Study of the reactivity of squarylferrocenes. Addition of amines and aminoesters

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Abstract
The reactivity of squarylferrocenes was studied in the addition of several *N*-centered nucleophiles. A total of seven simple amines (primary and secondary) were added to both monosquarylferrocene and 1,1′-bissquarylferrocene to generate 14 ferrocenylsquaramides in 85-98%. Likewise, five aminoesters were added to the same scaffolds to produce a novel family of 10 ferrocene-aminoester conjugates in good to excellent yields (57-95%).

Keywords: Ferrocene, squaryl esters, cyclobutenediones, α-aminoesters

Introduction

After over fifty years of its discovery, ferrocene has become the starting material for the preparation of compounds with applications in different fields.[1] One emergent area in which ferrocene is playing already a leading role is bioorganometallic chemistry.[2] Some of the features that render ferrocene a very attractive candidate for applications in bioorganometallic chemistry include: its electroneutrality, chemical stability, redox properties, and non-toxicity.[3] As a result, a large number of reports have appeared in the literature dealing with the synthesis and biological activity of ferrocene bioconjugates.[4] One example that stands out with respect to its antiproliferative activity on mammary tumors is a family of ferrocene-containing Tamoxifen analogues called Ferrocifen (Figure 1).[5]

Similarly, another class of important bioorganometallic compounds with significant medical applications is that of metal-peptide bioconjugates. Some of them have displayed interesting properties such as antiproliferative and anti-bacterial activity.[6] Within this type of compounds, a great deal of efforts has focused on the synthesis and study of the properties of ferrocene-peptides.

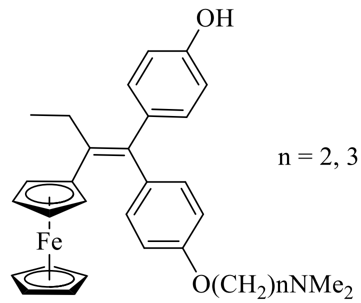
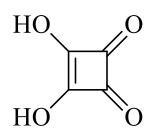


Figure 1. General structure of the Ferrocifen family.

These derivatives are important because they incorporate a redox-active moiety which is, at the same time, a scaffold that may hold two peptide strands within H-bonding distance. Several research groups have disclosed the synthesis of ferrocene-peptides and described their use as: electrochemical biosensors,[7] redox-switching centers, etc.[8]

A different organic fragment that has been attached to peptides is squaric acid or its derivatives. Squaric acid **1** is a very attractive molecule in its own right. It has been used in medicinal chemistry,[9] material science,[10] and organic synthesis.[11]



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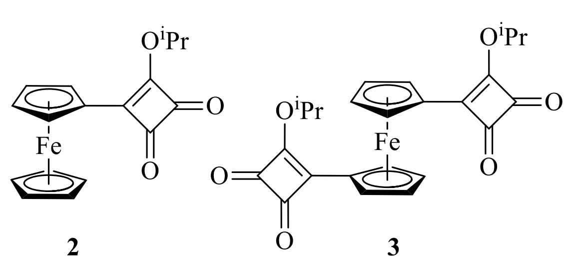
Squaric acid-peptide hybrids have been incorporated to protein conjugates which mimic the polysaccharides found on the cell surfaces of different pathogens.[12] In another example, these compounds have been utilized as inhibitors of Matrix Metalloprotease **1**.[13]

Our group has disclosed the synthesis of squarylferrocenes **2** and **3**[14] and shortly after that, building on our results, Zora *et al*. reported the synthesis of ferrocenylquinones from **2**.[15]



2 **3**

As can be appreciated, **2** and **3** already possess the two fragments whose attractive properties were aforementioned. We now report the initial study of the reactivity of these scaffolds with simple amines and aminoesters which can help pave the way for the preparation of more elaborate organometallic peptides.

The study began with the addition of simple amines to assess the reactivity of both **2** and **3** under mild conditions.[16] The survey was carried out with the amines shown in Figure 2.

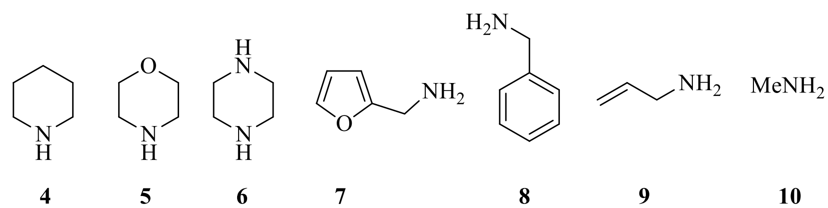


Figure 2. Amines used for reaction with **2** and **3**.

We were pleased with the excellent reactivity displayed by both **2** and **3**. The results are illustrated in Table 1.

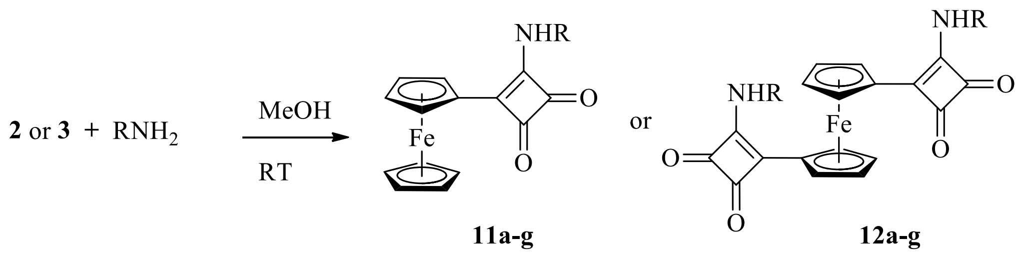


Table 1. Addition of amines **4-10** to squarylferrocenes **2** and **3**

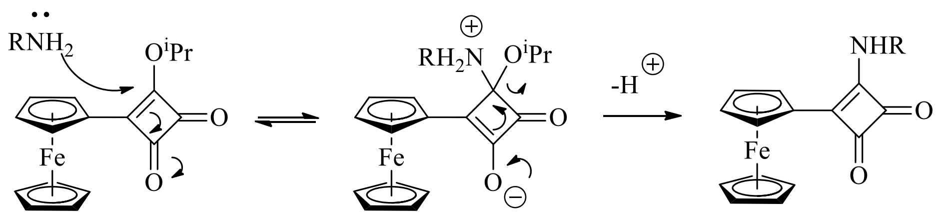
Entry	Amine	Product	Time	% yield[a]
1	**4**	**11a**	1 h	91
2	**5**	**11b**	1 h	98
3	**6**	**11c**	1 h	97
4	**7**	**11d**	30 min	93
5	**8**	**11e**	35 min	85
6	**9**	**11f**	45 min	96
7	**10**	**11g**	40 min	95
8	**4**	**12a**	3 h	95
9	**5**	**12b**	3 h	97
10	**6**	**12c**	2 h	80

Table 1. Continued

Entry	Amine	Product	Time	% Yield[a]
11	**7**	**12d**	2 h	94
12	**8**	**12e**	2 h	93
13	**9**	**12f**	2 h	97
14	**10**	**12g**	2 h	92

[a]Isolated yield. For the series **11a-g**, a 1:2 ratio of **2**:amine was used. For the series **12a-g**, a 1:4 ratio of **3**:amine was used.

The addition of the amines **4-10** to **2** and **3** took place smoothly approaching quantitative yields in several cases. The ^{i}PrO- group in the squarylferrocenes showed excellent reactivity as leaving group in this addition-elimination process (Figure 3).



2 **11**

Figure 3. Addition/elimination process that gives rise to squaramides.

As expected on the basis of steric hindrance, primary amines reacted more rapidly than secondary ones. However, the yield did not decomposedrease. This trend was observed in both **11a-g** and **12a-g** series. Due to the fact that an excess of the amines were used in all cases, no evidence of the double addition product was observed in the case of piperazine in the ^{1}H NMR spectrum of the crude material (entries 3 and 10). No inert atmosphere was required and the reactions took place at room temperature. All of the products were deep red solids that could be purified by simply triturating the crude material with hexanes and ethyl ether.

Next, we turned our attention to the addition of aminoesters to squarylferrocenes **2** and **3**. The aminoester hydrochlorides used are shown in Figure 4.

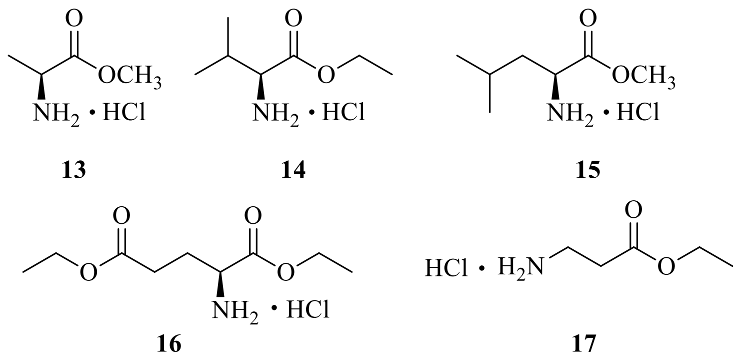


Figure 4. Aminoester hydrochlorides added to squarylferrocenes **2** and **3**.

The results of this study are displayed in Table 2.

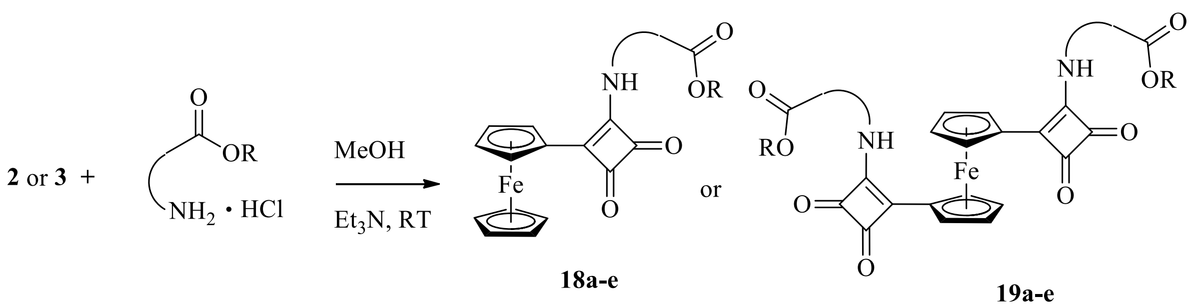


Table 2. Addition of aminoester hydrochlorides **13-17** to squarylferrocenes **2** and **3**

Entry	Aminoester	Product	Time (h)	% Yield[a]
1	**13**	**18a**	4	79
2	**14**	**18b**	4	81
3	**15**	**18c**	4	77
4	**16**	**18d**	4	78
5	**17**	**18e**	1.5	95
6	**13**	**19a**	24	57
7	**14**	**19b**	24	68
8	**15**	**19c**	24	80
9	**16**	**19d**	24	73
10	**17**	**19e**	2	88

[a]Isolated yield. For the series **18a-e**, a 1:2:2 ratio of **2**:aminoester:TEA was used. For the series **19a-e**, a 1:4:4 ratio of **3**:aminoester:TEA was used.

Commercially available aminoester hydrochlorides **13-17** were added to both **2** and **3**. The reaction conditions were basically the same as those specified in Table 1, except for the addition of a stoichiometric amount of Et_3N to liberate the aminoester. The yields were somewhat lower than the case of the addition of simple amines, however, they ranged from acceptable to good. Except for the case of β-alanine (entry 5), an increase in the reaction time was observed in all cases, especially in the addition of the aminoesters to the bis-squarylferrocene **3**. This general observation may be attributed to the increased steric bulk at the position adjacent to the amino group in the aminoesters. As in the case of the addition of simple amines, products **18-19** were dark red solids that were purified by simple trituration of the crude material with hexanes and ethyl ether.

Ferrocenyl derivatives **18a-e** and **19a-e**, once hydrolyzed to the corresponding free carboxylic acids, may be used to incorporate other aminoacids or peptide chains.

Conclusions

Squarylferrocenes **2** and **3** exhibited excellent reactivity toward the addition of both primary and secondary amines. Likewise, aminoester conjugates were prepared in the same fashion in high yields. The possibility to react free amino oligopeptides directly to **2** and **3** in a convergent manner is being currently investigated in our group and will be disclosed in due course.

Experimental Section

General. ^{1}H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) in DMSO-d_6 (2.49 ppm) as internal reference unless otherwise indicated. Data are reported in the following order: chemical shift in ppm (δ), multiplicities (br (broadened)), s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), hep (heptet), m (multiplet), exch (exchangeable), app (apparent), coupling constants, *J*, are reported (Hz), and integration. Infrared spectra were recorded on a Perkin-Elmer FTRI 1600 series spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong 67-100 %), m (medium 40-67 %), and w (weak 20-40%).

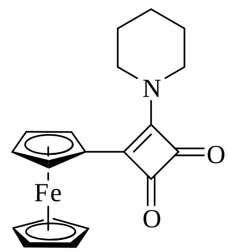
Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Accurate mass spectra were obtained on a Bruker microTOF fitted with an ESI.

General procedure for the synthesis of ferrocene monosquaramides (11a-g)

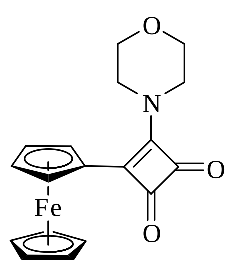
A 20-mL vial was charged with **2** (50 mg, 0.15 mmol, 1 equiv), the corresponding amine (0.30 mmol, 2 equiv), methanol (4 mL), and a magnetic stirrer. The vial was capped and the mixture was stirred until completion whereupon the solvent was removed under reduced pressure. The product was purified by simply trituration with hexanes and ethyl ether.

General procedure for the synthesis of ferrocene bissquaramides (12a-g)

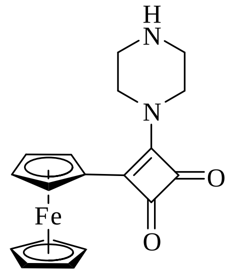
A 20-mL vial was charged with **3**[14b] (50 mg, 0.11 mmol, 1 equiv), the corresponding amine (0.43 mmol, 4 equiv), methanol (4 mL), and a magnetic stirrer. The vial was capped and the mixture was stirred until completion whereupon the solvent was removed under reduced pressure. The product was purified by simply trituration with hexanes and ethyl ether.



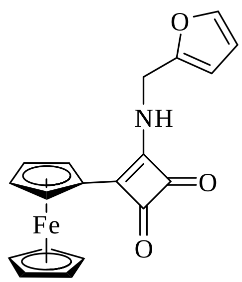
3-Ferrocenyl-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione (11a). Red solid (48 mg, 91 %). TLC (R_f = 0.7, 90% AcOEt/hexanes); mp: 262 ºC (decomposed); IR (KBr, cm^{-1}): 2937 (m), 2869 (m), 1772 (i), 1716 (s), 1603 (s), 1495 (s), 1454 (m), 1357 (m), 1032 (m), 934 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.7 (app t, J = 1.8 Hz, 2H), 4.6 (app t, J = 1.8, 2H), 3.9 (br, 2H), 3.8 (br, 2H), 1.6 (br, 6 H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.9, 188.1, 175.5, 165.1, 79.1, 70.9. 69,7, 68.9, 25.2, 23.0. HRMS FABS $(M+H)^+$ Calcd for $C_{19}H_{20}FeNO_2$: 350.0843. Found: 350.0844. Anal. Calcd for $C_{19}H_{19}FeNO_2$: C, 65.35; H, 5.48; Fe, 15.99; N, 4.01; O, 9.16. Found C, 65.63 ; H, 5.81; N, 3.94.



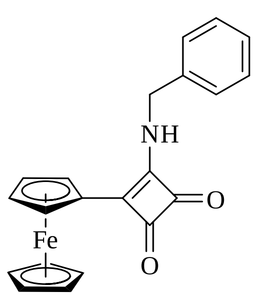
3-Ferrocenyl-4-morpholino-cyclobut-3-ene-1,2-dione (11b). Red solid (51 mg, 98%). TLC (R_f = 0.7, 90% AcOEt/hexanes); mp > 242 ºC (decomposed); IR (KBr): 2918 (m), 1771 (i), 1720 (s), 1604 (s),1498 (i), 1450 (s), 1309 (i)1287 (s), 1022, (m), 909 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.7 (br s, 2H), 4.6 (br s, 2H), 4.2 (s, 5H), 3.9 (br, 4H), 3.8 (br, 4H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.6, 188.1, 175.7, 165.5, 71.0, 70.5, 69.7, 69.1, 65.6. HRMS FABS $(M+H)^+$ Calcd for $C_{18}H_{18}FeNO_3$: 352.0636. Found: 352.0638. Anal. Calcd for $C_{18}H_{17}FeNO_3$: C, 61.56; H, 4.88; Fe, 15.90; N, 3.99; O, 13.67. Found C, 61.66 ; H, 4.95; N, 3.88.



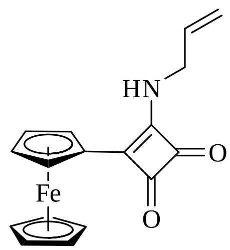
3-Ferrocenyl-4-(piperazin-1-yl)cyclobut-3-ene-1,2-dione (11c). Red solid (51 mg, 97%). TLC (R_f =0.4, 2% MeOH/CH_2Cl_2); mp: 285 ºC (decomposed); IR (KBr, cm^{-1}): 3320 (m), 2359 (m), 1770 (s), 1711 (s), 1602 (m), 1498 (m), 1270 (m), 1135 (m), 1006 (m), 817 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.7 (br, 2H), 4.6 (br, 2H), 4.2 (s, 5 H), 3.8 (br, 4 H), 2.8 (br, 4H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.8, 188.0, 175.4, 165.2, 70.9, 70.8, 69.7, 69.1, 49.6, 46.9, 45.4. HRMS FABS $(M+H)^+$ Calcd for $C_{18}H_{19}FeN_2O_2$: 351.0796. Found: 351.0789. Anal. Calcd for $C_{18}H_{18}FeN_2O_2$: C, 61.74; H, 5.18; Fe, 15.95; N, 8.00; O, 9.14. Found C, 61.69 ; H, 4.99; N, 8.15.



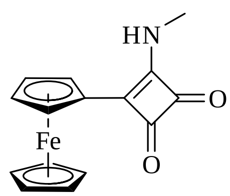
3-Ferrocenyl-4-(furan-2-ylmethyamino)cyclobut-3-ene-1,2-dione (11d). Red solid (50 mg, 93 %). TLC (R_f = 0.7, 90% AcOEt/hexanes); mp= 222 ºC (decomposed); IR (KBr, cm^{-1}): 3144 (m), 2927 (m), 1778 (s), 1712 (s), 1598 (s), 1577 (s), 1522 (s), 1423 (m), 1219 (m), 1148 (m), 1085 (m), 823 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.0 (br, 1H), 7.6 (s, 1H), 6.4 (d, J = 9 Hz, 2H), 5.0 (s, 2H), 4.8 (app d, J = 3.2 Hz, 2H), 4.6 (s, 2H), 4.14 (s, 5H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.6, 188.2, 177.8, 168.0, 151.3, 142.9, 110.6, 107.8, 71.4, 69.8, 67.5. HRMS FABS $(M+H)^+$ Calcd for $C_{19}H_{16}FeNO_3$: 362.0479. Found: 362.0462. Anal. Calcd for $C_{19}H_{15}FeNO_3$: C, 63.18; H, 4.19; Fe, 15.46; N, 3.88; O, 13.29. Found C, 63.28 ; H, 4.24; N, 3.97.



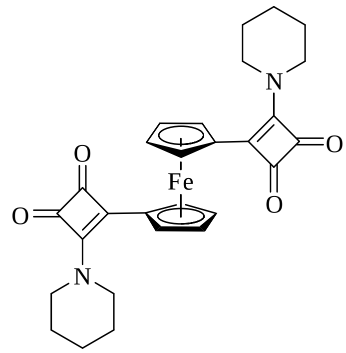
3-Benzylamino-4-ferrocenylcyclobut-3-ene-1,2-dione (11e). Red solid (47 mg, 85%). TLC (R_f = 0.90, 90% AcOE/hexanes); mp= 266 ºC (decomposed); IR (KBr, cm^{-1}): 3109 (m), 2927 (m), 1777 (s), 1706 (s), 1576 (s), 1515 (s), 1455 (m), 1440 (m), 1228 (m), 1170 (m), 1028 (m), 925 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.1 (br, 1H), 7.3 (s, 5H), 5.1 (s, 2H), 4.9 (d, *J* = Hz, 2H), 4.6 (s, 2H), 4.2 (s, 5H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.8, 188.0, 177.6, 167.8, 138.5, 128.6, 127.4, 127.3, 71.3, 69.9, 69.7, 67.4, 47.1. HRMS FABS $(M+H)^+$ Calcd for $C_{21}H_{18}FeNO_2$: 372.0687. Found: 372.0678. Anal. Calcd for $C_{21}H_{17}FeNO_2$: C, 67.95; H, 4.62; Fe, 15.04; N, 3.77; O, 8.62. Found C, 68.18 ; H, 4.37; N, 3.61.



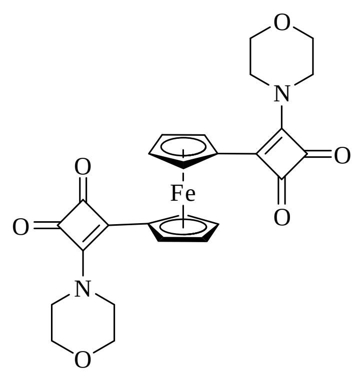
3-Allylamino-4-ferrocenylcyclobut-3-ene-1,2-dione (11f). Red solid (46 mg, 96%). TLC (R_f =0.8, 90% AcOEt/hexanes); mp: 235 ºC (decomposed); IR (KBr, cm^{-1}): 3153 (m), 1777 (s), 1709 (s), 1580 (s), 1514 (s), 1422 (m), 925.4 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.7 (br, 1H), 5.9 (m, 1H), 5.2 (d, *J*= 7 Hz, 1H), 5.2 (s, 1H), 5.1 (s, 2H), 4.6 (s, 2H), 4.3 (br s, 2H), 4.2 (s, 5H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.7, 188.2, 177.8, 167.5, 135.2, 116.0, 71.3, 70.0, 69.7, 67.4, 45.8. HRMS FABS $(M+H)^+$ Calcd for $C_{17}H_{16}FeNO_2$: 322.0530. Found: 322.0519. Anal. Calcd for $C_{17}H_{15}FeNO_2$: C, 63.58; H, 4.71; Fe, 17.39; N, 4.36; O, 9.96. Found C, 63.36 ; H, 4.53; N, 4.33.



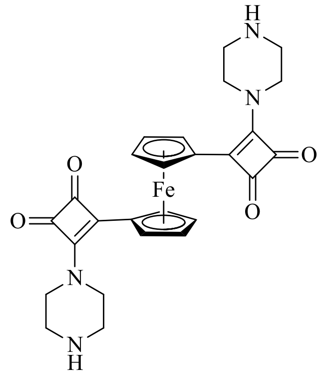
3-Ferrocenyl-4-methylaminocyclobut-3-ene-1,2-dione (11g). Red solid (42 mg, 95%). TLC (R_f = 0.7, 90% AcOEt/hexanes); mp: 271 ºC (decomposed); IR (KBr, cm^{-1}): 3155 (m), 2931 (m), 1777 (s), 1715 (s), 1586 (s), 1521 (s), 1412 (s), 1393 (s), 1003 (m), 927 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.4 (br s, 1H), 5.0 (br s, 2H), 4.6 (br s, 2H), 4.2 (s, 5H), 3.3 (d, *J*= 5, 3H). ^{13}C NMR (50 MHz, DMSO-d_6): 192.2, 188.1, 178.1, 167.0, 71.1, 70.2, 69.7, 67.3, 30.8. HRMS FABS $(M+H)^+$ Calcd for $C_{15}H_{14}FeNO_2$: 296.0374. Found: 296.0365. Anal. Calcd for $C_{15}H_{13}FeNO_2$: C, 61.05; H, 4.44; Fe, 18.92; N, 4.75; O, 10.84. Found C, 61.35; H, 4.29; N, 4.56.



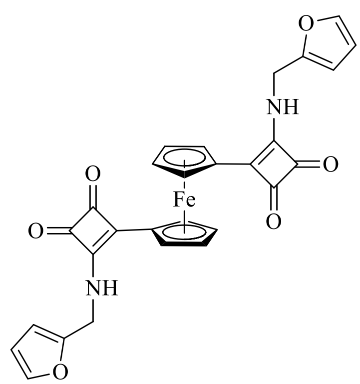
4,4′-(1,1′-Ferrocenyl)bis(3-(piperidin-1-yl)cyclobut-3-ene-1,2-dione) (12a). Red solid (52 mg, 95%). TLC (R_f = 0.2, CH_2Cl_2 / MeOH / CH_3CO_2H, 7:4:1); mp: 288 ºC (decomposed); IR (KBr, cm^{-1}): 3090 (w), 2945 (m), 2864 (m),1769 (s), 1722 (s), 1618 (s), 1499 (s), 1451 (s), 1397 (m), 1284 (m), 1025 (m), 933 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.9 (app t, J = 1.8 Hz, 4H), 4.5 (app t, J = 1.8 Hz, 4H), 3.9 (app d, J = 5.4 Hz, 4H), 3.4 (app d, J = 5.2 Hz, 4H), 1.7 (br s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): 192.5, 188.6, 177.3, 161.9, 76.0, 72.2, 70.7, 50.3, 48.3, 25.9, 25.3, 23.5. HRMS FABS $(M+H)^+$ Calcd for $C_{28}H_{29}FeN_2O_4$: 513.1477. Found: 513.1500. Anal. Calcd for $C_{28}H_{28}FeN_2O_4$: C, 65.64; H, 5.51; Fe, 10.90; N, 5.47; O, 12.49. Found C, 65.36; H, 5.73; N, 5.38.



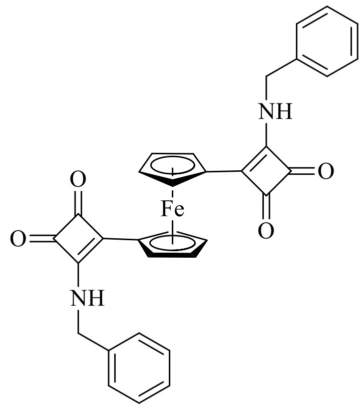
4,4′-(1,1′-Ferrocenyl)bis(3-morpholinocyclobut-3-ene-1,2-dione) (12b). Red solid (54 mg, 97%). TLC (R_f = 0.5, CH_2Cl_2/MeOH/CH_3CO_2H); mp: 276 ºC (decomposed); IR (KBr, cm^{-1}): 2963 (m), 2865 (m), 1774 (s), 1724 (s),1615 (s)1498 (s), 1399 (m), 1277 (m), 1071 (m), 908 (m). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.9 (br s, 4H), 4.5 (br s, 4H), 4.0 (br s, 2H), 3.88 (br s, 4H), 3.5 (br s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 192.1, 188.7, 177.5, 162.3, 75.6, 72.6, 70.8, 66.7, 65.8, 49.1, 47.3. HRMS FABS $(M+H)^+$ Calcd for $C_{26}H_{25}FeN_2O_6$: 517.1062. Found: 517.1032. Anal. Calcd for $C_{26}H_{24}FeN_2O_6$: C, 60.48; H, 4.69; Fe, 10.82; N, 5.43; O, 18.59. Found C, 60.40; H, 4.71; N, 5.48.



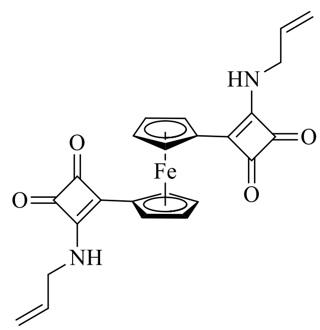
4,4′-(1,1′-Ferrocenyl)bis(3-(piperazin-1yl)cyclobut-3-ene-1,2-dione) (12c). *Six equiv of piperazine were used*. Red solid (44 mg, 80%). TLC (R_f = 0.15, CH_2Cl_2 / MeOH / CH_3CO_2H, 7:4:1); mp: 247 ºC (decomposed); IR (KBr, cm^{-1}): 3344 (w), 2921 (m), 2831 (m), 1770 (s), 1721 (s), 1615 (s), 1496 (s), 1273 (m). ^1H NMR (200 MHz, DMSO-d_6): δ 4.82 (br s, 4H), 4.65 (br s, 4 H), 3.76 (br s, 4 H), 2.83 (br s, 10 H). ^{13}C NMR (50 MHz, DMSO-d_6): 192.3, 189.1, 176.7, 167.3, 72.2, 71.8, 70.4, 50.4, 47.9, 46.2. HRMS FABS $(M+H)^+$ Calcd for $C_{26}H_{27}FeN_4O_4$: 515.1382. Found: 515.1395. Anal. Calcd for $C_{26}H_{26}FeN_4O_4$: C, 60.71; H, 5.10; Fe, 10.86; N, 10.89; O, 12.44. Found C, 60.48; H, 5.31; N, 10.95.



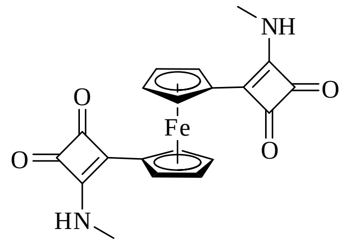
4,4′-(1,1′-Ferrocenyl)bis(3-(furan-2-ylmethylamino)cyclobut-3-ene-1,2-dione) (12d). Red solid (54 mg, 94%). TLC (R_f = 0.15, CH_2Cl_2 / MeOH / CH_3CO_2H, 7:4:1); mp: 263 ºC (decomposed); IR (KBr): 3259 (m), 2953 (m), 1775 (i), 1720 (s),1578 (s), 1515 (s), 1425 (m), 1082 (m), 1012 (m), 923 (m), 496 (m). ^1H NMR (200 MHz, DMSO-d_6): δ 9.01(br s, 2H), 7.63 (s, 2H), 6.42 (s, 4H), 5.07 (br s, 4H), 4.76 (d, J = 5 Hz, 4H), 4.63 (br s, 4H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.9, 187.9, 177.2, 163.9, 150.9, 142.9, 110.6, 108.1, 72.6, 72.4, 68.7. HRMS FABS $(M+H)^+$ Calcd for $C_{28}H_{21}FeN_2O_6$: 537.0749. Found: 537.0765. Anal. Calcd for $C_{28}H_{20}FeN_2O_6$: C, 62.71; H, 3.76; Fe, 10.41; N, 5.22; O, 17.90. Found C, 62.66; H, 3.79; N, 5.11.



4,4′-(1,1′-Ferrocenyl)bis(3-(benzylamino)cyclobut-3-ene-1,2-dione) (12e). Violet solid (56 mg, 93%). TLC (R_f = 0.2, CH_2Cl_2 / MeOH / CH_3CO_2H, 7:4:1); mp: 256 ºC (decomposed); IR (KBr, cm^{-1}): 3154 (m), 3050 (m), 1775 (m), 1718 (s), 1584 (m), 1514 (m), 1436 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.0 (t, *J* = 6 Hz, 2H), 7.4 (s, 10H), 5.1 (br s, 4H), 4.8 (d, *J* = 6 Hz, 4H), 4.6 (br s, 4H). ^{13}C NMR (50 MHz, DMSO-d_6): 192.3, 187.9, 177.2, 163.7, 138.2, 128.6, 127.5, 72.9, 72.4, 68.6, 47.4. HRMS FABS $(M+H)^+$ Calcd for $C_{32}H_{25}FeN_2O_4$: 557.1164. Found: 557.1137. Anal. Calcd for $C_{32}H_{24}FeN_2O_4$: C, 69.08; H, 4.35; Fe, 10.04; N, 5.03; O, 11.50. Found C, 68.75; H, 3.02; N, 4.96.



4,4′-(1,1′-Ferrocenyl)bis(3-(allylylamino)cyclobut-3-ene-1,2-dione) (12f). Red solid (47 mg, 97%). TLC (R_f = 0.2, CH_2Cl_2 / MeOH / CH_3CO_2H, 7:2:1); mp: 272 ºC (decomposed); IR (KBr): 3440 (s), 3072 (m), 3008 (m), 2249 (s), 2123 (s), 1772 (s), 1715 (s), 1659 (m), 1603 (m), 1508 (m) 1226 (s), 1027 (s), 679 (s), 668 (s), 474 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.7 (t, *J* = 6.2 Hz, 2H), 6.0 (m, 2H), 5.2 (d, *J* = 11 Hz, 4H), 5.1 (d, *J* = 3.2 Hz, 4H), 5.0 (s, 4H), 4.6 (s, 4H), 4.2 (t, *J* = 5.4, 4H). ^{13}C NMR (50 MHz, DMSO-d_6): 191.9, 187.8, 177.1, 163.2, 134.8, 116.5, 72.9, 72.1, 68.42, 46.0. HRMS FABS $(M+H)^+$ Calcd for $C_{24}H_{21}FeN_2O_4$: 457.0851. Found: 457.0877. Anal. Calcd for $C_{24}H_{20}FeN_2O_4$: C, 63.18; H, 4.42; Fe, 12.24; N, 6.14; O, 14.03. Found C, 63.28; H, 4.22; N, 6.25.



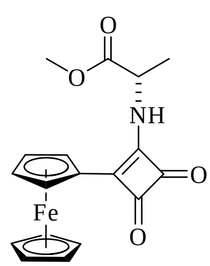
4,4′-(1,1′-Ferrocenyl)bis(3-(methylamino)cyclobut-3-ene-1,2-dione) (12g). Red solid (40 mg, 92%). TLC (R_f =0.3, CH_2Cl_2 / MeOH / CH_3CO_2H, 7:4:1); mp: 230 ºC (decomposed); IR (KBr, cm^{-1}): 3446 (s), 3070 (s), 3009 (s), 1772 (s), 1715 (s), 1654 (m), 1617 (m), 1514 (m), 1057 (s), 1028 (s), 1008 (s), 760 (m), 474 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.32 (d, J = 4.6Hz, 2H), 5.02 (br s, 4H), 4.64 (br s, 4H), 3.142 (d, J = 4.6 Hz, 6H). ^{13}C NMR (50 MHz, DMSO-d_6): 192.5, 187.9, 177.2, 162.2, 73.7, 72.1, 68.2, 30.7. HRMS FABS $(M+H)^+$ Calcd for $C_{20}H_{17}FeN_2O_4$: 405.0538. Found: 405.0562. Anal. Calcd for $C_{20}H_{16}FeN_2O_4$: C, 59.43; H, 3.99; Fe, 13.82; N, 6.93; O, 15.83. Found C, 59.08; H, 3.71, N, 6.82.

General procedure for the synthesis of ferrocene monosquaramides (18a-e)

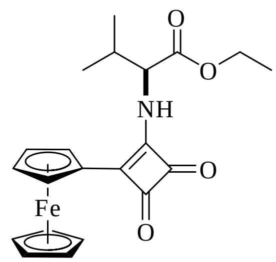
A 20-mL vial was charged with **2** (50 mg, 0.15 mmol, 1 equiv), the corresponding aminoester hydrochloride (0.30 mmol, 2 equiv), triethylamine (0.30 mmol, 2 equiv), methanol (4 mL), and a magnetic stirrer. The vial was capped and the mixture was stirred until completion whereupon the solvent was removed under reduced pressure. The product was purified by simply trituration with hexanes and ethyl ether.

General procedure for the synthesis of ferrocene bissquaramides (19a-e)

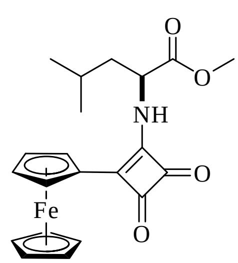
A 20-mL vial was charged with **3** (50 mg, 0.11 mmol, 1 equiv), the corresponding aminoester hydrochloride (0.43 mmol, 4 equiv), triethylamine (0.43 mmol, 4 equiv), methanol (4 mL), and a magnetic stirrer. The vial was capped and the mixture was stirred until completion whereupon the solvent was removed under reduced pressure. The product was purified by simply trituration with hexanes and ethyl ether.



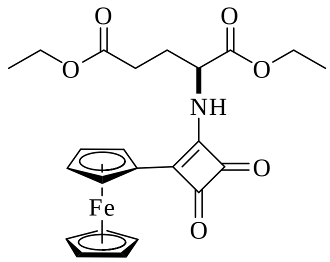
Methyl (*R*)-2-(3,4-dioxo-2-ferrocenylcyclobut-1-enylamino)propanoate (18a). According to GP. Red solid (43 mg, 79%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.7); mp = 170-171 ºC. $[\alpha]^{20}_D$= +27.7 (c = 0.01, CH_3CN). IR (KBr, cm^{-1}): 3334 (m), 2967 (m), 1776 (s), 1731 (s), 1598 (s), 1509 (s), 1463 (s), 1333 (m), 1266 (m), 1122 (m), 1026 (m), 818 (m). ^{1}H NMR (200 MHz, CD_3CN): δ 6.8 (br s, 1H), 5.1 (q, *J*= 7.2 Hz, 1H), 4.92 (br s, 2H), 4.6 (app d, *J* =1.6 Hz, 2H), 4.22 (s, 5H), 3.74 (s, 3H), 1.63 (d, *J*= 7.4 Hz, 3H); ^{13}C NMR (50 MHz, CD_3CN): δ 192.3, 190.0, 179.5, 173.2, 169.9, 72.8, 71.1, 68.9, 68.8, 53.7, 53.4, 18.8. Anal. Calcd for $C_{18}H_{17}FeNO_4$: C, 58.88; H, 4.67; N, 3.81. Found: C, 58.79; H, 4.56; N, 3.79.



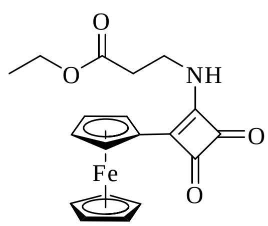
Ethyl (*R*)-2-(3,4-dioxo-2-ferrocenylcyclobut-1-enylamino)-3-methylbutanoate (18b). According to GP. Red solid (50 mg, 81%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.7); mp = 135-136 ºC. $[\alpha]^{20}_D$ = -4.11 (c= 0.01, CH_3CN). IR (KBr, cm^{-1}): 3309 (m), 2967 (m), 1780 (i), 1736 (s), 1717 (s), 1597 (s) 1505 (s), 1465 (s), 1330 (m), 1222 (m), 1119 (m), 1041 (m), 1024 (m), 863 (m). ^{1}H NMR (200 MHz, CD_3CN): δ 6.7 (d, *J* = 9.4 Hz, 1H), 4.9 (br s, 2H), 4.8 (t, *J* = 6.4 Hz, 1H), 4.6 (app t, *J* = 2 Hz, 2H), 4.2 (q, overlapped, 2H), 4.2 (s, 5H), 2.4 (m, 1H), 1.3 (t, *J* = 7 Hz, 3H), 1.1 (d, *J* =2 Hz, 6H). ^{13}C NMR (50 MHz, CD_3CN): δ 192.3, 179.5, 171.6, 170, 72.7, 71.1, 70.6, 69.0, 68.8, 63.4, 62.5, 32.5, 19.3, 18.4, 14.6. Anal. Calcd for $C_{21}H_{23}FeNO_4$: C, 61.63; H, 5.66; N, 3.42. Found: C, 61.71; H, 5.54; N, 3.49.



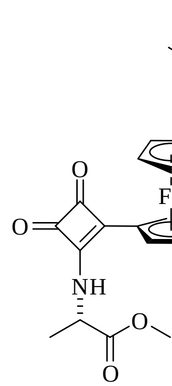
Methyl (*R*)-2-(3,4-dioxo-2-ferrocenylcyclobut-1-enylamino)-4-methylpentanoate (18c). According to GP. Red solid (47 mg, 77%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.7); mp = 162-164 ºC. $[\alpha]^{20}_D$ = -18.11 (c= 0.01, CH_3CN); IR (KBr, cm^{-1}): 3309 (m), 2967 (m), 1780 (s), 1736 (s), 1717 (s), 1597 (s), 1505 (s), 1465 (s), 1330 (m), 1222 (m), 1119 (m), 1024 (m), 863 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.7 (d, *J* = 8.6 Hz, 1H), 5. (app d, *J* =5 Hz, 2H), 5.0 (q, *J*= 3 Hz, 1H), 4.6 (app t, *J* =1.8 Hz, 2H), 4.2 (s, 5H), 3.7 (s, 3H), 1.9 (m, 1H), 1.7 (app t, *J* = 5.2 Hz, 2H), 0.97 (two d, *J* = 5.8 Hz, 6H). ^{13}C NMR (50 MHz, CD_3CN): δ 192.3, 189.9, 179.5, 173.1, 170.2, 72.8, 71.1, 70.5, 69.0, 68.7, 56.5, 53.3, 41.5, 25.6, 23.4, 21.3. Anal. Calcd for $C_{21}H_{23}FeNO_4$: C, 61.63; H, 5.66; N, 3.42. Found: C, 61.52; H, 5.45; N, 3.71.



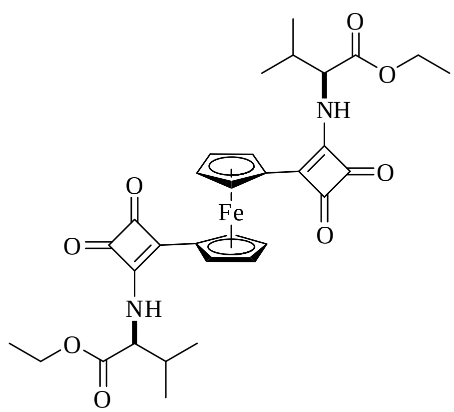
Diethyl (*R*)-2-(3,4-dioxo-2-ferrocenylcyclobut-1-enylamino)pentanedioate (18d). According to GP**.** Red solid (55 mg, 78%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.7); mp= 131-132 ºC. $[\alpha]^{20}_{D}$= -26.04 (c=0.01, CH_3CN). IR (KBr, cm^{-1}): 3193 (m), 2980 (m), 1776 (s), 1738 (s), 1738 (s), 1711 (s), 1582 (s), 1464 (s), 1227 (m), 1110 (m), 1026 (m), 820 (m). ^{1}H NMR (200 MHz, CD_3CN): δ 6.9 (d, *J*= 8.2 Hz, 1H), 4.9 (br s, 2 H), 4.6 (br s, 2 H), 4.2 (s, 5H), 4.2 (overlapped, 2H), 4.1 (q, *J* = 7 Hz, 2H), 2.56 (t, *J*=7.2 Hz, 2H), 2.3 (t, *J*= 6.8 Hz, 1H), 2.1(app q, *J*= 6.4 Hz, 2H), 1.3 (m, *J* = 7 Hz, *J* = 6.6 Hz, 6H). ^{13}C NMR (50 MHz, CD_3CN): δ 192.2, 190.0, 179.8, 173.7, 171.8, 170.2, 72.8, 71.1, 70.4, 68.9, 68.8, 62.8, 61.5, 57.4, 31.2, 28.0, 14.5. Anal. Calcd for $C_{23}H_{25}FeNO_6$: C, 59.12; H, 5.39; N, 3.00;. Found: C, 59.02; H, 5.51; N, 3.28.



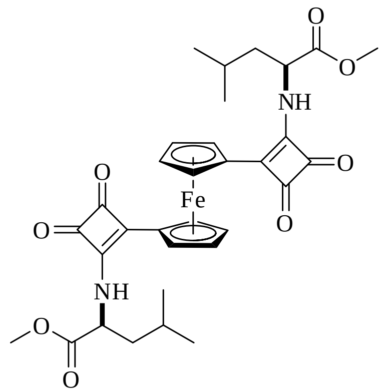
Ethyl 3-(3,4-dioxo-2-ferrocenylcyclobut-1-enylamino)propanoate (18e). According to GP**.** Red solid (53 mg, 94%; TLC (4% MeOH/CH_2Cl_2, R_f = 0.5); mp = 154-155 ºC; IR (KBr, cm^{-1}): 3161 (m), 2934 (m), 1777 (s), 1739 (s), 1708 (s)1580 (s), 1518 (s), 1433 (s),1373 (s), 1265 (s),1105 (m),1043 (m), 840 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.5 (br s, 1H), 5.0 (app t, *J* = 2 Hz, 2H), 4.6 (app t, *J* = 2 Hz, 2H) 4.1 (s, 5H), 4.1 (q, *J* = 7.2 Hz, 2H), 3.9 (q, *J* = 6.6 Hz, 2H), 2.7 (t, *J* = 6.4 Hz, 2H), 1.2 (t, *J* = 7 Hz, 3H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 191.5, 188.0, 177.9, 170.6, 167.0, 71.2, 69.8, 69.6, 67.3, 60.0, 34.7, 15.1. Anal. Calcd for $C_{19}H_{19}FeNO_4$: C, 59.86; H, 5.02; N, 3.67. Found: C, 59.67; H, 4.13; N, 3.79.



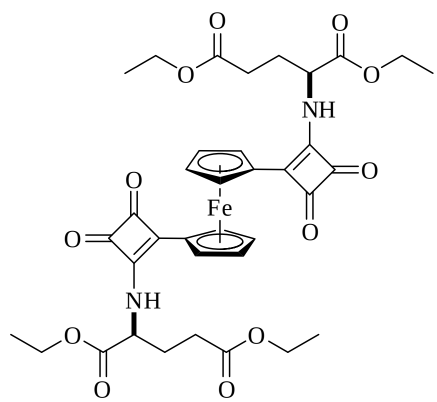
Dimethyl (*2R,2′R*)-2,2′-[2,2′-(1,1′-ferrocenyl)bis(3,4-dioxocyclobut-1-ene-2,1-diyl)]bis(azanediyl) dipropanoate (19a). According to GP. Violet solid (33 mg, 57%); TLC (4% MeOH/ CH_2Cl_2, R_f = 0.5); mp = 270 ºC (decomposed). $[\alpha]^{20}_D$ = +47.7 (c = 0.01, CH_3CN). IR (KBr, cm^{-1}): 3329 (m), 1778 (s), 1728 (s), 1599 (s), 1467 (s), 1395 (m), 1339 (m), 1120 (m). ^1H NMR (200 MHz, DMSO-*d*$_6$): δ 8.6 (d, *J* = 8.2 Hz, 2H), 4.8 (q, *J* = 7.2 Hz, 2H), 4.7 (br s, 4H), 4.6 (br s, 4H), 3.6 (s, 6H), 1.5 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (50 MHz, DMSO-*d*$_6$): δ 192.3, 191.6, 191.0, 174.4, 172.1, 79.6, 74.2, 70.2, 69.5, 52.5, 22.4. Anal. Calcd for $C_{26}H_{24}FeN_2O_8$: C, 56.95; H, 4.41; N, 5.11. Found: C, 56.69; H, 4.68; N, 5.37.



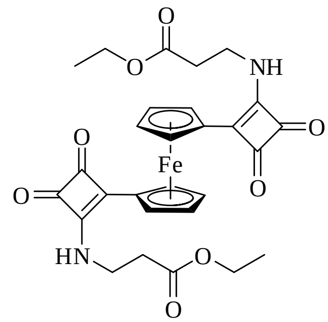
Diethyl (*2R,2′R*)-2,2′-(2,2′-(1,1′-ferrocenyl)bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl) bis(3-methylbutanoate) (19b). According to GP. Red solid (46 mg, 68%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.5); mp = 277 ºC (decomposed). $[\alpha]^{20}_D$ = -32.2 (c= 0.01, CH_3CN); IR (KBr, cm^{-1}): 3335 (m), 2968 (m), 1775 (s), 1731 (s), 1598 (s) 1513 (s), 1462 (m), 1333 (m), 1039 (m), 842 (m). ^1H NMR (200 MHz, CD_3CN): δ 6.9 (d, *J* = 9 Hz, 2H), 4.9 (app d, *J* = 5.2 Hz, 4H), 4.8 (dd, *J* = 6 Hz, *J* = 3.2 Hz, 2H), 4.6 (br s, 4 H), 4.3 (q, *J* = 6.6 Hz, 4H), 2.3 (m, 2H), 1.3 (t, *J* = 7 Hz, 6H), 1.1 (dd, *J* = 3.4 Hz, 12 H). ^{13}C NMR (50 MHz, DMSO-*d*$_6$): δ 191.7, 188.1, 178.1, 170.3, 165.5, 73.0, 71.6, 69.6, 69.1, 62.1, 61.0, 30.6, 18.7, 18.5, 14.0. Anal. Calcd for $C_{32}H_{36}FeN_2O_8$: C, 60.77; H, 5.74; N, 4.43. Found: C, 60.90; H, 5.68; N, 4.59.



Dimethyl (*2R,2′R*)-2,2′-(2,2′-(1,1′-ferrocenyl)bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis (azanediyl)bis(4-methylpentanoate) (19c). According to GP. Red solid (54 mg, 80%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.4); mp= 235 ºC (decomposed). $[\alpha]^{20}_D$ = -33.39 (c= 0.01, CH_3CN); IR (KBr, cm^{-1}): 3263 (m), 2958 (m), 1775 (s), 1746 (s), 1720 (s), 1589 (s), 1510 (s) 1460 (m)1213 (m), 830 (m). ^1H NMR (200 MHz, CD_3CN): δ 7.2 (d, *J* = 9.4 Hz, 2H), 5.0 (q, 2H), 4.9 (d, 1.8 Hz, 4H), 4.6 (d, 1.8H, 4H), 3.7 (s, 6H), 1.8 (t, *J*= 10.4 Hz, 4H), 1.6 (m, 1H), 1.0 (t, *J* = 4.2 Hz, 12 H). ^{13}C NMR (50 MHz, CD_3CN): δ 192.48, 190, 180.12, 173.28, 167.49, 74.82, 74.61, 70.25, 69.8, 56.6, 53.3, 41.6, 25.5, 23.3, 21.5. Anal. Calcd for $C_{32}H_{36}FeN_2O_8$: C, 60.77; H, 5.74; N, 4.43. Found: C, 60.90; H, 5.68; N, 4.58.



Tetraethyl (*2R,2′R*)-2,2′-(2,2′-(1,1′-ferrocenyl)bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis (azanediyl)dipentanoate (19d). According to GP. Red solid (59 mg, 73%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.5); mp = 129-130 ºC. $[\alpha]^{20}_D$ = -59.07 (c = 0.01, CH_3CN); IR (KBr): 3340 (m), 2981 (m), 1777 (s), 1733 (s), 1601 (s), 1513 (s), 1461 (m), 1329 (m), 1027 (m), 927 (m). ^1H NMR (200 MHz, CD_3CN): 7.3 (d, *J* = 8.6 Hz, 2H), 4.9 (d, *J* = 8.6 Hz, 4H), 4.7 (d, *J* = 10.2 Hz, 4H), 4.3 (m, 8H), 2.6 (t, *J* = 6.6 Hz, 4H), 2.4 (m, 2H), 2.2 (m, 4H), 1.3 (m, 12H). ^{13}C NMR (50 MHz, CD_3CN): δ 192.4, 189.9, 180.3, 173.9, 171.8, 74.7, 74.4, 72.7, 70.2, 69.7, 62.9, 61.5, 57.6, 31.2, 27.9, 14.5. Anal. Calcd for $C_{36}H_{40}FeN_2O_{12}$: C, 57.76; H, 5.39; N, 3.74. Found: C, 57.91; H, 5.12; N, 3.89.



Diethyl 3,3′-(2,2′-(1,1′-ferrocenyl)bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl) dipropanoate (19e). According to GP. Red solid (55 mg, 88%); TLC (4% MeOH/CH_2Cl_2, R_f = 0.3); mp = 210-211 ºC; IR (KBr): 3290 (m), 2985 (m), 1770 (s), 1729 (s), 1576 (s), 1513 (s), 1389 (m), 1319 (m), 1044 (m), 924 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.4 (br s 2H), 5.0 (s, 4H), 4.6 (s, 4H), 4.1 (q, *J* = 7 Hz, 4H), 3.8 (q, *J* = 6 Hz, 4H), 2.7 (t, *J* = 7 Hz, 4H), 1.2 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 191.8, 187.8, 177.2, 170.6, 162.5, 73.0, 72.2, 68.3, 60.1, 34.5, 13.9. Anal. Calcd for $C_{28}H_{28}FeN_2O_8$: C, 58.35; H, 4.90; N, 4.86. Found: C, 58.62; H, 4.98; N, 4.79.

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