



Technology Opportunity, Ref. No. UZ-09/532

Novel nanomolar inhibitor of Eph tyrosine kinases

New small molecule inhibitors of Eph kinases have been developed which have potential therapeutic application in angiogenesis dependent cancers. The selectivity of the compound is comparable to that of marketed kinase inhibitors (e.g. Gleevec). The other kinases that are inhibited by the compound (Abl, Src, Lck) are also known to be relevant in a variety of human cancers.

Keywords Angiogenesis dependent cancers, Intraocular neovascular syndromes, Kinase inhibitor, Nanomolar

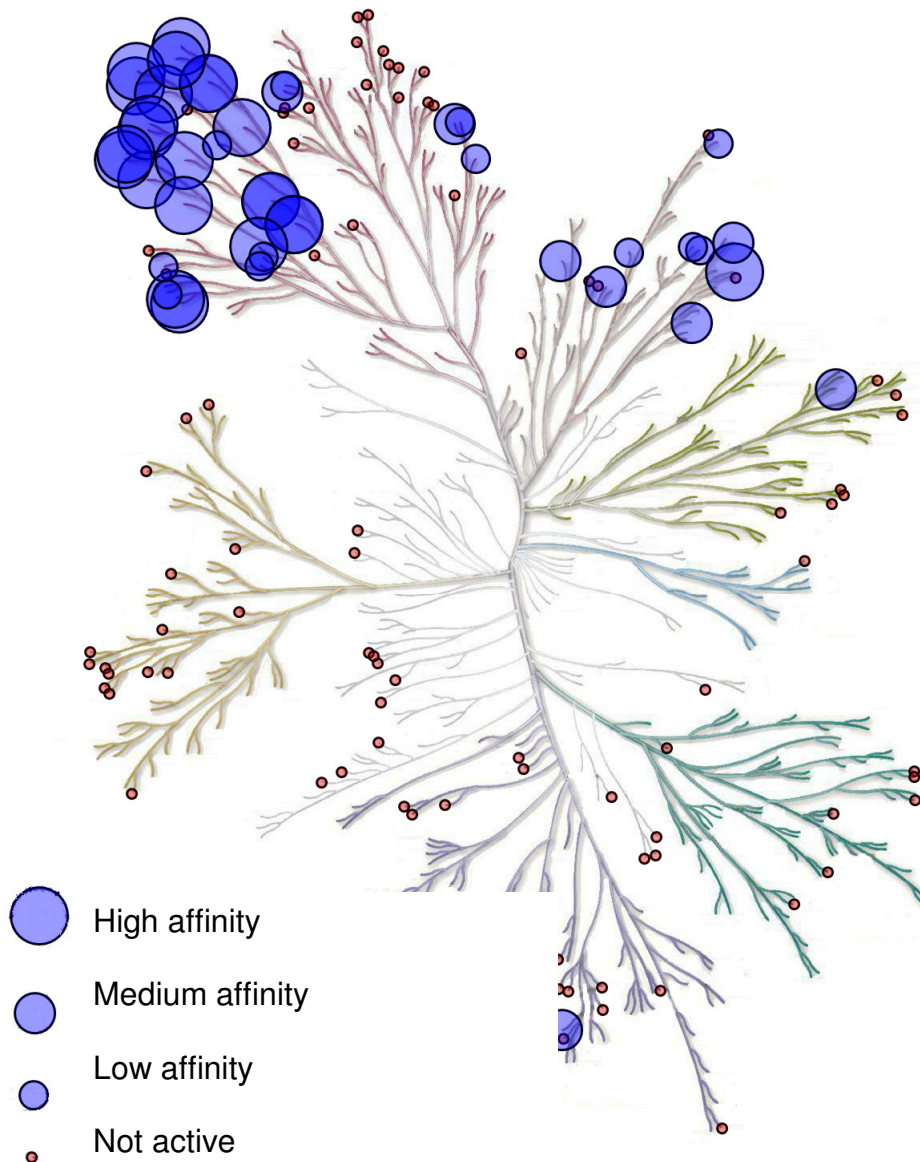
Inventors Prof. Caflisch, Institute of Biochemistry, and Prof. Nevado, Institute of Organic Chemistry, University of Zurich

Background Angiogenesis has been identified as one of the key steps in human carcinogenesis. Because of low toxicity and resistance potential, as well as the possibility to treat a large spectrum of solid tumor types, angiogenesis inhibition is considered a promising target in anticancer therapies. Several studies show involvement of Eph signaling in sprouting angiogenesis and blood vessel remodelling during vascular development. Furthermore, overexpression of several of the 14 Eph receptors has been linked to tumors and the associated vasculature, suggesting a critical role in tumor-related angiogenesis. Inhibition of binding of EphB4 to its natural ligand EphrinB2 using soluble extracellular domains of EphB4 has indeed been shown to reduce tumor growth in murine tumor xenograft models. Thus, inhibition of Eph angiogenic activity has been recognized as an effective strategy for blocking tumor progression and metastasis.

Invention A new class of small molecule inhibitors of Eph kinases has been developed. Fragment-based high-throughput docking followed by structure-guided improvement resulted in the discovery of compounds with single-digit ($IC_{50}=5nM$) inhibition of Eph kinases in biochemical assays. The selectivity of the compounds (see next page) and the inhibition concentration in cell-based assays (CHO cells overexpressing the targets) are comparable to that of marketed kinase inhibitors (e.g. Gleevec). Besides Eph kinases, the compounds inhibit an attractive combination of targets: SRC and Lck are overexpressed in a variety of human cancers. The Abl family kinases plays a crucial role in different human leukemias.

Patent Status Patent filed

Contact *Unitecra, Technology Transfer of University Zurich, Wolfgang Henggeler, Möhrlistrasse 23, CH-8006 Zürich, +41 1 634 44 01, henggeler@unitecra.ch*



Selectivity profile of compound **66** ($IC_{50}=5nM$). The circles correspond to all kinases tested: inhibition of activity was measured in enzymatic assays with radiolabeled ATP at Reaction Biology Corporation and University of Dundee for 11 and 85 kinases, respectively, while binding affinity of 50 kinases was measured at Ambit Biosciences Corporation. Enzymatic assays: high, medium, low, and no compound affinity for kinase activity (with respect to DMSO control) of <10%, 10%-30%, 30%-60%, and >60%, respectively. Binding assay: high, medium, low, and no compound affinity for kinase activity (with respect to DMSO control) of <1%, 1%-10%, 10%-30%, and >30%, respectively. The dendrogram is adapted from a previously reported picture (Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. The protein kinase complement of the human genome. *Science* 2002, 298, 1912-1934)