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C-H Functionalization and Antibacterial Activity of Heteroleptic Palladium Complexes Bearing Dithiocarbamates Moiety

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The catalytic and antibacterial activity of heteroleptic palladium (Pd) complexes bearing dithiocarbamates (DTC) moiety is described. Various spectroscopic techniques, including multinuclear nuclear magnetic resonance (NMR), Fourier Transform–Infrared (FT-IR), elemental analysis, and thermogravimetric analysis (TGA), were employed to characterize both DTC salt and heteroleptic Pd complexes. An excellent catalytic performance was observed in the C-H functionalization of benzo[*h*]quinoline to 10-methoxy benzo[*h*]quinoline in the presence of a sacrificial oxidant. The heteroleptic Pd complex provided an almost quantitative yield of product (89%) under a milder condition (50°C, 3 mol% Pd loading) and shorter reaction times (2 hrs). The antibacterial activity of DTC salt and heteroleptic Pd complexes was investigated against six bacterial strains: 4 Gram-negative [*Escherichia coli, Salmonella thyphimurium, Klebsiella aerogenes, and Klebsiella pneumoniae*] and 2 Gram-positive [*Bacillus subtilis, and Bacillus cereus*]. Herein, we highlight that the heteroleptic Pd complex exhibited more significant inhibition activity than the DTC ligand against Gram-negative bacteria as compared to Gram-positive bacteria. Further analysis showed that both tested compounds possessed moderate bacteriostatic (MIC) effects against all tested strains. The heteroleptic Pd complex's bactericidal (MBC) potency was more significant than the ligand's.

Keywords: Antimicrobial activity; catalysis; dithiocarbamates; palladium complexes

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Since the discovery of the dithiocarbamates (DTC) compound, it has received substantial interest and found application in areas including lubricants, accelerators, and biological applications [1]. DTCs are generally synthesized by the reaction of carbon disulphide with a secondary amine in the presence of a base to yield ammonium or alkali salt. Further reaction with a metal salt through simple metathesis produces corresponding metal DTC complexes [2]. Malatesta and co-workers reported the first bis(dithiocarbamate) [$Pd(S_2CNR_2)_2$] complex, and many other complexes have been studied to date [3-5]. The utilization of Pd(II) complexes bearing S, S chelating DTC moiety in catalysis is still uncommon, probably due to concerns about catalyst poisoning [6]. Despite this, Pd(II) complexes containing bidentate sulphur ligands have been reported as excellent catalysts in C-H functionalization. This is demonstrated by good conversion of product in the methoxylation of benzo[*h*]quinoline employing palladium imidazolium-2-dithiocarboxylate complexes [7]. Furthermore, the investigation was extended to a series of monometallic and bimetallic Pd catalysts supported by DTC ligands, which showed a high catalytic activity in the alkoxylation of benzo[*h*]quinoline and methoxylation of 8-methyl quinoline [8]. The reported Pd complex's catalytic performance competed favourably with the commercially available $Pd(OAc)_2$ previously reported for a similar reaction employing a high-temperature setup [9].

The prolonged misuse of antibiotics has led to the persistent rise and swift dissemination of antibiotic-resistant bacterial species, posing a significant global threat to human health. Therefore, developing a new strategy using metal complexes to combat antibiotic-resistant bacterial species is crucial. Palladium (II) complexes have been investigated for several applications in medicinal chemistry, including their potential as antibacterial agents [10, 11]. Several studies have reported moderate to good antibacterial activity of Pd(II) complexes-bearing DTC complexes against various bacterial strains, including Gram-positive and Gram-negative bacteria [12-14]. Keeping in mind all these points, Pd(II) complexes hold promise as potential antibacterial agents, and more studies in this

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field may lead to the development of cutting-edge antimicrobial treatments to combat bacterial infections. Therefore, we reported synthesizing and characterizing a novel DTC ligand and heteroleptic Pd(II) complexes in this contribution. The antibacterial activity was evaluated using Gram-positive and Gram-negative bacteria. The catalytic activity was assessed towards methoxylation of benzo[*h*]quinoline by varying catalyst loading against reaction time.

EXPERIMENTAL

Chemicals and Measurement

All chemicals and solvents were purchased from commercial sources with analytical grade and used without further purification unless stated otherwise. The infrared (IR) spectra were collected on Nicolet 6700 spectrometer (Thermo Fisher Scientific) fitted with attenuated total reflectance (ATR) sampling equipment. Spectral was collected on 32 scan averages in the range of 4000 cm^{-1} to 600 cm^{-1} with a spectral resolution of 4 cm^{-1}. ^{1}H, $^{31}P\{^{1}H\}$ and $^{13}C\{^{1}H\}$ NMR spectra analysis of DTC salt and heteroleptic Pd complexes was recorded on 400 MHz spectrometers using Varian Bruker AV400 at room temperature. The product yield for C-H functionalization was determined using Varian Bruker AV300 spectrometers at 25°C in deuterated $CDCl_3$. The samples's carbon, hydrogen, nitrogen, and sulfur content were analyzed using a Model 2400 Perkin-Elmer Series II CHNS/O analyzer. TGA analysis of heteroleptic Pd complex was conducted in an inert environment between 30°C and 750°C at a scan rate of 10°C/min with a Mettler Toledo TGA/DSC 1LF/UMX instrument.

Synthesis of Dithiocarbamates Salt $\{(EtO)_3SiCH_2CH_2CH_2\}_2NCS_2K$ (1)

Bis-(3-triethoxysilylpropyl)amine (500 mg, 1.175 mmol) and K_2CO_3 (649 mg, 4.698 mmol) were dissolved in acetonitrile (20 mL) and stirred for 30 minutes. Carbon disulfide (0.085 mL, 6.20 mmol) was added to the solution, and stirring continued for 2 hours. The solution was filtered to remove excess salt, and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (10 mL) and filtered through diatomaceous earth (Celite). The solvent was removed to give a yellow oily product [4]. Yield: 584 mg (90%). IR (ATR): 2972, 2885, 1462 (νC-N), 1250 (νC=S), 1163, 1070, 955 (νC-S), 758 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.59 (t, 4H, CH_2, J_{HH} = 7.6 Hz), 1.20 (triplet, 18H, OCH_3, J_{HH} = 6.8 Hz), 1.82 (m, 4H, CH_2), 3.79 (m, 12H, OCH_2, J_{HH} = 6.8 Hz), 3.93 (m, 4H, CH_2) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): δ 6.8 (s, CH_2), 18.3 (s, OCH_2), 20.0 (s, CH_2), 50.5 (s, OCH_3), 56.0 (s, CH_2), 58.4 (s, OCH_3), 210.9 (s, CS_2) ppm.

Synthesis of $[\{(EtO)_3SiCH_2CH_2CH_2\}_2NCS_2Pd(PPh_3)_2]PF_6$ (2)

DTC ligand (**1**) (45 mg, 0.17 mmol) was treated with ammonium hexafluorophosphate (23 mg, 0.29 mmol) in methanol (10 mL). A chloroform solution (10 mL) of *cis*-$[PdCl_2(PPh_3)_2]$ (50 mg, 0.14 mmol) was added to the reaction mixture and refluxed at 80 °C overnight. The reaction mixture was filtered through Celite, and the solvent was removed by a rotary evaporator. The collected residue was dissolved in a minimum amount of chloroform and filtered through Celite. All the solvent was removed by reduced pressure. Diethyl ether (20 mL) was added and triturated in a sonic water bath to give a pale yellow solid. The product was filtered and washed with diethyl ether (10 mL) [4]. Yield: 76 mg (65%). IR (ATR cm^{-1}): 3052, 1514, 1480 (νC-N), 1433, 1311, 1267 (νC=S), 1168, 1094, 1052, 996 (νC-S), 887, 744 and 689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.50 (m, 4H, CH_2), 1.17 (triplet, 18H, OCH_3), 1.65 (m, 4H, CH_2), 3.54 (m, 12H, OCH_2), 3.76 (m, 4H, CH_2), 7.31-7.44 (m, 30H, PPh_3) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz): δ 15.3 (s, CH_2), 18.4 (s, OCH_2), 20.9 (s, CH_2), 51.7 (s, OCH_3), 58.6 (s, CH_2), 65.9 (s, OCH_3), 129.0 (t, *o/m*-PC_6H_5), 131.8 (s, p-PC_6H_5), 134.1 (t, *ipso*-PC_6H_5, obscured), 201.9 (s, CS_2) ppm. $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2): δ 30.4 (s, PPh_3) ppm. Elem. Anal. Calcd. for $C_{55}H_{72}F_6NO_6P_3PdS_2Si_2$ (Mw = 1276.81): C, 51.7; H, 5.7; N, 1.1; Found: C, 51.3; H, 5.9; N, 1.0.

General Catalysis Procedure

The catalysis general setup followed the method from previous literature [15]. Benzo[*h*]quinoline (50.0 mg, 0.28 mmol), iodobenzene diacetate (180.4 mg, 0.56 mmol), and compound **2** (1.0 - 3.0 mol %) were dissolved in methanol solution (2.5 mL) using the individual reaction bottles. The reaction flask was sealed and transferred into a Radleys Carousel 12 Place Reaction Station at 50 °C for a designated time frame (2, 4, and 6 hours). The solvent was then removed under reduced pressure, followed by the dissolution of a yellow crude oil residue in the $CDCl_3$ for ^{1}H NMR analysis. The product yield was calculated by comparing the peak of 10-methoxybenzo[*h*] quinoline at 9.15 ppm to the integration of the H_2 or H_{10} protons of benzo[*h*]quinoline at 9.30 ppm and 9.05 ppm, respectively. ^{1}H NMR: δ = 9.15 (dd, 1H, J = 4.0 Hz, 2.0 Hz), 8.16 (dd, 1H, J = 8.0 Hz, 2.0 Hz), 7.80 (d, 1H, J = 8.5 Hz), 7.67 (d, 1H, J= 8.5 Hz), 7.64 (t, 1H, J = 8.0 Hz), 7.56 (dd, 1H, J = 8.0 Hz, 1.0 Hz), 7.50 (dd, 1H, J = 8.0 Hz, 2.0 Hz), 7.26 (dd, 1H, J = 8.0 Hz, 1.0 Hz), 4.19 (s,3H).

Antibacterial Studies

The biological activity of compounds **1** and **2** was examined against six bacterial strains; 4 Gram-

negative [*Escherichia coli* (ATCC25922), *Salmonella thyphimurium* (ATCC14028), *Klebsiella aerogenes* (ATCC13048), and *Klebsiella pneumoniae* (ATCC 700603)] and 2 Gram-positive [*Bacillus cereus* (ATCC11778), and *Bacillus subtilis* (ATCC13124)]. The bacterial strain was obtained from the Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), Shah Alam, and cultured onto a nutrient agar media plate at 37°C.

Following our published procedure, the anti-bacterial activity of **1** and **2** were determined using the disk diffusion method on Muller-Hinton Agar (MHA) medium [15]. Each bacterium inoculum was cultured in MHA broth for 18 to 20 hours at 37°C. The density of each bacteria inoculum required for the test was adjusted to 0.5 McFarland standard (1.0 x 10^8 CFU/ml) measured using the Turbidometer (Oxoid, UK). A bacteria culture was used to lawn MHA plates evenly using a sterile cotton swab, followed by the sterile Whatmann filter papers (6 mm) placement to mimic conventional antibiotic disc. Zone of microbial growth inhibition at various concentrations of **1** (40, 60, 80, and 100 mg/ml) and **2** (10, 20, 30, and 40 mg/ml) in dichloromethane (DCM) were evaluated by injecting the solution (20 µL) into sterile Whatmann filter papers. Sterilized distilled water (or DCM) was used as a negative control. Gentamicin (10µg) was placed at the center of the petri dish as a positive control reference. All the plates were incubated at 37°C overnight. The diameter of the clear zone around the tested disc was measured in mm as a reflection of antibacterial activity. The experiment was performed in triplicate per condition.

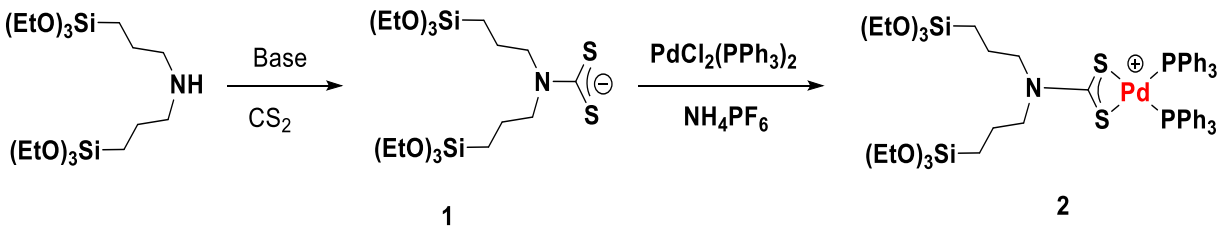
The minimum inhibitory concentration (MIC) was determined using Muller-Hinton broth (MHB) macrodilution assays. The colonies of each strain were prepared and adjusted to McFarland standards. Before each experiment, aliquots of adjusted inoculum (1 mL) were transferred to 8 sterilized glass tubes. Compounds **1** and **2** were dissolved in DCM (1 mL) and were added to the first tube. Serial two-fold dilutions of **1** ranging from 200 to 1.56 mg/mL and **2** ranging from 140 to 1.09 mg/ml were used to determine the MIC. Two additional test tubes containing only inoculated MHB (negative control) and a combination of MHB and bacteria (positive control) were prepared. All tubes were then incubated overnight at 37°C. The MIC endpoint was chosen as the lowest concentration of compounds **1** and **2**, where no visible growth of bacteria is seen in the test tubes. The visual turbidity of the tubes was noted, both before and after incubation, to confirm the MIC value. The minimum bactericidal concentration (MBC) of compounds **1** and **2** were determined by taking an aliquot from all the test tubes, which showed no visible bacterial growth, and were subcultured onto the MHA plate and incubated overnight at 37°C. No evidence of bacterial growth following incubation was confirmed as MBC values.

All the biological statistical tests were performed using GraphPad Prism, version 8. Experimental data of the zone of inhibition are expressed as means ± standard error of the means (SEM). The results show the mean of three tested cultures plus SEM. Data were further analyzed with a two-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparison post-test. In all tests, p-values <0.05 and asterisks indicate statistically significant differences.

RESULTS AND DISCUSSION

Synthesis and Characterization of DTC Ligands and Heteroleptic Pd Complexes

An efficient route to synthesizing DTC salt and heteroleptic Pd complexes bearing DTC moiety was summarized in Scheme 1. Triethoxysilyl-DTC ligand (**1**) was prepared by treating *Bis*-(3-triethoxysilylpropyl) amine with CS_2 in the presence of a base in acetonitrile solution. The reaction mixture was stirred magnetically for 2 hours at ambient temperature to yield a sticky yellow oil of **1**. The solid-state infrared spectrum of **1** exhibits characteristic bands at 1462 cm^{-1}, assigned to *ν*(C-N) stretching vibrations [16]. A single double bond trait presence at 1250 cm^{-1} is comparable with the range (1250 -1350 cm^{-1}) for the *ν*(C=S) previously reported [17]. The presence of only one band (*ν*(C-S), 955 cm^{-1}) in the region of 1060-940 cm^{-1} suggested a symmetric bonding of DTC ligand, acting in a bidentate chelating mode, was obtained [18].



1 2

Scheme 1. Synthesis of DTC ligands (**1**) and palladium DTC complexes (**2**).

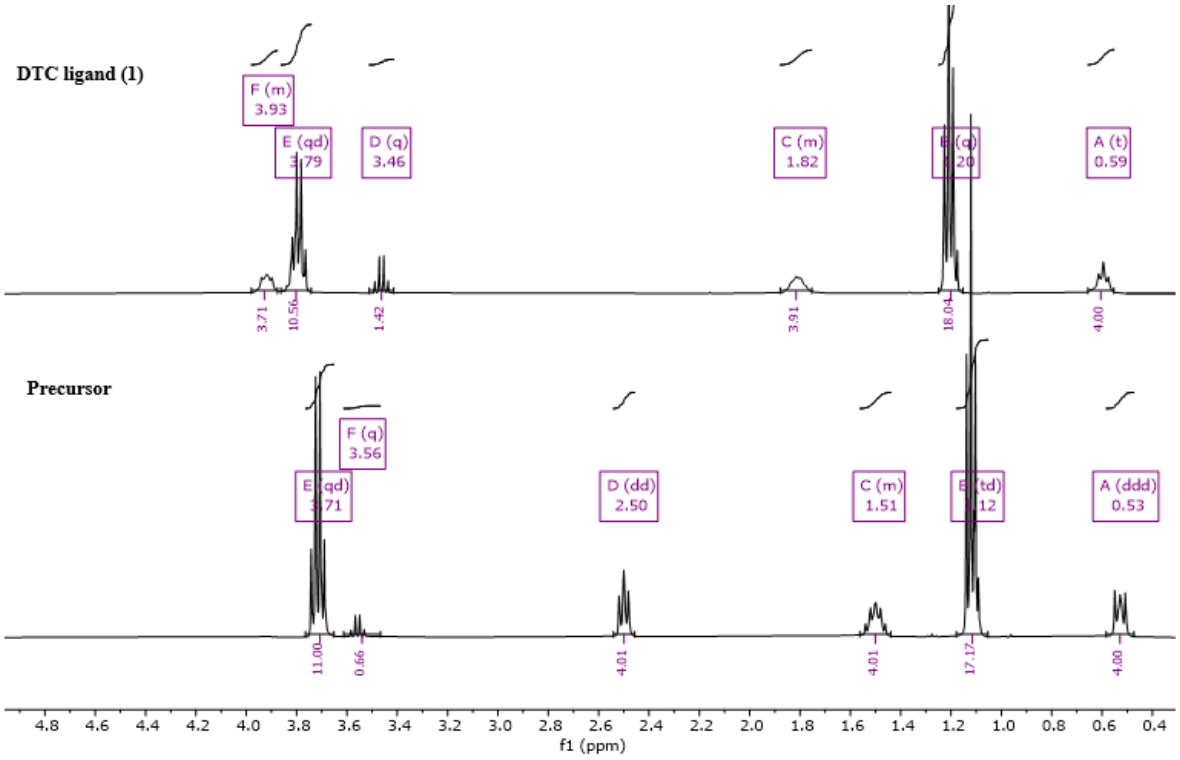


Figure 1. ^{1}H NMR spectrum comparison between precursor and DTC ligand (**1**).

The disappearance of the diagnostic resonances of the secondary amine protons for precursor at 2.50 ppm in ^{1}H NMR spectrum (Figure 1) further confirms the formation of **1**. The retention of the propyl chain belonging to DTC moiety was indicated by a downfield shift of chemical resonances at 0.59, 1.82, and 3.93 ppm, as compared to the same features in the precursor (0.53, 1.51 and 3.71 ppm). Furthermore, the triplet and multiplet resonances at 1.20 and 3.79 ppm confirmed the presence of the triethoxy (O-CH_2CH_3) -group. The chemical resonance of the CS_2 unit was observed at 211 ppm in $^{13}C\{^{1}H\}$ NMR spectrum that can be ascribed to the bidentate nature of DTC salts [19].

A pale yellow product of heteroleptic Pd complex (**2**) was synthesized by reacting *cis*-[$PdCl_2(PPh_3)_2$] with **1** in the presence of NH_4PF_6 while stirring magnetically and under reflux conditions in a mixture of methanol and chloroform solution. The solid-state infrared data of *ν*(C-N) vibration shifted to a higher frequency in **2** (1480 cm^{-1}), presumably due to an increase in C-N double bond character related to the chelating effect of nitrogen lone pair of DTC ligand toward palladium ion upon coordination. Similarly, a single absorption band (νC-S) was shifted from 955 cm^{-1} to 996 cm^{-1} upon coordination, indicating a symmetrical bidentate binding mode of DTC ligands to the palladium center [20]. In addition, the bands associated with hexafluorophosphate anions (887 cm^{-1}) were observed.

^{1}H NMR analysis of **2** showed an upfield shift in their resonances due to back donation from the palladium center to the DTC ligand. For instance, the retention of propyl chains resonating at new chemical shifts (0.50, 1.65, and 3.54 ppm) compared to the precursor (0.59, 1.82, and 3.93 ppm) alongside multiplet resonances (1.17 ppm and 3.76 ppm) of triethoxy group. The protons due to the phenyl ring of triphenylphosphine appeared at 7.30-7.45 ppm. An essential CS_2 peak in ^{13}C NMR spectra resonated slightly upfield (202 ppm) compared to the precursor (211 ppm) associated with the accumulation of electron density after complexation [21]. ^{31}P NMR frequency of **2** shifted considerably downfield from 23.3 ppm (precursor: *cis*-[$PdCl_2(PPh_3)_2$]) to 30.4 ppm after the coordination of the phosphine ligand to a metal moiety (Figure 2). This phenomenon might relate to the electronic density flow from the phosphorus atom to the palladium center after the formulation of the complex [19]. A singlet resonance recorded confirmed chemically equivalent phosphorus atoms, indicating symmetrical structures of **2**. The retention of hexafluorophosphate anions (PF_6^-) was proven by a septet signal from -136 ppm to -153 ppm in the ^{31}P NMR spectrum. Elemental analysis of the pale yellow product (C, 51.3; H, 5.9; N, 1.0) was satisfactory with theoretical values (C, 51.7; H, 5.7; N, 1.1) predicted, further confirming the formulation of **2**.

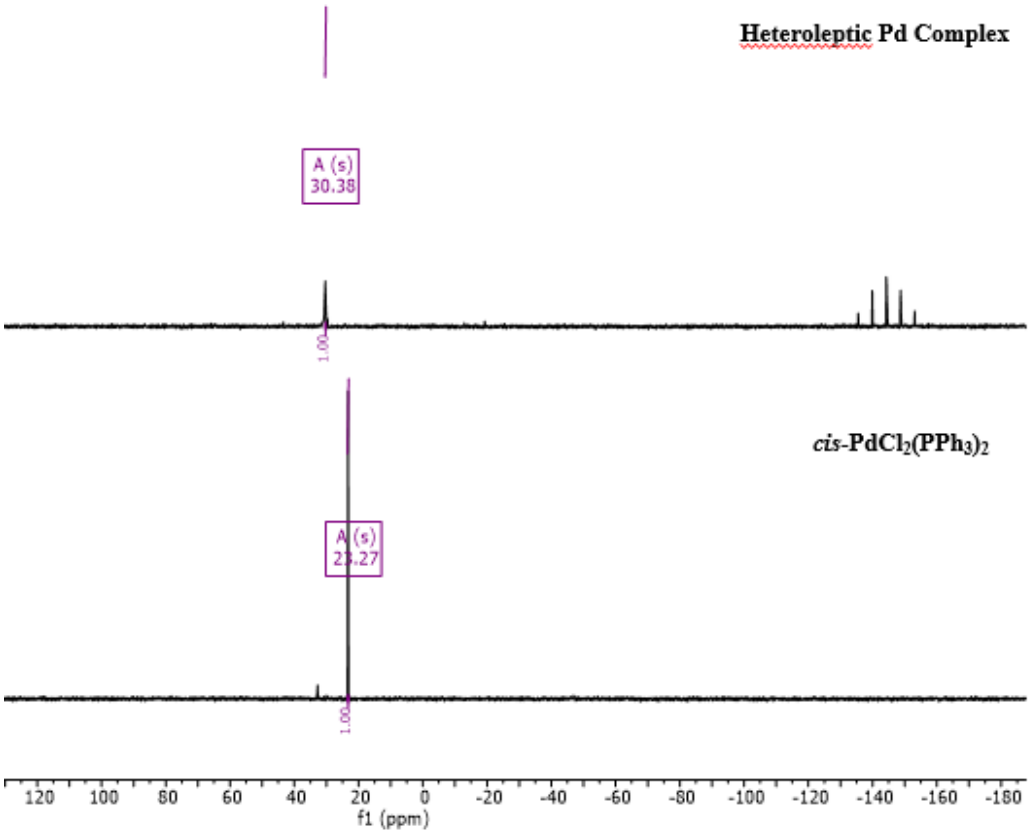


Figure 2. ^{31}P NMR spectrum comparison between cis-$PdCl_2(PPh_3)_2$ with heteroleptic Pd complex (**2**).

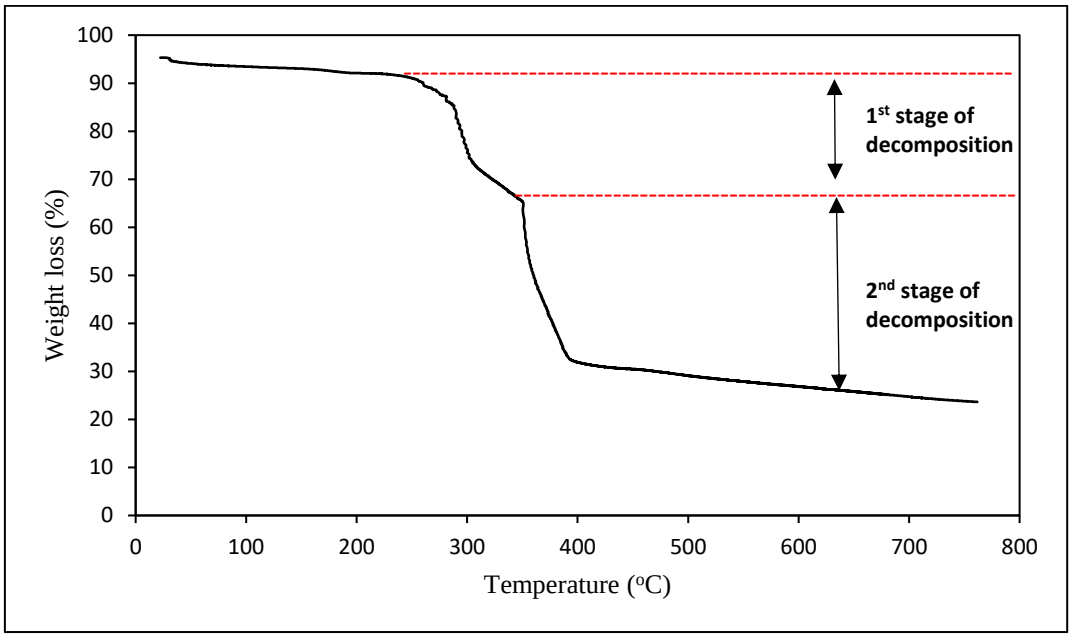


Figure 3. TGA isotherm of **2**.

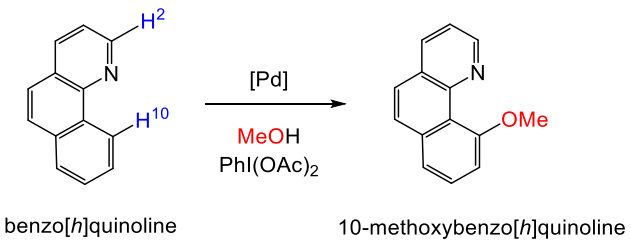
The thermal stability of **2** was investigated from 30 °C to 750 °C using a heating rate of 10 °C per minute using TGA. The TGA isotherm (Figure 3) revealed a steady mass decline within 30 °C to 250 °C. It was followed by a rapid mass decline from 250 °C to 350 °C, indicating a first stage of decomposition with a total of 36% weight loss. The mass continued to drop from 351 °C to 400 °C with 23% weight loss (second stage of decomposition). Approximately 30% of metallic palladium remained after heating. The

TGA analysis confirmed compound **2** is stable unless the catalysis setup required a heating procedure of more than 250 °C.

Methoxylation of Benzo[*h*]quinoline

To access the catalytic performances of **2**, the C-H functionalization of benzo[*h*]quinoline to 10-methoxy-benzo[*h*]quinoline was employed as a model reaction (Scheme 2). The substrate was chosen because of the presence of a single bond [C-H(10)] for directed C-H functionalization, and a mild condition was required for cyclopalladation to occur. The possible mechanism of the reaction involves the formation of a cyclopalladated intermediate, followed by the oxidation of Pd(II) to Pd(IV), finished by reductive elimination to afford a product [22].

Complex **2** was tested as a homogeneous catalyst by mixing substrate (benzo[*h*]quinoline), sacrificial oxidant ((diacetoxy)iodobenzene), and solvent (methanol) inside the reaction flask. The reaction flask was sealed and placed in a Radleys Carousel 12 Place Reaction Station. Initial studies were carried out with **2** as a catalyst at 50 °C and a loading of 1 mol% in a similar manner advised by the literature, giving yields of only 27% after 2 hours (Figure 4). However, increasing the reaction time to 6 hours resulted in approximately twice the yield (63%) when Pd loading is fixed at 1 mol%. It was decided to investigate the effects of increasing the catalyst loading even if a further improvement could be anticipated over longer reaction times. Product yield improves from 51% to 97% in 2 to 6 hours with a 2 mol% loading. This finding implies that a milder approach (50 °C) inhibits the dissociation of the triphenylphosphine ligand to generate an active catalytic intermediate, resulting in a decreased product yield [6]. However, a quantitative product yield (90%) was obtained with 3 mol% catalyst loading after 2 hours and was chosen as the optimum for the reaction.



Scheme 2. Model reaction of methoxylation of benzo[*h*]quinoline.

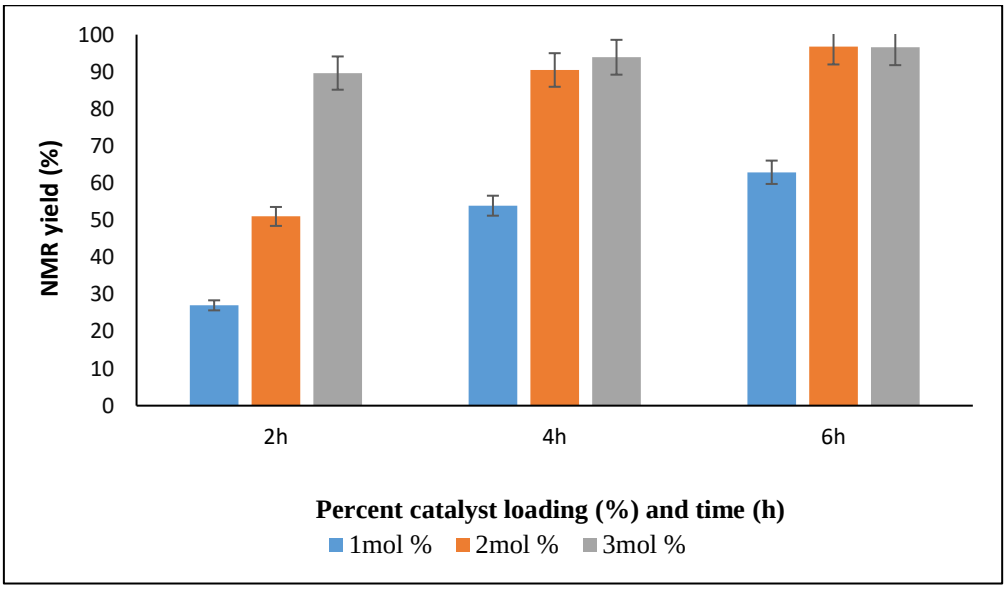


Figure 4. Comparison of catalyst loading results for methoxylation of benzo[*h*]quinoline. Pd loading = 1-3 mol%, time = 2,4 and 6 hours and T = 50 °C.

Antibacterial Activity

Metal complexation has an enormous impact on biological activity. Complexation increases the antibacterial potency compared to a neat ligand, providing new opportunities for combating antibiotic resistance [23]. Pd(II) complex-bearing DTC ligands have been associated with elevated biological activity [24]. Therefore, the present study investigated the antibacterial activity of **1** and **2** against six bacterial strains. In general, all bacteria tested were inhibited by both compounds **1** and **2**. By utilizing DTC salts (**1)** as an antibacterial agent, *E. coli*, *S. typhimurium*, and *K. aerogenes* cultures showed a moderate increase of inhibitory zone from the lowest to the highest concentrations (40 to 100 mg/mL) in comparison to *K. pneumoniae, B. subtilis*, and *B. cereus* which recorded no discernible difference (Figure 5).

Klebsiella sp. showed a greater inhibition zone amongst all of the other bacterial strains against heteroleptic Pd-DTC complex (**2**). However, the inhibition zone was not significantly different; *E. coli* exhibited a slightly lower inhibition zone than those *Klebsiella* sp. While *S. typhimurium* and *B.subtilis* exhibited comparable inhibition zones against increasing concentration, *B. cereus* displayed no inhibition. The slightly reduced antibacterial activity of both compounds against *B.subtilis and B. cereus* can be attributed to the thick cell wall (20-80 nm) of Gram-positive bacteria [25], which resists the antimicrobial effect of the compounds. Gentamicin inhibited the growth of all tested bacterial strains, with a zone of inhibition of 20 - 25 mm, whereas the solvent (dichloromethane) showed no zone of inhibition against the tested organisms. This implies that the antibacterial activity seen in screenings **1** and **2** was due to the DTC ligands and heteroleptic palladium complexes, respectively, rather than the DCM employed to prepare various compound concentrations.

In conclusion, the Pd complex's average inhibition zone was slightly more significant than that of the DTC ligand against the tested species of Gram-positive and Gram-negative bacteria. The biological effects of the Pd complex incorporating the DTC moiety add to the evidence that metal complexes are effective antibacterial agents. These findings align with previous literature reports which demonstrated palladium(II) complexes bearing picolyl amine dithiocarbamate [26], pyrrolidinedithiocarbamate, N,N-diethyldithiocarbamate [27], and N,N-bis(3,3-dimethyl-allyl)-dithiocarbamate [28] were found to induce susceptible activity against Gram-positive and Gram-negative bacteria.

Determination of MIC and MBC

Both compounds that showed susceptible activity were further evaluated for their minimum inhibitory concentration (MIC) values. The MIC for **1** was 50 mg/mL against *Bacillus* species and *K. aerogenes*, 25 mg/mL against *S. typhimurium* and *K. pneumoniae*, and 6.25 mg/mL against *E. coli* (Table 1). Comparatively to Pd complexes (**2**), *K. pneumoniae* and *K. aerogenes* inhibited bacterial growth at 8.75 mg/mL. The MIC values for the remaining tested strains were at 17.5 mg/mL, respectively (Table 2).

In terms of antibacterial activity, the heteroleptic Pd-DTC complex surpassed the DTC ligand, which already has a low inhibitory influence. The explanation is ascribed to chelation theory, which states that when metal complexation occurs, polarity decreases, resulting in an increase in the lipophilicity of the metal complexes, allowing them to easily pass through the bacteria cell membrane [29]. Another plausible explanation of metal complexes' exacerbated antibacterial activity as compared to their respective ligands is correlated to ion neutralizing the complexes, nuclearity of the metal center in the complexes, and chelate effects [30].

Table 1. The MIC of **1** against selected bacterial strains.

Bacteria	Concentrations of **1** (mg/ml)								
	200	100	50	25	12.5	6.25	3.12	1.56	Control
E. coli	-	-	-	-	-	-	+	+	+
S. thypimurium	-	-	-	-	+	+	+	+	+
K. pneumoniae	-	-	-	-	+	+	+	+	+
K. aerogenes	-	-	-	+	+	+	+	+	+
B. subtilis	-	-	-	+	+	+	+	+	+
B. cereus	-	-	-	+	+	+	+	+	+

Note: (+) = bacterial growth, (-) = no bacterial growth

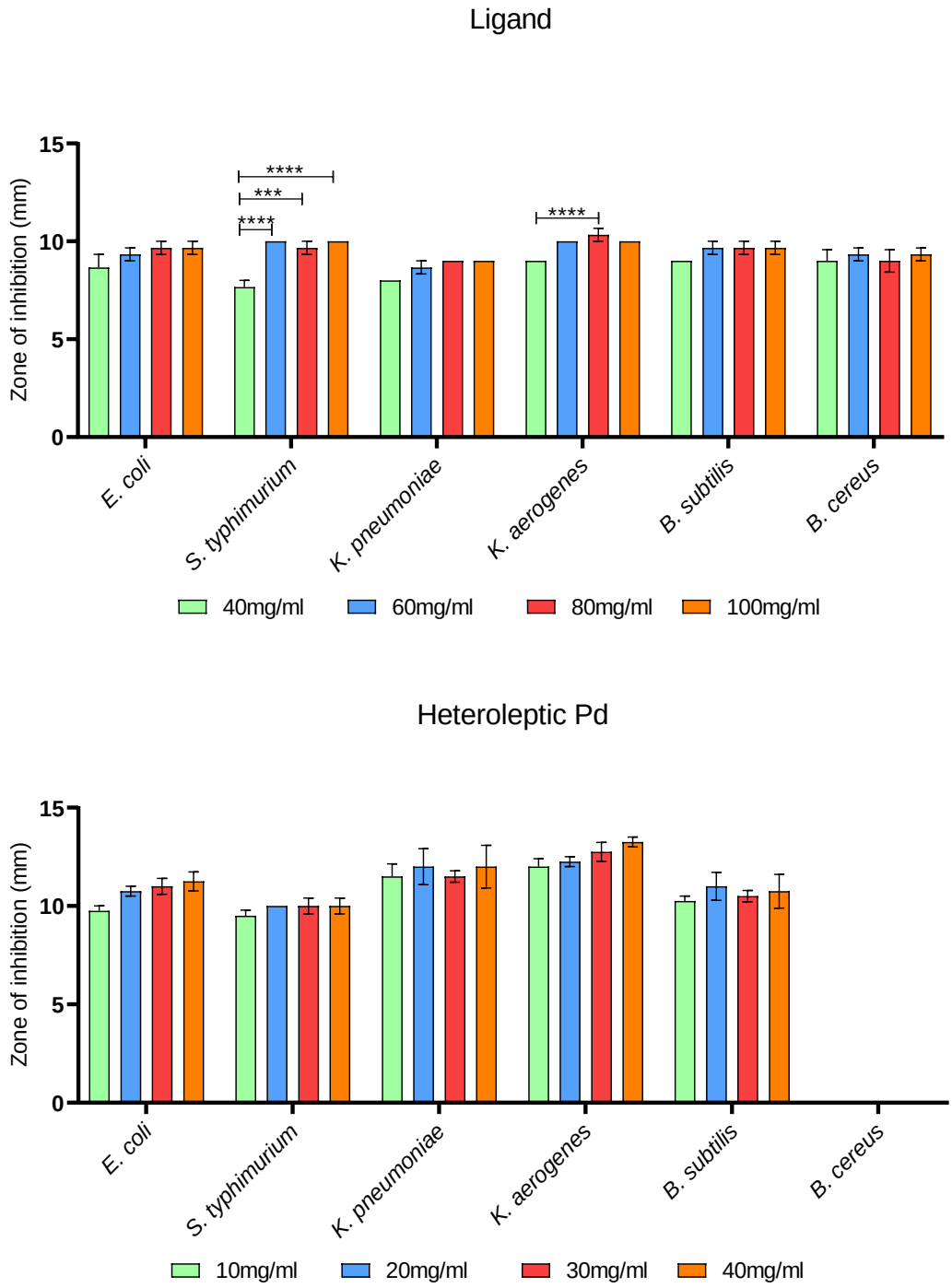


Figure 5. The inhibition zones of the DTC ligand (**1**) and heteroleptic Pd complex (**2**) against selected bacterial strains. The levels displayed are the mean of three tested cultures ± SEM. The asterisks indicate statistically significant differences analyzed with two-way ANOVA followed by Tukey's multiple comparison post-test

The macrodilution assay revealed various MBC values of compounds **1** and **2** against all the tested bacteria species. In general, both of these compounds are capable of inhibiting bacterial growth (Table 3, Figure 6). Except for *K. aerogenes*, both **1** and **2** efficiently killed the bacteria at 50 mg/ml and 8.75mg/ml, respectively. *S. typhimurium*, *K. pneumoniae*, *B. subtilis*, and *B. cereus* displayed only inhibition of bacteria with high MBC values of 140 mg/mL against compound **2**. To summarize the bacterial eradication, the heteroleptic Pd-DTC complex consistently outperformed the DTC ligand.

Table 2. The MIC of **2** against selected bacterial strains.

Bacteria	Concentrations of **2** (mg/ml)								
	140	70	35	17.5	8.75	4.37	2.18	1.09	Control
E. coli	-	-	-	-	+	+	+	+	+
S. thypimurium	-	-	-	-	+	+	+	+	+
K. pneumoniae	-	-	-	-	-	+	+	+	+
K. aerogenes	-	-	-	-	-	+	+	+	+
B. cereus	-	-	-	-	+	+	+	+	+
B. subtilis	-	-	-	-	+	+	+	+	+

Notes: (+) = bacterial growth, (-) = no bacterial growth

Table 3. Summarized MBC values of **1** and **2**.

Bacteria	Minimum bactericidal concentration (mg/ml)	
	1	**2**
E. coli	+	+
S. thypimurium	+	140
K. pneumoniae	+	140
K. aerogenes	50	8.75
B. subtilis	+	140
B. cereus	+	140

Note: + = Bacteria growth

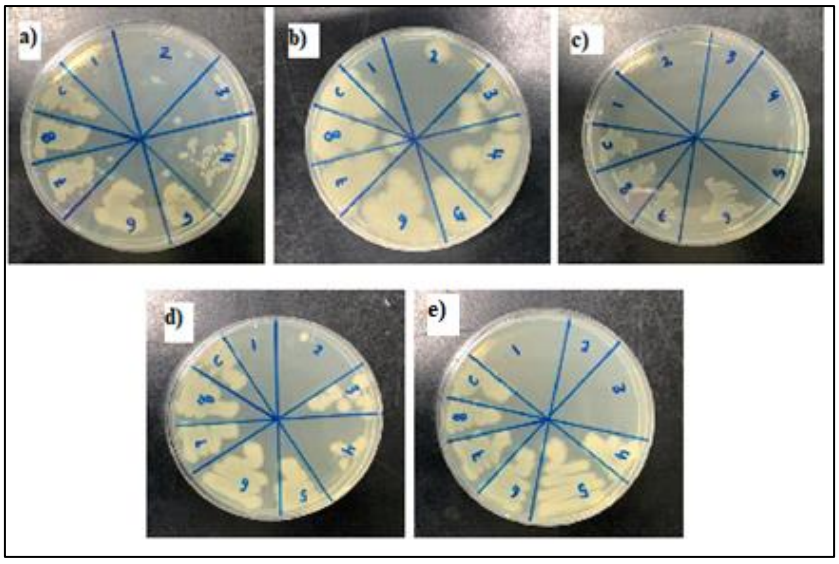


Figure 6. MBC plates of successful bactericidal effect complex **2** against bacteria a) *Klebsiella pneumoniae*, b) *Salmonella typhimurium*, c) *Klebsiella aerogenes*, d) *Bacillus cereus*, and e) *Bacillus subtilis.*

CONCLUSION

A novel DTC ligand and heteroleptic Pd-DTC complexes were synthesized. A combination of characterization results, including ^{1}H, $^{31}P\{^{1}H\}$ and $^{13}C\{^{1}H\}$ NMR, FT-IR, and elemental analysis, suggested the coordination of the DTC ligand with Pd precursor in a square-planar geometry through the sulfur bidentate to formulate the heteroleptic Pd-DTC complex. These complexes demonstrated high catalytic activity in the C-H functionalization of benzo[*h*] quinoline to 10-methoxybenzo[*h*]quinoline using 3 mol% of Pd loading at lower temperatures. DTC ligand and heteroleptic Pd-DTC complexes exhibited antibacterial activity towards Gram-positive and Gram-negative bacteria species. This preliminary finding could pave the way for developing antibacterial agents based on dithiocarbamate-metal complexes against various bacterial pathogens.

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