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抑制 CIP2A 之小分子對抗乳癌細胞之結構活性研究
Design and Synthesis of Quinoxaline Derivatives as CIP2A Inhibitors

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Abstract：
Cancerous inhibitor of PP2A (CIP2A) is a human oncoprotein that stabilizes c-Myc expression and activates Akt signaling pathway through the inactivation of PP2A, and consequently promotes tumor cell survival and proliferation. The overexpression of CIP2A has been found in various types of cancers and correlates with poor prognosis; thus, it has become a promising target for the development of anticancer agents. Previously, we have shown that erlotinib and its di-substituted quinazoline derivatives possess the ability against cell proliferation and inhibit CIP2A expression in hepatocellular carcinoma (HCC) cells. Here, a new scaffold, quinoxaline, is applied to the development of CIP2A inhibitors. We have demonstrated that the quinoxaline-based small molecule, TD-52, is a more potent inhibitor of CIP2A. Therefore, we chose TD-52 as the lead compound for structural modification. Based on the skeleton of TD-52, 3 series of novel quinoxaline derivatives were synthesized and their bioactivities were evaluated. Di-substituted quinoxaline derivatives with electron-withdrawing groups at C2 and C3 are favored for the HCC cells proliferation inhibitory activity. By comparison, mono-substituted quinoxaline derivatives showed no activity against HCC cells. Among the 44 compounds we have synthesized, TD-92 is the most potent drug in the inhibition of HCC cell (IC_{50}: 0.85 μM). These results demonstrated that the structural modification of quinoxaline is a promising strategy for the development of CIP2A inhibitors.