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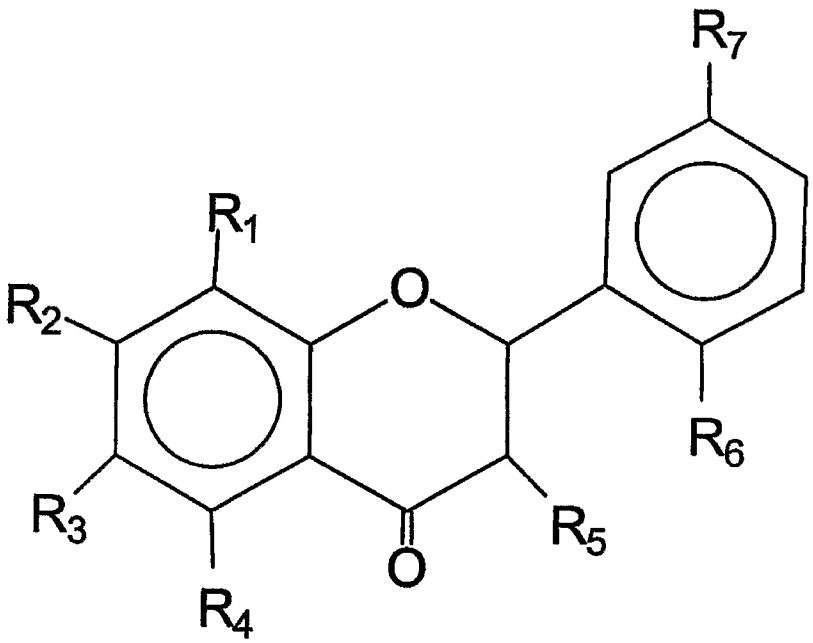
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[Continued on next page]

(54) Title: INCLUSION COMPOUNDS OF DIOCLEIN, FLORANOL OR ANALOGS WITH CYCLODEXTRIN AND THEIR USE FOR TREATING CARDIOVASCULAR DISEASES



(57) Abstract: The present invention relates to dioclein, floranol or natural or synthetic analogs; associated to inclusion compounds with the cyclodextrins and to controlled-release devices using biodegradable or non-biodegradable polymer, such as PLGA, PLA, PGA or mixtures thereof; their respective pharmaceutical compositions for the study and treatment of cardiovascular diseases and associated products. The substances developed in the present invention have been tested for their ability of inhibiting different isoforms of PDE' s. These are also the first substances, and their pharmaceutical compositions, in the therapeutical arsenal, capable of inhibiting, in a potent and selective manner, the isoform of type-1 (PDEl) phosphodiesterase. The present invention used two flavonoids as forms that inhibits phosphodiesterases of types 1 to 5: dioclein and floranol, as well as their analogs and pharmaceutical compositions, using the cyclodextrins and their inclusion compounds, as well as pharmaceutical and pharmacologically acceptable excipients.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/BR2006/000060

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61K47/40 A61K47/34 A61K9/16 A61P9/00

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)
A61K A61P

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, BIOSIS, EMBASE, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TOMMASINI SILVANA ET AL: "Improvement in solubility and dissolution rate of flavonoids by complexation with beta-cyclodextrin." JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS 16 APR 2004, vol. 35, no. 2, 16 April 2004 (2004-04-16), pages 379-387, XP002433373 ISSN: 0731-7085 abstract page 379, column 1 - page 380, column 1 page 386, column 2 ----- -/--	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"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)
"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
"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
"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	Date of mailing of the international search report
14 May 2007	11/06/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Nyeki, Agnes

INTERNATIONAL SEARCH REPORT

International application No
PCT/BR2006/000060

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CALDERONE VINCENZO ET AL: "Vasorelaxing effects of flavonoids: investigation on the possible involvement of potassium channels." NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY OCT 2004, vol. 370, no. 4, October 2004 (2004-10), pages 290-298, XP002433370 ISSN: 0028-1298 the whole document	1-13
Y	REZENDE BRUNO A ET AL: "Mechanisms involved in the vasodilator effect of the flavanol floranol in rat small mesenteric arteries." PLANTA MEDICA MAY 2004, vol. 70, no. 5, May 2004 (2004-05), pages 465-467, XP002433371 ISSN: 0032-0943 the whole document	1-13
Y	FREIBERG S ET AL: "Polymer microspheres for controlled drug release" INTERNATIONAL JOURNAL OF PHARMACEUTICS, AMSTERDAM, NL, vol. 282, no. 1-2, 10 September 2004 (2004-09-10), pages 1-18, XP004543665 ISSN: 0378-5173 the whole document	1-13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-13 (claims searched incompletely)

The subject-matter of Claims 1-13 is not clear in the sense of Article 6 PCT. Claims 1-13 relate to processes and to compositions obtained by these processes. However, Claim 1 does not define clear process steps and therefore do not allow the skilled man to determine the scope of this claim. The search was consequently limited to pharmaceutical compositions comprising the complex of the compound of Figure 1. and cyclodextrin and to the use of such a complex for the treatment of cardiovascular diseases. The controlled-release formulation of such a complex comprising PLGA, PGA or PLA has been also included in the scope of the search.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR2006/000060

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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. ☒ Claims Nos.: 1-13 (claims searched incompletely)
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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 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.