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Design, synthesis and biological evaluation of novel combretastatin A-4 derivatives – potential antimitotic agents

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Microtubules are key components of the cytoskeleton consisting of αβ-tubulin heterodimers and are involved in a wide range of various cellular functions, such as cell division, where they are responsible for mitotic spindle formation and proper chromosomal separation [1]. The biological importance of microtubules in mitosis and cell division makes them an interesting target for the development of anticancer agents: many of them are already in clinical use (epothilone, paclitaxel) or in clinical trials such as combretastatin A-4 (3′-hydroxy-3,4,4′,5-tetramethoxy-*cis*-stilbene, CA-4), however the search of new potent agents is still continued [2].

A series of sixteen CA-4 thioanalogs was prepared as a part of our on-going search for novel tubulin inhibitors. They were designed using parallel virtual screening protocol of reaction based combinatorial library. Antitubulin properties of the obtained compounds were studied *in vitro* with the use of tubulin polymerization assay kit (Cytoskeleton, USA). Cytotoxic activity was estimated against a panel of eight cancer and normal human cell lines with the use of MTT test.

In a series of oxazole CA-4 thioanalogs two potent inhibitors of tubulin polymerization were found: 4-(3,5-dimethoxy-4-methylthiophenyl)-5-(3-hydroxy-4-methoxyphenyl)oxazole (KomOx3) and 4-(3-bromo-4,5-dimethoxyphenyl)-5-(4-methoxy-3-methylthiophenyl)oxazole (KomOx7) with IC_{50} values of 1.05 and 0.80 μM, respectively, showing a stronger inhibition of tubulin polymerization than CA-4 (IC_{50} = 2.5 μM). Potency of antitubulin activity of studied compounds correlated well with their cytotoxic action on cell lines.

[1] Honore S., Pasquier E., Braguer D. *Cell. Mol. Life Sci*. 62 (2005) 3039-3056
[2] Kingston D. G. I. *J. Nat. Prod*. 72 (2009) 507-515

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