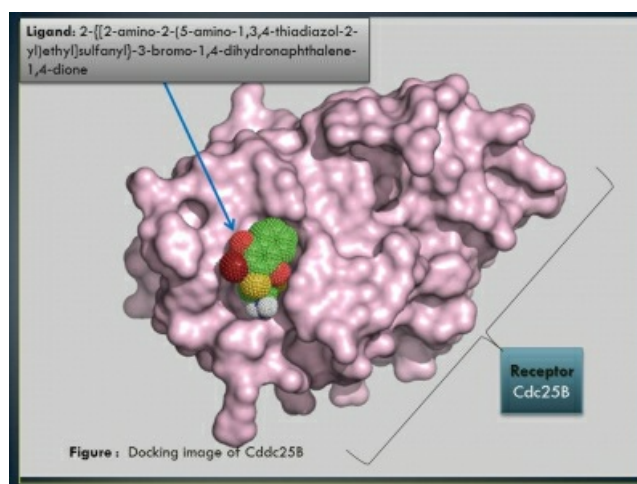


*Discovery of new inhibitors of Cdc25B by structure-based docking studies*Upendra Nayek¹, Dhanya Sunil², Abdul Ajees Abdul Salam¹¹Atomic And Molecular Physics, Manipal University, Manipal, India, ²Department of Chemistry, Manipal Institute of Technology, Manipal, India

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The cdc25 family of phosphatases plays a vital role in cell cycle regulation. The role of Cdc25B (one of the isoforms of Cdc25) in tumor cell growth is well recognized. All the active site of the Cdc25 proteins has the consensus Cys-X5-Arg motif. Based on the three-dimensional structural studies, the role of the cysteine and arginine residues in Cdc25B proteins are accurately established. Alteration of either the cysteine and arginine residues of the Cys-X5-Arg motif led to the loss of both reductase and phosphatase activities. R is a highly conserved arginine that hydrogen bonds to the phosphorylated amino acid of the substrate. Structural evidence suggests that the toxic metals like arsenic bind strongly to cysteine the carbonyl group of residue Cys477 in Cdc25B points toward the location where phosphate should bind. Recently Lund et al. [1] have identified two potential inhibitors for Cdc25B (PDB ID: 4WH7, and 4WH9). Interestingly these small molecules [2-fluoro-4-hydroxybenzoxazole and 2-[(2-cyano-3-fluoro-5-hydroxyphenyl) sulfanyl] ethanesulfonic acid] bound to a different pocket primarily comprised of Phe386, Leu398, Cys484, Arg488, and Met505 on Cdc25B located approximately 15 Angstrom away from the Cys-X5-Arg active site. This alternative active site is relatively more polar and connects well with water hydrogen bonding network. Currently, we have proposed a set of 34 novel compounds, which may be the potential inhibitors for Cdc25B. The molecular docking technique has been employed to identify the affinity of the molecules, and all the compounds were docked in all major active sites. The result suggest that 3-[(pyridin-4-yl)methyl]-3-azatricyclo[7.3.1.0^{5,13}] trideca-1(12),5,7,9(13),10-pentaene-2,4-dione&8-bromo-3-[(pyridin-4-yl)methyl]-3-azatricyclo[7.3.1.0^{5,13}] trideca-1(12),5,7,9(13),10-pentaene-2,4-dione) (-7.1 kcal/mol, -6.4 kcal/mol) has better affinity than the molecules identified by Lund et al. (-5.1kcal/mol) [1]. And these molecules also have better hydrogen bonding and hydrophobic interactions with several amino acids in the secondary active site. The proposed molecules docked at Cys-X5-Arg active site, revealed some interesting protein interactions. In summary, we identified some novel high-affinity inhibitor molecules to block the activity of Cdc25b phosphatases, which may provide an opportunity to target this important class of proteins.

[1] Lund G. et al.(2015).Acs Chem.Biol. 10: 390-394

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