

# 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 30763025" 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 ( $IC_{50} = 9.29 \text{ } \mu\text{M}$ ). Moreover, compound 9c showed excellent VEGFR-2 inhibitory activity, at the sub-micromolar level with  $IC_{50}$  value  $0.2 \text{ } \mu\text{M}$ , 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  $R^2 = 0.814$ . 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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