Bioorganic & Medicinal Chemistry Letters 26 (2016) 3295–3299

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Synthesis, crystal structures, molecular docking, and in vitro biological activities of transition metals with 4-(2,3-dichlorophenyl) piperazine-1-carboxylic acid

Dan-Dan Yang [a], Ya-Nan Chen [a], Yu-Shan Wu [a], Rui Wang [a], Zhi-Jian Chen [a], Jie Qin [a], Shao-Song Qian [a,*], Hai-Liang Zhu [a,b]

[a] School of Life Sciences, Shandong University of Technology, Zibo 255049, People's Republic of China
[b] State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, People's Republic of China

ARTICLE INFO

*Article history:*
Received 9 March 2016
Revised 20 April 2016
Accepted 18 May 2016
Available online 19 May 2016

*Keywords:*
Metal complexes
Crystal structure
Molecular docking
Telomerase inhibitor
Antiproliferative

ABSTRACT

Four novel mononuclear complexes, [Cd(**L**)$_2$·2H$_2$O] (**1**), [Ni(**L**)$_2$·2H$_2$O] (**2**) [Cu(**L**)$_2$·H$_2$O] (**3**), and [Zn(**L**)$_2$·2H$_2$O] (**4**) (CCDC numbers: 1444630–1444633 for complexes **1**–**4**) (HL = 4-(2,3-dichlorophenyl) piperazine-1-carboxylic acid) were synthesized, and have been characterized by IR spectroscopy, elemental analysis, and X-ray crystallography. Molecular docking study preliminarily revealed that complex **1** had potential telomerase inhibitory activity. In accordance with the result of calculation, in vitro tests of the inhibitory activities of complex **1** against telomerase showed complex **1** ($IC_{50}$ = 8.17 ± 0.91 μM) had better inhibitory activities, while complexes **2**, **3** and **4** showed no inhibitory activities. Antiproliferative activity in human cancer cell line HepG2 was further determined by MTT assays. The $IC_{50}$ value (6.5 ± 0.2 μM) for the complex **1** having good inhibitory activity against HepG2 was at the same micromolar concentrations with *cis*-platinum (2.2 ± 1.2 μM). While the $IC_{50}$ value for the metal-free ligand, complex **2**, **3** and **4** was more than 100 μM. These results indicated that telomerase was potentially an anticancer drug target and showed that complex **1** was a potent inhibitor of human telomerase as well as an antiproliferative compound.



The clinical success and drawbacks of Pt anticancer drugs have stimulated the exploration of other metal-based anticancer compounds.[1,2] A number of metal-based compounds with promising antiproliferative activity toward a wide range of tumors with novel mechanisms of action have recently been described.[3–5] Metal-containing compounds offer many advantages over conventional carbon-based compounds in the development of new medicinal compounds. These advantages are due to their ability to coordinate ligands in a three dimensional configuration, thus allowing functionalization of groups that can be tailored to defined molecular targets. In medicinal chemistry—traditionally dominated by organic chemistry—metal complexes have gained favor as diagnostic tools and anticancer agents.[6] Telomere maintenance is a universal cancer hallmark, and small molecules that disrupt telomere maintenance generally have anticancer properties. Since the vast majority of cancer cells utilize telomerase activity for telomere maintenance, the enzyme has been considered as an anticancer drug target.[7–9] Many heterocyclic structure contained compounds are reported had antitumor or antiproliferative activities.[10–14]

The piperazine derivatives are important pharmacophores that can be found in biologically active compounds across a number of different therapeuticareas.[15–18] MST-16 [4,4-1,2-(ethanediyl)bis(1-isobutoxycarbonyloxy-methyl-2,6-piperazinedione)] was recently approved as an oral anticancer drug for clinical use in Japan.[19] Based on all the above, a novel ligand containing piperazine ring (4-(2,3-dichlorophenyl)piperazine-1-carboxylic acid) was designed and synthesized, the ligand reacted with transition metal salts to give four novel complexes, [Cd$^{II}$(**L**)$_2$·2H$_2$O] (**1**), [Ni$^{II}$(**L**)$_2$·2H$_2$O] (**2**), [Cu$^{II}$(**L**)$_2$·H$_2$O] (**3**) and [Zn(**L**)$_2$·2H$_2$O] (**4**) and structurally characterized by X-ray diffraction. Molecular docking study preliminarily revealed that complex **1** had potential telomerase inhibitory activity. In accordance with the result of calculation, in vitro tests of the inhibitory activities of complexes **1** against telomerase showed complex **1** had better inhibitory activities. Antiproliferative activity in human cancer cell line HepG2 was further determined by MTT assays. The $IC_{50}$ value for the complex **1** having good inhibitory activity against telomerase was at the same micromolar concentrations with *cis*-platinum. These results

* Corresponding author.
*E-mail address:* sdutqss@163.com (S.-S. Qian).

http://dx.doi.org/10.1016/j.bmcl.2016.05.051
0960-894X/

indicated that telomerase was potentially an anticancer drug target and showed that complex **1** was a potent inhibitors of human telomerase.

Synthesis of 4-(2,3-dichlorophenyl)piperazine-1-carboxylic acid (HL) was efficiently performed starting from commercially available compounds. 1-(2,3-Dichlorophenyl)piperazine (1.00 g), 2-bromoaceticacid (2.50 g) and potassium hydroxide (1.50 g) were added to a round bottom flask containing 40 ml ethanol and the solution was refluxed at 75 °C for 10 h using an oil bath. The reaction mixture was then cooled to room temperature, and neutralized with hydrochloric acid to form the precipitate. The solution was filtered, transferred to a clean pre-weighed round bottom flask and dried. The yield of dry product was 64% (Scheme 1).

General method for the preparation of complexes **1**–**4**: 0.02 M 4-(2,3-dichlorophenyl)piperazine-1-carboxylic acid–water solution (4 ml) were added to a methanol solution (4 ml) containing mental irons. Adjust the pH value to 7 with potassium hydroxide water solution. The resulting mixture was heated at 120 °C in a kettle for 48 h with a incubator. The solution was cooled for 24 h and filtrated. The filtrate was left to stand at room temperature for a few days to give the corresponding crystals suitable for X-ray diffraction analysis. The elemental analyses and characteristic IR data (FT-IR Nicolet 5700 Spectrometer from 4000 to 400 $cm^{-1}$ with transmission of infrared system, no of scans: 32, resolution: 4) for the complexes were as follows:

(**1**) [$Cd^{II}$(**L**)$_2$·2$H_2O$]: Colorless block crystal, yield 52%. Calcd for $C_{24}H_{30}Cl_4N_4O_6Cd$: C, 40.59; H, 4.50; N, 7.57. Found: C, 41.25; H, 4.36; N, 7.68. Characteristic IR data (KBr, $cm^{-1}$): 3281; 2841; 1585; 1451; 1415; 1252; 1112; 960; 782.

(**2**) [$Ni^{II}$(**L**)$_2$·2$H_2O$]: Green block crystal, yield 62%. Calcd for $C_{24}H_{30}Cl_4N_4O_6Ni$: C, 43.77; H, 4.85; N, 8.17. Found: C, 44.58; H, 4.76; N, 8.49. Characteristic IR data (KBr, $cm^{-1}$): 3288; 2846; 1589; 1448; 1417; 1235; 1107; 958; 781.

(**3**) [$Cu^{II}$(**L**)$_2$·$H_2O$]: Blue needle crystal, yield: 72%. Calcd for $C_{24}H_{27}Cl_4N_4O_5Cu$: C, 44.62; H, 4.64; N, 8.33. Found: C, 45.58; H, 4.58; N, 8.61. Characteristic IR data (KBr, $cm^{-1}$): 3381; 2956; 1637; 1452; 1379; 1244; 1117; 953; 784.

(**4**) [$Zn^{II}$(**L**)$_2$·2$H_2O$]: Colorless block crystal, yield: 47%. Calcd for $C_{24}H_{30}Cl_4N_4O_6Zn$: C, 43.34; H, 4.08; N, 8.09. Found: C, 44.58; H, 3.91; N, 8.31. Characteristic IR data (KBr, $cm^{-1}$): 3295; 2993; 1594; 1450; 1419; 1252; 1111; 961; 782.

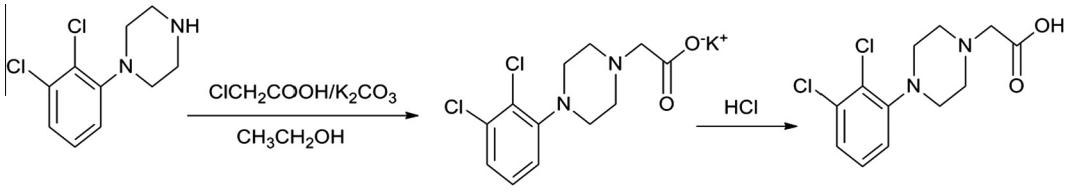
Single crystals of complexes **1**–**4** were mounted on a thin glass fiber at room temperature. The reflection data were collected on a Bruker D8 VENTURE PHOTON diffract meter with graphite monochromatic Mo-Ka radiation ($\lambda$ = 0.71073 Å) using the generic omega scan technique. The structures were solved by direct methods and refined on $F^2$ by full matrix least-squares with SHELXS-97 program.[20,21] All of the non-hydrogen atoms were refined anisotropically. The water H atoms were located in a difference Fourier map and refined freely. The remaining H atoms were placed in idealized positions and constrained to ride on their parent atoms. Selected bond lengths and angles were given in Tables 1–3.

*Description of crystal structures:* Metal ions in complexes **1**, **2** and **4** exhibit similar coordination geometries, **1** is taken as an example to depict in detail.

**Table 3**
Hydrogen-bonds (Å, °) for complexes **1**–**4**

| Complex | D—H | d(D—H) | d(H...A) | <DHA | d(D...A) | A |
|---|---|---|---|---|---|---|
| **1** | $O_1W$—$H_1W$ | 0.812 | 1.960 | 169.04 | 2.761 | O1 |
| | $O_1$ W—$H_2W$ | 0.776 | 2.626 | 124.75 | 3.134 | O2 |
| **2** | $O_1W$—$H_1W$ | 0.820 | 1.993 | 162.32 | 2.785 | O1 |
| | $O_1W$—$H_2W$ | 0.832 | 2.651 | 129.14 | 3.241 | O2 |
| **3** | $O_1W$—$H_1W$ | 0.820 | 1.984 | 172.76 | 2.800 | O1 |
| **4** | $O_1W$—$H_1W$ | 0.820 | 1.855 | 160.20 | 2.641 | O1 |

Symmetry transformations used to generate equivalent atoms: (i) $-x+1, -y+3, -z+2$; (ii) $x, -y+5/2, z-1/2$; (iii) $-x+1, -y+3, -z+1$; (iv) $x, -y+5/2, z+1/2$; (v) $-x, -y+1, -z$; (vi) $-x+1, -y+3, -z$.




**Scheme 1.** Synthesis of 4-(3,4-dichlorophenyl)piperazine-1-carboxylic acid.

**Table 1**
Selected bond angles/° in complexes **1**–**4**

| Complex **1** | | Complex **2** | | Complex **3** | | Complex **4** | |
|---|---|---|---|---|---|---|---|
| O1W—Cd1—O2 95.05 | 95.05 | O1W—Ni1—O2 | 92.78 | O1W—Cu1—O2 | 92.11 | O1W—Zn1—O2 | 92.83 |
| O1W—Cd1—O2a | 84.955 | O1W—Ni1—O2a | 91.12 | O1W—Cu1—O2a | 92.11 | O1W—Zn1—O2a | 81.17 |
| O1W—Cd1—N1 | 89.396 | O1W—Ni1—N1 | 88.88 | O1W—Cu—N1 | 97.60 | O1W—Zn1—N1 | 88.67 |
| O1W—Cd1—N1a | 90.616 | O1W—Ni1—N1a | 91.12 | O1W—Cu1—N1a | 97.60 | O1W—Zn1—N1a | 91.33 |
| O2—Cd1—N1 | 74.43 | O2—Ni1—N1 | 79.95 | O2—Cu1—N1 | 82.87 | O2—Zn1—N1 | 79.10 |
| N1—Cd1—N2a | 180.00 | N1—Ni1—N2a | 180.00 | N1—Cu1—N2a | 164.80 | N1—Zn1—N1a | 180.00 |
| O2—Cd1—O2a | 180.00 | O2—Ni 1—O2a | 180.00 | O2—Cu1—O2a | 175.78 | O2—Zn1—O2a | 180.00 |
| O1W—Cd1—O1Wa | 180.00 | N1—Ni 1—N2a | 180.00 | | | O1W—Zn1—O1Wa | 180.00 |

**Table 2**
selected bond distances/A° for complexes **1**–**4**

| Complex **1** | | Complex **2** | | Complex **3** | | Complex **4** | |
|---|---|---|---|---|---|---|---|
| Cd1—O2 | 2.1990 | Ni1—O2 | 1.9922 | Cu1—O2 | 1.924 | Zn1—O2 | 1.990 |
| Cd1—N1 | 2.4619 | Ni1—N2 | 2.2913 | Cu1—N2 | 2.077 | Zn1—N1 | 2.376 |
| Cd1—O1W | 2.3337 | Ni1—O1W | 2.0803 | Cu1—O1W | 2.214 | Zn1—O1W | 2.144 |