

Design, synthesis and crystal structure of novel chalcone derivatives as potential microtubule targeting agents

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The microtubular system with its dynamic nature characterized by the polymerization and depolymerization of α,β -tubulin heterodimers, is essential in a variety of cellular processes, including maintenance of cell shape, regulation of motility and cell division [1]. Because of the latter function microtubules are one of the significant and more successful molecular target for designing of new active molecules possessing anticancer activity. Among this group of compounds chalcones (1,3-diphenylprop-2-en-1on derivatives) represent a promising class of compounds with a simple structure, taking the possibility of extensive structural modifications that improve their natural anticancer properties.

Their mechanism of action including the inhibition of tubulin assembly by binding to the colchicine binding domain resulting from their structural similarity to other active ligands that have the same molecular target (e.g. combretastatin A-4, CA-4). Our successful investigation on novel potent inhibitors of tubulin polymerization from group of CA-4 thioderivatives prompted us to extend our research on chalcone scaffold. Herein we present synthesis, docking studies and X-ray structural characteristics of novel chalcone thioderivatives. Their biological activity will be further determined using series of a cancer cell lines, tubulin inhibition, cell cycle and pro-apoptotic analyses.

The multidisciplinary research methodology supported by computer aided drug design methods, standard and high-resolution X-ray structural analysis combined with modelling of the multipole electron density distribution [2] enable to develop of a new, effective chemotherapeutics from the group of chalcone derivatives and for the better understanding of their interaction with tubulin at the molecular level.

[1] Mikstacka, R., Stefański, T., Róžański, J. *Cell. Mol. Biol. Lett.* 2013, 18, 368-397.

[2] Poulain-Paul, A., Nassour, A., Jelsch, C., Guillot, B., Kubicki, M., Lecomte, C. *Acta Cryst. A*, 2012, 68, 715-728.

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