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FULL PAPER

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# Facile synthesis, characterisation and anti-inflammatory activities of ferrocenyl ester derivatives of 4-arylidene-5-imidazolinones

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This article describes the synthesis, optoelectronic properties and anti-inflammatory activities of a series of seven ferrocenyl ester-linked 4-arylidene-5-imidazolinone conjugates. Three different types of *ortho*-, *meta*- and *para*-substituted ferrocenyl esters have been prepared. Their UV–Vis spectra and electrochemical studies are described. The structure of one of the conjugates was confirmed by single-crystal X-ray diffraction study. These conjugates exhibited moderate anti-inflammatory activities.

**KEYWORDS**
anti-inflammatory, arylidene, ferrocene, imidazolinones

## 1 | INTRODUCTION

Nitrogen-containing heterocyclic compounds occur in a wide variety of natural products and biologically active compounds, such as hormones, vitamins, alkaloids, as well as in numerous fine and speciality chemicals.[1] Imidazolinone, a prominent naturally occurring heterocycle, has been one of the most extensively studied moieties due to its presence in nature as a component of fluorescent proteins.[2] Some of the overwhelmingly popular ones are green fluorescent proteins,[3] cyan fluorescent proteins,[4] blue fluorescent proteins[5] and the red kaede fluorescent proteins (Figure 1).[6] Imidazolinones have significant potential as anticonvulsant,[7] anti-parkinson[8] and anti-inflammatory agents.[9] These moieties have also been examined for their enzyme inhibition activities, for instance, monoamine oxidase inhibitors,[10] as dual inhibitors of p38α MAPK and ERK1/2 enzymes,[11] as well as angiotensin II receptors.[12] The photochemical phenomena of fluorescent proteins have also been investigated and interpreted by means of these imidazolinones as chemical models.[13,14]

On the other hand, in recent times, the biomolecular conjugates of ferrocene have been extensively studied for several bioactivities, such as antimalarial, anticancer, antimicrobial, anti-tuberculosis, etc.[15] Recognition of biomolecules, bio-sensors and bio-imaging are also some of the applications of ferrocene-based compounds.[16] Our group has been involved in the synthesis and bioactivity of ferrocene-based biomolecules, such as

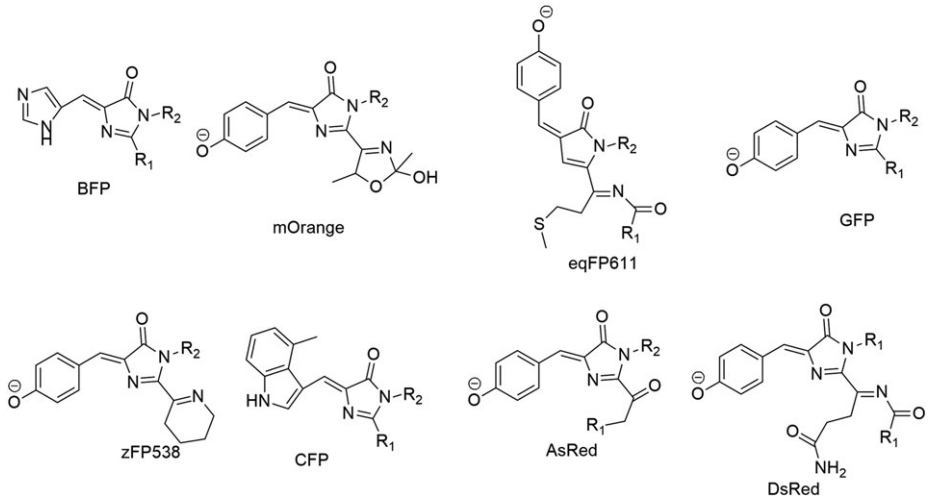



**FIGURE 1** Some of the imidazolinone fragments present in naturally occurring fluorescent proteins.

carbohydrates, pseudo-peptides, as well as chalcogeno triazole conjugates.[17]

During a thorough literature search, it was observed that there were no reports on the influence of an organometallic redox-active unit on imidazolinones. Hence, it was anticipated that coupling of a biologically active redox unit such as ferrocene on to the imidazolinones might augment interesting optoelectronic as well as biological properties. Herein, we describe the synthesis, optoelectronic as well as anti-inflammatory activity of a series of seven different ferrocene-based 4-arylidene 5-imidazolinone conjugates. These include the *ortho*-, *meta*- and *para*-substituted ferrocenyl esters of two different derivatives of imidazolinones.

## 1.1 | Experimental section

$^{1}$H–NMR spectra were recorded in $CDCl_3$ solutions using a 500 MHz (Inova 500) and 400 MHz (Bruker Avance 400) instrument. The chemical shifts for the protons were reported using tetramethylsilane as an internal standard. $^{13}$C–NMR spectra were recorded at 125 MHz on an Inova 500 and 100 MHz on a Bruker Avance 400 instrument, and the carbon shifts are referenced to the $^{13}$C signal of $CDCl_3$ at 77.0 ppm. Coupling constants ($J$) are expressed in Hz. Infrared spectra were obtained with a Thermo Nicolet Nexus 670 spectrometer using KBr discs. Melting points were determined with a Toshniwal melting point apparatus and are uncorrected. Cyclic voltammetric (CV) measurements were performed on a PC-controlled CH instruments model CHI 620C electrochemical analyzer. CV experiments were performed on 1 mM sample solution in $CH_2Cl_2$ solvent at a scan rate of 100 mV s$^{-1}$ using 0.1 M tetrabutylammonium perchlorate (TBAP) as supporting electrolyte. The working electrode is glassy carbon, standard calomel electrode (SCE) is reference electrode and platinum wire is an auxiliary electrode. After that, CV were been recorded. The optical absorption spectra were recorded on a Shimadzu (Model UV-3600) spectrophotometer with about $10 \times 10^{-5}$ M concentrations of solutions. Steady-state fluorescence spectra were recorded (Spex model Fluorlog-3) for solutions having optical density at the wavelength of excitation ($\lambda_{ex}$). The ferrocenecarboxylic acid and 4-arylidene-5-imidazolinones were prepared according to reported literature.[18,19]

## 1.2 | General procedure for the esterification

To a solution of 4-arylidene-5-imidazolinones (1.0 eq.) in $CH_2Cl_2$ (10 ml mmol$^{-1}$) was added ethylcarbodiimide hydrochloride (EDCHCl; 1.2 eq.), dimethyl aminopyridine (DMAP; 0.2 eq.) and ferrocenecarboxylic acid (1.2 eq.). The mixture was stirred for 2 h at room temperature, diluted with water (10 ml) and the layers were separated. The aqueous layer was extracted with dichloromethane ($2 \times 10$ ml) and the combined organic layer was washed with brine (10 ml), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the corresponding ester.

### 1.2.1 | Compound 5a

According to the general procedure documented above, the reaction of (Z)-4-(2-hydroxybenzylidene)-1,2-dimethyl-1H-imidazol-5(4H)-one (216 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) afforded the corresponding ferrocenyl ester **5a** as a yellow solid (312

mg, 73% yield), m.p. 188–189 °C; $^1$H–NMR (500 MHz, $CDCl_3$): $\delta$ = 8.87 (d, $J$ = 7.9 Hz, 1H, Ar), 7.49 (s, 1H, =CH), 7.41 (t, $J$ = 7.6 Hz, 1H, Ar), 7.33 (t, $J$ = 7.6 Hz, 1H, Ar), 7.25 (d, $J$ = 7.9 Hz, 1H, Ar), 5.03 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.53 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.39 (s, 5H, $C_5H_5$), 3.17 (s, 3H, $NCH_3$), 2.39 (s, 3H, $CH_3$) ppm; $^{13}$C–NMR (75 MHz, $CDCl_3$): $\delta$ = 170.49 (C = O amide), 170.0 (C = O ester), 163.3 (=$CCH_3$), 150.3 (Ar), 139.5 (Ar), 132.7 (Ar), 130.7 (Ar), 126.7 (=C), 125.8 (Ar), 122.7 (=CH), 119.5 (Ar), 72.0 (Fc), 70.5 (Fc), 70.1 (Fc), 69.5 (Fc), 26.5 ($NCH_3$), 15.7 ($CH_3$) ppm; (ESI): $m/z$ 429 $[M + H]^+$; HR-MS (ESI): calcd for $C_{23}H_{21}FeN_2O_3$: 429.0896 $[M + H]^+$; found: 429.0890; IR (neat): 3426, 3094, 2924, 1792, 1640, 1555, 1483, 1445, 1397, 1368, 1294, 1266, 1223, 1191, 1135, 1099, 909 $cm^{-1}$.

### 1.2.2 | Compound 6a

According to the general procedure documented above, the reaction of (*Z*)-4-(3-hydroxybenzylidene)-1,2-dimethyl-1H-imidazol-5(4H)-one (216 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) afforded the corresponding ferrocenyl ester **6a** as a yellow solid (333 mg, 78% yield), m.p. 201–202 °C: $^1$H–NMR (500 MHz, $CDCl_3$): $\delta$ = 8.22 (t, $J$ = 1.8 Hz, 1H, Ar), 7.84 (d, $J$ = 7.7 Hz, 1H, Ar), 7.45 (t, $J$ = 7.9 Hz, 1H, Ar), 7.20–7.17 (m, 1H, Ar), 7.10 (s, 1H, =CH), 4.99 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.51 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.35 (s, 5H, $C_5H_5$), 3.17 (s, 3H, $NCH_3$), 2.33 (s, 3H, $CH_3$) ppm; $^{13}$C–NMR (75 MHz, $CDCl_3$): $\delta$ = 170.6 (C = O amide), 170.2 (C = O ester), 163.0 (=$CCH_3$), 151.0 (Ar), 139.3 (Ar), 135.6 (=C), 129.5 (=CH), 129.4 (Ar), 125.9 (Ar), 124.9 (Ar), 123.4 (Ar), 71.9 (Fc), 70.6 (Fc), 69.9 (Fc), 69.9 (Fc), 26.5 ($NCH_3$), 15.6 ($CH_3$) ppm; (ESI): $m/z$ 429 $[M + H]^+$; HR-MS (ESI): calcd for $C_{23}H_{21}FeN_2O_3$: 429.0896 $[M + H]^+$; found: 429.0892; IR (neat): 2926, 2860, 1718, 1647, 1566, 1445, 1368, 1267, 1149, 1100, 1026, 921, 821 $cm^{-1}$.

### 1.2.3 | Compound 6b

According to the general procedure documented above, the reaction of (*Z*)-4-(3-hydroxybenzylidene)-2-methyl-1-propyl-1H-imidazol-5(4H)-one (244 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) afforded the corresponding ferrocenyl ester **6b** as a yellow solid (342 mg, 75% yield), m.p. 168–169 °C; $^1$H–NMR (500 MHz, $CDCl_3$): $\delta$ = 8.23 (t, $J$ = 1.8 Hz, 1H, Ar), 7.83 (d, $J$ = 7.7 Hz, 1H, Ar), 7.45 (t, $J$ = 7.9 Hz, 1H, Ar), 7.20–7.17 (m, 1H, Ar), 7.08 (s, 1H, =CH), 4.99 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.52 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.36 (s, 5H, $C_5H_5$), 3.56 (t, $J$ = 7.3 Hz, 2H, $NCH_2$), 2.34 (s, 3H, $CH_3$), 1.70–1.62 (m, 2H, $CH_2$), 0.96 (t, $J$ = 7.4 Hz, 3H, $CH_3$) ppm; $^{13}$C–NMR (75 MHz, $CDCl_3$): $\delta$ = 170.6 (C = O amide), 170.2 (C = O ester), 163.1 (=$CCH_3$), 151.1 (Ar), 139.2 (Ar), 135.7 (=C), 129.5 (=CH), 129.4 (Ar), 125.7 (Ar), 124.8 (Ar), 123.4 (Ar), 71.9 (Fc), 70.6 (Fc), 70.0 (Fc), 42.1 ($NCH_2$), 22.5 ($CH_3$), 15.7 ($CH_2$), 11.1 ($CH_3$) ppm; (ESI): $m/z$ 457 $[M + H]^+$; HR-MS (ESI): calcd for $C_{25}H_{25}FeN_2O_3$: 457.1209 $[M + H]^+$; found: 457.1201; IR (neat): 3422, 3075, 2963, 2931, 2871, 1722, 1642, 1577, 1554, 1481, 1437, 1401, 1355, 1288, 1248, 1153, 1097, 1016, 996, 814 $cm^{-1}$.

### 1.2.4 | Compound 7a

According to the general procedure documented above, the reaction of (*Z*)-4-(4-hydroxybenzylidene)-1,2-dimethyl-1H-imidazol-5(4H)-one (216 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) afforded the corresponding ferrocenyl ester **7a** as a yellow solid (376 mg, 88% yield), m.p. 196–197 °C, $^1$H–NMR (400 MHz, $CDCl_3$): $\delta$ = 8.21 (d, $J$ = 8.6 Hz, 2H, Ar), 7.24 (d, $J$ = 8.6 Hz, 2H, Ar), 7.11 (s, 1H, =CH), 4.97 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.51 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.30 (s, 5H, $C_5H_5$), 3.19 (s, 3H, $NCH_3$), 2.38 (s, 3H, $CH_3$) ppm; $^{13}$C–NMR (100 MHz, $CDCl_3$): $\delta$ = 170.6 (C = O amide), 169.9 (C = O ester), 162.5 (=$CCH_3$), 152.1 (Ar), 138.5 (Ar), 133.3 (Ar), 131.6 (=C), 126.2 (=CH), 121.9 (Ar), 72.0 (Fc), 70.6 (Fc), 69.9 (Fc), 69.7 (Fc), 26.5 ($NCH_3$), 15.6 ($CH_3$) ppm; (ESI): $m/z$ 429 $[M + H]^+$; HR-MS (ESI): calcd for $C_{23}H_{21}FeN_2O_3$: 429.0898 $[M + H]^+$; found: 429.0902; IR (neat): 3442, 3090, 2927, 2856, 1729, 1704, 1643, 1595, 1447, 1269, 1202, 1093, 1015, 905 $cm^{-1}$.

### 1.2.5 | Compound 7b

According to the general procedure documented above, the reaction of (*Z*)-4-(4-hydroxybenzylidene)-2-methyl-1-propyl-1H-imidazol-5(4H)-one (244 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) afforded the corresponding ferrocenyl ester **7b** as a yellow solid (405 mg, 89% yield), m.p. 157–158 °C; $^1$H–NMR (500 MHz, $CDCl_3$): $\delta$ = 8.21 (d, $J$ = 8.6 Hz, 2H, Ar), 7.25 (d, $J$ = 8.6 Hz, 2H, Ar), 7.10 (s, 1H, =CH), 4.97 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.52 (t, $J$ = 1.9 Hz, 2H, $C_5H_4$), 4.31 (s, 5H, $C_5H_5$), 3.58 (t, $J$ = 7.4 Hz, 2H, $NCH_2$), 2.40 (s, 3H, $CH_3$), 1.71–1.63 (m, 2H, $CH_2$), 0.97 (t, $J$ = 7.4 Hz, 3H, $CH_3$) ppm; $^{13}$C–NMR (75 MHz, $CDCl_3$): $\delta$ = 170.7 (C = O amide), 169.9 (C = O ester), 162.6 (=$CCH_3$), 152.1 (Ar), 138.4 (Ar), 133.3 (Ar), 131.6 (=C), 126.1 (=CH), 121.9 (Ar), 72.0 (Fc), 70.6 (Fc), 69.9 (Fc), 69.7 (Fc), 42.1 ($NCH_2$), 22.5($CH_3$), 15.7 ($CH_2$), 11.1 ($CH_3$) ppm; (ESI): $m/z$ 457 $[M + H]^+$; HR-MS (ESI): calcd for

$C_{25}H_{25}FeN_2O_3$: 457.1210 [M + H]$^+$; found: 457.1209; IR (neat): 3422, 2958, 2926, 2854, 1722, 1705, 1645, 1595, 1555, 1450, 1404, 1269, 1245, 1199, 1163, 1100, 1018, 911, 822 cm$^{-1}$.

### 1.2.6 | Compound 8a

According to the general procedure documented above, the reaction of (*Z*)-4-(4-hydroxy-3-methoxybenzylidene)-1,2-dimethyl-1H-imidazol-5(4H)-one (246 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) afforded the corresponding ferrocenyl ester **8a** as a yellow solid (384 mg, 84% yield), m.p. 217–219 °C; $^1$H–NMR (400 MHz, $CDCl_3$): $\delta$ = 8.06 (d, $J$ = 1.6 Hz, 1H, Ar), 7.64 (dd, $J$ = 1.8, 8.1 Hz, 1H, Ar), 7.12 (d, $J$ = 8.1 Hz, 1H, Ar), 7.07 (s, 1H, =CH), 4.96 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.49 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.35 (s, 5H, $C_5H_5$), 3.94 (s, 3H, $OCH_3$), 3.18 (s, 3H, $NCH_3$), 2.37 (s, 3H, $CH_3$) ppm; $^{13}$C–NMR (75 MHz, $CDCl_3$): $\delta$ = 170.6 (C = O amide), 169.4 (C = O ester), 162.5 (=$CCH_3$), 151.5 (Ar), 141.3 (Ar), 138.5 (Ar), 132.9 (=C), 126.5 (=CH), 125.5 (Ar), 123.3 (Ar), 115.4 (Ar), 71.8 (Fc), 70.6 (Fc), 70.1 (Fc), 69.7 (Fc), 55.7 ($OCH_3$), 26.5 ($NCH_3$), 15.7 ($CH_3$) ppm; (ESI): *m/z* 459 [M + H]$^+$; HR-MS (ESI): calcd for $C_{24}H_{23}FeN_2O_4$: 459.1001 [M + H]$^+$; found: 459.1005; IR (neat): 3385, 3086, 3005, 2933, 1728, 1700, 1664, 1595, 1505, 1448, 1416, 1365, 1264, 1131, 1097, 1024, 909, 810 cm$^{-1}$.

### 1.2.7 | Compound 8b

According to the general procedure documented above, the reaction of (*Z*)-4-(4-hydroxy-3-methoxybenzylidene)-2-methyl-1-propyl-1H-imidazol-5(4H)-one (274 mg, 1 mmol) with ferrocenecarboxylic acid (276 mg, 1.2 mmol) delivered the corresponding ferrocenyl ester **8b** as a yellow solid (413 mg, 85% yield); m.p. 181–182 °C; $^1$H–NMR (500 MHz, $CDCl_3$): $\delta$ = 8.08 (d, $J$ = 1.6 Hz, 1H, Ar), 7.64 (dd, $J$ = 1.8, 8.2 Hz, 1H, Ar), 7.12 (d, $J$ = 8.2 Hz, 1H, Ar), 7.07 (s, 1H, =CH), 4.96 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.49 (t, $J$ = 1.8 Hz, 2H, $C_5H_4$), 4.35 (s, 5H, $C_5H_5$), 3.95 (s, 3H, $OCH_3$), 3.58 (t, $J$ = 7.3 Hz, 2H, $NCH_2$), 2.39 (s, 3H, $CH_3$), 1.71–1.64 (m, 2H, $CH_2$), 0.97 (t, $J$ = 7.4 Hz, 3H, $CH_3$) ppm; $^{13}$C–NMR (75 MHz, $CDCl_3$): $\delta$ = 170.6 (C = O amide), 169.4 (C = O ester), 162.5 (=$CCH_3$), 151.5 (Ar), 141.3 (Ar), 138.5 (Ar), 132.9 (=C), 126.5 (=CH), 125.5 (Ar), 123.3 (Ar), 115.4 (Ar), 71.8 (Fc), 70.6 (Fc), 70.1 (Fc), 69.7 (Fc), 55.7 ($OCH_3$), 42.1 ($NCH_2$), 26.5 ($CH_3$), 15.7 ($CH_2$), 11.1 ($CH_3$) ppm; (ESI): *m/z* 509 [M + Na]$^+$; HR-MS (ESI): calcd for $C_{26}H_{26}FeN_2NaO_4$: 509.1138 [M + Na]$^+$; found: 509.1140; IR (neat): 3419, 2925, 2862, 1713, 1645, 1594, 1556, 1504, 1456, 1409, 1367, 1268, 1201, 1132, 1024, 912, 804 cm$^{-1}$.

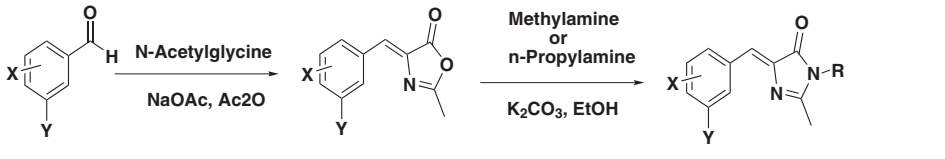
## 2 | RESULTS AND DISCUSSION

### 2.1 | Synthesis and characterisation

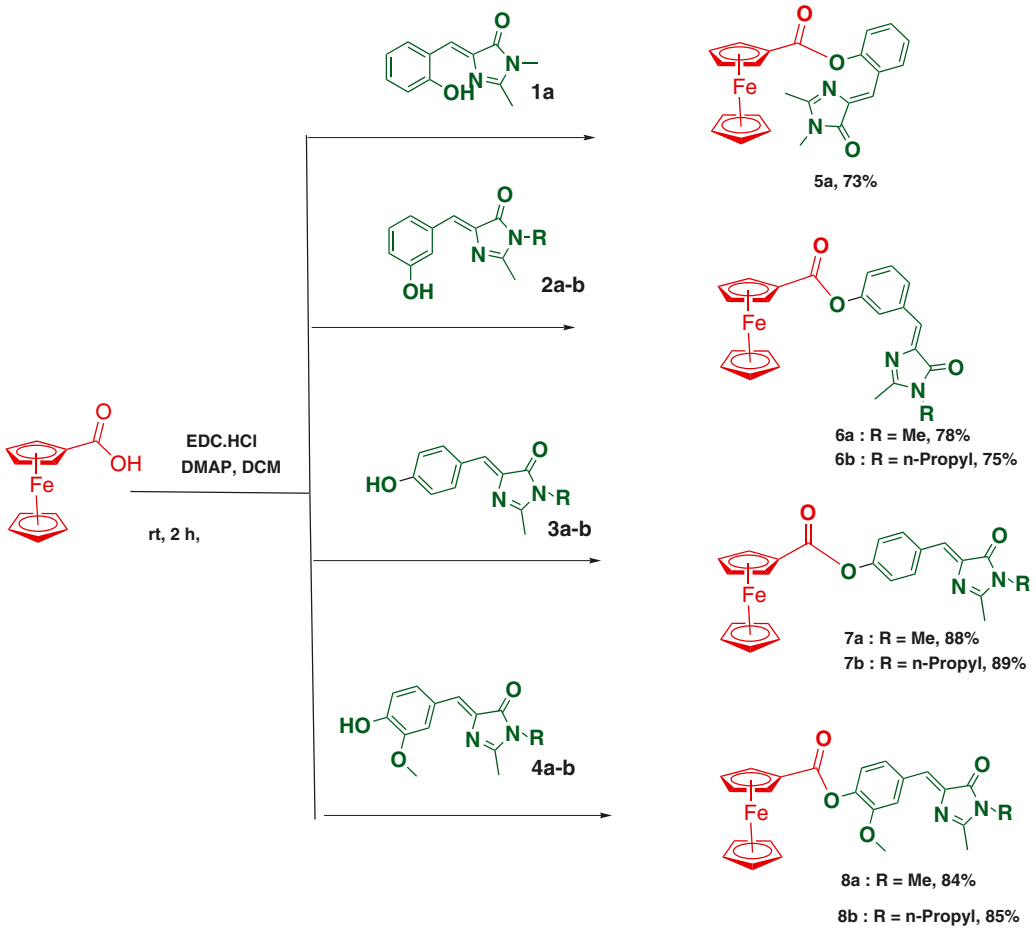
A simple condensation of various phenolic aldehydes with N-acetylglycine followed by alkyl amine exchange led to the formation of 4-arylidene-5-imidazolinones (**1a**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**) (Scheme 1) according to reported literature.[19]

These 4-arylidene-5-imidazolinones on reaction with ferrocenecarboxylic acid formed the ferrocenyl ester-derived 4-arylidene-5-imidazolinones. Accordingly, a series of 4-arylidene-5-imidazolinone compounds (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**) (Scheme 2) were synthesised by the following literature procedure,[20] wherein the free phenolic hydroxyl group was coupled with ferrocenecarboxylic acid in the presence of EDCHCl accompanied by a catalytic amount of DMAP employing dichloromethane as an appropriate solvent.

All the compounds were characterised by $^1$H- and $^{13}$C–NMR. In the $^1$H–NMR spectrum of all the compounds (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**), a singlet at about $\delta$ 7.07–8.22 ppm was observed, which could be attributable to the >C = C-H proton, and a singlet at 2.3 ppm for $CH_3$ linked to C-2 in all ferrocenyl ester-linked 4-arylidene-5-imidazolinones. In the $^1$H–NMR spectra of all the ferrocenyl derivatives, substituted cyclopentadienyl (Cp) ring protons appeared as triplets at about $\delta$ 4.96–5.03 ppm and 4.49–4.53 ppm, while a sharp singlet was




**SCHEME 1** Synthesis of 4-arylidene-5-imidazolinones, (**1a–4b**).




**SCHEME 2** Synthesis of ferrocenyl esters of 4-arylidene-5-imidazolinones (**5a–8b**)

observed for the unsubstituted cyclopentadienyl (Cp) ring at about 4.30–4.39 ppm. In the $^{13}$C–NMR spectra, the signals at about $\delta$ 15.6–15.7 ppm and $\delta$ 162.5–163.3 ppm were due to –$CH_3$ linked to C-2 and tertiary C-2 bonded to two N atoms, respectively, and the characteristic peak at about $\delta$ 115.4–123.4 ppm was assigned for allylic C attached to imidazolinone.[21] The FT-IR spectra of (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**) shows carbonyl (C═O) vibration bands at 1730–1750 $cm^{-1}$ and 1630–1680 $cm^{-1}$, which clearly indicates the substituted ester group and unsaturated amide, respectively, in ferrocenyl 4-arylidene-5-imidazolinone compounds. The bands at about 1580–1700 $cm^{-1}$ in the IR spectra can be assigned to the aromatic region.

## 2.2 | Optical studies: UV–Vis spectroscopy

The UV–Vis absorption spectra of ferrocenyl esters derivatives (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**) were recorded in $CH_2Cl_2$ over a wavelength range of 300–425 nm, as shown in Figure 2.

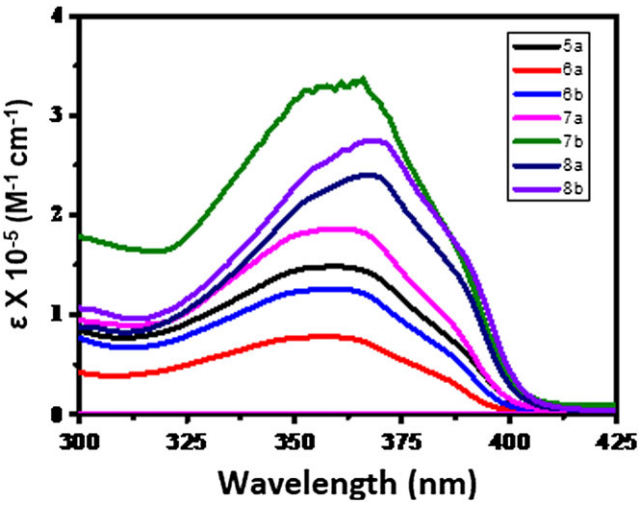



**FIGURE 2** Absorption spectra of ferrocenyl esters (**5a–8b**) in $CH_2Cl_2$

These ferrocene conjugates (**5a–8b**) exhibited strong absorption in the UV–Vis region (290–400 nm). The high-energy band with maxima at about 356 nm corresponds to the $\pi \rightarrow \pi^*$ electronic transition of the

ligand (**5a–7a**), and the low energy band at about 369 nm might arise from the localised metal-to-ligand charge transfer [Fe(d) → Cp($\pi^*$)] transition (**7b–8b**). The presence of a low-energy band confers the yellow colour for the conjugates.[17,22] Because the ferrocene moiety also depicts the metal-to-ligand charge transfer (MLCT) band between 320 and 360 nm, the low-energy band might also possess some ferrocene character.[23] The absorption spectra of *para*-substituted compounds such as (**7a**, **7b**, **8a**, **8b**) displayed high intensity as compared with the *ortho*- (**5a**) and *meta*- (**6a**, **6b**) substituted compounds. Such spectral changes can be attributed to the elongation of the $\pi$-conjugation in *para*-substituted compounds, when compared with *ortho*- and *meta*-substituted compounds.[24]

It is known in the literature that imidazolinone compounds are weakly fluorescent and, in the presence of fluorescence tags like Spinach, its fluorescence properties are enhanced.[25] We have carried out the steady-state emission studies of the present series of molecules in dichloromethane solvent at room temperature by exciting at 360 nm, and the resulted emission spectra are displayed in Figure 3. The fluorescence emission spectra of the ferrocenyl conjugates esters (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**) display two peaks at 409 and 432 nm, with a Stokes shift of 50–60 nm. It was also expected that the presence of the imidazolinone moiety should display interesting fluorescence behaviour. The lower enhancement of emission intensity may perhaps be due to a possible electron transfer from donor ferrocene to acceptor imidazolinone. It was also observed that the intensity of the fluorescence spectra of (**7b**) was slightly lowered as compared with the other compounds, this could perhaps be due to better charge transfer between ferrocene and 4-arylidene-5-imidazolinones.[19,26]

## 2.3 | Electrochemical studies

The electrochemical behaviours of ferrocenyl ester 4-arylidene-5-imidazolinones (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**) were studied by using the CV technique in $CH_2Cl_2$ at room temperature. The resultant CV is displayed in Figure 4, and data are presented in Table 1.

From Figure 4 and Table 1, it is suggested that all substituted ferrocenyl ester 4-arylidene-5-imidazolinones undergo a reversible one-electron oxidation similar to ferrocene, except the oxidation potentials of all compounds are anodically shifted by 0.30 V. The shift in oxidation potential might be due to the presence of the electron-withdrawing nature of imidazolinones, which is explained in the fluorescence spectra.[27]

## 2.4 | X-ray crystallography

The molecular structure of ferrocenyl ester derivative **6b** was determined by means of single-crystal X-ray diffraction studies, and its crystallographic data and structural refinement parameters are given in Table 2. Orange crystals of **6b** were grown by slow diffusion of hexane over a saturated dichloromethane solution. The compound crystallised in the monoclinic, space group $P2_1/n$. The absolute configuration and the atom numbering scheme are given in Figure 5, which shows a perspective view of compound **6b**. The pertinent bond length and bond angle data are listed in the Supporting Information. The crystal structure confirms the formation of a ferrocenyl ester-substituted imidazolinone moiety. The crystallographic structure reveals the orientation of the ferrocene group and imidazolinone with respect to the benzene ring.

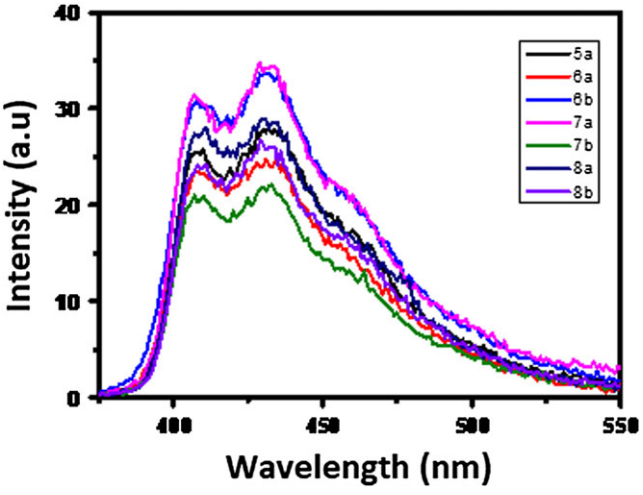



**FIGURE 3** Fluorescence spectra of ferrocenyl ester (**5a–8b**) in $CH_2Cl_2$

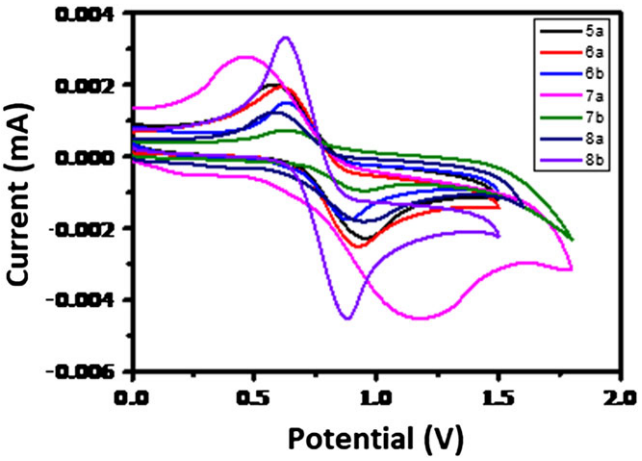



**FIGURE 4** Electrochemical oxidative potential curves of (**5a–8b**) in $CH_2Cl_2$ at RT.

**TABLE 1** CV data for ferrocenyl ester compounds (**5a**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**) obtained from voltammograms (vs. SCE)[a]

| Comp. Code | $E^0_{ox}$ (mV) | $\Delta E_p$ (mV) | $i_{pc}/i_{pa}$ | λabs max (nm) ($\varepsilon \times 10^4$) | λem max (nm) | Stokes shift (nm) |
|---|---|---|---|---|---|---|
| 5a | 763 | 364 | 0.90 | 359 (3.81) | 433 | 74 |
| 6a | 763 | 298 | 0.76 | 356 (3.51) | 434 | 78 |
| 6b | 760 | 266 | 0.88 | 359 (3.73) | 431 | 72 |
| 7a | 811 | 705 | 0.77 | 361 (3.92) | 432 | 71 |
| 7b | 777 | 305 | 0.77 | 362 (4.16) | 431 | 69 |
| 8a | 764 | 367 | 0.70 | 367 (4.00) | 432 | 65 |
| 8b | 750 | 259 | 0.75 | 369 (4.04) | 430 | 61 |

[a]All compounds in DCM with TBAP (supporting electrolyte) at 25 °C at a scan rate of 100 mV $s^{-1}$. $E^0_{ox} = (E_{pc} + E_{pa}/2)$, $\Delta E_p = (E_{pc} - E_{pa})$, $i_{pc}/i_{pa}$ (ratio between cathodic and anodic peak current), $E^0$red (reduction potential), $\varepsilon$ (extinction coefficient).

**TABLE 2** Crystal structure data and refinement parameters

| Crystal parameters | 6b |
|---|---|
| Empirical formula | $C_{25}$ $H_{24}$ Fe $N_2$ $O_3$ |
| Formula weight (g $mol^{-1}$) | 456.31 |
| Temperature *K* | 100(2) |
| Wavelength Å | 0.7107 |
| Crystal system | Monoclinic |
| Space group | $P2_1/n$ |
| *a* Å | 7.6610(10) |
| *b* Å | 27.323(4) |
| *c* Å | 10.6691(14) |
| α (°) | 90 |
| β (°) | 109.4770(10) |
| γ (°) | 90 |
| Volume $Å^3$ | 2105.5(5) |
| *Z* | 4 |
| Density (calculated)mg $m^{-3}$ | 1.440 |
| Absorption coefficient $mm^{-1}$ | 0.746 |
| *F*(000) | 952 |
| Crystal size mm | 0.180 × 0.150 × 0.090 |
| θ range (°) | 2.158–28.322 |
| *h*, *k*, *l* max | 10, 36, 14 |
| Reflections collected | 27 903 |
| Independent reflections | 5187 [*R*(int) = 0.0413] |
| Completeness to θ = 25.242° | 98.2% |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 5187/82/326 |
| Goodness-of-fit on $F^2$ | 1.350 |
| Final *R* indices [$I > 2$sigma($I$)] | $R1 = 0.0475$, w$R2 = 0.1337$ |
| *R* indices (all data) | $R1 = 0.0622$, w$R2 = 0.1510$ |
| Extinction coefficient | 0.n(7) |
| Largest diff. Peak and hole | 1.164 and −1.390 e.$Å^{-3}$ |

## 2.5 | Anti-inflammatory activity:

### 2.5.1 | In vitro assay by protein denaturation method

The protein denaturation method was followed for performing anti-inflammatory activity of synthesised compounds according to Mizushima and Kobayashi.[28] Bovine serum albumin (1% solution) in 50 mM sodium phosphate buffer (pH 6.4) was used. The reaction mixture consists of 0.1 ml of test sample (1 mg $ml^{-1}$), 0.2 ml of albumin protein, and was made up to a final volume of 5 ml with buffer. The reaction mixture was incubated at 37 °C for 20 min, and then heated to 95 °C for 20 min. After cooling the samples to room temperature, the turbidity was measured at 660 nm using a UV–Vis spectrophotometer (Model SL 210, Elico India). The experiment was performed in triplicate and average values were reported. The percentage inhibition of protein denaturation was calculated as follows:

$$\text{Percentage inhibition} = [(\text{Abs control} - \text{Abs sample})/\text{Abs control}] \times 100.$$

Compounds that inhibit the denaturation or increase the stability of proteins may be termed as anti-inflammatory. Proteins lose their complex tertiary structure (denaturation) by application of external stress during the denaturation process. The denaturation of these proteins may be via different routes, which include acid or alkaline reactions, heat treatment or radiation reactions, etc. The data presented in Table 3 clearly indicate that anti-inflammatory activity of the compound depends on the position of the 4-arylidene-5-imidazolinone on the ferrocene as well as aryl substituent. This can be evidenced from the fact that 4-arylidene-5-imidazolinone with methyl substitution at the *ortho* position (**5a**) resulted in only 21%

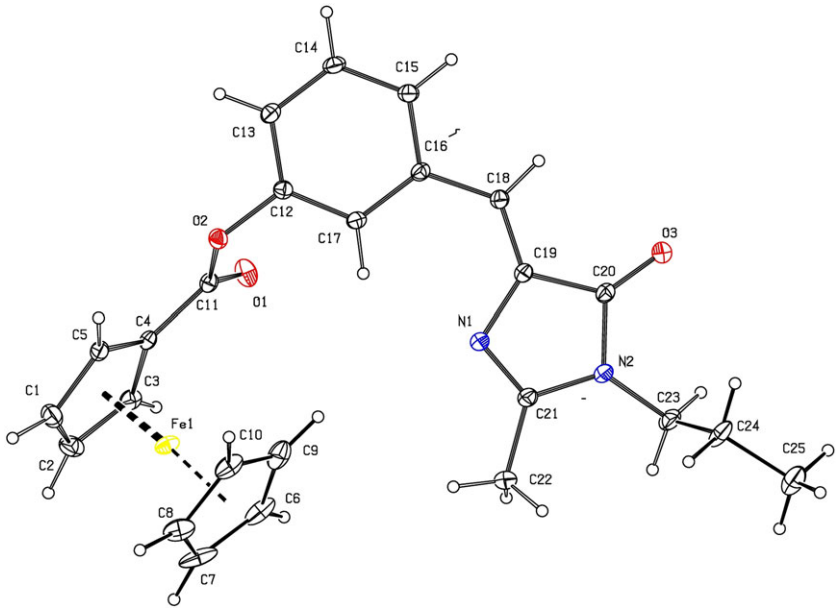



**FIGURE 5** A view of **6b**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are represented by circles of arbitrary radii.

**TABLE 3** Anti-inflammatory activity

| Compound | % inhibition |
|---|---|
| 5a | 21 |
| 6a | 55 |
| 6b | 31.14 |
| 7a | 44.26 |
| 7b | 27.86 |
| 8a | 3.27 |
| 8b | 47.54 |
| Std (Diclofenac) | 81.96 |

[a]Method used: protein denaturation method; protein used: bovine serum albumin); % inhibition: [(Control OD − test OD)/Control OD] × 100.

anti-inflammatory activity, while this increased more than double with 4-arylidene-5-imidazolinone substituted at the *meta* and *para* positions (**6a** and **7a**; Table 3). Replacing the methyl moiety with propyl decreased the anti-inflammatory activity [31% and 27% for (**6b**) and (**7b**), respectively; Table 3] either at *meta* or *para* positions. This suggests that the substituted carbon chain may be playing a role in protein interaction during protein structure denaturation or protection i.e. anti-inflammatory functionality. Further substitution of the methoxy moiety at the *meta* position on to methyl (**8a**) 4-arylidene-5-imidazolinone drastically reduced the anti-inflammatory activity (3%), whereas its substitution to propyl (**8b**) 4-arylidene-5-imidazolinone showed little change (47%; Table 3). However, the synthesised compounds were less effective than diclofenac (standard).

## 3 | CONCLUSIONS

This article describes the synthesis of ferrocene-conjugated 4-arylidene-5-imidazolinones via ester linkages. The molecular structure of one of the conjugates (**6b**) was established using single-crystal X-ray diffraction studies. The UV–Vis and electrochemical studies display characteristic transitions and reversible oxidation behaviour, respectively. These conjugates have also exhibited moderate to good anti-inflammatory activities. Further studies to modulate the optoelectronic properties of these 4-arylidene 5-imidazolinone conjugates are in progress.

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