REFERENCES

Abbasi, M., Sadeghi-Aliabadi, H., Hassanzadeh, F., and Amanlou, M., 2015 Prediction of dual agents as an activator of mutant p53 and inhibitor of Hsp90 by docking, molecular dynamic simulation and virtual screening, *J. Mol. Graph.*, 61, 186-195.

Abedinifar, F., Babazadeh Rezaei, E., Biglar, M., Larijani, B., Hamedifar, H., Ansari, S., and Mahdavi, M., 2021, Recent strategies in the synthesis of thiophene derivatives: highlights from the 2012–2020 literature, *Mol. Divers.*, 25(4), 2571 - 2604.

Abosalim, H. M., Nael, M. A., and El-Moselhy, T. F., 2021, Design, synthesis and molecular docking of chalcone derivatives as potential anticancer agents, *ChemistrySelect*, 6(4), 888–895.

Achutha, D. K., Vagish, C. B., Renuka, N., Lokeshwari, D. M., and Kariyappa, A. K., 2020, Green synthesis of novel pyrazoline carbothioamides: A potent antimicrobial and antioxidant agents, *Chem. Data. Collect.*, 28, 100445.

Adelusi, T. I., Oyedele, A. Q. K., Boyenle, I. D., Ogunlana, A. T., Adeyemi, R. O., Ukachi, C. D., Idris, M. O., Olaoba, O. T., Adedotun, I. O., Kolawole, O. E., Xiaoxing, Y., and Abdul-Hammed, M., 2022, Molecular modeling in drug discovery, *Inform. Med. Unlocked,* 29, 100880.

Ahmad, M. R., and Bano, N., 2011, Conventional and Microwave assisted Synthesis of 1, 3-Diphenyl-2-Propenone derivatives and cytotoxic, antibacterial activities*, Int. J. Chemtech Res.,* 3(3), 1470-1478.

Ahmad Mir, S., Meher, R. K., Baitharu, I., and Nayak, B., 2022, Molecular dynamic simulation, free binding energy calculation of Thiazolo-[2,3-b]quinazolinone derivatives against EGFR-TKD and their anticancer activity, *Results Chem.,* 4*,* 100418.

Aksöz, B.E. and Ertan, R., 2012. Spectral properties of chalcones II. *Fabad J. Pharm. Sci*, *37*(4), 205-216.

Alidmat, M. M., Khairuddean, M., Kamal, N. N. S. N. M., Muhammad, M., Wahab, H. A., Althiabat, M. G., and Alhawarri, M. B., 2022, Synthesis, characterization, molecular docking and cytotoxicity evaluation of new thienyl chalcone derivatives against breast cancer cells, *Syst. Rev. Pharm.,* 13(1), 1 – 11.

Alex, J. M., Singh, S., and Kumar, R., 2014, 1-Acetyl-3, 5-diaryl-4, 5-dihydro (*1H*) pyrazoles: exhibiting anticancer activity through

intracellular ROS scavenging and the mitochondria-dependent death pathway, *Archiv der Pharmazie*, 347(10), 717-727.

Amin, K.M., Eissa, A.A.M., Seri, S.M.A., Awadallah, F.M., and Hassan, G.S., 2013, Synthesis and Biological Evaluation of Novel Coumarin-Pyrazoline Hybrids Endowed With Phenylsulfonyl Moiety as Antitumor Agents, *Eur. J. Med. Chem.*, 60, 187-198.

Anonim, 2020, *Cancer incidence in Indonesia,* The Global Cancer Observatory, International Agency for Research on Cancer, World Health Organization, Lyon.

Arora, P., Arora, V., Lamba, H. S., and Wadhwa, D., 2012, Importance of heterocyclic chemistry: a review, *Int. J. Pharm. Sci.*, 3(9), 2947–2954.

Arteaga, C.L., Ramsey, T.T., Shawver, L.K., Guyer, C.A., 1997, Unliganded epidermal growth factor receptor dimerization induced by direct interaction of quinazolines with the ATP binding site, *J. Biol. Chem.,* 272(37), 23247–23254.

Bakar, A. A., Akhtar, M. N., Ali, N. M., Yeap, S. K., Quah, C. K., Loh, W. S., Alitheen, N. B., Zareen, S., Ul-Haq, Z., and Shah, S. A. A., 2018, Design, synthesis and docking studies of flavokawain B type chalcones and their cytotoxic effects on MCF-7 and MDA-MB-231 cell lines, *Molecules*, 23(3), 1–14.

Basnet, A., Thapa, P., Karki, R., Choi, H., Choi, J. H., Yun, M., Jeong, B. S., Jahng, Y., Na, Y., Cho, W. J., Kwon, Y., Lee, C. S., and Lee, E. S., 2010, 2,6-Dithienyl-4-furyl pyridines: Synthesis, topoisomerase I and II inhibition, cytotoxicity, structure-activity relationship, and docking study, *Bioorg. Med. Chem. Letters*, 20(1), 42–47.

Bekker, H., Berendsen, H. J. C., Dijkstra, E. J., Achterop, S., Vondrumen, R., Vanderspoel, D., and Renardus, M. K. R., 1993, Gromacs-a parallel computer for molecular-dynamics simulations, *Proceeding: 4th International Conference on Computational Physics,* 92, 252-256.

Bennett, C. H., 1976, Efficient estimation of free energy differences from Monte Carlo data*, J. Comput. Phys.,* 22(2), 245–268.

BIOVIA, Dassault Systemes, Discovery Studio 2017. San Diego: Dassault Systemes, 2020.

Bondi, A., 1964, Van der Waals volumes and radii, *J. Phys. Chem.* 68, 441–451.

Bruckner, S., and Boresch, S., 2011, Efficiency of alchemical free energy simulations. I. A practical comparison of the exponential formula,

thermodynamic integration, and Bennett's acceptance ratio method, *J. Comput. Chem.*, 32(7), 1303-1319.

Buganim, Y., Solomon, H., Rais, Y., Kistner, D., Nachmany, I., Brait, M., Madar, S., Goldstein, I., Kalo, E., Adam, N., Gordin, M., Rivlin, N., Kogan, I., Brosh, R., Sefadia-Elad, G., Goldfinger, N., Sidransky, D., Kloog, Y., and Rotter, V., 2010, P53 Regulates the Ras Circuit To Inhibit the Expression of a Cancer-Related Gene Signature by Various Molecular Pathways, *Cancer Res.*, 70(6), 2274–2284.

Burry, R. W., 2011, Controls for immunocytochemistry: An update, *J. Histochem. Cytochem.*, 59(1), 6–12.

Bussi, G., Donadio, D., and Parrinello, M., 2007, Canonical sampling through velocity rescaling, *J. Chem. Phys*., 126(1), 014101.

Carradori, S., Secci, D., Bolasco, A., De Monte, C., and Yáñez, M., 2012, Synthesis and selective inhibitory activity against human COX-1 of novel 1-(4-substituted-thiazol-2-yl)-3,5-di(hetero)aryl-pyrazoline derivatives, *Archiv. Der. Pharmazie*, 345(12), 973–979.

CavigLia, J. M., and Schwabe, R. F., 2014, Experimental Hepatocarcinogenesis. In *Pathobiology of Human Disease: A Dynamic Encyclopedia of Disease Mechanisms*, Academic Press: Oxford.

CCRC, 2009, *Prosedur Uji Sitotoksik Metode MTT*, Cancer Chemoprevention Research Center, Yogyakarta, Universitas Gadjah Mada, 1–7.

Chernyshov, V. V., Popadyuk, I. I., Yarovaya, O. I., and Salakhutdinov, N. F., 2022, Nitrogen-containing heterocyclic compounds obtained from monoterpenes or their derivatives: Synthesis and properties, *Top. Curr. Chem., 380*(5), 42.

Chicco, D., Warrens, M. J., and Jurman, G., 2021, The coefficient of determination R-squared is more informative than SMAPE, MAE, MAPE, MSE and RMSE in regression analysis evaluation, *PeerJ Comput. Sci.,* 7, e623.

Childers, M. C., and Daggett, V., 2017, Insights from molecular dynamics simulations for computational protein design, *Mol. Syst. Des. Eng.*, 2(1), 9–33.

Chouiter, M. I., Boulebd, H., Pereira, D. M., Valentão, P., Andrade, P. B., Belfaitah, A., and Silva, A. M. S., 2020, New chalcone-type compounds and 2-pyrazoline derivatives: Synthesis and caspase-dependent anticancer activity. *Future Med. Chem*., 12(6), 493–509.

Chunaifah, I., 2022, Synthesis of thiophene-based chalcone and *N*-phenylpyrazoline derivatives and cytotoxic activity against cancer cell lines, *Thesis*, Department of Chemistry, Universitas Gadjah Mada, Yogyakarta.

Chunaifah, I., Venilita, R.E., Jiwamurwa, P., Tjitda, P., Astuti, E., and Wahyuningsih, T.D., 2024. Thiophene-based N -phenyl pyrazolines : Synthesis , anticancer activity , molecular docking and ADME study, *J. Appl. Pharm. Sci.,* 14, 63–71.

Clusan, L., Ferrière, F., Flouriot, G. and Pakdel, F., 2023. A basic review on estrogen receptor signaling pathways in breast cancer, *Int. J. Mol. Sci.,* 24(7), p.6834.

Cornell, W. D., Cieplak, P., Bayly, C. I., Gould, I. R., Merz, K. M., Ferguson, D. M., Spellmeyer, D. C., Fox, T., Caldwell, J. W., and Kollman, P. A., 1995, A second generation force field for the simulation of proteins, nucleic acids, and organic molecules, *J. Am. Chem. Soc.*, 117(19), 5179–5197.

Darden, T., York, D., and Pedersen, L., 1993, Particle mesh Ewald: An N-log(N) method for Ewald sums in large systems, *J. Chem. Phys*., 98(12), 10089–10092.

Dash, B., and Karim, S., 2021, Pyrazoline heterocyclic : A Review, *Int. J. Pharm. Sci.,* 12*(6),* 2570–2588.

Daura, X., Mark, A. E., and Van Gunsteren, W. F., 1998, Parametrization of aliphatic CH_n united atoms of GROMOS96 force field, *J. Comput. Chem.* 19(5), 535–547.

DeLano, W.L., 2002. Pymol: An open-source molecular graphics tool. *CCP4 Newsl. Protein Crystallogr.*, *40*(1), pp.82-92.

De Ruiter, A., Boresch, S., and Oostenbrink, C., 2013, Comparison of thermodynamic integration and Bennett acceptance ratio for calculating relative protein-ligand binding free energies, *J. Comput. Chem.*, 34(12), 1024-1034.

De Vasconcelos, A., Campos, V. F., Nedel, F., Seixas, F. K., Dellagostin, O. A., Smith, K. R., De Pereira, C. M. P., Stefanello, F. M., Collares, T., and Barschak, A. G., 2013, Cytotoxic and apoptotic effects of chalcone derivatives of 2-acetyl thiophene on human colon adenocarcinoma cells, *Cell Biochem. Func.*, 31(4), 289–297.

De Vivo, M., Masetti, M., Bottegoni, G., and Cavalli, A., 2016, Role of molecular dynamicss and related methods in drug discovery, *J. Med.*

Chem., 59(9), 4035–4061.

Dowarah, J., Patel, D., Marak, B. N., Yadav, U. C. S., Shah, P. K., Shukla, P. K., and Singh, V. P., 2021, Green synthesis, structural analysis and anticancer activity of dihydropyrimidinone derivatives, *RSC Adv.*, 11(57), 35737-35753.

Duddukuri, N. K., Thatikonda, S., Godugu, C., Kumar, R. A., and Doijad, N., 2018, Synthesis of novel thiophene-chalcone derivatives as anticancer-and apoptosis-inducing agents, *ChemistrySelect,* 3(24), 6859-6864.

Durrant, J. D., and McCammon, J. A., 2011, Molecular dynamics simulations and drug discovery, *BMS Biol.*, 9(1).

E, J., Liu, Y., Guan, S., Luo, Z., Han, F., Han, W., Wang, S., and Zhang, H., 2020, How different substitution positions of f, cl atoms in benzene ring of 5-methylpyrimidine pyridine derivatives affect the inhibition ability of $EGFRL^{858r/t790m/c797s}$ inhibitors: a molecular dynamics simulation study, *Molecules*, 25(4), 895.

Eisenhaber, F., Lijnzaad, P., Argos, P., Sander, C., Scharf, M., 1995. The double cubic lattice method: Efficient approaches to numerical integration of surface area and volume and to dot surface contouring of molecular assemblies, *J. Comput. Chem*., 16, 273–284.

El-Bakary, N. M., Hagag, S. A., Ismail, M. A., and El-Sayed, W. M., 2022, New thiophene derivative augments the antitumor activity of γ-irradiation against colorectal cancer in mice via anti-inflammatory and pro-apoptotic pathways, *Discov. Oncol.*, 13(1), 119.

El-Borai, M. A., Rizk, H. F., Ibrahim, S. A., Fares, A. K., and Beltagy, D. M., 2021, Assessment of anti-hemolytic, cytotoxicity, antioxidant activities and molecular docking study based on thienopyrazole scaffold as pharmacophore, *J. Mol. Struct.,* 1240, 130602.

Elkaeed, E. B., Yousef, R. G., Elkady, H., Gobaara, I. M., Alsfouk, A. A., Husein, D. Z., and Eissa, I. H., 2022, The assessment of anticancer and vegfr-2 inhibitory activities of a new 1*H*-indole derivative: *in silico* and *in vitro* approaches, *Processes*, 10(7), 1391.

Fayyazi, N., Fassihi, A., Esmaeili, S., Taheri, S., Ghasemi, J. B., and Saghaie, L., 2020, Molecular dynamics simulation and 3D-pharmacophore ana lysis of new quinoline-based analogues with dual potential against EGFR and VEGFR-2, *Int. J. Biol. Macromol*., 142, 94–113.

Flynn, J. F., Wong, C., and Wu, J. M., 2009, Anti-EGFR therapy: mechanism and advances in clinical efficacy in breast cancer, *J. Oncol.*, 2009, 1–16.

Friedman, H. L., 1951, Influence of isosteric replacements upon biological activity, *NAS-NRS Publication*, *206*, 295-358.

Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T. A., Klicic, J. J., Mainz, D. T., and Shenkin, P. S., 2004, Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy, *J. Med. Chem*., 47(7), 1739-1749.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Mennucci B., Petersson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng G., Sonneberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery Jr., J.A., Peralta, J.E., Ogliaro, F., Bearpark M., Heyd, J.J., Brothers E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Rega N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Sratmann, R.E., J., Fox, D.J., 2009, Gaussian 09 Revision D.01.

Forli, S., Huey, R., Pique, M. E., Sanner, M. F., Goodsell, D. S., and Olson, A. J., 2016, Computational protein–ligand docking and virtual drug screening with the AutoDock suite, *Nat. Protoc.*, 11(5), 905–919.

Fotakis, G., and Timbrell, J. A., 2006, *In vitro* cytotoxicity assays: Comparison of LDH, neutral red, MTT and protein assay in hepatoma cell lines following exposure to cadmium chloride, *Toxicol. Lett.*, 160(2), 171–177.

Fogaça, T. B., Martins, R. M., Begnini, K. R., Carapina, C., Ritter, M., de Pereira, C. M., and Collares, T., 2017, Apoptotic effect of chalcone derivatives of 2-acetylthiophene in human breast cancer cells, *Pharmacol. Rep.,* 69(1), 156-161.

Freire, E., 2008, Do enthalpy and entropy distinguish first in class from best in class?, *Drug Discov.,* 13(19–20), 869–874.

Ganesan, A., Coote, M. L., and Barakat, K., 2017, Molecular dynamics-driven drug discovery: leaping forward with confidence, *Drug Discov.*, 22(2), 249–269.

Garcia-Mayea, Y., Mir, C., Masson, F., Paciucci, R., and Leonart, M. E.,

2020, Insights into new mechanisms and models of cancer stem cell multidrug resistance, *Semin. Cancer Biol.,* 60, 166–180.

Gitlitz, B. J., Bernstein, E., Santos, E. S., Otterson, G. A, Milne, G., and Syto, M., 2014, A randomized, placebo-controlled, multicenter, biomarker-selected, phase 2 study of apricoxib in combination with erlotinib in patients with advanced non-small-cell lung cancer, *J. Thorac. Oncol.*, 9, 577–582.

Genheden, S. and Ryde, U., 2015. The MM/PBSA and MM/GBSA methods to estimate ligand-binding affinities, *Expert Opin. Drug Discov.*, 10(5), pp.449-461.

Ghorab, M. M., Bashandy, M. S., and Alsaid, M. S., 2014, Novel thiophene derivatives with sulfonamide, isoxazole, benzothiazole, quinoline and anthracene moieties as potential anticancer agents, *Act. Pharm.,* 64(4), 419–431.

Gomes, M. N., Muratov, E. N., Pereira, M., Peixoto, J. C., Rosseto, L. P., Cravo, P. V. L., Andrade, C. H., and Neves, B. J., 2017, Chalcone derivatives: Promising starting points for drug design, *Molecules*, 22(8).

Gomtsyan, A., 2012, Heterocycles in drugs and drug discovery, *Chem. Heterocycl.*, *48*(1), 7–10.

Guo, Z., Guozhang, H., Wang, H., Li, Z., and Liu, N., 2019, Ampelopsin inhibits human glioma through inducing apoptosis and autophagy dependent on ROS generation and JNK pathway, *Biomed Pharmacother.,* 116, 108524.

Gutierrez, M., Vallejos, G. A., Cortes, M. P., and Bustos, C., 2019, Bennett acceptance ratio method to calculate the binding free energy of BACE1 inhibitors: Theoretical model and design of new ligands of the enzyme, *Chem. Biol. Drug. Des.*, 93(6), 1117–1128.

Haider, K., Shafeeque, M., Yahya, S., and Yar, M. S., 2022, A comprehensive review on pyrazoline-based heterocyclic hybrids as potent anticancer agents. *Eur. J. Med. Chem. Reports*, 5, 100042.

Hanahan, D., and Weinberg, R. A., 2000, The hallmarks of cancer, *Cell,* 100(1), 57-70.

Hanahan, D., and Weinberg, R. A., 2011, Hallmarks of cancer: The next generation, *Cell*, 144(5), 646–674.

Hanahan, D., 2022, Hallmarks of cancer: new dimensions, *Cancer Discov.*, 12(1), 31-46.

Harmastuti, N., Herowati, R., Susilowati, D., Pranowo, H. D., and Mubarika, S., 2012, Synthesis and cytotoxic activity of chalcone derivatives on human breast cancer cell lines, *Indones. J. Chem.,* 12(3), 261-267.

Hashmi, H.F., Xuan, X., Chen, K., Zhang, P., Shahab, M., Zheng, G., Younous, Y.A., Salamatullah, A.M. and Bourhia, M., 2024, Molecular modeling and simulation approaches to characterize potential molecular targets for burdock inulin to instigate protection against autoimmune diseases, *Sci. Rep.,*14(1), p.11291.

Haq, K.U., Sa'adah, N.L., Siswanto, I. and Suwito, H., 2023, Bioactivity of dihydropyrimidinone derivatives as inhibitors of cyclooxygenase-2 (COX-2): an in silico approach, *RSC Adv.,* 13(49), pp.34348-34357.

Hollingsworth, S.A., and Dror, R.O., Molecular dynamics simulation for all, *Neuron*, 99, 1129-1143.

Holmseth, S., Lehre, K. P., and Danbolt, N. C., 2006, Specificity controls for immunocytochemistry, *Anat. Embryol.,* 211(4), 257–266.

Homeyer, N., Stoll, F., Hillisch, A. and Gohlke, H., 2014, Binding free energy calculations for lead optimization: assessment of their accuracy in an industrial drug design context, *J. Chem. Theory Comput.,* 10(8), 3331-3344.

Hospital, A., Goni, J.R., Orozco, M., dan Gelpi, J.L., 2015, Molecular dynamics simulations: advances and applications, *An. Acad. Bras. Ciênc.,* 8, 37-47.

Hornak, V., Abel, R., Okur, A., Strockbine, B., Roitberg, A., and Simmerling, C., 2006, Comparison of multiple AMBER force fields and development of improved protein backbone parameters viktor, *PROTEINS Struct. Funct. Bioinforma.,* 65, 712–725.

Housman, G., Byler, S., Heerboth, S., Lapinska, K., Longacre, M., Snyder, N., and Sarkar, S., 2014, Drug resistance in cancer: an overview. *Cancers*, *6*(3), 1769-1792.

Hu, C., Gao, Y., and Du, W., 2016, Design, synthesis, and biological evaluation of pyrazole derivatives, *Chem. Biol. Drug. Des.*, 87(5), 673–679.

Huang, W., Lin, Z., and Van Gunsteren, W. F., 2011, Validation of the GROMOS 54A7 force field with respect to b-peptide folding, *J. Chem. Theory Comput.*, 7(5), 1237–1243.

Huey, R., Morris, G. M., Olson, Arthur, J., and Goodsell, D. S., 2006,

Software news and update a semiempirical free energy force field with charge-based desolvation, *J. Comput. Chem.*, 28(6), 1145–1152.

Humphrey, W., Dalke, A., and Schulten, K., 1996, VMD: Visual molecular dynamics, *J. Mol. Graph.,* 14(1), 33–38.

Jagtap, A.R., Satam, V.S., Rajule, R.N., and Kanetkar, V.R., 2011, Synthesis of highly fluorescent coumarinyl chalcones derived from 8-acetyl-1,4-diethyl-1,2,3,4-tetrahydro-7H-pyrano[2,3-g]quinoxalin-7-one and their spectral characteristics, *Dyes. Pigm.,* 91, 20–25.

Jainey, P. J., and Bhat, I. K., 2012, Antitumor, analgesic, and anti-inflammatory activities of synthesized pyrazolines, *J. Young Pharm.,* 4(2), 82–87.

Jin, M., Liang, Y. J., Lu, R., Chuai, X. H., Yi, Z. H., Zhao, Y., and Zhang, H. J., 2004, Synthesis and properties of photoluminescence and electroluminescence of pyrazoline derivatives, *Synth. Met*., 140(1), 37-41.

Kabsch, W., and Sander, C., 1983, Dictionary of protein secondary struc ture: Pattern recognition of hydrogen-bonded and geometrical features, *Biopolymers*, 22(12), 2577–2637.

Karplus, M., and McCammon, J. A., 2002, Molecular dynamics simulations of biomolecules, *Nat. Struct. Mol. Biol*., 9(9), 646-652.

Karthikeyan, C., SH Narayana Moorthy, N., Ramasamy, S., Vanam, U., Manivannan, E., Karunagaran, D., and Trivedi, P., 2015, Advances in chalcones with anticancer activities, *Recent Pat. Anticancer Drug Discov*., 10(1), 97–115.

Khan, J., Deb, P. K., Priya, S., Medina, K. D., Devi, R., Walode, S. G., and Rudrapal, M., 2021, Dietary flavonoids: Cardioprotective potential with antioxidant effects and their pharmacokinetic, toxicological and therapeutic concerns, *Molecules*, 26(13), 1–24.

Kharbanda, C., Alam, M. S., Hamid, H., Javed, K., Bano, S., Dhulap, A., Ali, Y., Nazreen, S., and Haider, S., 2014, Synthesis and evaluation of pyrazolines bearing benzothiazole as anti-inflammatory agents, *Bioorg. Med. Chem.*, 22(21), 5804–5812.

Khaw, K. Y., Choi, S. B., Tan, S. C., Wahab, H. A., Chan, K. L., and Murugaiyah, V., 2014, Prenylated xanthones from mangosteen as promising cholinesterase inhibitors and their molecular docking studies, *Phytomedicine*, 21(11), 1303–1309.

Kollman, P.A., Massova, I., Reyes, C., Kuhn, B., Huo, S., Chong, L., Lee,

M., Lee, T., Duan, Y., Wang, W. and Donini, O., 2000. Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum models, *Acc. Chem. Res.,* 33(12), pp.889-897.

Kuete, V., Karaosmanoğlu, O., and Sivas, H., 2017, *Medicinal Spices and Vegetables from Africa: Therapeutic Potential Against Metabolic, Inflammatory, Infectious and Systemic Diseases*, Academic Press, Cambridge.

Kufareva, I., and Abagyan, R., 2012, Methods of protein structure comparison, *Methods Mol. Biol.*, 857, 231–257.

Kulkarni, R. R., Tupe, S. G., Gample, S. P., Chandgude, M. G., Sarkar, D., Deshpande, M. V., and Joshi, S. P., 2014, Antifungal dimeric chalcone derivative kamalachalcone e from Mallotus philippinensis, *Nat. Prod. Res.*, 28(4), 245–250.

Kumar, G., Tanwar, O., Kumar, J., Akhter, M., Sharma, S., Pillai, C. R., Alam, M. M., and Zama, M. S., 2018a, Pyrazole-pyrazoline as promising novel antimalarial agents: A mechanistic study, *Eur. J. Med. Chem.*, 149, 139–147.

Kumar A.D., Prabhudeva M. G., Bharath S., Kumara K., Lokanath N. K., and Kumar K. A., 2018b, Design and Amberlyst-15 mediated synthesis of novel thienyl-pyrazole carboxamides that potently inhibit Phospholipase A2 by binding to an allosteric site on the enzyme, *Bioorg. Chem.,* 444-452.

Kumar, A., Singh, A. K., Singh, H., Vijayan, V., Kumar, D., Naik, J., and Kumar, P., 2023, Nitrogen-containing heterocycles as anticancer agents: A medicinal chemistry perspective, *Pharmaceuticals*, 16(2), 299.

Krawczyk-Łebek, A., Żarowska, B., Dymarska, M., Janeczko, T., and Kostrzewa-Susłow, E., 2024. Synthesis, fungal biotransformation, and evaluation of the antimicrobial potential of chalcones with a chlorine atom, *Sci. Rep.,* 14, 1–22.

Laskowski, R. A., Jabłonska, J., Pravda, L., Varekova, R. S., and Thornton, J. M., 2018, PDBsum: Structural summaries of PDB entries, *Protein Sci.,* 27(1), 129–134.

Leão, M., Soares, J., Gomes, S., Raimundo, L., Ramos, H., Bessa, C., and Saraiva, L., 2015, Enhanced cytotoxicity of prenylated chalcone against tumour cells via disruption of the p53–MDM2 interaction, *Life Sci.,* 142, 60-65.

Lellek, V., Chen, C. Y., Yang, W., Liu, J., Ji, X., and Faessler, R., 2018, An efficient synthesis of substituted pyrazoles from one-pot reaction of ketones, aldehydes, and hydrazine monohydrochloride, *Synlett.*, 29(8), 10f71–1075.

Lam, K. W., Uddin, R., Liew, C. Y., Tham, C. L., Israf, D. A., Syahida, A., and Lajis, N. H., 2012, Synthesis and QSAR analysis of chalcone derivatives as nitric oxide inhibitory agent, *Med. Chem. Res.*, 21(8), 1953–1966.

Lebedeva, O. P., Zhukova, I. O., Ivashova, O. N., Pakhomov, S. P., and Churnosov, M. I., 2017, Proteins P53 and BCL-2 in pathogenesis of missed and spontaneous abortions, *DIT., 9(3),* 65-8.

Lengauer, T., and Rarey, M., 1996, Computational methods for biomolecular docking, *Curr. Opin. Struct. Biol*., 6(3), 402–406.

Li, J., Ma, C., Huang, Y., Luo, J., and Huang, C., 2003, Differential requirement of EGF Receptor and Its Tyrosine Kinase for AP-1 Transactivation Induced by EGF and TPA, *Oncogene*, 22, 211-219.

Li, W., Zhou, J., and Xu, Y.,2015, Study of the *in vitro* cytotoxicity testing of medical devices, *Biomed. Rep.*, 3(5), 617–620.

Li, M., Cong, Y., Li, Y., Zhong, S., Wang, R., Li, H. and Duan, L., 2019. Insight into the binding mechanism of p53/pDIQ-MDMX/MDM2 with the interaction entropy method, *Front. Chem.*, 7, 33.

Lima, L., and Barreiro, E., 201, Bioisosterism: a useful strategy for molecular modification and drug design, *Curr. Med. Chem.,* 12(1), 23–49.

Lionta, E., Spyrou, G., Vassilatis, D., and Cournia, Z., 2014, Structure-based virtual screening for drug discovery: principles, applications and recent advances, *Curr. Top. Med. Chem.*, 14(16), 1923–1938.

Liu, M., Wilairat, P., Croft, S. L., Tan, A. L. C., and Go, M. L., 2003, Structure-activity relationships of antileishmanial and antimalarial chalcone, *Bioorg. Med. Chem.*, 11(13), 2729–2738.

MacKerell, A. D., Bashford, D., Bellott, M., Dunbrack, R. L., Evanseck, J. D., Field, M. J., Fischer, S., Gao, J., Guo, H., Ha, S., Joseph-McCarthy, D., Kuchnir, L., Kuczera, K., Lau, F. T. K., Mattos, C., Michnick, S., Ngo, T., Nguyen, D. T., Prodhom, B., and Karplus, M., 1998, All-atom empirical potential for molecular modeling and dynamics studies of proteins, *J. Phys. Chem. B*, 102(18), 3586–3616.

Mahadevaswamy, L.D., and Kariyappa, A.K., 2017, An environmentally

benign lemon juice mediated synthesis of novel furan conjugated pyrazole derivatives and their biological evaluation, *Pharm. Chem. J.,* 8(51), 670-677.

Mahapatra, D. K., Bharti, S. K., and Asati, V., 2015, Chalcone scaffolds as anti-infective agents: Structural and molecular target perspectives, *Eur. J. Med. Chem.*, 101, 496–524.

Malde, A. K., Zuo, L., Breeze, M., Stroet, M., Poger, D., Nair, P. C., Oostenbrink, C., and Mark, A. E., 2011, An automated force field topology builder (ATB) and repository: Version 1.0*, J. Chem. Theory Comput.,* 7(12), 4026–4037.

Mark, P., and Nilsson, L., 2001, Structure and dynamics of the TIP3P, SPC, and SPC/E water models at 298 K, *J. Chem. Theory Comput.,* 105(43), 9954–9960.

Mathew, B., Haridas, A., Uçar, G., Baysal, I., Adeniyi, A. A., Soliman, M. E. S., Joy, M., Mathew, G. E., Lakshmanan, B., and Jayaprakash, V., 2016, Exploration of chlorinated thienyl chalcones: A new class of monoamine oxidase-B inhibitor, *Int. J. Biol. Macromol.*, 91, 680–695.

Mathew, B., Suresh, J., Anbazghagan, S., Paulraj, J., and Krishnan, G. K., 2014,. Heteroaryl chalcones: Mini review about their therapeutic voyage, *Biomed. Prev. Nutr.*, 4(3), 451–458.

Matiadis, D., and Sagnou, M., 2020, Pyrazoline hybrids as promising anticancer agents: An up-to-date overview, *Int. J. Mol. Sci.,* 21(15), 1–41.

McConkey, B. J., Sobolev, V., and Edelman, M., 2002, The performance of current methods in ligand-protein docking, *Curr. Sci*., 83(7), 845–856.

Meanwell, N. A., 2011, Synopsis of some recent tactical application of bioisosteres in drug design, *J. Med. Chem.*, 54(8), 2529–2591.

Meng, X. Y., Zhang, H. X., Mezei, M., and Cui, M., 2011, Molecular docking: a powerful approach for structure-based drug discovery, *Curr. Comput.-Aided Drug Des.*, 7(2), 146-157.

Merkel, O., Taylor, N., Prutsch, N., Staber, P.B., Moriggl, R., Turner, S.D. and Kenner, L., 2017, When the guardian sleeps: Reactivation of the p53 pathway in cancer, *Mutat. Res. Rev. Mutat. Res.,* 773, 1-13.

Miller, B.R., McGee, T.D., Swails, J.M., Homeyer, N., Gohlke, H., Roitberg, A.E., 2012, MMPBSA.py: An efficient program for end-state free energy calculations, *J. Chem. Theory Comput.,* 8, 3314–3321.

Misra, M., Yadav, A.K., 2023. Assessment of available AMBER force fields to model DNA-ligand interactions, *Biointerface Res. Appl. Chem.,* 13.

Mohareb, R. M., Abdallah, A. E. M., Helal, M. H. E., and Shaloof, S. M. H., 2016, Synthesis and structure elucidation of some novel thiophene and benzothiophene derivatives as cytotoxic agents, *Acta Pharm.*, *66*(1), 53–68.

Moreira, J., Almeida, J., Saraiva, L., Cidade, H., and Pinto, M., 2021, Chalcones as promising antitumor agents by targeting the p53 pathway: An overview and new insights in drug-likeness, *Molecules*, 26(12), 3737.

Morgillo, F., Della Corte, C. M., Fasano, M., and Ciardiello, F., 2016. Mechanisms of resistance to EGFR-targeted drugs: lung cancer, *ESMO open*, 1(3), e000060.

Mori, T., Morimoto, T., Komaki, K. and Monden, Y., 1991. Comparison of estrogen receptor and epidermal growth factor receptor content of primary and involved nodes in human breast cancer, *Cancer*, 68(3), pp.532-537.

Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., and Olson, A. J., 2009, AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility, *J. Comput. Chem.,* 30(16), 2785-2791.

Muhseen, Z. T., and Li, G., 2019, Promising terpenes as natural antagonists of cancer: An *in silico* approach, *Molecules,* 25(1), 155.

Murray, J.B., Davidson, J., Chen, I., Davis, B., Dokurno, P., Graham, C.J., Harris, R., Jordan, A., Matassova, N., Pedder, C. and Ray, S., 2019. Establishing drug discovery and identification of hit series for the anti-apoptotic proteins, Bcl-2 and Mcl-1, *ACS Omega*, 4(5), pp.8892-8906.

Mustofa, Satriyo, P. B., Suma, A. A. T., Waskitha, S. S. W., Wahyuningsih, T. D., and Sholikhah, E. N., 2022, A potent EGFR inhibitor, *N*-phenyl pyrazoline derivative suppresses aggressiveness and cancer stem cell-like phenotype of cervical cancer cells, *Drug Des. Devel. Ther.*, 16, 2325–2339.

Nagy, M. I., Darwish, K. M., Kishk, S. M., Tantawy, M. A., Nasr, A. M., Qushawy, M., and Salama, I., 2021, Design, synthesis, anticancer activity, and solid lipid nanoparticle formulation of indole-and benzimidazole-based compounds as pro-apoptotic agents targeting Bcl-2 protein, *Pharmaceuticals,* 14(2), 113.

Nasab, R.R., Mansourian, M., Hassanzadeh, F., and Shahlaei, M., 2018, Exploring the Interaction between Epidermal Growth Factor Receptor Tyrosine Kinase and some of the synthesized inhibitors using combination of in-silico and in-vitro cytotoxicity methods, *Res. Pharm. Sci.,* 13(6), 509-522.

Nehra, B., Rulhania, S., Jaswal, S., Kumar, B., Singh, G., and Monga, V., 2020, Recent advancements in the development of bioactive pyrazoline derivatives, *Eur. J. Med. Chem.*, 205, 112666.

Neto, R. de A. M., Santos, C. B. R., Henriques, S. V. C., Machado, L. de O., Cruz, J. N., da Silva, C. H. T. d. P., Federico, L. B., Oliveira, E. H. C. d., de Souza, M. P. C., da Silva, P. N. B., Taft, C. A., Ferreira, I. M., and Gomes, M. R. F., 2022, Novel chalcones derivatives with potential antineoplastic activity investigated by docking and molecular dynamics simulations, *J. Biomol. Struct. Dyn.,* 40(5), 2204–2216.

Nguyen, T.T., Viet, M.H., Li, M.S., 2014, Effects of water models on binding affinity: Evidence from all-atom simulation of binding of tamiflu to A/H5N1 neuraminidase, *Sci. World J.,* 2014.

Normanno N., De Luca A., Bianco C., Strizzi L., Mancino M., and Maiello MR., 2006, Epidermal growth factor receptor (EGFR) signaling in cancer, *Gene*, 366, 2–16.

Noori, Z., Solà, M., Viñas, C., Teixidor, F., and Poater, J., 2025, Unraveling aromaticity: the dual worlds of pyrazole, pyrazoline, and 3D carborane, *Beilstein J. Org. Chem.,* 21(1), 412-420.

O'callaghan, G., and Houston, A., 2015, Prostaglandin E2 and the EP receptors in malignancy: possible therapeutic targets?, *Br. J. Pharmacol.,* 172(22), 5239-5250.

Opo, F.D.M., Moulay, M., Zari, A., Alqaderi, A., Alkarim, S., Zari, T., Bhuiyan, M.A., Mahmoud, M.M., Aljoud, F., Suhail, M. and Edris, S., 2022, Pharmacophore-based virtual screening approaches to identify novel molecular candidates against EGFR through comprehensive computational approaches and in-vitro studies, *Front. Pharmacol.,* 13, p.1027890.

Orlikova, B., Tasdemir, D., Golais, F., Dicato, M., and Diederich, M., 2011, Dietary chalcones with chemopreventive and chemotherapeutic potential, *Genes Nutr.*, 6(2), 125–147.

Ornnork, N., Kiriwan, D., Lirdprapamongkol, K., Choowongkomon, K., Svasti, J. and Eurtivong, C., 2020, Molecular dynamics, MM/PBSA and in vitro validation of a novel quinazoline-based EGFR tyrosine

kinase inhibitor identified using structure-based in silico screening, *J. Mol. Graph. Model*, 99, 107639.

Özdemir, A., Altintop, M. D., Kaplancikli, Z. A., Turan-Zitouni, G., Çiftçi, G. A., and Yildirim, Ş. U., 2013, Synthesis of 1-acetyl-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives and evaluation of their anticancer activity, *J. Enzyme Inhib. Med. Chem.*, 28(6), 1221–1227.

Pai, R., Soreghan, B., Szabo, I. L., Pavelka, M., Baatar, D., Tarnawski, A. S., 2002, Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy, *Nat. Med.*, 8, 289–293.

Palusiak, M., and Grabowski, S. J., 2002, Methoxy group as an acceptor of proton in hydrogen bonds, *J. Mol. Struct*., 642(1-3), 97-104.

Park, H. G., Bak, E. J., Woo, G. H., Kim, J. M., Quan, Z., Kim, J. M., Yoon, H. K., Cheon, S. H., Yoon, G., Yoo, Y. J., Na, Y., and Cha, J. H., 2012, Licochalcone E has an antidiabetic effect, *J. Nutr. Biochem.*, 23(7), 759–767.

Parrinello, M., and Rahman, A., 1981, Polymorphic transitions in single crystals: A new molecular dynamics method, *J. Appl. Phys.,* 52(12), 7182–7190.

Peng, F., Liao, M., Qin, R., Zhu, S., Peng, C., Fu, L., and Han, B., 2022, Regulated cell death (RCD) in cancer: key pathways and targeted therapies, *Signal Transduct. Target. Ther.,* 7(1), 286.

Pereira, D., Lima, R. T., Palmeira, A., Seca, H., Soares, J., Gomes, S., and Cidade, H., 2019, Design and synthesis of new inhibitors of p53–MDM2 interaction with a chalcone scaffold, *Arab. J. Chem*., 12(8), 4150-4161.

Petrov, D., Margreitter, C., Grandits, M., Oostenbrink, C., and Zagrovic, B., 2013, A systematic framework for molecular dynamics simulations of protein post-translational modifications, *PLoS Comput. Biol.,* 9(7), e1003154.

Pettersen, E.F., Goddard, T.D., Huang, C.C., Couch, G.S., Greenblatt, D.M., Meng, E.C., Ferrin, T.E., 2004, UCSF Chimera - A visualization system for exploratory research and analysis*, J. Comput. Chem.,* 25, 1605–1612.

Pinto, P., Machado, C. M., Moreira, J., Almeida, J. D. P., Silva, P. M. A., Henriques, A. C., Soares, J. X., Salvador, J. A. R., Afonso, C., Pinto, M., Bousbaa, H., and Cidade, H., 2019, Chalcone derivatives targeting

mitosis: synthesis, evaluation of antitumor activity and lipophilicity, *Eur. J. Med. Chem*., 184, 111752.

Pinzi, L., and Rastelli, G., 2019, Molecular docking: Shifting paradigms in drug discovery, *Int. J. Mol. Sci.*, 20(18), 4331.

Pola, S., Banoth, K. K., Sankaranarayanan, M., Ummani, R., and Garlapati, A., 2020, Design, synthesis, *in silico* studies, and evaluation of novel chalcones and their pyrazoline derivatives for antibacterial and antitubercular activities. *Med. Chem. Res.*, 29(10), 1819–1835.

Polo-Cuadrado, E., Acosta-Quiroga, K., Rojas-Pena, C., Rodriguez-Nuñez, Y. A., Duarte, Y., Brito, I., and Gutierrez, M., 2022, Molecular modeling and structural analysis of some tetrahydroindazole and cyclopentanepyrazole derivatives as COX-2 inhibitors, *Arab. J. Chem.,* 15(2), 103540.

Prabhudeva, M. G., Naveen, S., Raghavendra, K. R., Dileep Kumar, A., Kumara, K., Lokanath, N. K., and Ajay Kumar, K., 2017a, 1-(3-Chlorophenyl)-5-(4-chlorophenyl)-3-(5-chlorothiophen-2-yl)-4, 5-dihydro-1H-pyrazole, *IUCrData*, 2(1), x162048.

Prabhudeva, M. G., Bharath, S., Kumar, A. D., Naveen, S., Lokanath, N. K., Mylarappa, B. N., and Kumar, K. A., 2017b, Design and environmentally benign synthesis of novel thiophene appended pyrazole analogues as anti-inflammatory and radical scavenging agents: Crystallographic, *in silico* modeling, docking and SAR characterization, *Bioorg. Chem.,* 73, 109-120.

Prabhudeva, M. G., Kumara, K., Dileep Kumar, A., Ningappa, M. B., Lokanath, N. K., and Ajay Kumar, K., 2018a, Amberlyst-15 catalyzed synthesis of novel thiophene–pyrazoline derivatives: spectral and crystallographic characterization and anti-inflammatory and antimicrobial evaluatio, *Res. Chem. Intermed.,* 44, 6453-6468

Prabhudeva, M., Renuka, N., and Kumar, K., 2018b, Synthesis of thiophene-pyrazole conjugates as potent antimicrobial and radical scavengers, *Curr. Chem. Lett*., 7(3), 73-80.

Prabhudeva, M. G., Vivek, H. K., and Kumar, K. A., 2019, Synthesis of novel pyrazole carboxamides using reusable catalyst as antimicrobial agents and molecular docking studies, *Chem. Data Collect*., 20, 100193.

Ranganathan, K., Suresh, R., Vanangamudi, G., Thirumurthy, K., Mayavel, P., and Thirunarayanan, G., 2014, $SOCl_2$ catalyzed cyclization of chalcones: Synthesis and spectral studies of some bio-potent 1H

pyrazoles, *Bull. Chem. Soc. Ethiop.*, 28(2), 271-288.

Ramadan, M. A., Shawkey, A. E., Rabeh, M. A., and Abdellatif, A. O., 2019, Expression of P53, BAX, and BCL-2 in human malignant melanoma and squamous cell carcinoma cells after tea tree oil treatment *in vitro*, *Cytotechnology*, 71(1), 461–473.

Ramirez-Tagle, R., Escobar, C. A., Romero, V., Montorfano, I., Armisén, R., Borgna, V., Jeldes, E., Pizarro, L., Simon, F., and Echeverria, C., 2016, Chalcone-induced apoptosis through caspase-dependent intrinsic pathways in human hepatocellular carcinoma cells, *Int. J. Mol. Sci.*, 17(2), 260.

Rana, M., Arif, R., Khan, F. I., Maurya, V., Singh, R., Faizan, M. I., and Ahmad, T., 2021, Pyrazoline analogs as potential anticancer agents and their apoptosis, molecular docking, MD simulation, DNA binding and antioxidant studies, *Bioorg. Chem.*, 108, 104665.

Rana, M., Faizan, M. I., Dar, S. H., Ahmad, T., and Rahisuddin., 2022, Design and synthesis of carbothioamide/carboxamide-based pyrazoline analogs as potential anticancer agents: apoptosis, molecular docking, ADME assay, and DNA binding studies, *ACS Omega*, 7(26), 22639–22656.

Raval, K., and Ganatra, T., 2022, Basics, types and applications of molecular docking: A review, *IP Int. J. Compr. Adv. Pharmacol.,* 7(1), 12-16.

Razzaghi-Asl, N., Mirzayi, S., Mahnam, K., and Sepehri, S., 2018, Identification of COX-2 inhibitors via structure-based virtual screening and molecular dynamics simulation, *J. Mol. Graph. Model*, 83, 138–152.

Reddy, L. S. S., Raju, M. B., and Sridhar, C., 2016, Novel pyrazolines: Synthesis and evaluation of their derivatives with anticancer and anti-inflammatory activities, *Int. J. Pharm. Pharm.*, 8(1), 247–254.

Rizvi, S. U. F., Siddiqui, H. L., Johns, M., Detorio, M., and Schinazi, R. F., 2012, Anti-HIV-1 and cytotoxicity studies of piperidyl-thienyl chalcones and their 2-pyrazoline derivatives, *Med. Chem. Res.,* 21(11), 3741–3749.

Rudrapal, M., Khan, J., Dukhyil, A. A. Bin, Alarousy, R. M. I. I., Attah, E. I., Sharma, T., Khairnar, S. J., and Bendale, A. R., 2021, Chalcone scaffolds, bioprecursors of flavonoids: Chemistry, bioactivities, and pharmacokinetics, *Molecules*, 26(23), 1–21.

Safaa, I. E., Mansour, E., Nassar, I. F., and Mekawey, A. A. I., 2020,

Synthesis of some new pyrazoline-based thiazole derivatives and evaluation of their antimicrobial, antifungal, and anticancer activities, *Russ. J. Bioorganic Chem.*, 46(3), 382–392.

Salem, M. M., Gerges, M. N., and Noser, A. A., 2022, Synthesis, molecular docking, and *in-vitro* studies of pyrimidine-2-thione derivatives as antineoplastic agents via potential RAS/PI3K/Akt/JNK inhibition in breast carcinoma cells, *Sci. Rep.,*12(1), 1–20.

Sahu, N. K., Balbhadra, S. S., Choudhary, J., and Kohli, D. V., 2012, Exploring pharmacological significance of chalcone scaffold: a review, *Curr. Med. Chem.*, 19(2), 209–225.

Schmid, N., Eichenberger, A. P., Choutko, A., Riniker, S., Winger, M., Mark, A. E., and Van Gunsteren, W. F., 2011, Definition and testing of the GROMOS force-field versions 54A7 and 54B7, *Eur. Biophys. J.*, 40(7), 843–856.

Schüttelkopf, A. W., and Van Aalten, D. M. F., 2004, PRODRG: A tool for high-throughput crystallography of protein-ligand complexes, *Acta Crystallogr. D,* 60(8), 1355–1363.

Sethi, A., Sanam, S., Alvala, R., and Alvala, M., 2021, An updated patent review of galectin-1 and galectin-3 inhibitors and their potential therapeutic applications (2016–present), *Expert Opin. Ther. Pat.*, 31(8), 709-721.

Shaik, A. B., Bhandare, R. R., Nissankararao, S., Edis, Z., Tangirala, N. R., Shahanaaz, S., and Rahman, M. M., 2020, Design, facile synthesis and characterization of dichloro substituted chalcones and dihydropyrazole derivatives for their antifungal, antitubercular and antiproliferative activities, *Molecules*, 25, 3188–3203.

Sharma, P., Kumar, S., Ali, F., Anthal, S., Gupta, V. K., Khan, I. A., Singh, S., Sangwan, P. L., Suri, K. A., Gupta, B. D., Gupta, D. K., Dutt, P., Vishwakarma, R. A., and Satti, N. K., 2013, Synthesis and biologic activities of some novel heterocyclic chalcone derivatives, *Med. Chem. Res.*, 22(8), 3969–3983.

Siegel, R. L., Miller, K. D., Fuchs, H. E., and Jemal, A., 2021, Cancer Statistics 2021, *CA Cancer J. Clin.*, 71(1), 7–33.

Simanshu, D. K., Nissley, D. V, and McCormick, F., 2017, RAS Proteins and Their Regulators in Human Disease, *Cell*, 170(1), 17–33.

Singh, U.C., Kollman, P.A., 1984, An approach to computing electrostatic charges for molecules, *J. Comput. Chem.,* 5, 129–145.

Sousa Da Silva, A.W., Vranken, W.F., 2012. ACPYPE - AnteChamber PYthon Parser interfacE, *BMC Res.,* Notes 5, 1–8.

Srinivasan, B., Johnson, T. E., Lad, R., and Xing, C., 2009, Structure - Activity relationship studies of chalcone leading to 3-hydroxy-4,3′,4′,5′-tetramethoxychalcone and its analogues as potent nuclear factor κB inhibitors and their anticancer activities, *J. Med. Chem.,* 52(22), 7228–7235.

Sugamoto, K., Matsusita, Y. I., Matsui, K., Kurogi, C., and Matsui, T., 2011, Synthesis and antibacterial activity of chalcones bearing prenyl or geranyl groups from Angelica keiskei, *Tetrahedron*, 67(29), 5346–5359.

Suma, A. A. T, Wahyuningsih, T. D., and Mustofa., 2019, Synthesis, cytotoxicity evaluation, and molecular docking study of *N*-phenylpyrazoline derivatives, *Indones. J. Chem.*, 19(4), 1081–1090.

Suma, A. A. T., 2019, Synthesis, cytotoxicity and immunocytochemistry evaluation of *N*-phenylpyrazoline derivatives from 4-chloroacetophenone as anticancer compounds, *Dissertation,* Department of Chemistry, Universitas Gadjah Mada, Yogyakarta.

Sun, R., Hou, Z., Zhang, Y., and Jiang, B., 2022, Drug resistance mechanisms and progress in treating EGFR-mutated lung adenocarcinoma, *Oncol. Lett., 24*(5), 408.

Szweda, M., Rychlik, A., Babińska, I., and Pomianowski, A., 2019, Significance of cyclooxygenase-2 in oncogenesis, *J. Vet. Res.*, 63(2), 215–224.

Tai H. H., Ensor C. M., Tong M., Zhou H., and Yan F., 2002, Prostaglandin catabolizing enzymes, *Prostaglandins Other Lipid. Mediat.*, 68, 483–493.

Tam, N. M., Vu, K. B., Vu, V. V., and Ngo, S. T., 2018, Influence of various force fields in estimating the binding affinity of acetylcholinesterase inhibitors using fast pulling of ligand scheme, *Chem. Phys. Lett.,*701, 65–71.

Tanamatayarat, P., Limtrakul, P.N., Chunsakaow, S., and, Duangrat, C., 2003, Screening of Some Rubiaceous Plants for Cytotoxic Activity Against Cervix Carcinoma (KB-3-1) Cell Line, *Thai J. Pharm. Sci.*, 3(4), 167-172.

Tanwer, N., Kaur, R., Rana, D., Singh, R., Singh, K., Tanwar, N., Rana, D., Kaur, R., Singh, R., and Singh, K., 2015, Synthesis and characterization of Pyrazoline derivatives, *Int. J. Integr. Sci. Technol*., 3(2), 39–41.

Tripathi, A. C., Upadhyay, S., Paliwal, S., Saraf, S. K., Banarasi, B., Northern, D., Vidyapith, B., Chemistry, P., Banarasi, B., Northern, D., and Road, F., 2018, N1-benzenesulfonyl-2-pyrazoline hybrids in neurological disorders : syntheses*, Biological*, 0008, 126–148.

Trott, O., and Olson, A. J., 2010, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, *J. Comput. Chem.,* 31(2), 455-461.

Valdés-Tresanco, M.S., Valdés-Tresanco, M.E., Valiente, P.A., Moreno, E., 2021, Gmx_MMPBSA: A New Tool to Perform End-State Free Energy Calculations with GROMACS, *J. Chem. Theory Comput.,* 17, 6281–6291.

Venilita, R. E., 2022, Synthesis and anticancer activity tests of chalcone and pyrazoline compounds based on 2-acetylthiophene and methoxy benzaldehyde derivatives, *Thesis,* Department of Chemistry, Universitas Gadjah Mada, Yogyakarta.

Verdonk, M. L., Cole, J. C., Hartshorn, M. J., Murray, C. W., and Taylor, R. D., 2003, Improved protein–ligand docking using GOLD, *Proteins: Struct. Funct. Genet.*, 52(4), 609-623.

Waskitha, S. S. W., 2022, Design of pyrazoline derivatives as anti-colon cancer compounds based on three-dimensional quantitative structure-activity relationship (3D-QSAR) and molecular docking, *Thesis*, Department of Chemistry, Universitas Gadjah Mada.

Wang, H., 2010, *Comprehensive Organic Name Reactions*, John Wiley and Sons Inc., Hoboken.

Warner, W.A., Sanchez, R., Dawoodian, A., Li, E. and Momand, J., 2012. Identification of FDA-approved drugs that computationally bind to MDM2, *Chem. Biol. Drug Des.,* 80(4), pp.631-637.

Wu, X., Liu, Y., Zhang, E., Chen, J., Huang, X., Yan, H., and Cai, Z., 2020, Dihydroartemisinin Modulates Apoptosis and Autophagy in Multiple Myeloma through the P38/MAPK and Wnt/β-Catenin Signaling Pathways. *Oxidative Medicine and Cellular Longevity*, *2020*(1), 6096391.

Yan, W., Zhao, Y., and He, J., 2018, Anti-breast cancer activity of selected 1, 3, 5-triazines via modulation of EGFR-TK, *Mol. Med. Rep.,* 18(5), 4175-4184.

Zamri, A., Frimayanti, N., and Teruna, H. Y., 2016, Docking and molecular dynamics simulations: Study of 1, 3, 4-oxadiazolechalcone hybrid

derivatives to search new active anticancer agents, *Thai J. Pharm. Sci.*, 40(4), 179–184.

Zayed, M. F., 2023, Medicinal chemistry of quinazolines as anticancer agents targeting tyrosine kinases*, Sci. Pharm.,* 91(2), 18.

Zhang, H., Cheng, S., Zhang, M., Ma, X., Zhang, L., Wang, Y., 2014, Prostaglandin E2 promotes hepatocellular carcinoma cell invasion through upregulation of YB-1 protein expression, *Int. J. Oncol.*, 44, 769–780

Zhang, H., Jiang, Y., Yan, H., Yin, C., Tan, T., and van der Spoel, D., 2017, Free-energy calculations of ionic hydration consistent with the experimental hydration free energy of the proton*, J. Phys. Chem. Lett.,* 8(12), 2705–2712.

Zhang, N., Peng, F., Wang, Y., Yang, L., Wu, F., Wang, X., and., He, G., 2020, Shikonin induces colorectal carcinoma cells apoptosis and autophagy by targeting galectin-1/JNK signaling axis, *Int. J. Biol. Sci*., 16(1), 147.

Zhu, B., Ferry, C. H., Blazanin, N., Bility, M. T., Khozoie, C., Kang, B. H., Glick, A. B., Gonzalez, F. J., and Peters, J. M., 2014, PPARβ/δ promotes EGFR-induced senescence and tumor suppression by potentiating p-ERK and repressing p-AKT signaling, *Oncogene*, 33(46), 5348–5359.