Supporting Information for:

Synthesis, Characterization, and Anticancer Activity of Folate γ-ferrocenyl conjugates

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1. General Information

1.1 Materials

All chemicals were purchased from Sigma-Aldrich and used without further purification except when mentioned. Folate deficient RPMI-1640 and 0.25% trypsin−ethylenediaminetetraacetic acid (EDTA) solution were purchased from Gibco. Fetal bovine serum (FBS) and Dulbecco's modified phosphate-buffered saline (DMPBS) (pH 7.4) were purchased from Nutricell Nutrientes Celulares (Campinas, SP, Brazil). FBS was inactivated by heating at 56 °C for 30 min as described by Gibco. Reactions dealing with air and moisture sensitive compounds were carried out using the Schlenk line technique. Pteroyl azide **14** and its intermediates (compounds **15**, **16**, and **17**) were prepared according to the literature.[1] Dried tetrabutylammonium fluoride was prepared according to the literature.[2]

1.2 Nuclear Magnetic Resonance (NMR) Spectroscopy

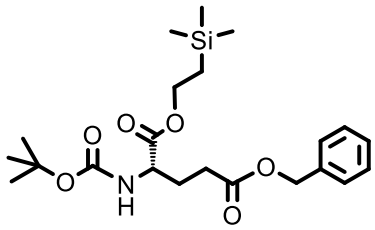
One-dimensional NMR spectra (^{1}H and ^{13}C) and two-dimensional NMR contour maps ([^{1}H-^{1}H]-COSY, and [^{1}H-^{13}C]-HSQC) were recorded on a Bruker AVANCE 400, Bruker AVANCE 500 or a Bruker Avance-III 600 MHz spectrometer at 298 K. Deuterated solvents were used as the lock. Chemical shifts (δ) are reported in parts per million (ppm) using the deuterated solvent residual peaks as the reference. The following abbreviations were used to denote the peak multiplicities: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *qui* = quintet, *m* = multiplet, and *br* = broad.

1.3 Mass Spectrometry (MS)

Mass spectra were obtained in a Waters Xevo Q-TOF (ESI-QTOF) mass spectrometer, in positive or negative mode depending on the target product. Samples solution in methanol or acetonitrile with 0.1% (v/v) of formic acid were injected into the mass spectrometer. Before each analysis, the spectrometer was externally calibrated with phosphoric acid ranging from 99 to 980 m/z.

2. Syntheses

2.1 Compound 1



Chemical Formula: $C_{22}H_{35}NO_6Si$
Exact Mass: 437.22
Molecular Weight: 437.61

In an air-free Schlenk flask, Boc-Glu(OBzl)-OH (4.45 mmol, 1.5 g), 4-(dimethylamino)pyridine (0.1 eq, 0.44 mmol, 54.4 mg) and 2-(trimethylsilyl)ethanol (1.5 eq, 6.68 mmol, 789 mg, 957 μL) were dissolved in 100 mL of anhydrous dichloromethane. The mixture was stirred under nitrogen atmosphere at 0 °C, and N,N′-dicyclohexylcarbodiimide (1.2 eq, 5.34 mmol, 1.1 g) was added. The solution was stirred overnight at room temperature. The mixture was filtered to remove the dicyclohexylurea and further purified by column chromatography using silica gel and hexane:ethyl acetate (solvent mixture gradient from 90:10 until 30:70) as eluent. Compound **2** was obtained as a colorless oil in 90% yield (1.700 g).

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.34 (*m*, Ar-*H*, 5H), 5.13 (*m*, N*H*Boc, OBzlC*H*$_2$, 3H), 4.30 (*m*, C*H*NHBoc, 1H), 4.21 (*m*, CO_2CH_2, 2H), 2.45 (*m*, CH_2CO_2, 2H), 2.24-2.16 (*m*, CHC*H*$_2$, 1H), 2.00-1.90 (*m*, CHC*H*$_2$', 1H), 1.43 (*s*, $CO_2C(CH_3)_3$), 9H), 1.00 (*m*, C*H*$_2$Si, 2H), 0.04 (*s*, Si(C*H*$_3$)$_3$, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz), δ (ppm): 172.6 (CO_2), 172.4 (CO_2), 155.4 (HN*C*O), 80.0 ($C_q(CH_3)_3$), 66.6 ($CO_2CH_2CH_2Si$), 64.0 (CO_2CH_2OBzl), 53.1 (N*C*H), 30.4 (CH_2CO_2), 28.0 ($C_q(CH_3)_3$), 28.0 ($CH_2CH_2CO_2$), 17.5 (CH_2Si), -1.4 ($Si(CH_3)_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{22}H_{35}NO_6Si$: 438.23, found 438.56.

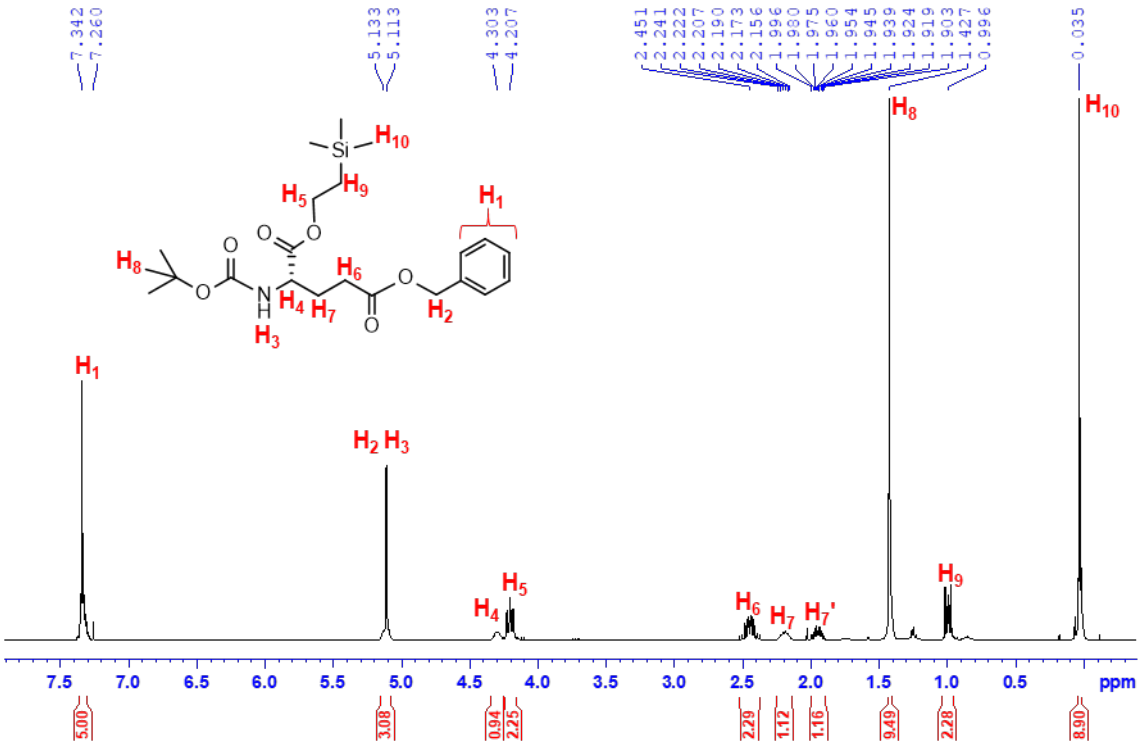


Figure S1. ^{1}H NMR spectrum of compound **1** (400 MHz, $CDCl_3$, 298 K).

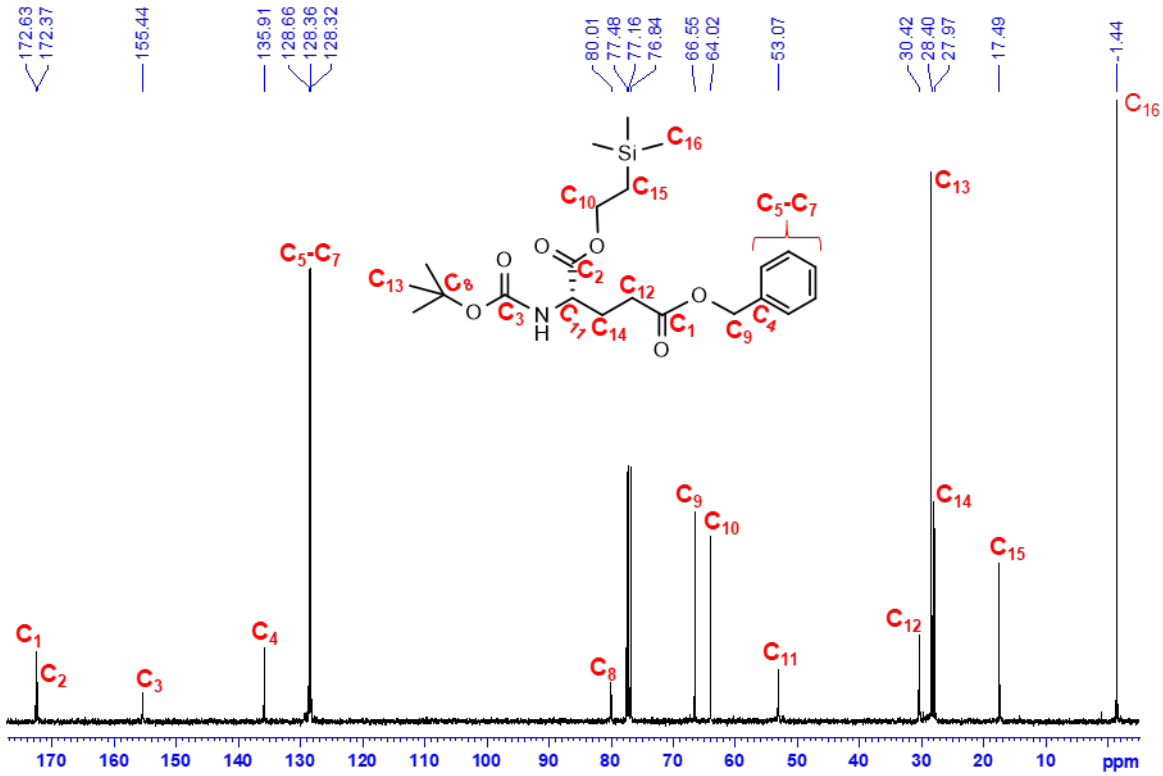


Figure S2. ^{13}C NMR spectrum of compound **1** (100 MHz, $CDCl_3$, 298 K).

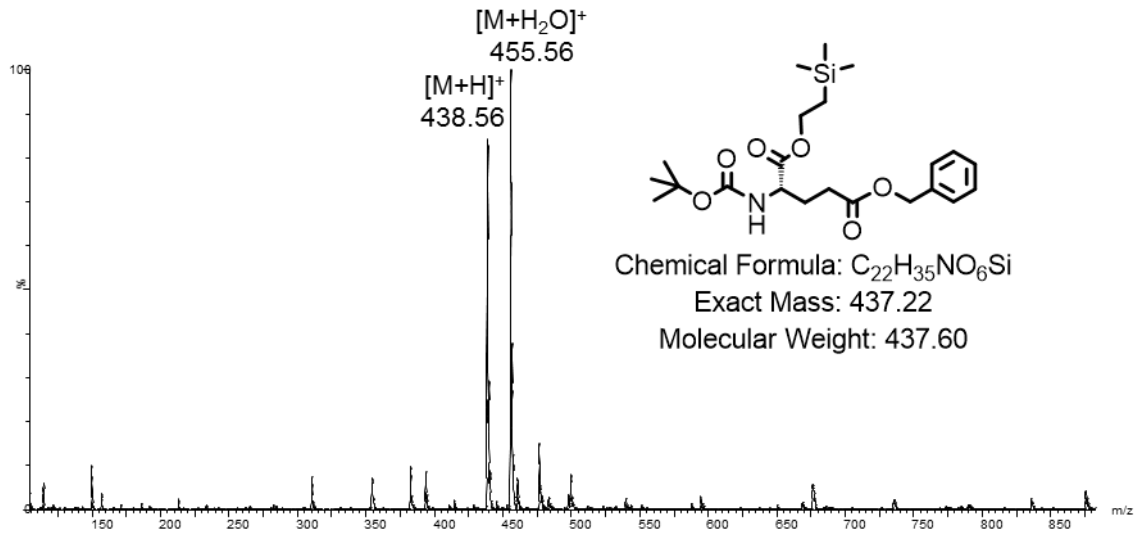
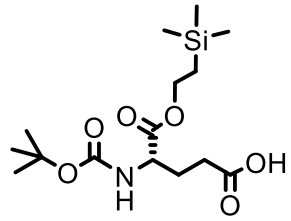


Figure S3. ESI mass spectrum of compound **1**.

2.2 Compound 2



Chemical Formula: $C_{15}H_{29}NO_6Si$
Exact Mass: 347.18
Molecular Weight: 347.48

Compound **1** (6.04 mmol, 2.644 g) was dissolved in 80 mL of ethanol and palladium on carbon (Pd/C 5%) catalyst (0.05 eq, 0.302 mmol, 0.643 g) was added. The solution was stirred under H_2 atmosphere at room temperature for 6 h. The solution was filtered through celite and concentrated under vacuum. The crude product was further purified by flash column chromatography using silica gel and dichloromethane:methanol (solvent mixture 95:5) as eluent. Compound **2** was obtained as a colorless oil in 83% yield (1.743g).

^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 5.17 (*d*, *J* = 7.3 Hz, N*H*Boc, 1H), 4.31 (*q*, *J* = 7.3 Hz, C*H*NHBoc, 1H), 4.22 (*m*, CO_2CH_2, 2H), 2.51-2.39 (*m*, CH_2CO_2H, 2H), 2.21-2.15 (*m*, $CHCH_2$, 1H), 1.96-1.89 (*m*, $CHCH_2$', 1H), 1.43 (*s*, $CO_2C(CH_3)_3$, 18H), 1.01 (*m*, CH_2Si, 2H), 0.04 (*s*, $Si(CH_3)_3$, 9H). **^{13}C NMR** ($CDCl_3$, 125 MHz), δ (ppm): 177.8 (CO_2H), 172.4 (CO_2CH_2), 155.7, (HNCO), 80.3 ($C_q(CH_3)_3$), 64.2 ($CO_2CH_2CH_2Si$), 53.0 (NCH), 30.2 (CH_2CO_2H), 28.4 ($C_q(CH_3)_3$), 28.0 ($CH_2CH_2CO_2H$), 17.5 (CH_2Si), -1.4 ($Si(CH_3)_3$). **ESI-MS** $[M]^-$ m/z calcd for $C_{15}H_{29}NO_6Si$: 346.17, found 347.05.

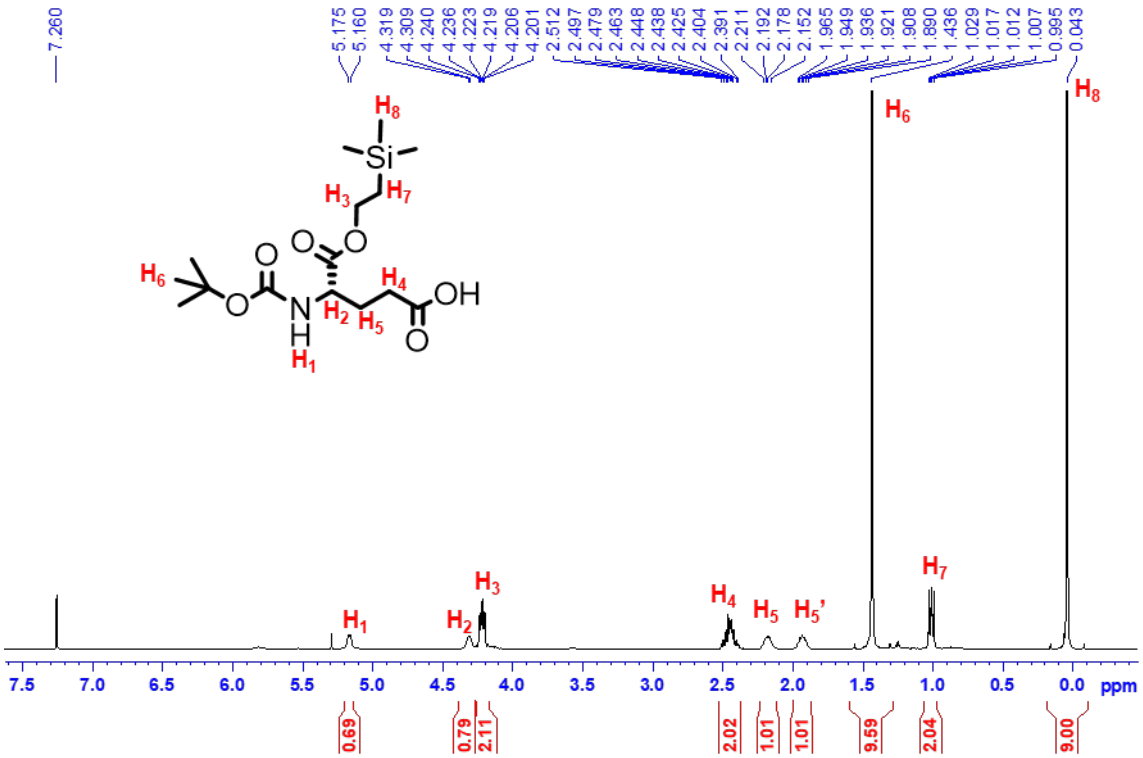


Figure S4. ^{1}H NMR spectrum of compound **2** (500 MHz, $CDCl_3$, 298 K).

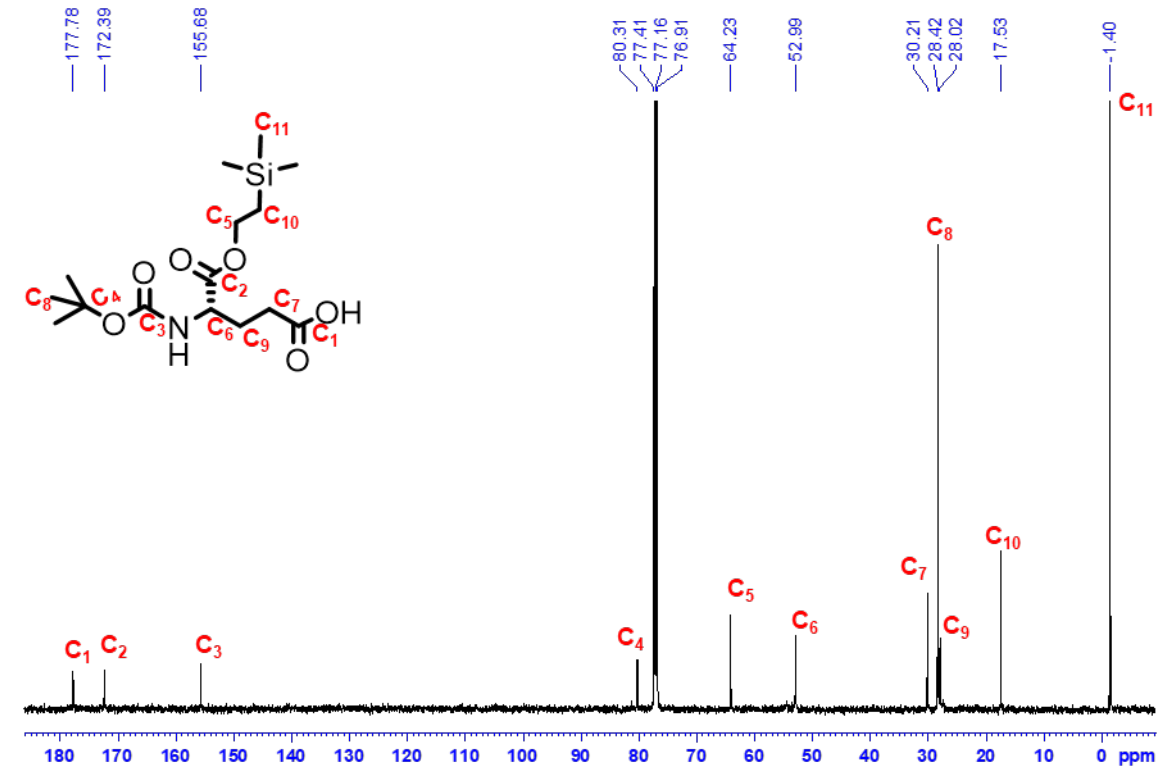


Figure S5. ^{13}C NMR spectrum of compound **2** (125 MHz, $CDCl_3$, 298 K).

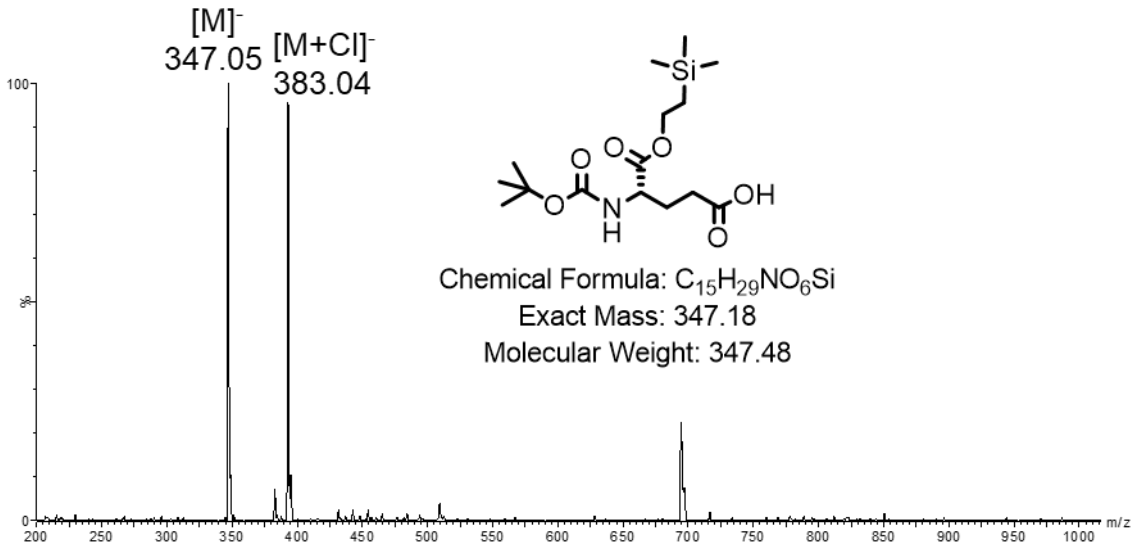
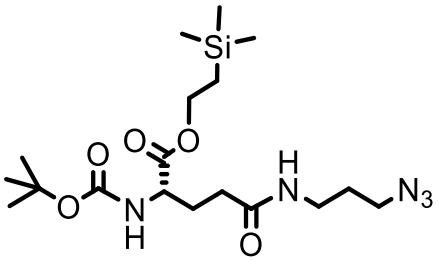


Figure S6. ESI mass spectrum of compound **2**.

2.3 Compound 3



Chemical Formula: $C_{18}H_{35}N_5O_5Si$
Exact Mass: 429.24
Molecular Weight: 429.59

In an air free Schlenk flask, compound **2** (0.29 mmol, 100 mg), N,N-diisopropylethylamine (4 eq, 1.2 mmol, 149 mg, 0.2 mL), HATU (1.1 eq, 0.32 mmol, 120.4 mg) and 3-azido-1-propanamine (3 eq, 0.86 mmol, 86 mg) were dissolved in 10 mL of anhydrous N,N-dimethylformamide. The mixture was stirred for 12 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was further purified by column chromatography using silica gel and hexane:ethyl acetate (solvent mixture gradient from 20:80 until 40:60) as eluent. Compound **3** was obtained as a colorless oil in 71% yield (88 mg).

^{1}H NMR ($CDCl_3$, 600 MHz), δ (ppm): 6.46 (*s*, CON*H*, 1H), 5.29 (*d*, *J* = 6.0 Hz, N*H*Boc, 1H), 4.23-4.20 (*m*, C*H*NHBoc and CO_2CH_2, 3H), 3.40-3.31 (*m*, CH_2NH and CH_2N_3), 2.27 (*t*, CH_2CON, 2H), 2.20-2.17 (*m*, $CHCH_2$, 1H), 1.87-1.83 (*m*, $CHCH_2$', 1H), 1.82 (*qui*, *J* = 6.6 Hz, $CH_2CH_2CH_2$, 2H), 1.44 (*s*, $CO_2C(CH_3)_3$, 9H), 1.00 (*m*, CH_2Si, 2H), 0.04 (*s*, $Si(CH_3)_3$, 9H). **^{13}C NMR** ($CDCl_3$, 150 MHz), δ (ppm): 172.4 (CO_2CH_2), 172.3 (*C*ONH), 155.2 (HN*C*O), 80.4 ($C_q(CH_3)_3$, 64.3 ($CO_2CH_2CH_2Si$), 53.1 (N*C*H), 49.4 (CH_2N_3), 37.2 (CH_2NH), 32.9 (CH_2CONH), 29.9 (CH_2CH_2CONH), 28.9 ($CH_2CH_2CH_2$), 28.4 ($C_q(CH_3)_3$), 17.6 (CH_2Si), -1.4 ($Si(CH_3)_3$). **ESI-MS** $[M+Na]^+$ m/z calcd for $C_{18}H_{35}N_5O_5Si$: 453.23, found 453.18.

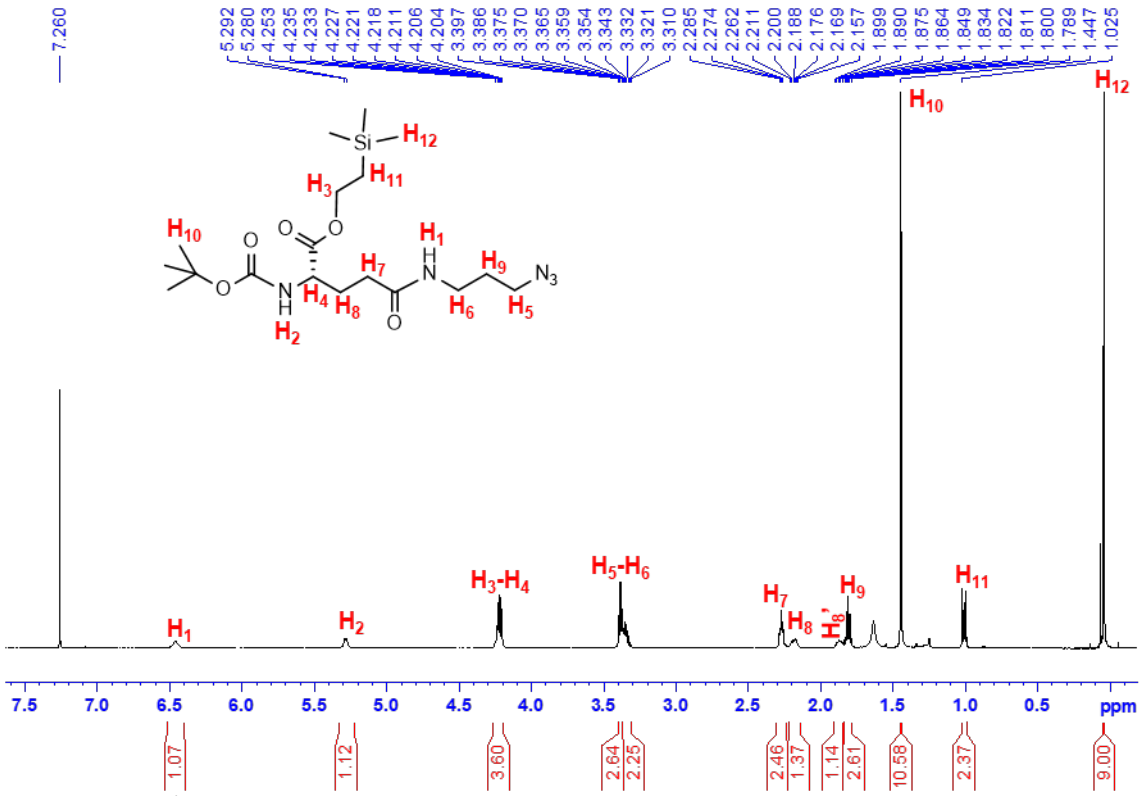


Figure S7. ^{1}H NMR spectrum of compound **3** (600 MHz, $CDCl_3$, 298 K).

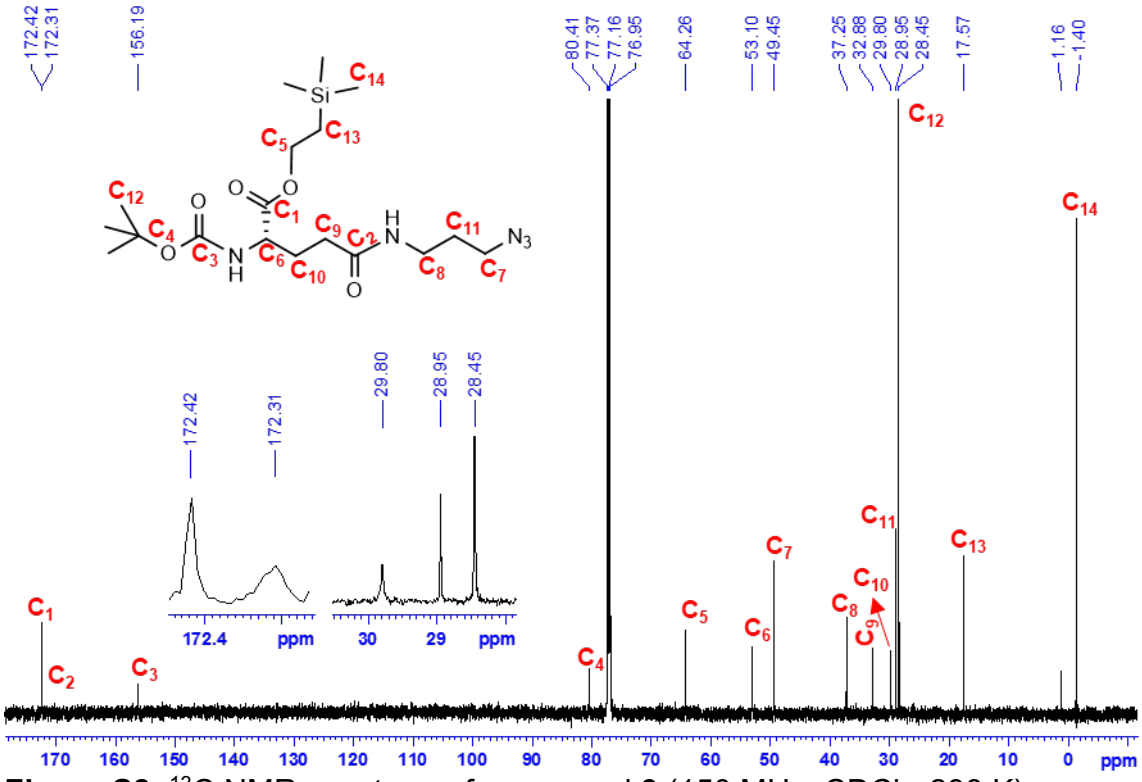


Figure S8. ^{13}C NMR spectrum of compound **3** (150 MHz, $CDCl_3$, 298 K).

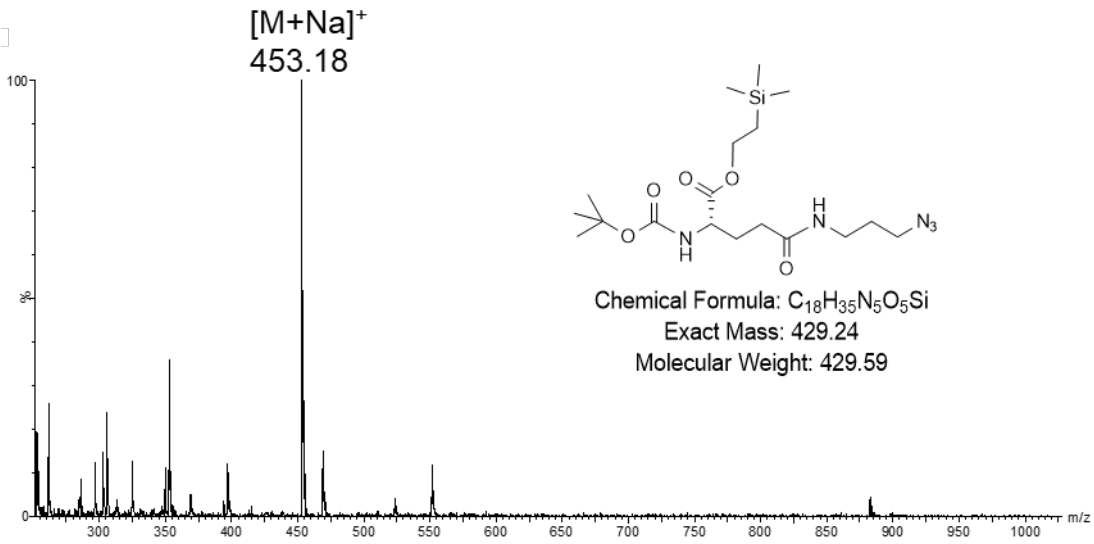
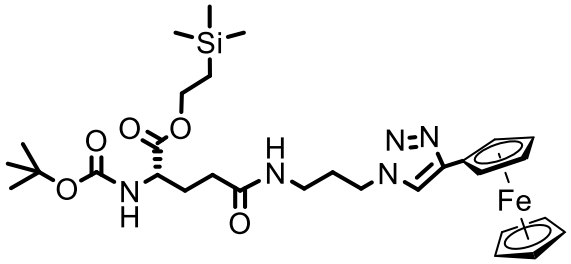


Figure S9. ESI mass spectrum of compound **3**.

2.4 Compound 4



Chemical Formula: $C_{30}H_{45}FeN_5O_5Si$
Exact Mass: 639.25
Molecular Weight: 639.65

In an air free Schlenk flask, compound **3** (0.14 mmol, 60 mg), ethenylferrocene (1 eq, 0.14 mmol, 29 mg) and copper(II) sulfate (0.05 eq, 0.1 M, 1.7 mg, 70 μL) were added into 12 mL of water and tetrahydrofuran 6/4 (v/v). After complete dissolution, sodium ascorbate (0.1 eq, 0.14 μmol, 2.8 mg) was added. The mixture was stirred for 24 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography using silica gel and dichloromethane:methanol (solvent mixture gradient from 100:00 until 95:5) as eluent. Compound **4** was obtained as a red oil in 84% yield (75 mg).

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.50 (*s*, triazole-*H*), 7.00 (*s*, CON*H*, 1H), 5.30 (*d*, *J* = 7.7 Hz, N*H*Boc, 1H), 4.93 (*br*, Fc-*H*, 2H), 4.51 (*br*, Fc-*H*, 2H), 4.40 (*m*, triazole-C*H*$_2$, 2H), 4.23-4.9 (*m*, C*H*NHBoc, Fc-*H*, CO_2CH_2, 8H), 3.28-3.21 (*m*, C*H*$_2$NH, 2H), 2.27 (*t*, *J* = 6.4 Hz, C*H*$_2$CON, 2H), 2.24-2.10 (*m*, CHC*H*$_2$ and $CH_2CH_2CH_2$, 3H), 1.88-1.85 (*m*, CHC*H*$_2$', 1H), 1.44 (*s*, $CO_2C(CH_3)_3$, 9H), 1.00 (*m*, C*H*$_2$Si, 2H), 0.04 (*s*, Si(C*H*$_3$)$_3$, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz), δ (ppm): 172.6 (CO_2CH_2), 172.4 (*C*ONH), 155.2 (HN*C*O), 156.1 (C_q-triazole), 119.7 (triazole-*C*H), 80.3 ($C_q(CH_3)_3$), 75.3 (FcAr-C_q), 69.4 (FcAr-*C*H), 68.8 (FcAr-*C*H), 66.8 (FcAr-*C*H), 64.1 ($CO_2CH_2CH_2Si$), 53.2 (N*C*H), 47.8 (triazole-*C*H$_2$), 36.5 (*C*H$_2$NH), 32.7 (*C*H$_2$CONH), 30.4 ($CH_2CH_2CH_2$), 29.3 (*C*H$_2$CH$_2$CONH), 28.4 ($C_q(CH_3)_3$, 17.5 (*C*H$_2$Si), -1.4 (Si(*C*H$_3$)$_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{30}H_{45}FeN_5O_5Si$: 640.26, found 640.34.

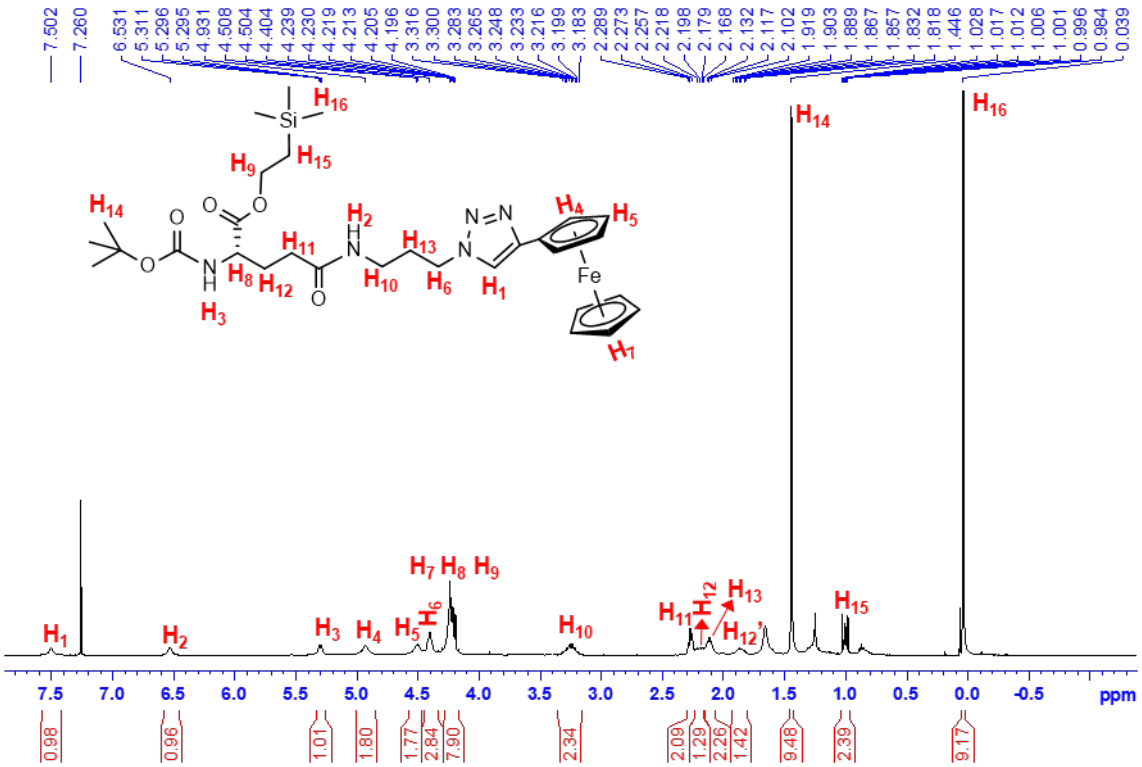


Figure S10. ^{1}H NMR spectrum of compound **4** (400 MHz, $CDCl_3$, 298 K).

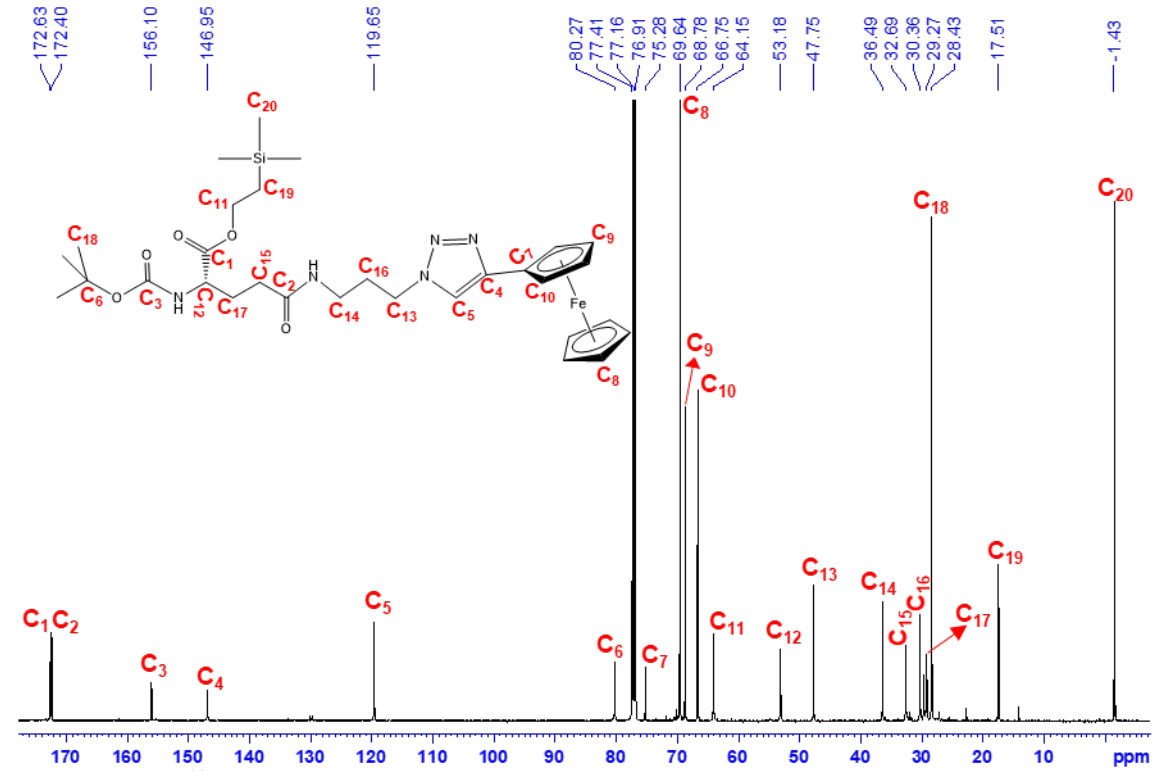


Figure S11. ^{13}C NMR spectrum of compound **4** (100 MHz, $CDCl_3$, 298 K).

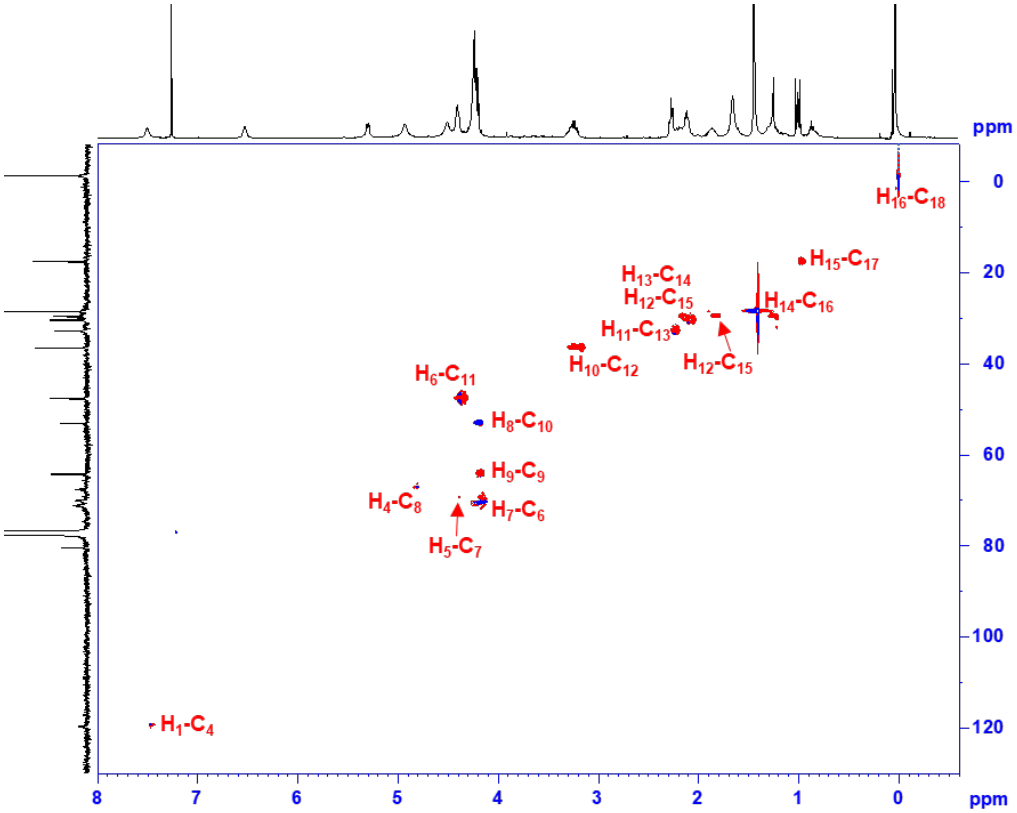


Figure S12. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of compound **4** recorded in $CDCl_3$ at 298 K (400 MHz).

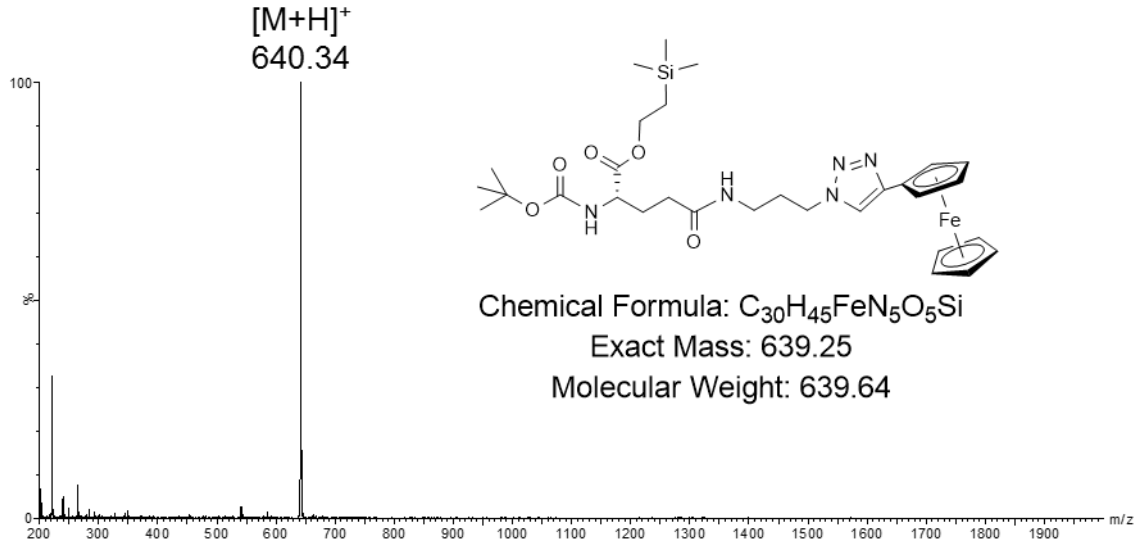
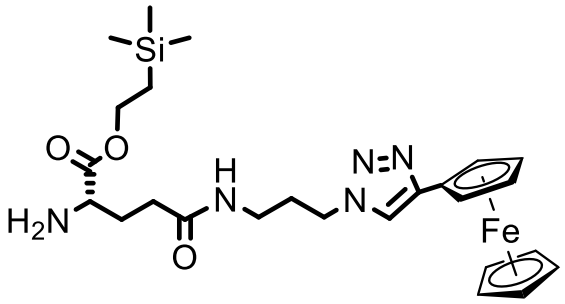


Figure S13. ESI mass spectrum of compound **4**.

2.5 Compound 5



Chemical Formula: $C_{25}H_{37}FeN_5O_3Si$
Exact Mass: 539.20
Molecular Weight: 539.53

In an air free Schlenk flask, compound **4** (0.12 mmol, 77 mg) was dissolved in 40 mL of water and 160 mL of formic acid. The mixture was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3 x 30 mL) and hexane (3 x 30 mL). Compound **5** was obtained as red oil in quantitative yield (65 mg).

^{1}H NMR (CD_3OD, 400 MHz), δ (ppm): 8.05 (*s*, triazole-*H*), 7.00, 4.73 (*br*, Fc-*H*, 2H), 4.45 (*t*, *J* = 6.7 Hz, triazole-C*H*$_2$, 2H), 4.32-4.27 (*m*, CO_2CH_2, Fc-*H*, 4H), 4.06 (*s*, Fc-*H*, 5H), 3.83 (*br*, H_2NCH, 1H), 3.24 (*t*, *J* = 6.4 Hz, CH_2NH, 2H), 2.41 (*t*, *J* = 6.6 Hz, CH_2CON, 2H), 2.16-2.01 (*m*, $CHCH_2$ and $CH_2CH_2CH_2$, 3H), 1.07 (*m*, CH_2Si, 2H), 0.01 (*s*, $Si(CH_3)_3$), 9H). **^{13}C NMR** (CD_3OD, 100 MHz), δ (ppm): 174.6 (CO_2CH_2), 172.8 (*C*ONH), 148.0 (C_q-triazole), 121.6 (triazole-*C*H), 76.1 (FcAr-C_q), 70.5 (FcAr-*C*H), 69.8 (FcAr-*C*H), 67.6 (FcAr-*C*H), 65.5 ($CO_2CH_2CH_2Si$), 54.1 (N*C*H), 37.6 (CH_2NH), 32.6 (CH_2CONH), 31.0 ($CH_2CH_2CH_2$), 28.9 (CH_2CH_2CONH), 18.3 (CH_2Si), -1.6 ($Si(CH_3)_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{25}H_{37}FeN_5O_3Si$: 540.21, found 540.22.

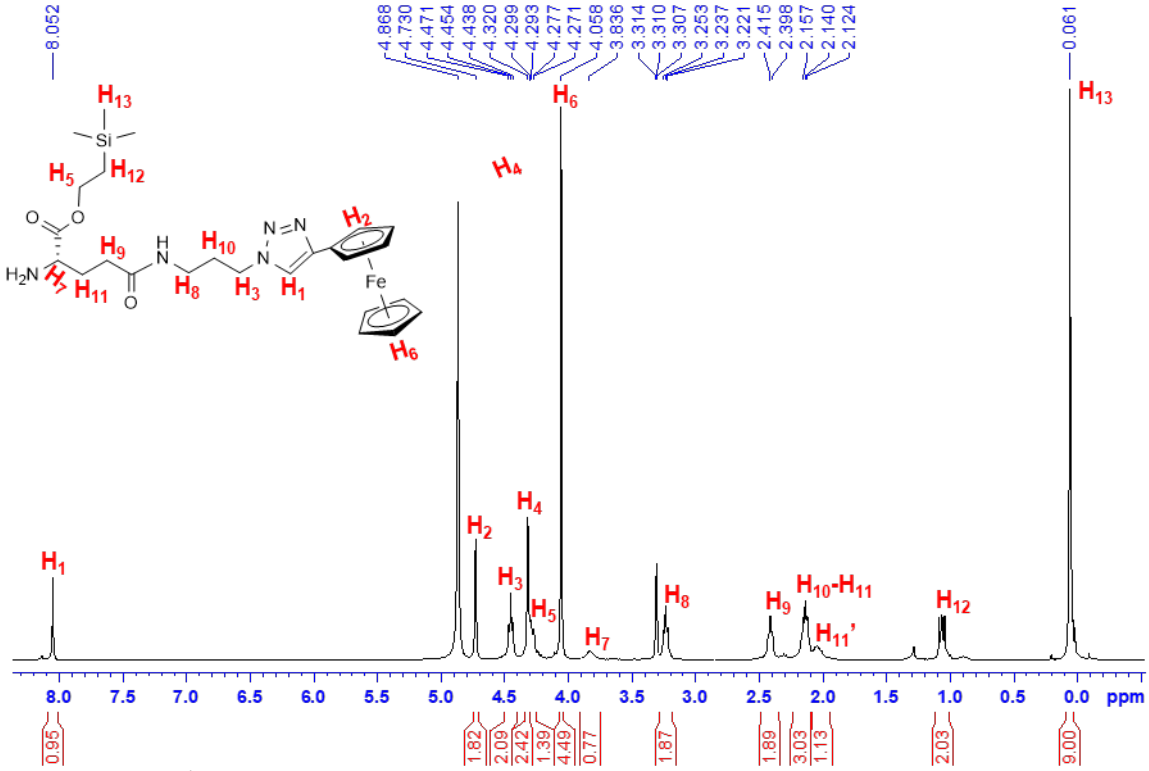


Figure S14. ^{1}H NMR spectrum of compound **5** (400 MHz, CD_3OD, 298 K).

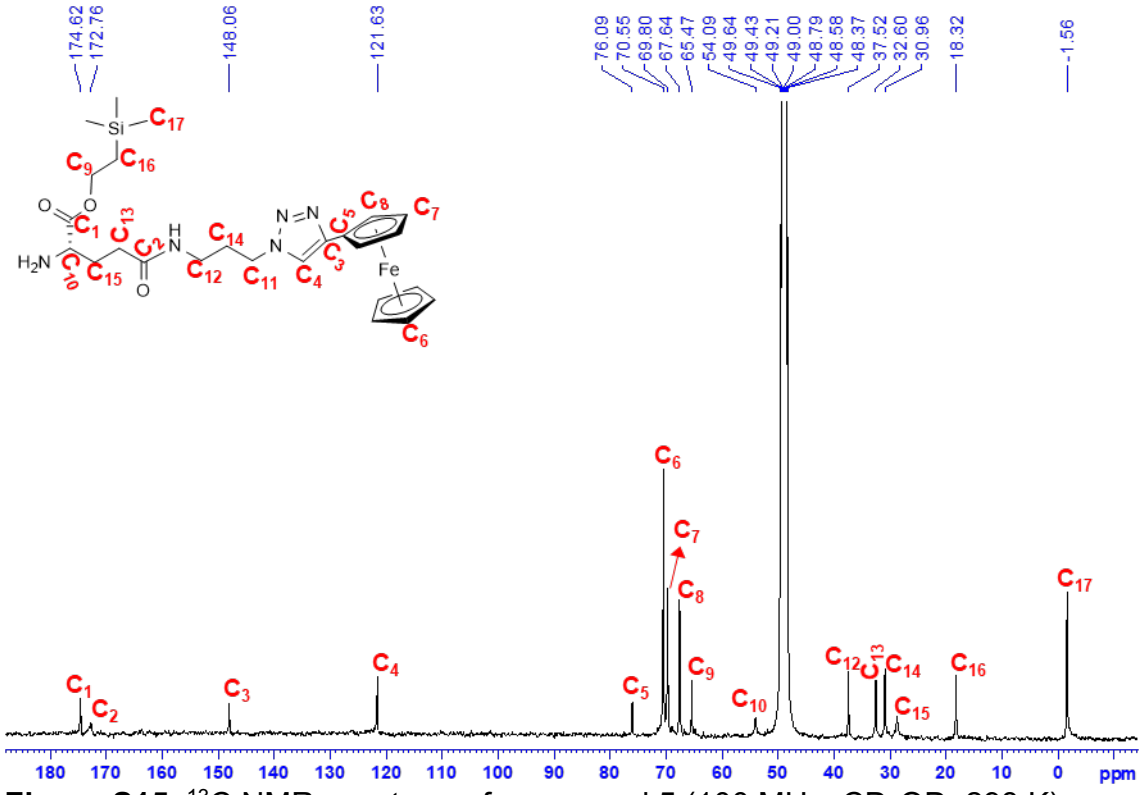


Figure S15. ^{13}C NMR spectrum of compound **5** (100 MHz, CD_3OD, 298 K).

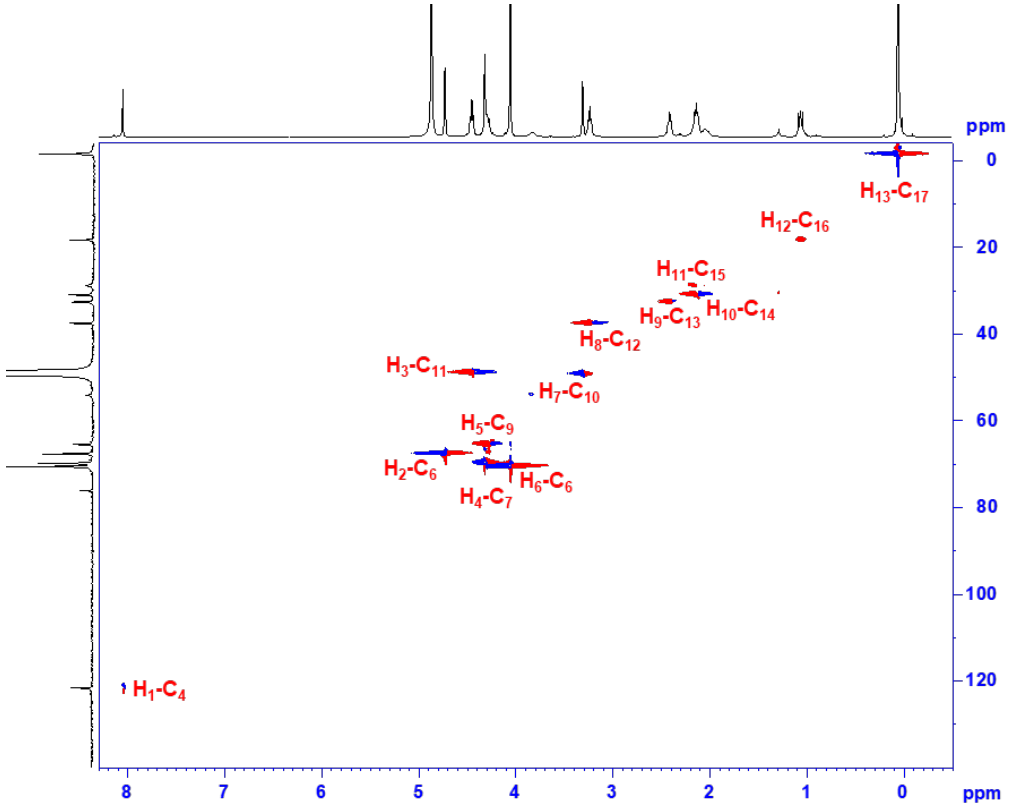


Figure S16. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of compound **5** recorded in CD_3OD at 298 K (400 MHz).

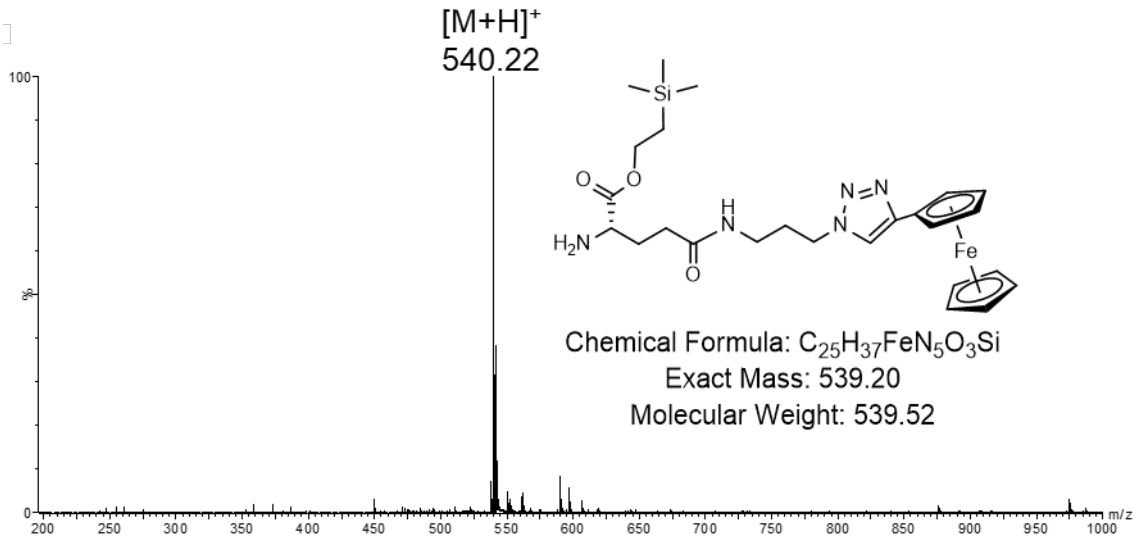
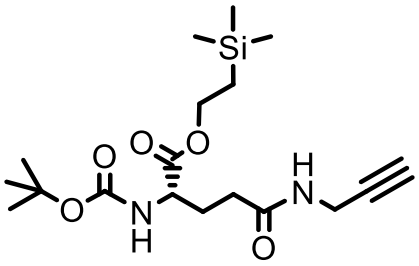


Figure S17. ESI mass spectrum of compound **5**.

2.6 Compound 6



Chemical Formula: $C_{18}H_{32}N_2O_5Si$
Exact Mass: 384.21
Molecular Weight: 384.55

In an air free Schlenk flask, compound **2** (0.58 mmol, 200 mg), N,N-diisopropylethylamine (3 eq, 1.6 mmol, 202 mg, 0.273 mL), HATU (1.2 eq, 0.7 mmol, 265 mg) and propargylamine (1.5 eq, 0.87 mmol, 48 mg) were dissolved in 5 mL of anhydrous N,N-dimethylformamide. The mixture was stirred for 12 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was further purified by column chromatography using silica gel and hexane:ethyl acetate (solvent mixture gradient from 100:00 until 50:50) as eluent. Compound **6** was obtained as an yellowish oil in 97% yield (215 mg).

^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 6.38 (*br*, CON*H*, 1H), 5.26 (*d*, *J* = 7.2 Hz, N*H*Boc, 1H), 4.27-4.17 (*m*, C*H*NHBoc and CO_2CH_2, 3H), 4.05 (*dd*, *J* = 5.2 Hz, *J* = 2.6 Hz, CONHCH_2), 2.29 (*t*, *J* = 7.5 Hz, CH_2CON, 2H), 2.22 (*t*, *J* = 2.6 Hz, alkyne-*H*, 1H), 2.21-2.16 (*m*, CHCH_2, 1H), 1.94-1.87 (*m*, CHCH_2', 1H), 1.44 (*s*, $CO_2C(CH_3)_3$, 9H), 1.00 (*m*, CH_2Si, 2H), 0.04 (*s*, $Si(CH_3)_3$), 9H). **^{13}C NMR** ($CDCl_3$, 125 MHz), δ (ppm): 172.4 (CO_2CH_2), 171.8 (*C*ONH), 155.0 (HN*C*O), 80.3 ($C_q(CH_3)_3$), 79.7 (alkyne-C_q), 71.7 (alkyne-*C*H), 64.2 ($CO_2CH_2CH_2Si$), 53.1 (N*C*H), 32.6 (CH_2CONH), 29.8 (CONHCH_2-alkyne), 29.4 (CH_2CH_2CONH), 28.5 ($C_q(CH_3)_3$), 17.6 (CH_2Si), -1.4 ($Si(CH_3)_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{18}H_{32}N_2O_5Si$: 385.22, found 385.18.

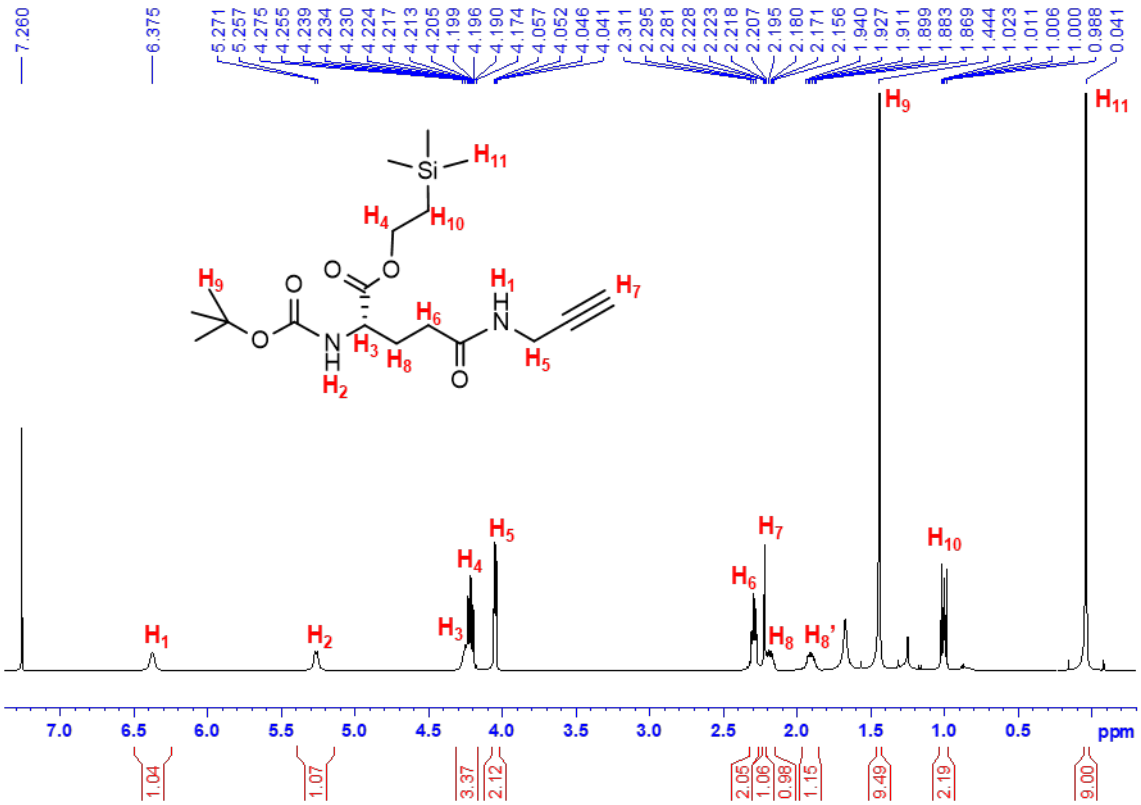


Figure S18. ^{1}H NMR spectrum of compound **6** (500 MHz, $CDCl_3$, 298 K).

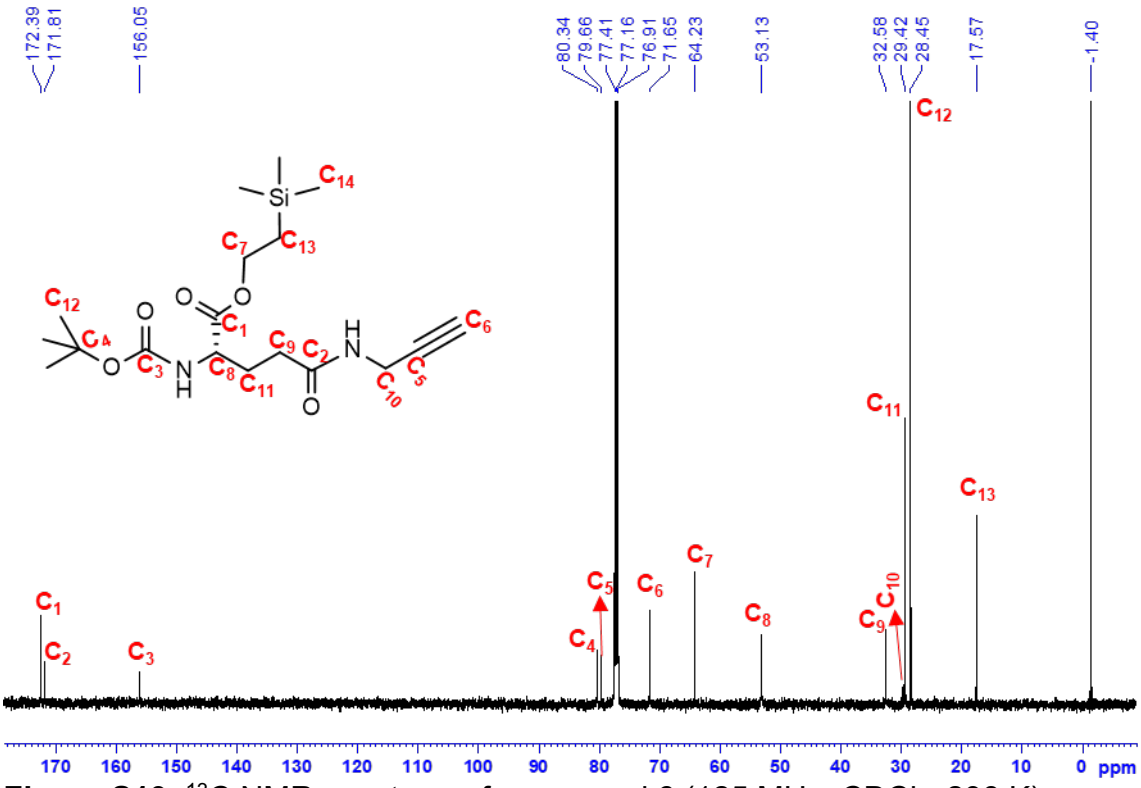


Figure S19. ^{13}C NMR spectrum of compound **6** (125 MHz, $CDCl_3$, 298 K).

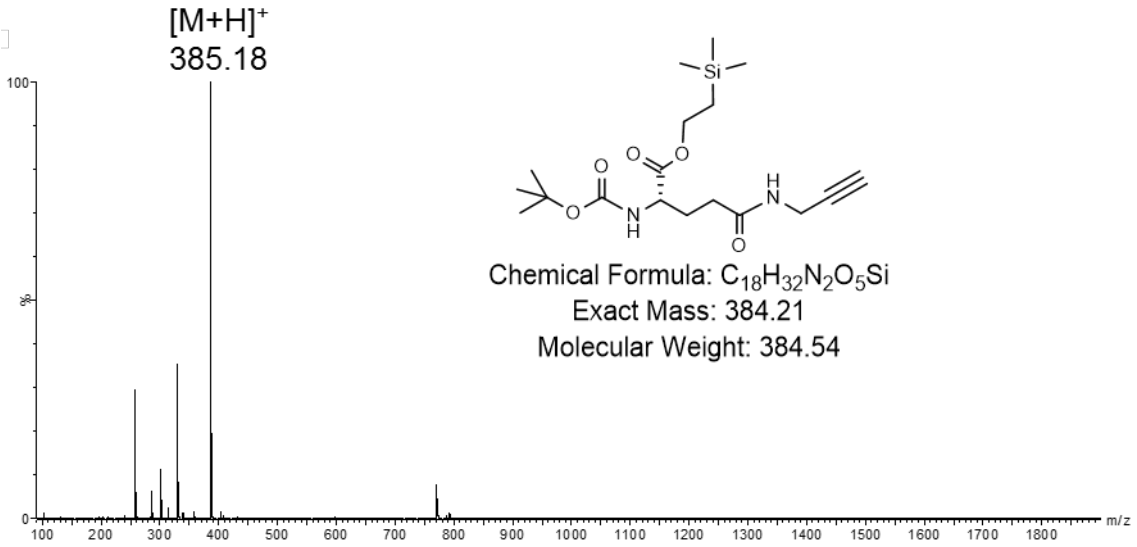
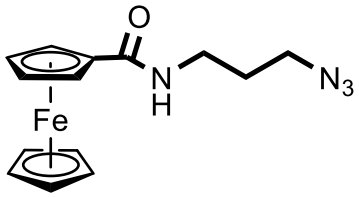


Figure S20. ESI mass spectrum of compound **6**.

2.7 Compound 7



Chemical Formula: $C_{14}H_{16}FeN_4O$
Exact Mass: 312.07
Molecular Weight: 312.15

In an air free Schlenk flask, ferrocenecarboxylic acid (0.43 mmol, 100 mg), N,N-diisopropylethylamine (5 eq, 2.2 mmol, 281 mg, 0.380 mL), HATU (1.1 eq, 0.48 mmol, 182 mg) and azido-1-propanamine (1.5 eq, 0.65 mmol, 89 mg) were dissolved in 5 mL of anhydrous N,N-dimethylformamide. The mixture was stirred for 12 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography using silica gel and hexane:ethyl acetate (solvent mixture 70:30) as eluent. Compound **7** was obtained as a red solid in 88% yield (120 mg).

^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 5.96 (CON*H*), 4.66 (*br*, Fc-*H*, 2H), 4.34 (*br*, Fc-*H*, 2H), 4.20 (*s*, Fc-*H*, 5H), 3.49-3.39 (*m*, CH_2NH, C$H_2$$N_3$, 4H), 1.88 (*q*, *J* = 6.6 Hz, $NHCH_2CH_2CH_2N_3$, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz), δ (ppm): 170.6 (*C*ONH), 76.2 (ArFc-C_q), 70.6 (ArFc-*C*H), 69.9 (ArFc-*C*H), 68.2 (ArFc-*C*H), 49.8 (N_3CH_2), 37.5 ($HNCH_2$), 22.2 ($NHCH_2CH_2CH_2N_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{14}H_{16}FeN_4O$: 313.07, found 313.70.

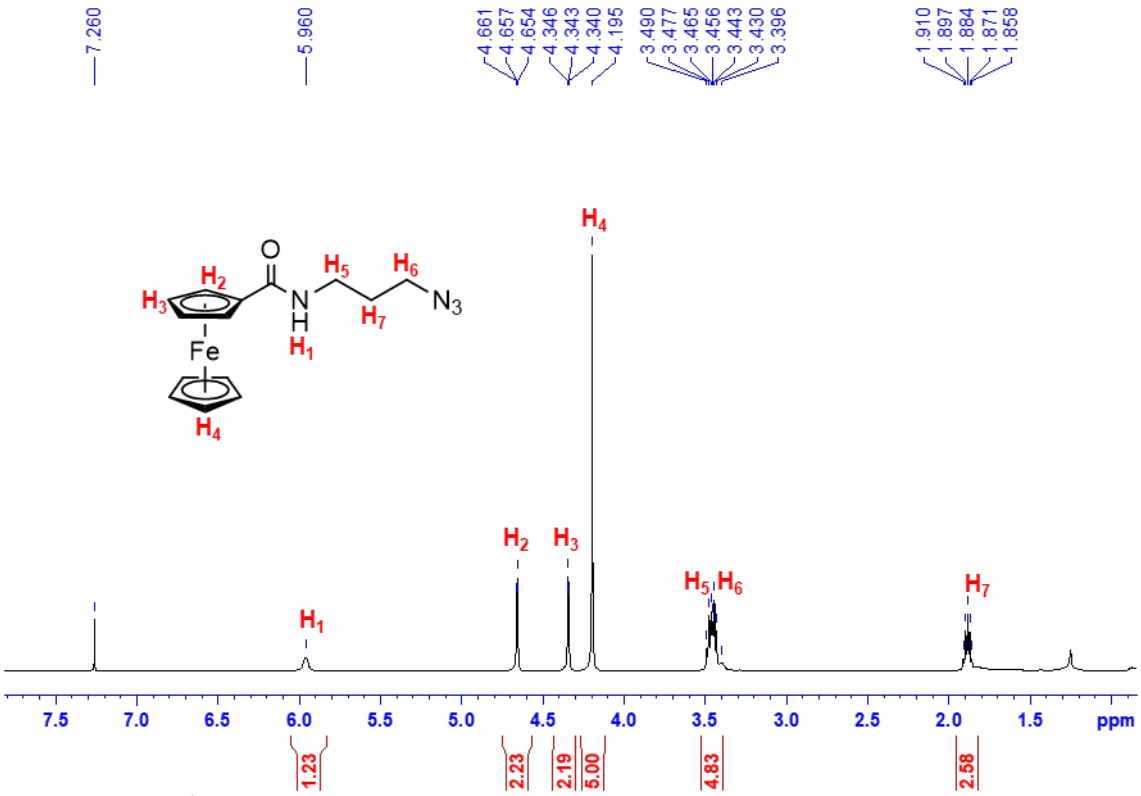


Figure S21. ^{1}H NMR spectrum of compound **7** (500 MHz, $CDCl_3$, 298 K).

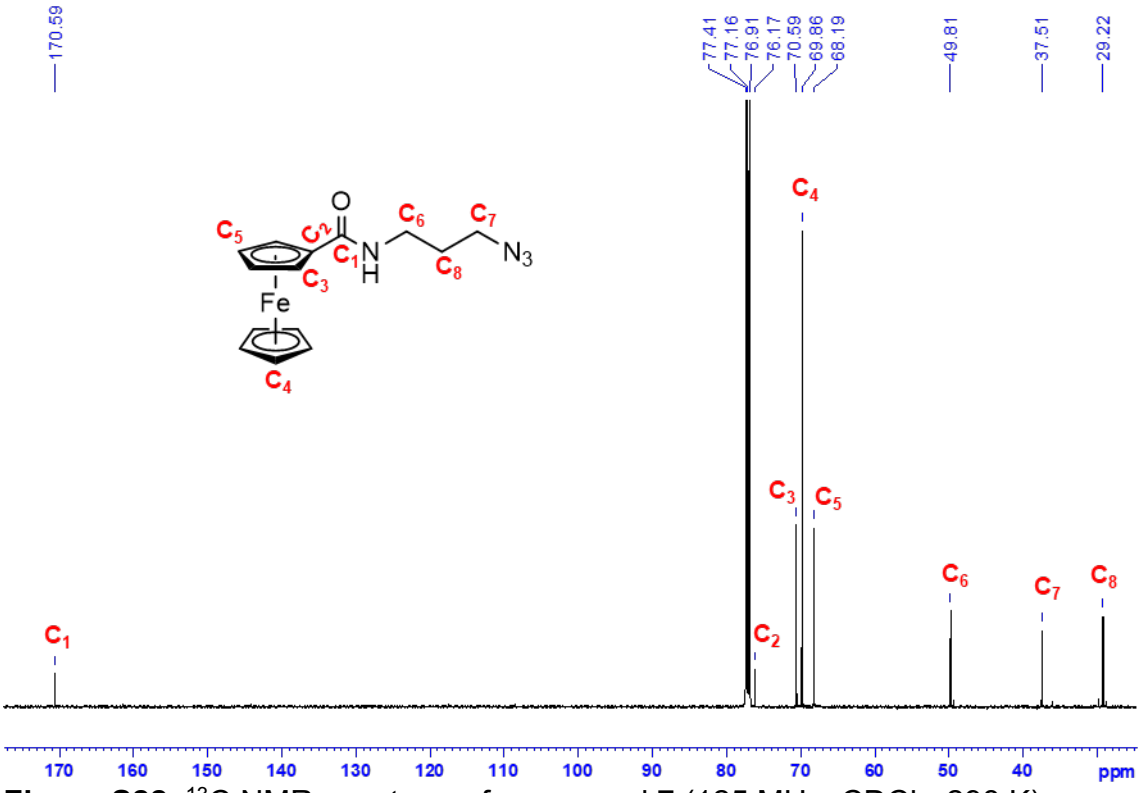


Figure S22. ^{13}C NMR spectrum of compound **7** (125 MHz, $CDCl_3$, 298 K).

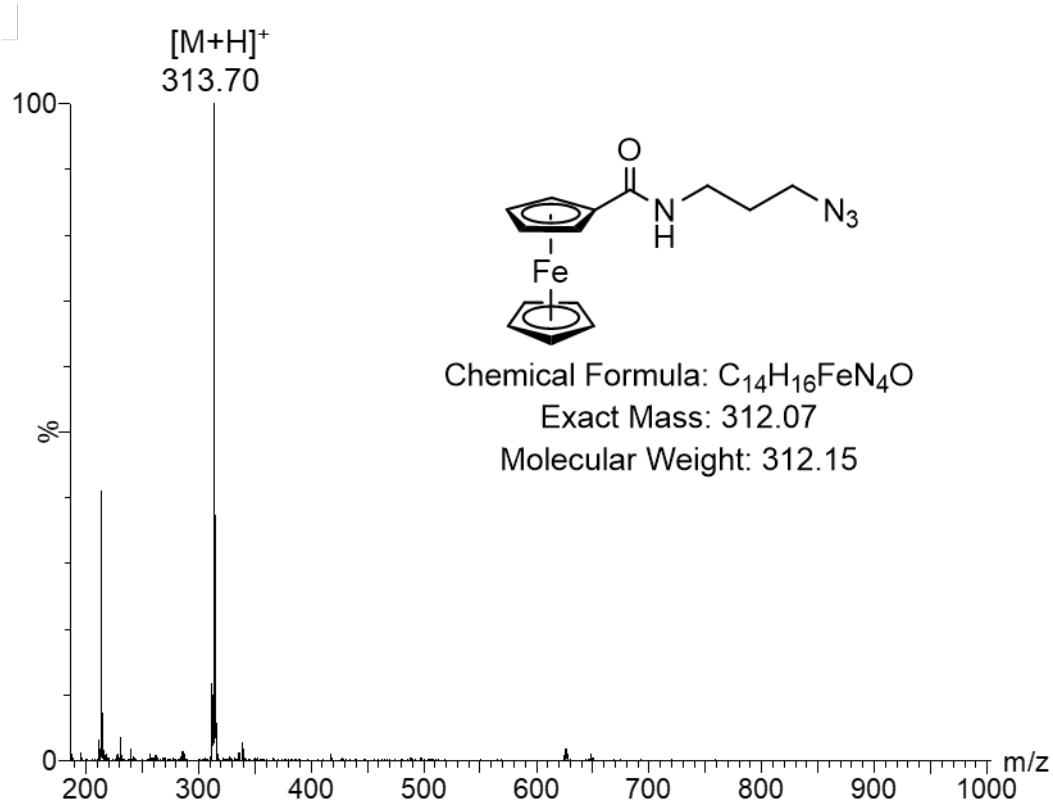
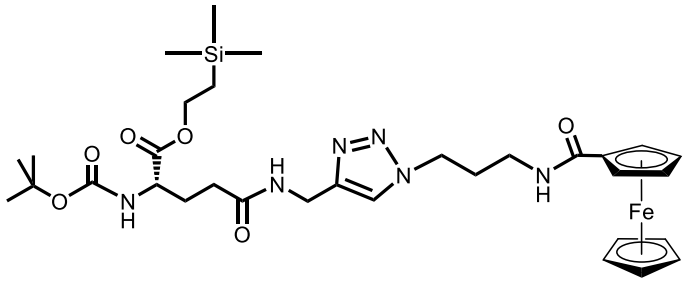


Figure S23. ESI mass spectrum of compound **7**.

2.8 Compound 8



Chemical Formula: $C_{32}H_{48}FeN_6O_6Si$
Exact Mass: 696.28
Molecular Weight: 696.70

In an air free Schlenk flask, compound **6** (0.23 mmol, 90 mg), compound **7** (1.2 eq, 0.28 mmol, 88 mg) and copper(II) sulfate (0.1 M, 0.05 eq, 11.7 μmols, 1.9 mg, 0.117 mL) were added into 12 mL of water and tetrahydrofuran 6:4 (v/v). After complete dissolution, sodium ascorbate (0.1 eq, 23.4 μmol, 4.6 mg) was added. The mixture was stirred for 24 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography using silica gel and dichloromethane:methanol (solvent mixture 100:5) as eluent. Compound **8** was obtained as a red oil in 83% yield (135 mg).

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.65 (*s*, triazole-*H,* 1H), 7.26 (*br*, CON*H*, 1H), 6.61 (*br*, CON*H*, 1H), 5.52 (*d*, *J* = 7.6 Hz, N*H*Boc, 1H), 4.68 (*br*, Fc-*H*, 2H), 4.43-4.38 (*m*, CH_2-trazole-CH_2, 4H), 4.28 (*br*, Fc-*H*, 2H), 4.13 (*br*, NHC*H*, CO_2CH_2, Fc-*H*, 8H), 3.32 (*m*, CH_2NH, 2H), 2.29 (*t*, *J* = 6.5 Hz, CH_2CON, 2H), 2.13 (*m*, CHCH_2 and $CH_2CH_2CH_2$, 3H), 1.90 (*m*, CHCH_2', 1H), 1.40 (*s*, $CO_2C(CH_3)_3$, 9H), 0.94 (*m*, CH_2Si, 2H), -0.01 (*s*, Si(CH_3)$_3$, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz), δ (ppm): 172.5 (CO_2CH_2), 172.4 (*C*ONH), 170.9 (*C*ONH), 155.9 (HN*C*O), 145.3 (C_q-triazole), 122.9 (triazole-*C*H), 80.2 ($C_q(CH_3)_3$), 75.9 (FcAr-C_q), 70.7 (FcAr-*C*H), 69.8 (FcAr-*C*H), 68.3 (FcAr-*C*H), 64.1 ($CO_2CH_2CH_2Si$), 53.2 (N*C*H), 48.1 (triazole-CH_2), 36.7 (triazole-CH_2NH), 35.3 (CH_2NH), 32.5 (CH_2CONH), 30.3 ($CH_2CH_2CH_2$), 29.1 (CH_2CH_2CONH), 28.5 ($C_q(CH_3)_3$), 17.6 (CH_2Si), -1.4 (Si(CH_3)$_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{32}H_{48}FeN_6O_6Si$: 697.28, found 697.28.

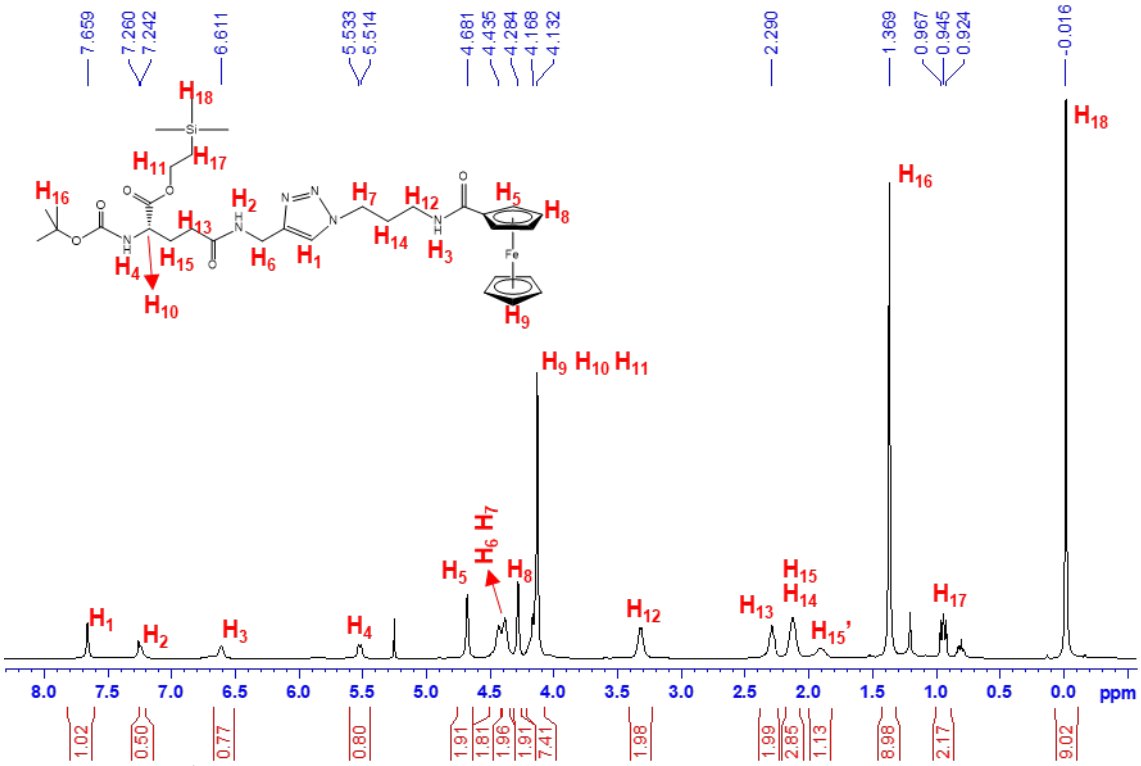


Figure S24. ^{1}H NMR spectrum of compound **8** (400 MHz, $CDCl_3$, 298 K).

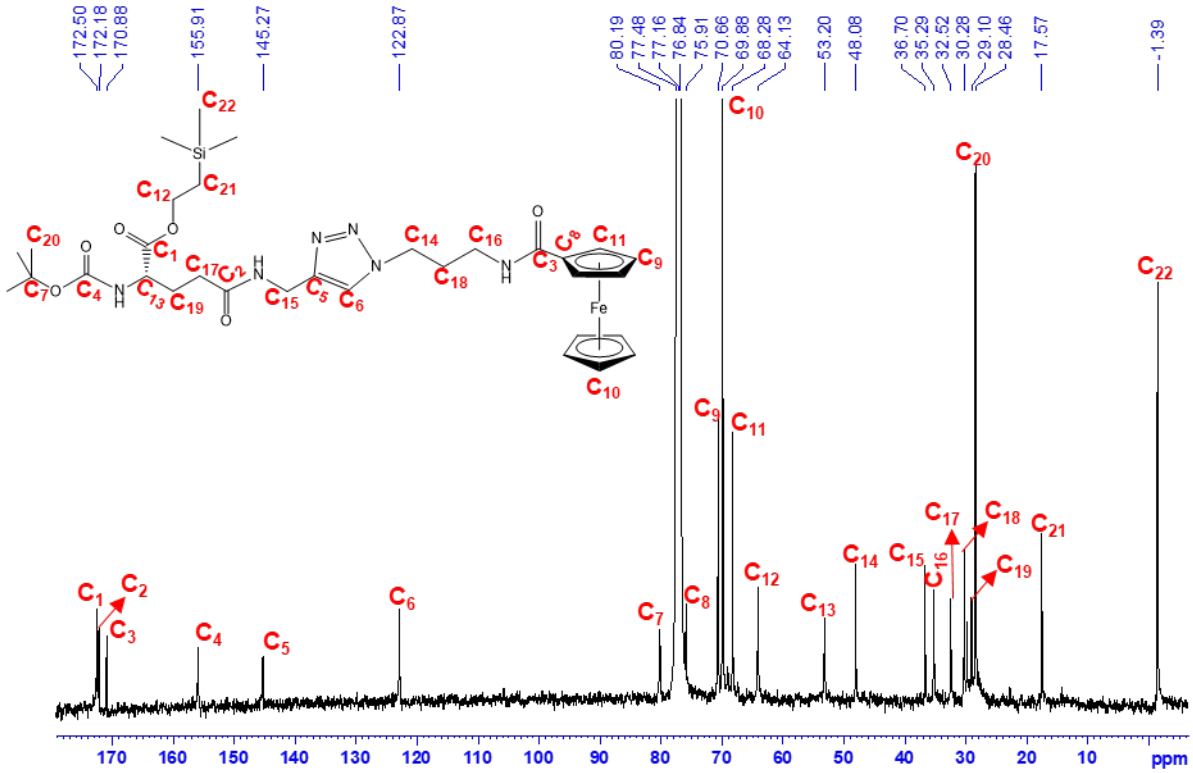


Figure S25. ^{13}C NMR spectrum of compound **8** (100 MHz, $CDCl_3$, 298 K).

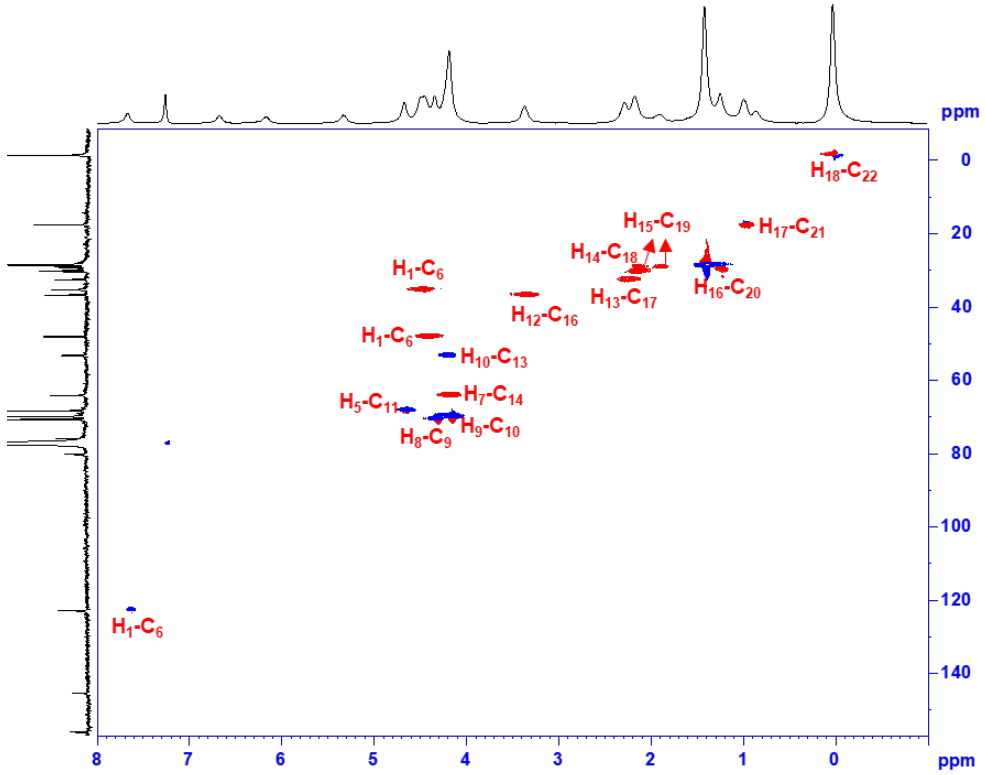


Figure S26. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of compound **8** recorded in $CDCl_3$ at 298 K (400 MHz).

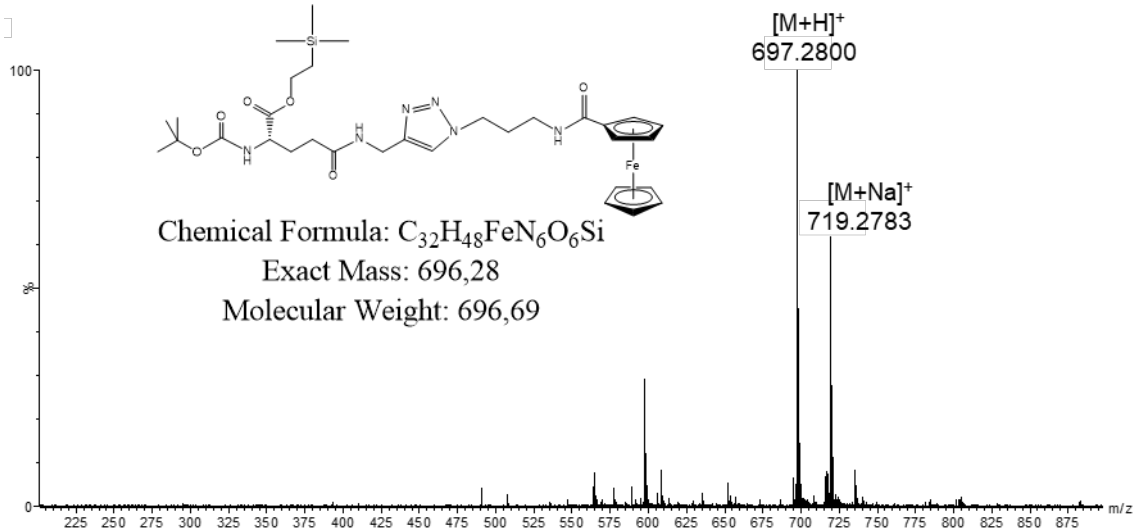
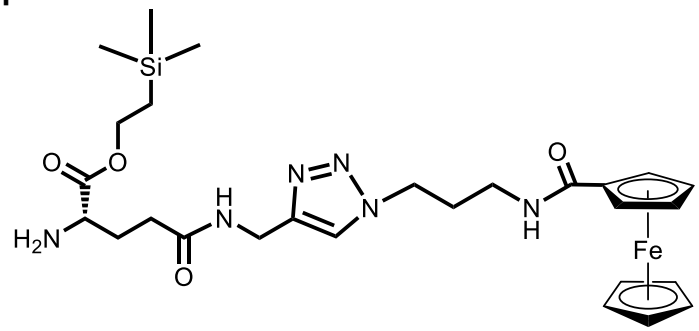


Figure S27. ESI mass spectrum of compound **8**.

2.9 Compound 9



Chemical Formula: $C_{27}H_{40}FeN_6O_4Si$
Exact Mass: 596.22
Molecular Weight: 596.59

In an air free Schlenk flask, compound **8** (0.13 mmol, 90 mg) was dissolved in 40 mL of water and 160 mL of formic acid. The mixture was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3 x 30 mL) and hexane (3 x 30 mL). Compound **9** was obtained as red oil in quantitative yield (77 mg).

^{1}H NMR (CD_3OD, 600 MHz), δ (ppm): 7.95 (*s*, triazole-*H,* 1H), 4.80 (*br*, Fc-*H*, 2H), 4.48 (*t*, *J* = 6.5 Hz, triazole-C*H*$_2$, 2H), 4.45 (*s*, NHC*H*$_2$-triazole, 2H), 4.41 (*br*, Fc-H, 2H), 4.31 (*br*, CO_2C*H*$_2$, 2H), 4.20 (*s*, Fc-*H*, 5H), 3.95 (*br*, H_2NC*H*, 1H), 3.34-3.33 (*m*, C*H*$_2$NH, 2H), 2.47 (*t*, *J* = 6.4 Hz, C*H*$_2$CON, 2H), 2.18 (*m*, CHC*H*$_2$ and CH_2C*H*$_2$$CH_2$, 3H), 2.10 (*m*, CHC*H*$_2$', 1H), 1.07 (*m*, C*H*$_2$Si, 2H), 0.06 (*s*, Si(C*H*$_3$)$_3$, 9H). **^{13}C NMR** (CD_3OD, 150 MHz), δ (ppm): 172.5 (*C*O_2CH_2), 172.4 (*C*ONH), 170.9 (*C*ONH), 155.9 (HN*C*O), 145.3 (*C*$_q$-triazole), 122.9 (triazole-*C*H), 80.2 (*C*$_q$(CH_3)$_3$), 75.9 (FcAr-*C*$_q$), 70.7 (FcAr-*C*H), 69.8 (FcAr-*C*H), 68.3 (FcAr-*C*H), 64.1 (CO_2*C*H_2CH_2Si), 53.2 (N*C*H), 48.1 (triazole-*C*H_2), 36.7 (triazole-*C*H_2NH), 35.3 (*C*H_2NH), 32.5 (*C*H_2CONH), 30.3 (CH_2C*H*$_2$$CH_2$), 29.1 (*C*$H_2CH_2$CONH), 28.5 ($C_q$(*C*$H_3$)$_3$, 17.6 (*C*$H_2$Si), -1.4 (Si(*C*$H_3$)$_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{27}H_{40}FeN_6O_4Si$: 597.23, found 597.22.

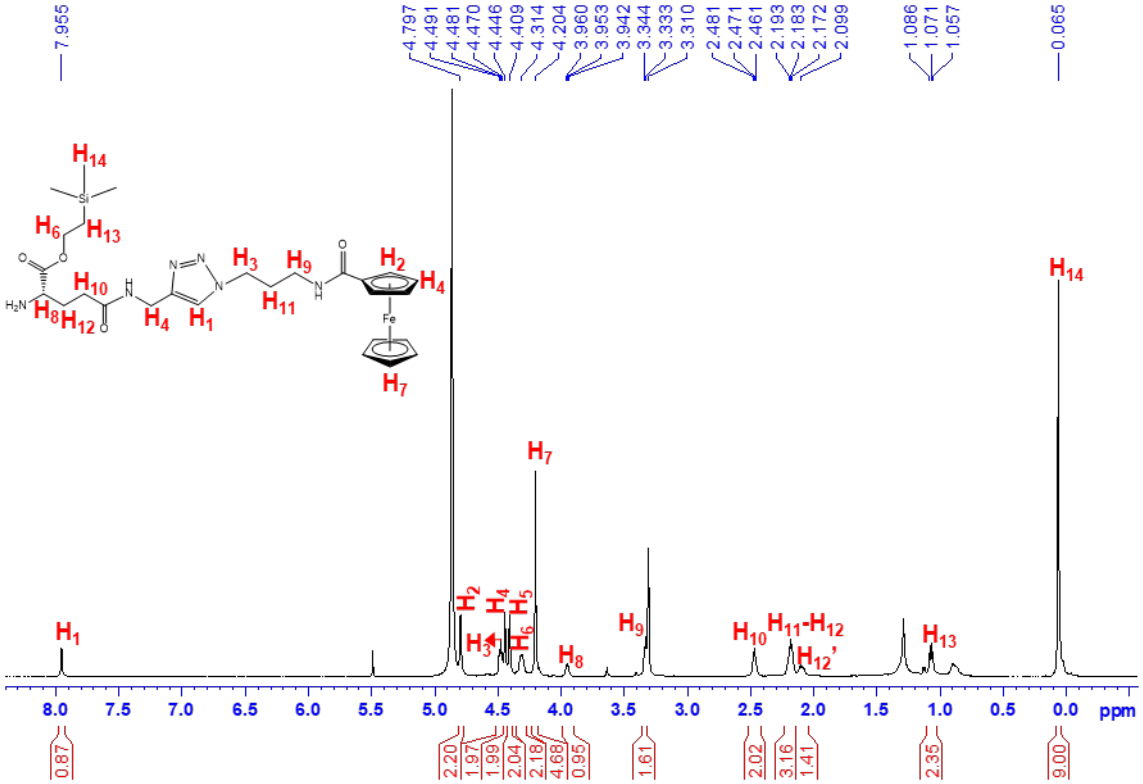


Figure S28. ^{1}H NMR spectrum of compound **9** (600 MHz, CD_3OD, 298 K).

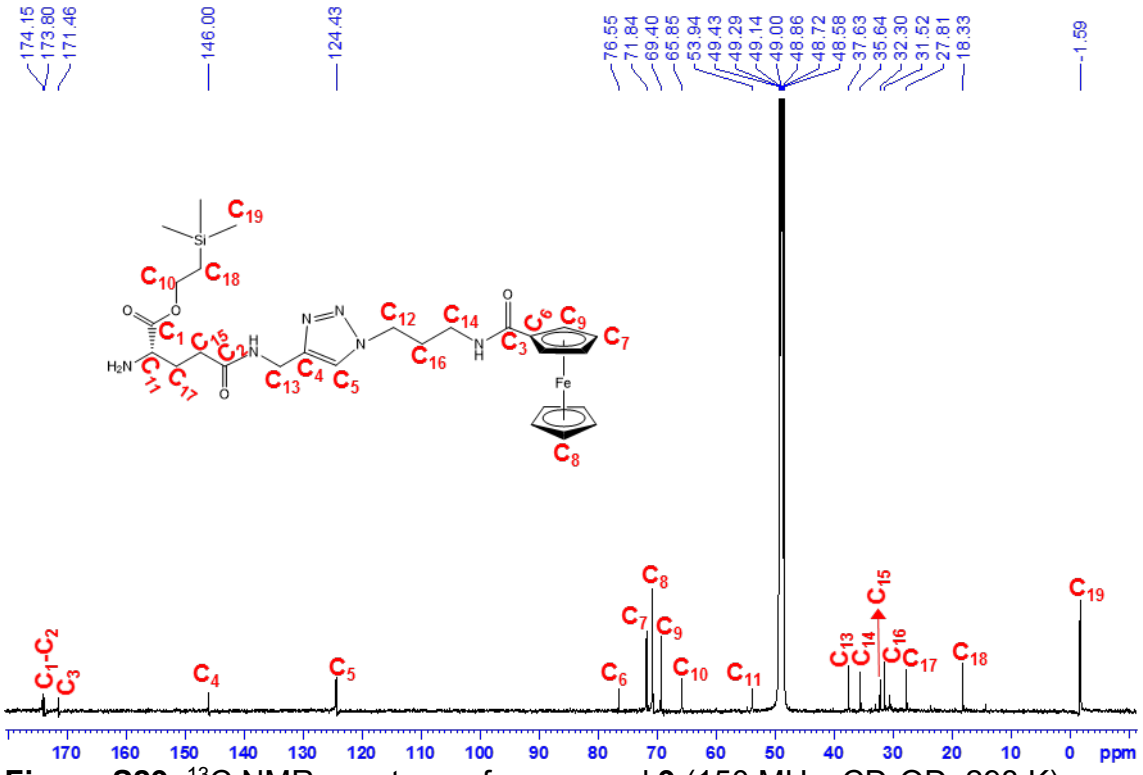


Figure S29. ^{13}C NMR spectrum of compound **9** (150 MHz, CD_3OD, 298 K).

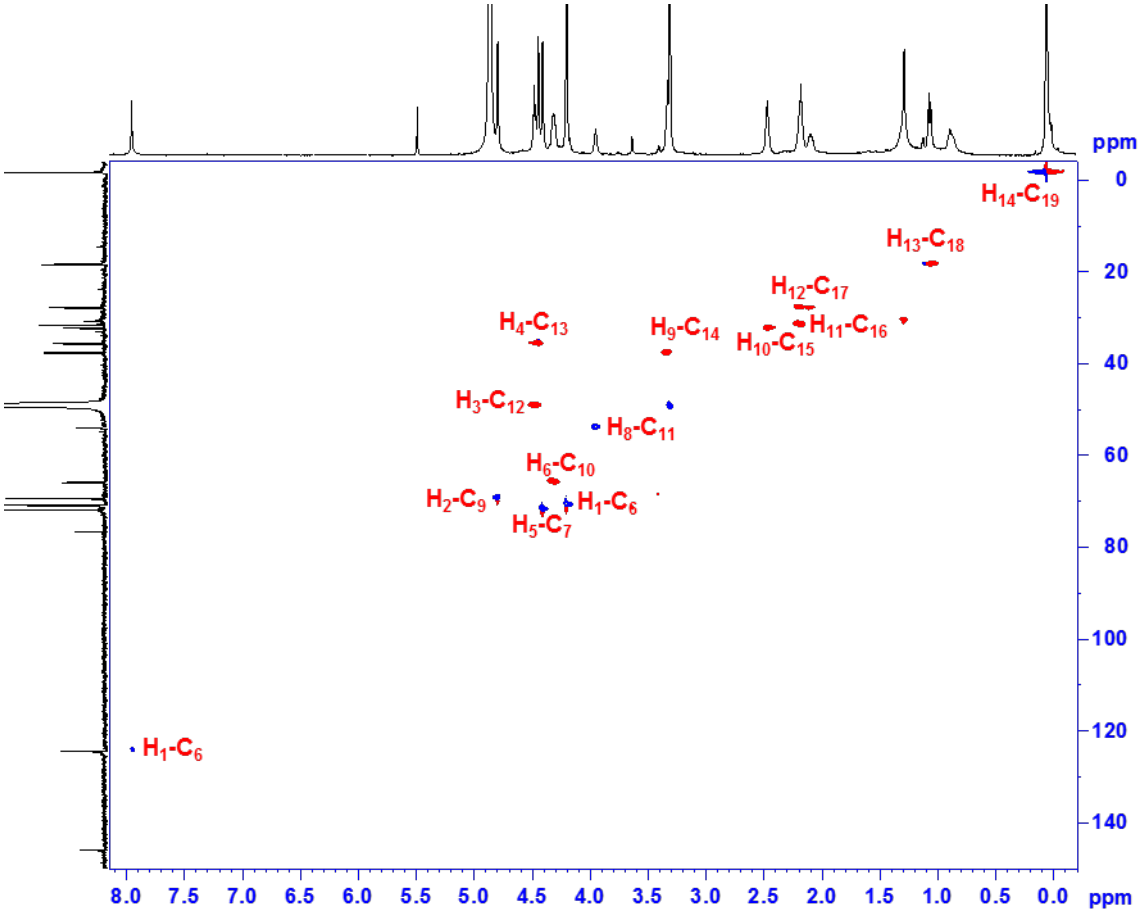


Figure S30. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of compound **9** recorded in CD_3OD at 298 K (600 MHz).

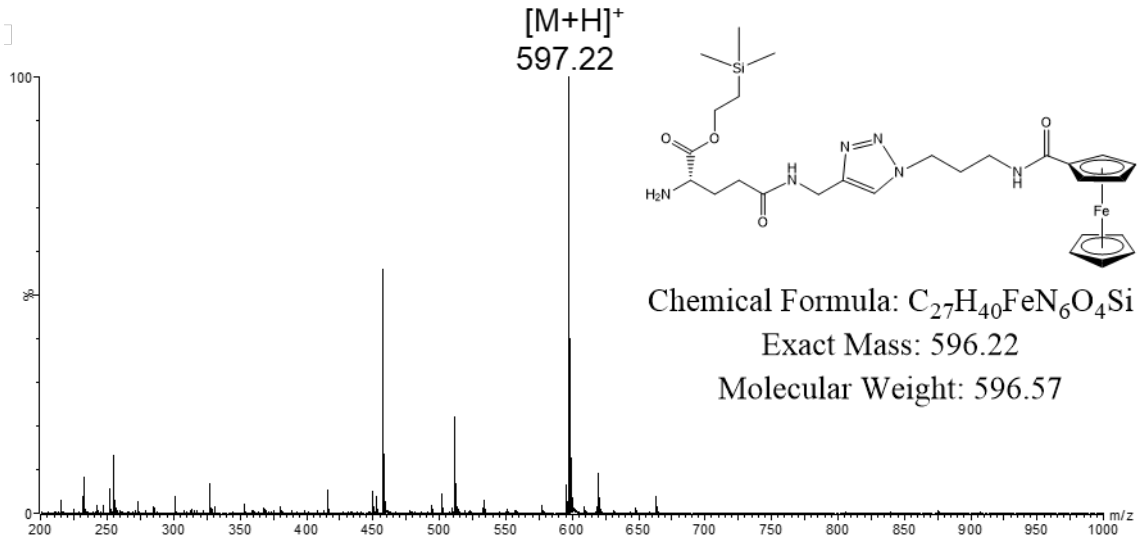
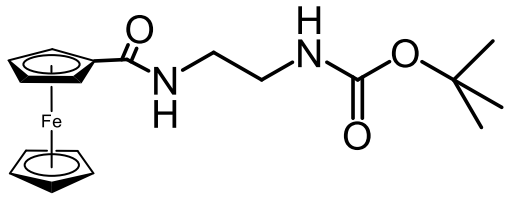


Figure S31. ESI mass spectrum of compound **9**.

2.10 Compound 10



Chemical Formula: $C_{18}H_{24}FeN_2O_3$
Exact Mass: 372.11
Molecular Weight: 372.25

In an air free Schlenk flask, ferrocenecarboxylic acid (0.43 mmol, 100 mg), N,N-diisopropylethylamine (3 eq, 1.3 mmol, 169 mg, 0.227 mL), HATU (1.1 eq, 0.48 mmol, 182 mg) and N-Boc-ethylenediamine (1.4 eq, 0.65 mmol, 104 mg, 103 μL) were dissolved in 5 mL of anhydrous N,N-dimethylformamide. The mixture was stirred for 12 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography using silica gel and hexane:ethyl acetate (solvent mixture gradient from 100:00 until 70:30) as eluent. Compound **7** was obtained as a red solid in 84% yield (137 mg).

^{1}H NMR ($(CD_3)_2CO$, 500 MHz), δ (ppm): 7.34 (*s*, CON*H*, 1H), 6.24 (*s*, CON*H*, 1H), 4.79 (*br*, Fc-*H*, 2H), 4.36 (*br*, Fc-*H*, 2H), 4.20 (*s*, Fc-*H*, 5H), 3.40 (*q*, *J* = 6.1 Hz, CH_2NH, 2H), 3.26 (*q*, *J* = 6.1 Hz, CH_2NH, 2H), 1.42 (*s*, C(CH_3)$_3$, 9H). **^{13}C NMR** ($(CD_3)_2CO$, 125 MHz), δ (ppm): 170.3 (*C*ONH), 156.4 (*C*ONH), 78.2 (*C*$(CH_3)_3$), 76.3 (ArFc-C_q), 70.1 (ArFc-*C*H), 69.5 (ArFc-*C*H), 68.2 (ArFc-*C*H), 40.3 (NH*C*H_2), 39.4 (HN*C*H_2), 27.5 (C(*C*H_3)$_3$). **ESI-MS** $[M+Na]^+$ m/z calcd for $C_{18}H_{24}FeN_2O_3$: 395.10, found 395.10.

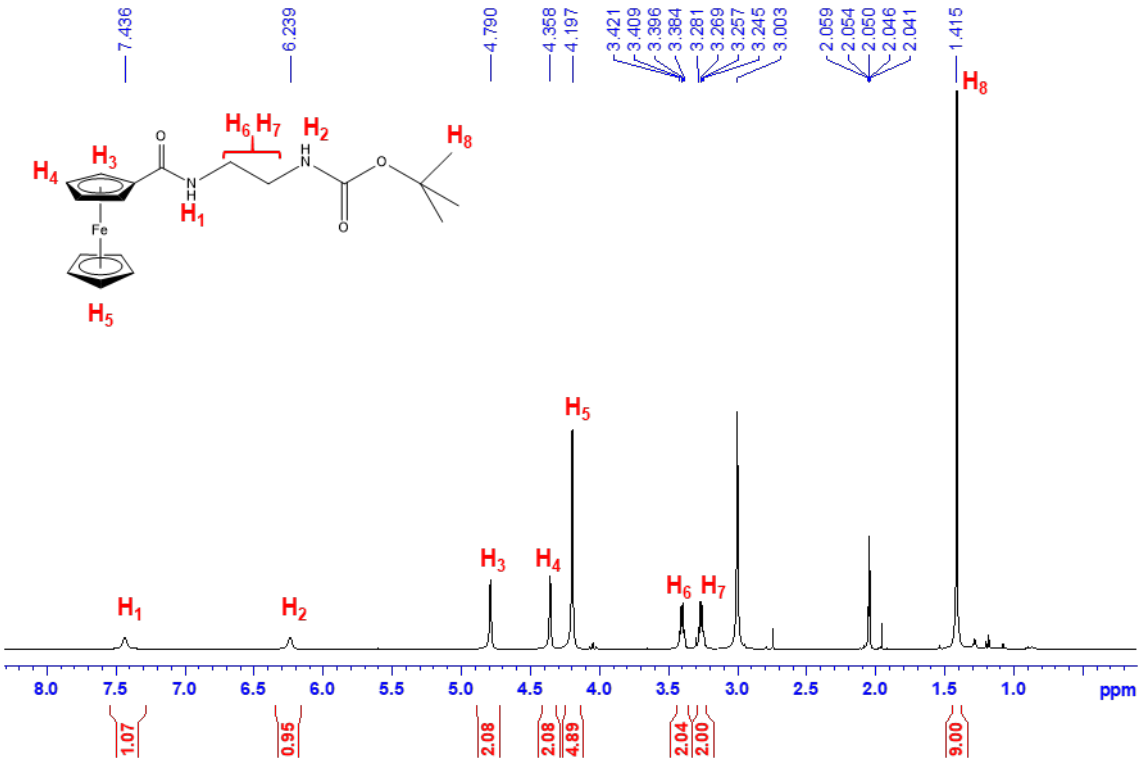


Figure S32. ^{1}H NMR spectrum of compound **10** (500 MHz, $(CD_3)_2CO$, 298 K).

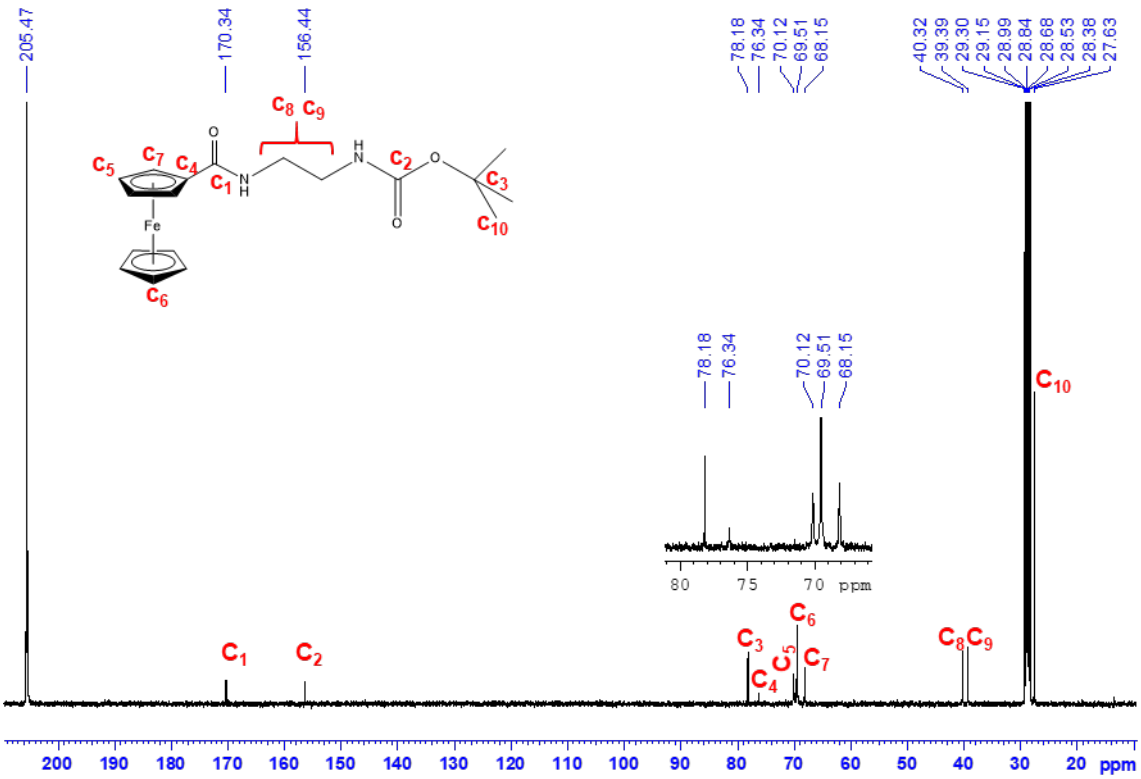


Figure S33. ^{13}C NMR spectrum of compound **10** (125 MHz, $(CD_3)_2CO$, 298 K).

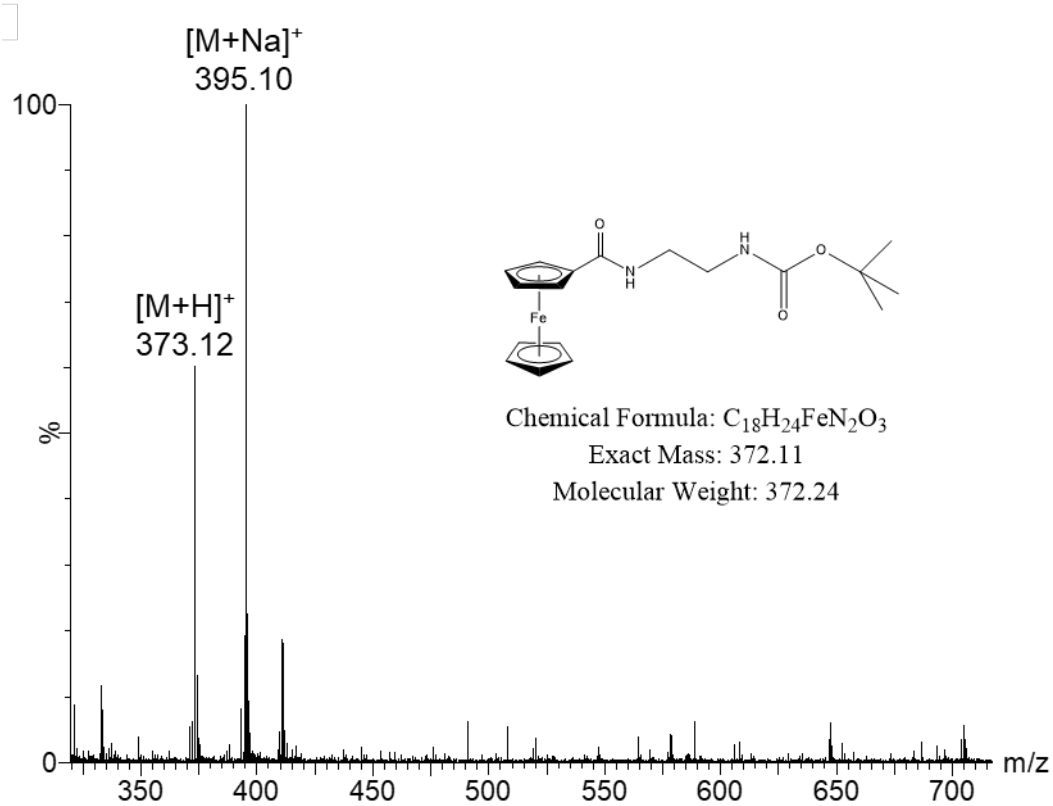
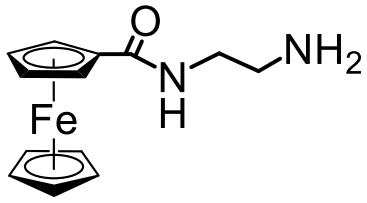


Figure S34. ESI mass spectrum of compound **10**.

2.11 Compound 11



Chemical Formula: $C_{13}H_{16}FeN_2O$
Exact Mass: 272.06
Molecular Weight: 272.13

In an air free Schlenk flask, compound **10** (0.27 mmol, 100 mg) was dissolved in 40 mL of water and 160 mL of formic acid. The mixture was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3 x 30 mL) and hexane (3 x 30 mL). Compound **11** was obtained as red oil in quantitative yield (73 mg).

^{1}H NMR (CD_3OD, 500 MHz), δ (ppm): 4.80 (*t*, *J* = 1.9 Hz, Fc-*H*, 2H), 4.44 (*t*, *J* = 1.9 Hz, Fc-*H*, 2H), 4.21 (*s*, Fc-*H*, 5H), 3.58 (*t*, *J* = 6.0 Hz, C*H*$_2$NH, 2H), 3.1 (*t*, *J* = 6.0 Hz, C*H*$_2$NH, 2H) **^{13}C NMR** ((CD_3OD, 125 MHz), δ (ppm): 175.0 (*C*ONH), 75.8 (ArFc-*C*$_q$), 72.1 (ArFc-*C*H), 70.9 (ArFc-*C*H), 69.5 (ArFc-*C*H), 41.1 (NH*C*H$_2$), 38.6 (HN*C*H$_2$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{13}H_{16}FeN_2O$: 273.07, found 273.10.

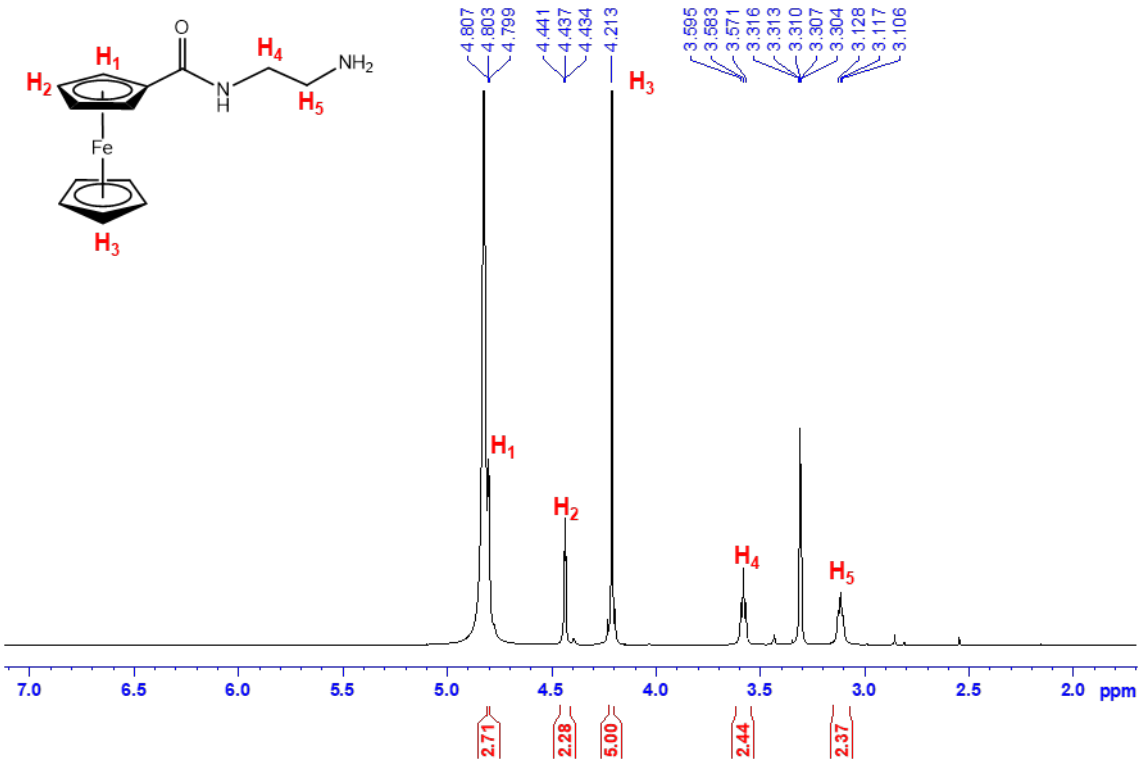


Figure S35. ^{1}H NMR spectrum of compound **11** (500 MHz, CD_3OD, 298 K).

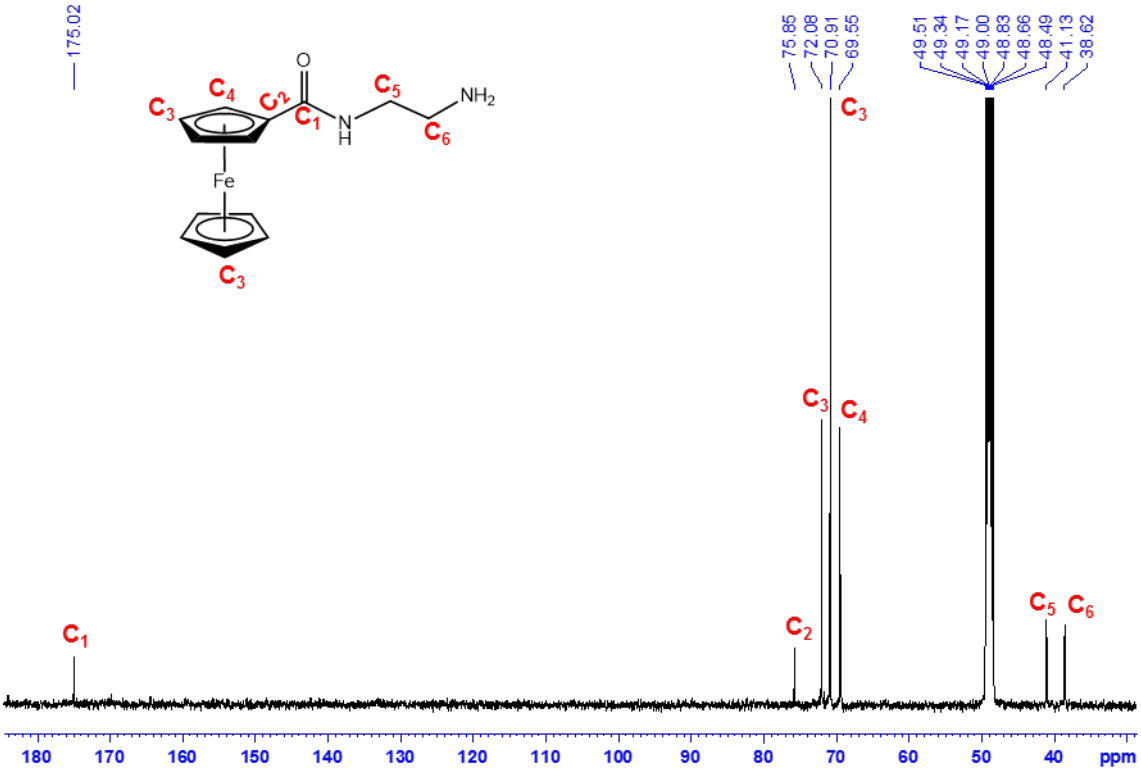


Figure S36. ^{13}C NMR spectrum of compound **11** (125 MHz, CD_3OD, 298 K).

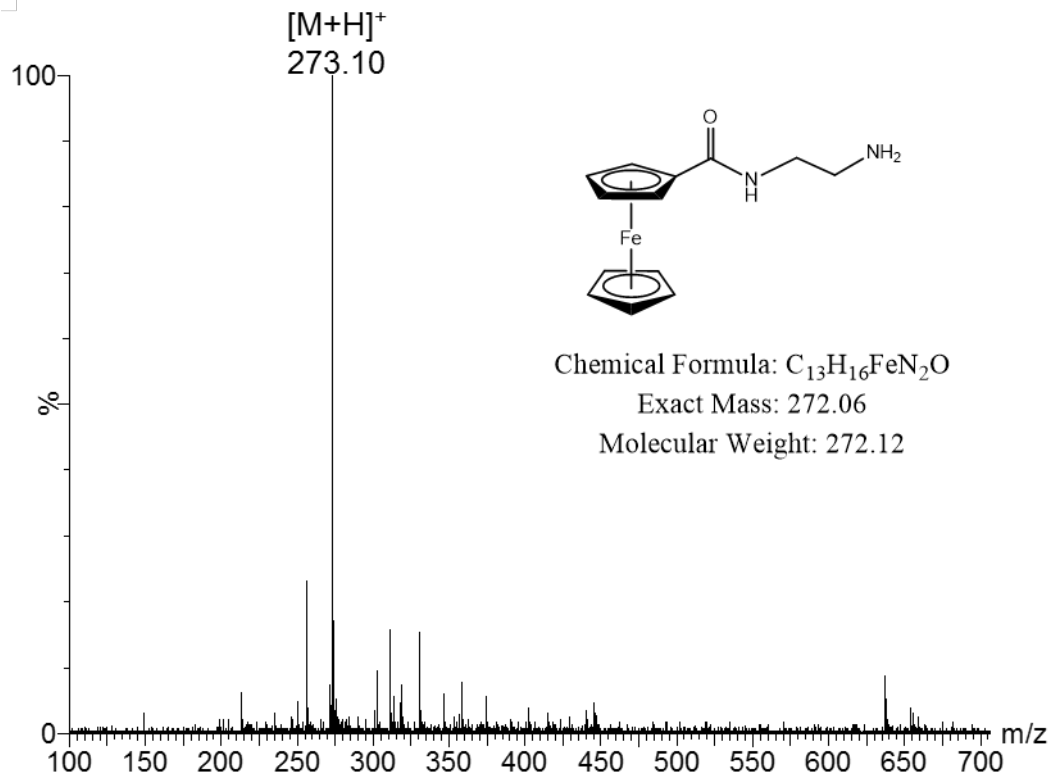
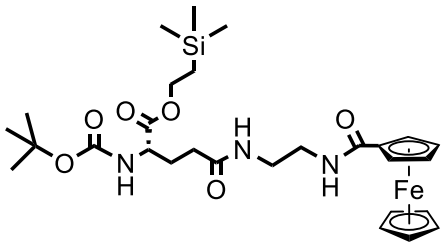


Figure S37. ESI mass spectrum of compound **11**.

2.12 Compound 12



Chemical Formula: $C_{28}H_{43}FeN_3O_6Si$
Exact Mass: 601.23
Molecular Weight: 601.60

In an air free Schlenk flask, compound **2** (0.24 mmol, 85 mg), N,N-diisopropylethylamine (6 eq, 1.47 mmol, 181 mg, 0.256 mL), HATU (1.1 eq, 0.27 mmol, 102 mg) and compound **11** (1.2 eq, 0.29 mmol, 0.080 mg) were dissolved in 5 mL of anhydrous N,N-dimethylformamide. The mixture was stirred for 12 h, at room temperature and under nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product was further purified by column chromatography using silica gel and hexane:ethyl acetate (solvent mixture gradient from 20:80 until 0:100) as eluent. Compound **12** was obtained as a red oil in 88% yield (156 mg).

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.06 (*s*, CON*H,* 1H), 7.01 (*s*, CON*H*, 1H), 5.41 (*d*, *J* = 7.7 Hz, N*H*, 1H), 4.76 (*br*, Fc-*H*, 2H), 4.34 (*br*, Fc-*H*, 2H), 4.21 (*br*, NHC*H*, CO_2CH_2, Fc-*H*, 8H), 3.46 (*m*, $NHCH_2CH_2NH$, 4H), 2.23 (*t*, *J* = 6.9 Hz, CH_2CON, 2H), 2.18-2.10 (*m*, $CHCH_2$, 1H), 1.96-1.86 (*m*, $CHCH_2$', 1H), 1.42 (*s*, $CO_2C(CH_3)_3$, 9H), 0.96 (*m*, CH_2Si, 2H), 0.01 (*s*, $Si(CH_3)_3$, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz), δ (ppm): 173.7 (CO_2CH_2), 172.5 (*C*ONH), 171.8 (*C*ONH), 156.0 (HN*C*O), 80.3 ($C_q(CH_3)_3$), 76.0 (FcAr-C_q), 71.0 (FcAr-*C*H), 70.2 (FcAr-*C*H), 68.7 (FcAr-*C*H), 64.2 ($CO_2CH_2CH_2Si$), 53.1 (N*C*H), 40.5 ($NHCH_2$), 40.1 ($NHCH_2$), 32.5 (CH_2CONH), 29.1 (CH_2CH_2CONH), 28.4 ($C_q(CH_3)_3$, 17.5 (CH_2Si), -1.4 ($Si(CH_3)_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{28}H_{43}FeN_3O_6Si$: 602.23, found 602.23.

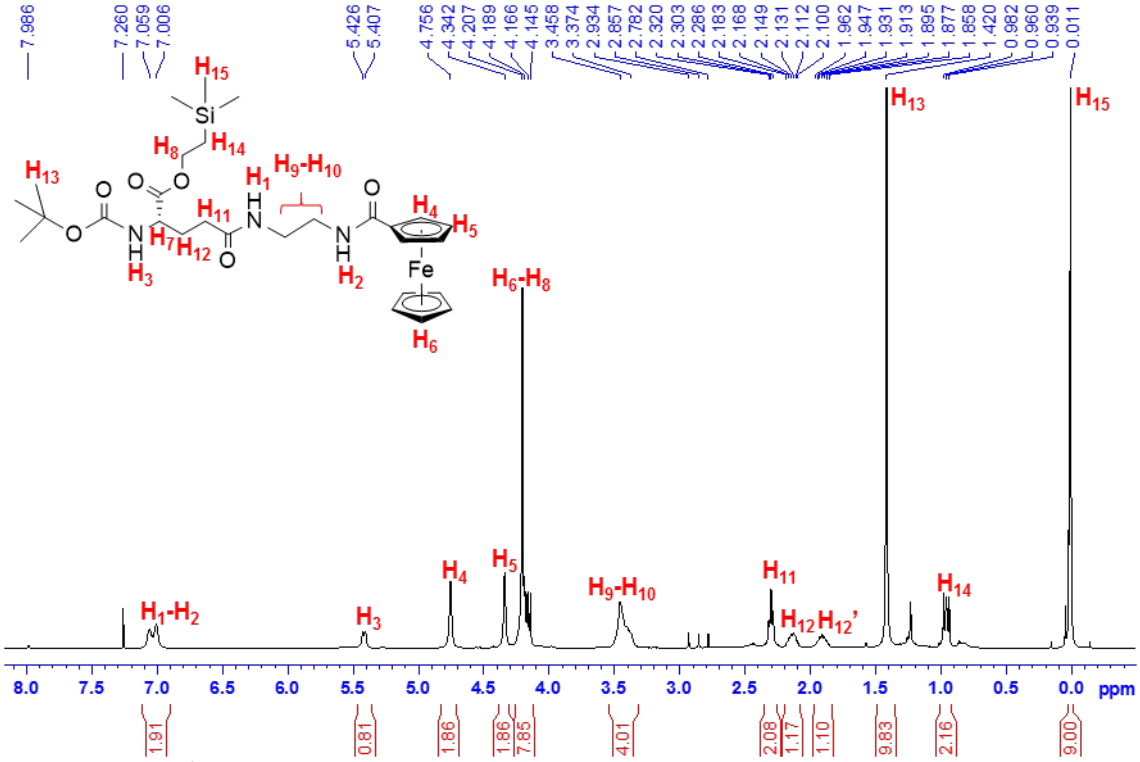


Figure S38. ^{1}H NMR spectrum of compound **12** (400 MHz, $CDCl_3$, 298 K).

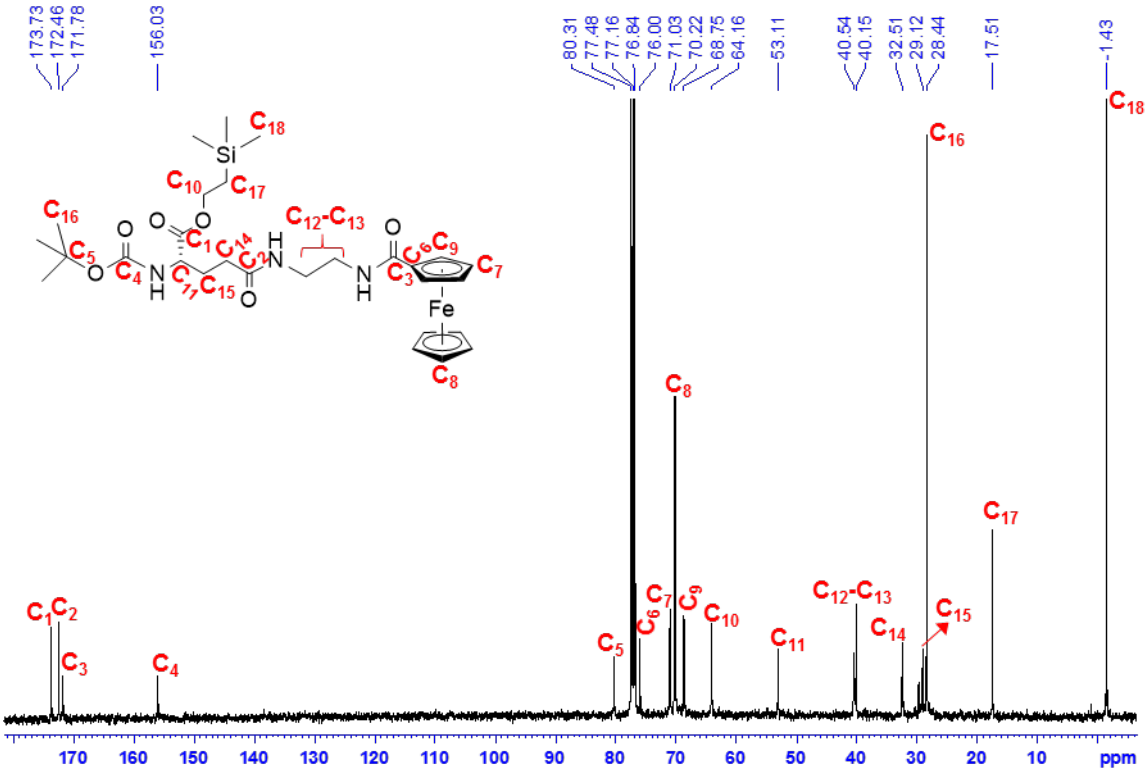


Figure S39. ^{13}C NMR spectrum of compound **12** (100 MHz, $CDCl_3$, 298 K).

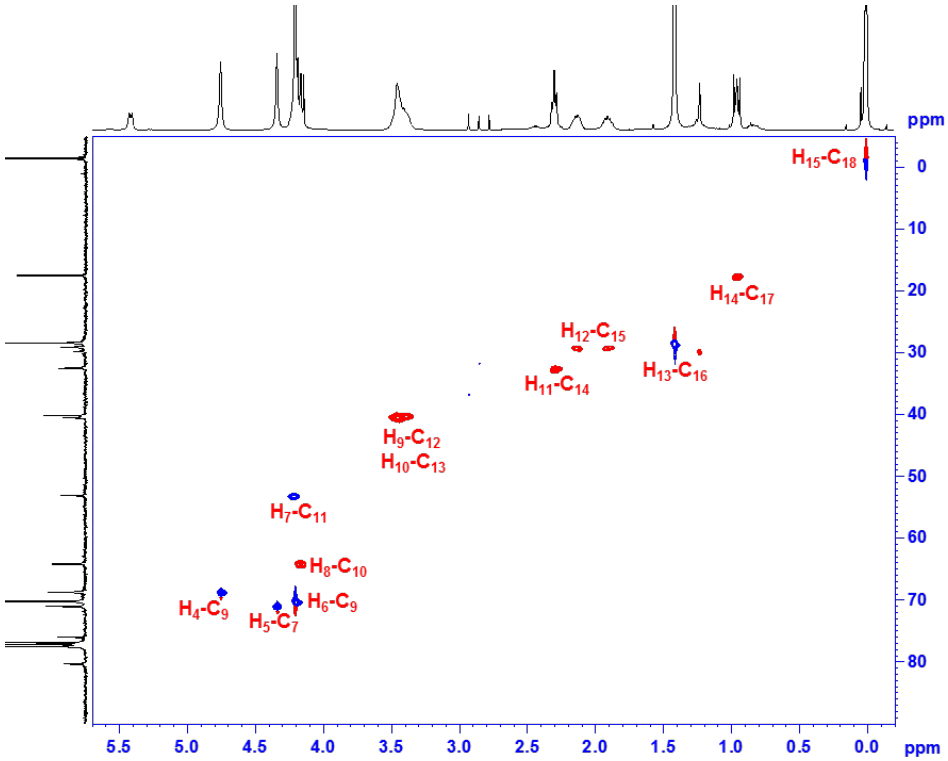


Figure S40. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of compound **12** recorded in $CDCl_3$ at 298 K (400 MHz).

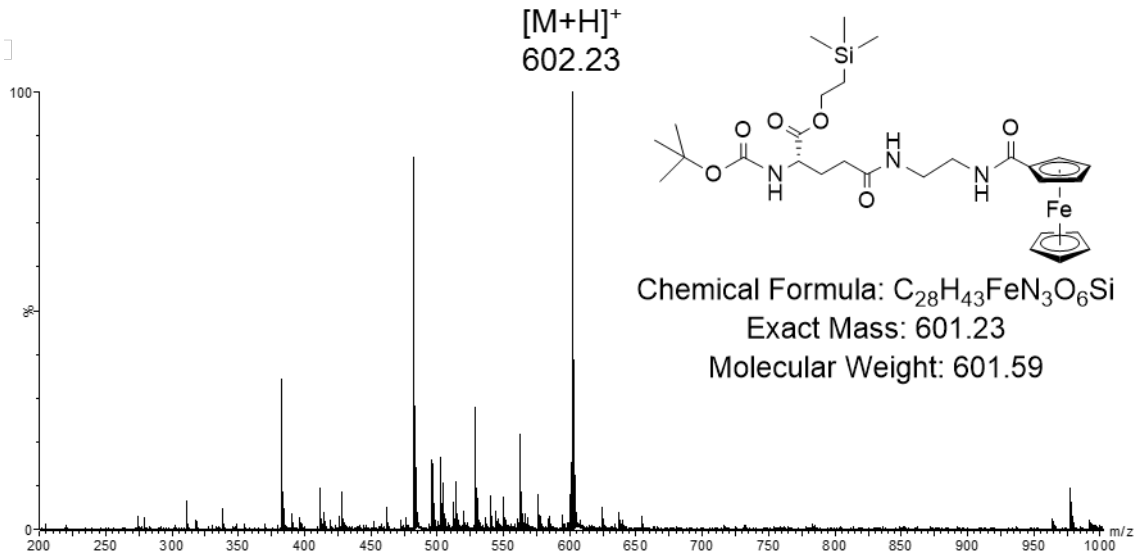
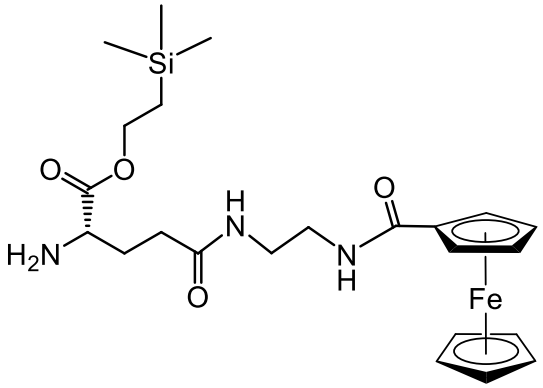


Figure S41. ESI mass spectrum of compound **12**.

2.13 Compound 13



Chemical Formula: $C_{23}H_{35}FeN_3O_4Si$
Exact Mass: 501.17
Molecular Weight: 501.48

In an air free Schlenk flask, compound **12** (0.27 mmol, 100 mg) was dissolved in 20 mL of water and 80 mL of formic acid. The mixture was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3 x 30 mL) and hexane (3 x 30 mL). Compound **13** was obtained as red oil in quantitative yield (73 mg).

^{1}H NMR (CD_3OD, 500 MHz), δ (ppm): 4.78 (*br*, Fc-*H*, 2H), 4.40 (*br*, Fc-*H*, 2H), 4.26 (*br*, $OCOC\mathit{H}_2$, 2H), 4.19 (*s*, Fc-*H*, 5H), 3.76 (*br*, $NHC\mathit{H}$, 1H), 3.43 (*m*, $C\mathit{H}_2NH$, 2H), 3.38 (*m*, $C\mathit{H}_2NH$, 2H), 2.40 (*br*, $C\mathit{H}_2CON$, 2H), 2.13 (*m*, $CHC\mathit{H}_2$, 1H), 2.02 (*m*, $CHC\mathit{H}_2$', 1H), 1.04 (*m*, $C\mathit{H}_2Si$, 2H), 0.06 (*s*, $Si(C\mathit{H}_3)_3$, 9H). **^{13}C NMR** (CD_3OD, 125 MHz), δ (ppm): 175.0 ($\mathit{C}O_2CH_2$), 173.9 ($\mathit{C}ONH$), 173.2 ($\mathit{C}ONH$), 76.5 (FcAr-C_q), 71.8 (FcAr-*C*H), 70.9 (FcAr-*C*H), 69.4 (FcAr-*C*H), 65.3 ($CO_2\mathit{C}H_2CH_2Si$), 54.2 ($N\mathit{C}H$), 40.5 ($NH\mathit{C}H_2$), 40.2 ($NH\mathit{C}H_2$), 32.7 ($\mathit{C}H_2CONH$), 29.2 ($\mathit{C}H_2CH_2CONH$), 18.3 ($\mathit{C}H_2Si$), -1.5 ($Si(\mathit{C}H_3)_3$). **ESI-MS** $[M+H]^+$ m/z calcd for $C_{23}H_{35}FeN_3O_4Si$: 502.18, found 502.18.

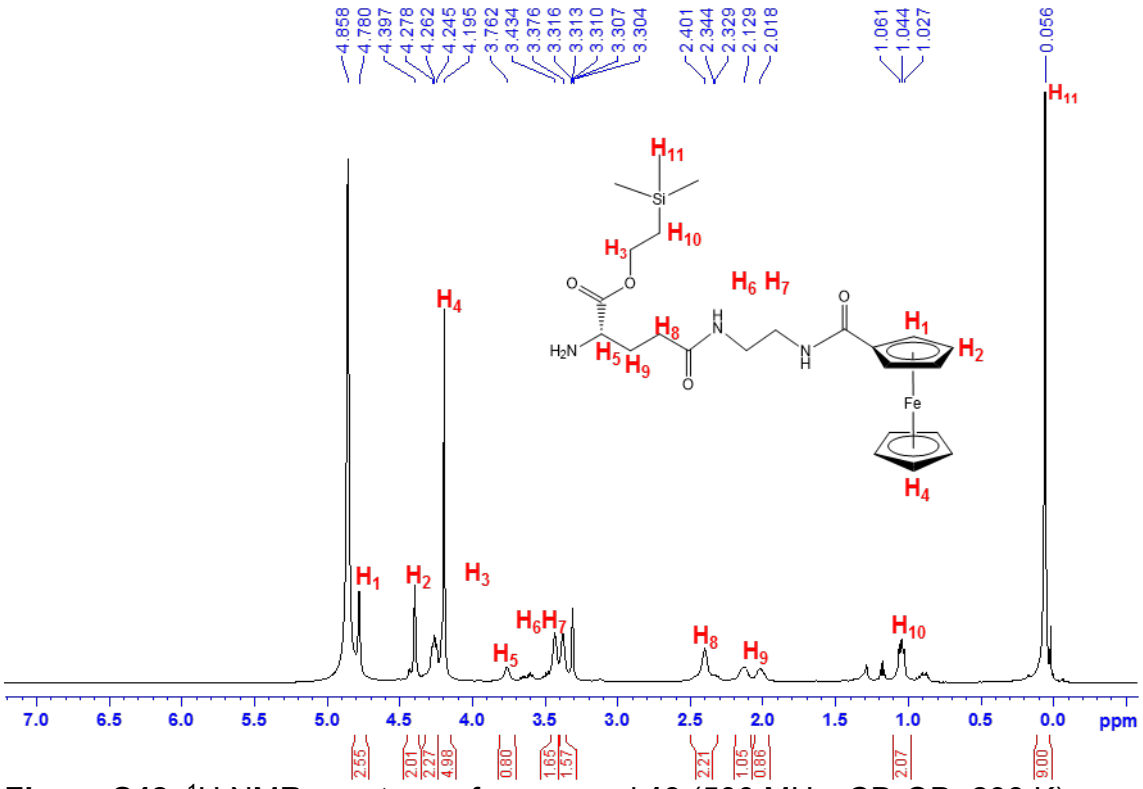


Figure S42. ^{1}H NMR spectrum of compound **13** (500 MHz, CD_3OD, 298 K).

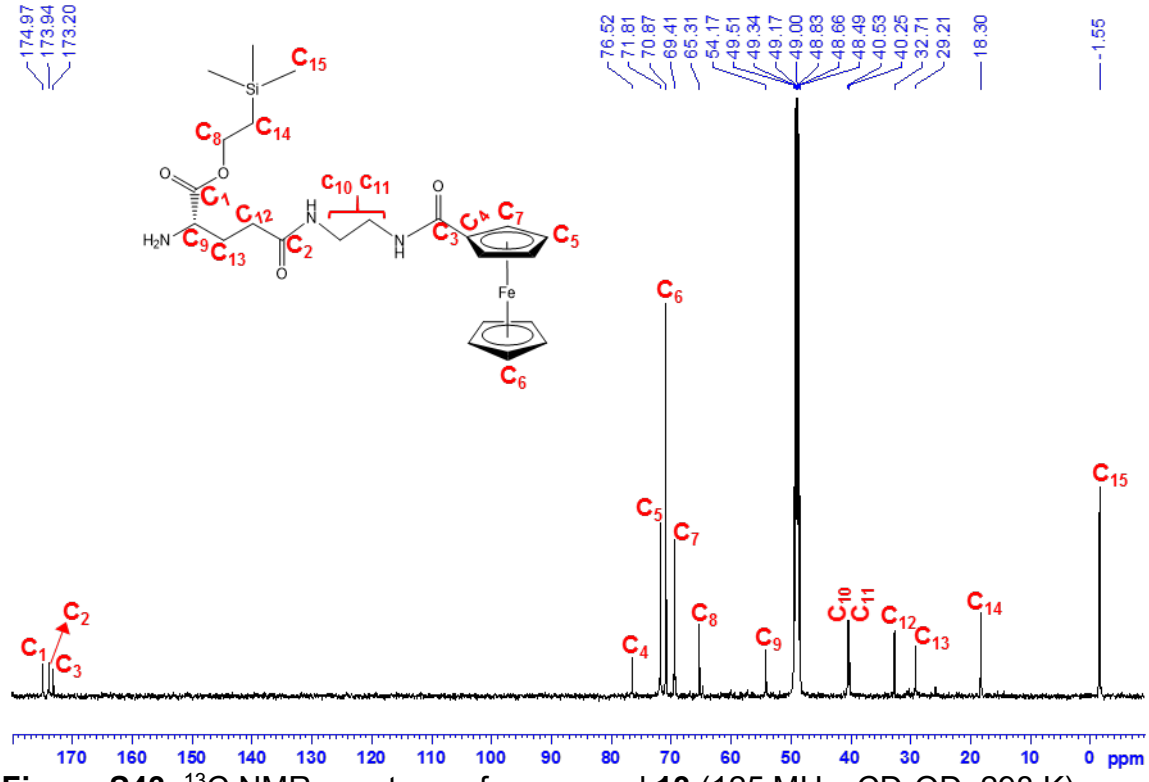


Figure S43. ^{13}C NMR spectrum of compound **13** (125 MHz, CD_3OD, 298 K).

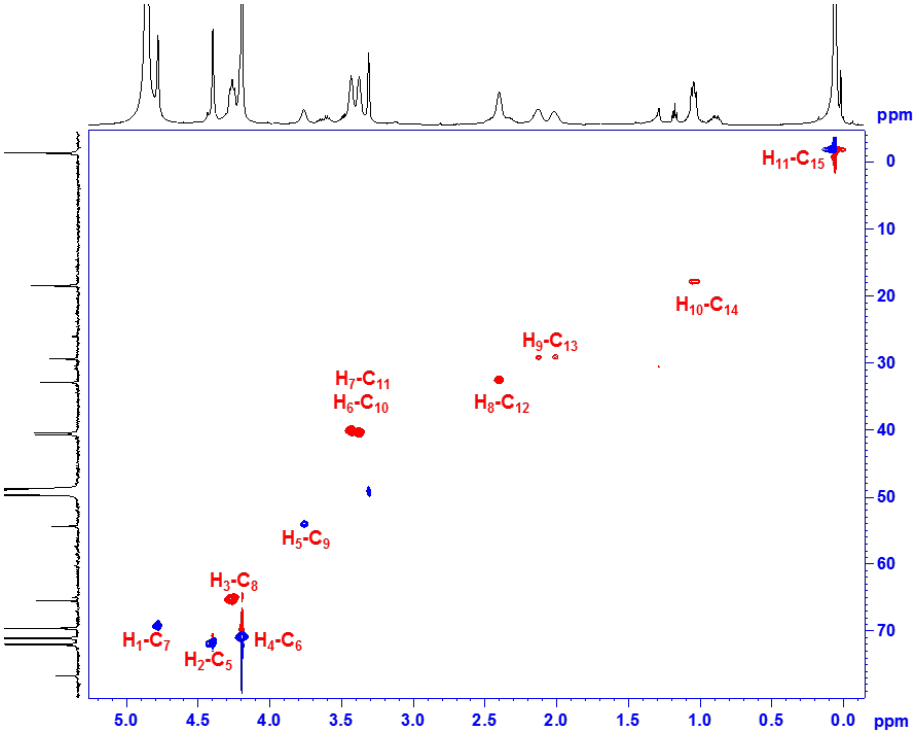


Figure S44. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of compound **13** recorded in CD_3OD at 298 K (500 MHz).

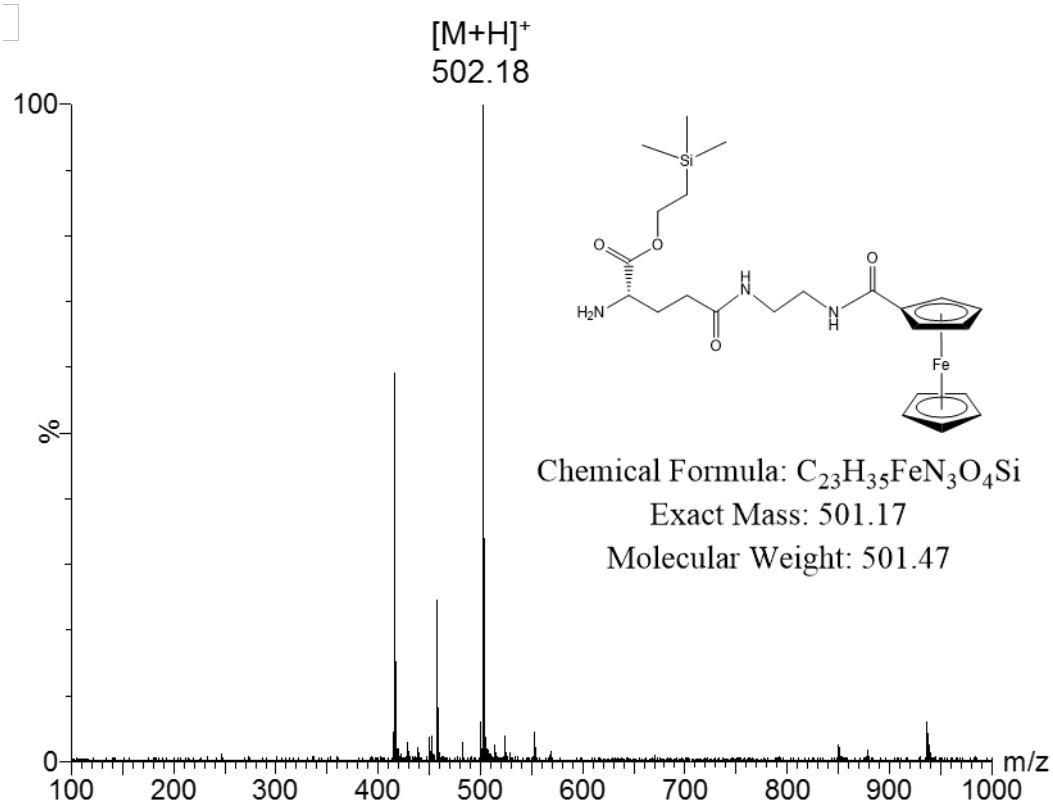
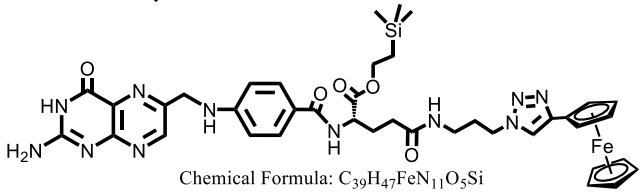


Figure S45. ESI mass spectrum of compound **13**.

2.14 Protected folate γ-Fc 18



Chemical Formula: $C_{39}H_{47}FeN_{11}O_5Si$
Exact Mass: 833.29
Molecular Weight: 833.81

In a Schlenk flask, Pte-N_3 **14** (50 mg, 0.14 mmol), Glu γ-Fc **5** (1.5 eq, 128 mg, 0.22 mmol) were dissolved in 7.5 mL of anhydrous dimethyl sulfoxide (DMSO). After complete dissolution, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (3 eq, 0.445 mmol, 68 mg, 64 μL) was slowly added. The mixture was stirred in the dark under nitrogen gas atmosphere for 12 h. The solution was precipitated in a mixture of diethyl ether and acetone (2:1, 100 mL). The solids was purified by column chromatography on silica gel with dichloromethane:methanol:trimethylamine (solvent mixture gradient from 99:0:1 until 79:20:1). Folate γ-Fc **18** was obtained as a brown solid in 60% yield (74 mg).

^{1}H NMR (DMSO-D_6, 500 MHz), δ (ppm): 8.65 (*s*, C(7)-*H*, 1H), 8.28 (*t*, *J* = 7.2 Hz, C(7')ON*H*, 1H), 8.14 (*s*, triazole-*H* ,1H), 7.94 (*t*, *J* = 5.4 Hz, CON*H*, 1H), 7.66 (*d*, *J* = 8.6 Hz, Ar(6'-2')-*H*, 2H), 6.93 (*br*, CON(3)*H* and N(2)H_2, 4H), 6.64 (*d*, *J* = 8.6 Hz, Ar(5'-3')-*H*, 2H), 4.96 (*t*, *J* = 1.5 Hz, Fc-*H*, 2H), 4.49 (*d*, *J* = 5.7 Hz, N(9)CH_2, 2H), 4.33 (*m*, C*H* and triazole-CH_2, 2H), 4.28 (*t*, *J* = 1.5 Hz, Fc-*H*, 2H), 4.11 (*m*, CO_2CH_2, 2H), 4.02 (*s*, Fc-*H*, 5H), 3.05 (*m*, CONHCH_2, 2H), 2.22 (*t*, *J* = 7.1 Hz, COCH_2, 2H), 2.08 (*m*, $COCH_2CH_2$', 1H), 1.98-1.91 (*m*, $COCH_2CH_2$'' and $NHCH_2CH_2$, 3H), 0.93 (*m*, SiCH_2, 2H), 0.00 (*s*, Si(CH_3)$_3$, 9H). **^{13}C NMR** (DMSO-D_6, 125 MHz), δ (ppm): 172.4 (CO_2CH_2), 171.5 (*C*ONH), 166.4 (*C*(7')ONH), 160.8 (*C*(4)ONH), 156.6 (Ar-C_q(2)), 153.7 (Ar-C_q(8a)), 150.8 (Ar-C_q(8')), 148.7 (Ar-*C*(7)), 145.1 (C_q-triazole), 131.1 (Ar-C_q(6)), 129.0 (Ar-*C*(6'-2')), 127.9 (Ar-C_q(4a)), 121.2 (Ar-C_q(1')), 120.7 (*C*-triazole), 111.2 (Ar-*C*(3'-5')), 76.1 (Ar-C_qFc), 69.2 (Ar-*C*Fc), 66.2 (Ar-*C*Fc), 69.3 (Ar*C*Fc), 62.4 (CO_2CH_2), 52.3 (HN*C*H), 47.1 (CH_2-triazole), 45.9 (*C*(9)H_2NH), 35.7 (CH_2NH), 31.8 (HNCOCH_2), 29.8 (CH_2 CH_2CH_2), 26.4 (CHCH_2), 16.8 (SiCH_2), -1.5 (Si(*C*H_3)$_3$). **ESI-QTOF-MS** $[M+H]^+$ m/z calcd for $C_{39}H_{47}FeN_{11}O_5Si$: 834.2960, found 834.2935.

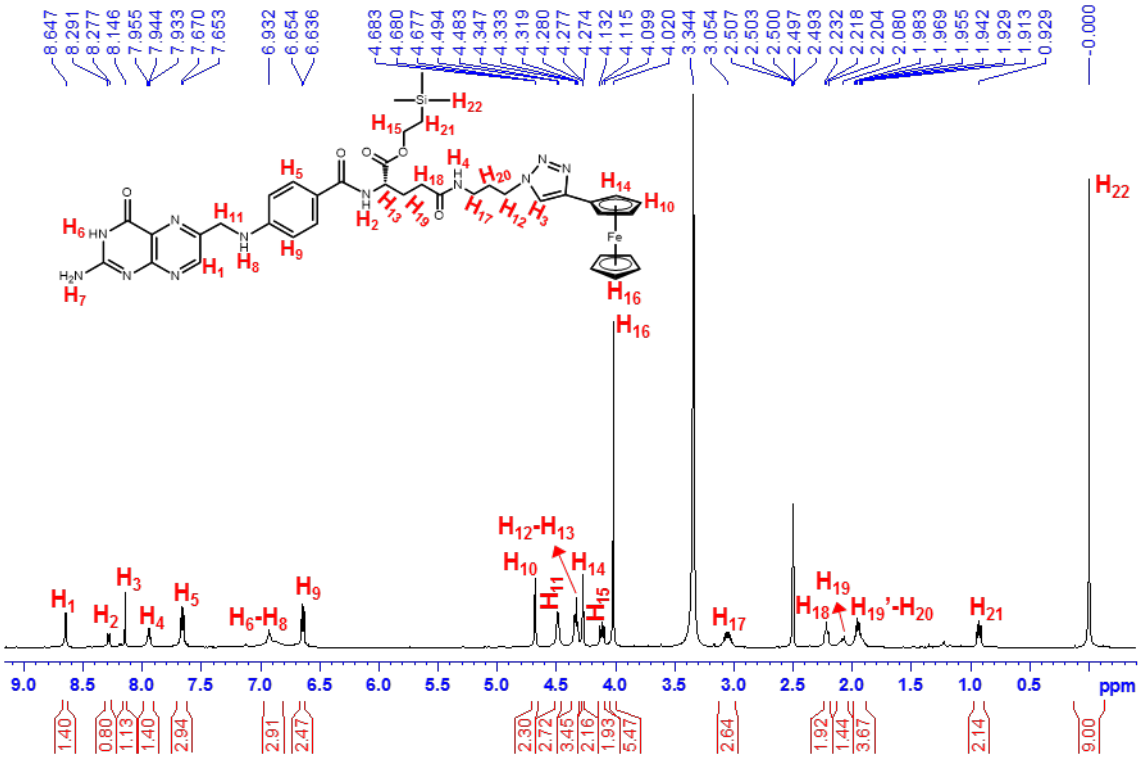


Figure S46. ^{1}H NMR spectrum of protected folate γ-Fc **18** (500 MHz, DMSO-D_6, 298 K).

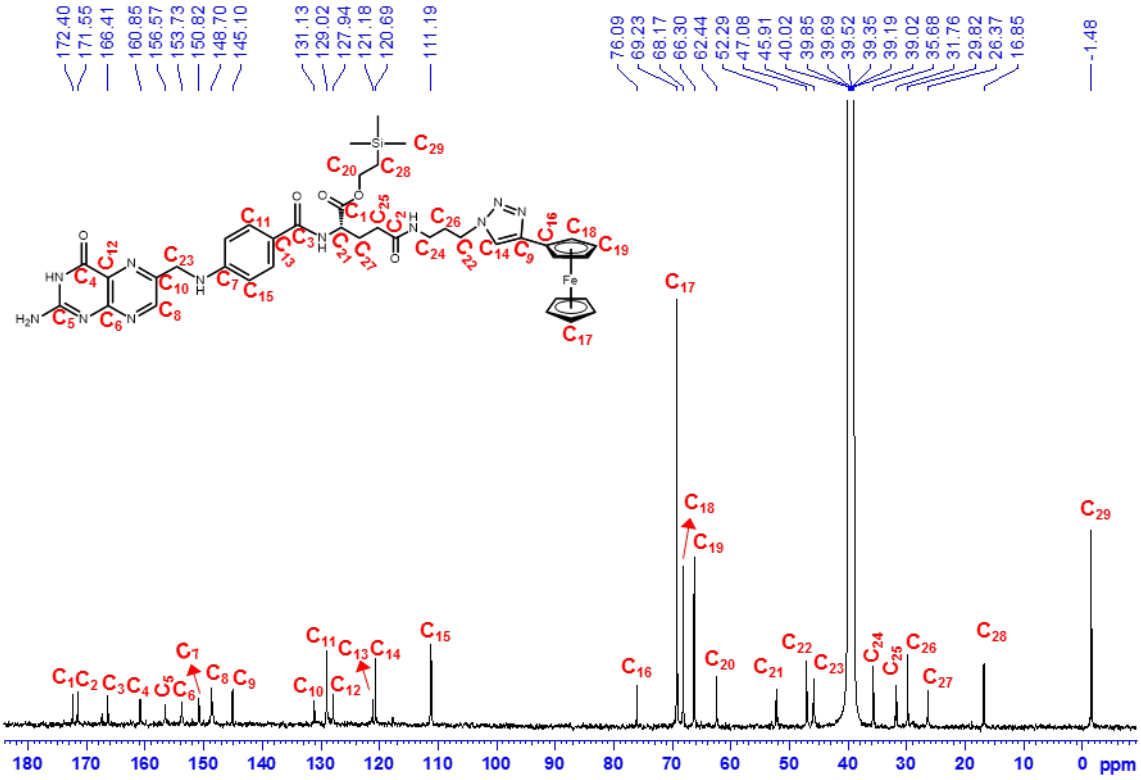


Figure S47. ^{13}C NMR spectrum of protected folate γ-Fc **18** (125 MHz, DMSO-D_6, 298 K).

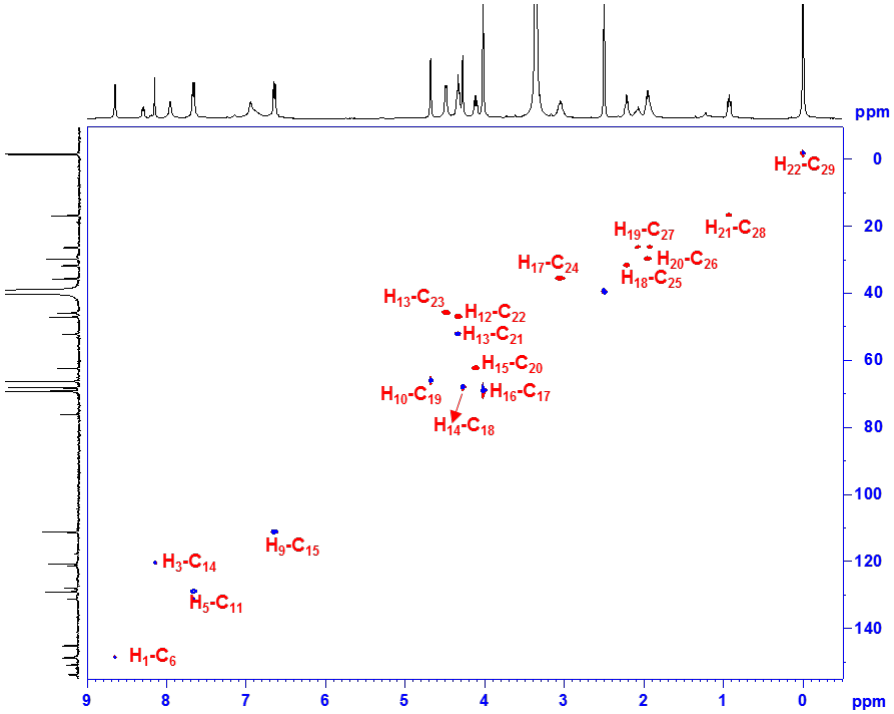


Figure S48. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of protected folate γ-Fc **18** recorded in DMSO-D_6 at 298 K (500 MHz).

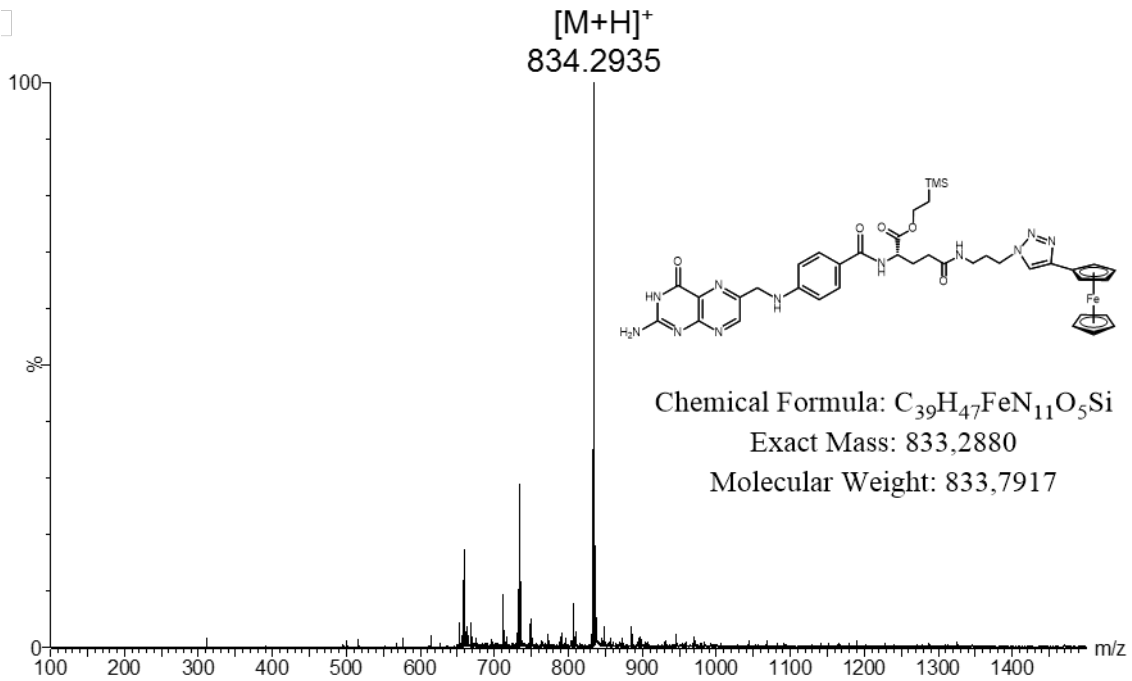


Figure S49. ESI-QTOF mass spectrum of protected folate γ-Fc **18**.

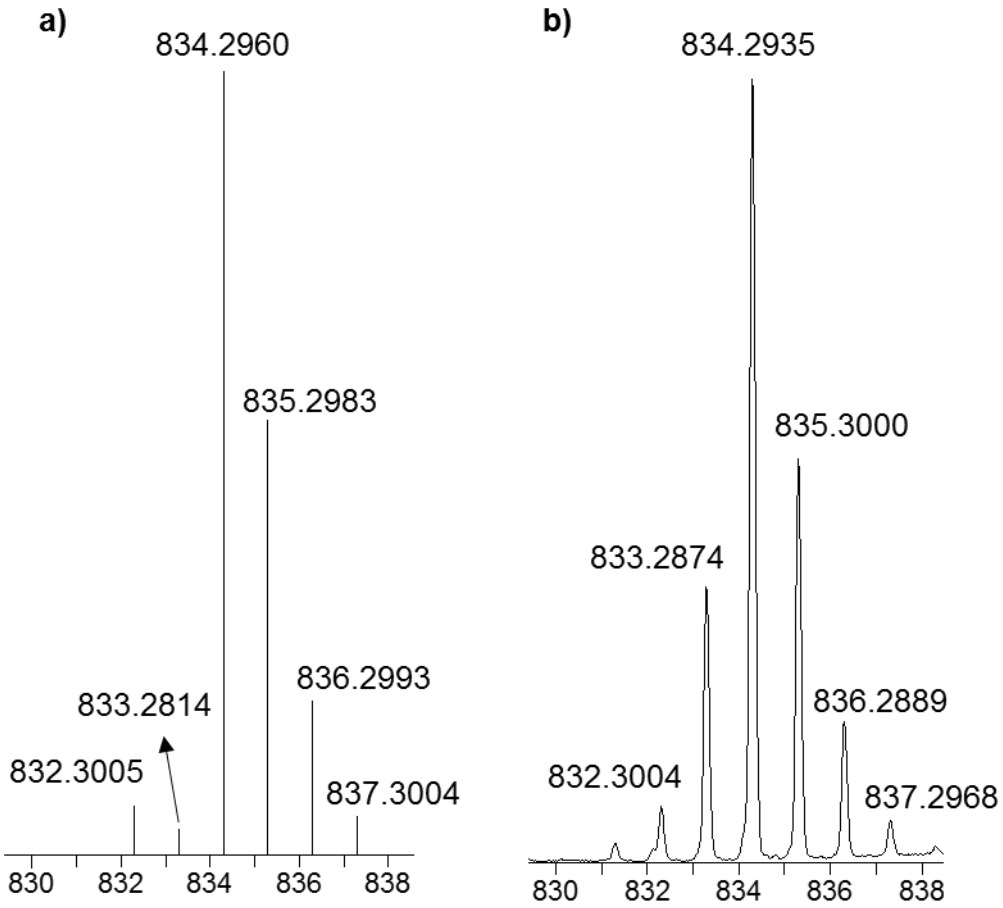
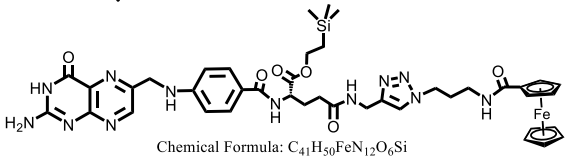


Figure S50. A zoom on the ESI-QTOF mass spectrum of protected folate γ-Fc **18**. Left: theoretical isotopic distribution for $[M+H]^+$. Right: experimental isotopic distribution for $[M+H]^+$.

2.15 Protected folate γ-Fc 19



Chemical Formula: $C_{41}H_{50}FeN_{12}O_6Si$
Exact Mass: 890.31
Molecular Weight: 890.86

In a Schlenk flask, Pte-N_3 **14** (70 mg, 0.21 mmol), Glu γ-Fc **9** (1.3 eq, 0.27 mmol, 161 mg) were dissolved in 1.4 mL of anhydrous DMSO. After complete dissolution, MTBD (2 eq, 0.42 mmol, 64 mg, 60 μL) was slowly added. The reaction mixture was stirred in the dark, under nitrogen gas atmosphere, for 12 h. The mixture was precipitated in a mixture of diethyl ether and acetone (2:1; 100 mL). The solid was purified by column chromatography on silica gel and dichloromethane:methanol:trimethylamine (solvent mixture gradient from 99:0:1 until 79:20:1) as eluent. Folate γ-Fc **19** was obtained as a brown solid in 56% yield (104 mg).

^{1}H NMR (DMSO-D_6, 500 MHz), δ (ppm): 8.64 (*s*, C(7)-*H*, 1H), 8.33 (*t*, *J* = 7.2 Hz, CON*H*, 1H), 8.28 (*d*, *J* = 5.5 Hz, CON*H*), 7.94 (*s*, triazole-*H* ,1H), 7.88 (*t*, *J* = 5.5 Hz, CON*H*, 1H), 7.65 (*d*, *J* = 8.6 Hz, Ar(6'-2')-*H*, 2H), 6.93 (*br*, CON(3)*H* and N(2)H_2, 4H), 6.64 (*d*, *J* = 8.6 Hz, Ar(5'-3')-*H*, 2H), 4.77 (*br*, Fc-*H*, 2H), 4.48 (*d*, *J* = 5.8 Hz, N(9)CH_2, 2H), 4.37 (*t*. *J* = 6.9 Hz, triazole-CH_2, 2H), 4.33-4.23 (*m*, NHC*H*, CONH-CH_2-triazole, Fc-*H*, 5H), 4.15 (*s*, Fc-*H*, 5H), 4.10 (*m*, CO_2CH_2, 2H), 3.19 (*q*, *J* = 6.4 Hz, CONHCH_2, 2H), 2.23 (*br* , COCH_2, 2H), 2.00-1.98 (*m*, $CH_2CH_2CH_2NH$, $COCH_2CH_2$', 3H), 1.95-1.88 (*m*, $COCH_2CH_2$'', 1H), 0.92 (*m*, SiCH_2, 2H), 0.00 (*s*, Si(CH_3)$_3$, 9H). **^{13}C NMR** (DMSO-D_6, 125 MHz), δ (ppm): 172.4 (CO_2CH_2), 171.4 (*C*ONH), 169.2 (*C*ONH), 166.5 (*C*(7')ONH), 160.8 (*C*(4)ONH), 156.6 (Ar-C_q(2)), 153.8 (Ar-C_q(8a)), 150.8 (Ar-C_q(8')), 148.7 (Ar-*C*(7)), 145.0 (C_q-triazole), 128.0 (Ar-*C*(6'-2') and Ar-C_q(6)), 128.0 (Ar-C_q(4a)), 122.8 (*C*-triazole), 121.2 (Ar-C_q(1')), 111.2 (Ar-*C*(3'-5')), 76.5 (Ar-C_qFc), 69.9 (Ar-*C*Fc), 69.3 (Ar-*C*Fc), 68.1 (Ar-*C*Fc), 62.4 (CO_2CH_2), 52.3 (HN*C*H), 47.1 (CH_2-triazole), 45.9 (*C*(9)H_2NH), 36.8 (CH_2NH), 34.3 ((*C*H_2NH)), 31.6 (HNCO*C*H_2), 30.3 ($CH_2CH_2CH_2$), 26.3 (CH*C*H_2), 16.8 (Si*C*H_2), -1.5 (Si(*C*H_3)$_3$). **ESI-QTOF-MS** $[M+H]^+$ m/z calcd for $C_{41}H_{50}FeN_{12}O_6Si$: 891.3174, found 891.3109.

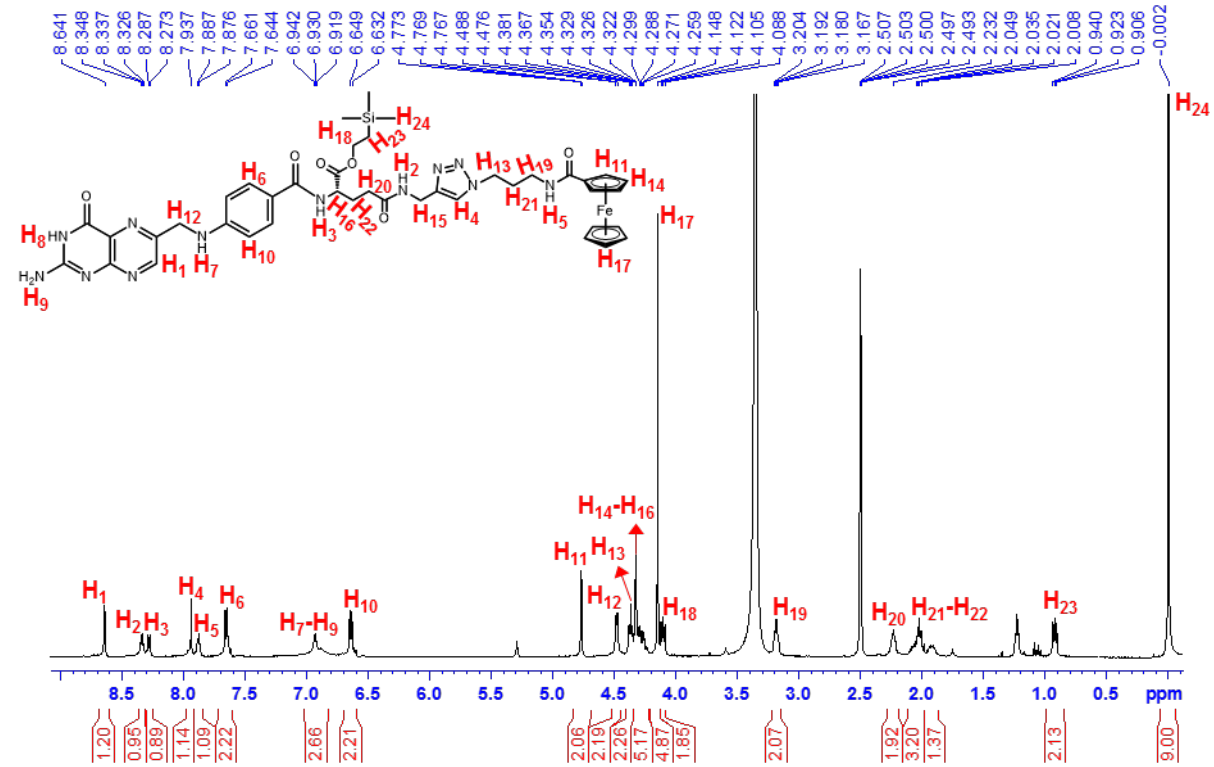


Figure S51. ^{1}H NMR spectrum of protected folate γ-Fc **19** (500 MHz, DMSO-D$_6$, 298 K).

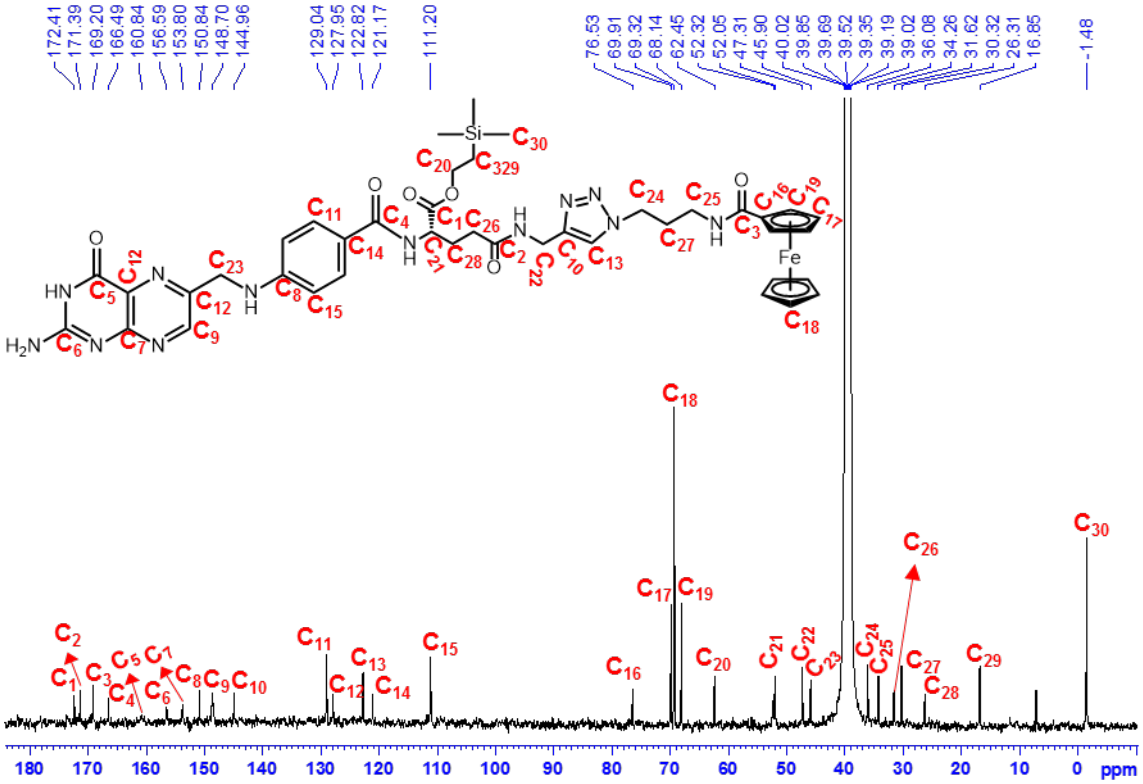


Figure S52. ^{13}C NMR spectrum of protected folate γ-Fc **19** (125 MHz, DMSO-D$_6$, 298 K).

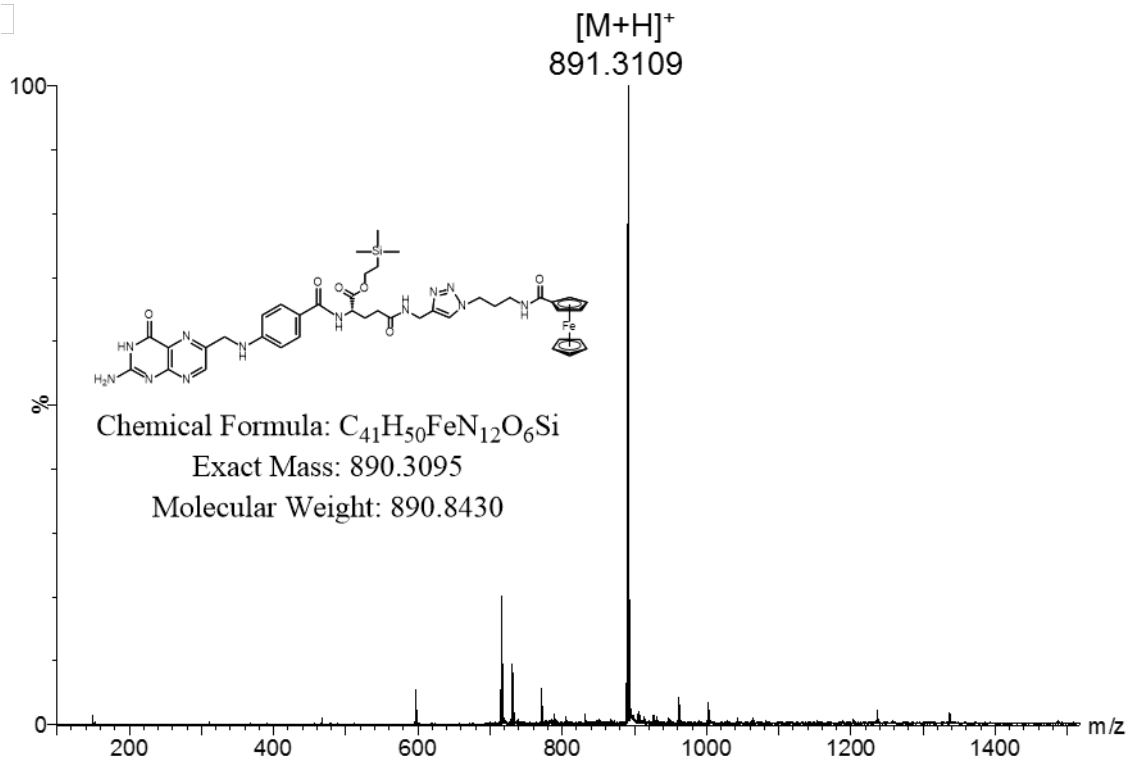


Figure S53. ESI-QTOF mass spectrum of protected folate γ-Fc **19**.

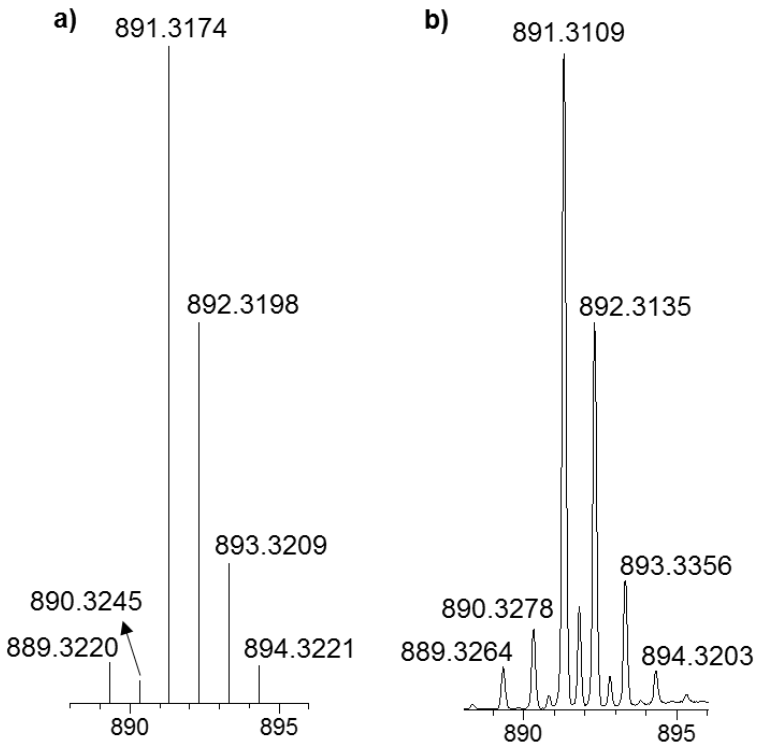
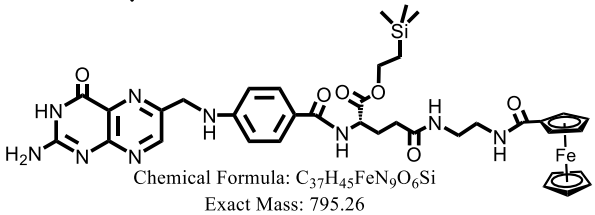


Figure S54. A zoom on the ESI-QTOF mass spectrum of protected folate γ-Fc **19**. Left: theoretical isotopic distribution for $[M+H]^+$. Right: experimental isotopic distribution for $[M+H]^+$.

2.16 Protected folate γ-Fc 20



Chemical Formula: $C_{37}H_{45}FeN_9O_6Si$
Exact Mass: 795.26
Molecular Weight: 795.75

In an air-free Schlenk flask, Pte-N_3 **14** (53 mg, 0.16 mmol), Glu γ-Fc **13** (1.3 eq, 0.2 mmol, 103 mg) were dissolved in 1 mL of anhydrous DMSO. After complete dissolution, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (2 eq, 0.32 mmol, 48 mg, 45 μL) was slowly added. The reaction mixture was stirred in the dark, under nitrogen gas atmosphere, for 12 h. The reaction mixture was precipitated in a cold mixture of diethyl ether and acetone (2:1; 100 mL). The crude product was purified by column chromatography using silica gel and dichloromethane:methanol:trimethylamine (solvent mixture gradient from 99:0:1 until 79:20:1) as eluent. Folate γ-Fc **20** was obtained as a brown solid in 58% yield (74 mg).

^{1}H NMR (DMSO-D_6, 500 MHz), δ (ppm): 8.64 (*s*, C(7)-*H*, 1H), 8.30 (*br*, N*H*, 1H), 7.92 (*br*, CON*H*, 1H), 7.80 (*br*, CON*H*, 1H), 7.65 (*d*, *J* = 8.5 Hz, Ar(6'-2')-*H*, 2H), 6.94 (*br*, CON(3)*H* and N(2)H_2, 4H), 6.64 (*d*, *J* = 8.5 Hz, Ar(5'-3')-*H*, 2H), 4.74 (*br*, Fc-*H*, 2H), 4.49 (*br*, N(9)CH_2, 2H), 4.31 (*m*, C*H* and Fc-*H*, 3H), 4.12-4.09 (*m*, Fc-*H* and CO_2CH_2, 7H), 3.21-3.13 (*m*, CONHCH_2, 4H), 2.20 (*br*, COCH_2, 2H), 2.01 (*m*, $COCH_2CH_2$', 1H), 1.94 (*m*, $COCH_2CH_2$'', 1H), 0.92 (*m*, SiCH_2, 2), 0.00 (*s*, Si(CH_3)$_3$, 9H). **^{13}C NMR** (DMSO-D_6, 125 MHz), δ (ppm): 172.3 (CO_2CH_2), 171.8, (*C*ONH), 169.2 (*C*ONH), 166.4 (*C*(7')ONH), 160.9 (*C*(4)ONH), 156.8 (Ar-C_q(2)), 153.8 (Ar-C_q(8a)), 150.8 (Ar-C_q(8')), 148.7 (Ar-*C*(7)), 131.1 (Ar-C_q(6)), 129.0 (Ar-*C*(6'-2')), 127.9 (Ar-C_q(4a)), 121.2 (Ar-C_q(1')), 111.2 (Ar-*C*(3'-5')), 76.5 (Ar-C_qFc), 69.8 (Ar-*C*Fc), 69.3 (Ar-*C*Fc), 68.1 (Ar-*C*Fc), 62.4 (CO_2CH_2), 52.2 (HN*C*H), 45.9 (*C*(9)H_2NH), 38.9 (*C*H_2NH), 38.6 (*C*H_2NH), 31.8 (HNCO*C*H_2), 26.4 (CH*C*H_2), 16.8 (*C*H_2Si), -1.52 (Si(*C*H_3)$_3$). **ESI-QTOF-MS** $[M+H]^+$ m/z calcd for $C_{37}H_{45}FeN_9O_6Si$: 796.2690, found 796.2601.

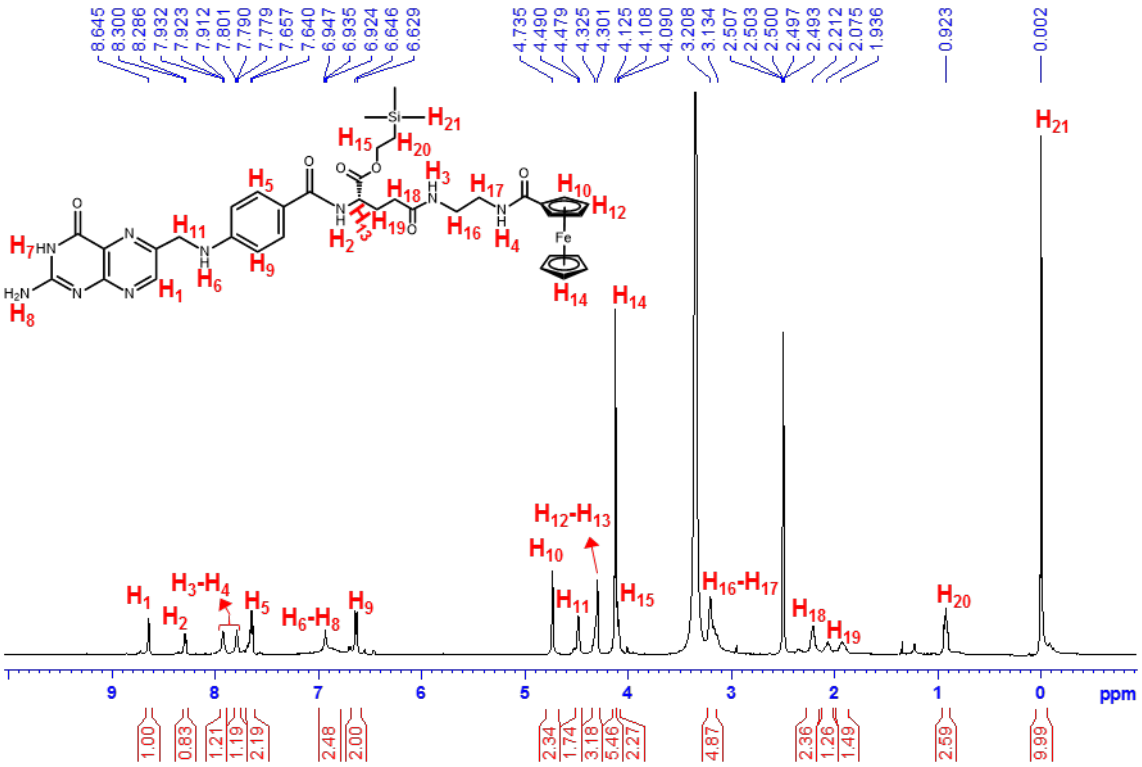


Figure S55. ^{1}H NMR spectrum of protected folate γ-Fc **20** (500 MHz, DMSO-D_6, 298 K).

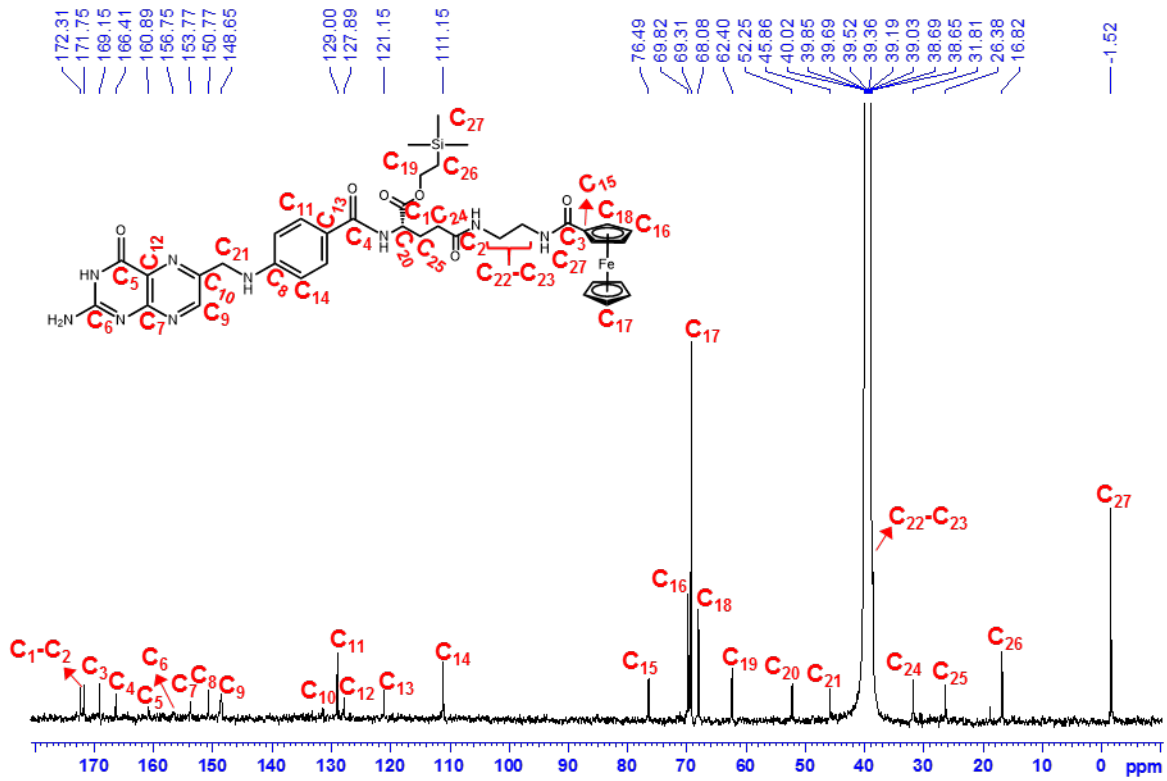


Figure S56. ^{13}C NMR spectrum of protected folate γ-Fc **20** (125 MHz, DMSO-D_6, 298 K).

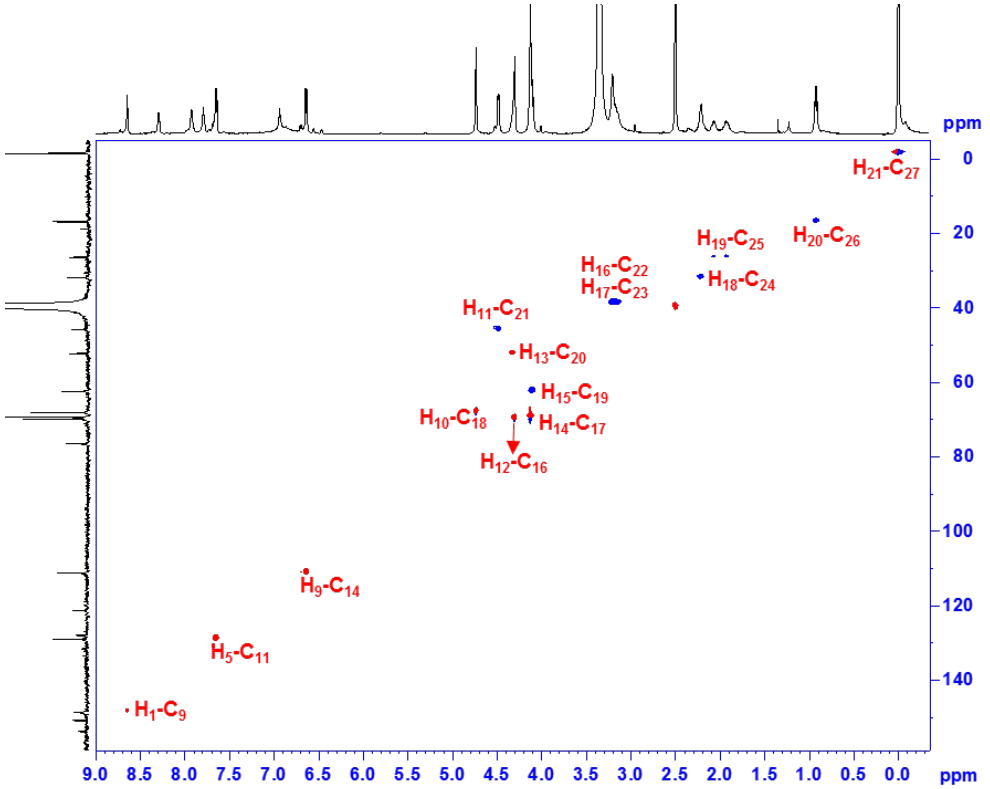


Figure S57. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of protected folate γ-Fc **20** recorded in DMSO-D_6 at 298 K (500 MHz).

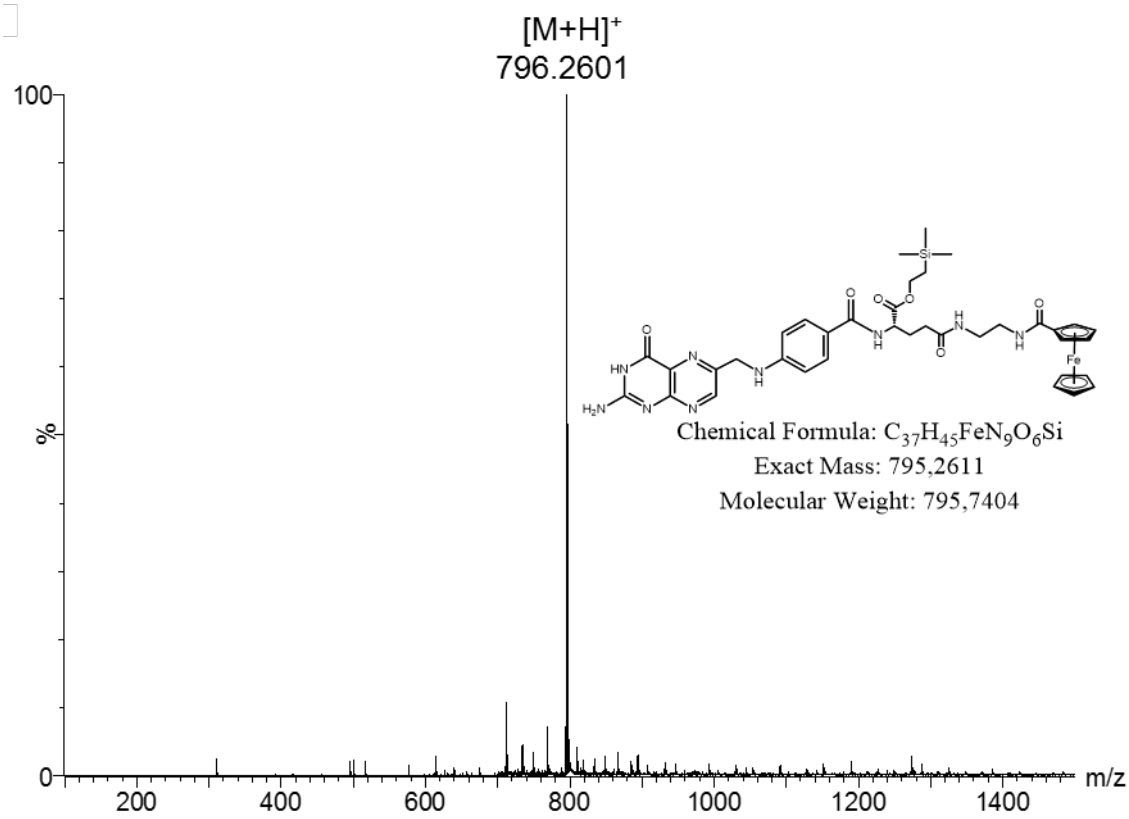


Figure S58. ESI-QTOF mass spectrum of protected folate γ-Fc **20**.

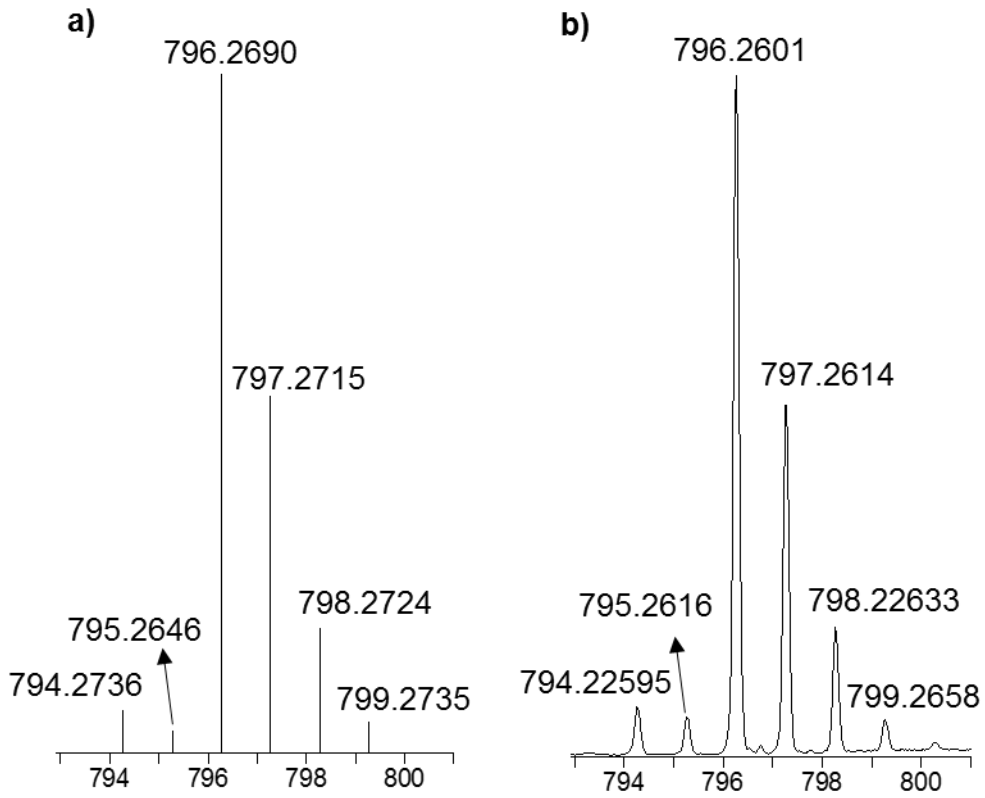
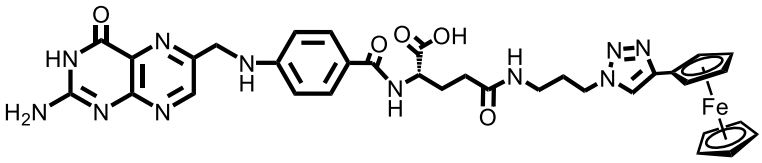


Figure S59. A zoom on the ESI-QTOF mass spectrum of protected folate γ-Fc **20**. Left: theoretical isotopic distribution for $[M+H]^+$. Right: experimental isotopic distribution for $[M+H]^+$.

2.17 Folate γ-Fc 21



Chemical Formula: $C_{34}H_{35}FeN_{11}O_5$
Exact Mass: 733.22
Molecular Weight: 733.57

Protected folate γ-Fc **18** (75 mg, 90 μmol) was dissolved in 1.5 mL of anhydrous DMSO and dried tetra-n-butylammonium fluoride (TBAF) solution in tetrahydrofuran (1.0 M, 4 eq, 36 mmol, 360 μL) was added. The reaction mixture was stirred for 4 hours under nitrogen gas atmosphere. The reaction mixture was precipitated in 100 mL of a cold mixture of diethyl ether and acetone (2:1) and the solids were collected after decantation. The solids were washed with cold HCl solution pH 2 (3×10 mL), cold water (3×10 mL) and cold acetonitrile (3×10 mL). folate γ-Fc **21** was obtained as a brown solid in 68% of yield (45 mg).

^{1}H NMR (DMSO-D_6, 500 MHz), δ (ppm): 11.48 (CO_2H), 8.64 (*s*, C(7)-*H*, 1H), 8.16 (*m*, triazole-*H* and C(7')ON*H*, 2H), 7.95 (*t*, *J* = 5.4 Hz, CON*H*, 1H), 7.66 (*d*, *J* = 8.6 Hz, Ar(6'-2')-*H*, 2H), 6.92 (*br*, CON(3)*H* and N(2)H_2, 4H), 6.64 (*d*, *J* = 8.6 Hz, Ar(5'-3')-*H*, 2H), 4.68 (*t*, *J* = 1.6 Hz, Fc-*H*, 2H), 4.47 (*d*, *J* = 5.8 Hz, N(9)CH_2, 2H), 4.33 (*m*, C*H* and triazole-CH_2, 2H), 4.28 (*t*, *J* = 1.6 Hz, Fc-*H*, 2H), 4.02 (*s*, Fc-*H*, 5H), 3.10-2.98 (*m*, CONHCH_2, 2H), 2.21 (*t*, *J* = 7.5 Hz, COCH_2, 2H), 2.12-2.07 (*m*, $COCH_2CH_2$', 1H), 1.98-1.88 (*m*, $COCH_2CH_2$'' and $NHCH_2CH_2$, 3H). **^{13}C NMR** (DMSO-D_6, 125 MHz), δ (ppm): 174.0 (CO_2H), 171.7, (*C*ONH), 166.3 (*C*(7')ONH), 160.9 (*C*(4)ONH), 156.6 (Ar-C_q(2)), 153.8 (Ar-C_q(8a)), 150.8 (Ar-C_q(8')), 148.6 (Ar-*C*(7)), 145.1 (C_q-triazole), 131.1 (Ar-C_q(6)), 128.9 (Ar-*C*(6'-2')), 127.9 (Ar-C_q(4a)), 121.4 (Ar-C_q(1')), 120.7 (*C*-triazole), 111.2 (Ar-*C*(3'-5')), 76.1 (Ar-C_qFc), 69.2 (Ar-*C*Fc), 68.2 (Ar-*C*Fc), 66.3 (Ar-*C*Fc), 52.2 (HN*C*H), 47.1 (CH_2-triazole), 45.9 ($C(9)H_2NH$), 35.7 (CH_2NH), 33.0 ($HNCOCH_2$), 29.8 ($CH_2CH_2CH_2$), 26.7 ($CHCH_2$). **ESI-QTOF-MS** $[M+H]^+$ m/z calcd for $C_{34}H_{35}FeN_{11}O_5$:734.2245, found 734.2252.

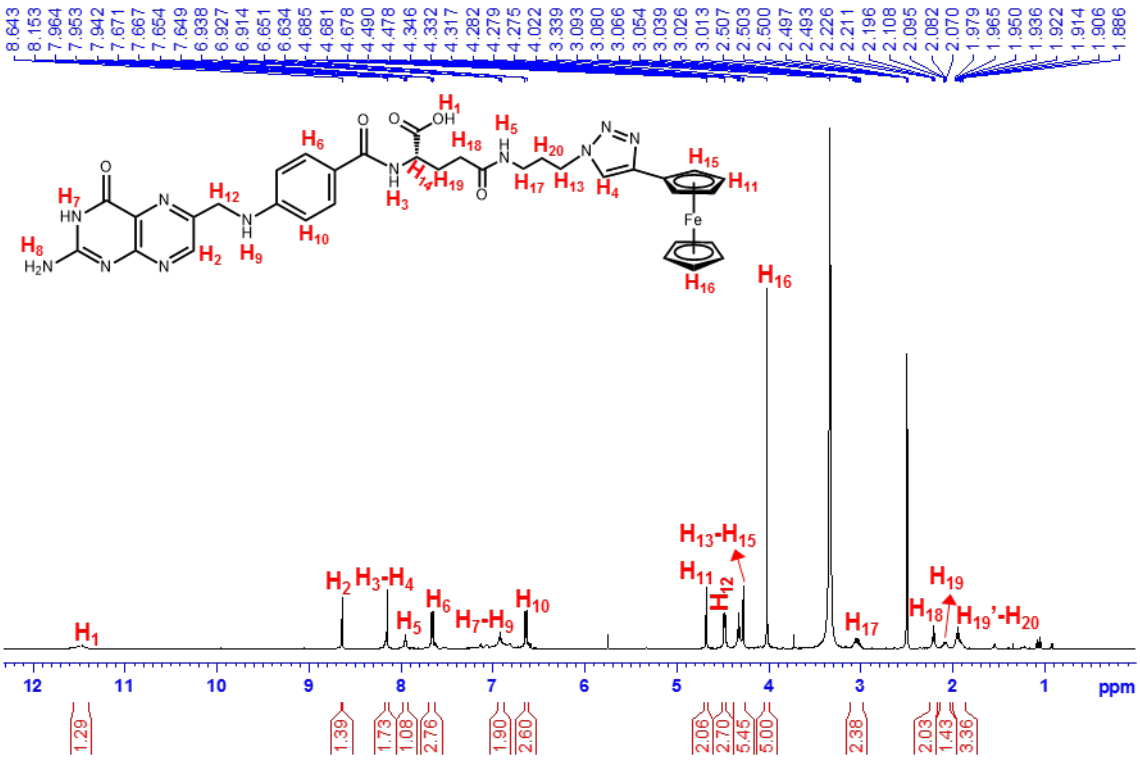


Figure S60. ^{1}H NMR spectrum of folate γ-Fc **21** (500 MHz, DMSO-D_6, 298 K).

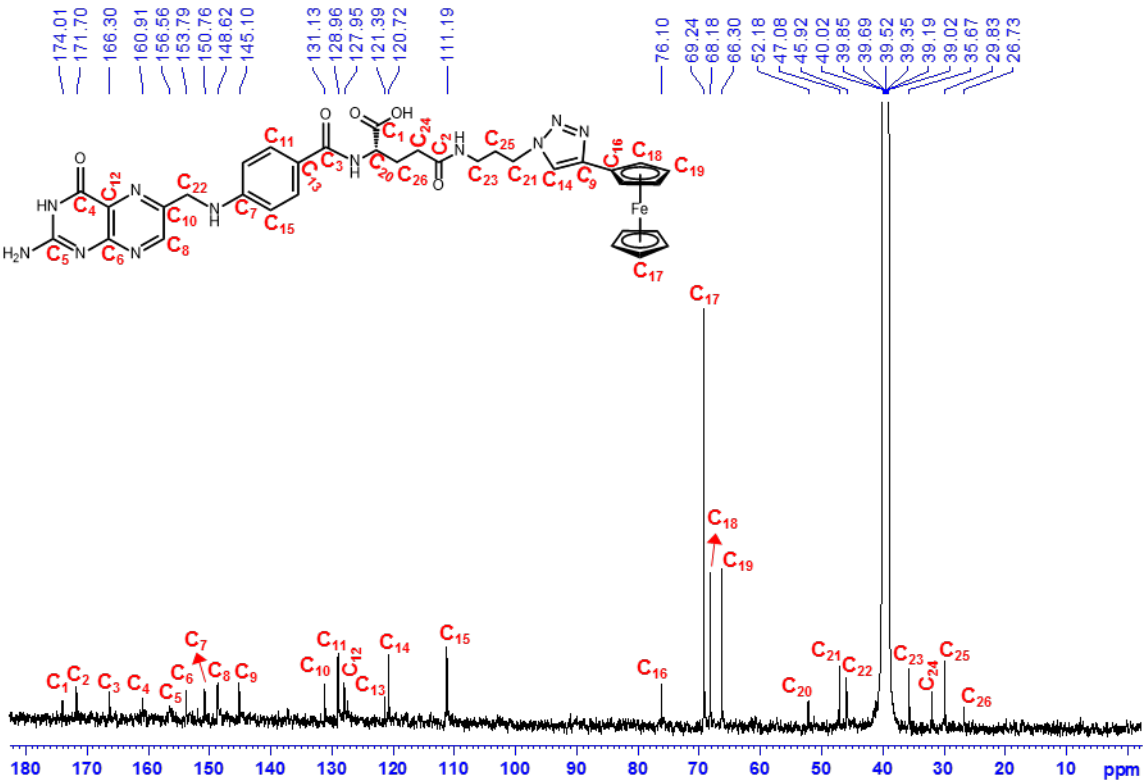


Figure S61. ^{13}C NMR spectrum of folate γ-Fc **21** (125 MHz, DMSO-D_6, 298 K).

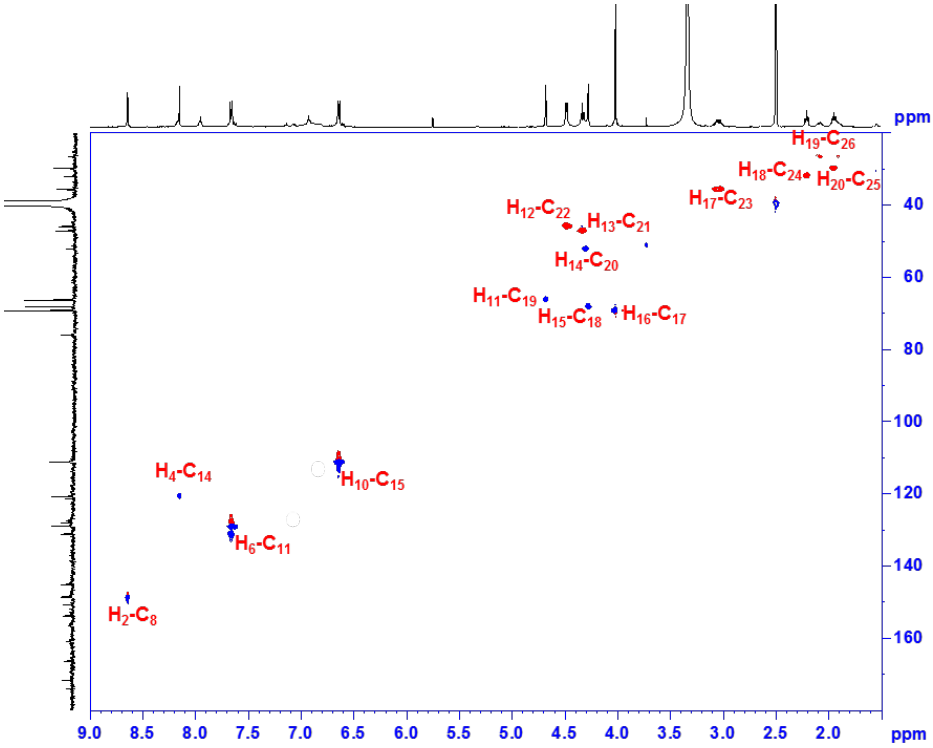


Figure S62. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of folate γ-Fc **21** recorded in DMSO-D_6 at 298 K (500 MHz).

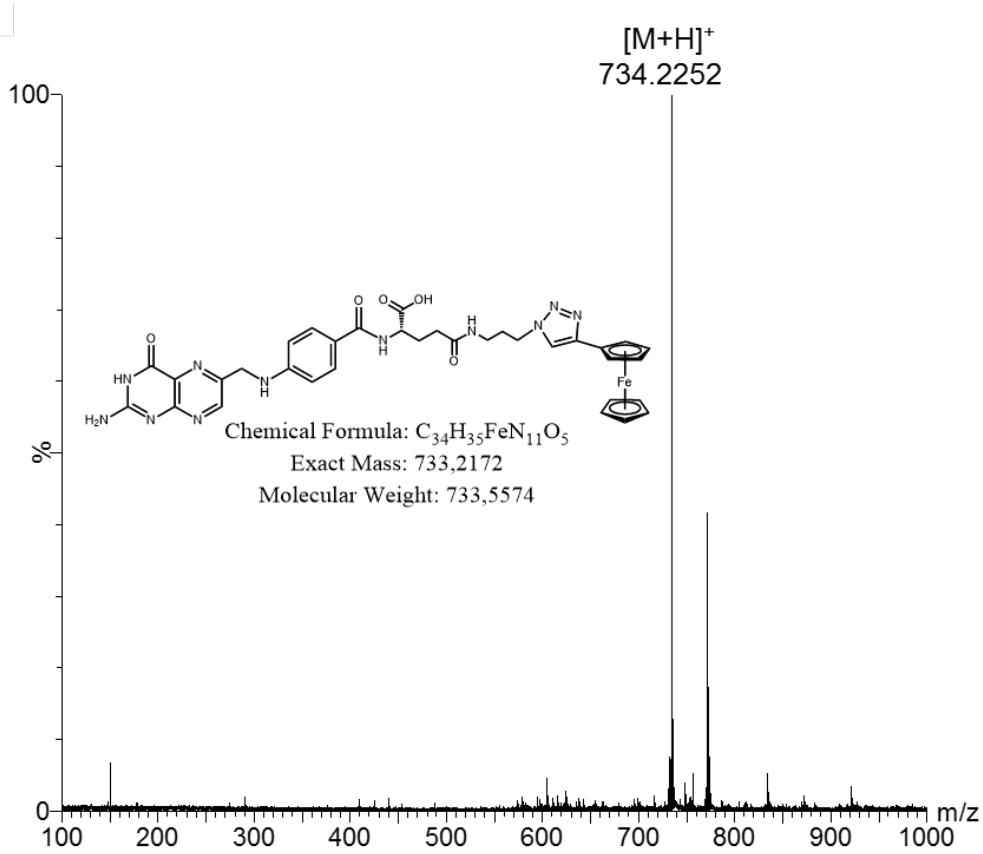


Figure S 63. ESI-QTOF mass spectrum of folate γ-Fc **21**.

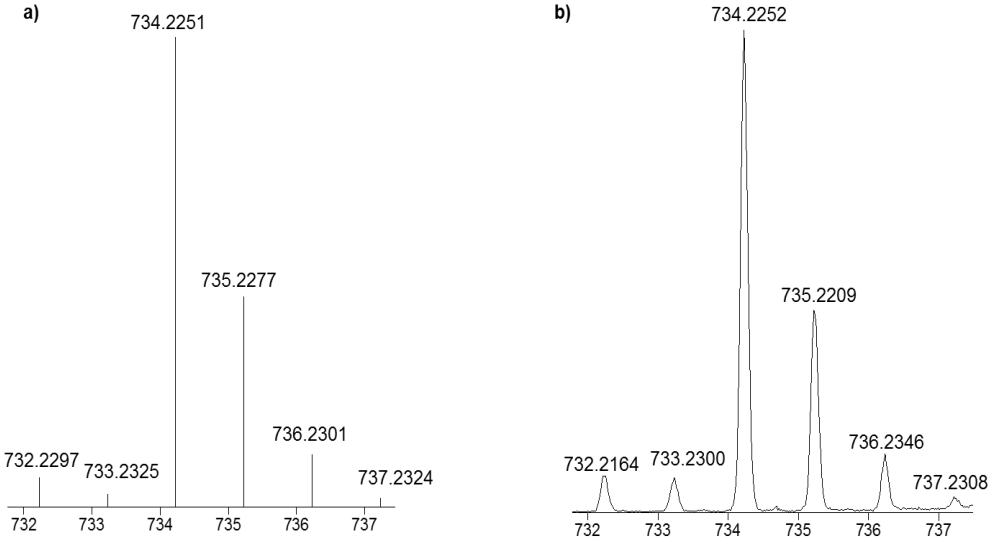
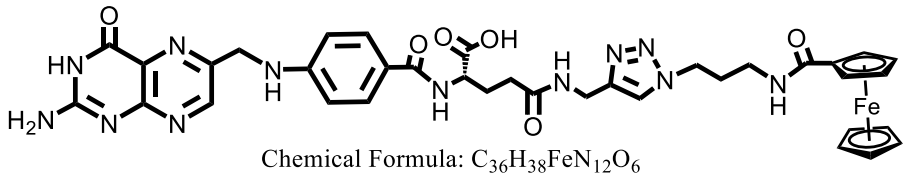


Figure S64. A zoom on the ESI-QTOF mass spectrum of folate γ-Fc **21**. Left: theoretical isotopic distribution for $[M+H]^+$. Right: experimental isotopic distribution for $[M+H]^+$.

2.18 Folate γ-Fc 22



Chemical Formula: $C_{36}H_{38}FeN_{12}O_6$
Exact Mass: 790.24
Molecular Weight: 790.62

Protected folate γ-Fc **19** (70 mg, 79 μmol) was dissolved in 1.5 mL of anhydrous DMSO and dried tetra-n-butylammonium fluoride (TBAF) solution in tetrahydrofuran (1.0 M, 3 eq, 24 mmol, 62 mg, 236 μL) was added. The reaction mixture was stirred for 4 hours under nitrogen gas atmosphere. The reaction mixture was precipitated in 50 mL of a cold mixture of diethyl ether and acetone (2:1) and the solids were collected after decantation. The solids were washed with cold HCl solution pH 2 (3×10 mL), cold water (3×10 mL) and cold acetonitrile (3×10 mL). folate γ-Fc **22** was obtained as a brown solid in 68% of yield (45 mg).

^{1}H NMR (DMSO-D_6, 500 MHz), δ (ppm): 11.43 (*s*, CO_2H, 1H), 8.64 (*s*, C(7)-*H*, 1H), 8.34 (*br*, CON*H*, 1H), 8.19 (*d*, *J* = 6.8 Hz, CON*H*), 7.94 (*s*, triazole-*H* ,1H), 7.87 (*br*, CON*H*, 1H), 7.65 (*d*, *J* = 8.1 Hz, Ar(6'-2')-*H*, 2H), 6.91 (*br*, CON(3)*H* and N(2)H_2, 4H), 6.64 (*d*, *J* = 8.1 Hz, Ar(5'-3')-*H*, 2H), 4.77 (*br*, Fc-*H*, 2H), 4.48 (*br*, N(9)CH_2, 2H), 4.38 (*t*. *J* = 6.3 Hz, triazole-CH_2, 2H), 4.33-4.24 (*m*, NHC*H*, CONH-CH_2-triazole, Fc-*H*, 5H), 4.15 (*s*, Fc-*H*, 5H), 3.18 (*m*, CONHCH_2, 2H), 2.23 (*br*, COCH_2, 2H), 2.10-2.01 (*m*, $CH_2CH_2CH_2NH$, $COCH_2CH_2$', 3H), 1.92 (*m*, $COCH_2CH_2$'', 1H). **^{13}C NMR** (DMSO-D_6, 125 MHz), δ (ppm): 173.9 (*C*O_2H), 171.5 (*C*ONH), 169.2 (*C*ONH), 166.4 (*C*(7')ONH), 160.9 (*C*(4)ONH), 156.6 (Ar-C_q(2)), 153.7 (Ar-C_q(8a)), 150.8 (Ar-C_q(8')), 148.8 (Ar-*C*(7)), 145.0 (C_q-triazole), 129.0 (Ar-*C*(6'-2') and Ar-C_q(6)), 128.0 (Ar-C_q(4a)), 122.8 (*C*-triazole), 121.4 (Ar-C_q(1')), 111.2 (Ar-*C*(3'-5')), 76.5 (Ar-C_qFc), 69.9 (Ar-*C*Fc), 69.3 (Ar-*C*Fc), 68.1 (Ar-*C*Fc), 52.1 (HN*C*H), 47.3 (*C*H_2-triazole), 45.9 (*C*(9)H_2NH), 36.1 (*C*H_2NH), 34.3 ((*C*H_2NH)), 31.8 (HNCO*C*H_2), 30.3 ($CH_2CH_2CH_2$), 26.5 (CH*C*H_2). **ESI-QTOF-MS** $[M+H]^+$ m/z calcd for $C_{36}H_{38}FeN_{12}O_6$: 791.2466, found 791.2253.

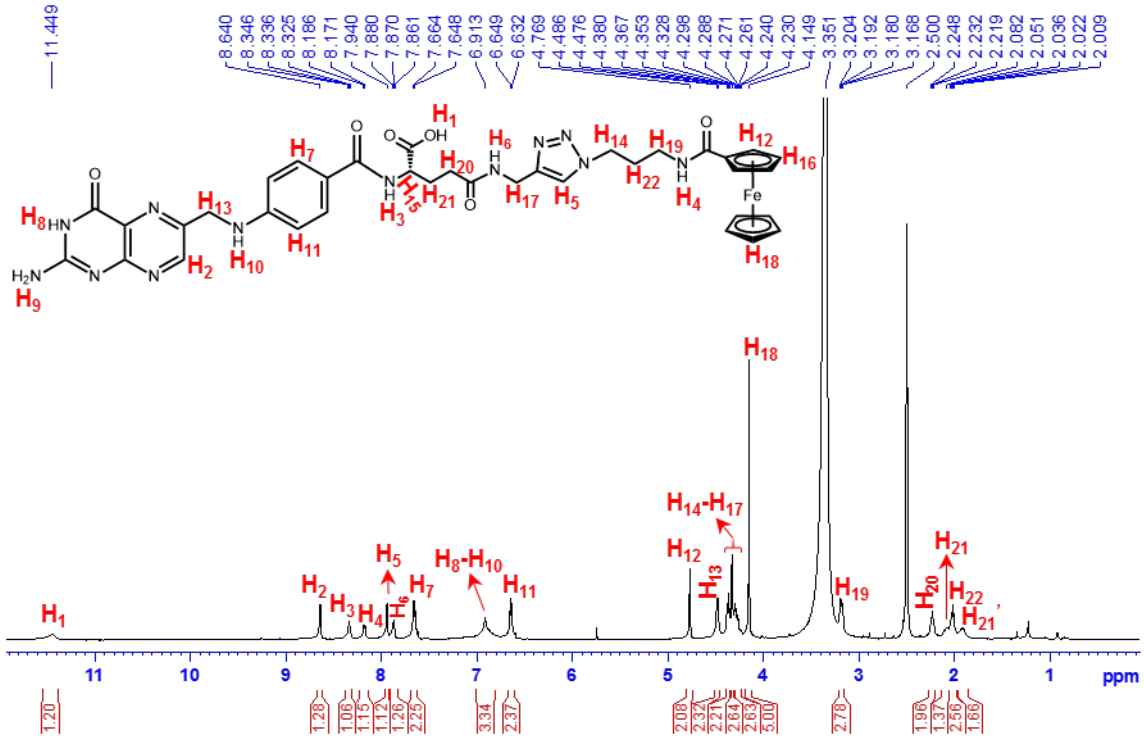


Figure S65. ^{1}H NMR spectrum of folate γ-Fc **22** (500 MHz, DMSO-D_6, 298 K).

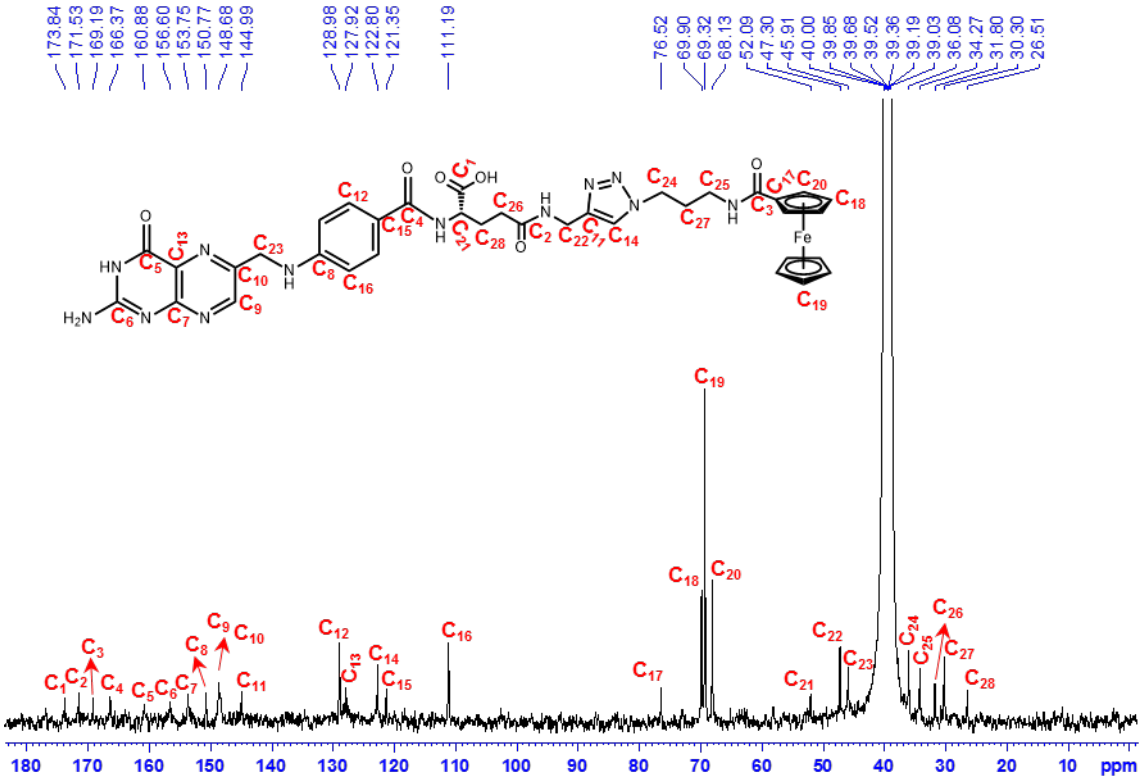


Figure S66. ^{13}C NMR spectrum of folate γ-Fc **22** (125 MHz, DMSO-D_6, 298 K).

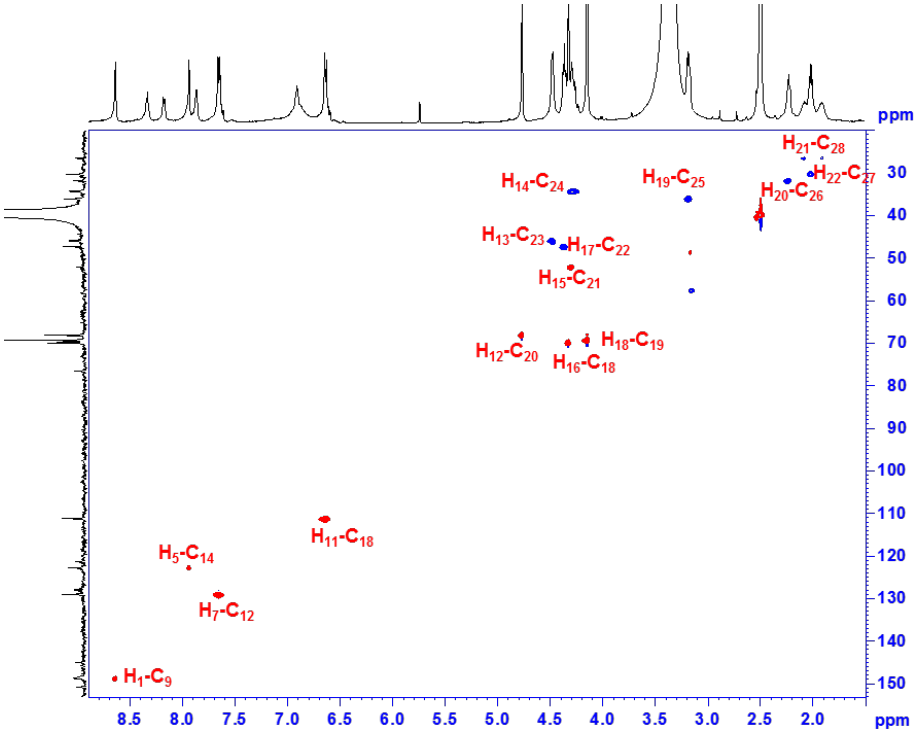


Figure S67. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of folate γ-Fc **22** recorded in DMSO-D_6 at 298 K (500 MHz).

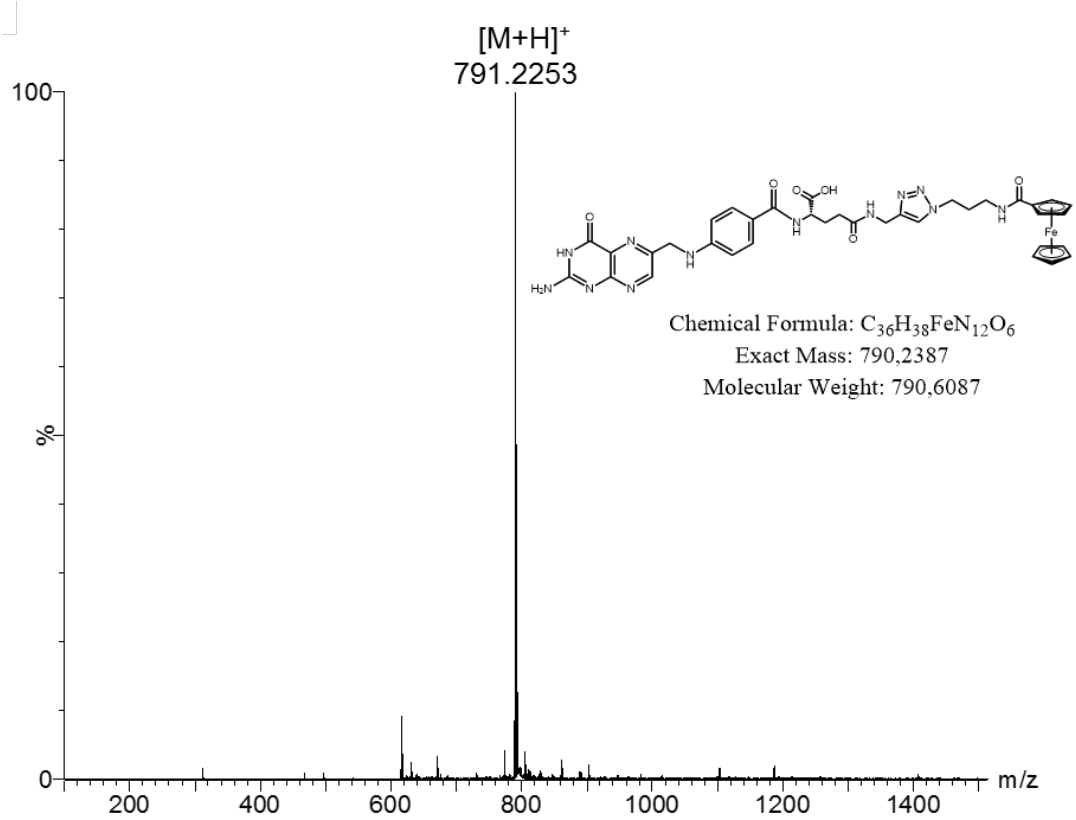


Figure S68. ESI-QTOF mass spectrum of folate γ-Fc **22**.

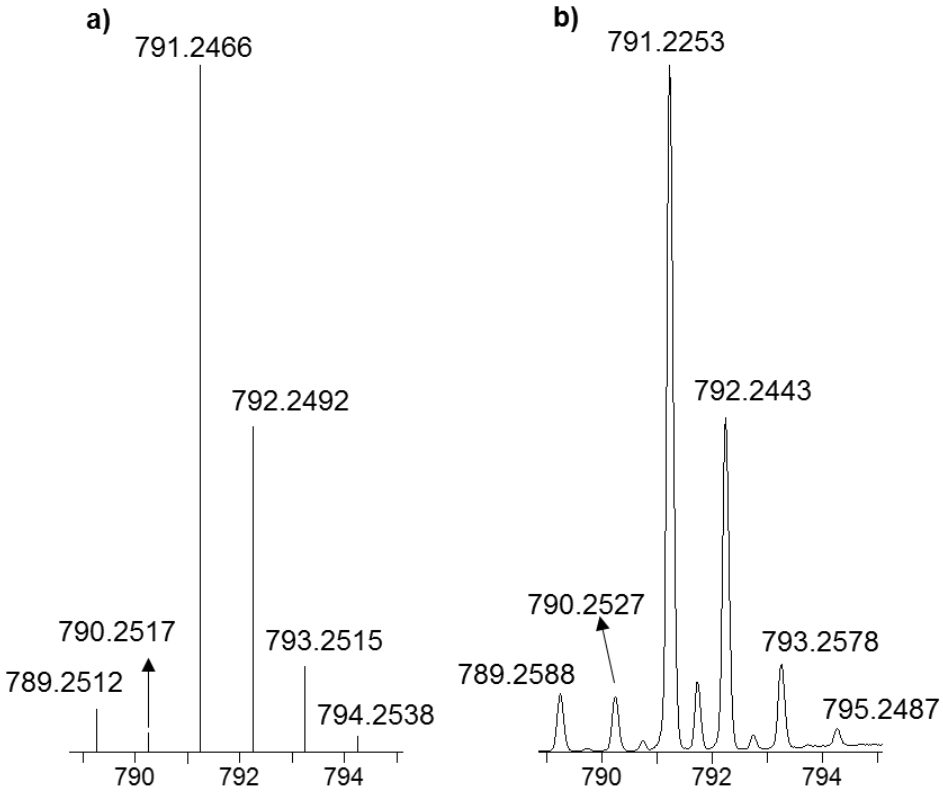
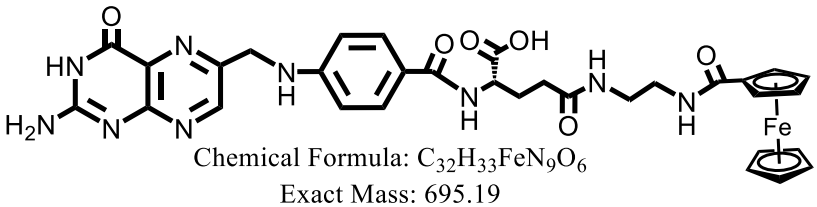


Figure S69. A zoom on the ESI-QTOF mass spectrum of folate γ-Fc **22**. Left: theoretical isotopic distribution for $[M+H]^+$. Right: experimental isotopic distribution for $[M+H]^+$.

2.19 Folate γ-Fc 23



Chemical Formula: $C_{32}H_{33}FeN_9O_6$
Exact Mass: 695.19
Molecular Weight: 695.52

Protected folate γ-Fc **20** (50 mg, 63 μmol) was dissolved in 1 mL of anhydrous DMSO and dried tetra-n-butylammonium fluoride (TBAF) solution in tetrahydrofuran (1.0 M, 3 eq, 0.19 mmol, 189 μL) was added. The reaction mixture was stirred for 4 hours under nitrogen gas atmosphere. The reaction mixture was precipitated in 50 mL of a cold mixture of diethyl ether and acetone (2:1) and the solids were collected after decantation. The solids were washed with cold HCl solution pH 2 (3×10 mL), cold water (3×10 mL) and cold acetonitrile (3×10 mL). folate γ-Fc **23** was obtained as a brown solid in 78% of yield (34 mg).

^{1}H NMR (DMSO-D_6, 500 MHz), δ (ppm): 11.44 (CO_2H), 8.64 (*s*, C(7)-*H*, 1H), 8.21 (*d*, *J* = 7.4 Hz, N*H*, 1H), 7.93 (*br*, CON*H*, 1H), 7.81 (*br*, CON*H*, 1H) 7.66 (*d*, *J* = 8.3 Hz, Ar(6'-2')-*H*, 2H), 6.94 (*br*, CON(3)*H* and N(2)H_2, 4H), 6.64 (*d*, *J* = 8.3 Hz, Ar(5'-3')-*H*, 2H), 4.74 (*br*, Fc-*H*, 2H), 4.48 (*br*, N(9)CH_2, 2H), 4.33 (*m*, C*H* and Fc-*H*, 3H), 4.12 (*s*, Fc-*H*, 5H), 3.20 (*m*, CONHCH_2, 4H), 2.21 (*t*, *J* = 6.13 Hz, COCH_2, 2H), 2.01 (*m*, $COCH_2CH_2$', 1H), 1.92 (*m*, $COCH_2CH_2$'', 1H). **^{13}C NMR** (DMSO-D_6, 125 MHz), δ (ppm): 173.4 (CO_2H), 171.8 (*C*ONH), 169.1 (*C*ONH), 166.1 (*C*(7')ONH), 160.7 (*C*(4)ONH), 156.4 (Ar-C_q(2)), 153.6 (Ar-C_q(8a)), 150.6 (Ar-C_q(8')), 148.6 (Ar-*C*(7)), 131.1 (Ar-C_q(6)), 128.9 (Ar-*C*(6'-2')), 127.8 (Ar-C_q(4a)), 121.2 (Ar-C_q(1')), 111.1 (Ar-*C*(3'-5')), 76.4 (Ar-C_qFc), 69.7 (Ar-*C*Fc), 69.2 (Ar-*C*Fc), 68.0 (Ar-*C*Fc), 51.9 (HN*C*H), 45.8 (*C*(9)H_2NH), 38.6 (*C*H_2NH), 38.5 (*C*H_2NH), 31.9 (HNCO*C*H_2), 26.4 (CH*C*H_2). **ESI-QTOF-MS** $[M]^-$ m/z calcd for $C_{32}H_{33}FeN_9O_6$: 694.1826, found 694.1859.

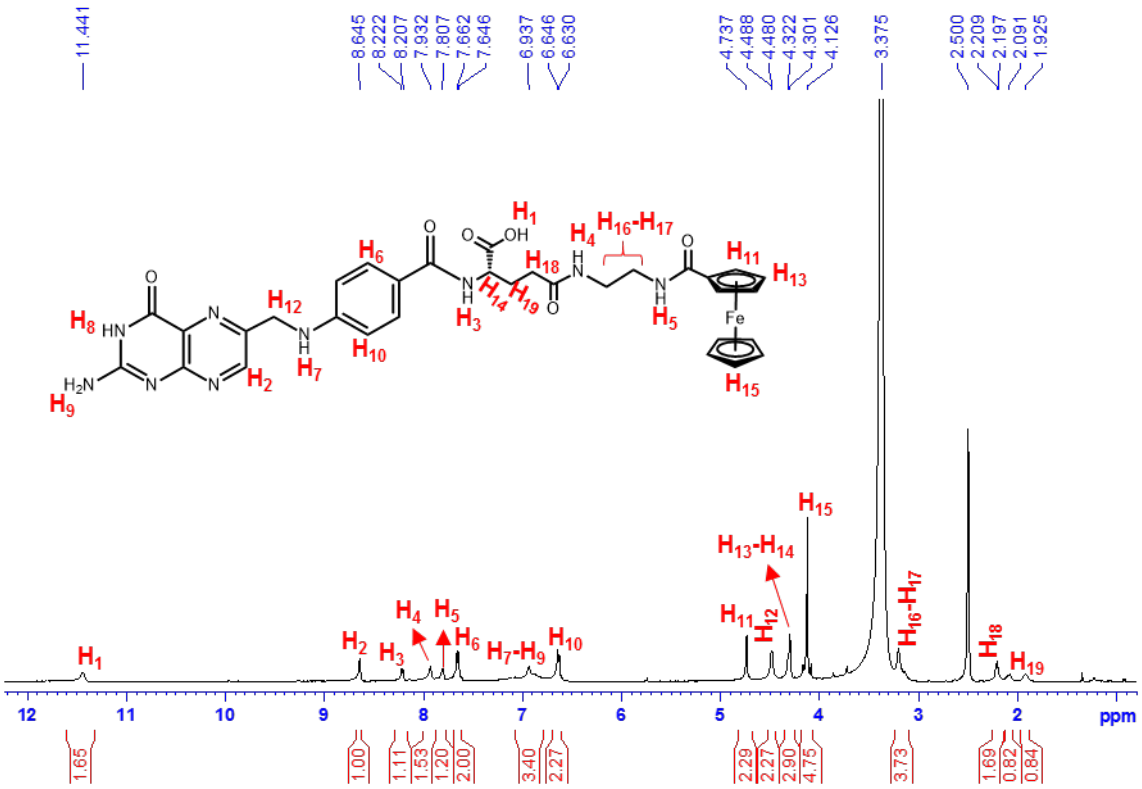


Figure S70. ^{1}H NMR spectrum of folate γ-Fc **23** (500 MHz, DMSO-D$_6$, 298 K).

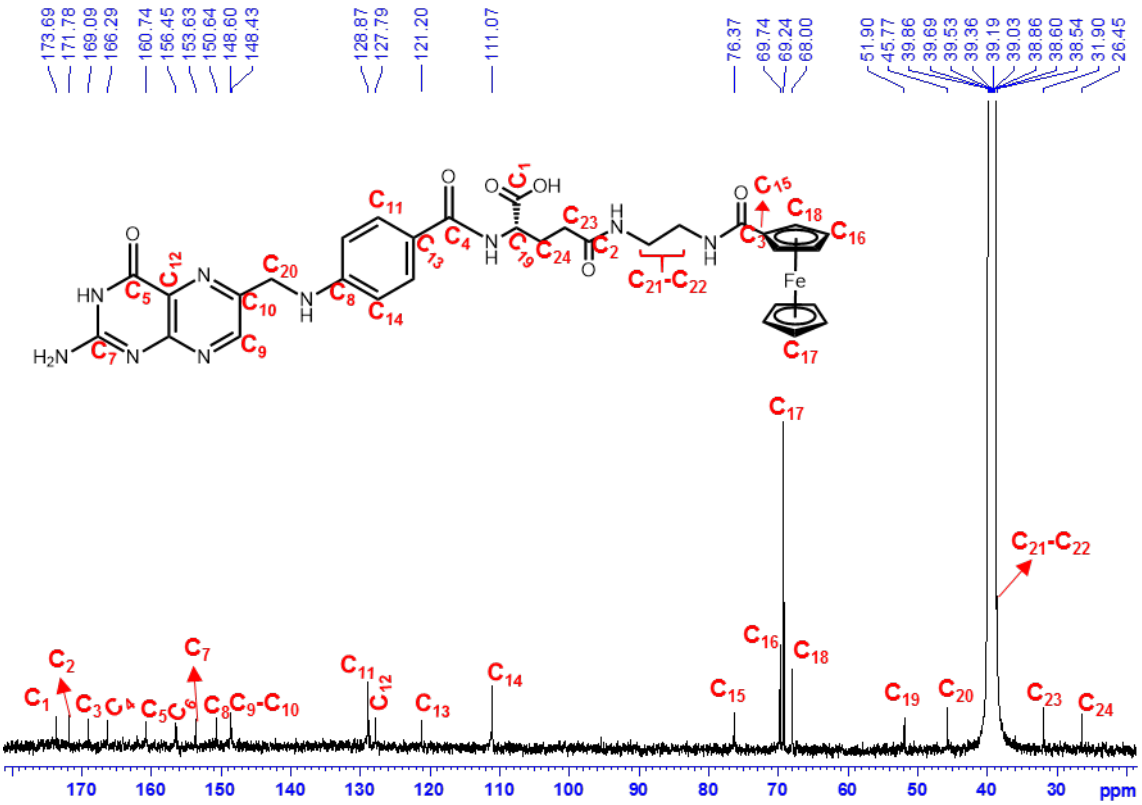


Figure S71. ^{13}C NMR spectrum of folate γ-Fc **23** (125 MHz, DMSO-D$_6$, 298 K).

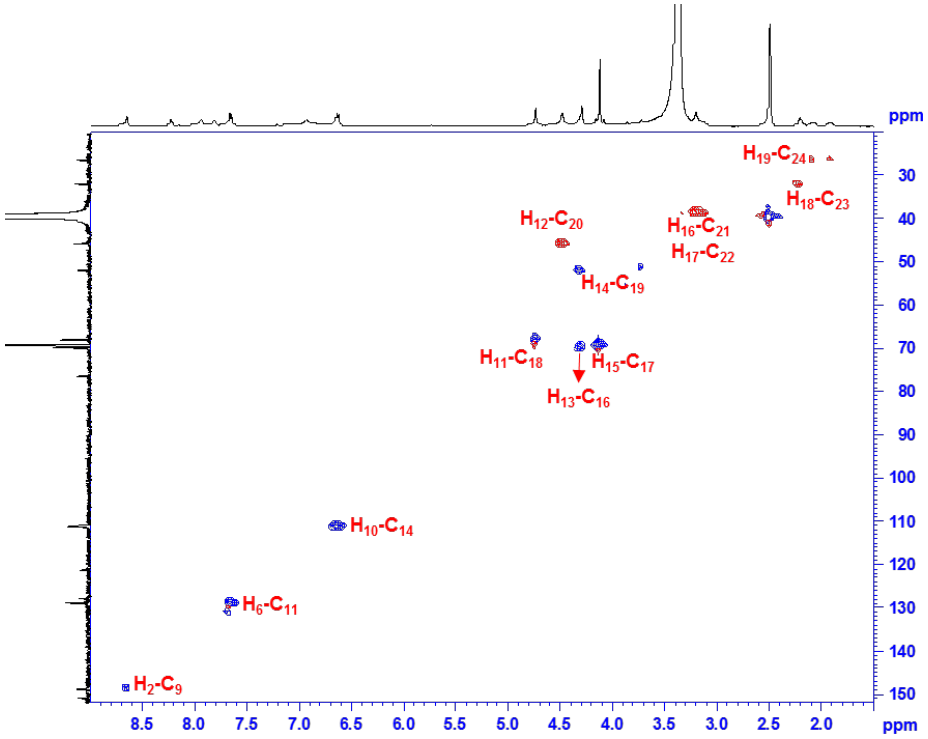


Figure S72. Two-dimensional [^{1}H-^{13}C]-HSQC NMR contour map of folate γ-Fc **23** recorded in DMSO-D_6 at 298 K (500 MHz).

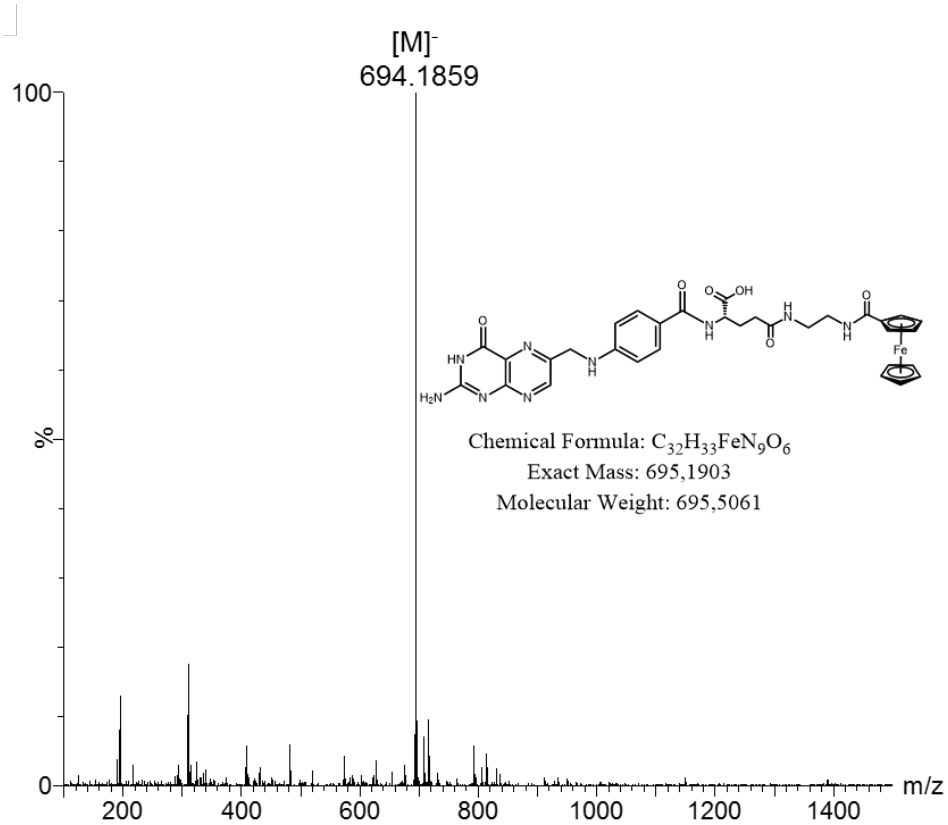


Figure S73. ESI-QTOF mass spectrum of folate γ-Fc **23**.

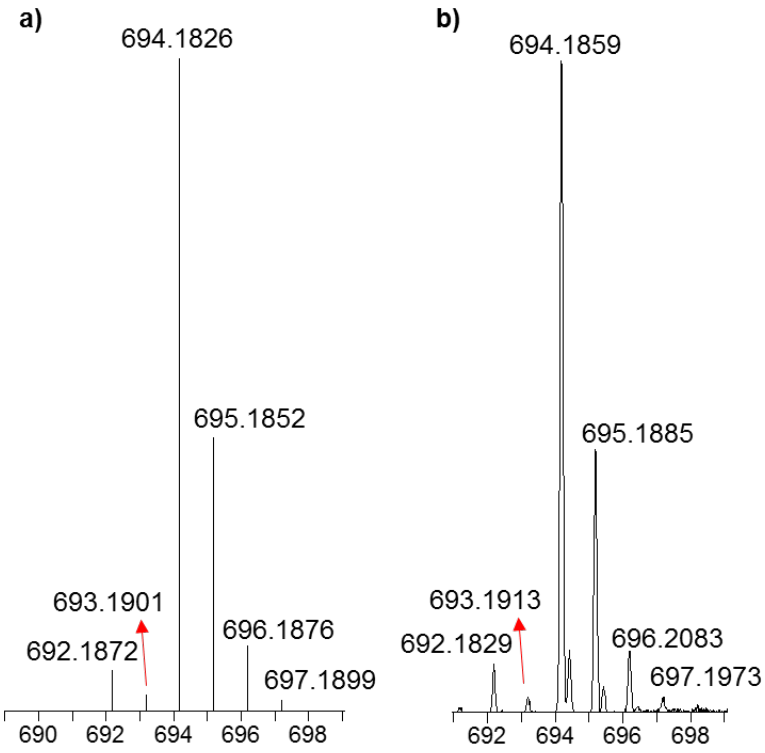
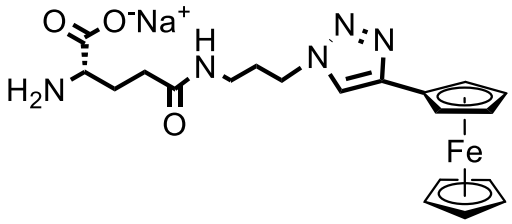


Figure S74. A zoom on the ESI-QTOF mass spectrum of folate γ-Fc **23**. Left: theoretical isotopic distribution for $[M]^-$. Right: experimental isotopic distribution for $[M]^-$.

2.20 Unprotected Glu γ-Fc 24



Chemical Formula: $C_{20}H_{24}FeN_5NaO_3$
Exact Mass: 461.11
Molecular Weight: 461.28

Compound **4** (0.12 mmol, 80 mg) was dissolved in 5 mL of anhydrous DMF and and dried TBAF solution in tetrahydrofuran (1.0 M, 3eq, 0.37 mmol, 98 mg, 0.375 mL) was added. The reaction mixture was stirred for 2 hours under nitrogen atmosphere. The solvents were evaporated to dryness and redissolved in 200 mL of ethyl acetate. The organic phase was washed with water (3×200 mL), brine (4×50 mL), dried over Na_2SO_4 and filtered. The crude intermediate was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3×30 mL) and hexane (3×30 mL). Compound **24** was obtained as a red oil in 93% of yield (55 mg).

^{1}H NMR (CD_3OD, 500 MHz), δ (ppm): 8.04 (*s*, triazole-*H*), 4.73 (*br*, Fc-*H*, 2H), 4.45 (*br*, triazole-C*H*$_2$, 2H), 4.32 (*br*, Fc-*H*, 2H), 4.06 (*s*, NHC*H*, Fc-*H*, 6H), 3.23 (*m*, C*H*$_2$NH, 2H), 2.46 (*br*, C*H*$_2$CON, 2H), 2.14 (*m*, CHC*H*$_2$ and $CH_2CH_2CH_2$, 4H), **^{13}C NMR** (CD_3OD, 125 MHz), δ (ppm): 175.3 (*C*O$_2$, *C*ONH), 148.0 (*C*$_q$-triazole), 121.7 (triazole-*C*H), 76.1 (FcAr-*C*$_q$), 70.6 (FcAr-*C*H), 69.8 (FcAr-*C*H), 67.6 (FcAr-*C*H), 55.8 (N*C*H), 37.5 (*C*H$_2$NH), 33.1 (*C*H$_2$CONH), 31.0 ($CH_2CH_2CH_2$), 27.9 (*C*H$_2$CH$_2$CONH). **ESI-MS** $[M]^-$ m/z calcd for $C_{20}H_{25}FeN_5O_3$: 438.1229, found 438.1233.

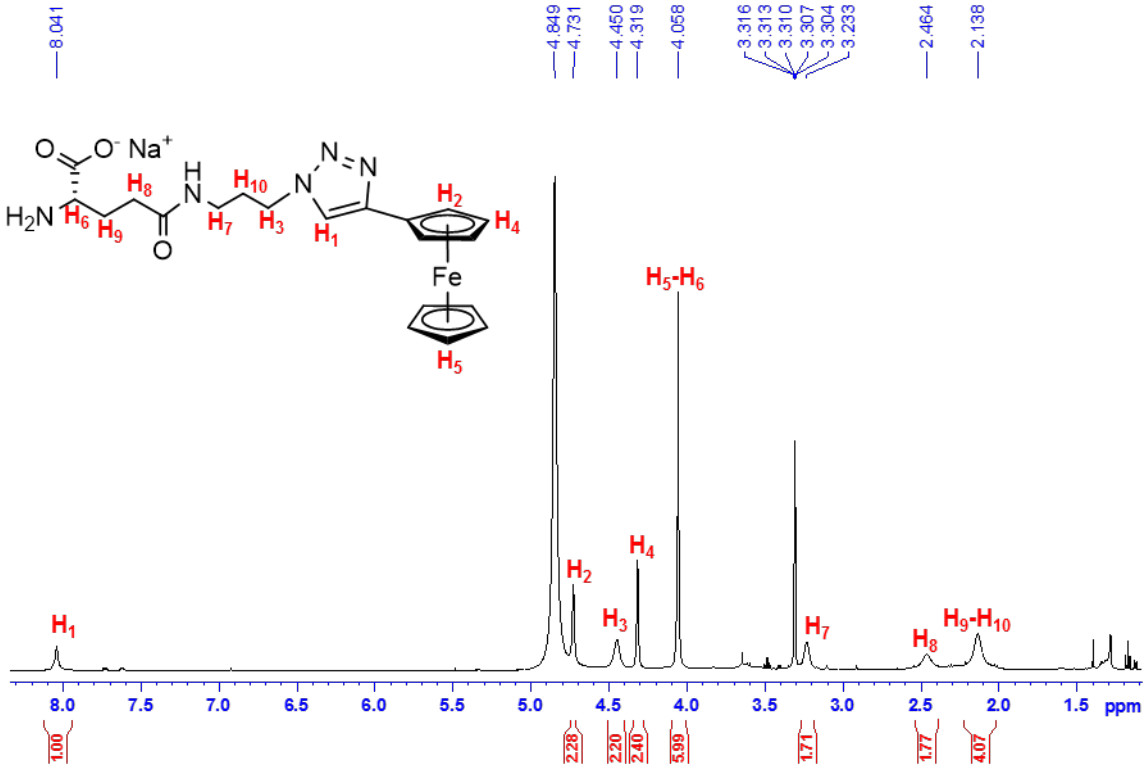


Figure S75. ^{1}H NMR spectrum of Glu γ-Fc **24** (500 MHz, CD_3OD, 298 K).

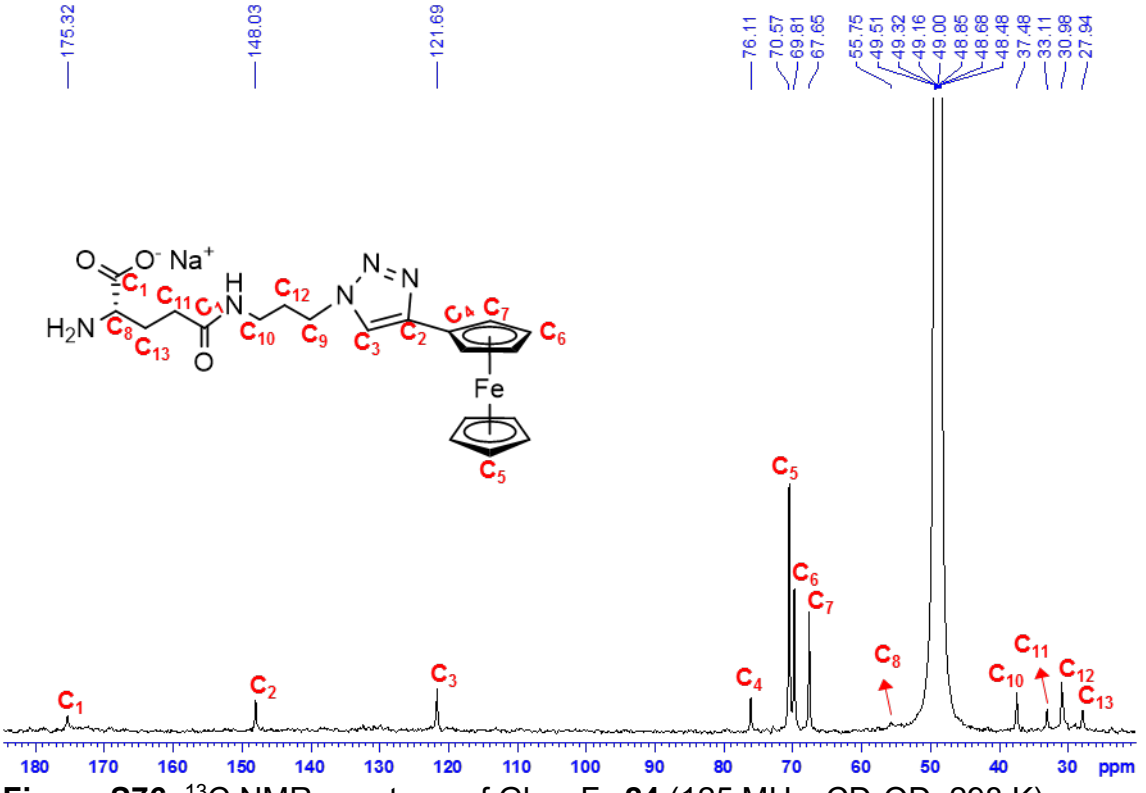


Figure S76. ^{13}C NMR spectrum of Glu γ-Fc **24** (125 MHz, CD_3OD, 298 K).

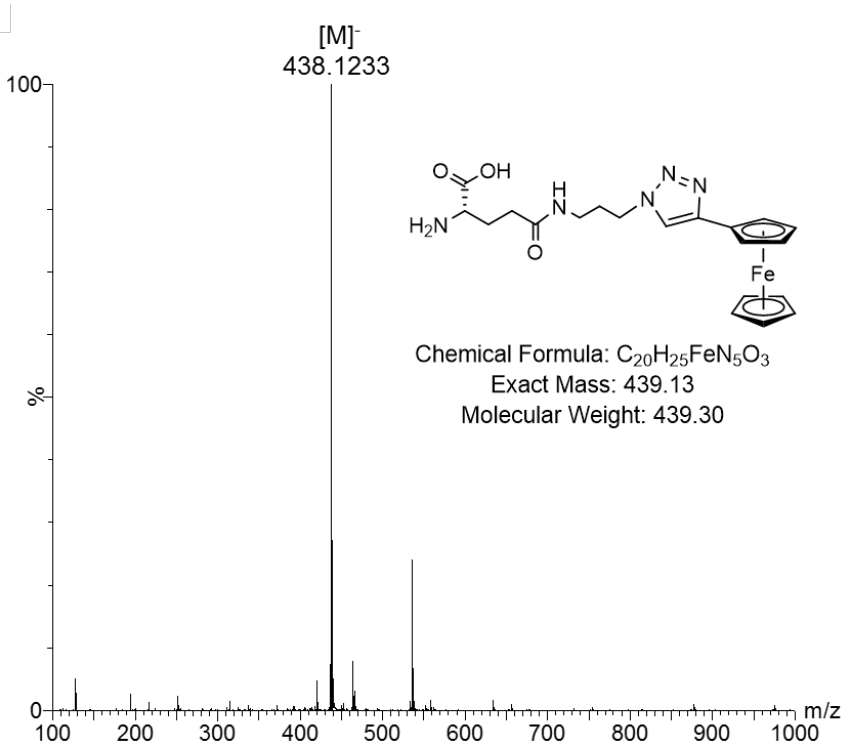


Figure S77. ESI-QTOF mass spectrum of unprotected Glu γ-Fc **24**

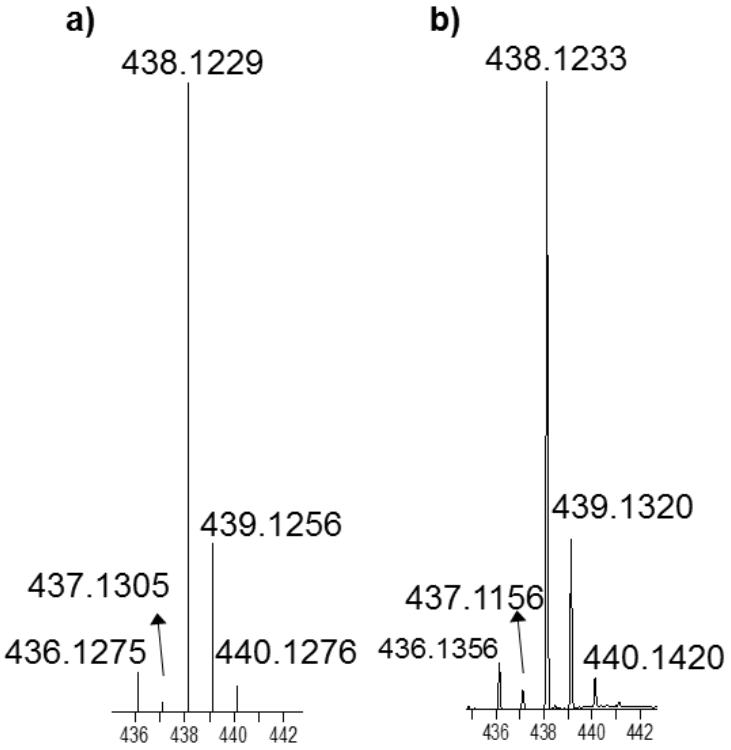
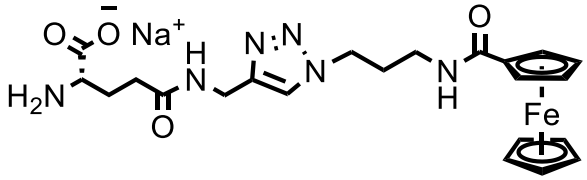


Figure S78. A zoom on the ESI-QTOF mass spectrum of Glu γ-Fc **24**. Left: theoretical isotopic distribution for $[M]^-$. Right: experimental isotopic distribution for $[M]^-$.

2.21 Unprotected Glu γ-Fc 25



Chemical Formula: $C_{22}H_{27}FeN_6NaO_4$
Exact Mass: 518.13
Molecular Weight: 518.33

Compound **8** (0.15 mmol, 80 mg) was dissolved in 5 mL of anhydrous DMF and and dried TBAF solution in tetrahydrofuran (1.0 M, 3eq, 0.34 mmol, 90 mg, 0.344 mL) was added. The reaction mixture was stirred for 2 hours under nitrogen atmosphere. The solvents were evaporated to dryness and redissolved in 200 mL of ethyl acetate. The organic phase was washed with water (3×200 mL), brine (4×50 mL), dried over Na_2SO_4 and filtered. The crude intermediate was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3×30 mL) and hexane (3×30 mL). Compound **25** was obtained as a red oil in 68% of yield (45 mg).

^{1}H NMR (CD_3OD, 400 MHz), δ (ppm): 7.96 (*s*, triazole-*H,* 1H), 4.80 (*br*, Fc-*H*, 2H), 4.47-4.45 (*br*, NHC*H*$_2$-triazole, triazole-C*H*$_2$, 4H), 4.40 (*br*, Fc-H, 2H), 4.20 (*s*, Fc-*H*, 6H), 3.64 (*m*, NHC*H*, 1H), 3.34 (*br*,HNC*H*$_2$, 1H), 2.48 (*br*, C*H*$_2$CON, 2H), 2.18 (*m*, CHC*H*$_2$ and $CH_2CH_2CH_2$, 4H). **^{13}C NMR** (CD_3OD, 100 MHz), δ (ppm): 175.2 (*C*O_2), 173.8 (*C*ONH), 146.2 (C_q-triazole), 124.5 (triazole-*C*H), 76.6 (FcAr-C_q), 71.8 (FcAr-*C*H), 70.8 (FcAr-*C*H), 69.4 (FcAr-*C*H), 59.7 (NH*C*H$_2$-triazole), 57.5 (triazole-*C*H$_2$), 56.1 (N*C*H), 48.1 (triazole-*C*H$_2$), 37.7 (*C*H$_2$NH), 35.7 (*C*H$_2$CONH), 33.1 ($CH_2CH_2CH_2$), 27.9 (*C*H$_2$CH$_2$CONH). **ESI-MS** $[M]^-$ m/z calcd for $C_{22}H_{28}FeN_6O_4$: 495.1443, found 495.1466.

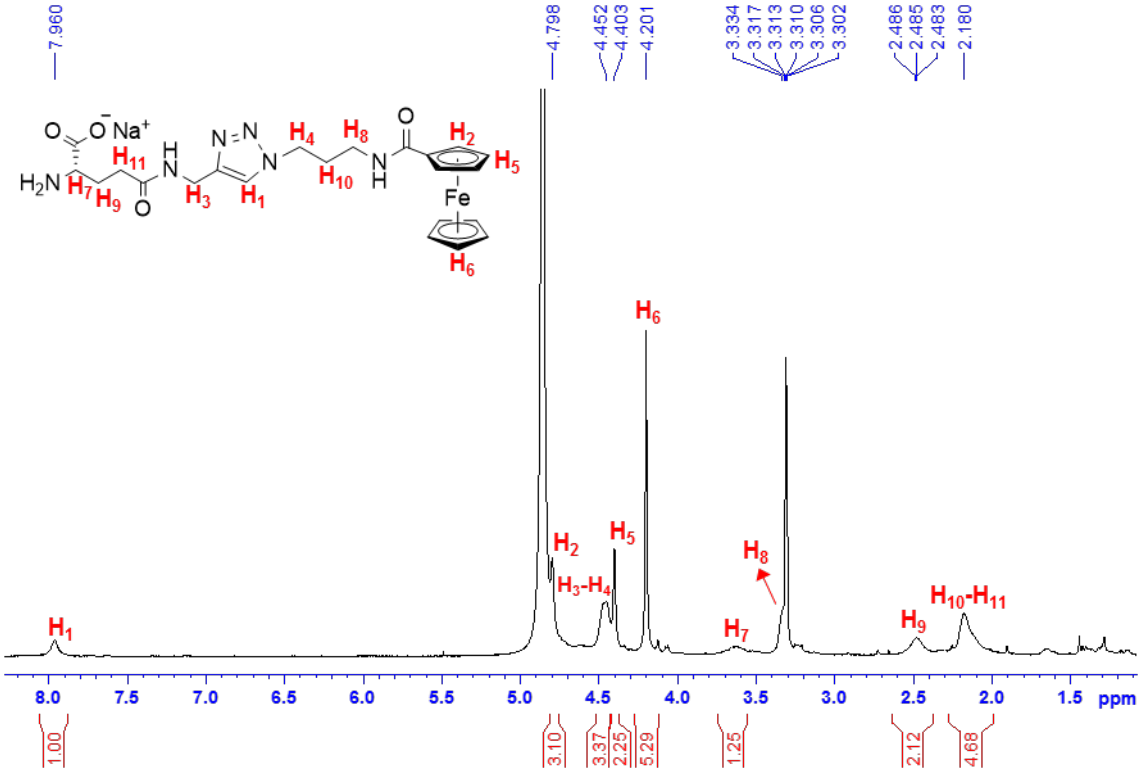


Figure S79. ^{1}H NMR spectrum of Glu γ-Fc **25** (400 MHz, CD_3OD, 298 K).

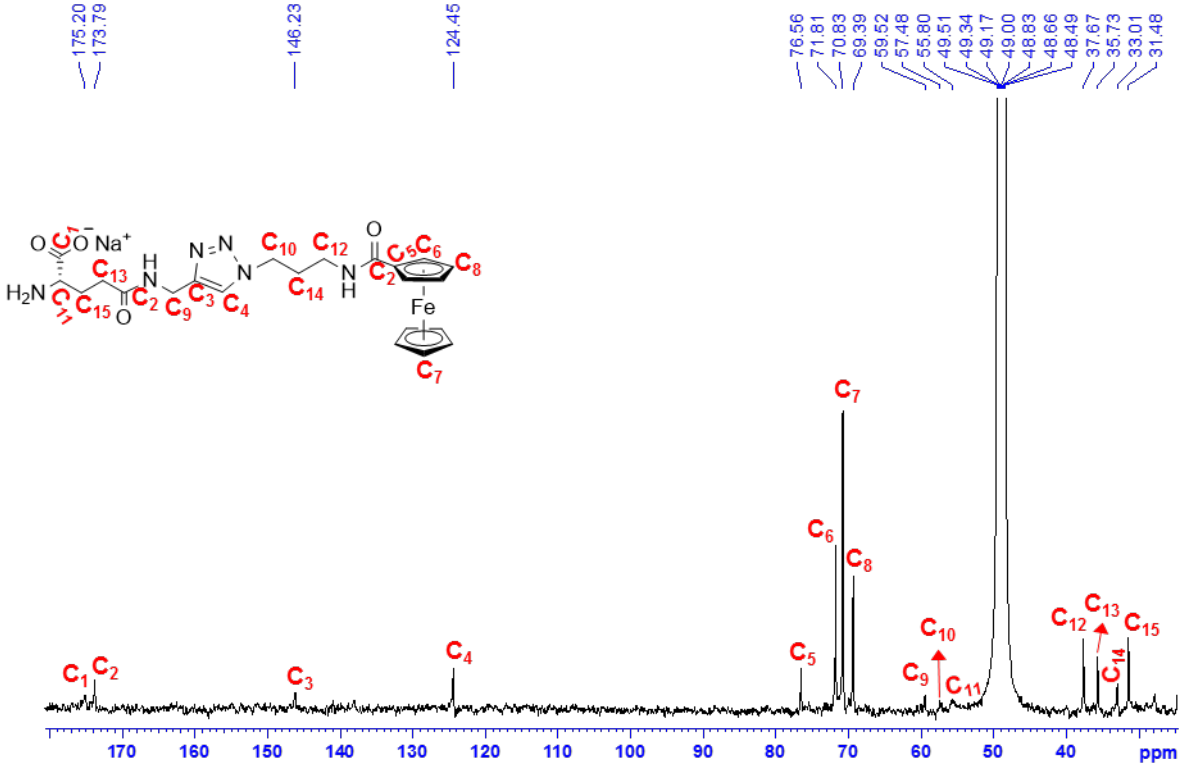


Figure S80. ^{13}C NMR spectrum of Glu γ-Fc **25** (100 MHz, CD_3OD, 298 K).

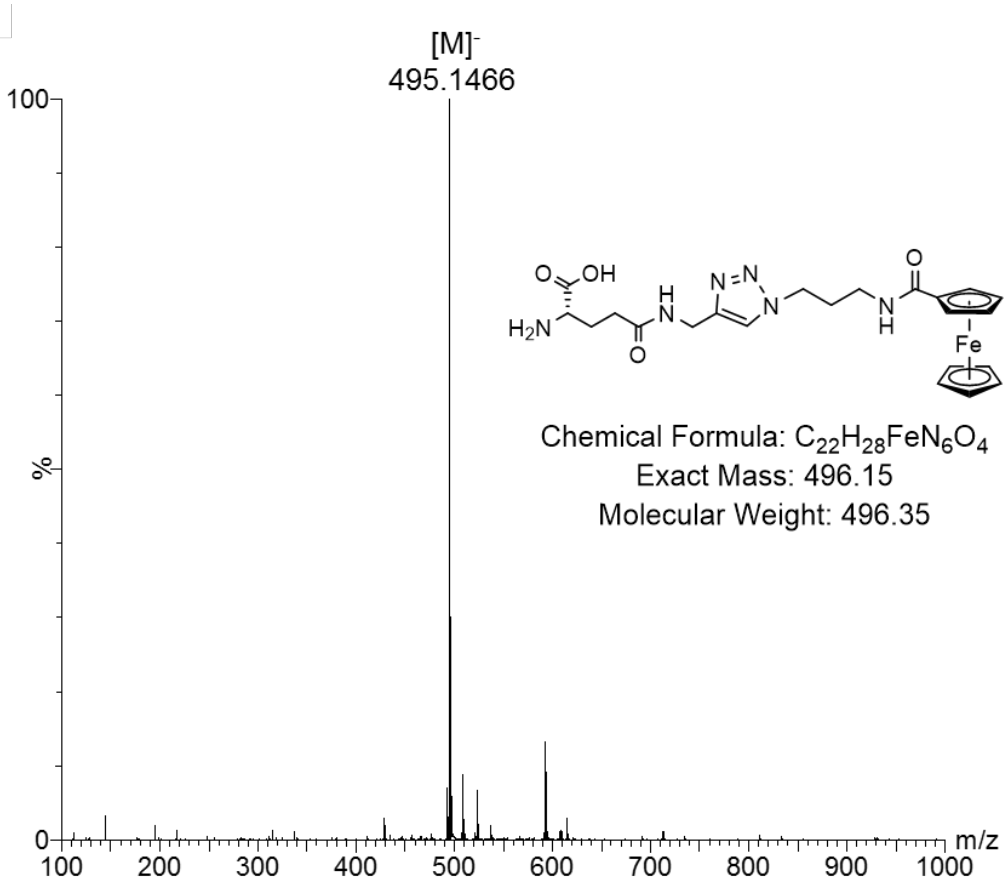


Figure S81. ESI-QTOF mass spectrum of unprotected Glu γ-Fc **25**.

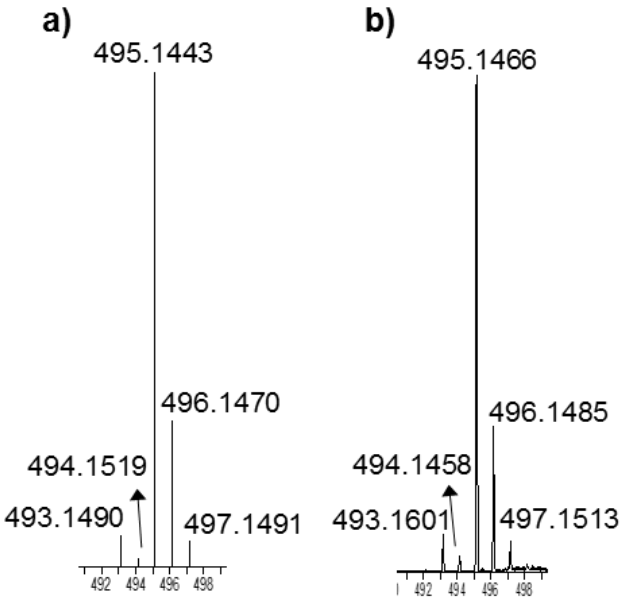
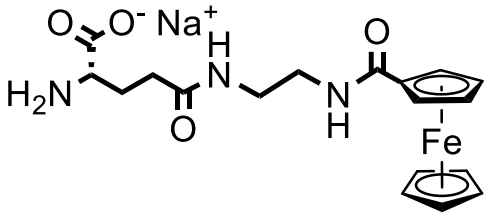


Figure S82. A zoom on the ESI-QTOF mass spectrum of Glu γ-Fc **25**. Left: theoretical isotopic distribution for $[M]^-$. Right: experimental isotopic distribution for $[M]^-$.

2.22 Unprotected Glu γ-Fc 26



Chemical Formula: $C_{18}H_{22}FeN_3NaO_4$
Exact Mass: 423.09
Molecular Weight: 423.23

Compound **12** (0.13 mmol, 80 mg) was dissolved in 5 mL of anhydrous DMF and and dried TBAF solution in tetrahydrofuran (1.0 M, 3 eq, 0.4 mmol, 104 mg, 0.400 mL) was added. The reaction mixture was stirred for 2 hours under nitrogen atmosphere. The solvents were evaporated to dryness and redissolved in 200 mL of ethyl acetate. The organic phase was washed with water (3×200 mL), brine (4×50 mL), dried over Na_2SO_4 and filtered. The crude intermediate was stirred at room temperature for 24 h under nitrogen atmosphere in the absence of light. The liquids were evaporated to dryness using rotary evaporation and the resulting solid was washed with diethyl ether (3×30 mL) and hexane (3×30 mL). Compound **26** was obtained as a red oil in 80% of yield (45 mg).

^{1}H NMR (D_2O, 400 MHz), δ (ppm): 4.88 (*br*, Fc-*H*, 2H), 4.61 (*br*, Fc-*H*, 2H), 4.38 (*s*, Fc-*H*, 5H), 3.73 (*t*, *J* = 5.2 Hz, NHC*H*, 1H), 3.37 (*br*, CH_2NH, 4H), 2.43-2.39 (*br*, CH_2CON, 2H), 2.13-2.06 (*m*, CHCH_2, 2H). **^{13}C NMR** (D_2O, 100 MHz), δ (ppm): 174.9 (*C*O_2), 174.3 (*C*ONH), 74.0 (FcAr-C_q), 71.7 (FcAr-*C*H), 70.2 (FcAr-*C*H), 68.4 (FcAr-*C*H), 54.3 (N*C*H), 39.0 (NH*C*H_2), 38.7 (NH*C*H_2), 31.6 (*C*H_2CONH), 26.4 (*C*H_2CH_2CONH). **ESI-MS** $[M]^-$ m/z calcd for $C_{18}H_{23}FeN_3O_4$: 400.0960, found 400.0902.

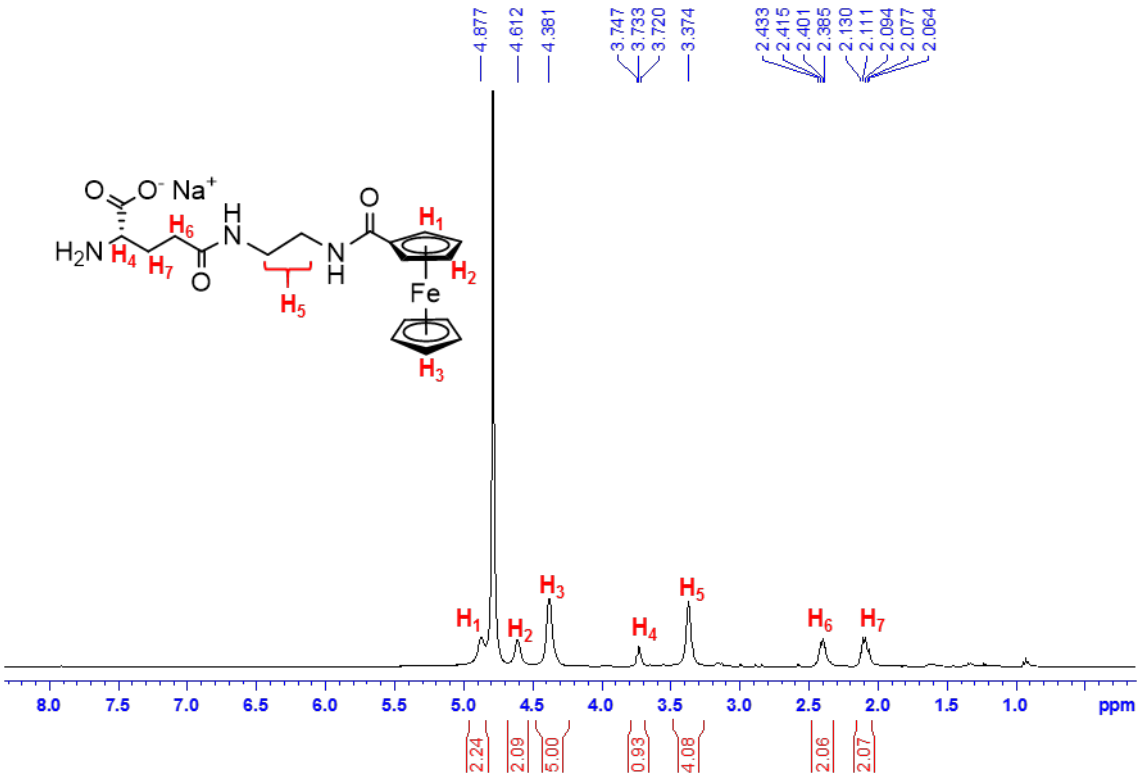


Figure S83. ^{1}H NMR spectrum of Glu γ-Fc **26** (400 MHz, D_2O, 298 K).

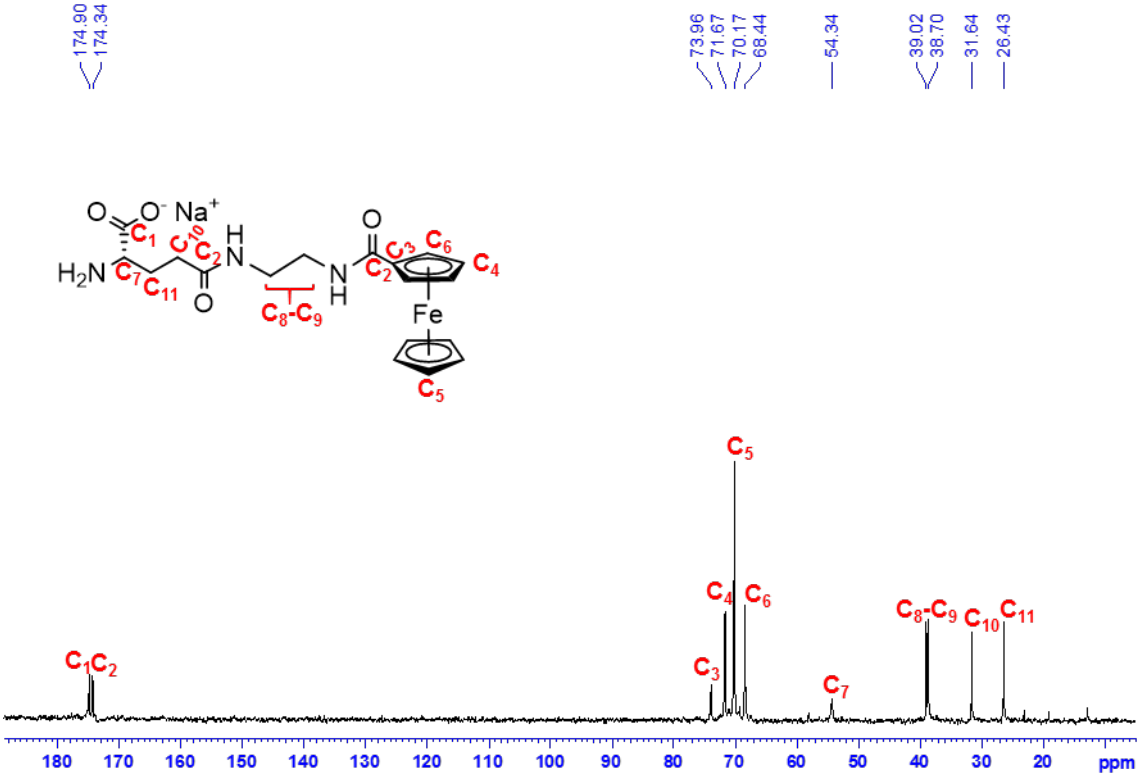


Figure S84. ^{13}C NMR spectrum of Glu γ-Fc **26** (100 MHz, D_2O, 298 K).

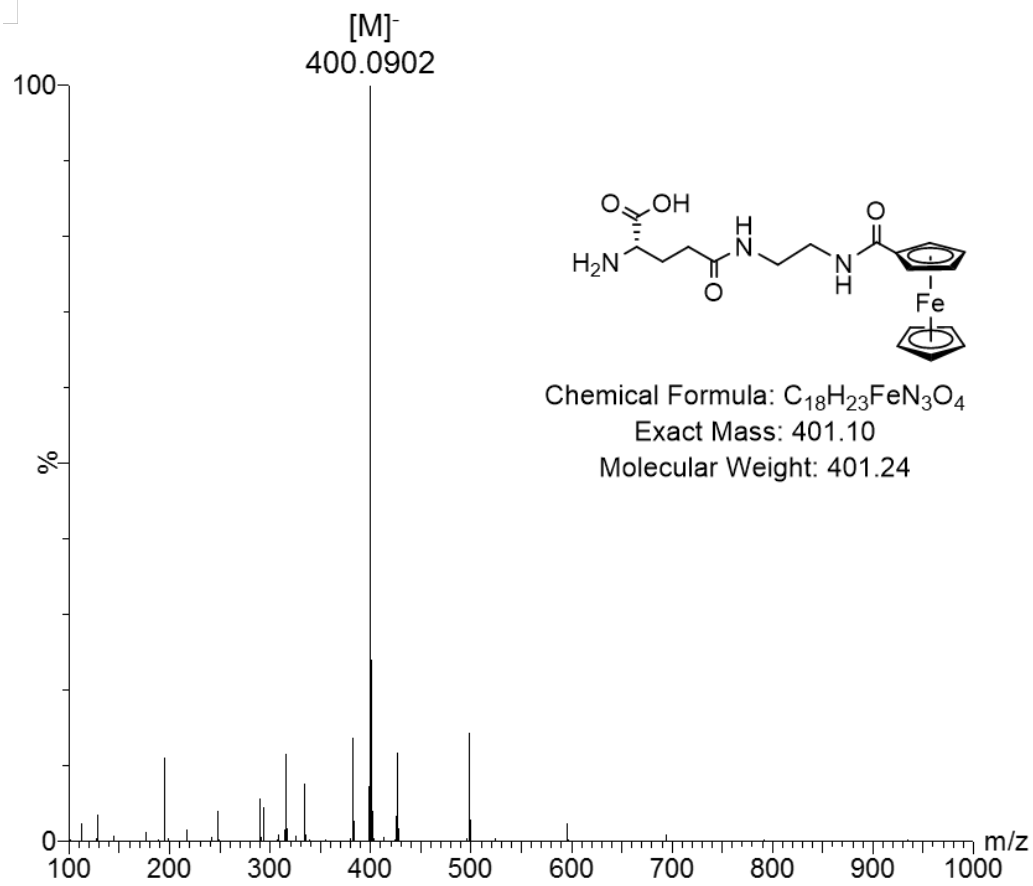


Figure S85. ESI-QTOF mass spectrum of unprotected Glu γ-Fc **26**.

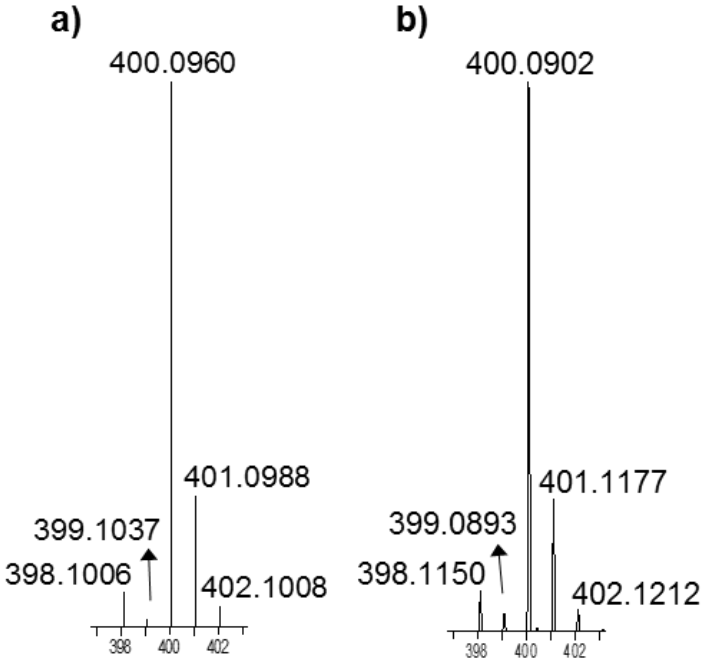


Figure S86. A zoom on the ESI-QTOF mass spectrum of Glu γ-Fc **26**. Left: theoretical isotopic distribution for $[M]^-$. Right: experimental isotopic distribution for $[M]^-$.

3. In vitro cytotoxicity supplementary data

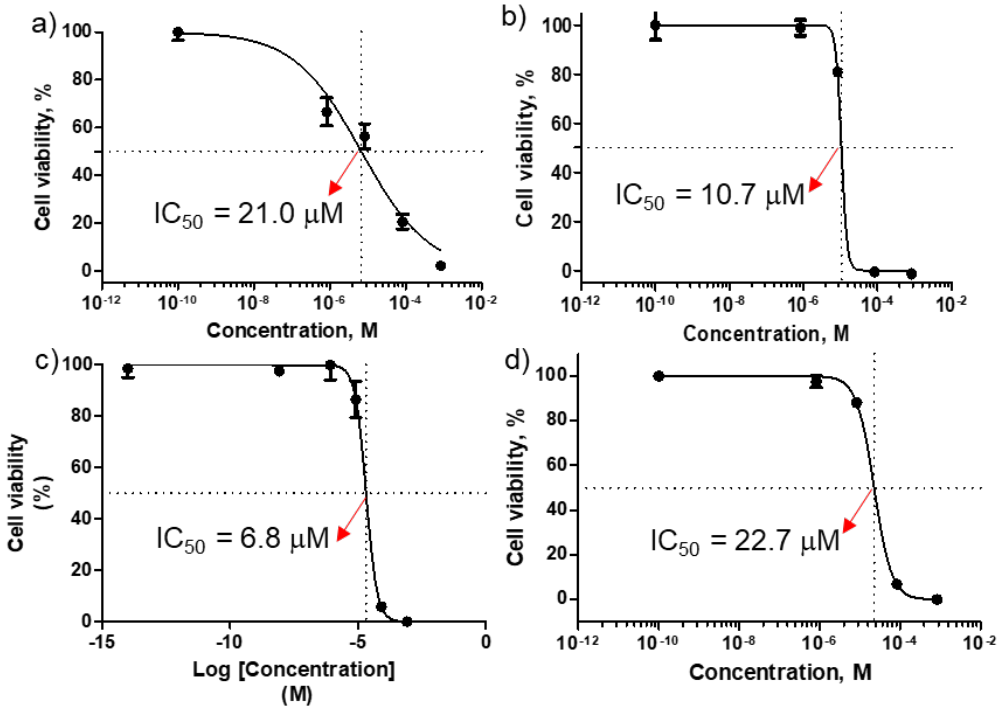


Figure S87. Dose-response curves of cisplatin on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

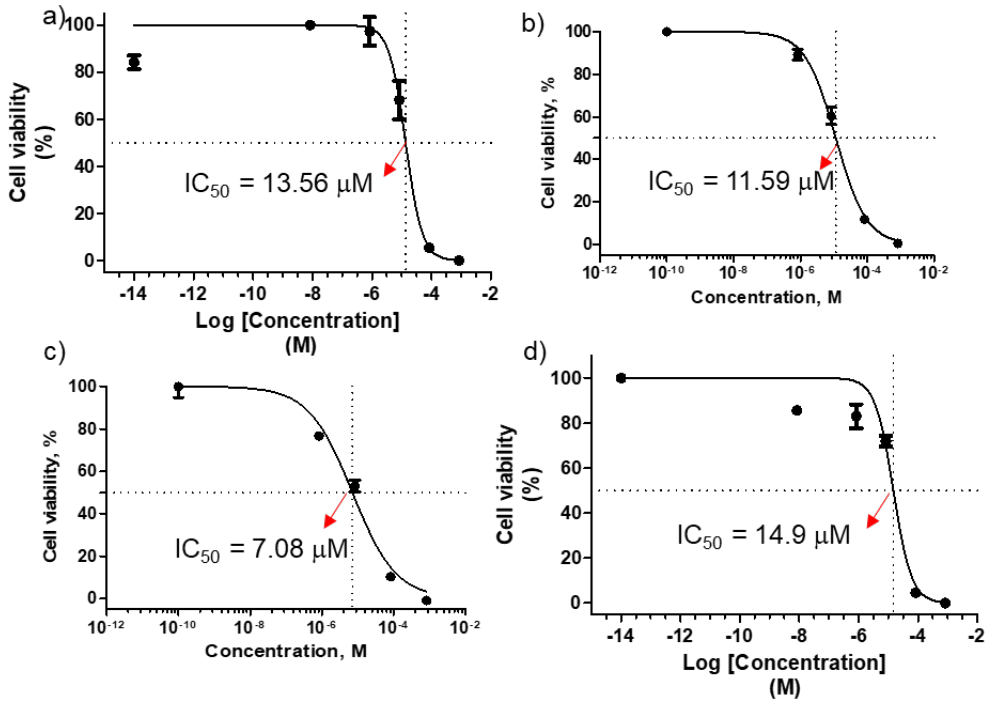


Figure S88. Dose-response curves of cisplatin on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

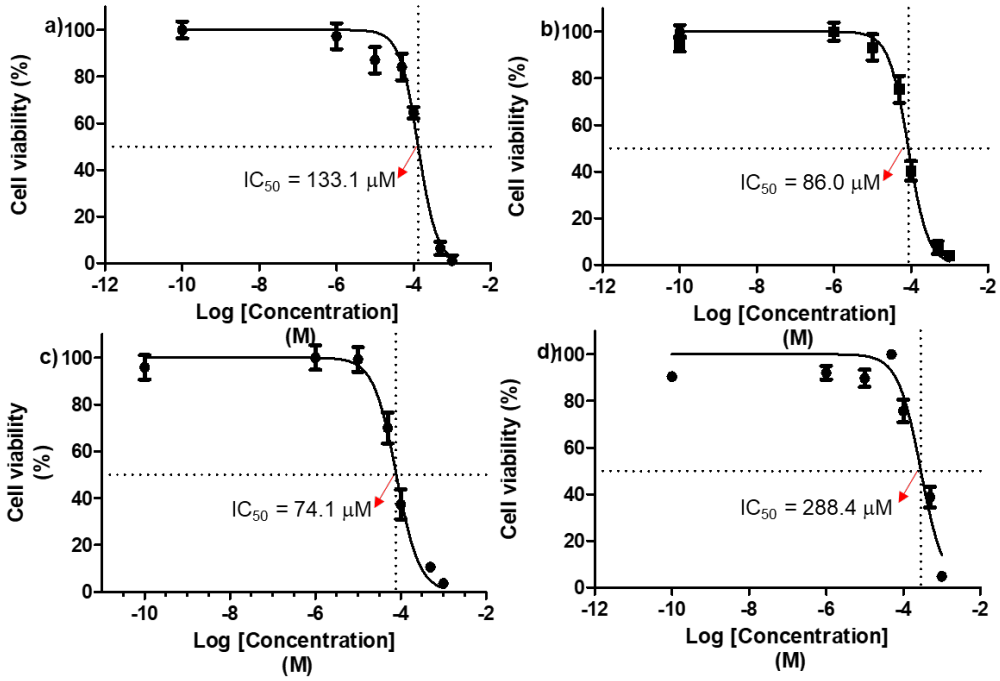


Figure S89. Dose-response curves of Glu γ-Fc **24** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

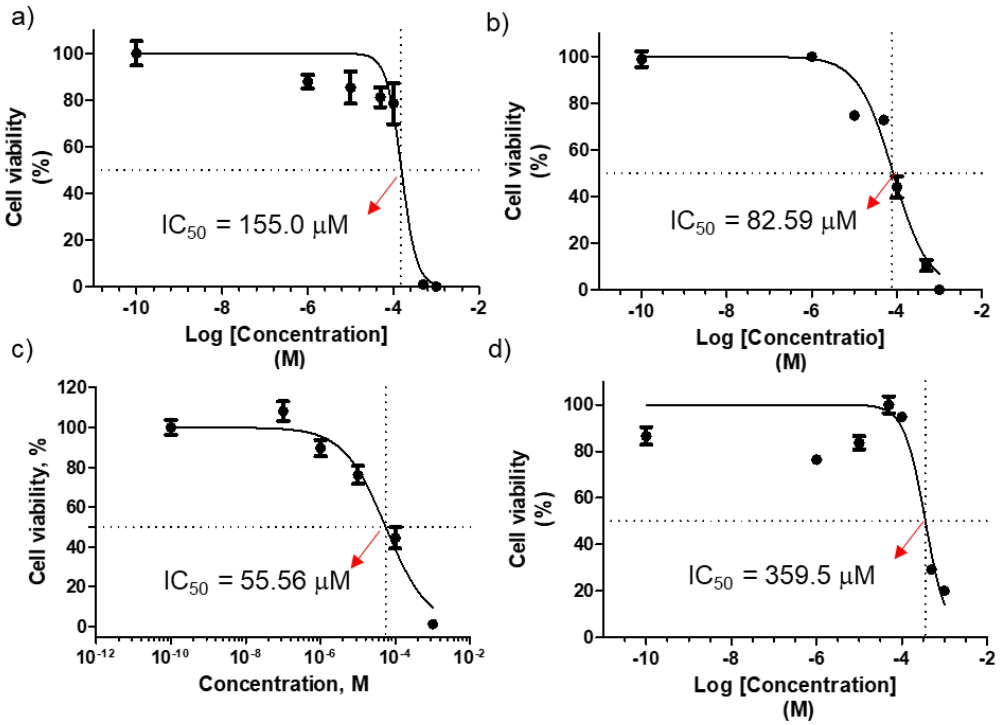


Figure S90. Dose-response curves of Glu γ-Fc **24** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

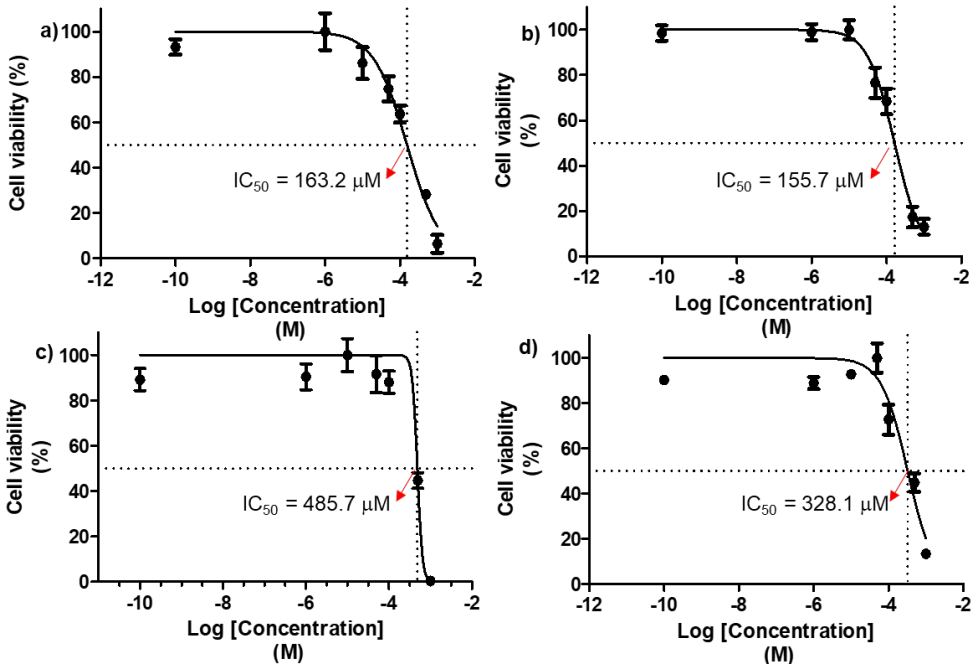


Figure S91. Dose-response curves of Glu γ-Fc **25** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

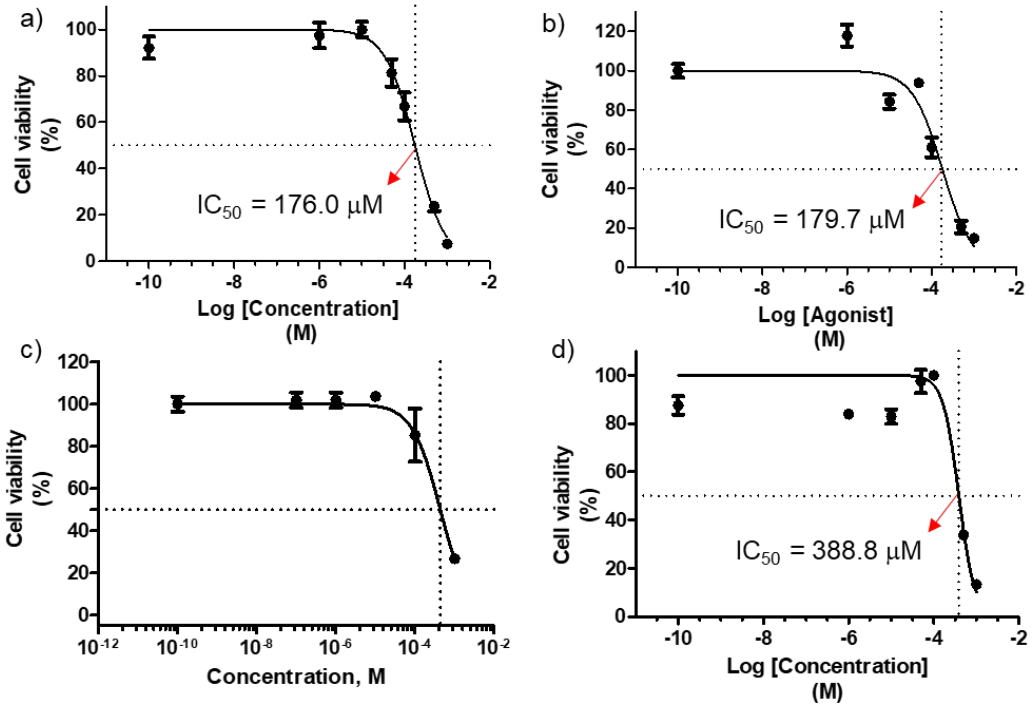


Figure S92. Dose-response curves of Glu γ-Fc **25** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

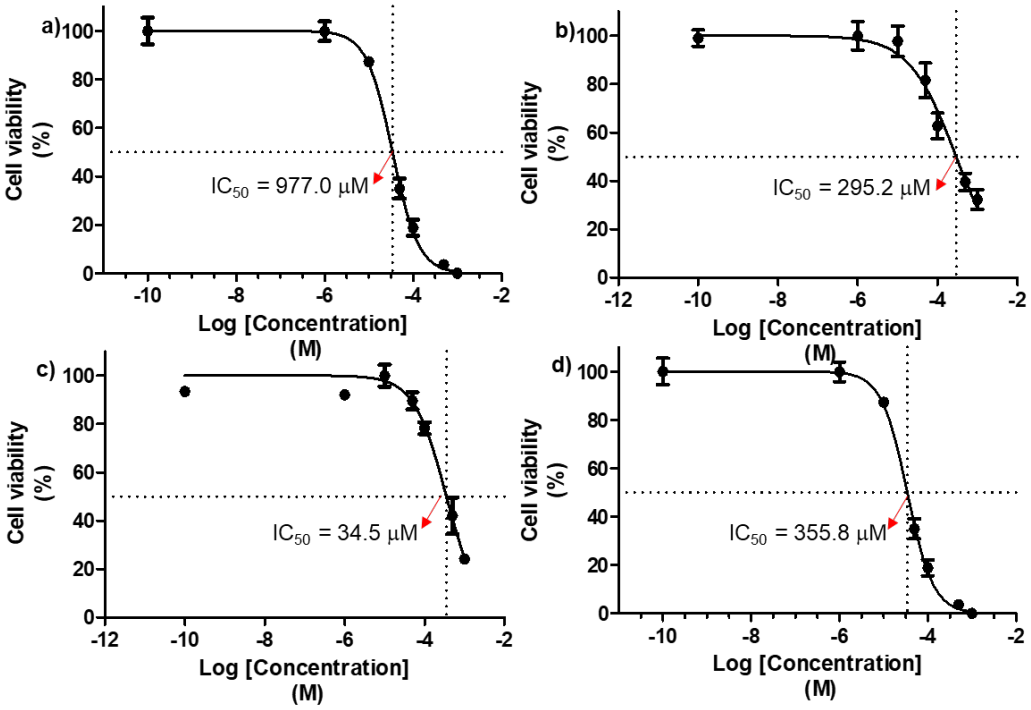


Figure S93. *In vitro* cell viability of Glu γ-Fc **26** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

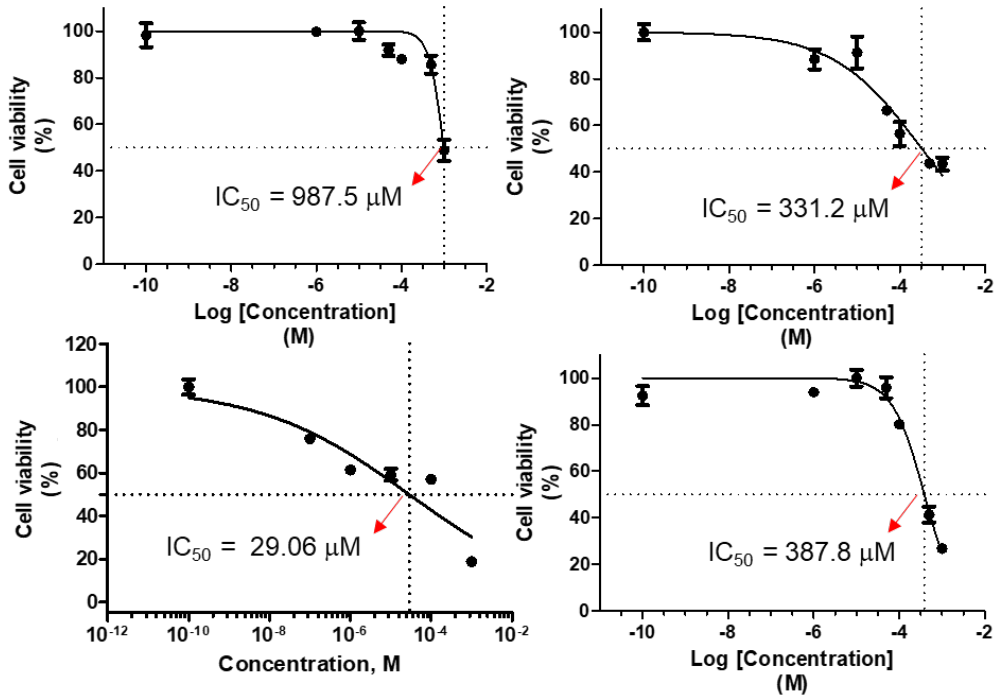


Figure S94. Dose-response curves of Glu γ-Fc **26** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

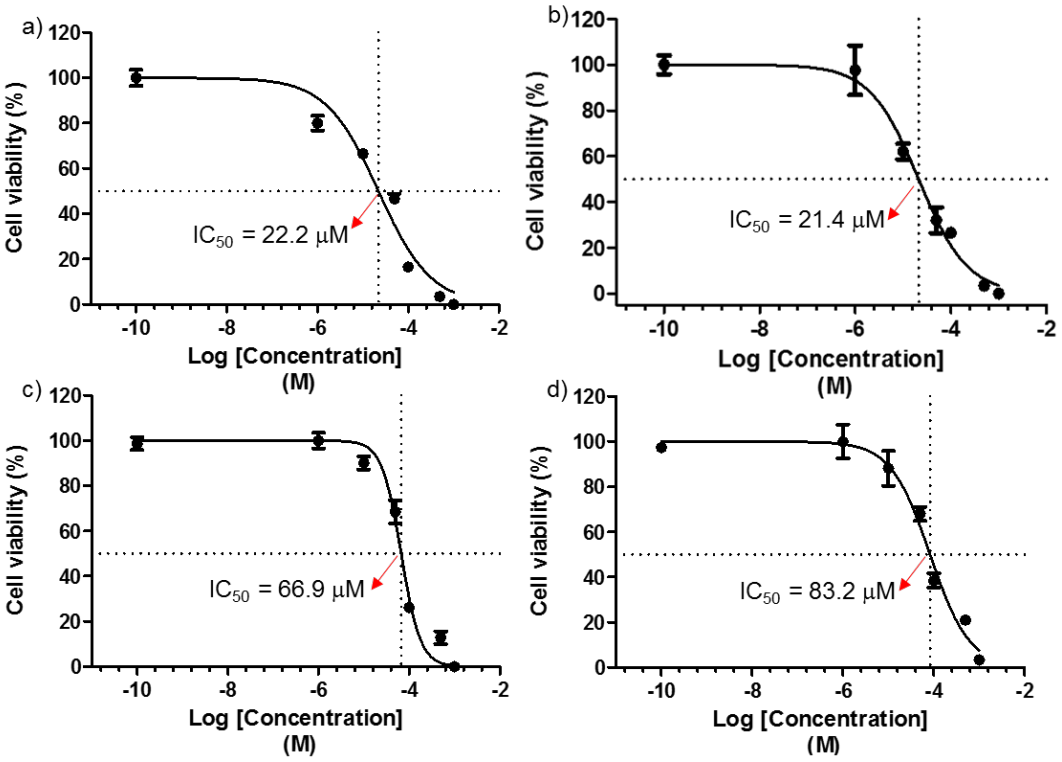


Figure 95. Dose-response curves of folate γ-Fc **21** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

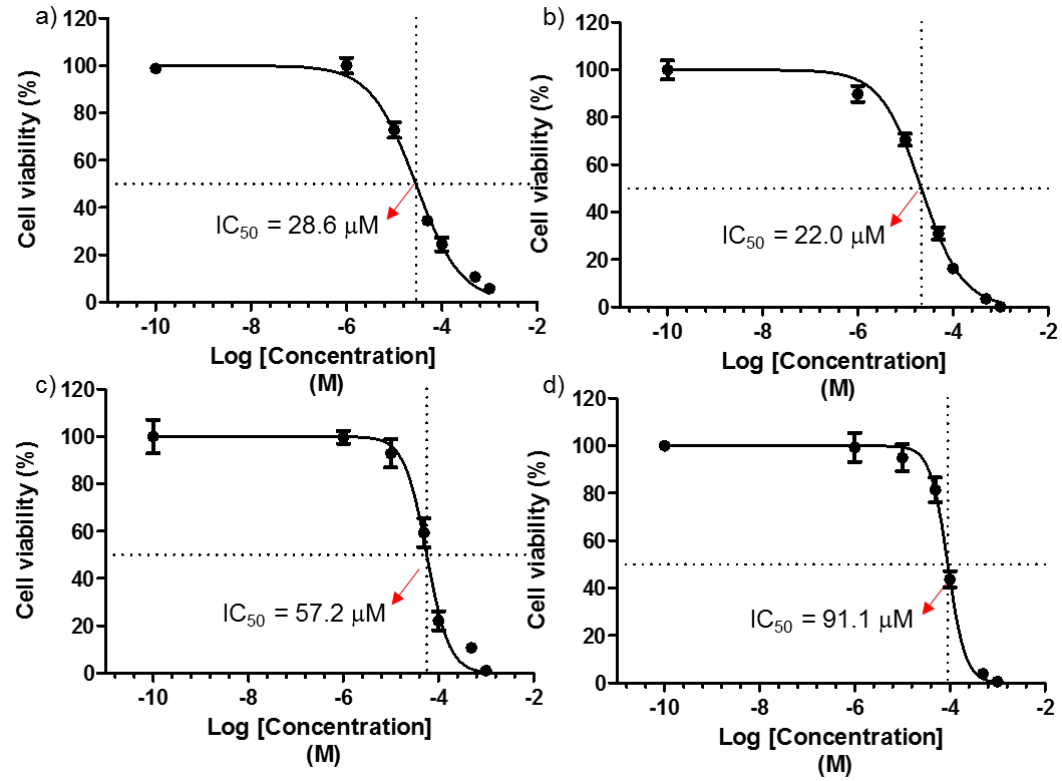


Figure S96. Dose-response curves of folate γ-Fc **21** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

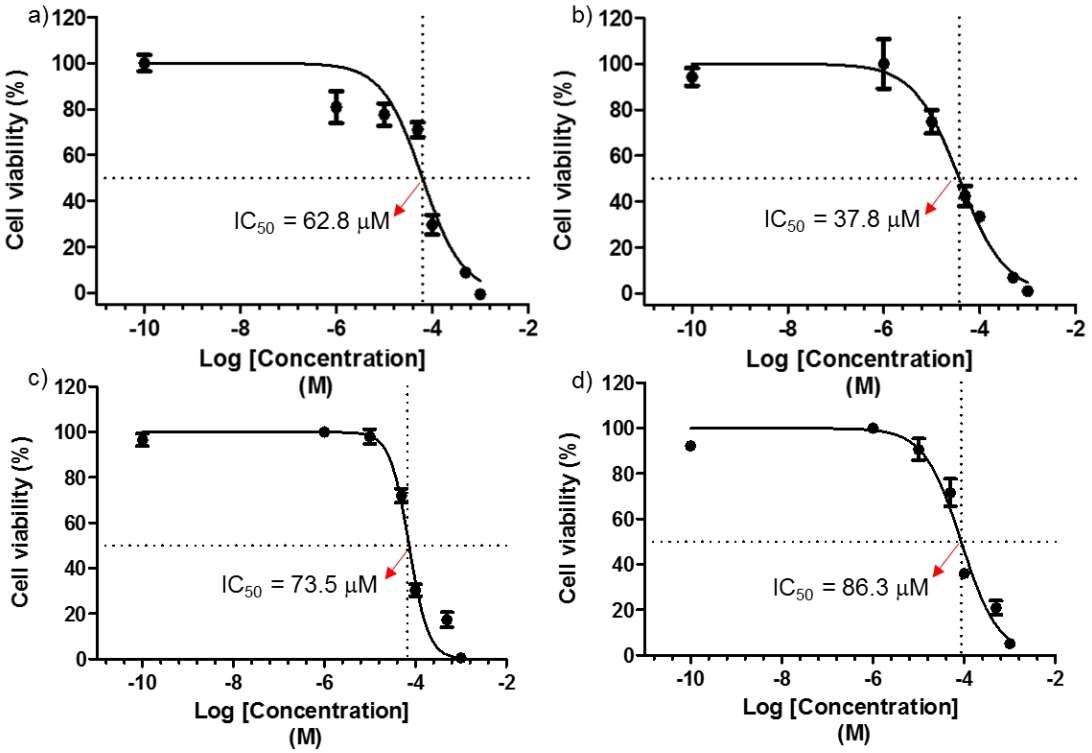


Figure S97. Dose-response curves of folate γ-Fc **22** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

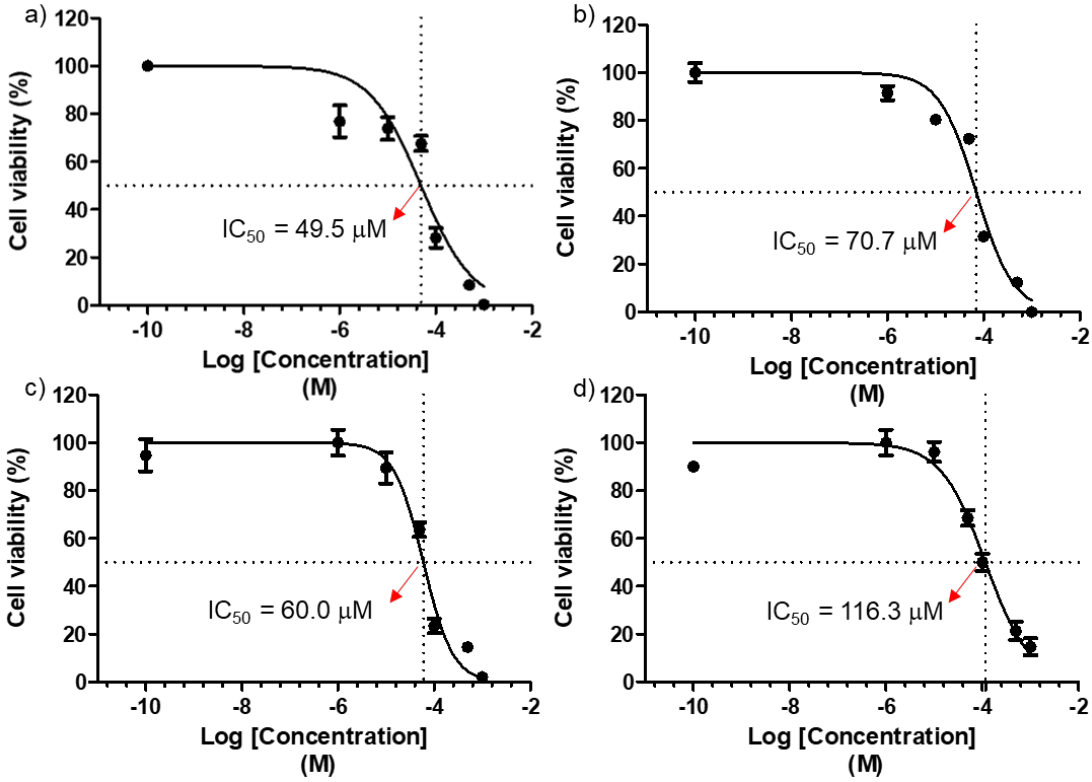


Figure S98. Dose-response curves of folate γ-Fc **22** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

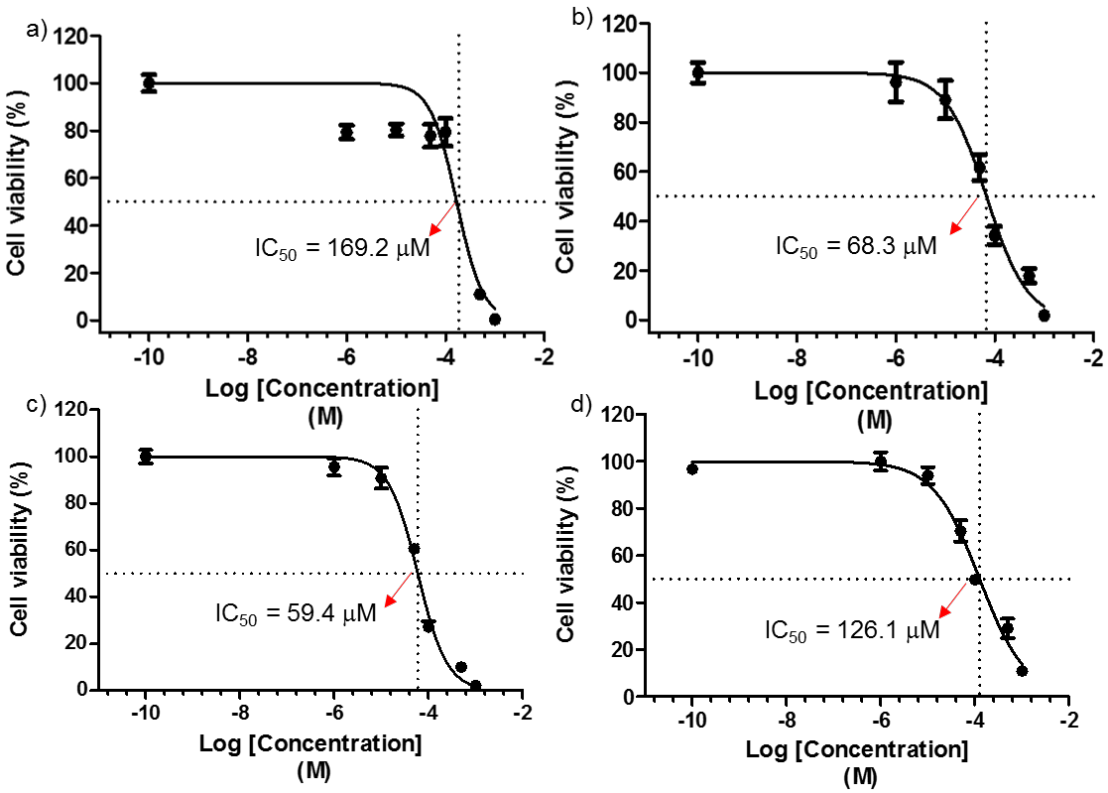


Figure S99. Dose-response curves of folate γ-Fc **23** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

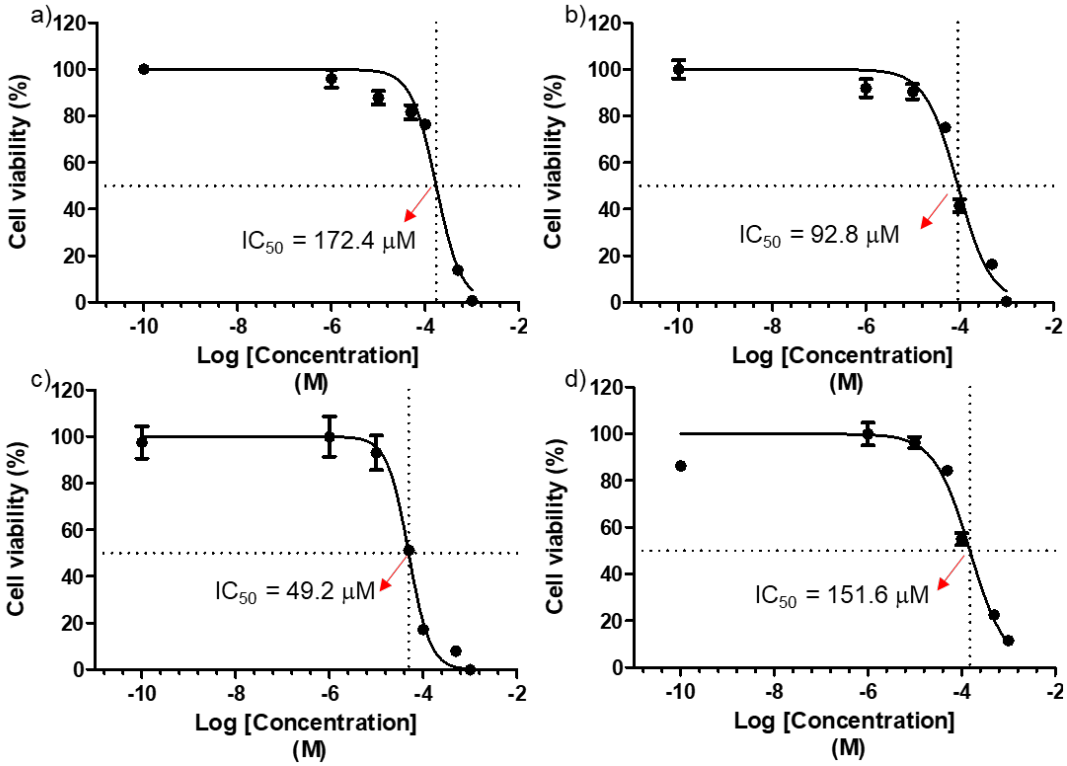


Figure S100. Dose-response curves of folate γ-Fc **23** on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

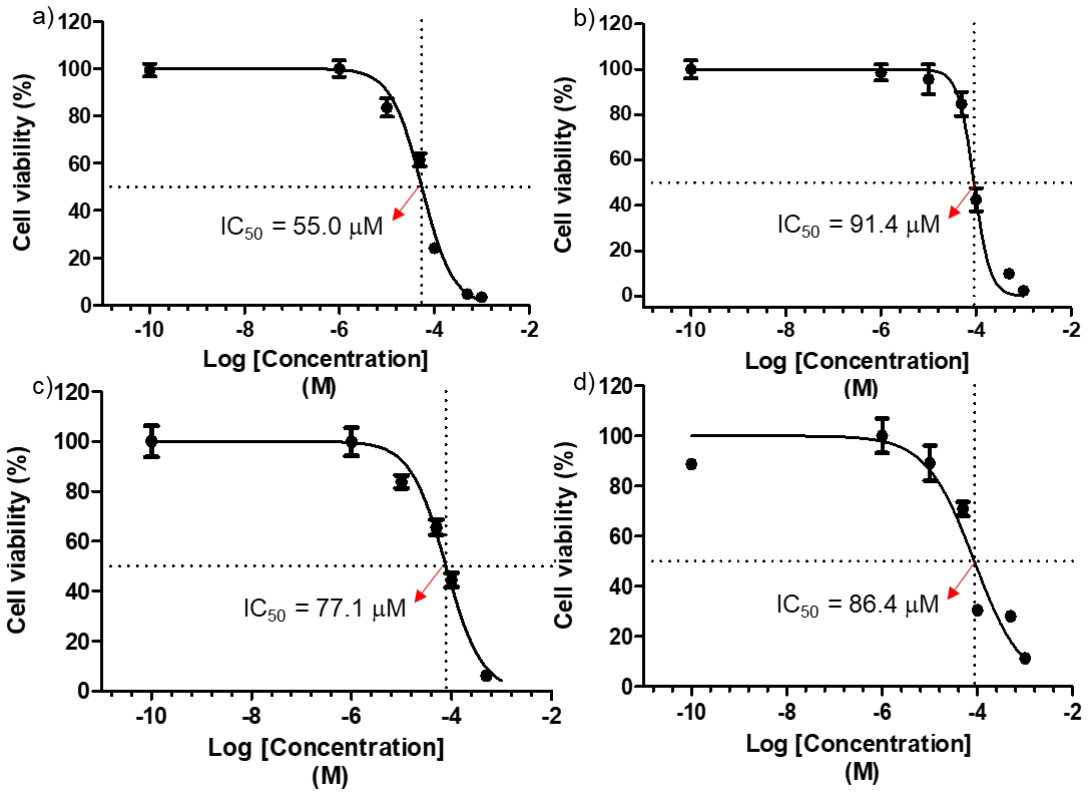


Figure S101. Dose-response curves of folate γ-Fc **21** with folic acid 1 mM on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

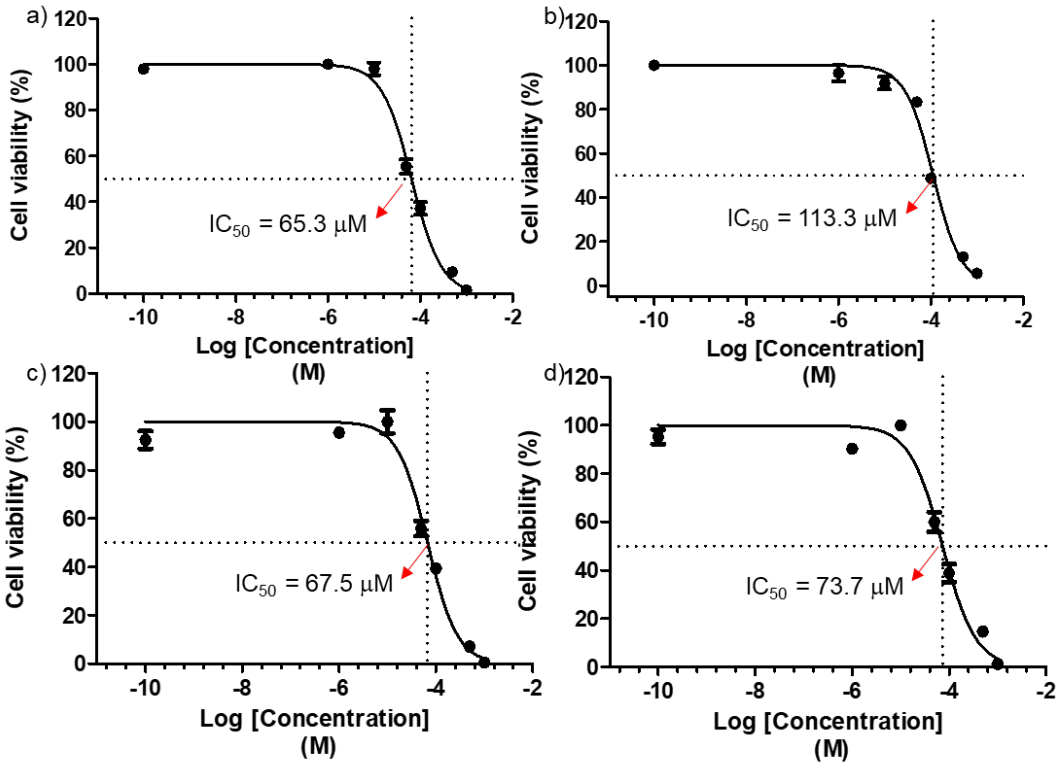


Figure S 102. Dose-response curves of folate γ-Fc **21** with folic acid 1 mM on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

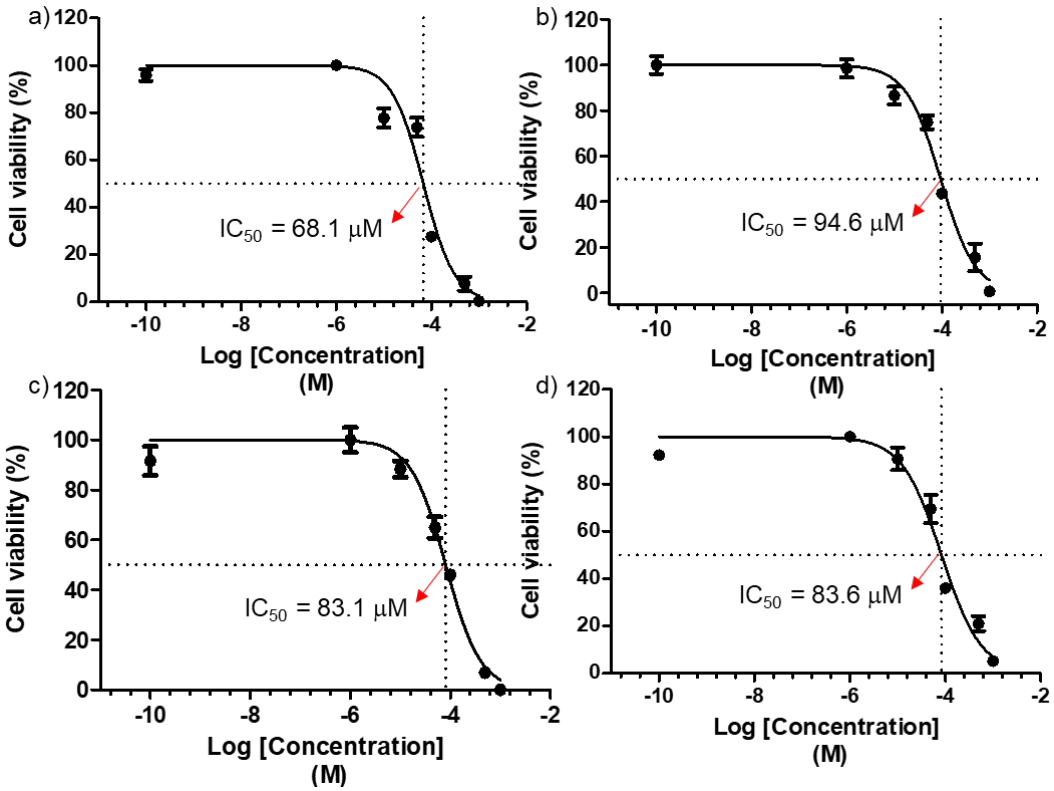


Figure S103. Dose-response curves of folate γ-Fc **22** with folic acid 1 mM on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

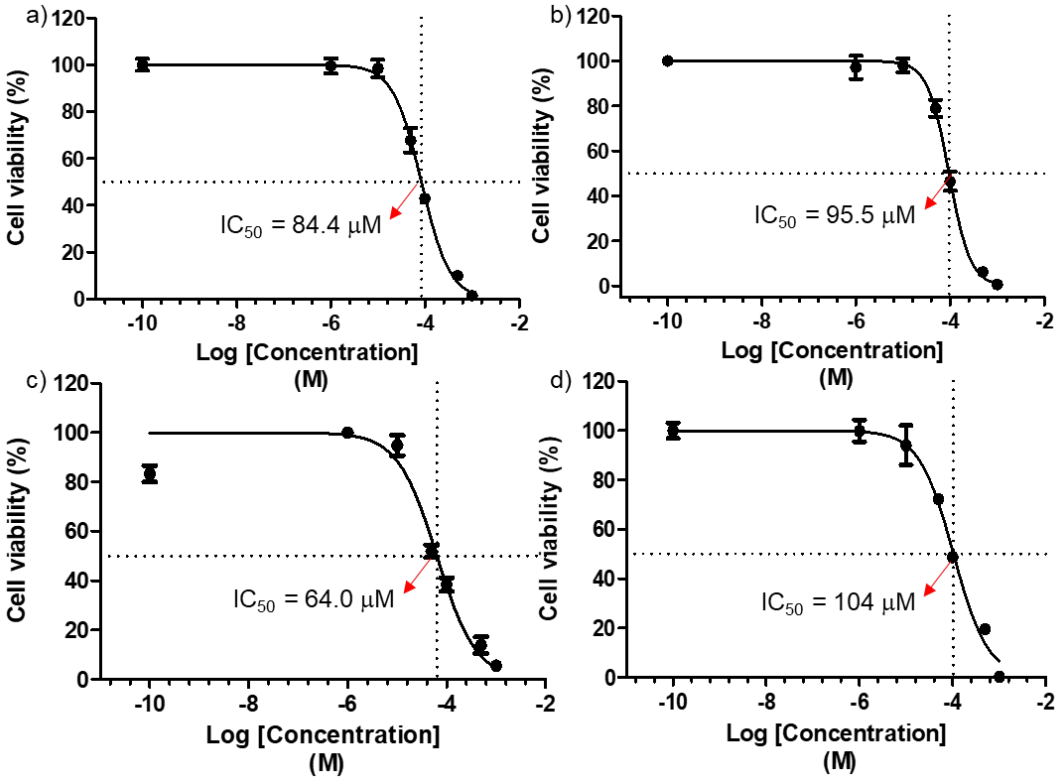


Figure S104. Dose-response curves of folate γ-Fc **22** with folic acid 1 mM on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

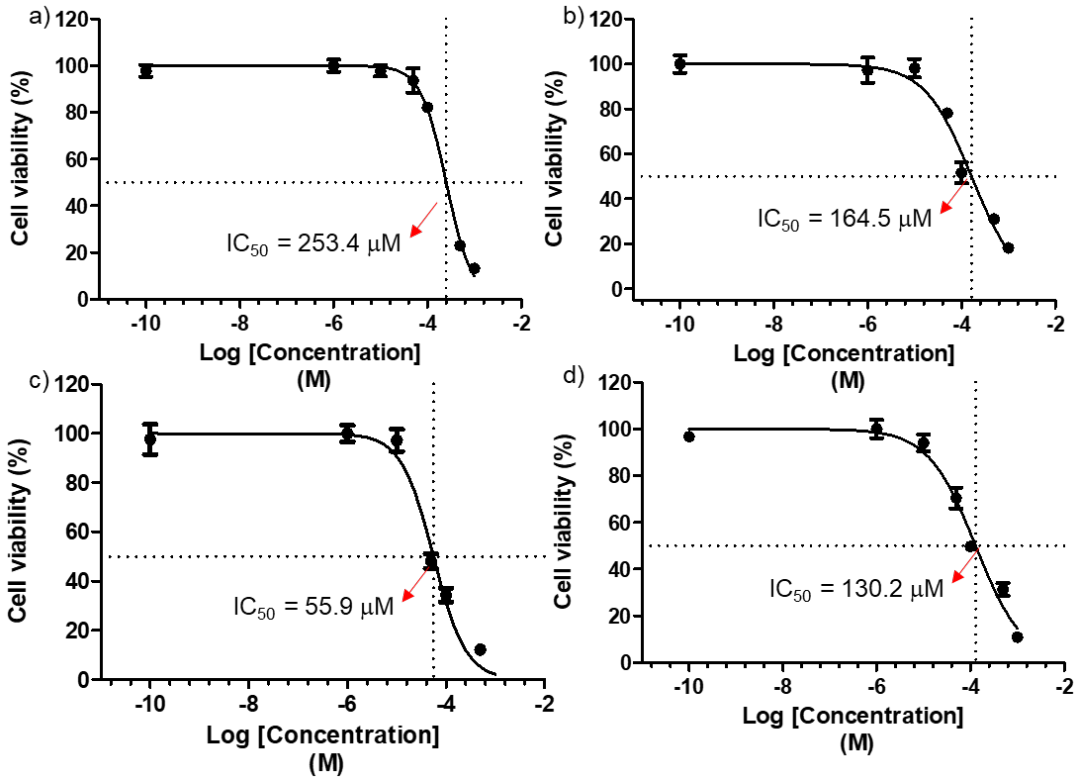


Figure S105. Dose-response curves of folate γ-Fc **23** with folic acid 1 mM on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line.

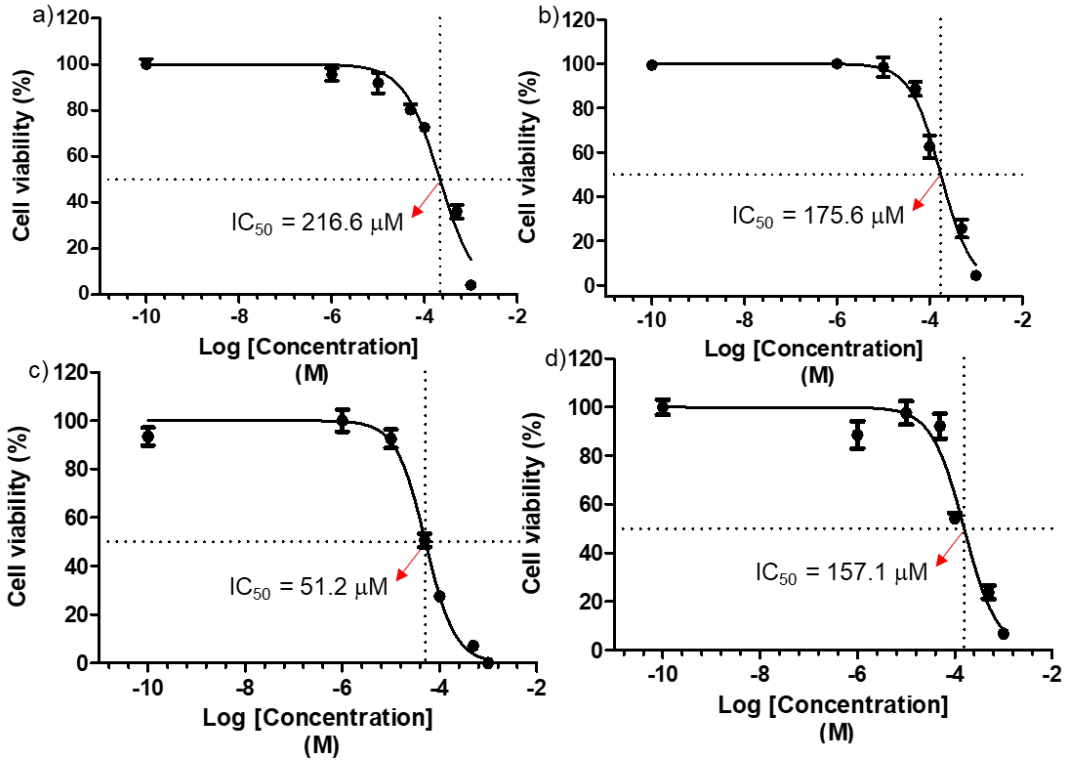


Figure S106. Dose-response curves of folate γ-Fc **23** with folic acid 1 mM on **(a)** HeLa, **(b)** MCF7, **(c)** PC-3 and **(d)** PNT2 cell line (duplicate).

4. References

1. J. Luo, M. D. Smith, D. A. Lantrip, S. Wang and P. L. Fuchs, *J. Am. Chem. Soc.*, 1997, **119**, 10004-10013.
2. D. P. Cox, J. Terpinski and W. Lawrynowicz, *J. Org. Chem.*, 1984, **49**, 3216-3219.