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Research paper

Pt(II) and Ni(II) complexes of octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthiourea derivatives: Synthesis, characterization, physical parameters and biological activity

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ABSTRACT

In this study, four novel Pt(II) and Ni(II) complexes of octahydropyrrolo[3,4-c]pyrrole, consisting of pyrrolidine fused to pyrrolidine-2,5-dione, *N*-benzoylthiourea derivatives were synthesized and their structural characterization was performed by NMR, FT-IR, MS, HRMS and elemental analysis techniques and single crystal X-ray diffraction studies. The octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthiourea compound **3c** crystallizes triclinic, with space group P-1. Pt(II) and Ni(II) ions created *cis*-complexes Pt(II) **4c** and Ni(II) **5a** forming distorted square-planar structures in orthorhombic space groups Pnma and Pbca, respectively. Furthermore, the ligands behave as bidentate and bind to the metal atom *via* the S and O atoms. Acid dissociation constants of the ligands were determined by potentiometric titration method in 25% (v/v) acetonitrile-water hydroorganic solvent at 25 ± 0.1 °C, at an ionic background of 0.1 mol/L of NaCl using the HYPERQUAD computer program and at least three acid dissociation constants were determined for each ligand. Stability constants of Pt(II) and Ni(II) complexes of the ligands were determined by potentiometric titration under the same conditions as stated above. Determination of the stability constant studies show that the ligands tend to form with Pt(II) ion in acidic medium as 1:1 (M:L) and in basic medium as 1:2 (M:L), but the ligands tend to form with Ni(II) ion in both acidic medium and basic medium as 1:2 (M:L). Antibacterial activity of the ligands and their complexes was investigated against *S. aureus*, *B. subtilis*, *A. hydrophila*, *E. coli* and *A. baumannii* standard bacterial strains. The ligands and their Pt(II) and Ni(II) complexes exhibited antibacterial activity against mentioned bacterial strains in the range of 62.5–125 μg/mL, 62.5–250 μg/mL and 62.5–125 μg/mL, respectively. Antimycobacterial activity of the compounds was investigated against the *M. tuberculosis* H37Rv strain. The compounds exhibit antimycobacterial activity in the range of 40–80 μg/mL.

1. Introduction

Metals play a very important role in living systems and pharmaceutical chemistry due to their chemical properties such as charge, interactions with ligands, structure and bonding, Lewis acid character, partially filled d-shell and redox activity [1]. Transition metals are vital in living systems, and many transition metal-based drugs have found clinical use nowadays [1,2]. The platinum-based complexes are gaining significance in bioinorganic chemistry due to the effectiveness of platinum-containing drugs such as cisplatin, carboplatin and oxaliplatin used for treatment of many types of cancer such as head and neck, etc [3–5]. Because cisplatin has various side effects and suffers from low solubility in water, recently, many platinum-based complexes have been intensively synthesized and their anticancer activities were investigated to overcome these negativities and to obtain new compounds with higher bioactivity [6–12]. In this context, several Pt(II) complexes with *N*-substituted-*N*′-aroyl(acyl)thioureas have been prepared and their anticancer properties were reported in the literature [13,14]. It is known that many Pt(II) complexes of *N*-substituted-*N*′-aroyl(acyl)thioureas have showed various other pharmacological activities such as antibacterial [15], antifungal [15–17], antimycobacterial [18] and antimalarial activities [19]. In addition, nickel-based complexes are also a very important area of pharmaceutical research [20–22] and Ni(II) complexes of *N*-substituted-*N*′-aroyl

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(acyl)thioureas have been intensively studied in the literature and are known to show a wide range of biological properties such as antimicrobial [23–27], antileishmanial [23] and anticancer activities [21,24,28].

The *N*-Substituted-*N′*-aroyl(acyl)thiourea moiety with general formula, $R^1C(O)NHC(S)NR^2R^3$, is a very useful scaffold in pharmaceutical chemistry and a unique ligand in coordination chemistry [29,30]. *N*-Substituted-*N′*-aroyl(acyl)thiourea derivatives are known to be effective against several types of cancer such as breast cancer [31], leukemia, colon and liver cancer [32] and exhibit other pharmacological properties such as G protein-coupled receptor 55 (GPR55) agonist activity [33], inhibitory activity against acetyl- and butyrylcholinesterases [34], antimicrobial [35–39], antitubercular [35,38] and analgesic activities [40]. In addition to their Pt(II) and Ni(II) complexes, many other metal complexes such as Pd(II) [15,41], Cu(I) [42], Cu(II) [24,43], Zn(II) [24,43], Co(II) [25,43] and Co(III) [44] of *N*-substituted-*N′*-aroyl(acyl)thioureas have been synthesized and were investigated for their various pharmacological activities.

The compounds containing nitrogen represent a major class of drug discovery studies [45]. Pyrrolidine contains nitrogen as heteroatom and is one of the most important scaffolds for pharmaceutical research [46,47]. The pyrrolidine moiety is present in the structures of many pharmacologically active compounds showing anticholinergic (procyclidine) [48], calcium channel blocker (bepridil) [49], anesthetic (rolicyclidine) [50] and antifungal (anisomycin) activities [51]. In addition, pyrrolidine-2,5-dione derivatives have also been reported to show various pharmacological activities such as antibacterial [52], antimycobacterial [53] and anticonvulsant activity [54]. Furthermore, heterocycles containing pyrrolidine fused to pyrrolidine-2,5-dione have been intensively studied and exhibit pharmacological activities such as antibacterial, antimycobacterial [55], anticancer [56], antiviral [57], thrombin inhibitor [58], *Escherichia coli* glycosyltransferase MurG and *Mycobacterium tuberculosis* galactosyltransferase GlfT2 inhibitor [59] activities.

In this study, we synthesized four novel Pt(II) and Ni(II) complexes of octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthiourea ligands and investigated their acid dissociation and stability constants and anti(myco)bacterial activity properties.

2. Experimental

2.1. Materials and instrumentation

All of the used chemicals were high-grade commercial products purchased from Merck or Aldrich and all solvents provided by commercial suppliers had reagent grade quality and were used without further purification.

A Varian Scimitar Series 1000 FT-IR spectrophotometer, using horizontal ATR, was used. Nuclear magnetic resonance spectra and decoupling experiments were determined at 400 MHz on a Bruker Ultrashield Plus Biospin GmbH. Chemical shifts are given in parts per million (δ) downfield from TMS as internal standard. Spectra were determined in deuterochloroform. The following abbreviations are used; s = singlet, d = doublet, m = multiplet and brd = broad doublet. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Kieselgel columns were packed with silica gel GF254. Melting points were determined on a Stuart SMP3 hot stage apparatus and are uncorrected. Mass spectra were recorded by an Agilent 6460 Triple Quad LC/MS/MS mass spectrometer. High resolution mass spectra were recorded by an LC-MS TOF electrospray ionization technique. Microanalyses were obtained using a LECO, CHNS-932 device. The X-ray crystal structure data were collected by a Rigaku R-Axis Rapid-S model X-ray diffractometer. pH-Metric titrations were performed using the Molspin pH meter™ with a Orion 8102BNUWP ROSS ultra combination pH electrode and the temperature was controlled using a thermostat (Digiterm 100, Selecta).

2.2. Synthesis

2.2.1. General procedure for synthesis of the octahydropyrrolo[3,4-c] pyrrole derivatives **1a–d**

The novel octahydropyrrolo[3,4-c]pyrrole derivatives **1a–d** were synthesized *via* 1,3-dipolar cycloaddition reaction according to literature methods [60–62]. The reaction was completed within 24 h and the structures of **1a–d** were determined by various analytical techniques. The analytical data of the compounds **1a–d** are given in the supporting information.

2.2.2. General procedure for synthesis of the octahydropyrrolo[3,4-c] pyrrole N-benzoylthioureas **3a–d**

The octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthioureas **3a–d** were prepared from the reaction of the corresponding octahydropyrrolo[3,4-c]pyrrole compound and benzoyl isothiocyanate according to the procedure given in the Refs. [27,63,64] (Scheme 1). After the reaction was completed (24–30 h), the mixture was purified by column chromatography (Et_2O:hexane/1:2). The analytical data of the compounds **3a–d** are given in the supporting information.

2.2.3. General procedure for the complex formation of **4a–d**

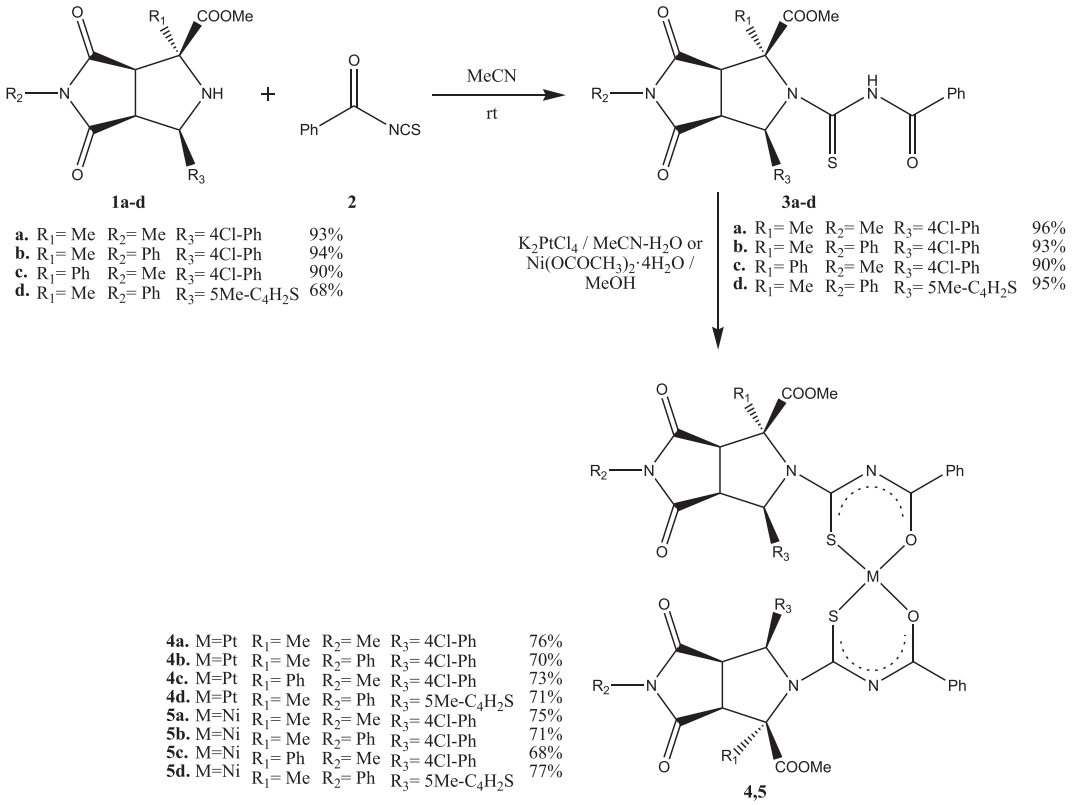
The Pt(II) complexes of ligands **3a–d** were prepared by modification of a literature method [17]. A solution of the ligand (2 mmol) in acetonitrile (30 mL) was added to a solution of K_2PtCl_4 (1.05 mmol) in water (20 mL), and the reaction mixture was stirred at ambient temperature for 24–36 h during which time the product precipitated as a yellow solid. Upon reaction completion, the solvent was filtered and the compound was washed with water and MeOH. The solvent was removed by filtration. After then the Pt(II) complexes were crystallized in DCM-MeOH. The analytical data of the compounds **4a–d** are given in the supporting information.

2.2.4. General procedure for the complex formation of **5a–d**

The Ni(II) complexes of ligands **3a–d** were prepared according to a literature method [16,17,27]. A solution of $Ni(OCOCH_3)_2{\cdot}4H_2O$ (1.05 mmol) in MeOH (30 mL) was added to a solution of the ligand (2 mmol) in MeOH (30 mL), and the reaction mixture was stirred at ambient temperature for 24–36 h during which time the product precipitated as a red solid. Upon reaction completion, the solvent was filtered and the compound was washed with MeOH several times. Finally, the Ni(II) complex **5a–d** was crystallized in DCM-MeCN-MeOH. The analytical data of the compounds **5a–d** are given in the supporting information.

2.3. X-ray crystallography

Single-crystal determination of **3c**, **4c** and **5a** was performed by using data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å) and oscillation scans technique with $\Delta w = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using Crystal Clear (Rigaku/MSC Inc., 2005) software [65]. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97 [66] programs. All non-hydrogen atoms were refined anisotropically. Methyl-H



Scheme 1. Synthesis of the octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthioureas and their Pt(II) and Ni(II) complexes.

atoms were derived from Fourier maps with the use of HFIX 137 command, others were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance.

2.4. Acid dissociation and stability constants studies

Apparatus and Materials. All reagents were analytical grade and were used without further purification. Potassium hydrogen phthalate (Fluka) (0.05 mol/kg) and sodium tetraborate solutions (Fluka) (0.01 mol/kg) were prepared and used for calibration of the electrode systems according to a literature method [67]. The ligand solutions were prepared as 1.10^{-3} mol/L in acetonitrile. Pt (II) and Ni(II) solutions were prepared as 1.10^{-3} mol/L from K_2PtCl_4 and $NiCl_2{\cdot}6H_2O$, respectively, in deionized water and then standardized with ethylenediaminetetraacetic acid (EDTA) [68]. A 0.025 mol/L NaOH solution served as titrant, and 0.1 mol/L HCl (Merck) and 1.0 mol/L NaCl (Merck) stock solutions were also prepared. Deionized water with a resistance of 18.2 MΩ.cm was obtained by an aquaMAX™-Ultra water purification system (Young Lin Inst.).

Titration was performed by using a set of the Molspin pH-mV-meter, with an Orion 8102BNUWP ROSS ultra combination pH electrode having an automatic micro burette, and the system was controlled by a PC computer. During the titrations, the temperature in the double-wall glass titration vessel was controlled using a thermostat (Digiterm 100, Selecta) and kept at 25.0 ± 0.1 °C, and the vessel solution was stirred. Calibration of the combination pH electrode was performed by using the buffer solutions of potassium hydrogen phthalate and sodium tetraborate at 25.0 ± 0.1 °C in water as required in the instructions of the Molspin Manual [67]. During each of the titrations, the titration vessel was purged through nitrogen (99.9%). In this study, HYPERQUAD, one of the most useful computer programs for determination of acid dissociation constants from potentiometric data with high precision and accuracy [69], was used to calculate the acid dissociation constants and stability constants from potentiometric data.

2.4.1. Procedure

The double-wall glass titration vessel was rinsed and dried before and after each titration process. The titration vessel was capped by a lid containing three holes. Air bubbles were removed during dropwise addition of the alkali solution. The syringe was rinsed once with deionized water and several times with the alkali solution before adding the alkali solution. In the first part of this study, to determine of the pK_a values of **3a–d** in 25% (v/v) acetonitrile-water hydroorganic solvent, added 10 mL of the ligand solution, 0.5 mL of the HCl solution and 5 mL of the NaCl solution from previously prepared their stock solutions to the titration cell. After that, 2.5 mL of acetonitrile was added to the titration cell and the titration cell was filled to 50.00 mL with deionized water and thus the 2.10^{-4} mol/L ligand solution was prepared. In the second part of this study, to determine the stability constants of the Pt(II) and Ni(II) complexes of ligands **3a–d** in 25% (v/v) acetonitrile–water hydroorganic solvent, 10 mL of the ligand solution, 5 mL of the K_2PtCl_4 or $NiCl_2{\cdot}6H_2O$ solution, 0.5 mL of the HCl solution and 5 mL of the NaCl solution were added to the titration cell. After that, 2.5 mL of acetonitrile was added to the titration cell and the titration cell was filled to 50.00 mL with deionized water and this way, the solution containing 2.10^{-4} mol/L ligand and 1.10^{-4} mol/L K_2PtCl_4 or $NiCl_2{\cdot}6H_2O$ was prepared. The data were obtained by titrating 50.00 mL of the prepared titration cell with a standardized NaOH solution and three titrations were performed for each compound. Standard deviations quoted only refer to random errors. The volume increment of the NaOH solution was 0.03 mL for each titration process. The pK_w value which is defined as $-\log[H^+][OH^-]$

for the aqueous system was obtained as 13.98 at the ionic strength employed.

2.5. Antibacterial activity

Antibacterial activity determination of the compounds was performed in duplicate against *Staphylococcus aureus* (ATCC 25925) and *Bacillus subtilis* (ATCC 6633) as Gram (+) bacterial strains and *Aeromonas hydrophila* (ATCC 95080), *Escherichia coli* (ATCC 25923) and *Acinetobacter baumannii* (ATCC 02026) as Gram (−) bacterial strains obtained from the Refik Saydam Hıfzıssıhha Institute, Ankara, Turkey. Stock solutions of **3a–d**, **4a–d**, **5a–d** were prepared by dissolving the compounds in DMSO and diluting in Mueller-Hinton broth and Triptic soy broth to give an initial concentration of 1000 μg/mL. Further dilutions of **3a–d**, **4a–d**, **5a–d** and ampicillin used as control drug were prepared at concentrations of 1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.8, 3.9 and 1.9 μg/mL. To ensure that the solvents had no effect on microbial growth, a control test was performed containing inoculated broth supplemented with DMSO at the same dilutions used for the test compounds and was determined to be inactive. The observed MIC values for each compound, **3a–d**, **4a–d**, **5a–d** and ampicillin are reported in Table 5.

2.6. Antimycobacterial activity

2.6.1. Agar proportion method

Antimycobacterial activity of **3a–d**, **4a–d**, **5a–d** were determined by agar dilution in duplicate as recommended by the Clinical Laboratory Standards Institute (CLSI) (NCCLS -M24-A 2003; NCCLS -M24-T 2002) and Isoniazid (INH) (Sigma I3377) and ethambutol (EMB) (Sigma E4630) were used as control agents. Positive and negative growth controls were studied in each assay. *M. tuberculosis* H37Rv was used as the standard strain and was provided by the Refik Saydam National Public Health Agency, National Tuberculosis Reference Laboratory, Ankara, Turkey. Stock solutions of **3a–d**, **4a–d**, **5a–d** and reference compounds were prepared in DMSO at a concentration of 1000 μg/mL. These solutions were then filtered through a 0.22 μm membrane filter (Millipore, USA). Middlebrook 7H10 agar medium (BBL, Becton Dickinson and Company, Sparks, MD, USA) was supplemented with oleic acid-albumin-dextrose-catalase (OADC, BBL, Becton Dickinson and Company, Sparks, MD, USA). The compounds **3a–d**, **4a–d**, **5a–d** and control agents were added to obtain an appropriate final concentration in the medium. The final concentrations of INH and EMB were 0.2–1 μg/mL and 5–10 μg/mL, respectively. Compounds **3a–d**, **4a–d**, **5a–d** were prepared at final concentrations of 5, 10, 20, 40, 80 and 160 μg/mL. Three mL of prepared medium without any references and synthesized compounds was dispensed into a sterile tube and it was used as growth control. The DMSO concentration in the final solutions was not above 1% for antimycobacterial activity.

2.6.2. Inoculum preparation

H37Rv was maintained in Lowenstein-Jensen medium. A culture suspension was prepared by subculturing in Middlebrook 7H9 broth (BBL, Becton Dickinson and Company, Sparks, MD, USA) supplemented with 10% OADC at 37 °C for 7–10 days, until a density corresponding to 10^{-2} dilutions was obtained from McFarland standard No. 1. Then 0.1 mL of the diluted suspension was inoculated onto the control and the other tubes with compounds **3a–d**, **4a–d**, **5a–d** in different concentrations. The tubes were incubated at 37 °C in an atmosphere of 5% CO_2 for 3 weeks. The MIC values were defined as the lowest concentration which inhibited bacterial growth and the results of INH and EMB were interpreted according to the CLSI.

3. Results and discussion

3.1. Synthesis and characterization of the complexes

The novel octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthioureas **3a–d** were synthesized by using a literature method [27,63,64] *via* reaction of the octahydropyrrolo[3,4-c]pyrroles **1a–d**, which were prepared by 1,3-cycloaddition reaction of the corresponding imine and *N*-substituted maleimide [60–62], and benzoyl isothiocyanate **2**. The structures and stereochemistry of **3a–d** were fully determined by ^{1}H and ^{13}C NMR, FT-IR, MS, HRMS and single crystal X-ray diffraction studies.

Pt(II) complexes **4a–d** were synthesized in a MeCN-water solvent system and their structures were analyzed on the basis of ^{1}H and ^{13}C NMR, FT-IR and HRMS studies. The structure of **4c** was fully characterized by single crystal X-ray diffraction. The X-ray structure shows that the amidic proton on the C(O)NHC(S) moiety is deprotonated prior to the complexation reaction, and ligands bind to the metal atom *via* S and O atoms as mutually *cis* to each other.

Ni(II) complexes **5a–d** were synthesized in MeOH and their structures were determined by various analytical techniques. The structure of **5a** was fully characterized by single crystal X-ray diffraction studies and similar to Pt(II) complexation, deprotonation of the amidic proton on the C(O)NHC(S) moiety is also observed. The Pt(II) and Ni(II) ions are coordinated by the S and O atoms, mutually *cis* to each other, of two ligands in a slightly distorted square planar coordination geometry and this geometry of the complexes is very important for their pharmaceutical properties [3].

The IR bands at 1671–1679 cm^{-1} in the spectra of the ligands **3a–d** are assigned to the ν (C=O) amide vibration bands, due to conjugation with the aromatic ring [23–27]. These bands disappear in the spectra of their Pt(II) or Ni(II) complexes, and a strong new peak is observed in the range of 1368–1401 cm^{-1}. The new peaks show that the delocalized amide oxygen atom coordinates to the Pt(II) and Ni(II). Similarly, the IR bands at 3268–3307 cm^{-1} in the spectra of the ligands **3a–d** are assigned to the ν (N—H) vibration bands and these bands also disappear in the spectra of their Pt (II) or Ni(II) complexes. These results show that the benzoylthiourea derivatives coordinate *via* O and S to the Pt(II) or Ni(II) atoms after deprotonation of the amidic proton of the C(O)NHC (S) moiety as described in the literature [23–27]. These results also indicate that the IR spectra are in accordance with the X-ray results.

The structures and stereochemistry of **3c**, **4c** and **5a** were fully characterized by X-ray crystallography. Structures were solved by

Table 2
pK_a values of the ligands (25% (v/v) acetonitrile-water, 25.0 ± 0.1 °C, I = 0.1 mol/L by NaCl).

Ligand	**3a**			**3b**			**3c**			**3d**			
Species	LH	LH_2	LH_3	LH	LH_2	LH_3	LH	LH_2	LH_3	LH	LH_2	LH_3	LH_4
pK_a Values	10.40 (±0.04)	7.66 (±0.04)	6.74 (±0.04)	9.68 (±0.07)	7.38 (±0.07)	6.46 (±0.07)	10.10 (±0.02)	7.48 (±0.02)	6.58 (±0.02)	10.40 (±0.08)	7.63 (±0.08)	6.74 (±0.08)	2.60 (±0.08)

Table 5
The MIC values (μg/mL) of the tested compounds against the (myco)bacterial strains.

Compound	*S. aureus*	*B. subtilis*	*A. hydrophila*	*E. coli*	*A. baumanii*	*M. tuberculosis H37Rv*
3a	125	62.5	125	125	62.5	40
3b	125	125	62.5	125	125	80
3c	125	125	62.5	125	62.5	40
3d	125	125	125	125	125	40
4a	125	125	250	125	62.5	40
4b	125	125	125	125	62.5	80
4c	125	62.5	62.5	125	62.5	40
4d	125	62.5	62.5	62.5	62.5	80
5a	125	62.5	125	125	62.5	40
5b	125	125	62.5	125	62.5	40
5c	125	62.5	62.5	125	62.5	80
5d	125	62.5	62.5	125	62.5	80
Ampicillin	31.25	0.9	31.25	15.62	125	
Isoniazid						0.2
Ethambutol						5

MIC: The minimal inhibitory concentrations.

direct methods, pertinent crystal and refinement data are given in Table 1 (see supporting information). The asymmetric unit of **3c** contains one target ligand (Fig. 1) and a disordered solvent molecule. Residual peaks in this structure (**3c**) could not be modelled successfully. There are four stereogenic carbon atoms, C16 has *S*-configuration and C9, C17 and C21 have *R*-configurations. The bond lengths of N2-C8 = 1.345(3) Å, N1-C8 = 1.393(3) Å and N1-C7 = 1.377(5) Å are shorter than the typical *N*-C single bond value (1.472 Å) [70], and the bond S-C8 = 1.665(3) Å and O1-C7 = 1.232 (3) Å are longer than C = S (1.611 Å) and C═O (1.208 Å) [71] double bonds lengths, respectively. These geometries indicate the existence of a partial electron delocalization in the *N*-C(S)-NH-C(O) fragment.

A view of the crystal structure of Pt(II) complex **4c** is depicted in Fig. 2. The Pt(II) complex **4c** crystallizes as dark yellow prisms and solve in the orthorhombic space group Pnma. The asymmetric unit contains half of the complex molecule, which is completed by a mirror plane through Pt along the *a*-axis. The square-planar geometry of the Pt(II) complex is formed *via* two sulfur and oxygen atoms as mutually *cis* to each other and ligands bind to the Pt(II) ion fully symmetric to each other. The bond lengths of N1-C8, 1.350(9) Å and N1-C1, 1.322(9) Å are shorter than the corresponding bonds of the **3c** ligand, but the bond length of N2-C8, 1.352(8) Å, S1-C8, 1.713(7) Å and O1-C1, 1.243(8) Å are longer than the corresponding bonds of the **3c** ligand.

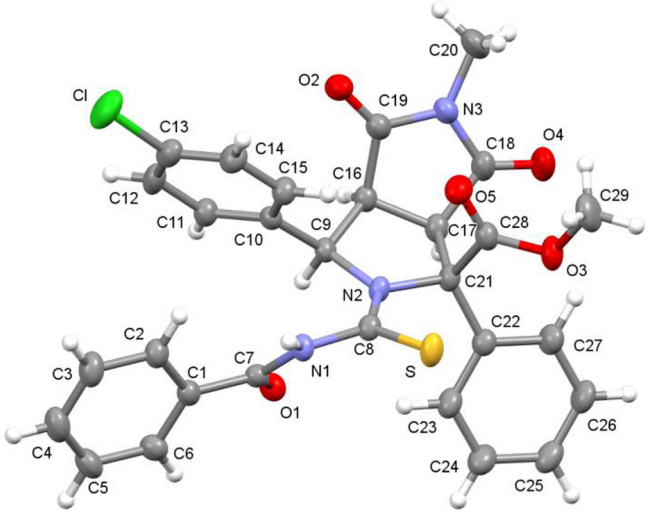


Fig. 1. Molecular structure of the compound **3c**. Anisotropic displacement ellipsoids are shown at 50% probability level. Selected interatomic distances [Å] and angles [°]: N2-C8 1.345(5), N1-C8 1.393(5), N1-C7 1.377(5), S-C8 1.665(4), O1-C7 1.232(5); C2-C8-N1 117.1(3), C8-N1-C7 126.5(3), N1-C7-C1 116.8(4), O1-C7-C1 121.6(4), O1-C7-N1 121.6(4), S-C8-N1 119.1(3), S-C8-N2 123.8(3).

A view of the Ni(II) complex **5a** is shown in Fig. 3. The Ni(II) complex **5a** crystallizes as dark red prisms and solved in the orthorhombic space group *P*bca and the asymmetric unit contains one complete molecule of the complex. The square-planar geometry was slightly distorted and the Ni(II) complex formed similar to the Pt(II) complex *via* two sulfur and oxygen atoms as mutually *cis* to each other. The angles S2–Ni1–O1 and S1–Ni1– O2 are 177.4(1)° and 179.6(1)°, respectively and less than 180°. On the other hand, the angles S1–Ni1–O1, 95.1(1)° and S2–Ni1–O2, 93.7(1)° are larger than 90° but the S2–Ni1–S1, 86.3(1)° and the O1–Ni1–O2, 84.9(2)° angles are less than 90°, revealing that the two octahydropyrrolo [3,4-c]pyrrole*N*-benzoylthiourea ligands have a steric effect on each other.

Crystallographic data that were deposited in CSD under CCDC-1500662 (**3c**), CCDC-1500490 (**4c**), CCDC-1500584 (**5a**) registration numbers contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (Fax: +441223 336033, e-mail: deposit@ccdc.cam.ac.uk).

3.2. Physical parameters

3.2.1. Acid dissociation constants of the ligands

Physicochemical parameters contain crucial information about the nature of molecules, and one of them is the acid dissociation constant (pK_a) which provides information about the acidity, solubility and hydrogen bonding capacity of molecules [72,73]. The acid dissociation constant is an indispensable parameter for the pharmaceutical scientist because the majority of drugs and numerous new organic molecules which have been synthesized for the determination of their pharmacological activities contain one or more acidic or basic groups [74,75]. Acid dissociation constants of the octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthiourea derivatives **3a–d** were potentiometrically determined at 25.0 ± 0.1 °C in a 25% (v/v) acetonitrile-water hydroorganic solvent system. Solutions of **3a–d** were prepared in acidic medium and NaCl solution was used to keep the ionic strength constant at 0.1. As a result of the calculations, three different pK_a values were found for **3a–c** and four pK_a values were found for **3d**. pK_{a1}, pK_{a2} and pK_{a3} values were obtained in a range of 10.40 (±0.08) – 9.68 (±0.07), 7.66 (±0.04) – 7.38 (±0.07) and 6.74 (±0.08) – 6.46 (±0.07), respectively (Table 2). In our previous study [76], we reported that three acid

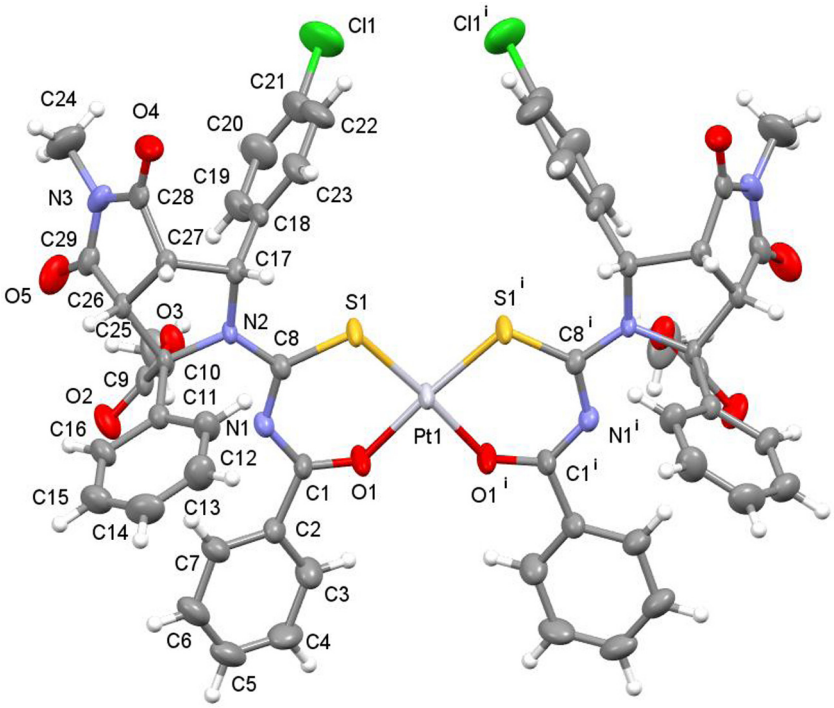


Fig. 2. Molecular structure of the compound **4c**. Anisotropic displacement ellipsoids are shown at 50% probability level. Selected inter atomic distances [Å] and angles [°]: Pt-O1 2.018(5), Pt-O1^{i} 2.018(5), Pt-S1 2.225(2), Pt-S1^{i} 2.225(2), S1-C8 1.713(7), O1-C1 1.243(8), N1-C8 1.350(9), N1-C1 1.322(9), N2-C8 1.352(8); O1-Pt-O1^{i} 81.5(3), S1-Pt-O1 94.7(2), S1^{i}-Pt-O1 176.1(2), S1–Pt–S1^{i} 89.1(1), Pt-S1-C8 107.2(2), Pt-O1-C1 129.4(5). *Symmetry-Code*; (i) x,y,1/2-z.

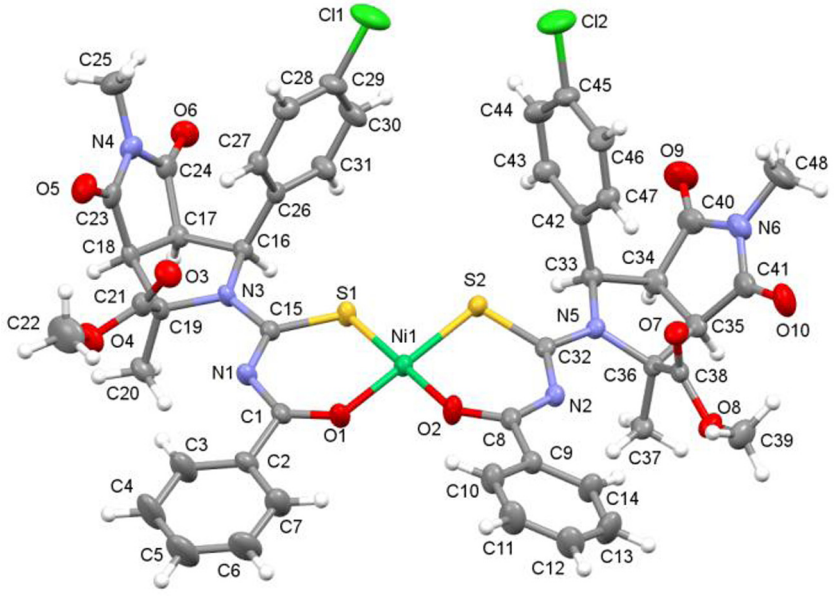


Fig. 3. Molecular structure of the compound **5a**. Anisotropic displacement ellipsoids are shown at 50% probability level. Selected interatomic distances [Å] and angles [°]: Ni1-O1 1.853(3), Ni1-O2 1.859(3), Ni1-S1 2.131(2), Ni1-S2 2.141(2), S1-C15 1.727(4), S2-C32 1.733(4), O(1)–C(1) 1.262(5), O(2)–C(8) 1.268(3), N(1)–C(1) 1.326(3), N(1)–C(15) 1.332(3), N(2)-C(8) 1.333(3), N(2)–C(32) 1.335(3), N(3)–C(15) 1.351(3), N(5)–C(32) 1.353(3); O1-Ni1-O2 84.9(2), S1-Ni1-O1 95.1(1), S1-Ni1-O2 179.6(1), S2-Ni1-O1 177.4(0), S2-Ni1-O2 93.7(1), S2-Ni1-S1 86.3(1), Ni1-S1-C15 108.2(2), Ni1-S2-C32 106.3(2), Ni1-O1-C1 133.2(3), Ni1-O2-C8 132.4(3).

dissociation constants exist for each fused ring thiohydantoin-pyrrolidine derivatives having a C(O)NHC(S)N cyclic moiety in 20% (v/v) ethanol-water mixture and suggested that the p*K*a values are related to carboxyl (in the range of 3.21 ± 0.02–3.80 ± 0.05), enol (in the range of 8.13 ± 0.01–8.66 ± 0.02) and amide NH (in the range of 10.87 ± 0.01–12.70 ± 0.05) groups. Binzet et al. reported a pK_a value, in the range of 9.62 (±0.05) – 8.79 (±0.02), for C(O)NHC(S)N type ligands in a dioxane-water (50% (v/v)) mixture, and they suggested that the pK_a values are related to amide NH groups [77]. In addition, Schröder et al. potentiometrically determined acid dissociation constants, in the range of 10.19–9.82, of the benzoylthioureas in 1,4-dioxane-water mixture (75% v/v) [78].. In this study, we propose that pK_{a1}, pK_{a2} and pK_{a3} values are related to amide NH group, enthiol and enol groups,

respectively. The pK_{a4} value is related to the carboxyl group which occurs by hydrolysis of the methyl ester of **3d** in acidic aqueous medium, and this is consistent with our previous study [76]. When comparing the pK_a values of **3a–c**, the highest pK_a values were obtained for **3a** containing one more methyl group than the others. It can be said that the Me group gives a basic character to the compound more than a Ph group for these compounds. Furthermore, the pK_a value of the carboxyl group was obtained only for **3d**, but we suggest that hydrolysis of the methyl ester of **3a–c** has occurred in the medium. The pK_a values of the carboxyl group of ligands **3a–c** couldn't be determined due to the fact that their pK_a values were not in the range of the limit of detection of the glass electrode. Hydrolysis of the methyl ester of the octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthioureas in acidic media and a proposed mechanism for their protonation is given in Scheme 2 (see supporting information).

The data was potentiometrically obtained by three individual measurements and used for calculation of the pK_a by using the HYPERQUAD computer program. Four deprotonated species formulated as LH_4, LH_3, LH_2 and LH were determined. The deprotonation equilibrium for the ligands is given in the following Eq. (1) (charges are omitted for simplicity) [79].

$$LH_n \rightleftharpoons LH_{n-1} + H \quad (1)$$

and the deprotonation constants (K_n) are given by Eq. (2);

$$K_n = [LH_{n-1}][H]/[LH_n] \quad (2)$$

The protonated ligand loses its protons with increasing pH and converts into another species of the ligand. The titration curves of **3a–d** and the distribution curves of species H are given in Fig. 4 (see supporting information).

3.2.2. Stability constants of the Pt(II) and Ni(II) complexes

Another crucial physicochemical parameter is the stability constant which provides information to understand the formation and stability of bonds in a complex. The stability constant also provides information about the bonding mechanisms and determines the concentration of the components present in a mixture in equilibrium [80,81]. The stability constants of Pt(II) and Ni(II) complexes of the octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthiourea derivatives were determined in 25% (v/v) acetonitrile-water hydroorganic solution and were interpreted with the HYPERQUAD computer program. The cumulative stability constants (β_{mlh}) are defined in the following Eqs. (3) and (4) [79]:

$$mM + lL + hH \rightleftharpoons MmLlHh \quad (3)$$

$$\beta mlh = [M_mL_lH_h]/[M]^m[L]^l[H]^h \quad (4)$$

M, L and H denote the metal ion, the ligand and H, respectively. Respective stoichiometric coefficients are specified as *m*, *l* and *h*. Pt(II)-ligand and Ni(II)-ligand titration curves are given in Figs. 5 and 6, respectively (see supporting information).

A number of species formulated as PtH_4L_2, PtH_3L_2, PtH_2L_2, $PtHL_2$, PtL_2, PtH_3L and PtH_2L of Pt(II)-**3a–d** are formed in acetonitrile-water solution at the different pH ranges (Fig. 5). During the complexation of the Pt(II) ions with **3a–d**, the first occurring species in acidic medium is PtH_2L and disappears around pH 7. During addition of the base to the titration cell, the second ligand binds to the PtH_nL complex and begins to form PtH_nL_2 species in the medium. While PtH_nL species are stable in the acidic medium, PtH_nL_2 species are stable mostly in basic medium. Furthermore, the PtL_2 type complexes are generally more stable above pH 11, except for complexation of **3d**. It can be said that the complexation of the Pt(II) ions with the **3a–d** type ligand under these conditions begins with the formation of PtH_nL type complexes, and PtH_nL_2 species begin to form with increase of the pH value of the medium. PtL_2 is the species with the lowest stability constant among the other species which are formed during complexation of the Pt(II) ions with **3a–d** (Table 3). Kumar et al. investigated the effects of pH of the medium, in the minimum volume of water followed by the addition of the appropriate amount of acetonitrile, on the Pt-benzoylthiourea (Pt-BTU) by ESI-MS technique and they found that the different Pt-BTU type species were Pt(BTU), $Pt(BTU)_2$ and $Pt(BTU)_3$ occurring with the changing of pH. The most abundant species at pH 3.0 is the Pt-BTU species and after increasing the pH value, the $Pt(BTU)_3$ type species is observed. After further increasing the pH value (pH > 6.0) the $Pt(BTU)_2$ becomes the dominant species in the medium [82]. In addition, Crisponi et al. examined potentiometrically and spectrophotometrically the complexation of Pt(II) with cimetidine and they reported that the occurring complexes were ML or ML_2 depending on the pH value [83]. When comparing the complexation of the Pt(II) ions with the ligands **3a–d** with literature, the observed PtL and PtL_2 species are the expected complexes during pH variation. Furthermore, we suppose that the PtL_3 species was not observed in the medium due to the fact that the **3a–d** ligands sterically do not allow this complexation.

A number of species formulated as NiH_5L_2, NiH_4L_2, NiH_3L_2, NiH_2L_2, $NiHL_2$, NiL_2 and $NiH_{-1}L_2$ of the Ni(II)-**3a–d** complex occurred in acetonitrile-water solution at the different ranges of the pH. During complexation of the Ni(II) ions with **3a**, **3b** and **3d**, the first occurring species in acidic medium is NiH_4L_2 and upon addition of the base to the titration cell, the NiH_3L_2 species begins to exist in the medium. As the pH value of the medium was further increased, NiH_2L_2, $NiHL_2$ and NiL_2 species were observed in the medium, respectively. The $NiH_{-1}L_2$ species begins to exist in the medium during complexation of the Ni(II) ions with **3a** and **3b** after the pH value of the medium was increased to around 10. It can be said that during complexation of the Ni(II) ions with **3a–d** under these conditions, solely the NiH_nL_2 type complex occurred in the medium (Fig. 6). In a fashion similar to the complexation of the Pt(II) ions with **3a–d**, the species having the lowest stability constant among the other species which are formed during complexation of the Ni(II) ions with **3a–d** is the NiL_2 species (Table 4). Schröder et al. examined the complexation of Ni(II) with benzoylthioureas and potentiometrically determined their stability constants in 1,4-dioxane-water mixture (75% v/v). They reported that only the NiL_2 species were formed during complexation of the Ni(II) ions with benzoylthioureas [78,84]. Beyer et al. reported that although the concentration of the *N,N*-diethyl-*N′*-benzoylthiourea in a 75% (v/v) 1,4-dioxane/water mixture was increased from 1:2, 1:4 up to 1:8 (M:L), only the NiL_2 species occurred in the medium. Furthermore, in the same study, they reported that during complexation of *N′,N′,N‴,N‴*-tetraethyl-*N,N″*-pyridine-2,6-dicarbonyl-bis(thiourea), containing two C(O)NHC(S)N moieties, with Ni(II) in a 75% (v/v) 1,4-dioxane/water mixture, only the Ni_2L_2 species occurred [85]. As a result, the formation of the Pt-**3a–d**, Pt-(**3a–d**)$_2$ and solely Ni-(**3a–d**)$_2$ type complexes during complexation of the Pt(II)/Ni(II) ions with **3a–d** is compatible with the literature.

3.3. Biological activity

Antibacterial activity studies of the octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthiourea derivatives **3a–d** and their Pt(II) **4a–d** and Ni(II) **5a–d** complexes were performed against five standard bacterial strains. **3a–d**, **4a–d** and **5a–d** exhibited antibacterial activity in the range of 62.5–125 μg/mL, 62.5–250 μg/mL and 62.5–125 μg/mL, respectively (Table 5). The synthesized ligands which have changeable substituents were selected to easily compare the relationship of the structure and bioactivity. All compounds **3a–d**, **4a–d** and **5a–d** exhibited antibacterial activity against the *S. aureus* strain with a MIC value of 125 μg/mL and ampicillin exhibited

activity with a MIC value of 31.25 μg/mL against the same bacteria strain. These results show that changing the position of the substituted groups in these compounds has no effect on the bioactivity against the *S. aureus* strain. Compounds **3a–d**, **4a–d** and **5a–d** exhibited antibacterial activity in the range of 62.5–125 μg/mL against the *B. subtilis* strain. When we compare the antibacterial activity of the compounds with ampicillin against the same strain, all compounds show moderate bioactivity. **3a**, containing a Me group as R_1 and R_2 and 4Cl-Ph as R_3, and its Ni(II) complex **5a** exhibited better antibacterial activity than the other ligands **3b**, **3c**, **3d** and its Pt(II) complex **4a** against the *B. subtilis* strain with a MIC value of 62.5 μg/mL. **3b**, containing a Me group as R_1, Ph as R_2 and 4Cl-Ph as R_3, exhibited the same antibacterial activity with its Pt(II) **4b** and Ni(II) **5b** complexes against the *B. subtilis* strain with a MIC value of 125 μg/mL. **3c**, containing a Ph group as R_1, Me as R_2 and 4Cl-Ph as R_3, exhibit lower antibacterial activity than its Pt(II) **4c** and Ni(II) **5c** complexes against the *B. subtilis* strain with a MIC value of 125 μg/mL. Similarly, **3d** also exhibited lower antibacterial activity than its Pt(II) **4d** and Ni(II) **5d** complexes against the *B. subtilis* strain with the same MIC value. The compound **3a** and its Ni(II) complex **5a** exhibited antibacterial activity against the *A. hydrophila* strain with a MIC value of 125 μg/mL and they showed better antibacterial activity than the Pt(II) complex **4a** against the same strain. Furthermore, **3b** and its Ni(II) complex **5b** exhibited antibacterial activity against the *A. hydrophila* strain with a MIC value of 62.5 μg/mL and they showed better antibacterial activity than the Pt(II) complex **4b** against the same strain. **3c** and its Pt(II) **4c** and Ni(II) **5c** complexes exhibited the same antibacterial activity against the *A. hydrophila* strain with a MIC value of 62.5 μg/mL. **3d** exhibited antibacterial activity against the *A. hydrophila* strain with a MIC value of 125 μg/mL and its Pt(II) **4d** and Ni(II) **5d** complexes exhibited better antibacterial activity than **3d** against the same strain with a MIC value of 62.5 μg/mL. Compared to ampicillin, it can be said that **3a–d** and their Pt(II) **4a–d** and Ni(II) **5a–d** complexes exhibited noteworthy bioactivity against the *A. hydrophila* strain. Except for **4d**, all ligands **3a–d** and their Pt(II) **4a–c** and Ni(II) **5a–d** complexes exhibited antibacterial activity against the *E. coli* strain with a MIC value of 125 μg/mL and **4d** exhibited better antibacterial activity against the *E. coli* strain with a MIC value of 62.5 μg/mL. Compared to ampicillin, it can be said that all of the compounds exhibited considerable bioactivity against the *E. coli* strain. **3b** and **3d** exhibited antibacterial activity with a MIC value of 125 μg/mL like ampicillin, and the other ligands **3a** and **3c** exhibited better antibacterial activity than the control group against the *A. baumanii* strain with a MIC value of 62.5 μg/mL.

Antimycobacterial activity studies of the ligands **3a–d** and their Pt(II) **4a–d** and Ni(II) **5a–d** complexes were performed against the *M. tuberculosis* H37Rv strain **(**Table 5**).** Ligands **3a**, **3c** and **3d** exhibited antimycobacterial activity with a MIC value of 40 μg/mL and **3b** exhibited antimycobacterial activity with a MIC value of 80 μg/mL against the same strain. Isoniazid and Ethambutol exhibited activity with a MIC value of 0.2 μg/mL and 5 μg/mL, respectively, against the *M. tuberculosis* H37Rv strain. Complexes **4a** and **4c** exhibited better antimycobacterial activity than **4b** and **4d** with a MIC value of 40 μg/mL. Similarly, complexes **5a** and **5b** exhibited better antimycobacterial activity than **5c** and **5d** with a MIC value of 40 μg/mL. **3a** and its Pt(II) **4a** and Ni(II) **5a** complexes exhibited antimycobacterial activity with a MIC value of 40 μg/mL. **3b** and its Pt(II) complex **4b** exhibited antimycobacterial activity with a MIC value of 80 μg/mL. At the same time, Ni(II) complex **5b** exhibited better antimycobacterial activity than **3b** and **4b** with a MIC value of 40 μg/mL. **3c** and its Pt(II) complex **4c** exhibited better antimycobacterial activity than its Ni(II) complex **5c** with a MIC value of 40 μg/mL. **3d** exhibits antimycobacterial activity with a MIC value of 40 μg/mL. At the same time, its Pt(II) **4d** and Ni(II) **5d** complexes exhibited antimycobacterial activity with a MIC value of 80 μg/mL. Compared to the reference compounds, it can be said that all of the compounds **3a–d**, **4a–d**, **5a–d** showed moderate antimycobacterial activity against the *M. tuberculosis* H37Rv strain. When we compare the antimycobacterial activity of **3a** and **3b** and their complexes among themselves, binding a Ph group as R_2 substituent instead of a Me group in the structure of **3a** and its Pt(II) **4a** and Ni(II) **5a** complexes, cause a decrease, decrease and no effect on antimycobacterial activity, respectively. When comparing the antimycobacterial activity of **3a** and **3c** and their complexes among themselves, binding a Ph group as R_1 substituent instead of a Me group in the structure of the **3a** and its Pt(II) **4a** and Ni(II) **5a** complexes, cause no effect**,** no effect and a decrease on antimycobacterial activity, respectively. Furthermore, comparing the antimycobacterial activity of **3b** and **3c** and their complexes among themselves, replacing the Me with a Ph group in the structure of **3b** and its Pt(II) **4b** and Ni(II) **5b** complexes, cause an increase, increase and decrease on antimycobacterial activity, respectively. Comparing the antimycobacterial activity of **3b** and **3d** and their complexes among themselves, binding a 5-methylthiophen-2-yl group as R_3 substituent instead of 4Cl-Ph in the structure of **3b** and its Pt(II) **4b** and Ni(II) **5b** complexes, cause an increase, no effect and a decrease on antimycobacterial activity, respectively.

4. Conclusion

The synthesis of novel Pt(II) and Ni(II) complexes of the octahydropyrrolo[3,4-c]pyrrole *N*-benzoylthioureas was performed in good yield, and their structural characterization in addition to the various analytical methods were fully performed by X-ray studies for the ligand **3c** and Pt(II) **4c** and Ni(II) **5a** complexes. X-ray studies of the Pt(II) and Ni(II) complexes showed that the amidic proton on the C(O)NHC(S) moiety was deprotonated prior to the complexation reaction, the ligands bound to Pt(II) and Ni(II) atoms *via* S and O atoms as mutually *cis* to each other and the complexes occurred in a slightly distorted square planar coordination geometry.

Due to the fact that these type of ligands have been used in a wide range of applications, the determination of at least three acid dissociation constants for the ligands in an acetonitrile-water mixture will provide very important contributions to the literature. Stability constant determination studies showed that although the ligands formed stable complex species with Pt(II) ions in acidic medium via binding as 1:1 (M:L) and in basic medium via binding as 1:2 (M:L), the ligands formed stable complex species with Ni(II) ions in both media via binding only as 1:2 (M:L).

The ligands and their complexes exhibited antibacterial and antimycobacterial activities in the range of 62.5–250 μg/mL and 40–80 μg/mL, respectively. Some of the free ligands exhibited better anti(myco)bacterial activity than their Pt(II) or Ni(II) complexes, but some of the free ligands exhibited less anti(myco) bacterial activity than their Pt(II) or Ni(II) complexes. The results of these anti(myco)bacterial activity studies are promising for future studies.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2017.04.026.

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