Supporting Information

‘Photorelease, Catch and Photorelease’ Strategies for Bioconjugation Utilizing *p*-Hydroxyphenacyl Group

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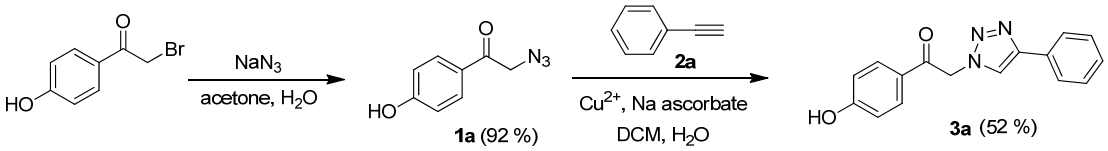
Contents

Materials and methods

Melting points were measured on a non-calibrated Kofler's hot stage melting point apparatus. NMR spectra were obtained on Bruker Avance II 300 MHz or Bruker Avance III 500 MHz spectrometers in chloroform-*d*, dimethylsulfoxide-d_6, acetonitrile-d_3, methanol-d_4 and water-d_2 or their mixtures, and they were referenced to the residual peak of the (major) solvent except for those of ^{19}F NMR. All NMR measurements were conducted at 30 °C. NMR spectra were processed using a program MestReNova v. 6.0.2. IR spectra were recorded on a Fourier transform spectrometer using solid samples. GC-MS spectra were recorded on a GC-coupled (30-m DB-XLB column) mass spectrometer in a positive mode with EI. HRMS spectra were obtained on a triple quadrupole ESI mass spectrometer in a positive and/or negative mode by Miroslava Bittová (Masaryk University). UV-Vis spectra were measured in 10.0 mm quartz fluorescence cuvettes using Agilent 8453 UV-VIS, Agilent Carry 5000 or GBC Scientific Equipment Cintra 2020 spectrometers. The spectral data were processed and plotted with an OriginPro 2015. The pH values of the solutions were determined using a glass electrode calibrated with certified buffer solutions at pH = 4.0, 7.0 and 10.0. All column chromatography procedures were performed on columns packed with silica gel (63−200 μm). Thin layer chromatography (TLC) was performed using silica gel plates Silica Gel 60 F254 (0.2 mm thickness, Merck) and visualized under a UV lamp (254 nm, 366 nm) or $KMnO_4$ stain. All solvents and chemicals used were used as purchased or purified/dried by standard procedures when necessary. Procedures involving dry solvents were carried out under nitrogen atmosphere.

Synthesis

Synthesis of *p*HP azide (1a) and model *p*HP triazole 3a



The bromide substituent in 4-hydroxyphenacyl bromide was substituted with an azide group in **1a**, which was allowed to react with phenylacetylene (**2a**) *via* the CuAAC (copper catalyzed alkyne-azide cycloaddition) to give the triazole **3a**.

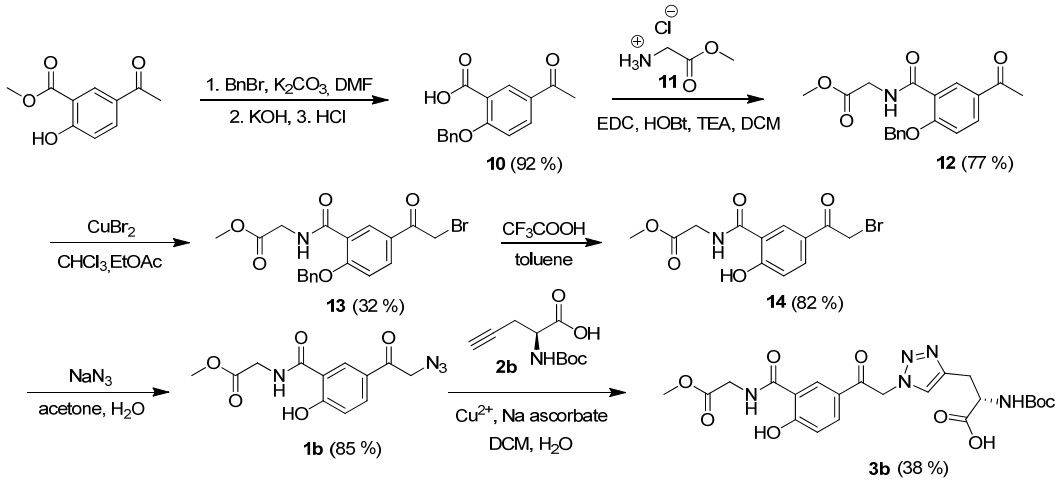
2-Bromo-1-(4-hydroxyphenyl)ethanone was prepared according to a known procedure.[1] ^{1}H NMR (300 MHz, DMSO): δ (ppm) 10.50 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.76 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, DMSO): δ (ppm) 189.85, 162.68, 131.44, 125.41, 115.43, 33.37.

2-Azido-1-(4-hydroxyphenyl)ethanone (1a). A 2-bromo-1-(4-hydroxyphenyl)ethanone (1.030 g, 4.79 mmol) was dissolved in an acetone/H_2O mixture (25 mL, 1:1, v/v). NaN_3 (0.605 g, 9.31 mmol) was dissolved in another portion of the same mixture (25 mL), and the solution of NaN_3 was added dropwise to a solution of the bromide under stirring. The reaction mixture was stirred at rt overnight. Subsequently, acetone was removed under reduced pressure and the

solution was extracted with dichloromethane (2 × 30 mL). Organic extracts were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by silica gel column chromatography (dichloromethane/ethyl acetate, 10:1, v/v) gave the title compound as white crystals. Yield 780 mg (92%). Mp >135 °C (decomp.; lit. 139–140 °C[2]). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.47 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.76 (s, 2H) (Figure S7). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ (ppm) 192.35, 162.68, 130.49, 125.84, 115.41, 54.13 (Figure S8). FTIR (neat, cm^{-1}): 3282.65, 2902.10, 2199.56, 2129.28, 2099.03, 1657.91, 1601.01, 1571.49, 1513.90, 1446.53, 1423.20, 1357.88, 1312.75, 1281.45, 1238.76, 1207.77, 1165.54, 1109.47, 1002.54, 987.61, 939.63, 905.56, 836.70, 810.06, 783.36, 722.74, 669.97, 634.65, 594.24, 563.69, 547.28, 499.20, 483.67, 468.70, 417.39. HRMS (ESI$^-$): calculated for $C_8H_7N_3O_2$ [M–H$^+$] 176.0466, found 176.0461. This compound has also been characterized elsewhere.[3]

1-(4-Hydroxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (3a). The azide **1a** (0.350 g, 1.976 mmol), $CuSO_4$ (0.016 g, 0.100 mmol) and sodium L-ascorbate (0.078 g, 0.395 mmol) were suspended in dichloromethane (25 mL). Phenylacetylene (**2a**, 0.22 mL, 1.98 mmol) was then added followed by addition of distilled water (25 mL) under vigorous stirring. The emulsion was stirred overnight at rt. Subsequently, the reaction mixture was extracted by ethyl acetate (5 × 20 mL). Organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product (0.524 g). Purification by silica gel chromatography eluting with hexane/ethyl acetate (1:1, v/v) gave the title compound as a pale yellow crystalline solid. Yield 0.290 g (52%). Mp 205–207 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.57 (s, 1H), 8.50 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.91–7.83 (m, 2H), 7.52–7.42 (m, 2H), 7.39–7.30 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.11 (s, 2H) (Figure S9). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ (ppm) 189.95, 162.98, 146.20, 130.84, 130.79, 128.89, 127.78, 125.61, 125.11, 123.04, 115.55, 55.40 (Figure S10). FTIR (neat, cm^{-1}): 3137.78, 3057.19, 2993.87, 2921.81, 2850.85, 2808.56, 2761.81, 2685.88, 2613.17, 2522.36, 1687.35, 1599.87, 1586.80, 1513.85, 1486.92, 1452.81, 1440.76, 1396.41, 1370.59, 1336.35, 1276.78, 1265.11, 1231.63, 1165.94, 1113.62, 1089.15, 1059.24, 1031.39, 982.48, 959.14, 886.40, 832.37, 763.98, 743.31, 707.02, 691.10, 675.77, 636.03, 595.86, 570.97, 509.18, 493.83, 465.32, 421.09. HRMS (ESI$^-$): calculated for $C_{16}H_{13}N_3O_2$ [M − H$^+$] 278.0935, found 278.0933.

Synthesis of 3b



The hydroxyl group of the starting material, methyl 5-acetylsalicylate, was protected by benzylation, and the ester was hydrolyzed to produce the acid **10**. Methyl 2-aminoethanoate hydrochloride (**11**) was connected with **10** *via* a peptide coupling protocol with ethyl-(*N*',*N*'-dimethylamino)propylcarbodiimide (EDC) hydrochloride. The resulting amide **12** was brominated in the α-position. The yield was quite low because the mixture of the products (starting material, monobrominated and dibrominated products) could not be separated by column chromatography. Also, the reaction had to be quenched soon after the start of refluxing (4 h) due to the decomposition of **13**. In fact, Br_2 caused deprotection of the benzyl group. The benzyl group was finally removed by treating **13** with trifluoroacetic acid in toluene for 2 days at room temperature. The first attempt of debenzylation utilized hydrogen with palladium on carbon as a catalyst. However, the reaction was unsuccessful. H_2 cleaved the benzyl group along with the bromide. The bromide substituent in **14** was replaced with azide to produce the *m*-substituted *p*-hydroxyphenacyl azide **1b**. Finally, the azide **1b** was connected to *N*-Boc-propargyl-L-glycine (**2b**) *via* a triazole linkage. We were unable to fully characterize the resulting triazole **3b**. The ^{1}H NMR signals of the Boc group in **3b** in different solvents (CD_3OD, $CDCl_3$, CD_3CN) were very complex and broad even at low temperatures (−30 to +50 °C; carbamates exist in two forms and the barrier to rotation is low already in simple Boc-protected amino acids at room temperature;[4] Figure S2).

5-Acetyl-2-(benzyloxy)benzoic acid (10). The title compound was prepared according to literature.[5] K_2CO_3 (6.53 g, 47.3 mmol) and benzyl bromide (4.68 mL, 39.4 mmol) were added to a solution of methyl 5-acetylsalicylate (3.06 g, 15.8 mmol) in DMF (50 mL). The solution was stirred overnight at rt. Then, it was diluted with 200 mL of ethyl acetate/H_2O (1:1, v/v), the organic phase was separated, concentrated and chromatographed on silica gel (hexane/ethyl acetate, 4:1, v/v) to obtain an oil, which was then dissolved in a mixture of 100 mL of methanol and 25 mL of aqueous KOH (6 M). The mixture was stirred overnight at rt, and concentrated HCl was added slowly until the solution become acidic (pH paper). The precipitated solid (KCl) was filtered off, and the solution was concentrated under reduced pressure to 30 mL. Solution was then extracted with $CHCl_3$ (150 mL), dried over $MgSO_4$, filtered and evaporated at reduced pressure to produce the title compound as a white solid. Yield 3.929 g (92%). Mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.46 (s, 1H), 8.76 (d, J = 2.3 Hz, 1H), 8.21 (dd, J = 8.8, 2.3 Hz, 1H), 7.48–7.40 (m, 5H), 7.22 (d, J = 8.8 Hz, 1H), 5.37 (s, 2H), 2.62 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 196.06, 165.52, 160.98, 134.83, 134.75, 134.17, 131.38, 129.35, 129.30, 127.90, 118.29, 113.51, 72.45, 26.56. This compound has already been described.[6]

Methyl 2-aminoethanoate hydrochloride (11). Compound was prepared according to the literature.[7] ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 8.67 (s, 3H), 3.73 (s, 2H), 3.70 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ (ppm) 167.94, 52.50, 39.45.

Methyl 2-(5-acetyl-2-(benzyloxy)benzamido)acetate (12). Methyl 2-aminoacetate hydrochloride (**11**, 0.352 g, 2.81 mmol), 1-hydroxybenzotriazole hydrate (0.417 g, 3.09 mmol), EDC•HCl (0.592 g, 3.09 mmol) and 5-acetyl-2-(benzyloxy)benzoic acid (**10**, 0.759 g, 2.81 mmol) were dissolved in dichloromethane (80 mL). Triethylamine (0.86 mL, 6.2 mmol) was added, and the solution was stirred overnight at rt. The most of dichloromethane was evaporated (~60 mL), and ethyl acetate (60 mL) was added to the residue. The solution was washed with water (2 × 10 mL), the organic phase was separated and dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford a crude product, pale yellow

crystals (0.916 g). Purification by column chromatography (ethyl acetate/hexane, 2:1, v/v) gave the amide **12** as white crystals. Yield 0.738 g (77%). Mp 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.81 (d, J = 2.4 Hz, 1H), 8.35 (s, 1H), 8.11 (dd, J = 8.7, 2.4 Hz, 1H), 7.52–7.33 (m, 5H), 7.13 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 4.21 (d, J = 5.2 Hz, 2H), 3.73 (s, 3H), 2.61 (s, 3H) (Figure S11). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 196.58, 170.15, 164.54, 160.36, 134.94, 133.82, 133.04, 130.96, 129.08, 128.93, 127.86, 121.00, 113.23, 71.78, 52.32, 41.95, 26.57 (Figure S12). FTIR (neat, cm^{-1}): 3387.38, 3040.76, 3003.66, 2957.35, 2916.24, 2849.48, 1753.68, 1678.56, 1635.61, 1594.66, 1517.99, 1462.64, 1439.58, 1391.30, 1358.63, 1303.60, 1260.58, 1204.75, 1129.75, 1097.51, 1083.39, 1029.48, 1011.25, 988.82, 965.14, 944.15, 930.45, 882.72, 852.50, 828.29, 781.64, 747.64, 730.36, 698.28, 653.01, 624.95, 614.35, 596.73, 556.76, 513.04, 494.56, 475.78, 457.46, 439.56. HRMS (APCI^{+}): calculated for $C_{19}H_{19}NO_5$ [M + H^{+}] 342.1336, found 342.1335.

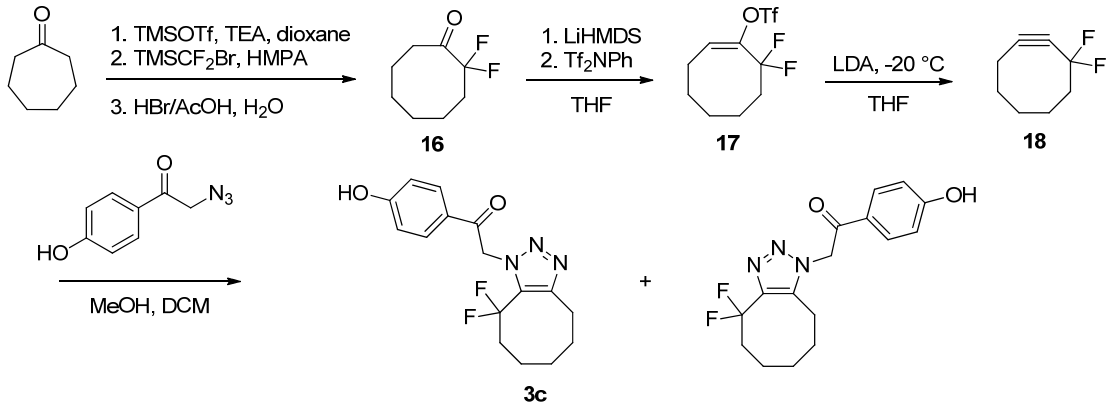
Methyl 2-(2-(benzyloxy)-5-(2-bromoacetyl)benzamido)acetate (13). A solution of **12** (0.993 g, 2.91 mmol) and $CuBr_2$ (1.455 g, 6.52 mmol) in 160 mL of ethyl acetate/$CHCl_3$ (1:1, v/v) was vigorously stirred and refluxed for 4 hours (the reaction progress was monitored by TLC). Then, the mixture was cooled to rt, filtered through a pad of silica and concentrated under reduced pressure to afford the crude title compound as a yellow solid. Purification of 1.06 g of crude material and 0.240 g from the previous run by silica gel chromatography (dichloromethane/ethyl acetate/hexane, 3:1:1, v/v) gave the product as white crystals. Yield 395 mg (32%). Mp 152–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.83 (d, J = 2.4 Hz, 1H), 8.32 (s, 1H), 8.14 (dd, J = 8.8, 2.4 Hz, 1H), 7.54–7.33 (m, 5H), 7.16 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.47 (s, 2H), 4.21 (d, J = 5.1 Hz, 2H), 3.73 (s, 3H) (Figure S13). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 189.84, 170.15, 164.19, 160.92, 134.76, 134.11, 134.09, 129.17, 129.07, 127.91, 127.75, 121.38, 113.63, 71.95, 52.40, 42.01, 30.98 (Figure S14). FTIR (neat, cm^{-1}): 3381.00, 3064.85, 2985.13, 2954.45, 2926.85, 2850.33, 2106.87, 1745.68, 1682.88, 1646.00, 1591.33, 1526.68, 1486.43, 1462.66, 1451.07, 1441.17, 1428.46, 1395.05, 1365.93, 1318.07, 1289.36, 1269.42, 1234.95, 1201.69, 1171.53, 1153.63, 1127.05, 1087.05, 1028.97, 1006.25, 994.50, 949.43, 912.25, 883.32, 872.65, 815.29, 782.67, 754.59, 736.56, 706.01, 696.55, 645.33, 592.99, 562.66, 500.93, 488.52, 455.67. HRMS (APCI^{+}): calculated for $C_{19}H_{18}BrNO_5$ [M + H^{+}] 422.0423, found 422.0425.

Methyl 2-(5-(2-bromoacetyl)-2-hydroxybenzamido)acetate (14). Trifluoroacetic acid (4.0 mL) was added to a stirred suspension of **13** (0.343 g, 0.816 mmol) in toluene (4.0 mL). The solution was stirred for 2 days at rt. Subsequently, the solvent was evaporated under reduced pressure to give a dark brown oil. Purification by silica gel chromatography eluting with dichloromethane/ethyl acetate (10:1, v/v) and then with ethyl acetate gave the title compound as a pale pink solid. Yield 220 mg (82%). Mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 12.75 (s, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 8.8, 2.0 Hz, 1H), 7.18 (s, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H), 4.26 (d, J = 5.2 Hz, 2H), 3.84 (s, 3H) (Figure S15). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 189.85, 170.50, 169.71, 166.41, 135.18, 128.30, 125.08, 118.89, 114.08, 52.94, 41.43, 30.37 (Figure S16). FTIR (neat, cm^{-1}): 3374.12, 2993.35, 2948.55, 2850.37, 2598.33, 1746.20, 1687.83, 1599.16, 1576.39, 1547.98, 1517.65, 1436.07, 1418.66, 1396.97, 1368.04, 1314.80, 1288.26, 1248.75, 1196.34, 1179.18, 1120.68, 1082.02, 1037.93, 1003.36, 978.84, 930.96, 879.16, 831.05, 780.53, 740.98, 697.00, 667.71, 645.24, 596.03, 571.37, 502.07, 468.62, 407.38. HRMS (ESI^{-}): calculated for $C_{12}H_{12}BrNO_5$ [M – H^{+}] 327.9826, found 327.9824.

Methyl 2-(5-(2-azidoacetyl)-2-hydroxybenzamido)acetate (1b). The bromide **14** (0.297 g, 0.900 mmol) and NaN_3 (0.113 g, 1.738 mmol) were dissolved in acetone/H_2O (30 mL, 2:1, v/v). The solution was stirred at rt overnight. Then, acetone was removed under reduced pressure, aq NH_4Cl (10%, 10 mL) was added, and the solution was extracted with ethyl acetate (3 × 10 mL). Organic extracts were combined, dried over $MgSO_4$ and evaporated under reduced pressure to give a crude product (yellow solid). This material was suspended in hexane and filtered through a pad of silica, which was rinsed several times with hexane (5 × 10 mL) to get rid of non-polar impurities. The filtrate was discarded and the title compound was obtained by rinsing a pad with several portions of ethyl acetate (5 × 10 mL) and evaporating the filtrate under reduced pressure. Yield 220 mg (85%). Pale yellow crystals. Mp >130 °C decomp. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 12.76 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 8.8, 2.1 Hz, 1H), 7.32 (s, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.51 (s, 2H), 4.26 (d, J = 5.3 Hz, 2H), 3.84 (s, 3H) (Figure S17). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 191.48, 170.44, 169.54, 166.35, 133.76, 127.26, 125.37, 118.82, 113.97, 54.60, 52.81, 41.26 (Figure S18). FTIR (neat, cm^{-1}): 3376.96, 2955.47, 2915.67, 2850.72, 2590.78, 2102.07, 1748.92, 1684.29, 1635.46, 1599.91, 1574.14, 1543.91, 1436.48, 1419.38, 1368.96, 1344.04, 1313.70, 1251.00, 1199.94, 1178.92, 1121.89, 1076.61, 1041.07, 1006.77, 983.50, 967.77, 926.99, 913.12, 842.51, 816.71, 782.69, 740.31, 708.97, 697.17, 624.14, 598.01, 577.01, 551.51, 493.19, 472.87, 413.62. HRMS (ESI$^-$): calculated for $C_{12}H_{12}N_4O_5$ [M – H$^+$] 291.0735, found 291.0736.

2-((*tert*-Butoxycarbonyl)amino)-3-(1-(2-(4-hydroxy-3-((2-methoxy-2-oxoethyl)-carbamoyl)phenyl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid (3b). The azide **1b** (45.7 mg, 156 μmol), $CuSO_4$ (7.9 mg, 50 μmol), sodium L-ascorbate (15.9 mg, 80.3 μmol) and *N*-Boc-propargyl-L-glycine (**2b**, 35.3 mg, 165.6 μmol) were suspended in dichloromethane (5 mL), and water (5 mL) was added. The emulsion was vigorously stirred overnight. After that, the reaction mixture was extracted by ethyl acetate (3 x 10 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give 61 mg of a pale yellow-green solid. This was dissolved in dichloromethane (5 mL), and hexane (~20 mL) was added to create a saturated solution. It was cooled at –78 °C and precipitated crystals were filtered and washed with hexane (10 mL). Yield 30 mg (38%). We were unable to analyze the ^{1}H NMR spectrum due to presence of many conformers of compound (the spectrum is shown in Figure S2). Mp 130–140 °C. FTIR (neat, cm^{-1}): 3372.57, 2957.41, 1742.02, 1695.99, 1644.86, 1593.58, 1545.54, 1501.21, 1437.46, 1367.89, 1311.96, 1220.79, 1163.23, 1056.72, 1023.33, 1003.72, 831.76, 782.65, 700.31, 606.88, 585.41, 507.60, 490.76. HRMS (ESI$^-$): calculated for $C_{22}H_{27}N_5O_9$ [M – H$^+$] 504.1736, found 504.1737.

Synthesis of 3,3-difluorocyclooctyne (18) and *p*HP triazole 3c



The first step of the synthesis involves formal insertion of the CF_2 group to the starting cycloheptanone according to the literature.[8] In the next steps, the procedure for the synthesis of difluorocyclooctyne derivative by Bertozzi and coworkers[9] was used. The ketone **16** was transformed to the enol triflate **17** using Tf_2NPh. Elimination of the triflate from **17** using LDA afforded 3,3-difluorocyclooctyne (**18**). **18** was used immediately in the subsequent reaction or was stored in a freezer. The triflate **17** and the alkyne **18** were not fully characterized because it was not possible to purify them thoroughly by silica gel chromatography. The acetylene **18** was unstable at room temperature and rapidly decomposed. Click reaction of **18** and *p*HP azide (**1a**) provided two isomers, from which the major **3c** was isolated and fully characterized.

2,2-Difluorocyclooctanone (16). The title compound was prepared according to a procedure from the literature.[8] Trimethylsilyl trifluoromethanesulfonate (1.07 mL, 5.91 mmol) was added to a solution of cycloheptanone (0.58 mL, 4.9 mmol) and Et_3N (0.96 mL, 6.9 mmol) in dry dioxane (5 mL) at 10 °C. A cooling bath was removed, and the solution was stirred for 40 min at room temperature. Then, the mixture was cooled to 10 °C, trimethyl(bromodifluoromethyl)silane (2.50 g, 12.3 mmol) was added followed by HMPA (2.2 mL, 12 mmol), and the mixture was stirred for 3 h at rt. Volatile components were evaporated under reduced pressure, and HBr (33% solution in acetic acid, 9.5 mL, 54 mmol) was added in one portion followed by H_2O (0.98 mL, 54 mmol). The reaction vessel was tightly closed and stirred for 1 h at 80 °C. The reaction was quenched with sat. aq $NaHCO_3$ (15 mL) and diluted with water. The mixture was extracted with hexane/Et_2O (3 × 20 mL, 1:1, v/v), the organic layers were dried over anhydrous $MgSO_4$, filtered and solvent was evaporated under reduced pressure to give a dark-orange oil (≈2 g). Purification by silica gel chromatography (hexane/dichloromethane, R_f = 0.35, 3:1, v/v) gave the title compound as a colorless oil. Yield 520 mg (65%). The analytical data are identical with those in the literature.[10] ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.70–2.58 (m, 2H), 2.30–2.11 (m, 2H), 2.02–1.91 (m, 2H), 1.75–1.52 (m, 4H), 1.51–1.39 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) −106.45 (t, $^3J_{H\text{-}F}$ = 15.8 Hz). GC-MS: *m/z* (%) = 162 (<1) $[M]^+$, 133 (5), 118 (17), 98 (39), 55 (100).

(*E*)-8,8-Difluorocyclooct-1-en-1-yl trifluoromethanesulfonate (17). Lithium bis(trimethylsilyl)amide (130 mg, 777 μmol) was added to a dried Schlenk flask followed by addition of dry THF (5 mL). The reaction mixture was cooled to −78 °C under stirring, and the ketone **16** (134 mg, 493 μmol) was added dropwise over 5 min. The reaction mixture was stirred for an additional 40 min, and then a solution of

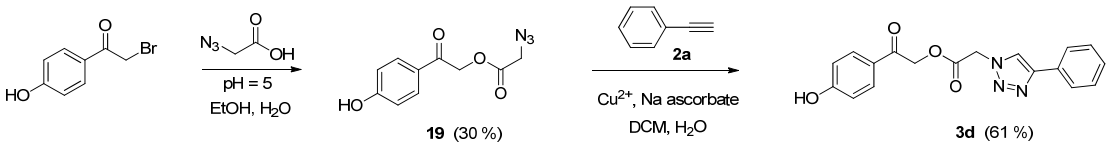
Tf_2NPh (242 mg, 677 μmol) in dry THF (4 mL) was added via syringe. The system was slowly warmed to rt, and the solution was stirred overnight. The solvent was evaporated under reduced pressure to give a pale yellow oil, which was filtered through a pad of silica and rinsed with a few portions of hexane/dichloromethane (3:1, v/v). The filtrate was evaporated under reduced pressure to give a colorless oil. Yield 170 mg (94%). Product was used without further purification in the subsequent step. ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) −70.62 (s, 3F), -73.92 (t, $^3J_{H\text{-}F}$ = 3.1 Hz, 2F). GC-MS: *m/z* (%) = 294 (3) $[M]^+$, 230 (22), 113 (22), 76 (33), 69 (100).

3,3-Difluorocyclooct-1-yne (18). The vinyl triflate **17** (0.300 g, 1.02 mmol) and THF (2 mL) were added to a dried Schlenk flask. The mixture was cooled to −20 °C under stirring. In a separate dried flask, a solution of LDA was prepared by addition of *n*-butyllithium (0.540 mL of a 2.2 M solution in hexanes, 1.19 mmol) dropwise to a solution of diisopropylamine (0.200 mL, 1.43 mmol) in dry THF (1 mL) under stirring at −78 °C. Then, the resulting solution of LDA was added dropwise to the solution of triflate over 1 h. The reaction mixture was then warmed to rt over 20 min and was quenched with methanol (4 mL). The mixture was concentrated under reduced pressure to ≈3 mL, mixed with 10 mL of pentane and filtered through a pad of silica, which was rinsed with several portions of pentane (20 mL). The filtrate was evaporated under reduced pressure to give a yellow oil (130 mg). The resulting compound was immediately used in a subsequent click reaction. ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) −88.83 (tt, $^3J_{H\text{-}F}$ = 13.5, $^5J_{H\text{-}F}$ = 5.1 Hz). GC-MS: *m/z* (%) = 144 (2) $[M]^+$, 129 (81), 115 (72), 109 (80), 88 (100), 79 (100).

2-(9,9-Difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (3c). The azide **1a** (48.0 mg, 271 μmol) was added to a solution of cyclooctyne **18** (40.0 mg, 277 μmol) in methanol/dichloromethane (10 mL, 1:1, v/v). The solution was stirred for 4 days at rt. Then, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (dichloromethane/ethyl acetate, 3:1, v/v) to give **3c** as a white solid. Yield 19.0 mg (22%). Mp 80–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.83 (bs, 1H), 7.88 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 5.94 (s, 2H), 3.07 (t, J = 6.9 Hz, 2H), 2.53–2.37 (m, 2H), 1.83–1.70 (m, 4H), 1.55–1.44 (m, 2H) (Figure S19). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ (ppm) 188.71, 162.76, 145.42 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 131.27 (t, $^2J_{C\text{-}F}$ = 28.7 Hz), 130.86, 126.35, 119.08 (t, $^1J_{C\text{-}F}$ = 236.4 Hz), 116.30, 55.75, 35.34 (t, $^2J_{C\text{-}F}$ = 24.0 Hz), 26.52, 24.27, 22.93, 21.14 (t, $^3J_{C\text{-}F}$ = 5.3 Hz) (Figure S20). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) −85.11 (t, $^3J_{H\text{-}F}$ = 15.8) (Figure S21). ^{1}H-^{13}C HSQCEDETGP (Figure S22). ^{1}H-^{13}C HMBC (Figure S23). FTIR (neat, cm^{-1}): 3074.27, 2923.99, 2854.44, 2691.17, 1687.78, 1601.05, 1579.90, 1516.18, 1467.01, 1446.18, 1346.28, 1310.74, 1286.51, 1223.13, 1166.87, 1111.01, 1086.49, 1044.95, 1016.53, 993.11, 918.40, 835.44, 753.78, 676.21, 634.23, 592.35, 570.59, 518.80, 497.05, 460.20, 427.00, 411.26. HRMS (ESI$^-$): calculated for $C_{16}H_{17}F_2N_3O_2$ $[M - H^+]$ 320.1216, found 320.1214.

*Note: According to ^{1}H and ^{19}F NMR, the ratio of the isomers formed was 5:3 in favor of **3c**, which was isolated.*

Synthesis of 3d



Substitution of the bromide in *p*HP bromide with a conjugated base of 2-azidoacetic acid gave **19** in acceptable yield. **3d** was prepared by a copper-catalyzed click reaction of **19** with phenylacetylene (**2a**).

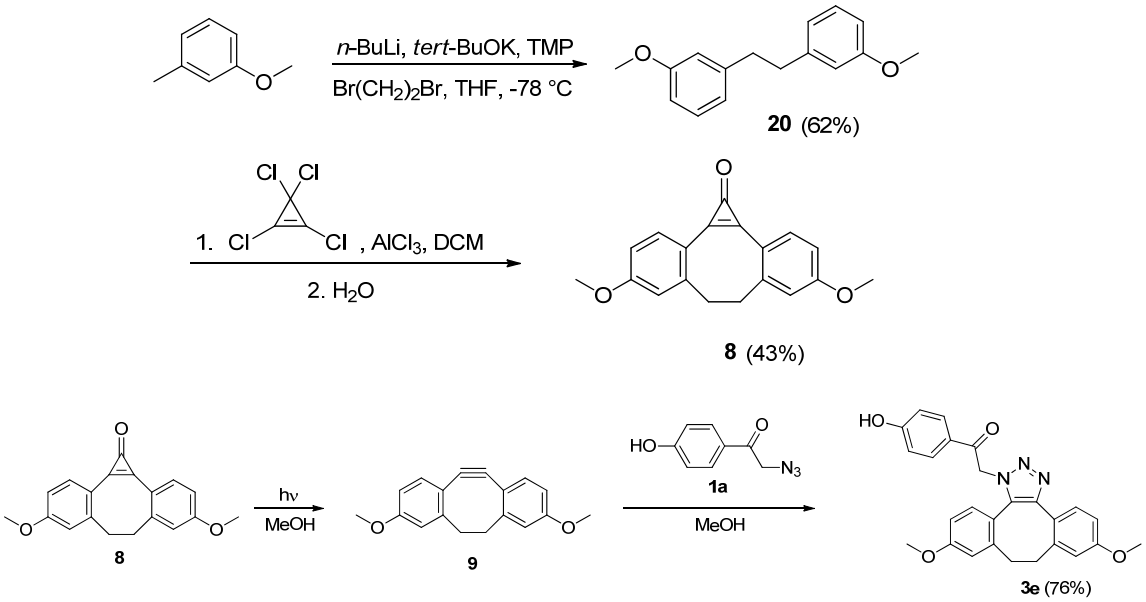
2-Azidoacetic acid was prepared according to a known procedure.[11] Sodium azide (2.28 g, 35.1 mmol) was added portionwise to a solution of bromoacetic acid (2.42 g, 17.6 mmol) in water (10 mL). The reaction mixture was stirred for 24 h at rt. The solution was acidified by conc. HCl to pH ~1 and extracted with Et_2O (2 × 10 mL). The organics extracts were combined, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to produce a colorless liquid. Yield 1.70 g (96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 3.96 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 173.56, 50.18.

2-(4-Hydroxyphenyl)-2-oxoethyl 2-azidoacetate (19). Sodium carbonate (~0.3 g) was added to a solution of azidoacetic acid (0.814 g, 8.06 mmol) in water (10 mL) until pH ~5 was reached (pH paper). Subsequently, ethanol (5 mL) was added. A solution of 2-bromo-1-(4-hydroxyphenyl)ethanone (1.014 g, 4.74 mmol) in ethanol/water (10 mL, 4:1, v/v) was added to the solution of azidoacetic acid under stirring, and the reaction mixture was stirred overnight at 50 °C. Then, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 × 15 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give a brownish oil (≈0.6 g), which crystalized under high vacuum. Purification using silica gel column chromatography (dichloromethane/ethyl acetate, 10:1, v/v) gave the title compound as a white solid. Yield 325 mg (30%). Mp 108–110 °C. ^{1}H NMR (300 MHz, DMSO): δ (ppm) 10.49 (s, 1H), 7.85 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 5.51 (s, 2H), 4.29 (s, 2H) (Figure S24). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO): δ (ppm) 189.95, 168.28, 162.74, 130.38, 125.22, 115.47, 66.90, 49.39 (Figure S25). FTIR (neat, cm^{-1}): 3358.44, 2940.06, 2104.78, 1748.35, 1687.35, 1603.00, 1576.95, 1519.67, 1439.11, 1424.05, 1380.55, 1280.35, 1248.66, 1207.93, 1170.92, 1107.43, 1063.33, 977.05, 949.53, 846.66, 818.77, 719.42, 644.54, 603.24, 577.54, 555.66, 512.53, 493.42, 442.01. HRMS (ESI^-): calculated for $C_{10}H_9N_3O_4$ [M–H^+] 234.0520, found 234.0520.

2-(4-Hydroxyphenyl)-2-oxoethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (3d). $CuSO_4$ (0.016 g, 0.100 mmol), sodium L-ascorbate (0.047 g, 0.238 mmol) and azide **19** (0.280 g, 1.191 mmol) were suspended in dichloromethane (10 mL), and phenylacetylene (**2a**, 0.131 mL, 1.191 mmol) and water (10 mL) were added under stirring. The emulsion was vigorously stirred overnight at rt. Then, the reaction mixture was extracted by ethyl acetate (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to give ~0.3 g of a gray solid. Purification by silica gel column chromatography (dichloromethane/ethyl acetate, 1:1, v/v) gave the title compound as white crystals. Yield 245 mg (61%). Mp 193–195 °C. ^{1}H NMR (500 MHz, DMSO): δ (ppm) 10.53 (s, 1H), 8.60 (s, 1H), 7.91–7.79 (m, 4H), 7.52–7.41 (m, 2H), 7.40–7.28 (m, 1H), 6.95–6.81 (m, 2H), 5.64 (s, 2H), 5.55 (s, 2H) (Figure S26). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO): δ (ppm) 189.85,

166.87, 162.81, 146.47, 130.49, 130.44, 128.96, 128.01, 125.22, 125.19, 122.80, 115.52, 67.25, 50.38 (Figure S27). FTIR (neat, cm^{-1}): 2948.11, 1774.50, 1680.07, 1603.58, 1516.80, 1471.13, 1443.17, 1417.69, 1373.93, 1361.24, 1286.91, 1239.14, 1202.23, 1165.82, 1108.64, 1088.67, 1053.22, 974.22, 834.01, 788.76, 770.96, 725.29, 712.10, 697.29, 676.46, 614.16, 562.61, 506.64, 489.69, 437.68. HRMS (ESI^-): calculated for $C_{18}H_{15}N_3O_4$ [M – H^+] 336.0990, found 336.0992.

Synthesis of cyclopropenone 8 and *p*HP triazole 3e



The cyclopropenone **8** was synthesized via a two-step procedure in an acceptable overall yield (27%). The three steps are required[12] to synthesize the diphenylethane intermediate **20**, but recently, a LiNK metalation coupling for connection of substituted toluenes has been developed by O'Shea and coworkers.[13] Next, electrophilic aromatic substitution reaction gave the compound **8**. **3e** was prepared by irradiation of **8**, and the resulting strained alkyne **9** underwent a click reaction with *p*HP azide (**1a**).

1,2-Bis(3-methoxyphenyl)ethane (20) was prepared according to a known procedure[13] in 62% yield. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30–7.19 (m, 2H), 6.88–6.74 (m, 6H), 3.83 (s, 6H), 2.95 (s, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 159.80, 143.51, 129.42, 121.00, 114.36, 111.46, 55.26, 37.95.

4,9-Dimethoxy-6,7-dihydro-1*H*-dibenzo[*a*,*e*]cyclopropa[*c*][8]annulen-1-one (8). The title compound was prepared according to a slightly modified reported procedure.[14] A suspension of $AlCl_3$ (0.193 g, 1.45 mmol) in dry dichloromethane (15 mL) was cooled to −78 °C, tetrachlorocyclopropene (0.169 mL, 1.38 mmol) was added, and the solution of 1,2-bis(3-methoxyphenyl)ethane (**20**, 0.334 g, 1.38 mmol) in dry dichloromethane (1 mL) was added slowly using a syringe. The mixture was stirred at −78 °C for 2 h and then for 1 h at room temperature. The reaction was quenched by addition of water (50 mL) under vigorous stirring. Dichloromethane (50 mL) was added to create a suspension. It was filtered through a pad of Celite, which was rinsed with several portions of dichloromethane. The organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give a crude product, which was purified by column

chromatography (dichloromethane/ethyl acetate, 1:1, v/v) to give the title compound as a white microcrystalline solid. Yield 172 mg (43%). Characterization data are consistent with those in the literature.[15] Mp 204–207 °C (lit. 197–199 °C)[12]. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.99–7.91 (m, 2H), 6.94–6.87 (m, 4H), 3.89 (s, 6H), 3.35 (d, J = 10.5 Hz, 2H), 2.64 (d, J = 10.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 162.58, 153.83, 147.92, 142.52, 135.93, 116.67, 115.94, 111.98, 55.65, 37.33.

2,9-Dimethoxy-5,6-didehydro-11,12-dihydrodibenzo[*a*,*e*]cyclooctyne (9). A solution of cyclopropenone **8** (5.3 mg, 18 μmol) in CD_3CN (0.25 mL) in an NMR cuvette was irradiated at 350 nm (a 450 W high pressure Hg(Xe) arc lamp equipped with a low-pass (Figure S40) and water IR filters) for 20 min. The starting material was quantitatively transformed into the alkyne **9**. The analytical data are consistent with those in the literature.[15] ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) 7.21 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.82 (dd, J = 8.4, 2.6 Hz, 1H), 3.81 (s, 3H), 3.27 (d, J = 11.4 Hz, 1H), 2.32 (d, J = 11.3 Hz, 1H). ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) 7.15 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 8.4, 2.6 Hz, 1H), 3.81 (s, 3H), 3.24 (d, J = 11.3 Hz, 1H), 2.33 (d, J = 11.2 Hz, 1H).

2-(6,11-Dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (3e). The cyclopropenone **8** (50.7 mg, 173 μmol) was dissolved in methanol (35 mL), and the solution was irradiated with a 450 W Hg(Xe) broad-band arc lamp equipped with a water IR filter for 25 min under stirring (the reaction progress was monitored by TLC). Then, the azide **1a** (30.7 mg, 173 μmol) was added to solution, and the reaction mixture was stirred overnight at rt. The solvent was removed under reduced pressure to give a crude product, which was purified by column chromatography (dichloromethane/ethyl acetate, 2:1, v/v). Yield 58 mg (76%). White microcrystalline solid. Mp >128 °C decomp. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.08 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.86–6.64 (m, 4H), 5.73 (s, 2H), 3.77 (s, 6H), 3.47–2.71 (m, 4H) (Figure S28). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 189.20, 163.36, 160.77, 159.56, 146.08, 143.66, 139.83, 135.88, 132.83, 130.79, 129.86, 125.89, 121.80, 117.72, 116.34, 116.05, 115.69, 112.39, 112.13, 55.31, 55.24, 54.05, 36.43, 33.18 (Figure S29). FTIR (neat, cm^{-1}): 3065.55, 3000.30, 2935.78, 2834.59, 2689.36, 2607.12, 1683.48, 1601.70, 1579.03, 1515.64, 1488.86, 1454.64, 1369.02, 1344.08, 1309.24, 1282.51, 1229.93, 1166.89, 1106.03, 1048.77, 1019.67, 984.75, 926.77, 894.88, 880.64, 816.03, 771.56, 742.30, 717.20, 689.91, 660.41, 621.44, 606.01, 589.58, 545.61, 490.14, 464.73, 450.95, 420.86. HRMS (ESI$^-$): calculated for $C_{26}H_{23}N_3O_4$ [M–H$^+$] 440.1616, found 440.1614.

4-Phenyl-1*H*-1,2,3-triazole (4a). This compound was isolated from the irradiated mixtures (see above). Purification by column chromatography (hexane/ethyl acetate, 1:1, v/v) gave the triazole **4a** as white crystals. The analytical data were in agreement with those reported in the literature.[16] ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 11.57 (bs, 1H), 7.97 (s, 1H), 7.83 (d, J = 7.1 Hz, 2H), 7.52–7.33 (m, 3H). HRMS (APCI$^+$): calculated for $C_8H_7N_3$ [M + H$^+$] 146.0713, found 146.0711. HRMS (APCI$^-$): calculated for $C_8H_7N_3$ [M – H$^+$] 144.0567, found 144.0560.

6,11-Dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (4e). This compound was isolated from the irradiated mixtures (see above). Purification using column chromatography (hexane/ethyl acetate, 1:1, v/v) gave the triazole **4e** as a white solid. Yield 7 mg (90%). Mp 105–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.35 (d, J = 8.4 Hz, 2H), 6.83–6.74 (m, 4H), 3.79 (s, 6H), 3.17 (s, 4H) (Figure S30). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ (ppm) 160.03, 144.10 (missing peak in ^{13}C NMR spectrum, but seen by ^{1}H–^{13}C HMBC (Figure S32)),

141.04, 132.08, 121.43, 115.50, 112.30, 55.38, 34.97 (Figure S31). FTIR (neat, cm^{-1}): 3128.00, 2922.29, 2834.93, 1607.46, 1575.34, 1517.27, 1498.13, 1461.78, 1427.26, 1258.41, 1233.91, 1158.57, 1110.23, 1079.14, 1050.83, 1028.24, 982.76, 895.59, 878.79, 844.79, 811.36, 746.76, 721.22, 616.53, 597.80, 544.88, 486.58, 461.38, 445.75. HRMS ($APCI^+$): calculated for $C_{18}H_{17}N_3O_2$ [M + H^+] 308.1394, found 308.1394.

9,9-Difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[d][1,2,3]triazole (4c). This compound was identified by an HRMS analysis from the mixture resulting from irradiation of the *p*HP triazole **3c** (see above). HRMS ($APCI^-$): calculated for $C_8H_{11}F_2N_3$ [M + Cl^-] 222.0615, found 222.0615.

Determination of the acid dissociation constant

A spectrophotometric titration was used to determine the acid dissociation constant of **3a** (pK_a = 7.98 ± 0.02). A solution of **3a** in aq HCl (0.01 M) was added to a solution of **3a** in aq NaOH (0.01 M, 100 mL) The UV-Vis spectra and corresponding pH of solutions were measured after each addition (Figures S33). The acid dissociation constants were obtained from the global analysis of the measured spectra using the program Specfit.

Quantum yields measurements

The quantum yields were determined in 10.0 mm quartz cuvettes. A 40 W medium pressure Hg arc lamp equipped with a monochromator (λ_{em} = 313 ± 1.5 nm, Figure S37) was used to determine the disappearance quantum yields of **3a** and **3d** (Table 1). The quantum yield of **3c** and **3e** was determined using a 450 W Hg(Xe) high pressure arc lamp equipped with 320 ± 10 nm band-pass filter (Table 1, Figure S36). The light sources were equilibrated at least for 60 min before the measurements started. The irradiance was determined using 4-hydroxyphenacyl fluoride[17] as an actinometer. The reaction conversions were determined by UV-vis spectroscopy and were kept below 10%. All measurements were repeated at least 4 times in order to calculate the standard deviations.

Irradiation experiments

Solutions of *p*HP derivatives **3a-e** (2-3 mg) in CD_3CN/D_2O (0.5 mL, 1:1, v/v) were irradiated in NMR tubes (5 mm diameter) using a 200 W medium pressure Hg lamp (Figures S1−S4, S38) until the full reaction conversions were achieved (**3b** was irradiated to >90% conversion). ^1H NMR spectra were recorded during the irradiation. The triazoles **4a** and **4e** formed were isolated and characterized. The triazole **4c** was identified by HRMS. The reaction mixture obtained upon irradiation of **3b** was analyzed by HRMS (Figure S41).

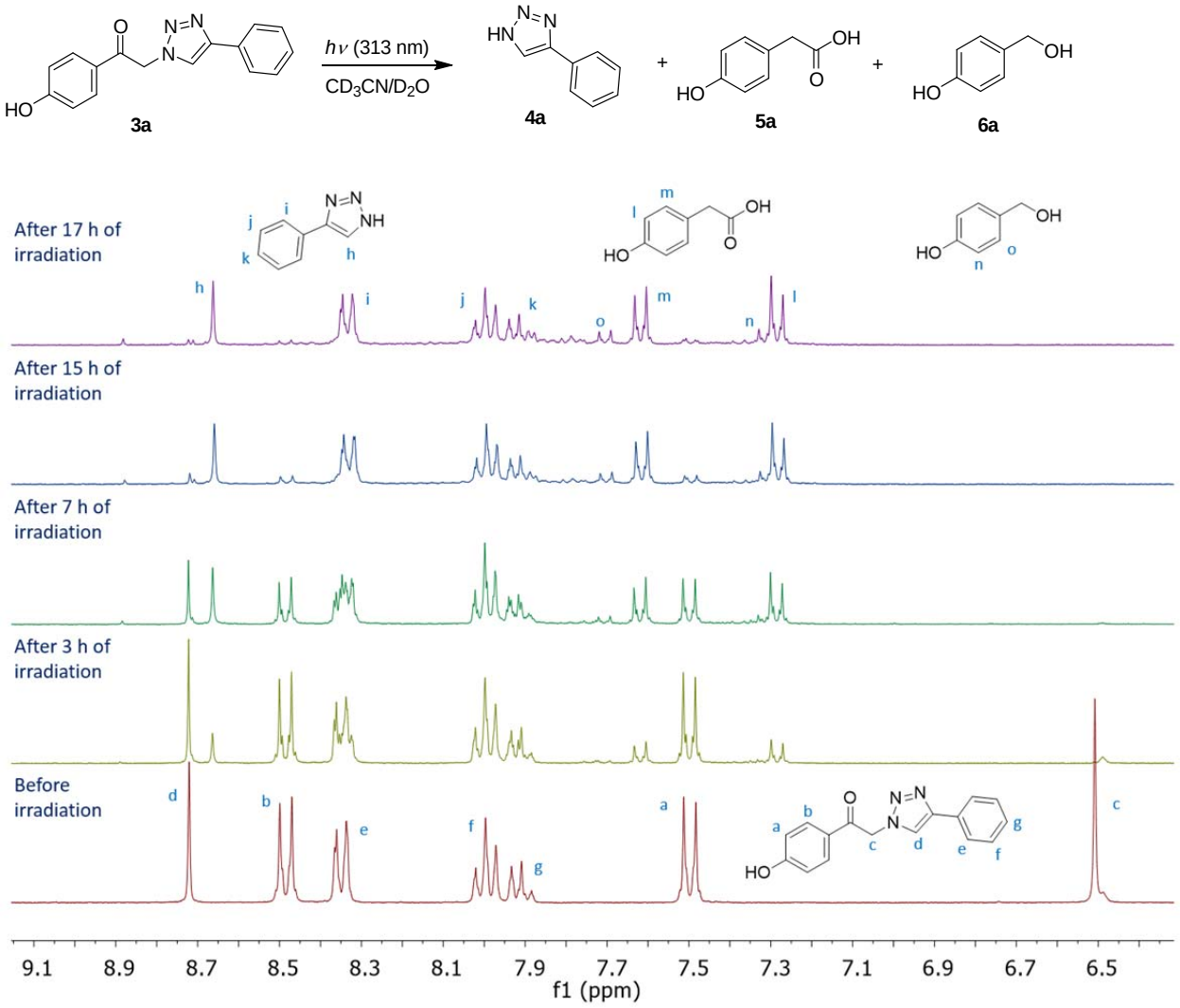


Figure S1. Irradiation of **3a**.

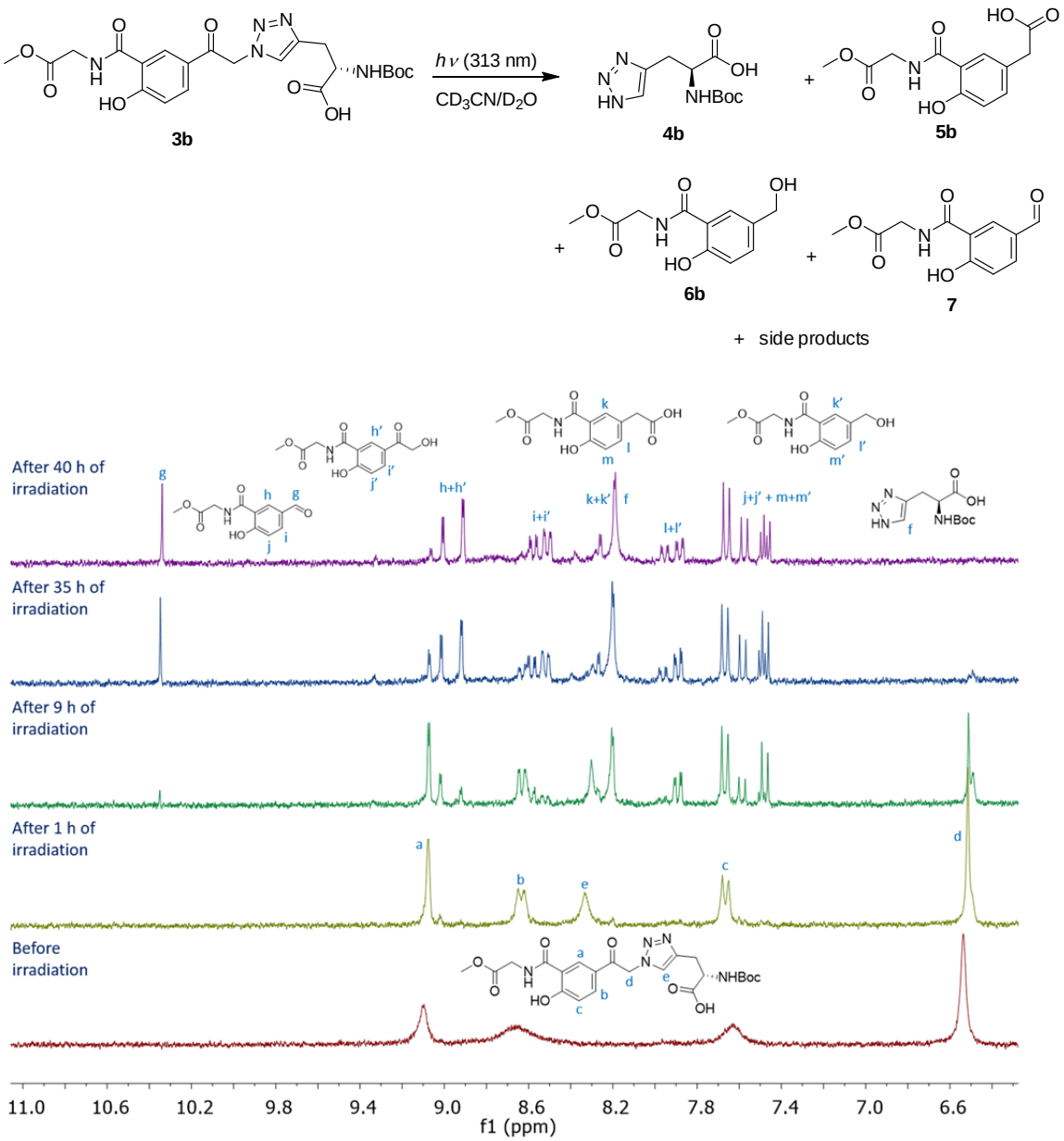


Figure S2. Irradiation of **3b**.

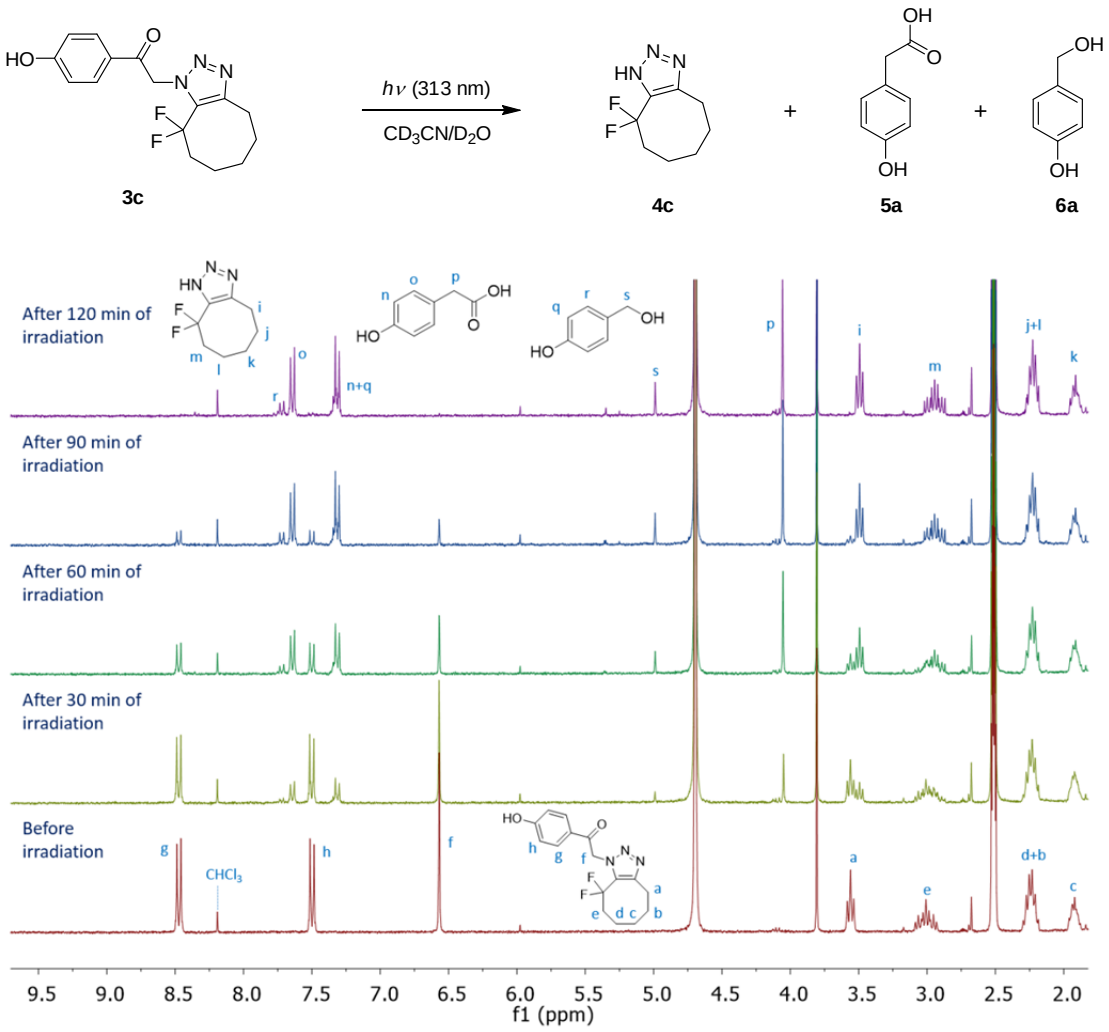


Figure S3. Irradiation of **3c**.

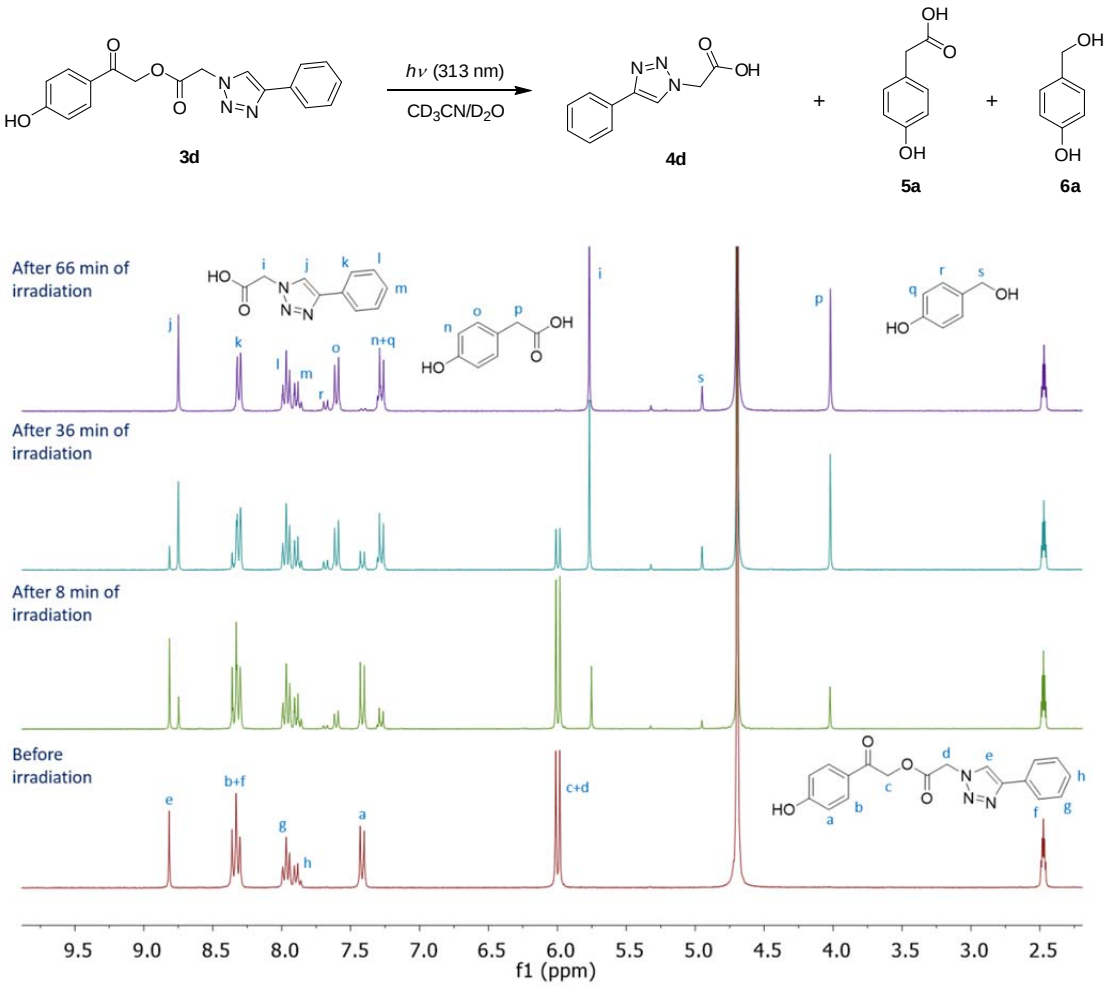


Figure S4. Irradiation of **3d**.

One pot reaction

A solution of the azide **1a** (2.6 mg, 1 equiv) and the cyclopropenone **8** (4.3 mg, 1 equiv) in CD_3CN (0.5 mL) was irradiated in an NMR tube (5 mm diameter) using a 450 W high pressure Hg(Xe) arc lamp equipped with a 350 nm low-pass (Figure S40) and a water IR filter for 25 min (Figure S5). Subsequently, cyclopropenone transformed to the alkyne **9**. The compound **1a** was not affected by irradiation because it does not absorb over 350 nm. The reaction mixture was kept in the dark for 2 days in order to **9** completely react with **1a** via a SPAAC process. The bimolecular rate constant for this reaction should be around 10^{-2} M^{-1} s^{-1} according to the literature[18] (it was not measured in this work). Then, D_2O (0.5 mL) was added. A 350 nm optical filter was changed to 300 nm low-pass filter (Figure S40) and the solution was irradiated using a 450 W high pressure Hg(Xe) arc lamp to full conversion (17 h). The triazole **4e** was successfully released from **3e** along with the byproducts **5a** and **6a** from the *p*HP moiety. All steps (photorelease, catch, and photorelease) were tested independently before the one pot reaction was carried out.

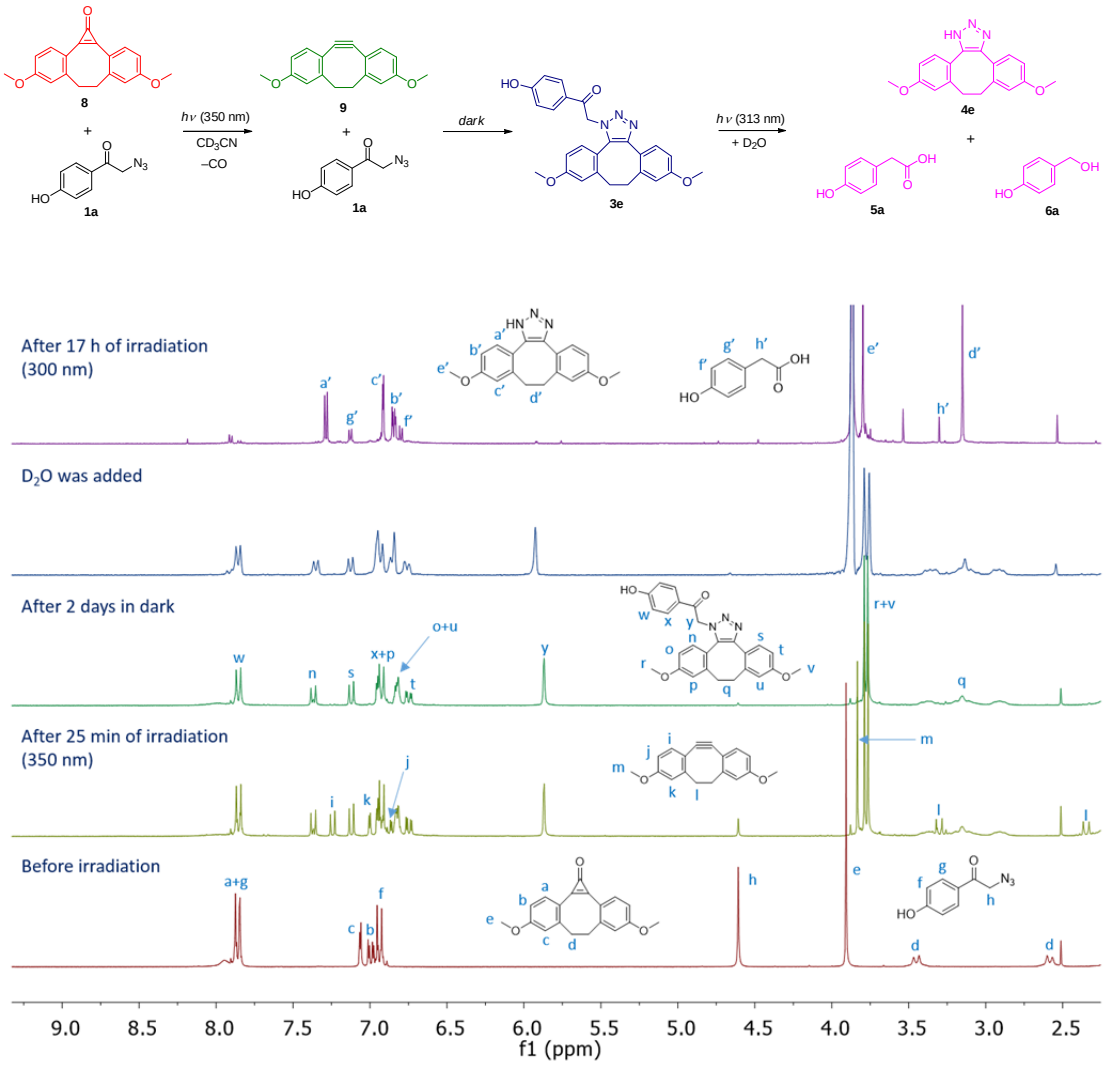


Figure S5. One pot reaction.

A solution of the cyclopropenone **8** (c = 5 × 10^{-5} M) in acetonitrile was irradiated for 5 s using a 450 W high pressure Hg arc equipped with 350 nm low-pass (Figure S40) and water IR filters to produce the acetylene **9**.

A solution of **3e** (c = 6 × 10^{-5} M) in aq acetonitrile (20%, v/v) was irradiated using a 450 W high pressure Hg arc lamp equipped with 300 nm (Figure S40) low-pass and water IR filters until the full conversion was reached (UV-vis, Figure S6).

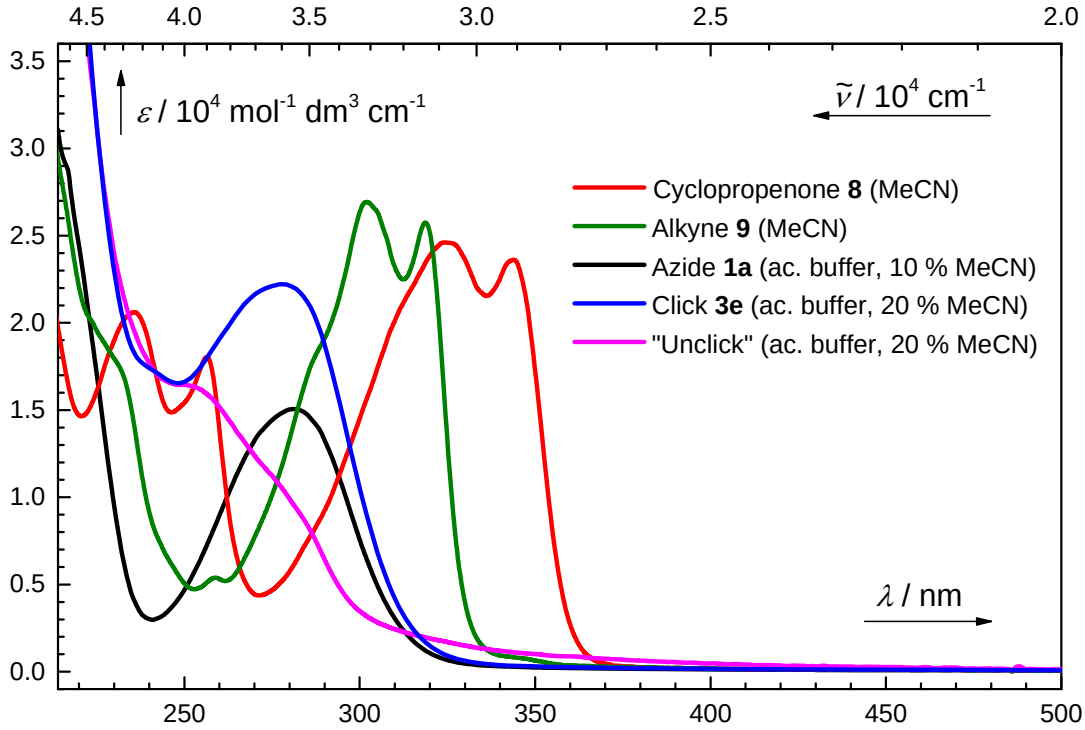


Figure S6. UV-Vis spectra of the cyclopropenone **8** (red line), alkyne **9** (green line), azide **1a** (black line), triazole **3e** (blue line) and the reaction mixture in a mixture of acetate buffer (I = 0.1 M, pH = 5.0) and aq acetonitrile (10–20%, v/v) after exhaustive irradiation by 313 nm UV light (magenta line).

Figure S7. ^{1}H NMR (300 MHz, DMSO-d_6): 2-azido-1-(4-hydroxyphenyl)ethanone (**1a**)

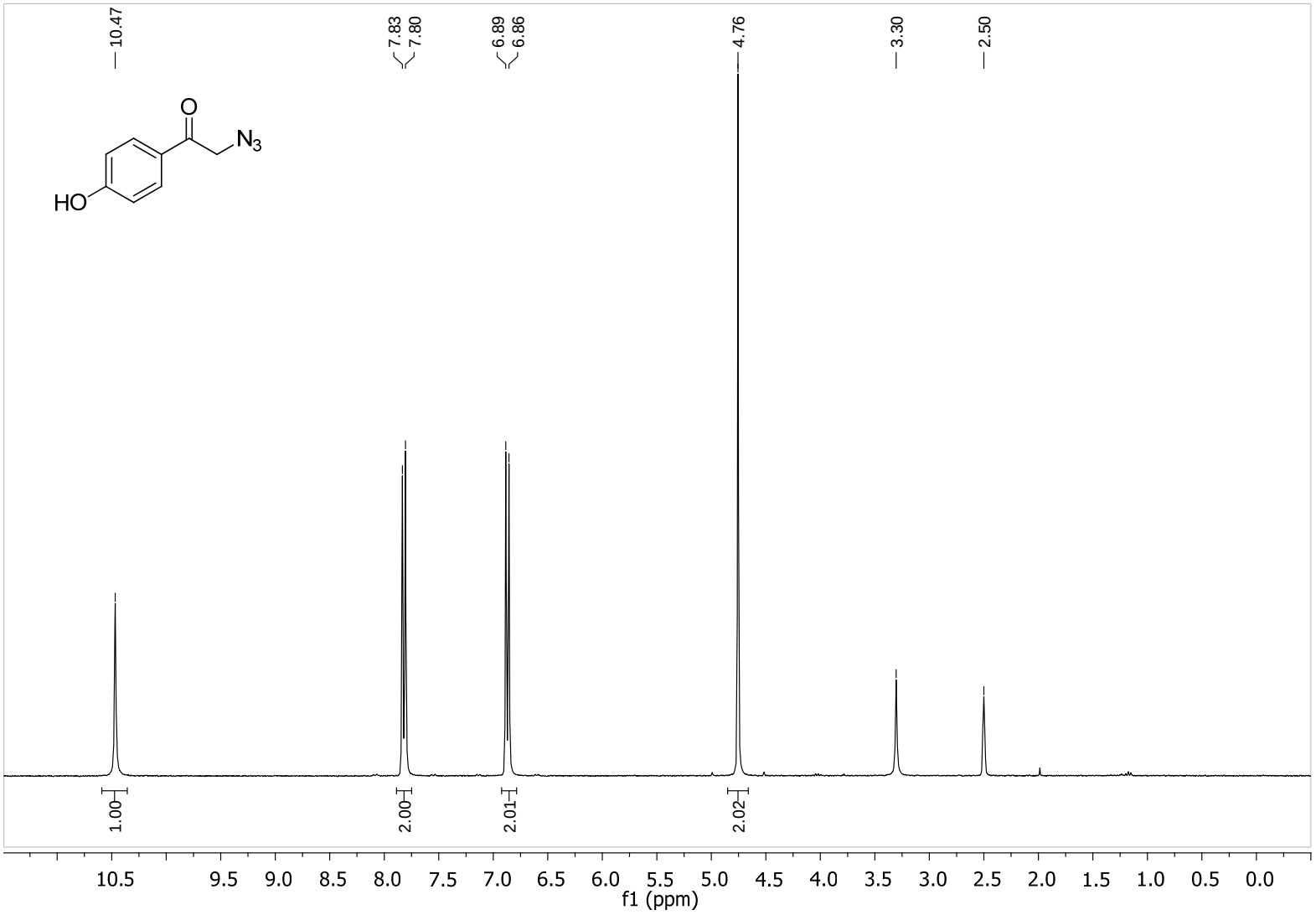


Figure S8. $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): 2-azido-1-(4-hydroxyphenyl)ethanone (**1a**)

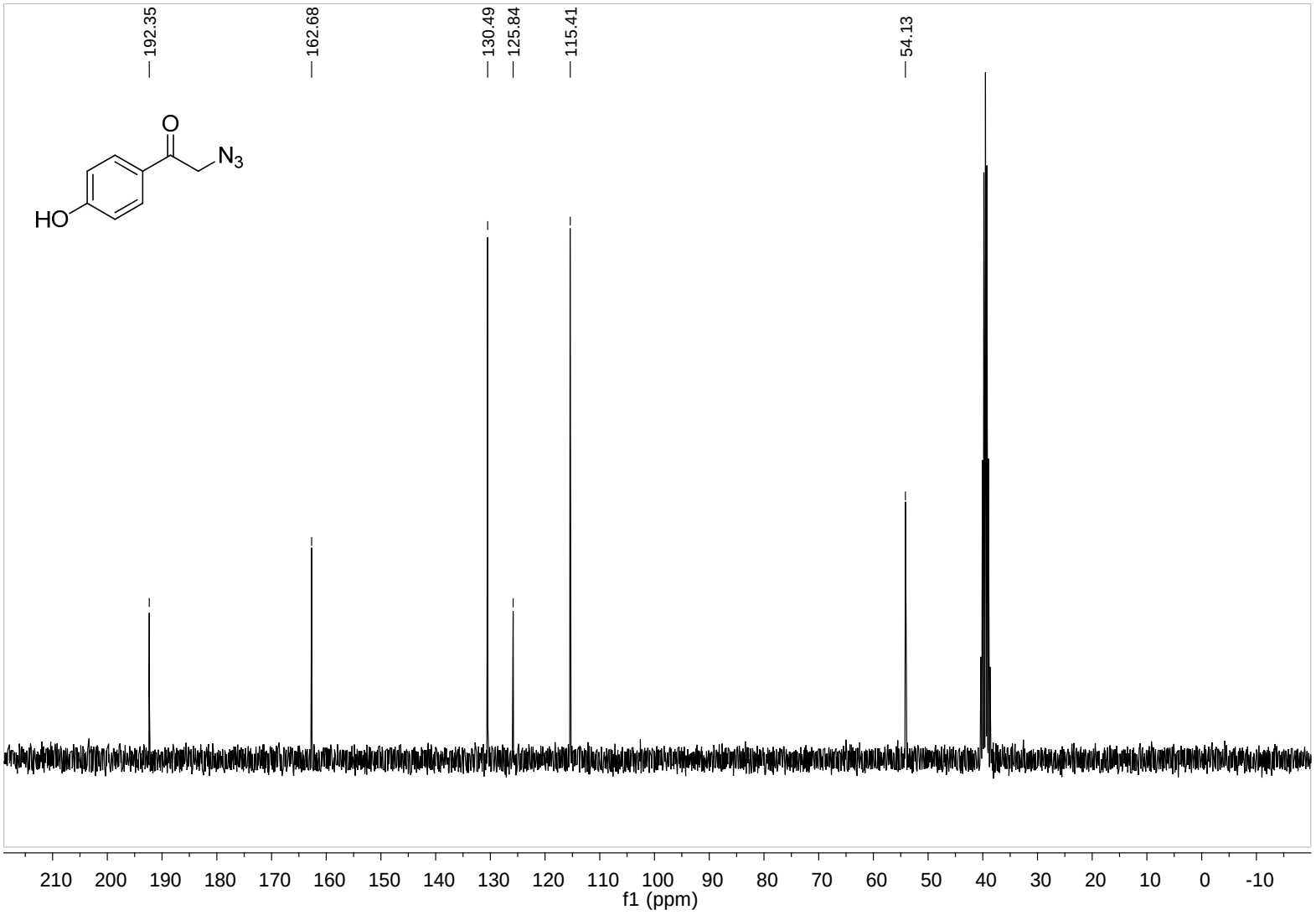


Figure S9. ^{1}H NMR (300 MHz, DMSO-d_6): 1-(4-hydroxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (**3a**)

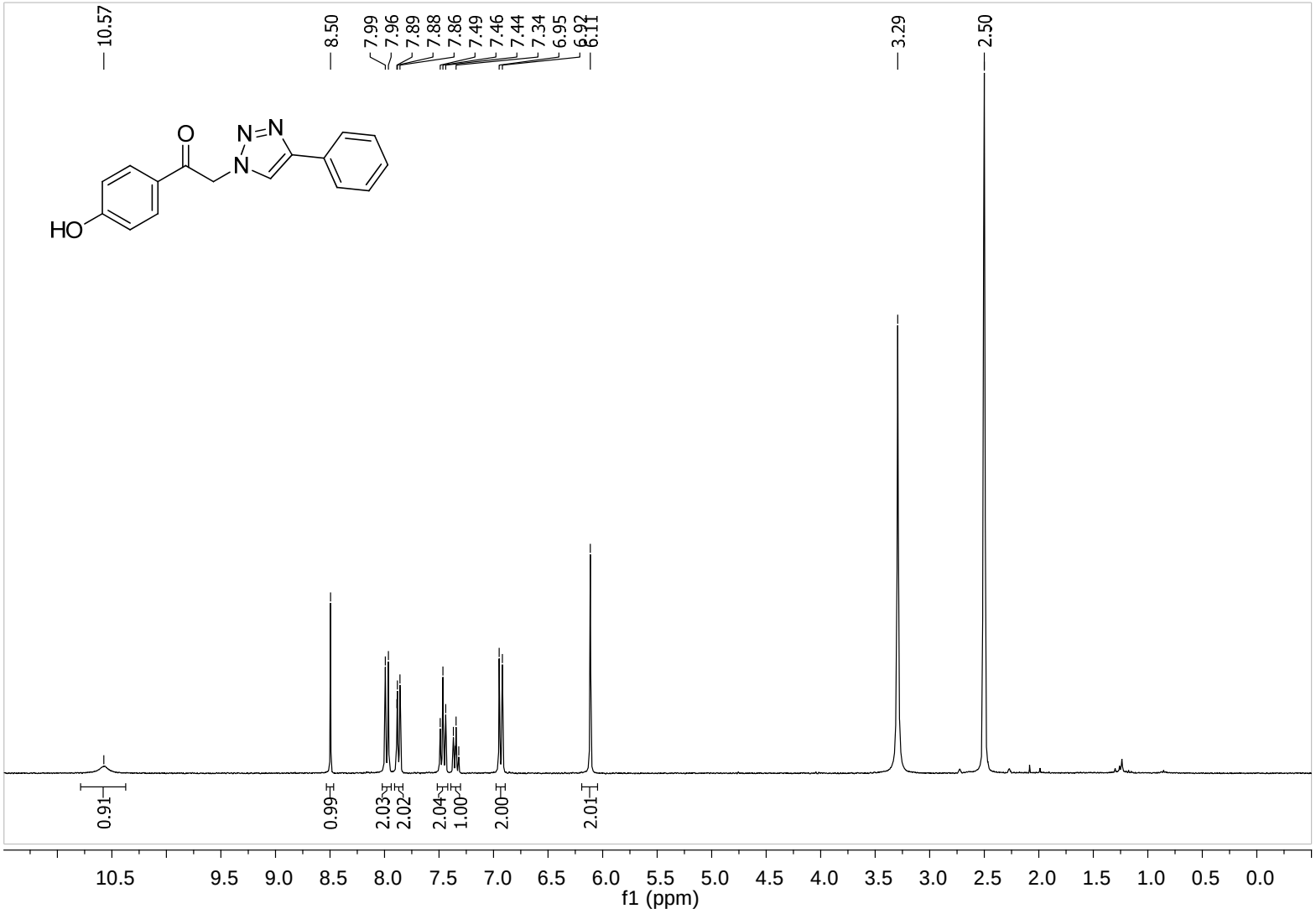


Figure S10. $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): 1-(4-hydroxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (**3a**)

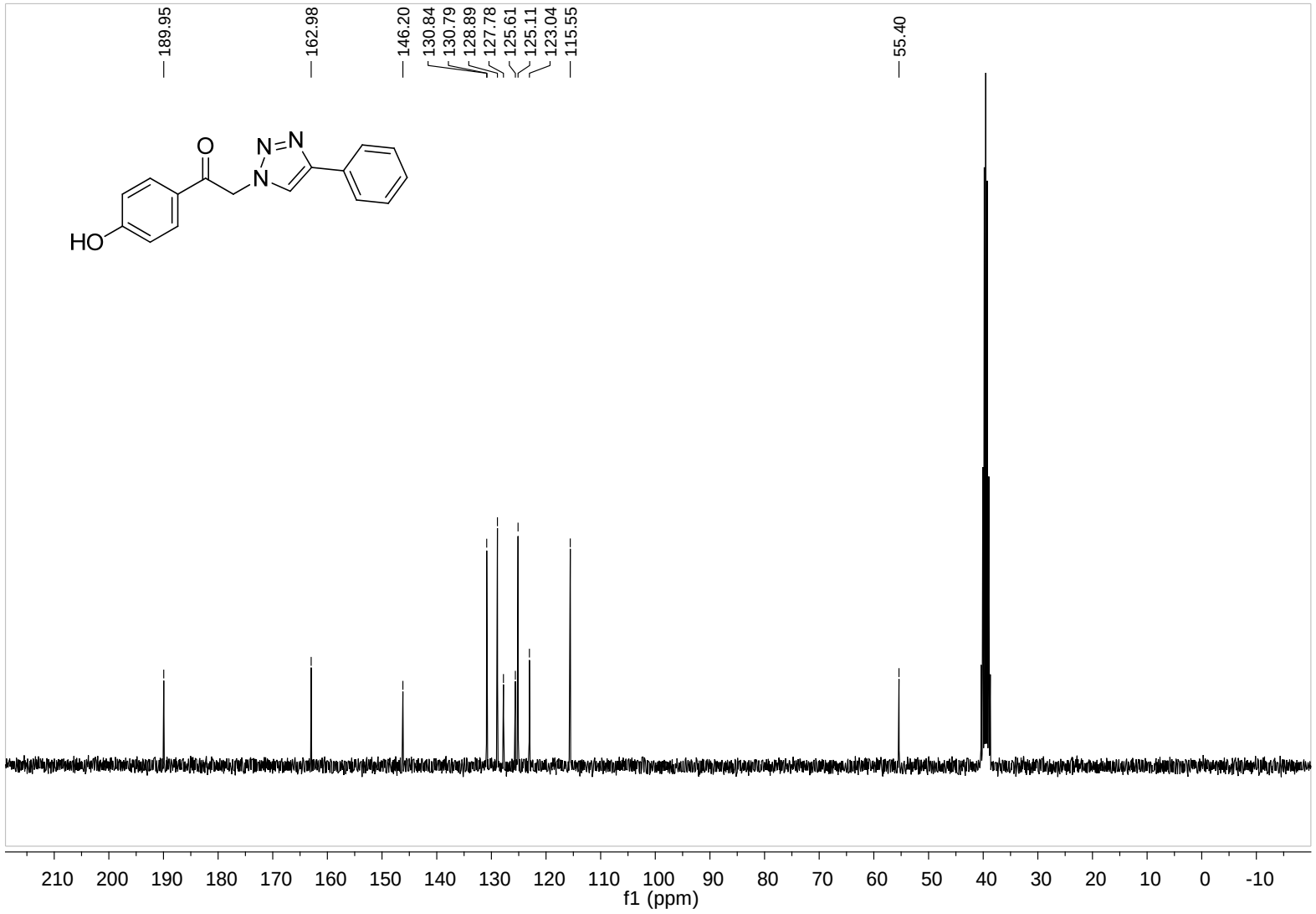


Figure S11. ^{1}H NMR (300 MHz, $CDCl_3$): Methyl 2-(5-acetyl-2-(benzyloxy)benzamido)acetate (**12**)

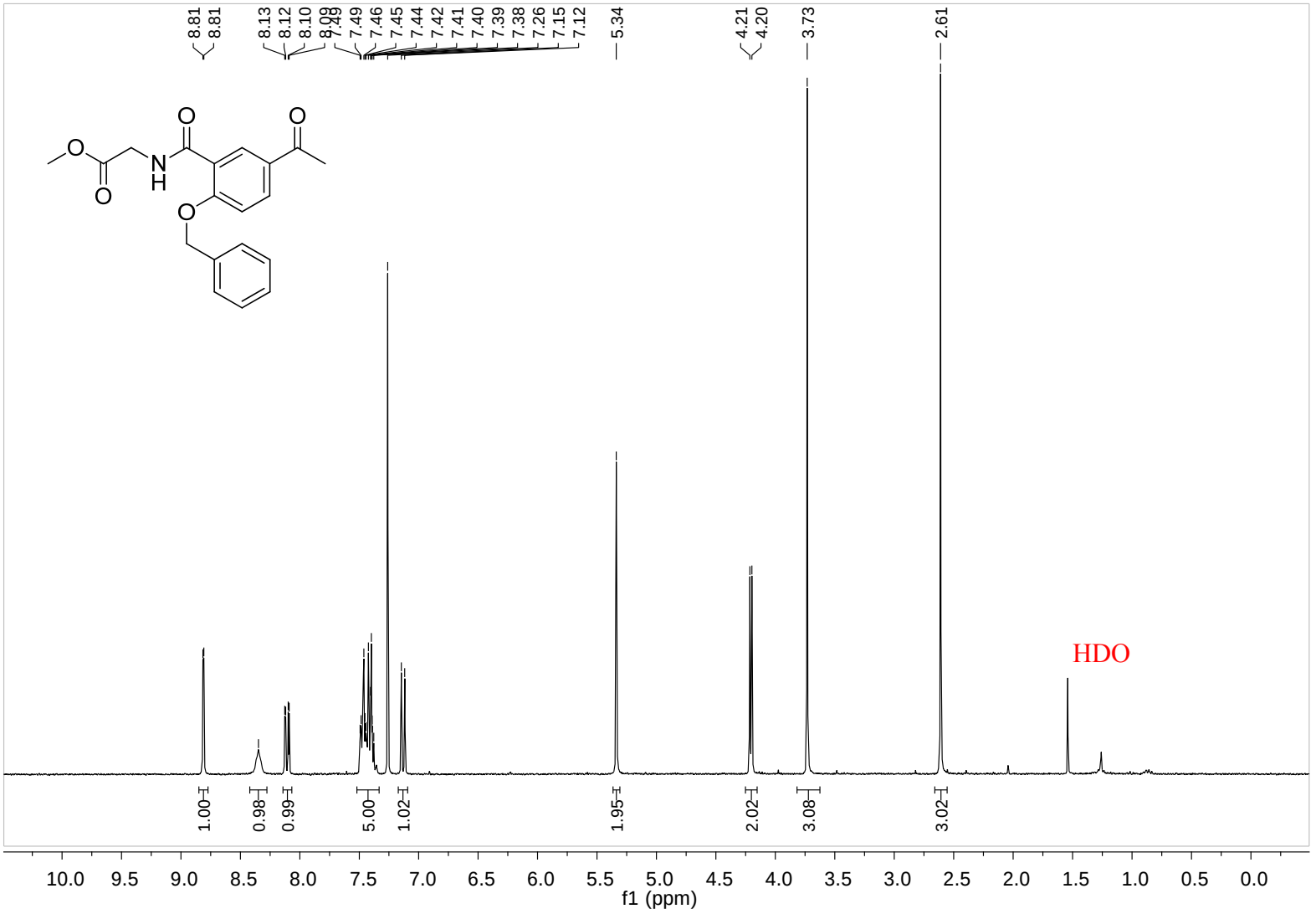


Figure S12. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): Methyl 2-(5-acetyl-2-(benzyloxy)benzamido)acetate (**12**)

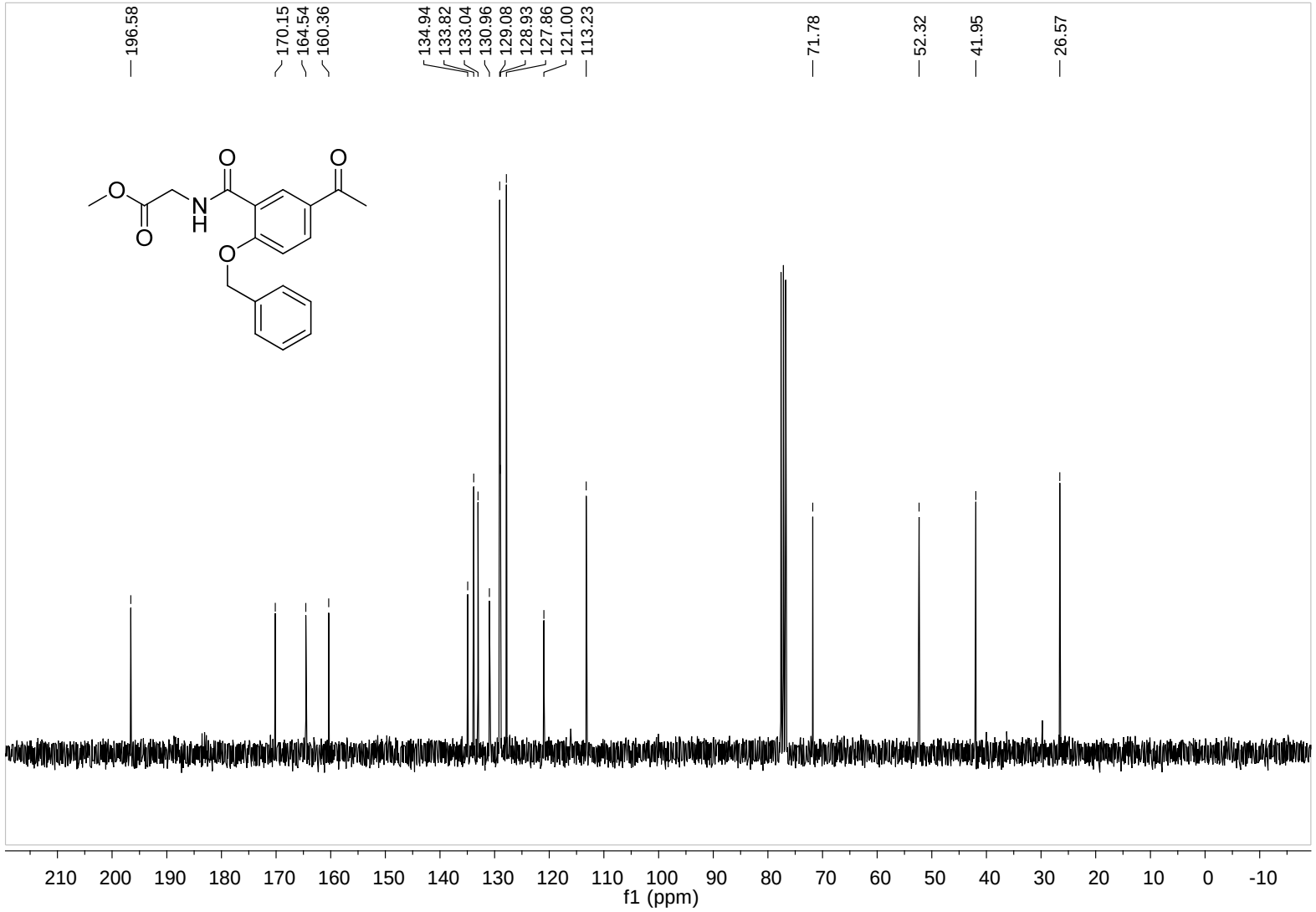


Figure S13. ^{1}H NMR (300 MHz, $CDCl_3$): Methyl 2-(2-(benzyloxy)-5-(2-bromoacetyl)benzamido)acetate (**13**)

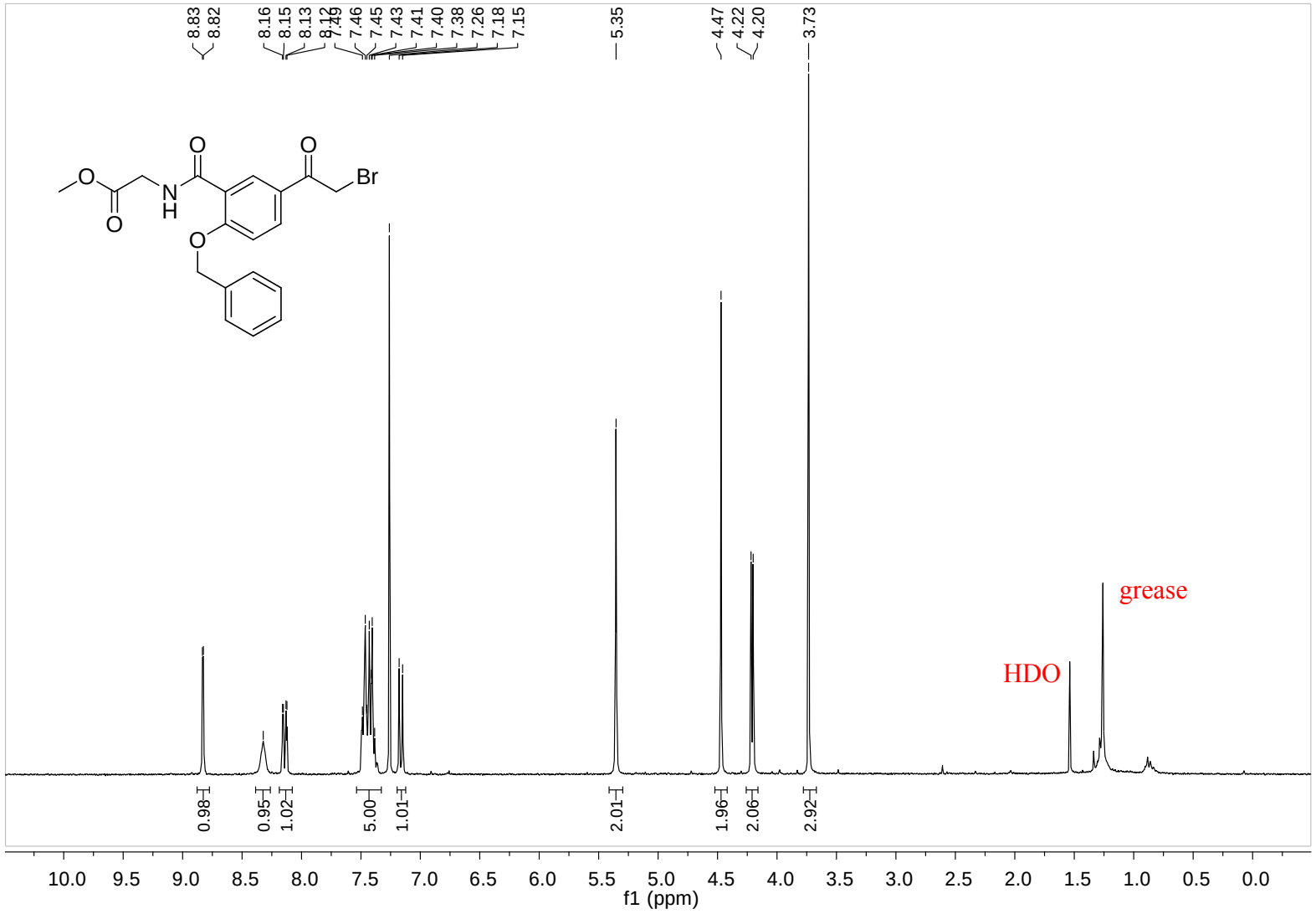


Figure S14. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): Methyl 2-(2-(benzyloxy)-5-(2-bromoacetyl)benzamido)acetate (**13**)

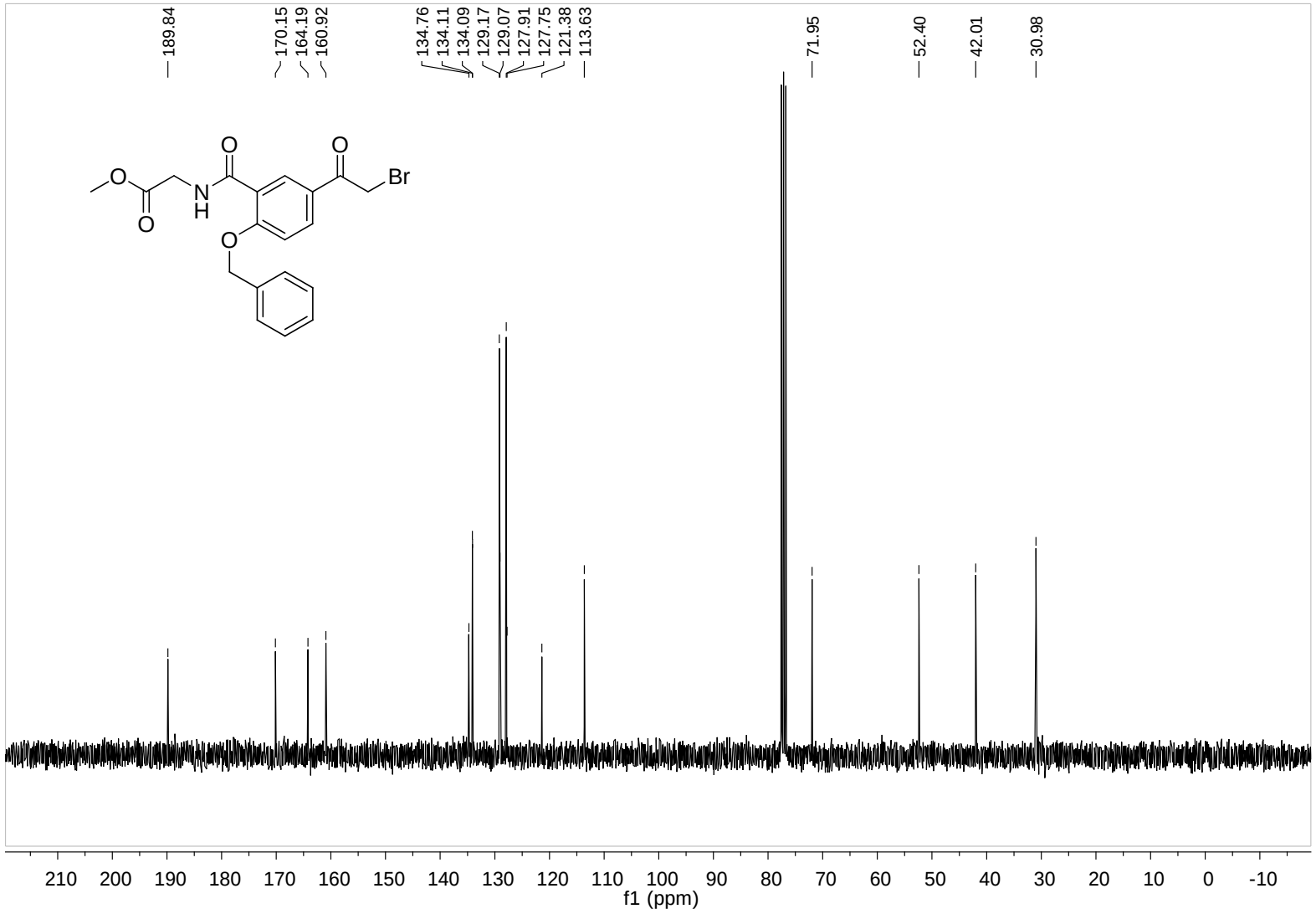


Figure S15. ^{1}H NMR (300 MHz, $CDCl_3$): Methyl 2-(5-(2-bromoacetyl)-2-hydroxybenzamido)acetate (**14**)

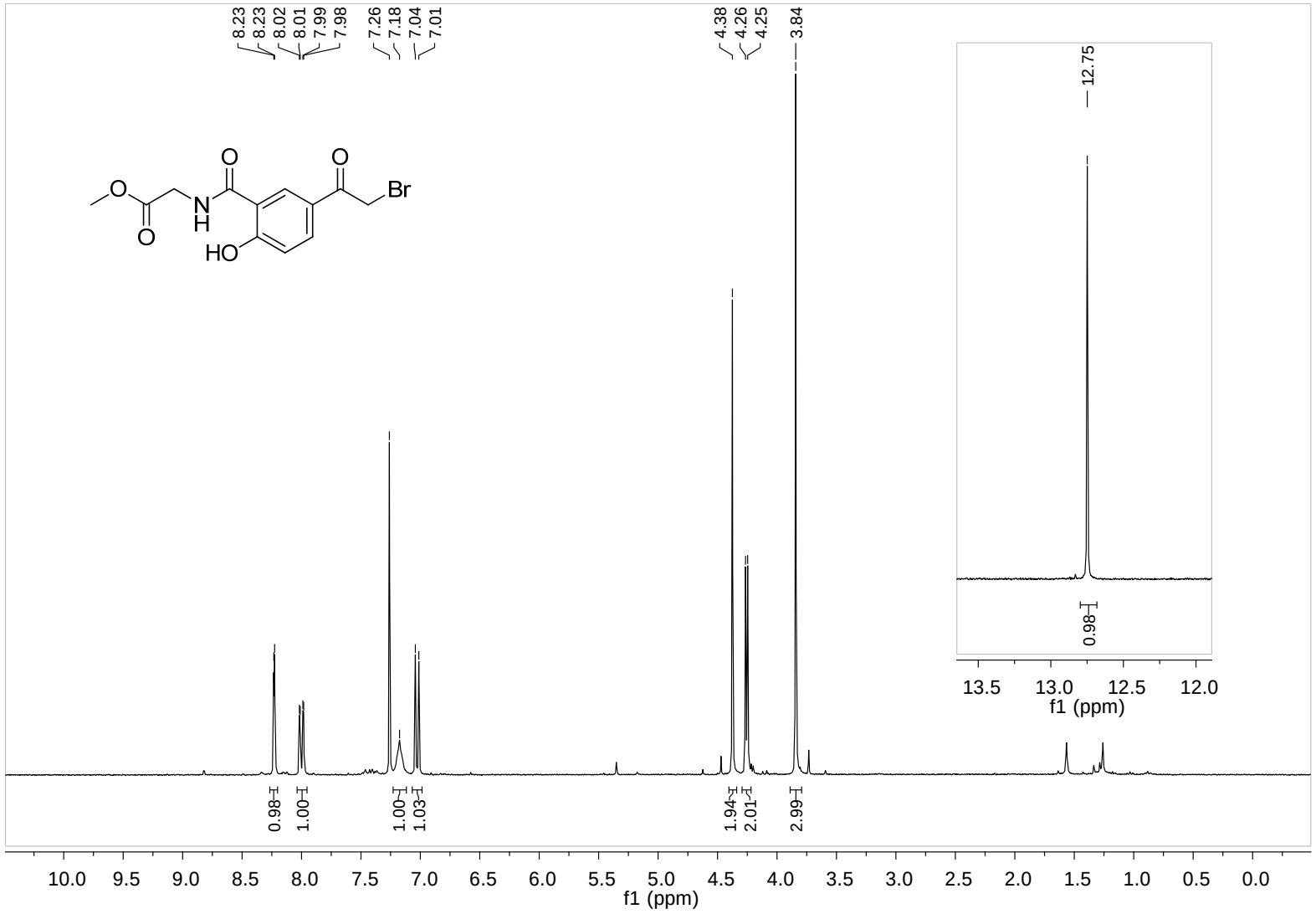


Figure S16. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): Methyl 2-(5-(2-bromoacetyl)-2-hydroxybenzamido)acetate (**14**)

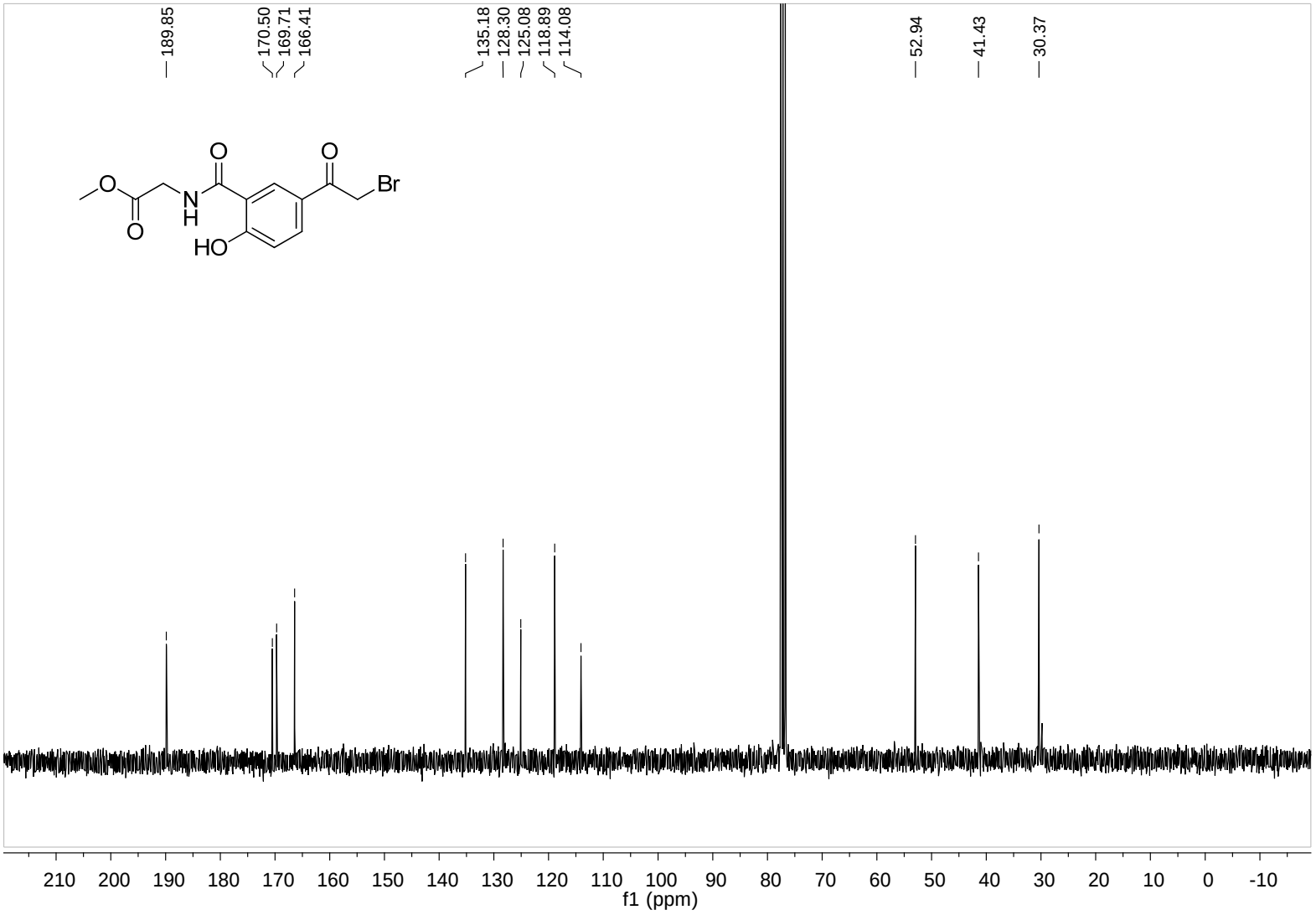


Figure S17. ^{1}H NMR (300 MHz, $CDCl_3$): Methyl 2-(5-(2-azidoacetyl)-2-hydroxybenzamido)acetate (**1b**)

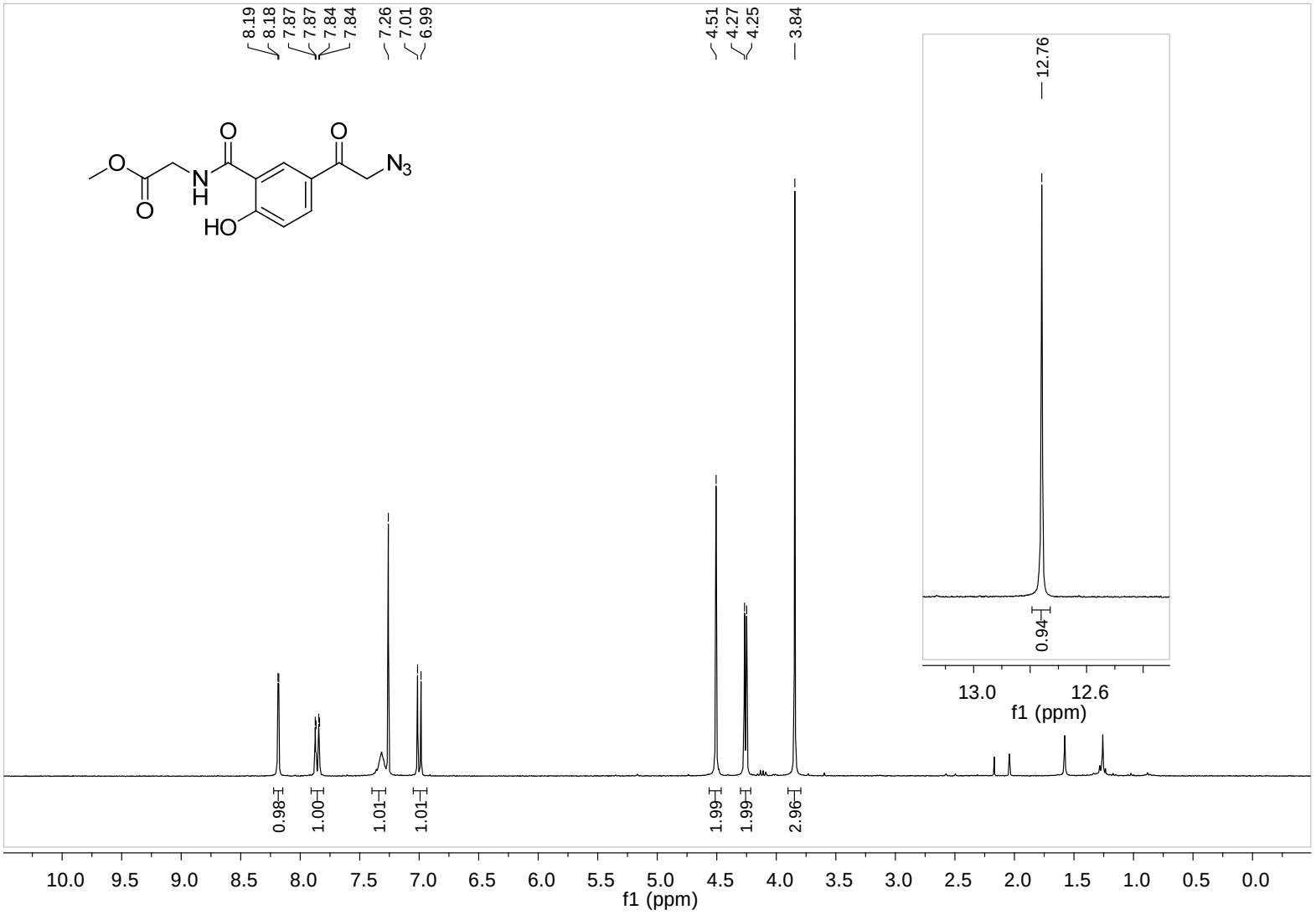


Figure S18. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): Methyl 2-(5-(2-azidoacetyl)-2-hydroxybenzamido)acetate (**1b**)

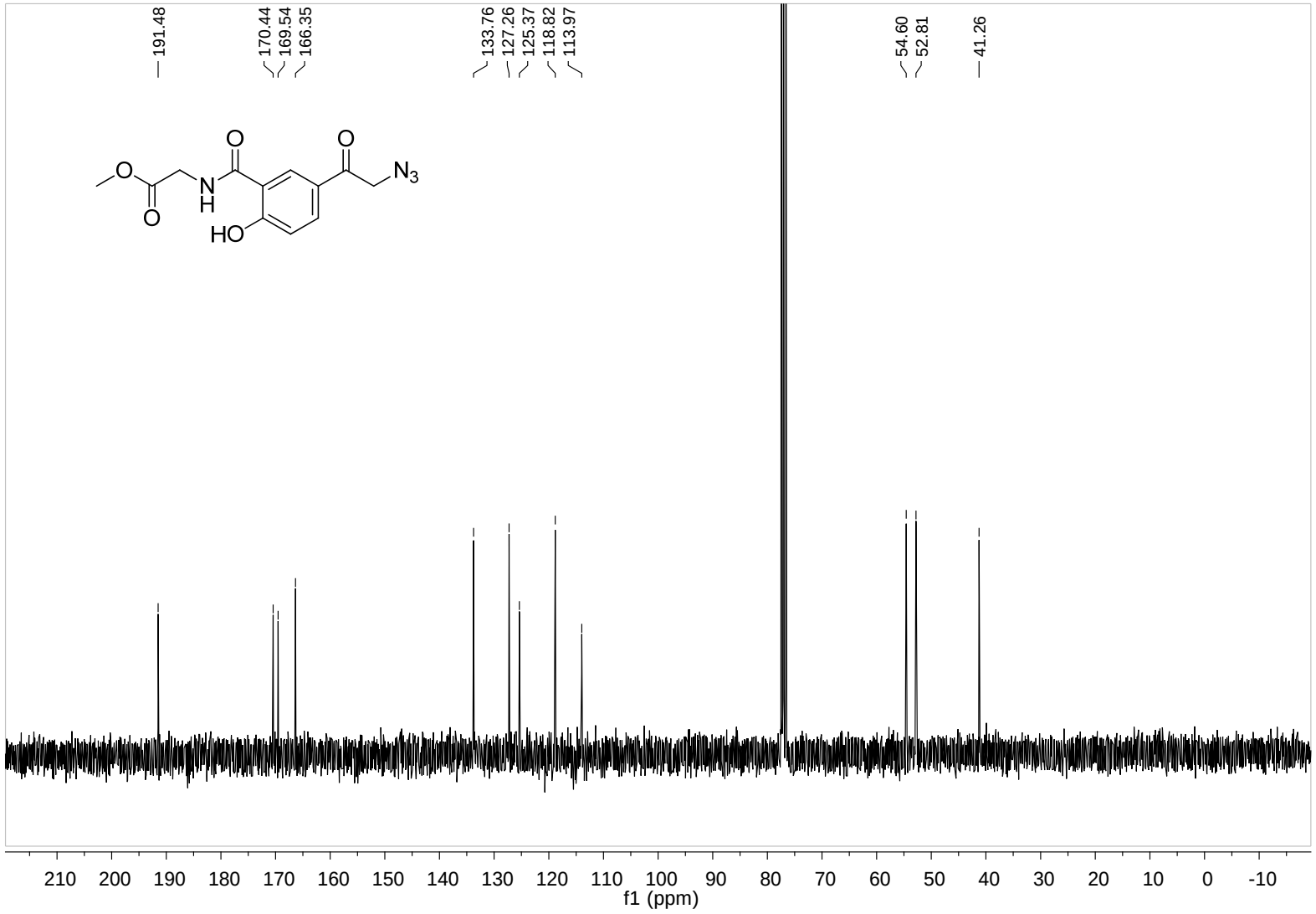


Figure S19. ^{1}H NMR (500 MHz, $CDCl_3$): 2-(9,9-difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3c**)

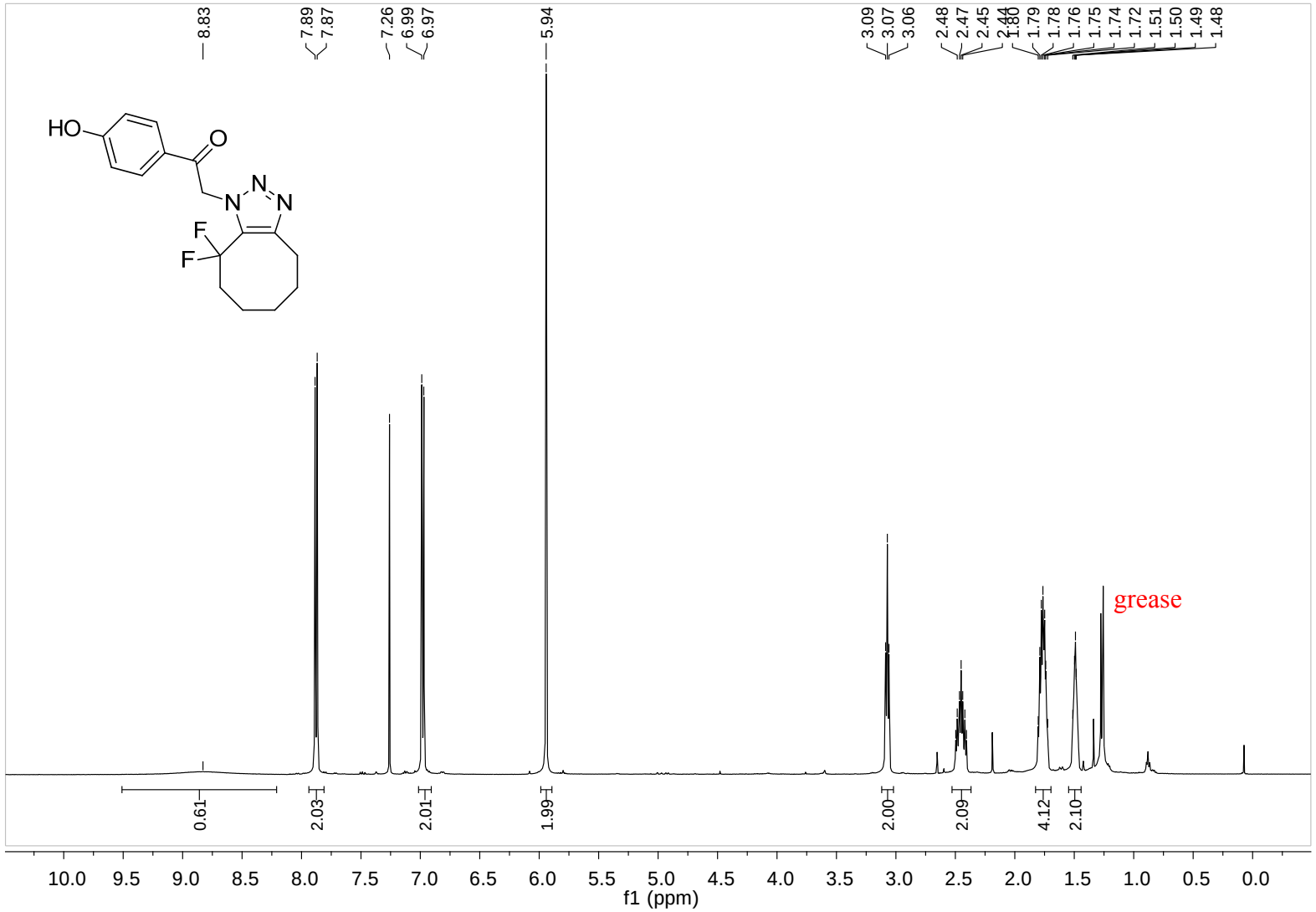


Figure S20. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): 2-(9,9-difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3c**)

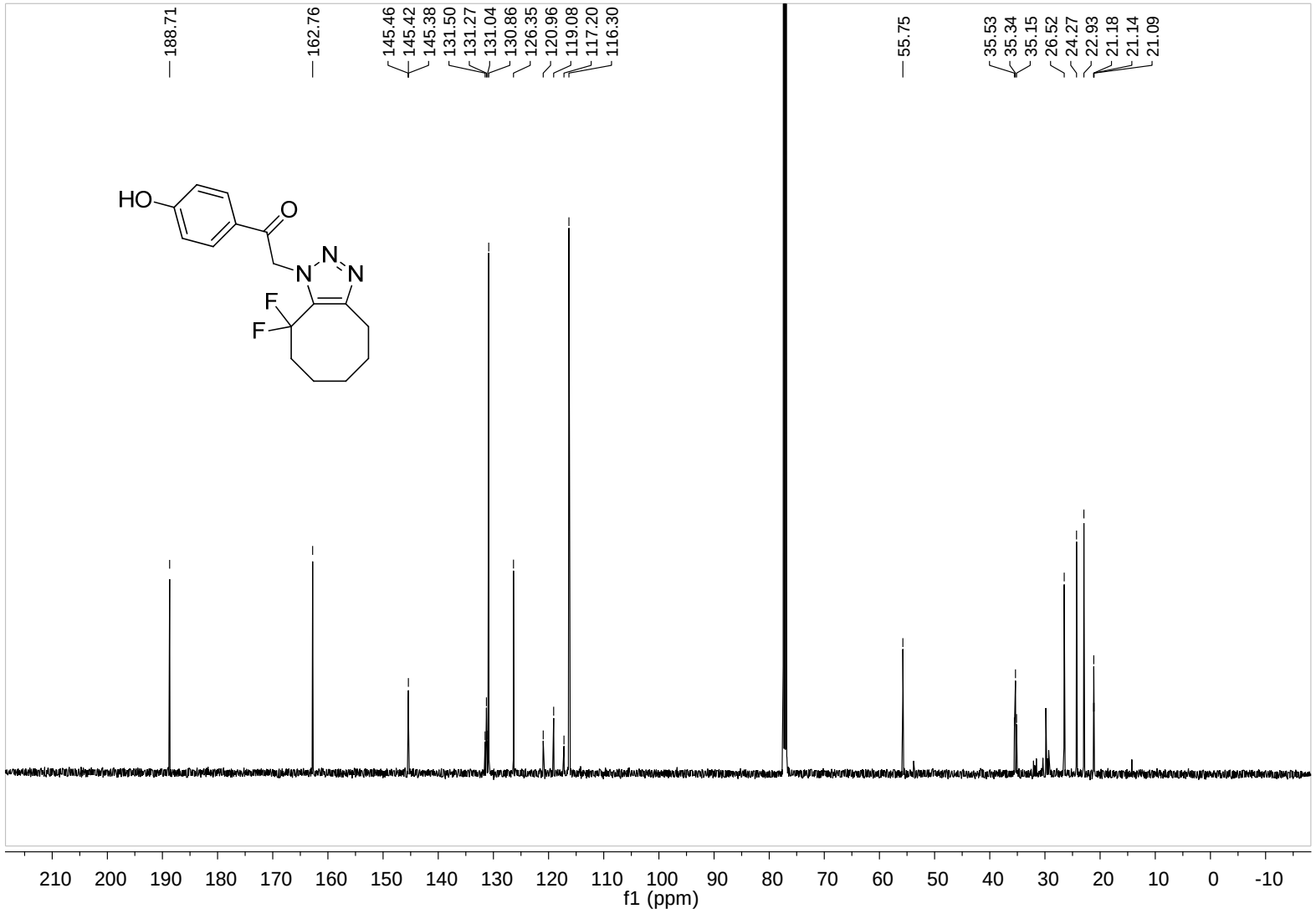


Figure S21. ^{19}F NMR (282 MHz, $CDCl_3$): 2-(9,9-difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3c**)

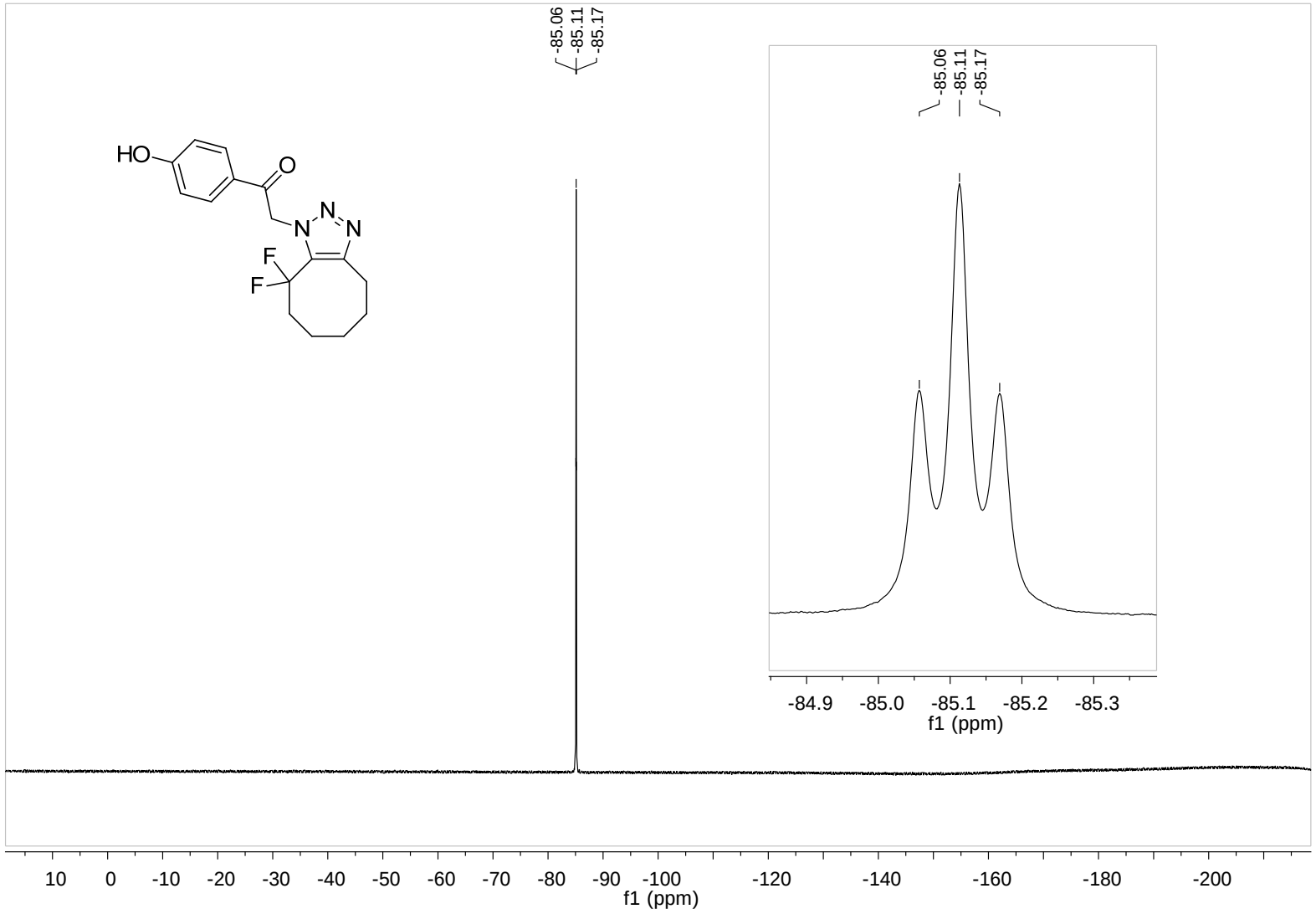


Figure S22. ^{1}H-^{13}C HSQCEDETGP (500 MHz, $CDCl_3$): 2-(9,9-difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3c**) (red cross-peaks belongs to the CH_2 groups and blue cross-peaks to the CH or CH_3 groups)

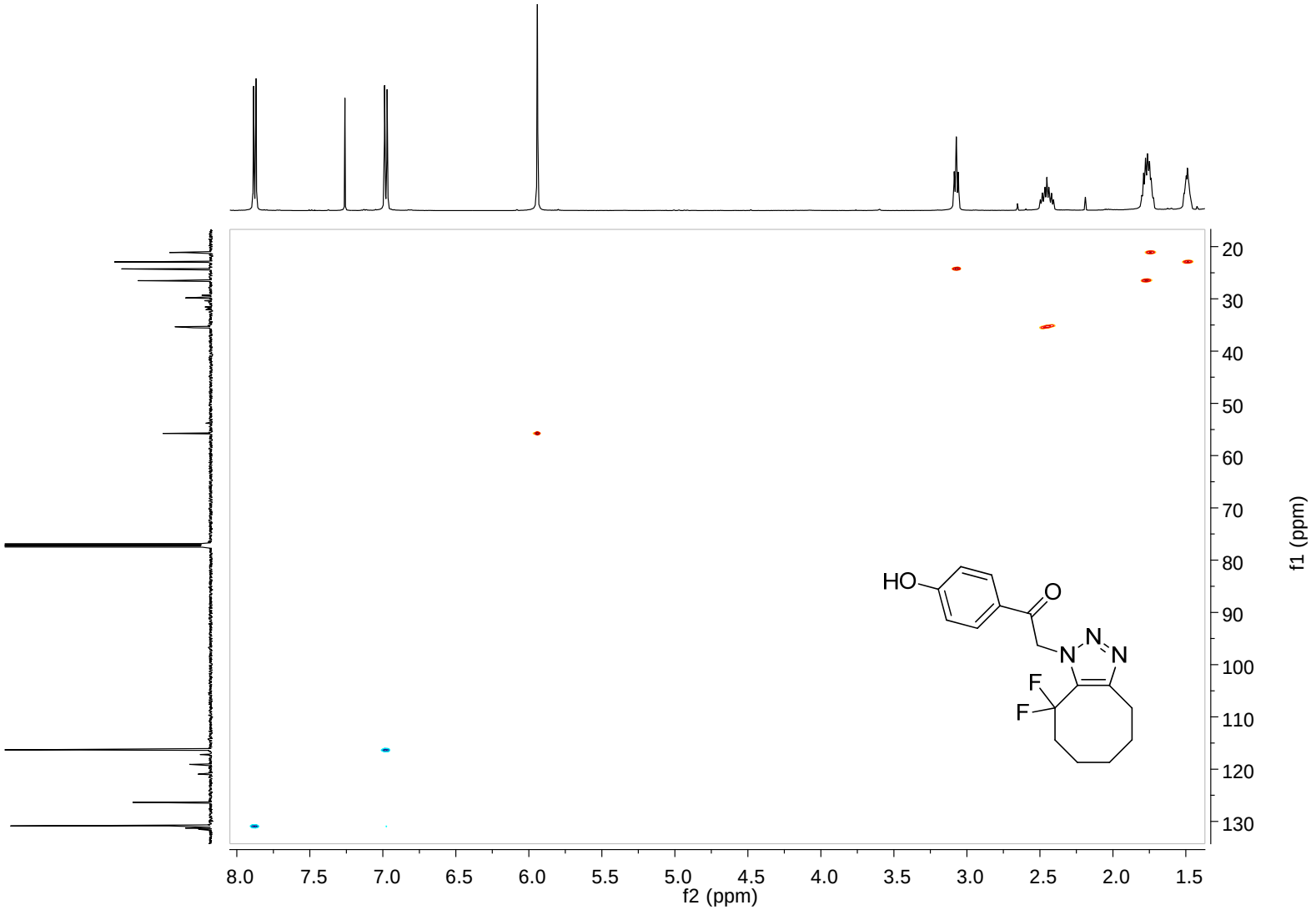


Figure S23. ^{1}H-^{13}C HMBC (500 MHz, $CDCl_3$): 2-(9,9-difluoro-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3c**). A depicted cross-peek (in circle) shows interaction between the *p*HP's α-hydrogen and carbon from the triazole core.

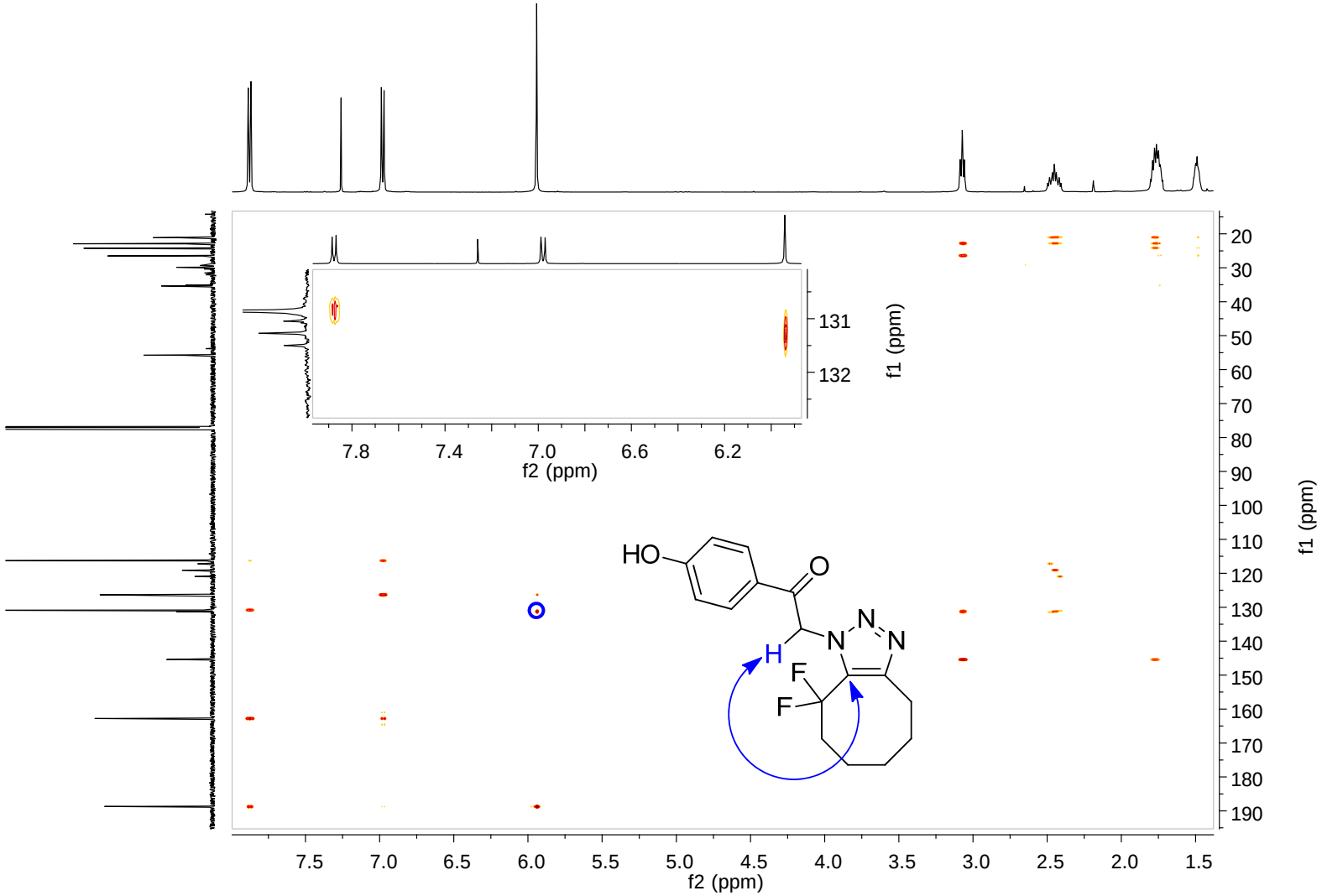


Figure S24. ^{1}H NMR (300 MHz, DMSO): 2-(4-hydroxyphenyl)-2-oxoethyl 2-azidoacetate (**19**)

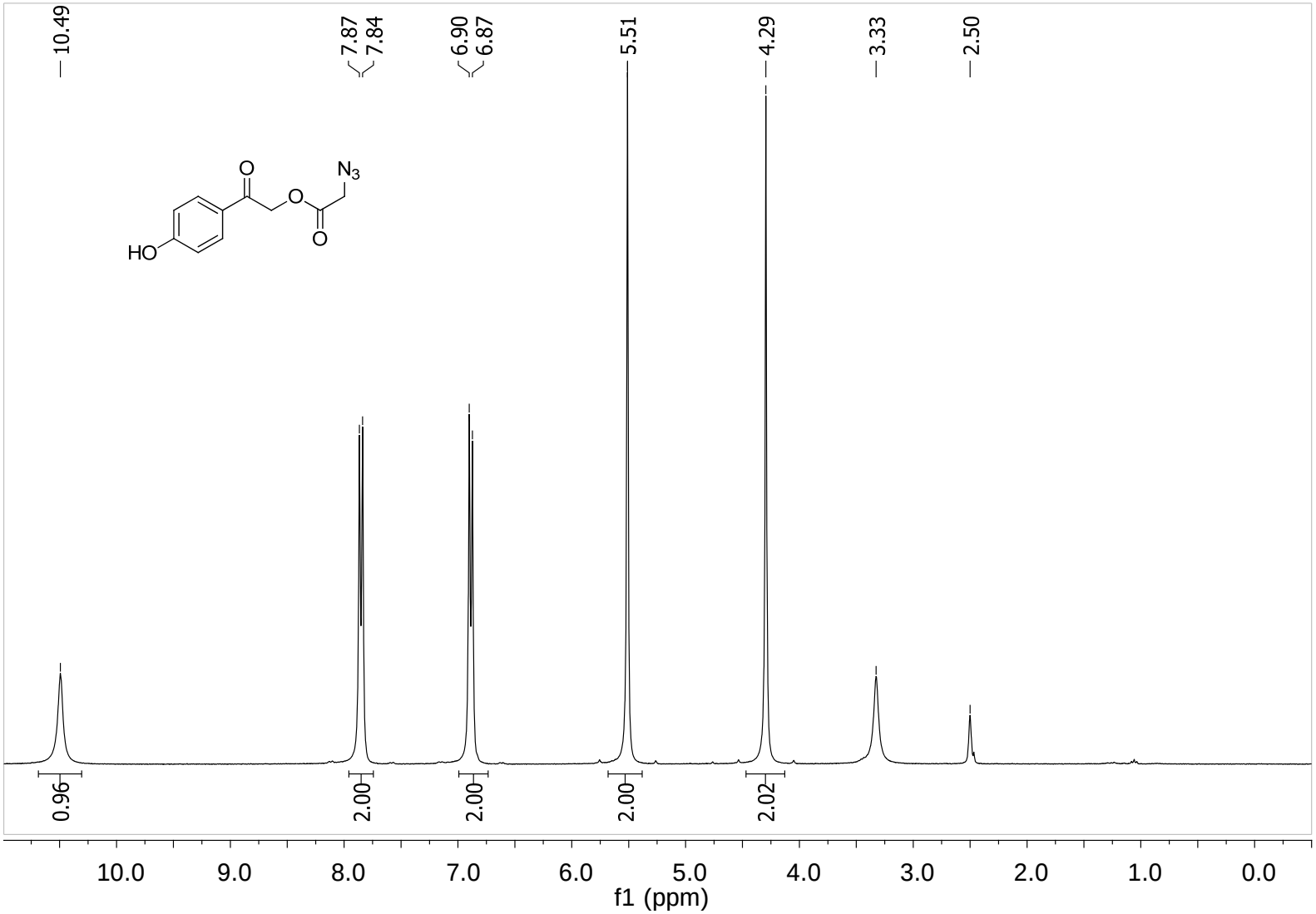


Figure S25. $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO): 2-(4-hydroxyphenyl)-2-oxoethyl 2-azidoacetate (**19**)

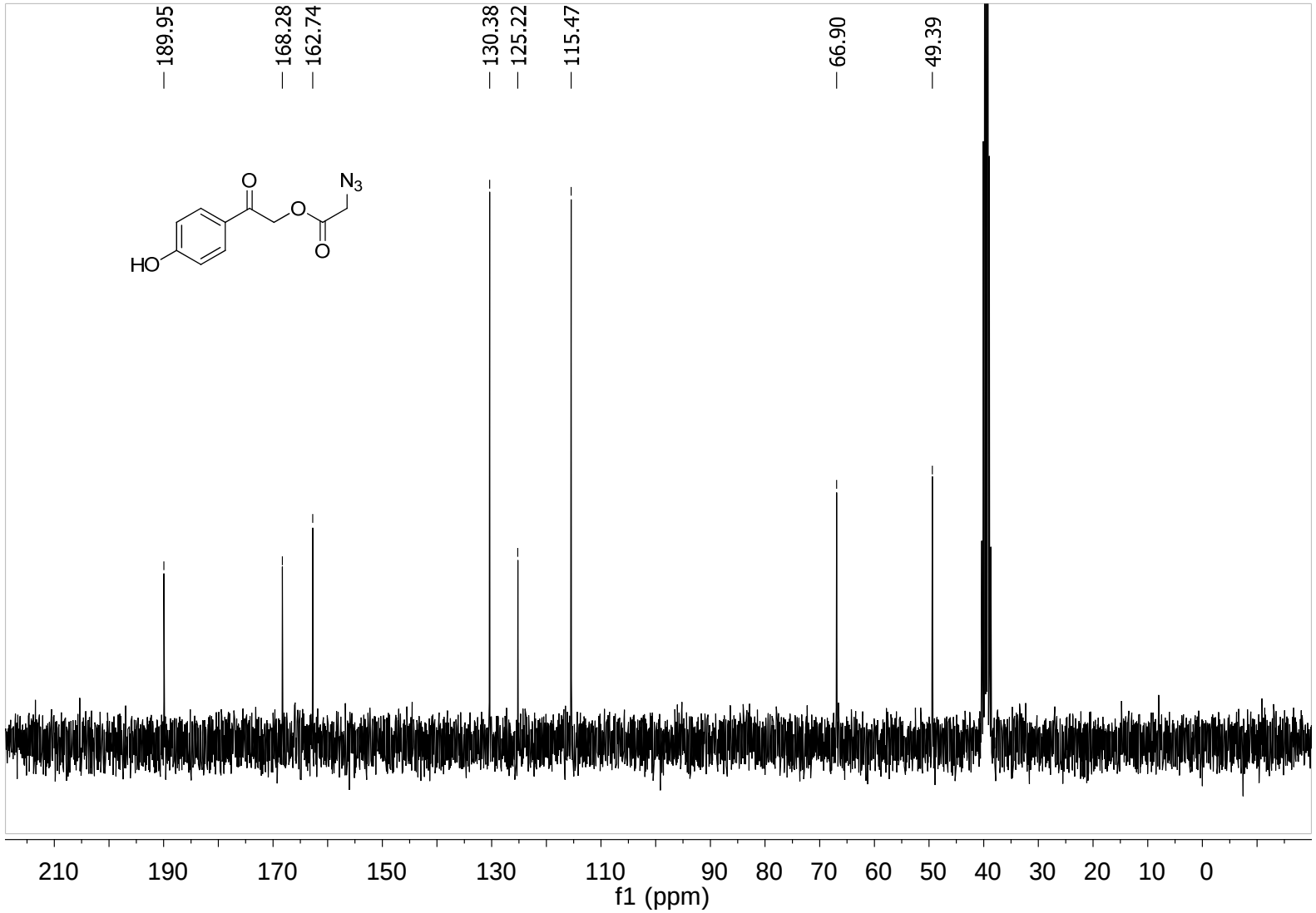


Figure S26. ^{1}H NMR (500 MHz, DMSO): 2-(4-hydroxyphenyl)-2-oxoethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (**3d**)

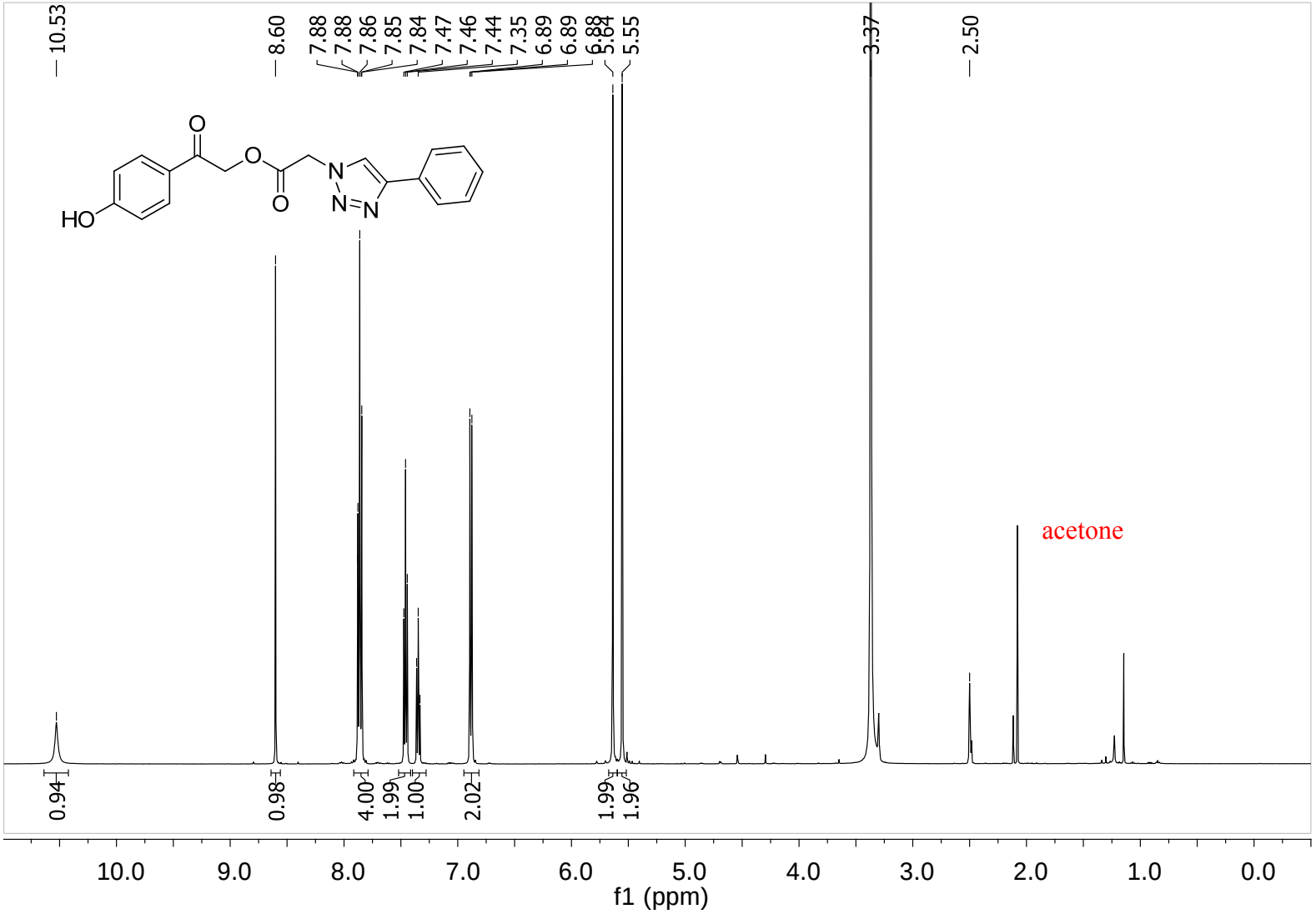


Figure S27. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO): 2-(4-hydroxyphenyl)-2-oxoethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (**3b**)

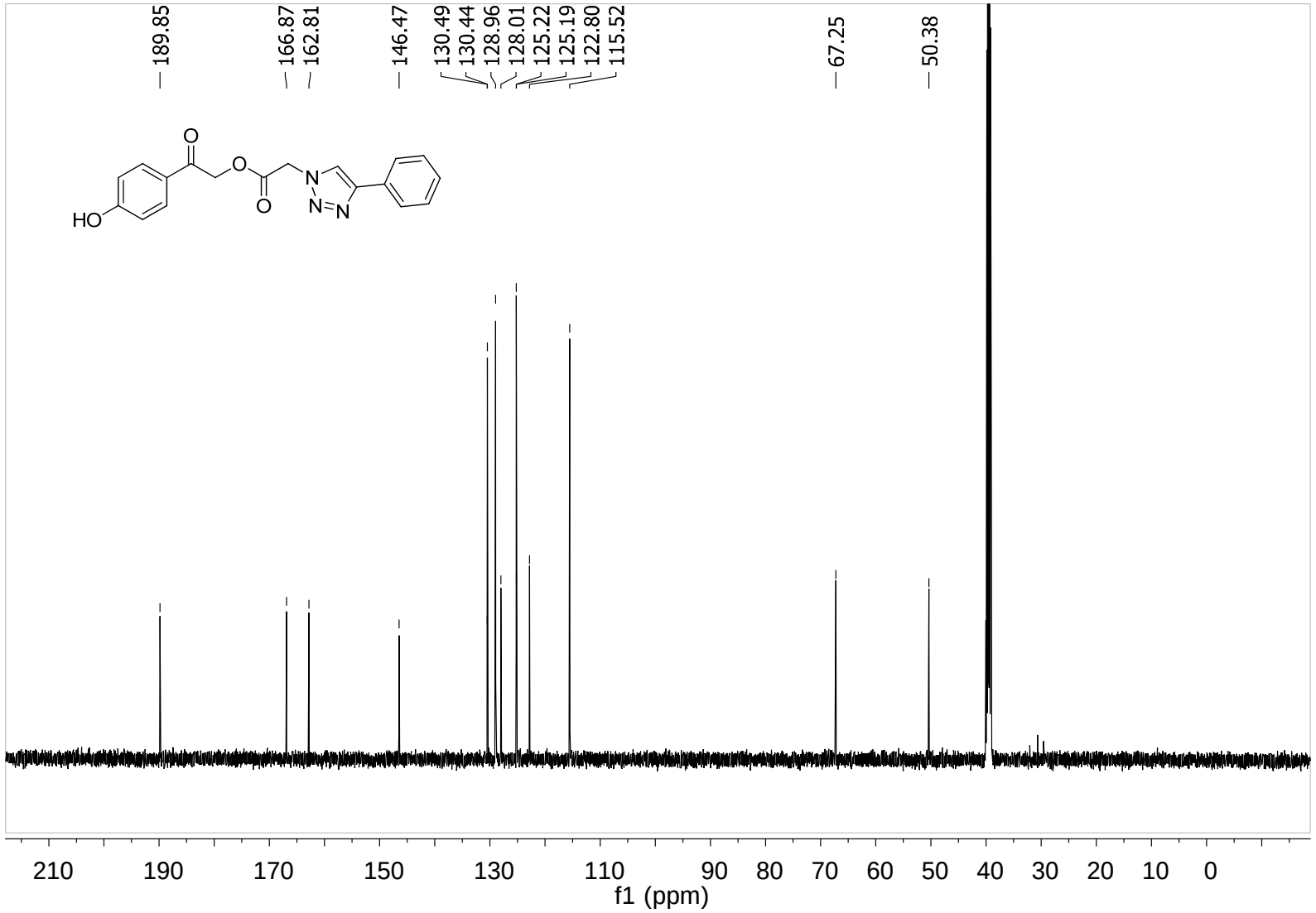


Figure S28. ^{1}H NMR (300 MHz, $CDCl_3$): 2-(6,11-dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3e**)

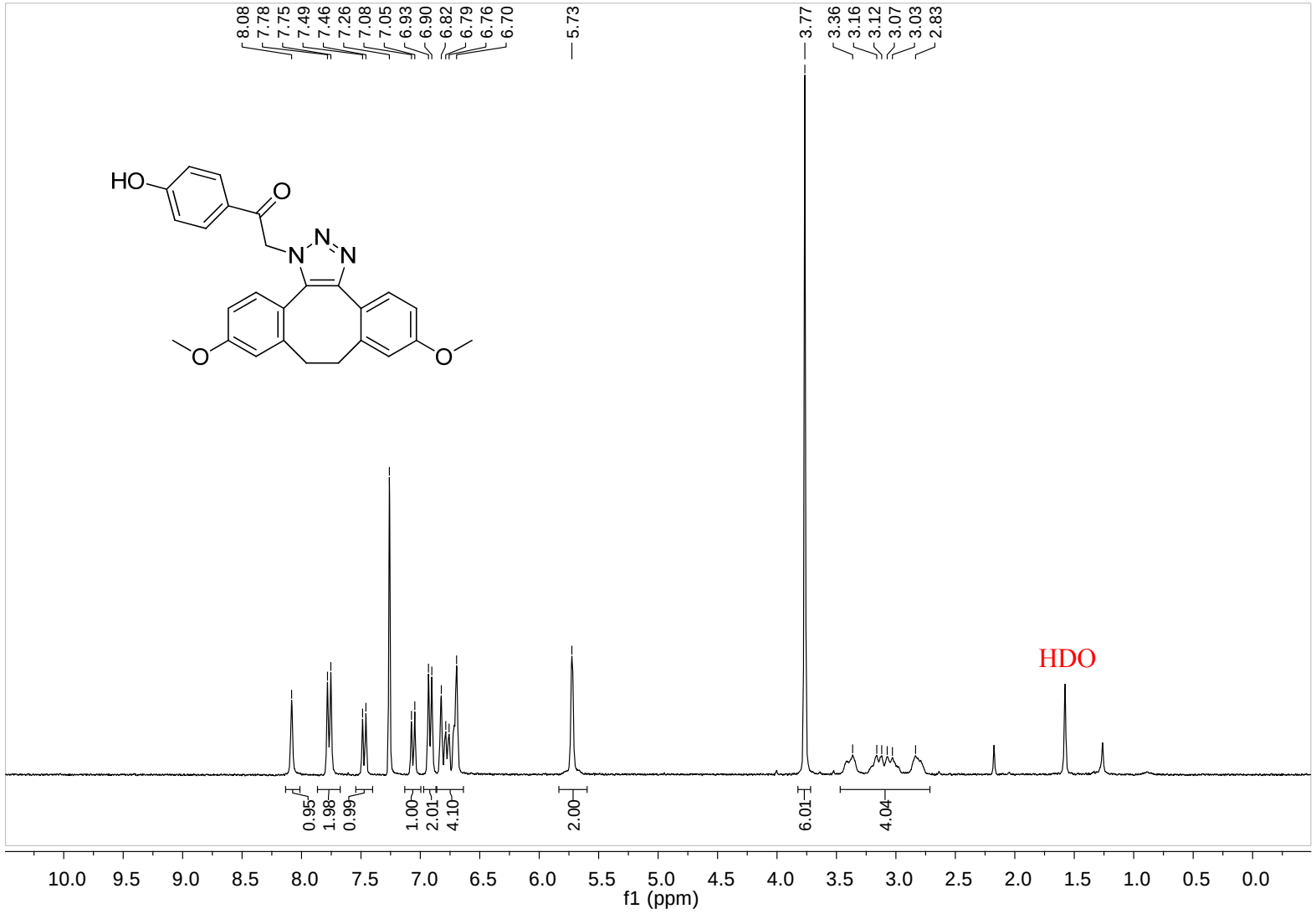


Figure S29. $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): 2-(6,11-dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)ethanone (**3e**)

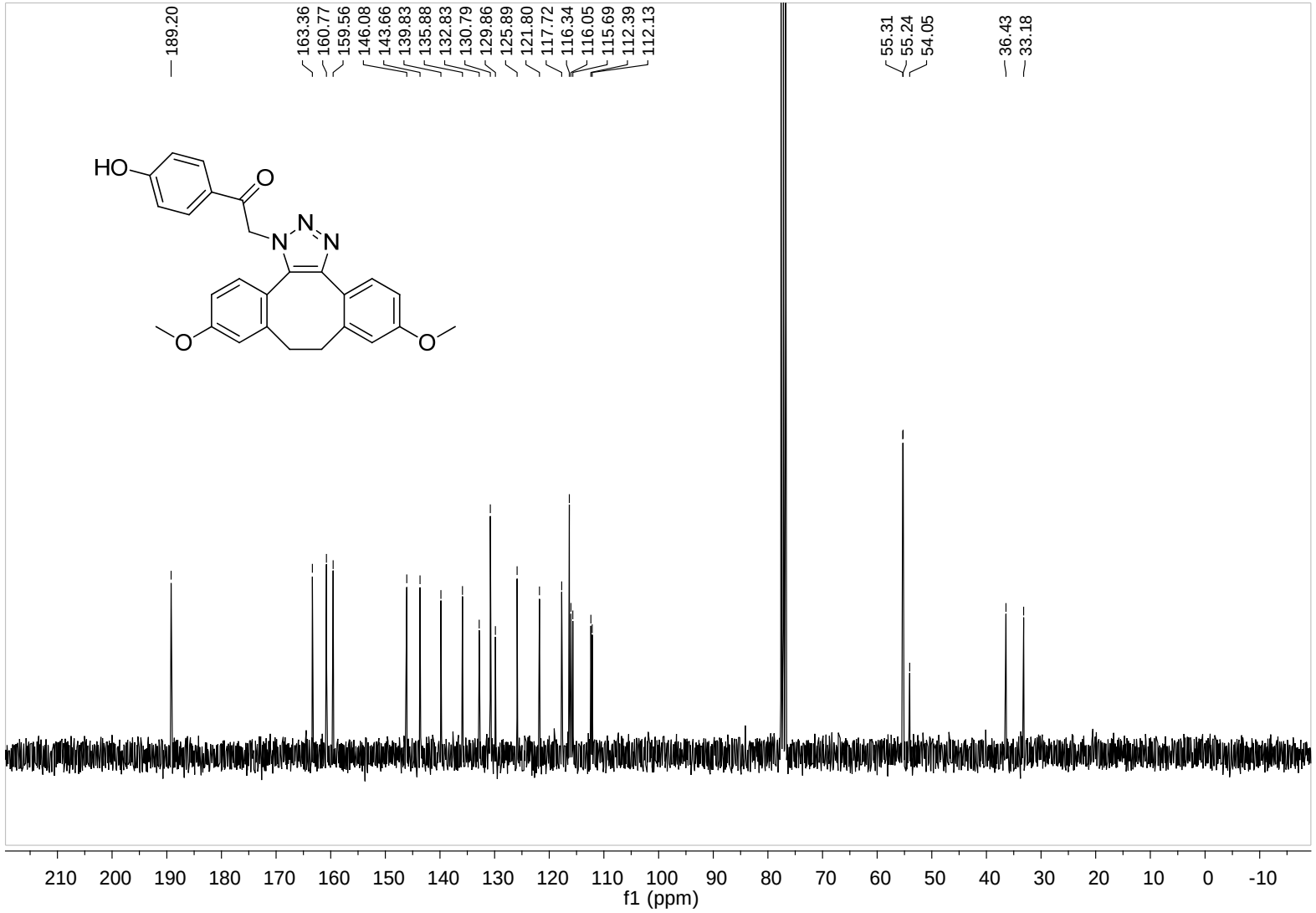


Figure S30. ^{1}H NMR (500 MHz, $CDCl_3$): 6,11-dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**4e**)

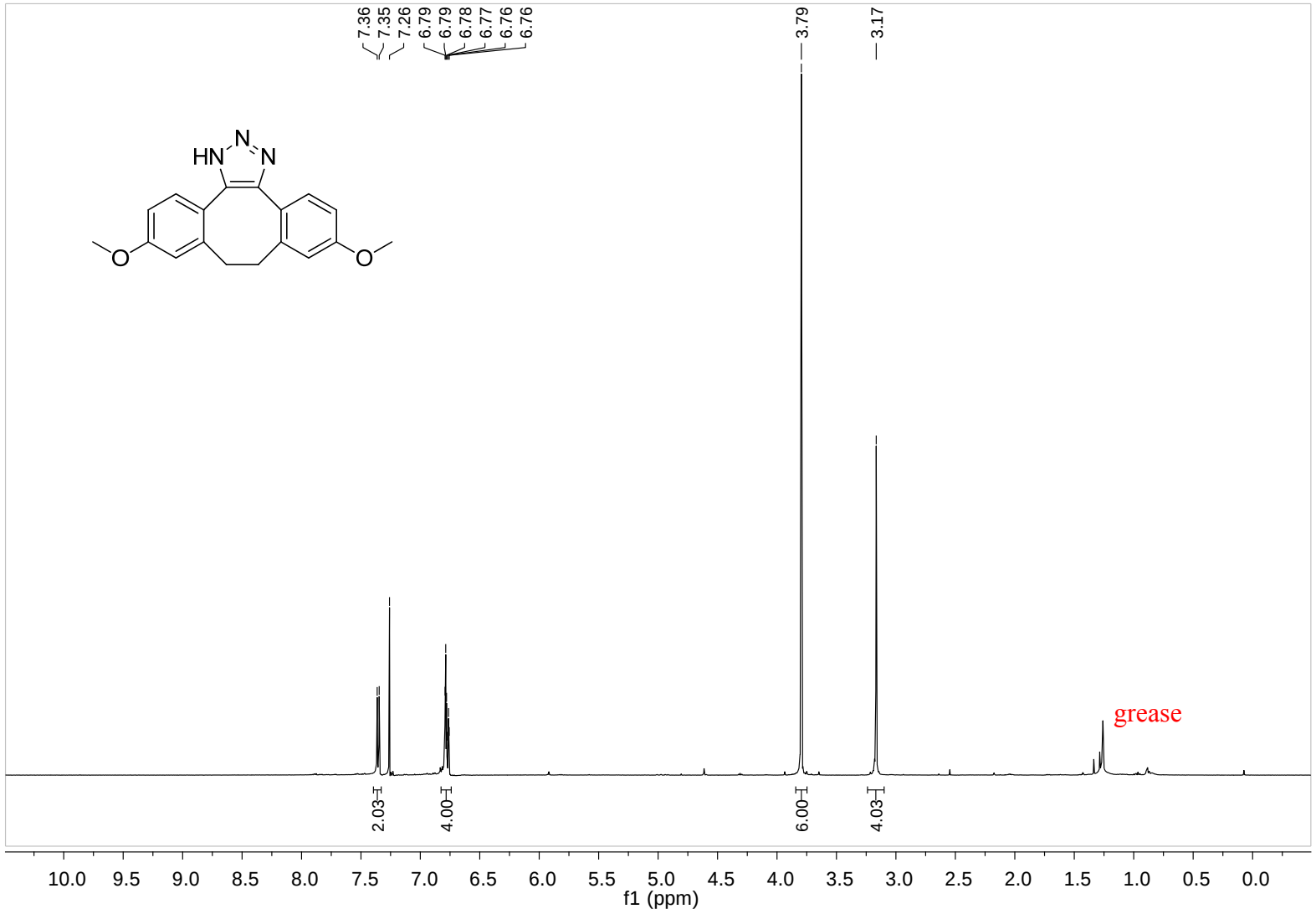


Figure S31. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): 6,11-dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**4e**)

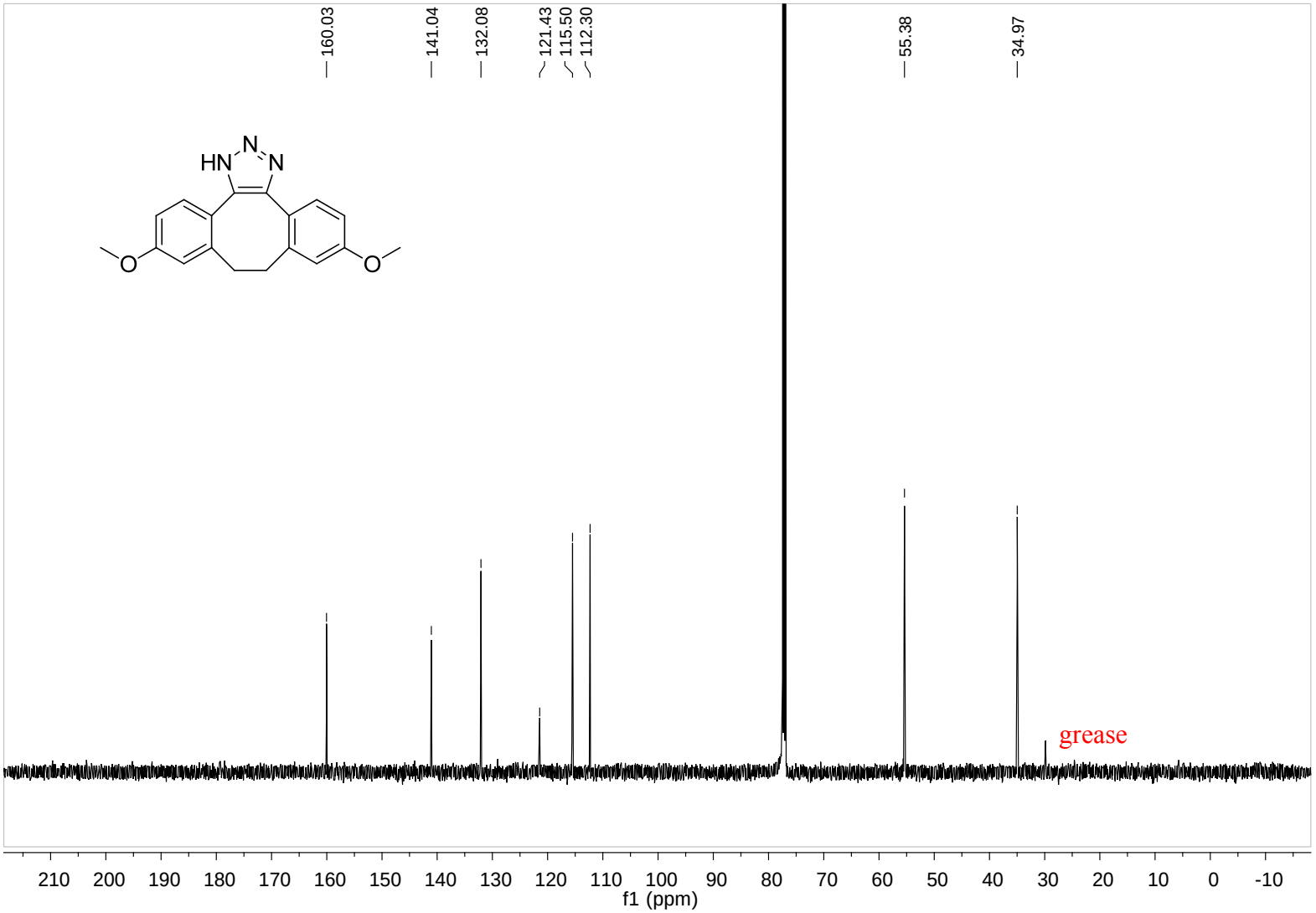


Figure S32. ^{1}H-^{13}C HMBC (500 MHz, $CDCl_3$): 6,11-dimethoxy-8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazole (**4e**). Depicted arrow points correspond to the missing signal of the carbon atom from the triazole core in the ^{13}C NMR spectrum.

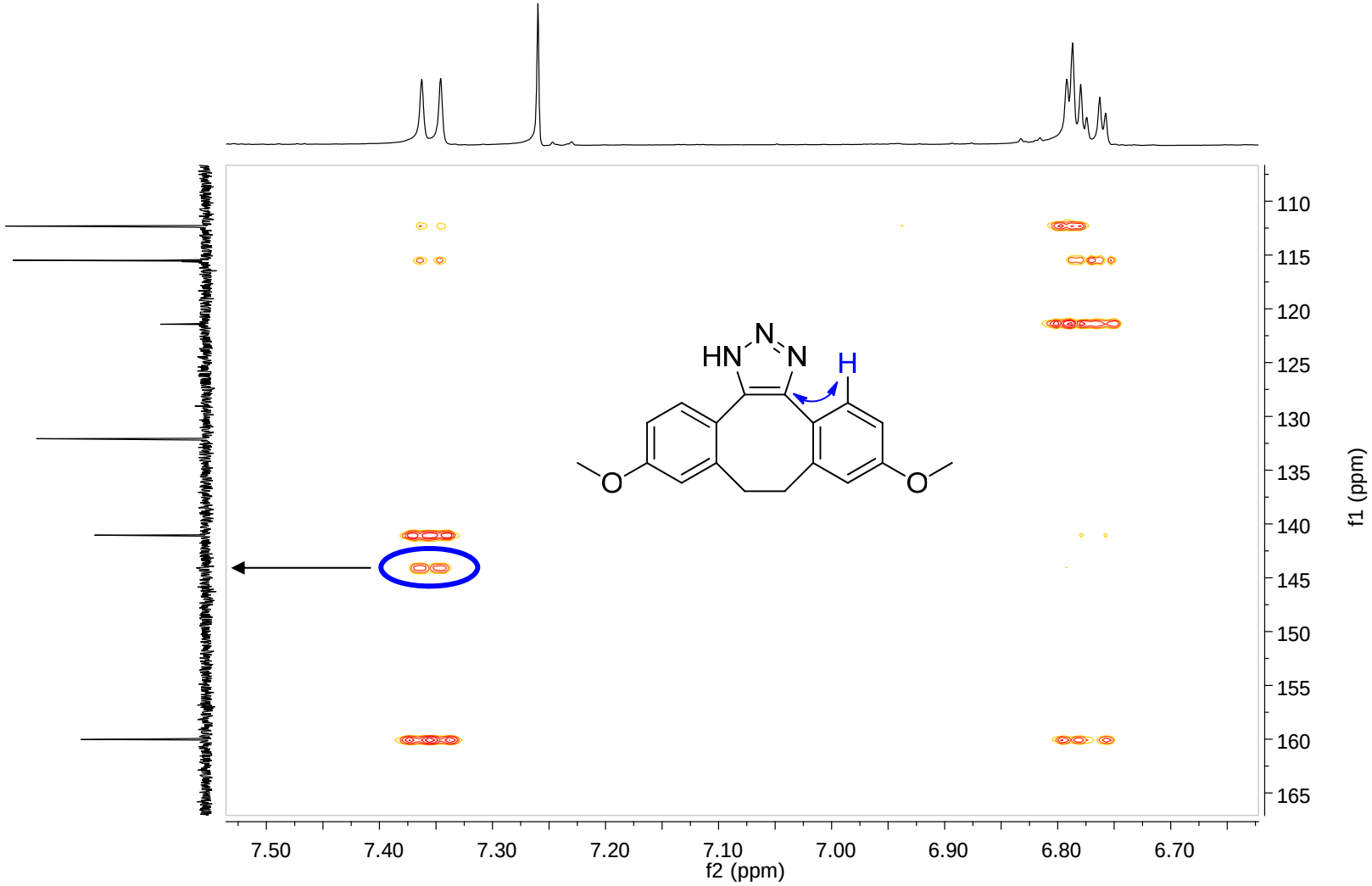


Figure S33. Acid-base titration of 1-(4-hydroxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (**3a**) in an aq acetonitrile (10%, v/v) solution ($c = 7.9 \times 10^{-5}$ mol dm^{-3})

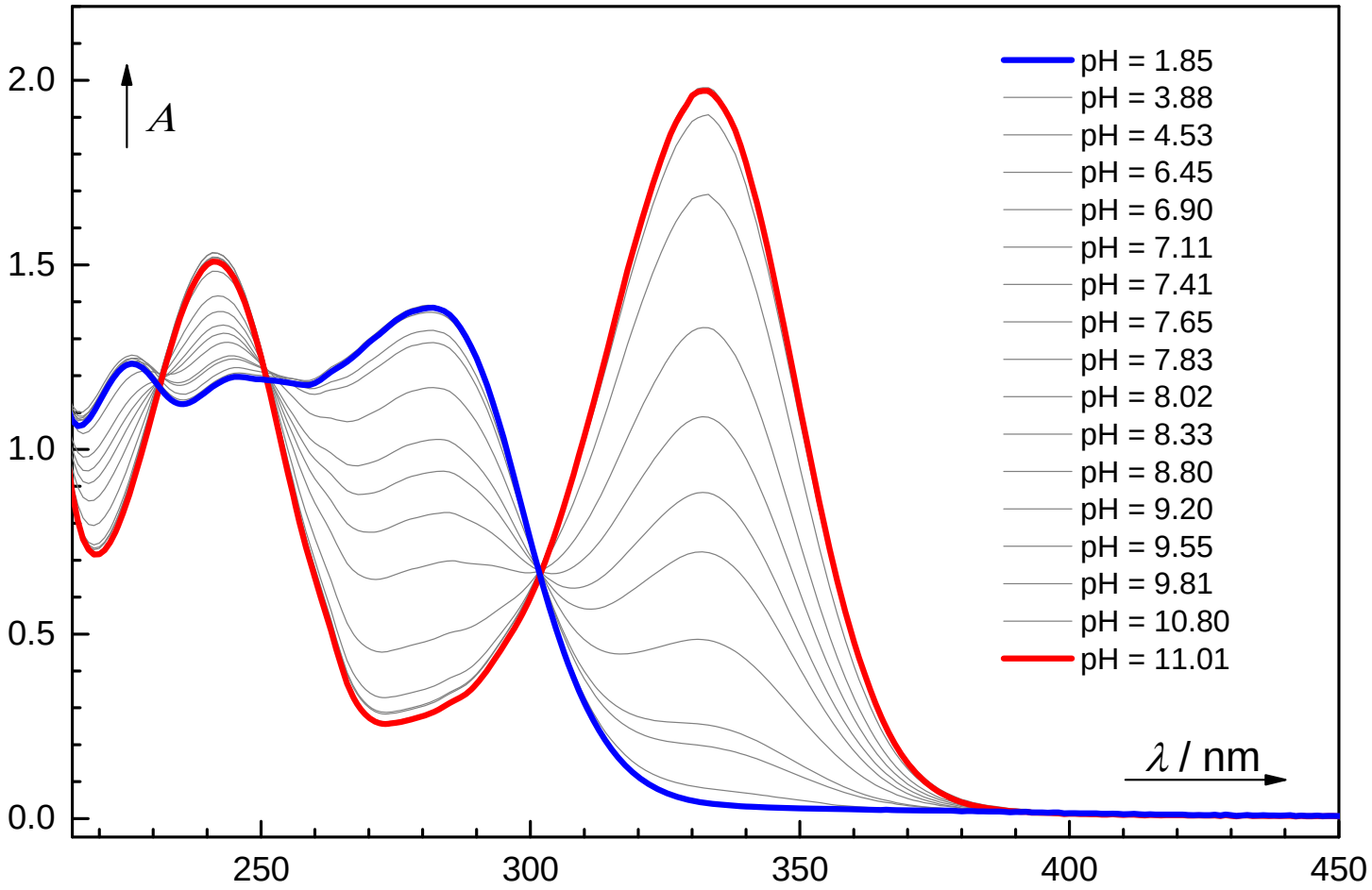
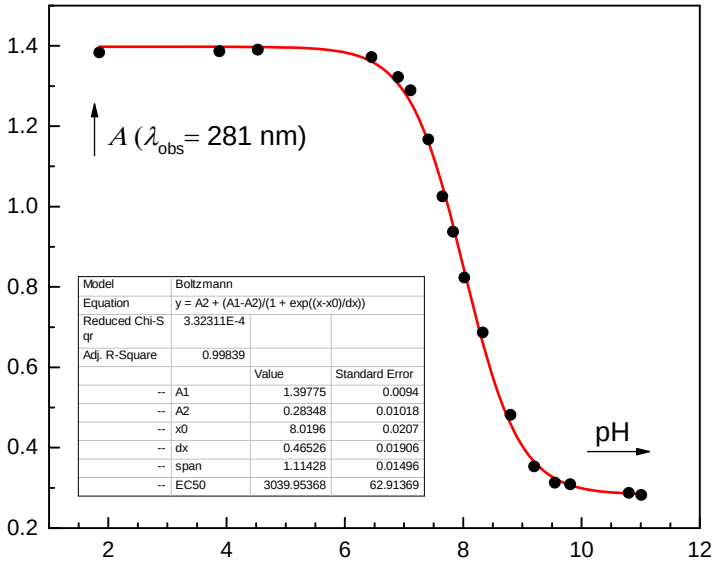


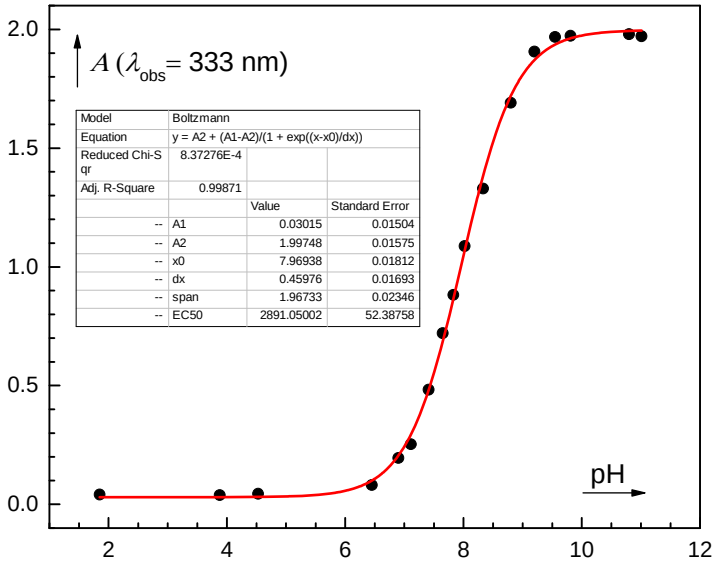
Figure S34. Acid-base titration of 1-(4-hydroxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (**3a**) in an aq CH_3CN (10%, v/v) solution ($c = 7.9 \times 10^{-5}$ mol dm^{-3}). The change in the absorbance at a) $\lambda_{obs} = 281$ nm that corresponds to the absorption maxima of **3a**, and b) $\lambda_{obs} = 333$ nm that corresponds to the absorption maxima of **3a**$^-$. Red line shows fitted data to the sigmoid Boltzmann function.

a)



Model	Boltzmann		
Equation	y = A2 + (A1-A2)/(1 + exp((x-x0)/dx))		
Reduced Chi-Sqr	3.32311E-4		
Adj. R-Square	0.99839		
		Value	Standard Error
--	A1	1.39775	0.0094
--	A2	0.28348	0.01018
--	x0	8.0196	0.0207
--	dx	0.46526	0.01906
--	span	1.11428	0.01496
--	EC50	3039.95368	62.91369

b)



Model	Boltzmann		
Equation	y = A2 + (A1-A2)/(1 + exp((x-x0)/dx))		
Reduced Chi-Sqr	8.37276E-4		
Adj. R-Square	0.99871		
		Value	Standard Error
--	A1	0.03015	0.01504
--	A2	1.99748	0.01575
--	x0	7.96938	0.01812
--	dx	0.45976	0.01693
--	span	1.96733	0.02346
--	EC50	2891.05002	52.38758

Figure S35. Acid-base titration of 1-(4-hydroxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (**3a**) in an aq acetonitrile (10%, v/v) solution ($c = 7.9 \times 10^{-5}$ mol dm^{-3}). A normalized speciation of **3a** and **3a**$^{-}$.

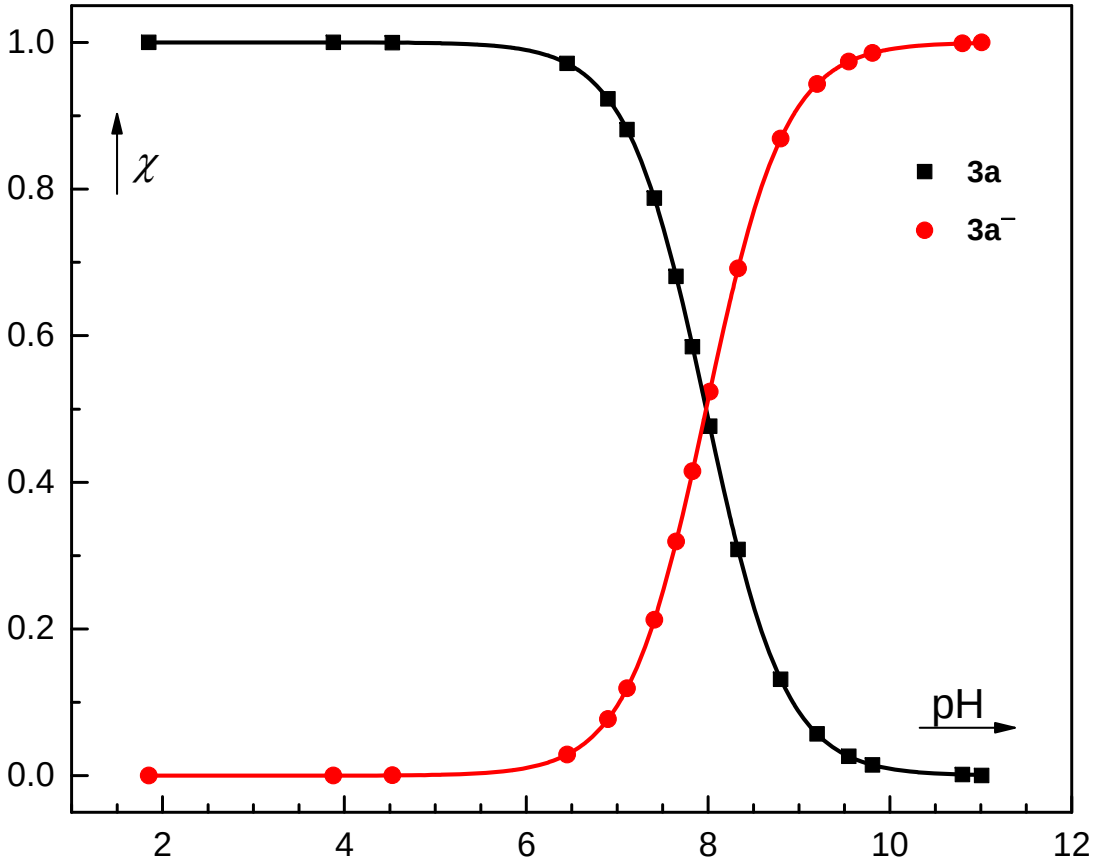


Figure S36. Normalized emission spectrum of a 450 W high pressure Hg(Xe) arc equipped with a λ_{em} = 320 ± 10 nm band-pass filter.

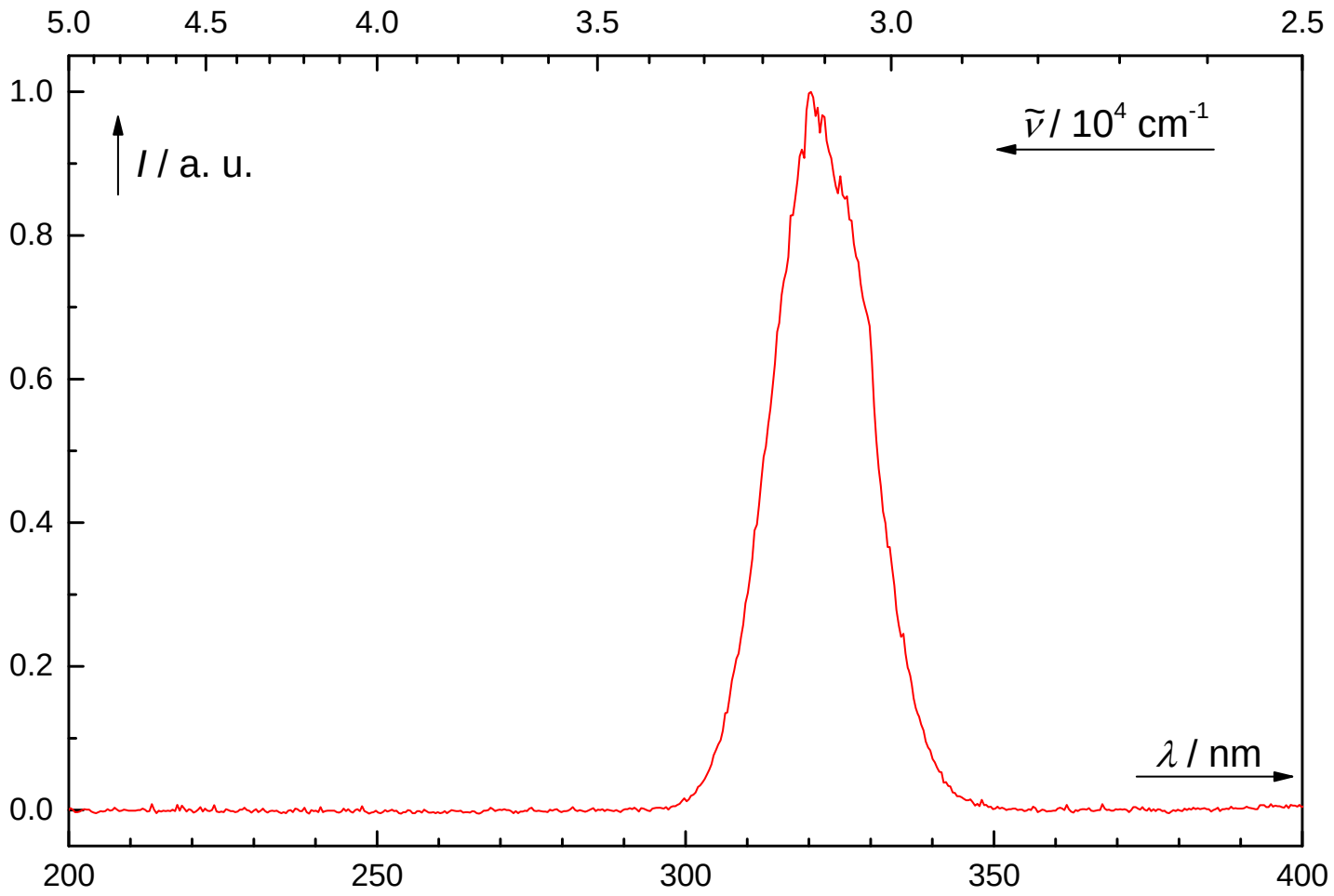


Figure S37. Normalized emission spectrum of a 40 W medium pressure Hg arc equipped with a monochromator: λ_{em} = 313 ± 1.5 nm.

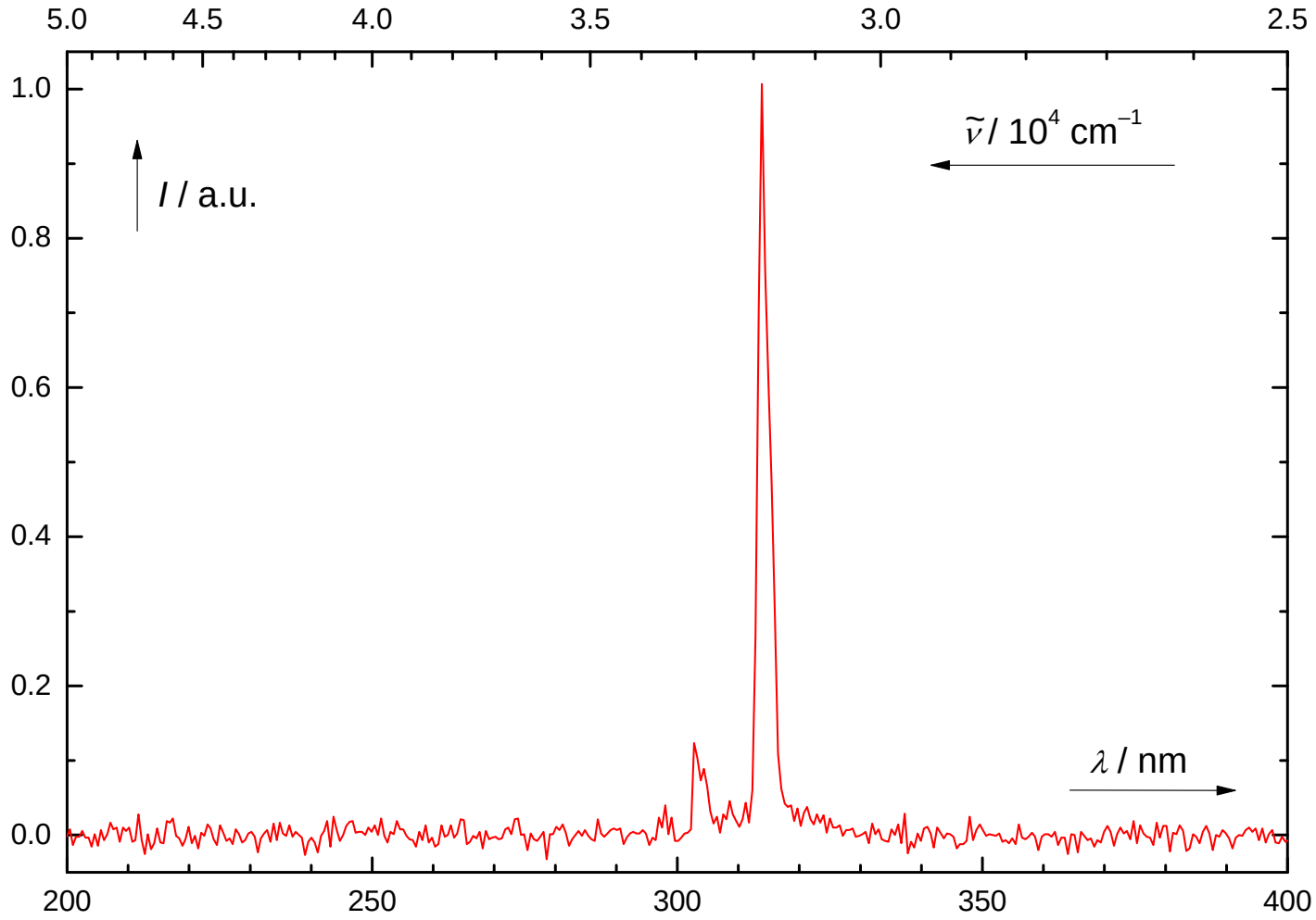


Figure S38. Normalized emission spectrum of a 200 W medium pressure Hg arc lamp.

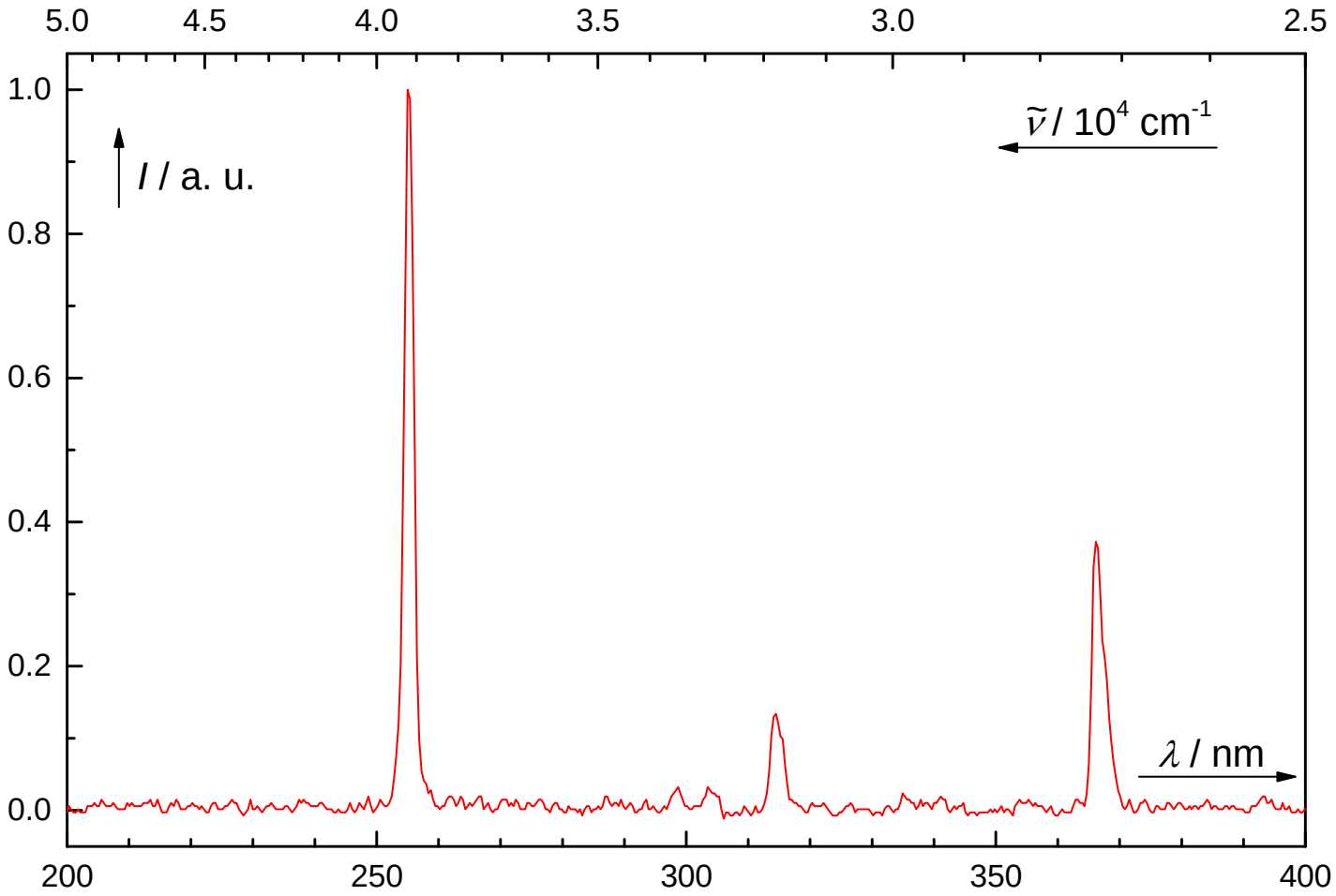


Figure S39. UV-vis absorption spectra in acetate buffer (pH = 5, I = 100 mmol dm^{-3}) of **3a** (blue line, acetonitrile (10 %, v/v) as a co-solvent), **3e** (green line, acetonitrile (20 %, v/v) as a co-solvent), **3c** (red line, acetonitrile (10%, v/v) as a co-solvent) and **3d** (black line, acetonitrile (10%, v/v) as a co-solvent).

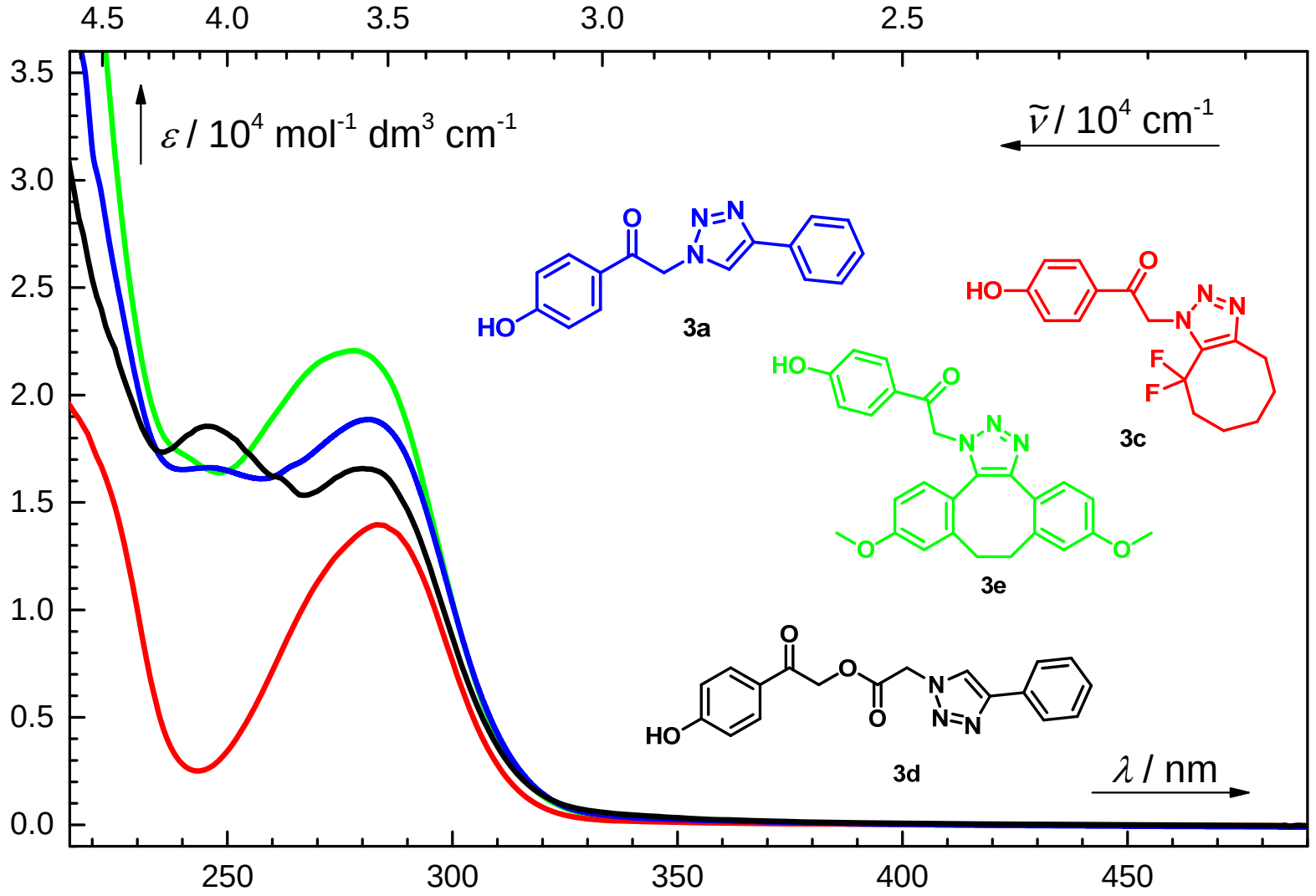


Figure S40. Transmittance spectra of 300 nm and 350 nm filters

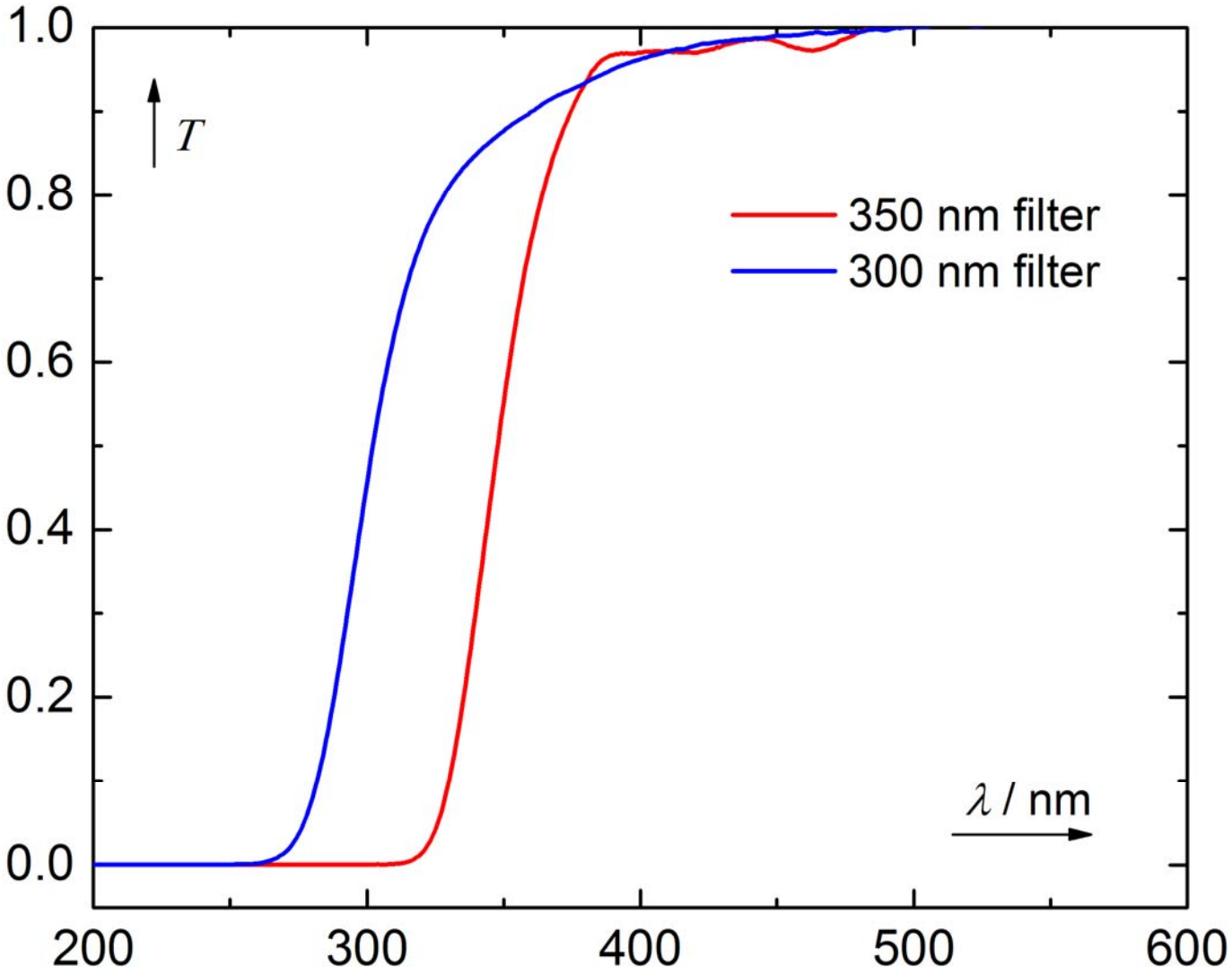
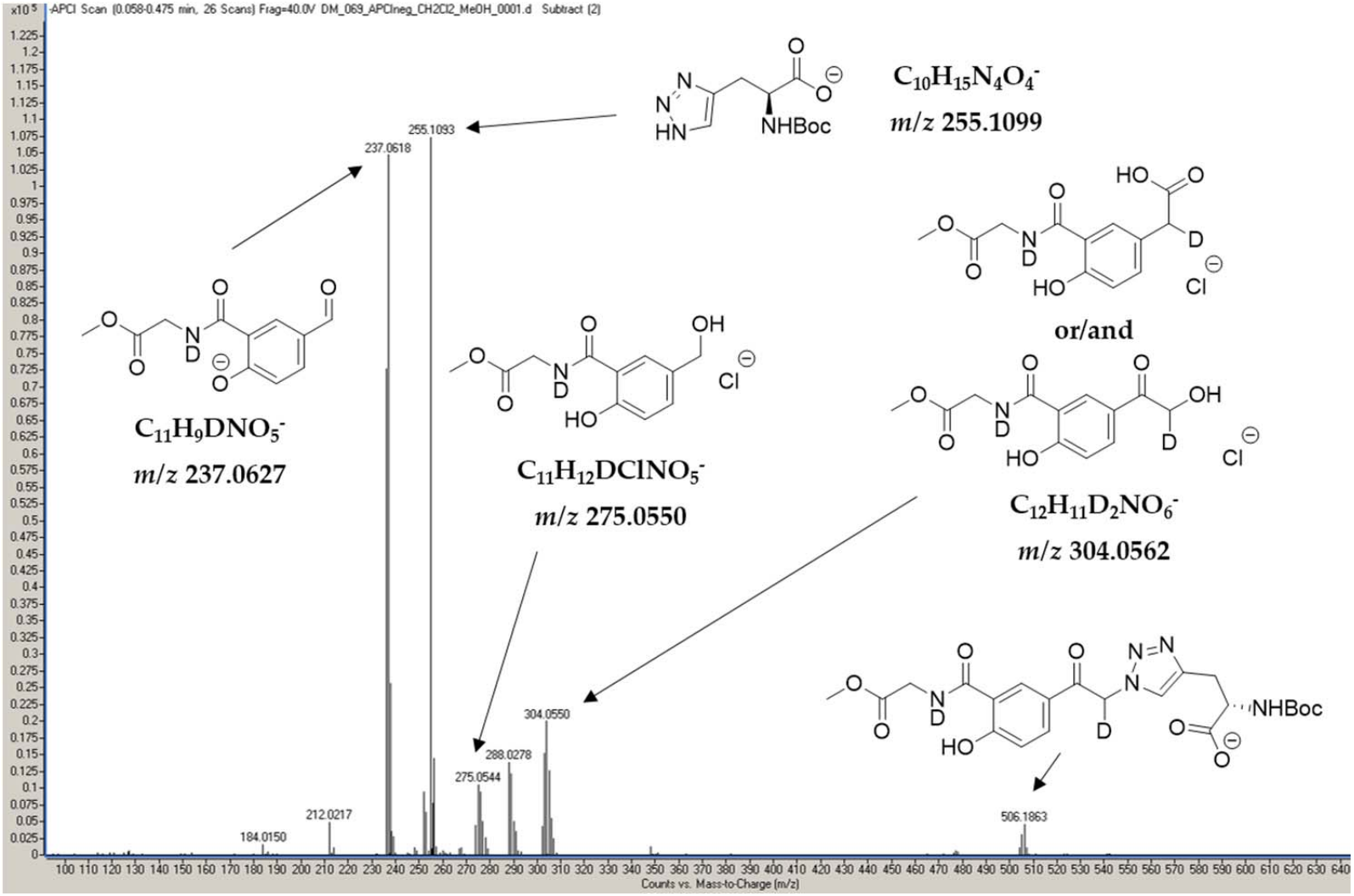


Figure S41. HRMS (APCI⁻) spectrum of the reaction mixture formed by irradiation of **3b** in CD_3CN/D_2O (1:1, v/v).



References

1. E. Bellale, M. Naik, V. B. Varun, A. Ambady, A. Narayan, S. Ravishankar, V. Ramachandran, P. Kaur, R. McLaughin, J. Whiteaker, S. Morayya, S. Guptha, S. Sharma, A. Raichurkar, D. Awasthy, V. Achar, P. Vachaspati, B. Bandodkar, M. Panda and M. Chatterji, *J. Med. Chem.*, 2014, **57**, 6572-6582.
2. J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, 1953, **75**, 2683-2684.
3. K. Edegger, C. C. Gruber, T. M. Poessl, S. R. Wallner, I. Lavandera, K. Faber, F. Niehaus, J. Eck, R. Oehrlein, A. Hafner and W. Kroutil, *Chem. Commun.*, 2006, 2402-2404.
4. D. Marcovici-Mizrahi, H. E. Gottlieb, V. Marks and A. Nudelman, *J. Org. Chem.*, 1996, **61**, 8402-8406.
5. J. Wintner, Dissertation, University of Basel, 2007.
6. S. Muto and A. Itai, EP1512396 A1, 2005.
7. G. Naturale, M. Lamblin, C. Commandeur, F.-X. Felpin and J. Dessolin, *Eur. J. Org. Chem.*, 2012, 5774-5788.
8. M. D. Kosobokov, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2015, **17**, 760-763.
9. J. A. Codelli, J. M. Baskin, N. J. Agard and C. R. Berozzi, *J. Am. Chem. Soc.*, 2008, **130**, 11486-11493.
10. Y. Kageshima, C. Suzuki, K. Oshiro and H. Amii, *Synlett*, 2015, **26**, 63-66.
11. V. Haridas, Y. K. Sharma, S. Sahu, R. P. Verma, S. Sadanandan and B. G. Kacheshwar, *Tetrahedron*, 2011, **67**, 1873-1884.
12. F. R. Fischer and C. Nuckolls, *Angew. Chem. Int. Ed.*, 2010, **49**, 7257-7260.
13. M. Blangetti, P. Fleming and D. F. O'Shea, *J. Org. Chem.*, 2012, **77**, 2870-2877.
14. D. W. Paley, D. F. Sedbrook, J. Decatur, F. R. Fischer, M. L. Steigerwald and C. Nuckolls, *Angew. Chem. Int. Ed.*, 2013, **52**, 4591-4594.
15. F. Friscourt, P. A. Ledin, N. E. Mbua, H. R. Flanagan-Steet, M. A. Wolfert, R. Steet and G.-J. Boons, *J. Am. Chem. Soc.*, 2012, **134**, 5381-5389.
16. X. Wang, C. Kuang and Q. Yang, *Eur. J. Org. Chem.*, 2012, 424-428.
17. T. Slanina, P. Sebej, A. Heckel, R. S. Givens and P. Klan, *Org. Lett.*, 2015, **17**, 4814-4817.
18. A. A. Poloukhtine, N. E. Mbua, M. A. Wolfert, G.-J. Boons and V. V. Popik, *J. Am. Chem. Soc.*, 2009, **131**, 15769-15776.