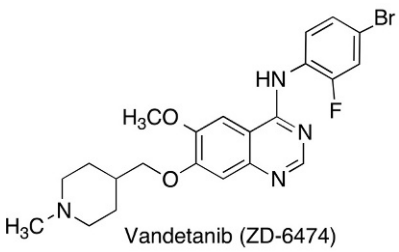
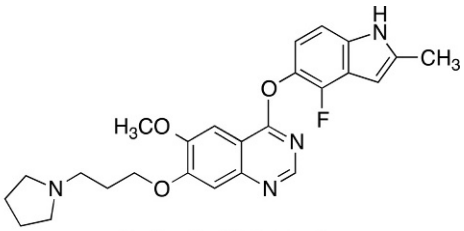
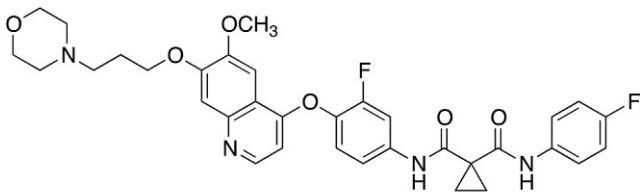


Vandetanib (ZD-6474)

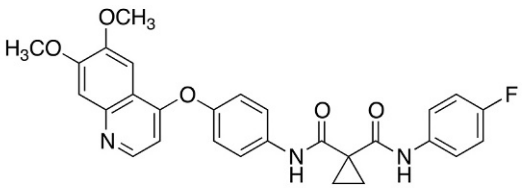


Cediranib (AZD-2171)

Because VEGF and HGF–c-Met signaling are activated in angiogenesis, the combined inhibition of both signaling has a major effect on the induction of endothelial cell apoptosis and reduction in the formation of capillaries as well as on the decreased microvessel density within tumors. Among a family of quinoline derivatives, foretinib (EXEL-2880, GSK-1363089, XL-880) inhibits several receptors, mainly VEGFR-2 and the hepatocyte growth factor receptor (HGFR, c-Met). Foretinib has entered phase II clinical trials in patients with estrogen, progesterone, and HER-2 receptor negative recurrent/metastatic breast cancer,[67] metastatic gastric cancer, and squamous cell cancer of the head and neck.[68] Its analog, cabozantinib (Cometriq®, XL184), is also a potent inhibitor of both c-Met and VEGFR-2 that showed promising signs of antitumor activity at doses not associated with toxicity in its early clinical experience. It was approved by the FDA in 2012 for the treatment of medullary thyroid cancers and is also in clinical trials for other malignancies, in which it has shown encouraging activity in castration-resistant prostatic cancers.



Foretinib (GSK-1363089, XL-880)



Cabozantinib (XL184)

Tivozanib (AV-951), which bears a high degree of structural similarity with foretinib and cabozantinib but has a urea group instead of a malonamide, is an orally active inhibitor that was designed to target all three VEGF receptors, and it also has shown high potency against c-Kit and PDGFR. This compound displayed promising activity in renal carcinomas, reaching phase III clinical studies, but it showed inferior overall survival rates in comparison with sorafenib. The closely related lenvatinib (E-7080, Lenvima®) is another quinoline/*N*-phenylurea hybrid that inhibits both VEGFR-2 and VEGFR-3. This compound was approved in 2012-2013 by several agencies as an orphan drug for several types of thyroid cancer not sensitive to radioiodine. In early 2015, it finally received FDA approval for radioactive iodine-refractary differentiated thyroid cancer. Linifanib (ABT-869), another urea derivative, is a multitargeted receptor tyrosine kinase inhibitor