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# Anti-leishmanial activity of Ni(II), Pd(II) and Pt(II) β-oxodithioester complexes

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New functionalized planar β-oxodithioester cis-chelate complexes, $[M(L)_2]$ (L= L1, methyl-3-hydroxy-3-(p-bromophenyl)-2-propenedithioate, M = Ni **1**, Pd **5**, Pt **9**; L2, methyl-3-hydroxy-3-(p-fluorophenyl)-2-propenedithioate, Ni **2**, Pd **6**, Pt **10;** L3, methyl-3-hydroxy-3-(naphthyl)-2-propenedithioate, Ni **3**, Pd **7**, Pt **11**; methyl-3-hydroxy-3-(p-methoxyphenyl)-2-propenedithioate, Ni **4**, Pd **8**, Pt **12**) have been synthesized and characterized by elemental analysis, IR, UV-Vis., $^{1}H$ and $^{13}C$ NMR spectroscopy; the structures of **2-4**, **8** and **11** have been elucidated by X-ray crystallography. In all crystal structures the metal has four-coordinate slightly distorted square planar geometry with cis-configuration of the ligands. These complexes have been assessed for their use as anti-leishmanial agents; **7** and **9** showed impressive anti-promastigote and anti-amastigote efficacy with $IC_{50}$ values of (0.59±0.10 μg/mL, 0.56±0.10 μg/mL) and ($IC_{50}$ 0.85±0.27, 1.99±0.08 μg/mL) respectively. Cytotoxicity assays on both compounds displayed toxicity on the promastigotes but less toxicity against RAW 264.7 cell lines at different concentration. The Pd and Pt complexes exhibit luminescent characteristics in solution originating from the intra ligand charge transfer state.

## Introduction

Inorganic complex based drugs are becoming increasingly important because of the co-operative influence of electronic and steric properties of the metal-organic ligand framework that may potentially modify their activity for medicinal applications. The advent of cis-platin, $PtCl_2(NH_3)_2$ the most effective anticancer drug until now, stimulated interest for the design and synthesis of metal complexes for their medicinal applications.[1] Also some Ni(II) and Pd(II) complexes have shown importance in biological systems.[2]

Leishmaniasis, a parasitic disease has become endemic in developing tropical and subtropical countries. Particularly in the North-East region of Bihar state, India, it has become epidemic due to drug resistance.[3] The onset of this disease is caused by the Leishmania genus and transmitted in human by bite of certain infected sand fly. Leishmaniasis is one of the most neglected disease[4] because of the limited resources available for diagnosis, treatment, and control and its strong association with poverty.[5] Until now there are no licensed vaccines against any form of leishmaniasis. Current treatment of the disease is based on chemotherapy, which depends on a few drugs with serious limitations such as high cost, toxicity, difficult route of administration, lack of efficacy in endemic areas and development of resistance.[6] Apart from the organic compounds, amphotericin B, paromomycin, the orally administered, miltefosine, pentavalent antimonial compound based drugs are in practice.[7] High toxicity and increasing resistance especially against pentavalent antimonials further complicate this issue in disease endemic regions of the world. The Bi(V) carboxylate, thiocarboxylate[8] and β-thioxoketone[9] complexes have been assessed for their antiparasitic activity against *Leishmania major* promastigotes and their cytotoxicity towards human fibroblasts. Recently some Ru(II) clotrimazole (CTZ) complexes have been screened against leishmania.[10] Many heteroleptic Pd, Pt and Ru nitrofuran- thiosemicarbazone complexes have served as potential anti-trypanosomal agents.[11] The Pd(II) and Pt(II) mixed-ligand, pyridine-2-thiol N-oxide

and dithiocarbazate complexes have shown anti *T.cruzi* activity.[12]

By comparison, despite synthetic versatility and practical utility,[13] the β-oxodithioester (O,S-donor) complexes somewhat similar to those with β-thioxoketone ligands have not been explored for their anti-leishmanial activity. It is critical to search for newer metal complex based drugs which will be effective and safe anti-leishmanial agents. The β-oxodithioester ligands (fig.1) used in this work present some interesting features: (i) oxygen is more electronegative than sulphur (ii) sulphur is larger than oxygen and has more diffused p and d orbitals whereas oxygen has no d-orbitals (iii) oxygen is a hard but sulphur is distinctly soft donor (iv) they form highly delocalized six-membered chelate ring about the metal centre (v) the functionalization of substituents on the dithio backbone may influence the electronic and steric properties and (vi) the additional donor atoms on the substituents may induce secondary interactions which are generally not associated with chelating ligands having identical donor atoms. The soft Pd(II) and Pt(II) ions differ from the borderline Ni(II) ion with regard to their preferential bonding with the soft S/hard O donor atoms in accordance of HSAB principle. These features may make significant differences in the stability and M-O/M-S bond polarity and hence the reactivity of the complexes. Furthermore, the metal based drugs are advantageous over organic drugs because of their inherent properties such as variable oxidation states (i.e. redox behaviour), coordination number and geometries and thermodynamic/kinetic characteristics associated with the metals which may induce their Lewis acid activity hence drug activity. Taking into account these facts it was considered worthwhile to undertake the synthesis, crystal structures and anti-leishmanial activity evalution of new cis-planar chelate β-oxodithioester complexes of Ni(II), Pd(II) and Pt(II). The potential anti-leishmanial activity observed for two complexes are described in this contribution.

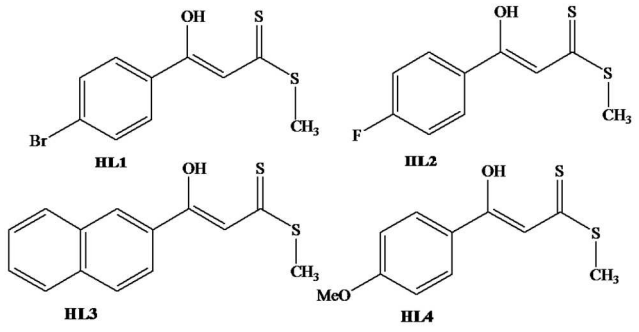



Fig. 1 Structure of ligands used in this work.

## Experimental Section

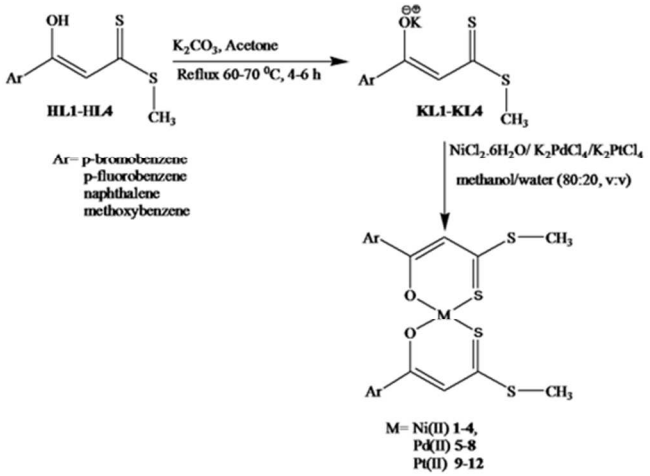
### Materials and general methods

All the experiments were carried out in the open at ambient temperature and pressure unless otherwise quoted. All chemicals used were reagent grade and obtained from the commercial sources. Solvents were distilled and purified by standard procedures. The ligands methyl-3-hydroxy-3-(p-bromophenyl)-2-propenedithioate (H**L1),** methyl-3-hydroxy-3-(p-fluorophenyl)-2-propenedithioate **(**H**L2)** methyl-3-hydroxy-(2-naphthyl)-2-propenedithioate **(**H**L3)** and methyl-3-hydroxy-3-(p-methoxyphenyl)-2-propenedithioate (H**L4)** and their corresponding potassium salts were synthesized as described elsewhere.[14] The experimental details dealing with the elemental analyses (C, H, S), IR, $^{1}$H and $^{13}$C{$^{1}$H} NMR, electronic absorption and luminescent spectra are the same as previously reported.[14]

### Synthesis of the complexes

**[M(L)$_2$]** (M=Ni(II), L = L1 **1**, L2 **2,** L3 **3,** L4 **4**; Pd(II), L1 **5**, L2 **6,** L3 **7,** L4 **8**; Pt(II), L1 **9**, L2 **10**, L3 **11**, L4 **12**)

The homoleptic complexes [M(**L**)$_2$] **1-12** were prepared adopting the general procedure as follows (Scheme 1). To a 10 mL stirred methanol-water ( 80:20, v/v) solution of K**L1** (0.28 g, 1 mmol), K**L2** (0.31 g, 1 mmol), K**L3** (0.27 g 1 mmol) or K**L4** (0.34 g, 1 mmol) was added separately a 10 mL solution of $NiCl_2.6H_2O$ (0.118 g, 0.5 mmol), $K_2PdCl_4$ (0.163 g, 0.5 mmol) or $K_2PtCl_4$ (0.207 g, 0.5 mmol) in the same solvent mixture and stirred for 4-8 h. The red-brown Ni(II) and orange coloured Pd(II) and Pt(II) complexes thus obtained as solids were filtered off, washed 3-4 times with methanol followed by diethyl ether. The compounds were purified by recrystallization in dichloromethane; the crystals of **2-4**, **8** and **11** were obtained within 3-4 weeks.




Scheme 1 Generalized synthesis of the complexes.

### Characterization data

[Ni(L1)$_2$] **1**

Yield: (69 %, 0.219 g). m. p. 275-279°C. Anal. Calcd. for $C_{20}H_{16}Br_2NiO_2S_4$ (635.70): C 37.82, H 2.54, S 20.20 %. Found: C 37.61, H 2.59, S 19.75 %. IR (KBr, cm$^{-1}$): $\nu$ = 1073 ($\nu_{C-O}$), 1256 ($\nu_{C=S}$), 1586 ($\nu_{C=C}$). $^{1}$H NMR (300.40 MHz, $CDCl_3$): δ 2.62 (s, 3H, $SCH_3$), 7.05 (s, 1H, =CH-C(S)-), 7.55 (m, 2H, Ar-H), 7.74-7.68 (m, 2H, Ar-H) ppm. $^{13}$C{$^{1}$H} NMR (75.45 MHz, $CDCl_3$): δ 23.07 (-$SCH_3$), 111.08 (=*C*H-C(S)-), 128.85, 132.68,

143.83, 147.24 (Ar-C), 180.49 (=C-O-), 192.42 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 275 (2.67 x $10^4$), 322 (3.28 x $10^4$), 351 (3.26 x $10^4$), 414 (7.9 x $10^3$), 672 (0.6 x $10^2$).

$[Ni(L2)_2]$ **2**

Yield: (72 %, 0.185 g). m. p. 279-282°C. Anal. Calcd. for $C_{20}H_{16}F_2NiO_2S_4$ (513.29): C 46.80, H 3.14, S 24.99 %. Found: C 46.41, H 3.25, S 24.65 %. IR (KBr, $cm^{-1}$): $\nu$ = 1100 ($\nu_{C-O}$), 1257 ($\nu_{C=S}$), 1561 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.66 (s, 3H, $SCH_3$), 6.88 (s, 1H, =CH-C(S)-), 6.96 (m, 2H, Ar-H), 7.87-7.82 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$): δ 18.7 (-$SCH_3$), 112.35 (=*C*H-C(S)-), 115.4, 127.8, 130.5, 145.72 (Ar-C), 183.0 (=C-O-), 209.7 (-C=S-) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 256 (4.49 x $10^4$), 285 (3.17 x $10^4$), 326 (6.18 x $10^4$), 368 (7.5 x $10^4$), 413 (2.35 x $10^4$), 668 (1.7 x $10^2$).

$[Ni(L3)_2]$ **3**

Yield: (78%, 0.225 g), m. p. 260-264°C. Anal. Calcd. for $C_{28}H_{22}O_2S_4Ni$ (577.43): C 58.24, H 3.84, S 22.21 %. Found: C 57.98, H 3.97, S 21.85 %. IR (KBr, $cm^{-1}$): $\nu$ = 1118 ($\nu_{C-O}$), 1248 ($\nu_{C=S}$), 1578 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.66 (s, 3H, $SCH_3$), 7.24 (s, 1H, =CH-C(S)-), 7.50 (m, 2H, Ar-H), 7.83 (m, 4H, Ar-H), 8.45 (d, 1H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45, $CDCl_3$): δ 18.3 (-$SCH_3$), 111.37 (=*C*H-C(S)-), 122.73-134.96 (Ar-C), 181.2 (=C-O-), 210.8 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$(nm), ε ($M^{-1}cm^{-1}$)): 264 (8.49 x $10^4$), 301 (4.84 x $10^4$), 324 (6.45 x $10^4$), 359 (6.32 x $10^4$), 416 (1.14 x $10^4$), 663 (1.5 x $10^2$).

$[Ni(L4)_2]$ **4**

Yield: (78%, 0.210 g), m. p. 217-220°C. Anal. Calcd. for $C_{22}H_{22}NiO_4S_4$ (537.36): C 49.17, H 4.13, S 23.87 %. Found: C 48.95, H 4.21, S 23.46 %. IR (KBr, $cm^{-1}$): $\nu$ = 1129 ($\nu_{C-O}$), 1251 ($\nu_{C=S}$), 1602 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.59 (s, 3H, -$SCH_3$), 3.85 (s, 3H, -$OCH_3$), 6.88 (s, 1H, =CH-C(S)-), 7.25 (m, 2H, Ar-H), 7.85 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (74.45 MHz, $CDCl_3$): δ 22.67 (-$SCH_3$), 55.40 (-$OCH_3$), 113.99 (=*C*H-C(S)-), 127.2, 129.14, 133.61, 163.2 (Ar-C), 184.0 (=C-O-), 204.90 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 282 (2.81 x $10^4$), 321 (4.81 x $10^4$), 358.5 (5.49 x $10^4$), 410 (1.79 x $10^4$), 668 (1.01 x $10^2$).

$[Pd(L1)_2]$ **5**

Yield: (81%, 0.277 g), m. p. 257-261°C. Anal. Calcd. for $C_{20}H_{16}Br_2PdO_2S_4$ (682.83): C 35.18, H 2.26, S 18.78 %. Found: C 34.86, H 2.35, S 18.45 %. IR (KBr, $cm^{-1}$): $\nu$ =1094 ($\nu_{C-O}$), 1317 ($\nu_{C=S}$), 1588 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.66 (s, 3H, -$SCH_3$), 6.88 (s, 1H, =CH-C(S)-), 6.95-6.97 (m, 2H, Ar-H), 7.86-7.83 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$): δ 23.40 (-$SCH_3$), 110.58 (=*C*H-C(S)-), 127.64, 133.64, 137.3 142.80 (Ar-C), 175.85 (=C-O-), 190.50 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 263 (3.74 x $10^4$), 346 (4.24 x $10^4$), 418 (1.87 x $10^4$).

$[Pd(L2)_2]$ **6**

Yield: (81%, 0.227 g), m. p. 247-251°C. Anal. Calcd. for $C_{20}H_{16}F_2PdO_2S_4$ (561.02) : C 42.82, H 2.87, S 22.86 %. Found: C 42.65, H 2.85, S 22.45 %. IR (KBr, $cm^{-1}$): $\nu$ = 1094 ($\nu_{C-O}$), 1259 ($\nu_{C=S}$), 1588 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.66 (s, 3H, -$SCH_3$), 6.87 (s, 1H, =CH-C(S)-), 6.96 (m, 2H, Ar-H), 7.86-7.83 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$): δ 21.83 (-$SCH_3$), 109.60 (=*C*H-C(S)-), 118.71, 124.32, 136.94, 148.57 (Ar-C), 186.58 (=C-O-), 198.08 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 303 (2.28 x $10^4$), 343 (2.62 x $10^4$), 415 (1.65 x $10^4$).

$[Pd(L3)_2]$ **7**

Yield: (84%, 0.263 g), m. p. 212-215°C. Anal. Calcd. for $C_{28}H_{22}PdO_2S_4$ (625.15): C 53.79, H 3.55, S 20.52 %. Found: C 53.68, H 3.66, S 20.35%. IR (KBr, $cm^{-1}$): $\nu$ = 1125 ($\nu_{C-O}$), 1286 ($\nu_{C=S}$), 1595 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.68 (s, 3H, $SCH_3$), 7.30 (s, 1H, =CH-C(S)-), 7.63 (m, 2H, Ar-H), 8.00 (m, 4H, Ar-H), 8.65 (d, 1H, Ar-H) ppm. $^{13}C\{^1H\}$NMR (75.45, $CDCl_3$): δ 21.06 (-$SCH_3$), 113.97 (=CH-C(S)-), 117.05, 121.44, 129.37, 132.83, 134.17, 141.61, 143.95 (Ar-C), 180.91 (=C-O-), 191.95 (-C=S-) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 259 (3.50 x $10^4$), 344 (3.06 x $10^4$), 431 (1.41 x $10^4$).

$[Pd(L4)_2]$ **8**

Yield: (73%, 0.212g), m. p. 253-256°C. Anal. Calcd. for $C_{22}H_{22}PdO_4S_4$ (585.09): C 46.16, H 3.79, S 21.92%. Found: C 45.85, H 3.78, S 21.45 %. IR (KBr, $cm^{-1}$): $\nu$ = 1124 ($\nu_{C-O}$), 1317 ($\nu_{C=S}$), 1594 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.59 (s, 3H, -$SCH_3$), 3.86 (s, 3H, -$OCH_3$), 6.79 (s, 1H, =CH-C(S)-), 6.93 (m, 2H, Ar-H), 7.91 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$) : δ 27.81 (-$SCH_3$), 59.79 (-$OCH_3$), 114.07 (=CH-C(S)-), 117.62, 122.73, 158.10, 158.91 (Ar-C), 187.87 (=C-O-), 197.61 (-C=S) ppm. UV-Vis.($CH_2Cl_2$, $\lambda_{max}$ (nm), ε 346 (3.84 x $10^4$), 413 (2.10x $10^4$).

$[Pt(L1)_2]$ **9**

Yield: (86%, 0.330 g), m. p. 219-223°C. Anal. calcd. for $C_{28}H_{22}PtO_2S_4$ (713.81): C 31.14, H 2.09, S 17.97 %. Found: C 30.96, H 2.17, S 17.52%. IR (KBr, $cm^{-1}$): $\nu$ = 1125 ($\nu_{C-O}$), 1287 ($\nu_{C=S}$), 1595 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.68 (s, 3H, -SMe), 6.81 (s, 1H, =CH-C(S)-), 7.25-7.87 (m, 2H, Ar-H), 7.87 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45, MHz, $CDCl_3$): δ 19.3 (-$SCH_3$), 110.26 (=CH-C(S)-), 126.3, 128.4, 133.7, 140.9 (Ar-C), 179.3 (=C-O-), 209.6 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 360 (6.94 x $10^4$).

$[Pt(L2)_2]$ **10**

Yield: (81%, 0.263g), m.p. 236-240°C. Anal. Calcd. for $C_{20}H_{16}F_2PtO_2S_4$ (649.67): C 36.97, H 2.48, S 19.74%. Found: C 36.75, H 2.45, S 19.42 %. IR( KBr, $cm^{-1}$ ): $\nu$ = 1164 ($\nu_{C-O}$), 1224 ($\nu_{C=S}$), 1595 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.66 (s, 3H, -$SCH_3$), 6.90 (s, 1H, =CH-C(S)-), 7.26 (m, 2H, Ar-H), 7.87 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45 MHz, $CDCl_3$): δ 27.80 (-$SCH_3$), 109.73 (=CH-C(S)-), 117.62, 129.740, 132.82, 137.61, 144.43, 147.57 (Ar-C), 183.30 (=C-O-), 201.61 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 255 (3.16 x $10^4$), 309 (3.1 x $10^4$), 368 (5.25 x $10^4$), 403 (3.95 x $10^3$).

$[Pt(L3)_2]$ **11**

Yield: (83%, 0.296 g), m. p. 205-208°C. Anal. Calcd. for $C_{28}H_{22}PtO_2S_4$ (713.81): C 47.11, H 3.11, S 17.97 %. Found: C 46.85, H 3.15, S 17.62 %. IR (KBr, $cm^{-1}$): $\nu$ = 1131 ($\nu_{C-O}$), 1302 ($\nu_{C=S}$), 1594 ($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.68-2.64 (s, 3H, $SCH_3$), 6.85 (d, 1H, =CH-C(S)-), 7.56 (m, 2H, Ar-H), 7.98 (m, 4H, Ar-H), 8.47 (d, 1H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (75.45, $CDCl_3$): δ 27.82 (-$SCH_3$), 109.38 (=CH-C(S)-),

126.84, 128.20, 131.04, 135.64, 141.82, 145.26, 146.27 (Ar-C), 184.31 (=C-O-), 200.80 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$ (nm), ε ($M^{-1}cm^{-1}$)): 296 (6.35 x $10^4$), 357 (7.49 x $10^4$).

[$Pt(L4)_2$ ] **12**

Yield: (76%, 0.256 g), m. p. 276-280 ºC. Anal. Calcd. for $C_{22}H_{22}PtO_4S_4$ (673.75): C 39.22, H 3.29, S19.04 %. Found: C 39.07, H 3.37, S 18.64 %. IR (KBr, $cm^{-1}$): $\nu$ = 1175($\nu_{C-O}$), 1253($\nu_{C=S}$), 1595($\nu_{C=C}$). $^1$H NMR (300.40 MHz, $CDCl_3$): δ 2.65 (s, 3H, -$SCH_3$), 3.87 (s, 3H, -$OCH_3$), 6.95-6.92 (m, 2H, Ar-H), 7.09 (s, 1H, =CH-C(S)-), 8.02 (m, 2H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (74.45 MHz, $CDCl_3$): δ 22.69 (-$SCH_3$), 55.6 (-$OCH_3$), 112.89 (-CH=C(-S)-), 117.62, 122.73, 158.10, 158.97 (Ar-C), 187.87 (=C-O-), 200.50 (-C=S) ppm. UV-Vis. ($CH_2Cl_2$, $\lambda_{max}$(nm), ε ($M^{-1}cm^{-1}$)): 344 (4.08 x $10^4$), 424 (1.72 x $10^4$).

**X-ray structure determinations**

Single crystals of the complexes **2-4, 8** and **11** were grown by slow evaporation of the $CH_2Cl_2$ solution of products. The X-ray diffraction data were collected on an Oxford X-calibur CCD diffractometer at 293 K using Mo Kα radiation. Data reduction were carried out using the CrysAlis program.[15] The structures were solved by direct methods using SHELXS-97[16] and refined on $F^2$ by full matrix least squares method using SHELXL-97.[17] Non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically fixed with thermal parameters equivalent to 1.2 times that of the atom to which they were bonded. Diagrams for all complexes were prepared using ORTEP[18] and Mercury software.[19]

**Bioevaluation methods: *In vitro* anti-leishmanial assay**

**Material and methods**

To evaluate anti-leishmanial activity a cloned line of *Leishmania donovani* promastigotes (2012) was used throughout this study, which is maintained in the laboratory. In order to assess the activity of compounds against the amastigote stage of the parasites, mouse macrophage cell lines (J-774A.1) were used. The promastigote forms of parasites were maintained *in vitro* in Dulbecco minimum essential medium (DMEM, Invitrogen, USA) supplemented with 10% FBS (Invitrogen, USA) and antibiotics (gentamycin 20 µg/mL, streptomycin 100 µg/mL, penicillin 100 U/mL, Sigma Chemicals, USA) at pH 7.2 in a BOD incubator at 25°C. For drug assays logarithmic phase parasites were harvested.

**Preparation of stock solutions.** Stock solutions of test samples were prepared initially in DMSO at 10 mg/mL concentration and further diluted with fresh complete medium and sterilized by filtration.

**A: *In vitro* antipromastigote activity**

For determination of the anti-leishmanial activity of compounds, promastigotes (1 × $10^6$ cells/100 µL/well) were seeded in a 96-well microtiter plate in the presence of 100 µL of compounds in each well (which were 2 fold serially diluted over seven points starting from 100 µg/mL, so final concentration of compounds in wells which ranges from 50 µg/mL to 0.78 µg/mL) and were further incubated for 48 h. After 48h, the anti-leishmanial activities were evaluated by a MTT (3-[4,5-methylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay, which is based on the reduction of the tetrazolium dye to insoluble formazan by the mitochondrial enzymes (Mosmann, 1983). Briefly, 30 µL (5 mg/mL) of MTT was added to each well, incubated for 2h at 37°C and centrifuged at 3000 rpm for 5 min. The supernatant was removed, the parasites were washed in PBS, and the precipitated formazan was dissolved in DMSO (150 µL). Cell viability was measured by absorbance at 540 nm on an ELISA plate reader. All experiments were repeated three times for each drug in duplicates.

**Data analysis**

The inhibition of parasitic growth is determined by comparison of the activity of treated parasites with that of untreated controls using the formula, Percentage Inhibition = N-n/N x 100, where N is the average OD of control wells and n is the average OD of treated wells. The cytotoxic effect are expressed as 50% lethal dose, i.e., as the concentration of a sample which provoked a 50% reduction in cell viability compared to cell in culture medium alone. Results were expressed as a concentration resulting in 50% inhibition ($IC_{50}$) ± standard deviation that was calculated by linear interpolation (Huber and Koella, 1993) as follows,

$$log\ (IC_{50}) = log\ (X1) + (50-Y1)/\ (Y2-Y1)\ [\ log\ (X2) - log\ (X1)]$$

where X1: Concentration of the drug that gives a % inhibition of the parasitaemia Y>50%,

X2: Concentration of the drug that gives a % inhibition of the parasitaemia Y<50%.

These cytotoxicity assay were performed for compounds having antipromastigote activity with $IC_{50}$<100.

**B. Macrophage-amastigote *in vitro* test model**

***In vitro* anti-amastigote activity.** J774.1 cells were seeded in 24 well plate at a density of $4\times10^5$ cells/100 µL/well in DMEM medium containing 10% FBS and plates were incubated at 37°C in 5% $CO_2$ incubator. After 24 h, the medium was replaced with fresh medium containing stationary phase promastigotes in 7:1 parasite to cell ratio, and incubated at 37°C in $CO_2$ incubator for 4-6 h. After incubation, cells were washed 2-3 times to remove non-internalized promastigotes. The test compounds (200 µL) were added two-fold serially diluted with complete DMEM medium over seven concentrations (50 - 0.78 µg/mL)) and then incubated for 48 h. After this period the cells were washed with phosphate buffer saline (0.02 M, pH 7.2), methanol fixed and stained with Giemsa to count live amastigotes in macrophage by bright-field microscopy.[20] The anti-amastigote activities of compounds were determined microscopically by counting number of amastigotes by examining at least 200 infected macrophages per experiment. $IC_{50}$ values were determined by monitoring the reduction in the mean percentage of infected

macrophages or by the mean reduction in the number of amastigotes per macrophage in drug treated cultures in relation to non treated cultures.[21] Miltefosine was used as the reference standard drug and as a control.

**C: Cytotoxicity assay**

The cell toxicity of compounds was evaluated on RAW264.7 cells as described elsewhere.[22] Briefly, RAW264.7 macrophage cells were maintained in DMEM medium supplemented with 10 % FBS at 37°C in a humidified mixture of 5% $CO_2$ atmosphere. Macrophages ($1 \times 10^6$ cells/mL) were seeded in 96-well microtiter plate in the presence of compounds, which were 2-fold serially diluted over six concentrations (100 to 0.78125 μg/mL) in DMEM medium and further incubated for 48 h. Cells without compounds (untreated cells) were used as control and considered as 100 percent viable cells. The cell viability were assayed using MTT, viability = mean absorbance of treated cells/mean absorbance of non-treated cells x 100. The cytotoxicity assays were performed for compounds having anti-promastigote activity, $IC_{50}$<100. The $IC_{50}$ values were calculated using nonlinear regression analysis.

## Results and Discussion

**Synthesis and characterization**

Treatment of a water- methanol solution containing two equivalents of the potassium salt of the ligands, K**L1**-K**L4** with one equivalent of $NiCl_2.6H_2O$, $K_2PdCl_4$ or $K_2PtCl_4$ in the same solvent mixture yielded air and moisture stable homoleptic complexes **1-12** in good yield (Scheme 1). The complexes have been characterized by elemental analysis, IR, UV-Vis., $^1$H and $^{13}$C NMR and their structures have been elucidated by X-ray crystallography. The luminescent behaviour of the complexes has been studied in $CH_2Cl_2$ solution. All the complexes were screened for activity against leishmanial parasite; only **7** and **9** have shown potential anti-leishmanial activity.

**Spectroscopy**

In the IR spectra, complexes **1-12** show bands at 1073-1175, 1224-1285 and 1578-1595 $cm^{-1}$ for the $\nu_{C-O}$ , $\nu_{C=S}$ and $\nu_{C=C}$ vibrations respectively diagnostic of O,S-coordination of β-oxodithioester ligands.[14, 23] In the $^1$H NMR spectra the ligands H**L1**- H**L4** (for details see ESI) display a single resonance in the $\delta$ 14.89-15.17 ppm range due to -OH proton, which is not observed in the complexes **1-12**. The peak for the vinylic proton is found at $\delta$ 6.72-7.10 ppm and $\delta$ 6.79-7.24 ppm for the ligands and complexes respectively. In the $^{13}C\{^1H\}$ spectra the resonances at $\delta$ 167.10-169.51 and $\delta$ 175.85-187.87 ppm correspond to the C-OH carbon in the free ligands and the complexes respectively. The vinylic carbon at $\delta$ 107.08-108.22 ppm for the ligands is observed at $\delta$ 109.38-114.07 ppm in the complexes with a downfield shift of approximately $\delta$ 4-6 ppm. The –C=S carbon at $\delta$ 215.02-218.0 ppm for the free ligands is significantly upfield shifted at $\delta$ 192.42-210.8 ppm in the complexes showing metal-ligand coordination.[23]

**Crystal Structures**

The single crystals of the complexes **2-4**, **8** and **11** were grown in dichloromethane solution. The crystal parameters and selected bond distances and angles are given in table 1 and 2 respectively. Their ORTEP diagrams are as shown in Figure 2. The asymmetric unit of **2-4** and **11** contains one discrete molecule whereas that of **8** contains half a molecule thus in this with the metal atom lying on a twofold axis. All the complexes show a distorted square planar geometry in a *cis* fashion coordinated *via* O15, S11, O35, S31 atoms. The distortion arises due to larger bite angles S11-M1-O15 and S31-M1-O35 at 95.59(6)–96.11(9)° for Ni complexes (**2-4**); 96.26(12) and 96.11(12)° respectively for **11** and S11-M1-O15 angle at 94.72(5)° for **8.** In the five structures, the $S_2O_2$ equatorial plane shows r.m.s. deviations of 0.0.36, 0.064, 0.013, 0.000, 0.026 Å with the metal 0.013(1), 0.006(1), 0.011(1), 0.000, 0.007(1) Å from the plane in **2-4, 8** and **11** respectively. As expected with their size, the M-O distances for Ni complexes, **2-4** are significantly shorter at (1.847(3)–1.860(2) Å) than the Pd complex **8**, at 2.022(1) and the Pt complex, **11** at (2.011(4), 2.022(4) Å). Similarly, the M-S distances of 2.126(1)–2.148(1) Å are shorter in **2-4** than **8** at 2.231(1) Å and **11** at 2.229(1) / 2.243(2) Å. The C12-C14 / C14-C15 distances at 1.352(5) - 1.376(4) / 1.383(6)–1.411(5) Å for **2-4**, 1.372(3) / 1.395(3) Å for **8** and 1.411(8) / 1.397 (8) Å for **11** are intermediate between single and double bond lengths. In all structures the C12-S11 bonds are shorter than the C12-S13 bonds with range of 1.683(4)-1.707(3) Å and 1.742(3)-1.762(3) Å respectively but both fall in the range between carbon-sulphur single and double bond lengths.[24]

The six-membered chelate ring is approximately planar in all structures with r.m.s deviations in the range 0.012-0.044 Å in the five structures. The two rings intersect at small angles 4.0, 8.9, 0.8 0.0, 4.9° with variations that are no doubt due to packing effects. As is apparent from figure 2, the substituents on the six-membered ring are approximately coplanar so that all molecules are essentially planar. The supramolecular structures of the complexes are sustained *via* weak intermolecular C-H···S, C-H···O and CH···π interactions (table 3, ESI).

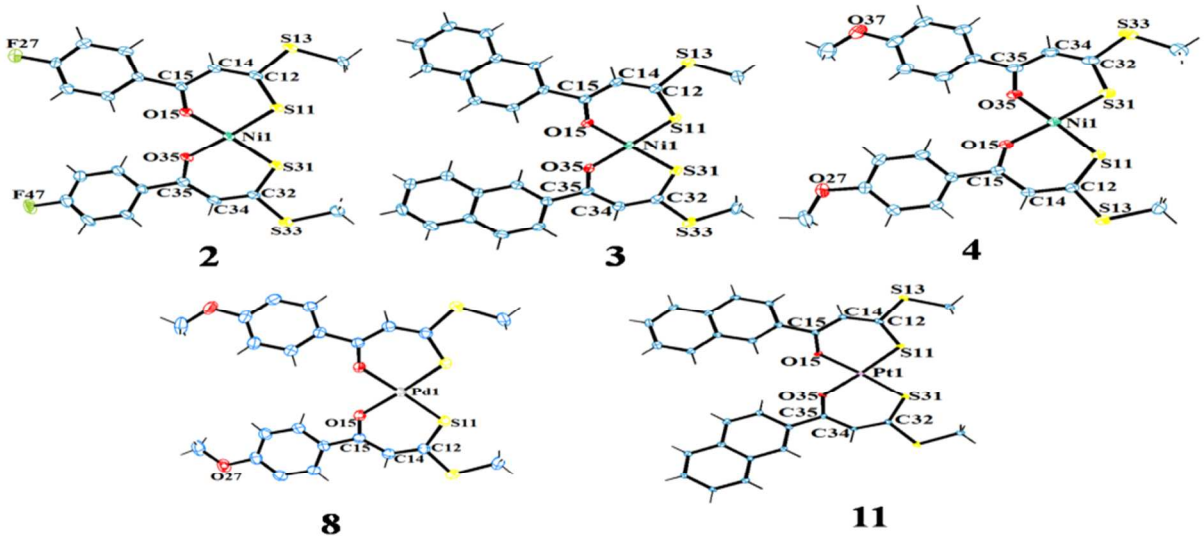



Fig-2. Molecular structures of **2-4**, **8** and **11** with displacement ellipsoids at 30% probability.

**Table 1** Crystal refinement parameters

| Compound | **2** | **3** | **4** | **8** | **11** |
|---|---|---|---|---|---|
| Chemical Formula | $C_{20}H_{16}F_2NiO_2S_4$ | $C_{28}H_{22}NiO_2S_4$ | $C_{22}H_{22}NiO_4S_4$ | $C_{22}H_{22}O_4PdS_4$ | $C_{28}H_{22}O_2PtS_4$ |
| Formula Weight | 513.28 | 577.41 | 537.35 | 585.04 | 713.78 |
| Crystal system | triclinic | monoclinic | monoclinic | tetragonal | monoclinic |
| Space group | P-1 | $P2_1/c$ | $P2_1$ | $I4_1/a$ | $P2_1/c$ |
| *a(Å)* | 12.2291(9) | 24.946(4) | 12.1110(4) | 17.4781(5) | 13.3438(5) |
| *b(Å)* | 4.0160(4) | 5.8062(10) | 7.1701(3) | 17.4781(5) | 16.6915(7) |
| *c(Å)* | 23.0003(15) | 17.003(3) | 13.5948(5) | 15.3714(4) | 11.6650(5) |
| *α (°)* | 75.300(7) | 90.00 | 90.00 | 90.00 | 90.00 |
| *β (°)* | 84.316(6) | 91.800(13) | 98.151(3) | 90.00 | 106.870(4) |
| *γ (°)* | 69.691(8) | 90 | 90 | 90 | 90 |
| $V(Å^3)$ | 1024.62(14) | 2461.5(7) | 1168.61(8) | 4695.7(2) | 2486.31(18) |
| *Z* | 2 | 4 | 2 | 8 | 4 |
| $\rho_{calc}(g\ cm^{-3})$ | 1.664 | 1.558 | 1.527 | 1.655 | 1.904 |
| T(K) | 293(2) | 293(2) | 293(2) | 293(2) | 150(2) |
| *μ (Mo Kα) (mm⁻¹)* | 1.387 | 1.154 | 1.214 | 1.173 | 6.005 |
| *F*(000) | 524 | 1192.0 | 556 | 2368 | 1392 |
| Reflections collected | 8853 | 18304 | 5096 | 9818 | 15140 |
| Independent reflns | 4468 | 5584 | 3660 | 2626 | 7087 |
| Reflections with $I > 2\sigma(I)$ | 2966 | 3643 | 3139 | 1980 | 5020 |
| Finalindices[$I>2\sigma(I)$]$R_1$[a],w$R_2$[b] | 0.0545, 0.1001 | 0.0664, 0.1555 | 0.0343, 0.0729 | 0.0327, 0.0750 | 0.0498, 0.0819 |
| $R_1$[a], w$R_2$[b][all data] | 0.0904, 0.1191 | 0.1046, 0.1780 | 0.0450, 0.0781 | 0.0526, 0.0811 | 0.0839, 0.0942 |
| GOF | 0.993 | 1.007 | 0.946 | 1.076 | 0.925 |
| CCDC | 1055639 | 1055640 | 925921 | 1055641 | 1055642 |

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $R^2 = \{[\Sigma w(F_o^2 - F_c^2)/\Sigma w(F_o^2)^2]\}^{1/2}$, $w = 1/[\sigma^2(F_o^2) + (xP)^2]$, where $P = (F_o^2 + 2F_c^2)/3$

**Table 2** Selected bond distances and angles for **2-4**, **8** and **11**.

| | **Bond lengths (Å)** | | | | |
|---|---|---|---|---|---|
| | **2** (M = Ni) | **3** (M = Ni) | **4** (M = Ni) | **8** (M = Pd)[a] | **11** (M = Pt) |
| M-O15 | 1.847(3) | 1.856(3) | 1.849(2) | 2.0223(2) | 2.011(4) |
| M-O35 | 1.860(2) | 1.853(3) | 1.848(2) | - | 2.022(4) |
| M-S11 | 2.148(1) | 2.132(1) | 2.137(1) | 2.2314(1) | 2.230(2) |
| M-S31 | 2.146(1) | 2.126(1) | 2.141(1) | - | 2.244(2) |
| C15-O15 | 1.269(4) | 1.254(5) | 1.269(3) | 1.266(3) | 1.285(7) |
| C15-C14 | 1.411(5) | 1.383(6) | 1.399(4) | 1.395(3) | 1.411(8) |
| C12-C14 | 1.352(5) | 1.368(5) | 1.376(4) | 1.372(3) | 1.397(8) |
| C12-S11 | 1.705(4) | 1.683(4) | 1.707(3) | 1.697(3) | 1.697(7) |
| C12-S13 | 1.762(3) | 1.749(4) | 1.744(3) | 1.757(3) | 1.742(6) |
| | **Bond Angles (°)** | | | | |
| O15-M-S11 | 95.68(8) | 96.11(9) | 95.59(6) | 94.72(5) | 96.26(12) |
| O15-M-S31 | 176.01(8) | 175.88(10) | 176.79(11) | 175.17(6) | 175.55(12) |
| O15-M-O35 | 81.21(11) | 83.29(12) | 81.49(9) | 82.88(10) | 79.58(16) |
| S11-M-S31 | 87.19(4) | 84.77(4) | 87.28(3) | 87.97(4) | 88.07(6) |
| S11-M-O35 | 176.58(9) | 176.52(10) | 177.08(7) | - | 175.46(13) |
| S31-M-O35 | 95.99(9) | 96.07(9) | 95.64(7) | - | 96.11(12) |

[a]in **8** S31 and O35 are S11$1, O31$1 where $1 represents symmetry element -x, 3/2-y,z.

**Absorption and emission spectra**

The UV-Vis. absorption and photoluminescence spectra of the complexes were recorded in dichloromethane solution at room temperature and displayed in Figure 4 and 5 respectively. The Ni (**1-4**) complexes exhibit bands near 260-415 nm (ε = 0.79-8.49 x $10^4$ $M^{-1}cm^{-1}$); the high energy bands are assigned to intra ligand (ILCT) whereas the low energy bands are assigned to ligand to metal (LMCT) charge transfer transitions. In these complexes a high energy band near 670 nm (ε = 0.6-1.01 x $10^2$ $M^{-1}cm^{-1}$) corresponds to the d-d transition. The analogous Pd and Pt complexes display absorptions near 250-431 nm (ε =1.40-6.94 x $10^4$ $M^{-1}cm^{-1}$) assignable to ILCT and metal perturbed ILCT transitions. When excited at 350 nm the Pd (**5-8**) and Pt (**9-12**) complexes show an unstructured emission band near 440 nm originating from the metal perturbed intra ligand charge transfer (ILCT) state. As expected all the Ni complexes are weakly luminescent due to their well known quenching behaviour because of the occurrence of d-d band in the visible region.[25]

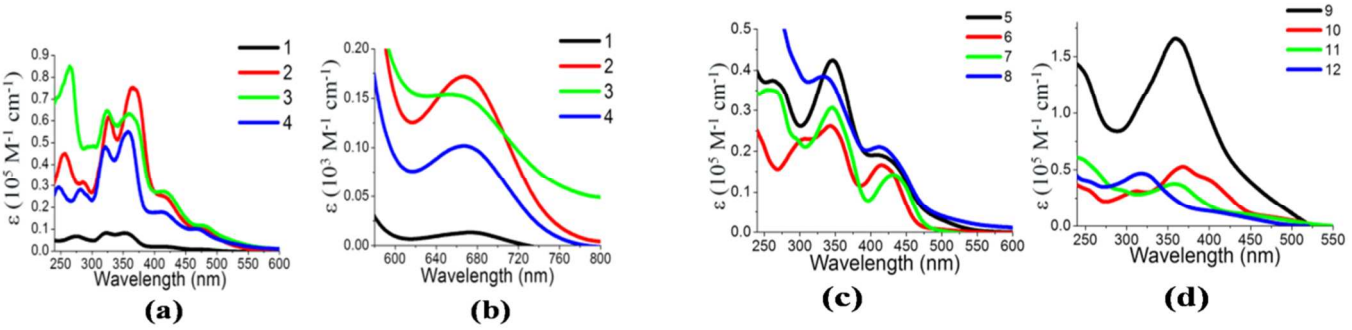



Fig.3 Absorption spectra for (a) Ni (**1-4**) and (b) d–d transitions in **1-4** (c) Pd (**5-8**) (d) Pt (**9-12**) complexes in dichloromethane solution at room temperature.

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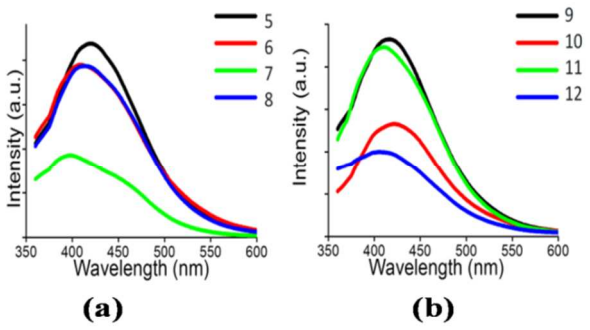


Fig. 4 Photoluminescence spectra of (a) Pd (**5**-**8**) and (b) Pt (**9**-**12**) complexes in dichloromethane solution at room temperature.

**Anti-leishmanial studies**

All the metal complexes were evaluated for their antileishmanial activities but out of these only two showed significant *in vitro* antileishmanial promastigote and intracellular amastigote activities than the standard drug Miltefosine. The antiparasitic activities of these metallic compounds have been demonstrated against *L. donovani* responsible for visceral leishmaniasis.

In this present study Pt (**9**) and Pd (**7**) complexes showed good anti-promastigote activity having $IC_{50}$ values 0.59±0.100 µg/mL and 0.56±0.10 µg/mL respectively (Table 3, Fig. 5). Pt and Pd containing compound showed 80% parasitic inhibition at 50 µg/mL and on visual observation it showed loss of flagellum, rounded morphology with substantial reduction in size as compared to control promastigotes, cell shrinkage and cell condensation may be cause of apoptosis, which may be possible cause of cell death, an exerted effect of Pt (**9**) and Pd (**7**) complex compounds. Anti-amastigote activity of these compounds has $IC_{50}$ 0.85±0.272 and 1.99±0.08 µg/mL respectively (Table 3, Fig. 5). Cytotoxicity assay on both the compounds showed toxicity on promastigotes but less toxicity against RAW 264.7 cell lines at different concentration (Table 3). This selectivity assay showed that the action of the compounds is specific for the protozoans and is not toxic for mammalian cells.

On the basis of their biological activities these compounds show potent leishmanicidal activity which may provide promising lead against leishmaniasis.

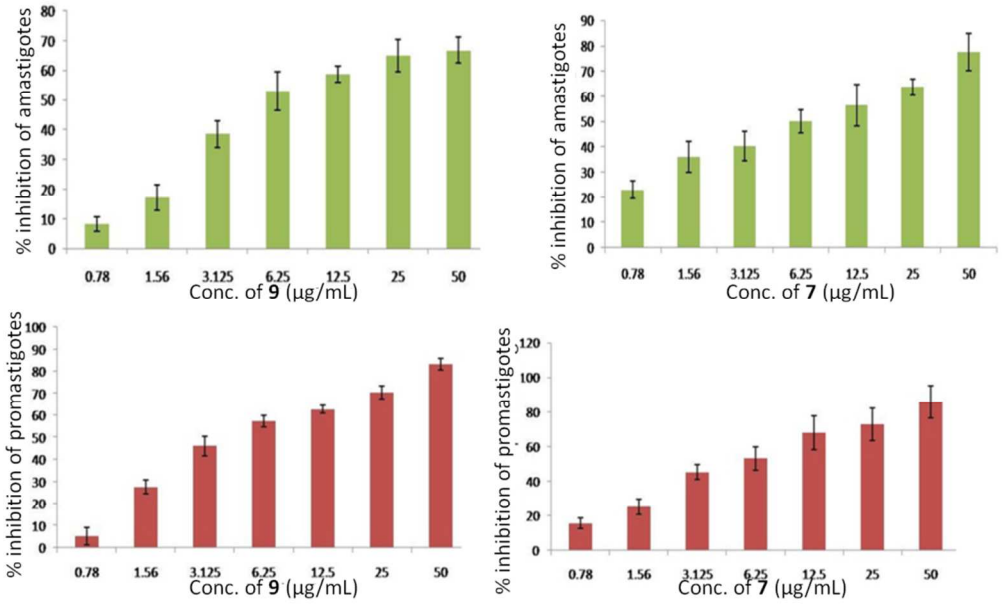


Fig.5 (a) Percentage inhibition in intracellular amastigote at different drug (complex **9**) concentrations range (0.78 µg/mL-50 µg/mL). (b) Percentage inhibition in intracellular amastigote at different drug (complex **7**) concentration range (0.78 µg/mL-50 µg/mL). (c) Percentage inhibition in promastigote at different drug (complex **9**) concentration range (0.78 µg/mL-50 µg/mL). (d) Percentage inhibition in promastigote on different drug (complex **7**) concentration range (0.78 µg/mL-50 µg/mL).

Table 3 Antileishmanial activity of compounds.

| Compound | mw | $IC_{50}$(μg/mL) ±SD on promastigote forms of *L. donovani* | $IC_{50}$(μg/mL) ±SD on *L. donovani* intra-macrophage amastigotes forms | $CC_{50}$ (μg/mL) ±SD on RAW 264.7 macrophage (μg/mL) | SI ($CC_{50}/IC_{50}$ of intramacrophage amastigotes forms) |
|---|---|---|---|---|---|
| $C_{20}H_{16}$ Pt $BrO_2S_4$ **9** | 771.47 | 0.59±0.100 | 0.85±0.272 | 41.58±5.10 | 48.91 |
| $C_{28}H_{22}PdO_2S_4$ **7** | 625.14 | 0.56±0.10 | 1.99±0.08 | 31.68±11.80 | 15.91 |
| Miltefosine | | - | 10.23±5.04 | 58.41±0.38 | 5.70 |

SI= Selectivity Index (SI defined by the ratio of $CC_{50}$ in RAW cells/$IC_{50}$ in intracellular *Leishmania* amastigotes).

## Conclusions

Out of twelve **1-12** new fully characterized planar cis-chelated β-oxodithioester ligand complexes of Ni(II), Pd(II) and Pt(II), **7** and **9** formed with distinctly soft Pd(II) and Pt(II) and the ligands L3 and L1 having naphthyl and Br substituents showed efficient anti-leishmanial activity against both forms of *L. donovani* parasite that causes visceral leishmaniasis. These compounds were also found less cytotoxic at different concentrations on RAW264.7 cells. The crystal structures of **2-4**, **8** and **11** revealed distorted square planar geometry about the metal centres. The Pd and Pt complexes showed luminescent characteristic in $CH_2Cl_2$ solution originating from metal perturbed ILCT state. This study demonstrates the scope of the metal complexes with a wider range of functionalized β-oxodithioester ligands for their possible applications as anti-leishmanial agents.

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*†Electronic Supplementary Information (ESI) available: [$^1$H NMR for ligand and weak interactions table ]. See DOI: 10.1039/b000000x/*

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