Supporting Information

cis-Amide promotion in α-ABpeptoid foldamers *via* triazolium side chains

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Materials and Methods

(1) Materials and General Methods:

All chemicals and reagents were purchased from commercial suppliers (Sigma-Aldrich, Saint Louis, Missouri, and Alfa Aesar, Haverhill, Massachusetts) and used without further purification unless specified. Rink amide MBHA resin (0.45 mmol/g) was purchased from Beadtech, Inc. (Seoul, South Korea). Analytical HPLC and LC/MS were conducted on Agilent systems with a C18 reversed phase HPLC column (Eclipse XDB, 3.5 μm, 4.6 mm × 150 mm). Linear gradients of A/B solvents (solvent A: 100% H_2O, 0.1% TFA; B: 100% acetonitrile (ACN), 0.1% TFA) were used with the flow rate of 0.7 ml/min (10 to 100% B gradient over 7 min followed by 100% B until 13-15 mins). Preparative HPLC purification was performed on an Agilent 1120 Compact LC system (Agilent Technology) with a C18 reversed-phase column (Agilent Technology, 5 μm, 21.2 mm × 150 mm) using a linear gradient from 20% B to 90% B by changing solvent composition over 50 minutes with the flow rate of 10 ml/min. High Resolution Mass Spectra (HRMS) were obtained using Agilent 7890 high-resolution mass spectrometer for oligomers (ESI-TOF), and JMS-700 high-resolution mass spectrometer coupled with a QQHQC type mass analyzer for monomers at Korea Basic Science Institute (KBSI), Ochang, Korea. CD spectra were recorded on a Jasco J-815 spectropolarimeter. The CD spectra were measured in the quartz cuvette with 2 mm path length. The spectra were averages of 5 successive accumulations, employing 100 nm/min scan rate. Data were expressed in terms of per-residue molar ellipticity (deg cm^2/dmol), as calculated per mole of amide groups present and normalized by the molar concentration of peptoids. Smoothing (10 points) and correction of the background spectra was performed afterwards. All NMR experiments were performed using at 300 K. ^{1}H NMR spectra were recorded at resonance frequencies either of 300, 500, and 600 MHz, using Bruker AVANCE III 300, Bruker AVANCE III 500, and Bruker AVANCE III 600, respectively. ^{13}C NMR spectra were recorded at resonance frequency of 125 MHz using Bruker AVANCE III 500.

(2) Synthesis of Monomer Building Blocks.

Methyl (S)-2-methyl-3-((4-nitrophenyl)sulfonamido)propanoate (2). Compound **2** was prepared according to our previously reported method (*Org. Lett.* **2016**, *18*, 3678–3681).

Methyl (S)-2-methyl-3-((4-nitro-N-(prop-2-yn-1-yl)phenyl)sulfonamido)propanoate (3). To a solution of **2** (2.5 g, 8.27 mmol) in THF (40 mL) was added triphenyl phosphine (4.34 g, 16.55 mmol), followed by propargyl alcohol (1.06 mL, 18.21 mmol) at 0 °C. Then a solution of diethyl azocarboxylate (7.5 mL of 40% solution in toluene, 16.55 mmol) was added to the reaction mixture at 0 °C in dropwise manner and left stirred at room temperature (rt) overnight. The mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL), extracted with EtOAc (2 × 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography to afford title compound **3** (2.55 g, 91%) as white powder. $[\alpha]_D20$ +30.6 (c 5.7, ACN); TLC R_f = ~0.5 (EtOAc/hexane 1:3); ^{1}H NMR (500MHz, $CDCl_3$): δ 8.35-8.32 (m, 2H), 8.05-8.02 (m, 2H), 4.15 (q, J = 18 Hz, 2H), 3.70 (s, 3H), 3.48-3.44 (dd, J = 8.5, 12 Hz, 1H), 2.97 (d, J = 7, 14 Hz, 1H), 2.89-2.85 (m, 1H), 2.00 (t, J = 2.5, 2 Hz, 1H), 1.22 (d, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 174.86, 150.45, 144.55, 129.31 (×2), 124.34 (×2), 75.90, 74.85, 52.31, 49.48, 39.04, 37.84, 15.21. HRMS (ESI-TOF MS) *m/z*: Calcd. for $C_{14}H_{16}N_2NaO_6S$ $[M + Na]^+$ 363.0627, found 363.0624.

Methyl (S)-3-((N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-nitrophenyl)sulfonamido)-2-methylpropanoate (4). To a stirred solution of **3** (2.5 g, 7.47 mmol) in *t*-BuOH (60 mL) under Ar were subsequently added a solution of freshly prepared aq. L-ascorbic acid (0.1 M, 22.4 mL, 0.3 equiv), a solution of aq. $CuSO_4$ (0.1 M, 7.5 mL, 0.1 equiv.) and benzyl azide (2.24 mL, 17.9 mmol, 2.4 equiv). The reaction mixture was degassed with Ar bubbling for 10 mins at rt and left for stirring overnight (~16 h) at 40 °C. On completion of reaction, the mixture was cooled down to rt, diluted with water to form a white precipitate. The obtained precipitate was filtered. The solid product was re-suspended into water and extracted with CH_2Cl_2 (5 × 100 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography to afford the desired product **4** (3.4 g, 96%) as white powder. $[\alpha]_D20$ +12.52 (c 3.8, ACN); TLC R_f = ~0.45 (2% MeOH/CH_2Cl_2); ^{1}H NMR

(500 MHz, $CDCl_3$): δ 8.21-8.19 (m, 2H), 7.88-7.86 (m, 2H), 7.42 (s, 1H), 7.37-7.35 (m, 3H), 7.24-7.21 (m, 2H), 5.44 (d, *J* =2.5 Hz, 2H), 4.51-4.50 (d, *J* =3.5 Hz, 2H), 3.58 (s, 3H), 3.51-3.47 (dd, *J* = 6.1, 8.1 Hz, 1H), 3.29-3.25 (dd, *J* = 6.7, 7.6 Hz, 1H), 2.89-2.85 (m, 1H), 1.06 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.90, 150.17, 145.51, 143.25, 134.49, 129.43 (×2), 129.24, 128.67 (×2), 128.29 (×2), 124.38 (×2), 123.25, 54.51, 52.15, 51.06, 43.69, 38.97, 15.15. HRMS (ESI-TOF MS) m/z: Calcd. For $C_{21}H_{24}N_5O_6S$ $[M + H]^+$ 474.1447, found 474.1446.

(S)-3-((N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-nitrophenyl)sulfonamido)-2-methylpropanoic acid (5). To a suspension of compound **4** (3.0 g, 6.33 mmol) in THF (24 mL) was added 1 N aq. solution of LiOH (12.6 mL, 2 equiv) at 0 °C. The mixture was stirred at 40 °C for 2-3 h. After complete consumption of starting material, volatiles were removed from the reaction mixture using rotary evaporator and the remaining aqueous layer was acidified with 1 N HCl solution until the pH of solution reached ~2-3. The white precipitate was stirred for 15 minutes and filtered. The solid product was washed with water and dried by applying high vacuum overnight. The desired product **5** (2.6 g, 89%) was obtained as a white powder. $[\alpha]D^{20}$ +18.34 (c 3.0, ACN); TLC R_f = ~0.2 (EtOAc/hexane/AcOH 1:1:0.02); ^1H NMR (500 MHz, CD_3CN): δ 9.68 (bs, 1H), δ 8.23-8.20 (m, 2H), δ 7.94-7.91 (m, 2H), 7.59 (s, 1H), 7.39-7.34 (m, 3H), 7.24-7.23 (m, 2H), 5.46 (s, 2H), 4.58-4.45 (d, *J* = 16.3, 34.5 Hz, 2H), 3.55-3.50 (dd, *J* = 7.5, 6.5 Hz, 1H), 3.26-3.2 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.89-2.82 (m, 1H), 1.06 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.32, 151.58, 146.37, 143.92, 137.02, 130.28 (×2), 130.01 (×2), 129.83, 129.33 (×2), 125.67 (×2), 124.98, 54.87, 52.34, 44.39, 39.56, 15.56. HRMS (ESI-TOF MS) m/z: Calcd. For $C_{20}H_{22}N_5O_6S$ $[M + H]^+$ 460.1291, found 460.1291.

(3) Synthesis of α-ABpeptoid Oligomers.

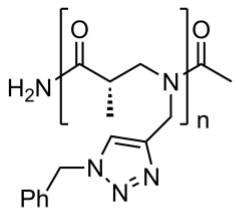
General Procedure for α-ABpeptoid Oligomer Synthesis:

Solid-phase syntheses were carried out in a 3 to 5 mL fritted syringe. The Rink amide MBHA resin (100 mg, 0.045 mmol) was swelled with DMF (1 mL) for 2 h. The Fmoc deprotection on resin (100 mg, 0.045 mmol) was carried out by 20 % piperidine in DMF (2 × 10 min). For the monomer coupling, resins were treated with the solution of synthesized monomer **5** (3.0 equiv), HATU (3.0 equiv), HOAt (3.0 equiv) and DIPEA (4.5 equiv) in DMF (1.0 mL) at room temperature. After shaking for 3 h, the reaction mixture was drained, and the resin was washed with DMF (×5) and CH_2Cl_2 (×5). Then to remove a nosyl protecting group, the resin was treated with 2-mercaptoethanol (2% in DMF, 0.6 ml) and 1,8-diazabicycloundec-7-ene (2.1% in DMF, 0.6 ml) for 45 min (×2) at room temperature. After a thorough washing cycle, the next monomer conjugation and nosyl deprotection steps were repeated to afford oligomers with the desired chain length. For *N*-terminal acetylation, acetic anhydrous (10 equiv) and DIPEA (10 equiv) in DMF (1 mL) was treated for 2 h at room temperature. For solid-phase quaternization reaction, an excess of MeI (~200 equiv) in ACN (0.2 mL) was added to the swollen resin in a glass vial and the reaction mixture was shaken at 70 °C for overnight. Final products were cleaved from the resin using a cleavage mixture (95% TFA, 2.5% TIS, and 2.5% H_2O) for 2 h (2 × 1 h) at room temperature and purified by reverse-phase HPLC. The purified α-ABpeptoids were characterized by mass spectrometry (Table S1).

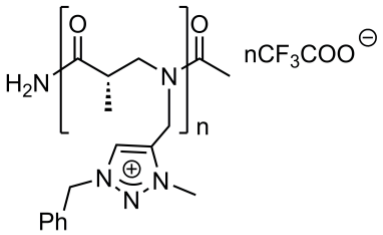
(4) NMR spectroscopic studies of α-ABpeptoids.

COSY and NOESY NMR spectra of **8a**, **9a**, and **9b** were recorded on Bruker AVANCE III 600. NOESY spectra were recorded with relaxation delay of 2 s and mixing time of 620 ms for **8a**, 450 ms for **9a**, and 600 msec for **9b**. ^{1}H-^{13}C HMBC NMR spectrum of **9b** was recorded on Bruker AVANCE III 500, with relaxation delay of 2 s.

Table S1. Purification and characterization of the synthesized α-ABpeptoids.



8a-h (n = 1-8)



9a-h (n = 1-8)

compound	chain length	% purity[a]		chemical formula	calcd mass	obsd mass[b]
		crude	purified			
8a	1	89	96	$C_{16}H_{22}N_5O_2$ $[M+H]^+$	316.1773	316.1773
8b	2	79	96	$C_{30}H_{38}N_9O_3$ $[M+H]^+$	572.3098	572.3096
8c	3	83	98	$C_{44}H_{54}N_{13}O_4$ $[M+H]^+$	828.4422	828.4419
8d	4	81	98	$C_{58}H_{70}N_{17}O_5$ $[M+H]^+$	1084.5746	1084.5747
8e	5	80	99	$C_{72}H_{86}N_{21}O_6$ $[M+H]^+$	1340.7070	1340.7067
8f	6	84	97	$C_{86}H_{102}N_{25}O_7$ $[M+H]^+$	1596.8394	1596.8394
8g	7	89	96	$C_{100}H_{118}N_{29}O_8$ $[M+H]^+$	1852.9718	1852.9706
8h	8	86	98	$C_{114}H_{134}N_{33}O_9$ $[M+H]^+$	2109.1042	2109.1052
9a	1	84	96	$C_{17}H_{24}N_5O_2$ $[M\text{-}CF_3COO^-]^+$	330.1930	330.1932
9b	2	84	99	$C_{34}H_{43}N_9O_5F_3$ $[M\text{-}CF_3COO^-]^+$	714.3339	714.3337
9c	3	77	97	$C_{51}H_{62}N_{13}O_8F_6$ $[M\text{-}CF_3COO^-]^+$	1098.4749	1098.4745
9d	4	84	99	$C_{68}H_{81}N_{17}O_{11}F_9$ $[M\text{-}CF_3COO^-]^+$	1482.6152	1482.6160
9e	5	80	99	$C_{85}H_{100}N_{21}O_{14}F_{12}$ $[M\text{-}CF_3COO^-]^+$	1866.7567	1866.7566
9f	6	74	99	$C_{102}H_{119}N_{25}O_{17}F_{15}$ $[M\text{-}CF_3COO^-]^+$	2250.8976	2250.8965
9g	7	90	97	$C_{119}H_{138}N_{29}O_{20}F_{18}$ $[M\text{-}CF_3COO^-]^+$	2635.0386	2635.0339
9h	8	93	97	$C_{136}H_{157}N_{33}O_{23}F_{21}$ $[M\text{-}CF_3COO^-]^+$	3019.1795	3019.1868

[a]Determined by analytical reversed-phase HPLC of purified products.
[b]High Resolution Mass Spectrometry (HRMS) data were acquired using Electrospray ionization (ESI) techniques.

Fig. S1 LC/MS spectra of purified α-ABpeptoid oligomers **8a-h** and **9a-h**.

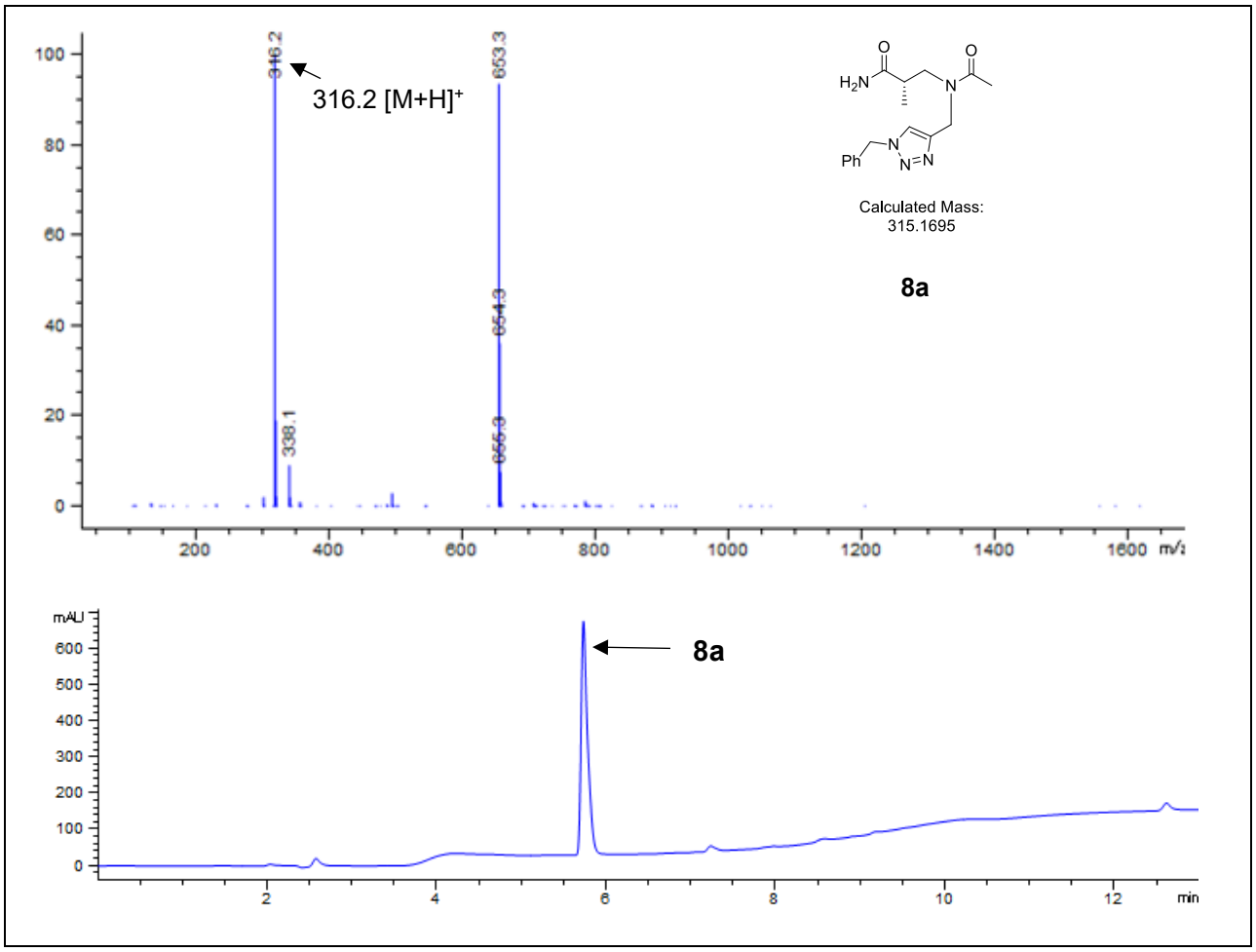
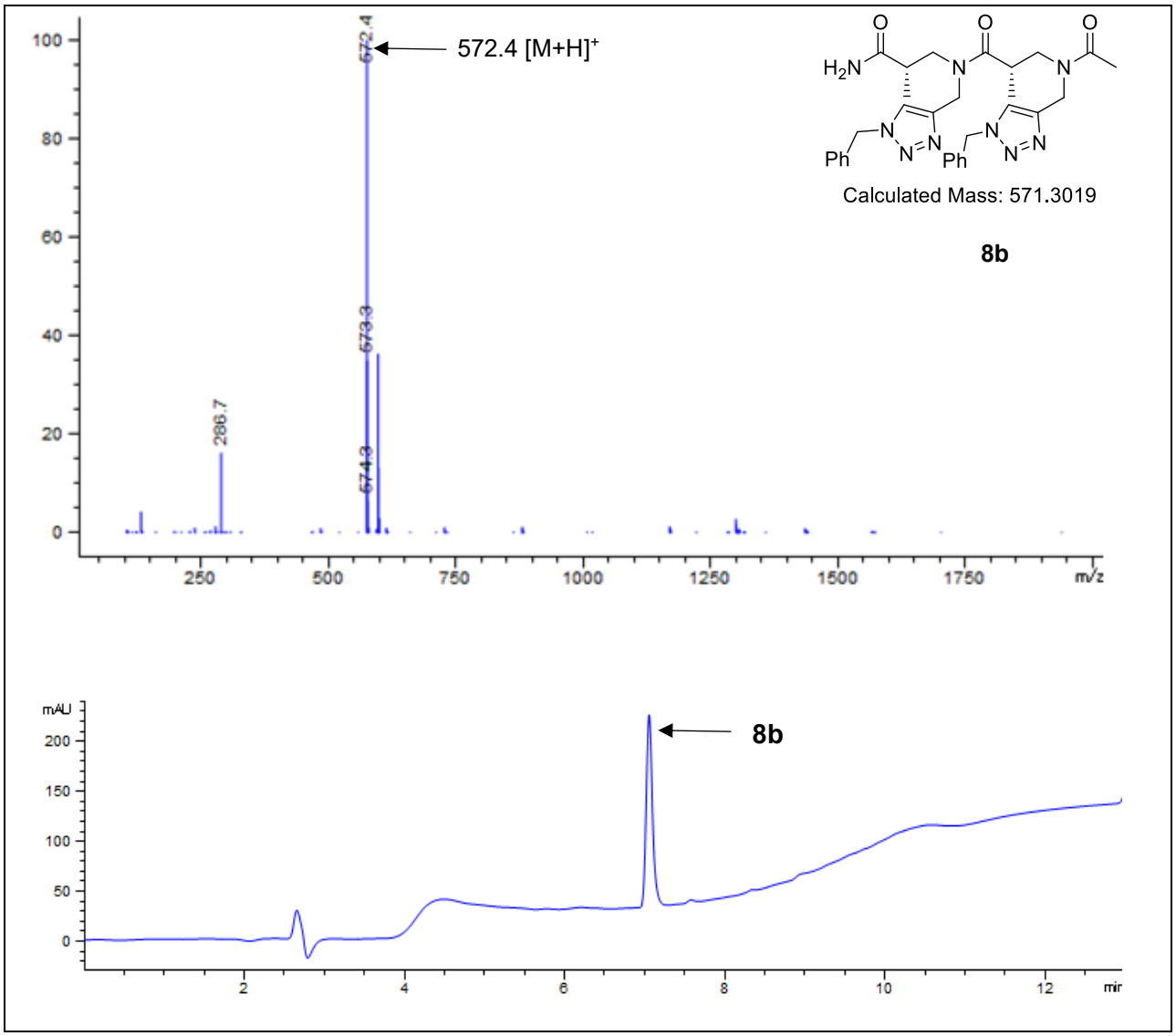


Fig. S1 (continued)



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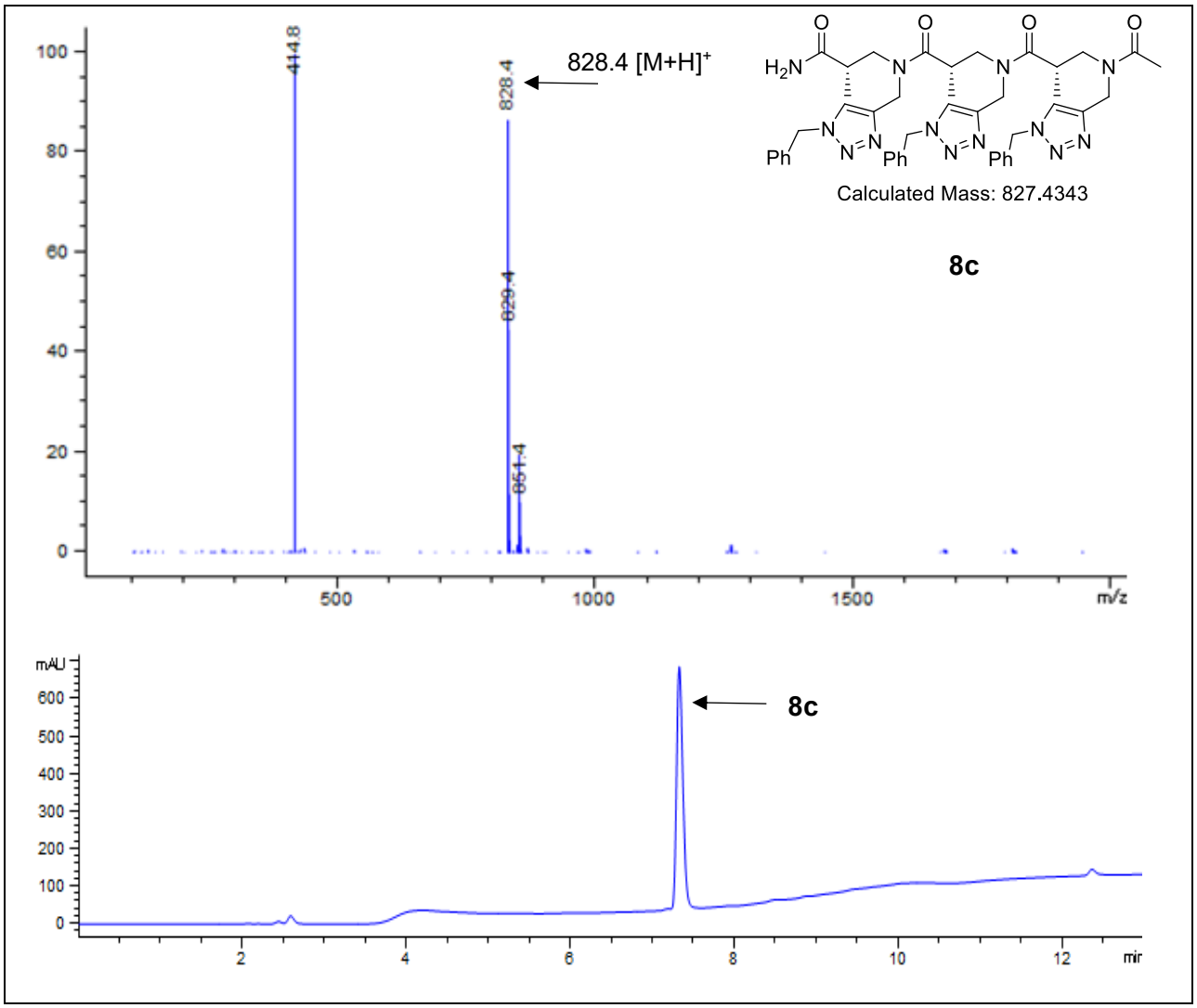

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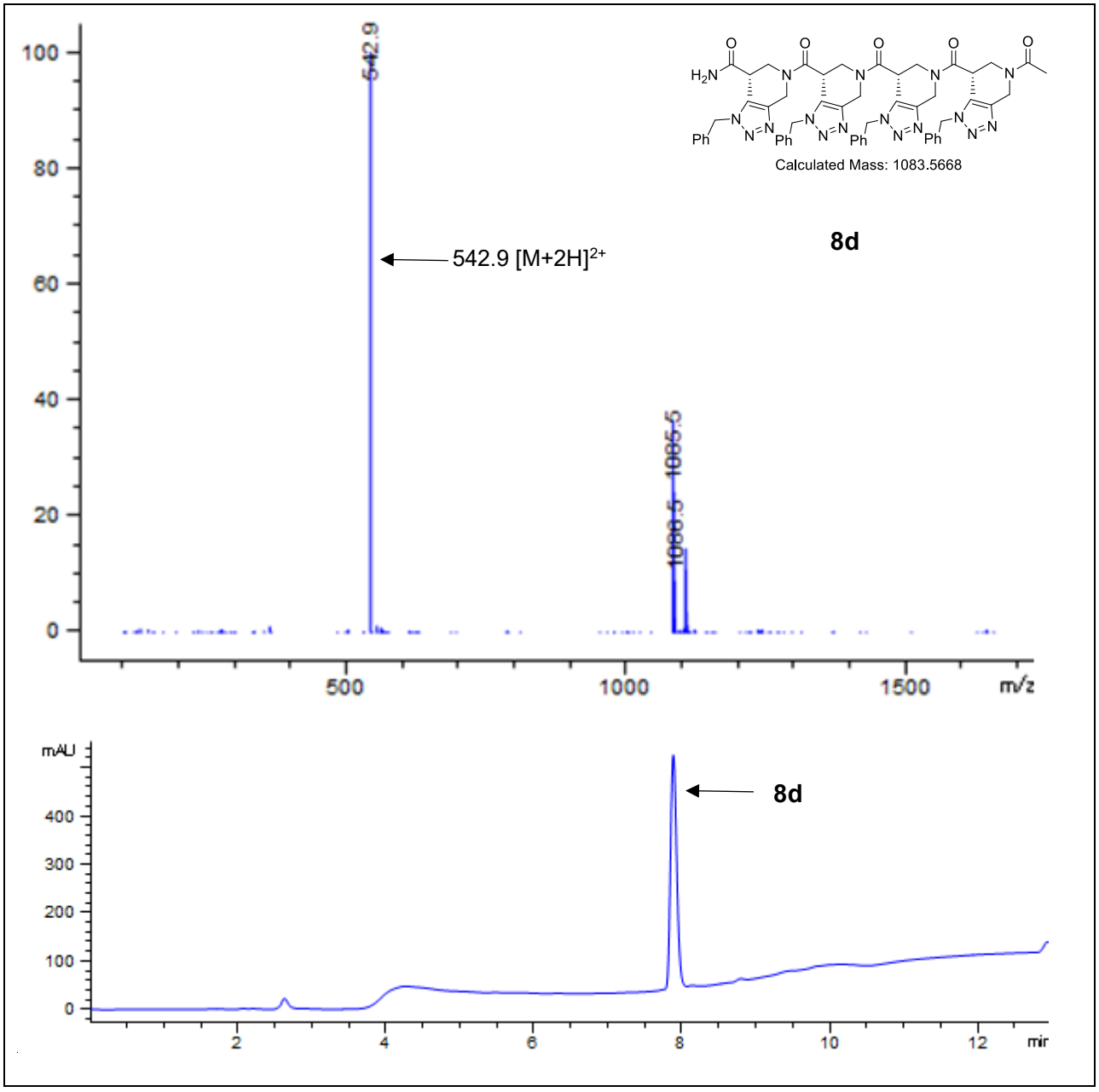

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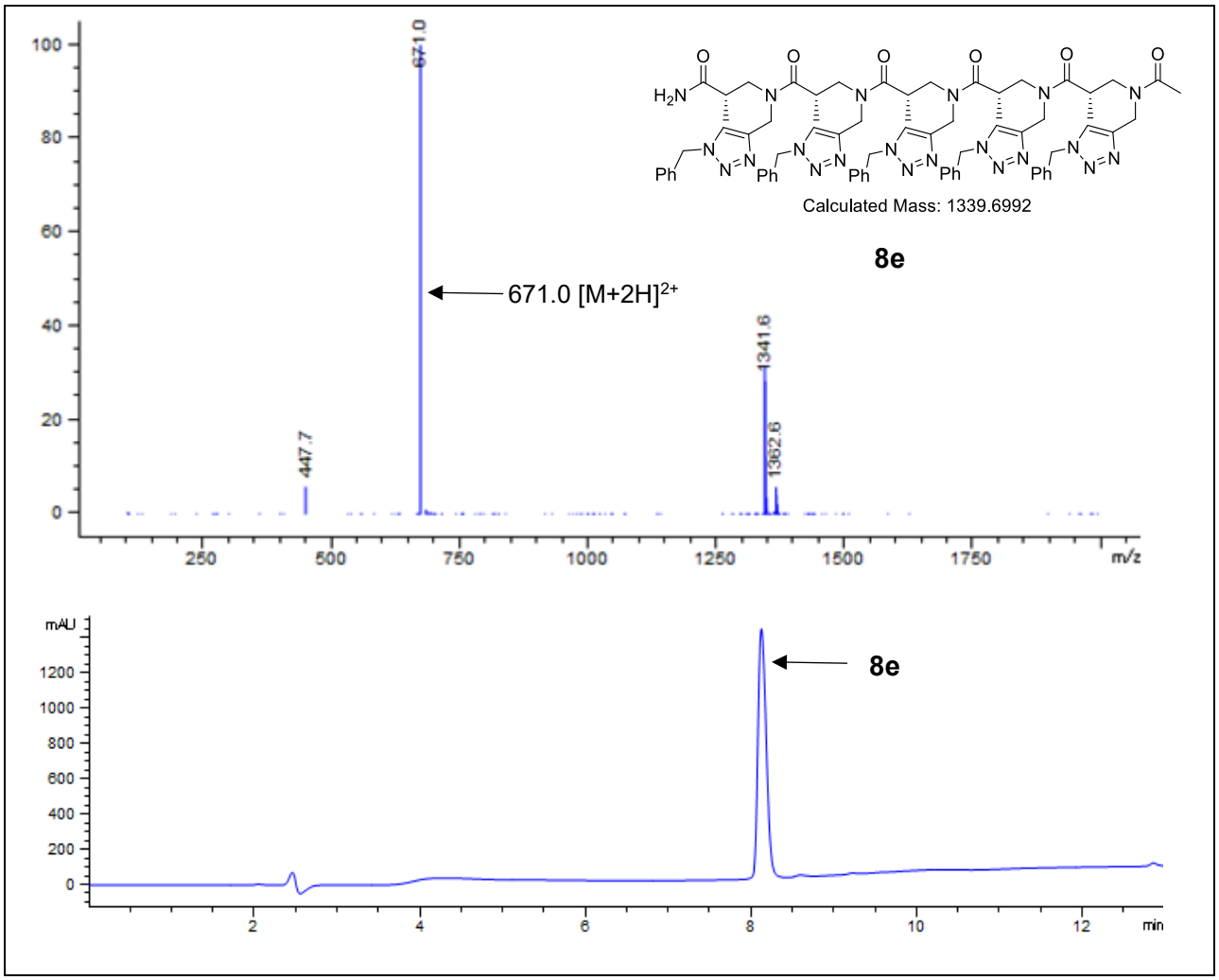

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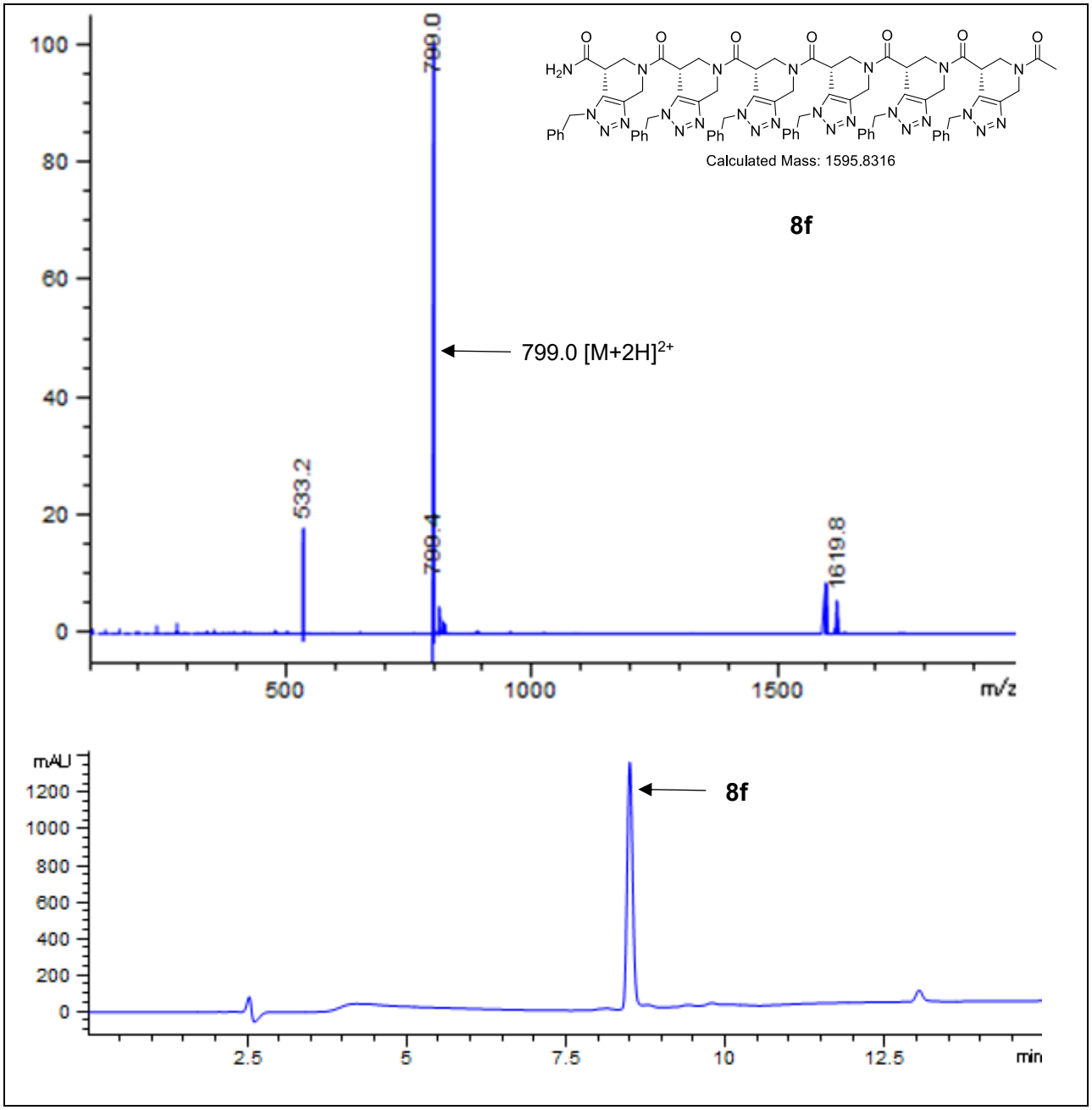

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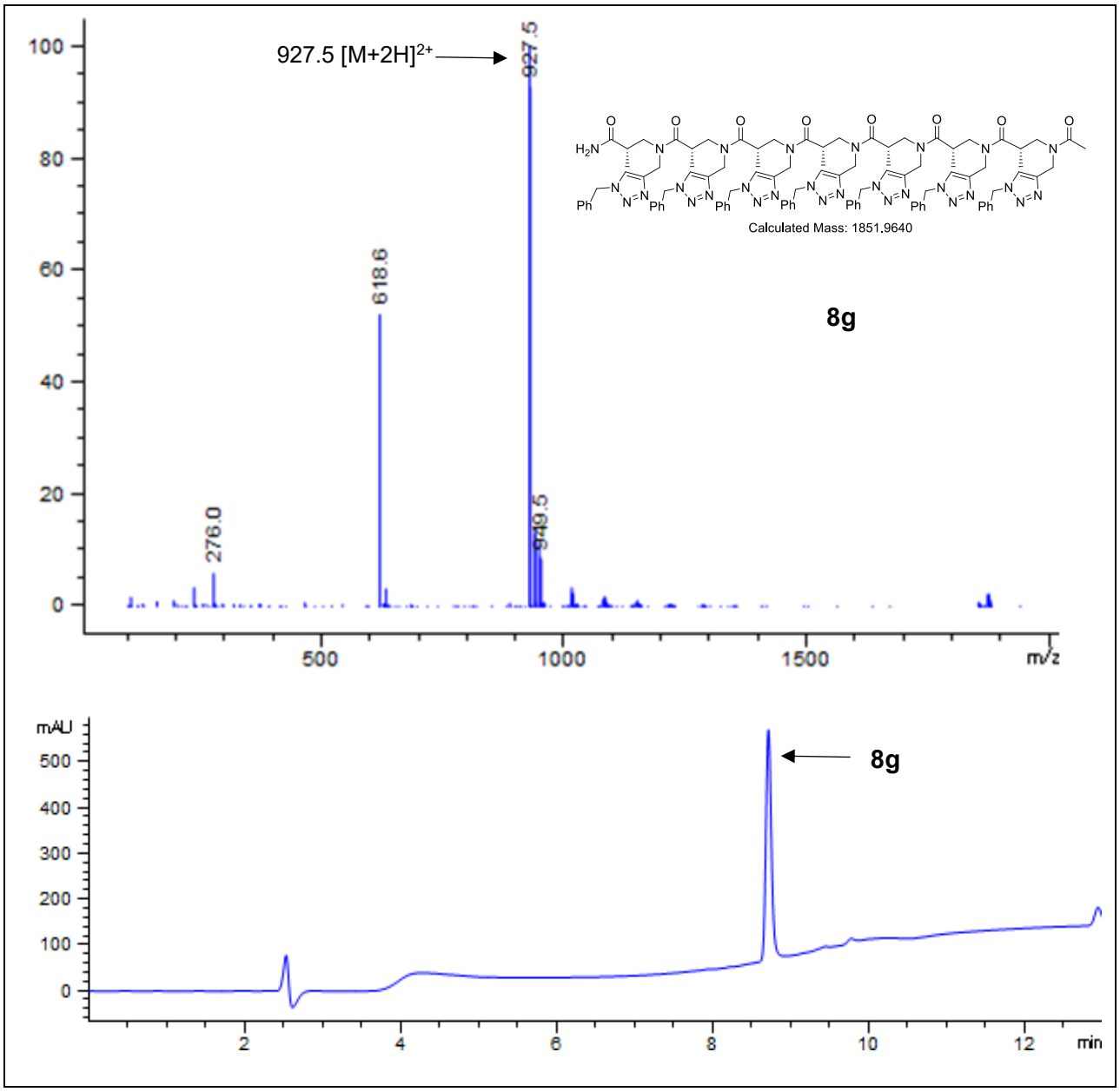

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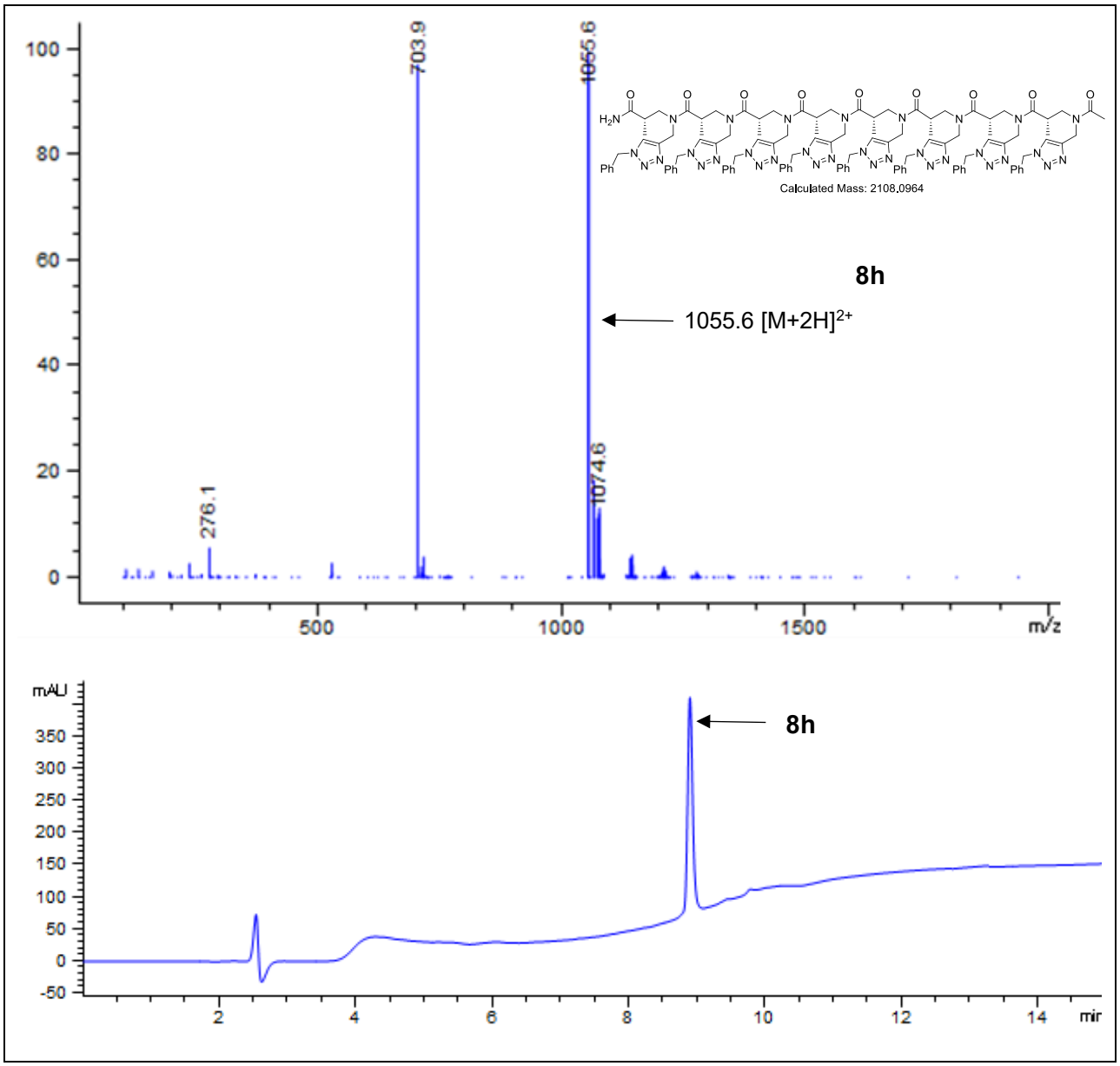

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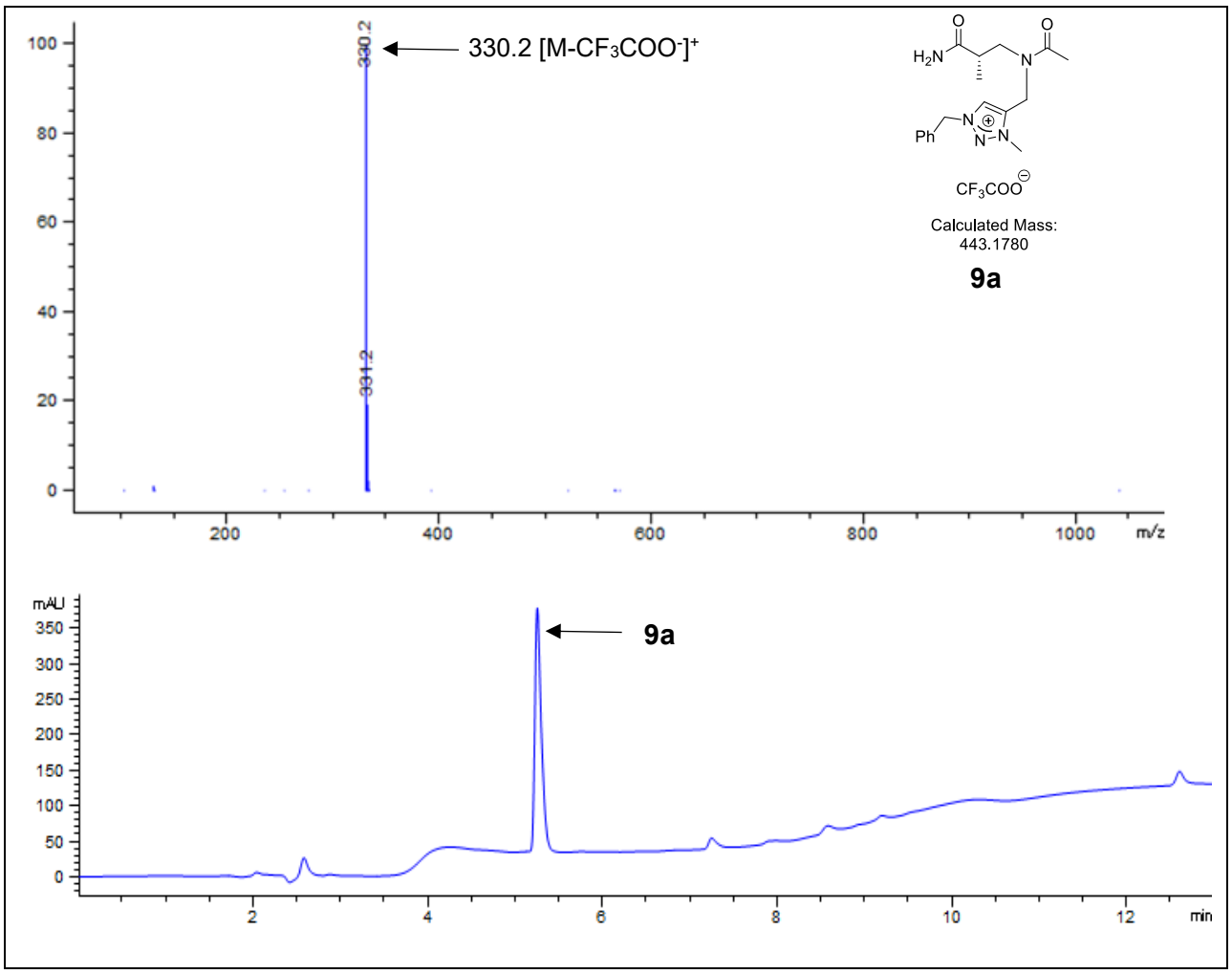

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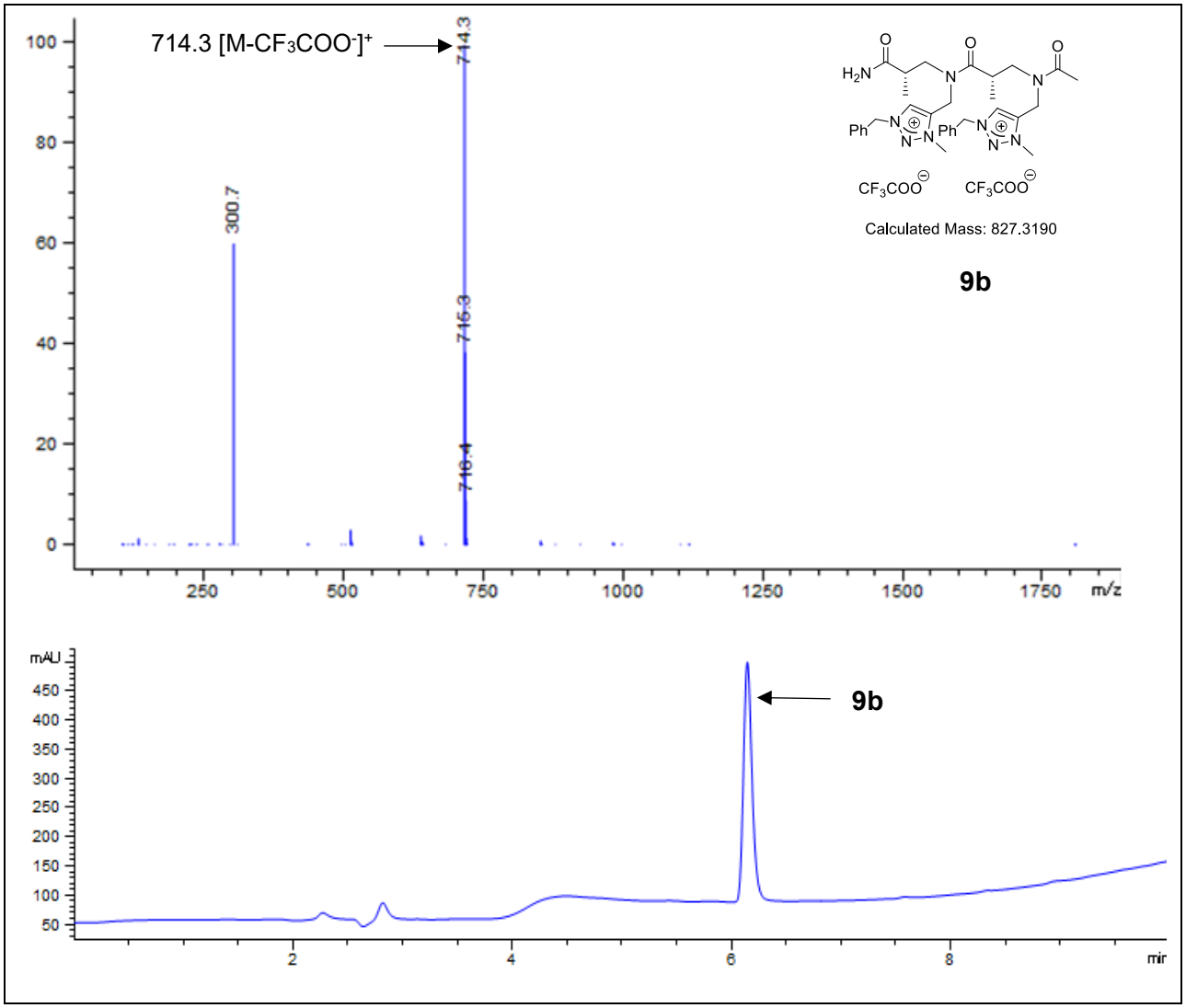

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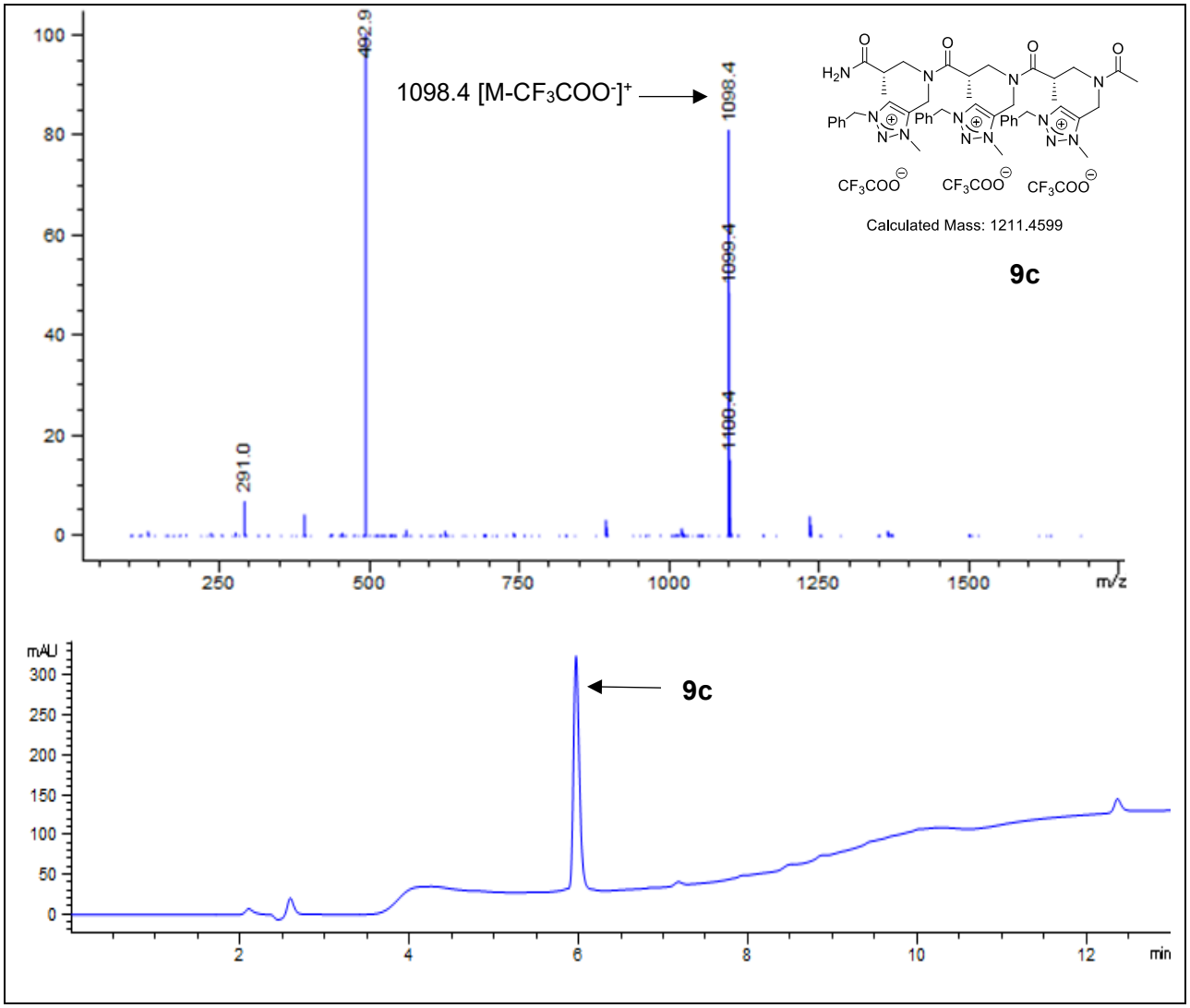

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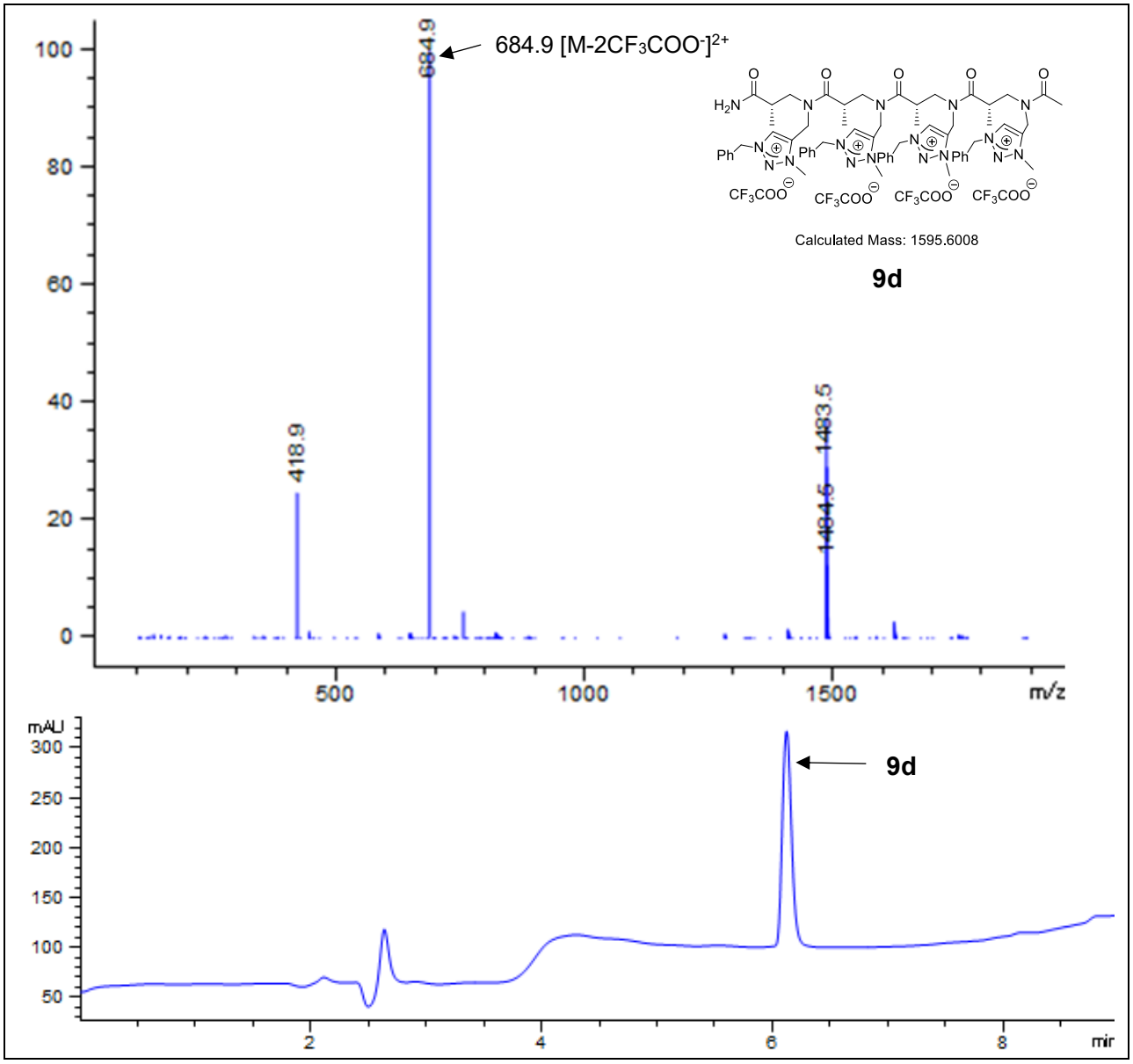

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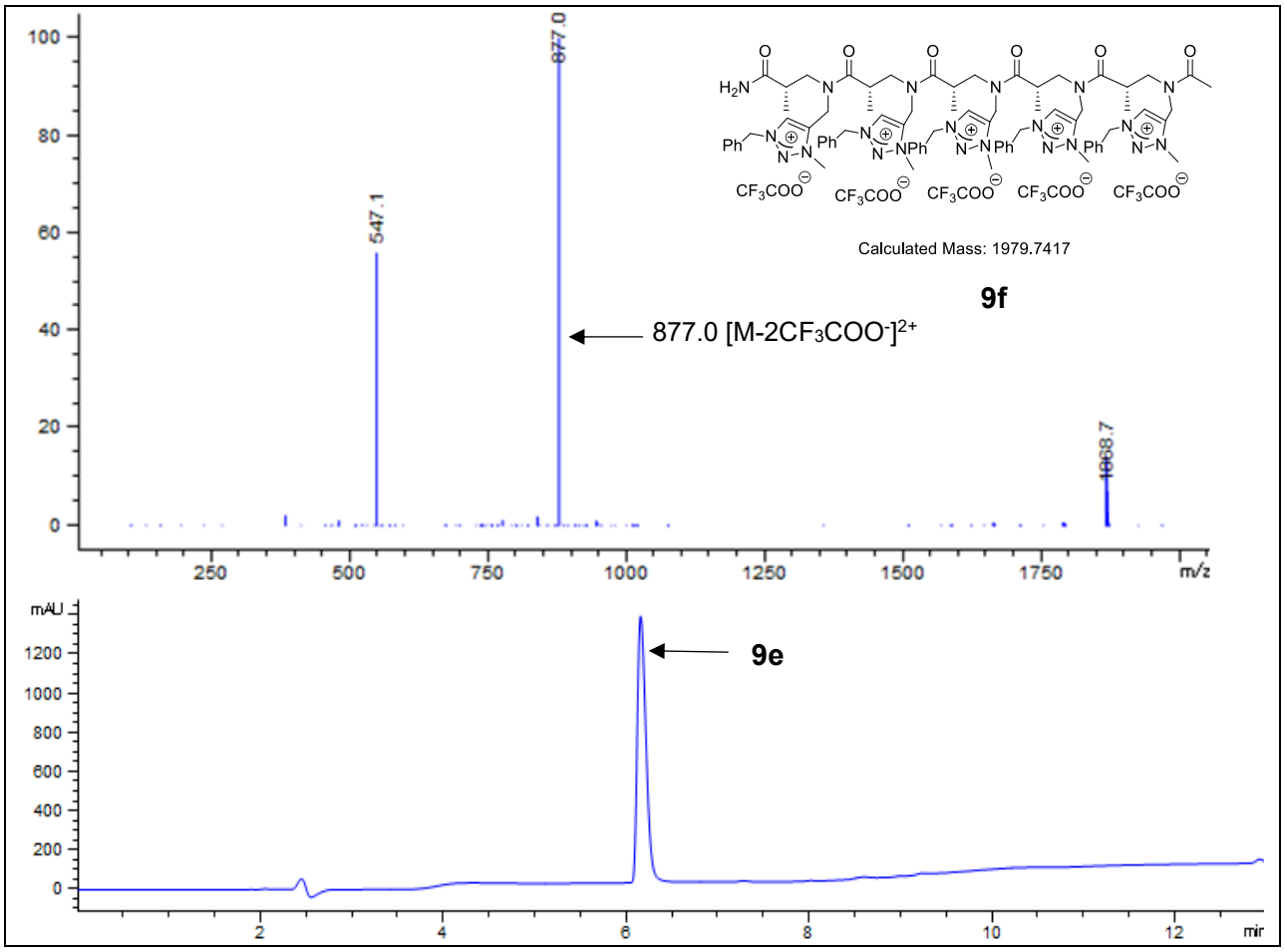

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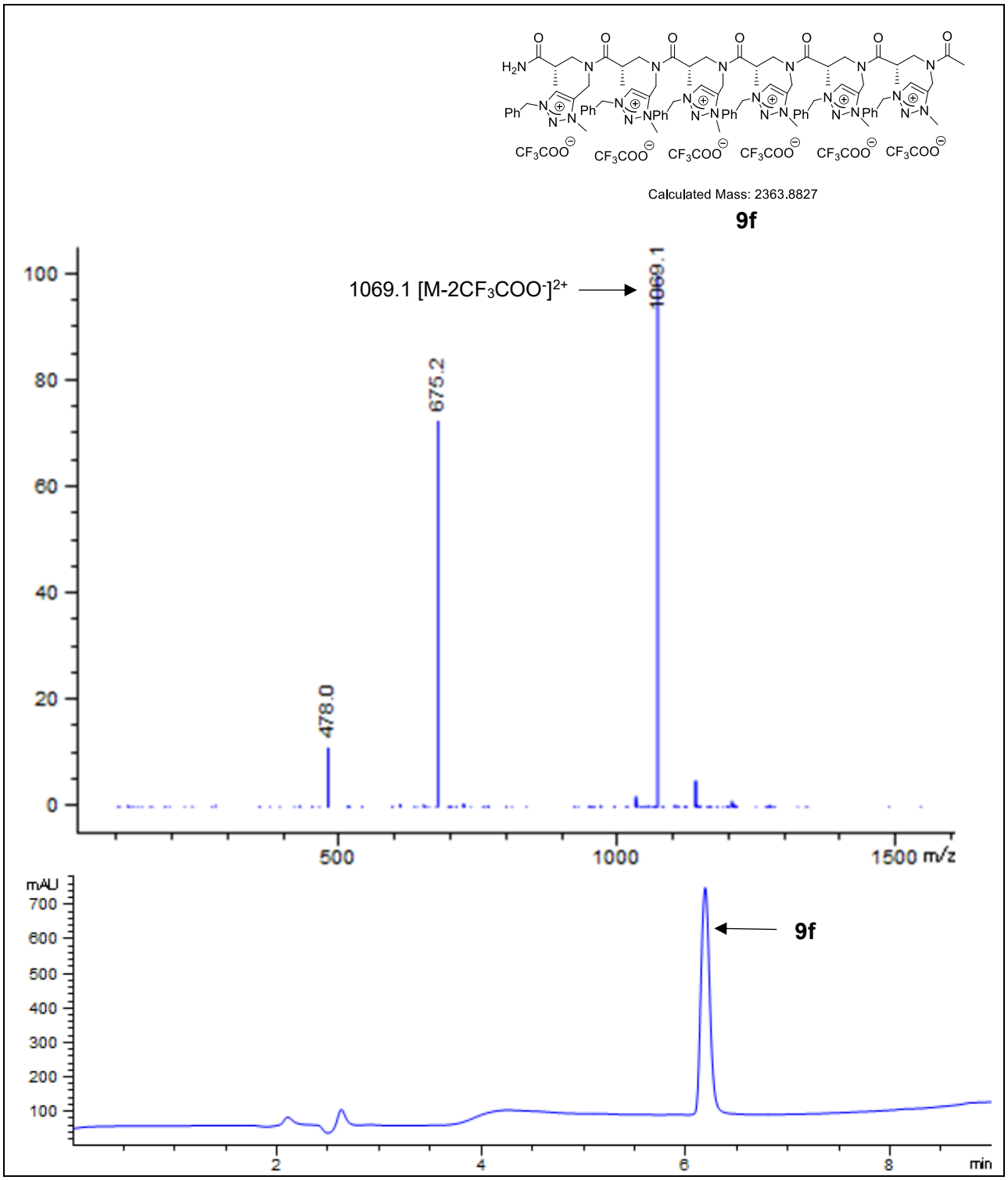

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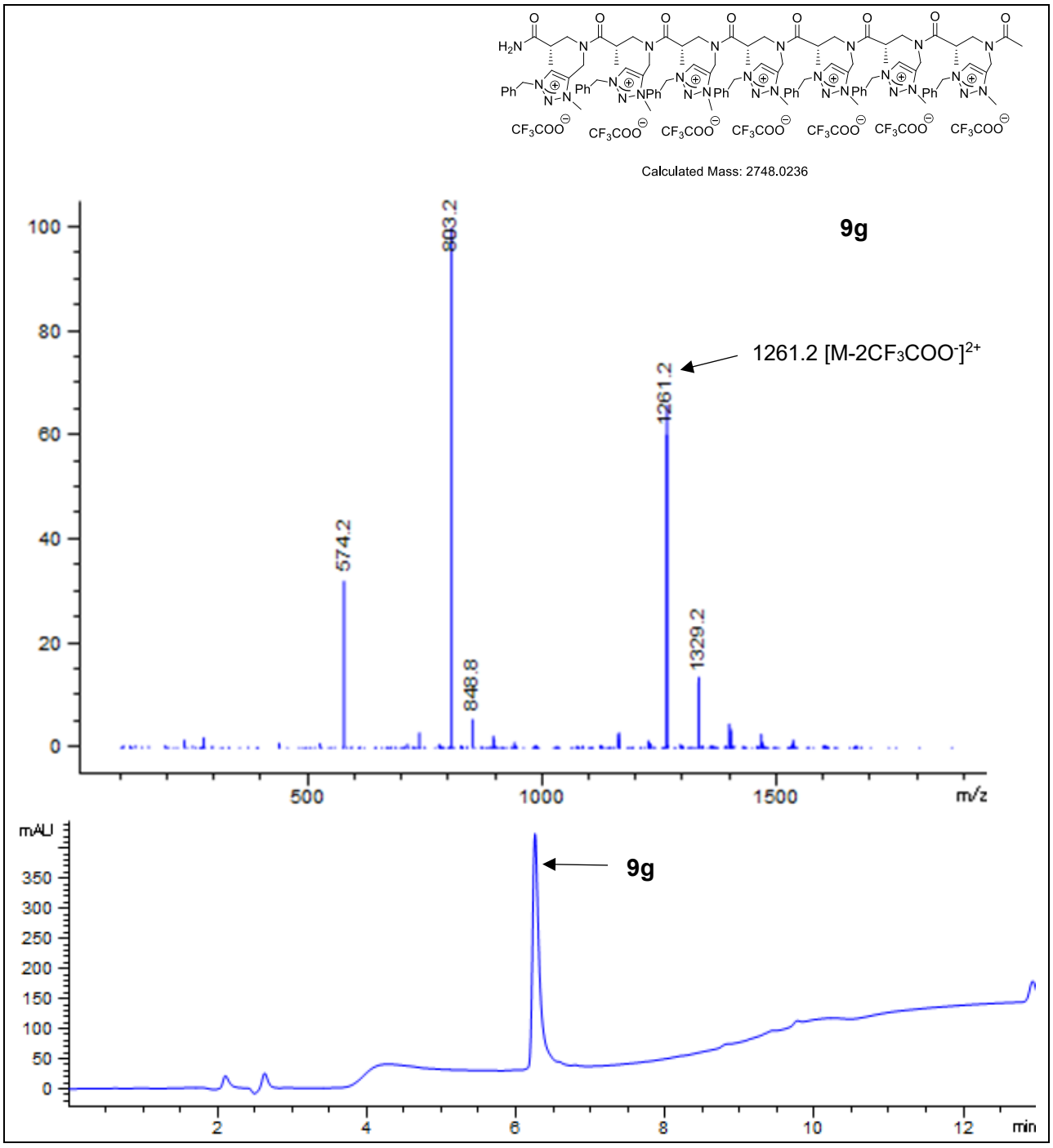

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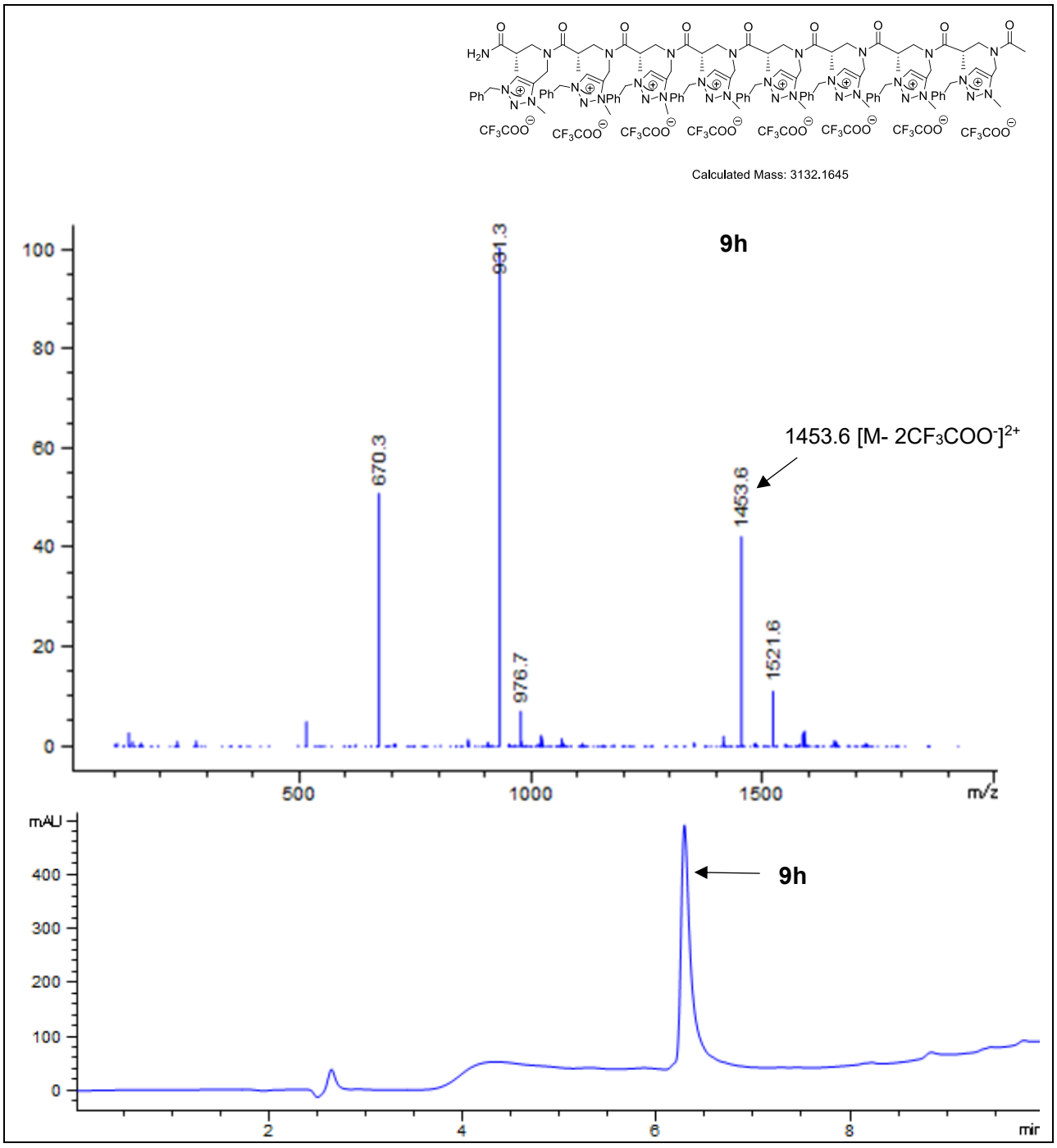
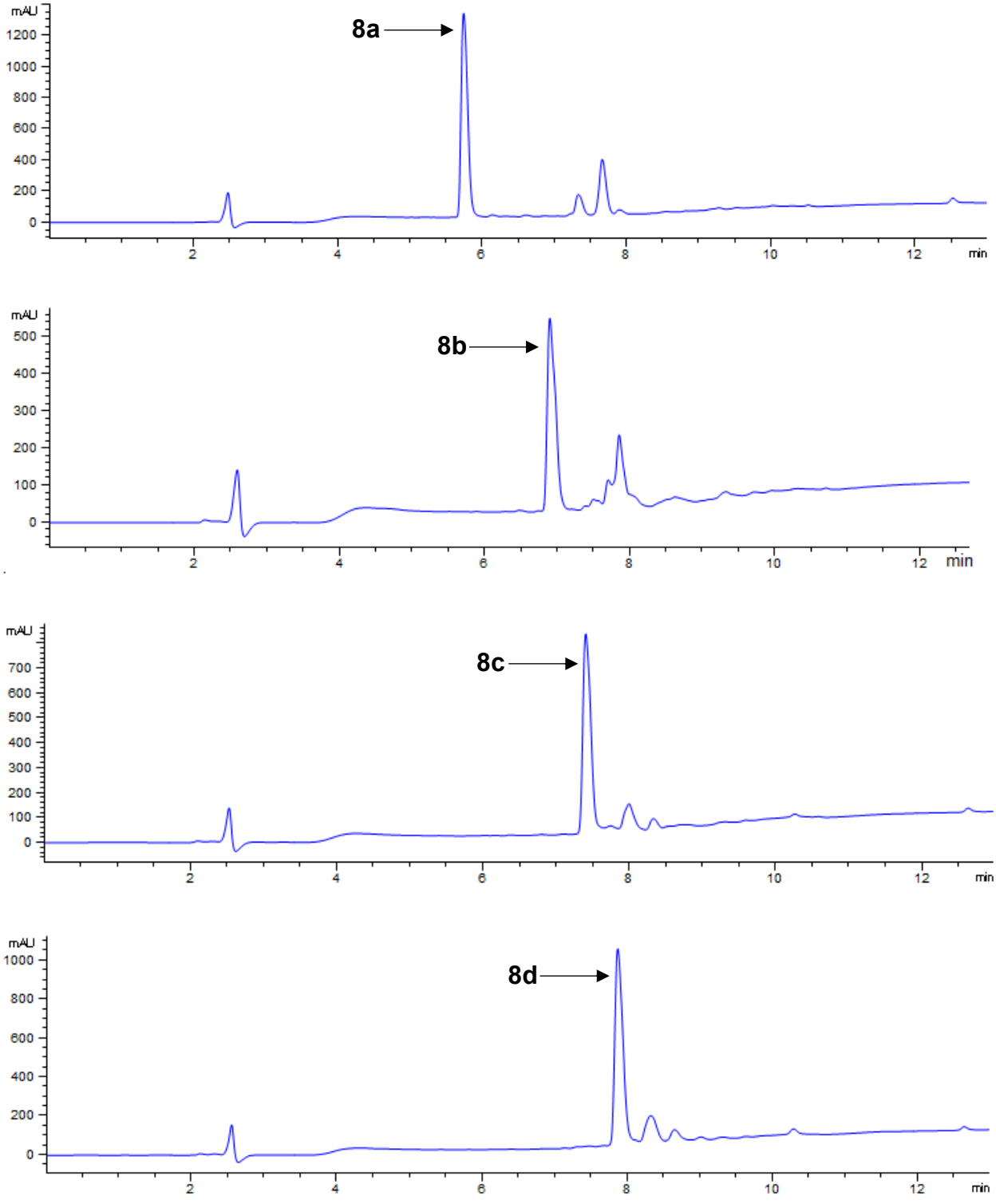


Fig. S2 HPLC chromatograms of crude products of **8a-h** and **9a-h**.



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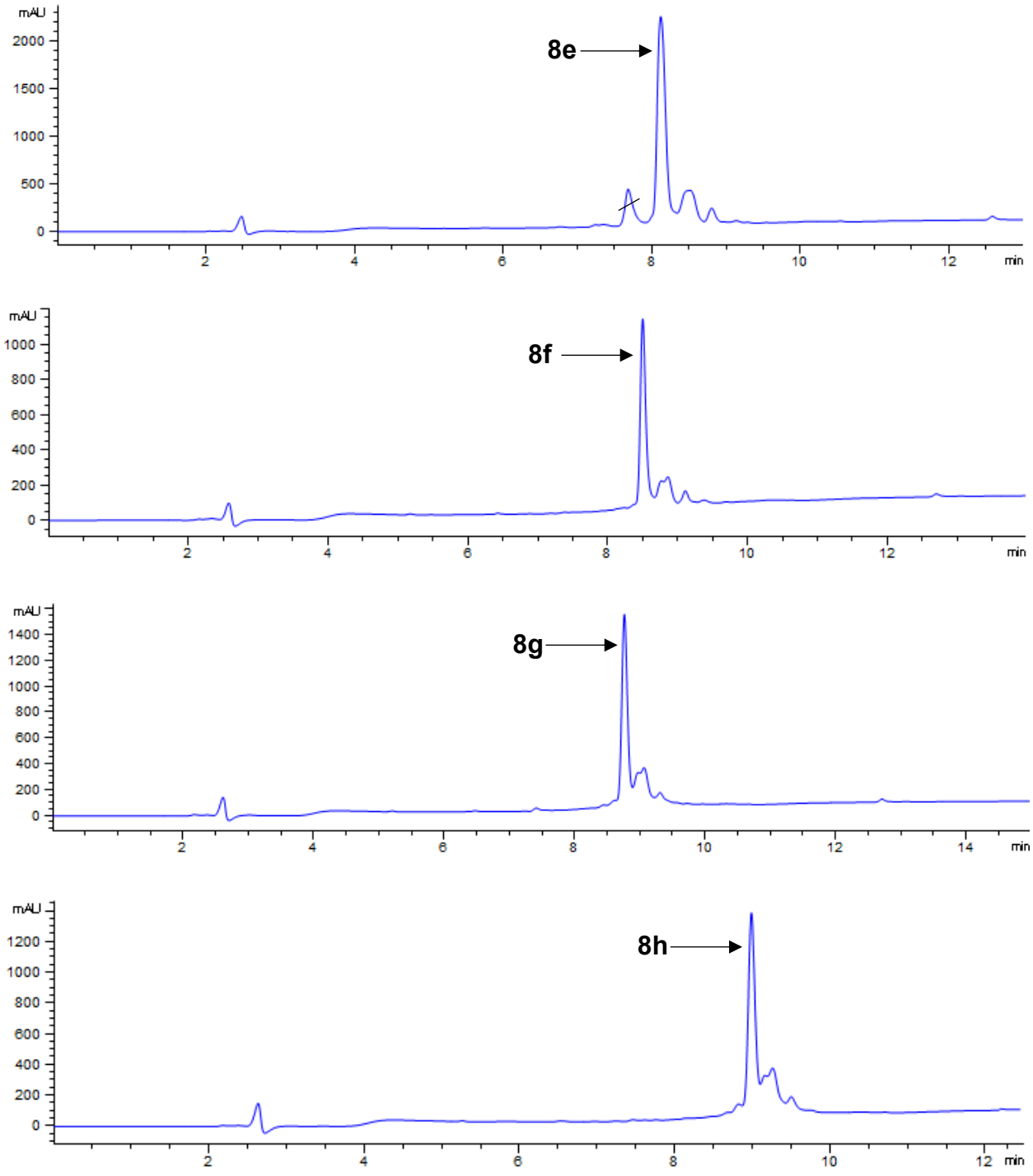

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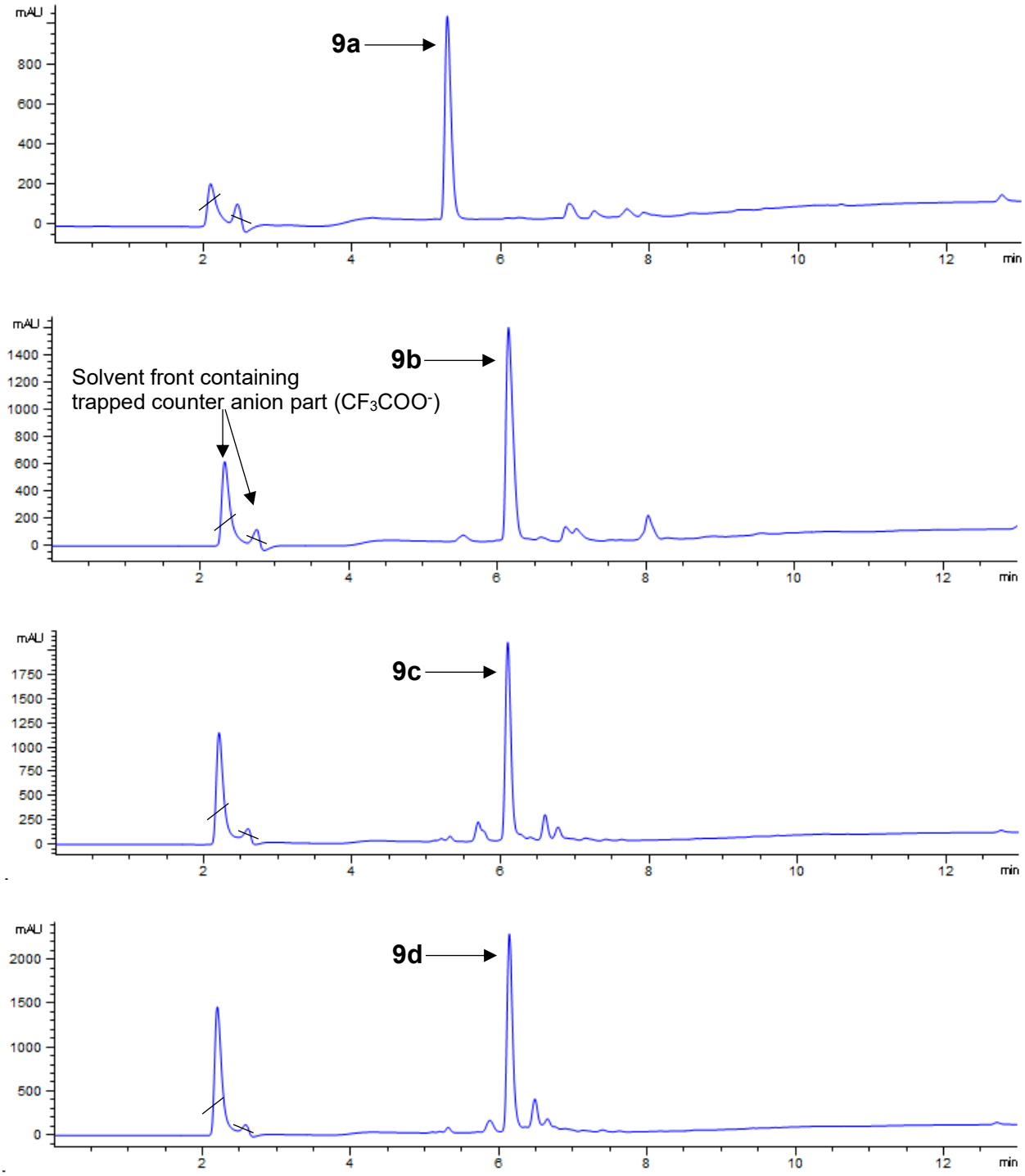

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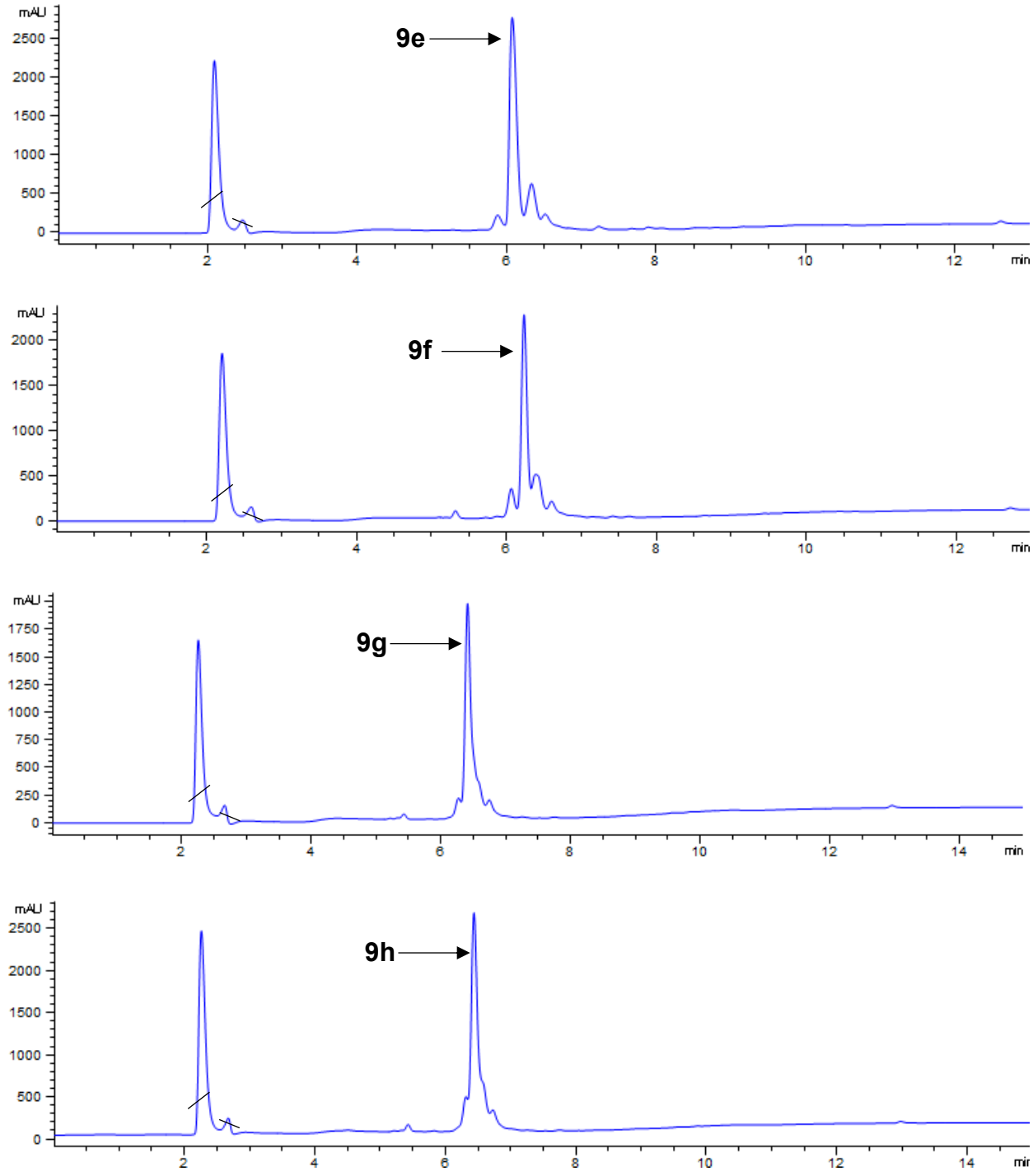
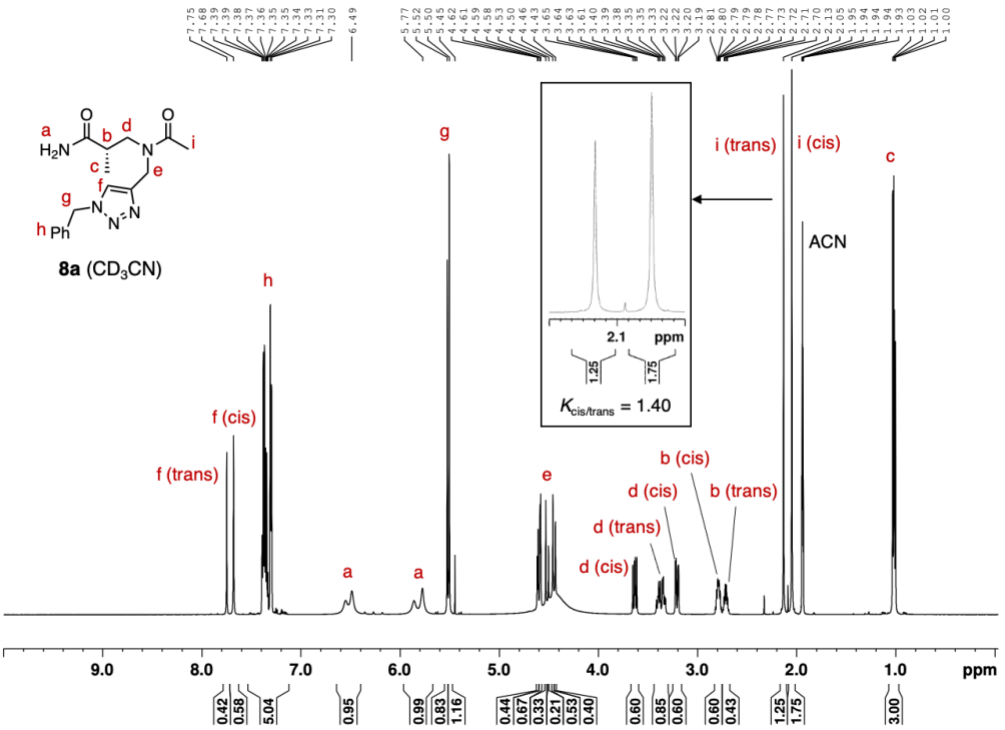


Fig. S3 ^{1}H NMR spectra of **8a** in CD_3CN, $CDCl_3$, and CD_3OD.

(a) CD_3CN (600 MHz)



(b) $CDCl_3$ (600 MHz)

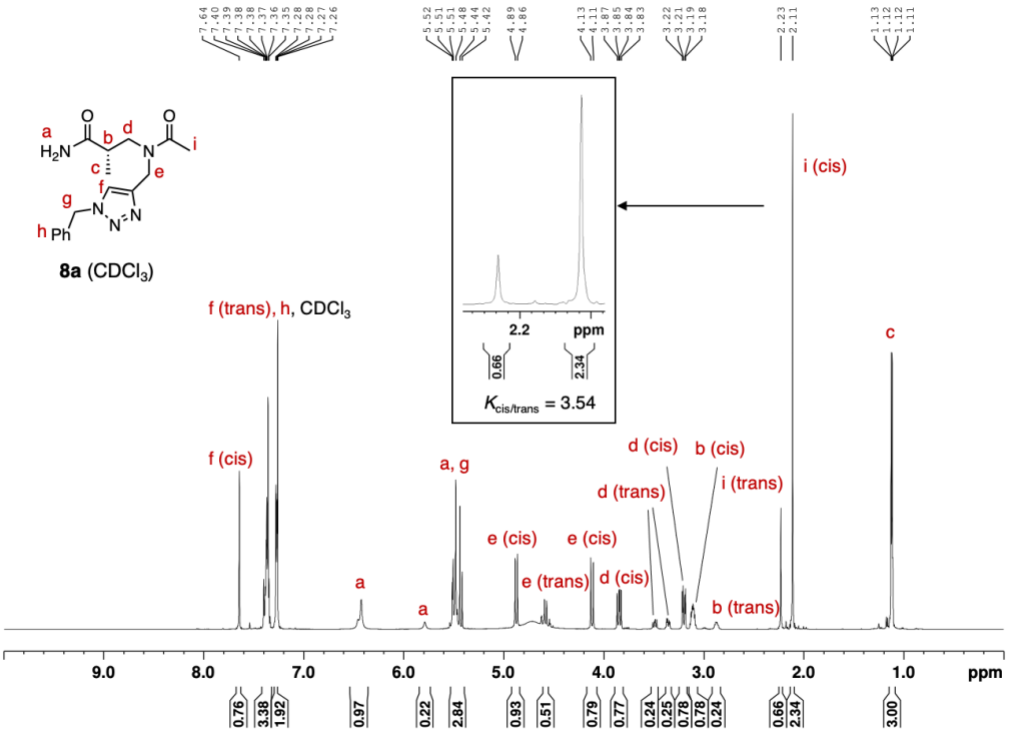


Fig. S3 (continued)

(c) CD_3OD (300 MHz)

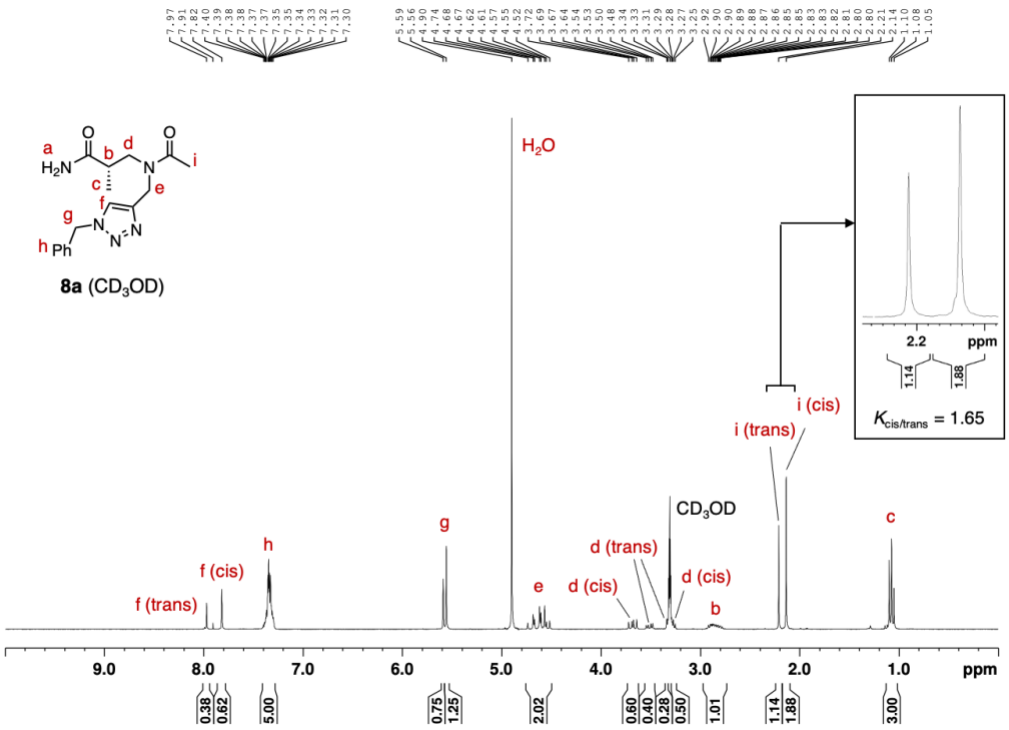


Fig. S4 COSY and NOESY spectra of **8a** in CD_3CN.

(a) COSY

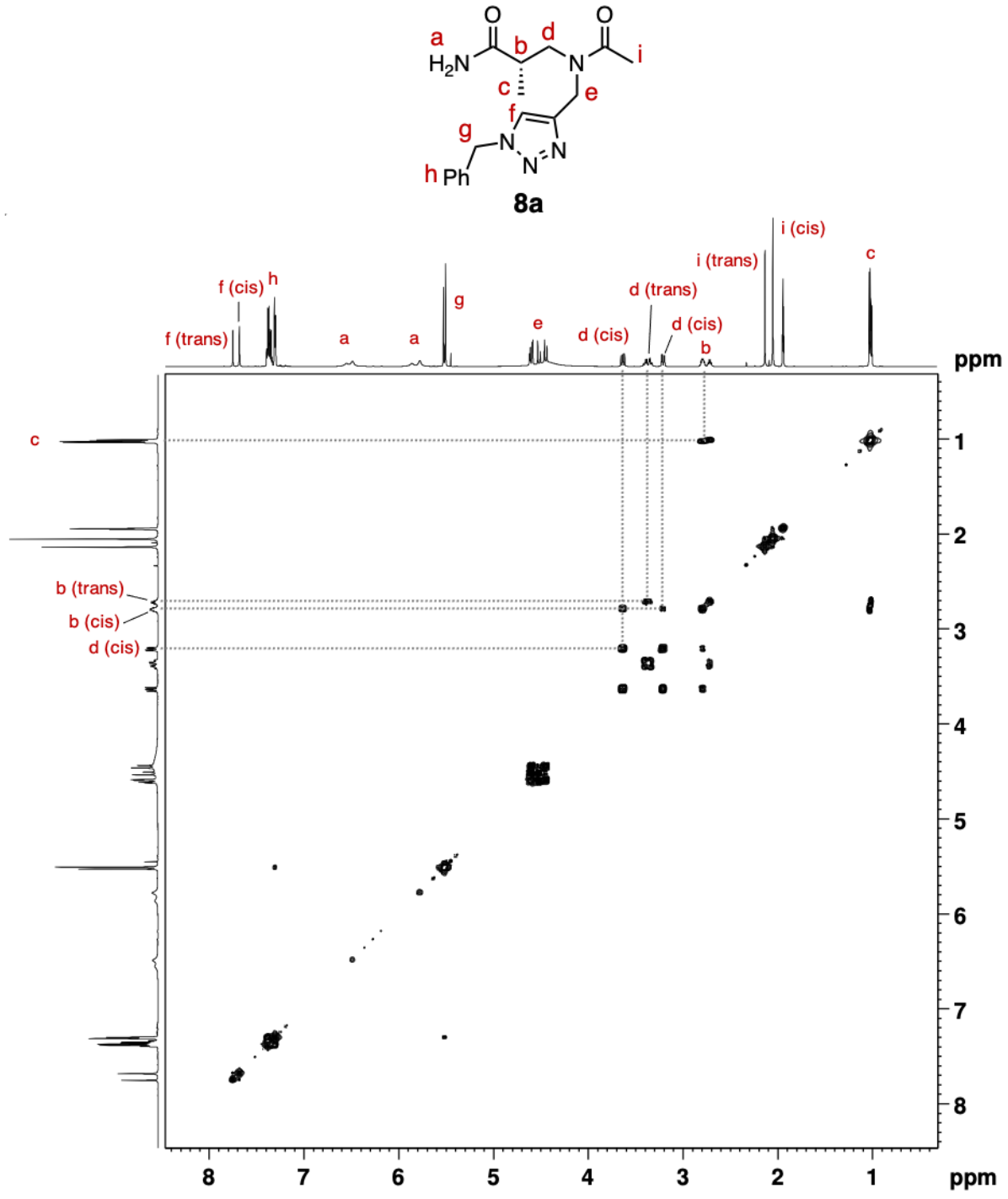


Fig. S4 (continued)

(b) NOESY

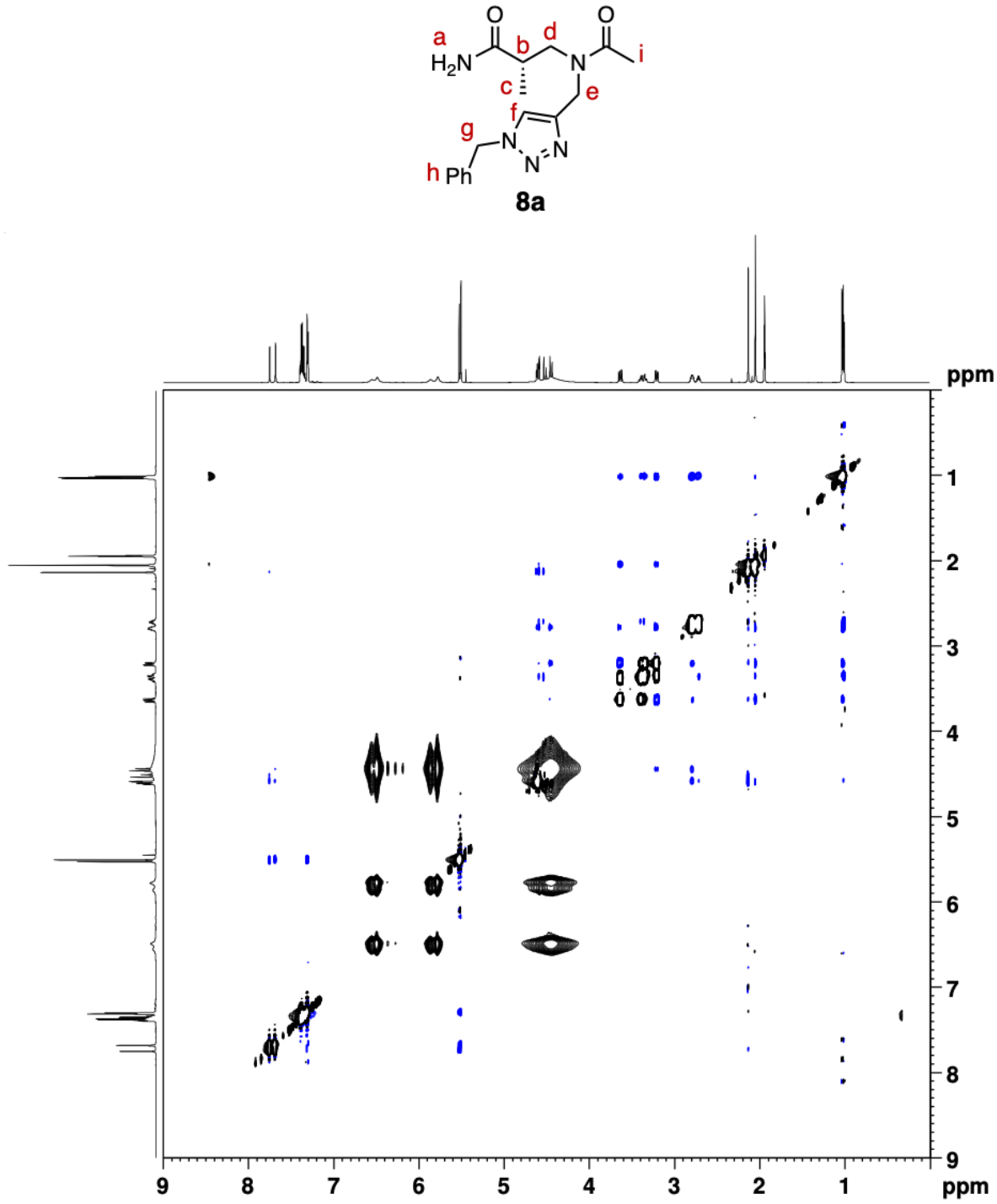


Fig. S4 (continued)

(c) Close-up views of NOESY spectrum of **8a**. NOEs indicating cis and trans amide geometries are shown in blue arrows.

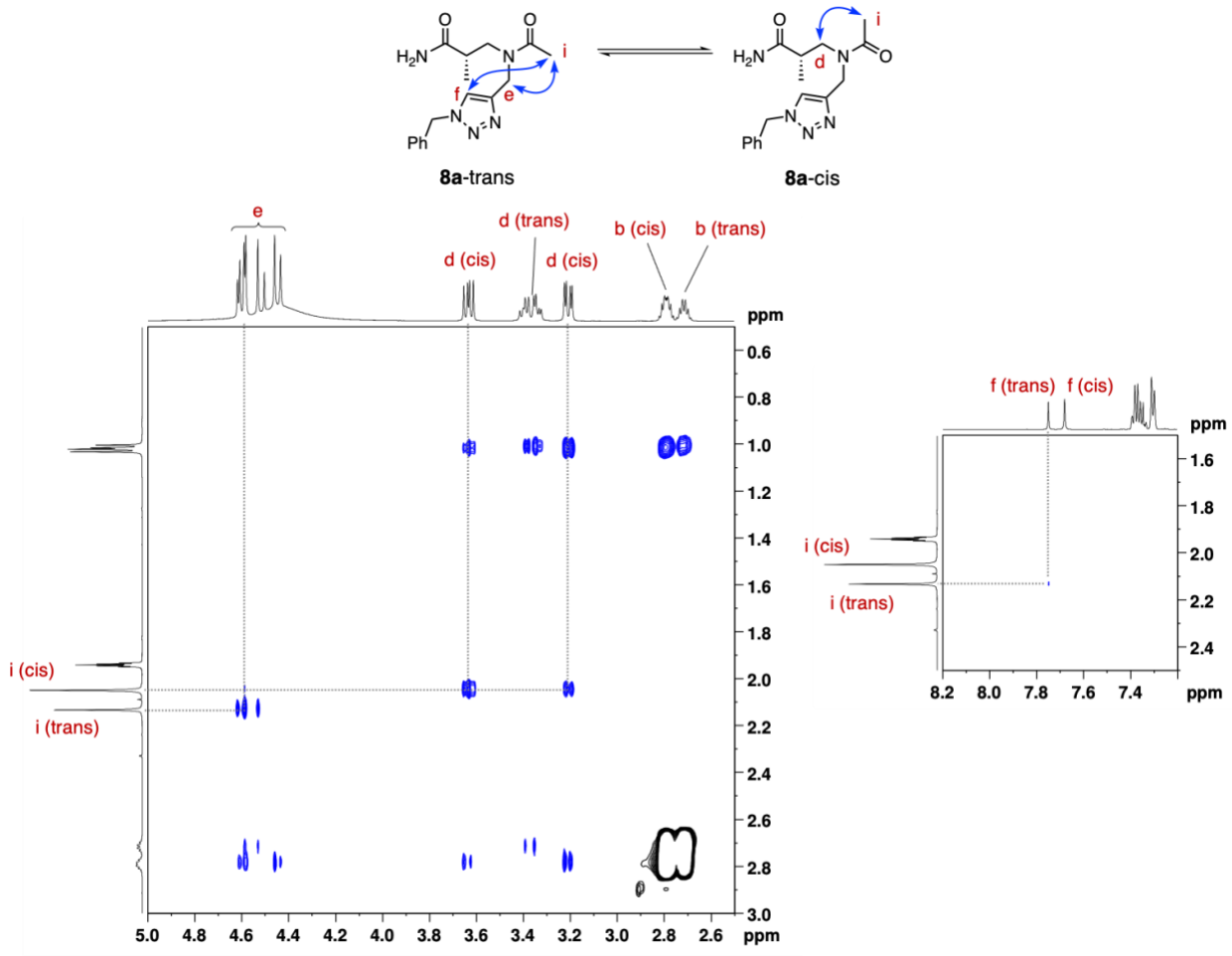
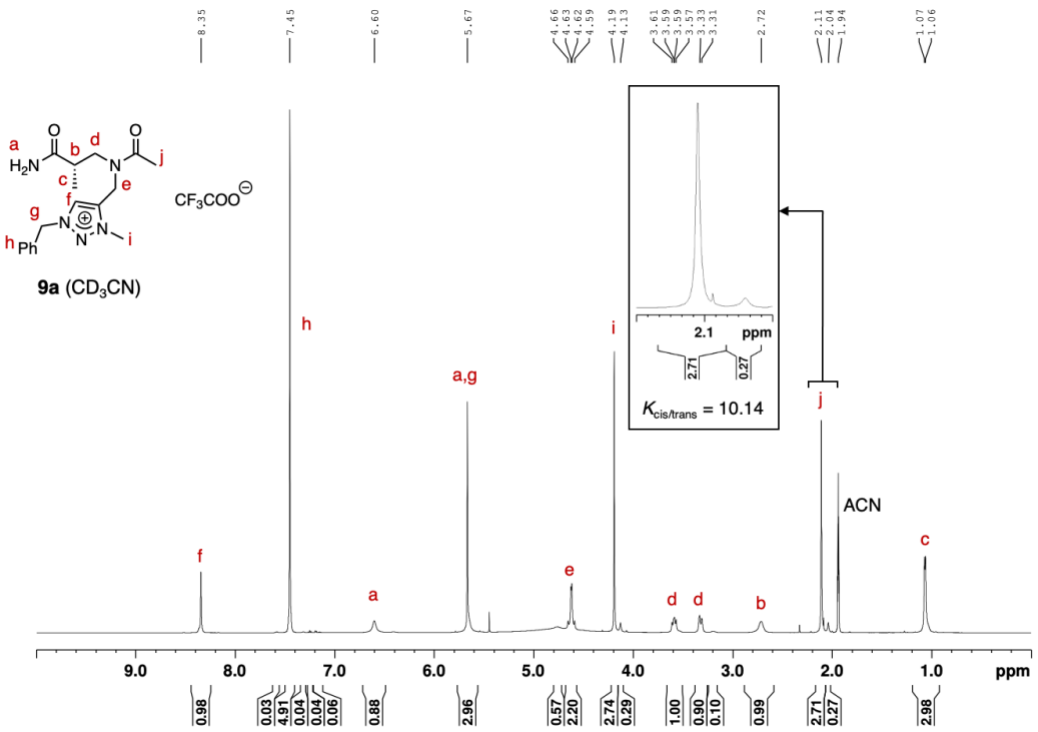


Fig. S5 ^{1}H NMR spectra of **9a** in CD_3CN, $CDCl_3$, and CD_3OD.

(a) CD_3CN (600 MHz)



(b) $CDCl_3$ (600 MHz)

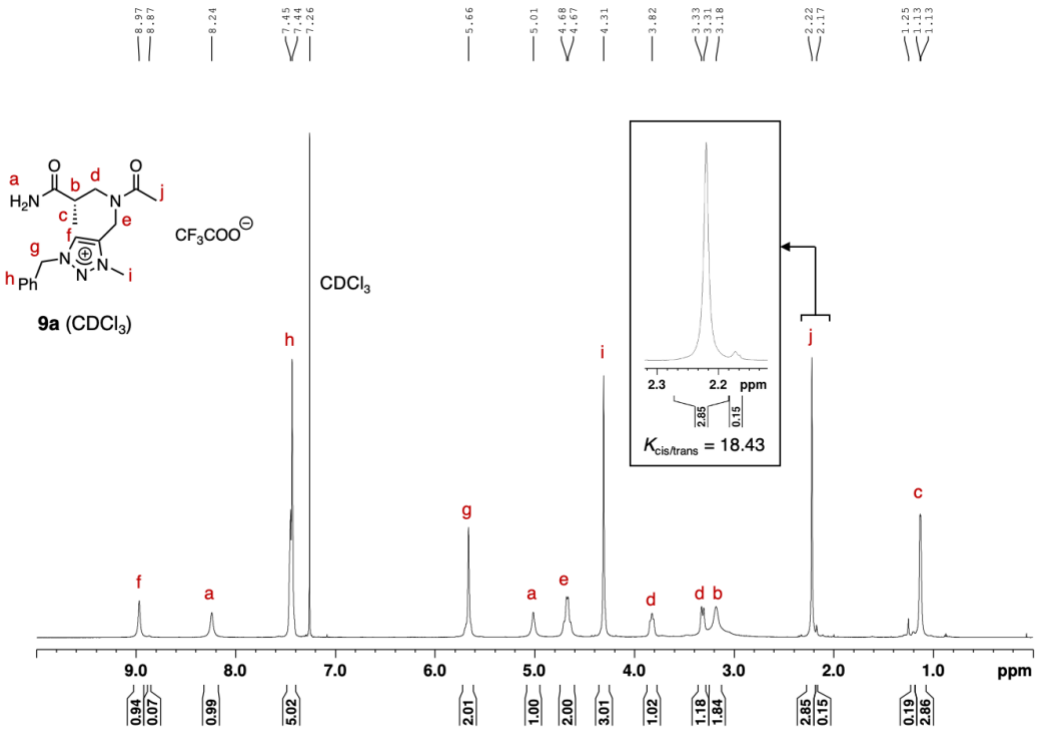


Fig. S5 (continued)

(c) CD_3OD (300 MHz)

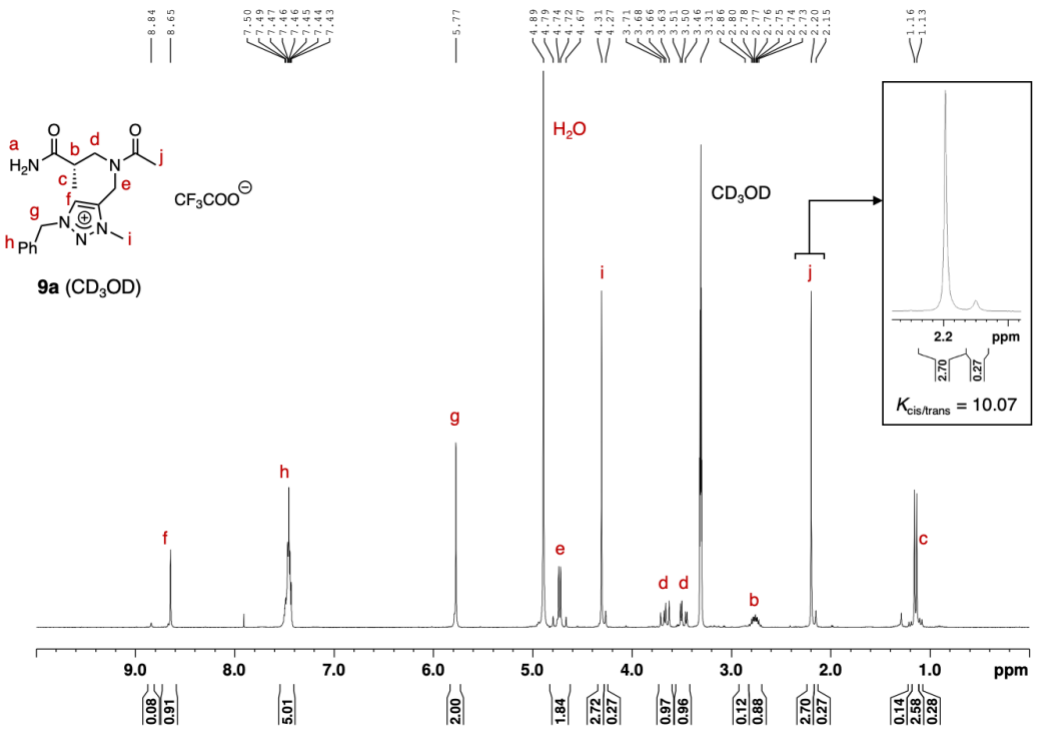


Fig. S6 COSY and NOESY spectra of **9a** in CD_3CN.

(a) COSY

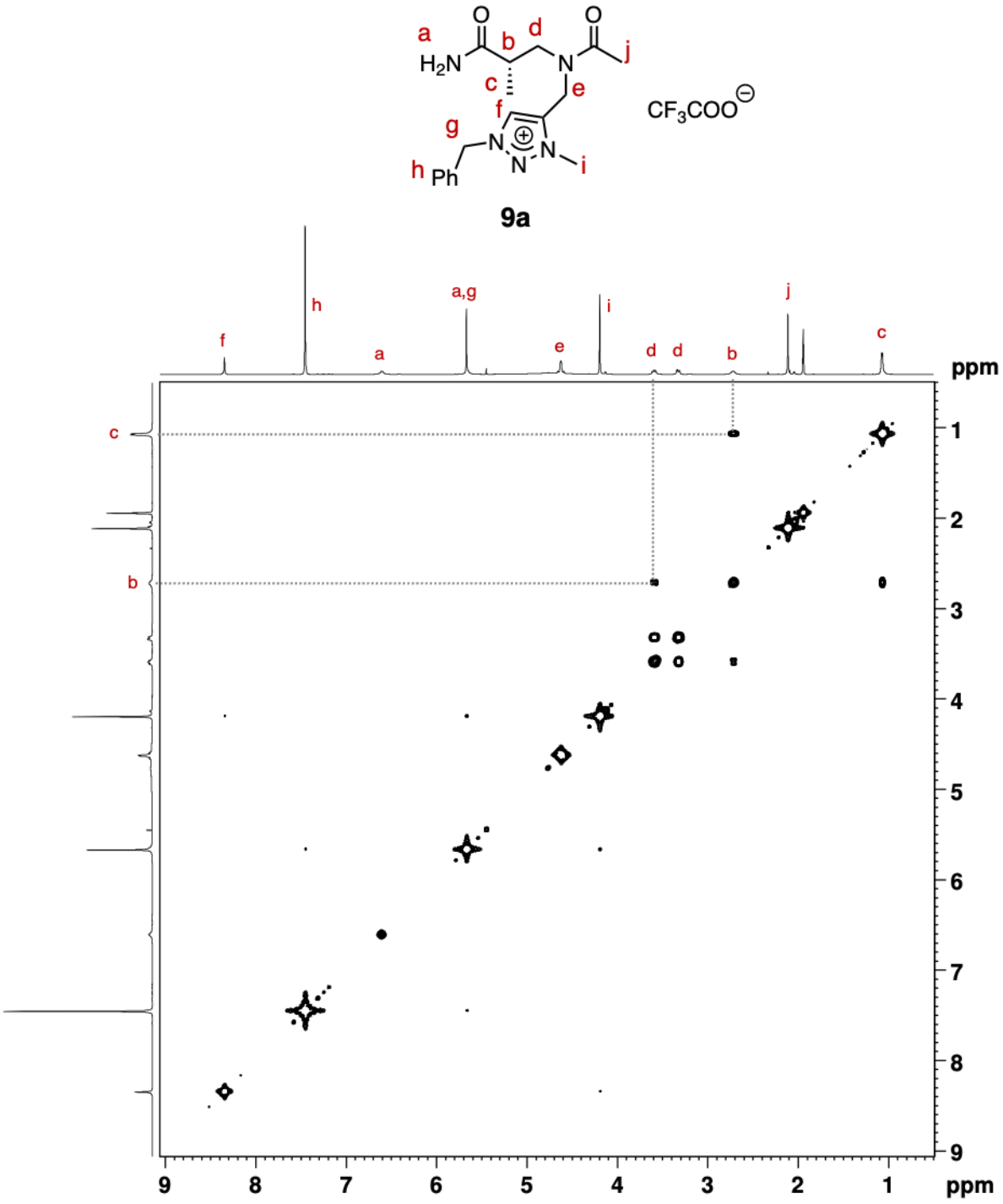


Fig. S6 (continued)

(b) NOESY. NOEs indicating cis amide geometry are shown in blue arrows.

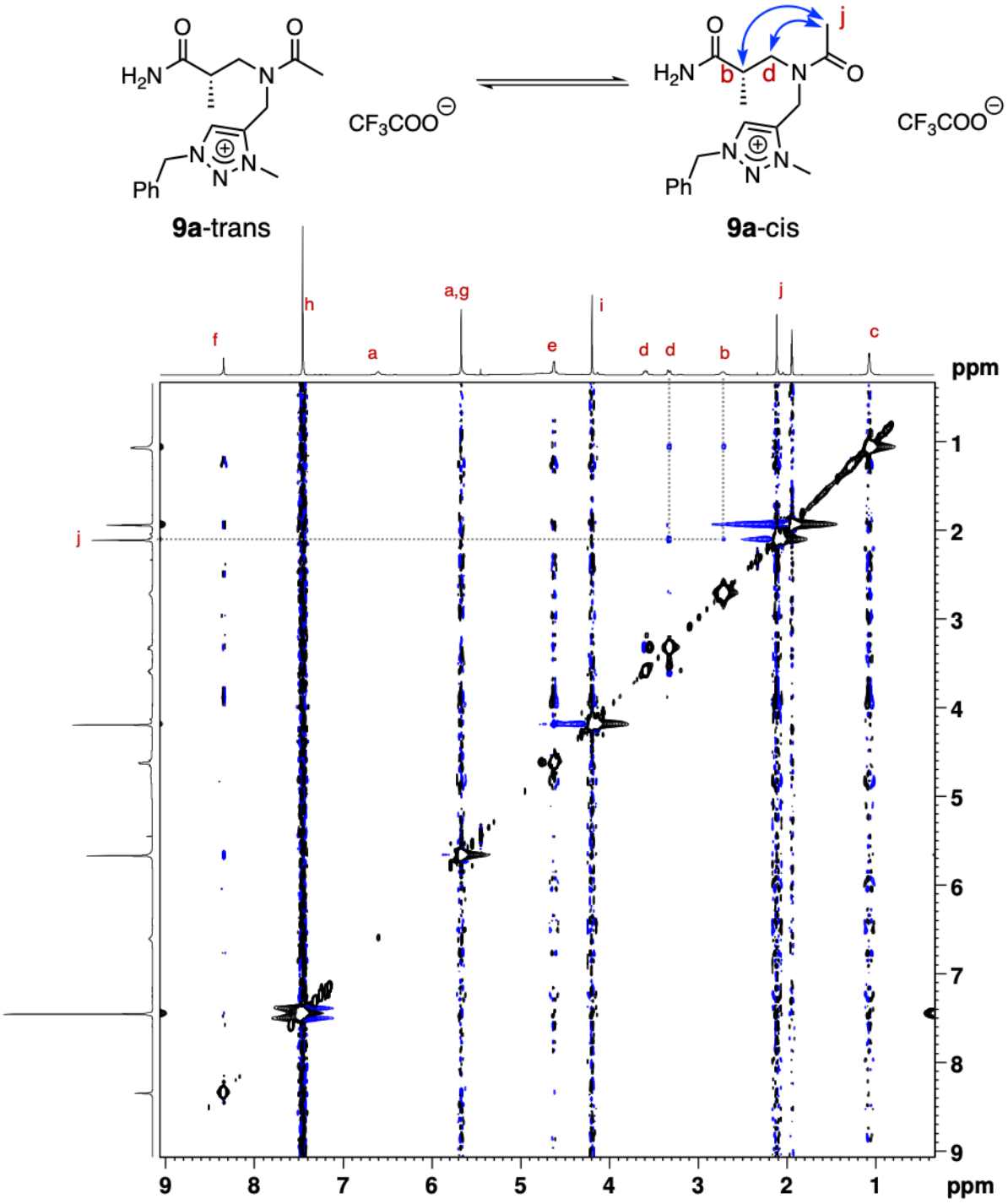
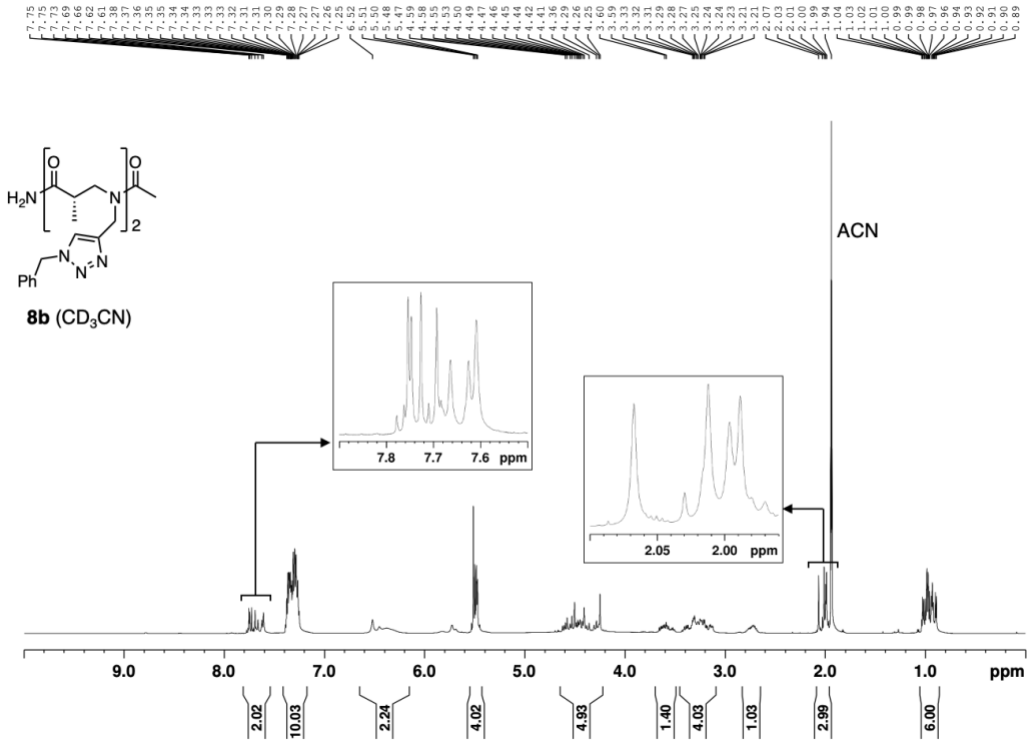


Fig. S7 ^{1}H NMR spectra of **8b** in CD_3CN, $CDCl_3$, and CD_3OD.

(a) CD_3CN (600 MHz)



(b) $CDCl_3$ (500 MHz)

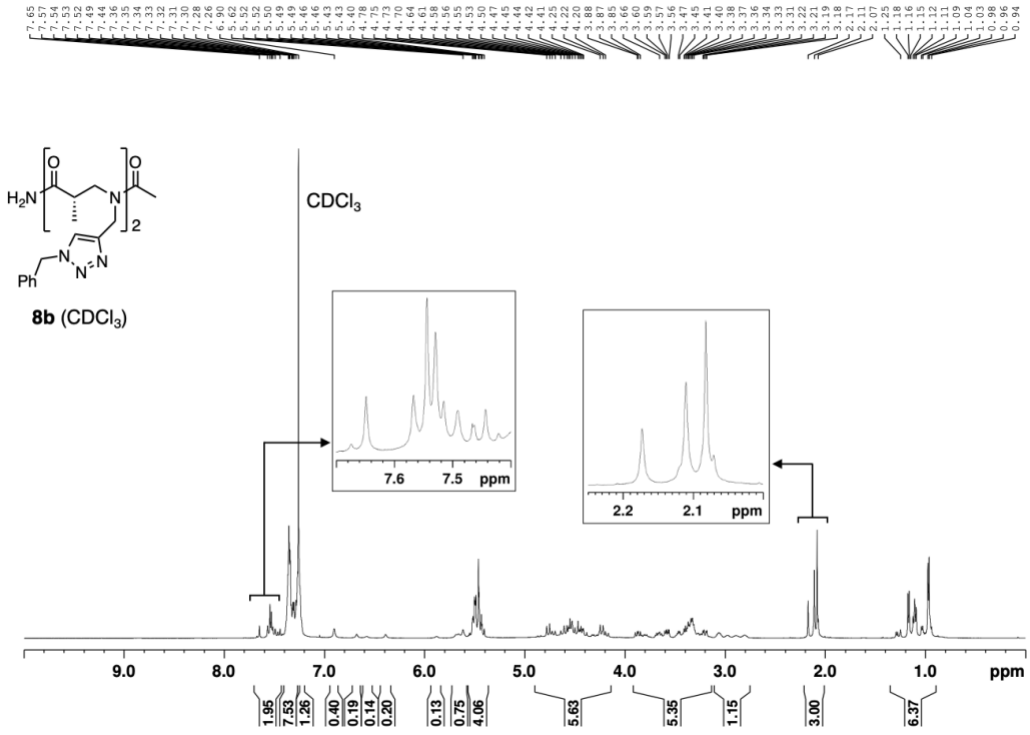


Fig. S7 (continued)

(c) CD_3OD (500 MHz)

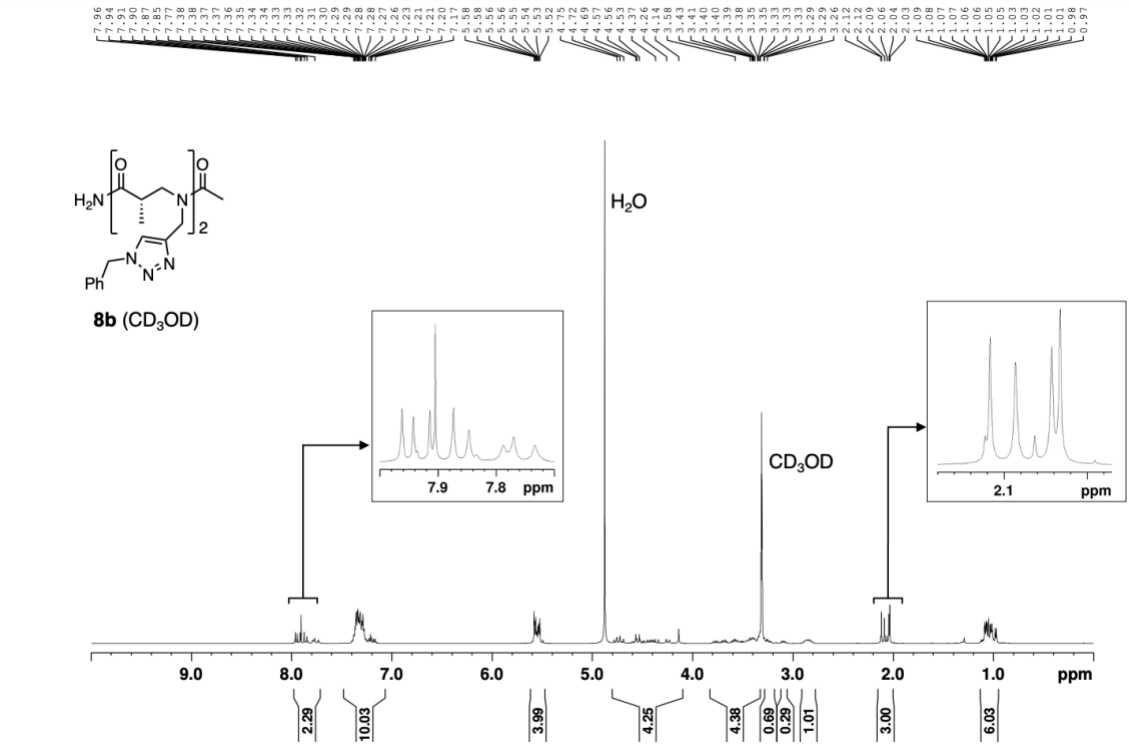
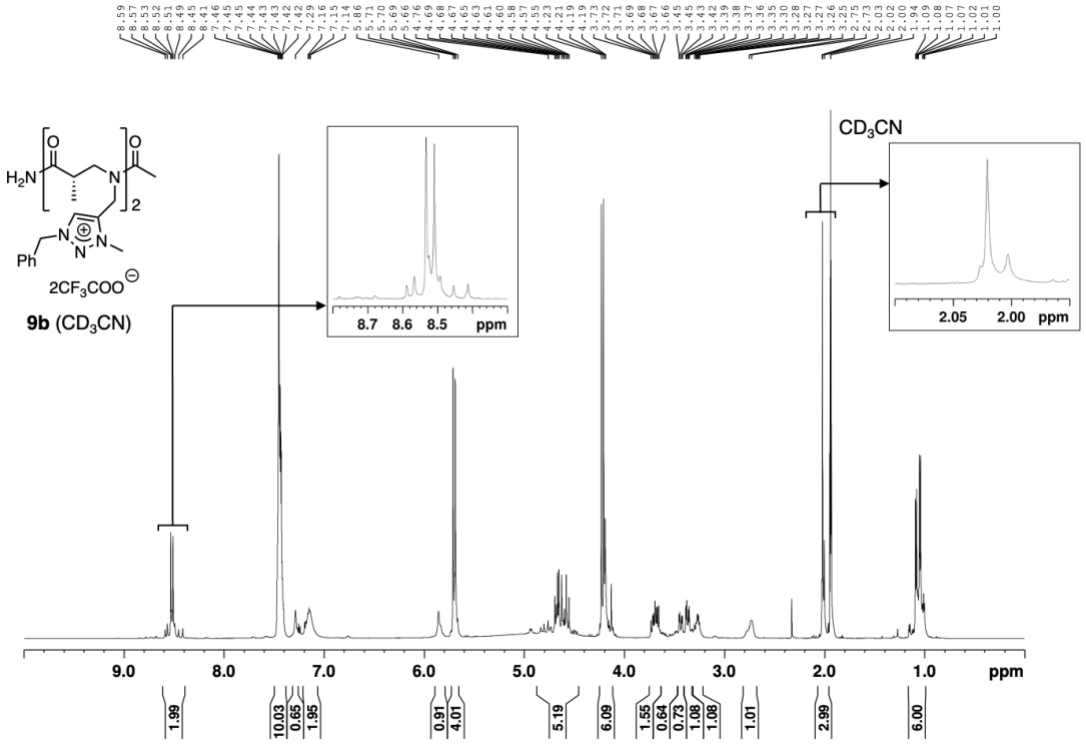


Fig. S8 ^{1}H NMR spectra of **9b** in CD_3CN, $CDCl_3$, and CD_3OD.

(a) CD_3CN (600 MHz)



(b) $CDCl_3$ (500 MHz)

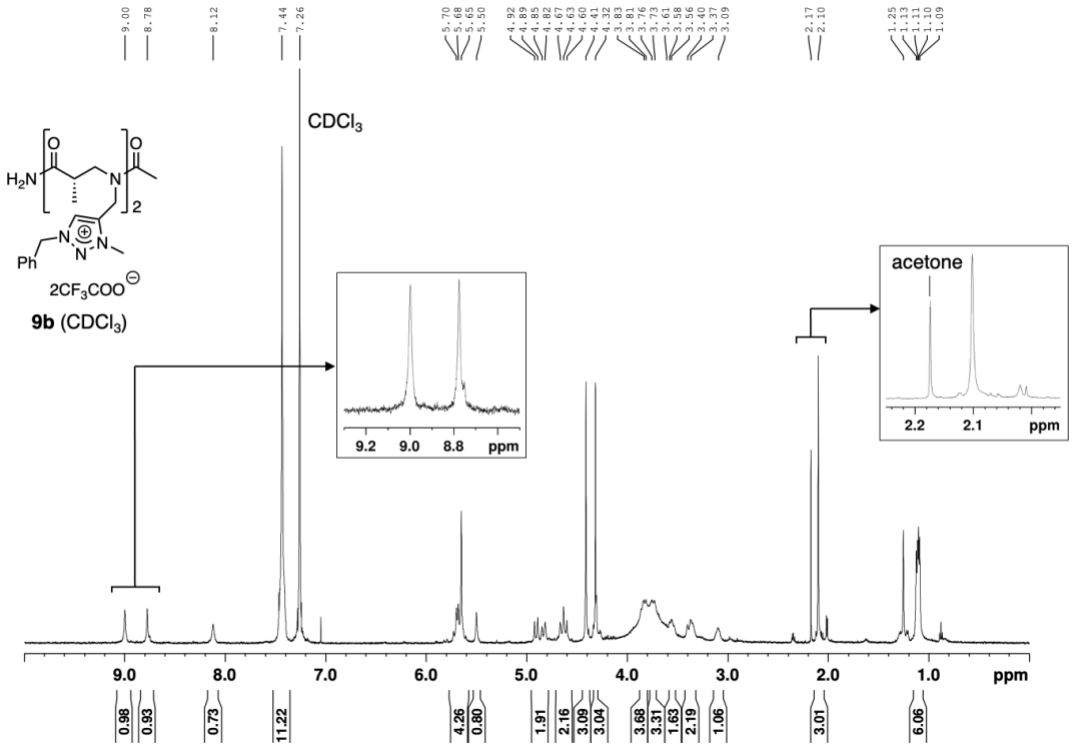


Fig. S8 (continued)

(c) CD_3OD (500 MHz)

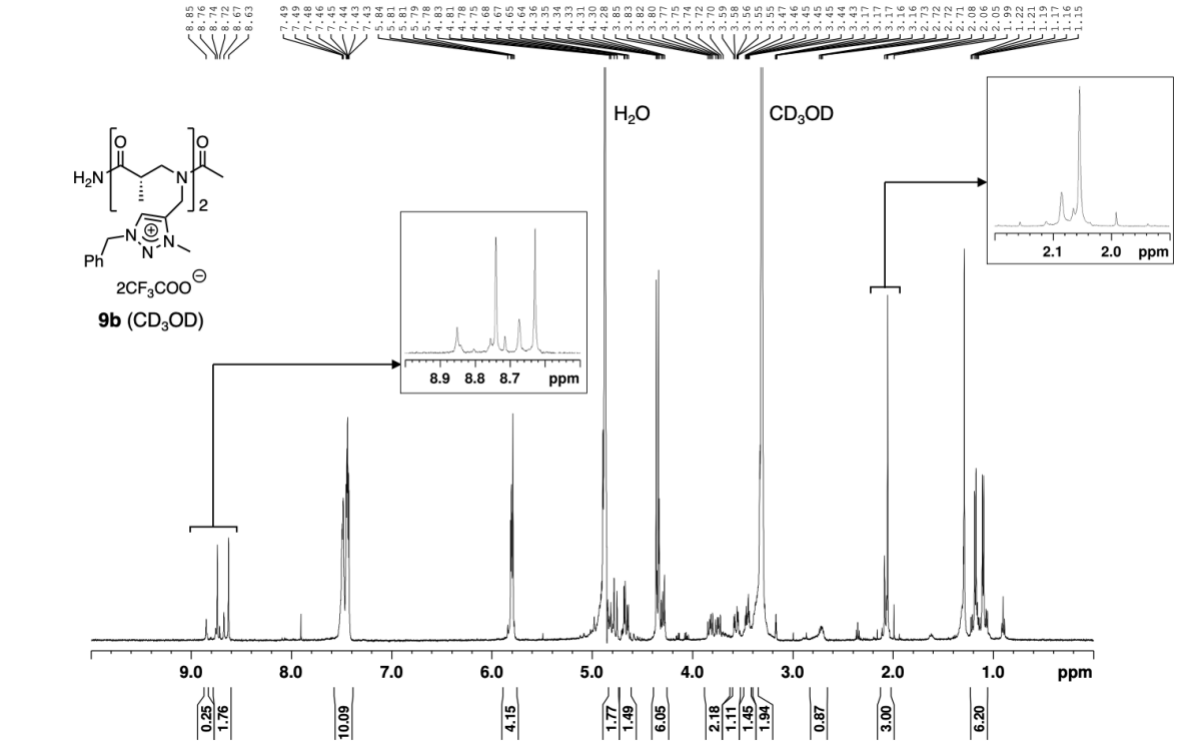
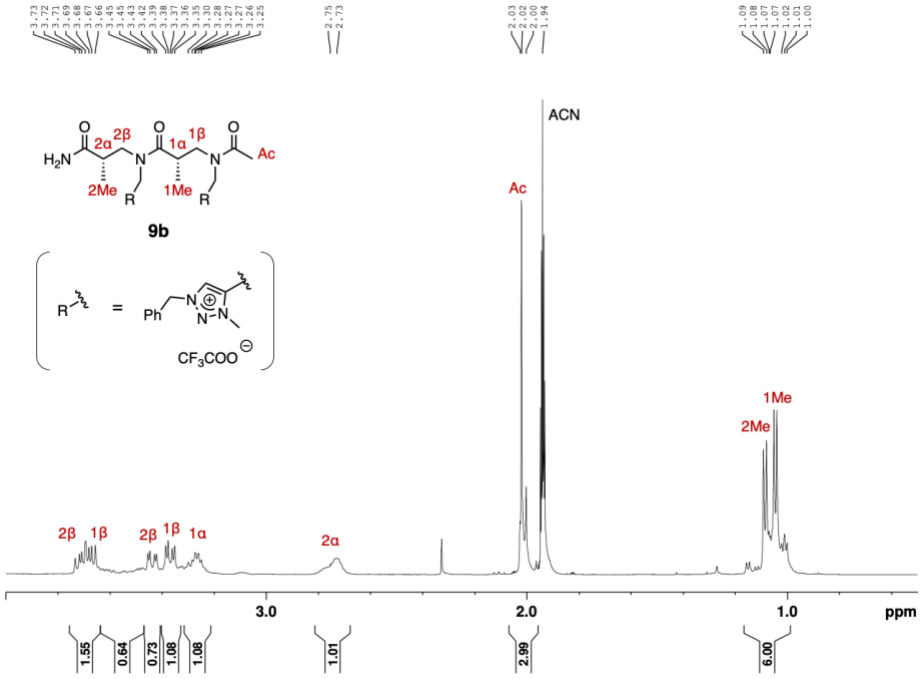


Fig. S9 ^{1}H, COSY, NOESY, and ^{1}H-^{13}C HMBC spectra of **9b** in CD_3CN.

(a) A close-up view of ^{1}H NMR spectrum of **9b** for backbone protons (4 to 0.5 ppm, 600 MHz)



(b) COSY

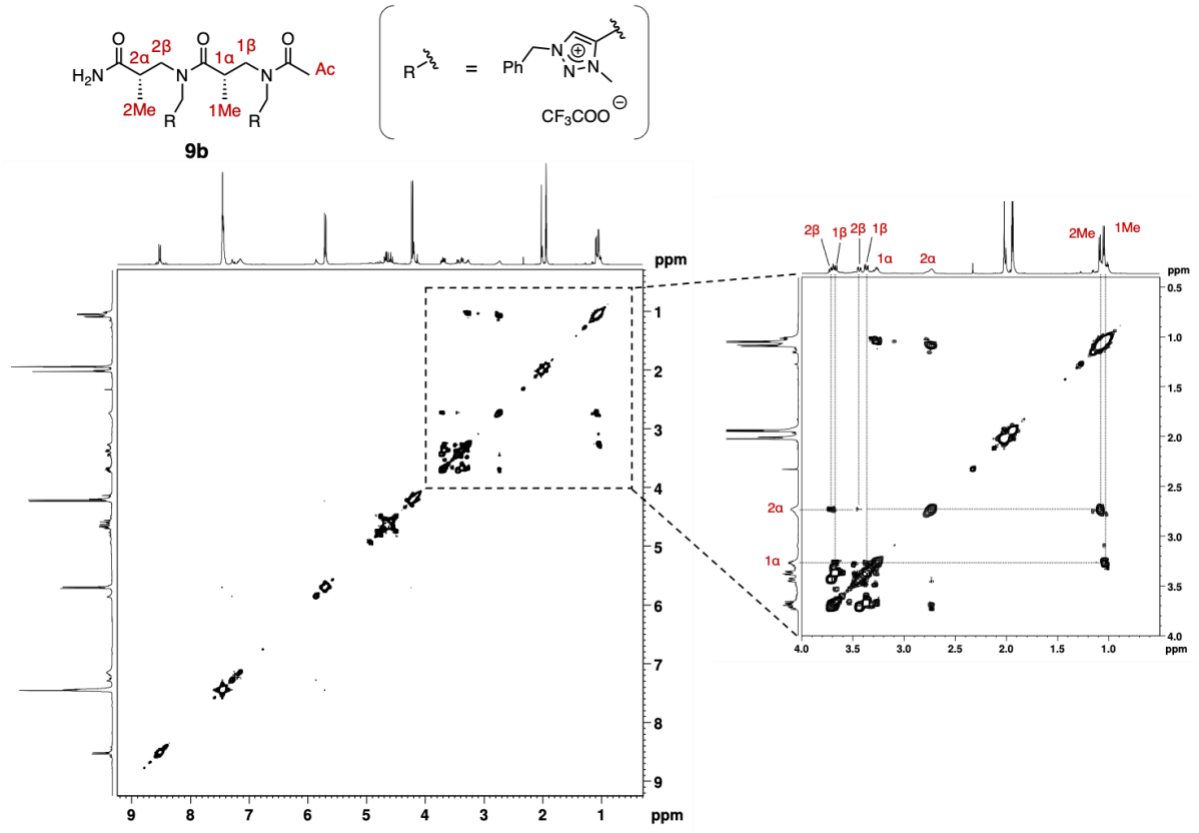


Fig. S9 (continued)

(c) ^{1}H-^{13}C HMBC

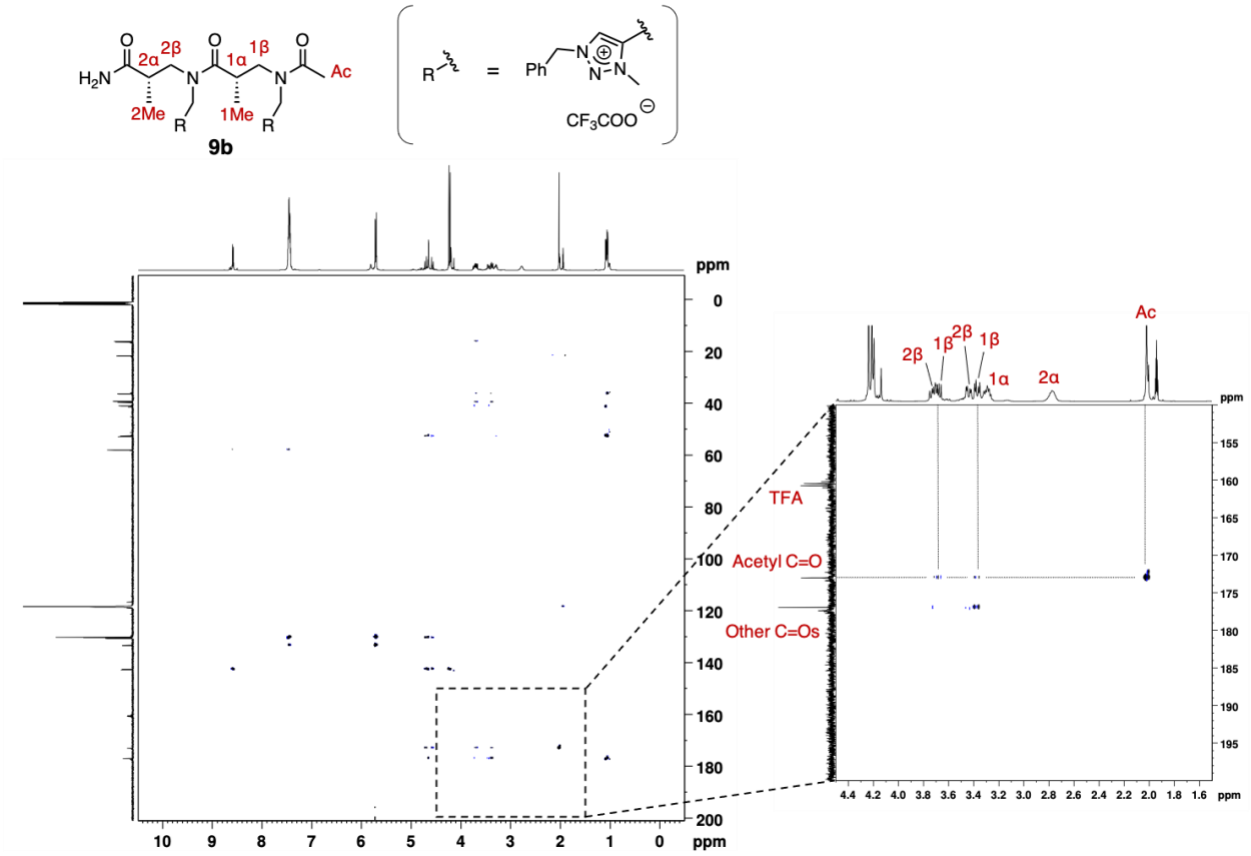


Fig. S9 (continued)

(d) NOESY

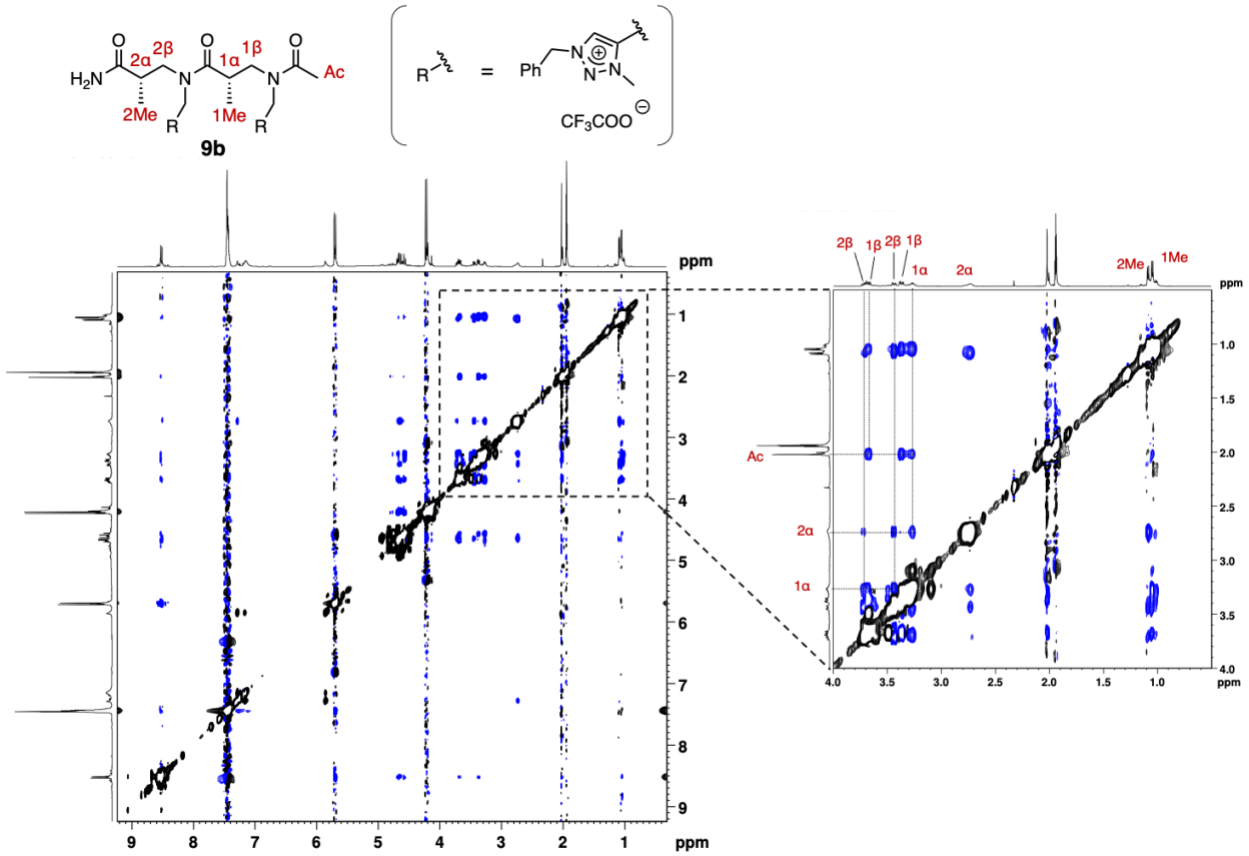
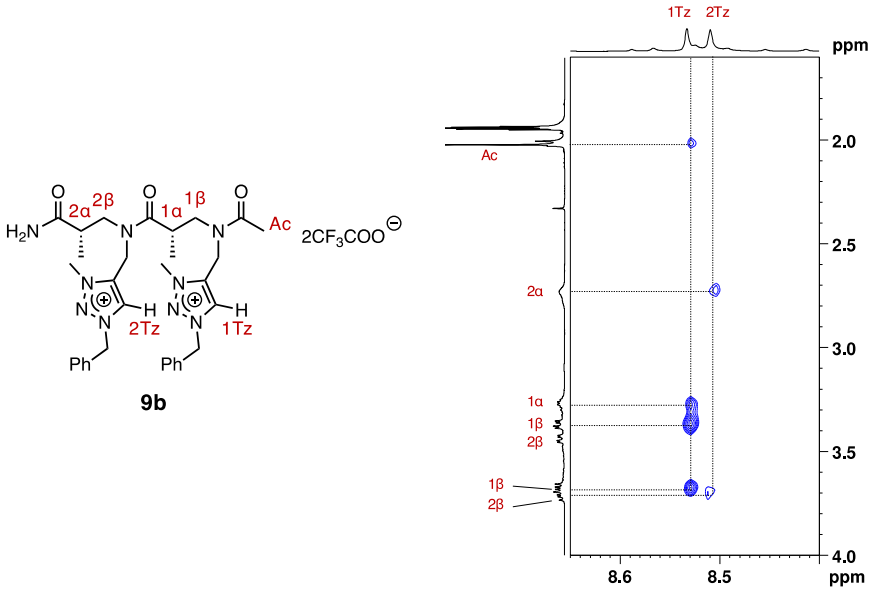


Fig. S9 (continued)

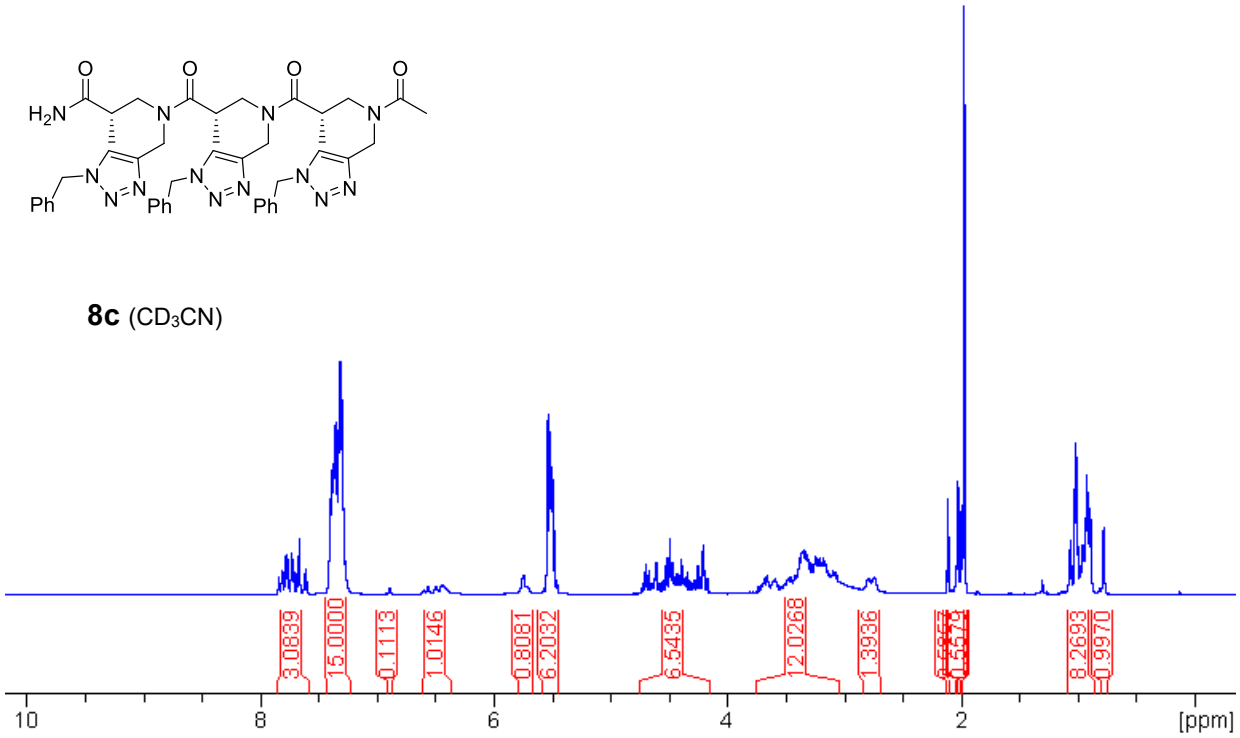
(e) NOESY, close up-view for triazolium C-H peaks.



9b

Fig. S10 ^{1}H NMR spectra of **8c**–**h** in CD_3CN.

(a) ^{1}H NMR spectrum of **8c** (600 MHz)



(b) ^{1}H NMR spectrum of **8d** (500 MHz)

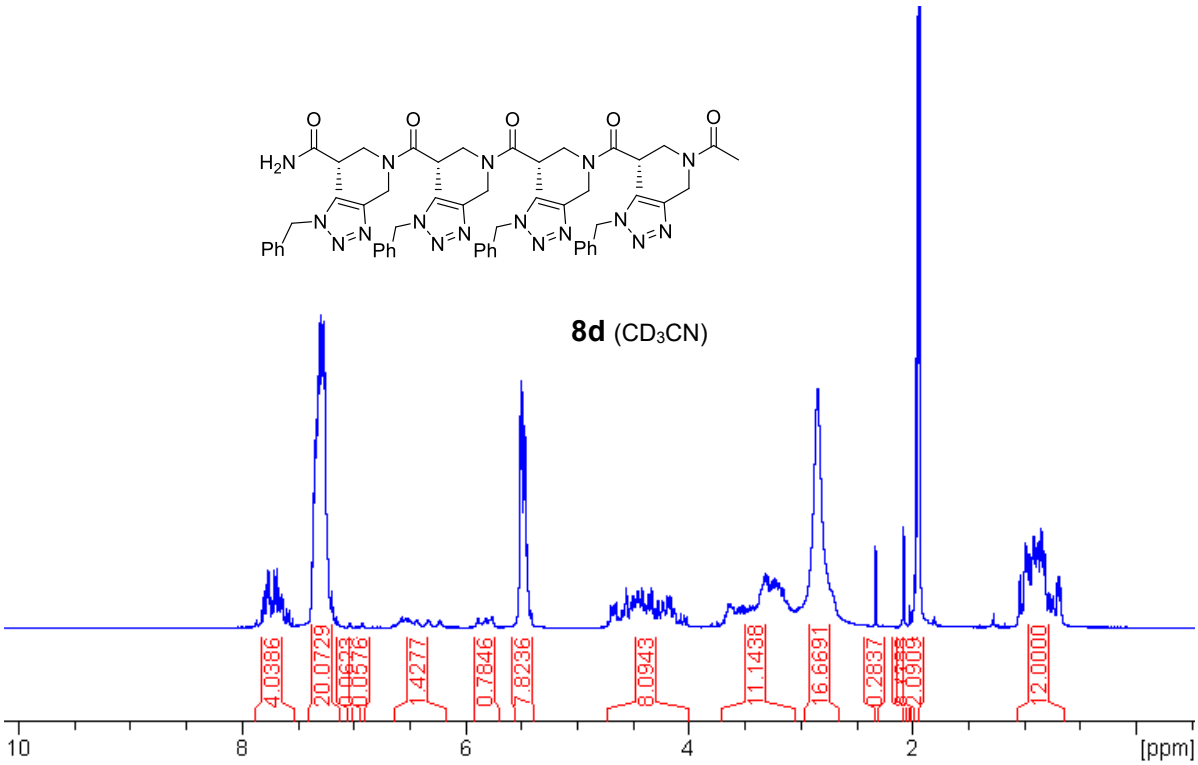
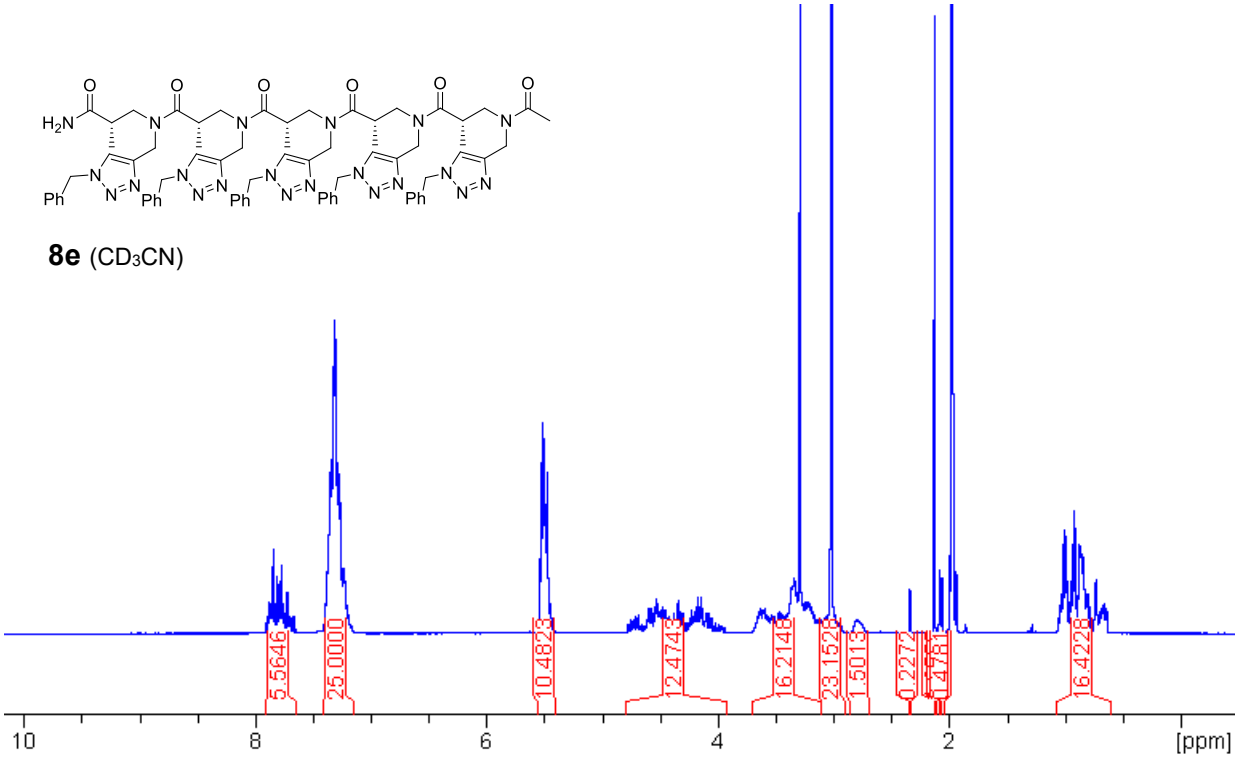


Fig. S10 (continued)

(c) ^{1}H NMR spectrum of **8e** (600 MHz)



(d) ^{1}H NMR spectrum of **8f** (500 MHz)

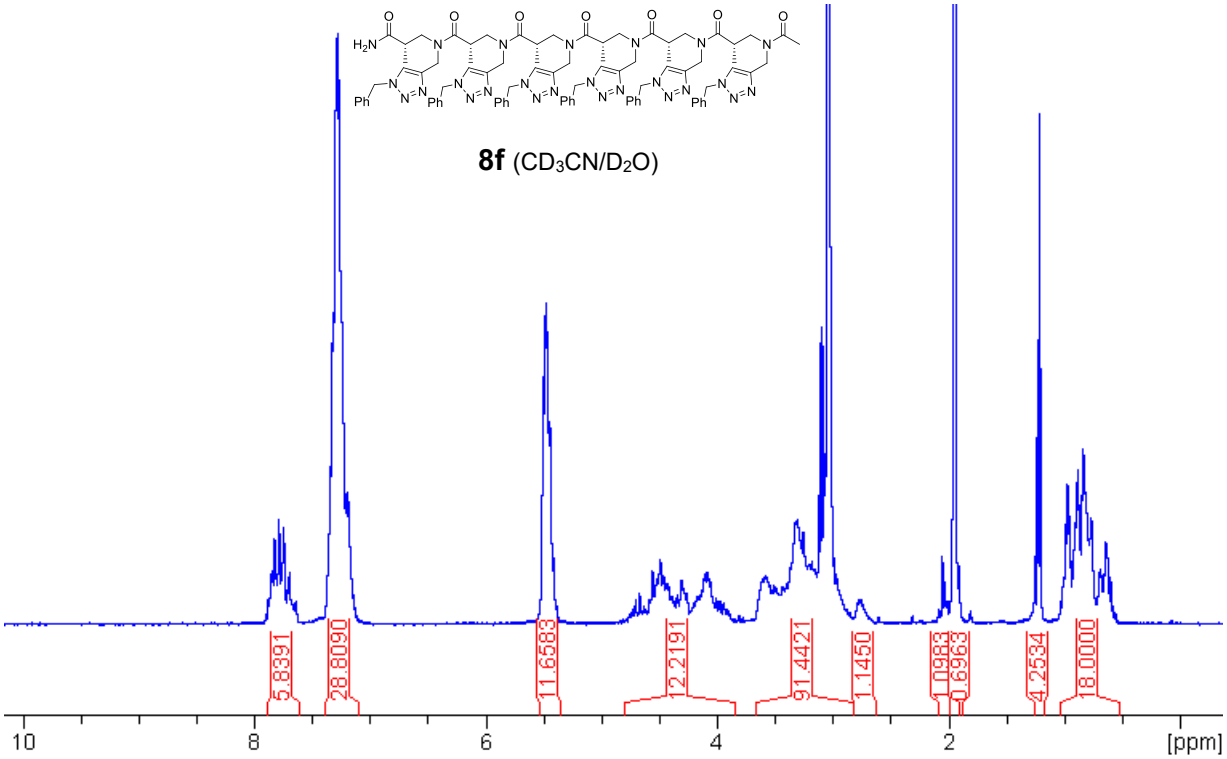
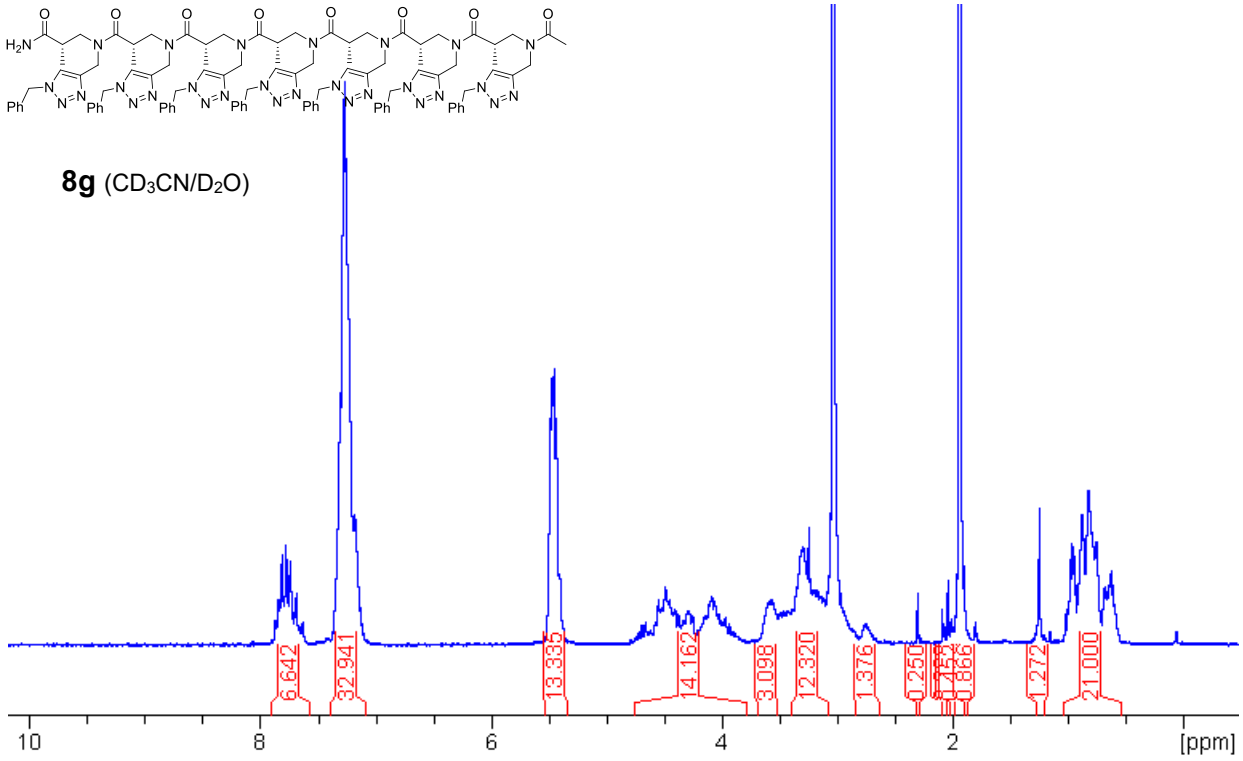


Fig. S10 (continued)

(e) ^{1}H NMR spectrum of **8g** (500 MHz)



(f) ^{1}H NMR spectrum of **8h** (500 MHz)

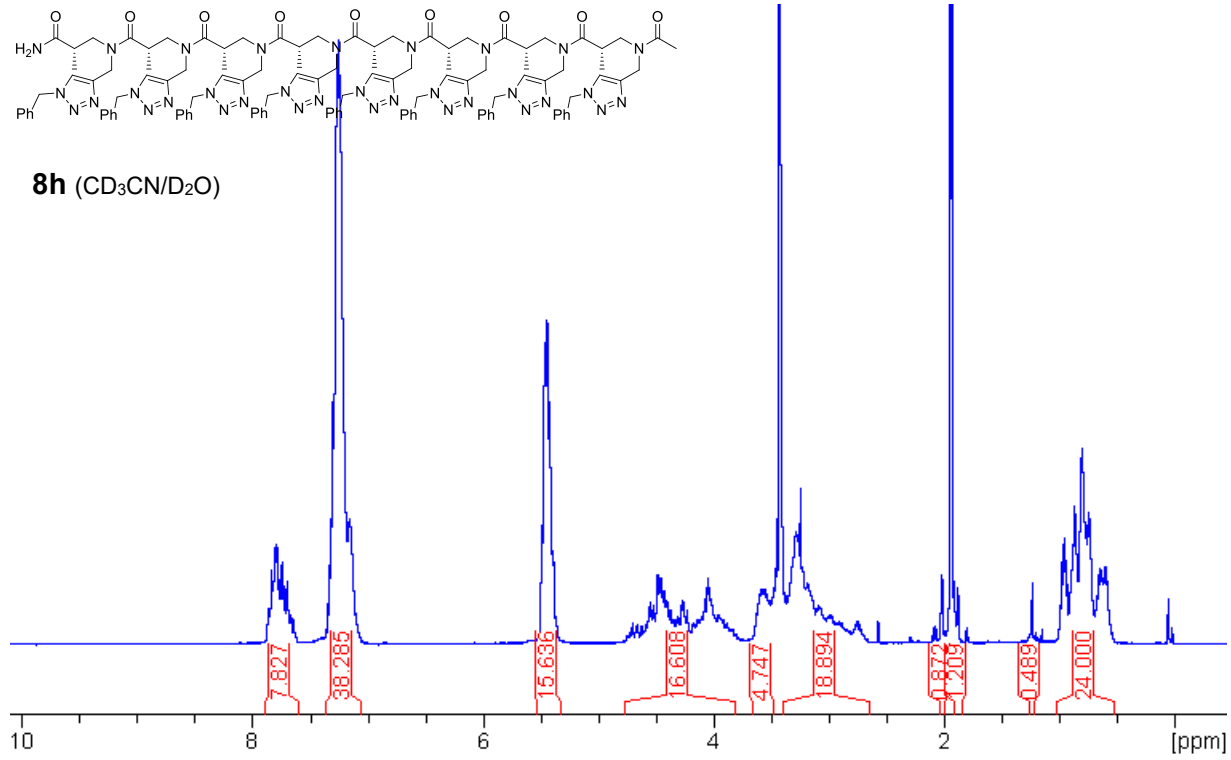
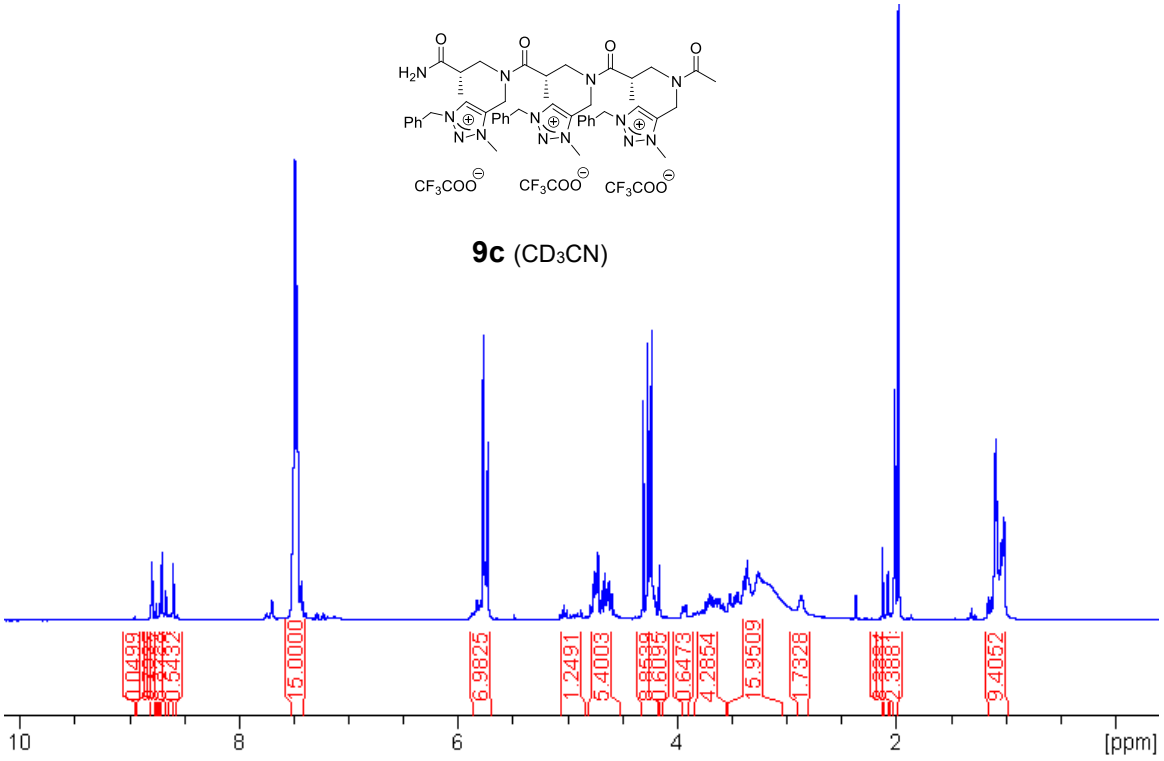


Fig. S11 ^{1}H NMR spectra of **9c**–**h** in CD_3CN.

(a) ^{1}H NMR spectrum of **9c** (600 MHz)



(b) ^{1}H NMR spectrum of **9d** (500 MHz)

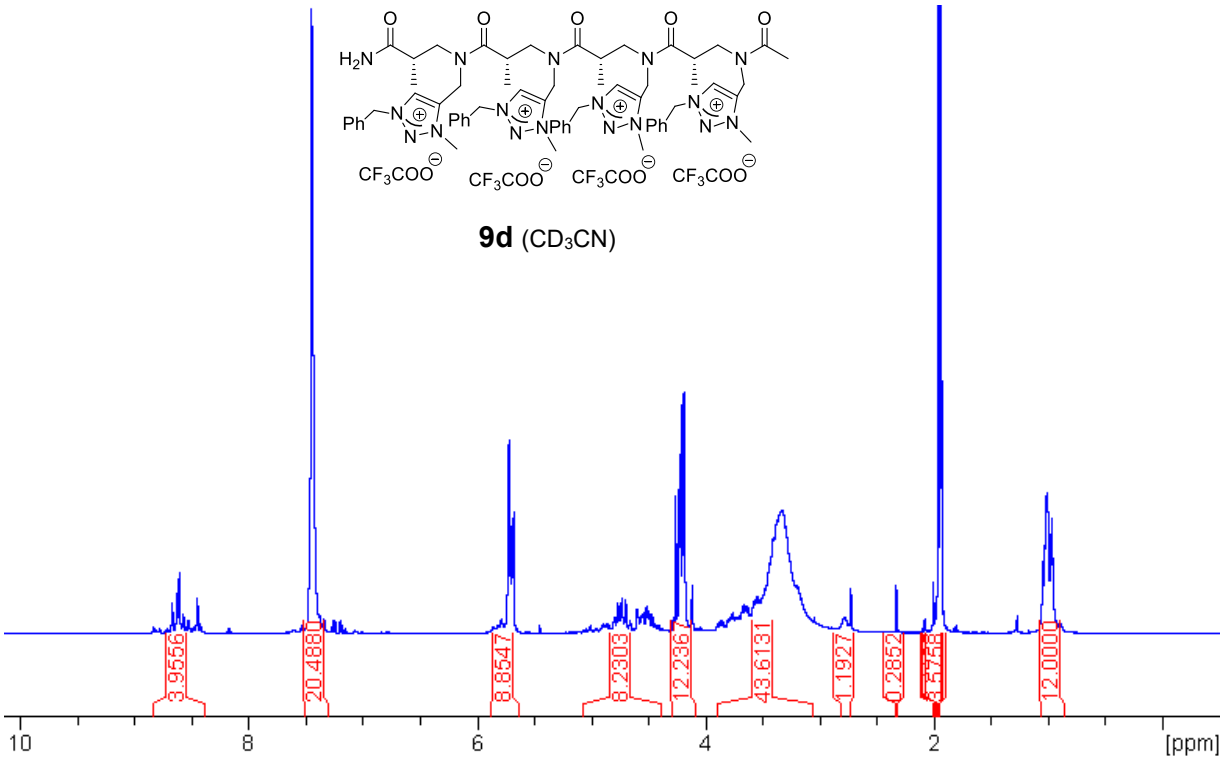


Fig. S11 (continued)
(c) ^{1}H NMR spectrum of **9e** (600 MHz)

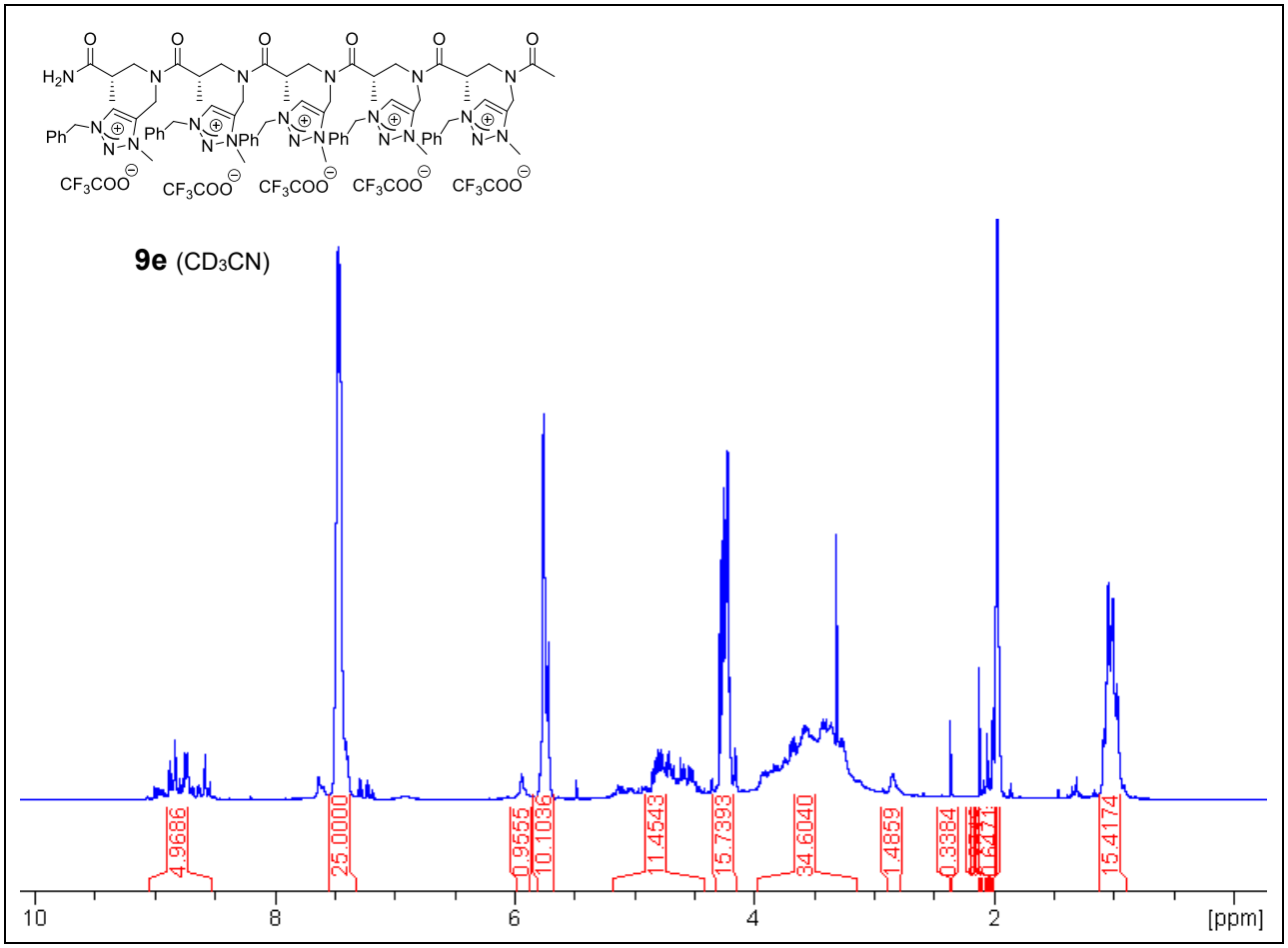


Fig. S11 (continued)

(d) ^{1}H NMR spectrum of **9f** (500 MHz)

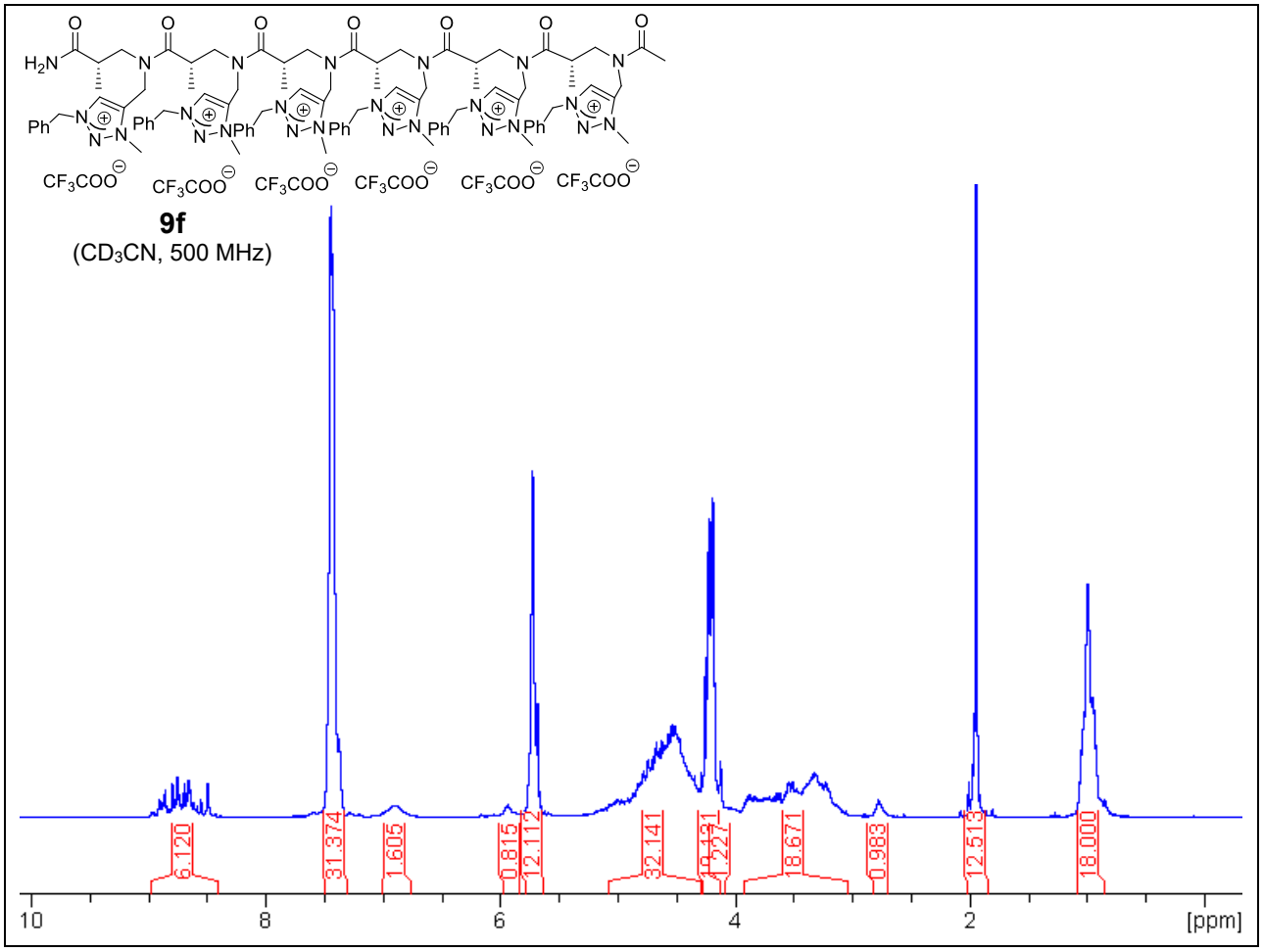


Fig. S11 (continued)

(e) ^{1}H NMR spectrum of **9g** (500 MHz)

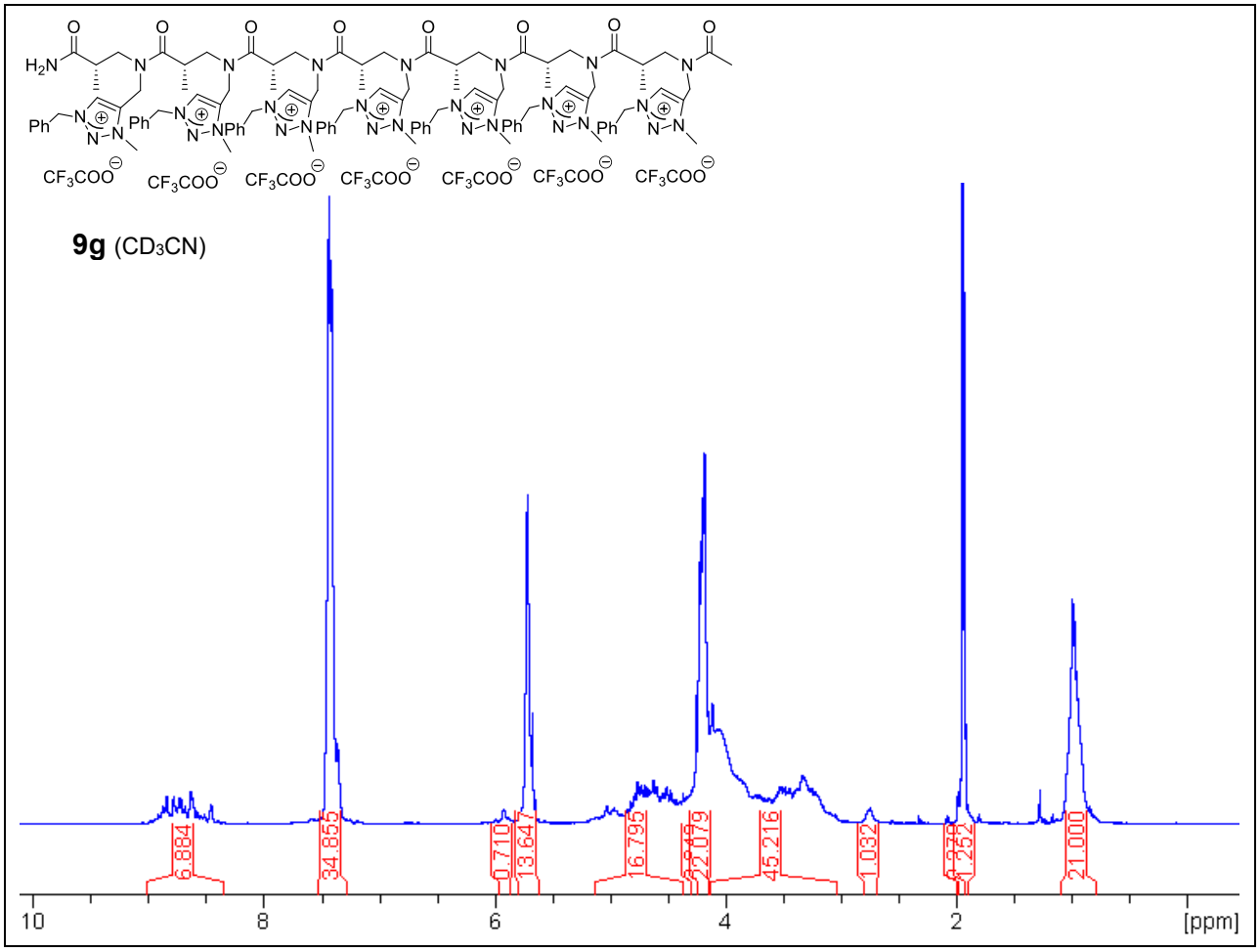


Fig. S11 (continued)

(f) ^{1}H NMR spectrum of **9h** (500 MHz)

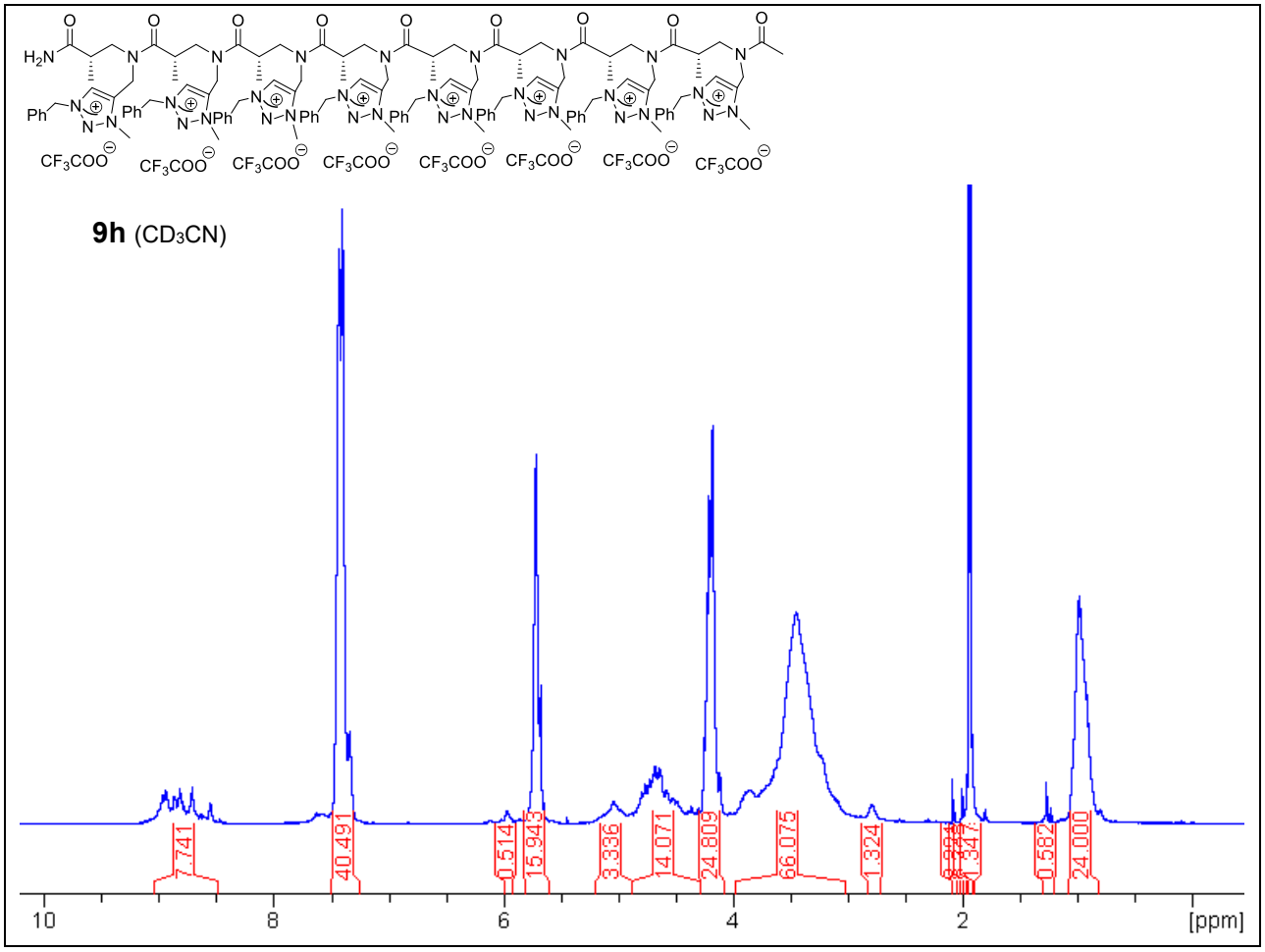


Fig. S12 CD melting curve of **9h** in TFE.

CD signal intensity of **9h** in TFE at 224 nm monitored at temperatures ranging from 5 to 65 ˚C.

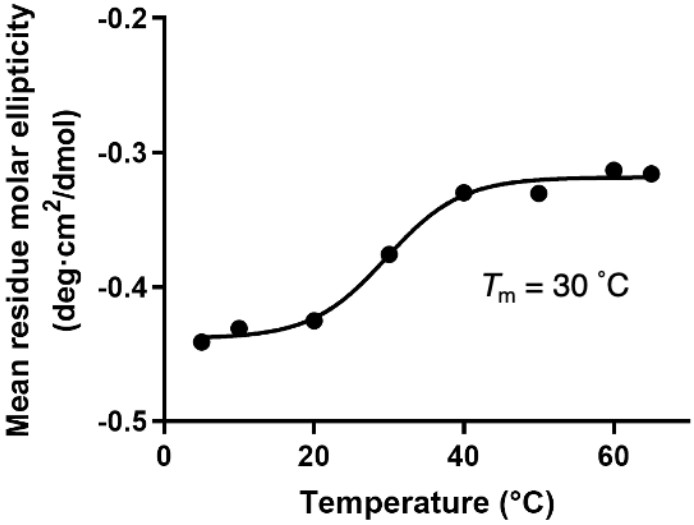


Fig. S13 Temperature dependence of CD spectrum of **8h** in TFE.

(a) CD spectra of **8h** in TFE recorded at various temperatures ranging from 5 to 65 ˚C. (b) CD spectra of **8h** in TFE before heating and after re-cooling (c, d) CD signal intensities of **8h** in TFE at 207 nm (c) and 228 nm (d) monitored at temperatures ranging from 5 to 65 ˚C.

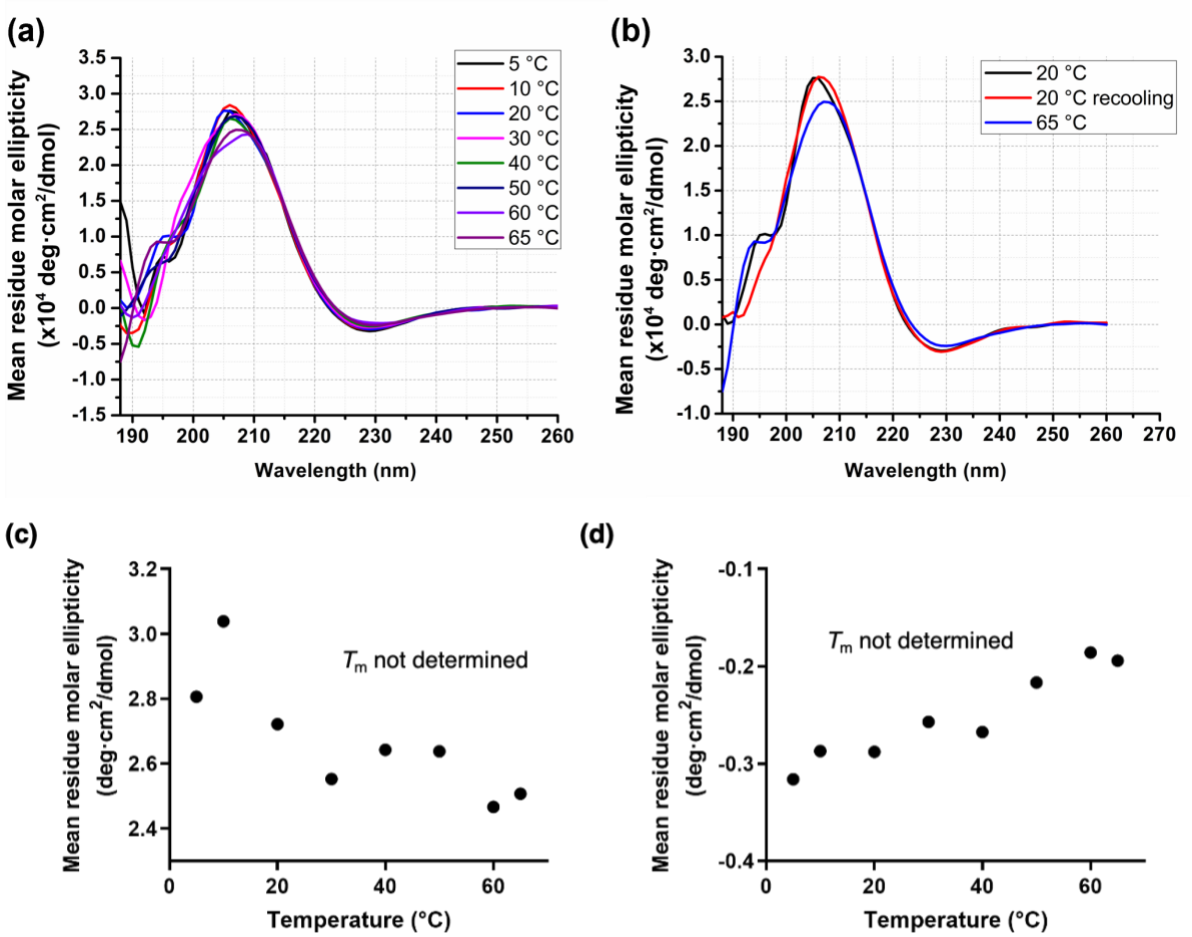


Fig. S14 ^{1}H and ^{13}C NMR spectra of nosyl-protected α-ABpeptoid monomer (**5**) and its intermediates (**3** and **4**).

(a) compound **3** (500 MHz for ^{1}H and 125 MHz for ^{13}C)

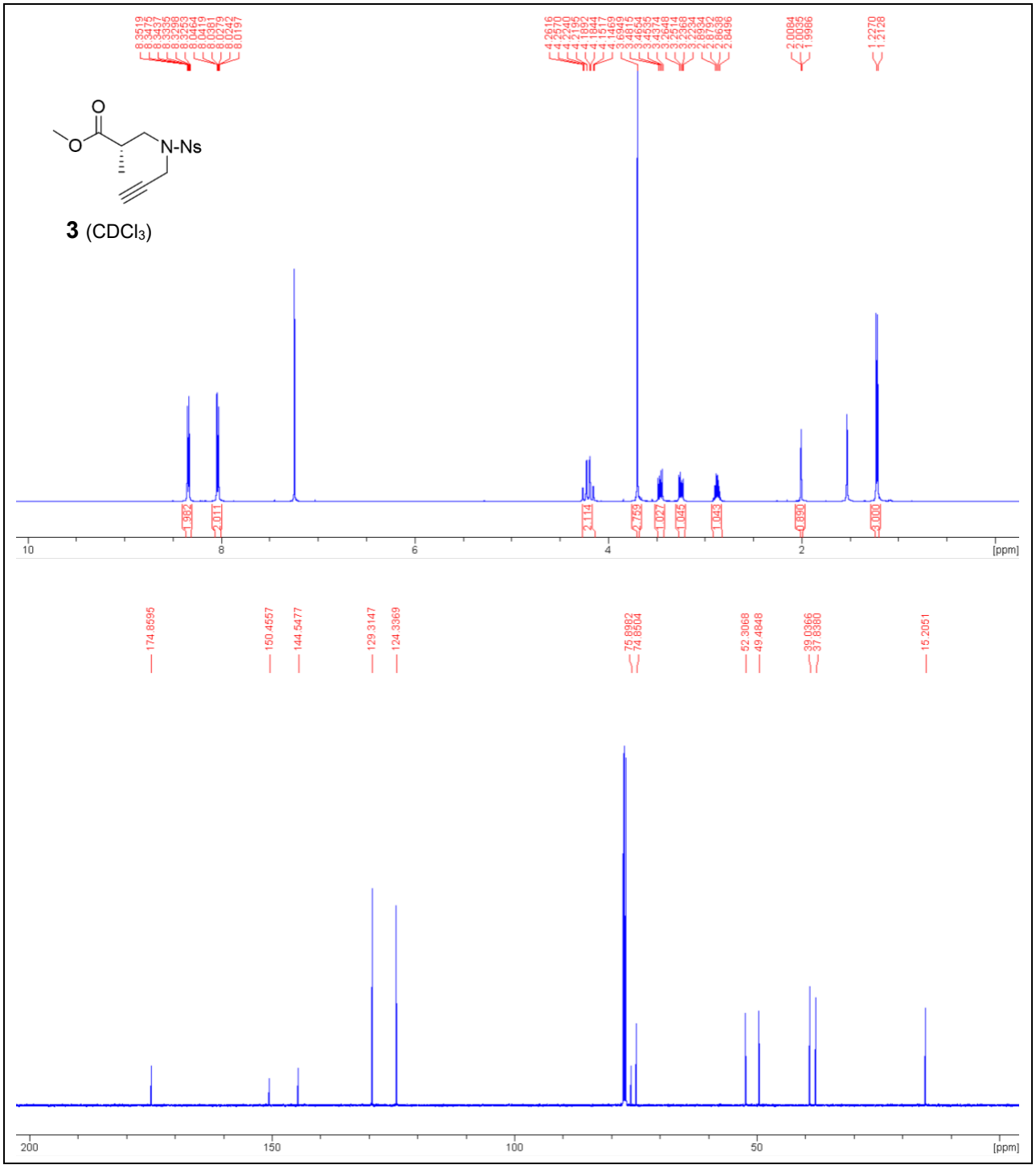


Fig. S14 (continued)

(b) compound **4** (500 MHz for ^{1}H and 125 MHz for ^{13}C)

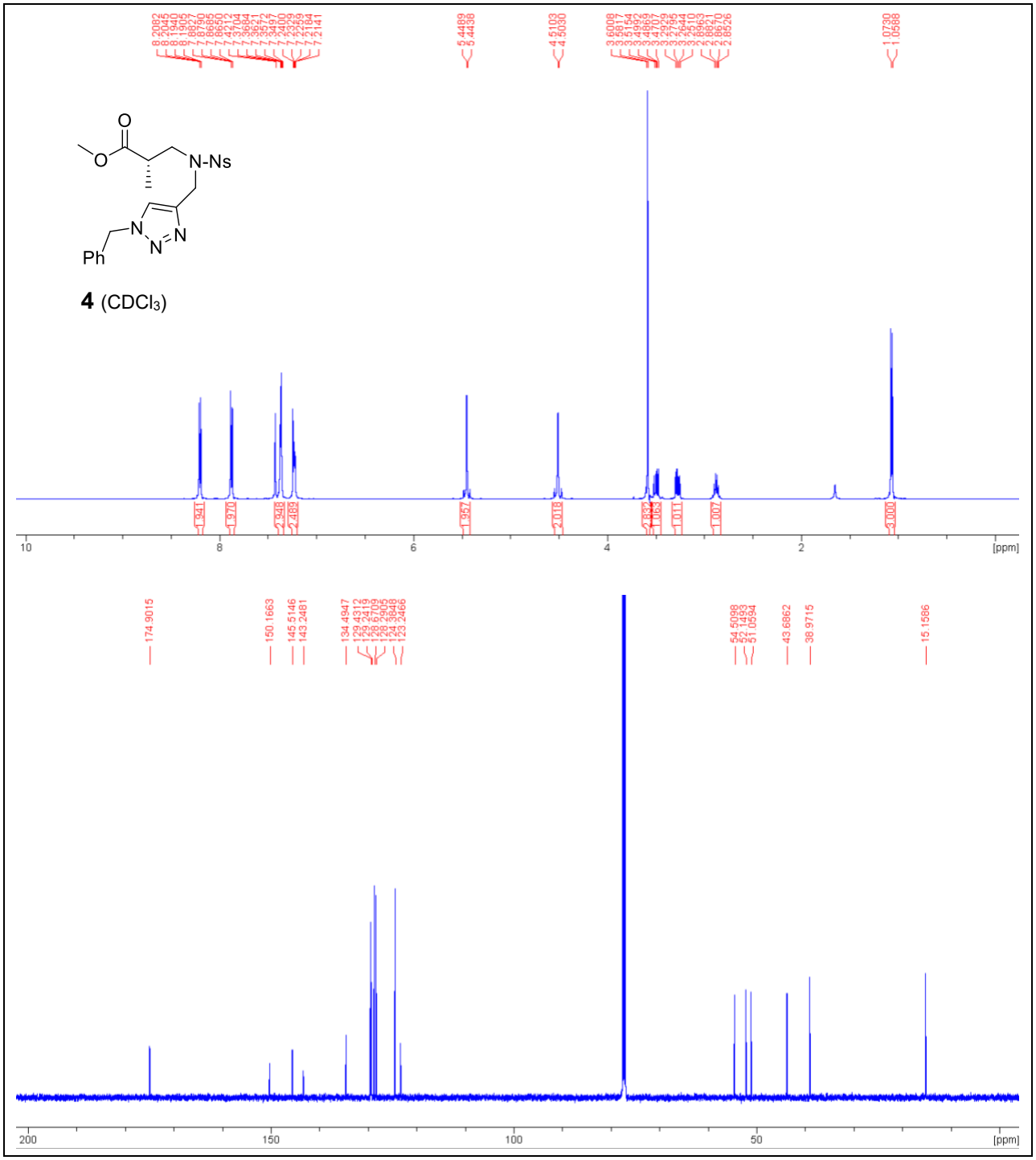


Fig. S14 (continued)

(c) compound **5** (500 MHz for ^{1}H and 125 MHz for ^{13}C)