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Synthesis, characterization and antibacterial studies of ferrocenyl and cymantrenyl hydrazone compounds

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ABSTRACT

Cymantrenyl Schiff base compounds $[(CO)_3Mn\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)R\}]$ (**4**–**7**) (R = C_6H_4–OH, C_5H_4N-*p*, C_6H_5, C_5H_4N-*o*) have been synthesized by room temperature reaction and their structural characterization was performed by single crystal X-ray diffraction studies. Room temperature reaction of mono- and di-acetyl ferrocene with salicyloyl and isonicotinyl hydrazides led to the formation of the some organometallic Schiff base compounds containing monosubstituted, disubstituted and unsymmetrically substituted ferrocenyl fragments, $[(\eta^5\text{-}C_5H_5)Fe\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)-R\}]$ (**8**, **9**), $[Fe\{(\eta^5\text{-}C_5H_4)C(CH_3)=NN(H)C(O)R\}_2]$ (**10**, **12**) (R = C_6H_4–OH, C_5H_4N), $[\{(\eta^5\text{-}C_5H_4)COCH_3\}Fe\{(\eta^5\text{-}C_5H_4)C(CH_3)=NN(H)C(O)(C_5H_4N)\}]$ (**11**) and $[Fe\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)(C_5H_4N)\}\{(\eta^5\text{-}C_5H_4)C(CH_3)=NN(H)C(O)C_6H_4-OH\}]$ (**13**) respectively. Antibacterial studies and electrochemical analysis were carried out for some of the compounds. Molecular structure determination was performed for compounds **4**, **5**, **8** and **9** by single crystal X-ray diffraction technique.

1. Introduction

The chemistry of hydrazone type Schiff-base compounds has received intense attention because of their unique coordination and structural properties and for their various biological applications related to antitumour, antibacterial, antifungal and other inhibitory activities [1–6]. Among them, studies of Schiff-base compounds with organometallic tags are increasingly drawing much interest due to their distinctive properties and features concerning both organometallic and coordination chemistry [7–15]. Molecular compounds containing organometallic tags have been found to be potential therapeutics against major diseases and can play a vital role as tracers in immunological analysis based on several analytical methods like FTIR, electrochemical, atomic absorption techniques etc [16–19,33–35]. Consequently, the research field of bio-organometallic chemistry is increasingly drawing much interest due to the development of a new class of organometallic compounds and their ability to play a leading role in the field of biology [20]. The use of ferrocenyl derivatives as bioactive molecule has been established recently and several reports show that a large number of ferrocene containing compounds display interesting cytotoxic and DNA cleaving activities [21–27]. A large part of the research is also concentrated on the synthesis of conjugates of peptides and peptide nucleic acids with organometallic fragments. Very recent studies on Schiff base compounds containing organometallic fragments reveal that ferrocenyl Schiff base compounds have exciting biological properties and are potential compounds for antitumour, antibacterial, antimalarial and antifungal activities [26–29]. Recently, some Cp based half sandwich organometallic fragments have been studied for their various biological properties ranging from antimalarial, antimicrobial, anticancer, enzyme inhibitors and phototoxicity [30–36]. Synthesis of cyrhetrenyl, $[CpRe(CO)_3]$, based Schiff base compounds have been carried out recently and shows comparable antichagasic properties with their ferrocenyl analogue [14]. Biologically active compounds of technicium, $[(CpR)^{99m}Tc(CO)_3]$ and rhenium have been synthesized in aqueous phase for their probable therapeutic and diagnostic applications [33,34]. Functionalization of peptides by cymantrene based organometallic fragment has been reported for their use in biological imaging applications and IR labelling studies [35]. Meggers et al. described the protein inhibitor property of an organo-ruthenium analogue of staurosporine, which contains a [CpRu(CO)] fragment attached to indolocarbazole heterocycle [31].

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In view of their enormous opportunity, we became interested to synthesize some Schiff base compounds containing [(η^5-C_5H_4R)M] organometallic tags and investigate their biological and electrochemical properties. Our aim was to prepare hydrazone type Schiff base compounds by the condensation of hydrazide derivative with appropriate organometallic species especially ferrocenyl and cymantrenyl derivatives. Some synthetic and biological studies on mono- and di-ferrocenyl hydrazone compounds have been carried out recently [7–13,27], but 1,1′-unsymmetrically substituted ferrocenyl hydrozone compounds are not known. We selected cymantrenyl moieties as because these compounds contain metal carbonyls, which show specific IR signals with intense absorption in the range 1900–2200 cm^{-1} and can be used as IR probes in various biological samples. Moreover, to our knowledge cymantrenyl Schiff base compounds have been rarely studied and one of the reports show the synthesis of cymantrenyl-biotine compounds for their use as tracer molecule [36], whereas cymantrenyl-hydrazone compounds have been largely unexplored and are yet to be investigated for their possible antibacterial activities. In this report, we describe the synthesis and characterization of four new cymantrenyl hydrazone Schiff base compounds (**4**–**7**) along with mono- and di-substituted (**8**–**10**, **12**) ferrocenyl hydrazones compounds. We have also attempted to synthesize hydrazone derivative containing unsymmetrically 1,1′ disubstituted ferrocenyl fragment (**11**, **13**). Compounds **4**, **5**, **8** and **9** have been characterized structurally by single crystal X-ray diffraction techniques. Antibacterial activity and electrochemical properties have been studied for some of the ferrocenyl and cymantrenyl compounds.

2. Experimental sections

2.1. General procedures

All reactions and manipulations were carried out under an inert atmosphere of dry, pre-purified argon using standard schlenk line techniques. Solvents were purified, dried and distilled under argon atmosphere prior to use. Infrared spectra were recorded on a Perkin Elmer Spectrum RX-I spectrometer as KBr pellet or CH_2Cl_2 solution and NMR spectra on a 400 MHz Bruker spectrometer in $CDCl_3$ or DMSO-d_6 solvent. Elemental analyzes were performed on a Vario El Cube analyzer. Mass spectra were obtained on a SQ-300 MS instrument operating in ESI mode. Cyclic voltammetric and differential pulse voltammetric measurements were carried out using a CH Instruments model 600D electrochemistry system. A platinum working electrode, a platinum wire auxiliary electrode and a silver/silver chloride reference electrode were used in a three-electrode configuration. The supporting electrolyte was 0.1 M $[NEt_4]ClO_4$ and the solute concentration was $\sim 10^{-3}$ M. The scan rate used was 50 mV s^{-1}. All electrochemical experiments were carried out under a nitrogen atmosphere and are uncorrected for junction potentials. TLC plates (20 × 20 cm, Silica gel 60 F254) were purchased from Merck. [(η^5-C_5H_5)Fe(η^5-$C_5H_4COCH_3$)], [Fe(η^5-$C_5H_4COCH_3$)$_2$], [$(CO)_3$Mn(η^5-$C_5H_4COCH_3$)], [$H_2NN(H)C(O)R$], (R = –C_6H_4–OH, C_6H_4N-*p*, C_6H_5, C_6H_4N-*o*) were prepared following reported procedures [37,38,39].

2.2. Synthesis of [$(CO)_3$Mn{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)–R}] {R = C_6H_4–OH (**4**), C_6H_4N-p (**5**), C_6H_5 (**6**), C_6H_4N-o (**7**)}

In a typical synthetic procedure, respective hydrazide (0.1 mmol) was taken in a two neck round bottomed flask and ethanol (10 ml) solvent was added. The solution was stirred under nitrogen atmosphere to obtain a clear solution. To the reaction mixture 0.1 mmol of monoacetyl cymantrene (25 mg, 0.1 mmol) and two drops of acetic acid was added at room temperature and under stirring condition and the reaction was continued for 3–4 h. After the reaction, the solution was filtered and the pale yellow precipitate was washed with cold ethanol and vacuum dried. The product was purified by preparative TLC in 5% ethanol:*n*-hexane solvent mixture. (Yield = 35 mg (92%) (**4**); 32 mg (88%) (**5**), 29 mg (81%) (**6**); 31 mg (86%) (**7**)).

4: Anal. Calcd. (found): C, 53.68 (53.45); H, 3.42 (3.37); N, 7.36 (7.45). IR (ν, cm^{-1}, CH_2Cl_2): 3278.7 (br), 3057.4 (br), 2010 (s), 1923.7 (vs), 1630.4 (s), 1601.5 (m). ^{1}H NMR (δ, $CDCl_3$): 2.15 (s, 3H, CH_3), 4.84 (s, 2H, η^5-C_5H_4), 5.38 (s, 2H, η^5-C_5H_4), 6.90–6.94 (t, 1H, C_6H_4), 7.04–7.06 (d, 1H, C_6H_4), 7.45–7.49 (t, 1H, C_6H_4), 9.01 (br, 1H, N*H*), 11.66 (br, 1H, O*H*). MS (ESI): *m*/*z* 381 $(M)^+$.

5: Anal. Calcd. (found): C, 52.60 (52.78); H, 3.28 (3.21); N, 11.50 (11.62). IR (ν, cm^{-1}, CH_2Cl_2): 3210 (br), 2019 (vs), 1929.8 (vs, br), 1669 (s), 1603 (w). ^{1}H NMR (δ, $CDCl_3$): 2.09 (s, 3H, CH_3), 4.79 (s, 2H, η^5-C_5H_4), 5.11–5.40 (m, 2H, η^5-C_5H_4), 7.67 (s, 2H, C_6H_4N), 8.78 (s, 2H, C_6H_4N), 8.95 (br, 1H, N*H*).

6: IR (ν, cm^{-1}, CH_2Cl_2): 3213 (br), 2018 (vs), 1926 (vs, br), 1658 (br), 1604 (w). ^{1}H NMR (δ, $CDCl_3$): 2.09 (s, 3H, CH_3), 4.79 (s, 2H, η^5-C_5H_4), 5.17–5.34 (m, 2H, η^5-C_5H_4), 7.49–7.84 (m, 5H, C_6H_5), 8.83 (br, 1H, N*H*). MS (ESI): *m*/*z* 365 $(M + 1)^+$.

7: IR (ν, cm^{-1}, CH_2Cl_2): 3195 (br), 2017 (vs), 1925.5 (vs, br), 1654 (br), 1590 (w). ^{1}H NMR (δ, $CDCl_3$): 2.1 (s, 3H, CH_3), 4.78 (s, 2H, η^5-C_5H_4), 5.15–5.36 (m, 2H, η^5-C_5H_4), 7.47 (s, 1H, C_6H_4N), 8.17 (s, 1H, C_6H_4N), 8.89 (br, 2H, C_6H_4N), 9.16 (br, 1H, N*H*). MS (ESI): *m*/*z* 366 $(M + 1)^+$.

2.3. Synthesis of [(η^5-C_5H_5)Fe{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)–R}] {R = C_6H_4–OH (**8**), C_6H_4N-p (**9**)}

In a two necked round bottomed flask respective hydrazide (0.1 mmol) was taken and 10 ml of ethanol solvent was added. To the reaction mixture, 23 mg (0.1 mmol) of monoacetyl ferrocene and two drops of acetic acid was added at room temperature under stirring condition. The reaction was continued for 6–12 h under nitrogen atmosphere and monitored using TLC. After the reaction, the solution was filtered and the orange precipitate was washed with cold ethanol and vacuum dried. The product was further purified by preparative TLC in 5% ethanol:*n*-hexane solvent mixture. (Yields: **8**: 31 mg (85%); **9**: 30 mg (87%)).

8: Anal. Calcd. (found): C, 62.98 (63.39); H, 4.97 (4.92); N, 7.73 (7.85). IR (ν cm^{-1}, KBr): 3446 (br), 2667.7 (m), 2577.7 (m), 1628 (s), 1607 (s), 1542 (s). ^{1}H NMR (δ, DMSO-d_6): 2.23 (s, 3H, CH_3) 4.23 (s, 5H, η^5-C_5H_5), 4.42 (t, 2H, η^5-C_5H_4), 4.69 (t, 2H, η^5-C_5H_4), 6.94–7.01 (m, 2H, C_6H_4), 7.39–7.42 (t, 1H, C_6H_4), 7.95–7.97 (d, 1H, C_6H_4), 11.16 (s, 1H, N*H*), 11.84 (br, 1H, O*H*). MS (ESI): *m*/*z* 363 $(M + 1)^+$.

9: Anal. Calcd. (found): C, 62.24 (62.68); H, 4.89 (4.81); N, 12.10 (12.26). IR (ν_{CO}, cm^{-1}, CH_2Cl_2): 3412 (br), 3146 (m), 1600 (vs), 1578 (vs). ^{1}H NMR (δ, DMSO-d_6): 2.30 (s, 3H, CH_3), 4.29 (s, 5H, η^5-C_5H_5), 4.50 (s, 2H, η^5-C_5H_4), 4.78 (s, 2H, η^5-C_5H_4), 7.85 (br, 2H, C_5H_4N), 8.82 (br, 2H, C_5H_4N), 10.95 (s, 1H, N*H*). MS (ESI): *m*/*z* 348 $(M + 1)^+$.

2.4. Synthesis of [Fe{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)C_6H_4–OH}$_2$] (**10**)

Ethanol solution of salicyloyl hydrazide (31 mg, 0.2 mmol) was taken in a two necked flask and 27 mg (0.1 mmol) of 1,1′-dicetyl ferrocene and one drop of HCl was added at room temperature under stirring condition. The reaction was continued for 3 h and monitored using TLC. After the reaction, the solution was filtered and the orange precipitate was washed with cold ethanol and dried under vacuum. The product was purified by preparative TLC in 20% ethanol:*n*-hexane solvent mixture. Yield: 50 mg (92%).

10: Anal. Calcd. (found): C, 62.45 (62.17); H, 4.83 (4.62); N, 10.41 (10.58). IR (ν, cm^{-1}, KBr): 3284 (m), 3078.3 (br), 1633.5 (vs), 1605.8 (s), 1558.7 (vs). ^{1}H NMR (δ, DMSO-d_6): 2.17 (s, 6H, CH_3) 4.46 (s, 4H,

η^5-C_5H_4), 4.77 (s, 4H, η^5-C_5H_4), 6.77–6.89 (m, 4H, C_6H_4), 7.25–7.29 (t, 2H, C_6H_4), 7.90–7.92 (d, 2H, C_6H_4), 11.14 (s, 2H, N*H*), 11.59 (br, 2H, O*H*). MS (ESI): *m*/*z* 539 $(M + 1)^+$, 521 $(M - OH)^+$.

2.5. Reaction of 1,1′-[Fe{(η^5-C_5H_4)$COCH_3$}$_2$] with isonicotinyl hydrazide

In a two necked flask, 10 ml ethanol was added to 1,1′-diacetylferrocene (135 mg, 0.5 mmol) and isonicotinyl hydrazide (62 mg, 0.5 mmol). The solution was stirred under nitrogen atmosphere for 15 min and two drops of acetic acid was added. The reaction was continued for 12 h at room temperature under inert atmosphere and continuously monitored using TLC. After the completion of the reaction, the solution was filtered, vacuum dried and preparative TLC was carried out with *n*-hexane:ethanol (75:25v/v) solvent mixture to separate trace amount of reactants and an orange compound [{(η^5-C_5H_4)$COCH_3$}Fe{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)(C_5H_4N)}] (**11**) (125 mg (64%)) in the order of elution.

11: Anal. Calcd. (found): C, 61.69 (61.93); H, 4.92 (4.84); N, 10.79 (10.64). IR (ν, cm^{-1}, CH_2Cl_2): 3450.8 (br), 3221.3 (br), 1659.2 (vs), 1636 (s), 1601.5 (s), 1549.7 (vs). ^{1}H NMR (δ, DMSO-d_6): 2.21 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.49 (s, 2H, η^5-C_5H_4), 4.62 (s, 2H, η^5-C_5H_4), 4.77 (s, 2H, η^5-C_5H_4), 4.81 (s, 2H, η^5-C_5H_4), 7.87 (br, 2H, C_5H_4N), 8.92 (br, 2H, C_5H_4N), 10.94 (s, 1H, N*H*). MS (ESI): *m*/*z* 390 $(M + 1)^+$.

2.6. Reaction of **11** with hydrazide

Ethanol solution (10 ml) of compound **11** (39 mg, 0.1 mmol) was taken in a two necked round bottomed flask and an equivalent amount of the respective hydrazide (0.1 mmol) (isonicotinyl hydrazide or salicyloyl hydrazide) and acetic acid (two drops) was added under stirring and inert atmospheric condition. The solution was stirred at room temperature and under nitrogen atmosphere for 2 h. The reaction was continuously monitored using TLC. After the completion of the reaction, the solution was filtered and the volume was reduced to minimum amount. Preparative TLC was carried out with the reaction mixture using *n*-hexane:ethanol (80:20v/v) solvent mixture to separate an orange coloured compound [Fe{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)(C_5H_4N)}$_2$] (**12**) (yield = 32 mg (62%)) or [{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)–C_6H_4–OH}Fe{(η^5-C_5H_4)C(CH_3)=N–N(H)C(O)(C_5H_4N)}] (**13**) (yield = 40 mg (78%)). Some amounts of unreacted compound and decomposition have also been observed after the reaction.

12: Anal. Calcd. (found): C, 61.41 (61.75); H, 4.70 (4.59); N, 16.53 (16.64). IR (ν, cm^{-1}, KBr): 3420 (vs), 1642 (vs), 1617, 1595. ^{1}H NMR (δ, DMSO-d_6): 2.29 (s, 6H, CH_3), 4.61 (s, 4H, η^5-C_5H_4), 4.81 (s, 4H, η^5-C_5H_4), 7.84 (m, 4H, C_5H_4N), 8.81 (m, 4H, C_5H_4N). MS (ESI): *m*/*z* 509 $(M + 1)^+$.

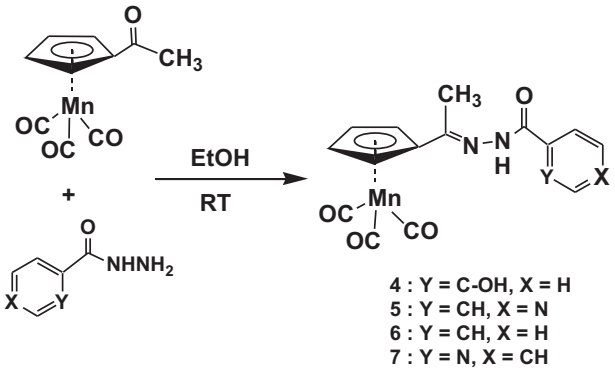
13: Anal. Calcd. (found): C, 61.95 (62.27); H, 4.78 (4.70); N, 13.38 (13.46). IR (ν, cm^{-1}, CH_2Cl_2): 3418 (m), 3274.5 (m), 1658.7 (s), 1642.4 (s), 1599.5 (s), 1564.7 (s), 1549.6 (vs). ^{1}H NMR (δ, DMSO-d_6): 2.15 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.43 (s, 2H, η^5-C_5H_4), 4.57 (s, 2H, η^5-C_5H_4), 4.74 (s, 2H, η^5-C_5H_4), 4.79 (s, 2H, η^5-C_5H_4), 6.52–7.82 (m, 8H, C_5H_4N, C_6H_4). MS (ESI): *m*/*z* 523 $(M)^+$.

2.7. Crystal structure determination for **4**, **5**, **8** and **9**

Single crystal X-ray structural studies of **4**, **5**, **8** and **9** were performed on a CCD Oxford Diffraction XCALIBUR-S diffractometer equipped with an Oxford Instruments low-temperature attachment. Data were collected at 150(2) K using graphite-monochromated Mo Kα radiation (λ_α = 0.71073 Å). The strategy for the data collection was evaluated by using the CrysAlisPro CCD software. The data were collected by the standard phi-omega scan techniques, and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on F^2 [40]. The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally 1.2 U_{eq} of their parent atoms. The crystallographic details are summarized in Table 1.

Table 1
Crystal data and structure refinement parameters for compounds **4**, **5**, **8** and **9**.

	4	**5**	**8**	**9**
Empirical formula	$C_{17}H_{13}MnN_2O_5$	$C_{16}H_{12}MnN_3O_4$	$C_{19}H_{18}FeN_2O_2$	$C_{36}H_{34}Fe_2N_6O_3$
Formula weight	380.23	365.23	362.20	710.39
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Tetragonal
Space group	*P 21/c*	*P b c a*	*P b c a*	*I*–4
a, Å	12.2632(6)	7.9517(3)	10.8288(5)	21.4833(4)
b, Å	10.5915(6)	18.8279(6)	12.7875(7)	21.4833(4)
c, Å	12.7224(7)	21.5734(7)	23.4845(12)	6.9735(2)
α deg	90	90	90	90
β deg	99.307(5)	90	90	90
γ deg	90	90	90	90
V, Å^3	1630.70(15)	3229.84(19)	3252.0(3)	3218.49(13)
Z	4	8	8	4
D_{calcd}, Mg m^{-3}	1.549	1.502	1.480	1.466
Abs coeff, mm^{-1}	0.840	0.842	0.941	0.948
F(000)	776	1488	1504	1472
Cryst size, mm	0.33 × 0.28 × 0.23	0.32 × 0.26 × 0.23	0.33 × 0.26 × 0.21	0.23 × 0.16 × 0.13
θ range, deg	3.17–25.00	2.94–24.99	3.01–25.00	3.00–24.98
Index ranges	$-14 < h < 14$, $-12 < k < 12$, $-15 < l < 15$	$-9 < h < 9$, $-20 < k < 22$, $-25 < l < 25$	$-12 < h < 11$, $-15 < k < 15$, $-27 < l < 21$	$-25 < h < 25$, $-20 < k < 25$, $-8 < l < 8$
Reflections collected/ unique	12,573/2869 [*R*(int) = 0.0305]	19,145/2820 [*R*(int) = 0.0496]	22,098/2855 [*R*(int) = 0.0666]	12,301/2849 [*R*(int) = 0.0420]
Data/restraints/ parameters	2869/0/231	2820/0/218	2855/0/222	2849/0/216
Goodness-of-fit on F^2	1.063	1.051	0.956	1.083
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0304, *wR*2 = 0.0832	*R*1 = 0.0387, *wR*2 = 0.0939	*R*1 = 0.0356, *wR*2 = 0.0787	*R*1 = 0.0322, *wR*2 = 0.0809
R indices (all data)	*R*1 = 0.0346, *wR*2 = 0.0867	*R*1 = 0.0478, *wR*2 = 0.1011	*R*1 = 0.0591, *wR*2 = 0.0849	*R*1 = 0.0350, *wR*2 = 0.0832
Largest diff. peak and hole, e Å^{-3}	0.236 −0.179	0.319 −0.381	0.266 −0.276	0.387 −0.408



Scheme 1.

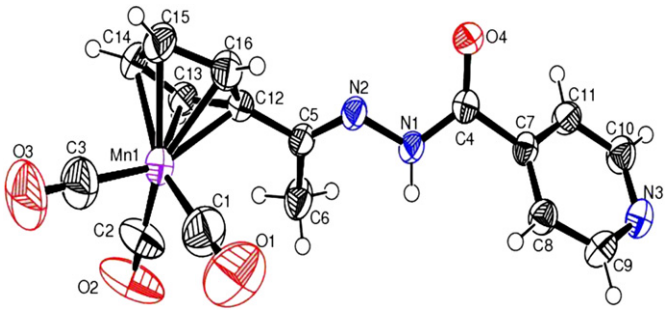


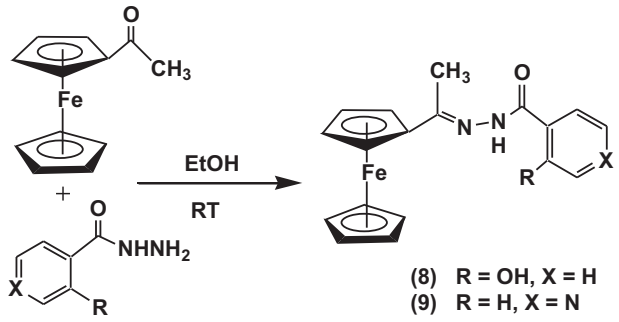
Fig. 2. ORTEP diagram of **5**. Selected bond lengths (Å) and bond angles (°): N(2)–C(5) = 1.280(3), N(1)–N(2) = 1.391(3), N(1)–C(4) = 1.340(3), O(4)–C(4) = 1.221(3), O(1)–C(1) = 1.144(4), C(5)–N(2)–N(1) = 116.3(2), C(4)–N(1)–N(2) = 118.3(2).

2.8. Antibacterial activity

Compounds **4**, **5**, **6**, **8**, **9** and **10** were screened for their antibacterial activity *in vitro* following the protocol described elsewhere [41]. The antibacterial effect was assayed against both Gram positive bacteria *viz*., *Staphylococcus aureus*, *Bacillus subtilis* and Gram negative bacteria *viz*., *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* by the agar well diffusion method [41]. The compounds were dissolved in DMSO at different concentrations ranging from 500 to 15.625 μg/ml. Mueller Hinton-agar (containing 1% peptone, 0.6% yeast extract, 0.5% beef extract and 0.5% NaCl, at pH 6.9–7.1) plates were prepared and 0.5 − McFarland culture (1.5×10^8 cells/ml) of the test organisms were swabbed onto the agar plate. 9 mm wells were made in the LB agar petri dishes. 100 μl of each of the compound with decreasing concentrations was added to separate wells. DMSO was used as the negative control and *Ampicillin* was used as positive control. The plates were incubated at 37 °C and observed for zones of inhibition around each well after 24 h. The results were compared with the activity of *Ampicillin* at identical concentrations. The MIC, defined as the lowest concentration of the test compound, which inhibits the visible growth, was determined visually after incubation for 24 h at 37 °C.

3. Results and discussion

Cymantrenyl based hydrazone compounds, $[(CO)_3Mn\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)-C_6H_4-OH\}]$ (**4**), $[(CO)_3Mn\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)-C_6H_4N\text{-}p\}]$ (**5**), $[(CO)_3Mn\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)-C_6H_5\}]$ (**6**), and $[(CO)_3Mn\{(\eta^5\text{-}C_5H_4)C(CH_3)=N-N(H)C(O)-C_6H_4N\text{-}o\}]$ (**7**) were synthesized by the room temperature reaction of $[Mn(CO)_3\{(\eta^5\text{-}C_5H_4)COCH_3\}]$ with the appropriate hydrazide compounds (salicyloyl hydrazide, isonicotinyl hydrazide, benzoyl hydrazide and nicotinyl hydrazide) (Scheme 1). All the compounds have been isolated and purified by preparative chromatography and characterized by spectroscopic techniques.



Scheme 2.

Infrared spectral analysis for compounds **4**–**7** reveals the presence of terminal metal carbonyl groups in the region 1923–2019 cm^{-1} and peaks corresponding to C=O and C=N in the range 1601.5–1669 cm^{-1}. ^1H NMR spectra shows the presence of protons corresponding to substituted cyclopentadienyl unit, methyl group, NH and aromatic ring protons for each of the four cymantrenyl hydrazone compounds. Compound **4** also shows a broad peak at δ 11.66 corresponding to −OH proton. Mass spectral analysis for **4** shows the characteristic molecular ion peak (M^+) at *m*/*z* 381 whereas for compounds **6** and **7**, ESI-MS peaks are observed at *m*/*z* 365 $[(M+1)^+]$ and 366 $[(M+1)^+]$ respectively.

Single crystal X-ray diffraction studies have been successfully carried out for **4** and **5** with the respective single crystals, grown from dichloromethane:*n*-hexane solvent mixture at −10 °C. The

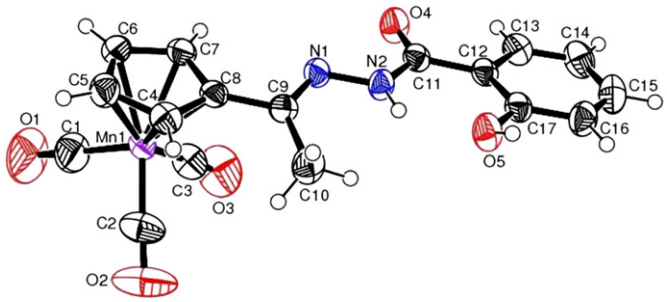


Fig. 1. ORTEP diagram of **4**. Selected bond lengths (Å) and bond angles (°): N(1)–C(9) = 1.273(3), N(1)–N(2) = 1.372(2), N(2)–C(11) = 1.338(3), O(4)–C(11) = 1.227(2), C(9)–N(1)–N(2) = 116.39(16), C(11)–N(2)–N(1) = 120.80(16).

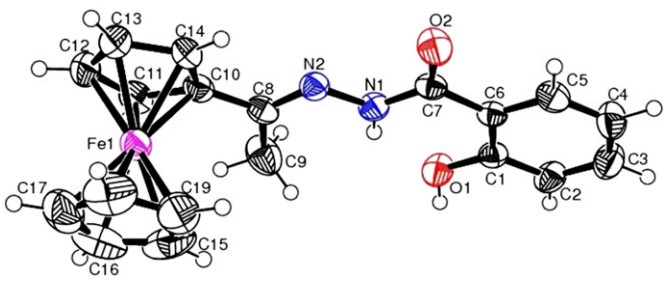


Fig. 3. ORTEP diagram of **8**. Selected bond lengths (Å) and bond angles (°): N(1)–N(2) = 1.380(2), N(2)–C(8) = 1.284(3), N(1)–C(7) = 1.340(3), O(2)–C(7) = 1.229(3), C(7)–N(1)–N(2) = 119.46(18), O(2)–C(7)–N(1) = 122.4(2), N(2)–C(8)–C(9) = 124.7(2).

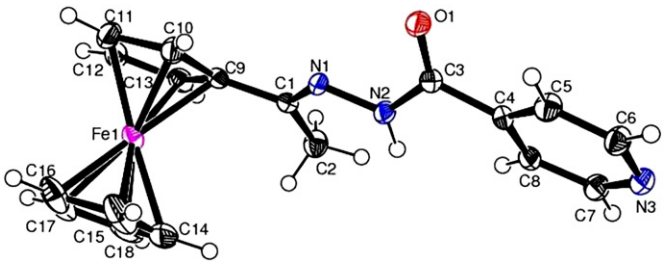


Fig. 4. ORTEP diagram of **9**. Water molecule has been removed for clarity. Selected bond lengths (Å) and bond angles (°): N(1)–N(2) = 1.391(3), N(2)–C(3) = 1.355(4), N(1)–C(1) = 1.291(4), O(1)–C(3) = 1.232(4), C(1)–N(1)–N(2) = 115.5(2), O(1)–C(3)–N(2) = 124.2(3), N(1)–C(1)–C(2) = 127.1(3).

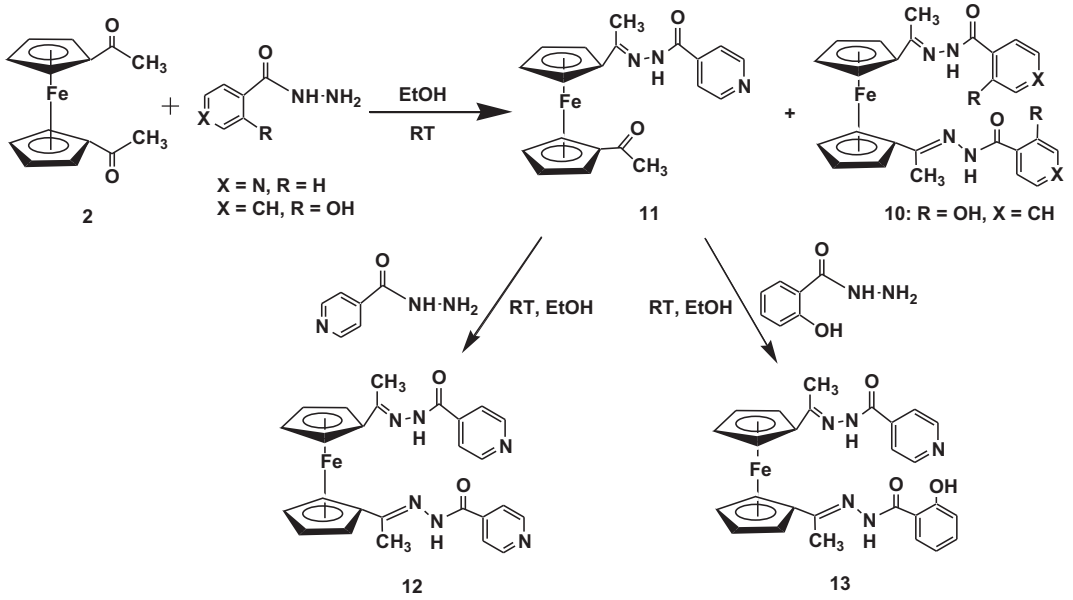
molecular structure of compound **4** and **5** confirms the presence of a cymantrenyl unit linked to the hydrazone chain, [C═NN(H)C(O)–R] involving a C═N bond (Figs. 1 and 2). In the molecule of **4**, the cyclopentadienyl and phenyl rings are almost coplanar, whereas in compound **5** the cyclopentadienyl ring and the pyridyl rings are perpendicular to each other forming a dihedral angle of around 72° between the cyclopentadienyl and pyridyl plane. The C═N bond distances for **4** and **5** are 1.279(2) Å and 1.280(3) Å respectively, which are comparable to that in ferrocenyl Schiff base compounds, [(η^5-C_5H_5)Fe{(η^5-C_5H_4)C(H)═NN(H)C(O)C_6H_5}] (1.277(4) Å) [10] and [Fe{(η^5-C_5H_4)C(CH_3)═NN═C(C_5H_4N)}$_2$] (1.241 (7)–1.300(7) Å) [42]. The N1–N2 single bond distance in **4** (1.377(2) Å) is shorter than that in **5** (1.391(3) Å) and in [(η^5-C_5H_5)Fe{(η^5-C_5H_4)C(H)═NN(H)C(O)C_6H_5}] [10]. In both the structures of **4** and **5**, the C═O and N–H bonds are trans to each other.

Monosubstituted ferrocenyl hydrazone compounds, [(η^5-C_5H_5)Fe{(η^5-C_5H_4)C(CH_3)═N–N(H)C(O)C_6H_4(OH)}] (**8**) and [(η^5-C_5H_5)Fe{(η^5-C_5H_4)C(CH_3)═N–N(H)C(O)(C_5H_4N)}] (**9**) have been obtained by a room temperature reaction of an ethanol solution of salicyloyl hydrazide or isonicotinyl hydrazide with monoacetyl ferrocene. Both the compounds have been isolated in pure form by preparative TLC using 80:20 (v/v) *n*-hexane:ethanol solvent mixture for characterization and antibacterial studies. Analogous reaction at room temperature was performed with 1,1′-diacetylferrocene and two equivalents of salicyloyl hydrazide to obtain the corresponding disubstituted hydrazone compound, [Fe{(η^5-C_5H_4)C(CH_3)═N–N(H)C(O)–C_6H_4(OH)}$_2$] (**10**) (Scheme 2). The above synthesis and purification procedure for compounds **8** and **10** involves slightly modified reaction and work-up conditions from the previously reported literature on the synthesis of the same compounds in thermal reaction condition [27,43]. We have been able to confirm the molecular structure for compound **8** by X-ray crystallography from a single crystal grown by evaporation techniques with ethanol/diethylether solvent mixture. Infrared spectra for **8** and **10** shows peaks at 1607, 1628, 1606, 1633 cm^{-1} corresponding to C═N and C═O groups. Presence of ferrocenyl protons have been confirmed by ^{1}H NMR spectral data in the range δ 4.23–4.69 for both the compounds and peaks at δ 11.84 (OH), δ 11.16 (NH) and δ 2.23 (CH_3) for **8** and δ 11.58 (OH), δ 11.14 (NH) and δ 2.16 (CH_3) for **10** reveals the presence of other functional protons. The NMR spectral analysis also reveals the presence of two hydrazone units attached to each of the ferrocenyl Cp ring in compound **10**, whereas in **8** one of the ferrocenyl Cp ring is linked to a hydrazone chain. The infrared and ^{1}H NMR spectra of compound **9** were compared with the reported values [28].

The molecular structures of **8** and **9** have been confirmed by single crystal X-ray analysis using crystals grown from ethanol/diethylether solvent mixture at −5 °C. Structure of compound **8** shows a ferrocenyl unit in which one of the Cp ring is attached to a hydrazone chain, [C═NN(H)C(O)C_6H_4–OH] via C═N linkage (Fig. 3). The C═N bond distance is 1.284(3) Å which is slightly longer than that in [(η^5-C_5H_5)Fe{(η^5-C_5H_4)C(H)═NN(H)C(O)C_6H_5}] (1.277(4) Å) [10] and comparable to that present in [Fe{(η^5-C_5H_4)C(CH_3)═NN═C(C_5H_4N)}$_2$] (1.241 (7)–1.300(7) Å) [42].

The molecular structure for **9** reveals the presence of a ferrocenyl unit linked to an isonicotinyl hydrazone chain [C═NN(H)C(O)C_5H_4N] by a Schiff base type C═N linkage (Fig. 4). The N–H and C═O bonds in the hydrazone fragment are in the opposite direction forming an E-isomer. The C1–N1 and C3–O1 bonds reveal double bond character with a bond distance of 1.291(4) Å and 1.232(4) Å respectively.

Unsymmetrically 1,1′-disubstituted ferrocenyl compounds have been of interest due to their multifunctional properties with unique structural features and tunable electrochemical responses. In the current study, we have been able to synthesize unsymmetrically 1,1′-disubstituted ferrocenyl compounds containing two different



Scheme 3.

Table 2
Cyclic voltammetric data for **8**, **9**, **10** and **13**.

Compounds	E_{pa}	E_{pc}	$E_{1/2}$ (V) (ΔE_p (mV))
8	0.332	0.260	0.296(72)
9	0.534	0.465	0.499(69)
10	0.656	0.548	0.602 (108)
13	0.660	0.547	0.604(113)

In DMF at a scan rate of 50 mV s^{-1}. $E_{1/2}$ (V) = $(E_{pa} + E_{pc})/2$, where E_{pa} and E_{pc} are the anodic and cathodic peak potentials Vs. Ag/AgCl respectively. ΔE_p (mV) = $E_{pa} - E_{pc}$.

hydrazone units by using simple synthetic methodology involving selective transformation of one of the Cp substituent. Reaction of 1,1′-diacetylferrocene with one equivalent of isonicotinyl hydrazide results in the formation of [{(η^5-C_5H_4)$COCH_3$}Fe{(η^5-C_5H_4)$C(CH_3)$=N–N(H)C(O)(C_5H_4N)}] (**11**) in which one of the Cp ring of the ferrocenyl moiety is attached to a hydrazone chain while the other Cp ring remains unchanged with an acetyl group (–$COCH_3$) (Scheme 3). To understand its reactivity, we added equivalent amount of isonicotinyl hydrazide to an ethanol solution of **11** under inert atmosphere to isolate the symmetrically disubstituted derivative [Fe{(η^5-C_5H_4)$C(CH_3)$=N–N(H)C(O)(C_5H_4N)}$_2$] (**12**). This reveals that the pendant acetyl group attached to one of the Cp ring in compound **11** is taking part in the reaction to form Schiff base type hydrazone linkage. Therefore, we carried out similar reaction technique to prepare 1,1′ unsymmetrically disubstituted ferrocenyl compounds containing two different hydrazone units. Thus, compound **11** was reacted with equivalent amount of salicyloyl hydrazide to obtain a new ferrocene containing mixed hydrazone compound [Fe{(η^5-C_5H_4)$C(CH_3)$=N–N(H)C(O)(C_5H_4N)}{(η^5-C_5H_4)$C(CH_3)$=N–N(H)C(O)–C_6H_4–OH}] (**13**) (Scheme 3).

Compounds **11**–**13** have been characterized by IR and ^{1}H NMR spectroscopy. Infrared spectra for compounds **11**–**13** show peaks corresponding to C=O and C=N stretching frequency in the range 1601–1659 cm^{-1}, 1595–1642 cm^{-1} and 1600–1659 cm^{-1} respectively. ^{1}H NMR spectra for **11** show peaks at δ 2.21 and δ 2.32 corresponding to two different methyl protons, δ 4.49–4.81 (four peaks) for disubstituted ferrocenyl Cp protons, δ 7.87 and δ 8.92 for pyridyl protons and δ 10.94 for NH proton of the hydrazone unit. Presence of CH_3, disubstituted ferrocenyl and pyridyl protons for compound **12** have been confirmed from their corresponding peaks at δ 2.29, δ 4.61–4.81and δ 7.84–8.81 respectively. Proton NMR spectra for compound **13** shows two methyl peaks at δ 2.28 and δ 2.15 region, four peaks in the range δ 4.43–4.79 corresponding to eight ferrocenyl protons and phenyl and pyridyl protons are observed in the range δ 6.52–7.82 as multiplet. ESI mass spectral analysis for **13** reveals the presence of M^+ fragment at 523 *m*/*z* region. To our knowledge 1,1′-unsymmetrically substituted ferrocenyl mixed hydrazone compounds are novel and the synthetic method described here can be used to prepare a varied range of ferrocenyl hydrazone compounds containing unsymmetrically Cp substituted side chains.

3.1. Electrochemical properties

The electrochemical properties of compounds **8**, **9**, **10** and **13** have been examined in DMF solution (0.1 M TBAP) by cyclic voltammetry. Compounds **8** and **9** showed reversible responses in the potential range 0.26–0.54 V involving single electron Fe(II)–Fe(III) oxidation when scanned in the positive potential side. The one-electron nature of these oxidations has been tentatively established by comparing its current height with that of the standard

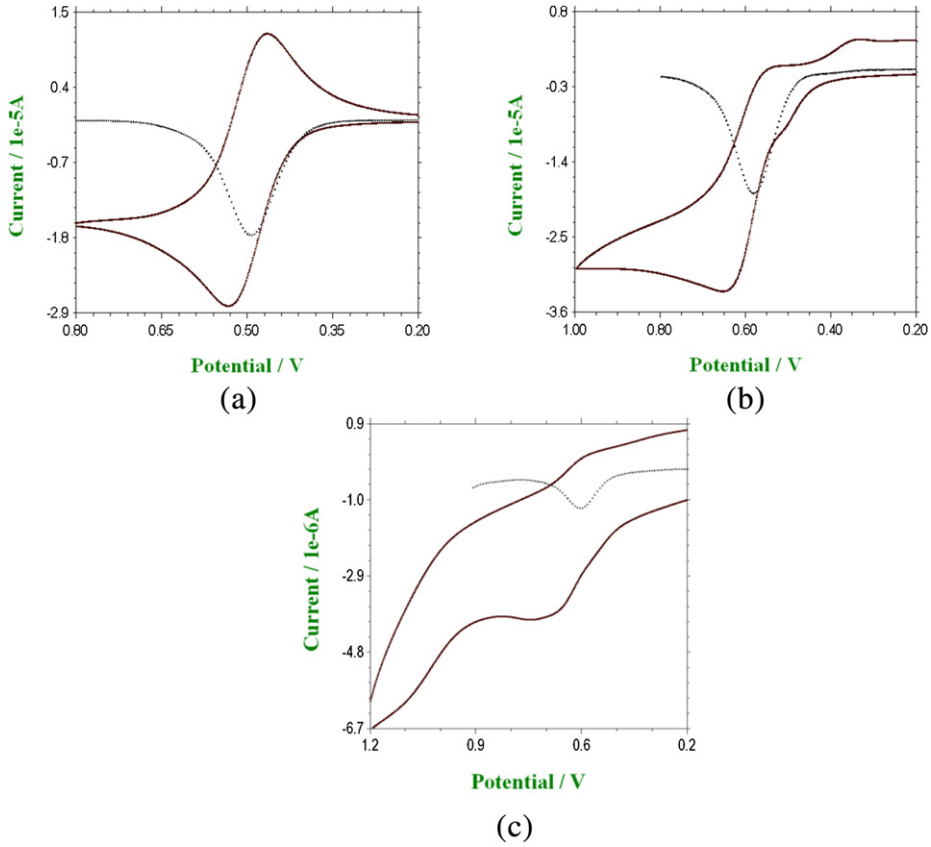


Fig. 5. Cyclic voltammograms (—) and differential pulse voltammograms (…) of compounds (a) **9**, (b) **10** and (c) **13** in DMF/0.1 M TEAP at 298 K. Ferrocene/ferrocenium was used as the standard.

Table 3
Minimum inhibitory concentration (MIC) value in μg/ml.

Compounds	*B. subtilis*	*E. coli*	*S. aureus*	*K. pneumoniae*	*P. aeruginosa*
4	125	250	125	–	125
5	250	125	–	62.5	250
6	–	62.5	–	125	31.25
8	62.5	250	–	–	250
9	31.25	62.5	–	125	–
10	15.62	–	–	–	62.5
Ampicillin	15.62	31.25	15.62	31.25	62.5

ferrocene/ferrocenium couple under the same experimental conditions. The one electron oxidation process at the positive potential for compound **9** shifted towards more positive side as compared to compound **8**. This may be due to the presence of a pyridyl group in **9** which makes the Fe(II)/Fe(III) oxidation more difficult than that in **8**. Disubstituted ferrocenyl compounds **10** and **13** showed irreversible oxidation steps in the positive potential range 0.547–0.660 V, which are higher than those for monosubstituted ferrocenyl compounds (**8**, **9**). The potential data are listed in Table 2, and some voltammograms are shown in Fig. 5.

3.2. Antibacterial activity

Antibacterial study was carried out for six of the synthesized compounds, **4**, **5**, **6**, **8**, **9** and **10**. All of them showed potential inhibition activity against the bacterial strains as shown in Table 3. Compound **10**, having two salicyloyl hydrazone chains attached to a ferrocene unit, showed promising antibacterial activity against *B. subtilis* and *P. aeruginosa* as compared to other compounds containing only one hydrazone chain linked to either cymantrenyl or ferrocenyl fragments. Among the cymantrenyl hydrazones, compound **6** has better MIC against *E. coli* and *P. aeruginosa* bacterial strain whereas cymantrenyl isonicotinyl hydrazone (**5**) showed better result when tested with *K. pneumoniae*. Ferrocenyl isonicotinyl hydrazone (**9**) is more active against *B. subtilis* and *E. coli* compared to the cymantrenyl analogue, whereas the later is more active in case of *K. pneumoniae*. Comparison of the inhibition activity for these ferrocenyl and cymantrenyl compounds with the reported antimicrobial properties of their organic analogue reveals increased inhibitory activity for the compounds containing organometallic fragments [44]. For example, the MIC for the hydroxyphenyl benzoylhydrazone, [(OH)C_6H_4CH=NNHC(O)Ph] has been found in the range 125–500, much higher than that for the ferrocenyl and cymantrenyl analogues [2]. Isonicotinic hydrazide and their hydrazone derivative, = [$C_6H_4N(CH_3)C(O)C$=NNHC(O)C_5H_4N] shows MIC greater than 200 μg/ml against *E. coli*, *S. aureus* and *B. subtilis* [45]. Antibacterial study on similar types of ferrocenyl compounds reported recently by other groups against some bacterial strains also showed promising results [27], whereas inhibition activity with cymantrenyl compound has been rarely studied. Significant antibacterial activity for the reported organometallic compounds could possibly be due to the presence of ferrocenyl or cymantrenyl groups that are playing a vital role to increase the cell permeability and lipophilicity of the compounds. Factors like better pi-electron delocalization and blocking of metal binding sites of the enzyme of microorganism may also result in better inhibition activity in metal containing compounds. The MIC data reported in Table 3 for cymantrenyl hydrazones will eventually help us in understanding the properties of these types of compounds.

4. Conclusion

In summary, ferrocenyl Schiff base compounds with monosubstituted and 1,1′-disubstituted cyclopentadienyl hydrazone fragments have been synthesized. Methodology has been designed to obtain unsymmetrically substituted ferrocenyl hydrazone compounds. Study of their electrochemical properties by cyclic voltammetric techniques shows responses corresponding to ferrocene-ferrocenium couple. Reactions were carried out to isolate four cymantrenyl hydrazone compounds and have been structurally characterized by single crystal X-ray studies. We explored the antibacterial activity for some ferrocenyl and cymantrenyl compounds against, *B. subtilis*, *E. coli*, *S. aureus*, *K. pneumoniae* and *P. aeruginosa* and MIC values have been reported. Among all, compounds **6**, **9** and **10** were found to have good antibacterial activity *in vitro* against the bacterial strains. These ferrocenyl and cymantrenyl Schiff base compounds are further suited for complexation reaction to obtain multimetallic compounds and various modification for their application in the field of bioorganometallic chemistry. We are currently engaged in the synthesis and reactivity of a variety of Cp based organometallic compounds and exploring their possibility for effective medicinal properties.

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Appendix A. Supplementary material

CCDC 882042, 882043, 882044 and 905674 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Appendix B

http://dx.doi.org/10.1016/j.jorganchem.2013.02.020.

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