Title: HETEROCYCLOIC COMPOUNDS, COMBINATORIAL LIBRARIES THEREOF AND METHODS OF SELECTING DRUG LEADS

Abstract: The present invention provides new heterocyclic compounds that have a relatively flexible backbone. These compounds may be used to produce new combinatorial libraries that will permit screening for lead compounds and selection of drug candidates for a variety of uses in human medicine, veterinary medicine and in agriculture. The members of libraries provided by the invention differ from each other (in addition to the conventional chemical and positional diversity attained by the different substituents on the ring) in two novel aspects: (a) the ring size; and (b) the chirality of the substituents on the ring. This leads to conformational diversity and flexibility that allows the selection of the most active compound, not only on the basis of the nature and proper arrangement of the substituents attained by the known chemical and positional diversity, but also based on the ability to undergo conformational complementarity attained by the conformational diversity. The present invention further provides combinatorial libraries comprising a plurality of the heterocyclic compounds of the present invention, and methods of screening the combinatorial libraries for compounds having a beneficial biological effect. The screening methods provided herein may be automated and/or computerized, for example by using a computer program to virtually screen the combinatorial libraries in order to identify compounds that are predicted to adopt bioactive conformations that will give rise to the desired biological effect.
### INTERNATIONAL SEARCH REPORT

#### A. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>IPC(7)</th>
<th>C07D 265/00</th>
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<tbody>
<tr>
<td>US CL</td>
<td>544/1, 63</td>
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</tbody>
</table>

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. | 544/1, 63 |

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 (structure search)

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<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</td>
<td>SCHMIDTZ E. Cyclische Peroxyde Aus Hydrazinverbindungen. Justus Liebig's Annalener Chemie 1960, Vol 635, pages 73-82.</td>
<td>1</td>
</tr>
</tbody>
</table>

* Further documents are listed in the continuation of Box C. See patent family annex.

- **"T"** Inter 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: 09 August 2003 (09.08.2003)

Date of mailing of the international search report: 10 OCT. 2003

Abandoned officer: Jon D. Epperson

Telephone No.: (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)
**INTERNATIONAL SEARCH REPORT**

**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 (in part)

**Remark on Protest**

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

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)
BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claim 1 (in part), drawn to a product described as a heterocyclic compound represented by the structure of formula 1 wherein A, B and D are all a bond; X and Y are both O; Z and Q are both -NH--; m and n are both 1 and a library that contains the "core structure" of said heterocyclic compound.

Groups 2-6, 901,200, claims 1 (in part) and 2-24, drawn to a product described as a heterocyclic compound an a library that encompasses said heterocyclic compound wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 1-24) read on their specifically elected compounds.

Groups 6,901,201-13,802,400, claims 25-42, drawn to a product described as a library that encompasses a "core structure" wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 25-42) read on their specifically elected compounds.

Groups 13,801,402-20,703,600, claims 43-52 (in part), drawn to a method of designing a combinatorial library wherein said library contains a "core structure" wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 43-52) read on their specifically elected compounds.

Groups 20,703,601-27,604,800, claims 43-52 (in part), drawn to a method of synthesizing a combinatorial library wherein said library contains a "core structure" wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 43-52) read on their specifically elected compounds.

Groups 27,604,801-34,506,000, claims 43-52 (in part), drawn to a method of screening a combinatorial library wherein said method uses a library that contains a "core structure" wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 43-52) read on their specifically elected compounds.

Groups 34,506,001-41,407,200, claims 53-57, drawn to a computer program product wherein said computer program product contains compounds with a "core structure" wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 53-57) read on their specifically elected compounds.

Groups 41,407,201-48,308,400, claims 58-64, drawn to a system for screening wherein said computer program for screening contains compounds with a "core structure" wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 58-64) read on their specifically elected compounds.
Groups 48,308,400-55,209,600, claims 65-68, drawn to a composition containing a compound represented by the structure in claim 1 wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 65-68) read on their specifically elected compounds.

Groups 55,209,600-62,110,800, claims 69-71, drawn to a method for treating a disease using a compound represented by the structure in claim 1 wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 69-71) read on their specifically elected compounds.

Groups 62,110,801-69,012,000, claims 71-73, drawn to a method for modulating a cellular component using a compound represented by the structure in claim 1 wherein A, B, D, X, Y, O, Z, Q, m and n are all independently varied as indicated in claim 1 (e.g., A, B, and D can be CH₃, C=O, a bond). The Examiner calculates that approximately 6,901,200 different core ring structures would be produced by formula 1 in claim 1. Applicant must indicate which cores structures (i.e., wherein A, B, D, X, Y, O, Z, Q, m and n are specifically defined) are elected and further must indicate which claims (i.e., 71-73) read on their specifically elected compounds.

Group 69,012,001, claims 74-75, drawn to a library of heterocyclic compounds.

The inventions listed as Groups 1-69,012,001 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:

The technical feature linking Groups 1-69,012,001 appears to be that they all represent, make and/or use compounds that have the structure of formula 1 in claim 1.


Consequently, Groups 1-69,012,001 are drawn to different special technical features because they are drawn to different products (e.g., they differ in respect to their properties, their use and the synthetic methodology for making them) and different methods (e.g., which are directed to different purposes, use different materials, rectify different method or process steps for the preparation of different product(s), screening of different characteristics, such as different binding affinities, different biochemical reaction conditions, etc. or lead to different final results). Therefore, the groups that describe these products and methods represent distinct subject matter. Art anticipating or rendering obvious each of the above-identified groups respectively would not necessarily anticipate or render obvious another group, because they are drawn to different inventions that have different distinguishing features and/or characteristics.

Therefore, the technical feature linking the inventions of groups 1-69,012,001 does not constitute a species technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

In addition, according to the guidelines in Section (f)(ii)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed sequences, the Markush group shall be regarded as being of similar nature when

(A) all alternatives have a common property or activity and
(B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or
(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The instant compounds of formula 1 are considered to be each separate inventions for the following reasons:

It is noted that each of the present claims has been presented in improper Markush format, as distinct products and/or distinct methods of using and or making and/or screening said products are improperly joined in the claims. Each compound of formula 1 is structurally and functionally distinct from each other and have a different special technical feature than each other (i.e., none of the compounds share a common "core" structure). As the products and methods encompassed by the claims do not share a special technical feature, the distinct products and methods may not be properly presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the invention of the elected group.
Specifically, the compounds do not meet the criteria of (A), common property or activity. Each compound behaves in a different way and has different physical and/or chemical properties as a result of their different "core" structures. Each compound cannot be substituted, one for the other, with the expectation that the same intended result will be achieved.

Further, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure, as each compound is unique. Accordingly, unity of invention between the compounds is lacking and each compound claimed is considered to constitute a special technical feature.

Consequently, the requirements for both part (a) and part (b) are NOT fulfilled. The alternatives do not have a common property and they do not have a common structure. Furthermore, the alternatives do not belong to any recognized class of compounds.

Finally, it is noted that different categories of invention may be considered to have unity in accordance with 37 CFR § 1.475 - Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage, cited in part below (especially sections (c) and (d)).

(a) An international and 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 (requirement of unity of invention). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression special technical features shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

A product and a process specially adapted for the manufacture of said product;

or

A product and process of use of said product; or

A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

A process and an apparatus or means specifically designed for carrying out the said process; or

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.

(c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.

(d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).

The instant international application contains multiple products and methods. However, the special technical feature that would join the first product (i.e., Group 1, claim 1) with a process of using and/or making said product is known in the art (see Shono et al., above) and, as a result, the feature that links these groups cannot be considered a special technical feature. Thus, the Groups that would fall within the categories of invention that would be considered to have unity of invention do NOT have unity of invention because the groups do not share a special technical feature.

Accordingly, groups 1-69,012,001 are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.