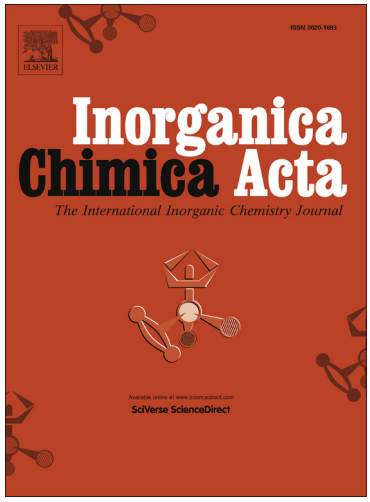


Synthesis, chemical characterization, DNA interaction and antioxidant studies of ortho, meta and para fluoro substituted ferrocene incorporated selenoureas

Raja Azadar Hussain, Amin Badshash, Manzar Sohail, Bhajan Lal, Atif Ali Altaf

PII: S0020-1693(13)00184-9
DOI: http://dx.doi.org/10.1016/j.ica.2013.04.003
Reference: ICA 15408

To appear in: *Inorganica Chimica Acta*

Received Date: 17 January 2013
Revised Date: 1 April 2013
Accepted Date: 5 April 2013

Please cite this article as: R.A. Hussain, A. Badshash, M. Sohail, B. Lal, A.A. Altaf, Synthesis, chemical characterization, DNA interaction and antioxidant studies of ortho, meta and para fluoro substituted ferrocene incorporated selenoureas, *Inorganica Chimica Acta* (2013), doi: http://dx.doi.org/10.1016/j.ica.2013.04.003

Synthesis, chemical characterization, DNA interaction and antioxidant studies of ortho, meta and para fluoro substituted ferrocene incorporated selenoureas

Raja Azadar Hussain[a], Amin Badshash*[a], Manzar Sohail[b], Bhajan Lal[a] and Atif Ali Altaf[c]

a. Coordination Chemistry Laboratory, Department of Chemistry, Quaid-i-Azam University (45320) Islamabad Pakistan.
b. Faculty of Science, Health, Education and Engineering ML12, University of the Sunshine Coast, Australia.
c. Department of Chemistry, University of Malakand KPK, Pakistan.

Abstract

We have reported a one pot synthesis of three new ferrocene incorporated selenoureas namely; 1-(2-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP2F), 1-(3-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP3F) and 1-(4-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP2F) by the reaction of corresponding carboxylic acid chlorides with potassium selenocyanate (KSeCN) and 3-methyl-4-ferrocenyl aniline in acetone under constant stirring. Synthesized compounds were characterized by FTIR, NMR (^{1}H and ^{13}C), CHNS and AAS. We have also presented X-rays single crystal structure for MeP2F. DNA binding studies were evaluated with the help of cyclic voltammetry in the presence of TBAP (tertiary butyl ammonium perchlorate) as supporting electrolyte in DMSO/water mixture of 70:30. Binding constant for MeP2F is 1.499 x 10^3 M^{-1}, MeP3F is 1.706 x 10^3 M^{-1} and MeP4F is 1.035 x 10^3 M^{-1}. Binding site size for MeP2F (0.334 bp) < MeP4F (0.410 bp) < MeP3F (0.463 bp). In all the compounds diffusion coefficients of drug-DNA adduct is lower than the free drug indicating slow diffusion of comparatively high molecular weight drug towards the electrode in cyclic voltammetry. Mode of interaction has further been reconfirmed with the help of viscometry. All the three compounds have good antioxidant activities against DPPH with IC_{50} values of 132 µg/ml, 108 µg/ml and 84 µg/ml for MeP2F, MeP4F and MeP3F respectively.

Keywords: Ferrocene; DNA binding constant; antioxidant

Introduction

After the discovery of elemental selenium in 1818 by Swedish chemist Berzelius it was named after the Greek goddess of moon (Selene). It was long considered to be an absolute biological poison that's why its use in organic synthesis, enzymology and bioinorganic chemistry was

limited. There are only a few reports for the use of selenium in organic synthesis before the discovery that it is a micronutrient in mammals birds and bacteria [1]. The most related to our topic among those is the work of Irwin B. Douglass in 1937 who synthesized the selenoureas for the first time by the reaction of anilines with isoselenocyanates [2]. Interest in the bioinorganic chemistry of selenium increased after the findings that organoselenium derivatives are far less toxic than the elemental selenium firstly and secondly due to its discovery in two bacterial enzymes i.e. formate dehydrogenase and glycine reductase. Uptil now efforts have been made for the applications of selenium derivatives in enzyme inhibition (nitirc oxide synthase inhibitors, ionosine monophosphate dehydrogenase inhibitors, lipoxygenase inhibitors, urdpase and thymidylate synthase inhibitors, antioxidant defense enzymes (reduction of hydroperoxides-GPx mimics, reduction of peroxinitriles, lipid peroxidation), tyrosine kinase and iodothyronine inhibitors) photochemotherapeutic agents, antitumor agents, anti-infective drugs, (antiviral, antifungal, antibacterial), cytokine inducers/immunomodulators, antihypertensive and cardiotonic agents [1].

Metal complexes of selenoureas are not, biocompatible and lipophilic. Introduction of ferrocene moiety not only resolves this problem but has its applications as antibiotic, antimalarial and anticancer agents [3]. Recently work has been reported on the interaction of ferrocene derivatives with DNA [4-5]. Inspired from synthetic chemistry and biological applications of selenoureas along with ferrocene incorporated derivatives we have combined both the functionalities i.e. ferrocene and selenoureas in ferrocene incorporated selenoureas for the first time (Scheme 1). In this article we have reported synthesis, chemical characterization and DNA binding studies of three new ferrocene incorporated selenoureas. We have provided X-rays single crystal structures for MeP2F and all the compounds have been completely characterized with ^{1}H and ^{13}C NMR, FT-IR, CHNS and AAS. We have also reported values for DNA binding constant (K), diffusion coefficient (D_o) and binding site size (s) with the help of cyclic voltammetry. The results obtained from cyclic voltammetry have been confirmed with viscometry as well. We have also reported antioxidant activity of the synthesized compounds.

Experimental

Material and Methods

Melting points were determined in a capillary tube using electro thermal melting point apparatus model MP-D Mitamura Riken Kogyo (Japan). Infrared spectra were taken on Thermoscientific NICOLET 6700 FTIR. ^{1}H and ^{13}C were recorded on Jeol JNM-LA 500 FT-NMR. $Si(CH_3)_4$ was used as internal reference. The elemental analysis was performed using a LECO-932 CHNS analyzer while the Fe concentrations were determined on an Atomic Absorption Spectrophotometer Perkin Elmer 2380.

Commercial Salmon DNA was solubalized in doubly distilled water to prepare a stock solution of 6×10^{-4} M from which working concentrations of DNA were prepared. Concentration of stock solution was measured by UV absorbance at 260 nm using an epsilon value of 6600 $M^{-1}cm^{-1}$. This DNA was protein free because $A_{260}/A_{280} > 1.8$.

Cyclic voltammetry was performed on Biologic SP-300 cyclic voltammeter running with EC-Lab Express V 5.40 software, Japan. Before every reading working electrode was polished with alumina powder and rinsed with distilled water. Analytical grade TBAP was used as supporting electrolyte and nitrogen gas (99.9 %) was purged through the mixture to avoid interference of oxygen.

The Ubbelohde vis-cometer was used for viscosity measurements at room temperature (25 ± 1 °C). Flow time was measured with a digital stopwatch. Flow time measurements were made in triplicate for the measurement of average flow time. Data were presented as relative viscosity (η/η_o), vs. binding ratio ([Drug]/[DNA]) where η is the viscosity of DNA in the presence of drug and η_o is the viscosity of DNA alone [5].

The reducing abilities of all the three ferrocene incorporated selenoureas were determined with the help of 1,1-diphenyl-2-picrylhydrazyl in DMSO to produce 1,1-diphenyl-2-picrylhydrazine. Decrease in the absorption of 1,1-diphenyl-2-picrylhydrazyl (DPPH) was monitored to calculate % age scavenging according to the following formula:

$$\text{Scavenging Activity (\%)} = A_o\text{-}A/A_o \times 100$$

Where A_o is the absorbance of free DPPH and A is the absorbance of DPPH-drug mixture with increasing concentration of drug. To a solution of DPPH (3.9 mg of DPPH in 100 mL DMSO) were added the increasing concentrations (12 μg/ml) of ferrocene incorporated selenoureas. The decrease in absorption of DPPH was monitored after every 5 minutes after the addition of drug at

a wavelength of 517 nm with the help of spectrophotometer. All the readings were taken in triplicate and the average of all the readings were used.

Ferrocene, 2-methyl-4-nitroaniline, sodium nitrite, diethyl ether, acetone, DMSO, Pd-charcoal, carboxylic acid chlorides and hydrazine were purchased from Sigma Aldrich. 3-methyl-4-ferrocenyl aniline was synthesized by a procedure reported by our group previously (Scheme 1) [6].

Synthesis

1-(2-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP2F): MeP2F was synthesized by reacting 0.3 g (0.00208 mol) of potassium selenocyanate (KSeCN) with 0.25 mL (0.00208 mol) of 2-fluorobenzoyl chloride in acetone [2]. The reaction was carried out in two neck round bottom flask for 3 hours under constant stirring at room temperature. After the formation of yellow colored product with a suspension of potassium chloride (KCl), 0.607 g (0.00208 mol) of 3-methyl-4-ferrocenylaniline were added into the reaction mixture. The reaction mixture was stirred under reflux for a further 4 hours and monitored with the help of thin layer chromatography (TLC). Orange colored product obtained in the solution state was mixed with cold water to remove the impurities and have the product in solid state, which was washed with n-hexane and recrystallized in acetone with 78 % yield. Decomposition temperature 154 °C ; Elemental analysis % Calc. (found): Carbon 57.83 (57.82), Nitrogen 5.39 (5.37), Hydrogen 4.04 (3.98), Fe 10.75 (10.72); ^{1}H-NMR (Benzene): δ (ppm) 13.41 (s, 1H), 9.15 (s, 1H), 8.80-6.54 (m, 7H), 4.49 (t, 2H), 4.44 (t,2H), 4.10 (s, 5H), 2.41 (s, 3H); ^{13}C-NMR (Benzene): δ (ppm) 178.5, 166.2, 136.9, 136.5, 135.3, 133.6, 132.2, 130.8, 130.4, 130.0, 129.8, 129.6, 87.0, 69.9, 69.7, 69.6-68.1, 21.4; FT-IR: υ (cm^{-1}) 3400-3100 (b), 3031, 2954, 2932, 1661, 1572, 1535, 1369, 1252, 1141.

1-(3-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP3F): MeP3F was synthesized by reacting 0.3 g (0.00208 mol) of potassium selenocyanate (KSeCN) with 0.25 mL (0.00208 mol) of 3-fluorobenzoyl chloride and then with 0.607 g (0.00208 mol) of 3-methyl-4-ferrocenylaniline in acetone [2] with 61 % yield following exactly the same procedure as was used for MeP2F. Decomposition temperature 149 °C; Elemental analysis % Calc. (found): Carbon 57.83 (57.79), Nitrogen 5.39 (5.36), Hydrogen 4.04 (4.01), Fe 10.75 (10.70); ^{1}H-NMR (Benzene): δ (ppm) 13.40 (s, 1H), 9.08 (s, 1H), 8.80-6.54 (m, 7H), 4.45 (t, 2H), 4.41 (t,2H), 4.12

(s, 5H), 2.44 (s, 3H); ^{13}C-NMR (Benzene): δ (ppm) 178.3, 167.3, 136.7, 136.6, 136.5, 134.8, 133.1, 131.7, 130.5, 130.0, 129.6, 129.5, 87.4, 69.1, 68.7, 69.6-68.1, 21.3; FT-IR: υ (cm^{-1}) 3400-3100 (b), 3029, 2953, 2929, 1657, 1561, 1541, 1377, 1250, 1140.

1-(4-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP4F): MeP4F was synthesized by reacting 0.3 g (0.00208 mol) of potassium selenocyanate (KSeCN) with 0.24 mL (0.00208 mol) of 4-fluorobenzoyl chloride and then with 0.607 g (0.00208 mol) of 3-methyl-4-ferrocenylaniline in acetone [2] with 74 % yield following exactly the same procedure as was used for MeP4F. Decomposition temperature 165 °C; Elemental analysis % Calc. (found): Carbon 57.83 (57.80), Nitrogen 5.39 (5.37), Hydrogen 4.04 (4.00), Fe 10.75 (10.74); ^{1}H-NMR (Benzene): δ (ppm) 13.41 (s, 1H), 9.13 (s, 1H), 8.80-6.54 (m, 7H), 4.48 (t, 2H), 4.43 (t,2H), 4.10 (s, 5H), 2.40 (s, 3H); ^{13}C-NMR (Benzene): δ (ppm) 178.5, 166.3, 136.9, 136.5, 136.3, 133.8, 132.1, 130.9, 130.6, 130.0, 129.9, 129.6, 87.2, 69.9, 69.8, 69.6-68.1, 21.3; FT-IR: υ (cm^{-1}) 3400-3100 (b), 3045, 2951, 2933, 1663, 1569, 1545, 1377, 1250, 1141.

Results and Discussions

All the three compounds have been synthesized in good yield and are orange brown in color. The products have been purified from possible impurities i.e. byproduct (amide, carboxylic acid, KCl) and unreacted material (3-methyl-4-ferrocenylaniline, KSeCN) due to their different solubilities in common organic solvents. All the three compounds have been analyzed with the help of FTIR, NMR (^{1}H & ^{13}C), CHNS and AAS. We have also provided X-Rays single crystal structure for MeP2F. In FTIR all the compounds provided a broad peak above 3200 cm^{-1} for their –NH protons owing to intramolecular hydrogen bonding between the protons of –NH, oxygen of carbonyl and fluorine. Ar-H appeared slightly above 3000 cm^{-1} and carbonyl group gave an intense band above ~1650 cm^{-1} whereas C=Se was available between 1050-1250 cm^{-1} for all the compounds. Elemental analysis provided the agreement between calculated and found values.

^{1}H and ^{13}C NMR data of all the three compounds (MeP2F, MeP3F, MeP4F) were recorded in deutrated benzene. Basically there are four different types of protons which are available in the compounds reported in this article i.e. –NH protons, aromatic protons, protons of methyl group and protons of ferrocene moiety. Both the –NH protons are available between 9-14

ppm whereas aromatic protons provide a multiplet between ~6-8 ppm in ^{1}H NMR spectra for all the three compounds. Methyl protons yield a singlet round about 2 ppm. Unsubstituted cyclopentadienyl (Cp) ring of ferrocene appears as a singlet approximately at 4 ppm whereas substituted Cp of ferrocene provides two triplets downfield from the singlet of substituted Cp for all the three compounds. In ^{13}C NMR spectra carbon attached with Se provides one signal at ~178 ppm and carbonyl carbon appears 10-12 ppm upfield from it. Aromatic and aliphatic carbons are available at 120-140 ppm and ~21 ppm respectively for all the three compounds. Carbons of unsubstituted Cp ring yielded one signal and substituted Cp gave three signals between 60-84 ppm.

Crystallography

Diffraction data of MeP2F were collected at 100(2) K on beamline MX1 at the Australian Synchrotron (λ = 0.71703 Å) [7]. The data reduction and indexing of diffraction pattern was performed by XDS software [8]. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of data using SHELXL97 (Sheldrick, 1997) software [7]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Basic crystal data and description of diffraction experiment are given in Table 1. ORTEP of MeP2F is given in Fig. 1 whereas selected bond lengths and bond angles have been given in Table 2. The structure reveals that the phenyl ring attached with Cp of ferrocene is not in plane with Cp moiety but almost in plane with the phenyl attached with carbonyl carbon. Hydrogens of the ferrocene are 100 % eclipsed with each other (Fig. 1b) and there is intramolecular hydrogen bonding at two positions as shown in Fig. 1 (Table 3).

Cyclic Voltammetry

A setup having three electrodes system i.e. working (platinum disc electrode with a geometric area of 0.071 cm^2/s,) reference (Ag/AgCl) and auxiliary electrodes (platinum electrode with geometric area much greater than working electrode) was used to evaluate cyclic voltammetric behavior. Mode of interaction was evaluated by viewing the changes in peak potentials and DNA binding constant was determined with the help of demolition in peak currents with the help of following equation [10]:

$$\log (1/[DNA]) = \log K + \log (I/I_o - I) \qquad \text{Eq 1}$$

Where I_o and I are the peak currents of free drug and DNA bound drug respectively and K is the binding constant. Binding site size was calculated with the help of following equation [11]:

$$C_b/C_f = K\{[\text{free base pairs}]/s \quad \textbf{Eq 2}$$

Where K is the binding constant, s is the binding site size in terms of base pair, C_b is the concentration of free species and C_f represents concentration of drug-DNA bound species. If we consider the concentration of DNA in terms of nucleotide phosphate, then the concentration of DNA base pairs will be equal to [DNA]/2 and Eq 2 will be written as:

$$C_b/C_f = K\{[DNA]/2s\} \quad \textbf{Eq 3}$$

and the value of C_b/C_f is equal [12] to (I_o - I/I) which are the values of experimental peak currents. The diffusion coefficient of free drug and DNA-bound drug provides best information about the molecular mass of drug-DNA adduct. Following form of Randles-Sevcik Equation [13] was used for the values of diffusion coefficients:

$$I_{pa} = 2.99 \times 10^5\, n\, (\alpha n)^{1/2}\, A\, C_o^{*} D_o^{1/2} \upsilon^{1/2} \quad \textbf{Eq 4}$$

Where I_{pa} is the anodic peak current C_o^* is the reductants's concentration in mol/cm^3, A is the geometric area of the electrode in cm^2, n is the number of electrons involved in the process, D_o is the diffusion coefficient in cm^2/s. All the three compounds provide quasi reversible behavior which is evident by a change in the peak potential when current (I/mA) is ploted Vs. potentials (E/V vs. Ag/AgCl) at different scan rates for all the three compounds (MeP2F, MeP3F, MeP4F (Fig. 2). MeP2F yields couple of well defined redox peaks with an oxidation maxima at 0.522 V and a reduction maxima at 0.337 V. Change in the current of oxidation peak was monitored with successive addition of DNA for the evaluation of drug-DNA binding constant. Oxidation current of free drug changes from 2.76 x 10^{-3} mA to 2.4759 x 10^{-3} mA with a 30 mV shift towards negative potential due to the addition of 1mL of 60 μM DNA solution. This negative shift in the peak potential represents the electrostatic interaction of positively charged ferrocene moiety with the negatively charged phosphate backbone of DNA. To another cyclic volammetric cell having the same drug with similar conditions was added 1 mL of 120 μM DNA with a further decrease in the peak current to 2.24 x 10^{-3} mA and a further 10 mV shift again favoring the electrostatic interactions. The addition of 180 μM DNA, 240 μM DNA and 300 μM DNA causes a decrease in peak current but with a positive shift in peak potential as compared with 120 μM DNA,

Although all the additions provide an overall negative shift as compared with free drug (Fig. 3). The positive shift after 120 μM DNA may be due to partial intercalation of the planner part of MeP2F into DNA helix at these concentrations of DNA and planarity of the organic part of the structure is also evident from the crystal structure of MeP2F. Another reason for partial intercalation may be a 30° twist in the Cp moieties of ferrocene which incorporates planarity in the ferrocene moiety as well. Binding constant of MeP2F was determined to be 1.4999×10^3 M^{-1} (Fig. 4). The diffusion coefficient of MeP2F-DNA adduct is 4.36×10^{-7} cm^2/s which is far less than the the diffusion coefficient of free MeP2F (6.42×10^{-5} cm^2/s). This low value of MeP2F-DNA adduct relative to free MeP2F indicates the slow diffusion of high molecular weight MeP2F-DNA moiety (Fig. 5). Low value of binding site size i.e 0.334 bp indicates overall electrostatic interactions (Fig. 6).

MeP3F also provides a couple of well defined redox peaks in the potential region of 0.0-0.9 V which provided the DNA binding constant of 1.706×10^3 M^{-1} (Fig. 7). Intercalative mode of interaction is more prominent for this compound than electrostatic interaction anyhow disturbance in the CV behavior is indicative of the possibility about two different types of interactions. Binding site size of 0.463 bp is higher than MeP2F and lower diffusion coefficient of MeP3F-DNA adduct (1.0×10^{-5} cm^2/s) than the free MeP3F (2.0×10^{-5} cm^2/s) is indicative for the formation of slow diffusing MeP3F-DNA adduct.

MeP4F behaves similar to MeP3F with a binding constant of 1.035×10^3 M^{-1} which is less than MeP2F and MeP3F. As mentioned above MeP4F-DNA adduct has a lower diffusion (1.34×10^{-6} cm^2/s) coefficient than MeP4F (1.55×10^{-6} cm^2/s) and binding site size was determined to be 0.410 bp. It is important to mention here that ferrocene derivatives generally show dominance of electrostatic interactions but an intercalative mode of interaction is not impossible according to our experience (Fig. 8) [15].

Viscometry

Mode of interaction was further confirmed with the help of viscometry as well. Results for the plot of η/η_o against [Drug]/[DNA] concentrations have been presented in Fig. 9. The increase in the viscosity of MeP3F-DNA and MeP4F-DNA adducts with increasing concentration of drug in the fixed concentration of DNA confirms the intercalative mode of

interaction. MeP2F shows a decrease in the relative viscosity with increasing concentration of the drug in the constant concentration of DNA proving the dominance of electrostatic mode of interaction (Fig. 9).

Antioxidant Studies

DPPH provides a strong absorption band at 517 nm due to its odd electron [14]. When any antioxidant reacts with DPPH it produces 1,1-diphenyl-2-picrylhydrazine. As a result the band intensity of DPPH decreases. This changes the color of DPPH and a corresponding decrease in the absorption. Fig. 10 shows a representative plot of absorbance vs. wavelength for MeP2F. IC_{50} values of 132 μg/ml, 108 μg/ml, and 84 μg/ml were determined for MeP2F, MeP4F and MeP3F respectively.

Conclusions

- Selenourea and ferrocene moieties have been successfully combined in ferrocene incorporated selenoureas.
- Synthesized compounds have shown DNA binding constant values in the range of 10^3 M^{-1} which indicates their potential applications as antitumor agents in the future.
- The synthesized compounds may be used as a single source iron and selenium precursors for the formation of FeSe thin films using aerosol assisted chemical vapor deposition because they have very good solubilities in toluene and THF.

Acknowledgements

We are thankful to Australian Synchrotron, Victoria, Australia for crystal analysis.

Associated content

Crystallographic Data

Crystallographic data for the structure reported in this paper have been deposited to the Cambridge Crystallographic Data Center as supplementary publication number CCDC-918928. Copies of the data will be available free of charge at deposit@ccdc.cam.ac.uk.

AUTHOR INFORMATION

Corresponding Author

*Tel: +923009780374. Office +92-051 9064-2131.E-mail: aminbadshah@yahoo.com.

References

[1] G. Mugesh, W.W. du Mont, H. Sies, Chem. Rev. 101 (2001) 2125-2179.

[2] I.B. Douglass, J. Am. Chem Soc. 59 (1937) 740-742.

[3] B. Lal, A. Badshah, A.A. Altaf, N. Khan, S. Ullah, Appl. Organometal. Chem. 25 (2011) 843-855.

[4] A. Shah, R. Qureshi, N.K. Janjua, S. Haque, S. Ahmad, Anal. Sci. 24 (2008) 1437-1441.

[5] F. Asghar, A. Badshah, A. Shah, M. K. Rauf, M.I. Ali, M.N. Tahir,; E. Nosheen, Z. Rehman, R. Qureshi, J. Organomet. Chem. 717 (2012) 1-8.

[6] A.A. Altaf, N. Khan, A. Badshah, B. Lal,; S. Ullah,; S. Anwar,; M. Subhan, J. Pak. Chem. Soc. 33 (2011) 691-693.

[7] M.G. Sheldrick, Siemmens Analytical X-Rays Instruments, Inc., Madison. Wisc, USA, 1996**.**

[8] T.M. McPhillips, S.E. McPhillips, H.J. Chiu, A.E. Cohen, A. M. Deacon, P.J. Ellis, E. Garman, A. Gonzalez, N.K. Sauter, R.P. Phizackerley, S. M. Soltis, P. Kuhn, J. Synchrotron Rad. 9 (2002) 401-406.

[9] W. Kabsch, XDS. Acta Cryst. D66 (2010) 125-132.

[10] Q. Feng, N.Q. Li,; Y.Y. Jiang, Anal. Chim. Acta. 344 (1997) 97-104.

[11] M. Aslanoglu, N. Oge, Turk. J. Chem. 29 (2005) 477-485.

[12] M. Aslanoglu, G. Ayne, Anal. Bioanal. Chem. 380 (2004) 658-663.

[13] C.M.A. Brett, A.M.O. Brett, Electrochemistry Principles, Methods and Applications, Oxford University Press, UK 1993.

[14] M. Sirajuddin, A. Saqib, N.A. Shah, M.R. Khan, M.N. Tahir, Spectrochemica Acta Part A 94 (2012) 134-142.

[15] B. Lal, A. Badshah, A.A. Altaf, M.N. Tahir, S. Ullah, F. Haq, Dalton Trans. 41 (2012) 14643-14650.

Table 1. Crystal Data of MeP2F.

	MeP2F
CCDC No.	918928
Empirical formula	C_{24} H_{21}FFeN2OSe
Formula weight	519.25
Temperature (K)	100 K
Wavelength Å	0.71073
a [Å]	9.9750 (8)
b [Å]	9.9990 (5)
c [Å]	11.1360 (3)
α [deg]	92.579 (2)°
β [deg]	102.078 (5)°
γ [deg]	99.957 (3)°
Volume Å^3	1065.95 (10)
Crystal System	Triclinic
Space group	P-1
Z	2
Density (calculated)	1.618 Mg/m^3
Index Ranges	-12<=h<=12, -12<=k<=12, -14<=l<=14
Absorption coefficient (μ)	2.444
F(000)	528
Goodness-of-fit on F^2 (S)	1.027
Largest diff. peak and hole	0.524 and -0.958 e.Å^{-3}
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0965
R indices (all data)	R1 = 0.0563, wR2 = 0.1187

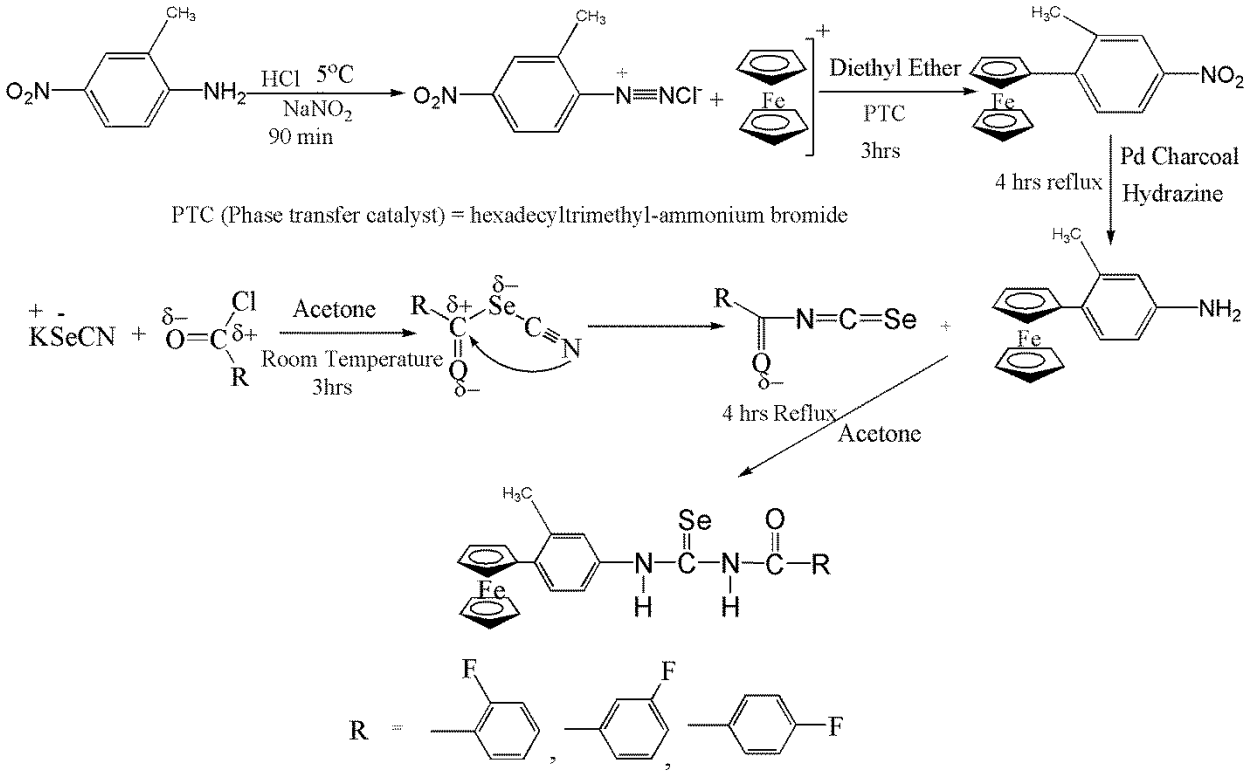
Table 2: Selected bond lengths (Å) and angles (°) for MeP2F.

Bond Type	Distance	Bond type	Angle
Se(1)-C(8)	1.831(3)	C(7)-N(1)-C(8)	128.8(2)
O(1)-C(7)	1.226(4)	C(7)-N(1)-H(1N)	117(3)
N(1)-C(7)	1.370(4)	C(8)-N(1)-H(1N)	115(3)
N(1)-C(8)	1.391(4)	C(8)-N(2)-C(9)	133.2(3)
N(1)-H(1N)	0.81(4)	C(8)-N(2)-H(2N)	103(2)
N(2)-C(8)	1.323(4)	C(9)-N(2)-H(2N)	124(2)
Fe(1)-C(19)	2.042(3)	Fe(1)-C(18)-H(18)	118(3)
Fe(1)-C(23)	2.042(3)	F(1)-C(2)-C(3)	116.7(3)
Fe(1)-C(16)	2.054(3)	F(1)-C(2)-C(1)	119.8(3)
		O(1)-C(7)-N(1)	122.6(3)
		O(1)-C(7)-C(1)	120.2(3)
		N(2)-C(8)-Se(1)	129.0(3)
		N(1)-C(8)-Se(1)	114.7(2)

Table 3: Hydrogen bonds for MeP2F (Å and °).

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...F(1)	0.81(4)	2.02(4)	2.691(3)	140(4)
N(2)-H(2N)...O(1)	0.70(3)	2.00(3)	2.659(4)	158(3)

Scheme 1. Synthetic scheme for ferrocene incorporated selenoureas.



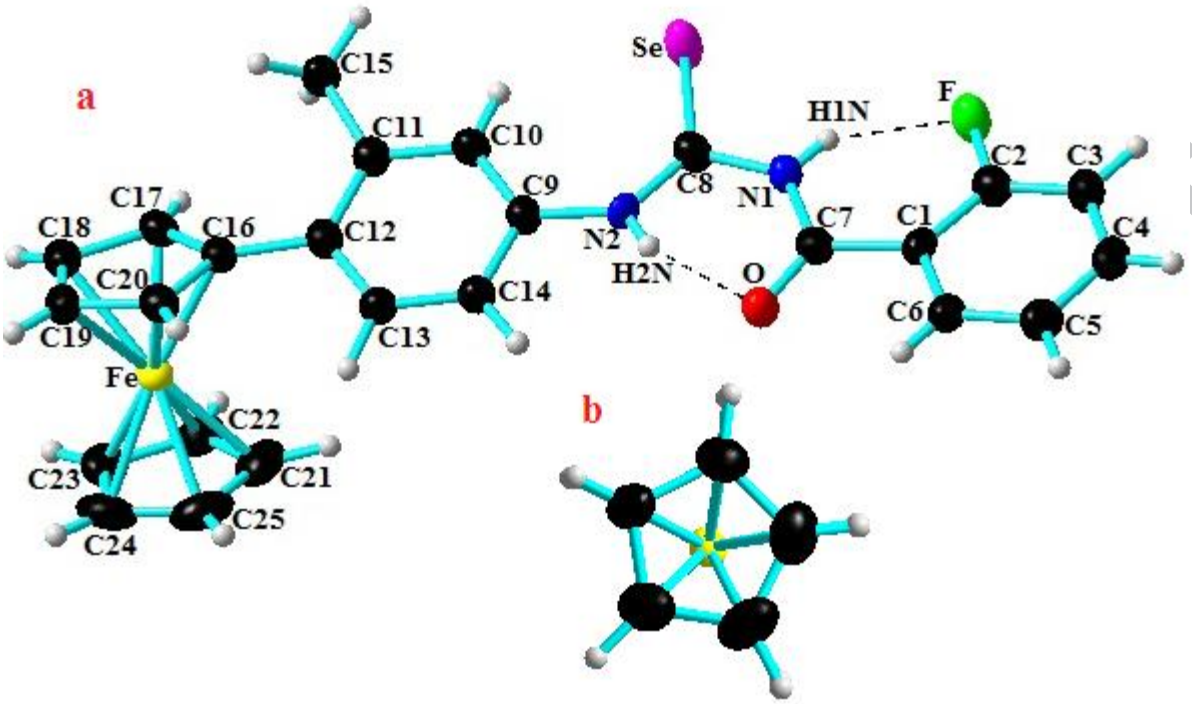


Fig. 1. Molecular diagram of MeP2F with ellipsoid displacement, non hydrogen atoms represented by 30 % probability boundary spheres and hydrogen atoms are sphere of arbitrary size. b) eclipsed ferrocene moiety.

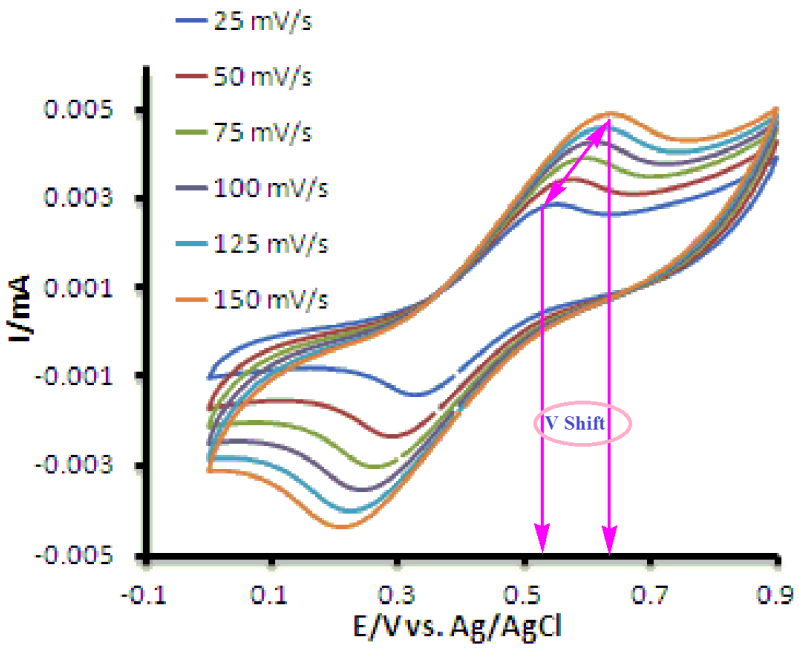


Fig. 2. Representative plots of I vs. E/V (Ag/AgCl) at different scan rates for MeP2F (quasi reversible).

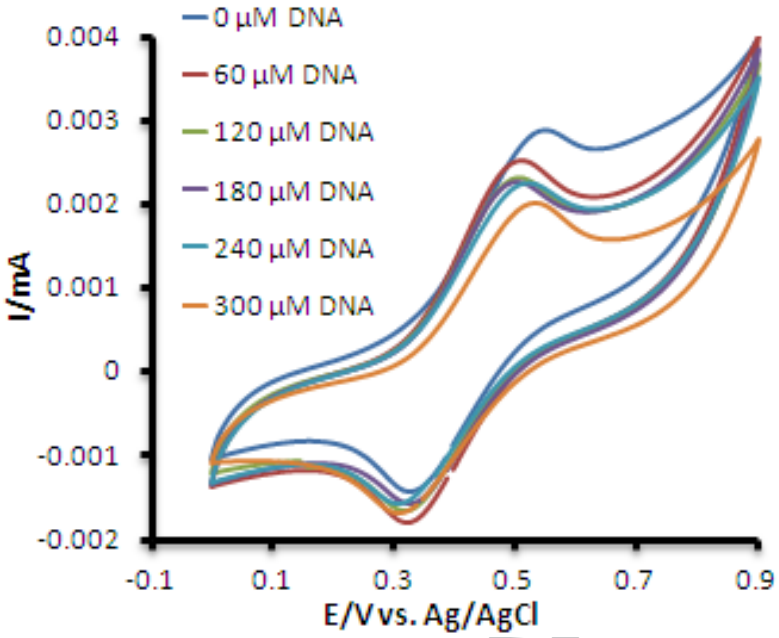


Fig. 3. Cyclic voltamograms of 1 mM MeP2F with 1mL of 0.5 M TBAP as supporting electrolyte in the absence and presence of 60-300 µM DNA showing a decrease in I from I_o and a concentration dependent shift in potential.

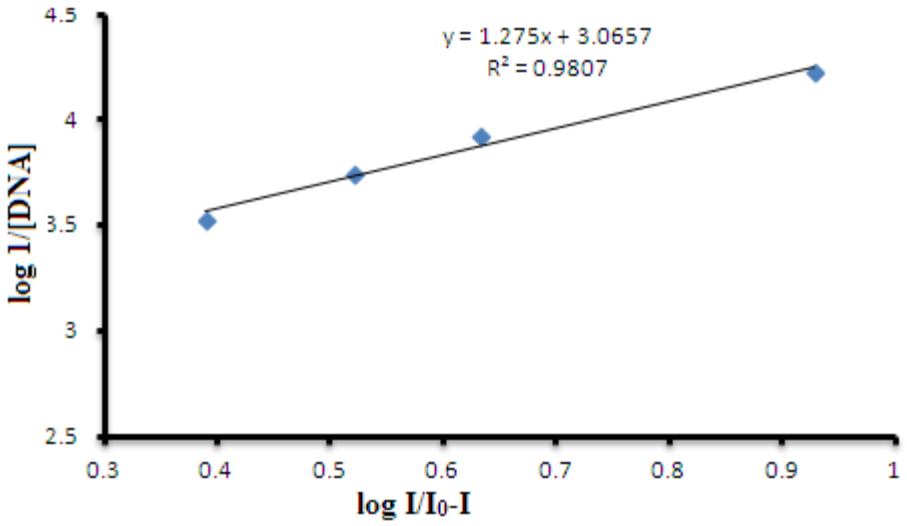


Fig. 4. Representative plot of log (I/I_o-I) vs. log (1/[DNA] for determination of binding constant of MeP2F.

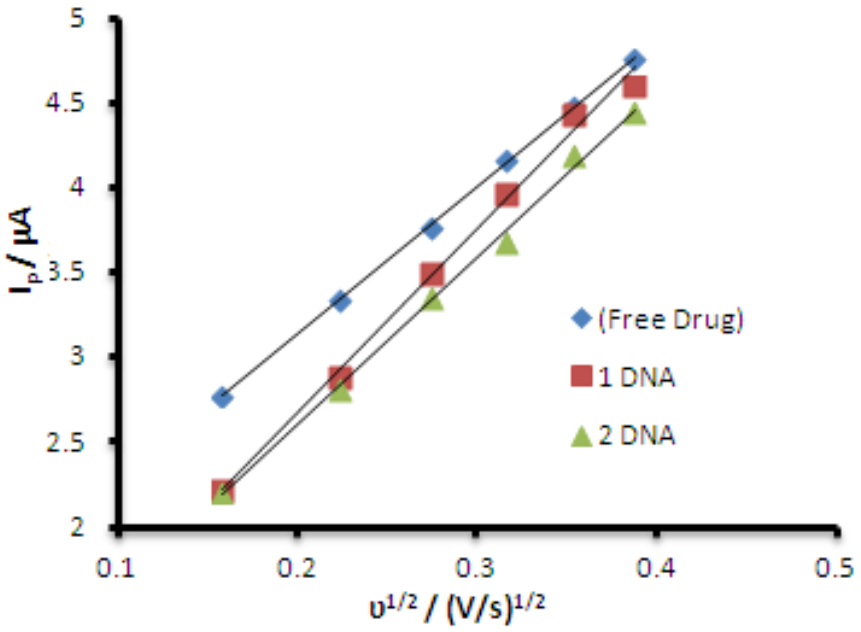


Fig. 5. Representative plots of I vs. υ ^{½}, for the determination of diffusion coefficient of free drug MeP2F and different drug-DNA adducts.

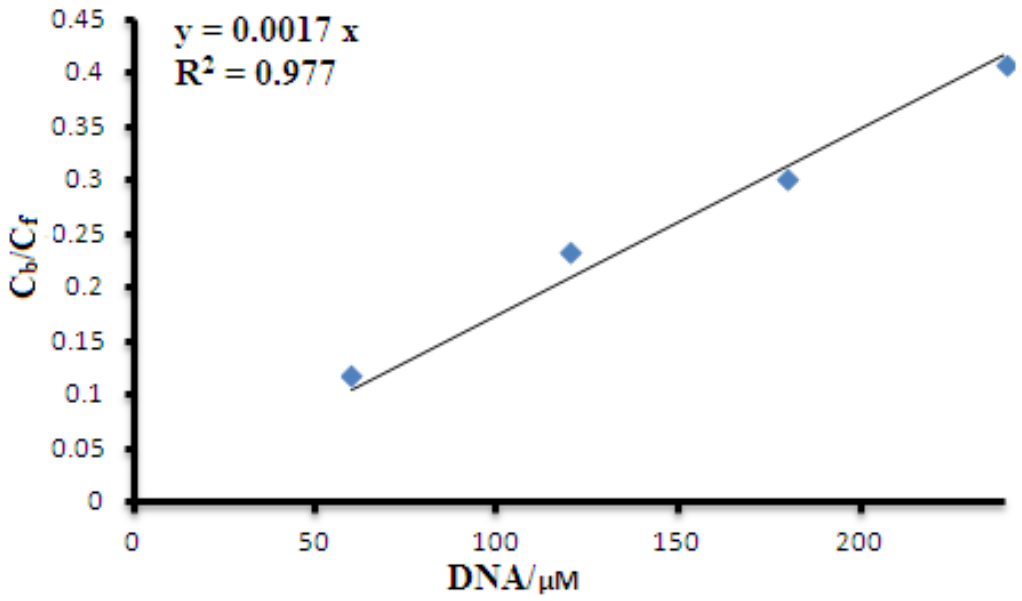


Fig. 6. Representative plots of C_b/C_f vs. [DNA]/μM for determination of binding site size for MeP2F.

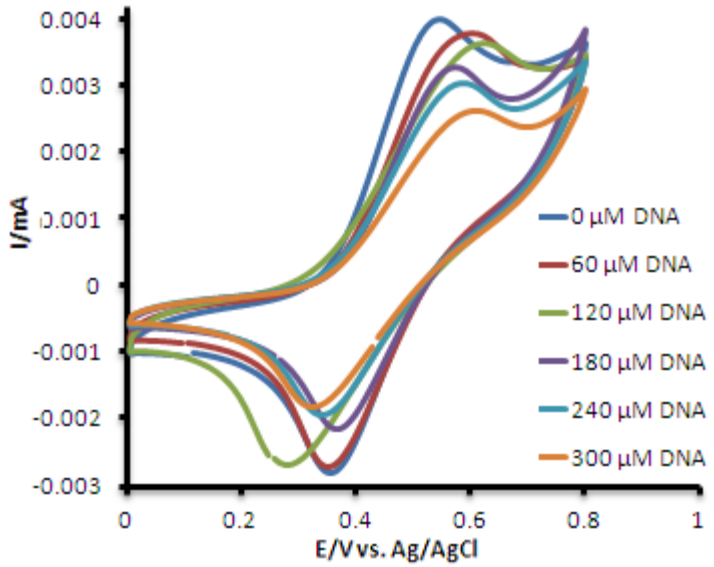


Fig. 7. Cyclic voltamograms of 1 mM MeP3F with 1mL of 0.5 M TBAP as supporting electrolyte in the absence and presence of 60-300 µM DNA showing a decrease in I from I_o and a concentration dependent shift in potential.

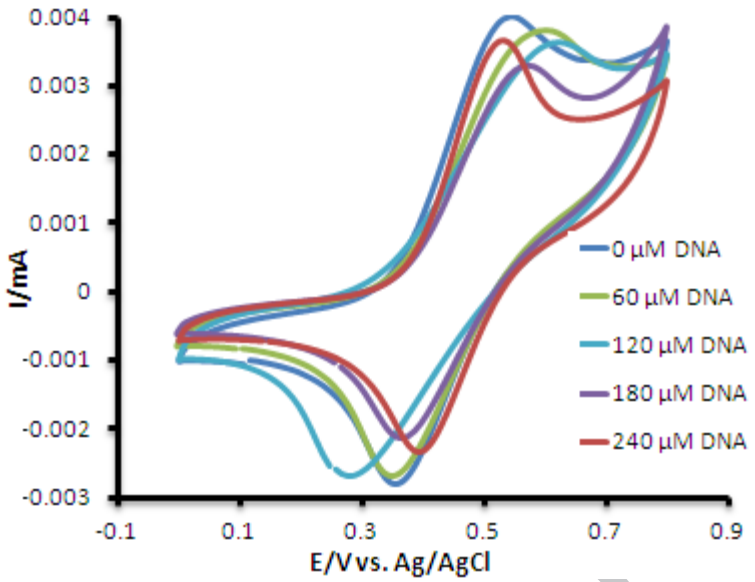


Fig. 8. Cyclic voltamograms of 1 mM MeP4F with 1mL of 0.5 M TBAP as supporting electrolyte in the absence and presence of 60-240 µM DNA showing a decrease in I from I_o and a concentration dependent shift in potential.

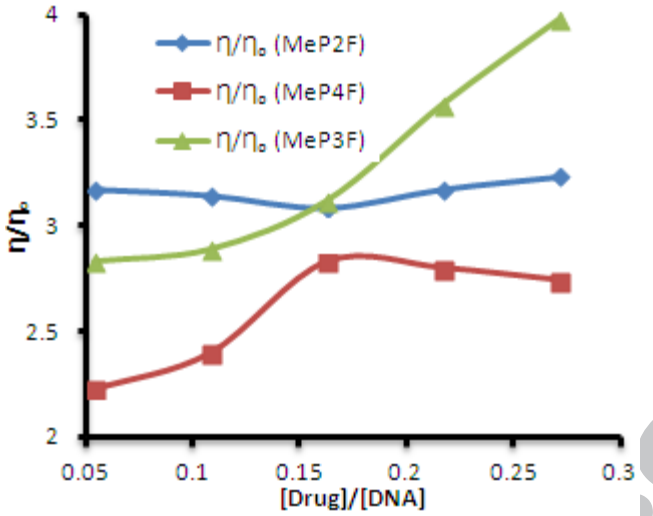


Fig. 9. Effects of increasing amount of drug on relative viscosity of drug-DNA at 25 ± 0.1 °C.

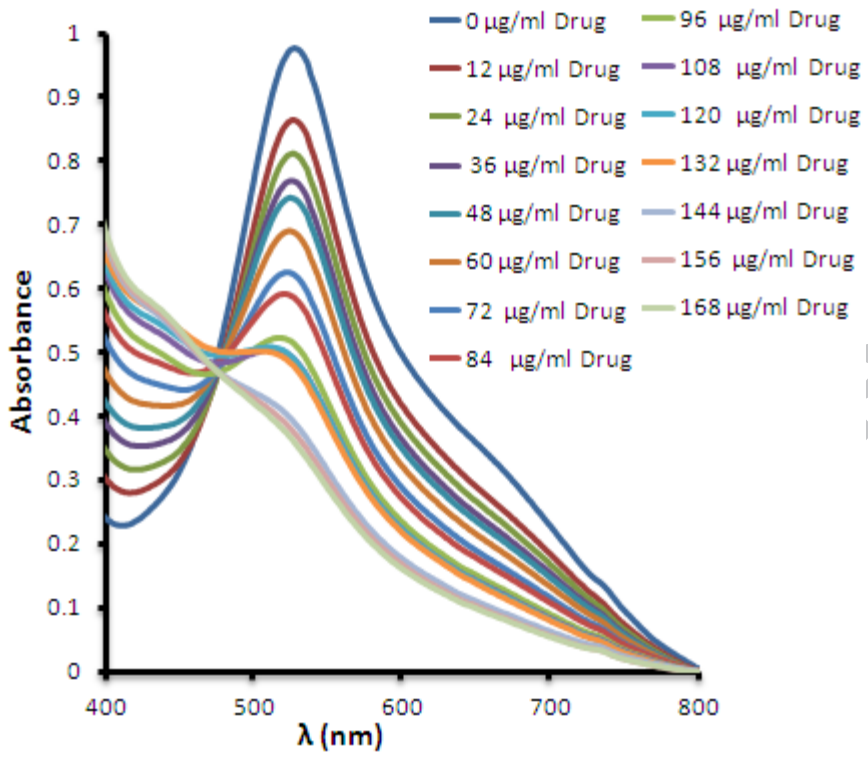
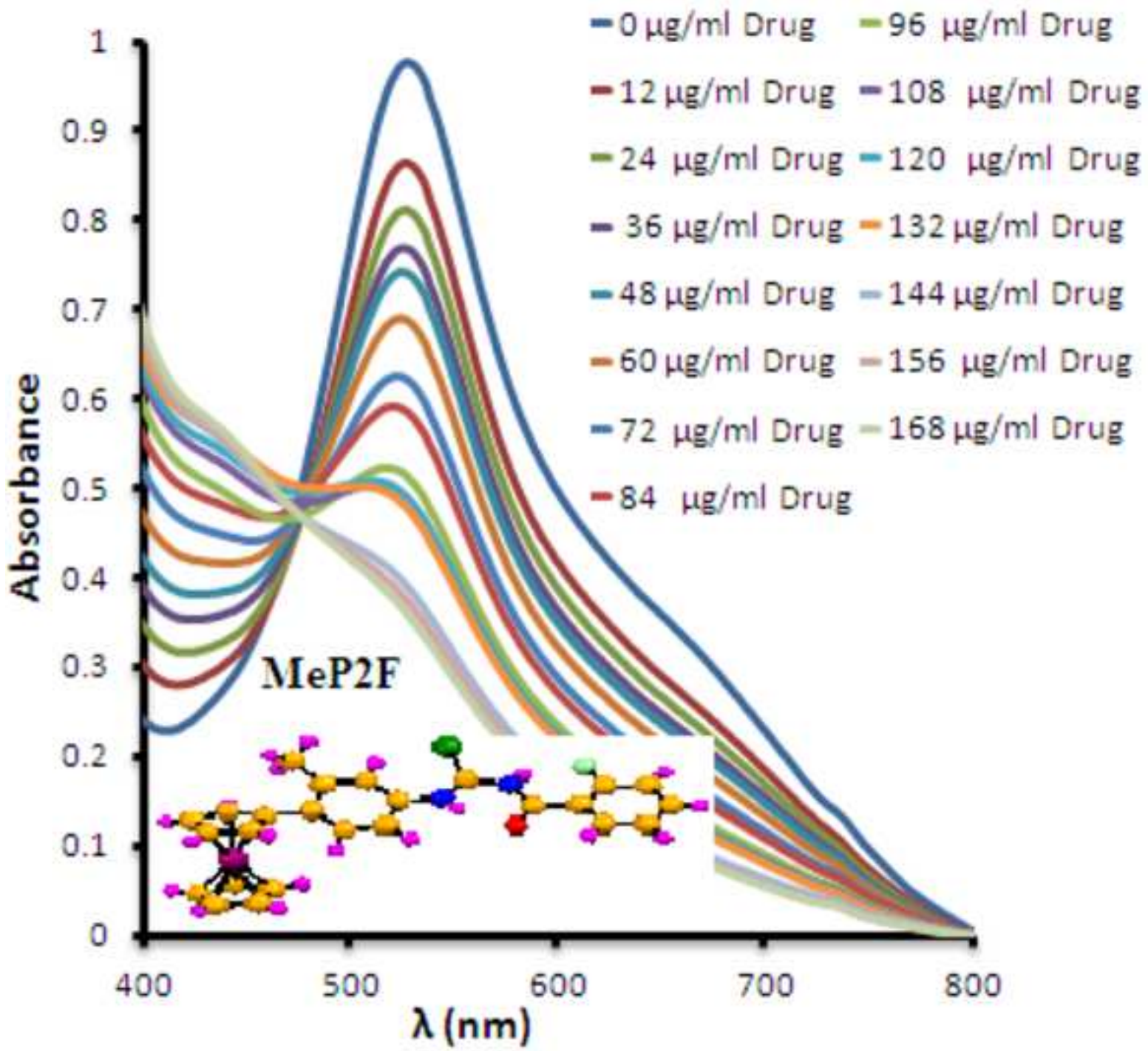


Fig. 10. Representative plot of absorbance vs. wavelength of MeP2F for DPPH scavenging activity.

Highlights (for review)

- Three new ferrocene incorporated selenoureas have been synthesized and characterized.
- Molecular structure of one compound has been determined by X-ray crystallography.
- All the compounds have DNA binding constant values in the range of 10^3 M^{-1}.
- IC_{50} values of the synthesized compounds have been found between 84-132 μg/ml against DPPH.

*Graphical Abstract (pictogram) (for review)



DPPH scavenging by its interaction with different concentrations of 1-(2-fluorobenzoyl)-3-(4-ferrocenyl-3-methylphenyl)selenourea (MeP2F).