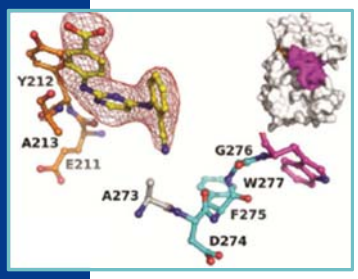
Novel Small Molecule Aurora A Kinase Inhibitor as a Cancer Therapeutic



A potent, selective, and water-soluble small molecule inhibitor of Aurora A kinase activity. Aurora kinase is overexpressed in at least half of patient tumor samples from a variety of cancers including those of the breast, prostate, lung, and colon. Our lead compound has an opportunity to be a first in class Aurora A kinase inhibitor with a novel mode of action for targeting Aurora kinases. In early preclinical studies, the lead compound displayed inhibition of Aurora A kinase activity in a human breast cancer cell line with efficacy similar to that of alisertib, which is an Aurora A kinase inhibitor currently in Phase III clinical trials.

COMMERCIAL OPPORTUNITY

- The Aurora A kinase oncogene is overexpressed in several cancers including breast (94%), colon (>50%), pancreatic (93%), ovarian (83%), prostate (98%), lung (69%), and gastric (>50%). Moreover, four of these are the most prevalent cancers in the US (lung, prostate, breast, and colon).
- Interest in this target is substantial as evidenced by numerous companies that have Aurora kinase inhibitors in development, including AstraZeneca, Amgen, Merck KGaA, EMD Serono, Nerviano, EntreMed, Inc., Takeda Millennium Pharmaceuticals, Boehringer-Ingelheim, Johnson & Johnson, Pfizer, Astex Pharmaceuticals, Sunesis, Glaxo Smith Kline, and Novartis.
- Two of the five Aurora kinase inhibitors currently in Phase II or III clinical trials are Aurora A kinase inhibitors, showing that Aurora A kinase inhibitors can successfully complete Phase I trials.
- Our lead compound targets the Aurora A kinase by the same mechanism that imatinib (Novartis) targets the Abl kinase—by binding to the inactive kinase and locking it in that state. This mechanism of action is what drives the potency and specificity of imatinib against Abl. Imatinib is FDA approved for 10 oncology indications and earned $4.6B in revenue in 2011.

TECHNOLOGY

Our Aurora A kinase inhibitor has a novel mode of action, which involves locking the aspartate-phenylalanine-glycine (DFG) residues of the ATP-binding pocket on Aurora kinase into an inactive conformation (DFG-out). By locking the Aurora kinase in this conformation, the active site becomes incompatible with substrate and ATP binding, resulting in enhanced potency and target selectivity. Our Aurora A kinase inhibitor is the only known DFG-out inhibitor of Aurora kinases. The lead compound is water-soluble and inhibits Aurora A kinase activity *in vitro* with an IC_{50} of 5.7nM with ~3-fold selectivity preference over Aurora B kinase (IC_{50}=15.6nM). It also inhibits Aurora A kinase activity in MDA-MB-468 human breast cancer cells with submicromolar potency to a similar extent as alisertib, which was used as a positive control.

PUBLICATION/PATENT

- *J. Med. Chem.* (2012), 55(17):7392−416; *ACS Chem. Biol.* (2012), 7(4):698-706
- PCT application filed March 30, 2012 for Drs. Schonbrunn, N. Lawrence, H. Lawrence, Sebti, & Martin

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