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SYNTHESIS AND CYTOTOXICITY OF METAL 4-METHYL-8-QUINOLINETHIOLATES

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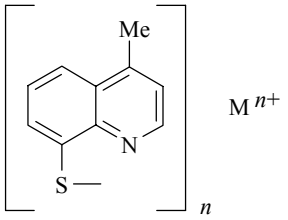
It has been shown that the introduction of a methyl group at position 4 of the quinoline ring in metal 8-quinolinethiolates brings about a significant increase in the selectivity of their cytotoxic activity. It was found that rhodium 4-methyl-8-quinolinethiolate is 46 times less toxic than the unsubstituted 8-quinolinethiolate but with comparable toxicity towards MG-22A tumor cells (LC_{50} 2 μg/ml).

Keywords: 4-methyl-8-quinolinethiolates of copper iridium, osmium, palladium, platinum, rhodium, ruthenium; synthesis, toxicity, cytotoxicity.

Many organic derivatives of copper [1], ruthenium [2], rhodium [3], and palladium [4] containing a metal to sulfur bond shown antitumor activity. We have shown that the 8-quinolinethiolates of copper, cadmium, indium, antimony, bismuth, ruthenium, rhodium, palladium, osmium, iridium, and platinum show high cytotoxicity towards HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), and B-16 (mouse melanoma) cells [5]. The highest activity to HT-1080 was shown by the iridium complex and to the MG-22A by the osmium complex. However, all of the metal 8-quinolinethiolates studied proved highly toxic towards normal NIH 3T3 mouse embryonic fibroblasts [5].

The introduction of substituents in the quinoline ring allowed us to decrease the toxicity and increase the selectivity of di(8-quinolyl) disulfides [6] and also to decrease the toxicity of the analogous metal 8-quinolineselenolates through introduction of a 4-methyl group into the quinoline ring [7]. We have therefore synthesized a series of metal 4-methyl-8-quinolinethiolates **1a-g** (Table 1) with the aim of decreasing the toxicity of the highly active complexes and studied their cytotoxicity on two tumour cell lines HT-1080 and MG-22A as well as on normal NIH 3T3 fibroblasts which served as a toxicity measure of the compounds (alternative method of determining LD_{50} [8]).



1 a M = Cu, **b** M = Ru, **c** M = Rh, **d** M = Pd, **e** M = Os, **f** M = Ir, **g** M = Pt;
a,d,g *n* = 2, **b, c, e, f** *n* = 3

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TABLE 1. Elemental Analysis and Yields of 4-Methyl-8-quinolinethiolates **1**.

Compound	Empirical formula	Found, % / Calculated, %			Yield, %
		C	H	N	
1a	$C_{20}H_{16}CuN_2S_2$	58.05 / 58.30	3.80 / 3.91	6.88 / 6.80	82
1b	$C_{30}H_{24}N_3RuS_3$	57.50 / 57.76	3.75 / 3.88	6.61 / 6.74	70
1c	$C_{30}H_{24}N_3RhS_3$	57.80 / 57.59	3.76 / 3.87	6.60 / 6.72	72
1d	$C_{20}H_{16}N_2PdS_2$	52.52 / 52.77	3.63 / 3.54	6.28 / 6.15	85
1e	$C_{30}H_{24}N_3OsS_3$	50.78 / 50.54	3.30 / 3.39	5.80 / 5.90	70
1f	$C_{30}H_{24}IrN_3S_3$	50.20 / 50.40	3.27 / 3.38	5.76 / 5.88	70
1g	$C_{20}H_{16}N_2PtS_2$	44.37 / 44.18	2.82 / 2.97	5.26 / 5.15	83

The introduction of a methyl group into position 4 of the quinoline ring decreases the toxicity of the metal 4-methyl-8-quinolinethiolates by more than one order when compared with that of the complexes with unsubstituted ligand [5]. This most significantly affects the toxicity of the iridium **1f** (LC_{50} 85 μg/ml), rhodium **1c** (LC_{50} 78 μg/ml), and palladium **1d** (LC_{50} 40 μg/ml) complexes. The decrease in toxicity of the metal complexes **1a-g** can be ordered as follows (Table 2):

$$Ru > Os > Pt > Cu > Pd > Rh > Ir$$

The most toxic complexes of ruthenium **1b** and osmium **1e** also show the greatest cytotoxicity towards tumor cells. The MG-22A cells proved to be somewhat more sensitive to the action of these compounds than the HT-1080 cells. The palladium complex **1d** has the least cytotoxicity. The platinum **1g**, rhodium **1c**, and iridium **1f** complexes caused the death of tumor cells even at a low concentration (LC_{50} ~ 2μg/ml) while the rhodium and iridium 4-methyl-8-quinolinethiolates proved to be 6-7 times less toxic than the platinum complex **1b** in relation to normal fibroblasts.

It should be noted that the rhodium complex **1c** is 46 times less toxic than the corresponding unsubstituted 8-quinolinethiolate [5] but shows comparable cytotoxicity towards MG-22A tumor cells (LC_{50} 2μg/ml). Hence we have shown that the introduction of a methyl group into the 4-position of the quinoline ring in metal 8-quinolinethiolates leads to a marked increase in the selectivity of their cytotoxic action.

TABLE 2. Cytotoxicity of 4-Methyl-8-quinolinethiolates **1***

Compound	LC_{50}, μg/ml					LD_{50}, mg/kg
	HT-1080		MG-22A		3T3	
	CV	MTT	CV	MTT	NR	
1a	11	10	2	2	22	494
1b	3	2	<1	<1	4	293
1c	6	2	2	2	78	1063
1d	44	21	15	17	40	681
1e	1	<1	<1	1	10	427
1f	7	2	2	2	85	1142
1g	4	2	2	2	12	434

* CV = crystal-violet; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NR = neutral-red.

EXPERIMENTAL

Elemental analysis was carried out using a Czechoslovakian CHN analyser.

4-Methyl-8-quinolinethiol Sodium Salt. $C_{10}H_8NSNa.H_20$ was prepared by a known method [9].

Preparation of Metal 4-Methyl-8-quinolinethiolates (see Table 1). The 4-methyl-8-quinolinethiol sodium salt (0.2 g, 0.86 mmol) was dissolved in 80% ethanol (10 ml), acetate buffer solution (pH 5, 5 ml) added, and then a solution of the appropriate metal salt in water (5 ml) was added with stirring: $CuSO_4.5H_2O$ (0.1 g, 0.4 mmol), $K_2[Ru(H_2O)Cl_5]$ (0.1 g, 0.27 mmol), $(NH_4)_3[RhCl_6].2H_2O$ (0.1 g, 0.26 mmol), $PdCl_2$ (0.1 g, 0.13 mmol), K_2OsBr_6 (0.18 g, 0.24 mmol), $(NH_4)_3[IrCl_6].H_2O$ (0.12 g, 0.25 mmol), or K_2PtCl_4 (0.16 g, 0.38 mmol). In the case of the Ru, Rh, Os, Ir, and Pt salts the reaction mixture was heated for 5 min on a water bath. The precipitated metal 4-methyl-8-quinolinethiolates were filtered off, washed with water, dried in air, and recrystallized from chloroform,

Cytotoxicity of Compounds 1a-g (Table 2), and also the acute toxicity (LD_{50}, mg/kg) were determined by methods [6, 8].

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