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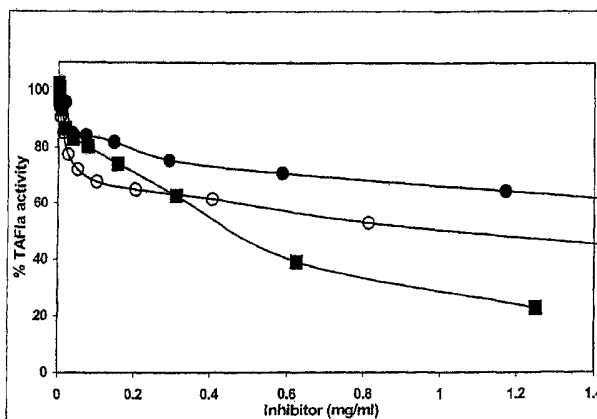
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[Continued on next page]

(54) Title: METHODS OF SCREENING FOR COMPOUNDS THAT MODULATE TAFIa ACTIVITY, COMPOUNDS, AND METHODS OF USING THE COMPOUNDS



(57) Abstract: Provided are methods of screening compounds for any aspirin-related activity other than TAFI inhibition, and also for non-inhibition of TAFI. Compounds identified by the screening methods can be used to treat, prevent or manage in a patient pain, fever, colon cancer, pancreatic cancer or an inflammatory, platelet aggregation, fibrinolytic or hemorrhagic disease or disorder. Also provided is a method of evaluating test compounds for TAFI inhibitory activity wherein the TAFI inhibitory activity of these test compounds is compared to the TAFI inhibitory activity of aspirin or its derivatives or metabolites. Further provided is a method of treating, preventing or managing in a patient, a hemorrhagic or thrombotic disease or disorder with high dose aspirin or aspirin derivatives or metabolites. Also contemplated is a method of treating, preventing or managing in a patient, pain, fever, colon cancer, pancreatic cancer or an inflammatory, platelet aggregation, fibrinolytic or hemorrhagic disease or disorder comprising administering aspirin or a derivative thereof or any other therapeutic having at least one desired therapeutic or prophylactic activity of aspirin to a patient in need thereof and administering to the patient a factor that promotes TAFIa activity, e.g. stabilized TAFIa, to ameliorate one or more adverse side effects of the therapeutic. Compounds identified by the methods of the invention are also provided.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/27070

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/00; A61K 38/28

US CL : 435/4; 514/12

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)

U.S. : 435/4; 514/12

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 practicable, search terms used)
STN (Medline, CAPLUS, PCTFULL), USPTO West, Google Scholar, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P	American Society of Hematology, 6-10 December 2002, Philadelphia, PA, entire document	1-9
A	US 20030035795 A1 (GARDELL et al.) 20 February 2003 (20.02.2003), entire document	1
A	WO 03/061653 (ALLERTON et al) 31 July 2003 (31.07.2003) entire document	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:		"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"B"	earlier application or patent published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/27070

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim 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. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation 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.: 1-9

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-9, as specifically drawn to the special technical feature of a method of identifying a compound which possess at least one aspirin activity and no TAFIa-inhibition.

Group 2, claim(s) 10, as specifically drawn to the special technical feature of a method of treating a disorder in a patient comprising administering a compound which possess one aspirin activity and no TAFIa inhibition.

Group 3, claim(s) 11 and 13-18, as specifically drawn to the special technical feature of a method of evaluating inhibition of TAFI activity by a test compound, in comparison with aspirin, salicylic acid, salicylic acid or gentisic acid.

Group 4, claim(s) 12, as specifically drawn to the special technical feature of a compound capable of inhibiting TAFI activity.

Group 5, claim(s) 19-23 and 29-32, as specifically drawn to the special technical feature of a method of treating or managing a thrombotic disorder.

Group 6, claim(s) 24-26 and 29-32, as specifically drawn to the special technical feature of a method of preventing a thrombotic disorder.

Group 7, claim(s) 27-32, as specifically drawn to the special technical feature of a method of reducing bleeding side-effects of aspirin in a patient comprising administering stabilized TAFIa.

Group 8, claim(s) 33, as specifically drawn to the special technical feature of a compound for inhibiting TAFI activity, having the chemical structure as shown in Claim 33.

Group 9, claim(s) 34, as specifically drawn to the special technical feature of a compound for inhibiting TAFI activity, having the chemical structure as shown in Claim 34.

Group 10, claim(s) 35, as specifically drawn to the special technical feature of a compound for inhibiting TAFI activity, having the chemical structure as shown in Claim 35.

Group 11, claim(s) 36-40 and 44-47, as specifically drawn to the special technical feature of a method of treating or managing a thrombotic disorder comprising administering an effective amount of a compound which inhibits TAFIa activity, wherein the compound has the chemical structure as shown in Claim 33.

Group 12, claim(s) 36-40 and 44-47, as specifically drawn to the special technical feature of a method of treating or managing a thrombotic disorder comprising administering an effective amount of a compound which inhibits TAFIa activity, wherein the compound has the chemical structure as shown in Claim 34.

Group 13, claim(s) 36-40 and 44-47, as specifically drawn to the special technical feature of a method of treating or managing a thrombotic disorder comprising administering an effective amount of a compound which inhibits TAFIa activity, wherein the compound has the chemical structure as shown in Claim 35.

Group 14, claim(s) 41-47, as specifically drawn to the special technical feature of a method of preventing a thrombotic disorder comprising administering an effective amount of a compound which inhibits TAFIa activity, wherein the compound has the chemical structure as shown in Claim 33.

Group 15, claim(s) 41-47, as specifically drawn to the special technical feature of a method of preventing a thrombotic disorder comprising administering an effective amount of a compound which inhibits TAFIa activity, wherein the compound has the chemical structure as shown in Claim 34.

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Group 16, claim(s) 41-47, as specifically drawn to the special technical feature of a method of preventing a thrombotic disorder comprising administering an effective amount of a compound which inhibits TAFIa activity, wherein the compound has the chemical structure as shown in Claim 35.

The inventions listed as Groups 1-16 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

A national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features, which define a contribution over the prior art. A national stage application containing claims to different categories of inventions will be considered to have unity of invention if the claims are drawn only to one of certain combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product; or
- (2) A product and process of use of said product; or
- (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
- (4) A process and an apparatus or means specifically designed for carrying out the said process; or
- (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process (see 37 CFR 1.475(b)-(d)). If there is no special technical feature, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

Accordingly, since the claims include different chemically unrelated products which do not share a common property or activity or a common structure, and multiple methods (identifying inhibitors of TAFI, non-inhibitors of TAFI, methods of treating a disorder and preventing a disorder) of using said products as delineated in the groups above, Groups 1-16 are not so linked as to form a single general inventive concept. Thus, a holding of lack of unity of invention is proper.