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Design, synthesis, molecular modeling and biological evaluation of 1,2,4-triazine-5(4H)-ones as antitubulin agents

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Background and Aims: Combretastatin (CA-4) is a potent tubulin polymerization inhibitor which first was extracted from the bark of willow tree. The cis isomer of CA-4 connects to the colchicine site on β-monomer of tubulin and distributes the assembling of microtubules. Therefore the mitosis steps of cancer cells especially methaphase are stopped. On the other hand, CA-4 makes the blood veins collapsed and decreases the blood flow into solid tumors. CA-4 is, thus, an effective treatment for solid and MDR cancers. According to structure-activity relationships (SAR) of CA-4, a new series of 1,2,4-triazine-5(4H)-ones were designed and synthesized in which the essential ring A is preserved while ring B carries different substituents with capability of hydrogen bond formation.
Methods: The synthesis was carried out using multistep reactions and the synthesized compounds were purified by flash chromatography. Their chemical structure was confirmed by IR, Mass, 1H NMR and CHN analysis. The molecular docking studies of synthesized compounds were performed by Autodock 4. The X-ray crystal structure αß-tubulin complexed with DAMA- colchicine was used in this study. The methoxy-substituted phenyls are positioned deep in the hydrophobic cavity surrounded by Cys241ß, Leu242ß, Ala354ß, Thr353ß, all of which contribute to favorable hydrophobic-hydrophobic binding. The cytotoxicity of these derivatives was evaluated on different cell lines such as MCF-7, PC-3, HCT116 and A594, using MTT assay.
Results: Some of the compounds showed satisfactory results.

Keywords: 1,2,4-triazine-5(4H)-ones; Cytotoxicity; Docking study; Antitubulin