

**Silver(I) complexes with quinazoline and phthalazine: synthesis,
structural characterization and evaluation of biological activities**

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Abstract

New silver(I) complexes with quinazoline (qz) and phthalazine (phtz), $[\text{Ag}(\text{NO}_3)(\text{qz})]_n$ (**1**) and $\{[\text{Ag}(\text{CH}_3\text{CN})]_2(\mu\text{-phtz})_2\}[\text{BF}_4]_2$ (**2**), have been synthesized and structurally characterized by using different spectroscopic and single crystal X-ray diffraction techniques. The obtained results revealed that the reaction of AgNO_3 with qz at room temperature in a 2 : 1 molar ratio led to the formation of the polynuclear complex **1**. However, the reaction of AgBF_4 with phtz under the same experimental conditions resulted in the formation of the dinuclear complex **2**. The solution behaviour and air/light stability of these silver(I) complexes have been investigated. The complexes **1** and **2**, alongside with the silver(I) salts used for their synthesis, were evaluated by *in vitro* antimicrobial studies against a panel of microbial strains that lead to many skin and soft tissue, respiratory, wound, and nosocomial infections. The obtained results indicate that all tested silver(I) compounds have good antibacterial activity with MIC values in the range from 1.5 to 15.6 $\mu\text{g mL}^{-1}$ against the investigated strains. On the other hand, their antifungal activity against *Candida albicans* was moderate. In order to determine the therapeutic potential of **1** and **2**, their antiproliferative effect on the normal human lung fibroblast cell line MRC5, the hemolytic effect on red blood cells and embryotoxicity on zebrafish (*Danio rerio*) have also been evaluated.

Keywords: Silver(I) complexes; Structural characterization; Antibacterial activity; Cytotoxicity; *Danio rerio*

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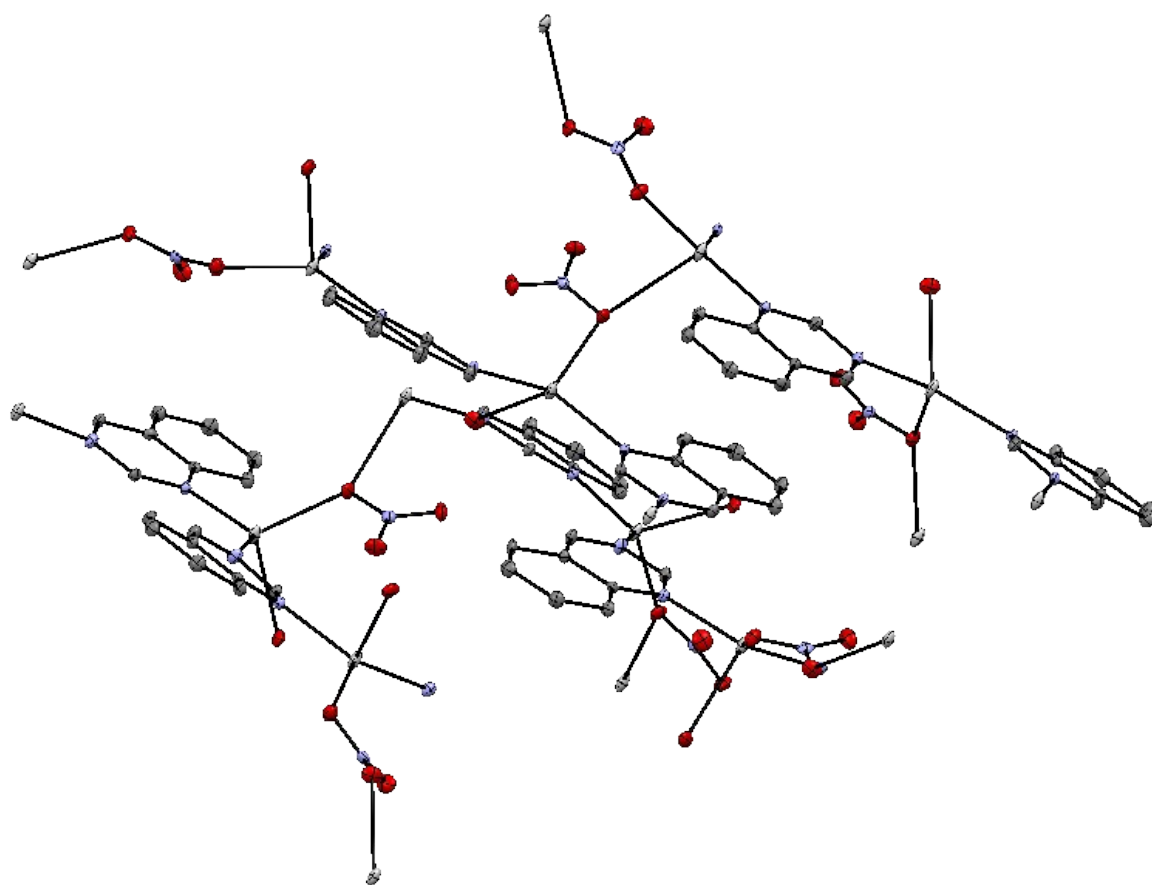


Fig. S1 An extended view of the polymeric complex **1**.

Table S1 Effect percentages for abnormal morphological characteristics evaluated in the zebrafish teratogenicity assay after 96 h exposure to silver(I) complexes and salts

Compound. concentration	Dead embryos	Teratogenic embryos	Normal embryos	Growth retardation	Notochord	Eyes	Otoliths	Pericardial edema	Yolk edema	Heart beat	Blood circulation	Hatching	Head malformation ^a	Skeletal deformities ^a
1														
15 µg mL ⁻¹	95.00	5.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	5.00	0.00	0.00
10 µg mL ⁻¹	83.33	1.67	15.00	0.00	0.00	0.00	0.00	10.00	0.00	0.00	0.00	16.67	0.00	0.00
5 µg mL ⁻¹	61.67	0.00	38.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	38.33	0.00	0.00
2.5 µg mL ⁻¹	36.67	0.00	63.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	63.33	0.00	0.00
2 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
1.5 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
1 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
0.5 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
AgNO₃														
15 µg mL ⁻¹	100.00	-	-	-	-	-	-	-	-	-	-	-	-	-
10 µg mL ⁻¹	100.00	-	-	-	-	-	-	-	-	-	-	-	-	-
5 µg mL ⁻¹	96.67	3.33	0.00	100.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	3.33	0.00	100.00
2.5 µg mL ⁻¹	80.00	3.33	16.67	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	20.00	0.00	16.67
2 µg mL ⁻¹	46.67	0.00	53.33	12.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	53.33	0.00	0.00
1.5 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
1 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
0.5 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
2														
15 µg mL ⁻¹	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10 µg mL ⁻¹	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5 µg mL ⁻¹	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.5 µg mL ⁻¹	91.67	0.00	8.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	8.33	0.00	0.00
2 µg mL ⁻¹	75.00	3.33	21.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.00	0.00	13.33
1.5 µg mL ⁻¹	65.00	0.00	35.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	35.00	0.00	0.00
1 µg mL ⁻¹	46.67	0.00	53.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	53.33	0.00	0.00
0.5 µg mL ⁻¹	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00
AgBF₄														
15 µg mL ⁻¹	100.00	-	-	-	-	-	-	-	-	-	-	-	-	-

Supplementary Material

10 µg mL ⁻¹	100.00	-	-	-	-	-	-	-	-	-	-	-	-	-
5 µg mL ⁻¹	100.00	-	-	-	-	-	-	-	-	-	-	-	-	-
2.5 µg mL ⁻¹	100.00	-	-	-	-	-	-	-	-	-	-	-	-	-
2 µg mL ⁻¹	83.33	6.67	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	16.67	40.00	40.00
1.5 µg mL ⁻¹	76.67	0.00	23.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	23.33	0.00	0.00
1 µg mL ⁻¹	68.33	0.00	31.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	31.67	0.00	0.00
0.5 µg mL ⁻¹	16.67	0.00	83.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	83.33	0.00	0.00

Abbreviation used: (hpf) hours post fertilization; (-) data not available due to 100% mortality.

^a Percentage of teratogenic effect based on all hatched embryos at the time of assessment.

Table S2 Details of the crystal structure determinations of complexes **1** and **2**

	1	2
formula	C ₈ H ₆ AgN ₃ O ₃	C ₂₀ H ₁₈ Ag ₂ B ₂ F ₈ N ₆
crystal system	orthorhombic	triclinic
space group	<i>Pna</i> 2 ₁	<i>P</i> $\bar{1}$
<i>a</i> /Å	13.678(5)	7.544(3)
<i>b</i> /Å	10.566(5)	8.109(4)
<i>c</i> /Å	12.076(5)	11.175(5)
<i>a</i> /°		110.495(12)
<i>b</i> /°		99.220(9)
<i>g</i> /°		98.036(11)
<i>V</i> /Å ³	1745.1(13)	617.7(5)
<i>Z</i>	8	1
<i>M_r</i>	300.03	731.76
<i>F</i> ₀₀₀	1168	356
<i>d_c</i> /Mg·m ⁻³	2.284	1.967
<i>μ</i> /mm ⁻¹	2.298	1.668
max., min. transmission factors	0.7464, 0.6698	0.7464, 0.6421
X-radiation, <i>λ</i> /Å	Mo- <i>Kα</i> , 0.71073	Mo- <i>Kα</i> , 0.71073
data collect. temperatur. /K	100(1)	100(1)
<i>θ</i> range /°	2.4 to 32.5	2.0 to 32.4
index ranges <i>h,k,l</i>	-19 ... 20, -15 ... 15, -18 ... 18	-11 ... 11, -12 ... 12, -16 ... 16
reflections measured	43039	15499
unique [<i>R</i> _{int}]	5992 [0.0394]	4134 [0.0225]
observed [<i>I</i> ≥ 2σ(<i>I</i>)]	5494	3860
data / restraints / parameters	5992 / 1 / 272	4134 / 0 / 192
GooF on <i>F</i> ²	1.056	1.071
<i>R</i> indices [<i>F</i> > 4σ(<i>F</i>)] <i>R</i> (<i>F</i>), <i>wR</i> (<i>F</i> ²)	0.0219, 0.0453	0.0196, 0.0460
<i>R</i> indices (all data) <i>R</i> (<i>F</i>), <i>wR</i> (<i>F</i> ²)	0.0269, 0.0474	0.0222, 0.0471
absolute structure parameter	0.45(3) ^a	
largest residual peaks /e·Å ⁻³	0.797, -0.458	0.640, -0.294

^a inversion twin, twin fractions 0.55 and 0.45.

Table S3 Lethal and teratogenic effects observed in zebrafish (*Danio rerio*) embryos at different hours post fertilization (hpf)

Category	Developmental endpoints	Exposure time (hpf)			
		24	48	72	96
Lethal effect	Egg coagulation ^a	●	●	●	●
	No somite formation	●	●	●	●
	Tail not detached	●	●	●	●
	No heart-beat		●	●	●
Teratogenic effect	Malformation of head	●	●	●	●
	Malformation of eyes ^b	●	●	●	●
	Malformation of sacculi/otoliths ^c	●	●	●	●
	Malformation of chorda	●	●	●	●
	Malformation of tail ^d	●	●	●	●
	Scoliosis	●	●	●	●
	Heart beat frequency		●	●	●
	Blood circulation		●	●	●
	Pericardial edema	●	●	●	●
	Yolk edema	●	●	●	●
	Yolk deformation	●	●	●	●
	Growth retardation ^e	●	●	●	●

^aNo clear organs structure are recognized.

^bMalformation of eyes was recorded for the retardation in eye development and abnormality in shape and size.

^cPresence of no, one or more than two otoliths per sacculus, as well as reduction and enlargement of otoliths and/or sacculi (otic vesicles).

^dTail malformation was recorded when the tail was bent, twisted or shorter than to control embryos as assessed by optical comparison.

^eGrowth retardation was recorded by comparing with the control embryos in development or size (before hatching, at 24 hpf and 48 hpf) or in a body length (after hatching, at and onwards 72 hpf) by optical comparison using a inverted microscope (CKX41; Olympus, Tokyo, Japan).