Electronic Supplementary Information

for

Vitamin B_{12} Derivatives as Activators of Soluble Guanylyl Cyclase

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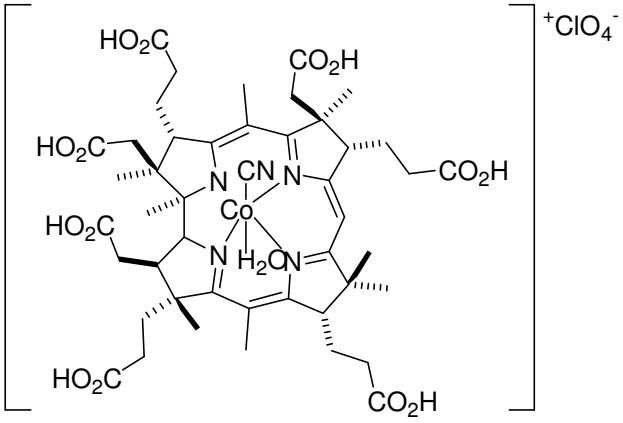
NMR Spectra:

General and Materials UV-vis absorption spectra were measured on a Hitachi U-3300 spectrometer and Perkin Elmer λ-25 at room temperature. High resolution ESI mass spectra were recorded on a Mariner spectrometer. MALDI-TOF-MS were measured using a Bruker Autoflex II, with dithranol as the matrix. ^{1}H and ^{13}C NMR spectra were recorded at RT on Bruker 400 or 500 and Varian 500 MHz instruments with TMS as an internal standard. Elemental analyses were obtained from the Service Center of Elementary Analysis of Organic Compounds at Kyushu University and from the Institute of Organic Chemistry PAS. DCVC (dry column vacuum chromatography) was performed using Merck Silica Gel (200-300 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.20 mm thickness.

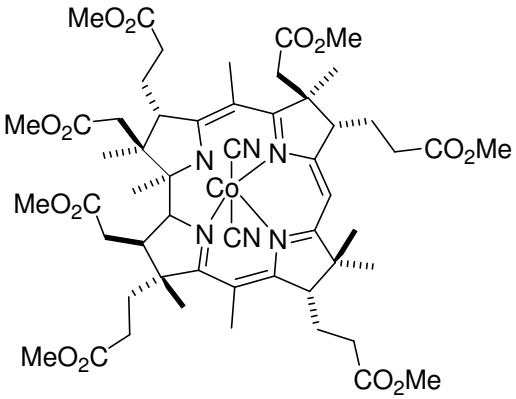
All solvents and chemicals used in the syntheses were of reagent grade and were used without further purification. Tested compounds were greater than 95% chemical purity as measured by HPLC analysis. HPLC analyses were carried out on a Hitachi High-Tech Fielding Co., Ltd., HPLC EZChrom Elite combined with an L-2455 DAD attachment, using three connected columns, Shodex KD-805, 804 and 802; DMF containing 5 mM LiBr was used as the eluent. Samples were treated with KCN (to effect dicyanation of the cobalt center of the vitamin B_{12} derivative in question) before HPLC analyses. Axial ligand exchange reactions involving the vitamin B_{12} derivatives of this study were monitored by UV-vis absorption spectroscopy.

Compound 2



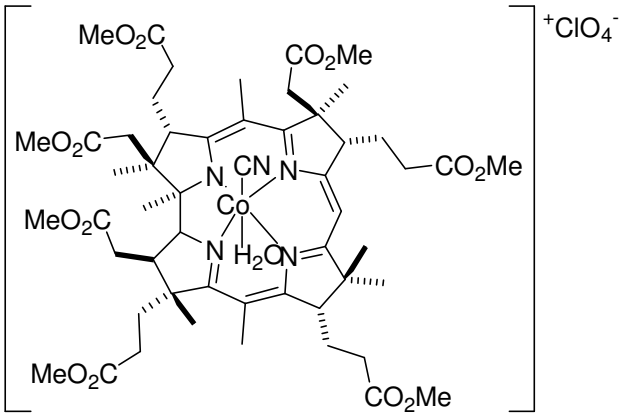
Compound **2** was prepared from heptamethylcobyrinate by hydrolysis, followed by treatment with the perchloric acid.[1]

Compound 3



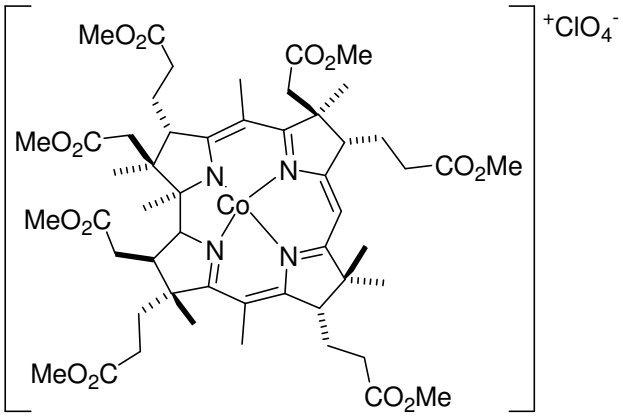
Compound **3** was prepared from cyanocobalamin using a method similar to that reported previously.[2] Anal. Calcd. for $C_{54}H_{73}CoN_6O_{14}$•H_2O: C, 58.58; H, 6.83; N, 7.59 %. Found: C, 58.46; H, 6.74; N, 7.58 %.

Compound 4



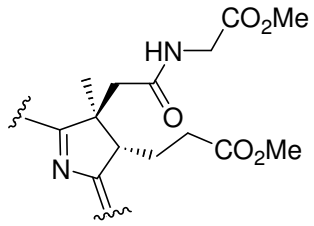
Compound **4** was prepared from derivative **3** using a method reported previously.[20] Anal. Calcd. for $C_{53}H_{75}ClCoN_5O_{19}$: C, 53.92; H, 6.40; N, 5.93 %. Found: C, 53.75; H, 6.40; N, 6.03 %.

Compound 5



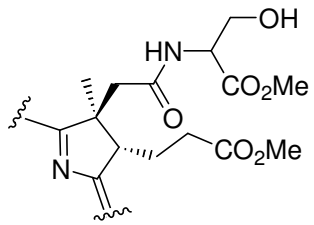
Compound **5** was prepared from **4** using a method reported previously.[3] Anal. Calcd. for $C_{52}H_{73}ClCoN_4O_{18}$: C, 54.95; H, 6.47; N, 4.93 %. Found: C, 54.68; H, 6.41; N, 5.00 %.

Preparation of compound 7



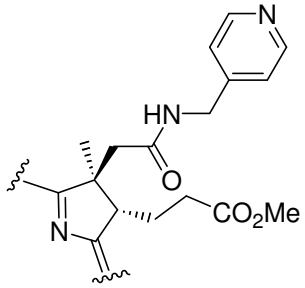
c-Acid (**6**) [4,5] (15 mg, 0.014 mmol) was dissolved in dimethylformamide (DMF; 1 mL) and cooled to 0 °C using an ice-bath under a nitrogen atmosphere. DEPC (9 µL, 0.06 mmol) was added to the solution, followed by Gly-OMe (4.0 mg, 0.04 mmol) and triethylamine (8 µL, 0.12 mmol). The reaction mixture was stirred for 6 h at 0 °C, and then 17 h at room temperature under a nitrogen atmosphere. The mixture was then diluted with dichloromethane (DCM) and washed with water. The organic layer was separated and dried over anhydrous Na_2SO_4, and evaporated to dryness. The product was purified using DCVC, 2.5% EtOH in DCM. After recrystallization from hexanes/AcOEt, compound **7** was isolated as a purple solid (14 mg, 86%). R_f 0.50, 5% EtOH in dichloromethane (DCM). Anal. calcd. for $C_{56}H_{76}CoN_7O_{15} + H_2O$: C 57.77, H 6.75, N 8.42; found: C 57.64, H 7.08, N 8.17. LRMS ESI (m/z) calcd. for $C_{55}H_{76}CoN_6O_{15}$ $[M-CN]^+$ 1120.1; found 1120.1. UV/Vis CH_2Cl_2, λ_{max}, ε ($L \cdot mol^{-1} \cdot cm^{-1}$): 588 ($1.05 \times 10^4$), 5.49 ($8.62 \times 10^3$), 422 ($2.72 \times 10^3$), 371 ($2.78 \times 10^4$), 317 ($9.52 \times 10^3$), 279 ($1.09 \times 10^4$). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.45 (t, *J* = 5.8 Hz, 1H), 5.55 (s, 1H), 3.91 (dd, *J* = 5.1 and 11.8 Hz, 1H), 3.74 (s, 4H), 3.69 (s, 4H), 3.67 (s, 4H), 3.65 (s, 3H), 3.61 (s, 7H), 3.04 (dd, *J* = 3.0 and 3.5 Hz, 1H), 2.81 (m, 1H), 2.69 (q, *J* = 7.0 Hz, 1H), 2.63-2.53 (m, 5H), 2.48-2.37 (m, 4H), 2.36-2.30 (m, 2H), 2.26-2.29 (m, 6H), 2.19-2.10 (m, 4H), 2.05 (s, 3H), 1.82-1.76 (m, 1H), 1.75 (s, 3H), 1.71-1.65 (m, 2H), 1.48 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.24 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.3, 176.1, 176.0, 173.9, 173.7, 173.1, 172.9, 172.1, 171.9, 171.6, 170.4, 170.2, 163.7, 161.2, 107.2, 102.6, 91.5, 83.1, 74.9, 58.9, 58.7, 57.3, 52.6, 52.1, 52.0, 51.9, 51.89, 51.83, 51.4, 47.0, 46.3, 41.9, 41.1, 39.6, 33.9, 32.6, 32.0, 31.7, 31.2, 31.1, 29.9, 26.2, 25.9, 25.1, 22.3, 19.8, 19.5, 18.3, 17.1, 15.7, 15.6.

Preparation of compound 8



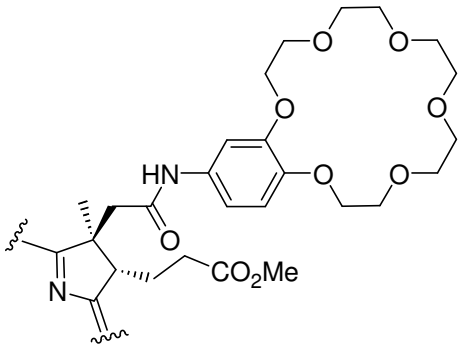
Following the procedure for compound **7**, *c*-acid **6** (90 mg, 0.084 mmol) was coupled with Ser-OMe (37 mg, 0.24 mmol). The product was purified using DCVC, 2.5% EtOH in DCM. After recrystallization from hexanes/ethyl acetate (AcOEt), compound **8** was isolated as a purple solid (51 mg, 54%). R_f 0.50, 5% EtOH in DCM. Anal. calcd. for $C_{57}H_{78}CoN_7O_{16}$ + $2H_2O$: C 56.48, H 6.82, N 8.09; found: C 56.13, H 6.55, N 7.93. LRMS ESI (m/z) calcd. for $C_{56}H_{78}CoN_6O_{16}$ $[M\text{-}CN]^+$ 1149.5; found 1149.9. UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 589 ($9.791x10^3$), 550 ($7.64x10^3$), 424 ($2.55x10^3$), 371 ($2.65x10^4$), 317 ($8.99x10^3$), 279 ($1.00x10^4$).^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm); 7.36 (m, 1H), 7.07 (d, *J* = 10.4 Hz, 1H), 5.58 (s, 1H), 4.31 (m, 1H), 4.08 (dd, *J* = 8.2 and 3.9 Hz, 1H), 3.82 (m, 1H), 3.77 (s, 3H), 3.71 (s, s, 6H), 3.69 (s, s, 6H), 3.63 (s, 3H), 3.58 (m, 1H), 3.05 (dd, *J* = 3.9 and 2.3 Hz, 1H), 2.80 (m, 1H), 2.60-2.51 (m, 5H), 2.49-2.40 (m, 6H), 2.35-2.26 (m, 3H), 2.28 (s, 3H), 2.17-2.11 (m, 4H), 2.08 (s, 3H), 2.04-1.99 (m, 1H), 1.80 (s, 4H), 1.74-1.69 (m, 1H), 1.63 (s, 3H), 1.51 (s, 3H), 1.37 (s, s, 6H), 1.25 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm); 176.1, 176.0, 173.7, 173.6, 172.8, 172.5, 171.6, 171.4, 170.3, 169.7, 163.5, 161.0, 128.3, 106.8, 102.4, 91.6, 82.6, 74.4, 61.7, 59.5, 58.4, 56.2, 55.8, 53.4, 52.4, 52.2, 52.0, 51.9, 51.8, 51.7, 51.6, 46.8, 46.1, 41.7, 39.2, 33.6, 32.1, 31.8, 31.5, 30.6, 29.5, 25.6, 25.3, 24.9, 22.0, 19.6, 18.9, 18.1, 17.1, 15.4, 15.2.

Preparation of compound 9



Following the procedure for compound **7**, *c*-acid **6** (410 mg, 0.38 mmol) was coupled with 4-(aminomethyl)pyridine (48 µL, 0.35 mmol). The product was purified by the columun chlomatography over silica gel 60N (spherical: 60–210 µm, neutral), using 5% MeOH in DCM. After recrystallization from hexanes/benzene compound **9** was isolated as a purple solid (190 mg, 45%.). Anal. calcd. for $C_{59}H_{77}CoN_8O_{13}$+$2H_2O$: C, 58.99; H, 6.80; N, 9.33 %. Found: C, 59.12; H, 6.56; N, 9.28 %. MALDI-TOF-MS (*m/z*): $[M-2CN]^+$, 1112. Selected IR features (□/cm^{-1}): 1734 (ester C=O, str.), 1664 (amide C=O, str.). UV/Vis CH_2Cl_2: 278, 312, 370, 421, 510(sh), 547 and 587. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm); 8.39 (d, 2H), 7.67 (t, 1H), 7.06 (d, 2H), 5.53 (s, 1H), 3.82 (t, 1H) , 3.78 (d, 1H), 3.61-3.75 (m, 20H) , 3.58 (t, 1H), 3.02 (t, 1H) , 2.81 (t, 1H), 2.22 (s, 3H), 2.11 (s, 3H), 2.69-1.72 (m, 22H) 1.65 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H).

Preparation of compound 10



Following the procedure for compound **7**, *c*-acid **6** (119 mg, 0.086 mmol) was coupled with 4'-aminobenzo 18-crown-6 ether (109 mg, 0.34 mmol). The product was purified by columun chlomatography over silica gel 60N (spherical: 60–210 µm, neutral), using 10% MeOH in DCM. After recrystallization from hexanes/benzene compound **9** was isolated as a purple solid (74 mg, 48%). Anal. calcd. for $C_{69}H_{94}CoN_7O_{19}$ and K and $2H_2O$: C, 56.78; H, 6.77; N, 6.72 %.Found: C, 56.94; H, 6.77; N, 6.63 %. MALDI-TOF-MS (*m/z*): $[M\text{-}CN]^+$, 1344. UV/Vis CH_2Cl_2: 371, 421, 510(sh), 547 and 587. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm); 8.80 (s, 1H), 7.34 (d, 1H), 7.09 (dd, 1H), 6.62 (dd, 1H), 5.74 (s, 1H), 4.21 (m, 4H), 4.05 (m, 4H), 3.87-3.80 (m, 6H), 3.75-3.62 (m, 24H), 3.46 (t, 1H), 3.05 (t, 1H), 2.77 (t, 1H), 2.30 (s, 3H), 2.22 (s, 3H), 1.68-2.64 (m, 22H), 1.62 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H).

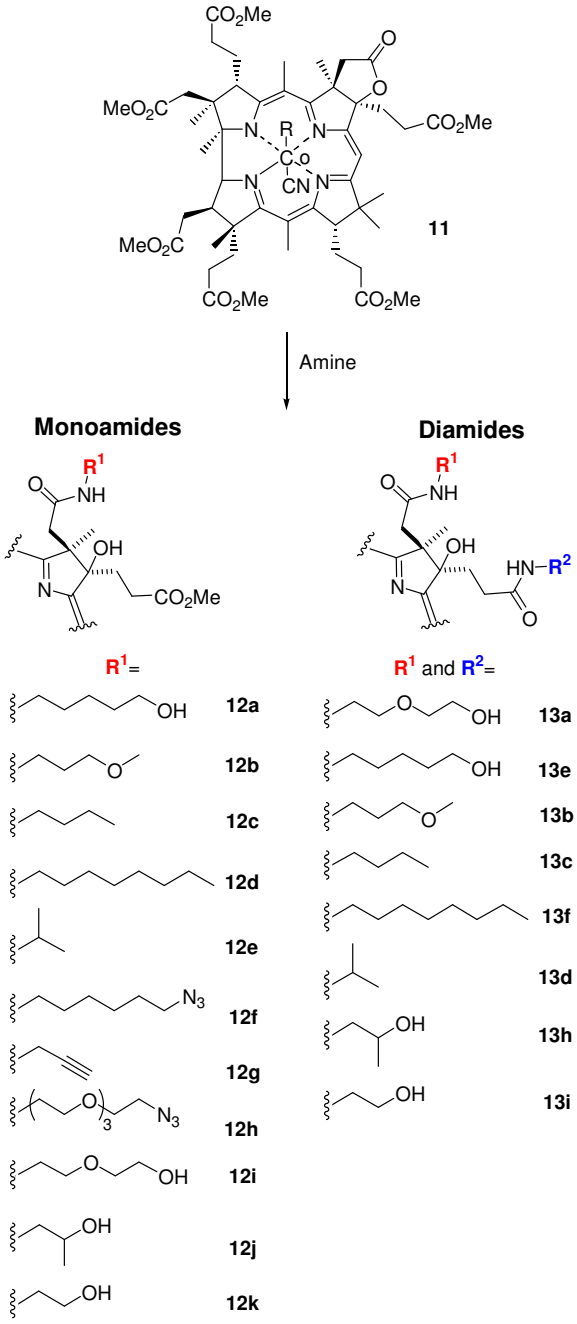


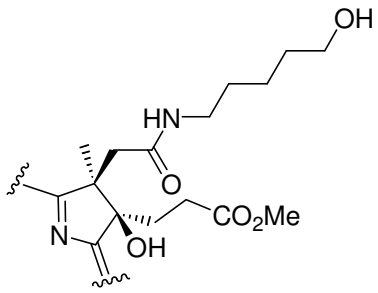
Figure 1 Full list of synthesized mono and di-amides from *c*-lactone.[6]

Table 1. Full list of Vitamin B_{12} derivatives with sGC-stimulating properties

Entry	Derivative	EC50	IC50	Activity ratio relative to compound 1
1	**1**	34.2	n/a[a]	1
2	**2**	20.5	547	0.48
3	**3**	9.3	n/a	0.92
4	**4**	14.1	39.8	1.34
5	**5**	4.5	12.6	0.96
6	**7**	17.4	n/a	0.71
7	**8**	20.5	547.6	0.74
8	**9**	5.3	n/a	0.53
9	**10**	10.1	n/a	0.42
10	**12a**	25.1	158.5	0.77
11	**12b**	12.6	316	0.84
12	**12c**	16.4	204.9	0.91
13	**12d**	3.8	n/a	0.57
14	**12e**	25	251	0.8
15	**12f**	34.7	316.2	0.88
16	**12g**	11.9	n/a	1.13
17	**12h**	12.7	n/a	0.71
18	**12i**	9.8	13.04	0.28
19	**12j**	32.5	40.7	0.23
20	**12k**	4.7	n/a	0.33
21	**13d**	101	n/a	2.5
22	**13h**	n/a	392	0.125
23	**14**	9	n/a	1.31
24	**15**	7.5	n/a	1.37

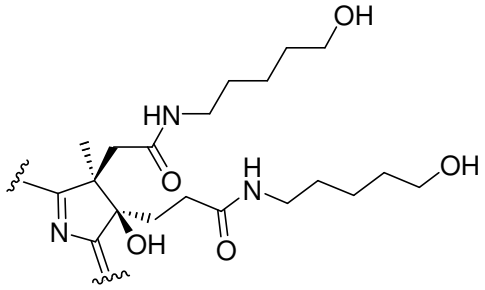
a not applicable

Preparation of compound 12a



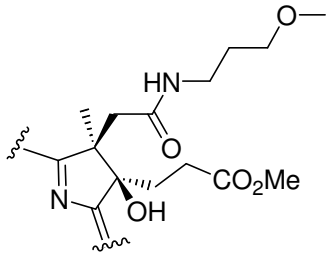
Following the reported procedure[6] for mono amide synthesis, *c*-lactone (15 mg, 13.9 µmol) and 5-aminopetanol (14 mg, 0.14 mmol) were stirred for 18 h. Compound **12a** was purified using DCVC, 5% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **12a** was isolated as a purple solid (14 mg, 87%). R_f 0.37, 5% EtOH in DCM. Anal. calcd. for $C_{58}H_{82}CoN_7O_{15} + H_2O$: C 58.33, H 7.09, N 8.21; found: C 58.42, H 7.26, N 7.76. HRMS ESI (m/z) calcd. for $C_{57}H_{82}CoN_6O_{15}$ $[M\text{-}CN]^+$ 1149.5164; found 1149.5177. UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 281 (9.50 x 10^3), 319 (9.45 x 10^3), 372 (2.68 x 10^4), 426 (2.68 x 10^3), 553 (8.29 x 10^3), 591 (1.01 x 10^4). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.26 (t, *J* = 5.4 Hz, 1H), 6.20 (s(br), 1H), 5.75 (s, 1H), 3.78 (d, *J* = 10.8 Hz, 1H), 3.74 (m, 4H), 3.68 (s, 6H), 3.67 (s, 3H), 3.65 (s, 3H), 3.61 (s, 3H), 3.45 (dt, *J* = 1.5 and 6.0 Hz, 2H), 3.26 (m, 1H), 3.05 (dd, *J* = 4.3 and 2.5 Hz, 1H), 2.91-2.85 (m, 1H), 2.81-2.77 (m, 1H), 2.73-2.66 (m, 2H), 2.64-2.52 (m, 4H), 2.47-2.41 (m, 5H), 2.36-2.31 (m, 3H), 2.24 (s, 3H), 2.21-2.13 (m, 5H), 2.11 (s, 3H), 2.09-2.02 (m, 4H), 1.85-1.66 (m, 6H), 1.63 (s, 3H), 1.47 (s, 3H), 1.36 (s, 6H), 1.26 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.7, 176.3, 175.8, 175.7, 174.0, 173.1, 172.8, 172.7, 172.2, 172.1, 171.9, 163.5, 160.1, 106.1, 102.9, 90.1, 85.3, 83.1, 75.0, 62.2, 58.9, 56.9, 56.2, 52.5, 52.0, 52.1, 52.0, 51.9, 51.8, 47.1, 46.5, 42.6, 42.2, 40.3, 39.7, 33.9, 32.7, 32.6, 32.4, 31.9, 31.6, 31.0, 30.0, 29.8, 25.9, 25.3, 23.4, 22.2, 19.7, 18.2, 17.2, 16.8, 15.7, 15.6.

Preparation of compound 13e



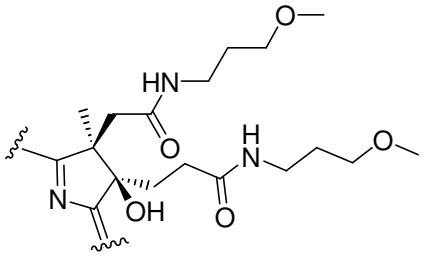
Following the reported procedure[6] used to prepare the mono amide derivatives, *c*-lactone (15 mg, 13.9 µmol) and 5-aminopetanol (0.1 mg, 0.9 mmol) were stirred for 18 h. Compound **13e** was purified using DCVC, 5-10% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **13e** was isolated as a purple solid (14 mg, 82%). R_f 0.36, 10% EtOH in DCM. Anal. calcd. for $C_{62}H_{91}CoN_8O_{15}$ + H_2O: C 58.85, H 7.41, N 8.86; found: C 58.52, H 7.69, N 8.66. HRMS ESI (m/z) calcd. for $C_{61}H_{91}CoN_7O_{15}$ $[M\text{-}CN]^+$ 1220.5882; found 1220.5899.UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 281 (8.60 x 10^3), 319 (8.67 x 10^3), 372 (2.47 x 10^4), 425 (2.80 x 10^3), 553 (7.65 x 10^3), 591 (9.01 x 10^3). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.08 (s(br), 1H), 6.93 (t, *J* = 4.8 Hz, 1H), 6.82 (s(br), 1H), 5.78 (s,1H), 3.81 (d, *J* = 10.3 Hz, 1H), 3.74 (s, 4H), 3.69-3.67 (m, 12H), 3.59 (s, 3H), 3.52 (t, *J* = 6.2 Hz, 2H), 3.46 (t, *J* = 5.7 Hz, 2H), 3.30-3.26 (m, 1H), 3.18-3.13 (m, 1H), 3.07-3.05 (m, 2H), 2.85-2.76 (m, 2H), 2.73-2.66 (m, 2H), 2.63-2.50 (m, 4H), 2.48-2.44 (m, 4H), 2.41-2.31 (m, 3H), 2.26 (s, 4H), 2.23-2.10 (m, 6H), 2.08 (s, 4H), 2.05-1.99 (m, 3H), 1.85-1.72 (m, 6H), 1.64 (s, 3H), 1.60-1.55 (m, 3H), 1.50-1.47 (m, 3H), 1.43 (s(br), 6H), 1.36 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.5, 176.4, 175.7, 174.4, 174.1, 173.8, 173.1, 173.0, 172.2, 172.0, 171.7, 163.2, 160.1, 106.4, 102.7, 96.4, 90.3, 85.8, 83.0, 74.9, 62.4, 62.1, 58.8, 56.9, 56.4, 52.6, 52.2, 52.1, 52.0, 51.9, 46.9, 46.4, 42.7, 42.1, 40.0, 39.7, 39.6, 34.0, 33.9, 32.6, 32.5, 32.4, 32.3, 30.8, 30.0, 29.0, 28.7, 25.6, 25.0, 23.3, 22.1, 19.5, 18.3, 17.1, 15.6, 15.5.

Preparation of compound 12b



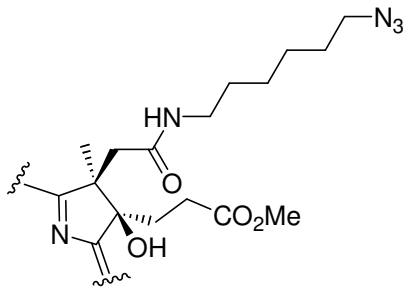
Following the reported procedure[6] used to prepare the mono amides, *c*-lactone (15 mg, 13.9 µmol) and 3-methoxy-propylamine (15 µL, 0.14 mmol) were stirred for 18 h. Compound **12b** was purified using DCVC, 2.5% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **12b** was isolated as a purple solid (12 mg, 75%). R_f 0.36, 5% EtOH in DCM. Anal. calcd. for $C_{57}H_{80}CoN_7O_{15} + H_2O$: C 58.01, H 7.00, N 8.31; found: C 58.07, H 7.15, N 8.08. HRMS ESI (m/z) calcd. for $C_{56}H_{80}CoN_6O_{15}$ $[M\text{-}CN]^+$ 1135.5028; found 1135.5008. UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 281 (9.73 x 10^3), 319 (9.57 x 10^3), 372 (2.77 x 10^4), 426 (2.93 x 10^3), 554 (8.50 x 10^3), 593 (1.06 x 10^4). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.27 (t, *J* = 5.8 Hz, 1H), 6.21, (s(br), 1H), 5.75 (s, 1H), 3.79 (d, *J* = 10.7 Hz, 1H), 3.74 (s, 3H), 3.68 (s(br), 6H), 3.67 (s, 3H), 3.65 (s, 3H), 3.61 (s, 3H), 2.31 (t, *J* = 6.4 Hz, 2H), 3.22 (s, 3H), 3.06-2.98 (m, 2H), 2.81-2.77 (m, 1H), 2.67-2.65 (m, 2H), 2.60-2.52 (m, 3H), 2.50-2.41 (m, 5H), 2.37-2.31 (m, 2H), 2.24 (s, 3H), 2.21-2.14 (m, 4H), 2.11 (s, 3H), 2.09-2.00 (m, 2H), 1.87-1.70 (m, 3H), 1.69-1.66 (m, 3H), 1.64 (s, 3H), 1.60 (t, *J* = 7.2 Hz, 2H), 2.90 (s, 3H), 1.36 (2 x s, 6H), 1.26 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.7, 176.2, 175.9, 175.7, 174.0, 173.1, 172.8, 172.7, 172.2, 172.0, 171.7, 163.5, 160.1, 106.0, 102.9, 90.1, 85.4, 83.1, 74.9, 70.8, 58.8, 58.6, 56.9, 56.0, 52.6, 52.2, 52.1, 52.0, 51.9, 51.8, 47.1, 46.5, 42.6, 42.1, 39.7, 37.8, 33.9, 32.7, 32.6, 31.9, 31.6, 31.0, 30.0, 29.8, 29.6, 25.9, 25.3, 22.2, 19.7, 18.2, 17.2, 15.7, 15.6.

Preparation of compound 13b



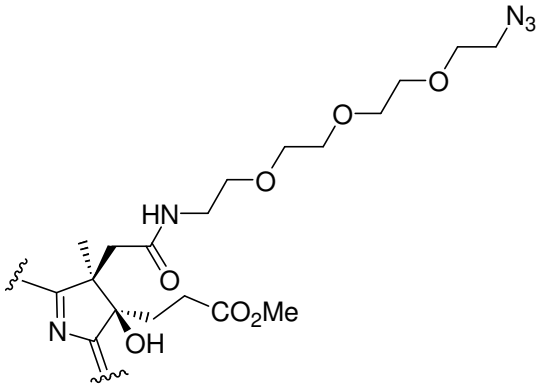
Following the reported procedure[6] used to prepare the mono amides, *c*-lactone (15 mg, 13.9 µmol) and 3-methoxy-propylamine (0.1 mL, 1.3 mmol) were stirred for 18 h. Compound **13b** was purified using DCVC, 2.5% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **13b** was isolated as a purple solid (9 mg, 52%). R_f 0.13, 5% EtOH in DCM. Anal. calcd. for $C_{60}H_{87}CoN_8O_{15} + H_2O$: C 58.24, H 7.25, N 9.06; found: C 58.24, H 7.44, N 8.74. HRMS ESI (m/z) calcd. for $C_{59}H_{87}CoN_7O_{15}$ $[M\text{-}CN]^+$ 1192.5572; found 1192.5586. UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 281 (9.61 x 10^3), 319 (9.46 x 10^3), 372 (2.65 x 10^4), 425 (3.15 x 10^3), 553 (8.40 x 10^3), 591 (9.82 x 10^3). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.14 (t, *J* = 5.7 Hz, 1H), 6.99 (s(br), 1H), 6.83 (t, *J* = 5.6 Hz, 1H), 5.77 (s, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 3.74 (s, 3H), 3.68-3.67 (m, 9H), 3.60 (s, 3H), 3.34 (t, *J* = 6.6 Hz, 2H), 3.26 (s, 4H), 3.25-3.24 (m, 2H), 3.21 (s, 3H), 3.17-3.11 (m, 2H), 3.06 (t, *J* = 4.4 Hz, 1H), 2.96-2.90 (m, 1H), 2.81-2.76 (m, 1H), 2.68-2.66 (m, 2H), 2.63-2.52 (m, 3H), 2.50-2.30 (m, 8H), 2.25 (s, 3H), 2.21-2.11 (m, 4H), 2.09 (s, 3H), 2.06-1.97 (m, 2H), 1.85-1.74 (m, 5H), 1.67-1.65 (m, 5H), 1.60-1.55 (m, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.5, 176.3, 175.7, 174.6, 174.1, 173.1, 172.9, 172.2, 172.0, 171.6, 163.3, 160.1, 106.4, 102.7, 90.3, 85.7, 83.1, 74.9, 70.8, 70.7, 58.9, 58.7, 58.6, 57.0, 56.4, 54.1, 52.6, 52.2, 51.1, 51.99, 51.92, 46.9, 46.5, 42.7, 42.1, 39.7, 37.6, 37.5, 33.9, 33.6, 32.7, 32.4, 31.6, 30.9, 30.0, 29.7, 25.7, 25.1, 22.1, 19.5, 18.3, 17.0, 16.6, 15.6, 15.5.

Preparation of compound 12f



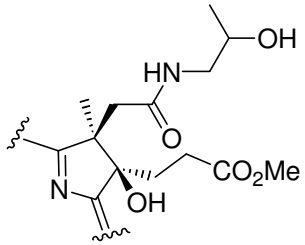
Following the reported procedure[6] used to prepare the mono amides, *c*-lactone (16 mg, 9.8 µmol) and 6-azido-hexylamine (20 mg, 0.14 mmol) were stirred for 24 h. Compound **12f** was purified using DCVC, 2.5% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **12f** was isolated as a purple solid (22 mg, 72%). R_f 0.32, 5% EtOH in DCM. Anal. calcd. for $C_{59}H_{83}CoN_{10}O_{14}$ + H_2O: C 57.46, H 6.95, N 11.36; found: C 57.48, H 7.02, N 11.36. HRMS ESI (m/z) calcd. for $C_{54}H_{76}CoN_6O_{15}$ $[M\text{-}CN]^+$ 1188.5389; found 1188.5386. UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 281 (8.85 x 10^3), 319 (9.11 x 10^3), 372 (2.26 x 10^4), 427.5 (3.12 x 10^3), 556 (7.15 x 10^3), 592 (8.62 x 10^3). ^{1}H NMR (500 MHz, toluene-d_8) δ (ppm); 8.11 (s(br), 0.5H), 8.02 (s(br), 0.5H), 6.09 (s, 0.6H), 6.01 (s, 0.1H), 5.96 (s, 0.2H), 4.04 (d, *J* = 9.4 Hz, 0.3H), 3.96 (s, *J* = 10.0 Hz, 0.7H), 3.91 (s, *J* = 8.5 Hz, 0.7H), 3.86 (d, *J* = 8.8 Hz, 0.3H), 3.52-3.51 (m, 3H), 3.46 (s, 3H), 3.45-3.44 (m, 1H), 3.40-3.36 (m, 9H), 3.33, (s, 5H), 3.32-3.31 (m, 2H), 3.14-3.05 (m, 1H), 2.86-2.81 (m, 3H), 2.77-2.75 (m, 2H), 2.73-2.69 (m, 4H), 2.68-2.59 (m, 3H), 2.56-2.50 (m, 5H), 2.47-2.32 (m 9H), 2.30 (s, 3H), 2.25-2.20 (m, 3H), 2.27 (s, 2H), 2.16 (s, 2H), 2.11 (s, 2H), 1.99-1.91 (m, 3H), 1.75-1.69 (m, 6H). ^{13}C NMR (125 MHz, toluene-d_8) δ (ppm); 176.6, 175.3, 173.7, 173.1, 172.7, 172.5, 172.3, 172.2, 172.0, 171.9, 163.4, 102.6, 85.6, 83.0, 75.1, 58.8, 58.7, 56.6, 54.1, 52.4, 51.6, 51.3, 51.2, 51.1, 51.0, 50.9, 46.9, 46.8, 46.7, 46.5, 42.4, 40.1, 39.9, 33.7, 33.6, 32.9, 31.7, 31.1, 30.5, 30.4, 30.3, 29.8, 26.8, 26.7, 26.6, 26.5, 25.9, 25.8, 25.0, 22.4, 20.9, 19.4, 19.3, 18.0, 17.3, 17.2, 16.9, 15.9, 15.5, 15.2.

Preparation of compound 12h



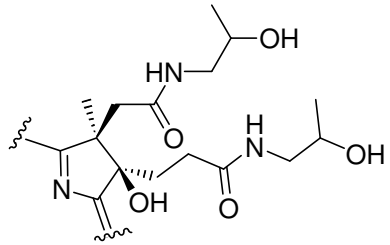
Following the reported procedure[6] used to prepare the mono amides, *c*-lactone (61 mg, 56.8 µmol) and 2-{2-[2-(2-azido-ethoxy)-ethoxy]-ethoxy}-ethylamine (120 mg, 0.55 mmol) were stirred for 16 h. Compound **12h** was purified using DCVC, 2.5% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **12h** was isolated as a purple solid (33 mg, 45%). R_f 0.48, 5% EtOH in DCM. Anal. calcd. for $C_{61}H_{87}CoN_{10}O_{17}$: C 57.74, H 6.79, N 10.85; found: C 56.70, H 7.02, N 10.58. HRMS ESI (m/z) calcd. for $C_{60}H_{87}CoN_9O_{17}$ $[M-CN]^+$ 1264.5512; found 1264.5546. UV/Vis CH_2Cl_2, λ_{max}, ε ($L \cdot mol^{-1} \cdot cm^{-1}$): 281 (9.42 x 10^3), 319 (9.09 x 10^3), 372 (2.57 x 10^4), 426 (2.92 x 10^3), 554 (7.84 x 10^3), 593 (9.96 x 10^3). ^{1}H NMR (500 MHz, toluene-d_8) δ (ppm); 8.11 (s(br), 1H), 6.08 (s, 1H), 3.92 (d, *J* = 10.8Hz, 1H), 3.82 (d, *J* = 8.6 Hz, 1H), 3.65-3.62 (m, 1H), 3.58 (s, 3H), 3.48 (s, 3H), 3.46 (t, *J* = 6.2 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 4H), 3.39-3.38 (m, 5H), 3.35 (s, 4H), 3.34 (s, 4H), 3.28 (t, *J* = 5.0 Hz, 3H), 2.90 (t, *J* = 5.2 Hz, 2H), 2.85-2.77 (m, 4H), 2.75-2.61 (m, 3H), 2.57-2.48 (m, 5H), 2.45-2.32 (m, 7H), 2.29 (s, 3H), 2.25-2.20 (s, 2H), 2.18 (s, 3H), 2.01-1.95 (m, 2H), 1.79-1.71 (m, 6H), 1.43 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (125 MHz, toluene-d_8) δ (ppm); 176.5, 175.8, 175.3, 174.7, 173.7, 172.7, 172.5, 172.3, 172.2, 171.1, 163.4, 161.0, 102.5, 96.5, 90.8, 85.6, 83.0, 75.1, 71.0, 70.9, 70.8, 70.5, 70.2, 69.6, 58.7, 56.8, 56.3, 54.1, 51.8, 51.7, 51.3, 51.2, 51.1, 50.9, 50.8, 46.7, 46.3, 42.7, 42.2, 40.0, 39.9, 33.7, 33.2, 32.9, 31.8, 31.1, 30.3, 29.8, 29.7, 25.8, 25.0, 22.3, 19.3, 18.0, 17.1, 16.9, 15.8, 15.5.

Preparation of compound 12j



Following the reported procedure[6] used to prepare the mono amides, *c*-lactone (20 mg, 18.6 µmol) and 1-Amino-propan-2-ol (14 µL, 0.18 mmol) were stirred for 18 h. Compound **12j** was purified using DCVC, 2.5-5.0% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **12j** was isolated as a purple solid (13 mg, 64%). R_f 0.36, 5% EtOH in DCM. Anal. calcd. for $C_{56}H_{78}CoN_7O_{15}$ + H_2O: C 57.67, H 6.91, N 8.41; found: C 57.67, H 6.84, N 8.25. HRMS ESI (m/z) calcd. for $C_{56}H_{78}CoN_7O_{15}$ $[M\text{-}CN]^+$ 1121.486; found 1121.486. UV/Vis CH_2Cl_2, λ_{max}, ε ($L{\cdot}mol^{-1}{\cdot}cm^{-1}$): 282 (9.07 x 10^3), 318 (9.29 x 10^3), 372 (2.85 x 10^4), 427 (2.93 x 10^3), 553 (8.16 x 10^3), 592 (1.05 x 10^4). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.04 (dd. *J* = 4.0 and 6.0 Hz, 0.6H), 6.92 (dd, *J* = 4.0 and 6.0 Hz, 0.4H), 5.86 (s(br), 1H), 5.72 (d, *J* = 4.5 Hz, 1H), 3.80-3.78 (m, 2H), 3.75 and 3.74 (2 x s, 1H), 3.70 and 3.69 (2 x s, 3H), 3.67 (m, 8H), 3.64 (s, 3H), 3.61 (s, 3H), 3.38 (ddd, *J* = 2.5, 7.0 and 14 Hz, 0.6H), 3.20 (ddd, *J* = 2.0, 6.0 and 14 Hz, 0.4H), 3.07 (m, 1H), 2.76-2.88 (m, 2H), 2.74-2.66 (m, 1H), 2.65 and 2.63 (2 x s, 3H), 2.62-2.38 (m, 5H), 2.31 and 2.29 (2 x d, *J* = 3.5 Hz, 1H), 2.25 and 2.24 (2 x s, 3H), 2.20-1.88 (m, 4H), 2.12 (s, 3H), 2.11 and 2.10 (2 x s, 3H), 1.88-1.80 (m, 1H), 1.73 (s, 3H), 1.67 and 1.66 (2 x s, 3H), 1.47 (s, 3H), 1.36 (s, 6H), 1.26 and 1.25 (2 x s, 4H), 1.20 (s, 3H), 0.99 and 0.97 (2 x d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.8, 176.7, 175.9, 174.0, 173.1, 173.0, 172.9, 172.7, 172.2, 172.1, 172.0, 171.9, 171.8, 163.5, 162.6, 159.5, 159.4, 112.6, 106.9, 106.8, 103.1, 103.0, 90.0, 85.6, 85.5, 83.1, 74.9, 67.4, 66.6, 66.4, 58.8, 56.8, 56.6, 56.4, 52.6, 52.4, 52.3, 52.2, 52.1, 51.9, 51.8, 48.6, 48.3, 47.2, 47.2, 46.5, 46.4, 42.9, 42.7, 41.9, 41.8, 39.7, 36.5, 34.0, 31.6, 32.2, 32.2, 32.0, 31.8, 31.7, 31.6, 31.4, 31.0, 30.9, 30.0, 25.9, 25.3, 22.3, 20.9, 20.6, 19.7, 18.2, 18.1, 17.3, 17.2, 17.0, 15.7, 15.65, 15.60.

Preparation of compound 13g



Following the reported procedure[6] used to prepare the mono amides, *c*-lactone (22 mg, 20.5 µmol) and 1-amino-propan-2-ol (0.1 mL, 1.2 mmol) were stirred for 18 h. Compound **13g** was purified using DCVC, 5.0% EtOH in DCM. After recrystallization from hexanes/AcOEt compound **13g** was isolated as a purple solid (12 mg, 57%). R_f 0.27, 5% EtOH in DCM. Anal. calcd. for $C_{58}H_{83}CoN_8O_{15}$ + H_2O: C 57.61, H 7.08, N 9.27; found: C 57.58, H 7.13, N 9.05. UV/Vis CH_2Cl_2, λ_{max}, ε ($L \cdot mol^{-1} \cdot cm^{-1}$): 282 (9.07 x 10^3), 318 (9.29 x 10^3), 372 (2.85 x 10^4), 427 (2.93 x 10^3), 553 (8.16 x 10^3), 592 (1.05 x 10^4). ^{1}H NMR (500 MHz, CD_2Cl_2) δ (ppm); 7.12 (s(br), 0.5H), 7.01-6.97 (m, 1.5H), 6.68 (d, *J* = 14.5Hz, 0.5H), 6.47 (d, *J* = 18.9 Hz, 0.5H), 5.81 (s, 0.5H), 5.80 (s, 0.5H), 3.83-3.76 (m, 3H), 3.74 (s,s, 3H), 3.68 (s, 5H), 3.67 (s, 6H), 3.58 (s, 1.5H), 3.57 (s, 1.5H), 3.51-3.46 (m, 1H), 3.34 (dd, *J* = 2.6 and 6.2 Hz, 0.5H), 3.28 (dd, *J* = 2.4 and 7.0 Hz, 0.5H), 3.23-3.15 (m, 1H), 3.09 (s (br), 1H), 2.94-2.86 (m, 1H), 2.83-2.75 (m, 2H), 2.72-2.58 (m, 4H), 2.54-2.39 (m, 7H), 2.34-2.31 (m, 2H), 2.26 (s, 3H), 2.21-2.14 (m, 4H), 2.12 (s, 3H), 2.11 (s(br), 3H), 2.08-1.98 (m, 1H), 1.90-1.85 (m, 3H), 1.79-1.72 (m, 1H), 1.63 (2 x s, 3H), 1.54-1.47 (m, 2H), 1.42 (s (br), 4H), 1.36-1.35 (m, 6H), 1.27 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm); 176.7, 176.1, 176.09, 176.04, 176.03, 174.8, 174.76, 174.74, 174.71, 174.1, 174.0, 173.9, 173.1, 173.08, 173.01, 172.96, 172.92, 172.44, 172.42, 172.3, 172.29, 172.21, 172.1, 172.0, 163.2, 163.17, 163.15, 159.9, 106.5, 106.4, 106.39, 106.35, 103.0, 90.6, 86.1, 86.02, 86.00, 83.3, 83.2, 75.1, 75.0, 67.0, 66.7, 66.5, 66.4, 58.9, 56.9, 56.8, 56.6, 56.3, 54.1, 52.63, 52.60, 52.2, 52.13, 52.11, 52.0, 51.9, 48.6, 48.4, 48.1, 48.0, 47.03, 47.01, 46.9, 46.5, 46.5, 46.37, 46.35, 42.9, 42.8, 41.9, 41.8, 39.7, 35.0, 33.9, 32.8, 32.77, 32.71, 31.9, 31.8, 31.7, 31.6, 30.7, 30.6, 30.0, 27.3, 25.5, 25.2, 25.1, 22.3, 20.9, 20.6, 20.54, 20.51, 19.5, 18.3, 18.2, 17.2, 15.7, 15.6, 15.5.

Purification of recombinant human sGC enzyme. This enzyme was purified from a culture of Sf9 cells infected with baculoviruses expressing α1 and β1 subunits of sGC as described previously.[7] Purified enzyme was aliquoted and stored at -80 ^{o}C in 50 mM TEA pH 7.4 containing 1 mM DTT, 1 mM EDTA and 1 mM EGTA. The quality of sGC preparations was assessed by measuring enzymatic activity in the presence of 10 μM DEA-NO donor using the α[^{32}P]GTP →cGMP conversion assay (see below). Only preparations with a specific activity higher than 5 μmole/min/mg were used for the studies reported herein.

Assay of sGC activity in vitro. Enzymatic activity was assayed by the formation of [^{32}P] cGMP from α[^{32}P]GTP at 37 °C as described previously.[8] In short, the reaction was initiated by the addition of 1 mM GTP/ α[^{32}P]GTP to 0.1μg sGC in 25 mM TEA, pH 7.5, 1 mg/ml BSA, 1 mM 3-isobutyl-1-methylxanthine (IBMX), 1 mM DTT, 1 mM cGMP, 3 mM $MgCl_2$, 0.05 mg/ml creatine phosphokinase and 5 mM creatine phosphate. To evaluate the effect of CN2-Cbi or BAY41-2272 on sGC activity, the enzyme was preincubated for 10 min at room temperature with the indicated concentration of the compound before initiating the reaction. The reaction was quenched by zinc acetate. The GTP was precipitated via the addition of Zn carbonate and the cGMP levels determined as described previously.[7]

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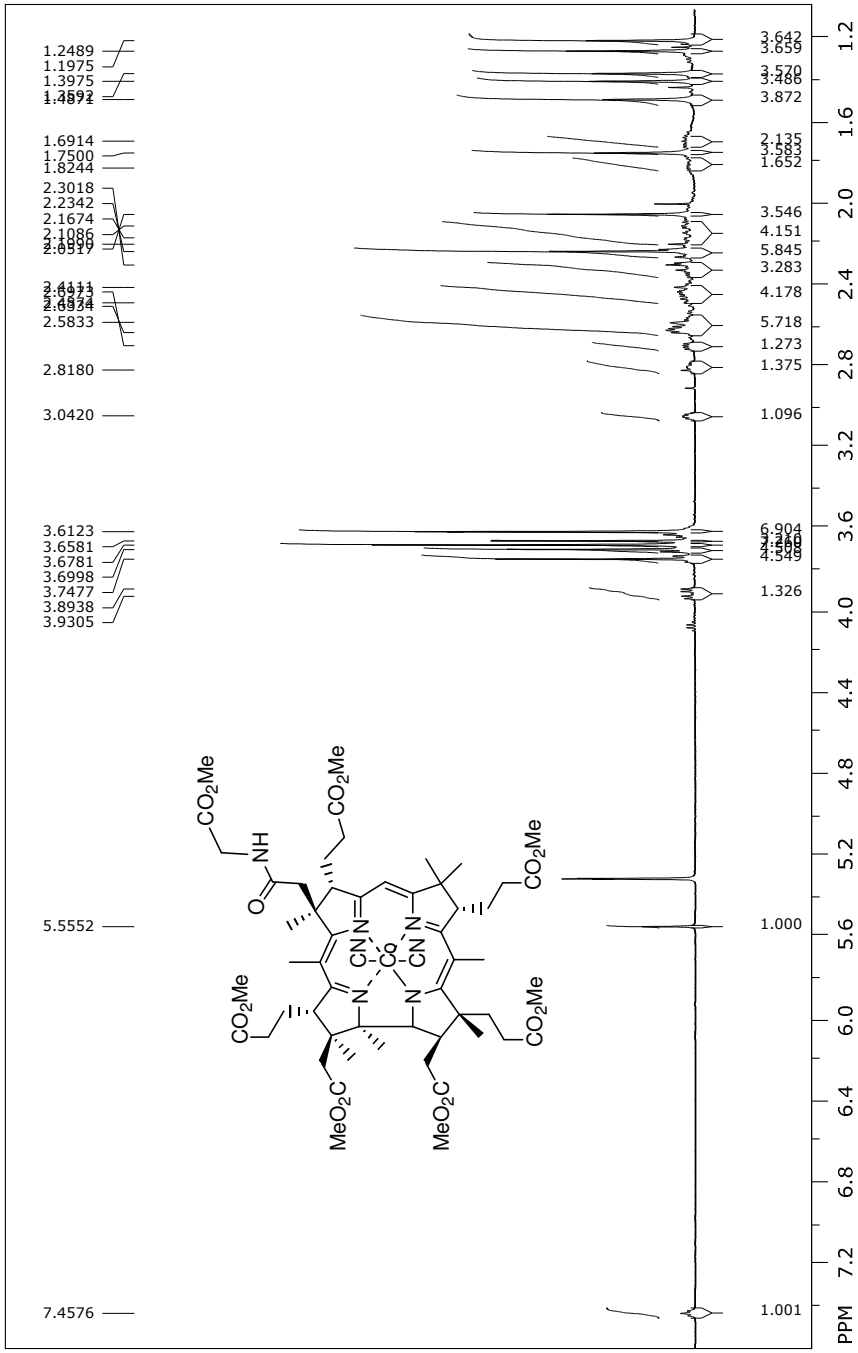
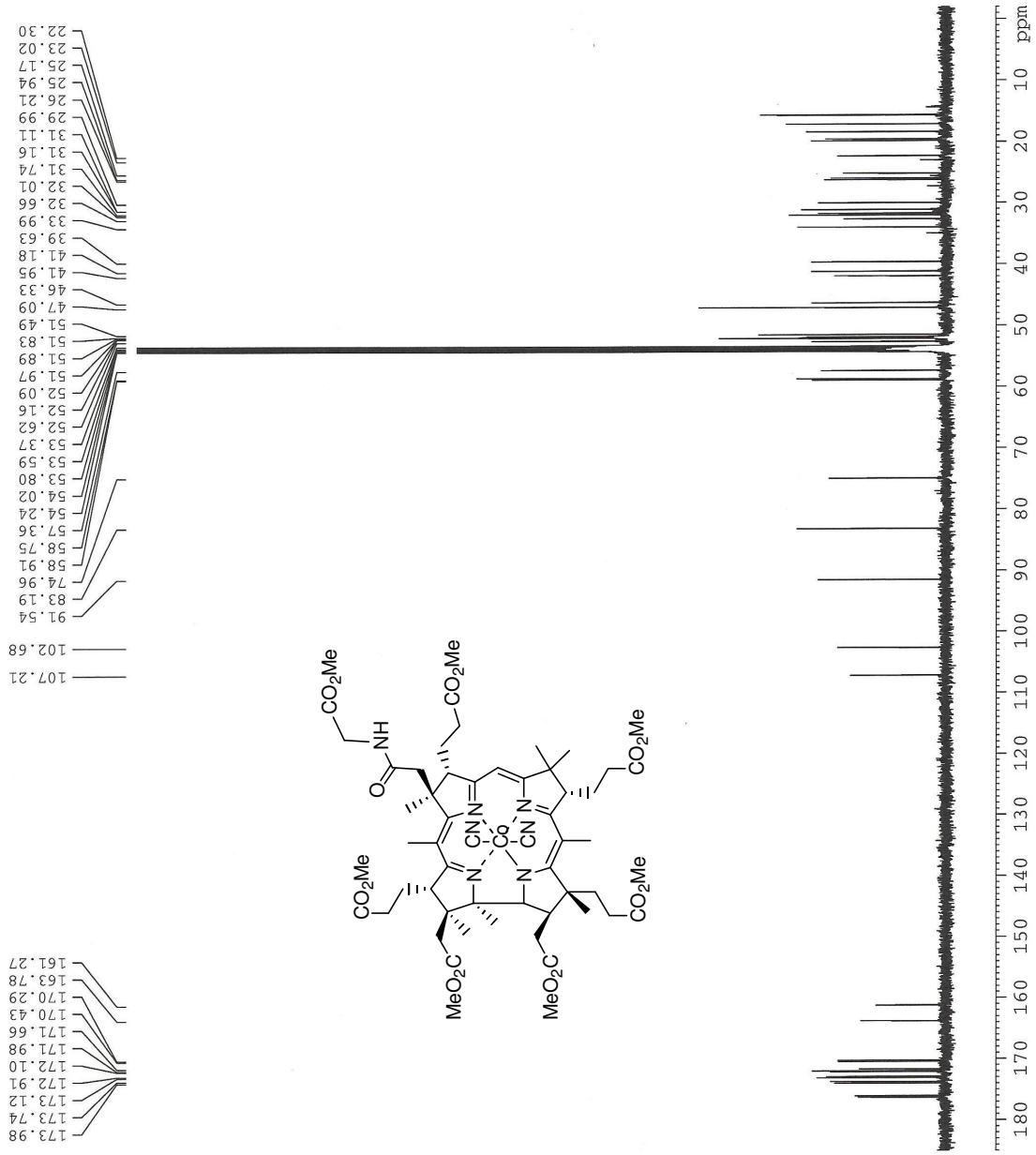
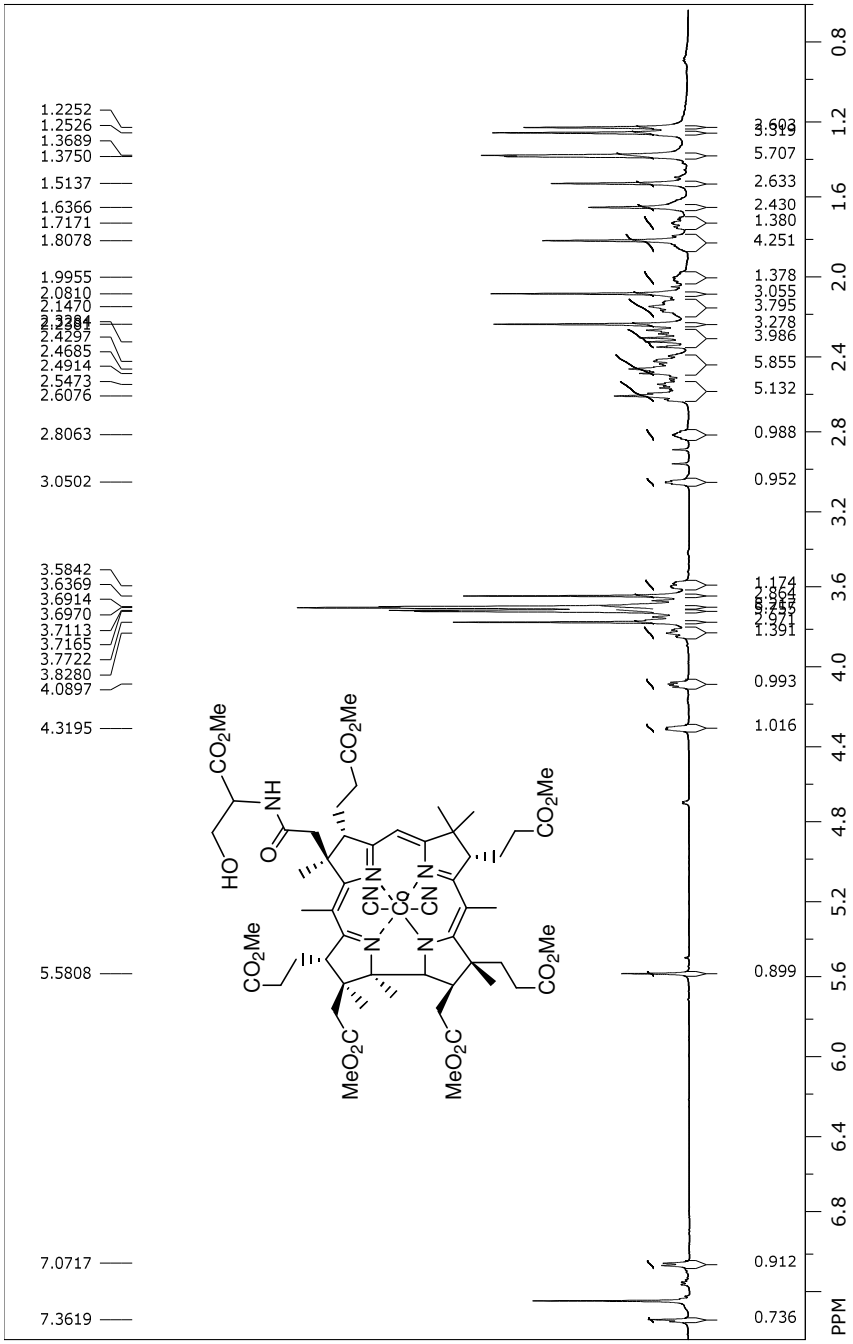
$(CN)_2$Cob(III)C1(Gly-OMe) 7



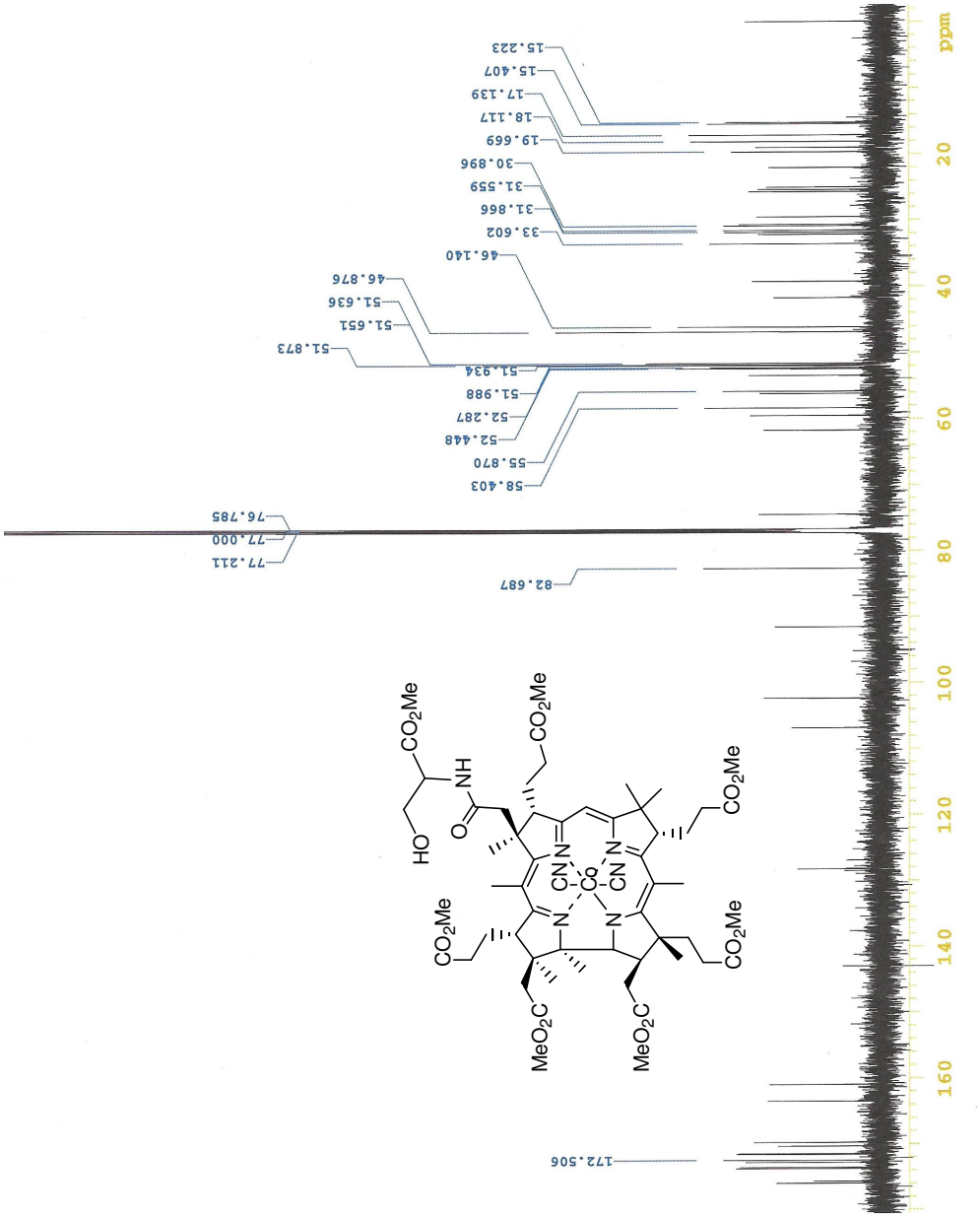
$(CN)_2$Cob(III)C1(Gly-OMe) 7



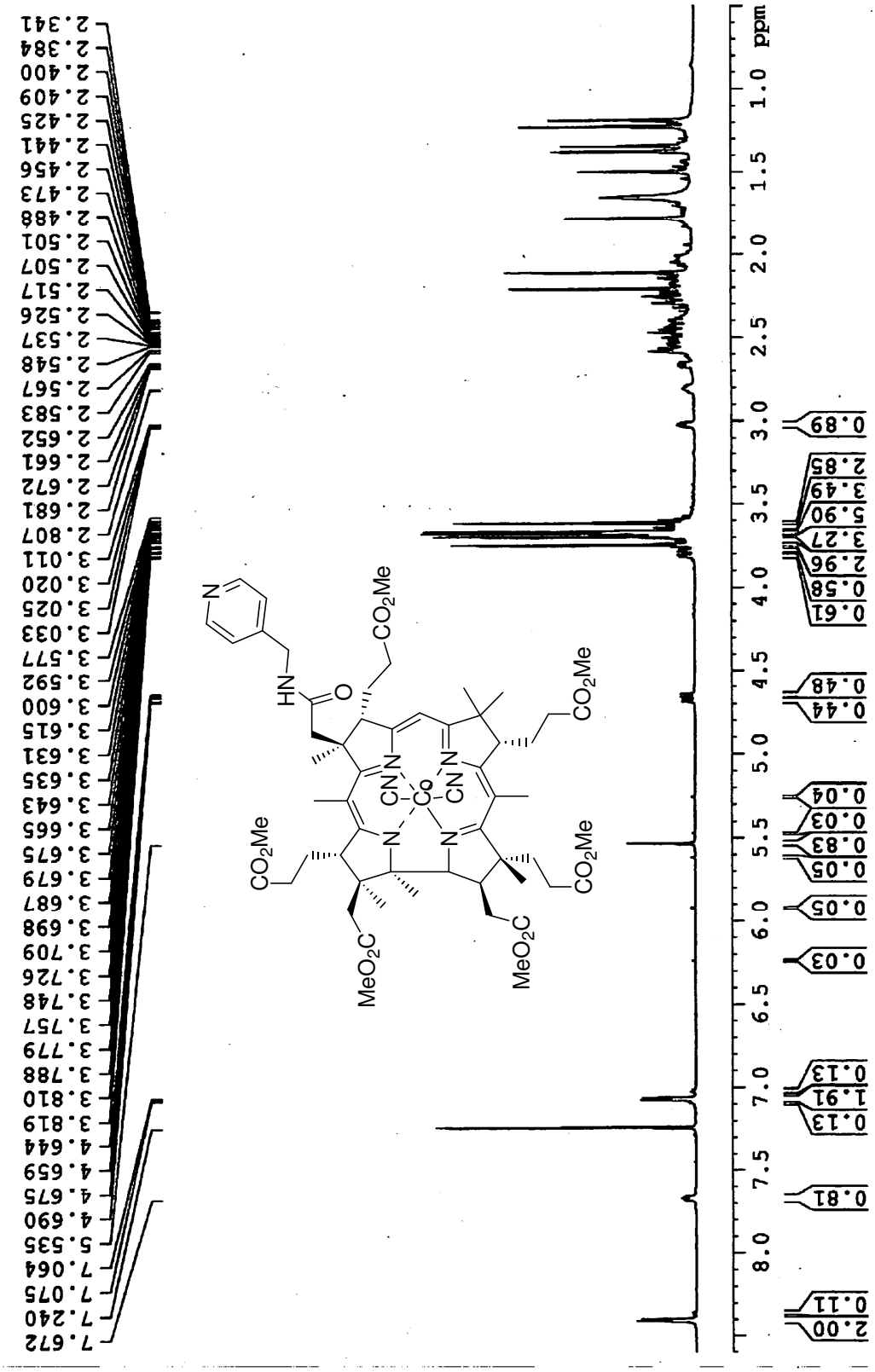
$(CN)_2$Cob(III)C1(Ser-OMe) 8



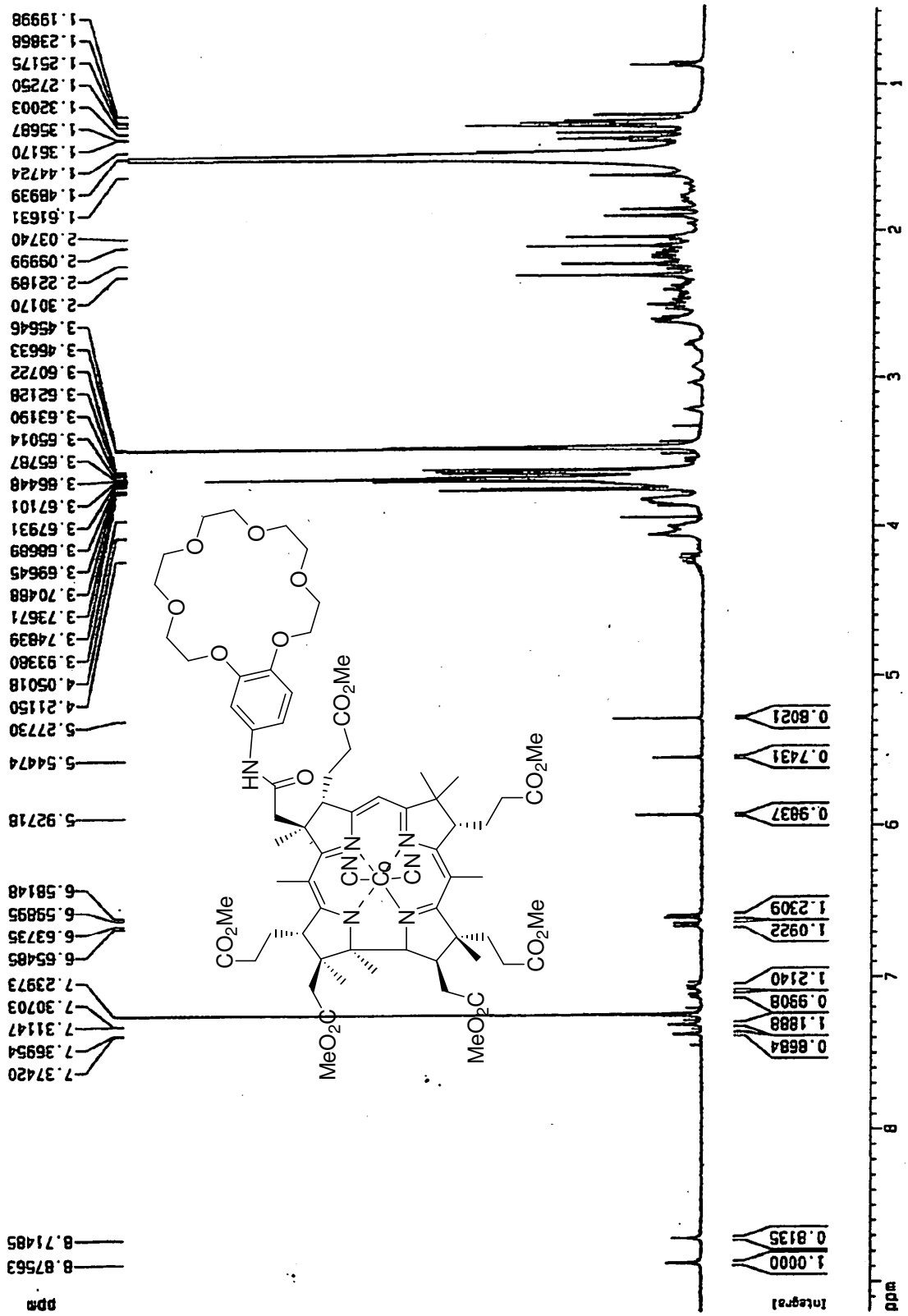
$(CN)_2$Cob(III)C1(Ser-OMe) 8



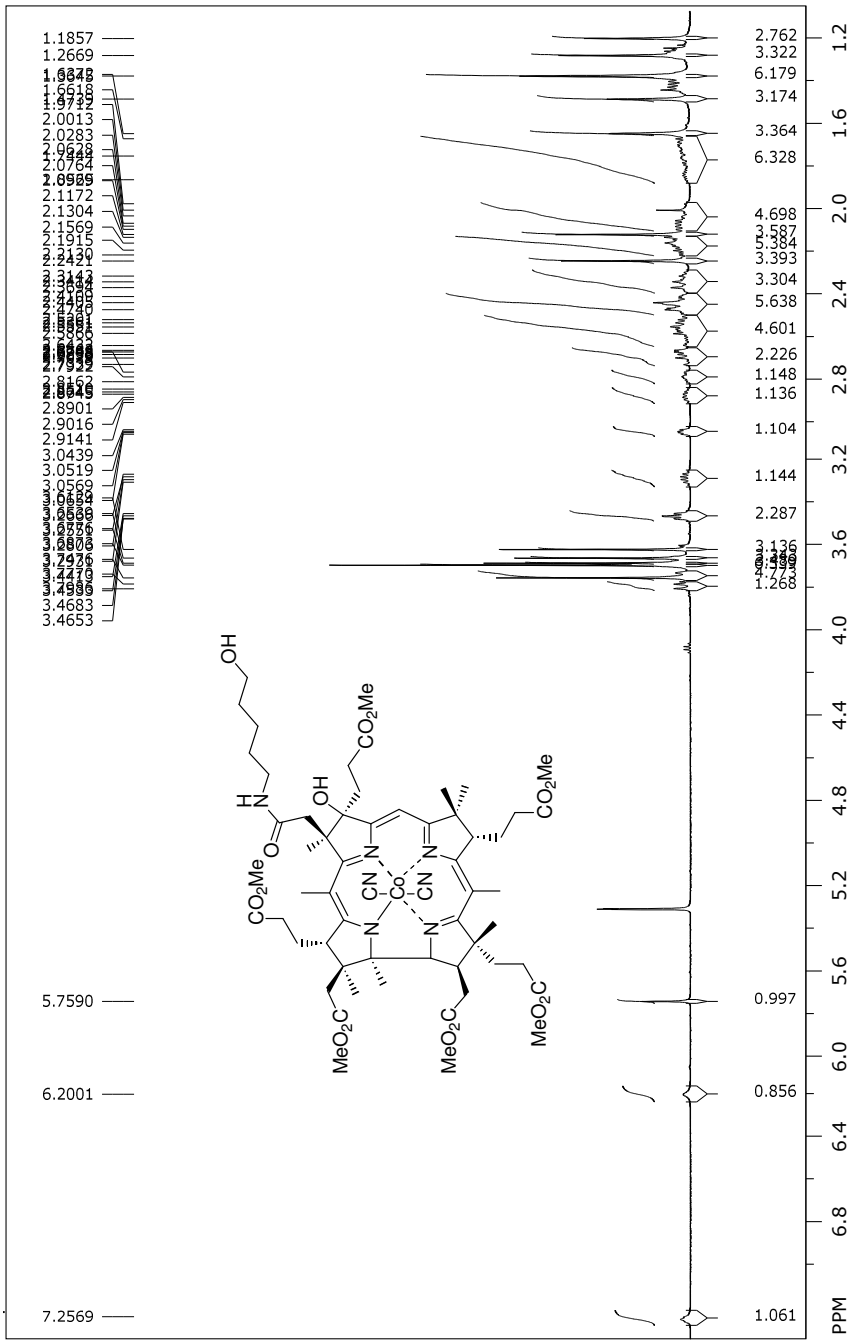
$(CN)_2$Cob(III)C1(Pyridine) 9



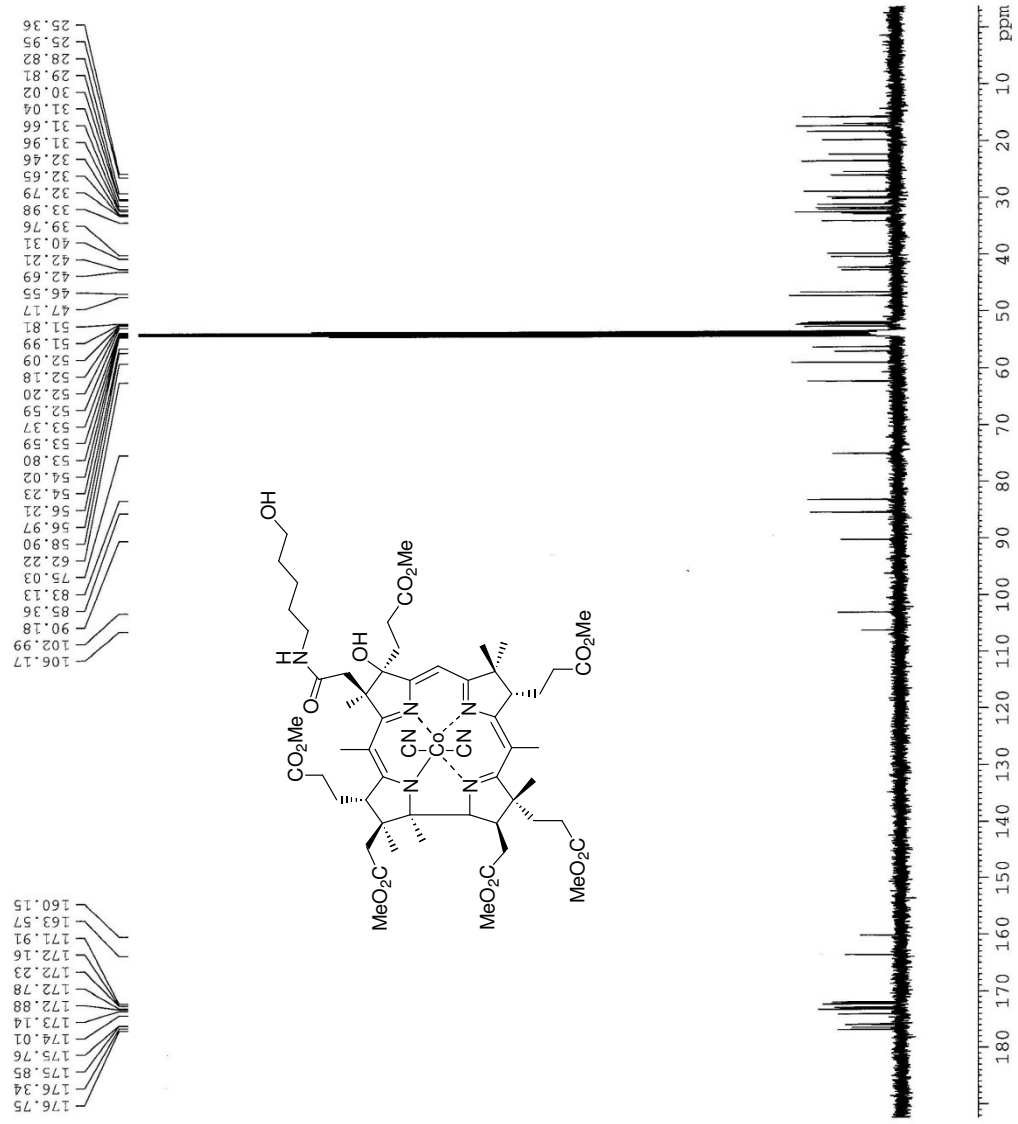
$(CN)_2$Cob(III)C1(Benzo-18-crown-6) 10



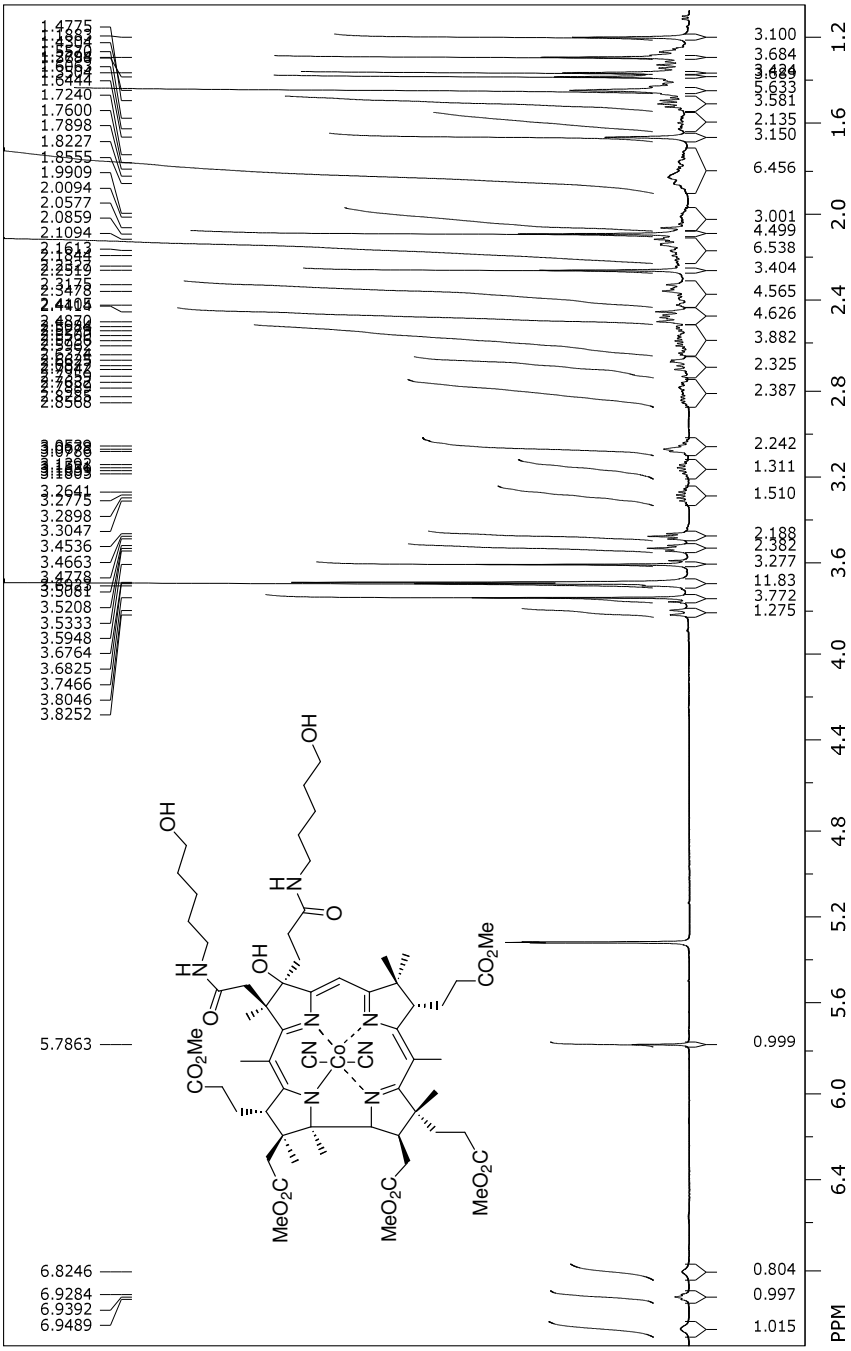
$(CN)_2$Cob(III)C1(5-pentanolamide) 12a



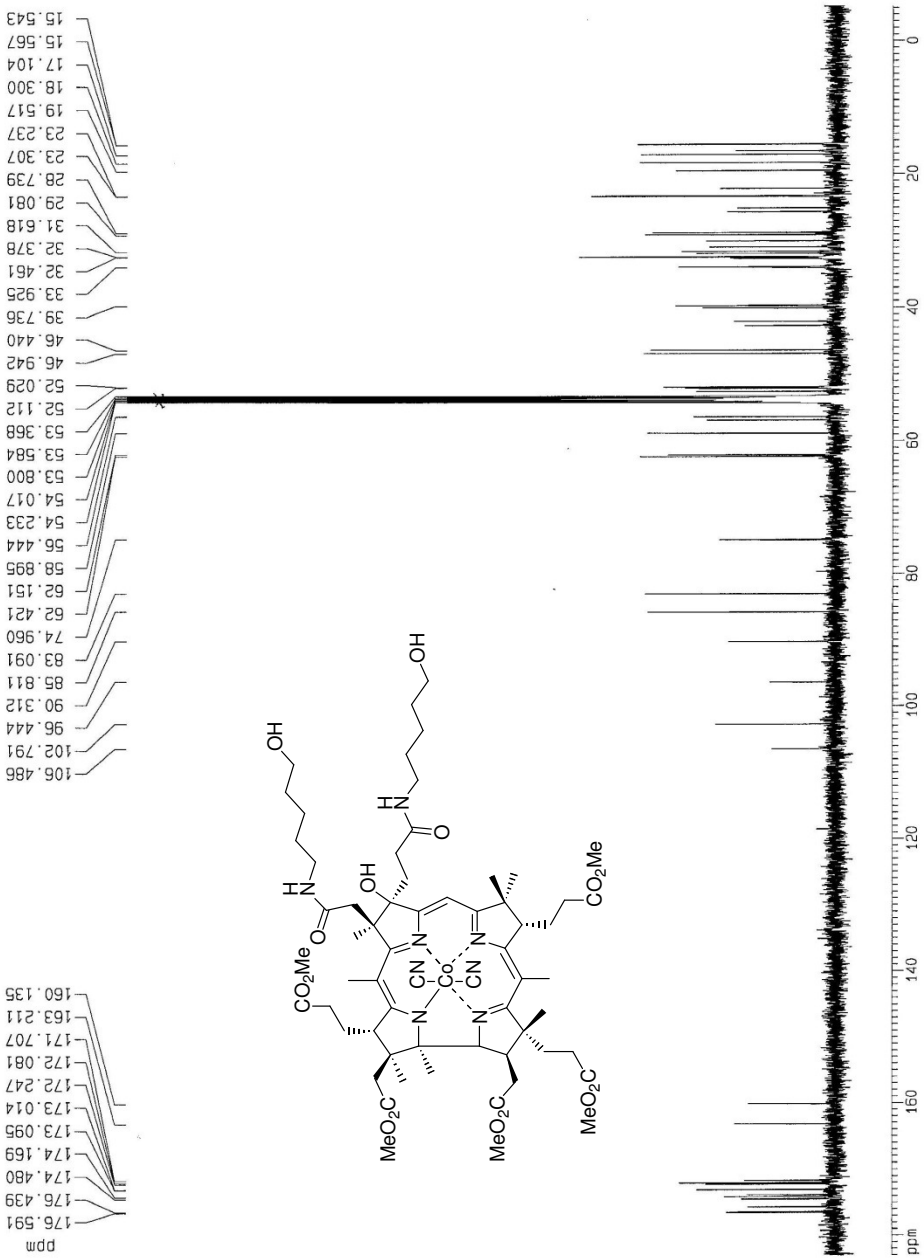
$(CN)_2$Cob(III)C1(5-pentanolamide) 12a



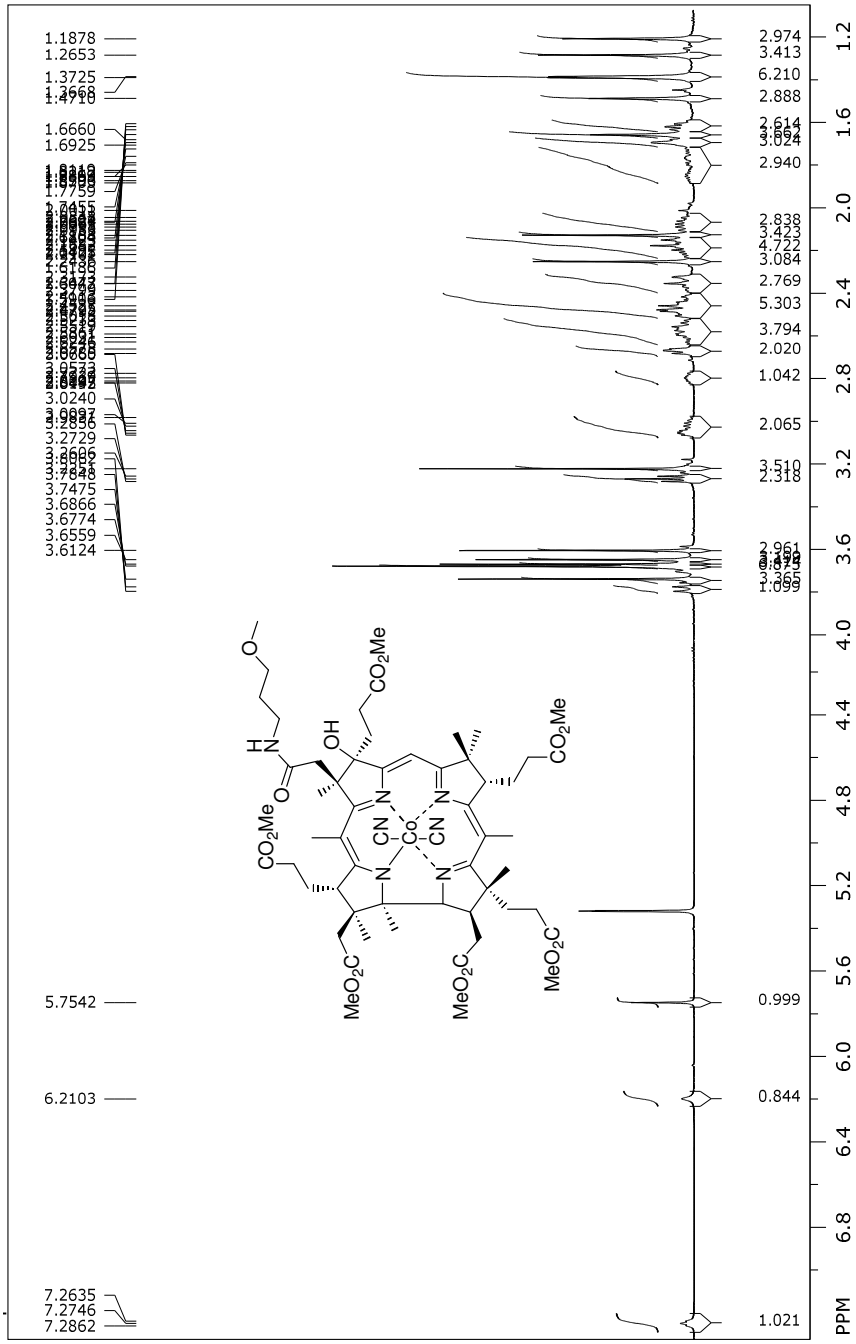
$(CN)_2$Cob(III)C1bis(5-pentanolamide) 13e



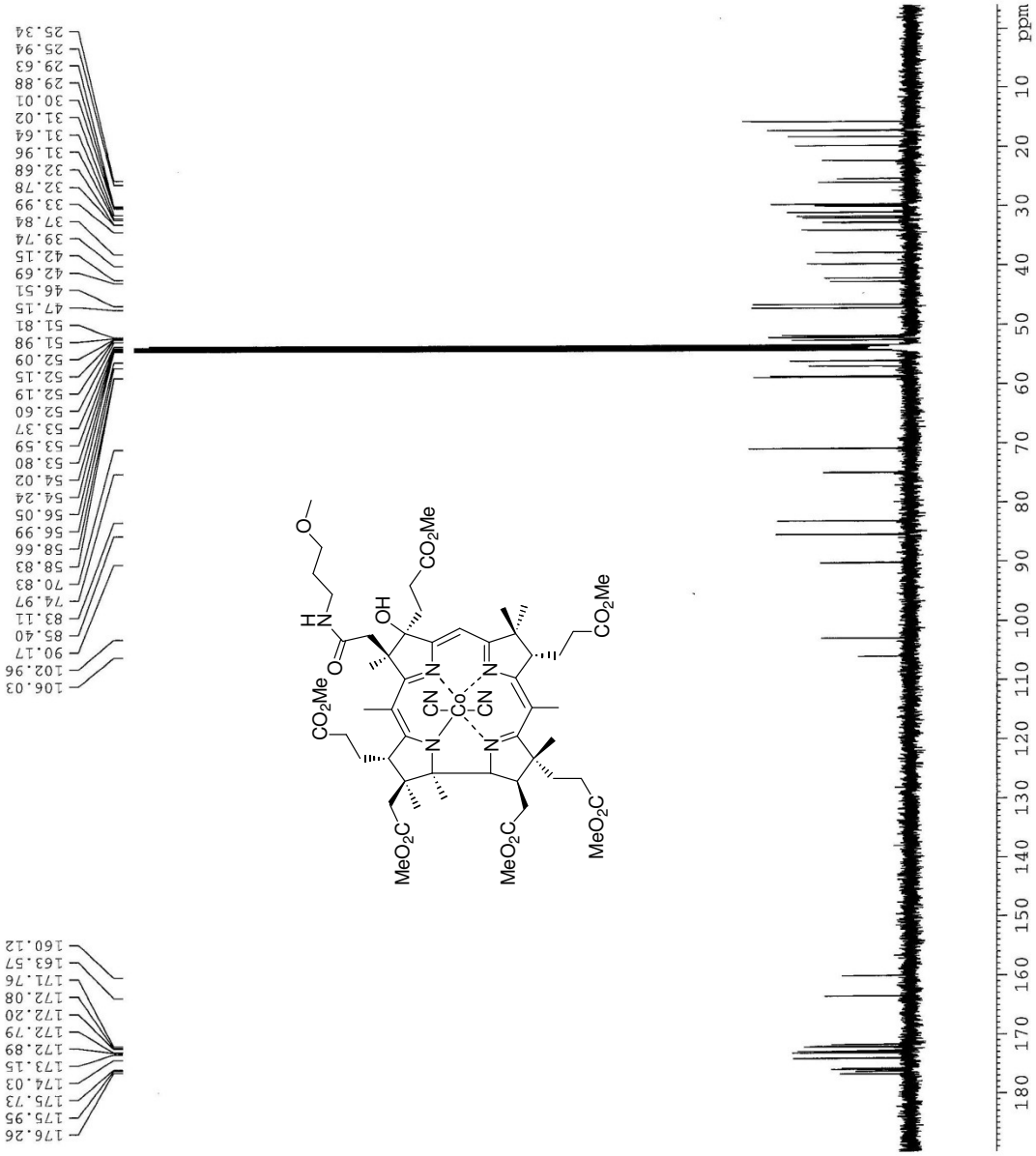
$(CN)_2$Cob(III)C1bis(5-pentanolamide) 13e



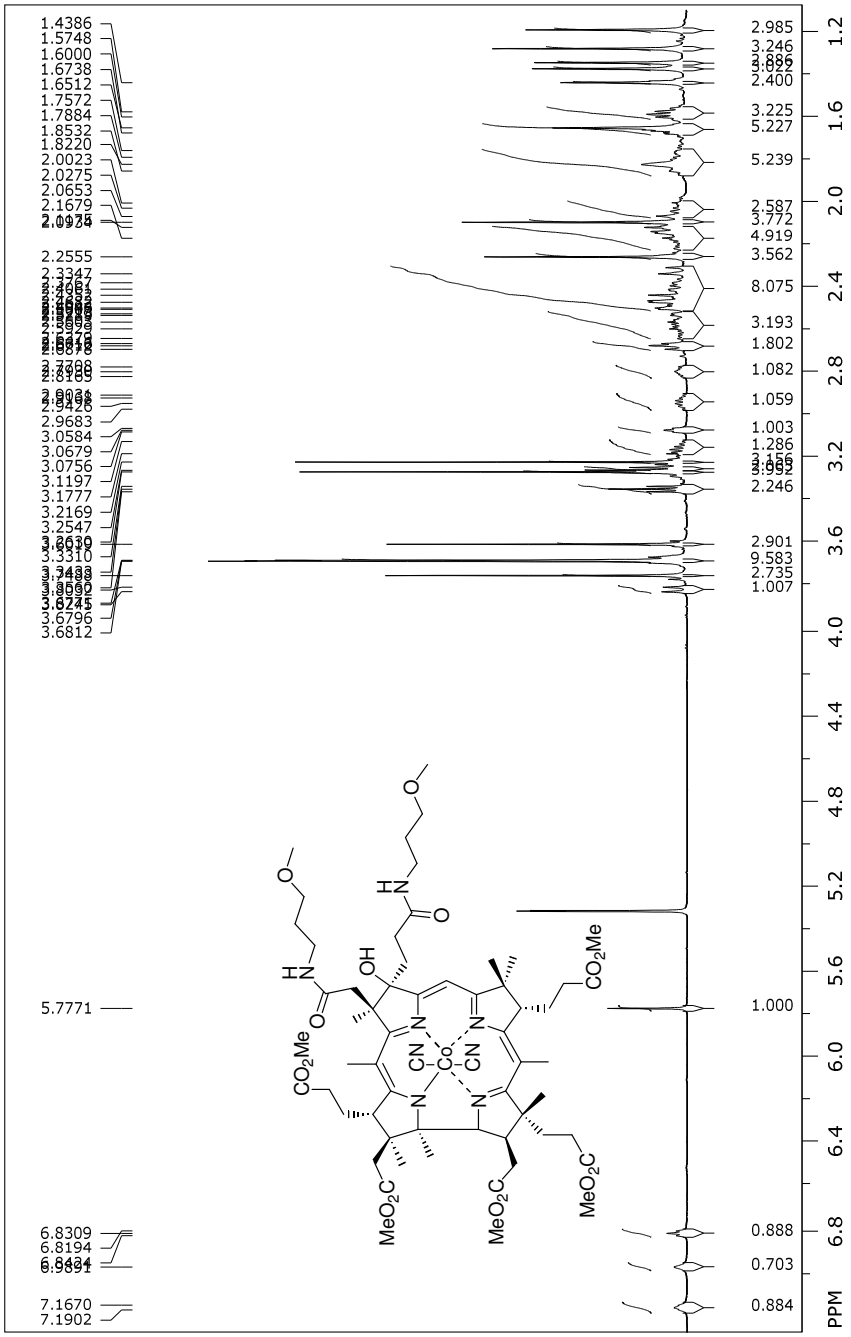
$(CN)_2$Cob(III)C1(3-methoxypropylamide) 12b



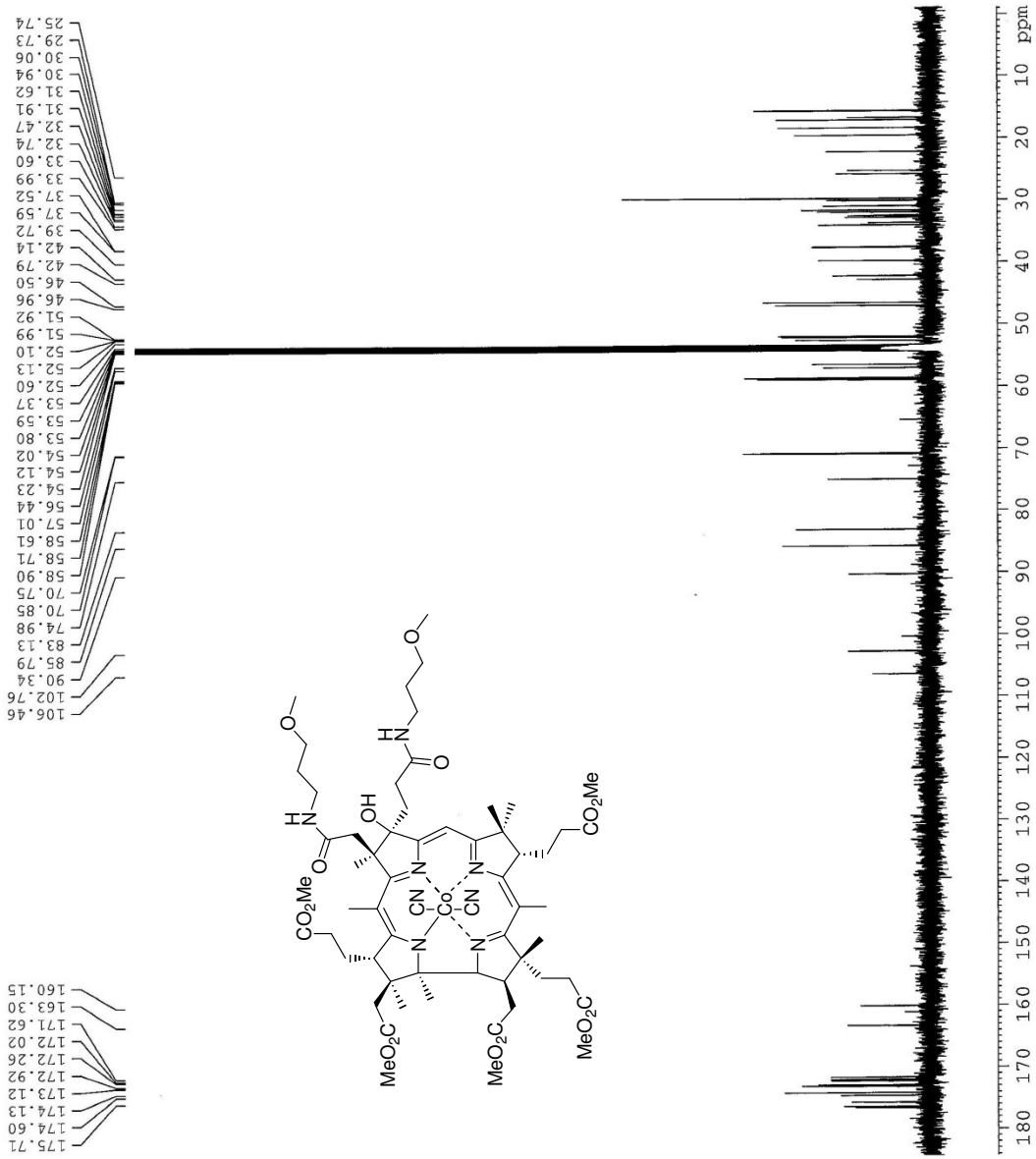
$(CN)_2$Cob(III)C1(3-methoxypropylamide) 12b



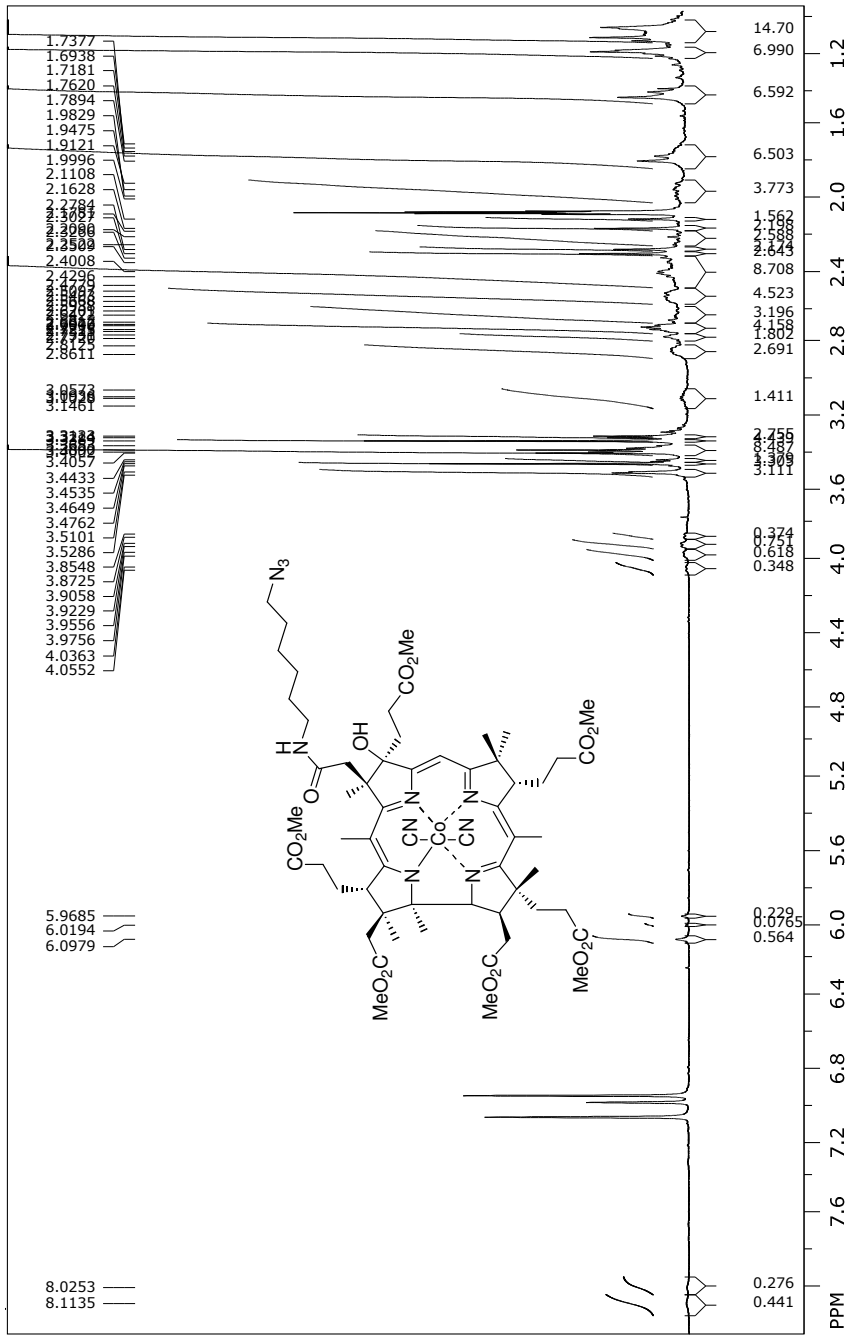
$(CN)_2$Cob(III)C1bis(3-methoxypropylamide) 13b



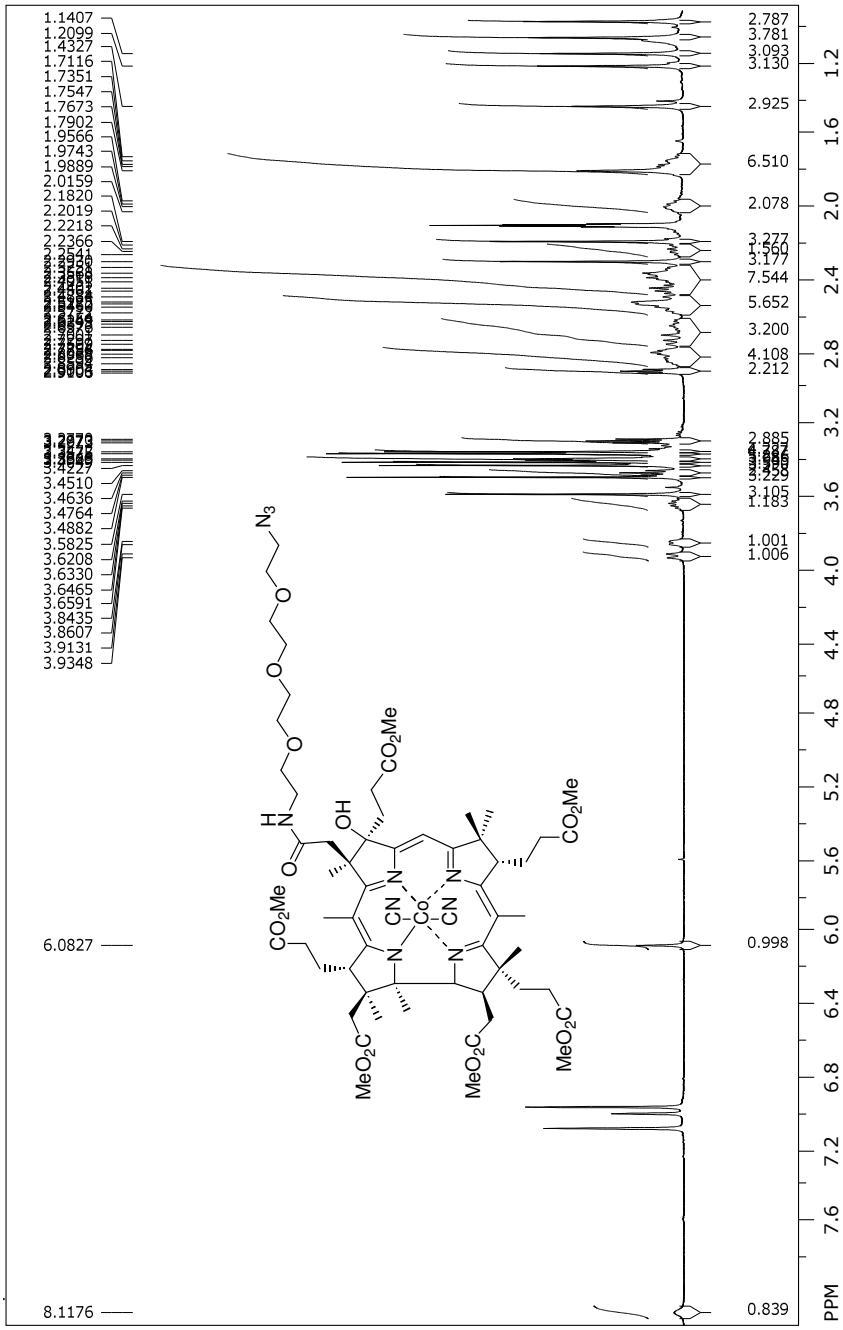
$(CN)_2$Cob(III)C1bis(3-methoxypropylamide) 13b



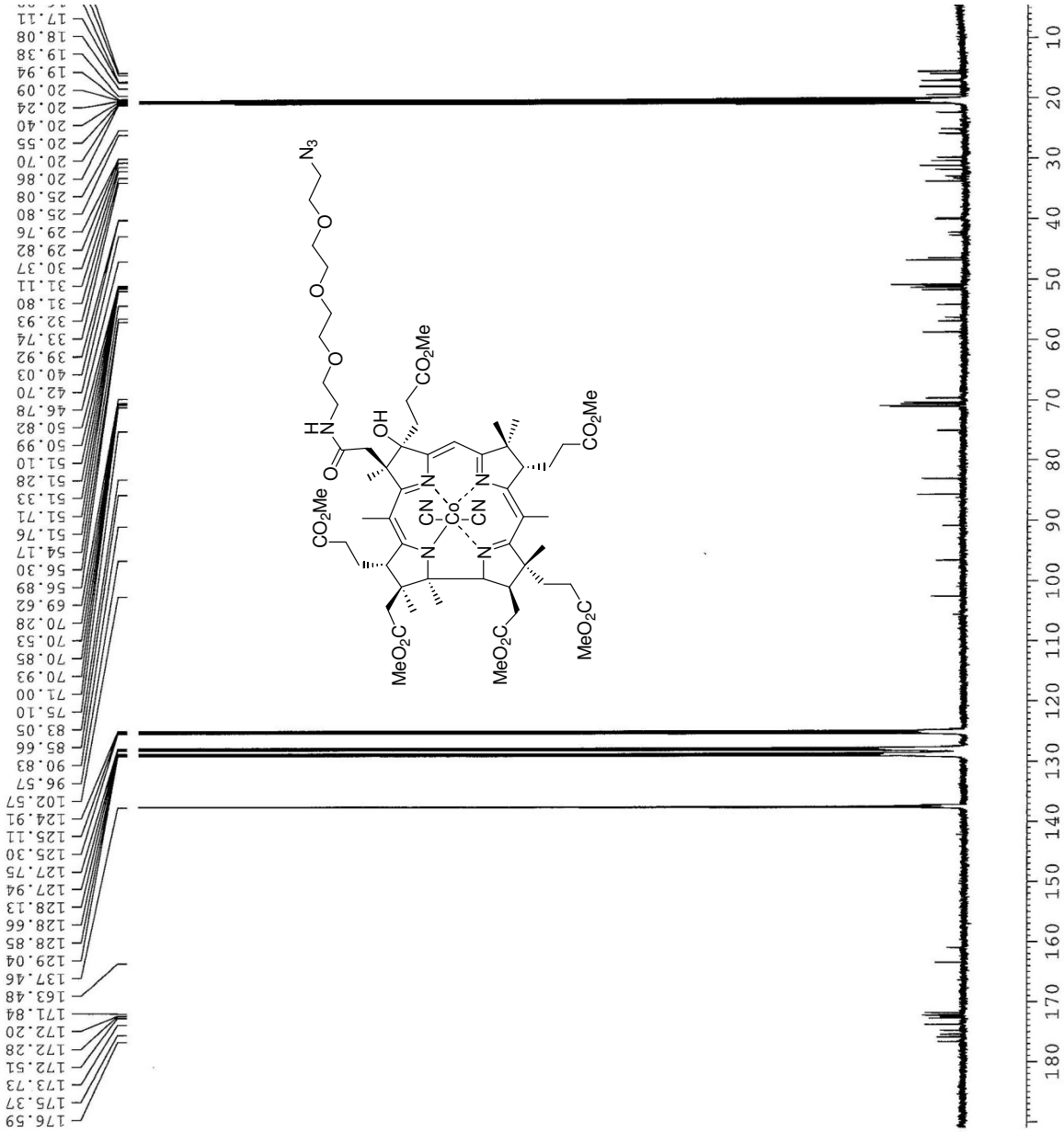
$(CN)_2$Cob(III)C1(6-azido-hexylamide) 12f



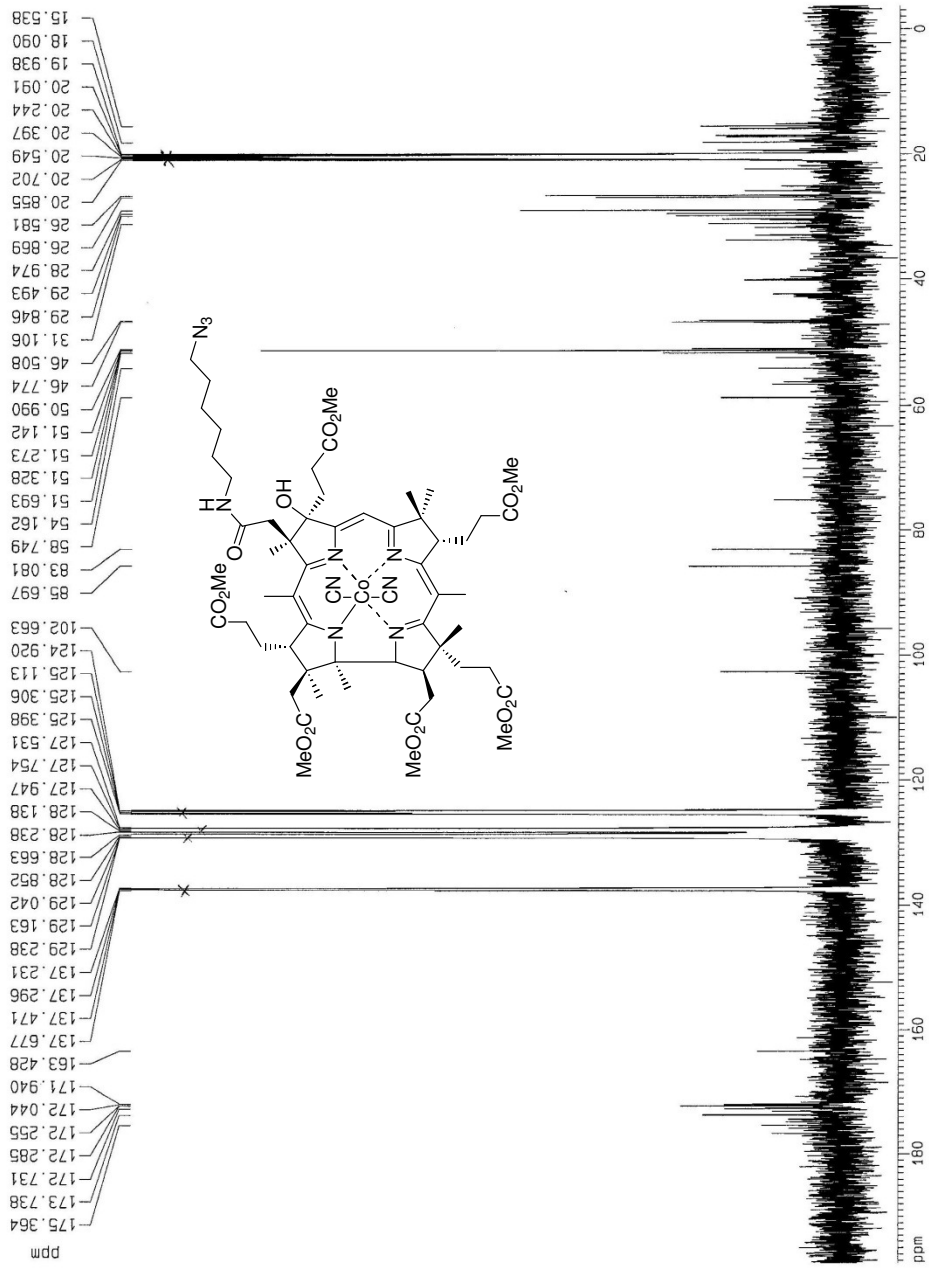
$(CN)_2$Cob(III)C1(2-{2-[2-(2-azido-ethoxy)-ethoxy]-ethoxy}-ethylamide)) 12h



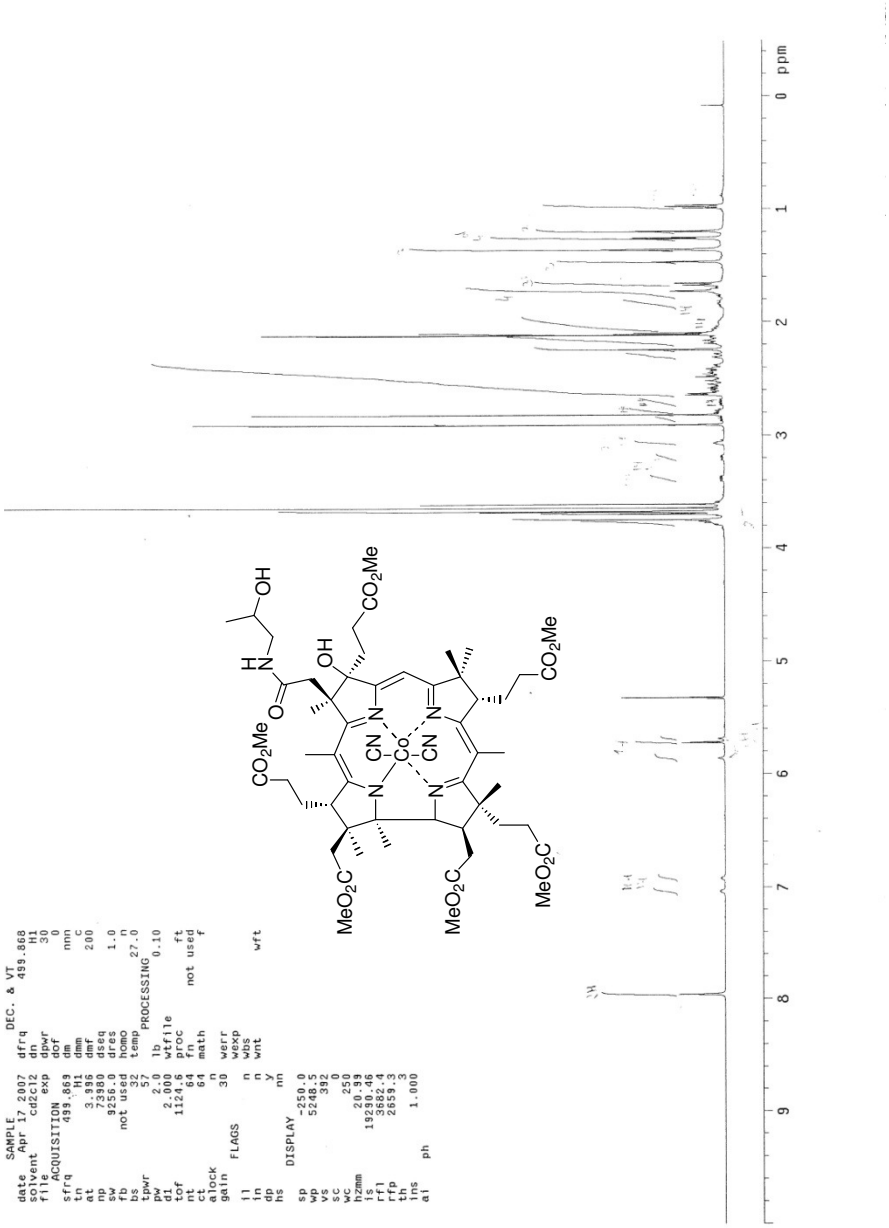
$(CN)_2$Cob(III)C1(2-{2-[2-(2-azido-ethoxy)-ethoxy]-ethoxy}-ethylamide) **12h**



$(CN)_2$Cob(III)C1(6-azido-hexylamide) 12f



$(CN)_2$Cob(III)C1(isopropanolamide) 12j



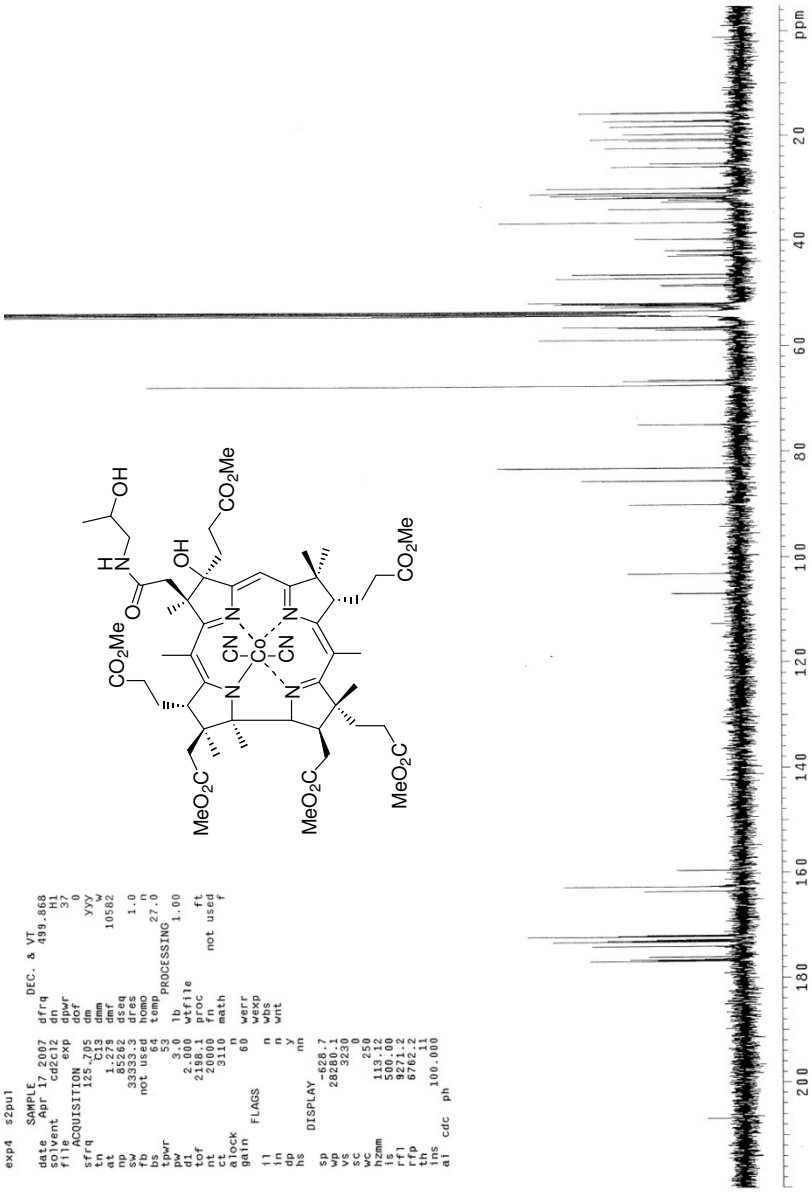
FREQUENCY	PPM	HEIGHT
932.249	1.865	4.5
927.023	1.855	5.0
921.939	1.844	6.4
917.843	1.836	6.1
911.488	1.823	4.6
907.815	1.816	6.5
889.455	1.779	6.1
884.229	1.769	7.6
877.026	1.755	7.6
874.060	1.749	9.5
871.518	1.744	10.6
863.044	1.727	52.9
854.711	1.710	13.4
847.649	1.696	8.2
836.774	1.674	40.5
828.299	1.657	48.9
733.248	1.467	70.5
724.067	1.449	4.1
721.666	1.444	4.0
678.589	1.358	120.2
668.138	1.337	6.1
664.889	1.330	4.7
661.358	1.323	3.5
650.766	1.302	3.8
646.670	1.294	3.6
630.569	1.261	91.9
626.049	1.252	89.5
597.520	1.195	116.8
501.621	1.004	3.8
495.547	0.991	41.1
489.050	0.978	53.7
488.203	0.977	57.9
481.847	0.964	48.1

FREQUENCY	PPM	HEIGHT
1140.007	2.281	9.8
1123.059	2.247	88.6
1121.788	2.244	103.5
1098.343	2.197	8.0
1094.671	2.190	19.2
1089.869	2.180	12.6
1088.033	2.177	12.5
1082.242	2.165	20.8
1073.768	2.148	10.9
1068.260	2.137	13.4
1066.847	2.134	12.6
1064.870	2.130	13.8
1060.633	2.122	13.4
1057.949	2.116	454.8
1053.853	2.108	108.2
1048.204	2.097	88.3
1044.108	2.089	17.3
1041.142	2.083	12.5
1038.600	2.078	10.5
1034.363	2.069	11.8
1032.103	2.065	12.2
1025.747	2.052	10.0
1017.556	2.036	8.3

FREQUENCY	PPM	HEIGHT
1912.427	3.826	3.5
1909.038	3.819	3.5
1900.846	3.803	3.2
1895.197	3.791	14.9
1890.112	3.781	17.2
1886.722	3.774	30.3
1880.508	3.762	38.2
1874.152	3.749	228.1
1872.740	3.746	285.8
1860.876	3.723	4.3
1855.368	3.712	12.7
1854.944	3.711	12.5
1848.024	3.697	205.0
1846.611	3.694	243.1
1844.917	3.691	44.7
1840.114	3.681	368.1
1836.725	3.674	488.8
1834.606	3.670	260.8
1832.205	3.665	32.3
1820.765	3.643	1106.9
1816.952	3.635	14.0
1815.257	3.631	12.0
1811.726	3.624	11.3
1803.958	3.609	457.5
1793.930	3.589	14.0
1791.812	3.585	12.5
1787.575	3.576	5.8
1778.677	3.558	2.9
1762.011	3.525	3.1
1702.409	3.406	6.1
1700.008	3.401	6.2
1695.630	3.392	6.5
1693.229	3.387	6.5
1688.709	3.378	7.0
1686.308	3.374	6.8
1681.930	3.365	6.6
1679.529	3.360	6.2
1609.759	3.220	4.8
1607.357	3.216	4.8
1603.403	3.208	5.1
1601.002	3.203	4.9
1596.059	3.193	5.8
1593.658	3.188	5.5
1589.703	3.180	5.5
1587.302	3.175	5.1
1538.717	3.078	12.7
1534.621	3.070	16.6
1529.254	3.059	12.4
1520.356	3.042	5.4

FREQUENCY	PPM	HEIGHT
1452.986	2.907	522.7
1452.704	2.906	515.4
1409.345	2.819	464.8
1408.780	2.818	448.0
1401.859	2.804	10.4
1395.786	2.792	7.7
1390.984	2.783	9.0
1321.919	2.645	38.1
1315.564	2.632	35.3
1308.643	2.618	11.6
1302.711	2.606	12.9
1300.452	2.602	9.8
1297.627	2.596	13.4
1291.836	2.584	16.3
1286.610	2.574	12.4
1280.961	2.563	8.6
1275.170	2.551	14.8
1273.617	2.548	16.3
1264.436	2.530	8.0
1259.776	2.520	18.3
1253.420	2.508	9.5
1249.607	2.500	6.8
1246.782	2.494	7.2
1242.968	2.487	28.0
1238.025	2.477	17.1
1233.082	2.467	9.4
1229.692	2.460	20.8
1227.009	2.455	11.4
1224.749	2.450	15.8
1222.207	2.445	11.7
1218.535	2.438	14.2
1212.179	2.425	13.4
1206.671	2.414	17.8
1201.304	2.403	11.6
1194.101	2.389	8.5
1189.299	2.379	10.3
1158.227	2.317	9.6
1154.837	2.310	11.7
1143.821	2.288	8.0

$(CN)_2$Cob(III)C1(isopropanolamide) 12j



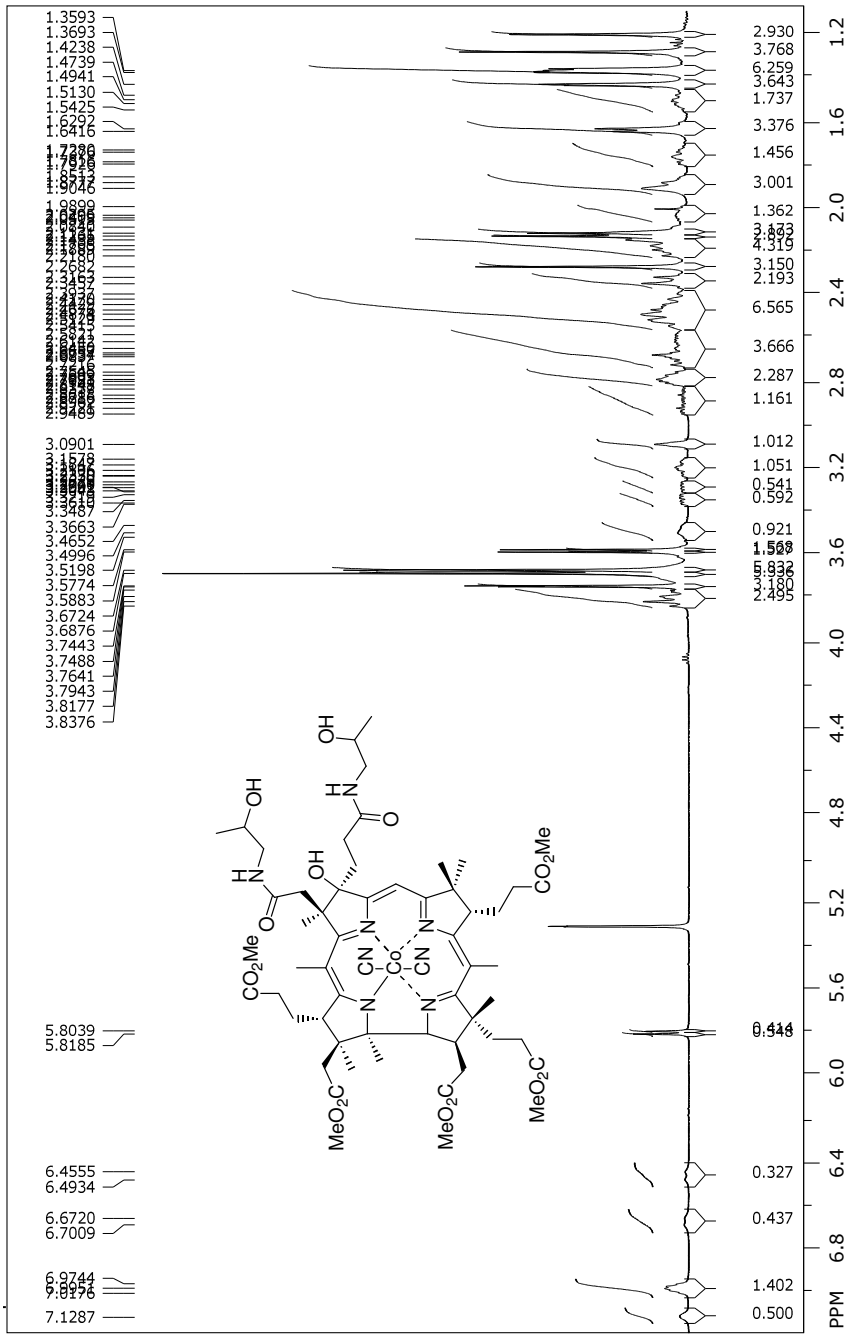
FREQUENCY	PPM	HEIGHT
22204.080	176.656	18.1
22179.666	176.462	24.0
22113.036	175.931	20.1
21867.370	173.977	31.9
21755.472	173.087	40.2
21734.110	172.917	26.6
21730.549	172.888	28.7
21706.135	172.694	18.3
21633.910	172.120	25.3
21630.858	172.095	45.5
21620.177	172.010	26.0
21618.651	171.998	26.5
21599.832	171.848	20.4
20551.553	163.508	20.9
20434.569	162.578	37.9
20052.591	159.539	13.6
20043.436	159.466	14.2
14157.612	112.638	6.7
13434.346	106.884	14.5
13427.733	106.831	15.2
12953.694	103.060	17.7
12951.659	103.043	24.3

FREQUENCY	PPM	HEIGHT
11314.391	90.017	23.9
10758.463	85.594	29.7
10747.273	85.505	34.0
10446.675	83.114	51.8
9419.250	74.940	22.2
8473.205	67.413	126.3
8368.428	66.579	25.3
8344.522	66.389	20.0

FREQUENCY	PPM	HEIGHT
5387.877	42.866	15.8
5361.938	42.660	13.8
5270.385	41.931	13.0
5257.160	41.826	16.4
4989.623	39.697	22.7
4591.369	36.529	51.5
4269.408	33.967	28.2
4095.458	32.583	17.0
4046.630	32.195	15.5
4019.673	31.981	14.0
4002.888	31.847	35.3
3989.155	31.738	18.6
3980.508	31.669	25.2
3942.362	31.365	40.5
3889.973	30.949	44.9
3883.869	30.900	38.6
3766.885	29.969	41.4

FREQUENCY	PPM	HEIGHT
3252.156	25.874	27.6
3174.844	25.259	19.5
2801.513	22.289	29.0
2628.071	20.909	23.9
2591.959	20.622	32.1
2470.397	19.654	25.2
2287.292	18.198	27.9
2282.205	18.157	21.8
2171.325	17.275	14.3
2159.118	17.178	29.1
2139.790	17.024	10.4
1970.417	15.677	27.7
1967.874	15.656	33.9
1960.245	15.596	34.6

$(CN)_2$Cob(III)C1bis(isopropanolamide) 13g



$(CN)_2$Cob(III)C1bis(isopropanolamide) 13g