Finally the third group of inducers includes tumor necrosis factor alpha and transforming growth factor beta that act indirectly, by promoting the release of the direct acting factors. Inhibitors of some of these processes have been developed and have entered clinical trial (Gao *et al.,* 2007).

1.6.5.3 VEGF Inhibitors

VEGF is the most important pro-angiogenic factor in the angiogenesis process. Four isoforms of VEGF exist, that bind to three receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3 (Flt-4) that are found on the surface of endothelial cells (Meyer and Penn 2008, Maeda *et al.,* 2000). Receptor binding triggers kinase activation through tyrosine phosphorylation and begins the signaling cascade that initiates angiogenesis.

The VEGF system can also be targeted through inhibition of VEGFR, by the use of monoclonal antibodies or specific tyrosine kinase inhibitors (Di Tomaso *et al.,* 2009).

The majority of the mitogenic, angiogenic, and permeability-enhancing properties of VEGF are mediated by VEGF receptor-2 (VEGFR2) (Jain *et al.,* 2007). Several inhibitors of this pathway have received FDA approval and are currently in clinical use; these include **bevacizumab** (**BV; Avastin; Genentech**), a monoclonal antibody that blocks human VEGF (Ferrara *et al.,* 2004, Dvorak 2002), and small-molecule inhibitors of the VEGFR2 tyrosine kinase (e.g., **sorafenib and sunitinib**) structures are drawn in (figure 6 and 9) (Chung *et al.,* 2010).

Recent studies suggest that blockade of the VEGFR2 signaling pathway may prompt some tumors to increase their expression of secondary molecules in order to sustain the neovascularization response. That although anti-VEGFR therapy initially blocks new blood vessel formation and tumor growth in a transgenic model of pancreatic islet cell tumors, both angiogenesis and tumor progression are eventually restored by