

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 March 2004 (04.03.2004)

PCT

(10) International Publication Number
WO 2004/018475 A3

(51) International Patent Classification⁷: **C07D 487/04**,
A61K 31/404, A61P 35/00, C07D 209/42, 209/08

(21) International Application Number:
PCT/US2003/025772

(22) International Filing Date: 15 August 2003 (15.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/224,979 20 August 2002 (20.08.2002) US

(71) Applicant: **SRI INTERNATIONAL** [US/US]; 333
Ravenswood Avenue, Menlo Park, CA 94025 (US).

(72) Inventors: **JONG, Ling**; 681 Endicott Drive, Sunnyvale,
CA 94087 (US). **CHAO, Wan-Ru**; 1510 Oriole Avenue,
Sunnyvale, CA 94087 (US).

(74) Agent: **REED, Dianne, E.**; Reed & Eberle LLP, Suite 210,
800 Menlo Avenue, 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, 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, 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.

(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, 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).

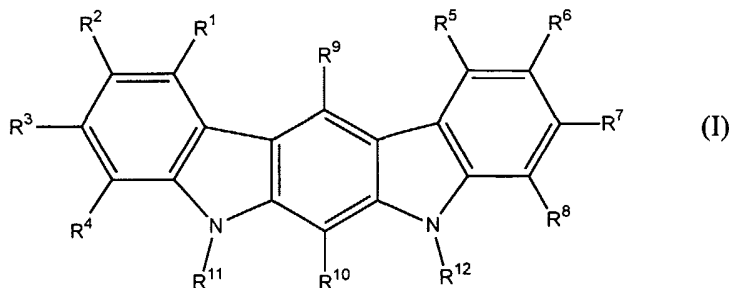
Published:

- 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

(88) Date of publication of the international search report:
1 April 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: ANALOGS OF INDOLE-3-CARBINOL METABOLITES AS CHEMOTHERAPEUTIC AND CHEMOPREVENTIVE AGENTS



(57) Abstract: Novel compounds useful as chemotherapeutic and chemopreventive agents are provided. The compounds are analogs of indole-3-carbinol metabolites wherein the structures and substituents of the compounds are selected to enhance the compounds' overall efficacy, particularly with respect to therapeutic activity, oral bioavailability, long-term safety, patient tolerability, and therapeutic window. The compounds are useful not only in treatment of cancer but also in prevention of cancer. One preferred class of the novel

compounds have the structure of formula (I), wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² are defined herein. Pharmaceutical compositions are provided as well, as are methods of synthesis and use.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/25772

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/404 A61P35/00 C07D209/42 C07D209/08

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 C07D 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)

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	DAVID STC. BLACK ET AL.: "Synthesis of indolo[3,2-b]carbazoles from 4,6-dimethoxyindole and aryl aldehydes" TETRAHEDRON, (INCL TETRAHEDRON REPORTS), vol. 51, no. 43, - 1995 pages 11801-11808, XP002265921 OXFORD GB * compounds 10 a-d * --- -/--	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.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 December 2003

Date of mailing of the international search report

12/02/2004

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

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 03/25772

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVID ST. C. BLACK ET AL.: "Calix[3]indoles, new macrocyclic tris(indolylmethylene)compounds with 2,7-linkages" CHEMICAL COMMUNICATIONS - CHEMCOM., vol. 10, - 1993 pages 819-821, XP002265922 ROYAL SOCIETY OF CHEMISTRY., GB ISSN: 1359-7345 * page 820, compound 12 *	14
X	ULF PINDUR ET AL.: "Reaktivität und Reaktionswege von methylsubstituierten Bisindolylcarbenium-Ionen" JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 24, no. 1, - 1987 pages 159-163, XP002265923 HETEROCORPORATION. PROVO., US ISSN: 0022-152X * page 161 and 163: compound 15 and 16 *	14
X	CHEMICAL ABSTRACTS, vol. 82, no. 17, 28 April 1975 (1975-04-28) Columbus, Ohio, US; abstract no. 111897k, HINO, TOHRU ET AL.: "Reaction of skatole with iodine in the presence of thiourea." XP002265931 & CHEM. PHARM. BULL., vol. 22, no. 11, - 1974 pages 2728-2731, -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 82:111897 XP002265933 compound with RN 55132-21-3	14

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/25772

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 80, no. 11, 18 March 1974 (1974-03-18) Columbus, Ohio, US; abstract no. 59818c, HINO, TOHRU ET AL.: "Preparation of 3-substituted 2-indolinethiones via diindolyl disulfides. Reaction of 3-substituted indoles with sulfur monochloride." XP002265932 abstract & CHEM. PHARM. BULL., vol. 21, no. 12, - 1973 pages 2739-2748, -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 80:59818 XP002265934 compound with RN 51206-69-0	14
X	ALPARSLAN AYGÜN ET AL.: "Synthesis and biological evaluation of structural variants of carbazoquinocin C" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 40, no. 3, - 2003 pages 411-417, XP002265924 * page 412, compound 24 and 25 *	25
X	WO 02 36561 A (SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S..A.) 10 May 2002 (2002-05-10) * example 2/11; claim 1, 10 *	25
X	GREGOR WILLE ET AL.: "Malassezin- a novel agonist of the arylhydrocarbon receptor from the yeast Malassezia furfur" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 4, - 2001 pages 955-960, XP002265925 * page 956, figure 1 *	25
X	ALLESSANDRA NAPOLITANO ET AL.: "Oxidation chemistry of 5,6-dihydroxy-2-methylindole" TETRAHEDRON, (INCL TETRAHEDRON REPORTS), vol. 49, no. 40, - 1993 pages 9143-9150, XP002265926 OXFORD GB * page 9145 and 9148: compound 7 *	25

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/25772

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTHONY H. JACKSON ET AL.: "Electrophilic substitution in indoles. Part 15. The reaction between methylenedi-indoles and p-nitrobenzenediazonium fluoroborate." JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., vol. 11, - 1987 pages 2543-2551, XP002265927 CHEMICAL SOCIETY. LETCHWORTH., GB ISSN: 0300-922X * page 2545 and 2549: compound 18a *	25
X	C. K. LAU ET AL.: "Reductive deoxygenation of aryl aldehydes and ketones and benzylic, allylic, and tertiary alcohols by ZnI₂-NaCNBH₃" JOURNAL OF ORGANIC CHEMISTRY., vol. 51, no. 15, - 1986 pages 3038-3043, XP002265928 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 * page 3040, compound 12 *	25
X	SIEGFRIED HÜNIG ET AL.: "Synthese vinyloger und azavinyloger Redoxsysteme mit Indolylresten als Endgruppen" JUSTUS LIEBIGS ANNALEN DER CHEMIE., vol. 6, - 1976 pages 1039-1059, XP002265929 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0075-4617 * page 1042 and 1052: compound 2 *	25
X	HENNING VON DOBENECK ET AL.: "Zur Chemie des Indols, VI. Alpha.beta'-Diindolylmethane und -methene. Der Urorosein-Chromophor" CHEMISCHE BERICHTE., vol. 102, no. 4, - 1969 pages 1347-1356, XP002265930 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0009-2940 * page 1349 and 1352: compound 4 *	25
A	WO 98 50357 A (THE TEXAS A & M UNIVERSITY SYSTEM) 12 November 1998 (1998-11-12) claims 15,20,25	1,44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/25772

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 60-123 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 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/25772

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0236561	A	10-05-2002	IT RM20000569 A1	03-05-2002
			AU 8439201 A	15-05-2002
			BR 0115139 A	30-09-2003
			CA 2427565 A1	10-05-2002
			CZ 20031178 A3	12-11-2003
			EP 1337511 A1	27-08-2003
			WO 0236561 A1	10-05-2002
			SK 5352003 A3	04-11-2003
WO 9850357	A	12-11-1998	US 5948808 A	07-09-1999
			AT 228502 T	15-12-2002
			AU 9102198 A	27-11-1998
			DE 69809726 D1	09-01-2003
			DE 69809726 T2	21-08-2003
			EP 0971890 A2	19-01-2000
			WO 9850357 A2	12-11-1998