Identification of potent leads for human cAMP dependent protein kinase catalytic subunit alpha:

A strategic application of virtual screening for cancer therapeutics

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Key points

- The advancement in therapeutic applications focused on specific macromolecules of deregulated cell signaling pathways bestowed novel approach to design the ligands as drug molecules against several life threatening diseases such as Cancer.
- Protein kinase A is one of the important protein in the cell signaling mechanism. cAMP, G-proteins and ATP molecules were required for activation of protein kinase A (PKA), upon activation, PKA catalytic subunits (PRKACA, PRKACB and PRKACG) undergoes many cellular functions like cell proliferations, cell cycle regulation, and survival of cells through acting on many substrates.
- Over expression of extracellular cAMP dependent protein kinase A catalytic subunits (PRKACA) causes severe tumorgenesis in different organs (prostate gland, breast, lungs and pancreas) leading to cancer.
- High throughput virtual screening was implemented herein to identify the potent leads for human PRKACA that stimulates chronic form of cancers.
- *In silico* functional and phylogenetic analysis of the PRKACA protein provided enough evidences towards its cancer stimulating nature.
- Fifteen published inhibitors were taken, ligand analogues were prepared. Lead identification, lead optimization was performed and finally best lead molecules were reported based on the docking scores.

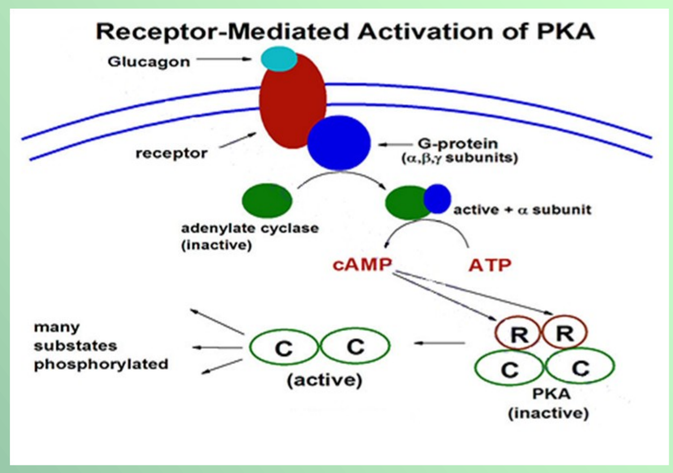


Figure 1. Activation of human PRKACA via G-protein and cAMP

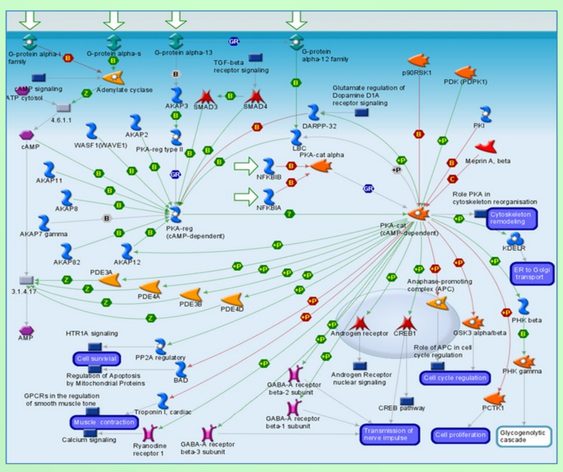
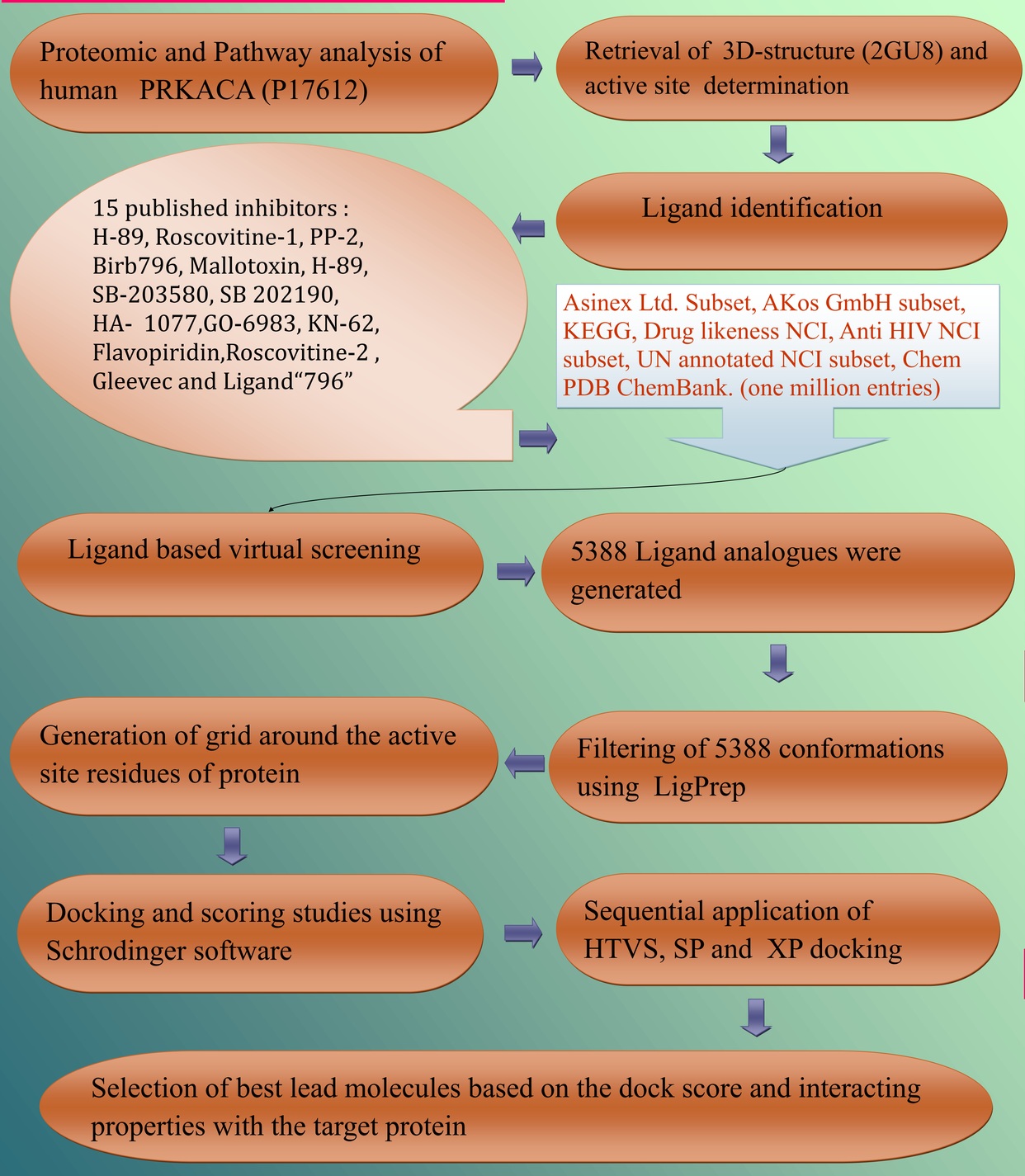


Figure 2: Human cAMP dependent PRKACA role in cell signaling mechanism

Materials and methods



Results and discussion

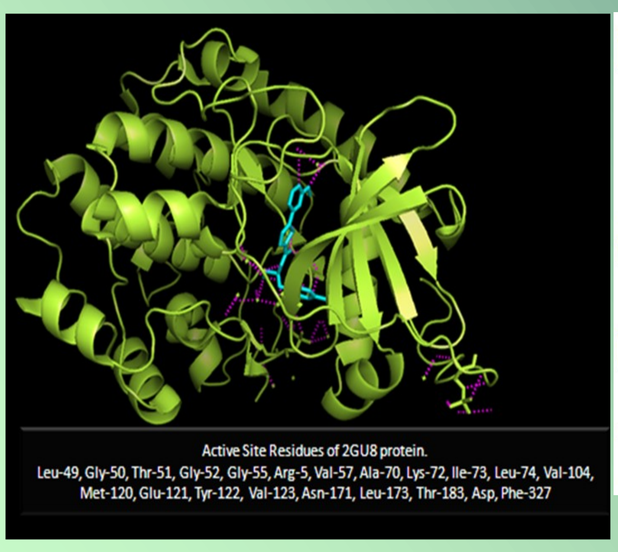


Figure3.Three- dimensional structure of 2GU8 protein

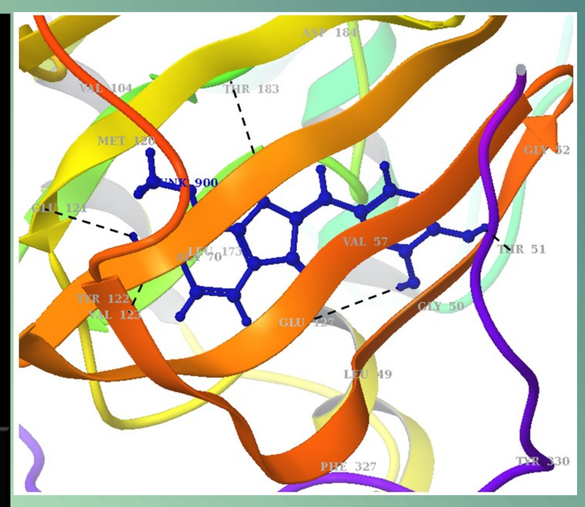


Figure4. Docking of lead‘**1**’ molecule with human PRKACA and hydrogen bonding network with the residues at Thr-51, Glu-121, Val-123, Glu-127 and Thr-183, blocking the functional activity of the protein.

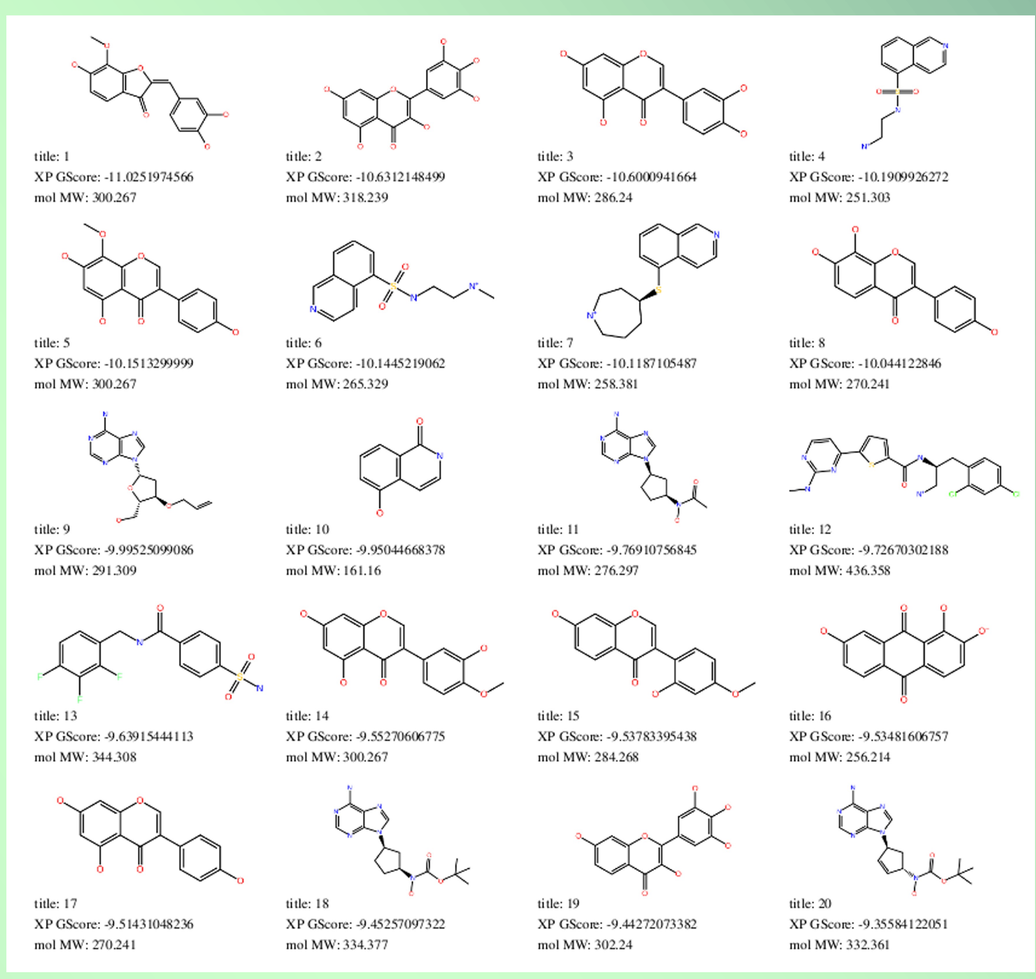


Figure 5. Predicted 20 best lead molecules based on the XP Gscore

- Proteomic analysis reveals that the functional properties of human cAMP dependent PRKACA.
- Pathway analysis reveals that the role of protein during signaling mechanism.
- Ligand based virtual screening was performed, and finally best 20 lead molecules were reported based on the XP Gscore.
- Lead ‘1’ (Leptosidin) with lowest docking score.-11.02 Kcal/mol was reported as a best lead molecule to inhibit functional activity of the protein.

Conclusion

- Signal transduction mechanisms were very important in the cell survival.
- Lead1 (Leptosidin) molecule forming five hydrogen bonds at Thr-51,Glu-121,Val-123,Glu-127 and Thr-183 which were reported earlier in co-crystallographic structure.
- The twenty lead molecules reported in the present study have good binding affinity towards human cAMP dependent PRKACA. However, Leptosidin with lowest XP Gscore and good binding orientation with the important active site residues is suggested as best lead for designing potential inhibitor.

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