



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 38/00, G01N 33/53, 33/567, 33/566, 33/543, C07K 5/00, C07C 233/00, 239/00, 241/00, 255/00, 259/04, 331/00, 381/00</p>	A3	<p>(11) International Publication Number: WO 00/04868</p> <p>(43) International Publication Date: 3 February 2000 (03.02.00)</p>
<p>(21) International Application Number: PCT/US99/16848</p> <p>(22) International Filing Date: 23 July 1999 (23.07.99)</p> <p>(30) Priority Data: 60/093,883 23 July 1998 (23.07.98) US</p> <p>(71) Applicant: METAPHORE, INC. [US/US]; Besthesda Hospital, Suite 256, 3655 Vista Avenue, St. Louis, MO 63110 (US).</p> <p>(72) Inventors: MARSHALL, Garland, R.; 85 Arundel Place, Clayton, MO 63105 (US). ROSIK, Leonard, O.; 1458 West Highway U, Troy, MO 63379 (US). SCHALL, Otto, F.; Apartment 2, 533 Clara Avenue, St. Louis, MO 63112 (US). SLOMCZYNSKA, Urszula, J.; 407C Mid Trail Drive, Ballwin, MO 63011 (US).</p> <p>(74) Agents: BLOSSER, G., Harley et al.; Senniger, Powers, Leavitt & Roedel, One Metropolitan Square, 16th Floor, St. Louis, MO 63102 (US).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 4 May 2000 (04.05.00)</p>	
<p>(54) Title: LIBRARIES OF POLYHYDROXAMATES AND THEIR ANALOGS</p>		
<p>(57) Abstract</p> <p>A method of synthesizing desired polyhydroxamates and polyhydroxamate analogs is provided. The method comprises linking a first component of the desired polyhydroxamate or polyhydroxamate analog to a support matrix under conditions effective to form a first matrix-bound intermediate of said desired polyhydroxamate or analog, extending said first matrix-bound intermediate using reagents and reaction conditions effective to form one or more additional matrix-bound intermediates of said desired polyhydroxamate or analog, thereby forming a matrix-bound precursor of the desired polyhydroxamate or polyhydroxamate analog. Protective groups used during synthesis of the precursor are removed and the matrix-bound precursor is cleared from the support matrix, thereby synthesizing the desired polyhydroxamate or polyhydroxamate analog. Methods of making, screening and selecting libraries of candidate polyhydroxamates, the libraries and polyhydroxamates, polyhydroxamate analogs, their intermediates, and methods for using such compounds and their compositions are also disclosed.</p>		


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EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16848

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :Please See Extra Sheet. US CL :Please See Extra Sheet. According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p>B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : Please See Extra Sheet. 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) Please See Extra Sheet.</p>														
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X - Y</td> <td>US 4,987,253 A (BERGERON) 22 January 1991 (22/01/91), see entire document, especially Abstract and compounds 10, 11, 14, 22, 23 & 24.</td> <td>34-39 ---- 1-33, 40-56</td> </tr> <tr> <td>Y</td> <td>WO 96/26223 A1 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 29 August 1996 (29/08/96), see entire document, especially pages 1-3, and claims 1 & 2.</td> <td>1-56</td> </tr> <tr> <td>Y</td> <td>GORDON et al. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies and Future Directions. J. Med. Chem. 13 May 1994, Vol. 37, No. 10, pages 1385-1401, see entire article, especially pages 1388-1390.</td> <td>1-44</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X - Y	US 4,987,253 A (BERGERON) 22 January 1991 (22/01/91), see entire document, especially Abstract and compounds 10, 11, 14, 22, 23 & 24.	34-39 ---- 1-33, 40-56	Y	WO 96/26223 A1 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 29 August 1996 (29/08/96), see entire document, especially pages 1-3, and claims 1 & 2.	1-56	Y	GORDON et al. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies and Future Directions. J. Med. Chem. 13 May 1994, Vol. 37, No. 10, pages 1385-1401, see entire article, especially pages 1388-1390.	1-44
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<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>														
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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														
Date of the actual completion of the international search 08 DECEMBER 1999		Date of mailing of the international search report 02 FEB 2000												
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer  MAURIE E. GARCIA Telephone No. (703) 308-0196												

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International application No.
PCT/US99/16848

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	NGU et al. A New and Efficient Solid Phase Synthesis of Hydroxamic Acids. J. Org. Chem. 17 October 1997, Vol. 62, No. 21, pages 7088-7089, see entire article.	1-44
Y	GOLEBIOASKI et al. Solid Supported Synthesis of Hydroxamic Acids. Tet. Lett. 21 May 1998, Vol. 39, No. 21, pages 3397-3400, see entire article, especially page 3397.	1-44
Y	FURKA et al. General Method for Rapid Synthesis of Multicomponent Mixtures. Int. J. Peptide Protein Res. 1991, Vol. 37, pages 487-493, see entire article, especially page 487.	1-44
Y	BERGERON et al. Synthesis and Biological Evaluation of Hydroxamate-Based Iron Chelators. J. Med. Chem. 1991, Vol. 34, No. 11, pages 3182-3187, see Scheme 1 and Figure 1.	1-56
Y	DIONIS et al. Synthesis and Analytical Characterization of a Major Desferrioxamine B Metabolite. J. Org. Chem. 1989, Vol. 54, No. 23, pages 5623-5627, see entire article, especially Scheme II.	1-56
Y	BERGERON et al. Structural Alterations in Desferrioxamine Compatible with Iron Clearance in Animals. J. Med. Chem. 1992, Vol. 35, No. 25, pages 4739-4744, see entire article.	1-56

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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. 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 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 Extra 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.:

Remark on Protest The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16848

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 38/00; G01N 33/53, 33/567, 33/566, 33/543; C07K 5/00; C07C 233/00, 239/00, 241/00, 255/00, 259/04, 331/00, 381/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

435/7.1, 7.2; 436/501, 518; 530/323; 558/390, 391, 394, 446, 451, 452; 560/312; 562/621-623; 564/153

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

435/7.1, 7.2; 436/501, 518; 530/323; 558/390, 391, 394, 446, 451, 452; 560/312; 562/621-623; 564/153

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

EAST, STN (REGISTRY, CAPLUS, MEDLINE, BIOSIS, SCISEARCH)

Search terms: structure, polyhydroxamate, hydroxamate, combinatorial, library, polymer, solid support, resin, bead, synthesis

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

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

Group I, claim(s) 1-14, drawn to a method of synthesizing a polyhydroxamate.

Group II, claim(s) 15-31 and 45-56, drawn to a method relating to libraries, libraries and methods of use of library compounds.

Group III, claim(s) 32 and 33, drawn to a matrix bound polyhydroxamate.

Group IV, claim(s) 34 and 35, drawn to an N-nosyl intermediate of a polyhydroxamate.

Group V, claim(s) 36-44, drawn to a polyhydroxamate.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

In Group I:

Species 1: Polyhydroxamate comprises a molecular scaffold

Species 2: Polyhydroxamate is a compound of specific structure

In Group II:

Subgroup 1: One species should be selected from the following:

Species A: Polyhydroxamate comprises a molecular scaffold

Species B: Polyhydroxamate is a compound of specific structure

Subgroup 2: One species should be selected from the following:

Species C-H: Methods of use of library compounds

In Group V:

Species 1: Polyhydroxamate comprises a molecular scaffold

Species 2: Polyhydroxamate is a compound of specific structure

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The claims are deemed to correspond to the species listed above in the following manner:

In Group I:

Species 1: Polyhydroxamate comprises a molecular scaffold
Claims 6,7,8

Species 2: Polyhydroxamate is a compound of specific structure
Claim 9

In Group II:

Subgroup 1: One species should be selected from the following:

Species A: Polyhydroxamate comprises a molecular scaffold
Claims 30,31

Species B: Polyhydroxamate is a compound of specific structure
Claim 29

Subgroup 2: One species should be selected from the following:

Species C-H: Methods of use of library compounds

Species C: Pharmaceutical, Claims 45,51,52

Species D: Imaging agent, Claims 46,53

Species E: Radiodiagnostic agent, Claims 47,53

Species F: X-ray contrast agent, Claims 58,63

Species G: System for separating metals, Claims 49,54

Species H: Metal chelator, Claims 50,55,56

In Group V:

Species 1: Polyhydroxamate comprises a molecular scaffold
Claims 38,41

Species 2: Polyhydroxamate is a compound of specific structure
Claim 39

The following claims are generic:

In Group I: Claims 1-5,10-14

In Group II: Claims 15-28

In Group V: Claims 36,37,40,42-44

The inventions listed as Groups I-V do not relate to a single 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:

Groups I, III, IV and V lack unity with each other because the technical feature that links the claims in all of these groups is the polyhydroxamate compounds. These compounds are known in the art as evidenced by BERGERON (US 4,987,253). See Abstract and compounds 10, 11, 14, 22, 23 and 24.

Groups I, III, IV and V lack unity with Group II because the technical feature that links the claims in Group II is the polyhydroxamate library. A compound is a different inventive concept than a library. Furthermore, the compounds are known in the art as described above. Therefore the groups lack unity.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

PCT Rule 13.2 states that unity of invention shall be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features". It further defines "special technical feature" as "those technical features that define a contribution which each of the claimed inventions, claimed as a whole, makes over the prior art". For example, unity of invention is fulfilled if:

(a) all alternatives have a common property; and

(b) (i) a common structure is present, i.e. a significant structural element is shared by all alternatives, or

(b) (ii) in cases where the common structure can not be the unifying criterion, all alternatives belong to a recognized class of compounds in the art to which the invention pertains. (MPEP Section 1850).

For the species elections between molecular scaffolds and compounds of specific structure, none of parts a-c are fulfilled.

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All of the claimed species of compound do not have a (known) common property. Also, the compounds encompassed by the instant formulas do not all possess a common structure (no shared significant structural element). Further, all of the species do not belong to a recognized class of compounds in the art to which they pertain. For the forgoing reasons, election under these rules is proper and required.

For the species elections between methods of use of library compounds, each of the claimed uses is different and there is no unifying technical feature that links all of the uses. Furthermore, they each would require different steps, i.e. the compounds would be identified in a different manner, and then the compounds are used in a different manner, depending on the specific use.