Synthesis and Electrochemical Characterization of Substituted Pyrrolo[1,2-c]pyrimidine Carboxylates

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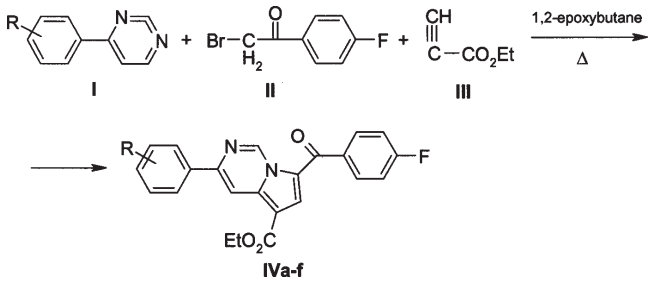
This work is devoted to the synthesis and characterization of new pyrrolo[1,2-c]pyrimidine derivatives. The electrochemical investigations have been done by cyclic voltammetry and differential pulse voltammetry. The redox processes for each compound were established, analyzed and an assessment was proposed to the particular functional groups at which they take place. It was based on comparison between the electrochemical behaviour of the compounds, similarities in their structure, as well as substituent effects.

Keywords: pyrrolo[1,2-c]pyrimidine derivatives, one-pot synthesis, three-component reaction, cyclic voltammetry, differential pulse voltammetry

Pyrrolo[1,2-*c*]pyrimidine is an *N*-bridgehead heterocyclic system of considerable interest because of several biological activities associated with this scaffold [1-3]. Some pyrrolo[1,2-*c*]pyrimidine derivatives exhibit therapeutic antioxidant effects in any disorders associated with oxidative stress, [4] others are useful for the treatment or prevention of cancer, inflammatory disorders and autoimmune diseases [3].

In order to establish the mechanism through which these antioxidant properties act, the electrochemical behaviour of several pyrrolo[1,2-c]pyrimidine derivatives has been investigated by cyclic voltammetry and differential pulse voltammetry. The obtained electrochemical data were found to be sensitive to the substituents identity. They allowed the characterization and the assessment of the principal redox processes that took place in each case.

The present paper is focused on the electrochemical behaviour of six structurally related pyrrolo[1,2-*c*]pyrimidine derivatives obtained according to Scheme 1, denoted **IVa-IVf**, in which various substituents are grafted on the same pyrrolo[1,2-c]pyrimidine skeleton. Two of them are newly synthesized compounds (**IVe, IVf**) .



Scheme 1. Synthetic route to the pyrrolo[1,2-c]pyrimidine carboxylates

Experimental part

Substituted pyrimidines **I** were obtained by condensation of the triformylaminomethane with substituted acetophenone in the presence of a catalytic amount of *p*-toluensulfonic acid [5].

Table 1
MELTING POINTS AND GLOBAL SYNTHESIS YIELDS OF PYRROLO[1,2-C]PYRIMIDINES **IVa-f**

Compound	R	mp (°C)	Yield (%)
IVa	CH_3 (*o*)	131-133	41 [4]
IVb	OCH_3 (*o*)	183-185	45 [4]
IVc	OCH_3 (*m*)	154-156	52 [4]
IVd	OCH_3 (*p*)	212-214	49 [4]
IVe	Br (*m*)	160-162	42
IVf	Br (*p*)	188-190	43

2-Bromo-4'-fluoroacetophenone (II), ethyl propiolate (III) and 1,2-epoxybutane were purchased from Aldrich. Acetonitrile (CH_3CN) and tetrabutylammonium perchlorate (TBAP) from Fluka were used as solvent and supporting electrolyte. All commercial reagents and solvents were used without further purification.

As a general procedure for synthesis of pyrrolo[1,2-c]pyrimidine derivatives **IVa - f,** a solution of 2.5 mmol of substituted pyrimidine **I**, 2.5 mmol of 2-bromo-4'-fluoroacetophenone **II** and 3.5 mmole ethyl propiolate **III** in 40 mL 1,2-epoxybutane was heated at reflux temperature for 24 h. The solvent was partly removed under vacuum, 10 mL of methanol was added under a gentle stirring and the mixture was left over night at room

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temperature. The solid formed was filtered off, washed on the filter with a mixture of methanol-diethyl ether 1:1 and crystallized from chloroform/methanol.

Melting points were determined on a Boëtius hot plate microscope. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets with absorptions in cm^{-1}. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H-NMR using $CDCl_3$ as solvent and TMS as internal standard.

The electrochemical experiments were carried out by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) using a PGSTAT12 AUTOLAB potentiostat connected to a three-compartment cell. The CV curves were generally recorded at 0.1 V/s or at various rates (0.1 - 1 V/s) - when studying the influence of the scan rate. DPV curves were recorded at 0.01 V/s with a pulse height of 0.025 V and a step time of 0.2 s. The working electrode was a glassy carbon disk (diameter of 3 mm). The active surface was polished before each determination with diamond paste (200 μm). The Ag/10 mM $AgNO_3$ in 0.1 M TBAP, CH_3CN was used as reference electrode. The potential was referred to the potential of the ferrocene/ferricinium redox couple (Fc/Fc^+) which in our experimental conditions was +0.07 V. A platinum wire was used as auxiliary electrode. The determinations were performed at 25°C under argon atmosphere.

Results and discussions

Synthesis of pyrrolo[1,2-c]pyrimidine derivatives

An efficient methodology for the synthesis of pyrrolo[1,2-c]pyrimidine derivatives *via* the one-pot, three component procedure starting from the readily available materials has already been reported [4]. The key components for the synthesis of pyrrolo[1,2-c]pyrimidines **IVe** and **IVf** via the one-pot, three component procedure are: the substituted pyrimidine derivative **I**, 2-bromo-4'-fluoroacetophenone **II** and ethyl propiolate **III** in 1,2-epoxybutane which acts both as solvent and acid scavenger (scheme 1). The reaction conditions are mild, involving only mixing of the components at reflux temperature for 24 h, followed by solvent evaporation and subsequent crystallization, as previously shown [4].

The structures of the pyrrolo[1,2-c]pyrimidines derivatives **IVe** and **IVf** were confirmed by chemical and spectral analysis. The melting points and the yields are presented in table 1.

Analytic and spectral data

Physico-chemical properties and spectral data of pyrrolo[1,2-*c*]pyrimidine derivatives **IVe** and **IVf** are presented here, while those for pyrrolo[1,2-*c*]pyrimidine derivatives **IVa-IVd** were already reported in literature [4].

Ethyl 3-(3-bromophenyl)-7-(4-fluorobenzoyl) pyrrolo[1,2-*c*]pyrimidine-5-carboxylate (IVe). Yellow crystals. Anal. calcd. for $C_{23}H_{16}BrFN_2O_3$: C: 59.12; H: 3.45; N: 5.99. Found: C: 58.87; H: 3.64; N: 6.21. IR (KBr): 1704, 1631, 1521, 1475, 1330, 1207 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, 3H, *J* = 7.1 Hz, CH_3), 4.43 (q, 2H, *J* = 7.1 Hz, CH_2), 7.23 (d, 2H, *J* = 8.7 Hz, Ph), 7.38 (t, 1H, *J* = 7.9 Hz, Ph), 7.57-7.61 (m, 1H, Ph), 7.81 (s, 1H, H-6), 7.90 (dd, 2H, *J* = 5.4, 8.8 Hz, Ph), 8.06-8.10 (m, 1H, Ph), 8.33 (t, 1H, *J* = 1.8 Hz, H-2'), 8.61 (d, 1H, *J* = 1.5 Hz, H-4), 10.55 (d, 1H, *J* = 1.5 Hz, H-1).

Ethyl 3-(4-bromophenyl)-7-(4-fluorobenzoyl) pyrrolo[1,2-*c*]pyrimidine-5-carboxylate (IVf). Yellow crystals. Anal. calcd. for $C_{23}H_{16}BrFN_2O_3$: C: 59.12; H: 3.45; N: 5.99. Found: C: 58.91; H: 3.63; N: 6.22. IR (KBr): 1704, 1618, 1480, 1333, 1203 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, 3H, *J* = 7.1 Hz, CH_3), 4.43 (q, 2H, *J* = 7.1 Hz, CH_2), 7.23 (d, 2H, *J* = 8.7 Hz, Ph), 7.64 (d, 2H, *J* = 8.7 Hz, Ph), 7.81 (s, 1H, H-6), 7.89, 7.92 (2d, 2H, *J* = 8.8 Hz, Ph), 8.04 (d, 2H, *J* = 8.8 Hz, Ph), 8.61 (d, 1H, *J* = 1.6 Hz, H-4), 10.55 (d, 1H, *J* = 1.6 Hz, H-1).

Electrochemical studies

CV and DPV anodic and cathodic curves were recorded individually, starting from the stationary potential, for various concentrations (in the range 0 - 3 mM) of the studied compounds in 0.1 M TBAP/CH_3CN. DPV and CV curves for different concentrations of each compound in 0.1M TBAP, CH_3CN are shown, as well as the CV curves for various scan domains at 0.1V/s and at different scan rates in the domains of the first anodic and cathodic electrode processes. The electrochemical nature of each peak was established from CV data (r - reversible; i - irreversible; q - quasi-reversible) and was given in addressed table for each compound.

Study of ethyl 7-(4-fluorobenzoyl)-3-o-tolylpyrrolo[1,2-c]pyrimidine-5-carboxylate, ***IVa***

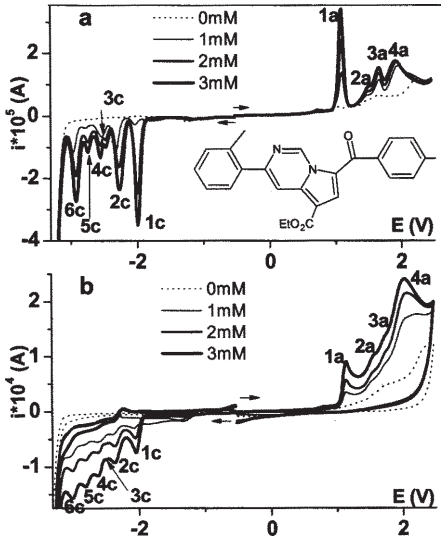


Fig. 1. (a) DPV and (b) CV curves for different concentrations of **IVa** (the structure is given in the inset) in 0.1M TBAP, CH_3CN

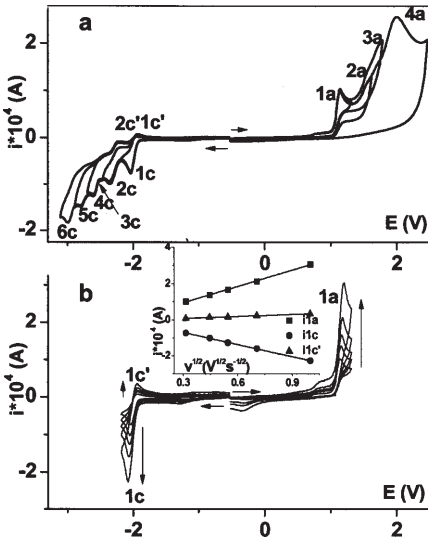


Fig. 2. CV curves for various scan domains at 0.1V/s (a) and at different scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s in the domains of the peaks 1c and 1a, respectively, (b) for **IVa** (3mM) in 0.1M TBAP, CH_3CN

Table 2
PEAK POTENTIALS (IN V) AND CHARACTERISTICS OF THE PEAKS FROM CV (r - REVERSIBLE; i - IRREVERSIBLE; q - QUASI-REVERSIBLE) AND THEIR ASSESSMENT FOR **IVa**

Peak	DPV	CV
1a	1.094	1.137 (i)
2a	1.494	1.562 (i)
3a	1.663	1.747 (i)
4a	1.916	2.031 (i)
1c	-1.990	-2.040 (r)
2c	-2.264	-2.368 (r)
3c	-2.475	-2.483 (i)
4c	-2.548	-2.616 (i)
5c	-2.738	-2.801 (i)
6c	-2.917	-3.005 (i)

Study of ethyl 7-(4-fluorobenzoyl)-3-(2-methoxyphenyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate, ***IVb***

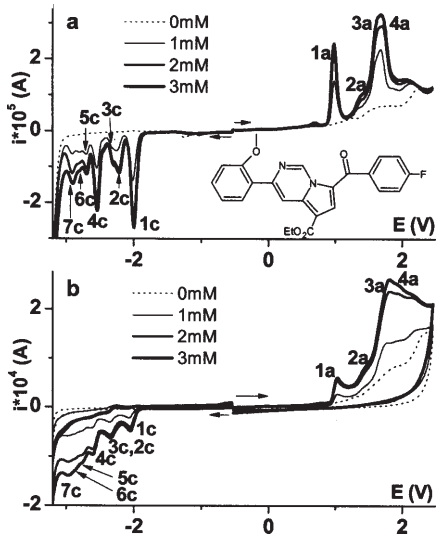


Fig. 3. (a) DPV and (b) CV curves for different concentrations of **IVb** (the structure is given in the inset) in 0.1M TBAP, CH_3CN

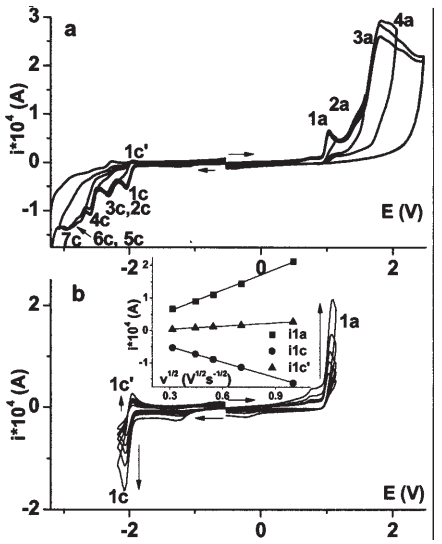


Fig. 4. CV curves for various scan domains at 0.1V/s (a) and different scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s in the domains of the peaks 1c and 1a, respectively, (b) for **IVb** (3mM) in 0.1M TBAP, CH_3CN

Table 3
PEAK POTENTIALS (IN V) AND CHARACTERISTICS OF THE PEAKS FROM CV (r - REVERSIBLE; i - IRREVERSIBLE; q - QUASI-REVERSIBLE) AND THEIR ASSESSMENT FOR **IVb**

Peak	DPV	CV
1a	0.985	1.035 (i)
2a	1.354	1.443 (i)
3a	1.627	1.814 (i)
4a	1.680	1.956 (i)
1c	-1.994	-2.044 (r)
2c	-2.216	*
3c	-2.321	*
4c	-2.542	-2.611 (i)
5c	-2.700	-2.761 (i)
6c	-2.805	-2.867 (i)
7c	-2.900	-2.965 (i)

** - not possible to be read*

Study of ethyl 7-(4-fluorobenzoyl)-3-(3-methoxyphenyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate, ***IVc***

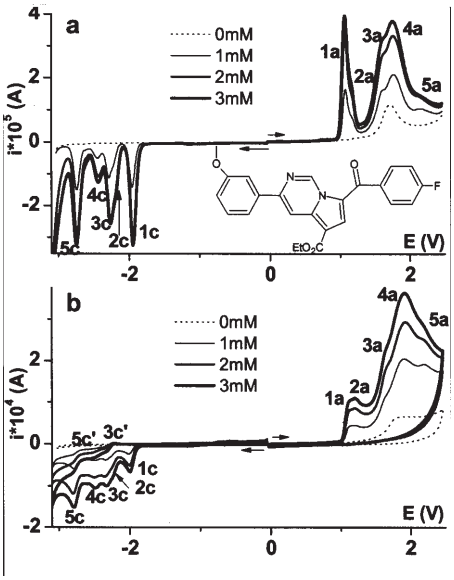


Fig. 5. (a) DPV and (b) CV curves for different concentrations of **IVc** (the structure is given in the inset) in 0.1M TBAP, CH_3CN

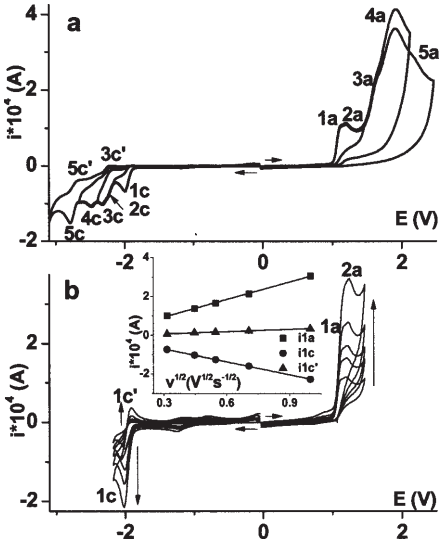


Fig. 6. CV curves for various scan domains at 0.1V/s (a) and at different scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s (b) in the domain of the peaks 1c and 1a-2a, respectively, for **IVc** (3mM) in 0.1M TBAP, CH_3CN

Table 4
PEAK POTENTIALS (IN V) AND CHARACTERISTICS OF THE PEAKS FROM CV (r - REVERSIBLE; i - IRREVERSIBLE; q - QUASI-REVERSIBLE) AND THEIR ASSESSMENT FOR **IVc**

Peak	DPV	CV
1a	1.065	1.119 (i)
2a	1.160	1.199 (i)
3a	1.592	1.668 (i)
4a	1.750	1.916 (i)
5a	2.171	2.181 (i)
1c	-1.946	-1.996 (r)
2c	-2.188	-2.253 (i)
3c	-2.262	-2.332 (q)
4c	-2.441	-2.483 (i)
5c	-2.746	-2.792 (q)

Study of ethyl 7-(4-fluorobenzoyl)-3-(4-methoxyphenyl) pyrrolo[1,2-c]pyrimidine-5-carboxylate, ***IVd***

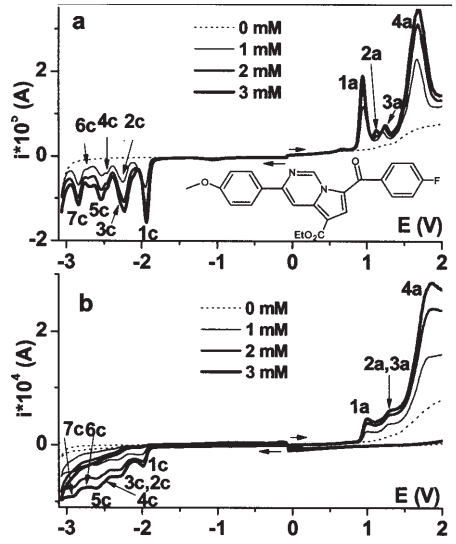


Fig. 7. (a) DPV and (b) CV curves for different concentrations of **IVd** (the structure is given in the inset) in 0.1M TBAP, CH_3CN

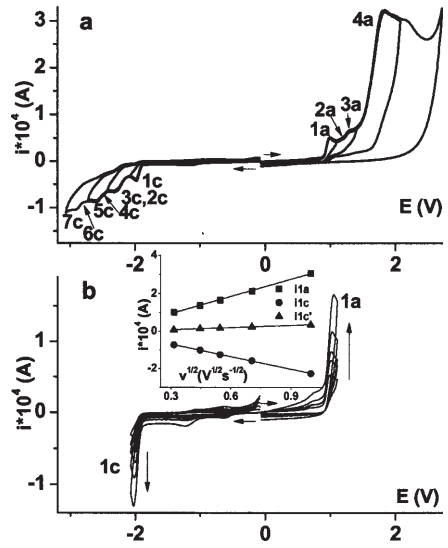


Fig. 8. CV curves for various scan domains at 0.1V/s (a) and at different scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s (b) in the domain of the peaks 1c and 1a, respectively, for **IVd** (3mM) in 0.1M TBAP, CH_3CN

Table 5
PEAK POTENTIALS (IN V) AND CHARACTERISTICS OF THE PEAKS FROM CV (r - REVERSIBLE; i - IRREVERSIBLE; q - QUASI-REVERSIBLE) AND THEIR ASSESSMENT FOR **IVd**

Peak	DPV	CV
1a	0.941	1.001 (i)
2a	1.120	* (i)
3a	1.246	1.293 (i)
4a	1.678	1.868 (i)
1c	-1.934	-1.990 (i)
2c	-2.228	*
3c	-2.281	*
4c	-2.460	-2.495 (i)
5c	-2.544	-2.610 (i)
6c	-2.692	-2.743 (i)
7c	-2.839	-2.911 (i)

* - not possible to be read

Study of ethyl 3-(3-bromophenyl)-7-(4-fluorobenzoyl) pyrrolo[1,2-c]pyrimidine-5-carboxylate, ***IVe***

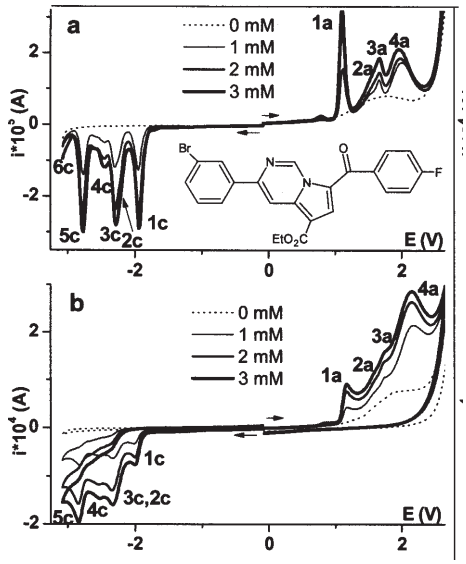


Fig. 9. (a) DPV and (b) CV curves for different concentrations of **IVe** (the structure is given in the inset) in 0.1M TBAP, CH_3CN

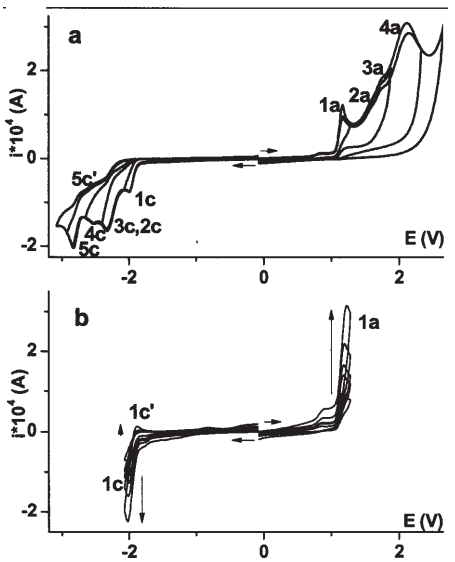


Fig. 10. CV curves for various scan domains at 0.1V/s (a) and at different scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s (b) in the domain of the peaks 1c and 1a, respectively, for **IVe** (3mM) in 0.1M TBAP, CH_3CN

Table 6

PEAK POTENTIALS (IN V) AND CHARACTERISTICS OF THE PEAKS FROM CV (r - REVERSIBLE; i - IRREVERSIBLE; q - QUASI-REVERSIBLE) AND THEIR ASSESSMENT FOR **IVe**

Peak	DPV	CV
1a	1.110	1.177 (i)
2a	1.531	1.584 (i)
3a	1.668	1.761 (i)
4a	1.963	2.160 (i)
1c	-1.933	-2.000 (r)
2c	-2.185	* (i)
3c	-2.280	* (i)
4c	-2.438	-2.522 (i)
5c	-2.764	-2.841 (q)
6c	*	*

** - not possible to be read*

Study of ethyl 3-(4-bromophenyl)-7-(4-fluorobenzoyl) pyrrolo[1,2-c]pyrimidine-5-carboxylate, ***IVf***

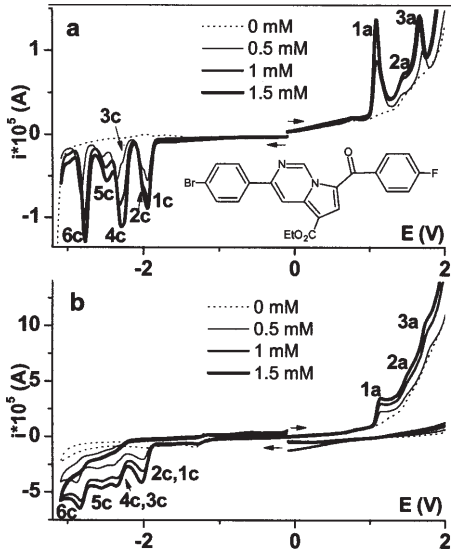


Fig. 11. (a) DPV and (b) CV curves for different concentrations of **IVf** (the structure is given in the inset) in 0.1M TBAP, CH_3CN

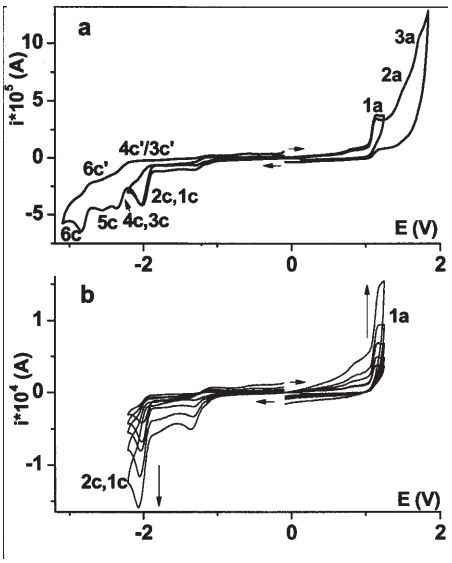


Fig. 12. CV curves for various scan domains at 0.1V/s (a) and at different scan rates: 0.1; 0.2; 0.3; 0.5; 1V/s (b) in the domain of the peaks 1c and 1a, respectively, for **IVf** (1.5mM) in 0.1M TBAP, CH_3CN

Table 7

PEAK POTENTIALS (IN V) AND CHARACTERISTICS OF THE PEAKS FROM CV (r - REVERSIBLE; i - IRREVERSIBLE; q - QUASI-REVERSIBLE) AND THEIR ASSESSMENT FOR **IVf**

Peak	DPV	CV
1a	1.084	1.144 (i)
2a	1.453	1.525 (i)
3a	1.663	1.737 (i)
1c	-1.948	* (i)
2c	-2.001	* (i)
3c	-2.264	*
4c	-2.295	-2.369
5c	-2.485	-2.564 (i)
6c	-2.769	-2.839 (q)

** - not possible to be read*

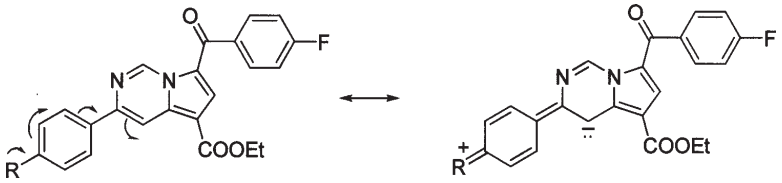
General considerations on the electrochemical behaviour of the compounds ***IVa – IVf***

Pyrrolo[1,2-c]pyrimidine is a complicate redox system due to its relatively low aromatic character, which confers it a higher reactivity than that of the common aryls. The difficulty of the peak interpretation is increased by the presence of stabilizing functional groups, which have close redox potentials with the aromatic moiety; therefore only partial peak assessments can be done (table 8).

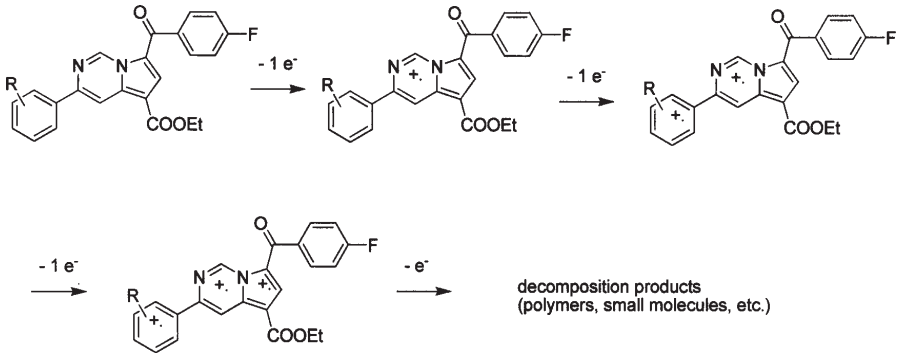
Table 8

PEAK POTENTIALS (IN V) FROM DPV AND THEIR ASSESSMENT FOR **IVa - IVf**

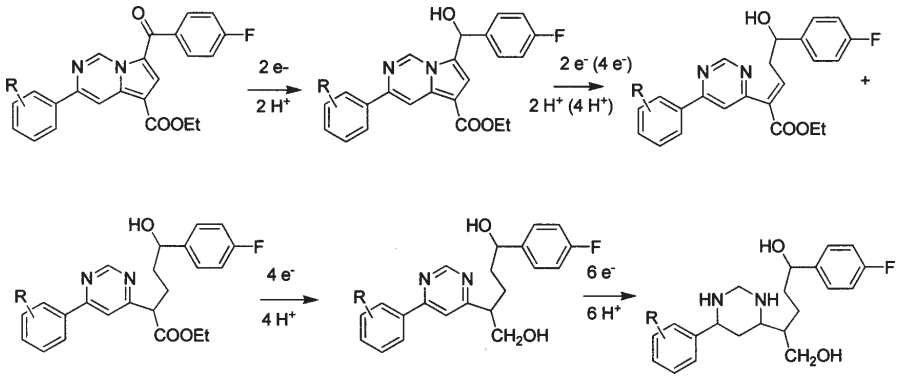
Compound	IVa	IVb	IVc	IVd	IVe	IVf	Functional group involved/process
Peak\R	o-Me	o-OMe	m-OMe	p-OMe	m-Br	p-Br	
1a	1.094	0.985	1.065	0.941	1.110	1.084	Py/$Py^{+\bullet}$
		1.354	1.160	1.120			Ph (in position 3)/
				1.246			oxidation
2a	1.494	1.627	1.592		1.531	1.453	Py/oxidation
3a	1.663	1.680	1.750	1.678	1.668	1.663	Py/oxidation
4a	1.916		2.171		1.963	2.110	Py/oxidation
5a							
1c	-1.990	-1.994	-1.946	-1.934	-1.933	-1.948	CO/ $CO^{-\bullet}$/CHOH/ reduction
2c					-2.185	-2.001	Br/Br^-/reductive elimination
3c	-2.264	-2.216	-2.188	-2.228	-2.280	-2.264	Pyrrole double
		-2.321	-2.262	-2.281		-2.295	bonds/reduction
4c	-2.475	-2.542	-2.441	-2.460	-2.438	-2.485	Ester/reduction
	-2.548			-2.544			
5c	-2.738	-2.700	-2.736	-2.692	-2.764	-2.769	Pyrimidine/reduction
6c	-2.917	-2.900		-2.839			Destructive reductions



Scheme 2. Effects of electron releasing groups on the electronic density in pyrimidine cycle



Scheme 3. Most probable oxidation path of substituted pyrrole[1,2-c]pyrimidines



Scheme 4. Most probable reduction path of substituted pyrrole[1,2-c]pyrimidines

At oxidation, the pyrimidine nitrogen looses one electron, leading to a radical-cation (**1a**). These potentials are observed around the value of 1 V, being slightly influenced by the phenyl substituents, R. The electron releasing groups like MeO or Br situated in *para* position reduce these peak potential values (by increasing the electron density on the central heterocycle as in the scheme 2), while those situated in *meta* position which have an inductive effect – I, like Br, increase this peak potential.

In oxidation only the first peak (**1a**) is clear, the rest being envelopes of peaks due to the overlapping of the several electrode processes. For instance, we can suppose that the anisole moiety is oxidized at 1.1-1.3 V, followed by the destructive oxidation of the pyrolopyrimidine at potentials higher than 1.5 V. The fluorophenylcarbonyl moiety should not be active in acetonitrile. The anodic processes are summarized in scheme 3.

In reduction the first process is the formation of the radical-anion localized at the keto group. The reduction of the fluorophenylcarbonyl group is followed by the formation of an alcohol. This first reduction potential is almost constant (-1.94 V) for all this series of compounds due to the fact that the substituents are too far away to induce a difference in the electron density of the keto group; however a small difference is observed for *ortho* isomers (-1.99 V), probably because of a steric effect. Further, the pyrrole-carboxylate group is attacked both as a Birch reduction of the double bonds and as a classical ester reduction to alcohol. The same behaviour was observed during the chemical reductions of esters which are not selective leading to mixtures of numerous products [7, 8]. Therefore, the multitude of peaks which are observed cannot be individually assessed to definite electrochemical reactions. The bromine group (in **IVe** and **IVf**) can be also reduced in this potential range (~ -2.1 V), while there is very low probability to remove the methoxy group (in **IVb**, **IVc**, **IVd**). Finally, at the most negative potentials, the pyrimidine system is reduced, while the phenyl or anisyl groups might remain unchanged. The cathodic processes are summarized in scheme 4.

The diffusion coefficients (D_0) of the new pyrrolo[1,2-*c*]pyrimidine carboxylates **IVa – IVf** were calculated (Table 9) from the dependence of the values of the first oxidation peak (**1a**) currents on the square root of the scan rate in CV [6]. The lowest value was obtained for **IVb**, probably due to the steric effect induced by a deviation from coplanarity due to the interaction between O (from methoxy group) and N (from the pyrimidine cycle).

Table 9
DIFFUSION COEFFICIENTS FOR **IVa – IVf**

Compound	R	D_0 / cm^2 s^{-1}
IVa	CH_3 (*o*)	4.5E-05
IVb	OCH_3 (*o*)	2.3E-05
IVc	OCH_3 (*m*)	4.5E-05
IVd	OCH_3 (*p*)	4.5E-05
IVe	Br (*m*)	5.1E-05
IVf	Br (*p*)	6.0E-05

Conclusions

The investigated pyrrolo[1,2-c]pyrimidine carboxylates present similar electrochemical characteristics. The electron transfers of the common functional groups occur at potentials which vary slightly, according to the effect of the substituent in the phenyl ring. Detailed investigation has been performed to assess the processes for each peak. The difficulty of the peak interpretation has been increased by the presence of stabilizing functional groups, which have close redox potentials with the aromatic moiety. The electrochemical data can be useful to establish the mechanism through which the antioxidant properties of pyrrolo[1,2-c]pyrimidine derivatives act.

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