Abstract:

Methods and compositions are described that comprise pyrone analogs such as flavonoids and cyclodextrins including quercetin and quercetin derivatives and sulfonalkyl ether cyclodextrins. In some cases the compounds of the invention are administered with a therapeutic agent such as an analgesic. In some cases, treatment with the compositions of the invention can result in the modulation of central nervous system and/or fetal effects of substances. Methods and compositions are described for the modulation of efflux transporter activity to increase the efflux of drugs and other compositions out of a physiological compartment and into an external environment. In particular, the methods and compositions disclosed herein provide for the increase of efflux transporter activity at blood-brain, blood-CSF and placental-maternal barriers to increase the efflux of drugs and other compositions from physiological compartments, including central nervous system and fetal compartments.
A CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 8/73 (2008.04)

USPC - 424/70 13

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)
USPC 424/70 13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC 424/99 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
Dialog, Google, Google Patents, USPTO website
Search Terms: Flavonoid, quercetin, rutin, chromosome, pyrone, cyclodextrin, complex, inclusion, captisol, sulfotolyl, sulfobutylyl, analgesic

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 Y</td>
<td>US 2006/01 11308 A1 (ROBBINS) 25 May 2006 (25 05 2006) para [0003]-[0004], [0006]-[0009], [0045], [0046], [0054], [0100], [0123], [0133], [0199], [0244], [0261]-[0262], [0264], [0309], [0327]</td>
<td>134 and 136-161 91-93, 135</td>
</tr>
<tr>
<td>Y</td>
<td>US 2007/0155695 A1 (WIRTH et al) 5 July 2007 (05 07 2007) Abstract, para [0002], [0039], [0125], [0127], [0131], [0230], [0300], [0326], [0333]</td>
<td>1-40, 77-93, 129-133</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

Date of the actual completion of the international search
29 December 2008 (29 12 08)

Date of mailing of the international search report
14 JAN

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No 571-273-3201

Author of the search report

Form PCT/ISA/210 (second sheet) (April 2007)
INTERNATIONAL SEARCH REPORT

This international search 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. [D] 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. [D] Claims Nos because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6(4(a))

This International Searching Authority found multiple inventions in this international application, as follows:

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 additional fees, this Authority did not invite payment of additional fees

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. [X] 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 claims 1-40, 77-93 and 129-161

Remark on Protest
- [□] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee
- [□] The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation
- [□] No protest accompanied the payment of additional search fees

Form PCT/ISA/210 (continuation of first sheet (2)) (Apr 2007)
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 I, claims 1-40, 77-93 and 129-161 drawn to methods for producing a stable aqueous composition comprising a pyrone analog (such as a flavonoid), etc.

Group II, claims 41-76, 94-128 and 181-198, drawn to pharmaceutical compositions comprising a therapeutic agent, a pyrone analog, etc.

Group III, claims 162-180, drawn to methods of treating an animal comprising administering an animal in need treatment an effective amount of a pyrone analog, etc.

Group IV, claims 199-213, methods of preparing a solution of a pyrone analog, etc.

The inventions listed as Groups I-III 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 special technical feature share by the inventions of the claims of groups I-IV appears to be compositions having a pyrone analog, such as a flavonoid Flavonoids and their derivatives in pharmaceutical compositions are well known in the art, as are such compositions in combination with cyclodextrins, etc. See for example US 2006/0002866 A1 to Gilles et al (5 January 2006), abstract It will be readily understood that the methods for producing compositions comprising pyrone analogs of the claims of groups I and IV are distinct from the compositions of the claims of group II not made by said methods, or the methods of treating an animal comprising administering to an animal in need thereof a pyrone analog, etc. of the claim of group III. It will also be understood that the methods of the claims of group I are distinct from the methods of the claims of group IV in that the methods of the claims of group IV require further inclusion of a basic amino acid or a sugar-amine with the cyclodextrn, which is not required in the methods of the claims of group I.

Thus, the inventions listed as Groups I-IV 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 feature. According to PCT Rule 13 2, unity of invention exists only when the same or corresponding technical feature is snared by all claimed inventions.

In this case the first named invention and first named species that will be searched without additional fees is Group I represented by claims 1-40, 77-93 and 129-161.