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Synthesis, electrochemical and biological studies on polyfunctionalized 4-ferrocenyl-4*H*-pyran and 4-ferrocenyl-1,4-dihydropyridine derivatives

José Marco-Contelles,[a,*] Rafael León,[a,b] Enrique Morales,[d] Mercedes Villarroya[b] and Antonio G. García[b,c]

[a]*Laboratorio de Radicales Libres, IQOG (C.S.I.C.), C/Juan de la Cierva 3, 28006 Madrid, Spain*
[b]*Departamento de Farmacología y Terapéutica, Instituto Teófilo Hernando, Facultad de Medicina, Universidad Autónoma de Madrid; C/Arzobispo Morcillo, 4, 28029 Madrid, Spain*
[c]*Servicio de Farmacología Clínica, Hospital Universitario de la Princesa, Madrid, Spain*
[d]*Instituto de Ciencia y Tecnología de Polímeros (C.S.I.C.), C/Juan de la Cierva 3, 28006 Madrid, Spain*

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This paper is dedicated to Professor José Luis Soto Cámara on the occasion of his retirement and in recognition of his research in heterocyclic chemistry

Abstract—The first synthesis of polyfunctionalized 4-ferrocenyl-4*H*-pyran and 4-ferrocenyl-1,4-dihydropyridine derivatives, as well as some of their relevant properties, including an electrochemical study and some aspects of their biological profile have been described.

Compounds containing ferrocene have been used in electrochemistry,[1] as molecular sensors[2] and in nonlinear optics.[3] In fact, it is now well established that the incorporation of ferrocene units in organic molecules introduces significant and new properties in these materials.[4] We are interested in ferrocene-containing molecules with *N*-donor groups, which may be able to work as ligands towards transition-metal ions[5] and new drugs.[6] Particularly, the stability and the nontoxicity of the ferrocenyl moiety have been invoked as a bonus in the designing of new biologically active molecules, as in a new ferrocene–chloroquine analogue[6b] or in novel ferrocenic artemisinin derivatives.[6c]

The synthesis of ferrocene-containing heterocycles is not new, and it has been reported several times in literature.[5,7] Our current interest in the synthesis of new pyran[8a] (or 1,4-dihydropyridine) derivatives[8b,c] and tacrine (Fig. 1) analogues,[9] we describe here our initial results on the synthesis, characterization, electrochemistry and biological evaluation of the new ferrocene-containing heterocycles, such as 6-amino-5-cyano-4-ferrocenyl-2-methyl-4*H*-pyran-3-carboxylic acid ethyl ester (**1**), 4-ferrocenyl-1,4-dihydropyridine-2,6-dimethyl-3,5-dicarboxylic acid diethyl ester (**5**) and some derivatives (**2**–**4**) of compound **1** (Fig. 1).

The synthesis of compound (**1**) has been carried out using the standard method[10] by reaction of ethyl acetoacetate and ferrocenemalonodinitrile,[11] catalyzed by piperidine. 4*H*-Pyran **1**, isolated as a solid in 51% yield,[12a] was transformed into imide **2** (62%) by simple treatment with acetic anhydride in pyridine. Friedländer reaction[13] of product **1** with cyclohexanone or cycloheptanone provided tacrine analogues **3** and **4** (Fig. 1), in 62% and 49% yields, respectively. Finally, Hantzsch[14] reaction between ferrocenecarboxaldehyde, ethyl acetoacetate and ethyl β-aminocrotonate gave the expected dihydropyridine **5**[12b] (Fig. 1) in 73% yield. All these new compounds showed analytical and spectroscopic data in good agreement with their structure.[12]

Keywords: Ferrocene; Heterocycles; 4*H*-Pyran; 1,4-Dihydropyridine; Tacrine.
* Corresponding author. Tel.: +33-91-5622900; fax: +34-91-5644853; e-mail: iqoc21@iqog.csic.es

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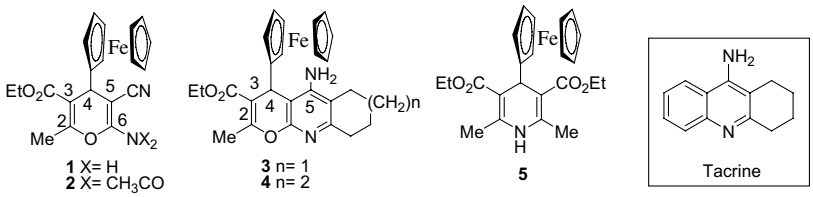

Figure 1.

Table 1. Formal electrode potentials (V vs Ag/Ag^+), peak to peak separations and i_{pc}/i_{pa} ratio exhibited by the ferrocene derivatives (**1**–**5**)[a]

Compound	E_p^a, V	E_p^c, V	ΔE_p, V	i_{pa}/i_{pc}
Ferrocene	0.554	0.423	0.131	1.45
1	0.565	0.416	0.149	1.07
2	0.579	0.409	0.170	1.14
3	0.582	0.422	0.160	1.16
4	0.490	0.344	0.146	1.07
5	0.631	0.498	0.133	1.07

[a] Methanol solution of compounds **1**–**5** (0.1 M in Et_4NBF_4, 1×10^{-3} M in sample). Scan rate 100 mV s^{-1}, sweep range 0–1 V.

With these compounds in hands we have investigated their electrochemical properties.[15]

The analysis of the cyclic voltammetric responses shows that all complexes exhibit the reversible ferrocene/ferrocenium oxidation, without any kind of geometrical reorganization after the electron removal process (the current ratio i_{pc}/i_{pa} is practically equal to unity, a deviation from unity only being detected for ferrocene itself) (Table 1). Electrode potentials were displaced towards lower or higher values depending on the nature of the substituents. Additionally, the value of the peak to peak separation (ΔE_p) increases when the sweep rate goes from 2 to 100 mV s^{-1}, being in all the cases higher than the value of 59 mV expected for an electrochemically reversible one-electron transfer process, probably due to uncompensated solution resistances.

Work is now in progress to synthesize and evaluate new heterocycles-containing ferrocene moieties having lower oxidation potential values than ferrocene itself looking for products with potential application as electrodes in electrochemical sensors.

Due to their close structural and functional relationship with tacrine (Fig. 1), the first acetylcholinesterase inhibitor used for Alzheimer's disease (AD) therapy, compounds **3** and **4** have been also subjected to biological evaluation, measuring a possible inhibitory effect of acetylcholinesterase (AChE) and/or butyrylcholinesterase (BuChE).[16,17] As expected, compounds **3** and **4** inhibited AChE with IC_{50}s of 39 and 29 μM, respectively (IC_{50} for tacrine, 0.14 μM), but the IC_{50} for products **1**, **2** and **5** was higher than 100 μM. Regarding BuChE compounds **1**–**5** were devoid of any activity ($IC_{50} > 100$ μM). To sum up, only compounds **3** and **4** are moderate AChE inhibitors, showing no inhibition on BuChE, with a strong selectivity for AChE. Since some of the new anticholinesterasic drugs used at present in the treatment of AD, like galanthamine, present neuroprotective effects,[18] we decided to find out whether our new compounds possessed also such effect on bovine chromaffin cells subjected to the action of veratridine, a toxin that causes a calcium overload and cell death, for 24 h. Cells were pre-incubated with compounds **1**–**5** for 24 h before application of the toxic stimulus and cell death was measured as LDH (lactic dehydrogenase) release to the medium. None of the compounds studied prevented cell death caused by veratridine.

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12. (a) Spectroscopic and analytical characterization of compounds **1** and **5**. (a) Compound **1**: mp 200–202 °C; IR (KBr) *v* 3394, 3325, 3217, 2187, 1698, 1673, 1646, 1605, 1334, 1257, 1058 cm^{-1}; ^1H NMR (DMSO, 200 MHz) δ 7.00 (s, 2H, NH_2), 4.16 (s, 9H, $2 \times Cp$), 4.12 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.81 (s, 1H, H-4), 2.20 (s, 3H, CH_3), 1.26 (t, 3H, OCH_2CH_3); ^{13}C (DMSO, 50.2 MHz) δ 166.2 (C=O), 161.3 (C6), 156.8 (C2), 121.2 (C3), 110.2 (CN), 95.0 (C, Cp), 69.1 ($5 \times$ CH, Cp), 67.8 (CH, Cp), 67.2 (CH, Cp), 66.1 (CH, Cp), 65.9 (CH Cp), 60.9 (OCH_2CH_3), 55.9 (C5), 32.5 (C4), 18.4 (CH_3), 14.4 (OCH_2CH_3); MS (APCI+) m/z $[M+1]^+$ 393, $[M+Na]^+$ 415, $[2M+Na^+]$ 807. Anal. Calcd for $C_{20}H_{20}N_2O_3Fe$: C, 60.31; H, 4.80; N, 7.41. Found: C, 60.18; H, 5.10; N, 7.39; (b) Compound **5**: mp 218–220 °C; IR (KBr) *v* 3342, 3091, 2978, 1690, 1484, 1446, 1333, 1297, 1095, 1019, 820 cm^{-1}; ^1H NMR (DMSO, 200 MHz) δ 8.74 (s, 1H, NH), 4.60 (s, 1H, H4), 4.04 (q, $J = 7.0$ Hz, 4H, $2 \times OCH_2CH_3$), 3.92 (s, 5H, Cp), 3.87 (br s, 2H, Cp), 3.71 (br s, 2H, Cp), 2.14 (s, 6H, $2 \times CH_3$), 1.15 (t, 6H, $2 \times OCH_2CH_3$); ^{13}C (DMSO, 50.2 MHz) δ 167.5 ($2 \times$ C, C=O), 144.6 ($2 \times$ C, C2/C6), 101.2 (C, Cp), 96.1 ($2 \times$ CH, C3, C5), 67.9 ($5 \times$ CH, Cp), 66.1 ($2 \times$ CH, Cp), 65.5 ($2 \times$ CH, Cp) 58.8 ($2 \times OCH_2CH_3$), 31.1 (C4), 17.8 ($2 \times CH_3$), 14.1 ($2 \times OCH_2CH_3$); MS (APCI+) m/z $[M+1]^+$ 438.3, $[M+Na]^+$ 460.3, $[2M+Na^+]$ 897.3. Anal. Calcd for $C_{23}H_{27}NO_4Fe$: C, 63.17; H, 6.22; N, 3.20. Found: C, 63.16; H, 6.35; N, 3.38.
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