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Computer aided design of small molecule inhibitors of Receptor Tyrosine Kinases (RTKs)

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Introduction: The development of drug resistance is a leading cause of treatment failures in many cancers. MAPK is an important cell signaling pathway. Many cancer drugs are designed to induce MAPK inhibition (MAPKi). Although MAPKi reduces cancer growth and migration, it is usually accompanied by the establishment of bypass signaling mediated by certain Receptor Tyrosine Kinases (RTKs). As a result, most patients acquire a resistance to MAPKi within a year. The simultaneous inhibition of implicated RTKs and MAPK is needed to overcome drug resistance. Most kinase inhibitors bind to the kinase ATP-binding site. The high homology of these sites among different kinases makes them challenging to target specifically. The specificity is important, since drugs that indiscriminately inhibit several kinases may harm healthy cells. Unlike ATP-competitive inhibitors, an allosteric inhibitor can retain its inhibitory effectiveness at various ATP concentrations. Allosteric sites vary between various kinases and thus allow a highly specific binding with fewer side effects. Patients that develop MAPKi resistance show a significant accumulation of certain RTKs, such as AXL and MET. AXL and MET are involved in many cellular processes. Several inhibitors of these kinases have been found. However, they all bind to the kinases' catalytic sites and, thus, lack selectivity. This work focuses on computational design of small druglike molecules that could potentially allosterically bind AXL and MET and, thus, prevent the creation of signaling that would bypass MAPK inhibition.

Materials and Methods: The following software and servers were used to analyze AXL and MET and their putative inhibitors: Protein Data Bank (PDB), Deep View, ArgusLab, Molinspiration, and Osiris Data Warrior. Three-dimensional structures of AXL and MET were obtained from the PDB (5TC0 and 5MJA, respectively). The DeepView program was used to simultaneously analyze the active sites, atomic distances, H-bonds, and charge densities of the molecules. The Argus Lab program was employed to analyze the docking sites and perform docking calculations. Druglike properties of designed small molecules were evaluated using the Molinspiration and Osiris Data Warrior programs. ATP-competitive inhibitors of AXL and MET were uploaded in ArgusLab and docked to the kinases. Fig. 1 a) and b) show the ATP pockets of AXL and MET, respectively, bound to their known ATP-competitive inhibitors. The figures show the AXL and MET residues within 6.0 Å from their respective inhibitors.The known inhibitors of AXL and MET were used as starting templates to computationally design new molecules that could potentially bind both AXL and MET. Atomic substitutions were done in the original inhibitors to achieve improved druglikeness of the newly designed molecules. Molecules that showed optimal druglike properties were chosen for further docking studies. The designed molecules were reconstructed and optimized in ArgusLab by using the Semiempirical Geometry Optimization. The Argus Dock function was used to dock the molecules in AXL and MET. The AScore function and a 0.4 Å grid resolution were used for the docking calculations. ArgusLab evaluated binding affinities of the designed molecules to the AXL and MET kinases.

Results and Discussion: One of the designed molecules was found to have optimal druglike properties and no indicated toxicities. The molecule formed stable complexes with AXL and MET, binding each allosterically. Fig. 2 shows the molecule docked to an allosteric site of AXL. The binding changed the configuration of the catalytic site and so prevented the binding of the ATP molecule in the site. The ATP molecule bonded in a new location. Fig. 3 shows the molecule docked allosterically in MET. The ATP molecule again bonded outside the catalytic site.

Conclusions: This work addresses computational design of putative allosteric inhibitors of the AXL and MET kinases. A designed molecule with promising druglike properties bonded to allosteric sites of the kinases. The binding caused conformational changes in the catalytic sites, which prevented the ATP molecule from binding there. The development of small molecule inhibitors that could simultaneously allosterically bind AXL and MET shows a promise for preventing the bypass signaling mediated by AXL or MET.

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