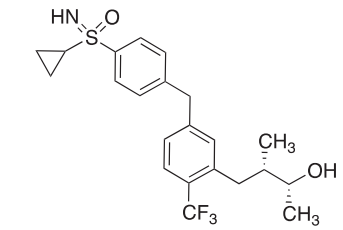
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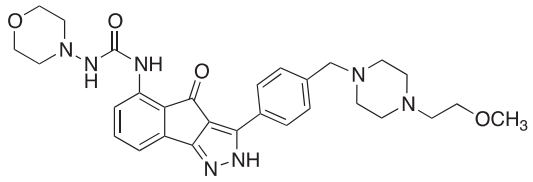
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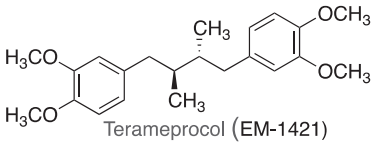
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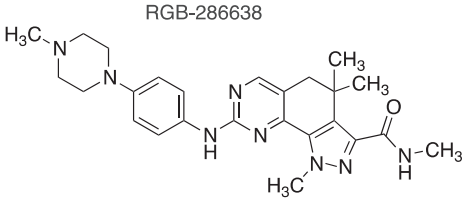
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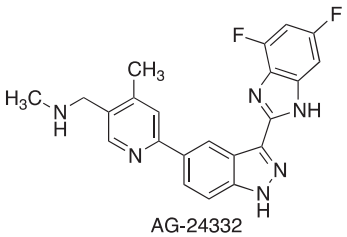
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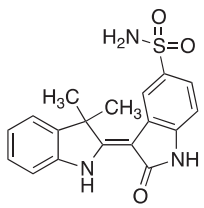
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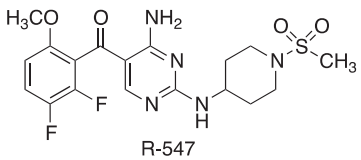
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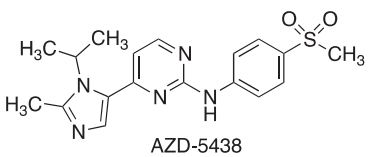
AZD-5438

5.2 POLO-LIKE KINASES (PLKs)

The serine/threonine protein kinase known as polo-like kinase 1 (PLK1) is an early trigger for G_2/M transition. Among other activities, PLK1 phosphorylates and activates the phosphatase cdc25C, which dephosphorylates and activates the cyclin B/cdc2 complex and activates components of the anaphase-promoting complex (APC/C). It is considered a proto-oncogene, and its overexpression is often observed in tumor cells. The loss of PLK1 expression can induce pro-apoptotic pathways and inhibition of cell growth. In cancer cells, PLK1 inhibition results in G_2/M cell cycle arrest followed by programmed cell death, whereas in normal cells this inhibition only causes reversible G_1 and G_2 arrest without programmed cell death. The PLK1 inhibitor volasertib (BI6727) blocks cell division by competitively binding to the ATP binding pocket of this kinase and is being developed to treat AML. The FDA has granted this drug a breakthrough therapy designation.[154]