Discovery of potent, selective and efficacious p38 MAPK inhibitor as clinical drug candidate

PH-797804 is a diarylpyridinone inhibitor of p38α mitogen-activated protein (MAP) kinase derived from a racemic mixture as the more potent atropisomer (αS). Based on structural analysis of dozens of high resolution crystal structures of p38α inhibitor complexes, PH-797804 is predicted to possess high level of specificity across the broad human kinase genome. We used a structural bioinformatics approach to identify two selectivity elements encoded by the TXXXG sequence motif on p38α kinase hinge. Kinome-wide sequence mining revealed rare presentation of the selectivity motif. Corroboratively, PH-797804 exhibited exceptionally high specificity against MAP kinases and the related kinases. No cross-reactivity was observed in large panels of kinase screens (selectivity ratio >500 fold). In cellular assays PH-797804 demonstrated superior potency and selectivity consistent with the biochemical measurements. Efficacy was achieved in animal models and certain human disease population. The compound is well-tolerated in phase I clinical trials, and is under phase II development for the treatment of several inflammatory diseases.

Biography

Dr. Xing is a senior principal scientist at Pfizer worldwide research and development. Upon fifteen years of pharmaceutical research experience she specializes in computer-aided drug design, medicinal chemistry, and PK-PD optimization. She has in-depth knowledge in multiple diseases areas including oncology, autoimmune diseases and cardiovascular disorders. In the past eleven years at Pfizer Dr. Xing made major contributions to the discovery of multiple clinical candidates targeting biological interventions as cures of inflammatory diseases. She has published more than forty scientific journal articles and patents, and has been an invited speaker in numerous drug discovery and scientific conferences. Dr. Xing received her Ph.D in Polymer Science from University of Akron, and double Bachelor degrees with a major in solid state physics and a minor in electrical and computer engineering from Tsinghua University.

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