Supplemental Information

Tripodal Amine Ligands for Accelerating Cu-Catalyzed Azide-Alkyne Cycloaddition: Efficiency and Stability against Oxidation and Dissociation

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A. General Methods

Reagents and solvents were purchased from Sigma-Aldrich, Fluka, Alfa-Aesar or VWR and used without further purification. The ultrapure Milli-Q water for all experiments was obtained by Milli-Q Water Purification Systems. Deoxygenated water was obtained by stirring the Milli-Q water in anaerobic chamber for two days. ESI-HRMS analyses were performed on Agilent 6150 instrument using methanol solutions. ESI-LC-MS analyses were performed on Thermo Finnigan LCQ Deca XP Plus LC/MSMS instrument using methanol solutions of the products through C18 column (Kinetex™ 5 μm XB-C18 100 Å, LC Column 50 × 4.6 mm, Phenomenex Inc.). Positive ion ESI-MS data were acquired using a Thermo Finnigan LCQ Deca XP ion trap mass spectrometer. NMR spectra were recorded on the JEOL ECX400 or ECA-500 spectrometer. All chemical shifts are reported in parts per million (ppm) with reference to solvent residual peaks. Coupling constants (*J*) are reported in hertz (Hz) and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; td, triplet of doublets; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; br, broad.

Table S1 Effects of ligands on dissociation constants (K_D) of ligand/Cu(I) 1:1 complexes and their activity in CuAAC (k_{obs}, yield) and air-oxidation of ascorbate (V_o)

ligand	Donor	Ring size/steric	K_D (10^{-10} M^{-1})[a]	k_{obs} ($M^{-1}s^{-1}$)[b]	% yield	V_o (10^{-8} M s^{-1})[c]	k_{obs}/V_o (10^8 M^{-2})
BTTAA	[Tr,Tr,Tr]	[5,5,5]	1.1 ± 0.2	29 ± 4	89	52 ± 1	0.56
1	[Tr,Tr,Tr]	[5,5,5]	1.1 ± 0.4	34 ± 7	89	27 ± 2	1.26
2	[Tr,Tr,Tr]	[6,6,6]	0.11 ± 0.02	0.9 ± 0.2	32	0.77 ± 0.07	1.17
3	[Tr,Tr,Tr]	[7,7,7]	0.26 ± 0.06	1.8 ± 0.6	22	14.6 ± 0.5	0.12
4	[Tr,Tr,Tr]	[5,5,6]	1.3 ± 0.2	10 ± 1	90	14.6 ± 0.2	0.68
5	[Tr,Tr,Tr]	[5,6,6]	0.18 ± 0.04	11 ± 3	97	13.0 ± 0.5	0.85
6	[Tr,Tr,Ph]	[5,5,5]	1.1 ± 0.2	17 ± 9	91	51 ± 2	0.33
7	[Tr,Tr,Tr,Tr]	[5,5,5,6]	0.60 ± 0.12	24 ± 2	90	26 ± 1	0.92
8	[Tr,Tr,Py]	[6,6,6]	0.12 ± 0.03	0.9 ± 0.4	25	11.5 ± 0.5	0.08
9	[Tr,Py,Py]	[6,6,6]	0.028 ± 0.005	0.1 ± 0.2	2	17.0 ± 0.5	0.01
10	[Py,Py,Py]	[6,6,6]	0.0082 ± 0.0007	0.6 ± 0.4	8	7.4 ± 0.5	0.08
11	[Py,Py,Py]	[5,5,5]	0.015 ± 0.006	5.1 ± 0.5	56	20 ± 2	0.26
12	[Py,Py,Ph]	[6,6,6]	1.4 ± 0.4	5 ± 1	46	14.9 ± 0.5	0.34
13	[Py,Py,Ph]	[6,6,6-Me][d]	0.54 ± 0.18	1.5 ± 0.8	15	9.4 ± 0.2	0.16
14	[Py,Py,Ph]	[6,6,6-Me_2][d]	0.34 ± 0.08	0.9 ± 0.5	14	6.7 ± 0.2	0.13
15	[Py,Py,Ph]	[5,6,6-Me][d]	0.79 ± 0.09	5.0 ± 0.7	53	21.6 ± 0.2	0.23
16	[Py,Py,Ph]	[5,6,6-Me_2][d]	13 ± 6	7 ± 1	56	6.2 ± 0.2	1.13
17	[Tr,Tr,Ph]	[6,6,6]	1.3 ± 0.3	1.4 ± 0.2	36	13.7 ± 0.5	0.10
18	[Tr,Tr,Ph]	[6,6,6-Me][d]	2.0 ± 0.3	0.8 ± 0.4	17	1.5 ± 0.1	0.53
19	[Tr,Tr,Ph]	[5,6,6-Me][d]	2.0 ± 1.6	5.0 ± 0.4	71	20 ± 1	0.25
20	[Tr,Tr,Ph]	[5,5,6-Me][d]	0.76 ± 0.08	15 ± 2	80	27 ± 1	0.56
21	[Tr,Tr,Ph]	[5,5,5-Me][d]	0.20 ± 0.11	7.9 ± 0.8	82	45.8 ± 0.2	0.17

[a] Measured by competitive binding assay with Bca. Values represent the mean ± standard deviation. [b] Apparent second-order rate constant (k_{obs}) and yield for the reaction of 3-azido-7-hydroxycoumarin (100 μM) with propargyl alcohol (50 μM) in the presence of the ligand (100 μM), $CuSO_4$ (100 μM) and sodium ascorbate (5 mM) in phosphate buffered saline (PBS, pH = 7.4) in air at 24 ± 1 °C for 60 min.[14, 48-50] [c] The air-oxidation rate (V_o) of sodium ascorbate (200 μM) by diffused O_2 in presence of Cu(I)-ligand complex (100 μM) in PBS (pH = 7.4) at 24 ± 1 °C. [d] Me/Me_2 represent the steric hindrance in ligands.

B. Measurement of the Dissociation Constant (K_D) of the Cu(I)-Ligand Complexes

Stock solutions:

MES buffer: 20 mM 2-(N-morpholino)ethanesulfonic acid (MES) in Milli-Q water, pH 6.15 (adjusted with NaOH and measured by digital pH meter W/RS-232).

$[Cu(MeCN)_4]PF_6$: 1 mM in MeCN/H_2O (5:95, v/v).

Na_2Bca: 1 mM in MES buffer.

Ligand: 10 mM in MES buffer.

Sodium ascorbate: 5 mM freshly prepared in MES buffer.

Final concentrations of reagents in the freshly prepared samples:

$[Cu(MeCN)_4]PF_6$: 16 μM

Na_2Bca: 40 μM

Ligand: 0–8 mM, listed in Table S2

Sodium ascorbate: 100 μM

Sample preparation for UV-vis spectrometry measurement:

Sample preparation was conducted in an anaerobic chamber (ALAC08-001, COY Laboratory products Inc.) filled with 5% H_2/N_2 circling through a pad of catalyst to maintain $[O_2] < 1$ ppm. Stock solutions were added by pipetting and mixed by aspiration with the pipette.

(1) Add 16 μL of the $[Cu^I(MeCN)_4]PF_6$ stock solution and 40 μL of the Na_2Bca stock solution into an empty cuvette (1 cm path).

(2) Add appropriate amount (0–800 μL) of the ligand stock solution according to the final ligand concentration listed in Table S2.

(3) Add 20 μL of the sodium ascorbate stock solution.

(4) Add the MES buffer to adjust the total volume to 1000 μL and mixed by aspiration with the pipette.

(5) Sealed the cuvette with a septum.

(6) After mixing all reagents, equilibrate the samples for 30 min including time for sample transport.

(7) Place the cuvettes in a flask and cap it with a rubber septum before taking it out from the anaerobic chamber. If the measurement is not performed immediately, pump the flask with pure nitrogen ($\geq$ 10 psi) through a needle connected to a schlenk line.

(8) The control solutions including everything except $[Cu^I(MeCN)_4]PF_6$ are prepared through the same steps 1–7.

UV-vis spectrometry:

UV-vis spectra of the samples in the septum-capped cuvettes (1 cm path) were obtained using a Varian Cary 50 Bio UV-vis spectrophotometer. The intensity of absorbance at λ_{max} = 358 nm was used for measurement of the concentration of Cu^IBca_2,[1] since it is much more sensitive than the one at 562 nm (the extinction coefficients ε_{358} = 42900 M^{-1} cm^{-1} *vs.* ε_{562} = 7900 M^{-1} cm^{-1}) and the background signals at 358 nm from the other components were low (Figure S1). The spectra of the components except Bca (Figure S1) were recorded as the following, which verifies that absence of absorbance at 358 nm.

(1) Use H_2O for baseline correction and obtain the spectrum of the MES buffer in a sealed cuvette (1000 μL, scan mode: survey, scan rate: fast).
(2) Use MES buffer for baseline correction and obtain the spectrum of a solution of 500 μM ligand **1**, 16 μM $[Cu^{I}(MeCN)_4]PF_6$ and 100 μM sodium ascorbate in 1000 μL MES buffer in a sealed cuvette (scan mode: survey, scan rate: fast).

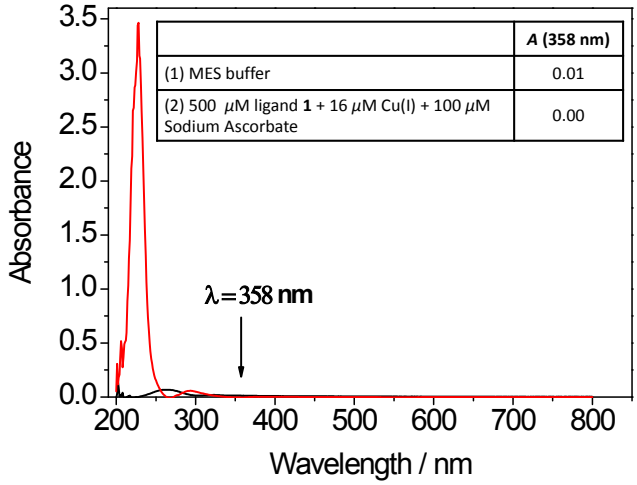


Figure S1 Spectra of the backgrounds, including the MES buffer (black line) and the mixture of 16 μM $[Cu^{I}(MeCN)_4]PF_6$, 500 μM ligand (**1**) and 100 μM sodium ascorbate in 1000 μL MES buffer (red line).

Spectra of the samples:

(1) Perform baseline correction using a solution of 40 μM Bca, ligand with the specified concentration (Table S2), and 100 μM sodium ascorbate (scan mode: survey, scan rate: fast).
(2) Obtain the spectrum of the test samples: a mixture of 16 μM $[Cu^{I}(MeCN)_4]PF_6$, 40 μM Bca, with the specified concentration (Table S2), and 100 μM sodium ascorbate (scan mode: survey, scan rate: fast).
(3) Repeat step (1) and (2) four times by varying ligand concentration corresponding to each sample.

Data treatment

Following the method described by Xiao *et al.*,[1] the dissociation constant (K_D) of Cu^{I} complex with the ligand **BTTAA** and **1**–**21** was determined using Bca as the probe. Bca forms 2:1 complex with Cu^{I} with a high stabilization constant ($\beta_2 = 10^{17.2}$ M^{-2}), which is essentially pH-independent at pH > 7.0,[1] and the competing binding of Cu(I) by the MES buffer can be ignored. Ligands with higher than nanomolar binding affinity to Cu(I) can effectively compete with Bca for Cu(I). Assuming the ternary complex Bca–Cu^{I}–L can be ignored as in the case of copper-binding proteins,[1] our system is composed of the following equilibrium, and the concentrations of the ligand [L], copper species [Cu^{I}], [Cu^{I}Bca], [$Cu^{I}Bca_2$], and Bca [Bca] are determined by the equilibrium constants K_D, K_1, K_2, β_2 in equations (1)–(4) and the initial concentrations of Cu^{I} ($[Cu^{I}]_{total}$), Bca ($[Bca]_{total}$) and ligand ($[L]_{total}$).

$Cu^{I}L \rightleftharpoons Cu^{I} + L$ $\quad K_D = \frac{[Cu^{I}][L]}{[Cu^{I}L]}$ (1)

$Cu^{I} + Bca \rightleftharpoons Cu^{I} + L$ $\quad K_1 = \frac{[Cu^{I}Bca]}{[Cu^{I}]}$ (2)

$Cu^{I}Bca + Bca \rightleftharpoons Cu^{I}(Bca)_2$ $\quad K_2 = \frac{[Cu^{I}Bca_2]}{[Cu^{I}Bca][Bca]}$ (3)

$Cu^{I} + 2\,Bca \rightleftharpoons Cu^{I}(Bca)_2$ $\quad \beta_2 = K_1K_2 = \frac{[Cu^{I}Bca_2]}{[Cu^{I}][Bca]^2}$ (4)

$[Cu^{I}]_{total} = [Cu^{I}Bca] + [Cu^{I}Bca_2] + [Cu^{I}L] + [CuI]$ (5)

from (2), (4): $\frac{[Cu^{I}Bca]}{[Cu^{I}Bca_2]} = \frac{1}{K_2[Bca]}$ (6)

since $\beta_2 > 10^{17}M^{-2}$ $\quad K_1 \approx K_2 > 10^{8}\,M^{-1}$

$[Bca] \approx 10^{-5}M$

then from (6): $\frac{[Cu^{I}Bca]}{[Cu^{I}Bca_2]} < 0.01$ (7)

from (4): $\frac{[Cu^{I}]}{[Cu^{I}Bca_2]} = \frac{1}{\beta_2[Bca]^2} \ll 0.01$ (8)

Therefore, $[Cu^{I}]_{total} \approx [Cu^{I}Bca_2] + [Cu^{I}L]$ (9)

from (1), (4): $\frac{[Cu^{I}Bca]}{[Cu^{I}Bca_2]} = \frac{1}{K_2[Bca]}$ (10)

$[L] = [L]_{total} - [Cu^{I}L]$ (ignoring Bca-Cu^{I}-L) (11)

$[Cu^{I}L] = [Cu^{I}]_{total} - [Cu^{I}Bca_2]$ from (9)

$[Bca] \approx [Bca]_{total} - 2[Cu^{I}Bca_2]$ ($\because [Cu^{I}Bca] \ll [Cu^{I}Bca_2]$) (12)

Derive (10), (11), (12): $K_D\beta_2 = (\frac{[L]_{total}}{[Cu^{I}L]} - 1)\frac{[Cu^{I}Bca_2]}{\{[Bca]_{total} - 2[Cu^{I}Bca_2]\}^2}$

$\therefore \quad K_D = \frac{\frac{[L]_{total}}{[Cu^{I}]_{total} - [Cu^{I}Bca_2]} - 1}{\left\{\frac{[Bca]_{total}}{[CuIBca_2]} - 2\right\}^2[CuIBca_2]\beta_2}$ (13)

In which β_2 = $10^{17.2}$ M^{-2},[1] $[Cu^{I}]_{total}$ = 16 × 10^{-6} M, $[Bca]_{total}$ = 40 × 10^{-6} M, $[L]_{total}$ is listed in Table S2, and $[Cu^{I}(Bca)_2]$ was measured by the absorbance at 358 nm A_{358} using formula $[Cu^{I}Bca_2] = \frac{A_{358}}{\varepsilon l}$ (ε_{358} = 42900 M^{-1} cm^{-1}, and l is the optical path length of the cuvette, l = 1 cm) and the values are listed below in Table S2. The standard deviation is obtained from four K_D values derived from data obtained with the specified ligand concentration.

Table S2 Average K_D of ligands

Entry	$[Bca]_{total}$ /μM	$[L]_{total}$ /μM	A_{358}	$[Cu^{I}$-$Bca_2]$/μM	$[Cu^{I}$-L]/μM	$K_D \times 10^{-11}$/M
1	40	0	0.66	15.39	0	-
2	40	500	0.56	13.05	2.33	9.1
3	40	1000	0.52	12.12	3.26	9.4
4	40	2000	0.49	11.42	3.96	12.3

5	40	3000	0.46	10.72	4.66		12.6
BTTAA						K_D =	11 ± 2
1	40	0	0.46	10.72	0		-
2	40	500	0.42	9.79	0.93		8
3	40	2000	0.36	8.39	2.33		8.4
4	40	4000	0.33	7.69	3.03		10.6
5	40	8000	0.31	7.22	3.5		16
Ligand **1**						K_D =	11 ± 4
1	40	0	0.5	11.7	0		-
2	40	250	0.4	9.32	2.33		1.37
3	40	500	0.33	7.69	3.96		1
4	40	750	0.32	7.5	4.2		1.33
5	40	1000	0.26	6.06	5.6		0.87
Ligand **2**						K_D =	1.1 ± 0.2
1	40	0	0.67	15.62	0		-
2	40	500	0.49	11.42	4.2		2.89
3	40	750	0.47	10.96	4.66		3.38
4	40	1000	0.4	9.32	6.3		2.04
5	40	1500	0.37	8.62	7		2.24
Ligand **3**						K_D =	2.6 ± 0.6
1	40	0	0.64	14.92	0		-
2	40	250	0.58	13.52	1.4		9
3	40	500	0.57	13.23	1.63		14.2
4	40	750	0.55	12.82	2.1		14
5	40	1000	0.53	12.35	2.56		13
Ligand **4**						K_D =	13 ± 2
1	40	0	0.63	14.69	0		-
2	40	250	0.48	11.19	3.5		1.6
3	40	500	0.42	9.79	4.9		1.5
4	40	750	0.4	9.32	5.36		1.79
5	40	1500	0.36	8.39	6.29		2.33
Ligand **5**						K_D =	1.8 ± 0.4
1	40	0	0.63	14.69	0		-
2	40	250	0.57	13.29	1.4		8.3
3	40	500	0.55	12.82	1.86		10.5
4	40	1000	0.51	11.89	2.8		10.2
5	40	2000	0.48	11.19	3.5		13
Ligand **6**						K_D =	11 ± 2
1	40	0	0.64	14.92	0		-
2	40	250	0.56	13.05	1.86		5.68
3	40	500	0.54	12.59	2.33		7.71
4	40	1250	0.45	10.49	4.43		5.14
5	40	1500	0.44	10.26	4.66		5.47
Ligand **7**						K_D =	6.0 ± 1.2
1	40	0	0.65	15.15	0		-
2	40	250	0.46	10.72	4.43		1.09
3	40	500	0.39	9.09	6.06		0.982
4	40	1000	0.37	8.62	6.53		1.6
5	40	2000	0.27	6.29	8.86		1.19
Ligand **8**						K_D =	1.2 ± 0.3
1	40	0	0.53	12.35	0		-
2	40	20	0.46	10.72	1.63		0.221
3	40	30	0.45	10.49	1.86		0.276
4	40	40	0.44	10.26	2.1		0.308
5	40	50	0.43	10.02	2.33		0.325
Ligand **9**						K_D =	0.28 ± 0.05
1	40	0	0.53	12.35	0		-
2	40	20	0.41	9.56	2.8		0.085
3	40	30	0.37	8.62	3.73		0.0741
4	40	40	0.36	8.39	3.96		0.0893
5	40	50	0.33	7.69	4.66		0.0779
Ligand **10**						K_D =	0.082 ± 0.007
1	40	0	0.61	14.22	0		-
2	40	50	0.38	8.86	5.36		0.0937

3	40	100	0.32	7.46	6.76		0.103
4	40	400	0.25	5.83	8.39		0.214
5	40	500	0.22	5.13	9.09		0.198
Ligand **11**						K_D =	0.15 ± 0.06
1	40	0	0.65	15.15	0		-
2	40	250	0.6	13.99	1.17		13
3	40	750	0.57	13.29	1.86		18.7
4	40	1500	0.52	12.12	3.03		15.2
5	40	2000	0.46	10.72	4.43		8.9
Ligand **12**						K_D =	14 ± 4
1	40	0	0.65	15.15	0		-
2	40	250	0.54	12.59	2.56		3.49
3	40	500	0.51	11.89	3.26		4.34
4	40	2000	0.43	10.02	5.13		6.18
5	40	3000	0.41	9.56	5.59		7.4
Ligand **13**						K_D =	5.4 ± 1.8
1	40	0	0.65	15.15	0		-
2	40	250	0.52	12.12	3.03		2.51
3	40	500	0.49	11.42	3.73		3.26
4	40	1000	0.44	10.26	4.9		3.46
5	40	3000	0.36	8.39	6.76		4.35
Ligand **14**						K_D =	3.4 ± 0.8
1	40	0	0.61	14.22	0		-
2	40	250	0.55	12.82	1.4		6.97
3	40	500	0.52	12.12	2.1		7,31
4	40	1000	0.49	11.42	2.8		8.73
5	40	1500	0.46	10.72	3.5		8.41
Ligand **15**						K_D =	7.9 ± 0.9
1	40	0	0.66	15.39	0		-
2	40	500	0.65	15.15	0.23		218
3	40	1000	0.63	14.69	0.7		117
4	40	2000	0.6	13.99	1.4		87.2
5	40	3000	0.59	13.75	1.63		102
Ligand **16**						K_D =	130 ± 60
1	40	0	0.55	12.82	0		-
2	40	500	0.51	11.89	0.93		15.3
3	40	750	0.49	11.42	1.4		13.1
4	40	1250	0.45	10.49	2.33		9.8
5	40	1500	0.44	10.26	2.56		21
Ligand **17**						K_D =	12 ± 3
1	40	0	0.68	15.85	0		-
2	40	250	0.64	14.92	0.93		24.3
3	40	750	0.59	13.76	2.1		19.8
4	40	1000	0.57	13.29	2.56		18.1
5	40	1500	0.55	12.82	3.03		19.4
Ligand **18**						K_D =	20 ± 3
1	40	0	0.65	15.15	0		-
2	40	250	0.63	14.69	0.47		43.9
3	40	750	0.57	13.29	1.86		18.7
4	40	1500	0.48	11.19	3.96		8.6
5	40	2000	0.47	10.96	4.2		10
Ligand **19**						K_D =	20 ± 16
1	40	0	0.68	15.85	0		-
2	40	750	0.54	12.59	3.26		8.27
3	40	1000	0.51	11.89	3.96		7.16
4	40	1500	0.49	11.42	4.43		8.27
5	40	2000	0.45	10.49	5.36		6.81
Ligand **20**						K_D =	7.6 ± 0.8
1	40	0	0.65	15.15	0		-
2	40	250	0.54	12.59	2.56		3.49
3	40	500	0.4	9.32	5.83		1.09
4	40	750	0.38	8.86	6.29		1.33
5	40	2000	0.32	7.46	7.69		1.94
Ligand **21**						K_D =	2.0 ± 1.1

C. Determine the Rate of Ascorbate Decomposition

Stock solutions:

PBS: Phosphate buffered saline (10× concentration) was diluted to 1× concentration with Milli-Q water to prepare 0.01 M PBS with NaCl concentration of 0.154 M upon adjustment of pH to 7.4 with NaOH.

Cu(I)-ligand:[2] All operations were done in anaerobic chamber ($[O_2]$ < 0.1 ppm) or in a schlenk line under argon atmosphere. Each ligand (**1**–**21** and **BTTAA**, 0.10 mmol) was treated with $[Cu^{I}(MeCN)_4]PF_6$ (37.3 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 30 min at room temperature, addition of ether (30 mL) resulted in formation of a white to pale yellow powder precipitate. After evaporation of the solvent under vacuum, the residue was dissolved in water (or DMSO/H_2O 8:92 v/v for **9**–**16** / Cu^{I}) to prepare the corresponding 4 mM Cu(I)-ligand stock solution. The fleshly prepared Cu(I)-ligand stock solution was used immediately.

Sodium ascorbate: 5 mM, freshly prepared in PBS.

Determine the λ_{max} of ascorbate in the samples:

Inject 40 μL of the 5 mM sodium ascorbate stock solution via microsyringe into the sealed test solution prepared by mixing 25 μL of the 4 mM Cu(I)-**1** stock solution and 935 μL PBS and vigorously shake the cuvette. Perform baseline correction using the solution (100 μM Cu(I)-**1**, 200 μM sodium ascorbate in PBS). The spectrum was recorded (scan mode: survey, scan rate: fast), which shows the λ_{max} for ascorbate to be approximately 265 nm.

Sample preparation:

Sample preparation was conducted in an anaerobic chamber filled with 5% H_2/N_2 circling through a pad of catalyst to maintain $[O_2]$ < 1 ppm. Stock solutions were added by pipetting and mixed by aspiration with the pipette.

(1) In an empty UV cuvette (1 cm path), add 25 μL of the 4 mM Cu(I)-ligand stock solution.

(2) Add PBS to adjust the total volume to 960 μL, giving a solution of 100 μM Cu(I)-ligand, 200 μM sodium ascorbate in PBS.

(3) Sealed with a septum cap.

(4) Place the cuvettes in a flask and cap it with a rubber septum before taking it out from the anaerobic chamber. If the measurement is not performed immediately, pump the flask with pure nitrogen ($\geq$ 10 psi) with a schlenk line through a needle.

(5) The control solutions are made with 25 μL of the 4 mM Cu(I)-ligand stock solution and 975 μL PBS without sodium ascorbate, and the preparation is through the same steps 1–4.

Protocol for monitoring the decomposition of ascorbate:

(1) Use the above control sample (100 μM Cu(I)-ligand in 1000 μL PBS) for baseline correction.

(2) Inject 40 μL of the 5 mM sodium ascorbate stock solution via microsyringe into the sealed test solution prepared by mixing 25 μL of the 4 mM Cu(I)-ligand stock solution and 935 μL PBS and vigorously shake the cuvette.

(3) Scan the sealed sample until the maximum absorption (λ_{max} = 265 nm) becomes constant (scan mode: cycle, scan rate: fast, scan time: 3 counts, 0.5 min/count).
(4) Open the cuvette to air and immediately monitor the optical density at 265 nm of the test samples for 30 min (scan mode: cycle, scan rate: fast, scan time: 60 counts, 0.5 min/count).

Delay of ascorbate oxidation due to O_2 diffusion:

The plots of the absorbance at λ_{max} = 265 nm corresponding to the concentration of ascorbate overtime show a fast decrease due to oxidative degradation of ascorbate following an initial delay of about 8 min (Figure S2, red curves). The following control experiments confirm that this delay was due to the oxygen diffusion to the optical path.
(a) In the first experiment, the mixed Cu(I)-**BTTAA** stock solution and sodium ascorbate stock solution were prepared and stored in anaerobic condition and used immediately. PBS solution (935 µL, saturated with O_2) was added to the mixture of 40 µL of the 5 mM sodium ascorbate stock solution and 25 µL of the 4 mM Cu(I)-**BTTAA** stock solution and vigorously shake the cuvette. Open the cuvette to air and immediately monitor the absorbance at 265 nm of the test samples for 30 min.
(b) In the second experiment, all the stock solutions were prepared in anaerobic condition and used immediately. Inject 40 µL of the 5 mM sodium ascorbate stock solution via microsyringe into the sealed test solution prepared by mixing 25 µL of the 4 mM Cu(I)-ligand stock solution and 935 µL PBS and vigorously shake the cuvette. 12 mL of air was injected to the above solution right before the measurement.

However, in these two control experiments, the starting point of the ascorbate decomposition was hard to identify. Thus, for the simplicity and accuracy of the measurement of the initial ascorbate oxidation rate (V_0), the method with the initial delay was applied.

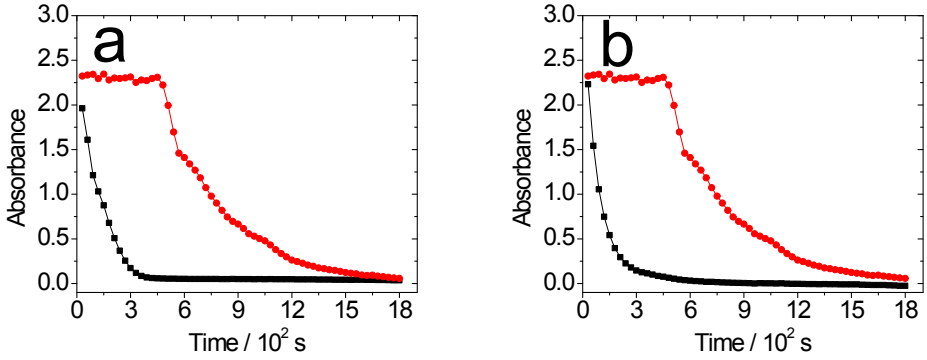


Figure S2 Plots of the absorbance of ascorbate at 265 nm monitoring its oxidative degradation by molecular oxygen diffused (red) *vs.* in situ added (black) to the reaction mixture in the optical path. The reaction mixture contained Cu(I)-**BTTAA** (100 µM), sodium ascorbate (200 µM) in 1000 µL PBS at 24 ± 1 °C and pH = 7.4. To obtain the red curve in a) and b), the solution was freshly prepared in a capped cuvette according to the above protocol and the cap was removed at the beginning of the measurement to allow diffusion of O_2 to the optical path. To obtain the black curve in a), PBS solution (935 µL, saturated with O_2) was added to the mixture of 40 µL of the 5 mM sodium ascorbate stock solution and 25 µL of the 4 mM Cu(I)-**BTTAA** stock solution. To obtain the black curve in b), 12 mL of air was injected to the above solution right before the measurement.

Data Treatment:

(1) Plot A_{265} *vs.* time for each ligand (Figure S3).

(2) Within the linear range applied to the Beer's law, the absorbance at 265 nm (A_{265}) is proportional to the concentration of ascorbate (c) by $A_{265} = \varepsilon_{265} l c$, in which the adsorption coefficient $\varepsilon_{265} = 1.5 \times 10^4$ $M^{-1}cm^{-1}$, optical length $l = 1$ cm.[3]

(3) The starting point of ascorbate decomposition is chosen from a four consecutively decreasing data points (120 seconds) in the curves.

(4) Examining the plots in Figure S3 reveals that the data points in the first 100 seconds of rapid decrease of A_{265} can be fit linearly as shown by the blue lines (the coefficient of determination (R^2) value is shown in the figure).

(5) The average velocity (V_0) of ascorbate oxidation within this time period is then calculated from

$$V_0 = m/\varepsilon l \qquad (14)$$

where m is the slope of the blue line, $\varepsilon = 1.5 \times 10^4$ $M^{-1}cm^{-1}$ is the ascorbate absorption coefficient at 265 nm, and $l = 1$ cm is the optical path length of the cuvette.

(6) Repeat steps 1–5 for each ligand to provide the initial ascorbate oxidation rate V_0 as given in Figure 3.

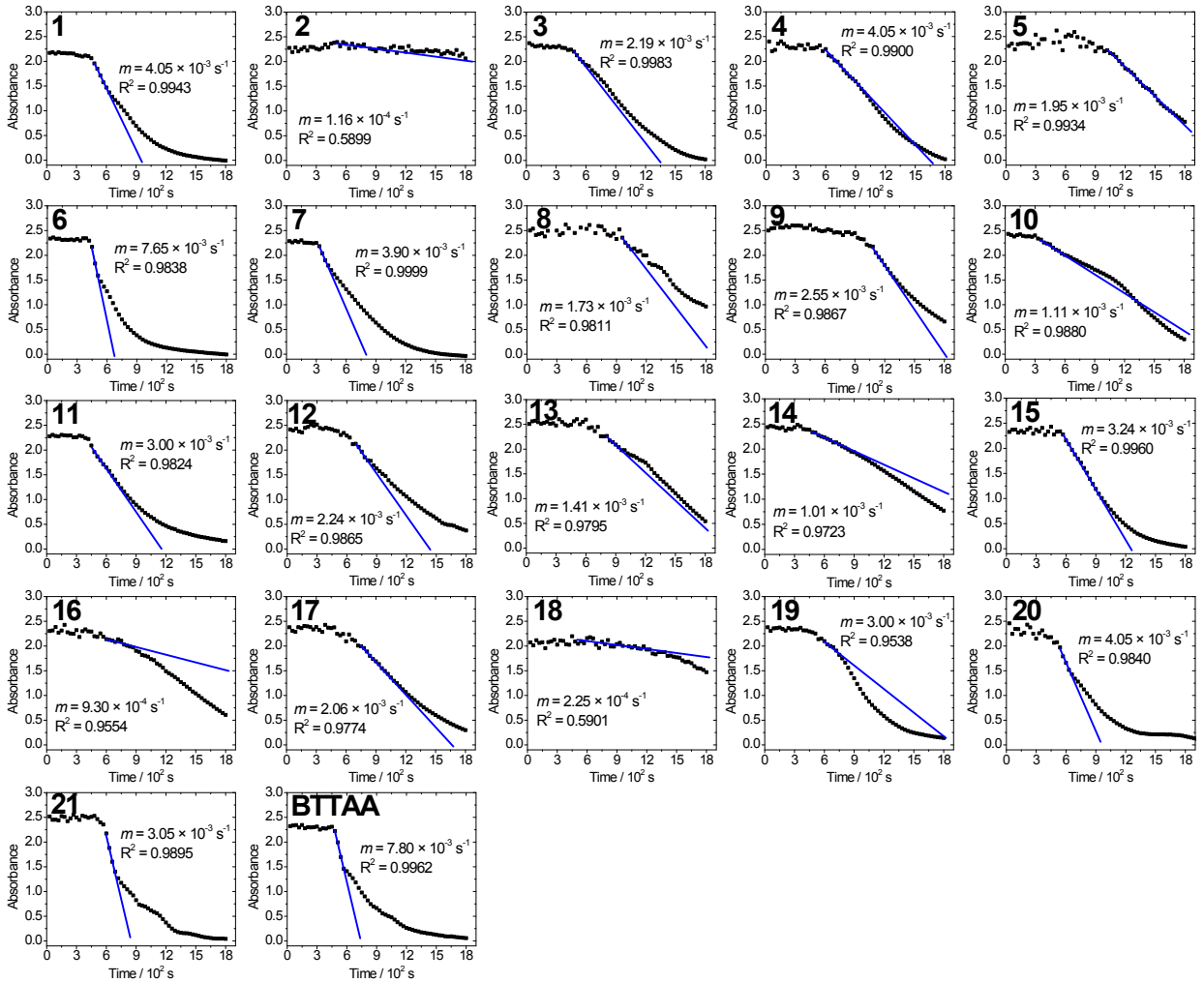


Figure S3 Plot of ascorbate absorbance (A_{265}) *vs.* time for the mixture of Cu(I) with ligand **1–21** and **BTTAA** (100 μM), sodium ascorbate (200 μM) in 1000 μL PBS at 24 ± 1 °C and pH = 7.4. The blue lines represent the best fit of data points in the first 100 seconds of rapid decrease of A_{265}. The slop (m) and the coefficient of determination (R_2) value are indicated next to the blue line.

D. Kinetic Measurement of a Fluorogenic CuAAC Reaction

Stock solutions:

PBS: Phosphate buffered saline (10× concentration) was diluted to 1× concentration with Milli-Q water to prepare 0.01 M PBS with NaCl concentration of 0.154 M upon adjustment of pH to 7.4 with NaOH.

$CuSO_4$: 1 mM stock solution in Milli-Q water.

Ligand: (for ligands **1**–**8**, **17**–**21** and **BTTAA**) 1 mM stock solution in PBS;
(for ligands **9**–**16**) 1 mM stock solution in 5% DMSO in PBS.

Azido-coumarin (3-azido-7-hydroxycoumarin[4]): 1 mM stock solution in 5% DMSO in PBS.

Propargyl alcohol: 0.5 mM stock solution in PBS.

Sodium Ascorbate: 25 mM stock solution in PBS.

Final concentrations of reagents in the 100 µL reaction mixture:

$CuSO_4$: 100 µM or 200 µM

Ligand: 100 µM

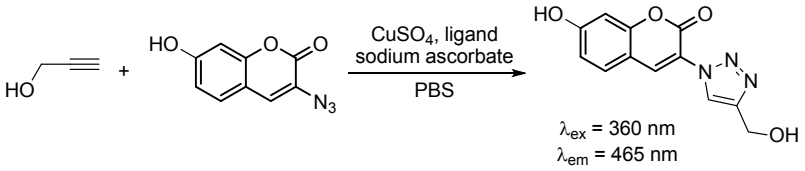
Azido-coumarin: 100 µM

Propargyl alcohol: 50 µM

Sodium ascorbate: 5 mM

Diethylenetriamine-pentaacetic acid pentasodium: 2.5 mM

Fluorogenic CuAAC reaction and measurement of apparent second order rate constant and yield:



The procedure was based on the method described by Wu *et al*.[5]

At 24 ± 1 °C, to a 96-well fluorescence plate add the reagents in the following order:

(1) 40 µL of PBS.

(2) 10 µL of 1.0 mM ligand stock solution.

(3) 10 µL of 1.0 mM $CuSO_4$ stock solution.

(4) 10 µL of 1.0 mM azido-coumarin stock solution.

(5) 10 µL of 0.5 mM propargyl alcohol stock solution.

(6) 20 µL of 25 mM sodium ascorbate stock solution. Rapidly aspirate the mixture and start measurement.

(7) At the specified time point, record the fluorescence intensity of the product (λ_{ex} = 360 nm, λ_{em} = 465 nm) with a Perkin Elmer HTS 7000 Bio Assay Reader. The data are plotted in Figure S6.

(8) The control groups are the samples including all the components except sodium ascorbate. As expected no product was observed in all control groups.

Standard curve for the product (Triazole-coumarin) concentration:

(1) Prepare a series of triazole-coumarin[4] standards by mixing the triazole-coumarin (various concentrations in the range of 0–50 μM), $CuSO_4$ (100 μM), ligand **1** (100 μM), sodium ascorbate (5 mM) in 100 μL PBS.

(2) Measure the fluorescence intensity of this series of triazole-coumarin mixture solution at 60 min. The mean fluorescence intensity (MFI) for each concentration was obtained from four replicate measurements and the error bar represented the standard deviation (SD).

(3) Plot the mean MFI ± SD *vs.* Product Concentration [P] (Figure S4) which can be linearly fit to give a linear relationship between MFI and Product Concentration [P].

(4) The fitting line MFI = 356 × [P] + 331 (R^2 = 0.9995) serves as the standard curve for estimating the yield of the reaction.

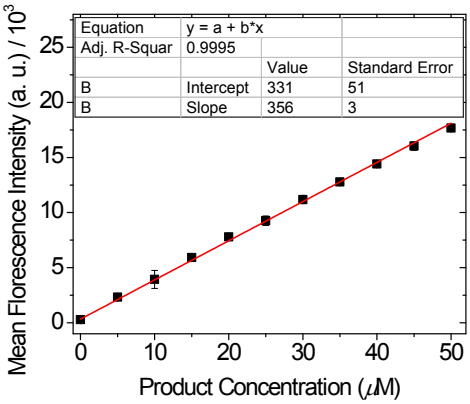


Figure S4 Standard curve for estimating the yield of the fluorogenic CuAAC reaction The mean fluorescence intensity was measured at λ_{ex} = 360 nm, λ_{em} = 465 nm from a series of solutions of triazole-coumarin with an concentration interval of 5 μM in the range of 0–50 μM representing 0–100% yield of the reaction. The solution also included most components in the reaction mixture: $CuSO_4$ (100 μM), ligand **1** (100 μM), sodium ascorbate (5 mM) in 100 μL PBS, measured at 60 min after mixing at temp = 24 ± 1 °C and pH = 7.4. Each data point is the mean of four replicates and the error bar represents the standard deviation. The red line is the best linear fit of the data point, which is expressed as MFI = 356 × (value of x-axis) + 331 (R^2 = 0.9995).

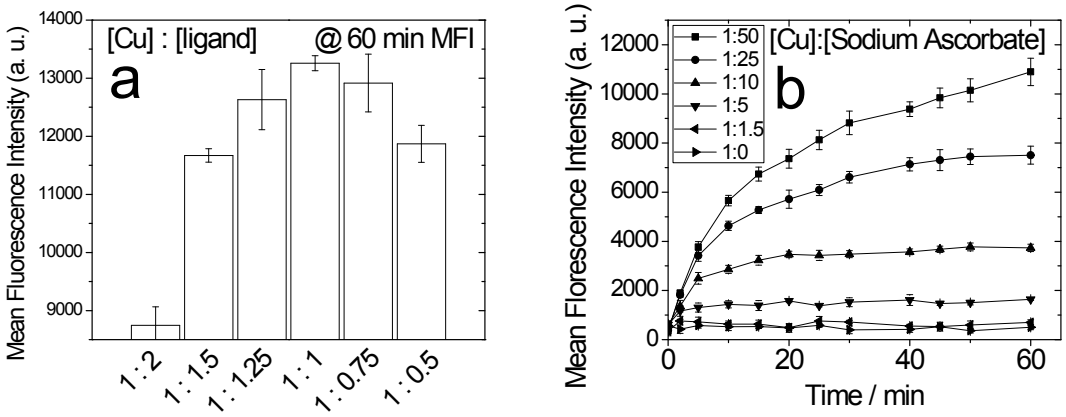


Figure S5 The screening of general condition for kinetic evaluation of catalyst efficiency. a) Optimized Cu/ligand ratio bar curve; b) Screening curves of Cu/ascorbate ratio.

Optimization of click condition:

In the optimization of reaction condition, a screening of Cu/ligand ratio was performed and the Cu/ligand ratio of 1:1 appeared to be the highest in catalytic activity for CuAAC reaction (Figure S5a). Moreover, an investigation of minimal ascorbate addition was accomplished, indicating an effective Cu/ascorbate ratio of 1:50 in this system (Figure S5b).

Data treatment:[6]

(1) Yield in Figure 3 was obtained from the mean fluorescence intensity (MFI) at 60 min with reference to the standard curve in Figure S6 using formula: $\text{Yield} = \frac{\text{MFI} - 331}{17800} \times 100\%$.

(2) The reaction rate constant (k_{obs}) in Figure 3 was determined as the following.

Following the method described by Finn *et al*.,[6] the apparent CuAAC reaction rate constant with ligand **BTTAA** and **1**–**21** was determined using the fluorogenic assay[4] with azido-coumarin and propargyl alcohol as a model CuAAC reaction. Assuming it is a bimolecular reaction between substrates azide and alkyne, the reaction rate constant can be derived from the equations (15)–(24) using the known initial concentrations of azide, alkyne and reaction time. The standard integrated rate law for a bimolecular reaction:

$$\mathrm{A(azide)} + \mathrm{B(alkyne)} \rightarrow \mathrm{P(triazole)}$$

was constructed for the present situation in which $[\mathrm{A}]_0 > [\mathrm{B}]_0$ as follows.

$$\text{Q} \quad \text{rate} = \frac{d[\mathrm{P}]}{d\mathrm{t}} = k[\mathrm{A}][\mathrm{B}] = k([\mathrm{A}]_0 - [\mathrm{P}])([\mathrm{B}]_0 - [\mathrm{P}]) \tag{15}$$

$$\text{from (15)}: \quad \frac{d[\mathrm{P}]}{([\mathrm{A}]_0 - [\mathrm{P}])([\mathrm{B}]_0 - [\mathrm{P}])} = k d\mathrm{t} \tag{16}$$

$$\text{integation on both sides from (15)}: \quad \int_0^{\mathrm{P}} \frac{d[\mathrm{P}]}{([\mathrm{A}]_0 - [\mathrm{P}])([\mathrm{B}]_0 - [\mathrm{P}])} = k\int_0^{\mathrm{t}} d\mathrm{t} \tag{17}$$

$$\text{from (17)}: \quad \int_0^{\mathrm{P}} \{\frac{1}{[\mathrm{A}]_0 - [\mathrm{B}]_0} \times [\frac{1}{([\mathrm{B}]_0 - [\mathrm{P}])} - \frac{1}{([\mathrm{A}]_0 - [\mathrm{P}])}]\} d[\mathrm{P}] = k\mathrm{t} \tag{18}$$

$$\text{then from (18)}: \quad \frac{1}{[\mathrm{A}]_0 - [\mathrm{B}]_0} \int_0^{\mathrm{P}} [\frac{1}{([\mathrm{B}]_0 - [\mathrm{P}])} - \frac{1}{([\mathrm{A}]_0 - [\mathrm{P}])}] d[\mathrm{P}] = k\mathrm{t} \tag{19}$$

$$\text{derive from (19)}: \quad \frac{1}{[\mathrm{A}]_0 - [\mathrm{B}]_0} \{[\ln[\mathrm{B}]_0 - \ln([\mathrm{B}]_0 - [\mathrm{P}])] - [\ln[\mathrm{A}]_0 - \ln([\mathrm{A}]_0 - [\mathrm{P}])]\} = k\mathrm{t} \tag{20}$$

$$\therefore \quad \frac{1}{[\mathrm{A}]_0 - [\mathrm{B}]_0} \ln \frac{([\mathrm{A}]_0 - [\mathrm{P}]) \times [\mathrm{B}]_0}{([\mathrm{B}]_0 - [\mathrm{P}]) \times [\mathrm{A}]_0} = k\mathrm{t} \tag{21}$$

$$\text{written as} \quad \frac{1}{[\mathrm{Azide}]_0 - [\mathrm{Alkyne}]_0} \ln \frac{([\mathrm{Azide}]_0 - [\mathrm{P}]) \times [\mathrm{Alkyne}]_0}{([\mathrm{Alkyne}]_0 - [\mathrm{P}]) \times [\mathrm{Azide}]_0} = k\mathrm{t} \tag{22}$$

$$\text{or solving for [P]}, \quad [\mathrm{P}] = \frac{[\mathrm{A}]_0 [\mathrm{e}^{k\mathrm{t} \times ([\mathrm{A}]_0 - [\mathrm{B}]_0)} - 1]}{\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0} \times \mathrm{e}^{k\mathrm{t} \times ([\mathrm{A}]_0 - [\mathrm{B}]_0)} - 1} \tag{23}$$

$$\text{written as,} \quad [\mathrm{P}] = \frac{[\mathrm{Azide}]_0 [\mathrm{e}^{k\mathrm{t} \times ([\mathrm{Azide}]_0 - [\mathrm{Alkyne}]_0)} - 1]}{\frac{[\mathrm{Azide}]_0}{[\mathrm{Alkyne}]_0} \times \mathrm{e}^{k\mathrm{t} \times ([\mathrm{Azide}]_0 - [\mathrm{Alkyne}]_0)} - 1} \tag{24}$$

In which $[Azide]_0$ = 100 μM, $[Alykne]_0$ = 50 μM, [P] is measured product (triazole-coumarin) concentration at each time point (t = 0–60 min) that is plotted in Figure S6 for all the ligands.

Based on the equation (22), $Y = \frac{1}{[Azide]_0 - [Alkyne]_0} \ln \frac{([Azide]_0 - [P]) \times [Alkyne]_0}{([Alkyne]_0 - [P]) \times [Azide]_0}$ *vs.* time (t) curve is plotted in Figure S7 and the slope is the apparent CuAAC reaction rate constant (k_{obs}).

Kinetics data of CuAAC reaction rate constants for Figure 3:

(1) Plots of triazole-coumarin concentration (as [P]) *vs.* time:

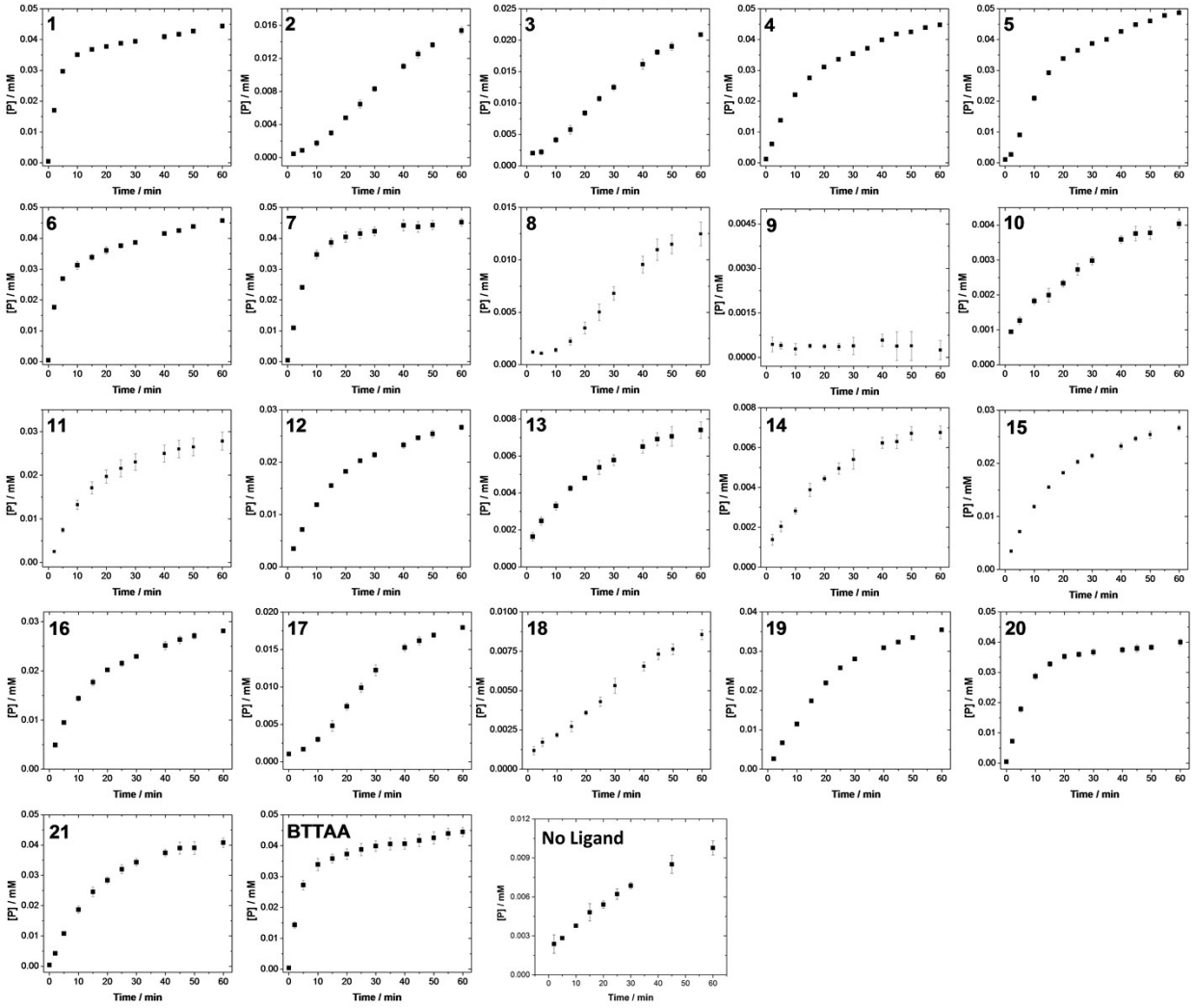


Figure S6 Fluorescence Assay for Measurement of Ligand Catalytic Activity. Propagyl alcohol (50 μM), azido-coumarin (100 μM), copper sulfate (100 μM), ligand (100 μM), sodium ascorbate (5 mM) in 100 μL PBS, 60 min, temp = 24 ± 1 °C and pH = 7.4. The dots represent the observed fluorogenic product concentration (converted by formula MFI = 356 × [P] + 331 (R^2 = 0.9995)) at each time point, each data point is the mean of four replicates and the error bar represents the standard deviation.

(2) Plots of $Y = \frac{1}{[Azide]_0 - [Alkyne]_0} \ln \frac{([Azide]_0 - [P]) \times [Alkyne]_0}{([Alkyne]_0 - [P]) \times [Azide]_0}$ *vs.* Time

Based on the equation (22), the slope is the apparent CuAAC reaction rate constant (k_{obs}). For ligands (**1**, **7**, **10**–**14**, **16**, **20**, **BTTAA**) with two linear fit lines, the first (initial) linear fit was applied for calculation the k_{obs}.

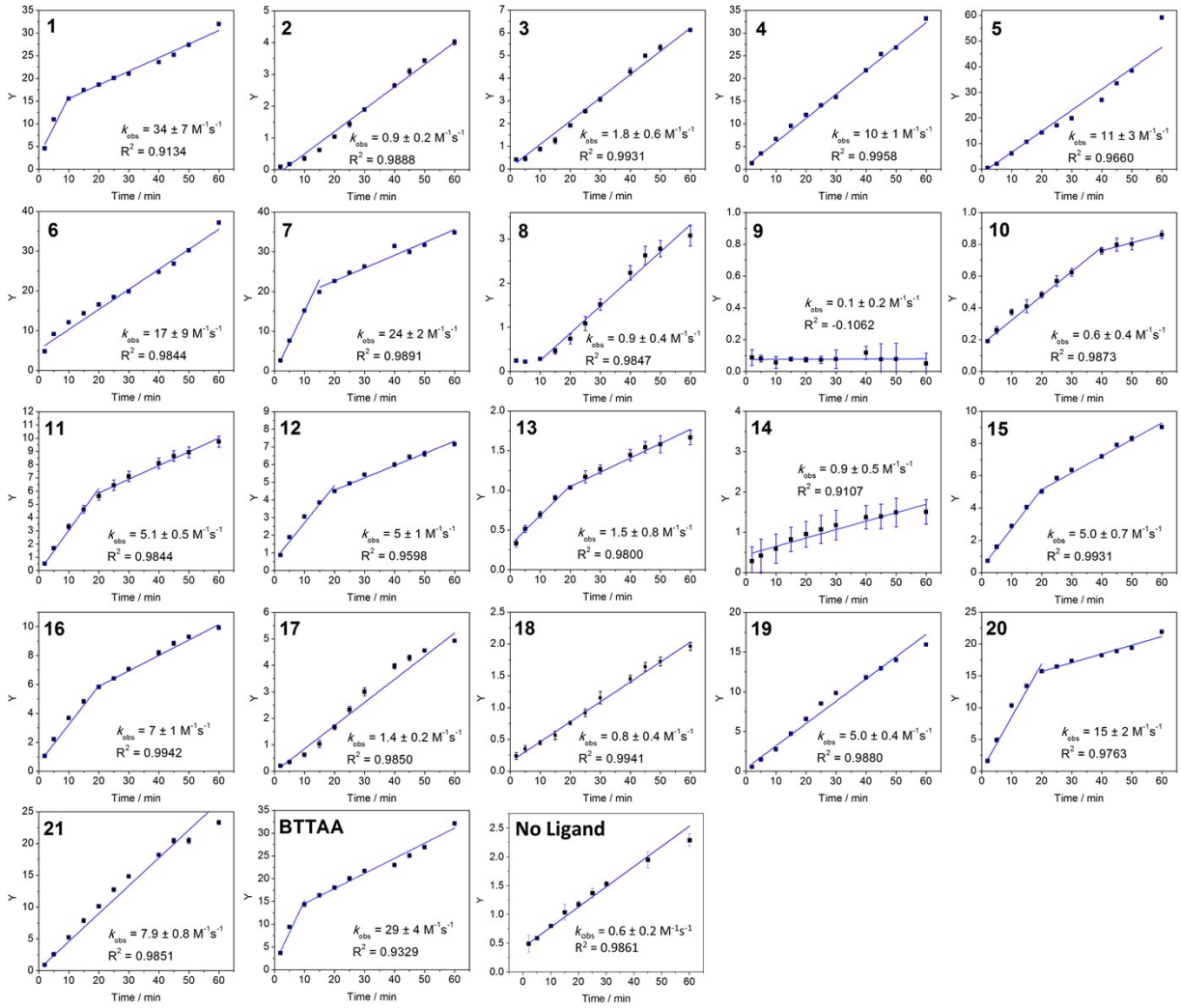


Figure S7 Fluorescence Assay for Measurement of Ligand Catalytic Activity. Propagyl alcohol (50 μM), azido-coumarin (100 μM), copper sulfate (100 μM), ligand (100 μM), sodium ascorbate (5 mM) in 100 μL PBS, 60 min, temp = 24 ± 1 °C and pH = 7.4. The dots mark observed data points, each data point is the mean of four replicates and the experimental error in rate constants upon repeat measurement is < 15% (usually ca. 10%), except ligands **9** and **15** where the catalytic activity is low; the solid blue line is the best second-order fit.

Tetraethylene glycol (TEG) Assay:

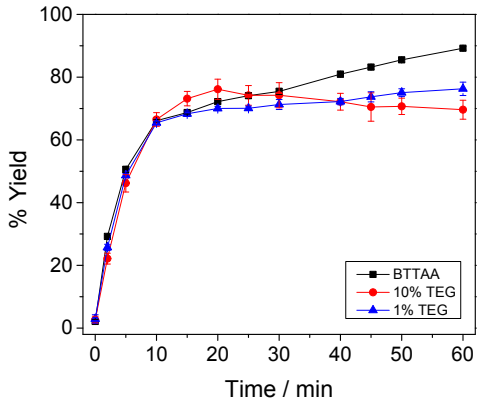


Figure S8. Fluorogenic Assay for Measurement of ligand catalytic activity. Propagyl alcohol (50 μM), azido-coumarin (100 μM), copper sulfate (100 μM), BTTAA (100 μM), sodium ascorbate (5 mM) in 100 μL PBS, 60 min, temp = 24 ± 1 °C and pH = 7.4. The data are converted to % yield using the calibration curve in Figure S4 for fluorescence intensity conversion) during the course of the reaction in 60 min. Each data point is the mean of four replicates and the error bar represents the standard deviation. 10% TEG represents 10 wt% tetraethylene glycol in solution.

E. Characterization of Cu(I)-Ligand-Alkyne Complexes

Stock solutions:

$CuSO_4$: 1 mM stock solution in Milli-Q water.

Ligand: 1 mM stock solution in Milli-Q water.

2-[2-(2-propyn-1-yloxyl)ethoxy]ethanol: 1 mM stock solution in Milli-Q water.

Sodium Ascorbate: 10 mM stock solution in Milli-Q water.

Final concentrations of reagents in the 1000 μL reaction mixture:

$CuSO_4$: 100 μM

Ligand: 100 μM

2-[2-(2-propyn-1-yloxyl)ethoxy]ethanol: 50 μM

Sodium ascorbate: 1000 μM

Sample preparation:

Sample preparation was conducted in an anaerobic chamber filled with 5% H_2/N_2 circling through a pad of catalyst to maintain $[O_2] < 1$ ppm. Stock solutions were added by pipetting and mixed by vortexing.

(1) In an empty Eppendorf tube (1.5 mL), add 100 μL of 1 mM ligand stock solution.
(2) Add 50 μL of 1 mM alkyne stock solution and mixed by aspiration with the pipette.
(3) Add 100 μL of 1 mM $CuSO_4$ stock solution and mixed by aspiration with the pipette.
(4) Add 100 μL of 10 mM sodium ascorbate stock solution and mixed by vortexing for 30 second.
(5) Use a 250 μL HPLC syringe to inject the sample solution into the ESI-MS instrument.

ESI-MS condition:

Positive ion ESI-MS data were acquired using a Thermo Finnigan LCQ Deca XP ion trap mass spectrometer operated with Xcalibur® software package (Thermo Fisher Scientific Inc.). The spectra were scaned in the *m/z* range from 400 to 1200. An optimization procedure carried out at the beginning of this work was conducted to achieve a good signal intensity. The ESI spray condition was: flow rate 10 μL/min; electrospray capillary voltage: 4.49 kV; source temperature: 40 ^oC. Typically, all MS measurements were carried out 3 min after mixing the reactants and the accumulated ESI-MS time is 5 min.

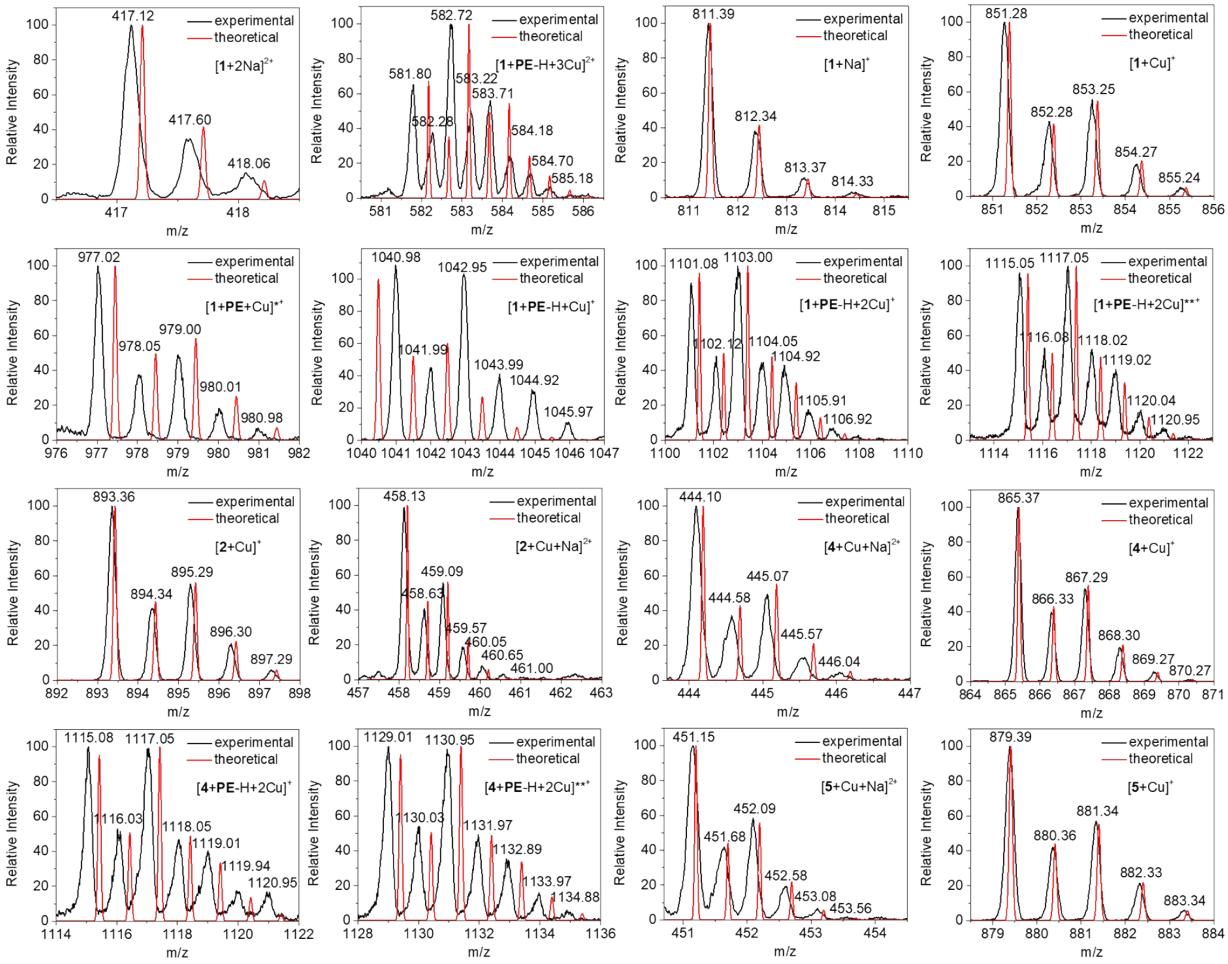


Figure S9 Isotopic pattern for Cu(I)-ligand-alkyne species in Figure 5. Experimental isotopic patterns were obtained by zoom scans centered on selected m/z. Theoretical isotopic patterns (red) of the proposed ions were calculated using IsoPro 3.0, and overlaid on the experimental isotope pattern (black).

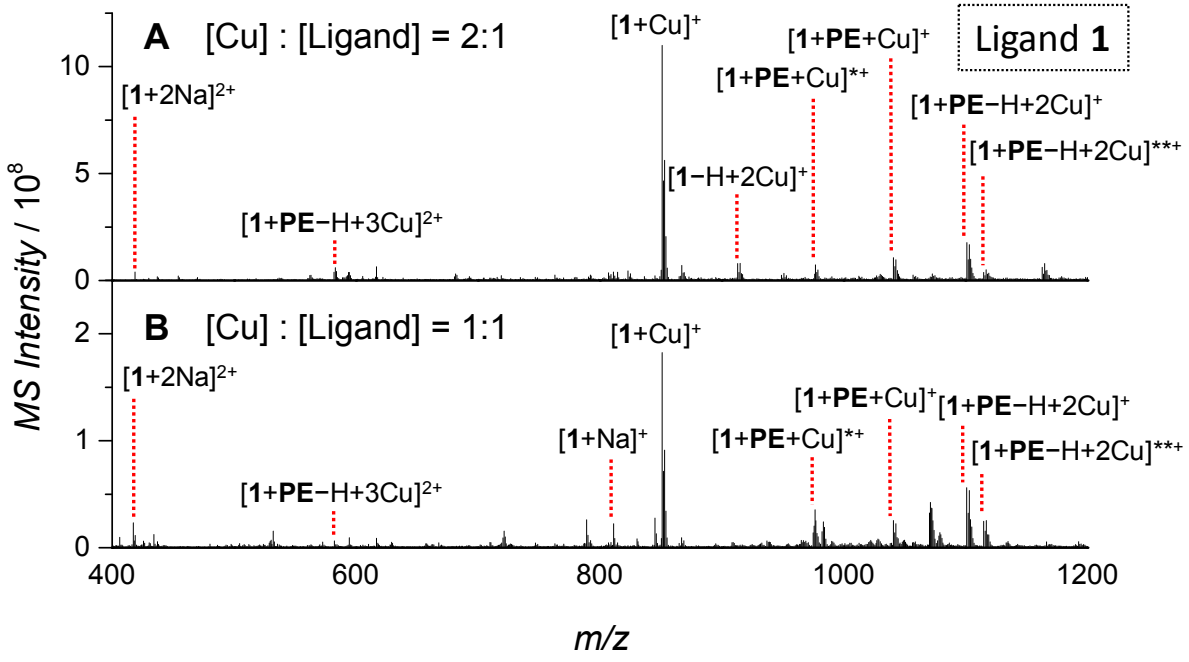


Figure S10 ESI-MS spectra of the Cu(I)-ligand-alkyne (A) 1:0.5:0.5 and (B) 1:1:0.5 mixture in water. $CuSO_4$ (100 μM), ligand **1** (100 μM in A and 50 μM in B), **PE** (50 μM), Na ascorbate (1 mM).

Table S3 The MS intensity of Cu(I)-acetylides in solution containing 100 μM Cu(I), 50/100 μM ligand **1**, and 50 μM **PE**; the molar fraction X_0–X_3 of free, mono-, di-, and tri-Cu(I) species calculated from the MS intensities

Cu/ligand	MS intensity / 10^7									Molar fraction			
	[**1**+**PE**+3Cu]$^{2+}$	[**1**+**PE**−H+2Cu]$^{+}$	[**1**+**PE**−H+2Cu]$^{**+}$	[**1**−H +2Cu]$^{+}$	[**1**+Cu]$^{+}$	[**1**+**PE**+Cu]$^{*+}$	[**1**+**PE**+Cu]$^{+}$	[**1**+2Na]$^{2+}$	[**1**+Na]$^{+}$	X_0	X_1	X_2	X_3
2:1	6.03	17.74	5.07	8.05	109.94	7.35	10.65	3.95	4.00	0.045	0.727	0.175	0.034
1:1	0.63	5.61	2.54	0.24	18.24	3.55	2.54	1.15	2.24	0.083	0.594	0.205	0.015

F. Peptide Oxidation Assay

Peptide synthesis, purification and characterization

The synthesis of azido-peptide AP: The peptide GGHGGH was synthesized manually through standard stepwise Fmoc-based solid-phase peptide synthesis (SPPS) protocols at 60 °C using conventional heating, with Rink Amide MBHA resin (Novabiochem, Darmstadt, Germany), 0.3 mmol of N-Hydroxybenzotriazole (HOBt) and 0.3 mmol of *N*,*N*′-diisopropylcarbodiimde (DIC, Sigma-Aldrich) (1:1) as the coupling reagents, and 20% dimethyl sulfoxide (DMSO)/*N*-Methyl-2-pyrrolidone (NMP) as the solvent. The coupling reaction was allowed to proceed for 2 h and each coupling step was repeated with a freshly prepared solution of HOBt and DIC before the peptide was deprotected. After coupling the last amino acid G, the amino group was deprotected, and coupled with 8-azido octanoic acid (30 equiv.) in the same condition. Then, the peptide was deprotected and cleaved from the resin in presence of 95% TFA/2.5% triisopropylsilane/2.5% water for 4 h at 37 °C. The crude peptides were precipitated from the mixtures with ice-cold diisopropyl ether, separated by centrifugation, extracted with 0.1% TFA/water and 50% acetonitrile/0.09% TFA/water and lyophilized to give 310 mg of the crude peptide. The crude peptide was dissolved in 500 uL of H_2O and purified with a Shimadzu C-18 RP-HPLC (LC-20AB) system using XTerra MS C18 OBD prep column (125 Å, 5 µm, 19 mm × 50 mm) with gradient elution (2-–70%, 0.1% formic acid in acetonitrile/0.1% formic acid in H_2O, 10 min). Yield 252 mg azido-peptide **AP** as white flocculence. The purified peptides were characterized by liquid chromatography/electrospray ionization–mass spectrometry (LC/ESI–MS) using a Thermo Finnigan LCQ Deca XP quadrupole (ESI) mass spectrometer. m/z: $[M+H]^+$ calculated for $C_{28}H_{43}N_{14}O_7$, 687.3; found: 687.2.

The synthesis of triazolyl-peptide TP: The azido-peptide N_3-GGHGGH was synthesized as above description. The CuAAC reaction of azido-peptide (0.02 mmol) with propargyl alcohol (1 mmol, 58 µL), tristriazolylmethylamine ligand **1** (0.05 mmol, 30 mg), $CuSO_4$ (0.05 mmol, 12.5 mg) and sodium ascorbate (0.3 mmol, 60 mg) was proceed for 12 h in H_2O at room temperature before the peptide was deprotected. After completing the solid phase CuAAC reaction, the triazolyl-peptide was deprotected and cleaved from the resin in presence of 95% TFA/2.5% triisopropylsilane/2.5% water for 4 h at 37 °C. The purification was the same as the protocol of azido-peptide **AP**. Yield 8 mg triazolyl-peptide **23** as white powder. The purified peptides were characterized by liquid chromatography/electrospray ionization–mass spectrometry (LC/ESI–MS) using a Thermo Finnigan LCQ Deca XP quadrupole (ESI) mass spectrometer. m/z: $[M+H]^+$ calculated for $C_{31}H_{47}N_{14}O_8$, 743.4; found: 743.4.

The CuAAC reaction of azido-peptide AP and propargyl alcohol with ligand 1, 5 or BTTAA

Preparation of stock solutions:

$CuSO_4$: 1 mM stock solution in H_2O.

Ligand: 1 mM stock solution in H_2O.

Azido-peptide (*Shep I* (15-20) Gly-Gly-His-Gly-Gly-His): 1 mM stock solution in H_2O.

Propargyl alcohol: 1 mM stock solution in H_2O.

Sodium Ascorbate: 3.3 mM stock solution in H_2O.

Diethylenetriamine-pentaacetic acid pentasodium salt (*Na_5DTPA):* 2.5 mM stock solution in H_2O.

Final concentrations of the reaction mixture (200 µL):

$CuSO_4$: 50 µM

Ligand: 100 µM (ligand to copper ratio = 2:1)

Azido-coumarin: 50 µM

Propargyl alcohol: 50 µM

Sodium ascorbate: 500 µM

Diethylenetriamine-pentaacetic acid pentasodium salt (Na_5DTPA): 250 µM

Protocol for peptide oxidation assay:

At 24 ± 1 °C, to a 0.5 mL microcentrifuge tube with locking lid, add the reagents in the following order:

(1) 100 µL of Milli-Q H_2O.

(2) 20 µL of 1.0 mM ligand stock solution.

(3) 10 µL of 1.0 mM $CuSO_4$ stock solution.

(4) 10 µL of 1.0 mM azido-peptide stock solution.

(5) 10 µL of 1.0 mM propargyl alcohol stock solution.

(6) 30 µL of 3.3 mM sodium ascorbate stock solution. Rapidly aspirate the mixture and start measurement.

(7) At the specified time point, quench the CuAAC reaction by adding 20 µL of 2.5 mM Na_5DTPA stock solution and analysis the reaction mixture immediately by LC/ESI-MS. For the LC-MS, 1 µL of the sample was injected and the separation condition is in a gradient elution (2–70%, 0.1% formic acid in acetonitrile/0.1% formic acid in H_2O, 10 min) through a C18 column (Kinetex™ 5 µm XB-C18 100 Å, LC Column 50 × 4.6 mm, Phenomenex Inc.). The data are summarized in Figure S12. Each data point represented the mean of three repeated experiments and standard deviation.

(8) The control groups are the samples including all the components except ligand (adding additional 20 µL H_2O to instead the ligand stock solution).

The liquid chromatograms of the reaction mixture at 60 min without/with ligands.

The liquid chromatography (LC) separation condition was in a gradient elution through a C18 column as described above. All the LC experiments were in the same separation condition. In Figure S12, the "MDS" represented the mean detector signal intensity obtained by three replicates. The mass spectra of each compound were obtained from the selected ion monitoring (SIM) chromatograms (Figure S11). The parameters in use were the plot type by mass range of the selected compound in a mass window of molecule weight (MW) ± 0.5 amu, see Figure S12.

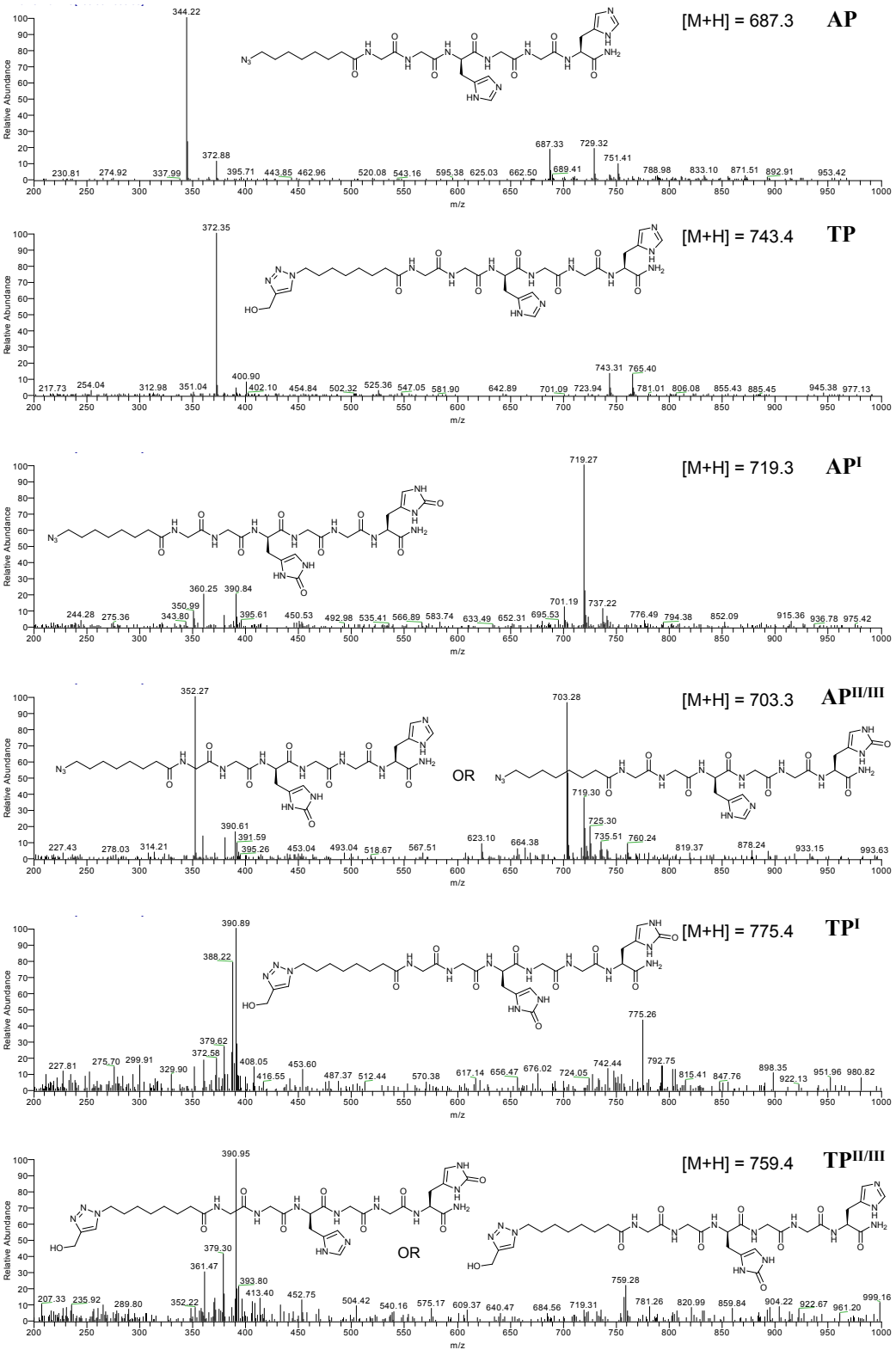


Figure S11 Mass spectra of peptides (**AP**, **TP**, $\mathbf{AP^{I/II/III}}$, and $\mathbf{TP^{I/II/III}}$) derived from the selected ion monitoring (SIM) LC-MS of the reaction mixture at 60 min without ligand.

Table S4 The liquid chromatogram parameters (mass and retention time) of the selected compounds

Compound	Mass [M+H]	Retention Time/min[a]
AP	687	5.94
TP	743	4.53
AP^{I} [b]	719	6.48
AP$^{II/III}$ [b]	703	5.63/6.71
TP^{I} [b]	775	6.19
TP$^{II/III}$ [b]	759	5.75/5.84
1	789	5.80
5	817	5.82
BTTAA	431	6.88

[a] All the liquid chromatograms were in the same condition described above. [b] The major oxidized peptides were derived from the CuAAC reaction mixture at 60 min with copper and ascorbate and without ligand.

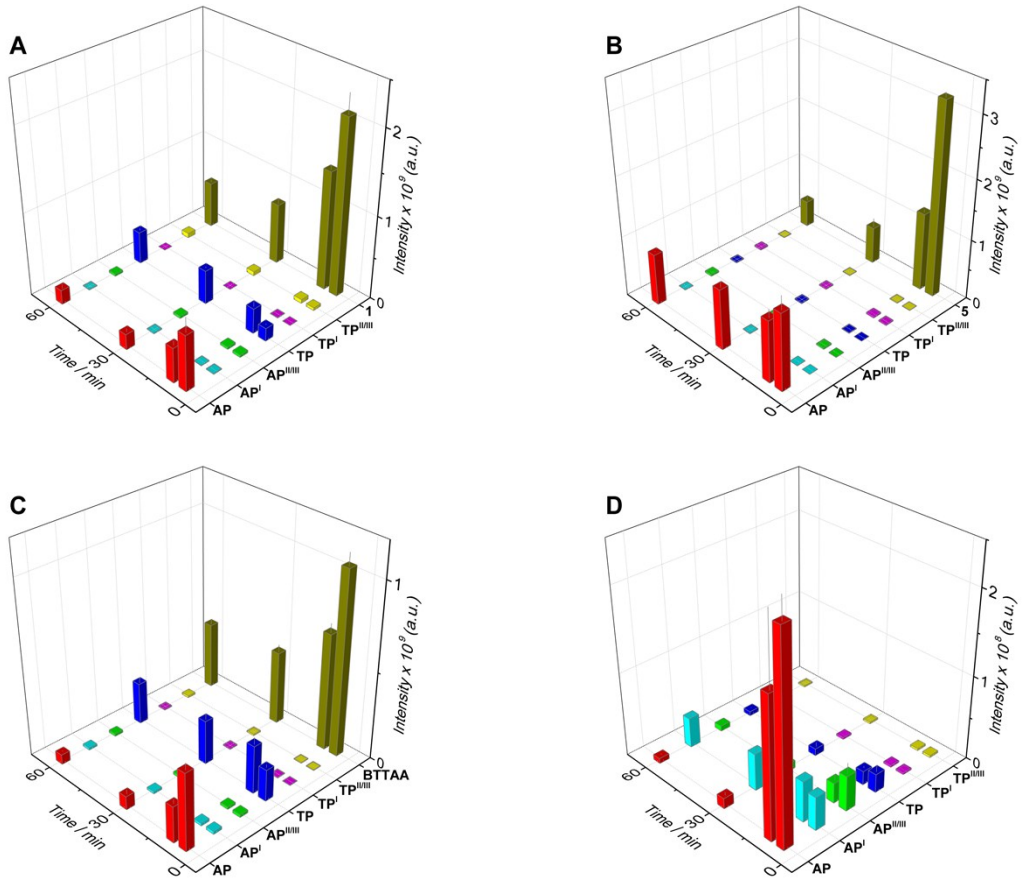


Figure S12 The LC-MS mean detector signal intensity and standard deviation (SD) of azido-peptide **AP**, triazolyl peptide **TP**, the oxidized peptides **AP^{I}**, **AP^{II}**, **AP^{III}**, **TP^{I}**, **TP^{II}** and **TP^{III}** during CuAAC reaction in the presence of ligands **1** (A), **5** (B), and **BTTAA** (C)/without ligand (D) at various time points.

Calibration curve correlating the mean detector signal (MDS) with the azido-peptide concentration:

(1) Prepare a serial dilution of the azido-peptide **AP**, from 0.5 μM, 5 μM, 10 μM, 25 μM, 50 μM to 100 μM in H_2O.

(2) Measure the detector signal (peak area) of this series of azido-peptide solution. The MDS for each concentration was obtained from three replicate measurements and the error bar represented the standard deviation (SD).

(3) Plot the mean MDS ± SD *vs.* [**AP**] (Figure S13) which can be linearly fit to give a linear relationship between MDS and [**AP**].
(4) The fitting line MDS = 2.90 × 10^7 × [**AP**] – 1.59 × 10^6 (R^2 = 0.9989) (Eq. 25) serves as the calibration curve for estimating the concentration of azido-peptide **AP** the data was summarized in Figure 6.

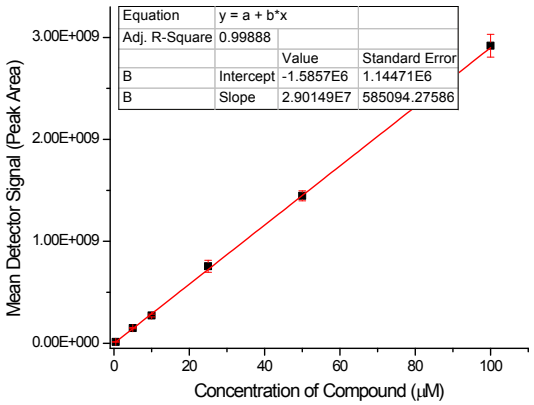


Figure S13 Standard curve for estimating the concentration of azido-peptide **AP**. The mean detector signal was obtained from a series of aqueous solutions of azido-peptide with the concentration from 0.5 to 100 μM. Each data point is the mean of three replicates and the error bar represents the standard deviation. The red line is the best linear fit of the data point, which is expressed as MDS = 2.90 × 10^7 × [**AP**] – 1.59 × 10^6 (R^2 = 0.9989).

Calibration curve correlating the mean detector signal (MDS) with triazolyl-peptide concentration:
(1) Prepare a serial dilution of the triazolyl-peptide **TP**, from 2 μM, 4 μM, 8 μM, 15 μM, 50 μM to 100 μM in H_2O.
(2) Measure the detector signal (peak area) of this series of triazolyl-peptide solution. The MDS for each concentration was obtained from three replicate measurements and the error bar represented the standard deviation (SD).
(3) Plot the mean MDS ± SD *vs.* [**TP**] (Figure S14) which can be linearly fit to give a linear relationship between MDS and [**TP**].
(4) The fitting line MDS = 2.52 × 10^7 × [**TP**] – 8.97 × 10^6 (R^2 = 0.9977) (Eq. 26) serves as the calibration curve for estimating the concentration of triazolyl-peptide **TP**. All the data was summarized in Figure 6.

Calibration curve correlating the mean detector signal (MDS) with the ligand 1 concentration:
(1) Prepare a serial dilution of the ligand **1**, from 5 μM, 10 μM, 25 μM, 100 μM to 200 μM, in the 50 μM azido-peptide **AP** and 50 μM propargyl alcohol solution.
(2) Measure the detector signal (peak area) of this series of ligand **1** solution. The MDS for each concentration was obtained from three replicate measurements and the error bar represented the standard deviation (SD).
(3) Plot the mean MDS ± SD *vs.* [**1**] (Figure S15) which can be linearly fit to give a linear relationship between MDS and [**1**].
(4) The fitting line MDS = 3.17 × 10^7 × [**1**] – 4.38 × 10^7 (R^2 = 0.9931) (Eq. 27) serves as the calibration curve for estimating the concentration of the ligand **1**.

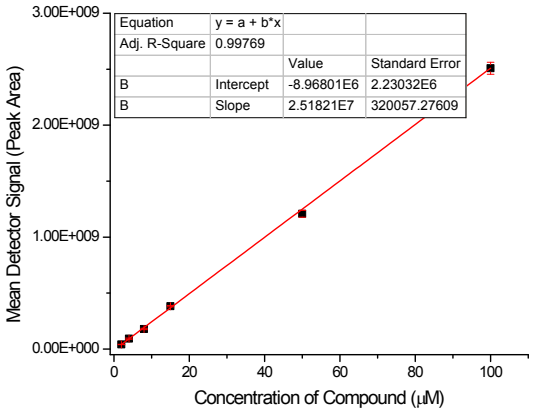


Figure S14 Standard curve for estimating the concentration of triazolyl-peptide **TP**. The mean detector signal was obtained from a series of aqueous solutions of triazolyl-peptide with the concentration from 2 to 100 μM. Each data point is the mean of three replicates and the error bar represents the standard deviation. The red line is the best linear fit of the data point, which is expressed as MDS = $2.52 \times 10^7 \times$ [**TP**] – 8.97×10^6 ($R^2 = 0.9977$).

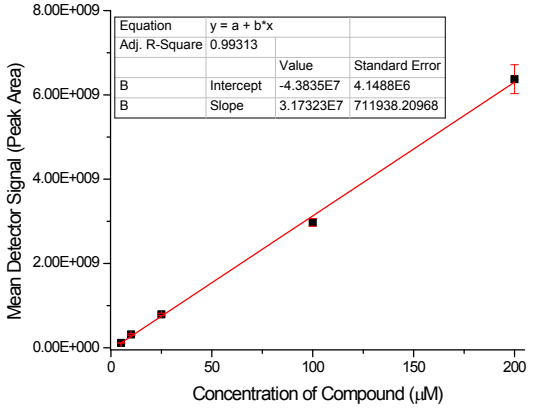


Figure S15 Standard curve for estimating the concentration of ligand **1**. The mean detector signal was obtained from a series of aqueous solutions of ligand **1** with the concentration from 5 to 200 μM, azido-peptide **AP** (50 μM) and propargyl alcohol (50 μM). Each data point is the mean of three replicates and the error bar represents the standard deviation. The red line is the best linear fit of the data point, which is expressed as MDS = $3.17 \times 10^7 \times$ [**1**] – 4.38×10^7 ($R^2 = 0.9931$).

Calibration curve correlating the mean detector signal (MDS) with the ligand 5 concentration:

(1) Prepare a serial dilution of the ligand **5**, from 5 μM, 10 μM, 20 μM, 40 μM, 100 μM to 200 μM, in the 50 μM azido-peptide **AP** and 50 μM propargyl alcohol solution.

(2) Measure the detector signal (peak area) of this series of ligand **5** solution. The MDS for each concentration was obtained from three replicate measurements and the error bar represented the standard deviation (SD).

(3) Plot the mean MDS ± SD *vs.* [**5**] (Figure S16) which can be linearly fit to give a linear relationship between MDS and [**5**].

(4) The fitting line MDS = $3.26 \times 10^7 \times$ [**5**] – 3.23×10^7 ($R^2 = 0.9984$) (Eq. 28) serves as the calibration curve for estimating the concentration of the ligand **5**.

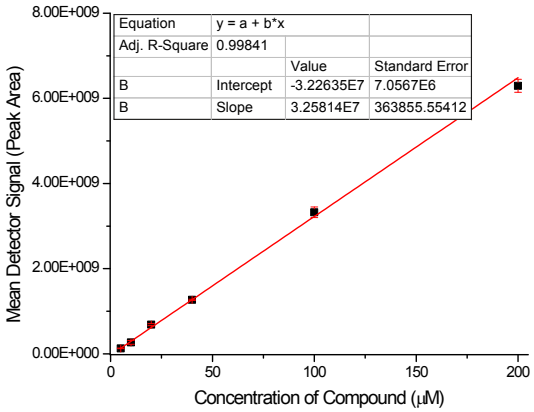


Figure S16 Standard curve for estimating the concentration of ligand **5**. The mean detector signal was obtained from a series of aqueous solutions of ligand **5** with the concentration from 5 to 200 μM, azido-peptide **AP** (50 μM) and propargyl alcohol (50 μM). Each data point is the mean of three replicates and the error bar represents the standard deviation. The red line is the best linear fit of the data point, which is expressed as MDS = $3.26 \times 10^7 \times$ [**5**] – 3.23×10^7 ($R^2 = 0.9984$).

Calibration curve correlating the mean detector signal (MDS) with the BTTAA concentration:

(1) Prepare a serial dilution of the ligand **BTTAA**, from 5 μM, 15 μM, 30 μM, 100 μM to 200 μM, in the 50 μM azido-peptide **AP** and 50 μM propargyl alcohol solution.

(2) Measure the detector signal (peak area) of this series of ligand **BTTAA** solution. The MDS for each concentration was obtained from three replicate measurements and the error bar represented the standard deviation (SD).

(3) Plot the mean MDS ± SD *vs.* [**BTTAA**] (Figure S17) which can be linearly fit to give a linear relationship between MDS and [**BTTAA**].

(4) The fitting line MDS = $1.51 \times 10^7 \times$ [**BTTAA**] – 1.43×10^7 ($R^2 = 0.9962$) (Eq. 29) serves as the calibration curve for estimating the concentration of the **BTTAA**.

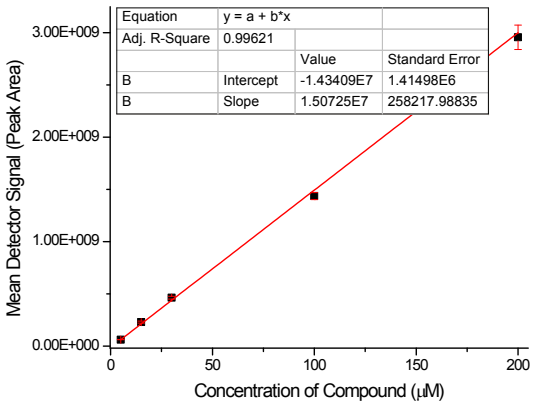


Figure S17 Standard curve for estimating the concentration of ligand **BTTAA**. The mean detector signal was obtained from a series of aqueous solutions of ligand **BTTAA** with the concentration from 5 to 200 μM, azido-peptide **AP** (50 μM) and propargyl alcohol (50 μM). Each data point is the mean of three replicates and the error bar represents the standard deviation. The red line is the best linear fit of the data point, which is expressed as MDS = $1.51 \times 10^7 \times$ [**BTTAA**] – 1.43×10^7 ($R^2 = 0.9962$).

% Ligand remaining

The concentrations of the remaining ligand were obtained based on the equation 27–29 above. Four different points were recorded, 5 min, 10 min, 30 min, and 60 min, respectively to access the changes of ligands during CuAAC reaction. All the data was summarized in Table 2.

Table S5 Mass spectrum of ligand **1** fragments

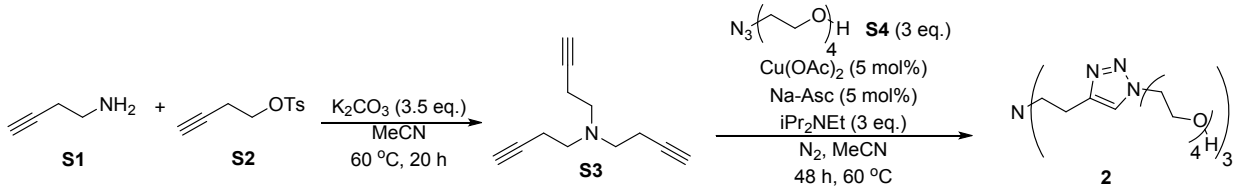
Fragment Mass	**Fragment Composition**		
Probable ligand fragment compositions of alcohol intermediates[a]			
745.4	OEG [4,4,3]		
701.4	OEG [4,3,3]	OEG [4,4,2]	
657.3	OEG [4,3,2]	OEG [3,3,3]	OEG [4,4,1]
613.3	OEG [4,3,1]	OEG [4,2,2]	OEG [3,3,2]
569.3 (581.3)	OEG [4,2,1]	OEG [3,3,1]	OEG [3,2,2]
Probable ligand fragment compositions of aldehyde intermediates[b]			
787.4	OEG [4,4,4]		
743.3	OEG [4,4,3]		
699.3	OEG [4,3,3]	OEG [4,4,2]	
655.3	OEG [4,3,2]	OEG [4,4,1]	OEG [3,3,3]
611.3	OEG [4,3,1]	OEG [4,2,2]	OEG [3,3,2]
Probable ligand fragment compositions of acid intermediates[c]			
803.4	OEG [4,4,4]		
759.4	OEG [4,4,3]		
671.3	OEG [4,3,2]	OEG [4,4,1]	OEG [3,3,3]
Probable ligand fragment compositions of ethyl ether intermediates[d]			
773.4	OEG [4,4,4]		
729.4	OEG [4,4,3]		
685.4	OEG [4,4,2]	OEG [4,3,3]	
641.3	OEG [4,4,1]	OEG [4,3,2]	OEG [3,3,3]
625.2	OEG [4,3,1]	OEG [4,2,2]	OEG [3,3,2]
597.3	OEG [4,3,1]	OEG [4,2,2]	OEG [3,3,2]
Selective probable ligand fragment compositions of mixed intermediates[e]			
683.3	OEG [3,2,1]	OEG [2,2,2]	

[a] Ligand fragments are labeled in the mass spectrum with red balls.
[b] Ligand fragments are labeled in the mass spectrum with yelow balls.
[c] Ligand fragments are labeled in the mass spectrum with blue balls.
[d] Ligand fragments are labeled in the mass spectrum with green balls.
[d] Ligand fragments are labeled in the mass spectrum with blue and yellow balls.

G. Synthesis of tripodal amine ligands

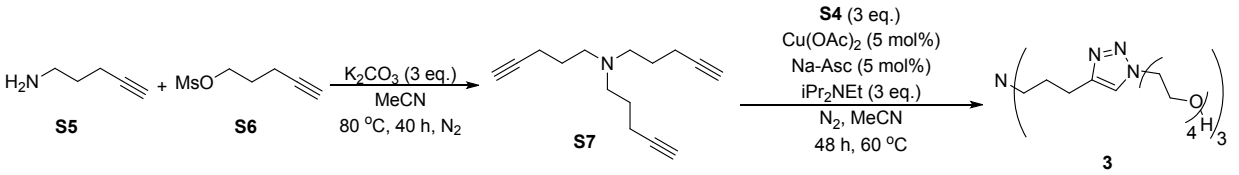
***Tris-triazole-(1-tetraethylene glycol-4-(but-3-yn-1-yl))amine* (2):** A mixture of **S1** (69 mg, 1.0 mmol), **S2** (493 mg, 2.20 mmol) and K_2CO_3 (483 mg, 3.50 mmol) in MeCN (4 mL) was stirred for 20 h at 60 °C. The solvent was removed with a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S3** (74 mg, 43%) that was used for the next step.

A stirred solution of **S3** (143.0 mg, 0.632 mmol) and **S4** (415.7 mg, 1.896 mmol) in MeCN (2.50 mL) was treated sequentially with diisopropylethylamine (81.8 mg, 0.632 mmol), $Cu(OAc)_2 \cdot H_2O$ (6.3 mg, 0.063 mmol) and sodium ascorbate (25.0 mg, 0.126 mmol). The mixture was stirred at 60 °C for 48 h under nitrogen, cooled down to room temperature, and treated with Chelex® 100 resin (Bio-Rad Laboratories, Inc.) with stirring for 30 min to remove copper. After the solvent was removed, the residue was purified by flash chromatography on silica gel with EtOAc / MeOH (9:1, v/v) as the eluent to give the product **2** (150 mg, 35.7 %) as a light yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 3H), 4.45 (t, *J* = 5 Hz, 6H), 3.79 (t, *J* = 5 Hz, 6H), 3.67 (t, *J* = 5 Hz, 6H), 3.61–3.59 (m, 6H), 3.56–3.53 (m, 24H), 2.88–2.79 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.00, 122.74, 72.65, 70.59, 70.52, 70.44, 70.31, 69.62, 61.53, 53.42, 50.13, 23.69. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{36}H_{66}N_{10}O_{12}$ 831.4934; found 831.4927.

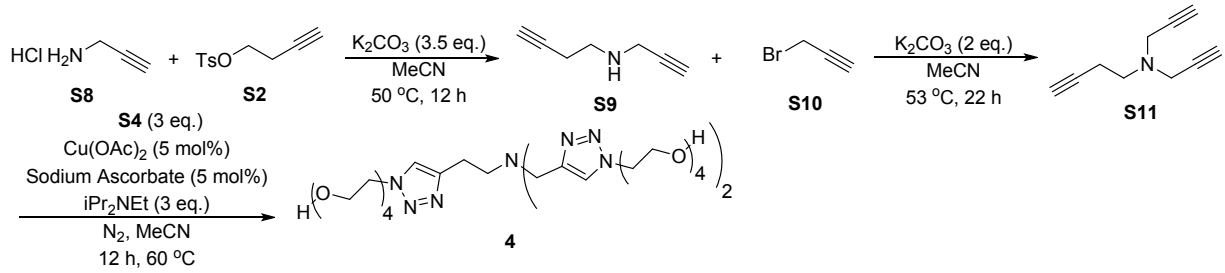


***Tris-triazole-(1-tetraethylene glycol-4-(pent-4-yn-1-yl))amine* (3):** A mixture of **S5** (83 mg, 1.0 mmol), **S6** (356 mg, 2.20 mmol) and K_2CO_3 (483 mg, 3.50 mmol) in MeCN (4 mL) was stirred for 40 h at 80 °C. The solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S7** (16 mg, 7.4 %) that was used for the next step.

A stirred solution of **S7** (143.0 mg, 0.632 mmol) and **S4** (415.7 mg, 1.896 mmol) in MeCN (2.50 mL) was treated sequentially with diisopropylethylamine (81.8 mg, 0.632 mmol), and $Cu(OAc)_2 \cdot H_2O$ (6.3 mg, 0.063 mmol) and sodium ascorbate (25.0 mg, 0.126 mmol). The mixture was stirred at 60 °C for 48 h under nitrogen, after then cooled down to room temperature and Chelex® 100 resin was added and stirred for 30 min to remove copper. The solvent was removed by a rotovap under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc / MeOH (9:1, v/v) as the eluent to give the product **3** (689 mg, 35.9 %) as a light yellow viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.56 (s, 3H), 4.52 (t, *J* = 5 Hz, 6H), 3.86 (t, *J* = 5 Hz, 6H), 3.72 (t, *J* = 4.5 Hz, 6H), 3.66 (d, *J* = 5 Hz, 6H), 3.61 (s, 24H), 2.71 (t, *J* = 7.5 Hz, 6H), 2.50 (t, *J* = 7.5 Hz, 6H), 1.81 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.80, 122.20, 72.65, 70.59, 70.51, 70.43, 70.31, 69.64, 61.52, 53.41, 50.10, 26.87, 23.57. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{39}H_{72}N_{10}O_{12}$ 873.5404; found 873.5392.



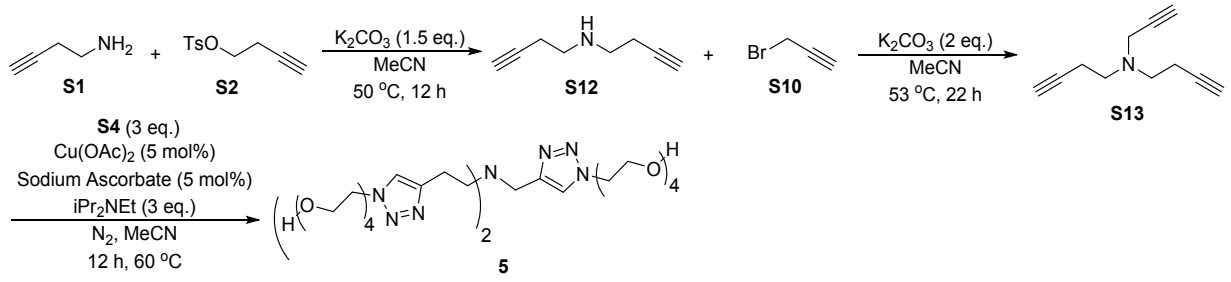
***N-(1-tetraethylene glycol)triazol-4-ethyl-N,N-bis(1-tetraethylene glycol)triazol-4-methylamine* (4):** A mixture of **S8** (92 mg, 1.0 mmol), **S2** (336 mg, 1.50 mmol) and K_2CO_3 (276 mg, 2.00 mmol) in MeCN (4 mL) was stirred for 12 h at 50 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S11** (145 mg, 52.2%) that was used for the next step. The synthesis procedure for compound **4** is similar to compound **2**. 572 mg of **4** was obtained as colorless oil in 71.2 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.78 (s, 2H), 7.59 (s, 1H), 4.48 (t, *J* = 5 Hz, 4H), 4.43 (t, *J* = 5 Hz, 4H), 3.82–3.78 (m, 6H), 3.75 (s, 4H), 3.66–3.63 (m, 6H), 3.58–3.56 (m, 6H), 3.53–3.51 (m, 24H), 2.93 (t, *J* = 7.75 Hz, 2H), 2.73 (t, *J* = 7.75 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.66, 143.65, 124.62, 122.84, 72.56, 72.54, 70.47, 70.46, 70.39, 70.34, 70.31, 70.19, 70.17, 70.17, 69.45, 69.43, 61.39, 52.65, 50.26, 50.11, 49.98, 47.48, 23.69. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{34}H_{62}N_{10}O_{12}$ 803.4621; found 803.4611.



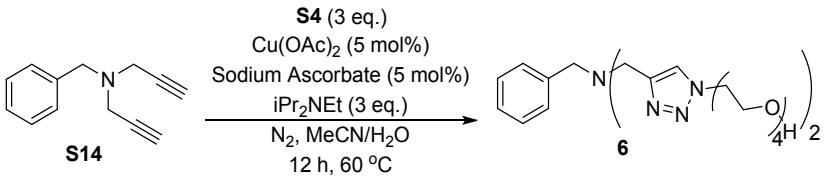
***N-(1-tetraethylene glycol)triazol-4-methyl-N,N-bis(1-tetraethylene glycol)triazol-4-ethylamine* (5):** A mixture of **S1** (69 mg, 1.0 mmol), **S2** (336 mg, 1.50 mmol) and K_2CO_3 (276 mg, 2.00 mmol) in MeCN (4 mL) was stirred for 12 h at 50 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S12** (71 mg, 41%) that was used for the next step. The triyne **S13** was prepared using the same procedure with **S10** (77 mg, 0.65 mmol) and K_2CO_3 (162 mg, 1.17 mmol) in MeCN (4 mL) at 53ºC for 22 h in 81 % yield (76 mg).

Compound **5** as a colorless oil was prepared similarly to compound **2** in 93.6 % yield (365 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 (s, 1H), 7.39 (s, 2H), 4.31 (t, *J* = 5 Hz, 2H), 4.27 (t, *J* = 5 Hz, 4H), 3.82 (br, 3H), 3.68 (s, 2H), 3.65–3.61 (m, 4H), 3.48 (t, *J* = 5 Hz, 6H), 3.40–3.39 (m, 6H), 3.37–3.34 (m, 26H), 2.69 (t, *J* = 6.75 Hz, 4H), 2.62 (t, *J* = 6.5 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.22, 143.39, 123.75, 122.34, 72.11, 72.09, 69.94, 69.91, 69.90, 69.88, 69.81, 69.69, 69.67, 68.97, 68.94, 60.77, 52.46,

49.63, 49.52, 49.47, 47.64, 23.09. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{35}H_{64}N_{10}O_{12}$ 817.4778; found 817.4775.



***N-benzyl-bis-(1-tetraethylene glycol)triazol-4-methylamine* (6):** A stirred solution of **S14**[7] (200 mg, 1.09 mmol) and **S4** (720 mg, 3.28 mmol) in mixed MeCN (2 mL) and H_2O (0.5 mL) was treated sequentially with diisopropylethylamine (300 mg, 2.32 mmol), $Cu(OAc)_2$ (11 mg, 0.055 mmol) and sodium ascorbate (12 mg, 0.050 mmol). The mixture was stirred at 60 °C 12 h under nitrogen and cooled down to room temperature. Curisorb^T (Seachem Laboratories, Inc.) was added and stirred for 30 min to remove copper. After filtration, the solvent was removed, and the residue was purified by flash chromatography on silica gel with EtOAc / MeOH (3:1, v/v) as the eluent to give the product **6** (279 mg, 41.2 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.40 (d, J = 7 Hz, 2H), 7.31, (t, J = 7 Hz, 2H) 7.23 (t, J = 7.5 Hz, 1H), 4.55 (t, J = 5 Hz, 4H), 3.88 (t, J = 5 Hz, 4H), 3.77 (s, 4H), 3.71 (t, J = 5 Hz, 4H), 3.65 (s, 2H), 3.61–3.56 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.39, 138.91, 128.98, 128.31, 127.04, 124.42, 72.58, 70.52, 70.40, 70.22, 69.55, 61.45, 57.42, 50.19, 47.72. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{29}H_{47}N_7O_8$ 622.3559; found 622.3561.

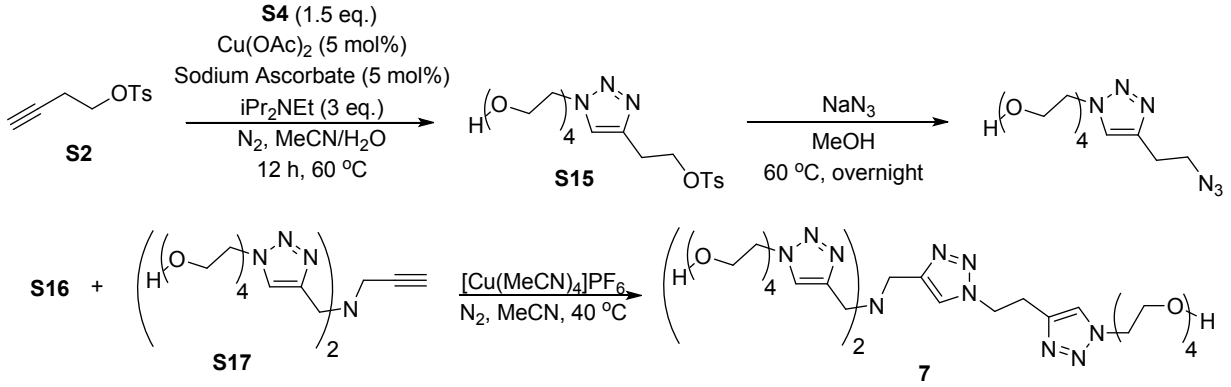


***Tetra-triazole-(1-tetraethylene glycol)-4-methylamine* (7):** A stirred solution of **S2** (224 mg, 1.00 mmol) and **S4** (329 mg, 1.50 mmol) in MeCN / H_2O (2.0 mL / 0.5 mL) was treated sequentially with diisopropylethylamine (150 mg, 1.16 mmol), and $Cu(OAc)_2$ (6 mg, 0.03 mmol) and sodium ascorbate (6 mg, 0.03 mmol). The mixture was stirred at 60 °C 12 h under nitrogen, and cooled down to room temperature. Curisorb^T was added and stirred for 30 min to remove copper. After the solvent was removed, the residue was purified by flash chromatography on silica gel with EtOAc / MeOH (3:1, v/v) as the eluent to give the product **S15** (448 mg, 99.0 %) that was directly used for the next step.

A mixture of **S15** (1.0 eq.) and sodium azide (1.5 eq.) in methanol was stirred overnight at 60 °C. The solvent was evaporated with a rotavap under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc / MeOH (3:1, v/v) as the eluent to give the product **S16** (99 %) that was directly used for the next step.

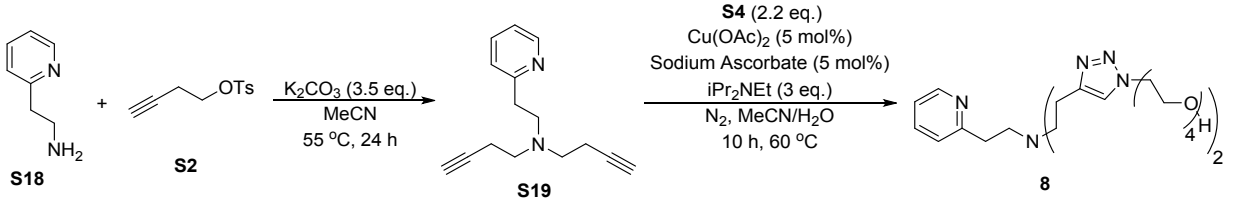
Compounds **S17** and **7** were prepared similarly to compound **2**. Purification of compound **7** was performed by flash chromatography on silica gel with CH_2Cl_2 / MeOH (3:1, v/v) as the eluent to give the product **7** (306 mg, 80.0 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.89 (s, 2H), 7.69 (s, 1H),

7.49 (s, 1H), 4.66 (t, J = 7.5 Hz, 2H), 4.49 (t, J = 5.0 Hz, 4H), 4.41 (t, J = 5.0 Hz, 2H), 3.82 (t, J = 5.0 Hz, 4H), 3.74 (t, J = 5.0 Hz, 2H), 3.66–3.65 (m, 12H), 3.59–3.56 (m, 6H), 3.55–3.49 (m, 24H), 3.29 (t, J = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.75, 143.72, 143.07, 125.10, 124.43, 123.38, 72.65, 70.63, 70.62, 70.61, 70.56, 70.48, 70.46, 70.40, 70.30, 70.29, 69.58, 69.48, 61.56, 61.54, 50.27, 50.21, 49.56, 47.34, 47.15, 26.84. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{37}H_{65}N_{13}O_{12}$ 884.4948; found 884.4938.



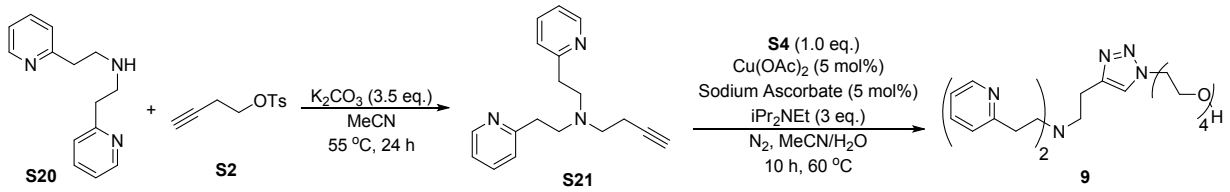
N-2-(pyridin-2-yl)ethyl-N,N-bis-(1-tetraethylene glycol) triazole-4-ethylamine **(8)**: A mixture of **S18** (122 mg, 1.00 mmol), **S2** (493 mg, 2.20 mmol) and K_2CO_3 (690 mg, 5.00 mmol) in MeCN (4 mL) was stirred for 24 h at 55 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S19** (143 mg, 63.2 %) that was used for the next step.

A stirred solution of **S19** (143.0 mg, 0.632 mmol) and **S4** (415.7 mg, 1.896 mmol) in MeCN / H_2O (0.5 mL / 2.0 mL) was treated sequentially with diisopropylethylamine (81.8 mg, 0.632 mmol), and $Cu(OAc)_2 \cdot H_2O$ (6.3 mg, 0.063 mmol) and sodium ascorbate (25.0 mg, 0.126 mmol). The mixture was stirred at 60 °C for 10 h under nitrogen and cooled down to room temperature. Curisorb^T was added and stirred for 30 min to remove copper. After the solvent was removed, the residue was purified by flash chromatography on silica gel with EtOAc / MeOH (9:1, v/v) as the eluent to give the product **8** (150 mg, 36.0 %) as a light yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40–8.37 (m, 1H), 7.50–7.45 (m, 1H), 7.38 (s, 1H), 7.37 (s, 1H), 7.04–6.98 (m, 2H), 4.38 (td, J_1 = 4.8 Hz, J_2 = 5.2 Hz, 4H), 3.86 (s, 2H), 3.72 (td, J_1 = 5.2 Hz, J_2 = 7.2 Hz, 4H), 3.61 (td, J_1 = 1.2 Hz, J_2 = 4 Hz, 4H), 3.55–3.47 (m, 20H), 2.88–2.74 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.44, 149.06, 146.00, 136.47, 123.57, 122.66, 121.23, 72.67, 70.54, 70.48, 70.39, 70.28, 69.57, 61.42, 53.64, 53.39, 50.06, 35.60, 23.73. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{31}H_{52}N_8O_8$ 665.3981; found 665.3977.

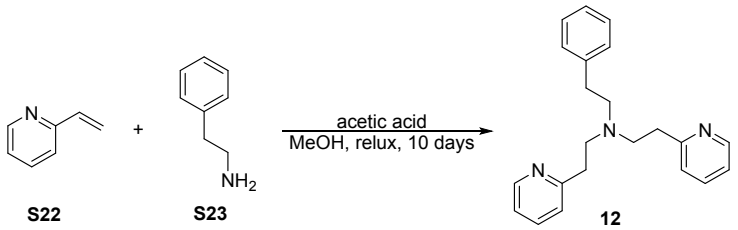


***N,N-Bis-2-(pyridin-2-yl)ethyl-N-(1-tetraethylene glycol) triazole-4-ethylamine* (9):** A mixture of **S20**[8] (85.2 mg, 0.375 mmol), **S2** (84.1 mg, 0.375 mmol) and K_2CO_3 (77 mg, 0.56 mmol) in MeCN (2 mL), was stirred for 24 h at 55 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL), dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S21** (60 mg, 57 %) that was used for the next step.

A stirred solution of **S21** (60.0 mg, 0.215 mmol) and **S4** (94.2 mg, 0.429 mmol) in MeCN / H_2O (0.5 mL / 2.0 mL) was treated sequentially with diisopropylethylamine (27.8 mg, 0.215 mmol), and $Cu(OAc)_2 \cdot H_2O$ (2.2 mg, 0.011 mmol) and sodium ascorbate (8.5 mg, 0.043 mmol). The mixture was stirred at 60 °C for 10 h under nitrogen and cooled down to room temperature. Curisorb^T was added and stirred for 30 min to remove copper. After the solvent was removed, the residue was purified by flash chromatography on silica gel with MeOH / EtOAc (1:1, v/v) as the eluent to give the product **9** (40 mg, 37 %) as a light brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47–8.46 (m, 2H), 7.51 (td, J_1 = 2 Hz, J_2 = 6 Hz, 2H), 7.34 (d, J = 2 Hz, 1H), 7.06–7.03 (m, 4H), 4.42 (d, J = 4.5 Hz, 2H), 3.79 (d, J = 4.5 Hz, 2H), 3.71–3.69 (m, 2H), 3.62–3.60 (m, 2H), 3.57–3.49 (m, 8H), 2.95–2.80 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.66, 149.18, 146.20, 136.36, 123.58, 122.70, 121.19, 72.75, 70.62, 70.58, 70.46, 70.37, 69.68, 61.53, 53.84, 53.53, 50.09, 35.92, 23.93. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{26}H_{38}N_6O_4$ 499.3027; found 499.3024.

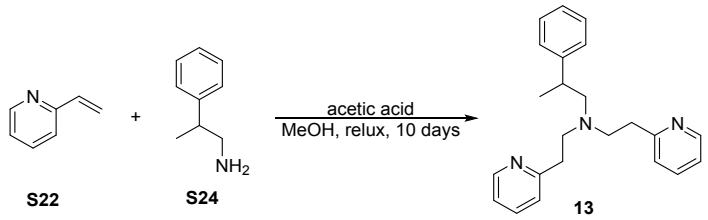


***N,N*-Bis[2-(2-pyridyl)ethyl]-phenylethylamine (12):** Compound **12** was prepared according to the reported method.[2] The mixture of **S22** (176 mg, 1.68 mmol) and **S23** (99 mg, 0.82 mmol) in MeOH (3 mL) containing acetic acid (100 mg, 1.68 mmol) was refluxed for 10 days. The solvent was removed by evaporation, and the resulting viscous material was dissolved in H_2O (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was dried with anhydrous K_2CO_3, filtered and evaporated to give pale brown oil. Flash column chromatography on silica gel with a mixture of EtOAc / MeOH (5:95, v/v). Yield 158 mg, 49.0 % as brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (ddd, J_1 = 0.7 Hz, J_2= 1.6 Hz, J_3 = 4.8 Hz, 2H), 7.53 (dt, J_1 = 2 Hz, J_2= 7.5 Hz, 2H), 7.27–7.23 (m, 2H), 7.19–7.16 (m, 1H), 7.13–7.08 (m, 4H), 7.01 (d, J = 7.5 Hz, 2H), 3.02–2.99 (m, 4H), 2.93–2.90 (m, 4H), 2.84–2.80 (m, 2H), 2.73–2.70 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.71, 149.22, 140.71, 136.18, 128.28, 125.85, 121.07, 56.04, 54.00, 36.18, 33.83. MS (ESI-Ion Trap) m/z: $[M+H]^+$ calculated for $C_{22}H_{26}N_3$ 332.2; found 332.2.



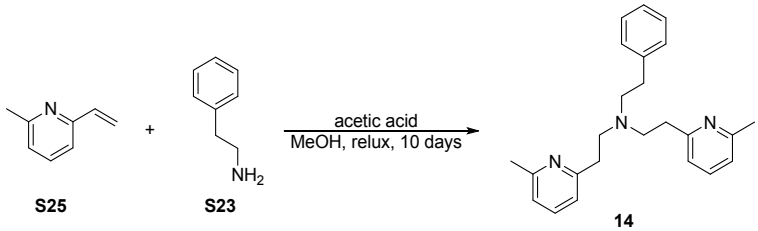
S22 S23 12

***N,N*-Bis[2-(2-pyridyl)ethyl]-*β*-methylphenylethylamine (13):** Compound **13** was prepared similarly to compound **12**. Yellow oil, 45 mg, 16 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J_1 = 4.9 Hz, J_2 = 0.9 Hz, 2H), 7.49 (td, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 2H), 7.27–7.22 (m, 2H), 7.19–7.14 (m, 1H), 7.13–7.06 (m, 4H), 6.91 (d, J = 7.8 Hz, 2H), 2.97–2.53 (m, 11 H), 1.12 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.81, 149.07, 149.07, 146.30, 136.08, 128.18, 127.31, 125.90, 123.57, 123.56, 123.55, 120.96, 62.39, 54.46, 38.38, 35.95, 19.67. MS (ESI-Ion Trap) m/z: $[M+H]^+$ calculated for $C_{23}H_{28}N_3$ 346.2; found 346.3.



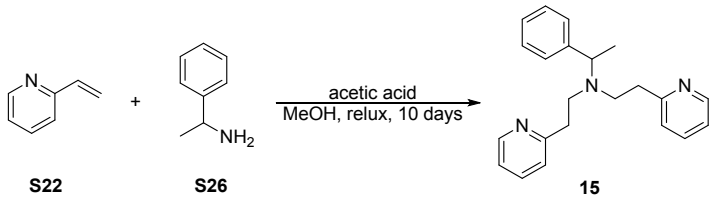
S22 S24 13

***N,N*-Bis[2-(6-methylpyridin-2-yl)ethyl]phenylethylamine (14):** Compound **14** was prepared similarly to compound **12**. Yellow oil, yield 92 mg, 26 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, J = 7.5 Hz, 2H), 7.10–7.27 (m, 5H), 6.95 (d, J = 7.5 Hz, 2H), 6.83 (d, J = 7.5 Hz, 2H), 2.93–2.98 (m, 4H), 2.85–2.90 (m, 4H), 2.77-2.83 (m, 2H), 2.67–2.72 (m, 2H), 2.51 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.05, 157.63, 140.74, 136.33, 128.77, 128.21, 125.77, 120.48, 120.20, 55.94, 54.06, 36.14, 33.84, 24.50. MS (ESI-Ion Trap) m/z: $[M+H]^+$ calculated for $C_{24}H_{30}N_3$ 360.2; found 360.2.

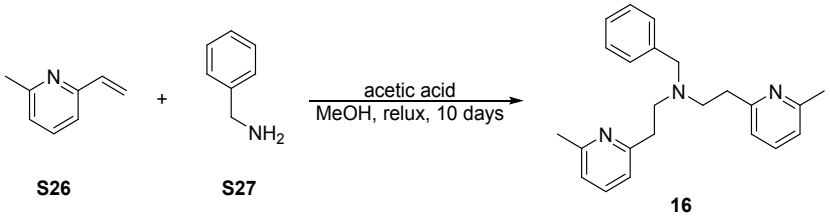


S25 S23 14

***1-Phenyl-N,N-bis(2-(pyridin-2-yl)ethyl)ethanamine* (15):** Compound **15** was prepared similarly to compound **12**. Dark brown oil, yield 60 mg, 18 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (ddd, J_1= 0.9 Hz, J_2 = 1.8 Hz, J_3 = 4.9 Hz, 2H), 7.50 (td, J_1 = 1.9 Hz, J_2 = 7.6 Hz, 2H), 7.21 (d, J = 4.4 Hz, 4H), 7.19–7.15 (m, 1H), 7.05 (ddd, J_1= 1.1 Hz, J_2 = 4.9 Hz, J_3 = 7.5 Hz, 2H), 6.98 (dd, J_1 = 3.9 Hz, J_2 = 4.8 Hz, 2H), 3.93 (q, J = 6.7 Hz, 1H), 2.99–2.78 (m, 8H), 1.32 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.82, 149.10, 144.25, 136.00, 127.95, 127.61, 126.50, 123.40, 120.93, 59.10, 50.31, 36.89, 16.63. MS (ESI-Ion Trap) m/z: $[M+H]^+$ calculated for $C_{22}H_{26}N_3$ 332.2; found 332.2.

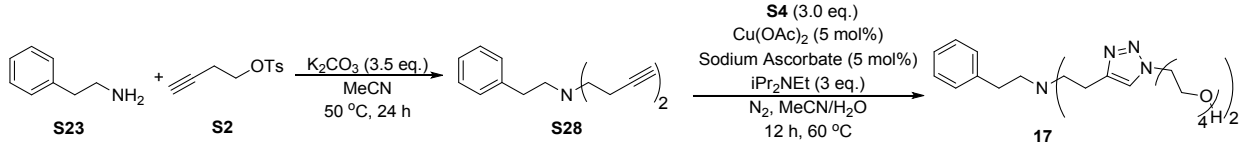


N-benzyl-2-(6-methylpyridin-2-yl)-N-(2-(6-methylpyridin-2-yl)ethyl)-ethanamine **(16)**: Compound **16** was prepared similarly to compound **12**. Dark oil, yield 91 mg, 32 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 8 Hz , 2H), 7.24–7.17 (m, 5H), 6.91 (d, *J* = 7.5 Hz, 2H), 6.79 (d, *J* = 7.5 Hz, 2H), 3.68 (br, 2H), 2.96–2.92 (m, 8H), 2.48 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.09, 157.59, 139.81, 136.25, 128.68, 127.98, 126.58, 120.44, 120.20, 58.39, 53.87, 36.02, 24.46. MS (ESI-Ion Trap) m/z: $[M+H]^+$ calculated for $C_{23}H_{28}N_3$ 346.2; found 346.3.



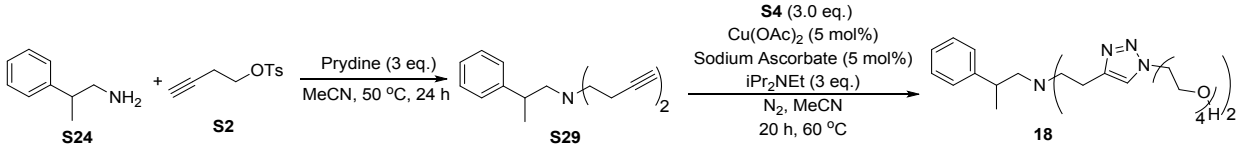
2-Phenyl-N,N-bis-(1-tetraethylene glycol)triazol-4-ethyl-1-amine **(17):** A mixture of **S23** (69 mg, 1.0 mmol), **S2** (493 mg, 2.20 mmol) and K_2CO_3 (483 mg, 3.50 mmol) in MeCN (4 mL) was stirred for 24 h at 50 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S28** (15.8 mg, 70.1%) that was used for the next step.

A stirred solution of **S28** (34 mg, 0.15 mmol) and **S4** (99 mg, 0.45 mmol) in MeCN / H_2O (2 mL / 0.5 mL) was treated sequentially with diisopropylethylamine (65 mg, 0.50 mmol), and $Cu(OAc)_2$ (3.0 mg, 0.015 mmol) and sodium ascorbate (3.0 mg, 0.015 mmol). The mixture was stirred at 60 °C 12 h under nitrogen, and cooled down to room temperature. Curisorb^T was added and stirred for 30 min to remove copper. After the solvent was removed, the residue was purified by flash chromatography on silica gel with CH_2Cl_2 / MeOH (10:1, v/v) as the eluent to give the product **17** (47 mg, 47 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 2H), 7.29–7.17 (m, 5H), 4.49 (t, *J* = 5.0 Hz, 4H), 3.84 (t, *J* = 5.0 Hz, 4H), 3.73–3.71 (m, 4H), 3.66–3.59 (m, 20H), 2.93–2.87 (m, 8H), 2.85–2.77 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.02, 140.54, 128.86, 128.42, 126.02, 122.71, 72.65, 70.61, 70.54, 70.46, 70.34, 69.65, 61.61, 55.66, 53.43, 50.12, 33.44, 23.75. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{32}H_{53}N_7O_8$ 664.4028; found 664.4020.



***2-Phenyl-N,N-bis-(1-tetraethylene glycol)triazol-4-ethyl)propan-1-amine* (18):** A mixture of **S24** (135 mg, 1.00 mmol), **S2** (493 mg, 2.20 mmol) and pyridine (237 mg, 3.00 mmol) in MeCN (4 mL) was stirred for 24 h at 50 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap and the residue was purified by flash chromatography on silica gel with EtOAc / hexane = (1:1, v/v) as the eluent to give the product **S29** (47 mg, 18 %) that was used for the next step.

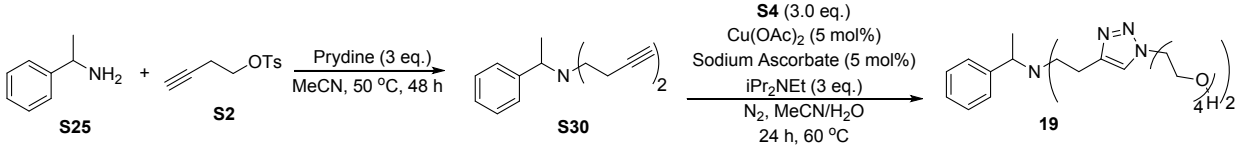
A stirred solution of **S29** (47 mg, 0.18 mmol) and **S4** (121 mg, 0.540 mmol) in MeCN (2 mL) was treated sequentially with diisopropylethylamine (70 mg, 0.54 mmol), and $Cu(OAc)_2$ (3.7 mg, 0.018 mmol) and sodium ascorbate (3.5 mg, 0.018 mmol). The mixture was stirred at 60 °C 20 h under nitrogen and cooled down to room temperature. Curisorb^T was added and stirred for 30 min to remove copper. The solvent was removed via rotovap. The residue was purified by flash chromatography on silica gel with CH_2Cl_2 / MeOH (5:1, v/v) as the eluent to give the product **18** (49 mg, 40 %) as a light yellow liquid. ^{1}H NMR (400 MHz, D_2O) δ 7.35 (s, 2H), 7.09 (t, J = 7.5 Hz, 2H), 7.02–6.98 (m, 3H), 4.32 (t, J = 5 Hz, 4H), 3.71 (t, J = 5 Hz, 4H), 3.51 (t, J = 4.5 Hz, 4H), 3.43–3.37 (m, 20H), 2.71 (dd, J_1 = 7.0 Hz, J_2 = 14.2 Hz, 1H), 2.60–2.53 (m, 9H), 2.42 (dd, J_1 = 6.1 Hz, J_2 = 13.1 Hz, 1H), 1.75 (s, 1H), 0.92 (d, J = 7 Hz, 3H); ^{13}C NMR (101 MHz, D_2O) δ 146.49, 146.16, 128.65, 127.29, 126.37, 123.72, 71.71, 69.66, 69.64, 69.45, 68.80, 60.33, 52.87, 49.85, 37.57, 21.73, 20.52. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{33}H_{55}N_7O_8$ 678.4185; found 678.4172.



***1-Phenyl-N,N-bis-(1-tetraethylene glycol)triazol-4-ethyl)ethanamine* (19):** A mixture of **S25** (121 mg, 1.00 mmol), **S2** (493 mg, 2.20 mmol) and pyridine (237 mg, 3.00 mmol) in MeCN (4 mL) was stirred for 48 h at 50 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S30** (15 mg, 6.0 %) that was used for the next step.

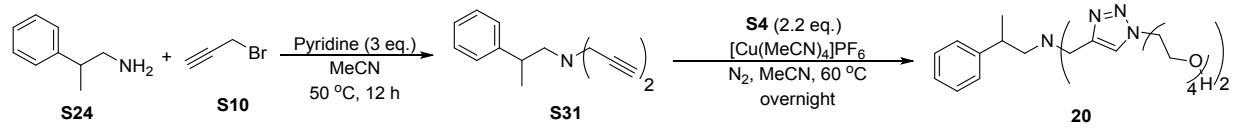
A stirred solution of **S30** (15 mg, 0.064 mmol) and **S4** (42 mg, 0.19 mmol) in MeCN / H_2O (0.4 mL / 0.1 mL) was treated sequentially with diisopropylethylamine (25 mg, 0.19 mmol), and $Cu(OAc)_2$ (1.3 mg, 0.0065 mmol) and sodium ascorbate (2.5 mg, 0.013 mmol). The mixture was stirred at 60 °C 24 h under nitrogen and cooled down to room temperature. Curisorb^T was added and stirred for 30 min to remove copper. After the solvent was removed, the residue was purified by flash chromatography on silica gel with CH_2Cl_2 / MeOH (10:1, v/v) as the eluent to give the product **19** (29 mg, 67 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 2H), 7.30–7.16 (m, 5H), 4.45 (dd, J_1 = 4.7 Hz, J_2 = 5.6 Hz, 4H), 3.93 (d, J = 6.6 Hz, 1H), 3.81 (t, J = 5.2 Hz, 4H), 3.69 (dd, J_1 = 4.0 Hz, J_2 = 5.2 Hz, 4H), 3.63–3.59 (m, 20H), 3.14 (br, 2H), 2.90–2.71 (m, 8H), 1.33 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.19, 143.98, 128.12, 127.85, 126.80, 122.55, 72.63, 70.62, 70.54, 70.47, 70.32, 69.67, 61.64, 59.21, 50.10, 49.95,

24.68, 16.54. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{32}H_{53}N_7O_8$ 664.4028; found 664.4020.



2-Phenyl-N,N-bis-(1-tetraethylene glycol)triazol-4-methyl)propan-1-amine **(20):** A mixture of **S24** (270 mg, 2.00 mmol), propargyl bromide **S10** (262 mg, 2.20 mmol) and pyridine (237 mg, 3.00 mmol) in MeCN (4 mL) was stirred for 12 h at 50 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S31** (63 mg, 15 %) that was used for the next step.

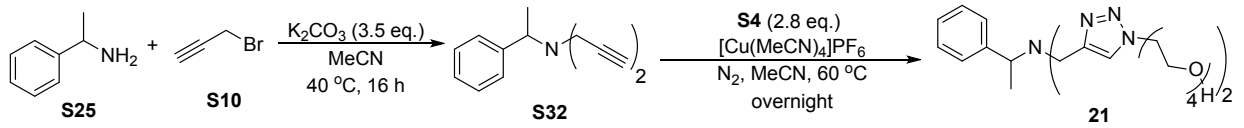
A stirred solution of **S31** (63 mg, 0.30 mmol) and **S4** (149 mg, 0.680 mmol) in MeCN (2 mL) was treated sequentially with diisopropylethylamine (70 mg, 0.54 mmol) and $[Cu(MeCN)_4]PF_6$ (3 mg, 0.008 mmol). The mixture was stirred at 60 °C overnight under nitrogen, cooled down to room temperature. Curisorb^T was added and stirred for 30 min. The solvent was removed via a rotovap under reduced pressure. The residue was purified by flash chromatography on silica gel with CH_2Cl_2 / MeOH (95:5, v/v) as the eluent to give the product **20** (144 mg, 74.1 %) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 2H), 7.27 (t, *J* = 8 Hz, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8 Hz, 2H), 4.50 (q, *J* = 5 Hz, 4H), 3.87 (t, *J* = 5 Hz, 4H), 3.76 (s, 4H), 3.71 (t, *J* = 4 Hz, 4H), 3.64–3.62 (m, 4H), 3.60–3.57 (m, 16H), 3.06 (q, *J* = 7 Hz, 1H), 2.58 (d, *J* = 7.5 Hz, 2H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.10, 144.60, 128.18, 127.51, 126.03, 124.16, 72.60, 70.57, 70.55, 70.43, 70.26, 69.56, 61.52, 60.80, 50.15, 48.53, 37.90, 19.74. HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{31}H_{51}N_7O_8$ 650.3872; found 650.3869.



1-Phenyl-N,N-bis-(1-tetraethylene glycol)triazol-4-methyl)ethylamine **(21):** A mixture of **S25** (242 mg, 2.00 mmol), **S10** (354 mg, 3.00 mmol) and K_2CO_3 (483 mg, 3.50 mmol) in MeCN (4 mL) was stirred for 16 h at 40 °C. The reaction mixture was cooled down to room temperature and the solvent was removed by a rotovap under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by a rotovap under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc / hexane (1:1, v/v) as the eluent to give the product **S32** (328 mg, 83.1 %) that was used for the next step.

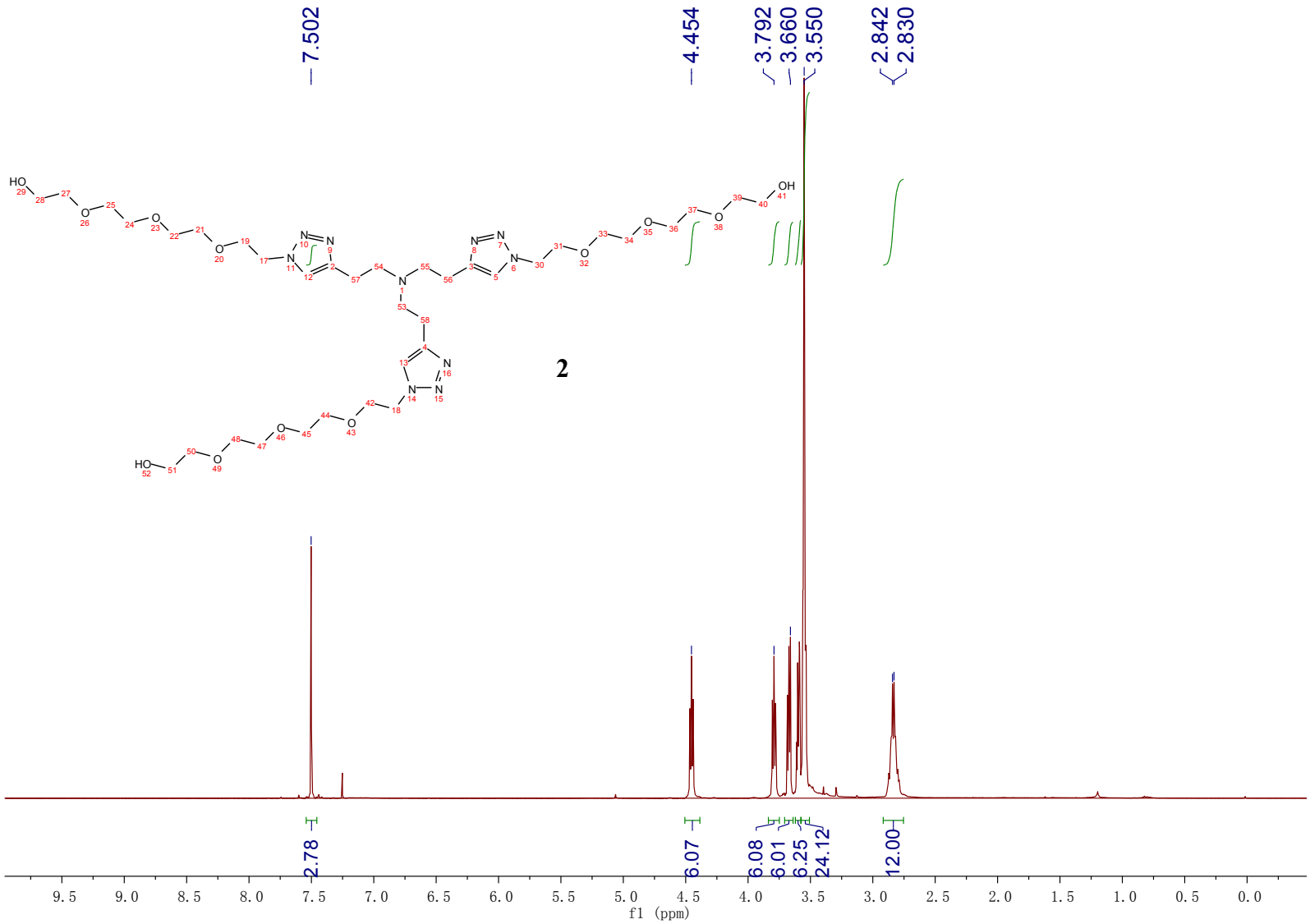
A stirred solution of **S32** (200 mg, 1.02 mmol) and **S4** (650 mg, 2.96 mmol) in MeCN (3 mL) was treated sequentially with diisopropylethylamine (25 mg, 0.19 mmol), and $[Cu(MeCN)_4]PF_6$ (19 mg, 0.050 mmol). The mixture was stirred at 60 °C overnight under nitrogen cooled down to room temperature. Curisorb^T was added and stirred for 30 min. The solvent was removed via rotovap. The residue was

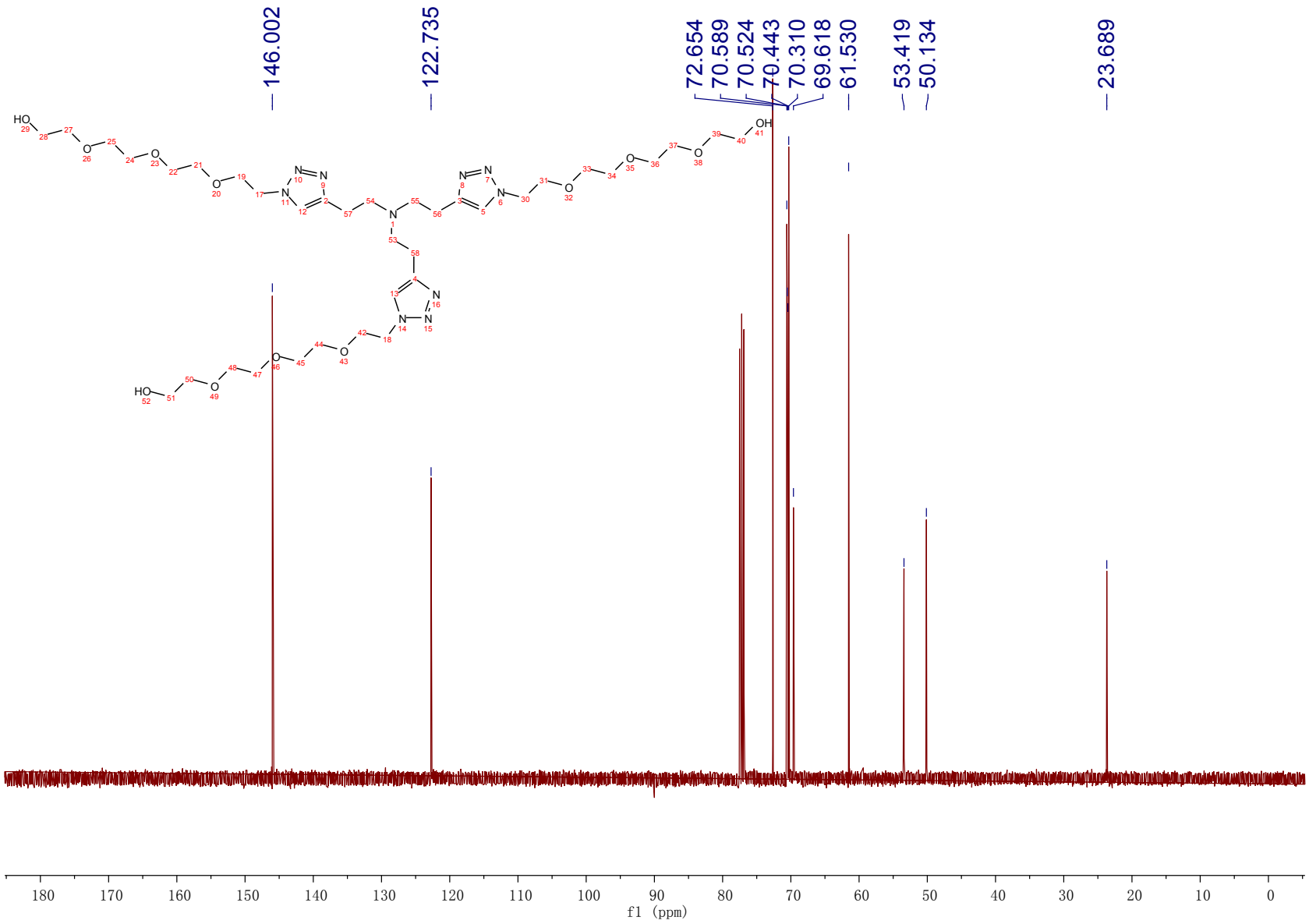
purified by flash chromatography on silica gel with CH_2Cl_2 / MeOH (10:1, v/v) as the eluent to give the product **21** (396 mg, 61.1 %) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.42 (d, J = 8 Hz, 2H), 7.31 (t, J = 6.75 Hz, 2H), 7.21 (t, J = 6.75 Hz, 2H), 4.53 (t, J = 5 Hz, 4H), 3.88–3.82 (m, 6H), 3.71–3.65 (m, 10H), 3.62–3.56 (m, 22H), 1.50 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.12, 144.22, 128.35, 127.62, 126.95, 124.39, 72.58, 70.55, 70.41, 70.23, 69.99, 69.54, 61.50, 59.22, 50.19, 44.41, 18.52. ESI- HRMS (ESI-Quadrupole) m/z: $[M+H]^+$ calculated for $C_{30}H_{49}N_7O_8$ 636.3715; found 636.3715.



S25 **S10** **S32** **21**

H. NMR spectrum

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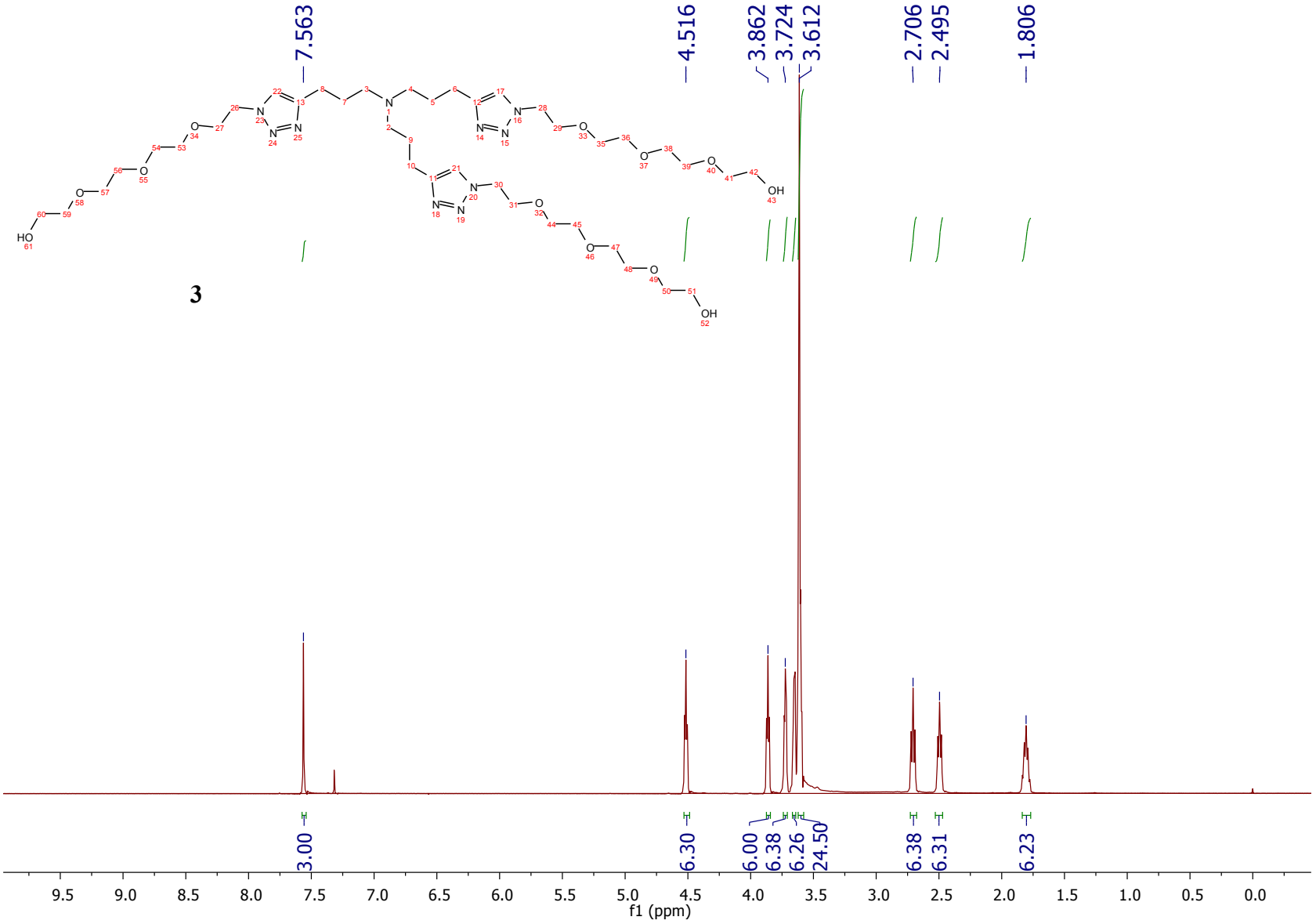
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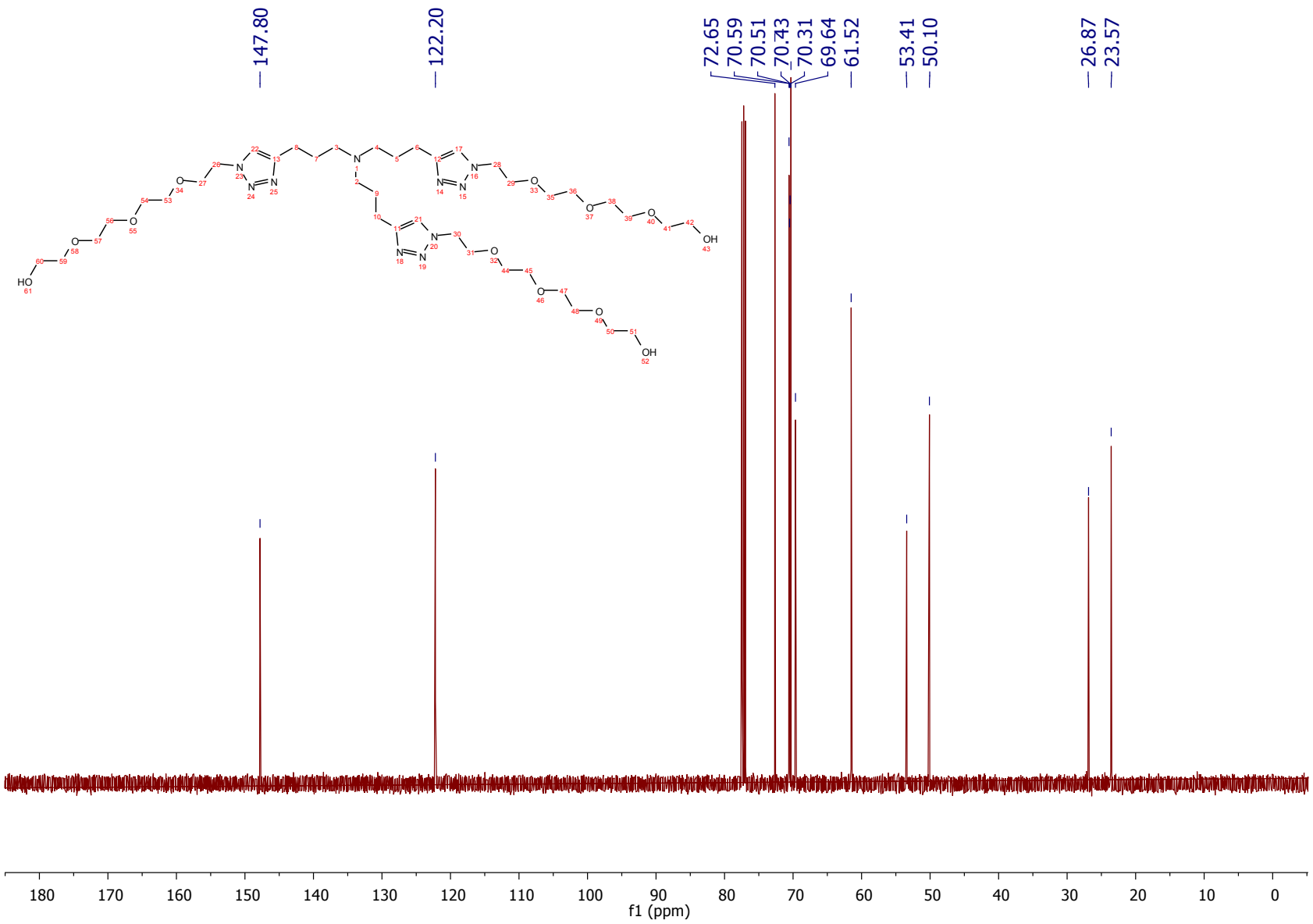
f1 (ppm)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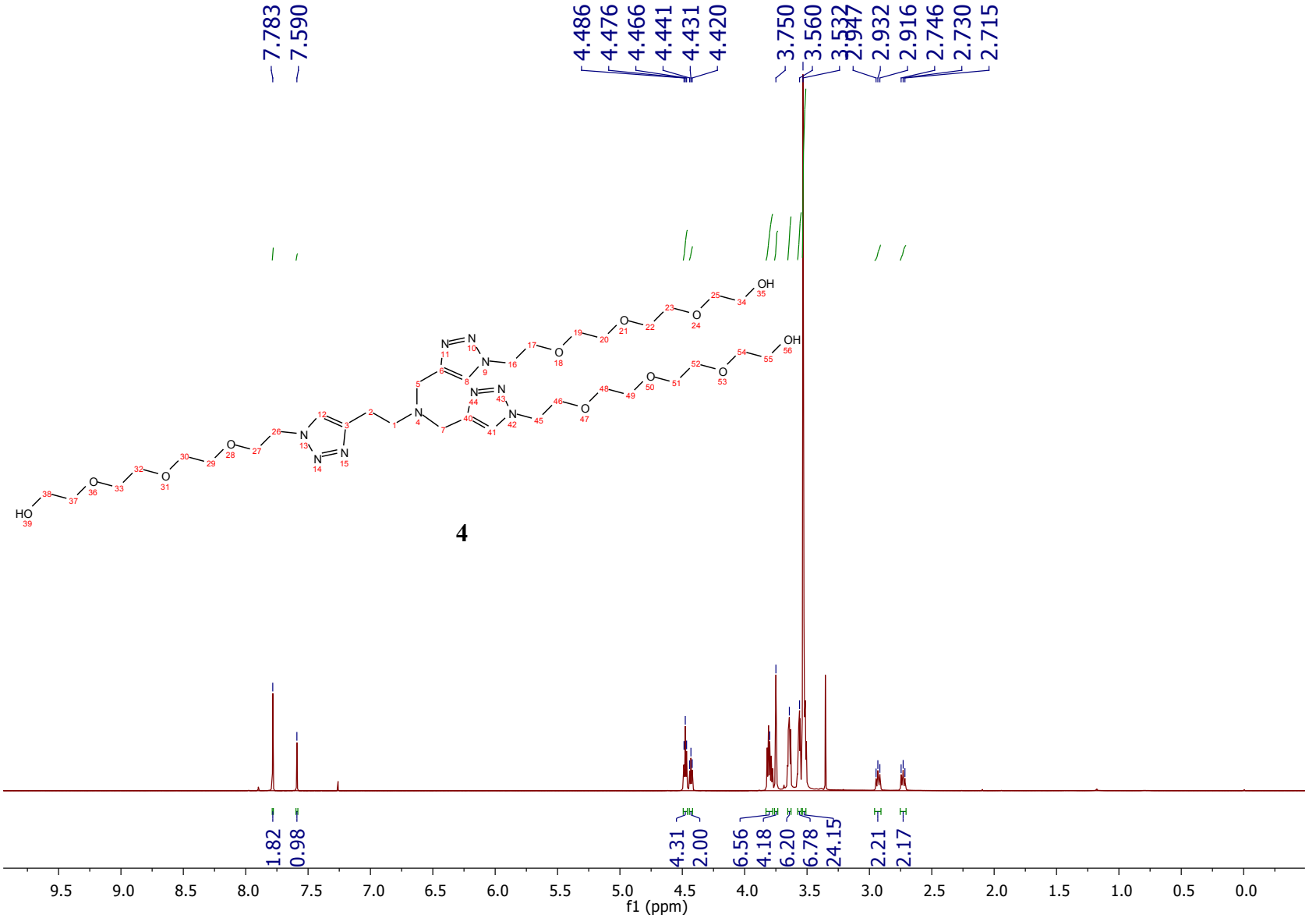
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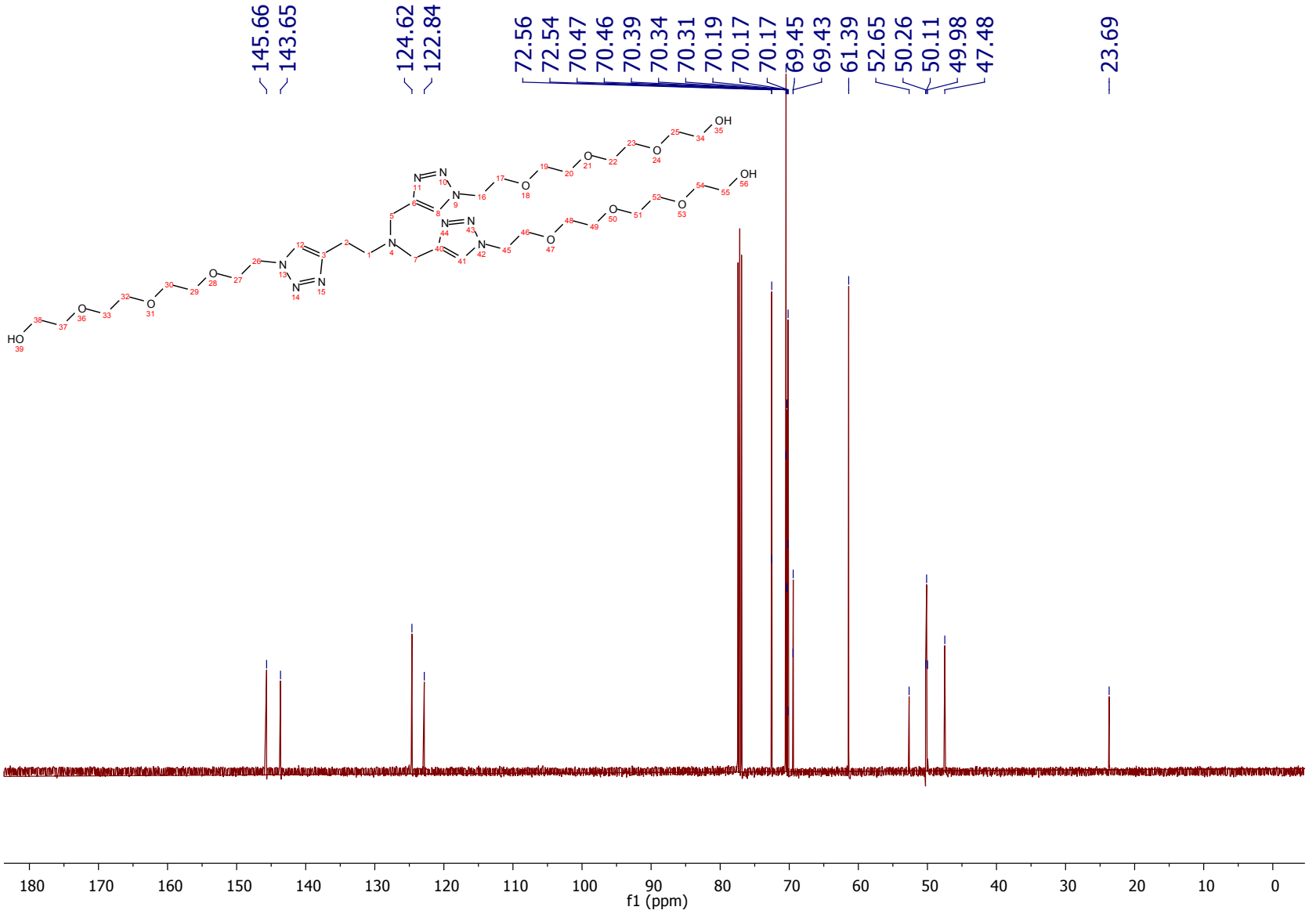
4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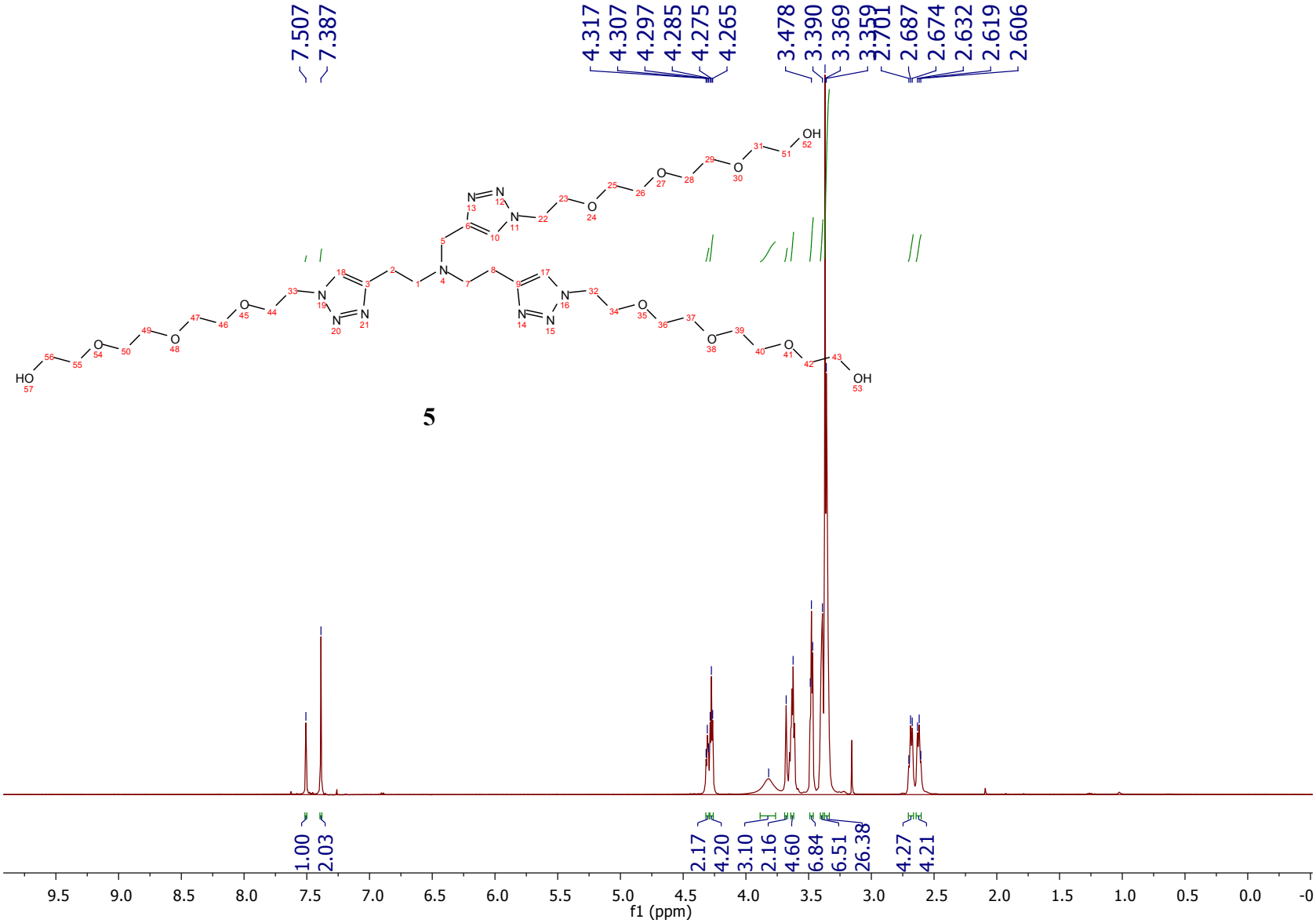
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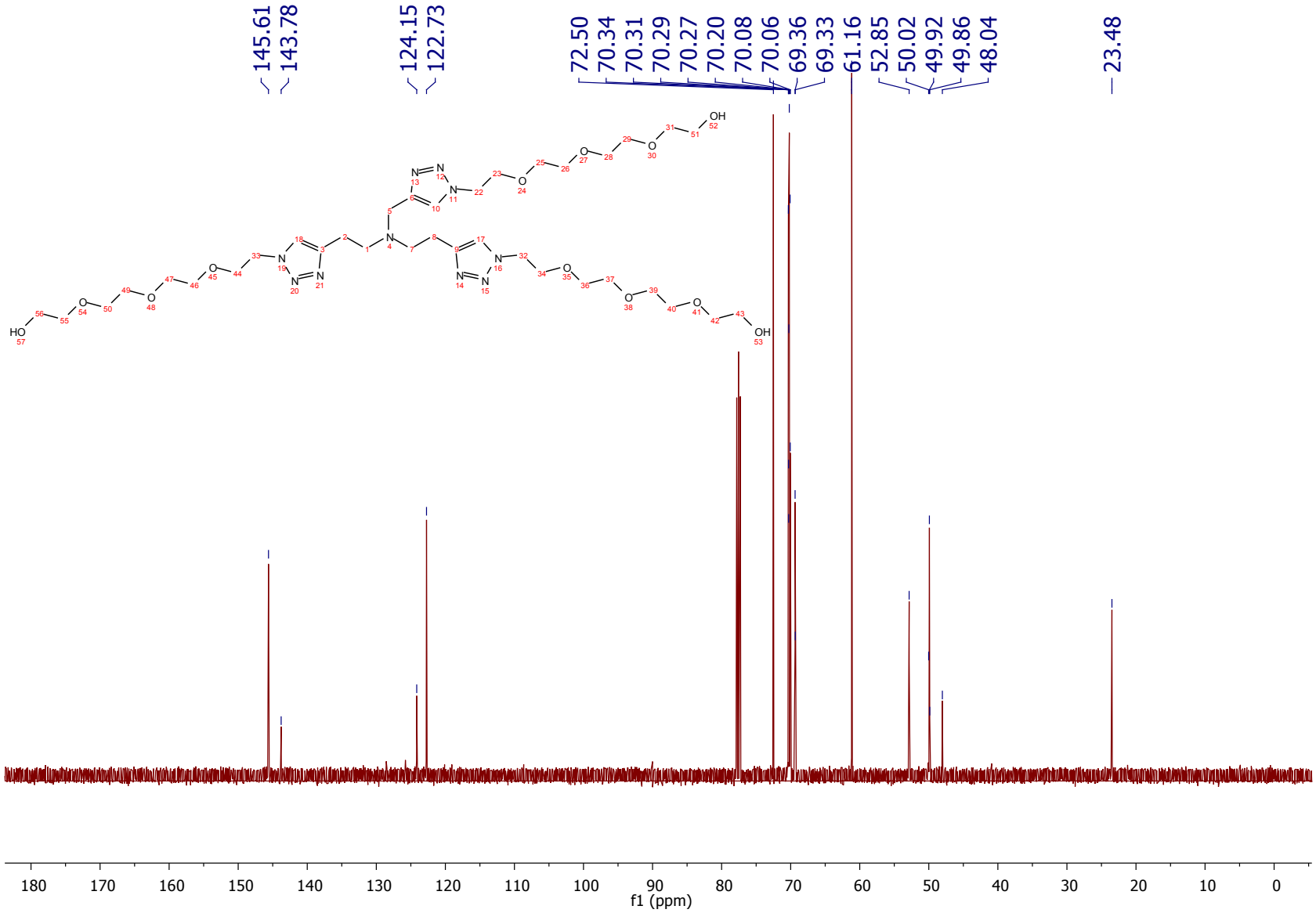
5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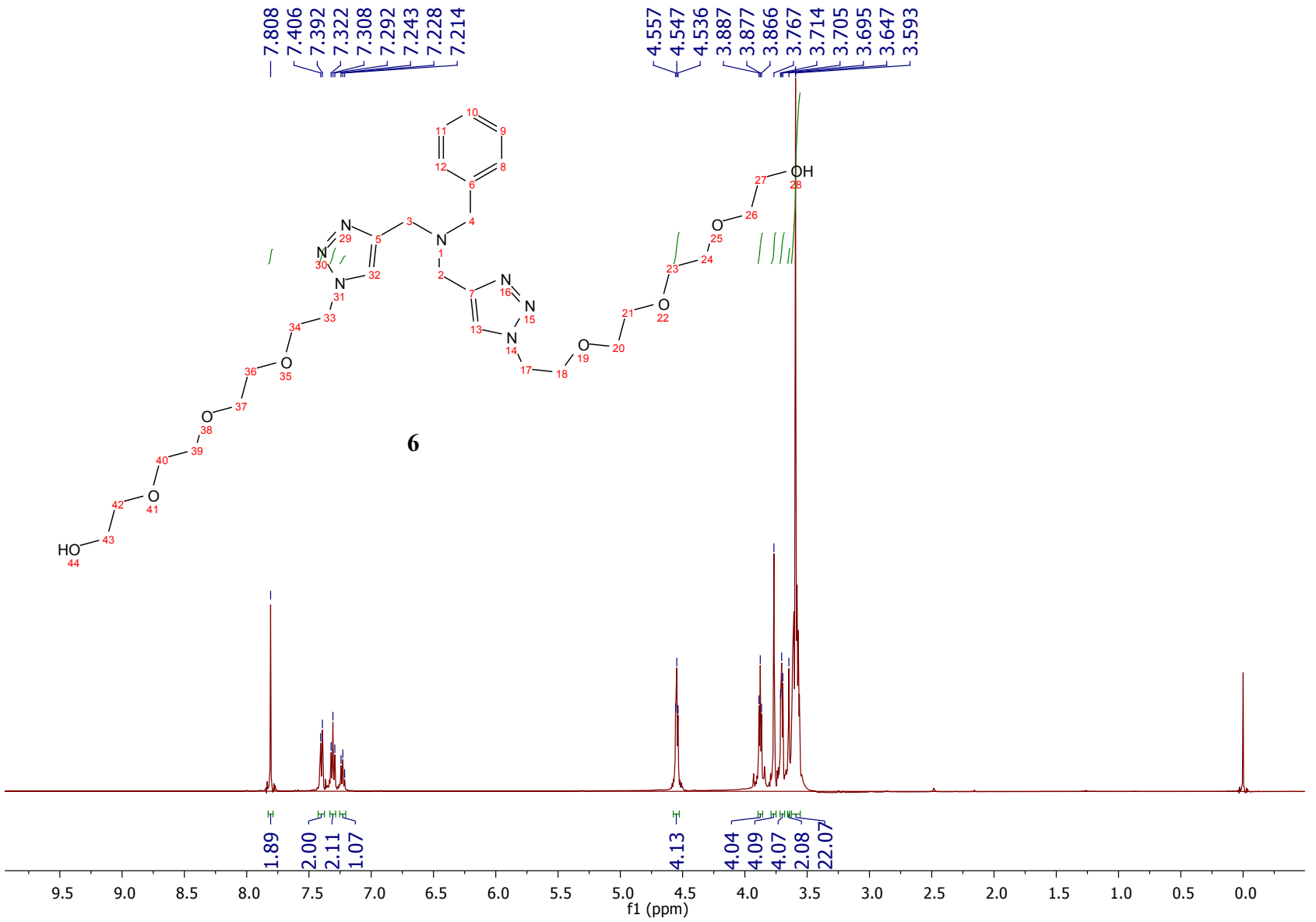
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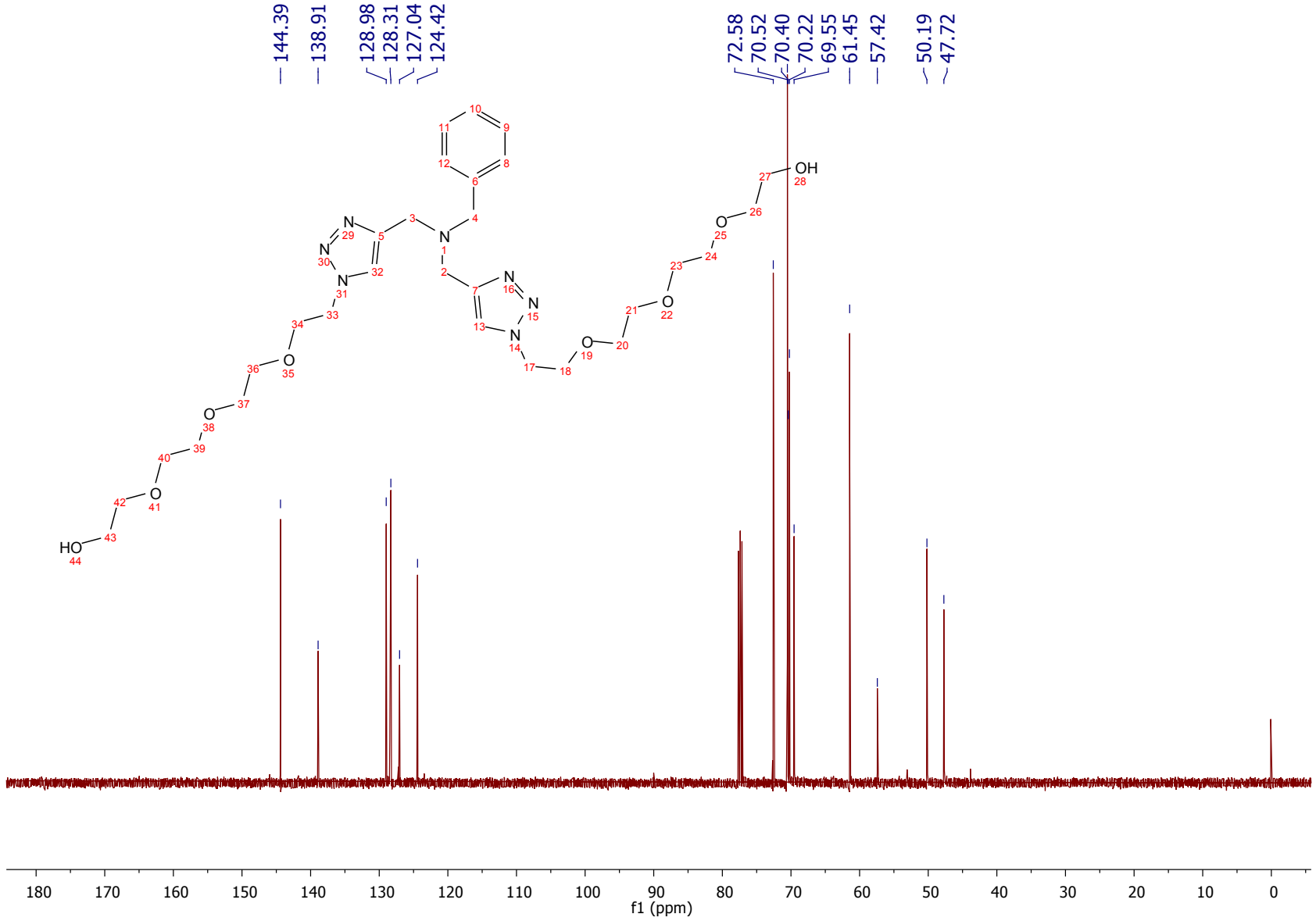
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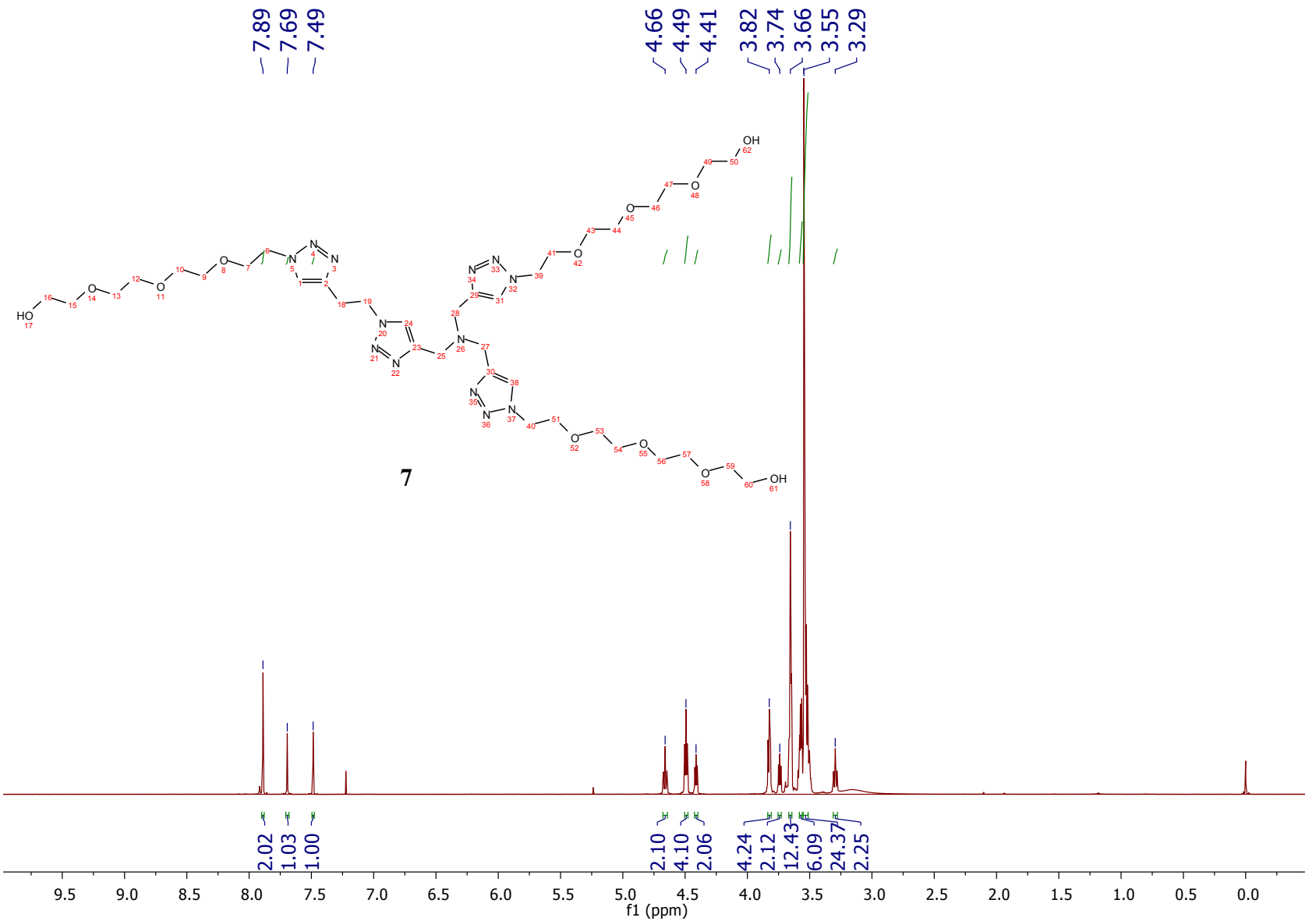
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2.25
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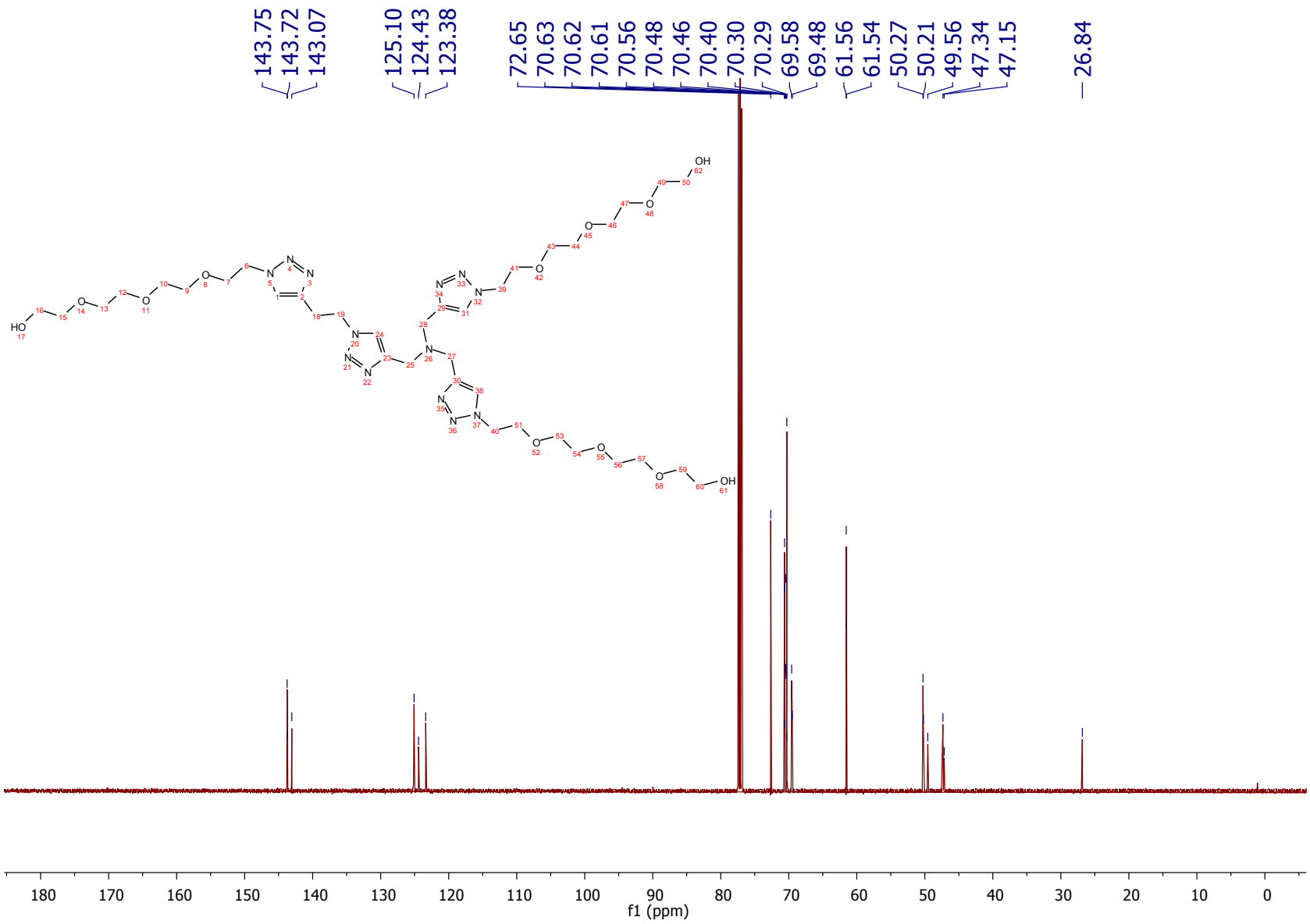
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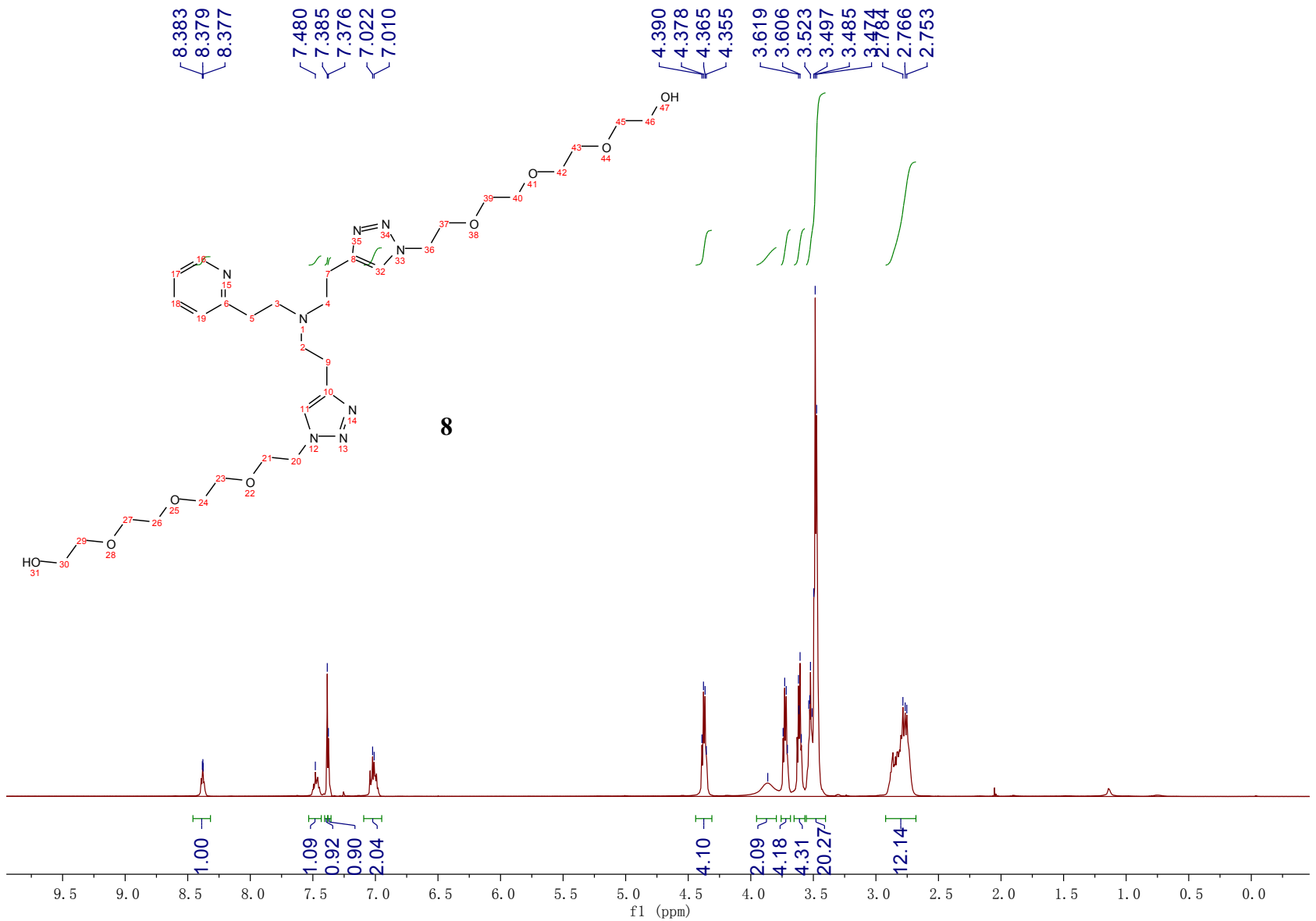
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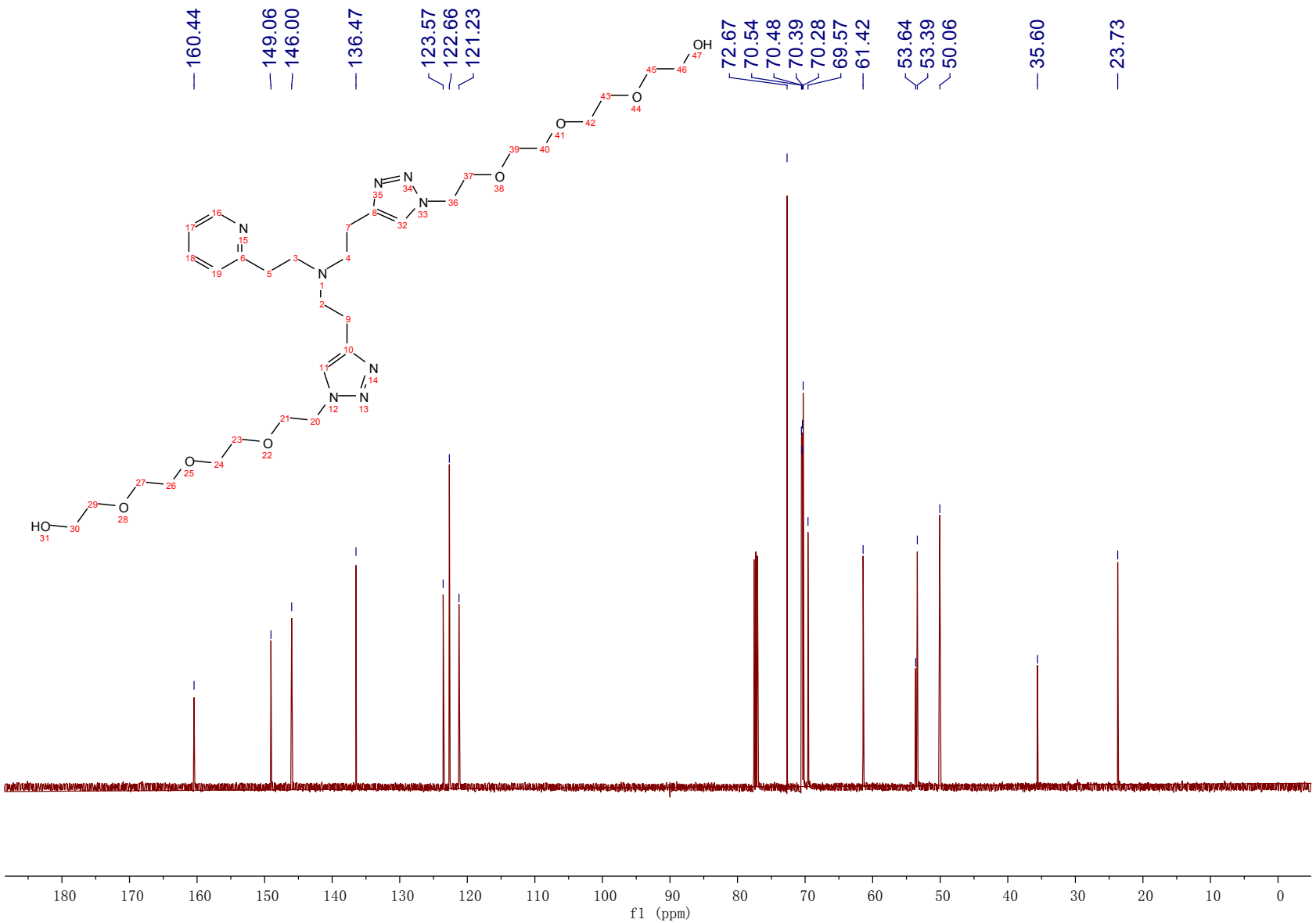
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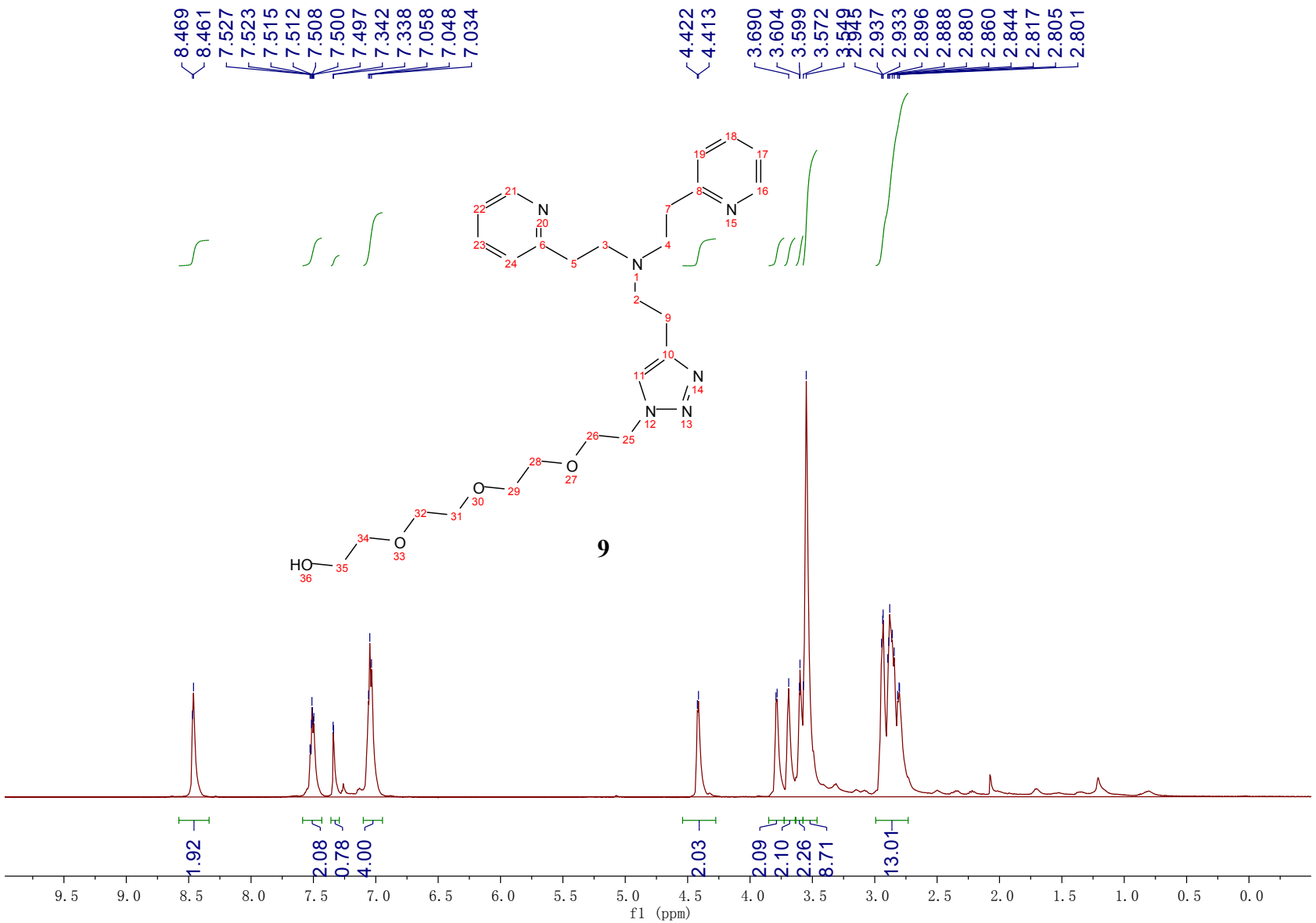
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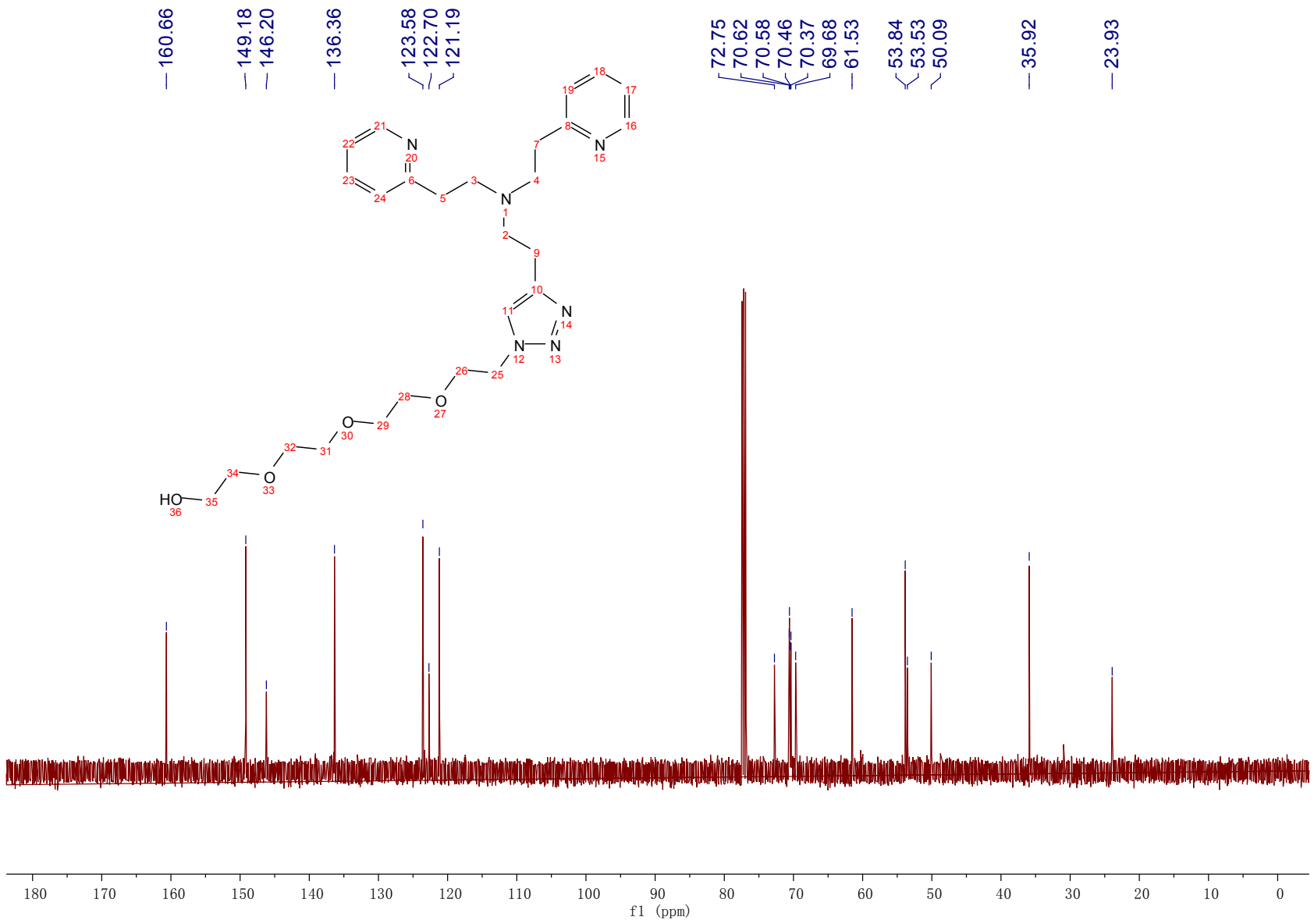
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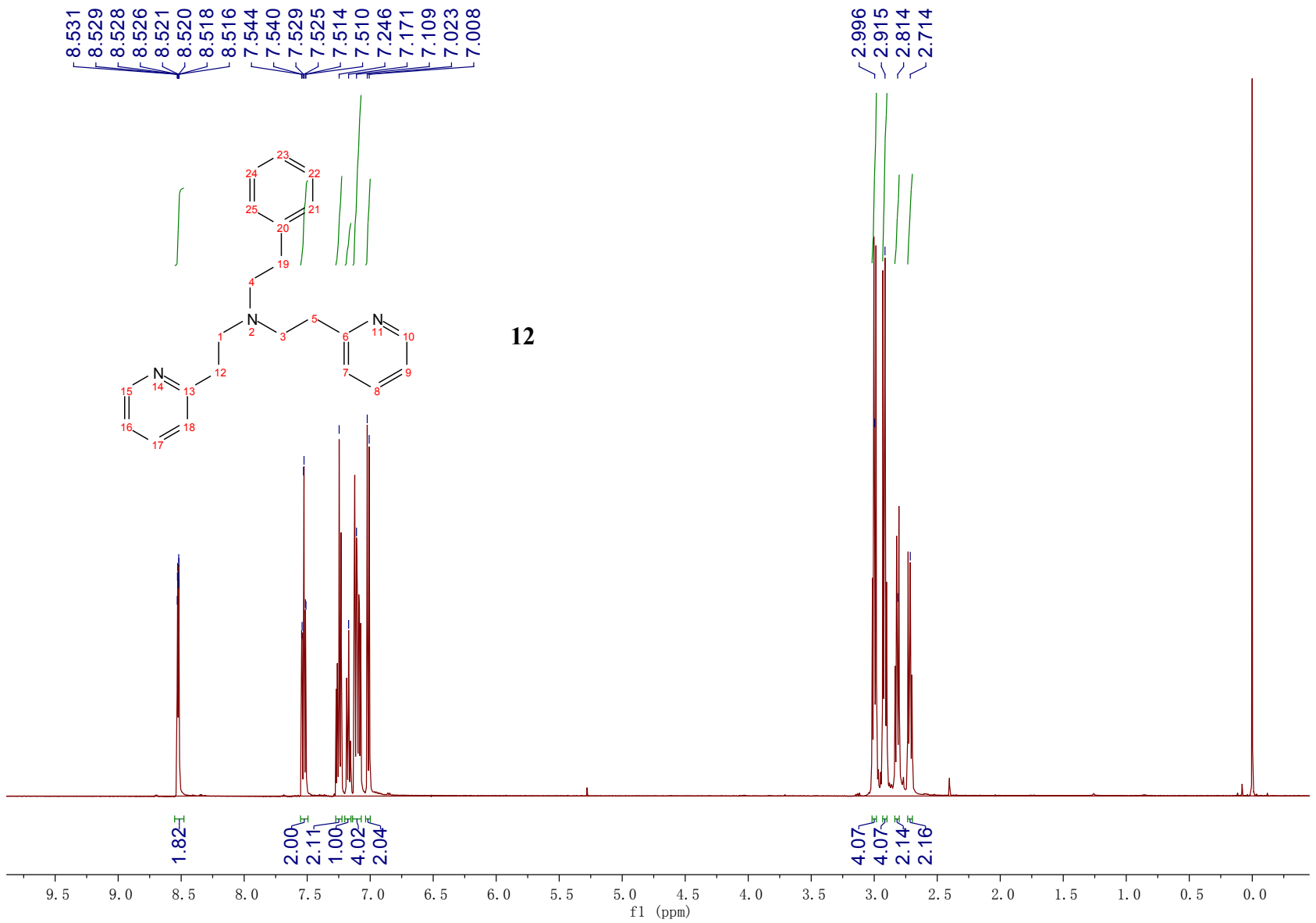
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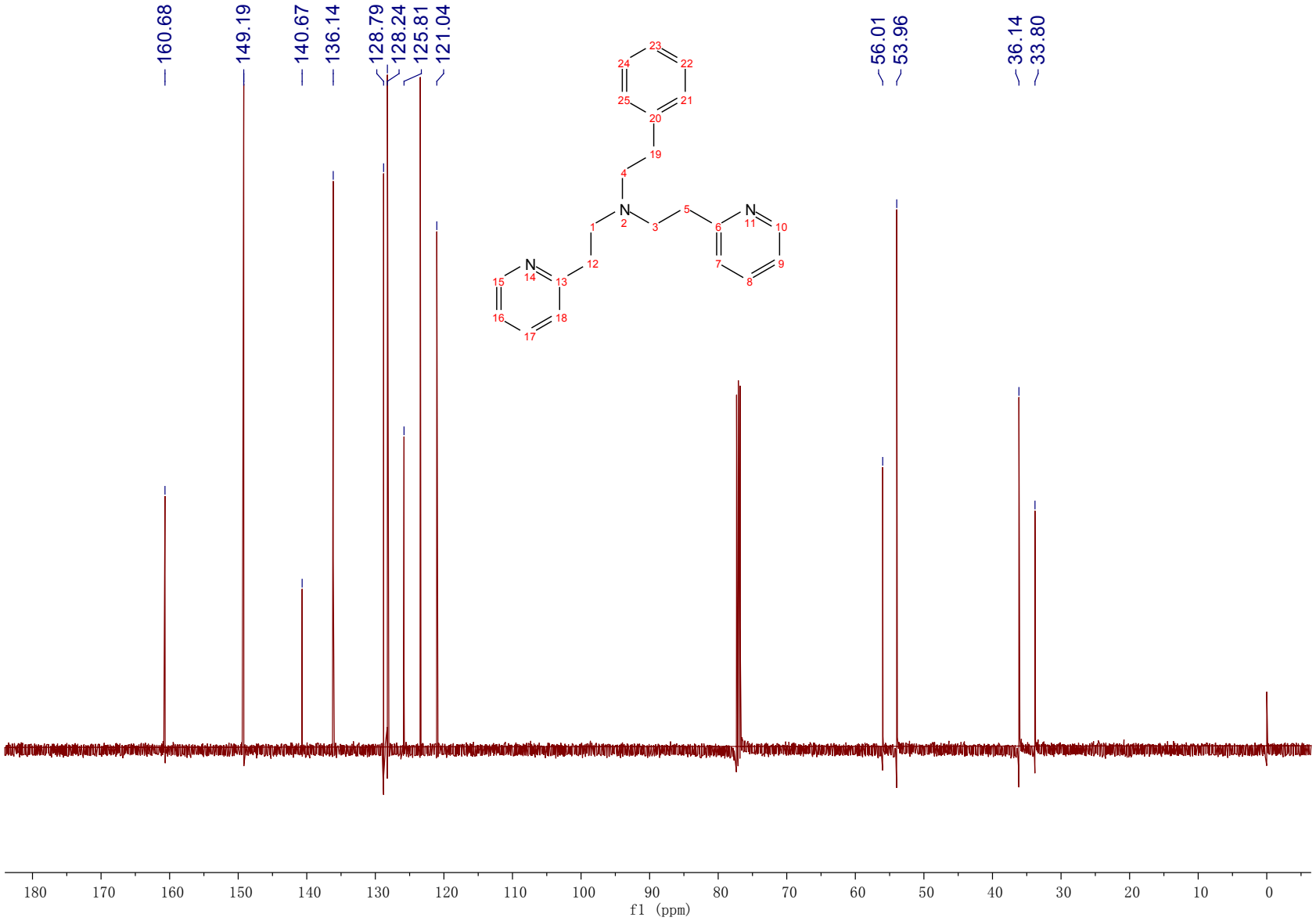
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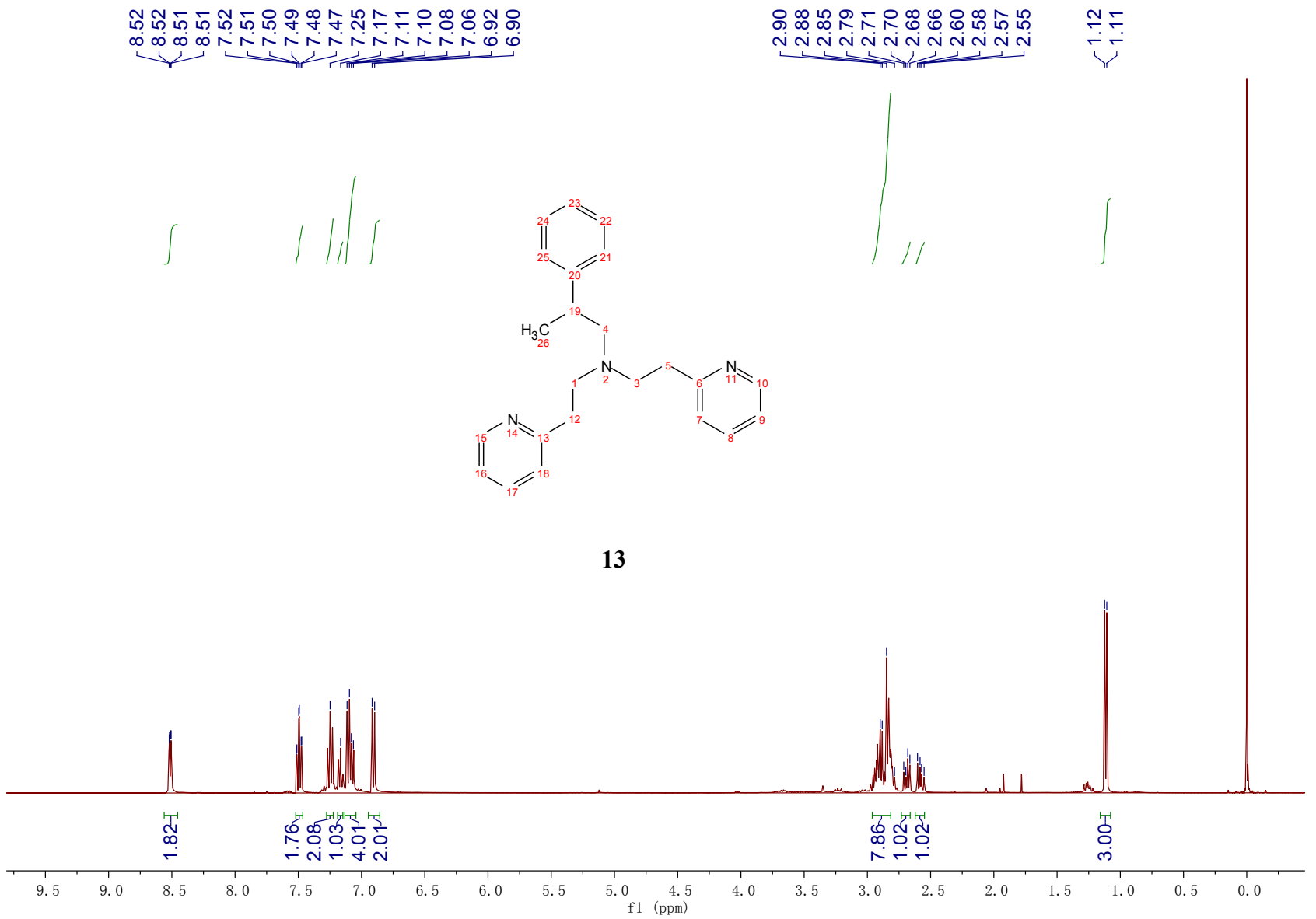
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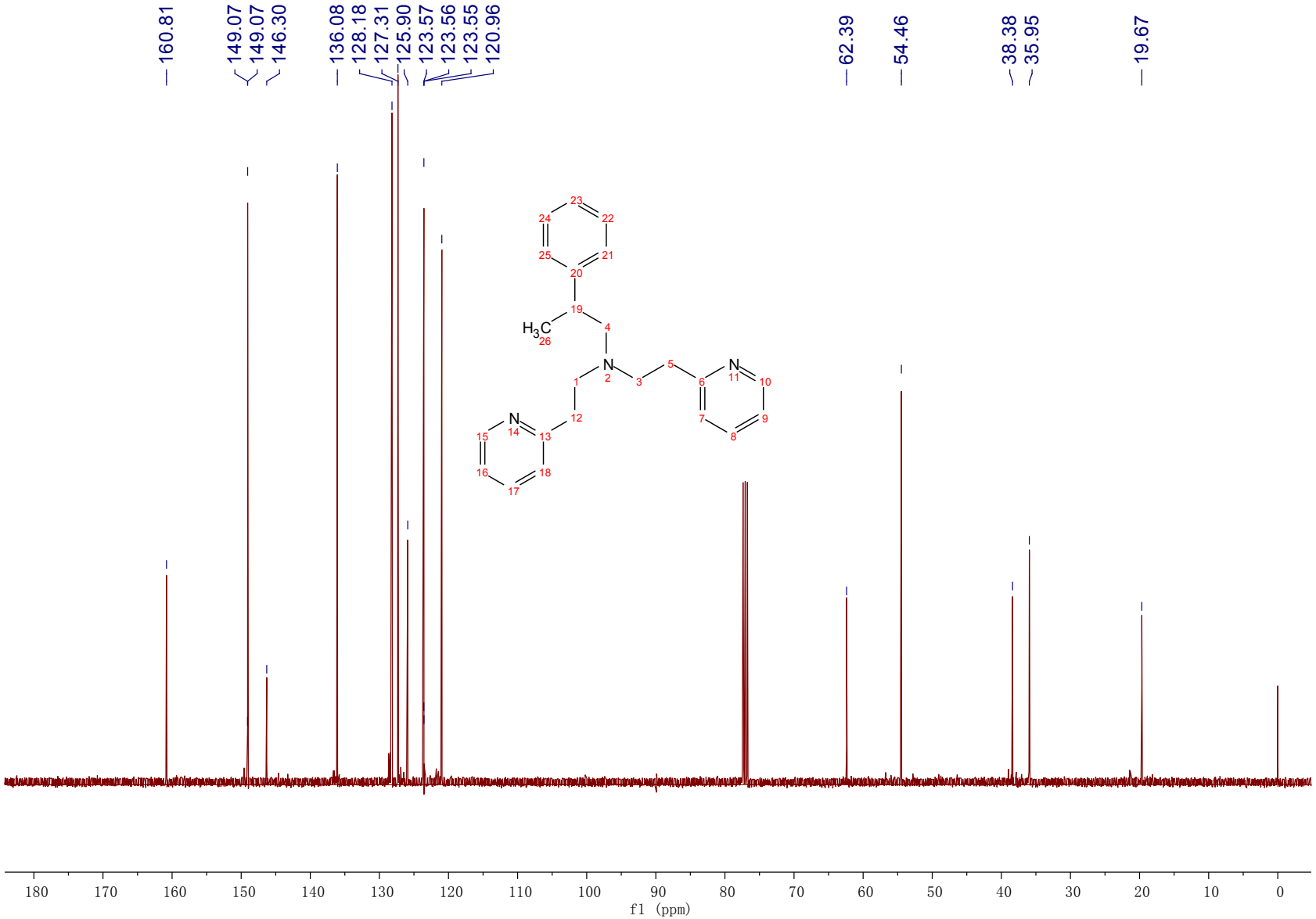
13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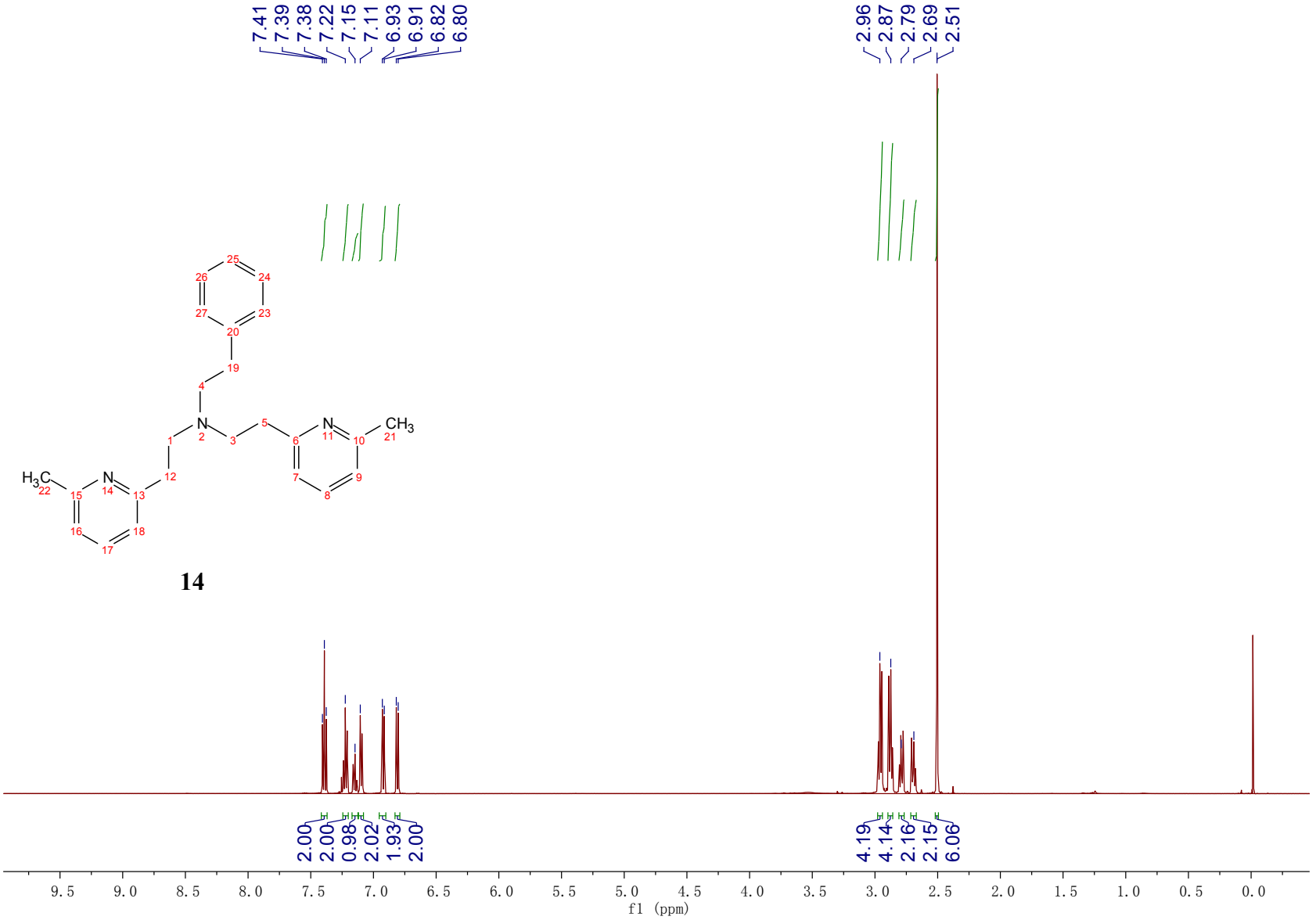
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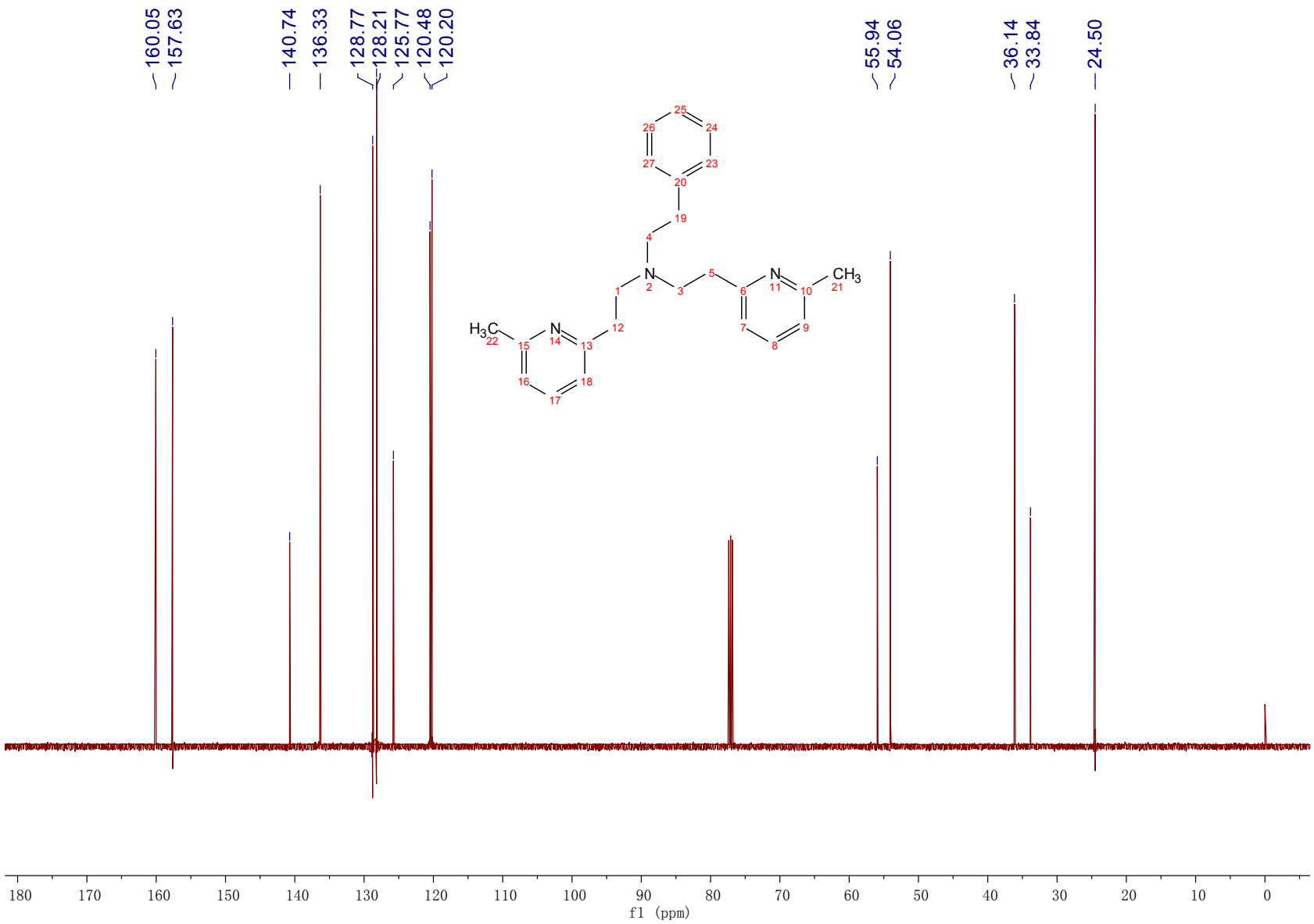
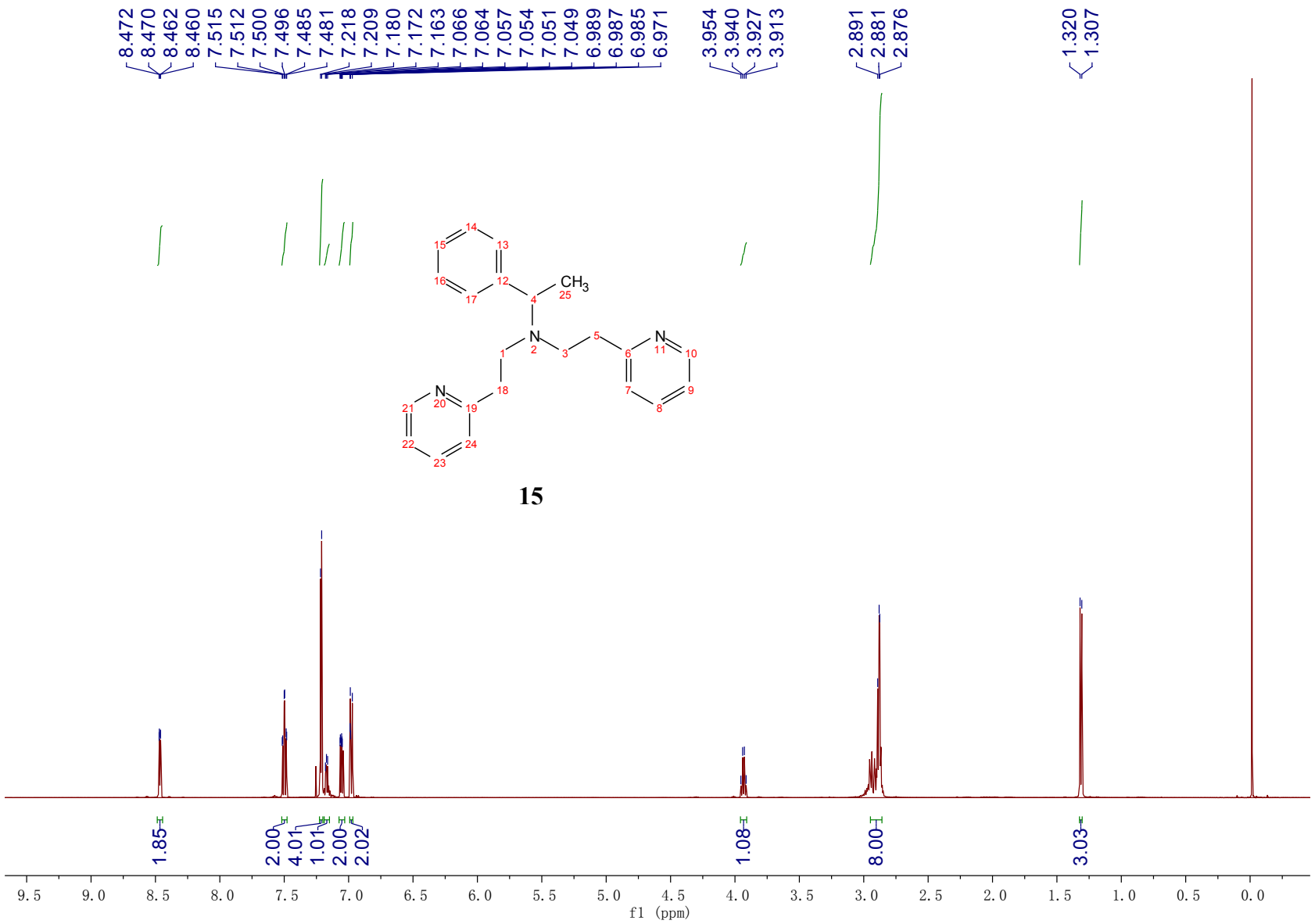
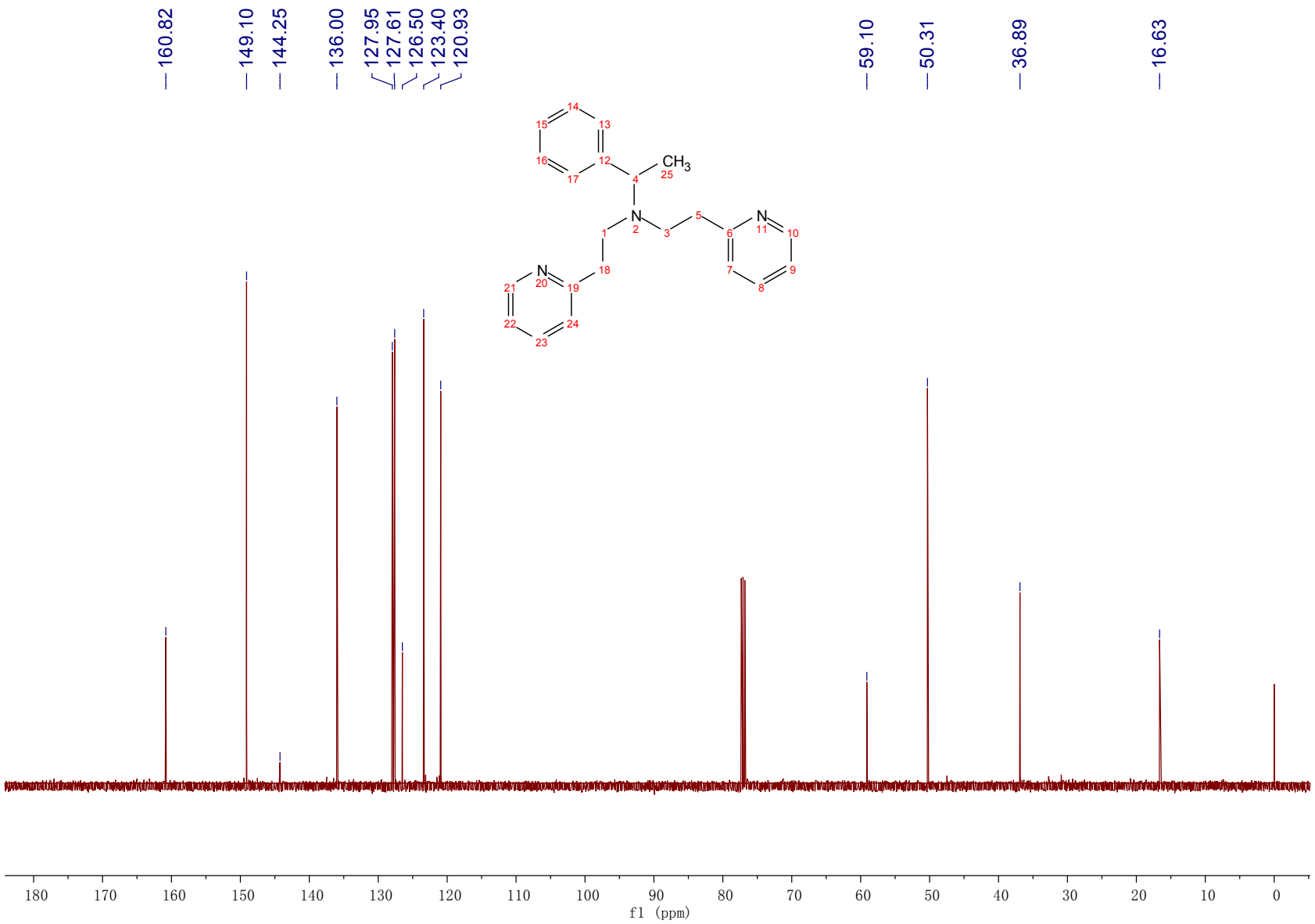
6.80
2.96
2.87
2.79
2.69
2.51
2.00
2.00
0.98
2.02
1.93
2.00
4.19
4.14
2.16
2.15
6.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

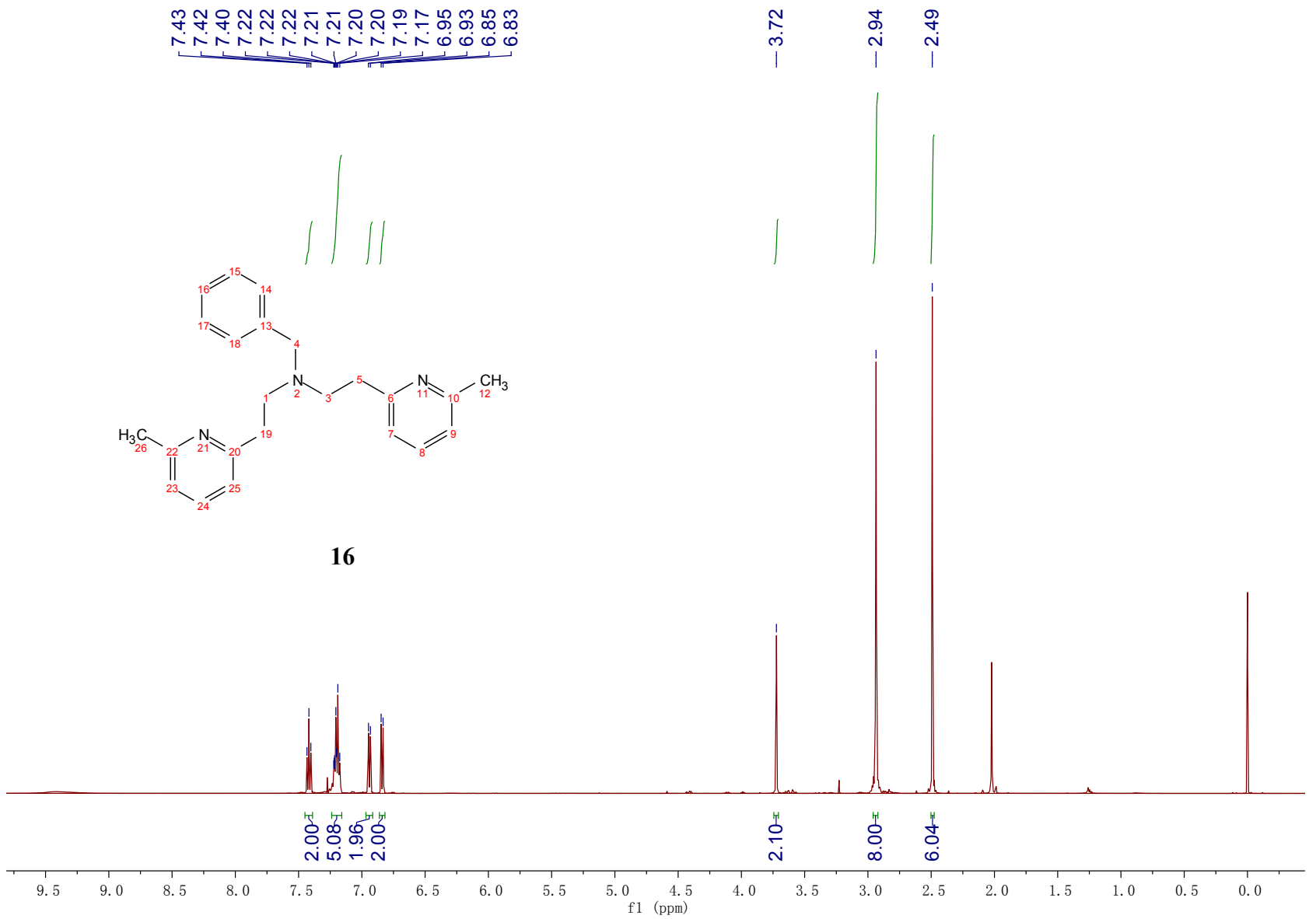
14


160.05
157.63
140.74
136.33
128.77
128.21
125.77
120.48
120.20
55.94
54.06
36.14
33.84
24.50
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

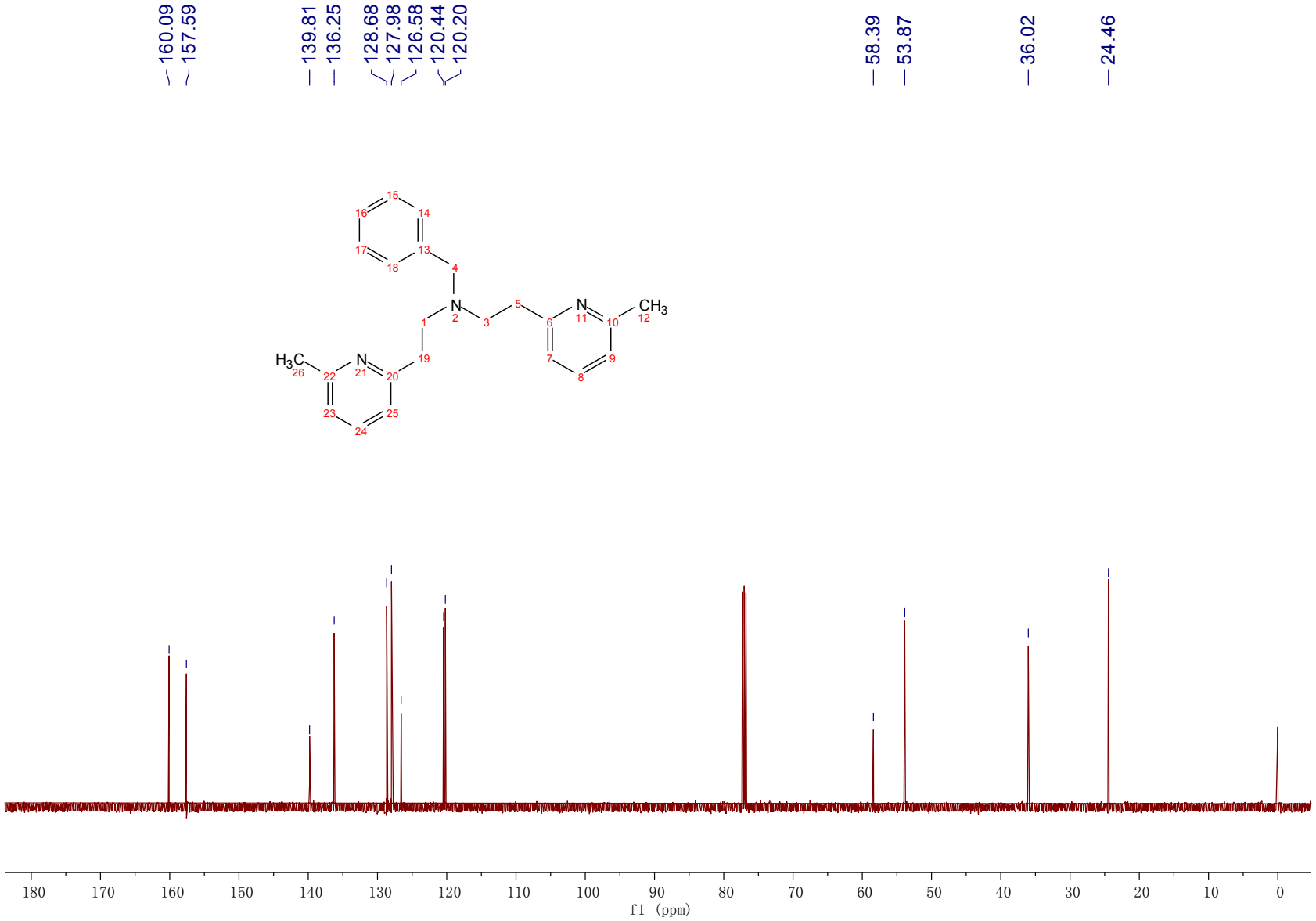

8.472
8.470
8.462
8.460
7.515
7.512
7.500
7.496
7.485
7.481
7.218
7.209
7.180
7.172
7.163
7.066
7.064
7.057
7.054
7.051
7.049
6.989
6.987
6.985
6.971
3.954
3.940
3.927
3.913
2.891
2.881
2.876
1.320
1.307
CH3
1.85
2.00
4.01
1.01
2.00
2.02
1.08
8.00
3.03
f1 (ppm)

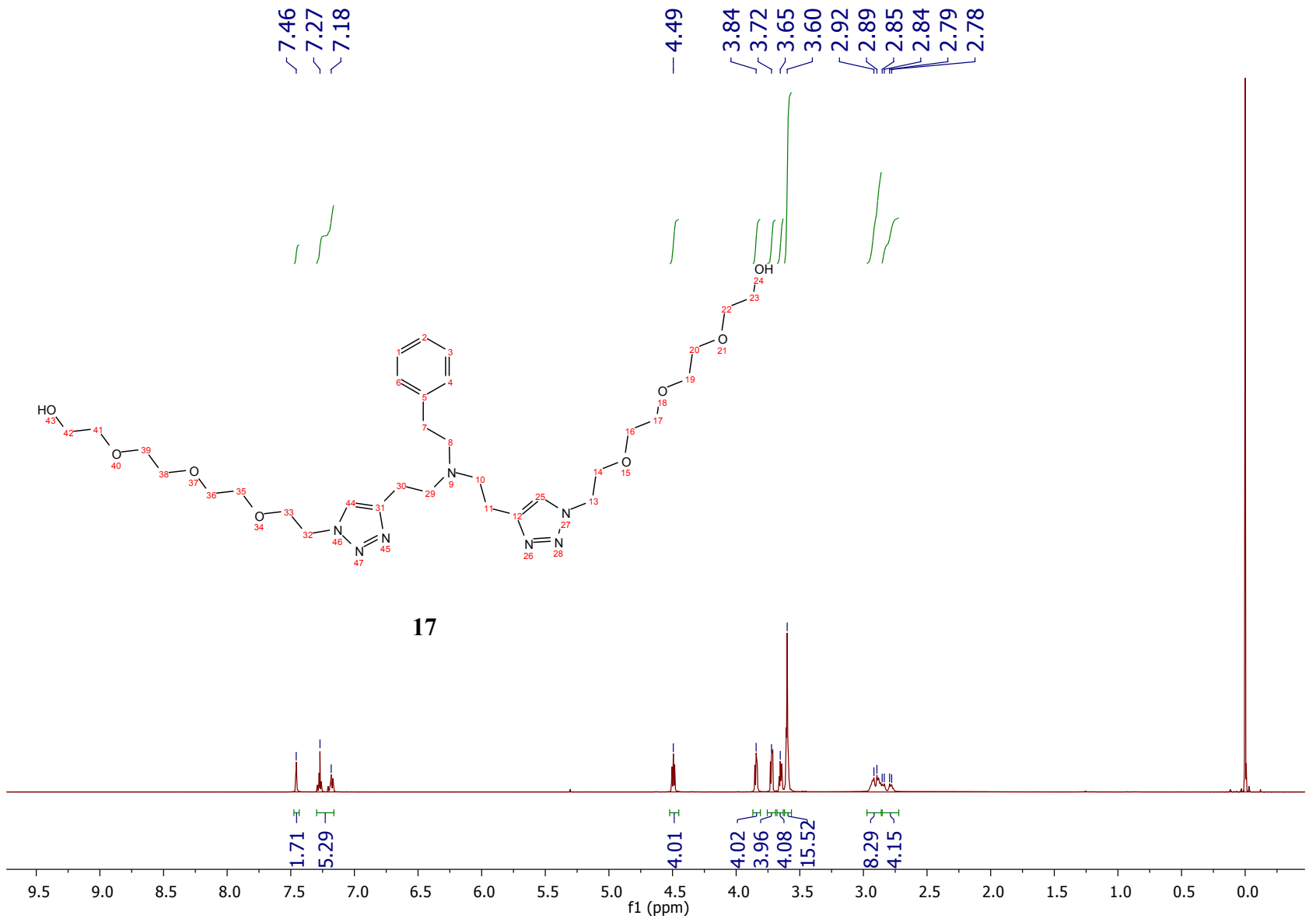
15


160.82
149.10
144.25
136.00
127.95
127.61
126.50
123.40
120.93
59.10
50.31
36.89
16.63
CH3
N
N
N
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

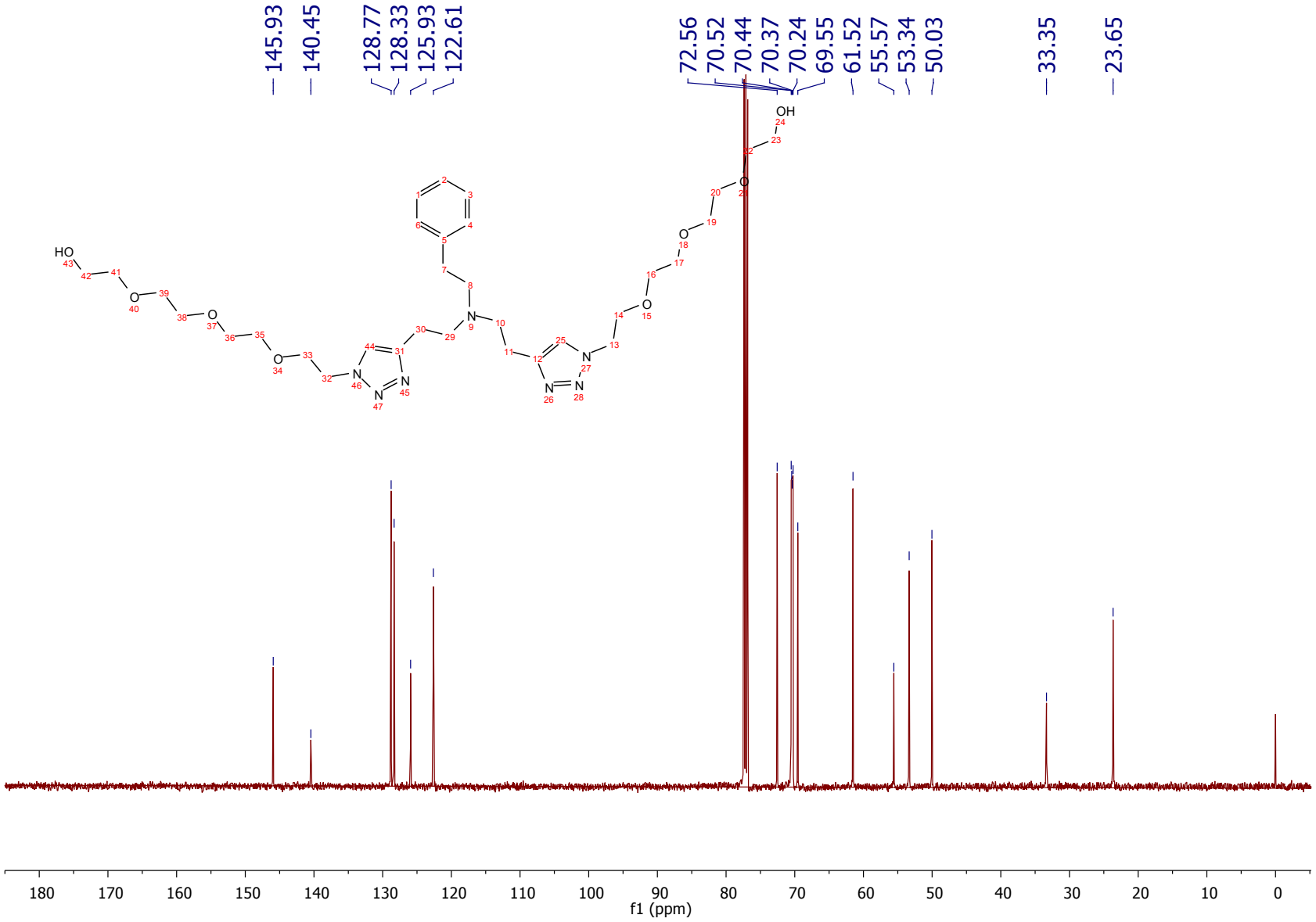

7.43
7.42
7.40
7.22
7.22
7.22
7.21
7.21
7.20
7.20
7.19
7.17
6.95
6.93
6.85
6.83
3.72
2.94
2.49
2.00
5.08
1.96
2.00
2.10
8.00
6.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

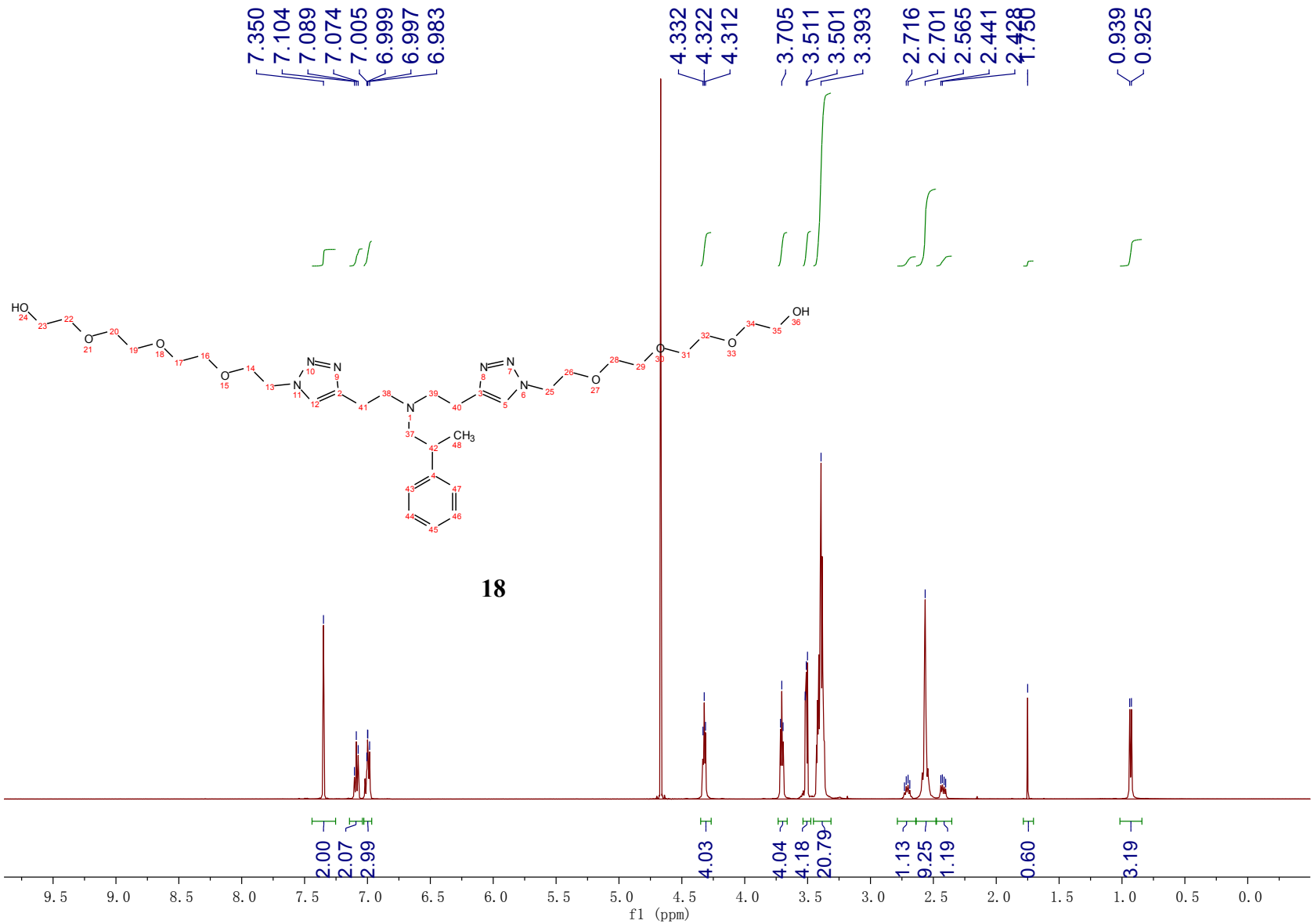
16


160.09
157.59
139.81
136.25
128.68
127.98
126.58
120.44
120.20
58.39
53.87
36.02
24.46
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

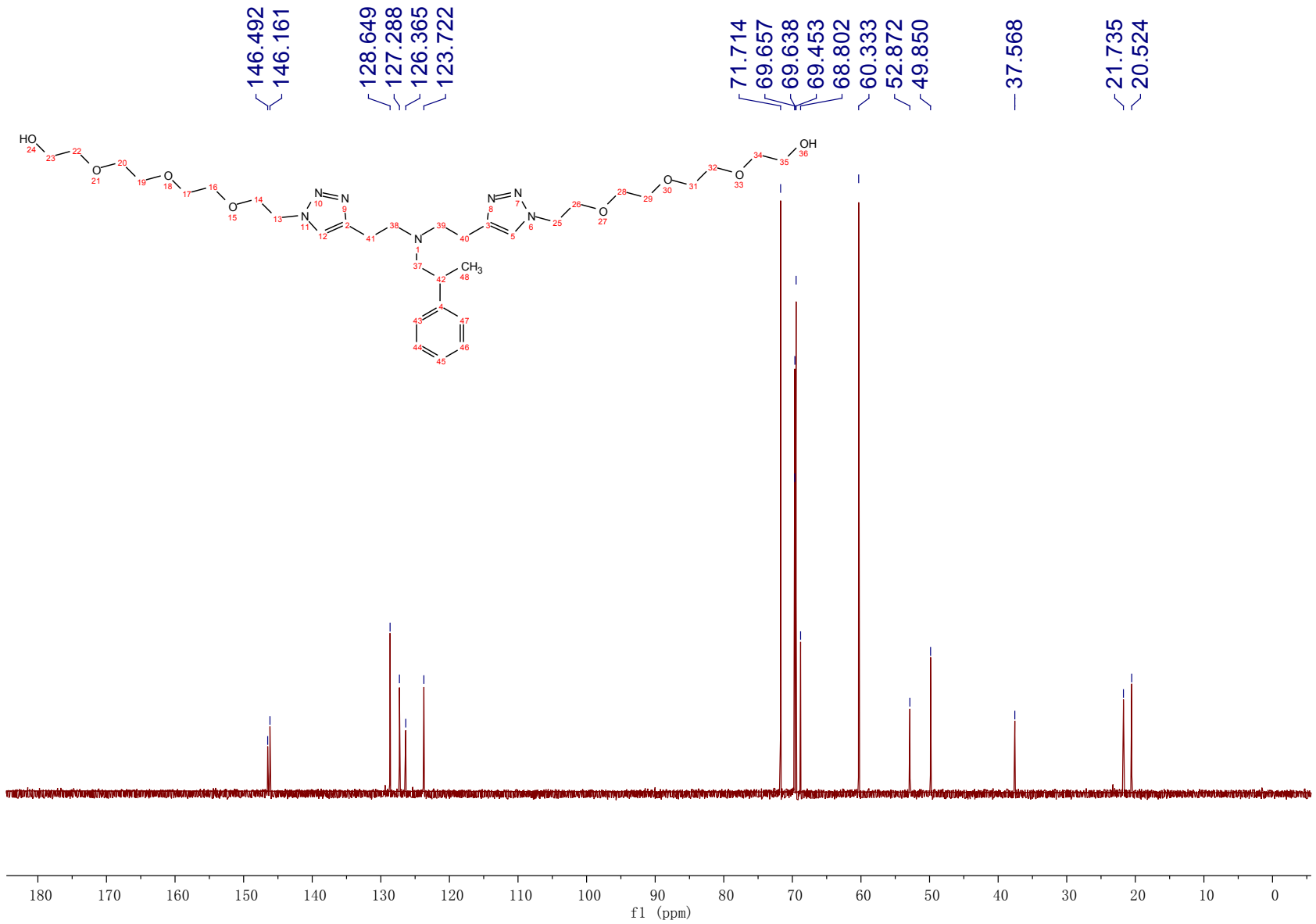

7.46
7.27
7.18
4.49
3.84
3.72
3.65
3.60
2.92
2.89
2.85
2.84
2.79
2.78
HO
OH
1.71
5.29
4.01
4.02
3.96
4.08
15.52
8.29
4.15
f1 (ppm)

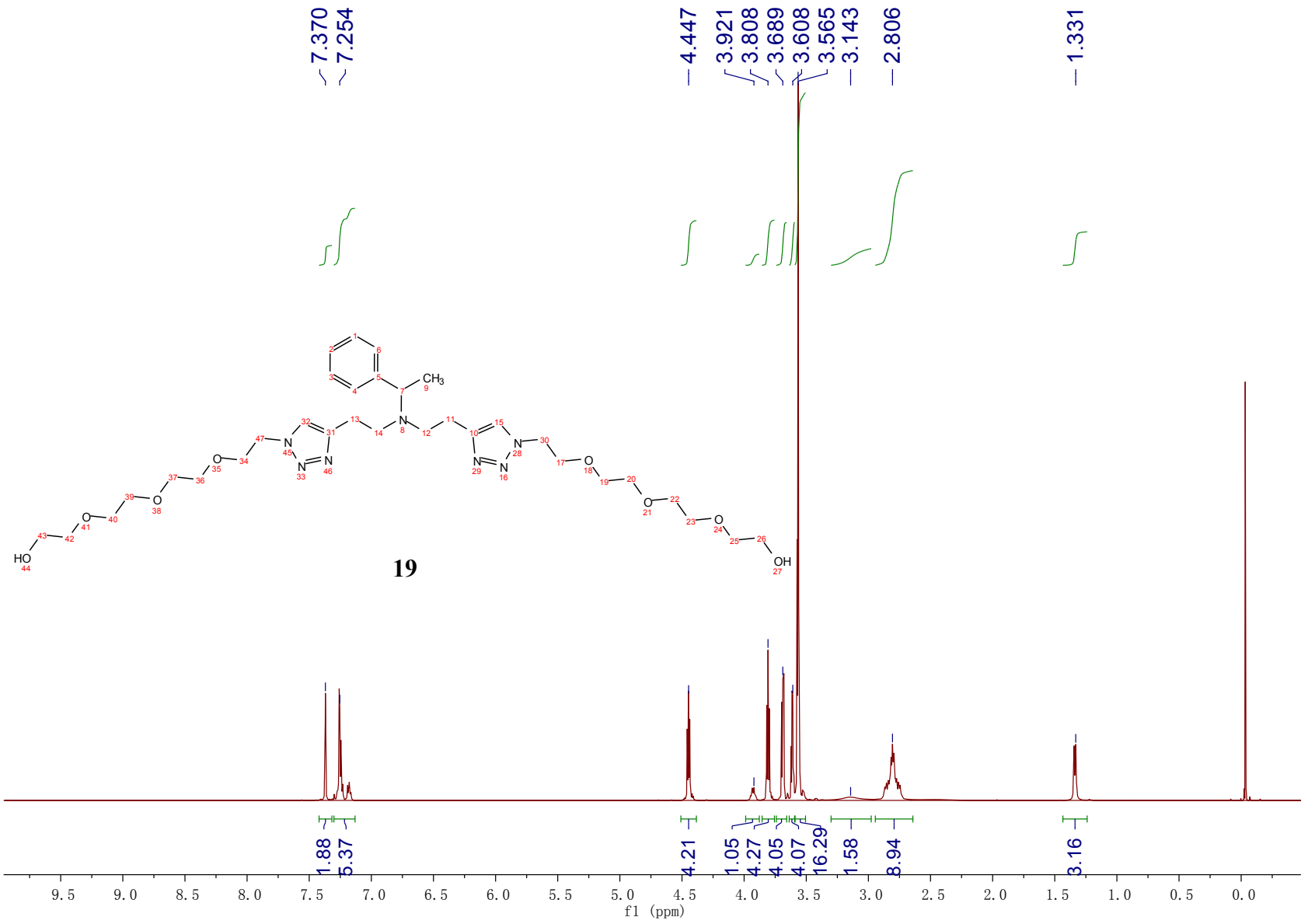
17

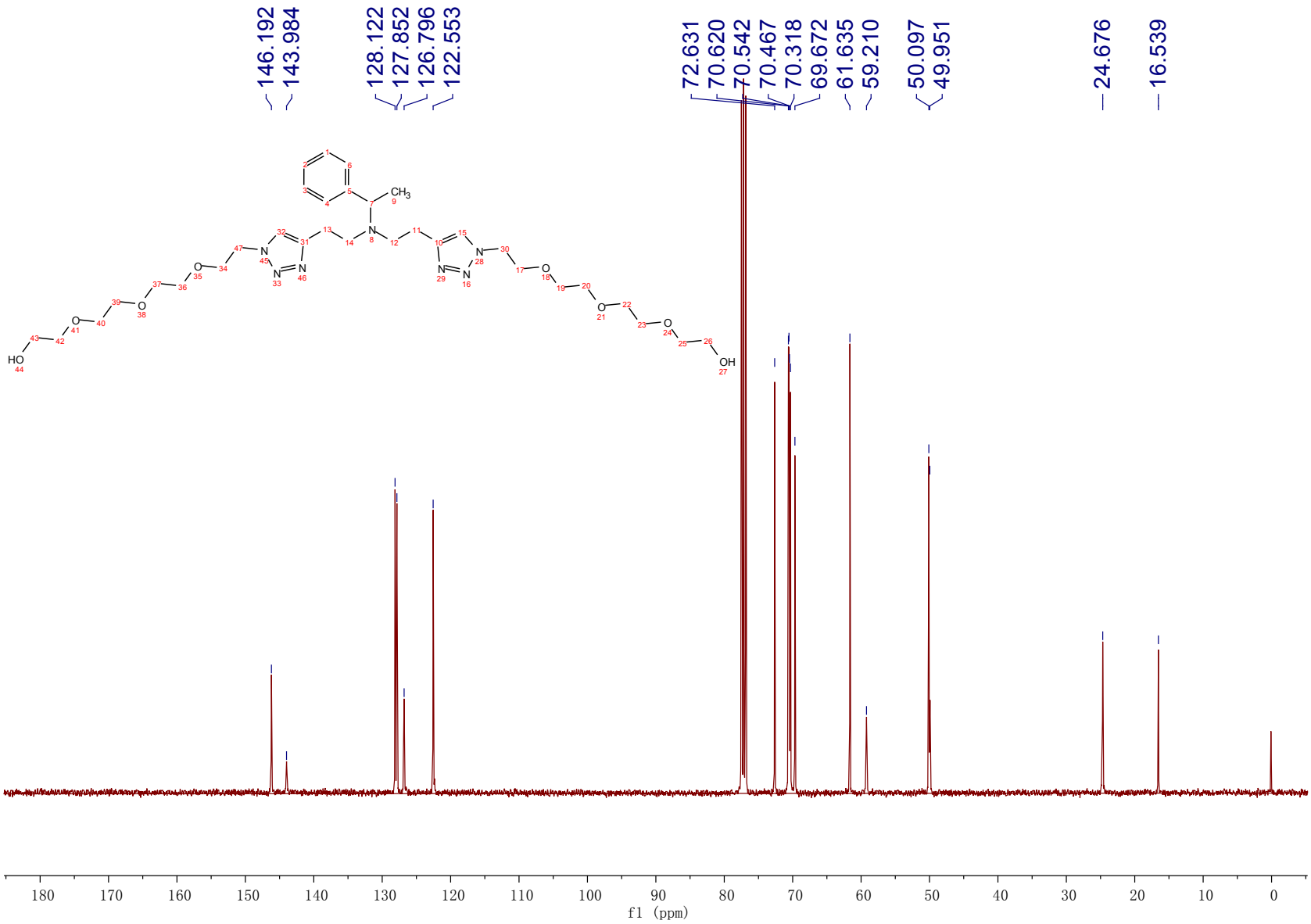

145.93
140.45
128.77
128.33
125.93
122.61
72.56
70.52
70.44
70.37
70.24
69.55
61.52
55.57
53.34
50.03
33.35
23.65
HO
OH
f1 (ppm)

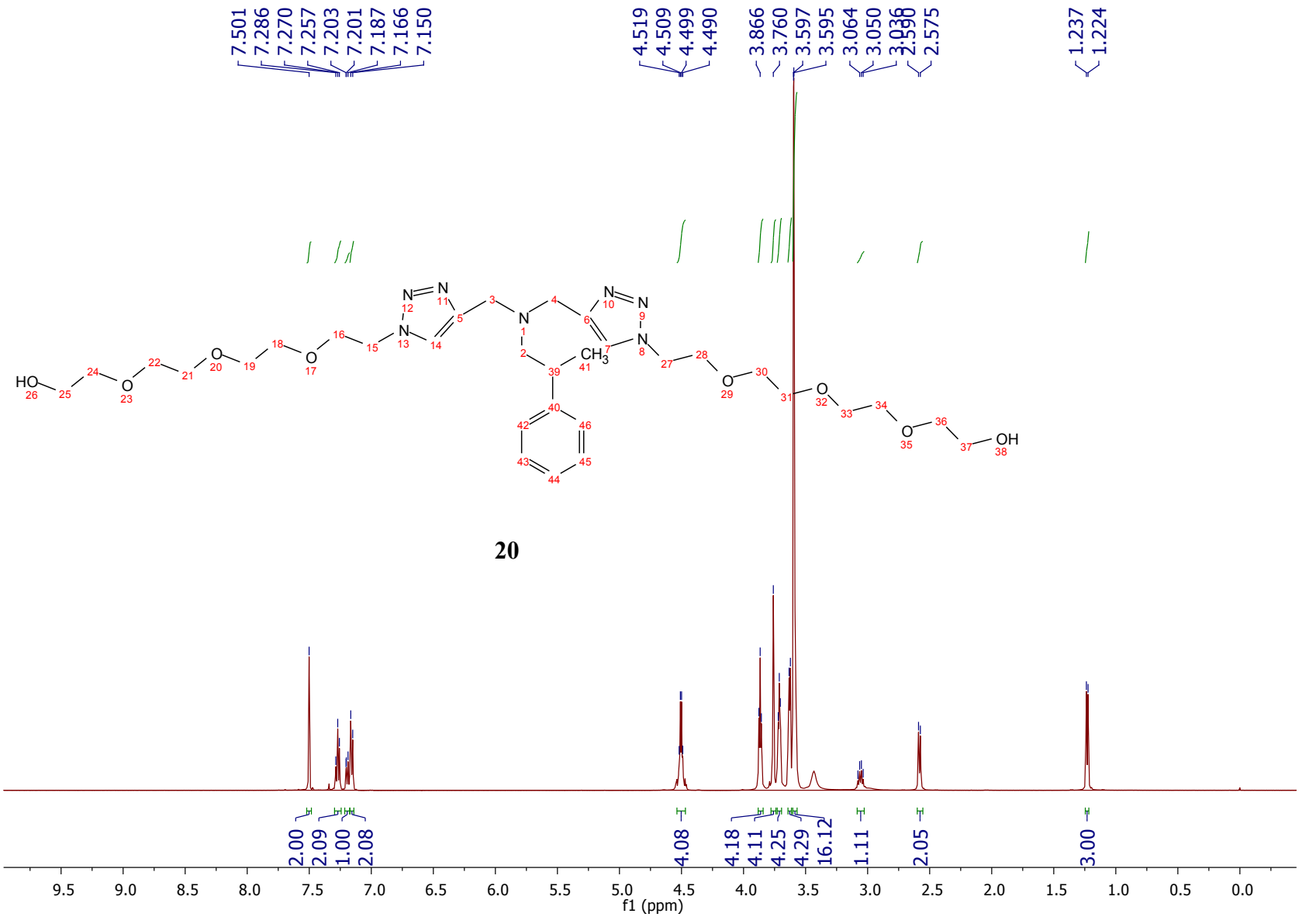

7.350
7.104
7.089
7.074
7.005
6.999
6.997
6.983
4.332
4.322
4.312
3.705
3.511
3.501
3.393
2.716
2.701
2.565
2.441
2.428
1.750
0.939
0.925
HO
OH
CH3
2.00
2.07
2.99
4.03
4.04
4.18
20.79
1.13
9.25
1.19
0.60
3.19
f1 (ppm)

18

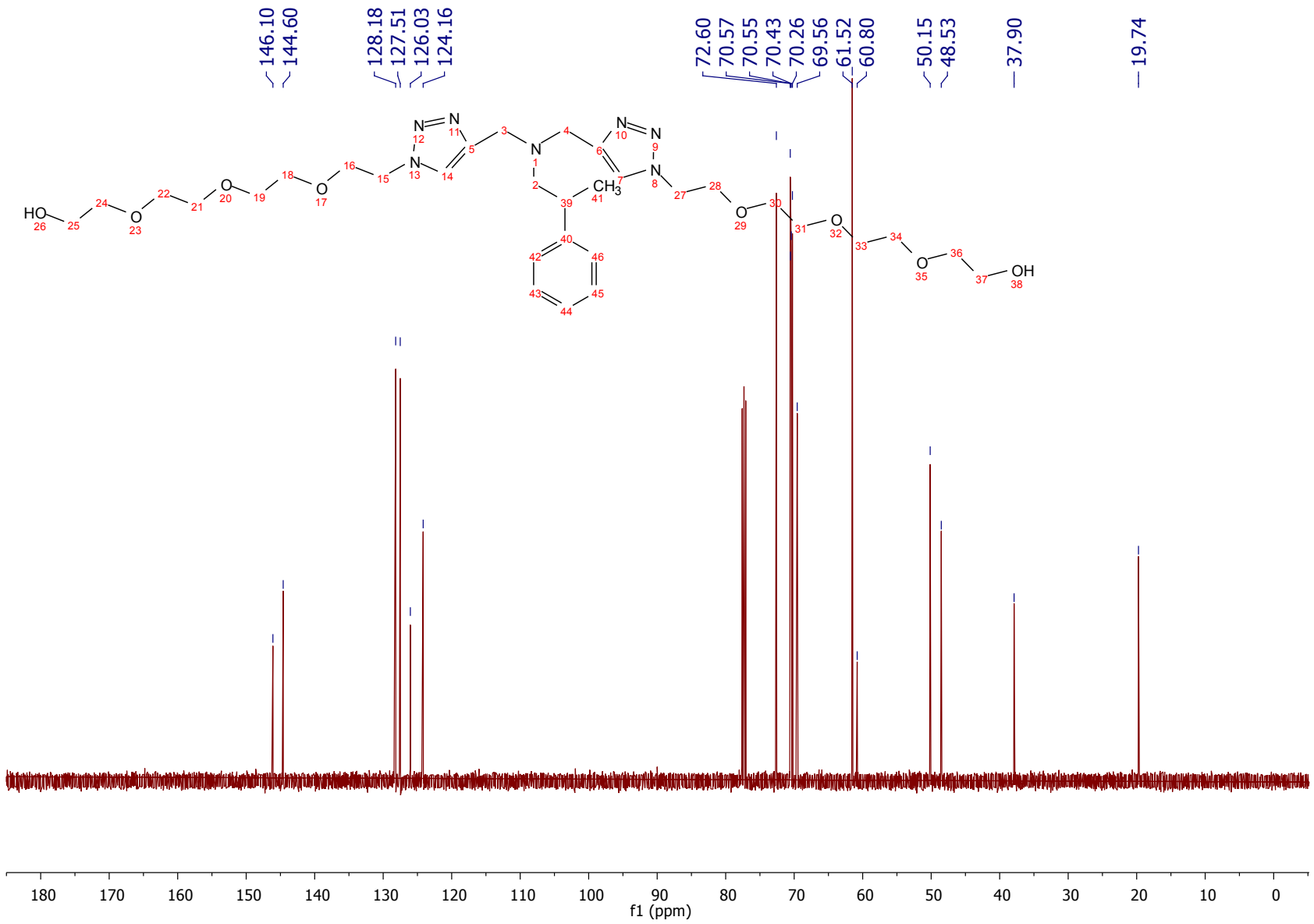

146.492
146.161
128.649
127.288
126.365
123.722
71.714
69.657
69.638
69.453
68.802
60.333
52.872
49.850
37.568
21.735
20.524
HO
OH
CH3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

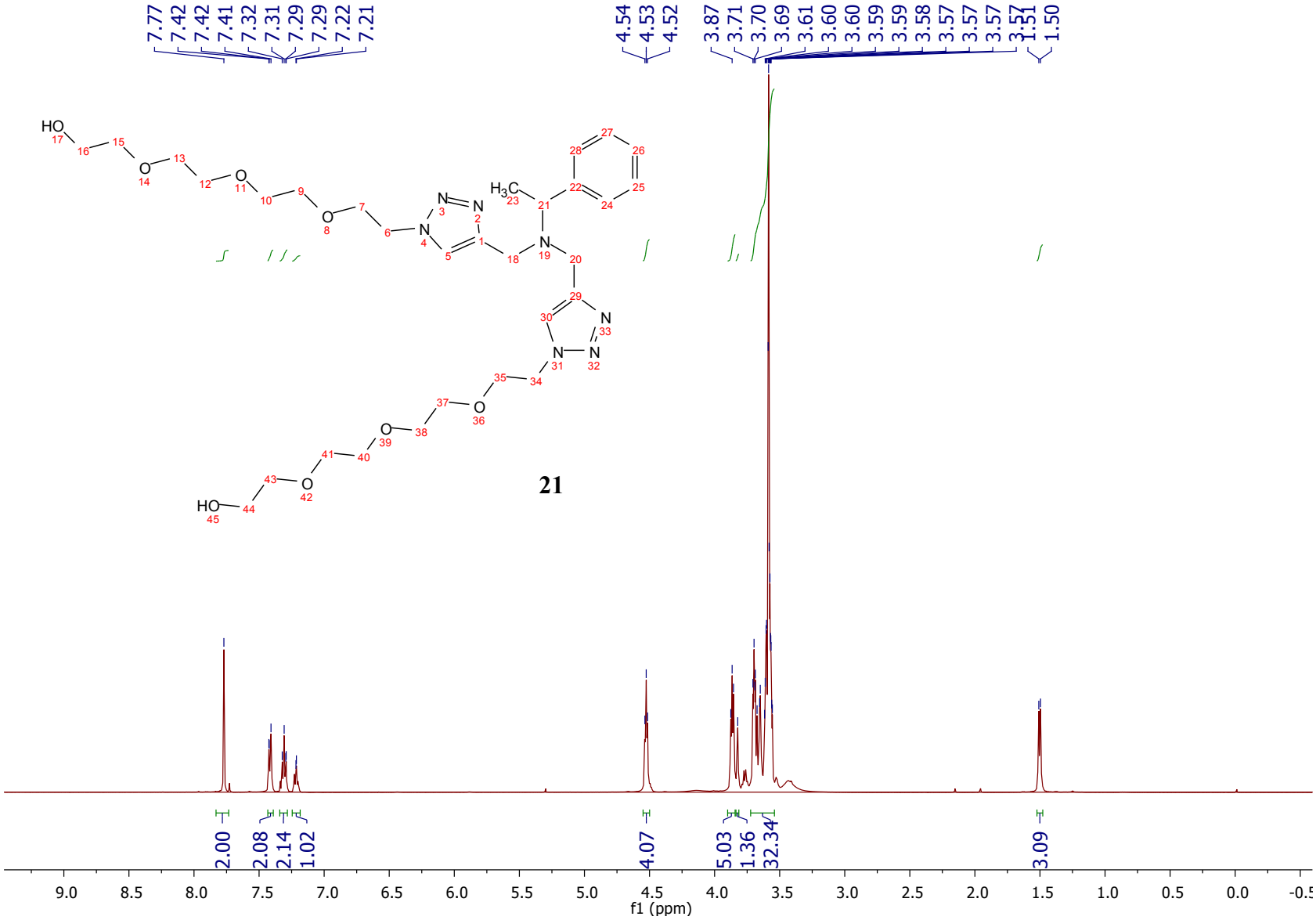

7.370
7.254
4.447
3.921
3.808
3.689
3.608
3.565
3.143
2.806
1.331
19
1.88
5.37
4.21
1.05
4.27
4.05
4.07
16.29
1.58
8.94
3.16
f1 (ppm)


146.192
143.984
128.122
127.852
126.796
122.553
72.631
70.620
70.542
70.467
70.318
69.672
61.635
59.210
50.097
49.951
24.676
16.539
CH3
HO
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

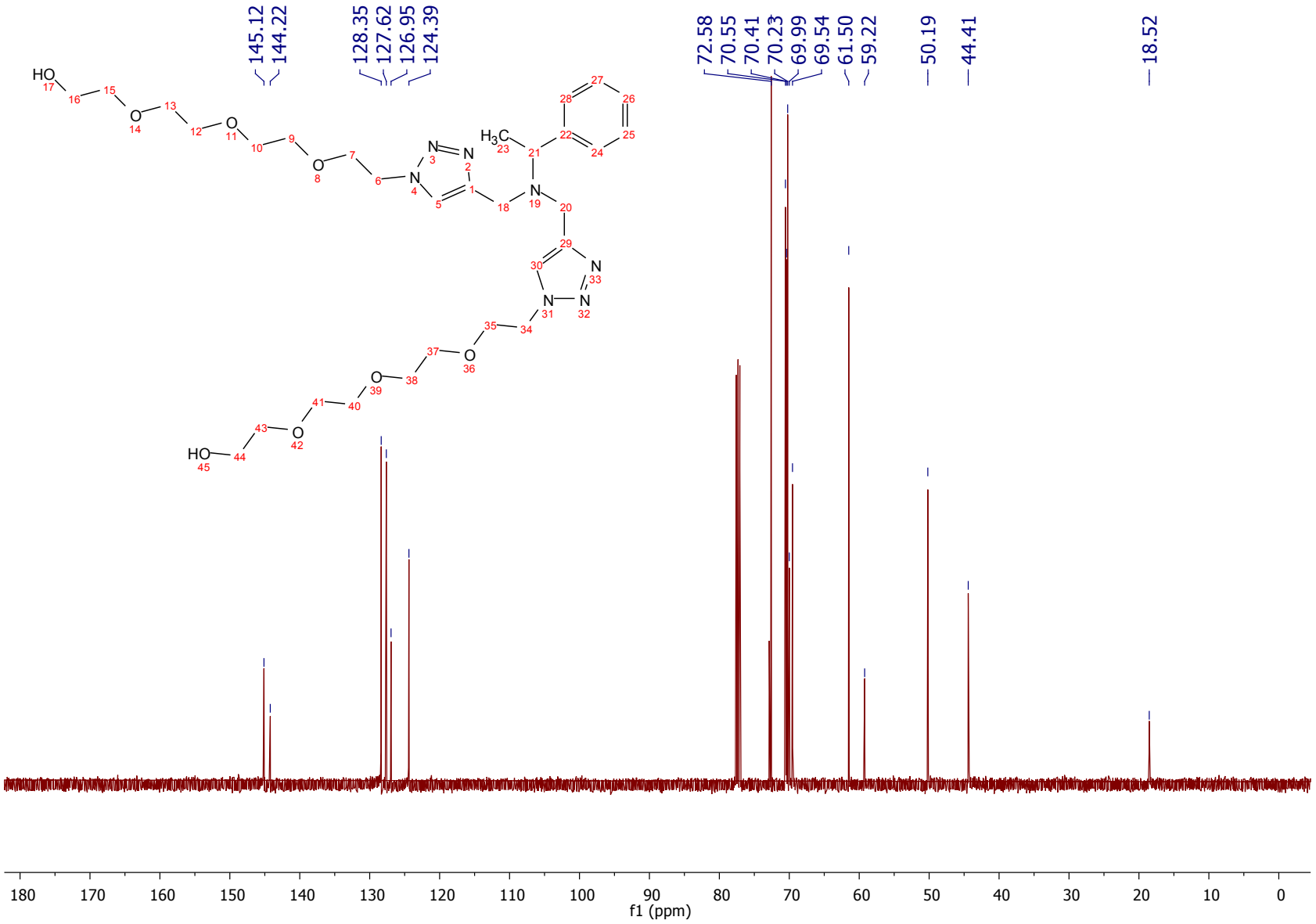

7.501
7.286
7.270
7.257
7.203
7.201
7.187
7.166
7.150
4.519
4.509
4.499
4.490
3.866
3.760
3.597
3.595
3.064
3.050
3.036
2.590
2.575
1.237
1.224
HO
OH
CH3
2.00
2.09
1.00
2.08
4.08
4.18
4.11
4.25
4.29
16.12
1.11
2.05
3.00
f1 (ppm)

20


146.10
144.60
128.18
127.51
126.03
124.16
72.60
70.57
70.55
70.43
70.26
69.56
61.52
60.80
50.15
48.53
37.90
19.74
HO
OH
CH3
f1 (ppm)


7.77
7.42
7.42
7.41
7.32
7.31
7.29
7.29
7.22
7.21
4.54
4.53
4.52
3.87
3.71
3.70
3.69
3.61
3.60
3.60
3.59
3.59
3.58
3.57
3.57
3.57
3.57
3.51
1.50
HO
O
O
O
N
N
N
N
N
N
N
O
O
O
O
HO
H3C
2.00
2.08
2.14
1.02
4.07
5.03
1.36
32.34
3.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

21


145.12
144.22
128.35
127.62
126.95
124.39
72.58
70.55
70.41
70.23
69.99
69.54
61.50
59.22
50.19
44.41
18.52
f1 (ppm)

I. Optimized Cartesian Coordinates of Selected Cu(I) Tripodal Amine Complexes

(1) Calculated atomic coordinates for Cu(I)-ligand 1 complex:

Standard Thermodynamic Quantities At 298.15 K and 1.00 ATM

This Molecule has 0 Imaginary Frequencies

Zero point vibrational energy: 206.502 kcal/mol

Total Enthalpy: 220.782 kcal/mol

Total Entropy: 157.374 cal/mol·K

N	0.01271009	-0.01637312	1.63975964
C	1.18229633	-0.87256910	1.92622263
H	0.83036445	-1.91089775	1.89402776
H	1.59043198	-0.70735215	2.93664352
C	0.17465882	1.42449714	1.92169590
H	-0.17242878	1.70032764	2.93083792
H	1.25051698	1.63473447	1.88993122
C	-1.31192933	-0.59565727	1.94200708
H	-1.35797169	-1.04323530	2.94815546
H	-2.02988418	0.23361830	1.93400686
C	2.26424955	-0.69100973	0.89696688
C	-1.72477923	-1.60836143	0.90791360
C	-0.51757418	2.27334893	0.88972257
N	3.06407018	-0.36589111	-1.15934846
N	1.95291659	-0.43739252	-0.42728664
N	4.10135976	-0.58169716	-0.28936447
C	3.64215942	-0.77951503	0.98425793
H	4.29664921	-0.96348154	1.81895096
C	-2.53128892	-2.72964794	0.99146772
H	-3.03417825	-3.19022750	1.82454779
N	-2.60889520	-3.21869792	-0.28399152
N	-1.87534115	-2.45173774	-1.15130701
N	-1.34571636	-1.47443400	-0.41612977
C	-1.11285686	3.51937331	0.97458689
H	-1.26956632	4.18315278	1.80750157
N	-1.51074739	3.82055181	-0.29934533
N	-1.19478018	2.80704169	-1.16692754
N	-0.58929389	1.87384625	-0.43333737
Cu	0.00913045	-0.02619094	-0.83388569
C	-3.33157323	-4.38895913	-0.78504630
H	-3.15071870	-4.44460515	-1.85781553
H	-2.96123066	-5.29653533	-0.30310527
H	-4.40207323	-4.27798076	-0.59906297
C	-2.19156415	5.01623354	-0.79866457
H	-2.32863970	4.88508675	-1.87135451
H	-3.16481022	5.12637077	-0.31509945
H	-1.58047656	5.90220605	-0.61287642
C	5.47836794	-0.56848784	-0.78552471
H	5.43231254	-0.39900886	-1.86062641
H	6.04300108	0.23728067	-0.31100279
H	5.95900399	-1.52864672	-0.58606064

(2) Calculated atomic coordinates for Cu(I)-ligand 2 complex:

Standard Thermodynamic Quantities At 298.15 K and 1.00 ATM

This Molecule has 1 Imaginary Frequencies

Zero point vibrational energy: 261.405 kcal/mol

Total Enthalpy: 277.351 kcal/mol

Total Entropy: 170.128 cal/mol·K

N	-0.05684049	-0.22759644	2.09832813
C	2.49068273	0.02485756	1.87227965
H	2.30542047	1.10586392	1.82716986
H	3.37148523	-0.10639793	2.51121460
C	-1.52359219	1.88315962	2.06247014
H	-1.94018799	2.58263389	2.79618360
H	-2.34493177	1.21141219	1.78074250
C	2.81584855	-0.48355226	0.50253715
C	-1.85336540	-2.25867947	0.22125177
C	-1.07820675	2.65828440	0.86291485
N	2.42048974	-1.00452885	-1.63143421
N	1.88009425	-0.51273176	-0.51317107
N	3.72505370	-1.28866089	-1.32264258
C	3.99852140	-0.98264660	-0.01852597
H	4.96838557	-1.12865504	0.42485356
C	-2.91519868	-2.94233946	-0.34816287
H	-3.47312803	-3.79999327	-0.01381941
N	-3.17336946	-2.30240261	-1.52829296
N	-2.31889607	-1.24693494	-1.71308016
N	-1.51984566	-1.23377001	-0.64251718
C	-1.17768284	4.00858264	0.56960469
H	-1.59999274	4.82946164	1.12328755
N	-0.60450070	4.15972447	-0.66240427
N	-0.14976211	2.95999417	-1.14408203
N	-0.44700792	2.05527021	-0.20728043
Cu	-0.03494686	0.08203939	-0.27492581
C	-0.43913902	5.37185864	-1.46351404
H	0.20569000	6.08449708	-0.94397438
H	0.02443153	5.07707536	-2.40424330
H	-1.41186840	5.82725571	-1.66207910
C	-4.18076241	-2.60656974	-2.54362120
H	-4.01307595	-3.60482600	-2.95432964
H	-5.18244401	-2.54614730	-2.11196318
H	-4.07755012	-1.86470267	-3.33474867
C	4.61037371	-1.83436751	-2.35068197
H	5.44570146	-1.15351902	-2.52987549
H	4.98788379	-2.81256451	-2.04413726
H	4.02241088	-1.93744434	-3.26197675
C	-1.08708365	-1.26276134	2.44892131
H	-2.06901166	-0.78237377	2.43417832
H	-0.91580866	-1.60883848	3.48282244
C	-0.40186033	1.07841538	2.75664896
H	0.50294952	1.69106635	2.78256398

H	-0.69156538	0.88932547	3.80471230
C	1.29900765	-0.68411346	2.55531381
H	1.37512728	-1.75761330	2.36523925
H	1.37742369	-0.54639179	3.64753577
C	-1.12291398	-2.48801536	1.50685634
H	-0.09964342	-2.82265794	1.29307544
H	-1.60794890	-3.31236444	2.04176089

(3) Calculated atomic coordinates for Cu(I)-ligand 3 complex:

Standard Thermodynamic Quantities At 298.15 K and 1.00 ATM

This Molecule has 0 Imaginary Frequencies

Zero point vibrational energy: 316.280 kcal/mol

Total Enthalpy: 335.007 kcal/mol

Total Entropy: 190.842 cal/mol·K

N	-1.24686029	-1.11107774	2.41513834
C	1.79129355	-1.13865937	1.68377580
H	1.08744077	-0.31658380	1.51806137
H	2.49756967	-0.80948830	2.45621184
C	-1.28214751	1.92009263	1.52502845
H	-2.20030768	2.51100736	1.63386351
H	-1.51820022	1.07947206	0.86425023
C	2.50453768	-1.36505808	0.38932905
C	-2.13025298	-1.43067831	-1.21904723
C	-0.22845507	2.73191869	0.84409146
N	2.76606640	-1.21935044	-1.82990396
N	1.98290983	-0.88014745	-0.80005921
N	3.80277590	-1.92720973	-1.29027185
C	3.67272327	-2.03645206	0.06753939
H	4.38983382	-2.55398115	0.68100446
C	-3.39293013	-1.34328679	-1.78433684
H	-4.21391328	-2.03891037	-1.80925273
N	-3.44651411	-0.11722591	-2.38928091
N	-2.27571309	0.56484729	-2.22444639
N	-1.47894743	-0.24329197	-1.51339024
C	0.20370222	4.03566512	1.02681983
H	-0.12758781	4.80901675	1.69801445
N	1.21698470	4.22098079	0.12626473
N	1.43656326	3.08969446	-0.60760151
N	0.55076510	2.19066709	-0.16489278
Cu	0.38217779	0.33349827	-0.97387257
C	2.02113871	5.41647727	-0.12606956
H	2.55745897	5.70786299	0.77975327
H	2.73470287	5.16735123	-0.91050781
H	1.38205309	6.23708449	-0.45998753
C	-4.53926873	0.48903084	-3.15027443
H	-4.76531564	-0.11619152	-4.03108449
H	-5.42928612	0.57979406	-2.52364986
H	-4.20726924	1.47839249	-3.46252121
C	4.86007246	-2.44182850	-2.16055525

H	5.82571533	-2.02629577	-1.86410168
H	4.89326928	-3.53250217	-2.10966781
H	4.62418877	-2.12936654	-3.17707003
C	-2.40564005	-1.89512588	1.91226184
H	-3.10916386	-1.17423361	1.48036314
H	-2.93379089	-2.39107050	2.75103803
C	-1.68247949	0.06626906	3.22481658
H	-1.61826774	-0.15780815	4.30154798
H	-2.74180844	0.25666152	3.01619499
C	-0.19970466	-1.91871946	3.09882900
H	-0.64978887	-2.81208386	3.56608535
H	0.20606462	-1.31469826	3.91987685
C	-1.44725608	-2.52584267	-0.46263731
H	-0.42833253	-2.18372173	-0.26757548
H	-1.35668827	-3.40770022	-1.11208300
C	-0.88069013	1.34113688	2.90769207
H	-1.05465540	2.08744080	3.69396958
H	0.19061945	1.10967854	2.92645582
C	0.97831646	-2.35317786	2.20255590
H	1.62893857	-3.02108222	2.78277834
H	0.61068974	-2.94170187	1.35795369
C	-2.11687197	-2.97802929	0.85816624
H	-1.49825483	-3.77470144	1.29047378
H	-3.08267039	-3.45085798	0.62939643

(4) Calculated atomic coordinates for Cu(I)-ligand 5 complex:

Standard Thermodynamic Quantities At 298.15 K and 1.00 ATM

This Molecule has 1 Imaginary Frequencies

Zero point vibrational energy: 242.727 kcal/mol

Total Enthalpy: 258.166 kcal/mol

Total Entropy: 168.977 cal/mol·K

N	-0.02408725	0.74800758	1.88211974
C	2.21776965	-0.52648455	1.83150212
H	2.65172651	0.36042683	1.35530968
H	2.95540194	-0.86769758	2.56731043
C	2.03443859	-1.61408165	0.81818639
C	-2.85761299	-0.37478099	0.66433785
C	1.23351804	2.42105014	0.50677904
N	1.15348372	-2.64705187	-0.95451804
N	1.10151363	-1.54619448	-0.19944503
N	2.13956241	-3.42734403	-0.41186421
C	2.69764622	-2.82329900	0.67976484
H	3.49221739	-3.26941034	1.25290265
C	-4.19247322	-0.39553570	0.29427065
H	-5.08860875	-0.55091153	0.87001269
N	-4.20558725	-0.17458434	-1.05454129
N	-2.93518469	-0.01333631	-1.53948494
N	-2.12471362	-0.13866470	-0.48459222
C	2.18726472	3.37767959	0.20327868

H	2.65551003	4.13979397	0.80233843
N	2.47107009	3.19785919	-1.12335218
N	1.73668651	2.16502897	-1.64854196
N	0.98555443	1.70612134	-0.64636185
Cu	-0.14529521	0.02717409	-0.47936723
C	3.39722790	3.93809483	-1.98068547
H	4.41366963	3.87082801	-1.58632973
H	3.35664638	3.48137847	-2.96885359
H	3.09310958	4.98508540	-2.04881781
C	-5.34403589	-0.11015391	-1.97077395
H	-5.87517735	-1.06464016	-1.97946419
H	-6.02382286	0.69115284	-1.67225473
H	-4.94837265	0.09689466	-2.96436432
C	2.46418769	-4.71581012	-1.02374038
H	3.49111760	-4.70879101	-1.39622306
H	2.33806134	-5.52040489	-0.29591331
H	1.77551201	-4.86221122	-1.85502382
C	-1.38908119	0.65593301	2.49374953
H	-1.93420924	1.57114248	2.24853720
H	-1.30917667	0.61126029	3.59268533
C	0.45502061	2.15895505	1.76366334
H	1.04845435	2.45633244	2.64399466
H	-0.42919746	2.80601475	1.75387865
C	0.94016246	-0.13182385	2.60899411
H	0.40981126	-1.04694170	2.88788136
H	1.24391823	0.36352440	3.54847673
C	-2.22030150	-0.55695272	2.00720037
H	-1.59058104	-1.45604116	1.99787835
H	-3.00988160	-0.74257857	2.74448685

(5) Calculated atomic coordinates for Cu(I)-ligand 10 complex:

Standard Thermodynamic Quantities At 298.15 K and 1.00 ATM

N	-0.04611543	0.08608157	-1.96643843
C	-0.74705668	-2.34990547	-1.66912188
H	-1.69036896	-1.90184035	-1.33120019
H	-1.01504845	-3.18342634	-2.32702616
C	-1.78908067	1.87209759	-1.42723931
H	-2.42795104	2.55510750	-1.99698436
H	-0.90934362	2.44893937	-1.11421090
Cu	0.02515161	-0.01420681	0.25626027
C	1.11624484	0.91127681	-2.43203011
H	0.83613530	1.96537118	-2.35206235
H	1.29947647	0.71086254	-3.50067699
C	-1.34260951	0.72601997	-2.36686879
H	-2.11464015	-0.04890302	-2.37881494
H	-1.25868508	1.10731662	-3.39779370
C	0.04722012	-1.31261704	-2.49723379
H	1.10209912	-1.59991910	-2.51043099
H	-0.30145369	-1.33175410	-3.54305053

C	2.42008801	0.67207912	-1.63407452
H	2.51681944	-0.39648996	-1.40125123
H	3.26733830	0.92639904	-2.28004810
C	2.53262671	1.47319320	-0.35741376
C	3.57977332	2.38416017	-0.15852841
C	3.66149933	3.10687578	1.03448049
C	2.68139556	2.91013448	2.01327671
C	1.65887414	1.99887703	1.75901869
N	1.58039374	1.28804774	0.60295581
H	4.47186042	3.80864609	1.19672833
H	4.32446218	2.51776598	-0.93467168
H	2.70577822	3.45022476	2.95203740
H	0.87303509	1.81881031	2.48218935
C	-0.00163254	-2.90404403	-0.47583865
C	0.27039407	-4.27443902	-0.35858825
C	0.96257626	-4.75699147	0.75504017
C	1.38260941	-3.85152383	1.73552695
C	1.09127416	-2.50007071	1.56372984
N	0.40873100	-2.02831451	0.48724155
H	1.17158249	-5.81622867	0.85444729
H	-0.06330605	-4.95257576	-1.13582454
H	1.92422609	-4.18261260	2.61333362
C	-2.54659120	1.41004593	-0.20413269
C	-3.88041400	1.78195372	0.01484954
C	-4.55442677	1.32837618	1.15164095
C	-3.87918441	0.49825050	2.05321787
C	-2.55647894	0.15547322	1.78183556
N	-1.89521288	0.60008666	0.68087303
H	-5.58473168	1.61547858	1.32943387
H	-4.37982873	2.42380733	-0.70183544
H	-4.36497603	0.12344345	2.94597990
H	1.40304647	-1.76035491	2.29106029
H	-1.99471466	-0.49096752	2.44477730

(6) Calculated atomic coordinates for Cu(I)-ligand 11 complex:

Standard Thermodynamic Quantities At 298.15 K and 1.00 ATM

N	-0.05098348	-0.01977894	-1.42541576
C	-0.93512434	-1.17514180	-1.67300124
H	-0.31014048	-2.07548046	-1.61974241
H	-1.37658031	-1.15514569	-2.68200483
C	-0.62222714	1.30307332	-1.74602505
H	-0.41814484	1.60452107	-2.78576359
H	-1.71218681	1.21560877	-1.65226948
C	1.36678275	-0.20767026	-1.79133348
H	1.48532189	-0.61380720	-2.80854811
H	1.83308087	0.78597270	-1.79537503
Cu	0.03865637	0.02881765	0.82391503
C	-2.04536959	-1.30885841	-0.63872901
C	-3.29062222	-1.84618621	-0.97928759

C	-4.25876709	-2.03114680	0.01335369
C	-3.95908081	-1.66522975	1.32934998
C	-2.70508386	-1.12035589	1.60475363
N	-1.76367431	-0.94300173	0.64418989
H	-5.22738153	-2.44859520	-0.23707550
H	-3.49656024	-2.11744423	-2.00899129
H	-4.68115492	-1.79187805	2.12673874
H	-2.43147403	-0.81257055	2.60601733
C	2.49434043	-1.72617260	1.41962011
C	3.58119708	-2.52298347	1.06065976
C	3.93961469	-2.60295048	-0.28870799
C	3.20232726	-1.87736921	-1.23019173
C	2.13225686	-1.08278468	-0.80713283
N	1.78078379	-1.01784601	0.50858152
H	4.77343028	-3.22022450	-0.60320978
H	2.17278936	-1.64287236	2.45002871
H	4.12533635	-3.07040779	1.82060684
H	3.45475413	-1.92290125	-2.28394562
C	-0.15276480	2.40168379	-0.80190571
C	-0.01645630	3.72233824	-1.24060982
C	0.33693274	4.72130769	-0.32757377
C	0.55444251	4.37230224	1.00911822
C	0.41795764	3.03559926	1.38324147
N	0.07228707	2.06563967	0.50001393
H	0.44376494	5.74925701	-0.65490940
H	-0.18814414	3.96366465	-2.28400557
H	0.83078145	5.11571353	1.74684191
H	0.58763741	2.71575047	2.40358072

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