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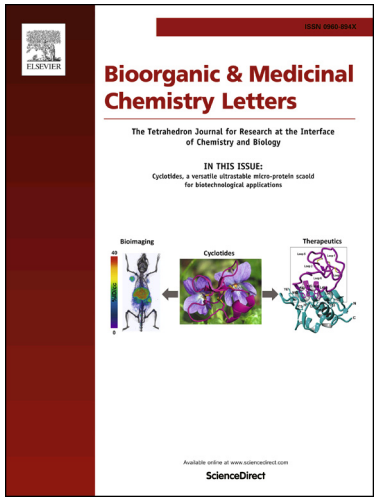

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Novel Thioureido-Benzenesulfonamide Derivatives with Enaminone Linker as Potent Anticancer, Radiosensitizers and VEGFR2 inhibitors

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Abstract

In this study, novel series of thioureido-benzenesulfonamide derivatives bearing an enaminone linker either *meta* or *para* oriented and having terminal linear or substituted aromatic or heteroaromatic ring system **5-16a,b** were designed and synthesized based on the general pharmacophoric features of type II VEGFR2 inhibitors. Evaluation of the synthesized compounds against HEPG2 hepatocellular carcinoma cells *in vitro* identified compounds **5b**, **6b** and **10-13b** as most active anticancer agents with IC_{50} equal to 0.12, 0.29, 0.58, 0.44, 0.42 and 0.66 µM, respectively. These compounds were evaluated for their ability to *in vitro* inhibit VEGFR2 kinase enzyme. The results demonstrated highly potent dose-related VEGFR2 inhibition with IC_{50} values in nanomolar range (33, 57, 210, 37, 37 and 220 nM, respectively). The radiosensitizing ability of the most promising compounds was studied which showed an increase in the cell killing effect of radiation after combination with the synthesized compounds which revealed lowered IC_{50} by nearly 50%. Molecular docking for the most potent compounds was performed to predict their possible binding mode within VEGFR2 active site and they showed binding affinity in a similar way to sorafenib.

Keywords: Benzenesulfonamides, HEPG2, VEGFR2.

Cancer remains to be one of the lethal diseases in the world; hepatocellular carcinoma (HCC) is considered the third type of cancer causing death [1]. The use of the common chemotherapeutic agents, although effective in cancer eradication, but also suffer from severe side effects arising from the lack of selectivity [2]. Therefore, finding new drugs that selectively target cancer cells is a today's goal [3, 4]. Inhibition of the VEGFR-2 signaling pathway was proved to have an antiangiogenic effect on human cancers as they exist predominately in vascular endothelial cells and hematopoietic stem cells and appears to mediate almost all of the known