Supporting Information

Synthesis and Evaluation of Tirbanibulin Derivatives: A Detailed Exploration of Structure-Activity Relationship for Anticancer Activity

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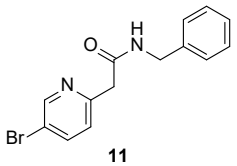
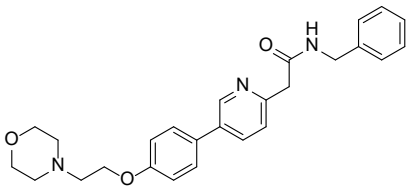
A. Experimental data analysis



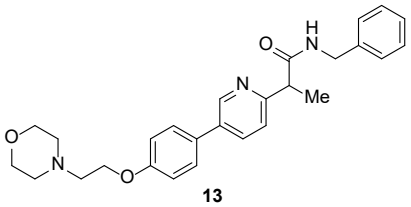
11

***N*-Benzyl-2-(5-bromopyridin-2-yl)acetamide (11).**[1] To a solution of 2-(5-bromopyridin-2-yl)acetic acid (1.0 equiv, 4.6 mmol, 1.0 g) in dichloromethane (15 mL), benzylamine (1.2 equiv, 5.6 mmol, 0.6 mL), EDCI·HCl (1.2 equiv, 5.6 mmol, 1.1 g), Et_3N (3.2 equiv, 15 mmol, 2.0 mL) and HOBt (1.2 equiv, 5.6 mmol, 750 mg) were added sequentially at 0 °C. The reaction mixture was stirred at room temperature for 18 h, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 3:1, R_f = 0.3) to give **11** (3.6 mmol, 1.1 g, 77%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64–8.57 (m, 2H), 7.99 (dd, J = 8.3, 2.5 Hz, 1H), 7.38–7.19 (m, 6H), 4.28 (d, J = 5.9 Hz, 2H), 3.67 (s, 2H).



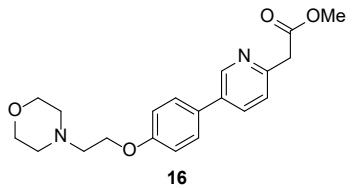
8 (tirbanibulin)

***N*-Benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (8, tirbanibulin).**[2] To a solution of **11** (1.0 equiv, 2.8 mmol, 870 mg) in DMF (18 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 3.4 mmol, 1.1 g), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.28 mmol, 230 mg), triphenylphosphine (0.1 equiv, 0.28 mmol, 73 mg), Cs_2CO_3 (1.5 equiv, 4.3 mmol, 1.4 g), and water (1.8 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 2 h, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **8** (2.3 mmol, 981 mg, 80%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (d, J = 2.3 Hz, 1H), 8.63 (t, J = 6.0 Hz, 1H), 7.97 (dd, J = 8.1, 2.5 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.35–7.20 (m, 5H), 7.06 (d, J = 8.8 Hz, 2H), 4.30 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.71 (s, 2H), 3.58 (t, J = 4.6 Hz, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.48 (br, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 158.5, 154.6, 146.4, 139.4, 133.9, 133.2, 129.3, 128.3 (2C), 127.9 (2C), 127.2 (2C), 126.8, 123.8, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.5, 42.2.



13

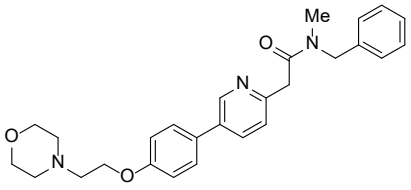
***N*-Benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)propanamide (13).** To a solution of **8** (1.0 equiv, 0.23 mmol, 100 mg) in DMF (2.3 mL), iodomethane (1.2 equiv, 0.28 mmol, 17 µL) and sodium hydride (60% dispersion in mineral oil, 1.5 equiv, 0.35 mmol, 14 mg) were added at 0 °C. The reaction mixture was stirred at room temperature for 30 min, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, Rf = 0.2) to give **13** (0.12 mmol, 53 mg, 51%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, J = 2.2 Hz, 1H), 8.55 (t, J = 6.0 Hz, 1H), 7.98 (dd, J = 8.2, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.32–7.18 (m, 5H), 7.06 (d, J = 8.8 Hz, 2H), 4.28 (d, J = 6.0 Hz, 2H), 4.14 (t, J = 5.7 Hz, 2H), 3.88 (q, J = 7.1 Hz, 1H), 3.58 (t, J = 4.7 Hz, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.49 (br, J = 5.8 Hz, 4H), 1.45 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 158.9, 158.7, 147.2, 138.6, 135.2, 134.8, 130.3, 128.7 (2C), 128.3 (2C), 127.5 (2C), 127.3, 122.4, 115.3 (2C), 66.5, 65.5, 57.6 (2C), 54.0 (2C), 49.03, 44.6, 18.9; HRMS (EI): calcd. for $C_{27}H_{31}N_3O_3$ ([M]$^+$) 445.2365, found 445.2344.



16

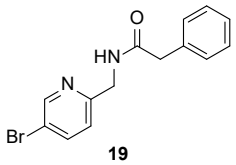
Methyl 2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetate (16).[1] To a solution of methyl 2-(5-bromopyridin-2-yl)acetate (1.0 equiv, 9.3 mmol, 2.1 g) in DMF (19 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 11 mmol, 3.7 g), $PdCl_2$(dppf)·CH_2Cl_2 (0.05 equiv, 0.47 mmol, 381 mg), triphenylphosphine (0.1 equiv, 0.93 mmol, 245 mg), potassium fluoride (1.5 equiv, 14 mmol, 814 mg), and water (2.0 mL) were added at room temperature. The reaction mixture was stirred at 100 °C. After 4 h, the mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **16** (9.26 mmol, 3.3 g, 99%) as brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (dd, J = 2.4, 0.8 Hz, 1H), 7.80 (dd, J = 8.1, 2.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.33 (dd, J = 8.0, 0.8 Hz,

1H), 7.00 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 5.7 Hz, 2H), 3.88 (s, 2H), 3.77–3.71 (m, 7H), 2.83 (t, J = 5.7 Hz, 2H), 2.64–2.55 (m, 4H).



14

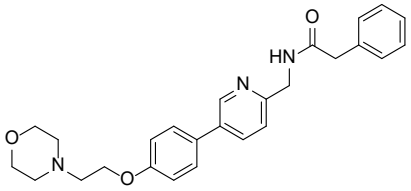
***N*-Benzyl-*N*-methyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (14).** To a solution of **16** (1.0 equiv, 0.28 mmol, 100 mg) in 1,4-dioxane (1.4 mL), *N*-methylbenzylamine (1.2 equiv, 0.033 mmol, 43 µL) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (1.2 equiv, 0.33 mmol, 46 mg) were added at room temperature. The reaction was stirred at 60 °C for 17 h, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10:1, R_f = 0.3) to give **14** (0.18 mmol, 78 mg, 63%) as a beige solid. ^{1}H NMR (two rotamers, 500 MHz, DMSO-d_6) δ 8.79–8.70 (m, 1H), 8.00–7.92 (m, 1H), 7.69–7.59 (m, 2H), 7.40–7.19 (m, 6H), 7.10–7.02 (m, 2H), 4.74–4.51 (m, 2H), 4.14 (t, J = 5.7 Hz, 2H), 4.01–3.91 (m, 2H), 3.58 (t, J = 4.7 Hz, 4H), 3.03–2.79 (m, 3H), 2.71 (t, J = 5.7 Hz, 2H), 2.49–2.45 (m, 4H); ^{13}C NMR (major rotamer, 125 MHz, DMSO-d_6) δ 169.8, 158.5, 154.5, 146.4, 137.7, 133.8, 133.1, 129.2, 128.4 (2C), 127.8 (2C), 127.4 (2C), 126.6, 123.9, 115.1 (2C), 66.1 (2C), 65.4, 57.00, 53.6 (2C), 50.0, 42.2, 35.2; ^{13}C NMR (minor rotamer, 125 MHz, DMSO-d_6) δ 169.8, 158.5, 154.4, 146.4, 137.3, 133.9, 133.2, 129.2, 128.6 (2C), 127.8 (2C), 127.2 (2C), 126.9, 123.9, 115.16 (2C), 66.1 (2C), 65.4, 57.0, 53.6 (2C), 52.7, 42.1, 33.4; HRMS (FAB): calcd. for $C_{27}H_{32}N_3O_3$ ($[M+H]^+$) 446.2444, found 446.2449.



19

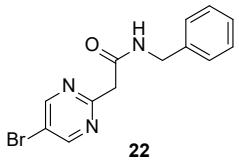
***N*-((5-Bromopyridin-2-yl)methyl)-2-phenylacetamide (19).** To a solution of 2-phenylacetic acid (1.0 equiv, 7.3 mmol, 1.0 g) in DMF (10 mL), (5-bromopyridin-2-yl)methanamine (1.2 equiv, 8.8 mmol, 1.6 g), HATU (1.5 equiv, 11.0 mmol, 4.2 g), and DIPEA (3.0 equiv, 22 mmol, 3.8 mL) were added sequentially at 0 °C. The reaction mixture was stirred at room temperature for 13 h, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1, R_f = 0.2) to give **19** (4.5 mmol, 1.4 g, 62%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.39–

7.27 (m, 5H), 7.12 (d, J = 8.4 Hz, 1H), 6.42 (br, 1H), 4.47 (d, *J* = 5.3 Hz, 2H), 5.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 163.6, 158.0 (2C), 138.2, 128.8 (2C), 127.8 (2C), 127.5, 118.8, 46.1, 43.8; HRMS (FAB): calcd. for $C_{13}H_{13}BrN_3O$ ([M+H]$^+$) 306.0242, found 306.0240.



17

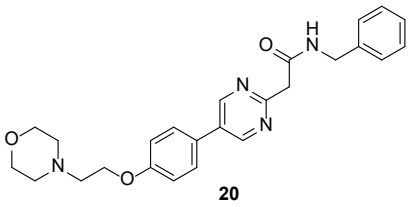
***N*-((5-(4-(2-Morpholinoethoxy)phenyl)pyridin-2-yl)methyl)-2-phenylacetamide (17).** To a solution of **19** (1.0 equiv, 3.6 mmol, 1.1 g) in DMF (23 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 4.3 mmol, 1.4 g), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.36 mmol, 294 mg), triphenylphosphine (0.1 equiv, 0.36 mmol, 94 mg), Cs_2CO_3 (1.5 equiv, 5.4 mmol, 1.7 g), and water (2.3 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 2 h, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **17** (3.0 mmol, 1.3 g, 82%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.5 Hz, 1H), 7.77 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.39–7.27 (m, 4H), 7.27–7.22 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.62 (br, 1H), 4.55 (d, *J* = 5.2 Hz, 2H), 4.17 (br, 2H), 3.75 (br, 4H), 3.67 (s, 2H), 2.84 (br, 2H), 2.60 (br, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 158.8, 154.7, 147.0, 135.0, 134.9, 134.7, 130.1, 129.5 (2C), 128.9 (2C), 128.2 (2C), 127.3, 121.9, 115.2 (2C), 66.8, 65.8, 57.6, 54.1 (2C), 44.5, 43.8, 29.7; HRMS (FAB): calcd. for $C_{26}H_{30}N_3O_3$ ([M+H]$^+$) 432.2287, found 432.2278.



22

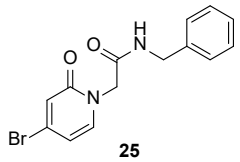
***N*-Benzyl-2-(5-bromopyrimidin-2-yl)acetamide (22).** To a solution of 2-(5-bromopyrimidin-2-yl)acetic acid (1.0 equiv, 0.46 mmol, 100 mg) in dichloromethane (15 mL), benzylamine (1.2 equiv, 0.55 mmol, 60 µL), EDCI·HCl (1.2 equiv, 0.55 mmol, 105 mg), Et_3N (2.5 equiv, 1.1 mmol, 0.16 mL) and HOBt (1.2 equiv, 0.55 mmol, 75 mg) were added sequentially at 0 °C. The reaction mixture was stirred at room temperature for 6 h, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1, Rf = 0.1) to give **22** (0.23 mmol, 72 mg, 51%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (s, 2H), 8.62 (t, *J* = 5.8 Hz, 1H), 7.38–7.20 (m, 5H), 4.30 (d, *J* = 5.9 Hz, 2H),

3.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 163.6, 158.0 (2C), 138.2, 128.8 (2C), 127.8 (2C), 127.5, 118.8, 46.1, 43.84; HRMS (FAB): calcd. for $C_{13}H_{13}BrN_3O$ ([M+H]$^+$) 306.0242, found 306.0240.



20

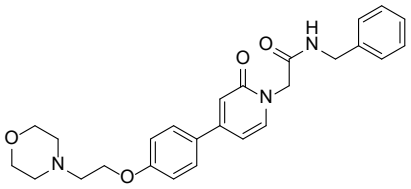
***N*-Benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyrimidin-2-yl)acetamide (20).** To a solution of **22** (1.0 equiv, 0.16 mmol, 50 mg) in DMF (1.6 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 0.19 mmol, 65 mg), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1 equiv, 0.016 mmol, 13 mg), triphenylphosphine (0.1 equiv, 0.016 mmol, 4.2 mg), Cs_2CO_3 (1.5 equiv, 0.24 mmol, 80 mg), and water (0.2 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 2 h. After reaction completion, the mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **20** (0.050 mmol, 25 mg, 36%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 2H), 7.65 (br, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.39–7.24 (m, 5H), 7.04 (d, *J* = 8.7 Hz, 1H), 4.53 (d, *J* = 5.7 Hz, 2H), 4.17 (t, *J* = 5.7 Hz, 2H), 4.05 (s, 2H), 3.80–3.71 (m, 4H), 2.84 (t, *J* = 5.7 Hz, 2H), 2.60 (t, *J* = 4.7 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 163.8, 159.0, 154.3 (2C), 139.3, 130.4, 128.2 (2C), 128.0 (2C), 127.2 (2C), 126.7, 126.0, 115.3 (2C), 66.2 (2C), 65.4, 56.9, 53.6 (2C), 46.0, 42.2; HRMS (FAB): calcd. for $C_{25}H_{29}N_4O_3$ ([M+H]$^+$) 433.2240, found 433.2244.



25

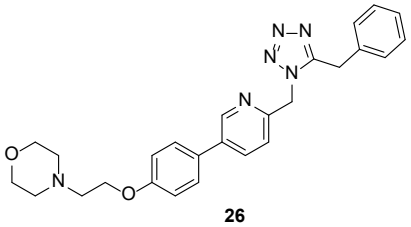
***N*-Benzyl-2-(4-bromo-2-oxopyridin-1(2*H*)-yl)acetamide (25).** A mixture of 4-bromopyridin-2(1*H*)-one (1.0 equiv, 0.57 mmol, 100 mg), *N*-benzyl-2-bromoacetamide (1.0 equiv, 0.57 mmol, 130 mg), and K_2CO_3 (3.0 equiv, 239 mg, 1.7 mmol) in DMF (1.4 mL) was stirred at 100 °C for 3 h. The reaction mixture was cooled to room temperature and quenched by saturated aqueous NH_4Cl, poured into water, and filtered with CH_2Cl_2. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 40:1, Rf = 0.25) to give **25** (0.048 mmol, 155 mg, 85 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (t, *J* = 5.9 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.36–7.21 (m, 5H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.48 (dd, *J* = 7.2, 2.2 Hz, 1H), 4.58 (s, 2H), 4.30 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100

MHz, DMSO-d_6) δ 166.4, 160.3, 140.9, 139.0, 135.3, 128.2 (2C), 127.2 (2C), 126.8, 120.9, 108.6, 50, 42.2; HRMS (FAB): calcd. for $C_{14}H_{14}BrN_2O_2$ ([M+H]$^+$) 321.0239, found 321.0245.



23

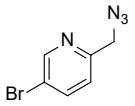
***N*-Benzyl-2-(4-(4-(2-morpholinoethoxy)phenyl)-2-oxopyridin-1(2*H*)-yl)acetamide (23).** To a solution of **25** (1.0 equiv, 0.16 mmol, 50 mg) in DMF (1 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 0.19 mmol, 62 mg), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1 equiv, 0.016 mmol, 13 mg), triphenylphosphine (0.1 equiv, 0.016 mmol, 4.3 mg), Cs_2CO_3 (1.5 equiv, 0.24 mmol, 80 mg), and water (0.1 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 20 h. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **23** (0.07 mmol, 33 mg, 47%) as a pale pink solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (t, J = 5.9 Hz, 1H), 7.71–7.64 (m, 3H), 7.36–7.22 (m, 5H), 7.04 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 2.1 Hz, 1H), 6.58 (dd, J = 7.2, 2.1 Hz, 1H), 4.60 (s, 2H), 4.32 (d, J = 5.9 Hz, 2H), 4.15 (t, J = 5.8 Hz, 2H), 3.58 (t, J = 4.7 Hz, 4H), 2.70 (t, J = 5.7 Hz, 2H), 2.48 (br, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.0, 161.7, 159.6, 150.4, 140.2, 139.1, 128.8, 128.2 (2C), 128.0 (2C), 127.2 (2C), 126.8, 114.9, 113.6 (2C), 103.4, 66.1 (2C), 65.4, 56.9, 53.6 (2C), 50.7, 42.2; HRMS (EI): calcd. for $C_{26}H_{29}N_3O_4$ ([M]$^+$) 447.2158, found 447.2134.



26

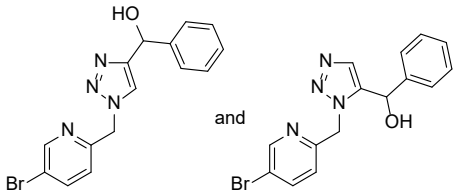
4-(2-(4-(6-((5-Benzyl-1H-tetrazol-1-yl)methyl)pyridin-3-yl)phenoxy)ethyl) morpholine (26). DPPA (2.0 equiv, 0.46 mmol, 100 μL) was added to a solution of **17** (1.0 equiv, 0.23 mmol, 100 mg) in 4-picoline (1.2 mL). The reaction mixture was stirred at 100 °C for 25 h. The mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **26** (0.15 mmol, 71 mg, 68%) as a brown oil. ^{1}H NMR (500

MHz, CD_3OD) δ 8.62 (d, *J* = 2.3 Hz, 1H), 7.90 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.23–7.09 (m, 8H), 5.74 (s, 2H), 4.46 (t, *J* = 4.9 Hz, 2H), 4.40 (s, 2H), 4.14–4.02 (br, 2H), 3.88–3.75 (br, 2H), 3.68 (t, *J* = 4.8 Hz, 2H), 3.65–3.56 (br, 2H), 3.40–3.42 (br, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.4, 156.4, 152.7, 148.3, 137.2, 136.4, 135.4, 131.8, 129.8 (2C), 129.8 (2C), 129.5 (2C), 128.3, 123.5, 116.4 (2C), 64.8 (2C), 62.9, 57.4, 53.7 (2C), 52.5, 29.9; HRMS (FAB): calcd. for $C_{26}H_{29}N_6O_2$ ($[M+H]^+$) 457.2352, found 457.2365.



28

2-(Azidomethyl)-5-bromopyridine (28).[3] To a solution of (5-bromopyridin-2-yl)methanol (1.0 equiv, 3.2 mmol, 600 mg) and Et_3N (1.5 equiv, 4.8 mmol, 0.67 mL) in THF (16 mL), methanesulfonyl chloride (1.2 equiv, 3.8 mmol, 0.30 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 30 min. After the reaction was complete, the mixture was poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The residue was dissolved in DMF (16 mL) and treated with NaN_3 (1.5 equiv, 4.8 mmol, 311mg). The reaction mixture was stirred for 2 h, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1, R_f = 0.3) to give **28** (2.8 mmol, 589 mg, 87%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, *J* = 2.3 Hz, 1H), 7.87 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.29 (s, 1H), 4.47 (s, 2H).



29 **30**

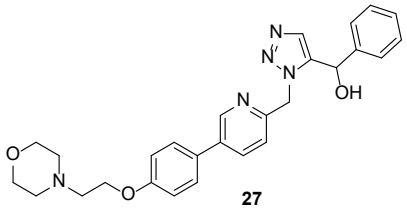
(1-((5-Bromopyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanol (29) and (1-((5-bromopyridin-2-yl)methyl)-1H-1,2,3-triazol-5-yl)(phenyl)methanol (30)

1-Phenylprop-2-yn-1-ol (1.0 equiv, 0.23 mmol, 31 mg) was added to a solution of **28** (1.0 equiv, 0.23 mmol, 50 mg) in toluene (1.2 mL). The reaction mixture was stirred at reflux temperature for 18 h. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3 for **29** and 0.4 for **30**) to give **29** (0.072 mmol, 25 mg, 31%) and **30** (0.087 mmol, 30 mg, 37%) as a beige solid.

29*: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (dd, J = 2.5, 0.7 Hz, 1H), 8.08 (dd, J = 8.3, 2.4 Hz, 1H), 7.94 (d, J = 0.6 Hz, 1H), 7.44–7.19 (m, 6H), 5.97 (d, J = 4.8 Hz, 1H), 5.81 (d, J = 4.7 Hz, 1H), 5.65 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 151.7, 150.1, 144.0, 139.9, 128.1 (2C), 127.0, 126.4 (2C), 124.2, 122.8, 119.6, 67.9, 53.6; HRMS (FAB): calcd. for $C_{15}H_{14}BrN_4O$ ([M+H]$^+$) 345.0351 found 345.0348

30: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br, 1H), 7.94 (dd, J = 8.2, 2.1 Hz, 1H), 7.47–7.31 (m, 7H), 6.10 (s, 1H), 5.64 (d, J = 15.1 Hz, 1H), 5.57 (d, J = 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 150.2, 140.9, 140.6, 140.1, 133.8, 128.7 (2C), 128.3, 126.3 (2C), 124.7, 120.8, 65.7, 52.6; HRMS (FAB): calcd. for $C_{15}H_{14}BrN_4O$ ([M+H]$^+$) 345.0351, found 345.0348.

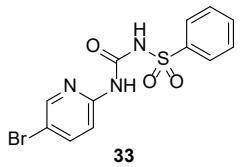
*The 1,4-triazole compound **29** was also selectively prepared by copper(I)-catalyzed alkyne-azide cycloaddition as follows: To a solution of 1-phenylprop-2-yn-1-ol (1.1 equiv, 0.18 mmol, 22 μL) and 2-(azidomethyl)-5-bromopyridine (1.0 equiv, 0.16 mmol, 35 mg) in CH_2Cl_2/H_2O (3:1) (1.0 mL), ascorbic acid (0.2 equiv, 0.030 mmol, 6.0 mg) and $CuSO_4$ (0.1 equiv, 0.015 mmol, 3.8 mg) were added at room temperature. The reaction mixture was stirred at room temperature for 14 h, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **29** (0.15 mmol, 50 mg, 94%) as a white solid.



27

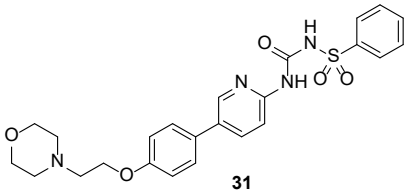
(1-((5-(4-(2-Morpholinoethoxy)phenyl)pyridin-2-yl)methyl)-1*H*-1,2,3-triazol-5-yl) (phenyl)methanol (27). To a solution of **30** (1.0 equiv, 0.096 mmol, 33 mg) in DMF (1.0 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 0.11 mmol, 38 mg), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.0096 mmol, 7.8 mg), triphenylphosphine (0.1 equiv, 0.010 mmol, 2.5 mg), Cs_2CO_3 (1.5 equiv, 0.14 mmol, 47 mg), and water (0.10 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 1 h. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.1) to give **27** (0.074 mmol, 35 mg, 79%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.99 (dd, J = 8.2, 2.3 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.46–7.30 (m, 6H), 6.99 (d, J = 7.9 Hz, 2H), 6.13 (s, 1H), 5.71 (q, J = 15.2 Hz, 2H), 4.46 (s, 2H), 4.01 (s, 4H), 3.69 (d, J = 12.1 Hz,

2H), 3.53 (t, J = 4.4 Hz, 2H), 3.07 (br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 153.1, 146.6, 141.4, 141.1, 134.4, 134.3, 132.2, 128.8, 128.2 (2C), 128.0 (2C), 127.6, 126.4 (2C), 121.7, 115.1 (2C), 66.1 (2C), 65.4, 65.1, 56.9, 53.6 (2C), 52.4; HRMS (EI): calcd. for $C_{27}H_{29}N_5O_3$ ([M]$^+$) 471.2270, found 471.2289.



33

***N*-((5-Bromopyridin-2-yl)carbamoyl)benzenesulfonamide (33).** 5-Bromopyridin-2-amine (1.0 equiv, 0.58 mmol, 100 mg) was added to a solution of benzenesulfonyl isocyanate (1.0 equiv, 0.58 mmol, 78 μL) in dichloromethane (3.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 min, poured into water, and filtered. The residual solid was washed with CH_2Cl_2 to give **33** (0.16 mmol, 57 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (br, 1H), 9.42 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 7.1 Hz, 2H), 7.99–7.92 (m, 1H), 7.75–7.68 (m, 1H), 7.68–7.59 (m, 2H), 7.58 (d, J = 8.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.2, 149.1, 148.2, 141.1, 139.4, 133.7, 129.2 (2C), 127.5 (2C), 114.1, 113.3; HRMS (FAB): calcd. for $C_{12}H_{11}BrN_3O_3S$ ([M+H]$^+$) 355.9704, found 355.9704.

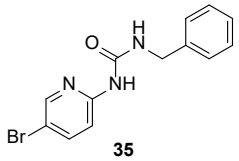


31

***N*-((5-(4-(2-Morpholinoethoxy)phenyl)pyridin-2-yl)carbamoyl)benzenesulfonamide (31).** To a solution of **33** (1.0 equiv, 0.28 mmol, 100 mg) in DMF (1.4 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 0.34 mmol, 112 mg), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.1 equiv, 0.028 mmol, 23 mg), triphenylphosphine (0.1 equiv, 0.028 mmol, 7.3 mg), Cs_2CO_3 (1.5 equiv, 0.42 mmol, 137 mg), and water (0.14 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 40 min. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **31** (0.16 mmol, 78 mg, 57%) as light yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.01 (dd, J = 8.8, 2.5 Hz, 1H), 7.95 (d, J = 7.1 Hz, 2H), 7.70–7.51 (m, 6H), 7.04 (d, J = 8.8 Hz, 2H), 4.17 (t, J = 5.6 Hz, 2H), 3.62 (t, J = 4.7 Hz, 4H), 2.85 (t, J = 5.6 Hz, 2H), 2.63 (t, J = 4.7 Hz,

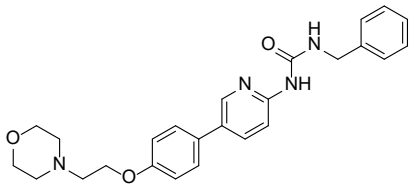
4H); ^{13}C NMR (100 MHz, DMSO-d_6 at 345 K) δ 158.3, 157.1, 144.8, 144.0, 134.6, 131.3, 130.5, 128.4, 126.2 (2C), 125.2 (2C), 123.9, 114.9 (2C), 107.6, 65.9, 65.5 (2C), 56.7, 53.3 (2C); HRMS (FAB): calcd. for $C_{24}H_{27}N_4O_5S$ ([M+H]$^+$) 483.1702, found 483.1695.

Note: The ^{13}C NMR spectrum of compound **31** was obtained at 345 K due to the presence of two rotamers in its ^{13}C NMR spectrum at room temperature. Interestingly, the urea carbon peak (152 ppm at room temperature) disappeared at the higher temperature (345 K).



35

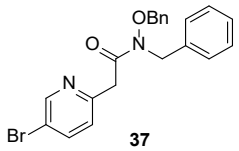
1-Benzyl-3-(5-bromopyridine-2-yl)urea (35).[4] To a solution of 5-bromopyridin-2-amine (1.0 equiv, 1.1 mmol, 200 mg) in THF (5.8 mL), (isocyanatomethyl)benzene (1.0 equiv, 1.1 mmol, 143 μL) was added at 0 °C. The reaction mixture was stirred at reflux temperature for 6 h. After cooled to room temperature, the mixture was quenched with water and filtered. The residual solid was washed with ethanol to give **35** (0.96 mmol, 294 mg, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.52 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.65 (dd, J = 8.9, 2.4 Hz, 1H), 7.40–7.28 (m, 5H), 6.72 (d, J = 8.8 Hz, 1H), 4.60 (d, J = 5.8 Hz, 2H).



34

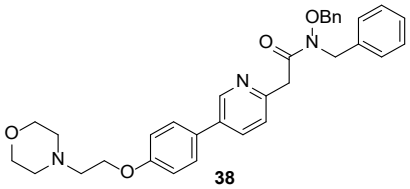
1-Benzyl-3-(5-(4-(2-morpholinoethoxy)phenyl)pyridine-2-yl)urea (34).[5] To a solution of **35** (1.0 equiv, 0.33 mmol, 100 mg) in DMF (1.7 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 0.39 mmol, 130 mg), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.039 mmol, 27 mg), triphenylphosphine (0.1 equiv, 0.039 mmol, 9 mg), Cs_2CO_3 (1.5 equiv, 0.49 mmol, 161 mg), and water (0.17 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 2 h. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **34** (0.12 mmol, 52 mg, 37%) as a light green solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.56 (s, 1H), 8.45 (d, J = 2.2 Hz, 1H), 7.96 (dd, J = 8.7, 2.6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.37–7.22 (m, 5H), 7.02 (d, J = 8.8 Hz, 2H), 4.42 (d, J = 5.9 Hz, 2H), 4.12 (t, J = 5.7 Hz, 2H), 3.58 (t, J = 4.6 Hz, 4H), 2.70

(t, J = 5.7 Hz, 2H), 2.48 (br, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 154.8, 152.1, 136.0, 129.3, 128.6, 128.4 (3C), 127.2 (2C), 127.1 (3C), 126.8, 115.1 (2C), 111.6, 66.2 (2C), 65.4, 57.0, 53.6 (2C), 42.6. HRMS (FAB): calcd. for $C_{25}H_{29}N_4O_3$ ([M+H]$^+$) 433.2240, found 433.2237.



37

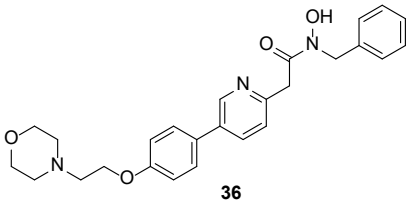
***N*-Benzyl-*N*-(benzyloxy)-2-(5-bromopyridine-2-yl)acetamide (37).** To a solution of 2-(5-bromopyridin-2-yl)acetic acid (1.0 equiv, 4.6 mmol, 1.0 g) in dichloromethane (15 mL), *N*, *O*-dibenzylhydroxylamine (1.1 equiv, 5.1 mmol, 1.0 mL), EDCI·HCl (1.2 equiv, 5.5 mmol, 1.1 g), Et_3N (2.5 equiv, 11 mmol, 1.6 mL), and HOBt (1.2 equiv, 5.5 mmol, 750 mg) were added sequentially at 0 °C. The reaction mixture was stirred at room temperature for 6 h, quenched by saturated aqueous NH_4Cl, poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 3:1, R_f = 0.3) to give **37** (3.6 mmol, 1.5 g, 78%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 8.3, 2.4 Hz, 1H), 7.38–7.27 (m, 10H), 7.12 (d, J = 8.3 Hz, 1H), 4.83 (s, 2H), 4.81 (s, 2H), 3.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 153.7, 149.8, 139.6, 136.2, 134.3, 129.5 (2C), 129.1, 128.8 (4C), 128.7 (2C), 127.9, 125.9, 119.2, 50.5, 41.2; HRMS (FAB): calcd. for $C_{21}H_{20}BrN_2O_2$ ([M+H]$^+$) 411.0708, found 411.0697.



38

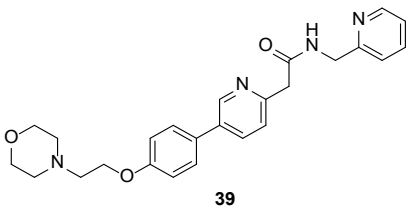
***N*-Benzyl-*N*-(benzyloxy)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridine-2-yl) acetamide (38).** To a solution of **37** (1.0 equiv, 0.49 mmol, 200 mg) in DMF (2.4 mL), 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine (1.2 equiv, 0.58 mmol, 194 mg), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.049 mmol, 40 mg), triphenylphosphine (0.1 equiv, 0.049 mmol, 13 mg), potassium hydride (1.5 equiv, 0.73 mmol, 43 mg), and water (0.24 mL) were added at room temperature. The reaction mixture was stirred at 100 °C for 16 h. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **38** (0.10 mmol, 56 mg, 22%) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (dd, J = 2.5, 0.8 Hz, 1H), 7.95 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.43–7.25 (m, 11H), 7.06 (d, J = 8.8 Hz, 2H), 4.98 (s,

2H), 4.89 (s, 2H), 4.14 (t, J = 5.8 Hz, 2H), 4.01 (s, 2H), 3.58 (t, J = 4.7 Hz, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.50–2.46 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.5, 153.8, 146.4, 136.7, 134.5, 133.8 (2C), 133.2, 129.5 (2C), 129.2, 128.7, 128.5 (2C), 128.3 (2C), 128.0 (2C), 127.8 (2C), 127.3, 124.1, 115.1 (2C), 75.7, 69.7, 66.1 (2C), 65.4, 56.9, 53.6 (2C), 41.0; HRMS (FAB): calcd. for $C_{33}H_{36}N_3O_4$ ([M+H]$^+$) 538.2706, found 538.2706.



36

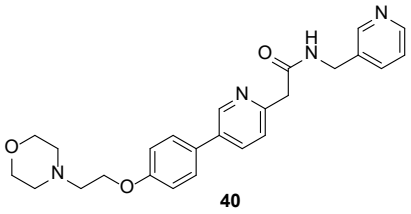
***N*-Benzyl-*N*-hydroxy-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridine-2-yl)acetamide (36).** To a solution of **38** (1.0 equiv, 0.10 mmol, 55 mg) in MeOH (1.0 mL), palladium 10% on carbon (10 wt.%, 5.5 mg) was added slowly at room temperature. The reaction mixture was stirred at room temperature under H_2 atmosphere for 6 h, and filtered with a Celite pad. The filtrate was concentrated in vacuo to give **36** (0.19 mmol, 37 mg, 84%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.74 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.40–7.22 (m, 6H), 7.07 (d, J = 8.7 Hz, 2H), 4.73 (s, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.98 (s, 2H), 3.63–3.54 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.47 (br, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 158.5, 154.3, 146.3, 137.0, 133.8, 133.2, 129.3, 128.3 (2C), 127.9 (2C), 127.8 (2C), 127.1, 124.1, 115.1 (2C), 66.1 (2C), 65.4, 57.0, 53.6 (2C), 51.3, 41.0; HRMS (FAB): calcd. for $C_{26}H_{30}N_3O_4$ ([M+H]$^+$) 448.2236, found 448.2242.



39

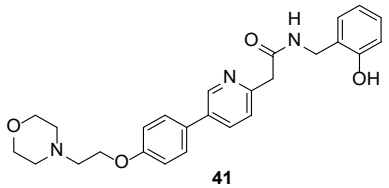
2-(5-(4-(2-Morpholinoethoxy)phenyl)pyridin-2-yl)-*N*-(pyridin-2-ylmethyl)acetamide (39). Compound **16** (1.0 equiv 0.281 mmol, 100 mg), 2-picolylamine (10.0 equiv, 2.81 mmol, 290 μL), and DBU (3.0 equiv, 0.842 mmol, 126 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2.5 h, with the reaction temperature controlled at 180 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to

give **39** (0.20 mmol, 87 mg, 72%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (dd, J = 2.5, 0.8 Hz, 1H), 8.73 (t, J = 6.0 Hz, 1H), 8.50 (ddd, J = 4.8, 1.9, 0.9 Hz, 1H), 7.97 (dd, J = 8.1, 2.5 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.41 (dd, J = 8.2, 0.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 4.39 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.7 Hz, 2H), 3.75 (s, 2H), 3.63–3.55 (m, 4H), 2.71 (t, J = 5.8 Hz, 4H), 2.49 (d, J = 2.1 Hz, 15H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 158.5, 158.5, 154.5, 148.8, 146.5, 136.7, 133.9, 133.3, 129.3, 127.9 (2C), 123.8, 122.1, 121.0, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.5, 44.4; HRMS (FAB): calcd. for $C_{25}H_{28}N_4O_3$ ([M+H]$^+$) 433.2240, found 433.2244



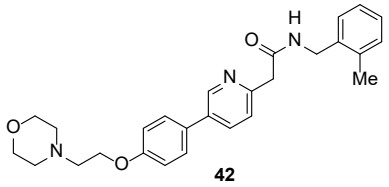
40

2-(5-(4-(2-Morpholinoethoxy)phenyl)pyridin-2-yl)-*N*-(pyridin-3-ylmethyl)acetamide (40). Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 3-picolylamine (10.0 equiv, 1.4 mmol, 143 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2.5 h, with the reaction temperature controlled at 180 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.1) to give **40** (0.097 mmol, 42 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 2.1 Hz, 1H), 8.69 (t, J = 5.8 Hz, 1H), 8.49 (s, 1H), 8.45 (d, J = 4.9 Hz, 1H), 7.97 (dd, J = 8.1, 2.5 Hz, 1H), 7.70–7.66 (m, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 7.8, 4.8 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 4.32 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.71 (s, 2H), 3.62–3.55 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.49–2.45 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.4, 158.5, 154.4, 148.7, 148.1, 146.5, 135.1, 134.9, 133.9, 133.3, 129.3, 127.9 (2C), 123.8, 123.4, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (3C), 44.4; HRMS (FAB): calcd. for $C_{25}H_{28}N_4O_3$ ([M+H]$^+$) 433.2240, found 433.2235



41

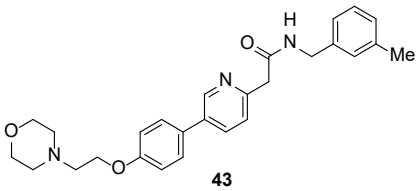
***N*-(2-Hydroxybenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)-2,3-dihydropyridin-2-yl)acetamide (41).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 2-(aminomethyl)phenol (10.0 equiv, 1.4 mmol, 345 mg), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **41** (0.081 mmol, 36 mg, 58%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.74 (d, *J* = 2.5 Hz, 1H), 8.52 (t, *J* = 5.9 Hz, 1H), 7.96 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.09–7.01 (m, 3H), 6.82–6.70 (m, 2H), 4.22 (d, *J* = 5.8 Hz, 2H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.72 (s, 2H), 3.58 (t, *J* = 4.6 Hz, 4H), 2.71 (t, *J* = 5.7 Hz, 2H), 2.49–2.45 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.6, 158.5, 154.9, 154.6, 146.4, 133.9, 133.2, 129.3, 128.6, 127.9 (2C), 127.9, 125.1, 123.8, 118.8, 115.2 (2C), 115.0, 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.3, 37.8; HRMS (EI): calcd. for $C_{25}H_{28}N_4O_3$ ([M]$^+$) 447.2158, found 447.2155



42

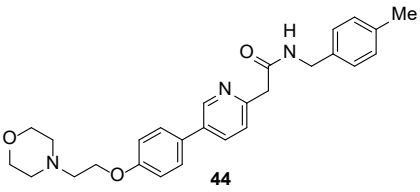
***N*-(2-Methylbenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (42).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 2-methylbenzylamine (10.0 equiv, 1.4 mmol, 174 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2.5 h, with the reaction temperature controlled at 180 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **42** (0.11 mmol, 47 mg, 75%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (dd, *J* = 2.5, 0.9 Hz, 1H), 8.48 (t, *J* = 5.7 Hz, 1H), 7.97 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.23 (dq, *J* = 5.1, 2.4 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 3H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.27 (d, *J* = 5.7 Hz, 2H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.71 (s, 2H), 3.62–3.55 (m, 4H), 2.71 (t, *J* = 5.7 Hz, 2H), 2.49–2.44 (m, 4H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 158.5, 154.6, 146.4, 136.9, 135.7,

133.8, 133.2, 129.9, 129.3, 127.8, 127.7 (2C), 126.9, 125.7, 123.7, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C)z, 44.4, 40.5, 18.6; HRMS (EI): calcd. for $C_{27}H_{31}N_3O_3$ ([M]$^+$) 445.2365, found 445.2354.



43

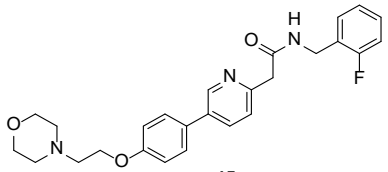
***N*-(3-Methylbenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (43).** Compound **16** (1.0 equiv, 0.14 mmol, 50 mg), 3-methylbenzylamine (10.0 equiv, 1.4 mmol, 174 µL), and DBU (3.0 equiv, 0.42 mmol, 64 µL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2.5 h, with the reaction temperature controlled at 180 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **43** (0.088 mmol, 39 mg, 63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (dd, J = 2.4, 0.8 Hz, 1H), 8.58 (t, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.40 (dd, J = 8.2, 0.8 Hz, 1H), 7.19 (td, J = 7.3, 1.1 Hz, 1H), 7.11–7.01 (m, 5H), 4.26 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.70 (s, 2H), 3.62–3.55 (m, 5H), 2.71 (t, J = 5.7 Hz, 2H), 2.49 – 2.45 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 158.5, 154.6, 146.4, 139.3, 137.3, 133.9, 133.2, 129.3, 128.1, 127.8 (2C), 127.8, 127.3, 124.3, 123.7, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.5, 42.2, 21.0; HRMS (EI): calcd. for $C_{27}H_{31}N_3O_3$ ([M]$^+$) 445.2365, found 445.2355.



44

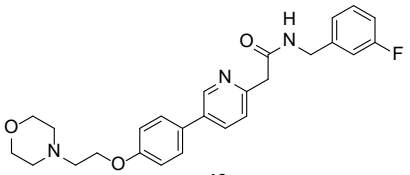
***N*-(4-Methylbenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (44).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 4-methylbenzylamine (10.0 equiv, 1.4 mmol, 174 µL), and DBU (3.0 equiv, 0.42 mmol, 64 µL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2.5 h, with the reaction temperature controlled at 180 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude

mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **44** (0.13 mmol, 56 mg, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (dd, J = 2.5, 0.8 Hz, 1H), 8.56 (t, J = 5.9 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.39 (dd, J = 8.2, 0.8 Hz, 1H), 7.14 (q, J = 8.1 Hz, 4H), 7.06 (d, J = 8.8 Hz, 1H), 4.25 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.69 (s, 2H), 3.62–3.55 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.50–2.45 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 158.5, 154.6, 146.4, 136.4, 135.8, 133.8, 133.2, 129.3, 128.8 (2C), 127.8 (2C), 127.2 (2C), 123.7, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.5, 42.0, 20.6; HRMS (EI): calcd. for $C_{27}H_{31}N_3O_3$ ([M]$^+$) 445.2365, found 445.2368.



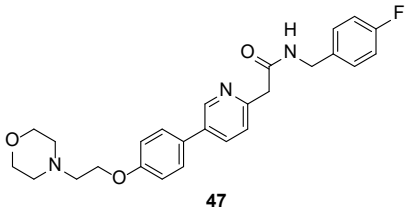
45

***N*-(2-Fluorobenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (45).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 2-fluorobenzylamine (10.0 equiv, 1.4 mmol, 159 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **45** (0.11 mmol, 49 mg, 78%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (dd, J = 2.5, 0.8 Hz, 1H), 8.62 (t, J = 5.8 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.41 – 7.26 (m, 3H), 7.22 – 7.13 (m, 2H), 7.06 (d, J = 8.8 Hz, 2H), 4.34 (d, J = 5.8 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.71 (s, 2H), 3.62–3.55 (m, 4H), 2.71 (t, J = 5.8 Hz, 2H), 2.50–2.44 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 160.0 (d, J = 244.3 Hz), 158.5, 154.5, 146.4, 133.9, 133.2, 129.6 (d, J = 4.4 Hz), 129.3, 128.9 (d, J = 8.1 Hz), 127.9 (2C), 125.9 (d, J = 14.9 Hz), 124.3 (d, J = 3.5 Hz), 123.8, 115.2 (2C), 115.0 (d, J = 21.2 Hz), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.4, 36.1 (d, J = 4.7 Hz); HRMS (EI): calcd. for $C_{26}H_{28}FN_3O_3$ ([M]$^+$) 449.2115, found 449.2113.



46

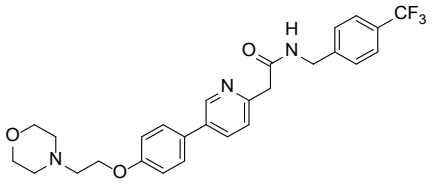
***N*-(3-Fluorobenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (46).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 3-fluorobenzylamine (10.0 equiv, 1.4 mmol, 159 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **46** (0.10 mmol, 46 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 2.5 Hz, 1H), 8.67 (br, 1H), 7.97 (dd, J = 8.0, 2.6 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.43–7.26 (m, 2H), 7.15–7.03 (m, 5H), 4.32 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.9 Hz, 2H), 3.72 (s, 2H), 3.58 (t, J = 4.6 Hz, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.48–2.44 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4, 162.2 (d, J = 243.1 Hz), 158.5, 154.5, 146.4, 142.6 (d, J = 7.0 Hz), 133.9, 133.3, 130.2 (d, J = 8.2 Hz), 129.3, 127.9 (2C), 123.8, 123.1 (d, J = 2.7 Hz), 115.2 (2C), 113.8 (d, J = 21.7 Hz), 113.4 (d, J = 21.1 Hz), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.5, 41.7; MS (EI): calcd. for $C_{26}H_{28}FN_3O_3$ ([M]$^+$) 449.2115, found 449.2119.



47

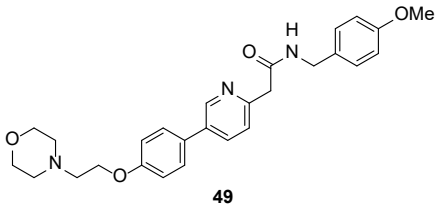
***N*-(4-Fluorobenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (47).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 4-fluorobenzylamine (10.0 equiv, 1.4 mmol, 159 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **47** (0.12 mmol, 53 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (dd, J = 2.5, 0.8 Hz, 1H), 8.63 (t, J = 6.0 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.39 (dd, J = 8.2, 0.8 Hz, 1H), 7.35–7.27 (m, 2H), 7.19–7.11 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.7 Hz, 2H), 3.70 (s, 2H), 3.62–3.55 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.49–2.45 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 161.1 (d, J = 242.1 Hz), 158.5, 154.5, 146.4, 135.6 (d, J = 3.1 Hz), 133.9, 133.2, 129.3, 129.2 (d, J = 8.1 Hz) (2C), 127.9 (2C), 123.7, 115.2 (2C), 115.0 (d, J = 21.2

Hz) (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 44.5, 41.5; MS (EI): calcd. for $C_{26}H_{28}FN_3O_3$ ([M]$^+$) 449.2115, found 449.2116.



48

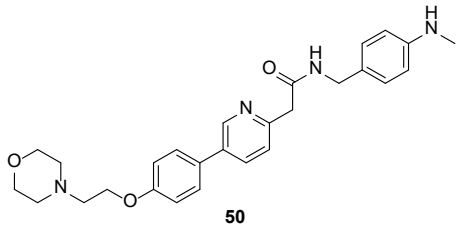
2-(5-(4-(2-Morpholinoethoxy)phenyl)pyridin-2-yl)-*N*-(4-(trifluoromethyl)benzyl)acetamide (48). Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 4-(trifluoromethyl)benzylamine (10.0 equiv, 1.4 mmol, 200 µL), and DBU (3.0 equiv, 0.42 mmol, 64 µL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **48** (0.092 mmol, 46 mg, 66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (dd, *J* = 2.5, 0.8 Hz, 1H), 8.74 (t, *J* = 6.1 Hz, 1H), 7.97 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.39 (d, *J* = 5.9 Hz, 2H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.74 (s, 2H), 3.62–3.55 (m, 4H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.51–2.44 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 158.5, 154.4, 146.5, 144.5, 133.9, 133.3, 129.3, 127.9 (2C), 127.8 (4C), 127.7 (d, *J* = 31.5 Hz), 125.2 (q, *J* = 3.7 Hz), 123.8, 115.2 (2C), 66.2, 65.4, 57.0 (2C), 53.6 (2C), 44.5, 41.9; MS (EI): calcd. for $C_{27}H_{28}F_3N_3O_3$ ([M]$^+$) 499.2083, found 499.2091.



49

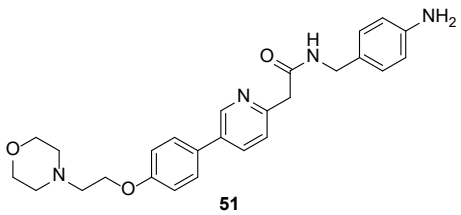
***N*-(4-Methoxybenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (49).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), 4-methoxybenzylamine (10.0 equiv, 1.4 mmol, 180 µL), and DBU (3.0 equiv, 0.42 mmol, 64 µL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with

the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **49** (0.043 mmol, 20 mg, 31%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (dd, J = 2.5, 0.8 Hz, 1H), 8.60 (t, J = 6.0 Hz, 1H), 7.97 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 8.2, 0.8 Hz, 1H), 7.33–7.18 (m, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.88–6.76 (m, 3H), 4.28 (d, J = 5.9 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 3.71 (d, J = 1.2 Hz, 5H), 3.62–3.55 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.49–2.45 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 159.3, 158.5, 154.6, 146.4, 141.0, 133.9, 133.2, 129.3 (2C), 127.9 (2C), 123.8, 119.3, 115.2 (2C), 112.7, 112.2, 66.2 (2C), 65.4, 57.0, 54.9, 53.6 (2C), 44.5, 42.1; MS (EI): calcd. for $C_{27}H_{31}N_3O_4$ ([M]$^+$) 461.2315, found 461.2313.



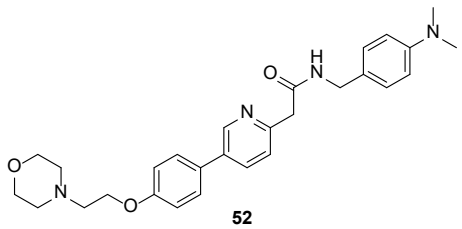
50

***N*-(4-(Methylamino)benzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (50).** To a solution of compound **16** (1.0 equiv, 0.14 mmol, 50 mg) in 1,4-dioxane (0.70 mL), 4-(aminomethyl)-*N*-methylaniline (1.2 equiv, 0.17 mmol, 23 mg) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (1.0 equiv, 0.14 mmol, 20 mg) were added at room temperature. The reaction was stirred at 60 °C for 15 h, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by preparative thin layer chromatography (CH_2Cl_2/MeOH, 10:1, R_f = 0.4) to give **50** (0.074 mmol, 34 mg, 53%) as a pale orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (d, J = 2.4 Hz, 1H), 8.42 (t, J = 5.7 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.53 (q, J = 5.0 Hz, 1H), 4.16 – 4.12 (m, 4H), 3.66 (s, 2H), 3.63 – 3.54 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.64 (d, J = 5.1 Hz, 3H), 2.51 – 2.47 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.8, 158.5, 154.7, 149.0, 146.4, 133.9, 133.2, 129.4, 128.4 (2C), 127.9 (2C), 126.0, 123.7, 115.2 (2C), 111.5 (2C), 66.2 (2C), 65.5, 57.0, 53.7 (2C), 44.5, 42.1, 29.9; MS (FAB): calcd. for $C_{27}H_{33}N_4O_3$ ([M+H]$^+$) 461.2553, found 461.2549



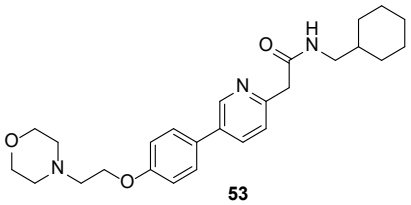
51

***N*-(4-Aminobenzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (51).** To a solution of compound **16** (1.0 equiv, 0.14 mmol, 50 mg) in 1,4-dioxane (0.7 mL), 4-aminobenzylamine (1.2 equiv, 0.17 mmol, 19 µL) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (0.3 equiv, 0.042 mmol, 5.9 mg) were added at room temperature. The reaction was stirred at 60 °C for 4 d, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by preparative thin layer chromatography (CH_2Cl_2/MeOH, 10:1, $R_f = 0.4$) to give **51** (0.054 mmol, 24 mg, 38%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (dd, J = 2.6, 0.7 Hz, 1H), 8.41 (t, J = 5.8 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 4.96 (s, 2H), 4.17–4.06 (m, 4H), 3.66 (s, 2H), 3.61–3.54 (m, 4H), 3.16 (d, J = 5.2 Hz, 2H), 2.71 (t, J = 5.7 Hz, 2H), 2.51–2.46 (m, J = 6.9 Hz, 2H); ^{13}C NMR (125z MHz, DMSO-d_6) δ 168.8, 158.5, 154.7, 147.5, 146.4, 133.9, 133.2, 129.4, 128.3 (2C), 127.9 (2C), 126.2, 123.7, 115.2 (2C), 113.7 (2C), 66.1 (2C), 65.4, 56.9, 53.6 (2C), 44.5, 42.1; MS (FAB): calcd. for $C_{26}H_{31}N_4O_3$ ($[M+H]^+$) 447.2396, found 447.2394



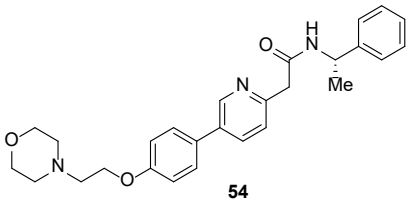
52

***N*-(4-(Dimethylamino)benzyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (52).** To a solution of compound **16** (1.0 equiv, 0.14 mmol, 50 mg) in 1,4-dioxane (0.7 mL), 4-(aminomethyl)-*N*,*N*-dimethylaniline (1.2 equiv, 0.17 mmol, 25 mg) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (1.0 equiv, 0.14 mmol, 20 mg) were added at room temperature. The reaction was stirred at 60 °C for 15 h, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by preparative thin layer chromatography (CH_2Cl_2/MeOH, 10:1, $R_f = 0.4$) to give **52** (0.097 mmol, 46 mg, 69%) as a pale orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73 (d, J = 2.4 Hz, 1H), 8.46 (t, J = 5.9 Hz, 1H), 7.96 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 8.5 Hz, 4H), 6.67 (d, J = 8.7 Hz, 2H), 4.20–4.09 (m, 4H), 3.67 (s, 2H), 3.62–3.55 (m, 4H), 2.85 (s, 6H), 2.71 (t, J = 5.7 Hz, 2H), 2.49–2.43 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.9, 158.5, 154.7, 149.6, 146.4, 133.9, 133.2, 129.3, 128.3 (2C), 127.9 (2C), 126.8, 123.7, 115.2 (2C), 112.4 (2C), 66.2 (2C), 65.5, 57.0, 53.7 (2C), 44.5, 41.9, 40.3 (2C); MS (FAB): calcd. for $C_{28}H_{35}N_4O_3$ ($[M+H]^+$) 475.2709, found 475.2709.



53

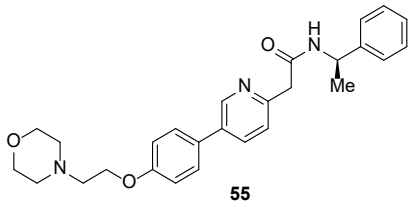
***N*-(Cyclohexylmethyl)-2-(5-(4-(2-morpholinoethoxy)phenyl)-2,3-dihydropyridin-2-yl)acetamide (53).** Compound **16** (1.0 equiv 0.14 mmol, 50 mg), cyclohexanemethylamine (10.0 equiv, 1.4 mmol, 182 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **53** (0.11 mmol, 46 mg, 75%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (dd, J = 2.5, 0.8 Hz, 1H), 8.06 (t, J = 5.8 Hz, 1H), 7.95 (dd, J = 8.1, 2.5 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 0.9 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 4.14 (t, J = 5.7 Hz, 2H), 3.63 (s, 2H), 3.60 – 3.56 (m, 4H), 2.92 (dd, J = 6.8, 5.8 Hz, 2H), 2.71 (t, J = 5.7 Hz, 2H), 2.50–2.41 (m, 4H), 1.70–1.57 (m, 5H), 1.38 (ddt, J = 11.2, 6.9, 3.4 Hz, 1H), 1.25–1.07 (m, 3H), 0.86 (q, J = 11.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 158.5, 154.8, 146.3, 133.8, 133.1, 129.3, 127.7 (2C), 123.6, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 45.0, 44.5, 37.4, 30.4 (2C), 26.0, 25.4 (2C); MS (EI): calcd. for $C_{26}H_{35}N_3O_3$ ($[M]^+$) 437.2678, found 437.2679.



54

2-(5-(4-(2-Morpholinoethoxy)phenyl)-2,3-dihydropyridin-2-yl)-*N*-((*S*)-1-phenylethyl)acetamide (54). Compound **16** (1.0 equiv 0.14 mmol, 50 mg), (*S*)-1-phenylethan-1-amine (10.0 equiv, 1.4 mmol, 181 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **54** (0.53 mmol, 24 mg, 38%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73

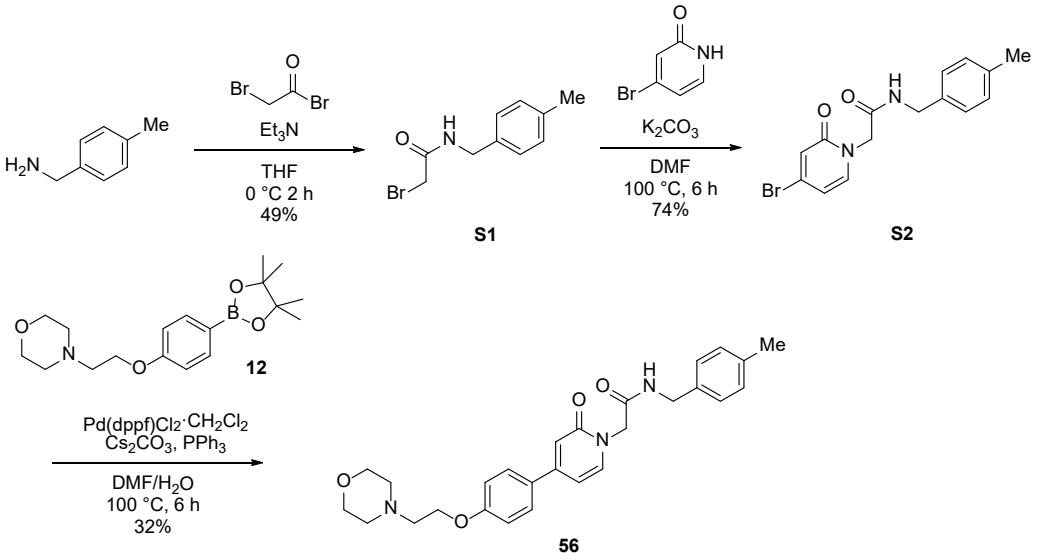
(dd, *J* = 2.5, 0.8 Hz, 1H), 8.60 (d, *J* = 8.1 Hz, 1H), 7.94 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.35 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.34–7.28 (m, 4H), 7.26–7.17 (m, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 4.92 (p, *J* = 7.1 Hz, 1H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.68 (s, 2H), 3.65–3.55 (m, 4H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.48–2.44 (m, 4H), 1.37 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.2, 158.5, 154.6, 146.4, 144.6, 133.8, 133.2, 129.3, 128.2 (2C), 127.9 (2C), 126.6, 126.0 (2C), 123.7, 115.2 (2C), 66.2, 65.4, 57.0, 53.6 (2C), 48.0, 44.4, 22.6; MS (EI): calcd. for $C_{27}H_{31}N_3O_3$ ([M]$^+$) 445.2365, found 445.2360.



55

2-(5-(4-(2-Morpholinoethoxy)phenyl)-2,3-dihydropyridin-2-yl)-*N*-((*R*)-1-phenylethyl)acetamide (55). Compound **16** (1.0 equiv 0.14 mmol, 50 mg), (*R*)-1-phenylethan-1-amine (10.0 equiv, 1.4 mmol, 181 μL), and DBU (3.0 equiv, 0.42 mmol, 64 μL) were combined with 1,4-dioxane (1.4 mL) in a vessel for microwave irradiation. The vessel was placed into a microwave reactor, and the microwave source was then turned on. The reaction mixture was irradiated under constant microwave conditions for 2 h, with the reaction temperature controlled at 200 °C. The reaction mixture was cooled to room temperature, poured into water, extracted twice with EtOAc, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.3) to give **55** (0.052 mmol, 23 mg, 37%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (dd, *J* = 2.5, 0.8 Hz, 1H), 8.60 (d, *J* = 8.1 Hz, 1H), 7.94 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.34–7.27 (m, 4H), 7.26–7.17 (m, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.92 (p, *J* = 7.2 Hz, 1H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.68 (s, 2H), 3.64–3.55 (m, 4H), 2.71 (t, *J* = 5.7 Hz, 2H), 2.51–2.44 (m, 4H), 1.37 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.2, 158.5, 154.6, 146.4, 144.6, 133.8, 133.2, 129.3, 128.2 (2C), 127.9 (2C), 126.6, 126.0 (2C), 123.7, 115.2 (2C), 66.2 (2C), 65.4, 57.0, 53.6 (2C), 48.0, 44.4, 22.6; MS (EI): calcd. for $C_{27}H_{31}N_3O_3$ ([M]$^+$) 445.2365, found 445.2362.

<Synthesis of pyridone analogs 56 and 57>

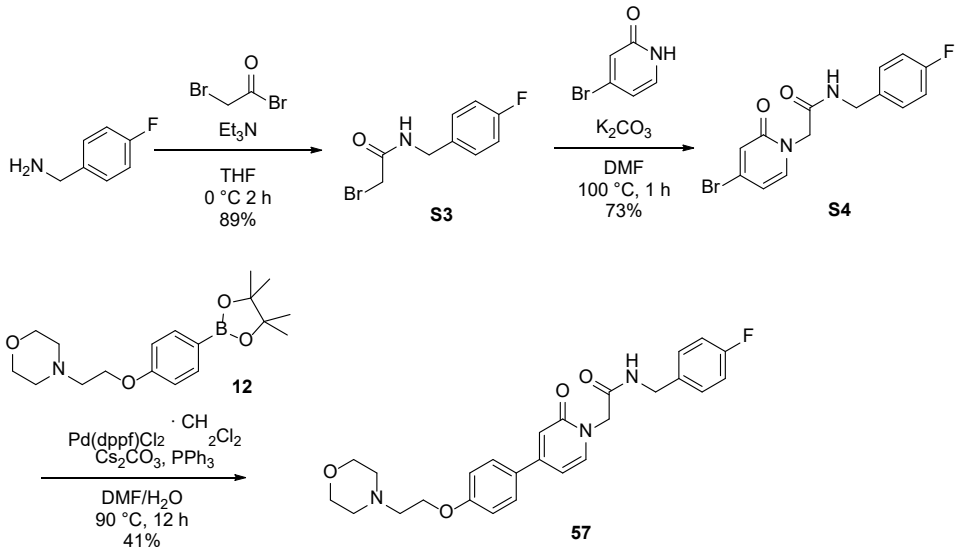


2-Bromo-*N*-(4-methylbenzyl)acetamide (S1).[6] To a solution of 4-methylbenzylamine (1.0 equiv, 2.5 mmol, 300 mg) in THF (12 mL), 2-bromoacetyl bromide (1.0 equiv, 2.5 mmol, 211 μL) and Et_3N (1.0 equiv, 2.5 mmol, 346 μL) were added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, poured in to water and extracted twice with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1, R_f = 0.3) to give **S1** (1.2 mmol, 294 mg, 49%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.14 (m, 4H), 6.71 (s, 1H), 4.44 (d, *J* = 5.7 Hz, 2H), 3.93 (s, 2H), 2.35 (s, 3H).

2-(4-Bromo-2-oxopyridin-1(2*H*)-yl)-*N*-(4-methylbenzyl)acetamide (S2). A mixture of 4-bromopyridin-2(1*H*)-one (1.0 equiv, 0.58 mmol, 100 mg), **S1** (1.1 equiv, 0.63 mmol, 153 mg), K_2CO_3 (3.0 equiv, 1.7 mmol, 238 mg) in DMF (2.9 mL) was stirred at 100 °C for 6 h. The reaction mixture was cooled to room temperature and poured into water. The precipitate was filtered and washed with CH_2Cl_2 to give **S2** (0.43 mmol, 142 mg, 74 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (t, *J* = 5.9 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.20–7.08 (m, 4H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.48 (dd, *J* = 7.2, 2.2 Hz, 1H), 4.56 (s, 2H), 4.25 (d, *J* = 5.8 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 160.4, 141.0, 136.0, 135.9, 135.4, 128.8 (2C), 127.3 (2C), 120.9, 108.7, 50.8, 42.0, 20.7; MS (FAB): calcd. for $C_{15}H_{16}BrN_2O_2$ ($[M+H]^+$) 335.0395, found 335.0388

***N*-(4-Methylbenzyl)-2-(4-(4-(2-morpholinoethoxy)phenyl)-2-oxopyridin-1(2*H*)-yl)acetamide (56).** To a solution of **S2** (1.0 equiv, 0.41 mmol, 138 mg) in DMF (2.0 mL), **12** (1.2 equiv, 0.49 mmol, 164 mg), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.041 mmol, 33 mg), triphenylphosphine (0.1 equiv, 0.041 mmol, 11 mg), Cs_2CO_3 (1.5 equiv, 0.62 mmol, 200 mg), and water (0.2 mL) were added at room temperature.

The reaction was stirred at 100 °C for 6 h. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.2) to give **56** (0.13 mmol, 61 mg, 32%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.63 (t, J = 5.9 Hz, 1H), 7.73–7.61 (m, 3H), 7.15 (q, J = 8.1 Hz, 4H), 7.04 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 7.2, 2.1 Hz, 1H), 4.59 (s, 2H), 4.26 (d, J = 5.8 Hz, 2H), 4.15 (t, J = 5.7 Hz, 2H), 3.62–3.53 (m, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.50–2.43 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.9, 161.7, 159.7, 150.4, 140.2, 136.1, 135.9, 128.9, 128.8 (2C), 128.0 (2C), 127.3 (2C), 115.0 (2C), 113.6, 103.4, 66.2 (2C), 65.5, 56.9, 53.6 (2C), 50.7, 42.0, 20.7; MS (FAB): calcd. for $C_{27}H_{32}N_3O_4$ ($[M+H]^+$) 462.2393, found 462.2394



2-Bromo-*N*-(4-fluorobenzyl)acetamide (S3).[6] To a solution of (4-fluorophenyl)methanamine (1.0 equiv, 2.4 mmol, 300 mg) in THF (12 mL), 2-bromoacetyl bromide (1.0 equiv, 2.4 mmol, 0.20 mL) and Et_3N (1.0 equiv, 2.4 mmol, 0.33 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, poured into water and extracted twice with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1, R_f = 0.3) to give **S3** (2.1 mmol, 525 mg, 89%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2H), 7.04 (t, J = 8.6 Hz, 2H), 6.76 (br, 1H), 4.45 (d, J = 5.8 Hz, 1H), 3.93 (s, 2H).

2-(4-Bromo-2-oxopyridin-1(2*H*)-yl)-*N*-(4-fluorobenzyl)acetamide (S4). A mixture of 4-bromopyridin-2(1*H*)-one (1.0 equiv, 1.1 mmol, 200 mg), **S3** (1.2 equiv, 1.4 mmol, 339 mg), K_2CO_3 (3.0 equiv, 3.4 mmol, 477 mg) in DMF (5.8 mL) was stirred at 100 °C for 8 h. The reaction mixture was

cooled to room temperature, poured into water, and filtered. The residual solid was washed with CH_2Cl_2 to give **S4** (0.840 mmol, 285 mg, 73 %) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.33 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.11–6.97 (m, 2H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.57 (dd, *J* = 7.2, 2.2 Hz, 1H), 4.66 (s, 2H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 161.2 (d, *J* = 242.3 Hz), 160.4, 141.0, 135.4, 135.3 (d, *J* = 3.0 Hz), 129.2 (d, *J* = 8.1 Hz), 120.9, 115.0 (d, *J* = 21.2 Hz), 108.7, 50.9, 41.5; MS (FAB): calcd. for $C_{14}H_{13}BrFN_2O_2$ ($[M+H]^+$) 339.0144, found 339.0141

***N*-(4-Fluorobenzyl)-2-(4-(4-(2-morpholinoethoxy)phenyl)-2-oxopyridin-1(2*H*)-yl)acetamide (57).** To a solution of **S4** (1.0 equiv, 0.295 mmol, 150 mg) in DMF (2.0 mL), **12** (1.2 equiv, 0.354 mmol, 118 mg), $PdCl_2$(dppf)·CH_2Cl_2 (0.1 equiv, 0.0295 mmol, 24 mg), triphenylphosphine (0.1 equiv, 0.0295 mmol, 8.0 mg), Cs_2CO_3 (1.5 equiv, 0.442 mmol, 144 mg), and water (0.2 mL) were added at room temperature. The reaction was stirred at 90 °C for 12 h. The mixture was cooled to room temperature, poured into water, extracted twice with CH_2Cl_2, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1, R_f = 0.1) to give **57** (0.122 mmol, 57 mg, 41%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (t, *J* = 5.9 Hz, 1H), 7.73–7.62 (m, 3H), 7.33 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.15 (t, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 2.0 Hz, 1H), 6.58 (dd, *J* = 7.1, 2.1 Hz, 1H), 4.59 (s, 2H), 4.30 (d, *J* = 5.9 Hz, 2H), 4.15 (t, *J* = 5.7 Hz, 2H), 3.62–3.53 (m, 4H), 2.71 (t, *J* = 5.8 Hz, 2H), 2.47 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 161.7, 161.2 (d, *J* = 242.2 Hz), 159.7, 150.5, 140.2, 135.4 (d, *J* = 3.0 Hz), 129.2 (d, *J* = 8.1 Hz) (2C), 128.8 (2C), 128.1, 115.0 (2C), 115.0 (d, *J* = 21.1 Hz) (2C), 113.7, 103.5, 66.2 (2C), 65.5, 56.9, 53.6 (2C), 50.8, 41.5; MS (FAB): calcd. for $C_{26}H_{29}FN_3O_4$ ($[M+H]^+$) 466.2142, found 466.2137

B. Pharmacokinetics data

< compound **44** >

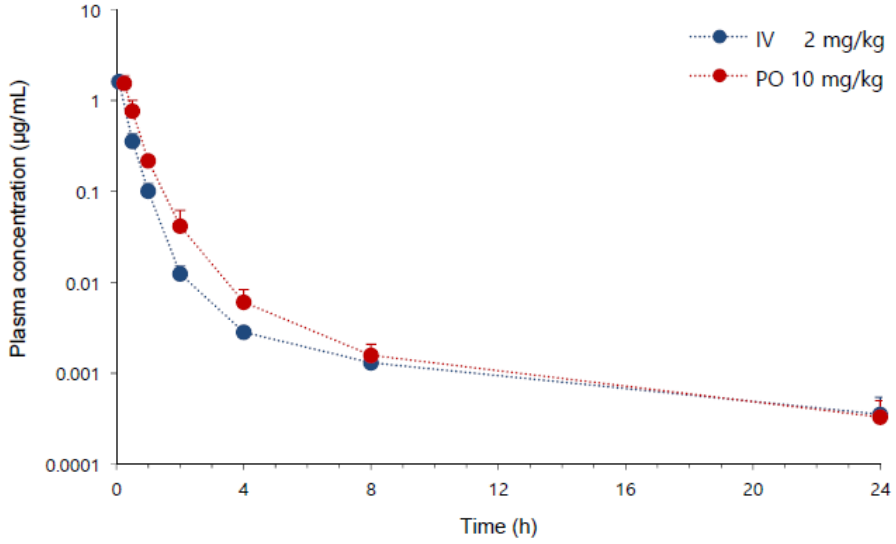


Figure S1. Plasma concentration-time profiles of compound **44** in male mice (n=3).

Table S1. Pharmacokinetic parameters of compound **44** in male mice.

Parameter	IV, 2 mg/kg	PO, 10 mg/kg
T_{max} (h)	NA	0.25 ± 0
C_{max} (μg/mL)	NA	1.54 ± 0.33
$T_{1/2}$ (h)	7.05 ± 1.92	5.45 ± 1.48
AUC_{last} (μg·h/mL)	0.77 ± 0.04	0.94 ± 0.16
AUC_{∞} (μg·h/mL)	0.78 ± 0.05	0.94 ± 0.17
CL (L/h/kg)	2.58 ± 0.15	NA
V_{ss} (L/kg)	1.89 ± 0.31	NA
MRT_{last} (h)	0.56 ± 0.03	0.86 ± 0.17
MRT_{∞} (h)	0.74 ± 0.14	0.95 ± 0.13
F_t (%)	NA	24.18

NA, not applicable; ND, not detected; NC, not calculated

Table S2. Plasma concentrations (ng/ml) of compound **44** after IV administration in male mice.

Time (h)	#1	#2	#3	Mean	S.D.
0.083	1878.8	1521.1	1449.0	1616.3	230.2
0.5	322.4	308.5	437.7	356.2	70.9
1	75.3	113.2	113.7	100.7	22.0
2	9.2	13.7	14.3	12.4	2.8
4	2.8	2.9	2.8	2.8	0.1
8	1.6	1.3	1.1	1.3	0.3
24	0.5	0.4	0.2	0.4	0.2

BQL, Below the quantification limit

Table S3. Plasma concentrations (ng/ml) of compound **44** after PO administration in male mice.

Time (h)	#1	#2	#3	Mean	S.D.
0.25	1730.9	1161.4	1742.6	1544.9	332.2
0.5	908.3	482.7	900.7	763.9	243.6
1	205.5	199.4	248.4	217.8	26.7
2	18.7	58.2	47.8	41.6	20.5
4	3.5	7.5	7.2	6.1	2.3
8	1.1	2.1	1.4	1.6	0.5
24	0.3	0.2	0.5	0.3	0.2

BQL, Below the quantification limit

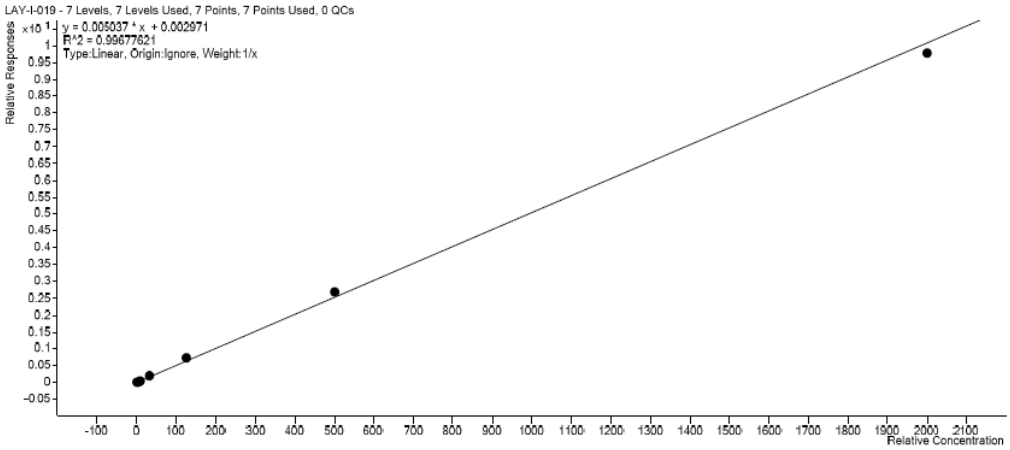


Figure S2. The calibration curve of compound **44**.

< compound **47** >

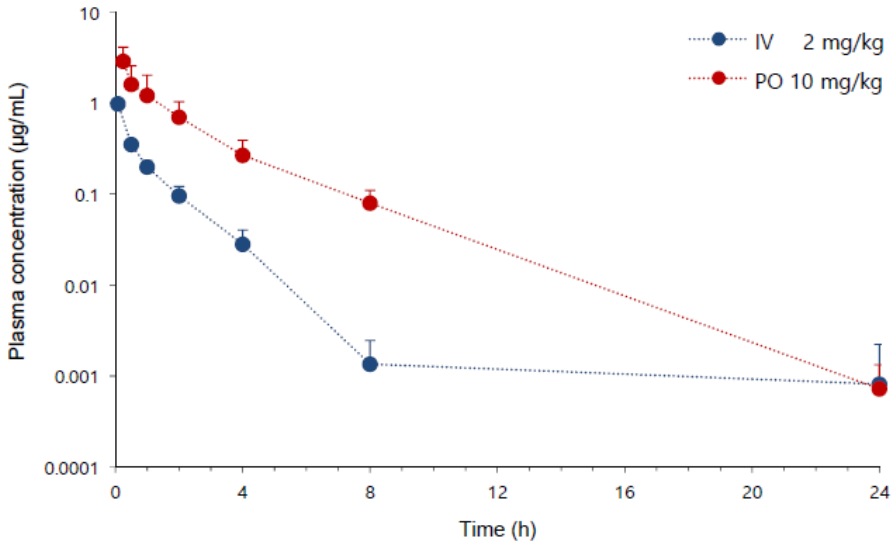


Figure S3. Plasma concentration-time profiles of compound **47** in male mice (n=3)

Table S4. Pharmacokinetic parameters of compound **47** in male mice

Parameter	IV, 2 mg/kg	PO, 10 mg/kg
T_{max} (h)	NA	0.25 ± 0
C_{max} (μg/mL)	NA	2.88 ± 1.22
$T_{1/2}$ (h)	1.69 ± 1.09	2.3 ± 0.23
AUC_{last} (μg·h/mL)	0.84 ± 0.11	4.88 ± 2.07
AUC_{∞} (μg·h/mL)	0.85 ± 0.11	4.88 ± 2.07
CL (L/h/kg)	2.39 ± 0.32	NA
V_{ss} (L/kg)	3.23 ± 0.81	NA
MRT_{last} (h)	1.24 ± 0.23	2.85 ± 0.86
MRT_{∞} (h)	1.37 ± 0.38	2.86 ± 0.86
F_t (%)	NA	115.97

NA, not applicable; ND, not detected; NC, not calculated

Table S5. Plasma concentrations (ng/ml) of compound **47** after IV administration in male mice

Time (h)	#1	#2	#3	Mean	S.D.
0.083	1091.7	891.3	960.6	981.2	101.8
0.5	361.1	330.1	360.0	350.4	17.6
1	184.8	172.2	236.4	197.8	34.0
2	86.9	75.3	124.1	95.4	25.5
4	21.0	21.3	42.2	28.2	12.2
8	0.2	1.6	2.3	1.4	1.1
24	2.5	0.0	0.0	0.8	1.4

BQL, Below the quantification limit

Table S6. Plasma concentrations (ng/ml) of compound **47** after PO administration in male mice

Time (h)	#1	#2	#3	Mean	S.D.
0.25	3156.3	1550.7	3944.4	2883.8	1219.9
0.5	1818.0	561.6	2433.8	1604.4	954.2
1	1278.0	360.9	1994.8	1211.3	819.0
2	506.9	514.6	1080.8	700.8	329.1
4	261.3	145.6	392.1	266.3	123.3
8	44.9	99.2	93.8	79.3	29.9
24	0.3	0.5	1.4	0.7	0.6

BQL, Below the quantification limit

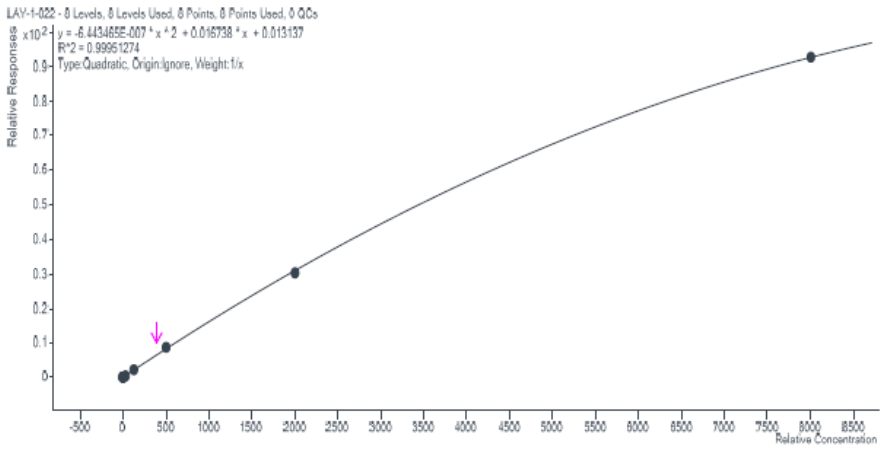
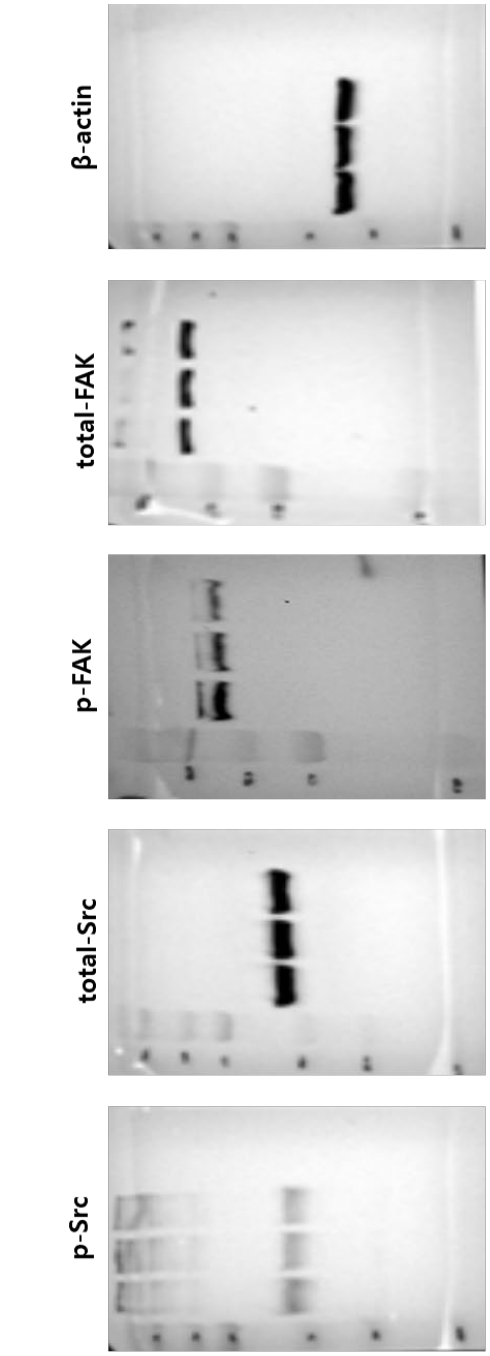


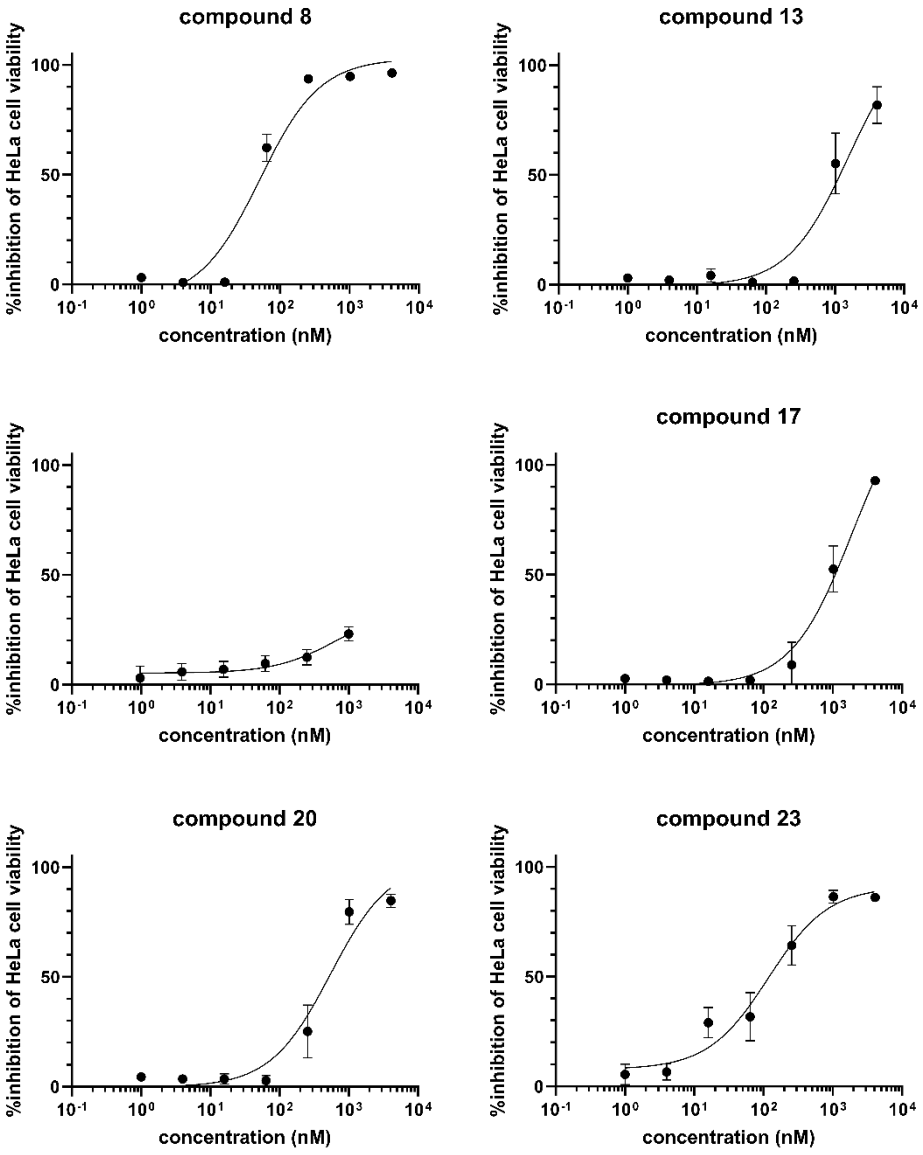
Figure S4. The calibration curve of compound **47**.

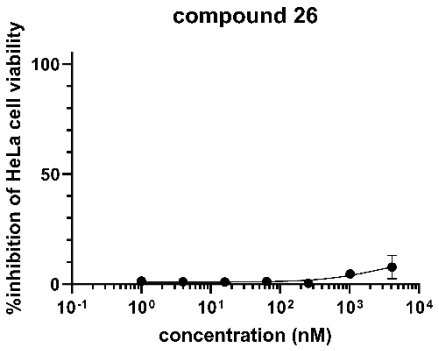
C. Original image of western blot

The order of sample loading is from left to right: PBS, compound **8**, compound **47**.



D. Dose-response curves of final compounds

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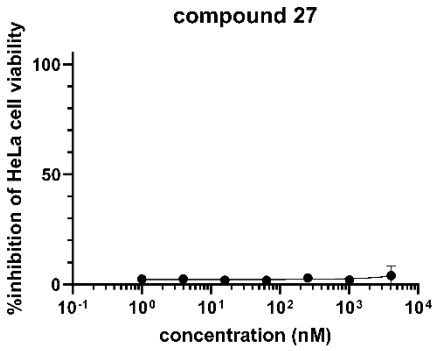
50
0
10-1
100
101
102
103
104
concentration (nM)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%inhibition of HeLa cell viability
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50
0
10-1
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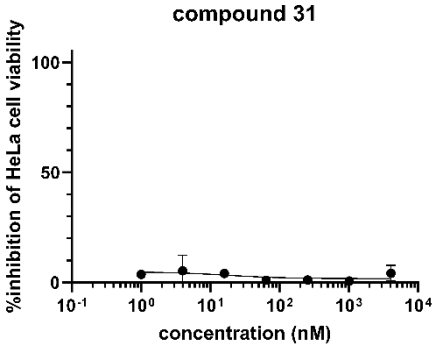
102
103
104
concentration (nM)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10-1
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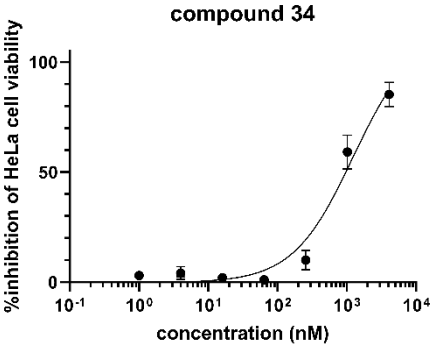
103
104
concentration (nM)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50
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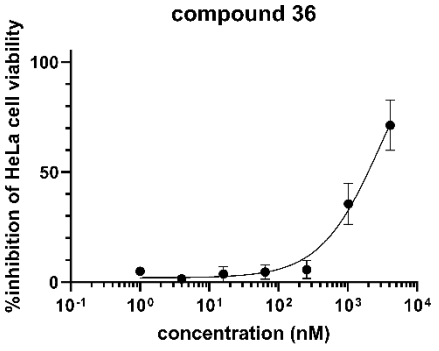
102
103
104
concentration (nM)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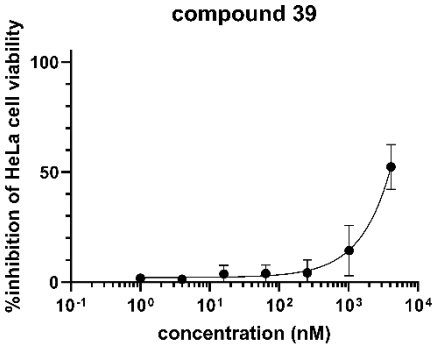
50
0
10-1
100
101
102
103
104
concentration (nM)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50
0
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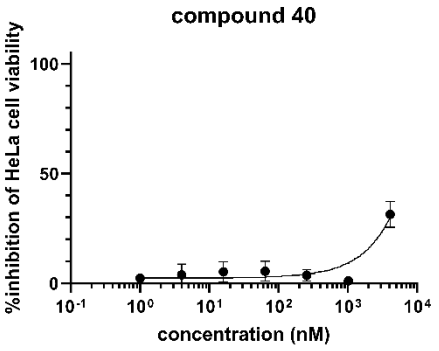
101
102
103
104
concentration (nM)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102
103
104
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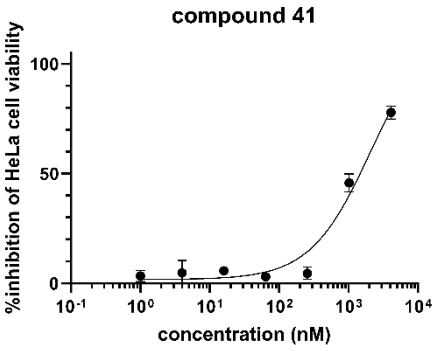
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10-1
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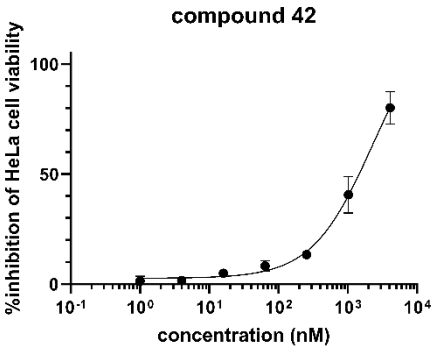
102
103
104
concentration (nM)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0
10-1
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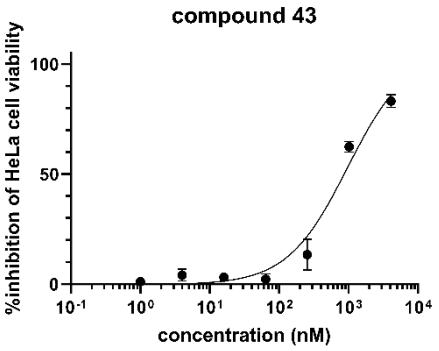
101
102
103
104
concentration (nM)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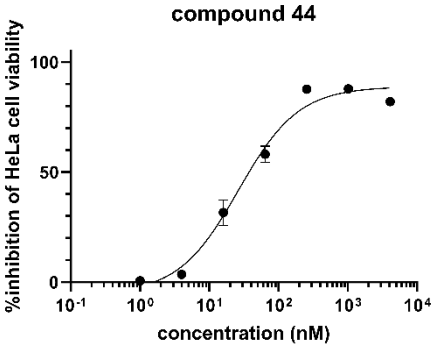
0
10-1
100
101
102
103
104
concentration (nM)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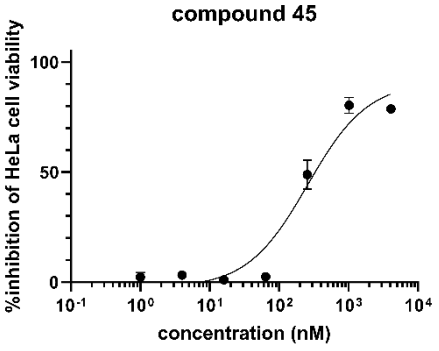
%inhibition of HeLa cell viability
100
50
0
10-1
100
101
102
103
104
concentration (nM)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50
0
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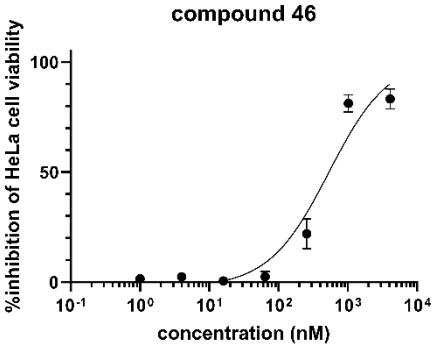
103
104
concentration (nM)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%inhibition of HeLa cell viability
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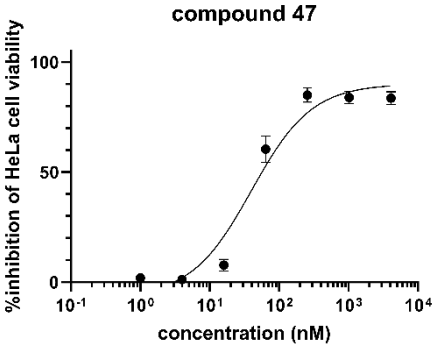
50
0
10-1
100
101
102
103
104
concentration (nM)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100
50
0
10-1
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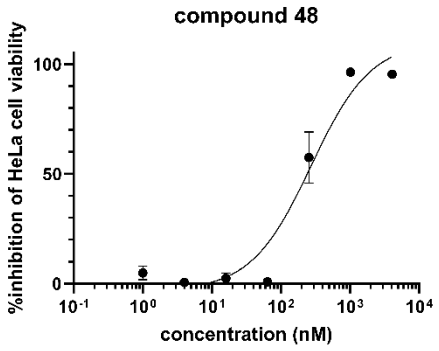
101
102
103
104
concentration (nM)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0
10-1
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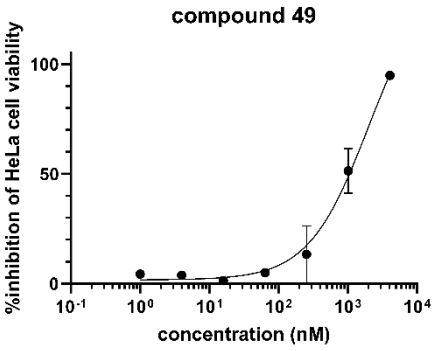
101
102
103
104
concentration (nM)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0
10-1
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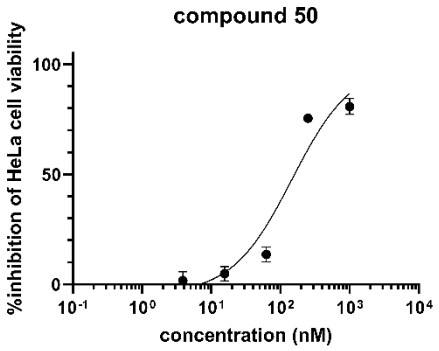
101
102
103
104
concentration (nM)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50
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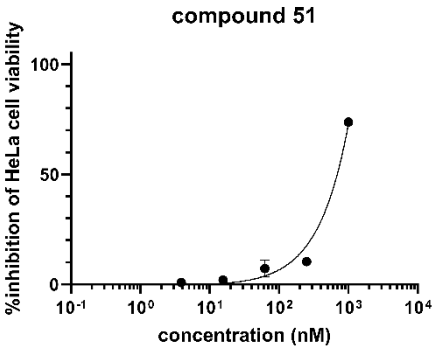
10-1
100
101
102
103
104
concentration (nM)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50
0
10-1
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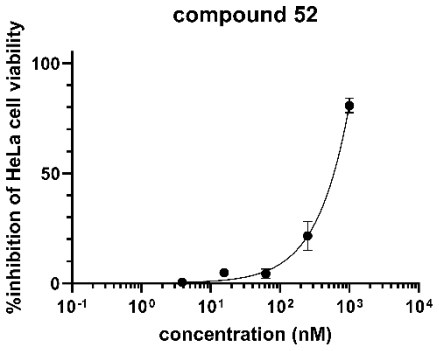
101
102
103
104
concentration (nM)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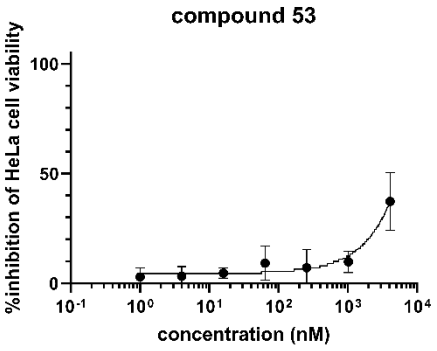
100
50
0
10-1
100
101
102
103
104
concentration (nM)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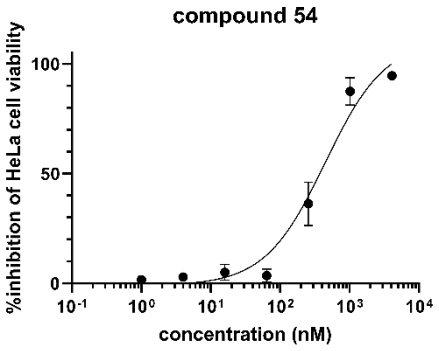
100
50
0
10-1
100
101
102
103
104
concentration (nM)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100
50
0
10-1
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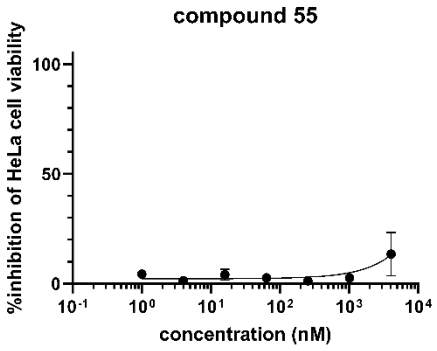
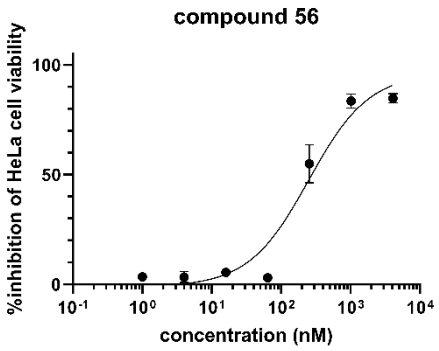
103
104
concentration (nM)


compound 55
%inhibition of HeLa cell viability
100
50
0
10-1
100
101
102
103
104
concentration (nM)


compound 56
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100
50
0
10-1
100
101
102
103
104
concentration (nM)

E. Biocompatibility test

Normal cell viability assay. MCF-10A (a breast epithelial line) cells were cultured in mammary epithelial cell growth medium (MEGM, Lonza, Switzerland). CCD-18Co (a colon fibroblast) and BJ (a skin fibroblast) cells were cultured with minimum essential medium (MEM, Gibco, Thermo Fisher Scientific, Waltham, MA) supplemented with 10% fetal bovine serum (Gibco) and 1% penicillin/streptomycin (Gibco) at 37 °C and 5% CO_2. A day before compound treatment, 5,000 cells from each cell line (MCF-10A, CCD-18Co, and BJ) were seeded into 96-well plates in 100 µL of cell culture medium. On the subsequent day, the cells were treated with test compounds dissolved in dimethyl sulfoxide (Sigma-Aldrich, St. Louis, MO). After 48 h of compound treatment, 10 µL of CCK-8 reagent was added to each well, and the absorbance at 450 nm was measured using a SpectraMax iD5 spectrophotometer (Molecular Devices, San Jose, CA). The absorbance signal at 450 nm is proportional to the number of viable cells.

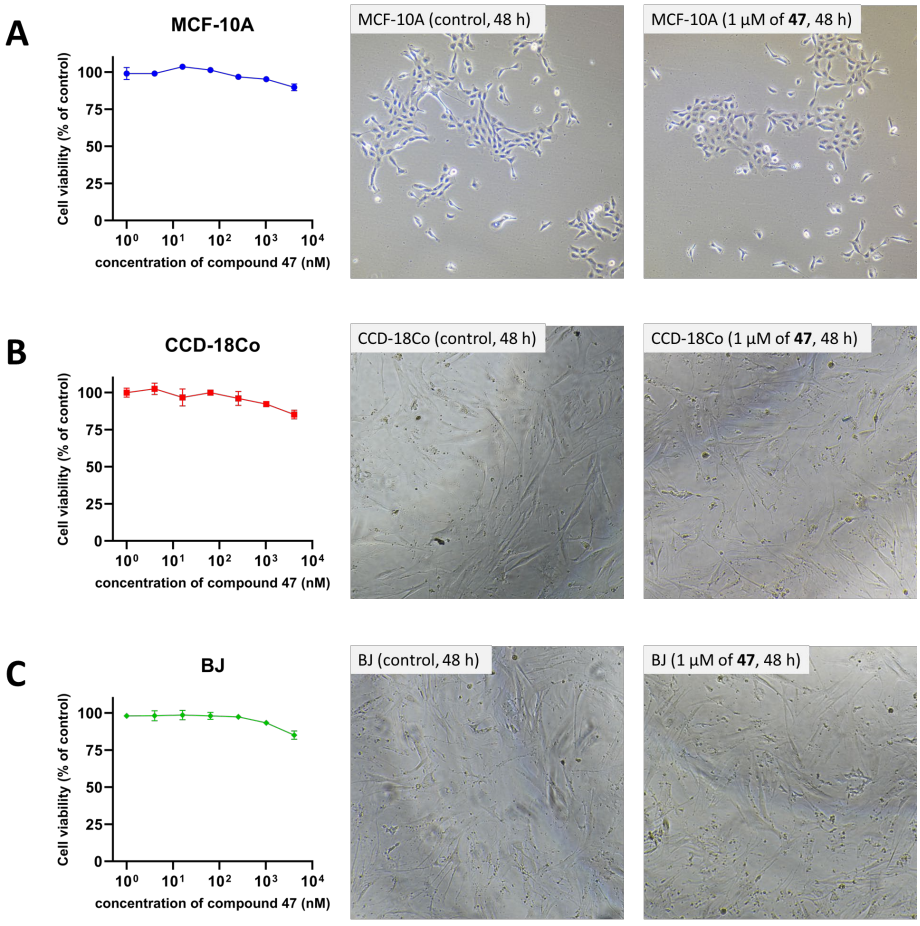
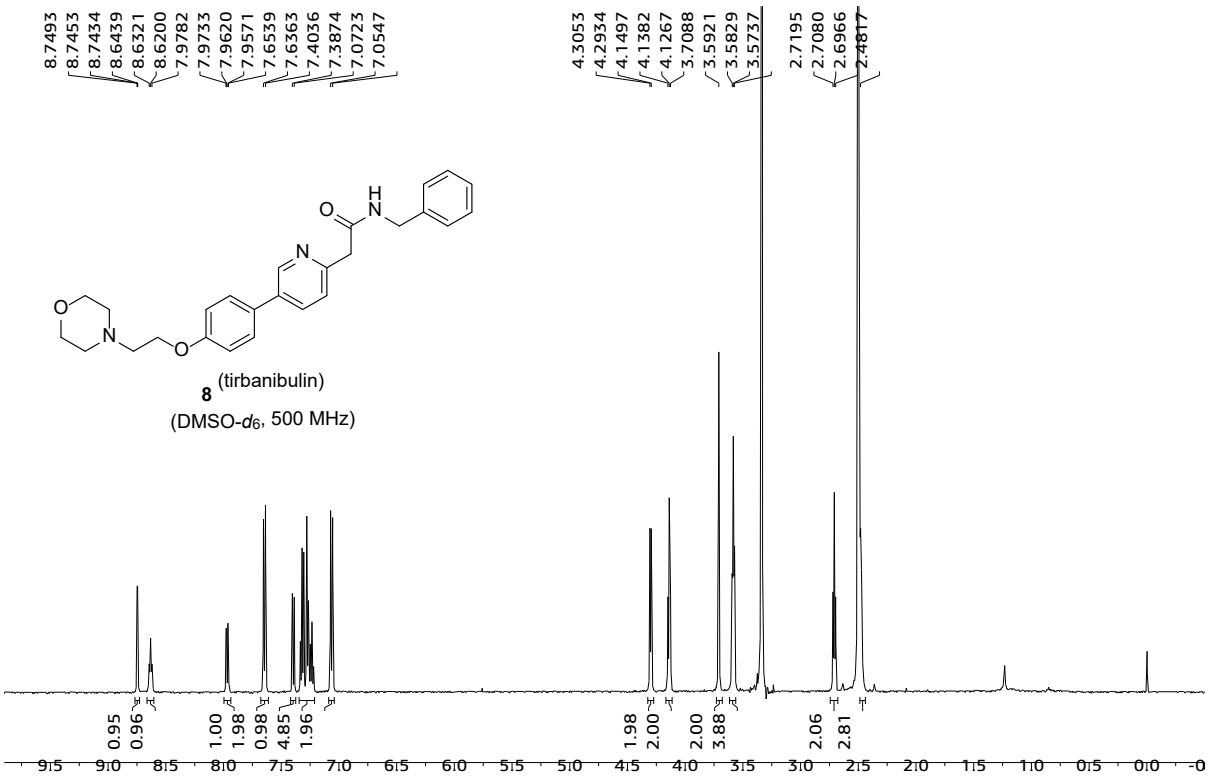


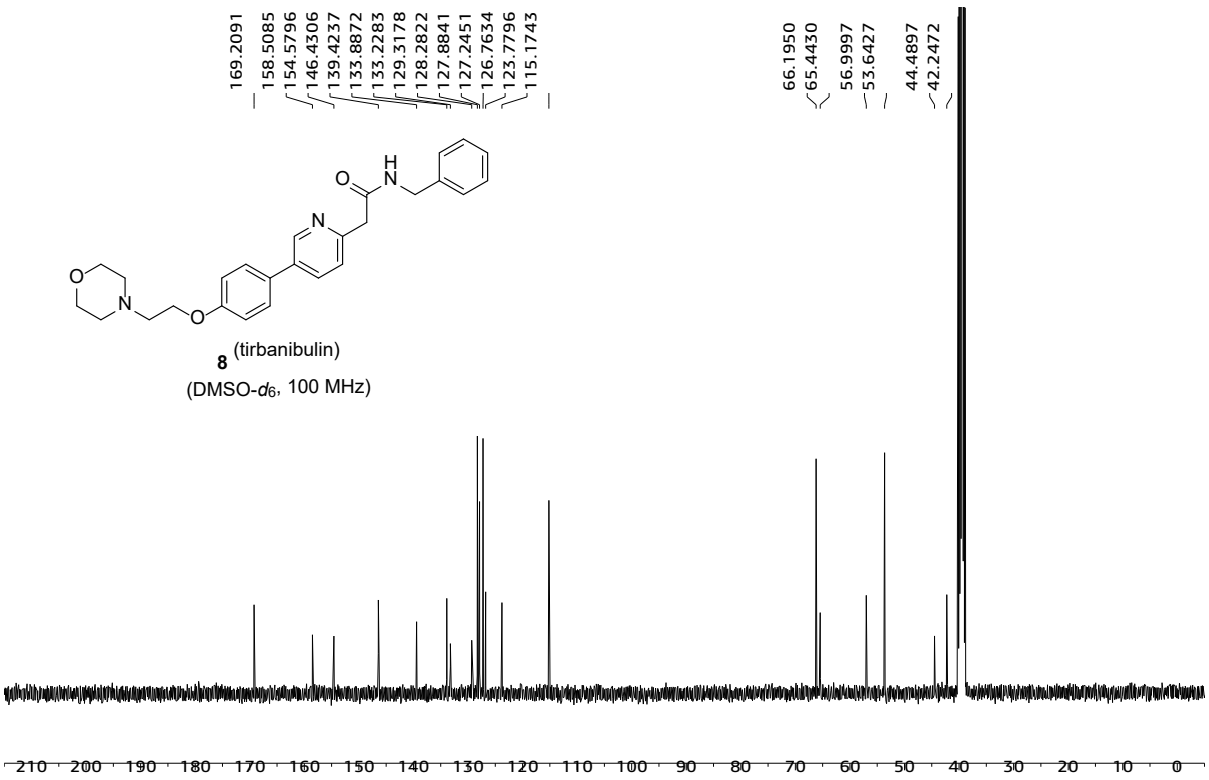
Figure S5. The cell viability graphs and bright-field images of (A) MCF-10A, (B) CCD-18Co, and (C) BJ cells treated with compound **47**.

F. Copies of ^{1}H and ^{13}C NMR, and LC/MS



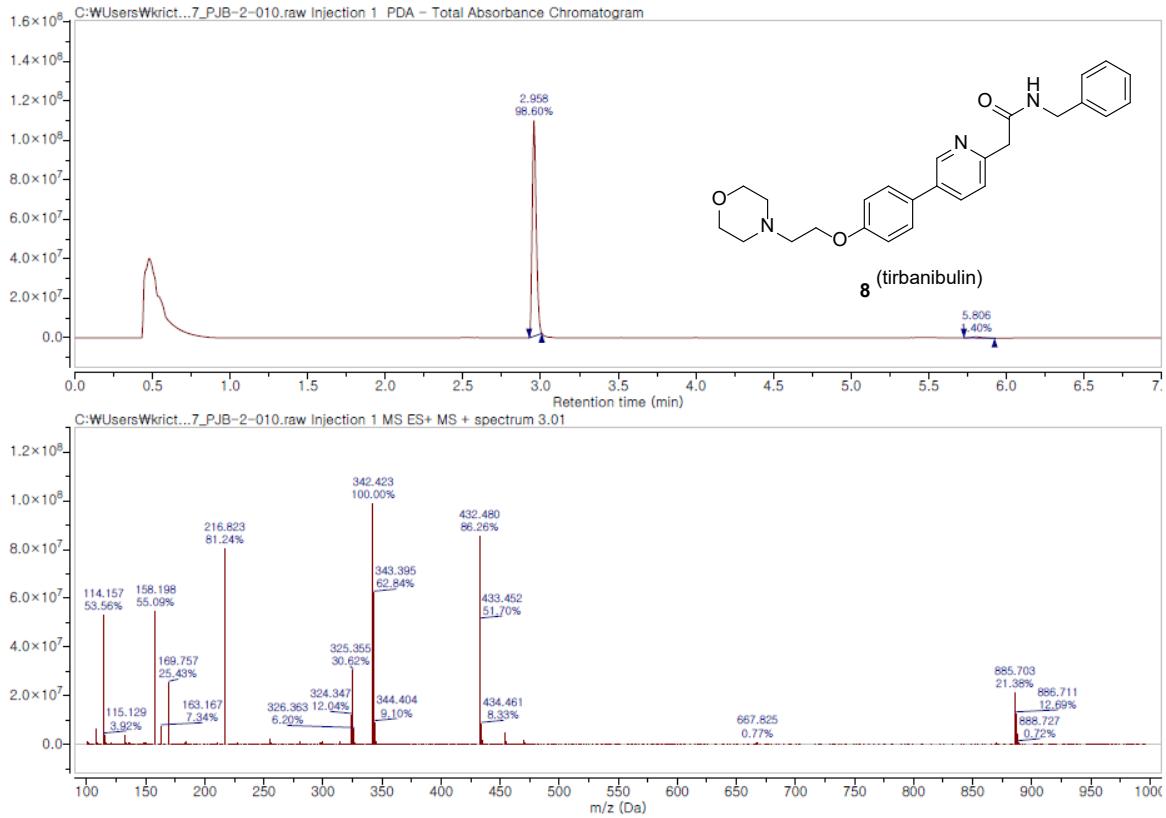
8 (tirbanibulin)

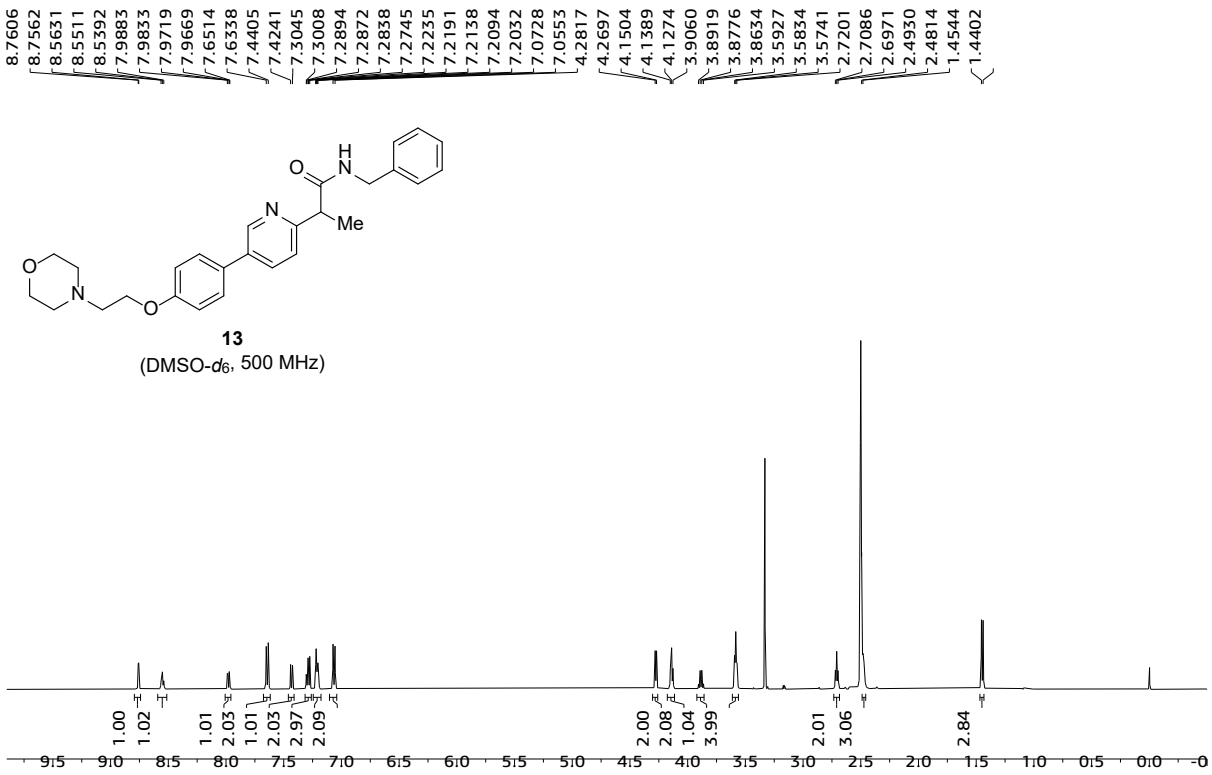
(DMSO-d_6, 500 MHz)



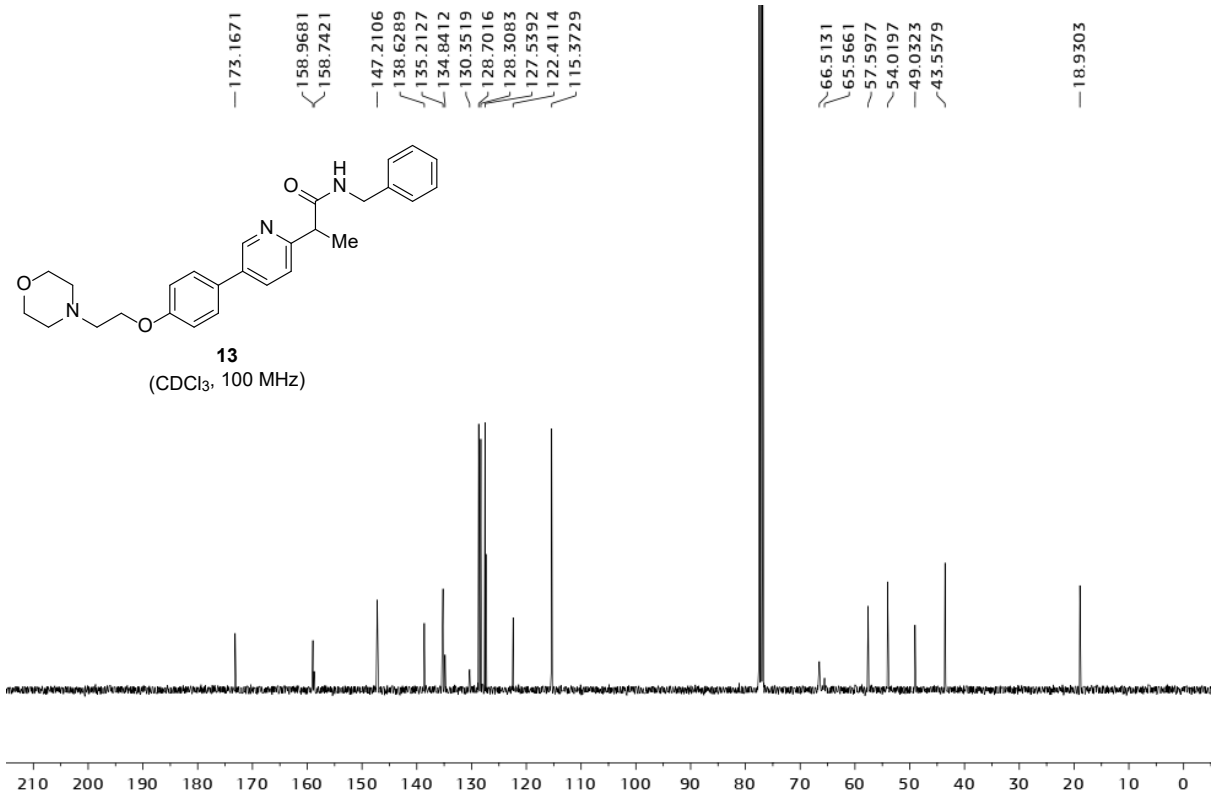
8 (tirbanibulin)

(DMSO-d_6, 100 MHz)

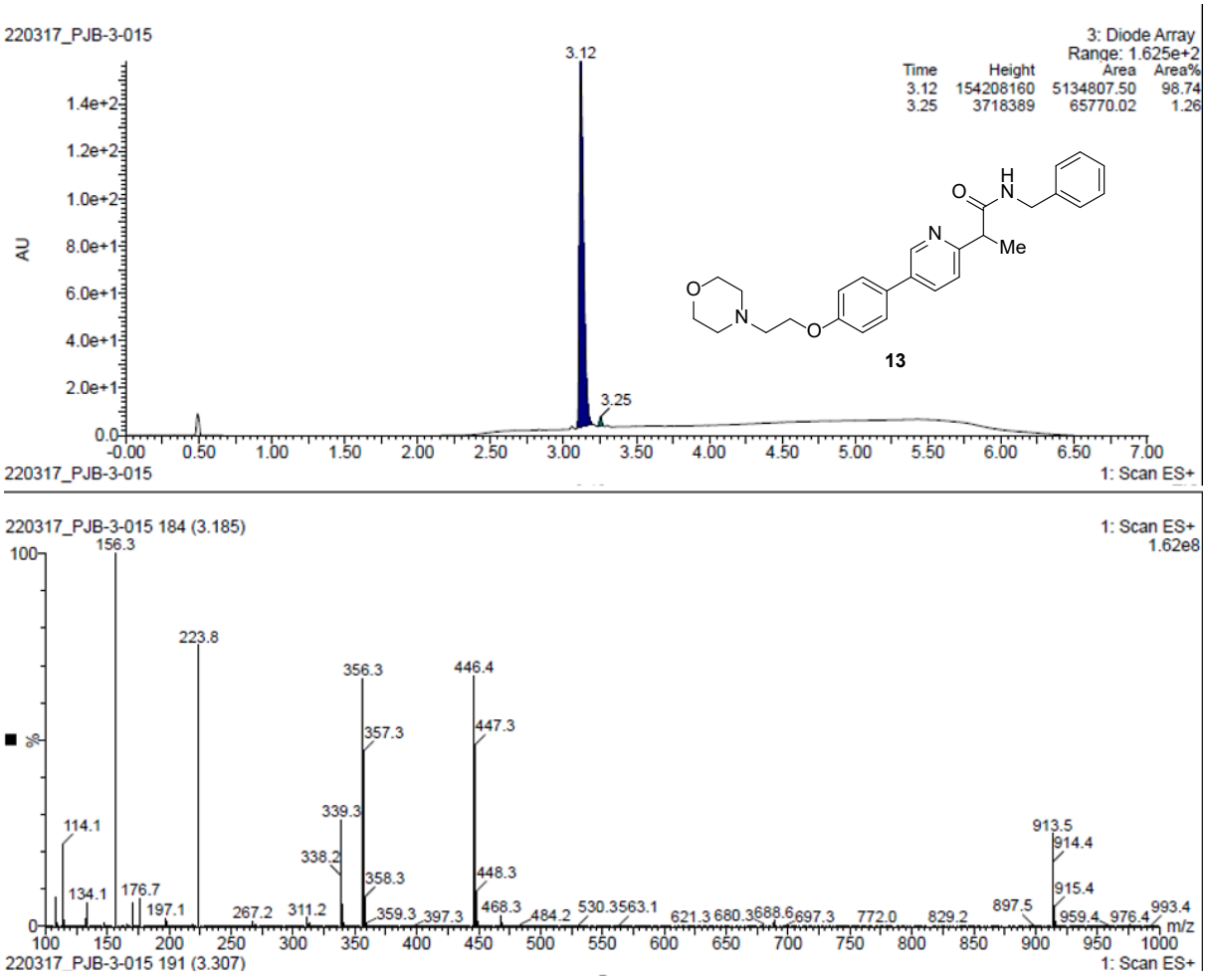

C:\Users\krict...7_PJB-2-010.raw Injection 1 PDA - Total Absorbance Chromatogram
2.958
98.60%
5.806
40%
Retention time (min)
8 (tirbanibulin)
C:\Users\krict...7_PJB-2-010.raw Injection 1 MS ES+ MS + spectrum 3.01
342.423
100.00%
216.823
81.24%
432.480
86.26%
343.395
62.84%
433.452
51.70%
114.157
53.56%
158.198
55.09%
169.757
25.43%
325.355
30.62%
324.347
12.04%
326.363
6.20%
344.404
9.10%
434.461
8.33%
163.167
7.34%
115.129
3.92%
667.825
0.77%
885.703
21.38%
886.711
12.69%
888.727
0.72%
m/z (Da)

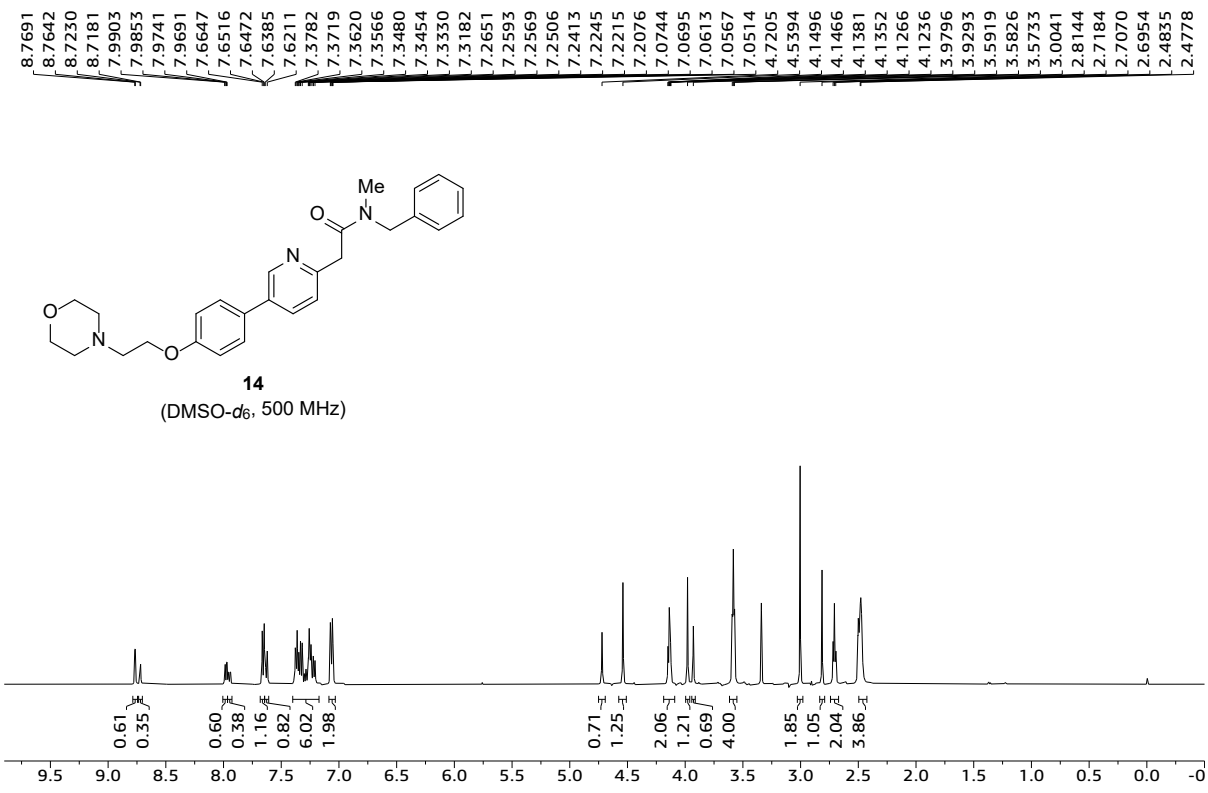


13
(DMSO-d_6, 500 MHz)

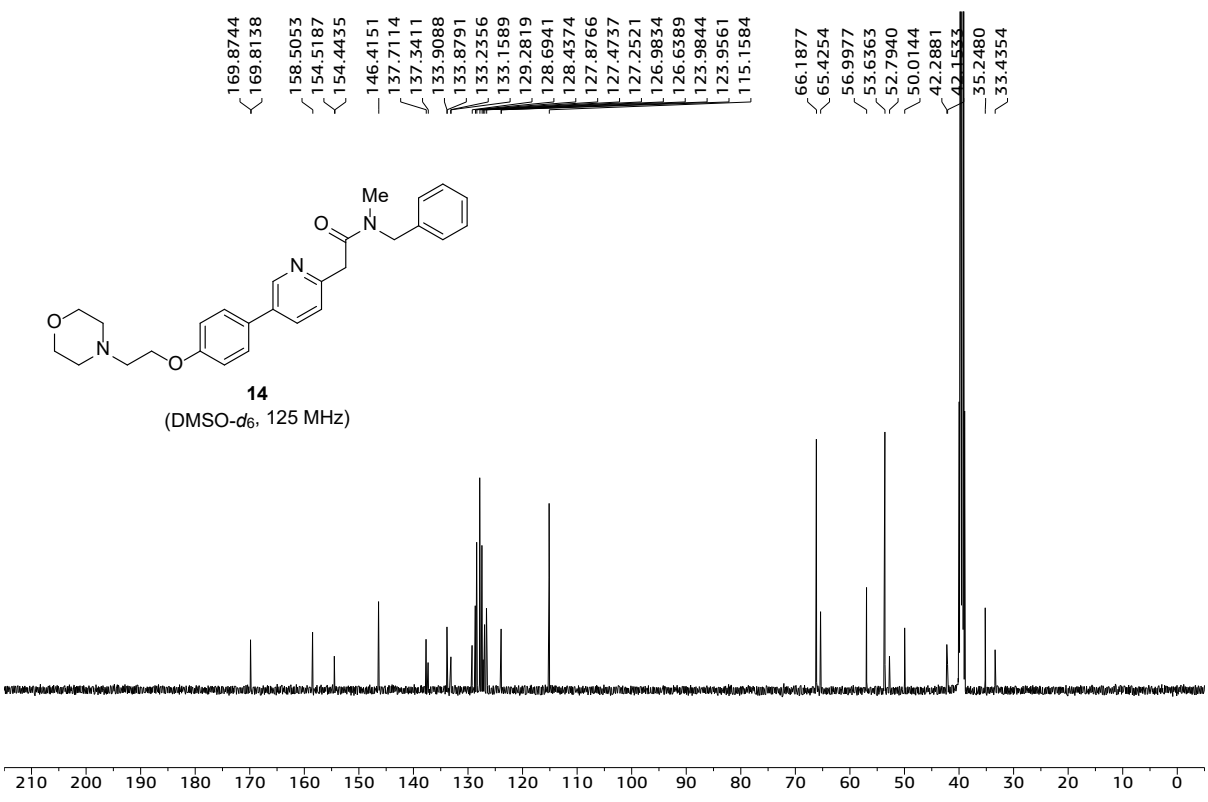


13
($CDCl_3$, 100 MHz)

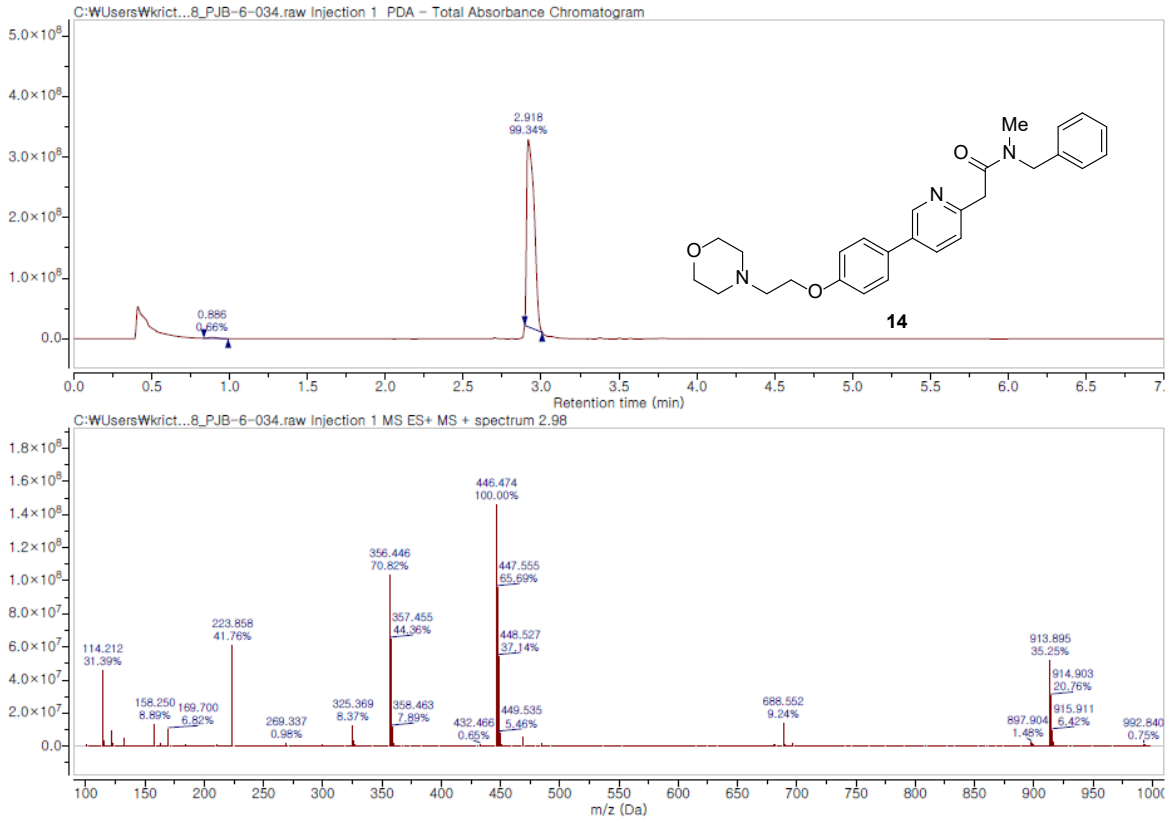

220317_PJB-3-015
3: Diode Array
Range: 1.625e+2
Time Height Area Area%
3.12 154208160 5134807.50 98.74
3.25 3718389 65770.02 1.26
3.12
3.25
AU
13
220317_PJB-3-015
1: Scan ES+
220317_PJB-3-015 184 (3.185)
1: Scan ES+
1.62e8
156.3
223.8
356.3
446.4
357.3
447.3
339.3
338.2
114.1
913.5
914.4
358.3
448.3
134.1
176.7
197.1
915.4
m/z
220317_PJB-3-015 191 (3.307)
1: Scan ES+

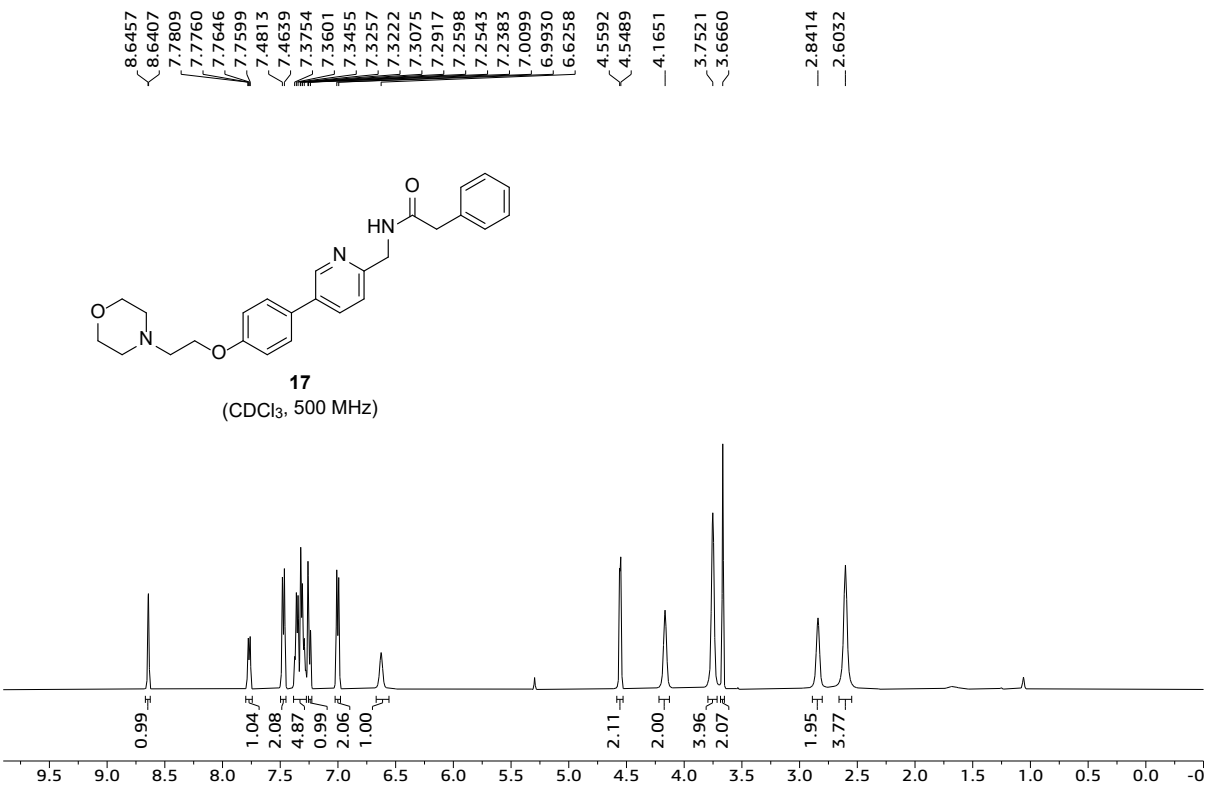


14
(DMSO-d_6, 500 MHz)



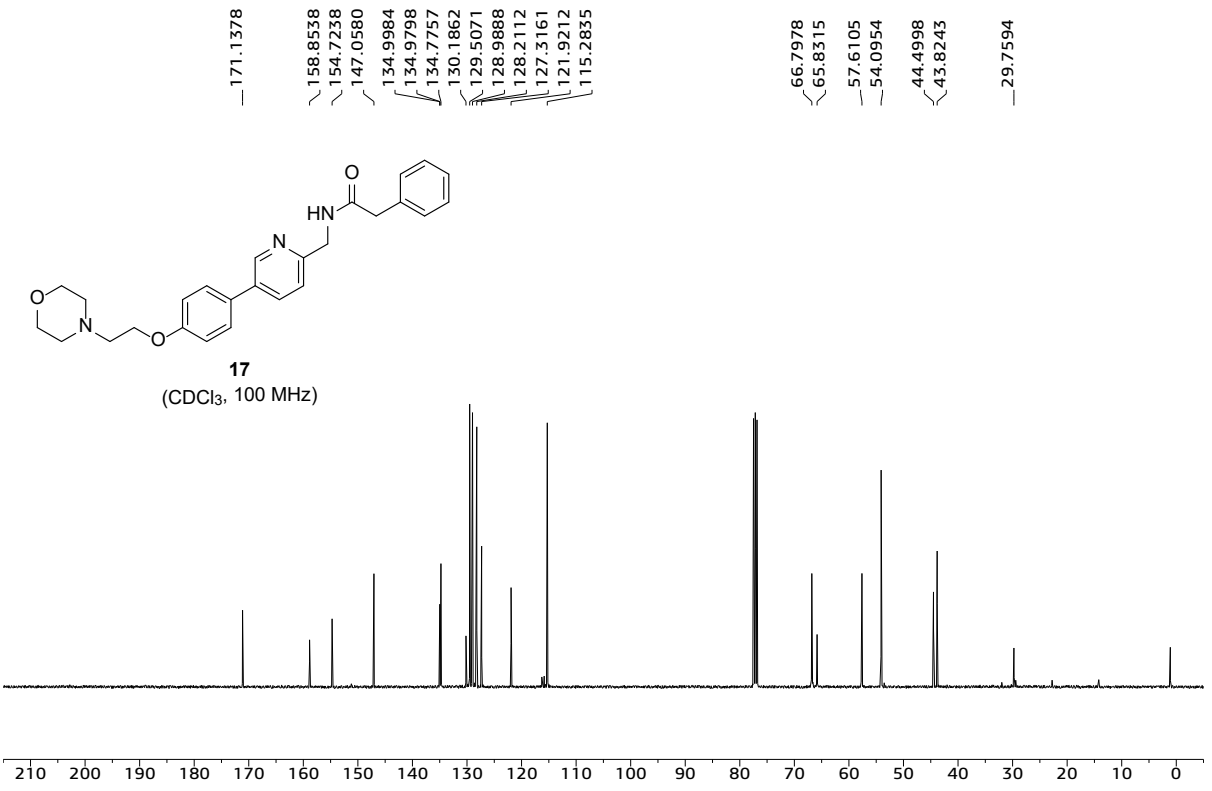
14
(DMSO-d_6, 125 MHz)


C:₩Users₩krict...8_PJB-6-034.raw Injection 1 PDA - Total Absorbance Chromatogram
2.918
99.34%
0.886
0.66%
Retention time (min)
14
C:₩Users₩krict...8_PJB-6-034.raw Injection 1 MS ES+ MS + spectrum 2.98
446.474
100.00%
356.446
70.82%
447.555
65.69%
357.455
44.36%
223.858
41.76%
448.527
37.14%
114.212
31.39%
913.895
35.25%
914.903
20.76%
158.250
8.89%
169.700
6.82%
325.369
8.37%
358.463
7.89%
449.535
5.46%
688.552
9.24%
915.911
6.42%
269.337
0.98%
432.466
0.65%
897.904
1.48%
992.840
0.75%
m/z (Da)



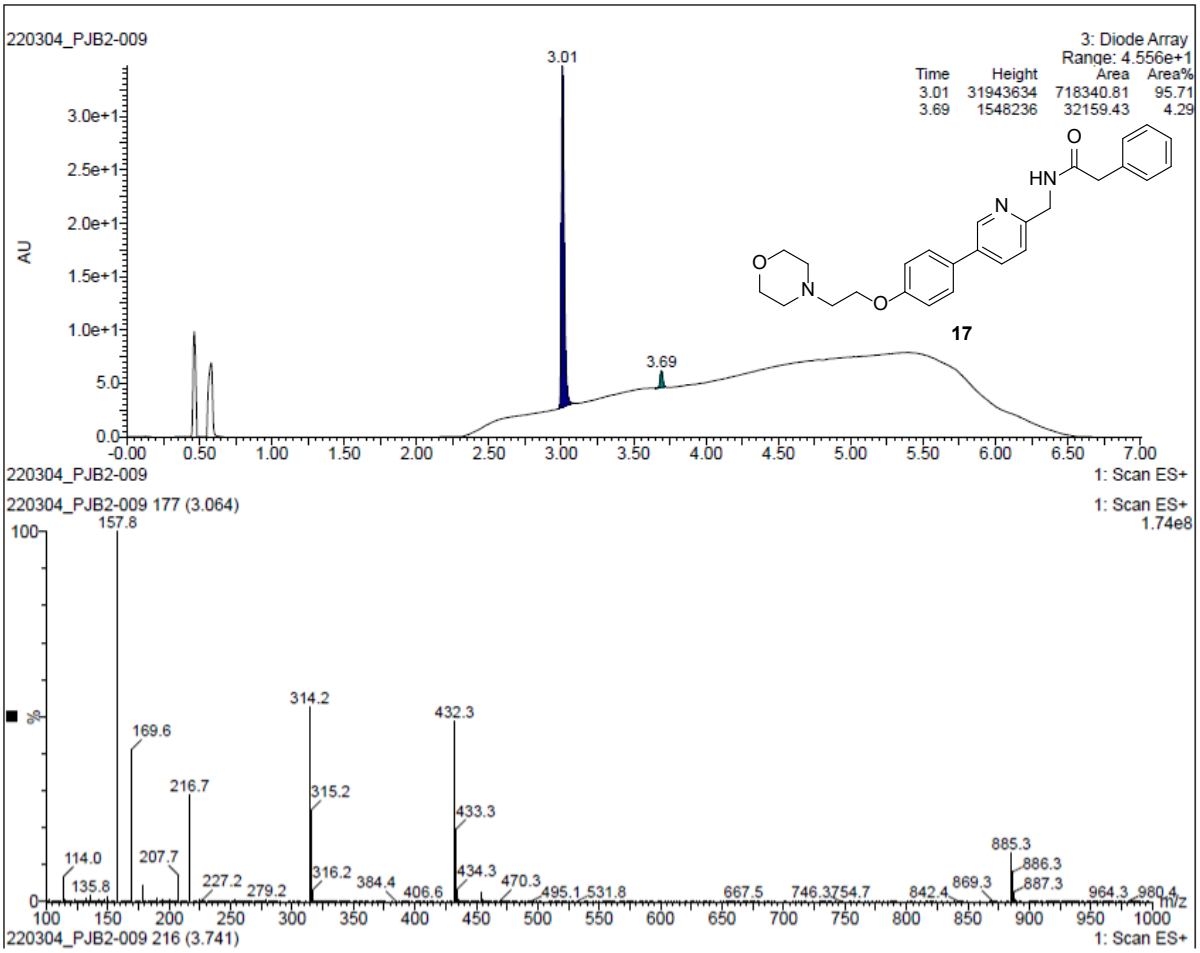
17

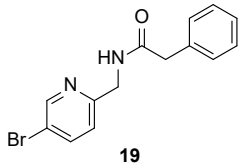
($CDCl_3$, 500 MHz)



17

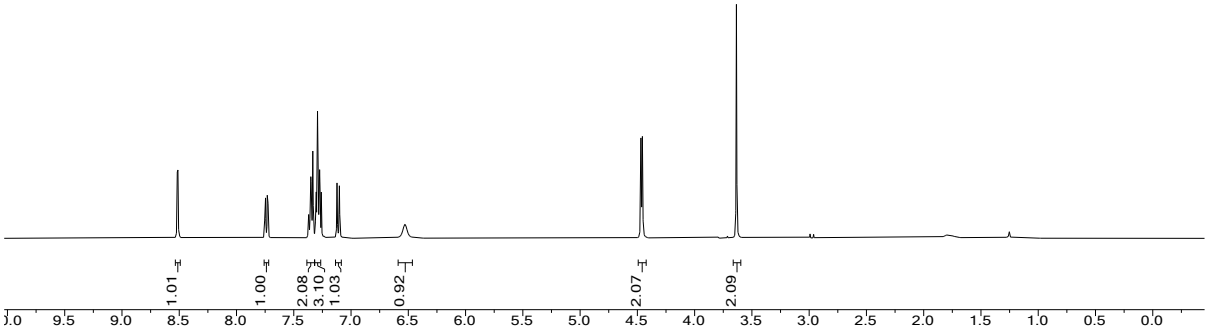
($CDCl_3$, 100 MHz)

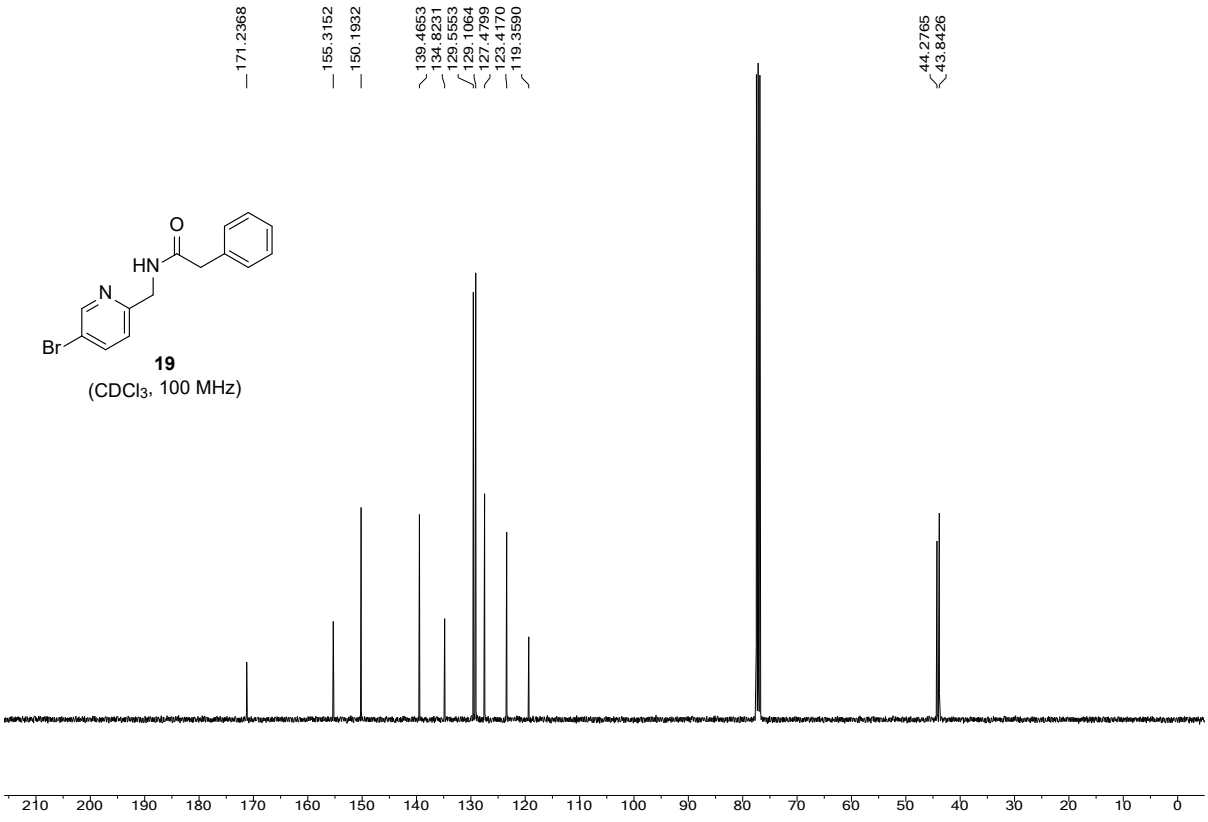

220304_PJB2-009
3: Diode Array
Range: 4.556e+1
Time Height Area Area%
3.01 31943634 718340.81 95.71
3.69 1548236 32159.43 4.29
3.01
3.69
AU
17
220304_PJB2-009
1: Scan ES+
220304_PJB2-009 177 (3.064)
1: Scan ES+
1.74e8
157.8
314.2
432.3
169.6
216.7
315.2
433.3
885.3
886.3
887.3
114.0
135.8
207.7
227.2
279.2
316.2
384.4
406.6
434.3
470.3
495.1
531.8
667.5
746.3
754.7
842.4
869.3
964.3
980.4
m/z
220304_PJB2-009 216 (3.741)
1: Scan ES+



19

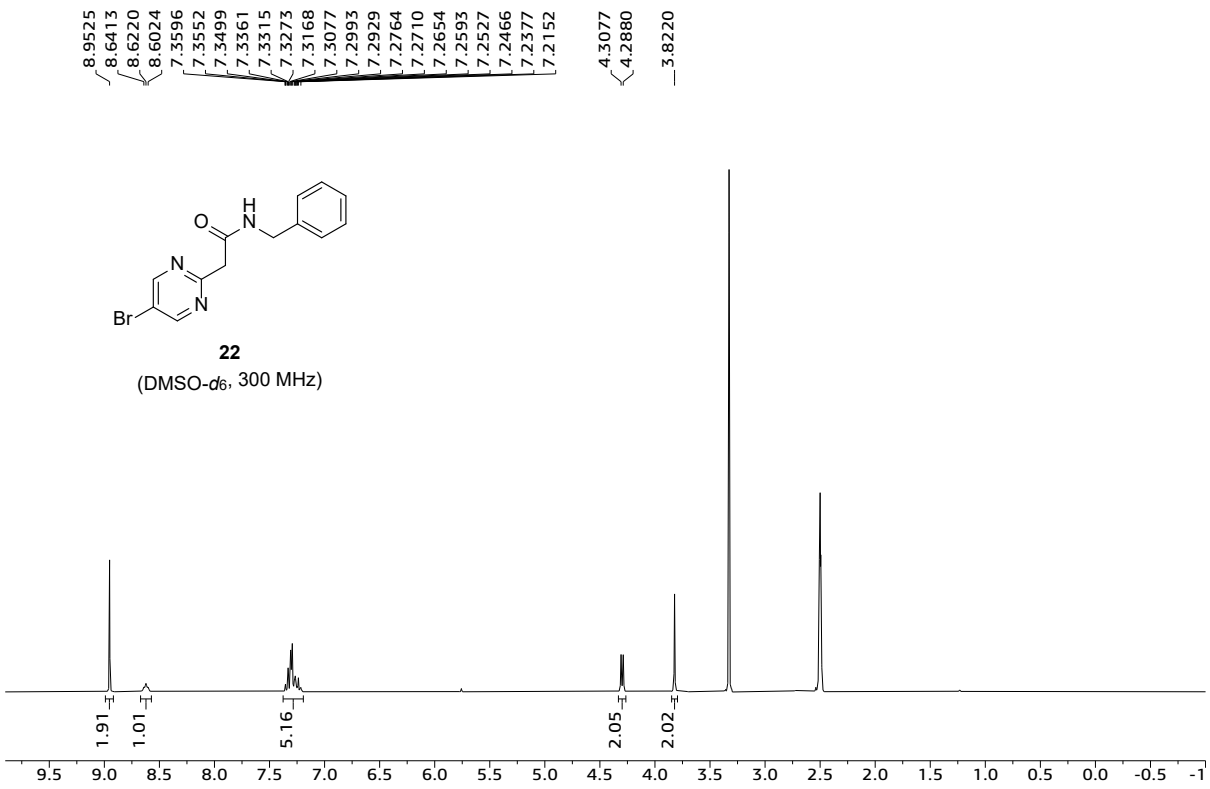
($CDCl_3$, 400 MHz)





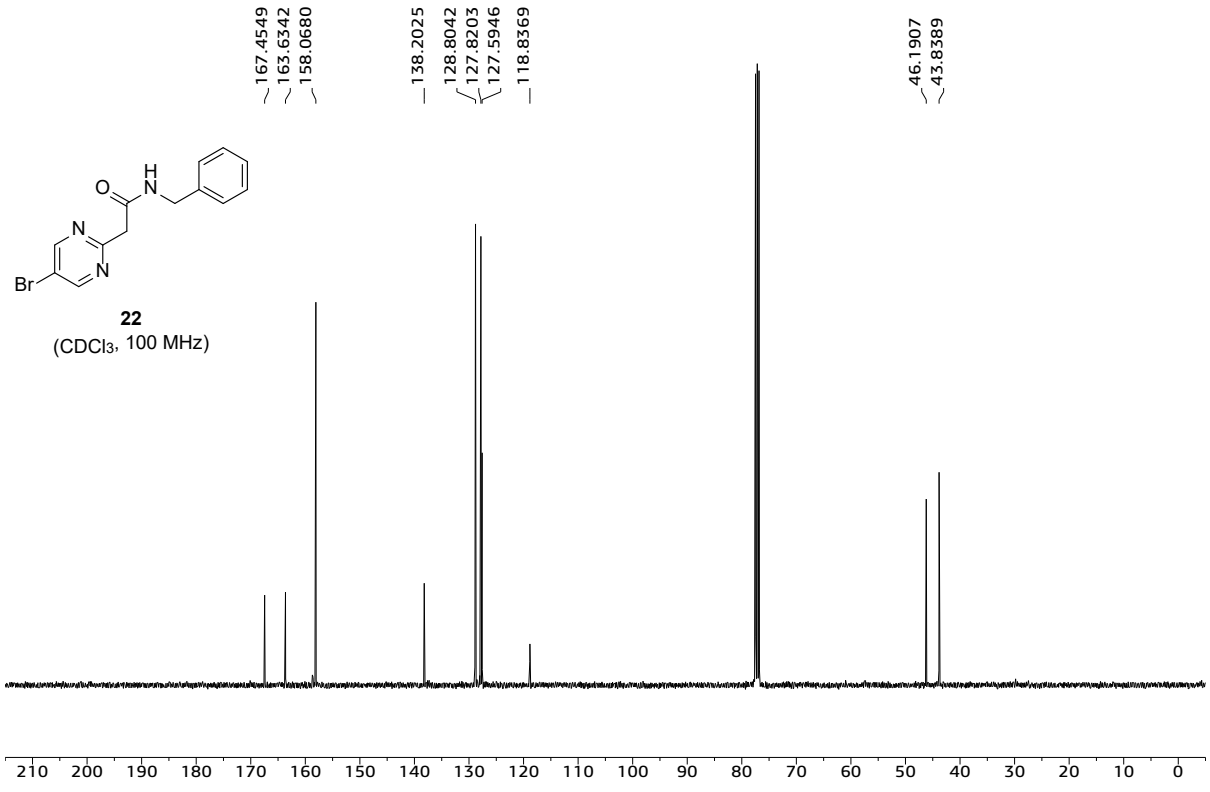
19

($CDCl_3$, 100 MHz)



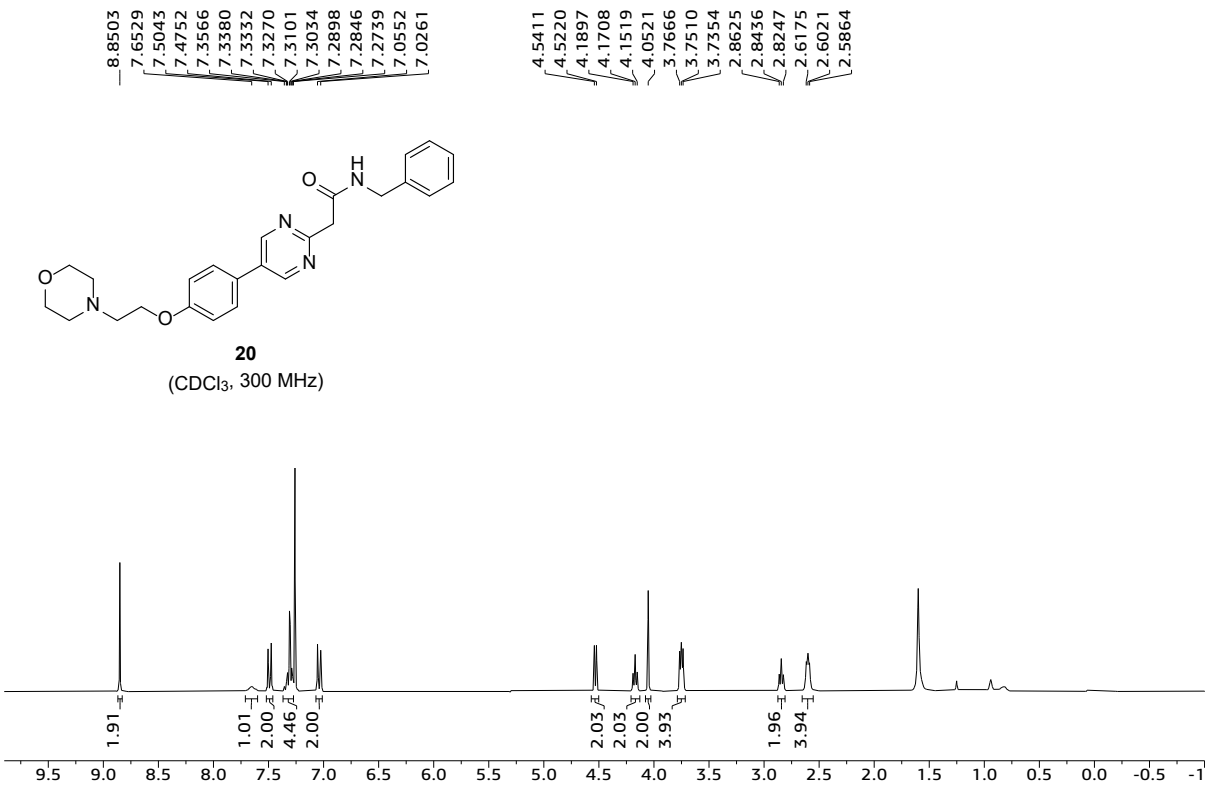
22

(DMSO-d_6, 300 MHz)



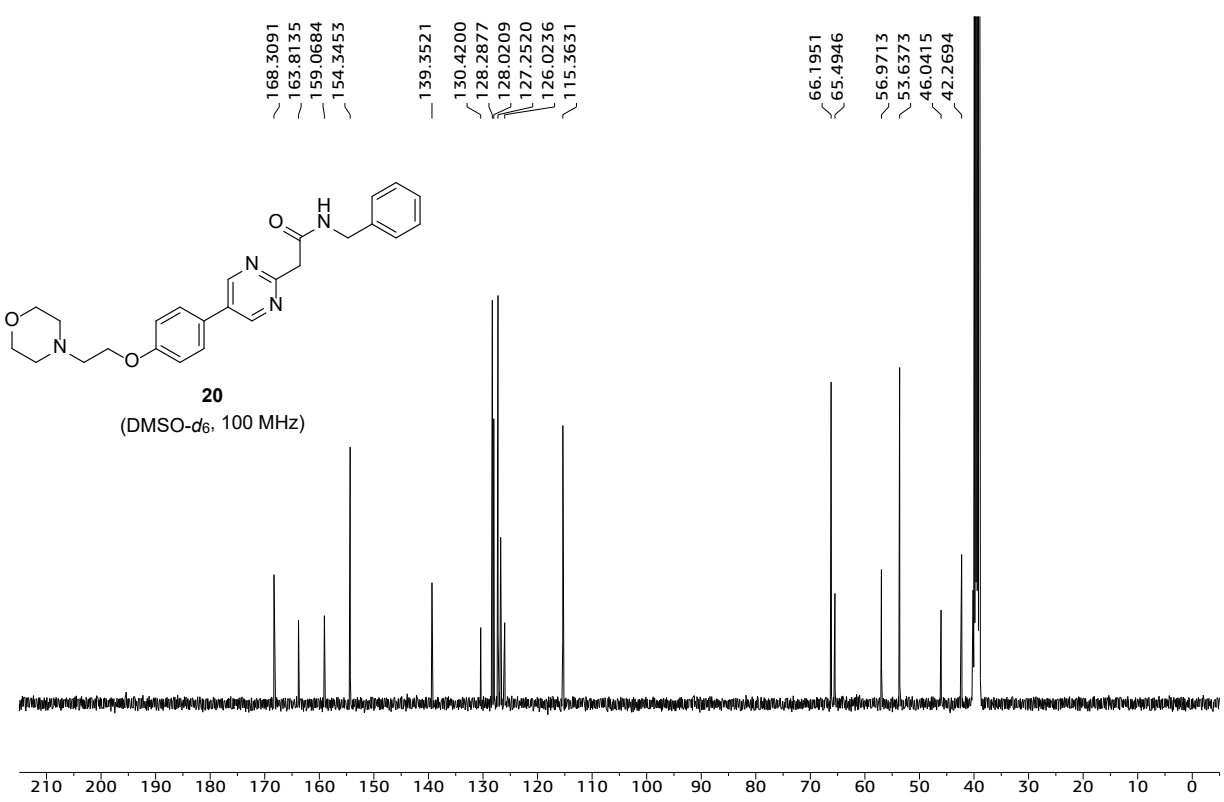
22

($CDCl_3$, 100 MHz)



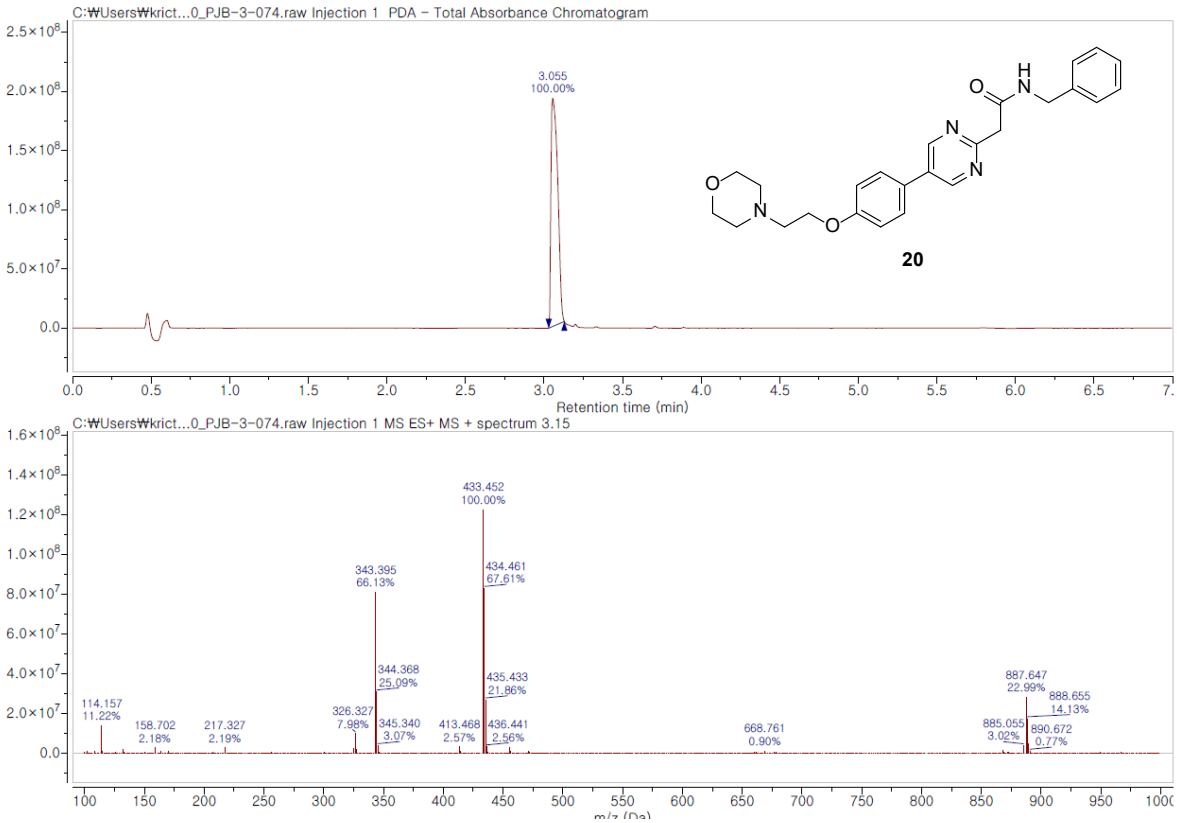
20

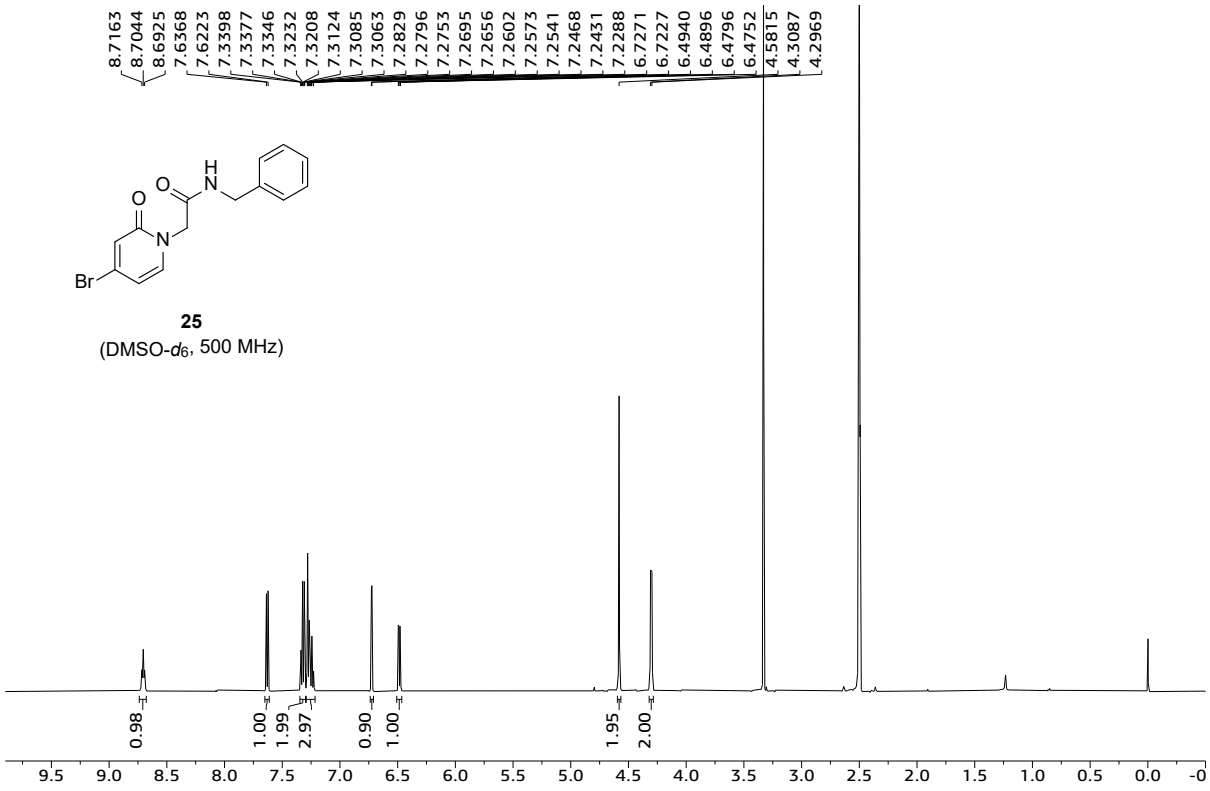
($CDCl_3$, 300 MHz)



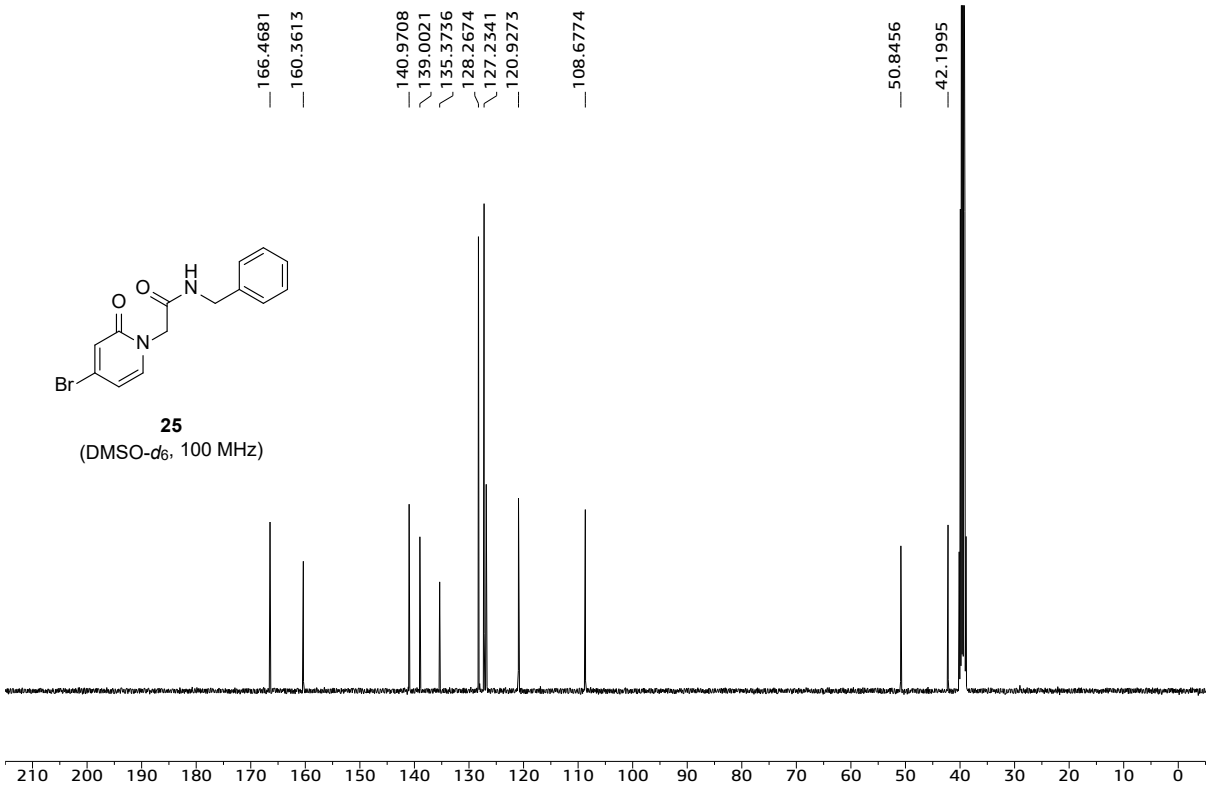
20

($DMSO\text{-}d_6$, 100 MHz)

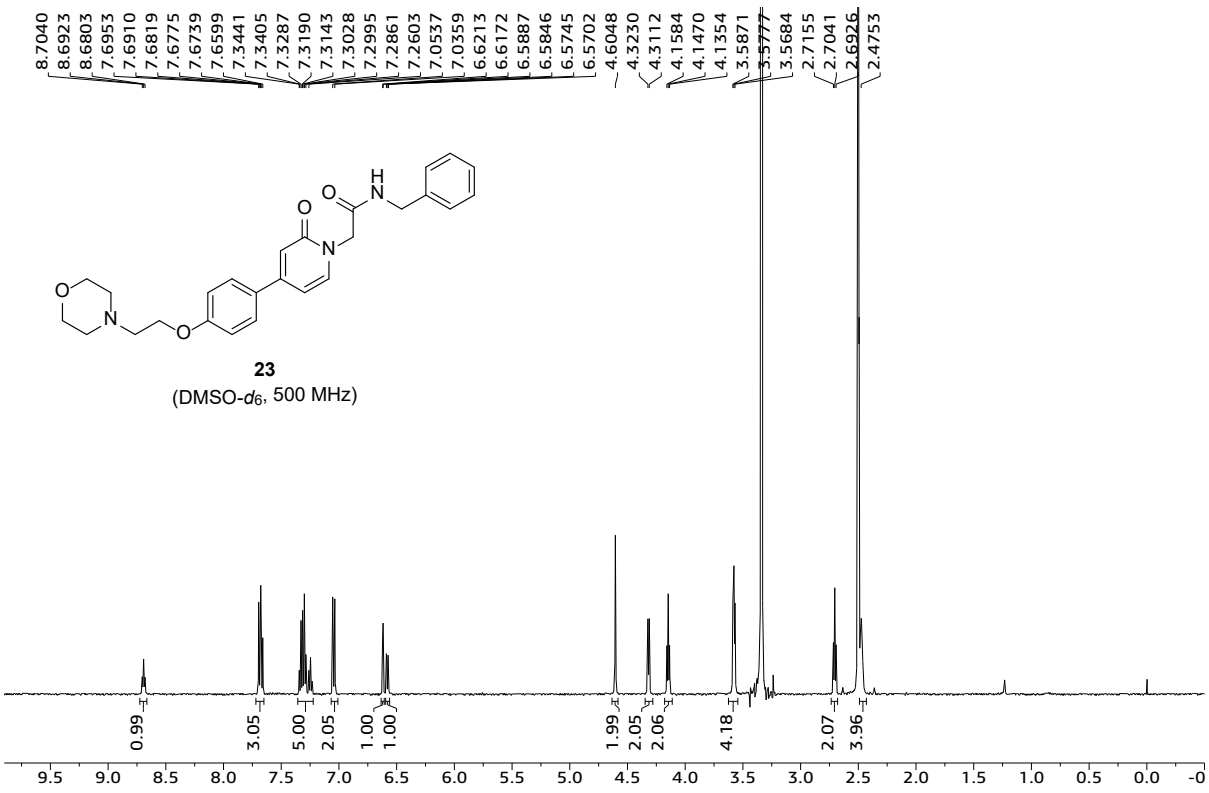

C:₩Users₩krict...0_PJB-3-074.raw Injection 1 PDA - Total Absorbance Chromatogram
3.055
100.00%
Retention time (min)
20
C:₩Users₩krict...0_PJB-3-074.raw Injection 1 MS ES+ MS + spectrum 3.15
433.452
100.00%
343.395
66.13%
434.461
67.61%
344.368
25.09%
435.433
21.86%
114.157
11.22%
158.702
2.18%
217.327
2.19%
326.327
7.98%
345.340
3.07%
413.468
2.57%
436.441
2.56%
668.761
0.90%
887.647
22.99%
888.655
14.13%
885.055
3.02%
890.672
0.77%
m/z (Da)



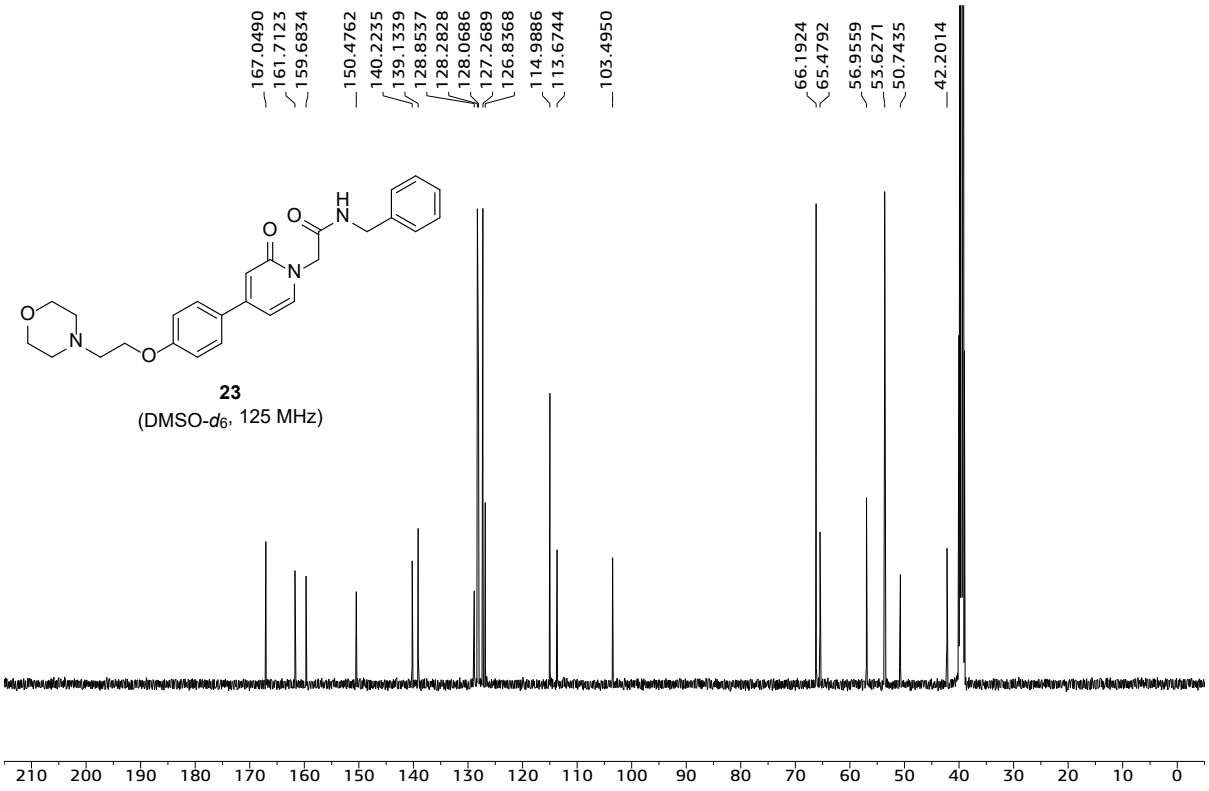
25
(DMSO-d_6, 500 MHz)



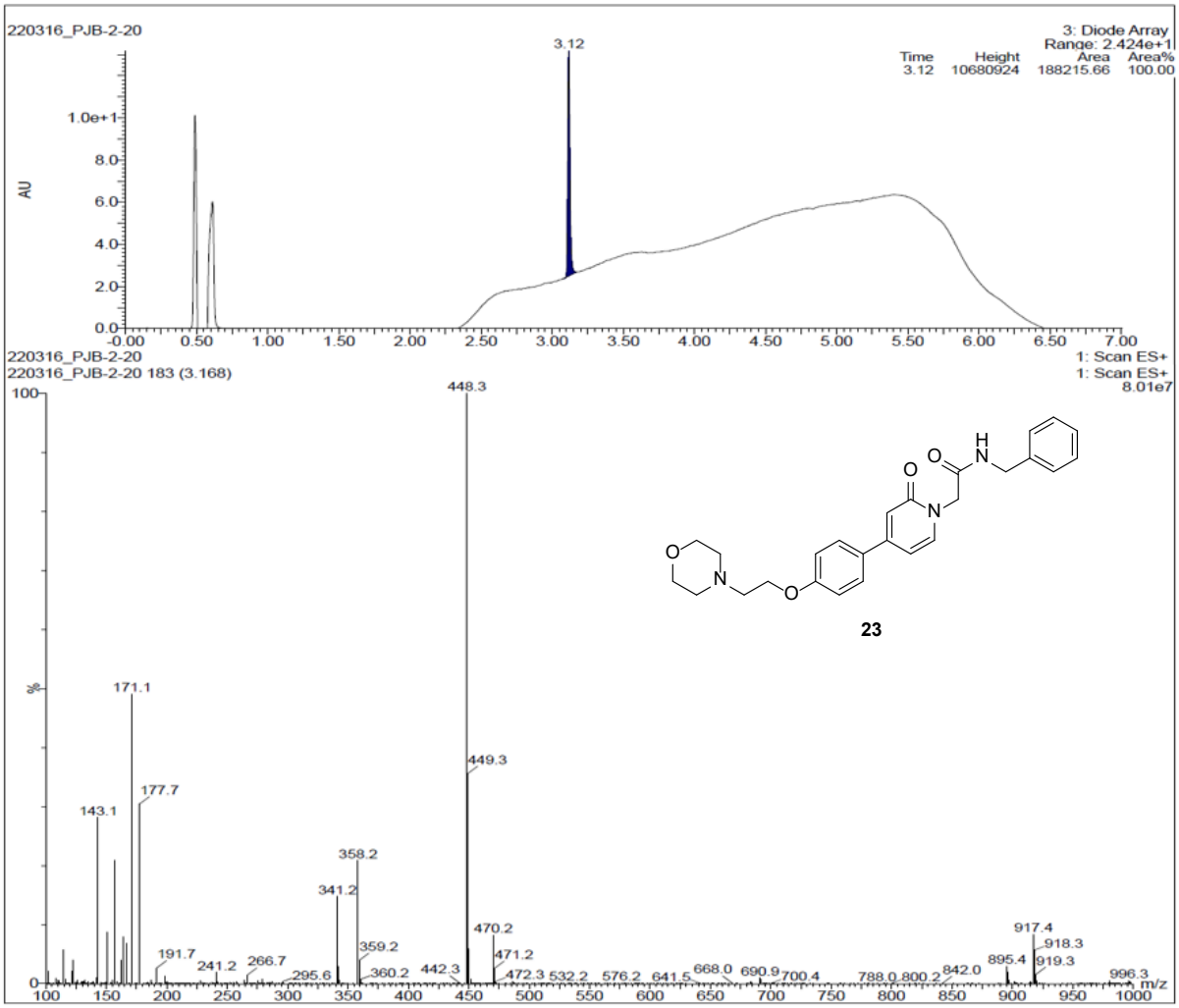
25
(DMSO-d_6, 100 MHz)

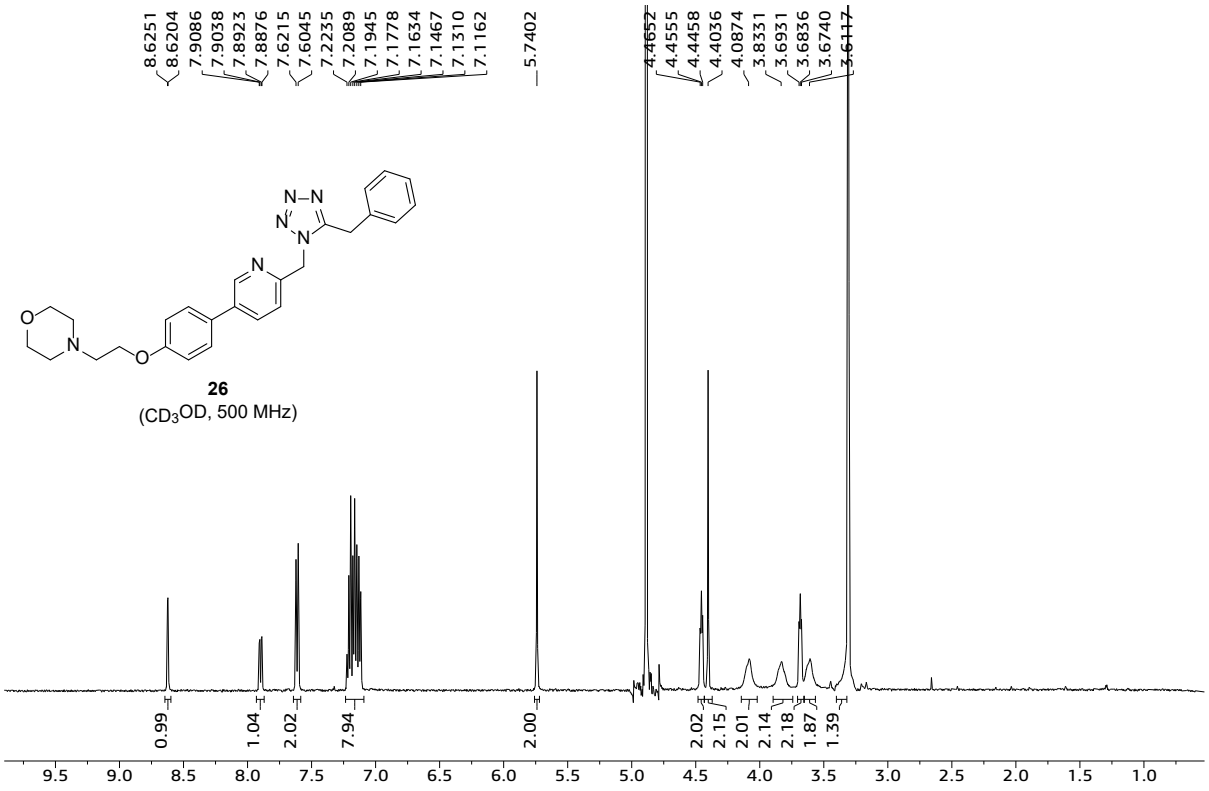


23
(DMSO-d_6, 500 MHz)

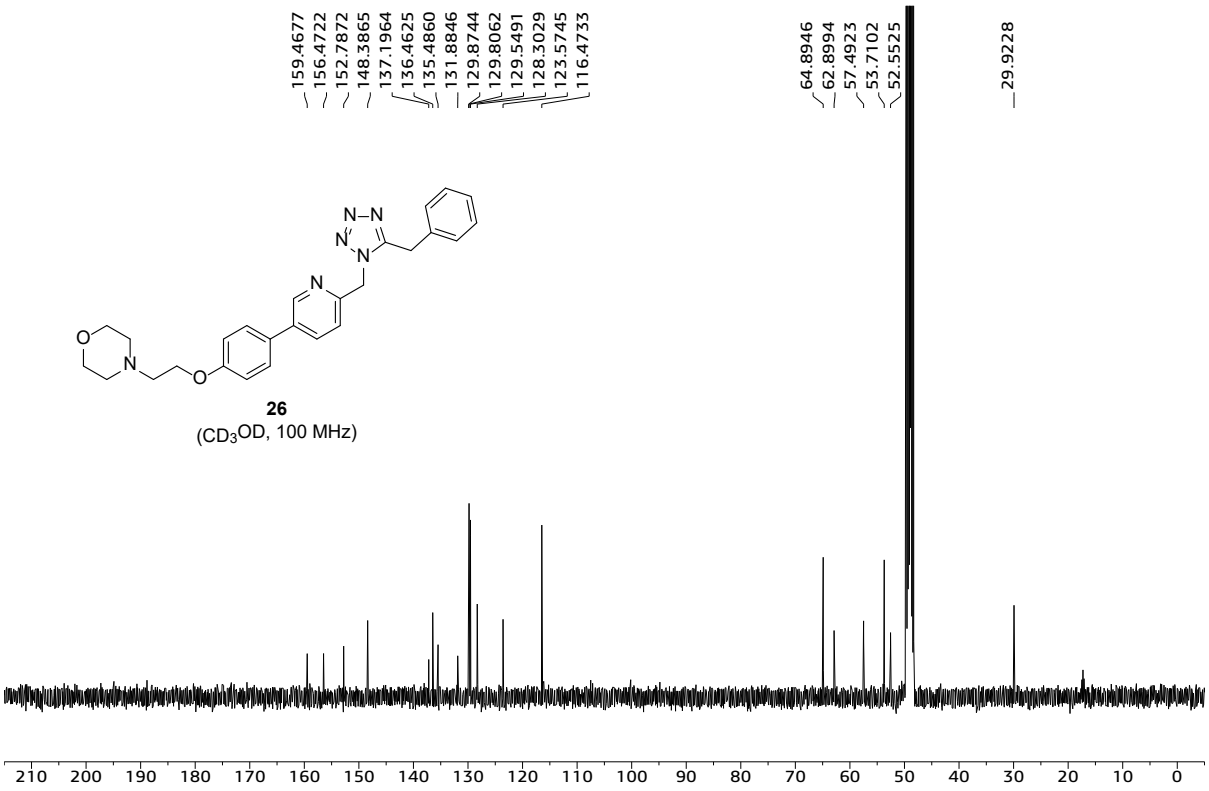


23
(DMSO-d_6, 125 MHz)

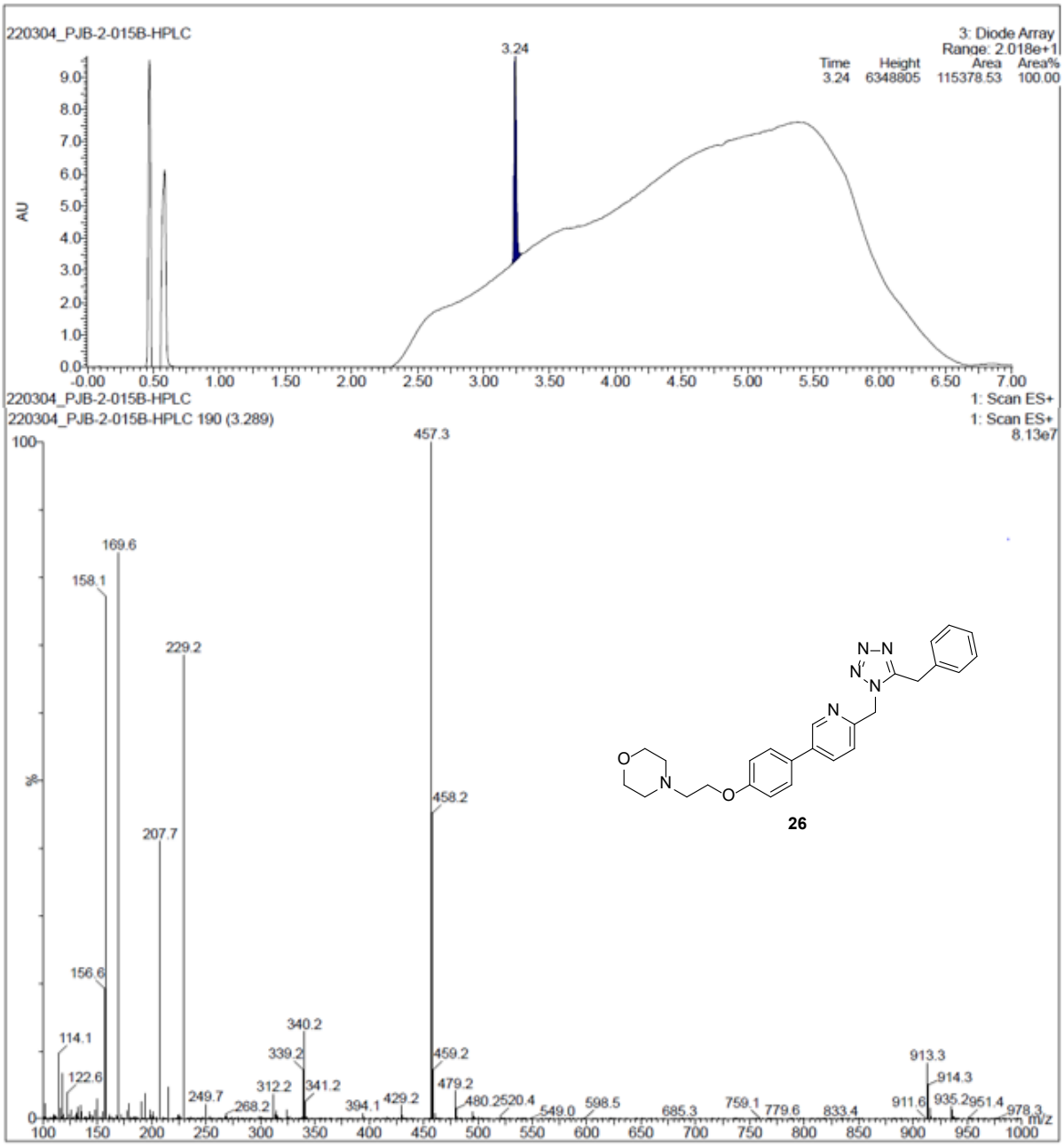

220316_PJB-2-20
3: Diode Array
Range: 2.424e+1
Time Height Area Area%
3.12 10680924 188215.66 100.00
3.12
AU
220316_PJB-2-20
220316_PJB-2-20 183 (3.168)
1: Scan ES+
1: Scan ES+
8.01e7
448.3
449.3
171.1
177.7
143.1
358.2
341.2
359.2
470.2
471.2
191.7
241.2
266.7
295.6
360.2
442.3
472.3
532.2
576.2
641.5
668.0
690.9
700.4
788.0
800.2
842.0
895.4
917.4
918.3
919.3
996.3
m/z
23

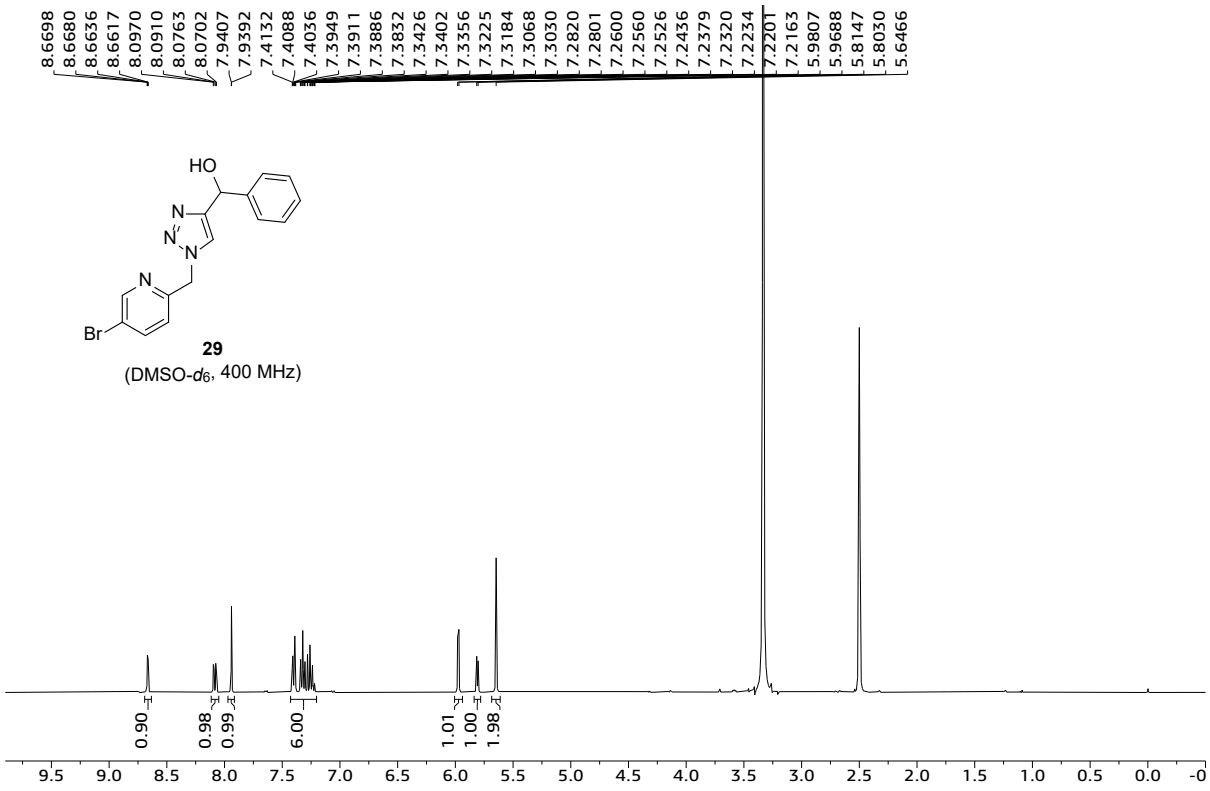


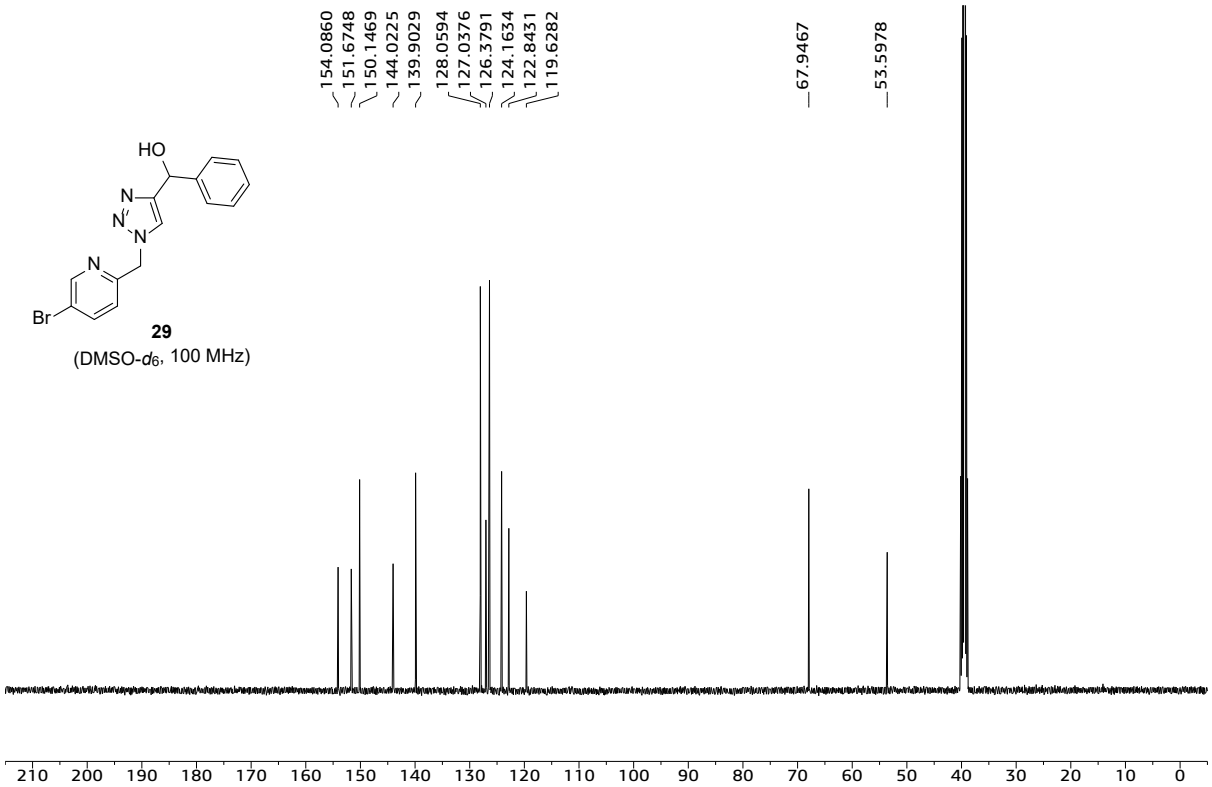
26
(CD_3OD, 500 MHz)

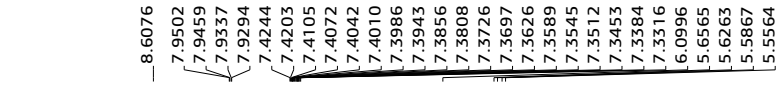


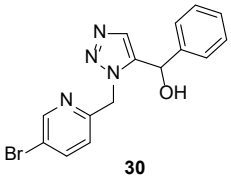
26
(CD_3OD, 100 MHz)


220304_PJB-2-015B-HPLC
3: Diode Array
Range: 2.018e+1
Time Height Area Area%
3.24 6348805 115378.53 100.00
3.24
AU
220304_PJB-2-015B-HPLC
220304_PJB-2-015B-HPLC 190 (3.289)
1: Scan ES+
1: Scan ES+
8.13e7
457.3
169.6
158.1
229.2
458.2
207.7
156.6
340.2
339.2
459.2
114.1
122.6
479.2
913.3
914.3
312.2
341.2
249.7
268.2
394.1
429.2
480.2
520.4
549.0
598.5
685.3
759.1
779.6
833.4
911.6
935.2
951.4
978.3
%
m/z
26


8.6698
8.6680
8.6636
8.6617
8.0970
8.0910
8.0763
8.0702
7.9407
7.9392
7.4132
7.4088
7.4036
7.3949
7.3911
7.3886
7.3832
7.3426
7.3402
7.3356
7.3225
7.3184
7.3068
7.3030
7.2820
7.2801
7.2600
7.2560
7.2526
7.2436
7.2379
7.2320
7.2234
7.2201
7.2163
5.9807
5.9688
5.8147
5.8030
5.6466
HO
N
N
N
N
Br
29
(DMSO-d6, 400 MHz)
0.90
0.98
0.99
6.00
1.01
1.00
1.98
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
0.0
-0

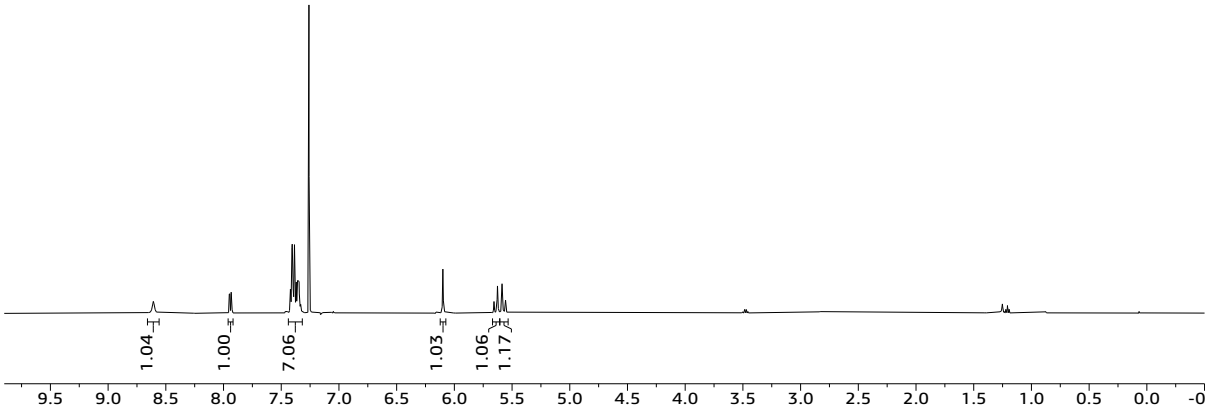

154.0860
151.6748
150.1469
144.0225
139.9029
128.0594
127.0376
126.3791
124.1634
122.8431
119.6282
67.9467
53.5978
HO
N
N
N
N
Br
29
(DMSO-d6, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

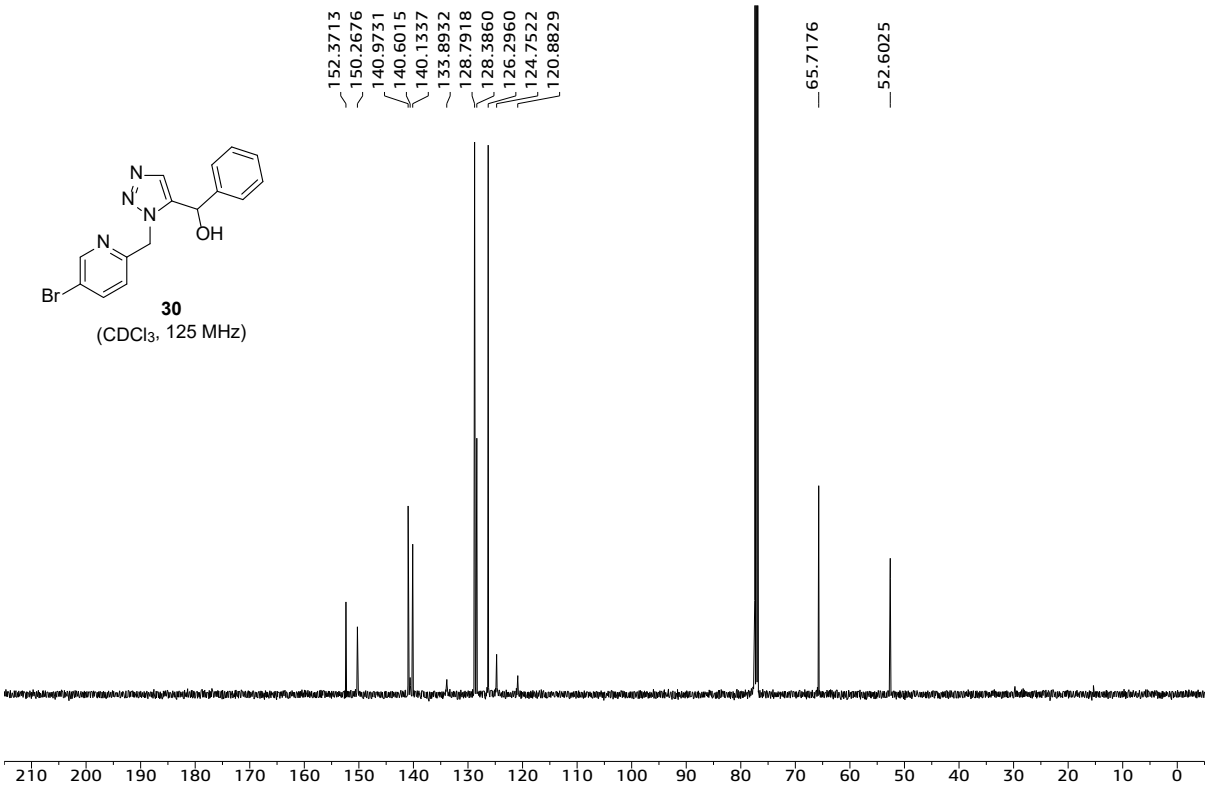




30

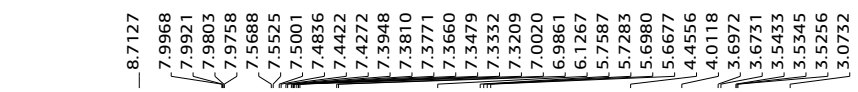
($CDCl_3$, 500 MHz)

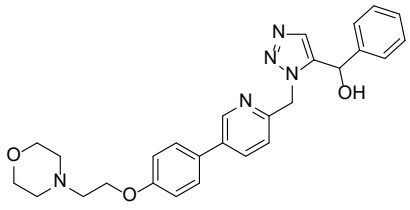




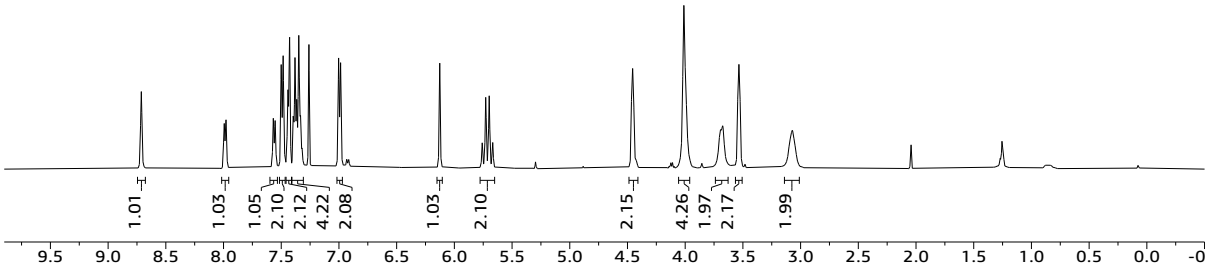
30

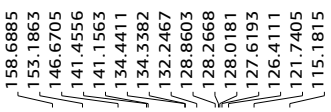
($CDCl_3$, 125 MHz)

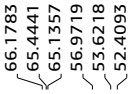


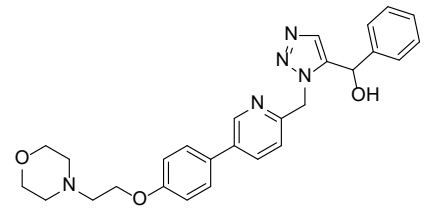


27
($CDCl_3$, 500 MHz)

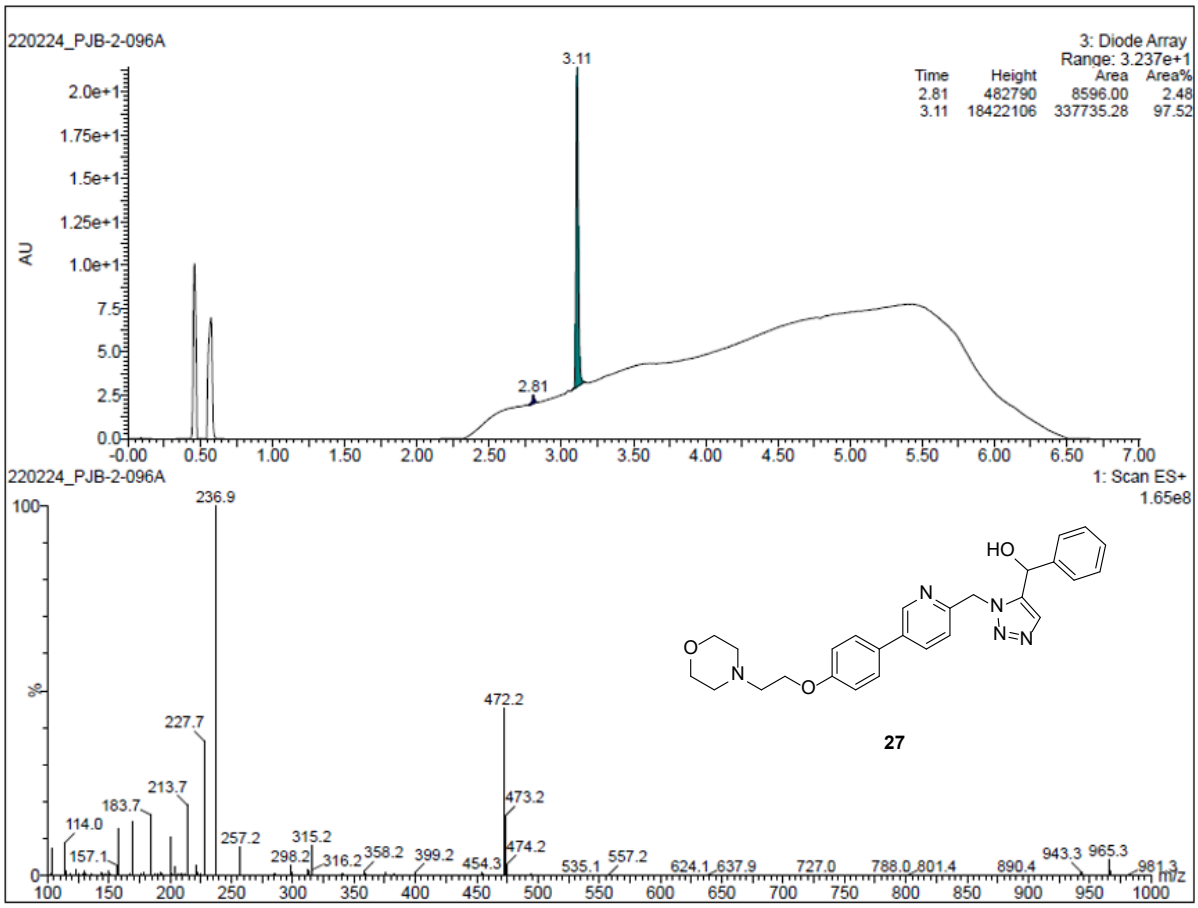




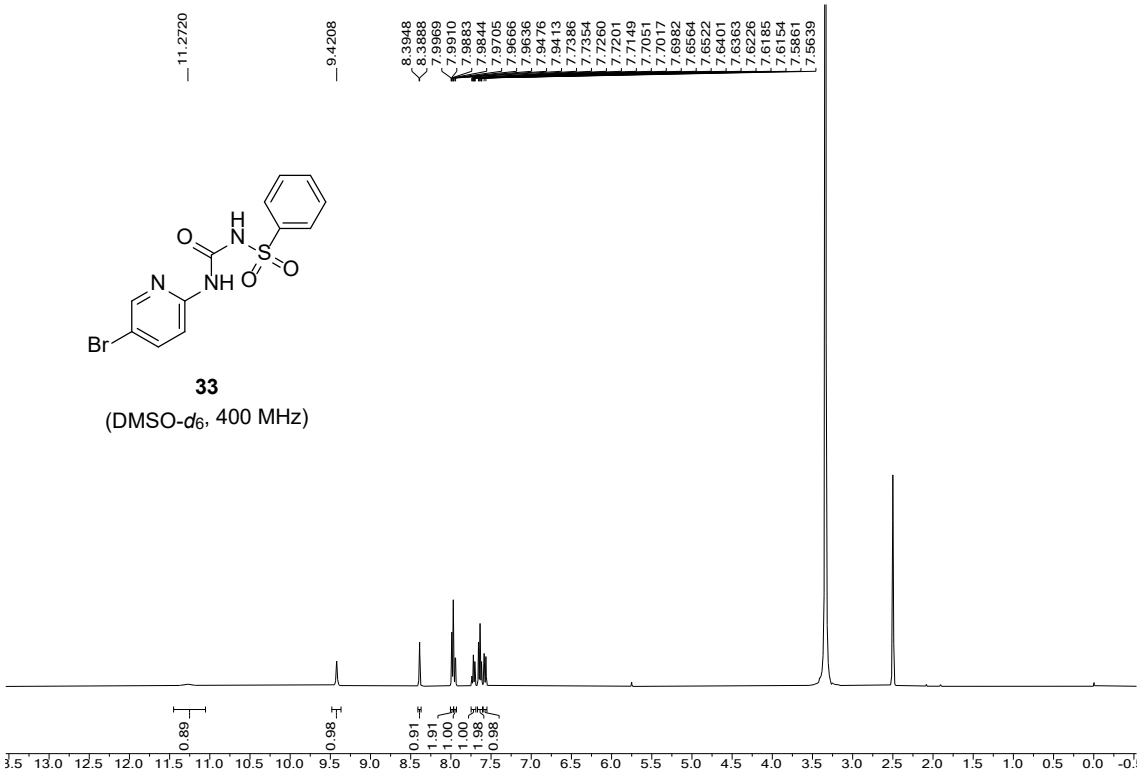




27
(DMSO-d_6, 100 MHz)

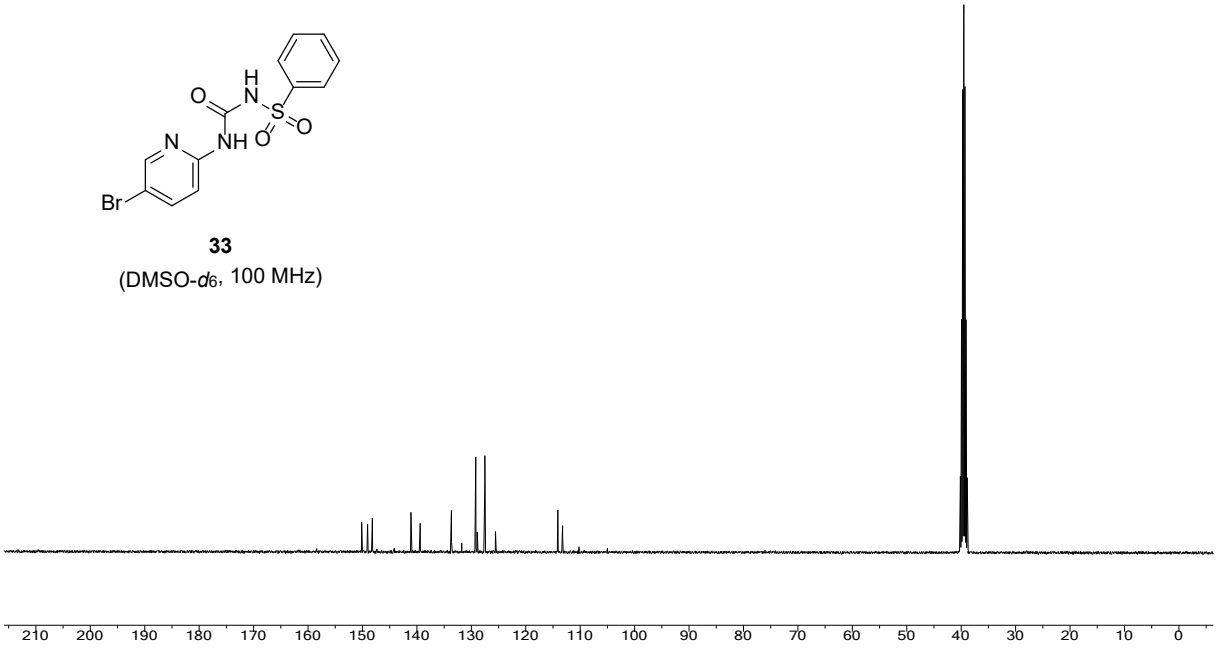

220224_PJB-2-096A
3: Diode Array
Range: 3.237e+1
Time Height Area Area%
2.81 482790 8596.00 2.48
3.11 18422106 337735.28 97.52
3.11
2.81
AU
220224_PJB-2-096A
1: Scan ES+
1.65e8
236.9
472.2
227.7
213.7
183.7
114.0
157.1
257.2
315.2
298.2
316.2
358.2
399.2
454.3
473.2
474.2
535.1
557.2
624.1
637.9
727.0
788.0
801.4
890.4
943.3
965.3
981.3
%
m/z
HO
N
N
N=N
O
N
O

27



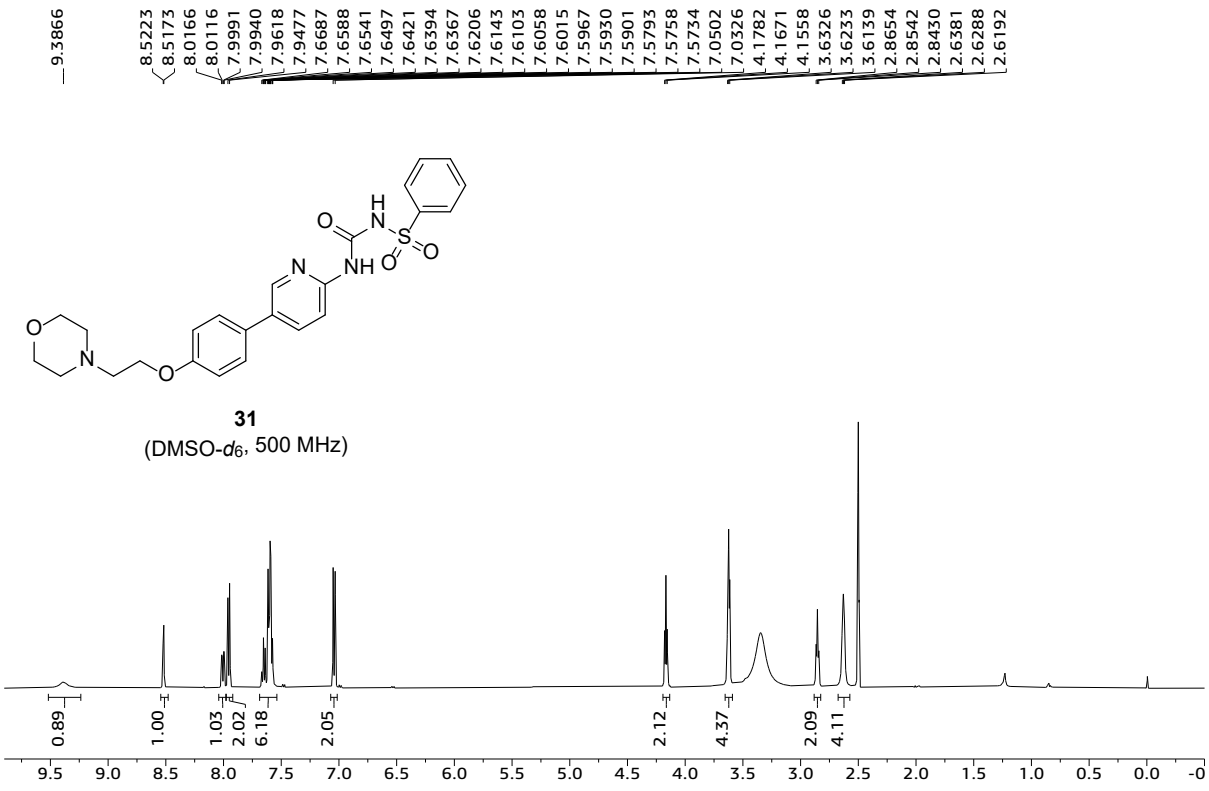
33

(DMSO-d_6, 400 MHz)

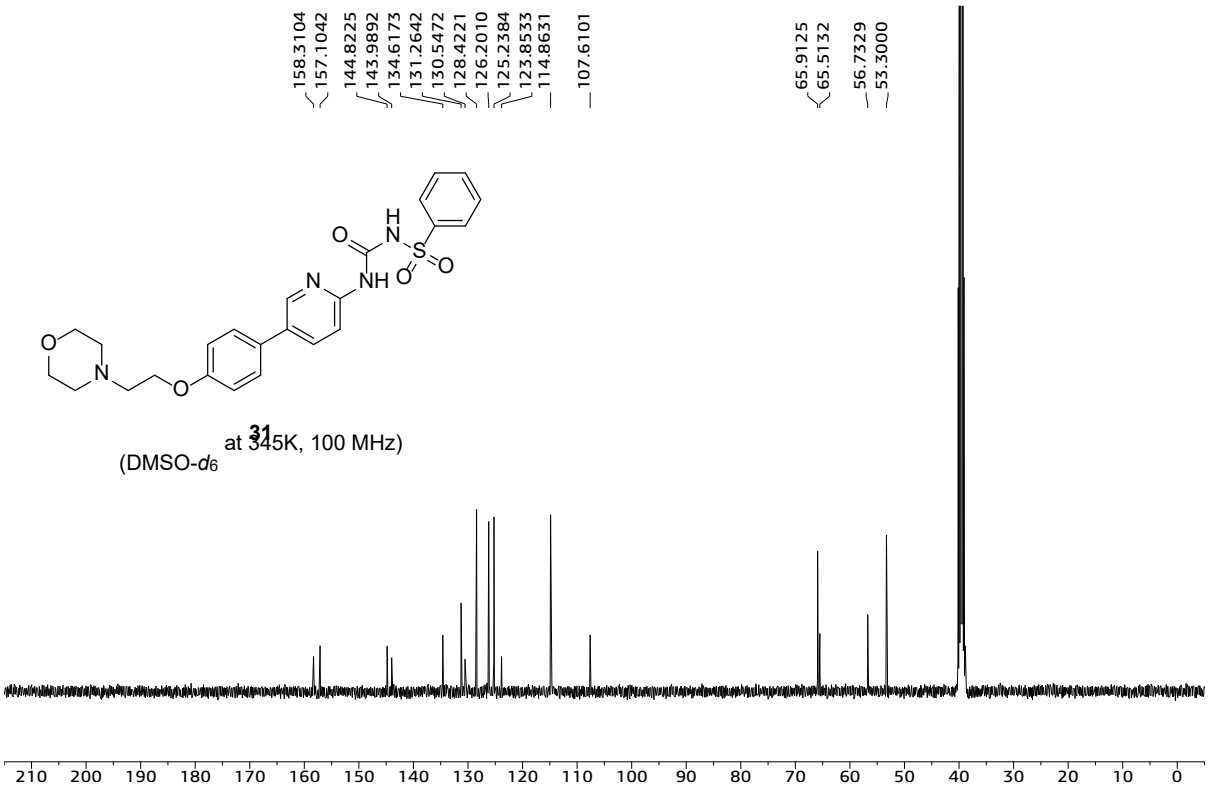


33

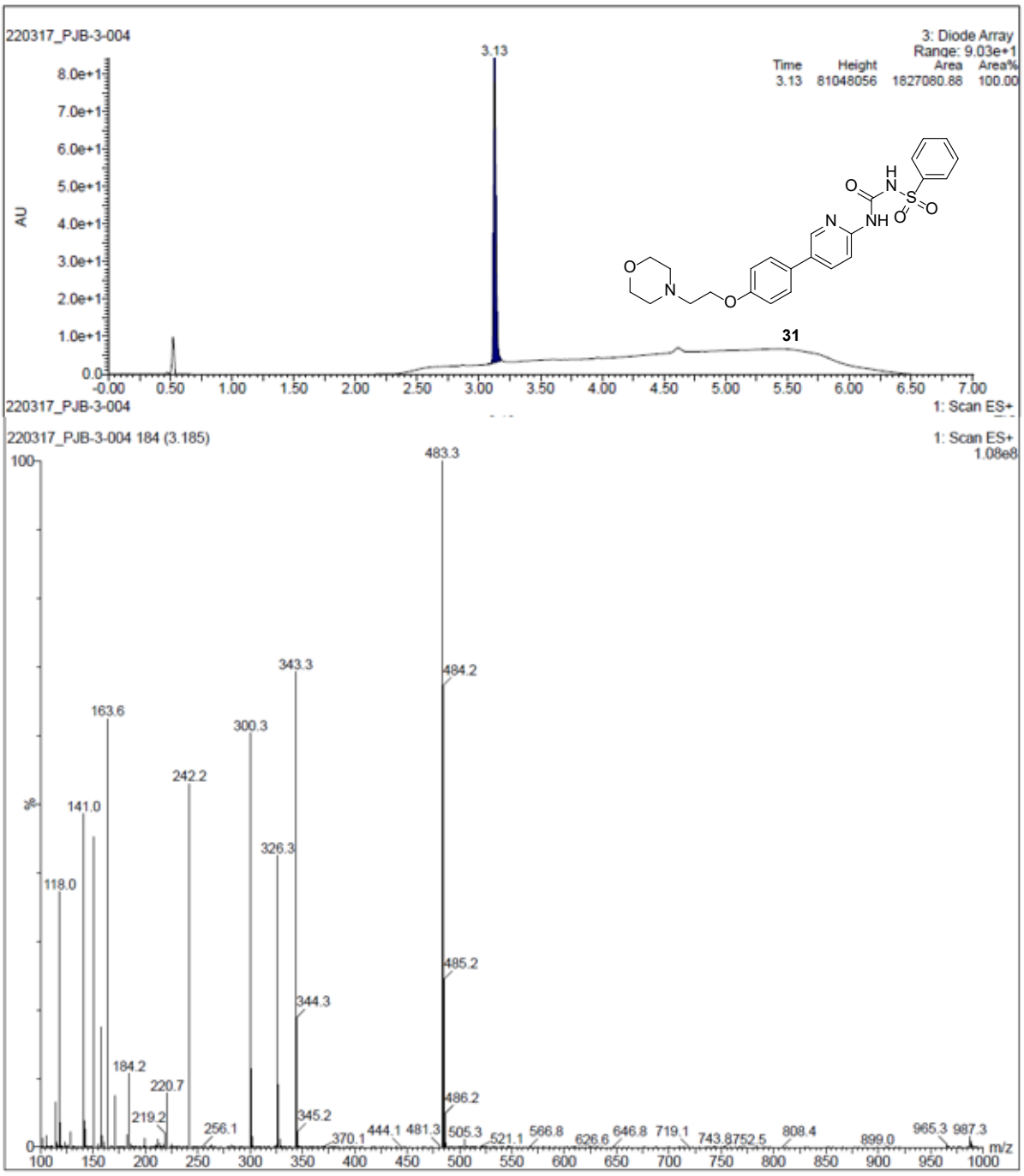
(DMSO-d_6, 100 MHz)

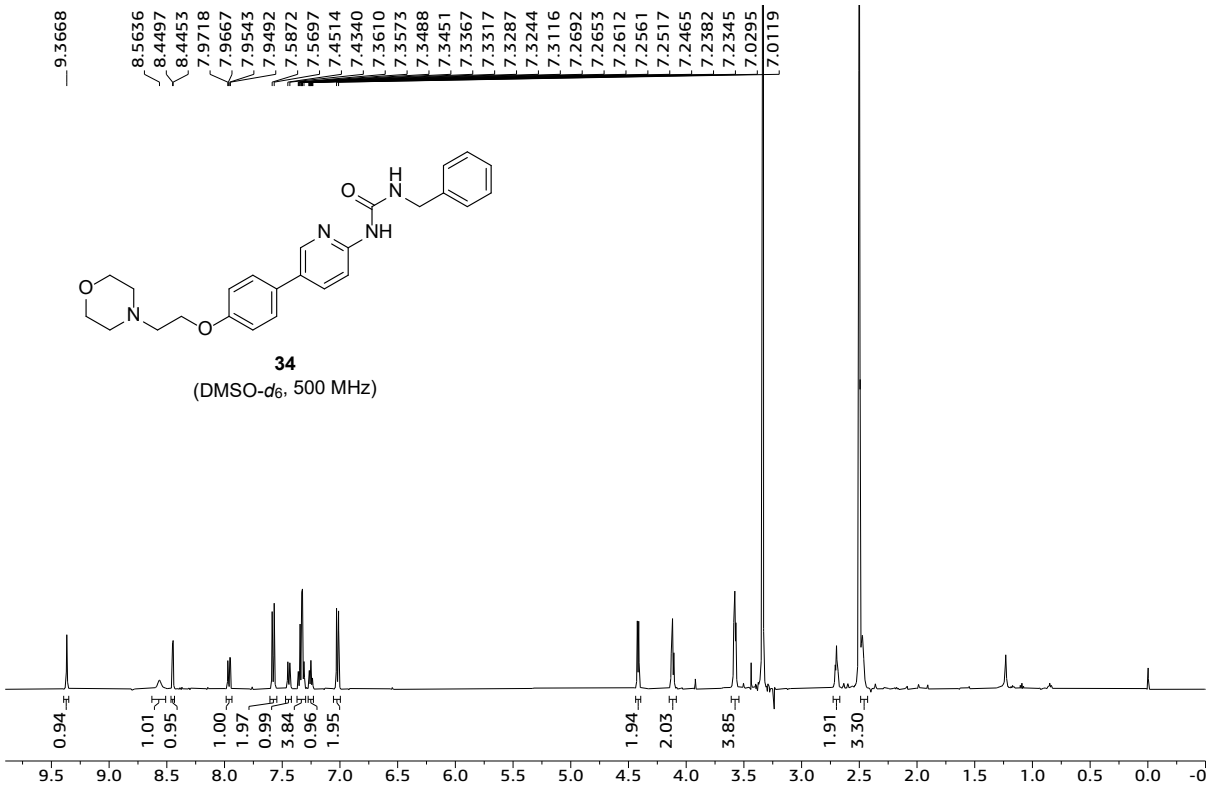


31
(DMSO-d_6, 500 MHz)

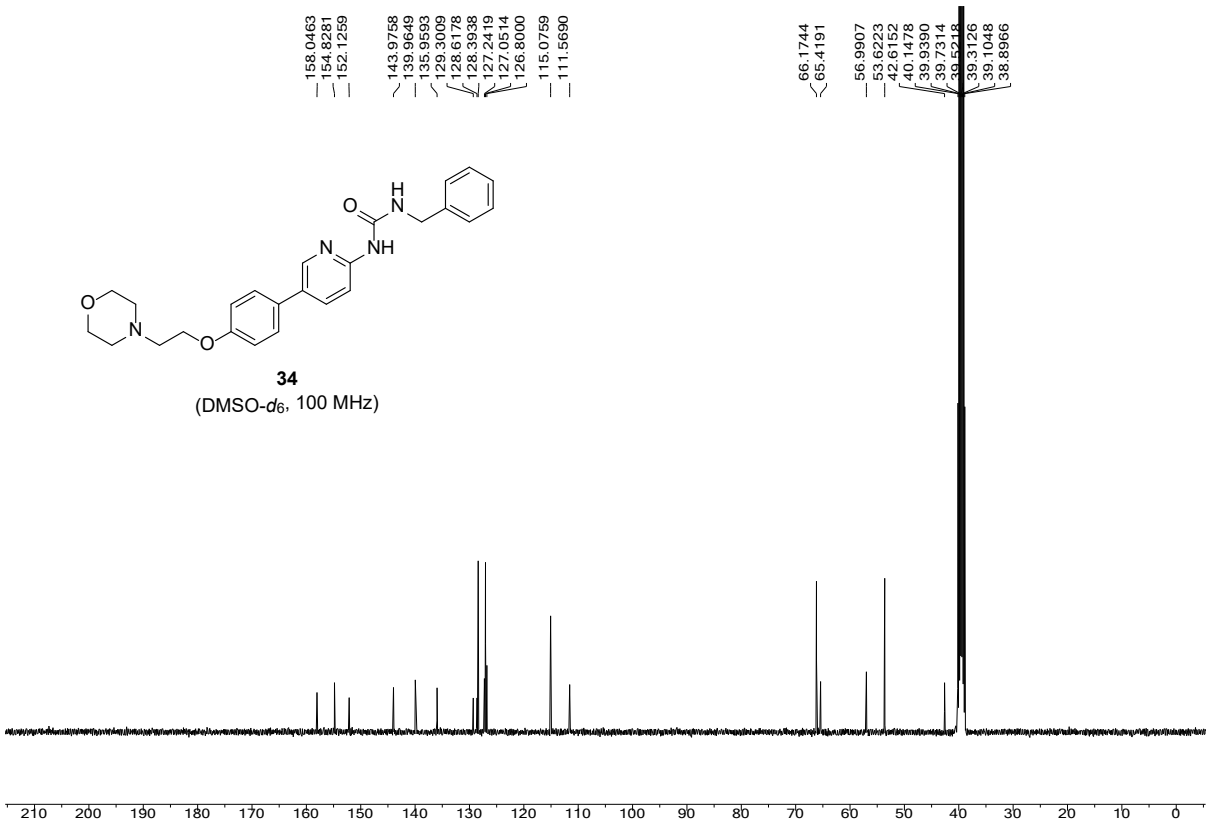


31
(DMSO-d_6 at 345K, 100 MHz)

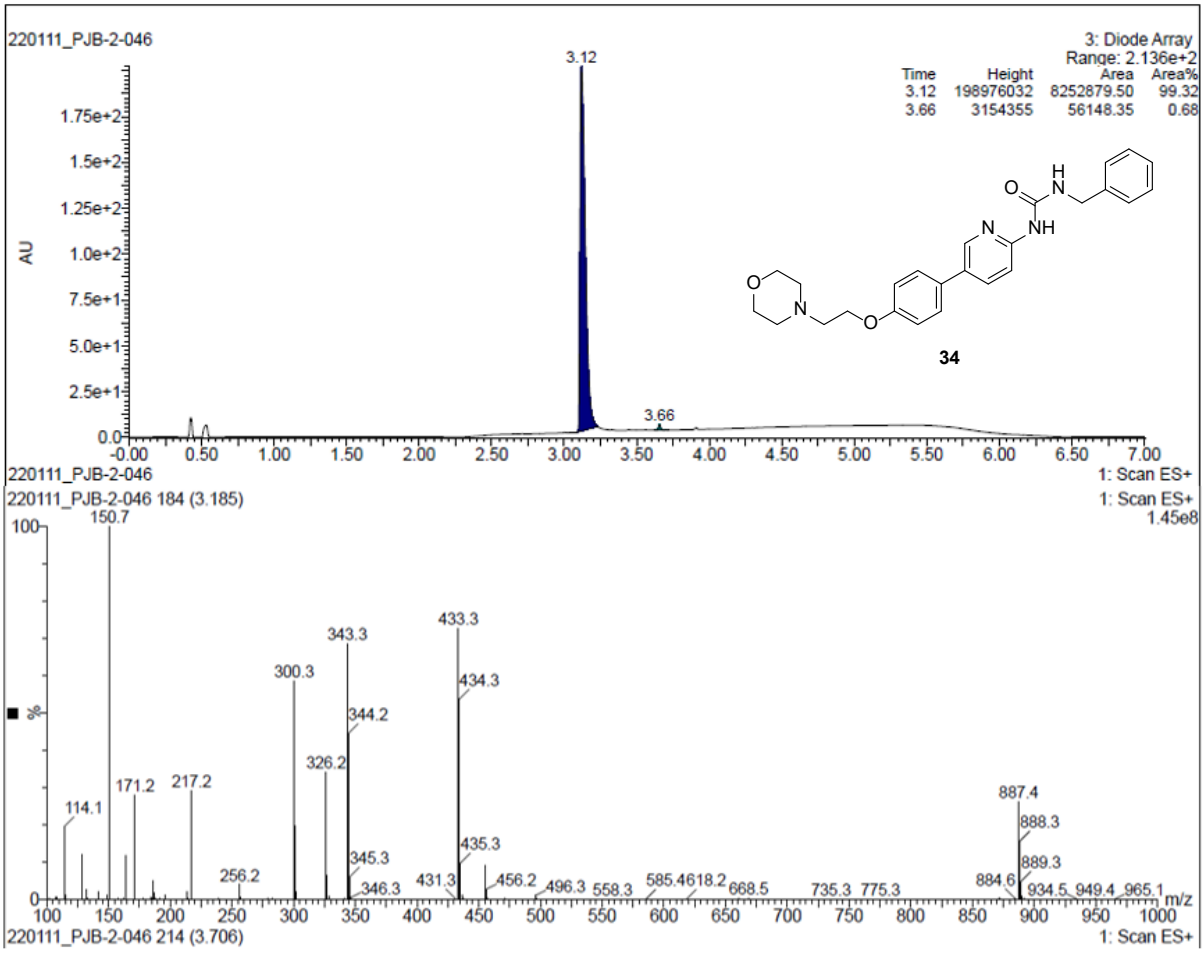

220317_PJB-3-004
3: Diode Array
Range: 9.03e+1
Time Height Area Area%
3.13 81048056 1827080.88 100.00
3.13
AU
31
220317_PJB-3-004
1: Scan ES+
220317_PJB-3-004 184 (3.185)
1: Scan ES+
1.08e8
483.3
484.2
343.3
163.6
300.3
242.2
141.0
326.3
118.0
485.2
344.3
184.2
220.7
486.2
219.2
345.2
256.1
%
m/z

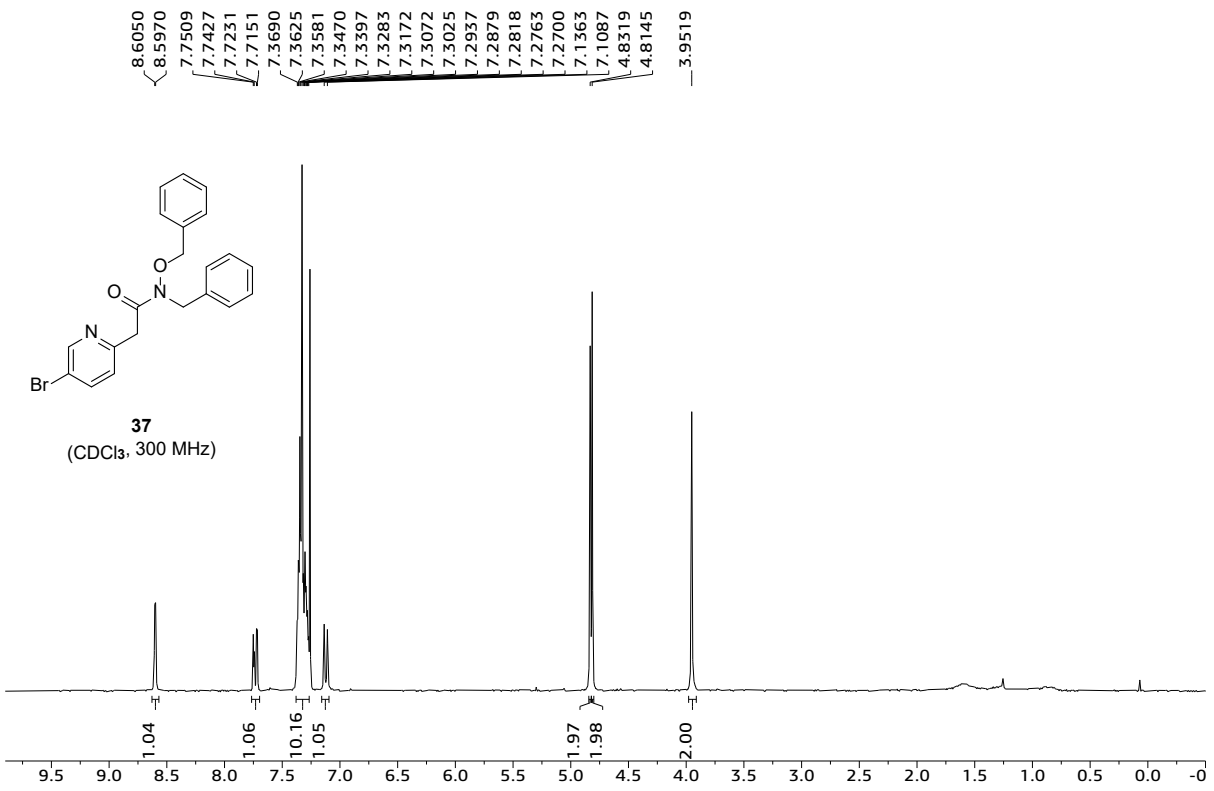


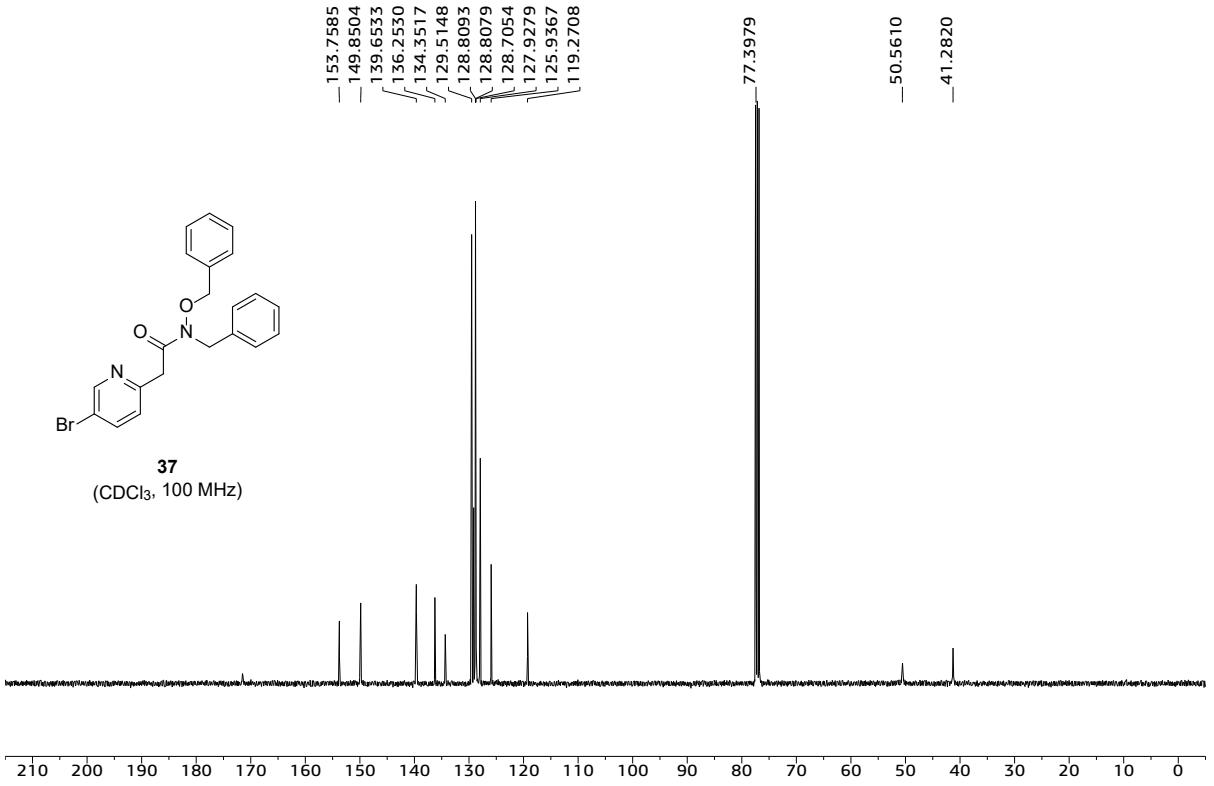
34
(DMSO-d_6, 500 MHz)

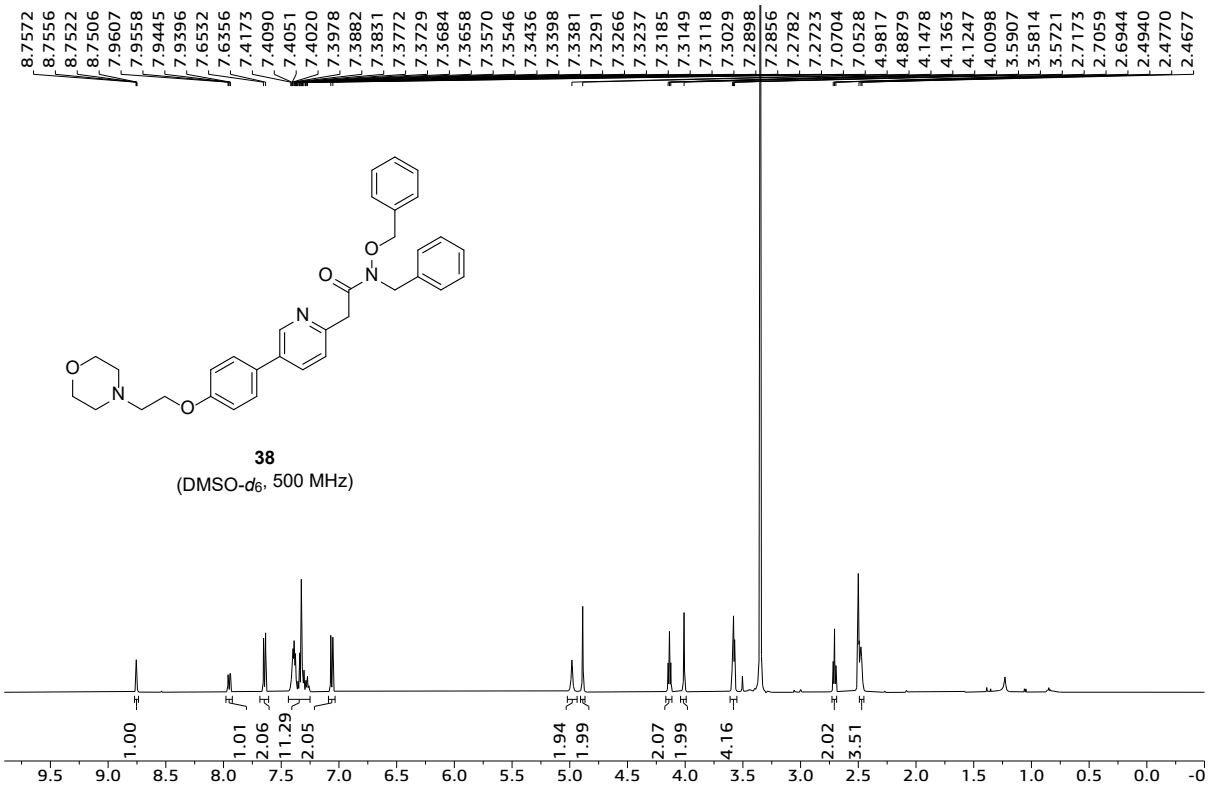


34
(DMSO-d_6, 100 MHz)

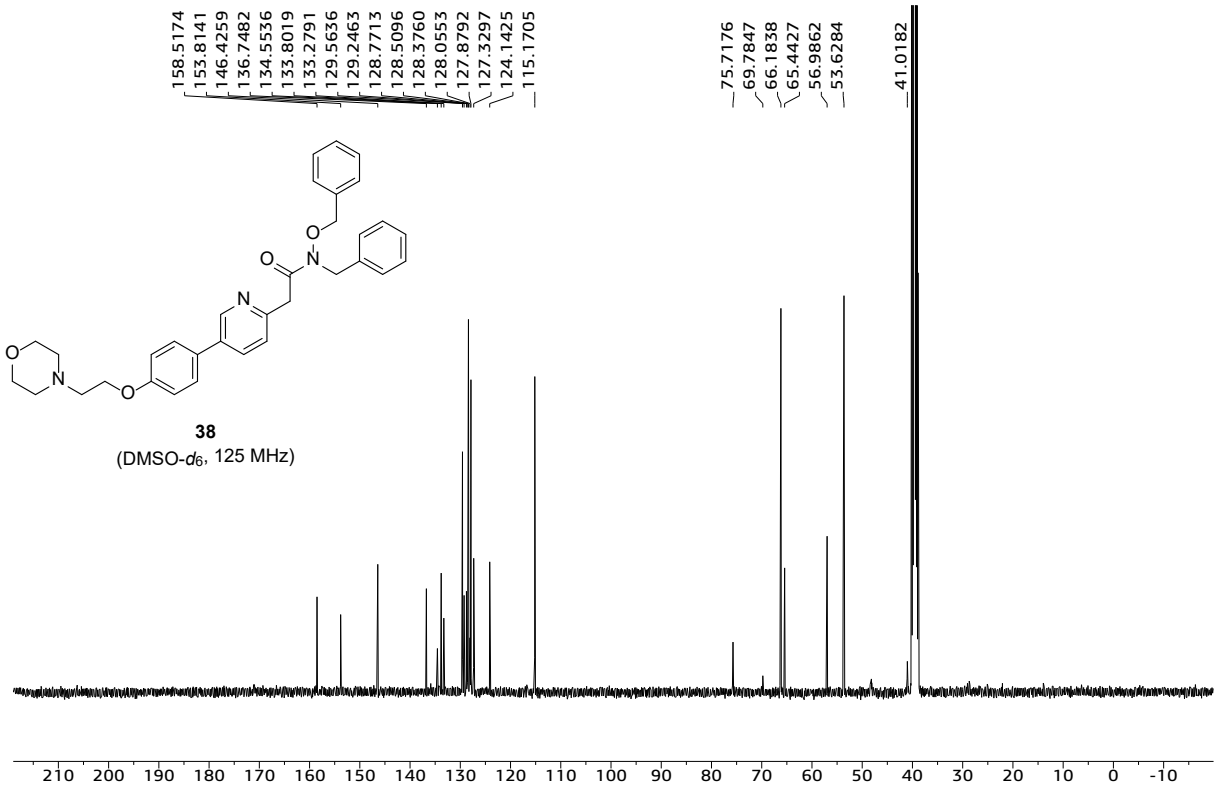

220111_PJB-2-046
3: Diode Array
Range: 2.136e+2
Time Height Area Area%
3.12 198976032 8252879.50 99.32
3.66 3154355 56148.35 0.68
3.12
3.66
AU
34
220111_PJB-2-046
1: Scan ES+
220111_PJB-2-046 184 (3.185)
1: Scan ES+
1.45e8
150.7
433.3
343.3
300.3
434.3
344.2
326.2
171.2
217.2
114.1
887.4
888.3
889.3
435.3
345.3
256.2
346.3
431.3
456.2
496.3
558.3
585.4
618.2
668.5
735.3
775.3
884.6
934.5
949.4
965.1
m/z
220111_PJB-2-046 214 (3.706)
1: Scan ES+


8.6050
8.5970
7.7509
7.7427
7.7231
7.7151
7.3690
7.3625
7.3581
7.3470
7.3397
7.3283
7.3172
7.3072
7.3025
7.2937
7.2879
7.2818
7.2763
7.2700
7.1363
7.1087
4.8319
4.8145
3.9519
O
N
O
N
Br
37
(CDCl3, 300 MHz)
1.04
1.06
10.16
1.05
1.97
1.98
2.00
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 0.0 -0

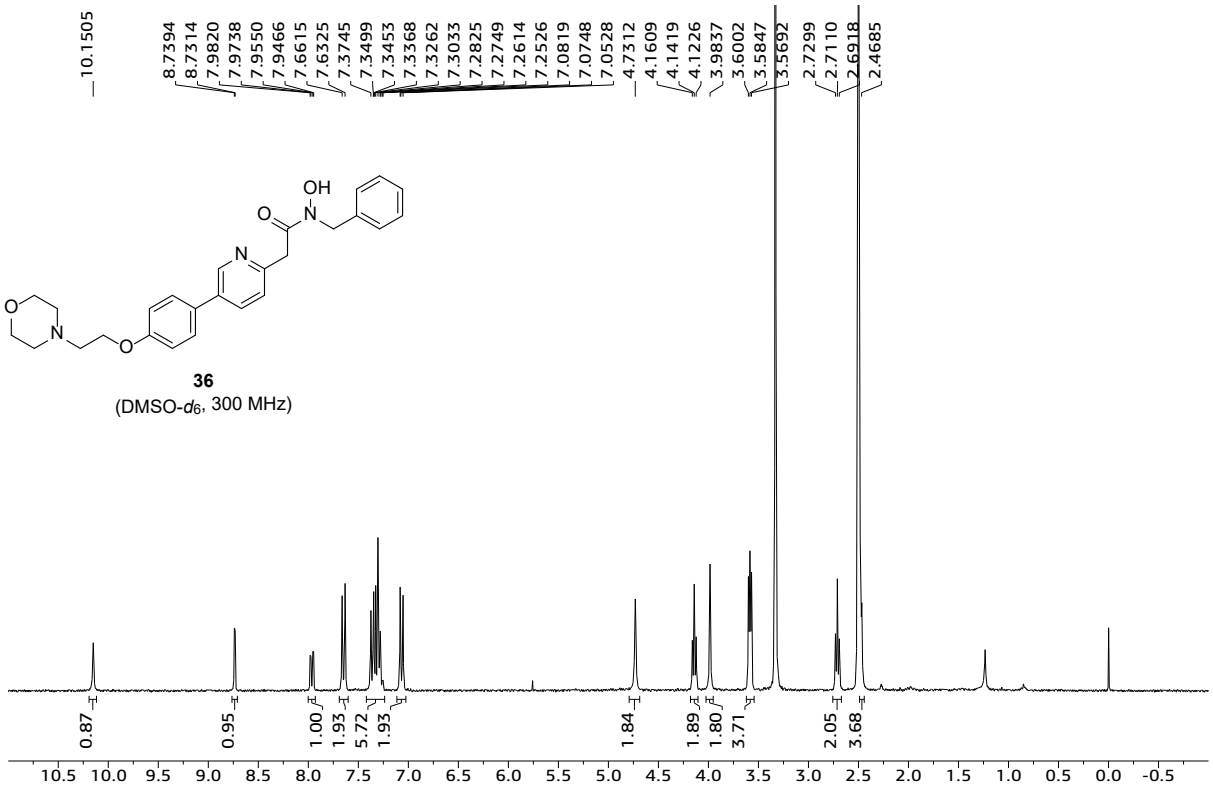

153.7585
149.8504
139.6533
136.2530
134.3517
129.5148
128.8093
128.8079
128.7054
127.9279
125.9367
119.2708
77.3979
50.5610
41.2820
O
N
O
N
Br
37
(CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



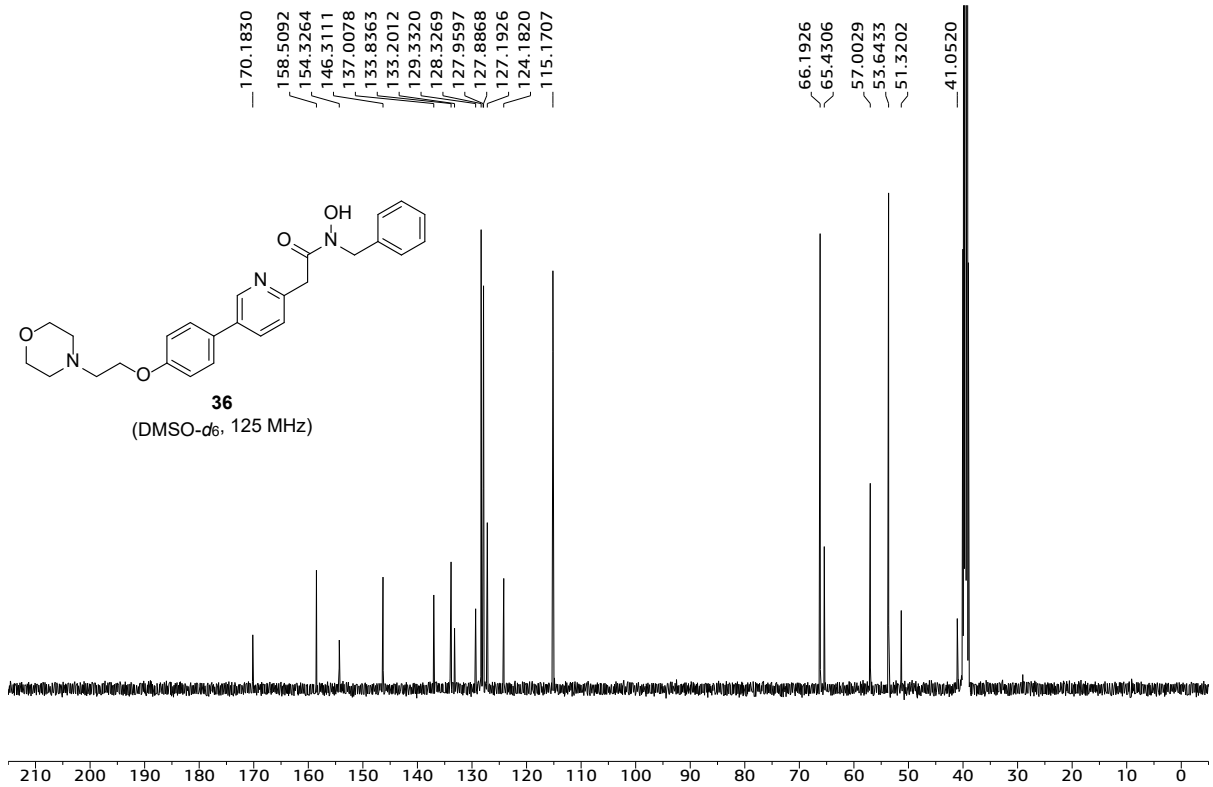
38
(DMSO-d_6, 500 MHz)



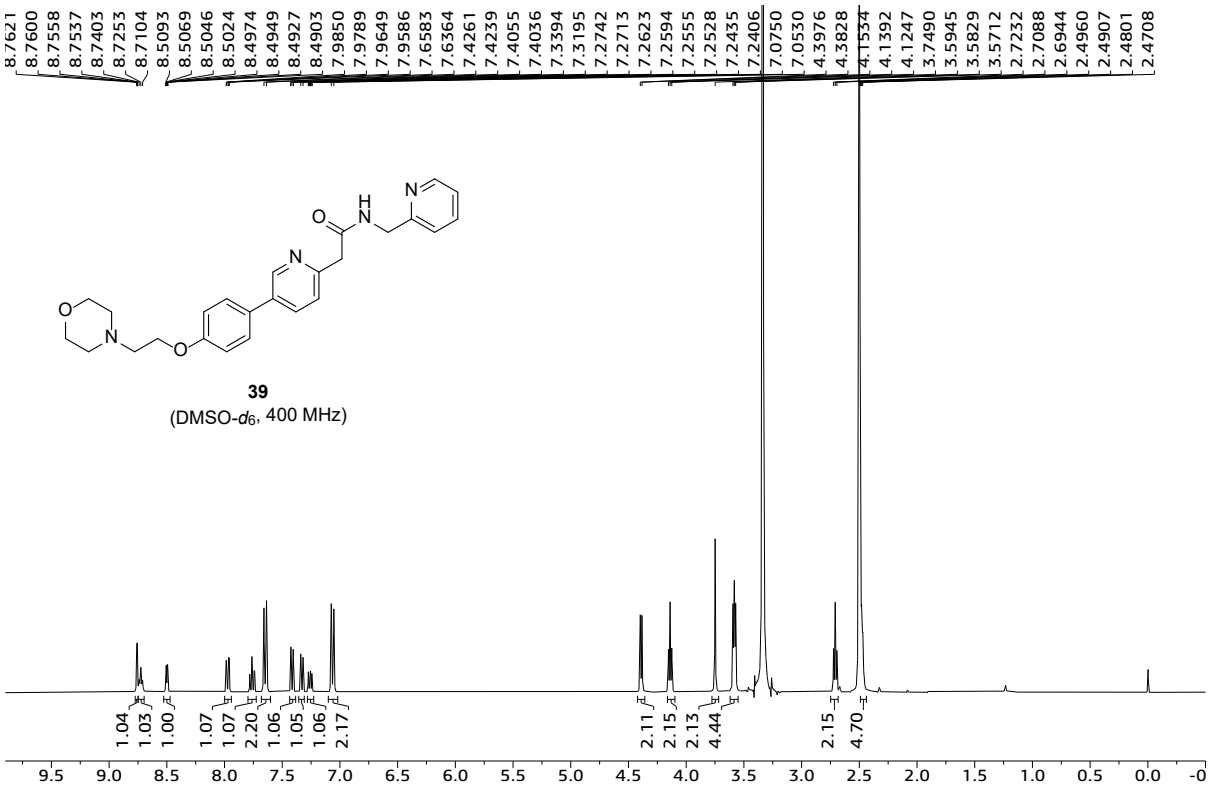
38
(DMSO-d_6, 125 MHz)



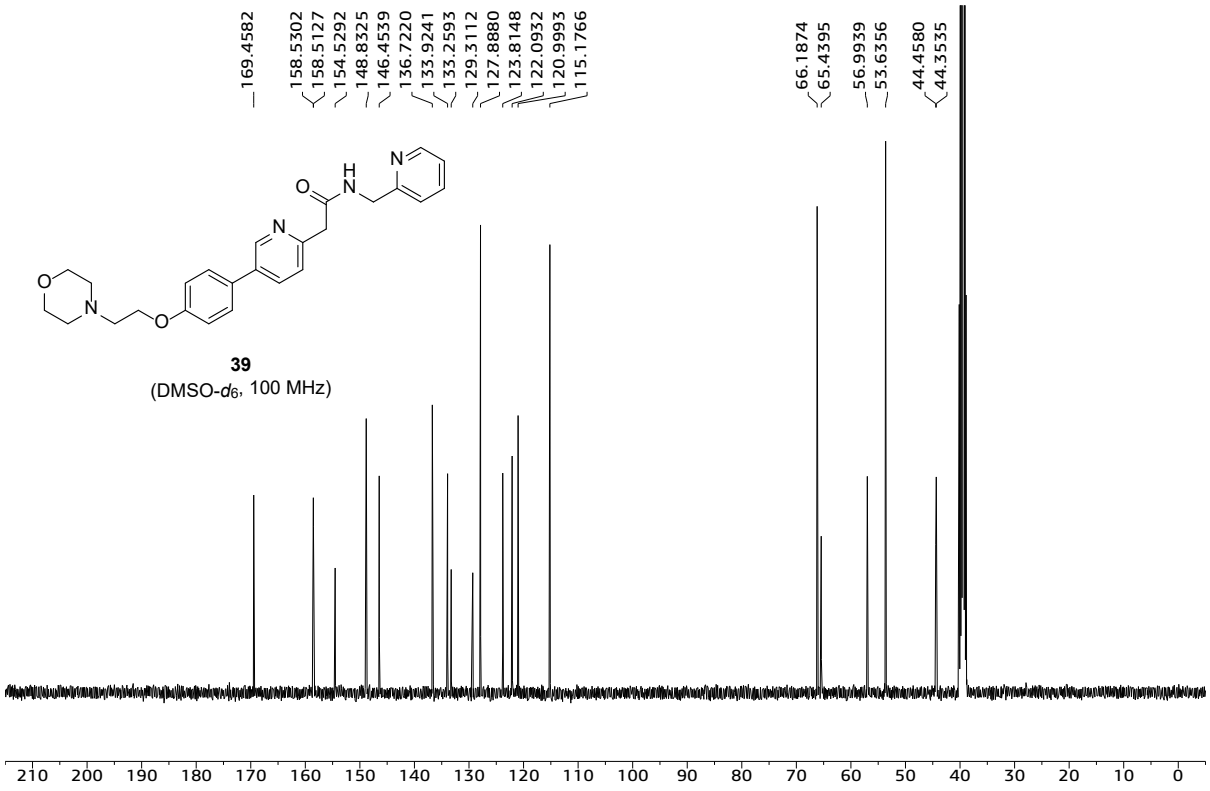
36
(DMSO-d_6, 300 MHz)



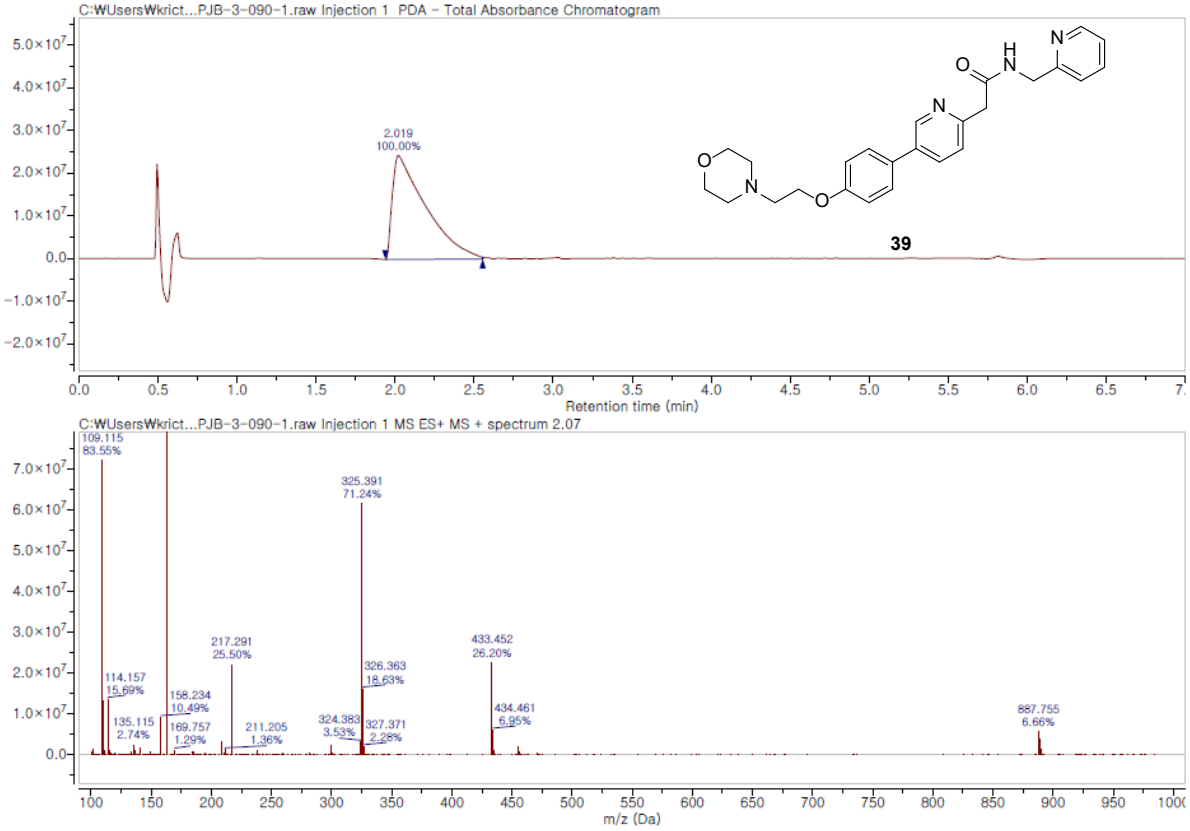
36
(DMSO-d_6, 125 MHz)

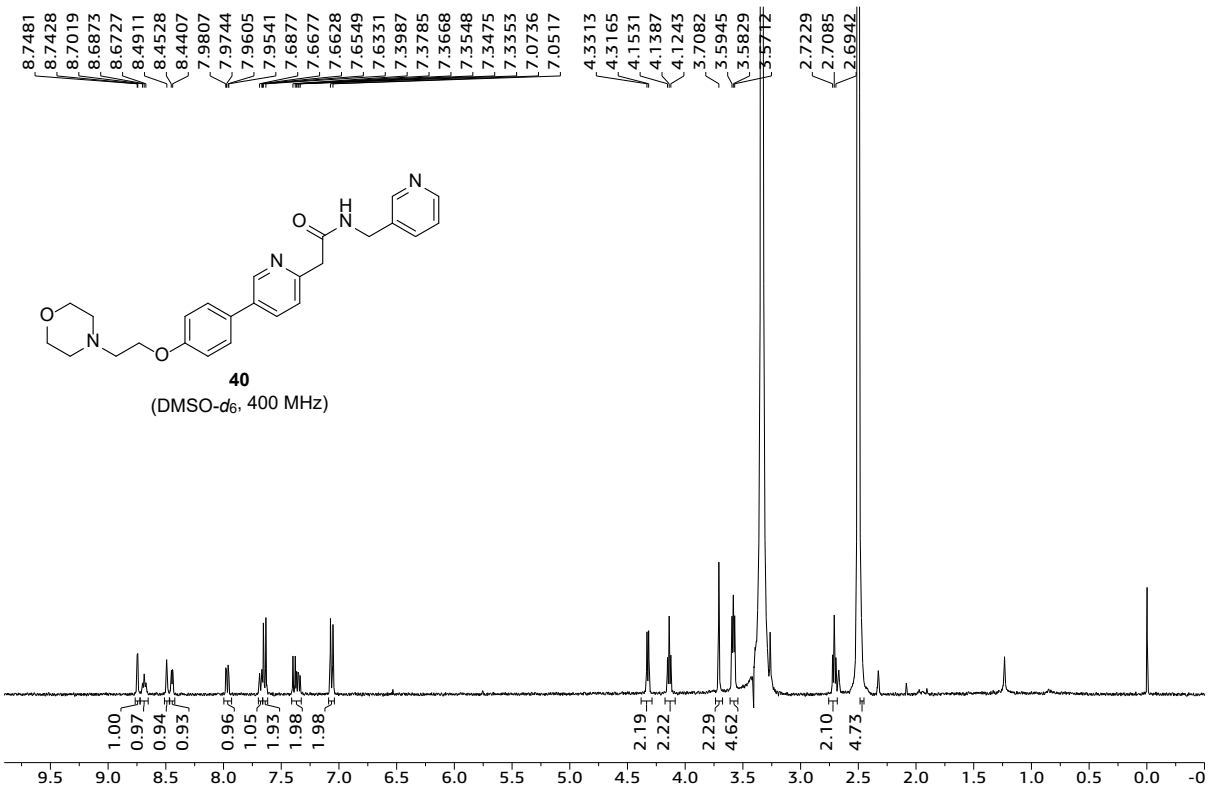


39
(DMSO-d_6, 400 MHz)

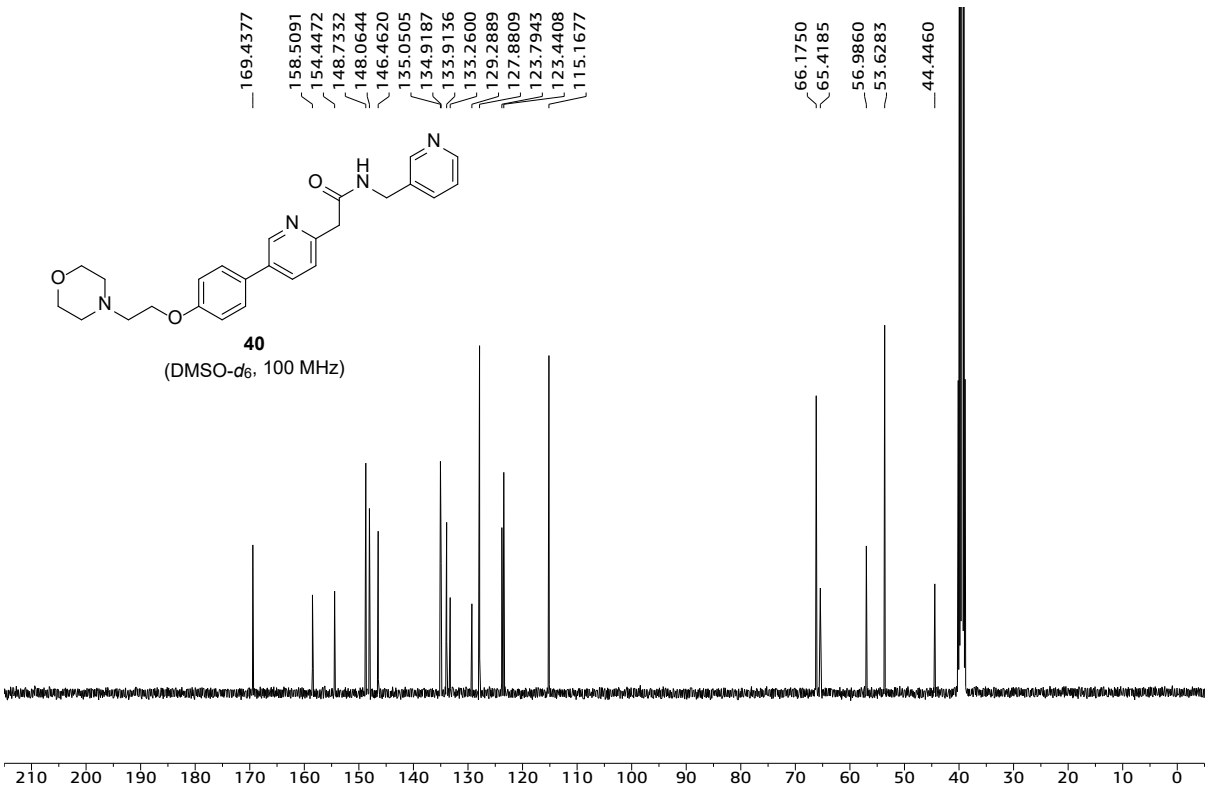


39
(DMSO-d_6, 100 MHz)

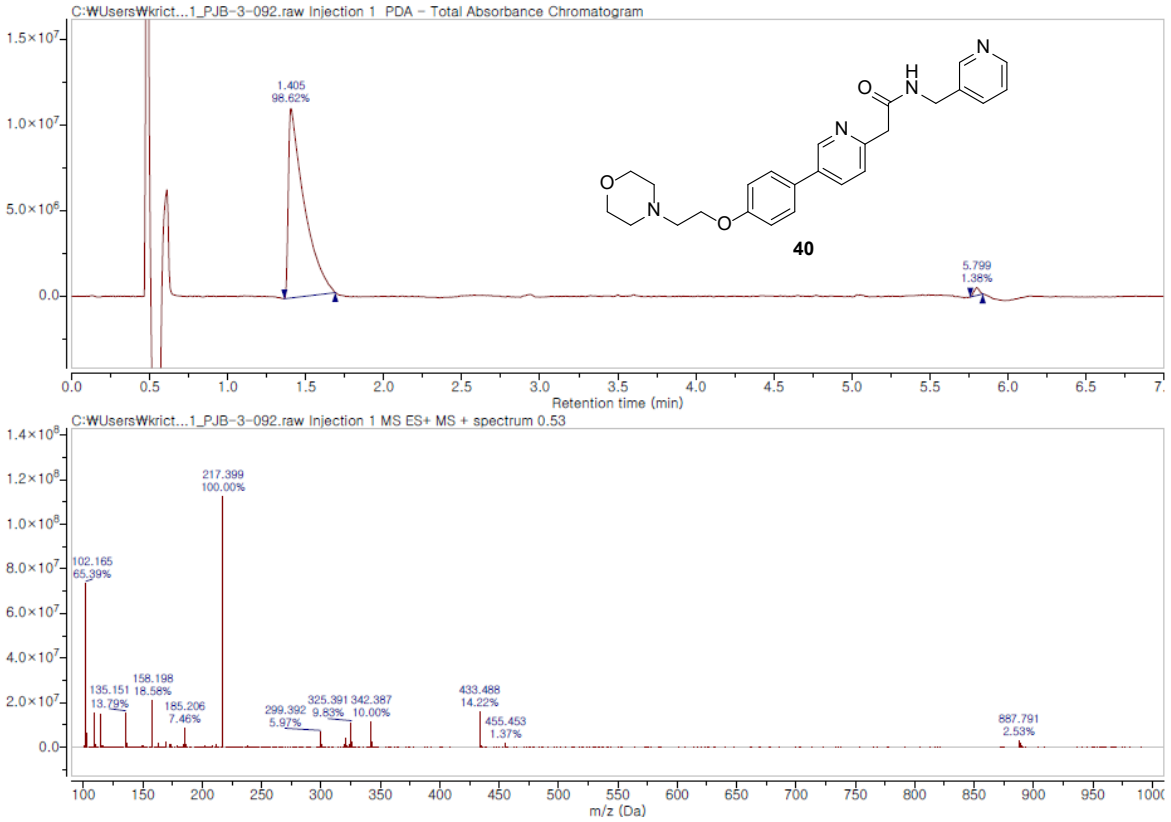

C:\Users\krict...PJB-3-090-1.raw Injection 1 PDA - Total Absorbance Chromatogram
2.019
100.00%
39
Retention time (min)
C:\Users\krict...PJB-3-090-1.raw Injection 1 MS ES+ MS + spectrum 2.07
109.115
83.55%
325.391
71.24%
217.291
25.50%
433.452
26.20%
326.363
18.63%
114.157
15.69%
158.234
10.49%
434.461
6.95%
887.755
6.66%
135.115
2.74%
169.757
1.29%
211.205
1.36%
324.383
3.53%
327.371
2.28%
m/z (Da)



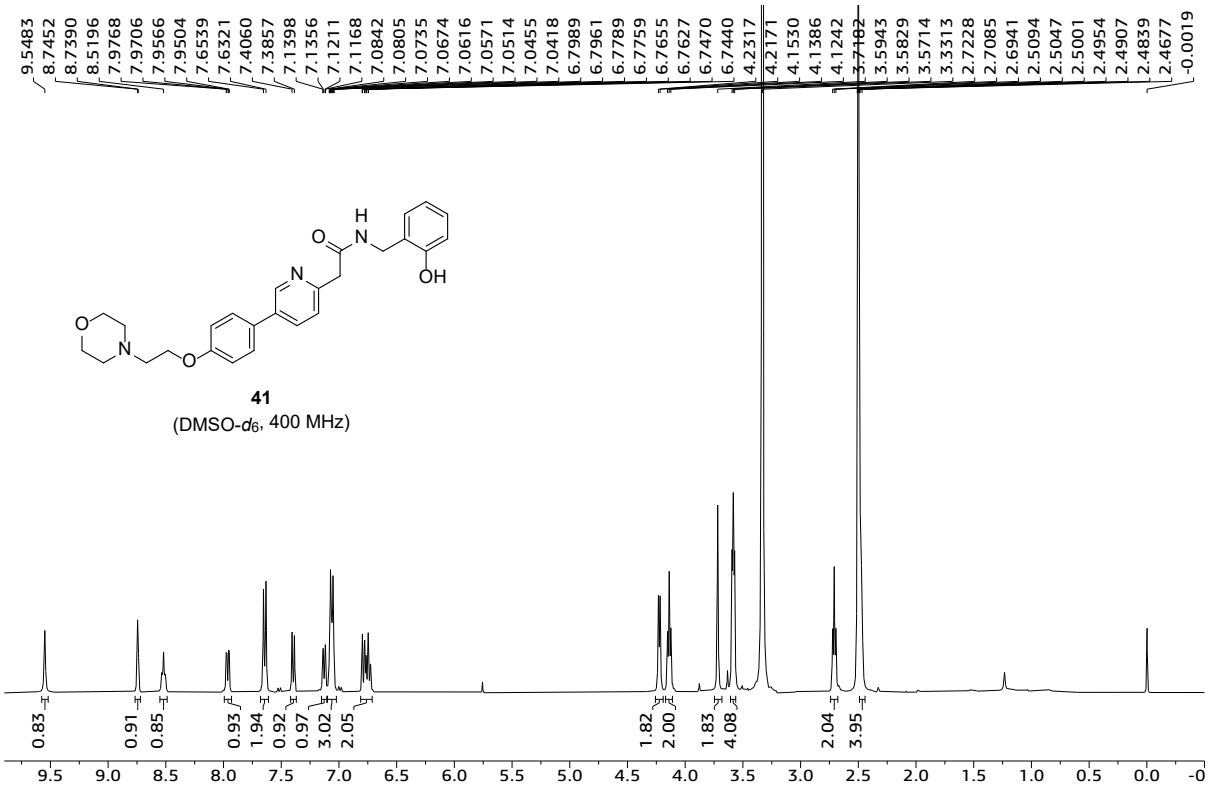
40
(DMSO-d_6, 400 MHz)



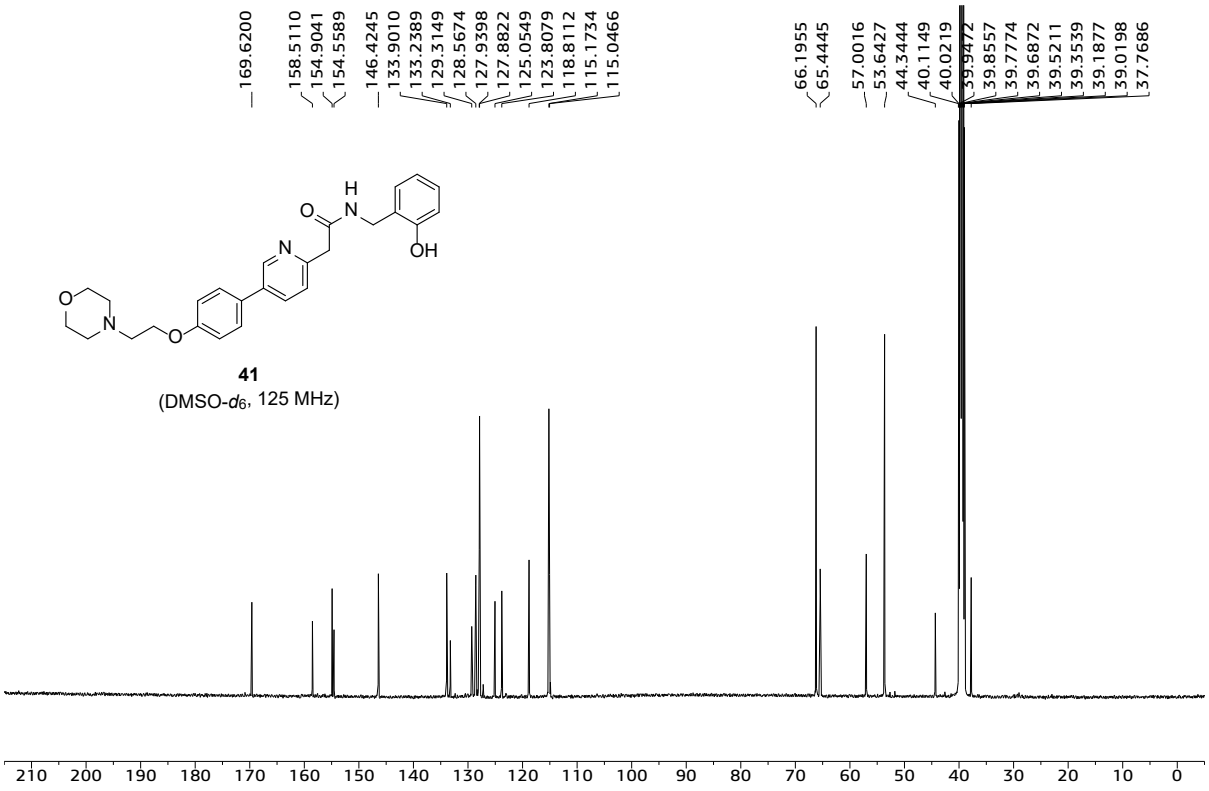
40
(DMSO-d_6, 100 MHz)


C:\Users\krict...1_PJB-3-092.raw Injection 1 PDA - Total Absorbance Chromatogram
1.405
98.62%
5.799
1.38%
Retention time (min)
C:\Users\krict...1_PJB-3-092.raw Injection 1 MS ES+ MS + spectrum 0.53
217.399
100.00%
102.165
65.39%
158.198
18.58%
135.151
13.79%
185.206
7.46%
299.392
5.97%
325.391
9.83%
342.387
10.00%
433.488
14.22%
455.453
1.37%
887.791
2.53%
m/z (Da)

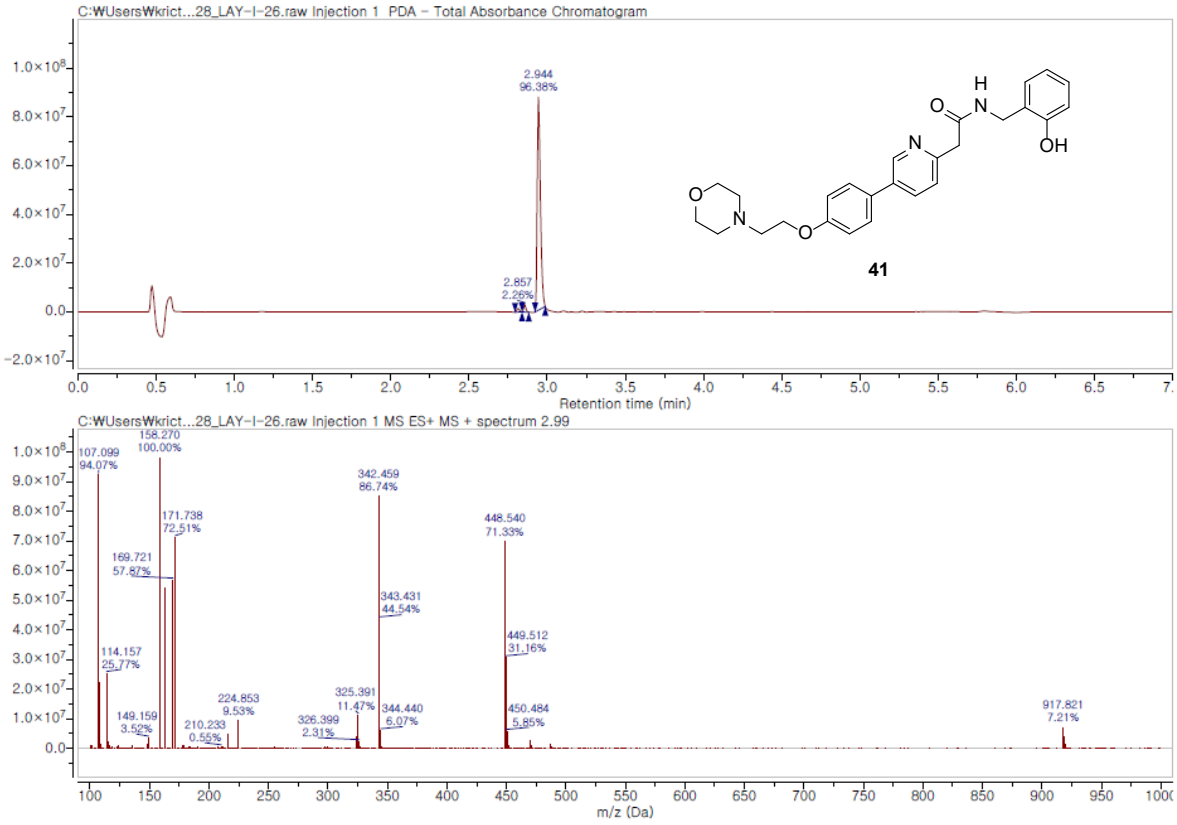
40

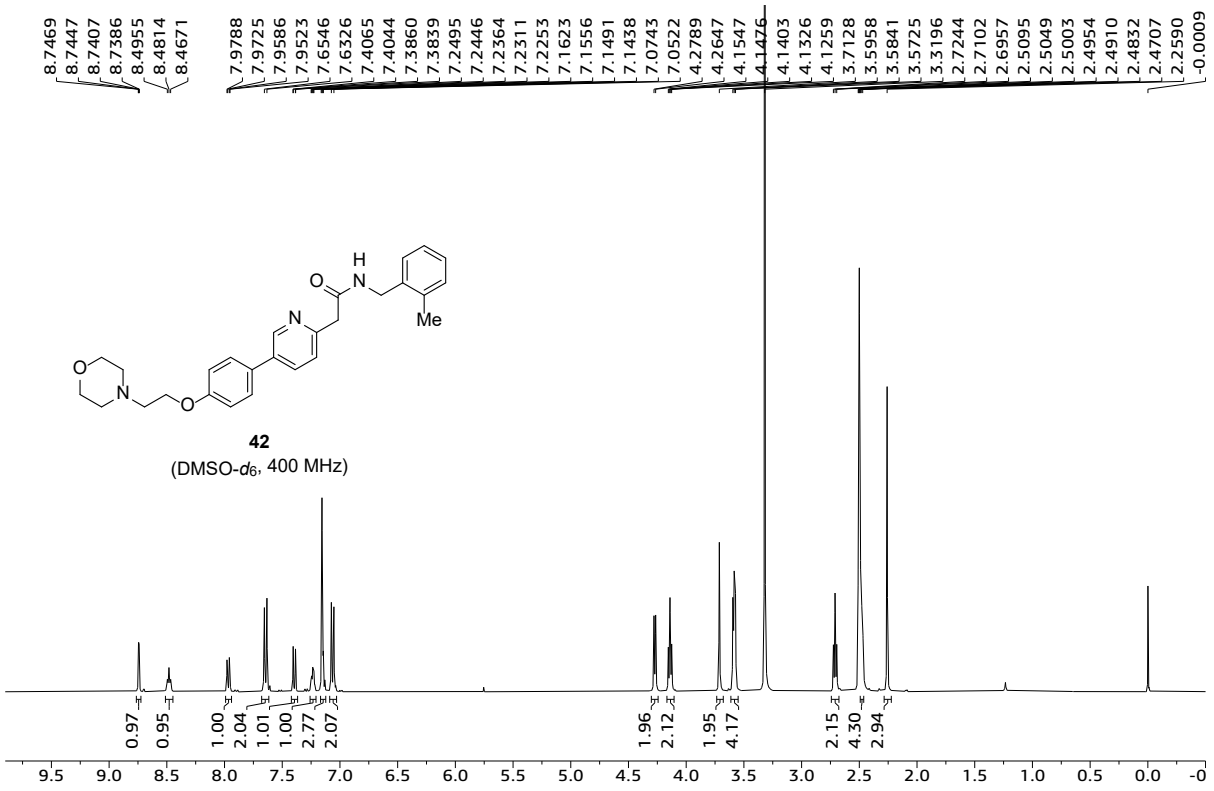


41
(DMSO-d_6, 400 MHz)



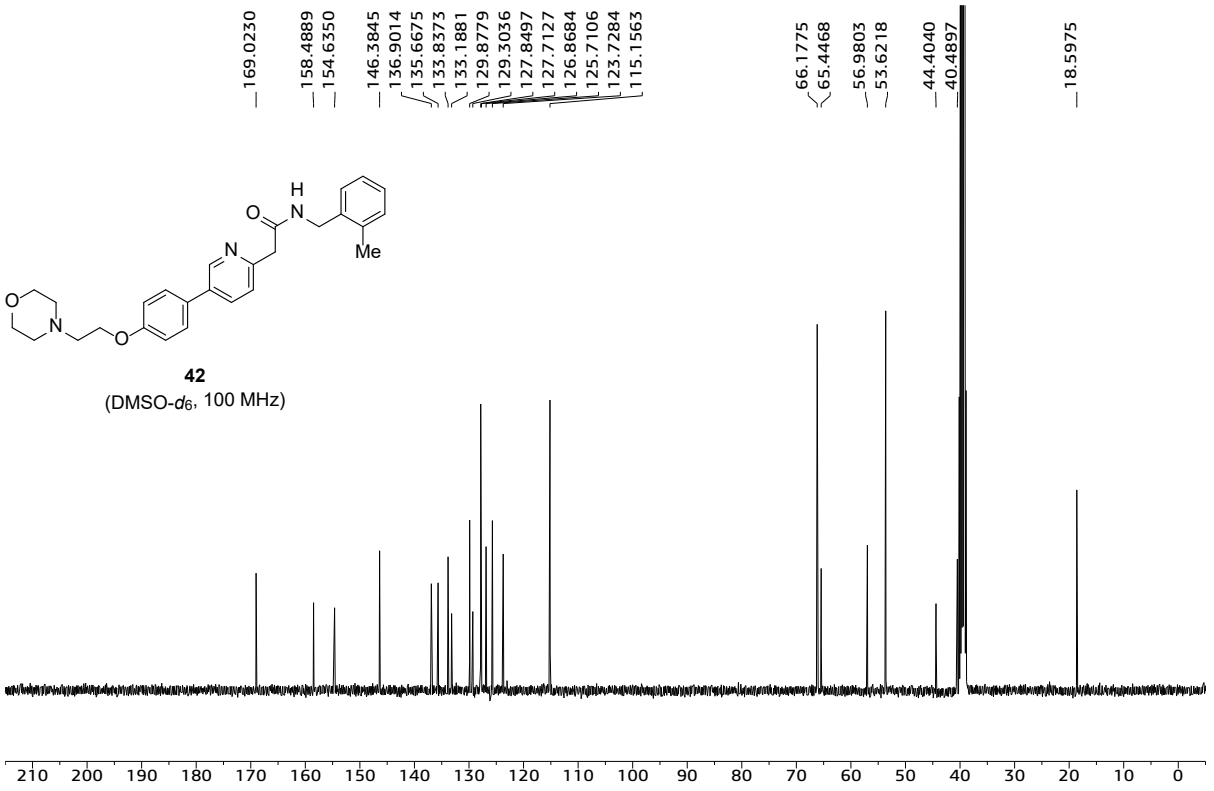
41
(DMSO-d_6, 125 MHz)


C:\Users\krict...28_LAY-I-26.raw Injection 1 PDA - Total Absorbance Chromatogram
2.944
96.38%
2.857
2.26%
Retention time (min)
41
C:\Users\krict...28_LAY-I-26.raw Injection 1 MS ES+ MS + spectrum 2.99
158.270
100.00%
107.099
94.07%
342.459
86.74%
171.738
72.51%
448.540
71.33%
169.721
57.87%
343.431
44.54%
449.512
31.16%
114.157
25.77%
224.853
9.53%
325.391
11.47%
344.440
6.07%
149.159
3.52%
210.233
0.55%
326.399
2.31%
450.484
5.85%
917.821
7.21%
m/z (Da)



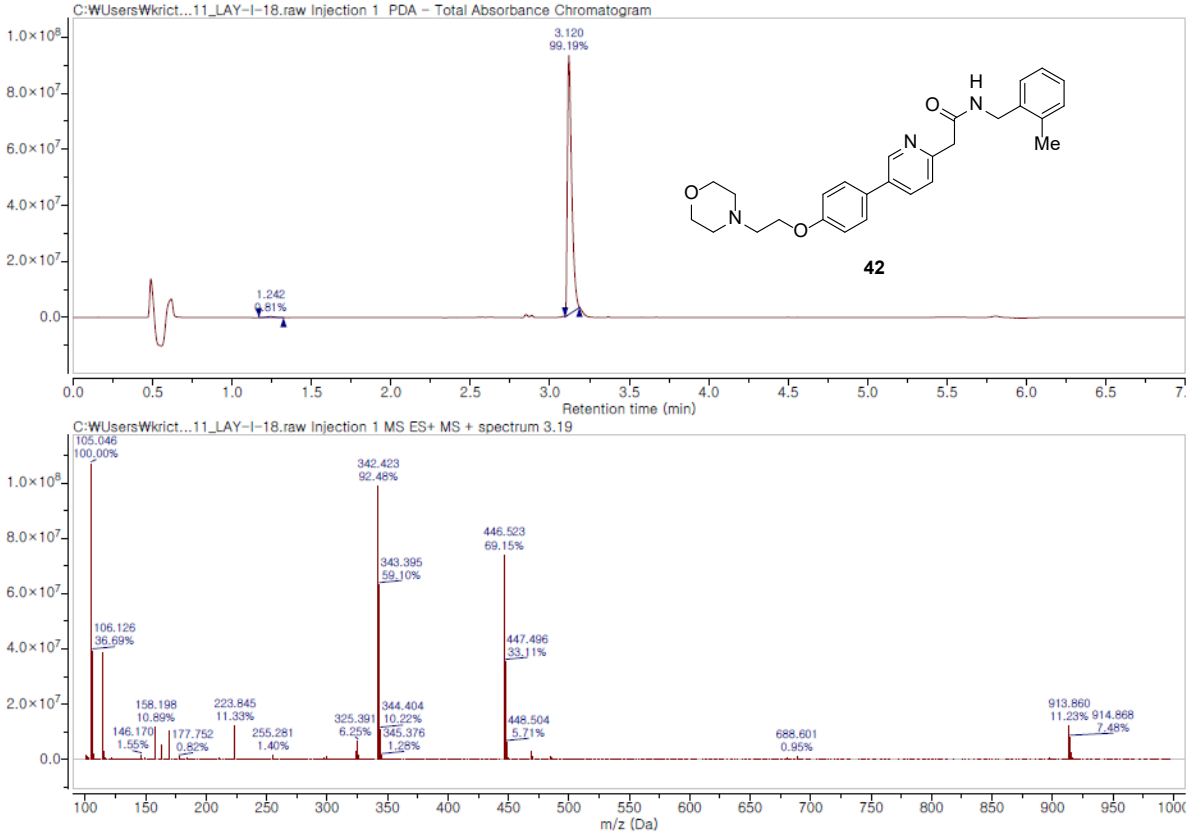
42

(DMSO-d_6, 400 MHz)

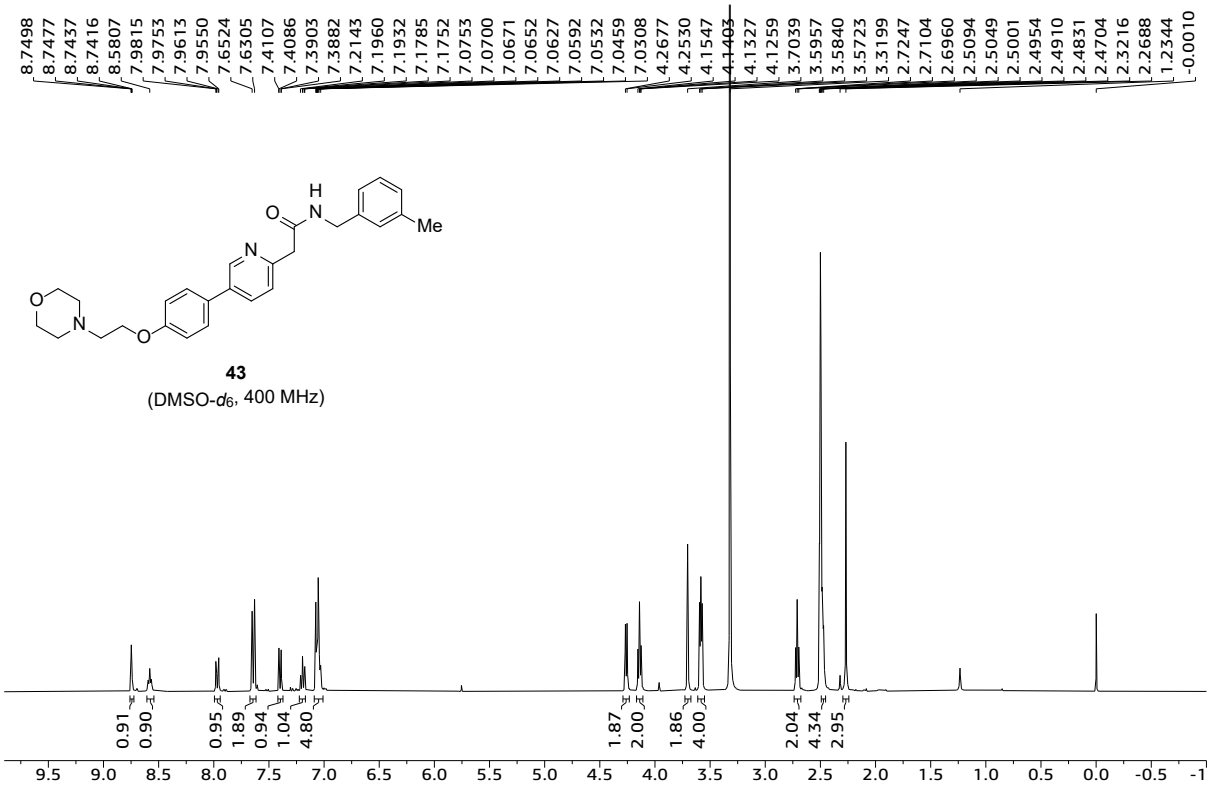


42

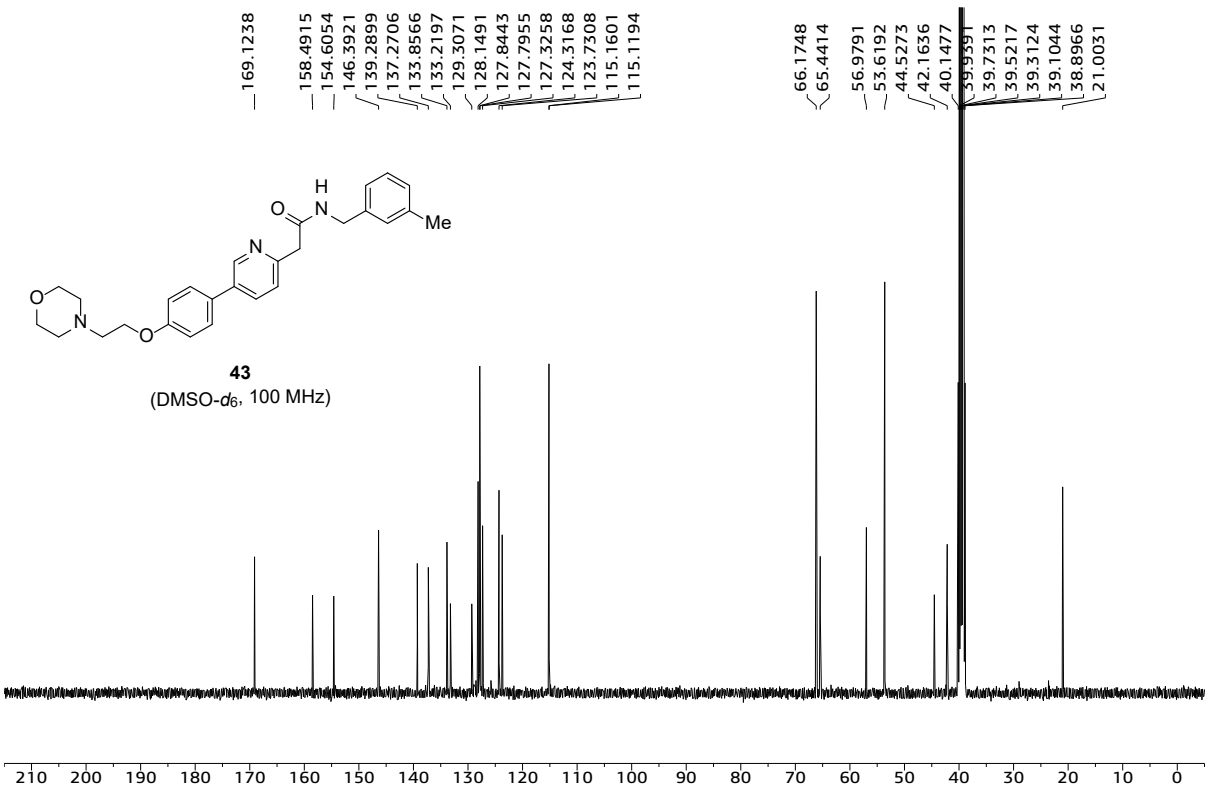
(DMSO-d_6, 100 MHz)


C:¥Users¥krict...11_LAY-I-18.raw Injection 1 PDA - Total Absorbance Chromatogram
3.120
99.19%
1.242
0.81%
Retention time (min)
C:¥Users¥krict...11_LAY-I-18.raw Injection 1 MS ES+ MS + spectrum 3.19
105.046
100.00%
342.423
92.48%
446.523
69.15%
343.395
59.10%
106.126
36.69%
447.496
33.11%
158.198
10.89%
223.845
11.33%
325.391
6.25%
344.404
10.22%
345.376
1.28%
448.504
5.71%
146.170
1.55%
177.752
0.82%
255.281
1.40%
688.601
0.95%
913.860
11.23%
914.868
7.48%
m/z (Da)

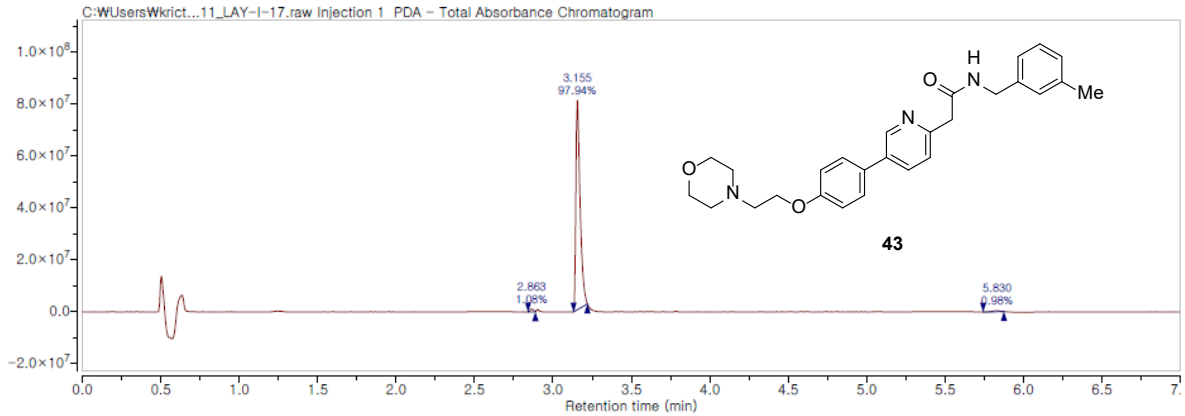
42



43
(DMSO-d_6, 400 MHz)

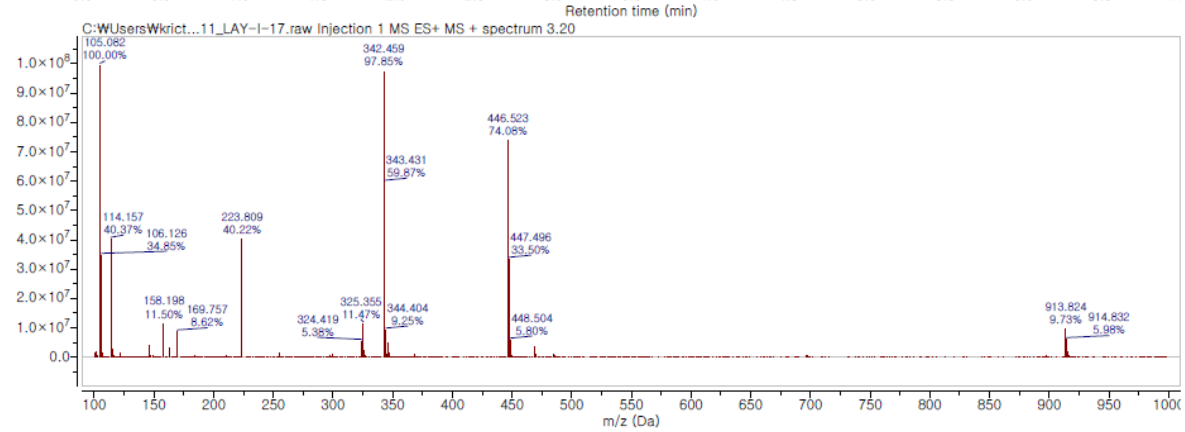


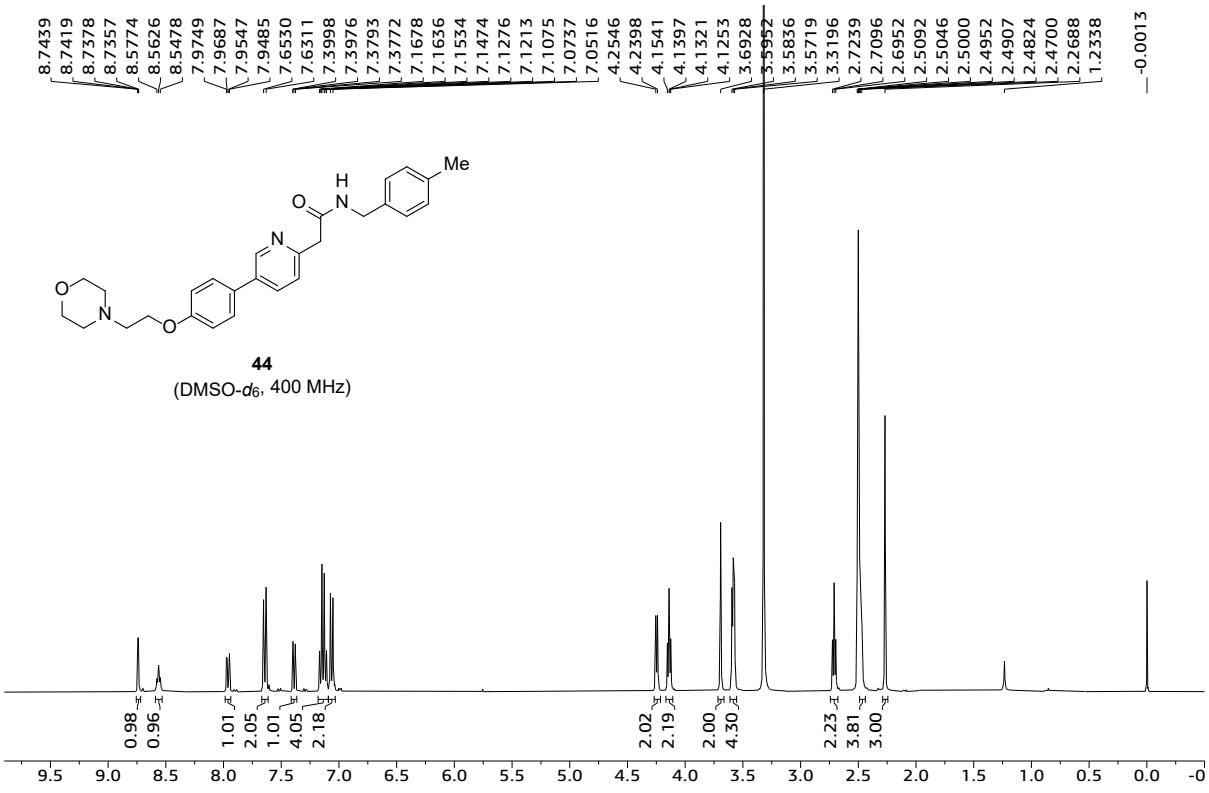
43
(DMSO-d_6, 100 MHz)

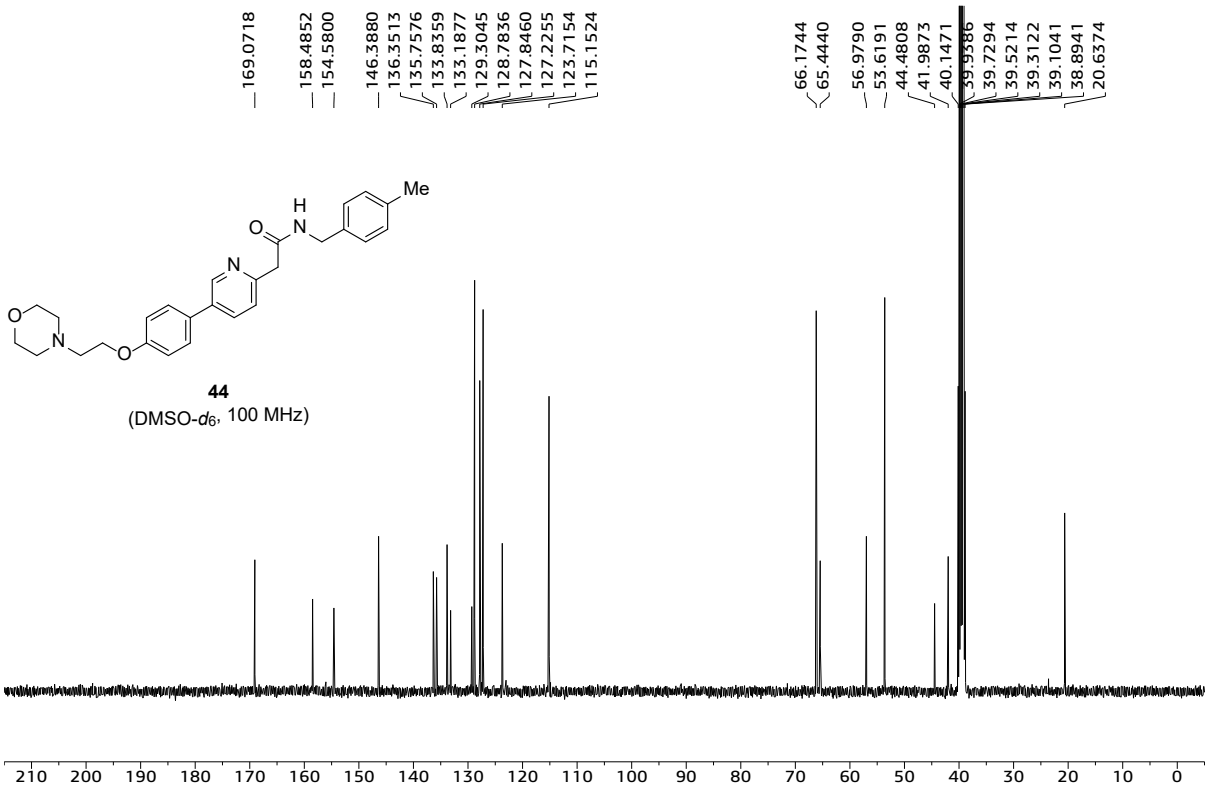

C:¥Users¥krict...11_LAY-I-17.raw Injection 1 PDA - Total Absorbance Chromatogram
3.155
97.94%
2.863
1.08%
5.830
0.98%
Retention time (min)

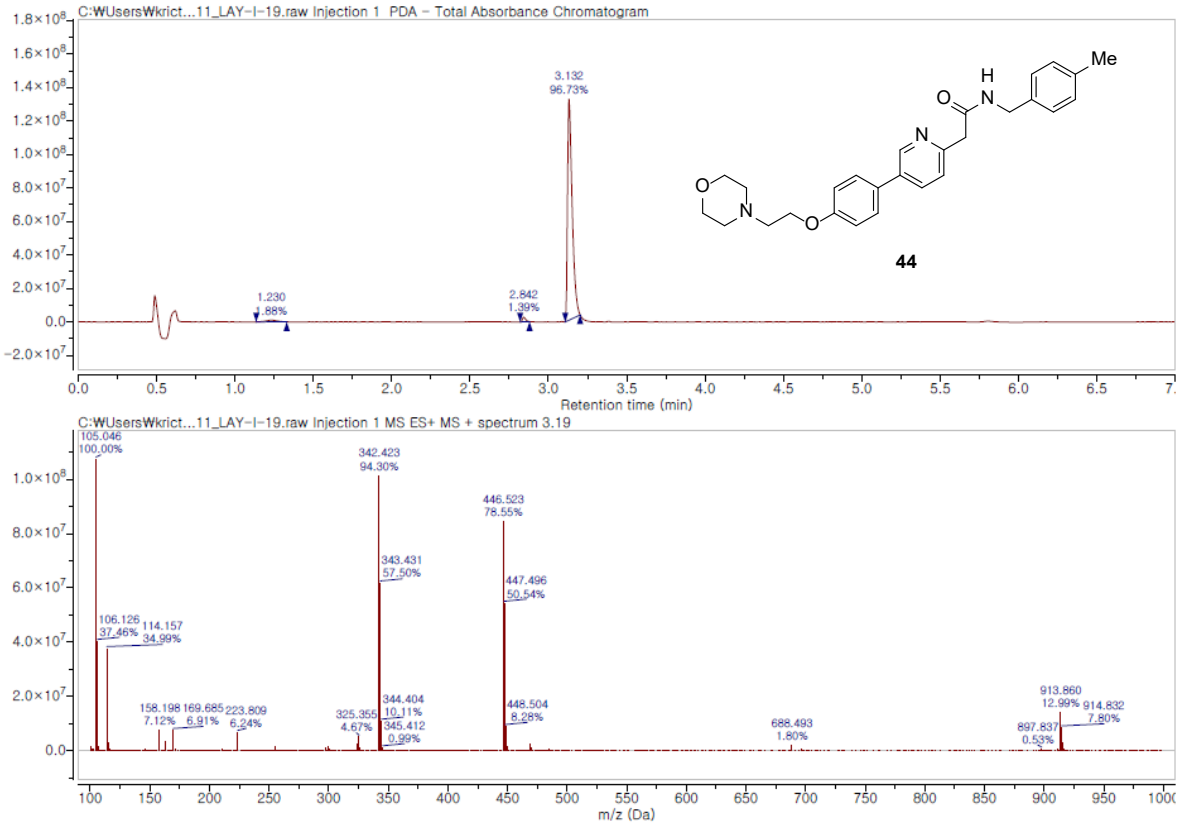
H
O
N
Me
N
O
N
O

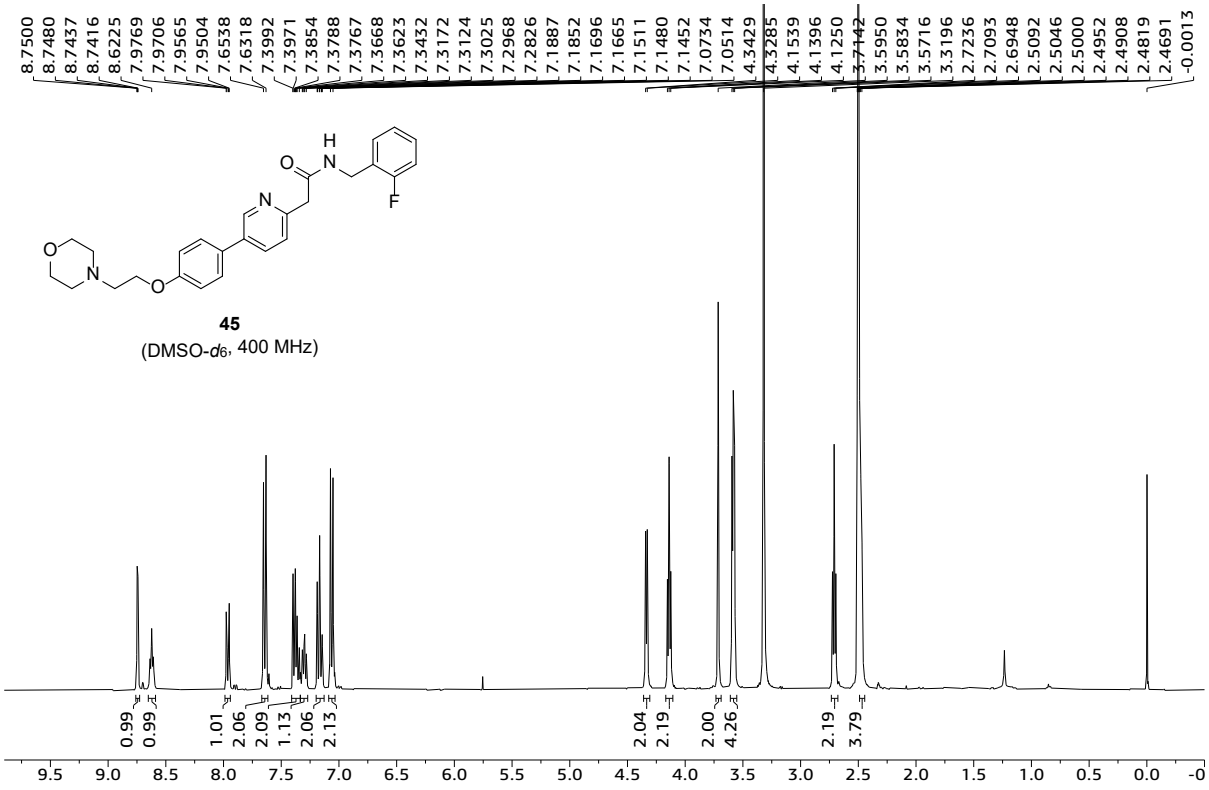
43


C:¥Users¥krict...11_LAY-I-17.raw Injection 1 MS ES+ MS + spectrum 3.20
105.082
100.00%
342.459
97.85%
446.523
74.08%
343.431
59.87%
114.157
40.37%
106.126
34.85%
223.809
40.22%
447.496
33.50%
158.198
11.50%
169.757
8.62%
325.355
11.47%
324.419
5.38%
344.404
9.25%
448.504
5.80%
913.824
9.73%
914.832
5.98%
m/z (Da)

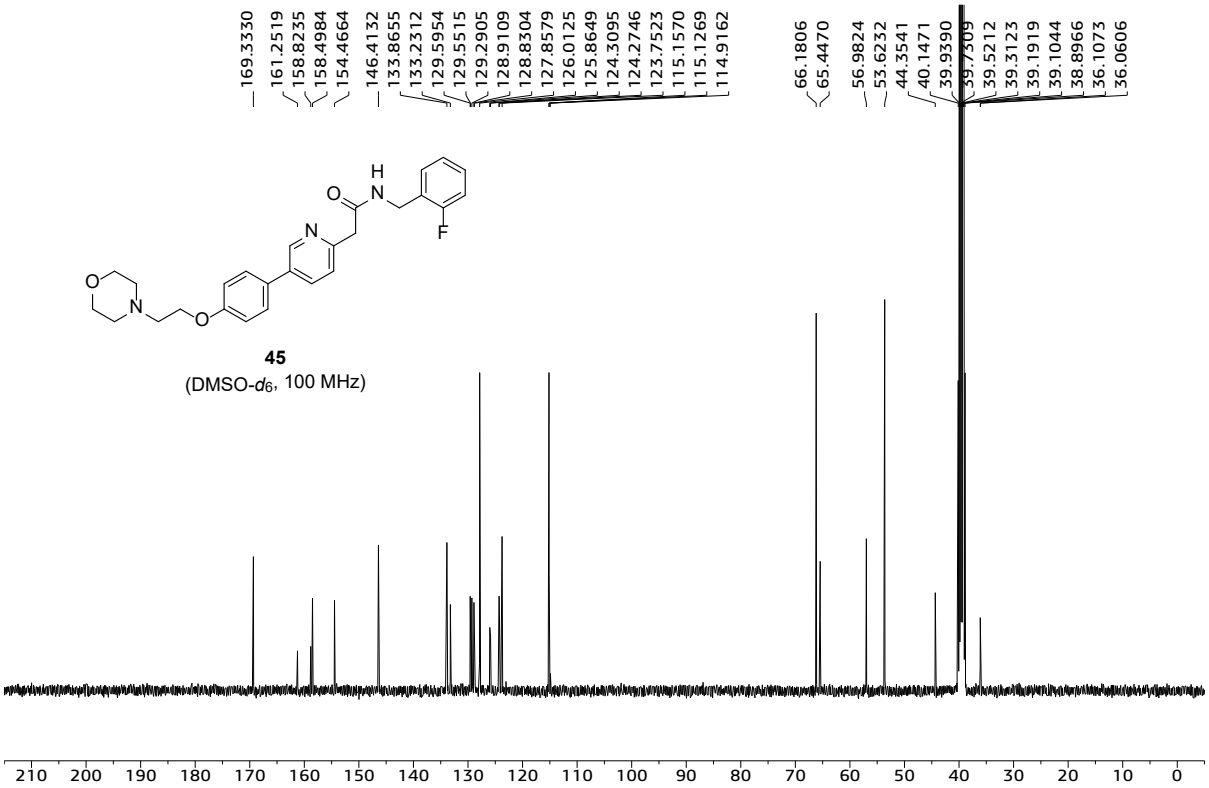

8.7439
8.7419
8.7378
8.7357
8.5774
8.5626
8.5478
7.9749
7.9687
7.9547
7.9485
7.6530
7.6311
7.3998
7.3976
7.3793
7.3772
7.1678
7.1636
7.1534
7.1474
7.1276
7.1213
7.1075
7.0737
7.0516
4.2546
4.2398
4.1541
4.1397
4.1321
4.1253
3.6928
3.5952
3.5836
3.5719
3.3196
2.7239
2.7096
2.6952
2.5092
2.5046
2.5000
2.4952
2.4907
2.4824
2.4700
2.2688
1.2338
-0.0013
Me
H
N
O
N
O
N
O
44
(DMSO-d_6, 400 MHz)
0.98
0.96
1.01
2.05
1.01
4.05
2.18
2.02
2.19
2.00
4.30
2.23
3.81
3.00
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 0.0 -0


169.0718
158.4852
154.5800
146.3880
136.3513
135.7576
133.8359
133.1877
129.3045
128.7836
127.8460
127.2255
123.7154
115.1524
66.1744
65.4440
56.9790
53.6191
44.4808
41.9873
40.1471
39.9586
39.7294
39.5214
39.3122
39.1041
38.8941
20.6374
Me
H
N
O
N
O
N
O
44
(DMSO-d_6, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

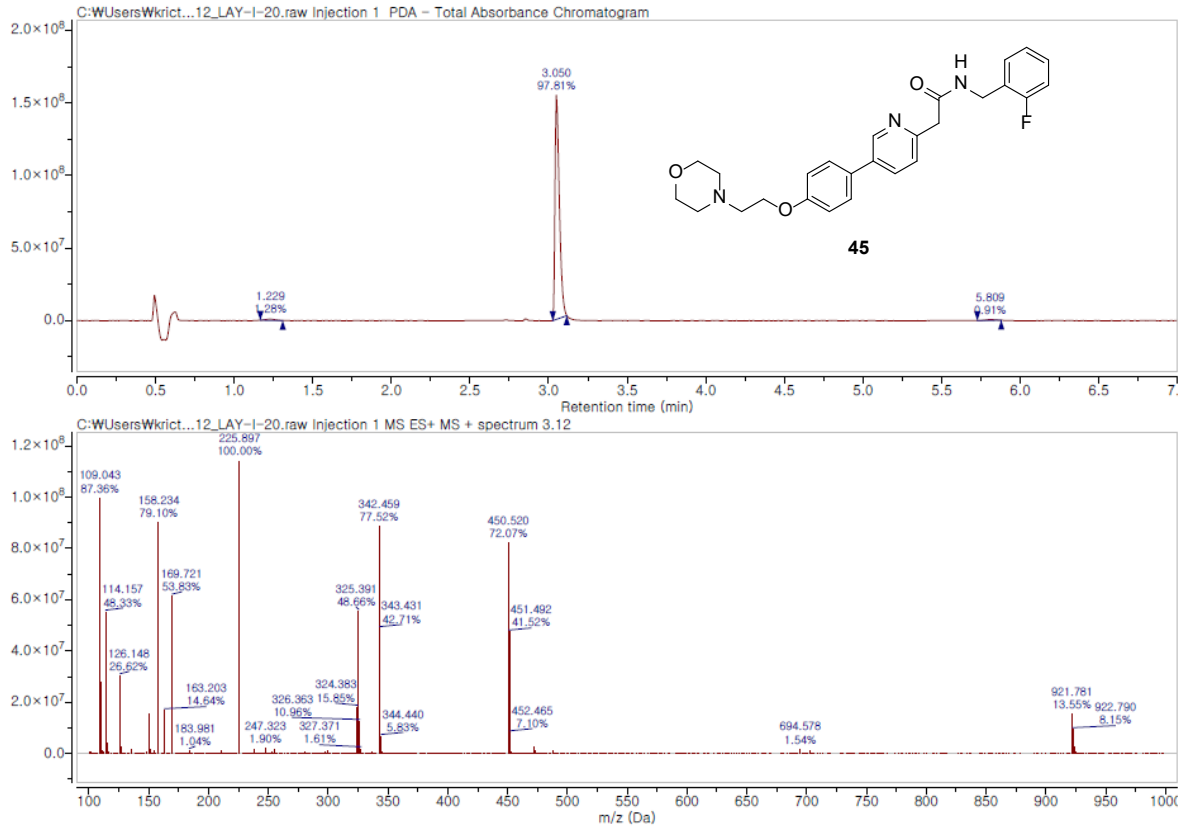

C:\Users\krict...11_LAY-I-19.raw Injection 1 PDA - Total Absorbance Chromatogram
3.132
96.73%
1.230
1.88%
2.842
1.39%
Retention time (min)
C:\Users\krict...11_LAY-I-19.raw Injection 1 MS ES+ MS + spectrum 3.19
105.046
100.00%
342.423
94.30%
446.523
78.55%
343.431
57.50%
447.496
50.54%
106.126
37.46%
114.157
34.99%
158.198
7.12%
169.685
6.91%
223.809
6.24%
325.355
4.67%
344.404
10.11%
345.412
0.99%
448.504
8.28%
688.493
1.80%
913.860
12.99%
914.832
7.80%
897.837
0.53%
m/z (Da)
Me
H
N
O
N
O
N
O
44



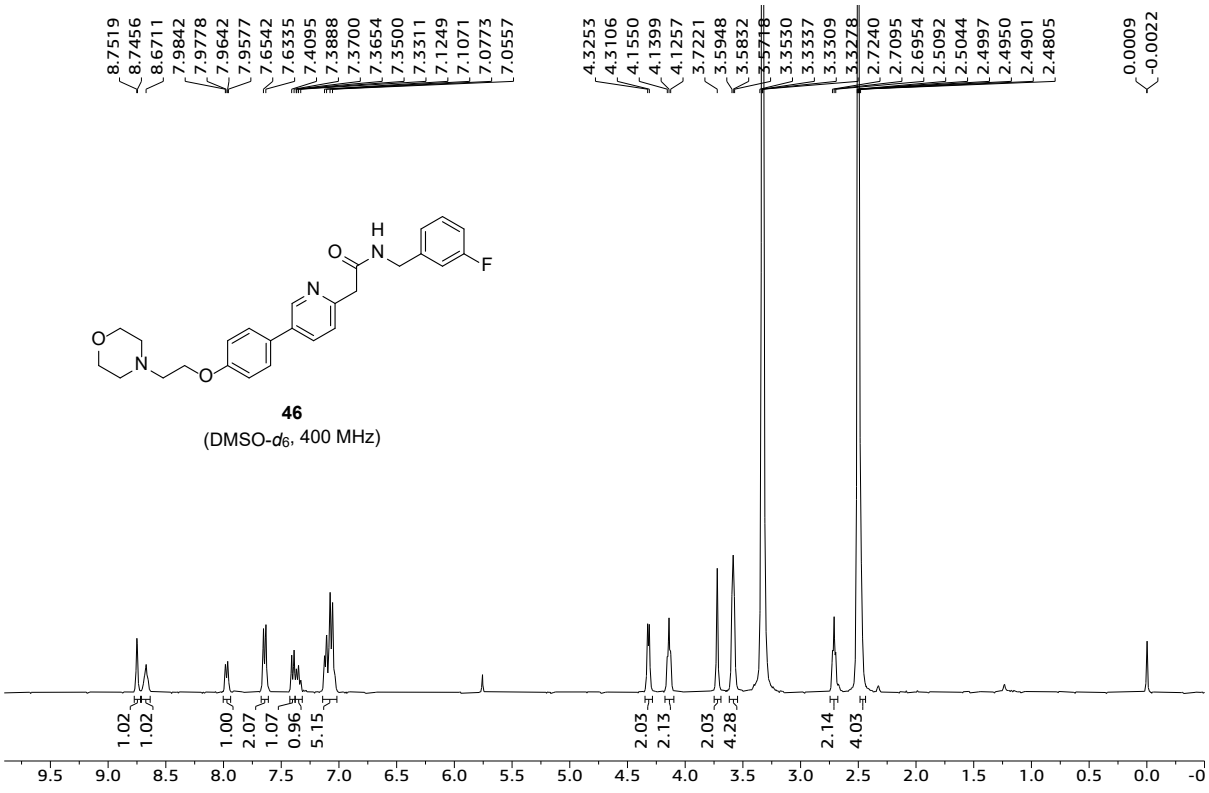
45
(DMSO-d_6, 400 MHz)



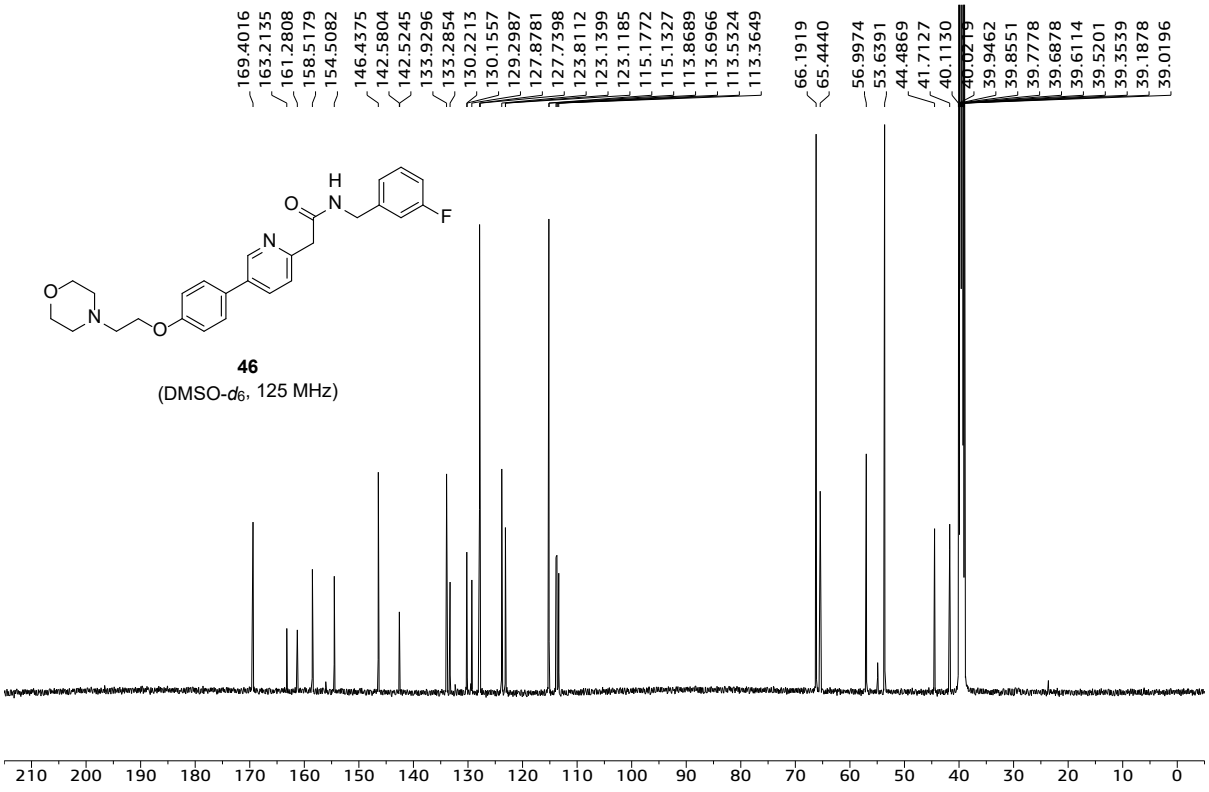
45
(DMSO-d_6, 100 MHz)


C:₩Users₩krict...12_LAY-I-20.raw Injection 1 PDA - Total Absorbance Chromatogram
3.050
97.81%
1.229
1.28%
5.809
0.91%
Retention time (min)
C:₩Users₩krict...12_LAY-I-20.raw Injection 1 MS ES+ MS + spectrum 3.12
225.897
100.00%
109.043
87.36%
158.234
79.10%
342.459
77.52%
450.520
72.07%
169.721
53.83%
114.157
48.33%
325.391
48.66%
343.431
42.71%
451.492
41.52%
126.148
26.62%
163.203
14.64%
324.383
15.85%
326.363
10.96%
344.440
5.83%
452.465
7.10%
183.981
1.04%
247.323
1.90%
327.371
1.61%
694.578
1.54%
921.781
13.55%
922.790
8.15%
m/z (Da)

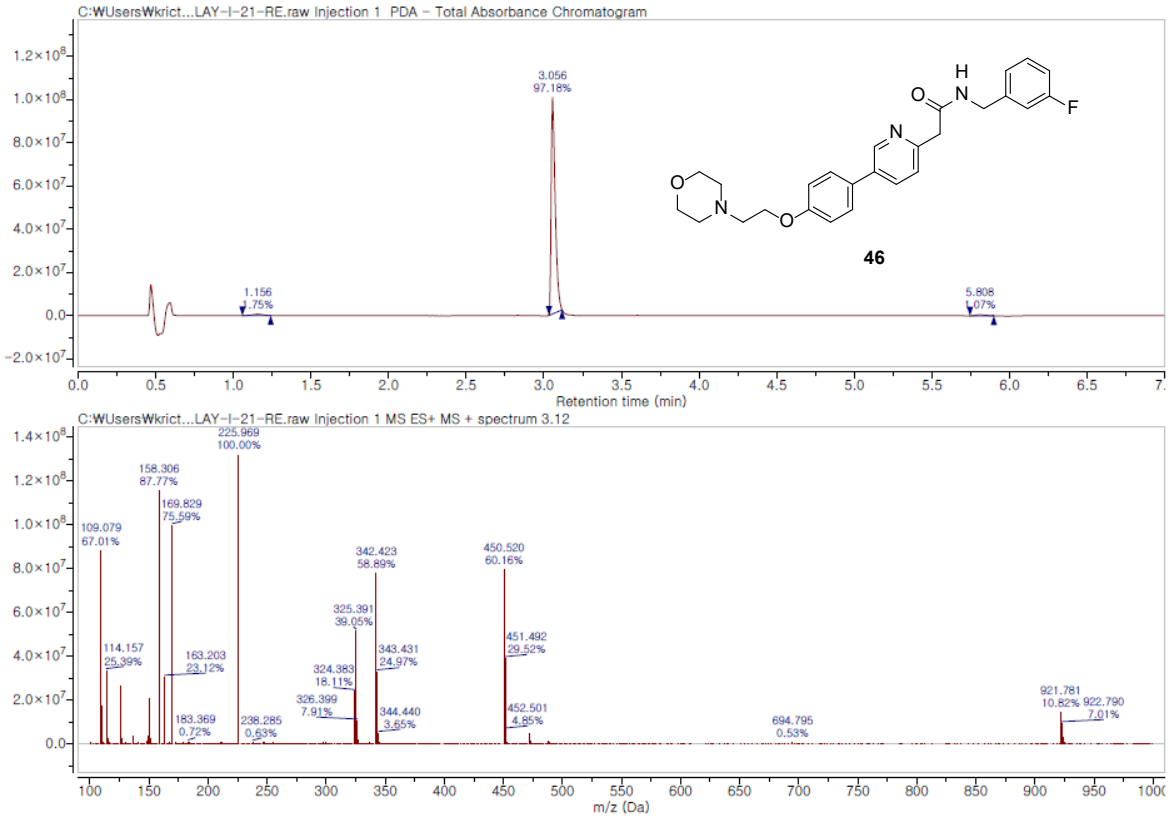
45

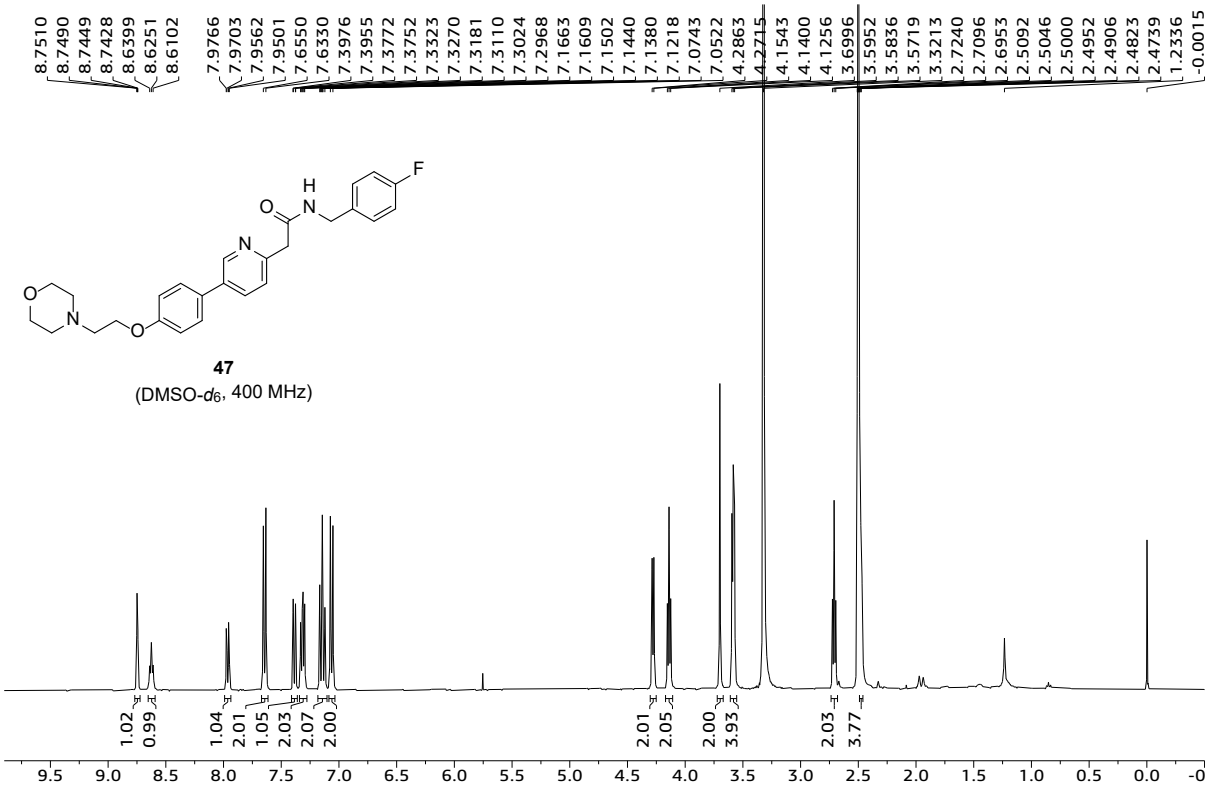


46
(DMSO-d_6, 400 MHz)

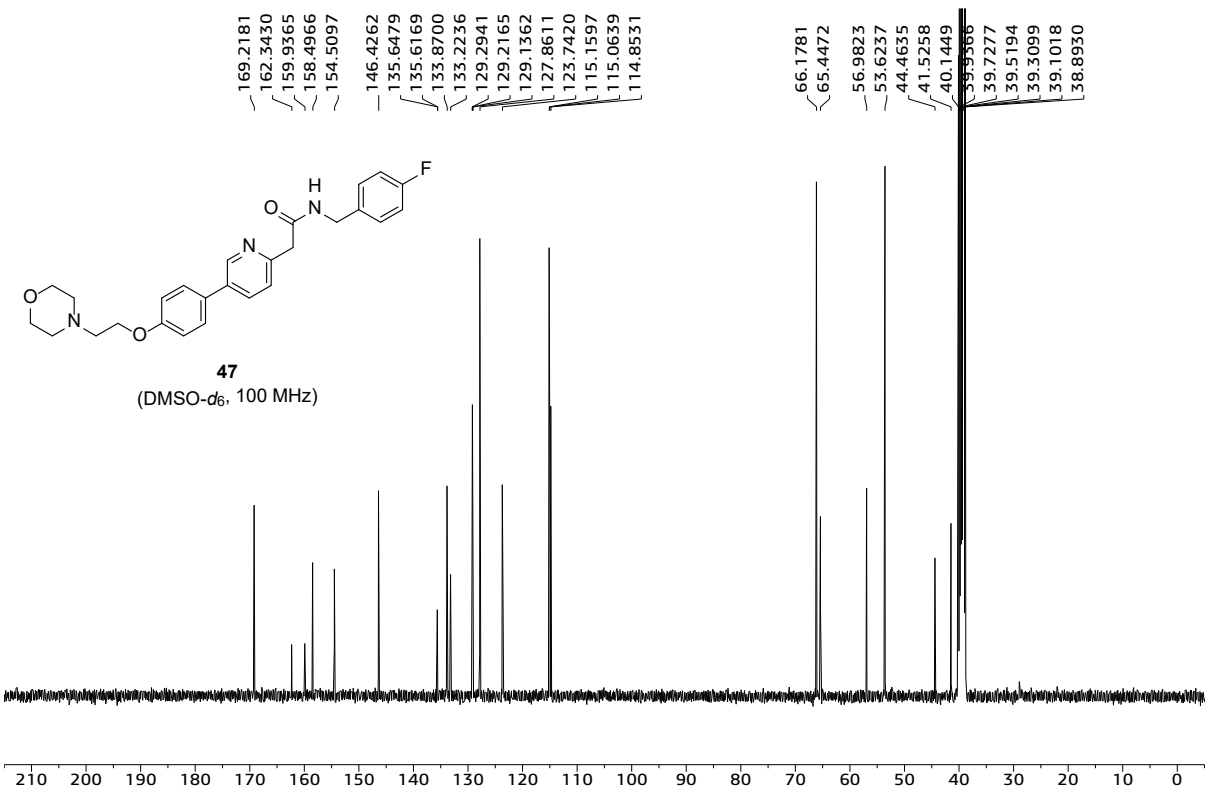


46
(DMSO-d_6, 125 MHz)

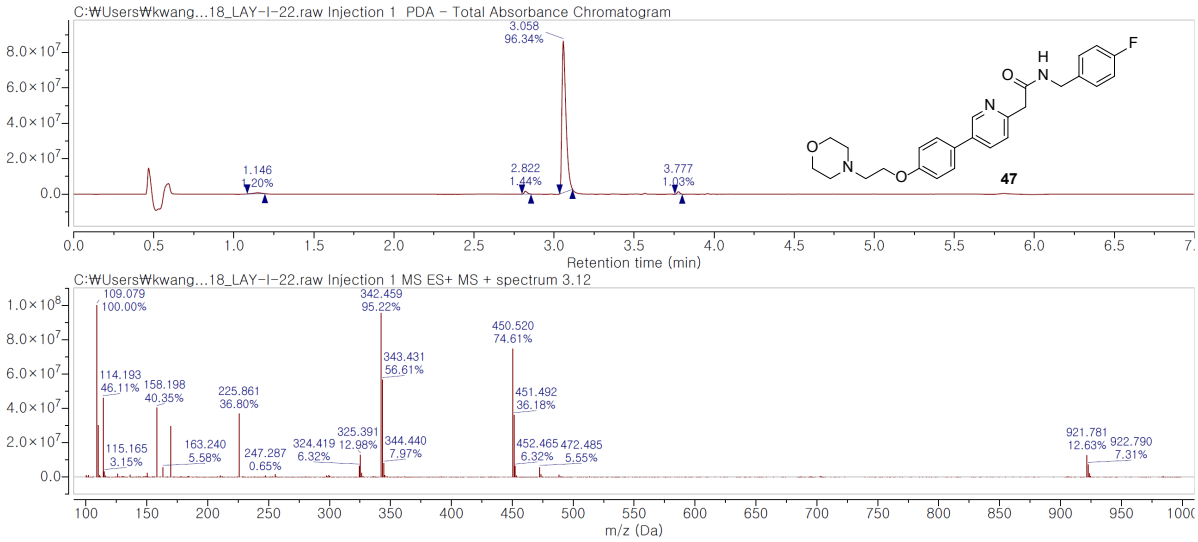

C:\Users\krict...LAY-I-21-RE.raw Injection 1 PDA - Total Absorbance Chromatogram
3.056
97.18%
1.156
1.75%
5.808
1.07%
Retention time (min)
C:\Users\krict...LAY-I-21-RE.raw Injection 1 MS ES+ MS + spectrum 3.12
225.969
100.00%
158.306
87.77%
169.829
75.59%
109.079
67.01%
342.423
58.89%
450.520
60.16%
325.391
39.05%
114.157
25.39%
163.203
23.12%
343.431
24.97%
451.492
29.52%
324.383
18.11%
326.399
7.91%
344.440
3.65%
452.501
4.85%
183.369
0.72%
238.285
0.63%
694.795
0.53%
921.781
10.82%
922.790
7.01%
m/z (Da)
46

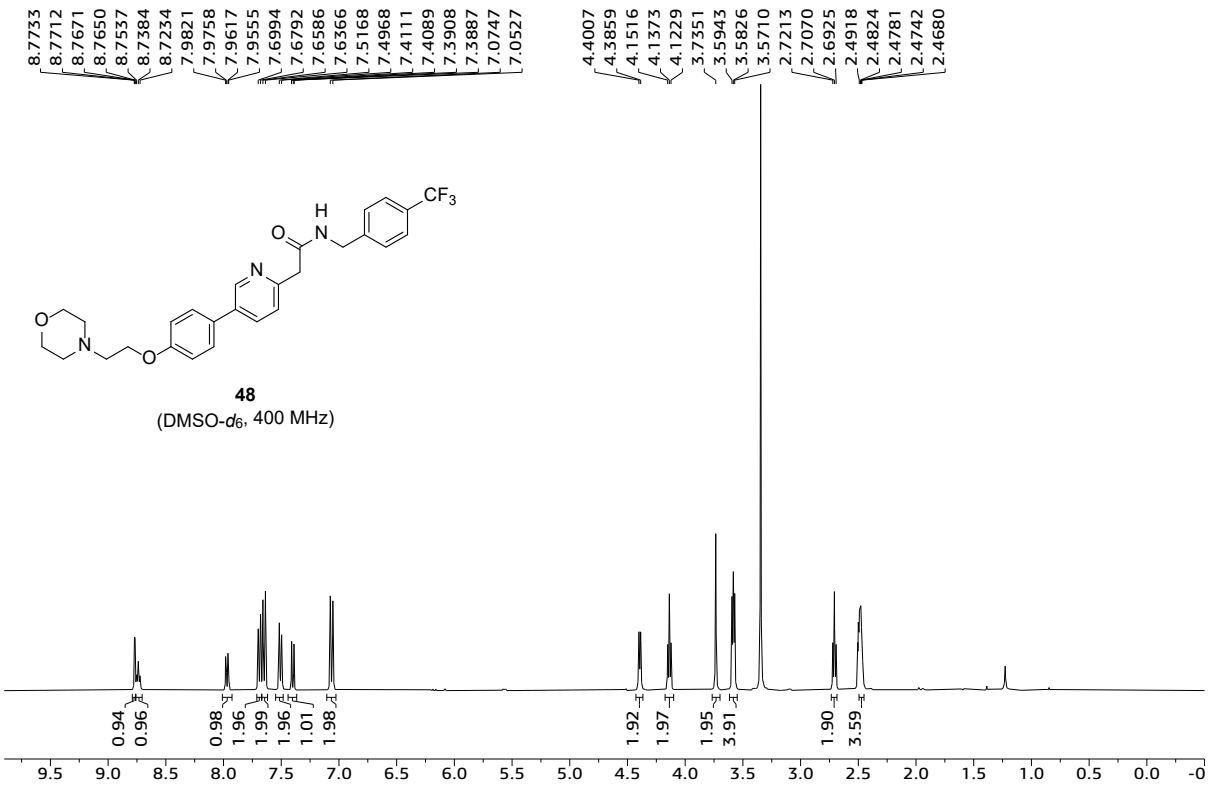


47
(DMSO-d_6, 400 MHz)

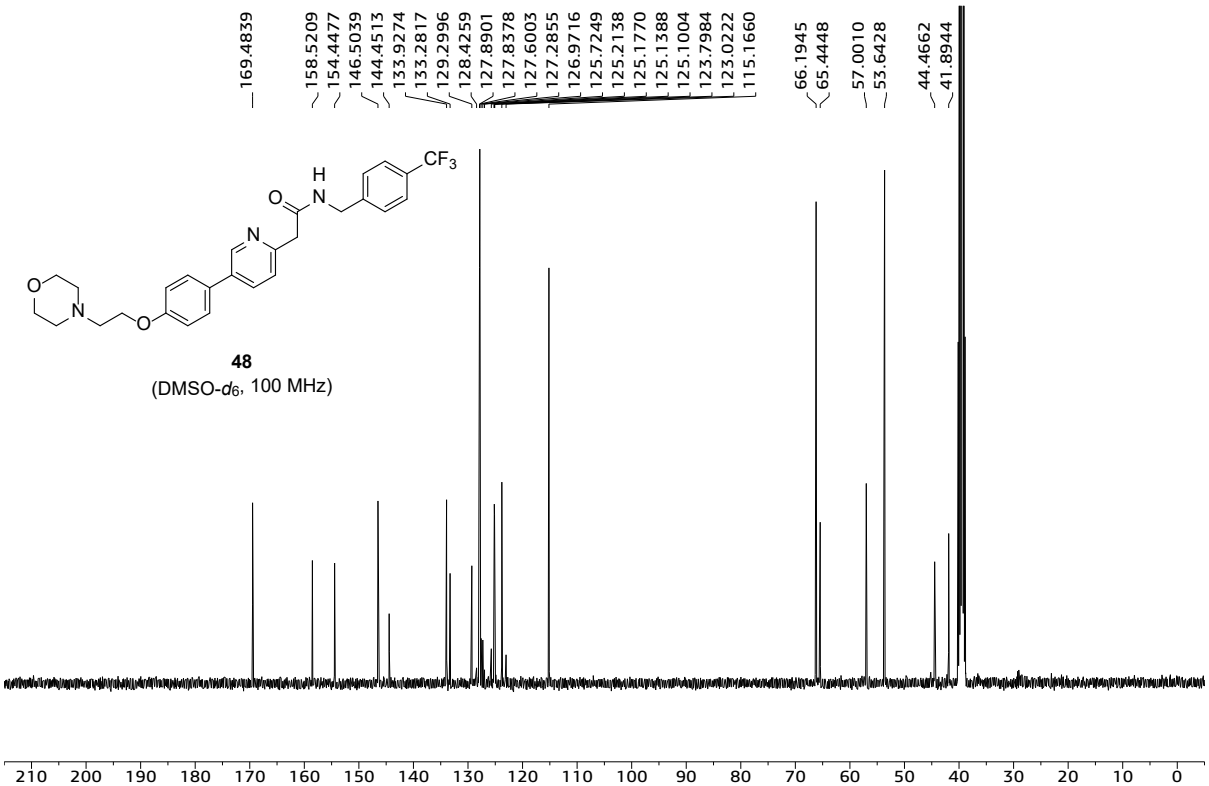


47
(DMSO-d_6, 100 MHz)

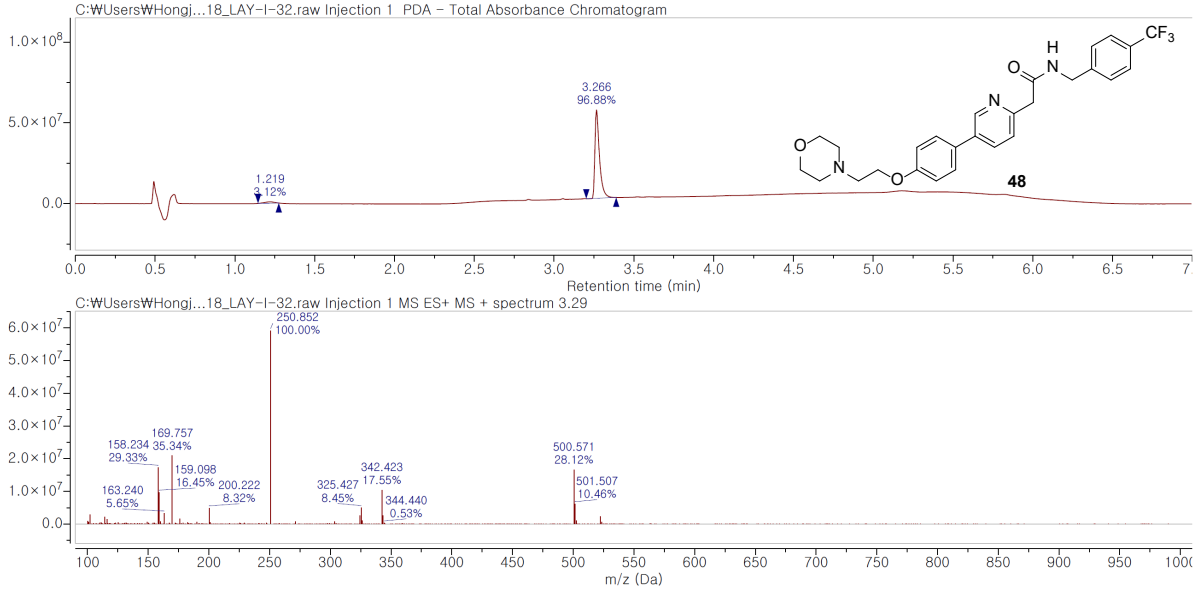

C:₩Users₩kwang...18_LAY-I-22.raw Injection 1 PDA - Total Absorbance Chromatogram
3.058
96.34%
1.146
20%
2.822
1.44%
3.777
1.03%
47
Retention time (min)
C:₩Users₩kwang...18_LAY-I-22.raw Injection 1 MS ES+ MS + spectrum 3.12
109.079
100.00%
342.459
95.22%
450.520
74.61%
343.431
56.61%
114.193
46.11%
158.198
40.35%
225.861
36.80%
451.492
36.18%
115.165
3.15%
163.240
5.58%
247.287
0.65%
324.419
6.32%
325.391
12.98%
344.440
7.97%
452.465
6.32%
472.485
5.55%
921.781
12.63%
922.790
7.31%
m/z (Da)

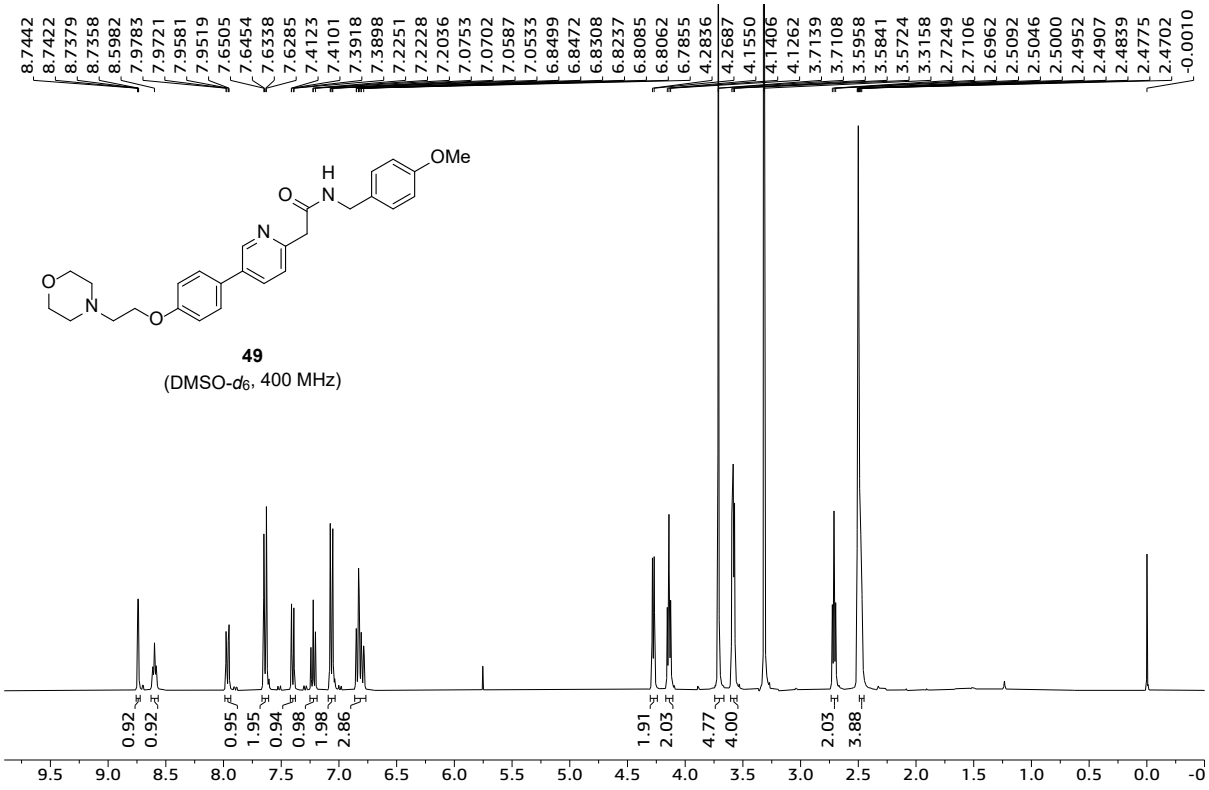


48
(DMSO-d_6, 400 MHz)



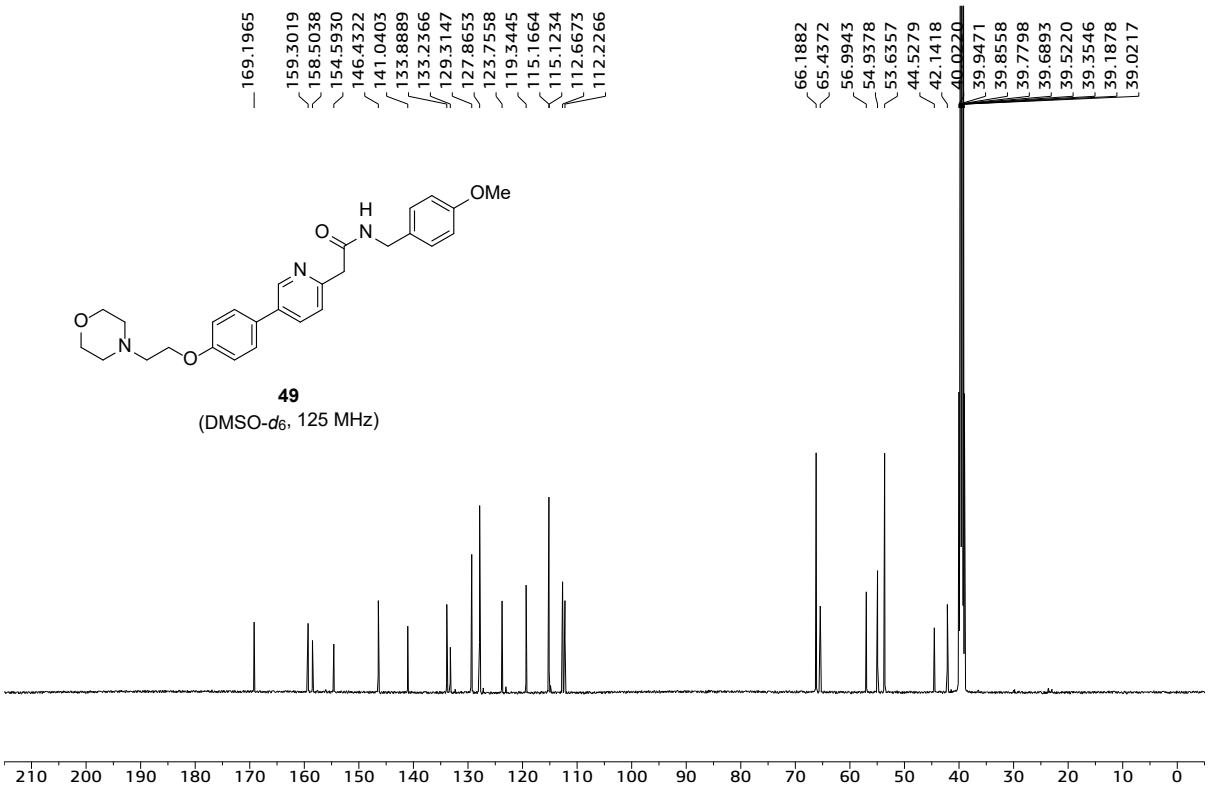
48
(DMSO-d_6, 100 MHz)


C:₩Users₩Hongj...18_LAY-I-32.raw Injection 1 PDA - Total Absorbance Chromatogram
1.0×10^8
5.0×10^7
0.0
1.219
3.12%
3.266
96.88%
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5
Retention time (min)
48
C:₩Users₩Hongj...18_LAY-I-32.raw Injection 1 MS ES+ MS + spectrum 3.29
6.0×10^7
5.0×10^7
4.0×10^7
3.0×10^7
2.0×10^7
1.0×10^7
0.0
250.852
100.00%
169.757
35.34%
158.234
29.33%
159.098
16.45%
200.222
8.32%
163.240
5.65%
342.423
17.55%
325.427
8.45%
344.440
0.53%
500.571
28.12%
501.507
10.46%
100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z (Da)



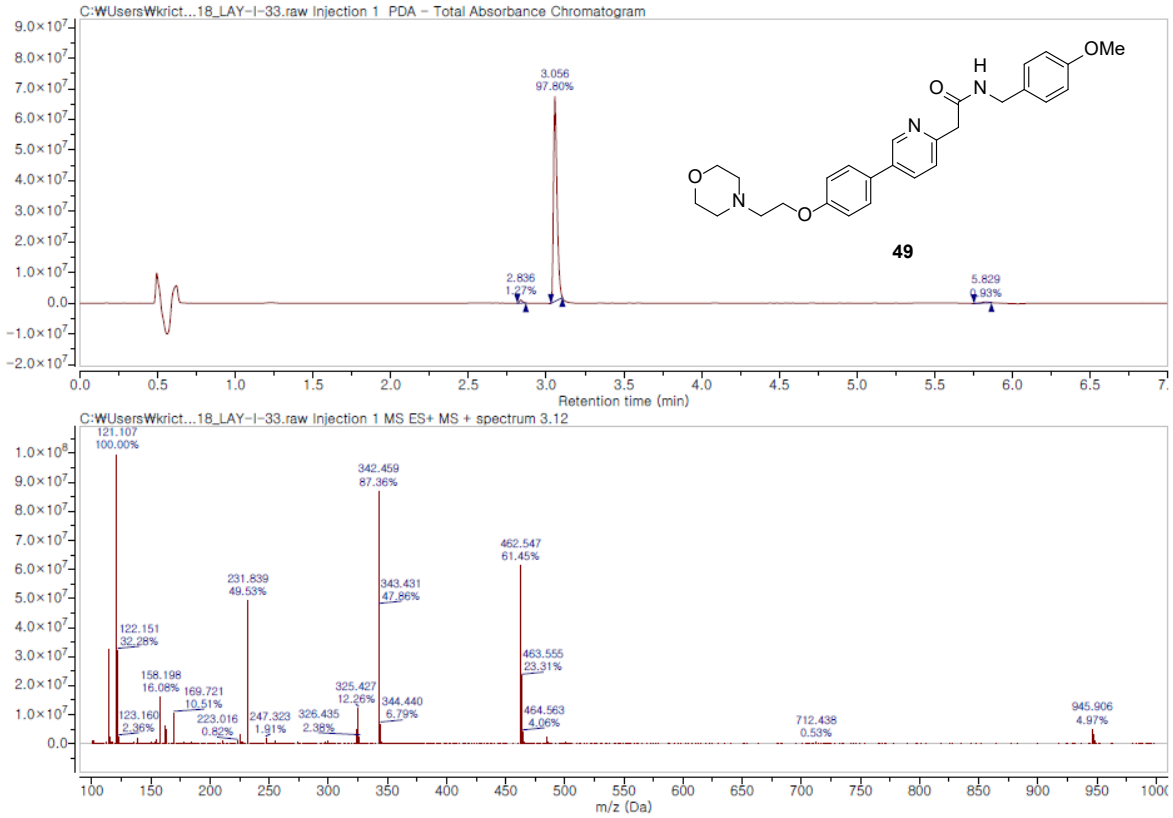
49

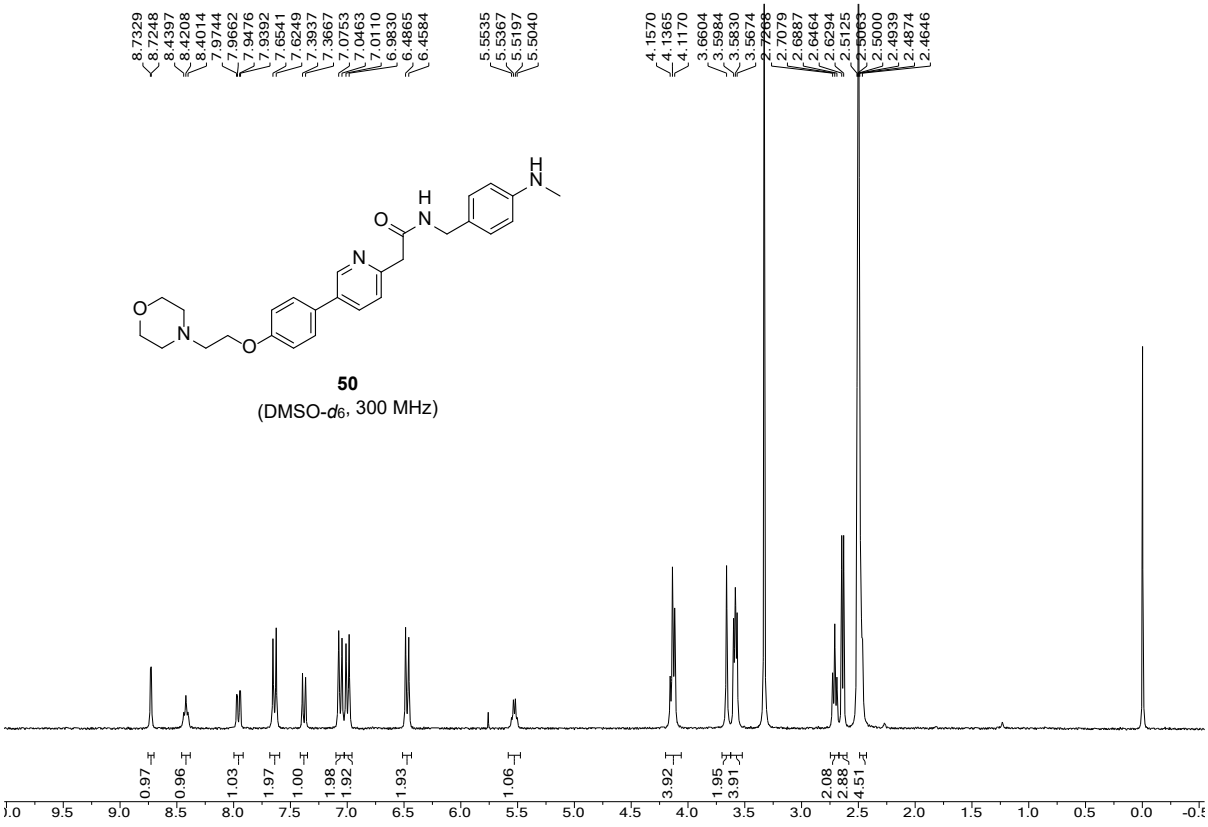
(DMSO-d_6, 400 MHz)



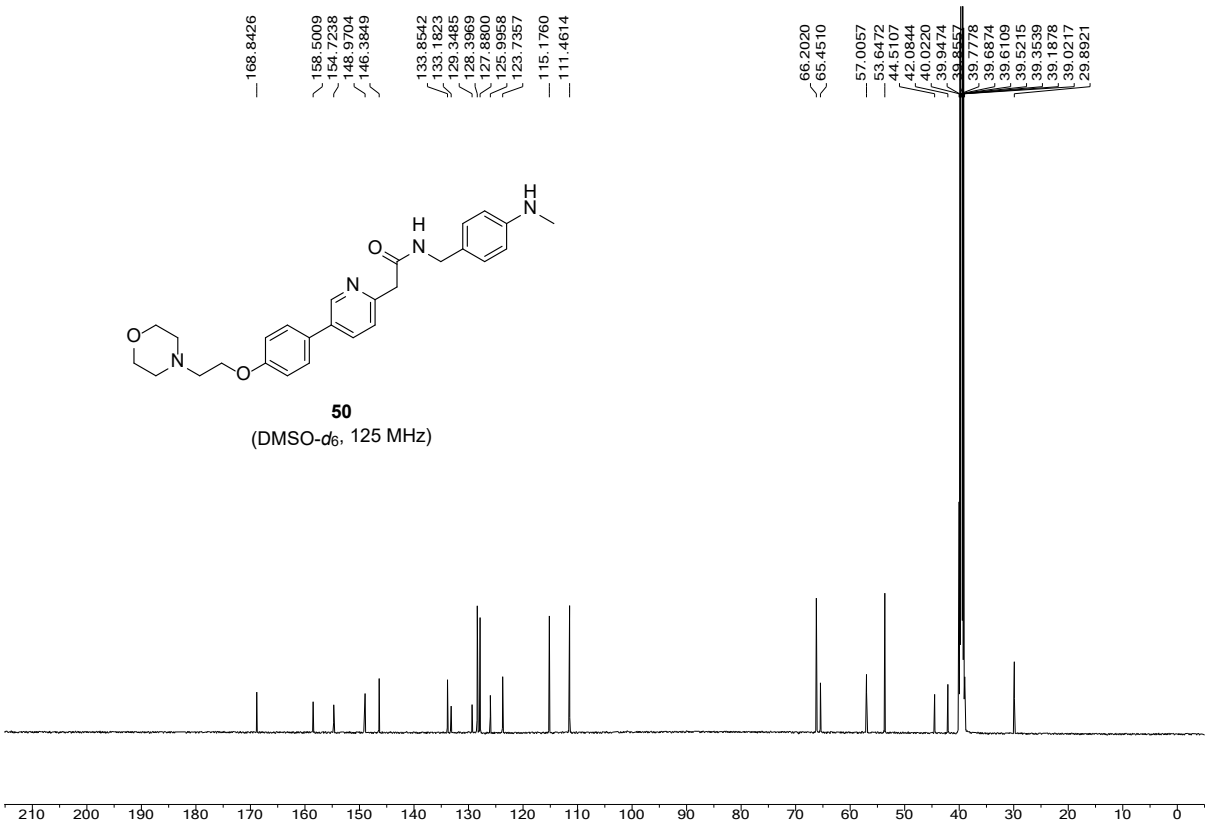
49

(DMSO-d_6, 125 MHz)

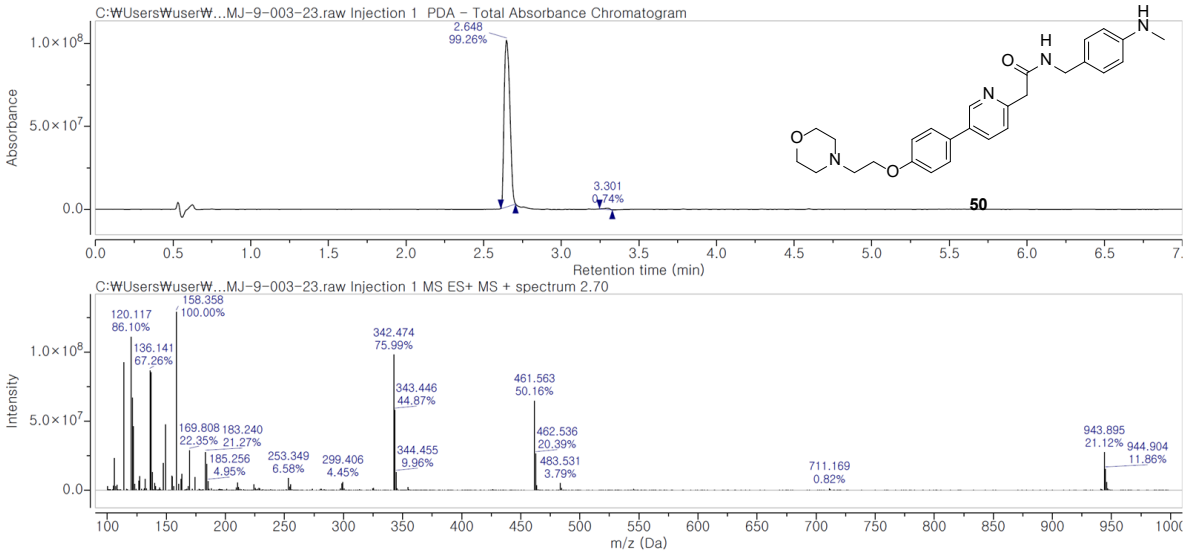

C:₩Users₩krict...18_LAY-I-33.raw Injection 1 PDA - Total Absorbance Chromatogram
3.056
97.80%
2.836
1.27%
5.829
0.93%
Retention time (min)
49
C:₩Users₩krict...18_LAY-I-33.raw Injection 1 MS ES+ MS + spectrum 3.12
121.107
100.00%
342.459
87.36%
462.547
61.45%
231.839
49.53%
343.431
47.86%
122.151
32.28%
463.555
23.31%
158.198
16.08%
169.721
10.51%
325.427
12.26%
344.440
6.79%
123.160
2.36%
223.016
0.82%
247.323
1.91%
326.435
2.38%
464.563
4.06%
712.438
0.53%
945.906
4.97%
m/z (Da)

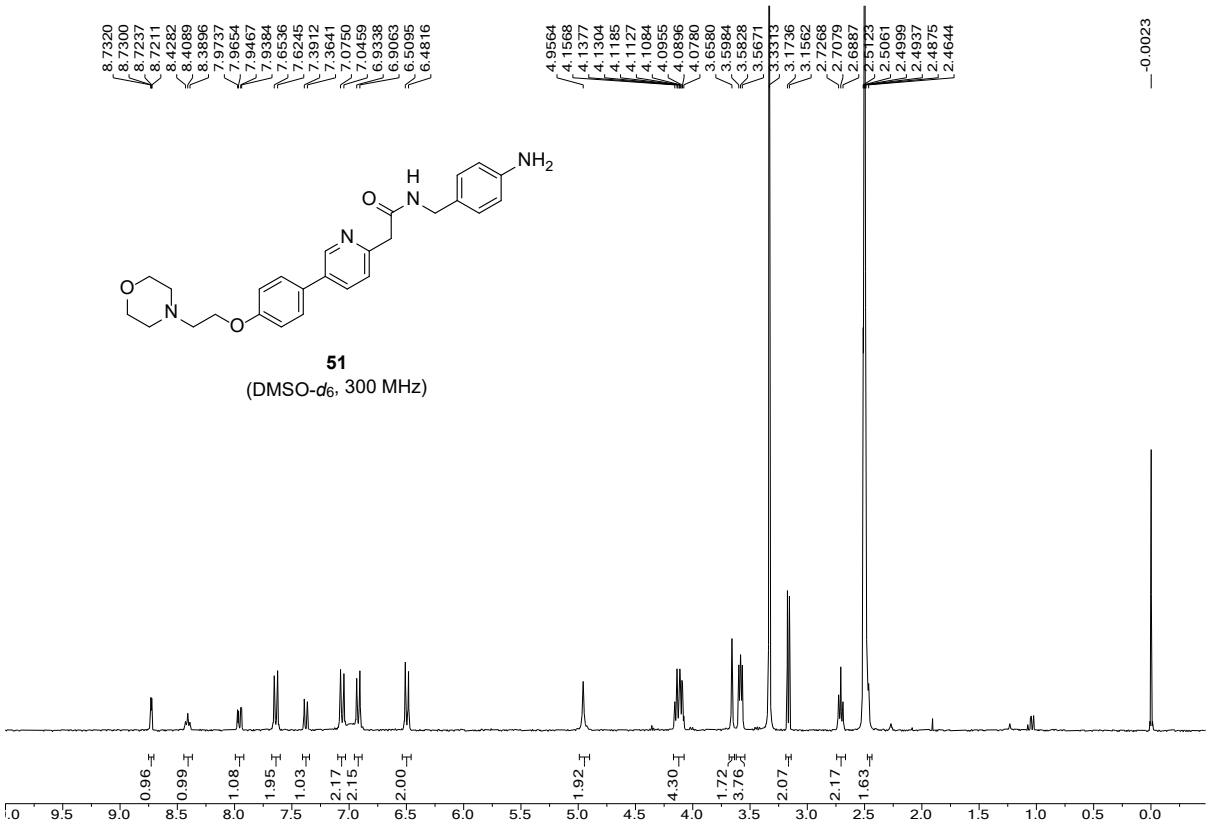


50
(DMSO-d_6, 300 MHz)

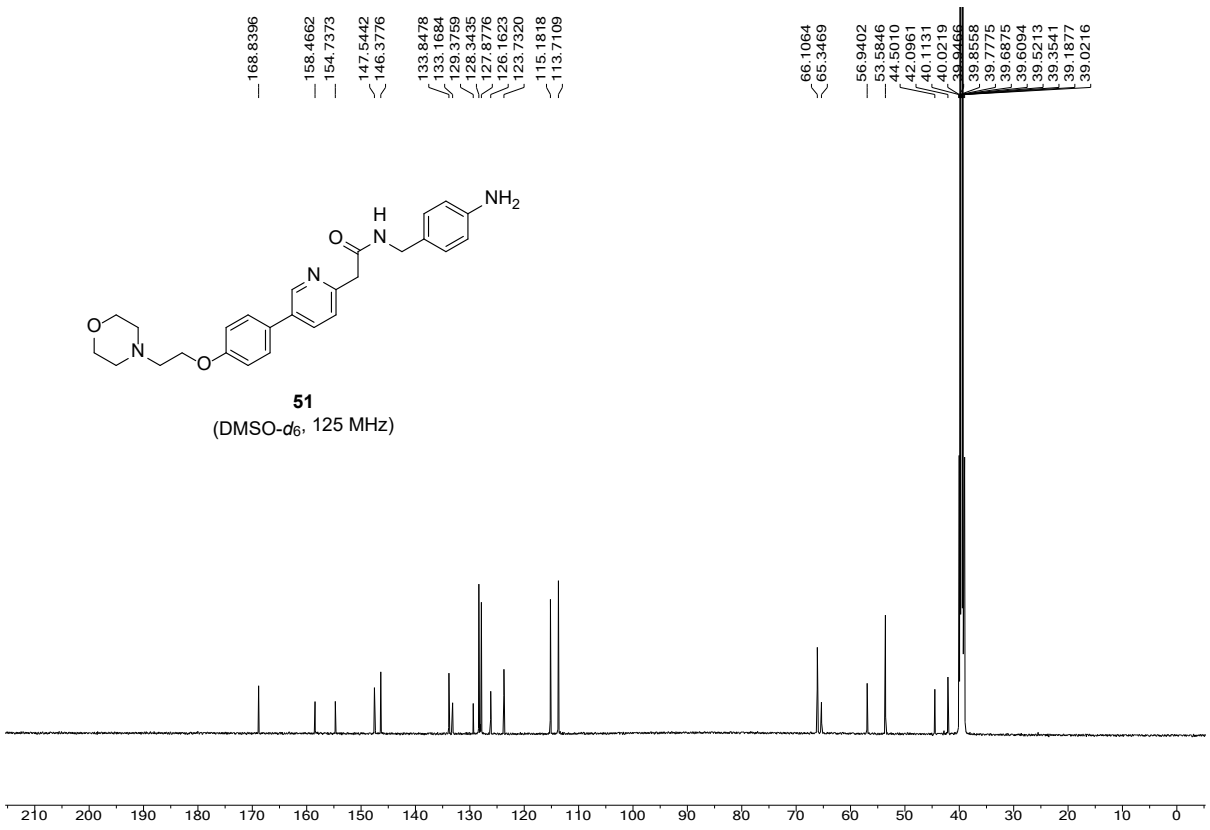


50
(DMSO-d_6, 125 MHz)

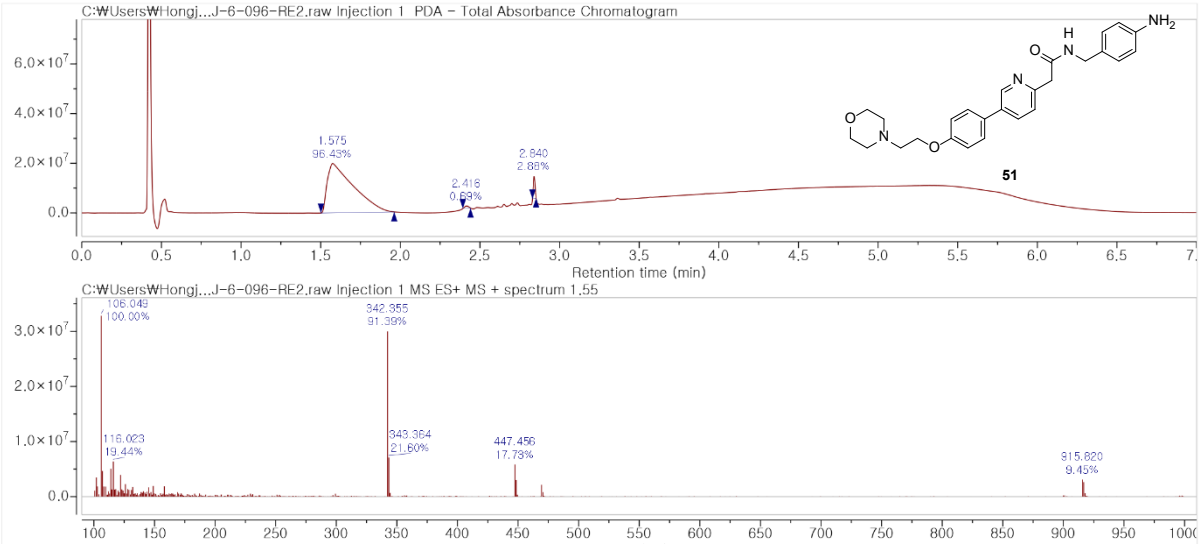

C:₩Users₩user₩...MJ-9-003-23.raw Injection 1 PDA - Total Absorbance Chromatogram
Absorbance
1.0×10^8
5.0×10^7
0.0
2.648
99.26%
3.301
0.74%
50
Retention time (min)
C:₩Users₩user₩...MJ-9-003-23.raw Injection 1 MS ES+ MS + spectrum 2.70
Intensity
158.358
100.00%
120.117
86.10%
136.141
67.26%
169.808
22.35%
183.240
21.27%
185.256
4.95%
253.349
6.58%
299.406
4.45%
342.474
75.99%
343.446
44.87%
344.455
9.96%
461.563
50.16%
462.536
20.39%
483.531
3.79%
711.169
0.82%
943.895
21.12%
944.904
11.86%
m/z (Da)

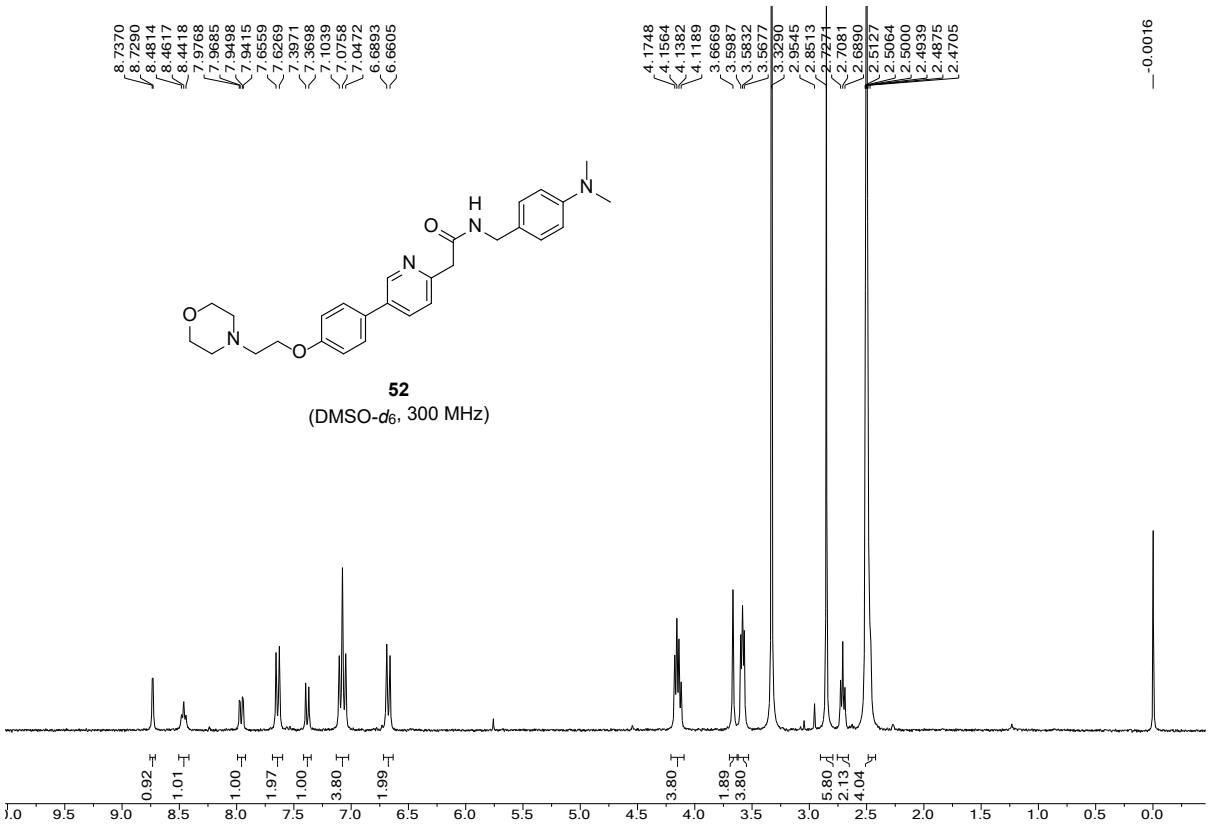


51
(DMSO-d_6, 300 MHz)

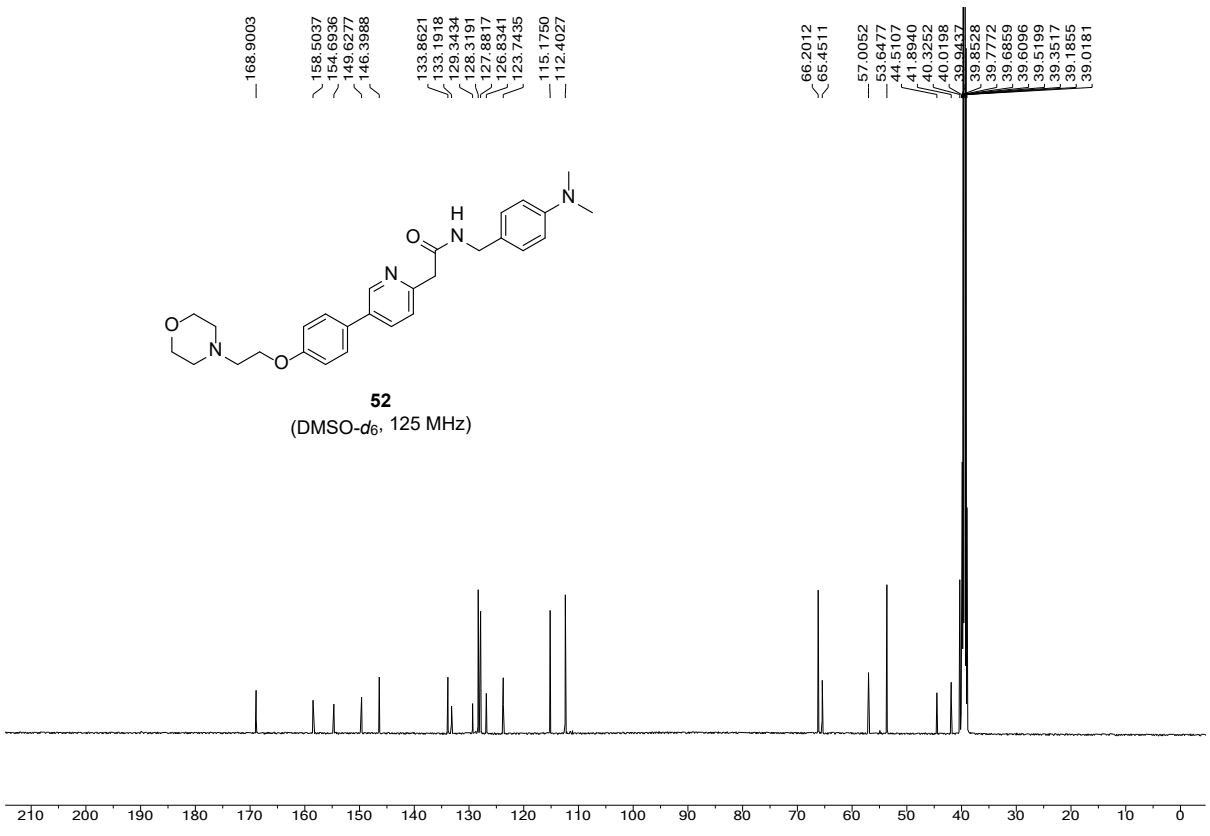


51
(DMSO-d_6, 125 MHz)

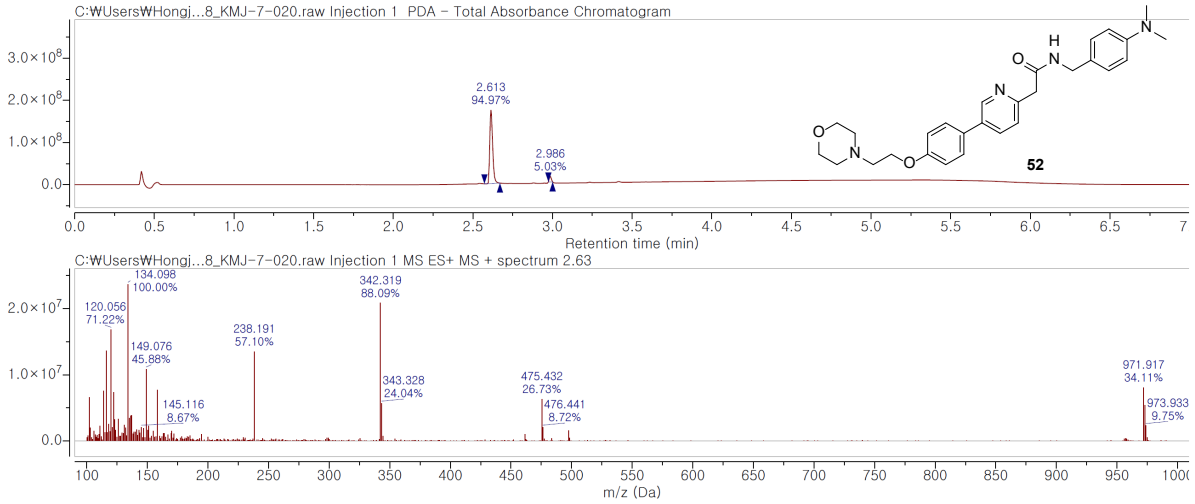

C:₩Users₩Hongj...J-6-096-RE2.raw Injection 1 PDA - Total Absorbance Chromatogram
1.575
96.43%
2.416
0.69%
2.840
2.88%
51
Retention time (min)
C:₩Users₩Hongj...J-6-096-RE2.raw Injection 1 MS ES+ MS + spectrum 1.55
106.049
100.00%
342.355
91.39%
116.023
19.44%
343.364
21.60%
447.456
17.73%
815.820
9.45%

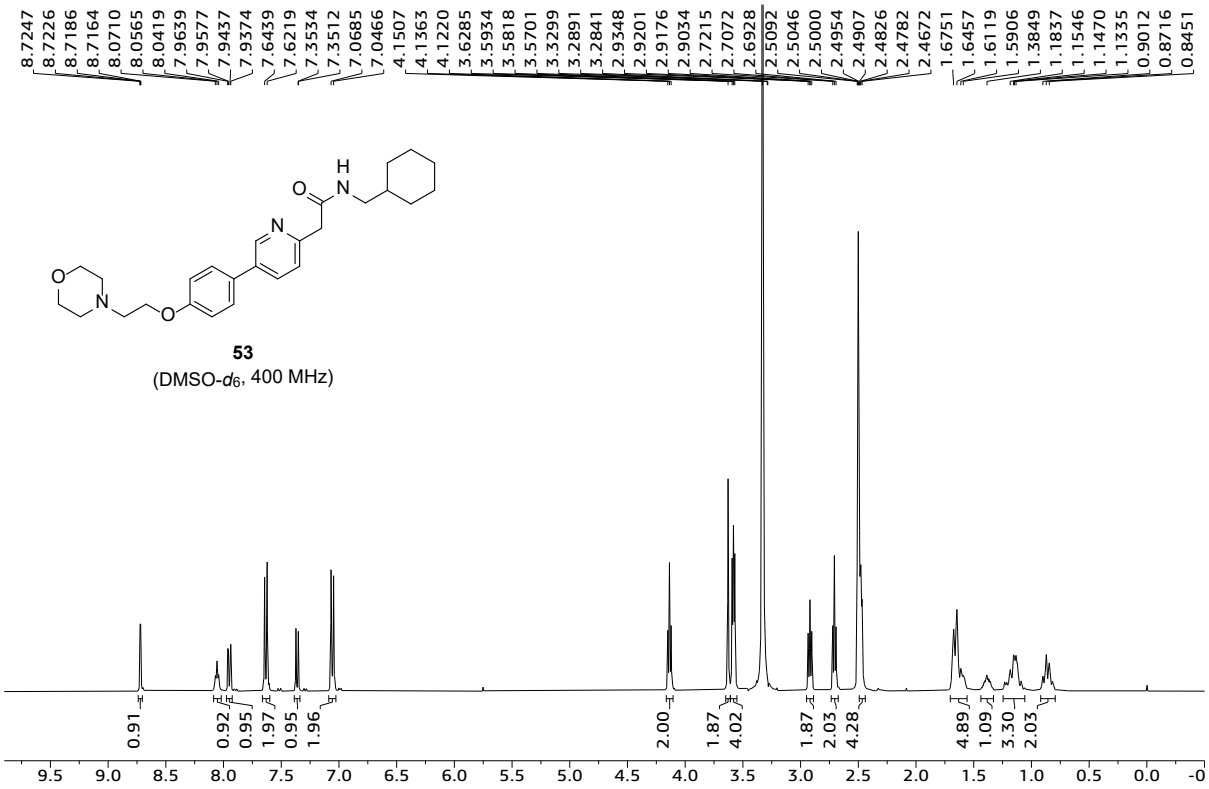


52
(DMSO-d_6, 300 MHz)

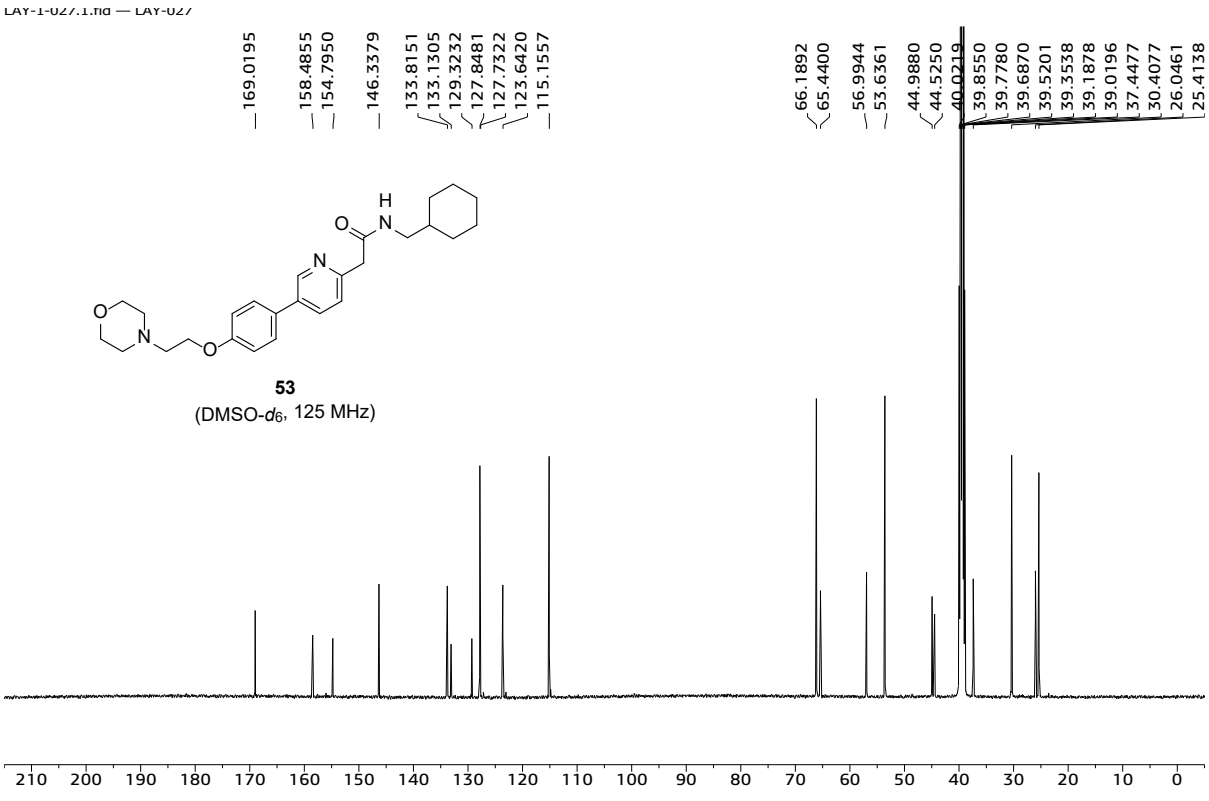


52
(DMSO-d_6, 125 MHz)

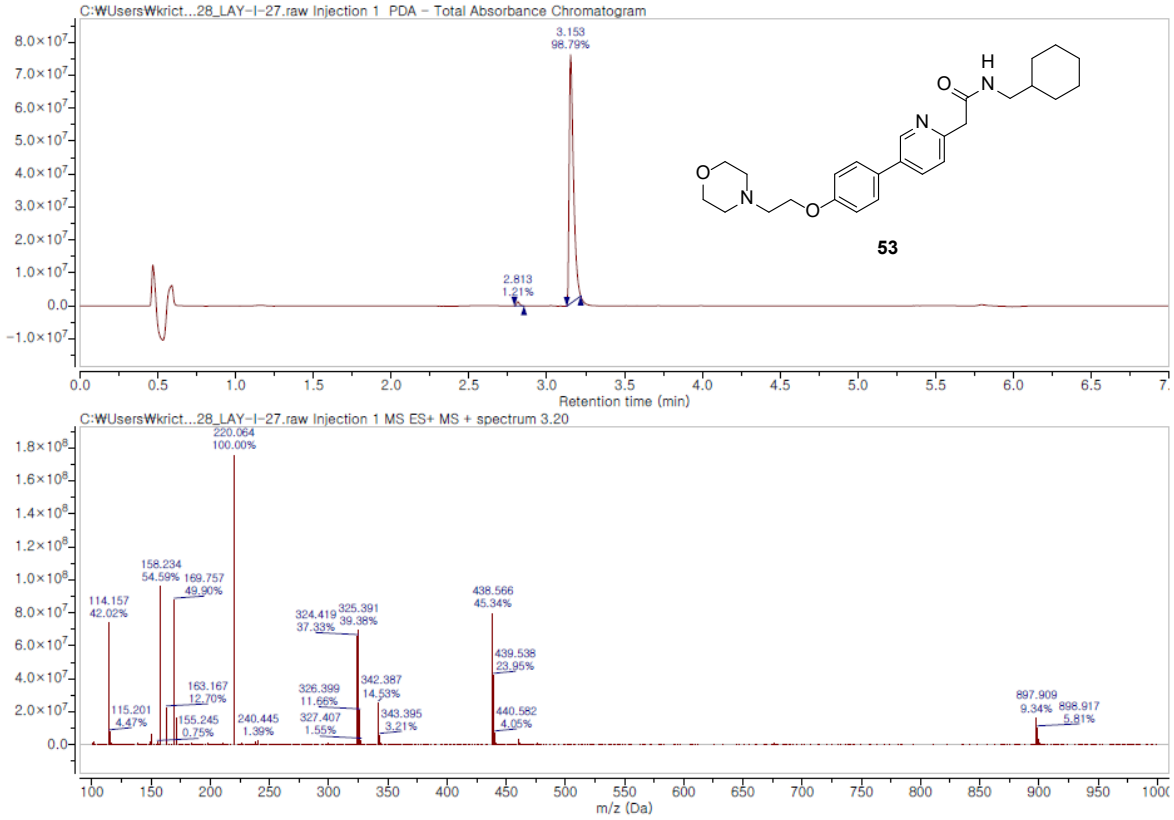

C:₩Users₩Hongj...8_KMJ-7-020.raw Injection 1 PDA - Total Absorbance Chromatogram
2.613
94.97%
2.986
5.03%
Retention time (min)
52
C:₩Users₩Hongj...8_KMJ-7-020.raw Injection 1 MS ES+ MS + spectrum 2.63
134.098
100.00%
120.056
71.22%
149.076
45.88%
145.116
8.67%
238.191
57.10%
342.319
88.09%
343.328
24.04%
475.432
26.73%
476.441
8.72%
971.917
34.11%
973.933
9.75%
m/z (Da)

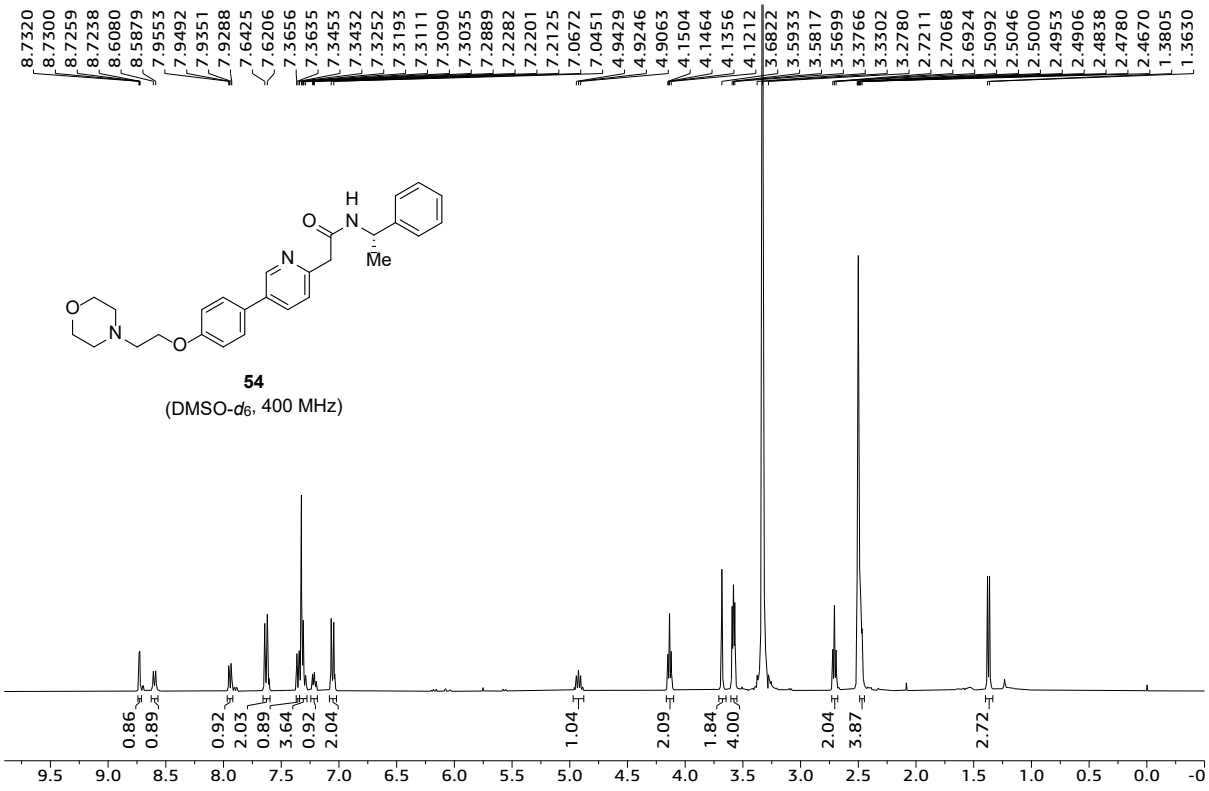


53
(DMSO-d_6, 400 MHz)



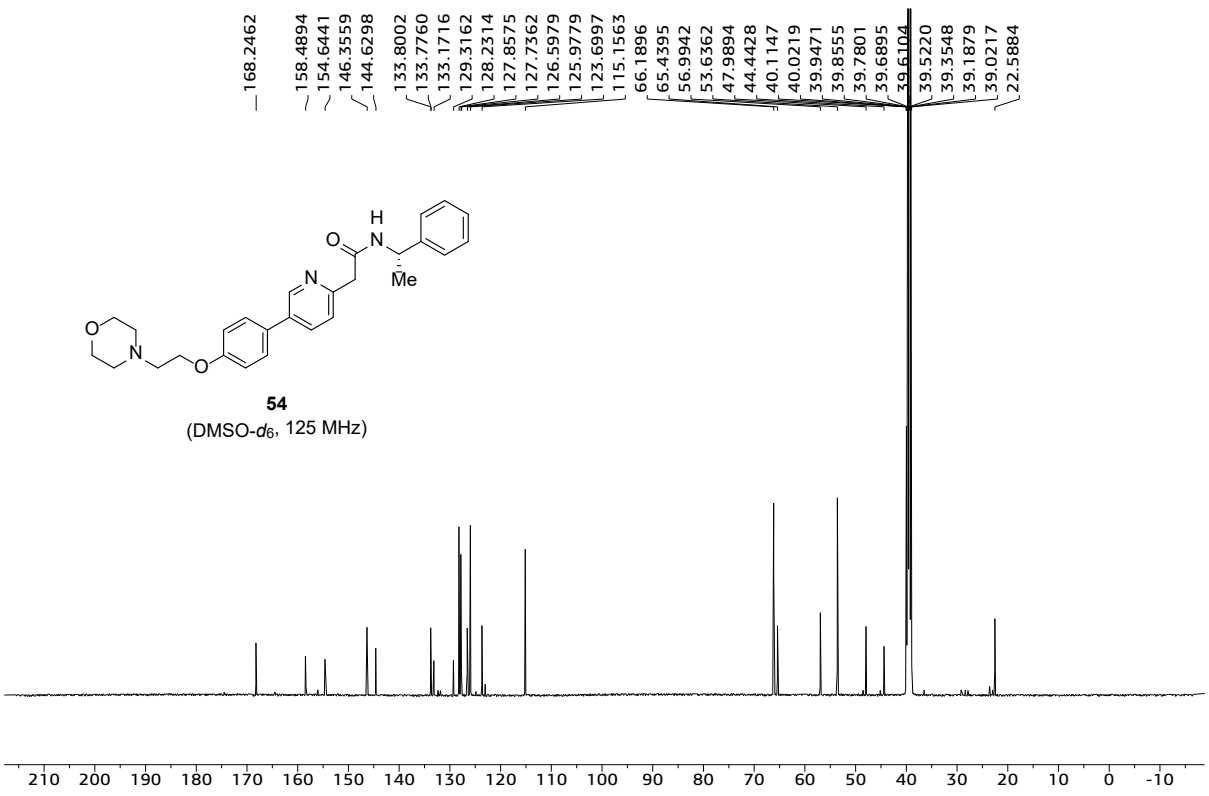
53
(DMSO-d_6, 125 MHz)


C:¥Users¥krict...28_LAY-I-27.raw Injection 1 PDA - Total Absorbance Chromatogram
3.153
98.79%
2.813
1.21%
Retention time (min)
53
C:¥Users¥krict...28_LAY-I-27.raw Injection 1 MS ES+ MS + spectrum 3.20
220.064
100.00%
158.234
54.59%
169.757
49.90%
114.157
42.02%
324.419
37.33%
325.391
39.38%
438.566
45.34%
439.538
23.95%
163.167
12.70%
326.399
11.66%
342.387
14.53%
115.201
4.47%
155.245
0.75%
240.445
1.39%
327.407
1.55%
343.395
3.21%
440.582
4.05%
897.909
9.34%
898.917
5.81%
m/z (Da)



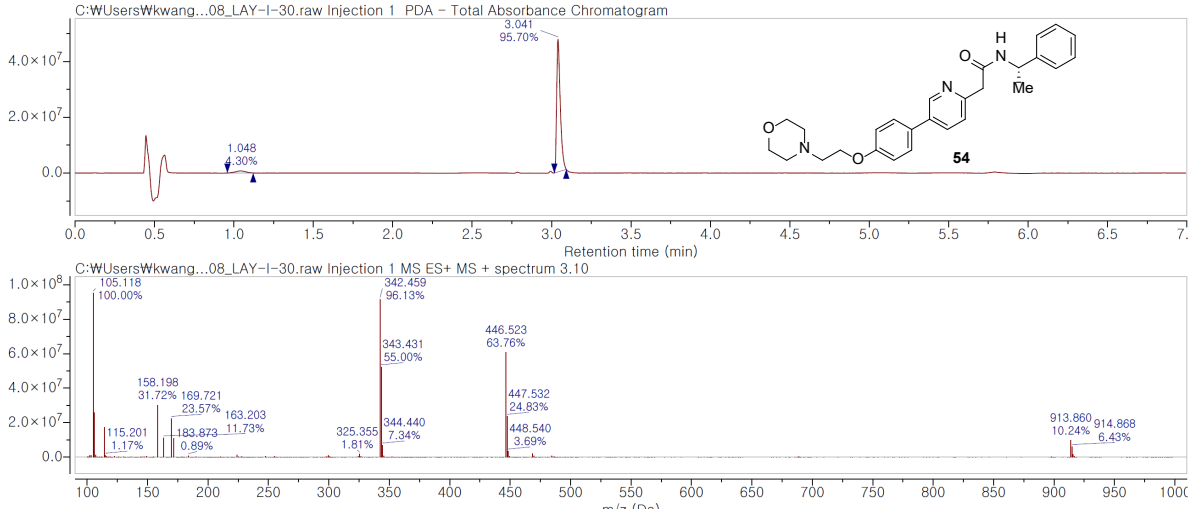
54

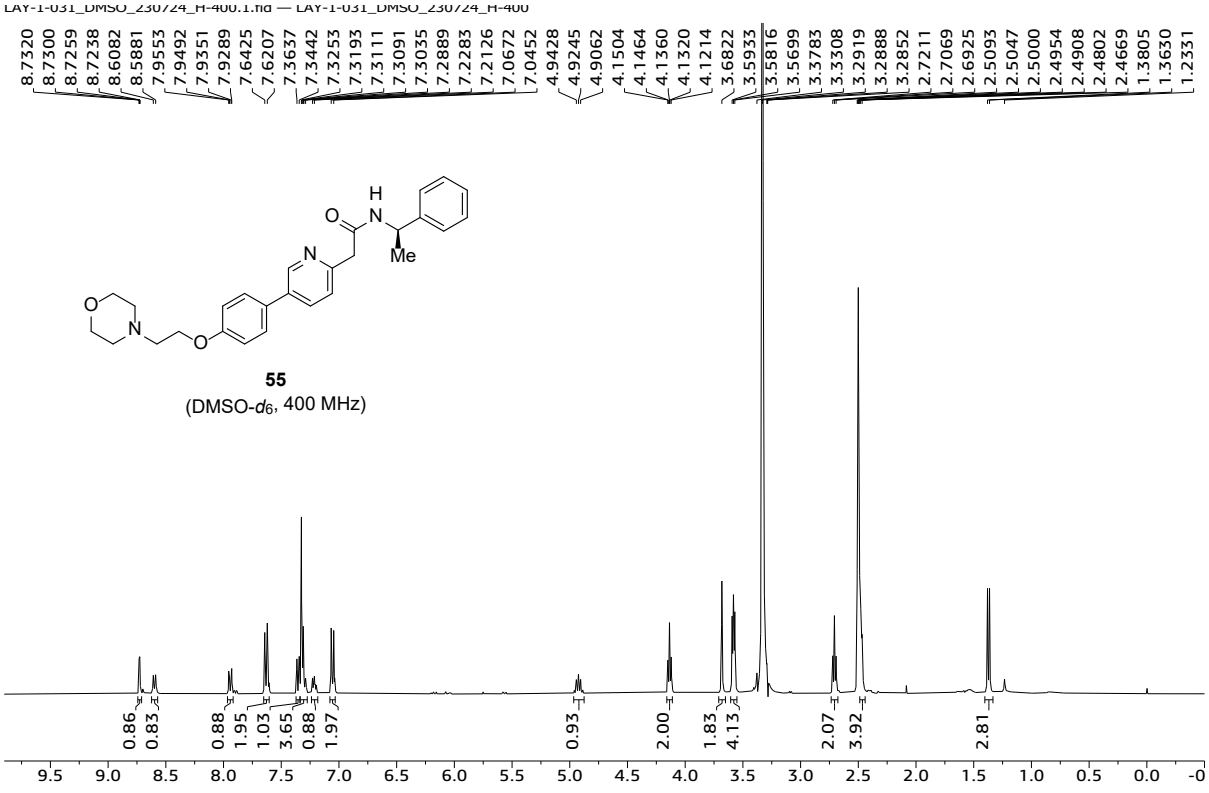
(DMSO-d_6, 400 MHz)



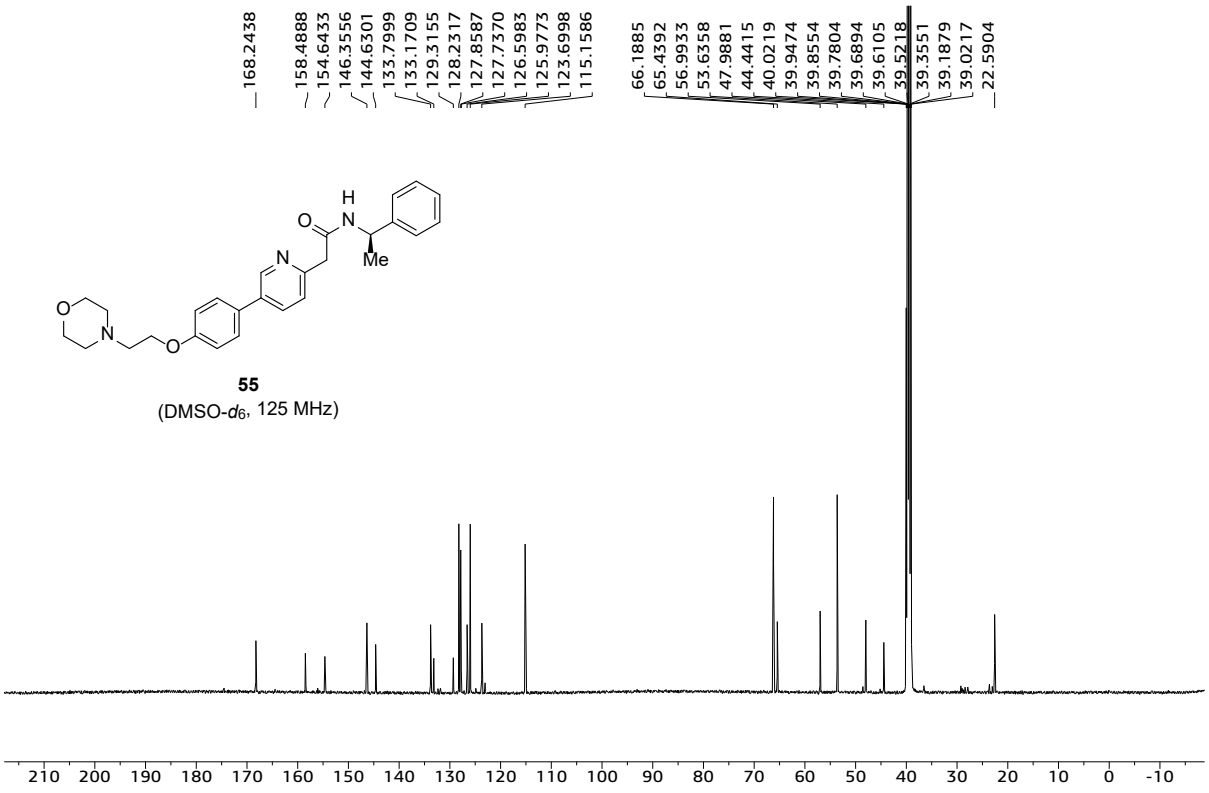
54

(DMSO-d_6, 125 MHz)

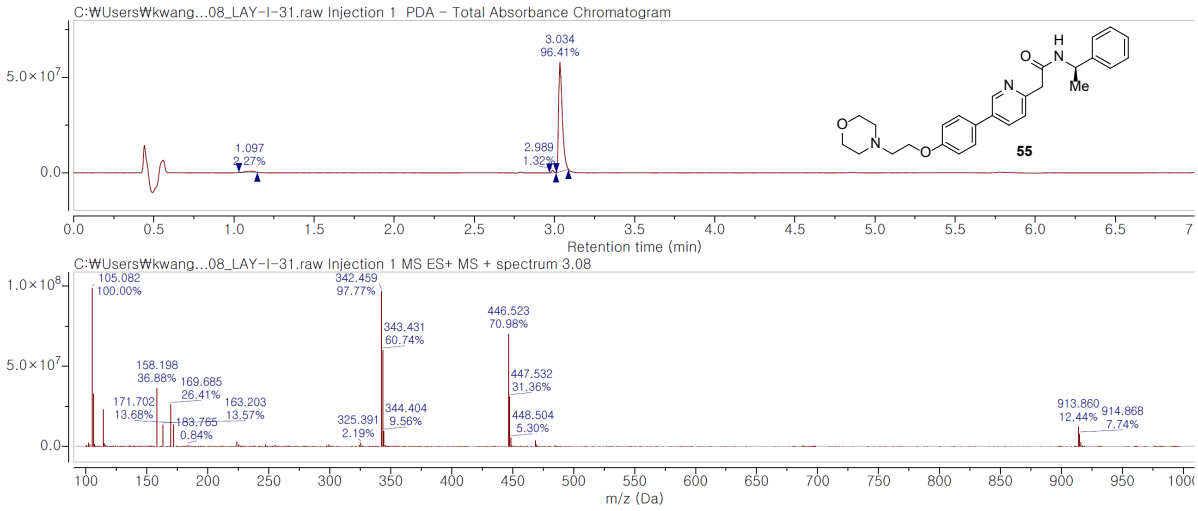

C:₩Users₩kwang...08_LAY-I-30.raw Injection 1 PDA - Total Absorbance Chromatogram
3.041
95.70%
1.048
4.30%
4.0×10^7
2.0×10^7
0.0
Retention time (min)
54
C:₩Users₩kwang...08_LAY-I-30.raw Injection 1 MS ES+ MS + spectrum 3.10
105.118
100.00%
342.459
96.13%
343.431
55.00%
446.523
63.76%
158.198
31.72%
169.721
23.57%
163.203
11.73%
447.532
24.83%
115.201
1.17%
183.873
0.89%
325.355
1.81%
344.440
7.34%
448.540
3.69%
913.860
10.24%
914.868
6.43%
1.0×10^8
8.0×10^7
6.0×10^7
4.0×10^7
2.0×10^7
0.0

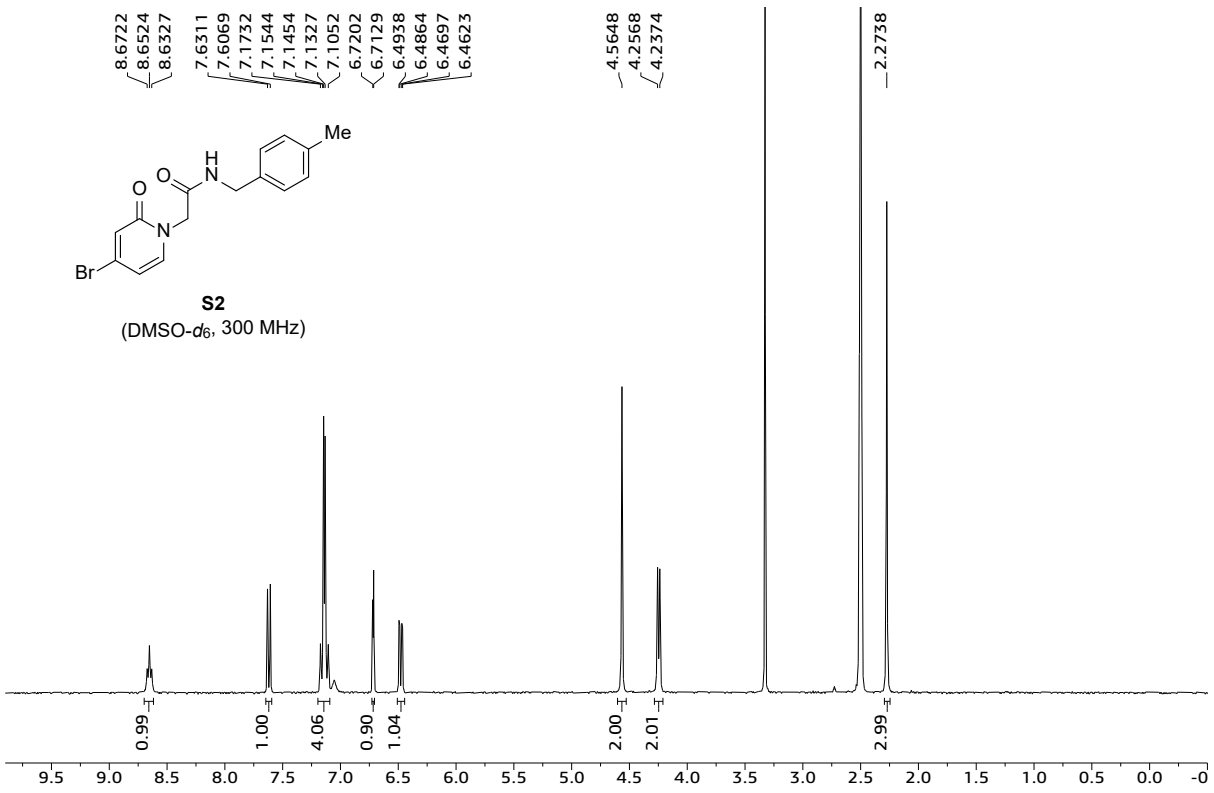


55
(DMSO-d_6, 400 MHz)

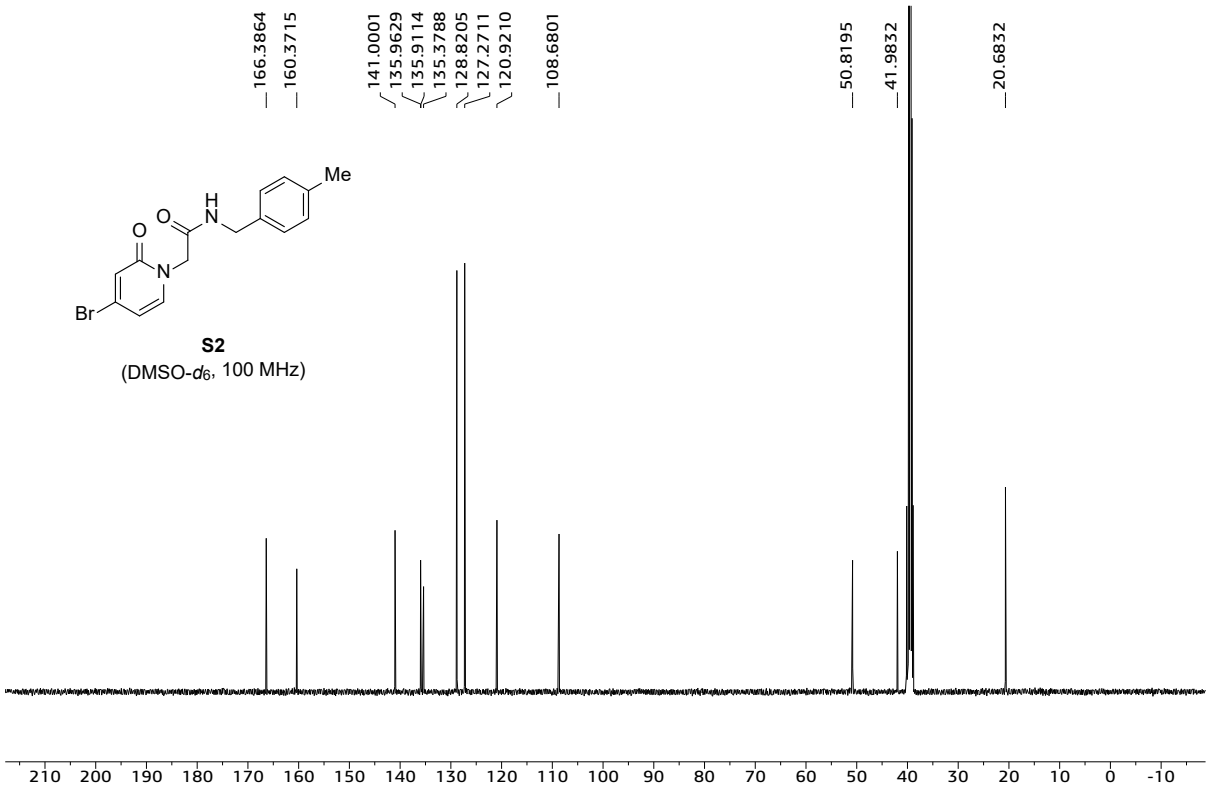


55
(DMSO-d_6, 125 MHz)

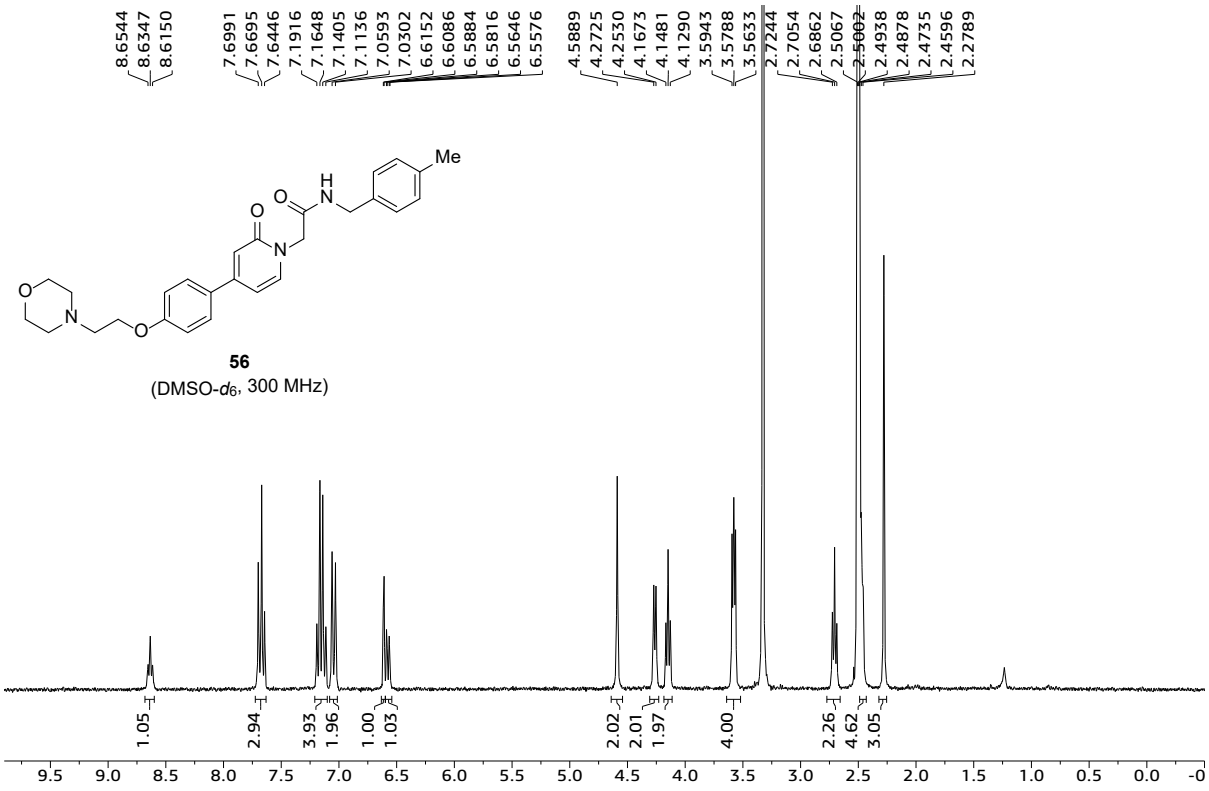

C:₩Users₩kwang...08_LAY-I-31.raw Injection 1 PDA - Total Absorbance Chromatogram
5.0×10^7
0.0
3.034
96.41%
1.097
2.27%
2.989
1.32%
55
Retention time (min)
C:₩Users₩kwang...08_LAY-I-31.raw Injection 1 MS ES+ MS + spectrum 3.08
1.0×10^8
5.0×10^7
0.0
105.082
100.00%
342.459
97.77%
343.431
60.74%
446.523
70.98%
158.198
36.88%
169.685
26.41%
171.702
13.68%
163.203
13.57%
183.765
0.84%
325.391
2.19%
344.404
9.56%
447.532
31.36%
448.504
5.30%
913.860
12.44%
914.868
7.74%
m/z (Da)



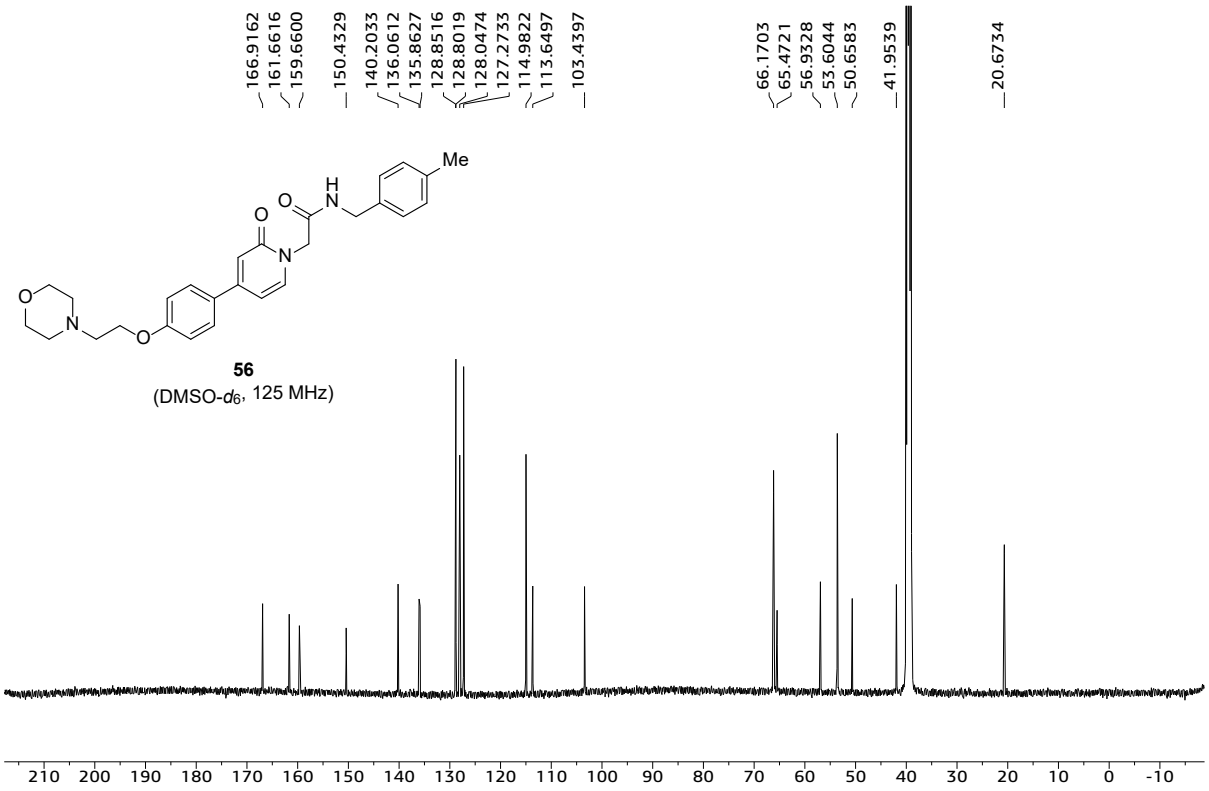
S2
(DMSO-d_6, 300 MHz)



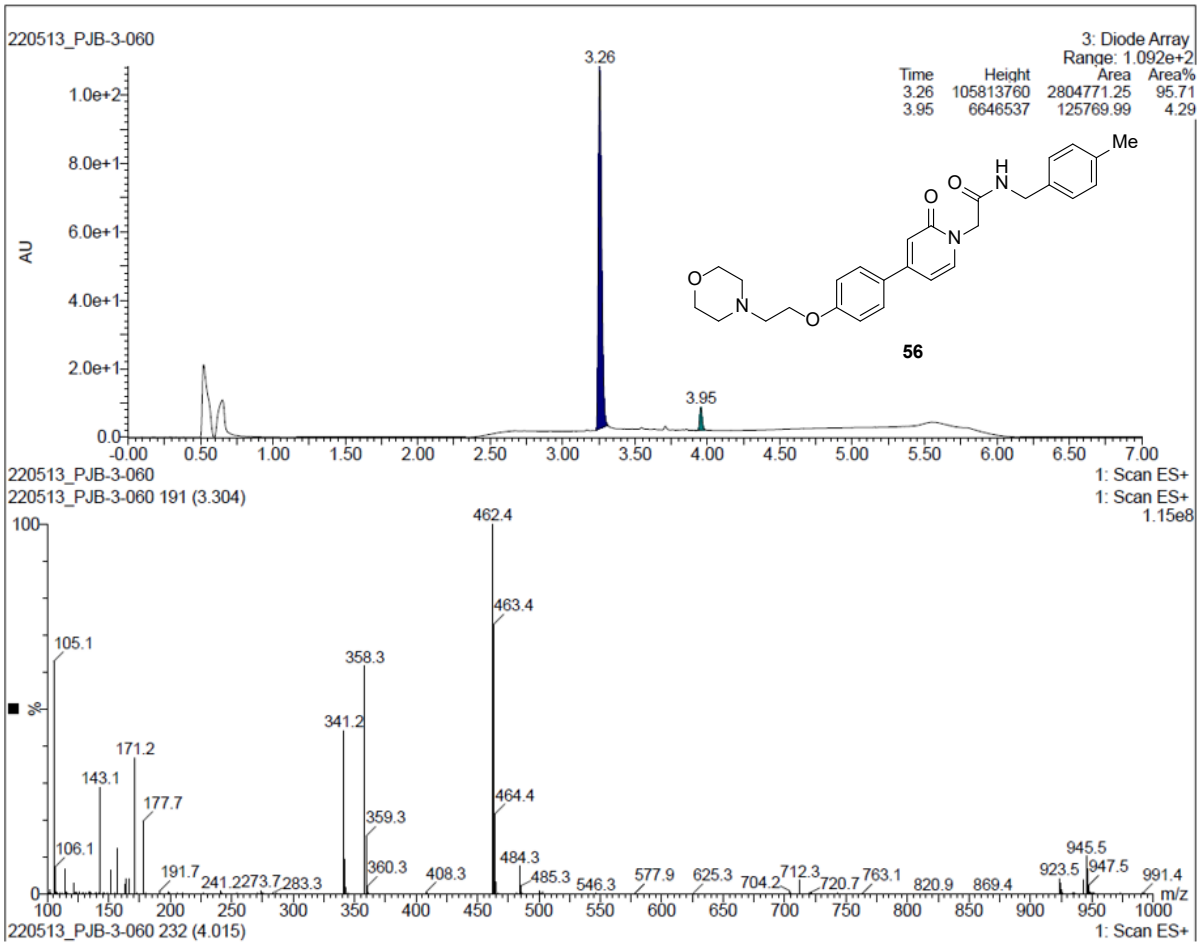
S2
(DMSO-d_6, 100 MHz)

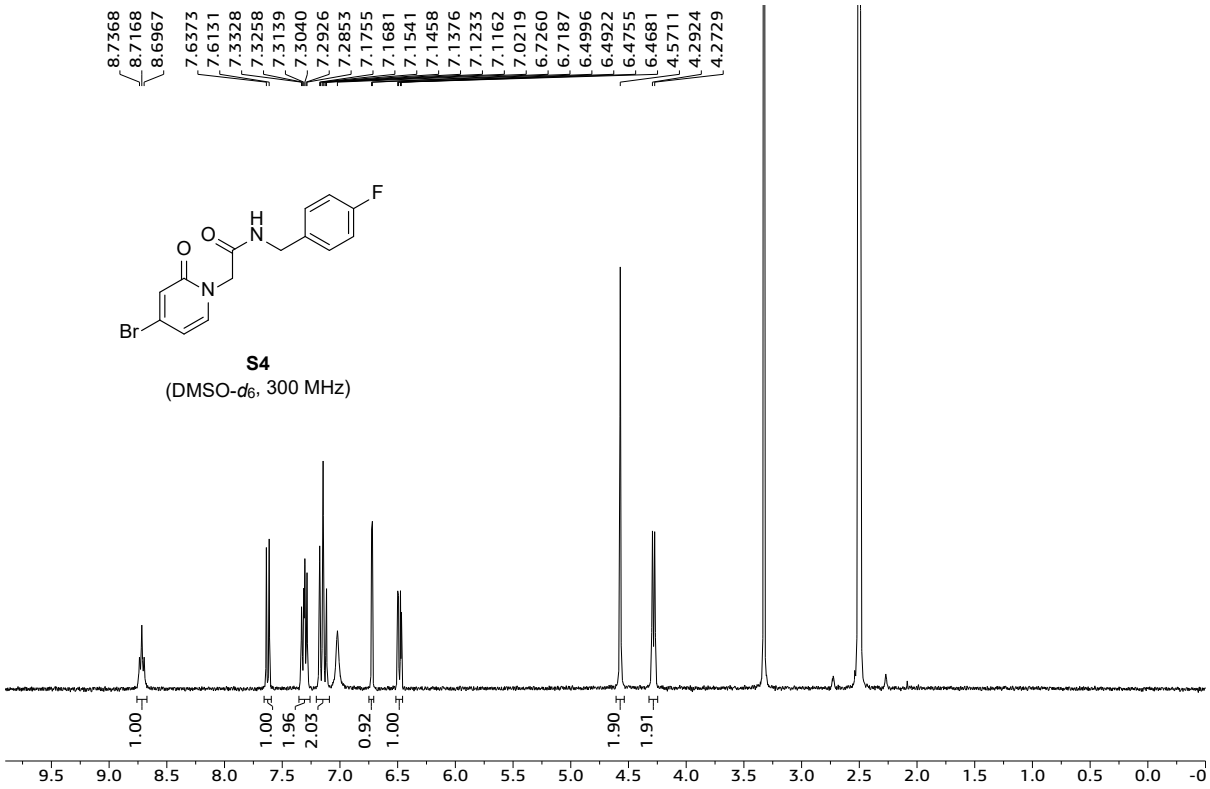


56
(DMSO-d_6, 300 MHz)

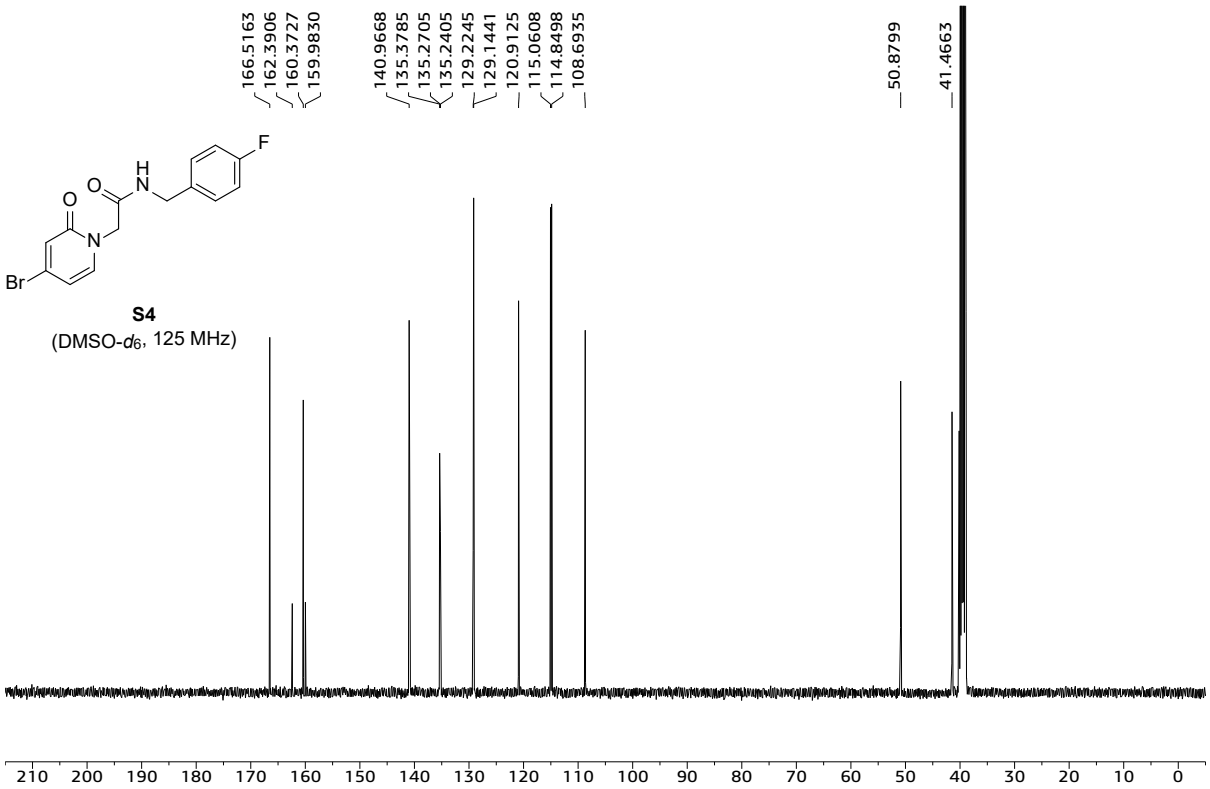


56
(DMSO-d_6, 125 MHz)

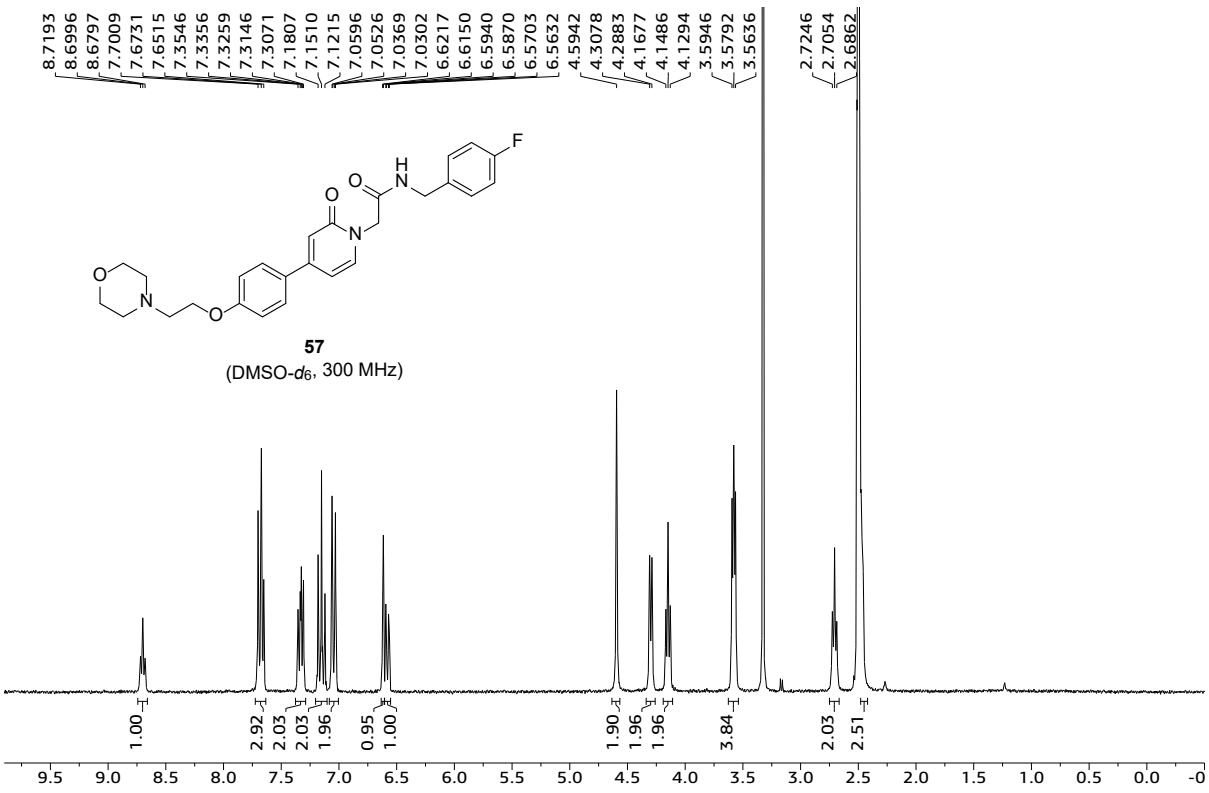

220513_PJB-3-060
3: Diode Array
Range: 1.092e+2
Time Height Area Area%
3.26 105813760 2804771.25 95.71
3.95 6646537 125769.99 4.29
3.26
3.95
AU
Me
56
220513_PJB-3-060
1: Scan ES+
220513_PJB-3-060 191 (3.304)
1: Scan ES+
1.15e8
462.4
463.4
105.1
358.3
341.2
171.2
143.1
177.7
464.4
359.3
106.1
484.3
945.5
947.5
m/z
220513_PJB-3-060 232 (4.015)
1: Scan ES+



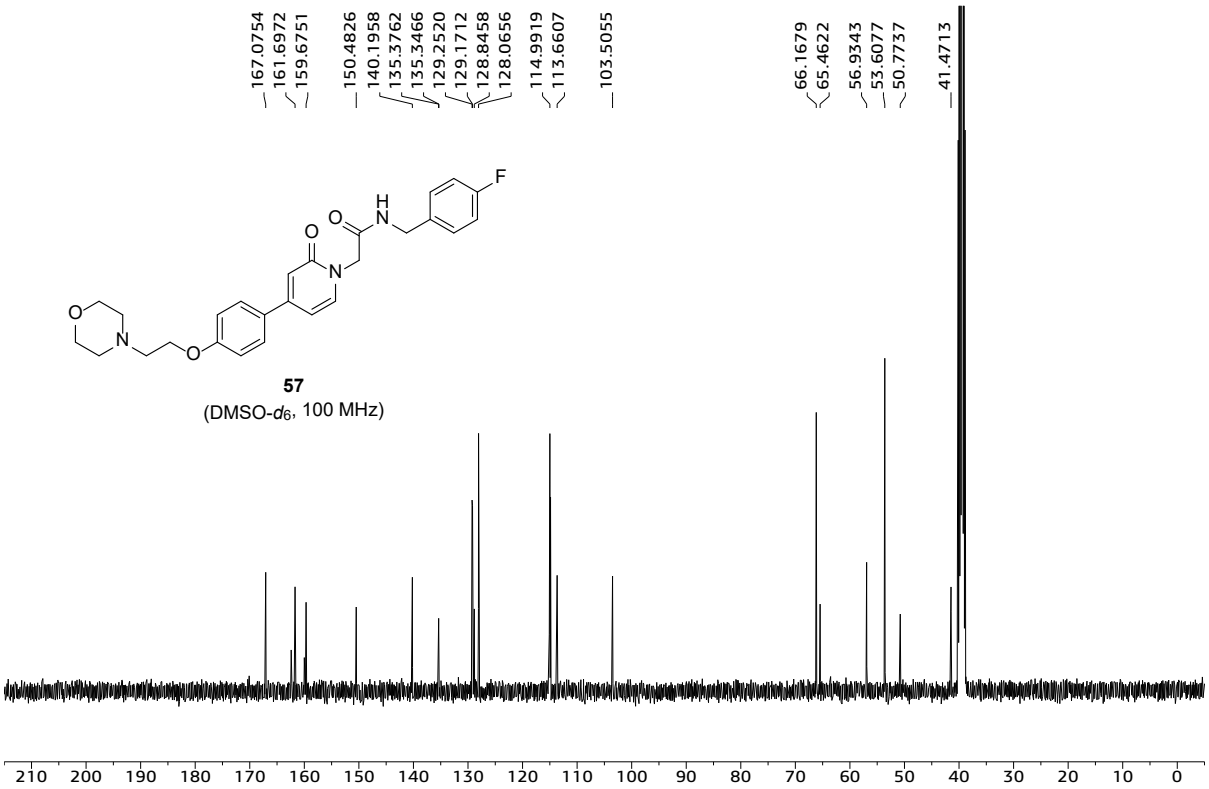
S4
(DMSO-d_6, 300 MHz)



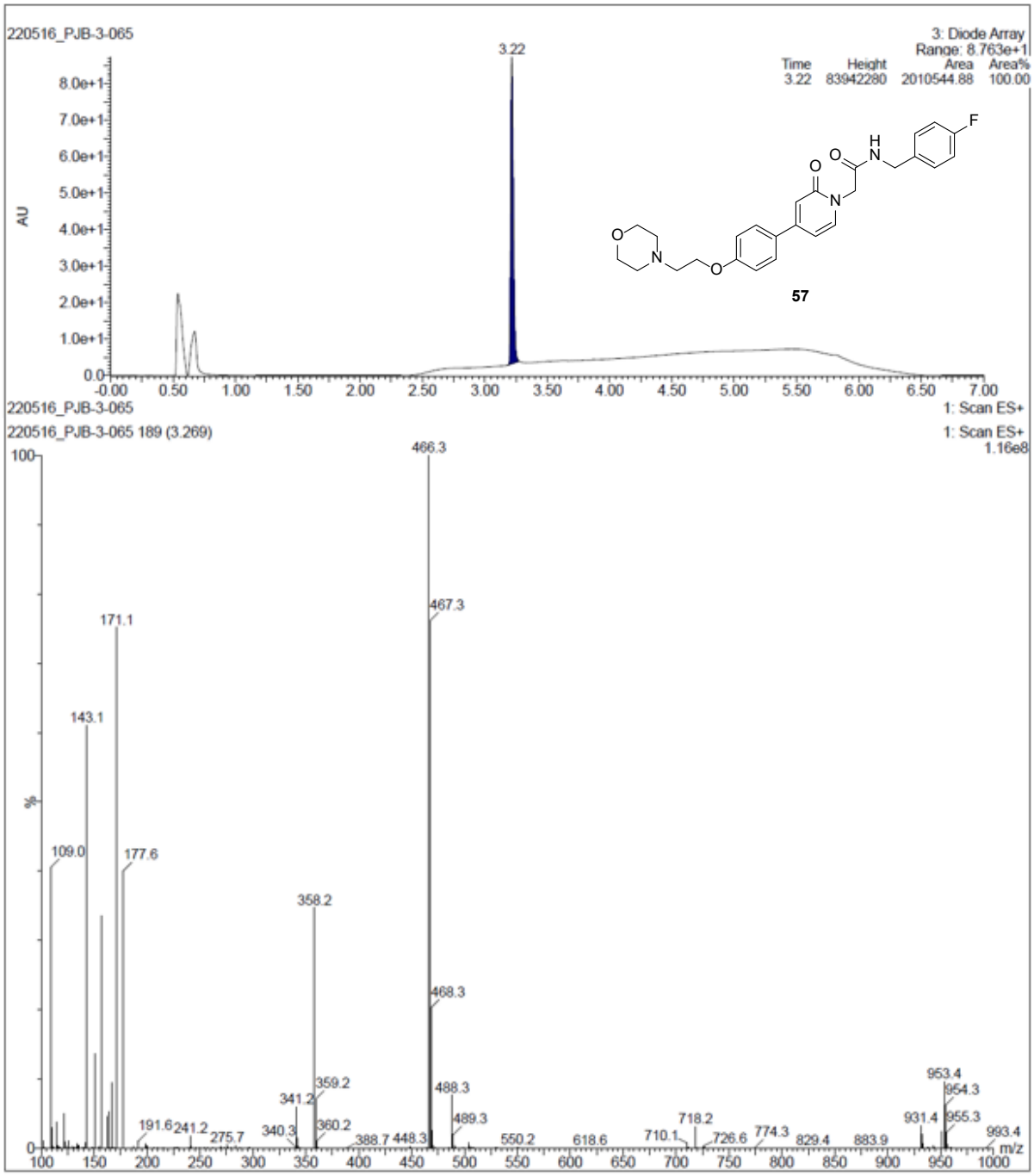
S4
(DMSO-d_6, 125 MHz)



57
(DMSO-d_6, 300 MHz)



57
(DMSO-d_6, 100 MHz)


220516_PJB-3-065
3: Diode Array
Range: 8.763e+1
Time Height Area Area%
3.22 83942280 2010544.88 100.00
3.22
AU
57
220516_PJB-3-065
1: Scan ES+
220516_PJB-3-065 189 (3.269)
1: Scan ES+
1.16e8
%
m/z
466.3
467.3
171.1
143.1
109.0
177.6
358.2
468.3
359.2
341.2
488.3
489.3
953.4
954.3
955.3
931.4
718.2
191.6
241.2
275.7
340.3
360.2
388.7
448.3
550.2
618.6
710.1
726.6
774.3
829.4
883.9
993.4

Compound #	LC/MS % purity
8	98.6
13	98.7
14	99.3
17	95.7
20	>99.5
23	>99.5
26	>99.5
27	97.5
31	>99.5
34	99.3
39	>99.5
40	98.6
41	96.4
42	99.2
43	97.9
44	96.7
45	97.8
46	97.2
47	96.3
48	96.9
49	97.8
50	99.3
51	96.4
52	95.0
53	98.8
54	95.7
55	96.4
56	95.7
57	>99.5

Table S7. The LC/MS purity of final compounds

G. References

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5. Z. Zhu, Y. Qiao, Z. Zhang, M. Gu, J. Wang, Z. Gao, W. Guo, M. Liu and R. Li, *Chin. J. Org. Chem.* 2020, **40**, 1983–1990.
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