

REFERENCES

- Abdul Hameed M.D.M., Hamza A., Zhan C-G., Microscopic modes and free energies of 3-phosphoinositide dependent kinas-1 (PDK1) binding with celecoxib and other inhibitors, *J. Phys. Chem. B.*, 110, 26365-26374, 2006.
- Ahmed N., Riley C., Quinn M. A., An immuno histochemical perspective of PPAR β and one of its putative targets PDK1 in normal ovaries, benign and malignant ovarian tumors, *Br. J. Cancer*, 98, 1415-1424, 2008.
- Akritopoulou-Zanze I., Hajduk P. J., Kinase-targeted libraries: The design and synthesis of novel, potent and selective kinase inhibitors. *Drug Discov. Today*, 14, 291-297, 2009.
- Alessi D.R., Deak M., Casamayor A., Caudwell F.B., Morrice N., Norman D.G., Gaffney P., Reese C.B., MacDougall C.N., Harbison D., Ashworth A., Bownes M., 3-P phosphoinositide-dependent protein kinase-1 (PDK1): structural and functional homology with the Drosophila DSTPK61 kinase, *Curr. Biol.*, 7, 776-789, 1997.
- Alessi D.R., James S.R., Downes C.P., Holmes A.B., Gaffney P.R.J., Reese C.B., Cohen P., Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Ba, *Curr. Biol.*, 7, 261-269, 1997.
- American Cancer Society. *Cancer Facts & Figures* 2008. Atlanta, American cancer society, 2008.
- Anderson A.C., The process of structure-based drug design, *Chem Biol*, 10, 787-797, 2003.
- Atmani D., Chaher N., Atmani D., Berboucha M., Debbache N., Boudaoud H., Flavonoids in human health: from structure to biological activity, *Curr Nutr Food Sci.*, 5, 225–237, 2009.
- Ballif B.A., Shimamura A., Pae E., Blenis J., Disruption of 3-Phosphoinositide-dependent kinase 1 (PDK1) signaling by the anti-

tumorigenic and anti-proliferative agent N- α -tosyl-L-phenylalanyl chloromethyl ketone, *J. Biol. Chem.*, 276, 12466-12475, 2002.

Balunas M.J., Kinghorn A.D., Drug discovery from medicinal plants, *Life Sci.*, 78, 431-441, 2005

Barnum D., Greene J., Smellie A., Sprague P., Identification of common functional configurations among molecules, *J. Chem. Inf. Comput. Sci.*, 36, 563-571, 1996.

Bayascas J.R., Leslie N.R., Parsons R., Fleming S., Alessi D.R., Hypomorphic mutation of PDK1 suppresses tumorigenesis in PTEN $^{+/-}$ mice, *Curr. Biol.*, 15, 1839-1846, 2005.

Bazzano L.A., He J., Ogden L.G., Loria C.M., Vupputuri S., Myers L., Whelton P.K., Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, *A J Clin Nutr.*, 76, 93-99, 2002.

Beecher GR., Overview of dietary flavonoids: nomenclature, occurrence and intake, *J Nutr.*, 133, 3248S-3254S, 2003

Belham C., Wu S., Avruch J., Intracellular signaling: PDK1 – a kinase at the hub of things, *Current Biology*, 9, R93-R96, 1999.

Bennett P. N., Brown M. J., Clinical Pharmacology, Churchill Livingstone, 10, 274-290, 2008

Berendsen H.J.C., Postma J.P.M., Van Gunsteren W.F., DiNola A., Haak J.R., Molecular dynamics with coupling to an external bath, *J. Chem. Phys.*, 81, 3681-3694, 1984.

Berendsen H.J.C., Grigera J.R., Straatsma T.P., The missing term in effective pair potentials, *J Phys Chem*, 91, 6269-71, 1987.

Berendsen H.J.C., van der Spoel D., van Drunen R., Gromac: a message passing parallel molecular dynamic implementation, *Comput. Phys. Commun.*, 91, 43-56, 1995.

Bianco R., Melisi D., Ciardiello F., Tortora G., Key cancer cell signal transduction pathways as therapeutic targets. *Eur. J. Cancer*, 42, 290-294, 2006.

Biondi R. M., Phosphoinositide-dependent protein kinase 1, a sensor of protein conformation, *Trends Biochem Sci.* ,29, 136-142,2004.

Biondi, R.M., Komander, D., Thomas C.C., Lizcano J.M., Deak M., Alessi, D.R., VanAalten D.M.F., High resolution crystal structure of the human PDK1 catalytic domain defines the regulatory phosphopeptide docking site, *EMBO J.*, 21, 4219-4228, 2002,

Bogoyevitch M. A., Fairlie D. P., A new paradigm for protein kinase inhibition:blocking phosphorylation without directly targeting ATP binding, *Drug. Discov.Today*, 12, 622-633, 2007.

Brazil D.P., Hemmings B.A., Ten years of protein kinase B signaling: a hard Akt to follow, *Trends Biochem. Sci.*, 26, 657-664, 2001.

Cao Y., Molecular mechanisms and therapeutic development of angiogenesis inhibitors, *Adv. Cancer Res.*, 100, 113-131, 2008.

Casamayor A., Morrice N., Alessi D. R., Phosphorylation of Ser 241 is essential for the activity of PDK1 identification of five sites of phosphorylation in vivo, *Biochem. J.*, 342, 287-292, 1999.

Cen L., Hsieh F-C., Lin H-J., Chen C-S., Qualman S. J., Lin J., PDK-1/AKT pathway as a novel therapeutic target in rhabdomyosarcoma cells using OSU-03012compound, *Br. J. Cancer.*, 97, 785-791,2007.

Chahar M.K., Sharma N., Dobhal M.P., Joshi Y.C., Flavonoids: versatile source of anticancer drugs, *Phcog Rev*, 5,1–12,2011.

Cheatham T.E., Kollman P.A., Molecular modeling of nucleic acid structure: Energy and sampling", *Ann Rev Phys Chem*, 51,435-451, 2000.

Cheng, Merz K.M., "Prediction of aqueous solubility of a diverse set of compounds using quantitative structure-property relationships." *J.Med Chem*, 46, 3572–3580, 2003.

Cherry M., Williams D. H., Recent kinase and kinase inhibitor X-ray structures: Mechanisms of inhibition and selectivity insights, Curr. Med. Chem., 11,663-673, 2004.

Chiang A.C., Massagué J., "Molecular basis of metastasis". The New England Journal of Medicine, 359, 2814–23, 2008.

Chiang Y.K., Kuo C.C., Wu Y.S., Chen C.T., Coumar M.S., Wu J.S., Hsieh H.P., Chang C.Y., Jseng H.Y., Wu M.H., Leou J.S., Song J.S., Chang J.Y., Lyu P.C., Chao Y.S., Wu S.Y., Generation of ligand-based pharmacophore model and virtual screening for identification of novel tubulin inhibitors with potent anticancer activity, J Med Chem, 52, 4221-4233, 2009.

Choy Y.B., Prausnitz M.R., The rule of five for non-oral routes of drug delivery, ophthalmic, inhalation and transdermal, Pharm. Res., 28, 943-948, 2011.

Clifford M.N., Diet-derived phenols in plasma and tissues and their implications for health, Planta Med, 12,1103–1114, 2004.

Coleman M. P., Quaresma M., Berrino F., Lutz J. M., Angelis R., Capocaccia R., baili P., Rachet B., Gatta G., hakulinen T., Micheli A., Sant M., Weir H. K., Elwood J. M., Tsukuma H., Koifman S., E Silva G. A., Franscisci S., Santaguilani M., Verdecchia A., Storm H. H., Young J. L., Concord working group. Cancer survival rate in five continents: a worldwide population-based study (CONCORD), Lancet Oncol., 9, 730-756, 2008.

Combs A.P., Structure-based drug design of new leads for phosphatase research, IDrugs ,10,112-115, 2007.

Congreve M., Murray C. W., Blundell T. L., Structural biology and drug discovery. Drug Discov. Today, 10, 895-907,2005.

Costanzi S., Tikhonova I. G., Harden T. K., Jacobson K. A., Ligand and structure based methodologies for the prediction of the activity of G protein-coupledreceptor ligands, J. Comput. Aided Mol. Des.,23,747-54, 2008.

Coumar M.S., Leou J.S., Shukla P., Wu J.S., Dixit A.K., Lin W.H., Chang C.Y., Lien TW, Tan UK, Chen C.H., Hsu J.T., Chao Y.S., Wu S.Y., Hsieh H.P., Structure-based drug design of novel Aurora kinase A inhibitors: structural basis for potency and specificity, *J Med Chem*, 52,1050-1062,2009.

Currie R.A., Walker K.S., Gray A., Deak M., Casamayor A., Downes C.P., Cohen P., Alessi D.R., Lucocq J., Role of phosphatidylinositol 3,4,5-triphosphate in regulating the activity and localization of 3-phosphoinositide dependent protein kinase-1, *Biochem. J.*, 337, 575-583, 1999.

Dancey J., Sausville E. A., Issues and progress with protein kinase inhibitors for cancer treatment, *Nat. Rev. Drug Discov.*, 2, 296-313, 2003.

Delano W. L., The case for open source software in drug discovery, *Drug Discov. Today*, 10, 213-217, 2005.

Dixon S.L., Merz K.M., "One-dimensional molecular representations and similarity calculations: methodology and validation," *Journal of Medicinal Chemistry*, 44 ,3795–3809, 2001.

Drews J., "Drug Discovery,A Historical Perspective", *Science* 287, 1960-3,2000.

Dror O., Shulman-Peleg A., Nussinov R., Wolfson H., Predicting molecular interactions in silico. I. An updated guide to pharmacophore identification and its applications to drug design, *Front. Med.Chem.* 3, 551–584, 2006.

Dong L. Q., Liu F., PDK2: the missing piece in the receptor tyrosine kinase signaling pathway puzzle, *Am. J. Physiol. Endocrinol. Metab.*, 289, E187-E196,2005.

Egan W.J., Merz K.M., Baldwin J.J., Prediction of Drug Absorption Using Multivariate Statistics, *J. Med. chem.* 43,3867-3877,(2000).

Ehrlich P., Ueber den jetzigen Stand der Chemotherapie. *Ber. Dtsch. Chem.Ges.* 42, 17–47,2006.

Ertl P., Rohde B., Selzer P., Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties, *J. Med. Chem.* 43,3714–3717, 2000

Essmann U., Perera L., Berkowitz M.L., Darden T., Lee H., Pedersen L.G., A smooth particle meso method, *J. Chem. Phys.*, 103, 8577-8595, 1995.

Fabian, M.A., Biggs III, W.H., Treiber, D.K., Atteridge, C.E., Azimioara, M.D., Benedetti, M.G., Carter, T.A., Ciceri, P., Edeen, P.T., Floyd, M., Ford, J.M., Galvin, M., Gerlach, J.L., Gortzfeld, R.M., Herrgard, S., Insko, D.E., Insko, M.A., Lai, A.G., Lelias, J.-M., Mehta, S.A., Milanov, Z.V., Velasco, A.M., Wodicka, L.M., Patel, H.K., Zarrinkar, P.P., Lockhart, D.J. A small molecule-kinase interaction map for clinical kinase inhibitors. *Nature Biotech.* 2005, 23, 329-336.

Fang S.C., Hsu C.L., Lin H.T., Yen G.C., Anticancer effects of flavonoid derivatives isolated from *Millettia reticulata* Benth in SK-Hep-1 human hepatocellular carcinoma cells, *J Agric Food Chem.* 58,814–820, 2010.

Feldman R.I., Wu J.M., Polokoff M.A., Kochanny M.J., Dinter H., Zhu D., Biroc S.L., Alicke B., Bryant J., Yuan S., Buckman B.O., Lentz D., Ferrer M., Whitlow M., Alder M., Finster S., Chang Z., Arnaiz D.O., Novel small molecule inhibitors of 3-phosphoinositide dependent kinase-1, *J. Biol. Chem.*, 280,19867-19874, 2005.

Fletcher R. (ed.), Optimization, Academic Press: New York and London, 1969.

Flynn P., Wong M., Zavar M., Dean N.M., Stokoe D., Inhibition of PDK-1 activity causes a reduction in cell proliferation and survival, *Curr. Biol.*, 10,1439-1442, 2000.

Fujita N., Tsuruo T., Survival-signaling pathway as a promising target for cancer chemotherapy, *Cancer Chemother. Pharmacol.*, 52, S24-S28, 2003.

Gane P.J., Dean P.M., Recent advances in structure-based rational drug design, *Curr Opin Struct Biol.*, 10, 401-404, 2000.

Gao N., Flynn D.C., Zhang Z., Zhong X.S., Walker V., Liu K.J., Shi X., Jiang B.H., G1 cell cycle progression and the expression of G1 cyclins

are regulated by PI3K/Akt/mTOR/p70S6K1 signaling in human ovarian cancer cells, Am. J. Physiol. Cell. Physiol., 287, C281-C291, 2004.

Gao X., Yo P., Harris T.K., Improved yields for baculovirus-mediated expression of human His6-PDK1 and His-PKB β /AKT2 and characterization of phosphor-specific isoforms for design of inhibitors that stabilize inactive conformations, Protein Expr. Purif., 43, 44-5, 2005.,

Garcia M., Jemal A., Ward E. M., Center M. M., Hao Y., Siegel R. L., Thun M. J., Global cancer facts & figures 2007, Atlanta, GA: American Cancer Society, 2007.

Gibbs J. B., Mechanism-based target identification and drug discovery in cancer research, Science, 287, 1969-1973, 2000.

Gill A. New lead generation strategies for protein kinase inhibitors-fragment based screening approaches, Mini Rev. Med. Chem. , 4, 301-311, 2004.

Gould K.S., Lister C, Flavonoid functions in plants. In: Andersen OM, Markham KR (eds) Flavonoids chemistry, biochemistry and applications, CRC Press Taylor & Francis Group, London, 397-442, 2005

Guend P., Evolution of the pharmacophore concept in pharmaceutical research. In Pharmacophore Perception, Development, and Use in Drug Design, Guñer

Guex N., Diemand A., Peitsch M.C., Protein modelling for all, Trends Biochem Science, 24, 364-367, 1999.

Halazy S., Signal transduction: An exciting field of investigation for small molecule drug discovery, Molecules, 8, 349-358, 2003.

Hammer B., “Recurrent Networks for Structured Data— A Unifying Approach and its Properties,” Cognitive Systems Research, 3, 145-165, 2002.

Harborne J.B. (ed), The flavonoids: advances in research since 1986. Chapman & Hall, London, 1994

Harborne J.B., Williams C.A., Advances in flavonoid research since 1992, *Phytochemistry*, 55,481–504, 2000.

Hassan S., Mathesius U., The role of flavonoids in root– rhizosphere signalling: opportunities and challenges for improving plant–microbe interactions, *J Exp Bot*, 63,3429–3444, 2012

Hennessy B.T., Smith D.L., Ram P.T., Lu Y., Mills G.B., Exploiting the PI3K/Akt pathway for cancer drug discovery, *Nature Rev. Drug Discov.*, 4, 988-1004, 2005.

Hess B., Bekker H., Berendsen H.J.C., Fraaije J.G.E.M. , LINCS: A linear constraint solver for molecular simulations, *J Comput Chem*,18,1463-1472,1997.

Hillisch A., Pineda L.P., Hilgenfeld R., “Utility of homology models in the drug discovery process” *Drug Discov. Today* ,9,659-669, 2004.

Hubbard R.E., “3D Structure and the Drug Discovery Process”, RSC Publishing, 2006.

Humphrey W., Dalke A., Schulten K., "VMD - Visual Molecular Dynamics", *J. Molec. Graphics*, 14, 33-38, 1996.

Jain R. K., Tomaso E. D., Duda D. G., Loeffler J. S., Sorensen A. G., Batchelor Panno J., *Cancer: The role of genes, lifestyle and environment*. Facts on file, Inc.New York. 2005

Karplus M., McCammon J.A., Molecular dynamics simulations of biomolecules, *Nat Struct Biol*,9,646-52,2002.

Kawai,S., Tomono T., Katase E., Ogawa,K. and Yano M., Quantitation of flavonoid constituents in Citrus fruits, *Journal Agricultural Food Chemistry*, 47,3565-3571,1999

Kerr J.F., Wyllie A.H., Currie A.R., "Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics", *Br. J. Cancer*, 26 239–57,1972.

Khan A., Prakash A., Kumar D., Rawat A., Srivastava R., Srivastava R., Virtual screening and pharmacophore studies for ftase inhibitors using

Indian plant anticancer compounds database,Bioinformation ,5,62-66, 2010.

Kim D., Chung J., Akt: Versatile mediator of cell survival and beyond, *J. Biochem. Mol. Biol.*, 35, 106-115,2002.

Klebe G., Recent developments in structure-based drug design,*J Mol Med*, 78, 269- 281, 2000.

Komander D., Kular G.S., Schuttelkopf A.W., Prakash K.R.C., Bain J., Elliott M., Garrido-franco M., Kozikowski A.P., Alessi, D.R., VanAalten, D.M.F.,Interaction of LY333531 and other bisindolyl maleimide inhibitors with PDK1.*Structure* ,12, 215-226, 2004.

Komander D., Kular G.S., Bain. J., Elliott, M., Alessi, D.R., Van Aalten, D.M.F.,Structural basis for UCN-01 (7-hydroxy staurosporine) specifically and PDK1 (3-phosphoinositide dependent protein kinase-1) inhibition. *Biochem. J.*,375,255-262, 2003, .

Komander, D., Kular, G., Deak, M., Alessi, D.R., VanAalten, D.M.F.,Role of T-loop phosphorylation in PDK1 activation, stability, and substrate binding, *J. Biol.Chem.*, 280, 18797-18802, 2005.

Lawlor M.A., Mora A., Ashby P.R., Williams M.R., Murray-trait V., Malone, L., Prescott A.R., Lucocq J.M., Alessi D.R., Essential role of PDK1 in regulating cell size and development in mice,*EMBO J.*, 21, 3728-3738, 2002.

Leeawen P.A.M.V., Flavonoids: a review of probable mechanisms of action and potential applications, *Am J Clin Nutr* ,74,418–425, 2001.

Lengauer T., Rarey M., Computational methods for biomolecular docking, *Curr. Opin. Struct. Biol.*,6,402–6,1996.

Leslie N.R., Downes C.P., PTEN: the downside of PI3-kinase signaling, *Cell.Sign.*,14, 285-29, 2002.

Li A. P., Screening for human ADME/Tox drug properties in drug discovery, *Drug Discov Today*, 6,357366, 2001.

Li D., Xie K., Wolff, R., Abbruzzesse J. L., Pancreatic Cancer. Lancet, 363, 1049-1057, ,2004.

Li, H., Sutter J., Hoffmann R., HypoGen:An Automated System for Generating Predictive 3D Pharmacophore Models., in Pharmacophore Perception, Development, and use in Drug Design, Iul Biotechnology Series 2, International University Line: La Jolla, CA,171–189.189In, Guner OF (ed), 2000.

Li,Z., Scheraga H.A., Monte Carlo-minimization approach to the multiple-minima problem in protein folding, Proc. Natl. Acad. Sci. U. S. A. ,84,6611–6615, 1987.

Liang K., Lu Y., Li X., Zeng X., Glazer R.I., Mills G.B., Fan Z., Differential roles of phosphoinositide-dependent protein kinase-1 and Akt1 expression and phosphorylation in breast cancer cell resistance to plaxitaxel, doxorubicin and gemcitabine, Mol. Pharmacol., 70, 1045-1052, 2006.

Lin H-J., Hsieh F-C., Song H., Lin J., Elevated phosphorylation and activation of PDK-1/AKT pathway in human breast cancer, British J. cancer, 93,1372-1381, 2005.

Liou J..P, Mahindroo N., Chang C.W., Guo F.M., Lee S.W., Tan U.K., Yeh T.K, Kuo C.C., Chang Y.W.,Lu P.H., Tung Y.S., Lin K.T., Chang J.Y., Hsieh H.P., Structure-activity relationship studies of 3-aryliindoles as potent antimitotic agents, ChemMedChem, 1,1106-1118, 2006.

Lipinski C. A.,Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Methods ,44, 235–249,2001.

Luo J., Manning B.D., Cantley L.C., Targeting the PI3K-Akt pathway in human cancer: Rationale and promise. Cancer Cell, 4, 257-262, 2003.

Manning G., Whyte D. B., Martinez R., Hunter T., Sudarsanam S., The proteinkinase complement of the human genome, Science, 298, 1912-1934,2002.

Martin G.S., Cell signaling and cancer, Cancer cell, 4, 167–174,2003.

Milne G.W.A., Nicklaus M.C., Driscoll J.S., Wang S., Zaharevitz D., The NCI Drug Information System 3D Database, *J. Chem. Inf. Comput. Sci.*, 34,1219-1224 1994.

Miyamoto S., Kollman P.A., Settle: An analytical version of the SHAKE and RATTLE algorithm for rigid water models, *J.Compu Chem*,13, 952-962,1992.

Mora A., Komander D., van Aalten D.M.F., Alessi D.R., PDK1, the master regulator of AGC kinase signal transduction, *Semin. Cell. Dev. Biol.*, 15, 161-170,2004.

Moraitakis G., Purkiss A.G., Goodfellow J.M., Interactive Essential Dynamics, *Rep Prog*,66,383-406 ,2003.

Mustata G., Li M., Zevola N., Bakan A., Zhang L., Epperly M., Greenberger J.S., Yu J., Bahar I., Development of small-molecule PUMA inhibitors for mitigating radiation induced cell death.,*Curr Top Med Chem*, 11, 281-290,2011.

Nakamura K., Sakaue H., Nishizawa A., Matsuki Y., Gomi H., Watanabe E., Hiramatsu R., Tamamori-Adachi M., Kitajima S., Noda T., Ogawa W., Kasuga M., PDK1 regulates cell proliferation and cell cycle progression through control of cyclin D1 and P27Kip1 expression, *J. Biol. Chem.*, 25, 17702-17711, 2008.

Newton A.C., Regulation of the ABC kinases by phosphorylation: protein kinase C as a paradigm, *Biochem. J.*, 370, 361-371, 2003.

Nijeveldt R., Nood E.V., Hoorn D.E.C.V., Boelens P.G., Norren K.V.,

Norberg J., Nilsson L.,*Acc Chem Res*, Molecular dynamics applied to nucleic acids,35,465-72, 2002.

O.F., Ed., International University Line (IUL), 171–189,2000.

Ong K.C., KhooH.E., " Bio logical effects of myricetin", *Gen Pharmacol*, 29,121 -126, 1997.

Ooms F., Molecular modeling and computer aided drug design. Examples of their applications in medicinal chemistry, Curr. Med. Chem. , 7, 141-158, 2000.

Orti L., Carbajo R.J., Pieper U., Eswar N., Maurer S.M., Rai A.K., Taylor G., Todd M.H., Pineda-Lucena A., Sali A., Marti-Renom M.A., A kernel for open source drug discovery in tropical diseases, PLoS Negl Trop Dis. 3,e418, 2009.

Parkin D. M., Bray F., Ferlay J., Pisani P., Estimating the world cancer burden: Globocan 2000, Int. J. Canc94, 153-156, 2001.

Pecorino L., Molecular biology of cancer. Mechanisms, targets and therapeutics. Oxford university press Inc. 2008.

Perrotti N., He R.A., Phillips S.A., Haft C.R., Taylor S.I., Activation of serum- and glucocorticoid-induced protein kinase (sgk) by cyclic AMP and insulin, J. Biol. Chem., 276, 9406-9412, 2001.

Pinner S., Sahai E., PDK1 regulates cancer cell motility by antagonising inhibition of ROCK1 by RhoE, Nature Cell Biol., 2, 127-137,2008.

Poste G., Fidler I.J., "The pathogenesis of cancer metastasis", Nature, 283, 139–46,1980.

Pouget C., Lauthier F., Simon A., Flavonoids: Structural requirements for antiproliferative activity on breast cancer cells, Bioorg Med Chem Lett,11,3095– 3097, , 2001.

Pullen N., Dennis P.B., Andjelkovic M., Dufner A., Kozma S.C., Hemmings B.A., Thomas G., Phosphorylation and activation of p70s6k by PDK1, Science,279, 707-710,1998.

Raguz S., Yague E.,Resistance to chemotherapy: new treatments and novel insights into an old problem, Br. J. Cancer, 99, 387-391, 2008.

Ramos S.,Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention, J Nutr Biochem, 18,427-442, 2007.

Reddy M.R., Erion M.D., "Computer aided drug design strategies used in discovery of fructose 1,6 biphosphatase inhibitors", Curr. Pharm. Des ,11, 283-294,2005.

Remers W. A., Antineoplastic agents. In Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry, Block, J. H., Beale Jr J. M. Eds.,Lippincott Williams & Wilkins. Philadelphia, 2004

Richards W.G., "Computer-Aided Drug Design," Pure P. P. KORE ET AL. 147 and Applied Chemistry, 66,1589- 1596, 1994.

Richards W.G., "Computer-aided drug design", Pure & Appl. Chern., 66, 1589-1596, 1994.

Ross J. A., olshan A. F., Pediatric cancer in the United States: The children's oncology group epidemiology research program, Cancer Epidemiol. Biomarkers Prev., 13, 1552-1554, 2004.

Ross J.A., Kasum C.M., Dietary flavonoids: bioavailability, metabolic effects, and safety,Annu Rev Nutr, 22,19-34, 2002.

Rother K., Dunkel M., Michalsky E., Trissl S., Goede A., Leser U., Preissner R., A structural keystone for drug design", Journal oIntegrative Bioinformatics, 22,1137-1143, 2006.

Sahoo S., Brickley D.R., Kocherginsky M., Conzen S.D., Coordinate expression of PI3-Kinase downstream effectors serum and glucocorticoid-induced kinase (SGK-1) and Akt-1 in human breast cancer, Eur. J. Canc., 41,2754-2759, 2005.

Samanta A., Das G., Das S.K., Roles of flavonoids in plants, Int J Pharm Sci Technol, 6,12–35, 2011

Savage S., Eraser: A Dynamic Data Race Detector for Multithreaded Programs, ACM Transactions on Computer Systems, 15,391-411, 1997.

Schafferhans A., Klebe G., "Docking Ligands onto Binding Site Representations Derived from Proteins built by Homology Modelling", J. Mol. Biol. 307, 407±427, 2001.

Schneider G., Giller T., Neidhart W., Schmid G., Scaffold-hopping” by topological pharmacophore search: a contribution to virtual screening, Angew. Chem. Int. 38, 2894–2896, 1999.

Shoichet B.K., Virtual screening of chemical libraries, Nature 432,862-865, 2004.

Sies H., Polyphenols and health: update and perspectives, Arch Biochem Biophys., 501, 2–5,2010.

Smith J.A., Poteet-Smith C.E., Xu Y., Errington T.M., Hecht S.M., Lannigan D.A., Identification of the first specific inhibitor of p90 ribosomal S6 kinase (RSK) reveals an unexpected role for RSK in cancer cell proliferation, Cancer. Res. 65, 1027-1034, 2005.

Stokoe D., Stephens L.R., Copeland T., Gaffney P.R., Reese C.B., Painter G.F., Holmes A.B., McCormick F., Hawkins P.T., Dual role of phosphatidylinositol-3,4,5-trisphosphate in the activation of protein kinase B, Science, 277,567–570, 1997

Susnow R.G.,Dixon S.L., “Use of robust classification techniques for the prediction of human cytochrome P450 2D6 inhibition,” Journal of Chemical Information and Computer Sciences, 43,1308–1315, 2003.

Szakacs G., Paterson J.K., Ludwig J. A., Booth-Genthe C., Gottesman M.M., Targeting multidrug resistance in cancer, Nat. Rev. Drug. Disc. 5, 219-234, 2006.

T. T., Angiogenesis in brain tumor, Nat. Rev. Neurosci., 8, 610-622, 2007.

Tanaka H., Fujita N., Tsuruo T., 3-Phosphoinositide dependent protein kinase-1 mediated I κ B kinase β (IKKB) phosphorylation activates NF- κ B signaling, J. Biol. Chem, 280, 40965-40973,2005.

The Spread of Tumors in the Human Body. London, Butterworth & Co, 1952.

Toker, A., Newton. A.C. Cellular signaling: pivoting around PDK-1. Cell. 2000,103, 185-188.

Ulf M., Povl K.L., Tommy L., Textbook of Drug Design and Discovery, Washington D.C.M, Taylor & Francis, 2002.

Van de Waterbeemd H., Smith D. A., Beaumont K., Walker D. K., Property-based design: Optimisation of drug absorption and pharmacokinetics, *J. Med. Chem.* 44, 1313–1333, 2001.

Van Montfort R.L., Workman P., Structure-based design of molecular cancer therapeutics, *Trends Biotechnol.* 27, 315-328, 2009.

Vanhaesebroeck B., Alessi D.R. ,The PI3K-PDK1 connection: more than just a road to PKB, *Biochem. J.*, 346, 561-576, 2000.

Vara J.A.F., Casado E., Castro J.D., Cejas P., Belda-Iniesta C.,Gonzalez-Baron M., PI3K/Akt signalling pathway and cancer, *Cancer Treat. Rev.*, 30, 193-204, 2004.

Venkatachalam C.M., Jiang X., Oldfield T. , Waldman M. , LigandFit: a novel method for the shape-directed rapid docking of ligands to protein active sites, *J Mol Graph Model.*, 4,289-307,2002.

Ververidis F., Trantas E., Douglas C., Vollmer G., Kretzschmar G., Panopoulos NBiotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I: chemical diversity, impacts on plant biology and human health, *Biotechnol J*, 2,1214–1234, 2007.

Veselovsky A. V., Ivanov A. S.,Strategy of computer-aided drug design, *Curr. drug targets infect. disord.*, 3, 33-40, 2003.

Vulpetti A., Bosotti R., Sequence and structural analysis of kinase ATP pocket residues, *IL Farmaco* , 59, 759-765, 2004.

Wang Y., Chiu J.F. , He Q.Y., “Proteomics in Computer-Aided Drug Design”, *Current Computer-Aided Drug Design*, 1, 43, 2005.

Waterbeemd H.V.,Smith DA, Jones BC, Lipophilicity in PK design: methyl, ethyl, futile, *J. Comput. Aid. Mol. Des.*,15,273–286, 2001

Waterbeemd H.V.D., Carter R. E., Grassy G., Kubiny H., Martin Y. C., Tute M. S., WILLETT P., “Glossary Of Terms Used In Computational Drug Design”, *Pure&Appl. Chem.*, 69, 1137-1152, 1997.

Waterbeemd H.V.D., Gifford E., ADMET in silico modeling: towards prediction paradise?, *Nature*, 2 192–204,2003.

Wermuth C.G., Ganellin C.R., Lindberg P., Mitscher L.A., Glossary of terms used in medicinal chemistry (IUPACRecommendations 1997), *Annu. Rep. Med. Chem.* 33, 385–395, 1998.

Wermuth C.G., Pharmacophores: historical perspective and viewpoint fromamedicinal chemist. In *Pharmacophores and Pharmacophore Searches*, In Langer T., Hoffmann R.D., Ed, Wiley–VCH, 3–13, 2006.

Wick M. J., Ramos F. J., Chen H., Quon M. J., Dong L. Q., Liu F., Mouse 3'-phosphoinositide-dependent protein kianse-1 undergoes dimerization and trans-phosphorylation in the activation loop, *J. Biol. Chem.*, 278,42913-42919, 2003.

Wong M.T., Chen Steve S-L, Emerging roles of interferon-stimulated genes in the innate immune response to hepatitis C virus infection, *Cellular & Molecular Immunology* ,1-25, 2014.

World Cancer Report 2014.

Wu G., Robertson D.H., Brooks C.L., Vieth M. III,Detailed analysis of grid-based molecular docking: A case study of CDOCKER—A CHARMM-based MD docking algorithm, *J. Comput Chem*, 24,1549-1562, 2003

Xia X., Maliski E.G., Gallant P., Rogers D., Classification of kinase inhibitors using a Bayesian model. *J Med Chem.*, 47, 4463-70, 2004.

Xiao C.W. ,Health effects of soy protein and isoflavones in humans, *J Nutr*, 138,1244S–1249S, 2008.

Young D.C. “Computational drug design. A guide for computational and medicinal chemists ,”John Wiley & Sons, Inc: Hoboken, NJ, 2009.

Yu J., Zhang L., PUMA, a potent killer with or without p53, *Oncogene*, 27, S71-S83,2009.

Zeng X., Xu H., Glazer R.I., Transformation of mammary epithelial cells by 3-Phosphoinositide dependent protein kinase-1 (PDK-1) is associated with the induction of protein kinase C α , Canc. Res., 62, 3538-3543,2002.

Zhang J., Yang P. L., Gray N. S., Targeting cancer with small molecule kinase inhibitors, Nat. Rev. Cancer, 9, 28-39, 2009.

Zhang Q., Thomas S.M., Lui V.W.Y., Xi S., Siegfried J.M., Fan H., Smithgall T.E., Mills G.B., Grandis J.R., Phosphorylation of TNF- α converting enzyme by gastrin releasing peptide induces amphiregulin release and EGF receptor activation, Proc. Natl. Acad. Sci. USA. ,103, 6901-6906, 2006.

