Two novel Co(II) complexes with two different Schiff bases: inhibiting growth of human skin cancer cells

Y.-J. Xiao1,2, Q.-C. Diao2, Y.-H. Liang3 and K. Zeng1

1Department of Dermatology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China
2Department of Dermatology, The Chongqing Hospital of Traditional Chinese Medicine (The First People’s Hospital of Chongqing City), Chongqing, China
3Department of Dermatology, Shenzhen Hospital, Southern Medical University, Shenzhen, Guangdong, China

Abstract

Using two flexible Schiff bases, H2L1 and H2L2, two new cobalt II (Co(II))-coordination compounds, namely, Py3CoL1 (1) and Py3CoL2 (2) (Py=pyridine, L1=3,5-ClC6H2(O)C=NC6H3(O)-4-NO2, L2=3,5-BrC6H2(O)C=NC6H3(O)-4-NO2) have been synthesized under solvothermal conditions. Single crystal X-ray structural analysis revealed that compounds 1 and 2 are both six-coordinate in a distorted octahedral geometry, and the 1D chain structure was formed by the π–π and C-H…O interactions or C-H…Cl interaction. The in vitro antitumor activities of 1, 2 and their corresponding organic ligands Py, L1, and L2 were studied and evaluated, in which three human skin cancer cell lines (A-431, HT-144 and SK-MEL-30) were used in the screening tests.

Key words: Schiff bases; Coordination compound; Antitumor activity

Introduction

Cancer is a proliferation disorder disease with apoptosis obstacles (1,2). It strikes more than one-third of the world’s population and causes over 20% of all deaths (3). Standard cancer treatment protocols include surgery, radiotherapy and chemotherapy (4). Unfortunately, chemotherapy is not effective in treating cancers associated with innate resistance to apoptosis and/or acquired resistance to drugs during treatment. Discovery of novel effective anticancer medicines is therefore of great importance (5).

Cobalt complexes with Schiff bases have received considerable attention in the fields of coordination chemistry and biological chemistry (6). Cobalt functions as the active site of hydrolytic enzymes, such as carboxypeptidase and carbonic anhydrase where it is in a hard-donor coordination environment of nitrogen and oxygen (7). Cobalt has been recognized as an important cofactor in biological molecules, either as a structural template in protein folding or as a Lewis acid catalyst that can readily adopt four-, five-, or six-coordination (7,8). The cobalt (Co) complexes with the Schiff bases derived from salicylaldehyde and its analogues have been extensively studied (9).

Correspondence: K. Zeng: <kang_zeng666@yeah.net>

Received February 8, 2017 | Accepted April 27, 2017

Braz J Med Biol Res | doi: 10.1590/1414-431X20176390
ISSN 1414-431X 1/5
solution continued to reflux for 2 h. The solution was cooled down to room temperature and filtered and the brown crystals of solution 1 were obtained. Analytical characteristics found for compound 1 \((C_{28}H_{21}Cl_2CoN_5O_4)\) were: C, 54.18; H, 3.39; N, 11.30%. Calculate: C, 54.13; H, 3.41; N, 11.27%.

The synthesis method for compound 2 was similar to that of compound 1. Analytical characteristics found for compound 2 \((C_{28}H_{21}Br_2CoN_5O_4)\) were: C, 47.40; H, 3.00; N, 9.85%. Calculate: C, 47.35; H, 2.98; N, 9.86%.

**Crystal structure determination**

Structural measurement was performed on the computer-controlled Mercury CCD diffractometer with graphite-monochromated Mo-\(K \alpha\) radiation (\(\lambda=0.71073\) Å) at \(T=293\) (2) K. Absorption correction was made using the SADABS (Bruker AXS Inc., USA) program. The structure was solved using the direct method and refined by full-matrix least-squares methods on \(F^2\) using the SHELXS-97 program package (10). Crystallographic data and structural refinements for compounds 1 and 2 are summarized in Table 1.

CCDC numbers for compounds 1 and 2 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; E-mail: E-mail: deposit@ccdc.cam.ac.uk)

**Antitumor activity**

Stock solutions of 1, 2 and their corresponding organic ligands Py, L1 and L2 were prepared in DMSO and kept at \(-20^\circ\)C. Appropriate dilutions of the compounds were freshly prepared just prior to the assays. Final concentrations of DMSO did not interfere with the cell growth.

Three human skin cancer cell lines (A-431, HT-144 and SK-MEL-30) grown as monolayer were routinely maintained in RPMI-1640 medium supplemented with 5% heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 \(\mu\)g/mL), at 37\(^\circ\)C in a humidified atmosphere containing 5% \(CO_2\). Exponentially growing cells were obtained by plating \(1.5 \times 10^5\) cells/mL for A-431 and HT-144 and \(0.75 \times 10^4\) cells/mL for SK-MEL-30, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all the experiments by exposing untreated control cells to the maximum concentration (0.5%) of DMSO used in each assay.

**Results and Discussion**

**Molecular structure**

The crystal structure determined by single-crystal X-ray diffraction showed that 1 and 2 both crystallize in the triclinic system, space group \(P\bar{1}\). The asymmetric unit

![Figure 1. Scheme representation of compounds Py3CoL1 (1) and Py3CoL2 (2).](image1)

![Table 1. Crystal data and structure refinement for Py3CoL1 (1) and Py3CoL2 (2).](image2)
comprises one Co(II) atom, three pyridine molecules, one 3,5-dichlorosalicylaldehyde-2-amino-4-nitrophenol or 3,5-dibromosalicylaldehyde-2-amino-4-nitrophenol Schiff base, respectively.

As shown in Figures 2A and 3A, the central Co1 atom is six-coordinate in a distorted octahedral geometry and is surrounded by two oxygen atoms (O1 and O2) and one amino nitrogen atom (N1) from the ligand, and three nitrogen atoms (N3, N4, and N5) from three different pyridines. The axes positions were occupied by two nitrogen atoms (N1 and N4 for 1; N1 and N5 for 2) from Shiff base ligand (3,5-dichlorosalicylaldehyde-2-amino-4-nitrophenol for 1; 3,5-dibromosalicylaldehyde-2-amino-4-nitrophenol for 2) and one pyridine molecule, respectively. The angle of N1-Co1-N4 and N1-Co1-N5 is 173.94° and 173.92°, respectively, which obviously deviates from linear angle 180°. The equatorial positions were occupied by four atoms (O1, O2, N3 and N5 for 1; O1, O2, N3 and N4 for 2). The bond lengths and bond angles between the four atoms in the equatorial plane and the center of the Co1 atom are also different [for 1, Co1-O1=2.0116 (14) Å, Co1-O2=2.0609 (15) Å, Co1-N3=2.2210 (18) Å, Co1-N5=2.2361 (16) Å, Co1-N4=2.2361 (16) Å, Co1-O2=2.0609 (15) Å, Co1-N3=2.2210 (18) Å, Co1-N5=2.2361 (16) Å, Co1-N4=2.2361 (16) Å].

Figure 2. A, Molecular structure of compound 1 (Py3CoL1); B, packing of compound 1 in unit cell; C, 1D infinite chain structure of compound 1 was formed by the π…π and C-H…O interactions; D, 1D infinite chain structure of compound 1 was formed by the C-H…Cl interactions.
N5=2.2029 (18) Å, O1-Co1-N3=93.85 (6)°, O2-Co1-N3=92.48 (7)°, O2-Co1-N5=88.57 (7)°; for 2, Co1-O1=2.0157 (19) Å, Co1-O2=2.0610 (19) Å, Co1-N3=2.217 (2) Å, Co1-N4=2.207 (2) Å, O1-Co1-N3=93.81 (8)°, O2-Co1-N3=92.92 (9)°, O1-Co1-N4=86.66 (8)°, O2-Co1-N4=88.39 (9)°, so the central Co1 atom is six-coordinate in a distorted octahedral geometry in the complexes 1 and 2.

The packing of the compounds 1 and 2 in unit cell is shown in Figures 2B and 3B, respectively. Moreover, for 1, the π...π and C-H...O interactions were observed between adjacent molecules, which led to the formation of an interesting 1D chain structure (Figure 2C). The C-H...Cl interaction in an adjacent molecule also resulted in the formation of a 1D chain structure (Figure 2D); for 2, the C-H...O hydrogen bonding interaction [H17...O4i 2.5939 (29) Å, C17-H17...O4i 171.995 (232)°, i: 1+x, y, z; H25...O3ii 2.5571 (36) Å, C25-H25...O3ii 136.210 (306)°, ii: 2-x, 2-y, -z; H23...O3iii 2.5816 (35) Å, C23-H23...O3iii 129.866 (198)°, iii: 1-x, 2-y, -z] were observed between adjacent molecules, which led to the formation of an interesting 1D ribbon-like structure (Figure 3C). The C-H...Br interaction...
proliferative activity of the test compounds against each of the title tumor cell lines may be arranged in a descending order according to the measured concentration required to inhibit tumor cell proliferation by 50% after continuous exposure of 48 h. *Doxorubicin was used as positive control.

### Antitumor activity

The tumor cell growth inhibition activities of 1, 2 and their corresponding organic ligands Py, L1 and L2 were assessed in vitro on 3 human skin cancer cell lines (A-431, HT-144, and SK-MEL-30) after continuous exposure for 48 h. The results were compared to the antiproliferative effects of the reference control doxorubicin. All compounds were dissolved in DMSO at 1 mg/mL immediately before use and diluted just before addition to the cell culture.

Data are reported as means ± SE of 3 independent experiments performed in duplicates. IC50: Drug concentration required to inhibit tumor cell proliferation by 50% after continuous exposure of 48 h.

| Compounds | IC50 (μM) |
|-----------|-----------|
|           | A-431     | HT-144    | SK-MEL-30 |
| Py        | 114.5 ± 6.2 | 120.5 ± 6.1 | 117.5 ± 4.9 |
| L1        | 93.2 ± 7.1  | 94.9 ± 6.9  | 98.8 ± 7.0  |
| L2        | 90.8 ± 3.5  | 112.6 ± 5.3 | 111.7 ± 5.9 |
| 1         | 11.3 ± 2.7  | 17.8 ± 3.1  | 19.8 ± 4.8  |
| 2         | 16.3 ± 1.8  | 17.1 ± 2.1  | 17.4 ± 2.6  |
| Doxorubicin* | 0.158 ± 0.067 | 0.141 ± 0.061 | 0.180 ± 0.041 |

Data are reported as means ± SE of 3 independent experiments performed in duplicates. IC50: Drug concentration required to inhibit tumor cell proliferation by 50% after continuous exposure of 48 h. *Doxorubicin was used as positive control.

### References

1. Borisova NE, Reshetova MD, Ustynyuk YA. Metal-free methods in the synthesis of macrocyclic Schiff bases. Chem Rev 2007; 107: 46–79, doi: 10.1021/cr0683616.
2. Guo XK, Sun HP, Shen S, Sun Y, Xie FL, Tao L, et al. Synthesis and evaluation of gambogenic acid derivatives as antitumor agents. Part III. Chem Biodivers 2013; 10: 73–85, doi: 10.1002/cbbd.201200126.
3. Götz M, Wortmann P, Schmid S, Hugel T. A multicolor single-molecule FRET approach to study protein dynamics and interactions simultaneously. Methods Enzymol 2016; 581: 487–516, doi: 10.1016/bs.meie.2016.08.024.
4. Chen Y, Bian Y, Sun Y, Kang C, Yu S, Fu T. Identification of 4-aminquinoline core for the design of new cholinesterase inhibitors. Peer J 2016; 4: e2140, doi: 10.7717/peerj.2140.
5. Diedrich B, Rigbolt KT, Röing M, Herr R, Kaeser-Pebbernard S, Grettzeimer C, et al. Discrete cytosolic macromolecular BRAF complexes exhibit distinct activities and composition. EMBO J 2017; 36: 646–663, doi: 10.15252/embj.201694732.
6. Han R, Sun Y, Kang C, Sun H, Wei W. Amphiphilic dendritic nanomicelle-mediated co-delivery of 5-fluorouracil and doxorubicin for enhanced therapeutic efficacy. J Drug Target 2017; 25: 140–148, doi: 10.1080/1061186X.2016.1207649.
7. Al-Harbi SA, Bashandy MS, Al-Saidi HM, Emara AA, Mousa TA. Synthesis, spectroscopic properties, molecular docking, anti-colon cancer and anti-microbial studies of some novel metal complexes for 2-amino-4-phenylthiazole derivative. Spectrochim Acta A Mol Biomol Spectrosc 2015; 145: 425–439, doi: 10.1016/j.saa.2015.03.054.
8. Ryckbosch SM, Wender PA, Pande VS. Molecular dynamics simulations reveal ligand-controlled positioning of a peripheral protein complex in membranes. Nat Commun 2017; 8: 6, doi: 10.1038/s41467-016-0015-8.
9. Greiss F, Kriegel F, Braun D. Probing the cooperativity of binding networks with high-throughput thermophoresis. Anal Chem 2017; 89: 2592–2597, doi: 10.1021/acs.analchem.6b04861.
10. Sheldrick GM. SHELXL-97. Program for crystal structure solution and refinement. Göttingen: University of Göttingen; 1997.