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Synthesis, crystal structure, and anticancer studies of organoruthenium(II) p-cymene N-phenyldithiocarbamate complex

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ABSTRACT

Organoruthenium(II) p-cymene *N*-phenyldithiocarbamate complex, $[Ru(phdtc)(\eta^6\text{-p-cym})]_2$, was synthesized and characterized by elemental analysis, spectroscopic techniques, and single crystal X-ray crystallography. The single crystal X-ray structure of the complex shows that the compound crystallizes in a monoclinic crystal system with a $P2_{1/c}$ space group to form a centrosymmetric binuclear complex. The structure consists of two divalent ruthenium(II) ions, two N-phenyldithiocarbamato anions and two p-cymene molecules. Each N-phenyldithiocarbamato anion acts as a chelating ligand to one ruthenium(II) and a bridging ligand to second ruthenium (II) ion in a classic "three-legged piano-stool" arrangement with a pseudo-tetrahedral geometry. The geometry around the ruthenium(II) ions is completed through η^6 coordination to the p-cymene carbon atoms. Anticancer studies showed that the compound is potently cytotoxic (complete kill between 10 and 50 μM) when tested up to 100 μM for up to 48 h against two cell lines, HeLa and MRC5-SV2, models of cervical and lung cancer, respectively, and in some instances outperformed the standard platinum-based anticancer drug cisplatin for cytotoxic potency, highlighting the anti-cancer prospect of the complex.

1. Introduction

Dithiocarbamates are versatile ligands with small bite-angles. They are well-known for stabilizing a wide range of metal ions in various oxidation states. This is due to their resonance form in which the nitrogen atom is positively charged, and each sulphur atom negatively charged and the existence of the partial double bond character of C−N and C−S of the thioureide moiety [1]. They are exceptionally stable and soluble in water due to the existence of hydrophilic moiety in their structural configuration. For decades, they have been used as metal chelates and found application in many fields such as medicine, agriculture, catalysis and so forth [2–5]. The chelating effect of dithiocarbamates results from the π-electron from the nitrogen to the sulphur atom via a delocalized π-orbital system which results in elevated electron density on the metal and this coordination mode is explained by k^2 hapticity [6].

Dithiocarbamates have been investigated for their potential antifungal, antibacterial, anti-inflammatory, and anticancer activities, etc. [7–11]. These chelating ligands are mostly employed in the synthesis of anticancer agents due to their enhanced stability, improved antitumor efficacy and low toxicity to normal cells [12]. As a result of this dithiocarbamate complexes have been prepared and their potential as therapeutic agents evaluated [13–16]. These have led to the identification of pharmacophores such as phenyl, piperidine and piperazine rings to be important for the development of dithiocarbamate ligands with potential anticancer property [17]. In a study that was done on Ru (III) dithiocarbamate complexes, it was proved that the cytotoxic activity of the compounds is influenced by the nature of the ligand coordinated to the ruthenium(III) ion [18]. Wang et al. [19] synthesized and investigated the antitumor activity of three novel dehydroabietyl piperazine dithiocarbamate ruthenium(II) polypyridyl complexes. Two of the compounds showed better in vitro antitumor activity in comparison with *cis*platin.

Amongst the ruthenium complexes that have been studied, Ru(II) arene complexes have also attracted interest as potential anticancer agents. This is due to their peculiar biological, chemical, and physical properties [20]. Arene ligands coordinate strongly with Ru(II) ion, resulting in an inert complex that stabilizes the Ru(II) ions at low oxidation states. Hence, arene coordination results in complexes with increased hydrophobicity compared to other Ru(II) complexes [21,22]. Subarkhan et al. [23] synthesized and evaluated in vitro anticancer activity of two organometallic tetranuclear Ru(II) arene complexes. The

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complexes showed enhanced cytotoxic activity in comparison to cisplatin. In continuation of our efforts to develop novel dithiocarbamate metal complexes [24–28], we present the synthesis, crystal structure and cytotoxicity evaluation of ruthenium(II) mixed N-phenyldithiocarbamate and p-cymene complex, against two cancer cell lines, HeLa and MRC5-SV2, models of cervical and lung cancer.

2. Materials and methods

2.1. Reagents and solvents

All the chemicals and solvents were of analytical grades purchased from Sigma-Aldrich chemical suppliers and were used without any further purification. The chemical reagents used are as follows: Aniline, carbon disulphide, aqueous ammonia, dichloro(p-cymene)ruthenium (II) dimer ($[RuCl_2(p\text{-}cym)]_2$.

2.2. Physical characterization

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Biospin 600 MHz spectrometer. The samples were prepared by dissolving small portion of the ligand in deuterated water (D_2O) and the complexes were dissolved in deuterated dimethylsulfoxide (DMSO-d_6). The residual signals of D_2O ($\delta = 4.79$ ppm for ^{1}H NMR) and DMSO-d_6 ($\delta = 39.52$ ppm for ^{13}C NMR) were used as the internal reference. Chemical shifts were reported in parts per million (ppm). The spectra were processed using Bruker Topspin 4.0.3 NMR prediction software. The FTIR spectra were recorded by an Agilent Technologies Cary 630 FTIR spectrometer (4000–650 cm^{-1}) on KBr pellet. Electronic spectra of the ligands and complexes were measured by a Perkin Elmer Lambda 25 spectrometer from 200–700 nm at room temperature. The ligand was prepared in distilled water whereas the complexes were prepared in DMSO. Each compound was dissolved in suitable amount of the solvent in a quartz cell of 1 cm path length. Mass spectra of the ligands and complexes were recorded on Water Micromass LCT Premier TOF-MS ES+/ ES-. Elemental composition of the ligands and complexes was examined using a Thermoscientific Flash 2000 elemental analyser.

2.3. Synthesis of ammonium N-phenyldithiocarbamate (phdtc) and Ru (ii) complex

Ammoinium salt of N-phenyldithiocarbamate ligands was prepared using a method reported in literature [24,29]. Colour: White. Yield (%): 59. M.pt (°C): 109. Λm (μS): 146.1. Molecular mass (*m/z*): Calc for $C_7H_6NS_2$ $[M\text{-}NH_4]^+$: 167.99, Found: 168. Selected FTIR, ν(cm^{-1}): N–C (1482), C–S (1279), C═S (988). ^{1}H NMR (400 MHz, D_2O, δ (ppm)): 7.30–7.26(t, $J = 7.56$ Hz, 2H), 6.92–6.88 (t, $J = 7.36$ Hz, 1H), 6.83–6.82 (d, $J = 4.24$ Hz, 2H), 4.04 (s, RN–H). ^{13}C NMR (400 MHz, D_2O, δ (ppm)): 126.14–140.70 (C_6H_5), 213.92 (C-S). Anal. Calc. for $NH_4(C_7H_6NS_2)$: C, 45.13; H, 5.41; N, 15.04. Found: C, 45.51; H, 5.40; N, 14.72.

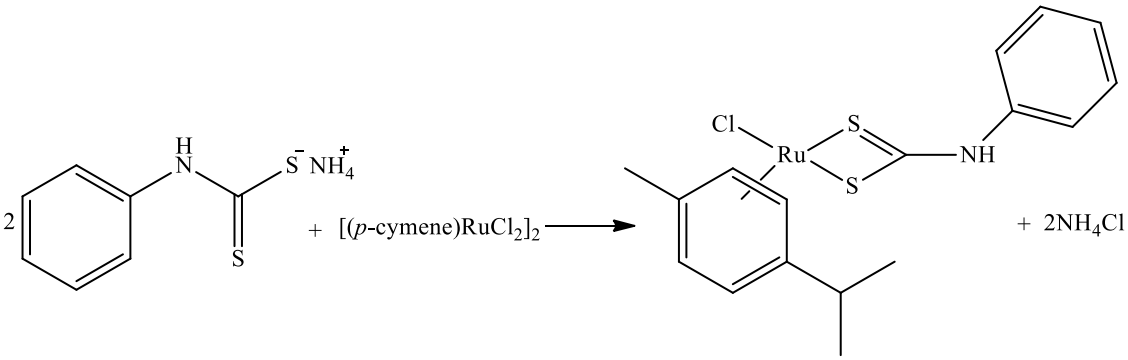
The ruthenium(II) p-cymene N-phenyldithiocarbamate complex was prepared by mixing solution of ammonium N-phenyldithiocarbamate (0.82 mmol, 0.15 g) and (p-cymene)ruthenium(II) dichloride dimer (0.41 mmol, 025 g) together and reflux in methanol for 12 h (Scheme 1). The dark brown solution was reduced, and the residue was extracted with dichloromethane. The extract was filtered, and the solution left to evaporate slowly in the fume-hood. Colour: Dark brown. Yield (%): 30. Molecular mass (*m/z*): Calc for $C_{17}H_{20}ClN_2RuS_2$ $[M\text{-}Cl]^+$: 403.54, Found: 403. Selected FTIR, ν(cm^{-1}): N–C (1481), C═S (1014). ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 7.16–6.91 (t, $J = 7.08$ Hz, 2H, –PhH), 6.89–6.86 (t, $J = 7.36$ Hz, 2H, –PhH), 6.85–6.84 (d, $J = 7.28$ Hz, 2H, –PhH), 5.93–5.92 (d, $J = 6.24$ Hz, 2H, –PhH), 5.74–5.72 (d, $J = 6.20$ Hz, 2H, –PhH), 2.49–2.48 (m, 1.84 Hz, 1H, $-CHCH_3CH_3$), 2.17 (s, 3H, $-PhCH_3$), 1.21–1.15 (t, $J = 21.20$ Hz, 6H, $-CHCH_3CH_3$). ^{13}C NMR (400 MHz, DMSO-d_6, δ (ppm)): 211.08 (C–S), 122.63, 106.07, 91.20, 88.89 (C_6H_5), 128.93, 111.13, 91.20, 88.89 (C_6H_4), 31.40 ($-CHCH_3CH_3$), 23.03 ($-CH_3CH_3-$), 19.13 ($-CH_3$). Anal. Calc. for $C_{17}H_{20}ClNRuS_2$: C, 46.51; H, 4.59; N, 3.19; S, 14.61. Found: C, 46.16; H, 4.51; N, 3.58, S; 14.63.

2.4. X-ray data collection

Single crystals of the compound were obtained by slow evaporation of the compound in dimethyl sulfoxide (DMSO) at room temperature. Block orange crystals of the compound was obtained after few days. The crystals were isolated under oil and fixed on a MITIGEN crystal mounter. The crystallographic data was obtained on a Bruker APEXII CCD diffractometer fitted with an Oxford Cryosystems instrument, running at $T = 296(2)$ K. The structures were resolved by the SHELXS-2013 [30] structure solution program using the Intrinsic Phasing solution method and by using Olex2 [31] as the graphical interface. The model was refined with version 2016/6 of ShelXL [32] using Least Squares minimization.

2.5. Cytotoxicity screening

The cytotoxicity of the complex was investigated against the human cervical adenocarcinoma cell line HeLa and the human foetal lung cell line MRC5-SV2. The platinum-based anti-cancer drug cisplatin was used as a positive control. The cells were cultured as adherent monolayer cells in 96-well plates, grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Foetal Calf Serum, 2 mM L-glutamine and 1% antibiotic-antimycotic solution (containing penicillin, streptomycin and amphotericin B). The seeding densities were 5×10^{-4} cells/mL and 7.5 × 10–4 cells/ml (100 μl of cell suspension per well), for HeLa and MRC5-SV2 cells, respectively. 24 h after the cultures were set up, when they had achieved a confluency between 80 and 90%, they were treated with complexes for up to 48 h, after which cell viability was assessed using the MTT (3-(4,5-Dimethyl-2-thiazolyl)−2,5-diphenyl-2H-tetrazolium bromide) assay, as previously reported [33]. Viability values are



Scheme 1. Synthesis of RuCl(N-phenyldithiocarbamate)(*p*-cymene) complex.

presented as Mean ± SEM (standard error of the mean). Statistical analyses were undertaken using GraphPad Prism (Version 9.3.1) (GraphPad Software, Inc., CA, USA). Statistical differences between means were assessed using analysis of variance (ANOVA) followed by a post-hoc test for multiple comparisons, with $P<0.05$ considered statistically significant.

3. Results and discussion

3.1. Synthesis

The ammonium salt of N-phenyldithiocarbamate ligand was synthesized using the nucleophilic addition method whereby aniline was reacted with carbon disulfide in the presence of aqueous ammonia. The ligand was obtained as a white powder. It was soluble in water and polar solvents such as methanol, ethanol, and acetonitrile. Ammonium salt of N-phenyldithiocarbamate ligand and (p-cymene)ruthenium dichloride dimer was reacted in 2:1 mole ratio to prepare the Ru(II) complex.

3.2. Crystal structure of the [Ru(N-phenyldithiocarbamate)(η⁶-p-cymene)]₂

The molecular structure of the complex is shown in Fig. 1 and the unit cell packing diagram in Fig. 2. Crystallographic and refinement data are presented in Table 1. Selected bond lengths and bond angles are provided in Table 2. The single crystal X-ray analysis shows that the complex crystallizes in a monoclinic crystal system with a $P2_1/c$ space group and is a centrosymmetric binuclear entity. The structure consists of two Ru(II) ions, two N-phenyldithiocarbamato anions and two p-cymene molecules. Each Ru(II) ions are in four coordinate environments consisting of one p-cymene, one molecule of N-phenyldithiocarbamato anion acting as bidentate chelating ligand and the ruthenium(II) ion coordinate an adjacent S-atom of the N-phenyldithiocarbamato anion. The molecular structure of this complex can be described as pseudotetrahedral, with a "piano stool"-like geometry [34] in which the two N-phenyldithiocarbamato anions act as chelating ligand to one Ru(II) and as a bridging ligand to the second Ru(II) ion [35] while each of the *p*-cymene molecule is coordinated to the Ru(II) ion through the η^6-carbon atoms. The Ru–S bond lengths are in the range 2.1886(18) - 2.2270 (18) Å, in agreement with values reported for related complexes [36, 37]. The Ru–S bond lengths are almost equidistant (2.317(5) and 2.3911(4)). The short C1–N1 bond length of 1.272(2) Å, which suggests a partial double-bond nature, that is characteristic bonding modes of dithiocarbamate ligand [38]. The packing diagram of the compound shown in Fig. 2 shows four molecules of the asymmetric unit in the crystal packing that occupies that four sides of the packing rectangle linked by non classical C—H···S intermolecular interactions between each unit cell. The η^6-*p*-cymene that occupied the length and width of the rectangle are parallel to each other.

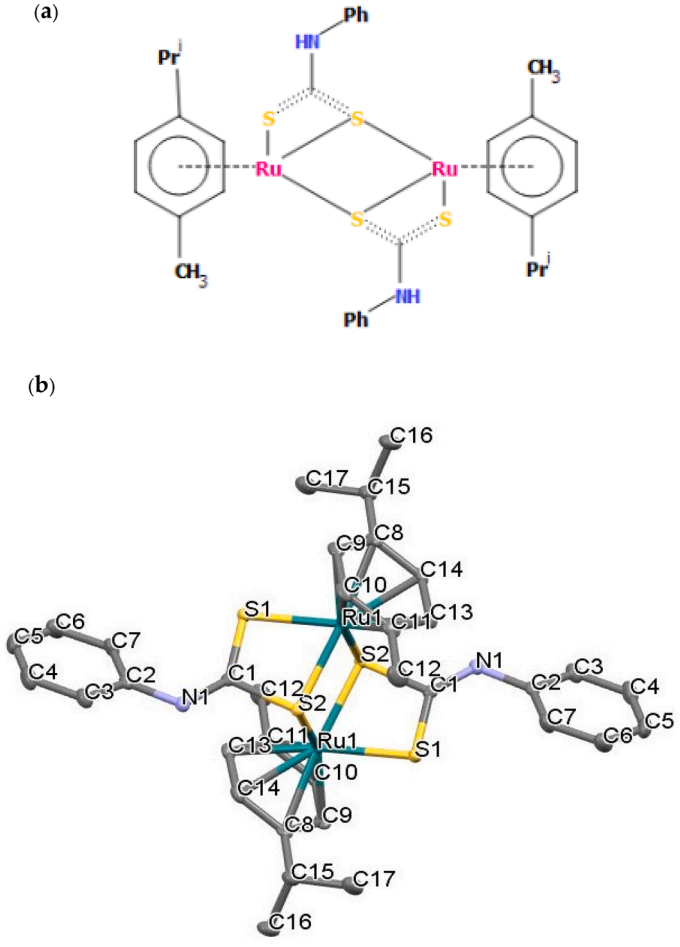


Fig. 1. (a) Chemical diagram of the title compound (b) Molecular structure of the complex showing 50% probability displacement ellipsoid and atom labelling. The hydrogen atoms are excluded.

3.3. FTIR spectra studies

In the FTIR spectra of dithiocarbamates, there are three main characteristic bands. Strong absorption bands in the region 1450 – 1550 cm^{-1} that is ascribed to the ν(C–N) of the N–C═S system; absorption bands in the region 1150 – 1280 cm^{-1}, which is attributed to ν(C–S), and single strong absorption bands in the region 950 – 1050 cm^{-1}, which is ascribed to the ν(C═S) stretching vibrations [39,40]. The ν (C═S) stretching vibrations is diagnostic and can be used to determine whether the ditiocarbamato anion coordinate the metal ion bidentately or monodentately [39,40]. The coordination of the metal ions to the dithiocarbmato anions lead to the delocalization of the electron cloud of the -NCSS group in the dithiocarbamate moiety [41,42]. In the bidentate chelating mode, two approximately equal metal-sulphur bonds give rise to a small bite-angle (S – M – S) of about 65–80 °C, depending on the size of the metal ion [43,44]. In the spectrum of the N-phenyl dithiocarbamate ligand, the ν(N—C) vibrational band was observed at 1482 cm^{-1}, ν (C–S) at 1279 cm^{-1} and ν(C = S) at 988 cm^{-1}. The band observed at 3450 cm^{-1} in the spectrum of the ligand is assigned to the N—H. In the spectrum of the complex, the ν(N–C), ν(C-S) and ν(C-S) stretching frequencies shifted to 1488, 1219 and 1007 cm^{-1} respectively. Of particular interest is the ν(C-S) stretching frequency that appear as a single band at 1007 cm^{-1} which confirmed bidentate coordination of the N-phenyldithiocarbamato anions as confirmed by the single crystal X-ray structure of the compound.

3.4. Electronic spectra studies

Dithiocarbamate ligands exhibit three transition bands in their electronic spectrum: The π→π* band ascribed to the intra-molecular and inter-ligand transitions of the N—C = S system, the π→π* of the S-C = S system and the n → π* located on the sulphur atom or ion [29,45]. The electronic spectrum of the N-phenyl dithiocarbamate ligand shows absorption band at 260 nm that is ascribed to the π → π* transitions of the N—C = S system. The second absorption band at 293 nm in the spectrum of the ligand is assigned to the π→π* transitions of the S-C = S moiety. This absorption band ascribed to the charge transfer transition did not appear in the ligand spectrum, this might be due to the presence of the N–H chromophore causing an interference and obstructing the observation of the expected band. Three absorption bands were observed in the electronic spectrum of organoruthenium(II) complex. The first band appeared at 265 nm was attributed to the π→π* transition of the N–C-S segment from the dithiocarbamate ligand that is coordinated to the Ru

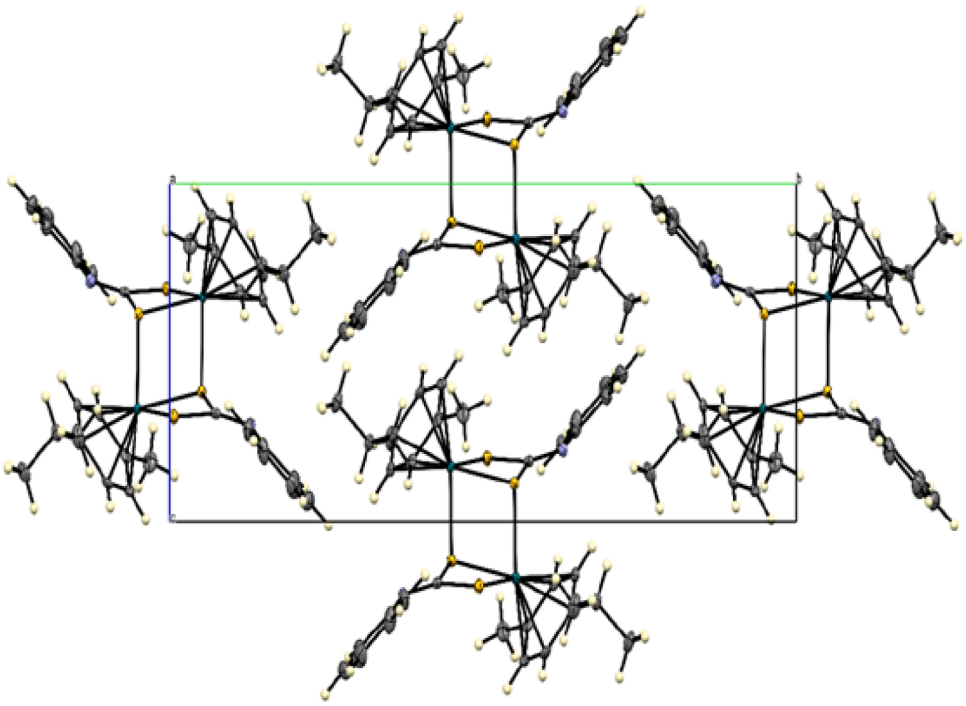


Fig. 2. Unit cells packing diagram of the complex.

Table 1
Crystal data and structure refinement for the complex.

Compound	[Ru(N-phenyldithiocarbamate)(η⁶-p-cymene)]₂
Empirical formula	$C_{34}H_{38}N_2Ru_2S_4$
Formula weight (g/mol)	805.04
Temperature (K)	296(2)
Wavelength (Å)	1.54178
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	8.7317(2)
b (Å)	22.1825(2)
c (Å)	8.5923(2)
α (°)	90
β (°)	99.1030(10)
γ (°)	90
Volume (Å^3)	1643(7)
Z	4
Calculated density (Mg/m^3)	1.627
Absorption coefficient (mm^{-1})	10.017
F(000)	816
Crystal size (mm^3)	0.185×0.120×0.085
Theta range for data collection	3.986 to 68.179°
Index ranges	−10<=*h*<=10, −26<=*k*<=26, −10<=*l*<=9
Reflections collected	29,086
Independent reflections	2992 [R(int) = 0.0321]
Data/ restraints/ parameters	2992 / 0 / 193
Goodness-of-fit on F^2	1.157
Final R indices [*I*>2sigma(I)]	R1 = 0.0183, wR2 = 0.0410
R indices (all data)	R1 = 0.0189, wR2 = 0.0412
Largest diff. peak and hole	0.316 and −0.320 e.Å^{-3}

Table 2
Bond lengths (Å) and angles (°) for complex.

Bond Length (Å)		Bond Angles (°)	
Ru1—C9	2.1886(18)	C9-Ru1-S1#1	91.70(5)
Ru1—C14	2.1915(18)	C14-Ru1-S1#1	137.96(5)
Ru1—C10	2.2049(19)	C10-Ru1-S1#1	105.74(6)
Ru1—C11	2.2174(19)	C11-Ru1-S1#1	138.68(6)
Ru1—C13	2.2255(18)	C13-Ru1-S1#1	170.82(5)
Ru1—C8	2.2270(18)	C8-Ru1-S1#1	104.74(5)
Ru1—S1#1	2.3817(5)	C9-Ru1-S2#1	131.72(5)
Ru1—S2#1	2.3911(4)	C14-Ru1-S2#1	147.79(5)
Ru1—S2	2.4020(4)	C10-Ru1-S2#1	102.25(5)
S1—C1	1.7614(18)	C11-Ru1-S2#1	93.79(5)
S1—Ru1#1	2.3818(4)	C13-Ru1-S2#1	113.00(5)
S2—C1	1.8056(19)	C8-Ru1-S2#1	169.50(5)
S2—Ru1#1	2.3912(4)	S1#1-Ru1-S2#1	73.244(15)
N1—C1	1.272(2)	C9-Ru1-S2	144.90(5)
N1—C2	1.416(3)	C14-Ru1-S2	91.36(5)
C2—C7	1.394(3)	C10-Ru1-S2	167.42(6)

Symmetry transformations used to generate equivalent atoms: #1 -*x* + 1,-*y* + 1,-*z* + 2.

(II) ion. The second band, a broad shoulder, between 298–340 nm, is assignable to M→LCT transition. The third absorption band at 435 nm in the electronic spectrum of the ruthenium(II) complex could be assigned to metal to ligand charge transfer transitions associated with electron transition from the filled orbitals of the ligands. Due to the low intensity, the electronic spectrum of ruthenium(II) are obscured by strong charge transfer transitions from the ligands and are thus not observable [46, 47].

3.5. NMR spectral studies

The ^{1}H NMR spectrum of N-phenyldithiocarbamate showed two triplets at 7.29–7.25 ppm (t, 4H) and 6.92–6.88 ppm (t, 1H), and a doublet at 6.83–6.82 ppm for the phenyl ring. The peak at 4.04 ppm was ascribed to the hydrogen atom of the RNH group and the in the ^{13}C-nmr spectrum, peak for the carbon atom of the C−S bond appeared at 213.92 ppm [44]. The ^{1}H NMR spectrum of the complex exhibited two triplets and a doublet in the region 7.16–6.84 ppm, which were assigned to the phenyl ring of the dithiocarbamate moiety. The protons due to the phenyl group of the p-cymene appeared as two doublets in the ranges 5.93–5.92 and 5.74–5.72 ppm [48]. A multiplet in the region 2.49–2.48 ppm was assigned to the proton atom attached to the tertiary carbon of the isopropyl group, while the $-CH_3$ protons of the isopropyl group were observed as a doublet around 1.25–1.21 ppm [49]. A singlet was observed at 2.17 ppm and assigned to the $-CH_3$ protons of p-cymene. The ^{13}C NMR spectrum showed a peak at 211.08 ppm which was

assigned to the C−S carbon of the dithiocarbamate moiety. The carbon atoms of the phenyl rings of p-cymene and dithiocarbamate ligand appear around 128.93–88.89 ppm. The tertiary carbon and methyl carbons of the isopropyl group appeared at 31.40 and 23.03 ppm, respectively. The methyl group of p-cymene appeared further upfield at 19.13 ppm.

3.6. Anticancer studies of complex

As shown in Fig. 3, both the complex and the positive control cisplatin when tested up to 100 μM for up to 48 h against HeLa or MRC5-SV2 cells reduced cell viability in a concentration- and mostly exposure time-dependent manner. The complex was significantly potent, such that at 50 μM HeLa cell viability at 48 h and MRC5-SV2 cell viability at 24 h were practically nil. Interestingly, comparing effects at an equimolar concentration of 100 μM, the complex was marginally more potent than cisplatin in HeLa cells and significantly more potent than cisplatin in MRC5-SV2 cells. This observation strongly supports the anti-cancer potential of the complex and justifies its further biological characterization.

4. Conclusions

Organoruthenium(II) p-cymene *N*-phenyldithiocarbamate complex, [Ru(phdtc)(η⁶-p-cym)]₂, was synthesized and characterized by spectroscopic techniques and single crystal X-ray crystallography. The complex crystallized in a triclinic $P2_1/c$ crystal system in which the ruthenium(II) coordinate N-phenyldithiocarbamate acts as chelating and bridging ligand between the ruthenium ions and two p-cymene molecules to form pseudotetrahedral, "piano stool"-like geometry. FTIR spectra

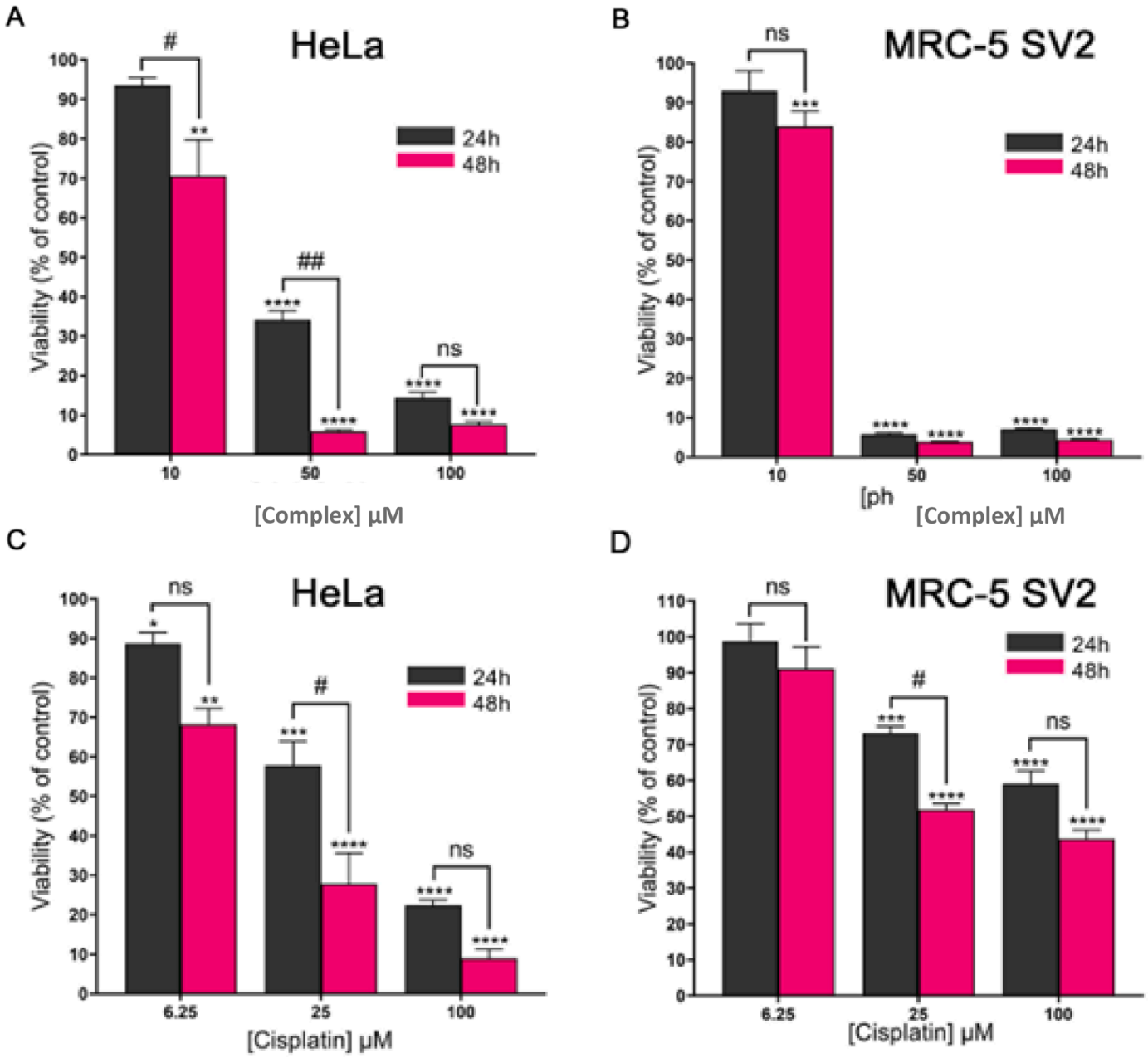


Fig. 3. Cytotoxic effects of the complex and the platinum-based anticancer compound cisplatin in cancer cell lines. Complex (A, B) and cisplatin (C, D) reduced the viability of HeLa and MRC5-SV2 cells, respectively, compared to the negative control. *P<0.05, **P<0.01, ***P<0.001 and ****P<0.0001 compared to the negative control; #P<0.05, ##P<0.01, and ns=non-significant, for comparison of the effects of the same concentration at 24 h and 48 h.

spectroscopy confirmed that the N-phenyldithiocarbamate anions coordinate bidentately to the Ru(II) ion. Anticancer potential of the compound was evaluated against two cancer cell lines, HeLa and MRC5-SV2. The complex was potently cytotoxic and, in some instances, outperformed cisplatin for cytotoxic potency when tested against two cancer cell lines, HeLa and MRC5-SV2, which are models of cervical and lung cancer, respectively, highlighting the anti-cancer prospect of the complex.

Supplementary Materials

CCDC 2,064,050 contains supplementary crystallographic data that can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: + 44–1223–336–033; or email: deposit@ccdc.cam.ac.uk.

CRediT authorship contribution statement

Peter A. Ajibade: Project administration, Supervision, Funding acquisition, Writing – review & editing. **Amos A. Fatokun:** Data curation, Formal analysis, Writing – review & editing. **Athandwe M. Paca:** Data curation, Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2023.136102.

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