DNA Binding and Anti-Cancer Activity of Redox-Active Heteroleptic *Piano-Stool* Ru(II), Rh(III) and Ir(III) Complexes containing 4-(2-Methoxypyridyl)-phenyldipyrromethene

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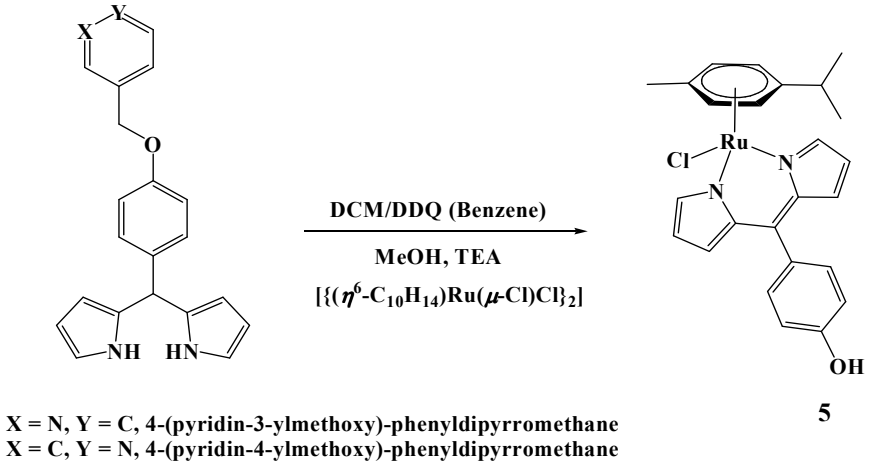
Contents

Synthesis of 4-(pyridin-3-ylmethoxy)-phenyldipyrromethane. It was prepared following the procedure for 4-(pyridin-2-ylmethoxy)-phenyldipyrromethane except that 4-(pyridin-3-ylmethoxy)-benzaldehyde (2.13 g, 10.0 mmol) was used in place of 4-(pyridin-2-ylmethoxy)-benzaldehyde (2.13 g, 10.0 mmol). Yield: 70% (2.29 g). Anal. Calc for $C_{21}H_{17}N_3O$, requires: C, 77.28; H, 4.94; N, 12.87. Found C, 77.18; H, 4.87; N, 12.89%. ^{1}H NMR ($CDCl_3$, δ ppm): 5.18 (s, 2H, OC*H*$_2$), 5.41 (s, 1H, C*H*, *meso*), 5.87 (s, 2H, pyrrolic), 6.14 (d, 2H, *J* = 3.0 Hz, pyrrolic), 6.70 (s, 2H, pyrrolic), 6.92 (m, 2H, phenyl), 7.15 (m, 1H, pyridyl), 7.27 (d, 2H, *J* = 10.2 Hz, phenyl), 7.64 (t, 1H, pyridyl), 7.96 (d, 2H, *J* = 8.1 Hz, phenyl), 8.15 (bs, 2H, N*H*, pyrrolic), 8.53 (d, 1H, *J* = 4.2 Hz, pyridyl). ^{13}C NMR ($CDCl_3$ δ ppm): 43.9 (C-5), 67.6 (C-10), 107.5 (C-2), 108.5 (C-3), 117.5 (C-1), 121.2 (C-4), 121.8 (C-11), 128.4 (C-7), 128.8 (C-8), 129.9 (C-6), 131.6 (C-12), 136.6 (C-13), 147.4 (C-14), 149.2 (C-15), 166.9 (C-9). IR (KBr pellets, cm^{-1}; % T): 584 (58), 671 (53), 735 (29), 823 (54), 999 (56), 1033 (36, *v*C-O$_{aliphatic}$), 1148 (54), 1219 (27, *v*C-O$_{aromatic}$), 1344 (36, *v*C=C$_{pyrrolic}$), 1389 (45, *v*C=C$_{pyridyl}$), 1545 (34, *v*C=N$_{pyrrolic}$), 1610 (27, *v*C=N$_{pyridyl}$), 1655 (45).

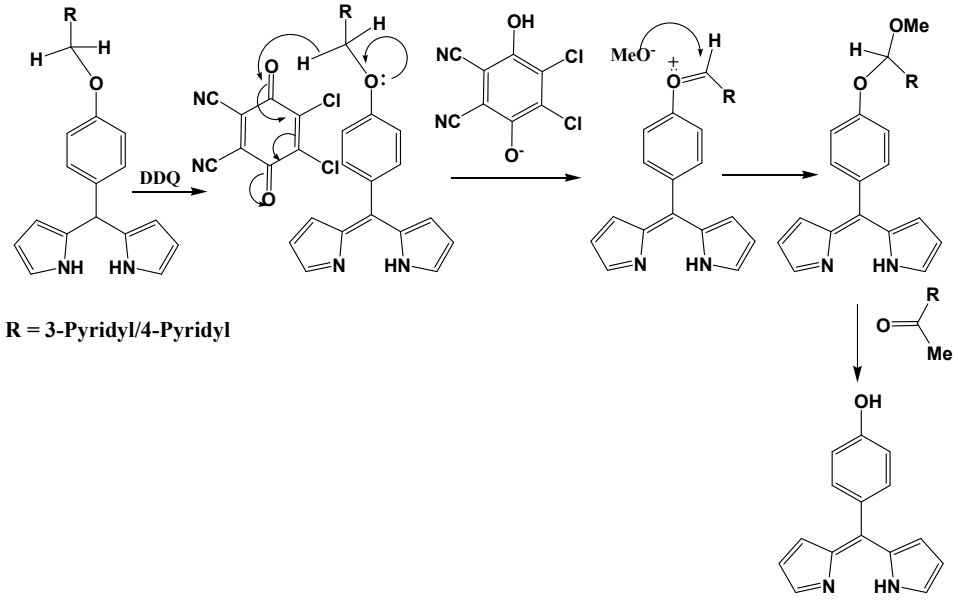
Synthesis of 4-(pyridin-4-ylmethoxy)-phenyldipyrromethane. It was prepared following the procedure for 4-(pyridin-2-ylmethoxy)-phenyldipyrromethane except that 4-(pyridin-4-ylmethoxy)-benzaldehyde (2.13 g, 10.0 mmol) was used in place of 4-(pyridin-2-ylmethoxy)-benzaldehyde (2.13 g, 10.0 mmol). Yield: 75% (2.46 g). ^{1}H NMR ($CDCl_3$, δ ppm): 5.07 (s, 2H, OC*H*$_2$), 5.43 (s, 1H, C*H*, *meso*), 5.89 (s, 2H, pyrrolic), 6.15 (d, 2H, *J* = 9.0 Hz, pyrrolic), 6.69 (s, 2H, pyrrolic), 6.89 (d, 2H, *J* = 8.4 Hz, phenyl), 7.14 (d, 2H, *J* = 8.4 Hz, phenyl), 7.34 (d, 2H, *J* = 8.4 Hz, pyridyl), 7.91 (bs, 2H, N*H*, pyrrolic), 8.59 (d, 1H, *J* = 6.9 Hz, pyridyl). ^{13}C NMR ($CDCl_3$, δ ppm): 43.5 (C-5), 68.5 (C-10), 107.0 (C-2), 108.8 (C-3), 114.2 (C-8), 118.0 (C-1), 129.0 (C-7a), 131.0 (C-6), 131.9 (C-7b), 135.5 (C-12), 147.2 (C-15), 151.2 (C-11), 154.1 (C-13), 157.7 (C-14), 161.6 (C-9). IR (KBr pellets, cm^{-1}; % T): 586 (56), 670 (48), 733 (20), 820 (50), 997 (54), 1032 (32, *v*C-O$_{aliphatic}$), 1143 (42), 1210 (23, *v*C-O$_{aromatic}$), 1340 (34, *v*C=C$_{pyrrolic}$), 1379 (42, *v*C=C$_{pyridyl}$), 1543 (32, *v*C=N$_{pyrrolic}$), 1603 (22, *v*C=N$_{pyridyl}$), 1649 (45).

Synthesis of [(η^6-$C_{10}H_{14}$)RuCl(4-OH-pdpm)] (5). It was prepared following the procedure for **2** except that 4-(3-methoxypyridyl)-phenyldipyrromethane (0.328 g, 1.0 mmol) was used in place of 4-(2-methoxypyridyl)-phenyldipyrromethane (0.328 g, 1.0 mmol). Yield: 25% (0.130

g). Anal. Calc for $C_{25}H_{25}ClN_2ORu$: requires: C, 59.34; H, 4.98; N, 5.54. Found: C, 59.27; H, 5.01; N, 5.51%. ^{1}H NMR ($CDCl_3$, δ ppm): 1.07 (d, 6H, J = 6.6 Hz, *p*-cymene $CH(CH_3)_2$), 2.11 (s, 3H, *p*-cymene CH_3), 2.43 (m, 1H, *p*-cymene $CH(CH_3)_2$), 5.28 (s, 4H, *p*-cymene C_6H_4), 5.70 (s, 2H, pyrrolic), 6.48 (s, 2H, pyrrolic), 6.73 (d, 2H, J = 4.2 Hz, pyrrolic), 6.83 (s, 2H, phenyl), 7.14 (s, 2H, phenyl), 7.99 (s, 1H, phenol). ^{13}C NMR ($CDCl_3$, δ ppm): 12.2 (*p*-cymene CH_3), 22.9 (*p*-cymene $CH(CH_3)_2$), 29.8 (*p*-cymene $CH(CH_3)_2$), 43.5 (C-5), 84.4, 84.6, 100.2 101.9 (ring C_6H_4) (*p*-cymene), 107.0 (C-2), 108.4 (C-3), 115.6 (C-1), 117.2 (C-4), 128.9 (C-6), 132.7 C-7, 142.2 (C-8), 191.0 (C-9).



Scheme S1. Synthesis of complexes of **5**

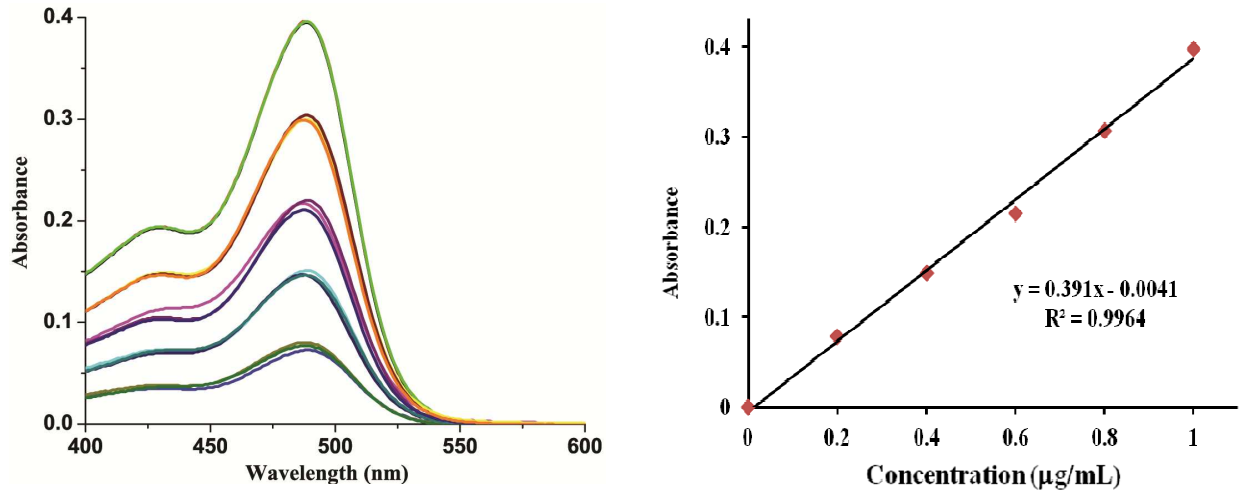


Scheme S2. Tentative cleavage mechanism of 4-(3-methoxypyridyl)-phenyldipyrromethene or 4-(4-methoxypyridyl)-phenyldipyrromethene.

It has been observed that the reaction between chloro bridged ruthenium complexes [{(η^6-arene)Ru(μ-Cl)Cl}$_2$] (η^6-arene = C_6H_6, $C_{10}H_{14}$) and structurally analogous rhodium/iridium dimers [{(η^5-C_5Me_5)M(μ-Cl)Cl}$_2$] [M = Rh, Ir] with 4-(pyridin-2-ylmethoxy)-phenyl-dipyrromethane with DDQ in CH_2Cl_2/CH_3OH (1:1, v/v) in presence of triethylamine at rt gave neutral heteroleptic dipyrrinato complexes [(η^6-arene)RuCl(2-pcdpm)] and [(η^5-C_5Me_5)MCl-(2-pcdpm)] (η^6-arene = C_6H_6, **1**; $C_{10}H_{14}$, **2**; M = Rh, **3**; Ir, **4**). Conversely, 4-(pyridin-3-ylmethoxy)-phenyldipyrromethane and 4-(pyridin-4-ylmethoxy)-phenyldipyrromethane undergo etheratic (C-O-C) bond cleavage with representative precursor [{(η^6-$C_{10}H_{14}$)Ru(μ-Cl)Cl}$_2$] leads to formation of the same complex [(η^6-$C_{10}H_{14}$)RuCl(4-OH-pdpm)], **5**. It is well known that such a ethers i.e. benzyl ethers and naphthylmethyl ethers have been acting as protecting groups in organic synthesis owing to their facile oxidative cleavage with either dichlorodicyanoquinone (DDQ) or ceric ammonium nitrate (CAN).[1] Based on the evidences one may propose a reaction mechanism for cleavage of ether bond (Scheme S2). Initially, one of the benzylic hydrogen was abstracted by DDQ to form the benzylic cation. Further, nucleophilic methoxide ion (MeO^-) attacks to the electrophilic carbon centre results in the formation of unstable intermediate which undergoes hydrolytic cleavage to form phenol and ketone. In contrary, the *insitu* oxidised species 2-pcdpm did not undergo etheratic bond cleavage which may be associated to the steric hindrance of the lone pairs of N (pyridyl) and oxygen (C-O-C, etheratic).

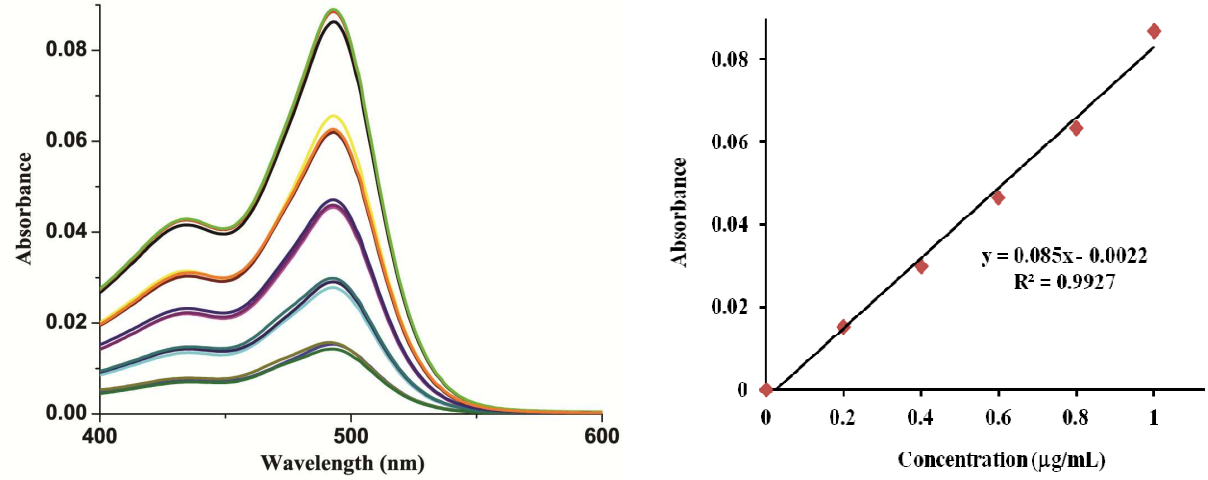
References:

1. (a) Crich, D.; Xia, O. V. *J. Org. Chem*. **2007**, *72*, 3581. (b) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833. (c) Lam, T. B. T.; Kadoya, K.; Iiyama, K. *Phytochemistry* **2001**, *57,* 987. (d) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169. (e) Liao, W.; Locke, R. D.; Matta, K. L. *Chem. Commun.* **2000**, 369. (f) Wuts, P. G. M. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, **2005**; pp 425-428. (g) Csavas, M.; Szabo, Z. B.; Borbas, A.; Liptak, A. In *Handbook of Reagents for Organic Synthesis: Reagents for Glycoside, Nucleotide, and Peptide Synthesis*; Crich, D., Ed.; Wiley: Chichester, **2005**; pp 459-460. (h) Greene, T. W.; Wuts, P. G. M. *Protecti*V*e Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**. (i) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, **2005**. (i) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033.



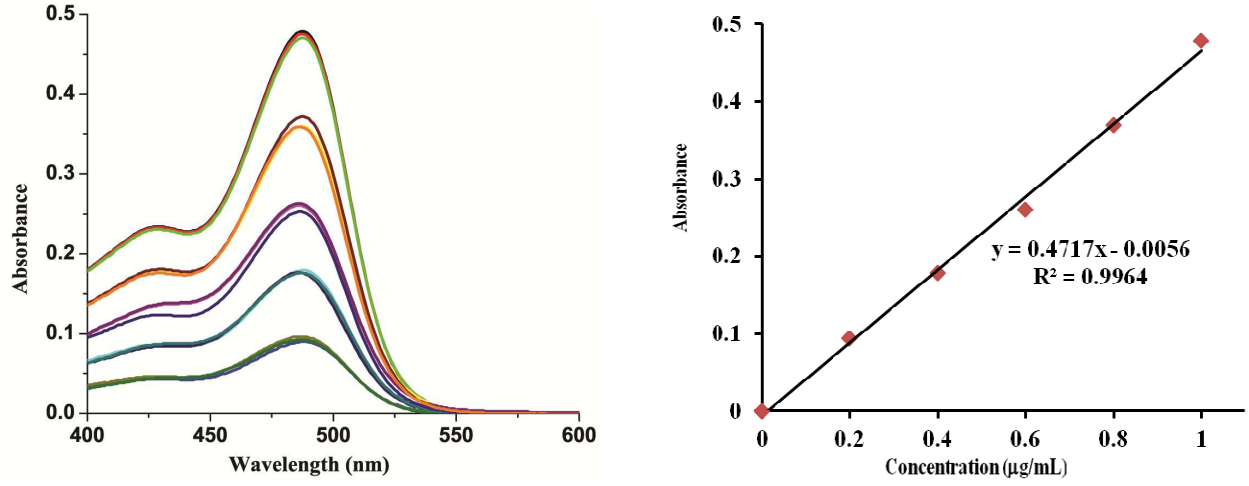
(a) (b)

Figure S1. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **1** (b) the calibration curve in *n*-octanol at ~ 487 nm



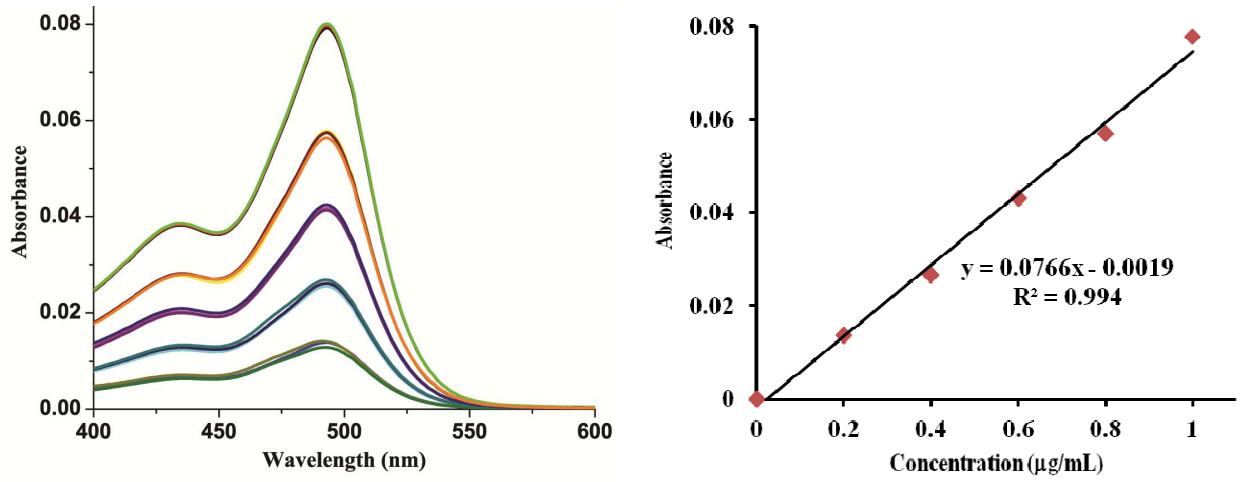
(a) (b)

Figure S2. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **1** (b) the calibration curve in water at ~ 492 nm



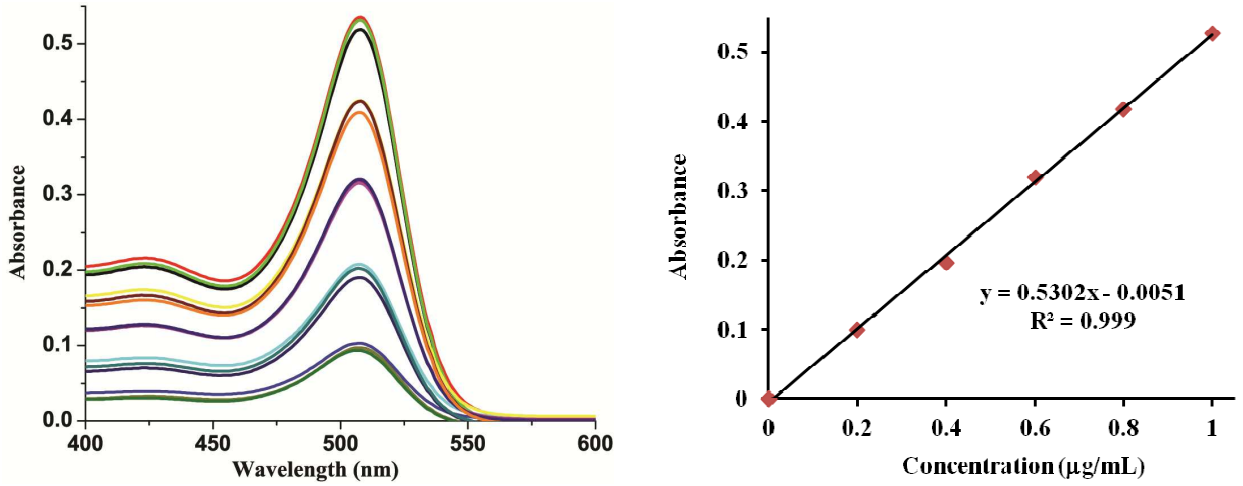
(a) (b)

Figure S3. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **2** (b) the calibration curve in *n*-octanol at ~ 489 nm



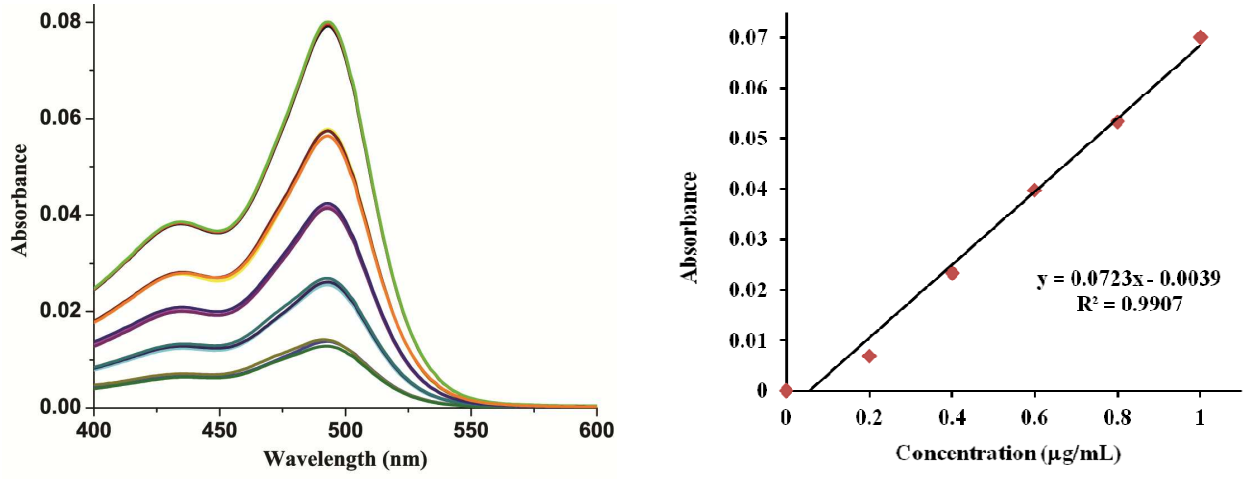
(a) (b)

Figure S4. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **2** (b) the calibration curve in water at ~ 493 nm



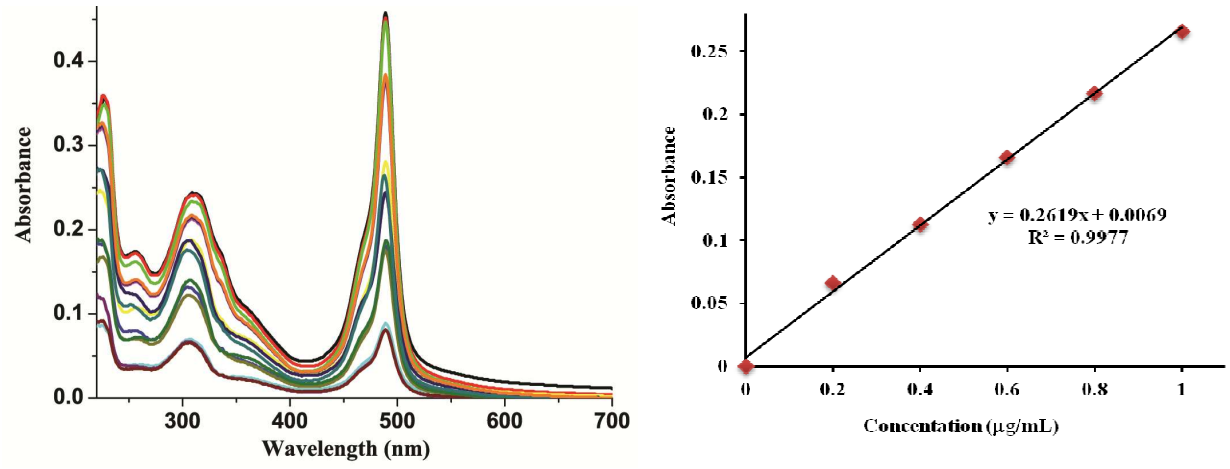
(a) (b)

Figure S5. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **3** (b) the calibration curve in *n*-octanol at ~ 507 nm



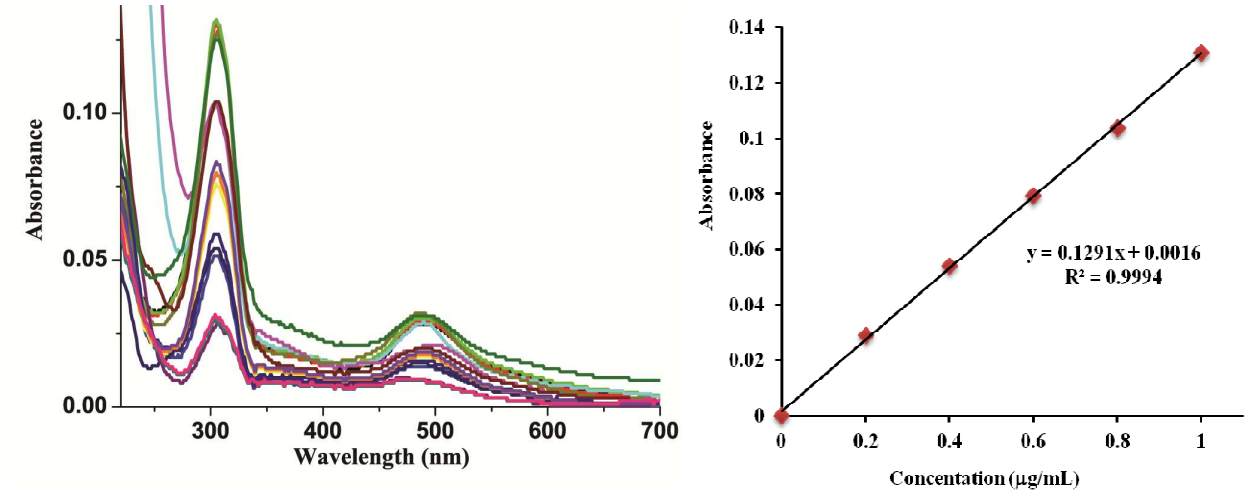
(a) (b)

Figure S6. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **3** (b) the calibration curve in water at ~ 498 nm



(a) (b)

Figure S7. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **4** (b) the calibration curve in *n*-octanol at ~ 309 nm



(a) (b)

Figure S8. Spectroscopic determination of lipophilicity (a) the absorption spectra upon varying concentration (2, 4, 6, 8, 10 μg/ml) of **4** (b) the calibration curve in water at ~ 305 nm

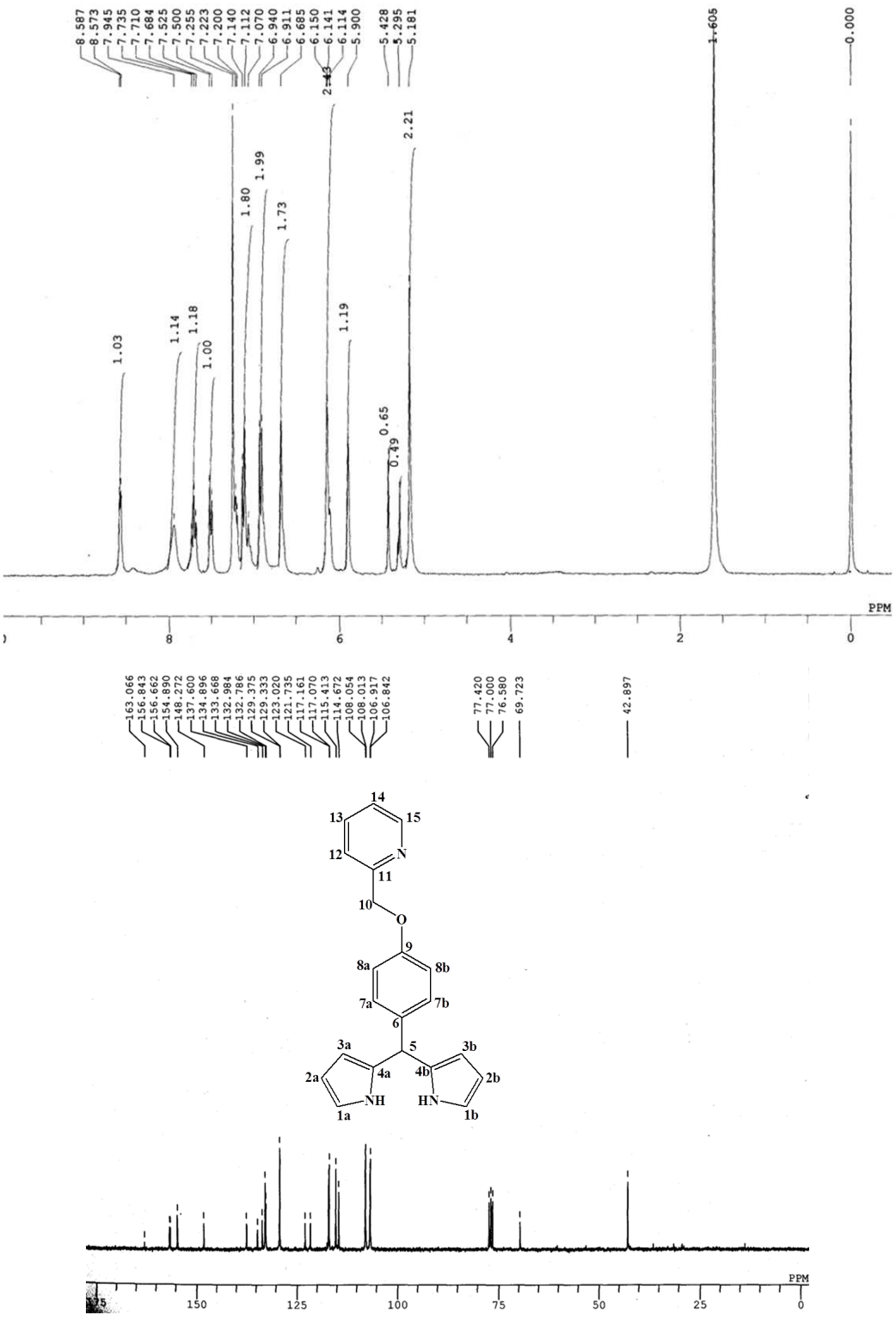


Figure S9. ^{1}H (top) and ^{13}C NMR (bottom) spectra of 4-(pyridin-2-ylmethoxy)-phenyldipyrromethane in $CDCl_3$

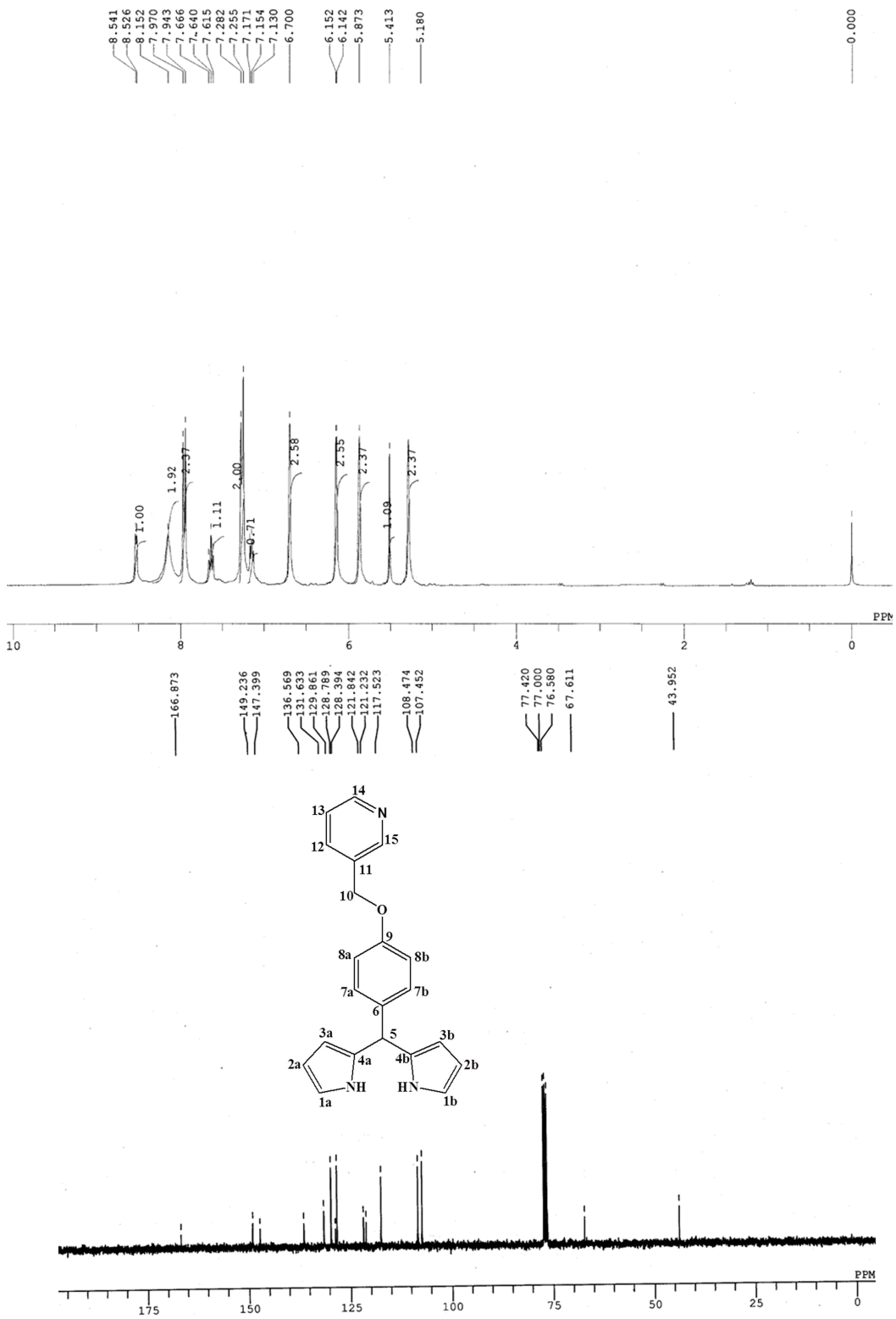


Figure S10. ^{1}H (top) and ^{13}C NMR (bottom) spectra of 4-(pyridin-3-ylmethoxy)-phenyldipyrromethane in $CDCl_3$

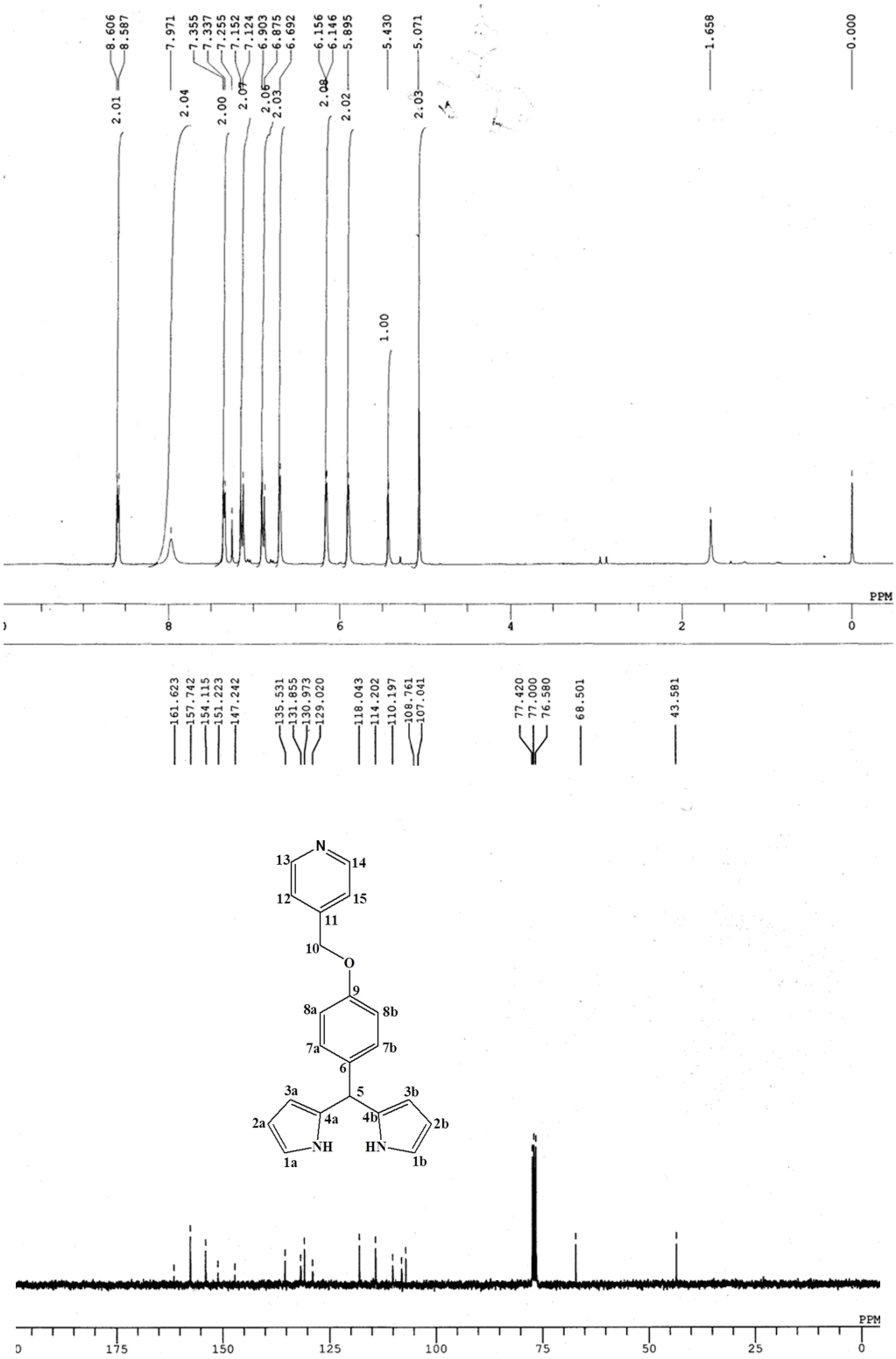


Figure S11. ^{1}H (top) and ^{13}C NMR (bottom) spectra of 4-(pyridin-4-ylmethoxy)-phenyldipyrromethane in $CDCl_3$

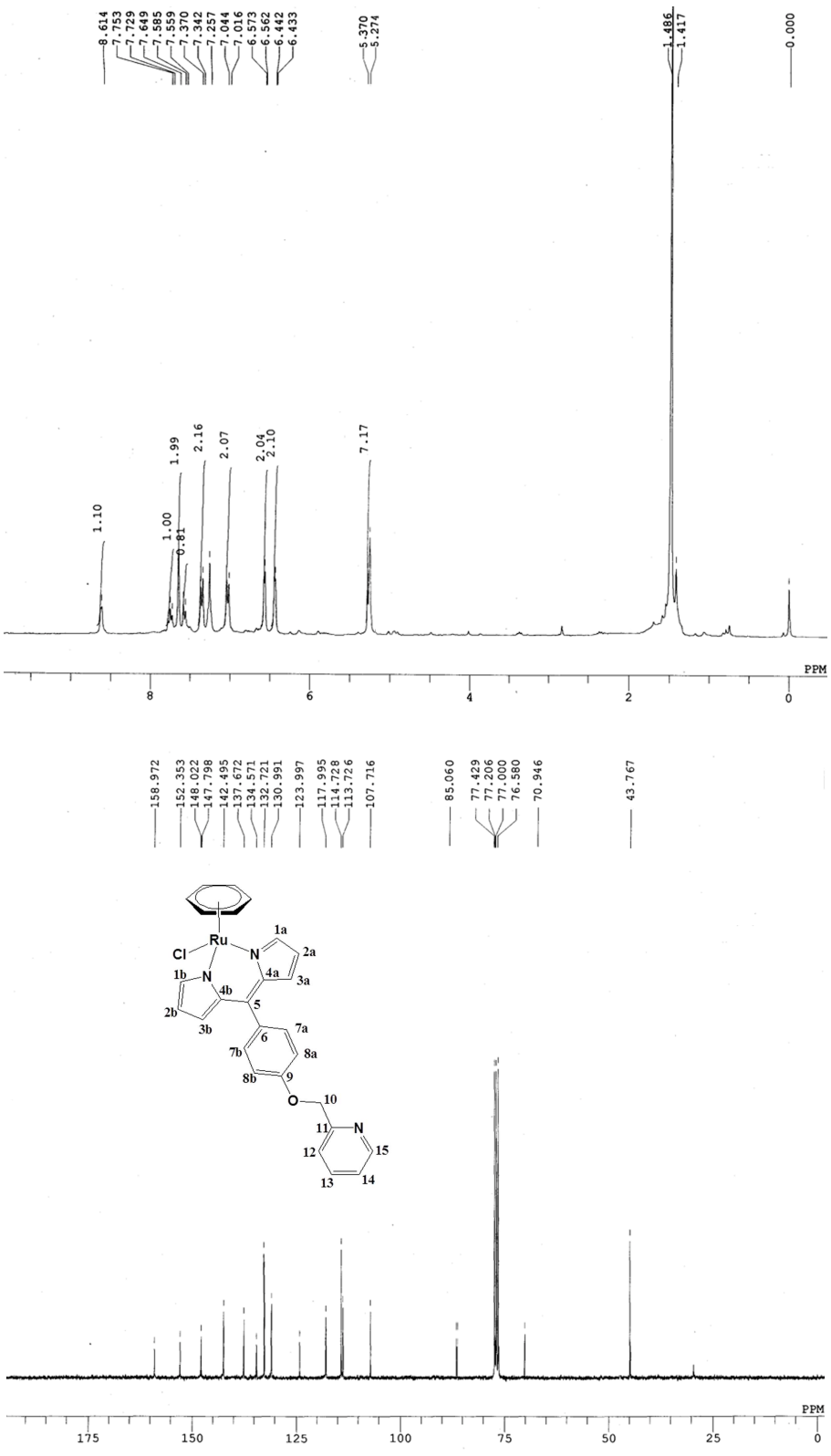


Figure S12. ^{1}H (top) and ^{13}C NMR (bottom) spectra of **1** in $CDCl_3$

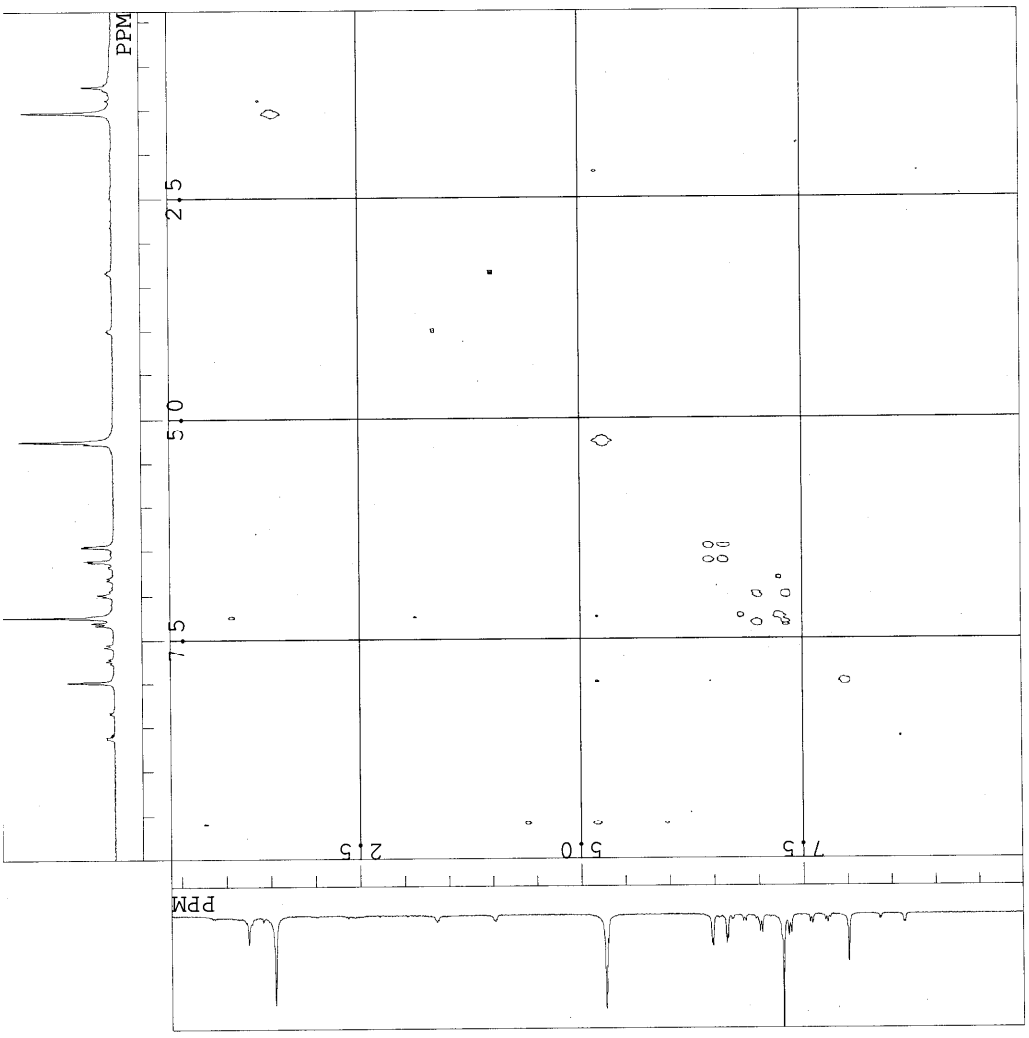


Figure S13. ^{1}H-^{1}H (COSY) NMR spectra of **1** in $CDCl_3$

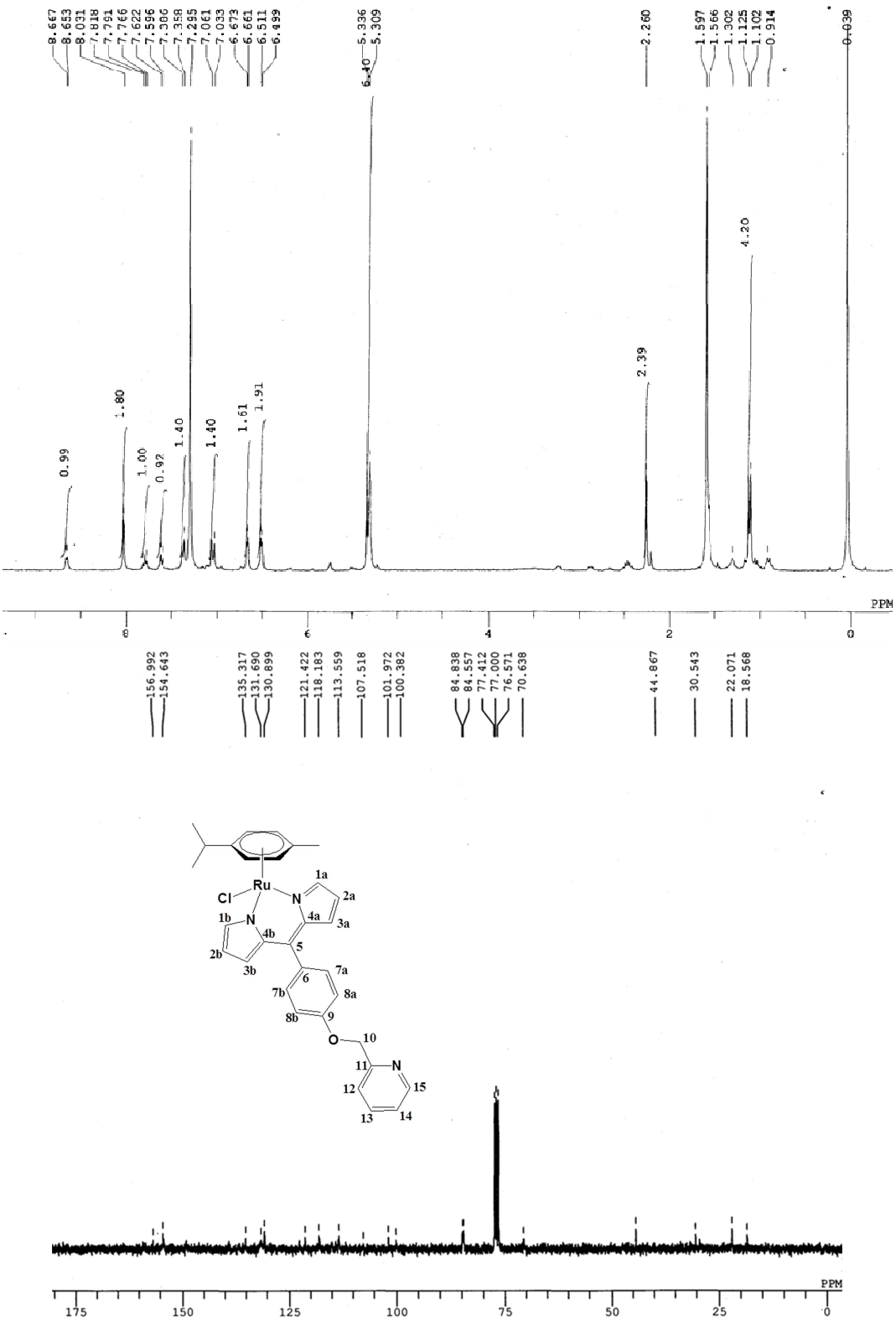


Figure S14. ^{1}H (top) and ^{13}C NMR (bottom) spectra of **2** in $CDCl_3$

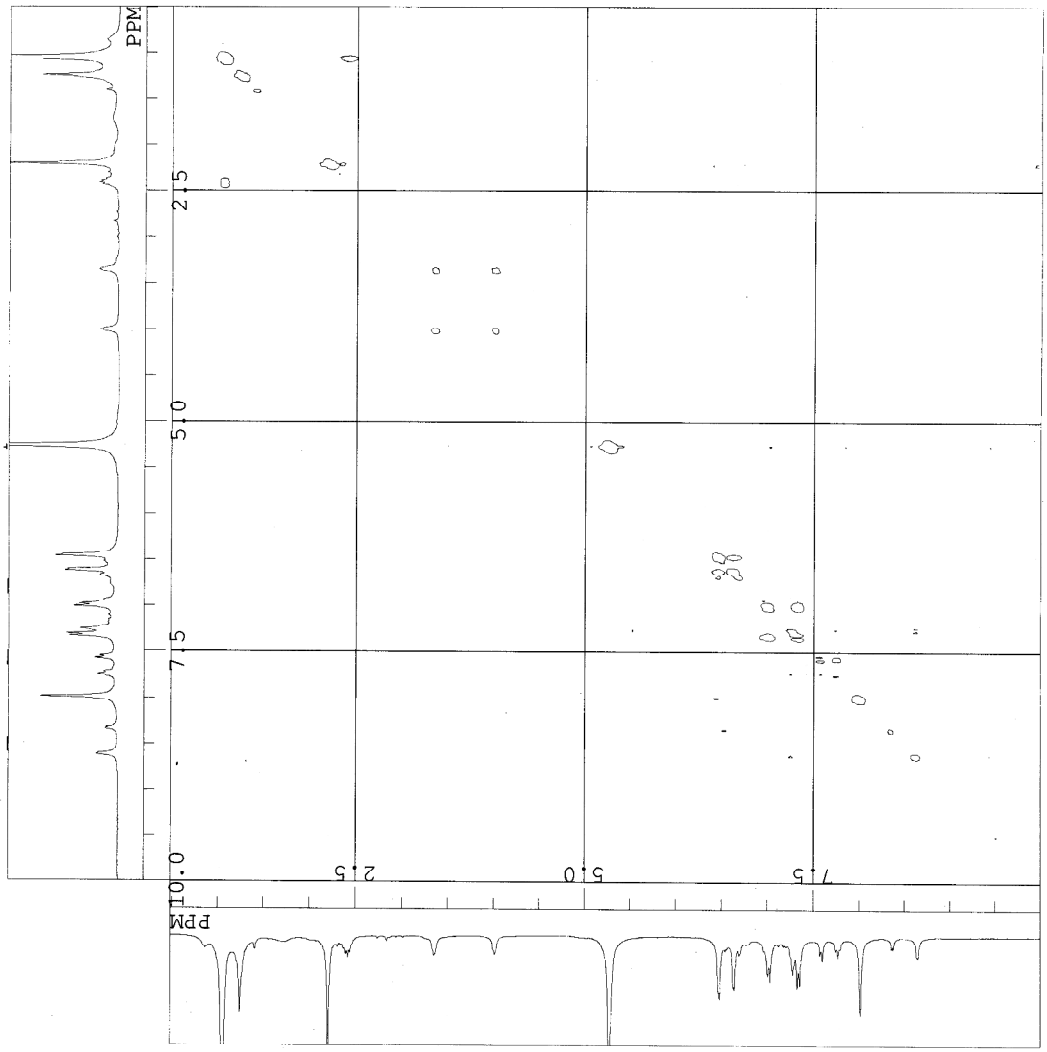


Figure S15. ^{1}H-^{1}H (COSY) NMR spectra of **2** in $CDCl_3$

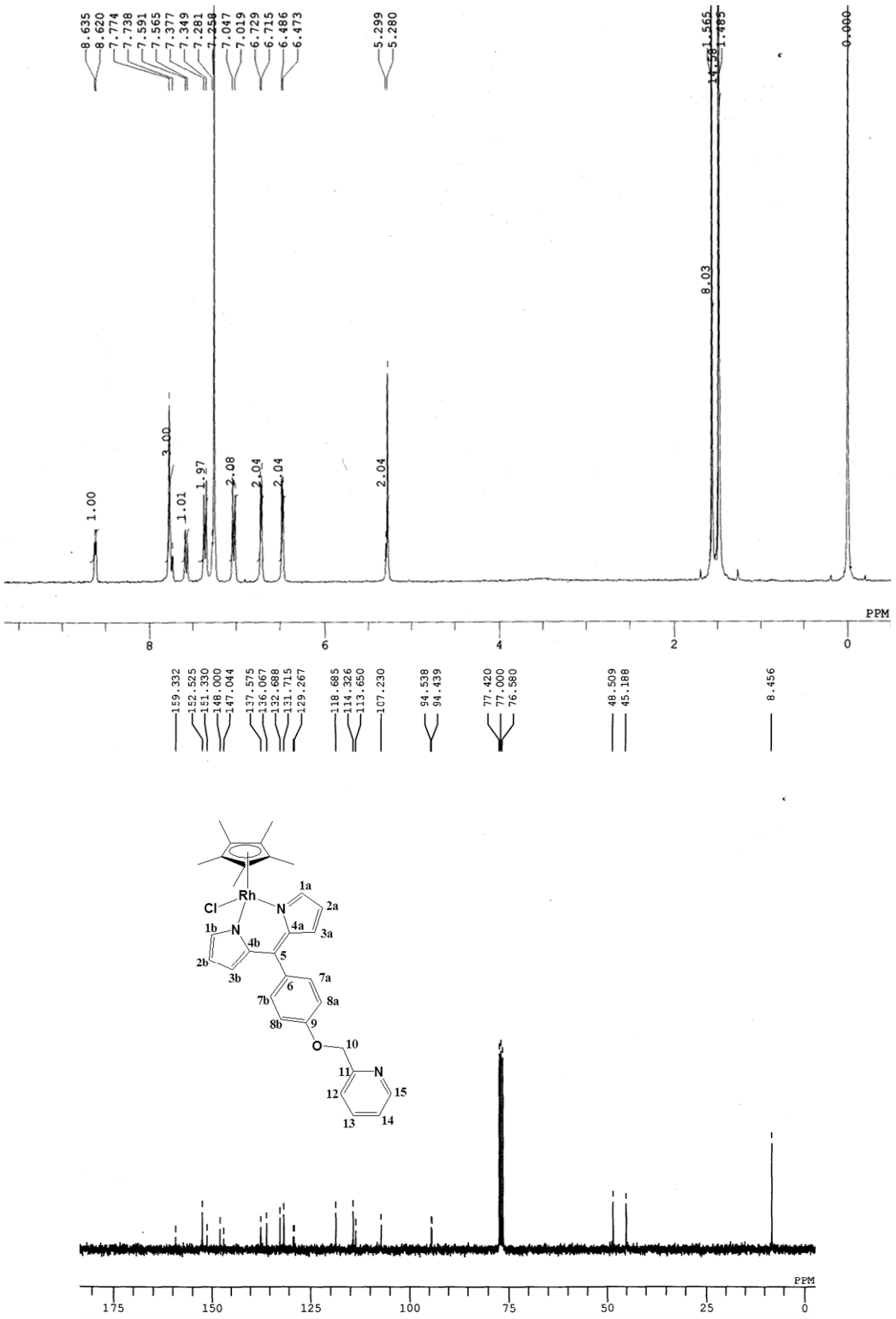


Figure S16. ^{1}H (top) and ^{13}C NMR (bottom) spectra of **3** in $CDCl_3$

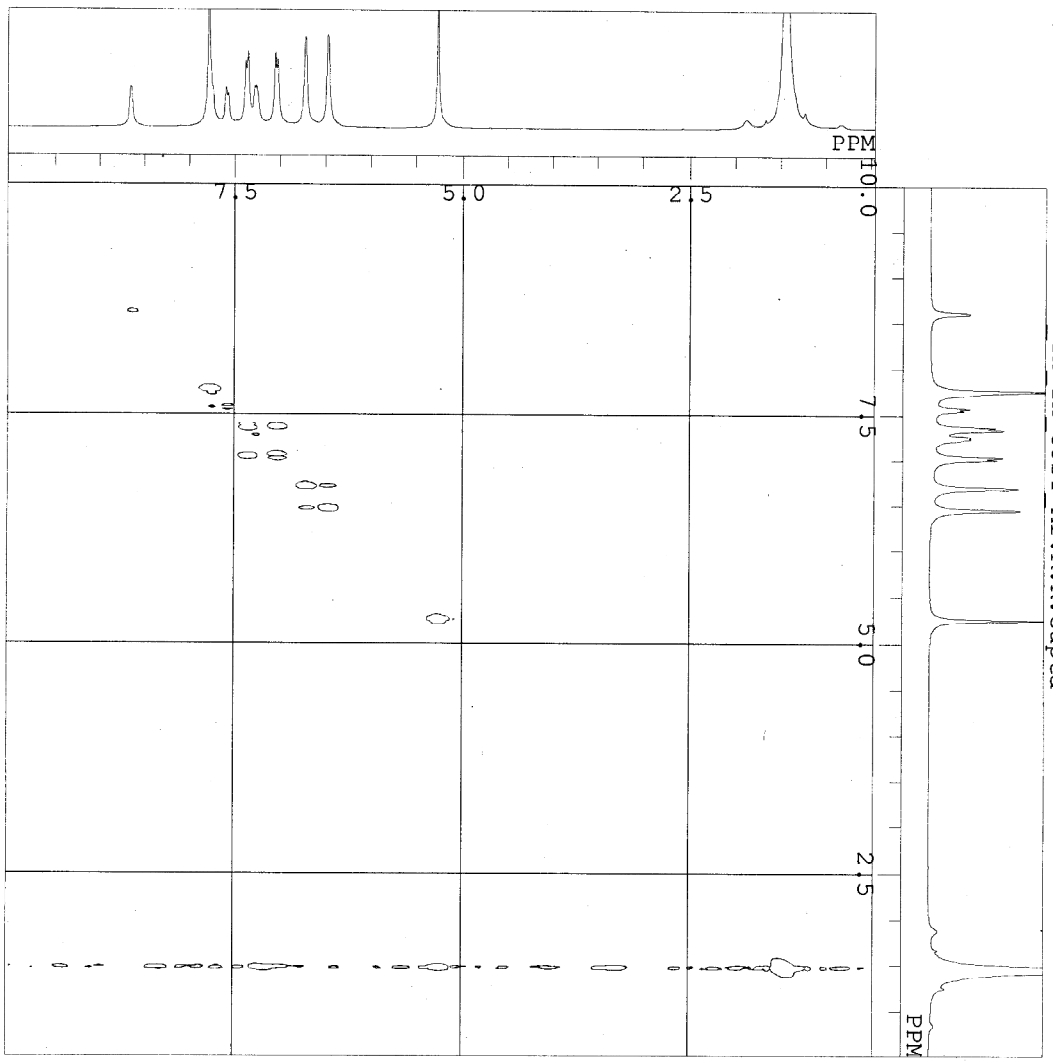


Figure S17. ^{1}H-^{1}H (COSY) NMR spectra of **3** in $CDCl_3$

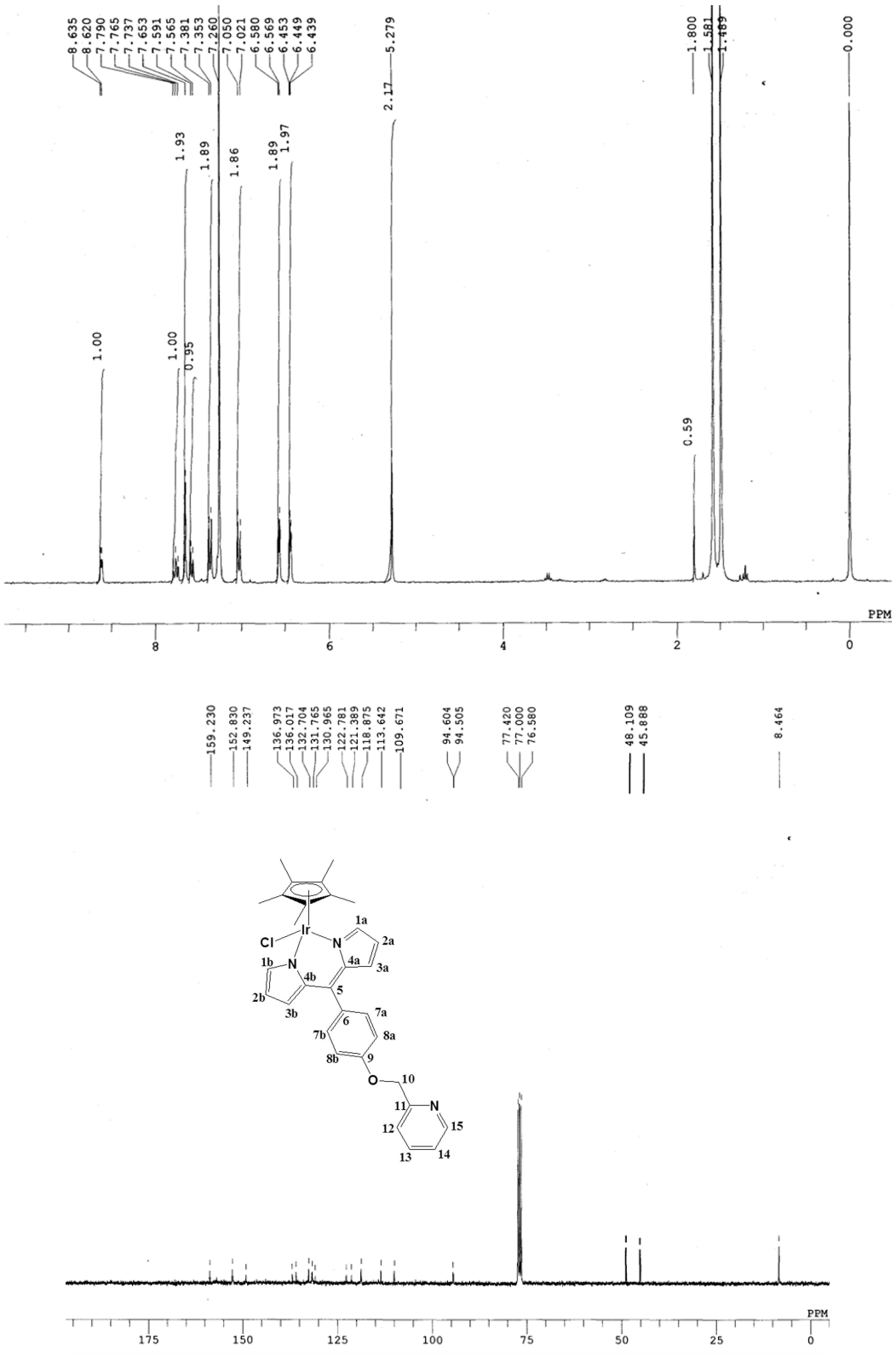


Figure S18. ^{1}H (top) and ^{13}C NMR (bottom) spectra of **4** in $CDCl_3$

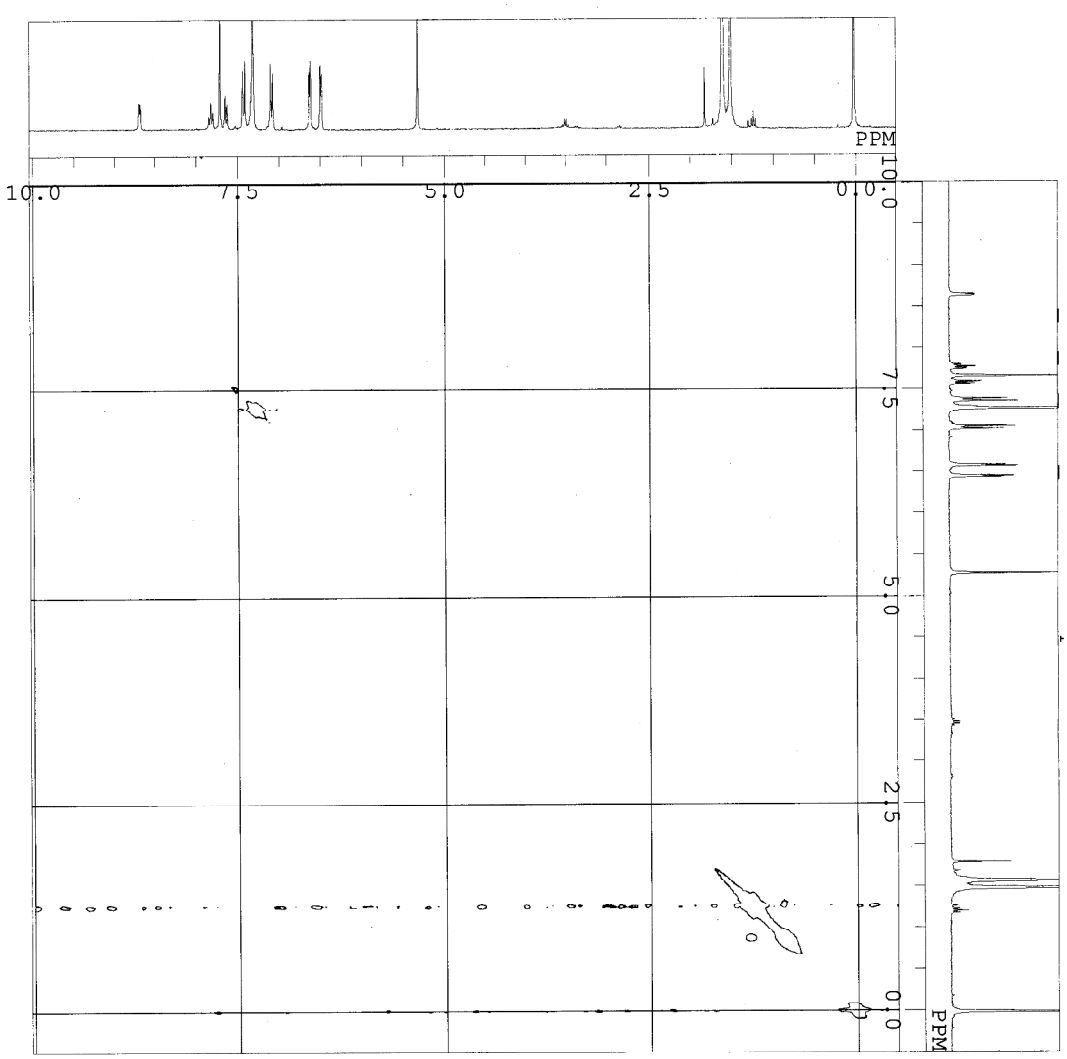


Figure S19. ^{1}H-^{1}H (COSY) NMR spectra of **4** in $CDCl_3$

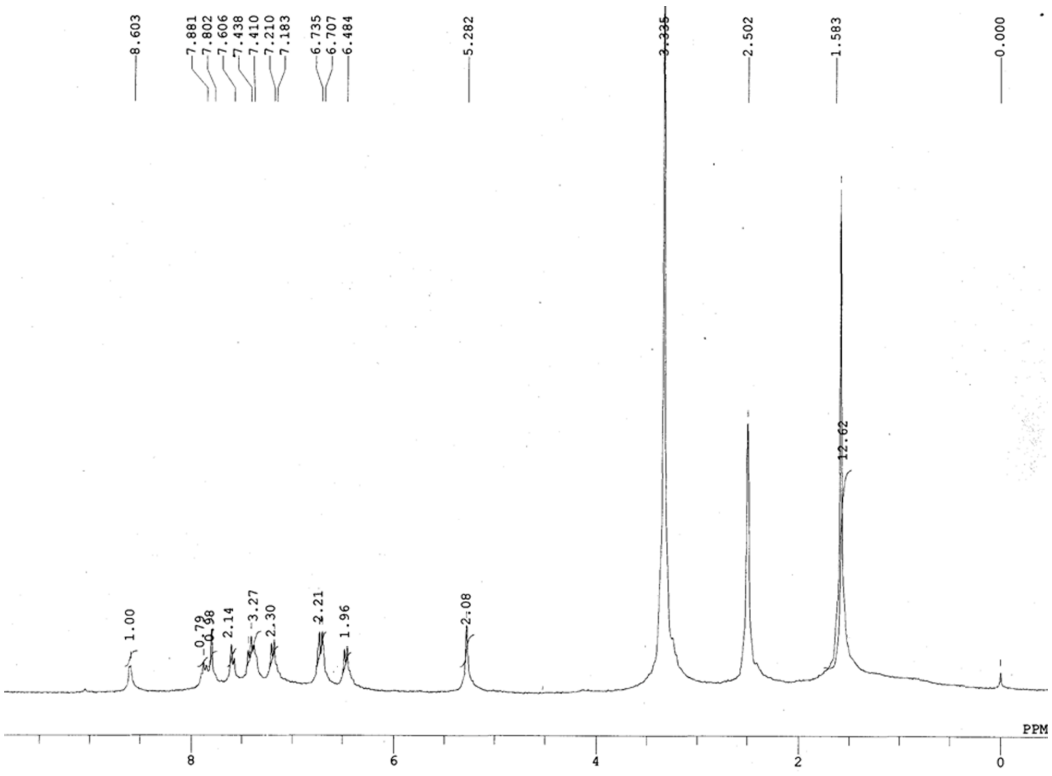


Figure S20. [1]H-NMR spectra of **4** in DMSO-*d*6

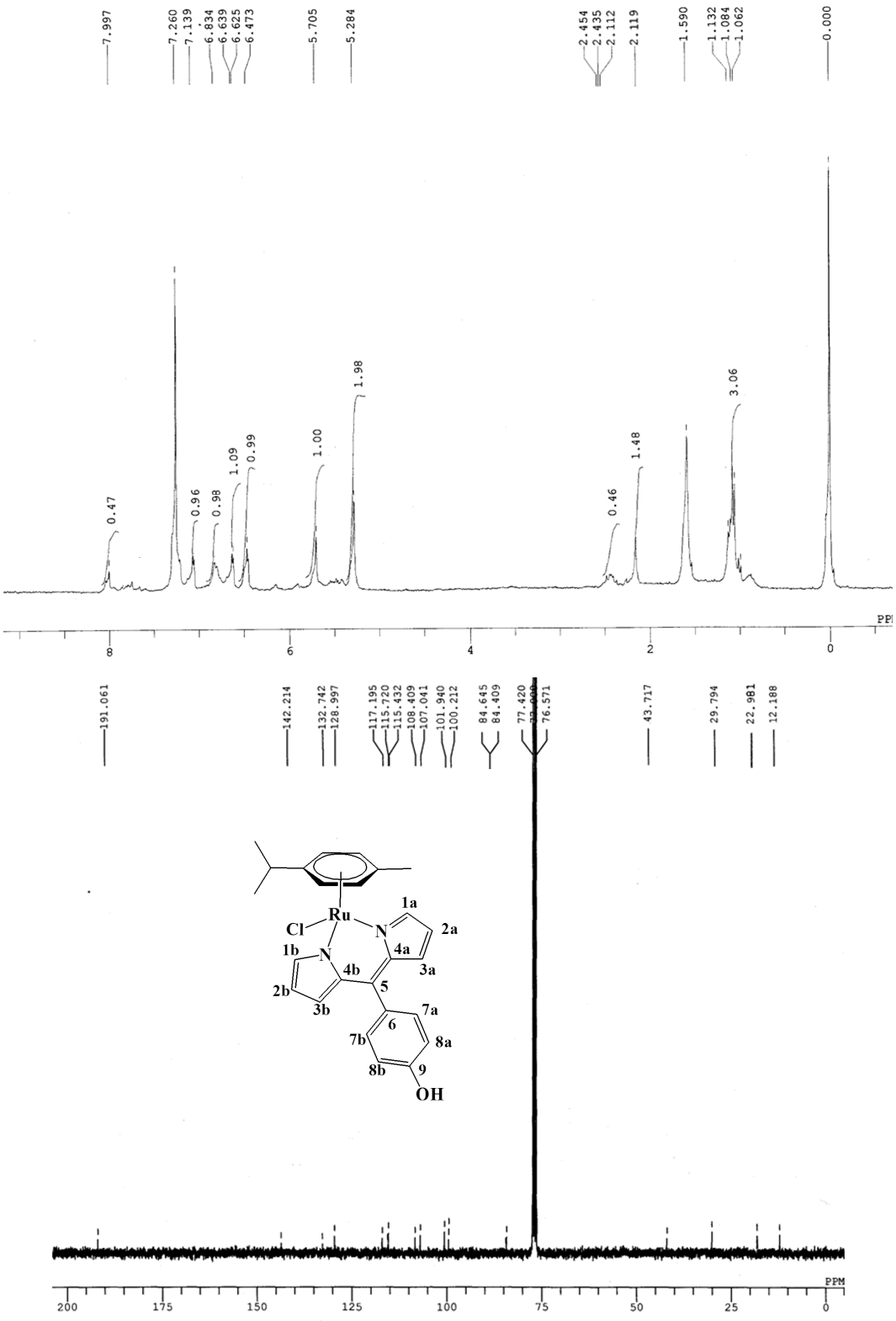
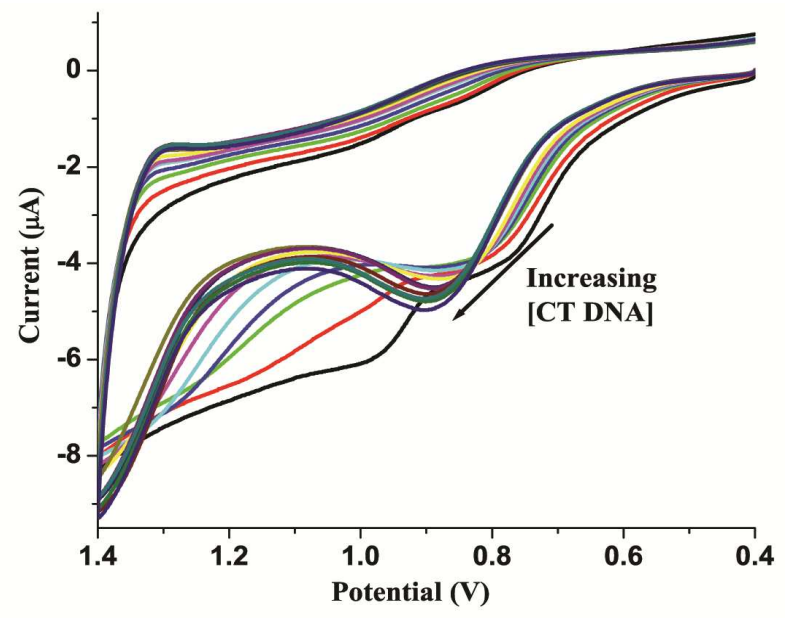
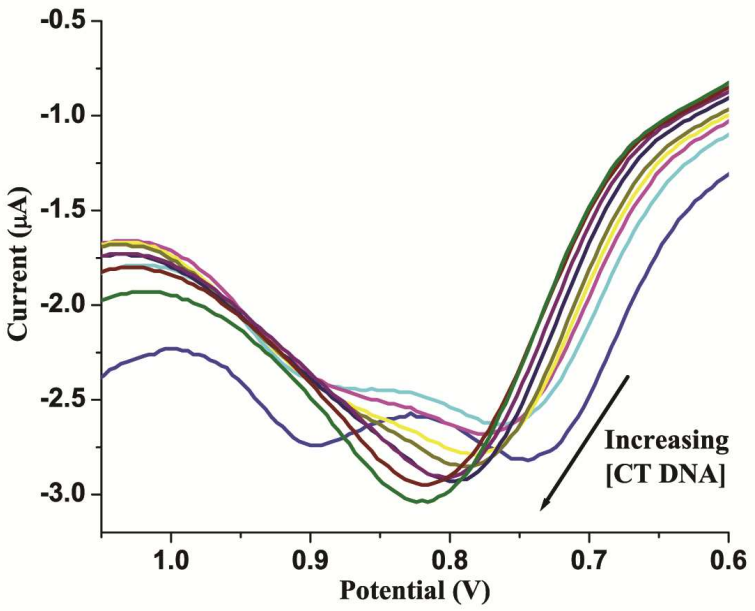


Figure S21. ^{1}H (top) and ^{13}C NMR (bottom) spectra of **5** in $CDCl_3$

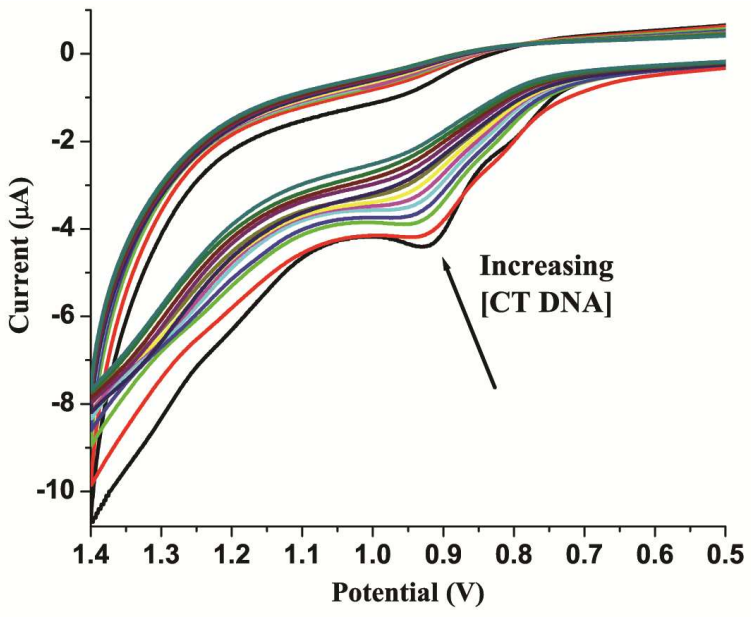


(a)

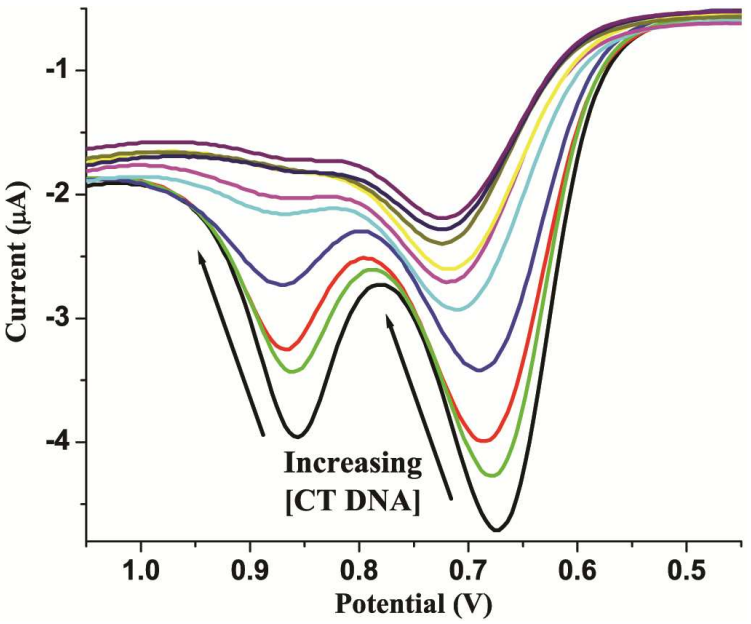


(b)

Figure S22. Evolution of the CV (a) and DPV (b) of **2** (*c*, 100 μM, MeCN) in presence of (0.0-1.0 μM CT DNA) at room temperature



(a)



(b)

Figure S23. Evolution of the CV (a) and DPV (b) of **3** (*c*, 100 μM, MeCN) in presence of (0.0-1.0 μM CT DNA) at room temperature

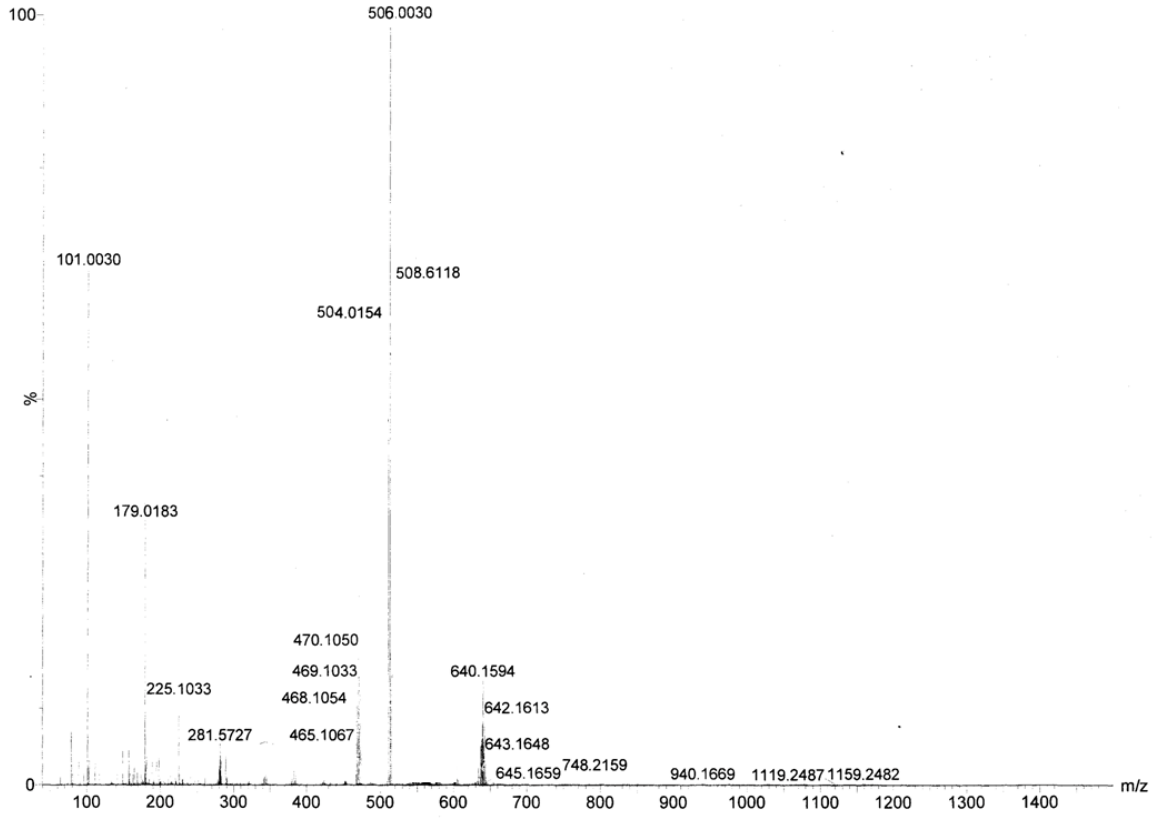


Figure S24. ESI-MS spectra of **1**

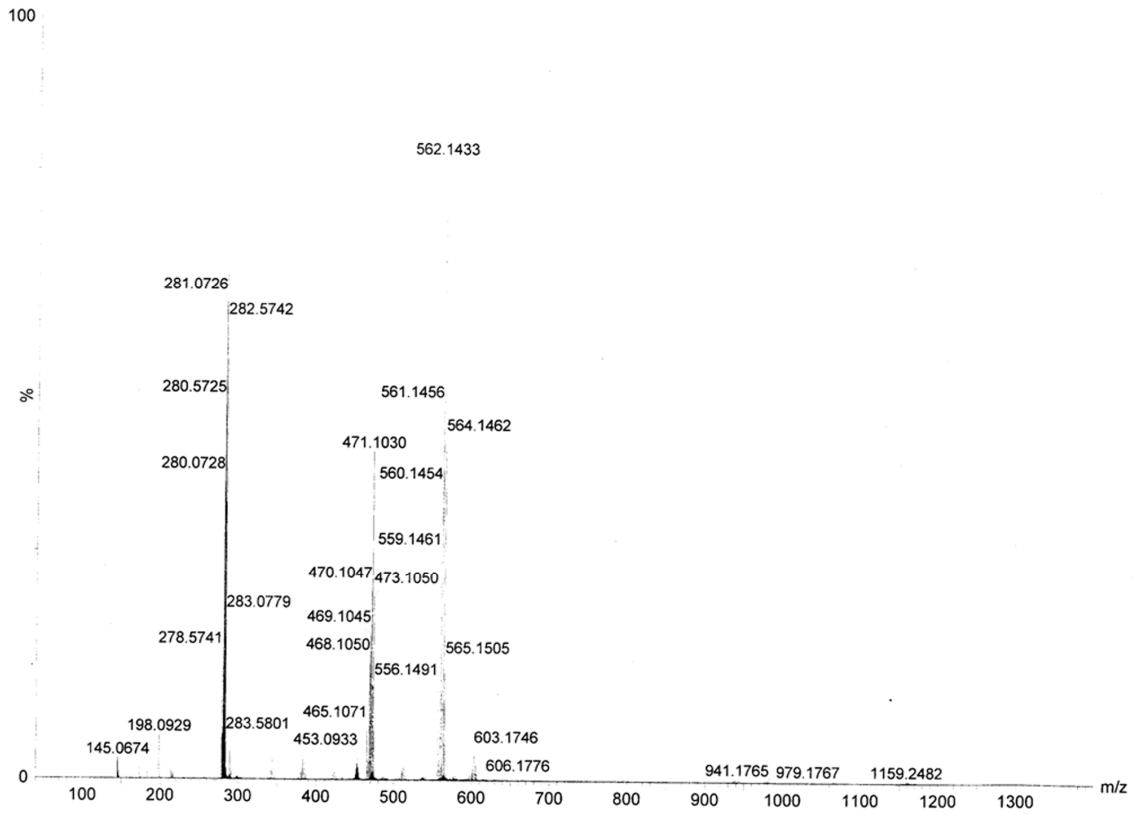


Figure S25. ESI-MS spectra of **2**

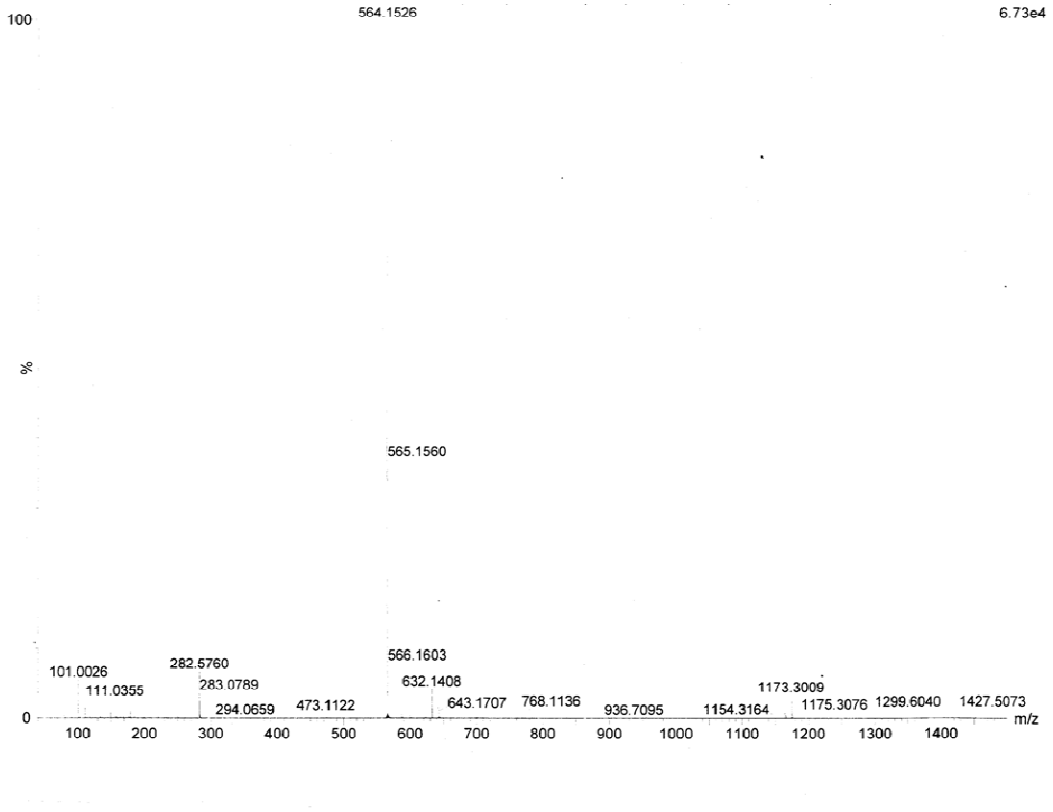


Figure S26. ESI-MS spectra of **3**

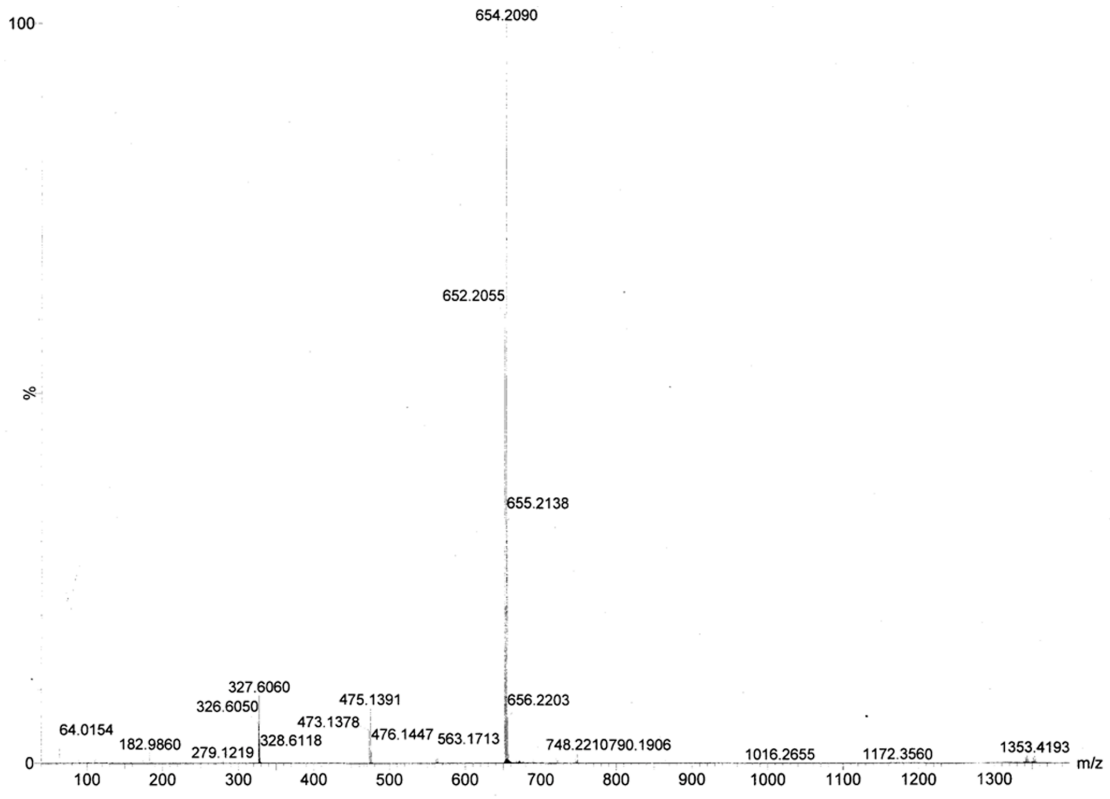


Figure S27. ESI-MS spectra of **4**

Table S5. **Electrochemical data of 1-4 (*c*, 100 μM, MeCN)**

(a) Changes in cyclic voltammetry after addition of CT DNA (1.0 μM) to a solution of **1**-**4**.

Compound	$E_{pa,}$ dpm/dpm^{+} (V),	$E_{pa,}$ Ru^{2+}/Ru^{3+} (V) or M^{3+}/M^{4+} (M = Rh, Ir)	E_{pa} = Complex + CT DNA (V)
1	0.744	0.985	
1 + CT DNA	Disappear	Disappear	0.891
2	0.760	0.982	
2 + CT DNA	Disappear	Disappear	0.897
3	0.803	0.916	
3 + CT DNA	0.967	Disappear	
4	0.662	0.843	
4 + CT DNA	0.751	0.935	

(b) Changes in differential pulse voltammetry after addition of CT DNA (1.0 μM) to a solution of **1**-**4**.

Compound	$E_{pa,}$ dpm/dpm^{+} (V),	$E_{pa,}$ Ru^{2+}/Ru^{3+} (V),	E_{pa} = Complex + CT DNA (V)
1	0.717	0.903	
1 + CT DNA	Disappear	Disappear	0.821
2	0.749	0.936	
2 + CT DNA	Disappear	Disappear	0.820
3	0.672	0.857	
3 + CT DNA	0.724	0.900	
4	0.666	0.855	
4 + CT DNA	0.727	0.881	