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Synthesis, characterization, biological activity, DNA and BSA binding study: novel copper(II) complexes with 2-hydroxy-4-aryl-4-oxo-2-butenoate†

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A serie of novel square pyramidal copper(II) complexes $[Cu(L)_2H_2O]$ (**3a–d**) with *O*,*O*-bidentate ligands [L = ethyl-2-hydroxy-4-aryl-4-oxo-2-butenoate; aryl = 3-methoxyphenyl-**2a**, (*E*)-2-phenylvinyl-**2b**, (*E*)-2-(4′-hydroxy-3′-methoxyphenyl)vinyl-**2c**, 3-nitrophenyl-**2d**, 2-thienyl-**2e**] were synthesized and characterized by spectral (UV-Vis, IR, ESI-MS and EPR), elemental and X-ray analysis. The antimicrobial activity was estimated by the determination of the minimal inhibitory concentration (MIC) using the broth microdilution method. The most active antibacterial compounds were **3c** and **3d**, while the best antifungal activity was showed by complexes **3b** and **3e**. The lowest MIC value (0.048 mg mL^{-1}) was measured for **3c** against *Proteus mirabilis*. The cytotoxic activity was tested using the MTT method on human epithelial carcinoma HeLa cells, human lung carcinoma A549 cells and human colon carcinoma LS174 cells. All complexes showed extremely better cytotoxic activity compared to cisplatin at all tested concentrations. Compound **3d** expressed the best activity against all tested cell lines with IC_{50} values ranging from 7.45 to 7.91 μg mL^{-1}. The type of cell death and the impact on the cell cycle for **3d** and **3e** were evaluated by flow cytometry. Both compounds induced apoptosis and S phase cell cycle arrest. The interactions between selected complexes (**3d** and **3e**) and CT-DNA or bovine serum albumin (BSA) were investigated by the fluorescence spectroscopic method. Competitive experiments with ethidium bromide (EB) indicated that **3d** and **3e** have a propensity to displace EB from the EB–DNA complex through intercalation suggesting strong competition with EB [K_{sv} = (1.4 ± 0.2) and (2.9 ± 0.1) × 10^4 M^{-1}, respectively]. K_{sv} values indicate that these complexes bind to DNA covalently and non-covalently. The achieved results in the fluorescence titration of BSA with **3d** and **3e** [K_a = (2.9 ± 0.2) × 10^6 and (2.5 ± 0.2) × 10^5 M, respectively] showed that the fluorescence quenching of BSA is a result of the formation of the **3d**– and **3e**–BSA complexes. The obtained K_a values are high enough to ensure that a significant amount of **3d** and **3e** gets transported and distributed through the cells.

Introduction

One of the fundamental goals in medicinal chemistry is the development of new anticancer and antimicrobial therapeutic agents. The use of metal containing compounds presents one of the most important strategies in the development of new anticancer and antimicrobial agents.[1–5]

One of the main health problems in our society, and one of the primary targets in medicinal chemistry is cancer. For a long time, platinum complexes have been at the centre of research studies as chemotherapy agents.[6–8] However, the treatment with platinum drugs is limited by several side effects such as nephrotoxicity and neurotoxicity.[9–13] The major interest in medicinal chemistry has been to develop and synthesize different non-platinum agents, with fewer side effects and/or lower cytotoxicity than platinum-based drugs.[14] A wide

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