Aurora B Kinase Targeted Library

The serine/threonine protein kinases of Aurora family genes play a critical role in the regulation of key cell cycle processes. Aurora B mediates chromosome segregation by ensuring orientation of sister chromatids, and overexpression of Aurora B in diploid human cells NHDF (normal human diploid fibroblast) induces multinuclearity.

In human thyroid carcinomas, cell lines originating from different histotypes showed an increase in Aurora B expression. Immunohistochemical analysis of archive samples showed a high expression of Aurora B in anaplastic thyroid carcinomas; conversely, Aurora B expression was not detectable in normal thyroid tissue. Real-time PCR analysis confirmed a strong expression of Aurora B in anaplastic thyroid carcinomas.

The blocking of Aurora B expression induced by RNA interference or by using an inhibitor of Aurora kinase activity significantly reduced the growth of thyroid anaplastic carcinoma cells. Therefore, developing Aurora B kinase inhibitors may lead to discovery of potent anti-cancer drugs.

Crystal structure of Human Aurora B in complex with VX680 inhibitor (4AF3 PDB entry) [1] was used for *in silico* screening of Life Chemicals stock compounds filtered by Lipinski and Veber Rules. Molecular docking was performed and its results were analyzed using DOCK 4.0-6.0 program. Molecular dynamics (MD) simulations and preparation of protein structures were carried out with GROMACS software. Ligand molecules were processed with GAMESS and GROMACS. Validation of the docking model and procedures were performed; RMSD value of 1.2 Å between crystallographic binding conformation and docked pose of co-crystallized ligand proved a good prediction ability of the virtual screening. The features of key amino acid residues: Ala157, Lue207, Phe88, Leu83, Val91 (Fig. 1) were defined as docking constraints.

The total number of compounds in the Library is about **1,000**.

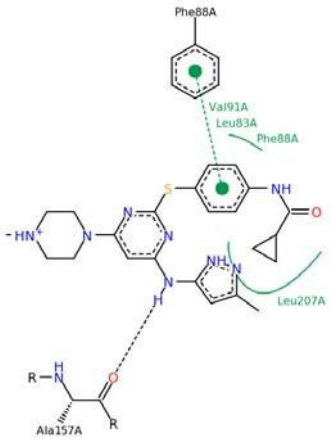

Fig. 1. Key amino acids responsible for the protein-ligand interaction.

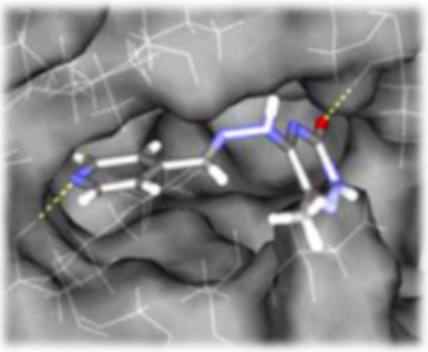

Fig. 2. The example of the docking binding mode of potential inhibitor from the Life Chemicals Library

References

1. Elkins J. M. et. al. Crystal structure of human aurora B in complex with INCENP and VX-680. **2012**, *J. Med. Chem.*, 55, pp. 7841–7848.