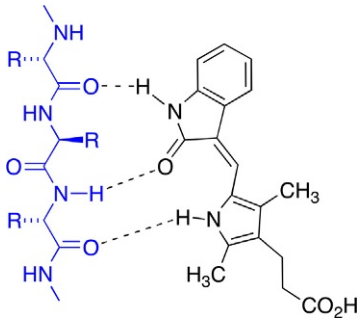
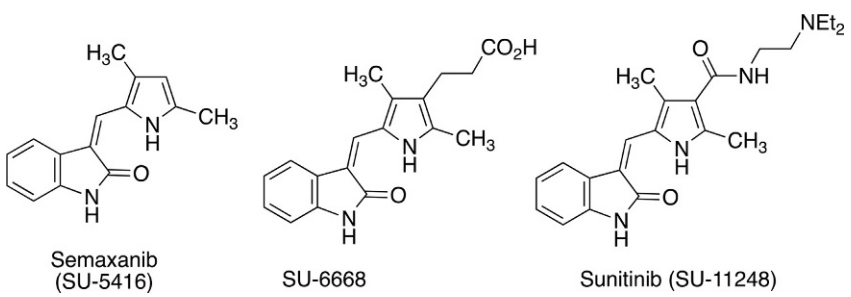


FIGURE 10.12

Binding of the indolinone sunitinib (SU-6668) to VEGFR-1.

propionic acid chain at the C-4′ position of semaxanib, was also a disappointment in clinical trials, but the (diethylaminoethyl)carbamoyl derivative sunitinib (SU-11248, Sutent®)[55] was approved by the FDA in 2006 and 2011 for gastrointestinal and renal cancer and for neuroendocrine pancreatic tumors, respectively. X-ray crystallographic studies of these pyrrole-derived indolinones co-crystallized with VEGFR-1 showed that these inhibitors occupy the same region as ATP and establish several hydrogen bond interactions in a side chain of the receptor as shown for SU-6668 (Figure 10.12).

Sunitinib inhibits multiple receptor kinases, including VEGFRs, PDGFRs, and c-Kit (CD117).[56] Because the latter kinase, when improperly activated by mutation, drives the majority of gastrointestinal stromal cell tumors,[57] sunitinib has been recommended as a second-line therapy for patients who become intolerant to imatinib.[58]



Vatalanib (PTK-787, ZK-222584) is an orally available aminophthalazine derivative that was identified through a screen of a chemical library against VEGFR-1.[59] It potently inhibits several VEGFR kinases, and also the tyrosine kinase activity of c-Kit and PDGFR, and has shown promising results in patients with metastatic colorectal cancer.[60] It is active in patients diagnosed with imatinib- or sunitinib-resistant gastrointestinal stromal tumors,[61] and it has been used as a starting point for the development of second-generation VEGFR inhibitors. Based on its binding mode to the receptors, an anthranilamide scaffold was selected for optimization, leading to the identification of AAL-993 as a potent and selective VEGFR-2 inhibitor. Motesanib (AMG-706) is a related inhibitor of VEGFR and PDGFR that has undergone clinical testing for non-squamous non-small cell lung carcinoma and breast cancer.[62]