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Synthesis, Characterization, Crystal Structures, and in vitro Antitumor Activity of Palladium and Platinum (II) Complexes with 2-Acetyl-4-Methylthiazole Thiosemicarbazone and 2-Acetylpyrazine Thiosemicarbazone

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Abstract

The novel Schiff bases I HAMTTSC (2-Acetyl-4-methylthiazole thiosemicarbazone), II HAPTSC(2-Acetylpyrazine thiosemicarbazone) and their complexes with Pt(II) and Pd(II): 1 [Pt(AMTTSC)Cl], 2 [Pt(AMTTSC)2], 3 [Pd(AMTTSC)Cl], 4 [Pd(AMTTSC)2], 5 [Pt(APTSC)Cl], 6 [Pt(APTSC)2], 7 [Pd(APTSC)Cl], and 8 [Pd(APTSC)2] have been synthesized, and characterized by elemental analysis and spectroscopic studies. The crystal structure of the Schiff bases I, II, and the complex 1 [Pt(AMTTSC)Cl], have been solved by single-crystal X-ray diffraction. The electronic, IR, UV/Vis, and NMR spectroscopic data of I and II and their complexes are reported. The in vitro antitumor activity of the Schiff bases and 1, 2, 4, 5 and 6 complexes against two different human tumor cell lines (HT-29 and HuTu-80) reveals that the complexes are more cytotoxic than their corresponding ligands with IC50 values at the range of 0.1–10 µM. These compounds can therefore be considered as agents with potential antitumor activity.

Molecular structure of 1 [Pt(AMTTSC)Cl]

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Introduction

Thiosemicarbazones (TSCNs) are very promising molecules in coordination chemistry because of their pharmacological properties of both ligands and complexes, (1–3) which include notably their antiparasital, (4) antibacterial (5, 6) and antitumor activities (7) depending on the parent aldehyde and ketone and, of course, metal ion. The thiosemicarbazone ligand usually coordinates with a metal through the imine nitrogen and the sulphur atom forming a five-membered ring chelate. Since cis-platin emerged as the most important antitumor drug (8), thousands of metal complexes have been synthesized and characterized in order to study the effect of the metal, the attached group on the structural and kinetic properties involved in the biological activity. (9) However significant problems are still extant, including side effects, toxicity, cancer specificity and acquired resistance. Consequently the development of new compounds outside the usual coordination sphere or of different structural properties is the challenge to cancer research.

Synthesis of the ligands

The ligands 2-Acetyl-4-methylthiazole thiosemicarbazone and 2-acetylpyrazine thiosemicarbazone, were prepared according to the literature (10).

Synthesis of Complexes Pt (AMTTSC)Cl Complex

A solution of K2PtCl4 (0.208 g, 0.5 mmol) in methanol, was added dropwise to a stirred solution of HAMTTSC (0.5 mmol) in 20 mL of methanol. The solution was refluxed for 2 hours and stirred for 24 hours at room temperature. The dark red precipitate was collected by filtration and dried in vacuo. Crystals suitable for X-Ray diffraction were obtained through slow evaporation of the DMF solvent.

Solid, yield: 70.59%, m.p. 236–237°C. Anal. Calc. For Pt(C7H9N4S2)Cl (443.84 g/mol): C, 18.94%; H, 2.04%; N, 12.62%. Found: C, 18.74%; H, 2.18%; N, 12.85%. I.R. (solid state, cm^{-1}): ν(NH2) 3395, 3267; ν(C=N) 1520.38; ν(C=S) 873.31; ν(N-N)1065.89. 1H-N.M.R (DMSO-d6): δ 2.21, 2.41 (s, 6H, 2CH3), 7.75 (s, 1H); 8.07(b, 2H, NH2).). 13C-N.M.R. (DMSO-d6): δ 13.93, 16.39 (2CH3); 148.59, –154.62(3C ring); 171.92 (HC=N); 183.20 (C=S). Electronic spectra (λmax nm): 270, 391, 531.

Pt (AMTTSC) 2 Complex

A solution of K2PtCl4 (0.208 g, 0.5 mmol) in methanol, was added dropwise to a stirred solution of HAMTTSC (1.0 mmol) in 30 mL of methanol. The solution was refluxed for 2 hours and stirred for 24 hours at room temperature. The pinkish red precipitate was collected by filtration and dried in vacuo.

Solid, yield: 74.36%, m.p. dec.>245°C.Anal. Calc. For Pt(C7H9N4S2)2 (621.69 g/mol): C, 27.05%; H, 2.92%; N, 18.02%. Found: C, 27.01%; H, 3.028%; N, 18.97%. IR (solid state, cm^{-1}): ν(NH2) 3354.48, 3265.78; ν(C=N) 1535.94; ν(C=S) 873.25; ν(N-N) 1075.01. 1H-N.M.R (DMSO-d6): δ 2.21, 2.39 (s, 6H,2CH3), 7.74, 7.34(s, 1H); 8.07 (b, 2H, NH2); 8.51, (b, 2H, NH2). 13C-N.M.R. (DMSO-d6): δ 13.51, 16.39 &13.91, 16.76 (4CH3); 144.02-152.49 &148.57-154.64 (3C ring); 166.07&171.93 (HC=N); 183.22 (C=S). Electronic spectra (λmax nm): 270, 363, 389, 53.

Pd (AMTTSC)Cl Complex

A solution of K2PdCl4 (0.163 g, 0.5 mmol) in methanol, was added dropwise to a stirred solution of HAMTTSC (0.5 mmol) in 20 mL of methanol. The solution was refluxed for 2 hours and stirred for 14 hours at room temperature. The orange precipitate was collected by filtration, washed with ethanol and ether, and dried in vacuo.

Solid, yield: 92.39%. m.p. 236–237°C. Anal. Calc. For Pd(C7H9N4S2)Cl (355.18 g/mol): C, 23.67%; H, 2.55%; N, 15.77%. Found: C, 22.94%; H, 2.68%; N, 15.09%. IR (solid state, cm^{-1}): ν(NH2) 3426.47, 3304.62; ν(C=N) 1552.37; ν(C=S) 867.85; ν(N-N) 1118.21. 1H-N.M.R. (DMSO-d6): δ 2.25, (s, 6H, 2CH3), 7.64 (s, 1H); 7.93 (d, 2H, NH2).13C-N.M.R. (DMSO-d6): δ 13.83, 16.36 (2CH3); 145.69, 147.79–154.36(3C ring); 169.58 (HC=N); 180.71 (C=S). Electronic spectra (λmax nm): 274, 313, 386,493.

Pd(AMTTSC)2 Complex

A solution of Pd(acac)2 (0.152 g, 0.5 mmol) in CH2Cl2/ CH3OH (30 mL, 2:1 v/v) was added dropwise to a stirred solution of HAMTTSC (1.0 mmol) in 30 mL of methanol. The solution was refluxed for 2 hours and stirred for 24 hours at room temperature. The red precipitate was collected by filtration, washed with ethanol and ether, and dried in vacuo.

Solid, yield: 79.54%. m.p. dec.>174°C. Anal. Calc. For Pd(C7H9N4S2)2, (533.03 g/mol): C, 31.55%; H, 3.4%; N, 21.02%. Found: C, 30.77%; H, 3.62%; N, 19.84%. IR (solid state, cm^{-1}): ν(NH2) 3308.98, 3257.77; ν(C=N) 1557.07; ν(C=S) 871.65; ν(N-N)1080.62. 1H-N.M.R. (DMSO-d6): δ 1.46, 1.62 (s, 6H, 2CH3), 7.04 (s, 1H); 8.04, 6.74 (d, 2H, NH2). 13C-N.M.R. (DMSO-d6): δ 13.66, 16.18 (2CH3); 147.49, 152.70& 148.44, 155.45 (3C ring); 169.62&171.19 (HC=N);, 182.38 (C=S). Electronic spectra (λmax nm): 289, 348, 448.

Conclusion

New potential anti-cancer Pt (II) and Pd(II) complexes were synthesized through the reaction of the heterocyclic thiosemicarbazone ligands with Pt (II) and Pd (II) ions in 1:1 and 1:2 ratios reactions.

The structures of the synthesized compounds were elucidated on the bases of spectroscopic data (IR. 1H and 13C N.M.R, UV-VIS and XRD).

As the experimental results show, the synthesized Schiff bases reacts with Pt(II) ion in different modes of bonding, they react as tridentate through the mercaptide sulfur ion, the azomethine nitrogen atom and the nitrogen of the ring.

All ligand and complexes tested show a concentration dependent reduction of cell proliferation. The test results show that the change of the ligand metal ratio has significant effects on the antiproliferative activities of the platinum(II) complexes. In general, it was found that complexes were more active than the corresponding ligand. The complex with the formula PtLCl was found to be slightly more active than the complexes with formula PtL2 against HT-29 and HuTu cancer cells line.

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