“Click” Synthesis of Non-symmetrical Bis-(1,2,3-Triazoles)

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SUPPORTING INFORMATION

1 Preparation Details and Physical and Spectroscopic Data of Compounds.

1.1 General.

All reactions were carried out under an atmosphere of nitrogen in oven or flame-dried glassware with magnetic stirring. Tetrahydrofuran and diethyl ether were dried through PS-MD-2 columns. Extra pure dichloromethane, hexane and ethyl acetate were dried over molecular sieves (4Å) and used without further purification. The aqueous solutions of copper (II) sulfate and sodium ascorbate were prepared using deoxygenated water. Purification of products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and phosphomolybdic acid-ammonium cerium (IV) nitric-sulfuric acid-water reagent. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, and they are reported as δ values (ppm) relative to residual $CDCl_3$ δ H (7.26 ppm), $CDCl_3$ δ C (77.16 ppm), CD_3OD δ H (3.31 ppm), CD_3OD δ C (49.0 ppm), D_2O δ H (4.79 ppm) DMSO-*d6* δ H (2.5 ppm) and DMSO-*d6* δ C (36.46 ppm) as internal standards. Mass spectra were obtained either under EI (70 eV) or CI conditions after direct injection (HRMS) or using GC-MS coupling (column: fused silica gel, 15 m, 0.25 mm, 0.25 nm phase SPB-5).

1.2 Preparation of Azides.

All azides except **6h** and **6n** are known compounds with identical spectroscopic data to previously described and they were prepared as previously reported in the literature. Benzyl azide (**6a**), *p*-nitrobenzyl azide (**6i**), 4-*tert*-butylbenzylazide (**6j**) and 2-azidoethanol (**6k**) were prepared starting from the corresponding bromides and NaN_3 in DMSO[1]. 4-Azidobenzonitrile (**6b**) and 4-azidotoluene (**6l**) were prepared by diazotation of the anilines with ^{t}BuONO and $TMSN_3$[2]. Benzyl 2-azidobutyrate (**6f**) and benzyl 2-azidoacetate (**6e**) were prepared from the corresponding aminoesters and freshly

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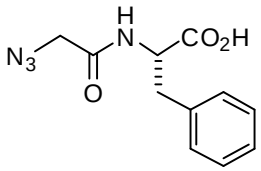
[1] Alvarez, S.G.; Alvarez M.T. *Synthesis*, **1997**, 413–414.

[2] (a) Liu, Q.; Tor, Y. *Org. Lett.,* **2003***, 5,* 2571-2572. (b) Barral, A. K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.,* **2007***, 9,* 1809-1811.

prepared triflyl azide[3]. Glycosyl azides were synthesized from *O*-benzyl or *O*-acetyl-protected monosaccharide-1-acetates using $TMSN_3$ under $SnCl_4$ catalysis: 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl-1-azide (**6d**)[4], 2,3,4-tri-*O*-acetyl-β-L-fucosyl-1-azide (**6m**)[4], 2,3,4,6-tetra-*O*-benzyl-α-D-mannosyl-1-azide (**6c**)[5] and β-L-fucosyl-1-azide (**6g**)[5].

N_3-Gly-Phe-OH (6h).



To a solution of H-Gly-Phe-OH (0.287 mmol, 64 mg) in H_2O:MeOH (1 ml: 2ml), $CuSO_4.5H_2O$ (0.003 mmol, 0.7 mg), K_2CO_3 (0.43 mmol, 60 mg) and freshly prepared solution of triflyl azide (0.574mmol) were added and the solution was stirred at rt for 4 hours. Then, the aqueous layer was acidified with HCl (1M) and the product was extracted twice with CH_2Cl_2. The collected organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to give a crude oil which was purified by column chromatography (eluent MeOH:CH_2Cl_2,1:9). Yield: 46.3 mg (65 %). Oil. $[\alpha]_D^{25}$ = + 47.29 (*c* = 1.05, CH_3OH). IR (cm^{-1}, KBr): 3308.2 (O-H), 1663.3 (C=O), 2106.4 (N_3). ^{1}H NMR (500 MHz, CD_3OD): δ 7.27-7.20 (m, 5H), 4.67-4.65 (m, 1H), 3.85 (d, 1H, *J* = 16.0 Hz), 3.80 (d, 1H, *J* = 16.0 Hz), 3.24 (dd, 1H, *J* = 13.9 Hz, *J* = 4.8 Hz), 3.00 (dd, 1H, *J* = 13.8 Hz, *J* = 8.5 Hz) . ^{13}C NMR (125 MHz, CD_3OD): δ 175.0, 169.6, 138.2, 130.3, 129.4, 127.7, 55.4, 49.5, 38.4. MS m/z (Ion Source Type: ESI positive polarity, 5 eV): MS+1= 249.1; MS2(249.1)= 90.8 (100), 146.0 (31), 90.9 (22), 119.9 (22).

[Preparation of **triflyl azide**: Tf_2O (0.574 mmol, 0.1 ml) was added to a solution of NaN_3 (2.81 mmol, 183 mg) in H_2O:CH_2Cl_2 (1.5 ml: 2.5 ml) at 0 ºC and the mixture was stirred vigorously for 2 hours. Then, the mixture was poured into a separation funnel and the product was extracted with CH_2Cl_2 (2 x 2 ml). The organic fraction was washed with Na_2CO_3 (sat.). The solution was used directly in the azido transfer reaction.]

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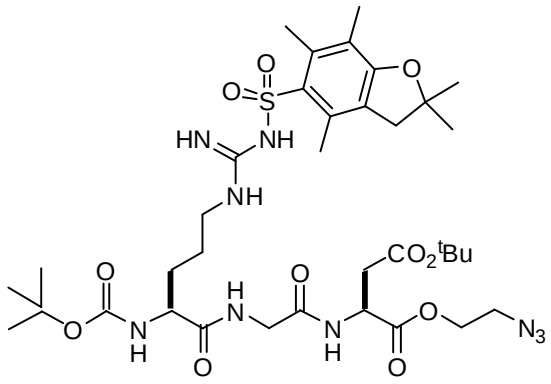
[3] Lundquist IV, J. T.; Pelletier. J. C. *Org. Lett.,* **2001***, 3,* 781-783.

[4] (a) Gyorgydeak, Z.; Paulsen, H.; Szilagyi L. *J. Carbohydrate Chem.,* **1993**, *12*, 139-163. (b) Kunz, H.; Pfrengle, W.; Ruck, K; Sager. W. *Synthesis*, **1991**, 1039-1042.

[5] Palomo, C.; Aizpurua, J. M.; Balentova, E.; Azcune, I.; Santos, J. I.; Jimenez-Barbero, J.; Cañada, J.; Miranda, J. I. *Org. Lett.,* **2008***, 10,* 2217-2230.

Boc-Arg(Pbf)-Gly-Asp(O^{t}Bu)-OCH$_2$CH$_2$-N$_3$ (6n).



To a solution of Boc-Arg(Pbf)-Gly-OH (0.56 mmol, 329 mg) and H-Asp-(O^{t}Bu)-O-$CH_2CH_2N_3$ (0.56 mmol, 145 mg) in CH_2Cl_2:DMF (20 mL: 1mL) at 0 ºC, Et_3N (0.84 mmol, 0.12 mL), HOBt (0.84 mmol, 114 mg) and EDC.HCl (0.84 mmol, 162 mg) were added. The stirring was continued for 1 hour at 0 ºC , and for 24 h at room temperature. After that time, the solution was washed with 1M aq. HCl (5 mL). The organic phase was dried over $MgSO_4$, solvents were evaporated under reduced pressure and the crude was purified by flash column chromatography (eluent EtOAc). Yield: 330 mg (71 %). Yellow solid (mp = 59-60 ºC). $[\alpha]_D^{25}$ = + 8.44 (*c* = 1.03, CH_3OH). IR (cm^{-1}, KBr): 3383, 3333 (N-H), 2106 (N_3), 1730, 1683 (C=O), 1551, 1455, 1368, 1251, 1158, 1107. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (bs, 1H), 7.09 (d, 1H, *J* = 9.3 Hz), 5.44 (bs, 1H), 4.85-4.81 (m, 1H), 4.31-4.29 (m, 2H), 4.03 (dd, 1H, *J* = 16.7 Hz, *J* = 6.04 Hz), 3.94 (dd, 1H, *J* = 16.8 Hz, *J* = 5.6 Hz), 3.51-3.42 (m, 2H), 3.28 (bs, 2H), 2.93 (dd, 1H, *J* = 17.0 Hz, *J* = 4.7 Hz), 2.58 (s, 3H), 2.52 (s, 3H), 2.10 (s, 3H), 1.95-1.86 (m, 1H), 1.74-1.55 (m,), 1.46 (s, 6H), 1.44 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ. 173.4, 170.6, 169.9, 169.5, 158.8, 156.6, 156.0, 133.0, 132.3, 124.7, 117.5, 86.4, 81.9, 64.3, 49.6, 49.0, 43.0, 37.3, 28.4, 25.4, 18.0, 12.5. MS m/z (Ion Source Type: ESI positive polarity, 5 eV): MS+1= 824.4 (100); MS2 (824.4) = 398.2 (100), 668.2 (46), 442.2 (23).

1.3 Preparation of 4-Ethynyl-1,2,3-triazoles.

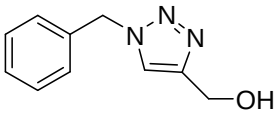
1.3.1 Stepwise Synthesis from 4-Hydroxymethyl-1,2,3-triazoles

1.3.1.1 General Procedure for the Preparation of 4-Hydroxymethyl-1,2,3-triazoles

To a solution of azide (1.0 eq.) and propargyl alcohol **7** (1.1 eq., ρ= 0.963 g/mL) in ^{t}BuO:H_2O (1:1) at rt, sodium ascorbate (1.0-0.4 eq.) and $CuSO_4$ (0.2 eq.) were added and

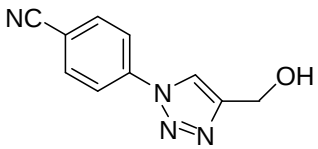
the resulting yellow mixture was stirred vigorously overnight. The reaction mixture was diluted and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The product was purified by column chromatography. TBTA catalyst has been used.

1-Benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole (8a).[6]



The general procedure 1.3.1.1. was followed starting from benzyl azide (**6a**) (10 mmol, 1.33 g), **7** (11 mmol, 0.64 mL), $CuSO_4$ (2 mmol, 0.5 g) and sodium ascorbate (4 mmol, 0.79 g). Yield: 1.81 g (96 %). Amorphous solid (mp = 78-79 ºC). IR (cm^{-1}, KBr): 3271 (OH), 3139.5, 3089.2, 3031.6, 1457.7 (triazole). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.40-7.27 (m, 5H), 5.52 (s, 2H), 4.79 (s, 2H), 2.17 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.6, 129.0, 128.8, 128.1, 56.0, 54.1. HRMS (m/z): $C_{10}H_{11}N_3O$, requires: 190.0980 [M+1]; found, 190.0981. MS (TOF CI) m/z: 91.1 (100), 190.1 (90), 144.1 (70), 172.1 (23).

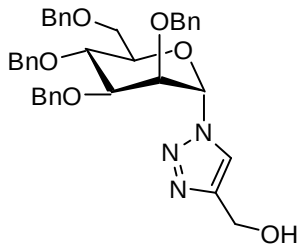
1-(4-Benzonitrile)-4-hydroxymethyl-1*H*-1,2,3-triazole (8b).



The general procedure 1.3.1.1 was followed starting from 4-azidobenzonitrile (**6b**) (3.33 mmol, 0.48 g), **7** (3.66 mmol, 0.212 mL), $CuSO_4$ (0.66 mmol, 0.165 g) and sodium ascorbate (1.33 mmol, 0.263 g). Yield: 0.636 g (95 %). Amorphous solid (mp = 165-167 ºC). IR (cm^{-1}, KBr): 3270 (OH), 3150, 2959, 2181 (C≡N), 1456 (triazole). ^{1}H NMR (500 MHz, DMSO): δ 8.83 (s, 1H), 8.16-8.07 (m, 4H), 5.35 (t, 1H, J = 5.3 Hz), 4.63 (d, 2H, J = 5.3 Hz). ^{13}C NMR (125 MHz, DMSO): δ 149.5, 139.5, 134.1, 121.0, 120.1, 117.9, 110.7, 54.8. HRMS (m/z): $C_{10}H_8N_4O$, requires: 201.0776 [M+1]; found, 201.0784. MS (TOF CI) m/z: 201.1 (100), 173.1 (76), 155.1 (71), 185.1 (41), 119.1 (34).

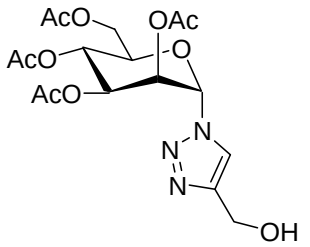
[6] Girard, C; Önen, E; Aufort, M; Beauvière, S; Samson, E; Herscovici, J. *Org. Lett.,* **2006**, *8,* 1689-1692.

1-(2,3,4,6-Tetra-O-benzyl-α-D-mannosyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (8c).



The general procedure 1.3.1.1 was followed starting from 2,3,4,6-tetra-*O*-benzyl-α-D-mannosyl-1-azide (**6c**) (0.304 mmol, 172 mg), **7** (0.334 mmol, 0.02 mL), TBTA (3 μmol, 1.6 mg), $CuSO_4$ (0.06 mmol, 15 mg) and sodium ascorbate (0.304 mmol, 60 mg). Yield: 186 mg (99 %). Oil. $[\alpha]_D^{25}$ = +35.07 (*c* = 1.36, CH_2Cl_2). IR (cm^{-1}, KBr): 3392.5 (OH), 3063.0, 3030.3, 2992.2, 1454 (triazole), 1113.0, 1027.8. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.37-7.13 (m, 20H), 5.92 (d, 1H, *J* = 3.7 Hz), 4.80 (t, 1H, *J* = 3.2 Hz), 4.78 (s, 2H), 4.73-4.45 (m, 8H), 4.06 (dd, 1H, *J* = 7.3 Hz, *J* = 2.9 Hz), 4.0 (dd, 1H, *J* = 8.0 Hz, *J* = 8.0 Hz), 3.71 (m, 1H), 3.68-3.65 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 138.2, 138.1, 138.1, 137.7, 128.6, 128.6, 128.5, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 121.6, 85.2, 78.3, 75.0, 74.5, 74.3, 73.5, 72.8, 67.0, 56.6. MS m/z (Ion Source Type: ESI positive polarity, 5 eV): MS+1 = 622.2360; MS2(622.2) = 181.2 (100), 90.8 (60), 90.8 (40), 179.1 (30). Anal. calcd. for $C_{37}H_{39}N_3O_6$: C, 71.48; H, 6.32; N, 6.76; Found: C, 71.46; H, 6.05; N, 6.44.

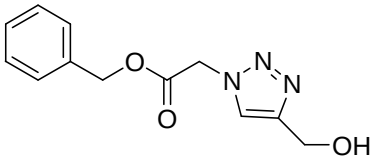
1-(2,3,4,6-Tetra-O-acetyl-α-D-mannosyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (8d).



The general procedure 1.3.1.1 was followed starting from 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl-1-azide (**6d**) (0.471 mmol, 176 mg), **7** (0.565 mmol, 0.032 mL), TBTA (4 μmol, 2.1 mg), $CuSO_4$ (0.094 mmol, 23 mg) and sodium ascorbate (0.188 mmol, 37 mg). Yield: 146 mg (72%). Oil. $[\alpha]_D^{25}$ = +43.46 (*c* = 0.8, CH_2Cl_2). IR (cm^{-1}, KBr): 3481.1 (OH), 2925.3, 1750.9 (C=O), 1436.5 (triazole), 1226.8. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 6.00 (d, 1H, *J* = 2.6 Hz), 5.93 (dd, 1H, *J* = 3.5 Hz, *J* = 2.8 Hz), 5.89 (dd, 1H, *J* = 8.8 Hz, *J* = 3.7 Hz), 5.36 (s, 1H, *J* = 8.9 Hz, *J* = 8.9 Hz), 4.83 (d, 2H, *J* = 3.7 Hz), 4.35 (dd, 1H, *J* = 12.5 Hz, *J* = 5.4 Hz), 4.06 (dd, 1H, *J* = 12.5 Hz, *J* = 2.6 Hz), 3.92-3.89 (m, 1H), 2.54 (bt, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 169.8, 169.7, 169.5, 148.5, 122.2, 83.7, 72.4, 69.0, 68.5, 66.3, 61.8, 56.7, 20.8, 20.69.

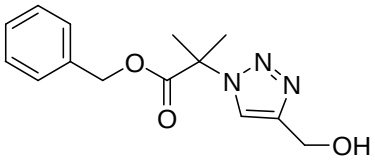
HRMS (m/z): $C_{17}H_{23}N_3O_{10}$, requires: 430.1462 [M+1]; found, 430.1461. MS (TOF CI) m/z: 331.1 (100), 169.0 (30).

1-(Benzyloxycarbonylmethyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (8e).



The general procedure 1.3.1.1 was followed starting from benzyl azidoacetate (**6e**) (3.56 mmol, 0.68 g), **7** (3.91 mmol, 0.228 mL), $CuSO_4$ (0.71 mmol, 178 mg) and sodium ascorbate (1.42 mmol, 282 mg). Yield: 0.734g (85 %). White solid (mp = 130-131 ºC). IR (cm^{-1}, KBr): 3256.7 (OH), 3149.2, 2920.2, 1748.7 (C=O), 1457.2 (triazole), 1231.5, 1220.2, 1209.0. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.39-7.33 (m, 5H), 5.24 (s, 2H), 5.21 (s, 2H), 4.86 (s, 2H), 1.90 (s, 1H). ^{13}C NMR (125 MHz, DMSO): δ 167.1, 147.9, 135.2, 128.3, 128.1, 127.9, 123.9, 66.5, 54.9, 50.1. HRMS (m/z): $C_{12}H_{13}N_3O_3$, requires: 248.1035 [M+1]; found, 248.1046. MS (TOF CI) m/z: 282.3 (100), 248.1 (86), 91.0 (37).

1-[1-(Benzyloxycarbonyl)isopropyl]-4-hydroxymethyl-1*H*-1,2,3-triazole (8f).

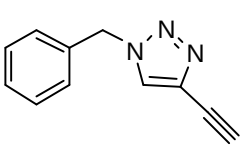


The general procedure 1.3.1.1 was followed starting from benzyl 2-azidoisobutirate (**6f**) (0.514 mmol, 0.114 g), **7** (1.54 mmol, 0.09 mL), TBTA (5 μmol, 2.6 mg), $CuSO_4$ (0.102 mmol, 26 mg) and sodium ascorbate (0.514 mmol, 102 mg). Yield: 115 mg (85 %). Oil. IR (cm^{-1}, KBr): 3346.1 (OH), 3153.2, 2995.4, 2945.6, 1743.9 (C=O), 1472.5 (triazole), 1270.9, 1153.5. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.35-7.24 (m, 5H), 5.17 (s, 2H), 4.81 (s, 2H), 3.14 (bs, 1H), 1.96 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 147.6, 135.0, 128.6, 128.5, 127.9, 120.9, 67.8, 64.6, 56.2, 25.6. HRMS (m/z): $C_{14}H_{17}N_3O_3$, requires: 276.1348 [M+1]; found, 276.1335. MS (TOF CI) m/z: 276.1 (100), 91.0 (46).

1.3.1.2 General Procedure for Swern Oxidation and Ohira-Bestmann Alkynylation.

To a solution of oxalyl chloride (1.1 eq.) in CH_2Cl_2 cooled at -55 ºC, DMSO (2.4 eq.) was added and the solution was stirred for 5 minutes. After this time, a solution of the corresponding alcohol (1.0 eq.) in CH_2Cl_2 was added *via* canula at the same temperature and the mixture was stirred for 15 min. Then, Et_3N (5.0 eq.) was added and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with 1M HCl and the product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, the solvent was evaporated under reduced pressure and the product was submitted to the Ohira-Bestmann alkynylation without any further purification. Thus, to a solution of the aldehyde in MeOH at 0 ºC, dimethyl acetyldiazomethylphosphonate[7] (1.0 eq.) and K_2CO_3 (2.0 eq.) were added. The reaction was stirred for 1 hour at 0 ºC and then, at rt for 3-5 hours. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (Hex/EtOAc).

1-Benzyl-4-ethynyl-1*H*-1,2,3-triazole (5a).

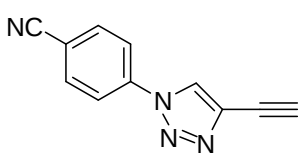


The general procedure 1.3.1.2 was followed starting from **8a** (9.05 mmol, 1.711 g), oxalyl chloride (9.96 mmol, 0.833 mL), DMSO (21.73 mmol, 1.546 mL), Et_3N (6.4 mL), K_2CO_3 (18.1 mmol, 2.5 g) and dimethyl acetyldiazomethylphosphonate reagent (9.05 mmol, 1.738 g). Yield: 2.340 g (75%). Amorphous solid (mp = 75-77 ºC). IR (cm^{-1}, KBr): 3275.3 (≡CH), 3123.3, 3068.5, 1454.0 (triazole). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.39-7.26 (m, 5H), 5.52 (s, 2H), 3.20 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.1, 130.3, 129.2, 128.9, 128.1, 126.7, 81.1, 73.1, 54.3. HRMS (m/z): $C_{11}H_9N_3$, requires: 184.0875 [M+1]; found, 184.0881. MS (TOF CI) m/z: 184.1 (100), 91.1 (70).

[**Aldehyde**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.99 (s, 1H), 7.42-7.30 (m, 5H), 5.59 (s, 2H)]

[7] Mueller, S.; Liepold, B.; Roth, G.; Bestmann, H. J. *Synlett*, **1996**, *6*, 521-522

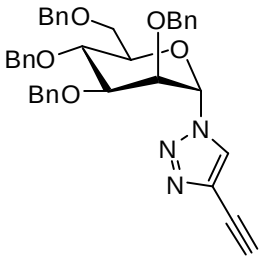
4-Ethynyl-1-(4-cyanophenyl)-1*H*-1,2,3-triazole (5b).



The general procedure 1.3.1.2 was followed starting from **8b** (9.27 mmol, 1.977 g), oxalyl chloride (10.2 mmol, 0.853 mL), DMSO (22.25 mmol, 1.583 mL), Et_3N (6.5 mL), K_2CO_3 (18.5 mmol, 2.5 g) and dimethyl acetyldiazomethylphosphonate reagent (9.27 mmol, 1.780 g). Yield: 1.621 g (80 %). Amorphous solid (mp = 154 ºC decomposition). IR (cm^{-1}, KBr): 3245 (≡CH), 3154, 3107, 2233 (C≡N), 2124 (C≡C), 1635, 1608, 1516, 1437 (triazole). ^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.92-7.85 (m, 4H), 3.35 (s, 1H). ^{13}C NMR (125 MHz, DMSO): δ 138.9, 134.1, 130.0, 126.6, 120.7, 117.8, 111.4, 84.9, 72.8. HRMS (m/z): $C_{11}H_6N_4$, requires: 195.0671 [M+1]; found, 195.0679. MS (TOF CI) m/z: 195.1 (100), 167.1 (90), 166.1 (23).

[**Aldehyde**, ^1H NMR (200 MHz, $CDCl_3$): δ 10.15 (s, 1H), 9.01 (s, 1H), 8.05 (d, 2H, *J* = 8.6 Hz), 7.83 (d, 2H, *J* = 8.6 Hz)]

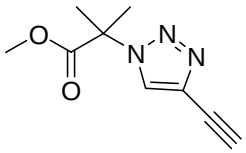
1-(2,3,4,6-Tetra-O-benzyl-α-D-mannosyl)-4-ethynyl-1*H*-1,2,3-triazole (5c).



The general procedure 1.3.1.2 was followed starting from **8c** (0.22 mmol, 136 mg), oxalyl chloride (0.24 mmol, 21 μL), DMSO (0.528 mmol, 0.037 mL), Et_3N (0.32 mL), K_2CO_3 (0.44 mmol, 60.8 mg) and dimethyl acetyldiazomethylphosphonate reagent (0.33 mmol, 63.3 mg). Yield: 68 mg (50 %). Oil. $[\alpha]_D^{25}$ = +56.04 (*c* = 0.53, CH_2Cl_2). IR (cm^{-1}, KBr): 3280.5 (≡CH), 3063.2, 3030.3, 2992.5, 2855.8, 1496.3 (triazole), 1099.8. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.35-7.13 (m, 20H), 5.91 (d, 1H, *J* = 4.1 Hz), 4.76 (dd, 1H, *J* = 3.0 Hz, *J* = 3.0 Hz), 4.70-4.44 (m, 8H), 4.00 (dd, 1H, *J* = 6.9 Hz, *J* = 2.8 Hz), 3.96 (dd, 1H, *J* = 6.9 Hz, *J* = 6.9 Hz), 3.72-3.64 (m, 3H), 3.25 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 138.0, 137.6, 138.7, 128.6, 128.6, 128.2, 128.2, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 126.7, 85.5, 81.6, 77.9, 75.2, 74.5, 74.3, 74.1, 73.6, 72.9, 68.9. Anal. calcd. for $C_{38}H_{37}N_3O_5$: C, 74.13; H, 6.06; N, 6.82. Found: C, 74.24; H, 6.36; N, 6.40.

[**Aldehyde**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.14 (s, 1H), 8.21 (s, 1H), 7.33-7.13 (m, 20H), 5.99 (d, 1H, *J* = 4.7 Hz), 4.70-4.31 (m, 9H), 3.96-3.92 (m, 2H), 3.74-3.60 (m, 3H)]

4-Ethynyl-1-[(1-methoxycarbonyl)-isopropyl]-1*H*-1,2,3-triazole (5i).



The general procedure 1.3.1.2 was followed starting from **8f** (1.02 mmol, 284 mg), oxalyl chloride (1.14 mmol, 95 μL), DMSO (2.45 mmol, 175 μL), Et_3N (0.7mL), K_2CO_3 (1.14 mmol, 283 mg) and dimethyl acetyldiazomethylphosphonate reagent (1.024 mmol, 216 mg). The crude of the reaction was acidified with 1 M aq. HCl and extracted with EtOAc. The solvents were evaporated under reduced pressure and the crude was treated with trimethylsilyldiazomethane (2.0 M in hexanes, >1.024 mmol, >0.512 mL) in dry methanol (12mL). After 15 minutes, the reaction mixture was directly evaporated and the product was purified by chromatography (eluent, Hex:EtOAc). Yield: 24 mg (15%). Oil. IR (cm^{-1}, KBr): 3278.5 (≡CH), 2995.8, 1743.8 (C=O), 1436.5 (triazole), 1280.7. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 3.74 (s, 3H), 3.23 (s, 1H), 1.95 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 129.9, 125.9, 81.2, 73.2, 64.9, 53.5, 25.8. HRMS (m/z): $C_9H_{11}N_3O_2$, requires: 194.0930 [M+1]; found, 194.0928. MS (TOF CI) m/z: 194.1 (100), 103.1 (52), 101.1 (26), 122.1 (21), 94.0 (20).

[**Aldehyde**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.14 (s, 1H), 8.28 (s, 1H), 7.35-7.23 (m, 5H), 5.16 (s, 2H), 1.98 (s, 6H)]

1.3.2 General Procedure from 1,4-Bis(trimethylsilyl)butadiyne

Preparation of 1-Trimethylsilyl-buta-1,3-diyne (10)

To a solution of 1,4-bis(trimethylsilyl)-buta-1,3-diyne (**9**)[8] (1.0 g, 5.14 mmol) in dry Et_2O (15 mL), was added MeLi·LiBr (1.5 M in Et_2O, 6.68 mmol, 4.45 ml) and the mixture was stirred overnight at rt. The reaction was quenched with aq. NH_4Cl (sat.) at 0 ºC and the product was extracted with Et_2O. The organic phase was dried over $MgSO_4$ and the solvent was carefully evaporated in vacuum to yield the product as dark oil. Yield: 345.5 mg (55 %).

General Procedure A: Cycloaddition under Sharpless Conditions

To a solution of the corresponding azide (1eq.), **10** (1.3 eq.) and TBTA (1 %) in ^{t}BuOH:THF under nitrogen atmosphere, were added deoxygenated aqueous solutions of Na ascorbate (0.4eq.) and $CuSO_4$ (0.2 eq.) were added. The homogenous solution (^{t}BuOH:THF:H_2O, 1:1:1) was stirred overnight. Subsequently, the solvents were evaporated under reduced pressure. The crude was dissolved in acetonitrile, CsF (1.0 eq.) was added, and the mixture was stirred for 1 hour. After this time, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography.

General Procedure B: Cycloaddition under Anhydrous Conditions

To a solution of the corresponding azide (1.0 eq.), **10** (1.3 eq.) and TBTA (1 %) in acetonitrile under nitrogen atmosphere, was added CuI (0.2 eq.) and DIPEA (5.0 eq.). The mixture was stirred overnight. Subsequently, CsF was added and the mixture was stirred for 1 hour. After this time, the solvent was evaporated under reduced pressure and the crude was purified by chromatography (Hex/EtOAc).

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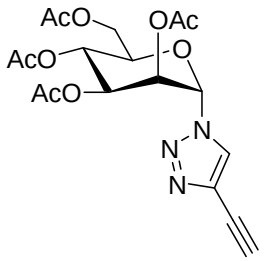
[8] Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **2003**, *44*, 9087-9090. (b) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H.; Akinde, B.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 840-842. (c) Holmes, A. B.; Jones, G. E. *Tetrahedron Lett.* **1980**, *21*, 3111-3112.

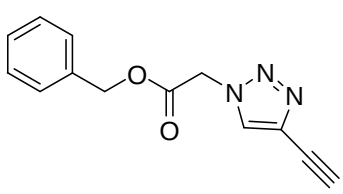
1-(2,3,4,6-Tetra-O-acetyl-α-D-mannosyl)-4-ethynyl-1*H*-1,2,3-triazole (5d).



The general procedure A was followed starting from 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl-1-azide (**6d**) (0.402 mmol, 150 mg), **10** (0.522 mmol, 64.0 mg), $CuSO_4$ (0.08 mmol, 20 mg), sodium ascorbate (0.402 mmol, 80 mg), TBTA (4 μmol, 2.1 mg) and CsF (0.402 mmol, 61 mg). Yield: 100 mg (60 %). Amorphous solid (mp = 55 ºC). $[\alpha]_D^{25}$ = +58.80 (*c* = 1.03, CH_2Cl_2). IR (cm^{-1}, KBr): 3270.9 (≡CH), 1749.0 (C=O), 1432.0 (triazole), 1370.2, 1224.8. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 6.01 (d, 1H, *J* = 3.2 Hz), 5.96 (dd, 1H, *J* = 3.5 Hz, *J* = 3.3 Hz), 5.82 (dd, 1H, *J* = 8.4 Hz, *J* = 3.6 Hz), 5.3 (dd, 1H, *J* = 8.4 Hz, *J* = 8.4 Hz), 4.41 (dd, 1H, *J* = 12.4 Hz, *J* = 5.9 Hz), 4.07 (dd, 1H, *J* = 12.4 Hz, *J* = 2.6 Hz), 3.93-3.90 (m, 1H), 3.29 (s, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 169.7, 169.6, 169.3, 127.0, 83.6, 82.1, 72.9, 68.7, 68.2, 66.4, 61.6, 20.8, 20.7. HRMS (m/z): $C_{18}H_{21}N_3O_9$, requires: 424.1356, [M+1]; found, 424.1351. MS (TOF CI) m/z: 331.1, 169.0, 332. 1.

[**Silylated-5d**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 5.99 (d, 1H, *J* = 3.1 Hz), 5.93 (dd, 1H, *J* = 3.3 Hz, *J* = 3.3 Hz), 5.79 (dd, 1H, *J* = 8.4 Hz, *J* = 3.5 Hz), 5.31 (dd, 1H, *J* = 8.5 Hz, *J* = 8.5 Hz), 4.39 (dd, 1H, *J* = 12.4 Hz, *J* = 5.8 Hz), 4.04 (dd, 1H, *J* = 12.4 Hz, *J* = 2.3 Hz), 3.90-3.86 (m, 1H), 3.14 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 0.25 (s, 9H).]

1-(Benzyloxycarbonylmethyl)-4-ethynyl-1*H*-1,2,3-triazole (5e).

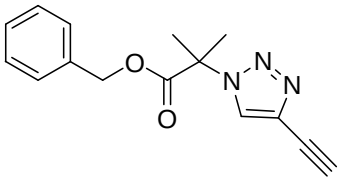


General procedure A was followed starting from benzyl 2-azidoacetate (**6e**) (0.392 mmol, 75 mg), **10** (0.510 mmol, 63 mg), $CuSO_4$ (0.078 mmol, 20 mg), sodium ascorbate (0.157 mmol, 31 mg), TBTA (4 μmol, 2.1 mg) and CsF (0.392 mmol, 59 mg). Yield: 60 mg (63 %). White solid (mp = 99-101 ºC). IR (cm^{-1}, KBr): 3297.6 (≡CH), 3270.4, 3150.4, 2996.1, 2956.2, 1749.7 (C=O), 1462.1 (triazole), 1394.4, 1223.8. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.39-7.33 (m, 5H), 5.24 (s,

2H), 5.20 (s, 2H), 3.25 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 134.5, 130.6, 129.0, 128.9, 128.7, 128.2, 81.4, 72.9, 68.3, 51.0. HRMS (m/z): $C_{13}H_{11}N_3O_2$, requires: 242.0930 [M+1]; found, 242.0918. MS (TOF CI) m/z: 242.1 (100), 91.1 (93).

[**Silylated-5e**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.39-7.33 (m, 5H), 5.23 (s, 2H), 5.18 (s, 2H), 0.26 (s, 9H)].

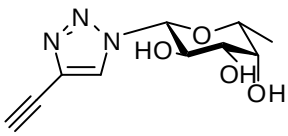
1-[1-(Benzyloxycarbonyl)-isopropyl]-4-ethynyl-1*H*-1,2,3-triazole (5f).



The general procedure A was followed starting from benzyl 2-azidoisobutyrate (**6f**) (0.515 mmol, 114 mg), **10** (0.668 mmol, 81.6 mg), $CuSO_4$ (0.103 mmol, 26 mg), sodium ascorbate (0.206 mmol, 40.7 mg), TBTA (5 μmol, 2.6 mg) and CsF (0.515 mmol, 78.2 mg). Yield: 79 mg (45 %). Oil. IR (cm^{-1}, KBr): 3284, 3151, 2917, 2849, 1744 (C=O), 1455, 1417. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.35-7.23 (m, 5H), 5.16 (s, 2H), 3.23 (s, 1H), 1.95 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 134.9, 128.8, 128.7, 128.1, 125.9, 81.18, 73.25, 68.14, 66.0, 25.8. HRMS (m/z): $C_{15}H_{15}N_3O_2$, requires: 270.1243 [M+1]; found, 270.1234. MS (TOF CI) m/z: 91.1 (100), 270.1 (81).

[**Silylated-5f**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.35-7.23 (m, 5H), 5.16 (s, 2H), 1.94 (s, 6H), 0.26 (s, 9H)].

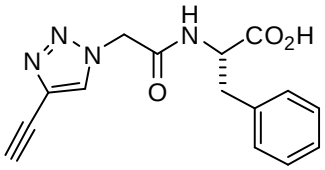
1-(β-L-Fucosyl)-4-ethynyl-1*H*-1,2,3-triazole (5g).



The general procedure B was followed starting from β-L-fucosyl-1-azide (**6g**) (0.26 mmol, 50 mg), **10** (0.34 mmol, 42 mg), CuI (0.05 mmol, 10 mg), DIPEA (1.32 mmol, 0.23 mL), TBTA (2.6 μmol, 1.4 mg) and CsF (0.26 mmol, 39 mg). The product was purified by PTLC (eluent MeOH:CH_2Cl_2 1:9). Yield: 41 mg (50 %). Oil. $[\alpha]_D^{25}$ = + 20.89 (*c* = 0.22, H_2O). IR (cm^{-1}, KBr): 3325 (OH). ^{1}H NMR (500 MHz, CD_3OD): δ 8.38 (s, 1H), 5.54

(d, 1H, *J* = 9.2 Hz), 4.05 (dd, 1H, *J* = 9.3 Hz), 3.98-3.94 (m, 1H), 3.78-3.75 (m, 1H), 3.68 (dd, 1H, *J* = 9.5 Hz, *J* = 3.2 Hz), 3.60 (s, 1H), 1.3 (d, 1H, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, D_2O): δ 130.5, 128.5, 88.7, 73.1, 73.7, 71.8, 70.0, 63.5, 63.1, 16.1. MS m/z (Ion Source Type: ESI positive polarity, 30 eV): MS+1= 240.1 (24); MS2 (240.1) = 93.9 (100), 56.6 (79), 74.8 (30).

4-Ethynyl-1-[N-(phenylalanyl)-glycinyl]-1*H*-1,2,3-triazole (5h).

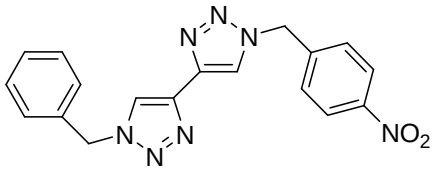


The general procedure B was followed starting from (S)-2-azidoacetamido-3-phenylpropanoic acid (**6h**) (0.173 mmol, 43 mg), **10** (0.346 mmol, 42 mg), CuI (0.865 mmol, 7 mg), DIPEA (0.86 mmol, 0.15 mL), TBTA (2 μmol, 1.1 mg), MeCN (2 ml). CsF (52 mg, 2 eq.). Yield: 40.6 mg (80 %). Oil. $[\alpha]_D^{25}$ = + 97.7 (*c* = 0.1, CH_3OH). IR (cm^{-1}, KBr): 3426.2, 3289.5 (O-H), 1605.1 (C=O). ^{1}H NMR (500 MHz, D_2O): δ 7.97 (s, 1H), 7.44-7.30 (m, 5H), 5.24 (s, 2H), 4.63-4.59 (m, 1H), 3.87 (s, 1H), 3.33 (dd, 1H, *J* = 13.9 Hz, *J* = 4.5 Hz), 3.01 (dd, 1H, *J* = 13.7 Hz, *J* = 9.3 Hz). ^{13}C NMR (125 MHz, D_2O): δ 178.0, 166.8, 138.0, 130.2, 129.6, 129.1, 127.3, 83.3, 56.9, 52.8, 38.1. MS m/z (Ion Source Type: ESI positive polarity, 5 eV): MS+1=299.1876; MS2(299.2)= 131.9 (100), 132.0 (42), 148.0 (30), 119.9 (20).

1.4 General Procedure for the Synthesis of Non-symmetric 1,1'-Disubstituted 4,4'-Bis-1*H*-1,2,3-triazoles

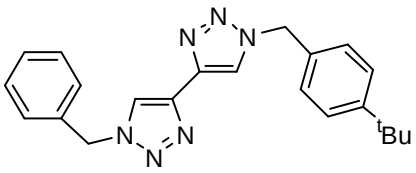
To a solution of the corresponding 4-ethynyl-1-substituted-1H-1,2,3-triazole (**5)** (1.0 eq.), azide (**6**) (1.1 eq.) and TBTA (1 %) in *t*-BuOH/THF under nitrogen atmosphere, was added deoxygenated aqueous solutions of Na ascorbate (0.4-1.0 eq.) and $CuSO_4$ (0.2 eq.). The homogenous solution (*t*-BuOH/THF/H_2O : 1/1/1) containing final concentrations of azide (0.07 M) and alkyne (0.06 M) was stirred overnight. After this time, the organic solvents were evaporated under reduced pressure and the crude was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the product was purified by column chromatography.

1-Benzyl-1'-(4-nitrobenzyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4a).



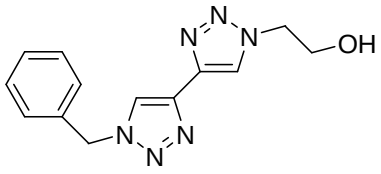
The general procedure 1.4 was followed starting from **5a** (0.215 mmol, 39.3 mg), *p*-nitrobenzyl azide (**6i**) (0.236 mmol, 42.1 mg), $CuSO_4$ (0.043 mmol, 10 mg) and Na ascorbate (0.086 mmol, 17 mg). Yield: 66 mg (85 %). Amorphous solid (mp = 190 ºC). IR (cm^{-1}, KBr): 3130, 3073, 2952, 2917, 2849, 1607, 1520, 1350. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 8.62 (s, 1H), 8.56 (s, 1H), 8.24 (d, 2H, *J* = 8.6 Hz), 7.57 (d, 2H, *J* = 8.6 Hz), 7.40-7.34 (m, 5H), 5.84 (s, 2H), 5.65 (s, 2H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ 147.1, 143.2, 139.3, 139.0, 135.8, 128.9, 128.6, 128.02, 127.8, 123.7, 122.1, 121.7, 52.8, 51.91. HRMS (m/z): $C_{18}H_{15}N_6O_2$, requires: 362.1365 [M+1]; found, 362.1376. MS (TOF CI) m/z: 362.1 (100), 108.1 (42), 107.1 (33), 106.1 (33).

1-Benzyl-1'-(4-*tert*-butylbenzyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4b).



The general procedure 1.4 was followed starting from **5a** (0.382 mmol, 70 mg), 4-*tert*-butylbenzylazide (**6j**) (0.420 mmol, 80 mg), $CuSO_4$ (0.076 mmol, 19 mg) and Na ascorbate (0.382 mmol, 75 mg). Yield: 140 mg (99 %). Amorphous solid (mp = 223 ºC decomposition). IR (cm^{-1}, KBr): 3131, 3076, 2962, 2866. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.94 (s, 1H), 7.43-7.28 (m, 9H), 5.58 (s, 2H), 5.55 (s, 2H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ 150.54, 139.1, 135.8, 132.8, 128.6, 128.0, 127.8, 127.6, 125.3, 121.6, 121.6, 52.8, 52.5, 30.87. HRMS (m/z): $C_{22}H_{24}N_6$, requires: 373.2141 [M+1]; found, 373.2142. MS (TOF CI) m/z: 373.2 (100), 147.1 (35).

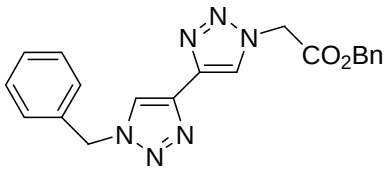
1-Benzyl-1'-(2-hydroxyethyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4c).



The general procedure 1.4 was followed starting from **5a** (0.36 mmol, 70 mg), 2-azidoethanol (**6k**) (0.39 mmol, 35 mg), $CuSO_4$ (0.072 mmol, 18 mg) and Na

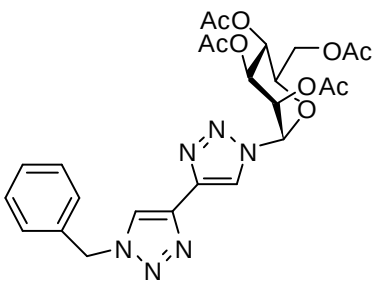
ascorbate (0.36 mmol, 71 mg). Yield: 95 mg (99 %). White solid (mp = 153 ºC). IR (cm^{-1}, KBr): 3374 (OH), 3138, 3101, 2969, 2934, 2887, 2505, 1494. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.93 (s, 1H), 7.39-7.31 (m, 5H), 5.57 (s, H), 4.54 (t, 2H, *J* = 4.7 Hz), 4.11 (t, 2H, *J* = 4.7 Hz. ^{13}C NMR (125 MHz, DMSO-*d6*): δ 139.3, 138.6, 135.8, 128.6, 128.0, 127.8, 121.9, 121.5, 59.6, 52.8, 52.2. HRMS (m/z): $C_{13}H_{14}N_6O$, requires 271.1307 [M+1]; found, 271.1309. MS (TOF CI) m/z: 271.1 (100).

1-Benzyl-1'-(benzyloxycarbonylmethyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4d).



The general procedure 1.4 was followed starting from **5a** (0.382 mmol, 70 mg), benzyl azidoacetate (**6e**) (0.42 mmol, 80 mg), $CuSO_4$ (0.076 mmol, 19 mg) and Na ascorbate (0.382 mmol, 76 mg). Yield: 121 mg (85%). White solid (mp = 160 ºC). IR (cm^{-1}, KBr): 3075.3, 2987.5, 1738.6 (C=O), 1455.1 (triazole), 1229.4, 1201.2. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 8.59 (s, 1H), 8.51(s, 1H), 7.40-7.35 (m, 10H), 5.67 (s, 2H), 5.54 (s, 2H), 5.23 (s, 2H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ 166.9, 138.9, 135.7, 135.2, 128.6, 128.3, 128.1, 128.0, 127.9, 127.8, 122.9, 121.8, 66.7, 52.9, 50.4. HRMS (m/z): $C_{20}H_{18}N_6O_2$, requires: 375.1569 [M+1]; found, 375.1573. MS (TOF CI) m/z: 91.0 (100), 375.2 (66), 93.1 (50), 92.1 (28).

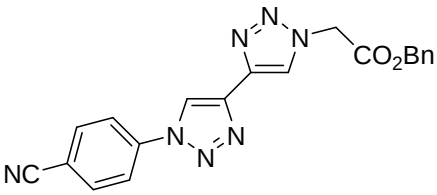
1-Benzyl-1'-(2,3,4,6-tetra-O-acetyl-α-D-mannosyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4e).



The general procedure 1.4 was followed starting from **5a** (0.38 mmol, 70 mg), 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl-1-azide (**6d**) (0.42 mmol, 156 mg), $CuSO_4$ (0.076 mmol, 19 mg) and Na ascorbate (0.38 mmol, 75 mg). Yield: 200 mg (95 %). Amorphous solid (mp = 63-68 ºC). $[\alpha]_D^{25}$ = +40.31 (*c* = 1.07, CH_2Cl_2). IR (cm^{-1}, KBr): 3147.9, 1752.5 (C=O), 1430.8 (triazole), 1225.5, 1049.1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.98 (s, 1H), 7.40.7.32 (m, 5H), 6.06 (d, 1H, *J* = 2.9 Hz), 6.04 (dd, 1H, *J* = 3.4 Hz, *J* = 3.1 Hz), 5.87 (dd, 1H, *J* = 8.7 Hz, *J* = 3.6 Hz), 5.60 (s, 2H), 5.35

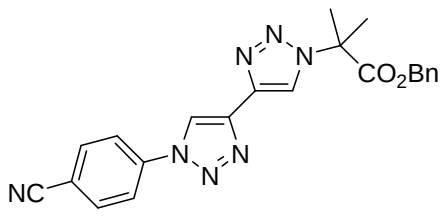
(dd, 1H, *J* = 8.8 Hz, *J* = 8.8 Hz), 4.38 (dd, 1H, *J* = 12.5 Hz, *J* = 5.8 Hz), 4.07 (dd, 1H, *J* = 12.5 Hz, *J* = 2.5 Hz), 3.90-3.86 (m, 1H), 2.18 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.6, 169.6, 169.3, 140.8, 134.4, 129.2, 128.9, 128.2, 120.8, 83.9, 77.4, 77.2, 76.9, 72.4, 68.8, 68.2, 66.2, 61.6, 54.4, 20.7, 20.6. HRMS (m/z): $C_{25}H_{28}N_6O_9$, requires: 557.1996 [M+1]; found, 557.1990. MS (TOF CI) m/z: 331.1 (100), 557.2 (51), 169.1 (29), 585.2 (22).

1-(Benzyloxycarbonylmethyl)-1'-(4-cyanophenyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4f).



The general procedure 1.4 was followed starting from **5b** (0.151 mmol, 29.3 mg), benzyl azidoacetate (**6e**) (0.166 mmol, 31.7 mg), $CuSO_4$ (0.03 mmol, 7.5 mg), Na ascorbate (0.151 mg, 29.9 mg) and TBTA (1.5 μmol, 0.8 mg). Yield: 40.0 mg (70 %). White solid (mp = 240 ºC). IR (cm^{-1}, KBr): 3128.8, 2997.3, 2962.4, 2230.4 (C≡N), 1728.2 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.27 (s, 1H), 7.99 (d, 2H, *J* = 8.4 Hz), 7.88 (d, 2H, *J* = 8.4 Hz), 7.40-7.35 (m, 5H), 5.29 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (125 MHz, DMSO-*d6*): δ 166.9, 140.2, 139.3, 138.1, 135.2, 134.1, 128.3, 128.1, 127.9, 123.5, 120.5, 120.4, 119.9, 117.9, 111.0, 66.7, 50.4. HRMS (m/z): $C_{20}H_{15}N_7O_2$, requires: 386.1365 [M+1]; found, 386.1372. MS (TOF CI) m/z: 386.1 (100), 330.1 (39), 387.1 (24), 358.1 (24).

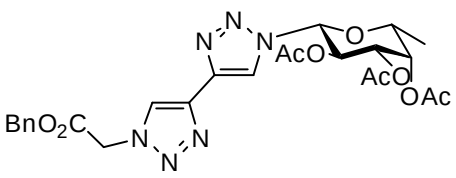
1-[1-(Benzyloxycarbonyl)isopropyl]-1'-(4-cyanophenyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4g).



The general procedure 1.4 was followed starting from **5b** (0.123 mmol, 23.8 mg), benzyl 2-azidoisobutirate (**6f**) (0.135 mmol, 29.7 mg), $CuSO_4$ (0.025 mmol, 6.1 mg), Na ascorbate (0.123 mmol, 24.4 mg) and TBTA (1.2 μmol, 0.6 mg). Yield: 40 mg (79 %). Amorphous solid (mp = 194-195 ºC). IR (cm^{-1}, KBr): 3144.2, 3126.6, 2232.0 (C≡N), 1743.8 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.38

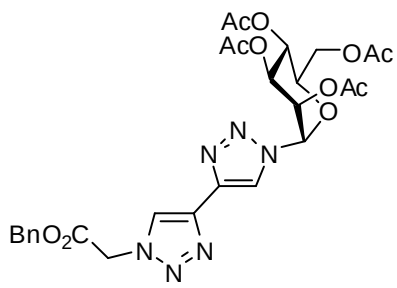
(s, 1H), 8.00 (d, 2H, *J* = 8.4 Hz), 7.88 (d, 2H, *J* = 8.4 Hz), 7.35-7.31 (m, 5H), 5.19 (s, 2H), 2.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 140.0, 135.0, 134.2, 128.8, 128.7, 128.1, 120.8, 117.8, 112.8, 68.1, 65.4, 25.9. HRMS (m/z): $C_{22}H_{19}N_7O_2$, requires: 414.1678 [M+1]; found, 414.1678. MS (TOF CI) (m/z): 91.0 (100), 414.2 (48), 358.2 (31), 328.1 (27).

1-(Benzyloxycarbonylmethyl)-1'-(2,3,4-tri-*O*-acetyl-β-L-fucosyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (**4h**).



The general procedure 1.4 was followed starting from **5e** (0.035 mmol, 8.5 mg), 2,3,4-tri-*O*-acetyl-α,β-L-fucosyl-1-azide (**6l**) (0.039 mmol, 12.2 mg), $CuSO_4$ (0.008 mmol, 2.0 mg), Na ascorbate (0.035 mmol, 7.0 mg) and TBTA (0.35 μmol, 0.2 mg). Yield: 17.5 mg (90 %). White solid (mp = 170-172 ºC). $[\alpha]_D^{25}$ = +38.26 (*c* = 1.08, CH_2Cl_2). IR (cm^{-1}, KBr): 1749.7 (C=O), 1734.1 (C=O), 1241.4, 1222.0. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.16 (s, 1H), 7.37-7.34 (m, 5H), 5.85 (d, 1H, *J* = 9.2 Hz), 5.57 (dd, 1H, *J* = 9.9 Hz, *J* = 9.5 Hz), 5.40 (d, 1H, *J* = 3.0 Hz), 5.29-5.26 (m, 1H), 5.25 (2s overlapped, 4H), 4.13 (dd, 1H, *J* = 12.7 Hz, *J* = 6.3 Hz), 2.25 (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.0, 169.1, 166.0, 140.5, 140.4, 134.7, 129.0, 128.9, 128.7, 122.3, 119.4, 86.6, 72.84, 71.40, 70.0, 68.4, 68.3, 51.1, 20.8, 20.7, 20.4, 16.2. HRMS (m/z): $C_{25}H_{28}N_6O_9$, requires: 557.1996 [M+1]; found, 557.2005. MS (TOF CI) m/z: 273.1 (100), 153.0 (42), 557.2 (39), 91.0 (39), 171.1 (34), 111.0 (20).

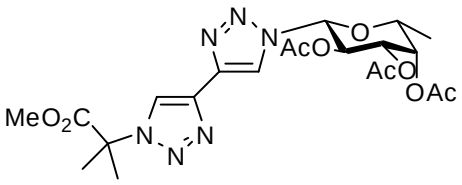
1-(Benzyloxycarbonylmethyl)-1'-(2,3,4,6-tetra-O-acetyl-α-D-mannosyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (**4i**).



The general procedure 1.4 was followed starting from **5e** (0.039 mmol, 9.5 mg), 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl-1-azide (**6d**) (0.045 mmol, 17 mg), $CuSO_4$ (0.008 mmol, 1.9 mg), Na ascorbate (0.040 mmol, 8.0

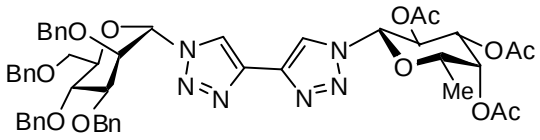
mg) and TBTA (0.4 μmol, 0.2 mg). Yield: 19.0 mg (79 %). Amorphous solid (mp = 56-58 ºC decomposition). $[\alpha]_D^{25}$ = +39.97 (*c* = 1.03, CH_2Cl_2) IR (cm^{-1}, KBr): 1751.2 (C=O), 1370.0 (triazole), 1223.4, 1049.0. ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.22 (s, 1H), 7.38-7.35 (m, 5H), 6.07-6.06 (m overlapped, 2H), 5.90 (dd, 1H, *J* = 8.8 Hz, *J* = 3.4 Hz), 5.36 (dd, 1H, *J* = 8.9 Hz, *J* = 8.8 Hz), 5.27 (d, 2H, *J* = 2.0 Hz), 5.24 (s, 2H), 4.38 (dd, 1H, *J* = 12.4 Hz, *J* = 5.6 Hz), 4.07 (dd, 1H, *J* = 11.4 Hz, *J* = 2.3 Hz), 3.91-3.88 (m, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.7, 169.6, 169.4, 166.0, 140.7, 139.9, 134.7, 128.9, 128.8, 128.6, 122.7, 121.0, 83.9, 72.4, 68.9, 68.3, 68.1, 66.2, 61.7, 51.1, 20.7, 20.7, 20.6. HRMS (m/z): $C_{27}H_{30}N_6O_{11}$, requires: 615.2051 [M+1]; found, 615.2029. MS (TOF CI) m/z: 331.1(100), 615.2(50), 169.1(42).

1-[1-(Methyloxycarbonyl)isopropyl]-1'-(2,3,4-tri-*O*-acetyl-β-L-fucosyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (**4j**).



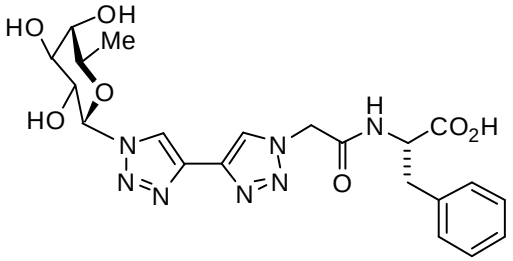
The general procedure 1.4 was followed starting from **5i** (0.202 mmol, 39 mg), 2,3,4-tri-*O*-acetyl-α,β-L-fucosyl-1-azide (**6l**) (0.222 mmol, 67.3 mg), $CuSO_4$ (0.04 mmol, 10 mg), sodium ascorbate (0.20 mmol, 40 mg) and TBTA (2 μmol, 1 mg). Yield: 94 mg (80%). White solid (mp = 175-177 ºC). $[\alpha]_D^{25}$ = +38.58 (*c* = 1.05, CH_2Cl_2). IR (cm^{-1}, KBr): 1750.6 (C=O), 1456.9 (triazole), 1370.0, 1243.6, 1222.4. ^1H NMR (500 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.18 (s, 1H), 5.84 (d, 1H, *J* = 9.1 Hz), 5.56 (dd, 1H, *J* = 9.7 Hz, *J* = 9.7 Hz), 5.40 (d, 1H, *J* = 3.1 Hz), 5.26 (dd, 1H, *J* = 10.2 Hz, *J* = 3.1 Hz), 4.13 (dd, 1H, *J* = 12.7 Hz, *J* = 6.3 Hz), 3.74 (s, 3H), 2.26 (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 170.5, 169.9, 169.0, 140.6, 139.3, 119.8, 119.2, 86.5, 72.7, 71.3, 70.0, 68.3, 64.7, 53.3, 25.8, 25.8, 20.7, 20.6, 20.3, 16.1. HRMS (m/z): $C_{21}H_{28}N_6O_9$, requires: 509.1996 [M+1]; found, 509.1989. MS (TOF CI) m/z: 509.2(100), 273.1(81), 537.2(26), 213.1(22).

1-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannosyl)-1'-(2,3,4-tri-*O*-acetyl-β-L-fucosyl)-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (**4k**).



The general procedure 1.4 was followed starting from **5c** (0.076 mmol, 47 mg), 2,3,4-tri-*O*-acetyl-α,β-L-fucosyl-1-azide (**6l**) (0.083 mmol, 26 mg), $CuSO_4$ (0.015 mmol, 4 mg), Na ascorbate (0.076 mmol, 15 mg) and TBTA (0.8 μmol, 0.4 mg). Yield: 63 mg (90 %). Oil. $[\alpha]_D^{25}$ = +56.27 (*c* = 0.935, CH_2Cl_2). IR (cm^{-1}, KBr): 3030.4, 2935.5, 2869.0, 1753.6 (C=O), 1454.3 (triazole), 1368.5, 1242.3, 1220.3, 1096.4, 1069.1. ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.20 (s, 1H), 7.38-7.14 (m, 20H), 6.02 (d, 1H, *J* = 3.2 Hz), 5.86 (d, 1H, *J* = 9.1 Hz), 5.59 (dd, 1H, *J* = 9.7 Hz, *J* = 9.6 Hz), 5.41 (d, 1H, *J* = 3.03 Hz), 5.27 (dd, 1H, *J* = 10.3 Hz, *J* = 3.2 Hz), 4.82 (m, 1H), 4.73-4.46 (m, 8H), 4.14 (dd, 1H, *J* = 12.4 Hz, *J* = 6.5 Hz), 4.09-4.04 (m, 2H), 3.76-3.67 (m, 3H), 2.27 (s, 3H), 2.02 (s, 3H), 1.90 (s, 3H), 1.29 (d, 3H, *J* = 6.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.0, 169.0, 138.2, 138.1, 137.7, 128.5, 128.5, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 127.7, 86.6, 85.4, 78.3, 75.1, 74.4, 74.10, 73.5, 72.9, 72.8, 71.3, 70.0, 68.7, 68.3, 20.7, 20.6, 20.3, 16.2. Anal. calcd. for $C_{50}H_{54}N_6O_{12}$: C, 64.50; H, 5.85; N, 9.03. Found: C, 64.66; H, 5.80; N, 8.67.

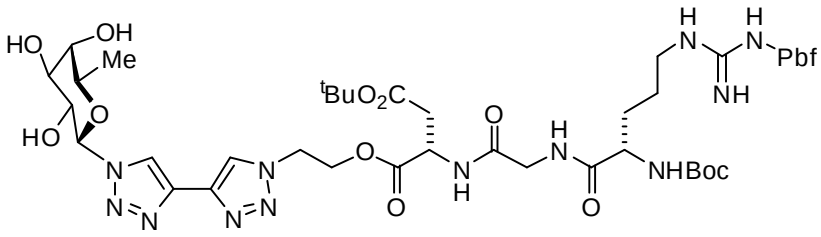
1-(β-L-Fucosyl)-1'-[N-(phenylalanyl)-glycinyl]-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4l).



The general procedure B was followed starting from **5h** (0.078 mmol, 23.4 mg), fucosyl-azide (**6g**) (0.078 mmol, 14.8 mg), CuI (0.015 mmol, 3 mg), DIPEA (0.39 mmol, 0.07 ml), TBTA (0.8 μmol, 0.4 mg) in acetonitrile (3ml). Yield: 74 mg (82 %). Oil. $[\alpha]_D^{25}$ = +22.91 (*c* = 0.51, CH_3OH). IR (cm^{-1}, KBr): 3446.6 (OH), 1700.0 (C=O). ^1H NMR (500 MHz, D_2O): δ 8.52 (s, 1H), 8.22 (s, 1H), 7.20-7.13 (m, 5H), 5.60 (d, 1H, *J* = 9.1 Hz), 5.19 (d, 1H, *J* = 16.2 Hz), 5.15 (d, 1H, *J* = 16.2 Hz), 4.55-4.52 (m, 1H), 4.18-4.14 (m, 1H), 4.01-3.98 (m, 1H), 3.78 (bs, 1H), 3.73-3.71 (m, 1H), 3.25 (dd, 1H, *J* = 13.8 Hz, *J* = 4.5 Hz), 3.25 (dd, 1H, *J* = 13.7 Hz, *J* = 8.1 Hz), 1.32 (d, 3H, *J* = 6.3 Hz).

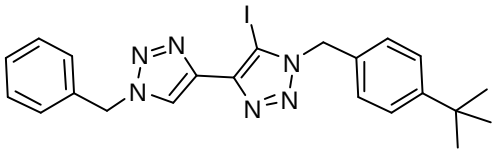
^{13}C NMR (125 MHz, D_2O): δ 178.1, 167.1, 139.3, 139.1, 138.1, 129.7, 129.1, 127.3, 124.6, 122.6, 88.7, 75.1, 73.8, 71.8, 70.1, 56.9, 53.1, 38.2, 16.1. MS m/z (Ion Source Type: ESI positive polarity, 5 eV): MS+1= 488.2 (100), 342.2 (29); MS2(448.2)= 342.2 (100).

1-(β-L-Fucosyl)-1'-[(Boc-Arg(Pbf)-Gly-Asp(O^{t}Bu)-ethoxy]-1*H*,1'*H*-4,4'-bis(1,2,3-triazole) (4m).



The general procedure 1.4 was followed starting from **5g** (0.121 mmol, 29 mg), RGD-azide (**6m**) (0.085 mmol, 70 mg), $CuSO_4$ (0.017 mmol, 4 mg), Na ascorbate (0.034 mmol, 7 mg) and TBTA (0.8 μmol, 0.4 mg). Yield: 74 mg (82 %). Oil. $[\alpha]_D^{25}$ = +8.77 (*c* = 0.35, CH_3OH). IR (cm^{-1}, KBr): 3327.1 (OH), 1682 (C=O), 1455.2 (triazole). ^{1}H NMR (500 MHz, D_2O): δ 8.60 (s, 1H), 8.57 (s, 1H), 8.27 (d, 1H, *J* = 7.2 Hz), 8.06 (bs, 1H), 6.70 (d, 1H, *J* = 7.6 Hz), 5.56 (d, 1H, *J* = 9.1 Hz), 4.75-4.73 (m, 2H), 4.66-4.62 (m, 1H), 4.58-4.50 (m, 2H), 4.13-4.08 (m, 1H), 3.97-3.93 (m, 2H overlapped), 3.76-3.75 (m, 2H), 3.61-3.60 (m, 2H overlapped), 3.05-3.04 (m, 2H), 2.70 (dd, 1H, *J* = 16.4 Hz, *J* = 5.7 Hz), 2.57 (dd, 1H, *J* = 16.4 Hz, *J* = 7.4 Hz), 2.52 (s, 3H), 2.46 (s, 3H), 2.04 (s, 3H), 1.61 (bb, 1H), 1.50-1.2 (m, 3H), 1.45 (s, 6H), 1.40 (s, 9H), 1.37 (s, 9H), 1.20 (d, 3H, *J* = 6.3 Hz) . ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 170.4, 170.2, 170.0, 158.9, 156.5, 156.4, 139.2, 139.0, 138.4, 132.8, 132.4, 124.8, 123.0, 121.4, 117.6, 88.7, 86.6, 81.8, 80.1, 74.3, 74.1, 71.8, 70.3, 63.7, 54.6, 49.5, 49.2, 43.3, 43.0, 37.0, 28.7, 28.4, 28.119.4, 18.0, 16.5, 12.5. MS m/z (Ion Source Type: ESI positive polarity, 15 eV): MS+1= 1063.5.

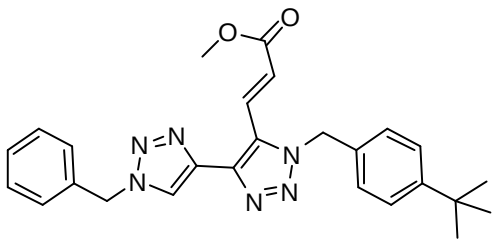
1-Benzyl-1'-(4-*tert*-butylbenzyl)-5'-iodo-1H,1'H-4,4'-bis(1,2,3-triazole) (11).



Previously dried CuI (2.2 mmol, 416.9 mg) was dissolved in dried CH_3CN (60 mL) and

5a (2 mmol, 365.0 mg) was added followed by 4-*tert*-butylbenzyl azide (**6j**) (2.2 mmol, 414.49 mg), NBS (2.4 mmol, 425.6 mg) and DIPEA (2.2 mmol, 381.5 µl). The mixture was kept stirring for 2 hours. The solvent was evaporated and the crude product was washed with aq. $Na_2S_2O_3/CH_2Cl_2$. The organic phase was dried over $MgSO_4$. The product was purified by column chromatography (eluent, Hex:EtOAc 1:1). Yield: 500 mg (50 %). Solid (mp = 143-144ºC). IR (cm^{-1}, KBr): 3117, 3103, 2956, 2867, 1434, 1427. ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.71 – 7.00 (m, 9H), 5.64 (s, 2H), 5.61 (s, 2H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0, 143.8, 140.0, 134.8, 131.6, 130.0, 129.6, 129.2, 128.6, 128.1, 126.8, 126.2, 122.2, 76.6, 54.7, 54.3, 35.0, 31.6. HRMS (m/z): $C_{22}H_{24}IN_6$, requires 499.1107 [M+1]; found, 499.1112. MS (TOF CI) m/z: 266.0(100), 285.0(68), 286.0(62), 147.1(59), 499.1(43).

1-Benzyl-1'-(4-*tert*-butylbenzyl)-5'-(*E*)-[2-(methoxycarbonyl)-ethenyl]-1*H*,1'*H*-4,4'-bi-1,2,3-triazole (12).



The iodotriazole **11** (0.1 mmol, 50 mg), $Pd(OAc)_2$ (0.01 mmol, 2.25 mg) and $NaHCO_3$ (0.25 mmol, 21.07 mg) were placed in a dried flask and anhydrous DMF (5 mL). Then methyl acrylate (0.5 mmol, 45 µl) was added and the mixture was kept stirring overnight at 120ºC. The DMF was evaporated and the crude product was filtered over celite. The crude product was purified by column chromatography (eluent, Hex:EtOAc 1:2). Yield: 30 mg (66%) as amorphous solid (mp = 144-146 ºC). IR (cm^{-1}, KBr): 2959, 2926, 2867,1718, 1457, 1436. ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.90 (d, J = 16.2, 1H), 7.46 – 7.32 (m, 8H), 7.18 (d, J = 8.1, 1H), 5.67 (s, 2H), 5.62 (s, 2H), 3.82 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 152.1, 141.0, 139.6, 134.6, 131.6, 131.3, 129.8, 129.6, 129.4, 128.7, 127.3, 127.0, 126.5, 125.6, 123.0, 65.9, 54.8, 53.0, 52.3, 35.0, 31.6. HRMS (m/z): $C_{26}H_{29}N_6O_2$ requires: 457.2352 [M+1]; found, 457.2364. MS (TOF CI) m/z: 398.2 (100), 457.2 (32), 398.2 (29).

2 ^{1}H and ^{13}C NMR Spectra of Compounds (Figures S1-S31)

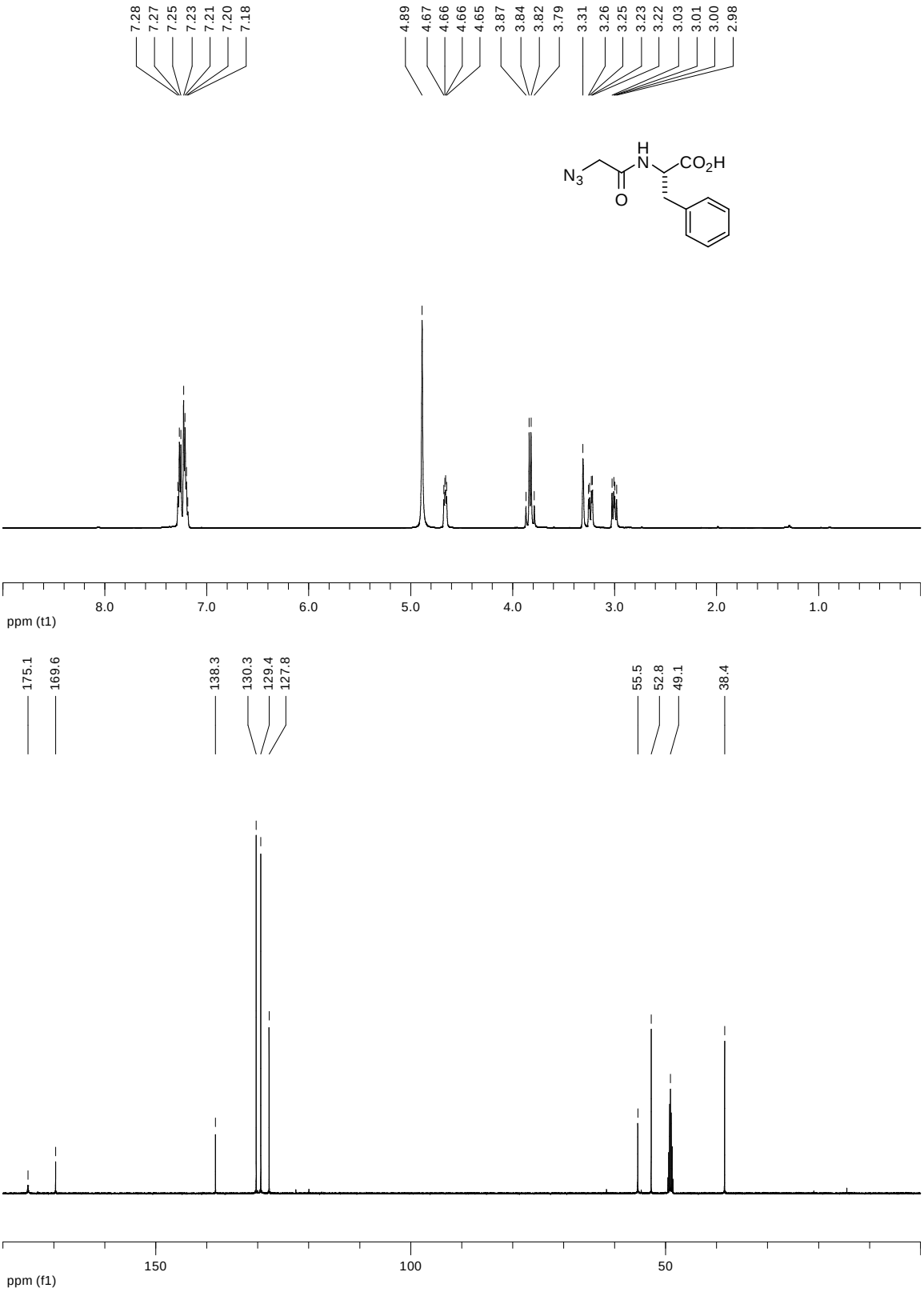


Figure S1: ^{1}H & ^{13}C NMR spectra of compound **6h** (CD_3OD)

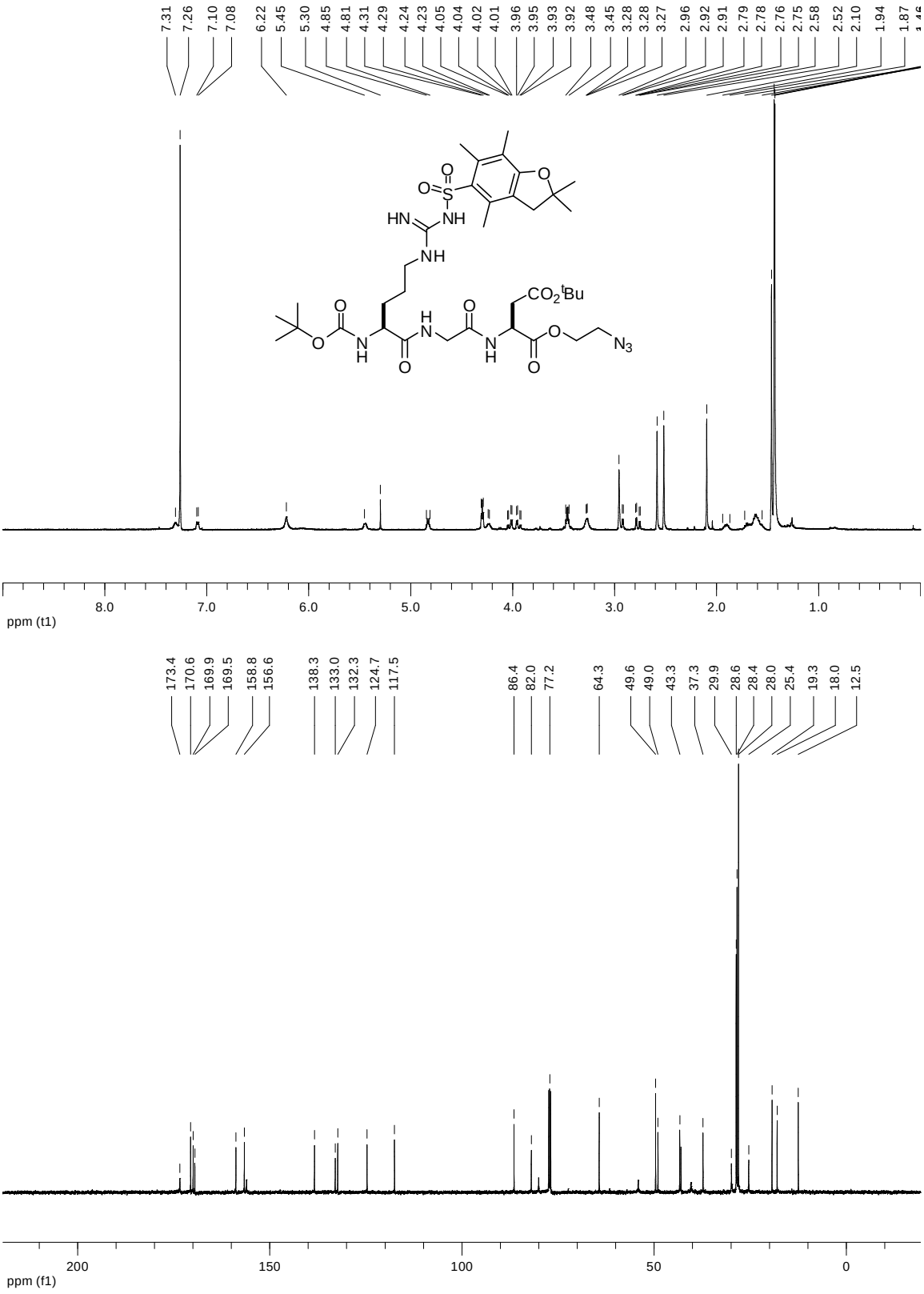


Figure S2: ^{1}H & ^{13}C NMR spectra of compound **6n** ($CDCl_3$)

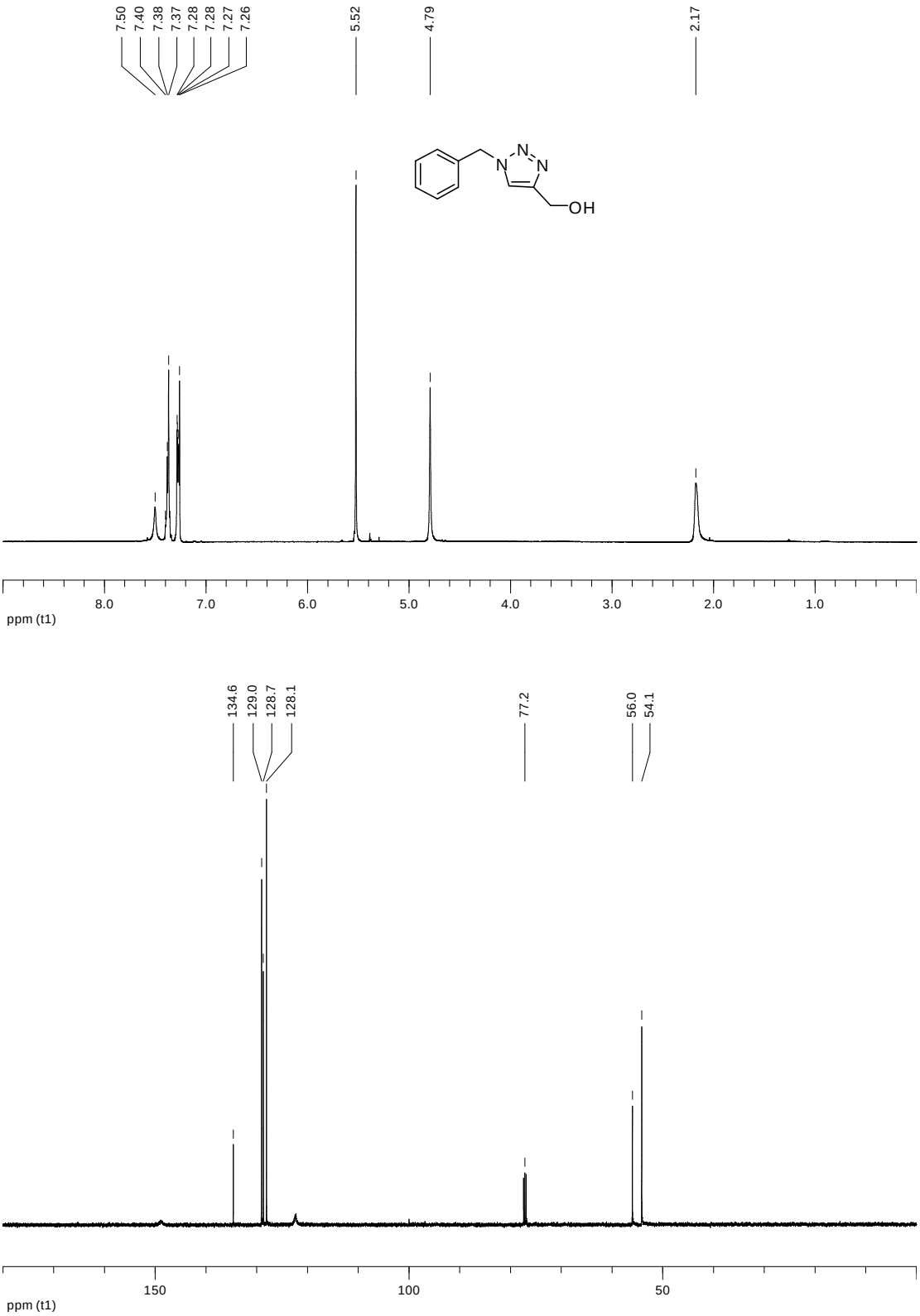


Figure S3: ^{1}H & ^{13}C NMR spectra of compound **8a** ($CDCl_3$).

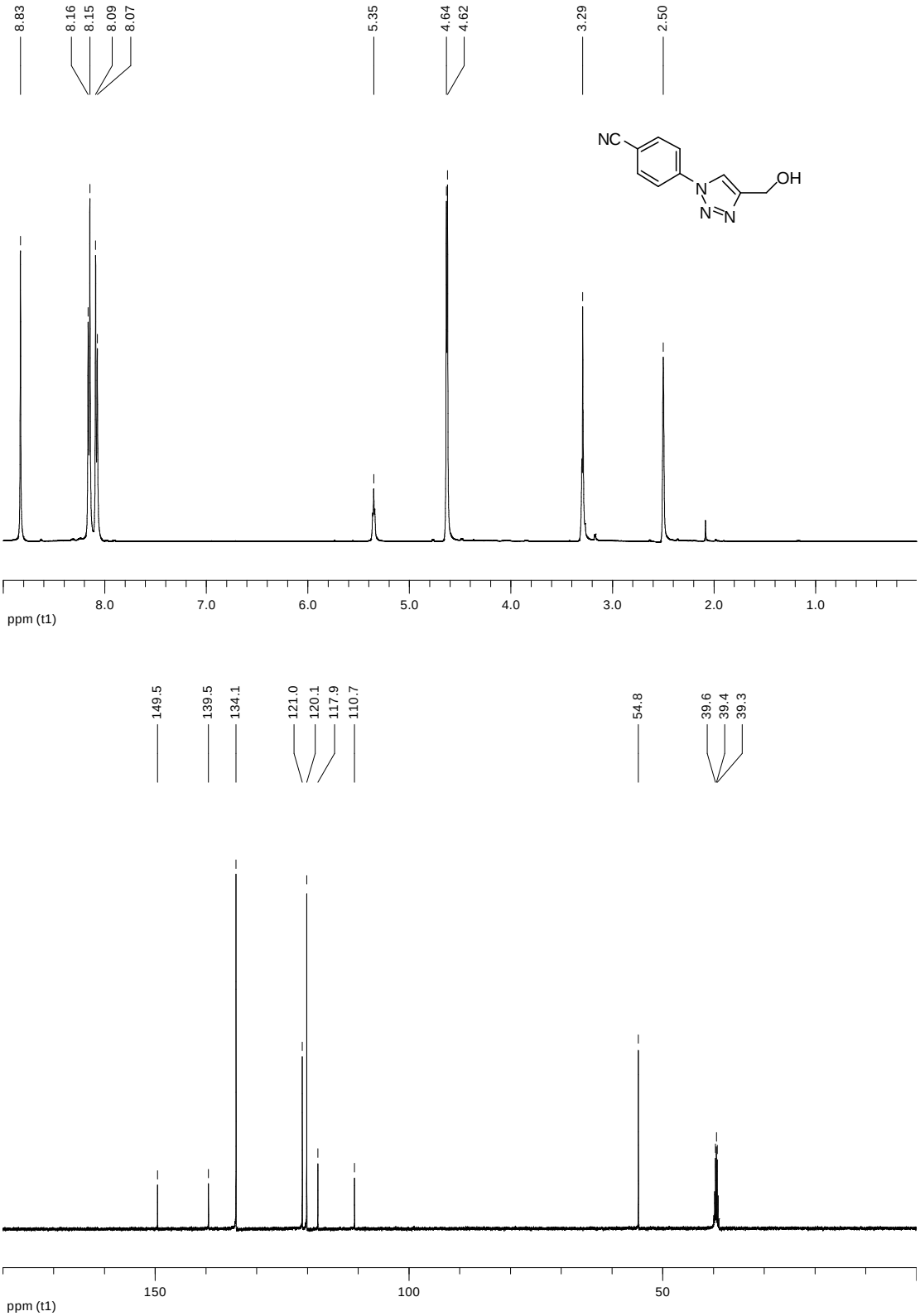


Figure S4: ^{1}H & ^{13}C NMR spectra of compound **8b** (DMSO).

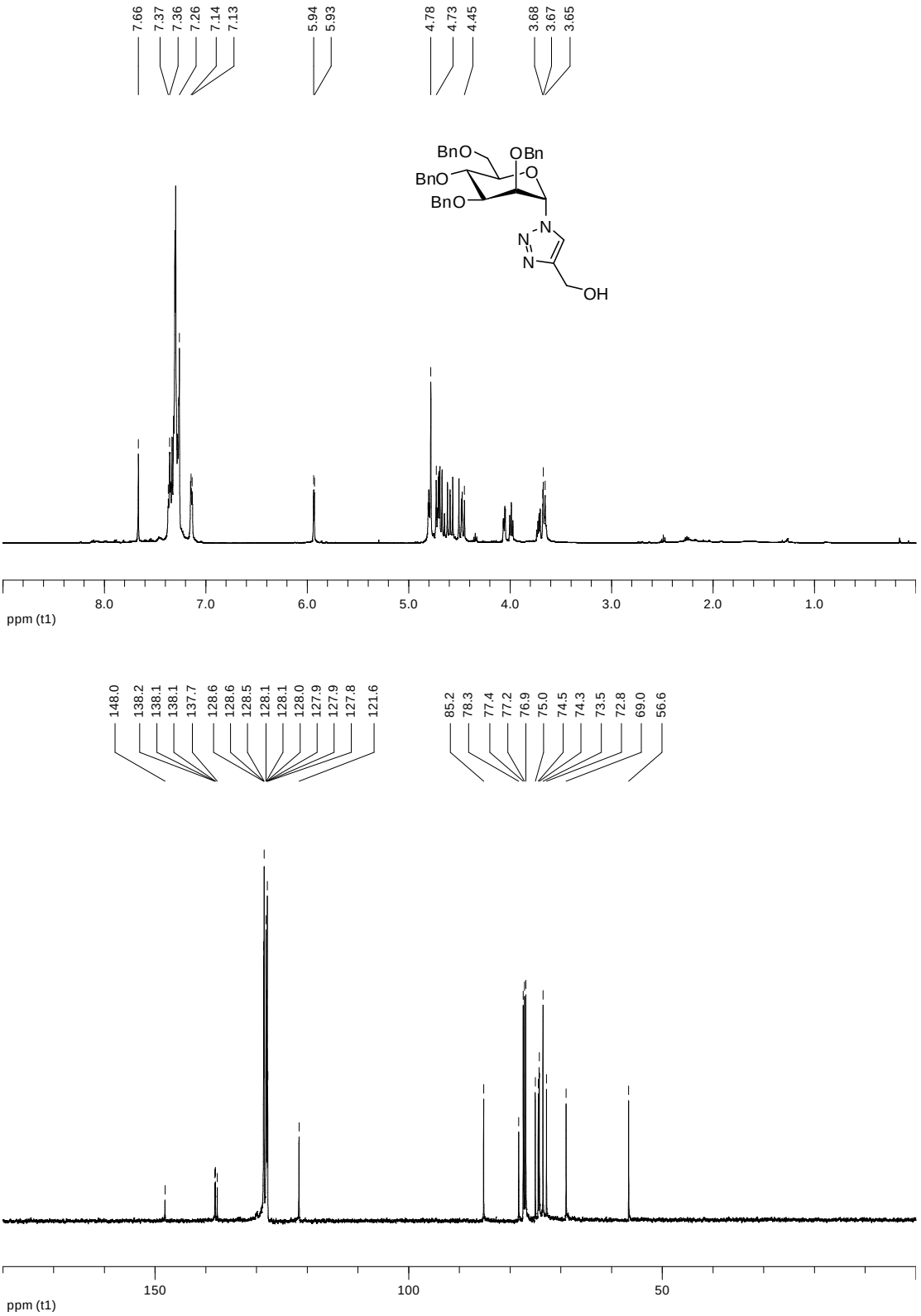


Figure S5: ^{1}H & ^{13}C NMR spectra of compound **8c** ($CDCl_3$).

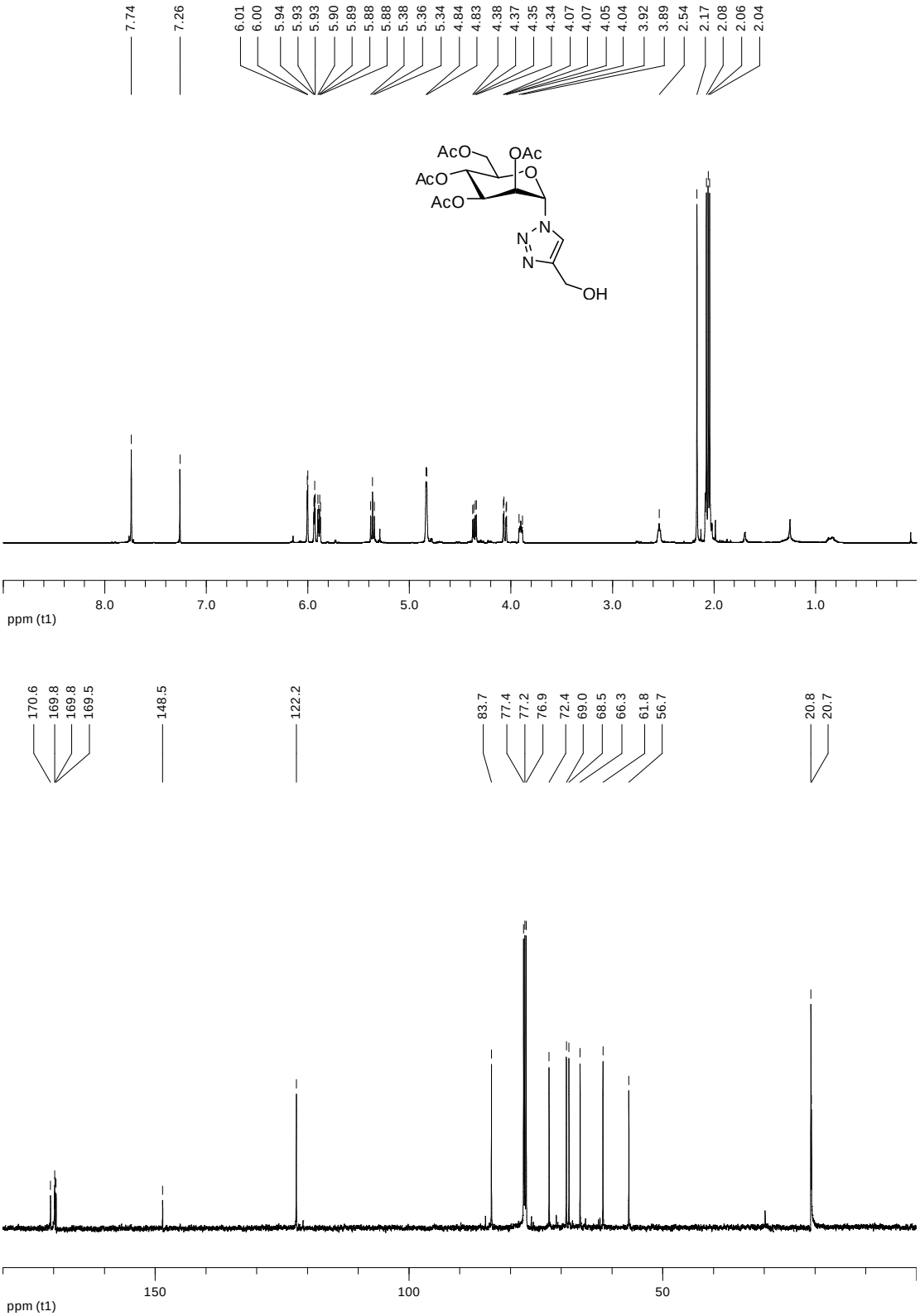


Figure S6: ^{1}H & ^{13}C NMR spectra of compound **8d** ($CDCl_3$).

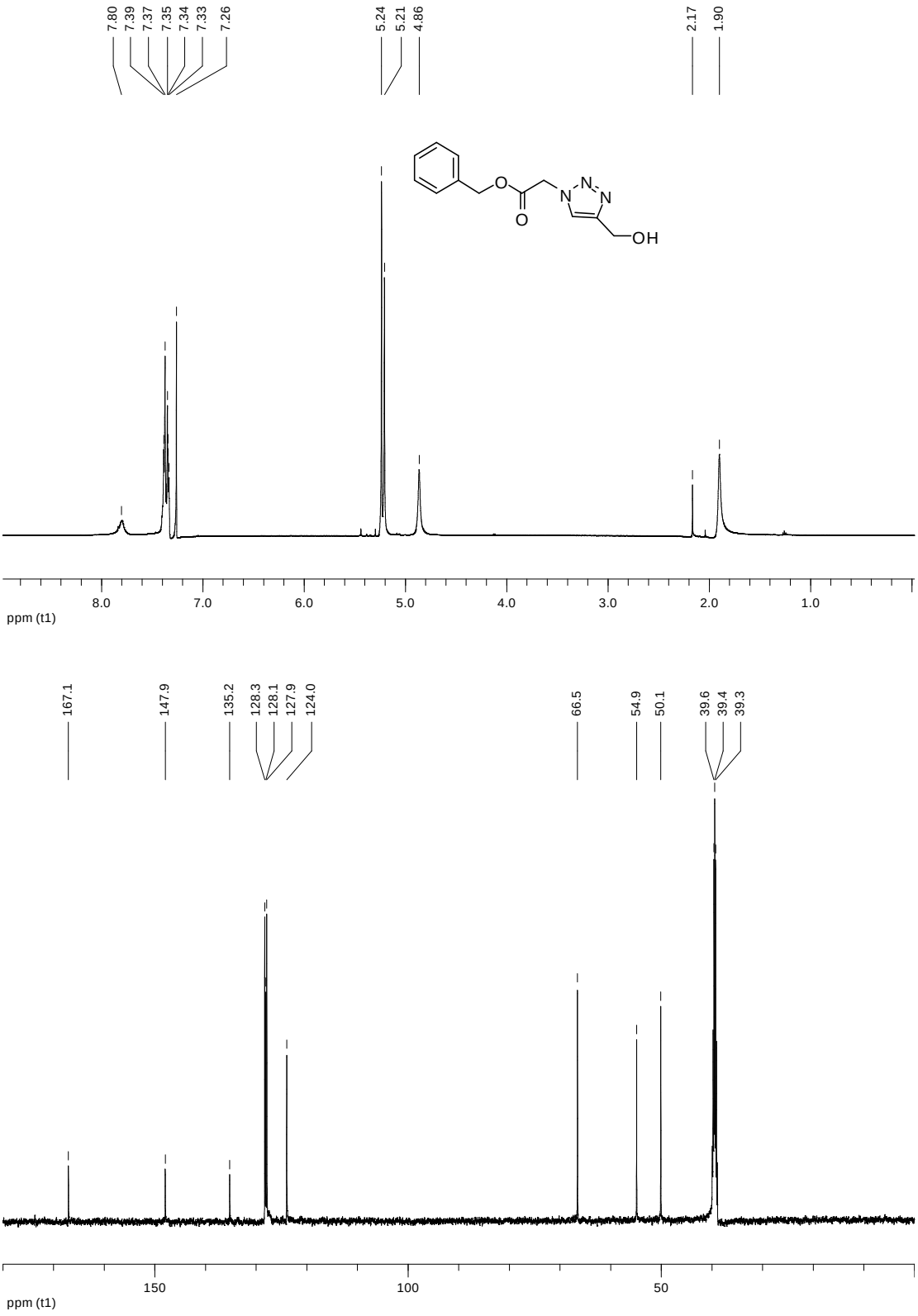


Figure S7: ^{1}H ($CDCl_3$) & ^{13}C (DMSO) NMR spectra of compound **8e**.

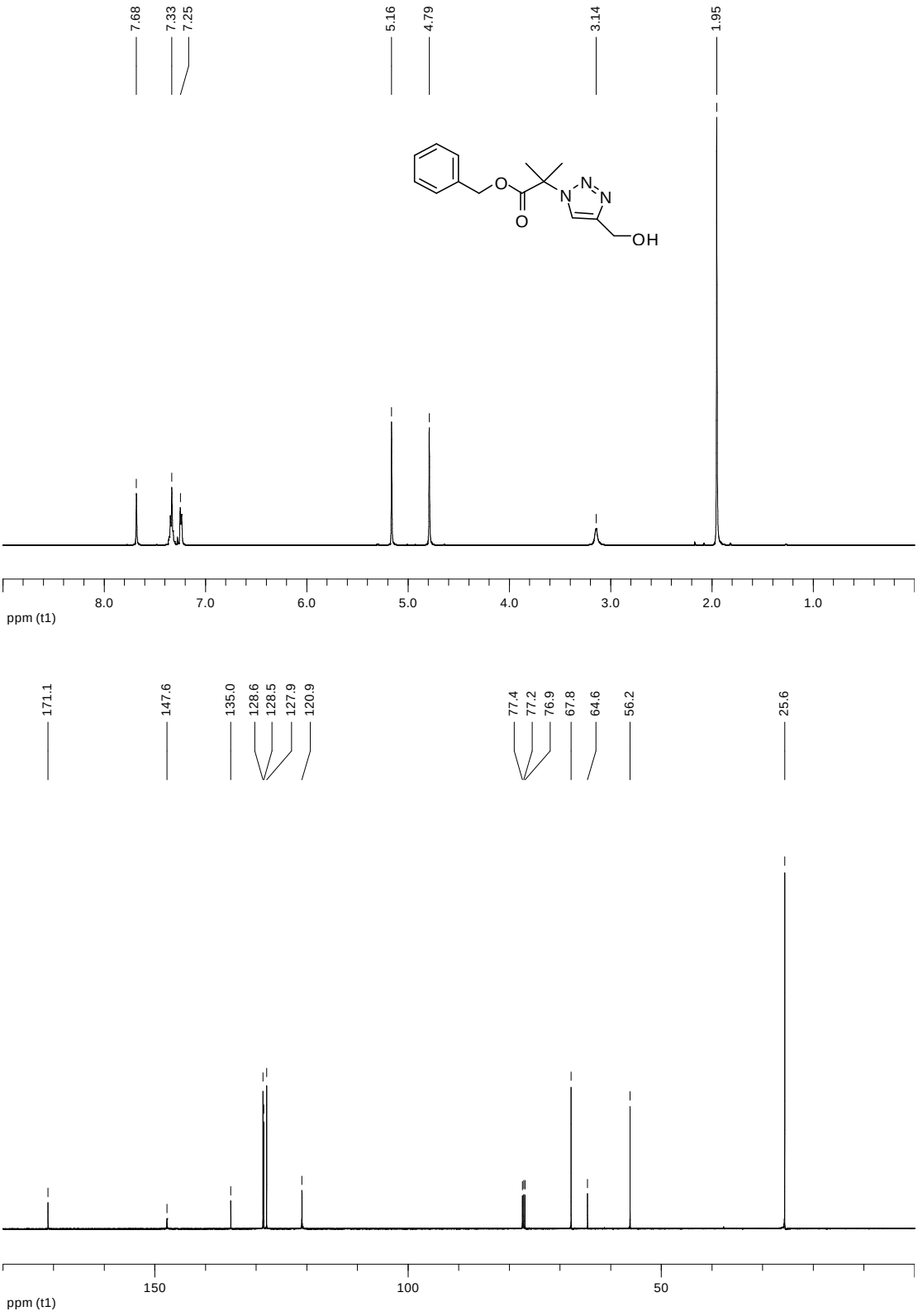


Figure S8: ^{1}H & ^{13}C NMR spectra of compound **8f** ($CDCl_3$).

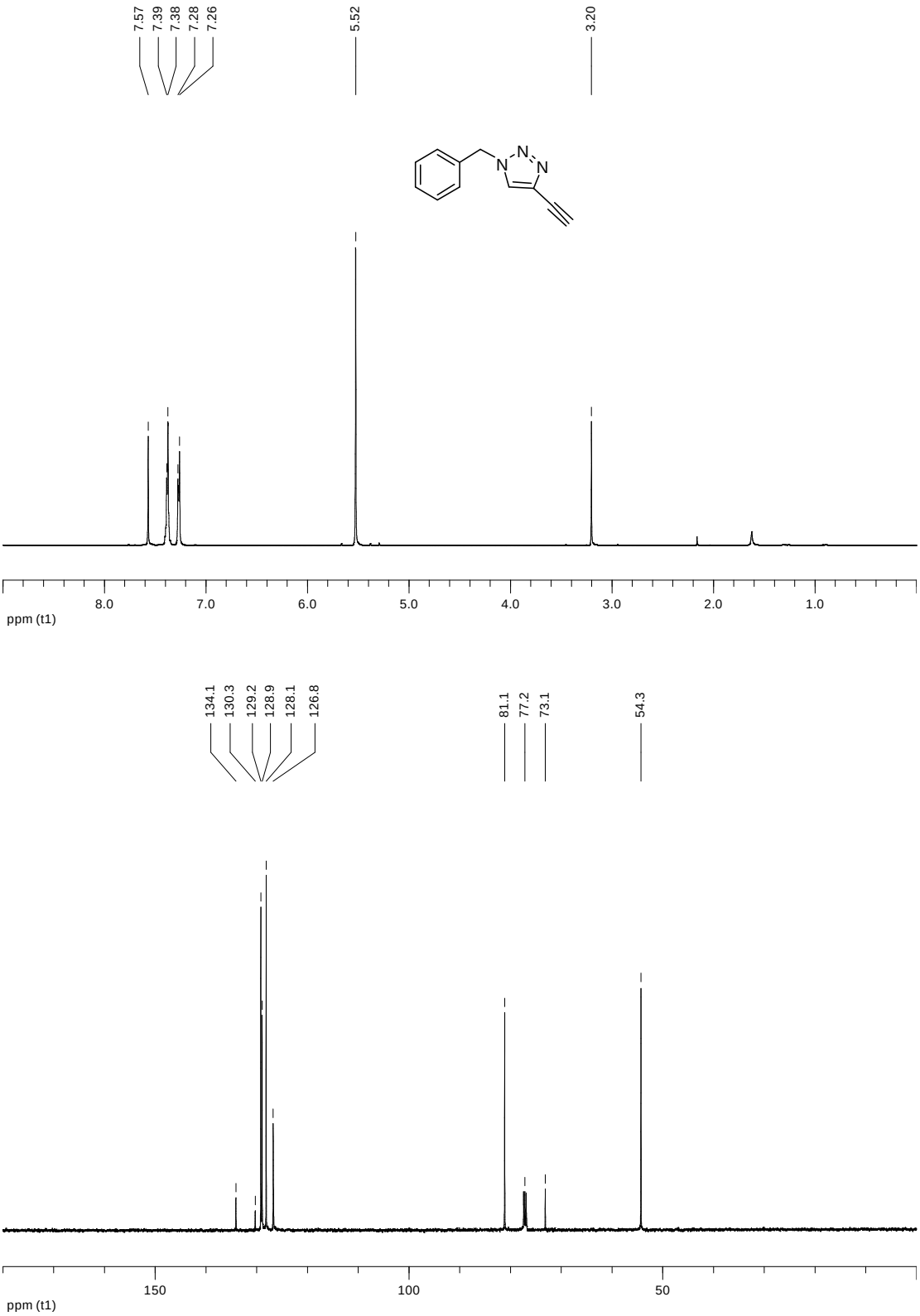


Figure S9: ^{1}H & ^{13}C NMR spectra of compound **5a** ($CDCl_3$).

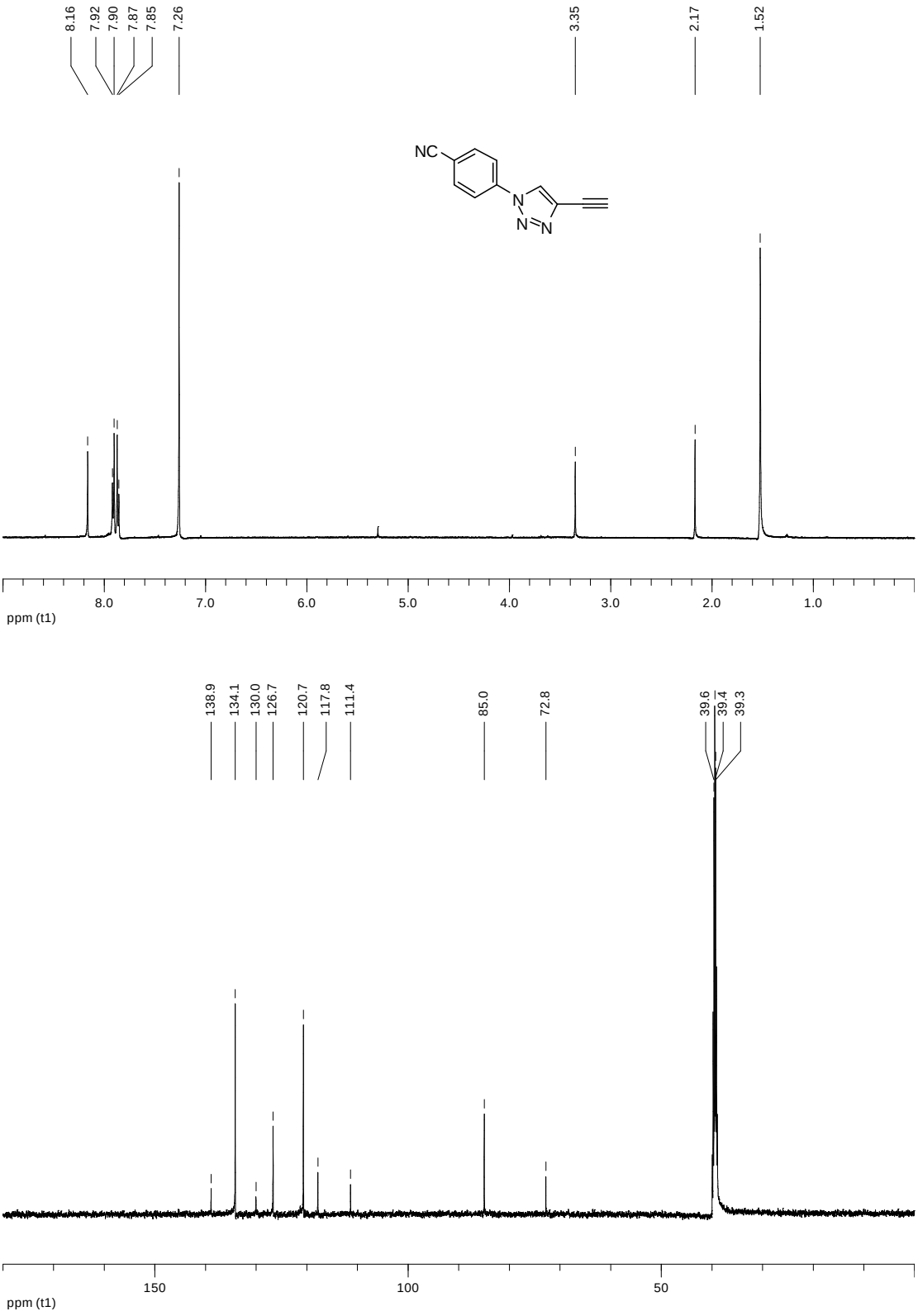


Figure S10: ^{1}H ($CDCl_3$) & ^{13}C (DMSO) NMR spectra of compound **5b**

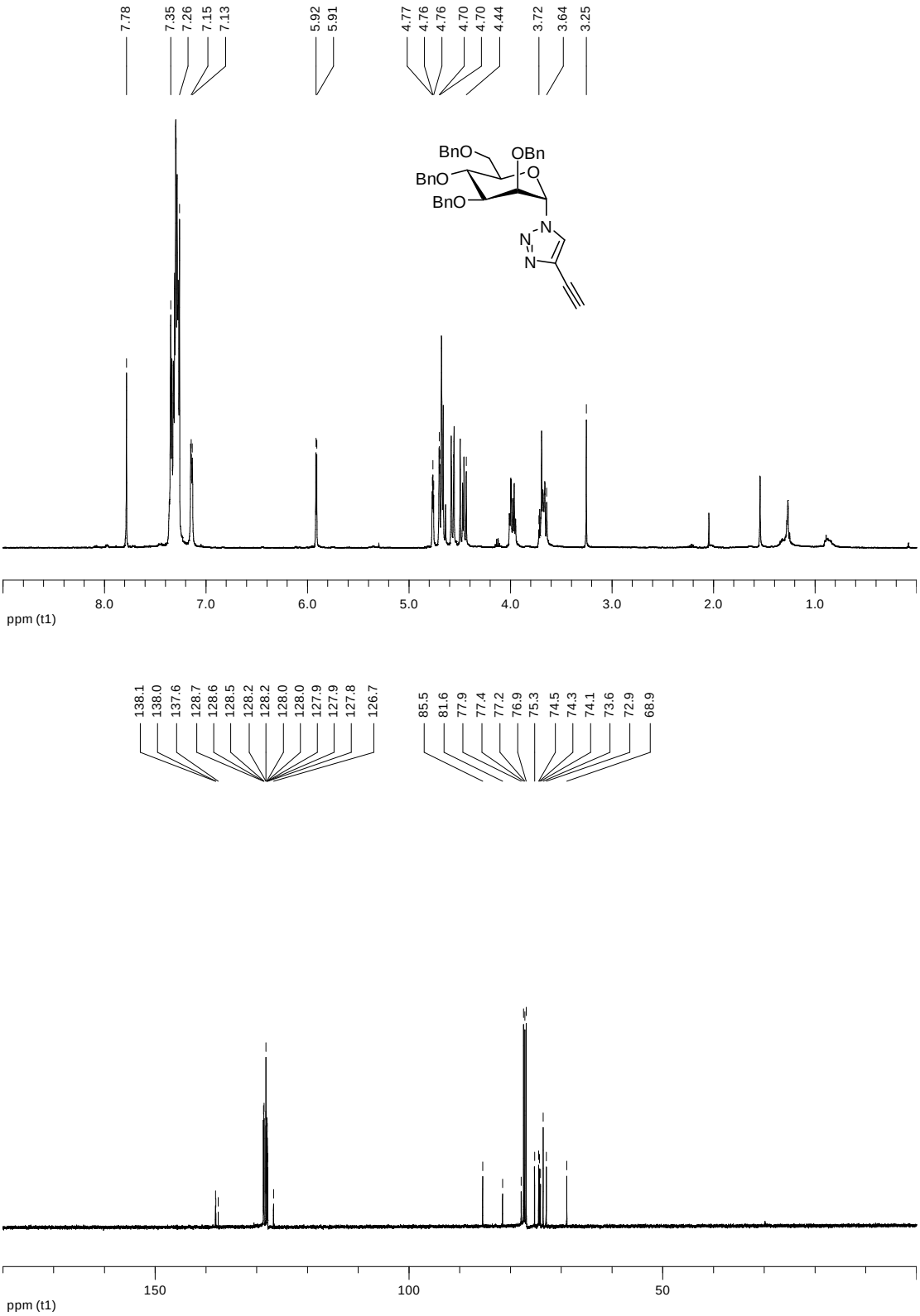


Figure S11: ^{1}H & ^{13}C NMR spectra of compound **5c** ($CDCl_3$).

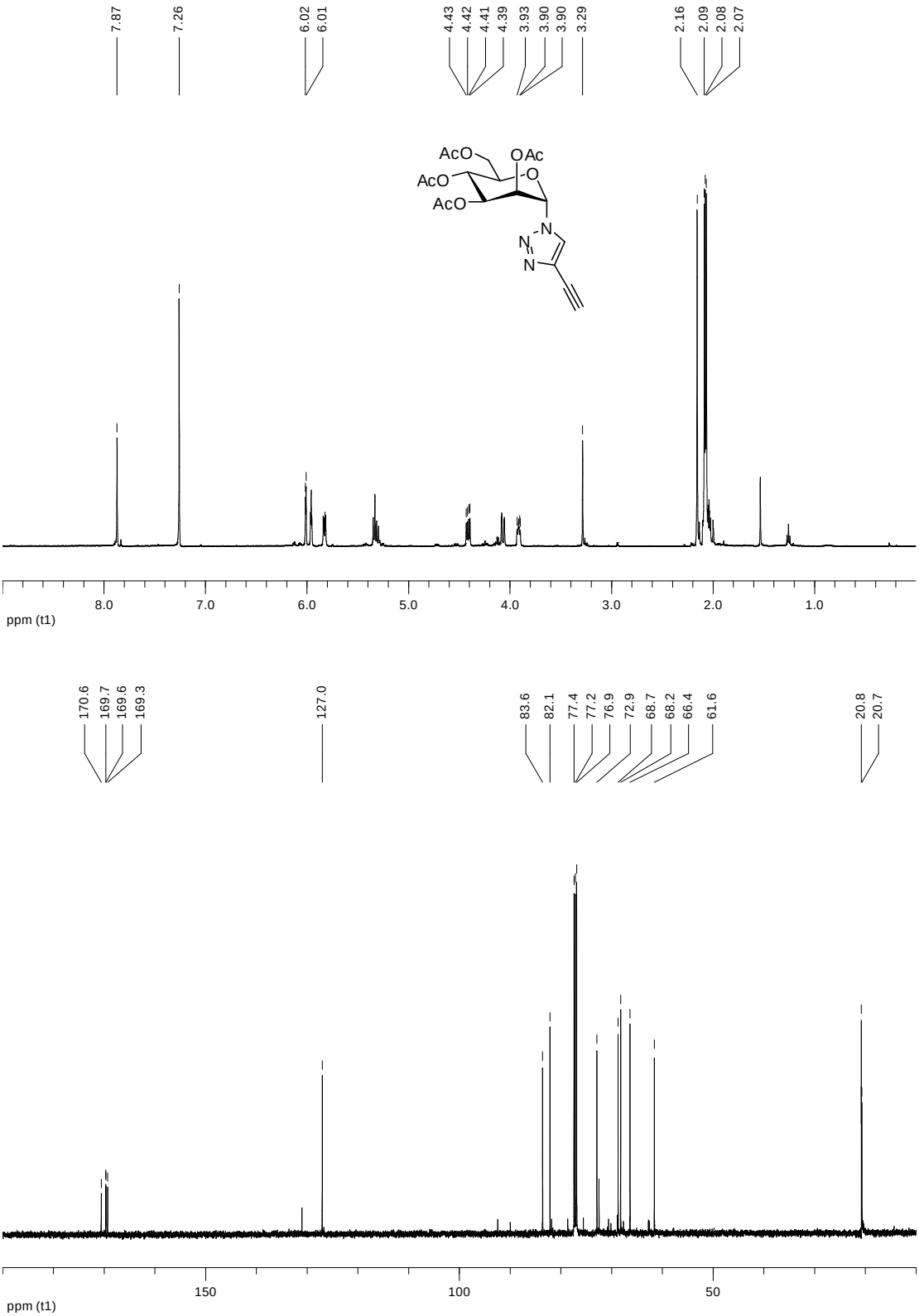


Figure S12: ^{1}H & ^{13}C NMR spectra of compound **5d** ($CDCl_3$).

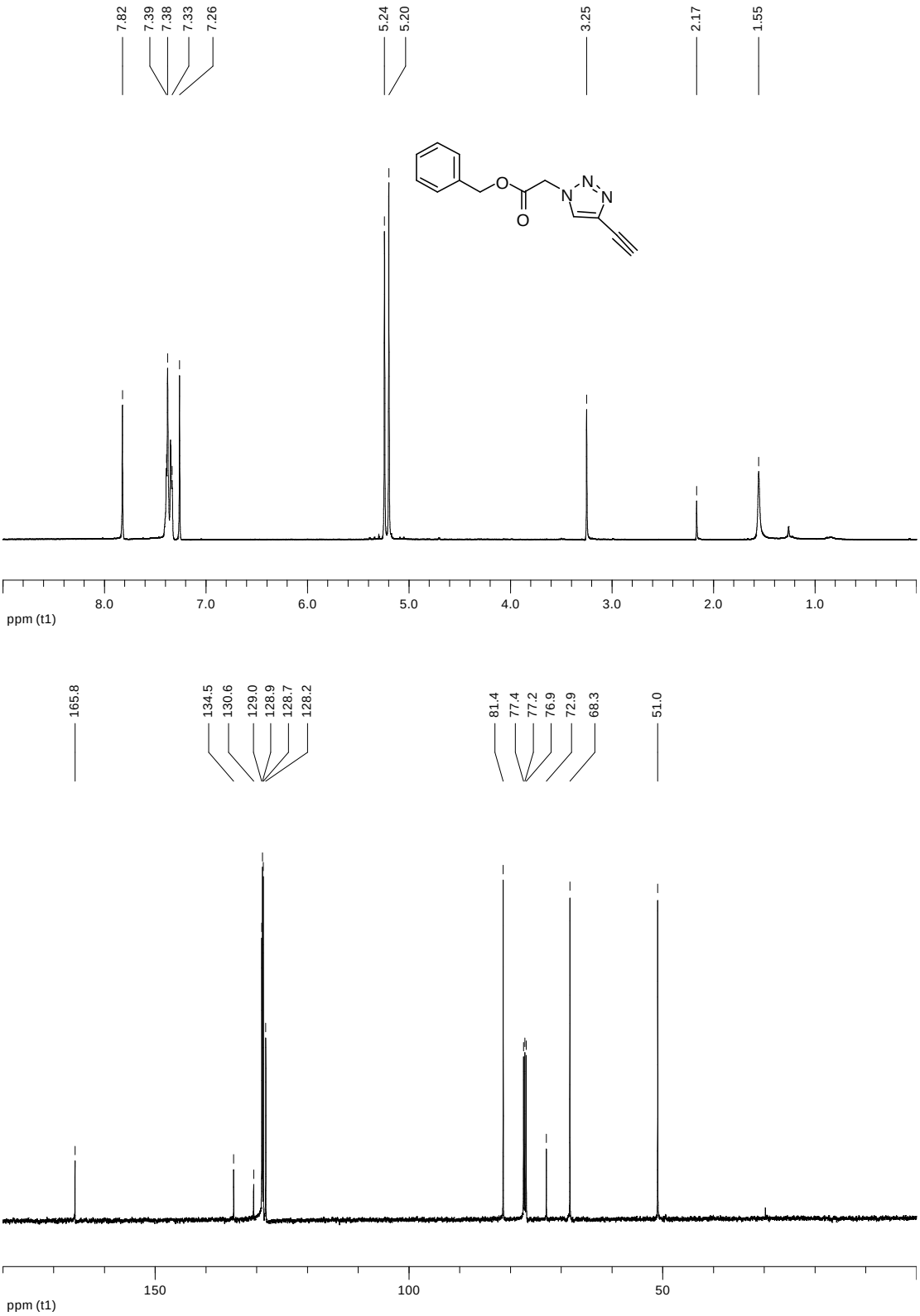


Figure S13: ^{1}H & ^{13}C NMR spectra of compound **5e** ($CDCl_3$).

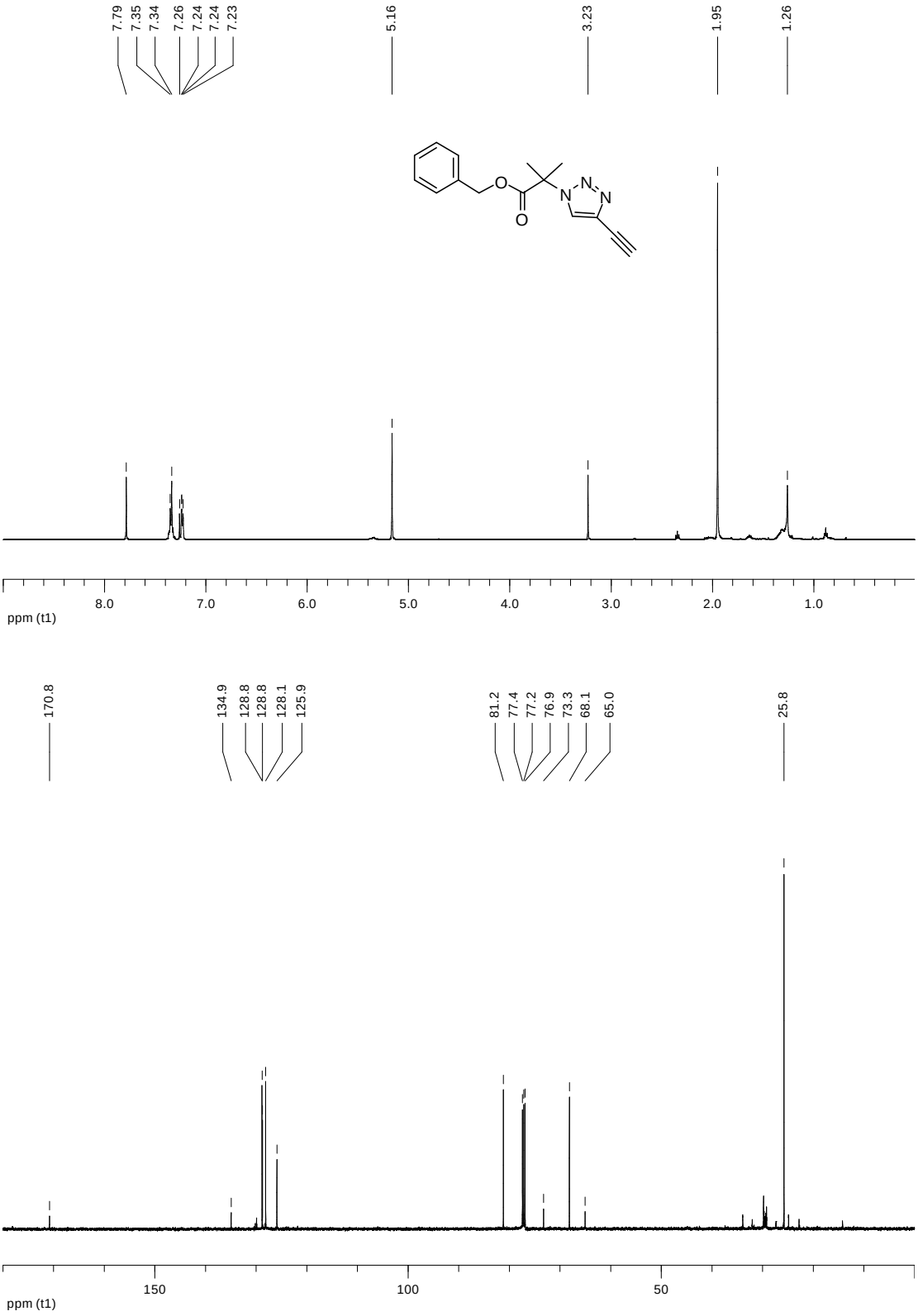


Figure S14: ^{1}H & ^{13}C NMR spectra of compound **5f** ($CDCl_3$).

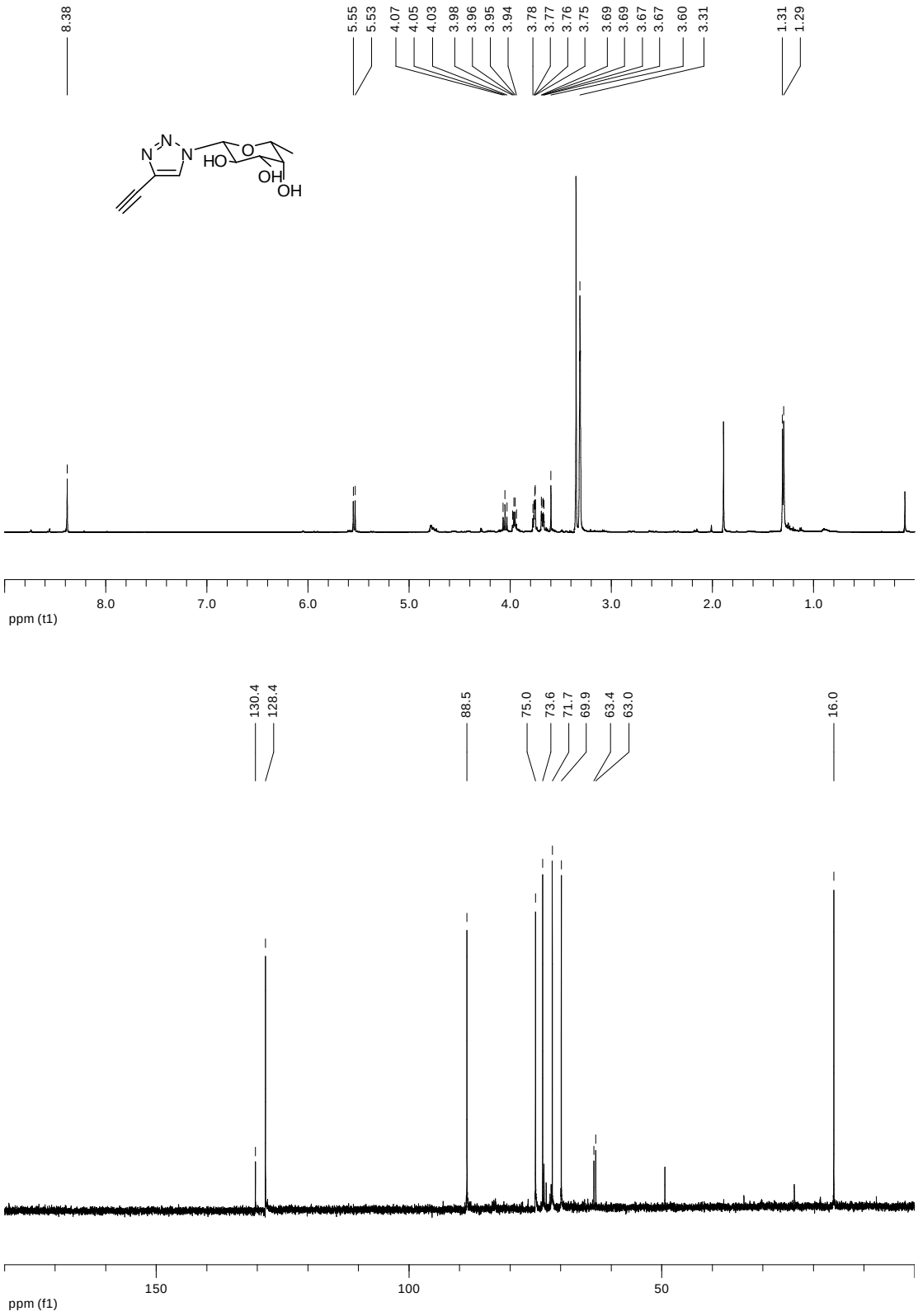


Figure S14: ^{1}H & ^{13}C NMR spectra of compound **5g** (CD_3OD).

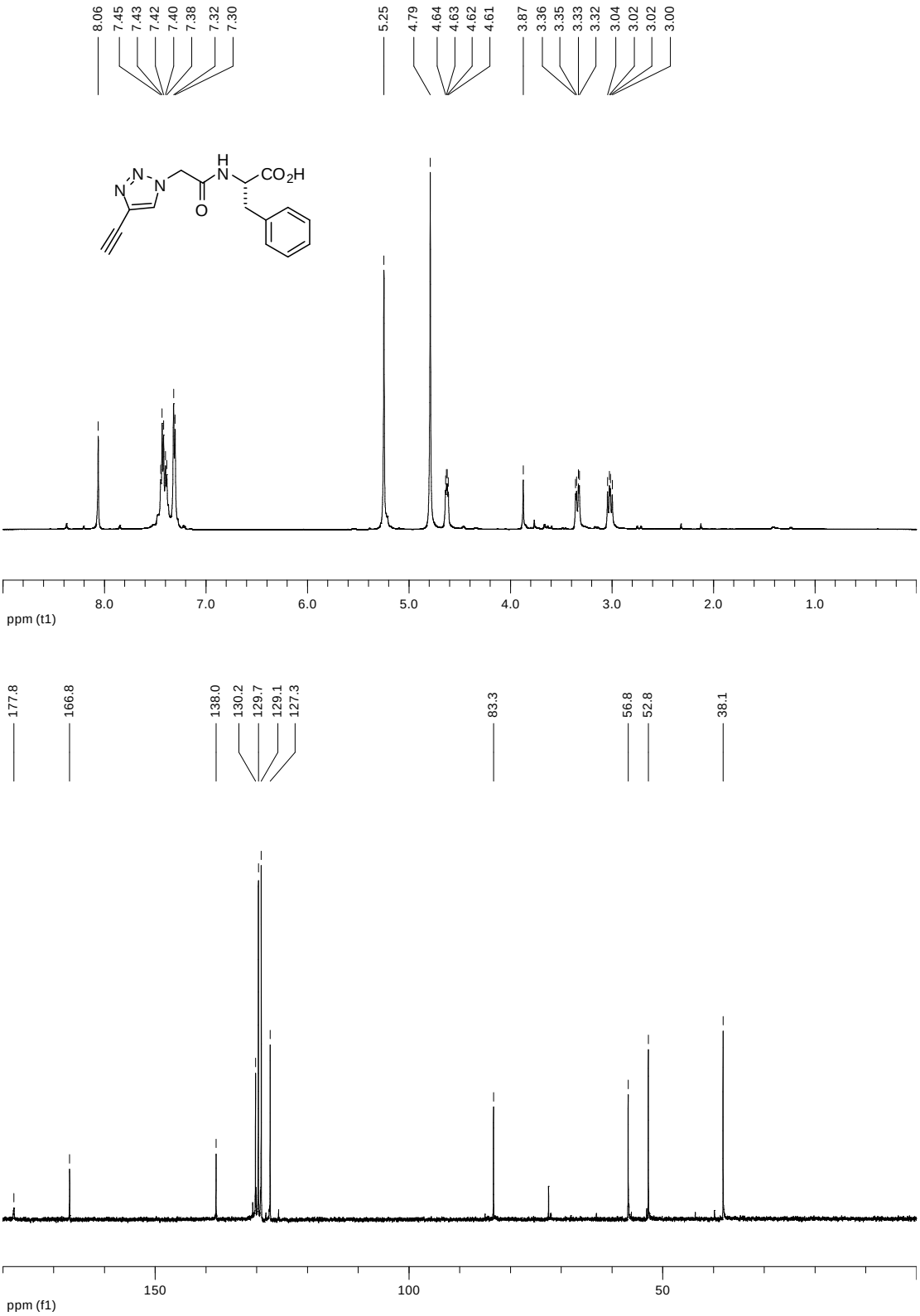


Figure S15: ^{1}H & ^{13}C NMR spectra of compound **5h** (CD_3OD).

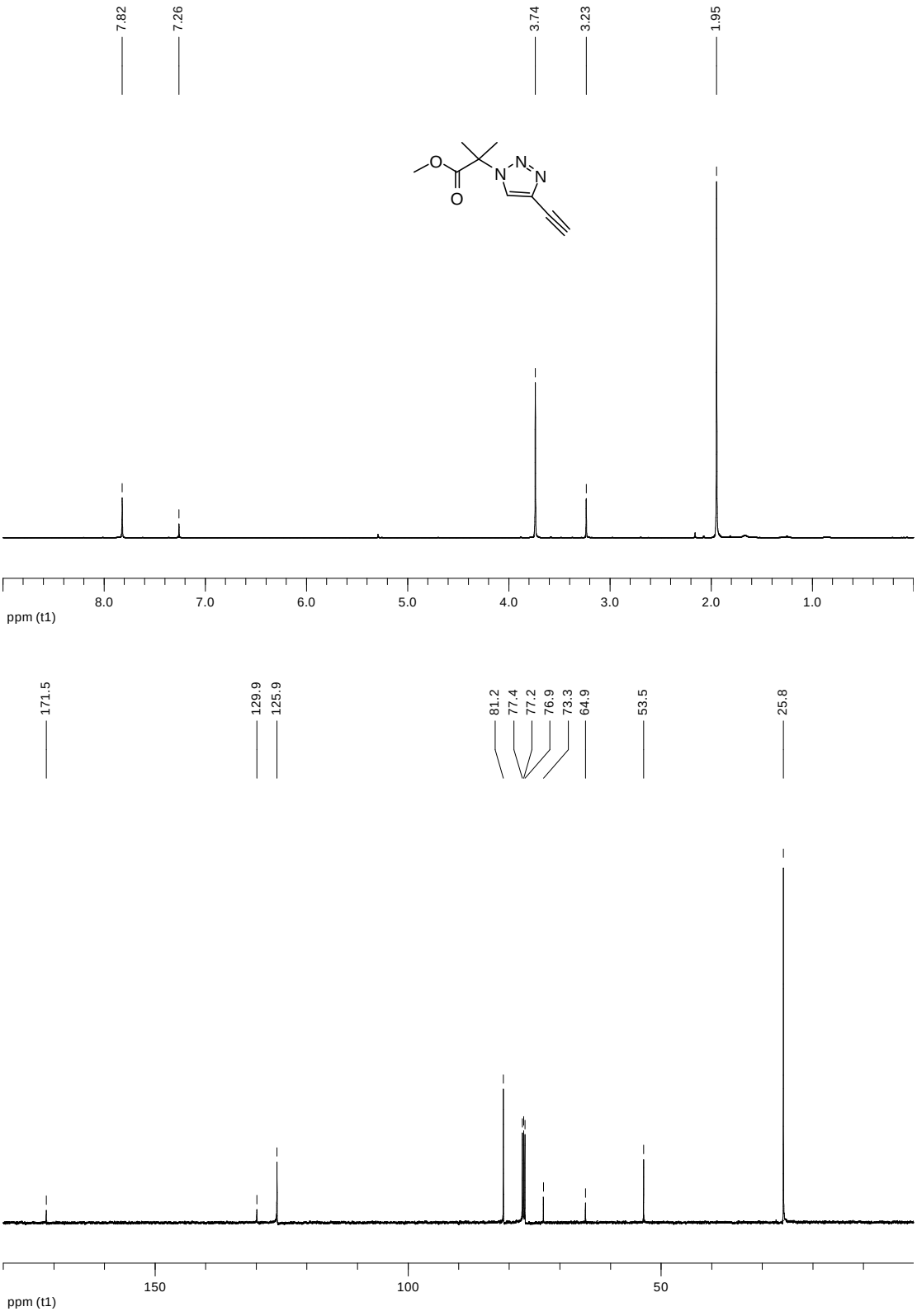


Figure S16: ^{1}H & ^{13}C NMR spectra of compound **5i** ($CDCl_3$).

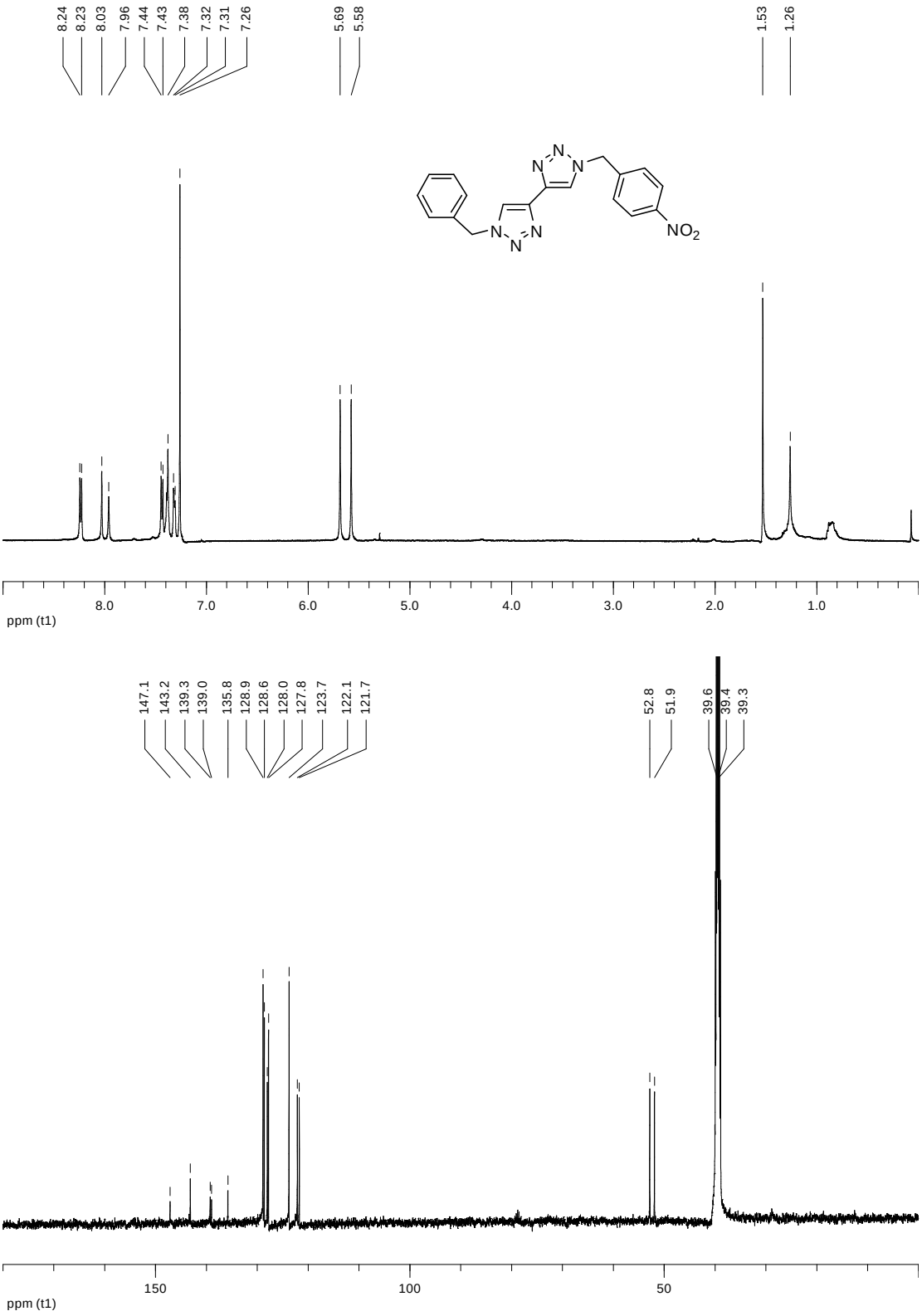


Figure S17: ^{1}H & ^{13}C NMR spectra of compound **4a** ($CDCl_3$).

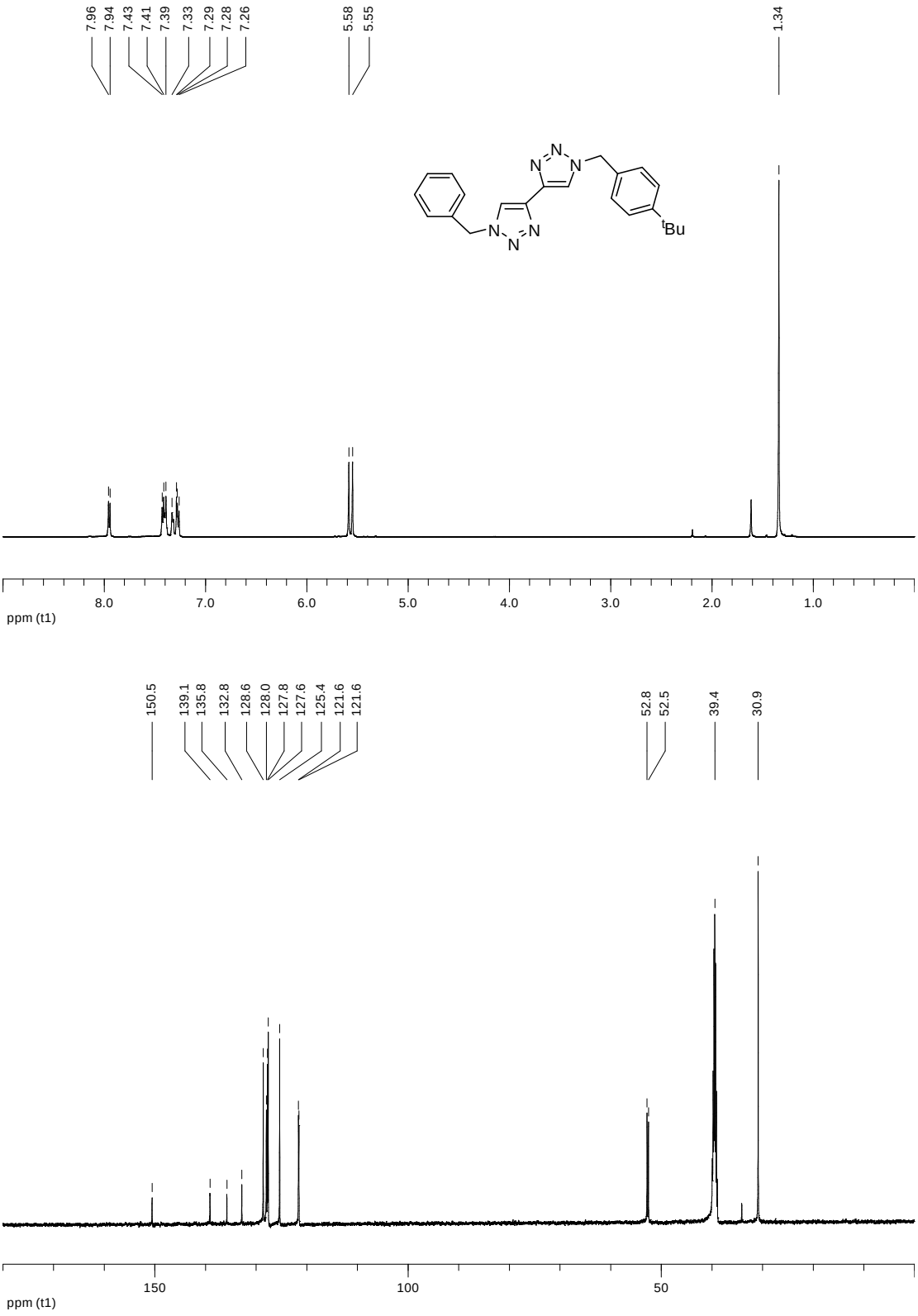


Figure S18: ^{1}H ($CDCl_3$) & ^{13}C (DMSO) NMR spectra of compound **4b**.

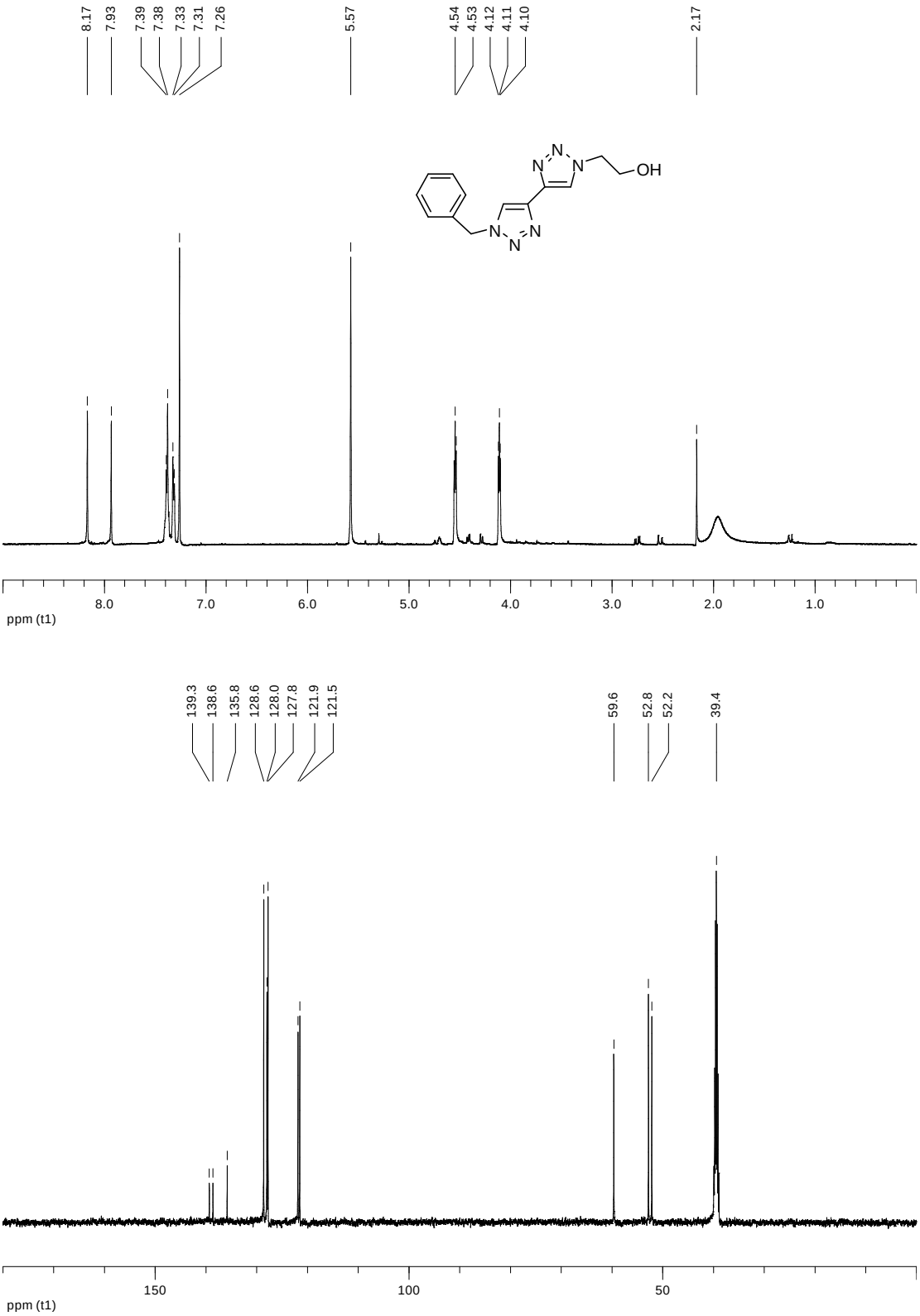


Figure S19: ^{1}H ($CDCl_3$) & ^{13}C (DMSO) NMR spectra of compound **4c**.

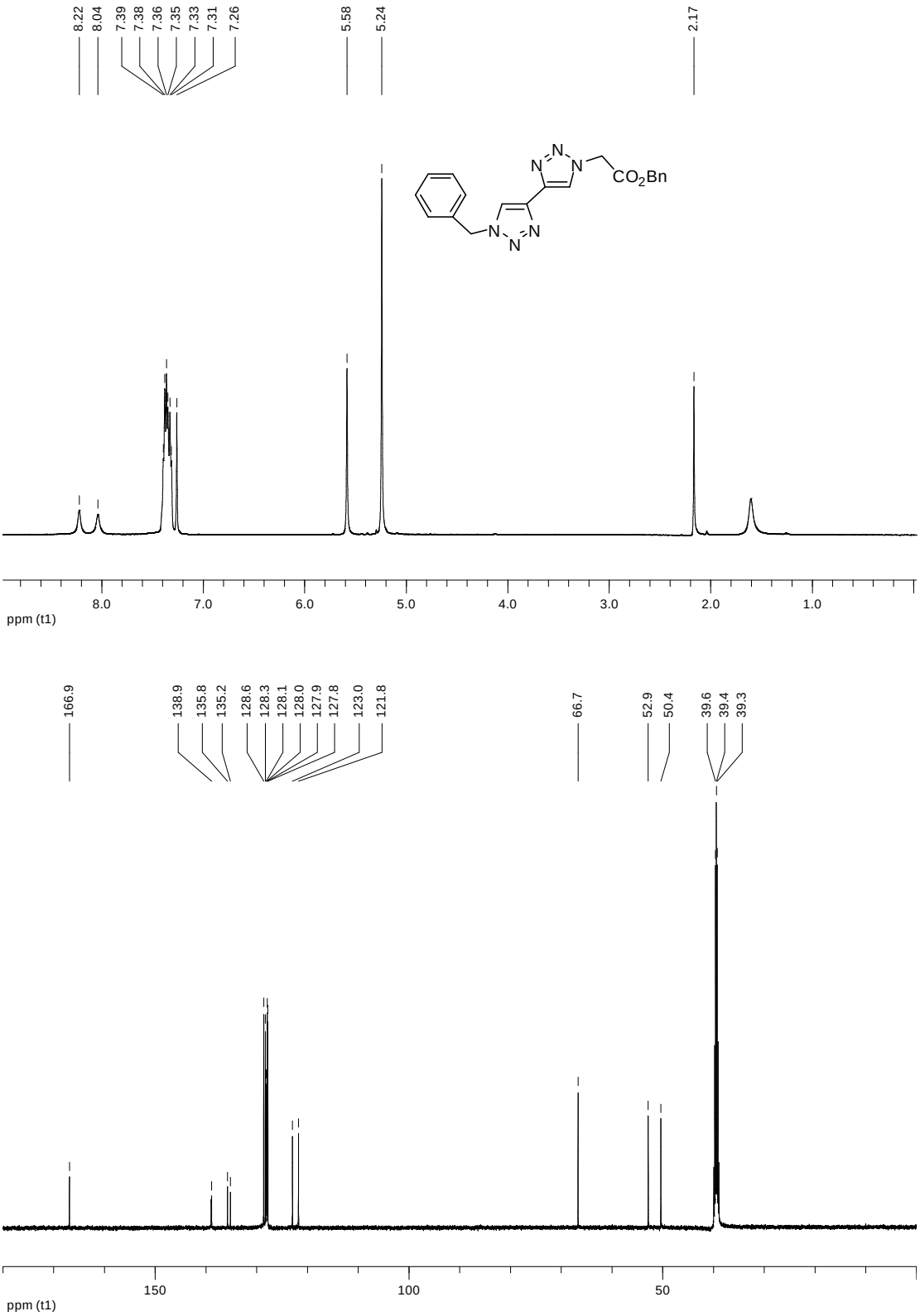


Figure S20: ^{1}H ($CDCl_3$) & ^{13}C (DMSO) NMR spectra of compound **4d**.

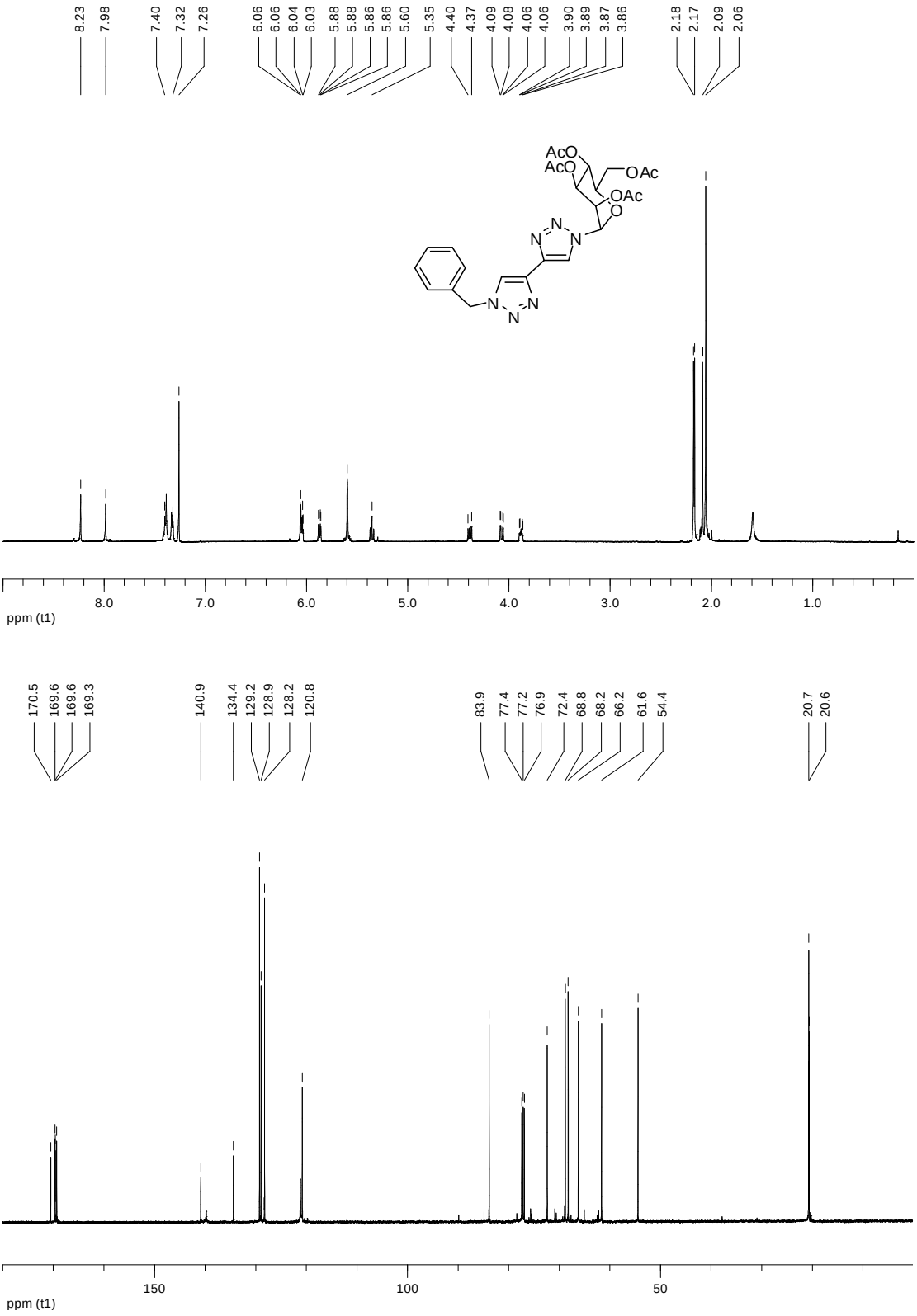


Figure S21: ^{1}H & ^{13}C NMR spectra of compound **4e** ($CDCl_3$).

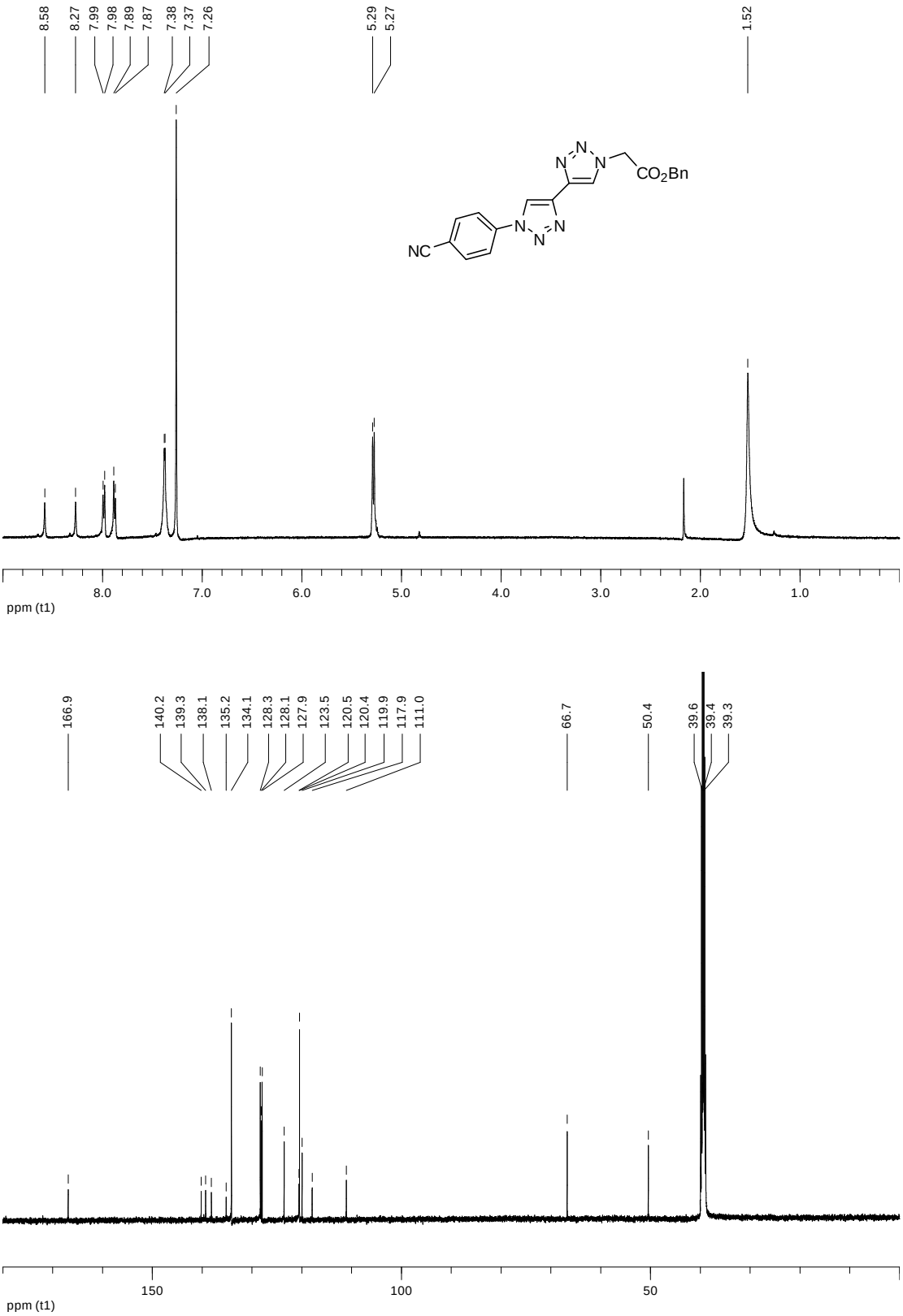


Figure S22: ^{1}H ($CDCl_3$) & ^{13}C (DMSO) NMR spectra of compound **4f**.

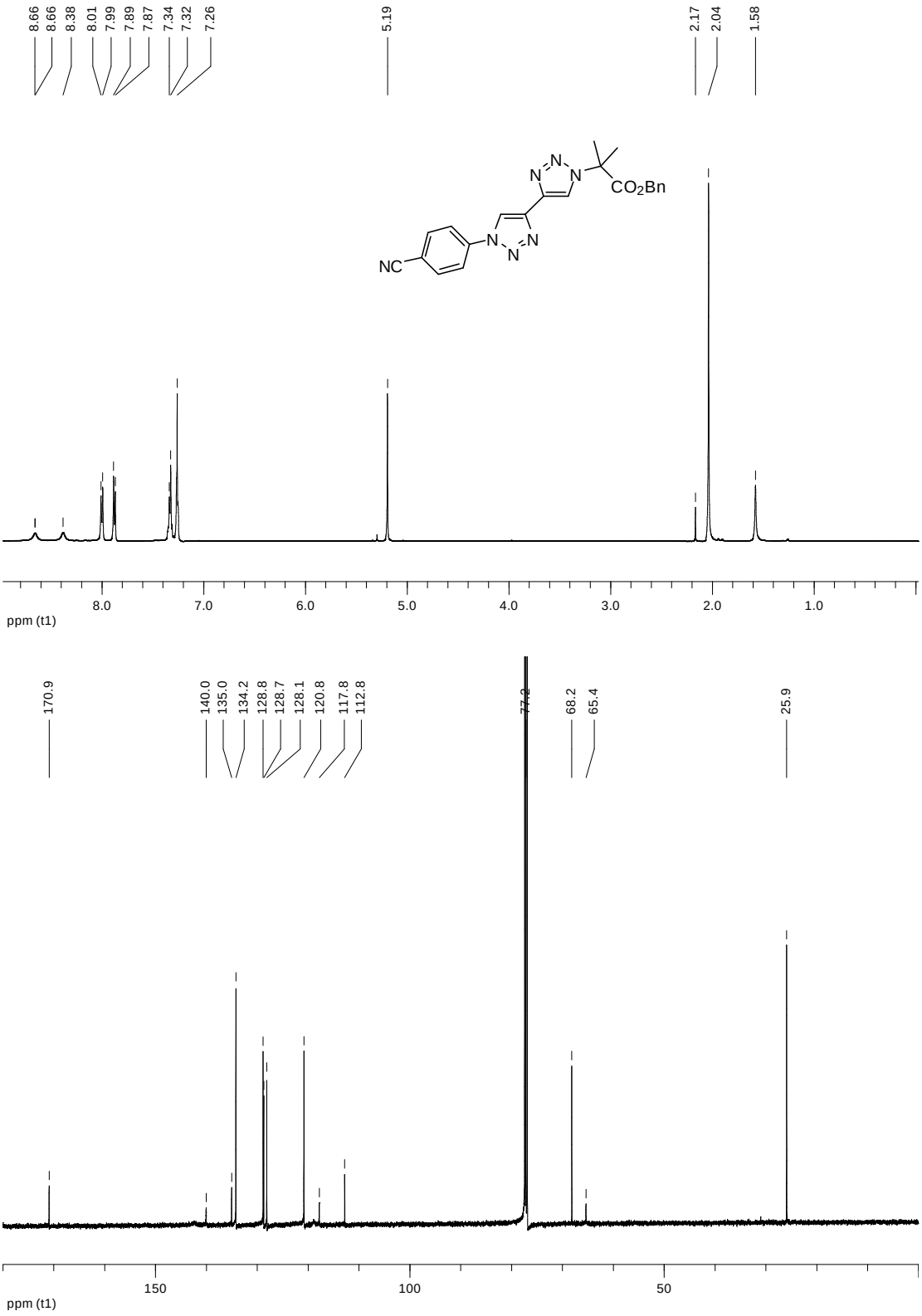


Figure S23: ^{1}H & ^{13}C NMR spectra of compound **4g** ($CDCl_3$).

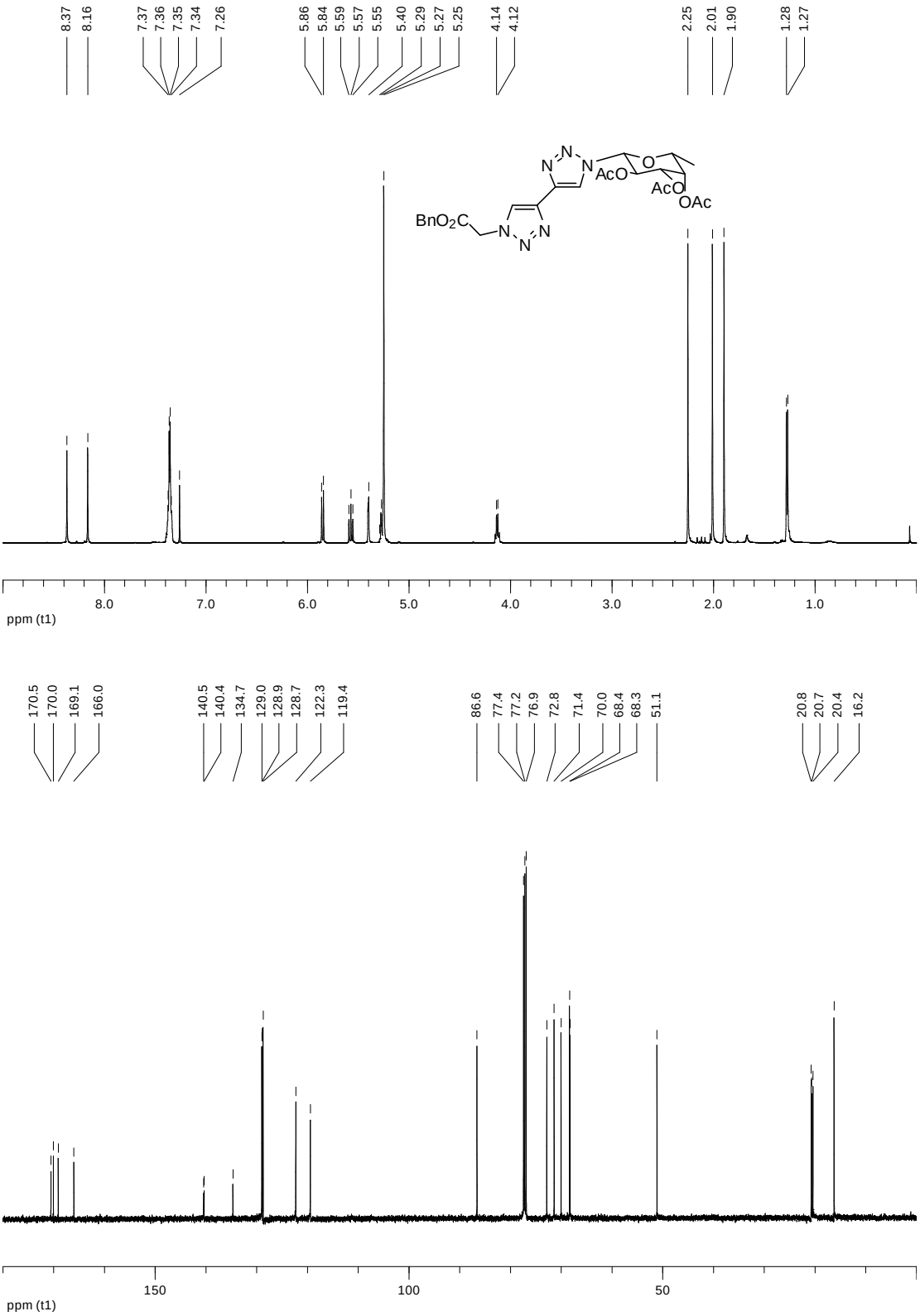


Figure S24: ^{1}H & ^{13}C NMR spectra of compound **4h** ($CDCl_3$).

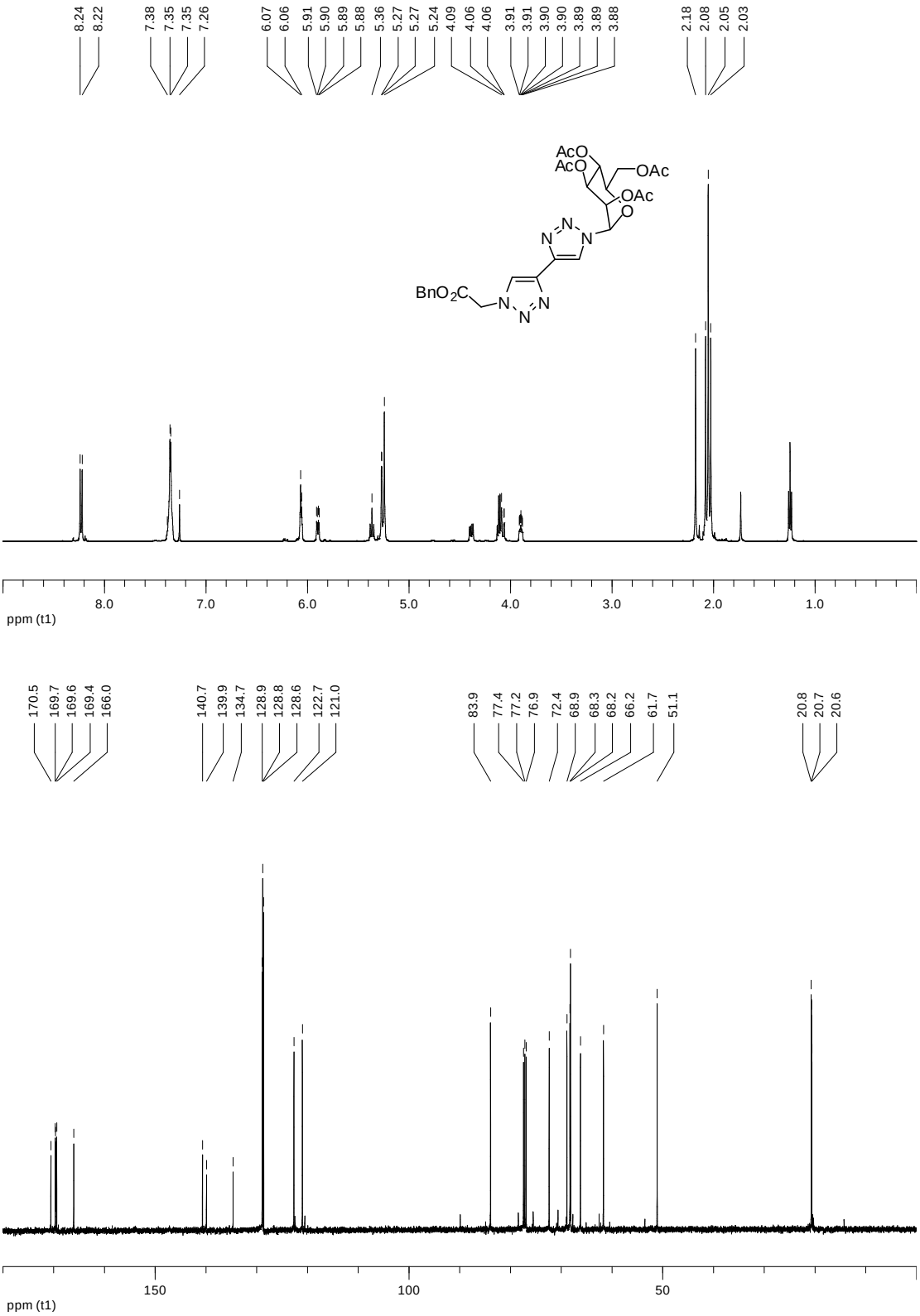


Figure S25: ^{1}H & ^{13}C NMR spectra of compound **4i** ($CDCl_3$).

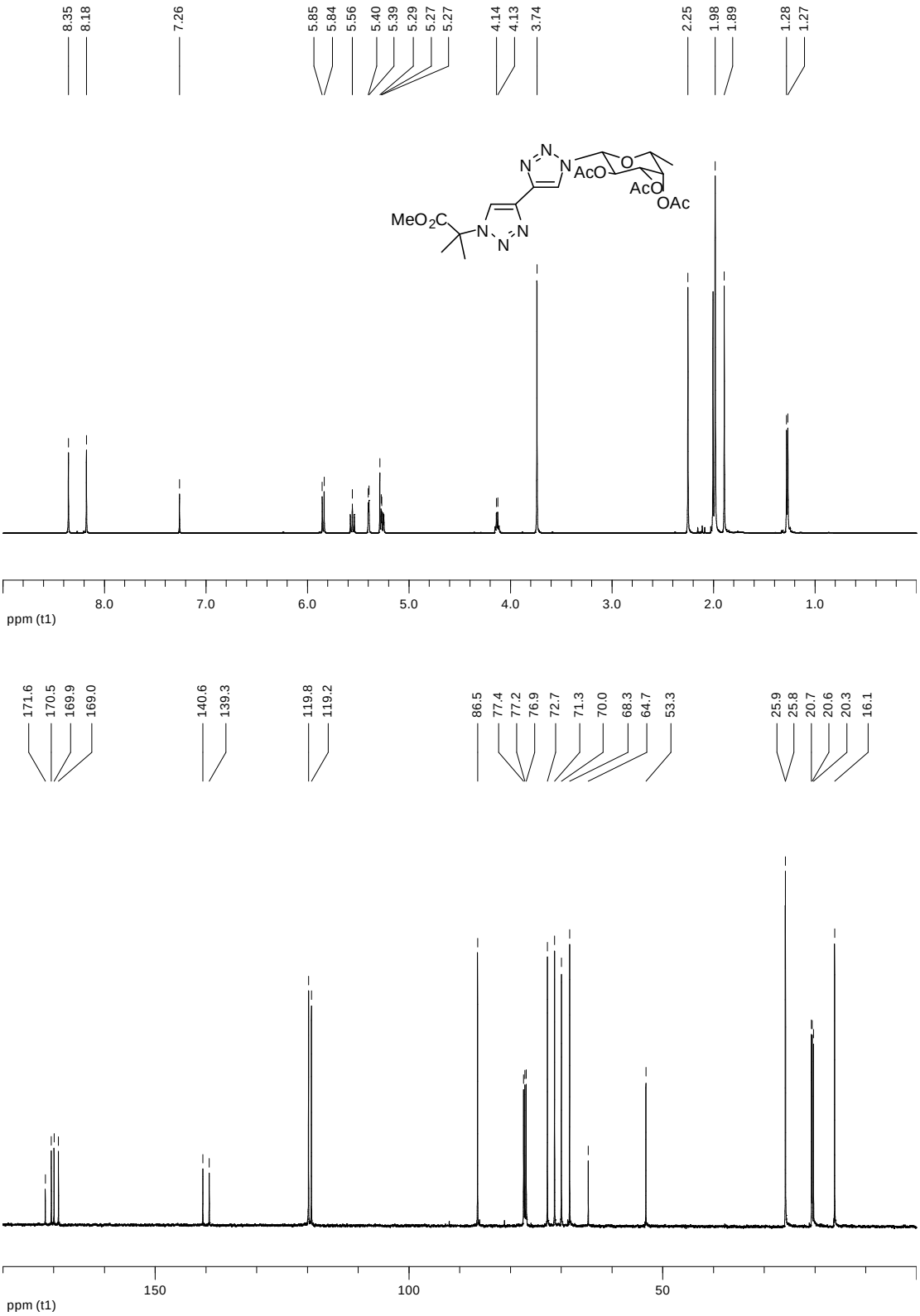


Figure S26: ^{1}H & ^{13}C NMR spectra of compound **4j** ($CDCl_3$).

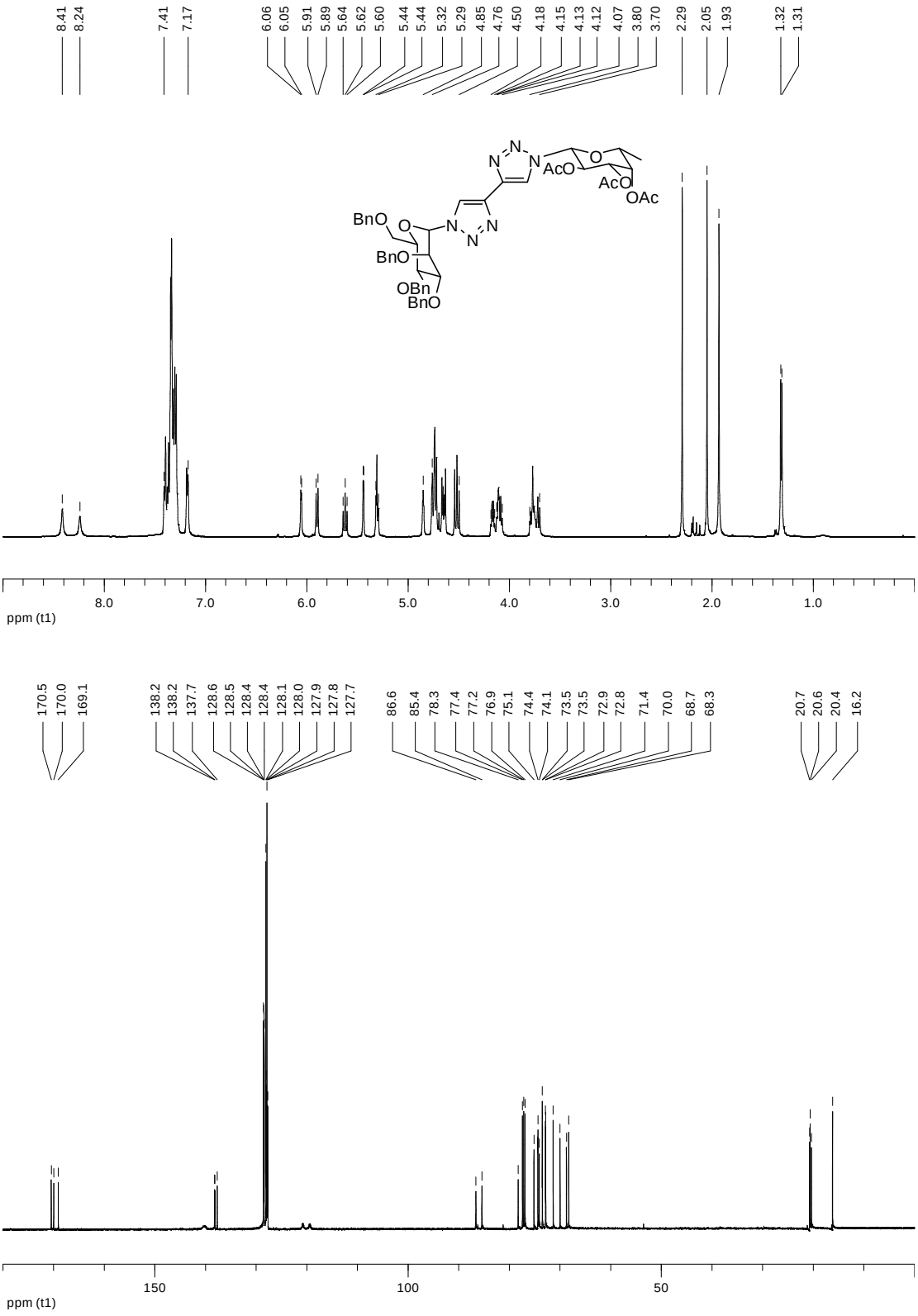


Figure S27: ^{1}H & ^{13}C NMR spectra of compound **4k** ($CDCl_3$).

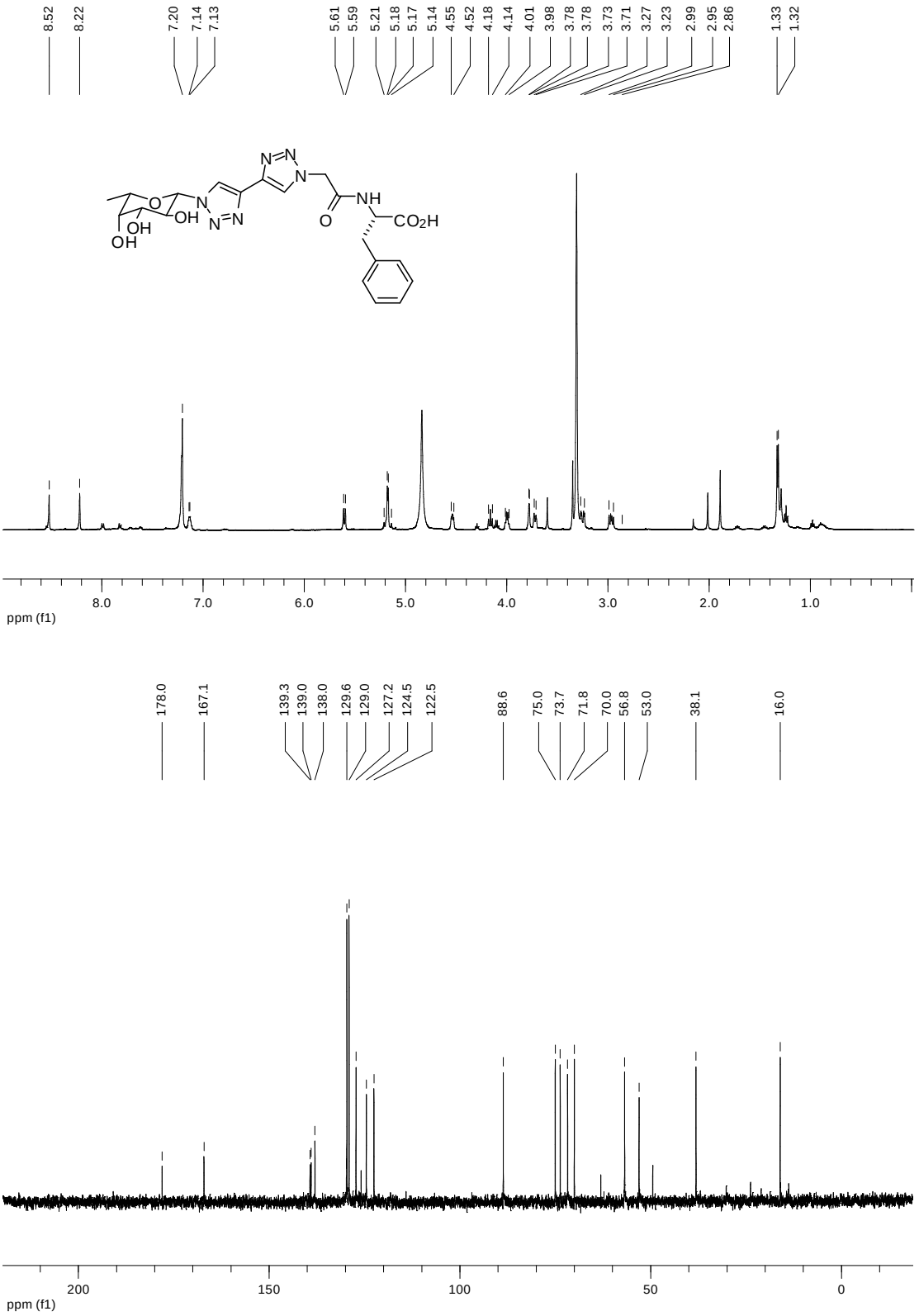


Figure S28: ^{1}H & ^{13}C NMR spectra of compound **4l** (D_2O).

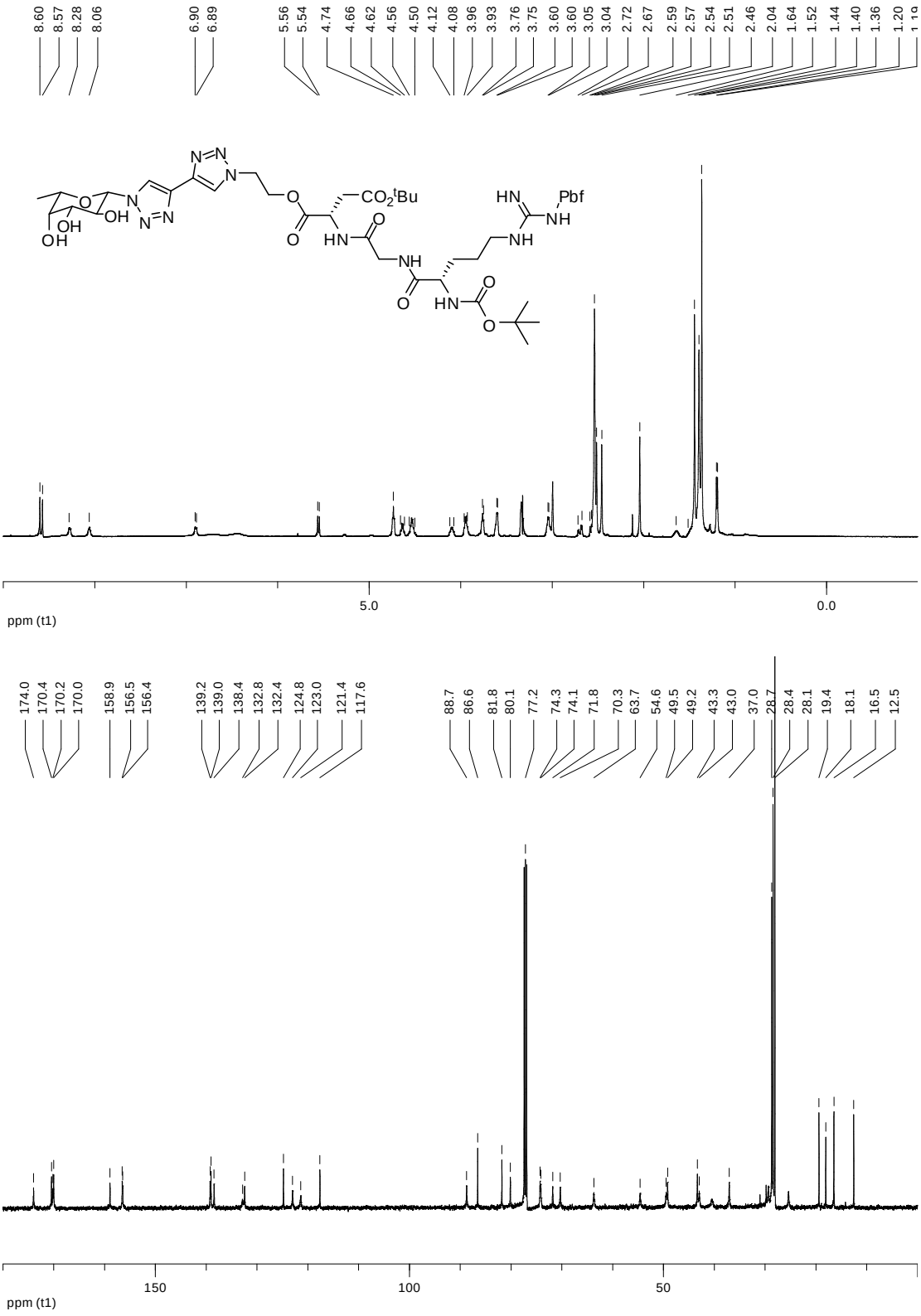


Figure S29: ^{1}H (D_2O) & ^{13}C ($CDCl_3$) NMR spectra of compound **4m**.

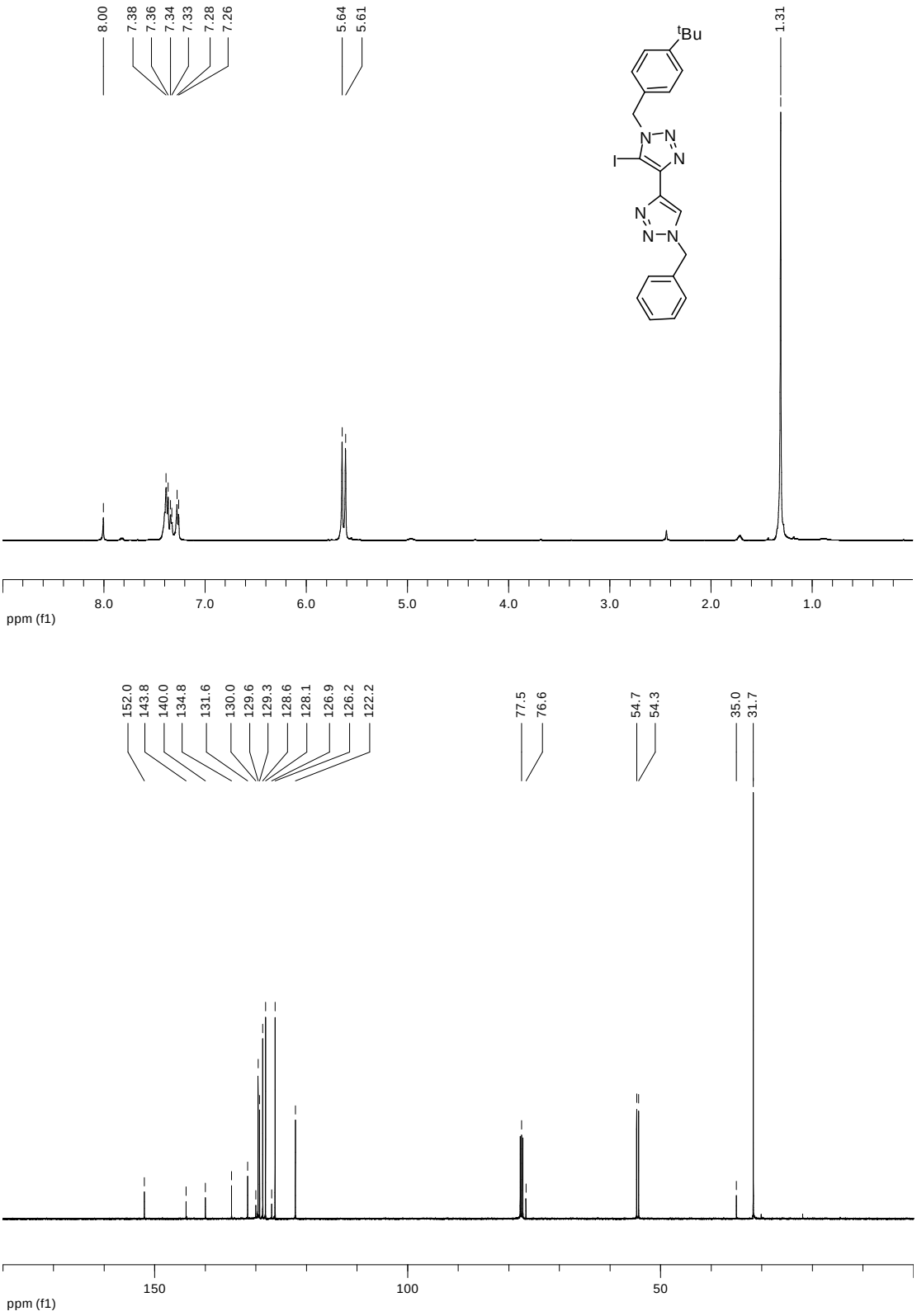


Figure S30: ^{1}H & ^{13}C NMR spectra of compound **11** ($CDCl_3$).

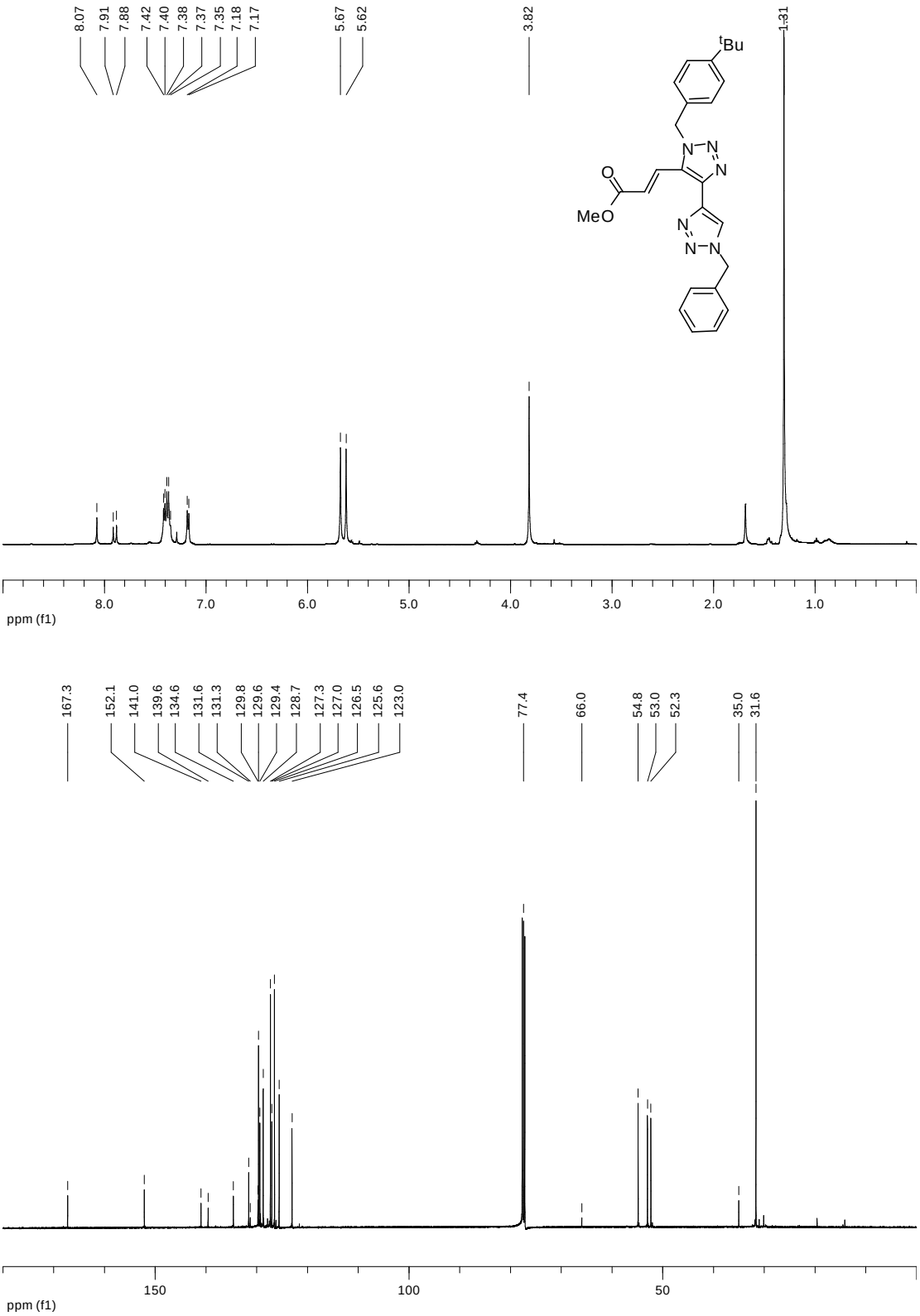


Figure S31: ^{1}H & ^{13}C NMR spectra of compound **12** ($CDCl_3$)