

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 1.5–1.03 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 μM). Moreover, compound 9c showed excellent VEGFR-2 inhibitory activity, at the sub-micromolar level with IC₅₀ value 0.2 μM, 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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