Design and synthesis of thienopyrimidine urea derivatives with potential cytotoxic and pro-apoptotic activity against breast cancer cell line MCF-7

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Abstract

A series of novel tetrahydrobenzothieno[2,3-d]pyrimidine urea derivatives was synthesized according to fragment-based design strategy. They were evaluated for their anticancer activity against MCF-7 cell line. Three compounds 9c, 9d and 11b showed 1.5ï1.03 folds more potent anticancer activity than doxorubicin. In this study, a promising multi-sited enzyme small molecule inhibitor 9c, which showed the most potent anti-proliferative activity, was identified. The anti-proliferative activity of this compound appears to correlate well with its ability to inhibit topoisomerase II (IC50 = 9.29 εM). Moreover, compound 9c showed excellent VEGFR-2 inhibitory activity, at the sub-micromolar level with IC50 value 0.2 εM, which is 2.1 folds more potent than sorafenib. Moreover, activation of damage response pathway of the DNA leads to cell cycle arrest at G2/M phase, accumulation of cells in pre-G1 phase and annexin-V and propidium iodide staining, indicating that cell death proceeds through an apoptotic mechanism. Compound 9c showed potent pro-apoptotic effect through induction of the intrinsic mitochondrial pathway of apoptosis. This mechanistic pathway was confirmed by a significant increase in the expression of the tumor suppressor gene p53, elevation in Bax/BCL-2 ratio and a significant increase in the level of active caspase-3. Quantitative structure-activity relationship (QSAR) studies delivered equations of five 3D descriptors with R2 = 0.814. This QSAR model provides an effective technique for understanding the observed antitumor properties and thus could be adopted for developing effective lead structures.

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