

BENZIMIDAZOLE DERIVATIVES, PREPARATION METHODS AND USES THEREOF

Technical Field

5 The present invention relates to benzimidazole compounds which are useful for inhibiting cyclin-dependent kinase. More specially, the invention provides compounds and pharmaceutical compositions thereof which are used as CDK4/6 inhibitors, and methods of treatment for diseases mediated by CDK4/6, such as cancer.

Background Art

10 Cyclin-dependent kinases (CDKs) mediate cell cycle progression, regulating transition from G1 to S phase and G2 to M phase. CDK activity is tightly controlled throughout the cell cycle by posttranscriptional modifications as well as the expression of cyclins and CDK inhibitors. There are four proliferative CDKs: CDK1, which predominantly regulates the transition from G2 to M phase, and CDK2/4/6, which regulate the transition from G1 to S phase.

15 Progression through the cell cycle is a highly regulated process. In the absence of appropriate growth signals, a family of pocket proteins including retinoblastoma protein (pRb) prevents cells from entering the DNA replication phase (S phase). The replication cycle begins when mitogens trigger signal transduction pathways, leading to increase of cellular levels of D-cyclins. D-cyclins, in turn, activate cyclin dependent kinases 4/6 (CDK4/6), which phosphorylates and inactivates pRb.

20 Uncontrolled cell proliferation is one of the hallmarks of cancer, and pRb inactivation is the key event that enables tumor cells to progress through the cell cycle unchecked. While some tumors delete the pRb gene itself, the majority maintains a functional pRb and instead activates CDK4/6 kinase activity. Ablation of CDK4/6 kinase activity led to complete tumor growth inhibition in many cancer types such as HR+ breast cancer, mantle cell lymphoma, glioblastoma and
25 squamous lung cancer. Furthermore, normal fibroblast cells were shown to overcome the absence of CDK4/6 due to compensation by CDK1, whose absence is not tolerated. Taken together, this evidence suggests that a selective inhibitor of CDK4/6 may have a wider therapeutic window than pan-CDK inhibitors.