Synthesis and biological evaluation of platinum complexes of highly functionalized aroylaminocarbo-*N*-thioyl prolinate containing tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione moieties

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Dedication ((optional))

Abstract: Platinum complexes derived from two families of bidentate funcionalized aroylaminocarbo-*N*-thyoyl prolinates are prepared using mild conditions from prolinates, which are available via 1,3-dipolar cycloadditions. The resulting four coordinated neutral square-planar platinum(II) complexes are very stable and are fully characterized. Their structures are determined by spectroscopic and analytical methods and one of them by single crystal X-ray diffraction analysis. In this pattern, the platinum exhibits distorted square planar geometry, with *cis*-bond angles ranging from 89.42(2) and 94.37(6)° and *trans*-bond angles of 176.19(6) and 177.08(6)°, respectively. Anti(myco)bacterial and antifungal studies of all these new compounds are carried out under standardized protocols.

Introduction

Apart from catalytic activity, platinum complexes exhibit important pharmacological and biological properties and attract the attention of many synthetic organic chemists. They are very important complexes in the medicinal chemistry area mainly displaying remarkable antitumor activity [1]. However, many other complexes showed antimicrobial, antiviral [2a] antileishmanial, and antitubercular [2b] activities. The modification of the nature of the ligand, anchored to the metal centre, can expand the interaction with microorganisms. For example, this effect is shown for some platinum(II) complexes bearing thiourea-type ligands, which possess interesting biological properties such as anticancer [3], antibacterial/antifungal [4,5,6], antimalarial [7] and antituberculosis [8] activities. Besides, the presence of a pyrrolidine ring is crucial due to the synergistic effects observed in the bioactivity of many compounds [9] and also this heterocycle was the core structure for the construction of biologically important entities [10].

With all these details in mind, we envisaged that the fusion of pyrrolidine and -C(O)NHC(S)- functional moieties into a platinum complex would be an attractive framework to study. In this context, our group has previously reported the synthesis of polysubstituted aroylaminocarbo-*N*-thioyl pyrrolidines and their Ni(II), Pd(II) and Cu(II) complexes [11]. Also, the presence of the (3-indolyl)methyl group attached to the quaternary carbon (C2 of the pyrrolidine ring) is an important aspect to survey. It was reported that this substituent was a key structural element for the stability of the final rearranged family of succinimides, increasing the biological activity of them [12a].

Here we will detail the synthesis of novel square-planar platinum(II)-complexes of cyclic and bicyclic highly functionalized aroylaminocarbo-*N*-thioyl prolinates from condensation of pyrrolidines with isothiocyanates. The biological activities of prepared compounds against M. tuberculosis H37Rv strain and Staphylococcus aureus (ATCC 25925), Bacillus subtilis (ATCC 6633), Escherichia coli (ATCC 25923), Acinetobacter baumannii (ATCC 02026), and Aeromonas hydrophila (ATCC 95080) standard strains and the anti-fungal activities against *Candida albicans* ATCC 14053, *C. tropicalis* ATCC 1369 and *C. glabrata* ATCC 15126 yeast strains are evaluated too.

Results and Discussion

Continuing with our research focussed on the structure activity relationship (SAR) of heterocyclic compounds and their metal complexes as bioactive agents, we know that molecules **1**, which were obtained from 1,3-dipolar cycloaddition reaction between the α-amino ester and the maleimide *via* imine-azomethine ylide in toluene or xylene [12] in 73-95% yields, resulted to be very attractive since the biological and chemical point of view [10]. In fact, their potential utility of them as bioactive agents has been demonstrated [10]. The bicyclic highly functionalized aroylaminocarbo-*N*-thioyl prolinate ligands **2a-e** were next synthesized by the condensation of phenyl isothiocyanate and the

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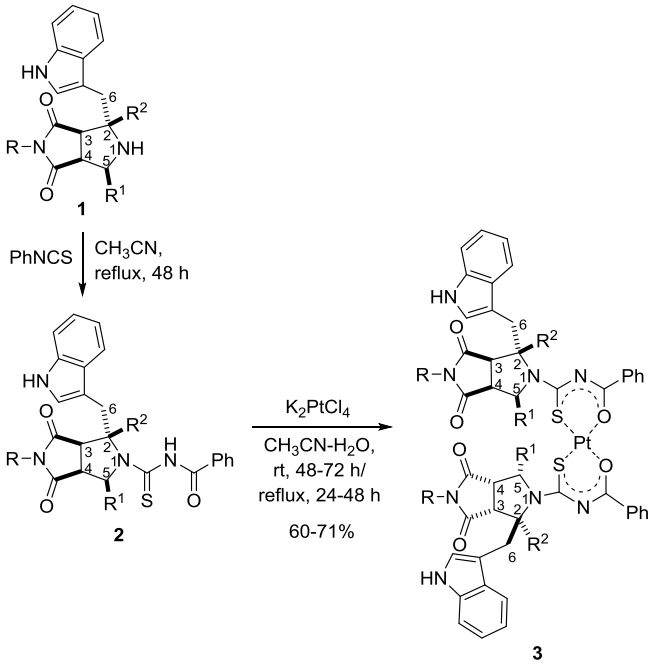
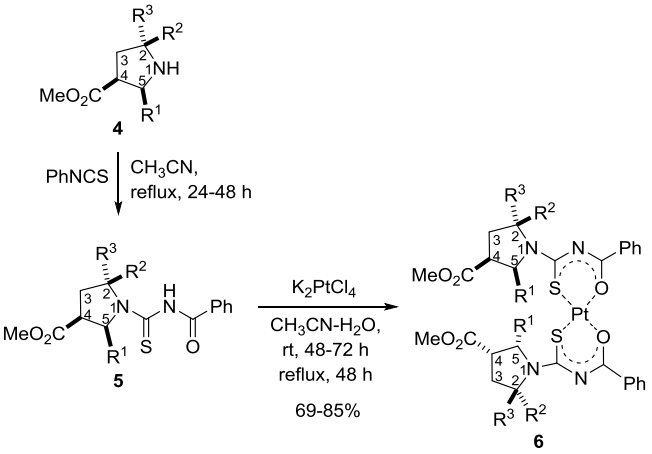
corresponding fused pyrrolidine **1** under refluxing acetonitrile for 48 h (Scheme 1) [10a]. Immediately, the square-planar platinum(II) complexes **3a-e** were prepared form molecules **2** (in 60-75% yield) by reaction with K_2PtCl_2 in acetonitrile-H_2O at room temperature for 48-72 h and recrystallized from DCM-MeOH as indicated in Scheme 1. The complexes **3a-e** were characterized using NMR, IR, microanalyses, mass spectrometry (MALDI-Tof), and HRMS experiments. Despite of their potential crystalline structure none of them gave satisfactory crystals to be analysed by X-ray diffraction.



1, **2**, **3a**. R = Ph, R^1 = 4-Chlorophenyl, $R^2 = CO_2CH_3$
1, **2**, **3b**. R = CH_3, R^1 = 4-Chlorophenyl, $R^2 = CO_2C_2H_5$
1, **2**, **3c**. R = CH_3, R^1 = 4-Methoxphenyl, $R^2 = CO_2C_2H_5$
1, **2**, **3d**. R = Ph, R^1 = 4-Methoxphenyl, $R^2 = CO_2C_2H_5$
1, **2**, **3e**. R= Cyclohexyl, R^1 = 4-Chlorophenyl, $R^2 = CO_2C_2H_5$

Scheme 1. Synthetic route for the preparation of platinum(II) complexes **3.**

Looking for an appropriate crystalline structure, prolinate derivatives incorporating other different groups at carbon atom number 4 were prepared. It is also known that this structural arrangement showed alternative activity against microorganisms [12,13]. In this sense, a new family of series of compounds **4**, **5** and **6** were designed. Starting compounds *endo*-prolinates **4**, were generated by 1,3-DC of the corresponding imino esters and methyl acrylate in 70-89% yields [12]. They were allowed to react with phenyl isothiocyanate in refluxing acetonitrile to obtain compounds **5a-c** in good yields. Following the reaction conditions of the Scheme 1 the synthesis of platinum(II) complexes **6** was successfully achieved in 69-85% yield (Scheme 2).



4, **5**, **6a**. R^1 = 2,4-Dimethoxyphenyl, $R^2 = CO_2CH_3$, $R^3 = CH_2Ph$
4, **5**, **6b**. R^1 = 4-Chlorophenyl, $R^2 = CO_2CH_3$, R^3 = indole
4, **5**, **6c**. R^1 = 2,4-Dichlorophenyl, $R^2 = CO_2CH_3$, $R^3 = CH_2Ph$

Scheme 2. Synthetic route for the preparation of platinum(II) complexes **6.**

Fortunately, the structure of **6a** was confirmed by a single crystal X-ray diffraction studies (Figure 1) [14]. Inspection of the crystallographic data confirmed that the platinum(II) complex **6a** was neutral square-planar molecule using the thioureido group/moiety as an efficient stabilizing bidentate ligand. In addition, crystal structural analysis of **6a** corresponded to a *meso*-compound, which is in agreement with the results reported in a previous work [11]. The data of crystal structure of **6a**, $[C_{31}H_{31}N_2O_7S]_2Pt$ are depicted in Figure. 1, crystallographic data with selected atomic distances and bond angles are listed in Table 1-3, and refined by a full matrix least squares technique based on F^2 using SHELXL2014.

The compound **6a** crystallised as yellow blocks in the *P* 1 space group with one molecule in the asymmetric unit. The molecular structure is shown in Figure 1. The bond lengths for Pt(1)-S(1) = 2.2184(7) Å , Pt(1)-O(1) = 2.0117(18) Å, Pt(1)-S(2) = 2.2346(7) Å and Pt(1)-O(8) =2.0260(18) Å and the angles between S(1)-Pt(1)-S(2) = 89.42(2), O(1)-Pt(1)-S(1) = 94.37(6), O(1)-Pt(1)-S(2) = 176.19(6), O(1)-Pt(1)-O(8) = 84.00(7), O(8)-Pt(1)-S(1) = 177.08(6) and O(8)-Pt(1)-S(2) = 92.24(5). The platinum exhibits the already mentioned distorted square planar geometry, with *cis* bond angles ranging from 89.42(2) and 94.37(6)° and *trans* bond angles of 176.19(6) and 177.08(6)° (Table 2 and 3). Minor disorder was observed around one of the phenyl rings, which was modelled in a 60:40 ratio, with thermal ellipsoids restrained using a rigid bond restraint. There is no evidence of hydrogen bonding or π-π interactions in the solid state.

Table 1: Crystallographic data for **6a**.

Empirical formula	$C_{62}H_{62}N_4O_{14}PtS_2$
Formula weight	1346.36
Temperature/K	121(1)
Crystal system	triclinic
Space group	P-1
a/Å	14.3323(2)
b/Å	14.3931(2)
c/Å	15.4532(2)
α/°	91.1570(10)
β/°	105.0220(10)
γ/°	90.4890(10)

Volume/Å^3	3077.90(7)
Z	2
ρ_{calc}g/cm^3	1.453
μ/mm^{-1}	2.414
F(000)	1368.0
Crystal size/mm^3	0.16 × 0.11 × 0.06
Radiation	Mo K_α (λ = 0.71073)
2Θ range for data collection/°	6.092 to 62.266
Index ranges	-20 ≤ h ≤ 20, -20 ≤ k ≤ 20, -21 ≤ l ≤ 22
Reflections collected	54186
Independent reflections	17532 [R_{int} = 0.0403, R_{sigma} = 0.0505]
Data/restraints/parameters	17532/63/774
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0358, wR_2 = 0.0668
Final R indexes [all data]	R_1 = 0.0509, wR_2 = 0.0728
Largest diff. peak/hole / e Å^{-3}	1.57/-0.78

Table 2: Selected bond lengths for **6a**.

Atom	Atom	Length/Å
Pt1	S1	2.2184(7)
Pt1	O1	2.0117(18)
Pt1	S2	2.2346(7)
Pt1	O8	2.0260(18)

Table 3: Selected bond angles for **6a.**

Atom	Atom	Atom	Angle/°
S1	Pt1	S2	89.42(2)
O1	Pt1	S1	94.37(6)
O1	Pt1	S2	176.19(6)
O1	Pt1	O8	84.00(7)
O8	Pt1	S1	177.08(6)
O8	Pt1	S2	92.24(5)

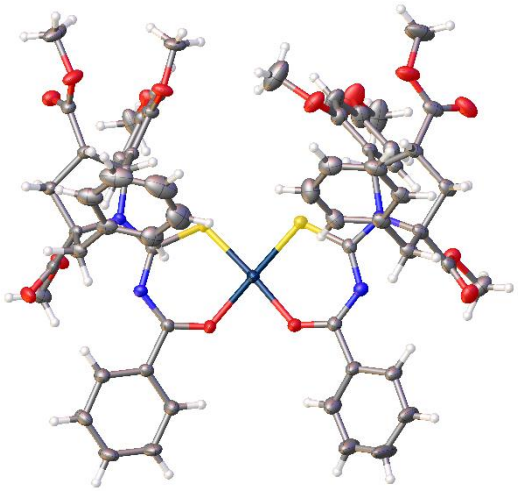


Figure 1. Crystal structure corresponding to compound **6a** [14].

Antibacterial activity. Stock solutions were prepared by dissolving the tested compounds in DMSO and then diluting in Mueller-Hinton broth and the test medium were prepared at concentrations of 500, 250, 125, 62.5, 31.25, 15.62, 7.8, 3.9 and 1.9 μg/mL. The minimum inhibitory concentrations (MIC) values was determined by broth dilution in duplicate as recommended by the Clinical Laboratory Standards Institute [15]. To ensure that the solvents had no effect on microbial growth, a control test was performed containing inoculated broth supplemented with DMSO which used for the test compounds **1a**, **2a**, **3a-e** and **6a-c**. The MIC values of the compounds were investigated against standard bacterial strains, obtained from the Refik Saydam Hıfzısıhha Institute, Ankara, Turkey. The antibacterial activity were assessed against two Gram (+) bacteria *Staphylococcus aureus* (ATCC 25925), *Bacillus subtilis* (ATCC 6633) and three Gram (–) bacteria *Escherichia coli* (ATCC 25923), *Acinetobacter baumannii* (ATCC 02026), and *Aeromonas hydrophila* (ATCC 95080). The MIC values for the compounds (**1a** and **2a)** were found in the range of 15,62 – 125 μg/ml and for the platinium complexes **(3a-e)** and **(6a-c)** in the range of 31,25 – 500 μg/mL. The control, ampicillin, showed activity with a range of 0.9-31.25 μg/mL against the tested bacteria as given in Table 1. The ligand molecule **2a** revealed the highest activities with the MIC values of 15.62 μg/mL when tested against *Aeromonas hydrophila* (ATCC 95080).

Anti-tuberculosis (TB) activity. Anti-TB activity of the tested compounds was performed according to literature method utilizing Microplate Alamar Blue assay [16]. The anti-tuberculosis activity of *t*he novel target compounds (**1a**, **2a**, **3a-3e**, **6a-6c**) were tested against *M. tuberculosis* H37Rv strain and measured by means of the minimum inhibitory concentrations (MIC) values (μg/mL). Thus Streptomycin (Sigma S6501), Izoniazid (INH) (Sigma I3377), Rifampicin (Sigma R3501), Ethambutol (EMB) (Sigma E4630) were used as standard known active reference drugs (Table 1). The bioactivity of the target compounds showed activity, in the range of 7.81-62.5 μg/mL (Table 2). The ligand molecule **2a** bearing phenyl, 4-chlorophenyl and methyl ester moieties revealed the highest activities with the MIC values of 7.81 μg/mL whereas the rest of molecules **1a**, **3a-3e**, **6a-c** showed moderate anti-TB activities in 62.5 μg/mL MIC values against M. tuberculosis H37Rv strain. Although biological target/ the mode of action of these novel molecules is unknown at the moment it seems that some molecules needs further alteration to increase their activity by modification of some part of the structure.

Anti-fungal activity. The anti-fungal activities of the target compounds (**1a**, **2a**, **3a-3e**, **6a-6c**) were tested against *Candida albicans* ATCC 14053, *C. tropicalis* ATCC 1369 and *C. glabrata* ATCC 15126 yeast strains according to the NCCLS standard document M27-A2 [17] using the microdilution broth procedure [18,19] and measured by means of MIC values (μg/mL). *Candida* strains were obtained from Refik Saydam Hıfzıssıhha Institute, Ankara, Turkey. Antifungal activities were performed in RPMI 1640 Medium (Sigma, R6504) which buffered to pH 7.0 with 0.165 M 3-(*N*-morpholino)-propanesulfonic acid (MOPS, Sigma, M1254) as outlined in document. Stock solutions of the tested compounds and reference antifungal agent were prepared in DMSO at a concentration of 1000 μg/mL. Standard strains is diluted by a 1:100 dilution followed by a 1:20 dilution of the stock suspension with RPMI 1640 medium which were then filtered *via* a 0.22 μm membrane. The fluconazole (Sigma, F8929) was used as standard known active reference drug and showed activity with a range of 3.90-31.25 μg/ml when tested against the indicated yeast. The novel tested molecules (**1a**, **2a**, **3a-3e**, **6a-c**) showed moderate anti-fungal activities in the range of 125-250 μg/mL MIC values (Table 2).

Table 1 Antibacterial and anti-*tuberculosis activities* (µg/mL)

	Staphylococcus aureus (ATCC 25925)	*Escherichia coli* (ATCC 25923)	*Acinetobacter baumannii* (ATCC 02026)	*Bacillus subtilis* (ATCC 6633)	*Aeromonas hydrophila* (ATCC 95080)	*M. tuberculosis* H37RV
1a	62,5 µg/mL	62,5 µg/mL	31,25 µg/mL	125 µg/mL	31,25 µg/mL	62,5 µg/mL
2a	62,5 µg/mL	62,5 µg/mL	31,25 µg/mL	125 µg/mL	15,62 µg/mL	7.81 µg/mL
3a	62,5 µg/mL	62,5 µg/mL	31,25µg/mL	125 µg/mL	31,25 µg/mL	62,5 µg/mL
3b	250 µg/mL	250 µg/mL	125 µg/mL	250 µg/mL	500 µg/mL	62,5 µg/mL
3c	62,5 µg/mL	62,5 µg/mL	31,25 µg/mL	125 µg/mL	31,25 µg/mL	62,5 µg/mL
3d	500 µg/mL	250 µg/mL	125 µg/mL	250 µg/mL	62,5 µg/mL	62,5 µg/mL
3e	250 µg/mL	250 µg/mL	125 µg/mL	62,5 µg/mL	62,5 µg/mL	62,5 µg/mL
6a	250 µg/mL	250 µg/mL	125 µg/mL	250 µg/mL	500 µg/mL	62,5 µg/mL
6b	62,5 µg/mL	62,5 µg/mL	31,25 µg/mL	125 µg/mL	31,25 µg/mL	62,5 µg/mL
6c	250 µg/mL	250 µg/mL	125 µg/mL	250µg/mL	125 µg/mL	62,5 µg/mL
Ampicillin	32.25	15.62	125	0.9	31.25	
Streptomycin						0,06 µg/mL
Izoniazid						0,12 µg/mL
Rifampicin						0,97 µg/mL
Etambutol						1,95 µg/mL

Table 2 Anti-fungal activity *(*µg/ml)

	Candida albicans ATCC 14053	*Candida tropicalis* ATCC 1369	*Candida glabrata* ATCC 15126
1a	125 µg/mL	125 µg/mL	125 µg/mL
2a	125 µg/mL	250 µg/mL	125 µg/mL
3a	250 µg/mL	125 µg/mL	250 µg/mL
3b	125 µg/mL	125 µg/mL	125 µg/mL
3c	250 µg/mL	250 µg/mL	125 µg/mL
3d	125 µg/mL	125 µg/mL	250 µg/mL
3e	250 µg/mL	250 µg/mL	125 µg/mL
6a	125 µg/mL	125 µg/mL	125 µg/mL
6b	125 µg/mL	125 µg/mL	125 µg/mL
6c	125 µg/mL	125 µg/mL	250 µg/mL
Fluconazole	31.25 µg/mL	15.62 µg/mL	3.90 µg/mL

Conclusions

The *N*-benzoylthiourea framework possessing pharmacophores containing prolinate units resulted to be a very strong bidentate ligand towards the platinum atom affording very stable planar dimeric entities. These series of highly pure complexes were isolated in good yields. Antibacterial, antituberculosis, and antifungal studies of all these new compounds revealed that molecule **2a** possesed the highest activity with the MIC values of 15.62 µg/mL when tested against *Aeromonas hydrophila*. This level is much more effective than the own shown by Ampicillin. In addition, the same molecule **2a** exhibited the highest activities with the MIC values of 7.81 µg/mL against M. tuberculosis H37Rv strain. All families of derivatives were tested as antigungals showing moderate activities in the range of 125-250 µg/mL MIC values, which are very high with respect to the effective fluconazole doses. At the moment, the biological properties and the mode of action for corresponding molecules is unknown, but we are currently modifying some substituents of the skeleton in order to increase their activities text of the article should appear here with headings as appropriate.

Experimental Section

General procedure for the synthesis of aminocarbothiolpyrrolidines (2 and 5): To a solution of the corresponding pyrrolidine (1.2 mmol) in dry acetonitrile (25 mL) was added dropwise benzoyl isothiocyanate (0.213 mL, 1.3 mmol) in dry acetonitrile (15 mL). The resulting solution was stirred at room temperature for 24-48 h or reflux 48 h. After completion of the reaction by monitoring TLC, the solvent removed and purified by flash chromatography.

General procedure for the synthesis of platinium complexes (3a-e, 6a-c): In a flask containing the corresponding aminocarbothiolpyrrolidine (2 mmol) in acetonitrile (20 mL), K_2PtCl_4 (1mmol) in water (10 mL) was added and the resulting solution was stirred at room temperature 48-72 h or under reflux for 24-48 h. The solvent was evaporated and the crude mixture was analysed by ^1H NMR and then crystallised in appropriate solvent to give a yellow solid.

X-Ray Crystallographic Analysis of 6a: Measurements were carried out at 120K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and connected to an Oxford Cryostream low temperature device using mirror monochromated /Mo K_α radiation (λ = 0.7107 Å) from a Microfocus X-ray source. The structure was solved by intrinsic phasing using SHELXT [20] and refined by a full matrix least squares technique based on F^2 using SHELXL2014 [21].

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Keywords: platinum complexes·aminocarbothiol·antibacterial·antifungal·antituberculosis

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