstract: Unit doses of factor Xa inhibitor compounds and methods of using these compounds for inhibiting blood coagulation in a human patient are taught herein. The unit dose of the factor Xa inhibitor compounds disclosed herein required to inhibit coagulation in a patient is lower than the unit dose required to obtain similar levels of coagulation inhibition in other animal models, such as rodents. Also taught are in vitro assays useful in predicting in vivo antithrombotic activity in humans.

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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

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, BIOSIS, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 376 515 B2 (ZHU BING-YAN [US] ET AL ZHU BING-YAN [US] ET AL) 23 April 2002 (2002-04-23) column 227, line 40 - line 45 paragraph [0843] column 62 - column 87 column 232 - column 498 -----	1-25
X	ZHANG P ET AL: "Design, synthesis, and SAR of anthranil amide-based factor Xa inhibitors with improved functional activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 4, 2004, pages 989-993, XP002414600 ISSN: 0960-894X the whole document ----- -/-	1-25



Further documents are listed in the continuation of Box C.



See patent family annex.

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- *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)
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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
- *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

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C(ConUnuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
X	ZHU ET AL: "Inhibitory effect of carboxylic acid group on hERG binding" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 16, no. 21, 1 November 2006 (2006-11-01), pages 5507-5512, XP005663480 ISSN: 0960-894X the whole document -----	1-25
X	ZHANG PENGLIE ET AL: "Design, synthesis, and SAR of anthranilamide-based factor Xa inhibitors incorporating substituted biphenyl P4 motifs." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 4, 23 February 2004 (2004-02-23), pages 983-987, XP002471265 ISSN: 0960-894X the whole document -----	1-25
X	WO 02/26731 A (COR THERAPEUTICS INC [US]; ZHU BING YAN [US]; HUANG WENRONG [US]; ZHAN) 4 April 2002 (2002-04-04) claims 1-16 -----	1-25
X	US 6 635 657 B1 (BEIGHT DOUGLAS WADE [US] ET AL) 21 October 2003 (2003-10-21) examples 278-280 -----	1-25
P, X	WO 2007/056517 A (MILLENNIUM PHARM INC [US]; GRANT CRAIG [GB]; KANTER JAMES P [US]; LANG) 18 May 2007 (2007-05-18) the whole document -----	1-25
Y	WO 02/18623 A (NOVARTIS FORSCHUNGSSTIFTUNG [CH]; ALBRECHT HUGO [CH]; HENGST ULRICH [C]) 7 March 2002 (2002-03-07) claims 14,15 -----	26-33
Y	US 5 153 176 A (ABE YOSHIHITO [JP] ET AL) 6 October 1992 (1992-10-06) column 28 -----	26-33

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

1. claims: 1-25

A method of inhibiting coagulation comprising the administration of compounds as claimed in claim 1-25 in specific dosages as well as unit dosage forms and pharmaceutical compositions comprising the compounds and the compounds PER SE.

2. claims: 26-33

An in vitro assay to determine whether a compound has in vivo antithrombotic activity comprising

- a) introducing a test compound into an in vitro sample of whole blood or plasma comprising tissue factor (TF) and a detectably-labeled thrombin substrate to form a test sample;
- b) determining the level of thrombin activity in the test sample by monitoring the cleavage of the detectably -labeled thrombin substrate in the test sample as a function of time;
- c) determining the level of thrombin activity in a control sample by monitoring the cleavage of the detectably-labeled thrombin substrate in the control sample as a function of time, wherein the control sample comprises whole blood or plasma comprising tissue factor (TF) and a detectably-labeled thrombin substrate;
- d) comparing the level of thrombin activity in the test sample and the control sample, wherein a lower level of thrombin activity in the test sample is an indication that the test compound has in vivo antithrombotic activity.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6376515	B2	23-04-2002	AT 311366 T 15-12--2005
		AU 4535301 A 12-09--2001	
		AU 5078301 A 12-09--2001	
		CA 2401778 A1 07-09--2001	
		DE 60115394 D1 05-01--2006	
		DE 60115394 T2 19-10--2006	
		DK 1259485 T3 10-04--2006	
		EP 1259485 A2 27-11--2002	
		ES 2254385 T3 16-06--2006	
		HK 1051539 A1 17-03--2006	
		WO 0164642 A2 07-09--2001	
		WO 0164643 A2 07-09--2001	
		US 2002002183 A1 03-01--2002	
WO 0226731	A	04-04-2002	AU 1128102 A 08-04-2002
			EP 1322637 A2 02-07-2003
us 6635657	B1	21-10-2003	US 2004029874 A1 12-02-2004
			US 2005282862 A1 22-12-2005
WO 2007056517	A	18-05-2007	AR 056787 A1 24-10-2007
			AU 2006311544 A1 18-05-2007
WO 0218623	A	07-03-2002	AU 1218402 A 13-03-2002
			CA 2420832 A1 07-03-2002
			EP 1315758 A2 04-06-2003
			JP 2004507471 T 11-03-2004
			US 2006177432 A1 10-08-2006
			US 2005037009 A1 17-02-2005
US 5153176	A	06-10-1992	JP 2094315 C 02-10-1996
			JP 4089498 A 23-03-1992
			JP 8013834 B 14-02-1996