ANTIPROLIFERATIVE EVALUATION OF QUINOLINE- AND COUMARIN-BASED LIGANDS WITH RHENIUM(I) TRICARBONYL COMPLEXES

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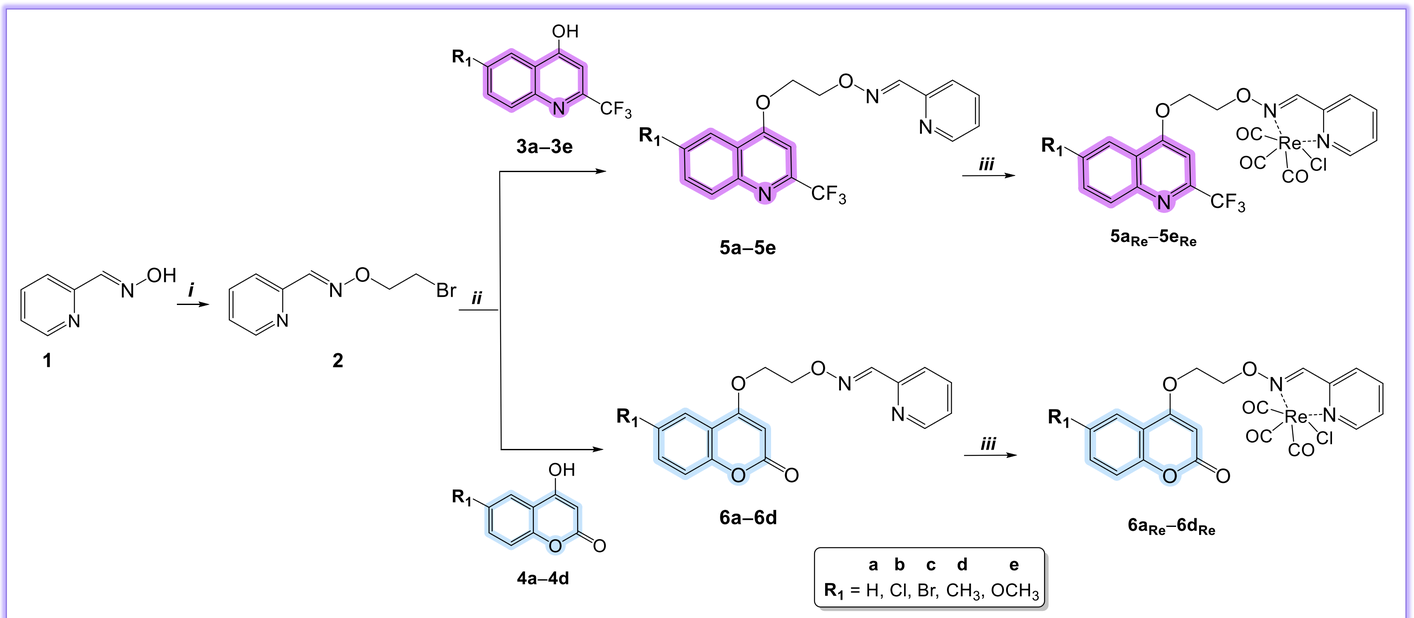
INTRODUCTION

Quinoline and coumarin derivatives, found in many biologically active compounds, exhibit notable anticancer activity [1,2]. In our previous studies, coumarin-triazole hybrid was found to have a pronounced inhibitory effect against HeLa cell lines with IC_{50} = 0.9 µm, while quinolone-ferrocene conjugate exhibited activity against K562 (IC_{50} = 7.9 µM) [1,2]. Furthermore, our results showed that coordination of coumarin ligands with Re(I) significantly enhanced antiproliferative activity [3].

SYNTHESIS AND SPECTROSCOPIC CHARACTERISATION

Quinoline and coumarin ligands were synthesized as described in Scheme 1. *O*-Alkylated (*E*)-picolinaldehyde oxime **2** was obtained by the base-promoted alkylation of syn-2-pyridinealdoxime with 1,2-dibromoethane. The reaction of quinoline **3a–3e** or coumarin **4a–4d** with *O*-alkylated (*E*)-picolinaldehyde oxime **2** and NaH yielded quinoline **5a–5e** and coumarin **6a–6d** ligands. These ligands then reacted with $[Re(CO)_5Cl]$ to form rhenium(I) tricarbonyl complexes $\mathbf{5a_{Re}–5e_{Re}}$ and $\mathbf{6a_{Re}–6d_{Re}}$. Both the ligands and complexes were fully characterized by ^1H and ^{13}C NMR, IR, UV-Vis spectroscopy, and single crystal diffraction. The ^1H NMR spectra of the rhenium(I) tricarbonyl complexes showed deshielding of the pyridine and aldoxime protons due to the electron-withdrawing inductive effects of the transition metal (Fig. 1.). Additionally, the crystal structures of the complexes confirmed the expected *fac*-stereochemistry, influenced by the back-bonding of the CO ligands.



Scheme 1. *Reagents and conditions:* (*i*) 1,1-dibromoethane, NaH, DMF, r.t, 24 h; (*ii*) K_2CO_3, DMF, 80 °C, 24 h (*iii*) $[Re(CO)_5Cl]$, $CHCl_3$, reflux, 24 h.

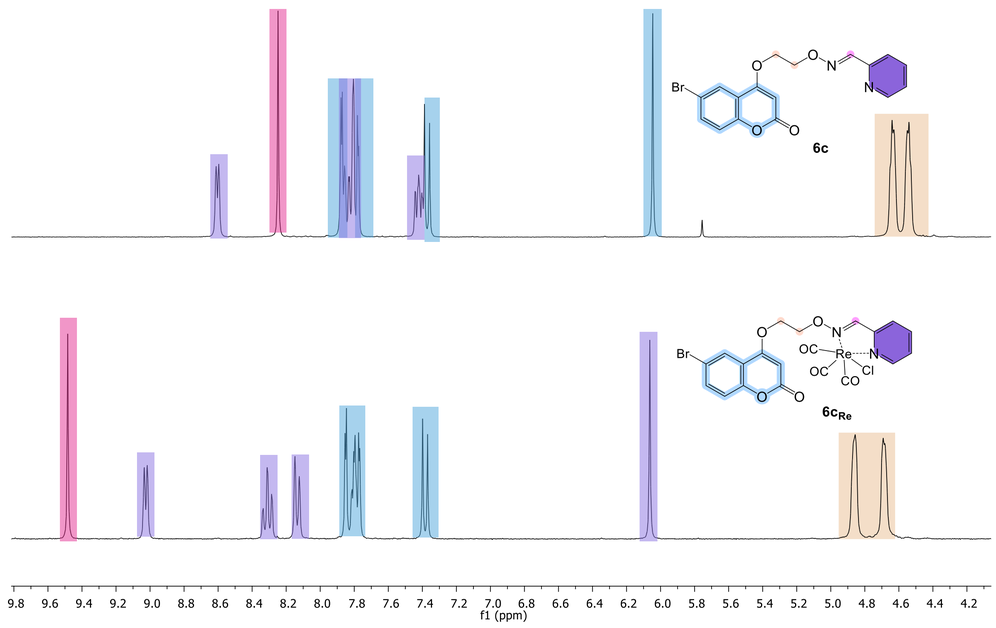


Fig. 1. Comparison of the proton NMR spectra of ligand **6c** and rhenium(I) tricarbonyl complex $\mathbf{6c_{Re}}$ in DMSO-d_6.

BIOLOGICAL EVALUATION

The antiproliferative evaluation of the new quinoline (**5a–5e**) and coumarin ligands (**6a–6f**) and their rhenium(I) tricarbonyl complexes ($\mathbf{5a_{Re}–5e_{Re}}$ and $\mathbf{6a_{Re}–6d_{Re}}$) on human tumour cell lines is shown in Table 1. Re(I) coordination significantly enhanced the activity of these complexes, with both quinoline and coumarin complexes exhibiting increased potency. Among the quinoline complexes, $\mathbf{5e_{Re}}$ showed the best growth inhibition in HuT78 cells (IC_{50} = 9.4 µM, SI = 5.8), while among the coumarin complexes, $\mathbf{6d_{Re}}$ had the strongest effect (IC_{50} = 2.4 µM, SI = 8.7).

Table 1. The growth–inhibition effects *in vitro* of compounds **5a–e** and **6a–f** and their rhenium(I) tricarbonyl complexes $\mathbf{5a_{Re}–5e_{Re}}$ and $\mathbf{6a_{Re}–6d_{Re}}$ on selected tumor cell lines.

		IC_{50}[a] (µM)						
R$_1$	Compd	CCRF-CEM	HeLa	CaCo-2	THP-1	HuT78	BJ	SI (HuT78)[b]
H	**5a**	94.9±40	>100	>100	86.4 ± 11.4	43.4±1.6	>100	2.3
	5a$_{Re}$	11.5±7.9	20.2±1.2	28.4±2.4	16.1±0.7	29.0±1.6	64.0±3.4	2.2
Cl	**5b**	>100	>100	>100	64.6±5.9	24.9±0.2	>100	4.1
	5b$_{Re}$	22.1±1.1	20.7±0.7	28.9±5.6	26.7±8.7	10.4±0.2	30.1±2.3	2.9
Br	**5c**	42.1±0.9	>100	>100	49.1±11.4	33.2±5.9	>100	4.3
	5c$_{Re}$	6.3±1.7	21.8±1.5	30.6±1.5	10.6±1.7	11.0±1.2	21.0±5.2	1.9
CH$_3$	**5d**	81.1±11.0	>100	<100	55.2±7.01	41.2±1.7	>100	2.4
	5d$_{Re}$	15.9±2.2	39.3±20.9	56.4±25.1	17.8±3.0	10.2±2.3	31.5±6.2	3.1
OCH$_3$	**5e**	**>100**	**>100**	**>100**	**76.4±7.5**	**48.7±3.3**	**>100**	**2.1**
	5e$_{Re}$	**17.2±6.6**	**27.9±11.7**	**29.4±7.4**	**36.1±3.7**	**9.4±0.1**	**54.5±2.7**	**5.8**
H	**6a**	46.5±7.1	>100	>100	46.2±5.1	49.2±5.5	>100	2.2
	6a$_{Re}$	26.0±10.5	>100	>100	71.0±5.7	40.5±7.1	>100	2.5
Cl	**6b**	89.5±33.4	>100	>100	56.2±5.9	44.8±37.3	>100	2.2
	6b$_{Re}$	24.4±0.8	>100	>100	25.8±1.6	34.9±1.4	78.1±2.5	2.2
Br	**6c**	94.0±11.1	>100	>100	39.6±7.2	44.7±0.3	>100	2.3
	6c$_{Re}$	9.5±2.7	19.1±2.3	33.2±6.2	15.4±2.1	10.6±1.0	59.1±5.9	5.6
CH$_3$	**6d**	**78.2±19.7**	**>100**	**>100**	**37.9±8.2**	**43.8±5.4**	**>100**	**2.3**
	6d$_{Re}$	**13.0±2.9**	**22.5±0.7**	**32.0±3.0**	**16.5±1.9**	**2.4±0.8**	**20.9±1.8**	**8.7**
	5Fu	52.2±0.8	8.2±1.9	5.9±0.7	76.4±0.5	>100	16.8 ± 7.0	/

[a]50% inhibitory concentration or compound concentration required to inhibit tumor cell proliferation by 50%. [b]SI, selectivity index, SI = IC_{50} for normal cell line/IC_{50} for cancer cell line (HuT78).

TREATMENT	GO/G1	S	G2/M
Control	30.9	26.5	35.9
(a) 5e	60.5	29.2	8.46
(b) 5e$_{Re}$	50.1	26.5	17.1
(c) 6d	57.1	30.8	8.96
(d) 6d$_{Re}$	47.3	29.5	20.4

Fig.2. Flow cytometric analysis of the cell cycle distribution of HuT78 cells exposed to compounds **5e** and **6d** (50 µM), $\mathbf{5e_{Re}}$ (10 µM), and $\mathbf{6d_{Re}}$ (2 µmol dm-3) for 24 hours. Data are presented as percentage (%) of cells in the cell cycle phase.

Ligands **5e** and **6d** and their complexes $\mathbf{5e_{Re}}$, and $\mathbf{6d_{Re}}$ were found to arrest the cell cycle of HuT78 cells, causing a significant accumulation of cells in the G0/G1 phase and a marked decrease in the number of cells in the G2/M phase (Fig. 2.). In addition, the rhenium(I) tricarbonyl complexes slightly increased ROS production and significantly reduced mitochondrial membrane potential by 50% ($\mathbf{5e_{Re}}$) and by 45% ($\mathbf{6d_{Re}}$) compared to untreated cells and cells treated with **5e** and **6d** (Fig.3.).

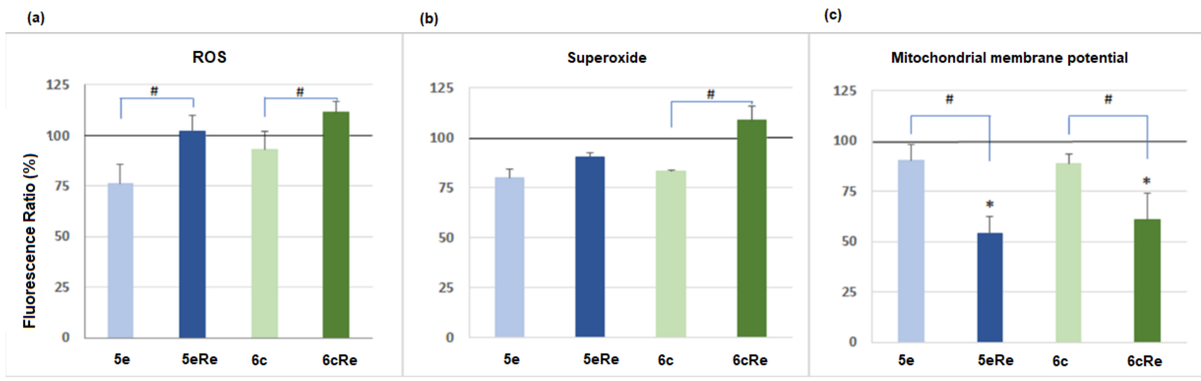


Fig.3. Data are presented as mean and standard deviation of three independent measurements in triplicate. A statistically significant *p* value is defined as $p < 0.05$ (*, #).

CONCLUSION

In summary, quinolines and coumarins were synthesised and coordinated with rhenium(I) to form complexes that exhibited markedly enhanced antiproliferative activity, particularly against T-cell lymphomas (HuT78). Among the complexes, $\mathbf{5e_{Re}}$ and $\mathbf{6d_{Re}}$ showed the strongest effect. They caused cell cycle arrest, increased ROS production and decreased mitochondrial membrane potential.

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FOUNDING

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