Ruthenium organometallic compounds as ABC drug efflux-targeted agents and collateral sensitizers

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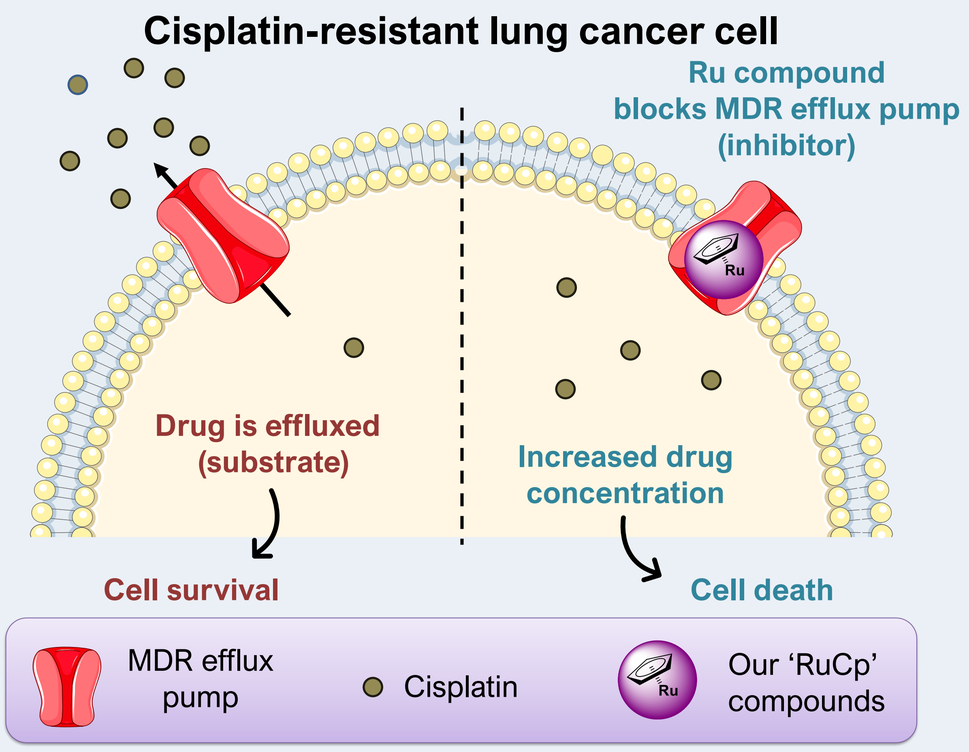
BACKGROUND

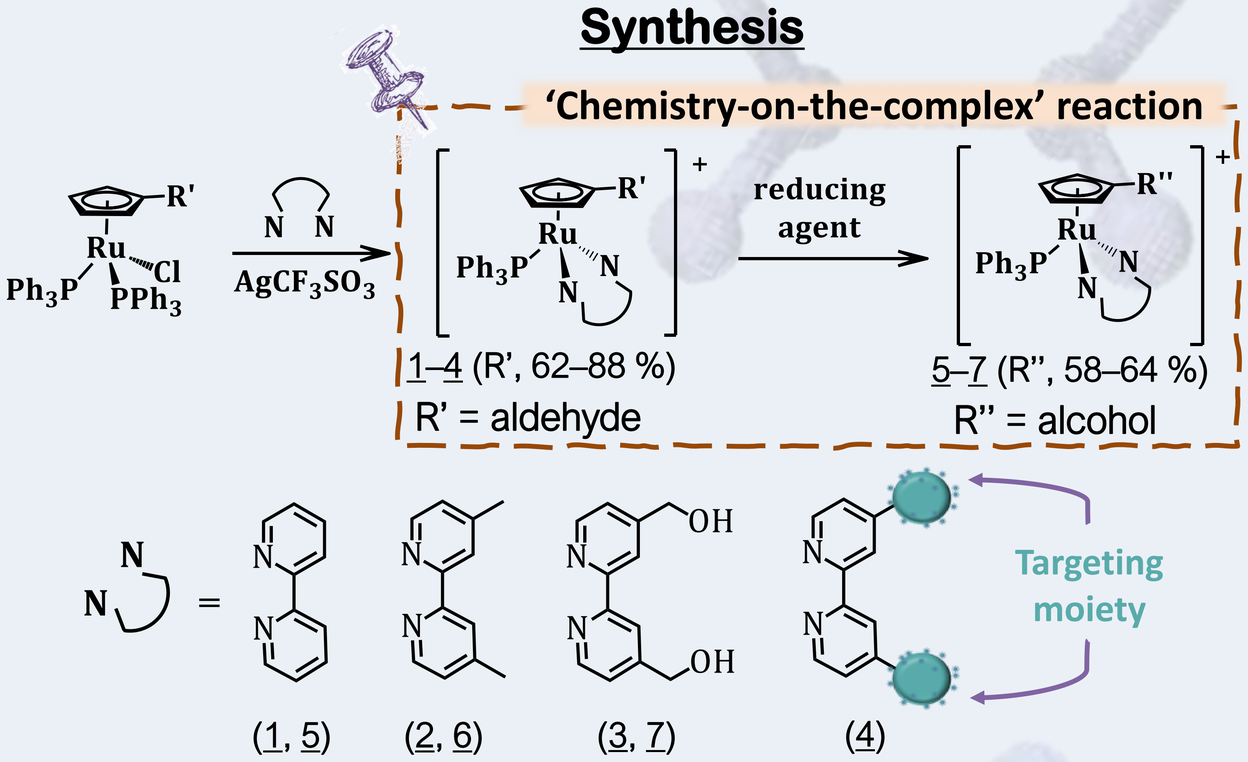
Our research group has been focused on exploring metal-based compounds, especially incorporating the "ruthenium-cyclopentadienyl" (*"RuCp"*) scaffold.[1] This moiety is an appealing and robust scaffold to build new molecules from where the judicious choice of co-ligands allows to impart different properties and to fine-tune the performance of the whole complex.

In this frame, we developed new compounds based on the functionalized *"RuCp"* moiety containing bipyridyl ligands which were tested against four non-small cell lung cancer (NSCLC) cell lines: A549, NCI-H228, Calu-3 and NCI-H1975. Our preliminary results show that the compounds are more cytotoxic in cisplatin-resistant than in cisplatin-sensitive cells, and increased cisplatin cytotoxicity by inhibiting MRP1 and P-gp transporters. This work unveils the mechanism of action of these compounds, suggesting that drug efflux transporters could be a potential target, and, more importantly, indicates that they induce collateral sensitivity in cisplatin-resistant lung cancer cells.



RESULTS

Synthesis



- Seven new compounds were synthesized and characterized by several spectroscopic techniques
- Crystallographic studies confirmed the proposed 'piano-stool' geometry
- All compounds are stable in aqueous solutions over 24 h

In vitro screening in NSCLC

Table 1. IC_{50} (μM) of the new ruthenium compounds and cisplatin in the cell lines analyzed after 72 h of incubation.

	1	2	4	6	Cisplatin
A549	10.8±1.3	12.4±3.6	15.4±2.6	12.5±2.1	>100
NCI-H228	4.3±0.7	3.8±1.4	16.5±1.3	7.8±1.2	>100
Calu-3	24.7±4.1	4.9±1.6	28.9±0.8	5.9±1.2	63.4 ± 8.7
NCI-H1975	91.8±10.4	>100	>100	>100	3.8 ± 1.1

- Compounds 1, 2, 4 and 6 show strong activity against cisplatin-resistant NSCLC A549 and NCI-H228
- Compounds 3, 5 and 7 were inactive in the cell lines studied

Collateral sensitivity

Table 2. Resistance factor (Rf = IC_{50}(cisplatin)/IC_{50}(cisplatin + IC_{25}compound)) of the cell lines treated with cisplatin *versus* cisplatin and Ru compounds.

	1	2	4	6
A549	71.4	555.6	**1250**	243.9
NCI-H228	333.3	**1389.9**	588.2	344.8
Calu-3	26.3	126	33.2	78.7
NCI-H1975	2.9	0.6	1.6	0.7

- The selected compounds were able to increase cisplatin cytotoxicity (up to **1390-fold**) when administrated at nontoxic doses

Inhibition of ABC transporters

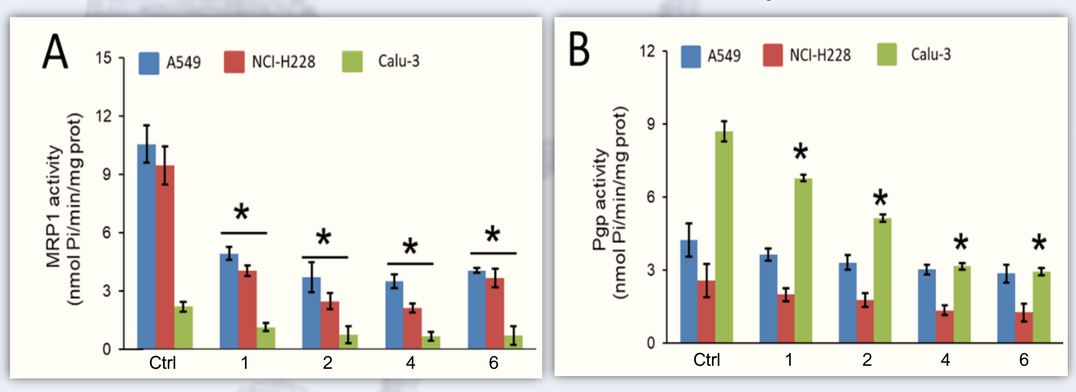


Figure 1. MRP1 (A) and P-gp (B) ATPase activity measured on the proteins immune-purified from cells treated without (ctrl) or with 1 μM of compounds 1, 2, 4 and 6 for 24 h.

- Compounds 1, 2, 4 and 6 inhibited MRP1 and P-gp activity in A549, NCI-H228 and Calu-3 cell lines, which overexpress these transporters.

CONCLUSIONS

- Seven new 'RuCp' compounds were successfully synthesized and characterized
- Compounds 1, 2, 4 and 6 were cytotoxic against NSCLC cell lines
- Our compounds increased the sensitivity to cisplatin in the resistant cell lines by inhibiting MRP1 and P-gp transporters

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References
[1] Garcia et al., *Future Medicinal Chemistry*, **2016**, 8(5), 527–544.