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An efficient one-pot method for the synthesis of novel ferrocene–triamide conjugates via pseudo five-component reaction

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ABSTRACT

A simple and efficient one-pot synthesis of novel ferrocene–triamide conjugates from the reaction of ferrocenecarboxaldehyde with Meldrum's acid and isocyanides in the presence of NH-containing compounds is described. This transformation proceeds through the creation of two C–C bonds, two C–N bonds, and one C=O bond, leading to three peptide bonds, and presumably occurs via a domino sequence involving Knoevenagel condensation, [1+4] cycloaddition, deacetonation, and aminolysis reactions.

1. Introduction

A suitable combination of the structural features of two small organic or organometallic, biologically active molecules may result in the creation of new molecules (hybrid or conjugates),[1–3] which are proving to be more efficacious, economical, and safe for their use as drugs. Hybrid molecules or conjugates are the constructs of different molecular entities, natural or unnatural, to generate functional molecules in which the characteristics of various components are modulated, amplified or give rise to entirely new properties.[4] The conjugation of biomolecules, such as amino acids, peptides, and DNA with organometallic compounds can provide novel systems that reflect properties of both the organometalic and the biologically derived moieties.[5]

Ferrocene and its derivatives are important on account of their fascinating sandwich structure and properties.[6] They have shown a broad variety of applications as complex material, pharmacology, organic synthesis, etc. Ferrocene itself exhibits interesting properties as an anti-anemic or cytotoxic agent.[7,8] The ferrocenyl group is incorporated into the structure of a number of biologically active molecules resulting in enhanced anticancer[9,10] and antimalarial[11,12] activities, among many others. Neuse and co-workers found highly enhanced activity of cytotoxic metal compounds including ferrocene when attached to polymers as prodrugs.[13,14] Conjugates of ferrocene with well-known drugs are reported, for example, with antibiotics, such as penicillins and cephalosporins.[15]

5-Arylidene Meldrum's acids are bis-electrophilic species and useful precursors in a variety of multicomponent reactions.[16] In our earlier publications,[17] we described three relatively facile routes to amidodiesters and triamides by taking advantage of Meldrum's acid derivatives. These compounds were obtained by treatment of Meldrum's acids with aldehydes (5-alkylidene or 5-arylmethylidene Meldrum's acids) and isocyanides in the presence of such nucleophiles as alcohols, phenols, and primary amines in dichloromethane. Based on these efficient and useful multicomponent reactions, more efforts were made to investigate the reactions of 5-alkylidene Meldrum's acids, isocyanides with other nucleophiles, such as water,[18] secondary amines,[19] arylhydroxylamines,[20] thiols,[21] diols,[22] 2-aminophenols,[22] pyrrole,[23] and indoles.[23]

Due to the biological significance of molecules with the ferrocenyl moiety we have combined triamides and ferrocene as molecular entities through carbon–carbon and carbon–heteroatom bond formation in order to create new hybrid molecules. Considering the versatile activities of these structures, we think it would be of interest to combine the ferrocenyl moiety and the triamide skeleton in view of their promising applications in organometallic synthesis and biological investigations.

2. Results and discussion

As part of ongoing research program on the development of new routes for the preparation of novel biologically active compounds,[24] we report a facile synthesis of triamide compounds **5** attached to

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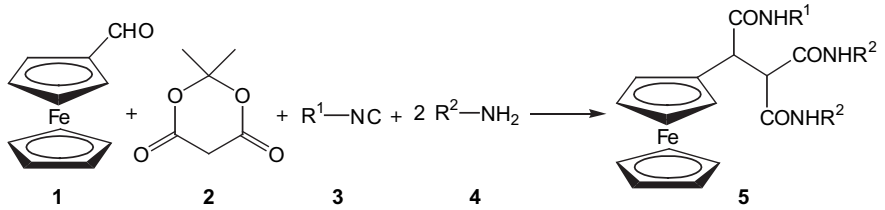
ferrocene via pseudo five-component reactions between ferrocenecarboxaldehyde **1**, Meldrum's acid **2** and isocyanides **3** in the presence of NH-containing compounds **4** to provide a library of novel ferrocene–triamide conjugates and the full results are summarized in Table 1.

The elucidation of the structure of **5** using ^{1}H and ^{13}C NMR spectroscopic data is discussed with **5a** as an example. The ^{1}H NMR spectrum of **5a** consisted of multiplet signals for the cyclohexyl rings (δ_H 1.03–1.59 ppm) and the NH–C*H* resonance (δ_H 3.50–3.60 ppm) and a doublet (δ_H 3.79 ppm, J_{AB}=10.8 Hz) for the

Table 1
Pseudo five-component condensation reactions of ferrocenecarboxaldehyde, Meldrum's acid and alkyl or aryl isocyanides in the presence of NH-containing compounds in anhydrous dichloromethane



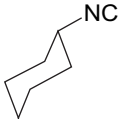
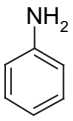
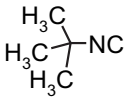
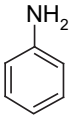
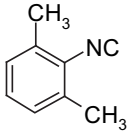
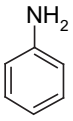
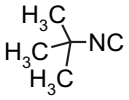
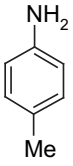
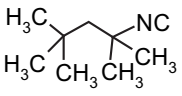
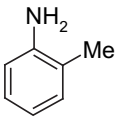
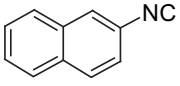
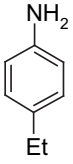
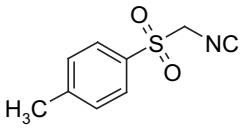
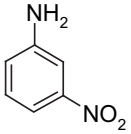
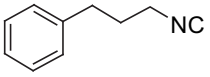
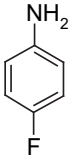
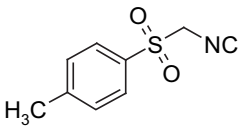
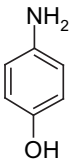
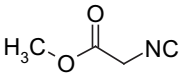
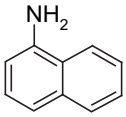
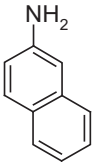
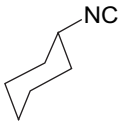
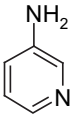
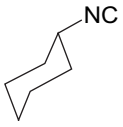
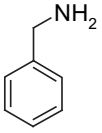
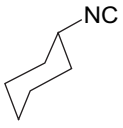
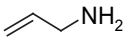
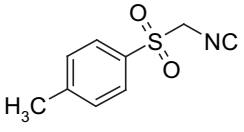
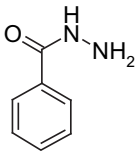
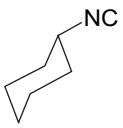
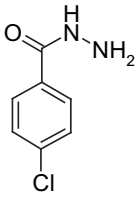
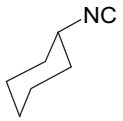
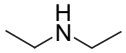
Entry	Isocyanide	NH-containing compound	Product	Yield[a] (%)
1			**5a**	95
2			**5b**	93
3			**5c**	80
4			**5d**	90
5			**5e**	75
6			**5f**	82
7			**5g**	83
8			**5h**	80

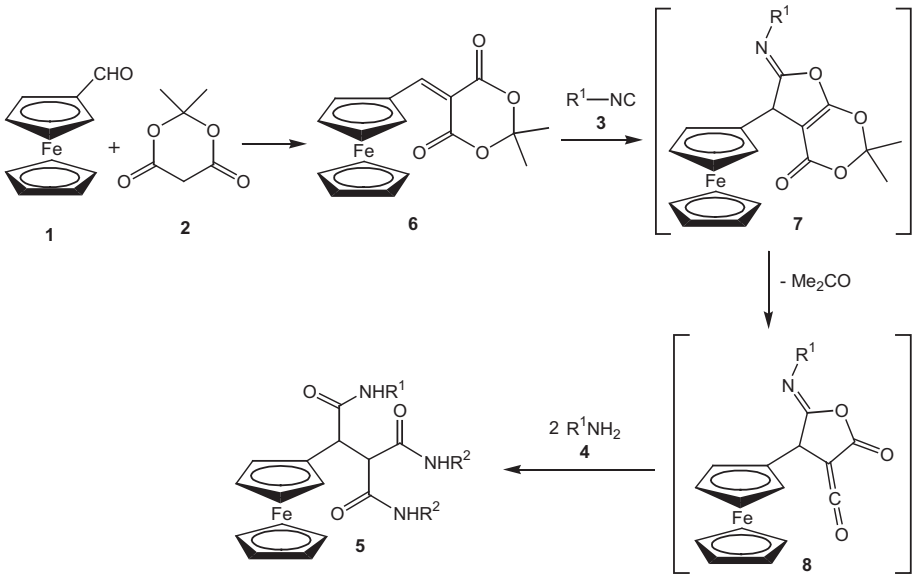
Table 1 (*continued*)

Entry	Isocyanide	NH-containing compound	Product	Yield[a] (%)
9			**5i**	77
10			**5j**	78
11			**5k**	90
12			**5l**	88
13			**5m**	85
14			**5n**	73
15			**5o**	86
16			**5p**	84
17			**5q**	74

[a] Refers to purified yield, which is >95% as determined by ^{1}H NMR spectroscopy.

methine protons. Multiplet signals were observed for the ferrocenyl hydrogens and another methine protons (δ_H 3.98–4.25 ppm). A fairly broad doublet resonance (δ_H 8.13 ppm, $^3J_{HH}$=7.8 Hz) was observed for the cyclohexyl–*NH* group. Two singlets (δ_H 9.56 and 9.71 ppm) were observed for the two Ph–*NH* protons. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 24 distinct resonances in agreement with the suggested structure.

The formation of ferrocene–triamide conjugate **5** could be accounted for by a plausible reaction pathway outlined in Scheme 1. The reaction may be rationalized as by initial formation of conjugated electron-deficient heterodiene by Knoevenagel condensation of the ferrocenecarboxaldehyde **1** and Meldrum's acid **2**, followed by a [1+4] cycloaddition reaction with isocyanide **3** to afford an iminolactone intermediate **7**. This intermediate first loses acetone



Scheme 1. Possible mechanism for the formation of products **5**.

to give acyl ketene **8**, which then reacts with two molecules of amines **4** to form the product **5**.

The scope and limitations of this process were explored by using eight alkyl or aryl isocyanides and fifteen NH-containing compounds. As shown in Table 1, allylic, benzylic, aromatic, aliphatic, and heteroaromatic amines are used in this protocol with excellent results. A variety of aryl amines carrying different functional groups were subjected to the coupling reactions and in all cases the desired product was obtained in good yields. It was observed that under similar conditions, a wide range of anilines containing electron-donating as well as electron-withdrawing groups, such as hydroxy, methyl, ethyl, phenyl, fluoro, and nitro underwent condensation with good isolated yields. It seems that the groups attached to the aromatic ring of the aryl amine do not affect the reaction significantly. To further examine the scope of the condensation reaction with respect to NH-containing compounds, two acyclic hydrazides (benzohydrazide and 4-chlorobenzohydrazide) were employed (entries 15,16). As we anticipated, 4-(2-benzoylhydrazino)-3-[(2-benzoylhydrazino)carbonyl]-2-(ferrocenyl)-*N*-{[(4-methylphenyl) sulfonyl]methyl}-4-oxobutanamide **5o** and 2-(ferrocenyl)-4-[2-(4-chlorobenzoyl)hydrazino]-3-{[2-(4-chlorobenzoyl)hydrazino]carbonyl}-*N*-cyclohexyl-4-oxobutanamide **5p** were successfully prepared under similar reaction conditions in 86% and 84% yields, respectively. Also, isocyanides with both sterically hindered and less hindered alkyl or aryl substituents were well tolerated and participated in the clean reactions, giving rise to the desired ferrocene–triamide conjugates in high yields.

3. Conclusion

In conclusion, we have developed a pseudo five-component domino process for the synthesis of novel ferrocene–triamide conjugates from simple and readily accessible starting materials. The reaction sequence consists of an initial Knoevenagel condensation of ferrocenecarboxaldehyde with Meldrum's acid, followed by [1+4] cycloaddition with isocyanides, then deacetonation and finally aminolysis to afford the products. This synthetic approach has the prominent features of high bond efficiency, good yields, operational simplicity, as well as broad scope of substrate tolerance, leading to a facile and straightforward access to brand-new conjugates.

4. Experimental

4.1. General

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an Elementar Vario EL *III* instrument. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively, with DMSO-d_6 as solvent and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal reference. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F_{254}) and visualized with UV light. All chemical reagents were obtained from Merck, Fluka or Acros and were used without further purification.

4.2. General procedure for preparation of the ferrocene–triamide conjugates 3a–q

Ferrocenecarboxaldehyde (0.5 mmol) and Meldrum's acid (0.5 mmol) were dissolved in 5 mL of anhydrous dichloromethane and the mixture was stirred at room temperature for 3 h. To this solution, the appropriate NH-containing compound (1.0 mmol) and the isocyanide (0.5 mmol) were added successively. The reaction mixture was stirred at ambient temperature for 12 h and the completion of reaction was confirmed by TLC (EtOAc/*n*-hexane 3:1). Subsequently, the precipitated product was filtered off and the solid washed with diethyl ether several times to give **5**. The crude product was purified by crystallization from hot ethanol to yield pure **5a–q**. The air-dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

*4.2.1. N^2-Cyclohexyl-2-(ferrocenyl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5a**).* Pale yellow solid (0.274 g, 95%); mp 306–308 °C; R_f (75% EtOAc/*n*-hexane) 0.28; IR (KBr) (ν_{max}, cm^{-1}): 3294 and 3268 (N–H), 1678 and 1636 (C=O), 1602 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.03–1.59 (10H, m, 5CH$_2$), 3.50–3.60 (1H, br s, NCH), 3.79 (1H, d, $^3J_{HH}$=10.8 Hz, CH), 3.98–4.25 (10H, m, ferrocene+CH), 6.99–7.51 (10H, m, arom.), 8.13 (1H, d, $^3J_{HH}$=7.8 Hz, NH), 9.56 and 9.71 (2H, 2s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 171.0, 167.1, 166.6, 139.9, 139.7, 130.1, 125.0, 124.8, 120.5, 120.3,

86.5, 69.9, 69.5, 68.4, 68.1, 68.0, 62.0, 48.8, 46.5, 33.6, 33.5, 26.5, 25.8, 25.7; Anal. Calcd for $C_{33}H_{35}FeN_3O_3$ (577.49): C, 68.63; H, 6.11; N, 7.28%. Found: C, 68.86; H, 6.09; N, 7.31%.

*4.2.2. N^2-(tert-Butyl)-2-(ferrocenyl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5b**).* Pale yellow solid (0.256 g, 93%); mp 264–266 °C; R_f (65% EtOAc/*n*-hexane) 0.60; IR (KBr) (ν_{max}, cm^{-1}): 3284 (N–H), 1672 and 1646 (C=O), 1601 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 1.24 (9H, s, 3Me), 3.75 (1H, d, $^3J_{HH}$=10.7 Hz, CH), 4.01–4.30 (10H, m, ferrocene+CH), 7.03–7.59 (10H, m, arom.), 7.86, 9.50 and 9.81 (3H, 3s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 170.5, 166.5, 165.9, 139.1, 138.9, 129.2, 124.2, 123.9, 119.8, 119.6, 85.9, 69.0, 68.4, 67.6, 67.2, 61.7, 50.6, 46.3, 28.8; Anal. Calcd for $C_{31}H_{33}FeN_3O_3$ (551.45): C, 67.52; H, 6.03; N, 7.62%. Found: C, 67.33; H, 6.01; N, 7.58%.

*4.2.3. N^2-(2,6-Dimethylphenyl)-2-(ferrocenyl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5c**).* Pale yellow solid (0.240 g, 80%); mp 302–304 °C; R_f (70% EtOAc/*n*-hexane) 0.56; IR (KBr) (ν_{max}, cm^{-1}): 3280 (N–H), 1675 and 1648 (C=O), 1600 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 2.15 (6H, s, 2Me), 4.09–4.33 (10H, m, ferrocene+CH), 3.89 (1H, d, $^3J_{HH}$=10.4 Hz, CH), 6.98–7.67 (13H, m, arom.), 9.65, 9.78 and 9.96 (3H, 3s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 170.4, 166.2, 139.2, 135.7, 135.5, 129.4, 129.3, 128.0, 126.6, 124.3, 123.9, 119.6, 119.2, 87.0, 69.3, 67.7, 67.4, 67.3, 66.8, 59.0, 45.1, 18.9; Anal. Calcd for $C_{35}H_{33}FeN_3O_3$ (599.49): C, 70.12; H, 5.55; N, 7.01%. Found: C, 69.88; H, 5.54; N, 6.99%.

*4.2.4. N^2-(tert-Butyl)-2-(ferrocenyl)-N^1,N^1-bis(4-methylphenyl)ethane-1,1,2-tricarboxamide (**5d**).* Pale yellow solid (0.260 g, 90%); mp 298–300 °C; R_f (65% EtOAc/*n*-hexane) 0.58; IR (KBr) (ν_{max}, cm^{-1}): 3284 (N–H), 1670 and 1644 (C=O), 1604 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 1.21 (9H, s, 3Me), 2.18 and 2.20 (6H, 2s, 2Me), 3.67 (1H, d, $^3J_{HH}$=11.0 Hz, CH), 3.97–4.27 (10H, m, ferrocene+CH), 7.03–7.44 (8H, m, arom.), 7.81, 9.36 and 9.68 (3H, 3s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 171.3, 167.2, 166.5, 137.5, 137.3, 133.9, 133.6, 130.4, 120.6, 120.4, 86.7, 69.8, 69.3, 68.4, 68.1, 68.0, 62.5, 51.4, 47.2, 29.6, 21.7; Anal. Calcd for $C_{33}H_{37}FeN_3O_3$ (579.51): C, 68.39; H, 6.44; N, 7.25%. Found: C, 68.12; H, 6.47; N, 7.28%.

*4.2.5. 2-(Ferrocenyl)-N^1,N^1-bis(2-methylphenyl)-N^2-(1,1,3,3-tetramethylbutyl)ethane-1,1,2-tricarboxamide (**5e**).* Pale yellow solid (0.238 g, 75%); mp 250–252 °C; (50% EtOAc/*n*-hexane) 0.76; IR (KBr) (ν_{max}, cm^{-1}): 3264 (N–H), 1668 and 1645 (C=O), 1588 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 0.92 (9H, s, CMe_3), 1.25 and 1.34 (6H, 2s, CMe_2), 1.66 and 1.80 (2H, AB-system, $^2J_{HH}$=14.3 Hz, CH_2), 2.06 and 2.17 (6H, 2s, 2Me), 3.94–4.28 (11H, m, ferrocene+CH–CH), 7.02–7.55 (8H, m, arom.), 7.75, 9.02 and 9.18 (3H, 3s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 171.1, 167.8, 167.1, 137.3, 137.0, 132.2, 131.6, 131.5, 131.4, 127.3, 127.2, 126.5, 126.1, 125.6, 124.9, 87.4, 69.9, 69.3, 68.2, 68.0, 67.9, 60.9, 55.8, 53.2, 47.3, 32.7, 32.3, 29.4, 29.3, 19.0, 18.9; Anal. Calcd for $C_{37}H_{45}FeN_3O_3$ (635.61): C, 69.92; H, 7.14; N, 6.61%. Found: C, 70.08; H, 7.11; N, 6.58%.

*4.2.6. 2-(Ferrocenyl)-N^1,N^1-bis(4-ethylphenyl)-N^2-2-naphthylethane-1,1,2-tricarboxamide (**5f**).* Pale yellow solid (0.277 g, 82%); mp 300–302 °C; (50% EtOAc/*n*-hexane) 0.82; IR (KBr) (ν_{max}, cm^{-1}): 3293, 3262 (N–H), 1671 and 1650 (C=O), 1601 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 1.05 and 1.08 (6H, 2 t, $^3J_{HH}$=7.5 Hz, $2CH_2CH_3$), 2.43–2.49 (4H, m, $2CH_2CH_3$), 3.93 (1H, d, $^3J_{HH}$=10.9 Hz, CH), 4.04–4.32 (10H, m, ferrocene+CH), 7.04–8.42 (15H, m, arom.), 9.62, 9.67 and 10.66 (3H, 3s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 171.9, 166.7, 166.4, 140.6, 140.4, 138.3, 137.5, 137.3, 134.8, 130.9, 129.7, 129.3, 129.2, 128.7, 128.5, 127.7, 125.7, 121.2, 120.7, 120.4, 116.0, 86.6, 70.2, 69.9, 68.6, 68.3, 67.6, 61.3, 47.0, 28.9, 28.8, 17.0, 16.9; Anal. Calcd for $C_{41}H_{39}FeN_3O_3$ (677.61): C, 72.67; H, 5.80; N, 6.20%. Found: C, 72.41; H, 5.78; N, 6.21%.

*4.2.7. 2-(Ferrocenyl)-N^1,N^1-bis(3-nitrophenyl)-N^2-[(phenylsulfonyl)methyl]ethane-1,1,2-tricarboxamide (**5g**).* Pale yellow solid (0.312 g, 83%); mp 220–222 °C; (75% EtOAc/*n*-hexane) 0.52; IR (KBr) (ν_{max}, cm^{-1}): 3298 (N–H), 1685 and 1646 (C=O), 1597 (C=C), 1325 and 1142 (SO_2); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 2.27 (3H, s, CH_3), 3.88–4.19 (11H, m, ferrocene+CH–CH), 4.56 and 4.79 (2H, 2 dd, $^3J_{HH}$=5.5 Hz, $^2J_{HH}$=13.8 Hz, $NHCH_2$), 7.15–8.63 (13H, m, arom.), 9.26 (1H, br t, $NHCH_2$), 10.18 and 10.25 (2H, 2s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 172.6, 167.3, 166.9, 149.2, 149.1, 145.4, 141.0, 140.7, 136.8, 131.5, 131.4, 130.7, 129.8, 126.8, 126.7, 119.7, 119.5, 115.0, 114.9, 85.5, 70.0, 69.9, 69.3, 68.5, 68.2, 61.9, 60.7, 45.9, 22.3; Anal. Calcd for $C_{35}H_{31}FeN_5O_9S$ (753.55): C, 55.79; H, 4.15; N, 9.29%. Found: C, 56.00; H, 4.14; N, 9.32%.

*4.2.8. 2-(Ferrocenyl)-N^1,N^1-bis(4-fluorophenyl)-N^2-(3-phenylpropyl)ethane-1,1,2-tricarboxamide (**5h**).* Pale yellow solid (0.259 g, 80%); mp 312–314 °C; (65% EtOAc/*n*-hexane) 0.63; IR (KBr) (ν_{max}, cm^{-1}): 3270 (N–H), 1671 and 1633 (C=O), 1600 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 1.66 (2H, dt, $^3J_{HH}$=7.0 Hz, $^3J_{HH}$=2.0 Hz, $NHCH_2CH_2Ph$), 2.55 (2H, t, $^3J_{HH}$=7.6 Hz, $NHCH_2CH_2Ph$), 2.93–3.01 and 3.20–3.27 (2H, 2 m, $NHCH_2CH_2Ph$), 3.80 (1H, d, $^3J_{HH}$=10.9 Hz, CH), 3.99–4.25 (10H, m, ferrocene+CH), 7.02–7.54 (13H, m, arom.), 8.33 (1H, t, $^3J_{HH}$=5.3 Hz, NH), 9.72 and 9.74 (2H, 2s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 172.1, 166.9, 166.7, 159.5 (d, $^1J_{CF}$=240.4 Hz, C_{ipso}–F), 159.4 (d, $^1J_{CF}$=240.2 Hz, C_{ipso}–F), 143.1, 136.2 (d, $^4J_{CF}$=2.2 Hz, C_{para}–F), 136.1 (d, $^4J_{CF}$=2.2 Hz, C_{para}–F), 129.6, 129.4, 126.9, 122.4 (d, $^2J_{CF}$=7.7 Hz, C_{meta}–F), 122.2 (d, $^2J_{CF}$=7.7 Hz, C_{meta}–F), 116.6 (d, $^2J_{CF}$=22.2 Hz, C_{ortho}–F), 116.5 (d, $^2J_{CF}$=22.3 Hz, C_{ortho}–F), 86.6, 69.9, 69.6, 68.5, 68.1, 68.0, 61.4, 46.5, 39.4, 33.7, 32.3; Anal. Calcd for $C_{36}H_{33}F_2FeN_3O_3$ (649.50): C, 66.57; H, 5.12; N, 6.47%. Found: C, 66.33; H, 5.14; N, 6.51%.

*4.2.9. 2-(Ferrocenyl)-N^1,N^1-bis(4-hydroxyphenyl)-N^2-{[(4-methylphenyl)sulfonyl]methyl}ethane-1,1,2-tricarboxamide (**5i**).* Pale yellow solid (0.267 g, 77%); mp 301–303 °C; (30% EtOH/*n*-hexane) 0.24; IR (KBr) (ν_{max}, cm^{-1}): 3319 (N–H), 1688 and 1649 (C=O), 1600 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 2.24 (3H, s, CH_3), 3.56–4.06 (11H, m, ferrocene+CH–CH), 4.58–4.74 (2H, m, CH_2), 6.33–7.66 (12H, m, arom.), 9.18–9.41 (5H, 4 br s, 3 NH+2 OH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 173.0, 166.2, 166.1, 154.9, 154.7, 145.3, 136.9, 131.8, 131.5, 130.7, 129.7, 122.2, 122.0, 116.8, 116.4, 116.3, 86.5, 69.9, 69.2, 68.2, 68.0, 67.8, 62.1, 60.2, 45.3, 22.3; Anal. Calcd for $C_{35}H_{33}FeN_3O_7S$ (695.56): C, 60.44; H, 4.78; N, 6.04%. Found: C, 60.20; H, 4.80; N, 6.01%.

*4.2.10. Methyl N-{2-(ferrocenyl)-4-(1-naphthylamino)-3-[(1-naphthylamino)carbonyl]-4-oxobutanoyl}glycinate (**5j**).* Pale yellow solid (0.260 g, 78%); mp 272–274 °C; (75% EtOAc/*n*-hexane) 0.78; IR (KBr) (ν_{max}, cm^{-1}): 3294 (N–H), 1755, 1742, 1673 and 1649 (C=O), 1597 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 3.55 (3H, s, CH_3), 3.73–4.32 (13H, m, ferrocene+CH–CH+CH_2), 7.15–8.63 (14H, m, arom.), 8.78–8.81 (1H, m, NH), 9.85 and 9.90 (2H, 2s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 172.9, 171.4, 168.0, 167.6, 134.9, 134.3, 134.1, 129.5, 128.9, 128.8, 127.4, 127.3, 127.0, 126.9, 123.6, 123.5, 122.8, 122.7, 86.5, 70.0, 69.6, 68.5, 68.2, 68.1, 60.1, 52.9, 46.9, 42.3; Anal. Calcd for $C_{38}H_{33}FeN_3O_5$ (667.53): C, 68.37; H, 4.98; N, 6.29%. Found: C, 68.62; H, 4.96; N, 6.31%.

*4.2.11. 2-(Ferrocenyl)-N^2-cyclohexyl-N^1,N^1-di-2-naphthylethane-1,1,2-tricarboxamide (**5k**).* Pale yellow solid (0.305 g, 90%); mp 312–314 °C; R_f (50% EtOAc/*n*-hexane) 0.61; IR (KBr) (ν_{max}, cm^{-1}): 3298 and 3280 (N–H), 1675 and 1639 (C=O), 1600 (C=C); ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 1.02–1.89 (10H, m, $5CH_2$), 3.68–3.74 (1H, m, NCH), 4.11–4.47 (11H, m, ferrocene+CH–CH), 7.50–8.11

(14H, m, arom.), 8.32 (1H, br d, $^3J_{HH}$=6.0 Hz, NH), 9.90 (2H, s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 170.3, 167.5, 166.9, 134.2, 134.1, 133.6, 133.3, 128.7, 128.1, 126.6, 126.4, 126.0, 122.8, 122.1, 121.6, 85.8, 69.1, 67.8, 67.4, 60.6, 48.2, 46.4, 33.0, 32.8, 25.7, 25.1, 25.0; Anal. Calcd for $C_{41}H_{39}FeN_3O_3$ (677.61): C, 72.67; H, 5.80; N, 6.20%. Found: C, 72.51; H, 5.77; N, 6.22%.

*4.2.12. N^2-Cyclohexyl-2-(ferrocenyl)-N^1,N^1-dipyridin-3-ylethane-1,1,2-tricarboxamide (**5l**).* Pale yellow solid (0.254 g, 88%); mp 276–278 °C; (50% EtOH/*n*-hexane) 0.78; IR (KBr) (ν_{max}, cm^{-1}): 3268 (N–H), 1680 and 1634 (C=O), 1596 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.01–1.76 (10H, m, 5CH$_2$), 3.52–3.57 (1H, m, NCH), 3.85 (1H, d, $^3J_{HH}$=10.6 Hz, CH), 3.90–4.30 (10H, m, ferrocene+CH), 7.26–8.57 (8H, m, pyridines), 8.70, 9.86 and 9.98 (3H, 3s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 170.7, 167.6, 167.0, 146.0, 145.8, 142.3, 142.2, 136.5, 136.3, 127.8, 127.6, 124.9, 86.0, 69.9, 69.5, 68.6, 68.2, 68.1, 61.8, 48.8, 46.9, 33.6, 33.5, 26.5, 25.8, 25.6; Anal. Calcd for $C_{31}H_{33}FeN_5O_3$ (579.47): C, 64.25; H, 5.74; N, 12.09%. Found: C, 64.07; H, 5.75; N, 12.12%.

*4.2.13. N^1,N^1-Dibenzyl-N^2-cyclohexyl-2-(ferrocenyl)ethane-1,1,2-tricarboxamide (**5m**).* Pale yellow solid (0.257 g, 85%); mp 284–286 °C; (80% EtOAc/*n*-hexane) 0.55; IR (KBr) (ν_{max}, cm^{-1}): 3295 (N–H), 1656 and 1638 (C=O), 1600 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.05–1.80 (10H, m, 5CH$_2$), 3.52–3.58 (2H, m, CH+NHC*H*), 3.90–4.35 (14H, m, ferrocene+CH+2C*H*$_2$Ph), 6.98–7.26 (10H, m, arom.), 7.87 (1H, t, $^3J_{HH}$=5.5 Hz, NHCH$_2$), 7.99 (1H, t, $^3J_{HH}$=5.5 Hz, NHCH$_2$), 8.03 (1H, d, $^3J_{HH}$=7.4 Hz, NHCH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 171.1, 168.7, 168.5, 140.4, 140.1, 129.5, 129.4, 128.2, 128.0, 86.9, 70.1, 69.8, 68.2, 68.1, 67.9, 60.6, 48.9, 46.3, 43.4, 33.7, 33.6, 26.6, 26.0, 25.9; Anal. Calcd for $C_{35}H_{39}FeN_3O_3$ (605.54): C, 69.42; H, 6.49; N, 6.94%. Found: C, 69.67; H, 6.52; N, 6.99%.

*4.2.14. N^1,N^1-Diallyl-N^2-cyclohexyl-2-(ferrocenyl)ethane-1,1,2-tricarboxamide (**5n**).* Pale yellow solid (0.184 g, 73%); mp 276–278 °C; (80% EtOAc/*n*-hexane) 0.57; IR (KBr) (ν_{max}, cm^{-1}): 3306 (N–H), 1663 and 1640 (C=O), 1536 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.09–1.76 (10H, m, 5CH$_2$), 3.41–3.44 (1H, m, NCH), 3.52 (4H, br s, 2 NCH$_2$), 3.64–4.19 (11H, m, ferrocene+CH–CH), 4.86–5.09 (4H, m, 2=CH$_2$), 5.55–5.60 and 5.67–5.72 (2H, 2 m, 2=CH), 7.52, 7.67 and 7.98 (3H, 3 br s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 171.0, 168.7, 168.2, 136.2, 136.0, 116.2, 116.1, 86.7, 69.9, 69.8, 68.2, 68.1, 67.8, 60.4, 48.7, 46.5, 42.0, 33.7, 33.6, 26.6, 25.9, 25.8; Anal. Calcd for $C_{27}H_{35}FeN_3O_3$ (505.43): C, 64.16; H, 6.98; N, 8.31%. Found: C, 63.92; H, 7.01; N, 8.28%.

*4.2.15. 4-(2-Benzoylhydrazino)-3-[(2-benzoylhydrazino)carbonyl]-2-(ferrocenyl)-N-{[(4-methylphenyl)sulfonyl]methyl}-4-oxobutanamide (**5o**).* Pale yellow solid (0.322 g, 86%); mp 224–226 °C; (30% EtOAc/*n*-hexane) 0.53; IR (KBr) (ν_{max}, cm^{-1}): 3258 and 3194 (N–H), 1677 and 1658 (C=O), 1614 (C=C), 1324 and 1142 (SO$_2$); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 2.33 (3H, s, CH$_3$), 3.90–4.16 (11H, m, ferrocene+CH–CH), 4.53–4.56 and 4.87–4.92 (2H, 2 m, NHC*H*$_2$), 7.37–7.90 (14H, m, arom.), 9.17, 10.02, 10.11, 10.64 and 10.72 (5H, 5 br s, 5 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 172.7, 166.9, 166.5, 166.2, 165.5, 145.6, 136.9, 133.4, 133.3, 133.2, 133.1, 131.1, 131.0, 129.7, 129.5, 128.9, 128.8, 86.7, 70.1, 69.1, 68.2, 68.1, 62.2, 55.2, 45.0, 22.3; Anal. Calcd for $C_{37}H_{35}FeN_5O_7S$ (749.61): C, 59.28; H, 4.71; N, 9.34%. Found: C, 59.51; H, 4.70; N, 9.31%.

*4.2.16. 2-(Ferrocenyl)-4-[2-(4-chlorobenzoyl)hydrazino]-3-{[2-(4-chlorobenzoyl)hydrazino]carbonyl}-N-cyclohexyl-4-oxobutanamide (**5p**).* Pale yellow solid (0.308 g, 84%); mp 320–322 °C; R_f (90% EtOAc/*n*-hexane) 0.52; IR (KBr) (ν_{max}, cm^{-1}): 3283 (N–H), 1673 and 1651 (C=O), 1587 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 1.05–1.91 (10H, m, 5CH$_2$), 3.44–3.60 (1H, m, NCH), 3.85 and 3.97 (2H, 2 d, $^3J_{HH}$=10.6 Hz, CH–CH), 4.05–4.28 (9H, m, ferrocene), 7.54–7.94 (8H, m, arom.), 8.06 (1H, d, $^3J_{HH}$=7.8 Hz, NHCH), 9.94, 10.02, 10.64 and 10.82 (4H, 4 br s, 4 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 170.2, 166.2, 165.8, 139.0, 129.2, 124.1, 123.9, 119.7, 119.5, 85.6, 69.0, 68.7, 67.6, 67.2, 61.2, 47.9, 45.8, 32.7, 25.7, 25.0; Anal. Calcd for $C_{35}H_{35}Cl_2FeN_5O_5$ (732.43): C, 57.39; H, 4.82; N, 9.56%. Found: C, 57.50; H, 4.80; N, 9.60%.

*4.2.17. N^2-Cyclohexyl-2-(ferrocenyl)-N^1,N^1,N^1,N^1-tetraethylethane-1,1,2-tricarboxamide (**5q**).* Pale yellow solid (0.198 g, 74%); mp 278–280 °C; (75% EtOAc/*n*-hexane) 0.24; IR (KBr) (ν_{max}, cm^{-1}): 3339 (N–H), 1655 and 1622 (C=O), 1534 (C=C); ^{1}H NMR (400.1 MHz, CDCl$_3$): δ_H 0.91 (6H, t, $^3J_{HH}$=6.7 Hz, 2CH$_3$), 1.05 (6H, t, $^3J_{HH}$=7.0 Hz, 2CH$_3$), 1.13–1.71 (10H, m, 5CH$_2$), 2.51–2.55 (1H, m, NCH), 2.91–3.37 (8H, m, 4CH$_2$), 3.73–4.54 (11H, m, ferrocene+CH–CH), 6.15 (1H, br s, 1 NH); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C 172.4, 168.1, 167.8, 69.7, 68.7, 68.5, 52.0, 49.3, 49.0, 42.5, 42.2, 41.7, 40.3, 33.9, 33.4, 26.4, 25.9, 25.7, 14.8, 14.1, 13.6, 13.1; Anal. Calcd for $C_{29}H_{43}FeN_3O_3$ (537.51): C, 64.80; H, 8.06; N, 7.82%. Found: C, 65.00; H, 8.09; N, 7.79%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.048.

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