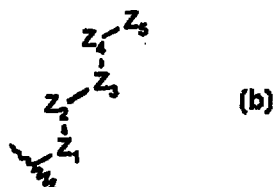
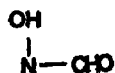
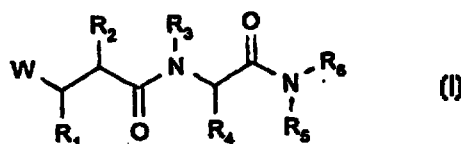




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(21) International Application Number: PCT/EP98/01015 (22) International Filing Date: 24 February 1998 (24.02.98) (30) Priority Data: 60/039,112 26 February 1997 (26.02.97) US (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ANDREWS, Robert, Carl [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). ANDERSEN, Marc, Werner [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). STANFORD, Jennifer, Badiang [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). BUBACZ, Dulcie, Garrido [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). CHAN, Joseph, Howing [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). COWAN, David, John [US/US]; 5121 Copper Ridge Drive #207, Durham, NC 27707 (US). GAUL, Michael, David		[US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). McDOUGALD, Darryl, Lynn [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). MUSSO, David, Lee [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). RABINOWITZ, Michael, Howard [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). WIETHE, Robert, William [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). (74) Agent: REED, Michael, A.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, 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 the receipt of amendments.

(54) Title: REVERSE HYDROXAMATE DERIVATIVES AS METALLOPROTEASE INHIBITORS



(57) Abstract

A family of compounds having general structural formula (I) wherein W is a reverse hydroxamic acid group (a); R₅ is hydrogen or lower alkyl; R₆ is (b); where Z₁ is heteroarylene; preferably: R₁ is methyl, ethyl, isopropyl, n-propyl or 3,3,3-trifluoro-n-propyl; R₂ is isobutyl or sec-butyl; R₃ is hydrogen; R₄ is tert-butyl, sec-butyl, 1-methoxy-1-ethyl or 2-(2-pyridylcarbonylamino)-1-ethyl; R₅ is hydrogen; and R₆ is 2-thiazolyl or 2-pyridyl. Such compounds show potent inhibition of MMP's, cell-free TNF convertase enzyme and TNF release from cells, and in some cases inhibit TNF convertase and TNF release from cells in preference to matrix metalloproteases.