Rational Design Approaches to Modeling Inhibitors of Kinesin Spindle Protein

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Kinesin spindle protein (KSP) is a motor protein that utilizes the energy from ATP hydrolysis to transport cellular cargo along microtubules and is essential for bipolar spindle formation during mitosis. Inhibition of KSP activates the spindle checkpoint and causes apoptosis, and thus KSP is considered an attractive cancer target for drug discovery. Although cancer drugs (*e.g.* taxol, taxotere) that inhibit mitosis by interfering with microtubule function are on the market, these often have side effects such as neuropathies. Targeting KSP offers a more specific mechanism of inhibition with potentially fewer off-target effects. GlaxoSmithKline (GSK) and Cytokinetics (CK) undertook a joint effort to find inhibitors for KSP just as I joined GSK, and I was the computational chemist for the program. For an ATP uncompetitive class of inhibitor, key insights from molecular visualization lead to successful predictions of inhibitor potency. Modeling was undertaken for a second ATP competitive inhibitor class towards determining the ligand binding site. A combination of docking, homology modeling, molecular dynamics, and photo affinity labeling lead to a model that rationalized SAR for this inhibitor. My learning's as a new computational chemist in the pharmaceutical industry will be shared.