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Synthesis, spectroscopic analysis and biological activity of the new derivatives of 3-formylchromone and complexes with Cu(II) ions

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ABSRTACT

Benzopyrones are widely represented by chromone, coumarin and flavone derivatives of natural and synthetical origin. Those derivatives are also studied worldwide. The hydrazone derivtives of benzopyrones are less extensively studied, but there are some reports in literature about their interesting coordination properties and biological activity. The preliminary studies of phosphorohydrazone derivatives of benzopyrones, synthesized in Department of Bioinorganic Chemistry are also confirm those properties.

The aim of my work was the synthesis of the new hydrazone derivatives of 3-formylchromone and their complexes with Cu(II). The next step was the physicochemical, biochemical, antimicrobial and cytotoxicity studies.

Within the presented study, three new hydrazone derivatives of 3-formylchromone (**4**, **5**, **14**), ten 2-amino-3-formylchromone derivatives (**1** – **3**, **6** – **8**, **10**, **11**, **13**, **15**) and two complexes with Cu(II) (**16** i **17**) were synthesized. Two phosphorohydrazone derivatives of coumarin (**18** i **19**) and one phosphorohydrazone derivative of 3-formylchromone (**20**) were used as a comparison in biological studies.

The acid dissociation constant (pK_a) studies confirm the presence of unprotonate form of studied compounds at basic pH. This study showed, that the -NH- group possesses the highest priority of protonation in case of non-aliphatic compounds, while in case of aliphatic compounds the protonation was not observed. The partition coefficients (log *P*) were determined at pH 7.0 – 8.7 range. The presence of -NH_2 at C-2 of chromone lead to decreasing of |log *P*| value.

During the microbiological screening (on 9 bacterial strains) no significant antimicrobial properties of the studied compounds were observed.

In vitro cytotoxicity assay (MTT test, towards the following cell lines: HL-60, HL-60 ADR and NALM-6) was perform using on 12 compounds. The relatively high cytotoxicity against HL-60 and NALM-6 was observed for six compounds. According to Kupchan's classification, 2-amino-6-chloro-3-[(2-hydroksyethyl)-hydrazonomethyl]-4*H*-chromen-4-one (**3**) possess a high anticancer potential ($IC_{50} \leq 15$ μmol/l). Three studied derivatives show similar cytotoxicity against HL-60 cells and its adriamycin-resistant subline HL-60 ADR. Probably, chromone derivatives

are poor substrates for transport by the MRP1 efflux pump. The selected compounds possess ability to induce apoptosis in the cytosolic cytochrome *c* levels study (by ELISA).

The influence of selected compounds on: total protein level (using BCA), the level of angiogenic factors (Western-blot analysis for bFGF, determination of bFGF and FGFR1 in cell lysates by ELISA) and cell proliferation of WM-115 and MCF-7 cell lines (by MTT test) was also investigated.

Compared to control, studied compounds affected the basic fibroblast growth factor (bFGF) level in cell lysates of melanoma WM-115 cells. The studied compounds in the range of concentrations $1 \cdot 10^{-9}$ - $1 \cdot 10^{-6}$ mol/l are affect on the cell proliferation as well as the total protein level, bFGF and FGFR1 content in WM-115 cell lysates in the range of concentrations $1 \cdot 10^{-9}$ - $5 \cdot 10^{-4}$ mol/l. The twofold influence of studied compounds on MCF-7 cell proliferation was observed – in the highest tested concentration ($1 \cdot 10^{-3}$ mol/l) the significant antiproliferative properties were noted, while at lowest tested concentrations ($1 \cdot 10^{-11}$ - $1 \cdot 10^{-10}$ mol/l) the same compounds significantly stimulated cell proliferation.