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Abstract

Synthesis, Structure and Biological Activity of Novel 4,5-dihydro-1*H*-imidazol-2-yl-phthalazine Derivatives and Their Copper(II) Complexes †

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Abstract: As a continuation of our previous investigations aimed at the synthesis of novel nitrogen-containing heterocycles and their metal complexes, we have now prepared two series of compounds incorporating a phthalazine ring at the position C_2 of 4,5-dihydro-1*H*-imidazole. The starting phthalazine (**I**) in the reaction with 2-chloroimidazoline (**II**) gives rise to the formation of pseudobase **III**. Then, compound **III** upon treatment with HOSA yields betaine which under basic conditions gives 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine (**IV**). In turn, the reactions of compound **IV** with a variety of acyl and sulfonyl chlorides lead to the formation of benzamides (**V**) and benzenesulfonamides (**VI**). Moreover, compounds **V** and **VI** can be transformed into corresponding 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-one derivatives **VII** and **VIII**. Such ligands are susceptible to the reaction with $CuCl_2$ giving rise to the formation of corresponding copper(II) complexes: dichloro[2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine]copper(II) (**1**), dichloro[2-(1-benzoyl-4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-one]copper(II) (**2**) and dichloro{bis-[2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-one]}copper(II) (**3**). The most promising results of biological studies were obtained for complex **1** towards the HeLa cell line (IC_{50} = 2.13 μM) without a toxic effect against fibroblasts BALB/3T3 (IC_{50} = 135.30 μM), which pointed towards its selectivity as a potential antitumor agent. It should be pointed out, that corresponding free ligand 2-(4,5-dihydro-1*H*-imidazol-2-yl)phthalazin-1(2*H*)-imine (**IV**) was less active than its metal complex (IC_{50} = 87.74 μM).

Keywords: phthalazine; imidazoline; copper(II) complexes; synthesis; structure; X-ray; cytotoxic activity

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