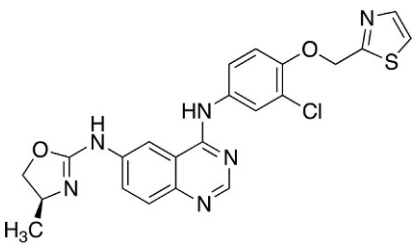
4.3 INHIBITORS OF HER-3

Recently, the use of more sensitive methods to analyze protein interactions has uncovered the relevance of the cell surface receptor HER-3, which can be up to 10 times more effective than HER-2 in recruiting accessory proteins that drive the rapid proliferation, enhanced survival, and distant spread of cancers.[41] HER-3 lacks a fully functional tyrosine kinase domain, but upon ligand binding, it heterodimerizes with other receptors of the EGFR family, forming a functional oncogenic signaling unit in many HER-2-driven breast cancers. Compared to the other EGFRs, HER-3 has a number of direct binding sites for the p85 subunit of phosphoinositide-3-kinase (PI3K), which enables more efficient signaling via the PI3K–AKT pathway. Overactivation of HER-3 accounts for some of the resistance to EGFR and HER-2 inhibitory agents via either increased receptor phosphorylation and cell surface localization or overexpression of the receptor or upregulation of the ligands. Therefore, the HER-3 receptor is an interesting target for new antitumor therapeutics, and currently several antibodies, including MM-121, U3-1287, and LJM716,[42] are in clinical trials. Affibody molecules, which are small three-helix proteins originally derived from one of the subunits of staphylococcal protein A, are promising candidates for future HER-3-targeted cancer therapy.[43]

4.4 PAN-HER INHIBITORS

Varlitinib (ARRY-543, ASLAN 001) is another anilinoquinazoline that acts as a HER inhibitor, in this case without selectivity. It has shown clinical activity in both HER2-positive and EGFR-positive tumors and is currently in clinical studies for gastric cancer, both alone and in combination.



Varlitinib (ARRY-543, ASLAN 001)

4.5 INHIBITORS OF INSULIN-LIKE GROWTH FACTOR RECEPTORS (IGF-1R)

The insulin-like growth factors (IGFs) are peptides with a high sequence homology with insulin which are part of a complex system (often referred to as the IGF "axis") that has a role in the promotion of cell proliferation and in the inhibition of apoptosis. Insulin-like growth factor-1 receptor (IGF-1R) is a membrane tyrosine kinase receptor with a 70% homology to the insulin receptor that, when activated by its ligands IGF-1, IGF-2, or insulin at supraphysiological concentrations, transmits a signal to its two major substrates, insulin receptor substrate-1 (IRS-1) and Shc, and the signal is subsequently transduced to the nucleus. Reduction of tumor invasion upon blockade of IGF-1R by several inhibitors indicated the critical function of this signaling for the acquisition of a malignant phenotype[44] and in chemotherapy resistance, but it has proven to be a tough target. It has been shown