COMPUTATIONAL DISCOVERY OF AURORA B KINASE ALLOSTERIC INHIBITORS

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The Aurora kinases are serine-threonine protein kinases crucial for the regulation of mitosis and cell cycle. Aurora-B is part of the chromosome passenger complex (CPC), together with the inner centromere protein (INCENP), borealin and survivin. INCENP forms a crown around the small lobe of Aurora B and their interaction is essential for activation and localization of the kinase. As aberrant levels of Aurora B are associated with tumorigenesis, these proteins have been explored as novel targets in cancer therapy. To date, there are no FDA-approved Aurora-B inhibitors, whereas most such bioactive compounds reported so far are ATP-competitive. Since the kinase ATP binding site is highly preserved, the INCENP–Aurora B interaction could be a promising target for selective inhibitor development.

This study aims to prioritize potential allosteric inhibitors of Aurora-B kinase through computational methodologies. Two allosteric sites important for Aurora-B-INCENP interaction, the ‘F pocket’, comprised by two sub-pockets, and the smaller ‘Y pocket’, have been described. A dataset of the reported Aurora-B inhibitors associated with the F pocket was used for the construction of a decoy set comprised of 28 active and 1850 inactive compounds (DUD-E), forming a validation tool. Development of a theoretical model was carried out, utilizing docking calculations of the decoy set against the crystallographic structure of human Aurora-B in complex with INCENP, druggability and hydration studies, as well as ROC curve analysis. Virtual screening of several chemical repositories, such as the NKUA in-house Pharmalab library (~2500 compounds, mainly natural products and semi-synthetic analogues), collections of fragments and NCI Repository subsets, as well as the bioactive compounds from LOPAC (1280 molecules) was performed. Promising drug-like compounds were selected in a consensus fashion by combining docking results (Glide software, Schrodinger Inc.) with 3D-similarity screening (ROCS, Openeye Software) based on CJ2-150, a known allosteric inhibitor with a hypothetically resolved binding mode, as a query. Furthermore, fragments with high predicted affinities and ligand efficiencies against the F pocket subsites were additionally identified. Subsequently, Molecular Dynamics and Free Energy Perturbation simulations were carried out, in an effort to further explore molecules which were top-ranked against their affinity for the F-pocket, toward validating their potential activities. High-throughput *in vitro* screening using thermal shift assays which is underway, will hopefully confirm the computationally identified hits and facilitate discovery of allosteric Aurora-B inhibitors as anti-cancer agents.