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(54) Title: CYCLOOXYGENASE-2 SELECTIVE INHIBITOR COMPOUNDS COMPRISING NITRIC OXIDE ENHANCING GROUPS, COMPOSITIONS AND METHODS OF USE

(57) Abstract: The invention describes compositions and kits comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor comprising at least one nitric oxide enhancing group, or pharmaceutically acceptable salts thereof, and novel compositions comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor comprising at least one nitric oxide enhancing group, and, optionally, at least one nitric oxide enhancing compound and/or at least one therapeutic agent. The invention also provides methods for (a) treating inflammation, pain and fever; (b) treating gastrointestinal disorders and/or improving the gastrointestinal properties of COX-2 selective inhibitors; (c) facilitating wound healing; (d) treating renal and/or respiratory toxicities; (e) treating disorders resulting from elevated levels of cyclooxygenase-2; (f) improving the cardiovascular profile of COX-2 selective inhibitors; (g) treating diseases resulting from oxidative stress; (h) treating endothelial dysfunctions; (j) treating diseases caused by endothelial dysfunctions; (k) treating inflammatory disease states and/or disorders; (l) treating ophthalmic disorders; and (m) treating peripheral vascular diseases. The cyclooxygenase 2 selective inhibitors of the invention are 2(2-((2-chloro-6-fluorophenyl) amino)5-methylphenyl)acetic acid derivatives comprising at least one nitric oxide enhancing group. The nitric oxide enhancing groups are nitroxides and/or heterocyclic nitric oxide donors.

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## INTERNATIONAL SEARCH REPORT

International application No.

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## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

<i>C07C 229/42</i> (2006.01)	<i>A61P 7/02</i> (2006.01)	<i>C07C 271/02</i> (2006.01)
<i>A61K 31/04</i> (2006.01)	<i>A61P 9/14</i> (2006.01)	<i>C07D 271/04</i> (2006.01)
<i>A61K 31/136</i> (2006.01)	<i>A61P 25/28</i> (2006.01)	<i>C07D 271/08</i> (2006.01)
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<i>A61P 1/04</i> (2006.01)	<i>A61P 35/00</i> (2006.01)	<i>C07D 413/04</i> (2006.01)

US Cl. 540/202

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)

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)

Chemical Abstracts: substructure search based on formula (I) of claim 1

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003/103602 A2 (NITROMED, INC.) 18 December 2003 See whole document	1, 2, 4-22
Y	WO 2003/094924 A1 (MERCK & CO., INC.) 20 November 2003 See whole document	3
Y	WO 2001/045703 A1 (NITROMED, INC.) 28 June 2001 See whole document	3

 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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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## INTERNATIONAL SEARCH REPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5703073 A (GARVEY D. S. ET AL.) 30 December 1997 See abstract; column 8, lines 35-40; Scheme XI	3

**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:  
See Extra 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 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.:

**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.

**Supplemental Box Sheet 1**

(To be used when the space in any of Boxes I to VIII is not sufficient)

**Continuation of Box No: III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, consideration was given to those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

The International Searching Authority has found that there are different inventions as follows:

- Claims 1-22 (all in part). It is considered that diphenylamine compounds having  $-\text{NO}$  as the nitric oxide enhancing group comprises a first distinguishing feature.
- Claims 1-22 (all in part). It is considered that diphenylamine compounds having  $-\text{NO}_2$  as the nitric oxide enhancing group comprises a second distinguishing feature.
- Claims 1-22 (all in part). It is considered that diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_3$  and is any one of moieties (1)-(12) comprises a third distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_3$  and is any one of moieties (13)-(14) comprises a fourth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_3$  and is any one of moieties (15)-(16) comprises a fifth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_3$  and is moiety (17) comprises a sixth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_3$  and is moiety (18) comprises a seventh distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_3$  and is moiety (19) comprises an eighth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_6$  and is moiety (1) comprises a ninth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_6$  and is moiety (2) comprises a tenth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_6$  and is moiety (3) comprises an eleventh distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $V_6$  and is moiety (4) comprises a twelfth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $E$  as  $Y_4$  and is moiety (1) or (2) comprises a thirteenth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $E$  as  $Y_4$  and is moiety (3) or (4) comprises a fourteenth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $E$  as  $Y_4$  and is moiety (5) or (6) comprises a fifteenth distinguishing feature.
- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within  $R_e$  and  $R_f$  taken together or  $R_o$  and  $R_p$  taken together and is moiety (1) comprises a sixteenth distinguishing feature.

**Supplemental Box Sheet 2**

(To be used when the space in any of Boxes I to VIII is not sufficient)

**Continuation of Box No: III**

- Claims 1-22 (all in part). It is considered that the diphenylamine compounds where the nitric oxide enhancing group is contained within R<sub>e</sub> and R<sub>f</sub> taken together or R<sub>o</sub> and R<sub>p</sub> taken together and is moiety (2) comprises a seventeenth distinguishing feature.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

The only feature common to all of the claims is the presence of at least one nitric oxide enhancing group linked to a diphenylamine framework. However this feature is not novel in the light of WO 2003/103602 (NITROMED, INC.) 18 December 2003 (see Formulae (II)-(IX)).

Because the common feature does not satisfy the requirement for being a special technical feature it follows that it cannot provide the necessary technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention *a posteriori*.

As the search and examination for the additional inventions would not require more than negligible additional search and examination effort over that for the first invention and each other, no additional search fees were warranted.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2006/028856

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. These particulars are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2003/103602	AU	2003248642	CA	2487414	EP	1539134
		US	7220749	US	2004072899		
WO	2003/094924	AU	2003229005	EP	1505985	US	2005215611
WO	2001/045703	AU	25928/01	BR	0017037	CA	2393724
		CN	1434712	EP	1246621	MX	PA02006312
		NZ	519781	RU	2002119574	US	6649629
		US	7166618	US	2001041726	US	2003220228
		US	2007060571	ZA	200205707		
US	5703073	AU	54493/96	CA	2218555	EP	0821589
		US	6043232	US	6043233	US	6048858
		US	6051588	US	6057347	US	6083515
		US	6143734	US	6323234	US	6482846
		US	6790864	US	2003109520	US	2005038029
		US	2006276439	WO	1996/032946		
END OF ANNEX							