

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number  
WO 02/009702 A3

(51) International Patent Classification<sup>7</sup>: A61K 31/404,  
A61P 27/06

(21) International Application Number: PCT/US01/24220

(22) International Filing Date: 27 July 2001 (27.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
200001916 28 July 2000 (28.07.2000) ES  
60/276,885 16 March 2001 (16.03.2001) US

(71) Applicants (for all designated States except US): **INSPIRE PHARMACEUTICALS, INC.** [US/US]; Suite 470, 4222 Emperor Boulevard, Durham, NC 27703 (US). **UNIVERSITY COMPLUTENSE DE MADRID** [ES/ES]; Avda. Seneca E-28040, Madrid (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PINTOR, Jesus, J.** [ES/ES]; c/o Francisco Silvela, 88 7 B, E-28002 Madrid (ES). **PERAL, Maria, A.** [ES/ES]; c/o Francisco Silvela, 88, 7 B, E-28002 Madrid (ES). **PETERSON, Ward, M.**

[US/US]; 332 Edinborough Drive, Durham, NC 27703 (US). **PLOURDE, Robert, Jr.** [US/US]; Suite 470, 4222 Emperor Boulevard, Durham, NC 27703 (US). **BROWN, Edward, G.** [US/US]; Suite 470, 4222 Emperor Boulevard, Durham, NC 27703 (US). **YERXA, Benjamin, R.** [US/US]; 3119 Birmanwood Road, Raleigh, NC 27607 (US).

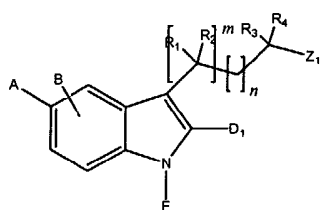
(74) Agent: **HALLUIN, Albert P.**; Howrey Simon Arnold & White LLP, 301 Ravenswood Avenue, Box 34, Menlo Park, CA 94025 (US).

(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, 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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

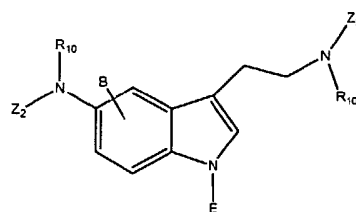
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

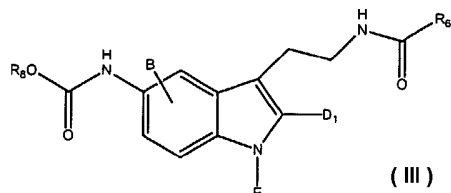
(54) Title: USE OF INDOLE DERIVATIVES FOR THE MANUFACTURE OF A MEDICAMENT FOR REDUCING INTRACULAR PRESSURE



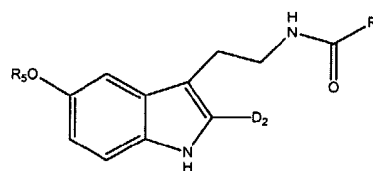
(I)



(II)



(III)



(IV)

(57) Abstract: The present invention provides a method of reducing intraocular pressure by administering pharmaceutical compositions comprising indole derivatives. The pharmaceutical compositions useful in this invention comprise indole derivatives and melatonin analogs of Formulae (I) (II) (III) (IV). A preferred embodiment is a method of lowering intraocular pressure using 5-(methoxycarbonylamino)-N-acetyltryptamine (5-MCA-NAT), also known as GR 135531, which has a prolonged duration of action and greater efficacy in lowering intraocular pressure compared to melatonin. The present invention further provides a method of treating disorders associated with ocular hypertension, and a method of treating various forms of glaucoma; the method comprises administering an effective dose of a pharmaceutical composition comprising an indole derivative with or without agents commonly used to treat such disorders.



WO 02/009702 A3



**Published:**

— *with international search report*

*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.*

**(88) Date of publication of the international search report:**

27 December 2002

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/24220

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/404 A61P27/06

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, CHEM ABS Data, EMBASE, BIOSIS, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 11685 A (WILSON ALAN BRIAN ;WYTHES MARTIN JAMES (GB); JONES SHIRLEY (GB); L) 25 April 1996 (1996-04-25) page 2, line 26 page 3, line 14 - line 23 claims 1,8,9,12,13 ---	1,7, 10-23
X	CURRENT EYE RESEARCH, vol. 7, no. 7, July 1988 (1988-07), pages 649-653, XP001098079 UK abstract page 649, left-hand column, line 1 -right-hand column, line 11 page 651, right-hand column, line 19 -page 652, right-hand column, line 25 --- -/--	1,5,6, 10-23

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.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

30 September 2002

Date of mailing of the international search report

07/10/2002

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  
 Economou, D

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/24220

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 89 01472 A (NELSON RES & DEV) 23 February 1989 (1989-02-23) the whole document claims 1-11 page 9, line 8 -page 12, line 26 ---	1-24
X	US 6 004 991 A (FOURTILLAN JEAN-BERNARD ET AL) 21 December 1999 (1999-12-21) cited in the application the whole document column 19, line 48 ---	1-24
P,X	PINTOR, J. ET AL.: "Involvement of melatonin MT3 receptors in the regulation of intraocular pressure in rabbits" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 416, no. 3, 30 March 2001 (2001-03-30), pages 251-254, XP001094033 the whole document ---	1-24
X	US 4 654 361 A (SAMPLES JOHN R ET AL) 31 March 1987 (1987-03-31) cited in the application the whole document -----	1,5,6, 10-23

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/24220

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9611685	A	25-04-1996	AT 210980 T	15-01-2002
			AU 3699795 A	06-05-1996
			BR 9504375 A	08-04-1997
			CA 2202484 A1	25-04-1996
			CA 2213241 A1	25-04-1996
			CN 1160347 A	24-09-1997
			CZ 9701118 A3	17-06-1998
			DE 69524780 D1	31-01-2002
			DE 69524780 T2	13-06-2002
			DK 785781 T3	18-03-2002
			WO 9611923 A1	25-04-1996
			WO 9611685 A2	25-04-1996
			EP 0804433 A1	05-11-1997
			EP 0785781 A2	30-07-1997
			ES 2167465 T3	16-05-2002
			FI 971527 A	11-04-1997
			FI 973382 A	18-08-1997
			HU 77317 A2	30-03-1998
			IL 115530 A	19-03-2001
			JP 2000080036 A	21-03-2000
			JP 9511755 T	25-11-1997
			JP 3096306 B2	10-10-2000
			NO 971606 A	08-04-1997
			PL 319868 A1	01-09-1997
			PT 785781 T	29-04-2002
			ZA 9508557 A	11-04-1997
			WO 8901472	A
AU 2309788 A	09-03-1989			
DK 42490 A	17-04-1990			
EP 0375726 A1	04-07-1990			
KR 9106124 B1	13-08-1991			
NO 900790 A ,B,	26-03-1990			
WO 8901472 A1	23-02-1989			
US 6004991	A	21-12-1999	FR 2737725 A1	14-02-1997
			AT 218547 T	15-06-2002
			AU 6823696 A	05-03-1997
			CN 1196049 A	14-10-1998
			DE 69621626 D1	11-07-2002
			EP 0851855 A1	08-07-1998
			WO 9706140 A1	20-02-1997
			JP 11510804 T	21-09-1999
			US 6140372 A	31-10-2000
			ZA 9606751 A	03-11-1997
			US 4654361	A