Inorganic Chemistry
Article
Cite This: Inorg. Chem. XXXX, XXX, XXX−XXX
pubs.acs.org/IC

Methyl-cyclopentadienyl Ruthenium Compounds with 2,2′-Bipyridine Derivatives Display Strong Anticancer Activity and Multidrug Resistance Potential

Leonor Côrte-Real,[†,○] Ricardo G. Teixeira,[†,○] Patrícia Gírio,[†,‡,○] Elisabeta Comsa,[‡] Alexis Moreno,[‡] Rachad Nasr,[‡] Hélène Baubichon-Cortay,[‡] Fernando Avecilla,[§] Fernanda Marques,[∥] M. Paula Robalo,[⊥,#] Paulo Mendes,[▽] João P. Prates Ramalho,[▽] M. Helena Garcia,[†] Pierre Falson,[*,‡] and Andreia Valente[*,†]

[†]Centro de Química Estrutural, Faculdade de Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal

[‡]Drug Resistance and Membrane Proteins Team, Molecular Biology and Structural Biochemistry Laboratory, UMR 5086 CNRS-UCBL1, IBCP 7 Passage du Vercors, 69 367 Lyon Cedex 07, France

[§]Grupo Xenomar, Centro de Investigacións Científicas Avanzadas (CICA), Departamento de Química, Facultade de Ciencias, Universidade da Coruña, Campus de A Coruña, 15071 A Coruña, Spain

[∥]Centro de Ciências e Tecnologias Nucleares, Instituto Superior Técnico (C^{2}TN/IST), Universidade de Lisboa, Estrada Nacional 10 (km 139.7), 2695-066 Bobadela LRS, Portugal

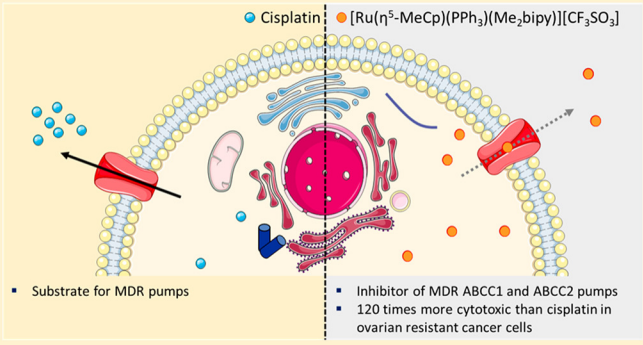
[⊥]Área Departamental de Engenharia Química, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Rua Conselheiro Emídio Navarro, 1, 1959-007 Lisboa, Portugal

[#]Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

[▽]Departamento de Química and Centro de Química de Évora, Escola de Ciências e Tecnologia, Universidade de Évora, Rua Romão Ramalho, 59, 7000-671 Évora, Portugal

Supporting Information

ABSTRACT: New ruthenium methyl-cyclopentadienyl compounds bearing bipyridine derivatives with the general formula [Ru(η^5-MeCp)(PPh_3)(4,4′-R-2,2′-bpy)]$^+$ (**Ru1**, R = H; **Ru2**, R = CH_3; and **Ru3**, R = CH_2OH) have been synthesized and characterized by spectroscopic and analytical techniques. **Ru1** crystallized in the monoclinic $P2_1/c$, **Ru2** in the triclinic $P\bar{1}$, and **Ru3** in the monoclinic $P2_1/n$ space group. In all molecular structures, the ruthenium center adopts a "piano stool" distribution. Density functional theory calculations were performed for all complexes, and the results support spectroscopic data. **Ru1** and **Ru3** were poor substrates of the main multidrug resistance human pumps, ABCB1, ABCG2, ABCC1, and ABCC2, while **Ru2** displayed inhibitory properties of ABCC1 and ABCC2 pumps. Importantly, all compounds displayed a very high cytotoxic profile for ovarian cancer cells (sensitive and resistant) that was much more pronounced than that observed with cisplatin, making them very promising anticancer agents.



INTRODUCTION

The increasing research in the area of metallodrugs has positioned ruthenium complexes as promising drugs for cancer therapy, particularly because of the progression through clinical trials of some inorganic ruthenium(III) complexes, namely NAMI-A, [ImH][trans-$RuCl_4$(DMSO) Im] (Im = imidazole), and KP1019, [Hind][trans-$RuCl_4(ind)_2$] (ind = indazole).[1−3] In addition, the growing research on ruthenium organometallic chemistry unveiled important features for the metallodrug field such as the lower toxicity of ruthenium drugs relative to platinum-based drugs (e.g., cisplatin, CDDP) and different cell targets than DNA.[4−6] Thus, different modes of action are possible, resulting in a better efficiency and less toxic side effects than those of the metallodrugs in clinical use.

Our research group has focused on the search for new Ru(II) and Fe(II) "piano stool" cationic complexes as anticancer agents. In this frame, diverse sets of complexes of the general formula [$M^{II}(\eta^5$-$C_5H_5)$(PP)(L)]$^+$ were designed and synthesized, with M^{II} = Ru, Fe; PP = monodentate or bidentate

Received: February 9, 2018

DOI: 10.1021/acs.inorgchem.8b00358
Inorg. Chem. XXXX, XXX, XXX−XXX