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Palladium (II) Mixed Ligand Complexes of Benzoisothiazol-3(2*H*)-Dithiocarbamate (Bit-dtc) and Tertiary Diphosphines: Synthesis, Characterization, Biological and Anticancer Studies

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Abstract

[Pd(bit-dtc)$_2$] complex was prepared by the reaction of sodium benzoisothiazol-3(*2H*)-dithiocarbamate (Nabit-dtc) with sodium tetrachloropalladate(II). Treatment of [Pd(bit-dtc)$_2$] with one mole equivalent of $Ph_2P(CH)_nPPh_2$ afforded complexes of the type [Pd(bit-dtc)$_2$($Ph_2(CH_2)_n$ PPh_2)] in good yield : n=1(dppm); n=2 (dppe), n=3 (dppp); n=4 (dppb); n=$(C_5H_4)_2Fe$ (dppf). The prepared complexes were characterized by elemental analysis, I.R., ^{1}H-{^{31}P} and ^{31}P-{^{1}H} NMR spectroscopy the dithiocarbamate ligand bonded as mono dentate with Pd ion. The NMR spectroscopic data suggested that the prepared complexes have mononuclear coordination mode with diphosphines binding as chelating ligands, except dppm which behaves as bridging ligand, afforded binuclear complex. The antimicrobial activities of the newly synthesized Pd(II) complexes were evaluated against two types of bacteria, namely *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*). Furthermore, the complexes where n= 2, 4 and 5 were screened against pancreatic adenocarcinoma (SNU-2469), human gastric-esophageal adenocarcinoma (SK-GT-5), and healthy cell(WRL68). The complex [Pd(bit-dtc)$_2$(dppe)] exhibited a significant activity against pancreatic adenocarcinoma of SNU-2469 cancer cells with IC_{50} value of 5.067 µM.

Keywords: Anticancer activity, Benzoisothiazol-3-dithiocarbamate, Mixed ligand complexes, Palladium, Phosphine.

Introduction

Metal complexes of S, N-donor ligands have been the focus of many studies, due to their interesting biological properties [1-3]. For instance, palladium complexes with dithiocarbamate, thione or thiourea moiety showed high anti-bacterial, anti-fungal and anti-cancer activity values [4-7]. In addition, these ligands have contributed to many applications. Thus, palladium dithiocarbamate complexes were used as a sulfur precursor for PdS nanoparticles [8]. These ligands have the ability to interact with heavy metals and form stable complexes due to their unique system, which allow the ligands to share their electron density on S and N atoms with the central metal [9] Fig. 1.

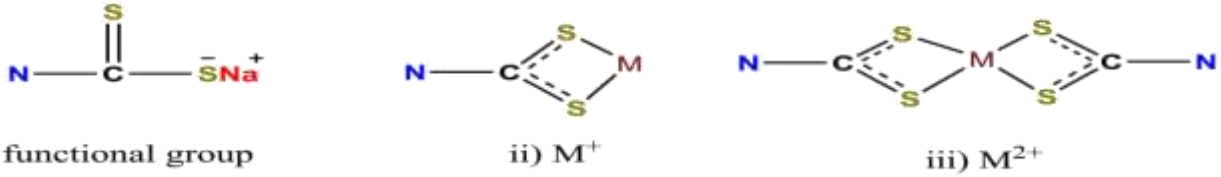

Figure 1. The dithiocarbamate group attached to heavy metal M. i) functional group, ii) M^+, iii) M^{2+}

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Tertiary diphosphine (diphos) ligands can react with divalent square planar dithiocarbamate complexes in several ways. The reaction mechanism can be summarized as follows; as the diphosphine ligand approaches the $[M(DTC)_2]$ complex, the metal-sulfur bond undergoes stepwise cleavage which result in either cationic $[M(K^2\text{-DTC})(diphos)]$ DTC or neutral complex $[M(K^1\text{-DTC})_2(diphos)]$ [10-13], Fig. 2. However, the cationic complex is believed to goes back to its stable neutral form via S_2^- nucleophilic attack on the central metal. In a previous publication, Al-jibori demonstrated the reaction of Pd-dithiocarbamate moiety with tertiary phosphine ligands [14].

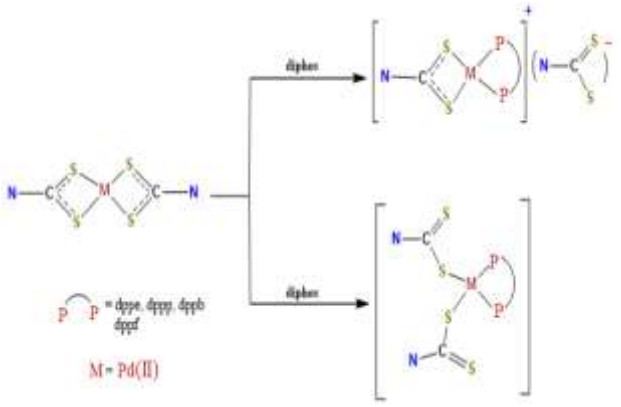

Figure 2. The reaction pathways of square planar dithiocarbamate complexes with tertiary phosphine ligands

In this study, palladium(II) mixed ligand complexes of dithiocarbamate derived from 1,2-benzisothiazol-3(*2H*)-one and diphosphine ligands were prepared. The antibacterial and anti-proliferative activities of the newly synthesized complexes were investigated.

Materials and Methods

The chemicals and solvents used in this project were purchased from commercial sources and used as they were. Melting points were measured on a Gallenkamp melting point apparatus and were uncorrected. The IR spectra (as KBr disk) were recorded on a Shimadzu FT-IR 8400 spectrophotometer in the 400-4000 cm^{-1} range. NMR spectra were recorded (DMSO-d_6) on a Bruker (400MHz) NMR spectrometer using TMS as an internal standard, sodium benzoisothiazol-3(*2H*)-dithiocarbamate (Nabit-dtc) was prepared by modified literature method [15].

Preparation of $[Pd(bit\text{-}dtc)_2]$ 1. To an aqueous solution of Na_2PdCl_4 (0.85 mmol, 0.250 g), was added an aqueous solution of Nabit-dtc (0.423 g, 1.7 mmol) resulted in the formation of red solution. The reaction mixture was stirred at room temperature for 24 hours furnished a red precipitate. The red precipitate was filtered-off, washed with cold EtOH and dried to give complex **1** (0.402 g, 85%) as a red powder, IR (KBr, cm^{-1}) 3063 υ(=C-H); 1631 υ(C=O); 1509 υ(C-N); 877 υ(C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.62 (d, 1H, Ha); 7.58 (d, 1H, Hd); 7.31 (t, 1H, Hc); 7.15 (t, 1H, Hb). Anal. Calc. $C_{16}H_8N_2O_2PdS_6$: C, 34.38; H, 1.44; N, 5.01. Found: C, 34.44, H, 1.51, N, 5.13 %.

General Procedure for Preparation of Complexes 2-4. Complex **1** (0.200 g, 0.358 mmol) was suspended in $CHCl_3$ (10 mL) followed by addition of a solution of diphosphine ligand (0.358 mmol) in $CHCl_3$ (10 mL). The suspension immediately turned into clear yellow, orange or red solution. The reaction mixture was refluxed for 1.5 hours and allowed to cool to room temperature. Evaporation of the resulting solution yielded gummy product, which was washed with diethyl ether to give the desired complex.

$[Pd(bit\text{-}dtc)_2(dppe)]$ **2**. From dppe (0.143 g, 0.358 mmol). Yield: 0.238 g (69%) as a yellow, orange or red powder, IR (KBr, cm^{-1}) 3053 υ(=C-H); 1662 υ(C=O); 1587 υ(C-N); 914 υ(C=S); 489 υ(P-C); 1099 υ(P-C); 1435 υ(P-Ph). $^{31}P\{^1H\}$- NMR (DMSO-*d6*, δ ppm): δP 31.53. ^{1}H NMR (DMSO-*d6*, $_\delta$ ppm): 6.9-8.30 (m, 28H, 5Ph); 2.76 (s, 4H, $2CH_2$). Anal. Calc. for $C_{42}H_{32}N_2P_2PdS_6$: C, 52.69; H, 3.37; N, 2.93. Found: C, 52.64; H, 3.55; N, 3.12 %

$[Pd(bit\text{-}dtc)_2(dppp)]$ **3**. From dppp (0.148 g, 0.358mmol). Yield: 221 mg (64%) as a yellow orange powder, IR (KBr, cm-1) 3055 υ(=C-H); 1665 υ(C=O); 1589 υ(C-N); 999 υ(C=S); 505 υ(P-C); 1101 υ(P-C); 1437 υ(P-Ph). $^{31}P\{^1H\}$- NMR (DMSO-*d6*, δ ppm): δP 31.14. ^{1}H NMR (DMSO-*d6*, δ ppm): 7.14-7.87 (m, 28H, 5Ph); 2.79 (m, 4H, $2CH_2$); 1.85

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(m, 2H, CH_2). Anal. Calc. for $C_{43}H_{34}N_2P_2PdS_6$: C, 53.16; H, 3.53; N, 2.88. Found: C, 53.04; H, 3.61; N, 2.91 %.

[Pd(bit-dtc)$_2$(dppb)] **4**. From dppb (0.153 g, 0.358mmol). Yield: 0.249 g (71%) as an orange red powder, IR (KBr, cm-1) 3035 υ(=C-H); 1665 υ(C=O); 1577 υ(C-N); 997 υ(C=S); 499 υ(P-C); 1101 υ(P-C); 1437 υ(P-Ph). $^{31}P\{^1H\}$- NMR (DMSO-*d6*, *δ* ppm): *δP* 31.24. ^1H NMR (DMSO-*d6*, *δ* ppm): 6.99-7.99 (m, 28H, 5Ph); 2.39 (s, 4H, $2CH_2$); 1.47 (s, 4H, $2CH_2$). Anal. Calc. for $C_{44}H_{36}N_2P_2PdS_6$: C, 53.63; H, 3.68; N, 2.84. Found: C, 53.61; H, 3.57; N, 2.89 %.

[Pd(bit-dtc)$_2$(dppf)] **5**. From dppf (0.198 g, 0.358mmol). Yield: 0.246 g (66%) as a red powder, IR (KBr, cm-1) 3053 υ(=C-H); 1579 υ(C=O); 1560 υ(C-N); 916 υ(C=S); 520 υ(P-C); 1095 υ(P-C); 1435 υ(P-Ph). $^{31}P\{^1H\}$- NMR (DMSO-*d6*, *δ* ppm): *δP* 28.38. ^1H NMR (DMSO-*d6*, *δ* ppm): 7.09-8.53 (m, 28H, 5Ph); 4.48 (s, 4H, Cp); 4.39 (s, 4H, Cp). Anal. Calc. for $C_{50}H_{36}FeN_2O_2P_2PdS_6$: C, 53.94; H, 3.26; N, 2.52. Found: C, 53.99; H, 3.31; N, 2.63 %.

[Pd(bit-dtc)$_2$(μ-dppm)]$_2$ 6. From dppm (0.138 g, 0.358mmol). Yield: 0.240 g (71%) as a red powder, IR (KBr, cm-1) 3053 υ(=C-H); 1662 υ(C=O); 1587 υ(C-N); 914 υ(C=S); 489 υ(P-C); 1099 υ(P-C); 1435 υ(P-Ph). $^{31}P\{^1H\}$- NMR (DMSO-*d6*, *δ* ppm): *δP* 25.14. ^1H NMR (DMSO-*d6*, *δ* ppm): 6.86-7.93 (m, 28H, 5Ph); 4.06 (t, 2H, CH_2). Anal. Calc. for $C_{82}H_{60}N_4O_4P_4Pd_2S_{12}$: C, 52.2; H, 3.21; N, 2.97. Found: C, 52.31; H, 3.31; N, 3.13 %.

Antimicrobial Activity Study

The synthesized complexes were evaluated for their biological activity using agar disc diffusion method, on following the Luria-Bertani Agar (LBA) medium[16]. The palladium complexes were tested against *Staphylococcus aureus* (*S. aureus*) as a Gram positive bacteria and *Escherichia coli* (*E. coli*) as a Gram negative bacteria. The obtained results were compared with Tetracycline as a standard antibiotic at 0.001 M concentration. The standard error for the experiments was ± 0.03%. The inhibition zones were determined using Luria-Bertani plates, after being incubated[17] for 24 hours at 37°C.

Results and Discussion

Synthesis and Characterization

Complex 1 was synthesized with an 85% yield through the reaction of an aqueous solution of NaBit-dtc with an equimolar aqueous solution of palladium (II) salt at room temperature, as depicted in Scheme 1 Subsequently, the obtained palladium (II) complex was further reacted with diphosphine ligands in equimolar ratios Scheme 2 to yield complexes 2-6 with yields ranging from 64% to 71%. Similarly, complex 6 was prepared in $CHCl_3$ with a yield of 71%.

The structures of ligand and the complexes 1-6 were assigned by IR, ^1H and $^{31}P\{^1H\}$- NMR spectra.

Infrared Spectra

In the IR spectrum of the Nabit-dtc ligand, no absorption band corresponding to υ(N-H) was observed in the distinctive region around 3200 cm^{-1}. The band at 1631 cm^{-1} was attributed to the stretching of the carbonyl group, while the strong absorption band at 1508 cm^{-1} indicated the presence of υ(C-N)[18]. The newly introduced CSS group exhibited an absorption at 877 cm^{-1}.In contrast, complex 1 displayed absorption bands similar to those of the bit-dtc ligand. Specifically, the absorption band at 1631 cm^{-1} was attributed to the carbonyl group, while the adjacent strong absorption was assigned to the υ(C-N) band. The υ(C=S) group was observed at 914 cm^{-1}. The addition of tertiary phosphine ligands to the palladium complexes was clearly discerned in the IR spectra, as the phosphine bands appeared in three distinctive regions of the spectrum [19-22]. The first phosphine band appeared within the range of 532-489 cm^{-1}. The second phosphine band was observed within 1103-1099 cm^{-1}, while the third phosphine band was noted within 1437-1433 cm^{-1}. A summary of all the results is provided in Table 1.

^1H and $^{31}P\{^1H\}$- NMR Spectra

In the ^1H NMR spectrum of Nabit-dtc, the amide proton (N-H) signal disappeared, while the benzene ring protons appeared as four distinct signals corresponding to the four protons of the benzene ring. The most deshielded proton manifested as a doublet at 7.84 ppm (Ha, d, 1H), while another doublet appeared at 7.68 ppm, attributed to the Hd proton (Hd, d, 1H). The remaining protons, namely

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Baghdad Science Journal

Hc and Hb, appeared as a triplet at 7.36 and 7.19 ppm, respectively. In the ^{1}H NMR spectrum of complex 1, the Ha and Hd protons were observed as two doublets adjacent to each other at 7.62 ppm and 7.58 ppm, respectively. Hc and Hb protons displayed as distinctive triplets at 7.31 ppm and 7.15 ppm, respectively.

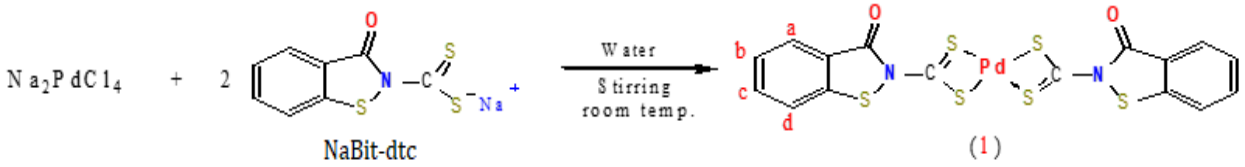
The ^{1}H-NMR spectra of Pd(II) dithiocarbamate and tertiary phosphine moieties revealed the following: complex 2 displayed the phenyl protons of both the dppe ligand and the bit-dtc ligand as a multiplet at 7.7 ppm, corresponding to 28 protons. The alkyl protons of the dppe ligand appeared as a singlet at 2.76 ppm (CH_2CH_2, s, 4H).

Complex **3** exhibited the 5 benzene protons, similar to complex 1, which appeared as a multiplet at 7.5 ppm (5Ph, m, 28H). The propyl moiety of dppp showed two signals at 2.79 and 1.85 ppm, respectively. Meanwhile, the dppb derived complex displayed the phenyl protons at 7.5 ppm (5Ph, m, 28H). Two signals appeared at 2.39 and 1.47 ppm, respectively, corresponding to the alkyl group ($4CH_2$), Fig.3.

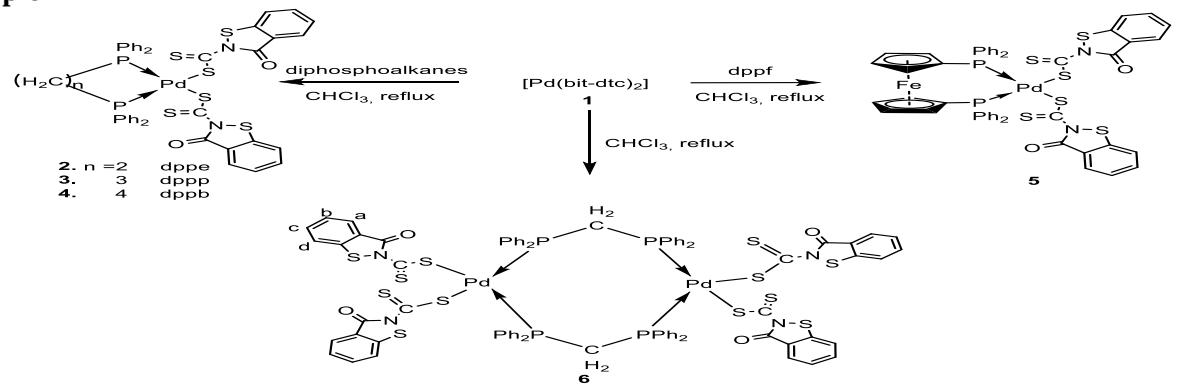
Complex **5** presented the 28 protons of the phenyl groups as a multiplet at 7.77 ppm, while the two Cps of the dppf moiety appeared as two singlets at 4.58 and 4.39 ppm, respectively, corresponding to four protons each.

Finally, complex **6** exhibited binuclear characteristics (A-Frame), evident in both the ^{1}H-NMR and ^{31}P{^{1}H}-NMR spectra [23-25]. The methylene protons appeared as a triplet at 4.06 ppm, indicating bridging behavior, as it displayed a deshielded signal. This behavior is anticipated from the dppm ligand due to the highly strained structure of its analogous mononuclear chelating compound. The protons of the 5 benzene rings appeared as expected at 7.5 ppm (5Ph, m, 28H).

The ^{31}P{^{1}H}-NMR spectra of the complexes (**2-6**) showed one signal which clearly indicates that the trans atoms to the P ligand are the same. Therefore, the final structure is a square planar complex with two (bit-dtc) ligands, S-bonded to the Pd(II) central metal. However, complex **6** showed bridging characteristic. Even though, the ^{31}P{^{1}H}-NMR spectrum of 6 showed one signal only, the positive value indicates that the ligand is attached to two Pd(II) ion in a bridging mode Fig. 4. If the dppm were to be bonded to a central metal in a chelating fashion, it would show highly negative values in the ^{31}P{^{1}H}-NMR, which could appear around -40 or -50 ppm [26].



Scheme 1. The reaction pathway for preparing palladium 1,2-benzisothiazol-3-one dithiocarbamate complex



Scheme 2. The reaction pathway for reacting [Pd(bit-dtc)$_2$] with diphosphine ligands

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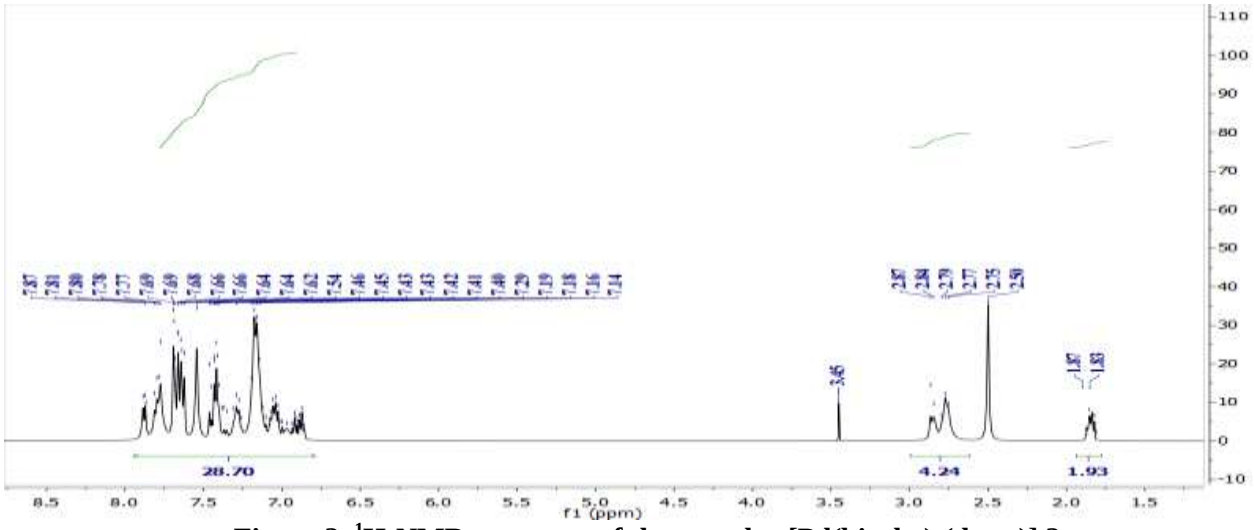

Figure 3. ^{1}H-NMR spectrum of the complex [Pd(bit-dtc)$_2$(dppp)] 3

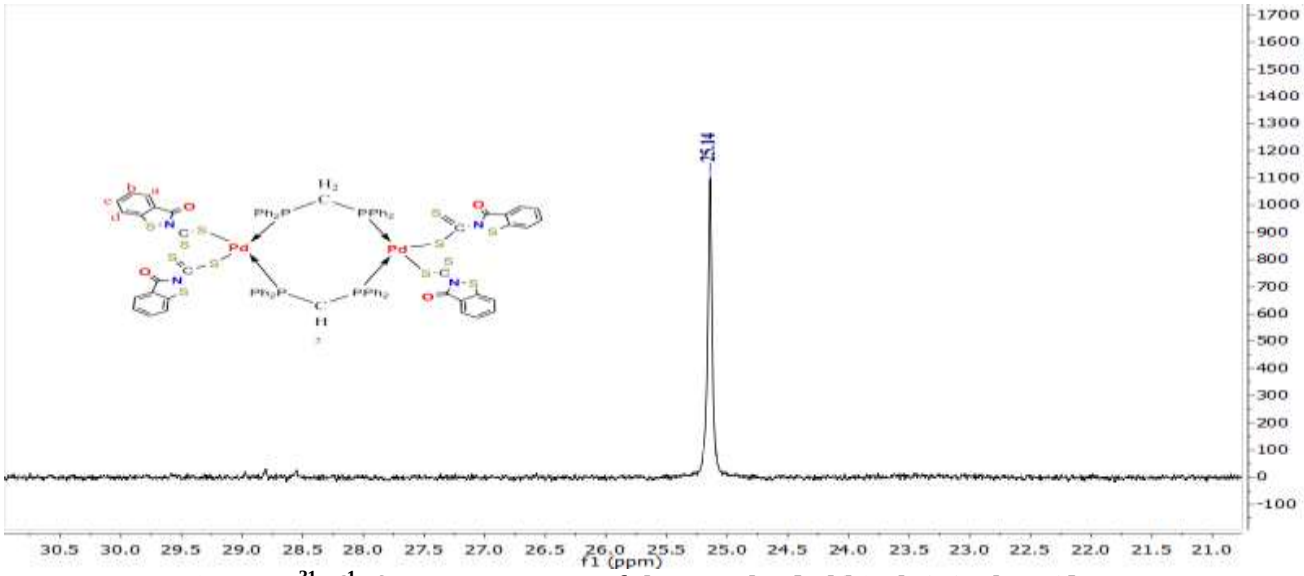

Figure 4. ^{31}P{^{1}H}-NMR spectrum of the complex [Pd(bit-dtc)$_2$(μ-dppm)]$_2$ 6

Table 1. Selected absorption bands for IR spectra of the Bit-dtcNa ligand and its complexes 1-6

Compd. No.	υ(C-H) cm^{-1} Arom.	υ(C-H) cm^{-1} aliphatic	υ(C=O) cm^{-1}	υ(C-N) cm^{-1}	υ(C=S) cm^{-1}	Phosphine bands cm^{-1}		
						υP-C	**υP-C**	**υPh-P**
NaBit-dtc	3050	-------	1639	1509	877	-----	-----	-----
1	3063	-------	1631	1585	914	-----	-----	-----
2	3053	2850-2920	1662	1587	918	489	1099	1435
3	3055	2850-2920	1665	1589	999	505	1101	1437
4	3035	2850-2960	1665	1577	997	499	1101	1437
5	3053	-------	1579	1560	916	520	1095	1435
6	3055	2908	1626	1570	995	532	1103	1433

Biological Activity

Antibacterial Activity

The newly synthesized Pd(II) complexes 1-5 were tested against two types of bacteria; *Staphylococcus aureus (S. aureus) and Escherichia coli (E. coli)*. and the results are presented in Table 2.

The antibacterial activities of these complexes demonstrated moderate biological properties against

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both targeted bacteria. The inhibition diameter zone for Staphylococcus aureus ranged from 12 to 20 mm, while for Escherichia coli, it ranged from 16 to 22 mm. Notably, complexes 1 and 5 exhibited greater activity against both selected bacteria than the other complexes. These results are consistent with findings from previously reported papers on dithiocarbamate complexes [19, 27, 28].

Table 2. Dimeter inhibition zone (mm) of the tested complexes against *S. aureus* and *E. Coli* bacteria

Complexes No.	Conc. (M)	Diameter inhibition zone (mm)	
		S. aureus	*E. coli*
1	10^{-3}	20	22
2	10^{-3}	17	18
3	10^{-3}	12	16
4	10^{-3}	14	19
5	10^{-3}	20	18
Tetracycline	10^{-3}	29	26

Anticancer Activity

Complexes **2**, **4**, and **5** were subjected to *in vitro* evaluation for their anticancer activity against pancreatic adenocarcinoma (SNU-2469), cervical carcinoma (SK-GT-5) and human gastric-esophageal adenocarcinoma (SK-GT-5) by using MTT assay [25,28, 29]. The results are summarized in Table 3.

Notably, among the tested complexes, [Pd(bit-dtc)$_2$(dppe)] 2 exhibited significant activity against the pancreatic adenocarcinoma cell lines of SNU-2469 with an IC_{50} value of 5.067 µM.

The enhanced anticancer activity of complex 2 may be attributed to the favorable fitting of its five-membered ring (dppe) within the amino acid pocket of SNU-2469, leading to greater stability compared to the other two complexes, 4 and 5, which contain the seven-membered ring (dppb) and ferrocene ligand, respectively.

Table 3. Anticancer activities of different Pd(II) complexes against three cancer cells in vitro

Complex No.	IC_{50} (µM)		
	SNU-2469	SK-GT-5	WRL-68
2	5.067	30.42	30.96
4	26.17	37.14	101.6
5	23.11	62.50	62.50

Conclusion

A new series of Pd(II) mixed ligand complexes derived from Benzoisothiazol-3(*2H*)-dithiocarbamate and tertiary diphisphine ligands have been synthesized and characterized by elemental analysis, IR and NMR spectroscopy. The IR spectra were effectively used to determine the formation of CSS group as well as showing the distinctive phosphine bands. In NMR, more specifically, $^{31}P\{^{1}H\}$- NMR techniques the complexes showed that diphosphine ligands attach as chelating mode except for dppm which showed as bridging ligand. The biological evaluation of the synthesized complexes **1-6** showed moderate activities against various cancer cells except complex **2** which exhibited significant activity against pancreatic adenocarcinoma. Complex **2** is considered as a new lead for treatment of pancreatic cancer.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration's approval.
- No animal studies are present in the manuscript.
- No potentially identified images or data are present in the manuscript.

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- Ethical Clearance: The project was approved by the local ethical committee at University of Sulaimani.

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معقدات البلاديوم الثنائي لليكاندات المختلطة بنزوايزوثيازول -3 (*2H*) ثنائي ثايوكرباميت و الفوسفينات الثالثية : تحضيرها وتشخيصها و دراسة فعاليتها الحيوية والمضادة للسرطان

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الخلاصة

تم تحضيرالمعقد [$Pd(bit\text{-}dtc)_2$] من تفاعل بنزوايزوثيازول -3 (*2H*)ثنائي ثايوكربامات الصوديوم (Nabit-dtc) مع ملح الصوديوم رابع كلوريد البلاديوم (II) .وبمعاملة معقد [$Pd(bit\text{-}dtc)_2$] مع ثنائي الفوسفينات $Ph_2P(CH)_nPPh_2$ بنسب مولية متساوية ادت للحصول على معقدات بنسب جيدة من نوع[$Pd(bit\text{-}dtc)_2(Ph_2(CH_2)_nPPh_2)$] حيث ان n تمثل؛

n=$(C_5H_4)_2Fe$ (dppf). n=4 (dppb); n=3 (dppp); n=2 (dppe); n=1(dppm)

وقد تم تشخيص المعقدات المحضرة باستخدام التحليل الدقيق للعناصروالتحليل الطيفي للأشعة تحت الحمراء علاوة على ذلك نتائج تحليل للطيف الرنين المغناطيسي للبروتون ^{1}H- NMR و$^{31}P\{^1H\}$-NMR حيث اتضح بان ليكند الثايوكاربامات يسلك سلوك احادي السن مع ايون البلاديوم. ومن خلال نتائج طيف الرنين المغناطيسي تم اقترح معقدات الليكندات المختلطة لها صيغ تناسقية أحادي النواة يسلك فيها ثنائي فوسفين كلكيند كيلتي (ثنائي المخلب) ماعدا اللكيند dppm حيث يسلك كليكند جسري وتكوين معقدات ثنائي النواة .

تم تقييم الأنشطة المضادة للميكروبات لمعقدات البلاديوم الثنائية المحضرة حديثا ضد نوعين من البكتيريا، وهما *ستافيلوكوكوس اوريس* (*S. aureus*) و*أشريشيا كولاي*(*E. coli*) . وتم فحص المعقدات 2 و 4 و 5 ضد سرطان البنكرياس (SNU-2469) وسرطان المعدة والمريء البشري (SK-GT-5) وخلايا البشرية الصحية (WRL68), أظهر المركب **2** [$Pd(bit\text{-}dtc)_2$] نشاطًا ملحوظا ضد سرطان البنكرياس الغدي للخلايا السرطانية SNU-2469 بقيمة IC_{50}حيث تبلغ 5.067 مايكرومولر.

الكلمات المفتاحية: الفعالية ضد السرطان، بنزوايزثايزول3-ثايوكابامات، معقدات للكيندات المختلطة، البلاديوم، الفوسفين.