Chemistry of Heterocyclic Compounds, Vol. 42, No. 6, 2006

CYTOTOXICITY OF METAL 8-QUINOLINETHIOLATES

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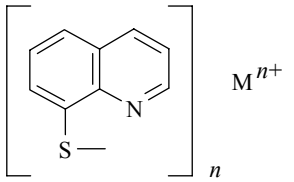
High cytotoxicity has been established for the 8-quinolinethiolates of copper, cadmium, indium, antimony, bismuth, ruthenium, rhodium, palladium, osmium, iridium, and platinum on HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), and B-16 (mouse melanoma) tumor cells. The greatest activity against HT-1080 was possessed by the iridium complex, and against MG-22A by the osmium complex. All the investigated metal 8-quinolinethiolates were highly toxic in relation to NIH 3T3 normal mouse embryo fibroblasts.

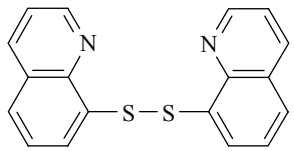
Keywords: 8-quinolinethiolates of metals, cytotoxicity.

We showed recently that 8-quinolineselenolates of metals possess high cytotoxicity on tumor cells HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), Neuro 2A (mouse neuroblastoma), and especially on B-16 mouse melanoma [1, 2]. However all these compounds, displaying high activity to tumor cells, are also toxic in relation to normal mouse embryo fibroblasta NIH 3T3 [2].

On the other hand, many organic derivatives of metals containing a metal–sulfur bond also possess antitumor activity, such as copper [3], gold [4], gallium [5], germanium [6], tin [7], rhodium [8], and palladium [9]. Consequently we decided to determine the cytotoxicity of 8-quinolinethiolates of metals in order to assess the effect of the nature of the ligand on the cytotoxicity of complexes and to compare the activity and toxicity of compounds analogous in structure containing a metal–sulfur and metal–selenium bond.



1a–k



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1 a M = Cu, **b** M = Cd, **c** M = In, **d** M = Sb, **e** M = Bi, **f** M = Ru, **g** M = Rh, **h** M = Pd, **i** M = Os, **j** M = Ir, **k** M = Pt; **1 a,b,h,k** $n = 2$, **c-g, i, j** $n = 3$

For this purpose we have synthesized a series of complexes of 8-quinolinethiol with metals **1a-k** (Table 1) by the interaction of sodium 8-quinolinethiolate with metal salts and have studied their cytotoxicity (Table 2) on three lines of tumor cells HT-1080, MG-22-A, and B-16. Action was also tested on normal mouse embryo fibroblasts NIH 3T3, which also served to determine the toxicity of compounds (alternative method of determining LD_{50}). The toxicity of the corresponding di(8-quinolinyl) disulfide was determined separately.

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TABLE 1. Results of Elemental Analysis and Yield of 8-Quinolinethiolates **1**

Compound	Empirical formula	Found, % / Calculated, %			Yield, %
		C	H	N	
1a	$C_{18}H_{12}CuN_2S_2$	56.02 / 56.30	3.27 / 3.15	7.36 / 7.29	83
1b	$C_{18}H_{12}CdN_2S_2$	49.54 / 49.26	2.61 / 2.76	6.43 / 6.34	85
1c	$C_{27}H_{18}InN_3S_3$	54.71 / 54.46	2.95 / 3.05	7.16 / 7.06	84
1d	$C_{27}H_{18}N_3S_3Sb$	53.50 / 53.83	3.15 / 3.01	6.82 / 6.98	80
1e	$C_{27}H_{18}BiN_3S_3$	47.28 / 47.02	2.51 / 2.63	6.20 / 6.09	75
1f	$C_{27}H_{18}N_3RuS_3$	55.93 / 55.74	3.06 / 3.12	7.12 / 7.22	70
1g	$C_{27}H_{18}N_3RhS_3$	55.75 / 55.57	3.05 / 3.11	7.15 / 7.20	75
1h	$C_{18}H_{12}N_2PdS_2$	50.93 / 50.61	2.92 / 2.83	6.42 / 6.56	87
1i	$C_{27}H_{18}N_3OsS_3$	48.53 / 48.34	2.61 / 2.70	6.16 / 6.26	89
1j	$C_{27}H_{18}IrN_3S_3$	48.29 / 48.19	2.64 / 2.69	6.14 / 6.24	80
1k	$C_{18}H_{12}N_2PtS_2$	42.20 / 41.92	2.20 / 2.35	5.20 / 5.43	95

TABLE 2. Cytotoxicity (LC_{50}, μg/ml) of 8-Quinolinethiolates **1***

Compound	M	n	HT-1080		MG-22A		B-16		3H3	
			CV	MTT	CV	MTT	CV	MTT	NR	LD_{50}, mg/kg
1a	Cu	2	0.3	0.3	0.3	0.3	0.6	0.7	1.4	154
1b	Cd	2	3	2	2	3	4	7	25	527
1c	In	3	0.3	0.3	0.3	0.2	0.2	0.5	<<0.3	<20
1d	Sb	3	0.3	0.3	0.3	0.2	0.2	0.3	<<0.3	<20
1e	Bi	3	0.3	0.3	0.3	0.2	0.3	0.3	<<0.3	<20
1f	Ru	3	0.8	0.4	0.2	0.3	0.2	0.2	<<0.3	<20
1g	Rh	3	1	1	2.6	2.2	1	1	1.7	175
1h	Pd	2	3	3	<1	<1	0.1	0.3	0.4	85
1i	Os	3	0.3	0.3	0.05	<0.1	0.2	0.2	<<0.3	<20
1j	Ir	3	0.06	0.1	0.2	0.2	0.2	0.3	<<0.3	<20
1k	Pt	2	0.4	0.4	0.4	0.2	0.4	0.3	0.3	83

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

The results of the investigation showed that the majority of the metal 8-quinolinethiolates display high cytotoxicity (0.2-0.5 μg/ml) towards all the tumor cell lines studied. Somewhat lower activity was possessed by the complexes of cadmium **1b** (2-7 μg/ml), rhodium **1g** (1-2.6 μg/ml), and also palladium **1h** (3 μg/ml on HT-1080). At the same time the complexes of iridium **1j** and osmium **1i** proved to be most active towards a definite type of cell, the iridium complex **1j** towards human fibrosarcoma cells HT-1080 (0.06 μg/ml according

to the CV test and 0.1 μg/ml according to MTT), the osmium complex **1i** towards mouse hepatoma MG-22A cells (0.05 μg/ml). The initial sodium 8-quinolinethiolate possessed the greatest cytotoxicity in relation to melanoma B-16 cells (0.003 μg/ml).

On comparing the cytotoxicity of analogous complexes of 8-quinolinethiol and 8-quinolineselenol [1] it was discovered that the cadmium complexes possess comparable activity on HT-1080 and MG-22A cells, and the complexes of indium and palladium on HT-1080 cells. In all the remaining cases the complexes with a metal-sulfur bond were significantly more active than their analogs with a metal-selenium bond. Disulfide **2** also displays higher cytotoxicity (0.4 μg/ml on HT-1080, 0.3 μg/ml on MG-22A and 0.025 μg/ml on B-16 according to the CV test), than the analogous di(8-quinolyl) diselenide [1].

Regrettably all the studied metal 8-quinolinethiolates displaying high cytotoxicity on tumor cells are simultaneously highly toxic towards normal NIH 3T3 cells (Table 2).

EXPERIMENTAL

Elemental analyses were carried out with the aid of a CHN Analyser (Czechoslovakia). The sodium salt of 8-quinolinethiol $C_9H_6NSNa.2H_2O$ and 8,8′-diquinolinyl disulfide (2) were obtained by the known procedure of [10].

Preparation of 8-Quinolinethiolates of Metals. The sodium salt of 8-quinolinethiol (0.2 g, 0.91 mmol) was dissolved in 80% ethanol (10 ml), acetate buffer solution (pH = 5) (5 ml) was added, and a solution of the metal salt in water (5 ml) was added with stirring as follows: $CuCl_2.2H_2O$ (0.11 g, 0.64 mmol), $Cd(OAc)_2·2H_2O$ (0.11 g, 0.41 mmol), $In_2(SO_4)_3·7H_2O$ (0.1 g, 0.16 mmol), $K(SbO)C_4H_4O_6·0.5H_2O$ (0.1 g, 0.3 mmol), $Bi(C_4H_4O_6)_3·6H_2O$ (0.2 g, 0.26 mmol), $K_2[Ru(H_2O)Cl_5]$ (0.1 g, 0.27 mmol), $(NH_4)_3[RhCl_6]·H_2O$ (0.1 g, 0.26 mmol), $PdCl_2$ (0.1 g, 0.56 mmol), K_2OsBr_6 (0.1 g, 0.13 mmol), $(NH_4)_3[IrCl_6]·H_2O$ (0.12 g, 0.25 mmol), K_2PtCl_4 (0.16 g, 0.38 mmol). In the case of the salts of Ru, Rh, Os, Ir, and Pt the reaction mixture was heated for 5 min on a water bath. The resulting solid metal 8-quinolinethiolate was filtered off, washed with water, dried in the air, and recrystallized from chloroform. Yields and results of elemental analysis of complexes **1a-k** are given in Table 1.

The Cytotoxicity of the obtained compounds **1a-k**, and of disulfide **2**, and also the acute toxicity (LD_{50}, mg/kg) were determined by the procedures of [1, 2]. Concentrations causing the death of 50% cells (LC_{50}, μg/ml) are given in Table 2.

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