Title: TUMOR NECROSIS FACTOR INHIBITORS

Abstract: The present invention is directed to compounds that are allosteric inhibitors of tumor necrosis factor receptor I, compositions comprising such compounds, and methods of using such compounds and compositions thereof in the treatment of TNF-α mediated conditions.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61K 31/222(2006.01);C07C 69/035(2006.01)
USPC: 514/548;560/140
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)
U.S.: 514/548;560/140

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)
CAS ONLINE-Structure search. Combined with the search role THU (stands for therapeutic use)

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</td>
<td>TAMAGNONE et al., &quot;Synthesis and laxative properties of esters of 1,1,1-[bis(4hydroxyphenyl) (2-pyridyl)] ethane and related compounds&quot;, Chimie Therapeutique, November 1973 No. 6, pages 682-685, especially page 682.</td>
<td>3</td>
</tr>
</tbody>
</table>

□ Further documents are listed in the continuation of Box C. □ See patent family annex.

Date of the actual completion of the international search
07 August 2006 (07.08.2006)

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

Form PCT/ISA/210 (second sheet) (April 2005)
## INTERNATIONAL SEARCH REPORT

**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:

Please See Continuation 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 any 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.: 1-10

**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)) (April 2005)
BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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, claim(s) 1-10, drawn to compound I-9 and pharmaceutical method of use claims using I-9 as active ingredient.

Group II, claim(s) 11-14, drawn to a TNF-1R1 inhibitor that binds to the allosteric site of TNF-R1 with an affinity of 100 nM or greater.

Group III, claim(s) 21, drawn to a TNF-R1 inhibitor that binds in the above manner and also reduces the TNF-alpha mediated activation of NF-kappaB and p38 kinase.

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: Compound I-9 is old and thus the presumption of a single general inventive concept is destroyed. See the Tamagnone et al article at page 682 which teaches the compound of instant claim 3.