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Synthesis, characterization and cytotoxicity of cyclopentadienyl ruthenium(II) complexes containing carbohydrate-derived ligands

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ABSTRACT

We here report the synthesis of new cyclopentadienyl ruthenium(II) complexes of general formula $[(\eta^5\text{-}C_5H_5)Ru(PP)(\mathbf{L})]^+$ (PP = two triphenylphosphine, 1,2-diphenylphosphinoethane), isolated as PF_6^- salts, with **L** being galactose and fructose carbohydrate derivative ligands, *N*-coordinated to the metal centre by nitrile, tetrazole and 1,3,4-oxadiazole moieties. The ten new organometallic compounds were fully characterized by FT-IR, ^1H, ^{13}C, and ^{31}P NMR spectroscopies, and by elemental analysis. The cytotoxicity of the ruthenium(II) compounds was tested on *HeLa* cancer cells (cervical carcinoma), unveiling IC_{50} values in the low micromolar range.

1. Introduction

Organometallic complexes containing monosaccharide ligands represent a small but challenging field in modern chemistry. Carbohydrates are the largest class of natural compounds and thereby readily available and renewable. They provide a large number of functional groups and several stereogenic centres per molecule, and each of the hydroxyl groups offers the opportunity of selective modification and coordination [1,2]. They can act as monodentate as well as polydentate chelating ligands with pronounced three-dimensional characteristics [3] and their coordination capability is not limited to oxophilic metal centres: the change of donor atoms from oxygen to others, e.g., nitrogen, enables the coordination to almost every metal atom [4]. They allow also some control over the lipophilicity/aqueous solubility of the complexes, by selective modification of the carbohydrate moiety.

Since the accidental discovery of the anticancer drug cisplatin by Rosenberg and co-workers in 1965 [5], metal complexes have attracted much interest as metallopharmaceuticals. Although cisplatin is still nowadays successfully used in the treatment of many cancer types, problems such as toxicity, side effects and drug resistance lead to investigation of alternative anticancer drugs.

Among the metal atoms used in anticancer metal complexes, ruthenium is most unique. Despite being a rare noble metal, unknown to living systems, ruthenium compounds show remarkable features, such as low general toxicity, the ability to mimic iron binding to biomolecules (transferrin, albumin) and stronger affinity for cancer tissues over normal tissues [6,7]. In particular, the families of half-sandwich organometallic complexes $[(\eta^6\text{-}C_6H_6)Ru(L)_3]$ [7–16] and $[(\eta^5\text{-}C_5H_5)Ru(L)_3]$ [17–23] in which three coordination sites are occupied by the aromatic rings, have been studied for their anticancer properties, evidencing cytotoxic properties in cisplatin resistant cancer cell lines, with IC_{50} values in nanomolar range. Apart from applications as anticancer drugs, other medical applications of ruthenium compounds have been explored. Uses include immunosupressants [24], nitric oxide scavengers [25], antimicrobial agents [26,27], malaria [28] and Chaga's disease treatment [29].

The synthesis of ruthenium compounds bearing carbohydrate derived ligands is a relatively unexplored area: our bibliographic search revealed some examples of ruthenium carbonyl clusters containing carbohydrate moieties [30–34], ruthenium-arene complexes containing a carbohydrate phosphite derivative with anticancer properties [35–37], and a report of ruthenium cyclopentadienyl complexes with coordinated thiomonosaccharides concerning their promising anti-inflammatory effects [38].

As part of our endeavour to produce a library of carbohydrate-containing organometallic compounds, we here report the

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synthesis and cytotoxic evaluation against human *HeLa* cells (cervical carcinoma) of ten new η^5-cyclopentadienyl ruthenium(II) complexes of general formula $[(\eta^5\text{-}C_5H_5)Ru(PP)(\mathbf{L})]^+$, isolated as PF_6^- salts, in which **L** are galactose and fructose carbohydrate derivative ligands, functionalized with nitrile, tetrazole and 1,3,4-oxadiazole *N*-coordinating moieties. The electronic density and the stereochemical environment of the metal centre are played by using two different phosphanes which were used as co-ligands, PPh_3 and Dppe. All new compounds were characterized by IR, ^1H, ^{13}C, ^{31}P NMR spectroscopies and by elemental analysis.

2. Results and discussion

2.1. Synthesis of the carbohydrate derivative ligands

The aldehyde precursors $\mathbf{P^2}$ and $\mathbf{P^4}$ (Scheme 1) were obtained by oxidation of the commercially available 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose ($\mathbf{P^1}$) and 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose ($\mathbf{P^3}$), prepared as described in the literature [39], respectively. The corresponding nitrile derivatives $\mathbf{L^1}$ and $\mathbf{L^4}$ were obtained in good yields by reaction with hydroxylamine hydrochloride and subsequent dehydration of the oximes with dicyclohexylcarbodiimide (DCC).

The tetrazole derivatives $\mathbf{L^2}$ and $\mathbf{L^5}$ were obtained quantitatively by 1,3-dipolar cyclo-addition of the corresponding nitriles with sodium azide, in DMF. Finally, acylation in boiling acetic anhydride of $\mathbf{L^2}$ and $\mathbf{L^5}$ afforded the 1,3,4-oxadiazole derivatives $\mathbf{L^3}$ and $\mathbf{L^6}$, respectively, in excellent yields.

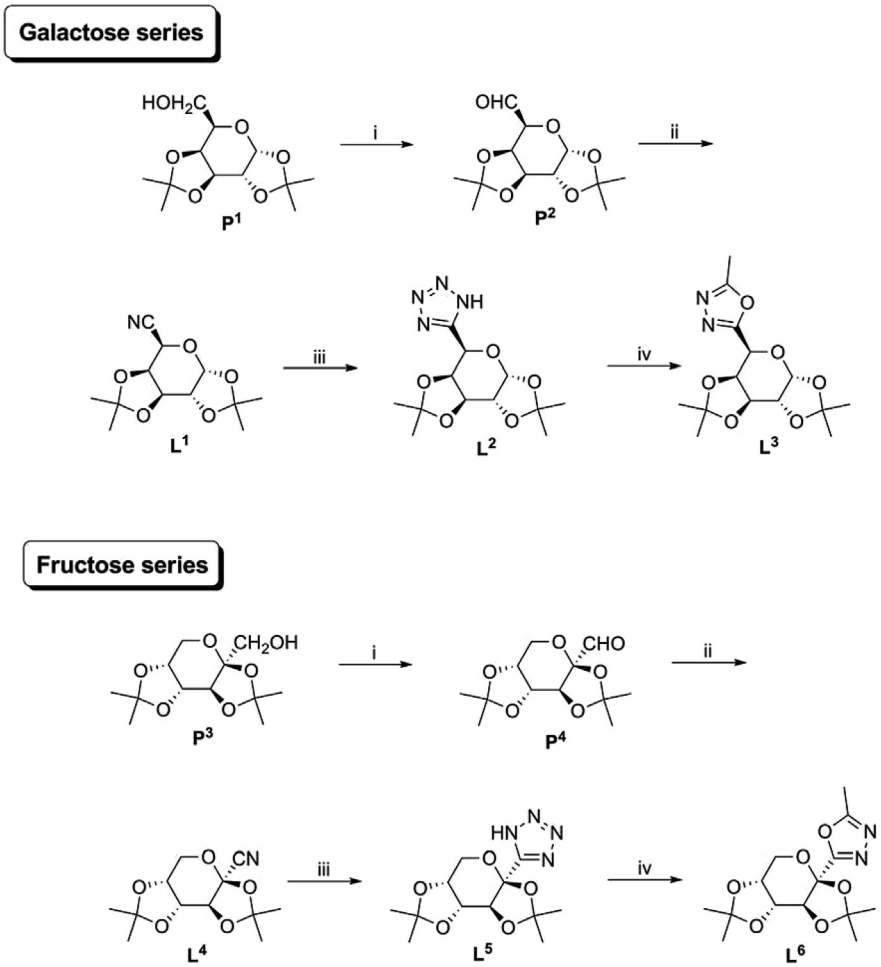
Compounds $\mathbf{P^2}$, $\mathbf{L^1}$, $\mathbf{L^2}$ and $\mathbf{L^3}$ were fully characterized ^1H, ^{13}C NMR and FTIR spectroscopies, and by elemental analysis. Compounds $\mathbf{P^4}$, $\mathbf{L^4}$, $\mathbf{L^5}$ and $\mathbf{L^6}$ were obtained and its ^1H, ^{13}C NMR spectra compared with the data described in the literature [40].

$\mathbf{L^5}$ and $\mathbf{L^6}$ are derivatives of topiramate, an anticonvulsant used in epilepsy treatment, and were in this case proposed as less toxic, more efficient alternative anticonvulsant drugs.

2.2. Synthesis of the Ru(II) complexes

The novel cationic complexes of general formula $[(\eta^5\text{-}C_5H_5)Ru(PP)(\mathbf{L})]^+$((PP) = $2PPh_3$ or Dppe), isolated as PF_6^- salts, were prepared by halide abstraction with $TlPF_6$ from the parent neutral complexes $[(\eta^5\text{-}C_5H_5)Ru(PP)Cl]$ in the presence of a slight excess of the corresponding carbohydrate-derived ligand, in dichloromethane at room temperature (Scheme 2). The compounds were recrystallized by slow diffusion of *n*-pentane or *n*-hexane in dichloromethane or acetone solutions.

The synthesis of compounds $[(\eta^5\text{-}C_5H_5)Ru(PPh_3)_2(\mathbf{L^3})][PF_6]$ and $[(\eta^5\text{-}C_5H_5)Ru(PPh_3)_2(\mathbf{L^6})][PF_6]$ was unsuccessfully attempted, resulting in product mixtures. Stereochemical hindrance, due to the methyl group in α position relatively to the coordinated nitrogen and the larger cone angle of PPh_3 over Dppe, may be the reason for the unsuccessful attempts. The same reactions were attempted in refluxing toluene, with similar results.



Scheme 1. Synthesis of the carbohydrate-derived ligands. i) PCC, CH_2Cl_2; ii) 1 – $H_2NOH{\cdot}HCl$, Pyridine; 2 – $CuSO_4{\cdot}5H_2O$, Et_3N, DCC, CH_2Cl_2; iii) NaN_3, NH_4Cl, DMF, 100 °C; iv) Ac_2O, Δ.