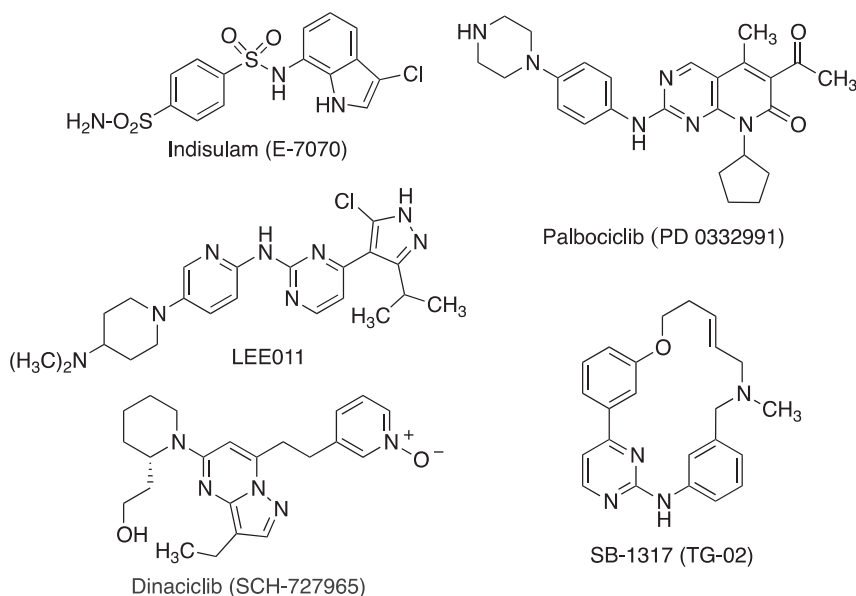


mutations that increase CDK4/6 activity. A phase I/II study of LEE011 in patients with solid tumors and lymphoma is currently ongoing.

Dinaciclib is another CDK inhibitor with nanomolar IC_{50} values for several kinases of the CDK family (CDK1, CDK2, CDK5, and CDK9).¹⁵² In preclinical work, this compound proved to be superior to flavopiridol in terms of both higher activity and an improved therapeutic index, and it is being evaluated in clinical trials for a variety of malignancies. SB-1357 (TG-02), which has an unusual macrocyclic structure, inhibits CDK1, -2, and -9 along with other kinase targets (JAK2, FLT3, and ERK5), and it has entered phase I clinical trials for advanced/refractory hematological malignancies.



BAY-1000394 is an orally bioavailable pan-CDK inhibitor that acts primarily by inhibiting the activity of the CDK1/cyclin B, CDK2/cyclin E, CDK4/cyclin D1, and CDK9/cyclin T1 kinases, thereby inducing cell cycle arrest at the G_1/S transition. This compound is under phase I/II clinical evaluation for small cell lung cancer. RGB-286638 is another multitargeted kinase inhibitor with anti-multiple myeloma activity triggered through inhibition of transcriptional CDKs¹⁵³ and is in phase II clinical evaluation. Terameprocol (EM-1421) is a semisynthetic tetra-*O*-methyl derivative of the previously mentioned nordihydroguaiaretic acid (INSM-18, NDGA), an inhibitor of IGFR-1 (see Section 4.5). Terameprocol inhibits CDK1 and survivin, and it has been clinically studied (phase I) in leukemia patients. Milciclib (PHA-848125) is another pan-CDK inhibitor that is under evaluation in phase II clinical trials. Additional CDK inhibitors that have at some point been in clinical trials, which have subsequently been terminated, include R-547, ZK-304709, AZD-5438, and AG-24322.