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(12) **United States Patent**
Straub et al.(10) **Patent No.:** US 7,585,860 B2
(45) **Date of Patent:** *Sep. 8, 2009(54) **SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION**(75) Inventors: **Alexander Straub**, Wuppertal (DE); **Thomas Lampe**, Wuppertal (DE); **Jens Pohlmann**, Wuppertal (DE); **Susanne Rohrig**, Essen (DE); **Elisabeth Perzborn**, Wuppertal (DE); **Karl-Heinz Schlemmer**, Wuppertal (DE); **Joseph Pernerstorfer**, Wuppertal (DE)(73) Assignee: **Bayer Schering Pharma Aktiengesellschaft**, Berlin (DE)

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(56) **References Cited**

U.S. PATENT DOCUMENTS

2,811,555 A 10/1957 Larive et al.
 3,279,880 A 10/1966 Straley et al.
 4,128,654 A 12/1978 Fugitt et al.
 4,250,318 A 2/1981 Dostert et al.
 4,327,725 A 5/1982 Cortese et al.
 4,500,519 A 2/1985 Lormeau et al.
 4,705,779 A 11/1987 Madi-Szabo et al.
 4,765,989 A 8/1988 Wong et al.
 5,002,937 A 3/1991 Bosies et al.
 5,254,577 A 10/1993 Carlson et al.
 5,349,045 A 9/1994 Jiang
 5,532,255 A 7/1996 Raddatz et al.
 5,561,148 A 10/1996 Gante et al.

5,654,435 A 8/1997 Barbachyn et al.
 5,688,792 A 11/1997 Barbachyn et al.
 5,756,732 A 5/1998 Barbachyn et al.
 5,792,765 A 8/1998 Riedl et al.
 5,801,246 A 9/1998 Barbachyn et al.
 5,827,857 A 10/1998 Riedl et al.
 5,910,504 A 6/1999 Hutchinson et al.
 5,922,708 A 7/1999 Riedl et al.
 5,929,248 A 7/1999 Barbachyn et al.
 5,972,947 A 10/1999 Tsaklakidis et al.
 6,069,160 A 5/2000 Stolle et al.
 6,251,869 B1 6/2001 Bohanon
 6,273,913 B1 8/2001 Wright et al.
 6,294,201 B1 9/2001 Kettelhoit et al.
 6,413,981 B1 7/2002 Paget et al.
 6,610,682 B2 8/2003 Tsujita et al.
 6,805,881 B1 10/2004 Kanikanti et al.
 6,818,243 B2 11/2004 Nagashima et al.
 7,034,017 B2 4/2006 Straub et al.
 7,045,631 B2 5/2006 Rosentreter et al.
 7,078,417 B2 7/2006 Rosentreter et al.
 7,109,218 B2 9/2006 Rosentreter et al.
 7,129,255 B2 10/2006 Rosentreter et al.
 7,157,456 B2 1/2007 Straub et al.
 7,351,823 B2 4/2008 Berwe et al.
 2001/0029351 A1 10/2001 Falotico et al.
 2003/0153610 A1 8/2003 Straub et al.
 2003/0161882 A1 8/2003 Waterman

(Continued)

FOREIGN PATENT DOCUMENTS

AU 744002 7/1999

(Continued)

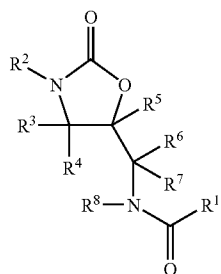
OTHER PUBLICATIONS

Riedl, B., Endermann, "Recent Developments with Oxazolidinone Antibiotics," R., Exp. Opin. Ther. Patents 1999, 9 (5), 625-633.

(Continued)

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(74) *Attorney, Agent, or Firm*—Connolly Bove Lodge & Hutz LLP(57) **ABSTRACT**

The invention relates to the field of blood coagulation. Novel oxazolidinone derivatives of the general formula (I)



(I)

processes for their preparation and their use as medicinally active compounds for the prophylaxis and/or treatment of disorders are described.

U.S. PATENT DOCUMENTS

2004/0162427 A1 8/2004 Rosentreter et al.
 2004/0242660 A1 12/2004 Straub et al.
 2005/0064006 A1 3/2005 Perzborn et al.
 2005/0182055 A1 8/2005 Berwe et al.
 2005/0261502 A1 11/2005 Rosentreter et al.
 2006/0154969 A1 7/2006 Rosentreter et al.
 2006/0258724 A1 11/2006 Straub et al.
 2007/0026065 A1 2/2007 Benke et al.
 2007/0149522 A1 6/2007 Thomas
 2008/0026057 A1 1/2008 Benke
 2008/0090815 A1 4/2008 Straub et al.
 2008/0200674 A1 8/2008 Straub et al.

FOREIGN PATENT DOCUMENTS

CA 2 437 587 8/2002
 CA 2 451 258 1/2003
 CA 2 464 290 5/2003
 DE 2836305 A1 3/1979
 DE 196 04 223 8/1997
 DE 19962924 A1 7/2001
 DE 10105989 A1 8/2002
 DE 10129725 A1 1/2003
 DE 10355461 A1 6/2005
 EP 0 127 902 12/1984
 EP 0 316 594 5/1989
 EP 0 352 781 1/1990
 EP 0350002 A1 1/1990
 EP 0 623 615 11/1994
 EP 0645376 3/1995
 EP 0 738 726 10/1996
 EP 0 785 200 7/1997
 EP 0930076 A1 7/1999
 EP 0950386 A2 10/1999
 GB 2140687 12/1984
 WO WO-93/09103 5/1993
 WO WO-93/23384 11/1993
 WO WO-97/03072 1/1997
 WO WO-97/09328 3/1997
 WO WO-97/10223 3/1997
 WO WO-98/01446 1/1998
 WO WO-98/54161 12/1998
 WO WO-99/02525 1/1999
 WO WO-99/03846 1/1999
 WO WO-99/06371 2/1999
 WO WO-99/21535 A1 5/1999
 WO WO-99/24428 5/1999
 WO WO-99/29688 6/1999
 WO WO-99/29688 A1 6/1999
 WO WO-99/31092 6/1999
 WO WO-99/37304 7/1999
 WO WO-99/37630 7/1999
 WO WO-99/37641 7/1999
 WO WO-99/40094 8/1999
 WO WO-99/59616 11/1999
 WO WO-00/16748 A1 3/2000
 WO WO-01/42242 A1 6/2001
 WO WO-01/44212 6/2001
 WO WO-01/46185 6/2001
 WO WO-01/47919 A1 7/2001
 WO WO-01/47949 A1 7/2001
 WO WO-02/25210 A1 3/2002
 WO WO-02/064575 8/2002
 WO WO-02/064575 A1 8/2002
 WO WO-02/070484 A1 9/2002
 WO WO-02/070485 A1 9/2002
 WO WO-02/070520 A1 9/2002
 WO WO-02/079195 A1 10/2002
 WO WO-02/079196 A1 10/2002

WO WO-03/035133 5/2003
 WO WO-03/035133 A1 5/2003
 WO WO-03/053441 A1 7/2003
 WO WO-2004/060887 A1 7/2004
 WO WO-2005/060940 A1 5/2005
 WO WO-2005/068456 A1 7/2005
 WO WO-2006/072367 A1 7/2006
 WO WO-2006/079474 A1 8/2006
 WO WO-2007/036306 A1 4/2007
 WO WO-2007/039122 A2 4/2007
 WO WO-2007/039132 A1 4/2007
 WO WO-2007/039134 A1 4/2007
 WO WO-2007/042146 A1 4/2007
 WO WO-2008/012002 A1 1/2008
 WO WO-2008/052671 A1 5/2008

OTHER PUBLICATIONS

Barbachyn, M.R. et al., "Identification of a Novel Oxazolidinone (U-100480) with Potent Antimycobacterial Activity," *J. Med. Chem.* 1996, 39, 680-685.
 Tucker, J.A. et al., "Piperazinyl Oxazolidinone Antibacterial Agents Containing a Pyridine, Diazene, or Triazene Heteroaromatic Ring," *J. Med. Chem.* 1998, 41, 3727-3735.
 Brickner, S.J. et al., "Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections," *J. Med. Chem.* 1996, 39, 673.
 Gregory, W.A. et al., "Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 1. The "B" Group," *J. Med. Chem.* 1989, 32, 1673-1681.
 Berry, C.N. et al., "Antithrombotic Actions of Argatroban in Rat Models of Venous, 'Mixed' and Arterial Thrombosis, and its Effects on the Tail Transection Bleeding Time," *Br. J. Pharmacol.* 1994, 113, 1209-1214.
 Meng, K. et al., "Effect of Acetylsalicylic Acid on Experimentally Induced Arterial Thrombosis in Rats," *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1977, 301, 115-119.
 Chern, J.W. et al., "Studies on Quinazolines IX: Fluorination versus 1,2-Migration in the Reaction of 1,3-Bifunctionalized amino-2-propanol with DAST," *Tetrahedron Lett.* 1998, 39, 8483-8486.
 Shakespeare, W.C., "Palladium-Catalyzed Coupling of Lactones with Bromobenzenes," *Tetrahedron Lett.* 1999, 40, 2035-2038.
 Renger, "Direct N-Arylation of Amides: An Improvement of the Goldberg-Reaction," *Synthesis Sep.* 1985, 856-860.
 Aebischer et al., "Synthesis of N-Arylrolipram Derivatives—Potent and Selective Phosphodiesterase-IV Inhibitors—By Copper Catalyzed Lactam-Aryl Halide Coupling," *Heterocycles.* 1998, 48, 2225-2229.
 Pfeil, E. et al., "Synthese von Oxalactamen aus Aziridinium-tetrafluorborat und Hydroxysäureestern," *Angew. Chem.* 79, 1967, 188.
 Ziegler, C.B., et al., "Synthesis of Some Novel 7-Substituted Quinolonecarboxylic Acids via Nitroso and Nitrono Cycloadditions," *J. Heterocycl. Chem.* 25, 2, 1988, 719-723.
 Bartoli et al., "Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide," *J. Org. Chem.* 1975, 40, 872-874.
 Reppe, et al., *Justus Liebigs Ann. Chem.* 596, 1955, p. 209.
 LuValle, J.E. et al., "Oxidation Processes. XXI. The Autoxidation of the p-Phenylenediamines," *J. Am. Chem. Soc.* 1948, 70, 2223.
 Snyder, H.R. et al., "Imidazo[4,5-f]quinolines III: Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-f]quinolines," *J. Pharm. Sci.* 1977, 66, 1204-1206.
 Adams, et al., "Sulfanilimide Derivatives," *J. Am. Chem. Soc.* 1939, 61, 2342-2349.
 Khanna, I.K. et al., "1,2-Diarylpyrroles as Potent and Selective Inhibitors of Cyclooxygenase-2," *J. Med. Chem.* 1997, 40, 1619-1633.
 Gutcalt, A. et al., "Studies on Quinazolines. 6. Asymmetric Synthesis of (S)-(+)- and (R)-(-)-3[[4-(2-Methoxyphenyl)piperazin-1-

- Grell, W., et al., "Repaglinide and Related Hypoglycemic Benzoic Acid Derivatives," *J. Med. Chem.* 1998, 41, 5219-5246.
- Artico, M. et al., "Research on Compounds with Antitlastic Activity," *Farmaco Ed. Sci.* 1969, 24, 179-190.
- Dankwardt et al., "Nonpeptide Bradykinin Antagonist Analogs Based on a Model of a Sterling-Winthrop Nonpeptide Bradykinin Antagonist Overlapped with Cyclic Hexapeptide Bradykinin Antagonist Peptides," *Bioorg. Med. Chem. Lett.* 1997, 1921-1926.
- Justus Liebigs Ann. Chem. 1955, 596, 204.
- Bouchet, et al., "o-Values of N-Substituted Azoles," *J. Chem. Soc. Perkin Trans. 2*, 1974, 449-451.
- Surrey, et al., "The Preparation of N-Benzyl-3-morpholones and N-Benzyl-3-homomorpholones from N-(Hydroxyalkyl)-chloroacetamides," *J. Amer. Chem. Soc.*, 77, 1955, 633-636.
- Tong, L.K.J., et al., "The Mechanism of Dye Formation in Color Photography. VII. Intermediate Bases in the Deamination of Quinonediimines," *J. Amer. Chem. Soc.* 1960, 82, 1988-2001.
- Delande, S.A., *Chem. Abstr.*, 1979, 90, 186926.
- Bono, F., et al., "Human Umbilical Vein Endothelial Cells Express High Affinity Receptors for Factor Xa," *Journal of Cellular Physiology*; 172:36-43 (1997); pp. 36-43.
- Cocks, T., et al., "Protease-activated receptors: sentries for inflammation?" *TIPS*; Mar. 2000 (vol. 21); pp. 103-108.
- Epstein, F., MD, "Atherosclerosis—An Inflammatory Disease," *The New England Journal of Medicine*; vol. 340, No. 2; pp. 115-126.
- Nakata, M., et al., "DX9065a, an Xa inhibitor, inhibits prothrombin-induced A549 lung adenocarcinoma cell proliferation," *Elsevier Science Ireland Ltd.*, *Cancer Letters* 122 (1998); pp. 127-133.
- Cirino, G., et al., "Inflammation-coagulation network: are serine protease receptors the knot?" *TIPS—May 2000* (vol. 21); pp. 170-172.
- Kaiser, B., et al., "A Synthetic Inhibitor of Factor Xa, DX-9065a, Reduces Proliferation of Vascular Smooth Muscle Cells in Vivo in Rats," *Elsevier Science Ltd.*, *Thrombosis Research* 98 (2000); pp. 175-185.
- Altieri, D., et al., "Identification of Effector Cell Protease Receptor-1: A Leukocyte-Distributed Receptor for the Serine Protease Factor Xa," *The Journal of Immunology* (1990); vol. 145, No. 1, Jul. 1, 1990; pp. 246-253.
- Coughlin, Shaun R., "Thrombin signalling and protease-activated receptors," *Nature*, vol. 407, Sep. 14, 2000; pp. 258-264.
- Ornstein, D., MD, et al., "Cancer, thrombosis, and anticoagulants," *Current Opinion in Pulmonary Medicine*, 2000, pp. 301-308.
- Dabbagh, K., et al., "Thrombin Stimulates Smooth Muscle Cell Procollagen Synthesis and mRNA Levels via a PAR-1 Mediated Mechanism" *Center for Cardiopulmonary Biochemistry and Respiratory Medicine*, (1997); pp. 405-409.
- Herault, J., et al., "Activation of Human Vascular Endothelial Cells by Factor Xa: Effect of Specific Inhibitors," *Biochemical Pharmacology*, vol. 57, pp. 603-610, 1999.
- Leveugle, B., et al., "Heparin Oligosaccharides that Pass the Blood—Brain Barrier Inhibit β -Amyloid Precursor Protein Secretion and Heparin Binding to β -Amyloid Peptide," *Journal of Neurochemistry*, vol. 70, No. 2, 1998; pp. 736-744.
- Molino, M., et al., "Differential Expression of Functional Protease-Activated Receptor-2 (PAR-2) in Human Vascular Smooth Muscle Cells," *Dept. of Medicine and Center for Experimental Therapeutics*; U. of Penn.; 1997; pp. 825-832.
- Plescia, J., et al., "Activation of Mac-1 (CD11b/CD18)-bound factor X by released cathepsin G defines an alternative pathway of leucocyte initiation of coagulation," *Journal of Biochemistry*, vol. 319 (1996); pp. 873-879.
- Howells, G., et al., "Proteinase-activated receptor-2: expression by human neutrophils," *Journal of Cell Science* 110 (1997); pp. 881-887.
- Herbert, J.-M., et al., "Effector Protease Receptor 1 Mediates the Mitogenic Activity of Factor Xa for Vascular Smooth Muscle Cells In Vitro and In Vivo," *J. Clin. Invest.*, vol. 101, No. 5 (1998); pp. 993-1000.
- Donnelly, K., et al., "Ancylostoma caninum Anticoagulant Peptide Ragosta, M., MD, et al., "Specific Factor Xa Inhibition Reduces Restenosis After Balloon Angioplasty of Atherosclerotic Femoral Arteries in Rabbits," *Circulation*, vol. 89, No. 3, Mar. 1994; pp. 1262-1271.
- Lindner, J., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice," *J. Immunology*, 2000, pp. 6504-6510.
- Zhang, Y., et al., "Tissue Factor Controls the Balance of Angiogenic and Antiangiogenic Properties of Tumor Cells in Mice," *J. Clin. Invest.*, vol. 94, Sep. 1994; pp. 1320-1327.
- Green, D., et al., "Lower mortality in cancel patients treated with low-molecular-weight versus standard heparin," *Letters to the Editor*, *The Lancet*, vol. 339, Jun. 13, 1992, p. 1476.
- Ko, F., et al., "Coagulation Factor Xa Stimulates Platelet-derived Growth Factor Release and Mitogenesis in Cultured Vascular Smooth Muscle Cells of Rat," *J. Clin. Invest.*, vol. 98, No. 6, Sep. 1996; pp. 1493-1501.
- Kakkar, A., et al., "Antithrombotic therapy in cancer," *BMJ*, vol. 318, Jun. 1999, pp. 1571-1572.
- Gasic, G., et al., "Coagulation factors X, Xa, and protein S as potent mitogens of cultured aortic smooth muscle cells," *Proc. Natl. Acad. Sci. USA*; vol. 89, Mar. 1992, *Cell Biology*, pp. 2317-2320.
- Cirino, G., et al., "Factor Xa as an Interface Between Coagulation and Inflammation," *J. Clin. Invest.*, vol. 99, No. 10, May 1997, pp. 2446-2451.
- Senden, N., et al., "Factor Xa Induces Cytokine Production and Expression of Adhesion Molecules by Human Umbilical Vein Endothelial Cells," *J. Immunology*, 1998, pp. 4318-4324.
- Papapetropoulos, A., et al., "Hypotension and inflammatory cytokine gene expression triggered by factor Xa-nitric oxide signaling," *Proc. Natl. Acad. Sci. USA*; vol. 95, *Pharmacology*, Apr. 1998, pp. 4738-4742.
- Camerer, E., et al., "Tissue factor- and factor X-dependent activation of protease-activated receptor 2 by factor VIIa," *PNAS*, vol. 97, No. 10, May 9, 2000; pp. 5255-5260.
- Donovan, F., et al., "Thrombin Induces Apoptosis in Cultured Neurons and Astrocytes via a Pathway Requiring Tyrosine Kinase and RhoA Activities," *J. Neuroscience*, Jul. 15, 1997, vol. 17, No. 14; pp. 5316-5326.
- Bouchard, B., et al., "Effector Cell Protease Receptor-1, a Platelet Activation-dependent Membrane Protein, Regulates Prothrombinase-catalyzed Thrombin Generation," *J. Biological Chemistry*, vol. 272, No. 14, Apr. 4, 1997; pp. 9244-9251.
- Molino, M., et al., "Endothelial Cell Thrombin Receptors and PAR-2," *J. Biological Chem.*, vol. 272, No. 17, Apr. 25, 1997; pp. 11133-11141.
- Nicholson, A., et al., "Effector Cell Protease Receptor-1 is a Vascular Receptor for Coagulation Factor Xa," *J. Biological Chem.*, vol. 271, No. 45, Nov. 8, 1996; pp. 28407-28413.
- Watson, D., et al., "Heparin-binding Properties of the Amyloidogenic Peptides A β and Amylin," *J. Biological Chem.*, vol. 272, No. 50, Dec. 12, 1997; pp. 31617-31624.
- Tuszynski, G., et al., "Isolation and Characterization of Antistatin," *J. Biological Chem.*, vol. 262, No. 20, Jul. 15, 1987; pp. 9718-9723.
- Kranzhöfer, R., et al., "Thrombin Potently Stimulates Cytokine Production in Human Vascular Smooth Muscle Cells but Not in Mononuclear Phagocytes," *Circulation Research*, vol. 79, No. 2, Aug. 1996; pp. 286-294.
- Schwartz, R., MD, et al., "Neointimal Thickening After Severe Coronary Artery Injury Is Limited by Short-term Administration of a Factor Xa Inhibitor," *Circulation*, vol. 93, No. 8, Apr. 15, 1996; pp. 1542-1548.
- Abendschein, D., Ph.D. et al., "Inhibition of Thrombin Attenuates Stenosis After Arterial Injury in Minipigs," *J. Am. Col. Card.*, vol. 28, No. 7, Dec. 1996; pp. 1849-1855.
- Carmeliet, P., MD, et al., "Gene Manipulation and Transfer of the Plasminogen and Coagulation System in Mice," *Sem. in Thrombosis and Hemostasis*, vol. 22, No. 6, 1996; pp. 525-542.
- Stouffer, G., MD, et al., "The Role of Secondary Growth Factor Production in Thrombin-Induced Proliferation of Vascular Smooth

- Bevilacqua, M., MD, Ph.D., et al., "Inducible Endothelial Functions in Inflammation and Coagulation," *Semin. in Thrombosis and Hemostasis*, vol. 13, No. 4, 1987; pp. 425-433.
- Bots, M., et al., Coagulation and Fibrinolysis Markers and Risk of Dementia, *Haemostasis*, vol. 28 (1998); pp. 216-222.
- Benzakour, O., et al., "Cellular and molecular events in atherogenesis; basis for pharmacological and gene therapy approaches to stenosis," *Cellular Pharmacology*, vol. 3., (1996); pp. 7-22.
- Kanthou, C., et al., "Cellular effects of thrombin and their signalling pathways," *Cellular Pharmacology*, vol. 2 (1995); pp. 293-302.
- Kaiser, B., et al., "Antiproliferation Action of Factor Xa Inhibitors in a Rat Model of Chronic Restenosis," Abstracts of the XVIII Congress of the International Society on Thrombosis and Haemostasis, Aug. 1999, p. 144.
- Tyrrell, D., et al., "Heperin in Inflammation: Potential Therapeutic Applications Beyond Anticoagulation," *Advances in Pharmacology*, vol. 46 (1999); pp. 151-208.
- Smirnova, I., et al., "Thrombin is an Extracellular Signal that Activates Intracellular Death Protease Pathways Inducing Apoptosis in Motor Neurons," *J. Neurobiology*, vol. 36 (1998); pp. 64-80.
- Bono, F., et al., "Factor Xa Activates Endothelial Cells by a Receptor Cascade Between EPR-1 and PAR-2," *Arterioscler Thromb Vasc Biol.*, Nov. 2000; pp. 1-6.
- Lala, P.K. et al., "Role of nitric oxide in tumor progression: lessons from experimental tumors," *Cancer and Metastasis Review*, vol. 17, pp. 91-106 (1998).
- Golub, T.R. et al., "Molecular classification of cancer: class discovery and class prediction by gene expression monitoring," *Science* (1999), vol. 286, pp. 531-537.
- FDA mulls drug to slow late-stage Alzheimer's [online], [retrieved on Sep. 23, 2003]. Retrieved from the internet, URL:<http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>.
- Ullman's Encyclopedia of Industrial Chemistry, Fifth Revised Ed., Editors: Elvers, B., Hawkins, S., VCH Verlagsgesellschaft mbH, Weinheim, 19985-1996, Ch. 5, 488-506.
- Zhu, B., Scarborough, R., "Recent Advances in Inhibitors of Factor Xa in the Prothrombinase Complex," *Curr. Opinions Card. Pul. Ren. Inv. Drugs*, 1:63-87 (1999).
- Uzan, A., "Antithrombotic Agents," *Emerging Drugs: The Prospect for Improved Medicines* 3: 189-208 (1998).
- Kaiser, B., "Thrombin and Factor Xa Inhibitors," *Drugs of the Future*, 23: 423-426 (1998).
- Al-Obeidi, F., Ostrem, J., "Factor Xa Inhibitors," *Expert Opin. Therapeutic Patents*, 9: 931-953 (1999).
- Al-Obeidi, F., Ostrem, J., "Factor Xa Inhibitors by Classical and Combinatorial Chemistry," *DDT*, 3: 223-231 (May 1998).
- Hauptmann, J., Sturzebecher, J., "Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside," *Thrombosis Research*, 93: 203-241 (1999).
- Pschyrembel, *Klinisches Wörterbuch*, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 199-200, Stichwort "Blutgerinnung."
- Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerinnung" Lubert Stryer, *Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg*, 1990, p. 259.
- Pschyrembel, *Klinisches Wörterbuch*, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 610, Stichwort "Heparin."
- Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin."
- Pschyrembel, *Klinisches Wörterbuch*, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 292, Stichwort "Cumarinderivate."
- Becker, M.R., et al., "Synthesis, Sar and in Vivo Activity of Novel Thienopyridine Sulfonamide Pyrrolidinones as Factor Xa Inhibitors," *Bioorganic and Medicinal Chemistry Letters*, 9:2753-2758 (1999).
- Reppe et al., *Justus Liebigs Ann. Chem.* 1955, vol. 596, p. 204.
- Wong et al. *The Journal of Pharmacology and Experimental Therapeutics*, vol. 295, No. 1, (2000), pp. 212-218.
- Ross, Russell, "Atherosclerosis—An Inflammatory Disease," *The*
- Perzborn, E. et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor. *Journal of Thrombosis and Haemostasis* 3, 3, Mar. 2005, pp. 514-521.
- Espinosa, G. et al. Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies. *Annals of the Rheumatic Diseases*, 63, 6, Jun. 2004, pp. 730-736.
- Bonomini, V. et al. A New Antithrombotic Agent in the Treatment of Acute Renal Failure Due to Hemolytic-Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. *Nephron* 37, 1984, 2, 144.
- Sinha, U. et al. Antithrombotic and hemostatic capacity of factor Xa versus thrombin inhibitors in models of venous and arteriovenous thrombosis. *European Journal of Pharmacology* 2000, 395, 51-59.
- Betz, A. Recent advances in Factor Xa inhibitors. *Expert Opinion Ther. Patents* 2001, 11, 1007-1017.
- Tac, K.T. et al. Factor X inhibitors. *Expert Opinion Investig. Drugs* 2003, 12, 799-804.
- Ruef, J. et al., New antithrombotic drugs on the horizon. *Expert Opinion Investig. Drugs* 2003, 12, 781-797.
- Samama, M.L. Synthetic direct and indirect factor Xa inhibitors. *Thrombosis Research* 2002, 106, V267-V273.
- Quan, M.L. The race to an orally active Factor Xa inhibitor: Recent advances. *Current Opinion in Drug Discovery & Development* 2004, 7, 460-469.
- The Ephesus Study, *Blood* 2000, 96, 490a.
- The Penthifra Study, *Blood* 2000, 96, 490a.
- The Pentamaks Study, *Blood* 2000, 96, 490a-491a.
- The Pentathlon 2000 Study, *Blood* 2000, 96, 491a.
- Leadley, R.J. Coagulation Factor Xa Inhibition: Biological Background and Rationale. *Current Topics in Medical Chemistry* 2001, 1, 151-159.
- Roehrig, S. et al. Discovery of the Novel Antithrombotic Agent 5-Chloro-N-((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methylthiophene-2-carboxamide (BAY 59-7939): An Oral, Direct Factor Xa Inhibitor. *J. Med. Chem.* 48, Sep. 22, 2005, pp. 5900-5908.
- Caira, M. Crystalline Polymorphism Of Organic Compounds. Springer Verlag Berlin Heidelberg 198, 1998, pp. 163-208.
- Hancock, B. et al. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. *Journal Pharmaceutical Science*. 86, 1 (Jan. 1997), pp. 1-12.
- Chiou, W.L. et al. Pharmaceutical Applications of Solid Dispersion Systems. *Journal of Pharmaceutical Sciences* 60, (1971). 128-1302.
- Ford, J.L. The Current Status of Solid Dispersions. *Pharm Acta Helv.* 61, (1986)69-88.
- Rasenack, N. et al. Poorly Water-soluble Drugs for Oral Delivery- A Challenge for Pharmaceutical Development. *Pharmazeutische Industrie* 67, Nr. 5 (2005), 583-591.
- Breitenbach, J. Melt extrusion: from process to drug delivery technology. *European Journal of Pharmaceutics and Biopharmaceutics* 54 (2002) 107-117.
- Breitenbach, J. Feste Loesungen durch Schmelzextrusion—ein integriertes Herstellkonzept. *Pharmazie in unserer Zeit* 29 (2000), 46-49.
- Gilligan, D.M. et al. The Management of Atrial Fibrillation. *The American Journal*, vol. 101, (4) 1996, 413-421.
- Kubitza, D. et al. Novel factor Xa inhibitors for prevention and treatment of thromboembolic diseases. *Expert Opinion on Investig. Drugs*, vol. 15, (8) 2006, pp. 843-855.
- Williams, E.M. Vaughan. Classifying anti-arrhythmic drugs. In: *Cardiac Arrythias-Proceedings of a symposium*, sandoe E., soedertaeje: Astra (1970), pp. 449-469.
- <http://familydoctor.org/online/famdocen/home/common/heartdisease/basics/290.html>.
- Kubitza, et al., Multiple dose escalation study Investigating the pharmacodynamic, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects, *Blood*, vol. 102:11:Nov. 16, 2003, p. 811a.
- Kubitza, et al., Abstract 3010, Single dose escalation study investigating the pharmacodynamic, safety, and pharmacokinetics of

Lerk, et al., Effect of Hydrophilization Drugs on Release Rate from Capsules, *J. of Pharma. Sciences*, 67(7), pp. 935-939 (1978).
Lerk, et al., In Vitro and In Vivo Availability of Hydrophilized Phenytoin from Capsules, *J. of Pharma. Sciences*, 68(5), pp. 634-638 (1979).

Greaves, et al., Novel Approaches to the Preparation of Low-Dose Solid Dosage Forms, *Pharmaceutical Technology*, Jan., pp. 60-64, (1995).
[Database Bielstein] Bielstein Institute for Organic Chemistry, Frankfurt-Main, DE. Database Accession No. 8822985.

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