References

REFERENCES

- Arruebo, M., Vilaboa, N., Sáez-Gutierrez, B., Lambea, J., Tres, A., Valladares, M., and González-Fernández, A., (2011), "Assessment of the evolution of cancer treatment therapies", Cancers, 3(3), pp. 3279–3330.
- Arendt, L. M., and Kuperwasser, C., (2015), "Form and function: how estrogen and progesterone regulate the mammary epithelial hierarchy", Journal of mammary gland biology and neoplasia, 20(1-2), pp. 9–25.
- Arcidiacono, B., Iiritano, S., Nocera, A., Possidente, K., Nevolo, M. T., Ventura, V., Foti, D., Chiefari, E., and Brunetti, A., (2012), "Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms", Experimental diabetes research, 2012, pp. 789174.
- Adriano, D.A., Lívia, B.S., and Donald, J.A., (2012), "Structure-Based Drug Design Strategies in Medicinal Chemistry", Current Topics in Medicinal Chemistry, 9(9), pp. 771-790.
- Alswah, M., Bayoumi, A.H., Elgamal, K., Elmorsy, A., Ihmaid, S., and Ahmed, H.E.A., (2018), "Design, Synthesis and Cytotoxic Evaluation of Novel Chalcone Derivatives Bearing Triazolo[4,3-a]- quinoxaline Moieties as Potent Anticancer Agents with Dual EGFR Kinase and Tubulin Polymerization Inhibitory Effects", Molecules, 23(1), pp. 48.
- Amany, S., Mostafa, Khalid, B., *et al.*, (2018), "Synthesis and anticancer activity of new dihydropyrimidinone derivatives", European Journal of Medicinal Chemistry, 156, pp. 304-315.
- Amin, K.M., Taha, A.M., George, R.F., Mohamed, N. M., and Elsenduny, F.F., (2018), "Synthesis, anti-tumor activity evaluation and DNAbinding study of coumarin based agents", Archive Der Pharmazie, 351(1), pp. 1700199.
- Avula, S., Komsani, J. R., Koppireddi, S., Yadla, R., Kanugula, A. K., & Kotamraju, S. (2012). Synthesis and cytotoxicity of novel 6H-indolo[2,3-b]quinoxaline derivatives. Medicinal Chemistry Research, 22(8), 3712–3718.
- Bhatia, R., and Rawal, R.K., (2019), "Coumarin Hybrids: Promising Scaffolds in the Treatment of Breast Cancer", Mini Reviews in Medicinal Chemistry, 19(17), pp. 1443-1458.

- Bissell, M.J., and Radisky, D., (2001), "Putting Tumours in Context," Nature Reviews Cancer., 1(1), pp. 46-54.
- Baylin, S. B., & Jones, P. A., (2016), "Epigenetic Determinants of Cancer", Cold Spring Harbor perspectives in biology, 8(9), a019505.
- Bajaj, J., Diaz, E., and Reya, T., (2020), "Stem cells in cancer initiation and progression", Journal of Cell Biology, 219(1), pp. e201911053.
- Becker, S., (2015), "A historic and scientific review of breast cancer: The next global health care challenge", International Journal of Gynecology and Obstetrics, 131, pp. S36-S39.
- Brisken, C., and O'Malley, B. (2010), "Hormone action in the mammary gland", Cold Spring Harbor perspectives in biology, 2(12), pp. a003178.
- Burns, K. A., and Korach, K. S. (2012), "Estrogen receptors and human disease: an update. Archives of toxicology", 86(10), pp. 1491–1504.
- Bhardwaj, P., Au, C. C., Benito-Martin, A., Ladumor, H., Oshchepkova, S., Moges, R., and Brown, K. A. (2019), "Estrogens and breast cancer: Mechanisms involved in obesity-related development, growth and progression", The Journal of steroid biochemistry and molecular biology, 189, pp. 161–170.
- Brueggemeier, R.W., Richards. J.A., and Petrel, T.A.. (2003), "Aromatase and cyclooxygenases: enzymes in breast cancer", Journal of Steroid Biochemistry and Molecular Biology, 2003, 86(3-5), pp. 501-7.
- Bollet, M.A., Savignoni, A., De Koning, L., *et al.*, (2011), "Tumor aromatase expression as a prognostic factor for local control in young breast cancer patients after breast-conserving treatment", Breast Cancer Research, 11, pp. R54.
- Bhatnagar, A.S., (2007), 'The discovery and mechanism of action of letrozole", Breast Cancer Research and Treatment, 105, pp. 7–17.
- Ballazhi, L., Popovski, E., Jashari, A., Imeri, F., Ibrahimi, I., Mikhova, B., and Mladenovska, K., (2015), "Potential antiproliferative effect of isoxazolo- and thiazolo coumarin derivatives on breast cancer mediatedbone and lung metastases", Acta Pharmaceutica, 65, pp. 53–63.
- Bhat, M.A., Al-Dhfyan, A., and Al-Omar, M.A., (2016). "Targeting Cancer Stem Cells with Novel 4-(4-Substituted phenyl)-5-(3,4,5-trimethoxy/3,4-

dimethoxy)-benzoyl-3,4-dihydropyrimidine-2(1H)-one/thiones", Molecules, 21(12), pp. 1746.

- Chow, A. Y., (2010), Cell Cycle Control by Oncogenes and Tumor Suppressors: Driving the Transformation of Normal Cells into Cancerous Cells. Nature Education, 3(9), pp. 7.
- Charmsaz, S., Collins, D.M., Perry, A.S., and Prencipe, M., (2019), "Novel Strategies for Cancer Treatment: Highlights from the 55th IACR Annual Conference". Cancers (Basel), 11(8), pp. 1125.
- Comşa, Ş,, Cîmpean, A.M., and Raica, M., (2015), "The Story of MCF-7 Breast Cancer Cell Line: 40 years of Experience in Research", Anticancer Research, 35(6), pp. 3147-54.
- Cronin, K.A., Lake, A.J., Scott, S., Sherman, R.L., et al., (2018), "Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics". Cancer, 124(13), pp. 2785-2800.
- Clezardin, P., (2011). "Therapeutic targets for bone metastases in breast cancer". Breast Cancer Research., 13, pp. 207-215
- Cardoso, F., Senkus-Kone, E., Fallowfield, L., Costa, A. and Castigilone, M., (2010), "Locally recurrent or metastatic breast cancer: ESMO Clinical practice guidelines for diagnosis, treatment and followup", Annals of Oncology, 21, pp. 15–19.
- Chen, S., Cho, M., Karlsberg, K., Zhou, D.Y., and Yuan, C., (2004), "Biochemical and biological characterization of a novel anti-aromatase coumarinderivative". Journal of Biology and Chemistry, 279, pp. 48071-48078.
- Chen, S., Cho, M., Karlsberg, K., Zhou, D., and Yuan, Y.C., (2004), "Biochemical and biological characterization of a novel anti-aromatase coumarin derivative". Journal of Biology and Chemistry, 279(46), pp. 48071-8.
- Chen, H., Li, S., Yao, Y., Zhou, L., Zhao, J., Gu, Y., Wang, K., and Li, X., (2013), "Design, synthesis and anti-tumor activities of novel triphenylethylene-coumarin hybrids, and their interactions with Ct- DNA". Bioorganic and Medicinal Chemistry Letters, 23(17), pp. 4785-4789.

- Chand, K., Shirazi, A.N., Yadav, P., Tiwari, R.K., Kumari, M., Parang, K., and Sharma, S.K., (2013), "Synthesis, anti-proliferative and c-Src kinase inhibitory activities of cinnamoyl- and pyranochromen-2-one derivatives". Canadian Journal of Chemistry, 91(8), pp. 741-754.
- Duss, S., André, S., Nicoulaz, AL., *et al.*, (2007), "An oestrogen-dependent model of breast cancer created by transformation of normal human mammary epithelial cells". Breast Cancer Research, 9, pp. R38.
- Durrani, I.A., Bhatti, A. and John, P., (2021), "The prognostic outcome of 'type 2 diabetes mellitus and breast cancer' association pivots on hypoxia-hyperglycemia axis", Cancer Cell International, 21, pp. 351.
- Daśko, M., Demkowicz, S., Rachon, J., Biernacki, K., Aszyk, J., Kozak, W., and Kubiński, K., (2020), "New potent STS inhibitors based on fluorinated 4-(1-phenyl-1 H-[1, 2, 3] triazol-4-yl)-phenyl sulfamates. Journal of Asian natural products research", 22(11), 1037-1044.
- Ding, J., Liu, J., Zhang, Z., Guo, J., Cheng, M., Wan, Y., Wang, R., Fang, Y., Guan, Z., Jin, Y., and Xie, S.S., (2020), "Design, synthesis and biological evaluation of coumarin-based N-hydroxycinnamamide derivatives as novel histone deacetylase inhibitors with anti-cancer activities". Bioorganic Chemistry, 101,pp. 104023.
- Drwal, M.N., Banerjee, P., Dunkel, M., Wettig, M.R., Preissner, R., (2014), "Protox: a Web Server for the In SilicoPrediction of Rodent Oral Toxicity," Nucleic Acid Research., 42(1), pp. 53-58.
- Esteller, M., (2002), "CpG island hypermethylation and tumor suppressor genes: a booming present, a brighter future". Oncogene, 21, pp. 5427–5440.
- Eketunde, A. O., (2020), "Diabetes as a Risk Factor for Breast Cancer", Cureus, 12(5), pp. e8010.
- El Newahie, A.M.S., Nissan, Y.M., Ismail, N.S.M., Abou El Ella, D.A., Khojah, S.M., and Abouzid, K.A.M., (2019), "Design and Synthesis of New Quinoxaline Derivatives as Anticancer Agents and Apoptotic Inducers. Molecules", **24**(6), pp. 1175.
- El Newahie, A.M.S., Ismail, N.S.M., Abou El Ella, D.A., and Abouzid, K.A., (2016), "Quinoxaline-Based Scaffolds Targeting Tyrosine Kinases and Their Potential Anticancer Activity", Archiv Der Pharmazie, 349(5), 309–326.

- Elmaghraby, A. M., Mousa, I. A., Harb, A. A., & Mahgoub, M. Y. (2013). Three component reaction: an efficient synthesis and reactions of 3, 4-dihydropyrimidin-2 (1H)-ones and thiones using new natural catalyst. *International Scholarly Research Notices*, *2013*.
- Ertl, P., Rohde, B., and Selzer, P., (2000), "Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties," Journal of Medicinal Chemistry., 43(20), pp. 3714–3717.
- Fares, J., Fares, M.Y., Khachfe, H.H., et al., (2019), "Molecular principles of metastasis: a hallmark of cancer revisited", Signal Transduction and Target Therapy, **5, pp.** 28.
- Fares, J., Fares, M. Y., Khachfe, H. H., Salhab, H. A., and Fares, Y. (2020), "Molecular principles of metastasis: a hallmark of cancer revisited. Signal transduction and targeted therapy", 5(1), pp. 28.
- Ferretti, G., Bria, E., Giannarelli, D., Felici, A., Papaldo, P., Fabi, A., Di, Cosimo. Et al., (2006), "Second- and third-generation aromatase inhibitors as first-line endocrine therapy in postmenopausal metastatic breast cancer patients: a pooled analysis of the randomised trials", British Journal of Cancer, 94(12), pp. 1789-96.
- Fan, J., Fu, A. and Zhang, L., (2019), "Progress in molecular docking", Quantitative Biology, 7, pp. 83–89.
- Fayed, E.A., Sabour, R., Harras, M.F., *et al.* (2019), "Design, synthesis, biological evaluation and molecular modeling of new coumarin derivatives as potent anti-cancer agents". Medicinal Chemistry Research, 28, pp. 1284–1297.
- Gonzalez, H., Hagerling, C., and Werb, Z. (2018), "Roles of the immune system in cancer: from tumor initiation to metastatic progression", Genes & development, 32(19-20), pp. 1267–1284.
- Guan, X., (2015), "Cancer metastases: challenges and opportunities", Acta Pharmaceutica Sinica B, 5(5), pp. 402-18.
- Greaves, M., and Maley, C. C., (2012), "Clonal evolution in cancer", Nature, 481(7381), pp. 306–313.
- Gao, Q., López-Knowles, E., Cheang, M.C.U., *et al.* (2020), "Impact of aromatase inhibitor treatment on global gene expression and its association

with antiproliferative response in ER+ breast cancer in postmenopausal patients", Breast Cancer Research, 22, pp. 1-20.

- Gutierrez, C., and Schiff, R., (2011), "HER2: biology, detection, and clinical implications. Archives of pathology & laboratory medicine", 135(1), pp. 55–62.
- Ghorab, M.M., Alsaid, M.S., Al-Ansary, G.H., Abdel-Latif, G.A., and Abou El Ella, D.A., (2016), "Analogue based drug design, synthesis, molecular docking and anti-cancer evaluation of novel chromene sulfonamide hybrids as aromatase inhibitors and apoptosis enhancers", European Journal of Medicinal Chemistry, 124, pp. 946-958.
- Goel, R., Luxami, V., and Paul, K., (2015), "Synthesis, in vitro anticancer activityand SAR studies of arylated imidazo[1,2-a] pyrazine-coumarin hybrids", RSC Advance, 5, pp. 37887-37895.
- Hao, T., Li-Talley, M., Buck, A. *et al.* (2019), "An emerging trend of rapid increase of leukemia but not all cancers in the aging population in the United States", Scientific Reports, 9, pp. 12070.
- Henske, E. P., (2003), "Metastasis of benign tumor cells in tuberous sclerosis complex", Genes, Chromosomes and Cancer, 38(4), pp.376-381.
- Harris, T., and McCormick, F., (2010), "The molecular pathology of cancer", Nature Reviews on Clinical Oncology, 7, pp. 251–265.
- Hapach, L.A., Mosier, J.A., Wang, W. *et al.* (2019), "Engineered models to parse apart the metastatic cascade". npj Precision Oncology, 3, pp. 20.
- Huang, C. Y., Ju, D. T., Chang, C. F., Muralidhar Reddy, P., and Velmurugan, B. K. (2017), "A review on the effects of current chemotherapy drugs and natural agents in treating non-small cell lung cancer", BioMedicine, 7(4), pp. 23.
- Hsiao, Y.H., Chou, M.C., Flower, C., Mason, J.T., and Man, Y.G., (2010), "Breast cancer heterogeneity: mechanisms, proofs and implications", Journal of Cancer, 1, pp. 6-13.
- Harada, K., Kubo, H., Tomigahara, K., Nishioka, K., Takahashi, J., Momose, M., Inoue, S., and Kojima, A., (2010), "Coumarins as novel 17β-hydroxysteroid dehydrogenase type 3 inhibitors for potential treatment of

prostate cancer", Bioorganic and Medicinal Chemistry Letters, 20, pp. 272-275.

- Hong-Zhen, Z., Jessica, M., *et al.* (2002), "Estrogen Mediates Mammary Epithelial Cell Proliferation in Serum-Free Culture Indirectly via Mammary Stroma-Derived Hepatocyte Growth Factor", Endocrinology, 143(9), 2002, pp. 3427–3434.
- Harbeck, N., Penault-Llorca, F., Cortes, J., *et al*. (2019), "Breast cancer", Nature Reviews Dis Primers, 5, pp. 66.
- 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), pp. 1769–1792.
- Hng, Y., Lin, M.H., Lin, T.S., Liu, I.C., Lin, I.C., Chen, M.J., Liang, P.H., *et al.* (2020), "Design and synthesis of 3-benzylaminocoumarin-7-O-sulfamate derivatives as steroid sulfatase inhibitors", Bioorganic Chemistry, 96, pp. 103618.
- Hussain, M.K. Sigh, D.K., Singh, A., Asad, M., Ansari, I., Shameem, M., Krishna, S., Valicherla, G.R., Makadia, V., Meena, S., Deshmukh, A.L., Gayen, J.R., Siddiqui, M.I., Datta, D., Hajela, K., and Banerjee, D.A., (2017), "Novel Benzocoumarin-Stilbene Hybrid as a DNA ligase I inhibitor with in vitro and in vivo anti-tumor activity in breast cancer models", Scientific Reports, 7, pp. 10715.
- Hosamani, K.M., Reddy, D.S., and Devarajegowda, H.C., (2015), "Microwave-assisted synthesis of new fluorinated coumarin–pyrimidine hybrids as potent anti-cancer agents, their DNA cleavage and X-ray crystal studies", RSC Advances, 5(15), pp. 11261-11271.
- Imran, A., Qamar, H. Y., Ali, Q., Naeem, H., Riaz, M., Amin, S., Kanwal, N., Ali, F., Sabar, M. F., & Nasir, I. A., (2017), "Role of Molecular Biology in Cancer Treatment: A Review Article. Iranian journal of public health", 46(11), pp. 1475–1485.
- Iqbal, N., and Iqbal, N., (2014), "Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications", Molecular biology international, 2014, pp. 852748.

- Ivashchenko, A.V. and Agafonova, I.F., (1981), "Synthesis and study of indolo[2,3-b]quinoxaline derivatives"., Chemistry of Heterocyclic Compounds, **17, pp.** 184–189.
- Jiang, W.G., Sanders, A.J., Katoh, M., Ungefroren, H., Gieseler, F., Prince, M, *et al.* (2015), "Tissue invasion and metastasis: Molecular, biological and clinical perspectives", Seminars in Cancer Biology, 35, pp. S244-S275.
- Kinzler, K.W., and Vogelstein, B., (1997), "Gatekeepers and Caretakers," Nature., 386, pp. 761-763.
- Kristensen, V., Harada, N., Yoshimura, N., *et al.* (2000) "Genetic variants of CYP19 (aromatase) and breast cancer risk", Oncogene, 19, pp. 1329–1333.
- Kim, S.C., Boggu, P.R., Yu, H.N., Ki, S.Y., Jung, J.M., et al. (2020), "Synthesis and biological evaluation of quinoxaline derivatives as specific c-Met kinase inhibitors", Bioorganic and Medicinal Chemistry Letters, 2020, pp. 127189.
- Kaur, R., Chaudhary, S., Kumar, K., Gupta, M.K., and Rawal, R.K., (2017), "Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review", European Journal of Medicinal Chemistry, 132, pp. 108-134.
- Karataş, M. O., Tekin, S., Alici, B., & Sandal, S., (2019), "Cytotoxic effects of coumarin substituted benzimidazolium salts against human prostate and ovarian cancer cells", Journal of Chemical Sciences, 131(8), pp. 1-12.
- Kahveci, B., Yilmaz, F., Mentese, E., and Ulker, S., (2017), "Design, synthesis and biological evaluation of coumarin–triazole hybrid molecules as potential antitumor and pancreatic lipase agents", Archiv der Pharmazie-Chemistry in Life Sciences, 350, pp. e1600369.
- Kamath, P.R., Sunil, D., Joseph, M.M., Salam, A., and Sreelekha, T., (2017), "Indole-coumarin-thiadiazole hybrids: An appraisal of their MCF-7 cell growth inhibition, apoptotic, antimetastatic and computational Bcl-2 binding potential", European Journal of Medicinal Chemistry, 136, pp. 442-451.
- Kamath, P.R., Sunil, D., Ajees, A., Pai, K.S.R., and Das, S., (2015), "Some new coumarin-indole hybrids: Synthesis, anti-cancer and Bcl-2 docking studies", Bioorganic Chemistry, 63, pp. 101-109.

- Kini, S.G., Choudhary, S., and Mubeen, M., (2012), "Synthesis, docking and anti-cancer activity of coumarin substituted derivatives of benzothiazole", Journal of Computational Methods and Molecular Design, 2 (1), pp. 51-60.
- Klein, L.L., and Tufano, M.D., (2013). "Synthesis of Substituted Isatins", Tetrahedron Letters, 54(8), pp. 1008-1011.
- Lievens, Y., Gospodarowicz, M.K., Grover, S., Jaffray, D., Rodin, D., Torode, J., and Zubizarreta, E. (2017), "Global Impact of Radiotherapy in Oncology: Saving One

  Million Lives by 2035," Radiotherapy and Oncology, 125(2), pp. 175-177.
- Lewis, J.S., and Jordan, V.C., (2005), "Selective estrogen receptor modulators (SERMs): mechanisms of anti-carcinogenesis and drug resistance". Mutation Research: Fundamental and Molecular Mechanisms, 591, pp. 247-263.
- Lingaraju, G.S., Balaji, K.S., Jayarama, S., Anil, S.M., Kiran, K.R., and Sadashiva, M.P., (2018), "Synthesis of new coumarin tethered isoxazolines as potential anti-cancer agents", Bioorganic and Medicinal Chemistry Letters, 28(23-24), pp. 3606-3612.
- Lu, X.Y., Wang, Z.C., Ren, S.Z., Shen, F.Q., Man, R.J., and Zhu, H.L., (2016), "Coumarin sulfonamides derivatives as potent and selective COX-2 inhibitors with efficacy in suppressing cancer proliferation and metastasis", Bioorganic and Medicinal Chemistry Letters, 26(15), pp. 3491-3498.
- Liu, H., Wang, Y., Sharma, A., Mao, R., Jiang, N., Dun, B., and She, J.X., (2015), "Derivatives containing both coumarin and benzimidazole potently induce caspase-dependent apoptosis of cancer cells through inhibition of PI3K-AKT-mTOR signalling", Anti-cancer Drugs, 26(6), pp. 667-677.
- Lipinski, C.A., Lombardo, F., Dominy, B.W., and Feeney, P.J., (2012), "Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings," Advanced Drug Delivery Review., 64, pp.4-17.
- Martin, T.A., Ye, L., Sanders, A.J, *et al.* Cancer Invasion and Metastasis: Molecular and Cellular Perspective. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013.
- Malone, E.R., Oliva, M., Sabatini, P.J.B. *et al.* (2020), "Molecular profiling for precision cancer therapies" Genome Medicine, 12, pp. 8.

- Mantovani, F., Collavin, L. and Del Sal, G., (2019), "Mutant p53 as a guardian of the cancer cell", Cell Death Differences, 26, pp. 199–212.
- Musa, A.M., Cooperwood, J.S. and Khan, M.O.F., (2008), "A Review of Coumarin Derivatives in Pharmacotherapy of Breast Cancer", Current Topics in Medicinal Chemistry, 15(26), pp. 2664-2679.
- Moyer, J.D., Barbacci, E.G., Iwata, K.K., Arnold, L., Boman, B., Cunningham, A., DiOrio. C., Doty, J., Morin, M.J., and Moyer, M.P., (1997), "Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase", Cancer Research, 57, pp. 4838-4848.
- Moasser, M., (2007), "The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis". Oncogene, 26(45), pp. 6469–6487.
- Mishra, S., and Singh, P., (2016), "Hybrid molecules: The privileged scaffolds for various pharmaceuticals", European Journal of Medicinal Chemistry, 124, pp. 500-536.
- Mohamed, M.F., Ibrahim, N.S., Elwahy, A.H.M. and Abdelhamid, I.A.,(2018), "Molecular Studies on Novel Antitumor Bis 1,4-Dihydropyridine Derivatives Against Lung Carcinoma and their Limited Side Effects on Normal Melanocytes", Anticancer Agents in Medicinal Chemistry, 18(15), pp. 2156-2168.
- Morris, G.M., Lim-Wilby, M., (2008), "Molecular docking". Methods in Molecular Biology, 443, pp. 365-82.
- Meng, X. Y., Zhang, H. X., Mezei, M., and Cui, M., (2011). "Molecular docking: a powerful approach for structure-based drug discovery". Current computer-aided drug design, 7(2), pp. 146–157.
- Mansoori, B., Mohammadi, A., Davudian, S., Shirjang, S., and Baradaran, B., (2017). The Different Mechanisms of Cancer Drug Resistance: A Brief Review, Advanced pharmaceutical bulletin, 7(3), pp. 339–348.
- Musiliyu, A.M., John, S.C., and Omar F.K., (2008), "A Review of Coumarin Derivatives in Pharmacotherapy of Breast Cancer", Current Medicinal Chemistry, 15(26), pp. 2664-2679.

- Mohamed, T.K., Batran, R.Z., Elseginy, S.A., Ali, M.M., and Mahmoud, A.E., (2019), Synthesis, anti-cancer effect and molecular modeling of new thiazolylpyrazolyl coumarin derivatives targeting VEGFR-2 kinase and inducing cell cycle arrest and apoptosis, Bioorganic Chemistry, 85, pp. 253-273.
- Chen-Chen, Ma., and Zhao-Peng, Liu., (2017), "Design and synthesis of coumarin derivatives as novel PI3K inhibitors," Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 17, pp. 395-403.
- Mosmann, T., (1983), "Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays," Journal of Immunological Methods., 65(1- 2), pp. 55-63.
- Nurgali, K., Jagoe, R. T., and Abalo, R., (2018), "Editorial: Adverse Effects of Cancer Chemotherapy: Anything New to Improve Tolerance and Reduce Sequelae?," Frontiers in pharmacology, 9, pp. 245.
- Nahta, R., and Esteva, F.J., (2006), "HER2 therapy: Molecular mechanisms of trastuzumab resistance". Breast Cancer Res, 8, pp. 215.
- Olshansky, S. J., and Hayflick, L., (2017), "The Role of the WI-38 Cell Strain in Saving Lives and Reducing Morbidity", AIMS public health, *4*(2), pp. 127–138.
- Ormazabal, V., Nair, S., Elfeky, O., *et al.* (2018), Association between insulin resistance and the development of cardiovascular disease. Cardiovascular Diabetology, 17, pp. 122.
- Pilleron, S., Sarfati, D., Janssen-heijnen, M., Vignat, J., Ferlay, J., Bray, F., (2018),"Global Cancer Incidence in Older Adults, 2012 and 2035: A Population-Based Study," International Journal of Cancer., 144(1), pp. 49-58.
- Mathur, P., Kumar, S.K., Chaturvedi, M., Das, P., Lakshminarayana, S., Stephen, S., Nallasamy, V., John, A., Narasimhan, S., Roselind, F.C. and on behalf of ICMR-NCDIR-NCRP, (2020), Investigator Group JCO Global Oncology, 6, pp. 1063-1075
- Pelosim, E., Castelli, G., and Testa, U., (2019), Understanding mechanisms of cancer initiation and development supports the need for an implementation of

primary and secondary cancer prevention, Annali dell'Istituto Superiore di Sanità, 55(4), pp. 371-379.

- Patel, K., Karthikeyan, C., Solomon, V.R., Moorthy, H.R., Lee, H., Sahu, K., Deora, G.S., and Trivedi, P., (2011), "Synthesis of some coumarinyl chalcones and their antiproliferative activity against breast cancer cell lines". Letters in Drug Design and Discovery, 8(4), pp. 308-311.
- Poloz, Y., and Stambolic, V., (2015), Obesity and cancer, a case for insulin signalling, Cell Death Discovery, 6, pp. e2037.
- Pagadala, N. S., Syed, K., and Tuszynski, J. (2017). Software for molecular docking: a review. Biophysical reviews, 9(2), pp. 91–102.
- Paul, K., Bindal, S., and Luxmi, V., (2013), "Synthesis of new conjugated coumarin– benzimidazole hybrids and their anticancer activity", Bioorganic and Medicinal Chemistry Letters, 23(12), pp. 3667-3672.
- PreADME Property Calculation Software. Available online: https://preadmet.bmdrc.kr/(Accessed on January, 2020)
- Protox Toxicity Prediction Software. Available online: http://tox.charite.de/tox (Accessed on January, 2020)
- Rajagopalan, H., Nowak, M.A., Vogelstein, B., and Lengauer, C., (2003), "The Significance of Unstable Chromosomes in Colorectal Cancer," Nature Reviews Cancer., 3(9), pp. 695-701.
- Ravnan, M.C., Ravnan, S.L., and Walberg, M.P., (2011), "Metastatic breast cancer: a review of current and novel pharmacotherapy", Formulary, 46, pp. 130–146.
- Robert, W., Brueggemeier, C., Hackett, S., and Diaz, C., (2005), "Aromatase Inhibitors in the Treatment of Breast Cancer", Endocrine Reviews, 26 (3), pp. 331–345.
- Reddy, O.R., Suryanarayana, V.C., Sharmila, N., Ramana, G.V., Anuradha, V., and Hari, B., (2013) "Synthesis and Cytotoxic Evaluation for Some New Dihydropyrimidinone Derivatives for Anticancer Activity", Letters in Drug Design & Discovery, **10**, pp. 699.
- RCSB Protein Data Bank. Avalaible online: http://www.rcsb.org/pdb (Accessed on 1 June 2019).

- Sainz, R.M., Lombo, F., Mayo, J. C., (2012), "Redical Decision in Cancer: Redox Control of Cell Growth and Death," Cancers., 4(2), pp. 442-474.
- Stratton, M. R., Campbell, P. J., & Futreal, P. A. (2009). The cancer genome. Nature, 458(7239), 719–724.
- Sieber, O.M., Heinimann, K., and Tomlinson, I. P., (2003), "Genomic Instability-The Engine of Tumorigenesis," Nature Reviews Cancer, 3(9), pp. 701-708.
- Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F., (2021), "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries", CA: A Cancer Journal for Clinicians, 71, pp. 209- 249
- Siegel, R.L., Miller, K.D., Fuchs, H., and Jemal, A., (2021), "Cancer Statistics", CA: A Cancer Journal for Clinicians,71, pp. 7- 33.
- Scott, W.L., and Athena, W.L., (2000), "Apoptosis in cancer," Carcinogenesis, 21(3), pp. 485–495.
- Shao, W., and Brown, M., (2003), "Advances in estrogen receptor biology: prospects for improvements in targeted breast cancer therapy", Breast Cancer Research. 6, pp. 39.
- Schlam, I., and Swain, S.M., (2003), "HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now, npj Breast Cancer", **7, pp.** 56.
- Silva, B.V., (2013), "Isatin, a Versatile Molecule: Studies in Brazil", Journal of Brazilian Chemical Society, 24(5), pp. 707-720.
- Stringlis, I. A., de Jonge, R., and Pieterse, C., (2019), "The Age of Coumarins in Plant-Microbe Interactions", Plant & cell physiology, 60(7), pp. 1405–1419.
- Sarker, S.D., and Nahar, L., (2017), "Progress in the Chemistry of Naturally Occurring Coumarins", Progress in the Chemistry of Organic Natural Products, 106, pp. 241-304.
- Srikrishna, D., Godugu, C., Dubey, P.K., (2018), "A Review on Pharmacological Properties of Coumarins". Mini Reviews in Medicinal Chemistry,18(2), pp.113-141.
- Sibiya, M.A., Raphoko, L., Mangokoana, D., Makola, R., Nxumalo, W., and Matsebatlela, T.M., (2019), "Induction of Cell Death in Human A549 Cells

Using 3-(Quinoxaline-3-yl) Prop-2-ynyl Methanosulphonate and 3-(Quinoxaline-3-yl) Prop-2-yn-1-ol", Molecules, 24(3), pp. 407.

- Soumyanarayanan, U., Bhat, V.G., and Kar, S.S., *et al.*, (2012), "Monastrol mimic Biginelli dihydropyrimidinone derivatives: synthesis, cytotoxicity screening against HepG2 and HeLa cell lines and molecular modeling study", Organic and Medicinal Chemistry Letters, **2,** 23.
- Stefanachi, A., Favia, A. D., Nicolotti, O., Leonetti, F., Pisani, L., Catto, M., and Carotti, A., (2011), "Design, synthesis, and biological evaluation of imidazolyl derivatives of 4, 7-disubstituted coumarins as aromatase inhibitors selective over 17-α-hydroxylase/C17− 20 lyase", Journal of medicinal chemistry, 54(6), pp. 1613-1625.
- Sanduja, M., Gupta, J., Singh, H., Pagare, P. P., and Rana, A., (2020), "Uracil-coumarin based hybrid molecules as potent anti-cancer and anti-bacterial agents", Journal of Saudi Chemical Society, 24(2), pp. 251-266.
- Sashidhara, K.V., Avula, S.R., Sharma, K., Palnati, K., Bathula, S.R., (2013), "Discovery of coumarin-monastrol hybrid as potential antibreast tumor-specific agent". European Journal of Medicinal Chemistry, 60, 120-127.
- Shibinskaya, M.O., Lyakhov, S.A., Mazepa, A.V., Andronati, S.A., Turov, A.V., Zholobak, N.M., and Spivak, N.Y., (2010), "Synthesis, cytotoxicity, antiviral activity and interferon inducing ability of 6-(2-aminoethyl)-6H-indolo [2, 3-b] quinoxalines", European Journal of Medicinal Chemistry, 45, pp. 1237–1243.
- Sohal. S.H., Goyal, A., Sharma, R., and Khare, R., (2014), "One-pot, multicomponent synthesis of symmetrical Hantzsch 1,4-dihydropyridine derivatives using glycerol as clean and green solvent", European Journal of Chemistry, 5 (1), pp. 171-175.
- Takeshima, H., and Ushijima, T., (2019), "Accumulation of genetic and epigenetic alterations in normal cells and cancer risk". npj Precision Oncology, 3, pp. 7.
- Topham, J.T., and Marra, M.A., (2016), "Sequencing Strategies to Guide Decision Making in Cancer Treatment," PLoS Med, 13(12), pp. e1002189.
- Unzue, A., Dong, J., Lafleur, K., Zhao, H., Frugier, E., Caflisch, A., and Nevado, C., (2014), "Pyrrolo[3,2-b]quinoxaline Derivatives as Types I1/2 and

II Eph Tyrosine Kinase Inhibitors: Structure-Based Design, Synthesis, and in Vivo Validation", Journal of Medicinal Chemistry, 57 (15), pp. 6834-6844.

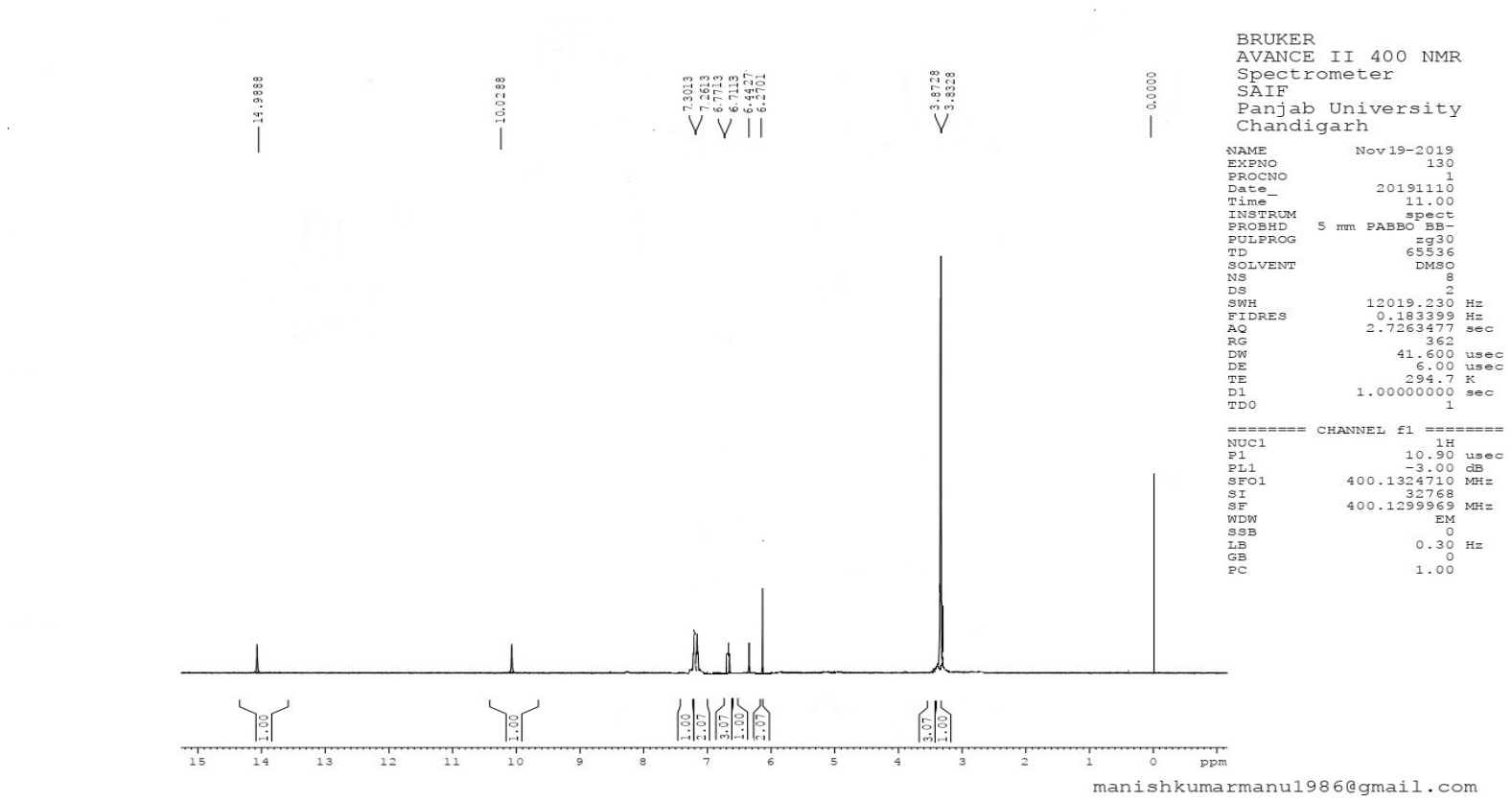
- Vogelstein, B., and Kinzler, K. W., (2002), "The Genetic Basis of Human Cancer," McGraw-Hill: New York.
- Venugopala, K. N., Rashmi, V., and Odhav, B., (2013), "Review on natural coumarin lead compounds for their pharmacological activity", BioMedical Research international, 963248. https://doi.org/10.1155/2013/963248
- Viradiya, D., Mirza, S, Shaikh, F., Kakadiya, R., Rathod, A., Jain, N., Rawal, R., and Shah, A., (2017), Design and Synthesis of 1,4-dihydropyridine Derivatives as Anti-cancer Agent, Anticancer Agents in Medicinal Chemistry, 17(7), pp.1003-1013.
- Vanhoefer, U., Müller, M., Hilger, R. *et al.*, (1999), "Reversal of MDR1-associated resistance to topotecan by PAK-200S, a new dihydropyridine analogue, in human cancer cell lines". British Journal of Cancer, 81, pp. 1304–1310.
- Vekariya, R. H., Patel, K. D., Rajani, D. P., Rajani, S. D., & Patel, H. D. (2017). A one pot, three component synthesis of coumarin hybrid thiosemicarbazone derivatives and their antimicrobial evolution. *Journal of the Association of Arab Universities for Basic and Applied Sciences*, *23*, 10-19.
- Weir, H.K., Anderson, R.N., Coleman King, S.M., Soman, A., Thompson, T.D., Hong, Y. *et al*., (2016), "Heart Disease and Cancer Deaths- Trends and Projections in the United States, 1969–2020". Preventing Chronic Diseases, 13, pp. 160211.
- WHO Fact Sheet, Tobacco-WHO, July-2021, www.who.int
- Waldman, A.D., Fritz, J.M. and Lenardo, M.J., (2020), "A guide to cancer immunotherapy: from T cell basic science to clinical practice". Nature Reviews of Immunology, 20, pp. 651–668.
- Wu, L., Wang, X., Xu, W., Farzaneh, F., Xu, R.; (2019), "The structure and pharmacological functions of coumarins and their derivatives", Current Medicinal Chemistry, 16(32), pp. 4236-60.
- Xu, J., Li, H., Wang, X., Huang, J., Li, S., Liu, C., Dong, R. *et al.*, (2020), "Discovery of coumarin derivatives as potent and selective cyclin-dependent

kinase 9 (CDK9) inhibitors with high antitumour activity", European Journal of Medicinal Chemistry, 200, pp. 112424.

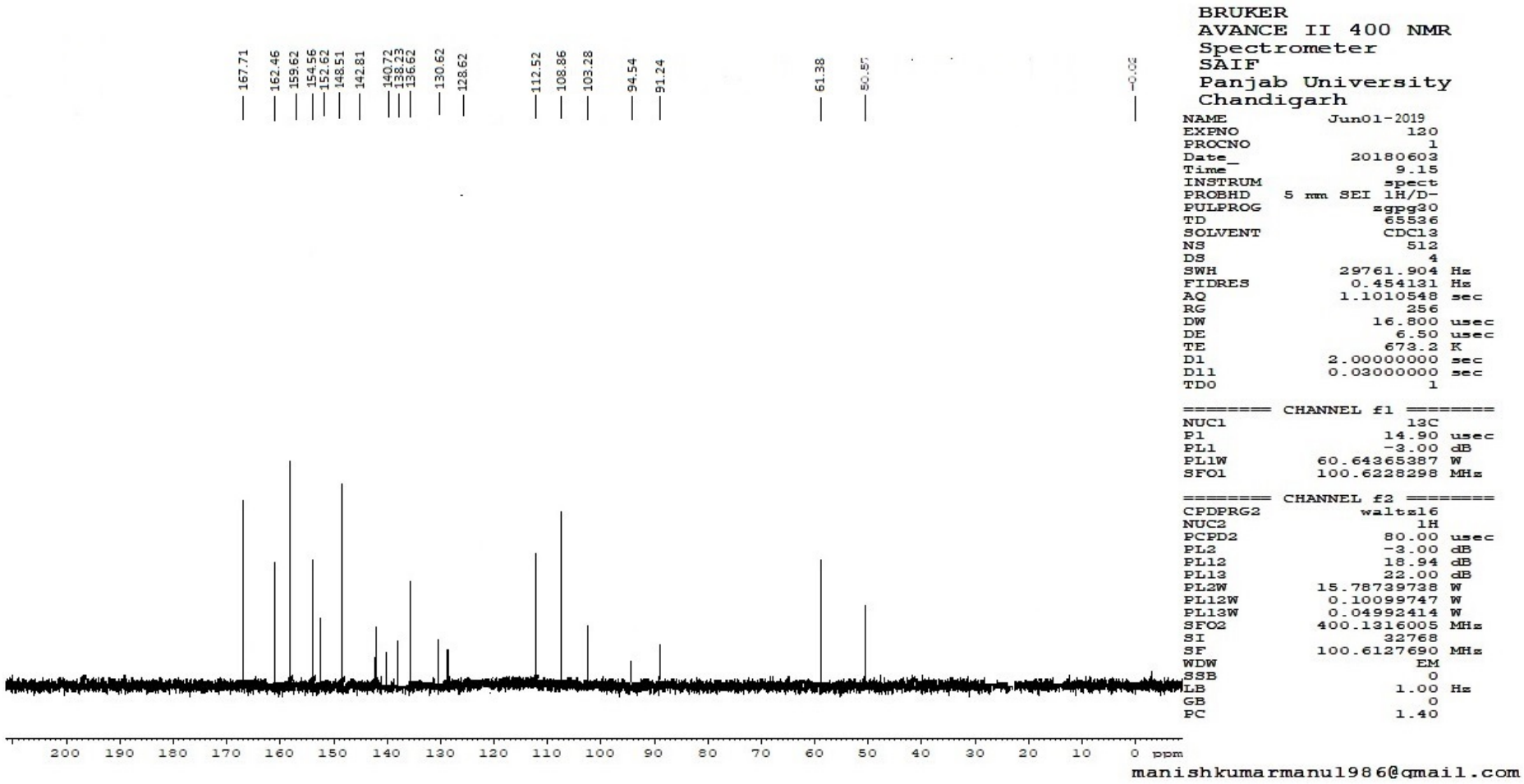
- Xiao, C.F., Tao, L.Y., Sun, H.Y., Wei, W., Chen, Y., Fu Li, W., Zou, Y., (2010), "Design, synthesis and antitumor activity of a series of novel coumarin-stilbenes hybrids, the 3-aryl Coumarins", Chinese Chemical Letters, 21, pp. 1295-1298.
- Yalaza, M., İnan, A., and Bozer, M. (2016), "Male Breast Cancer", The journal of breast health, 12(1), pp. 1–8.
- Yue, W., Wang, J. P., Li, Y., Fan, P., Liu, G., Zhang, N., Conaway, M., Wang, H., Korach, K. S., Bocchinfuso, W., and Santen, R, (2010), "Effects of estrogen on breast cancer development: Role of estrogen receptor independent mechanisms", International journal of cancer, 127(8), pp. 1748–1757.
- Yamaguchi, Y., Nishizono, N., Kobayashi, D., Yoshimura, T., Wada, K., and Oda. K., (2017), "Evaluation of synthesized coumarin derivatives on aromatase inhibitory activity", Bioorganic and Medicinal Chemistry Letters, 27(12), pp. 2645-2649.
- Yamaguchi, Y., Nishizono, N., and Oda, K., (2020), "Evaluation of Synthesized Ester or Amide Coumarin Derivatives on Aromatase Inhibitory Activity", Biological and Pharmaceutical Bulletin, 43(8), pp.1179-1187.
- Zaitceva, V., Kopeina, G.S., Zhivotovsky, B., (2021), "Anastasis: Return Journey from Cell Death," Cancers, 13, pp. 3671.
- Zhao, H., Zhou, L., Shangguan, A. J., and Bulun, S. E., (2016), "Aromatase expression and regulation in breast and endometrial cancer. Journal of molecular endocrinology", 57(1), pp. R19–R33.
- Zhang, Y.Y., Zhang, Q.Q., Song, J.L., Zhang, L., Jiang, C.S., Zhang, H., (2018), "Design, Synthesis, and Antiproliferative Evaluation of Novel Coumarin/2-Cyanoacryloyl Hybrids as Apoptosis Inducing Agents by Activation of Caspase-Dependent Pathway", Molecules, 23(8), pp. 1972.

Appendix

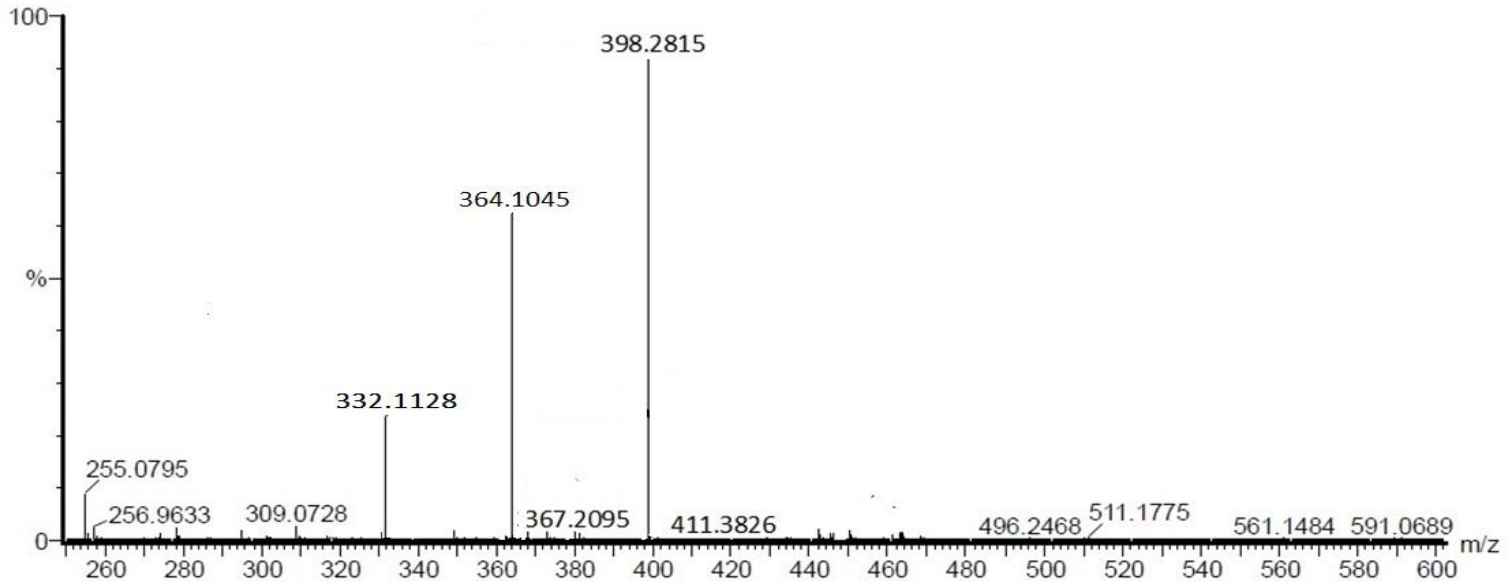
^{1}H NMR of Compound RB86



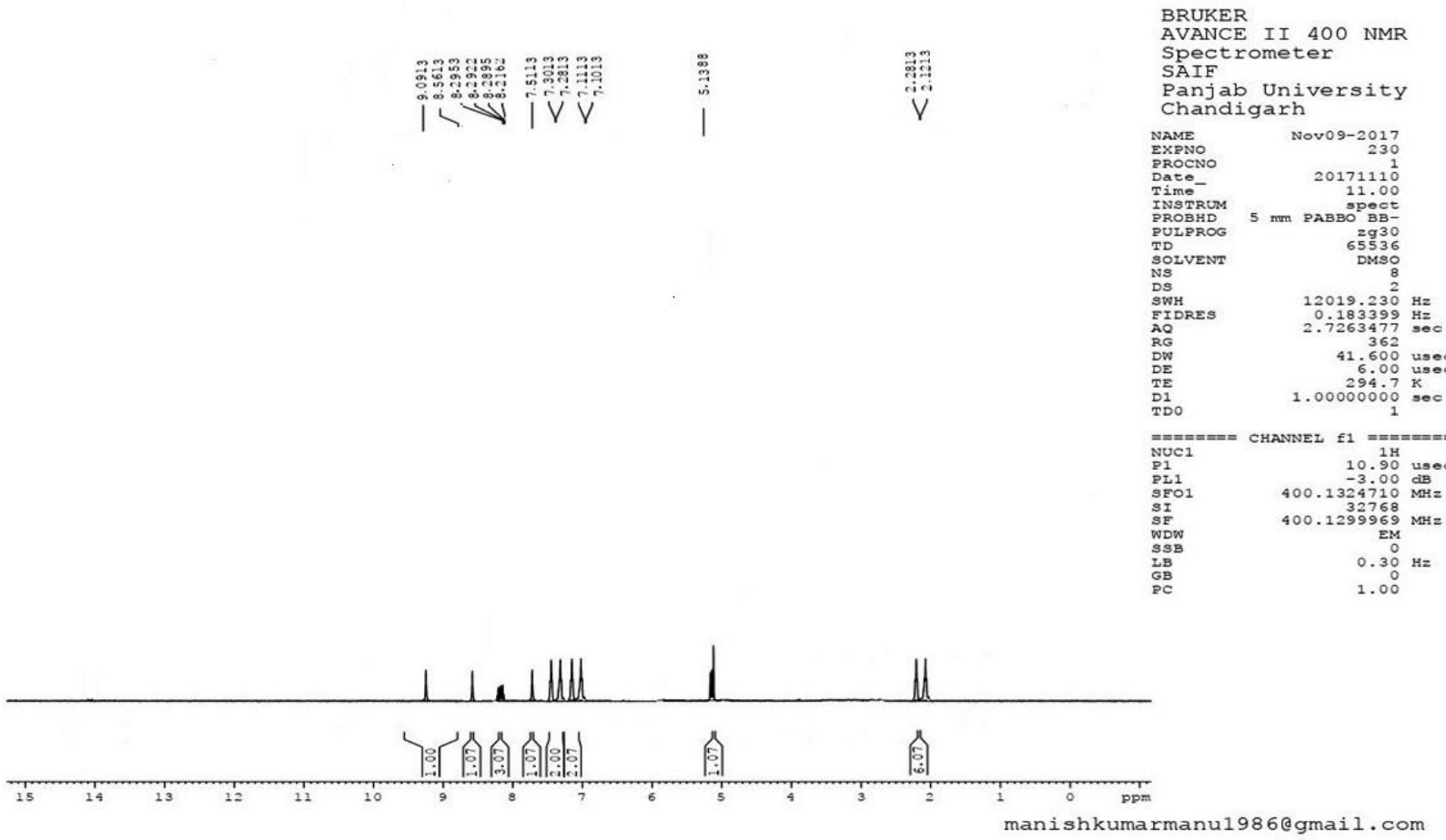
^{13}C NMR of Compound RB86



HRMS of Compound RB86



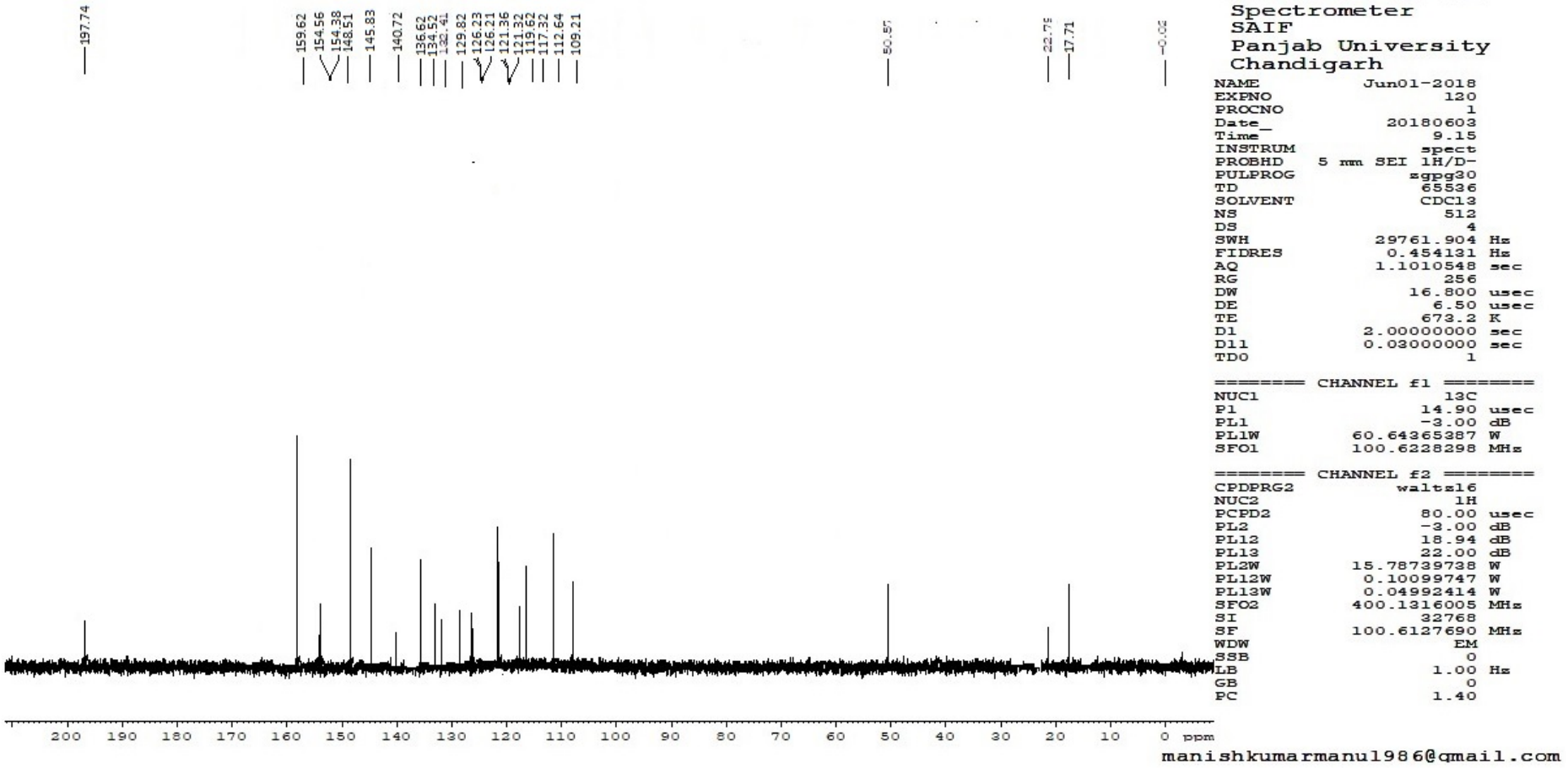
^{1}H NMR of Compound CD28




```
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

NAME                Nov09-2017
EXPNO                      230
PROCNO                       1
Date_                 20171110
Time                     11.00
INSTRUM                  spect
PROBHD   5 mm PABBO BB-
PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                          8
DS                          2
SWH                 12019.230 Hz
FIDRES                0.183399 Hz
AQ                    2.7263477 sec
RG                        362
DW                     41.600 usec
DE                      6.00 usec
TE                     294.7 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                      10.90 usec
PL1                     -3.00 dB
SFO1               400.1324710 MHz
SI                        32768
SF                 400.1299969 MHz
WDW                          EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                      1.00
```

manishkumarmanu1986@gmail.com

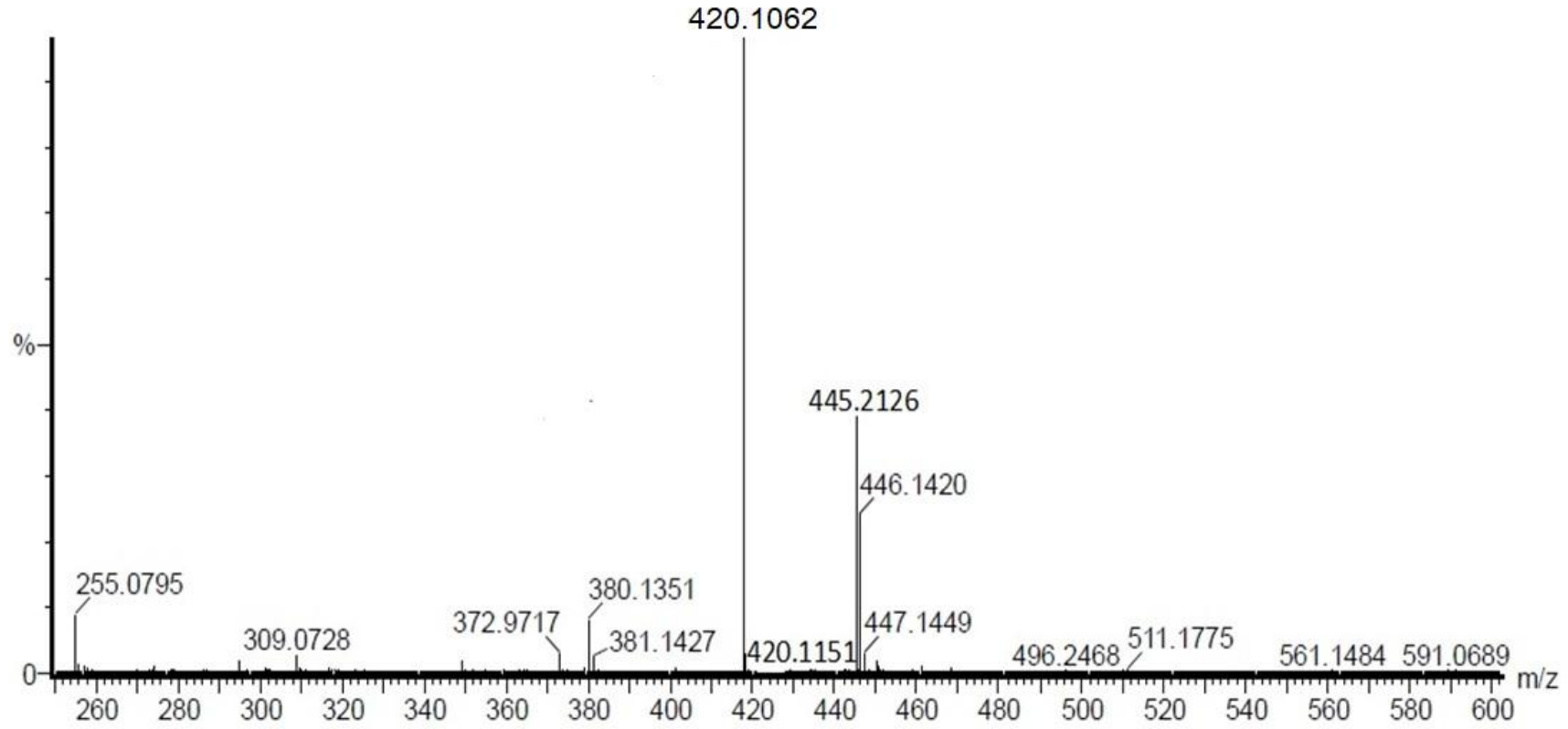
^{13}C NMR of Compound CD28



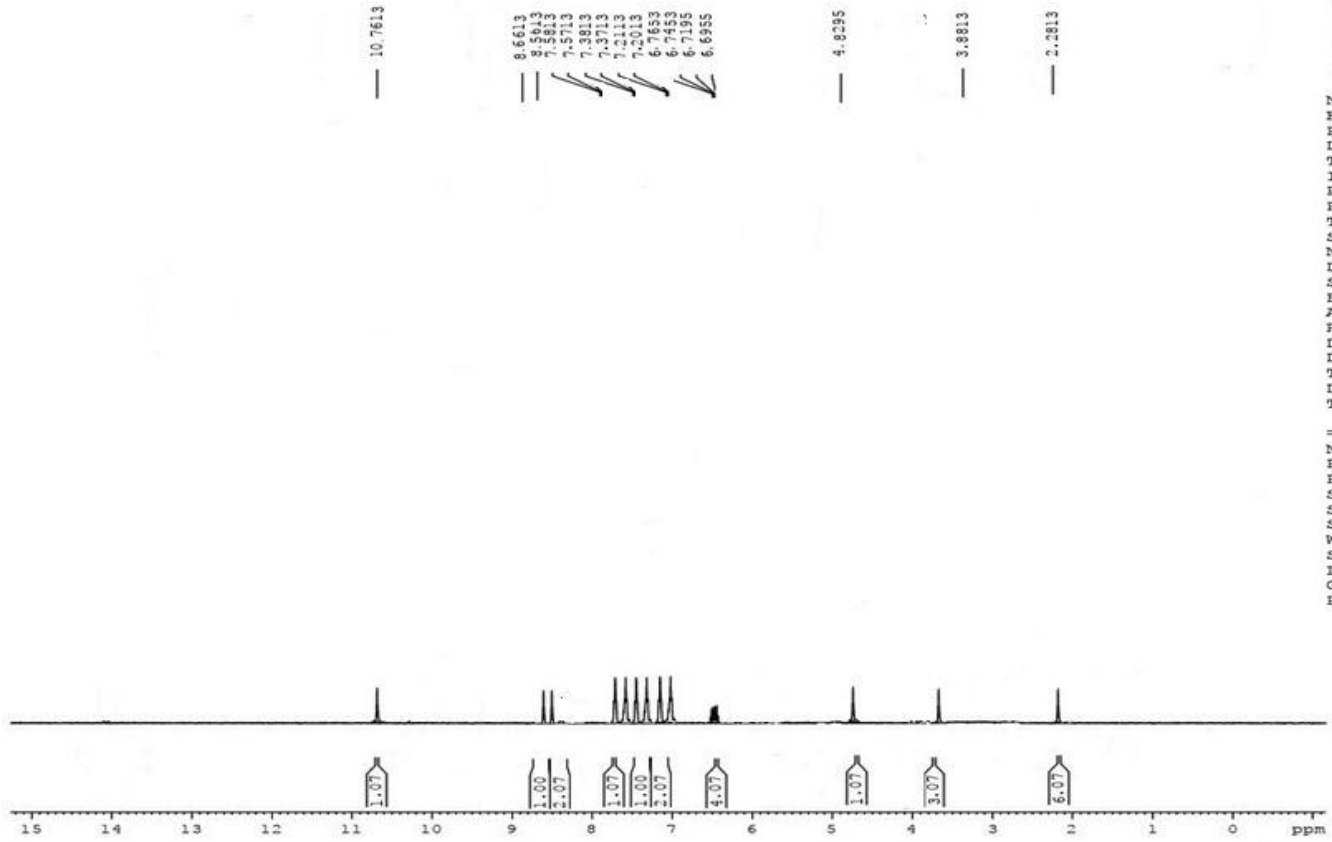

```
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh
NAME                Jun01-2018
EXPNO                      120
PROCNO                       1
Date_                 20180603
Time                      9.15
INSTRUM                  spect
PROBHD     5 mm SEI 1H/D-
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                         512
DS                           4
SWH                  29761.904 Hz
FIDRES               0.454131 Hz
AQ                   1.1010548 sec
RG                         256
DW                    16.800 usec
DE                     6.50 usec
TE                     673.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       13C
P1                    14.90 usec
PL1                    -3.00 dB
PL1W             60.64365387 W
SFO1            100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                 80.00 usec
PL2                    -3.00 dB
PL12                   18.94 dB
PL13                   22.00 dB
PL2W             15.78739738 W
PL12W             0.10099747 W
PL13W             0.04992414 W
SFO2            400.1316005 MHz
SI                       32768
SF              100.6127690 MHz
WDW                         EM
SSB                          0
LB                    1.00 Hz
GB                           0
PC                    1.40
```

manishkumarmanul986@gmail.com

HRMS of Compound CD28



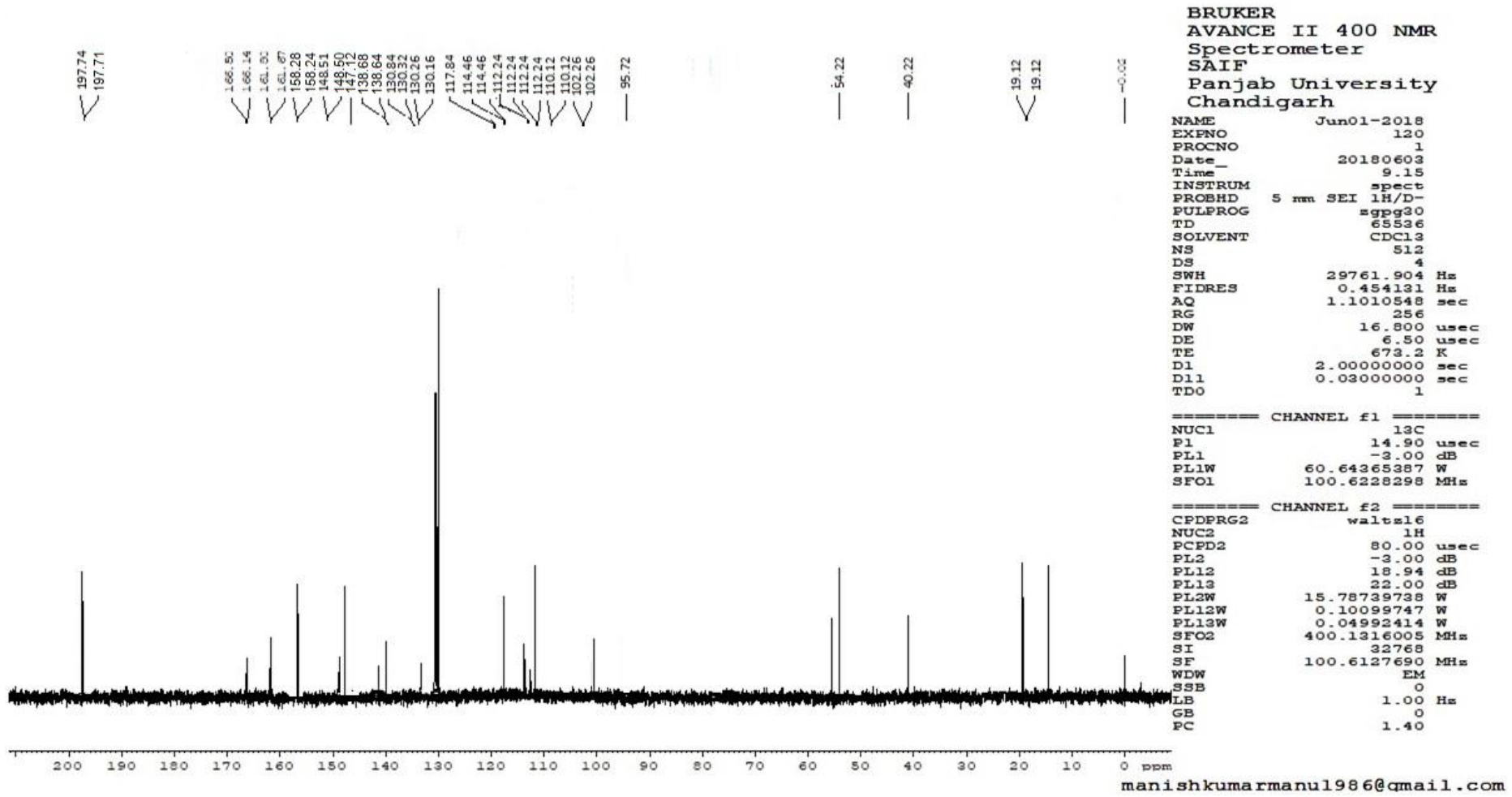
^{1}H NMR of Compound DP32



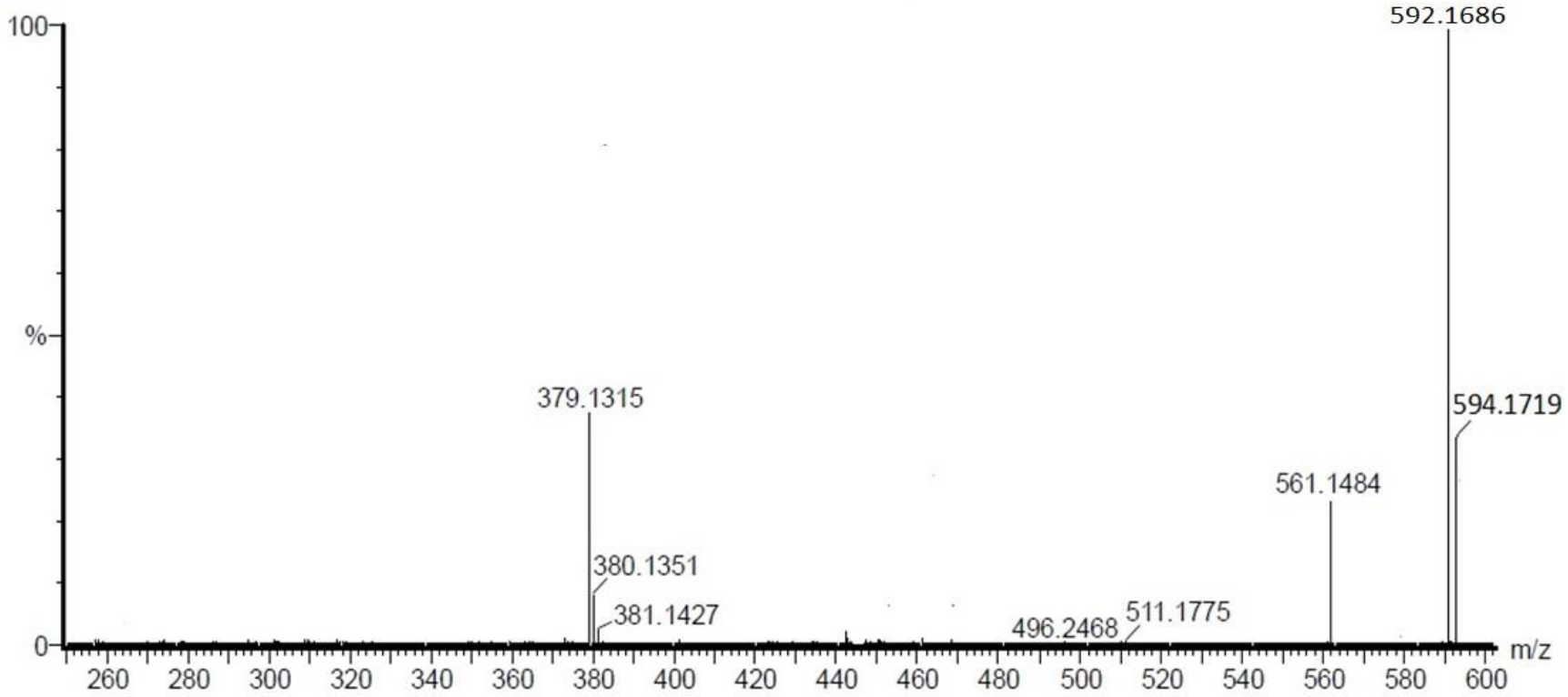

```
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

NAME                Nov09-2017
EXPNO                      230
PROCNO                       1
Date_                 20171110
Time                     11.00
INSTRUM                  spect
PROBHD    5 mm PABBO BB-
PULPROG                  zg30
TD                      65536
SOLVENT                  DMSO
NS                          8
DS                          2
SWH                 12019.230 Hz
FIDRES                0.183399 Hz
AQ                    2.7263477 sec
RG                        362
DW                     41.600 usec
DE                      6.00 usec
TE                     294.7 K
D1                  1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                      10.90 usec
PL1                     -3.00 dB
SFO1               400.1324710 MHz
SI                        32768
SF                 400.1299969 MHz
WDW                         EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                      1.00
```

manishkumarmanul986@gmail.com

^{13}C NMR of Compound DP32



HRMS of DP32


100
%
0
592.1686
594.1719
561.1484
379.1315
380.1351
381.1427
496.2468
511.1775
m/z
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600

List of Publications

Research Articles

- **Rohit Bhatia,** Raj Kumar Narang, Ravindra Kumar Rawal. *In silico* investigation of therapeutic potentials of coumarin-quinoxaline hybrids against breast cancer, synthesis and *in vitro* activity. ***Indian Journal of Heterocyclic Chemistry,*** 2020, 30(4), 489.
  Impact Factor: 0.339 **Indexing:** SCIE, SCOPUS.
- **Rohit Bhatia,** Raj Kumar Narang, Ravindra Kumar Rawal. Coumarin-dihydropyrimidinone hybrids: design, virtual screening, synthesis and cytotoxic activity against breast cancer. ***Journal of Advanced Scientific Research,*** 2020, 11(3), 220-233.
  Indexing: UGC Care List.

Review Articles

- **Rohit Bhatia**, Shelly Pathania, Virender Singh, R.K. Rawal. Metal catalyzed synthetic strategies toward coumarin derivatives. *Chemistry of Heterocyclic compounds*, 2018, 54 (3), 280-291.
  Indexing: SCIE, SCOPUS **Impact Factor:** 1.27
- **Rohit Bhatia,** R. K. Rawal. Coumarin Hybrids: Promising Scaffolds in the Treatment of Breast Cancer. *Mini Reviews in Medicinal Chemistry*, 2019, 19(17), 1443-1458.
  Indexing: SCIE, SCOPUS **Impact Factor:** 3.86

Indian Journal of Heterocyclic Chemistry
Vol. 30 - Number 04 (Oct-Dec 2020) 489-502
DocID: https://connectjournals.com/01951.2020.30.489

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

In silico Investigation of Therapeutic Potentials of Coumarin-Quinoxaline Hybrids against Breast Cancer, Synthesis and *In vitro* Activity

Rohit Bhatia[1,2], Raj K. Narang[2], Ravindra K. Rawal[3]*

[1]Department of Pharmaceutical Sciences and Technology, MRSPTU, Bathinda, Punjab, India
[2]Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Ferozepur G.T. Road, Moga, Punjab, India
[3]Department of Chemistry, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana, India

ABSTRACT To explore the aromatase and HER2 inhibitory activity and to develop newer drug candidates, we have designed a library of ninety compounds by hybridization of two heterocyclic scaffolds; coumarin and quinoxaline. The different derivatives were designed by making substitutions on both the moieties. The designed compounds were further subjected to molecular docking studies against aromatase (PDB Id: 3S7S) and HER2 (PDB Id: 3WSQ) using molecular operating environment 2019.0102 software. Seven compounds revealed best docking scores and their binding patterns in the pocket of aromatase were determined and compared with the standard drugs. Further, *in silico* drug likeliness properties and toxicity profile of best compounds were established using preADME, swissADME, and Protox softwares. The docking protocol was validated and the RMSD value was found to be 1.34. The best four compounds were further synthesized and evaluated for *in vitro* activity against breast cancer utilizing MCF7 and T47D cell lines. The compounds revealed moderate to good activity. The best four compounds were synthesized in the laboratory.

KEYWORDS Aromatase, Coumarin, Drug likeliness, Molecular operating environment, Quinoxaline.

How to cite this article: Bhatia, R., Narang, R.K., Rawal, R.K. *In silico* Investigation of Therapeutic Potentials of Coumarin-quinoxaline Hybrids against Breast Cancer, Synthesis and *In vitro* Activity, *Indian J. Heterocycl. Chem.*, **2020**, *30*, 489–502. *(DocID: https://connectjournals.com/01951.2020.30.489)*

INTRODUCTION

Breast cancer is one of the most frequent and insidious cancer in women.[1] It impacts about 2.1 million women per year and is one of the most lethal ailments in women. According to the WHO, about 627,000 women died globally in 2018 due to breast cancer which constituted 15% of all deaths due to cancer among women.[2] It has been estimated that about 66% postmenopausal women suffering from breast cancer are associated with estrogen dependent breast cancer. Estrogen binds to the estrogen receptors (present in mammary glands) and promotes the tumor growth in female breasts.[3] Estrogens cause enhancement of proliferation of breast epithelial cells and estrogen dependent mammary carcinoma cells and secrete various growth factors.[4] Aromatase is a cytochrome P450 enzyme complex which is present in large concentrations in ovaries of premenopausal women, in peripheral adipose tissues of postmenopausal women and in the placenta of pregnant women.[5] It has been also reported that aromatase activity is maximum in or near the tumor sites in breasts.[6,7] Aromatase enzyme acts on the androgens and produces the most potent endogenous estrogen estradiol.[8] A continuous research is in progress to develop newer drug candidates with promising activity against breast cancer. Many research groups have focused on inhibition of aromatase for drug design and development. A few aromatase inhibitors have been already available in market such as anastrozole, letrozole, exemestane, and testolactone.[9] Another enzyme

*Corresponding author: E-mail: rawal.ravindra@gmail.com

Bhatia et al., J Adv Sci Res, 2020; 11 (3) Suppl 7: 220-233 220

ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

COUMARIN-DIHYDROPYRIMIDINONE HYBRIDS: DESIGN, VIRTUAL SCREENING, SYNTHESIS AND CYTOTOXIC ACTIVITY AGAINST BREAST CANCER

Rohit Bhatia*[1, 2], Raj K. Narang[3], Ravindra K. Rawal[4]

[1]*Research Scholar, Department of Pharmaceutical Sciences & Technology, MRSPTU, Bathinda, Punjab, India*
[2]*Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Ferozepur G.T. Road, Moga, Punjab, India*
[3]*Department of Pharmaceutics, ISF College of Pharmacy, Ferozepur G.T. Road, Moga, Punjab, India*
[4]*Department of Chemistry, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana, India*
**Corresponding author: bhatiarohit5678@gmail.com*

ABSTRACT

Breast cancer is the most invasive form of cancer in women. It is characterized by over production of oestrogens which is mainly mediated by over-expression of aromatase. In the presented work we have designed a library of fifty coumarin-dihydropyrimidinone hybrids and screened them virtually for their aromatase inhibitory potentials through molecular docking tools. Docking was carried out against human aromatase (PDB Id: 3S7S) using exemestane as standard drug. Six compounds with best docking scores and interactions were selected and also analysed for *in silico* drug likeliness and toxicity. Further these six compounds were synthesized and characterized through spectrometric techniques. Further these were evaluated for cytotoxic potentials against breast cancer cell lines using MTT assay. Compounds **CD8** and **CD28** were found most potent among the all. The synthesized compounds must be explored further for discovery of a suitable therapeutic candidate against breast cancer.

Keywords: Breast cancer, Aromatase, Coumarin, Dihydropyrimidinone, Hybrids, MOE

1. INTRODUCTION

Despite of a great advancement in health and medical service sector, cancer is still a major life threatening disease around the globe [1-4]. Breast cancer is one of the most lethal forms of cancer in women and leading cause of death in post menopausal women. It has been reported that almost 66% of post menopausal breast cancer occurs due to over expression of oestrogen which leads to emergence of hormone-dependent tumors [5]. Oestrogen binds to its receptors present in mammary cells and is responsible for development of tumors in female breasts [6]. Aromatase belongs to cytochrome P450 enzyme class which is present in ovaries of premenopausal, adipose tissue of postmenopausal and placenta of pregnant women in higher concentrations [7]. It is evident that aromatase is highly expressed in tumor sites of breasts [8, 9]. Therefore aromatase has been identified as a significant target for development of therapeutic agents against breast cancer. There is a huge number of medicines/chemotherapeutic agents working through different targets/modes, already available in market against breast cancer and other cancers. Beyond this, there is still selectivity and normal cell toxicity issues are there which are limiting the use of existing therapeutic agents [10]. Many scientists, researchers, academicians and industries from all over the world are working continuously towards developing therapeutic candidates against cancer with least toxicity and high selectivity. Pathophysiology and progression of breast cancer involves a series of complex underlying events and many of the single targeted agents fail to achieve the therapeutic action. Therefore either high dose or a combination of multiple drugs is required to treat the ailment which generally leads to toxicity [11]. To combat this issue researchers and medicinal chemists have focussed their attention towards concept of molecular hybridization. This approach is based upon generation of new hybrid molecule by combining two or more scaffolds/sub unit of scaffold having different mode of actions [12] through suitable chemical approach. The hybrid molecule thus created possesses all the therapeutic potentials of individual moieties and is able to bind to more than one therapeutic target [13, 14]. Hence this is an ideal approach to design multi-target directed therapeutic agents against cancer.

Papers Presented in National/International Conferences

- Presented Paper on "Coumarin-dihydropyrimidinone hybrids: Design, virtual screening, synthesis and cytotoxic activity against Breast cancer" in International Conference "Chemistry Virtual 2020" conducted by Magnus Group, USA in 2020.
- Presented Paper on "Coumarin-quinoxaline hybrids against breast cancer: Structural insights through molecular docking tools" in National Conference "S & T Hathacon" conducted by GRD Institute of Technolgy and Management in May, 2020.
- **Received 1st Prize** for Verbal Presentation on "Design, Synthesis and Structural Insights of a New Series of Coumarin Hybrids as Anticancer Agents" in HPTU sponsored National Conference held at Himachal Institute of Pharmaceutical Sciences and Research, Nadoun, H.P. in February, 2020.
- **Received Best Project Award** for presentation on "Coumarin fused/tethered nitrogen containing heterocycles as anti-cancer agents" in Zonal Level **ANVESHAN-2018** program held at Manav Rachna Institute of Research and Studies, Faridabad in February, 2018.
- **Received Young Scientist Award for Paper presentation on "**Design strategies for newer coumarin fused/tethered nitrogen containing heterocycles as anticancer agents" in International Conference on Clinical Research Held at Baba Farid University of health Sciences, Faridkot, September, 2017.

CHEMISTRY VIRTUAL 2020

Rohit Bhatia[1],*, Raj K. Narang[2], Ravindra K. Rawal[3]
ISF College of Pharmacy, India

Coumarin-dihydropyrimidinone hybrids: design, virtual screening, synthesis and cytotoxic activity against breast cancer

Breast cancer is the most invasive form of cancer in women. It is characterized by over production of oestrogens which is mainly mediated by over-expression of aromatase. In the presented work we have designed a library of fifty coumarin-dihydropyrimidinone hybrids and screened them virtually for their aromatase inhibitory potentials through molecular docking tools. Docking was carried out against human aromatase (PDB Id: 3S7S) using exemestane as standard drug. Six compounds with best docking scores and interactions were selected and also analysed for in silico drug likeliness and toxicity. Further these six compounds were synthesized and characterized through spectrometric techniques. Further these were evaluated for cytotoxic potentials against breast cancer cell lines using MTT assay. Compounds CD8 and CD28 were found most potent among the all. The synthesized compounds must be explored further for discovery of a suitable therapeutic candidate against breast cancer.

Audience take Away:

- Audience will be able to know how to select drug design approaches.
- The presentation will be helpful to the audience to apply CADD tools in drug design by combining them with molecular hybridization approach to design multitarget directed therapeutic agents against cancer.

Biography:

Dr. Rohit Bhatia is currently working as Assistant Professor in Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga; India. He has pursued his PhD from MRSPTU, Bathinda; India. He has a total of 6 years of research experience. His area of expertise is computer aided drug design, medicinal chemistry and bio-analysis. He has more than 40 publications in reputed International and National Journals. He has won several awards in National and International awards.

GRD INSTITUTE OF MANAGEMENT & TECHNOLOGY

No.: STH2020 / 001

JAGANNATH UNIVERSITY NCR, HARYANA

CERTIFICATE OF PARTICIPATION

Is awarded to

ROHIT BHATIA

For participation in

S&T Hackthon-2020

"National e-Conference on Recent Advances in Science & Technology"

Organized by

GRD INSTITITE OF TECHNOLOGY AND MANAGEMENT, RAJPUR ROAD, DEHRADUN, UTTARAKHAND

&

UTTARANCHAL COLLEGE OF SCIENCE AND TECHNOLOGY, NAGAL HATNALA, DEHRADUN, UTTARAKHAND

In Collaboration With

DEPARTMENT OF BASIC SCIENCES, JAGANNATH UNIVERSITY, BAHADURGARH, HARYANA (INDIA)

on 18-05-2020 to 20-05-2020

Title of his/her Papers/Abstract is

"Coumarin-Quinoxaline Hybrids against Breat Cancer : Structural Insights through Molecular Modelling Tools"

(Dr. N.S.Rathee) Coordinator

(Dr. Preeti Handa Kakkar) Organizing Secretary

(Dr. Savita Goyal Aggarwal) Convener

INTERNATIONAL WEBINAR ON PHARMACY AND PHARMA NETWORKS

Pharmacy and Pharma Networks Leadership & Committee, USA

Certificate of Honour and Appreciation

This certificate is awarded to Prof./Dr./Mr./Mrs. Rohit Bhatia

of ISF College of Pharmacy, Moga has presented a paper

on In silico investigation of therapeutic potentials of coumarin-quinoxaline hybrids against breast cancer, synthesis and in vitro activity

In honour of your excellence as a **Speaker** for significant contribution to the success of International Webinar on Pharmacy and Pharma Networks, organized by **Helios Group Scientific Network** in association with Pharma Leadership and Committee, which was held on **September 21, 2020.**

Roger M. Leblanc, The University of Miami, USA.

Jonathan Sheng, American University of Health Sciences, USA

Remya Mohanraj, Houston Community College, Houston, Texas

Huang Wei Ling, MD, Medical acupuncture & pain management clinic, Brazil

MANAV RACHNA
Vidyanatariksha

Association of Indian Universities (AIU), New Delhi
&
Manav Rachna International Institute of Research & Studies
(Deemed to be University under section 3 of the UGC Act, 1956)
Faridabad - 121004, Haryana

ANVESHAN 2018

(NORTH ZONE)

STUDENTS RESEARCH CONVENTION

Certificate of Achievement

This is to certify that Mr./Ms./Dr. ROHIT BHATIA
Son/Daughter of Shri PIAR CHAND enrolled
in PHARMACY Department/Faculty of PHARMACEUTICAL CHEMISTRY
of NRSPTU, BATHINDA (ISFCP, MOGA) University/Institute
participated in North Zone Student Research Convention held at Manav Rachna International Institute of Research & Studies, Faridabad during February 26-27, 2018. His/Her proposal / project entitled COUMARIN FUSED ------AGENTS under the category of BASIC SCIENCES. and secured IInd position.

Dr. Pradeep K. Varshney
Director, MRIIC
Coordinator - Anveshan-2018 (North Zone)

Dr. M. K. Soni
PVC, MRIIRS and Exec. Director - MRIIC
Patron - Anveshan-2018 (North Zone)

Dr. N. C. Wadhwa
Vice - Chancellor, MRIIRS
Chief Patron - Anveshan-2018 (North Zone)

University Centre of Excellence in Resea
Baba [illegible] of Health Scienc

with all honors & privileges is pleased to confer

Young Scientist Award

Best Paper/ Best Poster (First/Second/Third)

upon

Prof. / Dr. / Mr. / Ms. Rohit Bhatia

in recognition of his paper / poster entitled

Coumarin Fused / Tethered Nitrogen containing Heterocycles as Anticancer Agents

"International Conference on Clinical Research -2017

on

Bridging gaps between industries, clinical research organizations, regulatory authorities for ground level problems in clinical trials of genetically modified products, vaccines, medicine and herbal drugs

September 8-9th , 2017.

8 credit hours have been awarded by The Punjab Medical Council
PMC/CME/2017/2968, Dated: 8/8/17

INCCR 2017

(Dr. Parveen Bansal)
Organizing Secretary

(Dr. Ram Charn Garg)
Nominee / Member
Punjab Medical Council