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Featured Letter

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Eighteen 5,7-Dihalo-8-quinolinol and 2,2′-Bipyridine Co(II) Complexes as a New Class of Promising Anticancer Agents

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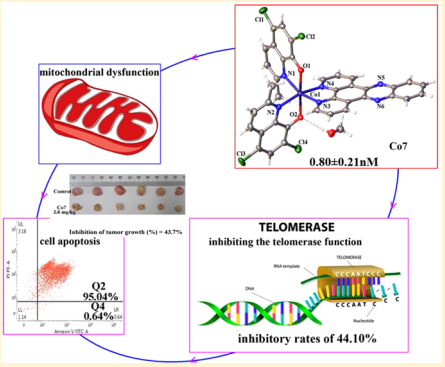
Supporting Information

ABSTRACT: Here we first report the design of a series of bis-chelate Co(II) 5,7-dihalo-8-quinolinol-phenanthroline derivative complexes, [Co(py)(QL1)$_2$] (**Co1**), [Co(py)(QL2)$_2$] (**Co2**), [Co(Phen)(QL1)$_2$] (**Co3**), [Co(Phen)(QL2)$_2$] (**Co4**), [Co(DPQ)(QL1)$_2$]·(CH$_3$OH)$_4$ (**Co5**), [Co(DPQ)(QL2)$_2$] (**Co6**), [Co(DPPZ)(QL1)$_2$]·CH$_3$OH (**Co7**), [Co(MDP)(QL1)$_2$]·3H$_2$O (**Co8**), [Co(ODP)(QL1)$_2$]·CH$_3$OH (**Co9**), [Co(PPT)(QL1)$_2$]·CH$_3$OH (**Co10**), [Co(ClPT)(QL1)$_2$] (**Co11**), [Co(dpy)(QL3)$_2$] (**Co12**), [Co(mpy)(QL1)$_2$] (**Co13**), [Co(Phen)(QL4)$_2$] (**Co14**), [Co(ODP)(QL4)$_2$] (**Co15**), [Co(mpy)(QL4)$_2$]I (**Co16**), [Co(ClPT)(QL4)$_2$] (**Co17**), and [Co(ClPT)(QL5)$_2$] (**Co18**), with 5,7-dihalo-8-quinolinol and 2,2′-bipyridine mixed ligands. The antitumor activity of **Co1**−**Co18** has been evaluated against human HeLa (cervical) cancer cells *in vitro* (IC$_{50}$ values = 0.8 nM−11.88 μM), as well as *in vivo* against HeLa xenograft tumor growth (TIR = 43.7%, $p < 0.05$). Importantly, **Co7** exhibited high safety *in vivo* and was more effective in inhibiting HeLa tumor xenograft growth (43.7%) than cisplatin (35.2%) under the same conditions (2.0 mg/kg). In contrast, the H-QL1 and DPPZ ligands greatly enhanced the activity and selectivity of **Co7** in comparison to **Co1**−**Co6**, **Co8**−**Co18**, and previously reported cobalt(II) compounds. In addition, **Co7** (0.8 nM) inhibited telomerase activity, caused G2/M phase arrest, and induced mitochondrial dysfunction at a concentration 5662.5 times lower than **Co1** (4.53 μM) in related assays. Taken together, **Co7** showed low toxicity, and the combination could be a novel Co(II) antitumor compound candidate.



KEYWORDS: *5,7-Dihalo-8-quinolinol, Co(II) complex, antitumor activity, telomerase activity, mitochondrial dysfunction*

Pt-based drugs were extensively used to treat a large number of tumors in the clinic.[1−10] However, cisplatin (*cis*-[PtCl$_2$(NH$_3$)$_2$]) and its derivatives were limited by drug resistance and some severe side effects,[1114] and consequently, the Ru, Ti, Au, Co, Ir, Os, Rh, Fe, Cu, etc., complexes have been designed and attracted attention.[16−38] In addition, cobalt has emerged as a key of vitamin B12 (cobalamin) metabolism and its metal complexes have been reported as DNA cleavage agents, antiviral, antifungal, antitumor antiproliferative, antioxidant, and have shown antimicrobial activity, such as oxoisoaporphine,[15] shydroxamic acids prodrugs,[16,17] 2-benzimidazole derivatives,[18] acetylene-hexacarbonyldicobalt,[19] 2-acetylpyridine and malonic acid dihydrazide,[20] antiulcer drug famotidine,[21] sparfloxacin,[23] valine-derived Schiff bases,[24] *N*-benzoyl-*N*′-dialkylthiourea derivatives,[25] nonsteroidal anti-inflammatory drugs,[28] non-steroidal anti-inflammatory drug tolfenamic acid,[30] 2-acetoxy-(2-propynyl)benzoate]hexacarbonyldicobalt,[31] a fluorescent coumarin,[32] and tetradentate phenolate-based ligand[35] cobalt-(II/III) complexes.

Recently, many novel hydroxyquinoline metal compounds, such as Zn, Cu, Ni, Ir, Os, Rh, Au, Co, Fe, Sn, Ru, Pt, Pd, and Ln metal complexes,[39−60] have proved to be promising anticancer drugs *in vitro* and *in vivo*. Among them, a small amount of copper(II) complexes of hydroxyquinolines were designed and preliminarily identified as anticancer drugs.[50−60] However, to date, Co(II) complexes bearing 5,7-dihalo-2-methyl-8-quinolinol and *o*-phenanthroline derivative mixed ligands have not been reported.

To gain the mixed chelating cobalt(II) complexes with high anticancer activity *in vitro* and *in vivo*, we first designed 18 novel Co(II) complexes **Co1**−**Co18** with 2,2′-bipyridine (py), 1,10-phenanthroline (Phen), 5,7-dichloro-2-methyl-8-quinolinol (H-QL1), dipyridoquinoxaline (DPQ), 5,7-dibromo-2-methyl-8-quinolinol (H-QL2), dipyridophenazine (DPPZ), 5,6-dimethyl-

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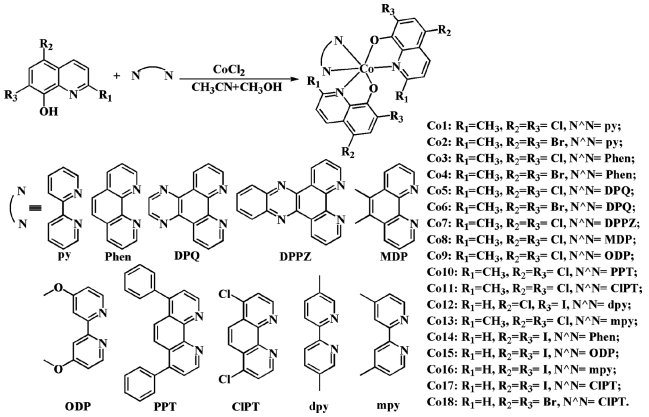
10-phenanthroline (MDP), 4,4′-dimethoxy-2,2′-bipyridyl (ODP), 4,7-diphenyl-10-phenanthroline (PPT), 4,7-dichloro-1,10-phenanthroline (ClPT), 5-chloro-7-iodo-8-hydroxy-quinoline (H-QL3), 5,5-dimethyl-2,2-dipyridine (dpy), 5,7-diiodo-8-hydroxyquinoline (H-QL4), 4,4′-dimethyl-2′-bipyridine (mpy), and 5,7-dibromo-8-quinolinol (H-QL5). Additionally, the biological properties of **Co1**−**Co18** have been evaluated.

First, the mononuclear complexes **Co1**−**Co18** were prepared by CH_3CN−CH_3OH (3.5 mL/1.5 mL) reflux of H-QL1 (or H-QL2, H-QL3, H-QL4, H-QL5) and py, Phen, DPQ, DPPZ, MDP, ODP, PPT, ClPT, dpy, and mpy with cobalt(II) acetate (2:1:1) at 80 °C for 24 h, respectively (Scheme 1). These 18 new Co(II) complexes were structurally fully characterized (Figures 1 and S1−S45).

Scheme 1. General Synthetic Pathway for Co1−**Co18**



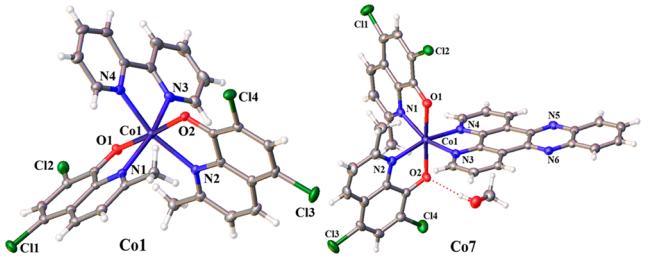


Figure 1. Crystal structures of **Co1** and **Co7**.

The Co(II) atoms in **Co1**−**Co18** were six-coordinated and surrounded by two deprotonated QL ligands (N^O-ligand) and one second ligand molecule (N^N-ligand) showing a distorted octahedral geometry (Figures 1 and S1−S16). In addition, a diagram of **Co1**−**Co18** is shown in Figures 1 and S1−S16, and selected bond distances (Å) and angles (deg) are listed in Tables S1−S54, and the bond lengths (Å) of **Co1**−**Co18** remained normal.

MTT assay was carried out to gauge the *in vitro* anticancer activity of **Co1**−**C o18**, H-QL1, H-QL2, py, Phen, DPQ, DPPZ, MDP, ODP, PPT, ClPT, H-QL3, dpy, H-QL4, $CoCl_2{\cdot}6H_2O$, mpy, and H-QL5 using BEL-7404 (hepatocellular), Hep-G2 (hepatocellular), HeLa (cervical), MCF-7 (breast) cancer cells, and normal HL-7702 (hepatocyte) cells. As a general observation (Table S55), **Co7** was more active (IC_{50} values = 0.80 nM) than the **Co1**−**Co6**, **Co8**−**Co18**, cisplatin, H-QL1, H-QL2, py, Phen, DPQ, DPPZ, MDP, ODP, PPT, ClPT, H-QL3, dpy, H-QL4, $CoCl_2{\cdot}6H_2O$, mpy, and H-QL5 in all tested cells, and the cytotoxicity of **Co1**−**Co18** against HeLa cells followed the order **Co7** > **Co5** > **Co8** > **Co11** > **Co3** > **Co10**> **Co9** > **Co13** > **Co1** > **Co6** > **Co4**> **Co2** > **Co12** > **Co18** > cisplatin > **Co15** > **Co17** > **Co14** > **Co16**. The higher *in vitro* anticancer activity for **Co7** may be due to the H-QL1 and DPPZ ligands. Such observed, different antitumor effects may be due to the electronic effect of the methyl group and the halogenated and more extended planar ligand of H-QL1 and DPPZ. Interestingly, **Co1**−**Co18** showed low toxicity (IC_{50} > 60.0 μM) to normal HL-7702 (hepatocyte) cells. Compared with previously reported 8-hydroxyquinoline metal complexes (IC_{50} ≥ 1.00 nM),[39−60] **Co7** exhibited higher cytotoxicity against HeLa cells (IC_{50} = 0.80 ± 0.21 nM).

Thus, ICP-MS assay showed that the Co(II) concentrations of **Co7** ((22.96 ± 0.15 nmol of Co)/10^6 cells) and **Co1** ((18.06 ± 0.05 nmol of Co)/10^6 cells) were significantly above those of control groups and cisplatin ((4.11 ± 0.59 nmol of Pt)/10^6 cells),[15] with **Co7** (0.80 nM) showing the highest cell accumulation of Co ((22.96 ± 0.15 nmol of Co)/10^6 cells) and a high extent in HeLa nuclear fraction (Table S56). Thus, **Co7** (0.80 nM) showed higher toxicity on the HeLa (cervical) cancer cells possibly due to its better cellular uptake.

Thus, the induction of the level of c-myc, hTERT, and thus, telomerase in HeLa cells by **Co1** (4.53 μM) and **Co7** (0.80 nM) was investigated using a TRAP-silver staining assay and Western blot. As shown in Figure 2, **Co7** (0.80 nM) showed a more

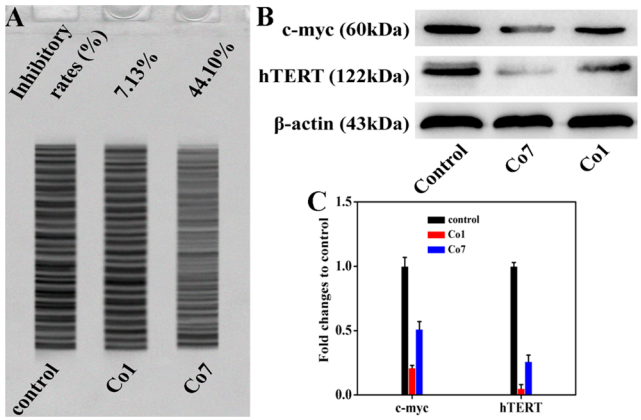


Figure 2. Level of telomerase (A) and related factors (B,C) in HeLa cells induced by **Co1** (4.53 μM) and **Co7** (0.80 nM) at 24 h.

inhibitory effect on c-myc, hTERT, and telomerase activity than that of **Co1** (4.53 μM), suggesting that **Co1** (4.53 μM) and **Co7** (0.80 nM) inhibited c-myc and hTERT, and thus, telomerase levels were related to a variety of malignant cancers.[61−65] Importantly, inhibition of telomerase in **Co7** (0.80 nM)-treated cells was 44.10%, while that caused by **Co1** (4.53 μM) only reached 7.13%.

Furthermore, a G2/M population of 22.89% was observed in **Co7** (0.80 nM)-treated cells, while the other corresponding G2/M populations of 20.27% and 12.35% were observed in the **Co1** (4.53 μM) treated and control cells (Figure 3), suggesting that **Co1** (4.53 μM) and **Co7** (0.80 nM) caused G2/M cycle arrest. In addition, **Co7** (0.80 nM) and **Co1** (4.53 μM) could inhibit the expression of cyclin B1 and CDK1 in HeLa (cervical) cells (Figure S46), mainly due to the G2/M phase arrest (Figure 3) that they cause and their ability to inhibit telomerase.[66−68] Further, immunofluorescence (Figure S47) and Western blot assays (Figure S46) were carried out. Clearly, **Co7** (0.80 nM) and **Co1** (4.53 μM) could up-regulate the H2A.X and cleaved-

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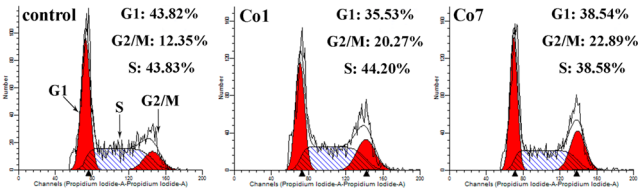

Figure 3. **Co7** (0.80 nM) and **Co1** (4.53 μM) caused G2/M phase arrest for 24 h.

PARP levels, indicating that **Co7** (0.80 nM) and **Co1** (4.53 μM) remarkably induced DNA damage (Figures S46 and S47) and caused G2/M phase arrest following the order of **Co7** > **Co1**.

In addition, **Co7** (0.80 nM) mainly accumulated in a nuclear fraction (Table S56) but also was distributed in the mitochondria. Thus, **Co7** (0.80 nM) and **Co1** (4.53 μM) caused obviously up-regulated reactive oxygen species (ROS, Figure S48), intracellular [Ca^{2+}] (Figure 4), and caspase-3/9

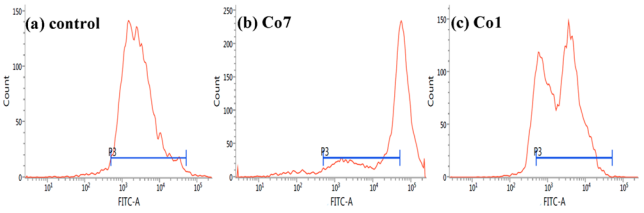

Figure 4. Effects of **Co7** (0.80 nM) and **Co1** (4.53 μM) on the [Ca^{2+}] level in HeLa cells at 24 h.

levels (Figure S49 and S50), and down-regulated mitochondrial membrane potential ($\Delta\Psi$m) (Figure S51) in HeLa cells, illustrating that the $\Delta\Psi$m, ROS generation, intracellular [Ca^{2+}], and caspase-3/9 played a key role in cancer mitochondrial function damage and apoptosis.[15,69−72]

Therefore, to clarify the antimigration effects of **Co7** (0.80 nM) and **Co1** (4.53 μM) in HeLa cells (Figure 5a−d), the transwell migration assay was carried out. It was found that **Co7** (0.80 nM) could significantly induce cell migration at 0.80 nM than that of **Co1** (4.53 μM).

For this, to further investigate the ability of **Co7** (0.80 nM) and **Co1** (4.53 μM) to induce HeLa cell apoptotic by flow cytometry (FCM). As shown in Figure 5e−g, the percentages of apoptotic cells treated with **Co7** (0.80 nM) and **Co1** (4.53 μM) were 95.68% and 34.42%, respectively, suggesting that Co complexes could cause cell death at higher rates than other 8-quinolinate metal complexes.[39−60]

Furthermore, treatment of HeLa xenografts by **Co7** (2.0 mg/kg/q2d) was related to significant reduction (TIR = 43.7%, p < 0.05) in tumor growth (Figure 6 and Tables S57−S59), which represents approximately 1.3-fold reduction compared with cisplatin-treated groups (IR = 35.2 ± 5.8%, p < 0.05).[51,55,56,72−74] In addition, **Co7** (2.0 mg/kg/q2d)-treated mice displayed no obvious signs of toxicity (Figure 6 and Tables S57−S59) as indicated by a relatively stable mouse body weight (m_{end}= 20.5 ± 1.3 g) compared to solvent control (m_{end}= 20.7 ± 1.4 g).

In conclusion, we have shown **Co1−Co18** complexes containing mixed 5,7-dihalo-8-quinolinol (H-QL1−H-QL5) and 2,2′-bipyridine derivative-based ligands as potential Co(II) complexes with superior cytotoxicity compared with previously reported Co compounds. MTT studies have demonstrated that **Co7** was ca. 300.6 times more cytotoxic than cisplatin (15.03 ± 1.05 μM), with IC_{50} values of 0.80 ± 0.21 nM while maintaining a high extent in HeLa nuclear fraction and targeting telomerase; thus, it was considerably less cytotoxic to normal HL-7702 (hepatocyte) cells. In addition, the antitumor activity of **Co7** has been evaluated *in vivo* against HeLa xenograft growth (TIR = 43.7%, p < 0.05). It also inhibited telomerase activity, caused G2/M phase arrest, and induced mitochondrial dysfunction at a 104.6-fold lower concentration than **Co1** (4.53 μM) in related assays. Thus, the superior cytotoxicity (IC_{50} = 0.80 ± 0.21 nM) and selectivity index of **Co7** in comparison to cisplatin could make it a novel antitumor cobalt(II)-based drug.

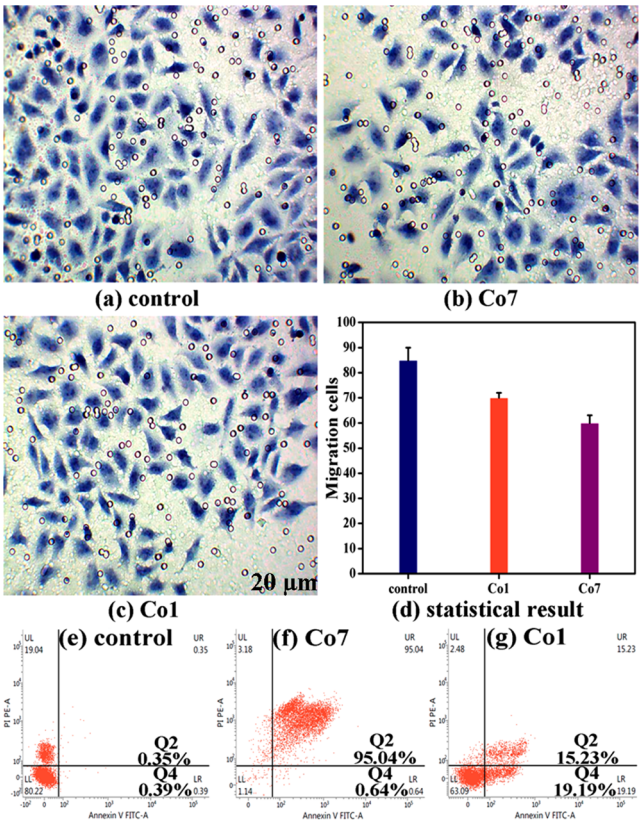

Figure 5. Antimigration (a−d) and apoptosis (e−g) effect of **Co7** (0.80 nM) and **Co1** (4.53 μM) on HeLa cells for 24 h.

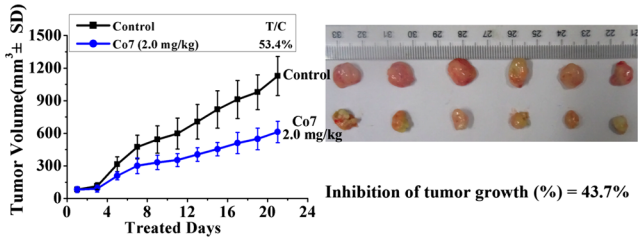

Figure 6. Tumor volume (A, mm^3 ± SD) and images (B) of the HeLa tumors of **Co7** (n = 6) for 21.0 days.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.9b00356.

Detailed experiments of **Co1−Co18** (PDF)

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The manuscript was written through contributions of all authors.

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Notes

The authors declare no competing financial interest.
The CCDC numbers for **Co1−Co18** are 1916696−1916700, 1916702, 1916703, 1917994, 1917997, 1917998, 1918000, 1918001, 1918004, 1918006, 1918007, 1918010, 1918012, and 1918014.

Biographies

Qi-Pin Qin received his Ph.D. degree from Guangxi Normal University in 2017 under the guidance of Prof. Zhen-Feng Chen and Hong Liang. Subsequently, he joined the faculty at Yulin Normal University in 2017 as a professor. His current research interest is focused on metal-based anticancer complexes, nanodrugs, and bioimaging agents. He has designed and synthesized over 300 new coordination compounds. The results have been published in over 70 research papers.

Hua-Hong Zou obtained his Ph.D. from Guangxi Normal University under the supervision of Prof. Fu-Pei Liang in 2015. Currently, he works at the State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry & Pharmacy of Guangxi Normal University. His research is focused on the design and mechanism of action of metal-based anticancer complexes, and assembly process and mechanism of polynuclear clusters in solution. He has published more than 120 papers related to the above research areas.

Fu-Pei Liang received his Ph.D. degree from the University of Zurich in 2001 and completed postdoctoral research at the University of Zurich in 2002. He is currently a Professor of the State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry & Pharmacy of Guangxi Normal University. His research interests include the design and mechanism of action of metal-based anticancer complexes, multifunctional complexes, and synthesis and properties of high-nuclearity lanthanide clusters.

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ABBREVIATIONS

SD, standard deviation; TIR, tumor growth inhibition rate

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