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Mendeleev Commun., 2022, **32**, 186–188

Mendeleev Communications

Ru^{II} and Ru^{III} complexes with imidazole ligands containing (benzyloxy)pyridinone moiety

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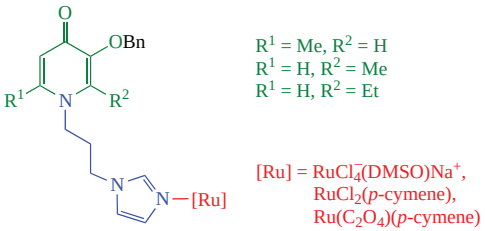
DOI: 10.1016/j.mencom.2022.03.011

Preparation of novel imidazole ligands containing 3-(benzyloxy)pyridinone moiety is described. The Ru^{III} and Ru^{II} leader-compounds containing the above-mentioned ligands were synthesized by coordination of imidazole group. The stability of the obtained compounds was explored in buffer solution and in the presence of DMSO, respectively, and their antiproliferative activity was assessed.



Keywords: pyridinone, imidazoles, ruthenium compounds, stability, antiproliferative activity.

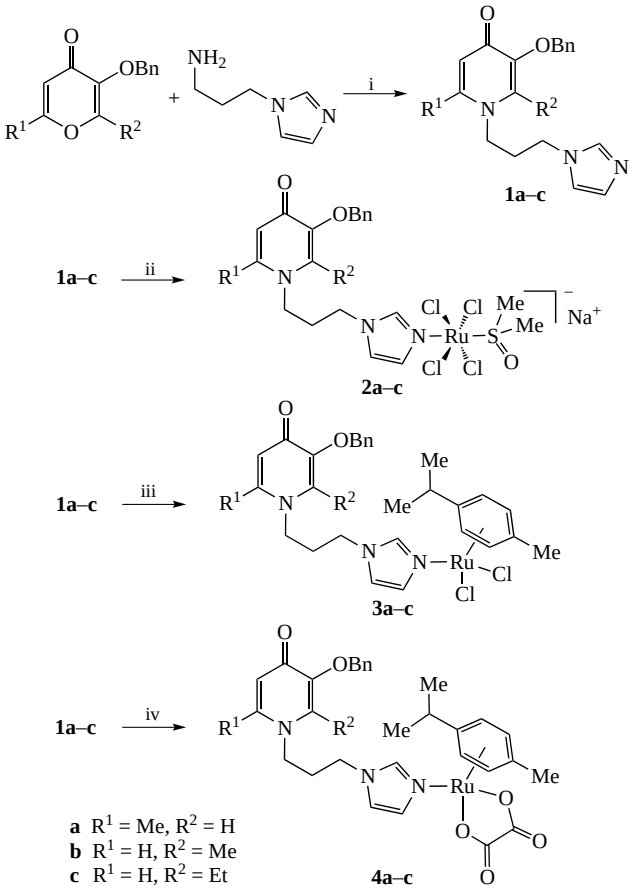
Since the 1980s, platinum drugs have been leading anticancer agents used for chemotherapy, with the most renowned of them being cisplatin and analogous carboplatin and oxaliplatin.[1–3] Being highly effective at fighting tumor development, they, however, bring severe side effects ranging from low selectivity and toxicity to different types of resistance.[4] These issues engender the need for a different kind of anticancer drugs possessing all strong qualities and having a milder effect on patient's organism in general. Such substances emerged in the late 1990s in the form of ruthenium-containing compounds similar to platinum ones. In contrast to their platinum predecessors, they demonstrated efficiency against cisplatin-resistant cancer types, reduced overall toxicity, and increased potential to hinder metastasis formation and distribution.[5–8]

Presently, some of the most promising candidates in ruthenium-containing anticancer drugs are Ru^{III} coordination compounds and organometallic Ru^{II} compounds.[9–13] It was determined that both types of substances hinder angiogenesis and are capable of influencing metastasis distribution.[14,15] Furthermore, some Ru anticancer compounds feature coordination of imidazole nitrogen to the metal and introduction of cymene into ruthenium coordination sphere, which are hypothesized to be essential for the drugs' effect.[9,16] Therefore, utilizing these scaffolds is considered a favorable strategy in designing ruthenium containing potential anticancer agents.[17,18]

Recently, hydroxypyrones were introduced as suitable ligands for ruthenium antiproliferative agents due to their favorable biocompatibility and toxicity characteristics.[19–21] They are generally obtained from natural sources or through simple well-known synthetic pathways;[22–24] hydroxypyrones can also be easily modified to give pyrones with different scaffolds in side chains, thiopyrones and hydroxypyridones,[20,25–27] which makes them propitious for use as ligands in drug development. Some of the ruthenium compounds containing hydroxypyridone ligands were previously reported to demonstrate similar or higher biological activity compared to cisplatin and his analogues.[28–31]

Here, we present the synthesis, characterization and stability study of the new imidazole ligands containing benzyl protected pyridinones, Ru^{II} and Ru^{III} compounds containing the above-mentioned ligands (Scheme 1). Additionally, we assess their stability and investigate their potential as antiproliferative agents. Ruthenium(III) complexes **2a–c** analogous to NAMI-A and two series of Ru^{II} compounds **3a–c**, **4a–c** similar to recently reported hybrid compounds[17] were prepared from benzyl-protected pyridinone ligands **1a–c**. Commercially available maltol and ethyl maltol were chosen as the initial compounds, as well as allomaltol obtained in a two-step synthesis from kojic acid.[32] Protective benzyl group was introduced into these three hydroxypyrone derivatives yielding compounds, which were then treated with 1-(3-aminopropyl)imidazole under alkaline conditions to afford the key pyridinone compounds **1a–c**. In published procedures, compounds similar to **1a–c** were isolated by treating the reaction mixture with hydrochloric acid;[27] however, it was not a suitable option due to the nitrogen protonation in the imidazole fragment of the ligands making consequent ruthenium coordination impossible. Ruthenium(III) complexes **2a–c** were obtained by a reaction between the ligands **1a–c** with sodium tetrachlorobis(dimethyl sulfoxide) ruthenate(III). Ruthenium(II) compounds **3a–c** with the chloride as a leaving group were accessed by treating the ligands with (η^6-*p*-cymene)ruthenium dichloride dimer. Compounds **4a–c** were obtained by treatment of ligands **1a–c** with (η^6-*p*-cymene) $Ru(C_2O_4)\cdot H_2O$ precursor obtained *in situ* by a reaction between $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ dimer and silver oxalate.

^{1}H NMR spectra and other data confirm the structures of the products. For complexes **1a–c**, in the recorded ESI-MS spectra, the peak was assigned to the $[M - Na^+]^-$ ion in the negative ion mode containing the characteristic isotope pattern for such types



Scheme 1 *Reagents and conditions*: i, NaOH, EtOH/H_2O, 100 °C, 12 h; ii, $[(Me_2SO)_2RuCl_4]^-Na^+$, acetone, 12 h; iii, $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$, acetone, 12 h; iv, $(\eta^6\text{-}p\text{-cymene})Ru(C_2O_4)\cdot H_2O$, MeOH, 12 h.

of ruthenium complexes. For all the mass spectra, experimental isotopic patterns are in good agreement with the calculated ones.

Stability in water/buffer solutions is a vital pharmacokinetic parameter for drug candidates. Therefore, we examined kinetic stability of Ru^{III} complexes in phosphate buffer (pH 7.4, NaCl 100 mM, 37 °C) using UV-VIS spectroscopy (Figure 1). We followed changes at 308 and 352 nm and were able to estimate the half-transformation time. Allomaltol based complex was found to be the most stable followed by ethyl maltol derivates; maltol based compounds were established to be the least stable ones.

It is known that ligand exchange reactions can affect biological activity of compounds;[33] for example, substitution by some solvents, like DMSO, often leads to activity decline. We demonstrated that such ligand exchange with DMSO takes place for compounds **3a–c** (^{1}H NMR monitoring, for the spectrum copies, see Online Supplementary Materials, Figure S11). The complexes are present in an equilibrium between different forms, with the exchange of the Cl ligands similar to the one observed for close related compounds.[18] In order to suppress the ligand exchange, Ru^{II} compounds **4a–c** with oxalate leaving group were prepared (see Scheme 1). ^{1}H NMR study showed that in the case of oxalate complexes **4a–c**, only signals for original compounds were detected in the presense of DMSO. Coordination of ligands to the ruthenium centre leads to changes in the chemical shifts of the imidazole protons. The N–CH=CH protons are shifted from 7.1 ppm in the ligands to 7.8–7.9 ppm in the complexes.

Proliferation inhibition of human cell lines by ligands **1a–c**, ruthenium compounds **2a–c**, **3a–c**, **4a–c** and cisplatin as a standard metal-based anticancer drug was evaluated on HCT116 colorectal carcinoma, MCF7 breast adenocarcinoma, A549 non-small cell lung carcinoma and WI38 nonmalignant lung fibroblast cell lines by means of the standard MTT colorimetric

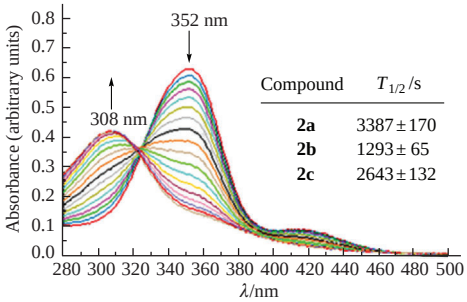


Figure 1 Transformation of Ru^{III} complex **2c** UV-spectra in phosphate buffer (pH 7.4, NaCl 100 mM, 37 °C, Δt = 2 min) and half-transformation times.

assay as the IC_{50} value after 72 h of incubation. The ligands demonstrated no antiproliferative activity. The ruthenium compounds were found only marginally active with IC_{50} close to 100 μM.

In summary, we have found that coordination of imidazole ligands containing (benzyloxy)pyridinone moiety to the Ru^{II} and Ru^{III} centers resulted in only marginally efficient antiproliferative compounds against cancer cells. The reasons for low activity remain unclear and require further investigation, which can help find ways to increase the antiproliferative potential of this class of complexes.

This research was supported by Russian Foundation for Basic Research (grants nos. 19-03-00394 and 19-33-90069).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.011.

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Received: 15th July 2021; Com. 21/6617