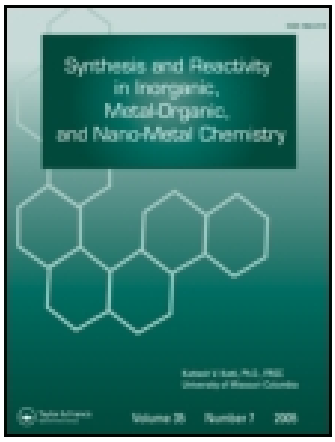


Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsrt20

A Diorganotin(IV) Complex of 2,6-Diacetylpyridine Bis(N^4- Cyclohexylthiosemicarbazone): Synthesis, Crystal Structure, and Cytotoxicity

Han Yu[a], Gaofeng Zhang[b], Mingxue Li[a], Yanli Lu[a] & Hechen Wu[a]

[a] Henan Key Laboratory of Polyoxometalates, Institute of Molecular and Crystal Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng, P. R. China

[b] Yancheng Experimental High School, Luohe, P. R. China

Accepted author version posted online: 29 Jun 2015.

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry (2015) 45, 1864–1869

ISSN: 1553-3174 print / 1553-3182 online
DOI: 10.1080/15533174.2013.867878

A Diorganotin(IV) Complex of 2,6-Diacetylpyridine Bis(N^4- Cyclohexylthiosemicarbazone): Synthesis, Crystal Structure, and Cytotoxicity

HAN YU[1], GAOFENG ZHANG[2], MINGXUE LI[1], YANLI LU[1], HECHEN WU[1]

[1]*Henan Key Laboratory of Polyoxometalates, Institute of Molecular and Crystal Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng, P. R. China*
[2]*Yancheng Experimental High School, Luohe, P. R. China*

Received 14 October 2013; accepted 10 November 2013

A diorganotin(IV) complex formulated as [$(Me)_2Sn(L)$] (**1**) (H_2L = 2,6-diacetylpyridine bis(N^4-cyclohexylthiosemicarbazone) has been synthesized and structurally characterized by elemental analysis, IR, UV, and NMR spectroscopy, and single-crystal X-ray diffraction. Complex **1** contains mononuclear neutral molecules composed of one N_3S_2 pentadentate anionic thiosemicarbazone ligand and one $(Me)_2Sn$(IV) group with a seven-coordinated tin ion. *In vitro* biological studies have indicated that complex **1** exhibited enhanced cytotoxicity compared to the thiosemicarbazone alone against human hepatocellular carcinoma HepG2 cells and could slightly distinguish HepG2 cells from normal hepatocyte QSG7701 cells.

Keywords: thiosemicarbazone, diorganotin(IV), crystal structure, cytotoxic activity

Introduction

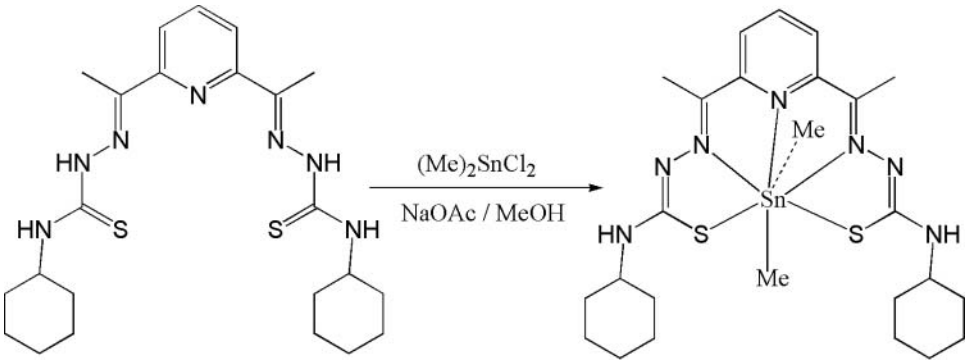
The search for new antitumor agents has immense importance for drug development. Considerable attention has been focused on heterocyclic thiosemicarbazones due to their coordination chemistry and biological activity.[1–6] The best known member of this family, 3-aminopyridine carboxaldehyde thiosemicarbazone (3-AP), is a potent ribonucleotide reductase inhibitor that is currently in phase II clinical trials for the treatment of a number of forms of cancer, including non–small-cell lung cancer and renal carcinoma.[7] This compound shows therapeutic activity over a certain range of dosages in preclinical tumor models without imposing intolerable host toxicity[8] and has led to a renewed interest in this class of compounds. The studies indicate that the biological activities of thiosemicarbazones often show a high dependence on their substituents. Minor modifications in thiosemicarbazones can lead to significant changes in biological activity.[9–11] Moreover, the biological properties of thiosemicarbazones are often related to metal ion coordination in different ways since some of them increase the biological activity by forming chelates with specific metal ions.[12,13] In some cases, the highest *in vivo* activity is associated with a metal complex rather than the parent ligand and some side effects may decrease upon complexation.[4,13–15]

Tin complexes are known for their multiple applications as antimicrobials and biocides.[16] Moreover, diorganotin(IV) compounds are known to exhibit important cytotoxic effects against tumor cells,[17–19] but are often very toxic.[20,21] Therefore, the syntheses of tin complexes with thiosemicarbazones could be a strategy of preparation of new drug candidates in which the metal and ligand could act synergistically.

In recent years we have been working on the structural and biological properties of heterocyclic thiosemicarbazones and their metal complexes.[22] Our chemical strategy focuses on modifications to the ligand substitutions and the types of metal ions with the aim of enhancing biological activities and reducing the potential toxicity of these compounds. These results have revealed that thiosemicarbazones derived from 2-acetylpyridine and their transition-metal complexes show significant cytotoxicity. After a careful literature search, N_3S_2 pentadentate 2,6-diacetylpyridine bis(N^4-cyclohexylthiosemicarbazone) and its metal complexes are not well documented. It is envisaged that they are likely to exhibit interesting properties both structurally and biologically.

As a part of our ongoing studies, we have synthesized and characterized 2,6-diacetylpyridine bis(N^4-cyclohexylthiosemicarbazone) and its tin(IV) complex [$(Me)_2Sn(L)$] (**1**) (Scheme 1). We have studied their *in vitro* cytotoxicity

Address correspondence to Mingxue Li, Henan Key Laboratory of Polyoxometalates, Institute of Molecular and Crystal Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, P. R. China. E-mail: limingxue@henu.edu.cn
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsrt.



Sch. 1. The reaction scheme for the synthesis of **1**.

against human hepatocellular carcinoma HepG2 cells. In addition, toxicity studies, on normal hepatocyte QSG7701 cells, have been carried out as an attempt to provide an insight into the pharmacological properties of the title compounds.

Experimental

Materials and Physical Measurements

All solvents and reagents used in this study were reagent grade and used without further purification. Human hepatocellular carcinoma HepG2 cells and normal hepatocyte QSG7701 cells were purchased from the Shanghai Institute for Biological Science, Chinese Academy of Science (Shanghai, China). Elemental analysis of C, H, and N was performed on a Perkin Elmer 240 analyzer. The infrared spectra were recorded from KBr discs on a Nicolet 170 FT infrared spectrophotometer. Electronic spectra were obtained with a Hitachi U4100 spectrometer. ^{1}H NMR spectra were recorded using a Bruker AV-400 spectrometer.

Synthesis of H_2L

A methanol solution of 4-cyclohexyl-3-thiosemicarbazide (2.08 g, 12 mmol) was refluxed with 2,6-diacetylpyridine (0.978 g, 6 mmol) in 30 mL methanol continuously for 4 h after adding a few drops of acetic acid. The mixture was allowed to cool to room temperature and kept for 12 h. The yellow precipitate was filtered off, washed with methanol and dried over P_4O_{10} *in vacuo*. Yield, 82 %. Elemental Anal. Calcd. (%) for $C_{23}H_{35}N_7S_2$: C, 58.32; H, 7.45; N, 20.70. Found: C, 58.48; H, 7.39; N, 20.57. -IR [KBr, ν (cm^{-1})]: 3335, 3298 and 3157 (N—H), 2930 and

Table 1. Summary of crystal data and refinement results for **1**

Empirical formula	$C_{25}H_{39}N_7S_2Sn$
Formula weight	620.44
T (K)	296(2) K
Crystal size (mm)	0.45 × 0.39 × 0.28
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	33.339 (3),
b (Å)	9.8003(10),
c (Å)	18.1785(17)
β (°)	99.216(2)
V (Å^3)	5862.8(10)
D_c (g cm^{-3})	1.406
Z	8
μ (mm^{-1})	1.040
θ range for data collections	0.62–26°
F(000)	2560
Limiting indices	$-40 \leq h \leq 44$, $-13 \leq k \leq 12$, $-24 \leq l \leq 15$
Reflections collected	14280
Independent reflections	7941 ($R_{int} = 0.0624$)
R_1, wR_2 [$I \geq 2\sigma(I)$]	0.0520, 0.1284
R_1, wR_2 (all date)	0.1121, 0.1758
Goodness-of-fit on F^2	0.885

Table 2. Selected bond lengths (Å) and angles (°) for **1**

Sn(1)–C(25)	2.127(6)	Sn(2)–N(10)	2.433(4)
Sn(1)–C(24)	2.141(6)	Sn(2)–S(4)	2.647(2)
Sn(1)–N(4)	2.371(5)	Sn(2)–S(3)	2.702(2)
Sn(1)–N(5)	2.438(4)	S(1)–C(7)	1.752(5)
Sn(1)–N(3)	2.442(5)	S(2)–C(17)	1.725(6)
Sn(1)–S(1)	2.658(2)	N(2)–N(3)	1.373(6)
Sn(1)–S(2)	2.689(2)	N(3)–C(8)	1.265(7)
Sn(2)–C(49)	2.119(6)	N(5)–C(15)	1.293(7)
Sn(2)–C(50)	2.130(6)	N(5)–N(6)	1.356(6)
Sn(2)–N(11)	2.390(4)	N(6)–C(17)	1.340(7)
Sn(2)–N(12)	2.432(5)		
C(25)–Sn(1)–C(24)	172.0(3)	N(12)–Sn(2)–S(4)	71.91(11)
C(25)–Sn(1)–N(4)	85.6(2)	N(10)–Sn(2)–S(3)	71.37(11)
N(4)–Sn(1)–N(5)	67.29(16)	N(11)–Sn(2)–N(10)	66.93(15)
N(3)–Sn(1)–S(1)	71.46(11)	C(49)–Sn(2)–C(50)	173.8(2)
N(5)–Sn(1)–S(2)	71.46(12)	S(4)–Sn(2)–S(3)	83.52(5)
S(1)–Sn(1)–S(2)	82.99(5)	N(11)–Sn(2)–N(12)	66.50(15)
N(4)–Sn(1)–N(3)	67.05(15)	C(49)–Sn(2)–N(11)	88.0(2)

2854 (cyclohexyl), 1635 (C=N), 1154 (N—N), 782 (C=S). -UV/Vis (MeOH, λ(nm)): 235, 314. -^{1}H NMR ($CDCl_3$, ppm): 14.20 (s, 2H, NH), 8.72 (s, 2H, NH), 8.65 (s, 2H, py), 7.77 (t, J = 7.8 Hz, 1H, py), 2.44 (s, 6H, Me), 2.42 (s, 2H, C_6H_{11}), 2.17–2.14 (m, 8H, C_6H_{11}), 1.79–1.76 (m, 8H, C_6H_{11}), 1.70–1.66 (m, 4H, C_6H_{11}).

Synthesis of [(Me)$_2$Sn(L)] (1)

A methanol solution containing $(Me)_2SnCl_2$ (0.044 g, 0.2 mmol) was added dropwise to a methanol solution (20 mL) of 2,6-diacetylpyridine bis(N^4- cyclohexylthiosemicarbazone) (0.068 g, 0.2 mmol) and NaOAc (0.032 g, 0.4 mmol). After refluxing for 1 h with stirring, the resulting mixture was filtered. Yellow crystals suitable for X-ray studies were obtained by the slow evaporation of an ethanol solution of **1**. The complex was recrystallized from methanol and dried over P_4O_{10} *in vacuo*. Yield, 79 %. Elemental Anal. Calcd. (%) for $C_{25}H_{39}N_7S_2Sn$: C, 48.39; H, 6.34; N, 15.80. Found: C, 48.26; H, 6.48; N, 15.62. -IR [KBr, ν (cm^{-1})]: 3390 and 3368 (N—H), 2930 and 2854 (cyclohexyl), 1563 (C=N), 1161 (N—N), 756 (C=S). −UV/Vis (MeOH, λ(nm)): 359, 416. -^{1}H NMR(DMSO-d_6, ppm): 8.27 (s, 2H, NH), 8.18 (t, J = 8.0 Hz, 1H, py), 8.08 (d, J = 8.0 Hz, 1H, py), 7.90 (d, J = 8.0 Hz, 1H, py), 2.51 (s, 6H, Me), 1.94–1.00 (m, 22H, C_6H_{11}), 0.51 (s, 6H, Sn-Me).

X-Ray Crystallographic Determination

A high-quality single-crystal was carefully selected under an optical microscope. The intensity data for **1** were collected at 296(2) K on a Bruker APEX–II CCD detector with Mo Kα radiation (λ = 0.71073 Å). Corrections for Lorentz and polarization effects and empirical absorption were applied. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F^2. All calculations were performed using the SHELXTL–97 software.[23,24] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to carbon and nitrogen atoms were geometrically placed in the idealized positions and refined with a riding model using default SHELXL parameters. The crystallographic data are listed in Table 1. The selected bond lengths and angles are given in Table 2. Hydrogen bond lengths and bond angles are listed in Table 3.

In Vitro *Cytotoxicity Assay*

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was carried out to evaluate cytotoxicity. Cells were plated into 96-well plates at a cell density of 1 × 10^4 cells per well and allowed to grow in a CO_2 incubator. After 24 h, the medium was removed and replaced by fresh medium containing the tested compounds which were

Table 3. Hydrogen bond lengths (Å) and bond angles (°) for complex **1**

D–H···A	*d*(H···A)	*d*(D···A)	∠(D–H···A)
N(1)–H(1A)–S(1)#1	2.97	3.637(5)	135.5
N(7)–H(7A)–N(9)#2	2.32	3.117(7)	153.4
N(8)–H(8A)–N(6)#3	2.40	3.145(7)	145.4
N(14)–H(14A)–S(4)#4	2.99	3.568(6)	126.9

Symmetry codes: #1: $-x, -y, -z+1$; #2: $x, y+1, z$; #3: $x, y-1, z$; #4: $-x+1, -y-1, -z+1$.

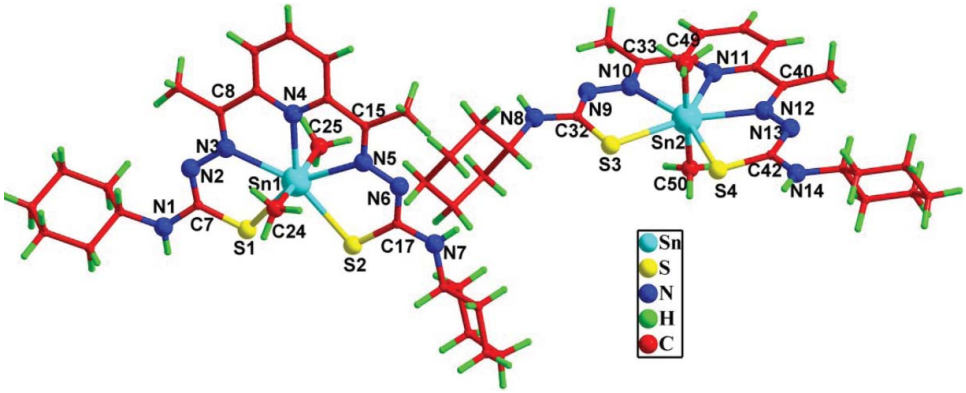


Fig. 1. Molecular structure of complex **1** with atomic numbering scheme.

dissolved in DMSO at 0.01 M and diluted to various concentrations with phosphate-buffered saline (PBS) before the experiment, and the final concentration of DMSO is lower than 1 %. After 24 h incubation, cultures were incubated in 100 μL of medium with 10 μL of 5 mg/mL MTT solution for 4 h at 37°C. The medium with MTT was removed, and 100 μL of DMSO was added to each well to dissolve the formazan. The absorbance at 570 nm was measured with microplate reader (Bio-Tek ELX800, USA). The inhibitory percentage of each compound at various concentrations was calculated, and the IC_{50} value was determined.

Results and Discussion

X-Ray Crystallography Diffraction Analysis

As shown in Figure 1, X-ray single-crystal structure analysis reveals that the asymmetric unit of the crystal of complex **1** consists of two slightly different crystallographically independent molecules with bond lengths and angles, which agree with each other and are within normal ranges (see Table 2). Each tin(IV) ion adopts a seven-coordinated distorted pentagonal bipyramidal geometry with the pentagonal plane defined by the pentadentate N_3S_2 thiosemicarbazone, whereas the axial positions are occupied by the two methyl groups. For an ideal pentagonal bipyramidal complex, each of the five angles subtended at the equatorial plane should be 72°. Therefore, the distortion from pentagonal bipyramidal geometry is evident from the bond angles N(4)–Sn(1)–N(5) 67.29(16), N(4)–Sn(1)–N(3) 67.05(15), N(3)–Sn(1)–S(1) 71.46 (11), N(5)–Sn(1)–S(2) 71.46(12), S(1)–Sn(1)–S(2) 82.99(5), N(11)–Sn(2)–N(12) 66.50(15), N(10)–Sn(2)–N(11) 66.93(15), N(10)–Sn(2)–S(3) 71.37(11), N(12)–Sn(2)–S(4) 71.91(11), S (3)–Sn(2)–S(4) 83.52(5), respectively. Although the azomethine nitrogen atoms are typically stronger donors than pyridine, the $Sn-N_{imine}$ bond distances in the present complex are longer than the $Sn-N_{pyridine}$ distance. While $M-N_{imine}$ bond distances in complexes of tridentate NNS thiosemicarbazone derived from heterocyclic aldehydes and ketones are invariably shorter than the $M-N_{pyridine}$ distances, the reverse appears to be true for metal complexes of pentadentate thiosemicarbazone ligands.[25] This is probably due to the geometrical requirements of the pentadentate N_3S_2 ligand and the fact that the pyridine nitrogen donor occupies the central position of the pentadentate ligand and is forced into a shorter than normal interaction with the metal because of the restraints of the two chelating arms. The measured C(7)–S(1) (1.752(5) Å), C(17)–S(2) (1.725(6) Å), C(32)–S(3) (1.714(5) Å) and C(42)–S(4) (1.735(6) Å) bond distances are longer than the typical thione double bond distance (1.56 Å) indicating that the ligand adopted a thiol tautomeric form and acted as a negative ligand.[26]

Since the thiosemicarbazone moieties have both the hydrogen bond donors and the hydrogen bond acceptors, the species provide the possibility of forming hydrogen bonds in the crys-

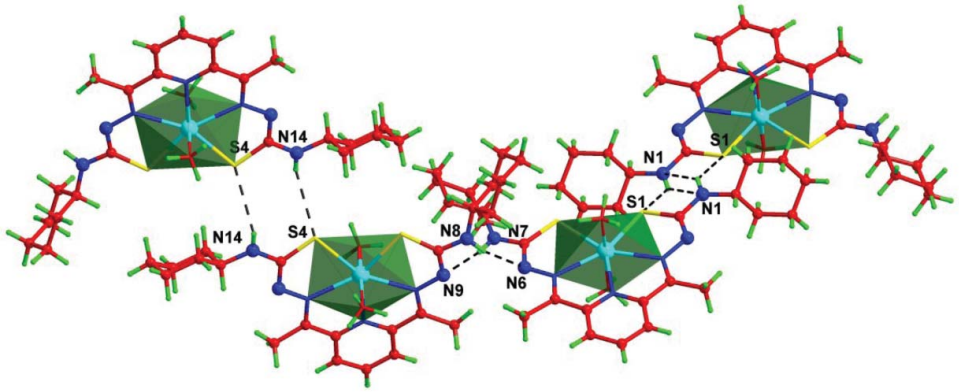


Fig. 2. Hydrogen bonds (dashed lines) in crystals of **1**.

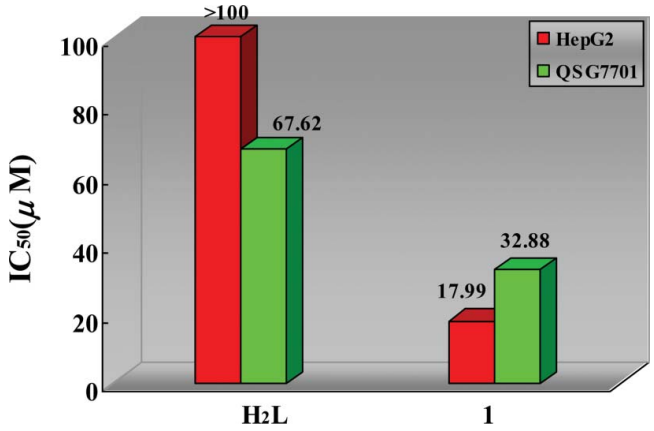


Fig. 3. The cytotoxicity of the title compounds against HepG2 cells and QSG7701 cells.

tal. The molecules of **1** are held together in the crystal packing through an extended network of intermolecular hydrogen bonds involving the terminal nitrogen atoms N(1), N(7), N(8), and N(14), the hydrazine nitrogen atoms N(6), N(9) and the coordinated sulfur atoms S(1), S(4), respectively (Figure 2). The separations for N(1)···S(1) (symmetry code: $-x, -y, -z + 1$) is 3.637(5) Å, with the N(1)−H(1A)···S(1) angle being 135.5°, the separations for N(7)···N(9) (symmetry code: $x, y + 1, z$) is 3.117(7) Å, with the N(7)−H(7A)···N(9) angle being 153.4°, the separation for N(8)···N(6) (symmetry code: $x, y - 1, z$) is 3.145(7) Å, with the N(8)−H(8A)···N(6) angle being 145.4° and the separations for N(14)···S(4) (symmetry code: $-x + 1, -y - 1, -z + 1$) is 3.568(6) Å, with the N(14)−H(14A)···S(4) angle being 126.9°, respectively (see Table 3).

In Vitro *Cytotoxicity*

In terms of the cytotoxic activity of thiosemicarbazones,[27–29] first we have evaluated the ability of H_2L and **1** to inhibit tumor cell growth against human hepatocellular carcinoma HepG2 cells. To explore the toxicity of these compounds, their effect on normal hepatocyte QSG7701 cells is also described. In our experiments, IC_{50} values (compound concentration that produces 50% of cell death) in micromolar units are calculated.

As shown in Figure 3, complex **1** indicates much lower IC_{50} values (17.99 μM) than H_2L (> 100 μM) against HepG2 cells indicating that coupling of the thiosemicarbazone to tin(IV) leads to enhancement of cytotoxicity of Schiff base ligand. Furthermore, IC_{50} values of **1** are higher in QSG7701 cells than in HepG2 cells, contrary to H_2L, indicating **1** has lower toxicity against QSG7701cells. Therefore, the further screening *in vitro* and *in vivo* of **1** will be essential for medical practice.

Conclusions

A diorganotin(IV) complex with 2,6-diacetylpyridine bis (N^4-cyclohexylthiosemicarbazone was synthesized and structurally characterized. It exhibited enhanced cytotoxicity compared to the thiosemicarbazone alone against human hepatoblastoma HepG2 cells and could slightly distinguish HepG2 cells from normal hepatocyte QSG7701 cells.

Funding

This work was financially supported by the National Natural Science Foundation of China (21071043), the Natural Science Foundation of Henan Province (132300410146), and Students' Innovation Training Program of Henan University (13NB052).

Supplementary Material

Crystallographic data for the structural analyses reported in this article have been deposited with the Cambridge Crystallographic Data Centre with CCDC 889493. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: t44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

References

1. Yu, Y.; Kalinowski, D. S.; Kovacevic, Z.; Siafakas, A. R.; Jansson, P. J.; Stefani, C.; Lovejoy, D. B.; Sharpe, P. C.; Bernhardt, P. V.; Richardson, D. R. Thiosemicarbazones from the old to new: iron chelators that are more than just ribonuclcotide reductase inhibitor. *J. Med. Chem*. **2009**, *52*, 5271–5294.
2. Singh, K; Barwa, M. S.; Tyagi, P. Synthesis, characterization and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate schiff bases derived by heterocyclic ketone. *Eur. J. Med. Chem*. **2006**, *41*, 147–153.
3. Karthikeyan, M. S.; Prasad, D. J.; Poojary, B.; Subramanya, B. K.; Holl, B. S.; Kumari, N. S. Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. *Bioorg. Med. Chem*. **2006**, *14*, 7482–7489.
4. Kowol, C. R.; Trondl, R.; Heffeter, P.; Arion, V. B.; Jakupec, M. A.; Roller, A.; Galanski, M.; Berger, W.; Keppler, B. K. Impact of metal coordination on cytotoxicity of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone(Triapine) and novel insights into terminal dimethylation. *J. Med. Chem*. **2009**, *52*, 5032–5043.
5. Beraldo, H.; Gambino, D. The wide pharmacological versatility of semicarbazones, Thiosemicarbazones and their metal complexes. *Mini-Rev. Med. Chem*. **2004**, *4*, 31–39.
6. Panneerselvam, P.; Nair, R. R.; Vijayalakshmi, G.; Subramanian, E. H.; Sridhar, S. K. Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents. *Eur. J. Med. Chem*. **2005**, *40*, 225–229.
7. Ma, B.; Goh, B. C.; Tan, E. H.; Lam, K. C.; Soo, R.; Leong, S. S.; Wang, L. Z.; Mo, F.; Chan, A. T.; Zee, B.; Mok, T. A. Redox-directed cancer therapeutics:mechanisms and opportunties. Invest. *New Drugs* **2008**, *26*, 169–173.
8. Finch, R. A.; Liu, M. C.; Grill, S. P.; Rose, W. C.; Loomis, R.; Vasquez, K. M.; Cheng, Y. C.; Sartorelli, A. C. Triapine (3-aminopyridine-2-carboxaldehyde- thiosemicarbazone): a potent inhibitor of ribonucleotide reductase activity with broad spectrum antitumor activity. *Biochem. Pharmacol*. **2000**, *59*, 983–991.

9. Singh, S.; Bharti, N.; Naqvi, F.; Azam, A. Synthesis, characterization and in vitro antiamoebic activity of 5-nitrothiophene-2-carboxaldehyde thiosemicarbazones and their Palladium (II) and Ruthenium (II) Complexes. *Eur. J. Med. Chem*. **2004**, *39*, 459–465.
10. Rebolledo, A. P.; Vieites, M.; Gambino, D.; Piro, O. E.; Castellano, E. E.; Zani, C. L.; Souza-Fagundes, E. M.; Teixeira, L. R.; Batista, A. A.; Beraldo, H. Palladium(II) complexes of 2-benzoylpyridine-derived thiosemicarbazones: spectral characterization, structural studies and cytotoxic activity. *J. Inorg. Biochem*. **2005**, *99*, 698–706.
11. Beraldo, H.; Gambino, D. Wide pharmacological versatility of semicarbazones, thiosemicarbazones and their metal complexes. Mini-Rev. *Med. Chem*. **2004**, *4*, 159–165.
12. Abram, U.; Ortner, K.; Gust, R.; Sommer, K. Gold complexes with thiosemicarbazones: reactions of bi- and tridentate thiosemicarbazones with dichloro[2-(dimethylaminomethyl)phenyl-C1,N] gold (III), [Au(damp-C1,N)Cl2]. *J. Chem. Soc., Dalton Trans*. **2000**, 735–744.
13. Murafuji, T.; Miyoshi, Y.; Ishibashi, M.; Mustafizur, R. A. F. M.; Sugihara, Y.; Miyakawa, I.; Uno, H. Antifungal activity of organobismuth compounds against the yeast saccharomyces cerevisiae: structure–activity relationship. *J. Inorg. Biochem*. **2004**, *98*, 547–552.
14. Mendes, I. C.; Moreira, J. P.; Ardisson, J. D.; Santos, R. G.; Silva, P. R. O.; Garcia, I.; Castineiras, A.; Beraldo, H. Organotin(IV) complexes of 2-pyridineformamide-derived thiosemicarbazones: antimicrobial and cytotoxic effects. *Eur. J. Med. Chem*. **2008**, *43*, 1454–1461.
15. Kovala-Demertzi, D.; Papageorgiou, A.; Papathanasis, L.; Alexandratos, A.; Dalezis, P.; Miller, J. R.; Demertzis, M. A. In vitro and in vivo antitumor activity of platinum(II) complexes with thiosemicarbazones derived from 2-formyl and 2-acetyl pyridine and containing ring incorporated at N(4)-position: synthesis, spectroscopic study and crystal structure of platinum(II) complexes with thiosemicarbazones, potential anticancer agents. *Eur. J. Med. Chem*. **2009**, *44*, 1296–1302.
16. Rebolledo, A. P.; Lima, G. M. D.; Gambi, L. N.; Speziali, N. L.; Maia, D. F.; Pinheiro, C. B.; Ardisson, J.D; Cortes, M. E.; Beraldo, H. Tin(IV) complexes of 2-benzoylpyridine N(4)-phenyl-thiosemicarbazone: spectral characterization, structural studies and antifungal activity. *Appl. Organomet. Chem*. **2003**, *17*, 945–951.
17. Gielen, M. Review: Organotin compounds and their therapeutic potential: a report from the Organometallic Chemistry Department of the Free University of Brussels. *Appl. Organomet. Chem*. **2002**, *16*, 481–494.
18. Gielen, M.; Biesemans, M.; Willem, R. Organotin compounds: from kinetics to stereochemistry and antitumour activities. *Appl. Organomet. Chem*. **2005**, *19*, 440–450.
19. Gielen, M. An overview of forty organotin chemistry developed at the free universities of brussels ULB and VUB. *J. Brazil. Chem. Soc*. **2003**, *14*, 870–877.
20. Jacobson, A. H.; Willingham, G. L.; Sea-nine antifoulant: an environmentally acceptable alternative to organotin antifoulants. *Sci. Total Environ*. **2000**, *258*, 103–110.
21. Abbott, A.; Abel, P. D.; Arnold, D. W.; Milne, A. Cost–benefit analysis of the use of TBT: the case for a treatment approach. *Sci. Total Environ*. **2000**, *258*, 5–19.
22. (a)Li, M. X.; Zhang, D.; Zhang, L. Z.; Niu, J. Y.; Ji, B. S. Synthesis, crystal structures and biological activities of 2-acetylpyridine N(4)-cyclohexylthiosemicarbazone and its manganese (II) and nickel(II) complexes. *Inorg. Chem. Commun*. **2010**, *13*, 1572–1575; b)Li, M. X.; Chen, C. L.; Zhang, D.; Niu, J. Y.; Ji, B. S. Mn(II), Co(II) and Zn(II) complexes with heterocyclic substituted thiosemicarbazones: synthesis, characterization, X-ray crystal structures and antitumor comparison. *Eur. J. Med. Chem*. **2010**, *45*, 3169–3177; c)Zhang, L. Z.; An, G. Y.; Yang, M.; Li, M. X.; Zhu, X. F. Synthesis, characterization, crystal structure and biological activities of the unusual main group 8-coordinate bismuth (III) complex derived from 2-acetylpyrazine N4-pyridylthiosemicarbazone. *Inorg. Chem. Commun*. **2012**, *20*, 37–40; d)Li, M. X.; Zhang, L. Z.; Zhang, D.; Ji, B. S.; Zhao, J. W. Synthesis, crystal structures, and biological evaluation of manganese(II) and nickel(II) complexes of 4-cyclohexyl-1-(1-(pyrazin-2-yl)ethylidene)thiosemicarbazide. *Eur. J. Med. Chem*. **2011**, *46*, 4383–4390; e)Li, M. X.; Zhang, L. Z.; Chen, C. L.; Niu, J. Y.; Ji, B. S. Synthesis, crystal structures, and biological evaluation of Cu(II) and Zn(II) complexes of 2-benzoylpyridine Schiff bases derived from S-methyl- and S-phenyldithiocarbazates. *Inorg. Biochem*. **2012**, *106*, 117–125.
23. Sheldrick, G. M. *SHELXS–97 Program for Crystal Structure Solution*; University of Göttingen, Germany, 1997.
24. Sheldrick, G. M. *SHELXL–97 Program for Crystal Structure Refinement*; University of Göttingen, Germany, 1997.
25. Battaglia, L. P.; Corradi, A. B.; Pelizzi, C.; Pelosi, G.; Tarasconi, P. Notes. Chemical and structural investigations on bismuth complexes of 2,6-di-acetylpyridine bis(2-thenoylhydrazone) and 2,6-diacetylpyridine bis(thiosemicarbazone). *J. Chem. Soc., Dalton Trans*. **1990**, *12*, 3857–3860.
26. Katti, K. V.; Singh, P. R.; Barnes, C. L. Transition-metal chemistry of main-group hydrazides. Part 2. A new oxime thiosemicarbazide framework as a novel SN multifunctional tripodal ligand for palladium(II): synthetic and X-ray crystal structural investigations. *J. Chem. Soc., Dalton Trans*. **1993**, 2153–2156.
27. Singh, S.; Bharti, N.; Mohapatra, P. P. Chemistry and biology of synthetic and naturally occurring antiamoebic agent. *Chem. Rev*. **2009**, *109*, 1900–1947.
28. Maurya, M. R.; Kumar, A.; Bhat, A. R.; Azam, A.; Bader, C.; Rehder, D. Dioxo- and oxovanadium(V) complexes of thiohydrazone ONS donor ligands: synthesis, characterization, reactivity, and antiamoebic activity. *Inorg. Chem*. **2006**, *45*, 1260–1269.
29. Bottari, B.; Maccari, R.; Monforte, F.; Ottana, R.; Vigorita, M. G.; Bruno, G.; Nicoloò, F. Rotondo, A.; Rotondo, E. Nickel(II) 2,6-diacetylpyridine bis(isonicotinoylhydrazonate) and bis(benzoylhydrazonate) complexes: structure and antimycobacterial evaluation. *Part XI. Bioorg. Med. Chem*. **2001**, *9*, 2203–2211.