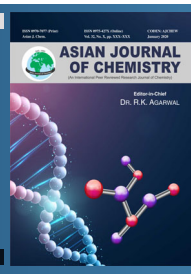
Asian Journal of Chemistry; Vol. 32, No. 8 (2020), 2091-2098

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.21870



Synthesis, Characterization and Bioactivity Study of Bidentate NS Schiff Base of *S*-Benzyl Dithiocarbazate and its Zn(II) and Pd(II) Complexes

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Received: 27 January 2019; *Accepted*: 30 June 2020; *Published online*: 27 July 2020; AJC-19996

The bis-chelated four coordinate complexes (ML_2, L = deprotonated ligand) of Zn(II) and Pd(II) ions were synthesized, derived from a new bidentate NS Schiff base called *S*-benzyl-β-N-(4-hydroxy-3-nitrophenyl)methylene dithiocarbazate (HL) which is the condensation product of *S*-benzyl dithiocarbazate (SBDTC) with 4-hydroxy-3-nitrobenzaldehyde. The synthesized ligand and complexes were characterized using conventional techniques like NMR, UV-visible, IR, mass spectroscopic techniques, magnetic susceptibility measurement and molar conductance. A single crystal X-ray crystallography data approved the proposed crystal structure of the ligand. Both in solid and solution phase, the ligand continues to exist in its thione tautomeric form. The chelates were formed by the reaction of ligand with the metal ions through the ligand azomethine nitrogen atom and the deprotonated thiolate sulfur anion. Magnetic susceptibility and electronic spectroscopic data suggested to have a tetrahedral geometry for ZnL_2 complex whereas a square planar structure for PdL_2 complex. The analgesic and anti-inflammatory bioactivity were assayed on both the ligand and its complexes by tail flick and carrageenan induced paw edema test. The ligand at the dose of 10 mg/kg, produced a significant (***$p < 0.001$) increase in pain threshold in tail flick methods when compared to control but in case of complexes, it showed moderate activity. At the same dose, the ligand and complexes significantly (***$p < 0.001$) reduced paw edema when compared to the control. Altogether, these results suggest that ligand and its complexes could be used as a potent anti-inflammatory agent.

Keywords: Schiff base, *S*-Benzyl Dithiocarbazate, Metal(II) complexes, Analgesic activity, Anti-inflammatory activity.

INTRODUCTION

S-Benzyl dithiocarbazate (SBDTC) Schiff bases comprise an essential part of nitrogen-sulfur donor ligands [1,2] occupied four potential donor atoms which coordinated with metal ions to create the chelate form approved by their structural formula. Exactly, transition reactions were completed through the main group of the metal with hard nitrogen and soft sulfur atoms facilitated of these ligands [3,4]. Principlally, both NS and SS complexes remain practicable [5]. After all, dithiocarbazic acid and its esters usually forming of five-membered chelate rings [3-6]. Typically, the bioactivity nature of Schiff bases depend on their stereochemistry, hydrogen bonding, substituents present on either side of the N_2S_2 chromophore [7,8] while for complexes, the bioactivity depends largely on its geometry, number of chelate rings, molecular packing, π-electron delocalization and lipophilicity [9,10].

Metal complexes of SBDTC Schiff bases have been reported to exhibit significant antibacterial [11-18], antifungal [17] and cytotoxic activities [17,18]. The mechanism of anticancer activity of SBDTC Schiff base and its metal complex has also been reported [19]. Natural plants have been investigated as potential source of anti-inflammatory and analgesic drugs [20]. Organometalic compounds sometimes behave as anti-inflammatory agents. Wide-ranging research supported that Au, Cu and Zn metal complexes used as anti-inflammatory drugs which have similar or higher efficacy with smaller side effects than the root organic drugs commonly in use. A recent study reported that bidentate NS Schiff base of SBDTC with 3-hydroxyacetophenone and its copper(II) and nickel(II) complexes showed signi-

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ficant analgesic and anti-inflammatory activities [21]. In continuation of our work, the coordination chemistry of a Schiff base synthesized from *S*-benzyl dithiocarbazate (SBDTC) and 4-hydroxy-3-nitro benzaldehyde with Zn(II) and Pd(II) ions is discussed and tested of their anti-inflammatory and analgesic activities.

EXPERIMENTAL

The solvents and chemicals used for the condensation reaction to form the Schiff base and metal complexes were of reagent grade. All of these solvent and chemicals were used without any further purification. Among these chemicals, metal salts and standard drugs *viz*. 4-hydroxy-3-nitrobenzaldehyde, palladium(II) nitrate hydrate, indomethacin were procured from Sigma-Aldrich (USA) and benzyl chloride was purchased from Sisco Research Laboratories (SRL) Pvt. Ltd, India.

Characterizations: IR spectra (4000-400 cm^{-1}) and UV-visible absorptions were scanned from Department of Chemistry, Rajshahi University of Engineering & Technology, Rajshahi, Bangladesh using IR Affinity 1S spectrometer, (Shimadzu, Japan) as KBr pellet and on a T60 UV-visible spectrophotometer (PG Instruments, UK) between 200-1100 nm in 10^{-5} M solution of DMSO using Win5 software. ^{1}H NMR (0-14 ppm, 500 MHz) and mass spectra were obtained from Venture Business Laboratory, Department of Environmental Applied Chemistry, University of Toyama, Japan on a JNM-A500 spectrometer in $CDCl_3$ and DMSO-d_6 (for complexes) using TMS as internal standard (for ^{1}H NMR spectra) and on a JEOL-JMS-700V mass spectrometer (scan range, mass-to-charge (*m/z*) ratio 0-850) (for mass spectra), respectively. Molar conductance and magnetic susceptibility measure-ments were also conducted at Department of Chemistry, Rajshahi University of Engineering & Technology (RUET) using molar conductance measurements with a heavy-duty conductivity/temperature meter (Extech Instruments, USA, model No. 407303) and on a magnetic susceptibility balance (Sherwood Scientific, UK).

X-ray crystal structure: Molecular structure of Schiff base (HL) was determined by single crystal X-ray crystallography on a Rigaku R-AXIS RAPID diffractometer from Water Quality Management Center, University of Toyama, Japan by using filtered Cu-Kα radiation (λ = 1.54187 Å). X-ray quality single crystals were grown at room temperature in to a mixture of chloroform and petroleum ether (2:1; v/v). Preliminary examination and intensity analysis for the proposed structure reported was taken at 173(1) K. The structure analysis was performed by direct process [22] and progressive Fourier techniques by the full-matrix least-squares techniques based on F^2 with all approved mirrors [23]. Hydrogen atoms were geometrically situated and refined using the riding model. The calculations were completed using the Crystal Structure package [24] without refinement for which SHELXL-97 was implemented [23].

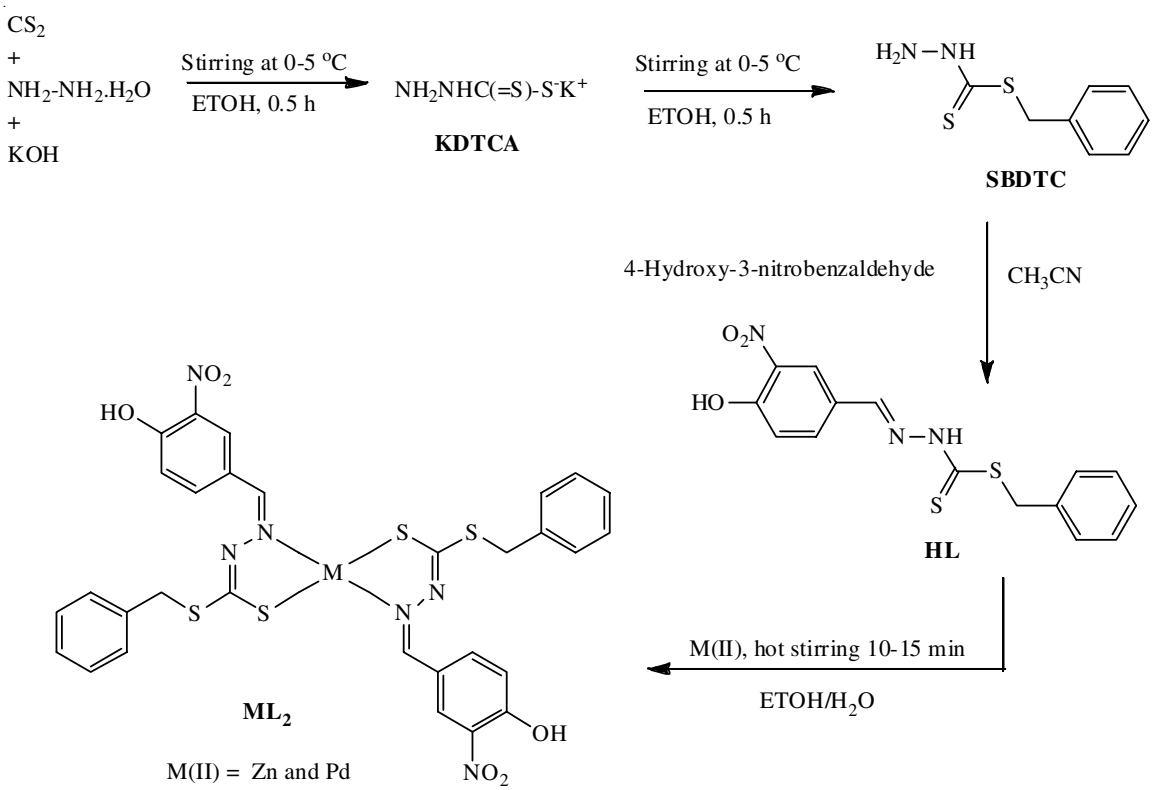
Animal ethics: In this research, synthesized compounds were applied to the test adult *Swiss albino* mice in moral acceptation theory and justified under animal rights and utilitarianism. The mice were collected from the animal resource branch of the International Centre for Diarrhea Disease Research, Bangladesh (ICDDRB). Experimental mice were accommodated in polypropylene cages containing clean wood chips as bedding materials. Maximum six mice/cage were maintained with controlled conditions (12:12 h light-dark with temperature 25 ± 2 ºC) along with utmost hygiene. The animal ethics were maintained under the conditions of Institute of Biological Sciences (IBSc), University of Rajshahi, Bangladesh, approved ethical clearance (license no: 225/320-IAMEBBC/IBSc).

Analgesic activity: Tail-flick method completed the analgesic activity using by Swiss albino mice (25-35g). Random sampling method was implemented to collect their sex [25,26]. When it was the comparison diclofenac sodium at a dose level of 10 mg/kg was applied orally as indicator. The test samples were applied orally at a dose level of 10 mg/kg body wt. It was recorded at 0, 30, 60 and 90 min after the implement and cut off time was 10 s.

Anti-inflammatory activity: The carrageenan induced paw edema test facilitated to measure the anti-inflammatory activity [27]. Only Group II received indomethacin (10 mg/kg, p.o.). After 1 h, 0.1 mL, 1% w/v carrageenan suspension in normal saline was injected into the subplantar tissue of the right hind paw. The paw volume was measured at 1, 2 and 3 h after carrageenan injection using the plethysmograph (Model: PLYAN; Buxco Electronics, Inc., USA).

Synthesis of *S*-benzyl-β-*N*-(4-hydroxy-3-nitrophenyl)-methylenedithiocarbazate (HL) (1): Schiff base was synthesized according to literature method [28]. Briefly, 4-hydroxy-3-nitrobenzaldehyde (1.67 g, 10 mmol) in acetonitrile (20 mL) was added in hot SBDTC (1.98 g, 10 mmol) in acetonitrile (40 mL) and refluxed for about 0.5 h. The resulting solution was cooled to room temperature (20-25 ºC). The orange-yellow solid which formed was separated, washed with ethanol and dried in vacuum over anhydrous $CaCl_2$. Yield: 2.96g (81%), m.p. 171-172 ºC. The synthesized compound was recrystallized from a mixture of chloroform and petroleum ether (2:1; v/v) as large orange pyramid shaped single crystals after 4 days of dissolution and slow evaporation at room temperature. IR (KBr, ν_{max}, cm^{-1}): 3273 (O-H), 3124 (N-H), 3082 (C-H, ring), 2985 (C-H, CH_2), 1622 (C=N), 1518 (C=C, ring), 1419 (C-H, CH_2, bend), 1485, 1305 (NO_2), 1236 (O-H, phenol), 1357 (O-H, in plane bending), 1035 (C=S), 972 (N-N), 943 (CSS). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.17 (s, 2H, H_2O), 4.56 (s, 2H, SCH_2), 7.19-7.44 (m, 5H, SCH_2Ph), 7.80 (s, 1H, H_{14}), 8.07 (dd, 1H, J_1 = 2.5 Hz, J_2 = 2.0 Hz, H(15), 8.29 (d, 1H, J = 2.0 Hz, H(11), 10.20 (s, 1H, OH), 10.80 (bs, 1H, NH), 7.42 (s, 1H, CH=N). UV-vis [DMSO, 10^{-5} M, nm (log ε)] λ_{max}: 248 (4.39), 282 (3.89), 348 (4.89). LRMS for $C_{15}H_{13}N_3O_3S_2$ (EI^+, 70 eV, %) *m/z*: 349 ($[M+2]^+$, 6.09), 247 ($M-C_3H_2NO_3$, 13.90), 231 ($M-C_4H_7NO_3$, 36.32), 215 ($M-C_4H_9N_2O_3$, 10.31), 132 ($M-C_4H_{13}N_3S_2$, 10.76); HRMS (EI^+) for $C_{15}H_{13}N_3O_3S_2$ calcd.: (M^+): 347.0398, found (M^+): 347.0395.

Synthesis of ML_2 (M = Zn(II) and Pd(II)) complexes: A mixture of Schiff base (0.174 g, 0.5 mmol) in ethanol (30 mL) and appropriate amount of corresponding metal salt (0.25 mmol) in ethanol (15 mL) was refluxed for 0.25 h. The precipitate formed was collected by filtration and washed with hot ethanol (10 mL) and chloroform (10 mL) and dried in vacuum (**Scheme-I**).



Scheme-I: Synthesis of Schiff base (**1**) and its metal complexes (**2**-**3**)

***bis*[Benzyl-*N*′-(4-hydroxy-3-nitrophenyl)methylene hydrazine carbodithioato-κ²-*N*′,*S*]zinc(II) (ZnL_2) (2):** Yield: 0.257 g (56 %), yellow powder, m.p. 143-146 ºC. IR (KBr, ν_{max}, cm^{-1}): 3257 (O-H), 3063, 3030 (C-H, ring), 2979, 2837 (C-H, CH_2), 1622 (C=C, ring), 1595 (C=N), 1436 (C-H, CH_2, bend), 1323 (NO_2), 1171 (O-H, phenol), 1045 (N-N), 966 (CSS), 546, 494 (M-N), 420 (M-S). ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm: 4.47 (s, 4H, SCH_2), 6.98-7.41 (m, 10H, SCH_2Ph), 7.92-7.99 (m, 6H, phenyl), 9.22 (s, 2H, OH), 8.20 (s, 2H, CH=N). UV-vis [DMSO, 10^{-5} M, nm (log ε)] λ_{max}: 259 (4.02), 358 (4.38), 455 (3.80). LRMS for $C_{30}H_{24}N_6O_6S_4Zn$ (FAB^+, 70 eV, %) *m/z*: 756 ($[M+2]^+$, 0.21), 540 (M-$C_8N_3O_3S$, 2.33), 307 (M-$C_{18}H_{15}N_3O_3S_2Zn$, 24.22), 289 (M-$C_{18}H_{17}N_3O_4S_2Zn$, 13.45), 154 (M-$C_{24}H_{20}N_5O_6S_2Zn$, 100). Λ (DMSO, 10^{-5} M, ohm^{-1} cm^2 mol^{-1}): 11.3 ; μ_{eff} = diamagnetic.

***bis*[Benzyl-*N*′-(4-hydroxy-3-nitrophenyl)methylene hydrazine carbodithioato-κ²-*N*′,*S*]palladium(II) (PdL_2) (3)**: Yield: 0.353 g (75%), brown powder, m.p. 256-257 ºC. IR (KBr, ν_{max}, cm^{-1}): 3302 (O-H), 1622 (C=C, ring), 1583 (C=N), 1419 (C-H, CH_2, bend), 1321 (NO_2), 1263 (O-H, phenol), 1001 (N-N), 964 (C=S), 509 (M-N), 418 (M-S). ^{1}H NMR (500 MHz, DMSO-d_6), δ ppm: 4.50 (s, 4H, SCH_2), 7.17-7.42 (m, 10H, SCH_2Ph), 8.11, 8.18 (s, 2H, H_{14}), 7.81, 7.79 (dd, 2H, J_1 = 2.0 Hz, H_{15}), 8.11 (d, 1H, J = 2.0 Hz, H_{11}), 9.22 (s, 2H, OH), 8.20 (s, 2H, CH=N). UV-vis [DMSO, 10^{-5} M, nm (log ε)] λ_{max}: 261 (4.23), 341 (4.27), 452 (3.51). LRMS for $C_{30}H_{24}N_6O_6S_4Pd$ (FAB^+, 70 eV, %) *m/z*: 799 (M^+, 0.12), 612 (M-$C_{12}H_{12}S$, 0.48), 460 (M-$C_{12}H_{12}N_2OSPd$, 2.26), 307 (M-$C_{15}H_{17}N_2O_2S_2Pd$, 25.56), 289 (M-$C_{15}H_{19}N_2O_3S_4Pd$, 13.90), 154 (M-$C_{22}H_{24}N_3O_5S_4Pd$, 100). Λ (DMSO, 10^{-5} M, ohm^{-1} cm^2 mol^{-1}): 12.7; μ_{eff} = diamagnetic.

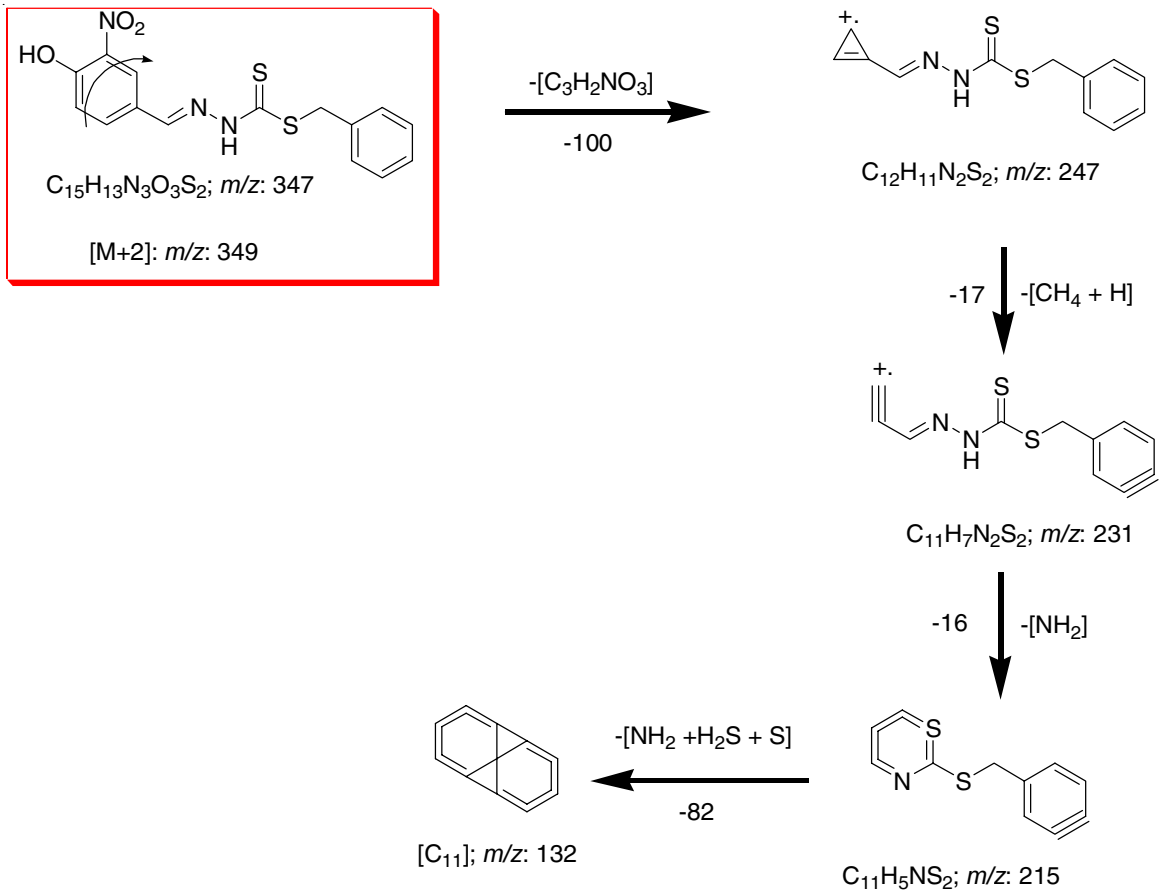
RESULTS AND DISCUSSION

Schiff base ligand HL was synthesized by condensation reaction of *S*-benzyl dithiocarbazate with 4-hydroxy-3-nitro benzaldehyde in acetonitrile under reflux, which on further reaction with respective divalent metal salts in 2:1 molar ratio, yielded their consisted metal chelates (ML_2). All spectroscopic analysis data support their proposed structures. The ligand was more or less soluble in most common organic solvents, whereas its complexes were only fairly soluble in DMSO. The result of molar conductivity of the complexes in solution referred their non-electrolytic nature.

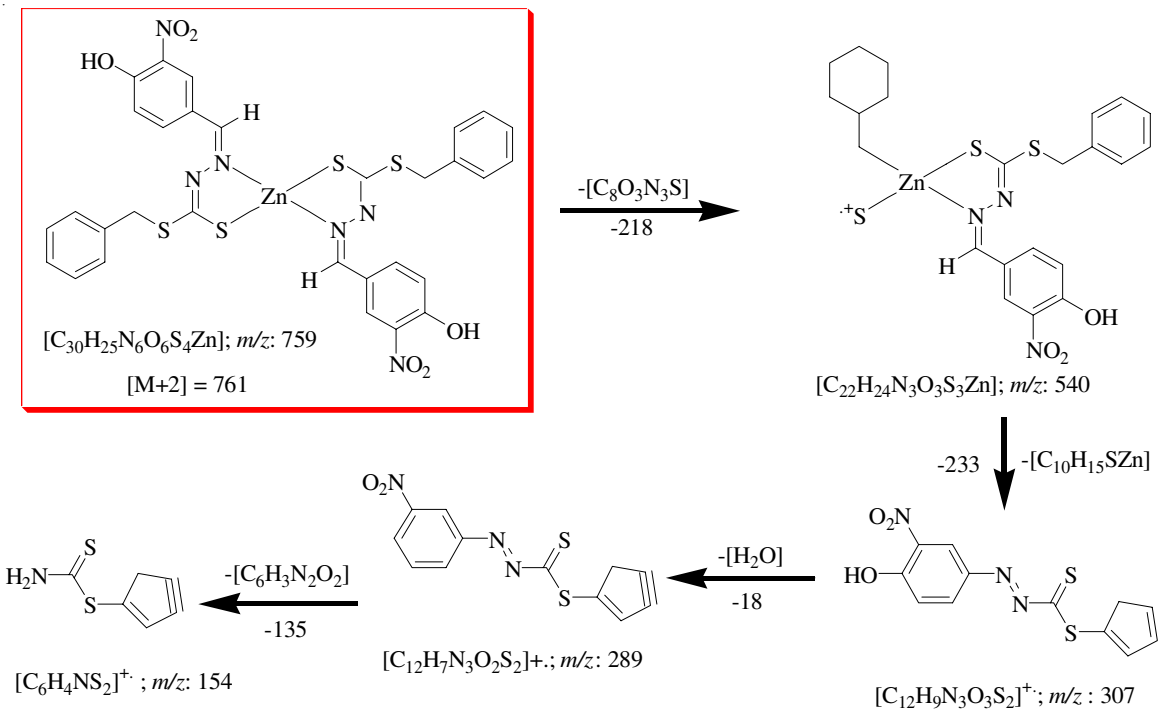
Characterization: The IR spectrum of free ligand as KBr pellet exhibited a weak and broad absorption at 3273 cm^{-1} for the phenolic ν(O-H) band as described by Joseph *et al*. [29]. This band was observed in significantly lower wave number that exhibited no significant change in the corresponding complexes [21], suggesting its non-involvement during complexation. The ligand exhibited another weak and sharp band at 3124 cm^{-1} and a medium to strong absorption at 1035 cm^{-1} assigned to the N-H and C=S stretching, respectively, which were not present in the complexes [21]. These indicated the coordination of ligand through the deprotonated thiolate sulfur anion [21]. The shifting of C=N stretching in the free ligand from 1620 cm^{-1} to lower frequency (1595-1583 cm^{-1}) in the complexes also indicated its coordination through azomethine nitrogen atom [21]. In addition, the ligand and its Zn(II) & Pd(II) complexes contained a strong band at 1323-1305 cm^{-1}, tentatively assigned to the symmetric stretching of the NO_2 group vibration [30]. In contrast, the asymmetric NO_2 group stretching mode might

have overlapped with the azomethine C=N vibration [30]. The ^{1}H NMR spectrum, of HL in $CDCl_3$ contained a broad singlet at 10.80 ppm for the imide (NH) proton that disappeared in its complexes, suggesting its thione tautomeric form in solution and coordinated with the metal ions *via* the deprotonation of the thiol form [31-34]. Additionally, a singlet at δ 7.42 ppm observed in the free ligand tentatively assigned to the azomethine (CH=N) proton, deshielded (*ca*. 0.6 ppm) in its respective complexes, also suggested its coordination through the β-nitrogen atom [31-34]. In contrast, a singlet at δ 4.56 ppm for SCH_2 protons of *S*-benzyl moiety of HL showed no significant change in its complexes [21]. The electronic spectrum of Schiff base showed a medium band at 248 nm as well as an intense broad band at 348 nm corresponding to the π→π* and n→π* transitions of phenyl ring and dithiocarbazate moiety, respectively that resulted in red shift in the complexes [21,31,32,34]. However, the ligand contained a shoulder band at 282 nm, assignable to the π→π* (azomethine) transition [35]. Additionally, the complexes showed a medium intensity absorption band in the visible region between 445-455 nm, attributable to the S→M charge transfer transition [35]. Generally, the square planar Pd(II) complexes are hoped to show three bands consisting to the $^1A_{1g}\rightarrow{}^1A_{2g}$, $^1A_{1g}\rightarrow{}^1B_{1g}$ and $^1A_{1g}\rightarrow{}^1E_g$ transitions, respectively, however with dithiocarbazate ligands, a long tail of strong charge transfer transitions invariably interfere with the observation of these bands was also observed [36]. The *d-d* transitions for zinc(II) complex with d^{10} configuration are normally not observed thus generally this *bis*-chelated complex is tetrahedral. The low resolution mass spectrum of HL was scanned by EI^+ method, which showed the molecular ion peak at *m/z* of 347 followed by the formation of fragment ions at *m/z* of 247, 231, 215, 205, 133, 117, 105 and 91. However, its ML_2 complexes were scanned for their low resolution mass spectrum by using FAB^+ method. The ZnL_2 and PdL_2 complexes exhibited molecular ion peak at *m/z* of 761 and 799 for [M+2] and [M+] ions respectively, suggesting the formation of *bis*-chelated four coordinate complexes (**Schemes II-IV**).

Crystal structure: The Schiff base crystal and molecular structure was determined by single crystal X-ray diffraction analysis. The data collection of the ligand is shown in Table-1. Moreover, selected bond distance and bond angles are shown in Table-2. Fig. 1 represents ORTEP drawing of Schiff base with atom numbering scheme. The single crystal X-ray diffraction study indicated that the ligand crystallizes in monoclinic system with space group $P2_1/c$. In ligand, dithiocarbazate group adopts an *E*-configuration with respect to the C=N bond of phenyl group. The β-nitrogen and the thioketo sulphur are *trans*-located with respect to the C(8)-N(2) bond. The molecule is in its thione tautomeric form with C(8)=S(1) bond length of 1.656(8) Å and the entire species has coplanar atoms with the exception of *S*-benzyl phenyl ring indicating an electron delocalization within it. An angle between the dithiocarbazate moiety and the *S*-benzyl phenyl ring is 0.56º. The bond lengths involving the dithiocarbazate moiety namely C(8)–S(1), C(8)–S(2), C(9)–



Scheme-II: Mechanism of fragmentation of Schiff base (**1**) by mass spectroscopy



Scheme-III: Mechanism of fragmentation of Zn(II) complex (**2**) by low resolution mass spectroscopy

TABLE-1
CRYSTALLOGRAPHIC DATA AND DETAILS OF REFINEMENT FOR (HL)

Empirical formula	$C_{15}H_{15}N_3O_4S_2$
Formula weight	365.42
Temperature (K)	173
Wavelength (Å)	1.54187
Crystal colour, habit	Orange, prism
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	4.63369(9)
b (Å)	9.6529(2)
c(Å)	36.1123(8)
α (°)	90.0000
β (°)	90.1162(13)
γ (°)	90.0000
V (Å^3)	1615.24(6)
Z, calculated density (g cm^{-3})	4, 1.503
Absorption coefficient (mm^{-1})	3.228
F(000)	760.00
Crystal size (mm)	0.85 × 0.18 × 0.03
θ range for data collection (°)	4.58-68.21
Limiting indices	-5 ≤ h ≤ 5; -11 ≤ k ≤ 11; -43 ≤ l ≤ 43
Reflections collected/unique	17828/2965
R_{int}	0.0803
θ max (°)	68.21
No. of reflections collected	17828
Maximum and minimum transmission	0.908 and 0.726
Data/restrains/parameters	2198/0/225
Goodness-of-fit on F^2	1.240
R_1 indices [I > 2σ(I)][a]	0.0908
wR_2	0.2546
Largest difference peak and hole (e/Å^3)	0.490, –0.460

[a]$R_1 = S||F_o| - |F_c|| / S|F_o|$, $wR_2 = [S(w(F_o^2 - F_c^2)^2)/Sw(F_o^2)^2]^{1/2}$

TABLE-2
SELECTED BOND LENGTHS (Å) AND ANGLES (°) FOR (HL)

Bond lengths		Bond angles	
C(8)–S(1)	1.656(8)	C(8)-S(2)-C(9)	100.7(4)
C(8)–S(2)	1.755(7)	S(1)–C(8)–S(2)	126.0(5)
C(9)–S(2)	1.820(8)	S(1)–C(8)–N(2)	120.2(6)
C(8)–N(2)	1.337(10)	S(2)–C(8)–N(2)	113.8(6)
N(1)–N(2)	1.377(9)	C(8)–N(2)–N(2)	122.7(7)
C(7)–N(1)	1.292(10)	N(2)–N(1)–C(7)	114.3(6)
C(1)–C(7)	1.454(10)	N(1)–C(7)–C(1)	121.1(7)

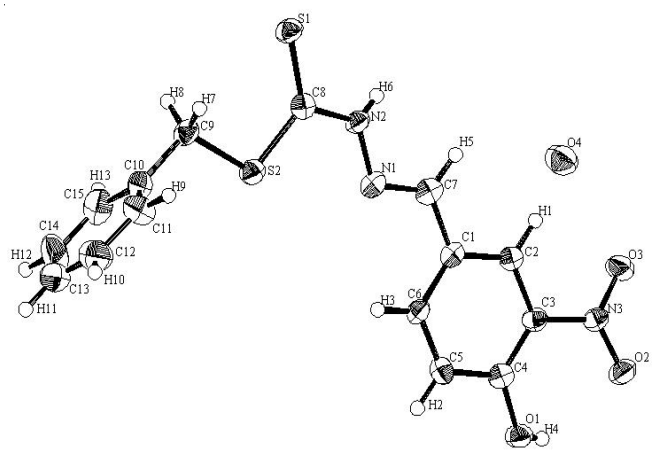
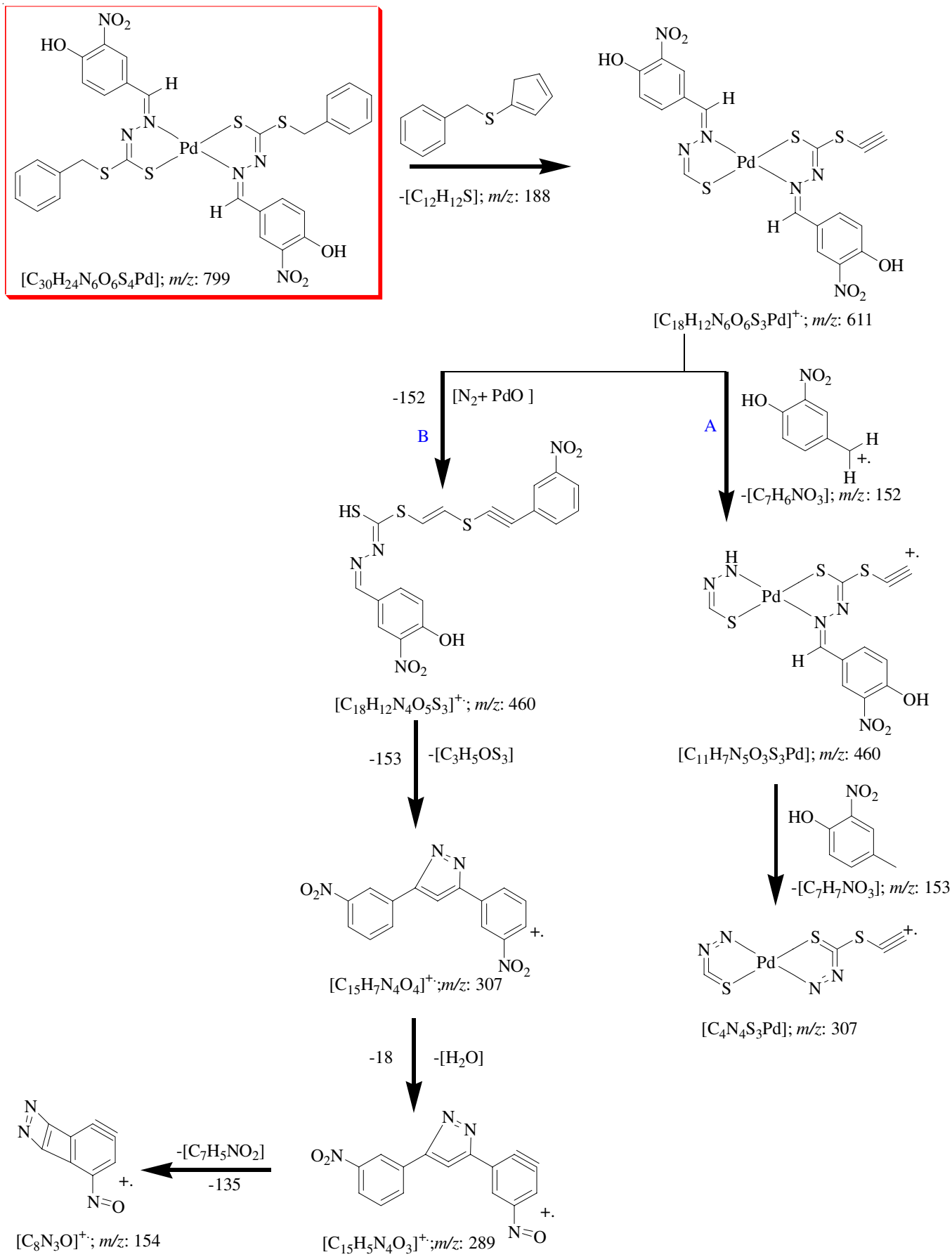


Fig. 1. ORTEP diagram (thermal ellipsoids at 40% probability level) of HL with atom numbering scheme

S(2), C(8)–N(2) and N(1)–N(2) were all in normal ranges of typical dithiocarbazate compounds [11,21,31-33,37]. Similarly, the bond angles in dithiocarbazate moiety like C(8)–S(2)–C(9), S(1)–C(8)–S(2) and C(8)–N(2)–N(1) were found at 100.7(4), 126.0(5) and 122.7(7)º, respectively and are comparable to the



Scheme-IV: Mechanism of fragmentation of Pd(II) complex (**3**) by low resolution mass spectroscopy

TABLE-3
ANALGESIC ACTIVITY OF HL AND ITS ZnL_2 AND PdL_2 COMPLEXES WITH A DOSE OF 10 mg/Kg BODY wt.

Compound	Tail flick time (s)			
	0 min	30 min	60 min	90 min
Control (vehicle)	2.60 ± 0.008	2.64 ± 0.005	2.67 ± 0.005	2.73 ± 0.018
HL	3.16 ± 0.008	3.47 ± 0.088	4.33 ± 0.300**	5.33 ± 0.369***
ZnL_2	2.77 ± 0.317	3.12 ± 0.305	3.24 ± 0.363	3.75 ± 0.456
PdL_2	2.80 ± 0.237	3.10 ± 0.305	3.57 ± 0.146	3.67 ± 0.142
Positive control (diclofenac-Na)	2.81 ± 0.005	3.31 ± 0.005	5.85 ± 0.020***	12.37 ± 0.035***

All values expressed as mean ± SEM (n = 6) one way analysis of variance (ANOVA) followed by Tucky test, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ significant compared to control.

TABLE-4
ANTI-INFLAMMATORY ACTIVITY OF THE TEST COMPOUNDS WITH A DOSE OF 10 mg/Kg BODY wt.

Compound	Paw edema volume (mm)				
	0 h	1 h	2 h	3 h	4 h
Control (vehicle)	1.92 ± 0.012	1.96 ± 0.008	2.07 ± 0.035	2.22 ± 0.014	2.22 ± 0.014
HL	0.42 ± 0.008	0.37 ± 0.031***	0.37 ± 0.029***	0.36 ± 0.030***	0.32 ± 0.014***
ZnL_2	0.42 ± 0.034	0.40 ± 0.023***	0.39 ± 0.026***	0.36 ± 0.014***	0.36 ± 0.011***
PdL_2	0.44 ± 0.020	0.40 ± 0.003***	0.38 ± 0.013***	0.36 ± 0.018***	0.33 ± 0.027***
Positive control (indomethacin)	1.54 ± 0.008	1.44 ± 0.008***	1.35 ± 0.014***	0.81 ± 0.005***	0.49 ± 0.039***

All the values indicated as mean ± SEM (n = 6) by one-way analysis of variance (ANOVA) followed by Tukey test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ significant compared to control.

literature values [11,21,38,39]. In contrast, S(2)–C(8)–N(2) bond angle is 7 to 14º smaller than values measured in other reported ligands [11,21,40]. A lattice water molecule was also detected in the crystal as shown in the ORTEP drawing (Fig. 1), thereby showing a variation in the molecular weight between mass and X-ray data (Table-1).

Analgesic activity: Table-3 depicted the analgesic activity and the test samples showed analgesic activity against radiant heat induced algesia. The brain and spinal cord play a major role in central pain mechanisms. The dorsal horn of the spinal cord is endowed with several neurotransmitters and receptors including: substance P, somatostatin, neuropeptide Y, inhibitory amino acid, nitric oxide, endogenous opioids and the monoamines, which are the major targets for pain and inflammation [41]. The tail immersion test was considered to be selective to examine compounds acting through opoid receptor; the ligand increased pain threshold, which mean basal latency which indicates that it may act *via* centrally mediated analgesic mechanism.

Anti-inflammatory activity: Table-4 indicated that the compounds significantly inhibited anti-inflammatory activity in second phase. Carrageenan induced oedema has been commonly used as an experimental animal model for acute inflammation and is believed to be biphasic. The early phase (1-2 h) of the carrageenan model is mainly mediated by histamine, serotonin and increased the synthesis of prostaglandins in the damaged tissue surroundings. The late phase is sustained by prostaglandin release and mediated by bradykinin, leukotrienes, polymorphonuclear cells and prostaglandins produced by tissue macrophages [42,43]. Since the ligand and complexes significantly inhibited paw edema induced by carrageenan in the second phase and this finding suggests a possible inhibition of cyclooxygenase synthesis by the test samples and this effect is similar to that produced by non-steroidal anti-inflammatory drugs such as indomethacin, whose mechanism of action is inhibition of the cyclooxygenase enzyme.

Conclusion

The results of the present study, indicate that the ligand HL afforded four coordinate bis-chelated neutral ML_2 complexes with zinc(II) and Pd(II) ions, respectively, binding through azomethine nitrogen atom and deprotonated thiolate sulfur anion. The Schiff base and its complexes showed significant analgesic and anti-inflammatory activities. As the OH group remains uncoordinated, it may play a vital role in biological activity of the test compounds.

Supplementary data: The supplementary crystallographic data for this article vide No. CCDC 972875 can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre.

ACKNOWLEDGEMENTS

The authors are grateful to the authorities of Institute of Biological Sciences (IBSc), University of Rajshahi, Rajshahi, Bangladesh for their kind research support for this research work. Thanks are also due to Mr. Atish Dipankar, University of Science & Technology, Dhaka, Bangladesh for conducting the biological activities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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