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Structure Based docking studies for the identification of small molecule targeting mTOR for the treatment of Breast cancer

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Breast cancer is the most common malignancy among women and accounts for second most common cause of the cancer related death [1]. This is majorlyreported as a heterogeneous disease with different subtypes defined by its hormone receptor such as estrogen (ER), progesterone (PR), human epidermal growth factor receptor-2(HER2) [2].Dysregulation in breast cancer most frequent associated with progression of PI3K/AKT/mTOR pathway. The routine activity of our body such as cell survival, cell division, cell proliferation,programmed cell death,protein synthesis, and integration of metabolismcontrols by this pathway [3]. The mammalian target of rapamycin is a conserved serine/threonine protein kinase, belongs to PI3K-kinase related family, which forms two distinct multi-protein complexes called mTORC1 and mTORC2 [4]. The mTOR signaling pathway integrates extracellular signals to intracellular and this signaling is activated in various cancer, directed by mutation in the gene-coding receptor tyrosine kinase, Ras, PI3K, and PTEN that is involved in numerous cellular processes [5]. The aberrant activation of mTOR signaling pathway identified in various malignancy including breast. Hyperactivation of mTOR commonly associated with cellular proliferation, and neogenesis [6]. In variety of cancer, phosphatase and tensin homologue deleted in chromosome 10(PTEN) is mutationally inactivated, leads to increase in overall mTOR activity. This hyperactivated mTOR gene produce mRNAs that encode various growth factors, cell death inhibitor, angiogenesis factors, inducer of cell growth which overall support carcinogenesis [7].Overall features of mTOR signaling pathway have provided a higher level of interest in targeting mTOR as a potential therapeutic agent for effective treatment. Present study aims to identify high affinity compound against mTOR for the treatment of breast cancer. Molecular docking studies was performed with 40 mTOR inhibitor using Schrodinger suite[8]. Out of 40 compounds, compound SF1126 found with the highest affinity with the targeted protein mTOR. This study was asserted with pharmacophore mapping discussed preferable interaction with mTOR. The compound determined in this study can be further used in vivo and in vitro studies to identify ADMET properties.

References

1. Cidado,J., & Park, B. H. (2012). Targeting the PI3K/Akt/mTOR pathway for breast cancer therapy. *Journal of mammary gland biology and neoplasia*, *17*(3-4), 205-216.

2. Chan, S., Scheulen, M. E., Johnston, S., Mross, K., Cardoso, F., Dittrich, C., Borner, M. (2005). Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. *Journal of Clinical Oncology*, *23*(23), 5314-5322.

3. Yardley, D. A. (2013). Combining mTOR inhibitors with chemotherapy and other targeted therapies in advanced breast cancer: rationale, clinical experience, and future directions. *Breast cancer: basic and clinical research*, *7*, 7.
4. Xie, J., Wang, X., & Proud, C. G. (2016). mTOR inhibitors in cancer therapy. F1000Research, 5.
5. Bhagwat, S. V., Gokhale, P. C., Crew, A. P., Cooke, A., Yao, Y., Mantis, C., ... & Epstein, D. M. (2011). Preclinical characterization of OSI-027, a potent and selective inhibitor of mTORC1 and mTORC2: distinct from rapamycin. *Molecular cancer therapeutics*, *10*(8), 1394-1406.
6. García-Echeverría, C. (2010). Allosteric and ATP-competitive kinase inhibitors of mTOR for cancer treatment. *Bioorganic & medicinal chemistry letters*, *20*(15), 4308-4312.

7. Dowling, R. J., Zakikhani, M., Fantus, I. G., Pollak, M., &Sonenberg, N. (2007). Metformin inhibits mammalian target of rapamycin–dependent translation initiation in breast cancer cells. *Cancer research*, *67*(22), 10804-10812.

8. Akare, U. R., Bandaru, S., Shaheen, U., Singh, P. K., Tiwari, G., Singare, P., ... & Banerjee, T. (2014). Molecular docking approaches in identification of High affinity inhibitors of Human SMO receptor. *Bioinformation*, *10*(12), 737.

9. Bandaru, S., Ponnala, D., Lakkaraju, C., Kumar, C., Bhukya, U. S., & Nayarisseri, A. (2014). Identification of high affinity non-peptidic small molecule inhibitors of MDM2-p53 interactions through structure-based virtual screening strategies. Asian Pac J Cancer Prev, 16, 3759-65.