



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification<sup>6</sup> : <b>C07D 401/04, 403/04, 405/04, 401/14, 409/14, 403/14, 417/14, 239/42, A61K 31/44, 31/505</b></p>	<p><b>A3</b></p>	<p>(11) International Publication Number: <b>WO 98/24782</b></p> <p>(43) International Publication Date: 11 June 1998 (11.06.98)</p>								
<p>(21) International Application Number: PCT/US97/22390</p> <p>(22) International Filing Date: 4 December 1997 (04.12.97)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/032,128</td> <td>5 December 1996 (05.12.96)</td> <td>US</td> </tr> <tr> <td>60/050,950</td> <td>13 June 1997 (13.06.97)</td> <td>US</td> </tr> <tr> <td>Not furnished</td> <td>21 November 1997 (21.11.97)</td> <td>US</td> </tr> </table> <p>(71) Applicant (for all designated States except US): AMGEN INC. [US/US]; Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): SPOHR, Ulrike, D. [CA/US]; 2925 Glenwood Drive #305, Boulder, CO 80301 (US). MALONE, Michael, J. [US/US]; 6054H Gunbarrel Avenue, Boulder, CO 80301 (US). MANTLO, Nathan, B. [US/US]; 2538 Ginny Way, Lafayette, CO 80026 (US).</p> <p>(74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US).</p>	60/032,128	5 December 1996 (05.12.96)	US	60/050,950	13 June 1997 (13.06.97)	US	Not furnished	21 November 1997 (21.11.97)	US	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b></p> <p><i>With international search report.</i></p> <p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 27 August 1998 (27.08.98)</p>
60/032,128	5 December 1996 (05.12.96)	US								
60/050,950	13 June 1997 (13.06.97)	US								
Not furnished	21 November 1997 (21.11.97)	US								
<p>(54) Title: SUBSTITUTED PYRIMIDINE COMPOUNDS AND THEIR USE</p>										
<p>(57) Abstract</p> <p>Selected novel substituted pyrimidine compounds are effective for prophylaxis and treatment of diseases, such as TNF-<math>\alpha</math>, IL-1<math>\beta</math>, IL-6 and/or IL-8 mediated diseases, and other maladies, such as pain and diabetes. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving inflammation, pain, diabetes and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.</p>										

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<b>EE</b>	Estonia						

# INTERNATIONAL SEARCH REPORT

International Application No

PCI/US 97/22390

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C07D401/04 C07D403/04 C07D405/04 C07D401/14 C07D409/14  
 C07D403/14 C07D417/14 C07D239/42 A61K31/44 A61K31/505

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 6 C07D

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)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 97 33883 A (SMITHKLINE BEECHAM CORP.) 18 September 1997 cited in the application see page 20, compound 5; see page 23, compound 5 see claims 10,16,19,26 ---	1-6,13
X	US 4 438 117 A (S. C. CHERKOFISKY) 20 March 1984 see claims 1,7; table 1 ---	1-6,13
X	EP 0 130 046 A (ELI LILLY AND CO.) 2 January 1985 see claims 1,5,6 ----- -/-	1-6,13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search  <b>26 May 1998</b>	Date of mailing of the international search report  <b>03.07.98</b>
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Name and mailing address of the ISA 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	Authorized officer  <p style="text-align: center;">Hass, C</p>
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22390

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. TAKAHASHI ET AL.: HETEROCYCLES, vol. 22, no. 3, 1984, pages 581-4, XP002064343 see page 582, compound 8g ---	1-6
X	DE 33 19 843 A (A.-A. POURZAL) 6 December 1984 see page 4, compound 1; page 10, example 4 ---	1-6
X	US 5 077 142 A (Y. SAKON ET AL.) 31 December 1991 see columns 67, 68, compound no. 146 ---	1-6
X	DE 20 56 407 A (SANDOZ AG) 27 May 1971 see page 29, example 5c, starting compound 5,6-diphenylpyrimidin-2-ol ---	1-6
A	DE 12 71 116 B (FARBENFABRIKEN BAYER ) 27 June 1968 cited in the application see columns 3-8, table ---	1
A	G. B. BENNETT ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, 1978, pages 623-8, XP000612140 cited in the application see page 625, table III, compounds 3a-c, 4a-p; page 626, table IV, compounds 7a, 7b ---	1
A	H.-J. KABBE: LIEBIGS ANNALEN DER CHEMIE, vol. 704, 1967, pages 144-9, XP002065898 cited in the application see tables 1,2 ---	1
A	L. GIAMMANCO: ATTI DELLA ACCADEMIA DI SCIENZE LETTERE E ARTI DI PALERMO, vol. 27, 1968, pages 469-83, XP002064350 see page 474, compound (XVII) ---	1
A	L. GIAMMANCO ET AL.: ANNALI DI CHIMICA, vol. 60, no. 3, March 1970, pages 188-97, XP002064349 see page 189, compound VI ---	1
A	WO 96 03387 A (G. D. SEARLE & CO.) 8 February 1996 cited in the application see abstract; claims 1,10; examples ---	1,13
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/22390

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 97 16442 A (MERCK & CO., INC.) 9 May 1997 cited in the application see abstract; claims 1,17-20,22,39 ---	1,13
A,P	WO 97 12876 A (MERCK & CO., INC.) 10 April 1997 cited in the application see claims 1,21,22,24,26 ---	1,13
A	R. J. IFE ET AL.: BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 6, 1995, pages 543-6, XP002065899 cited in the application see page 544, scheme 1; page 545, table 1 -----	1,13

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/22390

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 14-31  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
2.  Claims Nos.: 1-11, 13  
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 II Observations where unity of invention is lacking (Continuation of item 2 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 14-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Claims Nos.: 14-31

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Claims Nos.: 1-11,13

In view of the large number of compounds, which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was based upon though not limited to the examples and tables given in the description, and to the general idea underlying the application. (see Arts. 6, 15 and Rule 33 PCT).

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/US 97/22390
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Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 9733883	A	18-09-1997	NONE	
US 4438117	A	20-03-1984	NONE	
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WO 9716442	A	09-05-1997	AU 1120897 A	22-05-1997
WO 9712876	A	10-04-1997	AU 7514396 A	28-04-1997