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60/291,965 21 May 2001 (21.05.2001) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
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19 December 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/059080 A3

(54) Title: TRISUBSTITUTED CARBOCYCLIC CYCLOPHILIN BINDING COMPOUNDS AND THEIR USE

(57) Abstract: The present invention relates to novel, non-peptidic small organic compounds having an affinity for cyclophilin (CyP)-type immunophilin proteins, and to pharmaceutical compositions comprising one or more of the said compounds. The invention further relates to the uses of these compounds and compositions for binding CyP-type proteins, inhibiting their peptidyl-prolyl isomerase activity, and for research, development, and therapeutic applications in a variety of medical disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/02538

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C275/42 C07C235/56 A61K31/166 A61K31/17 A61K31/18 A61K31/435 A61P25/00 A61P17/00 A61P33/00 A61P31/00 A61P27/00 A61P9/00 C07C233/66 C07C235/42 C07C311/21					
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 7 C07C 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) BEILSTEIN Data, EPO-Internal, PAJ, WPI Data, CHEM ABS Data					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category °	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	US 5 741 819 A (ILLIG CARL R ET AL) 21 April 1998 (1998-04-21) column 3, line 56 -column 4, line 10 column 8, line 38 - line 41 examples				1-63
P, X	WO 01 17953 A (GUILFORD PHARM INC) 15 March 2001 (2001-03-15) page 12, compounds 4,7				1-63
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in 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 document 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 another 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 16 October 2002			Date of mailing of the international search report 29/10/2002		
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 O'Sullivan, P		

INTERNATIONAL SEARCH REPORT

In ternational Application No
PCT/US 02/02538

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C335/32 C07C335/20 C07C243/38 C07C255/54 C07C335/18
C07C311/48 C07C233/76 C07C233/75 C07D295/12 C07C233/29
C07C337/06 C07D209/48 C07D213/74 C07D213/56 C07D231/12

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 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.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2769377 XP002216926 abstract & ISHIKAWA ET AL: KOGYO KAGAKU ZASSHI, vol. 71, 1968, pages 519-20, NIPPON KAGAKUKAI, TOKYO, JP ISSN: 0023-2734 --- -/--	1

Further documents are listed in the continuation of box C.

Patent family members are listed in 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 document 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 another 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

16 October 2002

Date of mailing of the international search report

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/02538

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 469096 XP002216927 abstract & HOPFF; KAEPELLI: CHEMIA (BUENOS AIRES), vol. 19, 1965, pages 228-232, ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 7503934 XP002216928 abstract & KRAFT, ARNO: JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS., no. 1, 1996, pages 77-80, CHEMICAL SOCIETY. LETCHWORTH., GB ISSN: 0022-4936 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2164585 XP002216929 abstract & TALLEC: ANNALES DE CHIMIE., vol. 3, no. 14, 1968, pages 347-357, Paris ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2777922 XP002216930 abstract & ISHIKAWA ET AL: KOGYO KAGAKU ZASSHI, vol. 71, 1968, pages 519-520, NIPPON KAGAKUKAI, TOKYO, JP ISSN: 0023-2734 ---	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2685041 XP002216931 abstract & ALEKSANDROW: ORG. POLUPROD. KRASITELI., vol. 1, 1959, pages 196-206, ---	1

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/02538

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2798758 XP002216932 abstract & ALEKSANDROW: ORG. POLUPROD. KRASITELI., vol. 1, 1959, pages 196-206, ---	1
X	CH 459 172 A (WANDER AG DR A) 15 July 1968 (1968-07-15) table 1 ---	1
X	US 2 593 563 A (HUFFMAN MAX N) 22 April 1952 (1952-04-22) example 11 ---	1
A	WO 98 37882 A (GUILFORD PHARM INC) 3 September 1998 (1998-09-03) page 1, line 5 - line 11 page 5, line 12 -page 9, line 25 ---	1-63
A	WO 99 62511 A (SQUIBB BRISTOL MYERS CO) 9 December 1999 (1999-12-09) page 4, line 20 -page 8, line 13 examples ---	1-63
A	US 6 054 452 A (BURAK ERIC S ET AL) 25 April 2000 (2000-04-25) column 2, line 57 -column 3, line 3 table 1 ---	1-63
A	US 3 876 797 A (BIEL JOHN HANS ET AL) 8 April 1975 (1975-04-08) column 1, line 36 -column 2, line 26 examples 7-9 -----	1-63

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/02538

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 29-45, 48-63 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 compounds.
2. Claims Nos.: 21-26, 46, 47
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

Continuation of Box I.2

Claims Nos.: 21-26, 46, 47

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the use of the compounds as therapeutic agents for the treatment of well-defined conditions as defined in the claims (ie modes of action, such as "blocking the permeability transition pore in mitochondria", claim 46, have not been searched). Claims 21-26,46, and 47 have therefore not been searched. Many novelty destroying compounds for present claim 1 have been found - some representative examples have been cited in the Search Report. Disclaiming these compounds would serve no purpose as they only represent a small fraction of the prior art.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/02538

Patent document cited in search report		Publication date	Patent family member(s)	Publication date			
US 5741819	A	21-04-1998	AU 722384 B2	03-08-2000			
			AU 6273696 A	30-12-1996			
			BR 9609216 A	27-07-1999			
			CA 2223727 A1	19-12-1996			
			CZ 9703813 A3	17-06-1998			
			EP 0831800 A1	01-04-1998			
			HU 9901086 A2	30-08-1999			
			JP 11508242 T	21-07-1999			
			NO 975740 A	26-01-1998			
			NZ 311410 A	28-07-2000			
			PL 323473 A1	30-03-1998			
			WO 9640100 A1	19-12-1996			
WO 0117953	A	15-03-2001	AU 7353300 A	10-04-2001			
			EP 1214293 A1	19-06-2002			
			WO 0117953 A1	15-03-2001			
CH 459172	A	15-07-1968	NONE				
US 2593563	A	22-04-1952	NONE				
WO 9837882	A	03-09-1998	AU 6181698 A	18-09-1998			
			EP 1001762 A1	24-05-2000			
			JP 2001513772 T	04-09-2001			
			WO 9837882 A1	03-09-1998			
			US 6242468 B1	05-06-2001			
			ZA 9800825 A	19-10-1998			
WO 9962511	A	09-12-1999	AU 743199 B2	24-01-2002			
			AU 4197599 A	20-12-1999			
			CA 2333997 A1	09-12-1999			
			EP 1087763 A1	04-04-2001			
			JP 2002516857 T	11-06-2002			
			WO 9962511 A1	09-12-1999			
			US 6096762 A	01-08-2000			
			US 6239146 B1	29-05-2001			
			US 6054452	A	25-04-2000	US 5846979 A	08-12-1998
US 6251892 B1	26-06-2001						
US 2001036942 A1	01-11-2001						
AU 723374 B2	24-08-2000						
AU 6181598 A	18-09-1998						
CA 2229707 A1	28-08-1998						
CN 1249681 T	05-04-2000						
EP 0993299 A1	19-04-2000						
HU 0001461 A2	28-04-2001						
JP 10310581 A	24-11-1998						
TW 458976 B	11-10-2001						
WO 9837885 A1	03-09-1998						
ZA 9801474 A	08-06-1998						
US 3876797	A	08-04-1975				AU 476015 B	09-09-1976
						AU 3648871 A	07-06-1973
			CA 961046 A1	14-01-1975			
			CH 547782 A	11-04-1974			
			CH 547780 A	11-04-1974			
			DE 2160973 A1	22-06-1972			
			FR 2117953 A5	28-07-1972			

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/US 02/02538
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3876797	A	GB 1365702 A	04-09-1974
		JP 58050983 B	14-11-1983
		SE 374359 B	03-03-1975
		US 3801624 A	02-04-1974
		US 3864386 A	04-02-1975
		US 3869492 A	04-03-1975
		US 3876798 A	08-04-1975
