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(54) Title: HETEROCYCLIC CYTOKINE INHIBITORS

(57) Abstract: The present invention provides low molecular weight compounds useful as cytokine inhibitors, and compositions thereof. In particular, compounds of the invention are useful as anti-inflammatory, anti-pain or anti-cancer agents. There are further provided methods for the preparation of such agents and their use in preventing or treating conditions mediated by cytokines.

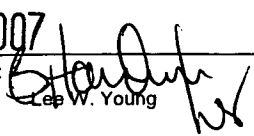


WO 2007/075896 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/48803

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/40 (2007.10); A61K 31/44 (2007.10) USPC - 514/356 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) IPC(8): A01N 43/40 (2007.10); A61K 31/44 (2007.10) USPC: 514/356 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched IPC(8): A01N 43/00, A61K 31/44 USPC: 514/183, 340 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST(USPT,PGPB,EPAB,JPAB); DialogPRO, GoogleScholar Search Terms: cytokine inhibitor, diabetes, triglyceride, fasting glucose, HbA1c, insulin, HOMA, bilirubin																
C. DOCUMENTS CONSIDERED TO BE RELEVANT																
<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>Y</td> <td>WO 2005/023761 A2 (BOMAN et al). 17 March 2005 (17.03.2005) entire document especially para[0164] and para[0040]</td> <td>1-79 and 85</td> </tr> <tr> <td>Y</td> <td>US 6,699,853 B2 (HARMSSEN et al.) 2 March 2004 (02.03.2004) entire document, especially col 3, ln 25-end</td> <td>1-79 and 85</td> </tr> <tr> <td>Y</td> <td>US 2004/0171659 A1 (MEDICHERLA et al.) 2 September 2004 (02.09.2004) entire document, especially para[0027], para[0055])</td> <td>69, 73-74 and 77</td> </tr> <tr> <td>Y</td> <td>US 2005/0256197 A1 (ENGBRETSON) 17 November 2005 (17.11.2005) entire document, especially para[0056]</td> <td>75</td> </tr> </tbody> </table>	Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	WO 2005/023761 A2 (BOMAN et al). 17 March 2005 (17.03.2005) entire document especially para[0164] and para[0040]	1-79 and 85	Y	US 6,699,853 B2 (HARMSSEN et al.) 2 March 2004 (02.03.2004) entire document, especially col 3, ln 25-end	1-79 and 85	Y	US 2004/0171659 A1 (MEDICHERLA et al.) 2 September 2004 (02.09.2004) entire document, especially para[0027], para[0055])	69, 73-74 and 77	Y	US 2005/0256197 A1 (ENGBRETSON) 17 November 2005 (17.11.2005) entire document, especially para[0056]	75	
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"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 5 November 2007 (05.11.2007)	Date of mailing of the international search report 20 DEC 2007															
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	Authorized officer:  Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 06/48803

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.:
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 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:
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 1, claims 1-79 and 85, drawn to compositions of cytokine inhibitors of formula I and methods of preparing and using the same.

Group 2, claim 80, drawn to method of preparing a compound of formula IV.

Group 3, claim 81, drawn to compound of formula VI.

Group 4, claim 82 and 84, drawn to compound of formula VII

(please see continuation in supplemental box)

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. 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.:
1-79 and 85

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 06/48803

continuation Box III Lack of unity:

Group 5, claim 83, drawn to compound of formula VIII.

The inventions listed as Groups 1-5 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:

Formulas I, IV, VI, VII and VIII are structurally distinct compounds. Specifically, formulas IV, VI, VII and VIII all lack the functionalized amido core of formula I. Formulas VI, VII and VIII lack the nitrogen and oxygen containing heterocyclic ring of formula IV. Formula VI has a carboxyl group lacking in formula VII and VIII. Formula VIII has a heterocyclic ring lacking in formula VII.

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 general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Species pertaining to Group 1:

The different species related to methods of use:

- a) methods of treating disorders mediated by cytokines
- b) methods to reduce level of cytokine
- c) method to reduce level of cytokine released from cell in response to pro-inflammatory stimulus
- d) method of inhibiting p38 activity
- e) method to reduce activity of pro-inflammatory mediator in subject
- f) method to reduce levels of C-reactive Protein or Rheumatoid Factor in blood
- g) method to increase HDL-level of subject
- h) method to decrease triglyceride-level in subject
- i) method to decrease fasting glucose-level in subject
- j) method of decrease HbA1c value in subject
- k) method to decrease insulin-level in subject
- l) method to decrease HOMA Insulin Resistance Index in subject
- m) method to increase indirect bilirubin-level in subject

The species listed above do not relate to a single general 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:

The methods of use are distinct methods of use which are pursued using different techniques and results are measured using different criteria.

The first named invention claims 1-79 and 85 limited to the compositions of formula I, methods of treating disorders mediated by cytokines with formula I and methods of preparing formula I.