

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 July 2004 (29.07.2004)

PCT

(10) International Publication Number
WO 2004/062653 A3

(51) International Patent Classification⁷: A61K 31/00,
31/4535, 31/138, 31/40, 31/55, A61P 37/00, 37/06

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(21) International Application Number:
PCT/US2004/000037

Declarations under Rule 4.17:

(22) International Filing Date: 5 January 2004 (05.01.2004)

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, 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, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/438,123 6 January 2003 (06.01.2003) US

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, 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, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(71) Applicant (for all designated States except US): WYETH [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ELLOSO, M., Merle [US/US]; 311 Spencer Road, Devon, PA 19333 (US). MITCHELL, Robert [US/US]; 26 Lenape Lane, Doylestown, PA 18901 (US). HARNISH, Douglas, C. [US/US]; 2715 Kutztown Road, Pennsburg, PA 18073 (US). ADELMAN, Steven, J. [US/US]; 342 Windy Run Drive, Doylestown, PA 18901 (US).

(74) Agent: WEBSTER, Darryl, L.; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,

(88) Date of publication of the international search report:
4 November 2004

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.

(54) Title: THE USE OF ESTROGEN RECEPTOR ALPHA MODULATORS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

(57) Abstract: The present invention provides methods of treating an autoimmune pathology in a mammal, comprising administering an agent with estrogen receptor agonist activity in particular a selective estrogen receptor modulator, to the mammal in an amount sufficient to decrease production of TH-1 and/or TH-2 cytokines. Also provided is a method of selecting compounds useful for the treatment of multiple sclerosis, comprising selecting a compound which has estrogen receptor agonist activity.

WO 2004/062653 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/000037

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7	A61K31/00 A61K31/4535 A61K31/138 A61K31/40 A61K31/55 A61P37/00 A61P37/06	
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 A61K A61P		
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) EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/85154 A (UNIV OREGON HEALTH SCIENCES ;OFFNER HALINA (US); US GOVERNMENT (US) 15 November 2001 (2001-11-15) abstract page 6, line 6 - page 7, line 30 page 12, line 11 - page 13, line 7 claims; examples I,IV -----	1-21,23, 25
X	WO 02/085374 A (UNIV CALIFORNIA ;VOSKUHLL RHONDA R (US)) 31 October 2002 (2002-10-31) abstract page 8, paragraph 34 - paragraph 35 claims; example 1 ----- -/--	1-21,23
<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		"I" 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 document 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		
Date of the actual completion of the international search 2 July 2004		Date of mailing of the international search report - 3. 09. 2004
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 Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/000037

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 724 879 A (LILLY CO ELI) 7 August 1996 (1996-08-07) whole document, in particular page 3, line 9 to page 4, line 6 -----	1-25
X	EP 0 664 123 A (LILLY CO ELI) 26 July 1995 (1995-07-26) the whole document -----	1-25
X	US 5 075 321 A (SCHREIBER ALAN D) 24 December 1991 (1991-12-24) the whole document -----	1-22
X	WO 96/05823 A (LILLY CO ELI) 29 February 1996 (1996-02-29) the whole document -----	1-25
X	EP 0 664 125 A (LILLY CO ELI) 26 July 1995 (1995-07-26) the whole document -----	1-25
X	EP 0 668 075 A (LILLY CO ELI) 23 August 1995 (1995-08-23) whole document, in particular page 8, lines 18-56 -----	1-25
X	EP 0 966 965 A (LILLY CO ELI) 29 December 1999 (1999-12-29) abstract page 3, line 56 - page 4, line 3; claims -----	1-22
X	APELGREN L D ET AL: "The effect of a selective estrogen receptor modulator on the progression of spontaneous autoimmune disease in MRL lpr/lpr mice" CELLULAR IMMUNOLOGY 1996 UNITED STATES, vol. 173, no. 1, 1996, pages 55-63, XP001190866 ISSN: 0008-8749 the whole document -----	1-22
A	EP 0 747 052 A (LILLY CO ELI) 11 December 1996 (1996-12-11) the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/000037

Box 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:

Although claims 1-25 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.
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 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 additional 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 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.:

1-25 (partially)

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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-25 (partially)

A method of treating an autoimmune pathology comprising administering an estrogen receptor alpha (ERalpha) agonist to a mammal in an amount sufficient to decrease production of TH-1 and/or TH-2 cytokines, wherein the ERalpha agonist is raloxifene.

Method of selecting compounds for the treatment of multiple sclerosis, comprising selecting an ERalpha agonist which is raloxifene.

2. claims: 1-25(partially)

A method of treating an autoimmune pathology comprising administering an estrogen receptor alpha (ERalpha) agonist to a mammal in an amount sufficient to decrease production of TH-1 and/or TH-2 cytokines, wherein the ERalpha agonist is selected from tamoxifen, idoxifene, droloxifen and toremifene.

Method of selecting compounds for the treatment of multiple sclerosis, comprising selecting an ERalpha agonist which is selected from tamoxifen, idoxifene, droloxifen and toremifene.

3. claims: 1-25(partially)

A method of treating an autoimmune pathology comprising administering an estrogen receptor alpha (ERalpha) agonist to a mammal in an amount sufficient to decrease production of TH-1 and/or TH-2 cytokines, wherein the ERalpha agonist is lasofoxifene.

Method of selecting compounds for the treatment of multiple sclerosis, comprising selecting an ERalpha agonist which is lasofoxifene.

4. claims: 1-25(partially)

A method of treating an autoimmune pathology comprising administering an estrogen receptor alpha (ERalpha) agonist to a mammal in an amount sufficient to decrease production of TH-1 and/or TH-2 cytokines, wherein the ERalpha agonist is bazedoxifene.

Method of selecting compounds for the treatment of multiple sclerosis, comprising selecting an ERalpha agonist which is bazedoxifene.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-25 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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/US2004/000037

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0185154	A	15-11-2001	AU 5984701 A	20-11-2001
			CA 2408935 A1	15-11-2001
			EP 1286664 A2	05-03-2003
			WO 0185154 A2	15-11-2001

WO 02085374	A	31-10-2002	US 2002183299 A1	05-12-2002
			EP 1397143 A1	17-03-2004
			WO 02085374 A1	31-10-2002

EP 0724879	A	07-08-1996	AU 708374 B2	05-08-1999
			AU 4916396 A	27-08-1996
			CA 2212232 A1	15-08-1996
			CN 1173819 A	18-02-1998
			CZ 9702465 A3	17-06-1998
			EP 0724879 A2	07-08-1996
			FI 973235 A	05-08-1997
			HU 9801829 A2	28-05-1999
			JP 10513470 T	22-12-1998
			NO 973609 A	11-09-1997
			WO 9624356 A1	15-08-1996
			ZA 9600897 A	05-08-1997

EP 0664123	A	26-07-1995	US 5521198 A	28-05-1996
			AU 699255 B2	26-11-1998
			AU 8153794 A	29-06-1995
			CA 2138509 A1	22-06-1995
			CN 1108102 A	13-09-1995
			CZ 9403206 A3	13-09-1995
			EP 0664123 A1	26-07-1995
			HU 71327 A2	28-11-1995
			IL 112031 A	22-12-1999
			JP 7215855 A	15-08-1995
			NO 944914 A	22-06-1995
			NZ 270164 A	22-08-1997
			US 6436958 B1	20-08-2002
			ZA 9410083 A	19-06-1996

US 5075321	A	24-12-1991	US 4902681 A	20-02-1990
			US 4908358 A	13-03-1990

WO 9605823	A	29-02-1996	US 5434166 A	18-07-1995
			AU 3368595 A	14-03-1996
			BR 9508732 A	11-11-1997
			CA 2198114 A1	29-02-1996
			EP 0769943 A1	02-05-1997
			JP 10505823 T	09-06-1998
			WO 9605823 A1	29-02-1996
			US 5530010 A	25-06-1996
			ZA 9506993 A	21-02-1997

EP 0664125	A	26-07-1995	US 5708009 A	13-01-1998
			AU 8154394 A	29-06-1995
			CA 2138513 A1	22-06-1995
			CN 1109884 A	11-10-1995
			CZ 9403227 A3	16-08-1995
			EP 0664125 A1	26-07-1995
			HU 72314 A2	29-04-1996
			JP 7242546 A	19-09-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/000037

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0664125	A		NO 944926 A	22-06-1995
			NZ 270184 A	29-07-1999
			US 5708010 A	13-01-1998
			ZA 9410096 A	19-06-1996
EP 0668075	A	23-08-1995	US 5492927 A	20-02-1996
			AU 701606 B2	04-02-1999
			AU 8153994 A	29-06-1995
			CA 2138457 A1	22-06-1995
			CN 1108096 A	13-09-1995
			CZ 9403228 A3	13-09-1995
			EP 0668075 A2	23-08-1995
			HU 71336 A2	28-11-1995
			IL 112029 A	28-10-1999
			JP 7215863 A	15-08-1995
			NO 944911 A	22-06-1995
			NZ 270187 A	27-07-1997
			RU 2146520 C1	20-03-2000
			US 5525624 A	11-06-1996
			ZA 9410085 A	19-06-1996
EP 0966965	A	29-12-1999	AU 753035 B2	03-10-2002
			AU 4819299 A	05-01-2000
			BR 9911224 A	20-02-2001
			CA 2333384 A1	23-12-1999
			CN 1305342 T	25-07-2001
			EP 0966965 A1	29-12-1999
			HR 20000860 A1	31-10-2001
			HU 0102383 A2	28-01-2002
			JP 2002518296 T	25-06-2002
			NO 20006086 A	30-11-2000
			PL 344841 A1	19-11-2001
			SK 18802000 A3	11-09-2001
			TR 200003713 T2	20-04-2001
			WO 9965306 A1	23-12-1999
			US 6353003 B1	05-03-2002
			ZA 200005884 A	22-10-2001
EP 0747052	A	11-12-1996	US 6545027 B1	08-04-2003
			AU 6175596 A	30-12-1996
			BR 9608585 A	05-01-1999
			CA 2223092 A1	19-12-1996
			EP 0747052 A2	11-12-1996
			JP 11507645 T	06-07-1999
			WO 9640137 A1	19-12-1996