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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/034266 A2

(51) International Patent Classification:
A61K 31/675 (2006.01) *C07F 9/28* (2006.01)
C07F 9/58 (2006.01)

(21) International Application Number:
PCT/US2005/033641

(22) International Filing Date:
21 September 2005 (21.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/611,623	21 September 2004 (21.09.2004)	US
60/615,419	1 October 2004 (01.10.2004)	US
60/616,500	6 October 2004 (06.10.2004)	US

(71) Applicant *(for all designated States except US)*: **VION PHARMACEUTICALS, INC.** [US/US]; Four Science Park, New Haven, CT 06511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LIN, Xu** [CN/US]; 16 Millwood Dr., Branford, CT 06405 (US). **KING, Ivan** [US/US]; 65 Blue Hills Rd., North Haven, CT 06573 (US). **BELCOURT, Michael, F.** [US/US]; 9 Algonquin Dr., Wallingford, CT 06492 (US). **DOYLE, Terrence, W.** [US/US]; 5 Wellsweep Lane, Killington, CT 06419 (US).

(74) Agent: **COLEMAN, Henry, D.**; Coleman Sudol Sapone, P.C., 714 Colorado Avenue, Bridgeport, CT 06605-1601 (US).

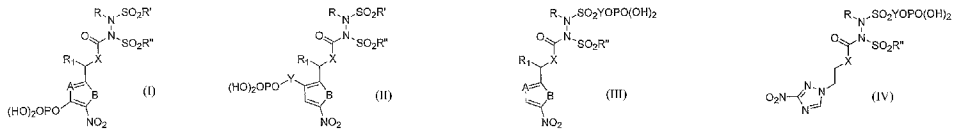
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, 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, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that 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.

(54) Title: PHOSPHATE-BEARING PRODRUGS OF SULFONYL HYDRAZINES AS HYPOXIA-SELECTIVE ANTINEOPLASTIC AGENTS



(57) Abstract: Novel phosphate-bearing prodrugs of sulfonyl hydrazines have the formulas (I), (II), (III) and (IV). Pharmaceutical compositions and uses thereof in the treatment of cancer are claimed. The aforementioned prodrugs include enantiomers, stereoisomers and tautomers thereof, as well as pharmaceutically acceptable salts or solvates and metabolites from all stages. The aforementioned prodrugs are preferentially activated in hypoxic tumors and can be given either alone, or in combination with other anticancer agents or with phototheraphy or radiotherapy. Where R = C_{1-10} alkyl, or C_{1-10} haloalkyl (preferably containing no more than 5 halogen groups, preferably 2-chloroethyl); R' and R" are independently C_{1-10} alkyl, or C_{5-20} aryl or heteroaryl (preferably methyl); R_1 is H, C_{1-10} alkyl, C_{1-10} alkoxyl, C_{5-20} aryl or heteroaryl or C_{5-20} aroxyl or heteroaroxyl (preferably methyl and ethyl); X is O, NH, or NR (preferably O); Y is $(CH_2)_n$, where n = 1, 2, 3, 4 or 5 (preferably n = 2 and 3); or Y = aryl or heteroaryl (preferably para-phenyl); A = CH, or N (preferably CH); and B = CH=CH, O, S, NH, or NR (preferably CH=CH); or pharmaceutically acceptable salts, solvates, polymorphs or metabolites, thereof.

WO 2006/034266 A2