cancer, MM, and CML, suggest that Hh signaling regulates cancer stem cells. This pathway activates the 7-pass transmembrane protein Smoothended (Smo), a G protein-coupled receptor whose activation results in the nuclear translocation of the Hh transcription factors Gli1 and Gli2, which initiate transcription of Hh-responsive genes. It is inactive in the absence of ligands because Smo is inhibited by the 12-pass transmembrane spanning receptor Patched 1 (Ptch 1). Its activation occurs when Ptch is bound by one of the Hh family of ligands, such as Sonic Hh (Shh).

Among Hh antagonists, the most developed are those targeting Smo. The discovery of cyclopamine, a highly teratogenic natural product, and the subsequent assignment of its activity to the Hh pathway, paved the way for the rapid development of synthetic inhibitors with druglike properties and improved bioactivity.

The semisynthetic derivative saridegib (IPI-926), which showed greater chemical stability, solubility, potency, selectivity, and bioavailability compared to cyclopamine,[135] entered clinical trials, but its development was interrupted. In order to identify small-molecule Hh antagonists of a different chemical class, a high-throughput screen based on murine embryonic fibroblast cells containing a plasmid with a luciferase reporter gene was performed. When these cells are stimulated with the ligand Shh, the luciferase activity can be optically measured, as can the reduction of this signal induced by antagonists of the Hh pathway. As shown in Figure 11.30, hit-to-lead optimization of the screening hits produced compound **11.1** that, after studying the replacement of the benzimidazole ring by a broad variety of heterocycles, led to the 2-piridylamide **11.2**, which eventually led to GDC-0449 (vismodegib, Erivedge®) following examination of a wide variety of amide substituents.[136]

Vismodegib is a competitive antagonist of the Smo receptor that was approved by the FDA for the treatment of basal cell carcinoma in 2012; it is also undergoing clinical trials for metastatic colorectal cancer, small cell lung cancer, advanced stomach cancer, pancreatic cancer, medulloblastoma, and chondrosarcoma.[137] Erismodegib (LDE-225, NVP-LDE225) is a selective, orally bioavailable Smo antagonist that inhibits the Hh- and Smo-dependent proliferation and is currently in a phase II trial in advanced basal cell carcinoma and in a phase I trial in medulloblastoma. Erismodegib monotherapy in chemonaive tumors seems to have little effect, but it is highly effective in preventing the recurrence

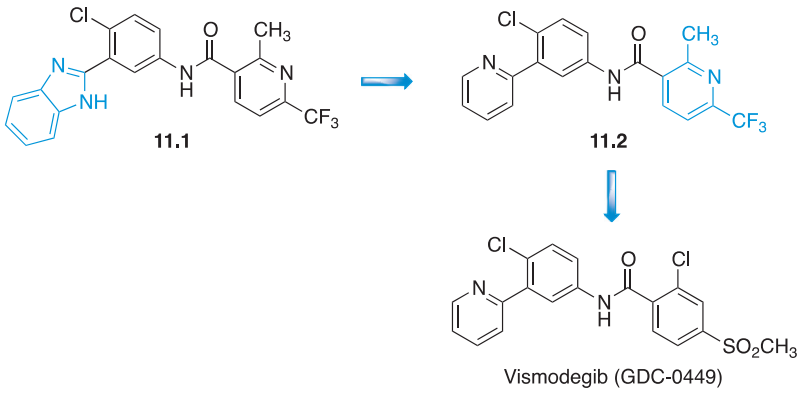

FIGURE 11.30

Development of vismodegib.