

(51) International Patent Classification:
A61K 31/497 (2006.01)(21) International Application Number:
PCT/US2011/064474(22) International Filing Date:
12 December 2011 (12.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/422,554 13 December 2010 (13.12.2010) US
61/471,395 4 April 2011 (04.04.2011) US(71) Applicant (for all designated States except US): **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 12th Floor, Oakland, California 94607 (US).

(72) Inventors; and

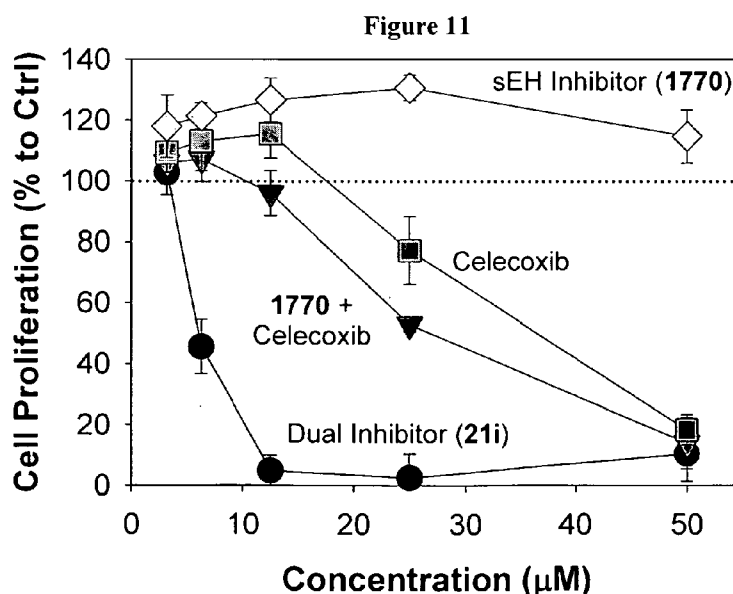
(75) Inventors/Applicants (for US only): **HAMMOCK, Bruce D.** [US/US]; Davis, California (US). **HWANG, Sung Hee** [KR/US]; Davis, California (US). **WAGNER, Karen M.** [US/US]; Davis, California (US). **MORISSEAU, Christophe** [FR/US]; West Sacramento, California (US). **WECKSLER, Aaron T.** [US/US]; Davis, California (US). **ZHANG, Guodong** [CN/US]; 1111 J Street, Apartment 79, Davis, California 95616 (US).(74) Agents: **TRIMBLE, Alexander R.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, California 94111 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,

[Continued on next page]

(54) Title: PYRAZOLE INHIBITORS OF COX-2 AND sEH



(57) **Abstract:** The present invention provides compounds and compositions, e.g., a series of compounds wherein a 1,5-bi-arylpyrazole group is conjugated to a urea group by a noncleavable covalent chain, that are useful as dual COX-2/sEH inhibitors. The activity of these compounds was demonstrated using a lipopolysaccharide (LPS) induced model of pain in the rat. The compounds of the present invention demonstrated superior anti-allodynic activity as compared to the same dose of celecoxib, i.e., a COX-2 inhibitor, also as compared to the same dose of t-AUCB, i.e., a sEH inhibitor, and also as compared to the co-administered same dose of both celecoxib and t-AUCB. The dual inhibitors of the present invention demonstrate enhanced in vivo anti-allodynic activity in a nociceptive behavior assay.



UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

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

10 April 2014

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/64474

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/497 (2012.01)

USPC - 514/254.05

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(8) - A61K 31/497 (2012.01)

USPC - 514/254.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/254.05, 252.05, 341, 563, 613 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest, Google Patent, Google Scholar, WIPO (pyrazole, sEH, COX, biarylpyrazole, inhibitor, urea, diaryl pyrazole, benzenesulfonamides, ureido, methanesulfonyl, without, inhibiting, activity, monitoring, fluorescence, umbilical, cell, proliferation)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 6,156,781 A (TALLEY, et al.) 05 December 2000 (05.12.2000) entire document, especially col 1, ln 15-19; col 2, ln 46-50; col 4, ln 66-col 5, ln 1; col 11, ln 4-6, 37-38, 66-col 12, ln 35; col 34, ln 56-66; col 41, ln 1-16; col 95, ln 66-col 96, ln 2 and col 97, ln 33-39.	1-3, 9, 14-16 ----- 4-8, 10-13, 17-23
Y	US 2005/0209297 A1 (SANNER, et al.) 22 September 2005 (22.09.2005) entire document, especially para[0007]-[0011] and [0466].	4-8
Y	US 2009/0227588 A1 (FLECK, et al.) 10 September 2009 (10.09.2009) entire document, especially para[0003], [0020] and [0656].	10-13
Y	US 2009/0326039 A1 (HAMMOCK, et al.) 31 December 2009 (31.12.2009) entire document, especially para[0008], [0087], [0106], [0111] and claim 92.	17, 19-22
Y	US 2005/0197338 A1 (HUANG, et al.) 08 September 2005 (08.09.2005) entire document, especially	18, 23
Y	US 2006/0178347 A1 (HAMMOCK, et al.) 10 August 2006 (10.08.2006) entire document, especially para[0028] and [0033].	13
Y	US 2008/0207699 A1 (HOELZEMANN, et al.) 28 August 2008 (28.08.2008) entire document, especially para[0045], [0076] and [0210]-[0211].	22

☐ Further documents are listed in the continuation of Box C.

* 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 application or patent 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

27 March 2012 (27.03.2012)

Date of mailing of the international search report

10 APR 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774