SYNTHESIS AND CHARACTERISATION OF NEW COORDINATION COMPOUNDS WITH WATER SOLUBLE PHOSPHINES: ANTICANCER PROPERTIES

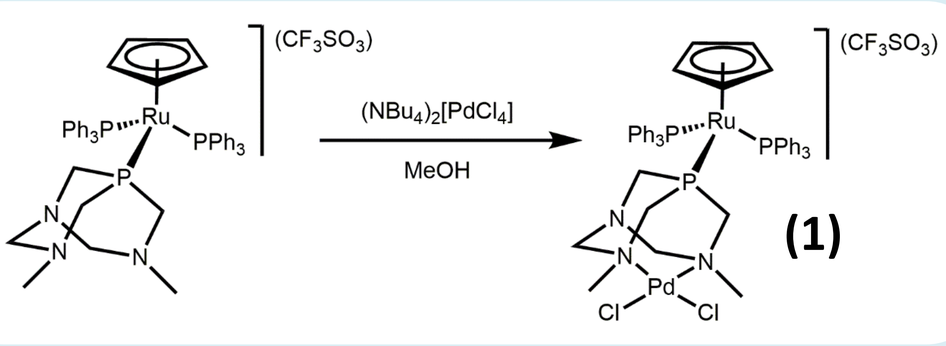
***Andrés Alguacil Alarcón*, Franco Scalambra and Antonio Manuel Romerosa Nievas**

Departamento de Química y Física, Facultad de Ciencias Experimentales, Universidad de Almería

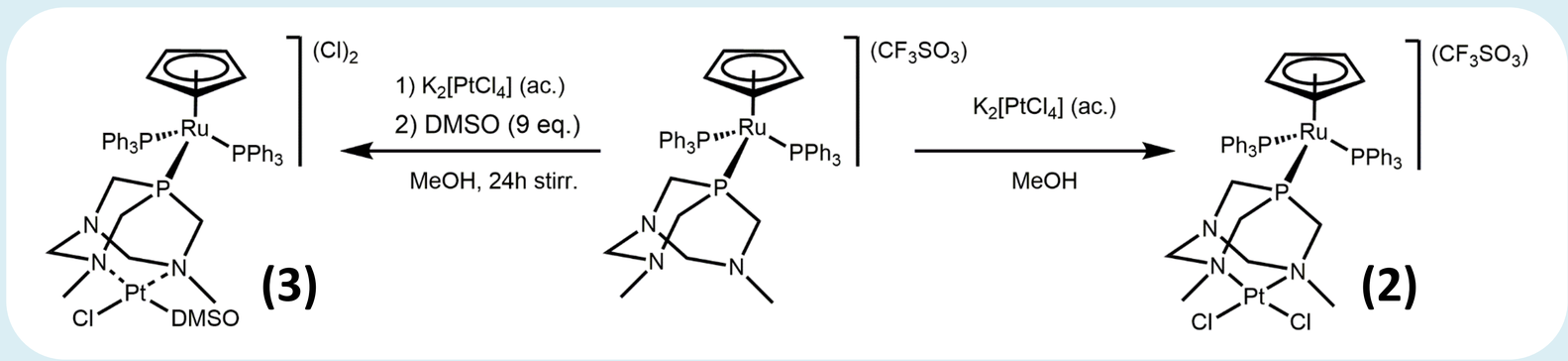
Introduction

The research on coordination compounds as anticancer drugs raised after the fortuitous discovery of *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) by Rosenberg in 1965.[1] From the approval of cisplatin as therapeutic drug in 1978 up to date, new metal complexes with different metals have been synthesized and studied for this purpose. Among these compounds those containing ruthenium(II) showed remarkable antiproliferative activity and low toxicity. Recently our group synthesised and fully characterized new Ru(II) complexes bearing the ligand dmoPTA (dmoPTA = 3,7-dimethyl-1,3,7-triaza-5-phosphabyciclo[3.3.1]nonane), which have shown better cytotoxic profile than those exhibited by cisplatin-like compounds.[2]

Synthesis



The azaphosphine dmoPTA can coordinate metals through the phosphorus atom and the chelating N_{CH3} atoms, offering the possibility to synthesise polymetallic species. So far, mono- and dimetallic complexes with general formula $[RuCp(PPh_3)_2$-μ-dmoPTA-1κ*P*:2κ²*N,N'*-$MCl_2]^+$ (M = metal) (2nd generation, **Figure 3**) displayed significant antiproliferative activity and also better selectivity against tumoral cells than cisplatin.[3]



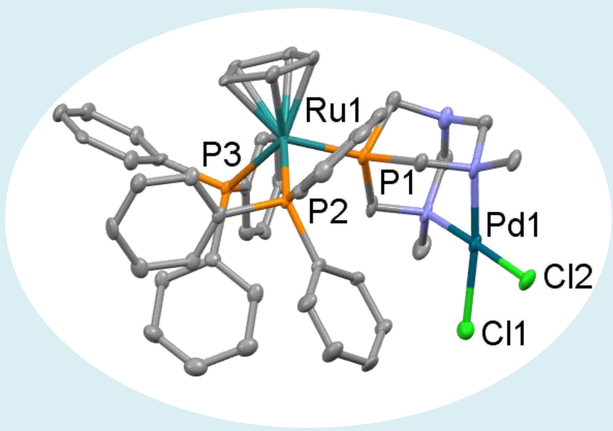


Figure 1. Crystal structure of $[RuCp(PPh_3)_2$-μ-dmoPTA-1κ*P*:2κ²*N,N'*-$PdCl_2)](CF_3SO_3)$ (**1**).

Substitution of a PPh_3 by a PTA ligand was accomplished, leading to a more hydrophilic derivatives based on the $[RuCp(PPh_3)(PTA)(dmoPTA\text{-}\kappa P)]^+$ scaffold (**Figure 2**).

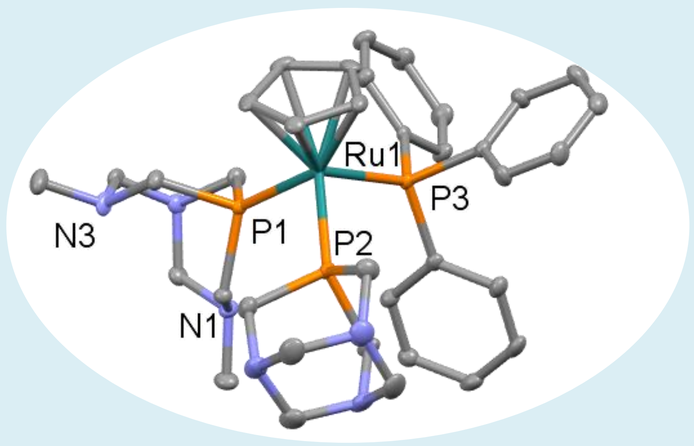
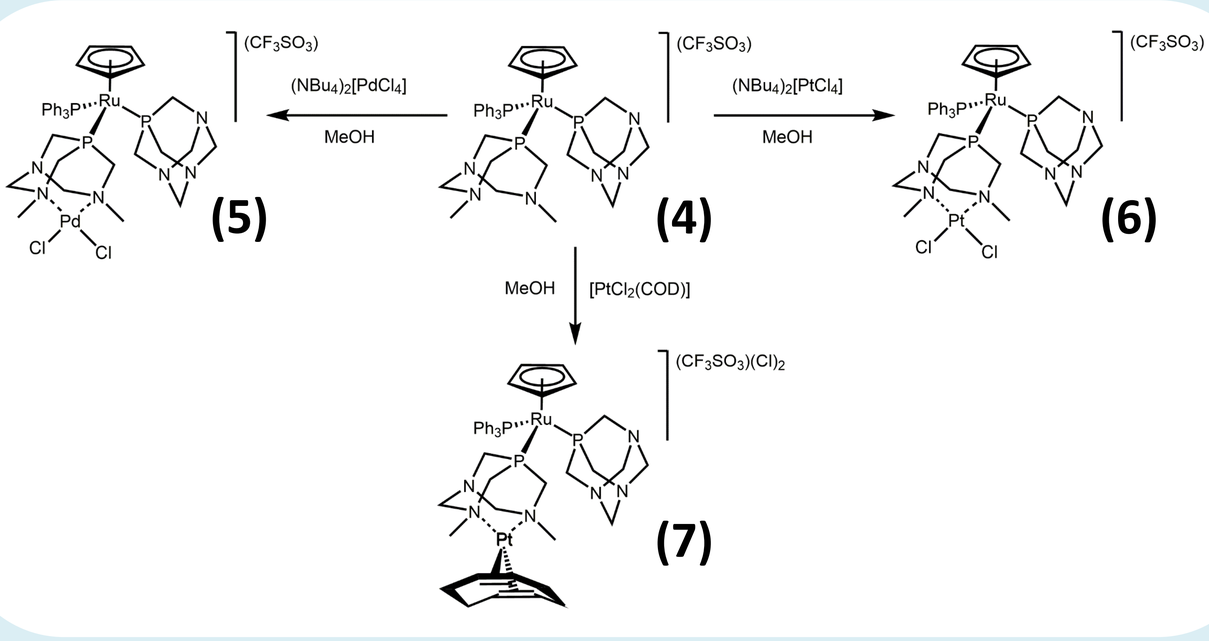


Figure 2. Crystal structure of $[RuCp(PPh_3)(PTA)(dmoPTA\text{-}\kappa P)](CF_3SO_3)$ (**4**).



Anticancer Properties

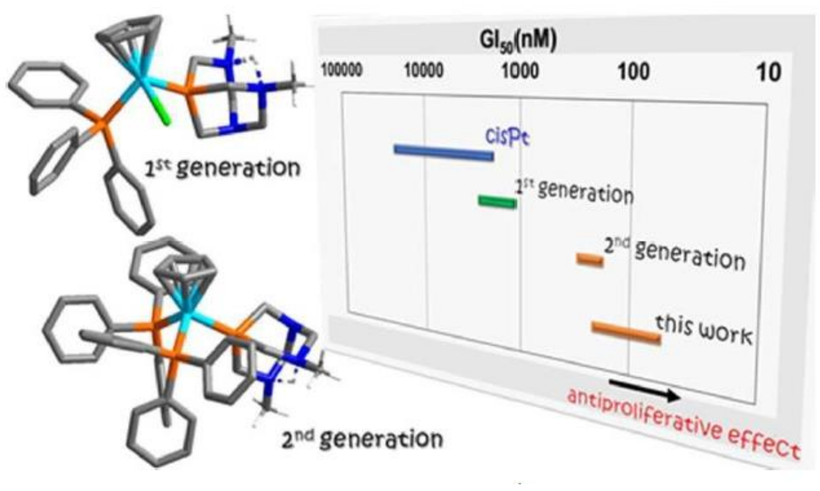


Figure 3. Antiproliferative activity of cisplatin, 1st, 2nd generation dmoPTA-Ru and the complexes presented in this work against human solid tumour cell lines

The antiproliferative activity of the synthesized complexes was evaluated against a panel of cancer cells sensitive and non-sensitive to cisplatin.

	cisplatin	1	2	3	4	5	6	7
A549 (lung)	4,9 (±0,2)	-	**1,3 (±0,12)**	**0,28 (±0,026)**	> 100	> 100	> 100	31 (±1,3)
HBL-100 (breast)	1,9 (±0,2)	-	**0,93 (±0,12)**	**0,25 (±0,052)**	> 100	> 100	> 100	> 100
HeLa (cervix)	1,8 (±0,5)	-	**0,08 (±0,014)**	**0,03 (±0,0034)**	86 (±19)	53 (±4,1)	> 100	97 (±4,4)
SW1573 (lung)	2,7 (±0,4)	-	**0,34 (±0,04)**	**0,028 (±0,012)**	61 (±6,7)	48 (±1)	> 100	33 (±2,9)
T-47D (breast)	17 (±3,3)	-	**2,2 (±0,29)**	**0,32 (±0,024)**	> 100	> 100	> 100	> 100
WiDr (colon)	23 (±4,3)	-	**1,4 (±0,2)**	**0,38 (±0,071)**	> 100	> 100	> 100	61 (±2,8)

Table 1. GI_{50} values (μM ± SD) of complexes 1-7 and cisplatin against human solid tumor tells lines.

Acknowledgements

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References

[1] B. Rosenberg, L. Van Camp, T. Krigas, Nature, **1965**, *205*, 698-699.
[2] Z. Mendoza, P. Lorenzo-Luis, M. Serrano-Ruiz, E. Martín-Batista, J. M. Padrón, F. Scalambra, A. Romerosa, *Inorg. Chem.*, **2016**, 55, 7820-7822.
[3] Z. Mendoza, P. Lorenzo-Luis, F. Scalambra, J. M. Padrón, A. Romerosa, *Dalton Trans.*, **2017**, 46, 8009–8012.