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Synthesis, characterization, and biological evaluation of Schiff base–platinum(II) complexes

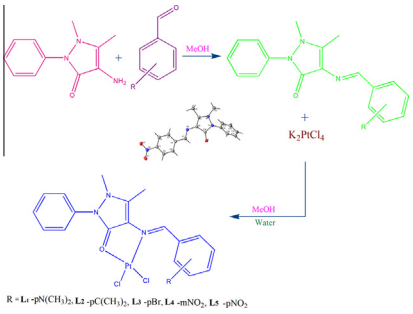
C. Shiju [a], D. Arish [a], N. Bhuvanesh [b], S. Kumaresan [c,*]

[a] Department of Chemistry, Manonmaniam Sundaranar University, Tirunelveli 627 012, TN, India
[b] Department of Chemistry, Texas A&M University, College Station, TX 77842, USA
[c] Department of Biotechnology, Manonmaniam Sundaranar University, Tirunelveli 627 012, TN, India

HIGHLIGHTS

- The platinum complexes of Schiff base ligands were synthesized and characterized.
- The structure of one of the ligands was confirmed by a single crystal XRD analysis.
- The geometrical structures of these complexes are found to be square planar.
- Antimicrobial studies indicate that these complexes exhibit better activity than the ligands.
- $[Pt(L_3)Cl_2]$ shows better activity towards *M. tuberculosis* H37Rv.

GRAPHICAL ABSTRACT



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ABSTRACT

The platinum complexes of Schiff base ligands derived from 4-aminoantipyrine and a few substituted aldehydes were synthesized and characterized by elemental analysis, mass, ^{1}H NMR, IR, electronic spectra, molar conductance, and powder XRD. The structure of one of the ligands **L_5** was confirmed by a single crystal XRD analysis. The Schiff base ligand crystallized in the triclinic, space group P-1 with $a = 7.032(2)$ Å, $b = 9.479(3)$ Å, $c = 12.425(4)$ Å, $\alpha = 101.636(3)°$, $\beta = 99.633(3)°$, $\gamma = 94.040(3)°$, $V = 795.0(4)$ Å^3, $Z = 2$, $F(000) = 352$, $D_c = 1.405$ mg/m^3, $\mu = 0.099$ mm^{-1}, $R = 0.0378$, and wR = 0.0967. The spectral results show that the Schiff base ligand acts as a bidentate donor coordinating through the azomethine nitrogen and the carbonyl oxygen atoms. The geometrical structures of these complexes are found to be square planar. Antimicrobial studies indicate that these complexes exhibit better activity than the ligand. The anticancer activities of the complexes have also been studied towards human cervical cancer cell line (HeLa), Colon Cancer Cells (HCT116) and Epidermoid Carcinoma Cells (A431) and it was found that the $[Pt(L_3)Cl_2]$ complex is more active.

Introduction

It has been well established that the platinum complexes are of biological importance due to their carcinostatic activity and interest in biological chemistry. The carcinostatic action of the platinum complexes is due to their interaction with nuclear DNA [1]. Platinum compounds are among the most important chemotherapeutic agents for treating cancer. Cisplatin (*cis*-diammin edichloroplatinum(II)), has a significant activity in ovarian, testicular, bladder, head and neck, and lung cancer, where it is most commonly used in combination with other drugs [2]. Thus, it has become one of the most successful anticancer drugs used worldwide in almost 50% of solid tumour chemotherapies. Although

* Corresponding author. Tel.: +91 9443182502.
E-mail address: skumarmsu@yahoo.com (S. Kumaresan).

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the initial response rates can be high with cisplatin-based regimen, the clinical utility of the drug is often limited by the onset of acquired or intrinsic resistance [3] and the number of side effects such as kidney damage, vomiting/nausea, and neurotoxicity [4]. The resistance of tumour cells to cisplatin remains a major cause of treatment failure in cancer patients, while the high toxicity of cisplatin limits the dose that can be given to patients. Developing metal complexes as drugs, however, is not an easy task. Schiff base metal complexes have received special attention because of their biological activity. Many Schiff bases are known to be medicinally important and are used to design medicinal compounds [5,6]. A wide range of Schiff bases have been synthesized and their complexation behavior studied in recent years. Because of the importance in the area of coordination chemistry, the pyrolozone chemistry of metals is developing very rapidly [7]. 4-Aminoantipyrine derivatives are very important in the field of coordination complexes and also these compounds are reported to exhibit analgesic and anti-inflammatory effects, antiviral, antibacterial, anti-cancer and herbicidal activities. [8–13]. In view of the above applications and importance, in the present paper we report the synthesis, characterization, and biological activity of platinum complexes with the Schiff bases derived from 4-aminoantipyrene and substituted benzaldehydes.

Experimental

Materials

4-Aminoantipyrene, N,N′-dimethylaminobenzaldehyde, 4-isopropylbenzaldehyde, 4-bromobenzaldehyde, 3-nitrobenzaldehyde, and 4-nitrobenzaldehyde were purchased from Merck. The human cervical cancer cell line (HeLa) and Colon Cancer Cells (HCT116) were obtained from National Centre for Cell Science (NCCS), Pune. K_2PtCl_4 was purchased from Sigma–Aldrich. All other reagents and solvents were purchased from commercial sources and were of analytical grade.

Physical measurements

Elemental analysis was done using a Perkin-Elmer elemental analyser. Molar conductance of the complexes was measured in DMSO (10–3 M) solutions using a Coronation Digital Conductivity Meter. The electrospray (ESI) mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer. Samples (10 μL) (dissolved in solvent such as methanol/chloroform/dichloromethane) were introduced into the ESI source through Finnigan surveyor autosampler. The ^{1}H NMR spectra were obtained on a JEOL GSX 400 FT-NMR spectrometer. IR(KBr) spectra were recorded on a JASCO FT/IR-410 spectrometer in the 4000–400 cm^{-1} region. The electronic spectra were recorded on a Perkin Elmer Lambda-25 UV–vis spectrometer. Powder XRD was recorded on a Rigaku Dmax X-ray diffractometer with Cu Kα radiation.

Synthesis of Schiff base ligands

4-Aminoantipyrene (1 mmol) in MeOH (20 mL) was taken in a 100 mL RB (Round Bottomed) flask. A solution of substituted benzaldehyde (1 mmol) in absolute MeOH (20 mL) was then added slowly to the flask. The reaction mixture was vigorously stirred for about 5 h. The volume of the mixture was reduced to half of the initial volume under reduced pressure and an excess of anhydrous ether was added. A yellow precipitate was formed, which was collected by vacuum filtration and washed several times with anhydrous ether and then dried *in vacuo* over anhydrous $CaCl_2$. The purity of the Schiff base ligand was checked by TLC. The yield of the isolated ligands was found to be 65–72%. The synthetic route for Schiff base ligands is shown in Scheme 1.

*{(E)-4-[4-N,N′dimethylbenzylideneamino]-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one}(**L_1**).*

Yellow crystals, yield 68%. ^{1}H NMR ($CDCl_3$) δ: 9.64 (s CH═N), 2.45 (s, C—CH_3), 3.24 (s, N—CH_3), 6.69–7.75 (m, ArH), 3.08 (s, N—$(CH_3)_2$). IR (KBr, cm^{-1}) ν: 1647 (C═O), 1610 (C═N), 1371 (C—N), 1455 (N—CH_3), 3047 (Ar CH). Anal. calcd for $C_{20}H_{22}N_4O$: C 71.83, H 6.63, N 16.75; found: C 72.15, H 6.21, N 16.52. UV–vis (CH_2Cl_2): λ/nm 362, 215.

*{(E)-4-[4-isopropylbenzylideneamino]-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one}(**L_2**).*

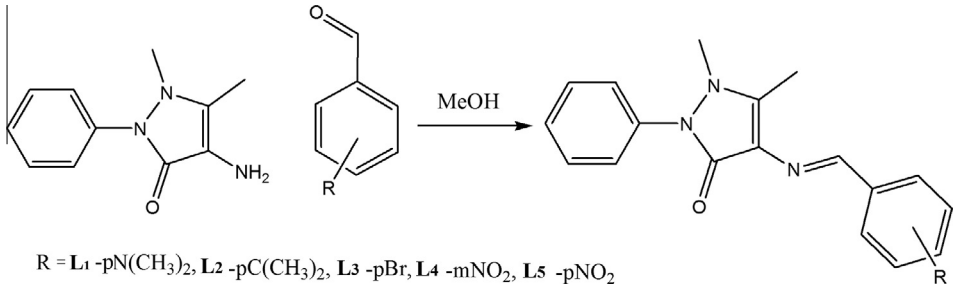
Pale yellow crystals, yield 65%. ^{1}H NMR ($CDCl_3$) δ: 9.55 (s CH═N), 3.16 (s, C—CH_3), 3.34 (s, —CH_3), 7.30–7.80 (m, ArH), 2.50 (s, C—$(CH_3)_2$). IR (KBr, cm^{-1}) ν: 1650 (C═O), 1595 (C═N), 1366 (C—N), 1455 (N—CH_3), 3048 (Ar CH). Anal. calcd for $C_{21}H_{23}N_3O$: C 75.65, H 6.95, N 12.60; found: C 76.02, H 7.18, N 12.21. UV–vis (CH_2Cl_2): λ/nm 329, 244, 215.

*{(E)-4-[4-bromobenzylideneamino]-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one}(**L_3**).*

Yellow crystals, yield 72%. ^{1}H NMR ($CDCl_3$) δ: 9.70 (s CH═N), 2.43 (s, C—CH_3), 3.16 (s, N—CH_3), 7.26–7.73 (m, ArH). IR (KBr, cm^{-1}) ν: 1649 (C═O), 1591 (C═N), 1376 (C—N), 1428 (N—CH_3), 3056 (Ar CH). Anal. calcd for $C_{18}H_{16}BrN_3O$: C 58.39, H 4.36, N 11.35; found: C 59.08,H 4.89, N 11.76. UV–vis (CH_2Cl_2): λ/nm 340, 255, 210.

*{(E)-4-[3-nitrobenzylideneamino]-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one}(**L_4**).*

Orange yellow crystals, yield 70%. ^{1}H NMR ($CDCl_3$) δ: 9.80 (s CH═N), 2.52 (s, C—CH_3), 3.21 (s, N—CH_3), 7.25–8.75 (m, ArH). IR (KBr, cm^{-1}) ν: 1647 (C═O), 1592 (C═N), 1382 (C—N), 1456 (N—CH_3), 3059 (Ar CH). Anal. calcd for $C_{18}H_{16}N_4O_3$: C 64.28, H



Scheme 1. Synthetic route for Schiff base ligands.