Sorafenib – A novel Inhibitor of Signal Transduction

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The discovery of Nexavar® (sorafenib tosylate) is the result of a collaboration between Bayer HealthCare and Onyx Pharmaceuticals. Sorafenib belongs to a novel class of kinase inhibitor exhibiting a dual mode of action. This compound inhibits Raf kinase, a key mediator of the MAP kinase pathway, thereby blocking tumor cell proliferation. In addition, sorafenib inhibits a series of receptor tyrosine kinases involved in angiogenesis and stromal activation, notably VEGFR and PDGFR. Therefore, the kinase profile of sorafenib results in inhibition of both tumor growth and tumor angiogenesis in xenograft models.

The medicinal chemistry program started from a lead structure identified via high-throughput screening. The confirmed hit, a thienyl-phenyl-urea (IC\(_{50}\) = 17 \(\mu\)M), was optimized using classical medicinal chemistry as well as combinatorial chemistry techniques.

Nexavar® was first approved in the US in late 2005 for the treatment of advanced renal cell carcinoma. In addition Nexavar® is the only approved drug for the treatment of advanced Liver Cancer. Additional Phase II and III clinical trials are currently ongoing, evaluating its potential in other cancer indications, either as a single agent or in combination therapeutics.