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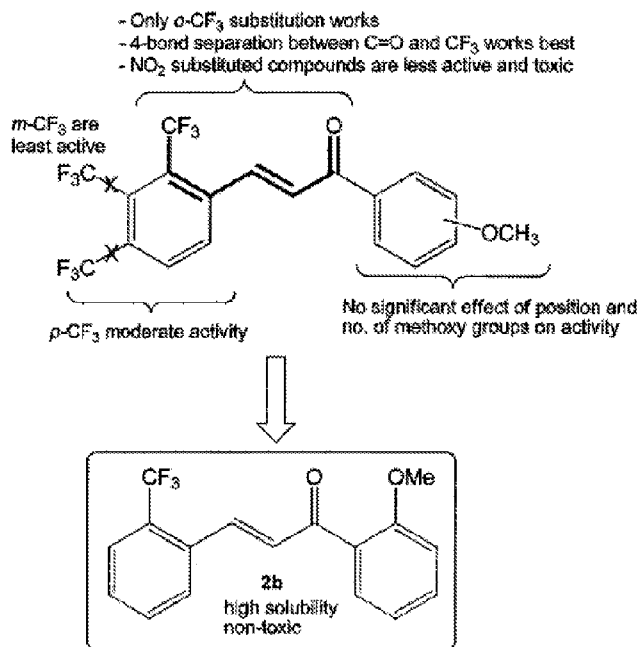
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[Continued on next page]

(54) Title: CHALCONE DERIVATIVES AS NRF2 ACTIVATORS



(57) Abstract: Compounds and methods for treating or preventing a disease, disorder or condition associated with an Nrf2-regulated pathway, including those associated with an autoimmune disease, comorbidity associated with diabetes, such as retinopathy and nephropathy, bone marrow transplant for leukemia and related cancers, bone marrow deficiencies, inborn errors of metabolism, and other immune disorders, oxidative stress, respiratory infection, ischemia, neurodegenerative disorders, radiation injury, neutropenia caused by chemotherapy, autoimmunity, and congenital neutropenic disorders, and for restoring a corticosteroid responsiveness, in a subject are provided.

Fig. 1



OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/026744**A. CLASSIFICATION OF SUBJECT MATTER***C07C 49/796(2006.01)i, C07C 205/31(2006.01)i, A61K 38/00(2006.01)i*

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)

C07C 49/796; A61K 31/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: chalcone, Nrf2, nuclear factor erythroid-2, ARE, autoimmune, neurodegenerative.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	KUMAR, VINEET et al., "Novel Chalcone Derivatives as Potent Nrf2 Activators in Mice and Human Lung Epithelial Cells", Journal of Medicinal Chemistry 2011, Vol. 54, 4147-4159. (03 May 2011) See the whole document, especially abstract & Table 1.	2-5
X	CHIARADIA, LOUISE DOMENEGHINI et al., "Synthesis and pharmacological activity of chalcones derived from 2,4,6-trimethoxyacetophenone in RAW 264.7 cells stimulated by LPS: Quantitative structure-activity relationships", Bioorganic & Medicinal Chemistry 2008, Vol. 16, 658-667.	2-3
A	See Table 2; Figure 3.	4-5
A	HENMI, KAYO et al., "Methoxy- and Fluoro-chalcone Derivatives Arrest Cell Cycle Progression and Induce Apoptosis in Human Melanoma Cell A375", Biol. Pharm. Bull. 2009, Vol. 32, 1109-1113. See Figure 1.	2-5
A	US 2003-0065039 A1 (KHARAZMI, ARSALAN et al.) 03 April 2003 See paragraph [0539].	2-5



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 application or patent 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 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

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Date of mailing of the international search report

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Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/026744

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003-0065039 A1	03.04.2003	None	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/026744**Box No. 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.: 10-58
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 10-58 relate to a method for treatment of the human body, which is a subject matter this International Searching Authority is not required to search under PCT Article 17(2)(a)i and Rule 39.1(iv).
2. ☒ Claims Nos.: 1, 6-9, 59-61
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 an extra sheet.
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 No. 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 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.

Box II.

The substituent R_8 in Formula (Ia) is defined twice in claim 1, each with different scope (' R_6 and R_7 R_8 are each independently selected from the group consisting of H, CF_3 , and NO_2 ' vs. ' R_8 is H'). Thus, in its current wording, the scope of R_8 is not clear. Consequently, the subject matter for which protection is sought is not clear in claim 1.

Claims 6 & 59-60 mention Formula (Ia), but it is not defined in each claim. (Even if the examiner infers its structure from the description, its substituent R_8 has a problem in its scope as stated in the above.) Claims 7-9 & 61, essentially dependent on either claim 6 or claim 60, have the same problem. Thus, the subject matter for which protection is sought is not clear for claims 6-9 & 59-61.

Consequently, no meaningful search could be carried out for claims 1, 6-9 & 59-61.

*Although claims 2-5 are dependent on claim 1, it is possible to define the subject matter of them because their chemical structures are fully presented.