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Synthesis, spectral characterization and *in vitro* antibacterial evaluation and Petra/Osiris/Molinspiration analyses of new Palladium(II) iodide complexes with thioamides

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Abstract The paper emphasizes on the synthesis of Palladium(II) iodide complexes containing based ligands. The new compounds of general formulae $[Pd(L)_4]I_2$ where L = Thiourea (Tu), Methylthiourea (Metu), Dimethylthiourea (Dmtu), Tetramethylthiourea (Tmtu), Imidazolidine-2-thione (Imt), Mercaptopyridine (Mpy), Mercaptopyrimidine (Mpm), and Thionicotinamide (Tna) were prepared simply by reacting $K_2[PdCl_4]$ with the corresponding thioamides in 1:2 M ratio and then with 2 equivalents Potassium iodide. The complexes were characterized by elemental analysis and spectroscopic techniques (IR, ^1H and ^{13}C NMR). All the synthesized complexes were screened for antibacterial activity and some of compounds have shown good activities against both gram positive and gram negative bacteria. POM analyses reveal that the compounds are only slightly toxic and present a potential for antibacterial activity. Moreover, they have 16–23% drug score which is an important parameter for the compound possessing the drug properties.

1. Introduction

The coordination and structural chemistry of Palladium based complexes with donor atoms, especially sulfur containing ligands have been extensively studied.[1–5] Palladium(II) complexes with heterocyclic thiones and thioureas as ligands

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showing a square-planar geometry have promising bio-relevant activities, particularly Mercaptopyrimidine, 6-Mercaptopurines, Imidazolidine-2-thione, and Diazinane-2-thione and their complexes with Palladium(II) are known to have antitumor activities.[6–16] In view of great potential, several complexes of thioamides with Au(I), Ag(I), Cu(I) Zn(II) Mo(II), Cd(II) Pd (II) and Hg(II) have been widely studied.[17–36]

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, possibly acting through mechanism of action, which is distinct from those of well-known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant. Due to the outbreak of infectious diseases caused by different pathogenic bacteria and the development of antibiotic resistance, researchers are searching for new antibacterial agents.

In continuation of our interest to further study the structural chemistry and biological properties of Palladium–sulfur interaction, in this paper, we describe the coordination of Palladium(II) iodide with a number of heterocyclic thiones as well as thioureas and their characterization by IR, ^{1}H and ^{13}C NMR spectroscopic techniques. Moreover, we have also investigated the antibacterial activities of these complexes. The knowledge of coordination behavior of thioamides toward Palladium(II) would be useful to understand the interactions of heavy metals to nucleotides and related compounds, which may have antitumor activity. The structures of the ligands used in this study are shown in Scheme 1.

2. Experimental

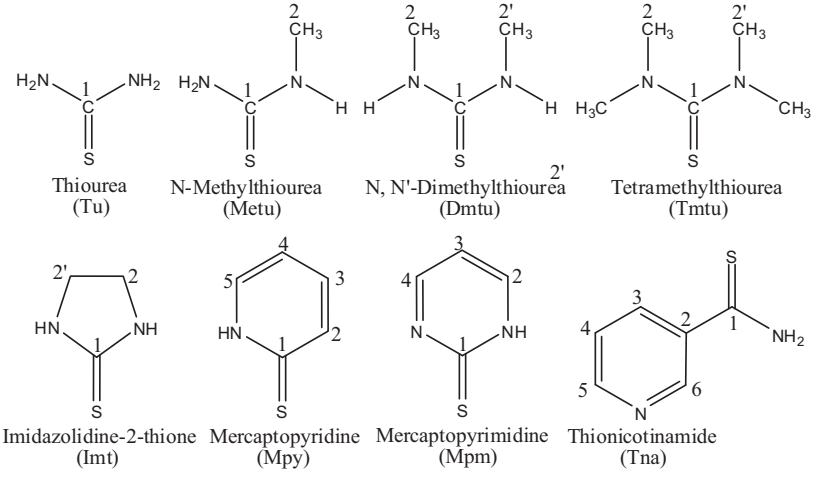
2.1. Chemicals

Palladium(II) chloride was purchased from Degussa AG 40474, Dusseldorf, Germany. The ligands, Thiourea (Tu), Methylthiourea (Metu), N,N′-Dimethylthiourea (Dmtu), Tetramethylthiourea (Tmtu), 2-Mercaptopyridine (Mpy), 2-Mercaptopyrimidine (Mpm), and Thionicotinamide (Tna) were purchased from ACROS Organics, USA. Imidazolidine-2-thione (Imt) was prepared according to the published procedure.[12]

2.2. Synthesis of the complexes

Potassium tetrachloropalladate (II) was prepared as described in the literature.[20] Slight excess of two equivalents of Potassium chloride 1:2.25 ratio was added into the solution of Palladium chloride in 25 cm^3 of distilled water with stirring for half an hour. The mixture was cooled in ice after few minutes yellowish-brown crystals of Potassium tetrachloropalladate (II) were formed which was separated by filtration and recrystallized from water containing few drops of HCl.

All the complexes were prepared by adding 2 equivalents of thioamides already dissolved in 15 mL methanol solution of $K_2[PdCl_4]$ (0.326 g) in 15 mL of water (Scheme 2). After half an hour stirring 2 equivalents of aqueous solution of Potassium iodide were added and stirred the solutions for one hour. On mixing dark brown or reddish color solutions were obtained except for $[Pd(Metu)_4]I_2$ complex, where a shows a pale yellow color solution was obtained. All these solutions were filtered and washed with methanol and were kept at room temperature for three to five days. Solid products were obtained from water–methanol mixture on slow evaporation.

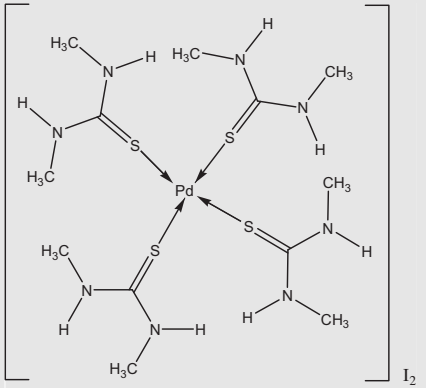
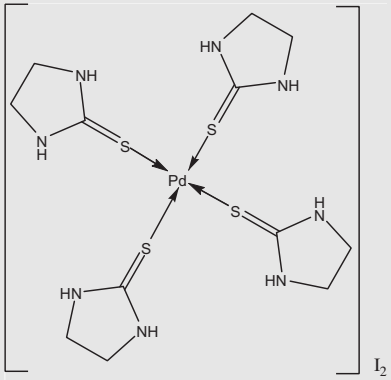
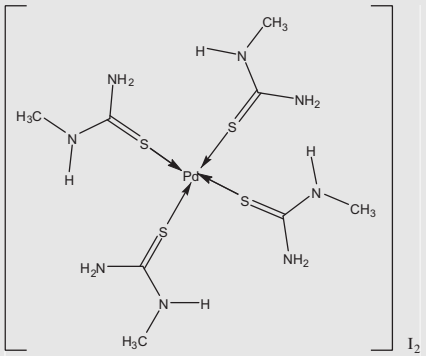
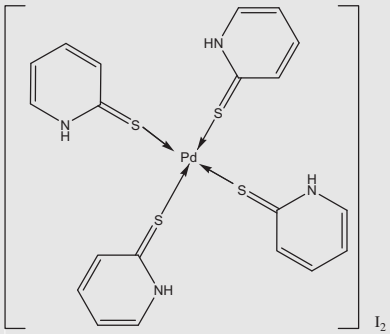
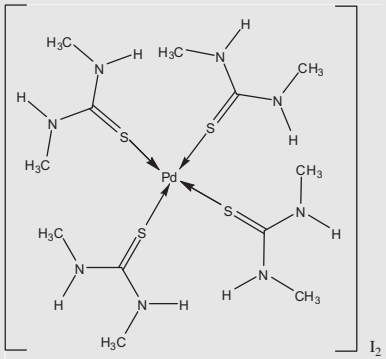
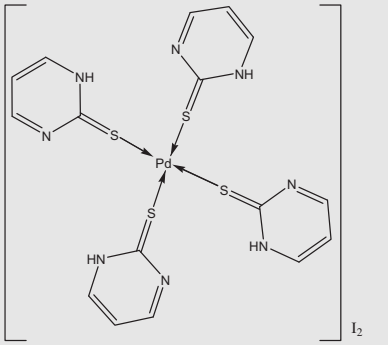


Scheme 1 Structures of the ligands used for complexation.

$$K_2[PdCl_4] + 2\,KI + 2(\text{Thioamide}) \xrightarrow[\text{Stirring 1 hour}]{\text{Water , Methanol}} [Pd(\text{Thioamide})_4]I_2 + 4\,KCl$$

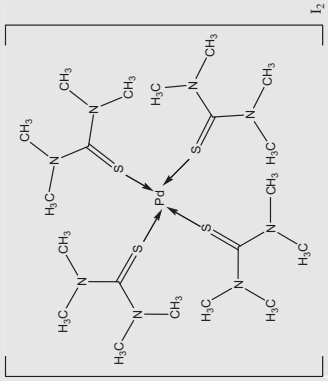
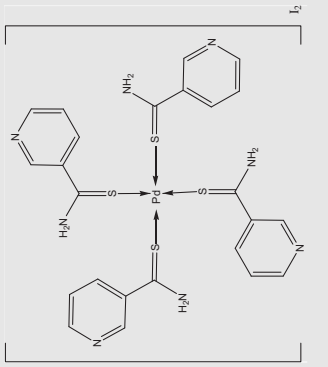
Scheme 2 General reaction for the synthesis of the complexes.

Table 1 Proposed structure of the synthesized compounds.

Comp. code	Structure	Comp. code	Structure
$[Pd(Dmtu)_4]I_2$		$[Pd(Imt)_4]I_2$	
$[Pd(Metu)_4]I_2$		$[Pd(Mpy)_4]I_2$	
$[Pd(Dmtu)_4]I_2$		$[Pd(Mpm)_4]I_2$	

(*continued on next page*)

Table 1 (*continued*)

Comp. code	Structure
$[Pd(Tmtu)_4]I_2$	
$[Pd(Tna)_4]I_2$	

The experimental yield of the products was around 60–75%. The proposed structures of the complexes are shown in Table 1. The elemental analysis and melting points (MP) of the complexes are given in Table 2.

2.3. Measurements

Elemental analysis was carried out on a Leco CHNS-932 Leco Corporation USA. Melting point was recorded on an Electrothermal IA 9000 Series, Essex SS2 5PH UK. FT-IR spectra were recorded on a Thermo Nicolet Nexus 6700 USA. The ^{1}H and ^{13}C NMR spectra of the ligands and their complexes in DMSO-d_6 were obtained on Bruker Avance 300 MHz NMR Spectrometer operating at frequencies of 300.00 MHz and 75.47 MHz respectively at 300 K. The spectral conditions were as follows: 32 K data points, 1.822 s acquisition time, 2.00 s pulse delay and 6.00 μs pulse width. The ^{13}C chemical shifts were measured relative to TMS.

2.4. Antibacterial activities of the complexes

The antibacterial activity of all synthesized metal complexes has been investigated against four bacteria, two G (+) bacterial strains i.e., *Staphylococcus aureus* ATCC 25923, and *Bacillus subtilis* DSM 3256, and two G (−) bacterial strains i.e., *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 10197 by the agar well diffusion method. Imipenem was used as standard antibiotic which is *β-Lactam* antibiotic effective against G (+ve) as well as G (−ve) bacteria. 3 mg of the test samples (ligands & complexes) was dissolved in 1 mL of DMSO. 2–3 mL nutrient broth (0.8 g/100 mL) was prepared in distilled water with pH 7 and was autoclaved at 121 °C, 15 psi pressure and for 20 min. 24 h fresh culture grown on nutrient broth at pH 7 was used for sensitivity testing. To compare the turbidity of bacterial cultures McFarland $BaSO_4$ solution was used as turbidity standard. To perform antibacterial assay, nutrient agar medium was prepared by dissolving 2 g/100 mL in distilled water with pH 7 and the medium was autoclaved. The nutrient agar medium was poured in Petri dishes and allowed to solidify. Using sterile cotton swabs lawns of test cultures were prepared on labeled plates. Four wells per plate were prepared with the help of sterile cork borer (2 mm). Using micropipette, 30 μL of test solution was poured in respective labeled wells. Now, these experimental plates were incubated for 24 h and zones of inhibition (%) were measured and compared with standard antibiotic imipenem having zone inhibition 21 mm, 18 mm, 16 mm and 18 mm, respectively.[37,38]

2.5. Petra/Osiris/Molinspiration (POM) analyses

Petra/Osiris/Molinspiration (POM) analysis is one of the well-known approaches that has been used regularly to produce the two dimensional models to identify and to indicate the type of pharmacophore site that affects biological activity with a change in the chemical substitution. The advantages of POM are the ability to predict the biological activities of the molecules and to represent the relationships between steric/electrostatic property and biological activity

Table 2 CHNS analysis, and MP of $[Pd(L)_4]I_2$ complexes.

Compound	Color	Found (calculated) %				MP (°C)
		C	H	N	S	
$[Pd(Tu)_4]I_2$	Dark brown	7.20 (7.22)	2.23 (2.41)	16.31 (16.85)	9.57 (9.63)	248–249
$[Pd(Metu)_4]I_2$	Pale yellow	13.41 (13.32)	3.36 (3.33)	15.62 (15.54)	8.90 (8.88)	214–216
$[Pd(Dmtu)_4]I_2$	Dark brown	18.48 (18.53)	4.10 (4.12)	14.39 (14.42)	8.21 (8.24)	202–204
$[Pd(Tmtu)_4]I_2$	Dark brown	27.01 (26.98)	5.42 (5.40)	12.57 (12.59)	7.21 (7.19)	245–247
$[Pd(Imt)_4]I_2$	Dark brown	18.75 (18.73)	3.15 (3.12)	14.51 (14.57)	8.33 (8.32)	242–244
$[Pd(Mpy)_4]I_2$	Dark brown	29.86 (29.82)	2.51 (2.48)	6.94 (6.96)	7.91 (7.95)	199–202
$[Pd(Mpm)_4]I_2$	Dark red	23.71 (23.74)	2.00 (1.98)	13.87 (13.85)	7.89 (7.91)	253–255
$[Pd(Tna)_4]I_2$	Dark brown	31.58 (31.56)	2.68 (2.63)	12.31 (12.27)	7.04 (7.01)	193–195

Table 3 Selected IR absorption (cm^{-1}) for free ligands and their Palladium(II) iodide complexes.

Compound	ν(C═S)	ν(N—H)	ν(N—H)	ν(C—N)	ν(Pd—S)	ν(Pd—I)
Tu	730	3156, 3365	1604	1473	–	–
$[Pd(Tu)_4]I_2$	706	3176, 3379	1608	1384	327	270
Metu	634	3163, 3245	1624	1488	–	–
$[Pd(Metu)_4]I_2$	762	3176	1619	1469	328	279
Dmtu	641	3203	1552	1521	–	–
$[Pd(Dmtu)_4]I_2$	717	3283, 3340	1573	1492	324	260
Tmtu	622	–	–	1491	–	–
$[Pd(Tmtu)_4]I_2$	675	2923, 3468	1553	1493	335	279
Imt	510	3200	1499	1307	–	–
$[Pd(Imt)_4]I_2$	562	3306	1507	1317	317	273
Mpy	613	3176	1578	1487	–	–
$[Pd(Mpy)_4]I_2$	754	2917, 3064	1498	1573	304	269
Mpm	624	3053	1602	1491	–	–
$[Pd(Mpm)_4]I_2$	748	3032	1525	1567	301	272
Tna	699	3180	1675	1455	–	–
$[Pd(Tna)_4]I_2$	671	3136, 3278	1613	1464	304	265

Table 4 ^1H NMR data of the ligands and their Palladium(II) iodide complexes.[a]

Compound	NH_2	NH	H-2	H-3	H-4	H-5	H-6	N—CH_3
Tu	7.06, s	–	–	–	–	–	–	–
$[Pd(Tu)_4]I_2$	7.88, s	–	–	–	–	–	–	–
Metu	7.45, s	7.60, s	–	–	–	–	–	2.80, s
$[Pd(Metu)_4]I_2$	8.63, s	7.65, s	–	–	–	–	–	2.82, s
Dmtu	–	7.38, s	–	–	–	–	–	2.81, s
$[Pd(Dmtu)_4]I_2$	–	8.51, s	–	–	–	–	–	2.84, 2.90, s
Tmtu	–	–	–	–	–	–	–	3.08, s
$[Pd(Tmtu)_4]I_2$	–	–	–	–	–	–	–	3.11, s
Imt	–	7.99, s	3.62, d	–	–	–	–	–
$[Pd(Imt)_4]I_2$	–	8.96, s	3.90, d	–	–	–	–	–
Mpy	–	10.12, s	7.53, d	7.40, d	7.90, t	7.23, d	–	–
$[Pd(Mpy)_4]I_2$	–	10.21, s	7.57, d	7.45, d	7.99, t	7.25, d	–	–
Mpm	–	8.28, t	8.30, d	–	8.20, d	–	–	–
$[Pd(Mpm)_4]I_2$	–	8.97, t	8.36, d	–	8.24, d	–	–	–
Tna	9.12, s	10.12, s	–	7.90, t	7.60, t	8.23, d	7.16, s	–
$[Pd(Tna)_4]I_2$	9.16, s	10.21, s	–	7.95, t	7.69, t	8.25, d	7.20, s	–

[a] Numbering is in accordance with Scheme 1.

Table 5 ^{13}C NMR data of the ligands and their Palladium(II) iodide complexes. [a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6
Tu	183.8	–	–	–	–	–
$[Pd(Tu)_4]I_2$	178.06	–	–	–	–	–
Metu	181.3	31.1	–	–	–	–
$[Pd(Metu)_4]I_2$	175.5	32.4	–	–	–	–
Dmtu	183.0	30.7	–	–	–	–
$[Pd(Dmtu)_4]I_2$	174.9	31.03	–	–	–	–
Tmtu	193.4	42.1	–	–	–	–
$[Pd(Tmtu)_4]I_2$	187.1	44.7	–	–	–	–
Imt	183.9	44.0	–	–	–	–
$[Pd(Imt)_4]I_2$	178.4	45.4	–	–	–	–
Mpy	177.7	133.2	113.9	137.5	137.9	–
$[Pd(Mpy)_4]I_2$	167.57	132.3	120.0	139.4	140.3	–
Mpm	181.9	155.0	154.8	110.0	–	–
$[Pd(Mpm)_4]I_2$	172.9	159.3	158.2	116.4	–	–
Tna	198.0	135.0	135.3	123.1	147.6	151.6
$[Pd(Tna)_4]I_2$	194.9	136.4	137.6	126.2	141.8	148.0

[a] Numbering is in accordance to the Scheme 1.

in the form of pharmacophore site, which gives key features on not only the ligand–receptor interaction, but also on the topology of the receptor.[39]

3. Results and discussion

3.1. Elemental analysis (CHN)

Elemental analysis data are given in Table 2. It can be seen that the observed values are in very good agreement with the calculated values that show the purity of the synthesized compounds.

3.2. IR studies

Selected IR spectroscopic vibrational bands for the free ligands and their Palladium(II) complexes are given in Table 3. Low frequency shifts in the ν(C═S) band at 506–739 cm^{-1}, ν(N—H) band at 1487–1675 cm^{-1}, ν(C—N) band at 1307–1602 cm^{-1} and high frequency shifts in ν(N—H) band at 3023–3379 cm^{-1} shifted to 562–762 cm^{-1}, 1498–1619 cm^{-1}, 1317–1573 cm^{-1} and 2917–3468 cm^{-1} respectively in the complexes were observed indicating coordination through sulfur compared with free ligands. The peaks at 301–335 cm^{-1} and 260–279 cm^{-1} were attributed to the ν(Pd—S) and ν(Pd—I) vibrations, respectively.[19,40,41]

3.3. NMR studies

The ^1H NMR data of the ligands and their complexes are given in Table 4. In ^1H NMR spectra of the complexes, the N—H signal of thiones becomes less intense upon coordination and shifted downfield by 0.03–1.74 ppm from their positions in free ligands. The downfield shifting of the N—H proton is related to an increase of the π electron density in the C—N bond upon complexation.[22] The appearance of N—H signal shows that the ligands are coordinated to Palladium(II) *via* the thioamide group. The N—H protons of Dmtu are equivalent but after coordination they become nonequivalent as NH_2 appears as triplets in Dmtu.

The ^{13}C NMR chemical shifts for the ligands and $[Pd(L)_4]I_2$ complexes are given in Table 5. Upfield shifts are observed in the >C═S resonance of ligands upon its complexation with Palladium(II). The upfield is attributed to the lowering of >C═S bond order and shifting of N → C electron density producing a partial double bond character in the C—N bond, as observed in the other metal complexes of thiourea.[14,19,20,36] In all complexes the C-2 resonance appears upfield by 2.97–10.12 ppm compared with the free ligands. Among these

Table 6 Antibacterial activity of the ligands and their Palladium(II) iodide complexes.

(% Zone of inhibition of Std. Drugs, Ligands and Complexes)

Compound	*Staphylococcus aureus* % value	*Bacillus subtilis* % value	*Escherichia coli* % value	*Pseudomonas aeruginosa* % value
Imipenem	100 (21 mm)	100 (18 mm)	100 (16 mm)	100 (18 mm)
Tu	0	0	13	0
$[Pd(Tu)_4]I_2$	43	45	57	17
Metu	0	17	45	33
$[Pd(Metu)_4]I_2$	14	17	13	33
Dmtu	10	11	13	11
$[Pd(Dmtu)_4]I_2$	0	0	6	0
Tmtu	0	11	0	0
$[Pd(Tmtu)_4]I_2$	10	17	13	22
Imt	0	22	38	28
$[Pd(Imt)_4]I_2$	14	22	0	17
Mpy	52	95	100	83
$[Pd(Mpy)_4]I_2$	14	39	44	50
Mpm	19	45	63	45
$[Pd(Mpm)_4]I_2$	48	56	69	67
Tna	0	0	19	0
$[Pd(Tna)_4]I_2$	33	0	0	0

Table 7 Osiris calculations of toxicity risks and drug-score of the selected compounds.

Compound #	Toxicity risks				Bioavailability and drug-score				
	Mutagenic	Tumorigenic	Irritant	Reproductive effective	cLog *P*	Solubility	TPSA	Druglikeness	Drug-score
$[Pd(Dmtu)_4]I_2$	+ +	+ +	+ +	+ +	−1.05	−1.97	52.04	−2.72	0.18
$[Pd(Imt)_4]I_2$	+ +	+ +	+ +	+ +	−1.05	−1.97	52.04	−2.72	0.18
$[Pd(Metu)_4]I_2$	+ +	+ +	+ +	+ +	−0.35	−1.08	24.06	−0.87	0.21
$[Pd(Mpy)_4]I_2$	+ +	+ +	+ +	+ +	0.18	−1.08	6.48	−4.23	0.16
$[Pd(Mpm)_4]I_2$	+ +	+ +	+ +	+ +	−0.32	−1.95	24.06	−0.20	0.23
$[Pd(Tmtu)_4]I_2$	+ +	+ +	+ +	+ +	−0.28	−3.13	12.03	−1.06	0.19
$[Pd(Tu)_4]I_2$	+ +	+ +	+ +	+ +	−0.13	−2.72	24.39	−0.83	0.20
$[Pd(Tna)_4]I_2$	+ +	+ +	+ +	+ +	0.31	−1.93	38.91	−1.36	0.18
Imipenem	+	+	+	+	−1.16	−0.97	139.0	−5.28	0.95

+ = not toxic; + + = slightly toxic.

Table 8 Molinspiration property and Molinspiration bioactivity score data of the selected compounds and reference drugs.

Data	$Pd(Dmtu)_4]I_2$	$Pd(Imt)_4]I_2$	$Pd(Metu)_4]I_2$	$Pd(Mpy)_4]I_2$	$Pd(Mpm)_4]I_2$	$Pd(Tmtu)_4]I_2$	$Pd(Tu)_4]I_2$	$Pd(Tna)_4]I_2$	Imipenem
miLog *P*	1.65	−0.019	0.901	4.208	2.361	1.65	0.152	−2.073	−0.734
TPSA	48.108	48.108	76.1	31.582	57.366	48.108	104.092	77.83	113.715
natoms	15.0	15.0	13.0	17.0	17.0	15	11	21.0	20.0
MW	568.584	564.552	540.53	582.566	584.542	568.584	512.476	636.618	299.352
nON	4	4	4	2	4	4	4	4	7
nOHNH	4	4	6	2	2	4	8	4	4
Nviolations	1	1	2	1	1	1	2	1	0
Nrotb	4	0	2	0	0	4	0	2	7
Volume	279.297	258.576	243.947	276.231	267.919	279.297	208.597	320.25	255.433
GPCR L	−0.63	−0.47	−1.00	−0.26	−0.35	−0.63	−1.20	0.01	0.32
ICM	−0.25	−0.19	−0.51	0.07	−0.13	−0.25	−0.57	−0.08	−0.21
KI	−0.55	−0.62	−0.72	−0.20	−0.34	−0.55	−1.01	−0.04	−0.56
NRL	−0.81	−0.86	−1.34	−0.38	−0.53	−0.81	−0.45	−0.21	−0.21
PI	−0.70	−0.66	−0.81	−0.46	−0.55	−0.70	−1.01	−0.18	0.97
EI	−0.27	−0.23	−0.36	−0.08	−0.12	−0.27	−0.50	−0.04	1.00

GPCR L = GPCR ligand, ICM = ion channel modulator, KI = kinase inhibitor, NRL = nuclear receptor ligand, PI = protease inhibitor, EI = enzyme inhibitor.

complexes the Mpy complexes are the most stable complex due to its most and significant shift in the C-2 resonance.

3.4. Antibacterial studies

Metal complexes with thioamides are capable of inhibiting bacterial growth and activity by interfering with the metabolic process in the bacteria.[1–3,14,20,33,36,38,41,42] In the present work, we have synthesized thioamides Palladium(II) iodide complexes and their. Antibacterial activities have been determined against four strains of bacteria *S. aureus* (ATCC 25923), *B. subtilis* (DSM 3256), *E. coli* (ATCC 25922), and *P. aeruginosa* (ATCC 10197). The results are shown in Table 6. Better antibacterial activities were observed as compared to a standard drug. The Palladium(II) complexes containing thiourea, mercaptopyridine and mercaptopyrimidine exhibited good activity against all bacteria *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*. The complexes of methylthioure, a tetramethylthiourea and imidazolidine-2-thione exhibited relatively low activity against all of these bacteria. The complexes of dimethylthiourea and thionicotinamide are ineffective against all bacteria i.e. all bacteria show resistance against these two complexes. The antibacterial activity of complexes may be attributed to their inhibition in the metabolic pathway which alter the replication of DNA. Moreover the Palladium(II) complexes have the ability to form hydrogen bonding with the constituents of cell and cell wall[43] or direct interaction with membrane, enzyme and proteins. The ligands have the capability to carry metal to the target (DNA) and allow it to interact with it. Weak coordinated ligands may be the best carrier for metal ions to the biological systems. The inactivity or decreased biological activity of some of the complexes may be related to the strongly coordinated ligands with the metal ions.[44,45] It has been observed that antibacterial activity decreases on complexation, while some ligands are biologically inactive but upon coordination showed biological activity. The complexes which exhibit significant biological activity show their potential to be used as antibacterial agents.

3.5. Petra/Osiris/Molinspiration (POM) analyses

Petra/Osiris/Molinspiration (POM) analyses were performed to investigate the potential pharmacophore sites of the synthesized compounds and reference drug (imipenem).

Modern drug discovery is based in large part on high throughput screening of small molecules against macromolec-

ular disease targets requiring that molecular screening libraries contain drug-like or lead-like compounds. We have analyzed the known standard references (SR) for drug-like properties. With this information in hand, we have established a strategy to design specific drug-like compounds.

3.5.1. Petra analysis

On the basis of the new finding, we can conclude that the synthesized compounds have the >C═S, —NH_2, >NH and —$N(CH_3)_2$ moieties which possess a potential for antibacterial/antifungal activities. For antiviral/antifungal activity, the compound possesses ($X^{\delta-}Y^{\delta+}$) pharmacophore site and also it was hypothesized that the difference in charge between X and Y of the same dipolar pharmacophoric site should facilitate the inhibition of bacteria more than viruses.[46]

3.5.2. Osiris calculations

Remarkably well behaved mutagenicity of divers synthetic molecules classified in database of Celeron Company of Swiss can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DNA. The Osiris calculations are tabulated in Table 7. Toxicity risks (mutagenicity, tumorigenicity, irritation, and reproduction) and physicochemical properties (cLog *P*, solubility, drug-likeness and drug-score) of compounds were calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. From the data evaluated in Table 7 it is observed that all the complexes are supposed to be slightly mutagenic, tumorigenic, irritant with slight reproductive effects when run through the mutagenicity assessment system in comparison with the standard/reference drugs. The reference drug (imipenem) is non-mutagenic, non-tumorigenic, non-irritant with no reproductive effect as shown in Table 7. Low hydrophilicities and low cLog *P* values may cause good absorption or permeation. It has been shown that for compounds to have a reasonable probability of good absorption, their cLog *P* value must not be greater than 5.0. On this basis, all the compounds possessed cLog *P* values are quite less than 5. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. Our estimated Solubility (*S*) value is a unit stripped logarithm (base 10) of a compound's solubility in mol/L. There are more than 80% of the drugs on the market having an (estimated) *S* value greater than −4.[47–49] In our case the *S* values for studied compounds are in the range of −1.08 and −3.13. Further, Table 7 shows drug likeness of the compounds which are almost in the comparable zone with that of standard drug used for comparison. The compounds also possess the drug-score though smaller than that of the reference drug.

3.5.3. Molinspiration calculations

cLog *P* (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (Table 8). The method is very stout and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area (TPSA) is calculated as a sum of fragment contributions. S-, N-, I and Pd centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood–brain barrier penetration. Prediction results of the studied compounds (molecular properties (TPSA and GPCR ligand)) are valued (Table 8). Lipophilicity (cLog *P* value) and polar surface area (TPSA) values are two important properties for the prediction of per oral bioavailability of drug molecules.[47–49] Therefore cLog *P* and TPSA values for compounds were calculated using molinspiration software programs and compared with the values obtained for standard drugs imipenem (for antibacterial activity). The calculated cLog *P* values for the investigated compounds are in the range of −0.13 to 0.31 which are in the acceptable range. So these compounds are expected to present good bioavailability.[47–49]

The polar surface area (TPSA) is calculated from the surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them and/or metal atom. Thus, the TPSA is closely related to the hydrogen bonding potential of a compound. Molecules with TPSA values around of 160 or more are expected to exhibit poor intestinal absorption. It is to be noted that cLog *P* and TPSA values are the two important parameters, although not sufficient criteria for predicting oral absorption of a drug. All the compounds (except $Pd(Metu)_4]I_2$ and $Pd(Tu)_4]I_2$) have one violation from the Rule of 5. Two or more violations of the Rule of 5 suggest the probability of problems in bioavailability of the standard drug.[48,49] Properties such as hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size, flexibility and presence of various pharmacophores features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. Activity of the synthesized compounds and standard drug was rigorously analyzed under four criteria of known successful drug activity in the areas of GPCR ligand activity, ion channel modulation, Kinase inhibition activity, and nuclear receptor ligand activity. Results are shown in Table 8 by means of numerical assignment. Thus, these compounds are expected to have near similar activity to the standard drug used based upon these four rigorous criteria (GPCR ligand, ion channel modulator, Kinase inhibitor and nuclear receptor ligand).[47–49]

4. Conclusion

The present study shows that the thioamide ligands coordinate with Palladium(II) iodide in the thione form in solution as well as in the solid state. All ligands behave as S-donors and are binding in a terminal mode and no bridging of groups between metal centers is found. The complexation was confirmed by the downfield shift of the N—H proton as a result of increase of π electron density in the C—N bond. In the ^{13}C NMR spectra of the complexes upfield shifts in the >C═S resonance also support the binding of ligands to Palladium(II). The shift difference of the >C═S resonance may be related to the strength of metal-sulfur bond. Some of the screened compounds have shown good antibacterial activity which has potential for their use in future as antibacterial agents.

Conflict of interest

The authors declare that they have no conflict of interest.

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