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Low-dimensional compounds containing bioactive ligands. Part XII: Synthesis, structures, spectra, *in vitro* antimicrobial and cytotoxic activities of zinc(II) complexes with halogen derivatives of quinolin-8-ol

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ABSTRACT

Seven new zinc(II) complexes, K[Zn(dClQ)$_3$]·2DMF (**1**), K[Zn(dClQ)$_3$]·2DMF·H$_2$O (**2**), [Zn(dBrQ)$_2$(H$_2$O)]$_2$·DMF·H$_2$O (**3**), [Zn(BrQ)$_2$(H$_2$O)]$_2$·H$_2$O (**4**), (HdClQ)$_2$[ZnCl$_4$]·2H$_2$O (**5**), [Zn(dClQ)$_2$(H$_2$O)$_2$]·H$_2$O (**6**) and [Zn(CQ)$_2$(H$_2$O)$_2$] (**7**) (5,7-dichloroquinolin-8-ol (dClQ), protonated 5,7-dichloroquinolin-8-ol (HdClQ), 5,7-dibromoquinolin-8-ol (dBrQ), 7-bromoquinolin-8-ol (BrQ), 5-chloro-7-iodoquinolin-8-ol (CQ)) have been prepared. All complexes were characterized by IR spectroscopy, elemental analysis and, except **7**, by X-ray structure analysis. Stability of complexes in dimethyl sulfoxide was verified by NMR spectra. Antimicrobial activity was tested against nine strains of pathogenic bacteria, five mould species and two yeast species. Cytotoxic activity was tested against colon cancer cell line HCT 116 and non-cancerous cell line CCD-18Co. While all complexes showed higher cytotoxicity than cisplatin, poor selectivity to normal cells was observed.

1. Introduction

The medical significance of metals has been known for many years, but the development of modern inorganic chemistry using metals as part of therapeutic drugs has been noticed after the discovery of cisplatin [1]. Cisplatin is one of the most commonly used anticancer drug based on metals, even though it has many side effects. Damage to kidney, liver and gastrointestinal tract is only a small group of undesirable effects [2,3], a notable problem is also the resistance of the cells to the cisplatin [4].

In addition to drugs of this type, therapeutics based on organic substances such as quinolines have been studied [5]. A variety of quinoline derivatives have usefulness as antimalarials, antibiotics, anti-inflammatory and anti-tumor drugs. An important anti-tumor effect exhibits quinolin-8-ol (8-HQ), which activity increases after binding to the complex. The most well-known substance is the tris (quinolin-8-ol) gallium complex, which attracts attention with great results, and is currently in the clinical trials stage as the KP46 drug [6,7]. 8-HQ derivatives, for example 5-chloro-7-iodoquinolin-8-ol (CQ), successful in the fight against Alzheimer's disease, cannot be omitted and entered to the second phase of clinical trials as the drug Clioquinol [8,9].

Zinc is an important cofactor essential to various cellular processes and can be a major regulator of cell metabolism. Therefore, many zinc complexes have been prepared in the last two decades, for example, with phthalocyanines [10], semicarbazones, or thiosemicarbazones [11,12], fenamates [13] but also quinolin-8-ol derivatives [14–16].

Promising biological activity results of mentioned zinc complexes and our previous work with [Zn(ClQ)$_2$(H$_2$O)$_2$] [17], motivated us to prepare new zinc complexes with halogen derivatives of 8-HQ and study their activity. Herein we describe synthesis, IR and NMR spectra and antimicrobial and cytotoxic activity of seven new Zn(II) complexes, namely K[Zn(dClQ)$_3$]·2DMF (**1**), K[Zn(dClQ)$_3$]·2DMF·H$_2$O (**2**), [Zn(dBrQ)$_2$(H$_2$O)]$_2$·DMF·H$_2$O (**3**), [Zn(BrQ)$_2$(H$_2$O)]$_2$·H$_2$O (**4**), (HdClQ)$_2$[ZnCl$_4$]·2H$_2$O (**5**), [Zn(dClQ)$_2$(H$_2$O)$_2$]·H$_2$O (**6**) and [Zn(CQ)$_2$(H$_2$O)$_2$] (**7**) (5,7-dichloroquinolin-8-ol (dClQ), protonated 5,7-dichloroquinolin-8-ol (HdClQ), 5,7-dibromoquinolin-8-ol (dBrQ), 7-bromoquinolin-8-ol (BrQ), 5-chloro-7-

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iodoquinolin-8-ol (CQ)). Moreover, crystal structures of all complexes but **7** are also described.

2. Materials and methods

2.1. Materials and chemicals

Investigated coordination compounds were prepared using halogen derivatives of quinolin-8-ol (XQ) (dClQ, 99%, dBrQ, 98%, BrQ, 97%, CQ, 95%) and zinc(II) chloride, 98% from Sigma-Aldrich, potassium hydroxide, p.a. from ITES Vranov, sodium hydroxide, p.a. from Lachema, N,N-dimethylformamide (DMF), p. a. from Alfa Aesar, ethanol, 96% from BGV Hniezdne, hydrochloric acid, 36% from Centralchem. All chemicals were used as received.

2.2. Syntheses

2.2.1. Syntheses of complexes *1–4*

Complexes **1–4** were prepared at room temperature. The appropriate amount of ligand XQ (78 mg (0.36 mmol) of dClQ (**1**); 39 mg of dClQ (**2**), 56 mg of dBrQ (**3**) and 41 mg of BrQ (**4**) what represents 0.18 mmol) was dissolved in 5 mL of DMF. While continuously stirring, KOH (60 mg), which had been previously dissolved in a small amount of water was added dropwise. Subsequently, an ethanolic solution of zinc chloride ($ZnCl_2$ in 5 mL of ethanol) was added (25 mg (0.18 mmol) for **1**, **2**; 50 mg (0.36 mmol) for **3**, **4**), thus the resulting ratio XQ:$ZnCl_2$ = 2:1 (**1**), 1:1 (**2**) and 1:2 (**3** and **4**).

The solutions were kept to crystallize at room temperature. After three (**1**), six (**2**), two (**3**) or one month (**4**), orange (**1–3**) or yellow crystals (**4**) were formed, filtered off, washed with water and dried on air.

K[Zn(dClQ)$_3$]·2DMF (**1**) – Calc. for $C_{33}H_{26}N_5O_5Cl_6ZnK$ (889.76 g·mol^{-1}): C, 44.54; H, 2.95; N, 7.87%. Found: C, 45.01; H, 2.72; N, 7.76%.

^{1}H NMR (DMSO-d$_6$): δ = 8.38 (1H, dd, J = 8.5, 1.5 Hz, H-4), 8.26 (1H, s, H-2), 7.95 (1H, s, H-9), 7.58 (1H, s, H-6), 7.56 (1H, dd, J = 8.5, 4.4 Hz, H-3), 2.89 (3H, s, CH_3), 2.73 (3H, d, J = 0.7 Hz, CH_3) ppm.

^{13}C NMR (DMSO-d$_6$): δ = 162.3 (C-9), 159.2 (C-8), 144.9 (C-2), 140.6 (C-8a), 134.3 (C-4), 129.4 (C-6), 126.0 (C-4a), 122.4 (C-3), 114.4 (C-7), 106.7 (C-5), 35.8 (C-12), 30.8 (C-11) ppm.

IR (ATR, cm^{-1}): ν(O—H) 3367(w, br), ν(C—H)$_{ar}$ 3061(w), ν(C—H)$_{al}$ 2944(vw), 2833(vw), ν(C=O) 1756(w), δ(H$_2$O) 1661(w), ν(C=C)$_{ar}$ 1556(s), 1489(m), ν(C=N)$_{ar}$ 1449(s), ν(C—C)$_{ar}$ 1395(m), 1381(s), 1358(m), δ_d(CH$_3$) 1194(w), δ(CCH)$_{ar}$ 1052(m), ν(C—O) 1113(w), ν(C$_5$—X) 969(m), ν(C$_7$—X) 881(s), γ(CCH)$_{ar}$ 804(m), 783 (s).

K[Zn(dClQ)$_3$]·2DMF·H$_2$O (**2**) – Calc. for $C_{33}H_{28}N_5O_6Cl_6ZnK$ (907.77 g·mol^{-1}): C, 43.66; H, 3.11; N, 7.71%. Found: C, 43.09; H, 2.64; N, 7.51%.

NMR spectra were not measured due to the obtained small amount of sample.

IR (ATR, cm^{-1}): ν(C—H)$_{ar}$ 3072(w), ν(C—H)$_{al}$ 2925(w), 2869(w), ν(C=O) 1748(w), ν(C=C)$_{ar}$ 1556(s), 1489(m), ν(C=N)$_{ar}$ 1448(s), ν(C—C)$_{ar}$ 1398(m), 1381(m), 1351(m), δ_d(CH$_3$) 1194(w), δ(CCH)$_{ar}$ 1052(w), ν(C—O) 1107(w), ν(C$_5$—X) 959(s), ν(C$_7$—X) 877(s), γ(CCH)$_{ar}$ 808(m), 790(m).

[Zn(dBrQ)$_2$(H$_2$O)]$_2$·DMF·H$_2$O (**3**) – Calc for $C_{39}H_{29}N_5O_8Br_8Zn_2$ (1465.72 g·mol^{-1}): C, 31.96; H, 2.00; N, 4.78%. Found: C, 31.59; H, 2.50; N, 5.06%.

^{1}H NMR (DMSO-d$_6$): δ = 8.48 (1H, dd, J = 4.5, 1.4 Hz H-2), 8.42 (1H, dd, J = 8.5, 1.5 Hz, H-4), 7.95 (1H, s, H-9), 7.93 (1H, s, H-6), 7.70 (1H, dd, J = 8.5, 4.5 Hz, H-3), 2.89 (3H, s, CH_3), 2.73 (3H, s, CH_3) ppm.

^{13}C NMR (DMSO-d$_6$): δ = 162.3 (C-9), 159.7 (C-8), 145.8 (C-2), 140.0 (C-8a), 137.4 (C-4), 134.7 (C-6), 127.3 (C-4a), 123.2 (C-3), 105.3 (C-7), 97.6 (C-5) ppm.

IR (ATR, cm^{-1}): ν(O—H) 3382(w, br), ν(C—H)$_{ar}$ 3067(w), ν(C—H)$_{al}$ 2923(w), ν(C=O) 1748(vw), δ(H$_2$O) 1660(m), 530(w), ν(C=C)$_{ar}$ 1552(m, sh), 1483(s), ν(C=N)$_{ar}$ 1452(s, br), ν(C—C)$_{ar}$ 1392 (m), 1377(s), 1358(s), δ_d(CH$_3$) 1198(w), δ(CCH)$_{ar}$ 1051(w), ν(C—O) 1112(m), ν(C$_5$—X) 949(m), ν(C$_7$—X) 877(w), γ(CCH)$_{ar}$ 860(m), 806 (m).

[Zn(BrQ)$_2$(H$_2$O)]$_2$·H$_2$O (**4**) – Calc. for $C_{36}H_{26}N_4O_7Br_4Zn_2$ (1077.05 g·mol^{-1}): C, 40.15; H, 2.43; N, 5.20%. Found: C, 39.66; H, 2.12; N, 5.07%.

^{1}H NMR (DMSO-d$_6$): δ = 8.59 (1H, d, J = 3.3 Hz, H-2), 8.43 (1H, dd, J = 8.3, 1.5 Hz, H-4), 7.65 (1H, d, J = 8.7, Hz, H-6), 7.62 (1H, dd, J = 8.3, 4.5 Hz, H-3), 6.89 (1H, d, J = 8.7 Hz, H-5) ppm.

^{13}C NMR (DMSO-d$_6$): δ = 159.3 (C-8), 145.7 (C-2), 139.6 (C-8a), 139.0 (C-4), 132.5 (C-6), 128.8 (C-4a), 121.8 (C-3), 109.3 (C-5), 106.0 (C-7) ppm.

IR (ATR, cm^{-1}): ν(O—H) 3307(w, br), ν(C—H)$_{ar}$ 3067(w), ν(C=O) 1765(vw), δ(H$_2$O) 1647(w), ν(C=C)$_{ar}$ 1563(m), 1485(s), ν(C=N)$_{ar}$ 1446(s, br), ν(C—C)$_{ar}$ 1372(s), δ(CCH)$_{ar}$ 1045(w), ν(C—O) 1110(m), ν(C$_7$—X) 915(w), γ(CCH)$_{ar}$ 856(m), 821(s).

2.2.2. Synthesis of complex *5*

Complex **5** was prepared at high temperature. 58 mg (0.27 mmol) of dClQ ligand was dissolved in 25 mL of ethanol while the system was heated to cca 60 °C. To the dissolved ligand, 18 mg (0.14 mmol) $ZnCl_2$ in 5 mL of ethanol was added. Subsequently, the mixture was acidified with three drops of 36% HCl, the mixture was boiled and slowly cooled to room temperature. After two months light yellow crystals of **5** were formed, filtered off, washed with water and dried on air.

(HdClQ)$_2$[ZnCl$_4$]·2H$_2$O (**5**) – Calc. for $C_{18}H_{16}N_2O_4Cl_8Zn$ (673.37 g·mol^{-1}): C, 32.11; H, 2.40; N, 4.16%. Found: C, 32.43; H, 2.12; N, 4.12%.

^{1}H NMR (DMSO-d$_6$): δ = 9.01 (1H, dd, J = 4.2, 1.5 Hz, H-2), 8.54 (1H, dd, J = 8.5, 1.5 Hz, H-4), 7.84 (1H, s, H-6), 7.78 (1H, dd, J = 8.5, 4.2 Hz, H-3) ppm.

^{13}C NMR (DMSO-d$_6$): δ = 149.8 (C-2), 149.1 (C-8), 138.8 (C-8a), 133.1 (C-4), 127.9 (C-6), 124.9 (C-4a), 123.2 (C-3), 119.0 (C-5), 115.7 (C-7) ppm.

IR (ATR, cm^{-1}): ν(O—H) 3390(w, br), ν(N—H) 3332(w), ν(C—H)$_{ar}$ 3050(w), 3009(w), δ(H$_2$O) 1624(m), ν(C=C)$_{ar}$ 1574(s), 1552(s), 1482(m, sh), ν(C—C)$_{ar}$ 1405(m), 1382(s), δ(COH) 1299(s), 1252 (m), δ(CCH)$_{ar}$ 1154 (m), 1045(w), ν(C—O) 1094(m), ν(C$_5$—X) 937 (m), ν(C$_7$—X) 877(s), γ(CCH)$_{ar}$ 818(s), 772(w).

2.2.3. Syntheses of complexes *6* and *7*

Complexes **6** and **7** were prepared under reflux conditions. 2 mmol of ligand XQ (428 mg of dClQ for **6**; 610 mg of CQ for **7**), 100 mL of water and 200 μL 1 M NaOH were put to round-bottom flask and heated one hour under reflux conditions. Then an additional 200 μL of NaOH was added to achieve pH 9. After another hour, 136 mg (1 mmol) $ZnCl_2$ dissolved in 50 mL of water was added. System was under reflux 24 hours. Subsequently, yellow powder products of **6** and **7** were filtered off, washed with water and dried on air. Yellow crystals of **6** were recrystallized from hot ethanol.

[Zn(dClQ)$_2$(H$_2$O)$_2$]·H$_2$O (**6**) – Calc. for $C_{18}H_{14}N_2O_5Cl_4Zn$ (545.54 g·mol^{-1}): C, 39.63; H, 2.59; N, 5.14%. Found: C, 39.98; H, 1.97; N, 5.06%.

^{1}H NMR (DMSO-d$_6$): δ = 8.56 (1H, dd, J = 4.5, 1.5 Hz, H-2), 8.50 (1H, dd, J = 8.6, 1.5 Hz, H-4), 7.70 (1H, dd, J = 8.5, 4.5 Hz, H-3), 7.69 (1H, s, H-6) ppm.

^{13}C NMR (DMSO-d_6): δ = 158.1 (C-8), 146.0 (C-2), 140.0 (C-8a), 135.1 (C-4), 129.5 (C-6), 125.7 (C-4a), 122.7 (C-3), 114.7 (C-7), 108.4 (C-5) ppm.

IR (ATR, cm^{-1}): ν(O—H) 3305(w, br), ν(C—H)$_{ar}$ 3105(w), δ(H_2O) 1647(w), 524(w), ν(C=C)$_{ar}$ 1567(m), 1493(m), ν(C=N)$_{ar}$ 1457(s), ν(C—C)$_{ar}$ 1398(s), 1380(s), 1364(s), δ(CCH)$_{ar}$ 1061(w), ν(C—O) 1114 (m), ν(C_5—X) 966(s), ν(C_7—X) 885(m), γ(CCH)$_{ar}$ 805(m), 781(m).

[Zn(CQ)$_2$(H_2O)$_2$] (**7**) – Calc. for $C_{18}H_{12}N_2O_4Cl_2I_2Zn$ (710.42 g·mol^{-1}): C, 30.43; H, 1.70; N, 3.94%. Found: C, 30.93; H, 1.87; N, 4.04%.

^{1}H NMR (DMSO-d_6): δ = 8.49 (1H, d, J = 4.5 Hz, H-2), 8.47 (1H, d, J = 8.6 Hz, H-4), 7.90 (1H, s, H-6), 7.71 (1H, dd, J = 8.6, 4.5 Hz, H-3) ppm.

^{13}C NMR (DMSO-d_6): δ = 162.0 (C-8), 145.8 (C-2), 137.6 (C-8a), 136.2 (C-6), 135.1 (C-4), 126.6 (C-4a), 123.0 (C-3), 109.7 (C-5), 80.0 (C-7) ppm.

IR (ATR, cm^{-1}): ν(O—H) 3378(w), ν(C—H)$_{ar}$ 3061(w), δ(H_2O) 1614(w), 578(m), ν(C=C)$_{ar}$ 1573(w), 1545(s), 1483(s), ν(C=N)$_{ar}$ 1440(s), ν(C—C)$_{ar}$ 1390(s), 1377(s), 1304(s), δ(CCH)$_{ar}$ 1049(w), ν(C—O) 1109(m), ν(C_5—X) 968(s), ν(C_7—X) 875(w), γ(CCH)$_{ar}$ 848 (m), 804(m).

2.3. Physical measurements

The infrared spectra of prepared compounds were recorded on a Nicolet 6700 FT-IR spectrophotometer from Thermo Scientific equipped with a diamond crystal Smart Orbit™ in the range 4000–400 cm^{-1}. To process the results, program OMNIC™ also from Thermo Scientific was used. Spectra were described in Origin2018b [18]. Elemental analyses of C, H and N were measured on CHNS Elemental Analyzer vario MICRO from Elementar Analysensysteme GmbH. 1D and 2D (gCOSY, gHSQC a gHMBC) NMR spectra were recorded at room temperature on a Varian VNMRS spectrometer operating at 599.87 MHz for ^{1}H and 150.84 MHz for ^{13}C. Spectra were recorded in DMSO-d_6 and the chemical shifts were referenced to the residual solvent signal (^{1}H NMR 2.50 ppm, ^{13}C NMR 39.5 ppm).

2.4. X-ray structure analysis

A summary of the crystal data and structure refinement for **1**–**6** is presented in Table 1. The data collection for **1**, **2** and **6** were carried out on Oxford Diffraction Xcalibur2 diffractometer equipped with Sapphire2 CCD detector; for **3** and **4** were carried out on SuperNova diffractometer from Rigaku OD equipped with Atlas2 CCD detector and data collection for sample **5** was carried out on Xcalibur Gemini diffractometer from Rigaku OD equipped with Atlas2 CCD detector. CrysAlisPro was used for data collection and also for cell refinement, data reduction and absorption correction [19]. The structures of prepared complexes were solved by SHELXT [20] and subsequent Fourier syntheses using SHELXL [21]. Anisotropic displacement parameters were refined for all non-H atoms. The H atoms of XQ molecules and DMF were placed in calculated positions and refined riding on their parent C atoms. H atoms of amine group and water molecules involved in hydrogen bonds were found in a Fourier difference map and refined by riding model. A geometric analysis was performed using SHELXL. DIAMOND [22] was used for molecular graphics. In **6** and **3** very high ADPs were observed and therefore the site disorder was performed. In **6**, Cl1 atom in position 5 on ligand dClQ was disordered over two positions, while in **3** all carbon atoms of DMF molecule were disordered over two positions. For **2**, Cl12 atom was disordered over several positions, however the partially occupied chlorine atoms were in physically unaccepted bond distances and, moreover, R-factors were not improved, therefore we have accepted the simpler model with Cl12 atom fully occupying one position.

2.5. In vitro antimicrobial assay

2.5.1. Test substances

The tested compounds were dissolved in DMSO and then diluted into nutrient liquid medium to achieve a concentration of 10%. DMSO was purchased from Acros Organics (New Jersey, USA). Resazurin was obtained from Alfa Aesar GmbH & Co. (KG, Karlsruhe, Germany). An antibiotic, doxycycline (Galenika A.D., Belgrade, Serbia), was dissolved in nutrient liquid medium, a Mueller–Hinton broth (Torlak, Belgrade, Serbia), while antimycotic, fluconazole (Pfizer Inc., USA) was dissolved in Sabouraud dextrose broth (Torlak, Belgrade, Serbia).

2.5.2. Test microorganism

The antimicrobial activity of the ligands and complexes was tested against 16 microorganisms. The experiment involved 9 strains of pathogenic bacteria, including five standard strains and four clinical isolates. Also, five mould species and two yeast species were tested. All clinical isolates were a generous gift from the Institute of Public Health, Kragujevac. The other microorganisms were provided from the collection held by the Microbiology Laboratory Faculty of Science, University of Kragujevac.

2.5.3. Suspension preparation

The bacterial suspensions were prepared by the direct colony method. The turbidity of the initial suspension was adjusted using densitometer (DEN-1, BioSan, Latvia). When adjusted to the turbidity of the 0.5 McFarland's standard [23] the bacteria suspension contains about 10^8 colony forming units (CFU)/mL and the suspension of yeast contains 10^6 CFU/mL. Ten-fold dilutions of the initial suspension were additionally prepared into sterile 0.85% saline. Bacterial inoculi were obtained from bacterial cultures incubated for 24 h at 37 °C on Mueller-Hinton agar substrate and brought up by dilution according to the 0.5 McFarland standard to approximately 10^6 CFU/ml. Suspensions of fungal spores were prepared from fresh mature (3-to 7-day-old) cultures that grew at 30 °C on a PD (Potato Dextrose) agar substrate. Spores were rinsed with sterile distilled water, used to determine turbidity spectrophotometrically at 530 nm, and then further diluted to approximately 10^6 CFU/ml according to the procedure recommended by NCCLS [24].

2.5.4. Microdilution method

Antimicrobial activity was tested by determining the minimum inhibitory concentrations (MIC) and minimum microbicidal concentration (MMC) using the microdilution plate method with resazurin [25]. The 96-well plates were prepared by dispensing 100 μL of nutrient broth, Mueller–Hinton broth for bacteria and Sabouraud dextrose broth for fungi, into each well. A 100 μL aliquot from the stock solution of the tested compound (with a concentration of 2000 μg/mL) was added into the first row of the plate. Then, two-fold serial dilutions were performed by using a multichannel pipette. The obtained concentration range was from 1000 to 7.8 μg/mL. The method is described in detail in the reported paper [26].

Doxycycline and fluconazole were used as a positive control. 10% DMSO (as solvent control test) was recorded not to inhibit the growth of microorganisms. Each test included growth control and sterility control. All the tests were performed in duplicate and the MICs were constant.

Minimum bactericidal and fungicidal concentrations were determined by plating 10 μL of samples from wells where no indicator color change, or no mycelia growth was recorded, on nutrient agar medium. At the end of the incubation period the lowest concentration with no growth (no colony) was defined as the minimum microbicidal concentration.

Table 1
Crystal data and structure refinement of **1–6.**

	1	**2**	**3**
Empirical formula	$C_{33}H_{26}N_5O_5Cl_6KZn$	$C_{33}H_{28}N_5O_6Cl_6KZn$	$C_{39}H_{29}N_5O_8Br_8Zn_2$
Formula weight [g mol^{-1}]	889.76	907.77	1465.69
T [K]	173(2)	173(2)	173(2)
λ [Å]	0.71073	0.71073	0.71073
Crystal system	triclinic	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Unit cell dimensions [Å, °]	a = 9.8021(4)	a = 9.9513(4)	a = 10.1200(3)
	b = 13.4109(7)	b = 11.7490(7)	b = 11.0756(5)
	c = 15.2014(10)	c = 17.1919(10)	c = 21.0222(9)
	α = 73.158(6)	α = 70.159(6)	α = 104.632(4)
	β = 73.978(4)	β = 80.442(4)	β = 93.844(3)
	γ = 74.768(4)	γ = 79.560(4)	γ = 94.390(3)
V [Å^3]	1801.65(12)	1847.51(19)	2264.04(16)
Z; calculated density [g·cm^{-3}]	2; 1.640	2; 1.632	2; 2.150
Absorption coefficient [mm^{-1}]	1.292	1.263	8.175
F(0 0 0)	900	920	1404
Crystal shape, colour	prism, orange	prism, orange	plate, orange
Crystal size [mm^3]	0.472 × 0.414 × 0.223	0.541 × 0.247 × 0.182	0.256 × 0.184 × 0.050
θ range for data collection [°]	2.945–26.500	2.983–26.500	2.980–26.500
Index ranges	$-11 \le h \le 12$, $-16 \le k \le 16$,	$-12 \le h \le 11$, $-14 \le k \le 14$,	$-12 \le h \le 12$, $-13 \le k \le 12$,
	$-18 \le l \le 19$	$-13 \le l \le 21$	$-26 \le l \le 26$
Reflections collected/independent	14364/7441	13376/7643	17585/9355
Data/restraints/parameters	7441/0/464	7643/0/473	9355/0/561
Goodness-of-fit on F^2	1.050	1.125	1.013
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0391,	$R1$ = 0.0762,	$R1$ = 0.0418,
	$wR2$ = 0.0834	$wR2$ = 0.2107	$wR2$ = 0.0652
R indices (all data)	$R1$ = 0.0529,	$R1$ = 0.0969,	$R1$ = 0.0798,
	$wR2$ = 0.0901	$wR2$ = 0.2107	$wR2$ = 0.0759
Largest diff. peak and hole [e Å^{-3}]	1.401 and −0.579	1.670 and −0.876	1.010 and −0.760
	4	**5**	**6**
Empirical formula	$C_{36}H_{26}N_4O_7Br_4Zn_2$	$C_{18}H_{16}N_2O_4Cl_8Zn$	$C_{18}H_{14}N_2O_5Cl_4Zn$
Formula weight [g mol^{-1}]	1076.99	673.30	545.48
T [K]	95(2)	173(2)	293(2)
λ [Å]	1.54184	0.71073	0.71073
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	Pc	$P2_12_12_1$	$C2/c$
Unit cell dimensions [Å, °]	a = 9.18090(10)	a = 10.4351(4)	a = 8.0422(10)
	b = 9.85220(10)	b = 13.2439(6)	b = 27.258(2)
	c = 19.9248(2)	c = 17.8809(8)	c = 10.0958(9)
	β = 91.6980(10)		β = 112.001(13)
V [Å^3]	1801.45(3)	2471.17(18)	2052.0(4)
Z; calculated density [g·cm^{-3}]	2; 1.985	4; 1.810	4; 1.766
Absorption coefficient [mm^{-1}]	7.311	1.889	1.752
F(0 0 0)	1052	1344	1096
Crystal shape, colour	block, yellow	prism, yellow	needle, yellow
Crystal size [mm^3]	0.153 × 0.144 × 0.110	0.492 × 0.380 × 0.200	0.458 × 0.066 × 0.02
θ range for data collection [°]	4.440–76.415	3.000–26.500	3.535–25.997
Index ranges	$-11 \le h \le 11$, $-12 \le k \le 12$, $-25 \le l \le 25$	$-13 \le h \le 9$, $-15 \le k \le 16$, $-22 \le l \le 13$	$-8 \le h \le 9$, $-33 \le k \le 32$, $-12 \le l \le 8$
Reflections collected/independent	29354/7365	10775/ 5093	4194/ 2024
Data/restraints/parameters	7365/2/479	5093/0/301	2024/0/154
Goodness-of-fit on F^2	1.094	0.982	1.054
Final R indices [I>2$\sigma(I)$]	$R1$ = 0.0351,	$R1$ = 0.0288,	$R1$ = 0.0363,
	$wR2$ = 0.0947	$wR2$ = 0.0581	$wR2$ = 0.0733
R indices (all data)	$R1$ = 0.0360,	$R1$ = 0.0331,	$R1$ = 0.0573,
	$wR2$ = 0.0983	$wR2$ = 0.0602	$wR2$ = 0.0817
Largest diff. peak and hole [e Å^{-3}]	1.033 and −0.448	0.418 and −0.455	0.377 and −0.404

2.6. Cytotoxic activity

For study of cytotoxicity, complexes were completely dissolved in DMSO (Sigma-Aldrich) at a concentration of 10 mM. Then complexes were diluted to different working concentrations in the range 1 μM–100 μM, so the final concentration of DMSO in cell culture medium never exceeded 0.5%.

2.6.1. Cell cultures

Human colorectal carcinoma cell line HCT 116 and human colon normal cell line CCD-18Co were purchased from the American Type Culture Collection (ATCC, Rockville, MD, USA). HCT 116 cells were grown in McCoy's 5A medium (Sigma-Aldrich) and CCD-18Co cells in MEM medium (Biosera, Boussens, France) supplemented with 10% foetal bovine serum (FBS; Biosera) and antibiotics (1% Antibiotic-Antimycotic 100× and 50 μg ml^{-1} gentamicin; Biosera) at 37 °C, 95% humidity and 5% CO_2.

2.6.2. MTT assay

The MTT assays were performed as previously reported by Kleban et al. [27] to evaluate changes in the metabolic activity of cells that occurred as the consequence of complexes treatment. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) (Sigma-Aldrich) was added to the cells in a 96-well plate (TPP, Trasadingen, Switzerland) (final concentration 0.5 mg ml^{-1}) 48 and 72 h after complexes treatment. The reaction was stopped

after 4 h incubation at 37 °C and the insoluble formazan was dissolved by addition of sodium dodecyl sulfate (SDS) at a final concentration of 3.3%. The absorbance (λ = 584 nm) was measured using a BMG FLUOstar Optima (BMG Labtechnologies GmbH, Offenburg, Germany). The results were evaluated as percentages of the absorbance of the untreated control. Experiments were performed in triplicates to obtain mean values. IC_{50} values were extrapolated from a sigmoidal fit to the metabolic activity data using Origin2018b [18].

3. Results and discussion

3.1. Syntheses

The preparation of the compounds **1**–**4**, **6** and **7** was performed in two different ways – at room temperature and under reflux (preparation of complex **5** will be discussed separately). Based on our knowledge, the halogen derivatives of quinolin-8-ol are not very well soluble in polar protic solvents, therefore DMF was used as a solvent of ligands in syntheses at rT. In syntheses under reflux, water was used as a common solvent, since the ligands are completely or partially dissolved at boiling point. Gradual formation of the product causes shift of the reactions balance, hence more of the ligand dissolves up to its complete dissolution. With the aim to deprotonate the hydroxyl group and thereby increase the chance of the ligands coordination to the zinc atom a base that shifted the pH of the solution to alkaline was used.

The preparation of **5** was carried out at high temperature, too. Contrary to previous syntheses, few drops of HCl were added to create acidic pH to increase the probability of the pyridine nitrogen atom protonation. The aim was to obtain compound with the analogous composition as in our previous work with palladium, $(HdClQ)_2[PdCl_4]$ [28].

3.2. Infrared spectroscopy

All prepared complexes were characterized by an infrared spectroscopy (Figs. S1 and S2). The presence of XQ ligands is proven by weak bands of stretching ν(C—H)$_{ar}$ vibrations observed in the range 3009–3105 cm^{-1} and by characteristic ν(C$_7$—X) bands observed at 830–915 cm^{-1} and ν(C$_5$—X) bands observed at 937–969 cm^{-1} (except **4**).

Five complexes (**1**, **3**, **4**, **6** and **7**) contain coordinated or uncoordinated water molecules that prove in spectra as a broad band in the range of 3382–3305 cm^{-1} [29]. Based on the structure analysis results, DMF molecules are present in **1**, **2** and **3**, and manifest themselves in IR spectra as weak bands of stretching ν(C—H)$_{al}$ vibrations between 2833 and 2944 cm^{-1}. These vibrations are very weak in **1** what could be caused by an overlap of a broad band of hydroxyl group involved in hydrogen bonds. Characteristic band of DMF is also at 1194 (**1** and **2**) and 1198 cm^{-1} (**3**) which corresponds to deformation vibration of methyl groups. In **5**, N- and O-protonated uncoordinated molecules of HdClQ form cationic part of its structure what is expressed in several differences in comparison with the spectra of other complexes: (1) due to the protonated nitrogen atom, stretching ν(N—H) vibration is observed at 3390 cm^{-1}; (2) contrary to all other compounds, ν(C=N)$_{ar}$ vibration is not present; (3) due to the protonated oxygen atom, two bands at 1299 and 1252 cm^{-1} occur which can be assigned to ν(COH) vibrations.

All other absorption bands in **1**–**7** are at characteristic wavenumbers very similar to those described in pure ligands [30,31].

3.3. X-ray structure analysis

Complexes **1**–**6** were prepared in crystalline form suitable for monocrystal X-ray structure analysis. Complexes **1** and **2** are ionic compounds with similar molecular structure, complex **2** contains one more water molecule, so we discuss their common properties for complex **1** preferentially (corresponding geometrical parameters for **2** are shown in parentheses). Complex **1** (Fig. 1) crystallizes in the triclinic space group $P\bar{1}$. The Zn(II) atom is hexa-coordinated by three N and three O donor atoms from three molecules of dClQ ligand forming a distorted octahedral geometry creating *fac* isomer. Bite chelate angles are in the range 78.58(8)–79.33(8)° (77.24(19)–79.7(2)°) and angles between coordinated molecules span from 85.65(7) to 100.43(8)° (87.7(2)–102.6(2)°) (Tables S1 and S2) (Fig. S3). The remaining angles range from 164.13(8) to 173.30(8)° (161.33(19)–169.4(2)°). The average Zn—O bond length is 2.078(2) Å (2.081(5) Å), while the average Zn—N bond length is longer (2.158(2) for **1** and 2.176(6) Å for **2**) due to the higher covalent radius of nitrogen. Such bond length difference is usual, e.g. in $[Zn(bpy)(NQ)_2]$ (bpy = 2,2′-bipyridine; NQ = 5-nitroquinolin-8-ol) the average Zn—O and Zn—N bond lengths from NQ are 2.100 and 2.148 Å, respectively [32]. Remaining geometrical parameters of the ligand are similar to those described in literature [33]. Negative charge of the complex anion in **1** is counterbalanced by uncoordinated potassium cation. In addition, the complex contains two solvated DMF molecules.

In the structure of **1**, interesting orientation of oxygen atoms to K^+ ion is observed. Uncoordinated potassium cation interacts with electronegative oxygen atoms from three dClQ ligands and two molecules of solvated DMF (Fig. 1c). Four interatomic K1···O distances are from range 2.641(2)–2.723(2) Å, while the fifth K1···O3 distance is longer (2.901(2) Å).

In the structure of **2**, distances between oxygen atoms and potassium ion are very similar as in **1** (2.641(6)–2.881(5) Å, additional distance K1···O6 from crystal water molecule is 2.694(7) Å).

Hydrogen bonds of C—H···Cl and C—H···O types for **1** and of C—H···Cl, C—H···O and O—H···O types for **2** along with π–π interaction between Cg-py(N1)···Cg-py(N1)^{v} for **1** and between Cg-py(N2)···Cg-ph(C27)^{vi} for **2** stabilize the structures (v: $2-x$, $1-y$, $1-z$; vi: $-x$, $1-y$, $1-z$) (Table S3). Thus, the 2D structure in the *ab* plane is created for **1**, while the structure of **2** propagates in all directions forming 3D net.

Complexes **3** with dBrQ (Fig. 2) and **4** with BrQ (Fig. 3) have very similar molecular structures, complex **3** contains one additional DMF molecule, so we discuss them together. Complex **3** crystallizes in the triclinic space group $P\bar{1}$, complex **4** in the monoclinic space group *Pc*. In both structures there are two independent Zn(II) atoms. Metal centers are penta-coordinated by two dBrQ or BrQ molecules, the fifth place is occupied by water molecule. The shape of coordination polyhedra is distorted between trigonal bipyramid and tetragonal pyramid as confirmed by τ parameters [34]. The distortion of the coordination polyhedra is confirmed also by the result from continuous shape measures of donor atoms positions relative to the vertices of an ideal trigonal bipyramid and tetragonal pyramid (CShM) [35] (Table 2). The structures of **3** and **4** are supplemented by one uncoordinated water molecule, DMF molecule in **3** is also present. Selected geometrical parameters for both complexes are given in Tables S4 and S5, all other geometrical parameters are very similar to those described in pure ligands [36,37].

In both complexes there are plenty of intermolecular interactions (Tables S6 and S7). There are strong hydrogen bonds of O—H···O type in **3** (Fig. 4). All but one tie all molecules in the asymmetric unit together creating packets in which two complexes (Zn1 and Zn2) are bundled to a dimer to which the DMF

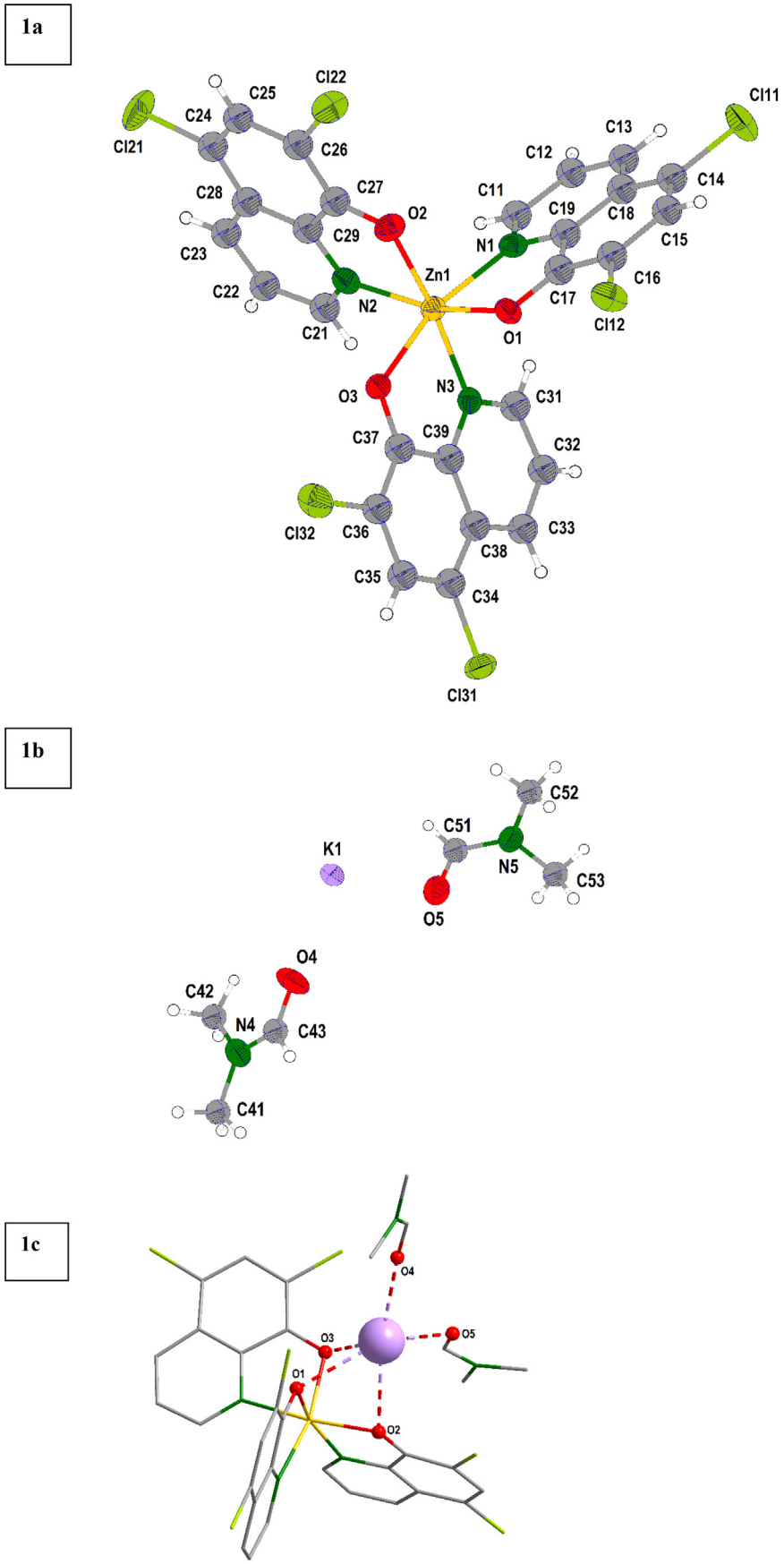

Fig. 1. Molecular structure of **1** with atom numbering scheme of complex anion (1a) and cationic part (1b). Displacement ellipsoids are drawn at 50% probability. 1c: Crystal structure of **1** with possible K1···O interactions.

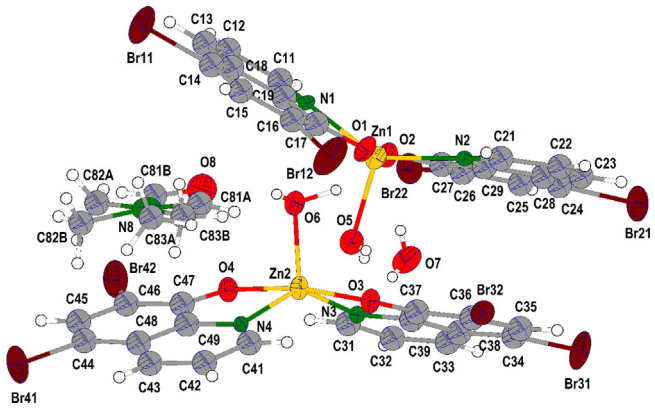

Fig. 2. Molecular structure with atom numbering scheme of **3**. Displacement ellipsoids are drawn at 50% probability.

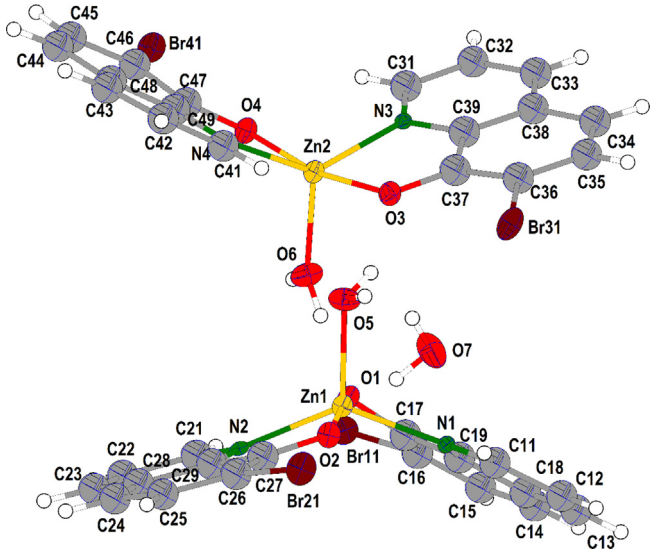

Fig. 3. Molecular structure with atom numbering scheme of **4**. Displacement ellipsoids are drawn at 50% probability.

Table 2
τ parameters and the CShM values for TBP and TP for **3** and **4**.

Compound/Zn atom	τ parameter	CShM TBP	CShM TEP
3/Zn1	0.508	1.945	2.014
3/Zn2	0.538	1.676	2.079
4/Zn1	0.536	1.623	2.128
4/Zn2	0.545	1.509	2.097

TBP = trigonal bipyramid, TP = tetragonal pyramid.

molecule is linked by O6—H2O6···O8 hydrogen bond. The only one hydrogen bond (O7—H1O7···O4^{i}, i: $x-1, y, z$) binds such packets together creating infinite chains in the *a* direction. The π–π interactions propagate the crystal structure in two other directions (Fig. 5). There is a similar topology of intermolecular interaction in the structure of **4**. The only difference is in directions in which the π–π interactions and hydrogen bonds propagate. While the π–π interactions dominate in the *ac* plane, the hydrogen bonds propagate in *b* direction.

The structure of the third ionic complex, **5**, is similar to that found in $(HdClQ)_2[PdCl_4]$ [28]. The Zn(II) atom in **5** is not coordinated by molecules of dClQ ligand, but is surrounded by four chlorido ligands (Fig. 6) forming slightly distorted tetrahedral geometry (Cl-Zn-Cl angles are in the range 107.05(3)–113.77(4)° (Table S8)). Negative charge of $[ZnCl_4]^{2-}$ anion is counterbalanced by two on nitrogen atoms protonated HdClQ molecules. All geometrical parameters of these cationic molecules are very similar to those described in [28] and in pure ligand [30].

Three-dimensional structure of **5** is formed by hydrogen bonds on which hydrogen atoms from HdClQ cations as well as from water molecules participate. Two cations are connected through hydrogen bonds of N—H···O and O—H···O types, while complex anion participates on crystal structure propagation through hydrogen bonds of O—H···Cl type (Table S9). Thus, layered structure parallel with the *ab* plane is created. The layers are further connected by π–π interactions between aromatic rings (Fig. 7).

Molecular complex **6**, which also contains dClQ ligand, crystallizes in the monoclinic space group *C*2/*c*. Zn(II) atom sits on the center of symmetry, therefore only half of the molecule is independent. The metal center is chelated by two dClQ ligands and the other two coordination places in *trans* positions occupy two aqua ligands, forming a distorted octahedral geometry. Moreover, one uncoordinated water molecule with O3 atom on twofold axis is present (Fig. 8). Bite angle O1—Zn1—N1 is 79.46(7)°, angles O1^{ii}—Zn1—N1 and O1—Zn1—N1^{ii} (ii: $1/2-x, 1/2-y, 1-z$) between coordinated molecules are 100.53(7) and 100.54(7)°, respectively (Table S10). These geometrical parameters are similar to those found in $\{[Zn(CQ)_2(H_2O)_2]_2[Zn(CQ)_2(H_2O)]_3\}\cdot 5DMF\cdot 2H_2O$ [38] or in $[Zn(dBrQ)_2(H_2O)_2]$ [15].

Due to hydrogen bonds (Table S11) and π–π interactions between pyridine and phenol rings the molecules of **6** are connected to a 3D net (Fig. 9).

3.4. Antimicrobial activity

The results of *in vitro* antimicrobial activity of complexes (**1**, **2**, **4**–**7**) against 16 strains of bacteria and fungi, with control results were determined by microdilution method. The results are presented in Tables 3 and 4. Antimicrobial activity of complex **3** was not measured due to the technical reasons. The results of antimicrobial activity of ligands for most of the tested microorganisms are shown in the previous manuscripts [39–41].

If we observe activity of different complexes in general, it can be concluded that the complexes **2** and **5** exhibited the same or better activity than the positive controls. These complexes also had better activity than their ligands, whereas this was not the case with the other complexes [40,41]. MIC values were obtained from <1.95 mg/mL to 1000 mg/mL. It was observed that the growth of microorganisms was not inhibited by 10% DMSO. There is no difference in sensitivity between G− and G+ bacteria according to the tested complexes.

The antifungal activity of all the tested complexes was better than the antibacterial activity, with some exceptions. All complexes had better antifungal activity than positive control (fluconazole).

The highest resistance among bacteria was demonstrated by *Pseudomonas aeruginosa*, clinical and standard strain, while, among fungi, by *Mucor mucedo* and *Aspergillus flavus* ATCC 9170.

It was noticed that 5-chloro-quinolin-8-ol derivatives are good antimicrobial agents [42]. Among metal complexes, zinc complex $[Zn(ClQ)_2(H_2O)_2]$ and cloxyquin (ClQ) as a ligand, were tested and they showed a significant antimicrobial activity. The complex showed the activity on fungi equal to the activity of the ligand and control [39], which is in accordance with our findings about complexes **2** and **5**.

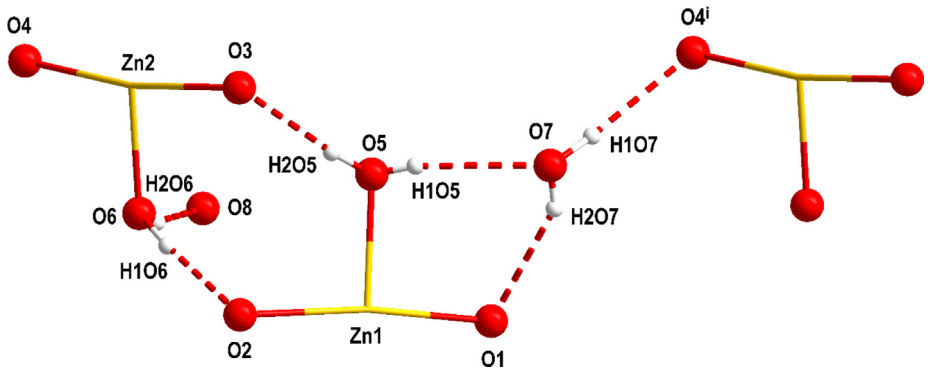

Fig. 4. Hydrogen bonds in **3** (dashed lines). Because of clarity, dBrQ ligands and DMF molecule are represented only by oxygen atoms. Symmetry code: (i) = $x - 1, y, z$.

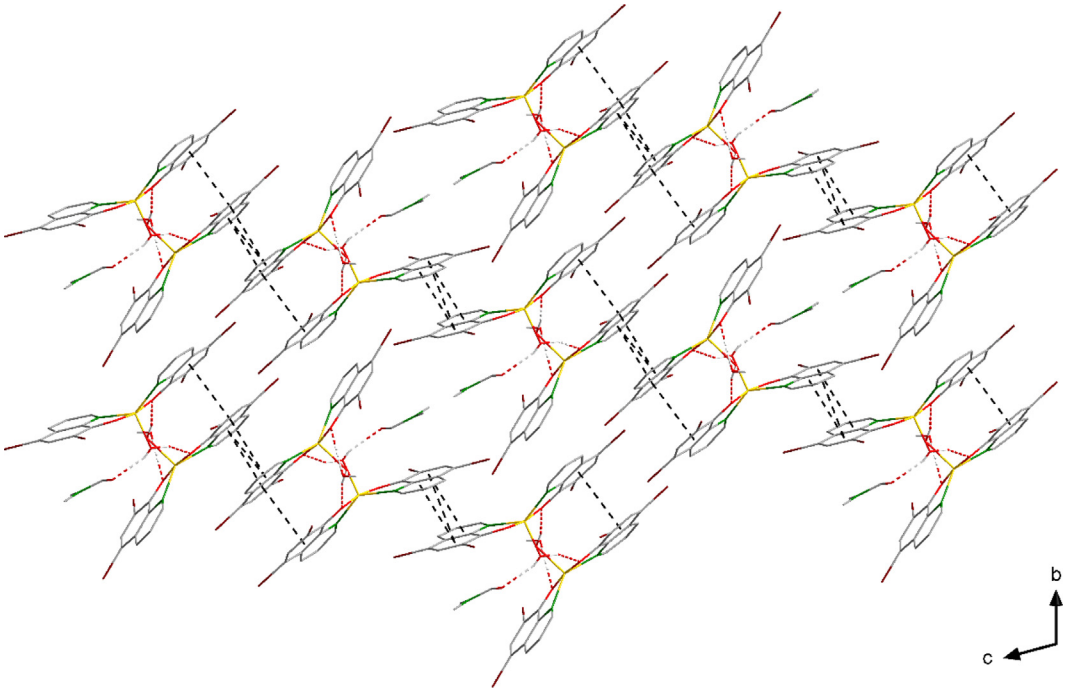

Fig. 5. π–π interactions (black dashed lines) in **3** which tie chains formed by hydrogen bonds (red dashed lines) into 3D structure. (Color online.)

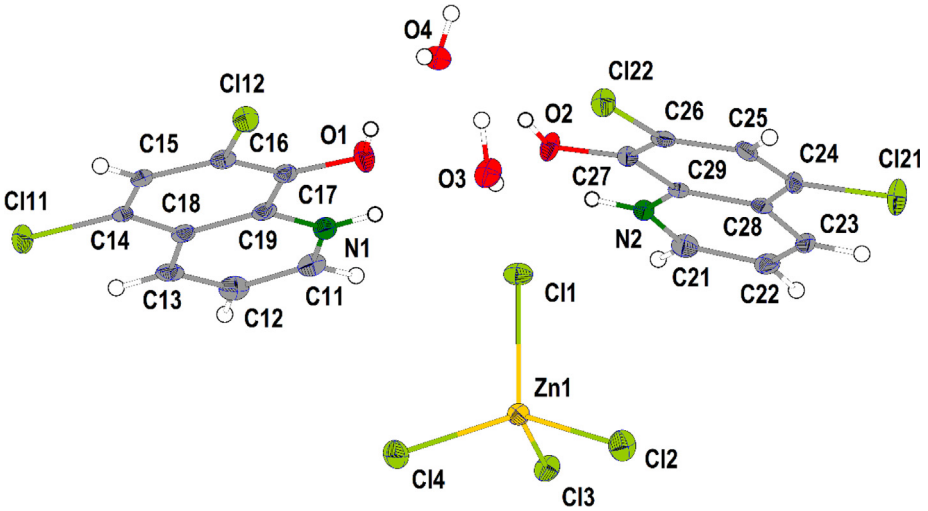

Fig. 6. Molecular structure with atom numbering scheme of **5**. Displacement ellipsoids are drawn at 50% probability.

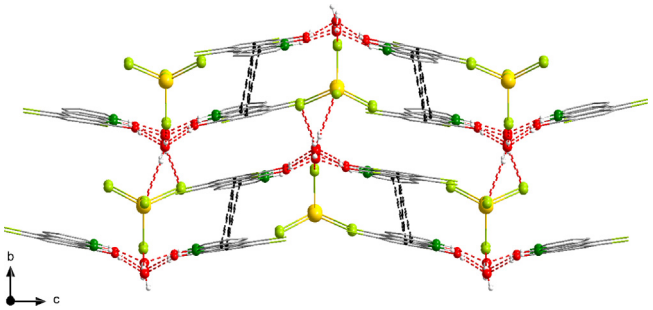

Fig. 7. Hydrogen bonds (red dashed lines) and π–π interactions (black dashed lines) creating a 3D structure of **5**. (Color online.)

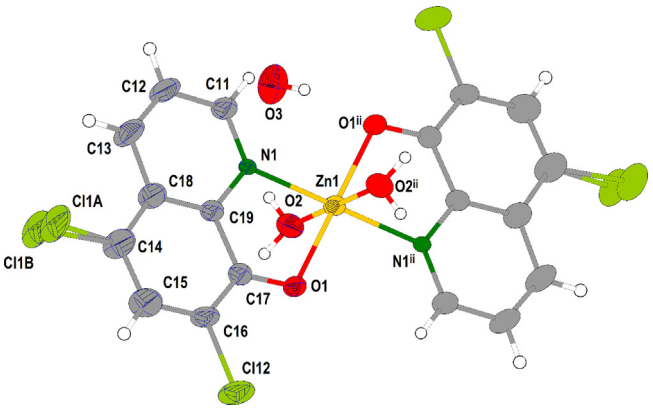

Fig. 8. Molecular structure with atom numbering scheme of **6**. Displacement ellipsoids are drawn at 50% probability. Symmetry code: (ii): 1/2 − *x*, 1/2 − *y*, 1 − *z*.

3.5. Cytotoxic activity

Cytotoxicity of the complexes **1**–**7** at several different concentrations (from 1 to 100 μM) was analyzed using MTT assays evaluated both 48 h and 72 h after their addition to colon cancer cell line HCT 116 and non-cancerous colon cell line CCD-18Co. Our results undoubtedly showed significant increase of cytotoxicity of all tested complexes against cancer cells, as compared to control group of untreated cells. As can be seen from the IC_{50} values (Table 5), all of the new zinc complexes showed significant cytotoxic activity against colon cancer cell line HCT 116. Higher cytotoxic effect was observed 48 h after complexes addition, IC_{50} values of the complexes are in the range from 1.7 to 7.1 μM while IC_{50} value of cisplatin is a lot of higher, 13.6 μM [39]. Unfortunately, selectivity of prepared complexes was not confirmed. After 48 h of complexes treatment, IC_{50} values obtained from non-cancerous colon cell line are in the range from 0.7 to 2.1 μM.

4. Conclusion

With the aim to continue in our previous work on biologically active 3*d* metal complexes with quinolin-8-ol derivatives, seven new zinc(II) complexes, $K[Zn(dClQ)_3]\cdot 2DMF$ (**1**), $K[Zn(dClQ)_3]\cdot 2DMF\cdot H_2O$ (**2**), $[Zn(dBrQ)_2(H_2O)]_2\cdot DMF\cdot H_2O$ (**3**), $[Zn(BrQ)_2(H_2O)]_2\cdot H_2O$ (**4**), $(HdClQ)_2[ZnCl_4]\cdot 2H_2O$ (**5**), $[Zn(dClQ)_2(H_2O)_2]\cdot H_2O$ (**6**) and $[Zn(CQ)_2(H_2O)_2]$ (**7**) (5,7-dichloroquinolin-8-ol (dClQ), protonated 5,7-dichloroquinolin-8-ol (HdClQ), 5,7-dibromoquinolin-8-ol (dBrQ), 7-bromoquinolin-8-ol (BrQ), 5-chloro-7-iodoquinolin-8-ol (CQ)) have been prepared. The complexes were characterized by elemental analysis, IR and NMR spectroscopies and six of them by X-ray structure analysis. Complexes **1**, **2** and **5** are ionic compounds, complexes **1** and **2** have similar molecular structure forming distorted octahedral geometry. Structure of complex **5** is different, the Zn(II) atom is not coordinated by molecules of dClQ ligand, but forming $[ZnCl_4]^{2-}$ anion and protonated HdClQ molecules represent cationic part. Complexes **3**, **4** and **6** are molecular compounds, in complexes **3** and **4** are two independent pentacoordinated Zn(II) atoms.

The results of *in vitro* antimicrobial activity have shown that complexes **2** and **5** had the same or better activity than the positive control and ligand. The antifungal activity of all the tested com-

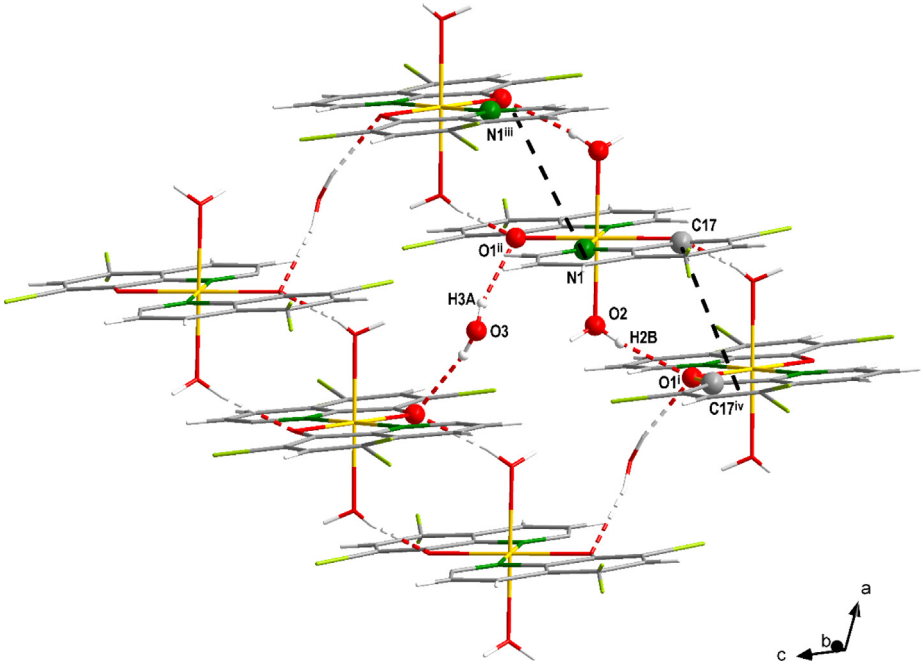

Fig. 9. Part of the 3D structure of **6** formed by hydrogen bonds (red dashed lines) and π–π interactions (black dashed lines). Symmetry codes: (i): −*x*, *y*, 1/2 − *z*; (ii): 1/2 − *x*, 1/2 − *y*, 1 − *z*; (iii): 1 − *x*, *y*, 3/2 − *z*; (iv): 1 − *x*, *y*, 1/2 − *z*. (Color online.)

Table 3
Antimicrobial activity of the tested complexes **1**, **2**, **4** and **5.**

Species/Tested compounds (μg/mL)	**1**		**2**		**4**		**5**	
	MIC	MMC	MIC	MMC	MIC	MMC	MIC	MMC
Bacillus subtilis ATCC 6633	1000	1000	<1.96	<1.96	250	500	<1.96	<1.96
Staphylococcus aureus ATCC 25923	500	500	<1.96	<1.96	125	125	<1.96	<1.96
Staphylococcus aureus	500	500	<1.96	<1.96	125	125	<1.96	<1.96
Pseudomonas aeruginosa ATCC 27853	1000	>1000	125	500	1000	1000	62.5	125
Pseudomonas aeruginosa	1000	>1000	125	250	500	1000	62.5	125
Escherichia coli	500	1000	<1.96	<1.96	125	125	<1.96	<1.96
Escherichia coli ATCC 25922	500	500	<1.96	<1.96	125	125	<1.96	<1.96
Proteus mirabilis ATCC 12453	1000	1000	15.76	15.76	500	500	15.78	15.78
Salmonella enterica	1000	1000	<1.96	<1.96	250	250	<1.96	<1.96
Candida albicans ATCC 10231	<1.96	<1.96	<1.96	<1.96	7.81	31.25	<1.96	<1.96
Saccharomyces boulardii	<1.96	<1.96	<1.96	15.78	<1.96	15.78	<1.96	<1.96
Mucor mucedo	1000	1000	<1.96	250	1000	1000	15.78	1000
Trichoderma viridae ATCC 13233	<1.96	15.78	<1.96	<1.96	<1.96	<1.96	<1.96	<1.96
Aspergillus flavus ATCC 9170	1000	1000	<1.96	<1.96	1000	1000	500	1000
Aspergillus fumigatus ATCC 1022	<1.96	<1.96	<1.96	<1.96	1000	1000	<1.96	<1.96
Aspergillus niger ATCC 16404	<1.96	<1.96	<1.96	<1.96	15.78	31.25	<1.96	<1.96

Table 4
Antimicrobial activity of the tested complexes **6** and **7** and positive controls.

Species/Tested compounds (μg/mL)	**6**		**7**		Doxycycline		Fluconazole	
	MIC	MMC	MIC	MMC	MIC	MMC	MIC	MMC
Bacillus subtilis ATCC 6633	31.25	31.25	15.78	15.78	1.953	31.25	–	–
Staphylococcus aureus ATCC 25923	31.25	31.25	<1.96	<1.96	0.224	3.75	–	–
Staphylococcus aureus	31.25	31.25	<1.96	<1.96	0.45	7.81	–	–
Pseudomonas aeruginosa ATCC 27853	1000	>1000	1000	>1000	62.5	125	–	–
Pseudomonas aeruginosa	1000	>1000	250	>1000	250	1000	–	–
Escherichia coli	31.25	31.25	<1.96	<1.96	7.81	15.625	–	–
Escherichia coli ATCC 25922	31.25	31.25	<1.96	<1.96	15.63	31.25	–	–
Proteus mirabilis ATCC 12453	62.5	125	125	125	15.63	62.5	–	–
Salmonella enterica	31.25	31.25	15.78	15.78	15.63	31.25	–	–
Candida albicans ATCC 10231	<1.96	<1.96	<1.96	<1.96	–	–	31.25	62.5
Saccharomyces boulardii	<1.96	<1.96	<1.96	<1.96	–	–	7.81	31.25
Mucor mucedo	1000	1000	<1.96	250	–	–	250	250
Trichoderma viridae ATCC 13233	<1.96	31.25	<1.96	<1.96	–	–	500	1000
Aspergillus flavus ATCC 9170	1000	>1000	31.25	250	–	–	500	500
Aspergillus fumigatus ATCC 1022	<1.96	<1.96	<1.96	<1.96	–	–	1000	1000
Aspergillus niger ATCC 16404	<1.96	<1.96	<1.96	<1.96	–	–	1000	1000

Table 5
IC_{50} values of prepared complexes.

IC_{50} [μM]								
Cell lines	Time [h]	**1**	**2**	**3**	**4**	**5**	**6**	**7**
HCT 116	48	2.1	1.8	4.8	1.7	2.8	3.1	7.1
	72	3.3	3.75	6.95	2.1	4.4	4.5	8.95
CCD-18Co	48	1.2	1.1	2.1	0.9	0.9	0.7	1.7
	72	0.9	0.9	1.05	0.6	0.3	0.35	1.3

plexes was better than the antibacterial activity, with some exceptions. All complexes had better antifungal activity than positive control (fluconazole).

The results of MTT assays have shown that all prepared complexes showed significant cytotoxic activity against colon cancer cell line HCT 116. Higher cytotoxic effect was observed after 48 h. Unfortunately, selectivity of prepared complexes evaluated using normal colon cell line CCD-18Co was not confirmed.

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Appendix A. Supplementary data

CCDC 1906595–1906600 contains the supplementary crystallographic data for **1**, **5**, **3**, **6**, **4**, **2**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data to this article can be found online at https://doi.org/10.1016/j.poly.2019.05.064.

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