

**REFERENCES**

1. Brunton, L. L.; Lazo, J. S.; Parker, K. L. *Goodman and Gillman's The pharmacological basis of therapeutics*, 11<sup>th</sup> edition, McGraw-Hill publication, New York, **2006**, pp. 855-910.
2. Madsen, U.; Krosggaard-Larsen, P.; Liljefors, T. *Textbook of Drug Design and Discovery*, 3<sup>rd</sup> edition, Washington, DC: Taylor & Francis, **2002**, pp. 1-36.
3. Reynolds, C.H.; Merz, K.M.; Ringe, D. *Drug Design: Structure- and Ligand-Based Approaches*, 1<sup>st</sup> edition, Cambridge, UK: Cambridge University Press, **2010**, pp. 61-180.
4. Paschalis Gavriilidisa, P.; Giakoustidisb, A.; Giakoustidisb, D. Aurora Kinases and Potential Medical Applications of Aurora Kinase Inhibitors: A Review. *J. Clin. Med. Res.* **2015**, 7, 742-751.
5. Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. The protein kinase complement of the human genome. *Science* **2002**, 298, 1912-1934.
6. Andrews, P. D. Aurora kinases: shining lights on the therapeutic horizon? *Oncogene* **2005**, 24, 5005–5015.
7. Bischoff, J. R.; Plowman, G. D. The Aurora/Ipl1p kinase family: regulators of chromosome segregation and cytokinesis. *Trends Cell Biol.* **1999**, 9, 454-459.
8. Honda, K.; Mihara, H.; Kato, Y.; Yamaguchi, A.; Tanaka, H.; Yasuda, H.; Furukawa, K.; Urano, T. Degradation of human Aurora2 protein kinase by the anaphase-promoting complex-ubiquitin-proteasome pathway. *Oncogene* **2000**, 19, 2812-2819.
9. Nigg, E. A. Mitotic kinases as regulators of cell division and its checkpoints. *Nat. Rev. Mol. Cell Biol.* **2001**, 2, 21-32.
10. Giet, R.; Petretti, C.; Prigent, C. Aurora kinases, aneuploidy and cancer, a coincidence or a real link? *Trends Cell. Biol.* **2005**, 15, 241-250.
11. Hansch, C. *Comprehensive medicinal chemistry – Quantitative drug design*. Vol-4. Pergamon Press, Elsevier, **2005**.
12. Aixia, Y.; Liyu, W. Aurora-A kinase inhibitor scaffolds and binding modes. *Drug Discovery Today* **2011**, 16, 260-269.
13. Castro, A.; Arlot-Bonnemains, Y.; Vigneron, S.; Labbe, J. C.; Prigent, C.; Lorca, T. APC/Fizzy-Related targets Aurora-A kinase for proteolysis. *EMBO Rep.* **2002**, 3, 457-462.

14. Taguchi, S.; Honda, K.; Sugiura, K.; Yamaguchi, A.; Furukawa, K.; Urano, T. Degradation of human Aurora-A protein kinase is mediated by hCdh1. *FEBS Lett.* **2002**, *519*, 59-65.
15. Brookmeyer, R.; Johnson, E.; Ziegler-Graham, K.; Arrighi, M. H. Forecasting the global burden of Alzheimer's disease. *Alzheimer's and Dementia* **2007**, *3*, 186–191.
16. Pal, P.; Gandhi, H.; Giridhar, R.; Yadav, M. R. ACAT Inhibitors: The Search for Novel Cholesterol Lowering Agents. *Mini-Reviews in Medicinal Chemistry* **2013**, *13*, 1195-1219.
17. World Health Organization. <http://www.who.int/mediacentre/factsheets/fs297/en/>.
18. Department of Epidemiology and Biostatistics, Kidwai Memorial Institute of Oncology. <http://kidwai.kar.nic.in/statistics.htm>.
19. Wermuth, C. G. *The practice of medicinal chemistry*, 3<sup>rd</sup> edition, Academic Press, **2003**.
20. Menendez, J. C.; Avendano, C. *Medicinal chemistry of anticancer drugs*, 1<sup>st</sup> edition, Elsevier, **2008**.
21. Anand, S.; Penrhyn-Lowe, S.; Venkitaraman, A. R. AURORA-A amplification overrides the mitotic spindle assembly checkpoint, including resistance to taxol. *Cancer Cell*, **2003**, *3*, 52-63.
22. Aliagas-Martin, I. *et al.* A class of 2,4-bisanilinopyrimidine Aurora A inhibitors with unusually high selectivity against Aurora B. *J. Med. Chem.*, **2009**, *52*, 3300-3307.
23. Aliagas-Martin, I.; Burdick, D.; Corson, L.; Dotson, J.; Drummond, J.; Fields, C.; Huang, O. W.; Hunsaker, T.; Kleinheinz, T.; Krueger, E.; Liang, J.; Moffat, J.; Phillips, G.; Pulk, R.; Rawson, T. E.; Ultsch, M.; Walker, L.; Wiesmann, C.; Zhang, B.; Zhu, B. Y.; Cochran, A. G. A class of 2,4-bisanilinopyrimidine Aurora A inhibitors with unusually high selectivity against Aurora B. *J. Med. Chem.* **2009**, *52*, 3300-3307.
24. Cheung, C.; Sarvagalla, S.; Lee, J. Y.; Huang, Y.; Coumar, M. S. Aurora kinase inhibitor patents and agents in clinical testing: an update (2011 – 2013). *Expert Opin. Ther. Pat.* **2014**, *24*, 1021-1038.
25. Kapetanovic, I. M. Computer-aided drug discovery and development (CADD): *in silico*-chemico-biological approach. *Chem Biol Interact* **2008**, *171*, 165-176.
26. Tropsha, A. "*QSAR in Drug Discovery*", 1<sup>st</sup> edition, Cambridge, UK: Cambridge University Press, **2010**, pp. 151-164.

27. Leach, A. R.; Harren, J. *Structure-based Drug Discovery*, 1<sup>st</sup> edition, Berlin: Springer, **2007**, pp. 49-123.
28. Wang, R.; Gao, Y.; Lai, L. LigBuilder: A Multi-Purpose Program for Structure-Based Drug Design. *J. Mol. Model.* **2000**, *6*, 498-516.
29. Schneider, G.; Fechner, U. Computer-based de novo design of drug-like molecules. *Nat. Rev. Drug. Discov.* **2005**, *4*, 649–63.
30. Lipkowitz, K. B.; Cundari, T. R.; Gillet, V. J. *Reviews in computational chemistry*, Vol. 22, John Wiley & Sons Inc., Hoboken, New Jersey, **2006**, pp. 57-168.
31. Shoichet, B. K.; Bodian, D. L.; Kuntz, I. D. Docking by least-squares fitting of molecular surface patterns. *J. Comput. Chem.* **1992**, *13*, 380-397.
32. Davis, A.; Teague, S. Hydrogen bonding, hydrophobic interactions, and failure of the rigid receptor hypothesis. *Angew. Chem.* **1999**, *38*, 737-749.
33. Fritz, T.; Tondi, D.; Finer-Moore, J.; Costi, M.; Stroud, R. Predicting and harnessing protein flexibility in the design of species-specific inhibitors of thymidylate synthase. *Chem. Biol.* **2001**, *10*, 981-995.
34. Lengauer, T.; Rarey, M. Computational methods for biomolecular docking. *Curr. Opin. Struct. Biol.* **1996**, *6*, 402–406.
35. Feig, M.; Onufriev, A.; Lee, M. S.; Im, W.; Case, D. A.; Brooks, C. L. Performance comparison of generalized born and Poisson methods in the calculation of electrostatic solvation energies for protein structures. *J. Comput. Chem.* **2004**, *25*, 265–84.
36. Jorgensen, W. L.; Tirado-Rives, J. Monte Carlo vs Molecular Dynamics for Conformational Sampling. *J. Phys. Chem.* **1996**, *100*, 14508-14513.
37. Wermuth, C. G.; Ganellin, C. R.; Lindberg, P.; Mitscher, L. A. "Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998)". *Pure and Applied Chemistry* **1998**, *70*, 1129–1143.
38. Qing, X. Y.; Lee, X. Y.; De Raeymaeker, J.; Tame, J. R. H.; Zhang, K. Y. J.; De Maeyer, M.; Voet, A. R. D. Pharmacophore modeling: advances, limitations, and current utility in drug discovery. *Dovepress* **2014**, *7*, 81-92.
39. Kier, L.B. *Molecular orbital theory in drug research*, Academy press: New York, **1971**, pp. 164-169.

40. Reddy, A. S.; Pati, S. P.; Kumar, P. P.; Pradeep, H. N.; Sastry, G. N. Virtual Screening in Drug Discovery – A Computational Perspective. *Current Protein and Peptide Science* **2007**, *8*, 329-351.
41. Glover, D. M.; Leibowitz, M. H.; McLean, D.A.; Parry, H. Mutations in Aurora prevent centrosome separation leading to the formation of monopolar spindles. *Cell* **1995**, *81*, 95–105.
42. Marumoto, T.; Hirota, T.; Morisaki, T.; Kunitoku, N.; Zhang, D.; Ichikawa, Y.; Sasayama, T.; Kuninaka, S.; Mimori, T.; Tamaki, N.; Kimura, M.; Okano, Y.; Saya, H. Roles of aurora-A kinase in mitotic entry and G2 checkpoint in mammalian cells. *Genes Cells* **2002**, *7*, 1173-1182.
43. Hirota, T.; Kunitoku, N.; Sasayama, T.; Marumoto, T.; Zhang, D.; Nitta, M.; Hatakeyama, K.; Saya, H. Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. *Cell* **2003**, *114*, 585-598.
44. Ouchi, M.; Fujiuchi, N.; Sasai, K.; Katayama, H.; Minamishima, Y. A.; Ongusaha, P. P.; Deng, C.; Sen, S.; Lee, S. W.; Ouchi, T. BRCA1 phosphorylation by Aurora-A in the regulation of G2 to M transition. *J. Biol. Chem.* **2004**, *279*, 19643-19648.
45. Wheatley, S. P.; Carvalho, A.; Vagnarelli, P.; Earnshaw, W. C. INCENP is required for proper targeting of Survivin to the centromeres and the anaphase spindle during mitosis. *Curr. Biol.* **2001**, *11*, 886-890.
46. Goto, H.; Yasui, Y.; Nigg, E. A.; Inagaki, M. Aurora-B phosphorylates Histone H3 at serine28 with regard to the mitotic chromosome condensation. *Genes Cells* **2002**, *7*, 11-17.
47. Sasai, K.; Katayama, H.; Stenoien, D. L.; Fujii, S.; Honda, R.; Kimura, M.; Okano, Y.; Tatsuka, M.; Suzuki, F.; Nigg, E. A.; Earnshaw, W. C.; Brinkley, W. R.; Sen, S. Aurora-C kinase is a novel chromosomal passenger protein that can complement Aurora-B kinase function in mitotic cells. *Cell Motil. Cytoskeleton* **2004**, *59*, 249-263.
48. Avo Santos, M.; van de Werken, C.; de Vries, M.; Jahr, H.; Vromans, M. J.; Laven, J. S.; Fauser, B. C.; Kops, G. J.; Lens, S. M.; Baart, E. B. A role for Aurora C in the chromosomal passenger complex during human preimplantation embryo development. *Hum. Reprod.* **2011**, *26*, 1868-1881.

49. Giles, F. J.; Swords, R.T.; Nagler, A.; Hochhaus, A.; Ottmann, O. G.; Rizzieri, D. A.; Talpaz, M.; Clark, J.; Watson, P.; Xiao, A.; Zhao, B.; Bergstrom, D.; Le Coutre, P. D.; Freedman, S. J.; Cortes, J. E. MK-0457, an Aurora kinase and BCRABL inhibitor, is active in patients with BCR-ABL T315I leukemia. *Leukemia* **2013**, *27*, 113-17.
50. Cheung, C. H.; Coumar, M. S.; Chang, J. Y.; Hsieh, H. P. Aurora kinase inhibitor patents and agents in clinical testing: an update (2009-10). *Expert Opin. Ther. Pat.* **2011**, *21*, 857-884.
51. Kantarjian, H. M.; Martinelli, G.; Jabbour, E. J.; Quintás-Cardama, A.; Ando, K.; Bay, J. O.; Wei, A.; Gröpper, S.; Papayannidis, C.; Owen, K.; Pike, L.; Schmitt, N.; Stockman, P. K.; Giagounidis, A.; SPARK-AML1 Investigators. Stage I of a phase 2 study assessing the efficacy, safety, and tolerability of barasertib (AZD1152) versus low-dose cytosine arabinoside in elderly patients with acute myeloid leukemia. *Cancer* **2013**, *119*, 2611-2619.
52. Meulenbeld, H. J.; Bleuse, J. P.; Vinci, E. M.; Raymond, E.; Vitali, G.; Santoro, A.; Dogliotti, L.; Berardi, R.; Cappuzzo, F.; Tagawa, S. T.; Sternberg, C. N.; Jannuzzo, M. G.; Mariani, M.; Petroccione, A.; de Wit, R. Randomized phase II study of danusertib in patients with metastatic castration-resistant prostate cancer after docetaxel failure. *BJU Int.* **2013**, *111*, 44-52.
53. Kelly, K. R.; Shea, T. C.; Goy, A.; Berdeja, J. G.; Reeder, C. B.; McDonagh, K. T.; Zhou, X.; Danaee, H.; Liu, H.; Ecsedy, J. A.; Niu, H.; Benaim, E.; Iyer, S. P. Phase I study of MLN8237-investigational Aurora A kinase inhibitor-in relapsed/ refractory multiple myeloma, Non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Invest. New Drugs* **2014**, *32*, 489-99.
54. Moy, C.; Oleykowski, C. A.; Plant, R.; Greshock, J.; Jing, J.; Bachman, K.; Hardwicke, M. A.; Wooster, R.; Degenhardt, Y. High Chromosome Number in hematological cancer cell lines is a Negative Predictor of Response to the inhibition of Aurora B and C by GSK1070916. *J. Transl. Med.* **2011**, *9*, 110-119.
55. Schöffski, P.; Jones, S. F.; Dumez, H.; Infante, J. R.; Van Mieghem, E.; Fowst, C.; Gerletti, P.; Xu, H.; Jakubczak, J. L.; English, P.A.; Pierce, K. J.; Burris, H. A. Phase I, open-label, multicentre, dose-escalation, pharmacokinetic and pharmacodynamic trial

- of the oral aurora kinase inhibitor PF-03814735 in advanced solid tumours. *Eur. J. Cancer* **2011**, *47*, 2256-2264.
56. Matulonis, U. A.; Lee, J.; Lasonde, B.; Tew, W. P.; Yehwalashet, A.; Matei, D.; Behbakht, K.; Grothusen, J.; Fleming, G.; Lee, N. K.; Arnott, J.; Bray, M. R.; Fletcher, G.; Brokx, R. D.; Castonguay, V.; Mackay, H.; Sidor, C. F.; Oza, A. M. ENMD-2076, an oral inhibitor of angiogenic and proliferation kinases, has activity in recurrent, platinum resistant ovarian cancer. *Eur. J. Cancer* **2013**, *49*, 121-131.
57. Arkenau, H. T.; Plummer, R.; Molife, L. R.; Olmos, D.; Yap, T. A.; Squires, M.; Lewis, S.; Lock, V.; Yule, M.; Lyons, J.; Calvert, H.; Judson, I. A phase I dose escalation study of AT9283, a small molecule inhibitor of aurora kinases, in patients with advanced solid malignancies. *Ann. Oncol.* **2012**, *23*, 1307-1313.
58. Shan, W.; Akinfenwa, P. Y.; Savannah, K. B.; Kolomeyevskaya, N.; Laucirica, R.; Thomas, D. G.; Odunsi, K.; Creighton, C. J.; Lev, D. C.; Anderson, M. L. A small-molecule inhibitor targeting the mitotic spindle checkpoint impairs the growth of uterine leiomyosarcoma. *Clin. Cancer Res.* **2012**, *18*, 3352-3365.
59. Kalous, O.; Conklin, D.; Desai, A. J.; Dering, J.; Goldstein, J.; Ginther, C.; Anderson, L.; Lu, M.; Kolarova, T.; Eckardt, M. A.; Langerød, A.; Børresen-Dale, A. L.; Slamon, D. J.; Finn, R. S. AMG 900, pan-Aurora kinase inhibitor, preferentially inhibits the proliferation of breast cancer cell lines with dysfunctional p53. *Breast Cancer Res. Treat.* **2013**, *141*, 397-408.
60. Ambit Biosciences Corp. Aurora kinase compounds and methods of their use. WO2011088045A1; **2011**.
61. Genosco and Oscotec, Inc. Kinase inhibitors. WO2011053861A1; **2011**.
62. Merck GMBH. Novel bicyclic urea compounds. WO2011017142A1; **2011**.
63. Shenzhen Salubris Pharmaceutical Co., Ltd. and Shanghai Institute of Pharmaceutical Industry. Polycyclic quinazolines, preparation thereof, and use thereof. US2011288086A1, WO2011144059A1; **2011**.
64. Boeringer Ingelheim International GMBH. Anticancer therapy with dual aurora kinase/MEK inhibitors. WO2012095505A1; **2012**.
65. H. Lee Moffitt Cancer Centre and Research Institute. Aurora kinase inhibitors and methods of making and using thereof. WO2012135641A2; **2012**.

66. Sanofi. Compound Ethyl 8-oxo-9-[3-[(1H-benzimidazol-2-yl)oxy]phenyl]-4,5,6,7,8,9-hexahydro-2H- pyrrolo[3,4-b]quinoline-3-carboxylate, salt, crystalline form, cocrystal, formulation, processes for preparation, application as medicaments, pharmaceutical compositions and new use particularly as inhibitors of Aurora kinases. WO2012066486A1; **2012**.
67. Cancer Research Technology Ltd. Pharmaceutically active compounds. WO2013190319A1; **2013**.
68. Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences. Preparation of 2,4-disubstituted thieno[3,2-d]pyrimidine compounds as anticancer agents. CN103242341A; **2013**.
69. Sun Yat Sen University. Preparation of pyrimidine derivatives as aurora kinase inhibitors for treatment of cancer. CN103059002A; **2013**.
70. Sun Yat Sen University. Application of pyrimidine derivative in preparing drug for prevention, treatment, and/or adjuvant treatment of tumor. CN103191120A; **2013**.
71. Sun Yat Sen University. Application of pyrimidine derivative in preparing drugs for prevention/treatment/auxiliary treatment of cancer. CN103202843A; **2013**.
72. Sunshine Lake Pharma Co., Ltd. Substitued pyrimidine derivatives as aurora kinase inhibitor. WO2013143466A1; **2013**.
73. Transtech Pharma, Llc. Benzimidazole carboxylic acid derivatives, compositions, and methods of use as aurora kinase inhibitors. WO 2014193696 A2; **2014**.
74. The Regents of the University of California. Aurora kinase inhibitors. WO 2014190207 A1; **2014**.
75. Regents of the University of Minnesota. Aurora kinase inhibitors WO 2014066840 A1; **2014**.
76. Belanger, D. B.; Curran, P. J.; Hruza, A.; Voigt, J.; Meng, Z.; Mandal, A. K.; Siddiqui, M. A.; Basso, A. D.; Gray, K. Discovery of imidazo[1,2-a]pyrazine-based Aurora kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5170-5174.
77. Meng, Z.; Kulkarni, B. A.; Kerekes, A.D.; Mandal, A. K.; Esposite, S. J.; Belanger, D. B.; Reddy, P. A.; Basso, A. D.; Tevar, S.; Gray, K.; Jones, J.; Smith, E. B.; Doll, R. J.; Siddiqui, M. A. Bioisosteric approach to the discovery of imidazo[1,2-a]pyrazines as potent Aurora kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 592-598.

78. Voss, M. E.; Rainka, M. P.; Fleming, M.; Peterson, L. H.; Belanger, D. M.; Siddiqui, A.; Hruza, A.; Voigt, J.; Gray, K.; Basso, A. D. Synthesis and SAR studies of imidazo-[1,2-a]-pyrazine Aurora kinase inhibitors with improved off-target kinase selectivity. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3544-3549.
79. Kwiatkowski, N.; Deng, X.; Wang, J.; Tan, L.; Villa, F.; Santaguida, S.; Huang, H. C.; Mitchison, T.; Musacchio, A.; Gray, N. Selective aurora kinase inhibitors identified using a taxol-induced checkpoint sensitivity screen. *ACS Chem. Biol.* **2012**, *7*, 185-196.
80. Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodshell, D. S.; Olson, A. J. AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility. *J. Comput. Chem.* **2009**, *30*, 2785-2791.
81. SYBYL 7.0; Tripos Inc., 1699 South Hanley Road, St. Louis, Missouri 63144, U.S.A.
82. Yu, T.; Tagat, J. R.; Kerekes, A. D.; Doll, R. J.; Zhang, Y.; Xiao, Y.; Esposito, S.; Belanger, D. B.; Curran, P. J.; Mandal, A. K.; Siddiqui, M. A.; Shih, N.; Basso, A. D.; Liu, M.; Gray, K.; Tevar, S.; Jones, J.; Lee, S.; Liang, L.; Ponery, S.; Smith, E. B.; Hruza, A.; Voigt, J.; Ramanathan, L.; Prosser, W.; Hu, M. Discovery of a Potent and Injectable Inhibitor of Aurora Kinases A and B based on the Imidazo-[1, 2-a]-Pyrazine Core. *ACS Med. Chem. Lett.* **2010**, *1*, 214-218.
83. Roy, P. P.; Paul, S.; Mitra, I.; Roy, K. On Two Novel Parameters for Validation of Predictive QSAR Models. *Molecules* **2009**, *14*, 1660-1701.
84. Golbraikh, A.; Tropsha, A. Beware of q<sup>2</sup>! *J. Mol. Graph. Model.* **2002**, *20*, 269-276.
85. Golbraikh, A.; Tropsha, A. Predictive QSAR modeling based on diversity sampling of experimental datasets for the training and test set selection. *J. Comput. Aid. Mol. Des.* **2002**, *16*, 357-369.
86. Saha, S.; Raghava, G. AlgPred: prediction of allergenic proteins and mapping of IgE epitopes. *Nucleic Acids Res.* **2006**, *34*, W202-W209.
87. Hopfinger, A. J.; Wang, S.; Tokarski, J. S.; Jin, B.; Albuquerque, M.; Madhav, P. J.; Duraiswami, C. Construction of 3D-QSAR Models Using the 4D-QSAR Analysis Formalism. *J. Am. Chem. Soc.* **1997**, *119*, 10509-10524.
88. Martins, J. P. A.; Barbosa, E. G.; Pasqualoto, K. F. M.; Ferreira, M. C. LQTA-QSAR: a new 4D-QSAR methodology. *J. Chem. Inf. Model* **2009**, *49*, 1428-1436.
89. GROMACS, Version 4.5, <http://www.gromacs.org>.

90. *Gaussian03*, Version 6.0, Gaussian Inc., Wallingford, USA.
91. O'Boyle, N. M.; Banck, M.; James, C. A.; Morley, C.; Vandermeersch, T.; Hutchison, G. R. Open Babel: An open chemical toolbox. *J. Cheminform.* **2011**, *3*, 33-47.
92. Schuttelkopf, A. W.; Van Aalten, D. M. F. PRODRG: a tool for high-throughput crystallography of protein-ligand complexes. *Acta Crystallogr D Biol. Crystallogr.* **2004**, *60*, 1355-1363.
93. MATLAB, Version 7.12, MathWorks, Inc.
94. Martins, J. P. A.; Ferreira, M. C. QSAR modeling: um novo pacote computacional open source para gerar e validar modelos QSAR. *Quim Nova* **2013**, *36*, 554-560.
95. Stahle, L.; Wold, S. Partial least squares analysis with cross validation for the two-class problem: A Monte Carlo study. *J. Chemom.* **1987**, *1*, 185-196.
96. Hoskuldsson, A. PLS regression methods. *J. Chemom.* **1988**, *2*, 211-228.
97. Melagraki, G.; Afantitis, A.; Sarimveis, H.; Koutentis, P. A.; Markopolus, J.; Igglessi-Markopoulou, O. Optimization of biaryl piperidine and 4-amino-2-biarylurea MCH1 receptor antagonists using QSAR modeling, classification techniques and virtual screening. *J. Comput. Aided Mol. Des.* **2007**, *21*, 251-267.
98. Ghasemi, J. B.; Safavi-Sohi, R.; Barbosa, E. G. 4D-LQTA-QSAR and docking study on potent Gram-negative specific LpxC inhibitors: a comparison to CoMFA modeling. *Mol. Divers.* **2012**, *16*, 203-213.
99. De Melo, E.B.; Ferreira, M. C. Four-dimensional structure-activity relationship model to predict HIV-1 integrase strand transfer inhibition using LQTA-QSAR methodology. *J. Chem. Inf. Model* **2012**, *52*, 1722-1732.
100. Selkoe, D. J. The origins of Alzheimer disease: A is for amyloid. *JAMA, J. Am. Med. Assoc.* **2000**, *283*, 1615-1617.
101. Selkoe, D. J. Alzheimer's disease: genes, proteins, and therapy. *Physiol. Rev.* **2001**, *81*, 41-766.
102. Small, D. H.; Cappai, R. Alois Alzheimer and Alzheimer's disease: a centennial perspective. *J. Neurochem.* **2006**, *99*, 708-710.
103. Carolan, C. G.; Dillon, G. P.; Gaynor, J. M.; Reidy, S.; Ryder, S. A.; Khan, D.; Marquez, J. F.; Gilmer, J. F. Structural Determinants of *Torpedo californica* Acetylcholinesterase

- Inhibition by the Novel and Orally Active Carbamate Based Anti-Alzheimer Drug Ganstigmine (CHF-2819). *J. Med. Chem.* **2008**, *51*, 6400-6409.
104. Butini, S.; Campiani, G.; Borriello, M.; Gemma, S.; Panico, A.; Persico, M.; Catalanotti, B.; Ros, S.; Brindisi, M.; Agnusdei, M.; Fiorini, I.; Nacci, V.; Novellono, E.; Belinskaya, T.; Saxena, A.; Fattorusso, C. Exploiting Protein Fluctuations at the Active-Site Gorge of Human Cholinesterases: Further Optimization of the Design Strategy to Develop Extremely Potent Inhibitors. *J. Med. Chem.* **2008**, *51*, 3154-3170.
105. Alipour, M.; Khoobi, M.; Foroumadi, A.; Nadri, H.; Moradi, A.; Sakhteman, A.; Grandi, M.; Shafiee, A. Novel coumarin derivatives bearing N-benzyl pyridinium moiety: Potent and dual binding site acetylcholinesterase inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 7214-7222.
106. Yang Hong-Qi, Y.; Zhi-Kun, S.; Sheng-Di, C. Current advances in the treatment of Alzheimer's disease: focused on considerations targeting A $\beta$  and tau. *Transl. Neurodegener.* **2012**, *1*, 21-32.
107. Medeiros, R.; Baglietto-Vargas, D.; LaFerla, F. M. The role of tau in Alzheimer's disease and related disorders. *CNS Neurosci. Ther.* **2011**, *17*, 514-524.
108. Rang, H. P.; Dale, M. M.; Ritter, J. M.; Moore, P. K. *Pharmacology*, 5<sup>th</sup> edition, Edinburgh: Churchill Livingstone; **2003**, pp. 508-522.
109. Chiou, S.; Huang, C.; Huang, C.; Hwang, M.; Lin, G. The Neuroprotective Role of Acupuncture and Activation of the BDNF Signaling Pathway. *J. Biochem. Mol. Toxicol.* **2009**, *23*, 303-308.
110. Bartus, R.; Dean, R.; Beer, B.; Lippa, A. The cholinergic hypothesis of geriatric memory dysfunction. *Science* **1982**, *217*, 408-414.
111. Terry, A. V. Jr.; Buccafusco, J. J. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 821-827.
112. Meunier, J.; Ieni, J.; Maurice, T. The anti-amnesic and neuroprotective effects of donepezil against amyloid  $\beta_{25-35}$  peptide-induced toxicity in mice involve an interaction with the sigma1 receptor. *Br. J. Pharmacol.* **2006**, *149*, 998-1012.
113. Marksteiner, J.; Schmidt, R. Treatment strategies in Alzheimer's disease with a focus on early pharmacological interventions. *Drugs Aging.* **2004**, *21*, 415-426.

114. Wilkinson, D. G.; Francis, P. T.; Schwam, E.; Payne-Parrish, J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging* **2004**, *21*, 453-478.
115. Tang, H.; Zhao, L. Z.; Zhao, H. T.; Huang, S. L.; Zhong, S. M.; Qin, J. K.; Chen, Z. F.; Huang, Z. S.; Liang, H. Hybrids of oxoisoaporphine-tacrine congeners: novel acetylcholinesterase and acetylcholinesterase-induced  $\beta$ -amyloid aggregation inhibitors. *Eur. J. Med. Chem.* **2011**, *46*, 4970-4979.
116. Keri, R.S.; Quintanova, C.; Marques, S.M.; Esteves, A.R.; Cardoso, S.M.; Santos, M.A. Design, synthesis and neuroprotective evaluation of novel tacrine-benzothiazole hybrids as multi-targeted compounds against Alzheimer's disease. *Bioorg. Med. Chem.* **2013**, *21*, 4559-4569.
117. Fernandez-Bachiller, M. I.; Perez, C.; Monjas, L.; Rademann, J.; Rodriguez-Franco, M. I. New tacrine-4-oxo-4*H*-chromene hybrids as multifunctional agents for the treatment of Alzheimer's disease, with cholinergic, antioxidant, and  $\beta$ -amyloid-reducing properties. *J. Med. Chem.* **2012**, *55*, 1303-1317.
118. Barreiro, E. J.; Camara, C. A.; Verli, H.; Brazil-Más, L.; Castro, N. G.; Cintra, W. M.; Aracava, Y.; Rodrigues, C. R.; Fraga, C. A. M. Design, Synthesis, and Pharmacological Profile of Novel Fused Pyrazolo[4,3-*d*]pyridine and Pyrazolo[3,4-*b*][1,8]naphthyridine Isosteres: A New Class of Potent and Selective Acetylcholinesterase Inhibitors. *J. Med. Chem.* **2003**, *46*, 1144–1152.
119. Marco-Contelles, J.; León, R.; de los Ríos, C.; Guglietta, A.; Terencio, J.; López, M. G.; García, A. G.; Villarroya, M. Novel Multipotent Tacrine–Dihydropyridine Hybrids with Improved Acetylcholinesterase Inhibitory and Neuroprotective Activities as Potential Drugs for the Treatment of Alzheimer's Disease. *J. Med. Chem.* **2006**, *49*, 7607–7610.
120. Savini, L.; Campiani, G.; Gaeta, A.; Pellerano, C.; Fattorusso, C.; Chiasserini, L.; Fedorko, J. M.; Saxena, A. Novel and potent tacrine-related hetero- and homobivalent ligands for acetylcholinesterase and butyrylcholinesterase. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1779-1782.
121. Hamulakova, S.; Janovec, L.; Hrabínova, M.; Spilovska, K.; Korabecny, J.; Kristian, P.; Kuca, K.; Imrich, J. Synthesis and Biological Evaluation of Novel Tacrine Derivatives

- and Tacrine–Coumarin Hybrids as Cholinesterase Inhibitors. *J. Med. Chem.* **2014**, *57*, 7073–7084.
122. Ozturan Ozer, E.; Tan, O. U.; Ozadali, K.; Kucukkilinc, T.; Balkan, A.; Ucar, G. Synthesis, molecular modeling and evaluation of novel *N*'-2-(4-benzylpiperidin-/piperazin-1-yl)acylhydrazone derivatives as dual inhibitors for cholinesterases and A $\beta$  aggregation. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 440-443.
123. Catto, M.; Berezin, A. A.; Lo Re, D.; Loizou, G.; Demetriades, M.; De Stradis, A.; Campagna, F.; Koutentis, P. A.; Carotti, A. Design, synthesis and biological evaluation of benzo[e][1,2,4]triazin-7(1H)-one and [1,2,4]-triazino[5,6,1-jk]carbazol-6-one derivatives as dual inhibitors of beta-amyloid aggregation and acetyl/butyryl cholinesterase. *Eur. J. Med. Chem.* **2012**, *58*, 84-97.
124. Karlsson, D.; Fallarero, A.; Brunhofer, G.; Guzik, P.; Prinz, M.; Holzgrabe, U.; Erker, T.; Vuorela, P. Identification and characterization of diarylimidazoles as hybrid inhibitors of butyrylcholinesterase and amyloid beta fibril formation. *Eur. J. Pharm. Sci.* **2012**, *45*, 169-183.
125. Brunhofer, G.; Fallarero, A.; Karlsson, D.; Batista-Gonzalez, A.; Shinde, P.; Gopi Mohan, C.; Vuorela, P. Exploration of natural compounds as sources of new bifunctional scaffolds targeting cholinesterases and beta amyloid aggregation: the case of chelerythrine. *Bioorg. Med. Chem.* **2012**, *20*, 6669-6679.
126. Galdeano, C.; Viayna, E.; Sola, I.; Formosa, X.; Camps, P.; Badia, A.; Clos, M. V.; Relat, J.; Ratia, M.; Bartolini, M.; Mancini, F.; Andrisano, V.; Salmona, M.; Minguillon, C.; Gonzalez-Munoz, G. C.; Rodriguez-Franco, M. I.; Bidon-Chanal, A.; Luque, F. J.; Munoz-Torrero, D. Huprine-tacrine heterodimers as anti-amyloidogenic compounds of potential interest against Alzheimer's and prion diseases. *J. Med. Chem.* **2012**, *55*, 661-669.
127. Mohamed, T.; Zhao, X.; Habib, L. K.; Yang, J.; Rao, P. P. Design, synthesis and structure-activity relationship (SAR) studies of 2,4-disubstituted pyrimidine derivatives: dual activity as cholinesterase and A $\beta$ -aggregation inhibitors. *Bioorg. Med. Chem.* **2011**, *19*, 2269-2281.
128. Mohamed, T.; Yeung, J. C.; Rao, P. P. Development of 2-substituted *N*-(naphth-1-ylmethyl) and *N*-benzhydrylpyrimidin-4-amines as dual cholinesterase and A $\beta$ -

- aggregation inhibitors: Synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 5881-5887.
129. Peng, D. Y.; Sun, Q.; Zhu, X. L.; Lin, H. Y.; Chen, Q.; Yu, N. X.; Yang, W. C.; Yang, G. F. Design, synthesis, and bioevaluation of benzamides: novel acetylcholinesterase inhibitors with multifunctions on butylcholinesterase, A $\beta$  aggregation, and  $\beta$ -secretase. *Bioorg. Med. Chem.* **2012**, *20*, 6739-6750.
130. Jiaranaikulwanitch, J.; Govitrapong, P.; Fokin, V. V.; Vajragupta, O. From BACE1 inhibitor to multifunctionality of tryptoline and tryptamine triazole derivatives for Alzheimer's disease. *Molecules* **2012**, *17*, 8312-8333.
131. Sinha, A.; Tamboli, R. S.; Seth, B.; Kanhed, A. M.; Tiwari, S. K.; Agarwal, S.; Nair, S.; Giridhar, R.; Chaturvedi, R. K.; Yadav, M. R. Neuroprotective Role of Novel Triazine Derivatives by Activating Wnt/ $\beta$  Catenin Signaling Pathway in Rodent Models of Alzheimer's Disease. *Mol. Neurobiol.* **2015**, *52*, 638-652.
132. (a) Rabjohn, N. *In organic synthesis*, Collective vol. 4, John Wiley & Sons, INC. **1963**;  
(b) Chauhan, S. M. S.; Singh, R.; Geetanjali. Microwave-Assisted Synthesis of 10-Substituted Isoalloxazines in the Presence of Solid Acids. *Synthetic Communication* **2003**, *33*, 1179-1184; (c) Cadogan, J. I. G.; Clark, B. A. J.; Ford, D.; MacDonald, R. J.; MacPherson, A. D.; McNab, H.; Nicolson, I. S.; Reed, D.; Sommerville, C. C. Reactions of 2-(pyrrol-1-yl)benzyl radicals and related species under flash vacuum pyrolysis conditions. *Org Biomol Chem.* **2009**, *21*, 5173-5183; (d) Janssens, F. E.; Kennis, L. E. J.; Hens, J. F.; Torremans, J. L. G.; Diels, G. S. M. 4-[(bicyclic heterocyclyl)-methyl and -hetero]-piperidines. US4695575 A; **1987**; (e) Hubbard, J. W.; Piegols, A. M.; Soderberg, B. C. G. Palladium-catalyzed N-heteroannulation of N-allyl- or N-benzyl-2-nitrobenzenamines: synthesis of 2-substituted benzimidazoles. *Tetrahedron* **2007**, *63*, 7077-7085; (f) Beaulieu, P. L. A Practical Oxone-Mediated, High-Throughput, Solution-Phase Synthesis of Benzimidazoles from 1,2-Phenylenediamines and Aldehydes and its Application to Preparative Scale Synthesis. *Synthesis* **2003**, *11*, 1683-1692; (g) Shelke, S. M.; Bhosale, S. H. Synthesis, antidepressant evaluation and QSAR studies of novel 2-(5H-[1,2,4]triazino[5,6-b]indol-3-ylthio)-N-(substituted phenyl)acetamides. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4661-4664; (h) El Ashry, E. H.; Ramadan, E. S.; Abdel Hamid, H. M.; Hagar, M. Microwave Irradiation for Accelerating

- each Step for the Synthesis of 1,2,4-Triazino[5,6-*b*]indole-3-thiols and their Derivatives from Isatin and 5-Chloroisatin. *Synlett* **2004**, *4*, 723-725; (i) Shmidt, M. S.; Reverdito, A. M.; Kremenichuzky, L.; Perillo, I. A.; Blanco, M. M. Simple and Efficient Microwave Assisted *N*-Alkylation of Isatin. *Molecules* **2008**, *13*, 831-840; (j) Bouhfid, R.; Joly, N.; Essassi, E. M.; Lequart, V.; Massoui, M.; Martin, P. Synthesis of New Spiro[1,4,2-dioxazole-5,3'-indolin]-2'-one by 1,3-Dipolar Cycloaddition. *Synthetic Communication* **2011**, *41*, 2096-2102.
133. Ellman, G. L.; Courtney, K. D.; Andres, V.; Feather-Stone, R. M. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. Pharmacol.* **1961**, *7*, 88-95.
134. Kwon, Y. E.; Park, J. Y.; No, K. T.; Shin, J. H.; Lee, S. K.; Eun, J. S.; Yang, J. H.; Shin, T. Y.; Kim, D. K.; Chae, B. S.; Leem, J. Y.; Kim, K. H. Synthesis, in vitro assay, and molecular modeling of new piperidine derivatives having dual inhibitory potency against acetylcholinesterase and A $\beta$ <sub>1-42</sub> aggregation for Alzheimer's disease therapeutics. *Bioorg. Med. Chem.* **2007**, *15*, 6596-6607.
135. Mohamed, T.; Zhao, X.; Habib, L. K.; Yang, J.; Rao, P. P. Design, synthesis and structure-activity relationship (SAR) studies of 2,4-disubstituted pyrimidine derivatives: Dual activity as cholinesterase and A $\beta$ -aggregation inhibitors. *Bioorg. Med. Chem.* **2011**, *19*, 2269-2281.
136. Klunk, W. E.; Jacob, R. F.; Mason, R. P. Quantifying amyloid beta-peptide (A $\beta$ ) aggregation using the Congo red-A $\beta$  (CR-A $\beta$ ) spectrophotometric assay. *Anal. Biochem.* **1999**, *266*, 66-76.
137. Kang, I. J.; Jeon, Y. E.; Yin, X. F.; Nam, J. S.; You, S. G.; Hong, M. S.; Jang, B. G.; Kim, M. J. *Food chem. toxicol.* Butanol extract of *Ecklonia cava* prevents production and aggregation of beta-amyloid, and reduces beta-amyloid mediated neuronal death. **2011**, *49*, 2252-2259.
138. Kakko, I.; Toimela, T.; Tahti, H. The toxicity of pyrethroid compounds in neural cell cultures studied with total ATP, mitochondrial enzyme activity and microscopic photographing. *Environ. Toxicol. Pharmacol.* **2004**, *15*, 95-102.
139. Glide version 5.5, Schrödinger, LLC, New York, NY, **2009**.
140. LigPrep Version 2.3, Schrödinger, LLC, New York, NY, **2009**.

141. Norata, G. D.; Catapano, A. L. Lipid lowering activity of drugs affecting cholesterol absorption. *Nutr. Metab. Cardiovasc. Dis.* **2004**, *14*, 42-51.
142. Mitchell, M. E., Sidawy, A. N. The pathophysiology of atherosclerosis. *Semin Vasc Surg.* **1998**, *11*, 134-141.
143. Jong, de A.; Plat, J.; Mensink, R. P. Metabolic effects of plant sterols and stanols. *J. Nutr. Biochem.* **2003**, *14*, 362-369.
144. Miyazaki, M.; Sakai, Y.; Sakamoto, S. H. Acyl coenzyme A: cholesterol acyltransferase inhibitors for controlling hypercholesterolemia and atherosclerosis. *Curr. Opin. Investig. Drugs.* **2003**, *4*, 1095-1099.
145. Wierzbicki, S. New lipid-lowering agents. *Exp. Opin. Emerg. Drugs.* **2003**, *8*, 365-376.
146. Altmann, W. S.; Davis, R. H. Jr.; Zhu, J. L.; Yao, X.; Hoos, M. L.; Tetzloff, G.; Iyer, P. S.; Maguire, M.; Golovko, A.; Zeng, M.; Wang, L.; Murgolo, N.; Graziano, P. M.; Niemann, Y. P. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science.* **2004**, *303*, 1201-1204.
147. Norum, K. R.; Lilljeqvist, A. C.; Helgerud, P.; Normann E. R.; Mo. A.; Selbekk. B. Esterification of cholesterol in human small intestine: the importance of Acyl CoA: cholesterol acyltransferase. *Eur. J. Clin. Invest.* **1979**, *9*, 55-62.
148. Heider. J. G.; Pickens, C. E.; Kelly, L. A. Role of Acyl CoA: cholesterol acyltransferase in cholesterol absorption and its inhibition by 57-118 in rabbit. *J. Lipid. Res.* **1983**, *24*, 1127-1134.
149. Field. F. J. Intestinal cholesterol esterase: intracellular enzyme or contamination of cytosol by pancreatic enzymes. *J. Lipid. Res.* **1984**, *25*, 389-399.
150. Helgerud, P.; Saarem, K.; Nonm, K. R. Acyl-CoA: cholesterol acyltransferase in human small intestine: its activity and some properties of enzymic action. *J. Lipid. Res.* **1981**, *22*, 271-277.
151. Chang, C.; Chen, J.; Thomas, M. A.; Cheng, D.; Del Priore, V. A.; Newton, R. S.; Pape, M. E.; Chang, T. Regulation and Immunolocalization of Acyl-Coenzyme A:Cholesterol Acyltransferase in Mammalian Cells as Studied with Specific Antibodies. *J. Biol. Chem.* **1995**, *270*, 29532-29540.
152. Joyce, C. W.; Shelness, G. S.; Davis, M. A.; Lee, R. G.; Skinner, K.; Anderson, R. A.; Rudel, L. L. ACAT1 and ACAT2 Membrane Topology Segregates a Serine Residue

- Essential for Activity to Opposite Sides of the Endoplasmic Reticulum Membrane. *Mol Biol Cell.* **2000**, *11*, 3675-3687.
153. Lin, S.; Cheng, D.; Liu, M. S.; Chen, J.; Cheng, T. Y. Human ACAT-1 in the endoplasmic reticulum contains seven transmembrane domains. *J. Biol. Chem.*, **1999**, *274*, 23276-23285.
154. Guo, Z. Y.; Lin, S.; Heinen, J. A.; Chang, C. C.; Chang, T. The active site His-460 of human Acyl-coenzyme A: cholesterol acyltransferase 1 residues in a hitherto undisclosed transmembrane domain. *J. Biol. Chem.* **2005**, *280*, 37814-37826.
155. Lin, S.; Lu, X.; Chang, C. C.; Chang, T. Y. Human acyl-coenzyme A: cholesterolase expressed in Chinese hamster ovary cells: membrane topology and active site location *Mol. Biol. Cell.*, **2003**, *14*, 2447-2460.
156. Liu, Y.; Guo, Z. Acyl coenzymeA: cholesterol acyltransferase family. *Front. Biol. China.* **2009**, *4*, 129-136.
157. Yang, J.; Yan, R.; Roy, A.; Xu, D.; Poisson, J.; Zhang, Y. The I-TASSER Suite: Protein structure and function prediction. *Nature Methods* **2015**, *12*, 7-8.
158. Roy, A.; Kucukural, A.; Zhang, Y. I-TASSER: a unified platform for automated protein structure and function prediction. *Nature Protocols* **2010**, *5*, 725-738.
159. Zhang, Y. I-TASSER server for protein 3D structure prediction. *BMC Bioinformatics* **2008**, *9*, 40-47.
160. Phase 3.1, Schrödinger, LLC, New York, **2009**.
161. Marti-Renom, M. A.; Stuart, A. C.; Fiser, A.; Sanchez, R.; Melo, F.; Sali, A. Comparative protein structure modeling of genes and genomes. *Annu. Rev. Biophys. Biomol.* **2000**, *29*, 291-325.