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Novel quinazoline derivative as RAF Inhibitor

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The oncogenic mutations of BRAF, occur most frequently in V600E, leading to constitutive activation of the MAPK signaling pathway, are common in a variety of human cancers. Recently, drugs targeting RAF kinase have been approved as an effective treatment for human malignancies that rely on this target for their growth. Thus, suppressing RAF kinase activity is a clinically meaningful approach in cancer patients harboring RAF driven oncogene. In this study, a series of quinazoline derivative was synthesized and evaluated for their RAF kinases inhibition activity. Several potent compounds displayed double-digit nanomolar IC50 values for RAF kinases including CRAF, BRAF, and $BRAF^{V600E}$. Preliminary profiling of one of the most active compounds in a panel of protein kinases revealed its selectivity for RAF kinases. In cells, the compound exhibited selective cytotoxicity against cancer cells harboring BRAF V600E mutation and dose-dependent inhibition of the phosphorylation of RAF downstream effectors MEK and ERK. Moreover, the compound was oral active in mice bearing A375 BRAFV600E-mutant melanoma xenograft. Therefore, the novel quinazoline derivative proved to be active as RAF inhibitor.

Biography

Shih-Chieh Yen has completed his PhD at the age of 30 years from Tsing-Hua University and postdoctoral studies from National Health Research Institutes, Institute of Biotechnology and Pharmaceutical Research. I am the research fellow of Development Center for Biotechnology, Institute of Pharmaceutics, an organic synthesis chemist service organization.

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