Inorganic Chemistry Communications 30 (2013) 178–181

Contents lists available at SciVerse ScienceDirect

Inorganic Chemistry Communications

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

Synthesis, characterization and cytotoxicity of the Au(III) complexes with cyclic amine-based dithiocarbamate ligands

Yanan Shi [a], Wenhao Chu [a], Yuechai Wang [a], Shuxiang Wang [a,b,*], Jianlong Du [a], Jinchao Zhang [a,b,**], Shenghui Li [a], Guoqiang Zhou [a], Xinying Qin [a], Chenliang Zhang [a]

[a] Key Laboratory of Chemical Biology of Hebei province, College of Chemistry and Environmental Science, Hebei University, Baoding 071002, China
[b] Key Laboratory of Medicinal Chemistry and Molecular Diagnosis of Ministry of Education, Hebei University, Baoding 071002, China

ARTICLE INFO

Article history:
Received 20 December 2012
Accepted 7 February 2013
Available online 14 February 2013

Keywords:
Au(III) complexes
Cyclic amine-based dithiocarbamate
Cytotoxicity

ABSTRACT

Seven new Au(III) complexes ([(PipDTC)$AuCl_2$] (**1**), [(MoDTC)$AuCl_2$] (**2**), [(BzoPizDTC)$AuCl_2$] (**3**), [(TsPizDTC)$AuCl_2$] (**4**), [(PizDTC)Au_2Cl_4] (**5**), [(MePizDTC)Au_2Cl_5] (**6**) and [(EtPizDTC)Au_2Cl_5] (**7**)) with cyclic amine-based dithiocarbamate have been synthesized, characterized and evaluated in vitro. The results indicate that these complexes exert selective cytotoxic effects against HL-60, BGC-823, Bel-7402 and KB cells lines. Complex **1** shows 11-, 5- and 1-folds higher cytotoxicity than cisplatin against KB, BGC-823 and Bel-7402 cell lines. Complex **2** exhibits higher cytotoxicity than cisplatin against BGC-823 and Bel-7402 cell lines. Complexes **3** and **4** display higher cytotoxicity than cisplatin against BGC-823 cell line. The nature of cyclic amine and the number of metal centers have important effects on cytotoxicity of these Au(III) complexes.

Nowadays, cisplatin and the follow-on drugs (carboplatin and oxaliplatin) are widely used to treat cancers, such as testicular cancer, ovarian cancer, esophageal cancer, bladder cancer, head and neck cancers, and small-cell lung carcinomas [1]. However, the effectiveness of cisplatin in the treatment cancer diseases is severely hindered by the frequent occurrence of initial and acquired drug resistance [2–5], and detrimental side effects, including nephrotoxicity, peripheral neuropathy, and ototoxicity [6,7]. Thus, it is critical to design other metal-based chemotherapeutic compounds to overcome tumor resistance to cisplatin.

During the last few years, there has been a renewed interest in the application of Au(III) compounds in cancer chemotherapy [8,9]. Attention was directed towards Au(III) compounds for two reasons: (1) Au(III) center is isoelectronic to Pt(II) compounds and adopt square-planar configuration; (2) Au(III) compounds have displayed strong tumor cell growth inhibition effects by a non-cisplatin-like mode of action. However, the high redox potential and poor stability of Au(III) compounds make their use rather problematic under physiological conditions. In recent years, by implementation of appropriate ligand selection strategies, a number of Au(III) compounds have been obtained, exhibiting sufficient stability under physiological-like conditions and manifesting cytotoxic properties towards several tumor cell lines [10,11]. The main types of Au(III) complexes endowed with improving stability and encouraging pharmacological properties are summarized as follows: coordination compounds with *N*-polydentate [12,13], macrocyclic ligands [14], chelating phosphines [15,16], and organometallic compounds with an Au–C bound or CNC-pincer backbone [17,18].

There has been a continuous interest in the synthesis of more potent Au(III) complexes containing S- and N-donor ligands that should have higher cytotoxic activity with minimum or no side effects compared to cisplatin [19]. In former work, we reported the synthesis and cytotoxicity of new Au(III) complexes with 5-aryl-3-(pyridin-2-yl)-4,5-dihydropyrazole-1-carbothioamide derivatives, which showed higher cytotoxicity than cisplatin against HeLa cell [20]. It was also reported that Au(III)-dithiocarbamato complexes displayed antitumor properties and no nephrotoxic side-effects [21]. Fregona and co-workers reported Au(III) complexes [Au(DMDT)X_2] and [Au(ESDT)X_2], which exhibited much more cytotoxic in vitro than cisplatin, with 1- to 4-folds higher cytotoxicity than reference drug, even toward human tumor cell lines intrinsically resistant to cisplatin itself [21–25]. Cyclic amine (such as piperidine, morpholine or piperazine) was able to select for improving activity in drug design [26]. In order to further explore the structure–activity relationships and discover new metal-based anticancer drugs, the synthesis, characterization and cytotoxicity of seven new Au(III) complexes with cyclic amine-based dithiocarbamate ligands are described in this paper.

The ligands **L1**–**L7** were prepared through reaction of the corresponding cyclic amine with CS_2 in a basic medium (NaOH), following the method as described in literature [27]. Au(III) complexes: [(PipDTC)$AuCl_2$] (**1**), [(MoDTC)$AuCl_2$] (**2**), [(BzoPizDTC)$AuCl_2$] (**3**),

* Correspondence to: S. Wang, Key Laboratory of Chemical Biology of Hebei province, College of Chemistry and Environmental Science, Hebei University, Baoding 071002, China. Tel./fax: +86 312 507 9359.
** Correspondence to: J. Zhang, Key Laboratory of Chemical Biology of Hebei province, College of Chemistry and Environmental Science, Hebei University, Baoding 071002, China. Tel./fax: +86 312 507 9005.
E-mail addresses: wsx@hbu.cn (S. Wang), jczhang6970@yahoo.com.cn (J. Zhang).

1387-7003/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.inoche.2013.02.010

[(TsPizDTC)$AuCl_2$] (**4**), [(PizDTC)Au_2Cl_4] (**5**), [(MePizDTC)Au_2Cl_5] (**6**) and [(EtPizDTC)Au_2Cl_5] (**7**) have been prepared as described in the experimental section (as shown in Scheme 1). Treatment of the cyclic-amine-based (such as piperidine, morpholine, *N*-benzoyl piperazine or *N*-(*p*-toluenesulfonyl)piperazine) dithiocarbamate ligands (**L1**–**L4**) with K[$AuCl_4$]·H_2O afford complexes (**1**–**4**) in 65–70% yields (Scheme 1, Route 1). Reaction of piperazine bis-dithiocarbamate (**L5**) with K[$AuCl_4$]·H_2O affords complex **5** in ~70% yield (Scheme 1, Route 2). Using *N*-alkyl piperazine dithiocarbamates (**L6** or **L7**) as ligands afford complexes (**6**, **7**) in 51–56% yields (Scheme 1, Route 3). Complexes **1**–**4** are mononuclear complexes, whereas complexes **5**–**7** are binuclear complexes [28].

The mode of coordination of complex **1** was confirmed by X-ray diffraction. The crystal was obtained by recrystallization complex **1** in acetonitrile and evaporating the solvent supernatant for a few weeks. Complex **1** crystallized in a monoclinic unit cell, space group P212121 (as shown in Fig. 1). Crystallographic data [29], selected bond lengths and angles for complex **1** are shown in Tables 1 and 2. The crystal data reveal that the dithiocarbamate ligands take place through the two sulfur atoms in an approximately square-planar geometry around the gold atom, while the other two coordination positions are occupied by the chlorine atoms, the -NCSS moiety acting as a symmetrical bidentate chelating group. The angle between planar S(1)–Au(1)–S(2) and planar Cl(1)–Au(1)–Cl(2) is 0.879(132)°, which indicates that the Au(1)–Cl(1)–Cl(2)–N(1)–N(2) plane is slightly distorted. The two Au–S bond lengths are 2.2821(19) and 2.290(3) Å. And, it is in good arrangement with the structure of [Au(MSDT)Br_2] obtained from GGA calculation reported by Fregona [22].

The elemental analysis data of **1**–**7** are in good agreement with the calculated values. All the complexes **1**–**7** are nonelectrolytes, as their molar conductance values (Λm) recorded in acetonitrile at 25.0 °C are in the range of 18.6–30.3 S m^2 mol^{-1} [30].

Optical electronic absorption spectra in acetonitrile generally show a similar pattern for all these complexes. Band I (226–228 nm) assign to an intraligand $\pi \rightarrow \pi^*$ transition located in the -NCSS moiety or intraligand $d \rightarrow p$ transition between levels originated by sulfur atoms. Bands II (266–275 nm) and Bands III (315–322 nm) show and correspond to $\pi \rightarrow \pi^*$ intraligand transitions mainly located in the -NCS and -CSS moieties, respectively [31].

Three regions in the IR spectrum of **1**–**7** are valuable in arguments concerning the electronic and structural characteristics of these compounds. The presence of the band in 1425–1456 cm^{-1} region is due to the ν(N-CSS). The bands present in the 1026–1087 cm^{-1} region are attributed to ν(C–S) vibration. The bands in the 391–420 cm^{-1} region are associated with ν(Au–S) vibration [32,33]. In addition, the most important change is that the peak of ligands due to the ν(N-CSS) vibration are shifted to higher frequency by about 20–25 cm^{-1} after coordination with Au(III) atom [34].

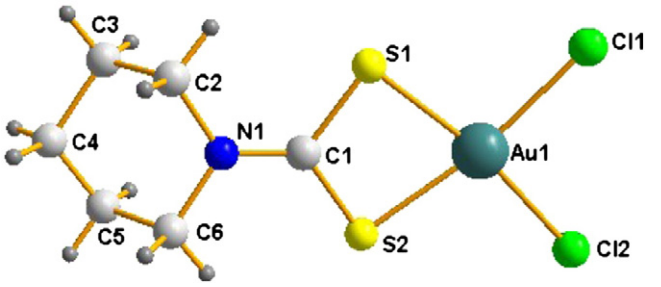
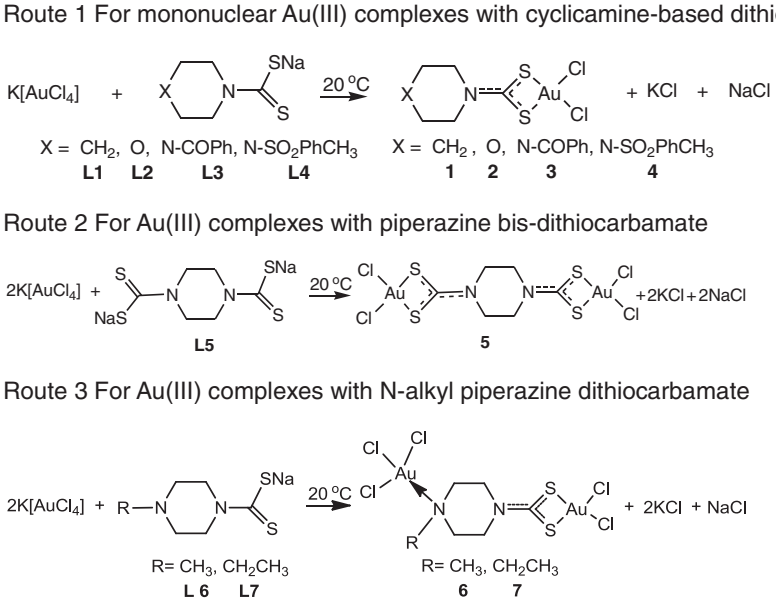


Fig. 1. Molecular structure for the complex **1**.

In comparison the ^{1}H NMR of the Au(III) complexes with those of free ligands, the δ of $-CH_2NCS_2$ shifts 0.3–0.5 ppm to the down field. For example, the proton signal at 3.55 ppm attributed to $-CH_2NCS_2$ (2H) of **L1** shift 0.37 ppm in complex **1.** This down field shift is caused by the lower electron density existing on theses protons in the complexes, in which the -NCSS moiety is neutral than in the free ligands, in which such a dithiocarbamic group is anionic.

^{13}C NMR of complexes **1**–**7** are recorded in DMSO-d_6, the δ of -N**C**S_2 carbon of all the complexes shifts 5–10 ppm to the down field in comparison to free ligands. This result is consistent with Fregona reported [35].

Complexes **1**–**7** are evaluated for their cytotoxic potency against four cell lines carried out by MTT assay [36], and the IC_{50} values are listed in Table 3. It can be seen that complexes **1**–**7** exert cytotoxic effect and selectivity against HL-60, BGC-823, Bel-7402 and KB cells lines. Complex **1** exhibits 11-, 5- and 1-folds higher cytotoxicity than cisplatin against KB, BGC-823 and Bel-7402 cell lines. Complex **2** shows higher cytotoxicity than cisplatin against BGC-823 and Bel-7402 cell lines. Complexes **1** and **2** display similar cytotoxicity to cisplatin against HL-60 cell line. Complexes **3** and **4** display higher cytotoxicity than cisplatin against BGC-823 cell line. In general, Complexes **1**–**4**



Scheme 1. The synthetic routines of the complexes **1**–**7**.

Table 1
Selected bond lengths and angles for complex **1**.

Length/Å or angle/°	
Au(1)–S(2)	2.2821 (19)
Au(1)–S(1)	2.290 (3)
Au(1)–Cl(1)	2.299 (3)
Au(1)–Cl(2)	2.309 (3)
S(2)–Au(1)–S(1)	75.58 (7)
S(2)–Au(1)–Cl(1)	171.01 (13)
S(1)–Au(1)–Cl(1)	95.45 (13)
S(2)–Au(1)–Cl(2)	94.39 (10)
S(1)–Au(1)–Cl(2)	169.96 (10)
Cl(1)–Au(1)–Cl(2)	94.57 (15)

Table 3
The cytotoxicity of the complexes **1**–**7** against HL-60, BGC-823, KB and Bel-7402 cell lines.

Complexes	IC_{50} (μM)			
	HL-60	BGC-823	KB	Bel-7402
1	2.88 ± 0.22	1.05 ± 0.26	0.64 ± 0.12	1.18 ± 0.16
2	2.85 ± 0.19	3.22 ± 0.25	8.52 ± 0.46	1.67 ± 0.35
3	3.60 ± 0.35	3.35 ± 0.29	11.85 ± 0.85	9.46 ± 0.24
4	12.89 ± 1.52	5.86 ± 0.48	17.01 ± 1.25	5.56 ± 0.48
5	18.60 ± 1.27	22.91 ± 1.68	15.24 ± 0.46	4.93 ± 0.50
6	17.90 ± 1.42	14.25 ± 1.17	55.65 ± 1.85	12.85 ± 0.75
7	28.28 ± 1.45	26.91 ± 0.64	59.74 ± 1.88	22.19 ± 1.42
Cisplatin [37]	2.89 ± 0.34	6.48 ± 0.81	8.12 ± 0.97	2.65 ± 0.33

show better cytotoxicity than cisplatin against BGC-823 cell line. It indicates that complexes **1**–**4** maybe exhibit selectivity cytotoxicity against BGC-823 cell line.

The structure–activity relationships are summarized as follows: (1) The number of metal centers affects on cytotoxicity. In general, mononuclear complexes **1**–**4** show higher cytotoxicity than binuclear complexes **5**–**7**. (2) The characteristic of cyclic amine has an important effect on cytotoxicity. For example, the cytotoxicity of **1**–**4** against HL-60, BGC-823 and KB cell lines decreases in the sequence: piperidine ≥ morpholine > *N*-benzoyl piperazine > *N*-(*p*-toluenesulfonyl) piperazine. The cytotoxicity of **1**–**3** against Bel-7402 cell line decreases in the sequence: piperidine > morpholine > *N*-benzoyl piperazine. It indicates that the steric hindrance has an important effect on the cytotoxicity, and the cytotoxicity decreases with increasing of the steric hindrance. In summary, when the cyclic amine is piperidine or morpholine, Au(III) complexes have better cytotoxicity.

Seven new potential anticancer Au(III) complexes with cyclic amine-based dithiocarbamate ligands were synthesized and elucidated on the basis of elemental analysis, IR, UV, and NMR, conductivity measurements and X-ray diffraction. The cytotoxicity results show that the Au(III) complexes with cyclic amine-based dithiocarbamate exert selective cytotoxicity against the tested cell lines. The nature of cyclic amine and the number of metal centers have important effects on cytotoxicity of the complexes. This study indicates that Au(III) complexes with dithiocarbamate derivative might be a promising source of metal-based antitumor agent.

Abbreviations

PipDTC piperidindithiocarbamate
MoDTC morfolindithiocarbamate
BzoPizDTC benzoylpiperazinedithiocarbamate
TsPizDTC tosyl piperazinedithiocarbamate
PizDTC piperazinedithiocarbamate
MePizDTC *N*-methylpiperazinedithiocarbamate
EtPizDTC *N*-ethylpiperazinedithiocarbamate
DMDT *N*,*N*-dimethyldithiocarbamate
ESDT ethylsarcosinedithiocarbamate
GGA generalized gradient approximation
MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
IC_{50} half maximal (50%) inhibitory concentration (IC) of a substance
OD optical density

Table 2
Crystallographic data for complex **1**.

Formula	$C_6H_{10}AuCl_2NS_2$
Fw	428.14
T (K)	296 (2)
Cryst syst	Orthorhombic
Space group	P212121
a (Å)	7.0103 (8)
b (Å)	12.3400 (15)
c (Å)	12.9741 (16)
V (nm^3)	1.1224 (2)
Z	4
Dc (Mg m^{-3})	2.534
F (000)	792
Cryst dimens (mm)	0.57 × 0.27 × 0.23
θ range (deg)	2.28–28.36
hkl ranges	−8 < *h* < 9 −16 < *k* < 16 −17 < *l* < 16
Data/parameters	2801/110
Goodness-of-fit on F^2	0.994
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0501$ $wR_2 = 0.1145$

Acknowledgments

This work was supported by Natural Science Foundation of Hebei Province (No. B2011201135), the Nature Science Foundation for Distinguished Young Scholars of Hebei Province (No. B2011201164), the Key Basic Research Special Foundation of Science Technology Ministry of Hebei Province (Grant Nos. 11966412D, 12966418D), the Key Research Project Foundation of Department of Education of Hebei Province (No. ZH2012041), the Pharmaceutical Joint Research Foundation of the Natural Science Foundation of Hebei Province and China Shiyao Pharmaceutical Group Co., Ltd (B2011201174), and the Science and Technology Support Project of Hebei Province (No. 11276431).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2013.02.010.

References

[1] A.M. Thayer, Chem. Eng. News 88 (2010) 24–28.
[2] L. Kelland, Nat. Rev. Cancer 7 (2007) 573–584.
[3] S.H. van Rijt, P.J. Sadler, Drug Discov. Today 14 (2009) 1089–1097.
[4] X.Y. Wang, Z.J. Guo, Chem. Soc. Rev. 42 (2013) 202–2247.
[5] S. Van Zutphen, J. Reedijk, Coord. Chem. Rev. 249 (2005) 2845–2853.
[6] B.W. Harper, A.M. Krause-Heuer, M.P. Grant, M. Manohar, K.B. Garbutcheon-Singh, J.R. Aldrich-Wright, Chem. Eur. J. 16 (2010) 7064–7077.
[7] Y.P. Ho, S.C.F. Au-Yeung, K.K.W. To, Med. Res. Rev. 23 (2003) 633–655.
[8] S. Nobili, E. Mini, I. Landini, C. Gabbiani, A. Casini, L. Messori, Med. Res. Rev. 30 (2010) 550–580.
[9] C.M. Che, R.W.Y. Sun, Chem. Commun. 47 (2011) 9554–9560.
[10] M. Serratrice, M.A. Cinellu, L. Maiore, M. Pilo, A. Zucca, C. Gabbiani, A. Guerri, I. Landini, S. Nobili, E. Mini, L. Messori, Inorg. Chem. 51 (2012) 3161–3171.
[11] M.A. Cinellu, L. Maiore, M. Manassero, A. Casini, M. Arca, H.H. Fiebig, G. Kelter, E. Michelucci, G. Pieraccini, C. Gabbiani, L. Messori, ACS Med. Chem. Lett. 1 (2010) 336–339.
[12] M. Serratrice, F. Edafe, F. Mendes, R. Scopelliti, S.M. Zakeeruddin, M. Grätzel, I. Santos, M.A. Cinellua, A. Casini, Dalton Trans. 41 (2012) 3287–3293.
[13] L. Maiore, M.A. Cinellu, S. Nobili, I. Landini, E. Mini, C. Gabbiani, L. Messori, J. Inorg. Biochem. 108 (2012) 123–127.
[14] R.W.Y. Sun, C.K.L. Li, D.L. Ma, J.J. Yan, C.N. Lok, C.H. Leung, N.Y. Zhu, C.M. Che, Chem. Eur. J. 16 (2010) 3097–3113.

[15] N. Shaik, A. Martin, I. Augustin, H. Giovinazzo, A. Varela-Ramirez, M. Sanaú, R.J. Aguilera, M. Contel, Inorg. Chem. 48 (2009) 1577–1587.
[16] L. Vela, M. Contel, L. Palomera, G. Azaceta, I. Marzo, J. Inorg. Biochem. 105 (2011) 1306–1313.
[17] J.J. Zhang, W. Lu, R.W.Y. Sun, C.M. Che, Angew. Chem. 124 (2012) 4966–4970.
[18] Y.B. Zhu, B.R. Cameron, R. Mosi, V. Anastassov, J. Cox, L. Qin, Z. Santucci, M. Metz, R.T. Skerlj, S.P. Fricker, J. Inorg. Biochem. 105 (2011) 754–762.
[19] P.D. Maia, H.H. Nguyen, D. Ponader, A. Hagenbach, S. Bergemann, R. Gust, V.M. Deflon, U. Abram, Inorg. Chem. 51 (2012) 1604–1613.
[20] S.X. Wang, W.Q. Shao, H.D. Li, C. Liu, K. Wang, J.C. Zhang, Eur. J. Med. Chem. 46 (2011) 1914–1918.
[21] M.N. Kouodom, L. Ronconi, M. Celegato, C. Nardon, L. Marchio, Q.P. Dou, D. Aldinucci, F. Formaggio, D. Fregona, J. Med. Chem. 55 (2012) 2212–2216.
[22] L. Giovagnini, L. Ronconi, D. Aldinucci, D. Lorenzon, S. Sitran, D. Fregona, J. Med. Chem. 48 (2005) 1588–1595.
[23] L. Ronconi, L. Giovagnini, C. Marzano, F. Bettio, R. Graziani, G. Pilloni, D. Fregona, Inorg. Chem. 44 (2005) 1867–1881.
[24] L. Ronconi, C. Marzano, P. Zanello, M. Corsini, G. Miolo, C. Macca, A. Trevisan, D. Fregona, J. Med. Chem. 49 (2006) 1648–1657.
[25] V. Milacic, D. Chen, L. Ronconi, K.R. Landis-Piwowar, D. Fregona, Q.P. Dou, Cancer Res. 66 (2006) 10478–10486.
[26] X.W. Chen, P. Zhan, C. Pannecouque, J. Balzarini, E.D. Clercq, X.Y. Liu, Eur. J. Med. Chem. 51 (2012) 60–66.
[27] C. Bolzati, M. Cavazza-Ceccato, S. Agostini, F. Refosco, Y. Yamamichi, S. Tokunaga, D. Carta, N. Salvarese, D. Bernardini, G. Bandoli, Bioconjugate Chem. 21 (2010) 928–939.
[28] General Procedure for the synthesis of **1**–**7**: Complexes were prepared by reaction $K[AuCl_4]\cdot H_2O$ and $\mathbf{L_1}$–$\mathbf{L_7}$ (1:1) or (2:1) in aqueous solution. After further 2 h at room temperature, the resulting yellow precipitate was filtered. The collected solid was washed with cold CH_3CN (3×1 mL) and dried to give **1**. Complex **1**: Yellow solid, yield: 66.7% IR (KBr, cm^{-1}): ν(N-CSS) 1430, ν(S–C–S) 1026, ν(S–Au–S) 408; UV (acetonitrile, nm): 228 (-NCSS), 275 (-NCS), 318 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.82 (m, 4H, CH_2), 1.72 (m, 6H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 23.9, 25.4, 51.2, 192.3; Anal. Calc. for $C_6H_{10}NS_2AuCl_2$: C, 16.83; H, 2.35; N, 3.27. Found: C, 16.93; H, 2.16; N, 3.10; Λm (CH_3CN) = 18.6 S m^2 mol^{-1}. Complex **2**: Yellow solid, yield: 65.2%; IR (KBr, cm^{-1}): ν(N-CSS) 1444, ν(S–C–S) 1072, ν(S–Au–S) 416; UV: (acetonitrile, nm) 226 (-NCSS), 273 (-NCS), 317 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.90 (q, 4H, CH_2), 3.81 (m, 4H, CH_2); ^{1}C NMR (150 MHz, DMSO-d_6) δ 50.1, 65.3, 197.4; Anal. Calc. for $C_5H_8NOS_2AuCl_2$: C, 13.96; H, 1.87; N, 3.26. Found: C, 14.04; H, 1.81; N, 3.14; Λm(CH_3CN) = 24.0 S m^2 mol^{-1}. Complex **3**: Yellow solid, yield: 68.7%; IR (KBr, cm^{-1}): ν(N-CSS) 1425, ν(S–C–S) 1083, ν(S–Au–S) 391; UV: (acetonitrile, nm) 227 (-NCSS), 271 (-NCS), 315 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (m, 5H, ph), 3.88 (m, 4H, CH_2), 3.68 (m, 4H, CH_2); ^{1}C NMR (150 MHz, DMSO-d_6) δ 46.0, 49.6,127.6, 129.0, 130.5, 135.4, 169.8, 194.7; Anal. Calc. for $C_{12}H_{13}N_2OS_2Au_2Cl_2$: C, 27.03; H, 2.46; N, 5.25. Found: C, 27.04; H, 2.88; N, 5.14; Λm(CH_3CN) = 23.2 S m^2 mol^{-1}. Complex **4**: Yellow solid, yield: 69.2%; IR (KBr, cm^{-1}): ν(N-CSS) 1436, ν(S–C–S) 1080, ν(S–Au–S) 399; UV: (acetonitrile, nm) 228 (-NCSS), 274 (-NCS), 315 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.78 (d, 2H, ph), 7.35 (d, 2H, ph), 3.81(m, 4H, CH_2), 3.75 (m, 4H, CH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 22.8, 48.5, 52.1, 128.3, 129.3, 137.6, 143,3, 198.8; Anal. Calc. for $C_{12}H_{15}N_2O_2S_3AuCl_2$: C, 24.71; H, 2.59; N, 4.80. Found: C, 24.45; H, 2.36; N, 4.54; Λm(CH_3CN) = 26.7 S m^2 mol^{-1}. Complex **5**: Yellow solid, yield: 70.1%. IR (KBr, cm^{-1}): ν(N-CSS) 1426, ν(S–C–S) 1078, ν(S–Au–S) 393; UV: (acetonitrile, nm) 227 (-NCSS), 277 (-NCS), 322 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.03 (s, 8H), ^{13}C NMR (150 MHz, DMSO-d_6) δ 52.3, 196.6; Anal. Calc. for $C_6H_8N_2S_6Au_2Cl_4$: C, 9.33; H, 1.04; N, 3.63. Found: C, 9.47; H, 1.36; N, 4.08; Λm(CH_3CN) = 29.8 S m^2 mol^{-1}. Complex **6**: Yellow solid, yield: 51.3%. IR (KBr, cm^{-1}): ν(N-CSS) 1448, ν(S–C–S) 1087, ν(S–Au–S) 398; UV: (acetonitrile, nm) 227 (-NCSS), 271 (-NCS), 315 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) 3.51(m, 4H, CH_2), 3.25 (m, 4H, CH_2), 3.01 (s, 3H, CH_3), ^{13}C NMR (150 MHz, DMSO-d_6) δ 43.4, 50.8, 51.7,190.4; Anal. Calc. for $C_6H_{11}N_2S_2Au_2Cl_5$: C, 9.65; H, 1.49; N, 3.75. Found: C, 9.77; H, 1.38; N, 4.14; Λm(CH_3CN) = 30.3 S m^2 mol^{-1}. Complex **7:** Yellow solid, yield: 56.3%. IR (KBr, cm^{-1}): ν(N-CSS) 1446, ν(S–C–S) 1074, ν(S–Au–S) 420; UV: (acetonitrile, nm) 227 (-NCSS), 266 (-NCS), 317 (-CSS); ^{1}H NMR (600 MHz, DMSO-d_6) 3.61 (m, 4H, CH_2), 3.45 (m, 4H, CH_2), 2.89 (q, 2H, CH_2), 1.15 (t, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.8, 41.2, 48.9, 50.3, 192.3; Anal. Calc. for $C_7H_{13}N_2S_2Au_2Cl_5$: C, 11.05; H, 1.72; N, 3.68. Found: C, 10.87; H, 1.29; N, 3.74; Λm(CH_3CN) = 29.3 S m^2 mol^{-1}.
[29] The data collection of the complex **1** was performed on a Bruker SMART APEX II CCD diffractometer equipped with a graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. Multi-scan absorption corrections were applied using the SADABS program. The structure was solved by the direct method using the SHELXS-97 program. Refinements on F2 were performed using SHELXL-97 by the full-matrix least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. Crystallographic data for the structural analysis of **1** have been deposited with the Cambridge Crystallographic Data Centre, CCDC-907890. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).
[30] W.J. Geary, Coord. Chem. Rev. 7 (1971) 81–122.
[31] C.C. Hadjikostas, G.A. Katsoulos, S.K. Shakhatreh, Inorg. Chim. Acta 133 (1987) 129–132.
[32] D.A. Brown, W.K. Glass, M.A. Burke, Spectrochim. Acta 32A (1976) 137–143.
[33] J.J. Criado, I. Fernandez, B. Macias, J.M. Salas, M. Medarde, Inorg. Chim. Acta 174 (1990) 67–75.
[34] F. Shaheen, A. Badshah, M. Gielen, G. Croce, U. Florke, D.D. Vos, S. Ali, J. Organomet. Chem. 695 (2010) 315–322.
[35] L. Ronconi, C. Maccato, D. Barreca, R. Saini, M. Zancato, D. Fregona, Polyhedron 24 (2005) 521–531.
[36] Four human carcinoma cell lines were used for cytotoxicity determination: HL-60, BGC-823, KB and Bel-7402 cell lines. The cells harvested from exponential phase were seeded equivalently into a 96-well plate, and then the complexes were added to the wells to achieve final concentrations. Control wells were prepared by addition of culture medium. Wells containing culture medium without cells were used as blanks. All experiments were performed in quintuplicate. The MTT assay was performed as described by Mosmann [30]. Upon completion of the incubation for 44 h, stock MTT dye solution (20 mL, 5 mg/mL) was added to each well. After 4 h incubation, 2-propanol (100 mL) was added to solubilize the MTT formazan. The OD of each well was measured on a microplate spectrophotometer at a wavelength of 570 nm. The IC_{50} value was determined from plot of % viability against dose of compounds added.
[37] J.C. Zhang, L.W. Li, L.W. Wang, F.F. Zhang, X.L. Li, Eur. J. Med. Chem. 45 (2010) 5337–5344.