

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

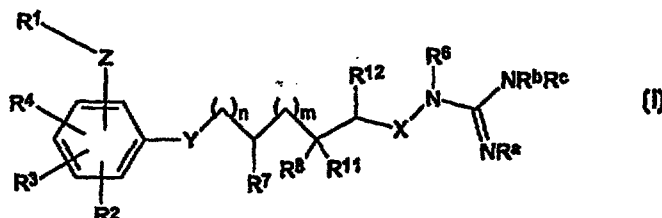


990227-6
18251

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 30/900, 27/900		A2	(11) International Publication Number: WO 98/23565
			(43) International Publication Date: 4 June 1998 (04.06.98)
(21) International Application Number: PCT/US97/21649		(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, 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, UZ, VN, YU, ZW, ARIPO patent (GH, 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).	
(22) International Filing Date: 26 November 1997 (26.11.97)			
(30) Priority Data: 60/031,822 26 November 1996 (26.11.96) US			
(71) Applicant: 3-DIMENSIONAL PHARMACEUTICALS, INC. [US/US]; Eagleview Corporate Center, Suite 104, 665 Stockton Drive, Exton, PA 19341 (US).			
(72) Inventors: TOMCZUK, Bruce, E.; 333 Sonnet Lane, Collegeville, PA 19426 (US). SOLL, Richard, M.; 324 Glenn Avenue, Lawrenceville, NJ 08648 (US). LU, Tianbao; 55 Heritage Lane, Exton, PA 19341 (US). FEDDE, Cynthia, L.; 211 Sassafra Court, Warrington, PA 18976 (US). IL-LIG, Carl, R.; 25 Jonathan Drive, Phoenixville, PA 19460 (US). MARKOTAN, Thomas, P.; Apartment S-23, 600 W. Schuylkill Road, Pottstown, PA 19465 (US). STAGNARO, Thomas, P.; 213 Ravenscliff Road, St. Davids, PA 19087 (US).		Published Without international search report and to be republished upon receipt of that report.	
(74) Agents: GOLDSTEIN, Jorge, A. et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).			

(54) Title: AMINOGUANIDINES AND ALKOXYGUANIDINES AS PROTEASE INHIBITORS.



(57) Abstract

Aminoguanidine and alkoxyguanidine compounds, including compounds of formula (I) wherein X is O or NR⁹ and R¹-R⁴, R⁶-R⁹, R¹¹, R¹², R^a, R^b, R^c, Y, Z, n and m are set forth in the specification, as well as hydrates, solvates or pharmaceutically acceptable salts thereof, that inhibit proteolytic enzymes such as thrombin are described. Also described are methods for preparing the compounds of Formula (I). The novel compounds of the present invention are potent inhibitors of proteases, especially trypsin-like serine proteases, such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa. Certain of the compounds exhibit antithrombotic activity via direct, selective inhibition of thrombin, or are intermediates useful for forming compounds having antithrombotic activity. The invention includes a composition for inhibiting loss of blood platelets, inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. Other uses of compounds of the invention are as anticoagulants either embedded in or physically linked to materials used in the manufacture of devices used in blood collection, blood circulation, and blood storage, such as catheters, blood dialysis machines, blood collection syringes and tubes, blood lines and stents.