

Cytotoxicity of arene ruthenium metalla-rectangles incorporating bis-pyridyl diimide linkers



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ABSTRACT

A series of tetranuclear arene ruthenium complexes of the general formula $[\text{Ru}_4(p\text{-cymene})_4(\mu_2\text{-L})_2(\mu_4\text{-OO}\eta\text{OO})_2][\text{CF}_3\text{SO}_3]_4$ ($\text{L}_1 = N,N'$ -bis(4-pyridylmethyl)-pyromellitic diimide, $\text{L}_2 = N,N'$ -bis(4-pyridylmethyl)-naphthalene diimide) were obtained from the corresponding dinuclear arene ruthenium complexes $\text{Ru}_2(p\text{-cymene})_2(\mu_4\text{-OO}\eta\text{OO})\text{Cl}_2$ ($\text{OO}\eta\text{OO} = \text{oxalato (oxa)}$, 2,5-dioxido-1,4-benzoquinonato (dobq), 2,5-dihydroxy-3-phenyl-1,4-benzoquinonato (dhpq), 2,5-dichloro-1,4-benzoquinonato (dClbq), 2,5-dioxido-3-undecyl-1,4-benzoquinonato (dubq), 2,5-dihydroxy-3,6-diphenyl-1,4-benzoquinonato (dhdb), 5,8-dioxido-1,4-naphtoquinonato (donq)) by reaction with the bidentate ligands (L_1 and L_2) and silver trifluoromethanesulfonate. The antiproliferative activity of the tetranuclear arene ruthenium metalla-rectangles was evaluated on cancerous (A2780 and A2780cisR) and non-cancerous (HEK293) cell lines, showing in all cases cancer cell selectivity. In general, the metalla-rectangles obtained with L_2 are more potent than those incorporating L_1 , and with the exception of $[\text{Ru}_4(p\text{-cymene})_4(\mu_2\text{-L}_1)_2(\mu_4\text{-dClbq})_2][\text{CF}_3\text{SO}_3]_4$, they are all more active than cisplatin on the cisplatin resistant A2780cisR cell line.

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1. Introduction

Rigid and semi-rigid bis-pyridyl linkers are widely-used building blocks in supramolecular chemistry [1]. Among bis-pyridyl spacers, bis-pyridyl diimide-based derivatives (Fig. 1) are good candidates for modulating the flexibility of the bidentate linkers, thus allowing modifications at a supramolecular level of the geometry and of the electronic property of the metal-based assemblies. These linkers have been extensively used to construct metal organic frameworks (MOFs) [2] and, to a lesser extent, to generate discrete metalla-assemblies (MAs) [3]. In recent years, several tetranuclear arene ruthenium metalla-cycles incorporating rigid bis-pyridyl ligands have been tested as anticancer agents [4]. They have been shown to interact with DNA [5] and with proteins [6], and apoptosis [7] was suggested to be the possible cell death mechanism, but their exact mode of action remains unclear [8]. Moreover, despite having similar sizes, components, structures and charges, the cytotoxicity and selectivity of metalla-cycles appear to

be unpredictable.

Herein, we describe a new series of tetranuclear arene ruthenium complexes bridged by the bis-pyridyl diimide-based linkers N,N' -bis(4-pyridylmethyl)-pyromellitic diimide (L_1) and N,N' -bis(4-pyridylmethyl)-naphthalene diimide (L_2). The cytotoxicity of the tetranuclear complexes on cancerous (A2780 and A2780cisR) and non-cancerous (HEK293) cell lines was evaluated and compared to cisplatin.

2. Results and discussion

The reaction between L_1 [9] and $\text{Ru}_2(p\text{-cymene})_2(\mu_4\text{-OO}\eta\text{OO})\text{Cl}_2$ ($\text{OO}\eta\text{OO} = \text{oxalato (oxa)}$, 2,5-dioxido-1,4-benzoquinonato (dobq), 2,5-dichloro-1,4-benzoquinonato (dClbq), 2,5-dioxido-3-undecyl-1,4-benzoquinonato (dubq), 5,8-dioxido-1,4-naphtoquinonato (donq)) in the presence of silver trifluoromethanesulfonate affords in good yields, the tetranuclear arene ruthenium metalla-rectangles (**1–5**) of the general formula $[\text{Ru}_4(p\text{-cymene})_4(\mu_2\text{-L}_1)_2(\mu_4\text{-OO}\eta\text{OO})_2]^{4+}$ (Scheme 1).

Similarly, five metalla-rectangles (**6–10**) were prepared with L_2 [10] and the dinuclear arene ruthenium complexes $\text{Ru}_2(p\text{-}$

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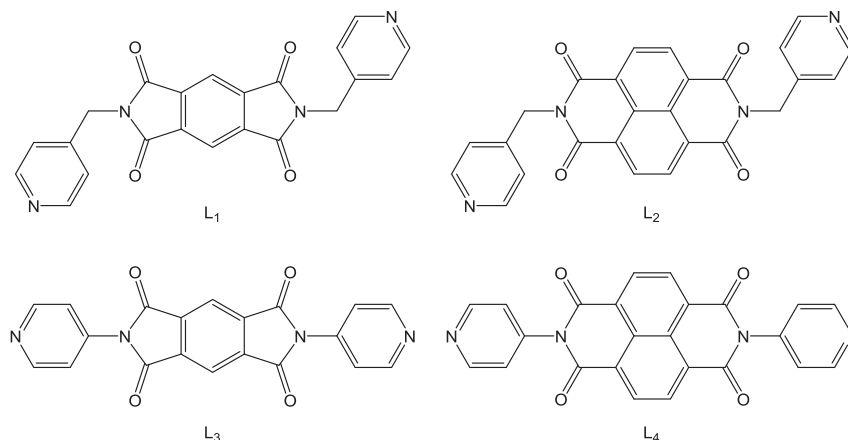
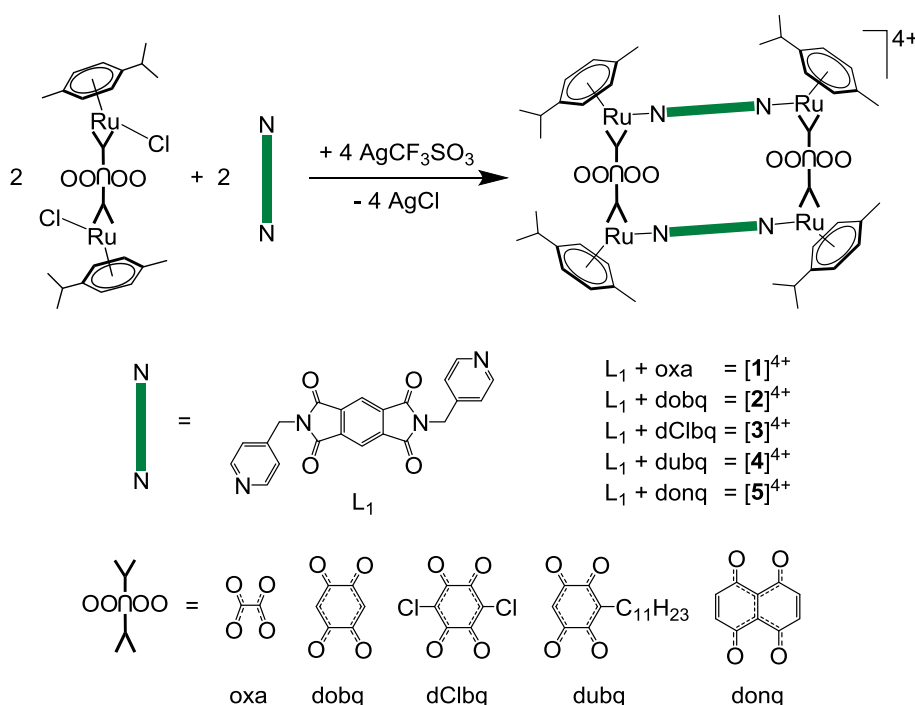


Fig. 1. Structures of semi-rigid (L₁ and L₂) and rigid (L₃ and L₄) bis-pyridyl diimide-based linkers.



Scheme 1. Synthesis of the arene ruthenium metalla-rectangles 1–5.

cymene)₂(μ₄-OOηOO)Cl₂ (OOηOO = oxa, dhp (2,5-dihydroxy-3-phenyl-1,4-benzoquinonato), dubq, dhdb (2,5-dihydroxy-3,6-diphenyl-1,4-benzoquinonato) and donq) in the presence of silver trifluoromethanesulfonate (Scheme 2). All metalla-rectangles were isolated and characterized as their triflate salts.

The nature of the tetradentate OOηOO bridging ligand in the dhp and dubq derivatives results in the formation of two isomers in which the side-arm of the dinuclear arene ruthenium units {Ru₂(*p*-cymene)₂(μ₄-OOηOO)}²⁺ is either on the same or opposite side of the metalla-rectangle. This feature is reflected in the ¹H NMR spectra, where broad or two sets of signals are observed for several protons of cations **4**, **7** and **8**. In these derivatives, a statistical ratio between the two isomeric rectangles is observed in accordance with analogous unsymmetrical arene ruthenium metalla-rectangles of the same or of analogous non-symmetrical ONηNO and OOηOO linkers [8f,11]. Unfortunately, we were unable to isolate the isomers and accordingly to assign the signals

associated to the specific isomers. Nevertheless, all ¹H NMR spectra show the expected signals for such tetranuclear metalla-assemblies.

The electrospray ionization mass spectra of complexes [1–10] [CF₃SO₃]₄ also confirm the formation of the tetranuclear metalla-rectangles (Fig. 2). In all cases, tricationic and dicationic peaks corresponding to the intact metalla-rectangles with one or two remaining trifluoromethanesulfonate anions were observed, {[Ru₄(*p*-cymene)₄(μ₂-L)₂(μ₄-OOηOO)₂]⁴⁺ + CF₃SO₃[−]]³⁺ and {[Ru₄(*p*-cymene)₄(μ₂-L)₂(μ₄-OOηOO)₂]⁴⁺ + 2 CF₃SO₃[−]]²⁺ respectively (see Experimental section). The isotopic pattern of these cationic peaks correlates exactly with the calculated theoretical isotopic distributions of Ru₄ species.

2.1. Cytotoxicity studies

The antiproliferative activity of the arene ruthenium metalla-

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