

References

- (1) <http://www.who.int/mediacentre/factsheets/fs317/en/> (Accessed on 22 December 2019).
- (2) <http://www.cdc.gov/ncbddd/dvt/data.html> (Accessed on 22 December 2019).
- (3) He, R.; Chen, D.; He, S. Factor XI: hemostasis, thrombosis, and antithrombosis. *Thromb. Res.* **2012**, *129*, 541-550.
- (4) Favalaro, E. J.; Lippi, G. Coagulation update: what's new in hemostasis testing? *Thromb. Res.* **2011**, *127*, S13-S16.
- (5) Palta, S.; Saroa, R.; Palta, A. Overview of the coagulation system. *Indian J. Anaesth.* **2014**, *58*, 515-523.
- (6) Sevinsky, J. R.; Mohan Rao, L. V.; Ruf, W. Ligand-induced protease receptor translocation into caveolae: a mechanism for regulating cell surface proteolysis of the tissue factor-dependent coagulation pathway. *J. Cell Biol.* **1996**, *133*, 293-304.
- (7) Chen, Y. J.; Lin-Chao, S.; Huang, T. S.; Yang, M. L.; Lu, F. J. Humic acid induced growth retardation in a Sertoli cell line, TM4. *Life Sci.* **2001**, *69*, 1269-1284.
- (8) Lawson, J. H.; Mann, K. G. Cooperative activation of human factor IX by the human extrinsic pathway of blood coagulation. *J. Biol. Chem.* **1991**, *266*, 11317-11327.
- (9) Osterud, B.; Rapaport, S. I. Activation of factor IX by the reaction product of tissue factor and factor VII: additional pathway for initiating blood coagulation. *Proc. Natl. Acad. Sci. U. S. A.* **1977**, *74*, 5260-5264.
- (10) Luchtman-Jones, L.; Broze, G. J. The current status of coagulation. *Ann. Med.* **1995**, *27*, 47-52.

- (11) Jackson, C. M. Models for reaction mechanisms in haemostasis-contributions from the study of prothrombin activation. *Thromb. Haemost.* **2007**, *98*, 24-35.
- (12) Corrigan, J. J.; Ray, W. L.; May, N. Changes in the blood coagulation system associated with septicemia. *N. Engl. J. Med.* **1968**, *279*, 851-856.
- (13) Gallus, A. S.; Lee, L. H.; Coghlan, D. W. New aspects of the blood coagulation cascade, anticoagulants and vein thrombosis in Asia. *Ann. Acad. Med. Singapore* **2002**, *31*, 685-696.
- (14) Morrissey, J.; Macik, B.; Neuenschwander, P.; Comp, P. Quantitation of activated factor VII levels in plasma using a tissue factor mutant selectively deficient in promoting factor VII activation. *Blood* **1993**, *81*, 734-744.
- (15) Vučelić, D.; Peško, P.; Stojakov, D.; Sabljak, P.; Bjelović, M.; Dunjić, M.; Špica, B. Systemic hemostatic drugs. *Acta Chir. Iugosl.* **2007**, *54*, 177-195.
- (16) Rao, L. V. M.; Rapaport, S. I. Activation of factor VII bound to tissue factor: a key early step in the tissue factor pathway of blood coagulation. *Proc. Natl. Acad. Sci. U. S. A.* **1988**, *85*, 6687-6691.
- (17) Chen, M. S.; Lincoff, A. M. Direct thrombin inhibitors. *Curr. Cardiol. Rep.* **2005**, *7*, 255-259.
- (18) Achneck, H. E.; Sileshi, B.; Parikh, A.; Milano, C. A.; Welsby, I. J.; Lawson, J. H. Pathophysiology of bleeding and clotting in the cardiac surgery patient: from vascular endothelium to circulatory assist device surface. *Circulation* **2010**, *122*, 2068-2077.
- (19) Tran, A. H.; Lee, G. Fondaparinux for prevention of venous thromboembolism in major orthopedic surgery. *Ann. Pharmacother.* **2003**, *37*, 1632-1643.

References

- (20) Sikka, P.; Bindra, V. K. Newer antithrombotic drugs. *Indian J. Crit. Care Med.* **2010**, *14*, 188-195.
- (21) Stein, P. D.; Grandison, D.; Hua, T. A.; Slettehaugh, P. M.; Henry, J. W.; Turlapaty, P.; Kerwin, R. Therapeutic level of oral anticoagulation with warfarin in patients with mechanical prosthetic heart valves: review of literature and recommendations based on international normalized ratio. *Postgrad. Med. J.* **1994**, *70*, S72-S83.
- (22) Weitz, J. I.; Linkins, L. A. Beyond heparin and warfarin: the new generation of anticoagulants. *Expert Opin. Investig. Drugs* **2007**, *16*, 271-282.
- (23) Belli, S.; Aytac, H. O.; Yabanoglu, H.; Karagulle, E.; Parlakgumus, A.; Nursal, T. Z.; Yildirim, S. Results of surgery in general surgical patients receiving warfarin: retrospective analysis of 61 patients. *Int. Surg.* **2015**, *100*, 225-232.
- (24) Alquwaizani, M.; Buckley, L.; Adams, C.; Fanikos, J. Anticoagulants: a review of the pharmacology, dosing, and complications. *Curr. Emerg. Hosp. Med. Rep.* **2013**, *1*, 83-97.
- (25) Blossom, D. B.; Kallen, A. J.; Patel, P. R.; Elward, A.; Robinson, L.; Gao, G.; Langer, R.; Perkins, K. M.; Jaeger, J. L.; Kurkjian, K. M. Outbreak of adverse reactions associated with contaminated heparin. *N. Engl. J. Med.* **2008**, *359*, 2674-2684.
- (26) Mekaj, Y. H.; Mekaj, A. Y.; Duci, S. B.; Miftari, E. I. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther. Clin. Risk Manag.* **2015**, *11*, 967-977.
- (27) Spinler, S. A.; Willey, V. J. A patient's guide to taking dabigatran etexilate. *Circulation* **2011**, *124*, 209-211.

- (28) Graff, J.; Harder, S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. *Clin. Pharmacokinet.* **2013**, *52*, 243-254.
- (29) Ufer, M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. *Thromb. Haemost.* **2010**, *103*, 572-585.
- (30) Krishnaswamy, S.; Mann, K. G.; Nesheim, M. E. The prothrombinase-catalyzed activation of prothrombin proceeds through the intermediate meizothrombin in an ordered, sequential reaction. *J. Biol. Chem.* **1986**, *261*, 8977-8984.
- (31) Kaiser, B. Factor Xa- a promising target for drug development. *Cell. Mol. Life Sci.* **2002**, *59*, 189-192.
- (32) Perzborn, E.; Roehrig, S.; Straub, A.; Kubitza, D.; Misselwitz, F. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. *Nat. Rev. Drug Discov.* **2011**, *10*, 61-75.
- (33) Lassen, M. R.; Davidson, B. L.; Gallus, A.; Pineo, G.; Ansell, J.; Deitchman, D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J. Thromb. Haemost.* **2007**, *5*, 2368-2375.
- (34) Lip, G. Y. H.; Agnelli, G. Edoxaban: a focused review of its clinical pharmacology. *Eur. Heart J.* **2014**, *35*, 1844-1855.
- (35) Cohen, A. T.; Harrington, R. A.; Goldhaber, S. Z.; Hull, R. D.; Wiens, B. L.; Gold, A.; Hernandez, A. F.; Gibson, C. M.; Bello, F.; Ferrari, A. E. Extended thromboprophylaxis with betrixaban in acutely III medical patients. *N. Engl. J. Med.* **2016**, *375*, 534-544.
- (36) Rao, P. S. S.; Burkart, T. Advances in oral anticoagulation therapy- what's in the pipeline? *Blood Rev.* **2017**, *31*, 205-211.

- (37) Vranckx, P.; Valgimigli, M.; Heidbuchel, H. The significance of drug-drug and drug-food interactions of oral anticoagulation. *Arrhythmia Electrophysiol. Rev.* **2018**, *7*, 55-61.
- (38) Chan, Y. H.; C.; Yeh, Y. H.; Tu, H. T.; Kuo, C. T.; Chang, S. H.; Wu, L. S.; Lee, H. F.; See, L. C. Bleeding risk with dabigatran, rivaroxaban, warfarin, and antiplatelet agent in Asians with non-valvular atrial fibrillation. *Oncotarget* **2017**, *8*, 98898-98917.
- (39) Alexander, J. H.; Lopes, R. D.; James, S.; Kilaru, R.; He, Y.; Mohan, P.; Bhatt, D. L.; Goodman, S.; Verheugt, F. W.; Flather, M. Apixaban with antiplatelet therapy after acute coronary syndrome. *N. Engl. J. Med.* **2011**, *365*, 699-708.
- (40) Vene, N.; Mavri, A.; Gubenšek, M.; Tratar, G.; Cuderman, T. V.; Perme, M. P.; Blinc, A. Risk of thromboembolic events in patients with non-valvular atrial fibrillation after dabigatran or rivaroxaban discontinuation - data from the Ljubljana Registry. *PLoS One* **2016**, *11*.
- (41) Padmanabhan, K.; Padmanabhan, K. P.; Tulinsky, A.; Park, C. H.; Bode, W.; Huber, R.; Blankenship, D. T.; Cardin, A. D.; Kisiel, W. Structure of human des(1-45) factor Xa at 2.2 Å resolution. *J. Mol. Biol.* **1993**, *232*, 947-966.
- (42) Roehrig, S.; Straub, A.; Pohlmann, J.; Lampe, T.; Pernerstorfer, J.; Schlemmer, K. H.; Reinemer, P.; Perzborn, E. Discovery of the novel antithrombotic agent 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. *J. Med. Chem.* **2005**, *48*, 5900-5908.
- (43) Maignan, S.; Mikol, V. The use of 3D structural data in the design of specific factor Xa inhibitors. *Curr. Top. Med. Chem.* **2005**, *1*, 161-174.

- (44) Schechter, I.; Berger, A. On the active site of proteases. III. mapping the active site of papain; specific peptide inhibitors of papain. *Biochem. Biophys. Res. Commun.* **1968**, *32*, 898-902.
- (45) Bode, W.; Schwager, P. The refined crystal structure of bovine β -trypsin at 1.8 Å resolution. II. Crystallographic refinement, calcium binding site, benzamidine binding site and active site at pH 7.0. *J. Mol. Biol.* **1975**, *98*, 693-717.
- (46) Bode, W.; Turk, D.; Karshikov, A. The refined 1.9-Å X-ray crystal structure of D-Phe-Pro-Arg chloromethylketone-inhibited human alpha-thrombin: structure analysis, overall structure, electrostatic properties, detailed active-site geometry, and structure-function relationships. *Protein science : a publication of the Protein Society* **1992**, *1*, 426-71.
- (47) Brandstetter, H.; Kühne, A.; Bode, W.; Huber, R.; Von der Saal, W.; Wirthensohn, K.; Engh, R. A. X-ray structure of active site-inhibited clotting factor Xa. implications for drug design and substrate recognition. *J. Biol. Chem.* **1996**, *271*, 29988-29992.
- (48) Dullweber, F.; Stubbs, M. T.; Musil, D.; Stürzebecher, J.; Klebe, G. Factorising ligand affinity: a combined thermodynamic and crystallographic study of trypsin and thrombin inhibition. *J. Mol. Biol.* **2001**, *313*, 593-614.
- (49) Katakura, S.; Nagahara, T.; Hara, T.; Kunitada, S.; Iwamoto, M. Molecular model of an interaction between factor Xa and DX-9065A, a novel factor Xa inhibitor: contribution of the acetimidoylpyrrolidine moiety of the inhibitor to potency and selectivity for serine proteases. *Eur. J. Med. Chem.* **1995**, *30*, 387-394.
- (50) Bhunia, S. S.; Roy, K. K.; Saxena, A. K. Profiling the structural determinants for the selectivity of representative factor-Xa and thrombin inhibitors using combined ligand-based and structure-based approaches. *J. Chem. Inf. Model.* **2011**, *51*, 1966-1985.

- (51) Stubbs, M. T.; Huber, R.; Bode, W. Crystal structures of factor Xa specific inhibitors in complex with trypsin: structural grounds for inhibition of factor Xa and selectivity against thrombin. *FEBS Lett.* **1995**, *375*, 103-107.
- (52) Straub, A.; Roehrig, S.; Hillisch, A. Oral, direct thrombin and factor Xa inhibitors: the replacement for warfarin, leeches, and pig intestines? *Angew. Chemie - Int. Ed.* **2011**, *50*, 4574-4590.
- (53) Dunwiddie, C. T.; Nutt, E. M.; Vlasuk, G. P.; Siegl, P. K. S.; Schaffer, L. W. Anticoagulant efficacy and immunogenicity of the selective factor Xa inhibitor antistasin following subcutaneous administration in the Rhesus Monkey. *Thromb. Haemost.* **1992**, *67*, 371-376.
- (54) Lapatto, R.; Kregel, U.; Schreuder, H. A.; Arkema, A.; De Boer, B.; Kalk, K. H.; Hol, W. G. J.; Grootenhuis, P. D. J.; Mulders, J. W. M.; Dijkema, R. X-ray structure of antistasin at 1.9 Å resolution and its modelled complex with blood coagulation factor Xa. *EMBO J.* **1997**, *16*, 5151-5161.
- (55) Waxman, L.; Smith, D. E.; Arcuri, K. E.; Vlasuk, G. P. Tick anticoagulant peptide (TAP) is a novel inhibitor of blood coagulation factor Xa. *Science* **1990**, 1473-1473.
- (56) Vlasuk, G. P.; Ramjit, D.; Fujita, T.; Dunwiddie, C. T.; Nutt, E. M.; Smith, D. E.; Shebuski, R. J. Comparison of the *in vivo* anticoagulant properties of standard heparin and the highly selective factor Xa inhibitors antistasin and tick anticoagulant peptide (TAP) in a rabbit model of venous thrombosis. *Thromb. Haemost.* **1991**, *65*, 257-262.
- (57) Pauls, H. W.; Ewing, W. R.; Choi-Sledeski, Y. M. The design of competitive, small-molecule inhibitors of coagulation factor Xa. *Front. Med. Chem. Online* **2005**, *1*, 129-152.

References

- (58) Nagahara, T.; Yokoyama, Y.; Inamura, K.; Katakura, S. ichi; Komoriya, S.; Yamaguchi, H.; Hara, T.; Iwamoto, M. Dibasic (amidinoaryl)propanoic acid derivatives as novel blood coagulation factor Xa inhibitors. *J. Med. Chem.* **1994**, *37*, 1200-1207.
- (59) Hara, T.; Yokoyama, A.; Ishihara, H.; Yokoyama, Y.; Nagahara, T.; Iwamoto, M. DX-9065a, a new synthetic, potent anticoagulant and selective inhibitor for factor Xa. *Thromb. Haemost.* **1994**, *71*, 314-319.
- (60) Guertin, K.; Choi, Y.-M. The discovery of the factor Xa inhibitor otamixaban: from lead identification to clinical development. *Curr. Med. Chem.* **2007**, *14*, 2471-2481.
- (61) Chu, V.; Brown, K.; Colussi, D.; Gao, J.; Bostwick, J.; Kasiewski, C.; Bentley, R.; Morgan, S.; Guertin, K.; Pauls, H. W. Pharmacological characterization of a novel factor Xa Inhibitor, FXV673. *Thromb. Res.* **2001**, *103*, 309-324.
- (62) Light, D.; Guilford, W. Discovery of the factor Xa Inhibitor, ZK 807834 (CI-1031). *Curr. Top. Med. Chem.* **2005**, *1*, 121-136.
- (63) Leitner, J. M.; Jilma, B.; Mayr, F. B.; Cardona, F.; Spiel, A. O.; Firbas, C.; Rathgen, K.; Stähle, H.; Schühly, U.; Graefe-Mody, E. U. Pharmacokinetics and pharmacodynamics of the dual fII/fX inhibitor BIBT 986 in endotoxin-induced coagulation. *BMC Pharmacol.* **2007**, *7*, A29.
- (64) Tamura, S. Y.; Levy, O. E.; Uong, T. H.; Reiner, J. E.; Goldman, E. A.; Ho, J. Z.; Cohen, C. R.; Bergum, P. W.; Nutt, R. F.; Brunck, T. K. Guanylpiperidine peptidomimetics: potent and selective bis-cation inhibitors of factor Xa. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 745-749.
- (65) Marlowe, C. K.; Sinha, U.; Gunn, A. C.; Scarborough, R. M. Design, synthesis and structure-activity relationship of a series of arginine aldehyde factor Xa Inhibitors. part 1: structures based on the (D)- Arg-

- Gly-Arg tripeptide sequence. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 13-16.
- (66) Zhu, B. Y.; Huang, W.; Su, T.; Marlowe, C.; Sinha, U.; Hollenbach, S.; Scarborough, R. Discovery of transition state factor Xa inhibitors as potential anticoagulant agents. *Curr. Top. Med. Chem.* **2005**, *1*, 101-119.
- (67) Huang, W.; Naughton, M. A.; Yang, H.; Su, T.; Dam, S.; Wong, P. W.; Arfsten, A.; Edwards, S.; Sinha, U.; Hollenbach, S.; Scarborough, R. M.; Zhu, B. Y. Design, synthesis, and structure-activity relationships of unsubstituted piperazinone-based transition state factor Xa inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 723-728.
- (68) Noguchi, T.; Tanaka, N.; Nishimata, T.; Goto, R.; Hayakawa, M.; Sugidachi, A.; Ogawa, T.; Asai, F.; Ozeki, T.; Fujimoto, K. Indoline derivatives II: synthesis and factor Xa (FXa) inhibitory activities. *Chem. Pharm. Bull.* **2007**, *55*, 393-402.
- (69) Tidwell, R. R.; Webster, W. P.; Shaver, S. R.; Geratz, J. D. Strategies for anticoagulation with synthetic protease inhibitors. Xa inhibitors versus thrombin inhibitors. *Thromb. Res.* **1980**, *19*, 339-349.
- (70) Noguchi, T.; Tanaka, N.; Nishimata, T.; Goto, R.; Hayakawa, M.; Sugidachi, A.; Ogawa, T.; Asai, F.; Matsui, Y.; Fujimoto, K. Indoline derivatives I: synthesis and factor Xa (FXa) inhibitory activities. *Chem. Pharm. Bull.* **2006**, *54*, 163-174.
- (71) Choi-Sledeski, Y. M.; Kearney, R.; Poli, G.; Pauls, H.; Gardner, C.; Gong, Y.; Becker, M.; Davis, R.; Spada, A.; Liang, G. Discovery of an orally efficacious inhibitor of coagulation factor Xa which incorporates a neutral P1 ligand. *J. Med. Chem.* **2003**, *46*, 681-684.
- (72) Matter, H.; Nazaré, M.; Güssregen, S.; Will, D. W.; Schreuder, H.; Bauer, A.; Urmann, M.; Ritter, K.; Wagner, M.; Wehner, V. Evidence for C-Cl/C-Br... π interactions as an important contribution to protein-ligand binding affinity. *Angew. Chemie* **2009**, *121*, 2955-2960.

- (73) Zhang, P.; Bao, L.; Zuckett, J. F.; Goldman, E. A.; Jia, Z. J.; Arfsten, A.; Edwards, S.; Sinha, U.; Hutchaleelaha, A.; Park, G.; Lambing, J. L.; Hollenbach, S. J.; Scarborough, R. M.; Zhu, B. Y. Design, synthesis, and SAR of anthranilamide-based factor Xa inhibitors incorporating substituted biphenyl P4 motifs. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 983-987.
- (74) Kleanthous, S.; Borthwick, A. D.; Brown, D.; Burns-Kurtis, C. L.; Campbell, M.; Chaudry, L.; Chan, C.; Clarte, M. O.; Convery, M. A.; Harling, J. D. Structure and property based design of factor Xa inhibitors: pyrrolidin-2-ones with monoaryl P4 motifs. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 618-622.
- (75) Young, R. J.; Adams, C.; Blows, M.; Brown, D.; Burns-Kurtis, C. L.; Chan, C.; Chaudry, L.; Convery, M. A.; Davies, D. E.; Exall, A. M. Structure and property based design of factor Xa inhibitors: pyrrolidin-2-ones with aminoindane and phenylpyrrolidine P4 motifs. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1582-1587.
- (76) Xue, T.; Ding, S.; Guo, B.; Zhou, Y.; Sun, P.; Wang, H.; Chu, W.; Gong, G.; Wang, Y.; Chen, X. Design, synthesis, and structure-activity and structure-pharmacokinetic relationship studies of novel [6,6,5] tricyclic fused oxazolidinones leading to the discovery of a potent, selective, and orally bioavailable FXa inhibitor. *J. Med. Chem.* **2014**, *57*, 7770-7791.
- (77) Yang, J.; Su, G.; Ren, Y.; Chen, Y. Design, synthesis and evaluation of isoxazolo[5,4-*d*]pyrimidin-4(5*H*)-one derivatives as antithrombotic agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 492-495.
- (78) Quan, M. L.; Pinto, D. J. P.; Rossi, K. A.; Sheriff, S.; Alexander, R. S.; Amparo, E.; Kish, K.; Knabb, R. M.; Luetgen, J. M.; Morin, P. Phenyltriazolinones as potent factor Xa inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1373-1377.

- (79) Orwat, M. J.; Qiao, J. X.; He, K.; Rendina, A. R.; Luetzgen, J. M.; Rossi, K. A.; Xin, B.; Knabb, R. M.; Wexler, R. R.; Lam, P. Y. S. Orally bioavailable factor Xa inhibitors containing alpha-substituted gem-dimethyl P4 moieties. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3341-3345.
- (80) Wang, Y.; Sun, X.; Yang, D.; Guo, Z.; Fan, X.; Nie, M.; Zhang, F.; Liu, Y.; Li, Y.; Wang, Y. Design, synthesis, and structure-activity relationship of novel and effective apixaban derivatives as FXa inhibitors containing 1,2,4-triazole/pyrrole derivatives as P2 binding element. *Bioorg. Med. Chem.* **2016**, *24*, 5646-5661.
- (81) Sun, X.; Hong, Z.; Liu, M.; Guo, S.; Yang, D.; Wang, Y.; Lan, T.; Gao, L.; Qi, H.; Gong, P. Design, synthesis, and biological activity of novel tetrahydropyrazolopyridone derivatives as FXa inhibitors with potent anticoagulant Activity. *Bioorg. Med. Chem.* **2017**, *25*, 2800-2810.
- (82) Al-Horani, R. A.; Mehta, A. Y.; Desai, U. R. Potent direct inhibitors of factor Xa based on the tetrahydroisoquinoline scaffold. *Eur. J. Med. Chem.* **2012**, *54*, 771-783.
- (83) Shi, Y.; O'Connor, S. P.; Sitkoff, D.; Zhang, J.; Shi, M.; Bisaha, S. N.; Wang, Y.; Li, C.; Ruan, Z.; Michael Lawrence, R. Arylsulfonamidopiperidone derivatives as a novel class of factor Xa inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7516-7521.
- (84) Hirayama, F.; Koshio, H.; Ishihara, T.; Hachiya, S.; Sugasawa, K.; Koga, Y.; Seki, N.; Shiraki, R.; Shigenaga, T.; Iwatsuki, Y. Discovery of *N*-[2-hydroxy-6-(4-methoxybenzamido)phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (darexaban, YM150) as a potent and orally available factor Xa inhibitor. *J. Med. Chem.* **2011**, *54*, 8051-8065.
- (85) Yang, J.; Su, G.; Ren, Y.; Chen, Y. Synthesis of 3,4-diaminobenzoyl derivatives as factor Xa inhibitors. *Eur. J. Med. Chem.* **2015**, *101*, 41-51.

- (86) Xing, J.; Yang, L.; Li, H.; Li, Q.; Zhao, L.; Wang, X.; Zhang, Y.; Zhou, M.; Zhou, J.; Zhang, H. Identification of anthranilamide derivatives as potential factor Xa inhibitors: drug design, synthesis and biological evaluation. *Eur. J. Med. Chem.* **2015**, *95*, 388-399.
- (87) Xing, J.; Yang, L.; Zhou, J.; Zhang, H. Design, synthesis and biological evaluation of anthranilamide derivatives as potential factor Xa (FXa) inhibitors. *Bioorg. Med. Chem.* **2018**, *26*, 5987-5999.
- (88) Patel, N. R.; Patel, D. V.; Murumkar, P. R.; Yadav, M. R. Contemporary developments in the discovery of selective factor Xa inhibitors: a review. *Eur. J. Med. Chem.* **2016**, *121*, 671-698.
- (89) Pinto, D. J. P.; Smallheer, J. M.; Cheney, D. L.; Knabb, R. M.; Wexler, R. R. Factor Xa inhibitors: next-generation antithrombotic agents. *J. Med. Chem.* **2010**, *53*, 6243-6274.
- (90) D'Souza, A. M.; Spiccia, N.; Basutto, J.; Jokisz, P.; Wong, L. S. M.; Meyer, A. G.; Holmes, A. B.; White, J. M.; Ryan, J. H. 1,3-Dipolar cycloaddition-decarboxylation reactions of an azomethine ylide with isatoic anhydrides: formation of novel benzodiazepinones. *Org. Lett.* **2011**, *13*, 486-489.
- (91) Wube, A. A.; Bucar, F.; Hochfellner, C.; Blunder, M.; Bauer, R.; Hüfner, A. Synthesis of *N*-substituted 2-[(1*E*)-alkenyl]-4-(1*H*)-quinolone derivatives as antimycobacterial agents against non-tubercular mycobacteria. *Eur. J. Med. Chem.* **2011**, *46*, 2091-2101.
- (92) Hardtmann, G. E.; Koletar, G.; Pfister, O. R. The chemistry of 2*H*-3,1-benzoxazine-2,4(1*H*)dione (isatoic anhydrides) 1. The synthesis of *N*-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)diones. *J. Heterocycl. Chem.* **1975**, *12*, 565-572.
- (93) Liu, L.; Zhang, Y.; Wang, Y. Phosphine-free palladium acetate catalyzed Suzuki reaction in water. *ChemInform* **2005**, *36*, 6122-6125.

- (94) Pradhan, S.; John, R. P. A discrete self-assembled palladium nano-cage catalyses Suzuki-Miyaura coupling heterogeneously and Heck-Mizoroki coupling homogeneously. *New J. Chem.* **2015**, *39*, 5759-5766.
- (95) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. Highly selective biaryl cross-coupling reactions between aryl halides and aryl Grignard reagents: a new catalyst combination of *N*-heterocyclic carbenes and iron, cobalt, and nickel fluorides. *J. Am. Chem. Soc.* **2009**, *131*, 11949-11963.
- (96) Asachenko, A. F.; Sorochkina, K. R.; Dzhevakov, P. B.; Topchiy, M. A.; Nechaev, M. S. Suzuki-Miyaura cross-coupling under solvent-free conditions. *Adv. Synth. Catal.* **2013**, *355*, 3553-3557.
- (97) Nazaré, M.; Matter, H.; Will, D. W.; Wagner, M.; Urmann, M.; Czech, J.; Schreuder, H.; Bauer, A.; Ritter, K.; Wehner, V. Fragment deconstruction of small, potent factor Xa inhibitors: exploring the superadditivity energetics of fragment linking in protein-ligand complexes. *Angew. Chemie - Int. Ed.* **2012**, *51*, 905-911.
- (98) Dash, R. C.; Zaino, A. M.; Hadden, M. K. A metadynamic approach to understand the recognition mechanism of the histone H3 tail with the ATRX ADD domain. *Biochim. Biophys. Acta - Gene Regul. Mech.* **2018**, *1861*, 594-602.
- (99) Dash, R. C.; Maschinot, C. R.; Hadden, M. K. A molecular dynamics approach to identify an oxysterol-based hedgehog pathway inhibitor. *Biochim. Biophys. Acta - Gen. Subj.* **2017**, *1861*, 168-177.
- (100) Serra, S.; Moineaux, L.; Vancraeynest, C.; Masereel, B.; Wouters, J.; Pochet, L.; Frédérick, R. Thiosemicarbazide, a fragment with promising indolamine-2,3-dioxygenase (IDO) inhibition properties. *Eur. J. Med. Chem.* **2014**, *82*, 96-105.

- (101) Tripathi, L.; Kumar, P.; Singh, R.; Stables, J. P. Design, synthesis and anticonvulsant evaluation of novel *N*-(4-substituted phenyl)-2-[4-(substituted) benzylidene]-hydrazinecarbothio amides. *Eur. J. Med. Chem.* **2012**, *47*, 153-166.
- (102) Raphael, E.; Joshua, C. P.; Koshy, L. Alkali catalyzed thermal cyclization of 1-substituted and 1,6-disubstituted 2,5-dithiobiureas: formation of 1,2,5-dithiones and/ or 1,3,4-thiadiazoline-5-thiones. *Indian J. Chem.* **1989**, *28B*, 635-638.
- (103) Wahab, A. Thiadiazole derivatives. IV. synthesis of some 5-mercapto-1,3,4-thiadiazoles and 5-ethylthio-2-arylamino-1,3,4-thiadiazoles. *Boll. Chim. Farm.* **1979**, *118*, 391-396.
- (104) Karl, G.; Elfriede, S.; Horst, B. Heterocyclen aus CH--aciden nitrilen, VIII. 2-amino-thiophene aus methylenaktiven nitrilen, carbonylverbindungen und schwefel. *Chem. Ber.* **1966**, *9*, 94-100.
- (105) Kathiravan, M. K.; Shishoo, C. J.; Kumar, K. G.; Roy, S. K.; Mahadik, K. R.; Kadam, S. S.; Jain, K. S. Synthesis and antihyperlipidemic activity of some novel condensed 2-chloroalkyl-4-chloro/hydroxy-5,6-disubstituted pyrimidines. *Arzneimittel-Forschung/Drug Res.* **2007**, *57*, 599-606.
- (106) Farahat, A. A.; Boykin, D. W. Copper (I) 3-methylsalicylate, an efficient catalyst for *N*-arylation of heterocycles under moderate reaction conditions. *Tetrahedron Lett.* **2014**, *55*, 3049-3051.
- (107) Zhou, Q.; Du, F.; Chen, Y.; Fu, Y.; Chen, G. "On water" promoted *N*-arylation reactions using Cu (0)/myo-inositol catalytic system. *Tetrahedron Lett.* **2019**, *60*, 1938-1941.
- (108) Pilkington, L. I.; Sparrow, K.; Rees, S. W. P.; Paulin, E. K.; van Rensburg, M.; Xu, C. S.; Langley, R. J.; Leung, I. K. H.; Reynisson, J.; Leung, E. Development, synthesis and biological investigation of a

- novel class of potent PC-PLC inhibitors. *Eur. J. Med. Chem.* **2020**, *191*, 112162.
- (109) Abdel-Atty, M. M.; Farag, N. A.; Kassab, S. E.; Serya, R. A. T.; Abouzid, K. A. M. Design, synthesis, 3D pharmacophore, QSAR, and docking studies of carboxylic acid derivatives as histone deacetylase inhibitors and cytotoxic agents. *Bioorg. Chem.* **2014**, *57*, 65-82.
- (110) Yang, Y. H.; Shi, M. Ring-expanding reaction of cyclopropyl amides with triphenylphosphine and carbon tetrahalide. *J. Org. Chem.* **2005**, *70*, 8645-8648.
- (111) Sugahara, M.; Ukita, T. A facile copper-catalyzed Ullmann condensation: *N*-arylation of heterocyclic compounds containing an -NHCO- moiety. *Chem. Pharm. Bull.* **1997**, *45*, 719-721.
- (112) Mali, A. C.; Deshmukh, D. G.; Joshi, D. R.; Lad, H. D.; Patel, P. I.; Medhane, V. J.; Mathad, V. T. Facile approach for the synthesis of rivaroxaban using alternate synthon: reaction, crystallization and isolation in single pot to achieve desired yield, quality and crystal form. *Sustain. Chem. Process.* **2015**, *3*, 11.
- (113) Yu, R. N.; Chen, C. J.; Shu, L.; Yin, Y.; Wang, Z. J.; Zhang, T. T.; Zhang, D. Y. Structure-based design and synthesis of pyrimidine-4,6-diamine derivatives as janus kinase 3 inhibitors. *Bioorg. Med. Chem.* **2019**, *27*, 1646-1657.
- (114) Bertrand, J.; Dostálová, H.; Krystof, V.; Jorda, R.; Castro, A.; Mella, J.; Espinosa-Bustos, C.; María Zarate, A.; Salas, C. O. New 2,6,9-trisubstituted purine derivatives as Bcr-Abl and Btk inhibitors and as promising agents against leukemia. *Bioorg. Chem.* **2020**, *94*, 103361.
- (115) Xing, J.; Yang, L.; Yang, Y.; Zhao, L.; Wei, Q.; Zhang, J.; Zhou, J.; Zhang, H. Design, synthesis and biological evaluation of novel 2,3-dihydroquinazolin-4(1*H*)-one derivatives as potential FXa Inhibitors.

- Eur. J. Med. Chem.* **2017**, *125*, 411-422.
- (116) Tang, Z.; Li, X.; Yao, Y.; Qi, Y.; Wang, M.; Dai, N.; Wen, Y.; Wan, Y.; Peng, L. Design, synthesis, fungicidal activity and molecular docking studies of novel 2-((2-hydroxyphenyl)methylamino)acetamide derivatives. *Bioorg. Med. Chem.* **2019**, *27*, 2572-2578.
- (117) Baraldi, P. G.; Preti, D.; Tabrizi, M. A.; Fruttarolo, F.; Saponaro, G.; Baraldi, S.; Romagnoli, R.; Moorman, A. R.; Gessi, S.; Varani, K. *N*⁶-[(Hetero)aryl/(cyclo)alkyl-carbamoyl-methoxy-phenyl]-(2-chloro)-5'-*N*-ethylcarboxamido-adenosines: The first example of adenosine-related structures with potent agonist activity at the human A₂B adenosine receptor. *Bioorg. Med. Chem.* **2007**, *15*, 2514-2527.
- (118) Im, J. H.; Jin, Y. R.; Lee, J. J.; Yu, J. Y.; Han, X. H.; Im, S. H.; Hong, J. T.; Yoo, H. S.; Pyo, M. Y.; Yun, Y. P. Antiplatelet activity of β -carboline alkaloids from *perganum harmala*: a possible mechanism through inhibiting PLC γ 2 phosphorylation. *Vascul. Pharmacol.* **2009**, *50*, 147-152.
- (119) Li, C.; Zhang, X.; Zhao, M.; Wang, Y.; Wu, J.; Liu, J.; Zheng, M.; Peng, S. A class of novel *N*-(1-methyl- β -carboline-3-carbonyl)-*N'*-(aminoacid-acyl)-hydrazines: aromatization leded design, synthesis, *in vitro* anti-platelet aggregation/*in vivo* anti-thrombotic evaluation and 3D QSAR analysis. *Eur. J. Med. Chem.* **2011**, *46*, 5598-5608.
- (120) Kim, J.; Jung, S. H.; Yun, E.; Cho, S. H.; Yuseok, O.; Kim, J. E.; Kim, Y. H.; Myung, C. S.; Song, G. Y. Synthesis of novel 3-*N*-substituted carbazole derivatives and evaluation of their abilities to inhibit platelet aggregation. *Bull. Korean Chem. Soc.* **2018**, *39*, 726-728.
- (121) Arnaiz, D. O.; Zhao, Z. (Spring); Liang, A.; Trinh, L.; Whitlow, M.; Koovakkat, S. K.; Shaw, K. J. Design, synthesis, and *in vitro* biological activity of indole-based factor Xa inhibitors. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 957-961.

References

- (122) Kikumoto, R.; Tamao, Y.; Ohkubo, K.; Tezuka, T.; Tonomura, S.; Okamoto, S.; Hijikata, A. Carboxyl-containing amide derivatives of *N* alpha-substituted L-arginine. *J. Med. Chem.* **1980**, 1293-1299.
- (123) Robertson, D. W.; Lacefield, W. B.; Bloomquist, W.; Pfeifer, W.; Simon, R. L.; Cohen, M. L. Zatosetron, a potent, selective, and long-acting 5HT₃ receptor antagonist: synthesis and structure-activity relationships. *J. Med. Chem.* **1992**, 35, 310-319.
- (124) Wang, T. C.; Chen, I. L.; Kuo, D. H.; Liao, C. H. Synthesis and cytotoxic and antiplatelet activities of dibenzofuran- and carbazole-substituted oximes. *Helv. Chim. Acta* **2004**, 87, 983-990.
- (125) <http://zinc12.docking.org/browse/subsets/>
- (126) Dixon, S. L.; Smondryev, A. M.; Rao, S. N. PHASE: a novel approach to pharmacophore modeling and 3D database searching. *Chem. Biol. Drug Des.* **2006**, 67, 370-372.
- (127) Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchins, S. M.; Strelitz, R. A.; Maccoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T. B. Nonpeptide angiotensin II antagonists derived from 4*H*-1,2,4-triazoles and 3*H*-imidazo[1,2-*b*][1,2,4]triazoles. *J. Med. Chem.* **1993**, 36, 591-609.
- (128) Zhao, Y.; Jiang, M.; Zhou, S.; Wu, S.; Zhang, X.; Ma, L.; Gong, P. Design, synthesis and structure-activity relationship of oxazolidinone derivatives containing novel S4 ligand as FXa inhibitors. *Eur. J. Med. Chem.* **2015**, 96, 369-380.
- (129) Pandya, V.; Jain, M.; Chakrabarti, G.; Soni, H.; Parmar, B.; Chaugule, B.; Patel, J.; Jarag, T.; Joshi, J.; Joshi, N. Synthesis and structure-activity relationship of potent, selective and orally active anthranilamide-based factor Xa Inhibitors: application of weakly basic sulfoximine group as novel S4 binding element. *Eur. J. Med. Chem.*

2012, 58, 136-152.

- (130) Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. UCSF Chimera-a visualization system for exploratory research and analysis. *J. Comput. Chem.* **2004**, 25, 1605-1612.
- (131) Tuckerman, M.; Berne, B. J.; Martyna, G. J. Reversible multiple time scale molecular dynamics. *J. Chem. Phys.* **1992**, 97, 1990-2001.
- (132) Bowers, K. J.; Chow, D. E.; Xu, H.; Dror, R. O.; Eastwood, M. P.; Gregersen, B. A.; Klepeis, J. L.; Kolossvary, I.; Moraes, M. A.; Sacerdoti, F. D. Scalable algorithms for molecular dynamics simulations on commodity clusters. **2007**, 43.