A highly efficient tandem [3+2] "click" cycloaddition /6-exo-cyclization strategy for the construction of triazole fused pyrazines

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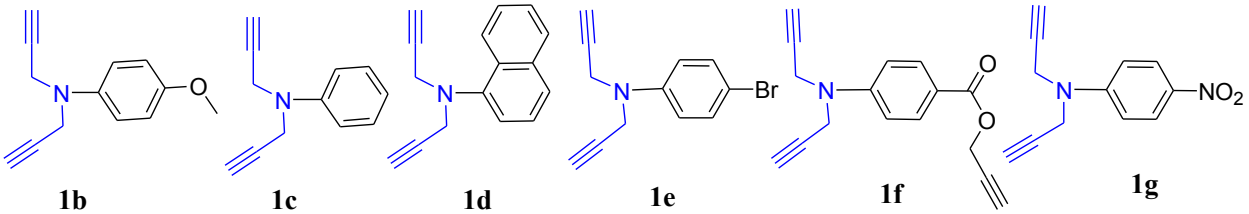
General information

All reactants and reagents were commercially available and were used without further purification unless otherwise indicated. The structures of the compounds were determined by 1D and 2D nuclear magnetic resonance spectroscopy and other spectroscopic techniques. ^{1}H and ^{13}C NMR spectra were recorded with 400 MHz Jeol and 500 MHz Bruker instruments. Chemical shifts are reported in δ values relative to an internal reference of solvent peak: $CDCl_3$ δ 7.26 ppm for the ^{1}H NMR, and δ 77.0 ppm for the ^{13}C NMR. Coupling constants are expressed in hertz (Hz). IR data were obtained with a FT-IR Perkin-Elmer spectrometer. UV spectra were recorded with a Cary 300Bio UV-vis spectrophotometer. ESI mass spectrometry data were obtained from an Acquity^{TM} Ultra Performance LCMS. Specific rotations of the amino acid derivatives were measured with a Perkin-Elmer Polarimeter, Model 341LC. Melting points were determined using a capillary method with a Secor (India) melting point apparatus. CHN analyses were performed using a Perkin Elmer 2400 CHN Elemental Analyzer. Reactions were monitored by thin layer chromatography using Merck plates (TLC Silica Gel 60 F254). Developed TLC plates were visualized with UV light (254 nm). Silica gel (100 ~ 200 mesh, Merck) was used for column chromatography. Yields refer to the chromatographically and spectroscopically pure compounds.

General Procedure for the synthesis of dipropargyl derivatives

A primary amine (1.0 mmol), K_2CO_3 (5.0 mmol) in DMF (5 mL) was stirred for 30 min at 25 °C. Propargyl bromide was added drop wise to the reaction mixture, and the mixture was stirred at 25 ^{o}C for 12−18 h depending on the substrate. The reaction was monitored by TLC. The volatiles of the reaction mixture were removed under reduced pressure and extracted with EtOAc (2 × 10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and again with water (2×10 mL), separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue on chromatography yielded the desired product.

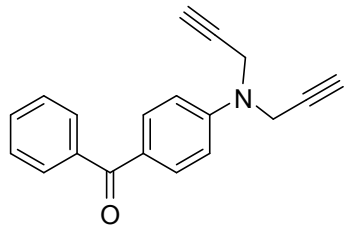
Dipropargyl compounds from reported literature



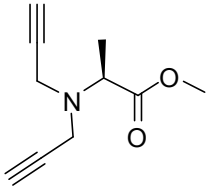
1b **1c** **1d** **1e** **1f** **1g**

The dipropargyl compounds **1b-1g** was synthesized based on the reported procedures and the spectroscopic characterization data were in well agreement with the literature reports.[1]

Experimental procedures and spectroscopic characterization of 1a, 3a–3d



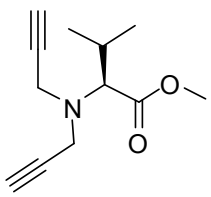
(4-(Diprop-2-ynylamino)phenyl)(phenyl)methanone (1a): Compound (**1a**) was synthesized from 4-amino benzophenone (0.50 g, 2.54 mmol), propargyl bromide (0.96 mL, 12.69 mmol) and K_2CO_3 (1.75 g, 12.69 mmol) in DMF (5 mL) at 25 ^oC for 12 h using the same general procedure described above. The column chromatography performed using ethyl acetate/hexane (10:90, v/v) afforded **1a** (0.64 g, 93%) as a yellow solid. mp 84–86 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (t, 2H, J = 2.3 Hz, ≡CH), 4.21 (d, 4H, J = 2.3 Hz, –CH_2N), 6.92-6.94 (m, 2H, –ArH), 7.45 (t, 2H, J = 7.5 Hz, –ArH), 7.52–7.55 (m, 1H, –ArH), 7.73–7.74 (m, 2H, –ArH), 7.82–7.84 (m, 2H, –ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.0, 72.9, 78.4, 112.9, 127.6, 128.0, 129.5, 131.4, 132.4, 138.6, 150.6, 195.2. FT−IR (KBr, cm^{-1}): 3284, 3261, 3053, 2924, 2106, 1635, 1599, 1522, 1323, 1167, 694, 647. λ_{abs} in MeOH (nm) 246, 331. ESI- MS (*m/z*): Calcd. for $C_{19}H_{16}NO$ $[M+H]^+$ 274.12, found 274.12. Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12; Found: C, 83.19; H, 5.63; N, 5.19.



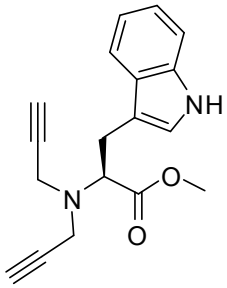
(*S*)-Methyl 2-(diprop-2-ynylamino)propanoate (3a): Compound (**3a**) was synthesized from methyl ester of alanine (0.50 g, 4.85 mmol), propargyl bromide (1.84 mL, 24.27 mmol) and K_2CO_3 (3.35 g, 24.27 mmol) in DMF (6 mL) at 25 ^oC for 12 h using the same general procedure described above. Column chromatography using ethyl acetate/hexane (10:90, v/v) yielded **3a** (0.67 g, 77%) as a colourless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.6 Hz,

–CH_3), 2.16 (t, 2H, *J* = 2.3 Hz, ≡CH), 3.47 (d, 4H, *J* = 2.3 Hz, –CH_2N), 3.48–3.50 (m, 1H, –C**H**CH_3), 3.60 (s, 3H, –OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 39.6, 51.6, 58.8, 72.9, 78.8, 173.4. FT−IR (neat, cm^{-1}): 3292, 2988, 2951, 2733, 2122, 2106, 1436, 1203, 1151, 654. λ_{abs} in MeOH (nm) 267; ESI MS (*m/z*): Calcd. for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.10, found 180.10. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82; Found: C, 66.92; H, 7.23; N, 7.92.

(*S*)-Methyl 2-(diprop-2-ynylamino)-3-methylbutanoate (3b): Compound (**3b**) was synthesized from methyl ester of valine (0.86 g, 6.56 mmol), propargyl bromide (2.48 mL, 32.82 mmol) and K_2CO_3 (4.53 g, 32.82 mmol) in DMF (8 mL) at 25 ^oC for 12 h using the same general procedure described above. Column chromatography using ethyl acetate/hexane (10:90, v/v) afforded **3b** (1.27 g, 94%) as a colourless liquid. $[\alpha]_D^{25.8}$ –84.12 (c 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, 3H, *J* = 6.0 Hz, –CH_3), 0.97 (d, 3H, *J* = 6.5 Hz, –CH_3), 1.99–2.03 (m, 1H, –C**H**$(CH_3)_2$), 2.2 (t, 2H, *J* = 2.3 Hz, ≡CH), 2.97–3.00 (m, 1H, –C**H**CH$(CH_3)_2$), 3.58 (d, 4H, *J* = 2.3 Hz, –CH_2N), 3.66 (s, 3H, –OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.4, 27.8, 39.4, 50.8, 70.6, 72.3, 79.6, 172.2. FT−IR (neat, cm^{-1}): 3293, 2963, 2874, 2840, 2122, 2107, 1732, 1433, 1149, 1001, 772, 655. λ_{abs} in MeOH (nm) 270. ESI-MS (*m/z*): Calcd. for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.13, found 208.13. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76; Found: $C_{12}H_{17}NO_2$: C, 69.74; H, 8.21; N, 6.86.

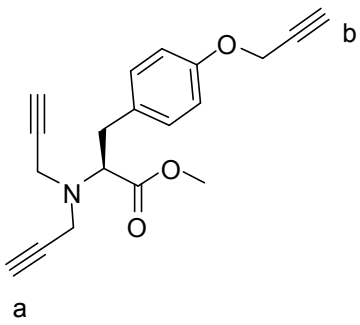


(*S*)-Methyl 2-(diprop-2-ynylamino)-3-(1H-indol-3-yl)propanoate (3c): Compound (**3c**) was synthesized from methyl ester of tryptophan (0.50 g, 2.29 mmol), propargyl bromide (0.86 mL, 11.4 mmol) and K_2CO_3 (1.58 g, 11.4 mmol) in DMF (5 mL) at 25 ^oC for 16 h using the same general procedure described above. Column chromatography using ethyl acetate/hexane (20:80, v/v) afforded **3c** (0.44 g, 66%) as a colourless viscous liquid. $[\alpha]_D^{25.8}$ –3.2 (c 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (t, 2H, *J* = 2.3 Hz, ≡CH), 3.20–3.34 (m, 2H, –ArCH_2), 3.56 (s, 3H, –OCH_3), 3.74 (d, 4H, *J* = 2.3 Hz, –CH_2N), 3.87–3.91 (m, 1H, –ArCH_2C**H**), 7.04 (d, 1H, *J* = 1.5 Hz, –ArH), 7.12–7.21 (m, 2H, –ArH), 7.32 (d, 1H, *J* = 8.4 Hz, –ArH), 7.65 (d, 1H, *J* = 7.6 Hz, –ArH), 8.14 (s, 1H, –NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 39.9, 51.4, 64.7, 73.2, 76.9, 77.1, 77.4, 79.3, 111.0, 111.2, 118.6, 119.4, 122.0, 122.9, 127.4,



136.1, 172.6. FT−IR (neat, cm^{-1}): 3287, 2950, 1733, 2121, 2107, 1437, 1340, 1214, 1130, 745, 653. λ_{abs} in MeOH (nm) 281. ESI-MS (*m/z*): Calcd. for $C_{18}H_{18}N_2NaO_2$ $[M+Na]^+$ 317.12, found 317.12. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.64; H, 6.10; N, 9.58.

(*S*)-Methyl 2-(diprop-2-ynylamino)-3-(4-(prop-2-ynyloxy)phenyl)propanoate (3d):

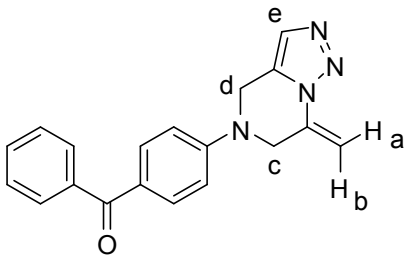


Compound (**3d**) was synthesized from methyl ester of tryptophan (0.70 g, 3.59 mmol), propargyl bromide (1.36 mL, 17.94 mmol) and K_2CO_3 (2.47 g, 17.94 mmol) in DMF (8 mL) at 25 ^oC for 20 h using the same general procedure described above. Column chromatography using ethyl acetate/hexane (10 : 90, v/v) yielded **3d** (0.78 g, 71%) as a colourless viscous liquid. $[\alpha]_D^{25.8}$ -3.1 (c 1.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 2H, H_a), 2.49 (s, 1H, H_b), 2.97 (d, 2H, J = 7.6 Hz, $-ArCH_2$), 3.54 (s, 3H, $-OCH_3$), 3.64 (d, 4H, J = 1.5 Hz, $-CH_2N$), 3.61–3.69 (m, 1H, $-ArCH_2C\mathbf{H}$), 4.63 (d, 2H, J = 2.3 Hz, $-OCH_2$), 6.86 (d, 2H, J = 8.4 Hz, –ArH), 7.10 (d, 2H, J = 8.4 Hz, –ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 39.8, 51.2, 55.7, 65.8, 72.9, 75.3, 78.5, 79.0, 114.7, 130.1, 130.2, 156.2, 171.9. FT−IR (neat, cm^{-1}): 3291, 2952, 2862, 2117, 1734, 1510, 1437, 1218, 1029, 658. λ_{abs} in MeOH (nm) 275. ESI-MS (*m/z*): Calcd. for $C_{19}H_{20}NO_3$ $[M+H]^+$ 310.14, found 310.14. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53; Found: C, 73.71; H, 5.99; N, 4.63.

General Procedure for synthesis of [1,2, 3]triazolo[1,5-a]pyrazine

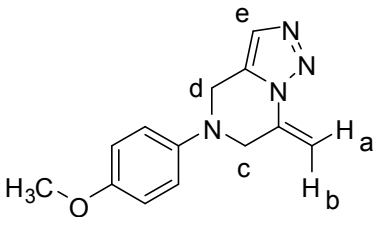
To a stirred solution of the diyene (1 equiv) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v), sodium ascorbate (40 mol%), copper sulphate pentahydrate (5 mol%), sodium azide (1.1 equiv) were added sequentially at room temperature. The reaction mixture was continued to stir at 70–80 ^oC for 24–36 h . The reaction was monitored by TLC. The volatiles were removed from the reaction mixture under reduced pressure and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and again with water (2×10 mL) and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using silica gel.

Experimental procedure and spectroscopic characterization of 2a–2g



(4-(7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)(phenyl) methanone (2a): Compound (**2a**) was prepared from (4-(diprop-2-ynylamino)phenyl) (phenyl) methanone (0.10 g, 0.36 mmol), sodium azide (0.026 g, 0.40 mmol), copper sulphate pentahydrate (0.003 g, 0.02 mmol) and sodium ascorbate (0.028 g, 0.14 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v) using the same general procedure described above. TLC (ethyl acetate/hexane, 75:25, v/v) and column chromatography using ethyl acetate/hexane (70:30, v/v) afforded **2a** (0.12 g, 86%) as a yellow solid. mp = 92–94 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (s, 2H, H_c), 4.76 (s, 2H, H_d), 5.11 (d, 1H, J = 1.6 Hz, H_b), 6.13 (d, 1H, J = 1.6 Hz, H_a), 7.00 (m, 2H, –ArH), 7.45–7.48 (m, 2H, –ArH), 7.54–7.58 (m, 1H, –ArH), 7.63 (s, 1H, H_e), 7.73–7.75 (m, 2H, –ArH), 7.81 (m, 2H, –ArH). ^{13}C (125 MHz, $CDCl_3$) δ 44.6, 50.2, 101.1, 115.0, 128.2, 129.6, 129.7, 129.8, 129.9, 131.9, 132.4, 133.7, 138.2, 151.5, 195.1. FT−IR (KBr, cm^{-1}): 2924, 2857, 1653, 1590, 1280, 1146, 701. λ_{abs} in MeOH (nm) 241, 328. ESI-MS (*m/z*): Calcd. for $C_{19}H_{17}N_4O$ $[M+H]^+$ 317.14, found 317.14. Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.03; H, 5.13; N, 17.51.

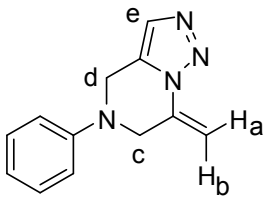
5-(4-methoxyphenyl)-7-methylene-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine (2b):



Compound (**2b**) was prepared from 4-methoxy-*N,N*-di(prop-2-ynyl)aniline (0.25 g, 1.25 mmol), sodium azide (0.09 g, 1.38 mmol), copper sulphate pentahydrate (0.01 g, 0.06 mmol) and sodium ascorbate (0.10 g, 0.5 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (25:75, v/v) yielded **2b** (0.28 g, 92%) as a yellowish orange solid, mp = 97–99 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H, $–OCH_3$), 4.13 (s, 2H, H_c), 4.48 (s, 2H, H_d), 4.98 (d, 1H, J = 1.6 Hz, H_b), 6.06 (s, 1H, H_a), 6.84 (t, 2H, J = 2.3 Hz, –ArH), 6.95 (t, 2H, J = 2.3 Hz, –ArH), 7.58 (s, 1H, H_e). ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.9, 53, 55.5, 100.2, 114.6, 119.8, 129.6, 130.8, 134.7, 142.5, 155.1. FT−IR (KBr, cm^{-1}): 2925, 1653, 1509, 1242, 1144, 1031, 903, 817. λ_{abs} in MeOH (nm) 239; ESI-MS

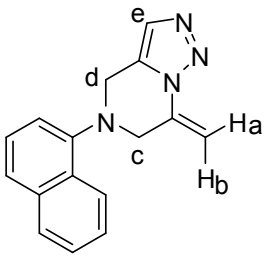
(*m/z*): Calcd. for $C_{13}H_{15}N_4O$ $[M+H]^+$ 243.12, found 243.12. Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13; Found: C, 64.33; H, 5.67; N, 23.06.

7-Methylene-5-phenyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine (2c): Compound (**2c**)



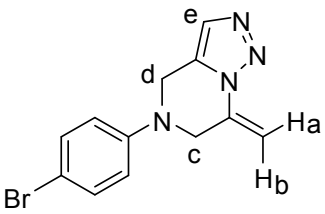
was prepared from *N,N*-di(prop-2-ynyl)aniline (0.16 mg, 0.95 mmol), sodium azide (0.07 g, 1.04 mmol), copper sulphate pentahydrate (0.007 g, 0.05 mmol) and sodium ascorbate (0.075 g, 0.38 mmol) in water/tertiary butyl alcohol (5.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (40:60, v/v) afforded **2c** (0.19 g, 94%) as a yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (s, 2H, H_c), 4.59 (s, 2H, H_d), 5.03 (s, 1H, H_b), 6.08 (s, 1H, H_a), 6.94–7.00 (m, 3H, –ArH), 7.27–7.31 (m, 2H, –ArH), 7.60 (s, 1H, H_e). ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.6, 51.7, 100.3, 117.4, 121.6, 129.4, 129.6, 130.6, 134.4, 148.5. FT−IR (film, cm^{-1}): 2926, 1667, 1599, 1221, 757, 694. λ_{abs} in MeOH (nm) 242; ESI-MS (*m/z*): for $C_{12}H_{13}N_4$ $[M+H]^+$ Calcd. 213.11, found 213.11; Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40; Found: C, 67.89; H, 5.78; N, 26.33.

7-Methylene-5-(naphthalen-1-yl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine (2d):



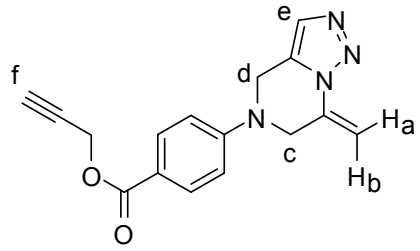
Compound (**2d**) was prepared from *N,N*-di(prop-2-ynyl)naphthalen-1-amine (0.10 g, 0.46 mmol), sodium azide (0.033 g, 0.50 mmol), copper sulphate pentahydrate (0.004 g, 0.23 mmol) and sodium ascorbate (0.036 g, 0.18 mmol) in water/tertiary butyl alcohol (5.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (75:25, v/v) yielded **2d** (0.090 g, 73%) as a pale yellow viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (s, 2H, H_c), 4.54 (s, 2H, H_d), 4.96 (s, 1H, H_b), 6.11 (s, 1H, H_a), 7.11 (d, 1H, J = 6.30 Hz, –ArH), 7.38 (t, 1H, J = 7.65 Hz, –ArH), 7.49–7.55 (m, 2H, –ArH), 7.61 (s, 1H, H_e), 7.64 (d, 1H, J = 8.4 Hz, –ArH), 7.85–7.88 (m, 1H, –ArH), 8.14–8.17 (m, 1H, –ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.9, 54.6, 99.9, 115.6, 122.9, 125.1, 125.5, 126.2, 126.3, 128.6, 129.5, 131.4, 134.7, 135.3, 146.3. FT−IR (film, cm^{-1}): 2924, 2862, 1647, 1538, 1048, 668. λ_{abs} in MeOH (nm) 289; ESI-MS (*m/z*): Calcd. for $C_{16}H_{15}N_4$ $[M+H]^+$ 263.13, found 263.13. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.46; H, 5.33; N, 21.21.

5-(4-Bromophenyl)-7-methylene-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine (2e):



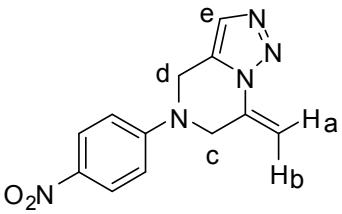
Compound (**2e**) was prepared from 4-bromo-*N,N*-di(prop-2-ynyl)aniline (0.11 g, 0.44 mmol), sodium azide (0.03 g, 0.48 mmol), copper sulphate pentahydrate (0.003 g, 0.02 mmol) and sodium ascorbate (0.036 g, 0.18 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (70:30, v/v) to afforded **2e** (0.09 g, 68%) as a yellow solid. mp = 113−115 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (s, 2H, H_c), 4.57 (s, 2H, H_d), 5.03 (d, 1H, J = 1.3 Hz, H_b), 6.09 (d, 1H, J = 1.3 Hz, H_a), 6.86 (d, 2H, J = 9.0 Hz, –ArH), 7.38 (d, 2H, J = 9.0 Hz, –ArH), 7.59 (s, 1H, H_e). ^{13}C (125 MHz, $CDCl_3$) δ 45.6, 51.7, 100.7, 114.2, 119.0, 129.8, 130.2, 132.4, 134.1, 147.5. FT−IR (KBr, cm^{-1}): 2929, 1658, 1493, 1221, 984, 825. λ_{abs} in MeOH (nm) 250. ESI-MS (*m/z*): Calcd. for $C_{12}H_{12}BrN_4$ $[M+H]^+$ 291.02, found 291.02; Anal. Calcd for $C_{12}H_{11}BrN_4$: C, 49.50; H, 3.81; N, 19.24; Found: C, 49.54; H, 3.93; N, 19.02.

Prop-2-ynyl 4-(7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)benzoate (2f):



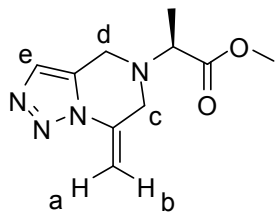
Compound (**2f**) was prepared from 4-(diprop-2-ynylamino)benzoic acid (0.13 g, 0.52 mmol), sodium azide (0.037 g, 0.57 mmol), copper sulphate pentahydrate (0.005 g, 0.03 mmol) and sodium ascorbate (0.041 g, 0.21 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v) using the same general procedure described above. TLC (ethyl acetate/hexane, 50/50) and column chromatography using ethyl acetate/hexane (50:50, v/v) afforded **2f** (0.135 g, 89%) as a pale yellow solid. mp = 125−127 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (d, 1H, J = 2.28 Hz, H_f), 4.37 (s, 2H, H_c), 4.73 (s, 2H, H_d), 4.88 (d, 2H, J = 1.52 Hz, –$COOCH_2$), 5.10 (s, 1H, H_b), 6.11 (s,1H, H_a), 6.96 (d, 2H, J = 10.5 Hz, –ArH), 7.63 (s, 1H, H_e), 7.99 (d, 2H, J = 10.5 Hz, –ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.5, 50.2, 52.2, 74.8, 77.9, 101.1, 115.2, 121.3, 129.8, 129.9, 131.7, 133.7, 152.1, 165.3. FT−IR (KBr, cm^{-1}): 3288, 2929, 1705, 1605, 1538, 1390, 1227, 827, 668. λ_{abs} in MeOH (nm) 290. ESI-MS (*m/z*): Calcd. for $C_{16}H_{15}N_4O_2$ $[M+H]^+$ 295.12, found 295.12. Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; Found: C, 65.38; H, 4.57; N, 18.88.

7-Methylene-5-(4-nitrophenyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine (2g):

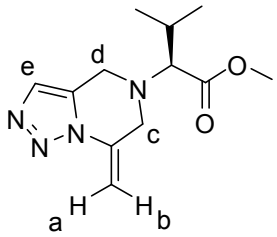


Compound (**2g**) was prepared from 4-nitro-*N,N*-di(prop-2-ynyl)aniline (0.08 g, 0.37mmol), sodium azide (0.027 g, 0.41 mmol), copper sulphate pentahydrate (0.003 g, 0.02 mmol) and sodium ascorbate (0.03 g, 0.15 mmol) in water/tertiary butyl alcohol (4.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (50:50, v/v) yielded **2g** (0.063 g, 66%) as a deep yellow solid. mp = 200–202 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (s, 2H, H_c), 4.81 (s, 2H, H_d), 5.16 (s, 1H, H_b), 6.15 (s, 1H, H_a), 6.97 (d, 2H, J = 9.5 Hz, –ArH), 7.65 (s, 1H, H_e), 8.17 (d, 2H, J = 9.5 Hz, –ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.3, 49.8, 101.7, 114.6, 125.9, 129.4, 129.9, 133.2, 140.6, 152.8. FT−IR (KBr, cm^{-1}): 2924, 2853, 1595, 1494, 1330, 1230, 1115, 832. λ_{abs} in MeOH (nm) 354. ESI-MS (*m/z*): Calcd. for $C_{12}H_{12}N_5O_2$ $[M+H]^+$ 258.09, found 258.09. Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22; Found: C, 55.83; H, 4.21; N, 27.08.

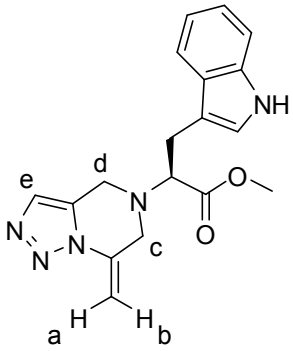
Experimental procedures and spectroscopic characterization of 4a-4d



(*S*)-Methyl 2-(7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)propanoate (4a): Compound (**4a**) was prepared from **3a** (0.13 g, 0.73 mmol), sodium azide (0.05 g, 0.80 mmol), copper sulphate pentahydrate (0.006 g, 0.040 mmol) and sodium ascorbate (0.063 g, 0.31 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (25:75, v/v) yielded **4a** (0.13 g, 79%) as a colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, 3H, J = 7.25 Hz, $–CH_3$), 3.52–3.56 (m, 1H, –C**H**CH_3), 3.59–3.62 (d, 1H, J = 14.15 Hz, H_c), 3.69–3.72 (m, 1H, J = 14.15 Hz, H_c), 3.70 (s, 3H, $–OCH_3$), 3.98 – 4.08 (m, 2H, H_d), 4.87 (d, 1H, J = 1.3 Hz, H_b), 5.95 (s, 1H, H_a), 7.47 (s, 1H, H_e). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 44.2, 50.6, 51.7, 60.4, 99.4, 129.4, 131.1, 135.0, 172.5. FT−IR (film, cm^{-1}): 2986, 2946, 1735, 1440, 1239, 1200, 1163, 986, 873. ESI-MS (*m/z*): Calcd. for $C_{10}H_{15}N_4O_2$ $[M+H]^+$ 223.12, found 223.12. Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21; Found: C, 54.14; H, 6.14; N, 25.31.

(*S*)-Methyl-3-methyl-2-(7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)butanoate (4b): 

Compound (**4b**) was prepared from **3b** (0.34 g, 1.64 mmol), sodium azide (0.12 g, 1.82 mmol), copper sulphate pentahydrate (0.013 g, 0.08 mmol) and sodium ascorbate (0.13 g, 0.66 mmol) in water/tertiary butyl alcohol (8.0 mL, 1:1, v/v)using the same general procedure described above. Column chromatography using ethyl acetate/hexane (35:65, v/v) afforded **4b** (0.34 g, 85%) as a yellowish orange liquid. $[\alpha]_D^{25.8}$ –44.80 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, 3H, –CHCH(C**H**$_3$)$_2$), 0.97 (d, 3H, –CHCH(C**H**$_3$)$_2$), 2.09–2.14 (m, 1H, –CHC**H**(CH$_3$)$_2$), 2.96–3.00 (m, 1H, –C**H**CH(CH$_3$)$_2$), 3.48 (d, 1H, *J* = 14.1 Hz, H$_c$), 3.64 (d, 1H, *J* = 14.1 Hz, H$_c$), 3.70 (s, 3H, –OCH$_3$), 3.94 (s, 2H, H$_d$), 4.88 (d, 1H, *J* = 1.3 Hz, H$_b$), 5.96 (d, 1H, *J* = 0.95 Hz, H$_a$), 7.49 (s, 1H, H$_e$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.5, 27.3, 44.8, 50.8, 51.2, 72.8, 99.1, 129.4, 131.6, 135.4, 171.4. FT−IR (fim, cm^{-1}): 3282, 2929, 1734, 1647, 1448, 1152, 1004, 668. λ_{abs} in MeOH (nm) 284. ESI-MS (*m/z*): Calcd. for $C_{12}H_{19}N_4O_2$ $[M+H]^+$ 251.15, found 251.15. Anal. Calcd for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38; Found: C, 57.38; H, 7.34; N, 22.08.

(*S*)-Methyl-3-(1H-indol-3-yl)-2-(7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)propanoate (4c): 

Compound (**4c**) was prepared from **3c** (0.31 g, 1.05 mmol), sodium azide (0.08 g, 1.18 mmol), copper sulphate pentahydrate (0.008 g, 0.05 mmol) and sodium ascorbate (0.08 g, 0.42 mmol) in water/tertiary butyl alcohol (8.0 mL, 1:1, v/v) using the same general procedure described above. TLC (ethyl acetate/hexane, 40:60 v/v) and column chromatography using ethyl acetate/hexane (40:60, v/v) yielded **4c** (0.26 g, 74%) as a colourless viscous liquid. $[\alpha]_D^{25.8}$ –7.42 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13–3.18 (m, 1H, –ArCH$_2$), 3.33–3.39 (m, 1H, –ArCH$_2$), 3.59–3.64 (m, 1H, H$_c$), 3.63 (s, 3H, –OCH$_3$), 3.67–3.70 (m, 1H, H$_c$), 3.78–3.82 (m, 1H, –ArCH$_2$C**H**), 4.06 (d, 1H, *J* = 15.2 Hz, H$_d$), 4.15 (d, 1H, *J* = 15.2 Hz, H$_d$), 4.91 (s, 1H, H$_b$), 6.02 (s, 1H, H$_a$), 7.02 (d, 1H, *J* = 2.3 Hz, –ArH), 7.10–7.14 (m, 1H, –ArH), 7.17–7.20 (m, 1H, –ArH), 7.35 (d, 1H, *J* = 7.6 Hz, –ArH), 7.49 (s, 1H, H$_e$), 7.57 (d, 1H, *J* = 7.6 Hz, –ArH), 8.07 (s, 1H, –NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 45.0, 51.1, 51.7,

66.6, 99.6, 111.0, 111.4, 118.4, 119.7, 122.3, 122.8, 127.2, 129.6, 131.5, 135.3, 136.1, 171.7. FT−IR (neat, cm^{-1}): 3293, 2924, 2857, 1723, 1441, 1339, 1236, 1167, 743. λ_{abs} in MeOH (nm) 324. ESI-MS (*m/z*): Calcd. for $C_{18}H_{20}N_5O_2$ $[M+H]^+$ 338.16, found 338.16. Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76; Found: C, 63.85; H, 5.78; N, 20.66.

(*S*)-Methyl 2-(7-methylene-6,7-dihydro-[1,2,3]triazolo[1,5a]pyrazin-5(4H)-yl)-3-(4-(prop-2-ynyloxy)phenyl)propanoate (4d): Compound (**4d**) was prepared from **3d** (0.35 g, 1.13 mmol), sodium azide (0.08 g, 1.24 mmol), copper sulphate pentahydrate (0.009 g, 0.05 mmol) and sodium ascorbate (0.089 g, 0.45 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v) using the same general procedure described above. Column chromatography using ethyl acetate/hexane (35:65, v/v) afforded **4d** (0.27 g, 67 %) as colourless viscous liquid. $[\alpha]_D^{25.8}$ −17.46 (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (t, 1H, *J* = 2.2 Hz, H_f), 2.93–2.99 (m, 1H, $-ArCH_2$), 3.07–3.11 (m, 1H, $-ArCH_2$), 3.56–3.60 (m, 1H, H_c), 3.62 (s, 3H, $-OCH_3$), 3.64–3.67 (m, 1H, H_c), 3.74–3.77 (m, 1H, $-ArCH_2C\mathbf{H}$), 4.0 (d, 1H, *J* = 15.5 Hz, H_d), 4.10 (d, 1H, *J* = 15.5 Hz, H_d), 4.65 (d, 2H, *J* = 2.2 Hz, $-OCH_2-$), 4.91 (s, 1H, H_b), 5.99 (s, 1H, H_a), 6.88 (d, 2H, *J* = 8.5 Hz, –ArH), 7.09 (d, 2H, *J* = 8.5 Hz, –ArH), 7.49 (s, 1H, H_e). ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.0, 45.0, 50.9, 51.5, 55.8, 67.8, 75.5, 78.5, 99.5, 115.0, 129.4, 129.8, 130.0, 131.2, 135.0, 156.4, 171.1. FT−IR (neat, cm^{-1}): 3285, 2923, 2851, 2119, 1732, 1673, 1608, 1511, 1219, 1023, 826. λ_{abs} in MeOH (nm) 223. ESI-MS (*m/z*): Calcd. for $C_{19}H_{21}N_4O_3$ $[M+H]^+$ 353.16, found 353.16. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90; Found: C, 64.66; H, 5.49; N, 15.93.

Experimental procedures and spectroscopic characterization of 5a–b

N,N-Di(but-2-ynyl)-4-methoxyaniline (5a): p-Anisidine (0.50 g, 4.07 mmol), K_2CO_3 (2.81 g, 20.33 mmol) in DMF (5 mL) was stirred for 30 min at 25 °C. 1-Bromobut-2-yne (1.08 mL, 12.21 mmol) was added drop wise to the reaction mixture, and the mixture was stirred at 25 ^oC for 12 h. The reaction was monitored by TLC. The volatiles of the reaction mixture were removed under reduced pressure and extracted with EtOAc (2 × 10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and again with water (2×10 mL), separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Column chromatography using ethyl acetate/hexane (10:90, v/v) yielded **5a** (0.88 g, 95%) as a colourless liquid. mp 73–74 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 1.81(s, 6H, ≡CC**H**$_3$), 3.77 (s, 3H, –OCH_3), 3.97 (s, 4H, –CH_2N), 6.84 (d, 2H, *J* = 9.16 Hz, –ArH), 6.98 (d, 2H, , *J* = 9.16 Hz, –ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 41.8, 55.5, 74.4, 80.5, 114.3, 119.0, 153.9. FT−IR (KBr, cm^{-1}): 2919, 1508, 1440, 1240, 1029, 914, 818, 707. λ_{abs} in MeOH (nm) 254; ESI-MS (*m/z*): for $C_{15}H_{17}NO$ $[M+H]^+$ Calcd. 228.14, found 228.10; Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; O, 7.04; Found: C, 79.50; H, 7.21; N, 6.26; O, 7.11.

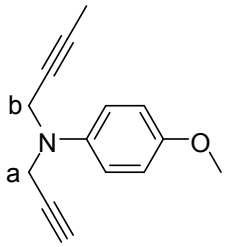
4-Methoxy-N,N-di(pent-2-ynyl)aniline (5b): p-Anisidine (0.50 g, 4.07 mmol), K_2CO_3 (2.81 g, 20.33 mmol) in DMF (5 mL) was stirred for 30 min at 25 °C. 1-Bromopent-2-yne (1.28 mL, 12.21 mmol) was added drop wise to the reaction mixture, and the mixture was stirred at 25 ^oC for 12 h. The reaction was monitored by TLC. The volatiles of the reaction mixture were removed under reduced pressure and extracted with EtOAc (2 × 10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and again with water (2×10 mL), separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Column chromatography using ethyl acetate/hexane (5:95, v/v) yielded **5b** (0.93 g, 90%) as a colourless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, 6H, *J* = 7.64 Hz, –CH_2C**H**$_3$), 2.18 (m, 4H, –C**H**$_2CH_3$), 3.76 (s, 3H, –OCH_3), 3.98 (s, 4H, –CH_2N), 6.83 (d, 2H, *J* = 9.16 Hz, –ArH), 6.97 (d, 2H, *J* = 9.16 Hz, –ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 13.9, 41.7, 55.39, 74.6, 86.3, 114.1, 119.0, 142.8, 153.8. FT−IR (film, cm^{-1}): 2975, 2936, 1509, 1441, 1317, 1241, 1044, 910, 819, 707. λ_{abs} in

MeOH (nm) 246; ESI-MS (*m/z*): for $C_{17}H_{21}NO$ $[M+H]^+$ Calcd. 256.17, found 256.12; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49; O, 6.27; Found: C, 79.80; H, 8.56; N, 5.39; O, 6.07.

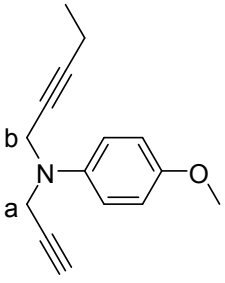
Experimental procedures and spectroscopic characterization of 7a–b, 8a–b

The monopropargyl compound **6** was synthesized based on the literature procedure and the spectral data were in well agreement with the reported ones.[2]

4-methoxy-N-(but-2-ynyl)-N-(prop-2-ynyl)aniline (7a): 4-methoxy-N-(prop-2-ynyl)aniline (0.20 g, 1.24 mmol), K_2CO_3 (0.42 g, 3.10 mmol) in DMF (5 mL) was stirred for 30 min at 25 °C. 1-Bromobut-2-yne (0.11 mL, 1.24 mmol) was added dropwise to the reaction mixture and it was continued to stirring at 25 °C for 12 h (the reaction was monitored by TLC). The volatiles of the reaction mixture were removed under reduced pressure and extracted with EtOAc (2×10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and water (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. TLC (ethyl acetate/hexane, 15/85, v/v) and column chromatography using ethyl acetate/hexane (10:90, v/v) yielded **7a** (0.25 g, 95%) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H, ≡CC**H**$_3$), 2.26 (t, 1H, *J* = 2.28 Hz, ≡CH), 3.75 (s, 3H, –OCH_3), 3.98 (s, 2H, H_b), 2.26 (d, 2H, *J* = 2.32 Hz, H_a), 6.85 (d, 2H, *J* = 9.16 Hz, –ArH), 6.97 (d, 2H, *J* = 9.16 Hz, –ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.3, 41.11, 41.14, 55.1, 72.5, 74.3, 79.3, 80.3, 114.1, 118.6, 142.2, 153.7. FT−IR (film, cm^{-1}): 2922, 1730, 1514, 1443, 1364, 1289, 1240, 1214, 1185, 1157, 1131, 1024, 912, 829. λ_{abs} in MeOH (nm) 246; ESI-MS (*m/z*): for $C_{14}H_{15}NO$ $[M+H]^+$ Calcd. 214.12, found 214.06; Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57; O, 7.50; Found: C, 78.72; H, 7.11; N, 6.49; O, 7.30.

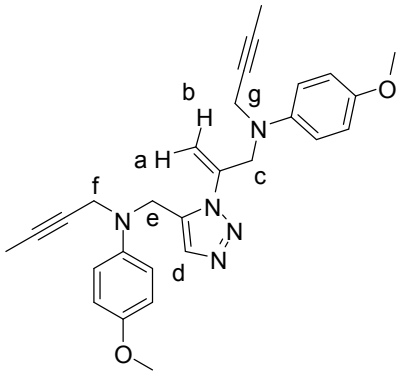


4-methoxy-N-(pent-2-ynyl)-N-(prop-2-ynyl)aniline (7b): 4-methoxy-N-(prop-2-ynyl)aniline (0.20 g, 1.24 mmol), K_2CO_3 (0.42 g, 3.10 mmol) in DMF (5 mL) was stirred for 30 min at 25 °C. 1-Bromopent-2-yne (0.13 mL, 1.24 mmol) was added dropwise to the reaction mixture and it was continued to stirring at 25 °C for 12 h (the reaction was monitored by TLC). The volatiles of the reaction



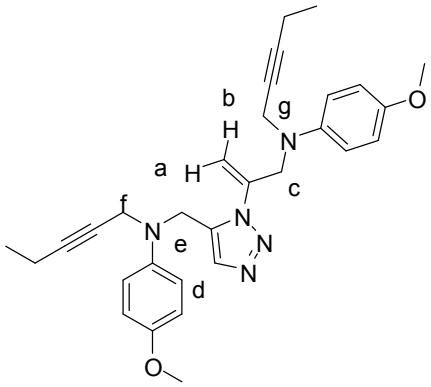
mixture were removed under reduced pressure and extracted with EtOAc (2×10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and water (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. TLC (ethyl acetate/hexane, 10/90, v/v) and column chromatography using ethyl acetate/hexane (5:95, v/v) yielded 7b (0.25 g, 90%) as a colourless liquid. . ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H, –$CH_2C\mathbf{H_3}$), 2.19 (m, 2H, –$C\mathbf{H}_2CH_3$), 2.23 (t, 1H, ≡CH), 3.77 (s, 3H, –OCH_3), 3.98 (s, 2H, H_b), 4.04 (d, 2H, J = 2.28 Hz), 6.85 (d, 2H, J = 9.16 Hz, –ArH), 6.97 (d, 2H, J = 9.16 Hz, –ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 13.8, 41.3, 41.7, 55.4, 72.5, 74.5, 79.4, 86.5, 114.2, 119.0, 142.5, 153.9. FT−IR (film, cm^{-1}): 3284, 2922, 2851, 1510, 1462, 1442, 1243, 1045, 1030, 820, 647. λ_{abs} in MeOH (nm) 250; ESI-MS (*m/z*): for $C_{15}H_{17}NO$ $[M+H]^+$ Calcd. 228.14, found 228.08; Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; O, 7.04; Found: C, 79.39; H, 7.26; N, 6.21; O, 7.09.

N-(but-2-ynyl)-N-(2-(5-((but-2-ynyl(4-methoxyphenyl)amino)methyl)-1H-1,2,3-triazol-1-yl)allyl)-4-methoxyaniline (8a): To a stirred solution of 4-methoxy-N-(but-2-ynyl)-N-(prop-2-ynyl)aniline (0.20 g, 0.94 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v), sodium ascorbate (0.074 g, 0.38 mmol), copper sulphate pentahydrate (0.012 g, 0.05 mol) and sodium azide (0.07g ,1.0 mmol) were added sequentially at room temperature. The reaction mixture was continued to stir at 80 ^{o}C for 24 h. The reaction was monitored by TLC. The volatiles were removed from the reaction mixture under reduced pressure and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and again with water (2×10 mL) and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. . TLC (ethyl acetate/hexane, 75:25, v/v) and column chromatography using ethyl acetate/hexane (70:30, v/v) afforded **8a** (0.02 g, 6%) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 6H, –OCH_3), 3.76 (s, 6H, ≡CCH_3), 3.90 (s, 2H, $H_{f/g}$) 3.94 (s, 2H, $H_{f/g}$) 4.42 (s, 2H, H_c), 4.60 (s, 2H, H_e), 5.21 (s, 1H, H_b), 5.53 (s, 1H, H_a), 6.81–6.92 (m, 8H, –ArH), 7.69 (s, 1H, H_d). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6, 41.3, 42.0, 47.7, 53.7, 55.6, 76.6, 76.7, 80.6, 105.8, 114.49, 114.53, 117.0, 117.5, 120.6, 139.6, 142.6, 145.7, 153.3. FT−IR (film, cm^{-1}): 2920, 2852, 1658, 1511, 1441, 1243, 1038, 944, 818.



λ_{abs} in MeOH (nm) 250; ESI-MS (*m/z*): for $C_{28}H_{31}N_5O_2$ $[M+Na]^+$ Calcd 492.24, found 492.25; Anal. Calcd for $C_{28}H_{31}N_5O_2$: C, 71.62; H, 6.65; N, 14.91; O, 6.81; Found: C, 71.52; H, 6.61; N, 14.90; O, 6.75.

4-methoxy-N-(2-(5-(((4-methoxyphenyl)(pent-2-ynyl)amino)methyl)-1H-1,2,3-triazol-1-yl)allyl)-N-(pent-2-ynyl)aniline (8b): To a stirred solution of 4-methoxy-N-(pent-2-ynyl)-N-(prop-2-ynyl)aniline (0.20 g, 0.88 mmol) in water/tertiary butyl alcohol (6.0 mL, 1:1, v/v), sodium ascorbate (0.069 g, 0.35 mmol), copper sulphate pentahydrate (0.011 g, 0.04 mol) and sodium azide (0.07 g ,1.0 mmol) were added sequentially at room temperature. The reaction mixture was continued to stir at 80 ^oC for 24 h. The reaction was monitored by TLC. The volatiles were removed from the reaction mixture under reduced pressure and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with water (10 mL), brine (2×10 mL) and again with water (2×10 mL) and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. . TLC (ethyl acetate/hexane, 70:35, v/v) and column chromatography using ethyl acetate/hexane (65:35, v/v) afforded **8b** (0.02 g, 4%) as a colourless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.01–1.06 (m, 6H, $-CH_2C\mathbf{H}_3$), 2.07–2.13 (m, 4H, $-C\mathbf{H}_2CH_3$), 3.87 (s, 2H, $H_{f/g}$), 3.90 (s, 2H, $H_{f/g}$), 4.38 (s, 2H, H_c), 4.55 (s, 2H, H_e), 5.16 (s, 1H, H_b), 5.47 (s, 1H, H_a), 6.77–6.80 (m, 8H, -ArH), 7.63 (s, 1H, H_d). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.0, 41.4, 42.1, 47.7, 53.7, 55.6, 74.4, 74.8, 86.6, 86.7, 105.8, 114.47, 114.51, 117.1, 117.6, 120.6, 139.6, 142.6, 145.9, 153.2, 153.3. FT−IR (film, cm^{-1}): 2934, 2833, 1658, 1509, 1440, 1317, 1239, 1036, 934, 813. λ_{abs} in MeOH (nm) 270; ESI-MS (*m/z*): for $C_{30}H_{35}N_5O_2$ $[M+H]^+$ Calcd. 498.28, found 498.12; Anal. Calcd for $C_{30}H_{35}N_5O_2$: C, 72.41; H, 7.09; N, 14.07; O, 6.43; Found: C, 72.35; H, 7.11; N, 14.14; O, 6.51.



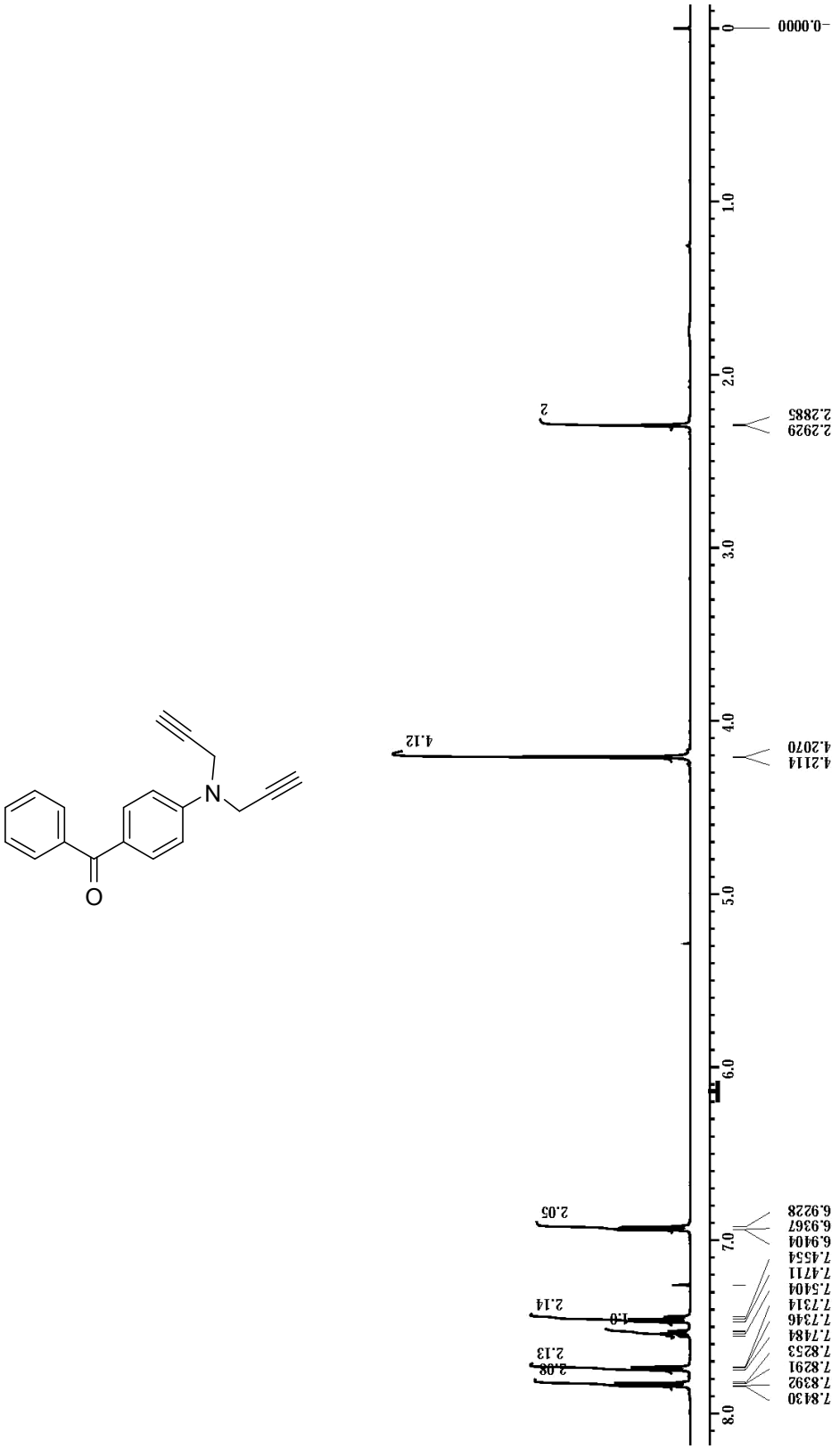


Figure S1. ^{1}H NMR spectrum of **1a**

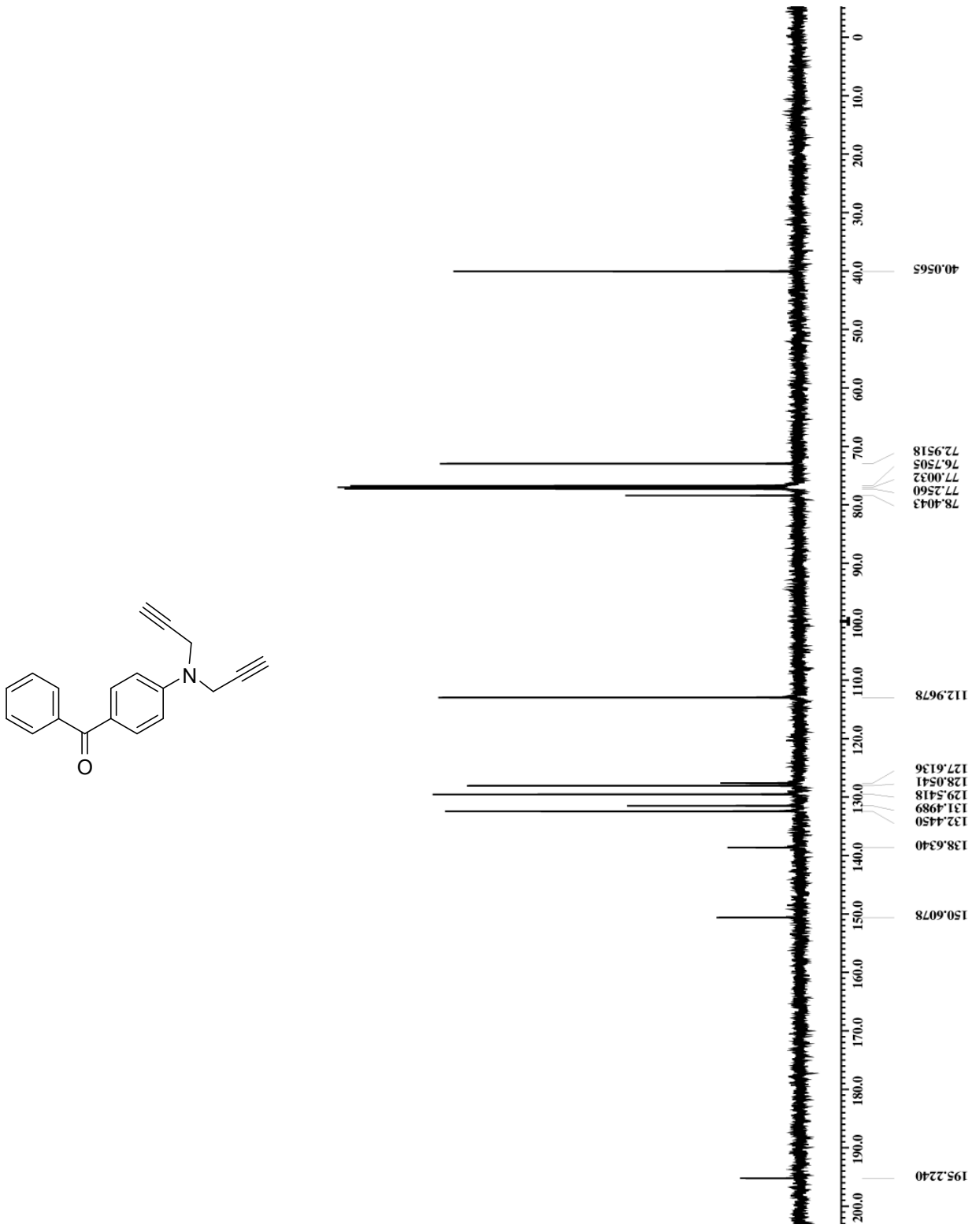


Figure S2. ^{13}C NMR spectrum of **1a**

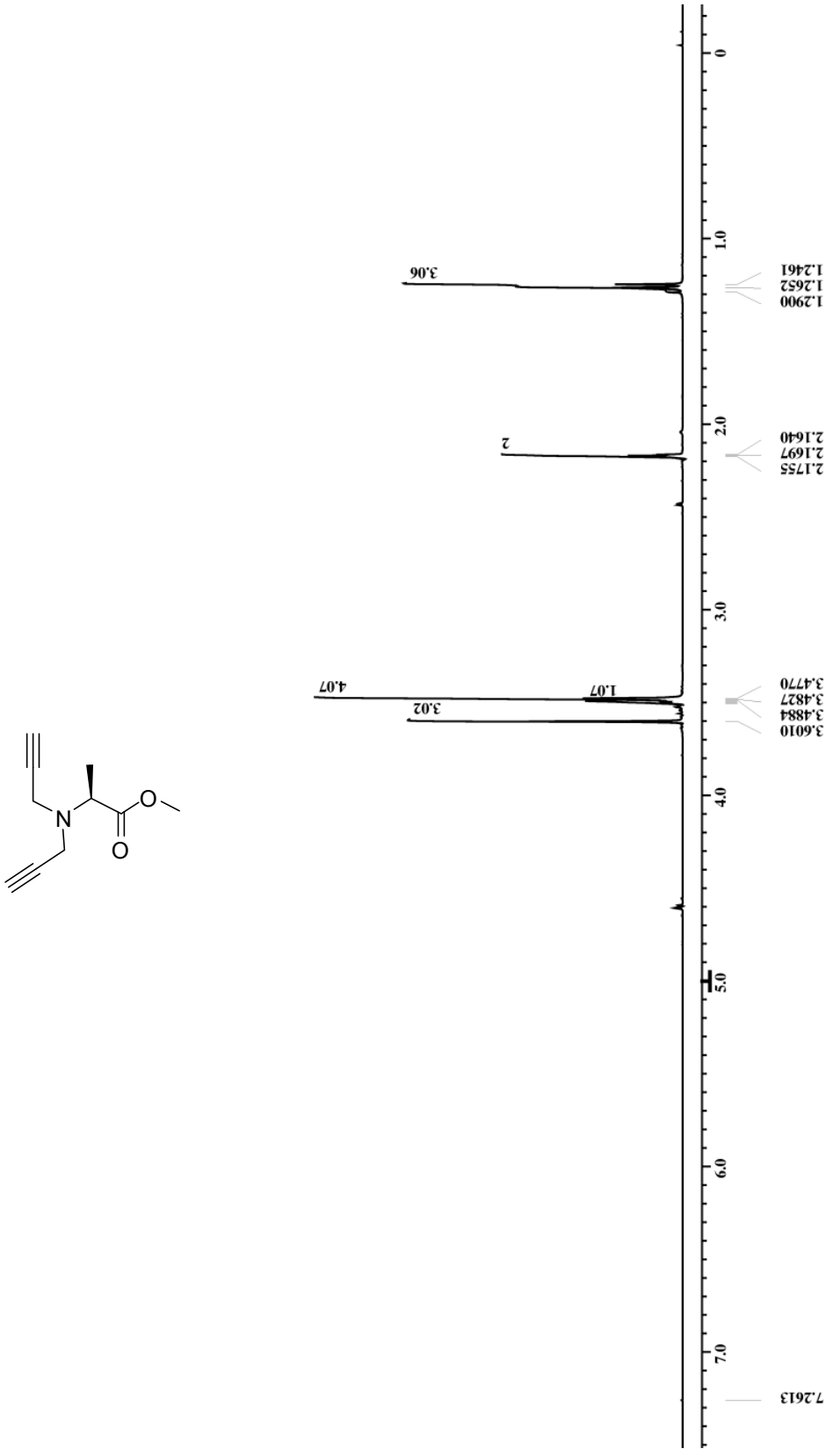


Figure S3. ^{1}H NMR spectrum of **3a**

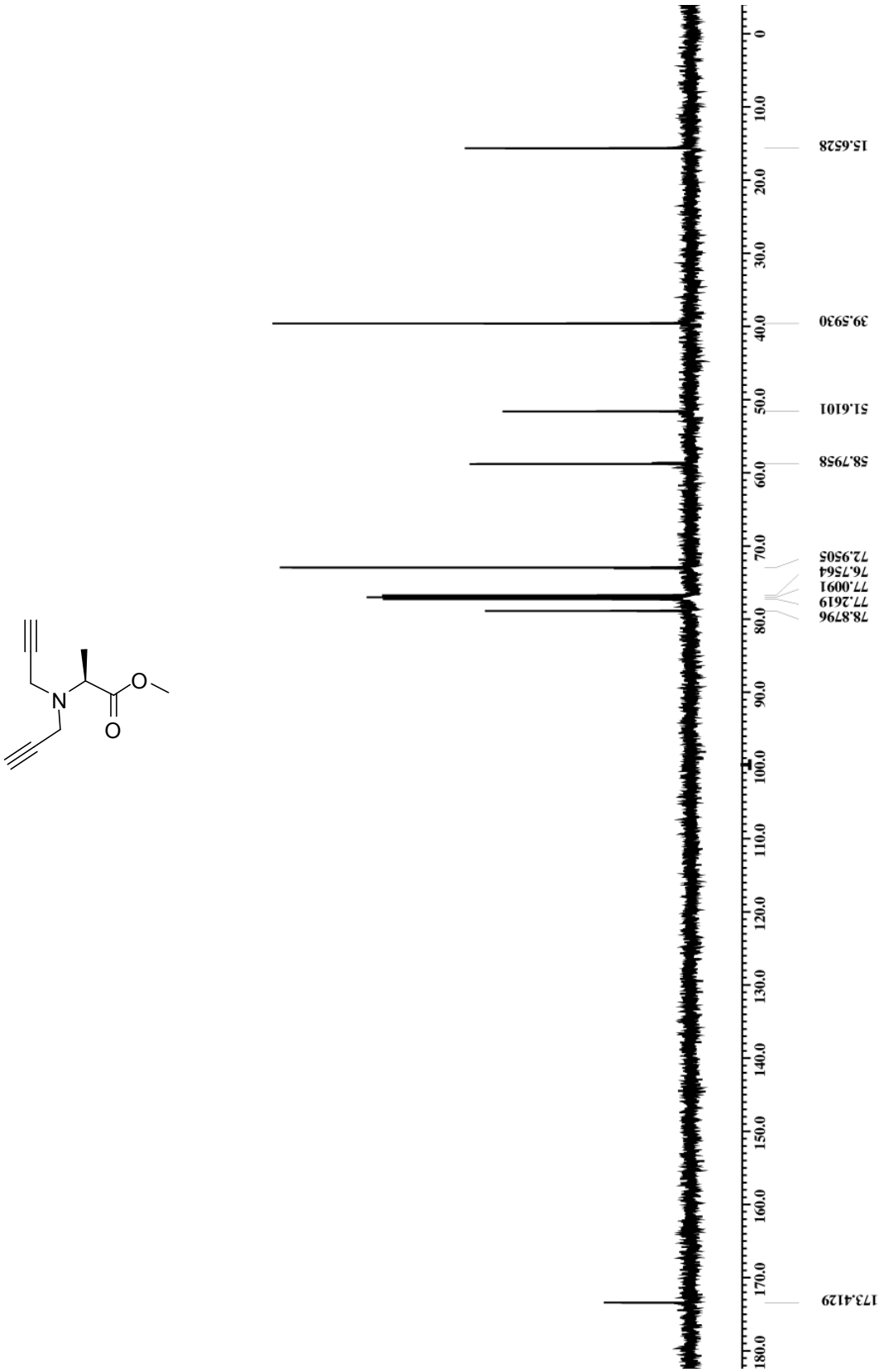


Figure S4. ^{13}C NMR spectrum of **3a**

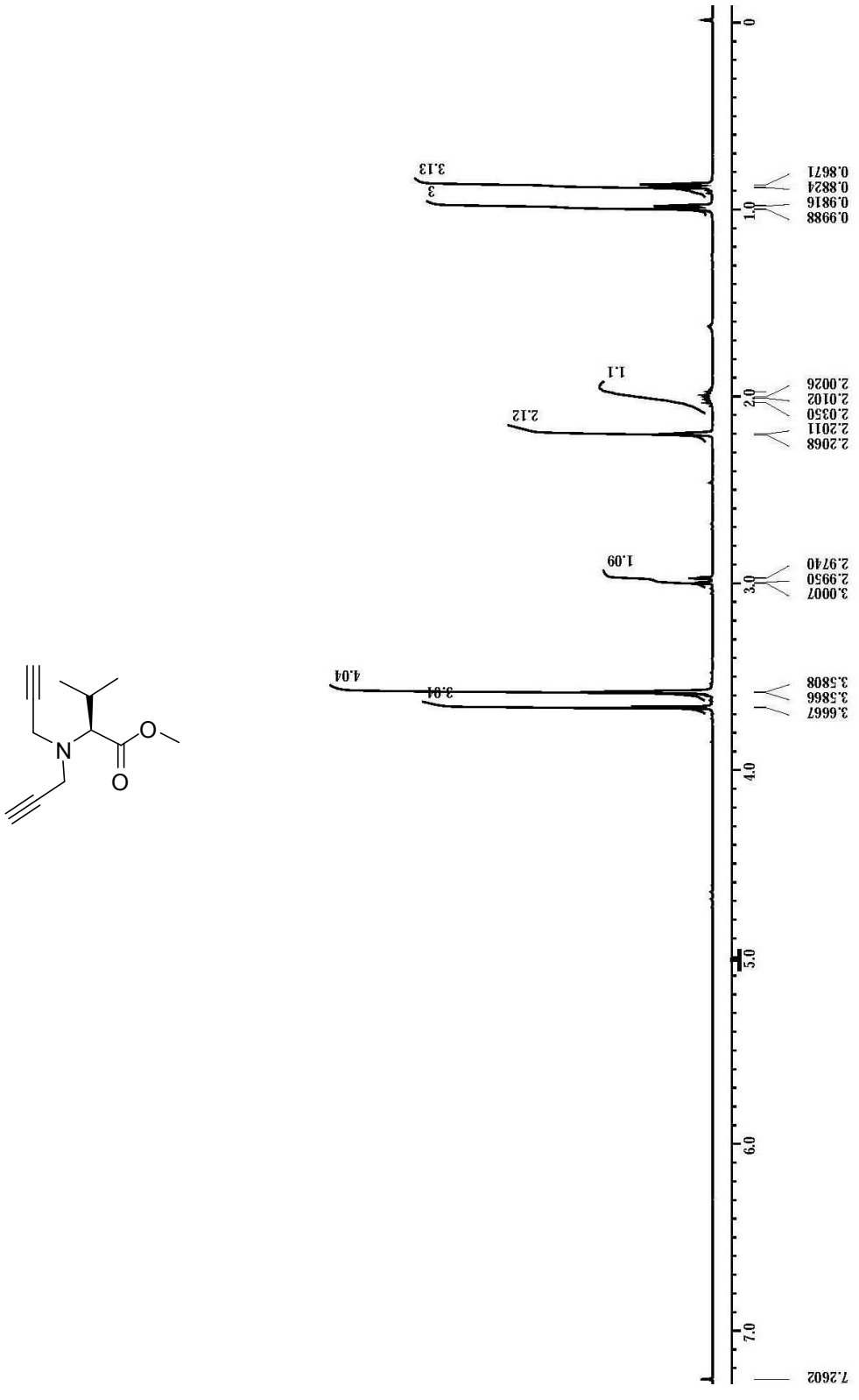


Figure S5. ^{1}H NMR spectrum of **3b**

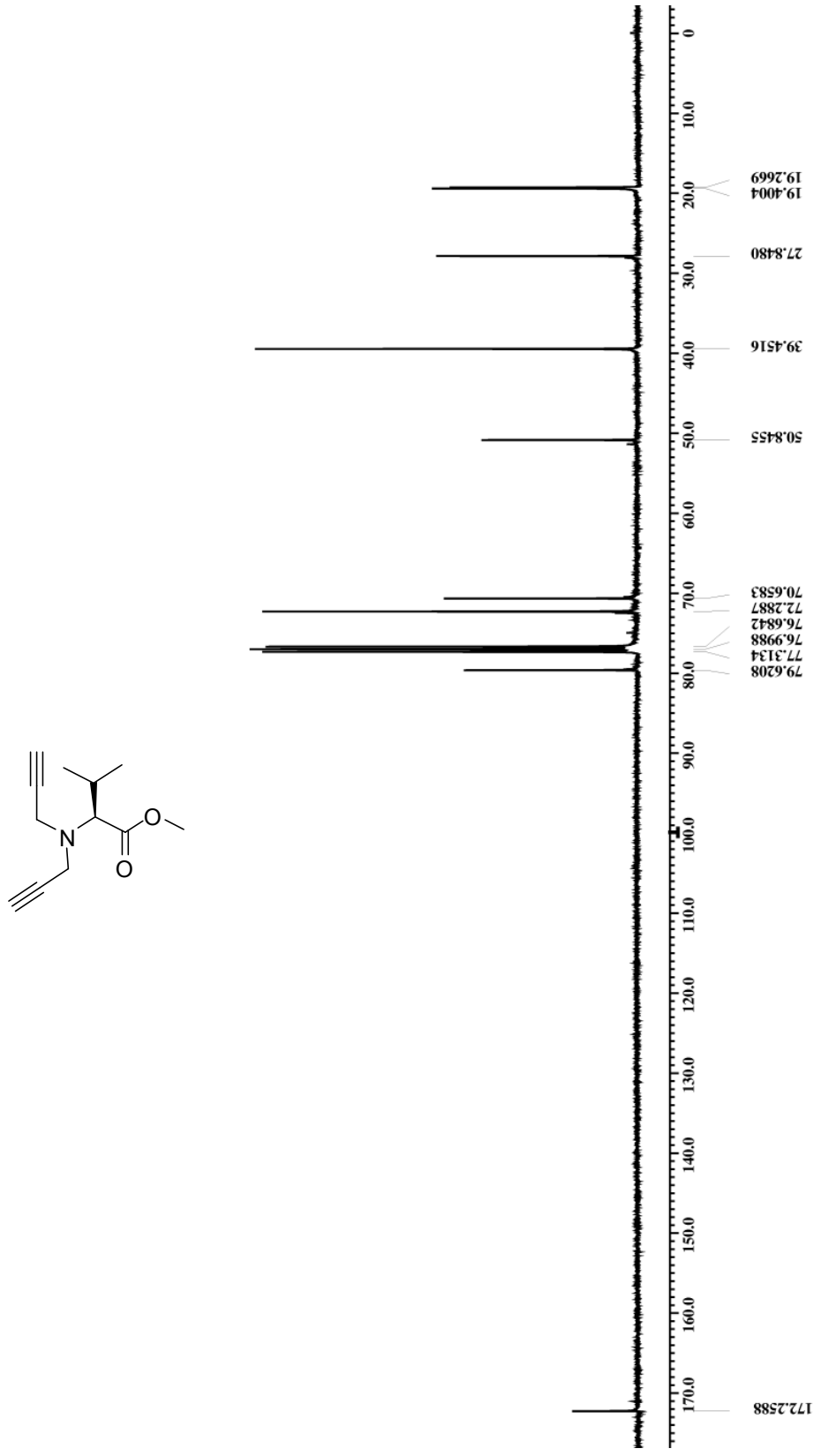


Figure S6. ^{13}C NMR spectrum of **3b**

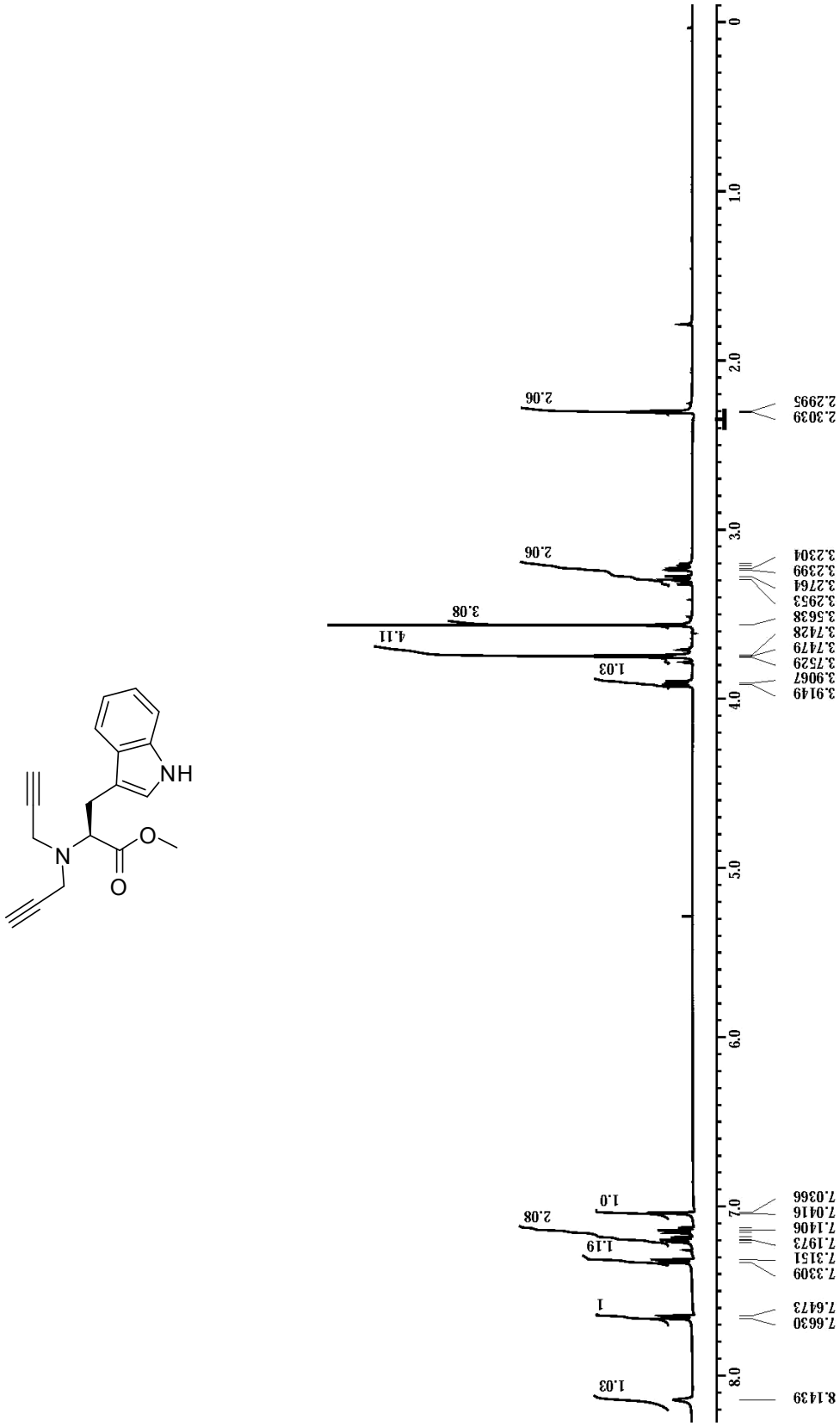


Figure S7. ^{1}H NMR spectrum of **3c**

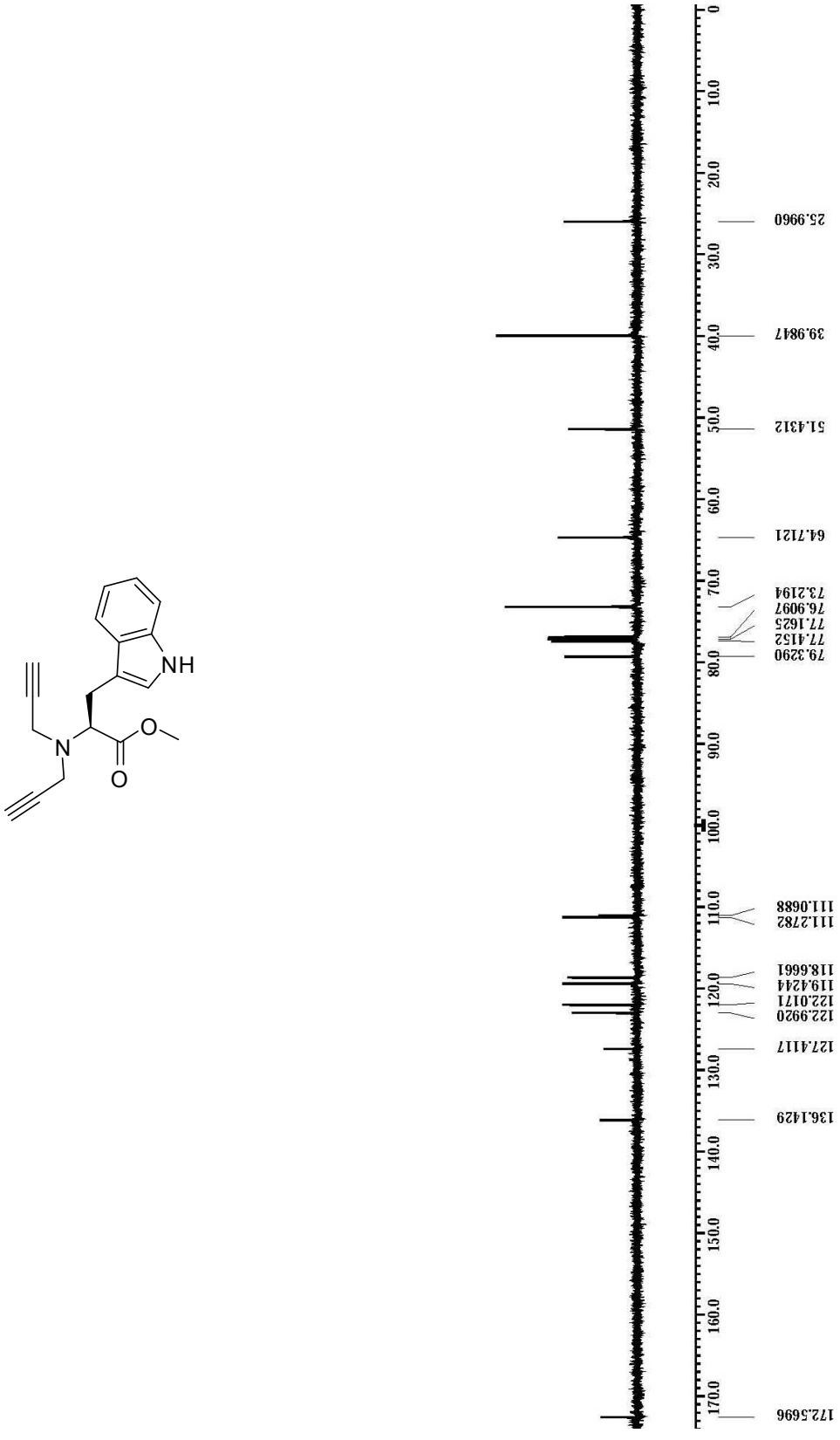


Figure S8. ^{13}C NMR spectrum of **3c**

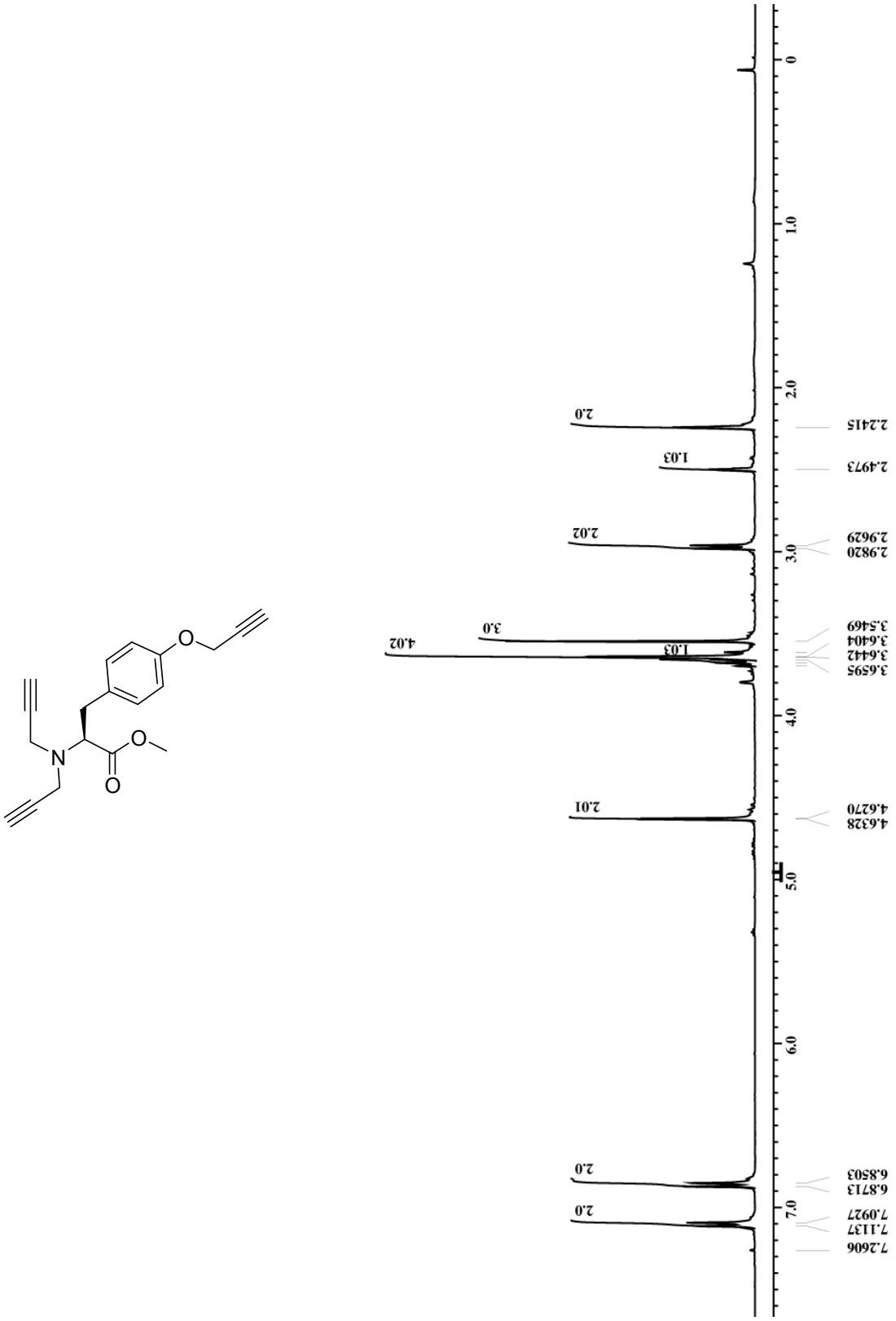


Figure S9. ^{1}H NMR spectrum of **3d**

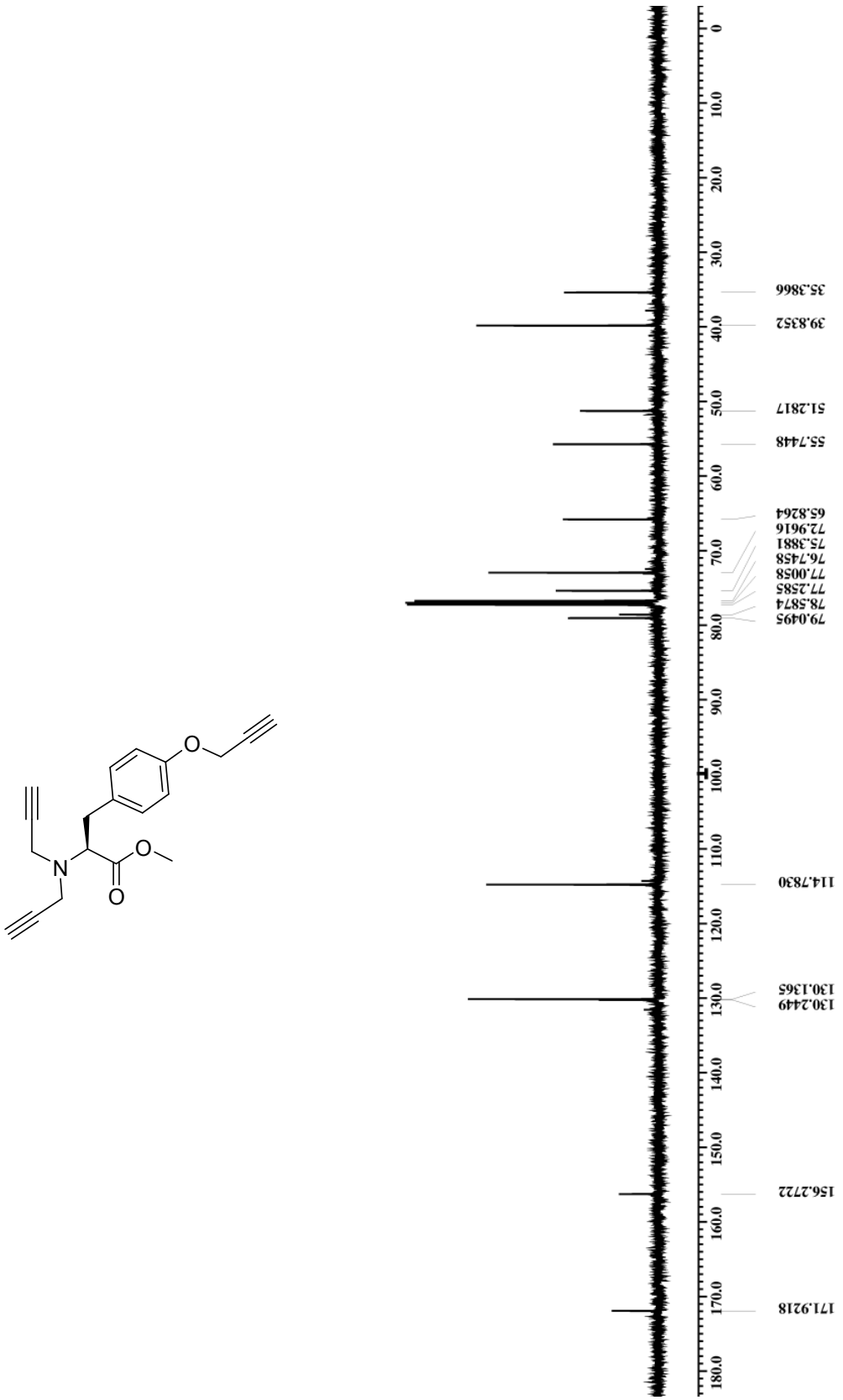


Figure S10. ^{13}C NMR spectrum of **3d**

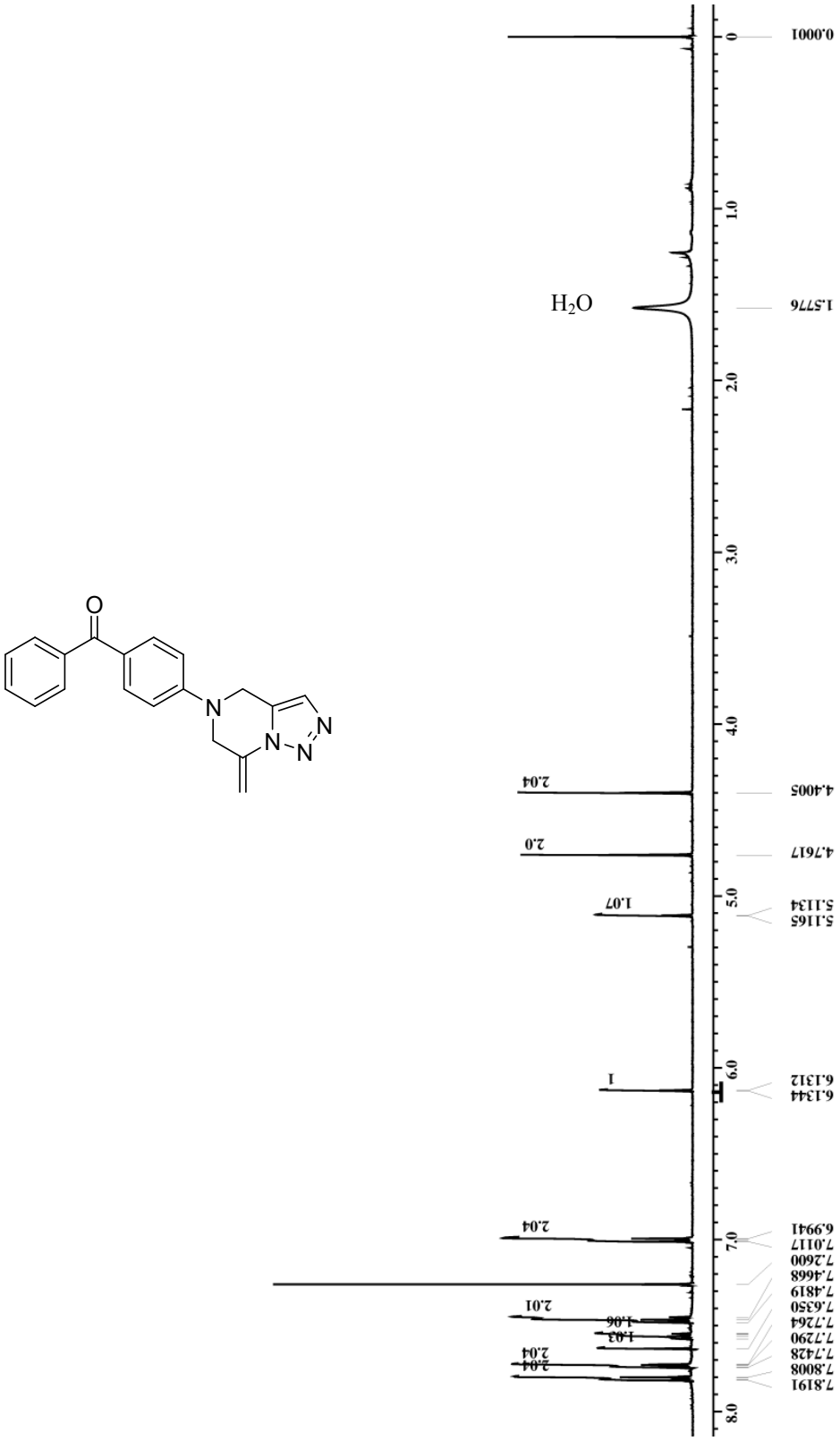


Figure S11. ^{1}H NMR spectrum of **2a**

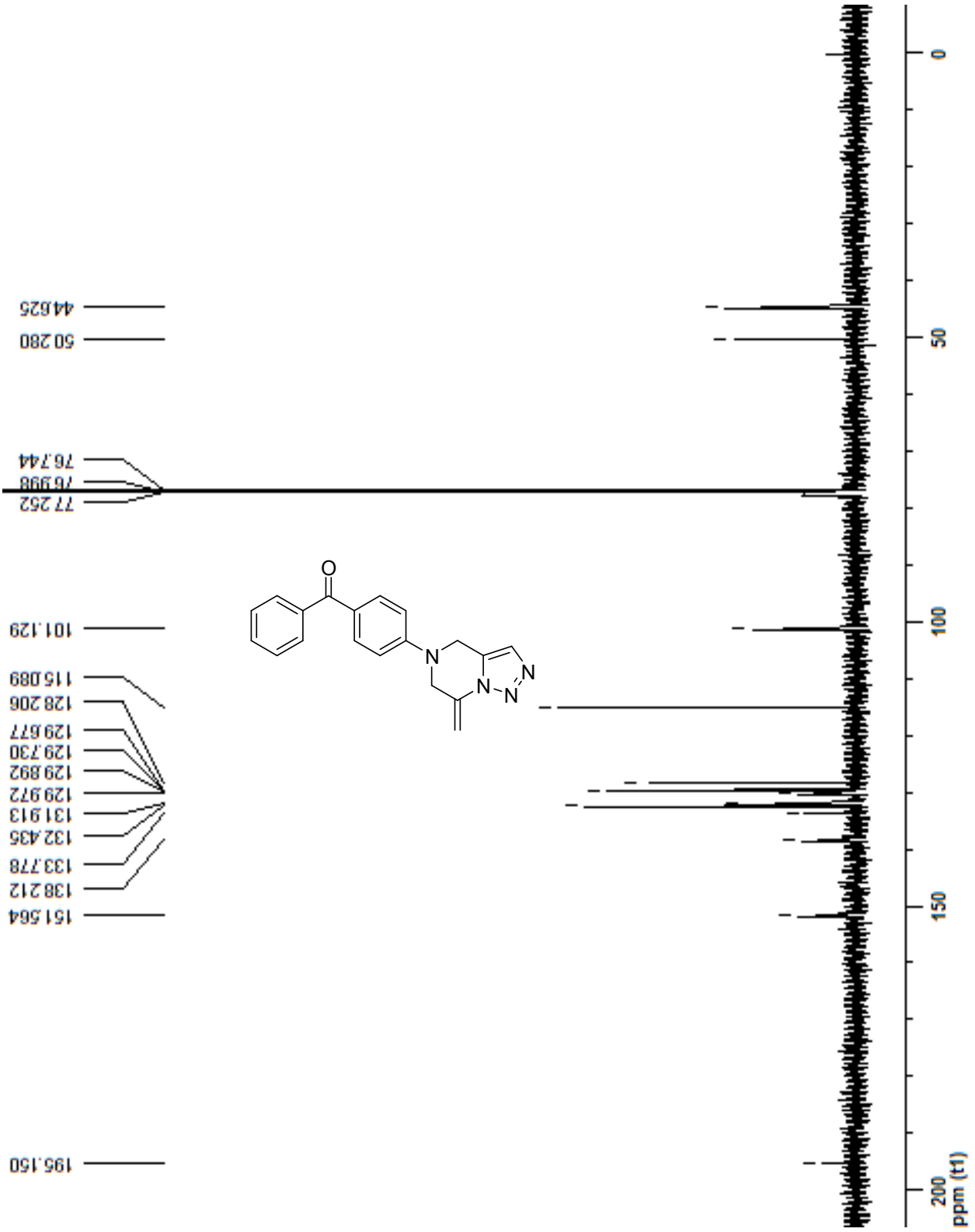


Figure S12. ^{13}C NMR spectrum of **2a**

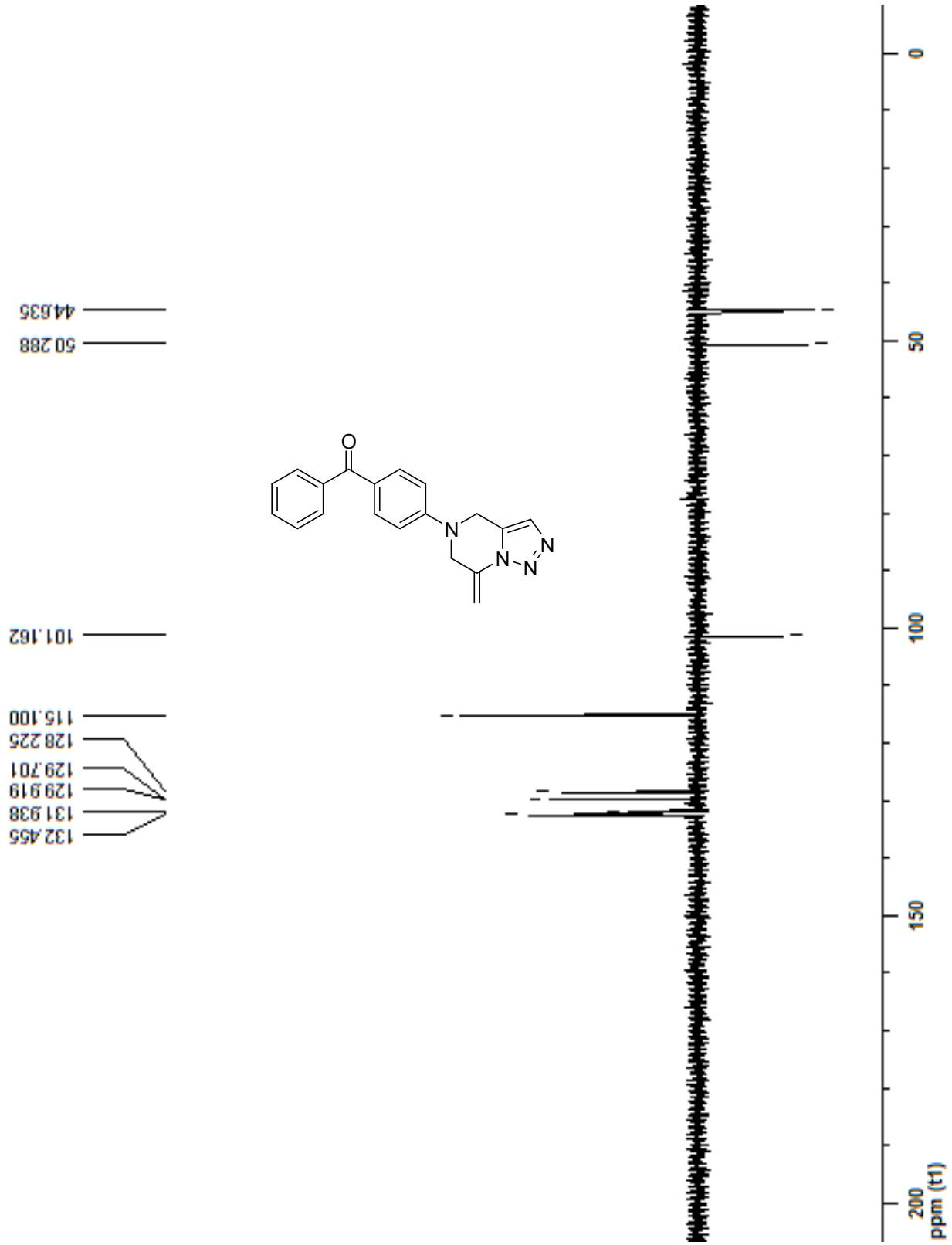


Figure S13. DEPT spectrum of **2a**

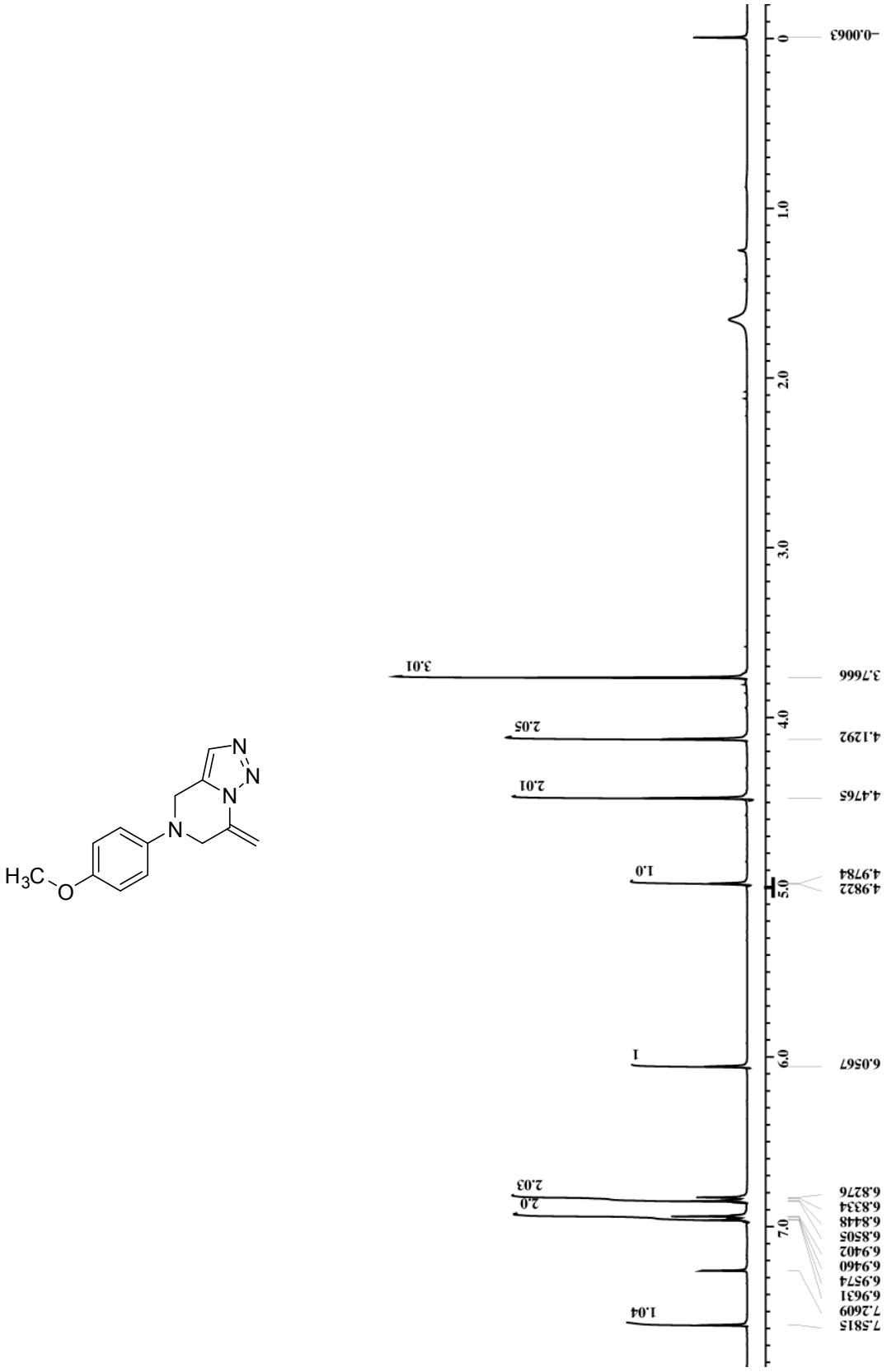


Figure S14. ^{1}H NMR spectrum of **2b**

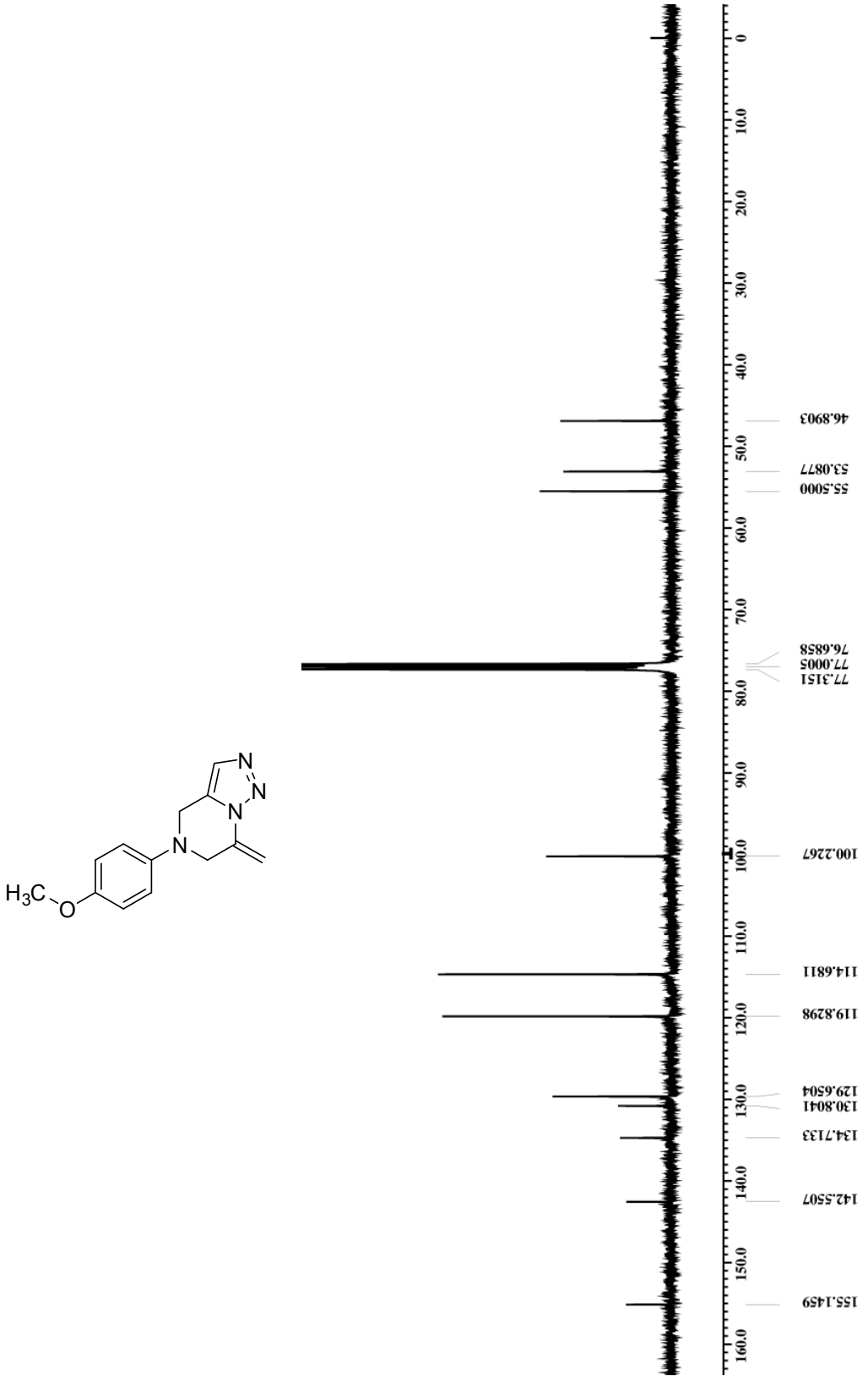


Figure S15. ^{13}C NMR spectrum of **2b**

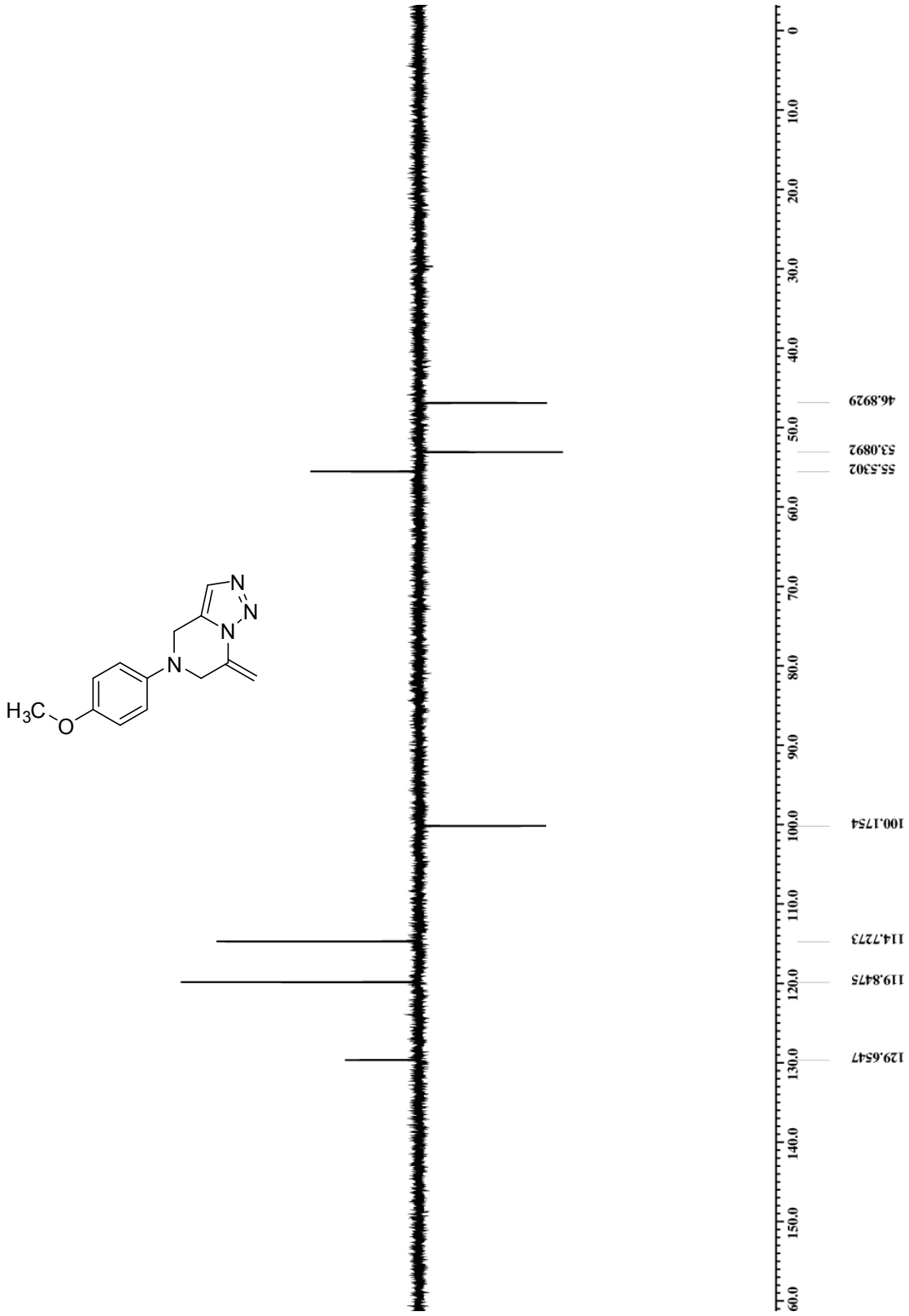


Figure S16. DEPT spectrum of **2b**

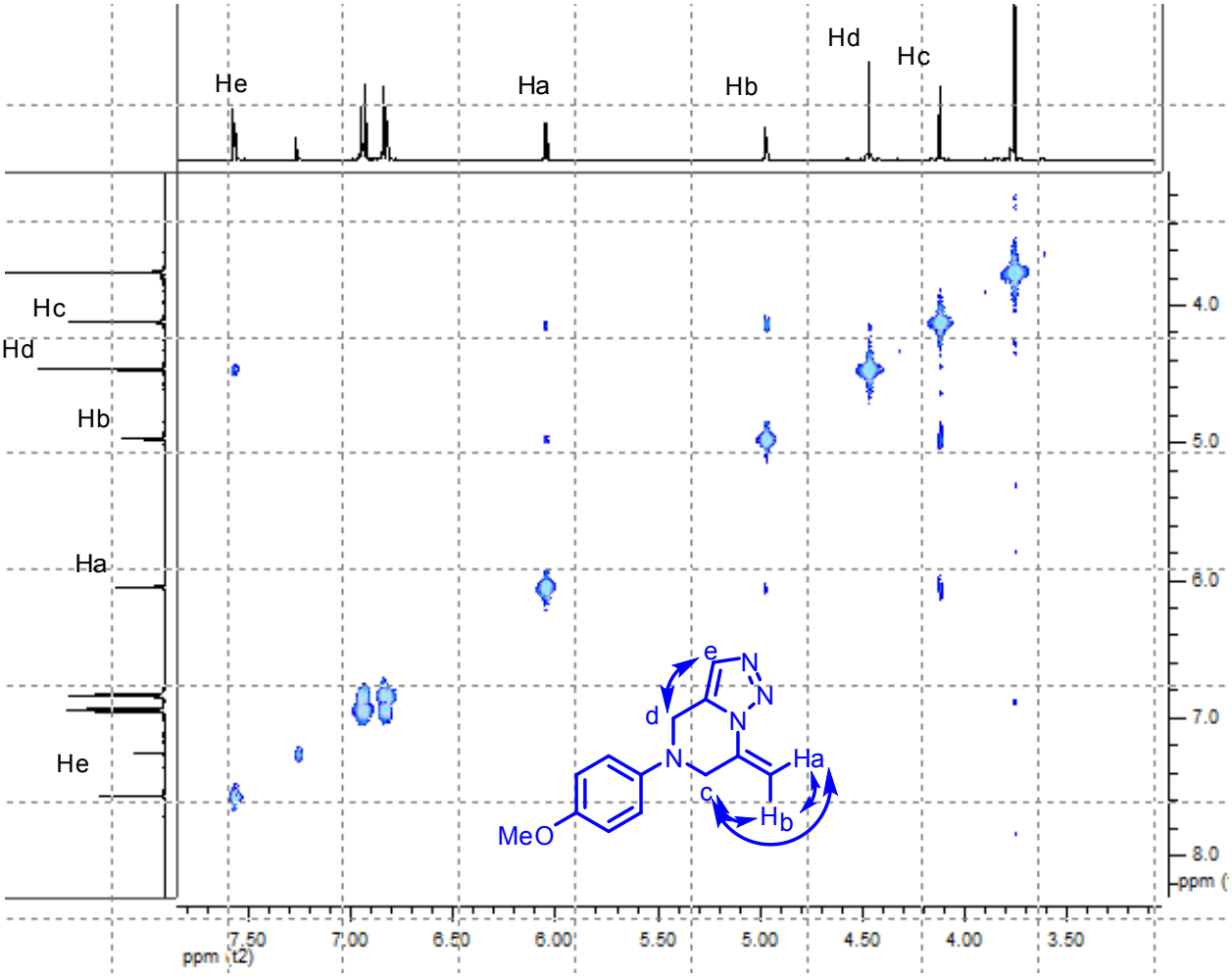


Figure S17. COSY spectrum of **2b**

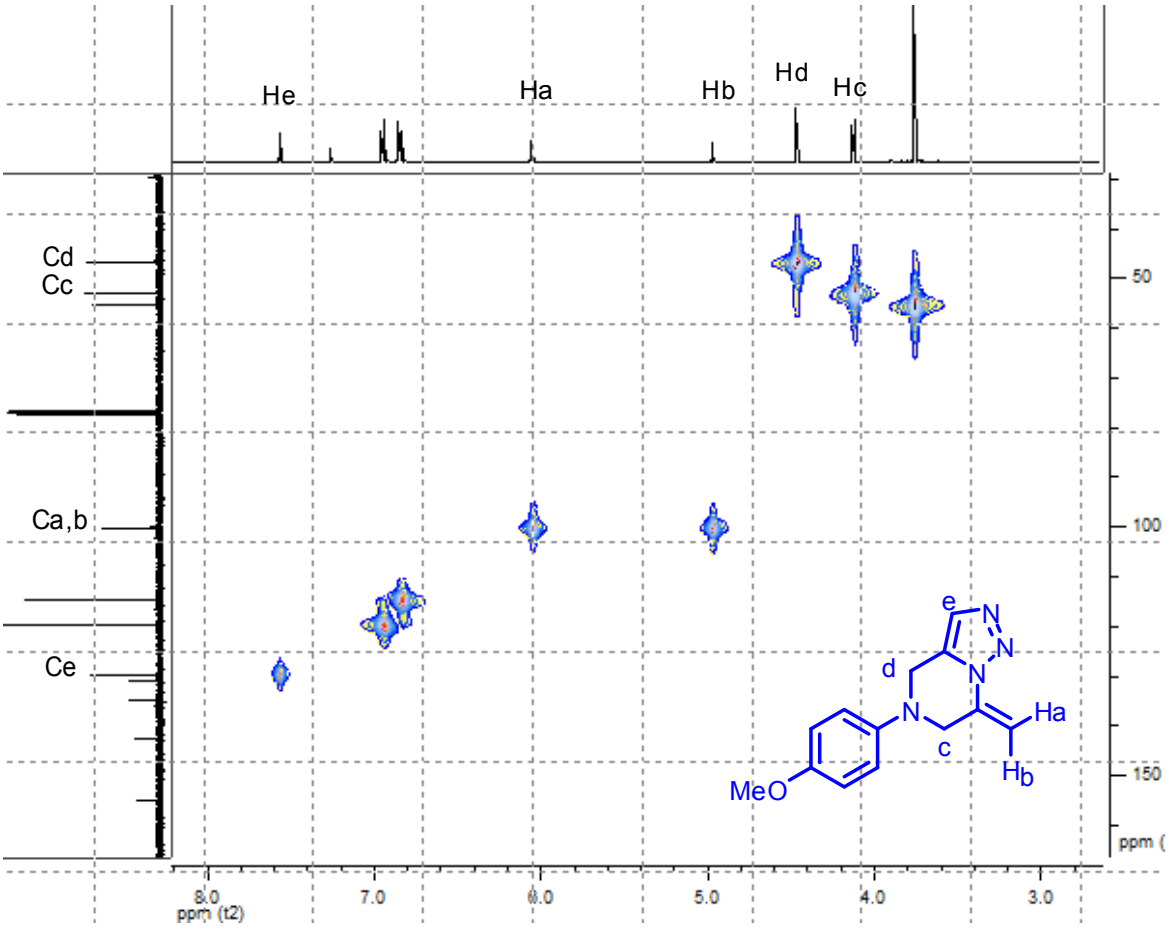


Figure S18. HMQC spectrum of **2b**

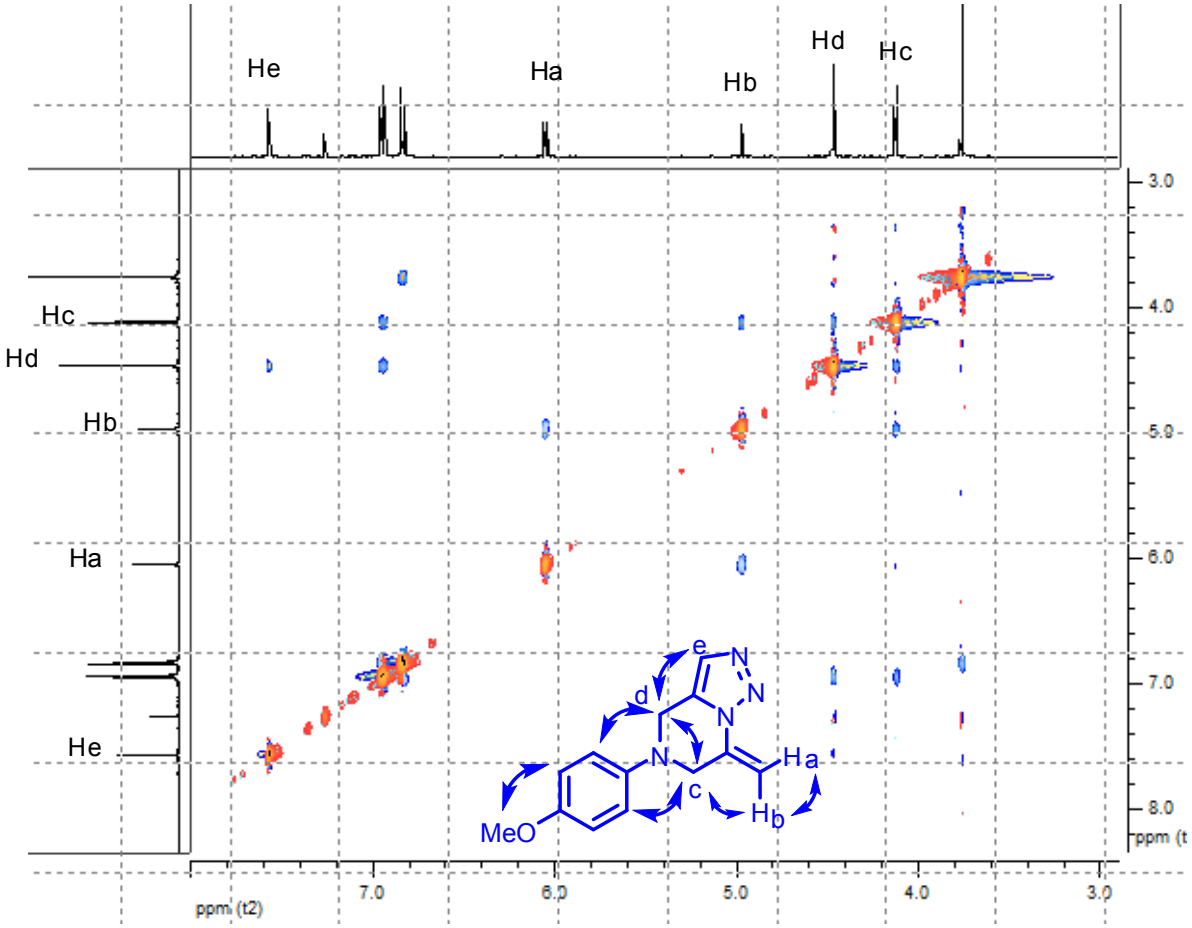


Figure S19. NOESY spectrum of **2b**

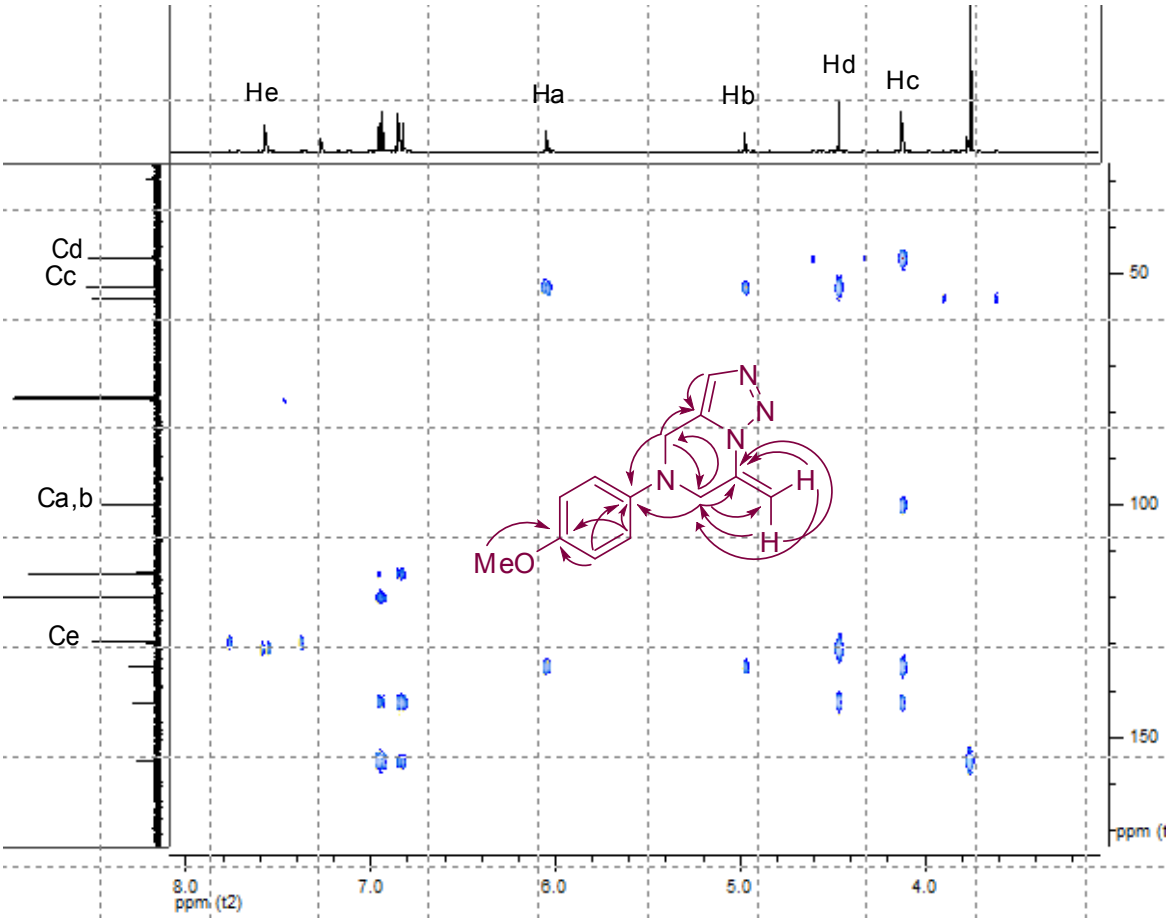


Figure S20. HMBC spectrum of **2b**

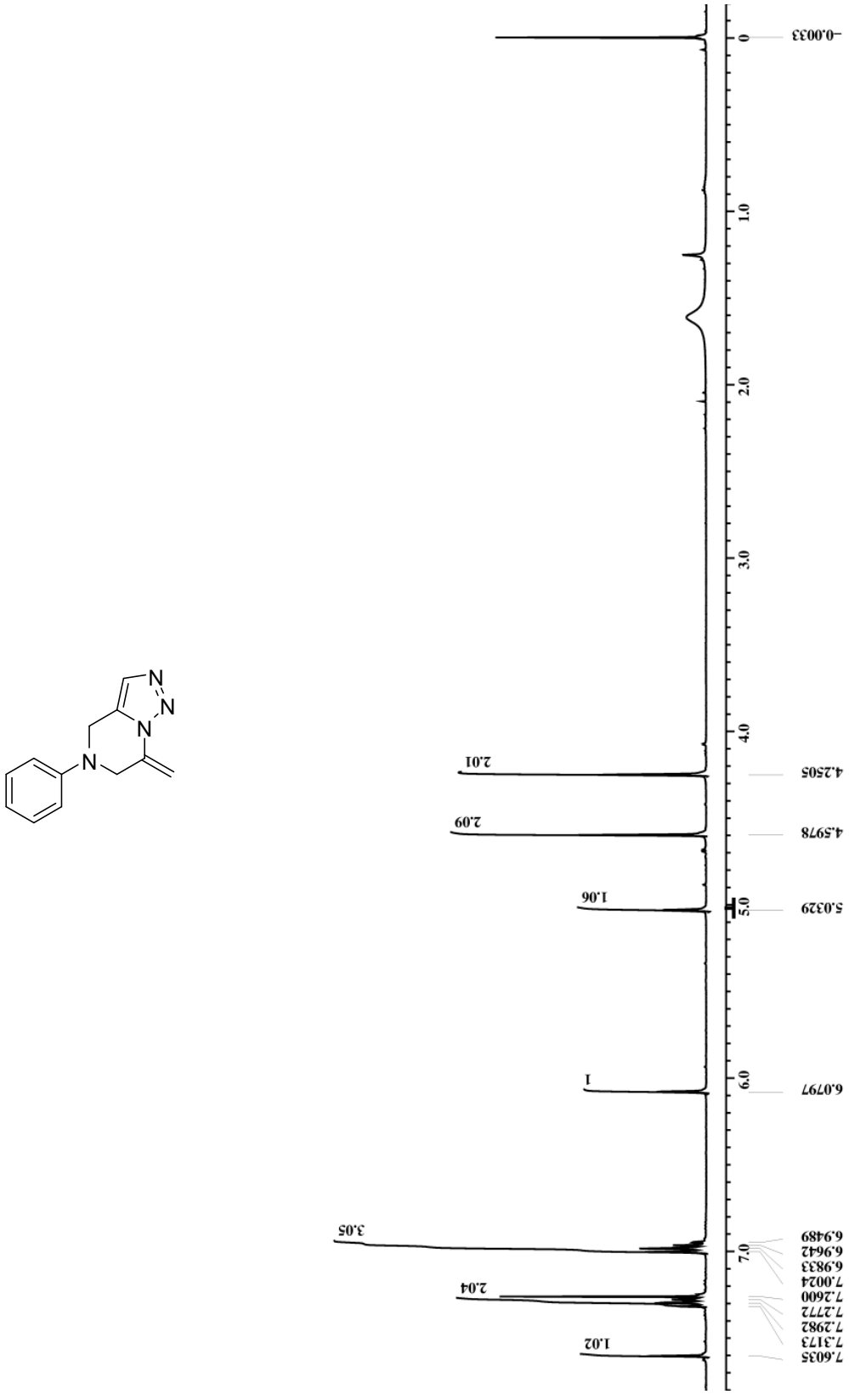


Figure S21. ^{1}H NMR spectrum of **2c**

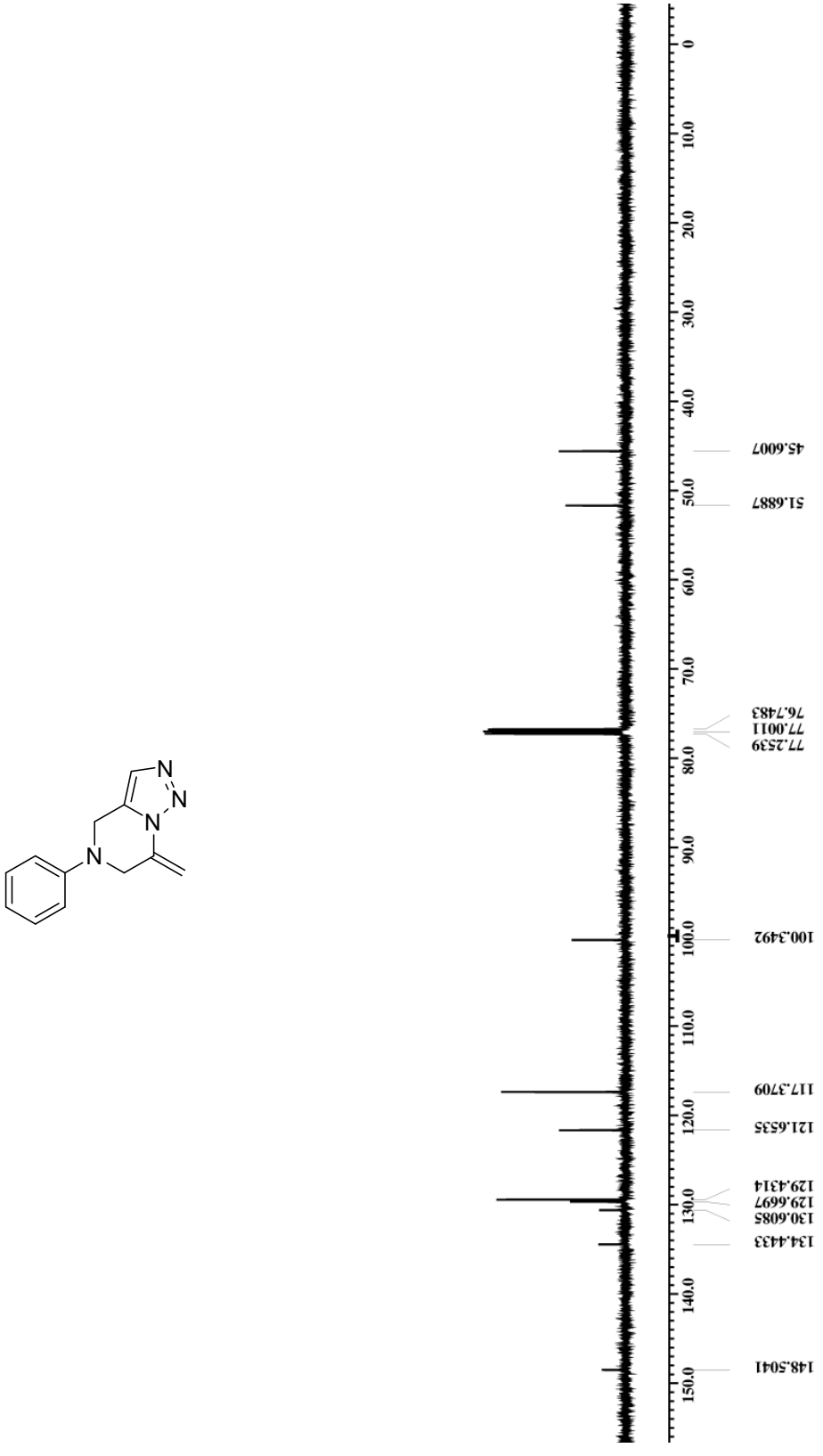


Figure S22. ^{13}C NMR spectrum of **2c**

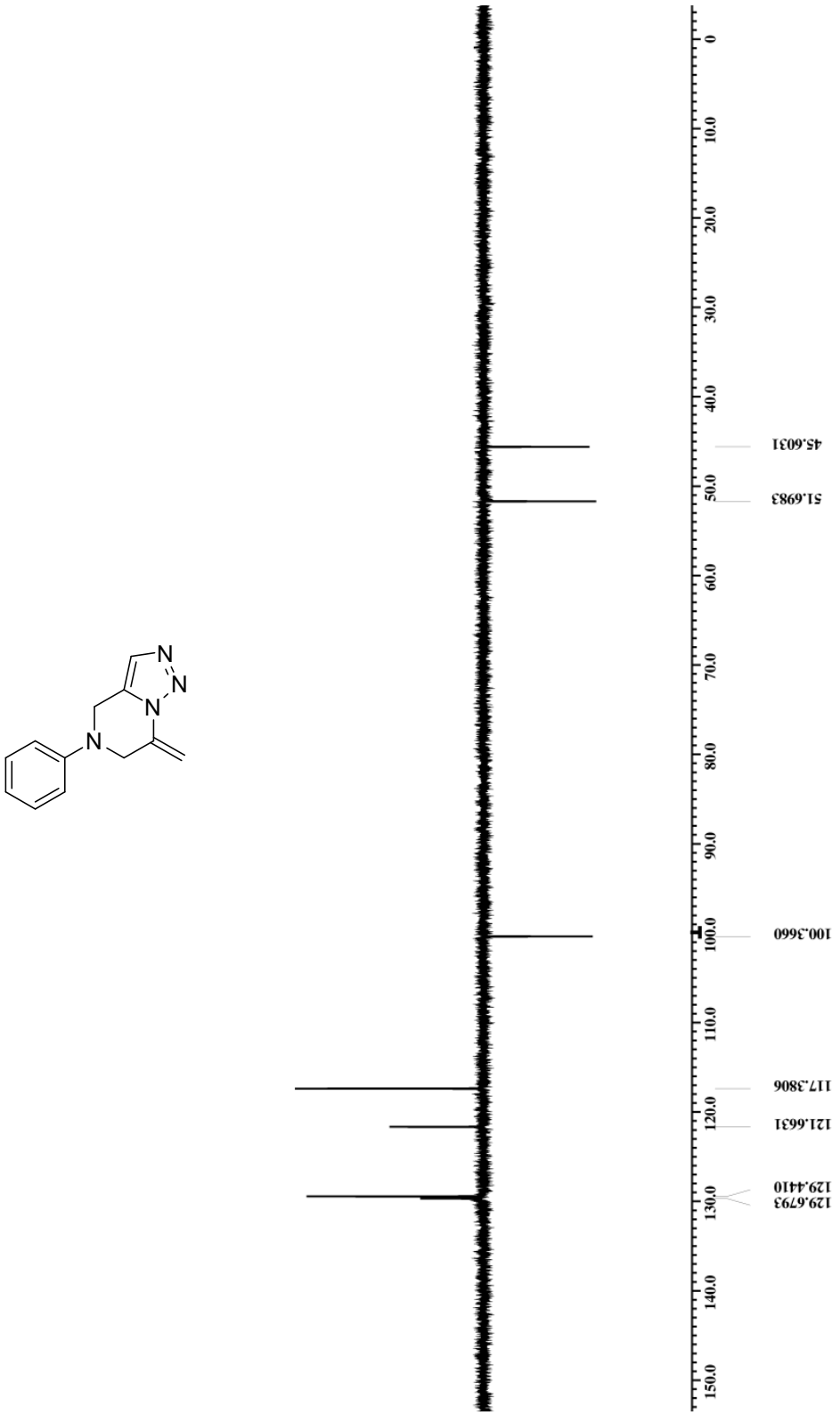


Figure S23. DEPT spectrum of **2c**

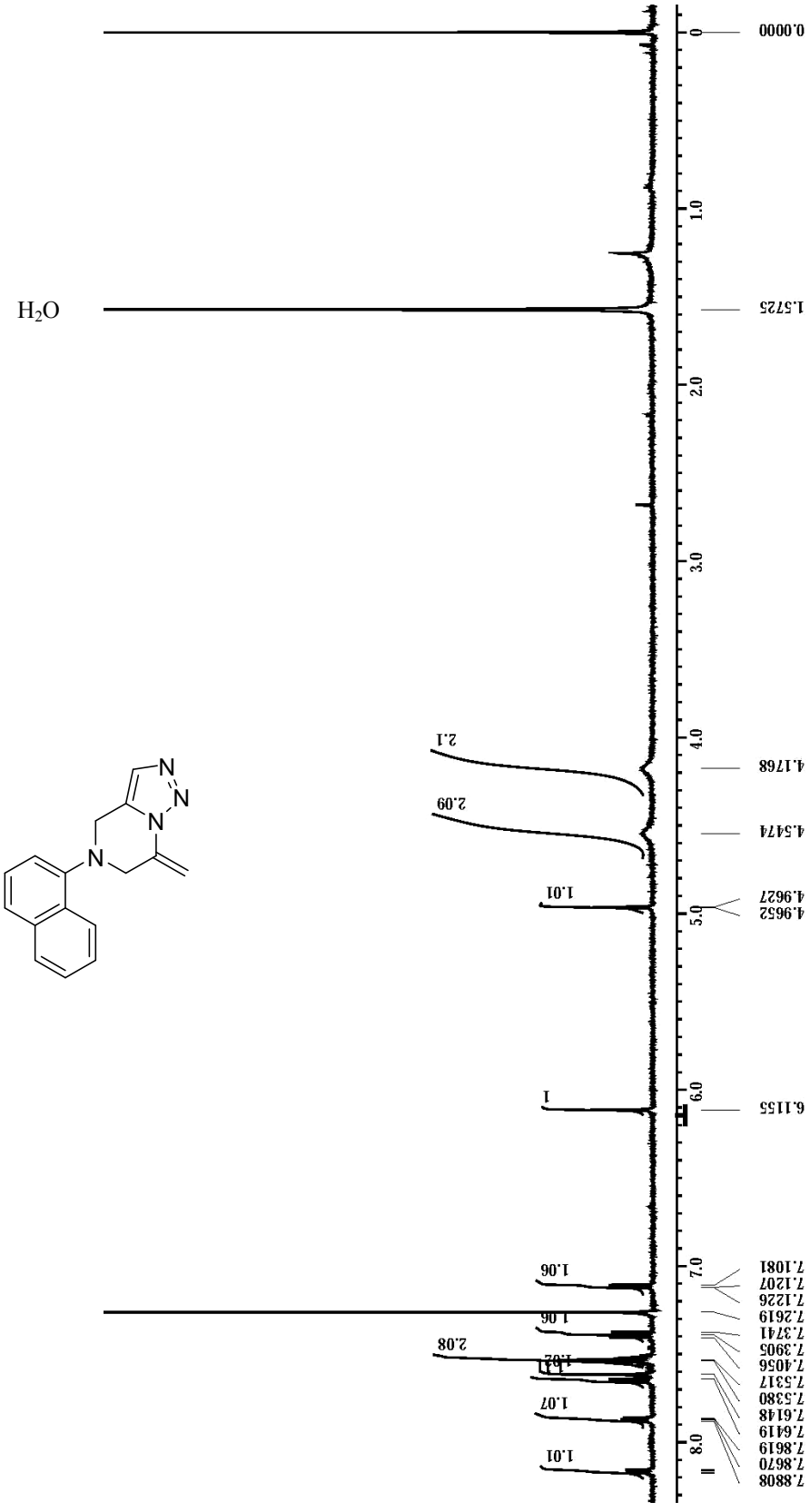


Figure S24. ^{1}H NMR spectrum of **2d**

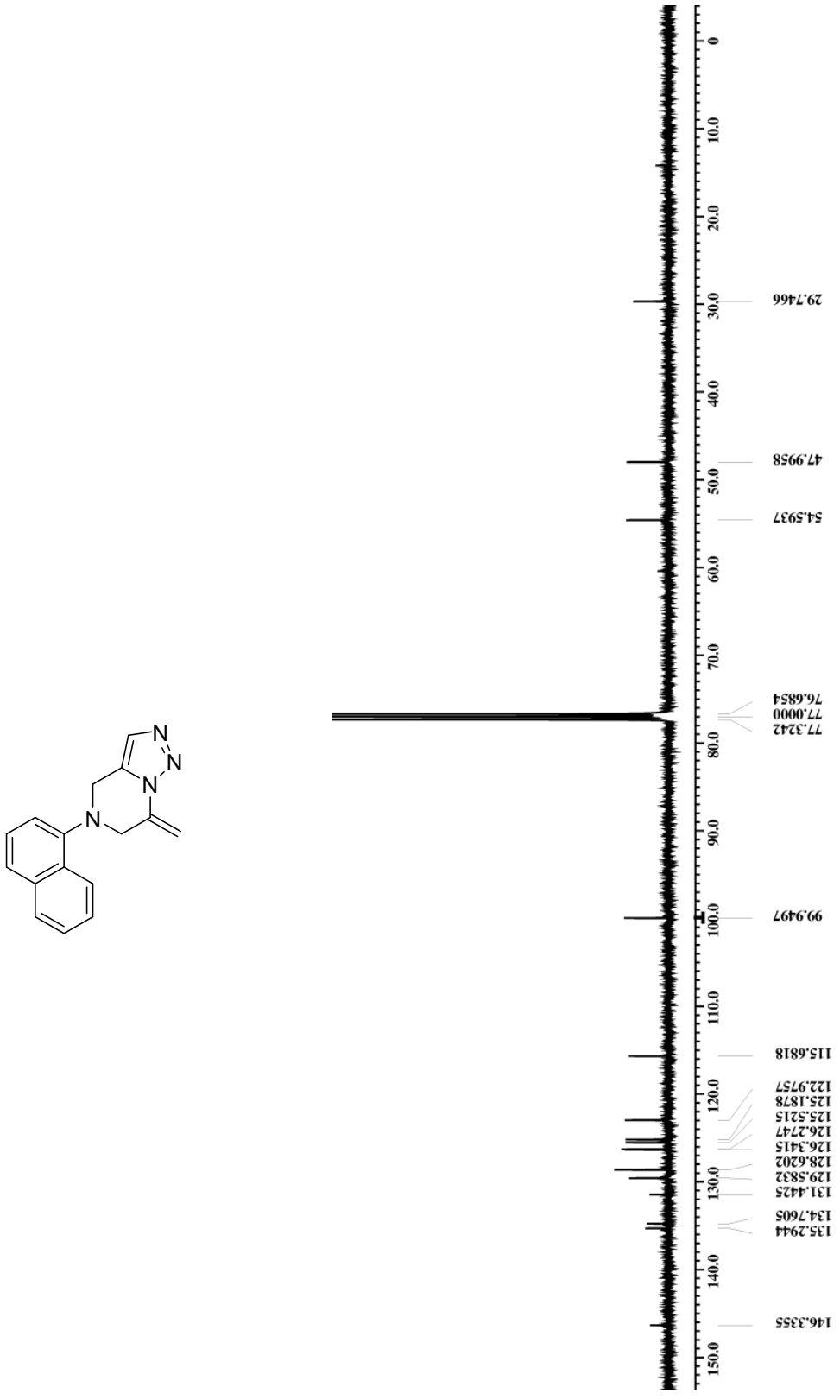


Figure S25. ^{13}C NMR spectrum of **2d**

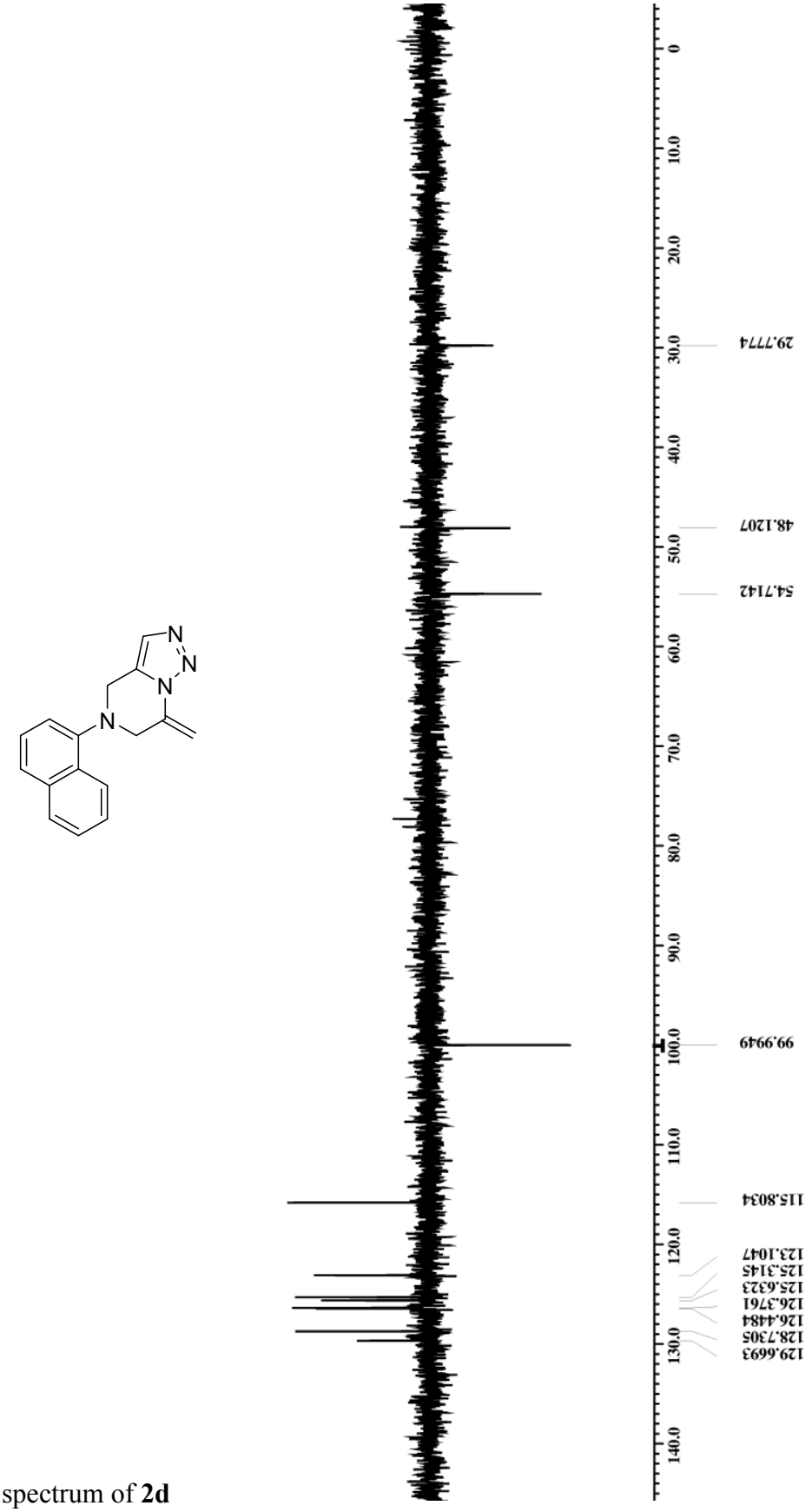


Figure S26. DEPT spectrum of **2d**

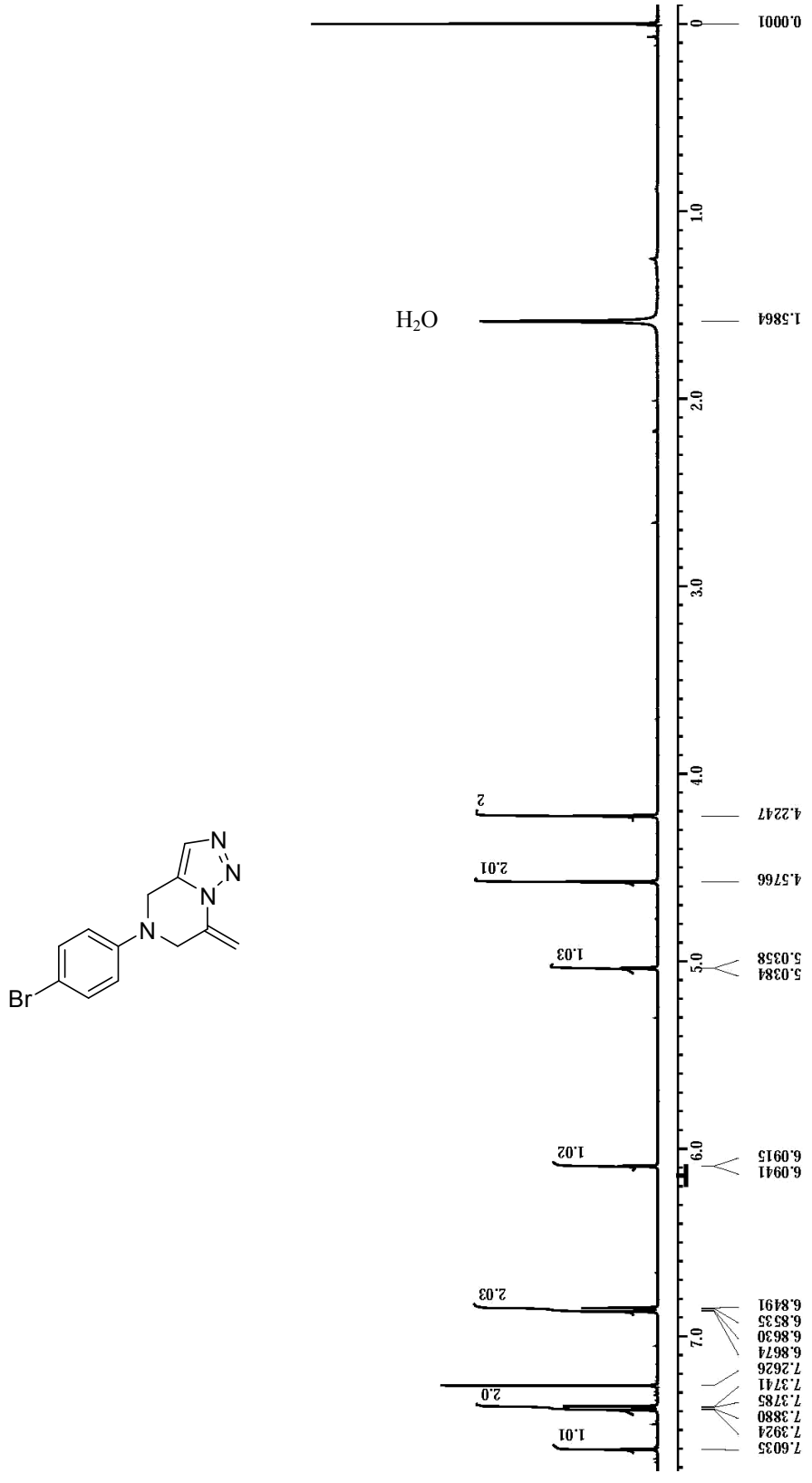


Figure S27. ^{1}H NMR spectrum of **2e**

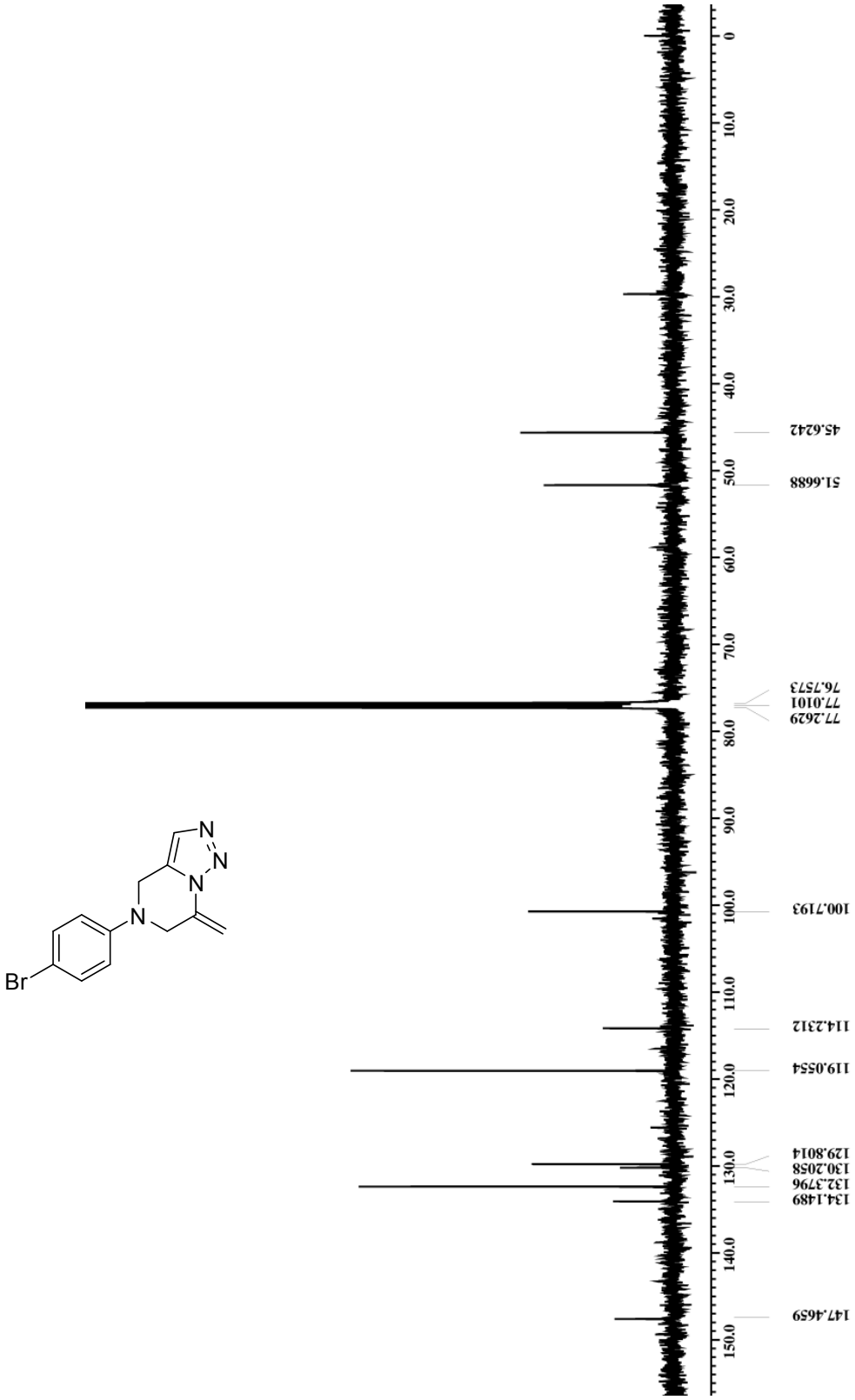


Figure S28. ^{13}C NMR spectrum of **2e**

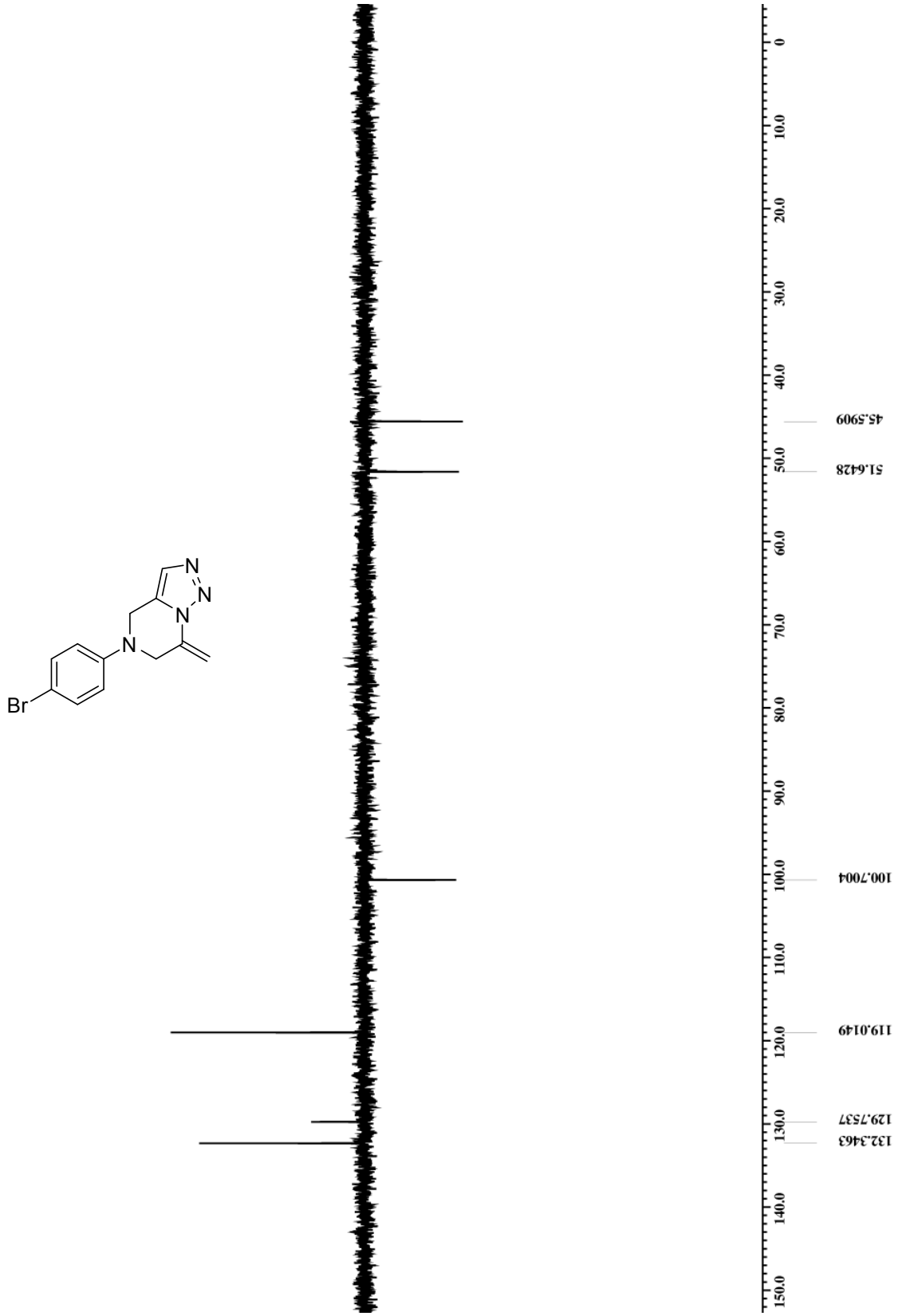


Figure S29. DEPT spectrum of **2e**

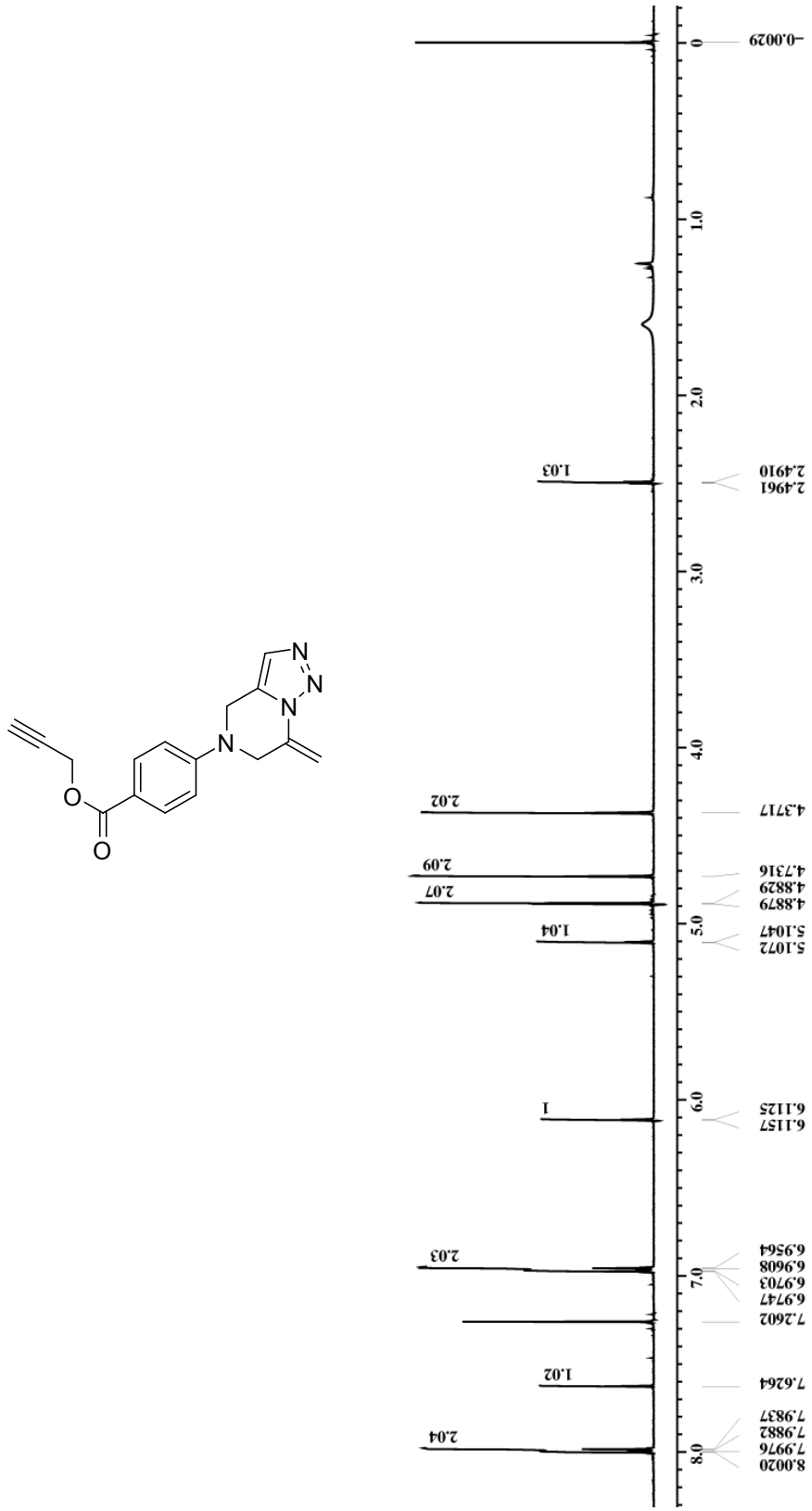


Figure S30. ^{1}H NMR spectrum of **2f**

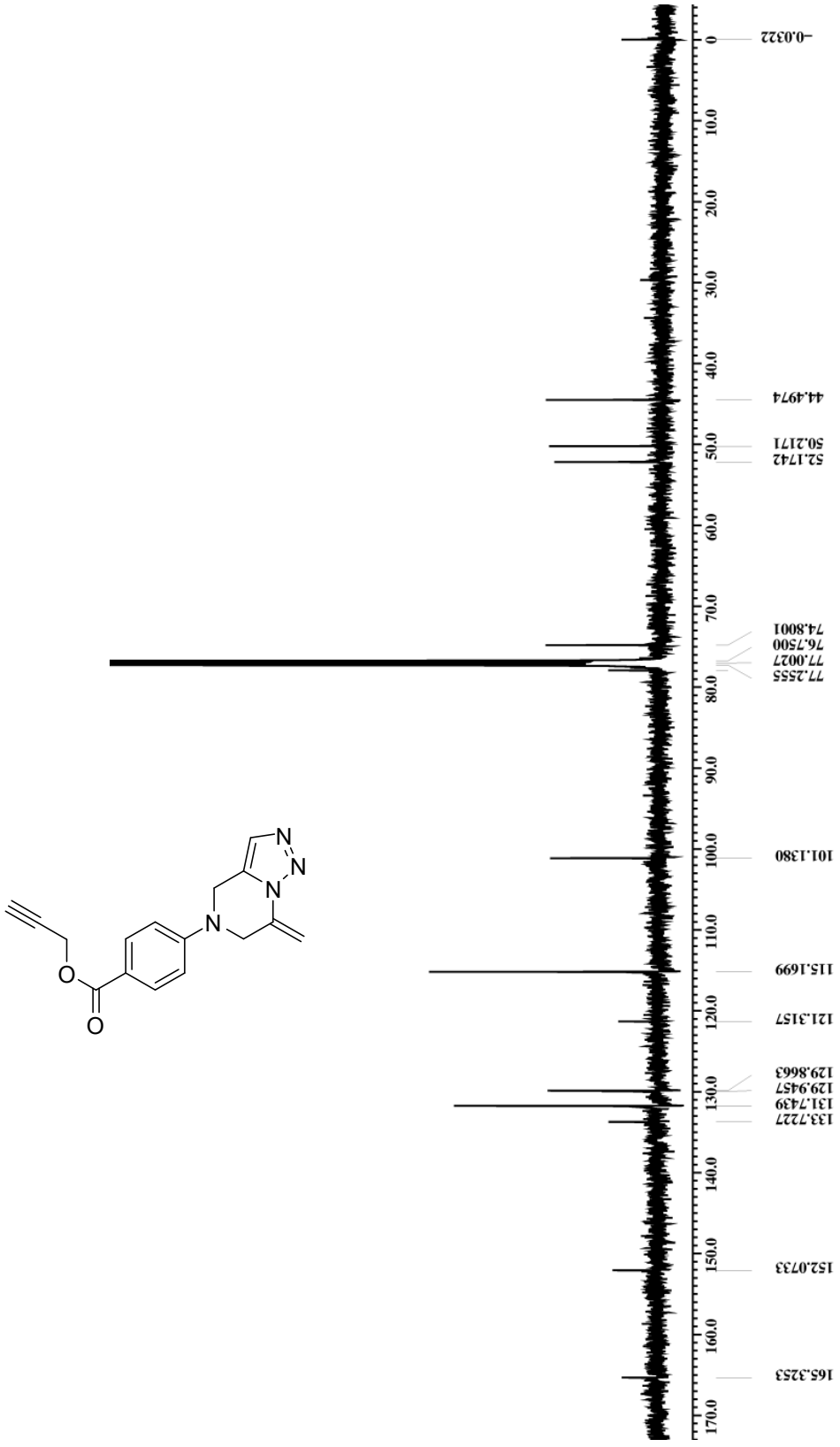


Figure S31. ^{13}C NMR spectrum of **2f**

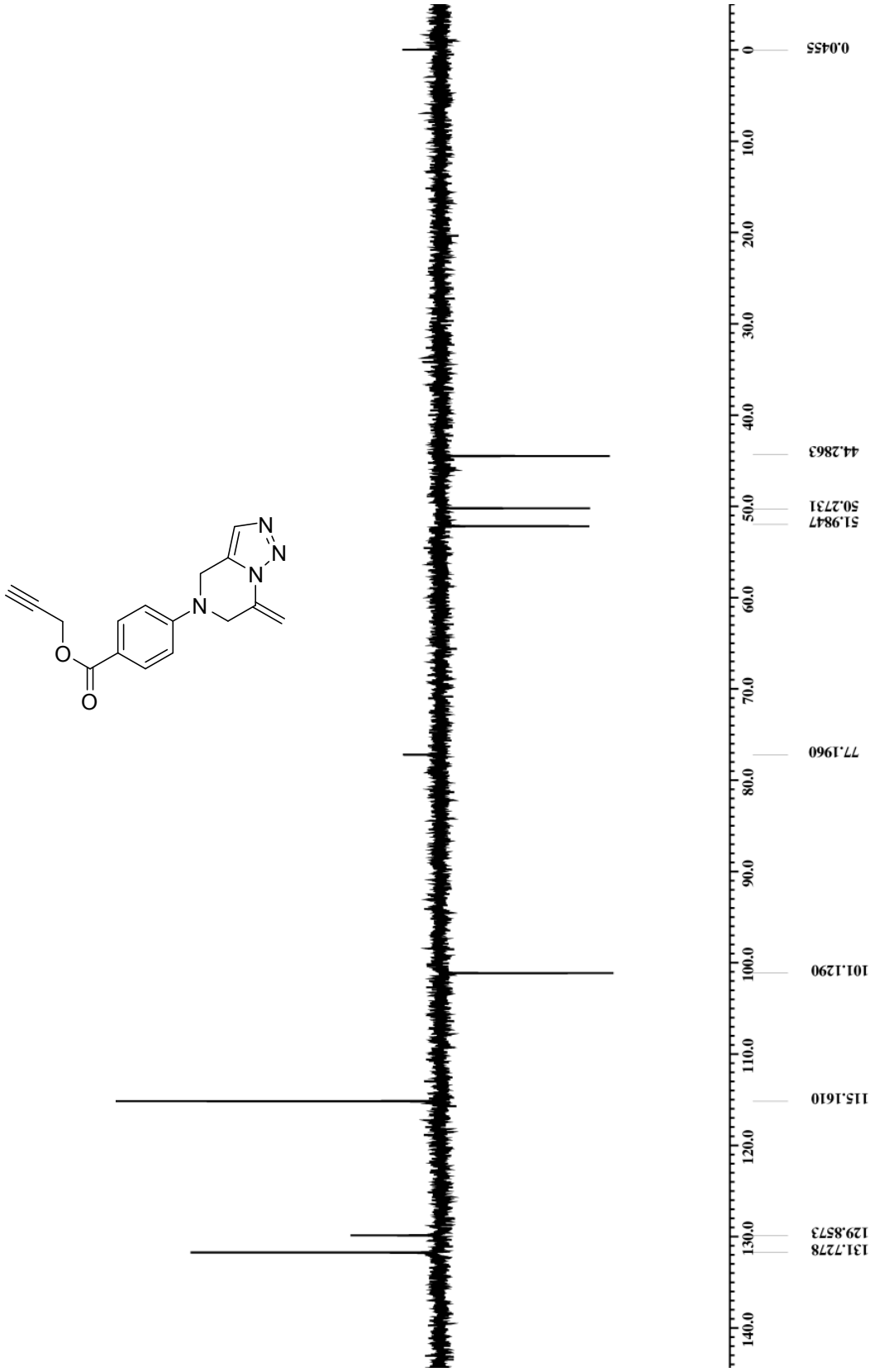


Figure S32. DEPT spectrum of **2f**

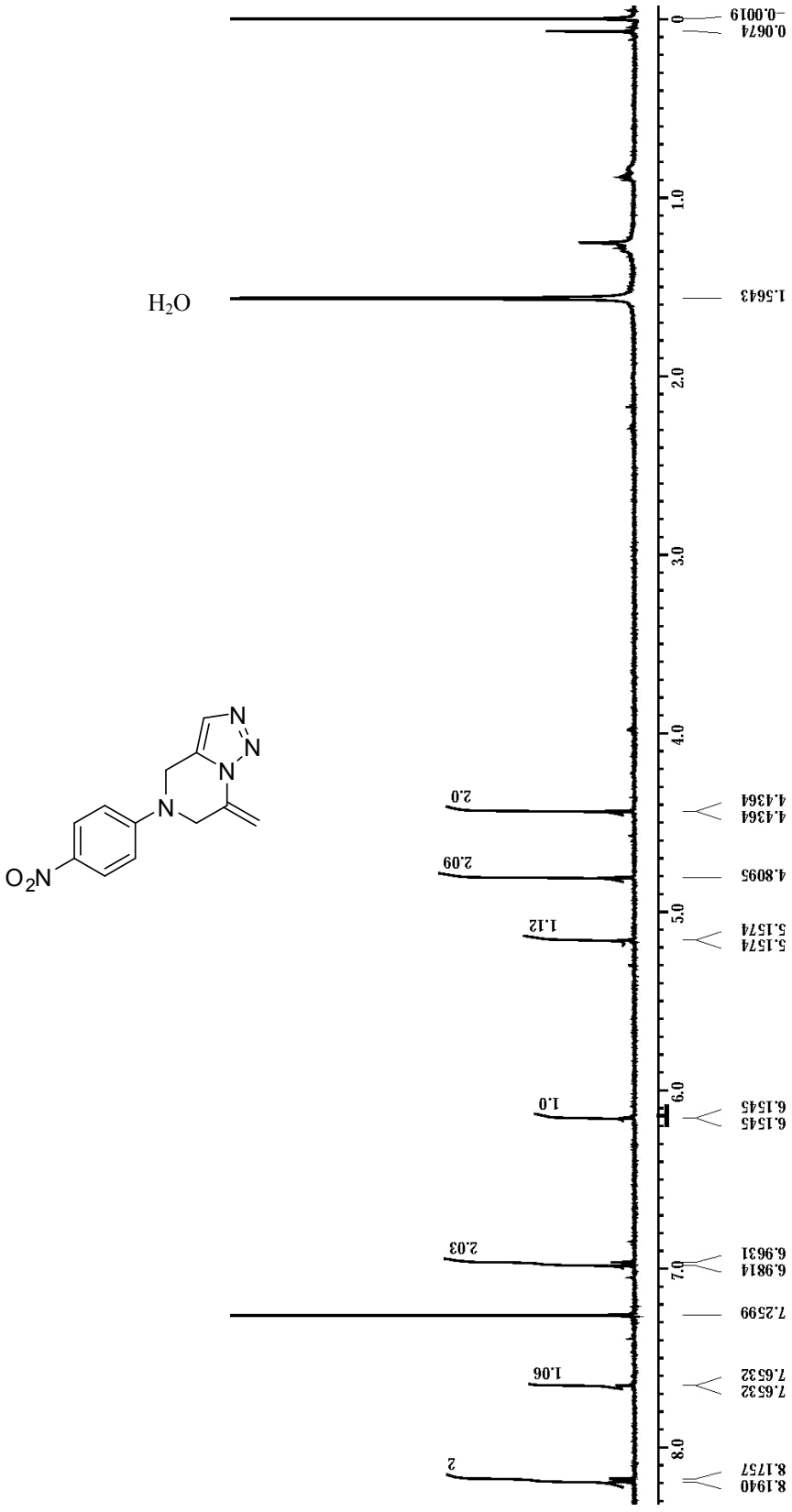


Figure S33. ^{1}H NMR spectrum of **2g**

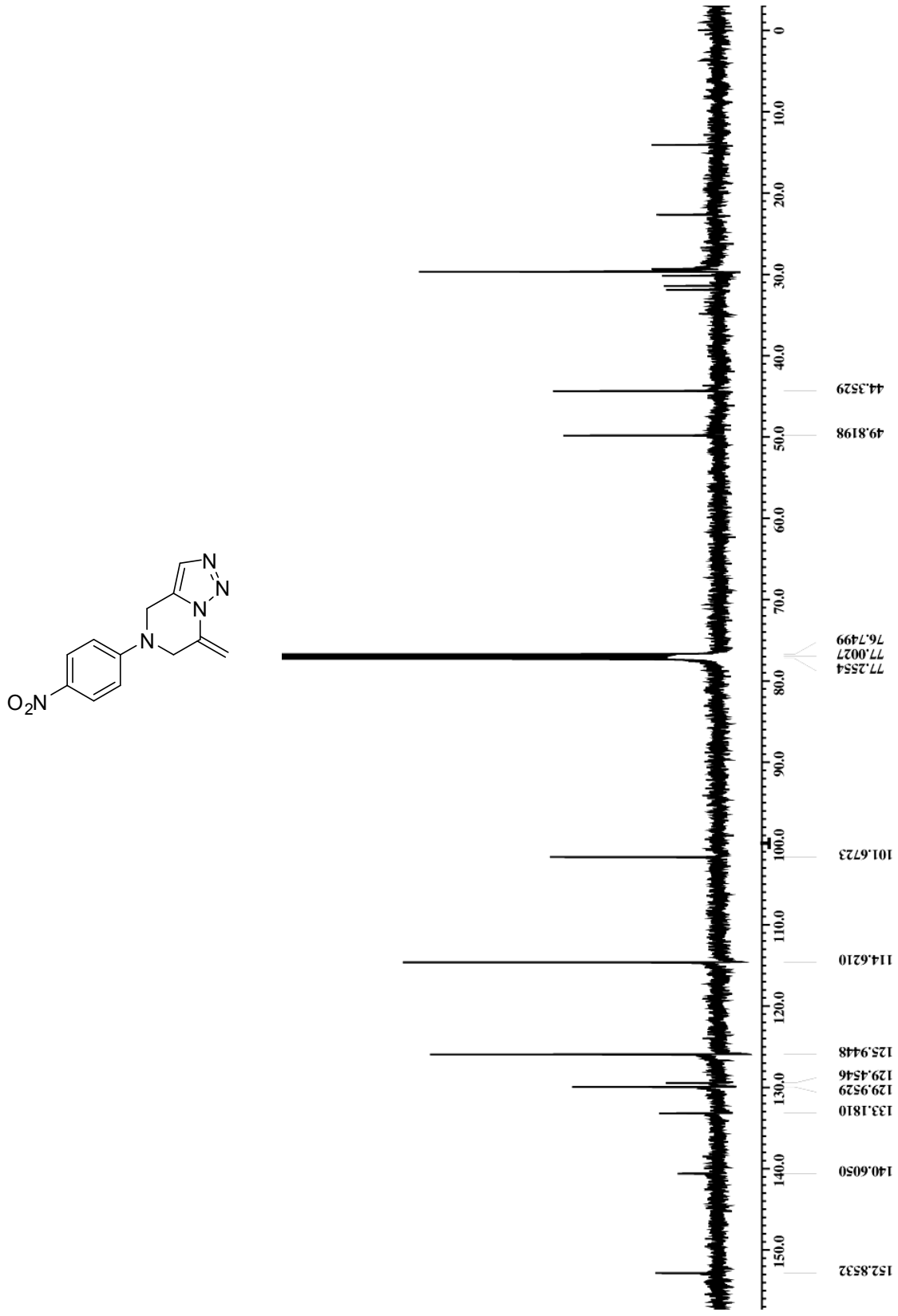


Figure S34. ^{13}C NMR spectrum of **2g**

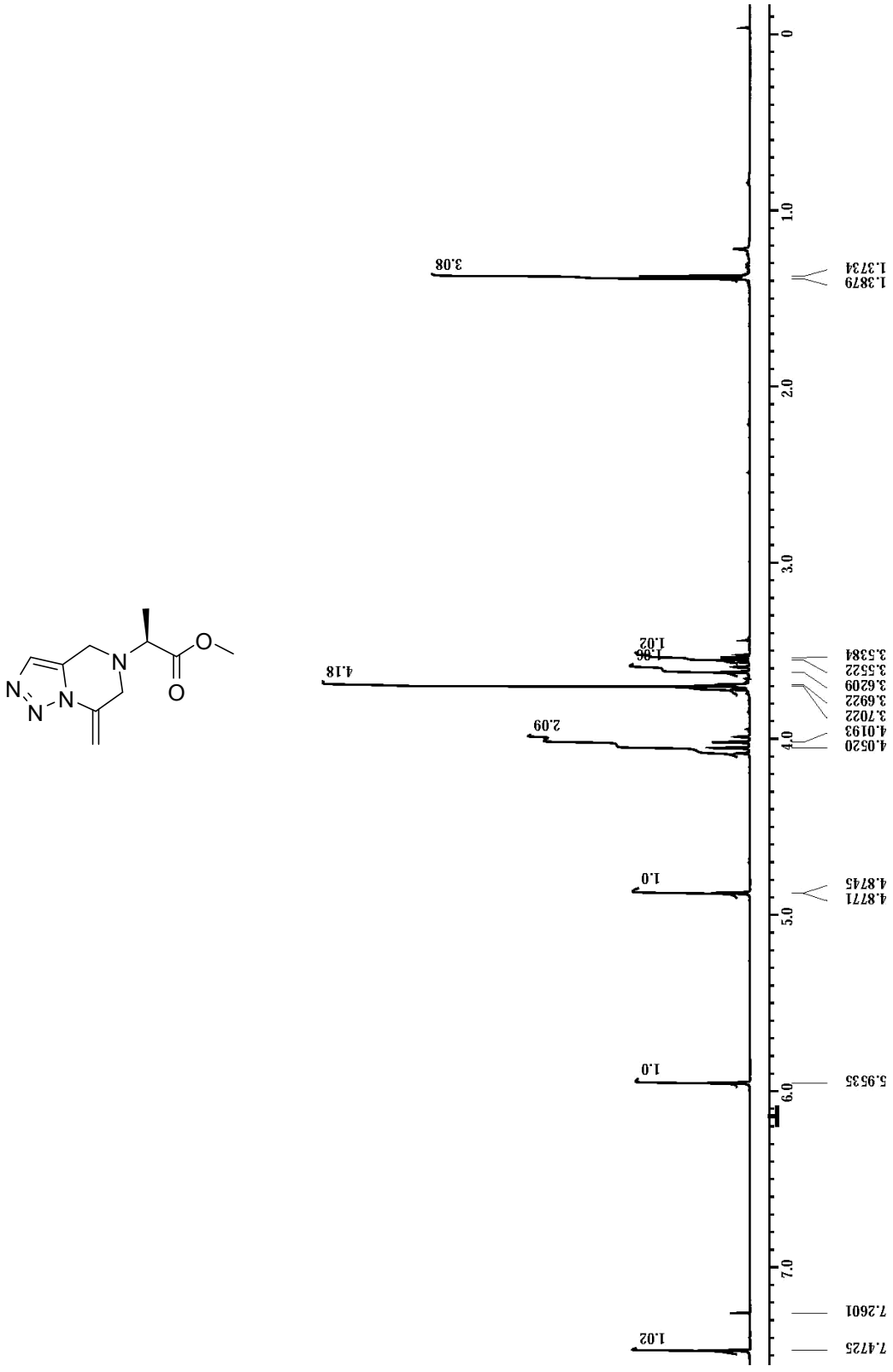


Figure S35. ^{1}H NMR spectrum of **4a**

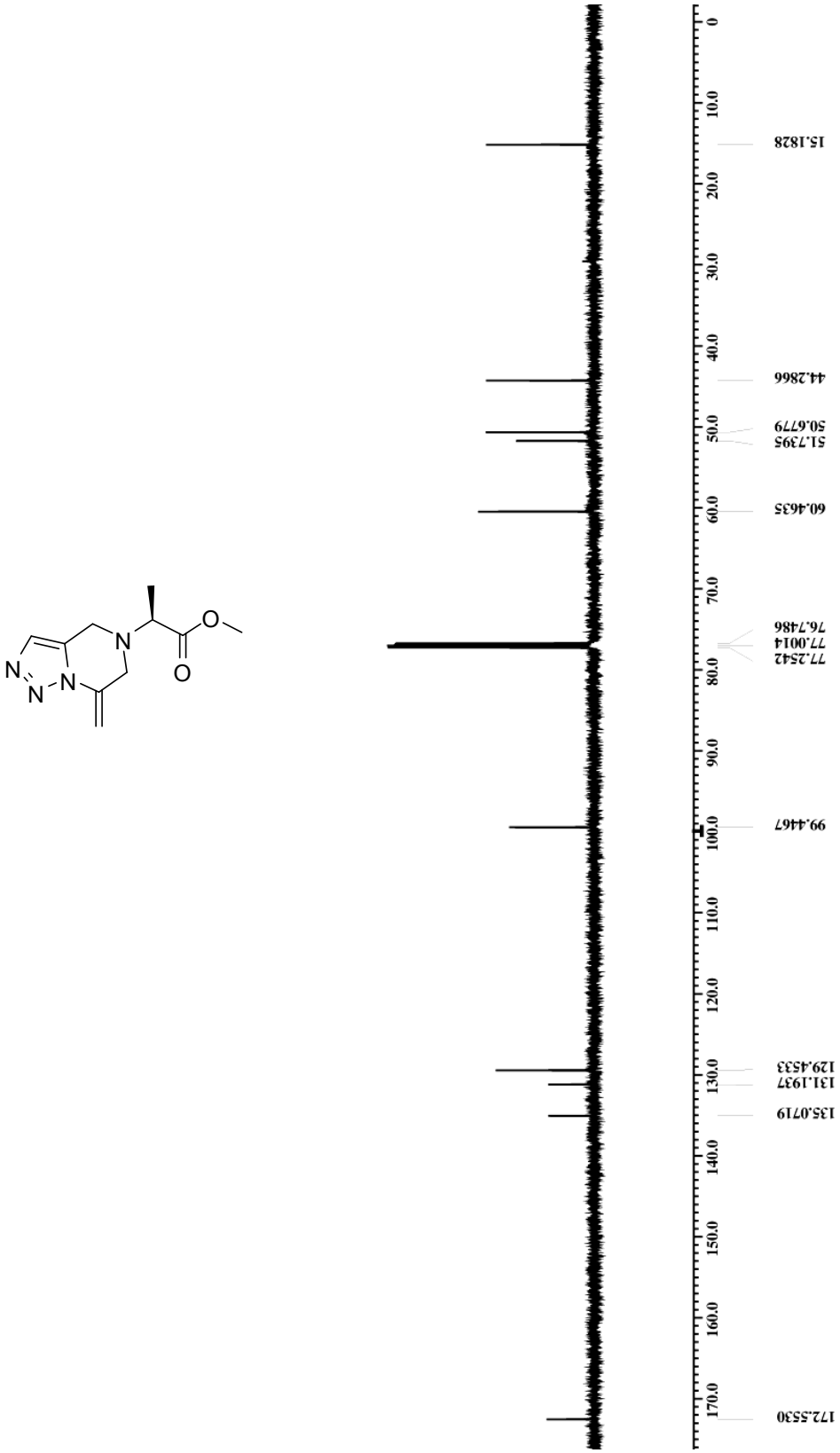


Figure S36. ^{13}C NMR spectrum of **4a**

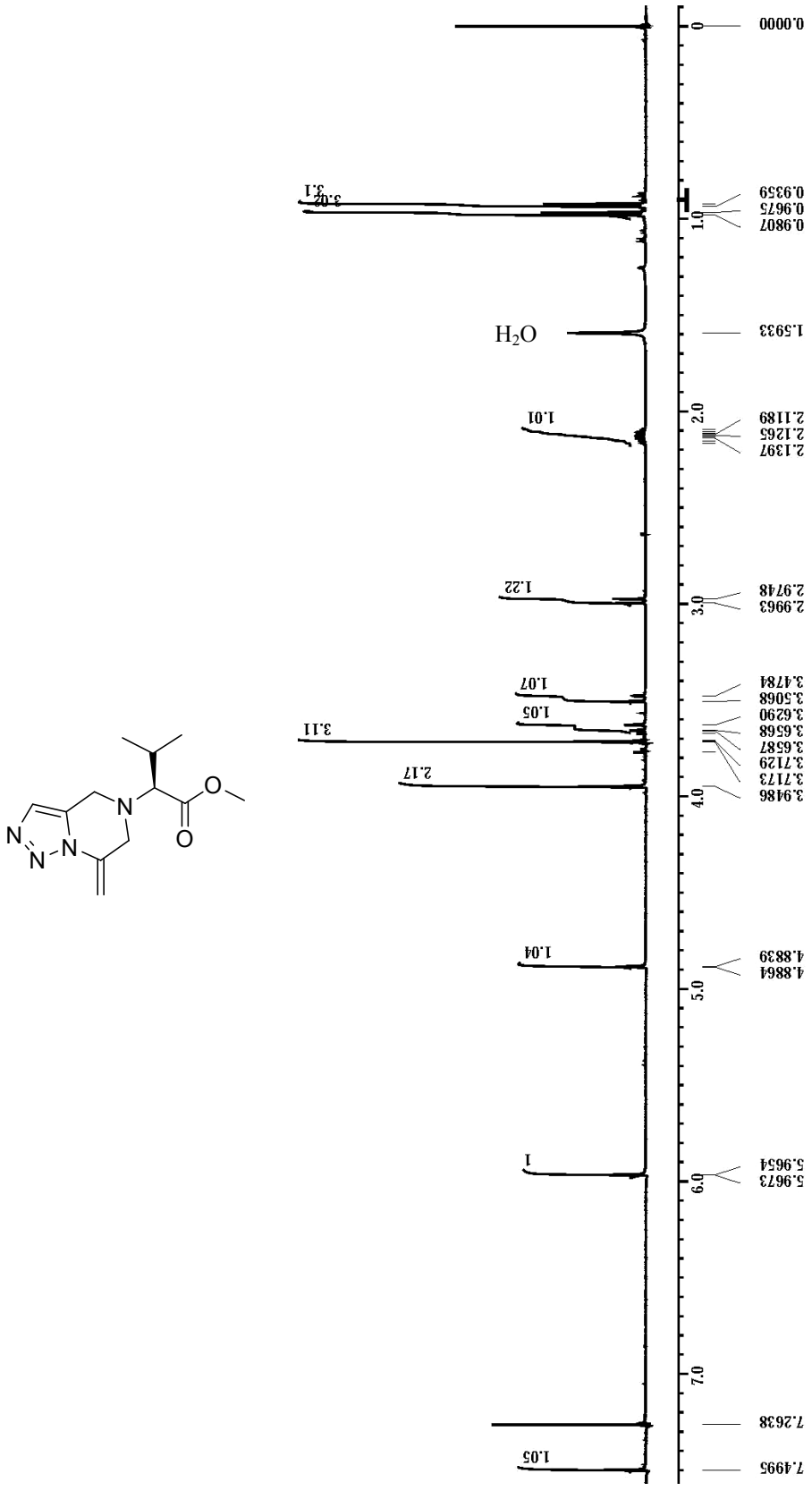


Figure S37. ^{1}H NMR spectrum of **4b**

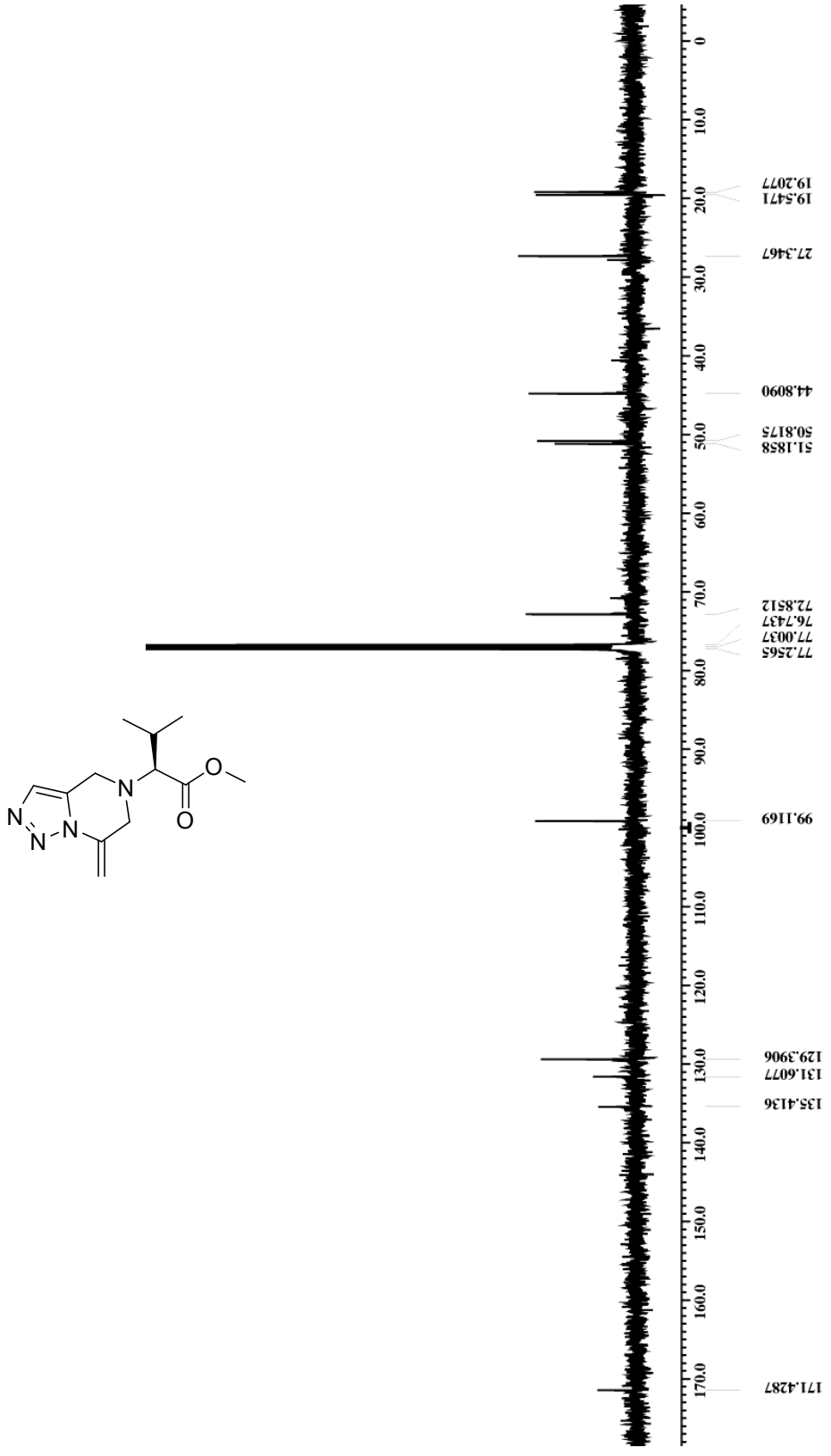


Figure S38. ^{13}C NMR spectrum of **4b**

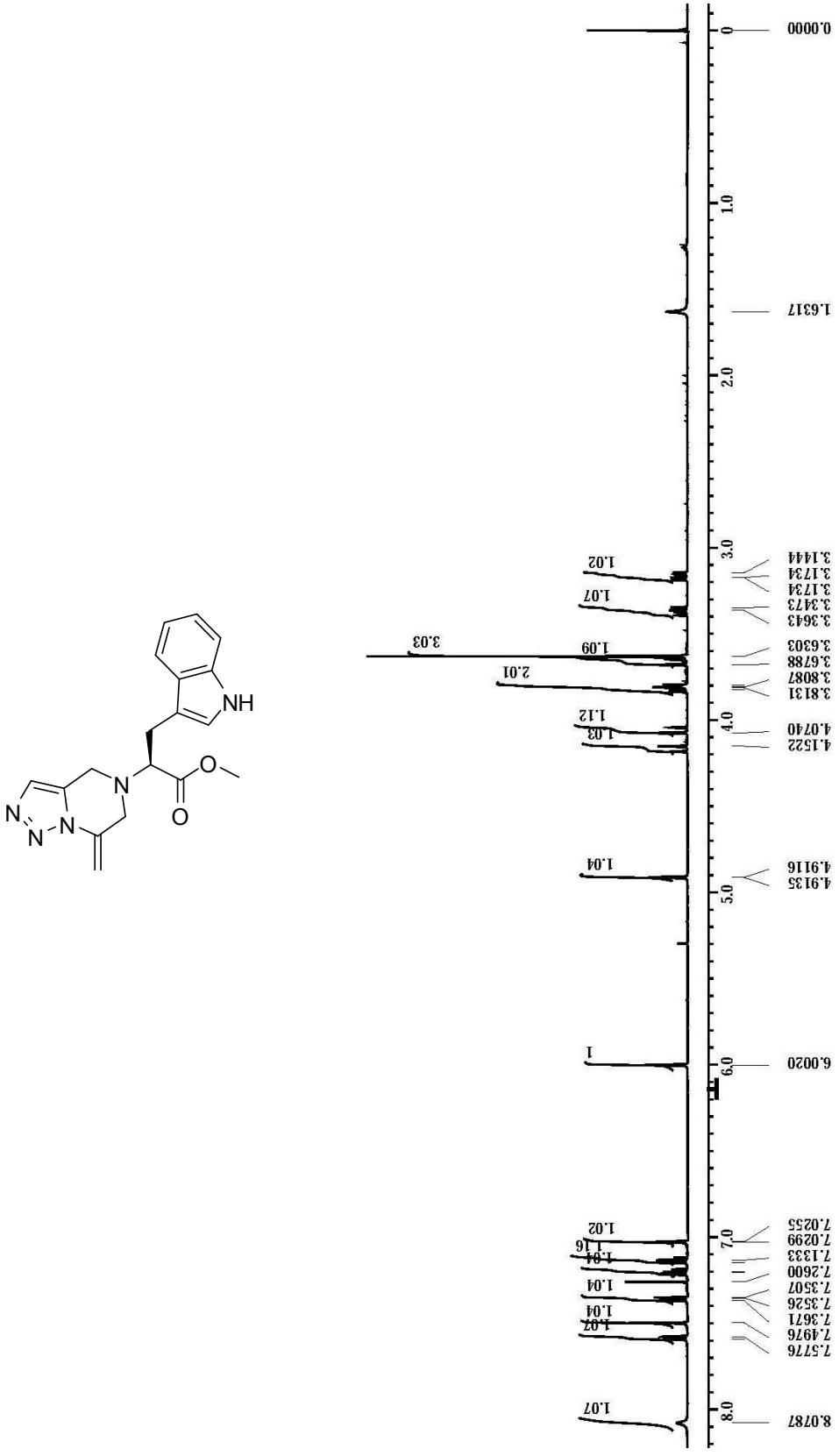


Figure S39. ^{1}H NMR spectrum of **4c**

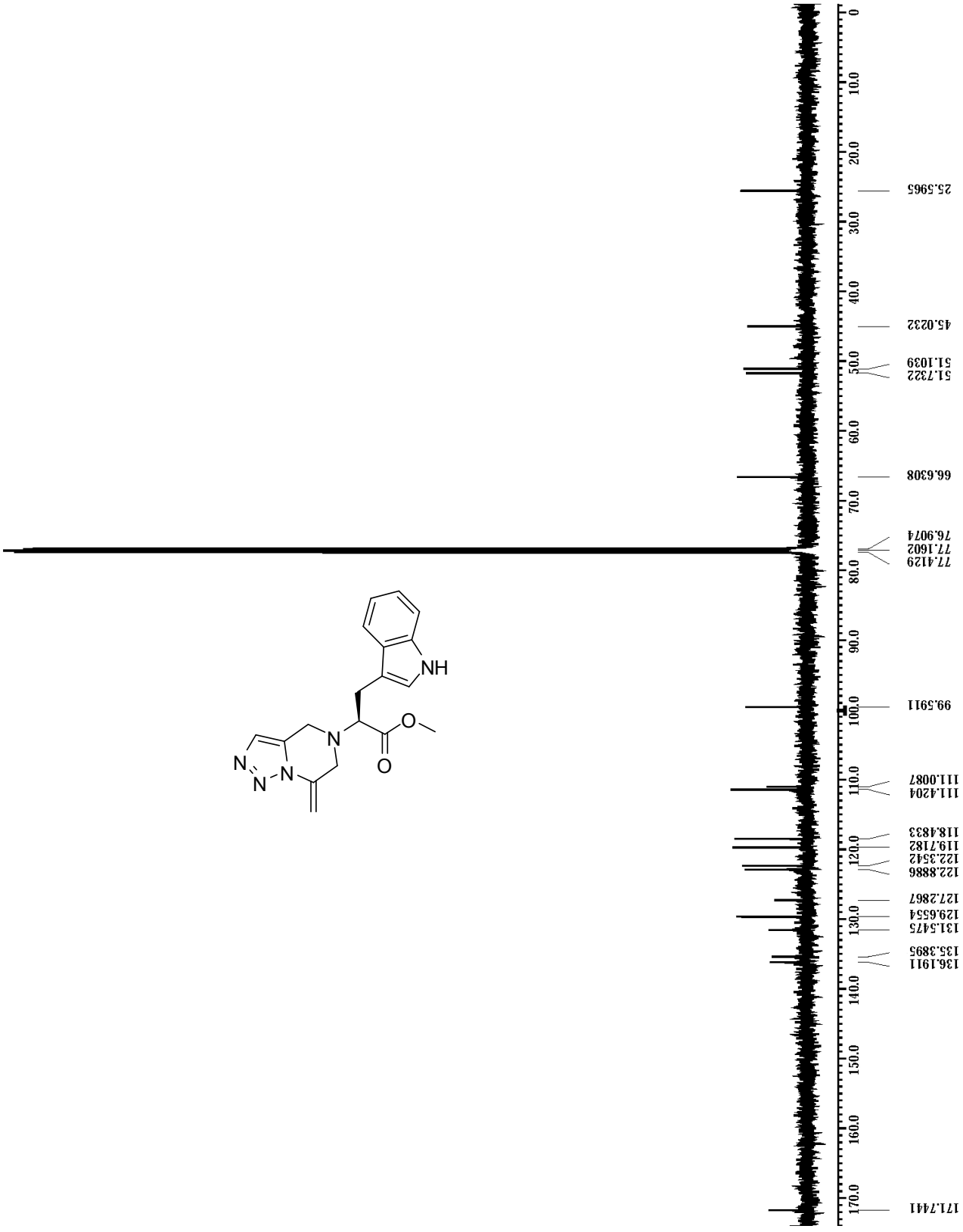


Figure S40. ^{13}C NMR spectrum of **4c**

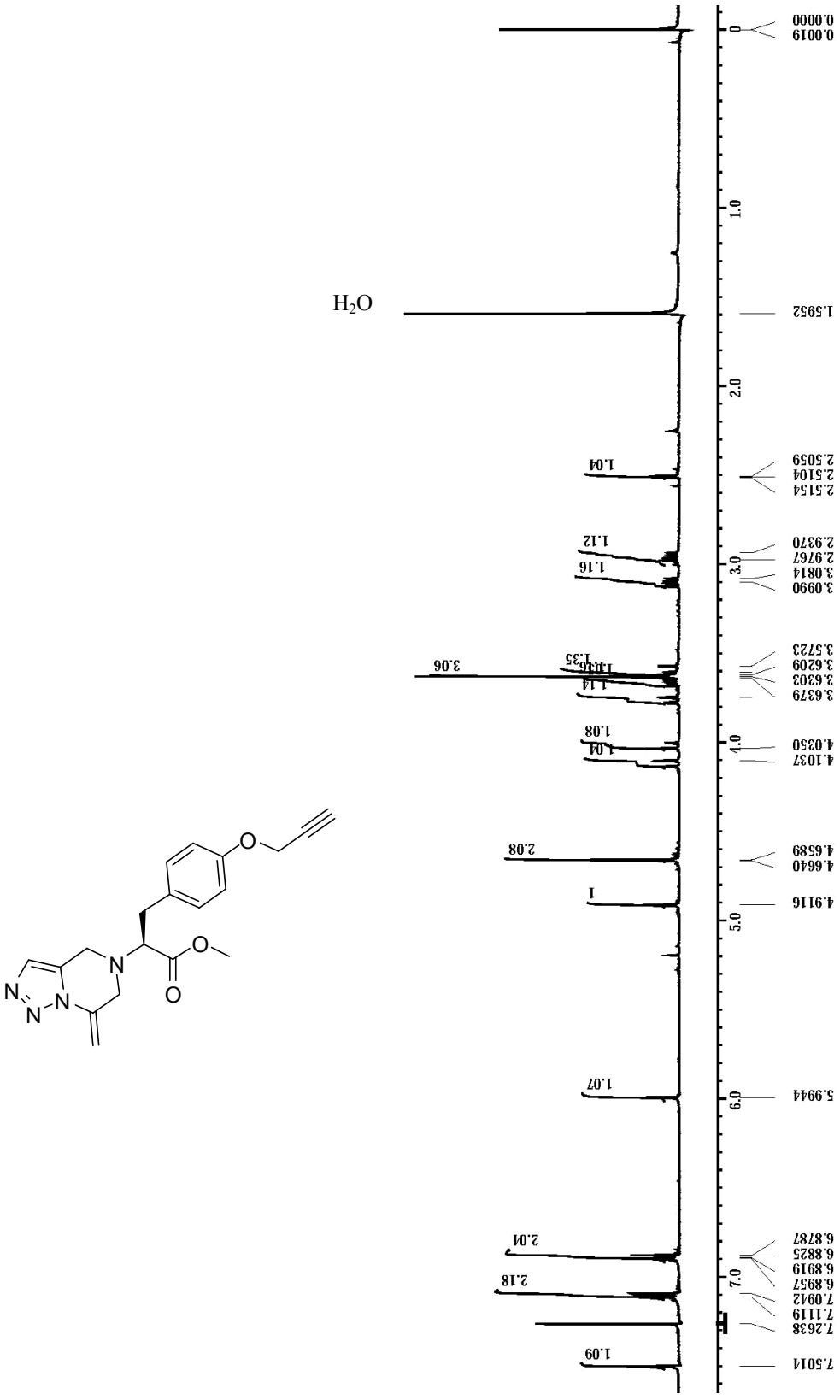


Figure S41. ^{1}H NMR spectrum of **4d**

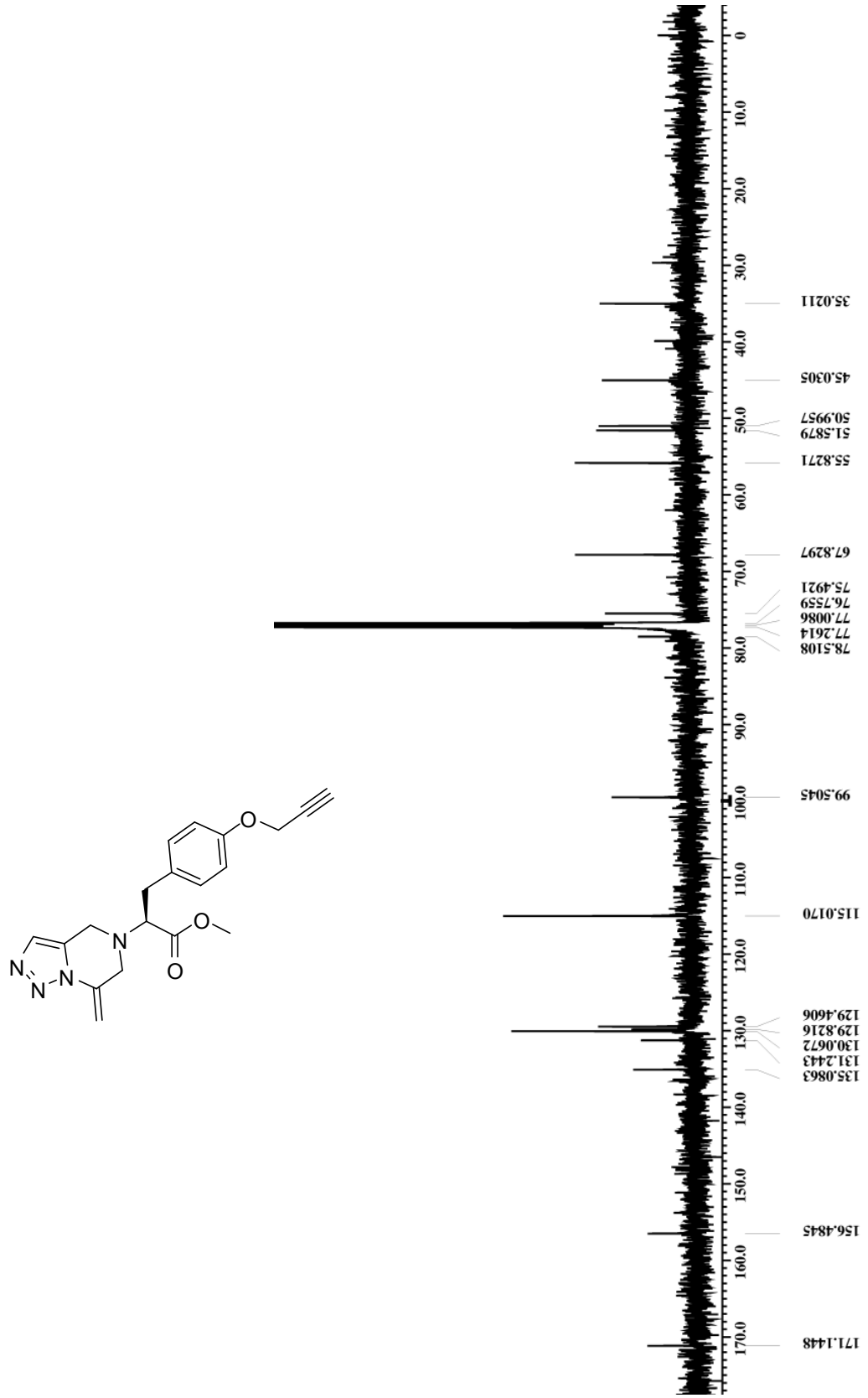


Figure S42. ^{13}C NMR spectrum of **4d**

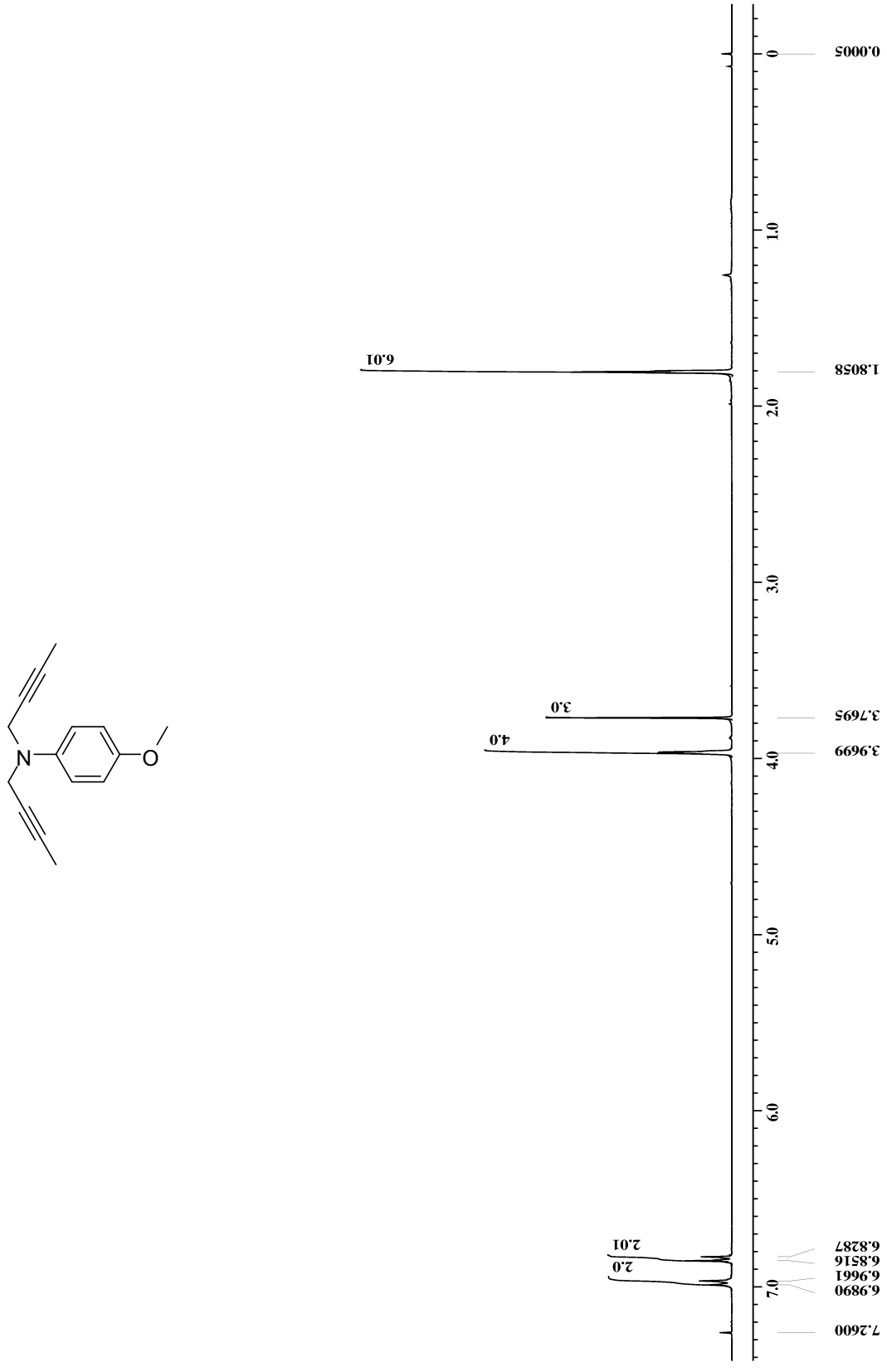


Figure S43. ^{1}H NMR spectrum of **5a**

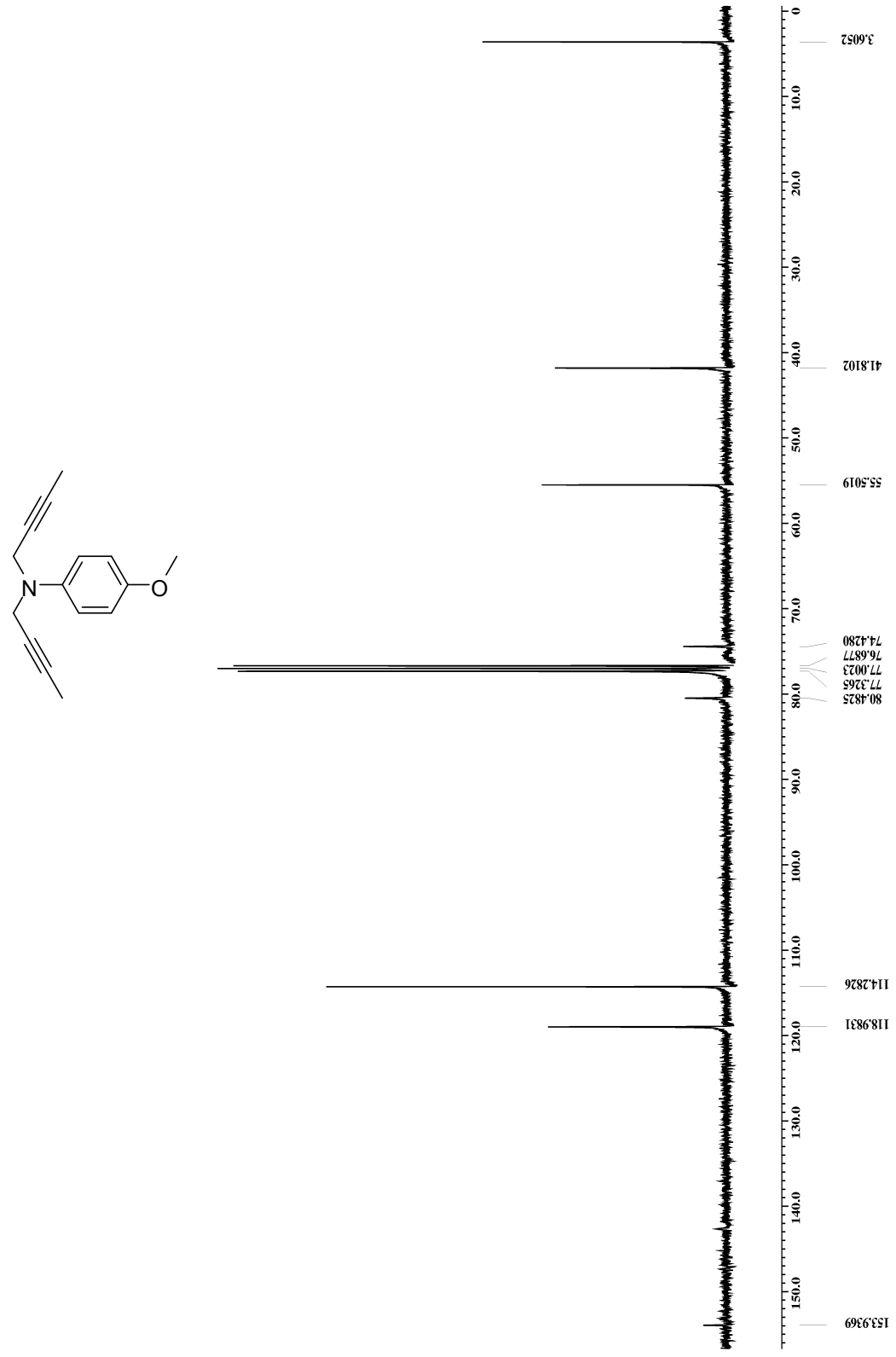


Figure S44. ^{13}C NMR spectrum of **5a**

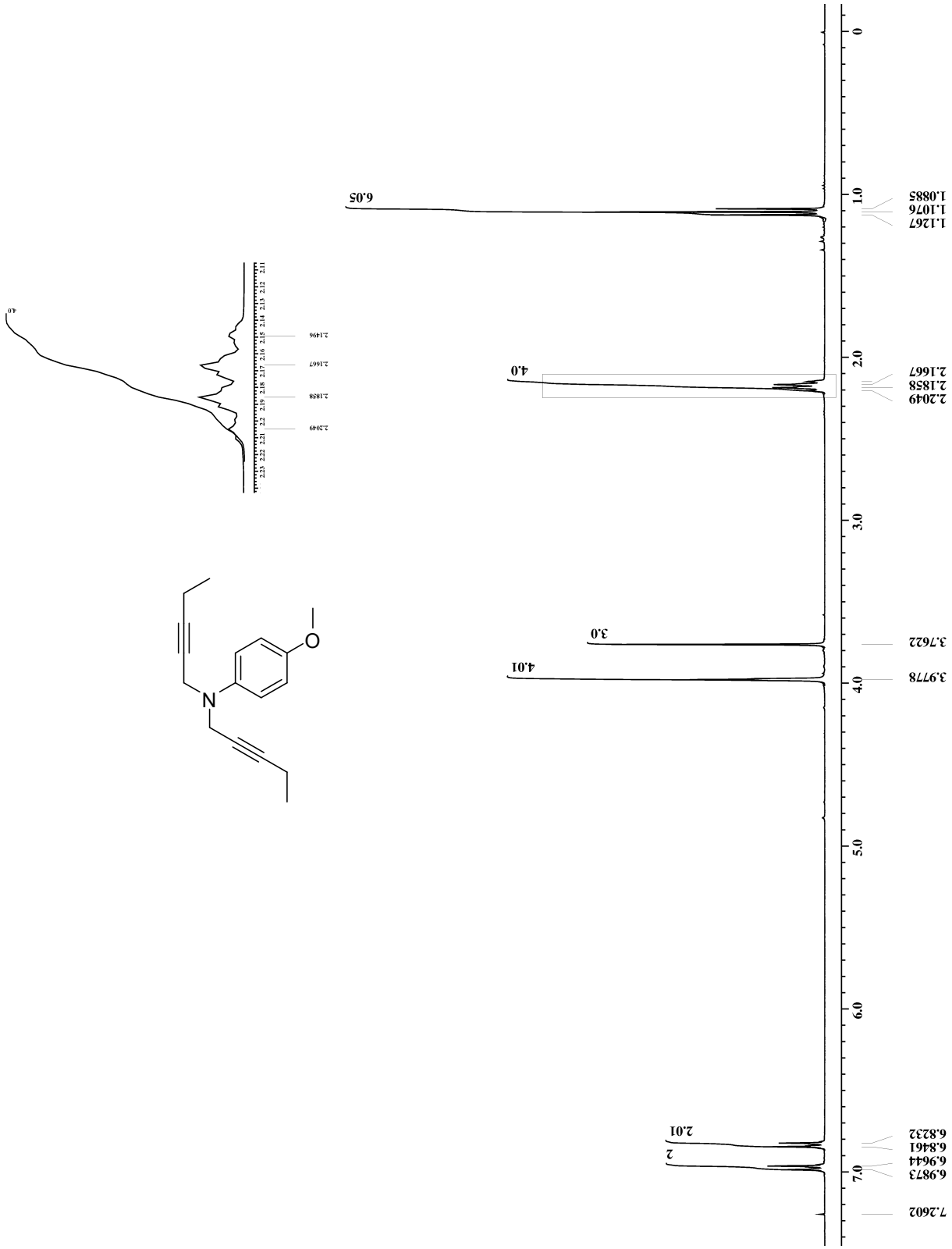


Figure S45. ^{1}H NMR spectrum of **5b**

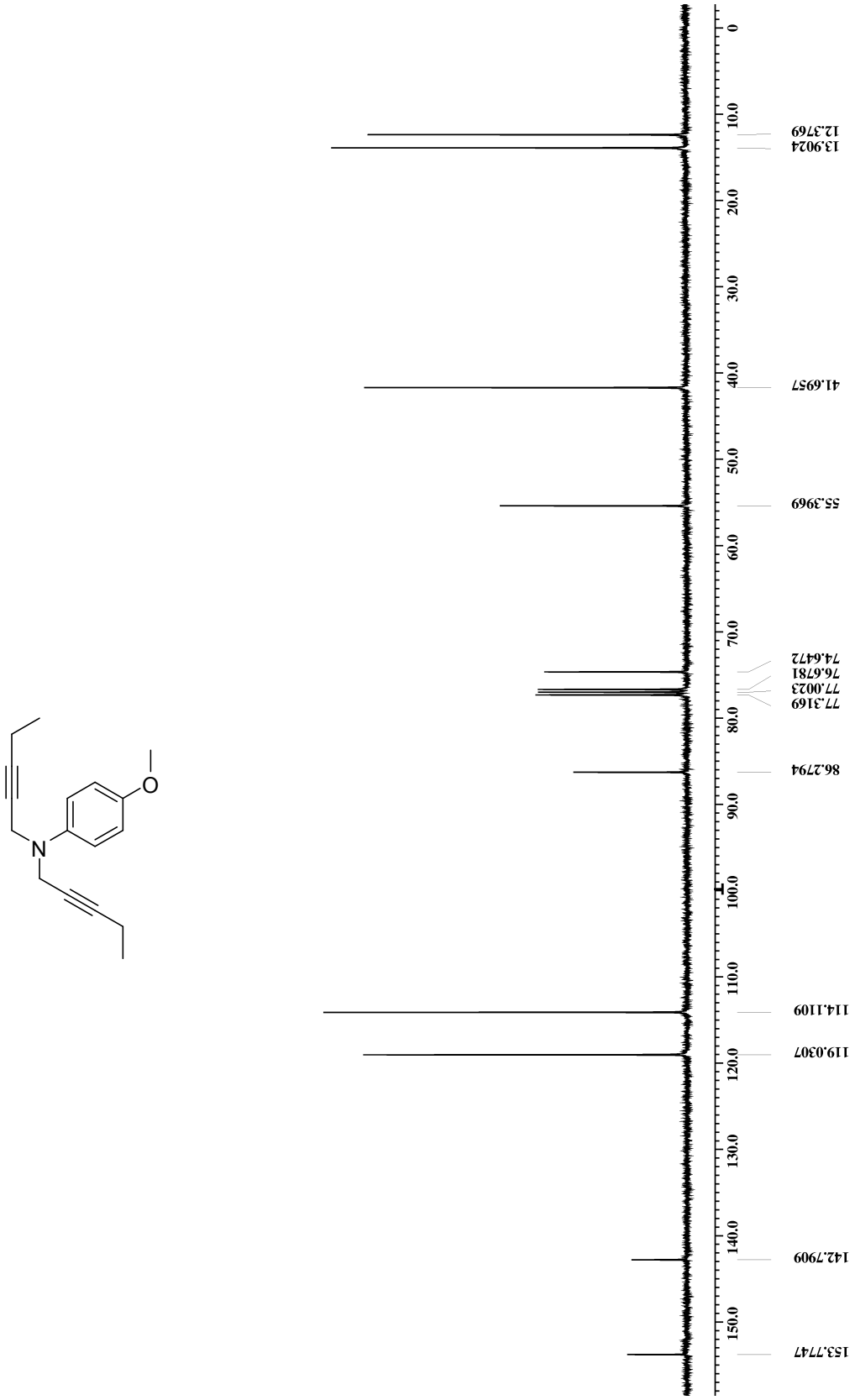


Figure S46. ^{13}C NMR spectrum of **5b**

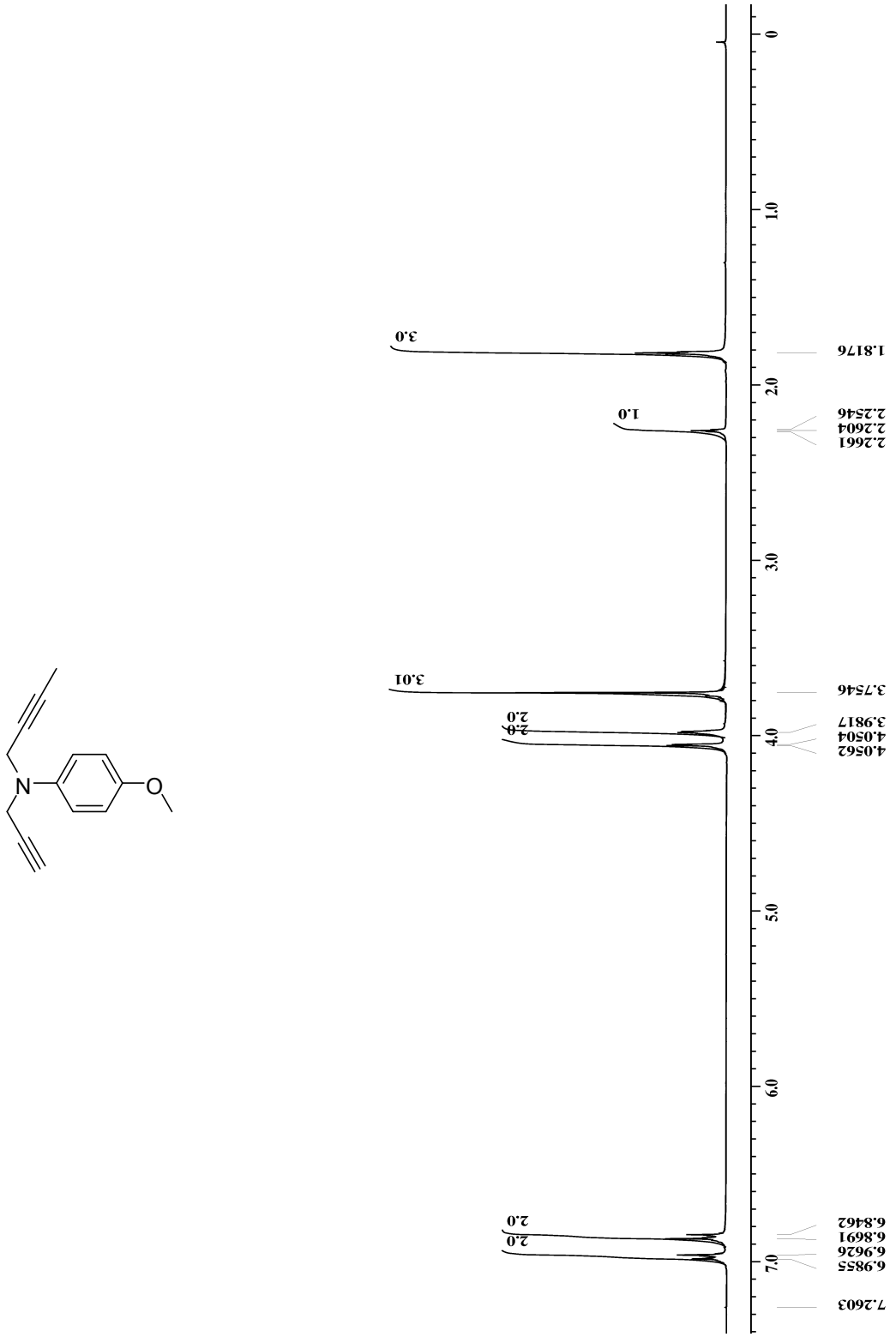


Figure S47. ^{1}H NMR spectrum of **7a**

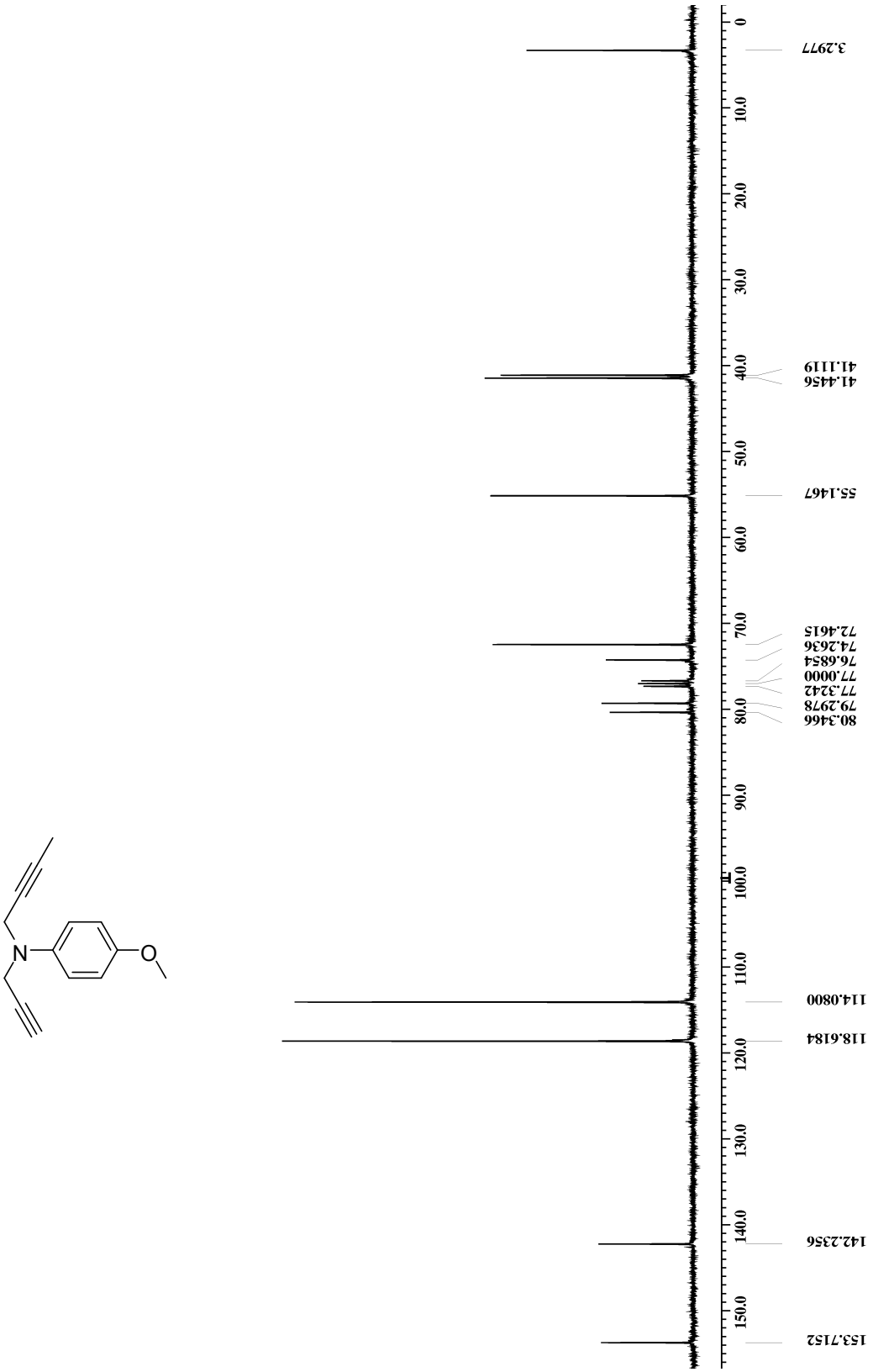


Figure S48. ^{13}C NMR spectrum of **7a**

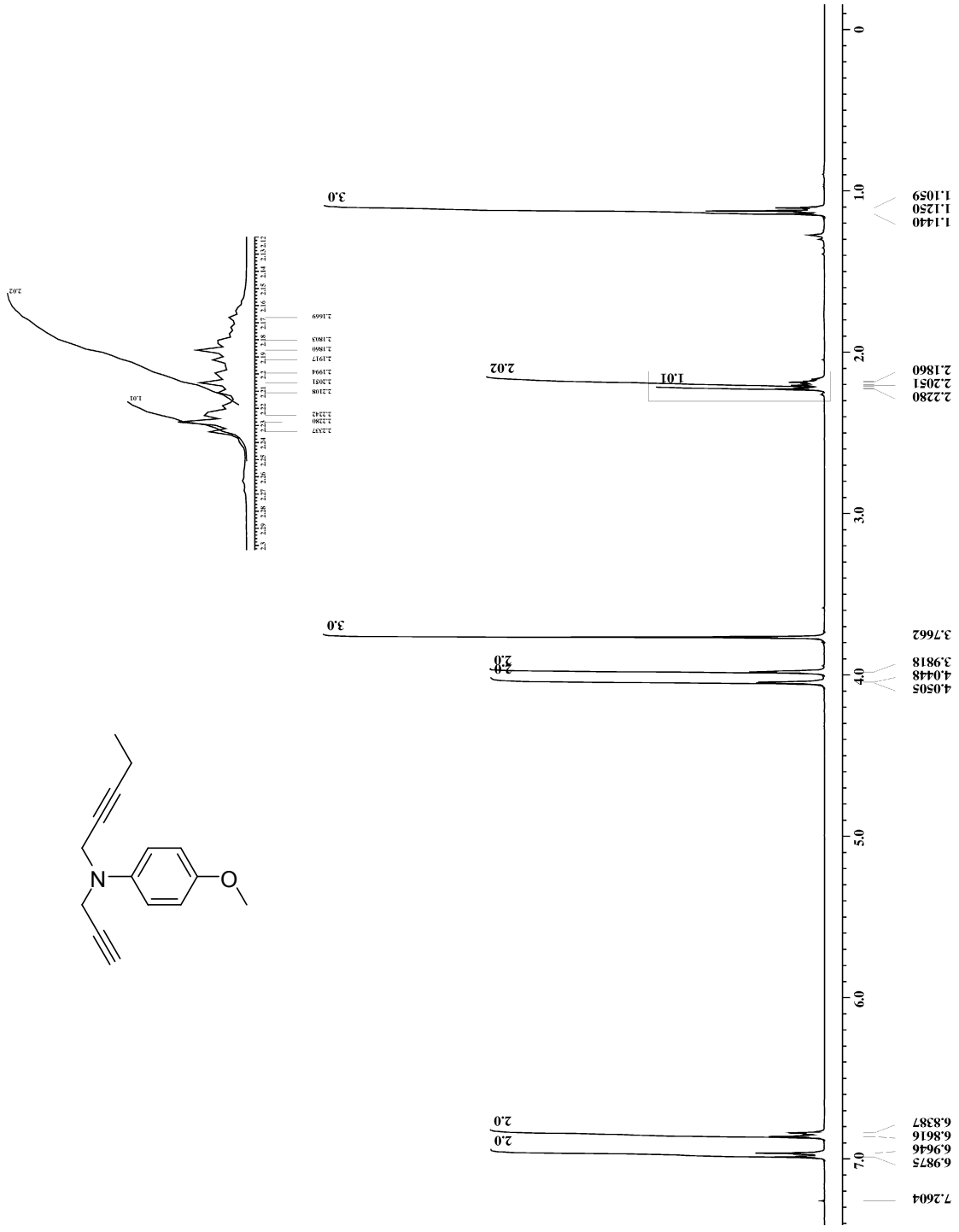


Figure S49. ^{1}H NMR spectrum of **7b**

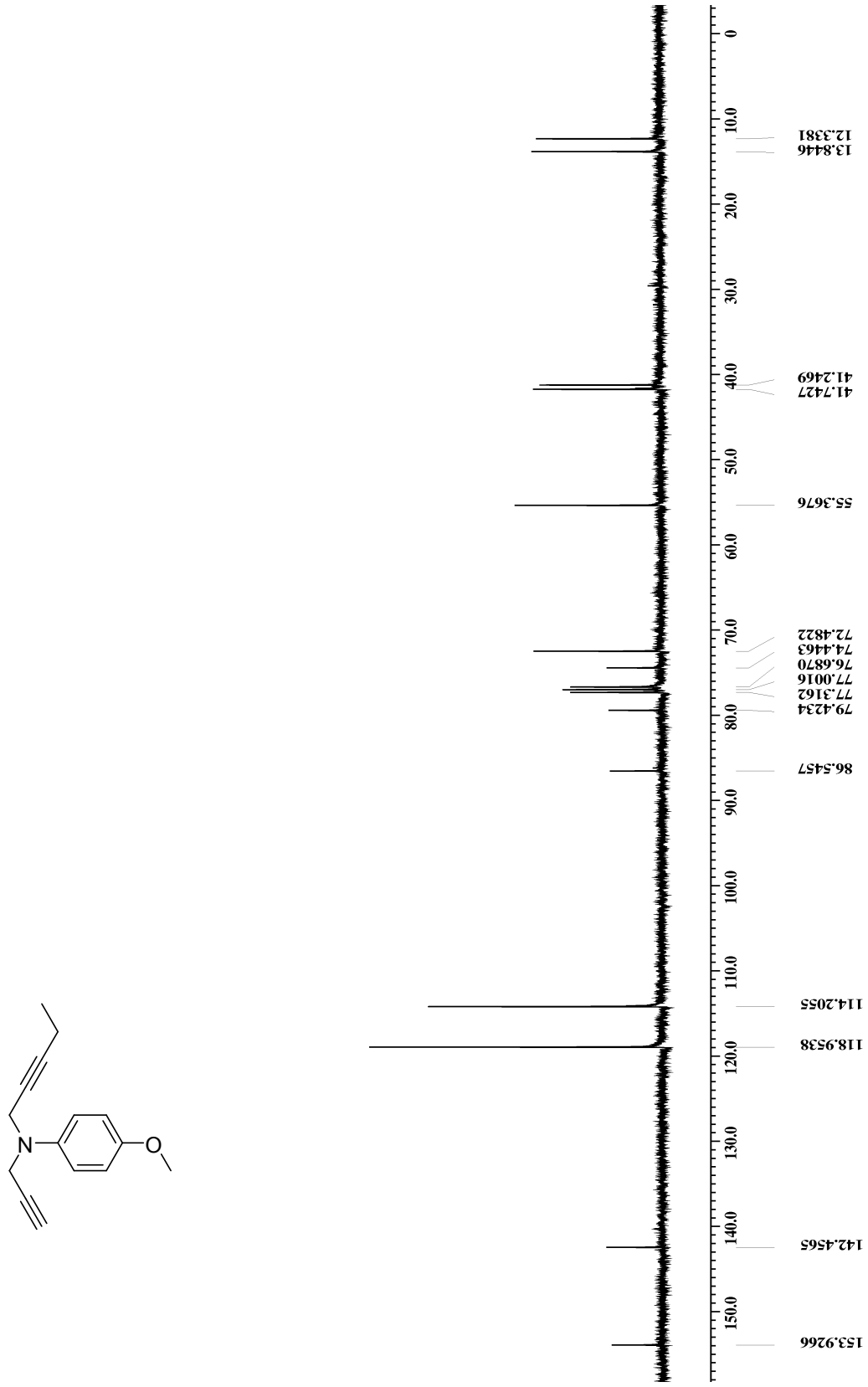


Figure S50. ^{13}C NMR spectrum of **7b**

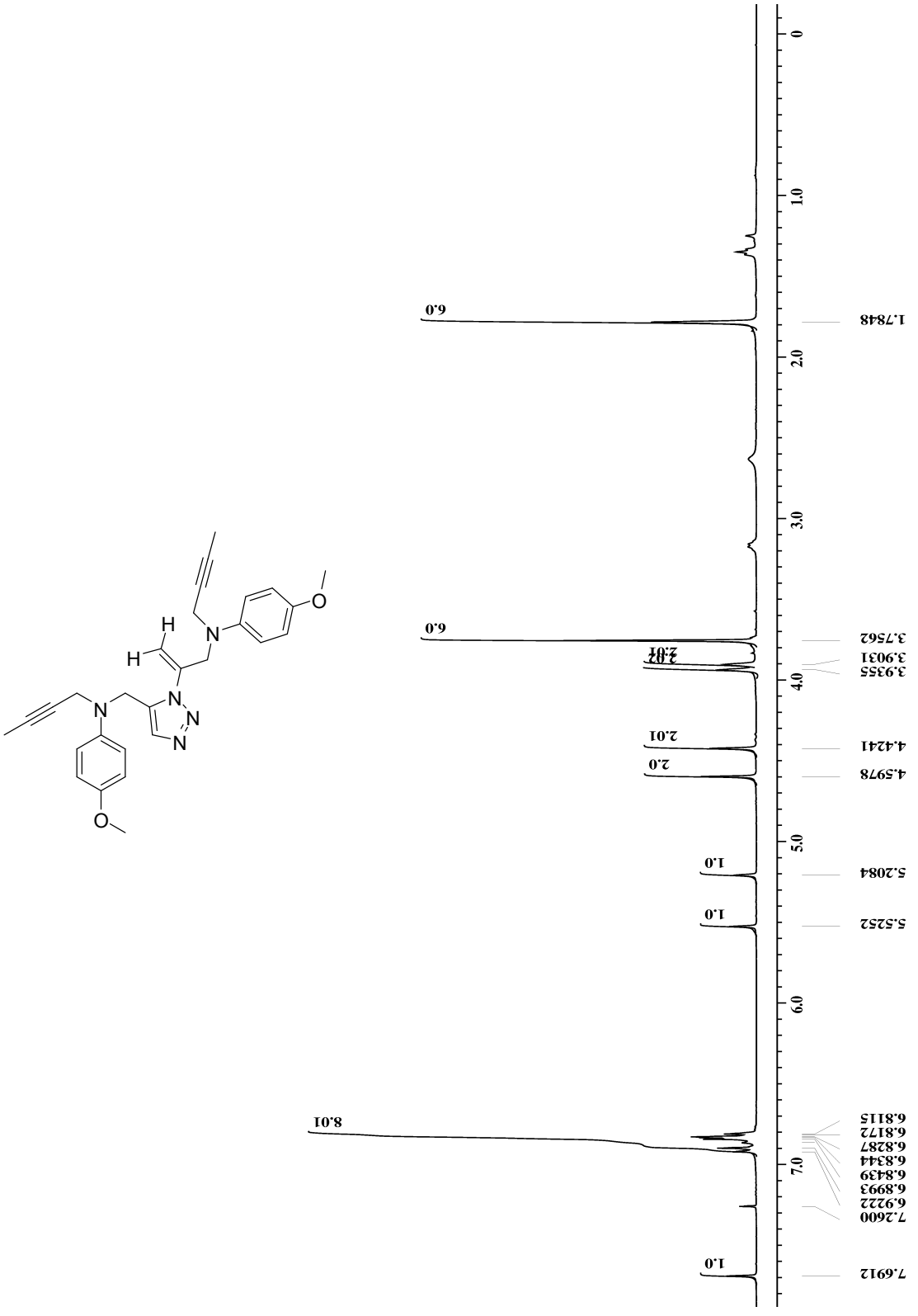


Figure S51. ^{1}H NMR spectrum of **8a**

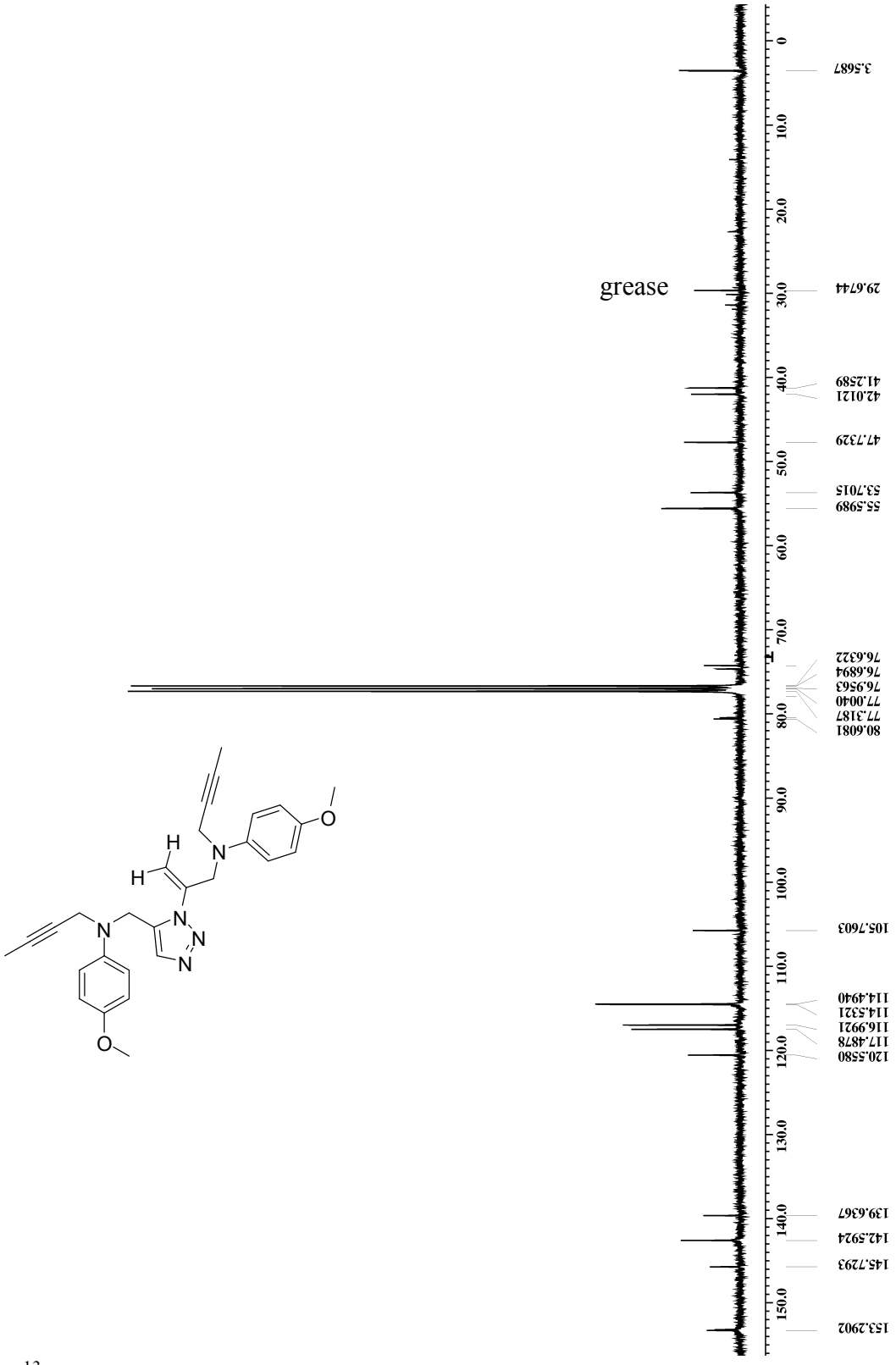


Figure S52. ^{13}C NMR spectrum of **8a**

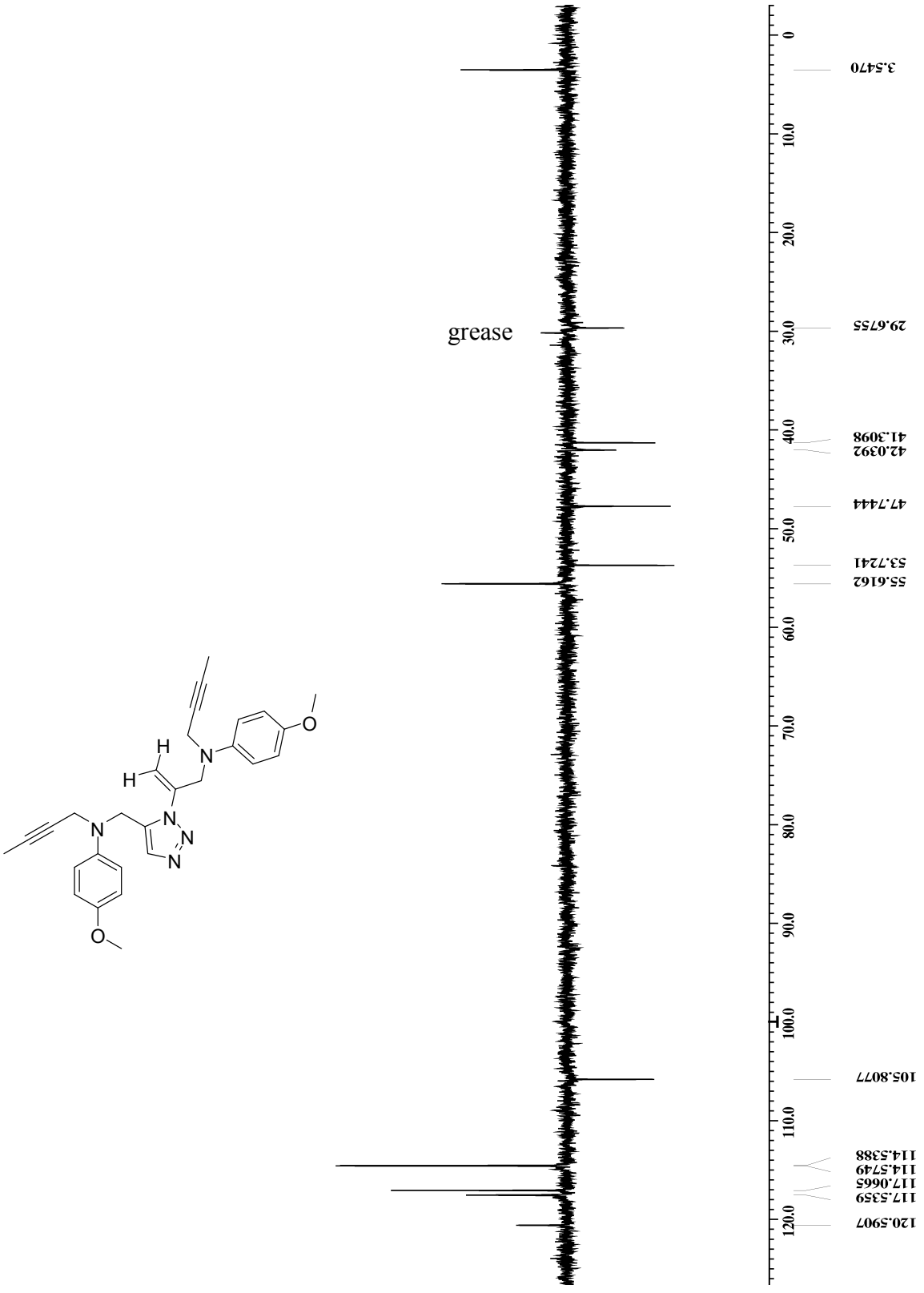


Figure S53. DEPT spectrum of **8a**

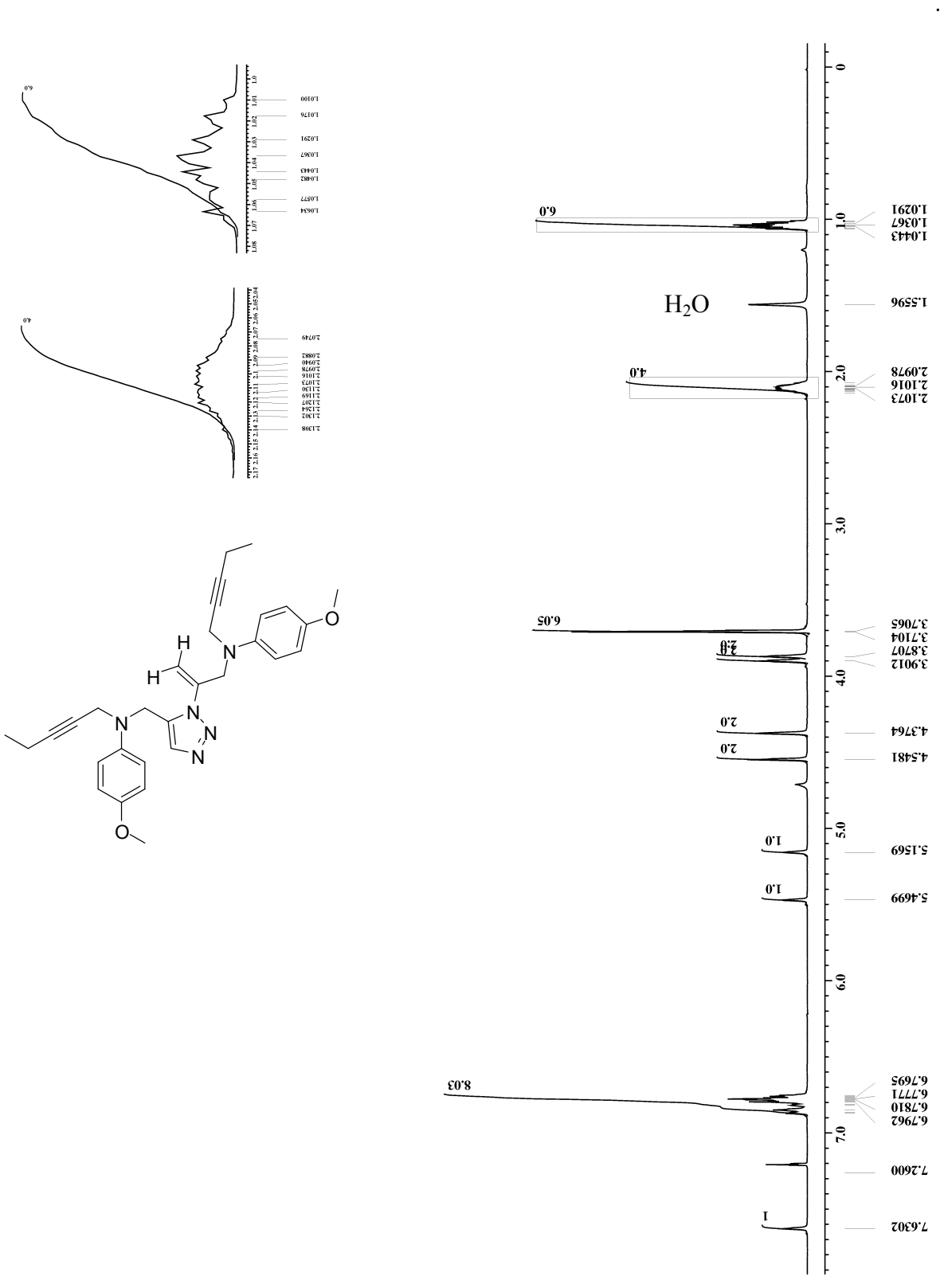


Figure S54. ^{1}H NMR spectrum of **8b**

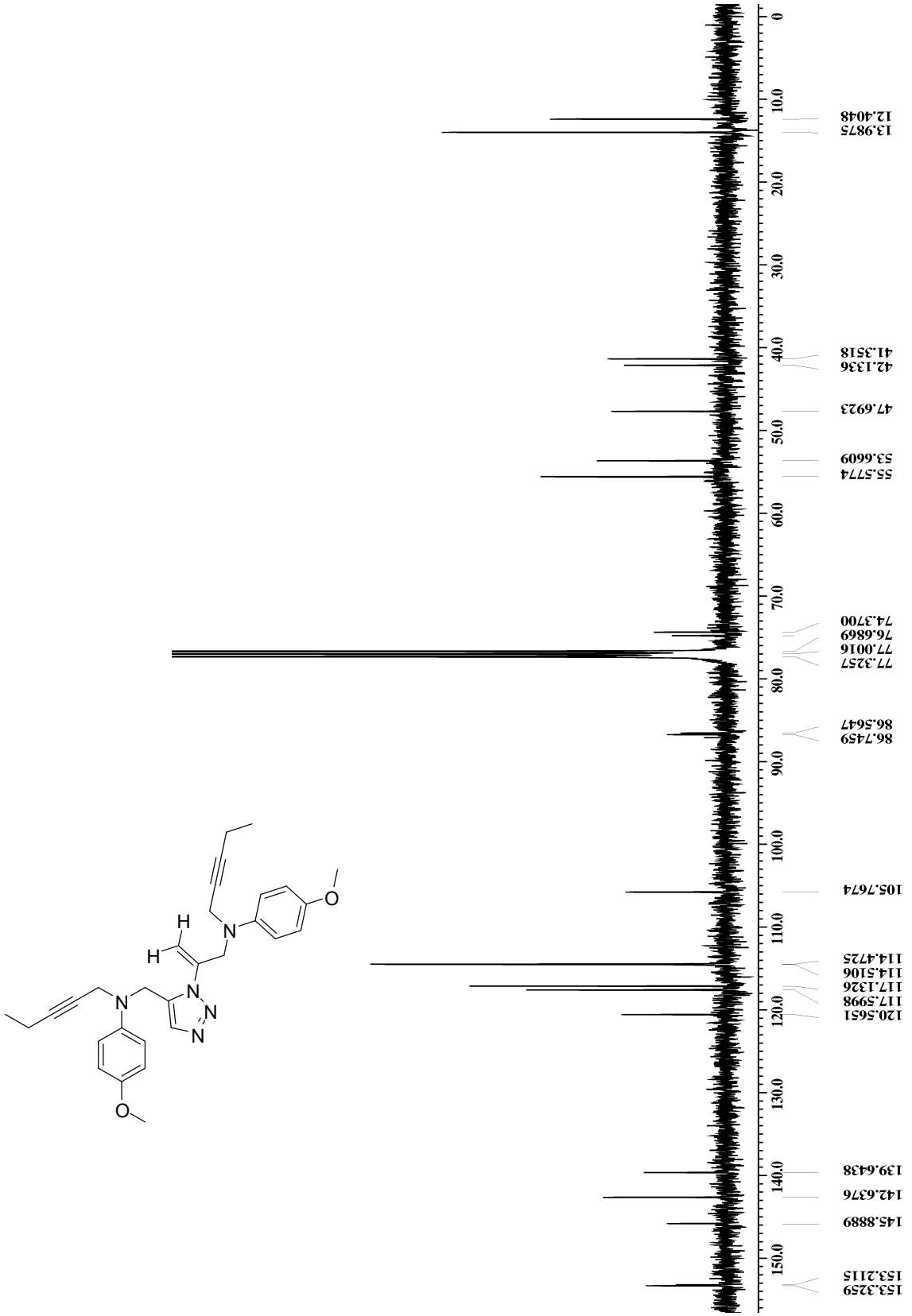


Figure S55. ^{13}C NMR spectrum of **8b**

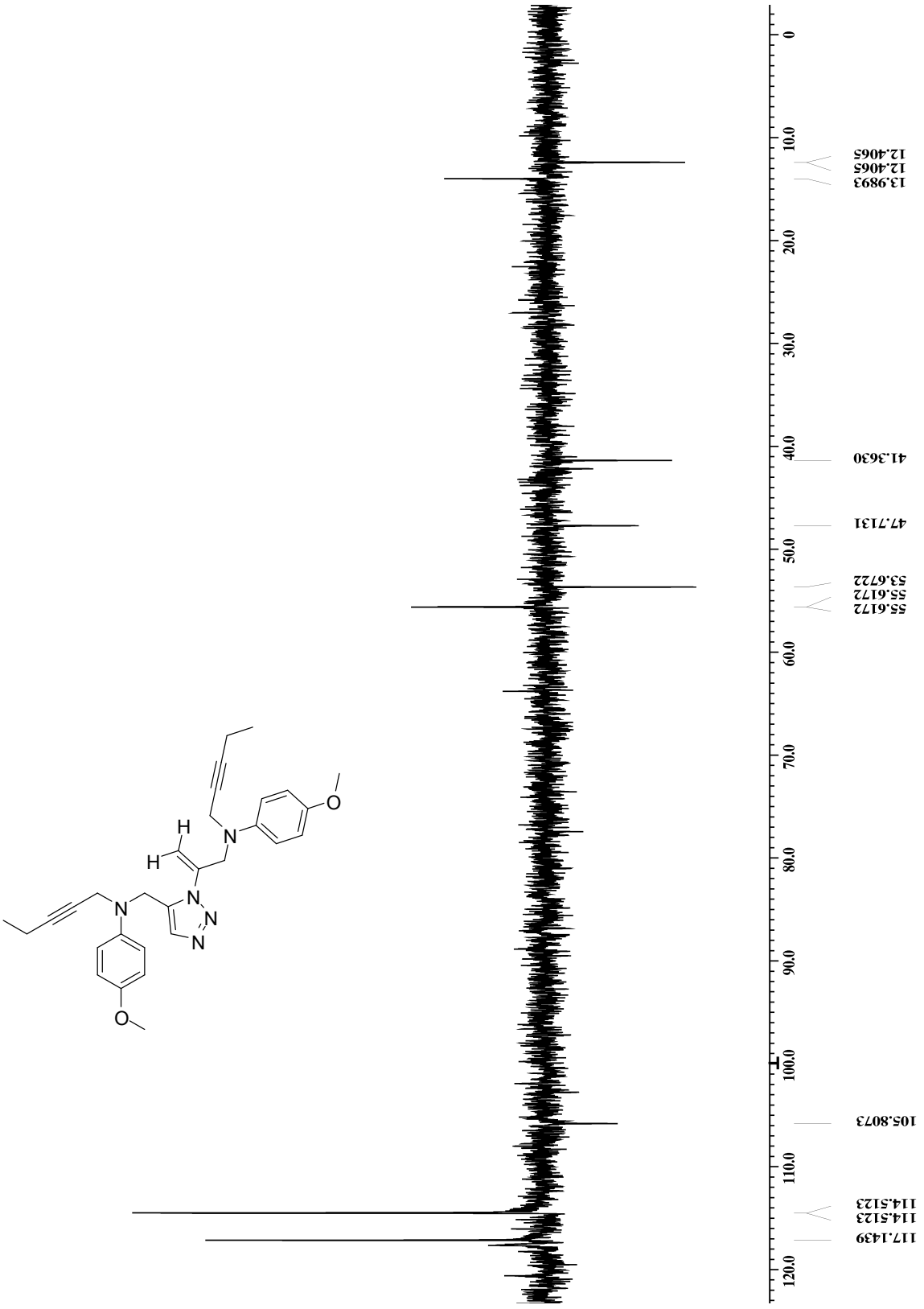


Figure S56. DEPT spectrum of **8b**

Crystallographic Details: **(CCDC Number 1026579)**

Compound **5a**: Single crystals were obtained by slow diffusion of CH_2Cl_2 solution. Crystal Data were collected on a SuperNova, Dual, Cu at zero, Eos diffractometer using graphite monochromated Mo Kα radiation (λ= 0.71073 Å). The crystal was kept at 100.00(10) K during data collection. Using Olex2[3], the structure was solved with the ShelXS[4] structure solution program using Direct Methods and refined with the ShelXL[5] refinement package using Least Squares minimisation. All hydrogen atoms were added according to the riding model. Crystallographic parameters for compound **5a** are given in **Table S1**. Selected bond lengths and bond angles of compound **5a** are given in **Table S2** and **Table S3** respectively.

Table S1: Crystallographic parameters for **5a**

Empirical formula	$C_{15}H_{17}NO$
F.W.	227.30
Crystal system	Orthorhombic
Space group	$Pca2_1$
a(Å)	23.9173 (15)
b(Å)	6.7330 (3)
c(Å)	7.7378 (5)
α(°)	90
β(°)	90
γ(°)	90
V, Å^3	1246.06 (13)
Z	4
λ, Å	0.710703
$\rho_{calc,}$ mg/mm^3	1.212
Crystal size, mm^3	0.14 × 0.08 × 0.06
T, K	100
μ, mm^{-1}	0.08
F(000)	488
2Θ range for data collection	3.4 to 50.08°
Index ranges	$-28 \le h \le 18$, $-8 \le k \le 4$, $-6 \le l \le 9$
Reflections collected	2554
Independent reflections	1575[R(int) = 0.0391]
Data/restraints/parameters	1575/1/157
Final R indexes [I>=2σ (I)]	R_1 = 0.0555, wR_2 = 0.1443
Final R indexes [all data]	R_1 = 0.0589, wR_2 = 0.1482
GOF	1.04
Largest diff. peak/hole / e Å^{-3}	0.26/-0.27
w	$1/[\sigma^2(F_o^2) + (0.0906P)^2 + 0.5005P]$ where $P = (F_o^2 + 2F_c^2)/3$

Table S2: Selected bond lengths (Å) of 5a

5a					
N1	C8	1.464 (4)	C9	C10	1.195 (6)
N1	C12	1.487 (4)	C13	C14	1.188 (5)

Table S3: Selected bond angles (deg) of 5a

5a							
C5	N1	C8	116.9 (2)	N1	C8	C9	114.4 (3)
C5	N1	C12	115.0 (2)	C13	C12	N1	111.5 (3)
C10	C9	C8	176.5 (4)	C14	C13	C12	177.1 (4)

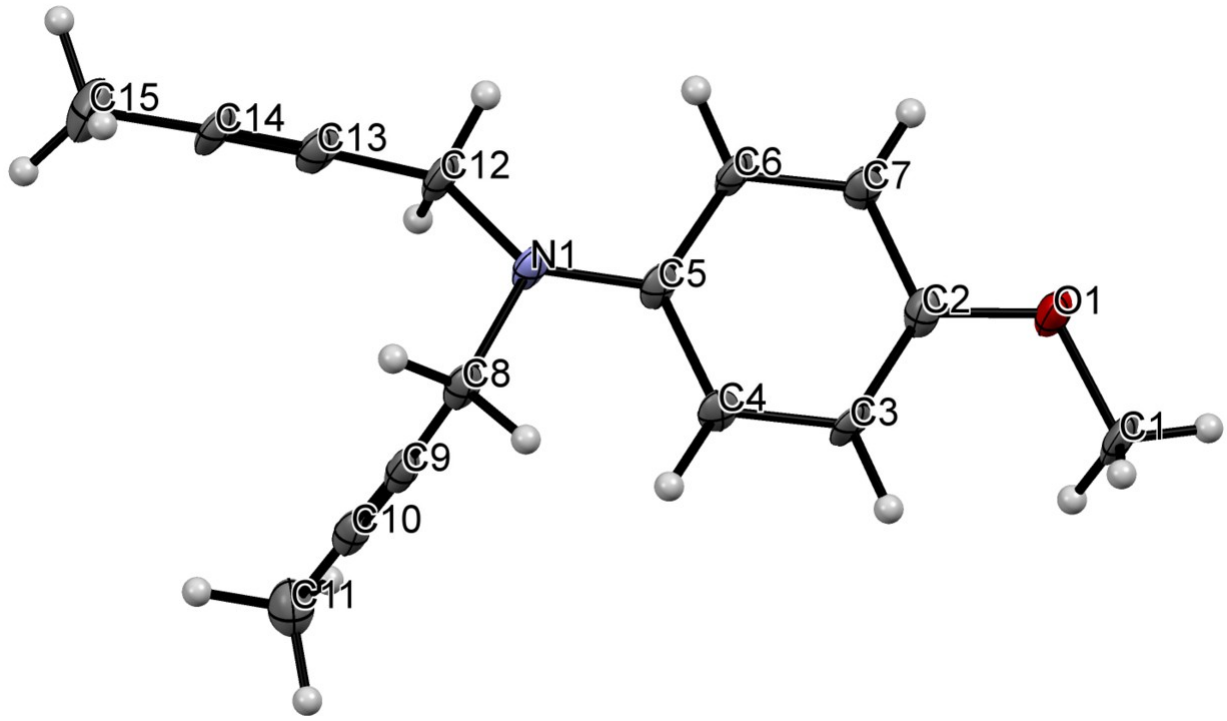


Figure S57: Crystal structure of **5a** (thermal ellipsoid plot with 50% probability)

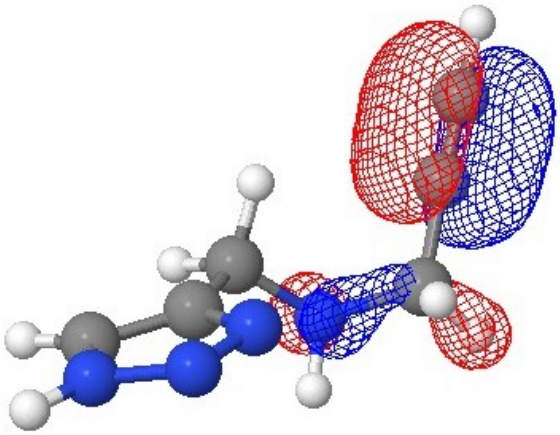


Figure S58. A RHF/STO-3G MO calculation on the geometry of the triazole-yne intermediate to visualize the π* of the alkyne moiety prior to the attack by the triazole N. Only the relevant part of the molecular architecture has been considered for simplicity of the calculation.

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