(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2003 (22.05.2003)

PCT

(10) International Publication Number
WO 03/041715 A1

(51) International Patent Classification[7]: A61K 31/5513, C07D 243/14, 401/04, 401/06, 403/04, 405/04, 407/04, 409/04, A61P 35/00, 37/02

(21) International Application Number: PCT/US02/36208

(22) International Filing Date:
13 November 2002 (13.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/331,235 13 November 2001 (13.11.2001) US

(71) Applicant *(for all designated States except US)*: **3-DIMENSIONAL PHARMACEUTICALS, INC.** [US/US]; Three Lower Makefield Corporate Center, 1020 Stony Hill Road, Suite 300, Yardley, PA 19067 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LU, Tianbao** [US/US]; 606 Monticello Lane, Kennett Square, PA 19348 (US). **LAFRANCE, Louis, V., III** [US/US]; 936 Cedarwood Avenue, West Chester, PA 19380 (US). **PARKS, Daniel, J.** [CA/US]; 106 North Severgn Drive, Exton, PA 19341 (US). **MILKIEWICZ, Karen, L.** [US/US]; 408 Cadwalader Circle, Exton, PA 19341 (US). **CALVO, Raul, R.** [US/US]; 72 Orchard Court, Royersford, PA 19468 (US). **CUMMINGS, Maxwell, David** [CA/US]; 659 West Valley Road, Wayne, PA 19087 (US). **KIM, Alexander, J.** [US/US]; 4708 Oxford Avenue, Philadelphia, PA 19124 (US). **GRASBERGER, Bruce, L.** [US/US]; 335 Meadowview Drive, Trappe, PA 19426 (US). **CARVER, Theodore, E., Jr.** [US/US]; 276 Meadowlake Drive, Downingtown, PA 19335 (US).

(74) Agents: **COVERT, John, M.** et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (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, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

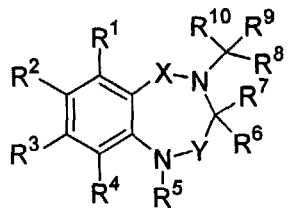
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, 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*

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 03/041715 A1

(54) Title: SUBSTITUTED 1,4-BENZODIAZEPINES AND USES THEREOF FOR THE TREATMENT OF CANCER



(I)

(57) Abstract: The present invention is directed to novel 1,4-benzodiazepines, pharmaceutical compositions thereof, and the use thereof as inhibitors of HDM2-p53 interactions. Compounds have formula (I) or a solvate, hydrate or pharmaceutically acceptable salt thereof; wherein: X and Y are independently -C(O)-, CH_2- or -C(S)-; R^1, R^2, R^3, R^4, R^7, R^8, R^b, R^c, R^d and M are defined herein, R^5 is hydrogen, alkyl cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroaryl, carboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl or alkylaminocarbonylalkyl; R^6 is cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, aralkyl, heteroarylalkyl, or a saturated or partially unsaturated heterocycle, each of which is optionally substituted; R^9 is cycloalkyl, aryl, heteroaryl, a saturated or partially unsaturated heterocycle, cycloalkyl(alkyl), aralkyl or heteroarylalkyl, each of which is optionally substituted; and R^{10} is $-(CH_2)_n-CO_2R^b$, $-(CH_2)_m-CO_2M$, $-(CH_2)_i-OH$ or $-(CH_2)_j-CONR^cR^d$ n is 0-8, m is 0-8, i is 1-8 and j is 0-8.