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Synthesis and unusual ring transformation of 1-acyl-3-(ferrocenylmethylidene)-piperazine-2,5-diones

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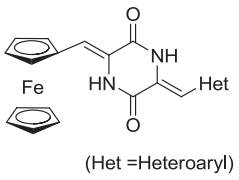
ABSTRACT

The reaction of 1,4-diacyl-piperazine-2,5-diones with ferrocenecarbaldehyde in the presence of ^{t}BuOK in ^{t}BuOH–DMF at room temperature afforded 1-acyl-3-(ferrocenylmethylidene)-piperazine-2,5-diones in 69–79% yields. The attempted *N*(4)-acylation of these compounds with carboxylic acids (2 equiv.) in the presence of *N*,*N*′-diisopropylcarbodiimide (2 equiv.) and 4-(dimethylamino)pyridine (3 equiv.) in dichloromethane at room temperature showed that the expected 1,4-diacylated products are initially formed, but undergo further transformations leading to compounds featuring conjugated ferrocenylmethylidene, azlactone (oxazolone) and oxazole units. As shown on the basis of one example, the azlactone ring in these compounds is opened in a room-temperature reaction with hydrazine, thus yielding the corresponding acyl hydrazide. The crystal structure of the starting material and the product of this reaction were confirmed by X-ray diffraction.

1. Introduction

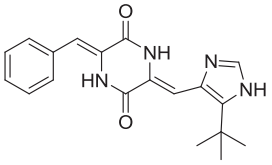
The search for ferrocenyl compounds exhibiting anticancer activity [1–5] continues to be an appealing current field within bioorganometallic chemistry [6–12]. From a synthetic viewpoint the main effort has been focused on modifying known anticancer drugs by introducing cytotoxic ferrocenyl groups into their structures. The best known example of such an approach is synthesis of the ferrocifene family, ferrocenyl analogs of an anti-breast cancer drug – tamoxifen [13].

By continuing our research on cytotoxic ferrocenyl compounds [14–17], we became interested in the synthesis of ferrocenyl derivatives of 2,6-dimethylenepiperazine-2,5-dione **1**. Compounds having this skeleton are abundant in nature [18,19] and display a wide spectrum of biological activities. Plinabulin (NPI-2355) **2** exhibits strong anti-microtubule activity and cytotoxicities in the nanomolar range [20–22]; it is currently under phase 2 clinical trials as a vascular disrupting agent (VDA) [23]. We thought that type **1** compounds having a cytotoxic ferrocene moiety attached to a 3,6-dimethylene-piperazine-2,5-dione template would have enhanced anti-microtubule and anticancer properties, similar to or higher than those of **2**.



(Het =Heteroaryl)

1



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We intended to prepare compounds **1** via a common route, a two-fold aldol condensation of 1,4-diacetyl-piperazine-2,5-dione (Scheme 1, **4a**) (prepared from glycine anhydride **3**) with appropriate aldehydes [18,21,24]. However, during the course of the synthetic work, we have found that the product of the condensation of **4a** with ferrocenecarbaldehyde, 1-acetyl-3-(ferrocenylmethylidene)-piperazine-2,5-dione **5a**, treated with acetic acid, *N*,*N*′-diisopropylcarbodiimide (DIC) and 4-(dimethylamino)pyridine (DMAP) underwent an unusual transformation into compound **7a** featuring two oxazole rings. Similar reaction was observed with various carboxylic acids. Herein we wish to report preliminary results concerning the scope and mechanism of this reaction.

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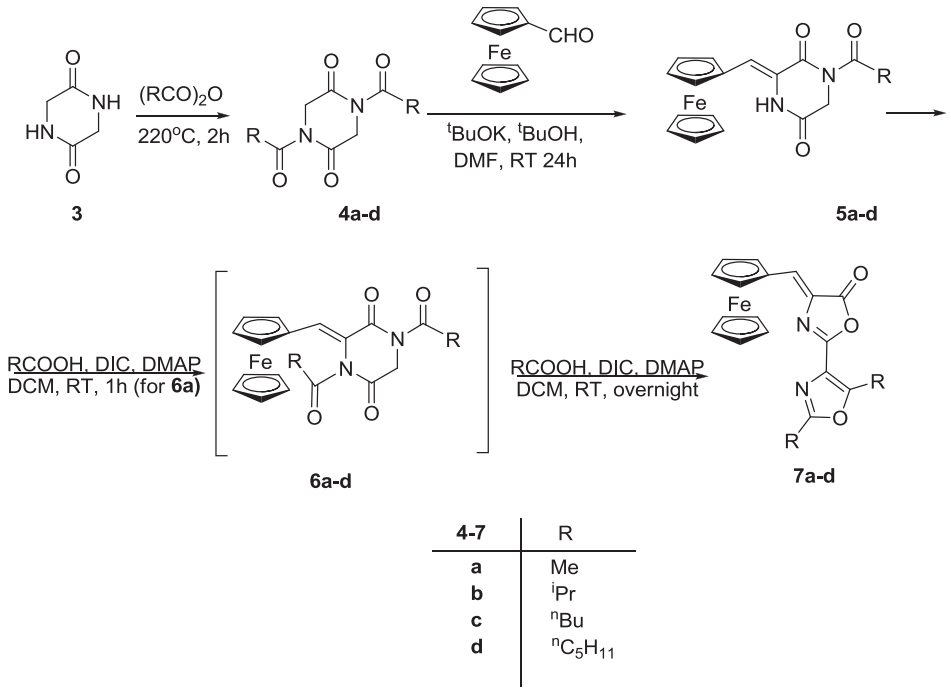


4-7	R
a	Me
b	^{i}Pr
c	^{n}Bu
d	$^{n}C_5H_{11}$

Scheme 1. Synthesis of compounds **5a**–**d** and their transformation into **7a**–**d**; DIC = *N*,*N*′-diisopropylcarbodiimide; DMAP = 4-(dimethylamino)pyridine.

2. Results and discussion

2.1. Chemical synthesis

We have found that **4a** reacts with ferrocenecarbaldehyde in the presence of ^{t}BuOK in ^{t}BuOH–DMF at room temperature to afford the expected 3-ferrocenylmethylidene derivative **5a** in 79% yield.

However, attempts to attach a second unsaturated group to C(6) via reaction of **5a** with various heteroaromatic aldehydes gave only trace amounts of the expected products. A similar decrease in reactivity of type **5** monounsaturated piperazine-2,5-diones in a second aldol condensation was reported earlier [21]. Since we thought that this may be due to decreased reactivity of the C(6) methylene group resulting from deacetylation of N(4), we tried to re-acetylate this nitrogen with acetic anhydride, but the reaction afforded only trace amount of the desired compound.

Therefore, we decided to check the reaction of **5a** with acetic acid in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) and 4-(dimethylamino)pyridine (DMAP). The reaction was performed in dichloromethane at room temperature at the molar ratio of **5a**:AcOH:DIC:DMAP = 1:2:3:3 and monitored by TLC. Surprisingly, we found that although the expected 1,4-diacetyl derivative **6a** was initially formed (and was isolated as red crystals in 40% yield when the reaction was quenched after 1 h), it underwent subsequent transformation on overnight standing into blue microcrystalline oxazole-substituted unsaturated azlactone **7a**, isolated in a 44% yield. Control experiment showed that transformation **6a** → **7a** takes place only in the presence of all reactants (i.e. acid, DIC and DMAP). We attempted to stop the reaction at the formation of **6a** using equimolar amounts of reactants, but under these conditions it was formed in a deceptively low yield (<5%).

The chemistry of piperazine-2,5-diones has been extensively studied and various ring-opening reactions were reported [18,24]. However, to the best of our knowledge what we report in this work – a ring opening followed by a domino reaction forming two conjugated oxazole rings – is unprecedented.

To gain insight into the substrate scope of the discovered reaction we synthesized a series of 1,4-diacyl-piperazine-2,5-diones **4b**–**d** by refluxing piperazine-2,5-dione (glycine anhydride) with corresponding acid anhydrides (reactions performed without a solvent). The desired **4b**–**d** were isolated in excellent yields. These compounds reacted with ferrocenecarbaldehyde under the conditions described above for the synthesis of **5a**, thus giving the expected 3-ferrocenylmethylene derivatives **5b**–**d** in good yields (72–77%). Then we performed a reaction of **5b**–**d** with carboxylic acids (having the same R group as the substrate to avoid the eventual formation of regioisomeric 2,5-disubstituted oxazoles) in the presence of DIC and DMAP. We isolated compounds **7b**–**d**, albeit in lower yields (10–13%).

A plausible mechanism for the transformation **6a**–**d** → 7**a**–**d** of is proposed in Scheme 2. Its key step involves C(6)-acylation, formation of a bicyclic oxazolo–piperazine intermediate, opening of the piperazine ring and re-cyclization yielding azlactone moiety.

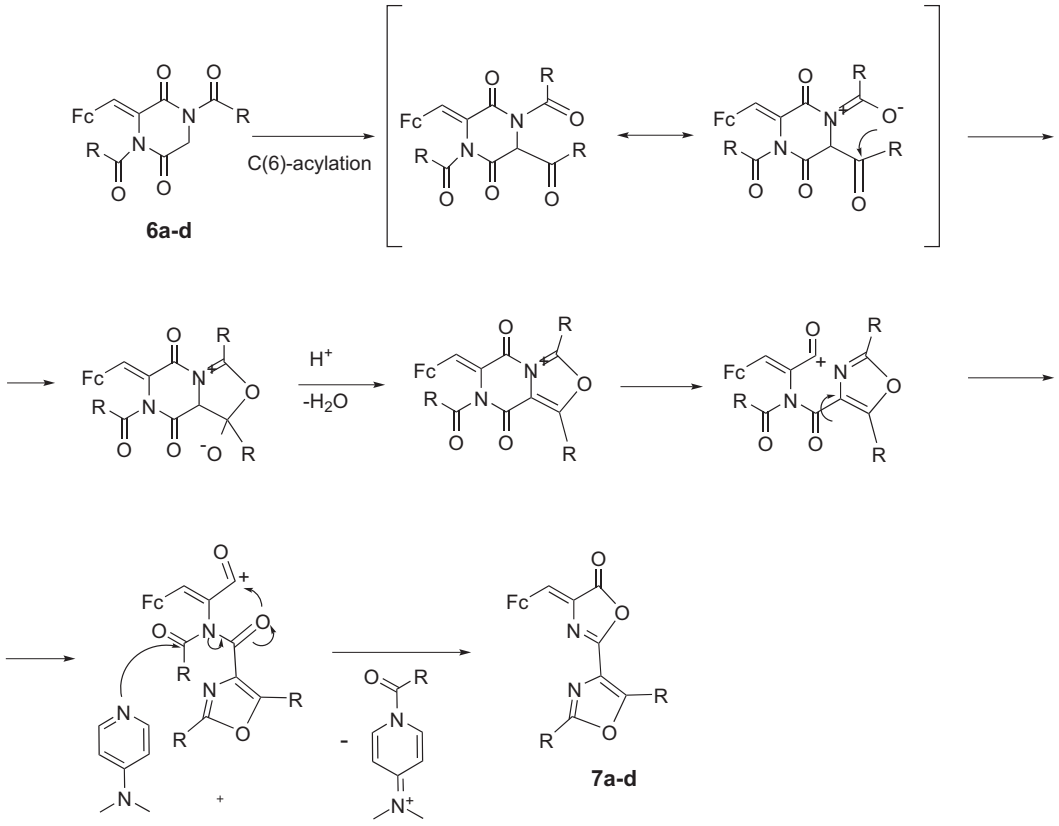
Compounds **7a**–**d** contain a reactive azlactone (oxazolone) ring which opens up numerous possibilities for synthetic transformations [25–28]. We performed a reaction of **7a** with hydrazine, yielding hydrazide **8** featuring an *N*-acylated ferrocenyl anhydroalanine skeleton in 96% yield (Scheme 3).

2.2. X-ray structure of *7a* and *8*

Unambiguous identification of compound **7a** and **8** required, apart from spectroscopic data, a single-crystal X-ray structure (Figs. 1 and 2, respectively).

The structure of **7a** shows the (*Z*)-configuration of the exocyclic (**C11**–**C12**) ethylene bond. The tricyclic system composed of a substituted Cp ring, **C11** and two oxazole rings is practically planar, thus indicating the π-conjugation between these units that brings about the intense color of this compounds (λ_{max} 544 nm, $\varepsilon = 4654$ dm^3 mol^{-1} cm^{-1} in 1,2-dichloroethane).

The structure of **8** reveals a distortion from the expected coplanarity of the Cp ligand with the adjacent unsaturated acyl

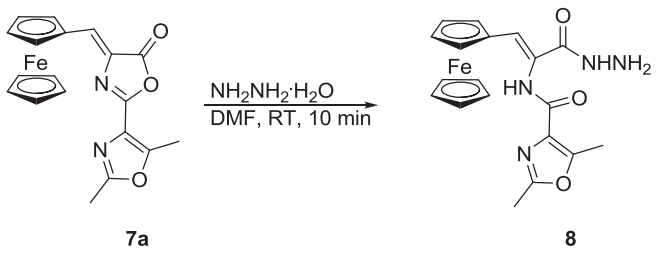


Scheme 2. Plausible mechanism for the transformation **6a–d** → **7a–d**.

hydrazide system; whereas the plane of the ethylenic (**C11–C12**) bond is twisted by about 9°, the carbonyl group plane forms an angle of about 55° with this plane. On the other hand, the carbonyl group is practically coplanar with the oxazole ring (an angle of about 6°). These distortions are probably of steric origin.

3. Conclusion

In conclusion, we discovered an unusual reaction of 1-acyl-3-ferrocenylmethylene-piperazine-2,5-diones involving ring-open ing followed by a domino cyclization that forms two oxazole rings. The reactive oxazolone moiety that is present in the products of this reaction (**7a–d**) is expected to undergo various ring-opening reactions (as evidenced by the reaction of **7a** with hydrazine) which may open up new routes to ferrocene–peptido conjugates. Furthermore, the oxazolone ring may also serve as a template in diversity-oriented synthesis of heterocycles [29–33] and natural products [25–34]. Finally, **7a–d** are potential redox-active bidentate ligands for metal ions.



Scheme 3. Ring-opening reaction of azlactone **7a** with hydrazine.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a *Bruker ARX 600* spectrometer (600 MHz for ^{1}H and 151 MHz for ^{13}C). Chemical shifts in ^{1}H spectra were referenced relative to the solvent signals: $CDCl_3$ $\delta = 7.27$ ppm for ^{1}H and $\delta = 77.20$ ppm for ^{13}C. Spectra were recorded at room temperature (291 K), chemical shifts are in ppm and coupling constants in Hz. EI and HR-EI and HRMS-EI analyses were performed in positive mode at 75 eV on mass spectrometer

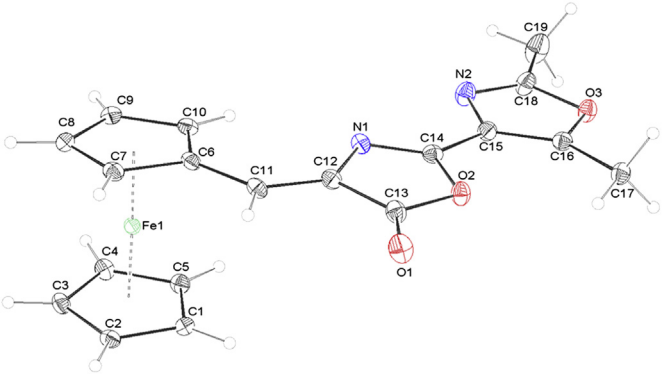


Fig. 1. ORTEP view of **7a**. Thermal ellipsoids have been set at the 50% probability level. Selected bond distances (Å) and dihedral angles (°): C11–C12 1.3545(19); C12–N1 1.4097(18); N1–C14 1.2892(18); C14–O2 1.3891(16); O2–C13 1.3891(16); C13–O1 1.2015(17); C14–C15 1.4461(19); C15–N2 1.4028(18); N2–C18 1.2907(18); C18–C19 1.482(2); C18–O3 1.3753(17); O3–C16 1.3740(16); C16–C17 1.478(2); C15–C16 1.3615(19); C12–C11–C6–C10 7.3(2); C6–C11–C12–N1 −1.4(2); N1–C14–C15–N2 0.2(2) (for detailed crystallographic data see the Supplementary materials).

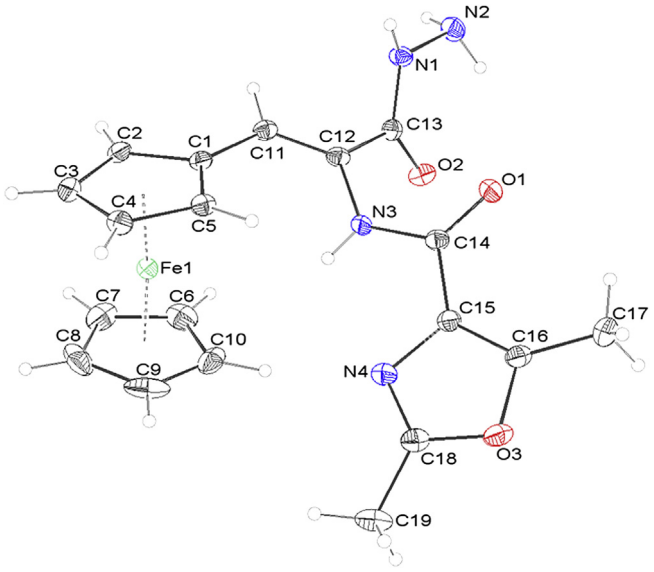


Fig. 2. ORTEP view of **8**. Thermal ellipsoids have been set at the 50% probability level. Selected bond distances (Å) and dihedral angles (°): C1–C11 1.465(3); C11–C12 1.339(3); C12–C13 1.498(3); C13–N1 1.331(3); N1–N2 1.419(2); C12–N3 1.410(2); N3–C14 1.360(3); C14–O1 1.227(2); C14–C15 1.470(3); C15–C16 1.347(3); C16–C17 1.473(3); C16–O3 1.378(2); O3–C18 1.369(3); C18–C19 1.487(3); C18–N4 1.284(3); N4–C15 1.403(3); C5–C1–C11–C12 25.4(3); C1–C11–C12–C13 171.17(19); C11–C12–C13–O2 −125.3(2); N3–C12–C13–O2 40.8(3); C13–C12–N3–C14 42.7(3); C12–N3–C14–O1 5.7(3); O1–C14–C15–C16–1.2(3) (for detailed crystallographic data see the Supplementary materials).

Finnigan MAT 95, Elemental analysis was performed by the Laboratory of Microanalysis at the Centre of Molecular and Macromolecular Studies in Łódź, Poland. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with Merck 5735 Kieselgel 60F254. Column chromatography was carried out on silica gel 60 (0.040–0.063 mm, 230–400 mesh, Fluka). Dichloromethane was distilled from calcium hydride and stored over activated molecular sieves 4 A (8–12 mesh). Reactions with ferrocenyl compounds were carried out under argon using the standard Schlenk technique. Chemicals and solvents (HPLC grade) were purchased from Sigma–Aldrich or AK Scientific (USA) and used as received.

*4.1.1. 1,4-Diacetylpiperazine-2,5-dione (**4a**)*

A mixture of glycine anhydride 1.50 g (13 mmol) and acetic anhydride (15 ml) was heated at 220 °C (oil bath temperature) for 2 h. The resulting solution was then cooled and an excess of acetic anhydride was removed under reduced pressure. The crude product was crystallized from *n*-hexane–ethyl acetate (1:1) Yield: 3.62 g (79%) of a bright yellow crystals. NMR and IR spectra of the product were identical with those of an authentic sample [34].

*4.1.2. 1,4-Diisobutyrylpiperazine-2,5-dione (**4b**)*

It was prepared using the same procedure as **4a**, starting from 3.00 g (26 mmol) of glycine anhydride and 30 cm^3 of isobutyric anhydride. Yield: 5.70 g (85%). Bright yellow powder. ^{1}H NMR: δ 4.58 (s, 4H, H-3 and H-6); 3.68 (dt, J = 13.5, 6.8, 2H, 2× CH); 1.21 (d, J = 6.8, 12H, 4× CH_3). ^{13}C NMR: δ 178.71 (CO); 165.93 (CO); 48.13 (C-3 and C-6); 36.04 (CH); 19.27 (CH_3); Elemental analysis: Found: C, 56.65; H, 7.13. N, 10.87. $C_{12}H_{18}N_2O_4$ requires: C, 56.68; H, 7.13, N, 11.02.

*4.1.3. 1,4-Divalerylpiperazine-2,5-dione (**4c**)*

It was prepared using the same procedure as **4a** starting from 1.50 g (13 mmol) of glycine anhydride and 15 cm^3 of valeric anhydride. Yield: 3.39 (89%). White powder. ^{1}H NMR: δ 4.58 (s, 4H, H-3 and H-6); 2.94 (t, J = 7.3, 4H, 2× CH_2-α); 1.65 (dt, J = 15.1, 7.53, 4H, 2× CH_2-β); 1.33–1.42 (m, 4H, 2× CH_2-γ); 0.93 (t, J = 7.3, 6H, 2× CH_3). ^{13}C NMR: δ 174.26 (CO); 166.05 (CO); 47.68 (C-3 and C-6); 38.71 (CH_2-α); 26.62 (CH_2-β); 22.37 (CH_2-γ); 13.95 (CH_3); Elemental analysis: Found: C, 59.52; H, 7.91; N, 9.89; $C_{14}H_{22}N_2O_4$ requires: C, 59.56; H, 7.85; N, 9.92.

*4.1.4. 1,4-Dihexanoylpiperazine-2,5-dione (**4d**)*

It was prepared using the same procedure as **4a** starting from 1.50 g (13 mmol) of glycine anhydride and 15 cm^3 of hexanoic anhydride. Yield: 3.80 g (94%). White powder. ^{1}H NMR: δ 4.58 (s, 4H, H-3 and H-6); 2.95 (t, J = 7.5, 4H, 2× CH_2-α); 1.63–1.71 (m, 4H, 2× CH_2-β); 1.31–1.37 (m, 8H, 2× CH_2-γ and 2× CH_2-δ); 0.87–0.94 (m, 6H, 2× CH_3). ^{13}C NMR: δ 174.30 (CO); 166.06 (CO); 47.69 (C-3 and C-6); 38.98 (CH_2-α); 31.42 (CH_2-γ or δ); 24.24 (CH_2-β); 22.57 (CH_2-γ or δ); 14.05 (CH_3). Elemental analysis: Found: C, 61.78; H, 8.42; N, 9.07. $C_{16}H_{26}N_2O_4$ requires: C, 61.91; H, 8.44; N, 9.03.

*4.1.5. 1-Acetyl-3-ferrocenylmethylidene-2,5-piperazinedione (**5a**)*

Potassium *t*-butoxide (0.74 g, 6.6 mmol) was added to a solution of **4a** (1.31 g, 6.6 mmol) and ferrocenecarbaldehyde (1.00 g, 4.7 mmol) in the mixture of DMF (12 ml) and *tert*-butanol (15 ml). The resulting mixture was stirred at room temperature overnight and the reaction was quenched by adding of H_2O (50 ml) and acetic acid (5 ml). The product was extracted with dichloromethane, the extract washed with water, brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel using dichloromethane–ethyl acetate (10:1) as eluent and then crystallized from ethyl acetate–*n*-hexane. Yield: 1.31 g (79%). Red crystals. ^{1}H NMR: δ 8.14 (br. s., 1H, NH); 6.95 (s, 1H, H-vinyl); 4.49 (s, 6H, 4× H-Cp and H-6); 4.24 (s, 5H, Cp); 2.63 (s, 3H, CH_3). ^{13}C NMR: δ 172.7 (CO); 162.5 (CO); 160.1 (CO); 123.5 (C-3); 121.0 (CH-vinyl); 75.9 (Cp-ipso); 71.2 (Cp); 69.9 (Cp); 69.6 (Cp); 46.4 (C-6); 27.3 (CH_3); Elemental analysis: Found: C, 57.95; H, 4.62; N, 7.92. $C_{17}H_{16}FeN_2O_3$ requires: C, 57.98; H, 4.58; N, 7.95.

*4.1.6. 3-Ferrocenylmethylidene-1-isobutyrylpiperazine-2,5-dione (**5b**)*

It was prepared using the same procedure as **5a** starting from **4b** (1.67 g, 6.6 mmol). Yield: 1.19 g (67%). Red crystals. ^{1}H NMR: δ 8.06 (s, 1H, NH); 6.96 (s, 1H, CH-vinyl); 4.49 (s, 2H, Cp); 4.48 (s, 2H, Cp); 4.47 (s, 2H, H-6); 4.25 (s, 5H, Cp); 3.71 (dt, J = 13.6, 6.8, 1H, CH); 1.24 (d, J = 6.8, 6H, 2× CH_3); ^{13}C NMR: δ 180.8 (CO); 162.9 (CO); 160.1 (CO); 123.8 (C-3); 120.9 (C-vinyl); 76.1 (Cp-ipso); 71.2 (Cp); 69.9 (Cp); 69.6 (Cp); 48.1; 46.8 (C-6); 36.2 (CH); 19.7 (CH_3); Elemental analysis: Found: C, 59.96; H, 5.51; N, 7.31. $C_{19}H_{20}FeN_2O_3$ requires: C, 60.02; H, 5.30; N, 7.37.

*4.1.7. 3-Ferrocenylmethylidene-1-pentanoylpiperazine-2,5-dione (**5c**)*

It was prepared using the same procedure as **5a** starting from **4c** (1.86 g, 6.6 mmol). Yield: 1.34 g (72%). Orange crystals. ^{1}H NMR: δ 8.1 (s, 1H, NH); 6.94 (s, 1H, CH-vinyl); 4.49 (s, 2H, H-6); 4.49 (d, J = 1.9, 2H, Cp); 4.48 (d, J = 1.9, 2H, Cp); 4.25 (s, 5H Cp); 3.00 (t, J = 7.2, 2H, CH_2-α); 1.69 (dt, J = 15.1, 7.5, 2H, CH_2-β); 1.37–1.45 (m, 2H, CH_2-γ); 0.96 (t, J = 7.3, 3H, CH_3); ^{13}C NMR: δ 176.1 (CO); 162.7 (CO); 160.1 (CO); 123.7 (C-3); 120.7 (CH-vinyl); 76.0 (Cp-ipso); 71.2 (Cp); 69.9 (Cp); 69.5 (Cp); 46.5 (C-6); 39.1 (CH_2-α); 27.1 (CH_2-β); 22.5 (CH_2-γ); 14.0 (CH_3); Elemental analysis: Found: C, 60.98; H, −5.71; N, 7.09. $C_{20}H_{22}FeN_2O_3$ requires: C, 60.93; H, 5.62; N, 7.11.

*4.1.8. 3-Ferrocenylmethylidene-1-hexanoylpiperazine-2,5-dione (**5d**)*

It was prepared using the same procedure as **5a** starting from **4d** (2.05 g, 6.6 mmol). Yield: 1.42 g (74%). Orange crystals. ^{1}H NMR: δ 8.09 (bs, 1H, NH); 6.94 (s, 1H, CH-vinyl); 4.49 (s, 2H, H-6); 4.49 (t,

Table 1
Crystal data and structure refinement for **7a** and **8**.

	7a	8
Empirical formula	$C_{19}H_{16}FeN_2O_3$	$C_{19}H_{20}FeN_4O_3$
Formula weight	376.19	408.24
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system, space group	Monoclinic, P-1	Monoclinic, P 1 21/c 1
Unit cell dimensions	$a = 7.0637(2)$ Å $\alpha = 75.546(3)^\circ$ $b = 10.7280(4)$ Å $\beta = 80.034(4)^\circ$ $c = 10.8421(4)$ Å $\gamma = 79.213(3)^\circ$	$a = 9.7340(12)$ Å $\alpha = 90^\circ$ $b = 23.8380(5)$ Å $\beta = 95.436(9)^\circ$ $c = 7.7331(4)$ Å $\gamma = 90^\circ$
Volume	774.62(5) Å^3	1786.3(2) Å^3
Z	2	4
Calculated density	1.613 mg/m^3	1.518 mg/m^3
Absorption coefficient	0.995 mm^{-1}	0.873 mm^{-1}
$F(000)$	388	848
Crystal size	0.16 × 0.04 × 0.04 mm	0.11 × 0.08 × 0.04 mm
Theta range for data collection	2.96–32.31°	2.10–28.72°
Limiting indices	$-10 \le h \le 10$, $-15 \le k \le 15$, $-15 \le l \le 16$	$-12 \le h \le 12$, $-31 \le k \le 31$, $-10 \le l \le 10$
Reflections collected/unique	19,709/5182 [R(int) = 0.0349]	27,218/4429 [R(int) = 0.0471]
Completeness to theta=	32.31; 93.9%	25.00; 99.8%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.96 and 0.95	1.0 and 0.97
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	5182/16/290	4429/0/273
Goodness-of-fit on F^2	1.036	1.062
Final R indices [$I > 2$sigma(I)]	$R1 = 0.0324$, $wR2 = 0.0690$	$R1 = 0.0348$, $wR2 = 0.0703$
R indices (all data)	$R1 = 0.0456$, $wR2 = 0.0739$	$R1 = 0.0532$, $wR2 = 0.0848$
Largest diff. peak and hole	0.515 and −0.329 e. Å^{-3}	0.419 and −0.346 e. Å^{-3}

J = 1.9, 2H, Cp); 4.48 (t, J = 1.9, 2H, Cp); 4.25 (s, 5H, Cp); 2.99 (t, J = 7.5, 2H, CH_2-α); 1.65–1.74 (m, 2H, CH_2-β); 1.28–1.41 (m, 4H, CH_2-γ and CH_2-δ); 0.84–0.96 (m, 3H, CH_3); ^{13}C NMR: δ 176.1 (CO); 162.7 (CO); 160.1 (CO); 123.7 (C-3); 120.7 (CH-vinyl); 76.0 (Cp-ipso); 71.2 (Cp); 69.9 (Cp); 69.5 (Cp); 46.5 (C-6); 39.3 (CH_2-α); 31.5 (CH_2-γ or δ); 24.7 (CH_2-β); 22.6 (CH_2-γ or δ); 14.1 (CH_3); Elemental analysis: Found: C, 61.80; H, 6.02; N, 6.82. $C_{21}H_{24}FeN_2O$ requires: C, 61.78; H, 5.93; N, 6.86.

4.1.9. 1,4-Diacetyl-3-ferrocenylmethylidenepiperazine-2,5-dione (**6a**)

To a solution of **5a** (352 mg, 1.0 mmol), DMAP (244 mg, 2.0 mmol), and acetic acid (172 μl, 3.0 mmol) in dichloromethane (10 ml), DIC 379 mg (470 μl, 3.0 mmol), was added and the resulting solution was stirred at 1 h at room temperature. Then the reaction was quenched by adding water (20 ml), and the product was extracted with dichloromethane. The organic solution was washed with water, brine, dried and evaporated. The crude product was purified by column chromatography on silica gel using dichloromethane–ethyl acetate (20:1) as eluent. Red crystals. Yield: 155 mg (40%). ^{1}H NMR 7.47 (s, 1H, CH-vinyl), 4.57 (br. s., 2H, H-6), 4.52 (t, J = 1.7 Hz, 2H, Cp-β), 4.36 (t, J = 1.7 Hz, 2H, Cp-α), 4.19 (s, 5H, Cp), 2.59 (s, 3H, 1-CO**C**H_3), 2.56 (s, 3H, 4-CO**C**H_3); ^{13}C NMR 171.36 (1-**C**OCH_3); 167.20 (C-5); 166.94 (4-**C**OCH_3); 165.11 (C-2); 138.28 (CH-vinyl); 121.02 (C-3); 75.67 (Cp-ipso); 72.22 (Cp-β); 70.77 (Cp-α); 70.17 (Cp); 47.00 (C-6); 27.05 (4-CO**C**H_3); 26.08 (1-CO**C**H_3); Elemental analysis: Found: C, 57.80; H, 4.58; N, 7.10. $C_{19}H_{18}FeN_2O_4$ requires: C, 57.89; H, 4.60; N, 7.11.

4.1.10. 1,4-Ferrocenylmethylidene-2′,5′-dimethyl-[2,4′-bioxazol]-5(4H)-one (**7a**)

Obtained using the procedure described above after overnight standing of the reaction mixture. Yield: 165 mg (44%). Dark blue crystals. ^{1}H NMR: δ 7.24 (s, 1H, CH-vinyl); 5.08 (s, 2H, Cp); 4.65 (t, J = 1.9, 2H, Cp); 4.20 (s, 5H, Cp); 2.69 (s, 3H, 2′-CH_3); 2.51 (s, 3H, 5′-CH_3). ^{13}C NMR: δ 166.7 (CO); 161.1 (C-5′); 155.8 (C-2); 154.2 (C-2′); 136.1 (CH-vinyl); 129.2 (C-4); 124.7 (C-4′); 76.5 (Cp-ipso); 73.2 (Cp); 72.6 (Cp); 70.4 (Cp); 14.0 (2′-CH_3); 12.4 (5′-CH_3); Elemental analysis: Found: C, 60.65; H, 4.32; N, 7.23. $C_{19}H_{16}FeN_2O_3$: requires: C, 60.66; H, 4.29; N, 7.45. EI-HRMS: Found: 376.0510 (M^+). $C_{19}H_{16}FeN_2O_3$ requires 376.0500 (M^+).

4.1.11. 4-Ferrocenylmethylidene-2′,5′-diisobutyryl-[2,4′-bioxazol]-5(4H)-one (**7b**)

It was prepared using the same procedure as **7a** starting from of **5b** (382 mg, 2.0 mmol) and of isobutyric acid (278 μl, 3.0 mmol). Yield: 59 mg (14%). Dark purple crystals. ^{1}H NMR: δ 7.22 (s, 1H, CH-vinyl); 5.06 (s, 2H, Cp); 4.66 (s, 2H, Cp); 4.20 (s, 5H, Cp); 3.83 (td, J = 7.0, 13.9, 1H, 2′-C**H**$(CH_3)_2$); 3.16 (td, J = 7.0, 13.9, 1H, 5′-C**H**$(CH_3)_2$); 1.40 (d, J = 7.2, 6H, 2′-CH(C**H**$_3)_2$); 1.39 (d, J = 7.2, 6H, 5′-CH(C**H**$_3)_2$); ^{13}C NMR: δ 168.1 (C-5′); 166.8 (CO); 162.2 (C-2′); 156.2 (C-2); 135.7 (CH-vinyl); 129.4 (C-4); 122.4 (C-4′); 73.1 (Cp); 72.5 (Cp); 70.4 (Cp); 28.7 (5′-**C**$H(CH_3)_2$), 26.7 (2′-**C**$H(CH_3)_2$); 20.7 (2′-CH(**C**$H_3)_2$); 20.4 (5′-CH(**C**$H_3)_2$); Elemental analysis: Found: C, 63.72; H, 5.74; N, 6.23. $C_{23}H_{24}FeN_2O_3$ requires: C, 63.90; H, 5.60; N, 6.48.

4.1.12. 4-Ferrocenylmethylidene-2′,5′-divaleryl-[2,4′-bioxazol]-5(4H)-one (**7c**)

It was prepared using the same procedure as **7a** starting from **5c** (394 mg, 2.0 mmol) and valeric acid (326 μl 3.0 mmol). Yield: 87 mg (16%). Purple crystals. ^{1}H NMR: δ 7.21 (s, 1H, H-vinyl); 5.07 (br. s., 2H, Cp); 4.64 (s, 2H, Cp); 4.20 (s, 5H, Cp); 3.11 (t, J = 7.7, 2H, 2′-CH_2-α); 2.81 (t, J = 7.7, 2H, 5′-CH_2-α); 1.69–1.83 (m, 4H, 2′- and 5′-CH_2-β); 1.40–1.47 (m, 4H, 2′- and 5′-CH_2-γ); 0.99 (t, J = 7.3, 3H, 2′-CH_3); 0.96 (t, J = 7.3, 3H, 5′-CH_3); ^{13}C NMR: δ 166.7 (CO); 164.6 (C-5′); 158.3 (C-2′); 156.1 (C-2); 135.7 (CH-vinyl); 129.4 (C-4); 124.1 (C-4′); 76.6 (Cp-ipso); 73.1 (Cp); 72.5 (Cp); 70.4 (Cp); 30.0 (2′-CH_2-β); 29.2 (5′-CH_2-β); 28.0 (5′-CH_2-α); 26.2 (2′-CH_2-α); 22.5 (2′- or 5′-CH_2-γ); 22.4 (2′- or 5′-CH_2-γ); 13.9 (2′- or 5′-CH_3); 13.8 (2′- or 5′-CH_3); Elemental analysis: Found: C, 65.31; H, 6.29; N, 6.01. $C_{25}H_{28}FeN_2O_3$requires C, 65.23; H, 6.13; N, 6.09.

4.1.13. 4-Ferrocenylmethylidene-2′,5′-dihexanoyl-[2,4′-bioxazol]-5(4H)-one (**7d**)

It was prepared by the same procedure as **7a** starting from of **5d** (408 mg, 2.0 mmol) and hexanoic acid (376 μl, 3.0 mmol). Yield: 73 mg (15.0%). Purple crystals. ^{1}H NMR: δ ppm 7.22 (s, 1H, H-vinyl); 5.07 (br. s., 2H); 4.65 (s, 2H); 4.20 (s, 5H); 3.11 (t, J = 7.5, 2H, 2′-CH_2-

α); 2.82 (t, $J = 7.7$, 2H, 5′-CH_2-α); 1.76–1.84 (m, 4H, 2′- and 5′-CH_2-β); 1.38–1.44 (m, 4H, 2′-CH_2-γ and CH_2-δ); 1.34–1.38 (m, 4H, 5′-CH_2-γ and CH_2-δ); 0.88–0.95 (m, 6H, 2× CH_3); ^{13}C NMR: δ 166.7 (CO); 164.6 (C-5′); 158.3 (C-4′); 156.1 (C-2); 135.7 (CH-vinyl); 129.4 (C-4); 124.1 (C-2′); 76.6 (Cp-ipso); 73.1 (Cp); 72.5 (Cp); 70.4 (Cp); 31.54 (2′- or 5′-CH_2-γ, or 2′- or 5′-CH_2-δ); 31.5 (2′- or 5′-CH_2-γ, or 2′- or 5′-CH_2-δ); 28.3 (5′-CH_2-α); 27.7 (2′- or 5′-CH_2-β); 26.8 (2′- or 5′-CH_2-β); 26.5 (2′-CH_2-α); 22.5 (2′- or 5′-CH_2-γ, or 2′- or 5′-CH_2-δ); 22.4 (2′- or 5′-CH_2-γ, or 2′- or 5′-CH_2-δ); 14.1 (CH_3); 14.1 (CH_3); Elemental analysis: Found: C, 66.38; H, 6.89; N, 5.61. $C_{27}H_{32}FeN_2O_3$ requires: C, 66.40; H, 6.60; N, 5.74.

4.1.14. *N-(3-Hydrazinyl-3-oxo-(1-ferrocenylprop-1-en-2-yl))-2,5-dimethyloxazole-4-carbox-amide (**8**)*

Hydrazine monohydrate (19 μl, 0.39 mmol) was added to a solution of **7a** (50 mg, 0.13 mmol) in DMF (4 ml), the resulting solution was stirred at room temperature for 10 min, and the solvent was evaporated to dryness. The crude product was dissolved in dichloromethane (10 ml), the solution was washed with brine, dried over Na_2SO_4, and evaporated. Crystallization from dichloromethane–*n*-hexane gave **8** as an orange solid. Yield: 51 mg (96%). ^{1}H NMR: δ 7.42 (bs, 1H, CH); 4.58 (bs, 4H, Cp, NH_2); 4.45 (bs, 2H, Cp); 4.28 (bs, 5H, Cp); 2.59 (s, 3H, CH_3); 2.56 (s, 3H, CH_3); ^{13}C NMR: 171.4; 167.2; 166.9; 165.2; 138.4; 121.0; 72.9; 71.4; 70.9; 47.2; 27.1; 26.1 Elemental analysis: Found: C, 56.01; H, 5.14. $C_{19}H_{20}FeN_4O_3$ requires: C, 55.90; H, 4.94. Unfortunately we were unable to obtain a correct value for nitrogen; HRMS (EI): Found: 408.0885 (M^+). $C_{19}H_{20}FeN_4O_3$ requires 408.0875 (M^+).

4.2. X-ray diffraction studies

The frames were collected on an Agilent Xcalibur system with CrysAlis171 [34] software and integrated with the CrysAlisPRO [35] software package. Data were corrected for absorption effects using the multi-scan method (SCALE3 ABSPACK [34]). The structures were solved and refined using the SHELXTL Software Package [36] (with a graphical interface provided by Olex2 [37]). Figures were produced by Ortep2v3. A summary of the crystallographic data is presented in Table 1.

The positions of all hydrogen atoms were picked from the Fourier map. The final positions of the hydrogen atoms were refined with restraint placed on the C–H distance only: 0.95(2) Å for hydrogens bound to aromatic C atoms and 0.98(2) Å for hydrogens bound to methyl C atoms, as suggested by SHELX for a given temperature.

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Appendix A. Supplementary material

CCDC 938751 and 938752 contain the supplementary crystallographic date for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif.

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