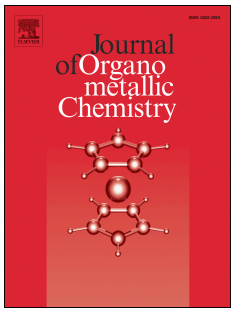
Accepted Manuscript



Some newly synthesized ferrocene based esters: Characterization, DNA interaction and DFT studies

Zaib un Nisa, Asghari Gul, Zareen Akhter, Muhammad Arif Nadeem, M. Nawaz Tahir, Moiz Uddin Ahmed

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Some newly synthesized ferrocene based esters: Characterization, DNA interaction and DFT studies

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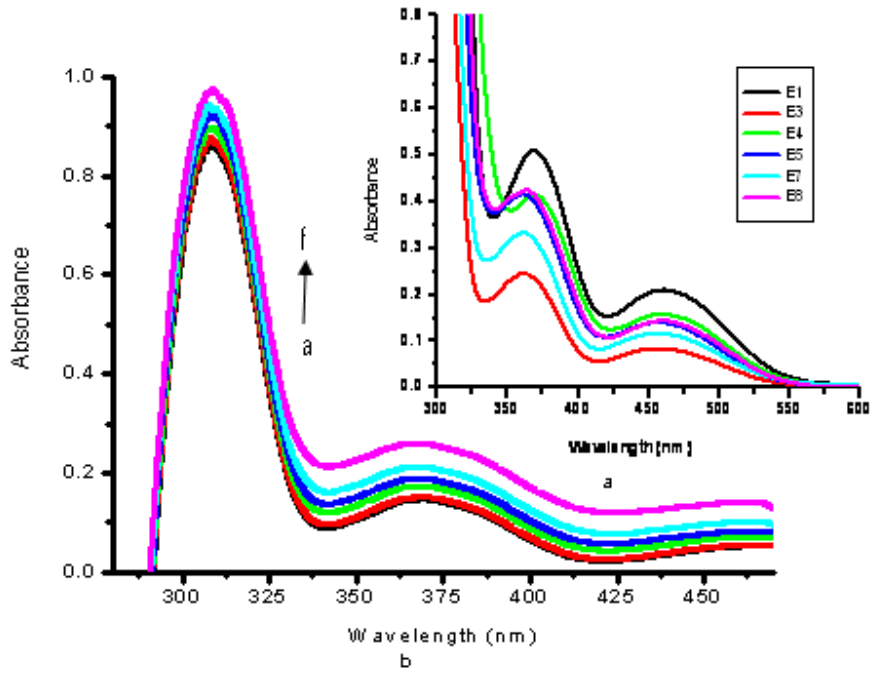
Graphical Abstract



(a) UV-Vis absorption spectra in Dichloromethane of representative ferrocenyl esters (b) UV-Vis spectra of 10 µM E4 for DNA Binding Study: (a) 0.00 µM (b) 1.1 µM (c) 2.2 µM (d) 3.3 µM (e) 4.4 µM (f) 5.5µM at room temperature.

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Highlights

- Ferrocenyl esters have been synthesized and characterized successfully.
- DFT calculations were carried out to support the experimental data.
- The interaction of these esters with double stranded chicken blood DNA was studied by cyclic voltammetry and absorption spectroscopic methods.

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Synopsis

- Synthesis and characterization of aromatic/aliphatic ferrocenyl ester.
- Electrochemical study of the products.
- UV spectroscopy and CV studies were planned in order to study their interaction with double stranded chicken blood DNA.

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Some newly synthesized ferrocene based esters: Characterization, DNA interaction and DFT studies

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Abstract

A series of aromatic/aliphatic ferroceneyl-esters (E1-E10) was synthesized by condensation of 4-ferrocenyl benzoic acid (FB) with various alcohols (A1-A10). Structural elucidation of these esters was carried out by FT-IR, ^{1}HNMR and UV-visible spectroscopic studies. Single crystal X-ray analysis was used to investigate solid state structure of E1, E4 and E8. DFT calculations were carried out at hybrid B3LYP level of theory using Density Gauss Double-Zeta with polarization functions full-electron basis sets to support the experimental data. Calculated structural parameters and FTIR vibrational frequencies of the optimized geometries were congruent to the experimental data. The interaction of the esters with double stranded chicken blood DNA was studied by cyclic voltammetry and absorption spectroscopic methods. Negative potential shift in cyclic voltammetric and the hyperchromic shift in UV-vis spectroscopy suggested external interaction

(groove binding). Interaction of ferrocenyl esters with DNA were found electrostatic in nature. Free energies of ferrocenyl esters-DNA complexes indicated spontaneity of their binding.

Keywords

Characterization, DFT calculations, Electrochemistry, Ferrocenyl esters, Synthesis, Thermal behavior

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1. Introduction

Discovery of bis(cyclopentadienyl) iron(II) has significantly influenced research in the advanced organometallic chemistry. Diverse coordination number, geometries, bonding modes, thermal stability, applications in catalysis, organic synthesis, and industry makes ferrocene (Cp_2Fe) most widely studied versatile compound in many research areas. It has also been investigated extensively for potential biological and medicinal applications from the beginning.[1-6]

In recent years, bio-organometallic chemistry has evolved as a rapidly emerging area which links classical organometallic chemistry to biology, molecular biotechnology and subsequently, with the preparation of novel peptide mimetic models and unnatural drugs. The oxidized species of ferrocene, ferrocenium (Cp^2Fe^+) was reported to be responsible for the cytotoxic properties on DNA mediated through its capacity to generate oxygen-free radical species. Presence of the ferrocenyl moiety enhances activity due to its relatively low reversible redox behavior.[6-11] This property is responsible for generating reactive oxygenated species under physiological conditions resulting in increase in anti-cancer activity as well as cell permeability due to its lipophilic nature.[12] Ferrocene has been recently reported to have antitumor properties due to the metabolic

formation of ferrocenium ions which induces oxidative damage to DNA. As a result, many functionalized ferrocenes have been prepared and tested in cancer cells.[7-12]

We report, herein, synthesis, structural characterization (experimental and calculated) of some newly synthesized ferrocenyl-esters. Different aliphatic and aromatic ferrocenyl esters were designed to study the effect of the presence of these groups on the DNA binding ability of the compounds, [7] which was performed using cyclic voltammertry and Uv-visible spectroscopic techniques.

2. Material and Methods

2.1 Materials and Reagents

Ferrocene (172.5 °C), hexadecyltrimethylammonium bromide sodium hydroxide (318 °C), N,N-dicyclohexylcarbodiimide (DCC, 34 °C), 4-N,N-dimethylaminopyridine (DMAP, 110-113 °C), 4-aminobenzoic acid (187–189 °C), sodium nitrite (271 °C), octadecan-1-ol (170-171 °C), hexadecan-1-ol (b.p. 150°C to 154), m-cresol (11 °C), decan-1-ol and conc. H_2SO_4 (10 °C) were purchased from Fluka, Switzerland and used without further purification. Anhydrous $MgSO_4$ (dec. 1124 °C) and benzoyl chloride were purchased from Panreac, Spain. 1-Napthol (95 to 96 °C), propan-1-ol (97 to 98 °C), propan-2-ol, silica gel 60-HF_{254} were obtained from Merck, Germany. $NaHCO_3$ and conc. HCl were obtained from Riedel-deHaen, Germany. The solvent dichloromethane purchased from Sigma Aldrich used were purified according to the standard reported method.

2.2 Synthesis

2.2.1 4-Ferrocenyl benzoic acid (FB)

FB was synthesized following a reported procedure out lined in the scheme 1. [14, 15]

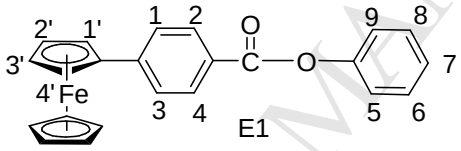
2.2.2 Synthesis of Ferrocenyl Ester Derivatives (E1-E10)

1.306 mmol 4-ferrrocenyl benzoic acid and 1.306 mmol alcohols (A1-A10, scheme 1) were added to a three- necked round-bottom flask fitted with reflux condenser, magnetic stirrer and inert gas

inlet/outlet. 50 ml anhydrous CH_2Cl_2 was added to the flask with constant stirring. After that a solution containing 0.296 g (1.436 mmol) N,N-dicyclohexylcarbodiimide (DCC) and a catalytic amount of N,N-dimethylaminopyridine (DMAP) in 10 ml anhydrous CH_2Cl_2 was added to the flask under N_2 atmosphere. The reaction mixture was stirred for 4 hours at room temperature. The dicyclohexylurea was filtered off and the solvent was removed under reduced pressure. The obtained products were purified by passing through a column of silica gel (ethyl acetate: n-hexanes), and then recrystallized from chloroform/ n-hexane (1:9).

2.2.3 Synthesis of phenyl 4-ferrocenyl benzoate (E1)

The ferrocenyl ester phenyl 4-ferrocenyl benzoate was synthesized and purified by above mentioned general method using phenol (0.122 g; 1.306 mmol). The product was purified by passing through a column of silica gel (ethyl acetate: n-hexane = 1:5).

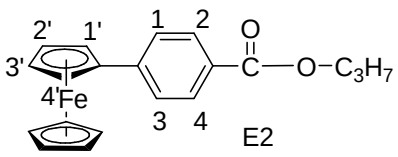


E1

Yield; 54.0%, m.p. 129°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.309 (2H, d, *J* = 8.4 Hz, 2,4), 7.754 (2H, d, *J* = 8.4 Hz, 1,3), 7.488 (2H, m, 5,9), 7.347-7.283 (3H, m, 6-8), 4.996 { 2H, t, *J* = 1.8 Hz, 1'4' (η^5-C_5H_4)}, 4.487 { 2H, t, *J* = 1.8 Hz, 2',3' (η^5-C_5H_4)}, 4.057 { 5H, s, (η^5-C_5H_5)}. UV/vis (CH_2Cl_2): λ_{max} 461 (ε=1500), 368 (ε=3000) nm. $C_{23}H_{18}FeO_2$ Calcd: C, 72.251, H, 4.712; Found; C, 71.39; H, 4.02.

2.2.4 Synthesis of n-propyl 4-ferrocenyl benzoate (E2)

n-Propyl 4-ferrocenyl benzoate was prepared by the procedure described above using (0.078 g; 1.306 mmol) propane-1-ol. Obtained ester was purified by passing through a column of silica gel (ethyl acetate: n-hexane = 1:6).

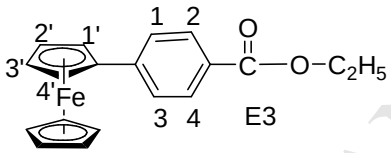


E2

Yield; 52.0%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.163 (2H, d, *J* = 8.4 Hz, 2,4), 7.981 (2H, d, *J* = 8.4 Hz, 1,3), 4.736 {2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.413 { 2H, t, *J* = 1.8 Hz, 2',3' (η^5-C_5H_4)}, 4.060 {5H, s, (η^5-C_5H_5)}, 4.127 (2H, t, *J* = 7.2 Hz, -OCH_2), 1.836 (2H, m, -CH_2-), 1.069 (3H, t, *J* = 7.2 Hz, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 455 (ε=2360), 344 (ε=9280) nm. 344. $C_{20}H_{20}FeO_2$ Calcd: C, 68.96, H, 5.747; Found; C, 67.88; H, 4.98.

2.2.5 Synthesis of ethyl 4-ferrocenyl benzoate (E3)

Ethyl 4-ferrocenyl benzoate was synthesized by above mentioned procedure using (0.060 g; 1.306 mmol) ethanol, obtained product was purified by passing through a column of silica gel (ethyl acetate: n-hexane = 1:5).

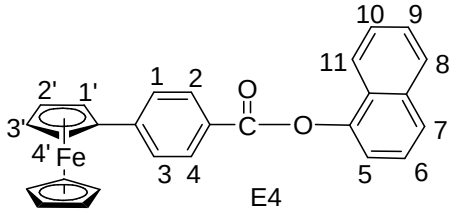


E3

Yield; 53.0%, m.p. 88^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.871 (2H, d, *J* = 8.4 Hz, 2,4), 7.669 (2H, d, *J* = 8.4 Hz, 1,3), 4.909 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.452 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 4.034 { 5H, s, (η^5-C_5H_5)}. 4.313 (2H, q, *J* = 7.2 Hz, -OCH_2), 1.332 (3H, t, *J* = 7.2 Hz, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 455 (ε=2630), 361 (ε=7890) nm. $C_{19}H_{18}FeO_2$ Calcd: C, 68.26, H, 5.38; Found; C, 67.88; H, 5.08.

2.2.6 Synthesis of 1-naphthyl 4-ferrocenyl benzoate (E4)

1-Naphthyl 4-ferrocenyl benzoate was synthesized by the procedure outlined in scheme 1 by using (0.18 g; 1.306 mmol) 1-napthol. Ferrocenyl ester obtained was purified by passing through a column of silica gel (ethyl acetate: n-hexane = 1:5).

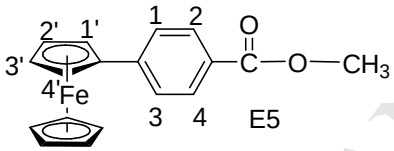


E4

Yield; 56.0%, m.p. 181-182°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.169 (2H, d, *J* = 8.4 Hz, 2,4), 7.811 (2H, d, *J* = 8.4 Hz, 1,3), 8.070-7.476 (7H, m, 5-11), 4.991 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.507 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 4.089 { 5H, s, (η^5-C_5H_5)}. UV/vis (CH_2Cl_2): λ_{max} 460 (ε=2000), 370 (ε=6550) nm. $C_{27}H_{20}FeO_2$ Calcd: C, 75.0, H, 4.62; Found; C, 73.88; H, 4.08.

2.2.7 Synthesis of methyl 4-ferrocenyl benzoate (E5)

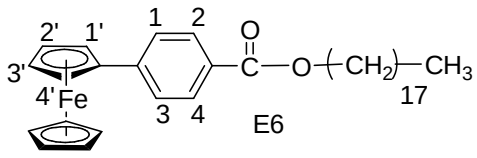
The specie methyl 4-ferrocenyl benzoate was prepared using (90.041 g; 1.306 mmol) methanol by the above mentioned procedure. Purification of resulting ester was done by column of silica gel (ethyl acetate: n-hexane = 1:7).



Yield; 55.0%, m.p. 100-101°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.64 (2H, d, *J* = 8 Hz, 2,4), 7.43 (2H, d, *J* = 8 Hz, 1,3), 4.21 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.061 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 3.79 {5H, s, (η^5-C_5H_5)} 4.13 (3H, s, -OCH_3). UV/vis (CH_2Cl_2): λ_{max} 455 (ε=2360), 361 (ε=6910) nm. $C_{18}H_{16}FeO_2$ Calcd: C, 67.5, H, 5.00; Found; C, 66.4; H, 4.88.

2.2.8 Synthesis of n-octadecanyl 4-ferrocenyl benzoate (E6)

The n-octadecanyl 4-ferrocenyl benzoate was synthesized by general procedure described above using (0.325 g; 1.306 mmol) n-octadecanol. Obtained product was purified by passing through a column of silica gel (n-hexane).

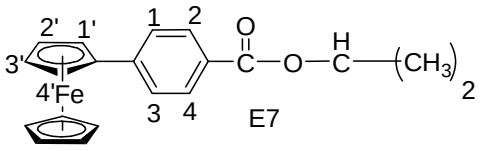


Yield; 65.0%, m.p. 66°C. ^{1}H NMR (300 MHz, $^{13}CHCl_3$): δ 7.970 (2H, d, *J* = 8.4 Hz, 2,4), 7.530 (2H, d, *J* = 8.4 Hz, 1,3), 4.726 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.403 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 4.049 { 5H, s, (η^5-C_5H_5)}, 4.324 (2H, t, *J* = 6.6 Hz, -OCH_2-), 1.785 (2H, m, -

CH_2-), 1.311-1.269 (30H, m, -CH_2-), 0.849 (3H, t, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 455 (ε=3440), 361(ε=9078) nm. $C_{35}H_{50}FeO_2$ Calcd: C, 75.26, H, 8.96; Found; C, 74.4; H, 8.08.

2.2.9 Synthesis of isopropyl 4-ferrocenyl benzoate (E7)

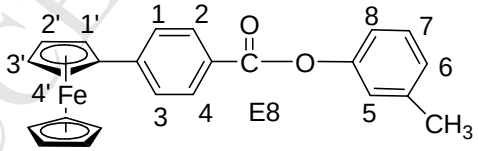
Isopropyl 4-ferrocenyl benzoate was prepared by using (0.078 g; 1.306 mmol) 2-propanol following the general procedure mentioned above. Obtained ferrocenyl ester was purified by passing through a column of silica gel (ethyl acetate: n-hexane = 1:6).



Yield; 57.0%, m.p. 71-73°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.873 (2H, d, *J* = 8.4 Hz, 2,4), 7.667 (2H, d, *J* = 8.4 Hz, 1,3), 4.904 {2H, t, *J* = 1.8 Hz, 1',4' (η^5-C_5H_4)}, 4.450 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 4.032 { 5H, s, (η^5-C_5H_5)} 4.345 (1H, m, -OCH-), 1.329 (6H, d, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 454 (ε=2520), 362 (ε=6360) nm. Calcd: C, 68.96, H, 5.747; Found; C, 67.4; H, 5.08. $C_{20}H_{20}FeO_2$ Calcd: C, 68.96, H, 5.747; Found; C, 67.4; H, 5.08

2.2.10 Synthesis of (3-methyl)-phenyl 4-ferrocenyl benzoate (E8)

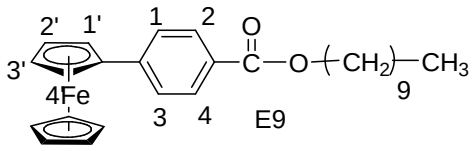
(3-Methyl)-phenyl 4-ferrocenyl benzoate was synthesized by above mentioned general procedure using m-cresol (0.140 g; 1.306 mmol), the produced ferrocenyl ester was purified by passing through a column of silica gel (ethyl acetate: n-hexane = 1:7).



Yield; 58.0%, m.p. 109-110°C. ^{1}H NMR (300 MHz, $^{13}CHCl_3$): δ 8.184 (2H, d, *J* = 8.7 Hz, 2,4), 7.605 (2H, d, *J* = 8.7 Hz, 1,3), 7.284-7.061 (4H, m, 5-8), 4.781 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.452 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 4.160 { 5H, s, (η^5-C_5H_5)}, 2.420 (3H, s, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 459 (ε=1070), 363 (ε=2893) nm. $C_{20}H_{20}FeO_2$ Calcd: C, 72.72, H, 5.05; Found; C, 71.4; H, 4.98.

2.2.11 Synthesis of n-decanyl 4-ferrocenyl benzoate (E9)

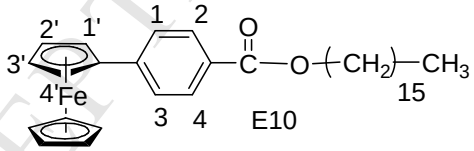
n-Decanyl 4-ferrocenyl benzoate was synthesized by above mentioned general method using (0.248 g; 1.306 mmol) n-decanol. ferrocenyl ester obtained was purified by passing through a column of silica gel (n-hexane).



Yield; 64.0%. ^{1}H NMR (300 MHz, $^{13}CHCl_3$): δ 7.898 (2H, d, *J* = 8.4 Hz, 2,4), 7.527 (2H, d, *J* = 8.4 Hz, 1,3), 4.729 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.407 { 2H, t, *J* = 1.8 Hz, 2',3'(η^5-C_5H_4)}, 4.052 { 5H, s, (η^5-C_5H_5)}, 4.326 (2H, t, *J* = 6.6 Hz, -OCH_2-), 1.784 (2H, m, -CH_2-), 1.279-1.251 (14H, m, -CH_2-), 0.849 (3H, t, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 455 (ε=2350), 369 (ε=3990) nm. $C_{21}H_{34}FeO_2$ Calcd: C, 67.37, H, 9.09; Found; C, 66.92H, 8.99.

2.2.12 Synthesis of n-hexadecanyl 4-ferrocenyl benzoate (E10)

The n-hexadecanyl 4-ferrocenyl benzoate benzoate was prepared by above mentioned procedure using (0.315 g; 1.306 mmol) n-hexadecanol. Obtained product was purified by passing through a column of silica gel (n-hexane).



Yield; 68.0%, m.p. 73^{o}C. ^{1}H NMR (300 MHz, $^{13}CHCl_3$): δ 7.971 (2H, d, *J* = 8.4 Hz,2,4), 7.529 (2H, d, *J* = 8.4 Hz, 1,2), 4.727 { 2H, t, *J* = 1.8 Hz, 1',4'(η^5-C_5H_4)}, 4.404 { 2H, t, *J* = 1.8 Hz, 2',3' (η^5-C_5H_4)}, 4.050 { 5H, s, (η^5-C_5H_5)}, 4.325 (2H, t, *J* = 6.6 Hz, -OCH_2-), 1.784 (2H, m, -CH_2-), 1.315-1.270 (26H, m, -CH_2-), 0.894 (3H, t, -CH_3). UV/vis (CH_2Cl_2): λ_{max} 455 (ε=2380), 368 (ε=4920) nm. $C_{33}H_{46}FeO_2$ Calcd: C, 74.70, H, 8.73; Found; C, 72.4; H, 7.98. Calcd: C, 74.71, H, 8.67; Found; C, 72.4; H, 7.98

2.3 Characterization

^{1}H NMR spectral analysis was carried out using Bruker Avance 300 MHz NMR instrument (in DMSO-d_6). Fourier transform infrared spectra were recorded on a FTIR instrument, Nicolet 6700, Thermoscientific company, USA using solid state analysis. Melting temperature of the esters was determined on a melting point apparatus, Mel-Temp., Mitamura Riken Kogyo, Inc., Tokyo, Japan, using open capillary tubes. Thermal characterization was carried out using Perkin-Elmer instrument TGA7 thermobalane, at a heating rate of 20-25 ^{o}C/min under N_2 atmosphere upto maximum temperature of 600 ^{o}C. Single crystal X-ray studies were performed at 150(2) K on a Bruker Apex II CCD diffractometer using MoK_α radiation (λ= 0.71073A^o). The cyclic voltammetry studies of representative ferrocene based esters were performed using Eco Chemie Auto lab. PGSTAT 12 potentiostat/galvanostat instrument with three electrode cells, glassy carbon (GC, 0.071 cm^2), Pt wire (0.1 cm thickness) and saturated calomel electrode (SCE)/ 3 M KCl were employed as working, counter and reference electrode respectively, using tetrabutylammonium perchlorate (TBAP) as a supporting electrolyte. The working electrode was polished with powdered α-alumina on a polishing pad and washed with doubly distilled water prior to each experiment. Absorption spectra of the esters were recorded on shimadzu 1700 spectrophotometer, Kyoto Japan. Purity of the product was monitored by TLC using pre-coated kieselgel 60-HF TLC platter using the eluent system that gave the best separation. Flash column chromatography was carried out using a forced flow of the indicated solvent on Kieselgel using pre-coated kieselgel 60-HF (0.02−0.045 mm).

3. Results and discussion

FB was synthesized following the reported method given in the scheme 1. It was then esterified with the aromatic and aliphatic alcohols (A1-A10, Scheme 1) producing ferrocenyl esters (E1-E10). The process was carried out in anhydrous dichloromethane using N,N-dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-N,N-dimethylaminopyridine (DMAP).

The viscous products obtained were further purified using flash column chromatography. FTIR, ^{13}C and ^{1}H-NMR analyses were carried out in order to confirm the syntheses of Es.

In FTIR spectra a broad band of carboxylic group (–COOH, 3500-2200 cm^{-1}) disappeared with the appearance of an intense carbonyl (C=O) peak at 1700-1740 cm^{-1} indicating the formation of ester linkage.[5,6] Typical Fe-Cp stretching vibration was found in range 470-490 cm^{-1}. The representative FTIR spectra are given in supporting information (SI). In order to support the experiental data, IR frequencies were calculated by using hybrid B3LYP with DFT-optimized DGDZVP basis sets. These frequencies were scaled according to the reported method and are given in supplementary information.[15]

^{1}H-NMR spectroscopic analysis of FB and ferrocenyl esters was carried out using TMS as an internal reference to support the FTIR results. Relevant peaks for FB [14] were found in the spectrum. ^{1}H-NMR spectra of Es were consistent with the proposed structures. Characteristic signals associated with the proton of ferrocene moiety were present in all spectra in the form of one upfield singlet 4.01-4.07 ppm and two downfield triplets [13] corresponding to unsubstituted and substituted cp ring protons respectively. Disappearance of signal because of carboxylic group (12.95 ppm) and appearance of signals due to aliphatic and aromatic substituents confirmed the formation of esters. Signals in ^{13}C-NMR spectra of all the synthesized compounds were in appropriate regions and confirmed the successful synthesis and purity of esters. [5-8] Their representative NMR spectra are given in SI. Single crystals suitable for X-ray analysis of E1, E4 and E8 were grown by slow evaporation from the solution. The data suggested that the compound **E1** was crystallized in the monoclinic space group $P2_1/c$. The Fe1-C bond lengths for η^5 (C_5H_4) ring of **E1** were in the range of 2.030(2) -2.051(2) Å (calc. 2.041-2.63 Å), similar to the η^5 (C_5H_5) ring, with a range of 2.017(3)-2.051(3) Å (calc. 2.023-2.059 Å). The cyclopentadienyl C-C bond lengths were in the range of 1.406(3)– 1.432(3) Å (calc. 1.411-1.441 Å) for η^5 (C_5H_4) ring whilst

for η^5 (C_5H_5) ring, these ranges from 1.371(3)–1.410(4) Å (calc. 1.383-1.421 Å). The representative bond length and angles are given in table 1.

The cyclopentadienyl rings were deviated slightly from an eclipsed geometry in **E1**. The alkyl benzoate chain is attached with the cyclopentadienyl ring in almost linear fashion as evidenced by the torsion angle of C9-C10-C11-C12, the value of which was 3.7(3)° (calc. 3.9). However, disposition of terminal phenyl (C_6H_5) ring, which gave a C17-O2-C18-C23 torsion angle of 126.9(2)° (calc. 127) mean that the phenyl moiety in **E1** was significantly out of the benzoate CO_2 plane. Analysis of hydrogen bonding in **E1** showed only two interactions, involving the un substituted ring and the ester O=C group as η^5-(C_5H_5) C-H....O=C (2.651 Å, calc. 2.682) interactions, together with C_{sp2}-H…..π(C_5H_5) interactions. The molecules were arranged as one dimensional column along a-axis through π…..π stacking interactions of two phenyl rings in the ester chain. The compound **E4** crystallized in the monoclinic space group *$P2_1/n$.* The Fe1-C bond lengths for η^5 (C_5H_4) ring of **E4** were in the range of 2.025(3)-2.048(2) Å (calc. 2.031-2.049 Å), similar to the η^5 (C_5H_5) ring, with a range of 2.027(3)-2.044(3) Å (calc. 2.029-2.051 Å), figure 1. The cyclopentadienyl C-C bond lengths were in the range of 1.399(5)– 1.428(4) Å (calc. 1.40-1.431 Å) for η^5 (C5H4) ring whilst for η^5 (C_5H_5) ring, these ranged from 1.395(4)– 1.416(4) Å (calc. 1.41-1.45 Å). Unlike **E1**, the cyclopentadienyl rings were in almost eclipsed geometry in **E4**. Similarly, unlike **E1**, the alkyl benzoate chain attached with the cyclopentadienyl ring was out of plane as evidenced by the torsion angle of C9-C10-C11-C12, the value of which was 148.1(3)° (calc. 149.2).

Similarly, disposition of terminal phenyl (C_6H_5) ring, which gave a C17-O2-C18-C23 torsion angle of 119.9(3)° (calc. 119.9), meant that the phenyl moiety in **E4** was also significantly out of the benzoate CO_2 plane. Analysis of hydrogen bonding in **E4** showed only two types of interactions, involving the un substituted ring and the ester O=C group as η^5-(C_5H_5)C-H....O=C (2.552 Å) interactions together with C-H…..π interactions. Due to these intermolecular attractions,

each molecule was linked with neighboring three molecules and arranged in zigzag fashion forming three dimensional supra-molecular architecture (figure 2).

The compound **E8** crystallized in the monoclinic space group $P2_1/n$. The Fe1-C bond lengths for η^5 (C5H4) ring of **E8** were in the range of 2.018(3) -2.036(2) Å (calc. 2.11-2.04 Å), similar to the η^5 (C5H5) ring, with a range of 2.009(3)-2.035(3) Å (calc. 2.010-2.041 Å). The cyclopentadienyl C-C bond lengths were in the range of 1.403(4) – 1.423(4) Å (calc. 1.410-1.438 Å) for η^5 (C5H4) ring whilst for η^5 (C5H5) ring, these ranges from 1.363(5)– 1.416(6) Å (calc. 1.371-1.422 Å). Unlike **E1**, the cyclopentadienyl rings were in almost eclipsed geometry in **E8**. The alkyl benzoate chain attached with the cyclopentadienyl ring was slightly out of plane as indicated by the torsion angle of C6-C10-C11-C12, the value of which was 13.0(4)° (calc. 13.3). However, disposition of terminal phenyl (C_6H_5) ring, which gave a C17-O2-C18-C23 torsion angle of 88.1(3)° (calc. 88.7) means that the phenyl moiety in **E8** wass almost at right angle to the benzoate CO_2 plane. Analysis of hydrogen bonding in **E8** showed two types of interactions, involving the CH_3 substituted on phenyl ring and the ester O=C group as (C_{sp3})C-H....O=C (2.692 Å, calc. 2.71 Å) interactions together with C-H….C-H and C-H…..π interactions between (C_6H_5) C-H and η^5-(C_5H_5) of neighboring molecules. The molecules were arranged as one dimensional column along b-axis, table 2. The geometric parameters of E1, E4 and E8 calculated by using hybrid B3LYP

With DFT-optimized DGDZVP basis set were found in the usual ranges.[15]] The X-ray data suggests that the bond angles and bond lengths are comparable with the previous reports on ferrocene derivatives. For example, Hongwei used FB for the synthesis of one dimensional coordination polymers and the FB showed similar structural features as E1, E4 and E8 [16]. Similarly, Gandrath synthesized some ferrocene esters and carboxylates, the C-C, Fe-C bond lengths and bond angles are comparable with their structural data [17]. Recently, Guoxiong synthesized errocenylphosphonofluoridodithioate derivatves and the data is again in agreement with the our ferrocene moety [18].

In order to study the reactions, electrostatic potential V(r) maps were calculated which are known for the identification of the electronic charge distribution around molecular surface and subsequently to predict sites for the reactions. These maps were calculated by using the same basis set as for IR frequencies. Attempt was made to predict the site for electrophilic/nucleophillic attacks. It can be seen that the FB is stable having almost uniform distribution of charge density, figure 3. However, oxygen and nitrogen atoms are surrounded by a greater negative charge surface, making these sites potentially more favorable for electrophilic attack (red). On the other hand the electrostatic potential map calculated for phenol showed positive (blue) mesh around OH group; however the aromatic ring seems neutral in terms of electron density. Thus distribution of potential in both esters is in favor of the esterification reaction. [15]

UV-visible spectroscopic technique was used to study the interaction (range 300-600 nm) and the binding mode of esters with double strand chicken blood DNA. It was found that the esterification of FB with various alcohols resulted in red shift with respect to the ferrocene due to the electron withdrawing nature of the ester linkage. [19] When compared to FB the aliphatic Es exhibited blue shift (hypsochromic effect, E2, E3, E5, E6, E7, E9 and E10) whereas aromatic compounds showed red shift (bathochromic effect, E1, E4, and E8) which was in accordance with the literature that the increase in conjugation results in the better overlap of π-orbitals and consequently decreases in the energy gap.

DNA binding study using UV-Vis spectroscopy between E4-DNA was investigated by studying interaction between 10 μM E4 and various concentrations (0.0–5.5 μM) of DNA, figure 4. It was found that there was an increase in absorbance (hyperchromism; figure. 4) with the increase in the concentration of DNA, based on the expected conformational changes of cyclopentadienyl rings in E4. [20,21] From literature it is known that NFC (4-nitrophenylferrocene), which is a potential anticancer drug exhibit similar behavior with DNA. NFC–DNA interactions reduce the face to face base stacking, causing extension and subsequently uncoiling of the DNA double helical

structure [7,8] or external interaction (groove binding or electrostatic) resulting in hyperchromic shift.[12,23] Therefore E4 is expected to exhibit groove binding with DNA. Binding constants for Es-DNA were determined at room temperature employing Benesi-Hildebrand equation.[24] Different solvent mixture were used to calculate these constants depending upon the solubility of the products like DMSO/H_2O (9:1) mixture for E4, E7 DMF/ H_2O (9:1) mixture for E10, E6 and EtOH/ H_2O (9:1) mixture for the remaining Es. The binding energy data for Es was found in range $6.21 \times 10^5\ M^{-1}$ to $2.48 \times 10^3\ M^{-1}$, table 3, figure 5 which was in agreement with the literature which showed that the typical range is between 10^2 -$10^5\ M^{-1}$ for ferrocenl esters. Negative ΔG values found in range -17.74 to −30.27 kJ/mol signified the spontaneity of interaction.

Electrochemical study was carried out to study redox behavior of the reactions. Cyclic voltammograms and approximately one value of Ipc/Ipa for all esters indicated reversible redox behavior. The selected CV data of the Es is given in table 4 and representative cyclic voltamograms are given in figure 9. The investigation carried out at different scan rates revealed that oxidation and reduction peaks showed a negligible shift in peak potential with the increase in scan rate (figure 7) which is a particular behavior related to reversible redox electro-active specie. [25,26] The Randles-Sevcik equation was used to calculate the diffusion coefficient values (D), Kochi's formula was used to calculate charge transfer coefficient(α) and Nicholson, Kochi method was used to calculate the Heterogeneous rate constant (table 5). Calculated α value, approximately 0.5 (figure 8, table 5) indicated reversibility of the redox process for E1-E10. [27] A straight line was obtained from the plot of peak current versus square root of scan rate (figure 8). This linear relationship suggested that processs is diffusion controlled.

DNA binding study using CV was used to elucidate the mechanism of their interaction with double strand chicken blood DNA in vivo figure 9, [28-30] the addition of various concentrations of DNA on fixed concentrations of E1 resulted in decrease in the current reduction peak values. Also a negative peak potential shift (cathodic shift) in the CV was observed which was attributed

to the electrostatic interaction of the positively charged ferrocene of E1 with polyanionic DNA molecule. The substantial diminution in peak current was due to the formation of slowly diffusing E1-DNA complex which lowered the concentration of free E1. The cathodic shift in peak also indicated that Fe (II) of E1 was easier to oxidize in the presence of DNA as its oxidized form was more strongly bound to DNA than its reduced form. [31-35] Using different concentrations of DNA, the binding constants, K_b for all the Es-DNA complexes were calculated at room temperature (25^oC), (figure 10, table 6). The binding energy data for Es was found in range 6.41×10^5 to 2.71×10^3. K_b and ΔG valves obtained from CV were in good agreement with the ones obtained from UV-vis techniques (table 6 and table 3 respectively).

4. Conclusion

A series of aromatic and aliphatic ferrocenyl ester E1-E10 was synthesized and characterized using standard protocols/procedures. Calculated bond distances, angles and vibrational IR frequencies showed excellent correlation with the experimental data**.** Their DNA interaction through UV-vis spectroscopy and Cyclic voltammetry were utilized in order to investigate their potential activity to be used as drugs. The observed hperchromism and cathodic shifts in peak potential suggested their different modes of interaction with DNA. Electrochemical studies showed that all the synthesized ester follow diffusion controlled one electron reversible redox behavior and formal potential values of compounds can be tailored by changing the substituent attached to the ferrocenyl moiety. Hence Es could be considered as a potential material for drugs. Among all, E3 showed greatest binding constant as well as Gibbs free energy thus it has greatest potential to be used as drug.

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Supplementary Information

CCDC number for the compounds $C_{23}H_{18}FeO_2$, $C_{27}H_{20}$ FeO_2 and C_{24} H_{20}FeO2 are 1053011, 1053012 and 1053013 respectively.

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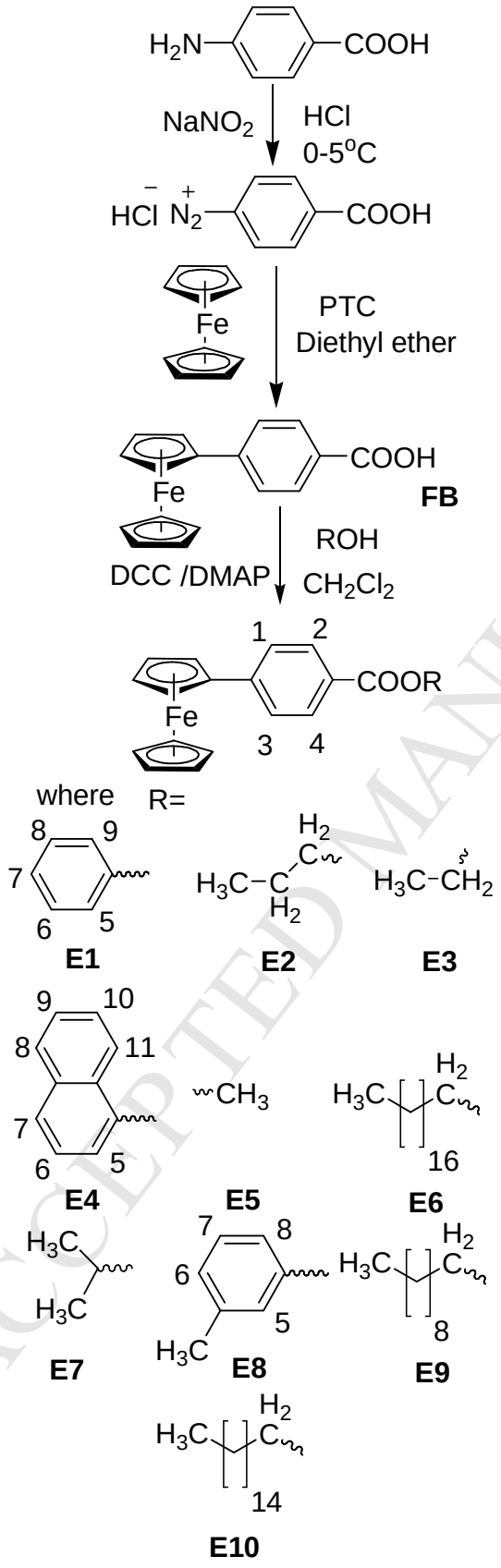
11. Figure 11. Plot of Ip^2 *vs* Ipo^2- Ip^2 /[DNA] for calculation of binding constant (using CV) of 1mM E1-DNA adduct at room temperature.



Scheme: 1 Synthesis of 4-Ferrocenyl benzoic acid (FB) and 4-ferrocenyl alkyl benzoate

Table 1. Selected bond lengths and bond angles of E1, E4 and E8

Important bond lengths and bond angles of E1($C_{23}H_{18}FeO_2$)			
Bond	**Bond length A°**	**Bond angle**	**Bond angle Measurement (º)**
Fe1—C1	2.017 (3)	C1—Fe1—C5	40.41 (13)
Fe1—C6	2.030 (2)	C5—Fe1—C7	125.80 (13)
Fe1—C10	2.046 (2)	C17—O2—C18	120.22 (18)
Fe1—C4	2.051 (3)	Fe1—C1—H1	124.6
C3—C4	1.374 (4)	C4—C5—Fe1	71.37 (16)
O2—C18	1.399 (3)	C7—Fe1—C2—C1	−165.9 (2)
C4—H4	0.9300	C19—C20—C21—C22	0.0 (4)
C21—C22	1.367 (4)	C18—O2—C17—O1	3.0 (3)
C18—C23	1.369 (3)	C13—C14—C17—O1	3.7 (3)
C11—C16	1.391 (3)	Fe1—C8—H8	126.5
Important bond lengths and bond angles of E4 ($C_{27}H_{20}FeO_2$)			
Bond	**Bond length A°**	**Bond a gle**	**Bond angle Measurement (º)**
Fe1—C6	2.025 (3)	C10—C6—H6	126.2

Fe1—C10	2.033 (3)	Fe1—C6—H6	125.9
Fe1—C4	2.038 (3)	C6—C7—H7	125.8
O1—C17	1.183 (3)	Fe1—C7—H7	126.4
O2—C18	1.413 (3)	C11—C12—H12	119.2
C4—H4	0.9300	O1—C17—O2	122.8 (3)
C2—C3	1.416 (4)	O2—C17—C14	112.1 (2)
C1—C2	1.395 (4)	C10—Fe1—C7—C6	38.19 (19)
C3—H3	0.9300	C6—C7—C8—Fe1	−58.7 (2)
C23—C24	1.411 (4)	C10—Fe1—C1—C5	−121.09 (19)
C1—C5	1.405 (4)	C23—C22—C27—C26	−1.9 (5)

Important bond lengths and bond angles of E8 ($C_{24}H_{20}FeO_2$)

Bond	**Bond length A°**	**Bond angle**	**Bond angle Measurement (º)**
Fe1—C10	2.018 (3)	C1—Fe1—C10	C1—Fe1—C10
Fe1—C4	2.035 (3)	C10—Fe1—C6	41.22 (10)
O2—C17	1.352 (3)	C10—Fe1—C4	158.43 (14)
C2—H2	0.9300	C17—O2—C18	117.9 (2)
C6—C7	1.415 (4)	C5—C1—Fe1	69.8 (2)
C11—C12	1.396 (4)	C3—C2—C1	108.9 (4)
C20—C21	1.351 (6)	C5—C1—H1	127.0
C24—H24C	0.9600	Fe1—C8—H8	126.4
O2—C18	1.396 (4)	O1—C17—O2	122.1 (3)
C14—C17	1.480 (4)	O2—C17—C14	111.9 (3)
Fe1—C9	2.029 (3)	C7—Fe1—C8—C9	119.8 (3)

Table 2 Crystallographic data and structure refinement results

	E1	**E4**	**E8**
Empirical formula	$C_{23}H_{18}FeO_2$	$C_{27}H_{20}FeO_2$	$C_{24}H_{20}FeO_2$
Formula weight	382.22	432.28	396.25
Temperature	296 K	296 K	296 K
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/n$
a / Å	5.8859 (2)	12.4697 (4)	11.4841 (5)
b / Å	21.1780 (9)	14.2173 (5)	8.8836 (4)
c / Å	13.9737 (5)	12.8412 (4)	18.7976 (8)
α	90°	90°	90°
β	98.353(2)°	118.243 (1)°	98.471 (2)°
Γ	90°	90°	90°
Volume / Å^3	1723.37 (11)	2005.53 (11)	1896.81 (14)
Z	4	4	4
Density Mg m^{-3}	1.473	1.432	1.388
S	1.05	1.04	1.02
F(000)	792	896	824
Limiting indices	$-7 \le h \le 5$	$-14 \le h \le 14$	$-14 \le h \le 14$
	$-24 \le k \le 25$	$-17 \le k \le 17$	$-10 \le k \le 7$
	$-14 \le l \le 16$	$-15 \le l \le 15$	$-23 \le l \le 23$
Reflections number	3109	3620	3718
R_{int}	0.027	0.041	0.024
T_{max}	25.3°	25.3°	26.0°
$wR(F^2)$	0.086	0.104	0.121

Table 3. Binding constant and free energy values for ferrocenyl esters-DNA complexes from UV-spectrophotometric data at room temperature.

Compounds	*Binding Constant †(K_b) M^{-1}	*Free energy (-ΔG= −RT ln K) Kj
E1	2.51×10^5	28.22
E2	1.87×10^5	27.55
E3	6.21×10^5	30.27
E4	1.83×10^5	27.50
E5	1.09×10^5	26.33
E6	8.22×10^3	20.46
E7	1.58×10^4	22.01
E8	8.62×10^4	25.79
E9	2.48×10^3	17.74
E10	5.20×10^3	19.42

Table 4. Selected CV data for compounds in mentioned solvents using KCl/TBAP *vs* Ag/AgBr: scan rate= 100mV/s

Compounds	E_p^a (V)	E_p^c (V)	*E^o (mV)	†ΔEp (mV)
E1 (Ethanol)	0.452	0.210	331	242
E2 (Ethanol)	0.352	0.170	261	182
E3 (Ethanol)	0.422	0.207	314	215
E4 (DMSO)	0.582	0.468	525	113
E5 (Ethanol)	0.291	0.198	244	93
E6 (DMF)	0.502	0.428	465	74
E7 (DMSO)	0.382	0.268	325	114
E8 (Ethanol)	0.321	0.248	499	73
E9 (Ethanol)	0.392	0.258	325	134
E10 (DMF)	0.572	0.448	510	124

*$E^o = E_p^a + E_p^c / 2$, †$\Delta Ep = E_p^a - E_p^c$

Table 5. Kinetic parameters calculated from CV data (Effect of scan rate on Es) of the compounds

Compounds	**†Diffusion coefficient D (cm^2s^{-1})**	**†Charge transfer coefficient α**	**†Heterogeneous rate constant $K_{s,h}$(cms^{-1})**
E1	1.66×10^{-5}	0.500	1.2×10^{-3}
E2	1.23×10^{-5}	0.501	1.74×10^{-3}
E3	1.549×10^{-5}	0.497	9.4×10^{-2}
E4	1.11×10^{-7}	0.499	1.05×10^{-3}
E5	1.03×10^{-5}	0.494	4.0×10^{-3}
E6	2.5×10^{-6}	0.500	2.3×10^{-3}
E7	2.7×10^{-7}	0.500	5.26×10^{-4}
E8	2.62×10^{-6}	0.499	2.4×10^{-3}
E9	2.62×10^{-6}	0.500	8.4×10^{-4}
E10	4.6×10^{-6}	0.500	1.48×10^{-3}

† $D^{1/2} = \frac{i_p}{(269{,}000)n^{3/2}A\,Cv^{1/2}}$, † $\alpha = E_{1/2} - E_P^c / E_p^a - E_P^c$, † $Ks,h = 2.18\,[\alpha v n F D_o/RT]^{1/2}\ \exp[-\frac{\alpha^2 nF\,\Delta Ep}{RT}]$

Table 6. Binding constant and free energy values for ferrocenyl esters-DNA complexes from voltametric data at room temperature

Compounds	Binding constant †*K_b (M^{-1})	Freee energy (-ΔG=RTlnK) Kj M^{-1}
E1	2.81×10^5	28.55
E2	2.07×10^5	27.86
E3	6.41×10^5	30.44
E4	1.99×10^5	27.77
E5	1.29×10^5	26.79
E6	8.40×10^3	20.57
E7	1.75×10^4	22.24
E8	8.82×10^4	25.92
E9	2.71×10^3	17.99
E10	5.42×10^3	19.57

†* $Ip^2 = \frac{1}{K_b[DNA]} (Ip_0^2 - Ip^2) + Ip_0^2 - [DNA]$

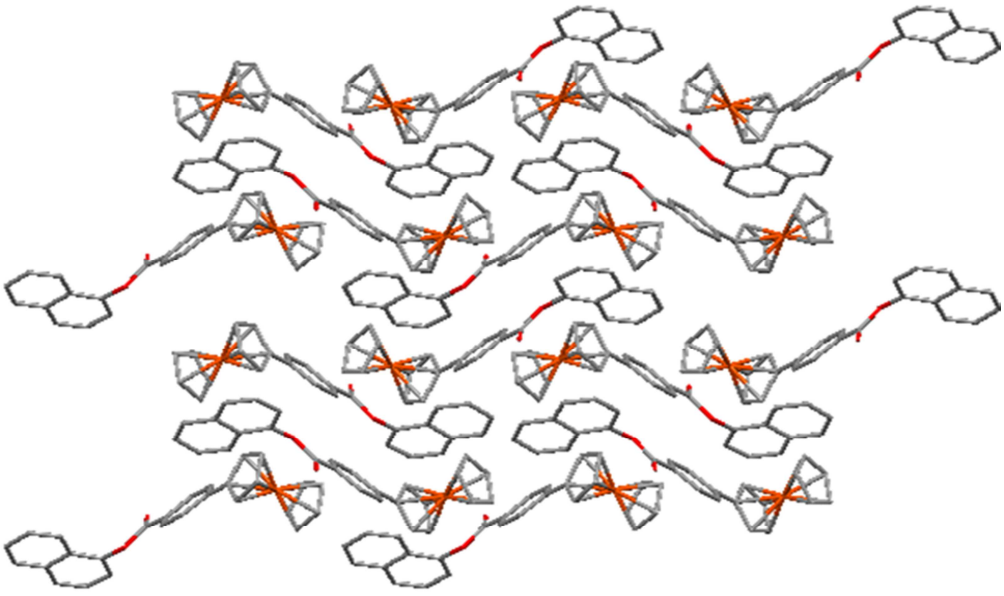


Figure 1. A packing diagram of E4 molecule.

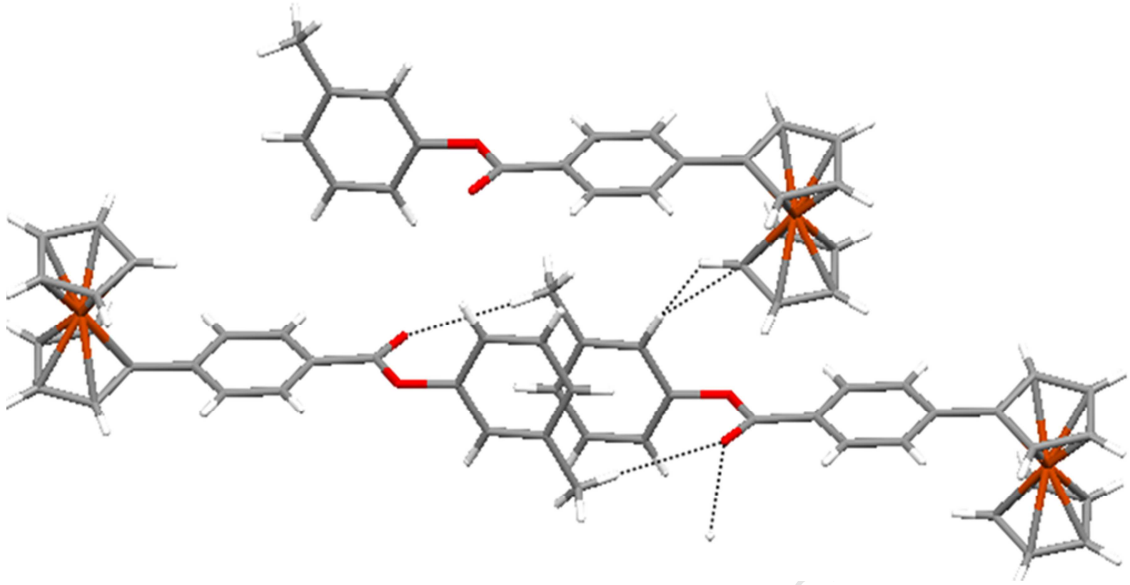


Figure 2. A diagram showing intermolecular attraction between E8 molecules

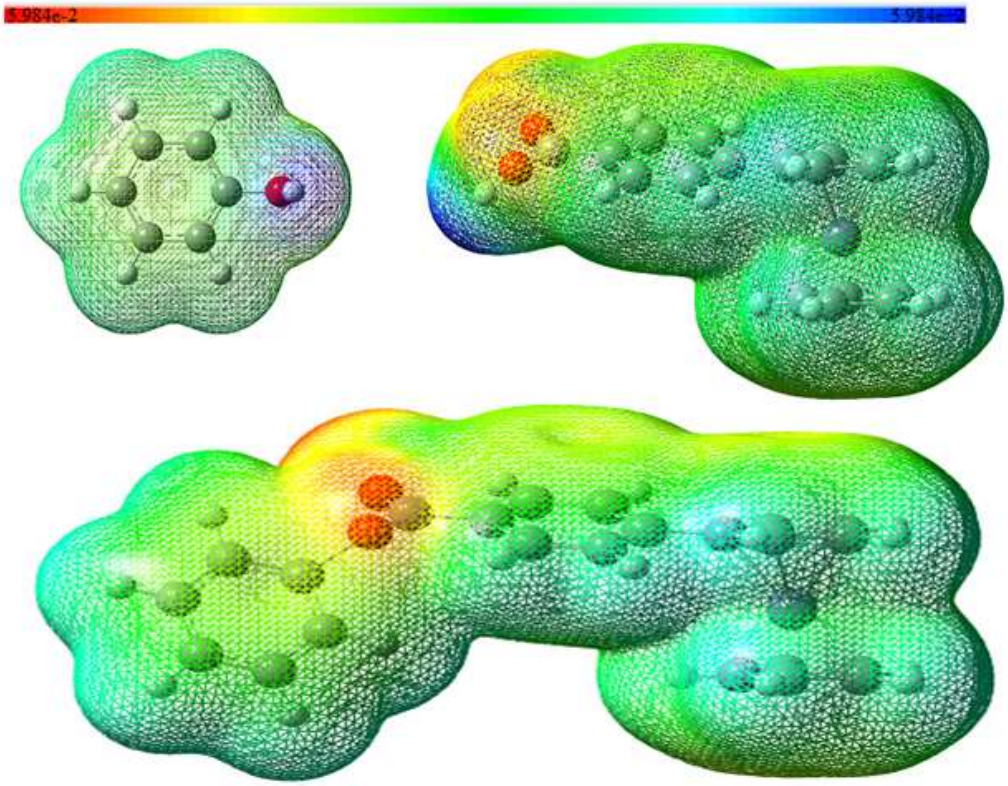


Figure 3. Electrostatic potential maps of phenol (A1), ferrocenyl benzoic acid (FB) and respective ferrocenyl ester (E1)

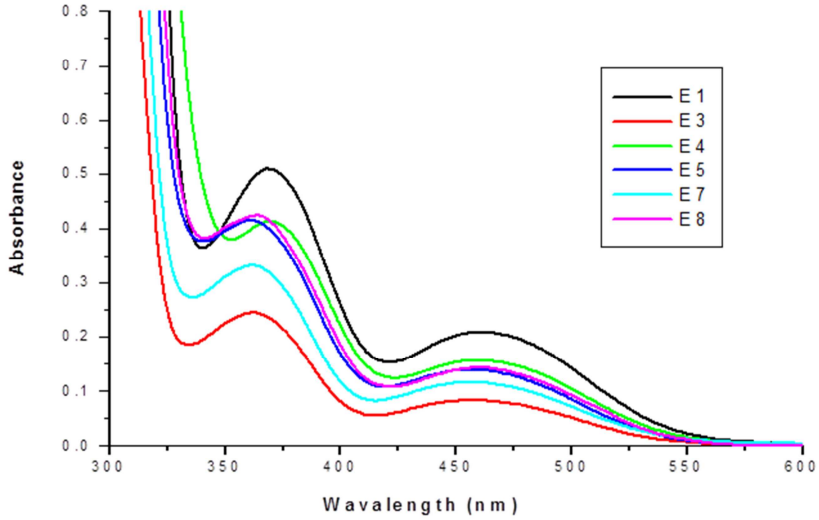


Figure 4. UV-Vis Absorption Spectra in Dichloromethane of Representative Ferrocenyl esters

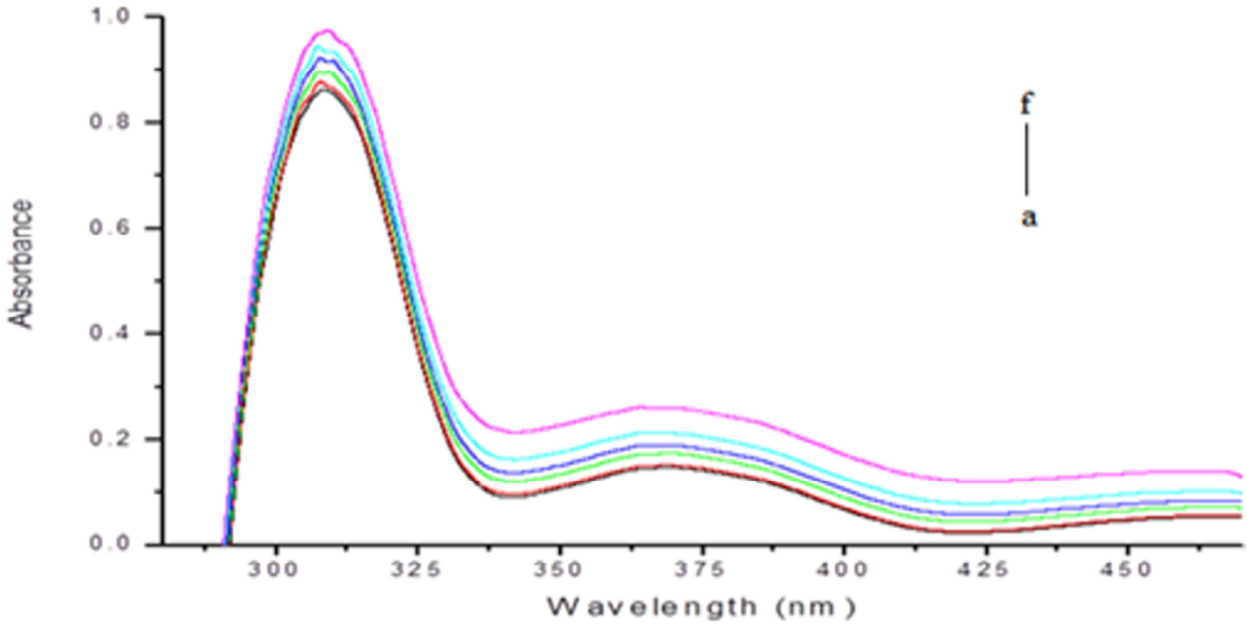


Figure 5. UV-Vis spectra of 10 µM E4 for DNA Interaction Study: (a) 0.00 µM (b) 1.1 µM (c) 2.2 µM (d) 3.3 µM (e) 4.4 µM (f) 5.5µM at room temperature.

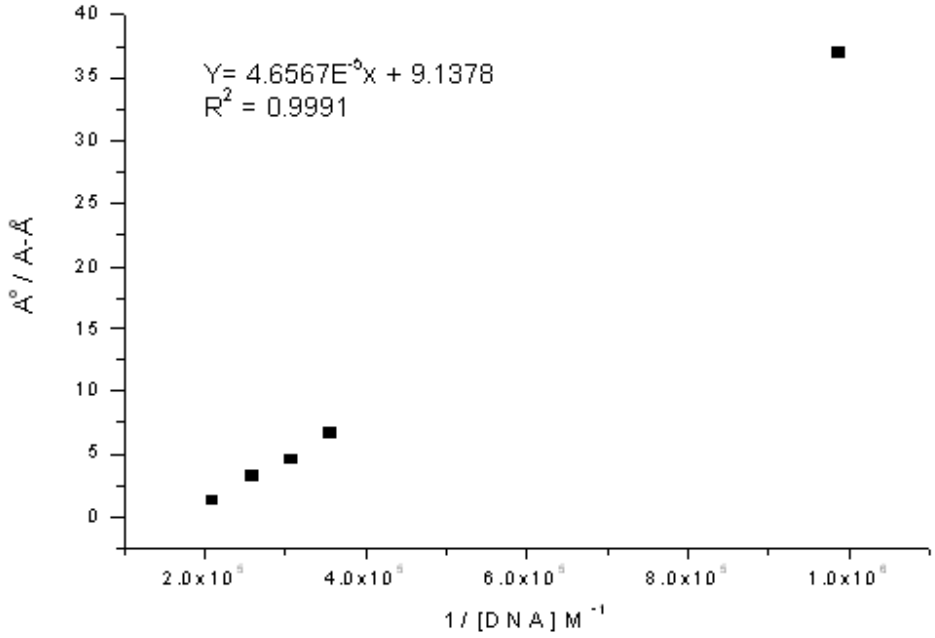
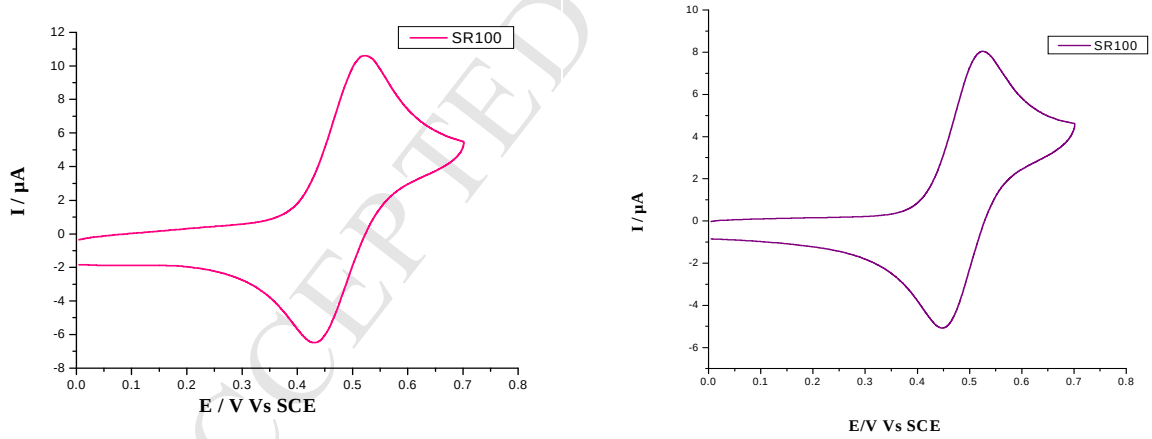


Figure 6. Plot of A^o / A-A^o *vs* 1/ [DNA] for 10 µM E4 with varying concentration of DNA to calculate the binding constant (using UV-Vis spectroscopy)



(a) (b)

Figure 7. Cyclicvoltamograms of Representative Esters at Scan rate 100 mv/s **(a)** E1 (1.3 mmol) **(b)** E3 (1mmol)

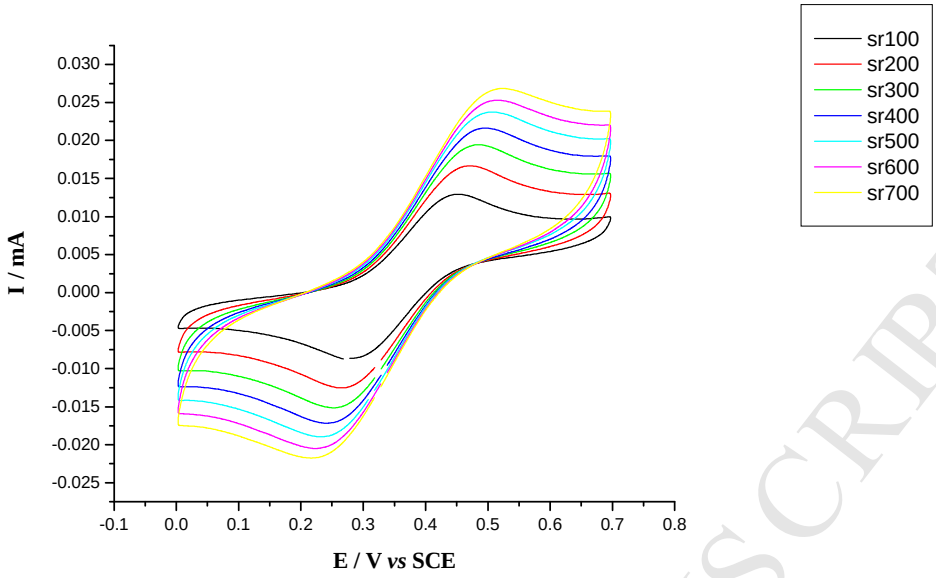


Figure 8. Effect of scan rate (using CV) on current-voltage profile of 1mM E1 at Pt disk electrode in10% aqueous ethanol and room temperature were: (a) 100 (b) 200 (c) 300 (d) 400 (e) 500 (f) 600 (g) 700 mV/s.

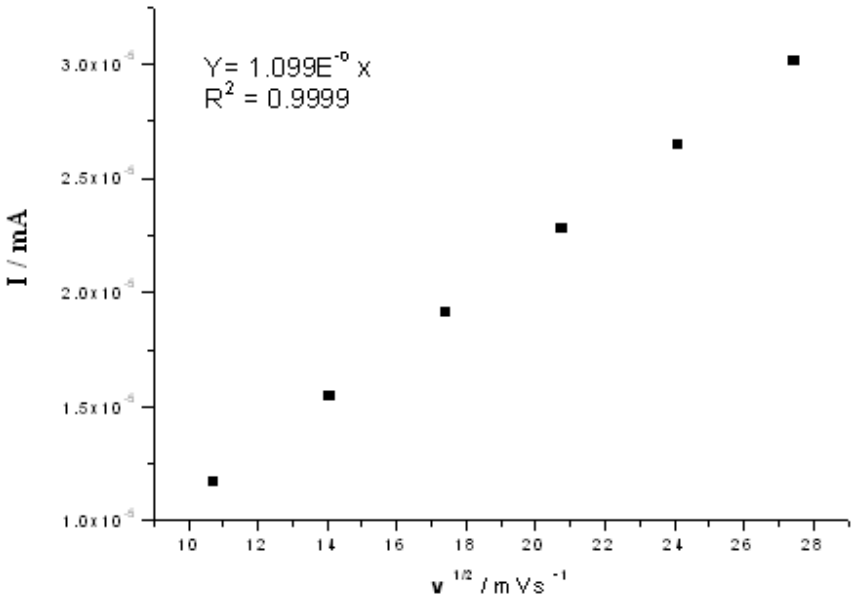


Figure 9. Plot of I *vs* $v^{1/2}$ for the determination of diffusion coefficient of 1mM E1(using CV)

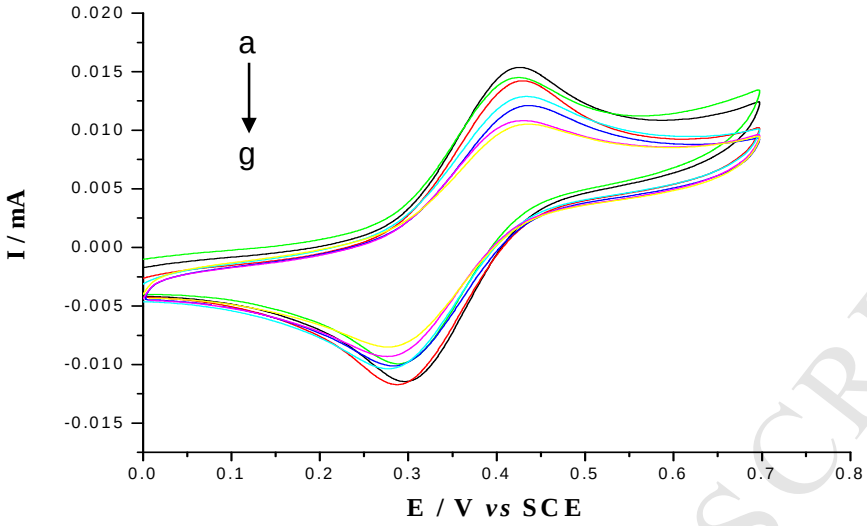


Figure 10. Effect of DNA on CV behaviour of 1mM E1 at 100mV/s: (a) 0.00 µM (b) 0.74 µM (c) 1.48 µM (d) 2.22 µM (e) 2.96 µM (f) 3.7µM (g) 555µM DNA

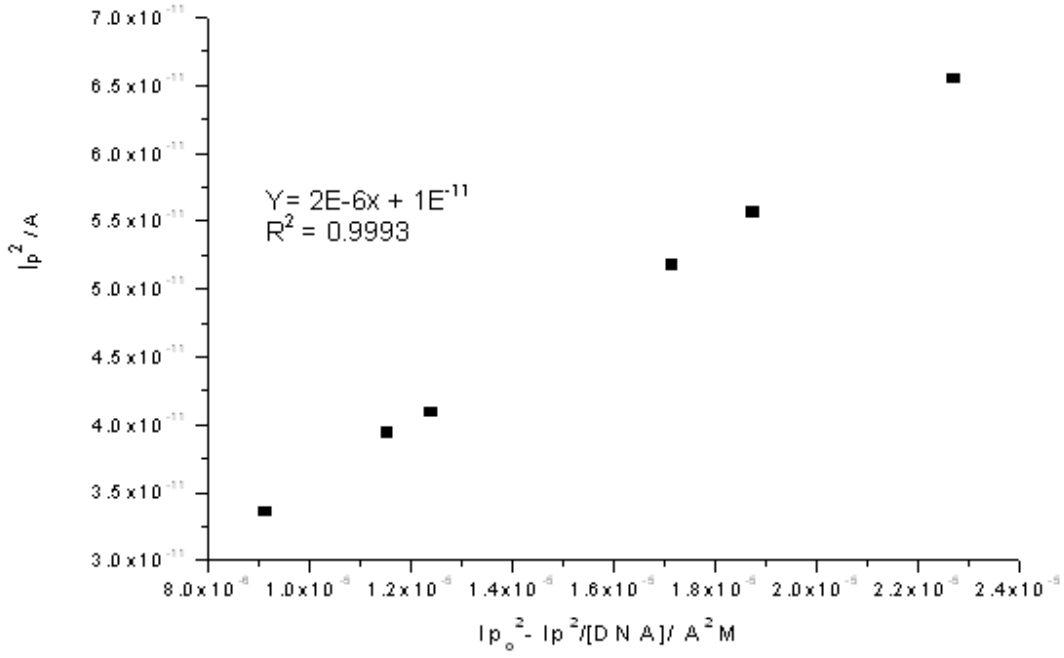
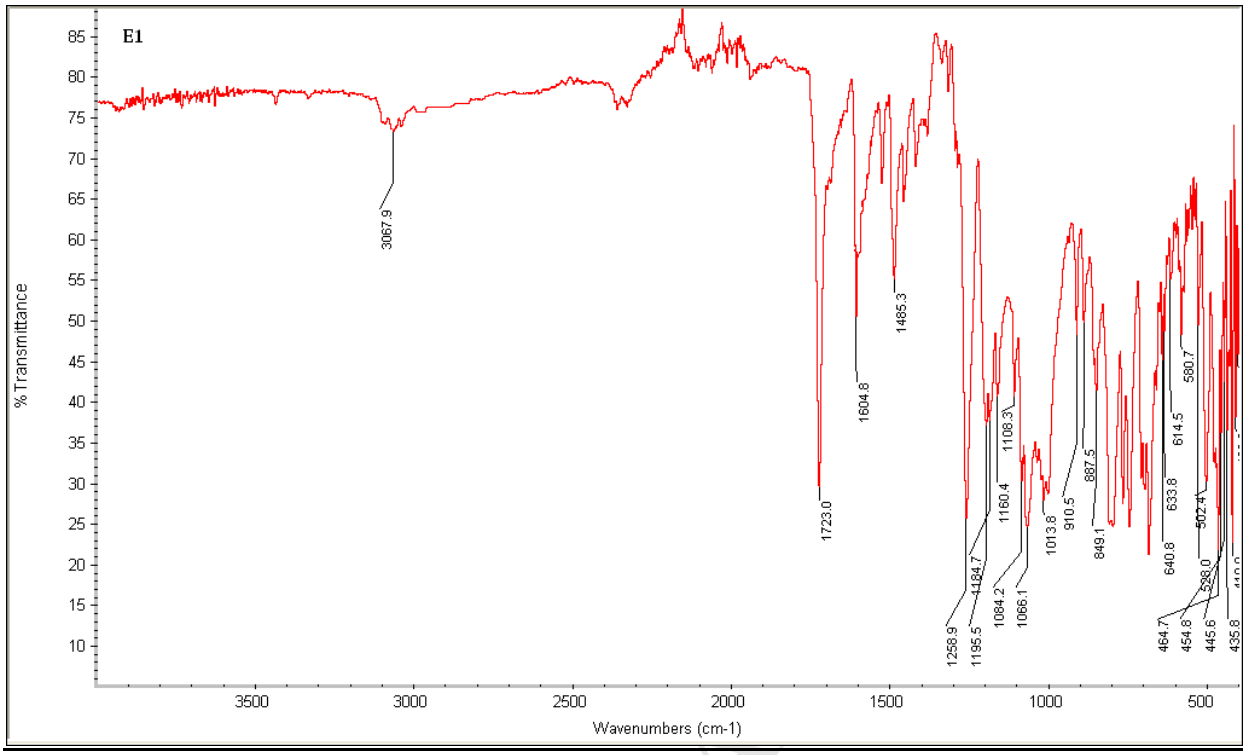
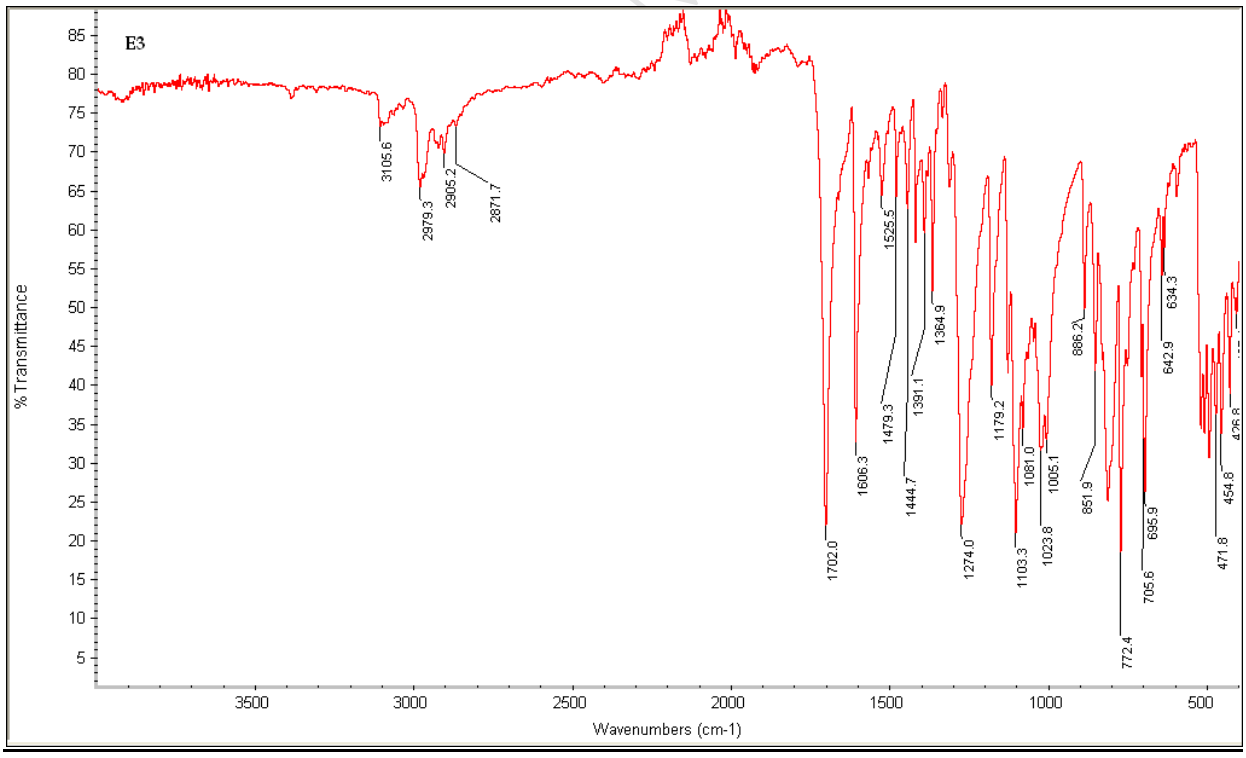


Figure 11. Plot of Ip^2 *vs* Ipo^2- Ip^2 /[DNA] for calculation of binding constant (using CV) of 1mM E1-DNA adduct at room temperature

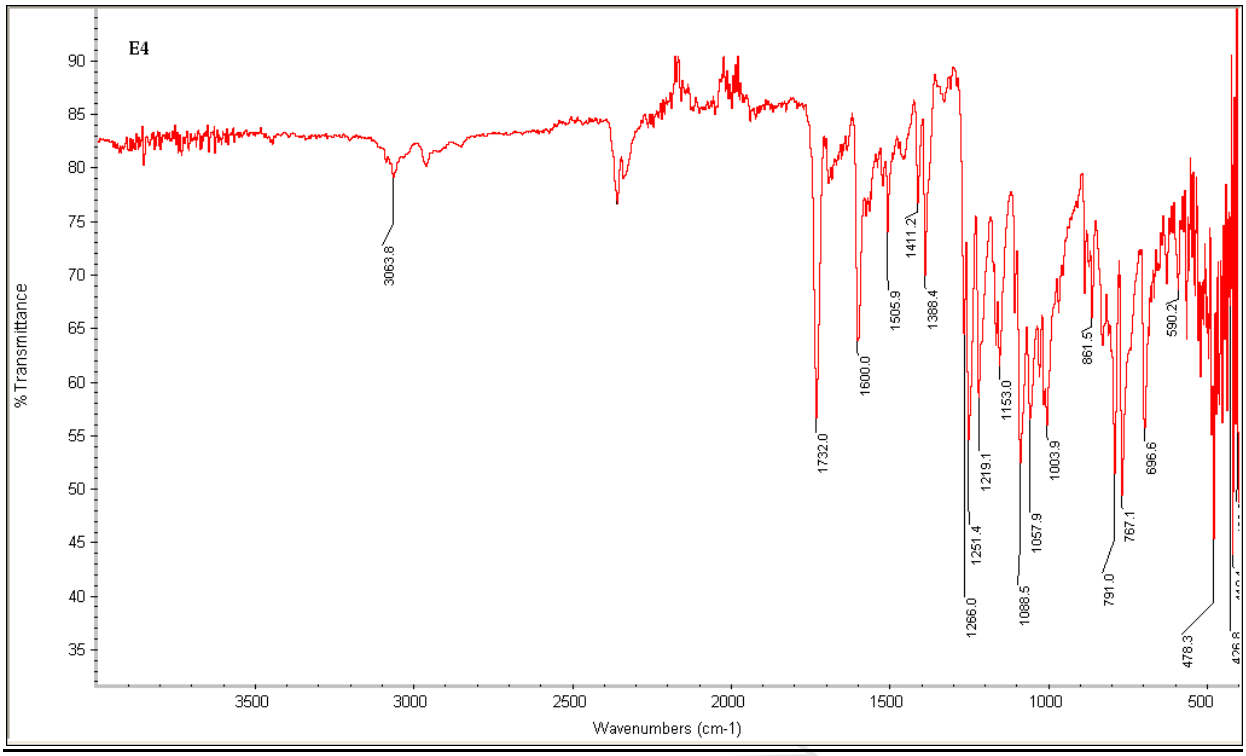
Electronic Supporting Information



(a) E1

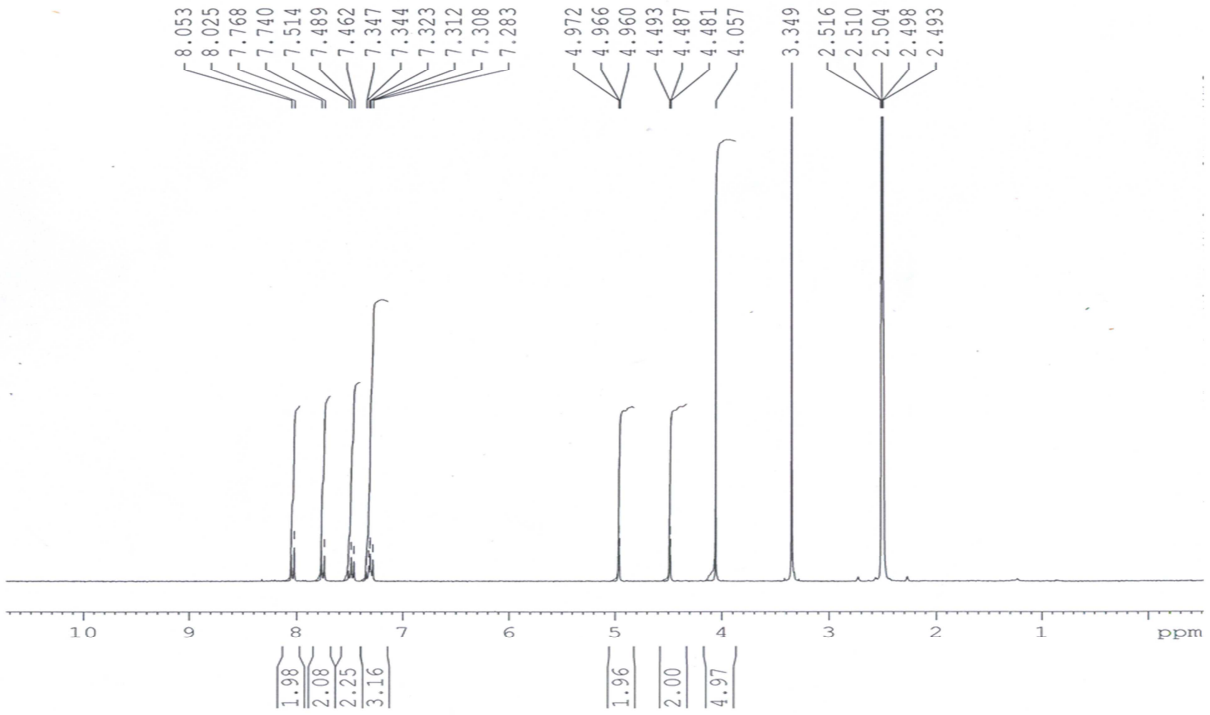


(b) E3

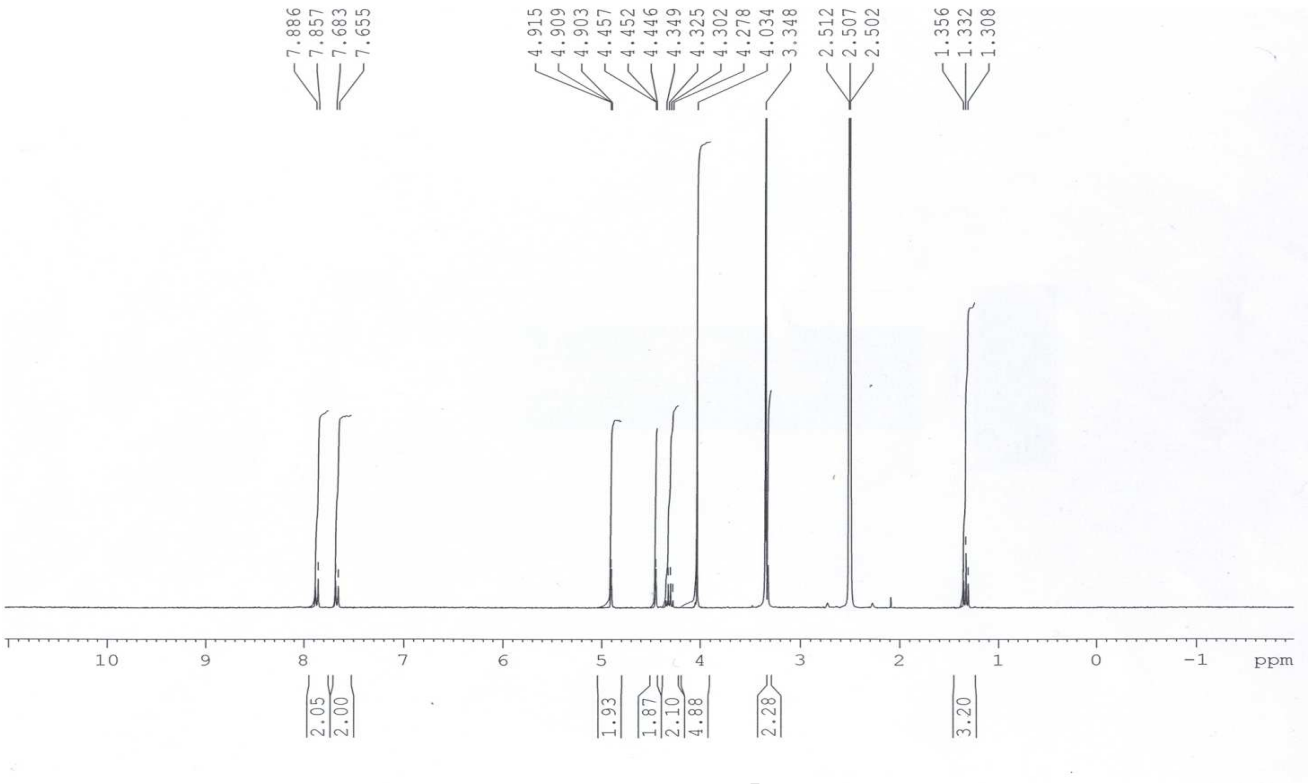


(c) E4

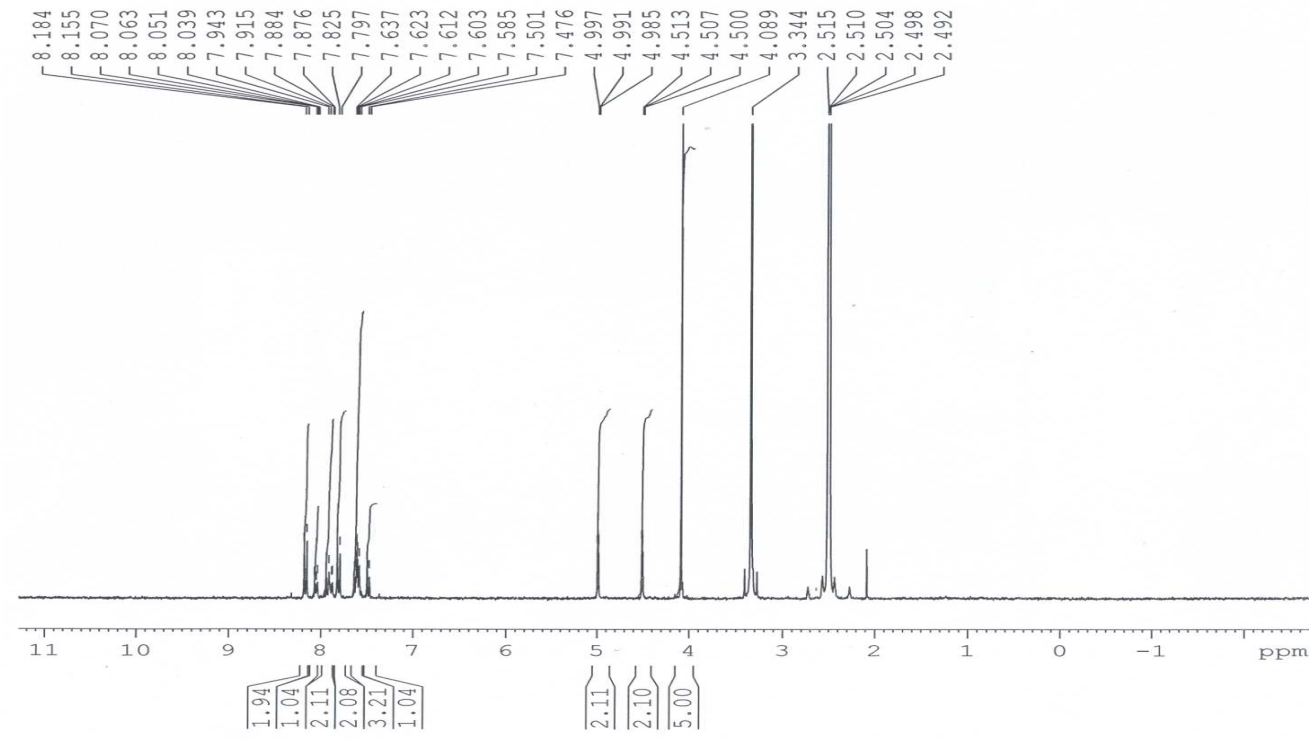
Figure 1. Representative FTIR spectra of Ferrocenyl esters **(a)** E1 **(b)** E3 (c) E4



(a) E1



(b) E3



(c) E4

Figure 2. Representative ^{1}HNMR Spectra (in DMSO-d_6) of Ferrocenyl esters **(a)** E3 **(b)** E4 **(c)** E1

Table 1: Experimental and calculated IR (cm^{-1}).

Codes	FTIR cm^{-1} Experimental	FTIR cm^{-1} Calculated (multiplied by scaling factor of 0.9654)
E1	3067(aromatic), 1723(C=O), 1604(C=C), 1485(C=C), 1258(C-O), 849(p-substitution), 473 (Fe-Cp)	3023(aromatic), 1769(C=O), 16051(C=C), 1201(C-O), 849(p-substitution), 421 (Fe-Cp)
E2	3090(aromatic), 2925(aliphatic), 1711(C=O), 1606(C=C), 1567(C=C), 1267(C-O), 857(p-substitution), 476(Fe-Cp)	3101(aromatic), 2977(aliphatic), 1732(C=O), 1641(C=C), 1277(C-O), 873(p-substitution), 486(Fe-Cp)
E3	3105(aromatic), 2905(aliphatic), 1702(C=O), 1606(C=C) , 1525(C=C), 1274(C-O), 851(p-substitution), 471(Fe-Cp)	3125(aromatic), 2977(aliphatic), 1752(C=O), 1656(C=C), 1214(C-O), 811(p-substitution), 431(Fe-Cp)
E4	3063(aromatic), 1732(C=O), 1600(C=C), 1505(C=C), 1251(C-O), 861(p-substitution), 478(Fe-Cp)	3099(aromatic), 1792(C=O), 1641(C=C), 1211(C-O), 891(p-substitution), 423(Fe-Cp)
E5	3063(aromatic), 2924(aliphatic), 1709(C=O), 1606(C=C), 1540(C=C), 1276(C-O), 859(p-substitution), 486(Fe-Cp)	3011(aromatic), 2994(aliphatic), 1789(C=O), 1676(C=C), 1199(C-O), 819(p-substitution), 410(Fe-Cp)
E6	3069(aromatic), 2915(aliphatic), 1716(C=O), 1606(C=C), 1541(C=C), 1272(C-O), 856(p-substitution), 729(-CH_2-bending), 479(Fe-Cp)	3099(aromatic), 2955(aliphatic), 1776(C=O), 1501(C=C), 1199(C-O), 892(p-substitution), 769(-CH_2-bending), 429(Fe-Cp)
E7	3019(aromatic), 2938(aliphatic), 1708(C=O), 1606(C=C), 1548(C=C), 1269(C-O), 857(p-substitution), 479(Fe-Cp)	3097(aromatic), 2988(aliphatic), 1768(C=O), 1676(C=C), 1295(C-O), 879(p-substitution), 491(Fe-Cp)
E8	3089(aromatic), 2912(aliphatic), 1717(C=O), 1602(C=C), 1528(C=C), 1263(C-O), 854(p-substitution), 477(Fe-Cp)	3101(aromatic), 2972(aliphatic), 1777(C=O), 1692(C=C), 1213(C-O), 881(p-substitution), 498(Fe-Cp)
E9	3090(aromatic), 2924(aliphatic), 1709(C=O), 1607(C=C), 1547(C=C), 1273(C-O), 856(p-substitution), 730(-CH_2-	3100(aromatic), 2994(aliphatic), 1779(C=O), 1697(C=C), 1211(C-O), 826(p-substitution), 783(-CH_2- bending),

	bending), 478(Fe-Cp)	458(Fe-Cp)
E10	3089(aromatic), 2916(aliphatic), 1709(C=O), 1608(C=C), 1528(C=C), 1270(C-O), 851(p-substitution), 721(-CH_2-bending), 479(Fe-Cp)	3109(aromatic), 2996(aliphatic), 1799(C=O), 1628(C=C), 1518, 1211(C-O), 811(p-substitution), 781(-CH_2-bending), 453(Fe-Cp)

[1] M. L. Laury, M. J. Carlson, A. K. Wilson, *J. Comput. Chem*. **2012** *33* 2380–2387.

^{13}CNMR

E1
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 165.27 (1C), 130 (3C), 134 (1C), 121.77(2C) (phenyl ring adjacent to ferrocenyl group), 83.08(ipso), 70.02 (2C), 69.44 (2C) (Cp-substituted), 67.02(5C, Cp-unsubstituted), 151.09 (1C)146.12 (4C) (phenyl ring).

E2
^{13}CNMR (75MHz, $^{13}CHCl_3$): δ 165.26 (1C)(C=O), 130.37(1C), 129.3 (2C), 128.2 (2), 121.83 (1C) (phenyl ring), 83.07(ipso),70.00 (2C), 67.00(2C) (Cp-substituted), 69.92 (5C) (Cp-unsubstituted), 22 (1C), 19.86 (1C)-10.3 (1C) (alkyl).

E3
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 166.70 (1C)(C=O), 130.37(1C), 130.00(2C),121.82 (2C)(phenyl ring), 83.38 (1C)(ipso), 70.00 (2C), 67.00 (2C) (Cp-substituted), 70.00 (5C) (Cp-unsubstituted), 77.51(1C) (O-CH2), 4.44 (1C) (methyl).

E4
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 165.2(C=O), 130.8 (3C),129.4 (2C), 127(1C) (phenyl ring), 84.38(1C)(ipso),71.00 (2C), 67.01(2C) (Cp-substituted), 71.3 (5C) (Cp-unsubstituted), 152.8(1C),134(IC), 127 (2C) 126.2 (4C), 121.0(1C), 109.4 (1C)(Naphthyl group).

E5
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 166.91 (1C)(C=O), 130.86(1C), 129.9(2C),-128.64 (2C), 127 (1C)(phenyl ring), 83.29 (1C)(ipso), 69.85 (2C), (2C)66.90 (Cp-substituted), 76.68 (5C)(Cp-unsubstituted), 77.51(1C)(methyl).

E6
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 166 (1C)(C=O), 130.4 (1C), 129.9(2), 128.7(2C),127.4(1C) (phenyl ring), 83.76 (1C)(ipso), 69.20(2C), 66.00(2C) (Cp-substituted), 76.68(5C) (Cp-unsubstituted), 60.9 (1C), 60.01 (16C) 59.9 (1C)(methylene), 14.1 (1C) (methyl).

E7
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 171.22 (1C)(C=O), 143.01(1C) 140 (2C), 135.0 (2C)-125.80 (1C) (phenyl ring), 83.52 (1C)(ipso), 69.64(2C), 66.72(2C) (Cp-substituted), 69.84(5C) (Cp-unsubstituted), 77.48 (1C) (-CH-), 24.51(1C) (methyl).

E8
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ165.36 (1C)(C=O), 129.91 (3C),118.69(2C)(phenyl ring adjacent to ferrocenyl group), 83.11(1C)(ipso), 69.93 (2C), 67.01(2C) (Cp-substituted), 77.50 (5C) (Cp-unsubstituted), 150.90(1C), 145(1C), 132.98 (2C),130.36(2C) (phenyl ring), 21.43(1C)(methyl group).

E9
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 167.65(1C)(C=O), 131.19 (1C), 129.99 (2C),127.61 (2C)(phenyl ring), 84.41(ipso)(1C), 67.88,(2C), 65.01(2C)(Cp-substituted), 69.87(5C)(Cp-unsubstituted), 78.48 (1C), 74.65(7C),76.53 (1C) (methylene), 15.18 (1C)(methyl)

E10
^{13}CNMR (75 MHz, $^{13}CHCl_3$): δ 166.75 (1C)(C=O), 130.19 (1C),129.98 (2C)125.61 (2C) (phenyl ring), 83.41(1C)(ipso), 66.88 (2C), 65.02 (2C) (Cp-substituted), 69.83 (5C) (Cp-unsubstituted), 77.48(1C), 76.63 (13C), 71.9 (1C)(methylene),14.18 (1C) (methyl).