Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information for:

Late-Stage Synthesis and Application of Photoreactive Probes Derived from Direct Benzoylation of Heteroaromatic C–H Bonds

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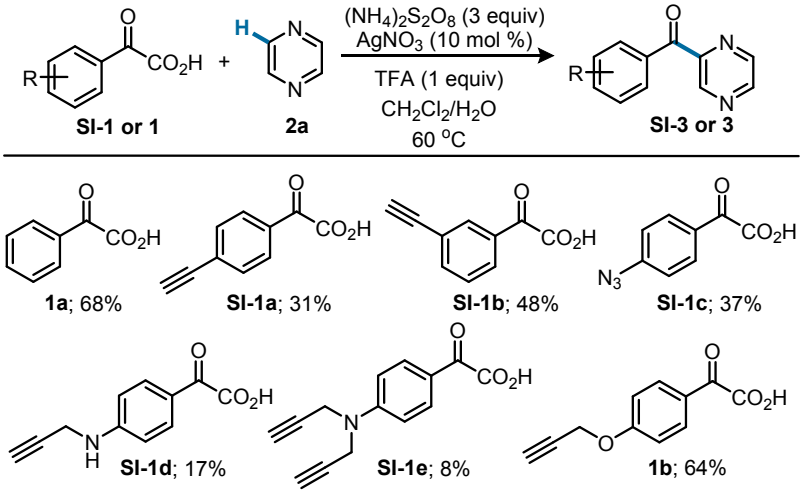
A. General Information

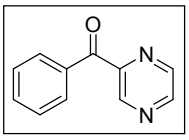
All reagents and solvents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Substituted aryl glyoxylic reagents **1b** and **SI-1a** through **SI-1e** were prepared using established procedures and strategies.[1-3] Biologically active compounds **2q**,[4] **2t**,[5] **2r**,[6] **2s**,[7] and **2u**[8] were prepared according to literature procedures. Silica gel chromatography was performed using medium pressure Biotage or ISCO systems employing columns pre-packaged by various commercial vendors including Biotage and ISCO. ^{1}H and $^{13}C\{^{1}H\}$ NMR characterization data were collected at 300 K on a Bruker AV-600 spectrometer operating at 600 and 151 MHz, respectively, or a Bruker AV-400 spectrometer operating at 400 and 101 MHz, respectively, with chemical shifts reported in parts per million relative to reference solvents. Representative IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer and only partial data are provided. High resolution mass spectroscopy (HRMS) was performed on an Agilent (6220) LC-MS TOF using a Xbridge C18 2.5 μm 3.0 X 5.0 mm at 60 ^{o}C; ammonium formate: water as mobile phase A1 and 50:50 Methanol:Acetonitrile as mobile Phase B1.

B. General Procedure for 2-Benzoyl Heterocycle Synthesis

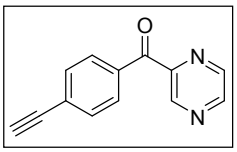
To a mixture of heterocycle (0.25 mmol), aryl glyoxylic acid reagent (1.5-2 equiv), and catalytic $AgNO_3$ (10 mol %) in degassed CH_2Cl_2 (2.5 mL) was added trifluoroacetic acid (1-2 equiv), followed by a freshly prepared solution of $NH_4S_2O_8$ (3 equiv) in degassed water (2.5 mL). The mixture was heated to 60 ^oC for 3h. The reaction was then cooled to room temperature, diluted with ethyl acetate and water (1:1), followed by filtration through Celite. The organic layer was removed and the aqueous fraction re-extracted with ethyl acetate three times. The combined organic extracts were washed with sat. $NaHCO_3$ followed by brine. The organic extracts were dried over $MgSO_4$, filtered, and evaporated to give the crude material, which was purified by silica gel column chromatography.

C. Optimization of Substituted Aryl Glyoxylic Acid Reagents

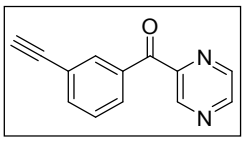




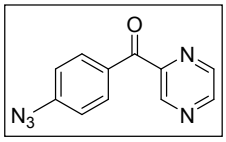
Equation 1, 3a. Using the general procedure with pyrazine (40 mg, 0.50 mmol) and phenyl glyoxylic acid **1a** (150 mg, 1.0 mmol), the benzophenone derivative was isolated as a pale yellow oil (63 mg, 0.34 mmol, 68%). IR (film): 3059, 1662, 1595, 1447, 1399, 1293, 1155, 931, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.24 (d, J = 1.2 Hz, 1H), 8.81-8.75 (m, 1H), 8.69 (dd, J = 2.3, 1.6 Hz, 1H), 8.12-8.06 (m, 2H), 7.67-7.61 (m, 1H), 7.55-7.48 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 192.1, 149.8, 146.7, 146.0, 142.8, 135.4, 133.5, 130.8, 128.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_9N_2O$: 185.0709. Found: 185.0707.



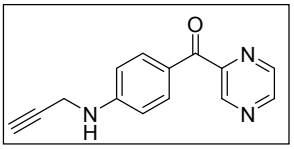
SI-3a. Using the general procedure with pyrazine (20 mg, 0.25 mmol) and aryl glyoxylic acid **SI-1a** (65 mg, 0.38 mmol), the benzophenone derivative was isolated as a light yellow oil (16 mg, 0.077 mmol, 31%). ^1H NMR (CD_3OD, 400 MHz): δ 9.28 (d, J = 1.6 Hz, 1H), 8.81 (d, J = 2.3 Hz, 1H), 8.61-8.75 (m, 1H), 8.02-8.17 (m, 2H), 7.58-7.69 (m, 2H), 3.29 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 191.3, 149.6, 147.0, 146.2, 142.9, 135.3, 132.0, 130.8, 127.4, 82.8, 80.8.



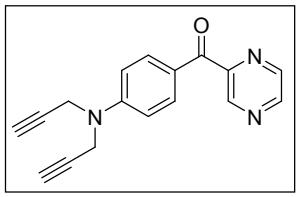
SI-3b. Using the general procedure with pyrazine (20 mg, 0.25 mmol) and aryl glyoxylic acid **SI-1b** (65 mg, 0.375 mmol), the benzophenone derivative was isolated as a white solid (25 mg, 0.12 mmol, 48%). IR (film): 3283, 1667, 1572, 1302, 1136, 1018, 725 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.30 (br s, 1H), 8.82 (br s, 1H), 8.72 (br s, 1H), 8.23 (t, J = 1.6 Hz, 1H), 8.10 (dt, J = 8.0, 1.3 Hz, 1H), 7.75 (dt, J = 7.7, 1.4 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 3.14 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 191.3, 149.5, 147.1, 146.2, 143.0, 136.7, 135.7, 134.6, 131.0, 128.5, 122.6, 82.6, 78.4; HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_8N_2O$: 209.0709. Found: 209.0707.



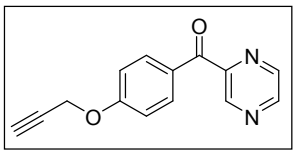
SI-3c. Using the general procedure with pyrazine (20 mg, 0.25 mmol) and aryl glyoxylic acid **SI-1c** (57 mg, 0.38 mmol), the benzophenone derivative was isolated as a tan solid (21 mg, 0.093 mmol, 37%). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.26 (d, J = 1.6 Hz, 1H), 8.79 (d, J = 2.3 Hz, 1H), 8.68 (dd, J = 2.3, 1.6 Hz, 1H), 8.18 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 190.4, 149.9, 146.9, 146.2, 145.5, 142.8, 133.1, 132.1, 118.9. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{11}H_7N_5O$: 248.0543. Found: 248.0536.



SI-3d. Using the general procedure with pyrazine (20 mg, 0.25 mmol) and aryl glyoxylic acid **SI-1d** (65 mg, 0.38 mmol), the benzophenone derivative was isolated as a pale yellow solid (10 mg, 0.042 mmol, 17%). IR (film): 3288, 1641, 1591, 1530, 1321, 1152 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.17 (d, J = 1.6 Hz, 1H), 8.74 (d, J = 2.3 Hz, 1H), 8.63-8.70 (m, 1H), 8.07 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 6.2 Hz, 2H), 4.54 (br s, 1H), 4.04 (dd, J = 5.9, 2.3 Hz, 2H), 2.28 (t, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101MHz): δ 189.8, 151.5, 151.4, 146.1, 146.0, 142.7, 133.6, 125.7, 112.2, 79.6, 72.1, 41.0. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{14}H_{11}N_3O$: 260.0794. Found: 260.0794.

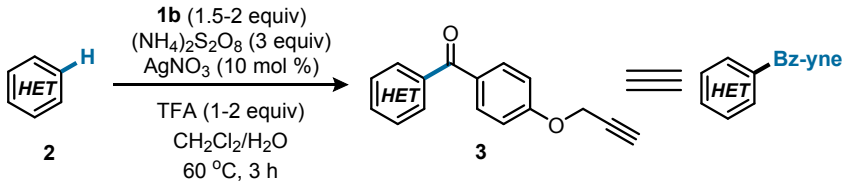


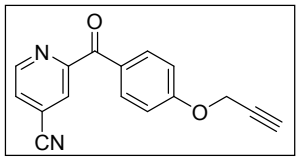
SI-3e. Using the general procedure with pyrazine (15 mg, 0.19 mmol) and aryl glyoxylic acid **SI-1e** (54 mg, 0.22 mmol) the benzophenone derivative was isolated as a pale yellow solid (5.0 mg, 0.015 mmol, 8%). IR (film): 3284, 1644, 1591, 1520, 1323, 1152 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 9.19 (d, J = 1.2 Hz, 1H), 8.75 (d, J = 2.3 Hz, 1H), 8.67 (dd, J = 2.3, 1.2 Hz, 1H), 8.16-8.11 (m, 2H), 6.99-6.94 (m, 2H), 4.24 (d, J = 2.3 Hz, 4H), 2.30 (t, J = 2.3 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 189.9, 151.4, 151.2, 146.2, 146.0, 142.7, 133.3, 125.9, 113.0, 78.3, 73.1, 40.1. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{17}H_3N_3O$: 298.0951. Found: 298.0957.



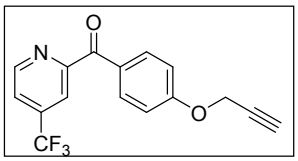
Equation 1, 3b. Using the general procedure with pyrazine (20 mg, 0.25 mmol) and aryl glyoxylic acid **1b** (61 mg, 0.38 mmol), the benzophenone derivative was isolated as a white solid (38 mg, 0.16 mmol, 64%). IR (film): 3259, 3216, 1642, 1602, 1570, 1316, 1255, 1012 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.24 (d, J = 1.2 Hz, 1H), 8.78 (d, J = 2.7 Hz, 1H), 8.68 (dd, J = 2.3, 1.6 Hz, 1H), 8.14-8.20 (m, 2H), 7.04-7.13 (m, 2H), 4.80 (d, J = 2.3 Hz, 2H), 2.57 (t, J = 2.3 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 190.4, 161.8, 150.4, 146.5, 146.1, 142.7, 133.3, 129.1, 114.6, 77.6, 76.3, 55.9. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{10}N_2O_2$: 239.0815. Found: 239.0814.

D. Preparation and Characterization of 2-Benzoyl Heterocycle Products

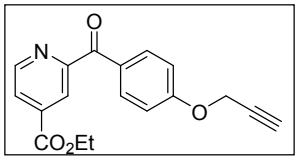




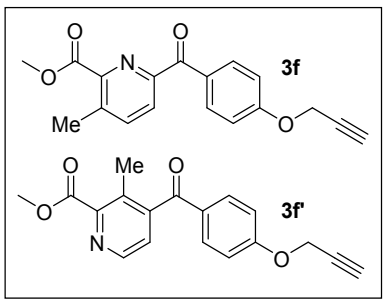
Scheme 1, 3c. Using the general procedure with 4-pyridinecarbonitrile (26 mg, 0.25 mmol) and aryl glyoxylic acid **1b** (102 mg, 0.50 mmol), the benzophenone derivative was isolated as a pale yellow solid (45 mg, 0.17 mmol, 68%). IR (film): 3286, 2241, 2131, 1643, 1596, 1569, 1297, 1250, 1009, 653 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.90 (d, J = 4.7 Hz, 1H), 8.25 (s, 1H), 8.20-8.11 (m, 2H), 7.70 (dd, J = 5.1, 1.6 Hz, 1H), 7.13-7.03 (m, 2H), 4.79 (d, J = 2.3 Hz, 2H), 2.57 (t, J = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 189.8, 161.9, 156.6, 149.2, 133.5, 128.7, 127.0, 126.3, 121.8, 115.9, 114.6, 77.6, 76.3, 55.9. HRMS (ESI/[M+Na]$^+$) calcd. for $C_{16}H_{10}N_2O_2Na$: 285.0634. Found: 285.0638.



Scheme 1, 3d. Using the general procedure with 4-(trifluoromethyl)pyridine (37 mg, 0.25 mmol) and aryl glyoxylic acid **1b** (102 mg, 0.50 mmol), the benzophenone derivative was isolated as a white solid (20 mg, 0.066 mmol, 26%). IR (film): 3315, 1645, 1599, 1571, 1280, 1170, 1131, 631 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.90 (d, J = 5.1 Hz, 1H), 8.22-8.18 (m, 1H), 8.14-8.08 (m, 2H), 7.92-7.87 (m, 1H), 7.14-7.08 (m, 2H), 4.86 (d, J = 2.3 Hz, 2H), 3.01 (d, J = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (CD_3OD, 101 MHz): δ 192.2, 163.7, 158.4, 151.2, 140.8 (q, J = 34 Hz), 134.7, 130.2, 122.8 (q, J = 3 Hz), 121.1 (q, J = 4 Hz), 115.8, 79.2, 77.6, 57.0. HRMS (ESI/[M+H]$^+$) calcd. for $C_{16}H_{11}F_3NO_2$: 306.0736. Found: 306.0737.

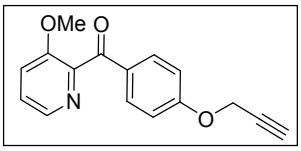


Scheme 1, 3e. Using the general procedure with ethyl isonicotinate (32 mg, 0.21 mmol) and aryl glyoxylic acid **1b** (87 mg, 0.42 mmol), the benzophenone derivative was isolated as a pale yellow solid (20 mg, 0.065 mmol, 31%). IR (film): 3312, 1726, 1644, 1597, 1570, 1245, 1017, 681, 657 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.87 (d, J = 5.1 Hz, 1H), 8.57-8.52 (m, 1H), 8.18-8.12 (m, 2H), 8.04 (dd, J = 5.1, 1.6 Hz, 1H), 7.10-7.04 (m, 2H), 4.79 (d, J = 2.3 Hz, 2H), 4.46 (q, J = 7.2 Hz, 2H), 2.57 (t, J = 2.3 Hz, 1H), 1.44 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 191.3, 164.5, 161.6, 156.5, 149.2, 139.1, 133.4, 129.4, 125.0, 123.8, 114.4, 77.7, 76.2, 62.1, 55.9, 14.2. HRMS (ESI/[M+H]$^+$) calcd. for $C_{18}H_{16}NO_4$: 310.1074. Found: 310.1078.

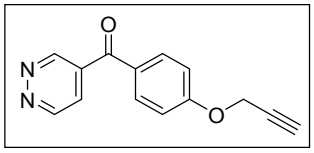


Scheme 1, 3f and 3f'. Using the general procedure with methyl 2-methylnicotinate (20 mg, 0.13 mmol) and aryl glyoxylic acid **1b** (54 mg, 0.26 mmol), the benzophenone derivatives were isolated as a mixture of two regiosiomers: **3f** as a tan solid (15 mg, 0.048 mmol, 37%) - IR (film): 3285, 1725, 1656, 1595, 1273, 1250, 1160, 802 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 4.78 (d, J = 2.3 Hz, 2H), 3.97 (s, 3H), 2.90 (s, 3H), 2.56 (t, J = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 191.2, 166.5, 161.6, 158.8, 157.1, 139.3, 133.6, 129.4, 126.9, 121.4, 114.4, 77.8, 76.1, 55.9, 52.5, 24.8. HRMS (ESI/[M+H]$^+$) calcd. for $C_{18}H_{15}NO_4$: 310.1074. Found: 310.1077. **3f'** as a tan solid (10 mg, 0.032 mmol, 25%) - IR

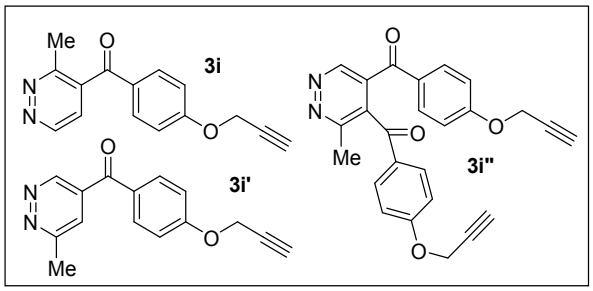
(film): 3283, 1730, 1665, 1597, 1262, 1169, 1018 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.69 (d, *J* = 4.7 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 5.3 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.77 (d, *J* = 2.3 Hz, 2H), 3.61 (s, 3H), 2.77 (s, 3H), 2.56 (t, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 193.3, 167.0, 161.9, 158.4, 150.6, 147.6, 131.9, 129.4, 125.5, 119.5, 114.9, 77.5, 76.3, 56.0, 52.3, 23.6. HRMS (ESI/[M+H]$^+$) calcd. for $C_{18}H_{15}NO_4$: 310.1074. Found: 310.1080.



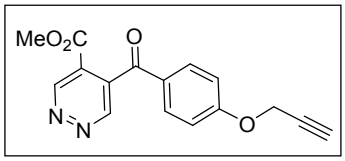
Scheme 1, 3g. Using the general procedure with 3-methoxypyridine (20 mg, 0.18 mmol) and aryl glyoxylic acid **1b** (76 mg, 0.36 mmol), the benzophenone derivative was isolated as a light yellow oil (13 mg, 0.049 mmol, 27%). IR (film): 3286, 1663, 1595, 1456, 1425, 1268, 1173, 1153, 1016, 937 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (dd, *J* = 4.3, 1.6 Hz, 1H), 7.85-7.90 (m, 2H), 7.32-7.45 (m, 2H), 6.99-7.04 (m, 2H), 4.76 (d, *J* = 2.7 Hz, 2H), 3.84 (s, 3H), 2.55 (t, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 192.1, 161.7, 154.1, 146.7, 140.5, 132.6, 130.0, 125.3, 119.2, 114.6, 77.7, 76.1, 55.9, 55.8. HRMS (ESI/[M+NH_4]$^+$) calcd. for $C_{16}H_{17}N_2O_3$: 285.1234. Found: 285.1247.



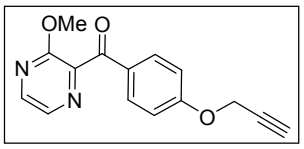
Scheme 1, 3h. Using the general procedure with pyridazine (20 mg, 0.25 mmol) and aryl glyoxylic acid **1b** (61 mg, 0.3 mmol), the benzophenone derivative was isolated as a white solid (11 mg, 0.046 mmol, 18%). IR (film): 3283, 1656, 1595, 1507, 1256, 132, 1160, 1016, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.47-9.43 (m, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.72 (dd, *J* = 5.0, 2.1 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 4.82 (d, *J* = 1.8 Hz, 2H), 2.59 (t, *J* = 2.2 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 191.3, 162.4, 151.7, 149.6, 135.1, 132.5, 128.7, 125.1, 115.2, 77.3, 76.6, 56.0. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{10}N_2O_2$:239.0815. Found: 239.0818.



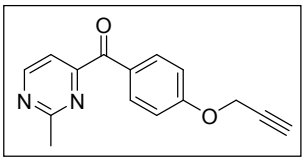
Scheme 1, 3i, 3i', and 3i". Using the general procedure with 3-methyl pyridazine (20 mg, 0.21 mmol) and aryl glyoxylic acid **1b** (87 mg, 0.42 mmol), the benzophenone derivatives were isolated as a mixture of regioisomers and bis-addition. Based on ^{1}H NMR integration the corrected yields of **3i**, **3i'**, and **3i"** are 29%, 15%, and 18%, respectively. **3i** as a gum (15 mg, 0.061 mmol, 29%) - IR (film): 3285, 1657, 1594, 1308, 1233, 1173, 1018, 847, 644 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.23 (d, *J* = 4.7 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 4.7 Hz, 1H), 7.07 (d, *J* = 9.4 Hz, 2H), 4.79 (d, *J* = 2.3 Hz, 2H), 2.69 (s, 3H), 2.57 (t, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 192.5, 162.7, 156.8, 149.3, 137.1, 132.4, 129.0, 123.7, 115.3, 77.3, 76.6, 56.1, 20.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{13}N_2O_2$: 253.0972. Found: 253.0978. **3i'** as a foam contaminated with 33% **3i** (12 mg, 0.048 mmol, 22%) - IR (film): 3284, 1659, 1593, 1257, 1231, 1158, 1016, 847, 643 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.26 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.57 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 4.81 (d, *J* = 2.3 Hz, 2H), 2.85 (s, 3H), 2.58 (t, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 191.7, 162.4, 147.4, 132.5, 132.4, 128.8, 125.7, 115.3, 115.2, 77.2, 76.6, 56.1, 22.5. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{13}N_2O_2$: 253.0972. Found: 253.0978. **3i"** as an off-white solid (15 mg, 0.037 mmol, 18%) - IR (film): 3287, 1659, 1594, 1260, 1231, 1168, 1015, 645 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.24 (s, 1H), 7.63-7.72 (m, 4H), 7.01 (m, 4H), 4.78 (d, *J* = 2.3 Hz, 2H), 4.76 (d, *J* = 2.3 Hz, 2H), 2.66 (s, 3H), 2.58 (t, *J* = 2.3 Hz, 1H), 2.57 (t, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 192.2, 191.1, 162.6, 157.2, 147.3, 136.6, 134.0, 132.6, 131.8, 129.6, 128.8, 115.2, 115.1, 77.3, 77.2, 76.5, 76.6, 56.1, 20.8. HRMS (ESI/[M+H]$^+$) calcd. for $C_{25}H_{18}N_2O_4$: 411.1339. Found: 411.1350.



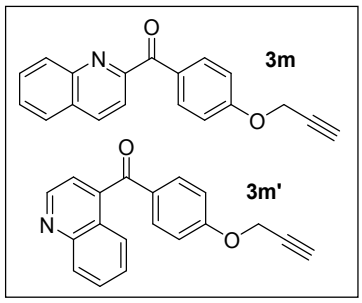
Scheme 1, 3j. Using the general procedure with methyl pyridazine-4-carboxylate (20 mg, 0.15 mmol) and aryl glyoxylic acid **1b** (59 mg, 0.29 mmol), the benzophenone derivative was isolated as a tan solid (37 mg, 0.12 mmol, 80%). IR (film): 3282, 2954, 1733, 1664, 1593, 1294, 1256, 1230, 1158, 731, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 9.72 (s, 1H), 9.30 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.78 (d, *J* = 2.3 Hz, 2H), 3.80 (s, 3H), 2.57 (t, *J* = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 190.6, 163.5, 162.5, 149.7, 149.1, 137.5, 131.7, 129.1, 125.3, 115.3, 77.3, 76.6, 56.1, 53.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{12}N_2O_4$: 297.087. Found: 297.0869.



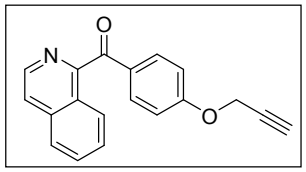
Scheme 1, 3k. Using the general procedure with 2-methoxypyrazine (28 mg, 0.25 mmol) and aryl glyoxylic acid **1b** (102 mg, 0.50 mmol), the benzophenone derivative was isolated as a white solid (61 mg, 0.23 mmol, 92%). IR (film): 3236, 1654, 1599, 1568, 1377, 1247, 1132, 1011, 667 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 2.7 Hz, 1H), 8.20 (d, *J* = 2.7 Hz, 1H), 7.90-7.84 (m, 2H), 7.05-6.99 (m, 2H), 4.76 (d, *J* = 2.7 Hz, 2H), 3.98 (s, 3H), 2.55 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 190.3, 161.9, 158.4, 142.2, 141.7, 135.3, 132.6, 129.3, 114.6, 77.6, 76.2, 55.8, 54.0. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{15}H_{12}N_2O_3Na$: 291.0740. Found: 291.0741.



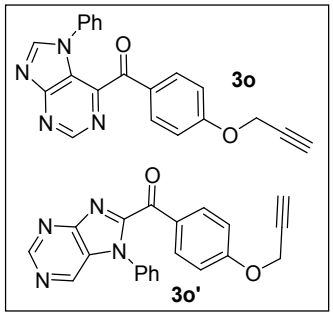
Scheme 1, 3l. Using the general procedure with 2-methyl pyrimidine (20 mg, 0.21 mmol) and aryl glyoxylic acid **1b** (87 mg, 0.42 mmol), the benzophenone derivative was isolated as an off-white solid (42 mg, 0.17 mmol, 81%). IR (film): 3287, 1661, 1596, 1567, 1311, 1257, 1231, 1165, 1019, 693, 646 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.90 (d, *J* = 5.3 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 5.3 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 4.80 (d, *J* = 2.3 Hz, 2H), 2.85 (s, 3H), 2.57 (t, *J* = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 190.7, 167.7, 162.4, 162.0, 158.5, 133.5, 128.5, 117.1, 114.6, 77.6, 76.3, 55.9, 26.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{13}N_2O_2$: 253.0972. Found: 253.0972.



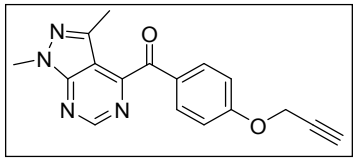
Scheme 1, 3m and 3m'. Using the general procedure with quinoline (15 mg, 0.12 mmol) and aryl glyoxylic acid **1b** (47 mg, 0.24 mmol), the benzophenone derivatives were isolated as a mixture of two regioisiomers: **3m** as a white solid (7.0 mg, 0.024 mmol, 20%) - IR (film): 3289, 1652, 1596, 1317, 1230, 1156, 1020, 924, 774 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.29-8.38 (m, 3H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.81 (d, *J* = 1.8 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 192.3, 161.7, 155.4, 146.9, 137.3, 134.0, 130.7, 130.3, 130.0, 129.0, 128.5, 127.9, 121.1, 114.6, 78.1, 76.3, 56.1. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{19}H_{13}NO_2$: 310.0838. Found: 310.0833. **3m'** as a white solid (11 mg, 0.038 mmol, 32%) - IR (film): 3287, 1656, 1592, 1503, 1251, 1228, 1167, 1015, 769 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ 9.03 (d, *J* = 4.1 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.82-7.90 (m, 3H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 4.1 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 4.78 (d, *J* = 1.8 Hz, 2H), 2.57 (t, *J* = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 194.5, 162.3, 149.5, 148.6, 145.0, 132.6, 130.4, 130.0, 129.9, 127.5, 125.5, 125.0, 119.2, 114.9, 77.5, 76.4, 56.0. HRMS (ESI/$[M+H]^+$) calcd. for $C_{19}H_{13}NO_2$: 288.1019. Found: 288.1030.



Scheme 1, 3n. Using the general procedure with isoquinoline (42 mg, 0.33 mmol) and aryl glyoxylic acid **1b** (112 mg, 0.55 mmol), the benzophenone derivative was isolated as a white solid (35 mg, 0.12 mmol, 36%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.60 (d, *J* = 5.9 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 5.9 Hz, 1H), 7.75 (t, *J* = 7.3 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.77 (d, *J* = 1.8 Hz, 2H), 2.55 (t, *J* = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 193.0, 161.7, 156.6, 140.9, 136.5, 132.9, 130.5, 130.1, 128.0, 126.8, 126.1, 126.0, 122.1, 114.4, 77.4, 76.0, 55.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{19}H_{13}NO_2$: 288.1019. Found: 288.1028.



Scheme 1, 3o and 3o'. Using the general procedure with 7-phenyl-*7H*-purine (42 mg, 0.21 mmol) and aryl glyoxylic acid **1b** (87 mg, 0.43 mmol), the benzophenone derivatives were isolated as a mixture of regioisomers. **3o** as a white solid (30 mg, 0.085 mmol, 40%) - IR (film): 3299, 3058, 1647, 1593, 1570, 1253, 1171, 763, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.30 (s, 1H), 8.42 (s, 1H), 7.82-7.76 (m, 2H), 7.46-7.34 (m, 3H), 7.21-7.15 (m, 2H), 7.03-6.96 (m, 2H), 4.78 (d, *J* = 2.3 Hz, 2H), 2.58 (t, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 188.8, 162.6, 162.4, 152.6, 149.3, 148.3, 135.2, 132.7, 129.7, 129.6, 128.6, 125.6, 123.0, 114.9, 77.4, 76.4, 56.0. HRMS (ESI/[M+H]$^+$) calcd. for $C_{21}H_{15}N_4O_2$: 355.1190. Found: 355.1196. **3o'** as a white solid (10 mg, 0.028 mmol, 13%) – IR (film): 3288, 1658, 1594, 1410, 1271, 1227, 1013, 914 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400MHz): δ 9.32 (s, 1H), 8.89 (s, 1H), 8.44-8.35 (m, 2H), 7.64-7.54 (m, 3H), 7.45-7.37 (m, 2H), 7.13-7.06 (m, 2H), 4.81 (d, *J* = 2.3 Hz, 2H), 2.58 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 182.6, 162.9, 158.7, 154.3, 151.1, 141.9, 134.7, 133.8, 130.1, 129.8, 128.9, 126.2, 115.0, 77.4, 76.5, 56.0. HRMS (ESI/[M+H]$^+$) calcd. for $C_{21}H_{15}N_4O_2$: 355.1190. Found: 355.1197.



Scheme 3, 3p. Using the general procedure with 1,3-dimethyl-1H-pyrazolo[3,4-d]pyrimidine (20 mg, 0.13 mmol) and aryl glyoxylic acid **1b** (55 mg, 0.27 mmol), the benzophenone derivative was isolated as a white solid (32mg, 0.10 mmol, 77%). IR (film): 3248, 1656, 1597, 1565, 1339, 1255, 1181, 1029, 680 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.06 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.80 (d, *J* = 2.3 Hz, 2H), 4.13 (s, 3H), 2.57 (t, *J* = 2.4 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 190.6, 162.4, 158.4, 154.4, 154.1, 142.1, 133.2, 128.6, 114.9, 111.1, 77.5, 76.4, 56.0, 33.6, 14.4; HRMS (ESI/[M+H]$^+$) calcd. for $C_{17}H_{15}N_4O_2$: 307.1190 . Found: 307.1193.

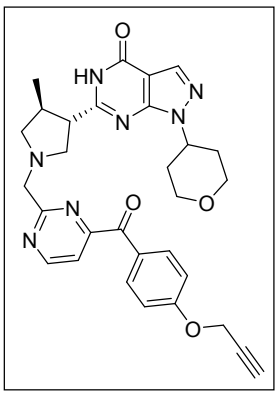


Figure 2, 3q. Using the general procedure with **2q** (180 mg, 0.46 mmol) and aryl glyoxylic acid **1b** (148 mg, 0.73 mmol), the benzophenone derivative was isolated as a white solid (36 mg, 0.054 mmol, 12%). IR (film): 2965, 2852, 1670, 1592, 1164, 1131, 789 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.27 (br s, 1H), 9.02 (d, *J* = 5.1 Hz, 1H), 8.12-8.03 (m, 3H), 7.80 (d, *J* = 5.1 Hz, 1H), 7.08-7.01 (m, 2H), 4.80-5.00 (m, 3H), 4.79 (d, *J* = 2.3 Hz, 2H), 4.38-3.76 (m, 4H), 3.68-3.44 (m, 3H), 2.95-3.10 (m, 1H), 2.59 (t, *J* = 2.3 Hz, 1H), 2.27-2.45 (m, 2H), 2.02 (s, 2H), 1.91 (d, *J* = 10.1 Hz, 2H), 1.26 (d, *J* = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 189.4, 162.8, 162.1, 160.0, 159.6, 159.1, 155.9, 151.1, 134.4, 133.1, 127.4, 119.4, 114.5, 104.4, 77.1, 76.1, 66.5, 60.3, 59.7, 57.4, 55.6, 53.8, 49.1, 38.1, 31.8, 31.7**.** HRMS (ESI/[M+Na]$^+$) calcd. for $C_{30}H_{31}N_7O_4$: 576.233. Found: 576.2331.

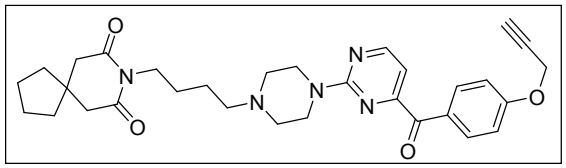


Figure 2, 3r. Using the general procedure with **2r** (77 mg, 0.20 mmol) and aryl glyoxylic acid **1b** (61 mg, 0.30 mmol), the benzophenone derivative was as a viscous yellow oil (10 mg, 0.018 mmol, 9%). IR (film): 3254, 2947, 1667, 1594, 1572, 1503, 1160, 1131, 844 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ 8.54 (d, J = 5.1 Hz, 1H), 8.10-8.02 (m, 2H), 7.14-7.07 (m, 2H), 6.93 (d, J = 4.7 Hz, 1H), 4.86 (d, J = 2.3 Hz, 2H), 3.89-3.82 (m, 4H), 3.80-3.73 (m, 2H), 3.02 (t, J = 2.5 Hz, 1H), 2.67-2.61 (m, 4H), 2.57-2.50 (m, 4H), 2.47 (m, 2H), 1.76-1.67 (m, 4H), 1.58-1.46 (m, 8H); $^{13}C\{^1H\}$ NMR (CD_3OD, 101 MHz): δ 193.4, 174.6, 164.6, 163.8, 162.4, 161.0, 134.4, 130.0, 115.8, 109.4, 79.2, 77.6, 59.4, 57.0, 54.2, 45.6, 44.7, 40.8, 40.3, 39.6, 27.2, 25.3, 25.0. HRMS (ESI/$[M+H]^+$) calcd. for $C_{31}H_{38}N_5O_4$: 544.2918. Found: 544.2917.

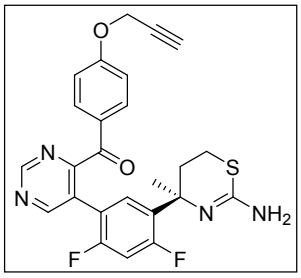


Figure 2, 3s. Using the general procedure with **2s** (64 mg, 0.20 mmol) and aryl glyoxylic acid **1b** (61 mg, 0.30 mmol), the benzophenone derivative was isolated as a pale yellow oil (10 mg, 0.021 mmol, 11%). IR (film): 3243, 3048, 1667, 1595, 1134, 756, 642 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ 9.34 (s, 1H), 9.04 (d, J = 1.2 Hz, 1H), 7.85-7.80 (m, 2H), 7.31-7.25 (m, 1H), 7.20 (dd, J = 11.9, 9.6 Hz, 1H), 7.12-7.07 (m, 2H), 4.87 (d, J = 2.3 Hz, 2H), 3.19-3.12 (m, 1H), 3.05 (t, J = 2.5 Hz, 1H), 2.87-2.79 (m, 1H), 2.67-2.58 (m, 1H), 2.20-2.11 (m, 1H), 1.77 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_3OD, 101 MHz): δ 192.5, 169.8, 164.4, 163.8, 160.7, 158.8, 133.9, 132.9, 131.9, 129.4, 128.0, 127.8, 119.9, 116.3, 115.8, 107.5, 79.0, 77.8, 25.6, 57.1, 33.7, 28.3, 24.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{25}H_{21}F_2N_4O_2S$: 479.1348. Found: 479.1357.

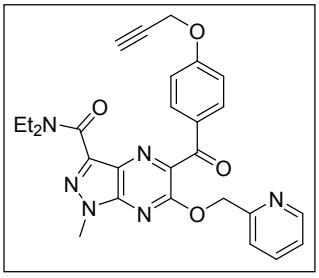


Figure 2, 3t. Using the general procedure with **2t** (155 mg, 0.46 mmol) and aryl glyoxylic acid **1b** (139 mg, 0.68 mmol), the benzophenone derivative was isolated as a yellow oil (90 mg, 0.18 mmol, 39%). IR (film): 2978, 1663, 1628, 1594, 1549, 1179, 1148, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.70-8.65 (m, 1H), 8.19 (dt, J = 7.8, 1.6 Hz, 1H), 7.90-7.84 (m, 2H), 7.77 (d, J = 8.2 Hz, 1H), 7.69-7.63 (m, 1H), 7.08-7.02 (m, 2H), 5.79 (s, 2H), 4.84 (d, J = 2.7 Hz, 2H), 4.10 (s, 3H), 3.62-3.49 (m, 4H), 3.03 (t, J = 2.3 Hz, 1H), 1.28-1.16 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 191.7, 164.4, 164.1, 157.6, 154.6, 146.7, 143.8, 142.6, 141.7, 140.4, 134.0, 130.6, 126.6, 126.4, 125.6, 116.1, 79.1, 77.8, 67.8, 57.1, 45.0, 41.8, 34.9, 15.0, 13.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{27}H_{27}N_6O_4$: 499.2088. Found: 499.2078.

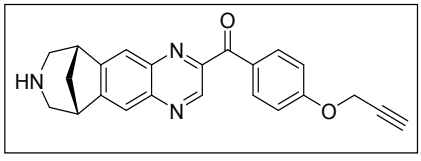
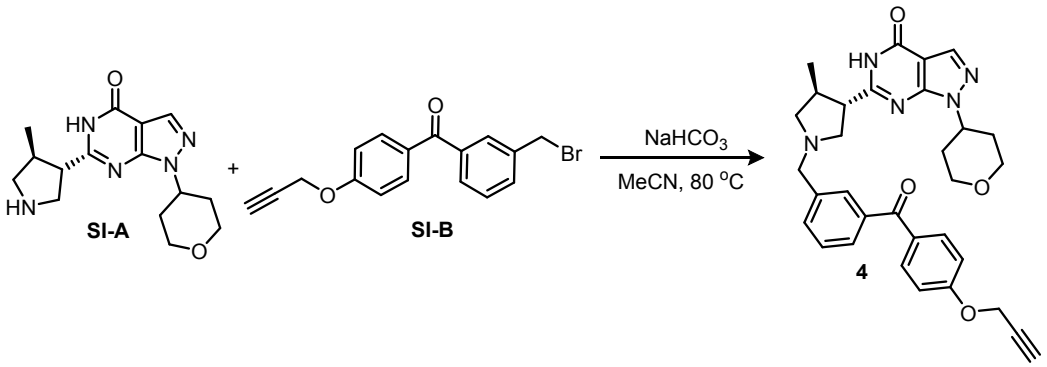


Figure 2, 3u. Using the general procedure with **2u** (63 mg, 0.30 mmol) and aryl glyoxylic acid **1b** (92 mg, 0.45 mmol), the benzophenone derivative was isolated as a yellow solid (36 mg, 0.097 mmol, 32%) - IR (film): 3233, 2974, 1669, 1595, 1571, 1182, 1123, 838 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ 9.35 (s, 1H), 8.29-8.22 (m, 2H), 8.19 (s, 1H), 8.17 (s, 1H), 7.19-7.12 (m, 2H), 4.89 (d, J = 2.3 Hz, 2H), 3.76-3.70 (m, 2H), 3.61-3.53 (m, 2H), 3.44-3.36 (m, 2H), 3.04 (t, J = 2.5 Hz, 1H), 2.58-2.50 (m, 1H), 2.35-2.29 (m, 1H); $^{13}C\{^1H\}$ NMR (CD_3OD, 101 MHz): δ 192.2, 163.8, 150.7, 149.2, 147.9, 146.0, 145.0, 142.7, 134.8, 130.4, 126.3, 125.1, 115.9, 79.2, 77.7, 57.1, 41.7, 40.4, 40.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{23}H_{20}N_3O_2$: 370.1550. Found: 370.1556.

E. Synthesis of Benzophenone Comparator 4



To solution of pyrrolidine **SI-A** (60 mg, 0.20 mmol) and benzyl bromide **SI-B** (72 mg, 0.22 mmol) in acetonitrile (2 mL) was added solid $NaHCO_3$ (50 mg, 0.59 mmol). The resulting mixture was heated in a heat block with stirring at 80 °C overnight. All solvent was evaporated and the crude material was partitioned between EtOAc and water. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude material was purified by reverse-phase chromatography (Column: Waters Sunfire C18 19x100, 5 uM; Mobile phase A: 0.05% TFA in water (v/v); Mobile phase B: 0.05% TFA in acetonitrile (v/v); Gradient: 80.0% H20/20.0% Acetonitrile linear to 60% H20/40% Acetonitrile in 8.5min to 0% H2O/100% MeCN to 9.0min, HOLD at 0% H20 / 100% Acetonitrile from 9.0 to 10.0min. Flow: 25mL/min.) to give the expected product **4** (trifluoroacetate salt) as an off-white solid (77 mg, 0.12 mmol, 60%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.40-12.24 (m, 1H), 10.75-10.39 (m, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.94 (s, 1H), 7.87-7.82 (m, 1H), 7.81-7.75 (m, 3H), 7.66 (t, J = 8.2 Hz, 1H), 7.19-7.11 (m, 2H), 4.96-4.91 (m, 2H), 4.87-4.71 (m, 1H), 4.69-4.53 (m, 2H), 4.04-3.93 (m, 2H), 3.92-3.69 (m, 1.5H), 3.68-3.55 (m, 2.5H), 3.52-3.40 (m, 2H), 3.39-3.28 (m, 0.5H), 3.27-3.03 (m, 1.5H), 2.92-2.79 (m, 0.5H), 2.72-2.57 (m, 0.5H), 2.21-2.03 (m, 2H), 1.93-1.75 (m, 2H), 1.12 (d, J = 6.2 Hz, 3H); HRMS (ESI/$[M+H]^+$) calcd. for $C_{32}H_{34}N_5O_4$: 552.2599. Found: 552.2605.

F. IC_{50} Determination of PDE Family for 3q and 4

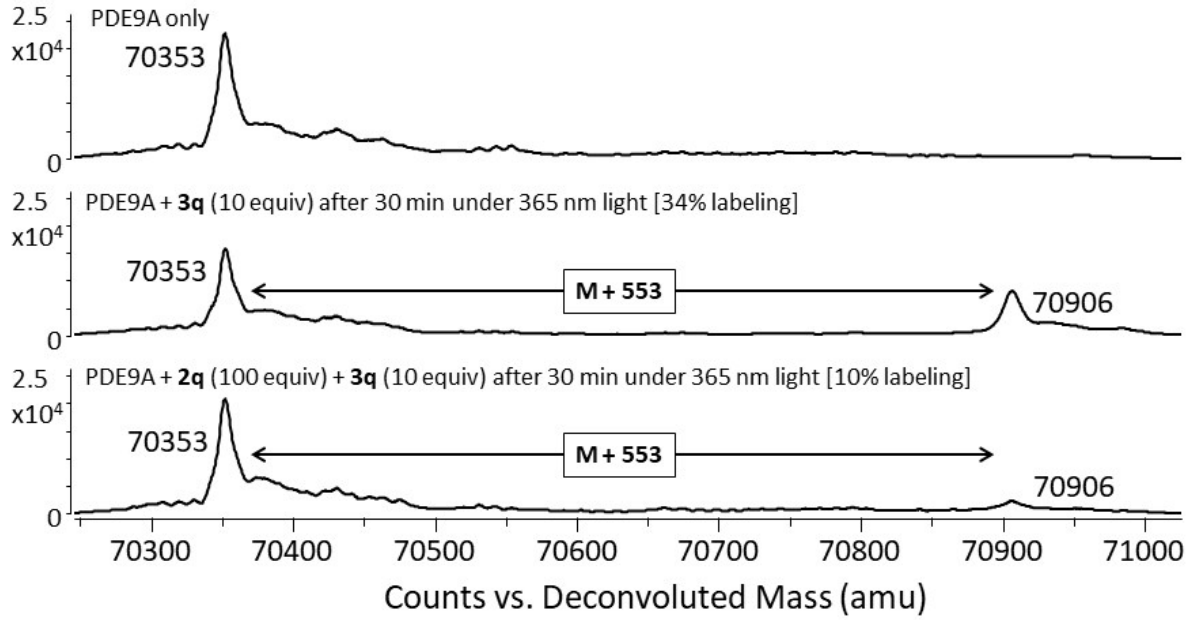
The PDE panel IC_{50} values for **3q** and **4** were obtained using previously described assay conditions; the IC_{50} value for the parent PDE9 inhibitor **2q** was obtained from published data.[4]

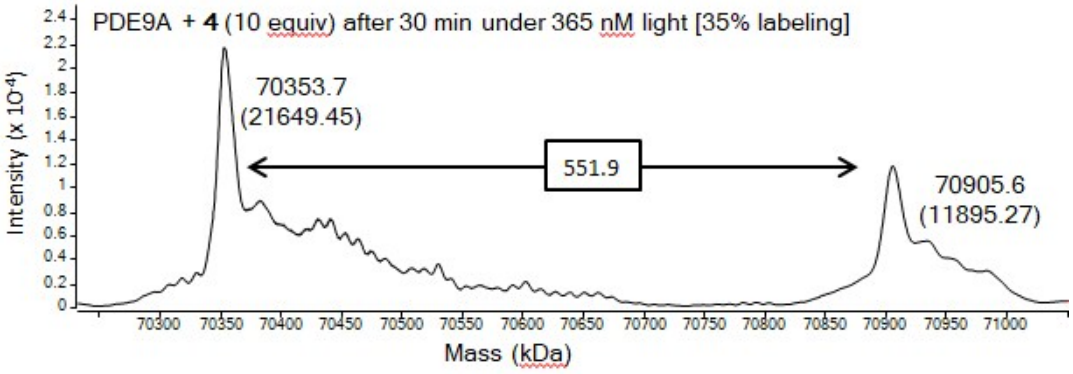
	PDE1B1	PDE2A1	PDE3A1	PDE4D3	PDE5A1	PDE6A (Bovine)	PDE7B	PDE8B	PDE9A1	PDE10A1	PDE11A4
Probe	IC50 (nM)										
4	1789.3	7357.5	584.5	2464.0	141.2	10.2	168.2	2455.3	0.4	2743.0	1236.1
3q	15588	123012	>200000	73556	10494	2561	16048	>200000	2	15133	46883

G. Photoaffinity Labelling and Digestion of PDE9A with probes 3q and 4

Procedure for photolabelling experiments

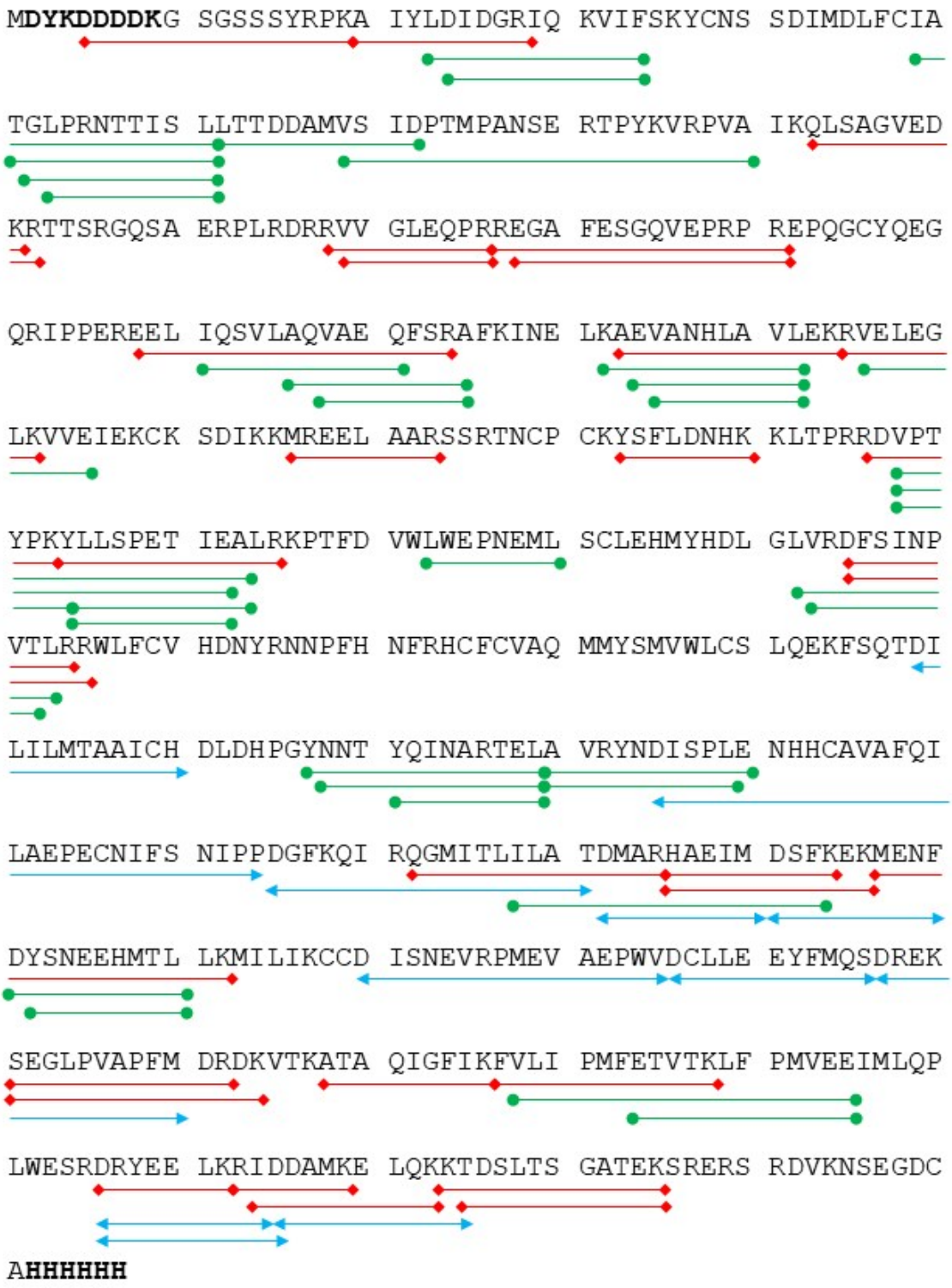
0.16 μM solutions of recombinant huPDE9A in Tris-HCl buffer with N-terminal flag and C-terminal His tags (expressed in Sf-9) were incubated in the presence of either 10% DMSO or 1.5 μM probe **3q** or 1.5 μM probe **3q** + 15 μM parent inhibitor **2q**. Solutions were allowed to equilibrate after addition of compound for 10 minutes before UV irradiation. For solutions where probe and parent were added, the parent compound was added first and allowed to equilibrate for 10 minutes before addition of the probe followed by another 10 minute equilibration. Exposure of UV irradiation was performed with a 365nm UV lamp for 30 minutes. 100 ng of protein samples were injected on column. Protein masses were determined by LC-MS performed using an Agilent 6530 Accurate-Mass Q-TOF LC/MS. Solvents for HPLC were A: 0.1% formic acid, and B: 0.1% formic acid in acetonitrile. Samples were eluted over an Agilent PLRP-S 1000A 5μm 50 x 2.1 mm column [p/n PL1912-1502] at a flow rate of 0.4 ml/min with a gradient from 1-22.5 min, 2-75%B. Mass spectra were collected in MS1 mode from 300-3200 m/z at a scan rate of 3 spectra per second. All spectra are normalized to the same intensity scale for comparative purposes.





Procedure for probe-PDE9A digestion experiments

Sequence coverage map for huPDE9A with N-terminal flag and C-terminal His tags. Digests were carried out using 1:100 ratio of protease:PDE9A using commercial FASP digestion kits (Expedeon #44250) following the manufacturer's protocol. Digested samples were desalted using C18 tips (100 µL bed volume, Thermo Fisher Scientific Pierce Biotechnology) using the manufacturer's instructions. 150fmols of digested protein were loaded onto a trap column (ACQUITY UPLC® M-Class Trap, V/V Symmetry® C18, pore size 100 Å, 5 µm spherical silica, 180 µm I.D. x 20 mm, Waters) and then separated over an analytical column (ACQUITY UPLC® M-Class peptide BEH C18 column, pore size 300 Å, particle size 1.7 µm, 75 µm I.D. x 100 mm, Waters) using a nanoAcquity Ultra Performance LC (Waters). Chromatography buffers consisted of 0.1% FA in water (A) and 0.1% FA in acetonitrile (B). Peptides were separated with a linear gradient from 0.5-30% B at a flow rate of 300 nL/min over 122 min. Mass spectra were acquired in positive ion mode using an Orbitrap Fusion mass spectrometer (Thermo Fisher Scientific) equipped with an EASY-SprayTM NG ion source and an EASY-SprayTM emitter (nanoflow, 7 µm I.D.). MS1 scan was conducted in the Orbitrap with a resolution of 120,000, and mass range of 400-1600 Th. MS2 data-dependent acquisition was performed in the ion trap at normal scan rate, using Top Speed mode with higher-energy collisional dissociation (HCD, CE=27%). A second injection of the same sample was run under the same settings but also using EThcD for fragmentation and a 240 min gradient. Raw data files were searched using Mascot v2.5.1.1 against an in-house database using the following parameters: MS tolerance 6 ppm, MSMS tolerance 0.6 Da, 1 missed cleavage allowed, variable oxidation of Met and fixed carbamidomethyl modification of Cys when iodoacetimide was used prior to digestion. The sequence of the huPDE9A construct is shown below. Colored bars below the sequence indicate peptides detected with a Mascot Ion score of 15 or greater. Tryptic peptides are indicated in red, peptic peptides are indicated in green and trypsin/AspN peptides are indicated in blue. In total, 69% of the sequence was covered in this approach.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KRTTSRGQSA ERPLRDRRVV GLEQPRREGA FESGQVEPRP REPQGCYQEG
QRIPPEREEL IQSVLAQVAE QFSRAFKINE LKAEVANHLA VLEKRVELEG
LKVVEIEKCK SDIKKMREEL AARSSRTNCP CKYSFLDNHK KLTPRRDVPT
YPKYLLSPET IEALRKPTFD VWLWEPNEML SCLEHMYHDL GLVRDFSINP
VTLRRWLFCV HDNYRNNPFH NFRHCFCVAQ MMYSMVWLCS LQEKFSQTDI
LILMTAAICH DLDHPGYNNT YQINARTELA VRYNDISPLE NHHCAVAFQI
LAEPECNIFS NIPPDGFKQI RQGMITLILA TDMARHAEIM DSFKEKMENF
DYSNEEHMTL LKMILIKCCD ISNEVRPMEV AEPWVDCLLE EYFMQSDREK
SEGLPVAPFM DRDKVTKATA QIGFIKFVLI PMFETVTKLF PMVEEIMLQP
LWESRDRYEE LKRIDDAMKE LQKKTDSLTS GATEKSRERS RDVKNSEGDC
AHHHHHH

H. References

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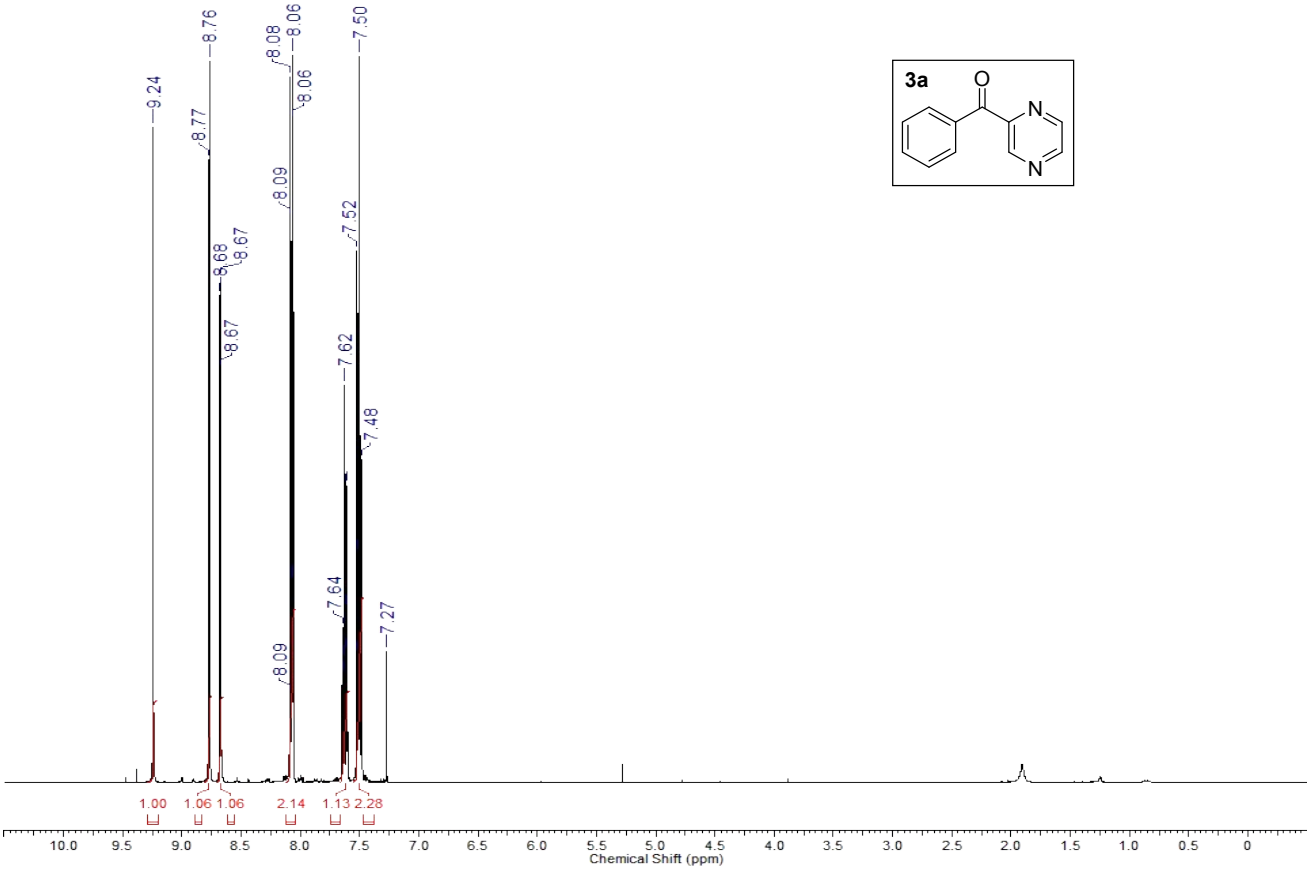
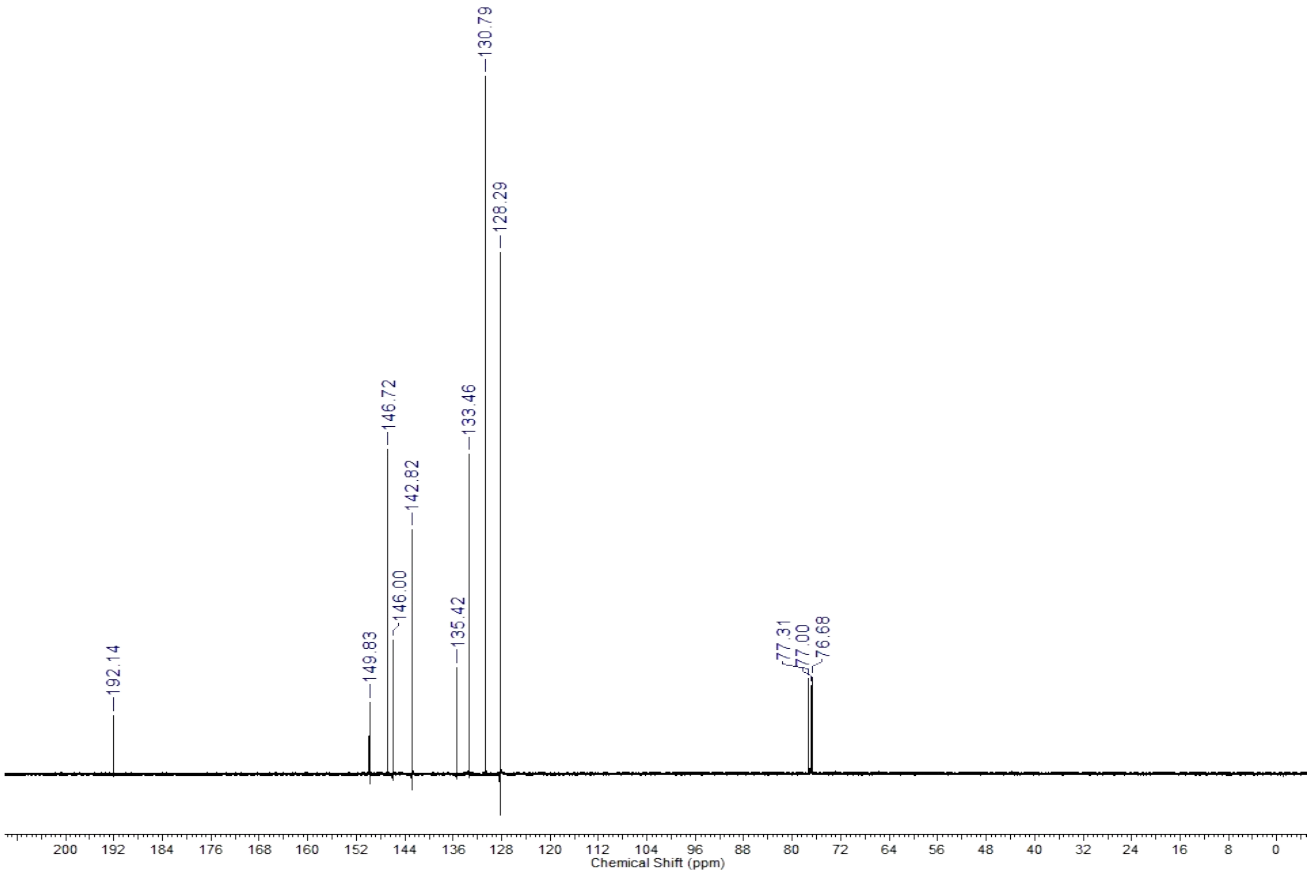
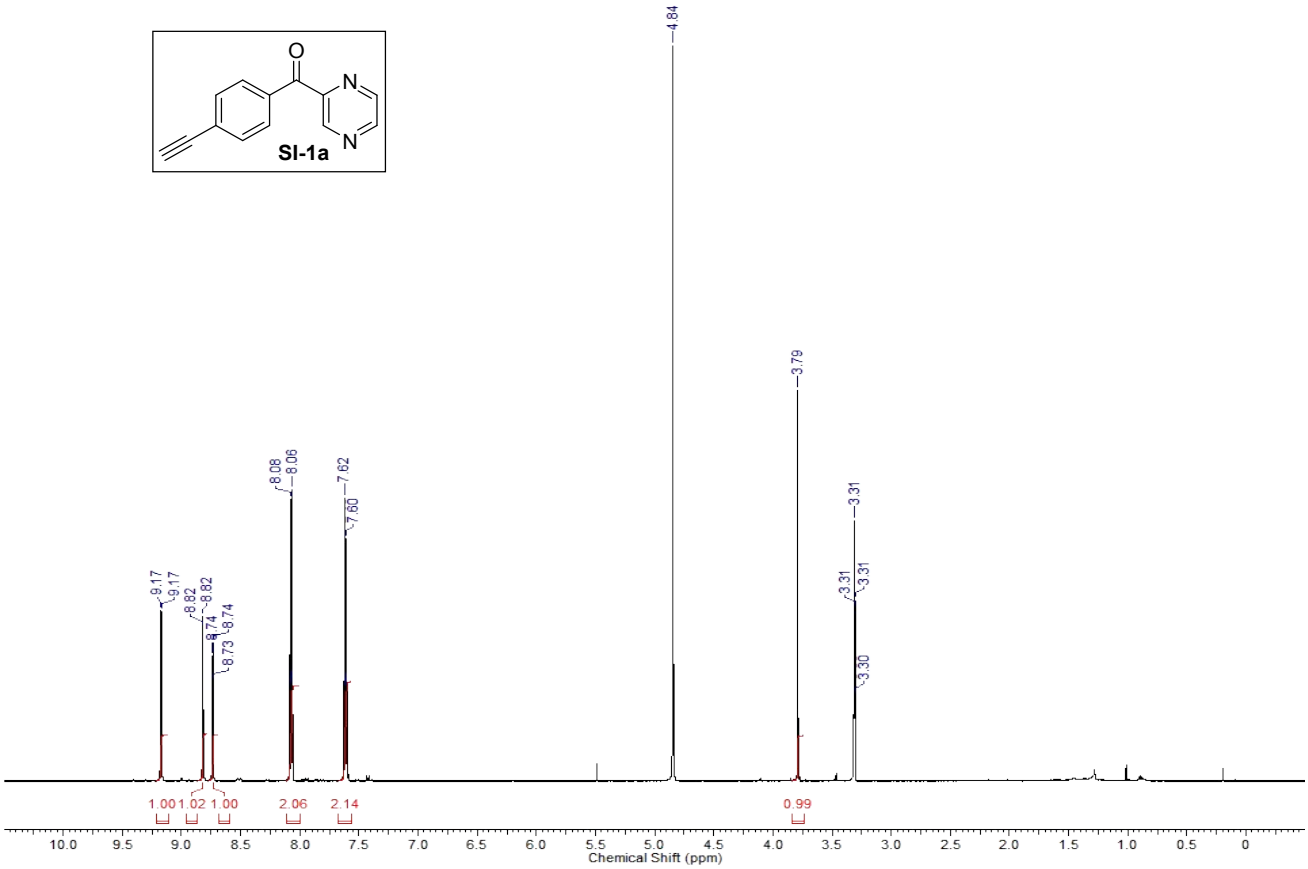
I. ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectra



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8.74
8.74
8.73
8.08
8.06
7.62
7.60
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3.79
3.31
3.31
3.31
3.30
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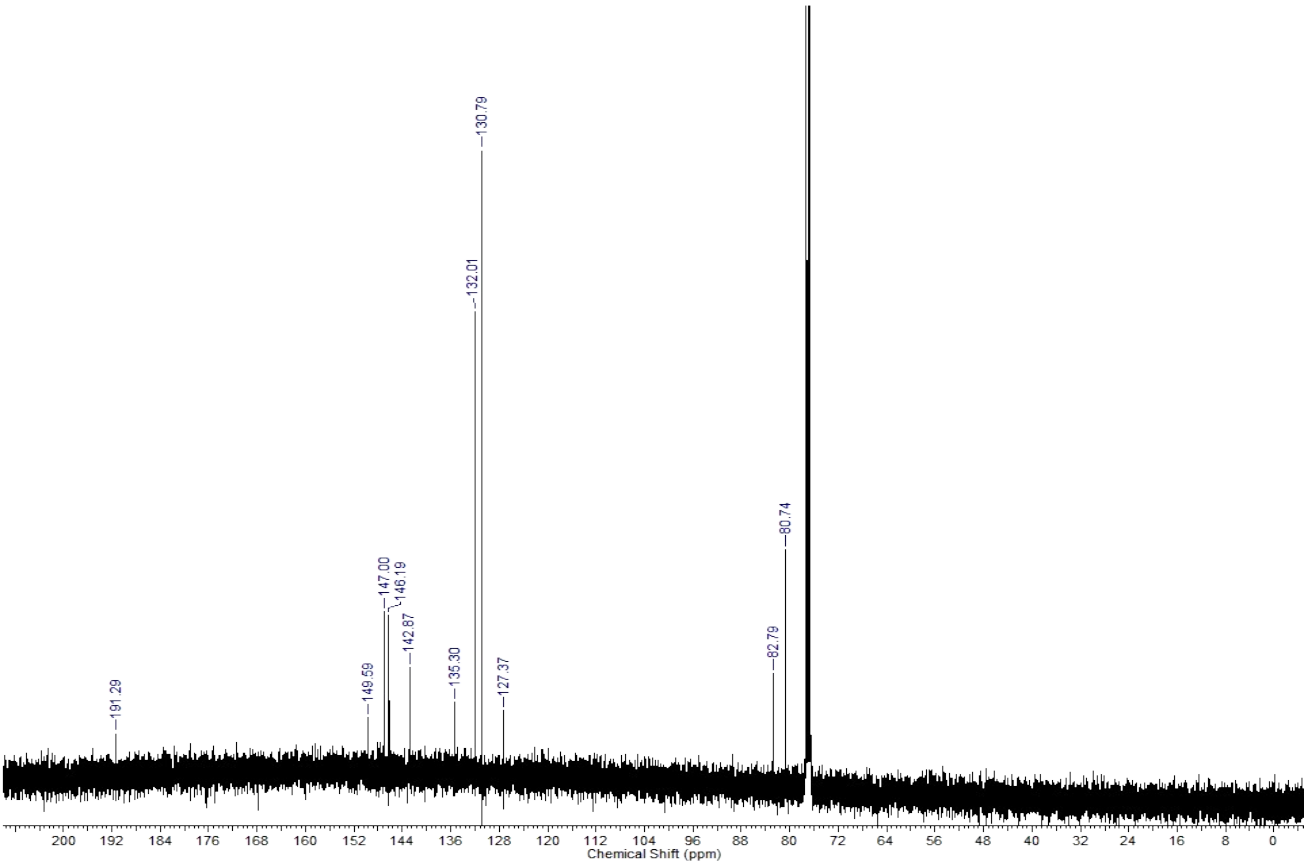
Chemical Shift (ppm)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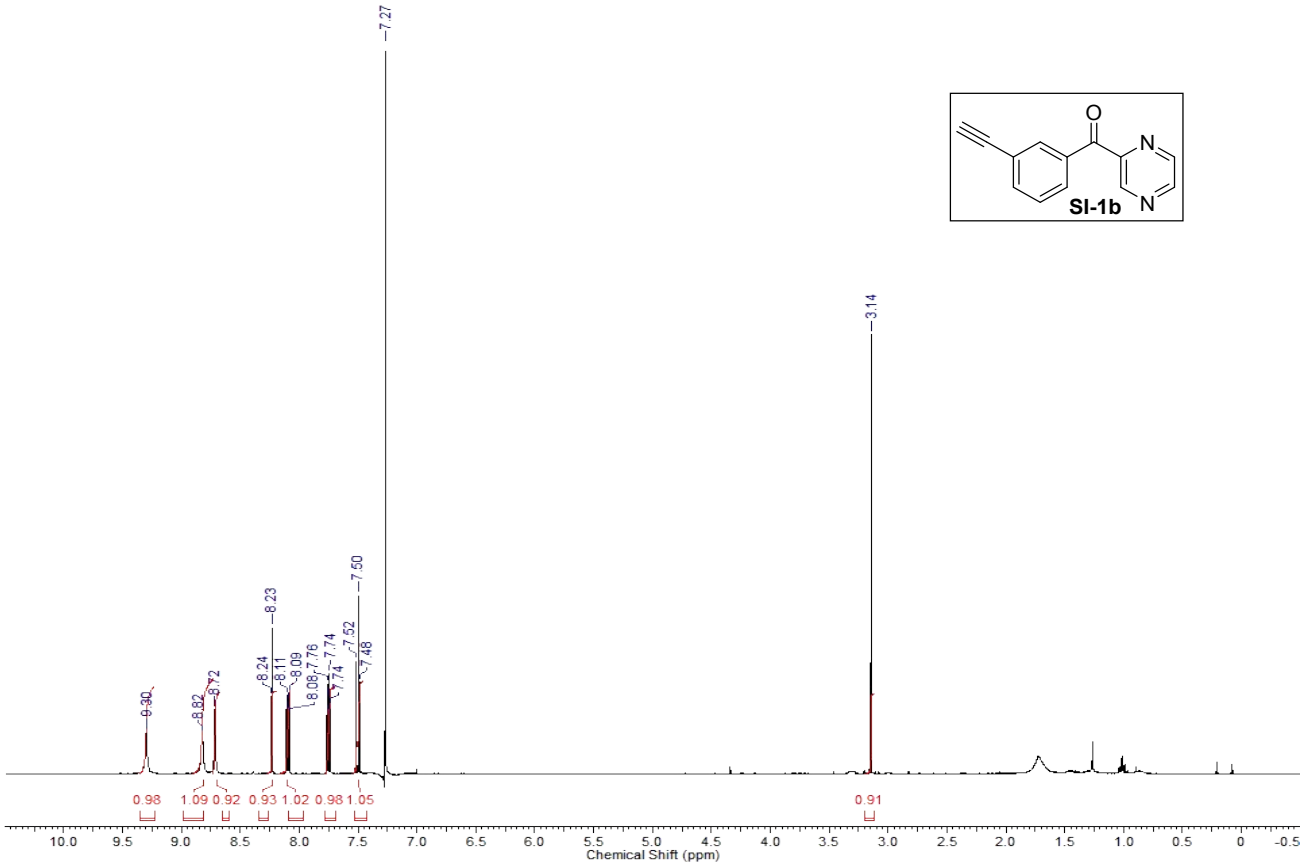
Chemical Shift (ppm)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8.08
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7.74
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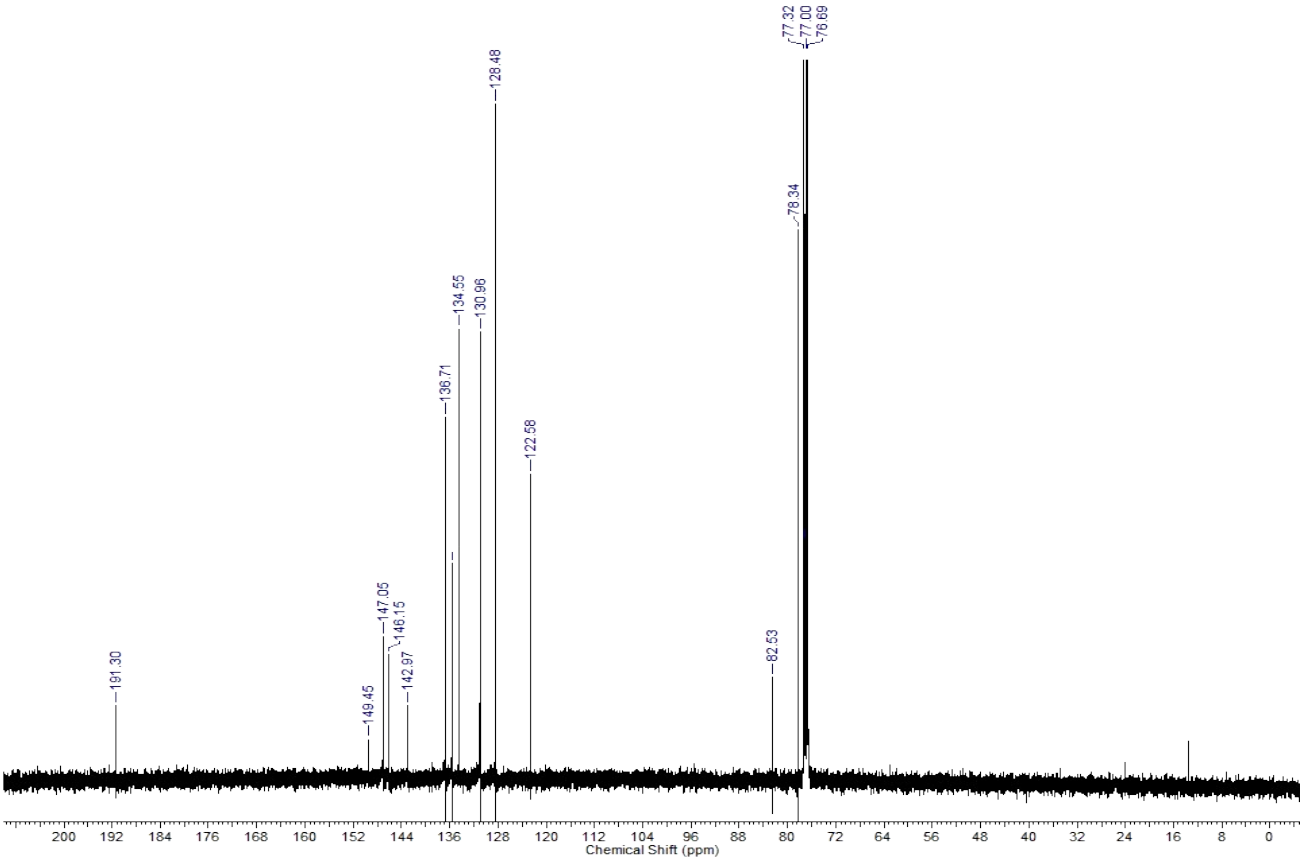
0.98
1.05
0.91
Chemical Shift (ppm)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122.58
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146.15
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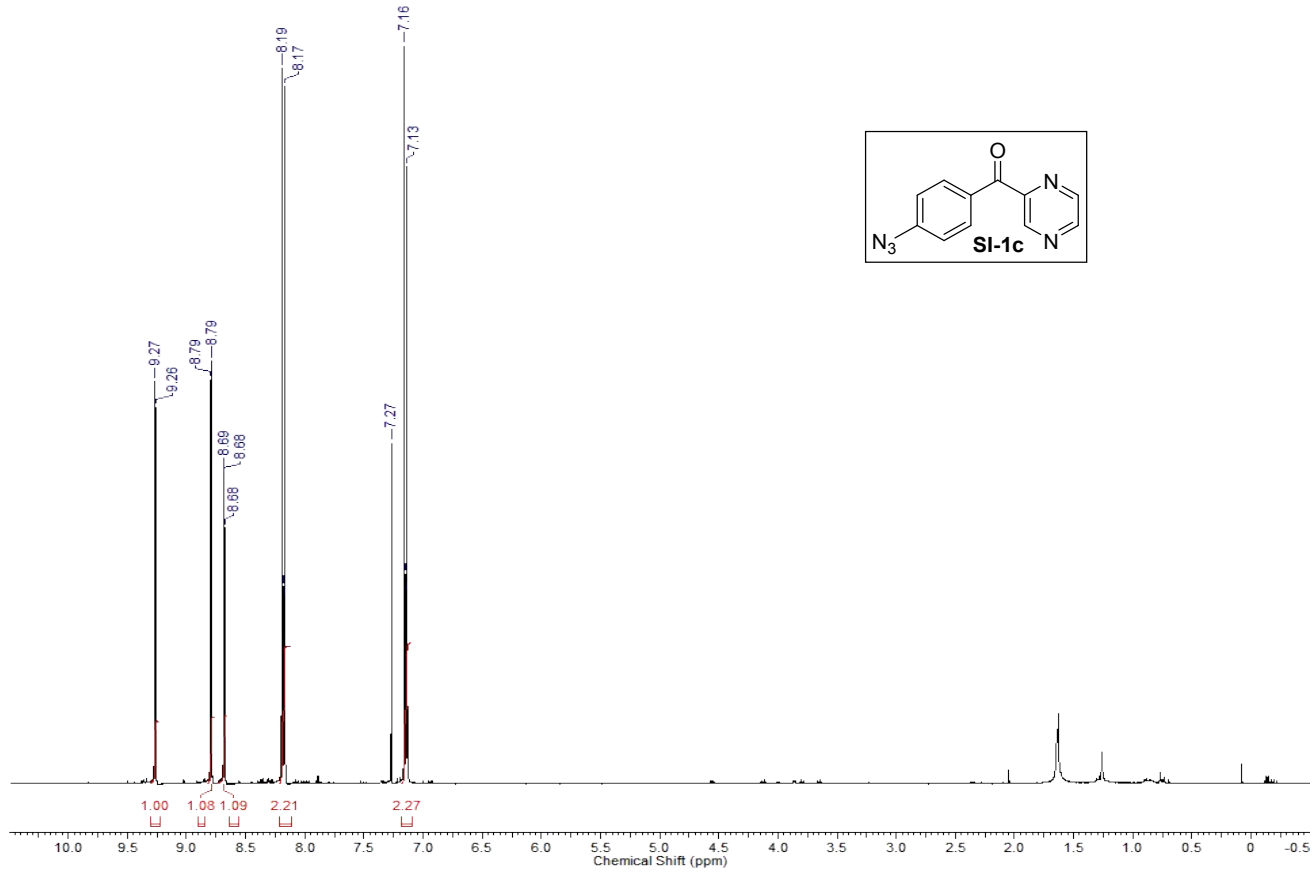
149.45
191.30
82.53
Chemical Shift (ppm)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2.21
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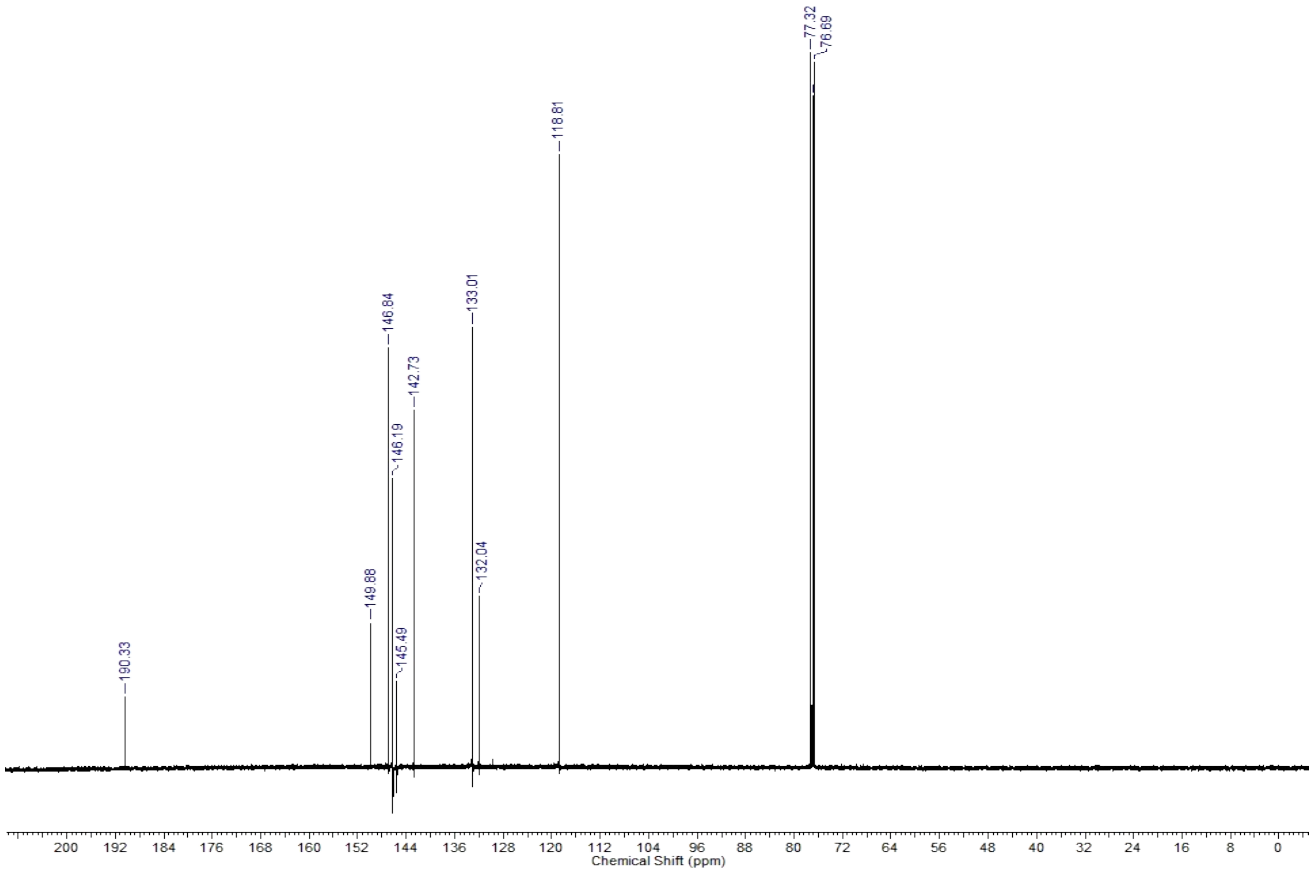
Chemical Shift (ppm)
SI-1c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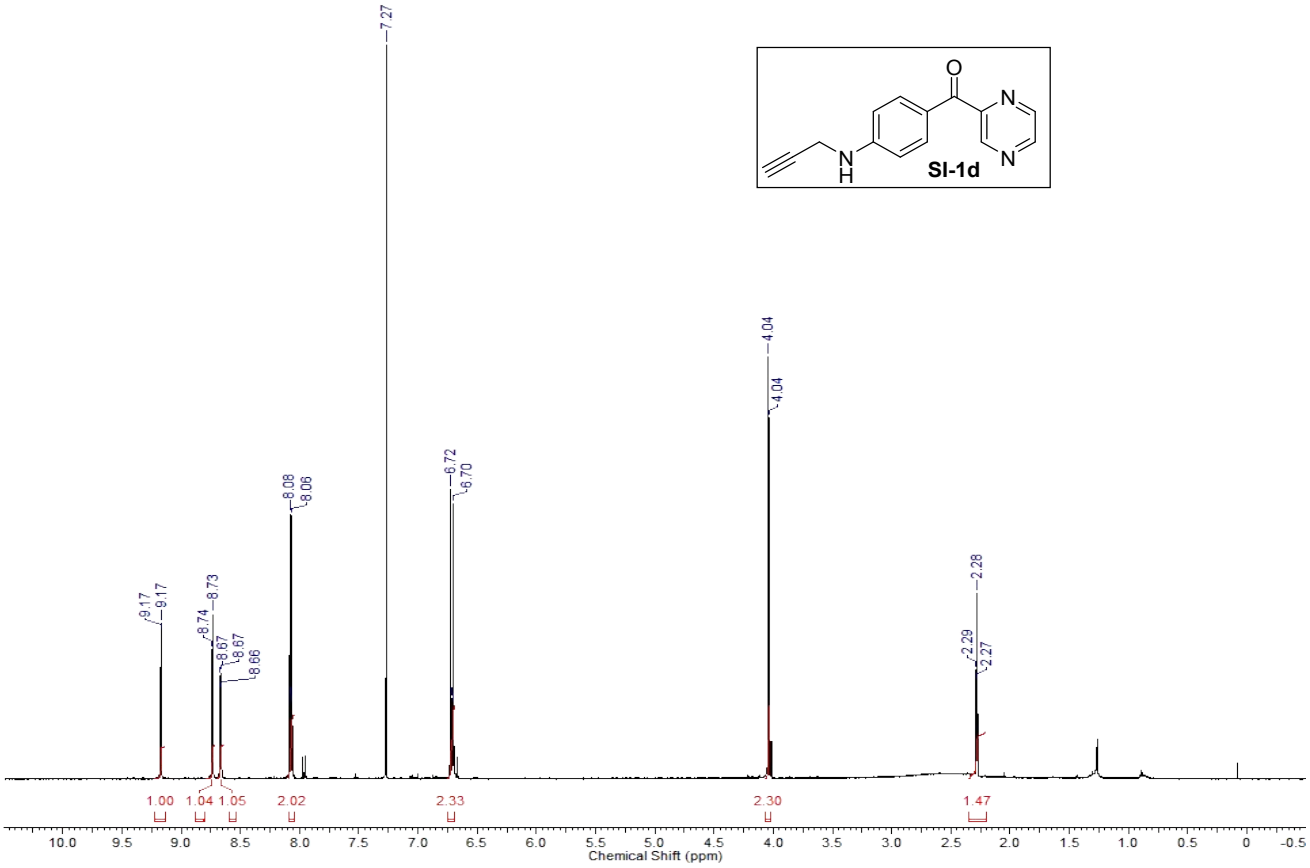
Chemical Shift (ppm)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8.08
8.06
6.72
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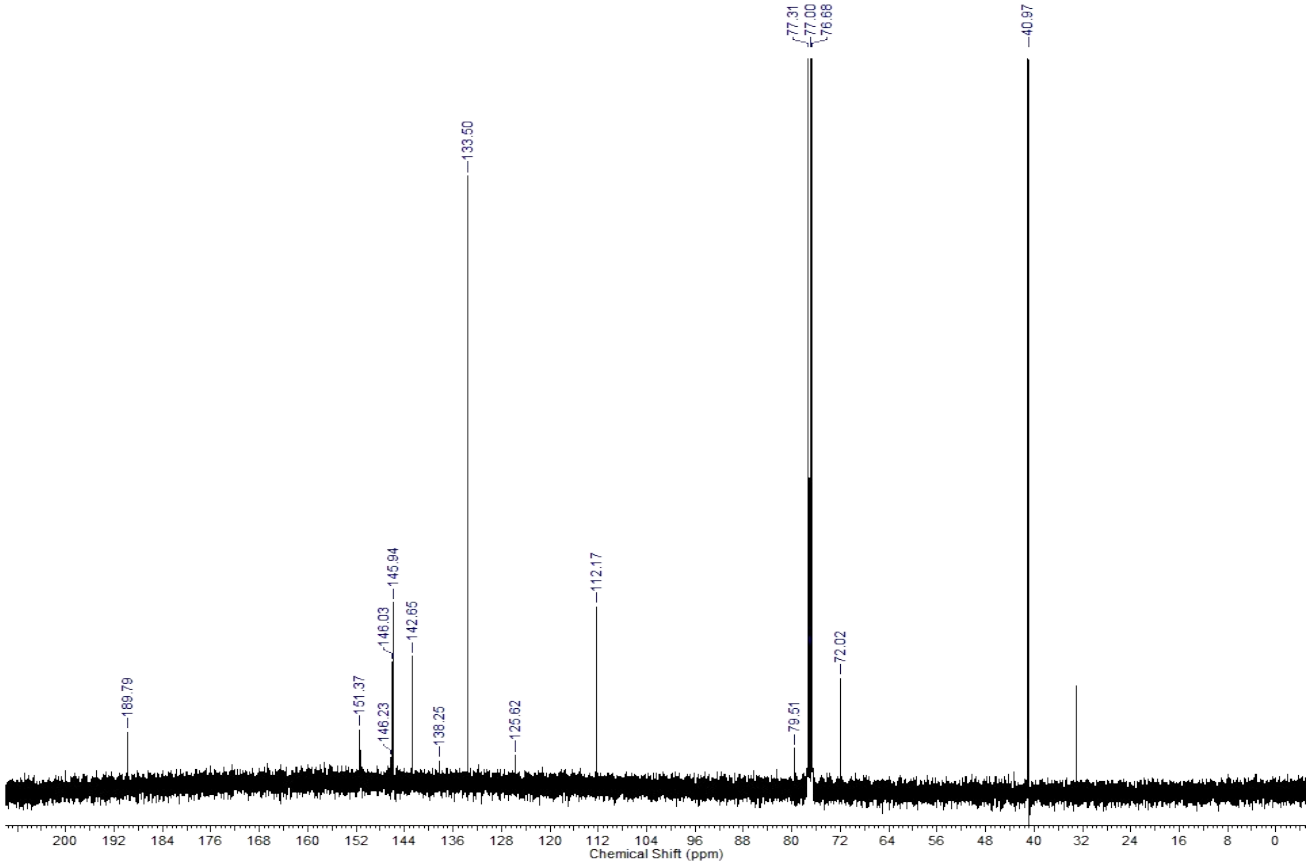
Chemical Shift (ppm)
O
N
N
N
H
SI-1d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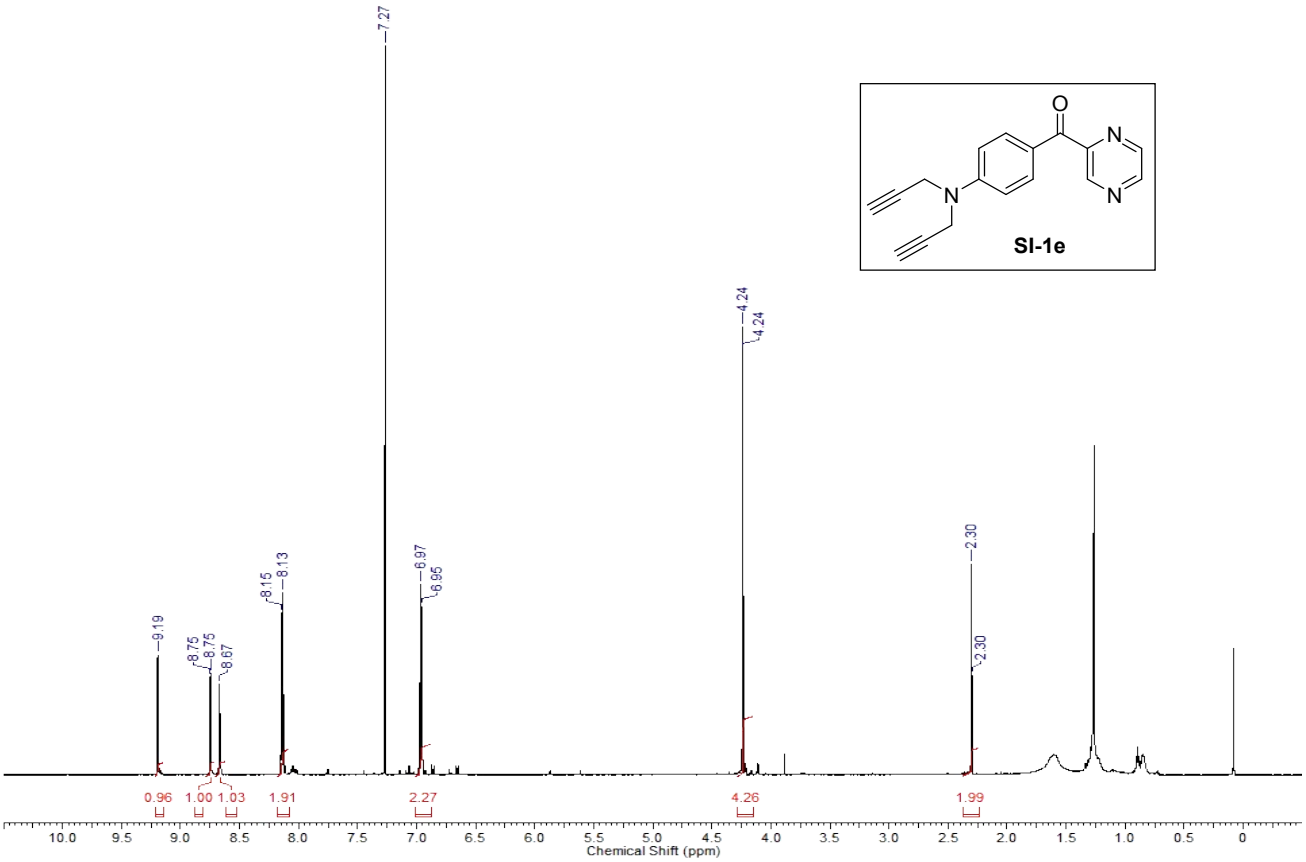
Chemical Shift (ppm)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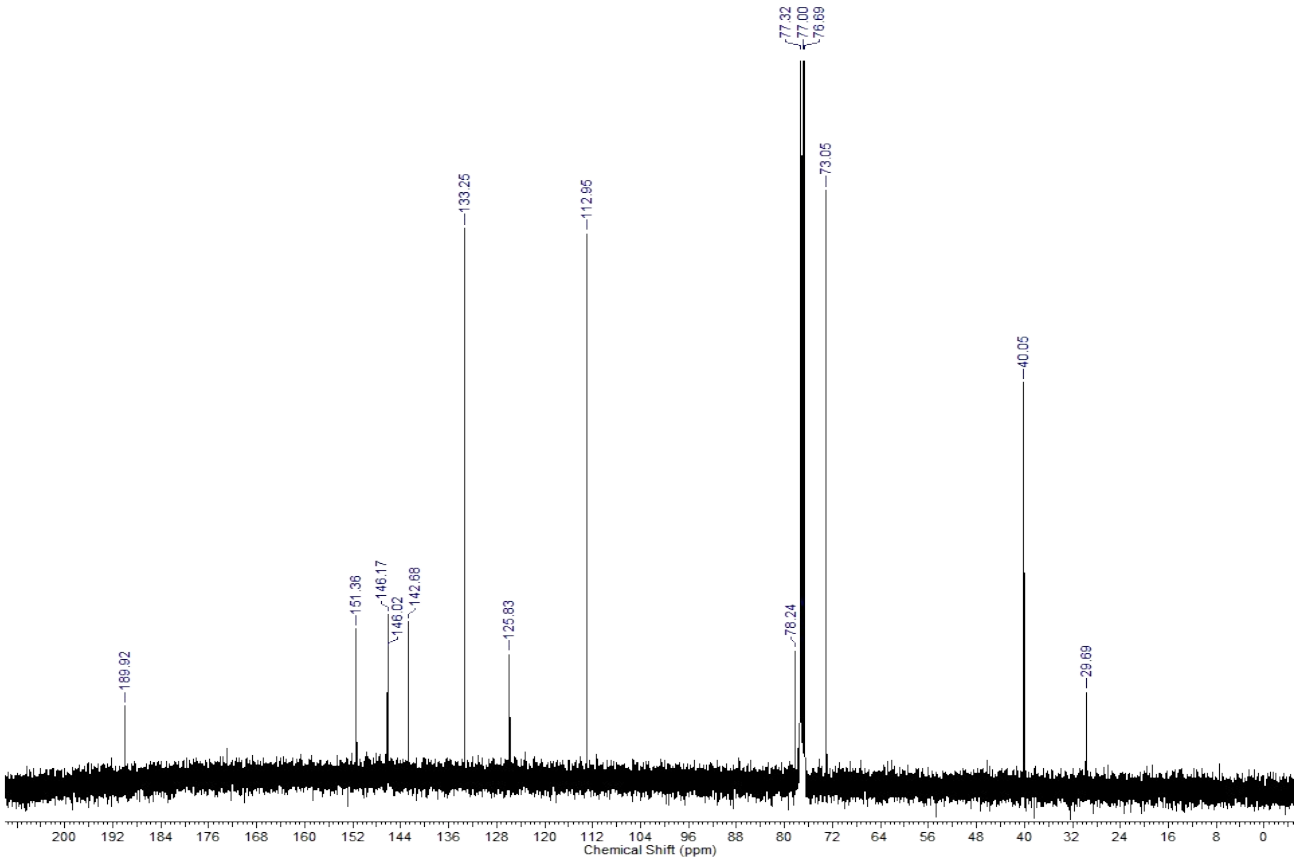
Chemical Shift (ppm)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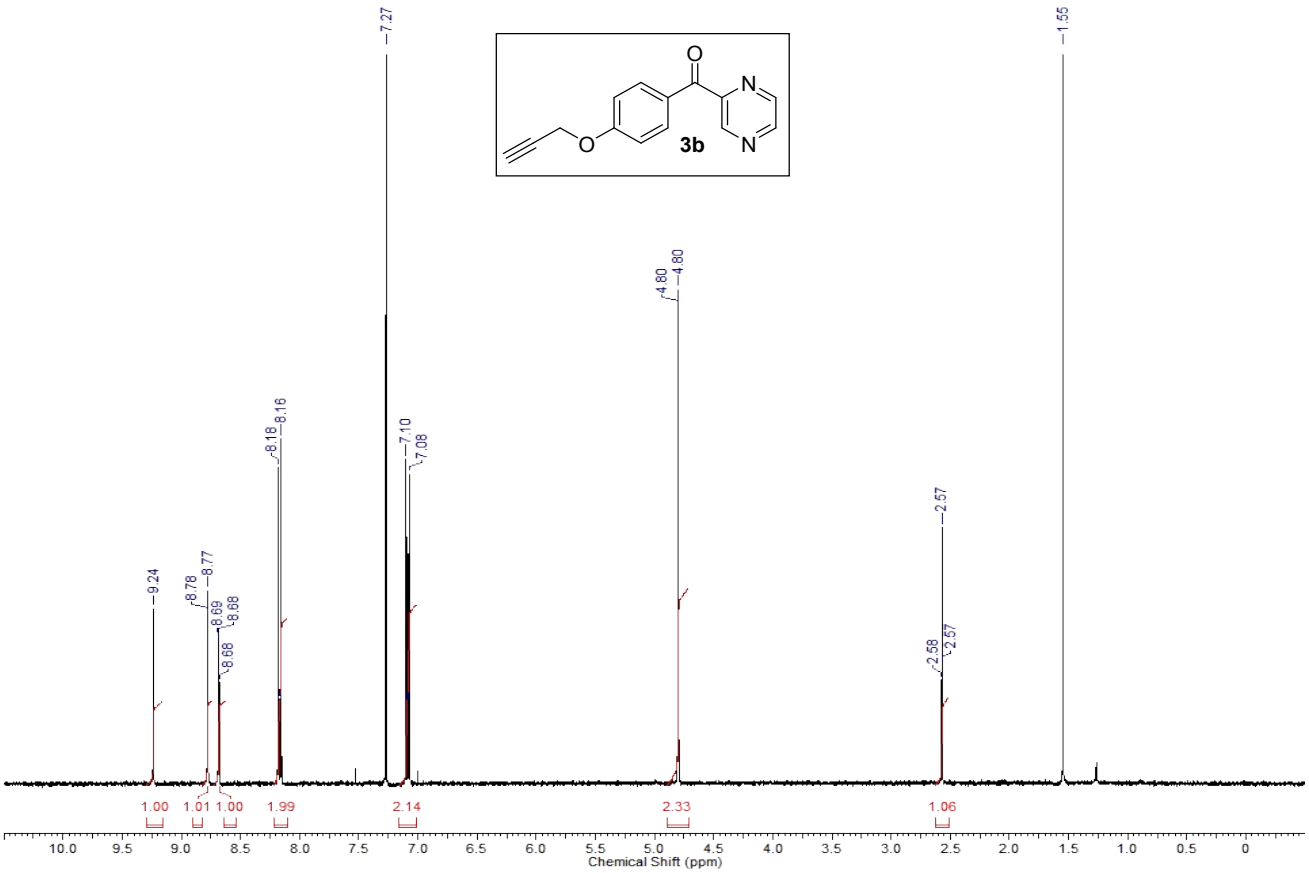
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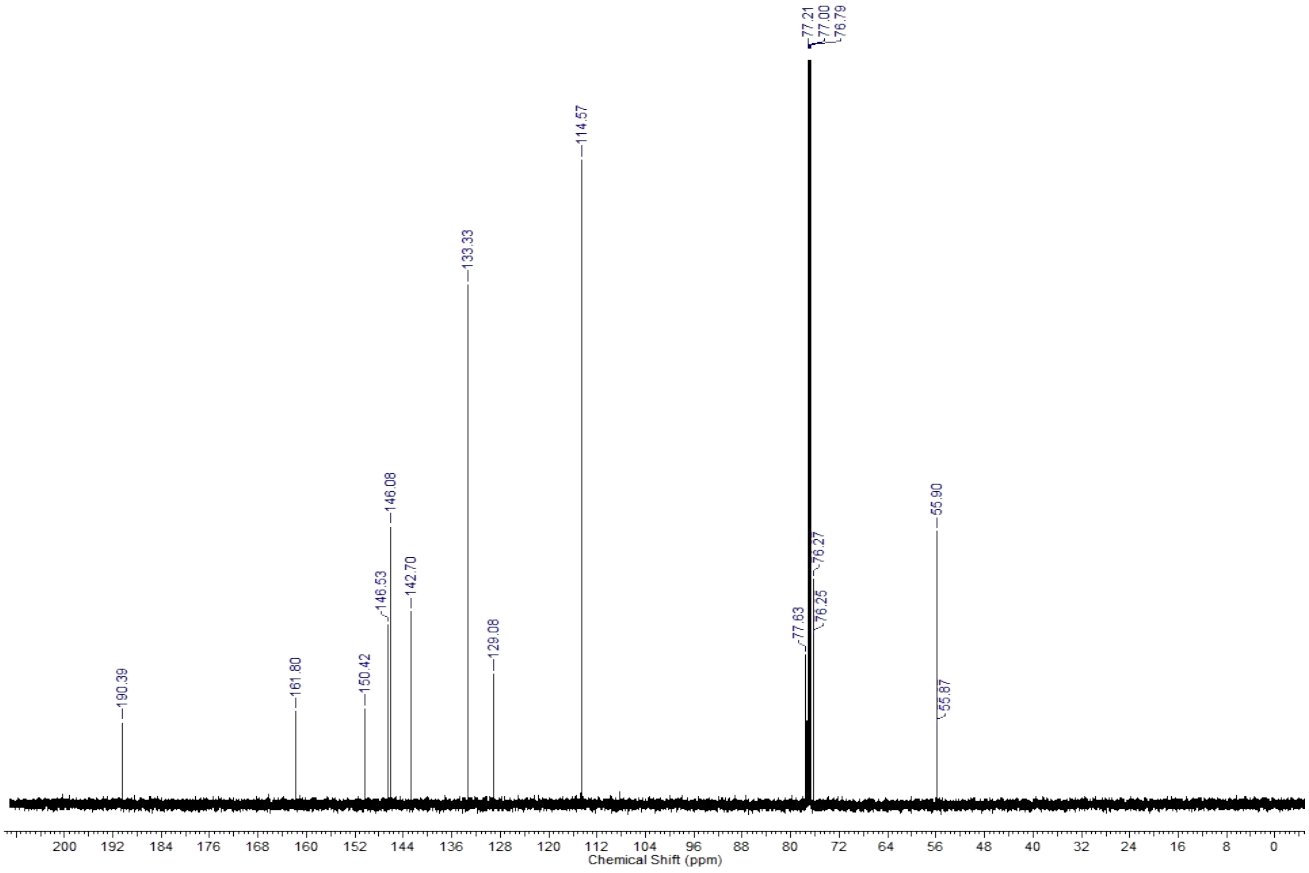
2.33
1.06
Chemical Shift (ppm)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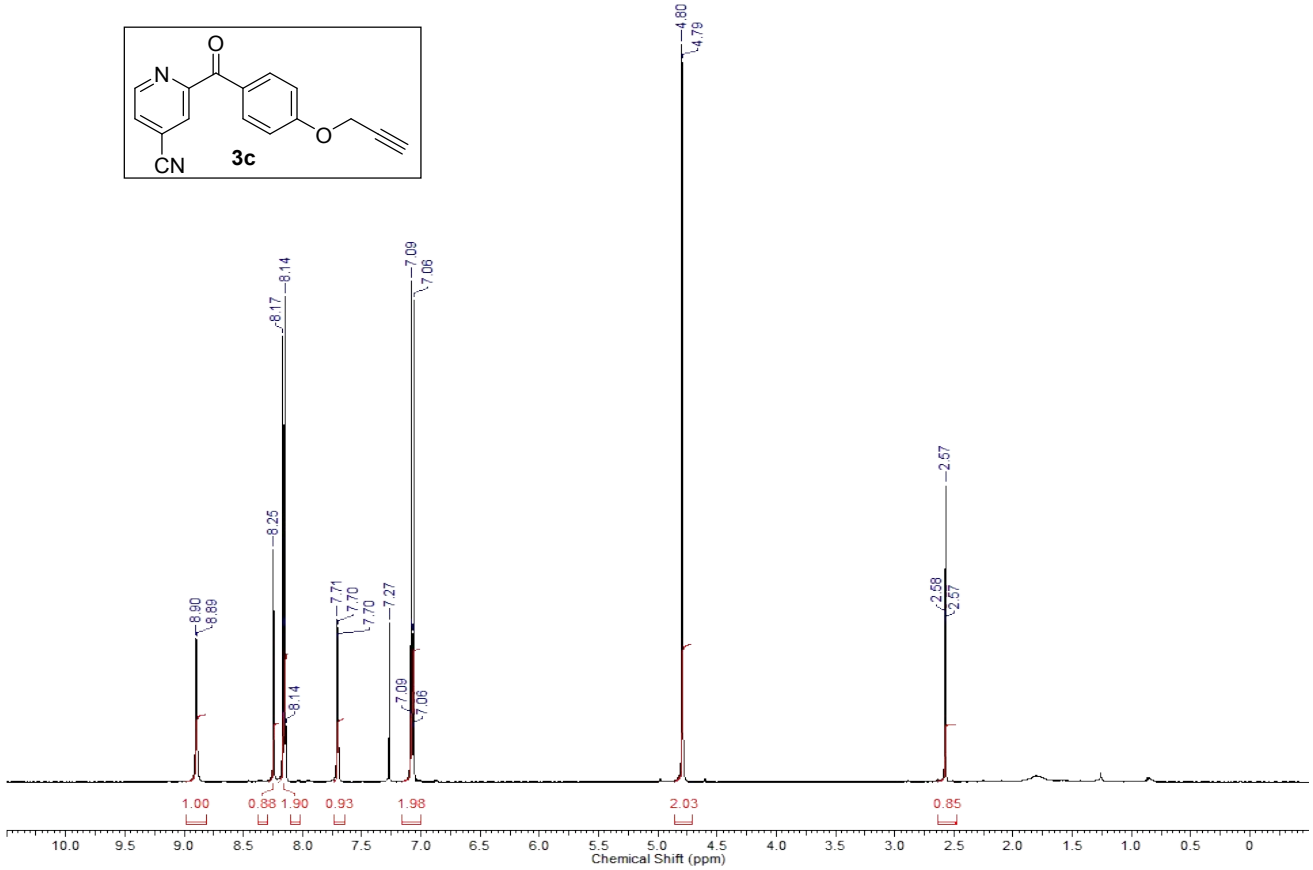
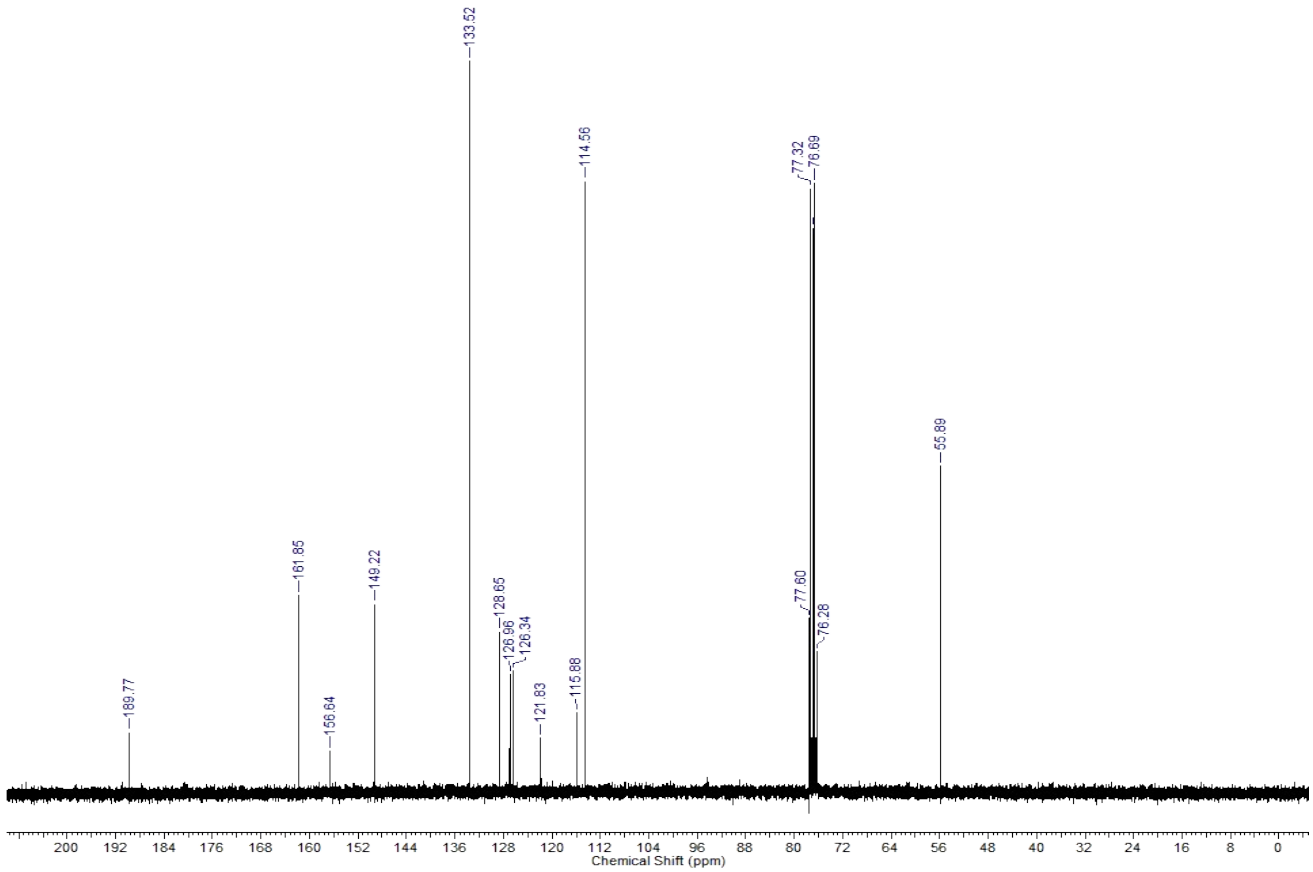
Chemical Shift (ppm)


3c
Chemical Shift (ppm)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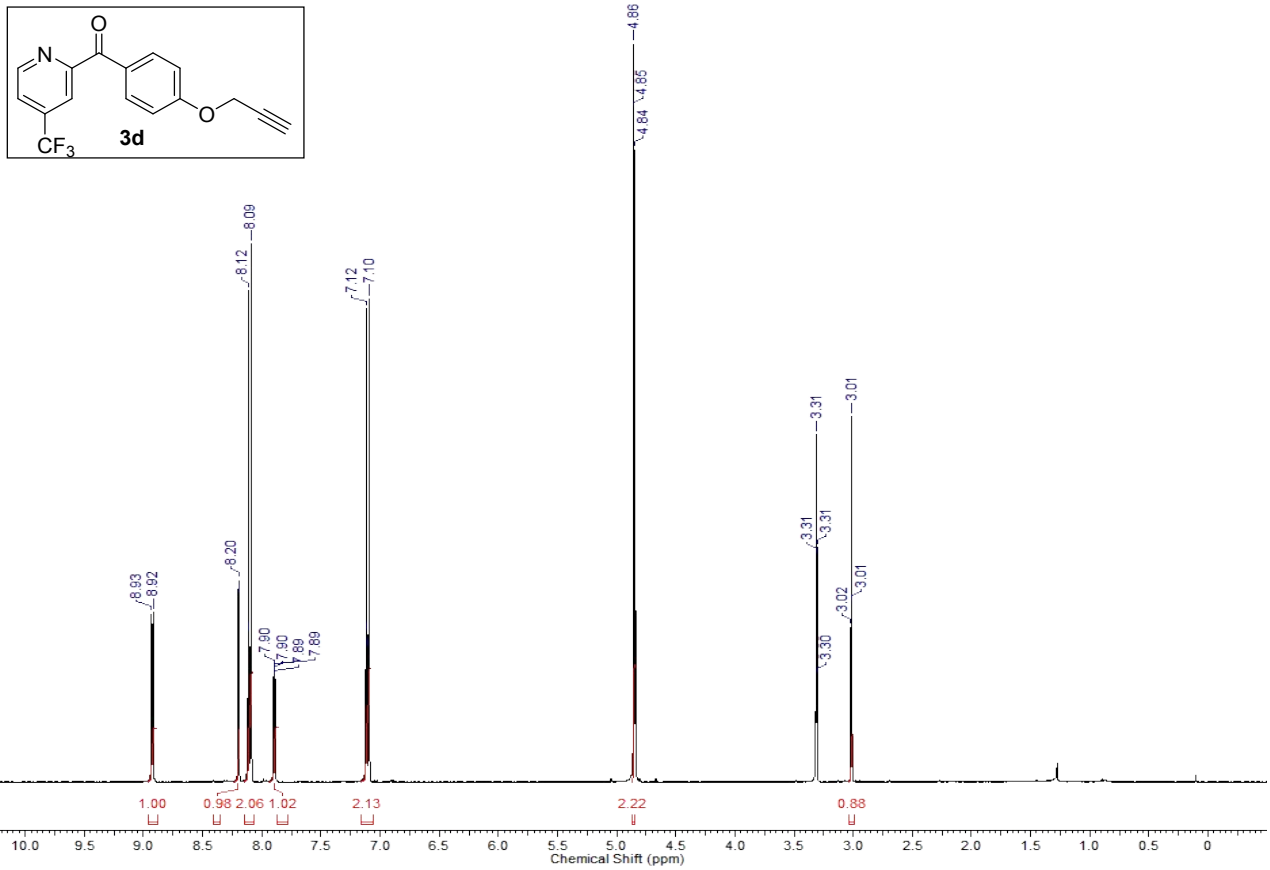
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7.89
7.12
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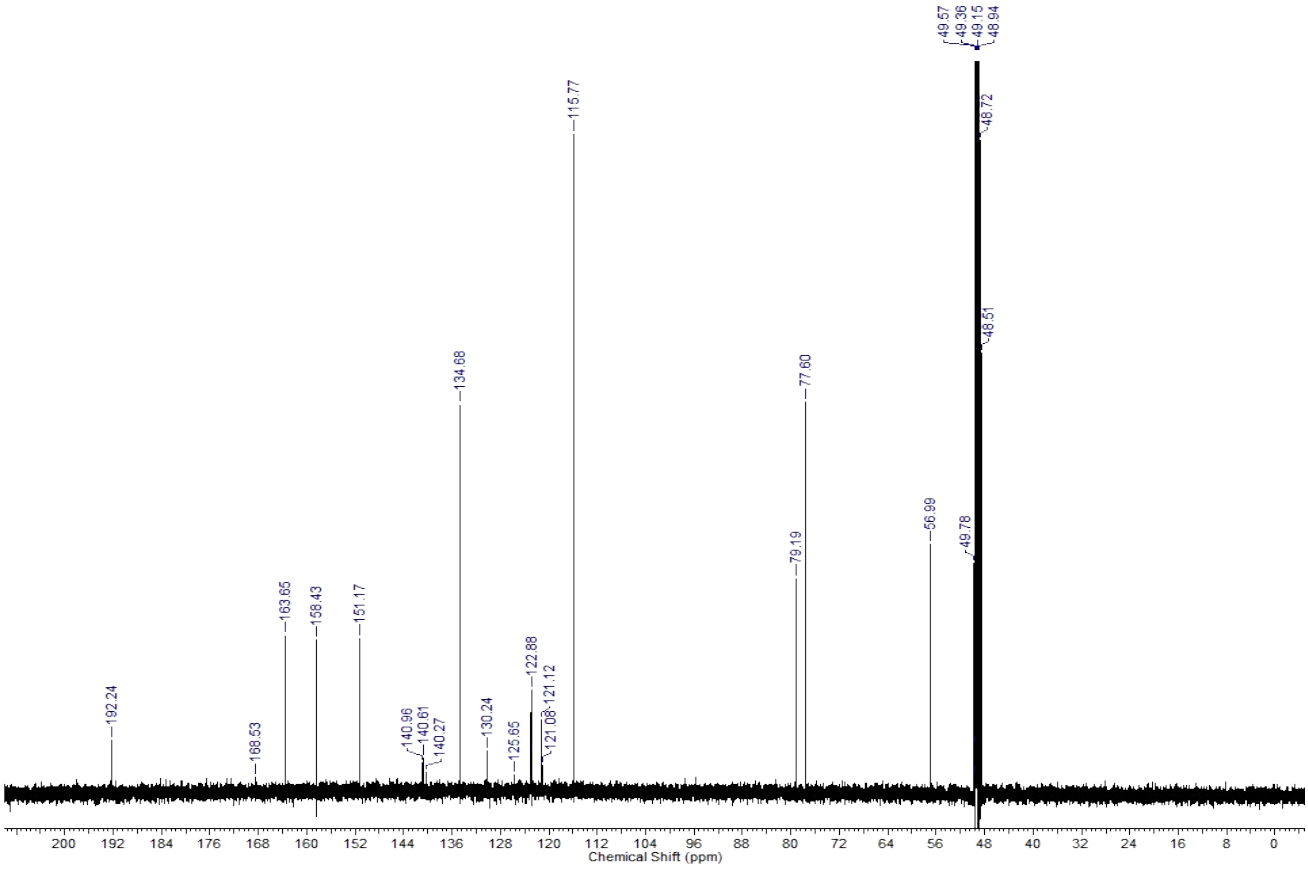
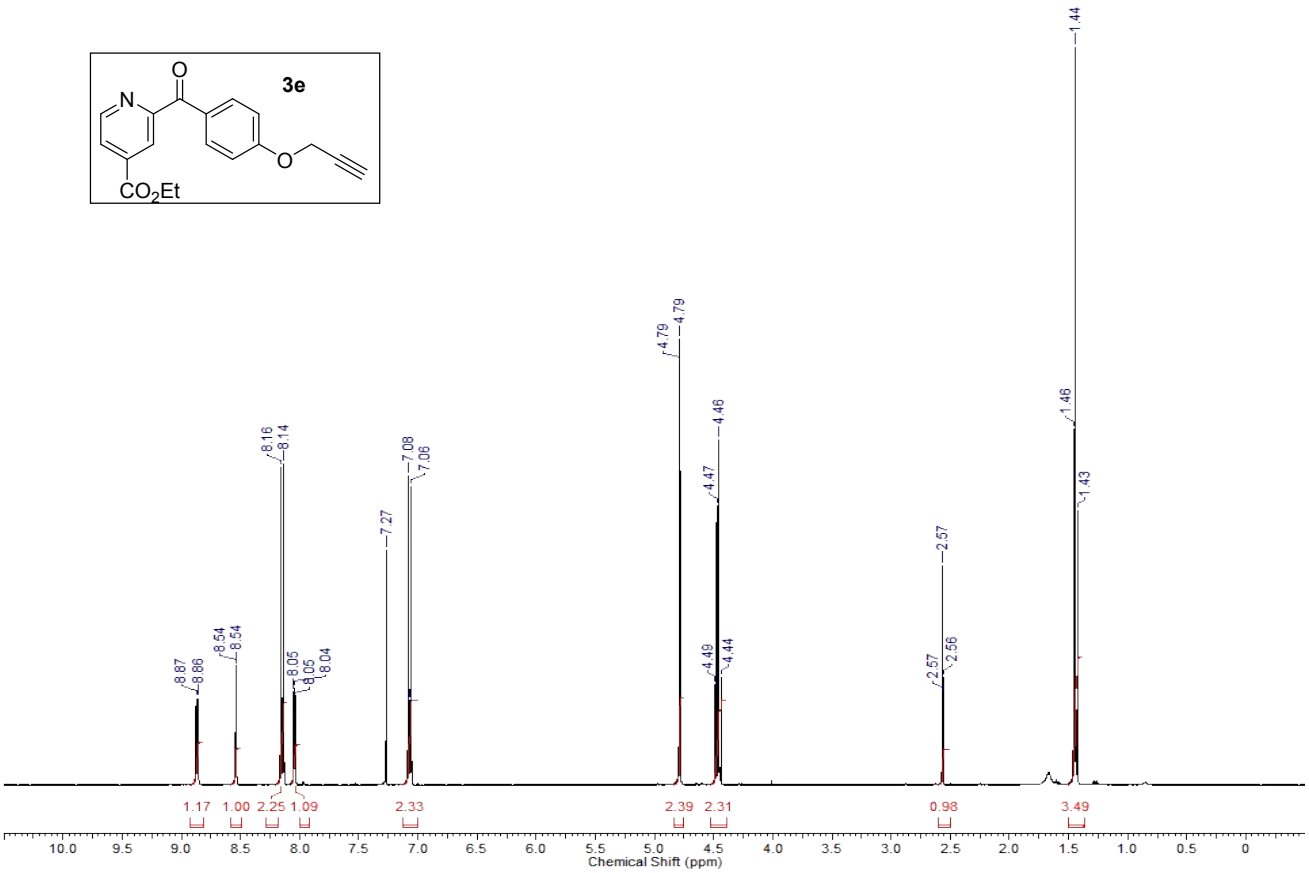
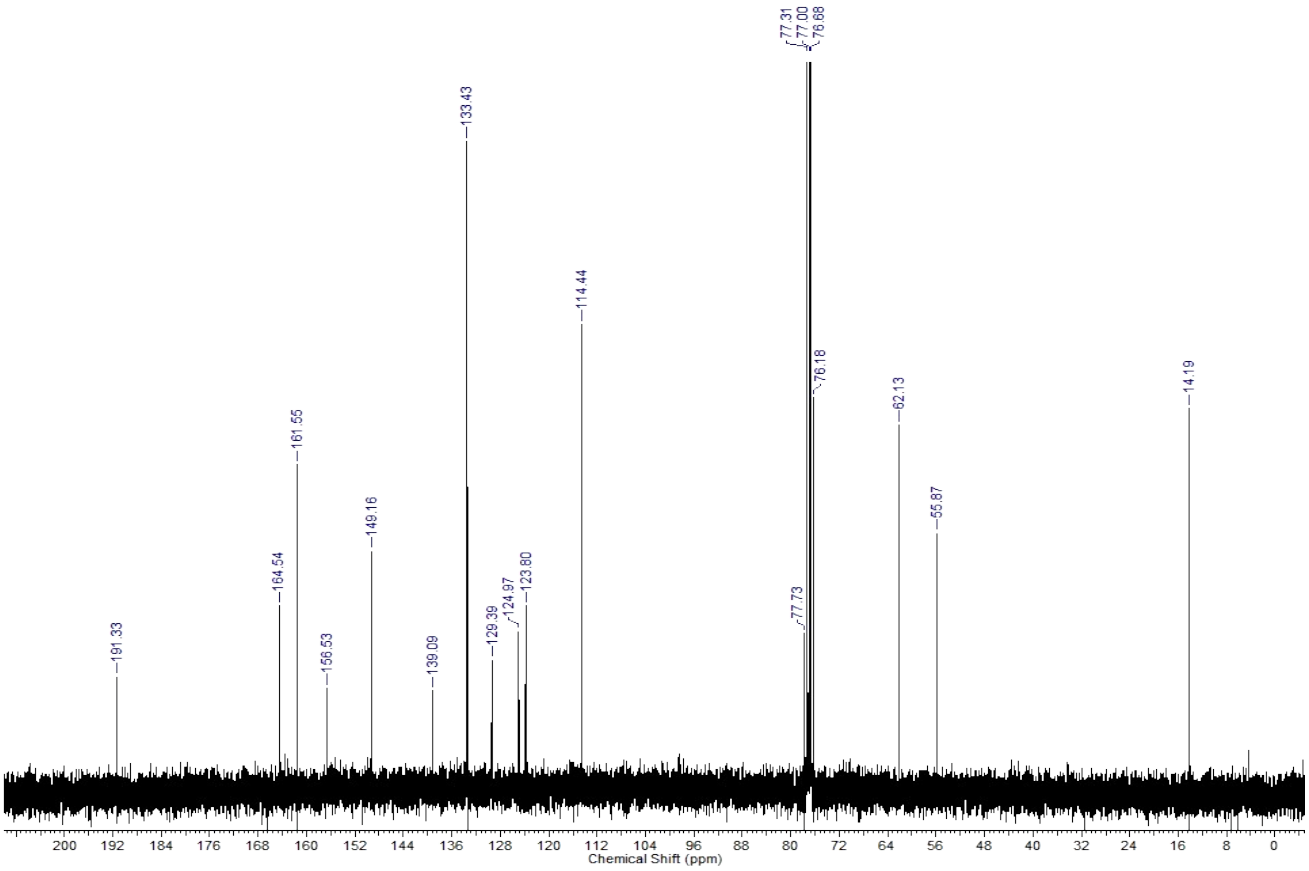
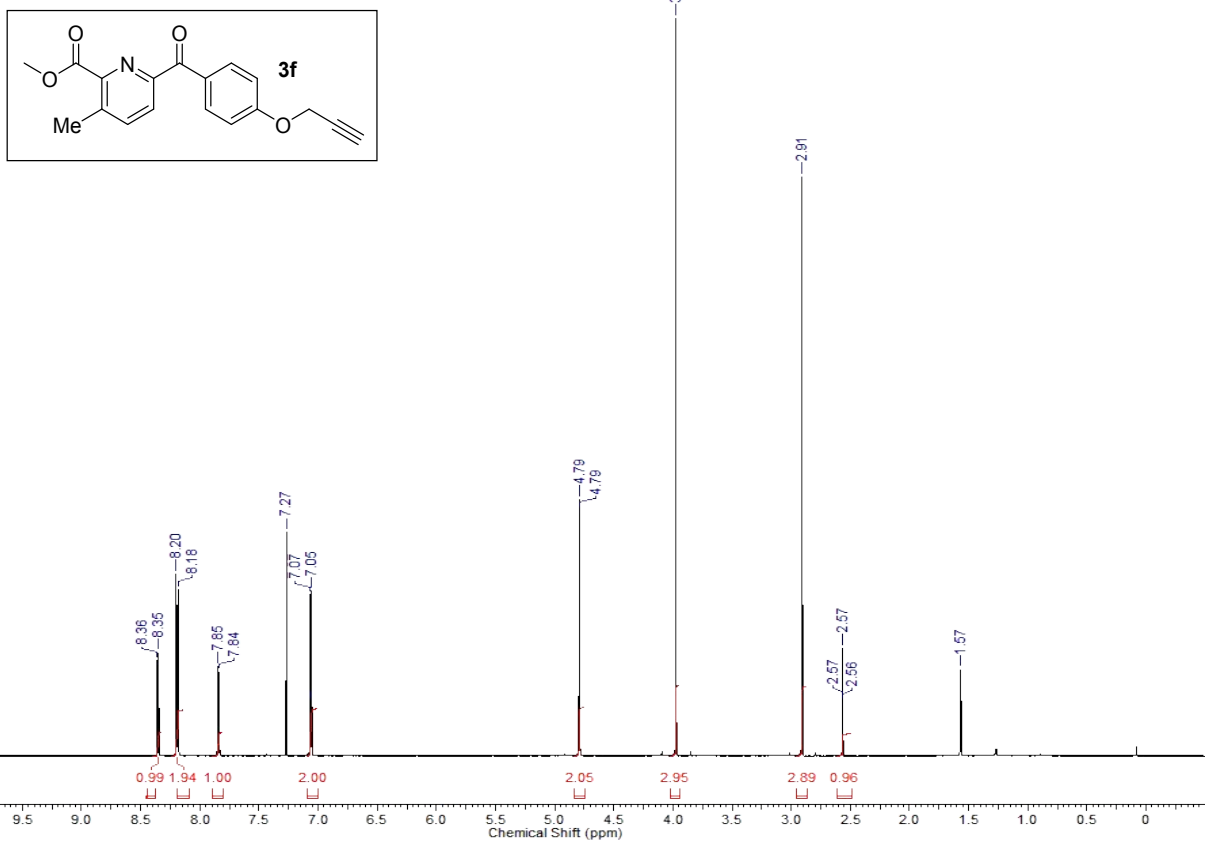
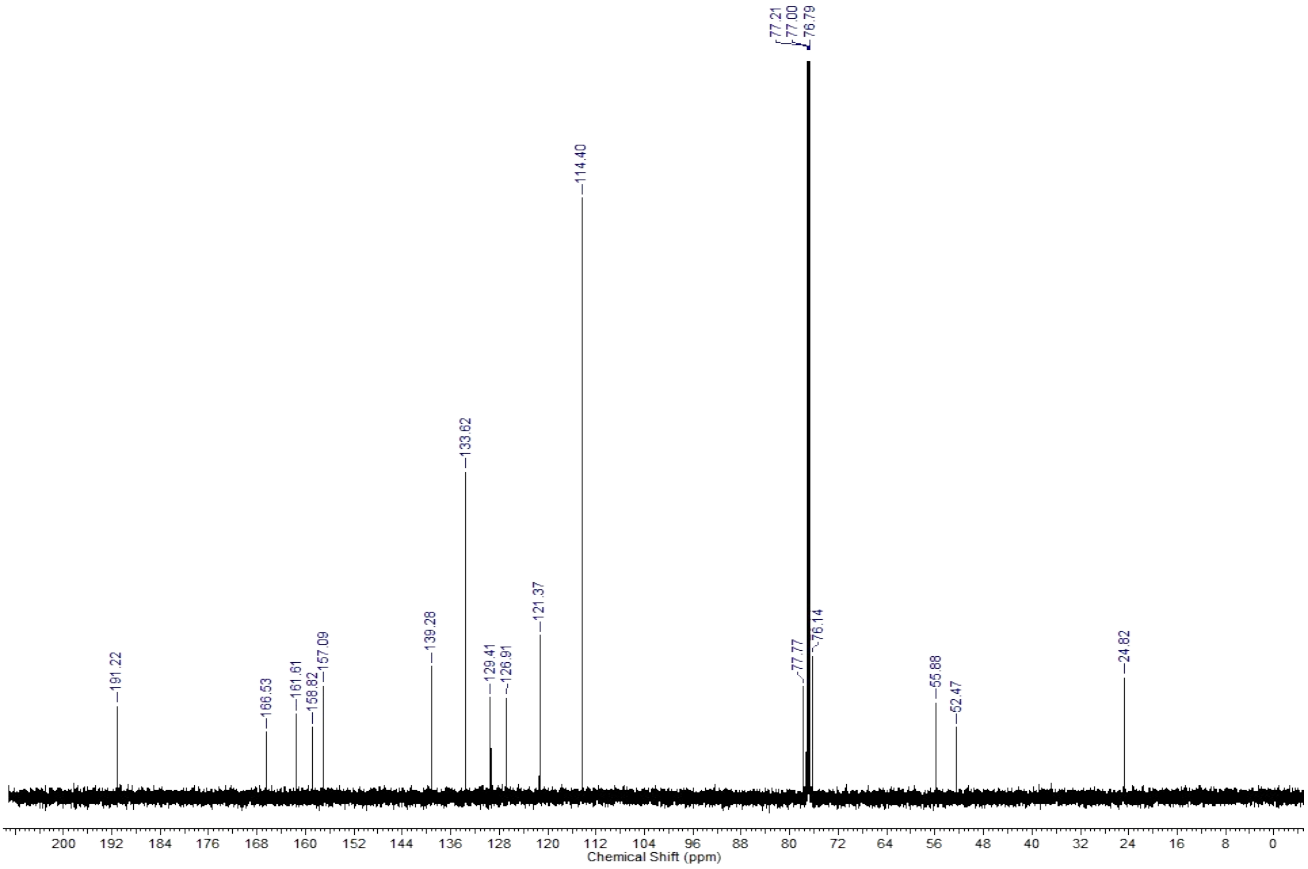
4.85
4.84
3.31
3.31
3.31
3.30
3.02
3.01
3.01
1.00
0.98
2.06
1.02
2.13
2.22
0.88
Chemical Shift (ppm)

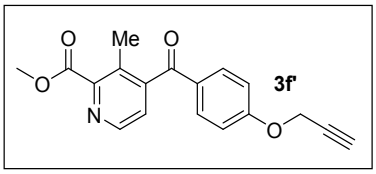

192.24
168.53
163.65
158.43
151.17
140.96
140.61
140.27
134.68
130.24
125.65
122.88
121.12
121.08
115.77
79.19
77.60
56.99
49.78
49.57
49.36
49.15
48.94
48.72
48.51
Chemical Shift (ppm)


3e
O
N
O
CO_2Et
8.87
8.86
8.54
8.54
8.16
8.14
8.05
8.05
8.04
7.27
7.08
7.06
4.79
4.79
4.47
4.46
4.49
4.44
2.57
2.57
2.56
1.46
1.44
1.43
1.17
1.00
2.25
1.09
2.33
2.39
2.31
0.98
3.49
Chemical Shift (ppm)

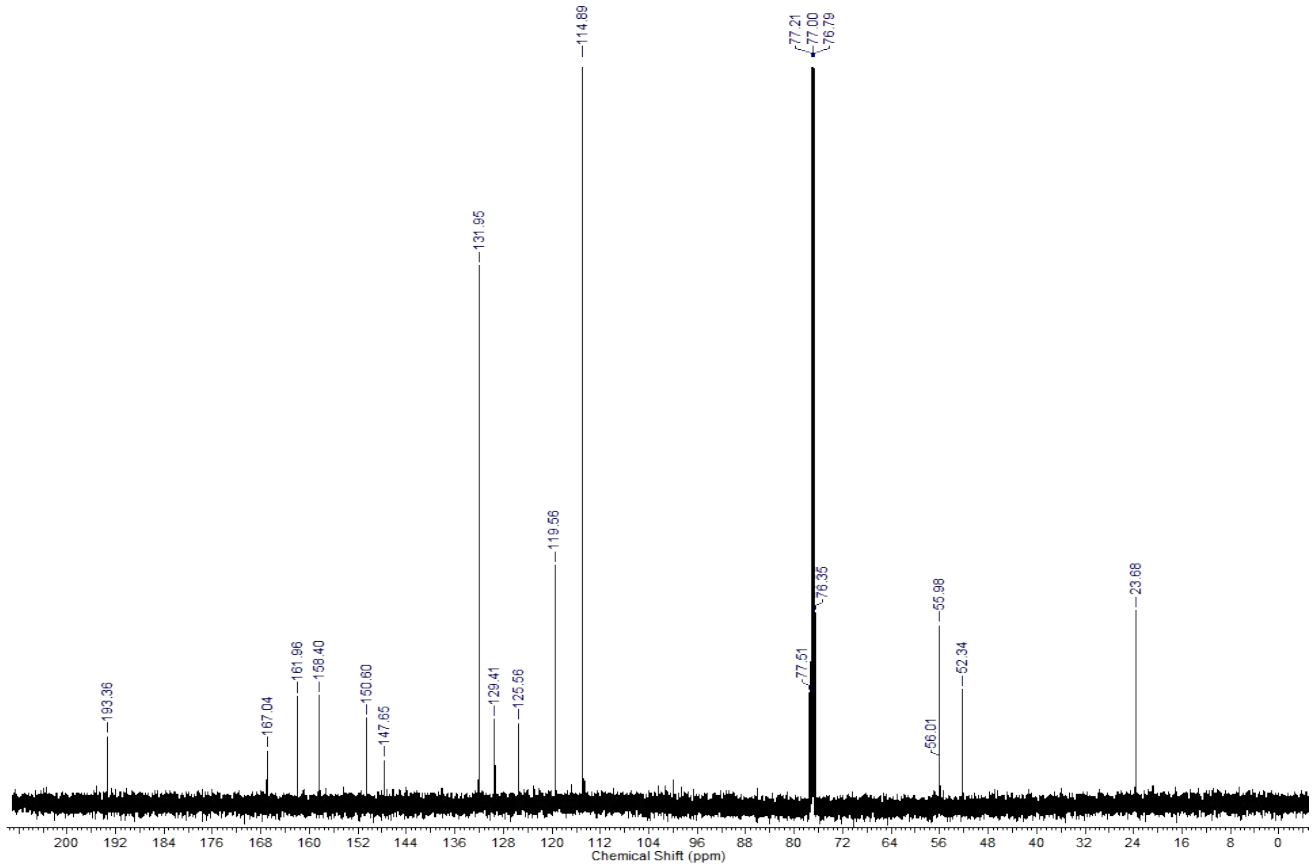

191.33
164.54
161.55
156.53
149.16
139.09
133.43
129.39
124.97
123.80
114.44
77.31
77.00
76.68
76.18
77.73
62.13
55.87
14.19
Chemical Shift (ppm)

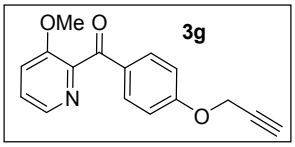

3f
Me
3.97
2.91
4.79
4.79
7.27
7.07
7.05
8.20
8.18
8.36
8.35
7.85
7.84
2.57
2.56
2.57
1.57
0.99 1.94 1.00 2.00 2.05 2.95 2.89 0.96
Chemical Shift (ppm)


77.21
77.00
76.79
114.40
133.62
191.22
166.53
161.61
158.82
157.09
139.28
129.41
126.91
121.37
77.77
76.14
55.88
52.47
24.82
Chemical Shift (ppm)

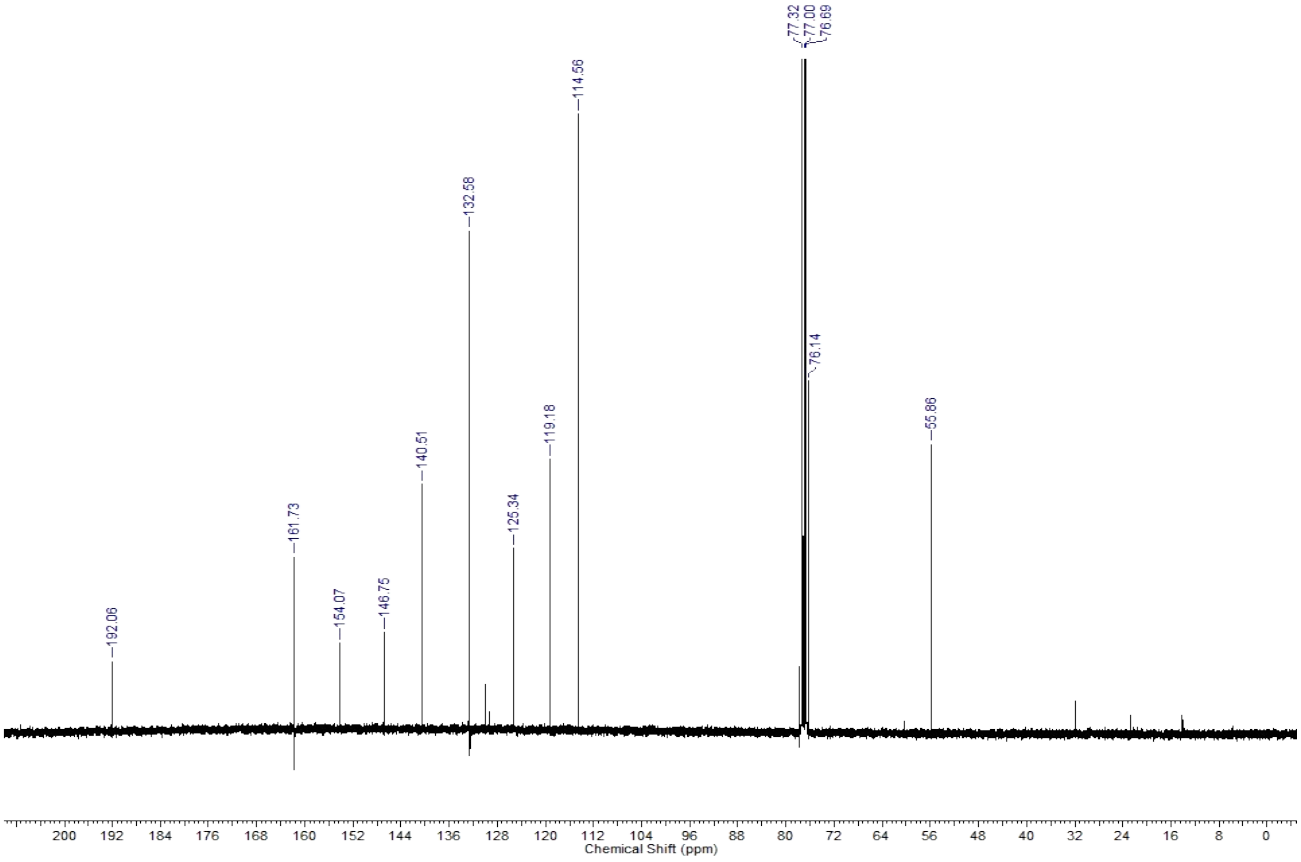

O
Me
O
O
N
O
3f'

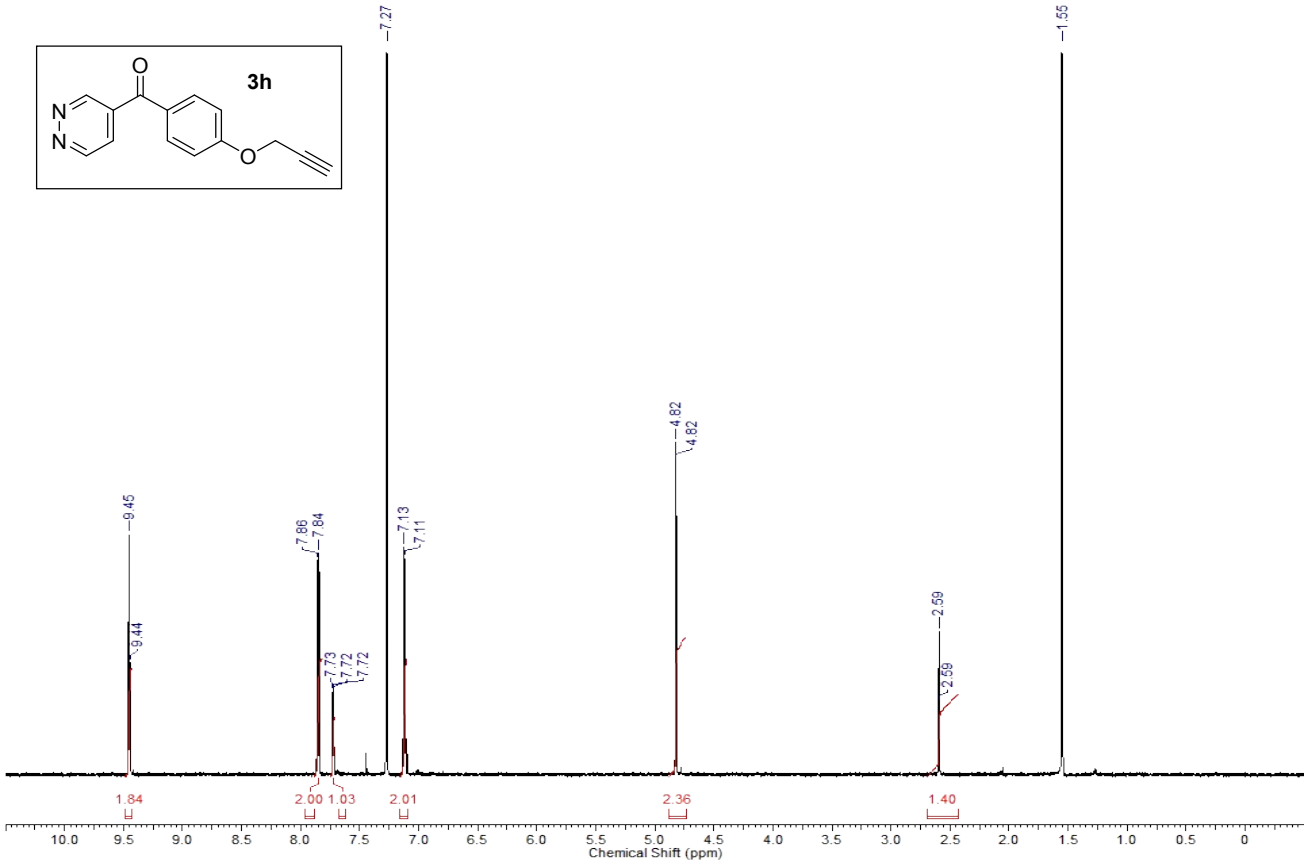
1.00
1.98
1.01
2.12
2.26
2.94
2.96
1.05
Chemical Shift (ppm)

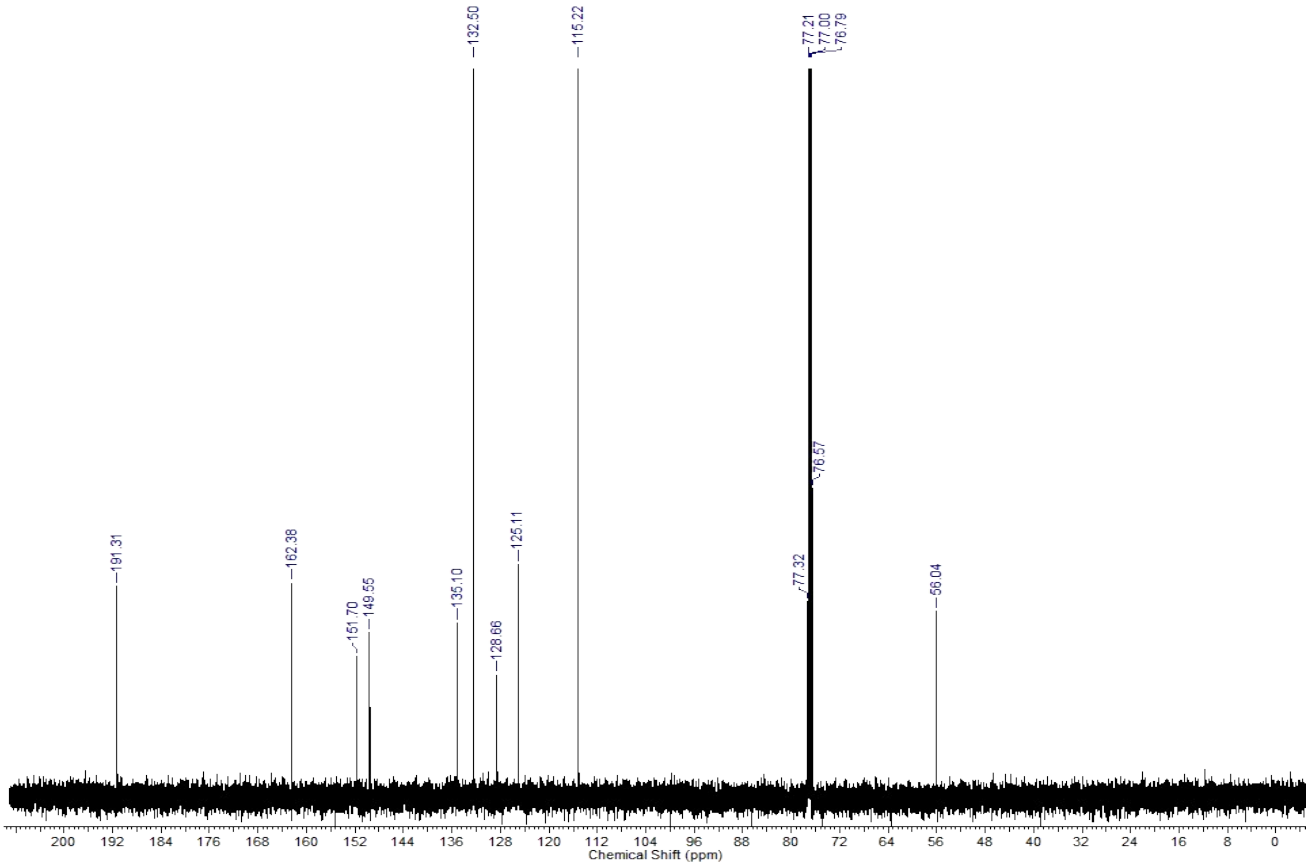

193.36
167.04
161.96
158.40
150.60
147.65
131.95
129.41
125.56
119.56
114.89
77.21
77.00
76.79
76.35
77.51
56.01
55.98
52.34
23.68
Chemical Shift (ppm)

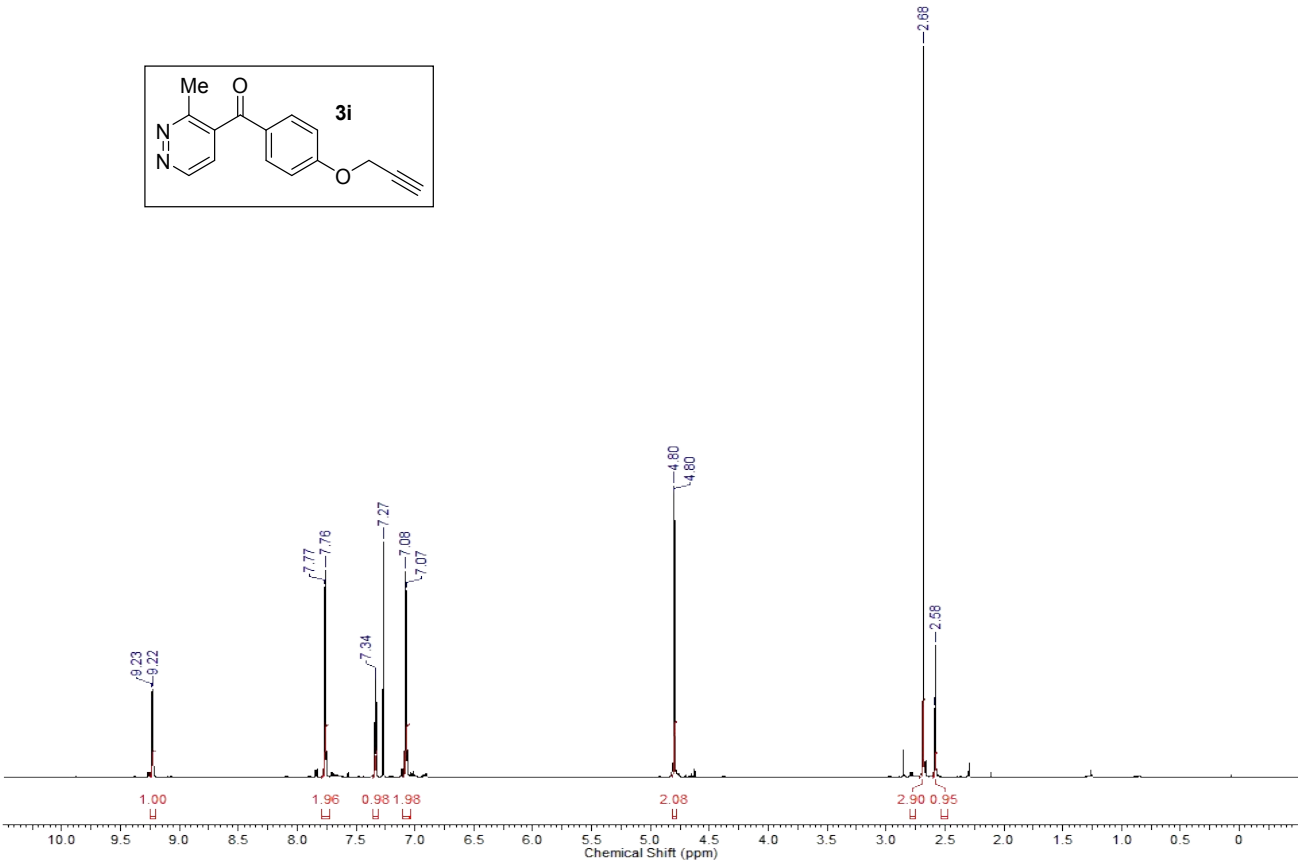

OMe O
3g
N
O

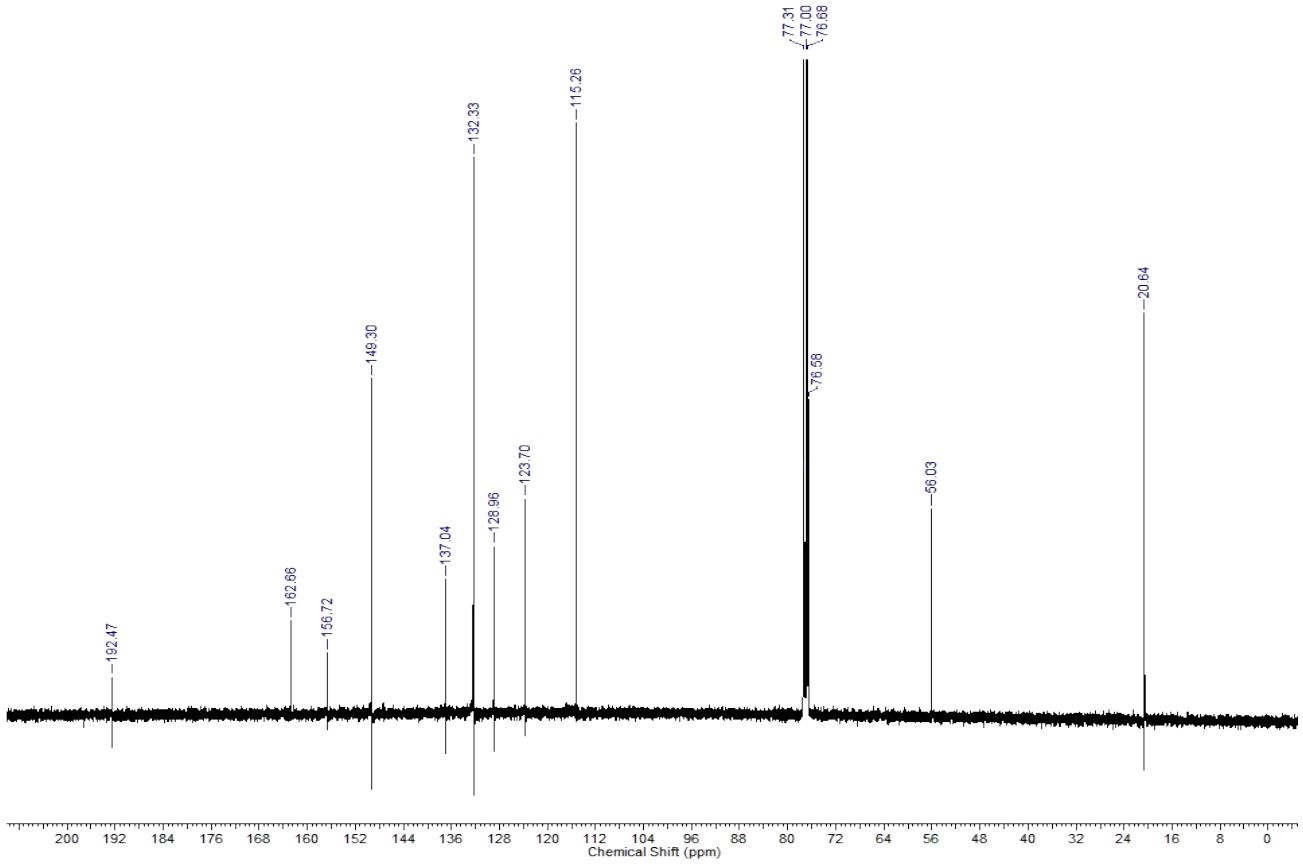
3.84
8.28
8.27
7.88
7.86
7.42
7.39
7.38
7.27
7.03
7.00
4.76
4.76
2.55
2.54
2.55
1.00
2.07
2.16
2.18
2.27
3.32
0.92
Chemical Shift (ppm)

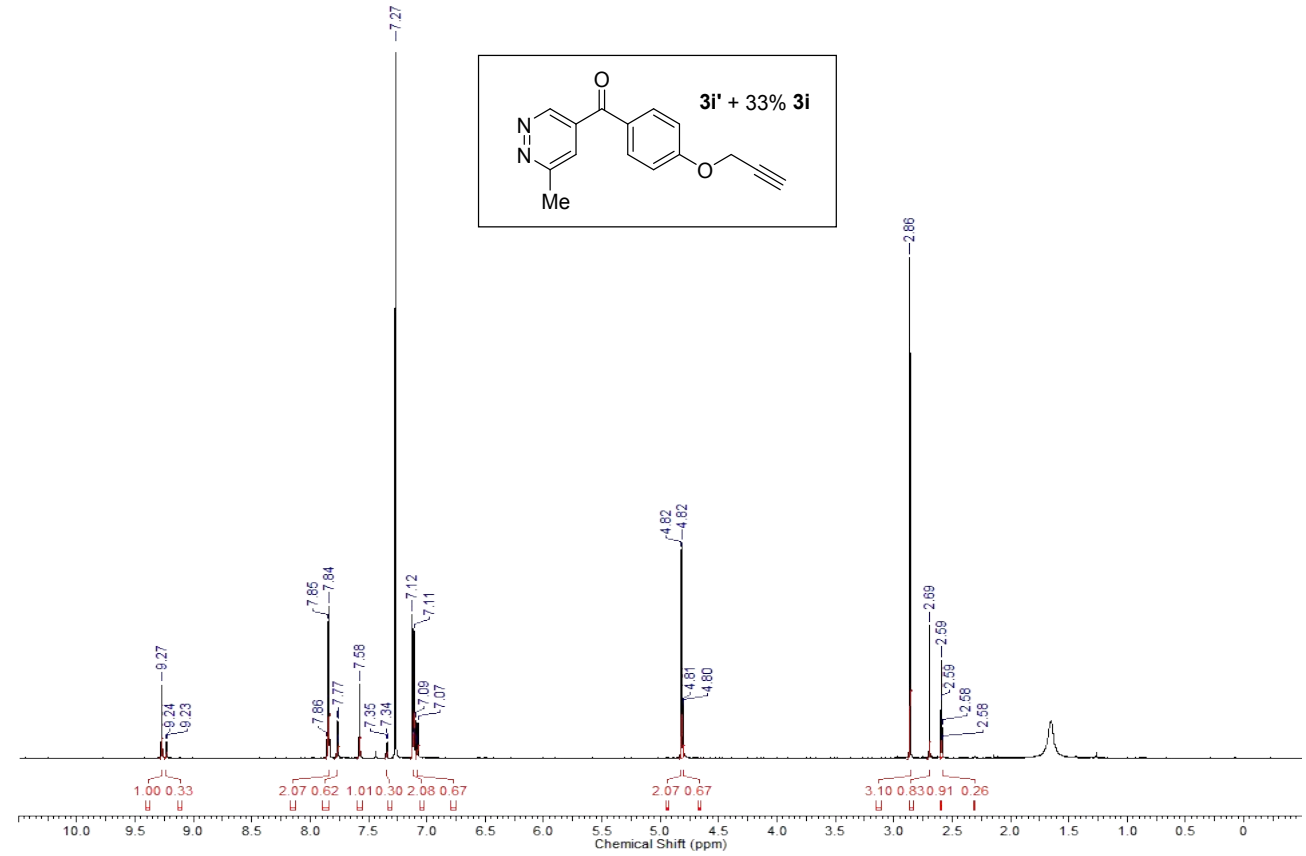

77.32
77.00
76.69
114.56
132.58
76.14
55.86
119.18
140.51
125.34
161.73
154.07
146.75
192.06
Chemical Shift (ppm)

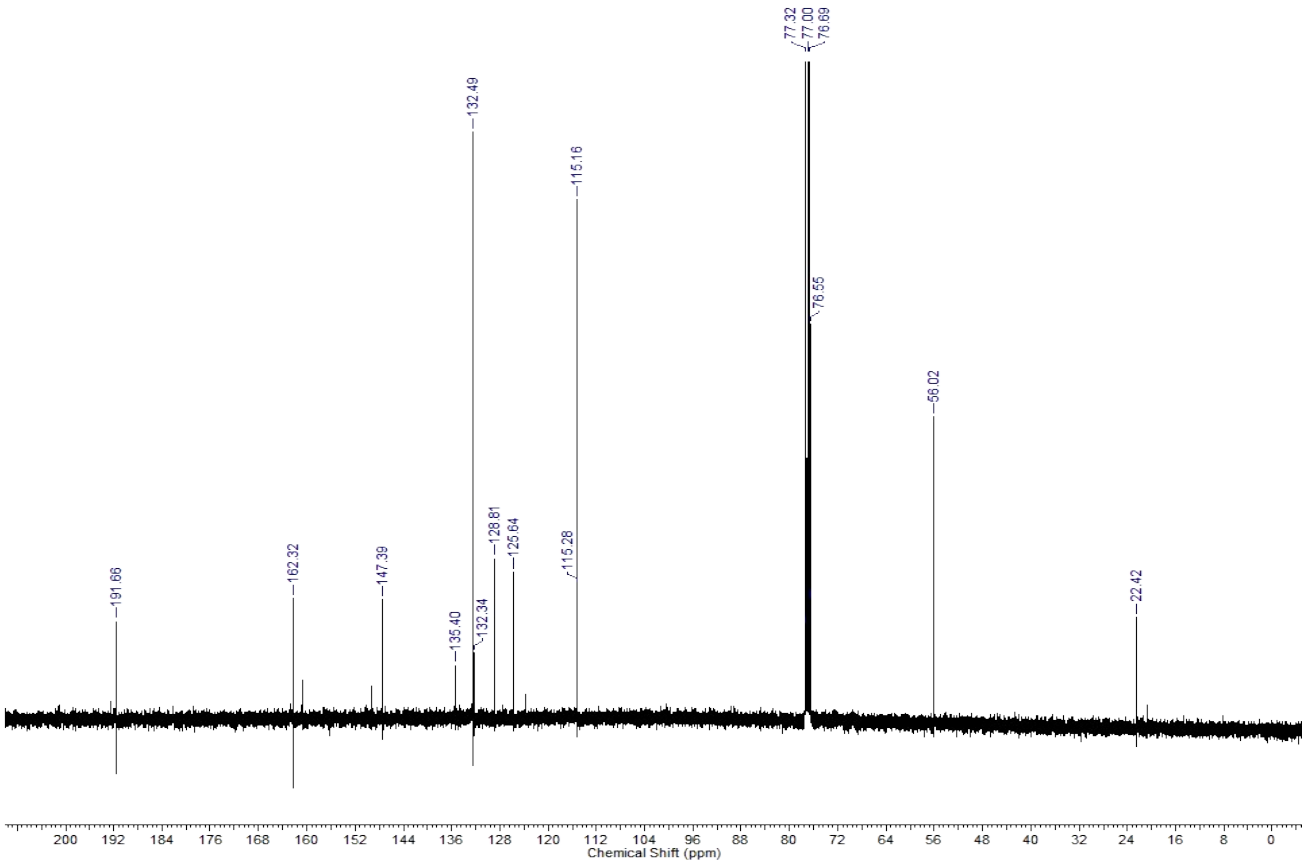

3h
9.45
9.44
7.86
7.84
7.73
7.72
7.72
7.27
7.13
7.11
4.82
4.82
2.59
2.59
1.55
1.84
2.00
1.03
2.01
2.36
1.40
Chemical Shift (ppm)

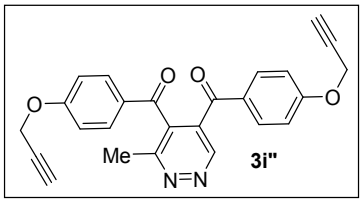

191.31
162.38
151.70
149.55
135.10
132.50
128.66
125.11
115.22
77.21
77.00
76.79
76.57
77.32
56.04
Chemical Shift (ppm)


Me
O
N
N
O
3i
2.88
4.80
4.80
7.77
7.76
7.27
7.08
7.07
7.34
9.23
9.22
2.58
1.00
1.96
0.98
1.98
2.08
2.90
0.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


77.31
77.00
76.68
115.26
132.33
20.64
149.30
76.58
56.03
123.70
128.96
137.04
162.66
156.72
192.47
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

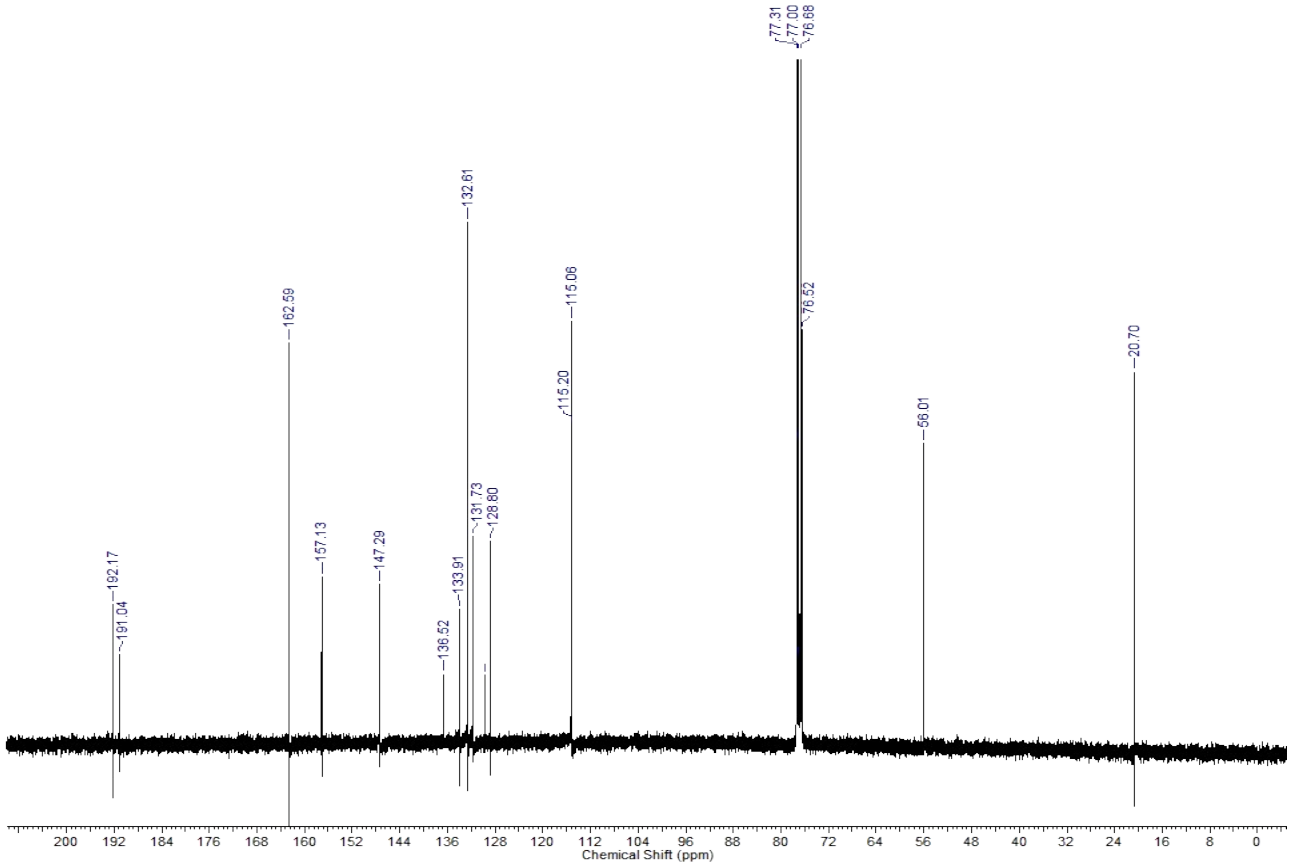

3i' + 33% 3i
Me
Chemical Shift (ppm)

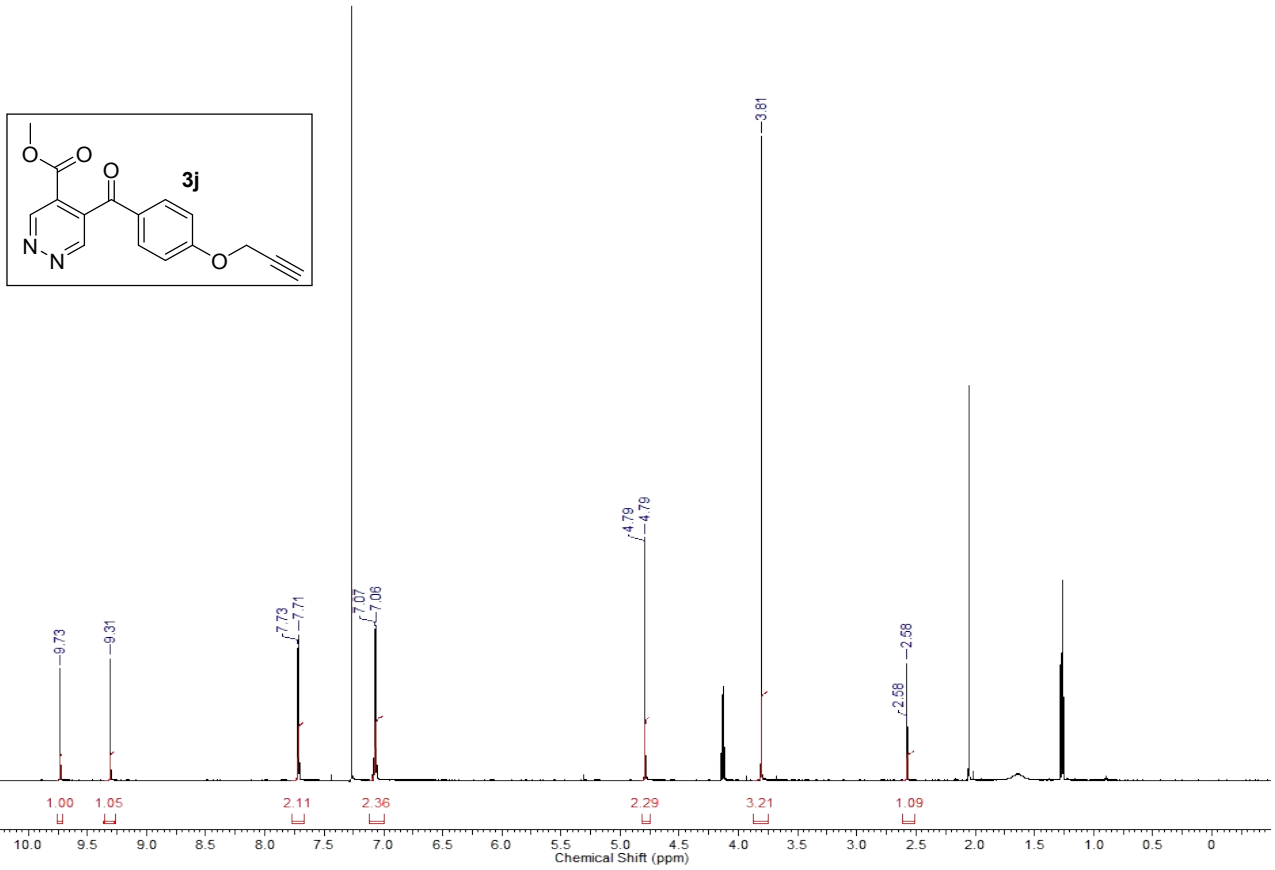

Chemical Shift (ppm)

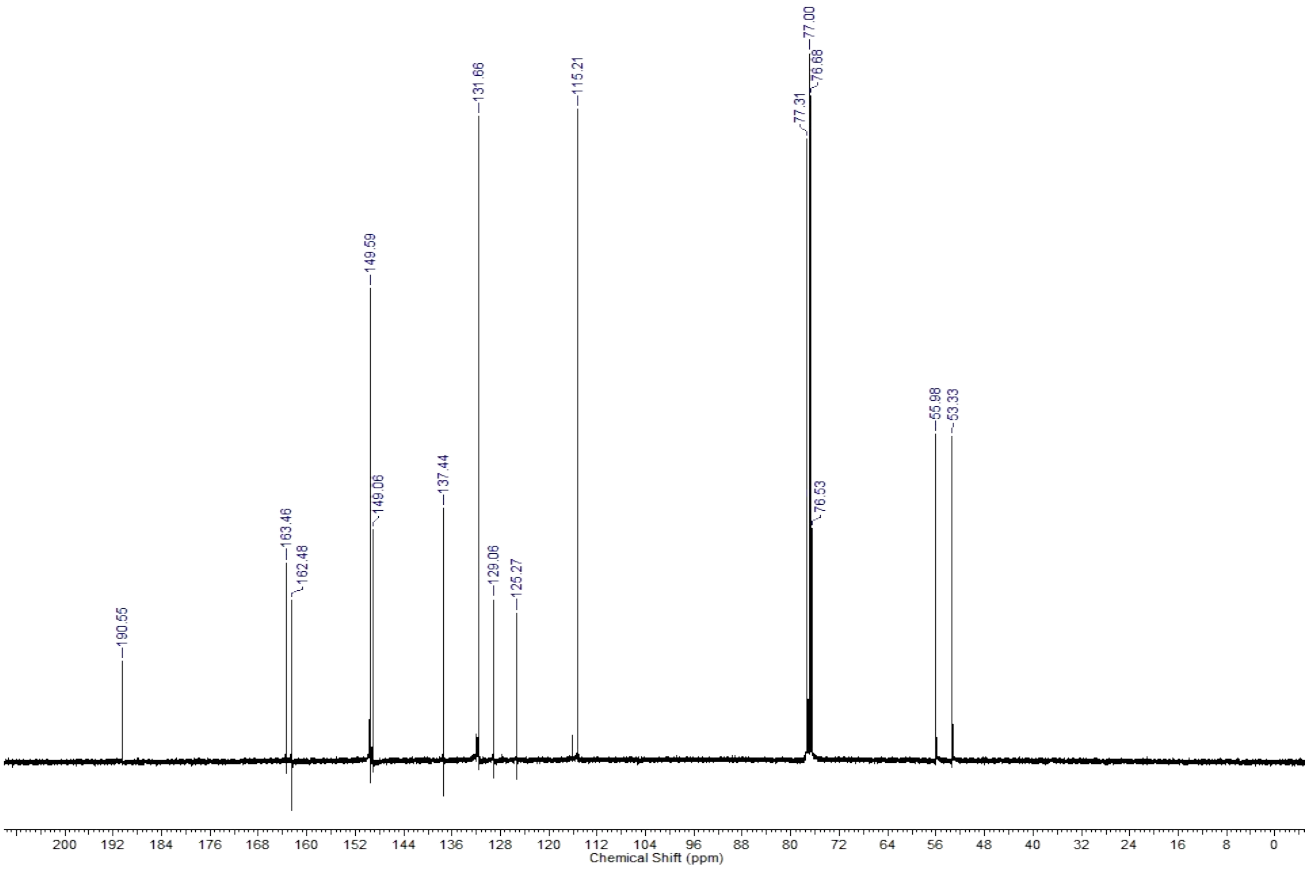

O
O
O
O
Me
N=N

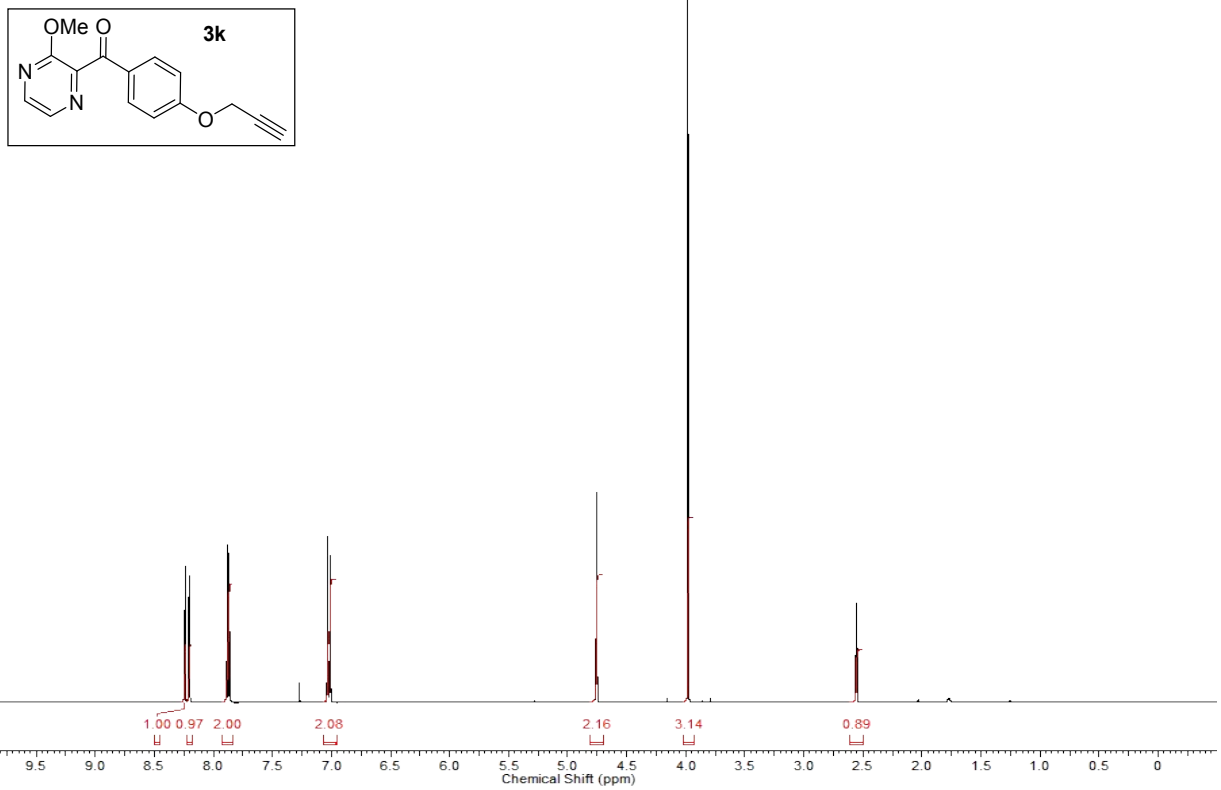
3i"

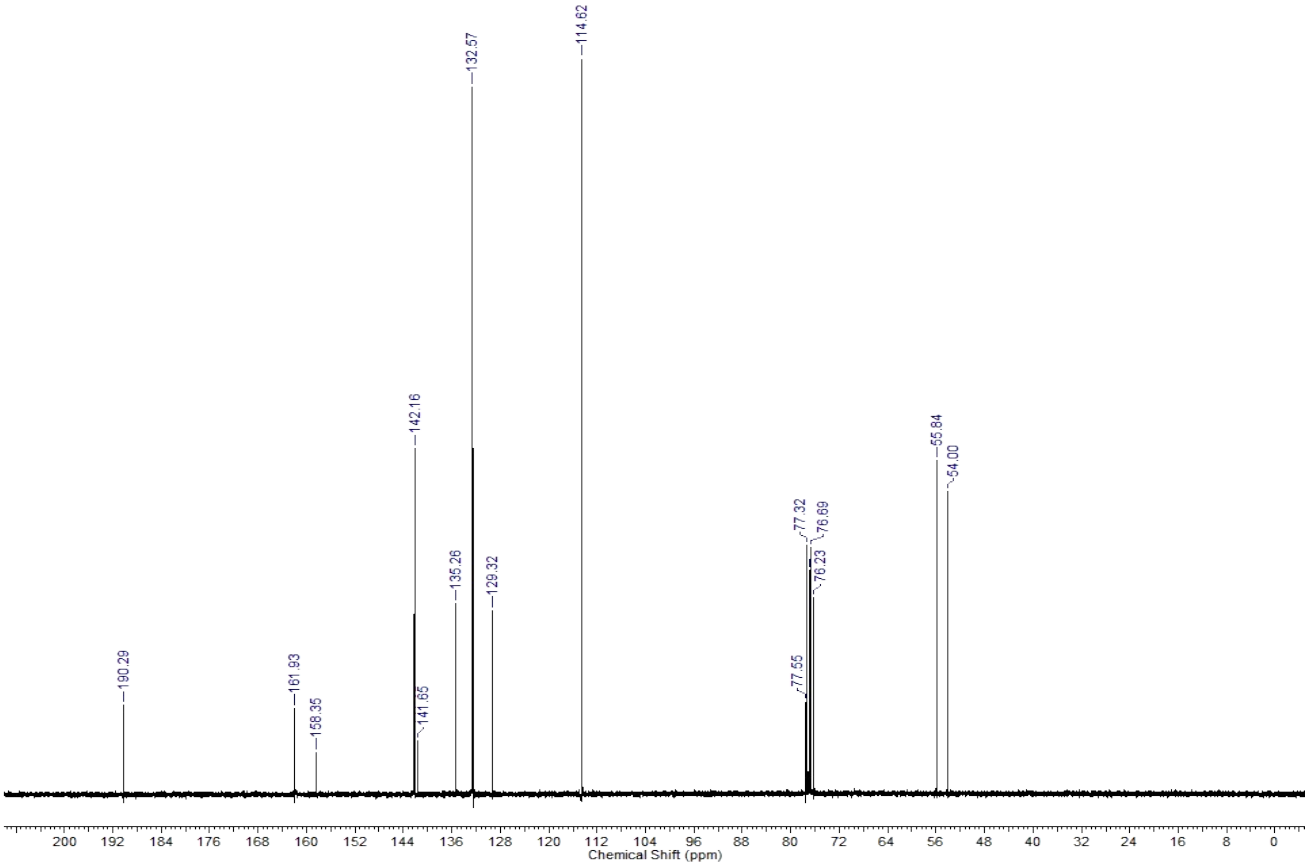
2.67
9.25
7.72
7.70
7.67
7.66
7.27
7.01
7.03
7.00
4.78
4.76
4.76
2.58
2.57
1.00
1.91
1.91
3.85
1.87
1.97
2.85
1.82
Chemical Shift (ppm)

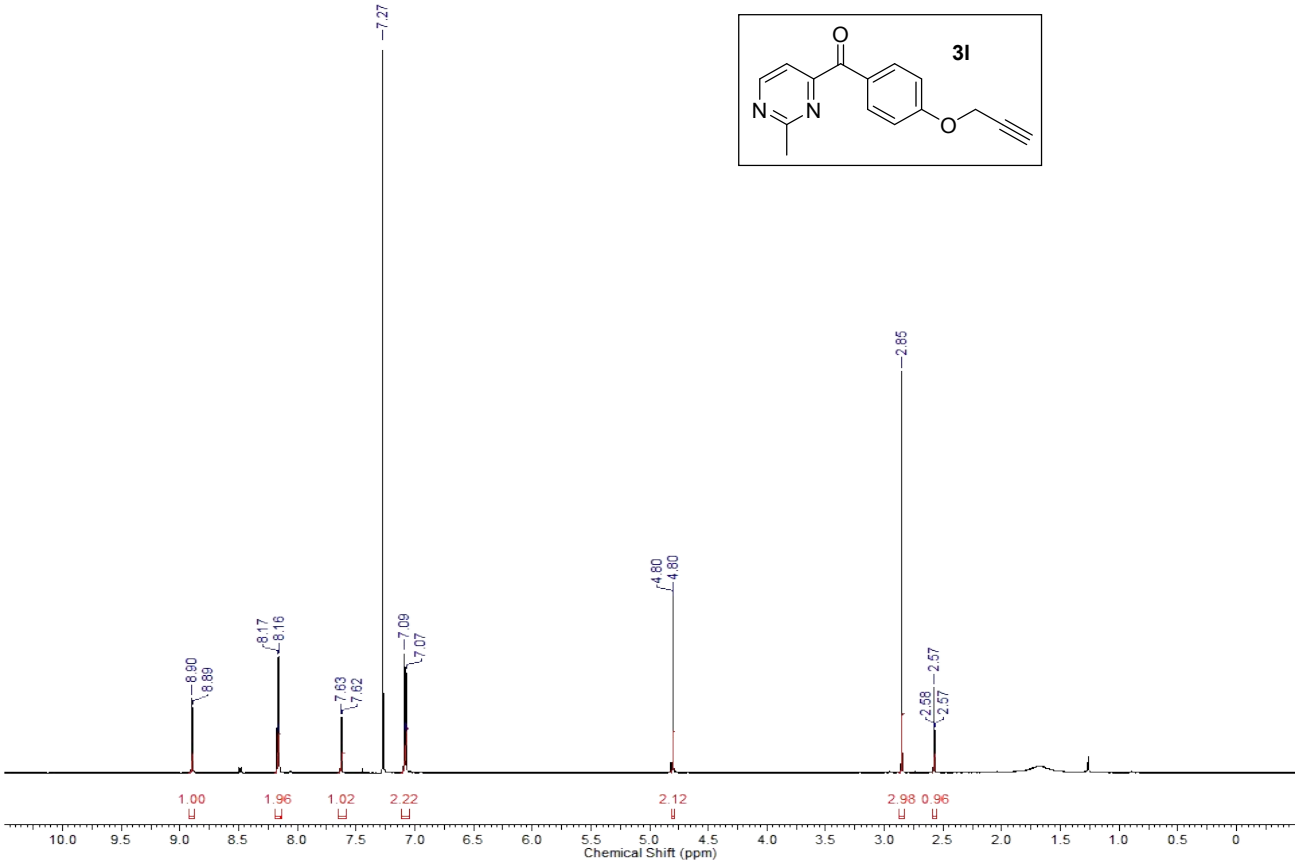

77.31
77.00
76.68
132.61
162.59
115.06
76.52
115.20
56.01
20.70
192.17
191.04
157.13
147.29
133.91
131.73
128.80
136.52
Chemical Shift (ppm)

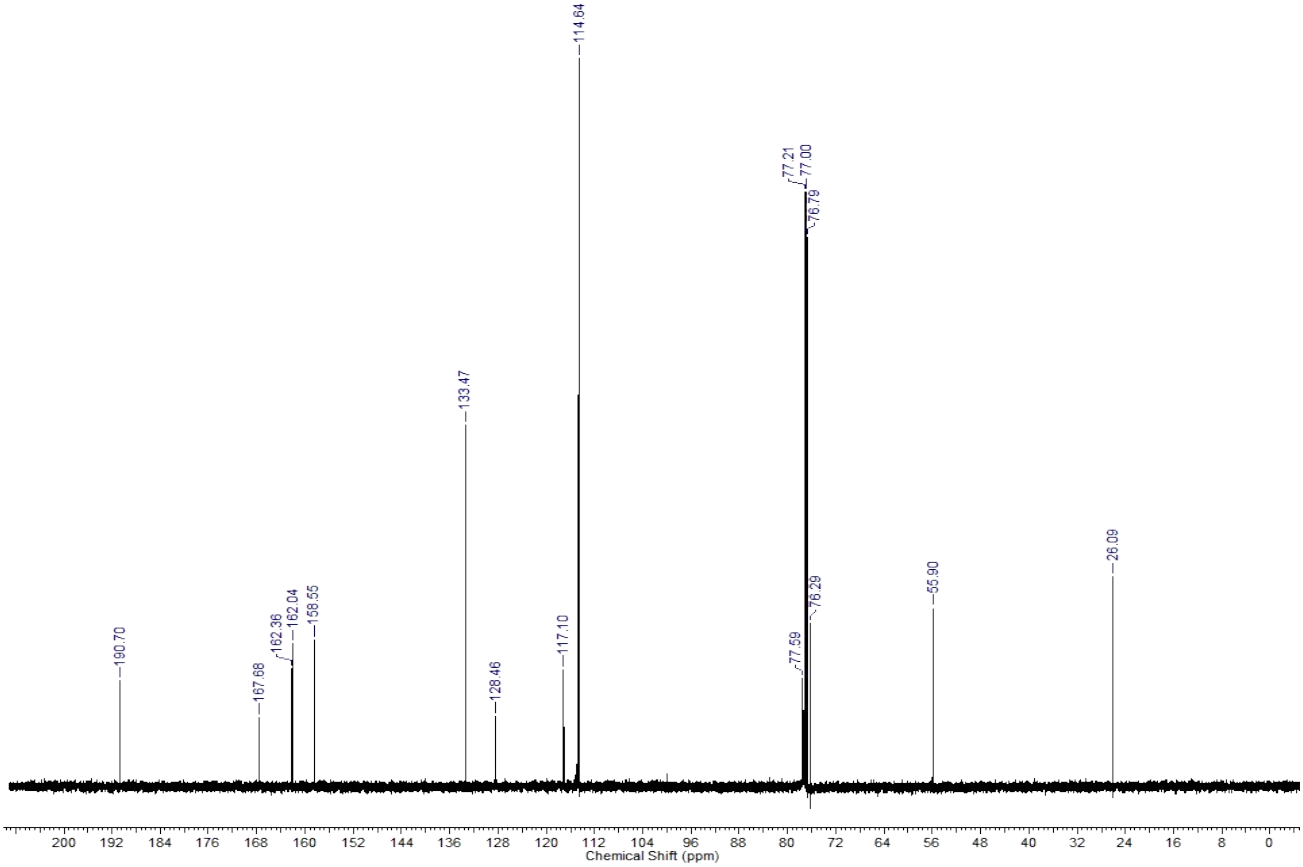

3j
9.73
9.31
7.73
7.71
7.07
7.06
4.79
4.79
3.81
2.58
2.58
1.00
1.05
2.11
2.36
2.29
3.21
1.09
Chemical Shift (ppm)

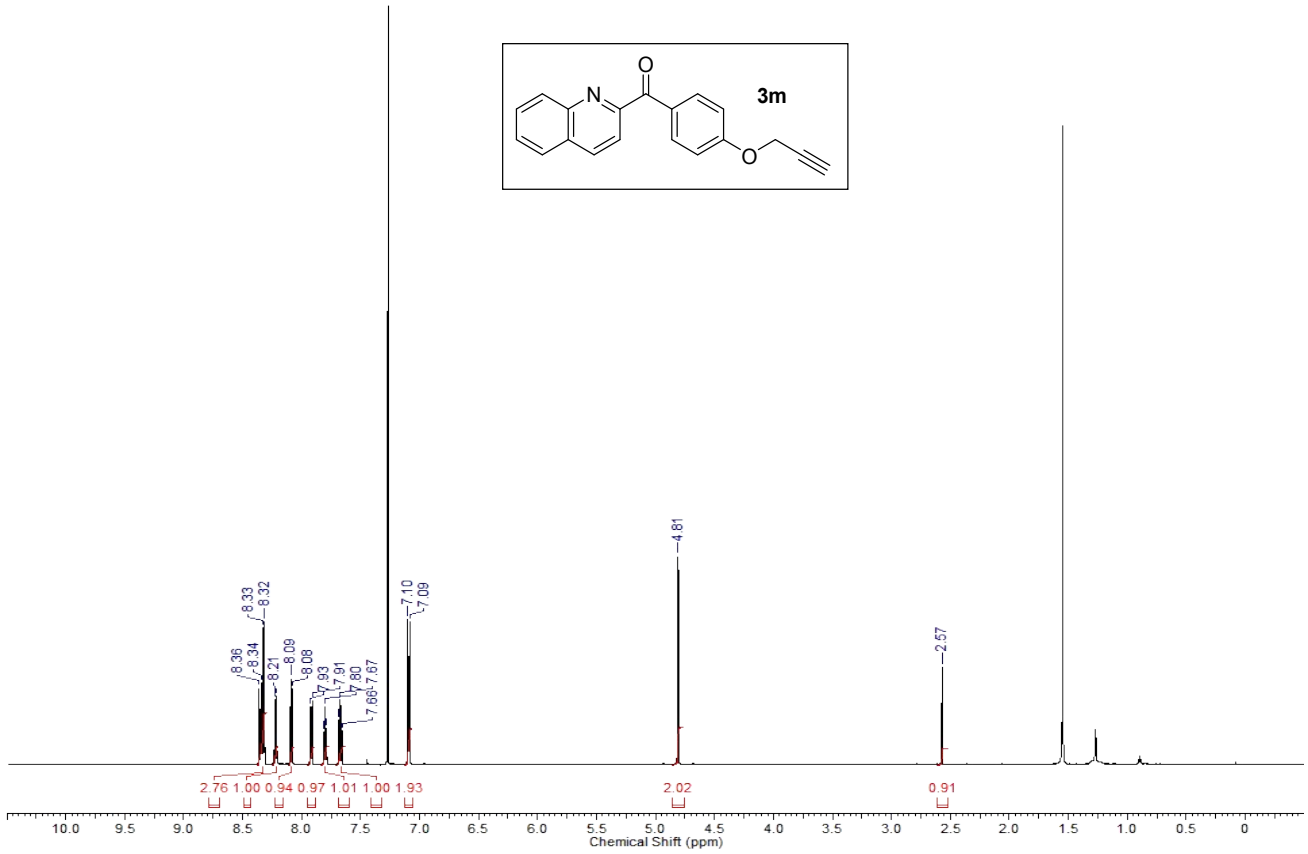

190.55
163.46
162.48
149.59
149.06
137.44
131.66
129.06
125.27
115.21
77.00
76.68
77.31
76.53
55.98
53.33
Chemical Shift (ppm)

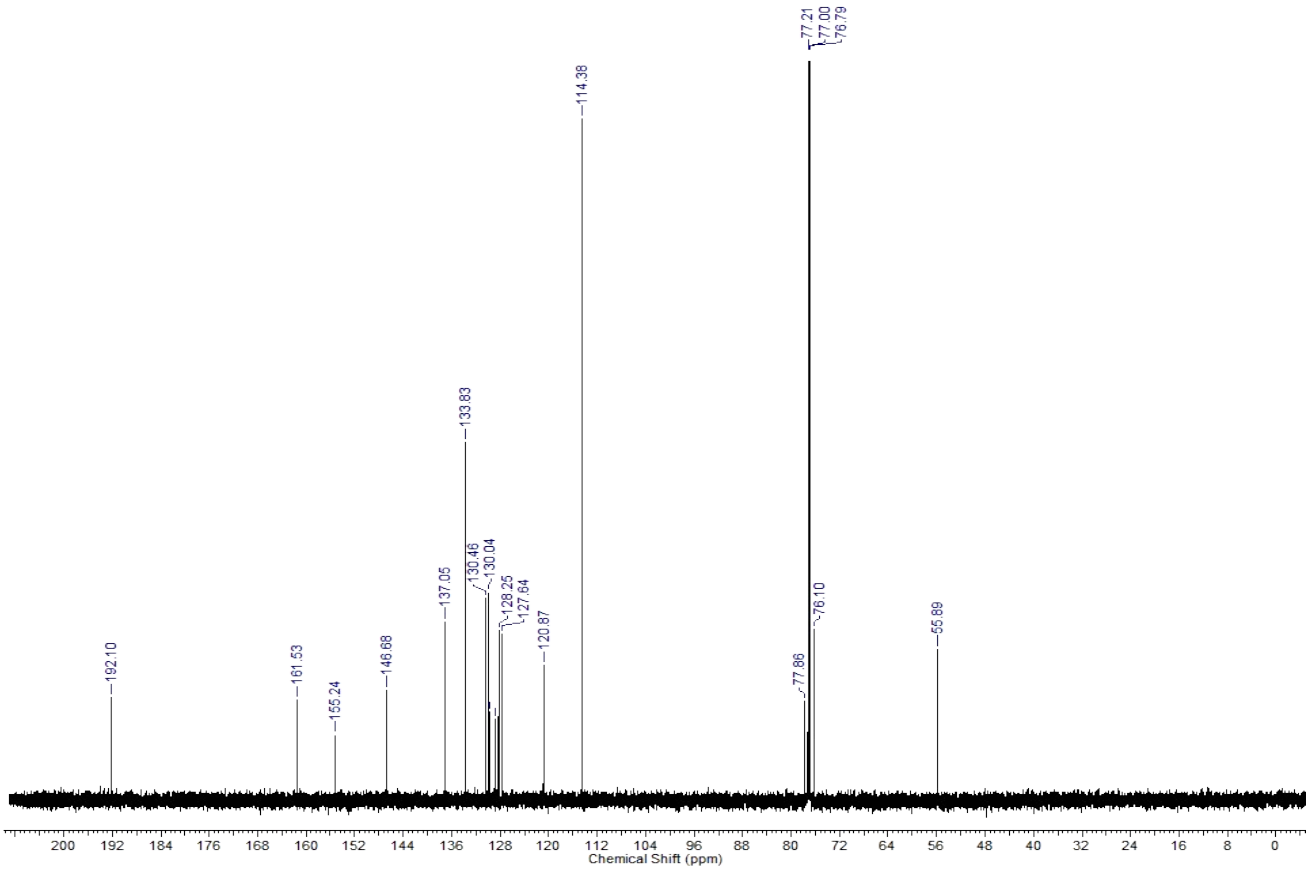

OMe O
3k
N
N
O
1.00 0.97 2.00 2.08 2.16 3.14 0.89
Chemical Shift (ppm)

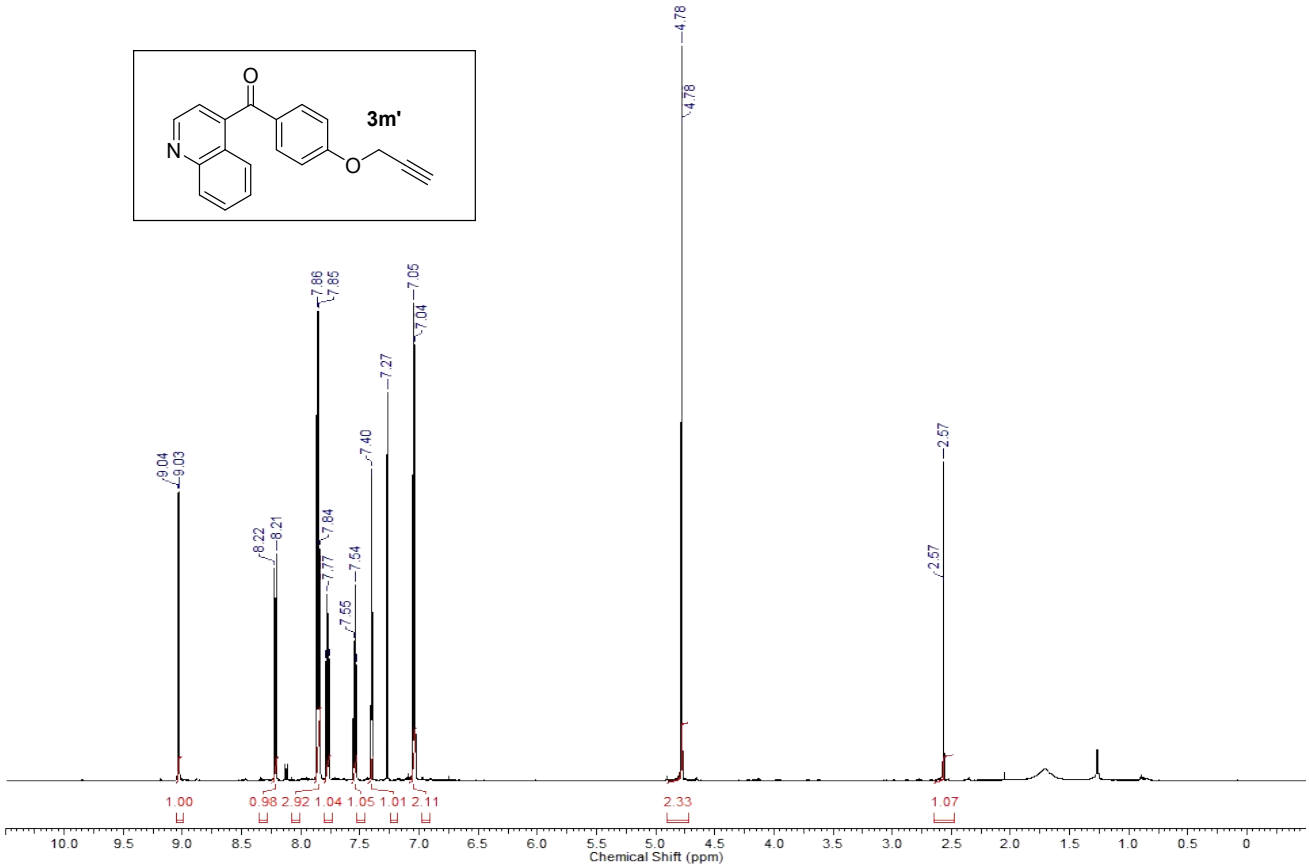

190.29
161.93
158.35
142.16
141.65
135.26
132.57
129.32
114.62
77.32
76.69
76.23
77.55
55.84
54.00
Chemical Shift (ppm)

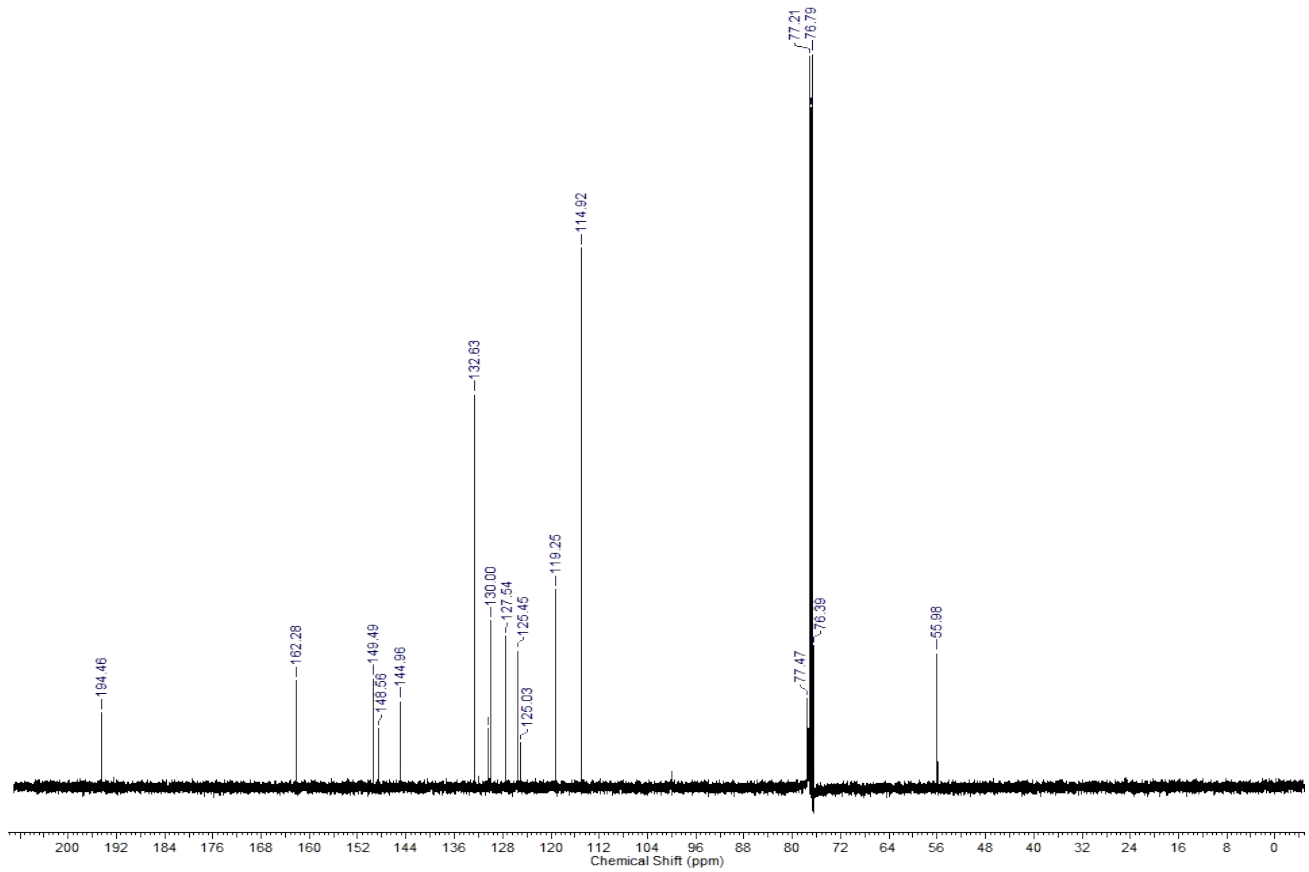

3l
7.27
8.90
8.89
8.17
8.16
7.63
7.62
7.09
7.07
4.80
4.80
2.85
2.58
2.57
2.57
1.00
1.96
1.02
2.22
2.12
2.98
0.96
Chemical Shift (ppm)

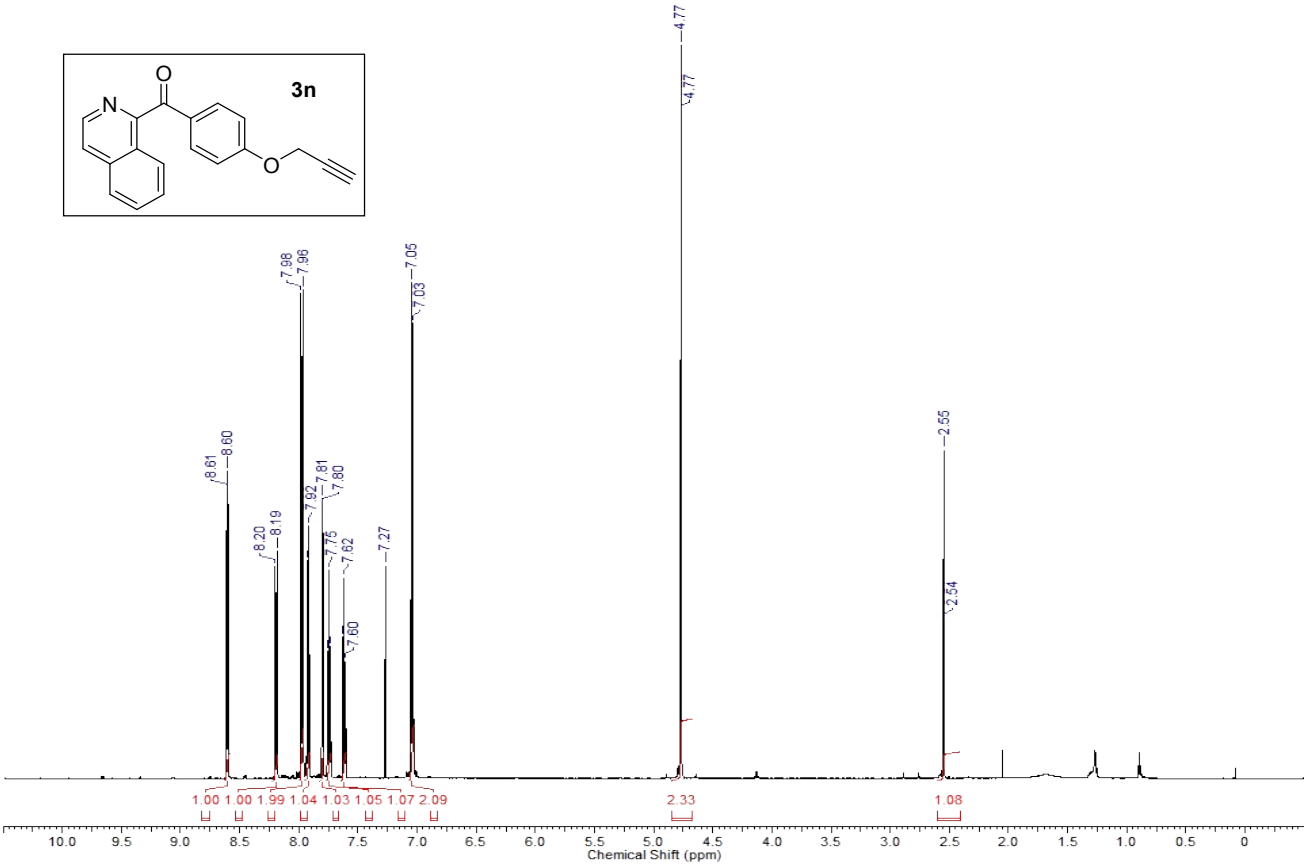

190.70
167.68
162.36
162.04
158.55
133.47
128.46
117.10
114.64
77.21
77.00
76.79
77.59
76.29
55.90
26.09
Chemical Shift (ppm)

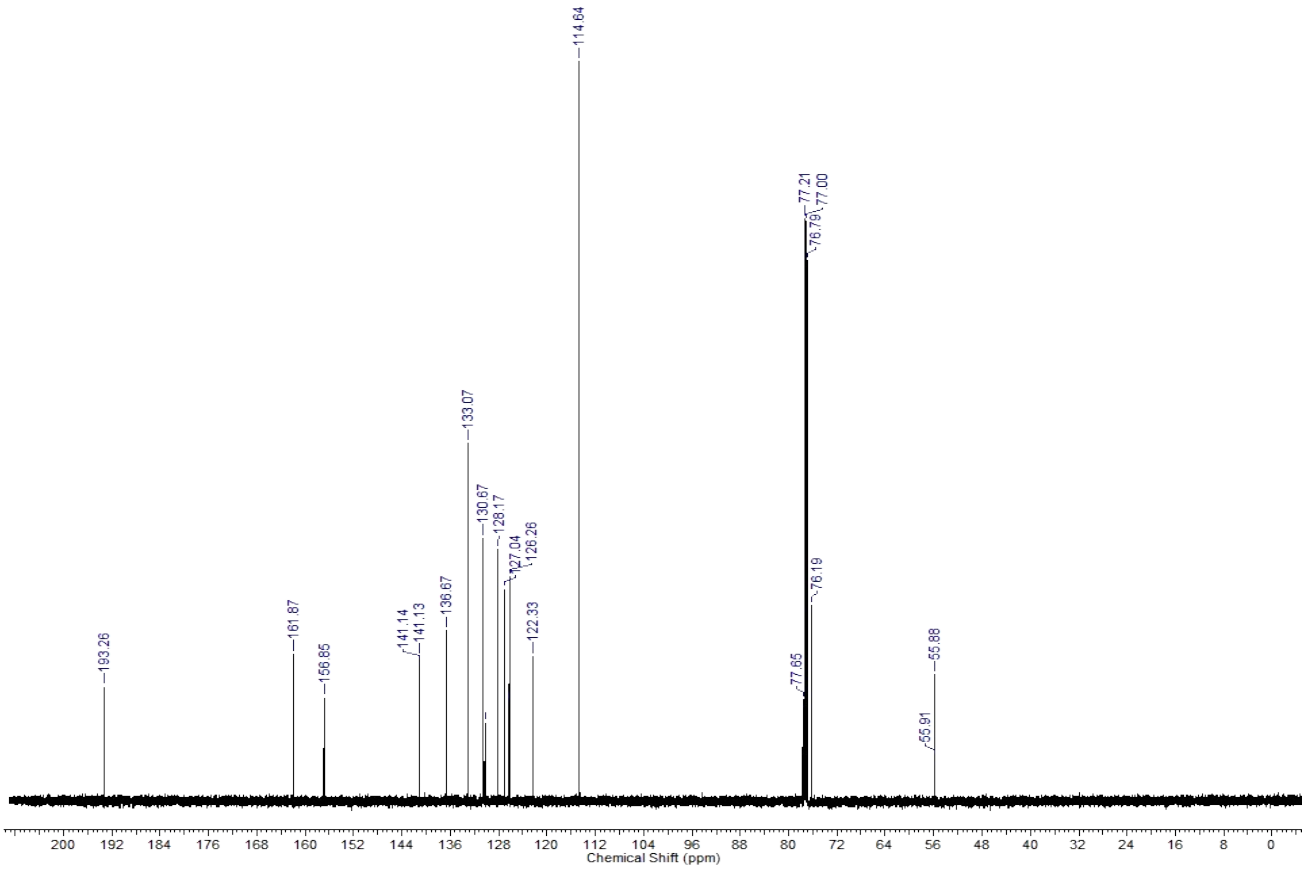

3m
8.36
8.34
8.33
8.32
8.21
8.09
8.08
7.93
7.91
7.80
7.67
7.66
7.10
7.09
4.81
2.57
2.76 1.00 0.94 0.97 1.01 1.00 1.93
2.02
0.91
Chemical Shift (ppm)

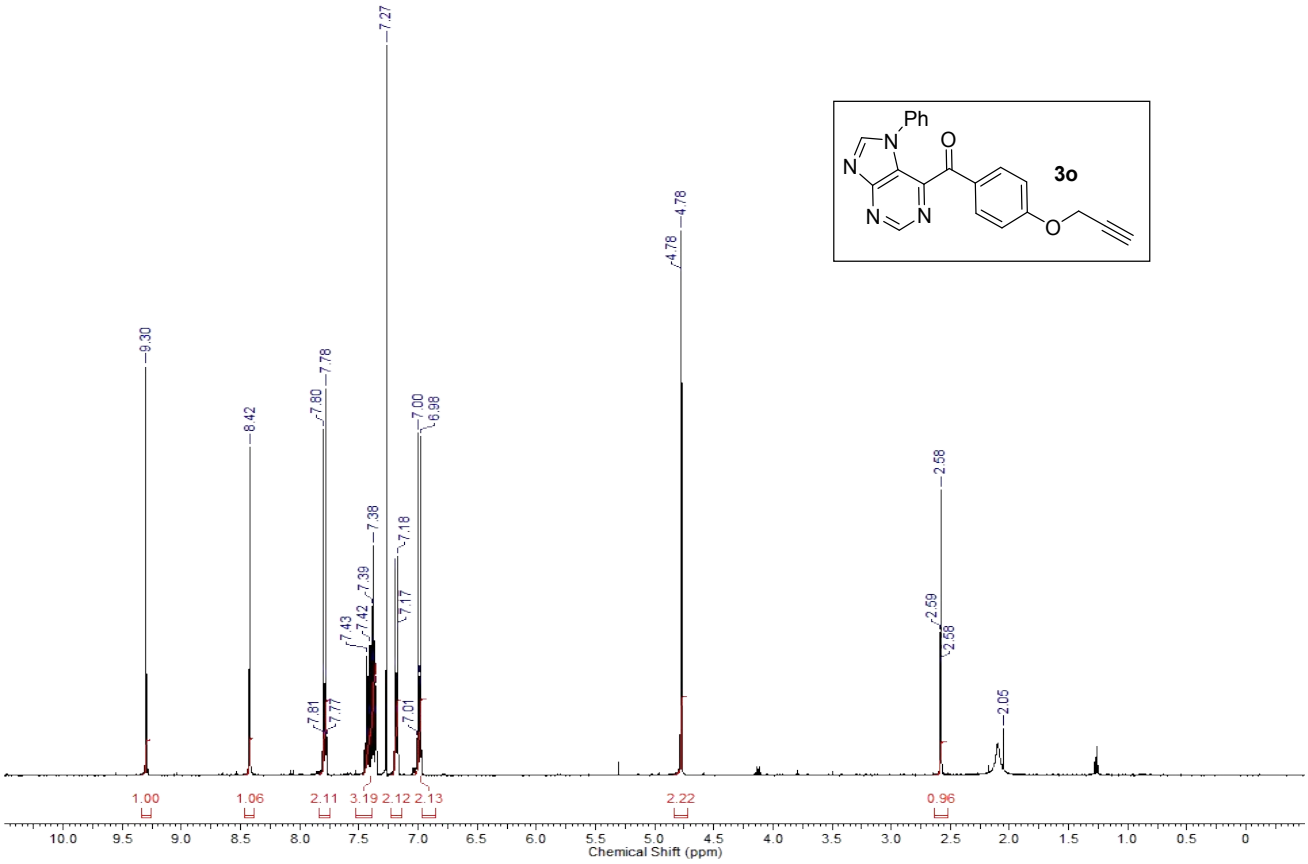

192.10
161.53
155.24
146.68
137.05
133.83
130.46
130.04
128.25
127.64
120.87
114.38
77.21
77.00
76.79
77.86
76.10
55.89
Chemical Shift (ppm)

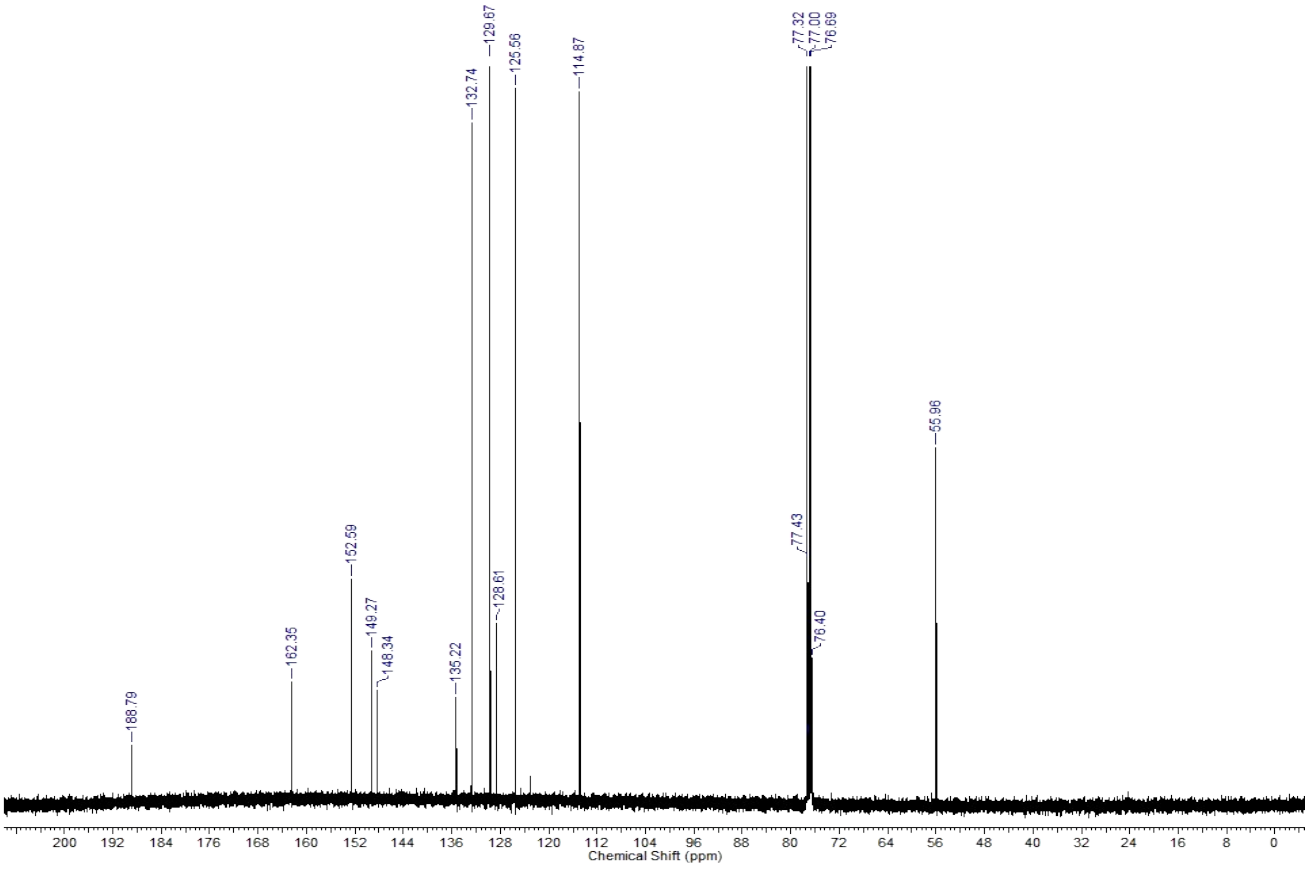

3m'
O
N
O
4.78
4.78
7.86
7.85
7.05
7.04
7.27
7.40
9.04
9.03
8.22
8.21
7.84
7.77
7.54
7.55
2.57
2.57
1.00
0.98
2.92
1.04
1.05
1.01
2.11
2.33
1.07
Chemical Shift (ppm)

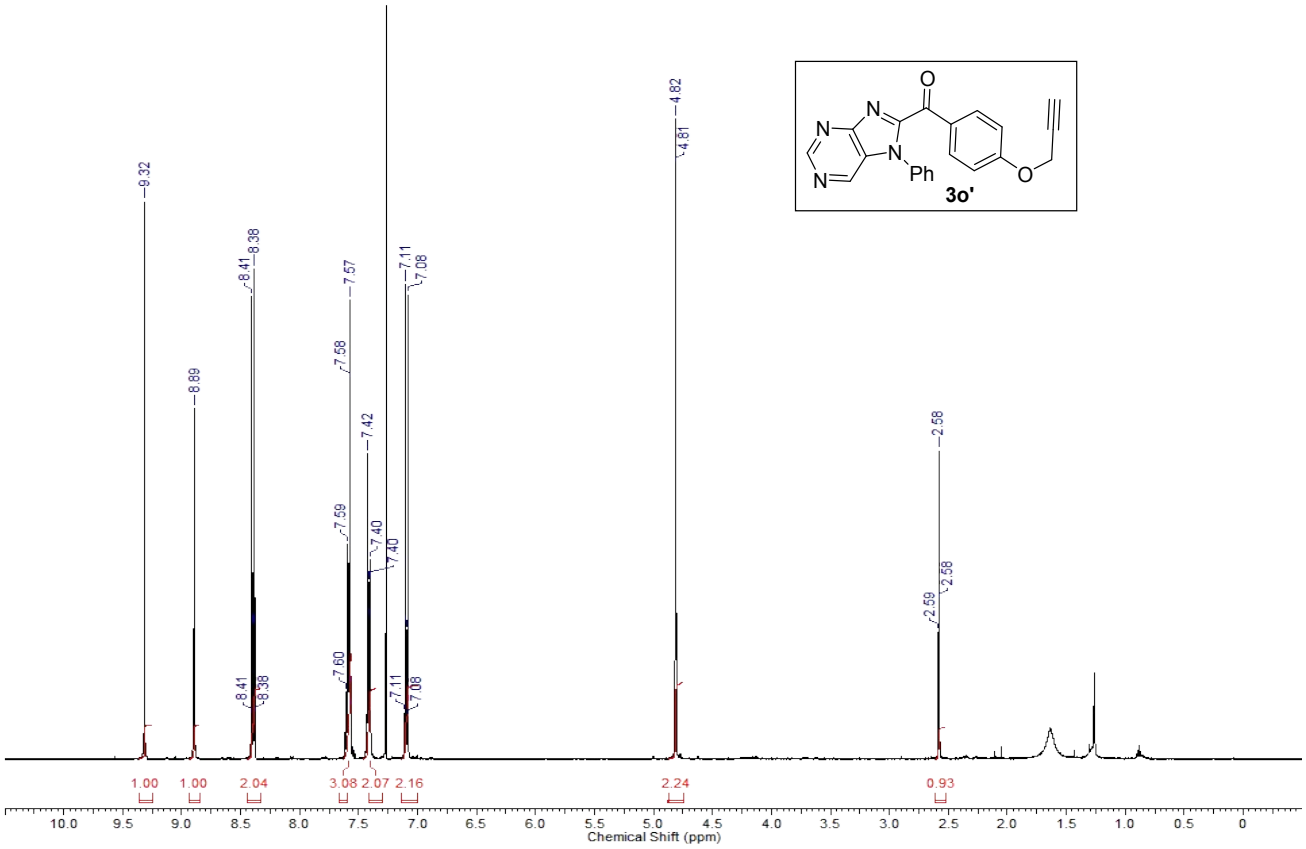

77.21
76.79
114.92
132.63
119.25
130.00
127.54
125.45
76.39
55.98
194.46
162.28
149.49
148.56
144.96
125.03
77.47
Chemical Shift (ppm)

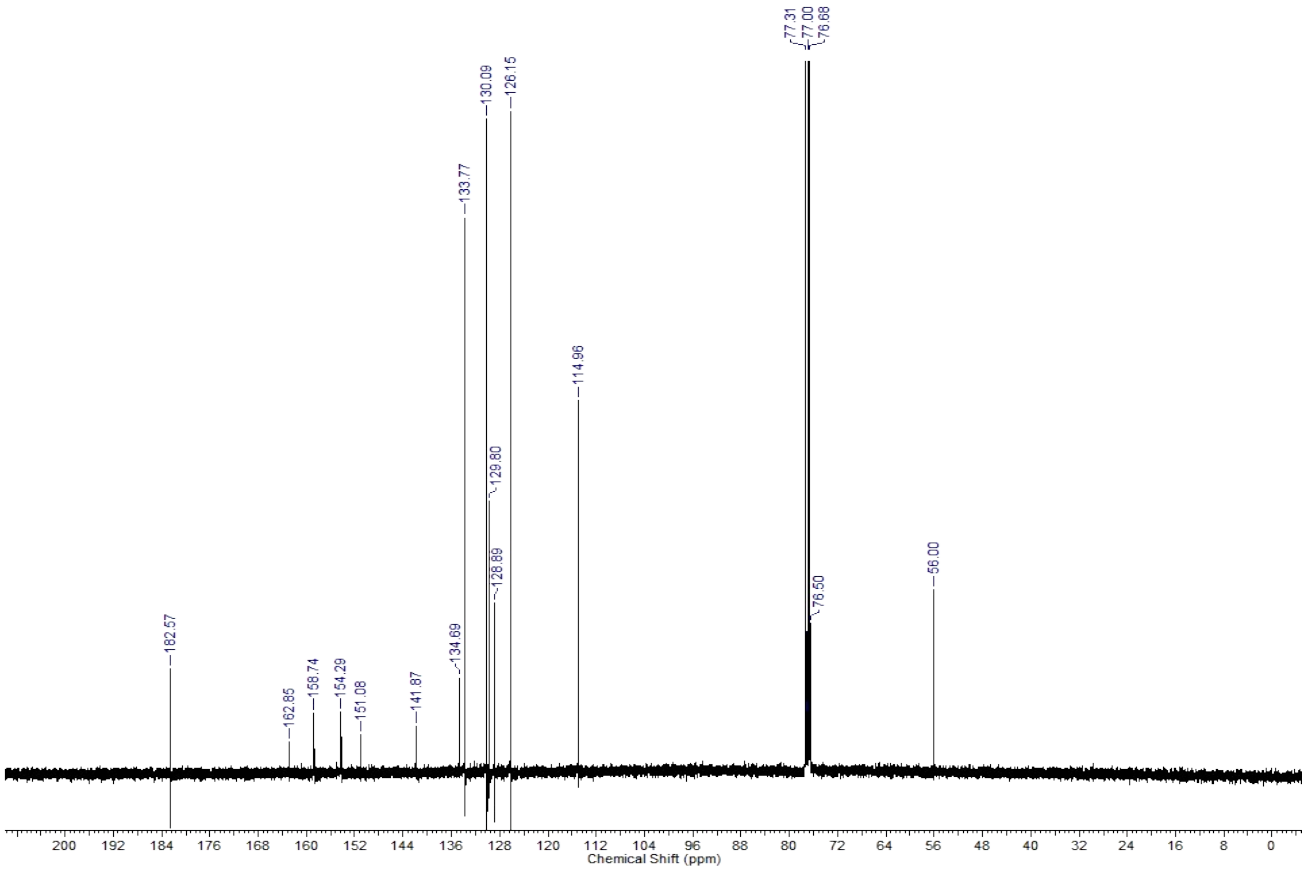

3n
O
N
O
4.77
4.77
7.98
7.96
7.05
7.03
8.61
8.60
8.20
8.19
7.92
7.81
7.80
7.75
7.62
7.27
7.60
2.55
2.54
1.00 1.00 1.99 1.04 1.03 1.05 1.07 2.09
2.33
1.08
Chemical Shift (ppm)

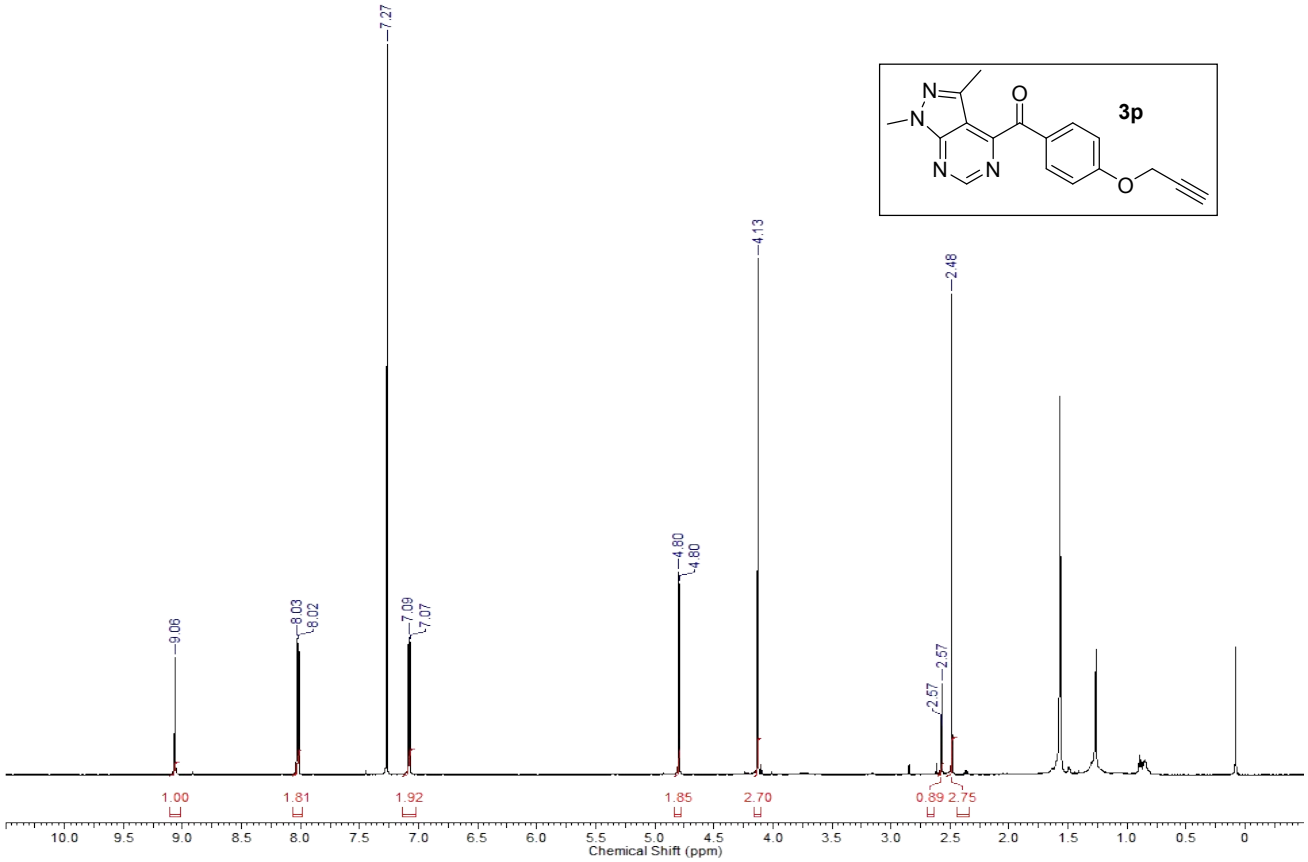

114.64
77.21
77.00
76.79
133.07
130.67
128.17
127.04
126.26
76.19
136.67
141.14
141.13
161.87
156.85
122.33
193.26
77.65
55.88
55.91
Chemical Shift (ppm)

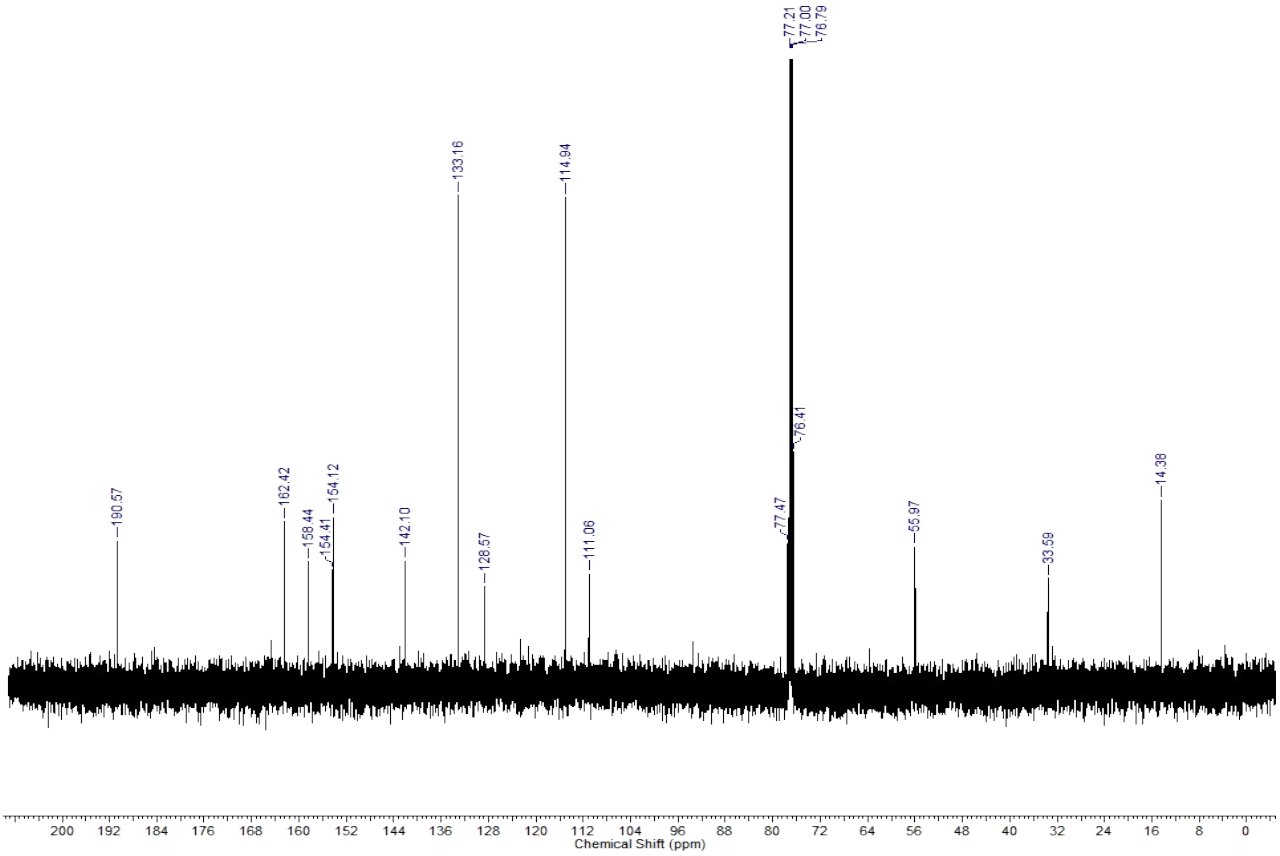

Ph
N
N
N
N
O
O
3o
9.30
8.42
7.81
7.80
7.78
7.77
7.43
7.42
7.39
7.38
7.27
7.18
7.17
7.01
7.00
6.98
4.78
4.78
2.59
2.58
2.58
2.05
1.00
1.06
2.11
3.19
2.12
2.13
2.22
0.96
Chemical Shift (ppm)

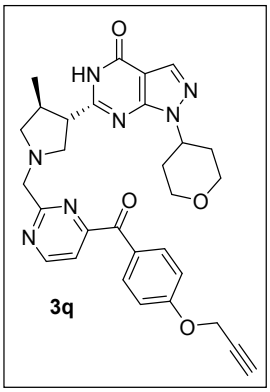

188.79
162.35
152.59
149.27
148.34
135.22
132.74
129.67
128.61
125.56
114.87
77.43
77.32
77.00
76.69
76.40
55.96
Chemical Shift (ppm)


3o'
9.32
8.89
8.41
8.38
7.58
7.57
7.42
7.59
7.40
7.11
7.08
4.82
4.81
2.58
2.59
1.00
1.00
2.04
3.08
2.07
2.16
2.24
0.93
Chemical Shift (ppm)

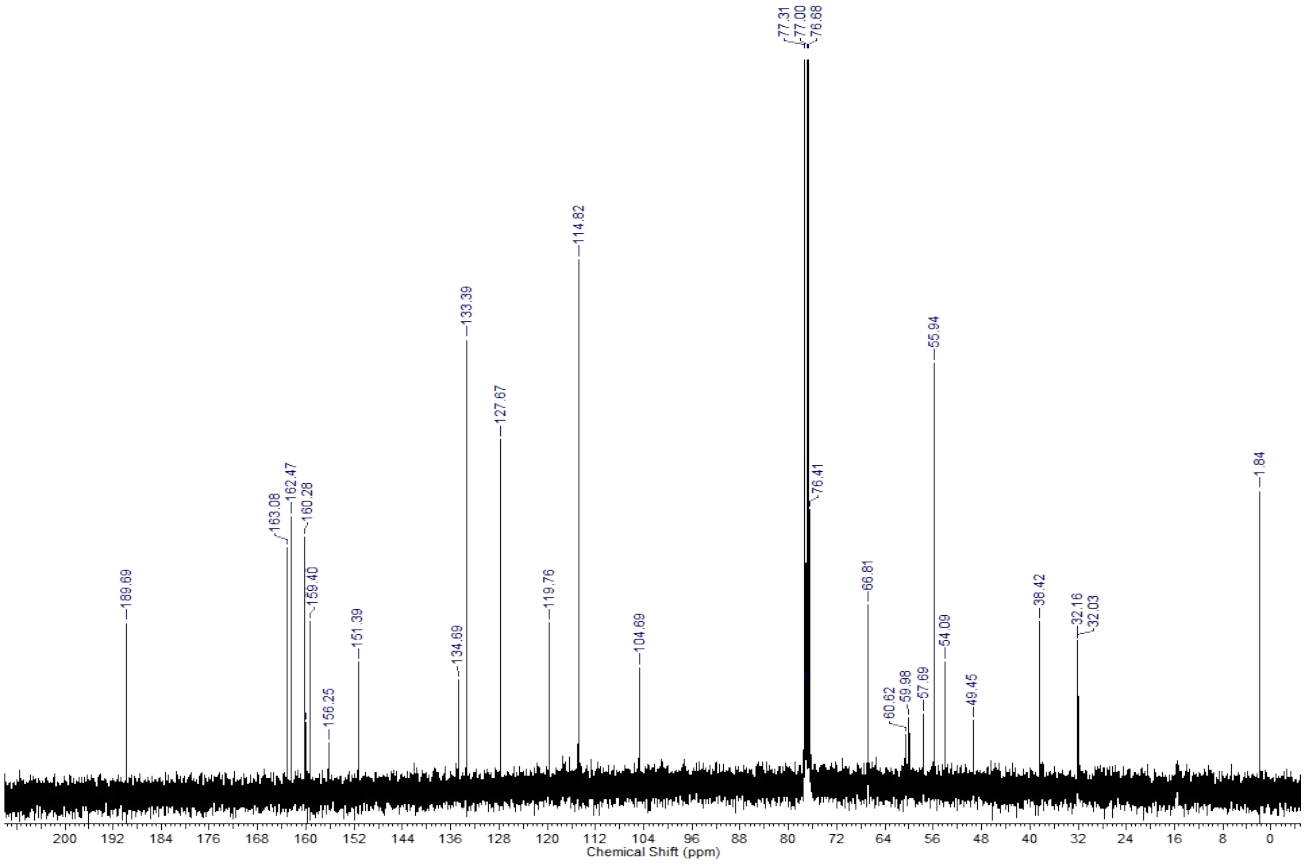

182.57
162.85
158.74
154.29
151.08
141.87
134.69
133.77
130.09
129.80
128.89
126.15
114.96
77.31
77.00
76.68
76.60
56.00
Chemical Shift (ppm)

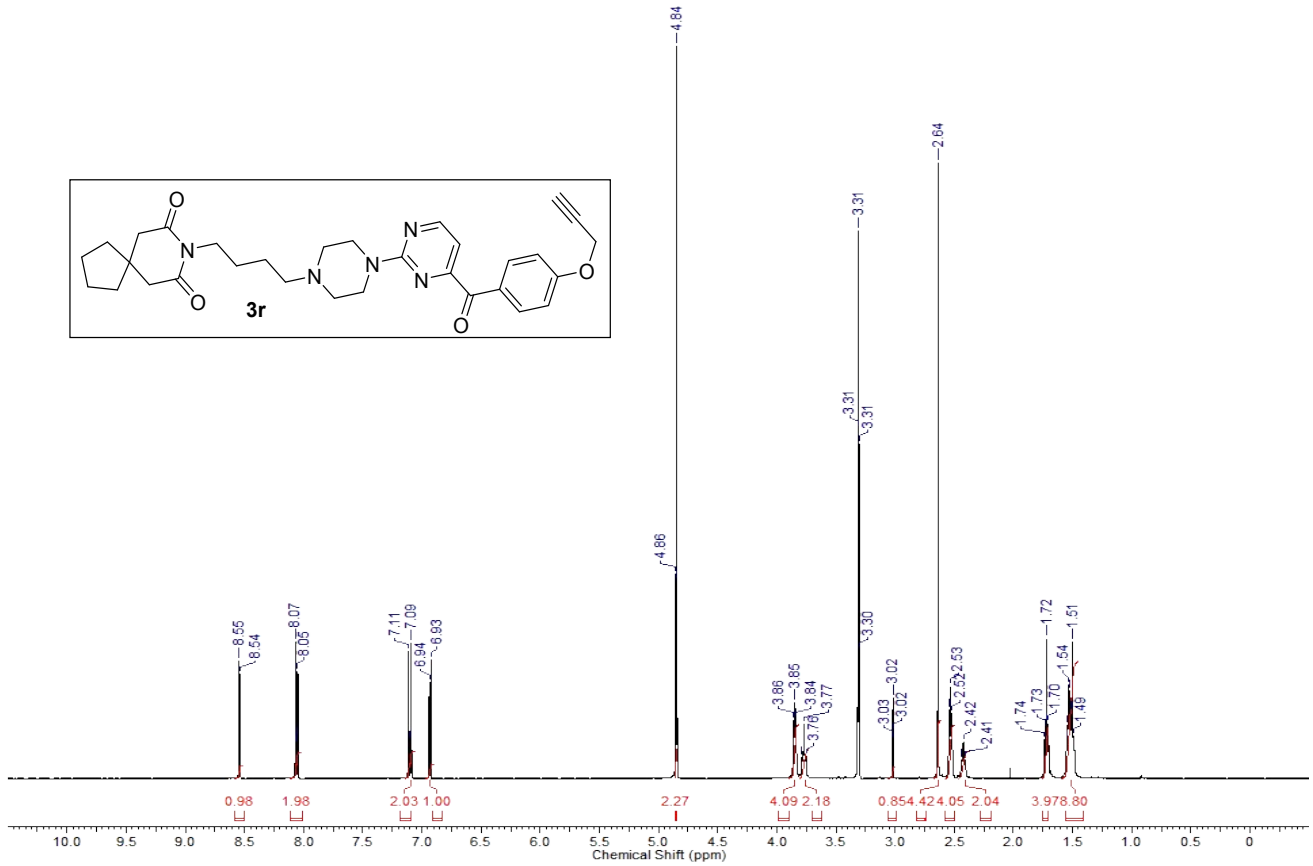

3p
9.06
8.03
8.02
7.27
7.09
7.07
4.80
4.80
4.13
2.57
2.57
2.48
1.00
1.81
1.92
1.85
2.70
0.89
2.75
Chemical Shift (ppm)

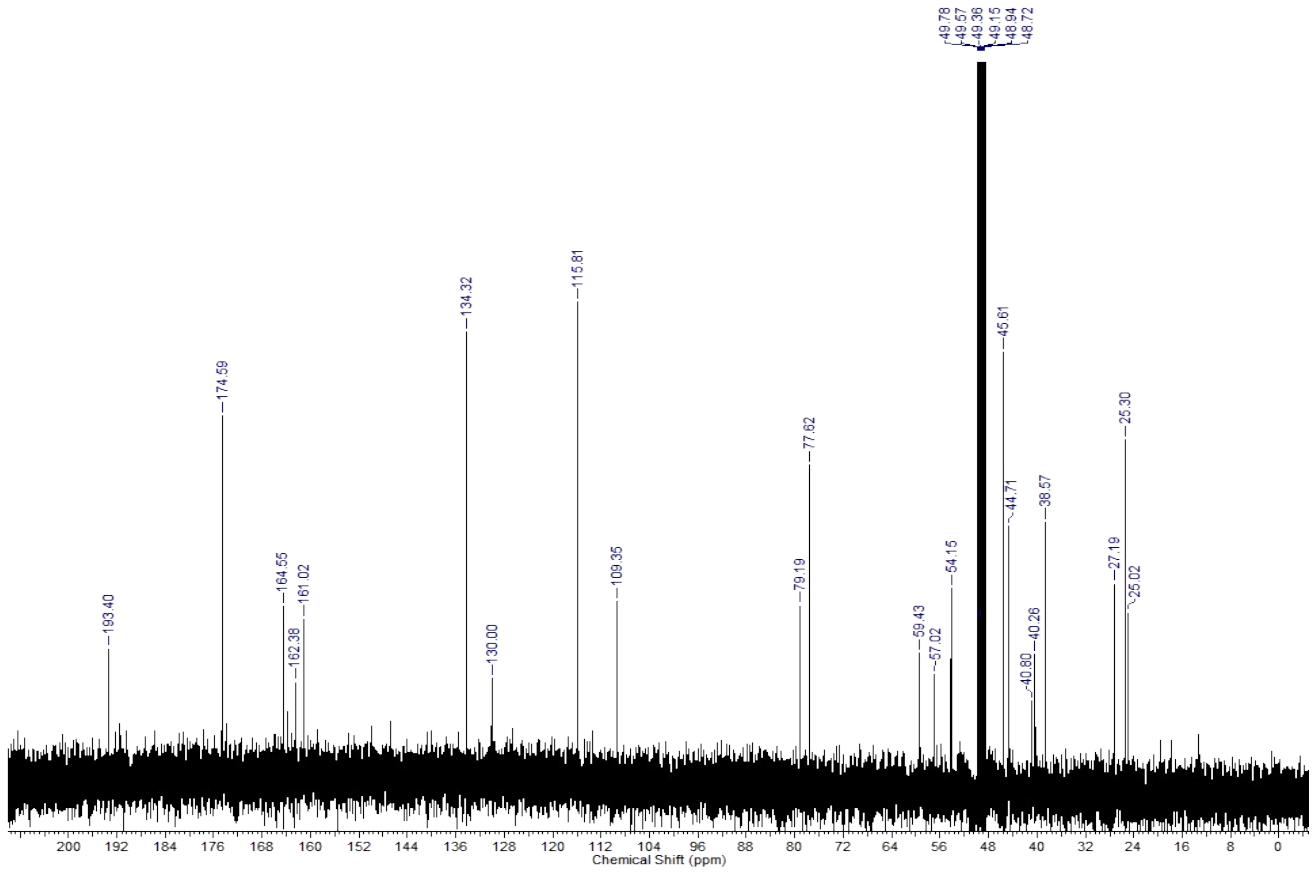

190.57
162.42
158.44
154.41
154.12
142.10
133.16
128.57
114.94
111.06
77.47
77.21
77.00
76.79
76.41
55.97
33.59
14.38
Chemical Shift (ppm)

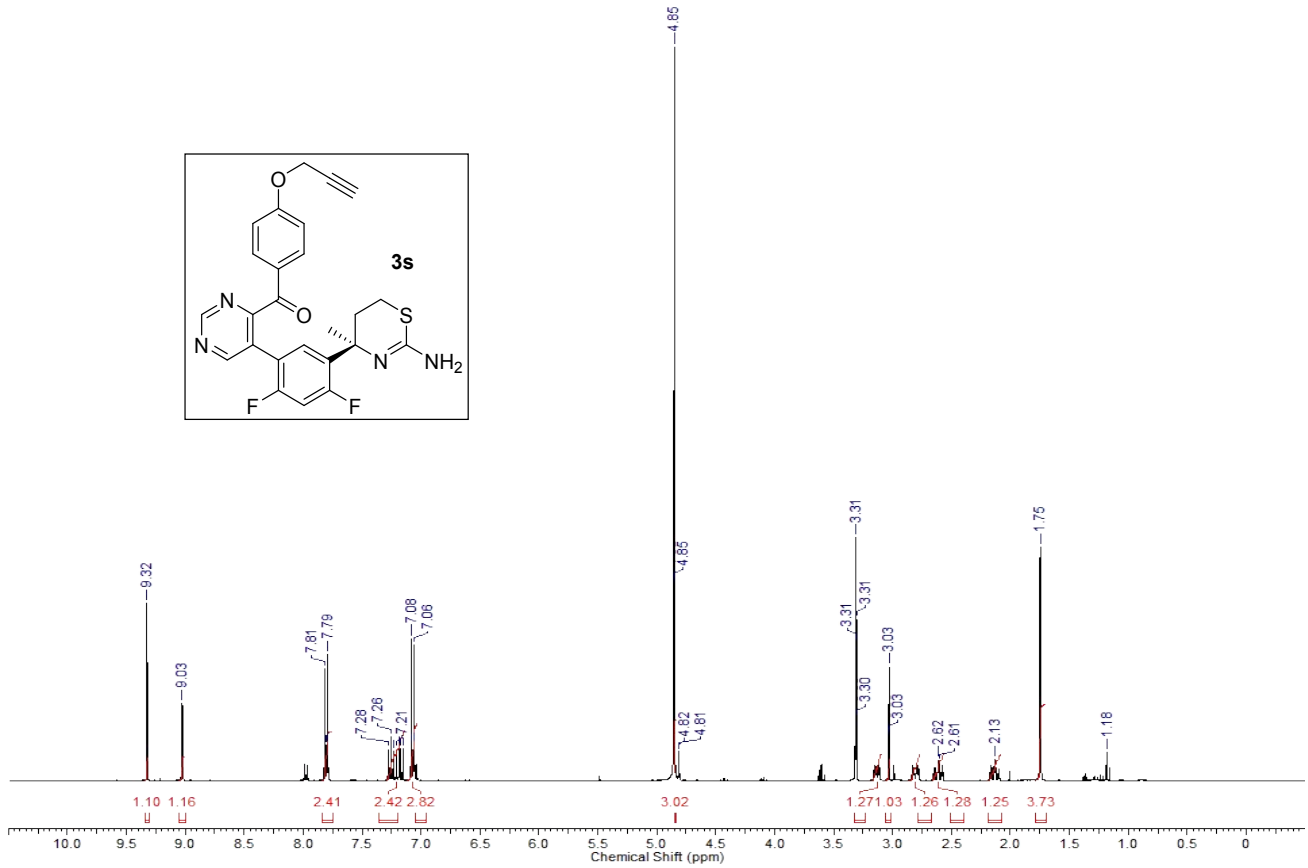

3q

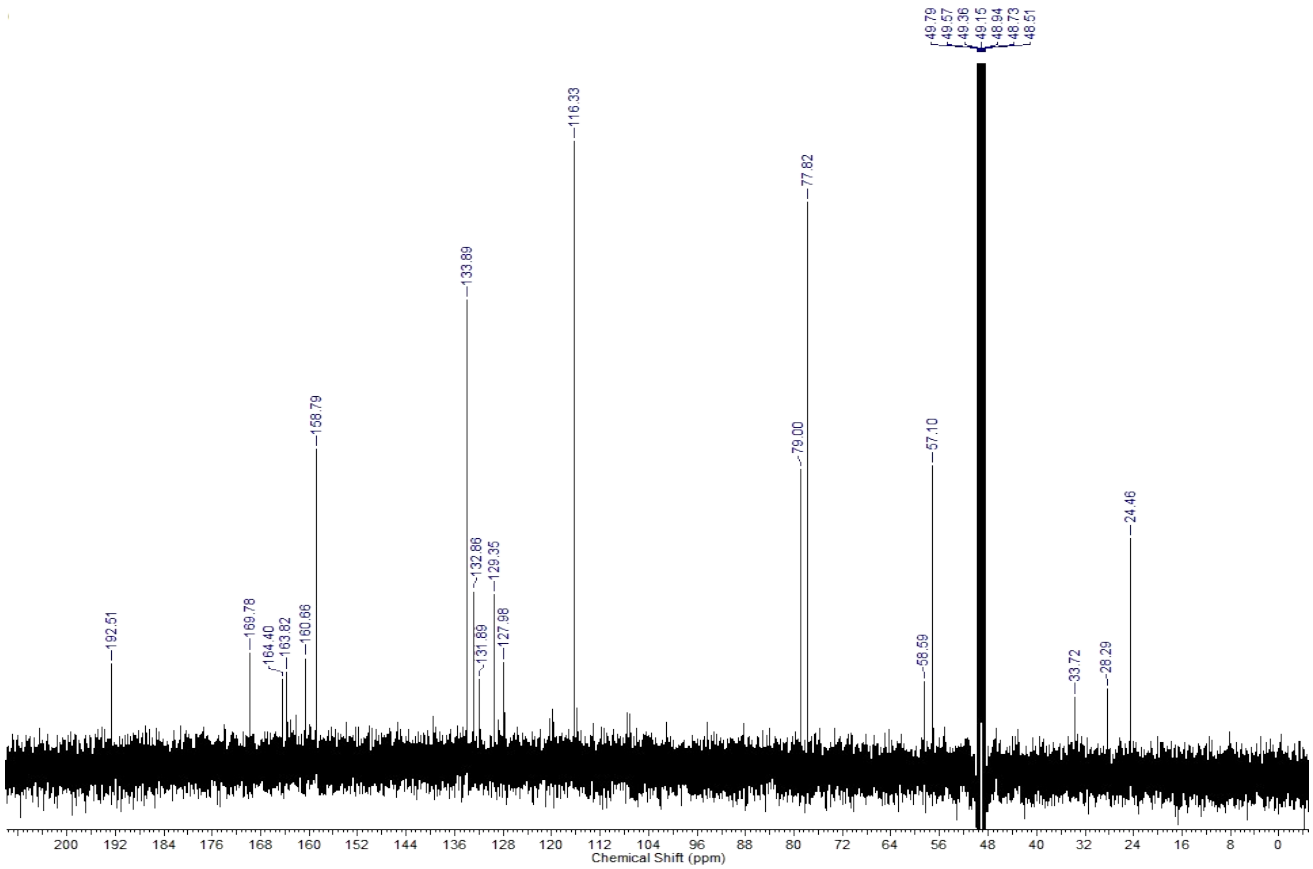
Chemical Shift (ppm)

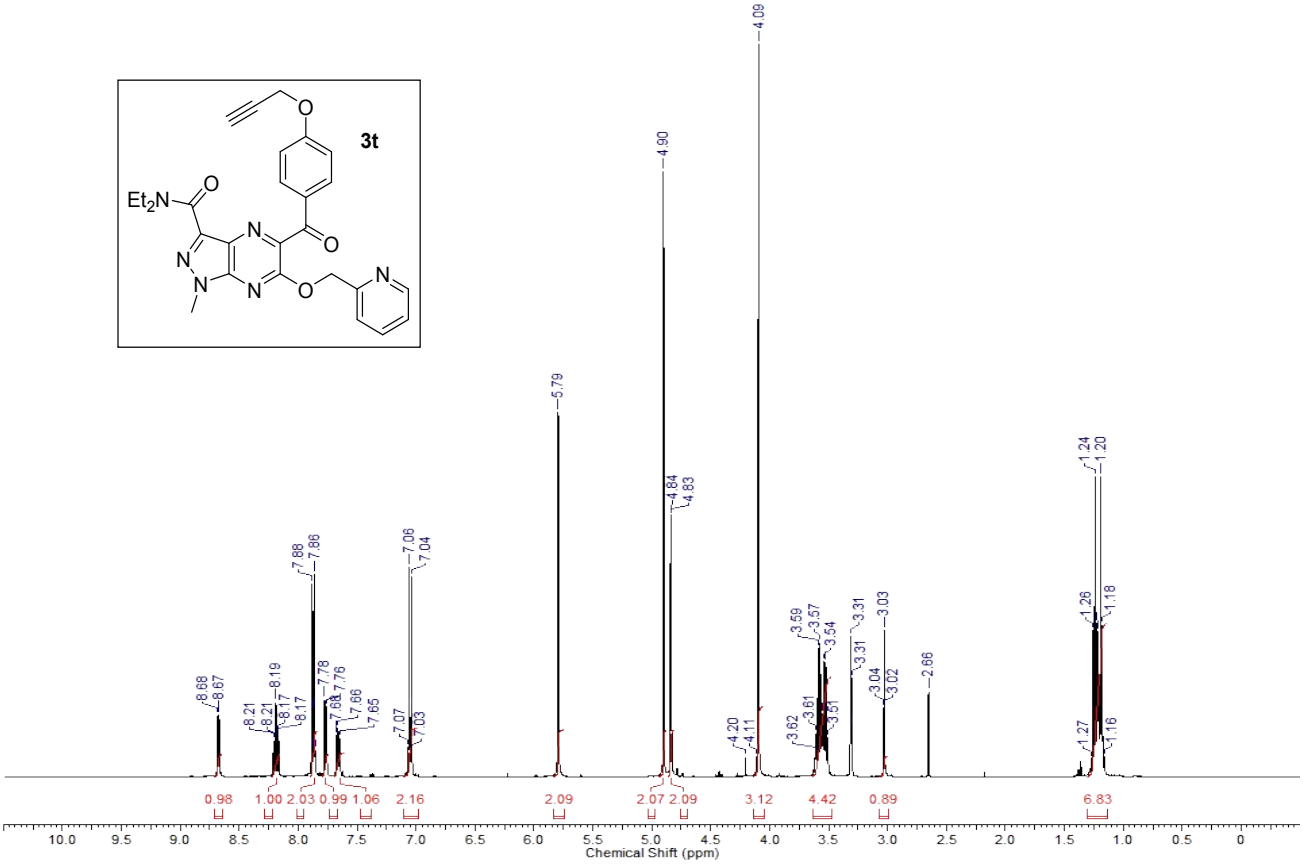

Chemical Shift (ppm)

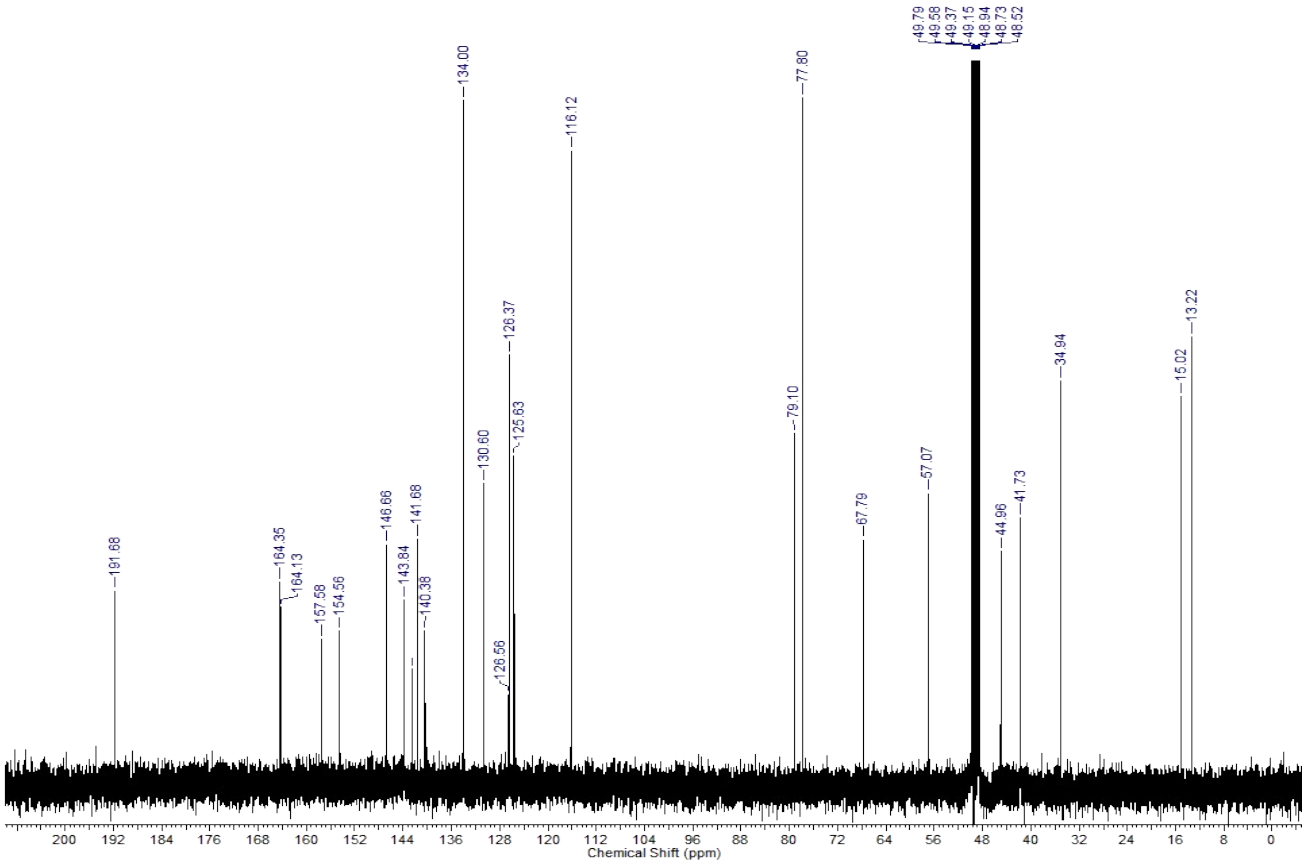

3r
Chemical Shift (ppm)

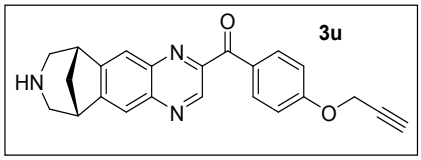

Chemical Shift (ppm)


3s
9.32
9.03
7.81
7.79
7.28
7.26
7.21
7.08
7.06
4.85
4.82
4.81
3.31
3.31
3.31
3.30
3.03
3.03
2.62
2.61
2.13
1.75
1.18
1.10 1.16
2.41
2.42 2.82
3.02
1.27 1.03 1.26 1.28 1.25 3.73
Chemical Shift (ppm)

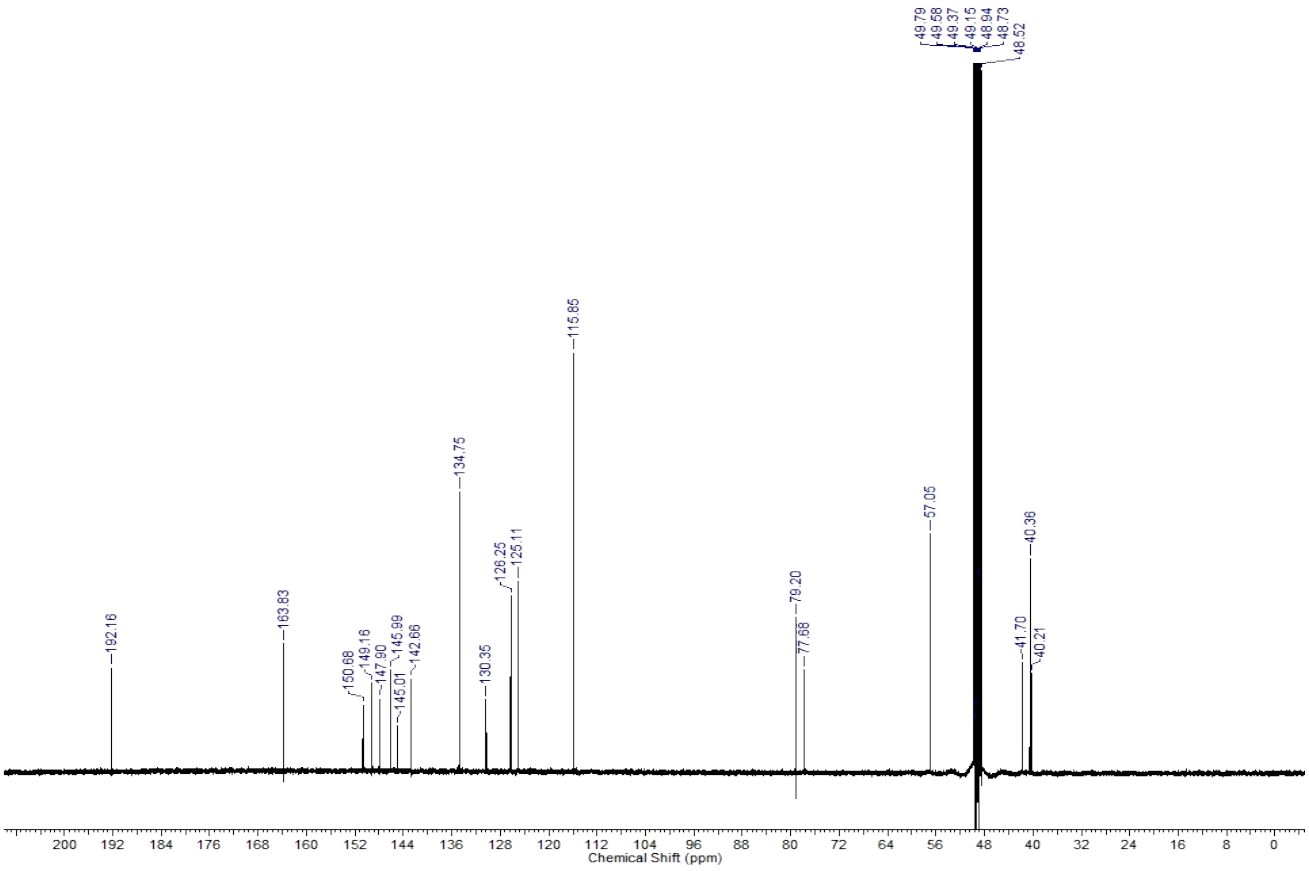

49.79
49.57
49.36
49.15
48.94
48.73
48.51
116.33
77.82
133.89
168.79
79.00
57.10
132.86
129.35
24.46
192.51
169.78
164.40
163.82
160.66
131.89
127.98
58.59
33.72
28.29
Chemical Shift (ppm)

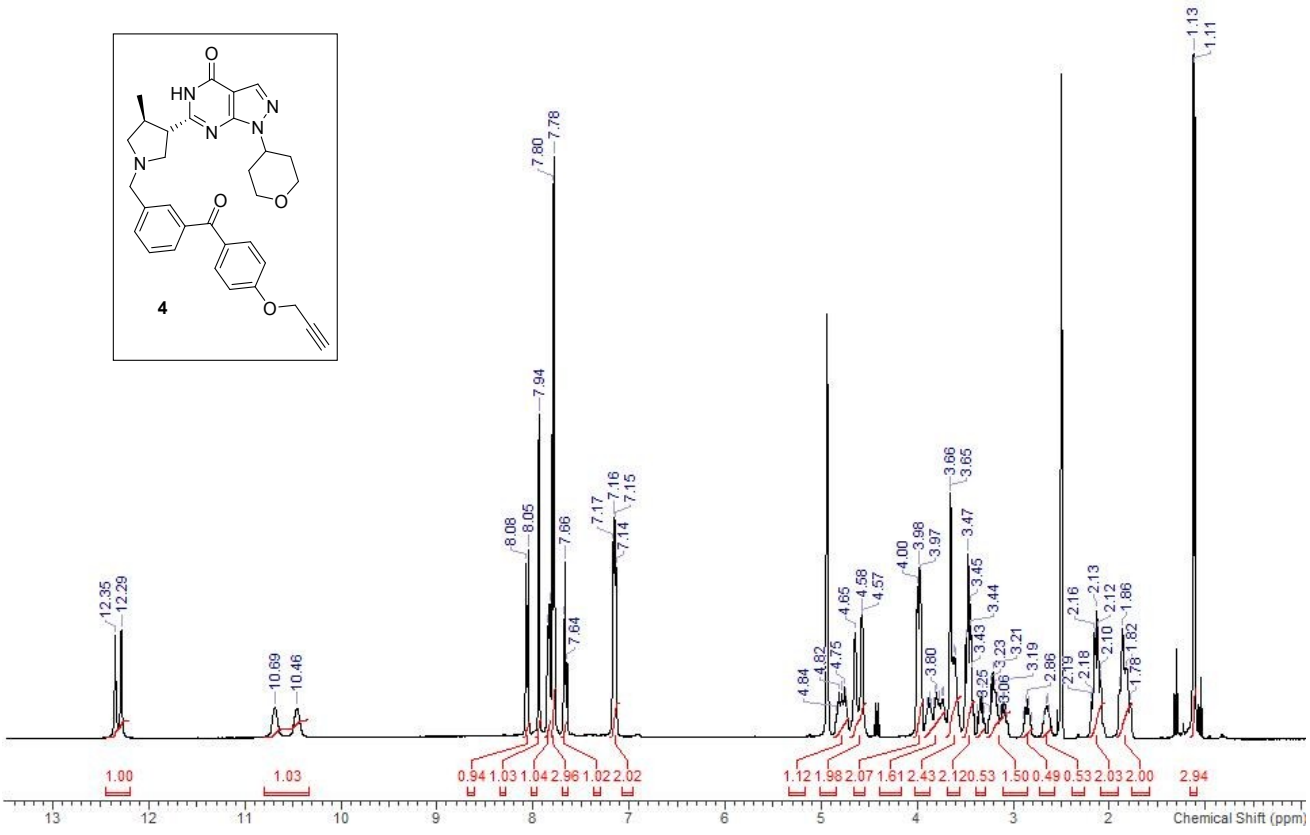

3t
Et2N
O
N
N
N
O
O
N
4.09
4.90
5.79
4.84
4.83
7.88
7.86
7.06
7.04
8.68
8.67
8.21
8.19
8.17
7.78
7.76
7.66
7.65
7.07
7.03
4.20
4.11
3.62
3.61
3.59
3.57
3.54
3.51
3.31
3.31
3.04
3.03
3.02
2.66
1.24
1.20
1.26
1.18
1.27
1.16
0.98
1.00
2.03
0.99
1.06
2.16
2.09
2.07
2.09
3.12
4.42
0.89
6.83
Chemical Shift (ppm)


191.68
164.35
164.13
157.58
154.56
146.66
143.84
141.68
140.38
134.00
130.60
126.56
126.37
125.63
116.12
77.80
79.10
67.79
57.07
49.79
49.58
49.37
49.15
48.94
48.73
48.52
44.96
41.73
34.94
15.02
13.22
Chemical Shift (ppm)


3u
HN
O
N
N
O

9.35
8.26
8.24
8.18
8.17
8.27
7.17
7.14
7.17
4.89
4.89
3.73
3.59
3.57
3.56
3.56
3.39
3.05
3.04
3.03
2.56
2.54
2.53
2.34
2.31
1.00
2.24
2.13
2.31
2.50
2.37
2.38
2.44
0.95
1.21
1.17
Chemical Shift (ppm)


49.79
49.58
49.37
49.15
48.94
48.73
48.52
115.85
134.75
57.05
40.36
126.25
125.11
163.83
79.20
192.16
150.68
149.16
147.90
145.99
145.01
142.66
130.35
77.68
41.70
40.21
Chemical Shift (ppm)


4
12.35
12.29
10.69
10.46
8.08
8.05
7.94
7.80
7.78
7.66
7.64
7.17
7.16
7.15
7.14
4.84
4.82
4.75
4.65
4.58
4.57
4.00
3.98
3.97
3.80
3.66
3.65
3.47
3.45
3.44
3.43
3.25
3.23
3.21
3.19
3.06
2.86
2.19
2.18
2.16
2.13
2.12
2.10
1.86
1.82
1.78
1.13
1.11
1.00
1.03
0.94 1.03 1.04 2.96 1.02 2.02
1.12 1.98 2.07 1.61 2.43 2.12 0.53 1.50 0.49 0.53 2.03 2.00
2.94
13
12
11
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)