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Synthesis and characterization of novel ferrocenyl chalcone ammonium and pyridinium salt derivatives

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Abstract

A novel series of ferrocenyl chalcone ammonium and pyridinium salt derivatives were synthesized in order to improve their solubility in aqueous media. Substituted ferrocenyl chalcones with amines and pyridines were synthesized using the base-catalyzed Claisen-Schmidt reaction, and their corresponding salts were prepared by a nucleophilic quaternization reaction at the nitrogen atom. Most of the synthesized ferrocenyl chalcone salts were soluble in water at room temperature. They were fully characterized by IR, NMR spectroscopy and HRMS spectrometry, and their electrochemistry was studied. The salt derivatives presented chemical reversibility, electrochemical quasi reversibility, and the slope of a plot of Log I_{pc} (or I_{pa}) versus Log v were almost 0.5 suggesting that their redox process was controlled by diffusion.

Keywords

ferrocenyl chalcones; ammonium and pyridinium salts; water-soluble ferrocenyl derivatives; *N*-alkylation reaction

1. Introduction

Many organometallic compounds studies in the last two decades have shown a broad range of biological activity. [1, 2, 3] While these discoveries are promising, a major challenge is that the majority of pharmaceutically active compounds exhibit low solubility in water, low bioavailability, or a combination of both. [4, 5, 6] Aqueous solubility can also be a valuable aid for decreasing dosage while increasing efficiency. [7] Orally administered drugs, which represent over 90% of medications [8], must be soluble at their absorption site [9] and in gastric media to achieve clinically significant bioavailability. [10]

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In honor of Dr. Luis Echegoyen, for his important contributions to the advancement of knowledge in science, exemplary scholarship, and for being a role model that has inspired many scientists.

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Organometallic compounds such as ferrocene and ferrocenyl derivatives have demonstrated low toxicity, DNA-cleaving activity, cytotoxic, antitumor, antimalarial, and antifungal properties. [11] Among the different ferrocenyl derivatives, ferrocenyl chalcones bearing a variety of substituents have been widely synthesized from acetyl ferrocene to produce 1-Ferrocenyl (1-Fc) chalcones or from ferrocenecarboxaldehyde obtaining the 3-Ferrocenyl (3-Fc) isomers, and then synthetically transformed into other derivatives with biological activity (Figure 1). [12] However, like many organometallic compounds with promising biological activity, the aforementioned ferrocenyl chalcone derivatives are insoluble in water. Despite their promising *in vitro* studies, ferrocenyl derivatives will not be clinically useful unless they are soluble at their biological absorption site. [9] Reports that detail the enhancement of solubility and the efficiency of known drugs with synthetic transformation are widespread [13], however, the use of quaternization reactions for this purpose is not common. Other reported strategies involve pH changes by protonating or deprotonating the nitrogen atom to improve their solubility in aqueous media. [8] This study is based on the alkylation of the nitrogen atom so the solubility would not be dependent or affected by the pH of the system.

The Claisen-Schmidt condensation is the most common method for the synthesis of ferrocenyl chalcones under homogeneous conditions in alcoholic media, using sodium or potassium hydroxide as the base. [14] This article is focused on the synthesis, characterization, and electrochemical properties of novel ferrocenyl chalcone salt derivatives. Using a Claisen-Schmidt condensation reaction, the synthesis of eight amine and pyridine substituted chalcones was achieved (Figure 2). The synthesis of the precursors chalcones (**1a–1d**) has been previously reported by us [15], whereas all the others are known. [11, 16–18]. Although different conditions have been employed for their synthesis, including solvent-free as well as ultrasound catalytic conditions. [19–24].

These eight ferrocenyl chalcones (**1a–d** and **2a–d**) were transformed into their corresponding salts to improve their solubility in aqueous media. (Figure 3) The *N*-alkylation of two lipophilic chains at the amine or pyridine nitrogen adds a positive charge to the framework and consequently, further enhances the solubility of the chalcones in aqueous media.

2. Results and Discussion

2.1 Synthesis of Ferrocenyl Chalcone Salt Derivatives

2.1.1 Methylated Salts—Synthesis of ferrocenyl derivatives **1e–1h** and **2e–2h** was done using DMS in toluene for 1 h (Scheme 1). Starting from ferrocenyl chalcones **1a–1d** and **2a–2d**, seven of the eight methylated salts were obtained in good to excellent yields (66 – 99%). (Table 1) The salts were successfully synthesized in 1 h under reflux conditions without the need for purification. Chalcone salt **1h** was previously reported by us [15] using 2-methyl THF, for 3 h at reflux under nitrogen atmosphere, albeit in a lower yield. Changing the solvent from 2-methyl THF to toluene produced a 73% yield of the salt. The four ferrocenyl chalcone salts from the 1-Fc system were obtained (**1e–h**), however, only three of the salts from the 3-Fc system were successfully synthesized (**2f–h**). Synthesis of compound

2e was attempted but only decomposition products were observed. The seven successfully synthesized ferrocenyl chalcone salts were soluble in water at room temperature.

2.1.2 Butylated Salts—The same method, using dibutylsulfate as alkylating agent, was used for the eight monosubstituted butylated ferrocenyl chalcone salts (**1i–l** and **2i–l**). (Scheme 2) Only four of these salts were obtained (**1j**, **1k**, **2j**, and **2k**). Yields ranging from 40 to 75% were produced after 3 hours of reflux. (Table 2) Two of the four butylated ferrocenyl chalcone salts from the 1-Fc system were obtained successfully (**1j** and **1k**). Products **1i** and **1l** were not produced in sufficient quantities for further characterization. Also, two of the salts from the 3-Fc system were successfully obtained (**2j** and **2k**). Decomposition of **2i** was observed and for **2l**, only starting material was recovered. From the four butylated ferrocenyl chalcone salts, only two compounds were soluble in water at room temperature (**1k** and **2k**).

2.2 Characterization

2.2.1 Spectral Analysis—All compounds were characterized and their structure confirmed by ^1H and ^{13}C NMR, FT-IR spectroscopy, and HRMS spectrometry. The ^1H NMR spectra for all the salts exhibited purities greater than 95%. In general, there were minimum variations between the regions of the spectral signals within the eight parental chalcones (**1a–d** and **2a–d**), regarding the 1-Fc or 3-Fc isomers. There are characteristic ^1H NMR chemical shifts for monosubstituted ferrocenes. These show shifts around 4–5 ppm that can be found on spectrum **A** shown in Figure 4. Aromatic peaks between 6.5–9 ppm can also be observed, which correspond to the aromatic protons and alkene protons from the chalcone. Coupling constants (J) consistently ranged from 14 to 16 Hz, which confirms an *E* configuration of the alkene. The ^{13}C NMR spectra revealed the four characteristic peaks of the monosubstituted ferrocene in the 65–80 and 110–160 ppm regions for the alpha, beta-unsaturated alkene carbons as well as the aromatic ring. The carbonyl signal resonated between 192–193 ppm for the 1-Fc chalcones and 187–188 ppm for those of the 3-Fc system, those signals correlate properly with the ketone carbonyl signals reported by S. Chatterjee, 2015. [25] The FT-IR spectra presented the characteristic band of the conjugated carbonyl around $1,650\text{ cm}^{-1}$, followed by the alkene band from the alpha, beta-unsaturated system around $1,600\text{ cm}^{-1}$. (See Appendix A)

The ^1H and ^{13}C NMR signals for the eleven ferrocenyl chalcones salts obtained are comparable to the spectra of their parental chalcones. All the peaks for the parental chalcones are present in each of the salts (see Figure 4), which proved that this part of the scaffold remained intact. For the ^1H NMR spectra of the methylated salts (spectrum **B** in Figure 4), the region around 3–5 ppm showed two peaks: one for the methyl of the quaternary methylated salt and the other accounts for the methyl of the counterion, which appears at lower field because it closeness to an oxygen atom. The same feature is exhibited by the butylated salts (spectrum **C** in Figure 4), with the difference that eight signals appeared in the 0.8 to 5 ppm range for the butyl connected to the chalcone nitrogen atom and the other butyl present in the counterion. Additional signals in the ^{13}C NMR spectra (Appendix A), appeared in the region between 60–70 ppm for the methylated salts and 10–70 ppm for the butylated salts. The FT-IR spectra (Appendix A) clearly showed the

difference in the 2,900–3,000 cm^{-1} region for the methylated salts compared with the butylated salts, which showed multiple bands in this region corresponding to the aliphatic CH stretching signals of the butyl group.

2.2.2 Electrochemical Studies—The electrochemical behavior of some of the synthesized monosubstituted ferrocenyl chalcone salt derivatives was studied for characterization purposes. The use of cyclic voltammetry was employed to obtain electrochemical parameters of the compounds and compare the two isomeric systems, 1-Fc vs 3-Fc. The results obtained are presented in Table 3 for the 1-Fc system and in Table 4 for the 3-Fc system.

The electrochemical parameters obtained demonstrated that the salts are electrochemically quasi-reversible. For all the cationic chalcones, the E_p is higher than 60 mV and oscillates between 61–109 mV, which is in the regime for a quasi-reversible electron transfer redox process. These salts also exhibited chemical reversibility. The peak currents ratio (I_{pc}/I_{pa}) is almost 1, which reveals that the redox process centered in the ferrocene nucleus is chemically stable, at least for voltages between 0 to 1000 mV vs Ag/AgCl (3M NaCl). From the slope of a plot of $\text{Log } I_{pc}$ (or I_{pa}) versus $\text{Log } v$, it is noticeable that the redox process is diffusion controlled due to the fact that the values are almost 0.5. If the value of the slope is higher than 0.5, there is a possibility that the redox process is controlled by the adsorption of the compound to the electrode surface. [15]

These results also demonstrate that the formal redox potential (E^0) for the 1-Fc salt derivatives is higher than the formal redox potential for the 3-Fc salts. There is a difference between the formal redox potential of structural isomers with the same substituent that varies between 140 to 255 mV. The carbonyl group closer to the ferrocene nucleus in the 1-Fc salts causes a polarization that accentuates the donor character of the ferrocene, causing it to be more resistant towards oxidation compared to the 3-Fc salts.

3. Conclusion

A simple method for the synthesis of monosubstituted ferrocenyl chalcone nitrogen salt-derivatives was developed for their potential use as oral drugs. Eleven out of sixteen possible salt derivatives were successfully synthesized in moderate to excellent yields (40–99%) by means of *N*-alkylation substitution reactions, and nine of the systems were soluble in water at room temperature. The identity, purity, and properties of all synthesized compounds were characterized by ^1H and ^{13}C NMR, FT-IR spectroscopy, cyclic voltammetry, and HRMS spectrometry. The electrochemical study of these new ferrocenyl salts showed an interesting tendency for the formal redox potential (E^0). This potential (E^0) between the 1-Fc system versus 3-Fc system is lower, suggesting an electronic effect caused by the proximity of the ferrocene to the carbonyl moiety as well as the position of the substituent on the aromatic ring. The enhanced solubility of the synthesized monosubstituted ferrocenyl chalcone salt derivatives is a promising drug-like property to further study their biological activity. Further analysis including their anticancer, antioxidant, antimalarial, and antibacterial properties are being studied and will be reported.

4. Experimental

4.1 Materials and Methods

All glassware was dried in an oven and assembled hot with a magnetic bar and stirrer. All reagents and solvents were used as purchased from Sigma-Aldrich, Aldrich Chemistry, Acros Organic, Alfa Aesar, PHARMCO-AAPER, Honeywell, B & J Brand, Strem Chemicals, Bean Town Chemical and TCI. All products were analyzed by ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) using a Bruker Avance DRX-500 or DRX-300 Spectrometer at room temperature. The samples were prepared dissolving 20–30 mg of the compounds in chloroform- d (CDCl_3), deuterated water (D_2O) or acetone- d_6 ($(\text{CD}_3)_2\text{CO}$), and the signals were calibrated with these solvent signals at δ 7.26, 4.80 and 2.05 ppm, respectively, for ^1H NMR and δ 77.00, or 29.92 ppm respectively for ^{13}C NMR. FT-IR spectra were obtained on a Shimadzu IRAffinity-1S Fourier Transform Infrared Spectrophotometer. The exact mass determination of the compounds was obtained by HRMS-ESI analysis on a Waters Xevo G2-S QToF MS/MS Spectrometer. The compounds were dissolved and diluted to a 1 ppm concentration in acetonitrile (HPLC grade 99.7%). Leucine enkephalin was used as a standard solution for the exact mass determination corrections. The acquisitions were conducted in ion spray mode by direct continuous pump infusion of the compound solutions at a flow rate of 20 mL/min in the mass spectrometer. Data acquisition was performed on the compounds in full scan, to choose the abundant ion $[\text{M}^+]$.

Electrochemical measurements were carried out using an Epsilon-BaSi® potentiostat, and cyclic voltammograms were collected in acetonitrile with LiClO_4 0.10 M as the supporting electrolyte. The concentration of the cationic chalcones was either 1 mM or 5×10^{-4} M. The solutions were protected from light and were not degassed before performing electrochemical characterization. A Ag/AgCl (3M NaCl) electrode and nichrome wire were used as reference and auxiliary electrodes, respectively. Platinum (0.02 cm^2) or glassy carbon (0.070 cm^2) electrodes were used as the working electrode. The working electrode was cleaned by polishing with diamond paste and Metadi fluid with a specialty polishing cloth. Afterwards, the electrode was subjected to ultrasound in a 1:1 water/acetone mixture for approximately 1 minute, rinsed with nanopure water, and dried with a Kim wipe.

The voltammograms were obtained at various scan rates from 0 to 5000 mV/s. From each voltammogram, the anodic and cathodic peak currents, and the anodic and cathodic peak potentials, were tabulated as a function of the scan rate. The electrochemical parameters (E° , E_p , I_{pc}/I_{pa} , and Slope of $\text{Log}(I_{pc} \text{ or } I_{pa})$ vs $\text{Log } \nu$) that produce useful information to characterize the redox process of the salt derivatives were determined from the voltammetric data.

4.2 Synthetic Procedures

4.2.1 1-Ferrocenyl Chalcones (1a–1d)

General Procedure: The acetylferrocene (2.0 mmol) and the pyridinecarboxaldehyde or benzaldehyde derivatives (2.0 mmol) were added to a round bottom flask at rt. Then, a freshly prepared NaOH soln (0.5 mmol in 1.0 mL each of H_2O and EtOH) was added

dropwise and left stirring at rt. When completed, the resulting product was filtered at reduced pressure, washing with cold water. The crude product was then recrystallized as described.

Compound 1a: 1-ferrocenyl-3-(2-pyridinyl) prop-2-en-1-one: Obtained as dark violet crystals after recrystallization using acetone:H₂O mixture. Yield: 0.41 g (64%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 8.69 (1H, s), 7.74 (s, 2H), 7.69 (s, 1H), 7.46 (s, 1H), 7.28 (d, 1H), 4.98 (s, 2H), 4.61 (s, 2H), 4.23 (s, 5H). ¹³C NMR (125 MHz, CDCl₃): δ = 193.3, 153.6, 150.2, 139.1, 136.9, 126.7, 125.5, 124.1, 80.6, 73.0, 70.2, 70.0. FT-IR (neat) ν_{max} (cm⁻¹): 1651 (m), 1597 (m), 1566 (w), 1462 (w), 1377 (m).

Compound 1b: 1-ferrocenyl-3-(3-pyridinyl) prop-2-en-1-one: Obtained as light violet crystals after recrystallization using acetone:H₂O mixture. Yield: 0.44 g (70%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 8.88 (s, 1H), 8.63 (s, 1H), 7.93 (s, 1H), 7.76 (d, *J* = 15.0 Hz, 1H), 7.37 (s, 1H), 7.17 (d, *J* = 16.0 Hz, 1H), 4.92 (s, 2H), 4.63 (s, 2H), 4.23 (s, 5H). ¹³C NMR (125 MHz, CDCl₃): δ = 192.3, 150.7, 149.7, 137.1, 134.7, 131.0, 124.8, 123.8, 80.3, 73.1, 70.2, 69.8. FT-IR (neat) ν_{max} (cm⁻¹): 1651 (m), 1593 (m), 1568 (w), 1477 (w), 1377 (m).

Compound 1c: 1-ferrocenyl-3-(4-pyridinyl) prop-2-en-1-one was obtained as violet crystals after recrystallization using EtOH:H₂O mixture. Yield: 0.44 g (70%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 8.68 (s, 2H), 7.67 (d, *J* = 15 Hz, 1H), 7.48 (s, 2H), 7.22 (d, *J* = 15 Hz, 1H), 4.92 (s, 2H), 4.64 (s, 2H), 4.23 (s, 5H). ¹³C NMR (125 MHz, CDCl₃): δ = 192.2, 150.6, 142.5, 137.7, 126.9, 122.0, 80.1, 73.3, 70.2, 69.8. FT-IR (neat) ν_{max} (cm⁻¹): 1651 (m), 1591 (m), 1548 (w), 1496 (w), 1375 (m).

Compound 1d: 1-ferrocenyl-3-(4-N, N-dimethylamino) prop-2-en-1-one was obtained as orange crystals after recrystallization using EtOH. Yield: 0.29 g (41%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 7.75 (d, *J* = 15 Hz, 1H), 7.55 (d, *J* = 8 Hz, 2H), 6.95 (d, *J* = 16 Hz, 1H), 6.71 (d, *J* = 8 Hz, 2H), 4.90 (s, 2H), 4.53 (s, 2H), 4.20 (s, 5H), 3.04 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ = 193.1, 151.8, 141.7, 130.1, 122.9, 118.1, 111.9, 81.3, 72.2, 70.0, 69.6, 40.2. FT-IR (neat) ν_{max} (cm⁻¹): 1639 (m), 1608 (m), 1570 (w), 1413 (m), 1363 and 1330 (m).

4.2.2 3-Ferrocenyl Chalcones (2a–2d)

General Procedure: The ferrocenecarboxaldehyde (2.0 mmol) and the acetyl pyridine or amino acetophenone derivatives (2.0 mmol) were added to a round bottom flask at rt. Then, a freshly prepared NaOH solution (0.5 mmol in 1.0 mL each of H₂O and EtOH) was added dropwise and left stirring at rt. When completed, the resulting product was filtered at reduced pressure, washing with cold water. The crude product was then recrystallized as described.

Compound 2a: 3-ferrocenyl-1-(2-pyridinyl) prop-2-en-1-one was obtained as dark violet crystals after recrystallization using acetone:H₂O mixture. Yield: 0.41 g (64%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 8.73 (s, 1H), 8.18 (d, *J* = 7 Hz, 1H), 7.89 (s, 1H), 7.86 (d, *J* = 4 Hz, 2H), 7.46 (s, 1H), 4.67 (s, 2H), 4.49 (s, 2H), 4.18 (s, 5H). ¹³C NMR (125 MHz, CDCl₃): δ = 188.5, 154.7, 148.8, 147.2, 137.0, 126.5,

122.9, 117.8, 79.5, 71.5, 69.9, 69.5. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1659 (m), 1591 (m), 1574 (w), 1462 (w), 1396 (m).

Compound **2b** *3-ferrocenyl-1-(3-pyridinyl) prop-2-en-1-one* was obtained as dark violet crystals after recrystallization using acetone:H₂O. Yield: 0.42 g (66%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 9.18 (s, 1H), 8.78 (d, J = 4 Hz, 1H), 8.25 (d, J = 8 Hz, 1H), 7.79 (d, J = 15 Hz, 1H), 7.43 (q, J = 5 Hz, 1H), 7.07 (d, J = 15 Hz, 1H), 4.62 (s, 2H), 4.53 (s, 2H), 4.20 (s, 5H). ¹³C NMR (125 MHz, CDCl₃): δ = 188.3, 152.8, 149.6, 148.4, 135.8, 133.9, 123.6, 118.4, 78.7, 71.8, 69.9, 69.3. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1649 (m), 1573 (m), 1558 (w), 1462 (w), 1398 (m).

Compound **2c** *3-ferrocenyl-1-(4-pyridinyl) prop-2-en-1-one* was obtained as dark violet crystals after recrystallization using EtOH:H₂O. Yield: 0.33 g (52%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 8.79 (s, 2H), 7.77 (d, J = 14 Hz, 1H), 7.72 (s, 2H), 6.99 (d, J = 14 Hz, 1H), 4.60 (s, 2H), 4.53 (s, 2H), 4.18 (s, 5H). ¹³C NMR (125 MHz, CDCl₃): δ = 188.9, 150.7, 149.4, 145.0, 121.5, 118.1, 78.5, 72.1, 70.0, 69.4. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1657 (m), 1580 (m), 1549 (w), 1468 (w), 1398 (m).

Compound **2d** *3-ferrocenyl-1-(4-N, N-dimethylamino) prop-2-en-1-one* was obtained as orange crystals after recrystallization using EtOH. Yield: 0.30 g (42%) of pure product. ¹H NMR (500 MHz, CDCl₃): δ = 7.97 (s, 2H), 7.68 (d, J = 15 Hz, 1H), 7.17 (d, J = 14 Hz, 1H), 6.70 (s, 2H), 4.58 (s, 2H), 4.43 (s, 2H), 4.17 (s, 5H), 3.07 (s, 6H). ¹³C NMR (500 MHz, CDCl₃): δ = 187.4, 153.2, 143.9, 130.6, 126.3, 119.3, 110.9, 80.0, 70.8, 69.7, 68.7, 40.1. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1643 (m), 1601 (m), 1574 (w), 1393 (m), 1360 and 1333 (m).

4.2.3 Methylated Salts (1e–h and 2e–h)

General Procedure: In a 50 mL round bottom flask dried in the oven and equipped with a magnetic stirring bar, 0.25 mmol of the corresponding ferrocenyl chalcone (1a–d or 2a–d) and 5 mL of the toluene were added. Then 2 mmol of dimethyl sulfate (DMS) were added dropwise to the round bottom flask, stirred vigorously and refluxed during 1 h. The solid was collected using vacuum filtration and washed with toluene.

Compound **1e** *1-ferrocenyl-3-(2-N-methylpyridinium) prop-2-en-1-one* was obtained as dark violet solid. Yield: 77 mg (69%) of pure product. HRMS-ESI (m/z): [M-SO₄CH₃]⁺ calcd for C₁₉H₁₈NOFe, 332.0738; found 332.0738. ¹H NMR (500 MHz, D₂O): δ = 8.61 (d, J = 5 Hz, 1H), 8.35 (s, 1H), 8.19 (d, J = 7 Hz, 1H), 7.81 (s, 1H), 7.68 (d, J = 15 Hz, 1H), 7.36 (d, J = 15 Hz, 1H), 4.84 (2H, s), 4.18 (3H, s), 4.14 (5H, s), 3.51 (3H, s). ¹³C NMR (125 MHz, D₂O): δ = 193.8, 150.5, 146.5, 145.4, 135.3, 127.6, 127.4, 126.7, 78.7, 76.3, 71.3, 70.5, 70.3, 55.2, 46.0. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1651, 1597, 1566, 1462, 1377.

Compound **1f** *1-ferrocenyl-3-(3-N-methylpyridinium) prop-2-en-1-one* was obtained as violet powder. Yield: 0.11 g (99%) of pure product. HRMS-ESI (m/z): [M-SO₄CH₃]⁺ calcd for C₁₉H₁₈NOFe, 332.0738; found 332.0742. ¹H NMR (500 MHz, D₂O): δ = 9.08 (s, 1H), 8.81 (s, 2H), 8.10 (s, 1H), 7.70 (d, J = 14 Hz, 1H), 7.50 (d, J = 15 Hz, 1H), 5.05 (s, 2H), 4.98 (s, 2H), 4.46 (s, 3H), 4.34 (s, 5H), 3.77 (s, 3H). ¹³C NMR (125 MHz, D₂O): δ = 195.3, 144.8, 144.6, 142.7, 135.6, 132.7, 129.4, 128.0,

78.9, 75.8, 71.2, 70.5, 55.4, 48.3. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1657, 1599, 1510, 1449, 1379.

Compound **1g** *1-ferrocenyl-3-(4-N-methylpyridinium) prop-2-en-1-one* was obtained as dark violet powder. Yield: 98 mg (88%) of pure product. HRMS-ESI (*m/z*): [M-SO₄CH₃]⁺ calcd for C₁₉H₁₈NOFe, 332.0738; found 332.0733. ¹H NMR (500 MHz, D₂O): δ = 8.72 (d, *J* = 4 Hz, 2H), 8.19 (d, *J* = 5 Hz, 2H), 7.67 (d, *J* = 16 Hz, 1H), 7.56 (d, *J* = 16 Hz, 1H), 4.98 (s, 2H), 5.02 (s, 2H), 4.35 (s, 3H), 4.31 (s, 5H), 3.73 (s, 3H). ¹³C NMR (125 MHz, D₂O): δ = 194.4, 150.5, 145.0, 133.6, 132.6, 125.8, 79.0, 71.1, 70.4, 55.2, 47.5. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1653, 1599, 1522, 1458, 1375.

Compound **1h** *1-ferrocenyl-3-(4-N,N,N-trimethylammoniumphenyl) prop-2-en-1-one* was obtained as orange powder. Yield: 89 mg (73%) of pure product. HRMS-ESI (*m/z*): [M-SO₄CH₃]⁺ calcd for C₂₂H₂₄NOFe, 374.1207; found 374.1208. ¹H NMR (500 MHz, D₂O): δ = 7.68 (d, *J* = 10, 4H), 7.43 (d, *J* = 16 Hz, 1H), 7.08 (d, *J* = 15 Hz, 1H), 4.09 (s, 3H), 4.68 (s, 2H), 3.58 (s, 5H), 3.48 (s, 9H). ¹³C NMR (125 MHz, D₂O): δ = 196.4, 147.1, 138.4, 136.5, 130.0, 125.5, 120.2, 79.0, 75.1, 70.8, 70.2, 56.7, 55.3. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1639, 1609, 1570, 1414, 1364 and 1331.

Compound **2f** *3-ferrocenyl-1-(3-N-methylpyridinium) prop-2-en-1-one* was obtained as violet powder. Yield: 103 mg (93%) of pure product. HRMS-ESI (*m/z*): [M-SO₄CH₃]⁺ calcd for C₁₉H₁₈NOFe, 332.0738; found 332.0737. ¹H NMR (500 MHz, D₂O): δ = 3.68 (s, 3H), 4.42 (s, 5H), 4.90 (s, 2H), 4.97 (s, 2H), 7.08 (d, *J* = 12 Hz, 1H), 7.85 (s, 1H), 8.12 (d, *J* = 3 Hz, 1H), 8.90 (s, 2H), 9.19 (s, 1H). ¹³C NMR (125 MHz, D₂O): δ = 185.5, 154.3, 147.1, 145.3, 143.8, 137.3, 128.1, 115.9, 78.9, 75.8, 72.1, 70.5, 55.4, 48.5. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1632, 1568, 1501, 1460, 1364.

Compound **2g** *3-ferrocenyl-1-(4-N-methylpyridinium) prop-2-en-1-one* was obtained as dark violet powder. Yield: 98 mg (88%) of pure product. HRMS-ESI (*m/z*): [M-SO₄CH₃]⁺ calcd for C₁₉H₁₈NOFe, 332.0738; found 332.0732. ¹H NMR (500 MHz, D₂O): δ = 8.35 (s, 2H), 8.95 (d, 2H), 7.90 (d, *J* = 15 Hz, 1H), 7.11 (d, *J* = 14 Hz, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 4.46 (s, 3H), 4.29 (s, 5H), 3.76 (s, 3H). ¹³C NMR (75 MHz, D₂O): 186.8, 154.9, 151.3, 146.3, 126.1, 116.8, 78.1, 74.2, 70.8, 70.6, 55.4, 48.4. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1663, 1568, 1516, 1464, 1364.

Compound **2h** *3-ferrocenyl-1-(4-N,N,N-trimethylammoniumphenyl) prop-2-en-1-one* was obtained as orange powder. Yield: 80 mg (66%) of pure product. HRMS-ESI (*m/z*): [M-SO₄CH₃]⁺ calcd for C₂₂H₂₄NOFe, 374.1207; found 374.1210. ¹H NMR (500 MHz, D₂O): δ = 3.56 (s, 9H), 3.65 (d, *J* = 3, 3H), 4.49 (s, 5H), 5.04 (s, 2H), 7.03 (s, 1H), 7.44 (s, 1H), 7.85 (s, 2H), 7.96 (s, 2H). ¹³C NMR (125 MHz, D₂O): δ = 189.6, 150.2, 149.4, 139.1, 130.3, 125.5, 120.4, 117.9, 73.7, 72.8, 72.5, 72.4, 56.9, 55.2. FT-IR (neat) $\nu_{\max}$ (cm⁻¹): 1643, 1574, 1543, 1379.

4.2.4 Butylated Salts (1i–l and 2i–l)

General Procedure: In a 50 mL round bottom flask dried in the oven and equipped with a magnetic stirring bar, 0.25 mmol of the corresponding ferrocenyl chalcone (**1a–d** or **2a–d**) and 5 mL of the toluene were added. Then 2 mmol of dibutyl sulfate (DBS) were added

dropwise to the round bottom flask, stirred vigorously and refluxed during 3 h. The solid was collected using vacuum filtration and washed with toluene.

Compound **1j** *1-ferrocenyl-3-(3-N-butylpyridinium) prop-2-en-1-one* was obtained as violet powder. Yield: 94 mg (71%) of pure product. HRMS-ESI (m/z): [M-SO₄(CH₂)₃CH₃]⁺ calcd for C₂₂H₂₄NOFe, 374.1207; found 374.1205. ¹H NMR (500 MHz, Acetone-d₆): δ = 9.92 (s, 1H), 9.20 (s, 1H), 9.07 (d, J = 7 Hz, 1H), 8.29 (s, 1H), 7.99 (d, J = 16 Hz, 1H), 7.73 (d, J = 16 Hz, 1H), 5.17 (d, J = 2 Hz, 2H), 4.96 (t, J = 7 Hz, 2H), 4.68 (d, J = 2 Hz, 2H), 4.27 (s, 5H), 3.94 (d, J = 6 Hz, 2H), 2.11 (t, J = 9 Hz, 2H), 1.55 (t, J = 7 Hz, 2H), 1.50 (t, J = 8 Hz, 2H), 1.37 (t, J = 5 Hz, 2H), 0.97 (t, J = 7 Hz, 3H), 0.88 (t, J = 8 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆): δ = 187.7, 151.8, 144.7, 144.1, 136.7, 131.9, 130.6, 128.4, 80.7, 77.9, 73.3, 70.2, 65.8, 61.9, 33.4, 31.8, 30.6, 19.1, 13.3, 13.0. FT-IR (neat) ν_{max} (cm⁻¹): 1657, 1599, 1510, 1454, 1377.

Compound **1k** *1-ferrocenyl-3-(4-N-butylpyridinium) prop-2-en-1-one* was obtained as dark violet powder. Yield: 99 mg (75%) of pure product. HRMS-ESI (m/z): [M-SO₄(CH₂)₃CH₃]⁺ calcd for C₂₂H₂₄NOFe, 374.1207; found 374.1207. ¹H NMR (500 MHz, D₂O): δ = 8.84 (s, 2H), 8.28 (s, 2H), 7.76 (d, J = 15 Hz, 1H), 7.65 (d, J = 16 Hz, 1H), 5.09 (s, 2H), 5.03 (s, 2H), 4.60 (s, 2H), 4.36 (s, 5H), 4.07 (s, 2H), 2.02 (s, 2H), 1.66 (s, 2H), 1.40 (s, 4H), 0.97 (s, 3H), 0.92 (s, 3H). ¹³C NMR (125 MHz, D₂O): δ = 195.2, 151.2, 144.3, 133.7, 133.1, 126.1, 79.1, 76.2, 71.3, 70.6, 69.2, 61.2, 32.4, 30.4, 18.7, 18.2, 12.8, 12.5. FT-IR (neat) ν_{max} (cm⁻¹): 1655, 1599, 1522, 1458, 1375.

Compound **2j** *3-ferrocenyl-1-(3-N-butylpyridinium) prop-2-en-1-one* was obtained as violet powder. Yield: 53 mg (40%) of pure product. HRMS-ESI (m/z): [M-SO₄(CH₂)₃CH₃]⁺ calcd for C₂₂H₂₄NOFe, 374.1207; found 374.1211. ¹H NMR (500 MHz, Acetone-d₆): δ = 9.91 (s, 1H), 9.44 (s, 1H), 9.22 (s, 1H), 8.42 (s, 1H), 7.96 (d, J = 15 Hz, 1H), 7.64 (d, J = 15 Hz, 1H), 5.01 (t, J = 8 Hz, 2H), 4.97 (t, J = 2 Hz, 2H), 4.63 (d, J = 2 Hz, 2H), 4.24 (s, 5H), 3.88 (d, J = 7 Hz, 2H), 2.13 (m, J = 8 Hz, 2H), 1.49 (t, J = 8 Hz, 4H), 1.35 (t, J = 8 Hz, 2H), 0.97 (t, J = 8 Hz, 3H), 0.87 (t, J = 7 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆): δ = 187.0, 151.0, 148.0, 144.7, 136.7, 128.6, 117.3, 79.0, 72.4, 70.2, 70.0, 65.7, 62.1, 33.5, 31.8, 19.2, 13.3, 12.9. FT-IR (neat) ν_{max} (cm⁻¹): 1633, 1506, 1464, 1364.

Compound **2k** *3-ferrocenyl-1-(4-N-butylpyridinium) prop-2-en-1-one* was obtained as dark violet powder. Yield: 81 mg (61%) of pure product. HRMS-ESI (m/z): [M-SO₄(CH₂)₃CH₃]⁺ calcd for C₂₂H₂₄NOFe, 374.1207; found 374.1214. ¹H NMR (500 MHz, D₂O): δ = 9.04 (d, J = 6 Hz, 2H), 8.41 (d, J = 5 Hz, 2H), 8.00 (d, J = 15 Hz, 1H), 7.16 (d, J = 15 Hz, 1H), 4.88 (s, 2H), 4.85 (s, 2H), 4.69 (t, J = 12 Hz, 2H), 4.34 (s, 5H), 4.06 (t, J = 7 Hz, 2H), 2.04 (t, J = 8 Hz, 2H), 1.65 (t, J = 7 Hz, 2H), 1.38 (q, J = 7 Hz, 4H), 1.04 (s, 3H), 0.98 (s, 3H). ¹³C NMR (125 MHz, D₂O): δ = 187.7, 155.7, 152.0, 145.4, 126.3, 116.8, 77.9, 74.2, 70.7, 70.5, 69.3, 62.0, 32.6, 30.4, 18.7, 18.3, 12.8, 12.6. FT-IR (neat) ν_{max} (cm⁻¹): 1661, 1576, 1516, 1464, 1364.

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Abbreviation

DBS	dibutylsulfate
DMS	dimethylsulfate

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Appendix A

Supplementary Material

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Highlights

- Eleven novel ferrocenyl chalcone salts were synthesized in yields from 40 to 99%.
- Nine compounds exhibited high water solubility, enhancing their drug potential.
- Used method for the salts' synthesis is simpler than previously reported methods.
- An interesting tendency for the E^0 parameter was showed for the ferrocenyl salts.

From Acetylferrocene

1-Ferrocenyl System (**1-Fc**)

From Ferrocenecarboxaldehyde

3-Ferrocenyl System (**3-Fc**)

Figure 1.
Ferrocenyl chalcones general core

Figure 2.
Monosubstituted ferrocenyl chalcones used as precursors

Figure 3.
Monosubstituted ferrocenyl chalcones salt derivatives

Figure 4. ^1H NMR spectra (500 MHz) of 4-pyridinyl (**1c**) and 4-pyridinium derivatives (**1g** and **1k**) of the 1-Fc system, (A) in CDCl_3 with TMS and (B and C) in D_2O at rt.

Scheme 1.

Synthesis of ferrocenyl chalcones salt derivatives by *N*-alkylation with DMS

Scheme 2.

Synthesis of ferrocenyl chalcones salt derivatives by *N*-alkylation with DBS

Table 1

Monosubstituted methylated ferrocenyl chalcone salt derivatives

ENTRY	PRODUCT ^A	YIELD (%)	SOLUBILITY IN WATER
1	1e	69	soluble
2	1f	99	soluble
3	1g	88	soluble
4	1h	73	soluble
5	2e	--- ^b	
6	2f	93	soluble
7	2g	88	soluble
8	2h	66	soluble

^aCompounds decomposed above 150 °C.^bDecomposition was obtained.

Table 2

Monosubstituted butylated ferrocenyl chalcone salt derivatives

ENTRY	PRODUCT ^A	YIELD (%)	SOLUBILITY IN WATER
1	1i ^b	4	insoluble
2	1j	71	insoluble
3	1k	75	soluble
4	1l ^b	5	insoluble
5	2i	--- ^c	---
6	2j	40	insoluble
7	2k	61	soluble
8	2l	--- ^d	---

^aCompounds decomposed above 150 °C.^bProduct has a sludge composition.^cDecomposition was obtained.^dNo reaction observed.

Table 3

Electrochemical parameters of the 1-ferrocenyl (1-Fc) system compounds at 100 mV/s of scan rate

Entry	Compound	E ^{o'} , mV	Ep, mV	I _{pc} /I _{pa}	Slope Log I _{pc} vs. Log v	Slope Log I _{pa} vs. Log v	Working Electrode ^c
1	1a^a	774	71	1.0	NR ^b	0.40	Pt
2	1b^a	732	75	1.1	NR ^b	0.47	Pt
3	1c^a	761	70	1.0	NR ^b	0.47	Pt
4	1e	744	80	0.94	0.50	0.46	GC
5	1f	776	75	1.1	-	-	GC
6	1g	673	71	0.97	0.50	0.49	Pt
7	1h	631	70	1.1	0.43	0.48	Pt
8	1i	800	73	0.94	-	-	GC
9	1j	768	61	1.2	-	-	Pt
10	1k	674	72	0.90	0.49	0.52	Pt

^aThese derivatives were synthesized and characterized by R. Cardona, M. Otaño, et. al., see *Journal of Electrochemical Society*, 2010, 157(8), F104–F110.^bNR = Not reported.^cGeometric area of the working electrode: Pt – 0.020 cm²; GC – 0.070 cm².

Table 4

Electrochemical parameters of the 3-ferrocenyl (3-Fc) system compounds at 100 mV/s of scan rate

Entry	Compound	E ^o , mV	E _p , mV	I _{pc} /I _{pa}	Slope Log I _{pc} vs. Log v	Slope Log I _{pa} vs. Log v	Working Electrode ^a
1	2f	524	67	1.0	0.47	0.49	Pt
2	2g	558	100	1.2	0.41	0.40	GC
3	2h	485	83	0.99	0.47	0.48	Pt
4	2j	643	109	1.1	-	-	GC
5	2k	482	80	1.0	0.45	0.47	Pt

^a Geometric area of the working electrode: Pt – 0.020 cm²; GC – 0.070 cm².