Supporting Information

Diverse Isoquinoline Scaffolds by Ugi/Pomeranz–Fritsch and Ugi/Schlittler-Müller Reactions

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Experiment procedures and Characterization Data of Products

General methods

All chemicals were purchased from commercial suppliers and used without any purification unless otherwise noted. Nuclear magnetic resonance spectra were recorded. Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double of doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR reported in ppm relative to the solvent peak. Thin layer chromatography was performed on silica gel plates (0.20 mm thick, particle size 25 μm). Flash chromatography was performed using RediSep R_f Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230-400 mesh). High resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

General procedure A: synthesis of isoquinoline **6**

To the stirred solution of oxo-component (1 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (1 mmol, 1.0 equiv.), acid (1 mmol, 1.0 equiv.) and isocyanide (1 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 15 h. Solvents were removed under vacuum. Then the crude Ugi-adduct (**5**) was dissolved in 3 mL acetonitrile and methanesulfonic acid (20 mmol, 20.0 equiv.) was added. The resulting mixture was stirred at room temperature for 18 h. The reaction was diluted with dichloromethane and quenched with saturated sodium bicarbonate solution at 0-5 ℃. The resulting solution was extracted with dichloromethane (10 mL x 3). The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**6**).

General procedure B: synthesis of benzo[*d*]azepinone **8**

To the stirred solution of oxo-component (1 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (1 mmol, 1.0 equiv.), pivalic acid (1 mmol, 1.0 equiv.) and isocyanide (1 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 15 h. Solvents were removed under vacuum. Then the crude Ugi-adduct (**7**) was dissolved in 37% HCl(aq) solution in dioxane (1 mL, 1:1, v/v) and was stirred at room temperature for 18 h. The reaction was diluted with dichloromethane and quenched with saturated sodium bicarbonate solution at 0-5 ℃. The resulting solution was extracted with dichloromethane (10 mL x 3). The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**8**).

General procedure C: synthesis of isoquinoline and carboline derivatives **10**

To a stirred solution of 2,2-dimethoxyacetaldehyde (1 mmol) in MeOH (1M) at room temperature, amine (1 mmol), benzoic acid (1 mmol) and isocyanide (1 mmol) were added. The resulting mixture was stirred at room temperature for 15 h. Upon completion, the solvent was evaporated under vacuum. Then, the crude Ugi-adduct (1) was dissolved in 37% $HCl_{(aq)}$ solution in dioxane (1 mL, 4:1, v/v) and was stirred at room temperature for 48 h. The reaction was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution (3 x 10 mL). Finally, the solvent was evaporated under vacuum and the crude product was purified by flash column chromatography using petroleum ether/ethyl acetate.

General procedure D: synthesis of tetrazole **12**

To the stirred solution of oxo-component (2 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (2 mmol, 1.0 equiv.), isocyanide (2 mmol, 1.0 equiv.) and trimethylsilyl azide (2 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 15 h. Solvents were removed under vacuum. Then the crude Ugi-adduct (**9**) was dissolved in 3 mL pyridine and *p*-tolunene sulfonyl chloride (2.4 mmol, 1.2 equiv.) was added. The resulting mixture was stirred at room temperature for 12 h. Solvents were removed

under vacuum. The residue was dissolved in dichloromethane (8 mL) and washed by 1M HCl solution (5 mL x 3). The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**12**).

General procedure E: synthesis of isoquinoline-tetrazole **13**

To the stirred solution of tetrazole **12** (0.5 mmol, 1.0 equiv.) in dioxane (4 mL) at room temperature, was added 6 M HCl solution (1 mL). The mixture was kept under reflux for 7 h. Solvents were removed under vacuum, the crude product was dissolved in dichloromethane (8 mL), washed by saturated sodium bicarbonate solution (5 mL x 3), saturated sodium chloride solution (5 mL x 1) and dried over $MgSO_4$. The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**13**).

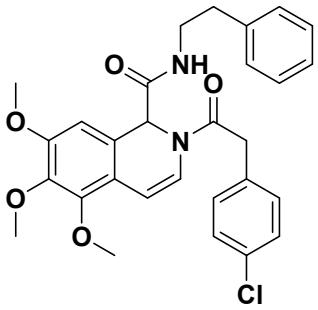
General procedure F: synthesis of tetrazole **14**

To the stirred solution of 3,5-dimethoxybenzaldehyde (3 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added 2,2-dimethoxyethylamine (3 mmol, 1.0 equiv.), Methyl isocyanoacetate (3 mmol, 1.0 equiv.) and trimethylsilyl azide (3 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 15 h. Then the sodium methoxide (3 mmol, 1.0 equiv.) was added. The resulting mixture was stirred at room temperature for 1 h. Solvents were removed under vacuum, the crude product was dissolved in dichloromethane (20 mL), washed by water (10 mL x 2), saturated sodium chloride solution (10 mL x 1) and dried over $MgSO_4$. The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**14**).

General procedure G: synthesis of tetracyclic product **15**

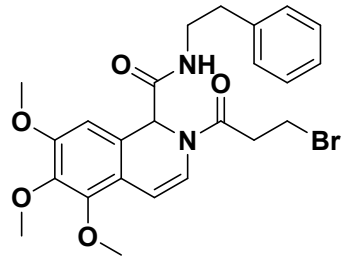
To the stirred solution of tetrazole **14** (1 mmol, 1.0 equiv.) in dioxane (2 mL) at room temperature, was added 37% HCl solution (1 mL). The resulting mixture was stirred at room temperature for 1 h. Solvents were removed under vacuum, the crude product was dissolved in dichloromethane (8 mL), washed by saturated sodium bicarbonate solution (5 mL x 3), saturated sodium chloride solution (5 mL x 1) and dried over $MgSO_4$. The solvents were removed under vacuum and the crude product was purified by flash column chromatography to give pure product (**15**).

6a: 2-(2-(4-chlorophenyl)acetyl)-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydro-isoquinoline-1-carboxamide



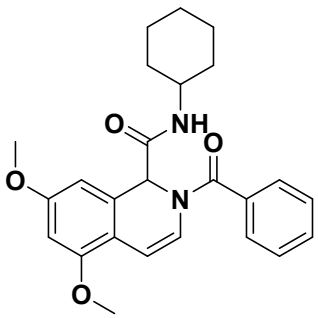
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (270 mg, 52% yield), M.P.= 160 –161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 5H), 7.19 – 7.15 (m, 2H), 7.06 – 7.01 (m, 2H), 6.59 – 6.55 (m, 1H), 6.51 (s, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 6.02 (s, 1H), 5.78 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.79 (s, 2H), 3.42 (q, *J* = 6.5 Hz, 2H), 2.78 – 2.62 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 168.6, 153.3, 148.8, 142.1, 138.6, 133.2, 132.2, 130.5, 129.0, 128.8, 128.6, 126.5, 124.1, 122.1, 117.1, 107.0, 106.4, 61.5, 61.0, 57.0, 56.2, 40.8, 39.6, 35.3; HRMS (ESI) m/z calculated for $C_{29}H_{30}ClN_2O_5$ $[M+H]^+$: 521.1838; found $[M+H]^+$: 521.1835.

6b: 2-(3-bromopropanoyl)-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydro-isoquinoline-1-carboxamide



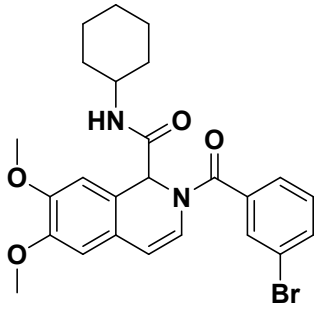
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (226 mg, 45% yield), M.P.= 153 –155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 3H), 7.09 – 7.03 (m, 2H), 6.57 – 6.50 (m, 2H), 6.23 (d, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 5.88 (t, *J* = 6.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.71 – 3.58 (m, 2H), 3.50 – 3.40 (m, 2H), 3.11 – 3.03 (m, 1H), 3.02 – 2.94 (m, 1H), 2.78 – 2.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.5, 153.4, 148.8, 142.1, 138.6, 128.8, 128.6, 126.5, 124.1, 121.5, 117.0, 107.1, 106.7, 61.5, 61.0, 56.9, 56.2, 40.7, 36.3, 35.2, 26.3; HRMS (ESI) m/z calculated for $C_{24}H_{28}BrN_2O_5$ $[M+H]^+$: 503.1176; found $[M+H]^+$: 503.1178.

6c: 2-benzoyl-*N*-cyclohexyl-5,7-dimethoxy-1,2-dihydroisoquinoline-1-carboxamide



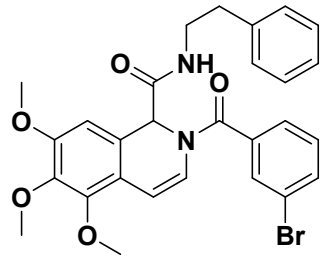
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (139 mg, 33% yield), M.P.= 241 – 243 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.52 – 7.48 (m, 1H), 7.46 – 7.41 (m, 2H), 6.54 – 6.36 (m, 3H), 6.26 (s, 1H), 6.18 (d, *J* = 7.7 Hz, 1H), 6.08 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 – 3.66 (m, 1H), 1.86 – 1.78 (m, 2H), 1.68 – 1.58 (m, 2H), 1.57 – 1.50 (m, 1H), 1.37 – 1.27 (m, 2H), 1.22 – 1.09 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 167.9, 160.5, 155.6, 134.0, 131.3, 130.8, 129.1, 128.6, 123.8, 113.3, 105.2, 104.1, 98.6, 58.5, 55.7, 48.4, 32.9, 32.8, 25.6, 24.6; HRMS (ESI) m/z calculated for $C_{25}H_{29}N_2O_4$ $[M+H]^+$: 421.2123; found $[M+H]^+$: 421.2122.

6d: 2-(3-bromobenzoyl)-*N*-cyclohexyl-6,7-dimethoxy-1,2-dihydroisoquinoline-1-carboxamide



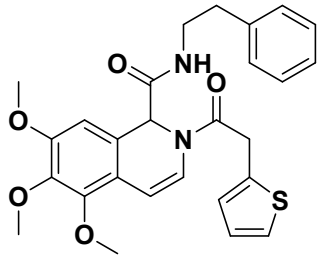
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as light yellow solid (269 mg, 54% yield), M.P.= 209 – 211 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (t, *J* = 1.8 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 6.67 (s, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 6.19 (s, 1H), 6.07 (s, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75 – 3.62 (m, 1H), 1.86 – 1.75 (m, 2H), 1.66 – 1.51 (m, 3H), 1.37 – 1.22 (m, 2H), 1.22 – 1.04 (m, 3H); ^{1}H NMR (500 MHz, Chloroform-*d*) ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 168.0, 149.3, 148.9, 135.8, 134.3, 131.8, 130.3, 127.4, 124.7, 123.4, 122.8, 120.8, 110.7, 110.6, 108.7, 58.1, 56.3, 56.1, 48.5, 32.8, 25.6, 24.6; HRMS (ESI) m/z calculated for $C_{25}H_{28}BrN_2O_4$ $[M+H]^+$: 499.1227; found $[M+H]^+$: 499.1225.

6e: *N*-benzyl-2-(3-bromopropanoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide



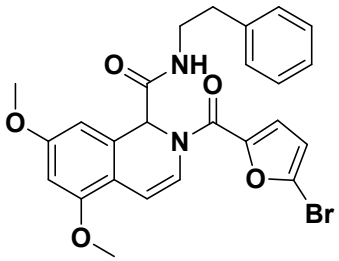
The product was synthesized according to procedure A in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (336 mg, 61% yield), M.P.= 167 – 169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.33 – 7.20 (m, 4H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.58 (s, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 6.19 – 6.09 (m, 2H), 6.01 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.50 (q, *J* = 6.4 Hz, 2H), 2.77 (q, *J* = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.1, 153.5, 149.0, 142.3, 138.8, 135.5, 134.4, 132.1, 130.1, 128.9, 128.8, 127.6, 126.7, 124.2, 124.0, 122.8, 117.5, 107.0, 105.8, 61.6, 61.1, 58.0, 56.3, 40.9, 35.4; HRMS (ESI) m/z calculated for $C_{28}H_{28}BrN_2O_5$ $[M+H]^+$: 551.1176; found $[M+H]^+$: 551.1177.

6f: 5,7-dimethoxy-*N*-phenethyl-2-(thiophene-2-carbonyl)-1,2-dihydro-isoquinoline-1-carboxamide



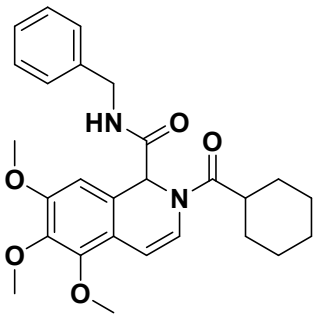
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (206 mg, 46% yield), M.P.= 187 – 189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 1H), 7.56 – 7.54 (m, 1H), 7.23 – 7.18 (m, 2H), 7.18 – 7.14 (m, 1H), 7.11 – 7.05 (m, 3H), 6.73 (d, *J* = 7.2 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 6.37 – 6.33 (m, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.53 – 3.41 (m, 2H), 2.84 – 2.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 162.6, 160.6, 155.6, 138.9, 136.3, 132.7, 131.8, 130.9, 128.9, 128.7, 127.4, 126.5, 123.3, 113.1, 106.6, 104.1, 98.7, 58.8, 55.7, 55.7, 41.0, 35.6; HRMS (ESI) m/z calculated for $C_{25}H_{25}N_2O_4S$ $[M+H]^+$: 449.1530; found $[M+H]^+$: 449.1531.

6g: 2-(5-bromofuran-2-carbonyl)-5,7-dimethoxy-*N*-phenethyl-1,2-dihydro-isoquinoline-1-carboxamide



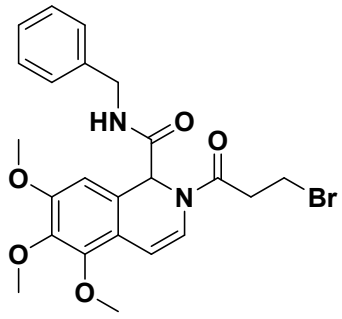
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (260 mg, 51% yield), M.P.= 142 – 144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H), 7.18 – 7.14 (m, 1H), 7.05 (d, *J* = 6.8 Hz, 3H), 6.84 – 6.78 (m, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H), 5.94 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.45 (q, *J* = 6.6 Hz, 2H), 2.80 – 2.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 160.6, 157.0, 155.6, 148.1, 138.8, 130.7, 128.9, 128.6, 127.1, 126.5, 122.2, 121.2, 113.8, 112.9, 107.0, 104.1, 98.7, 58.3, 55.7, 40.9, 35.5; HRMS (ESI) m/z calculated for $C_{25}H_{24}BrN_2O_5$ $[M+H]^+$: 511.0863; found $[M+H]^+$: 511.0864.

6h: *N*-benzyl-2-(cyclohexanecarbonyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline -1-carboxamide



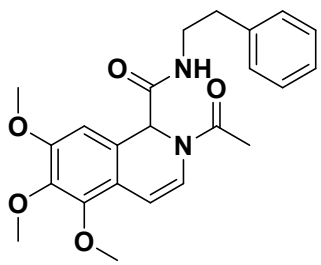
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as semi-solid (153 mg, 33% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 3H), 7.18 – 7.13 (m, 2H), 6.72 – 6.67 (m, 1H), 6.64 (s, 1H), 6.41 (t, *J* = 5.8 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 6.11 (s, 1H), 4.42 – 4.30 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.68 – 2.57 (m, 1H), 1.85 – 1.64 (m, 5H), 1.55 – 1.41 (m, 2H), 1.34 – 1.18 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 169.3, 153.3, 148.8, 142.1, 138.2, 128.7, 127.5, 127.5, 124.5, 122.1, 117.5, 107.2, 105.8, 61.6, 61.1, 57.0, 56.3, 43.6, 41.0, 29.1, 25.8; HRMS (ESI) m/z calculated for $C_{27}H_{33}N_2O_5$ $[M+H]^+$: 465.2384; found $[M+H]^+$: 465.2386.

6i: *N*-benzyl-2-(3-bromopropanoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide



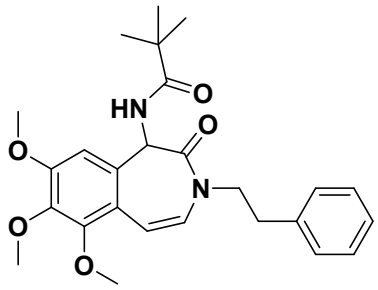
The product was synthesized according to procedure **A** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (210 mg, 43% yield), M.P.= 195 – 197 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.16 – 7.13 (m, 2H), 6.66 (s, 1H), 6.66 – 6.63 (m, 1H), 6.33 (t, *J* = 5.8 Hz, 1H), 6.28 (d, *J* = 7.8 Hz, 1H), 6.12 (s, 1H), 4.46 – 4.29 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.73 – 3.61 (m, 2H), 3.25 – 3.12 (m, 1H), 3.07 – 2.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 168.7, 153.6, 149.0, 142.2, 137.9, 128.8, 127.6, 124.2, 121.5, 117.1, 107.3, 107.0, 61.6, 61.1, 57.2, 56.4, 43.8, 36.4, 26.5; HRMS (ESI) m/z calculated for $C_{23}H_{26}BrN_2O_5$ $[M+H]^+$: 489.1020; found $[M+H]^+$: 489.1020.

6j: 2-acetyl-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydroisoquinoline-1-carboxamide



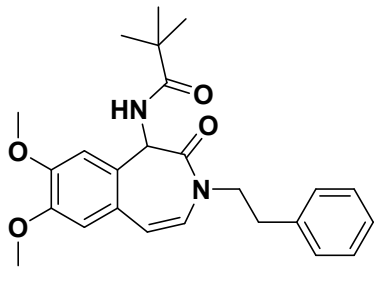
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (69 mg, 16% yield), M.P.= 108 – 110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 2H), 7.23 – 7.19 (m, 1H), 7.08 – 7.04 (m, 2H), 6.56 (s, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 6.18 (d, *J* = 7.9 Hz, 1H), 6.02 (s, 1H), 5.95 (t, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.49 – 3.38 (m, 2H), 2.79 – 2.66 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 168.9, 153.0, 148.5, 141.8, 138.6, 128.6, 128.4, 126.3, 124.0, 122.9, 117.0, 107.0, 105.1, 61.3, 60.8, 56.7, 56.0, 40.6, 35.1, 21.2; HRMS (ESI) m/z calculated for $C_{23}H_{26}N_2O_5Na$ $[M+Na]^+$: 433.1733; found $[M+Na]^+$: 433.1728.

8a: *N*-(6,7,8-trimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



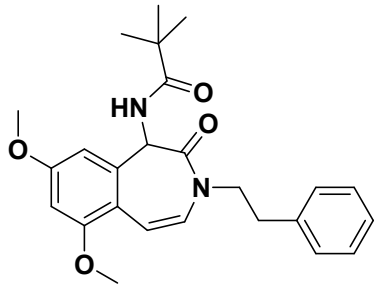
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (235 mg, 52% yield), M.P.= 111 – 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.1 Hz, 1H), 7.19 – 7.09 (m, 3H), 7.05 – 6.97 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.49 (s, 1H), 6.14 (d, *J* = 9.1 Hz, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.14 – 3.98 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.60 – 3.46 (m, 1H), 2.83 – 2.70 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 165.8, 155.0, 150.2, 140.9, 137.9, 130.3, 128.8, 128.5, 127.0, 126.5, 118.8, 114.7, 101.2, 61.2, 60.9, 55.7, 54.0, 49.8, 39.0, 34.6, 27.7; HRMS (ESI) m/z calculated for $C_{26}H_{33}N_2O_5$ $[M+H]^+$: 453.2384; found $[M+H]^+$: 453.2382.

8b: *N*-(7,8-dimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



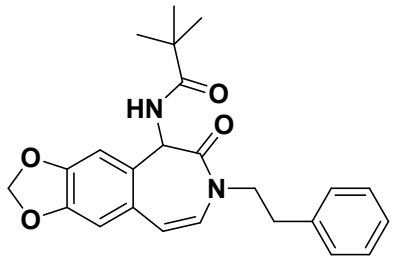
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as semi-solid (190 mg, 45% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.9 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.03 – 6.92 (m, 2H), 6.69 (d, *J* = 10.7 Hz, 2H), 6.43 (d, *J* = 8.9 Hz, 1H), 6.07 (d, *J* = 8.9 Hz, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.16 – 4.03 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.56 – 3.43 (m, 1H), 2.84 – 2.68 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 166.0, 150.6, 148.3, 138.1, 128.9, 128.5, 127.2, 126.9, 126.5, 124.6, 118.8, 110.0, 105.4, 56.2, 55.8, 53.9, 50.2, 39.1, 34.7, 27.8; HRMS (ESI) m/z calculated for $C_{25}H_{31}N_2O_4$ $[M+H]^+$: 423.2278; found $[M+H]^+$: 423.2278.

8c: *N*-(6,8-dimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



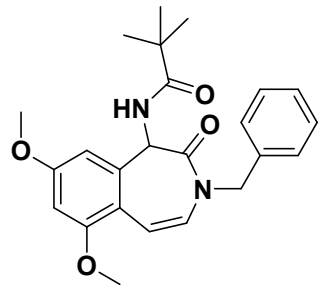
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (181 mg, 43% yield), M.P.= 156 – 158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 6.2 Hz, 1H), 7.19 – 7.12 (m, 3H), 7.05 – 6.96 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.1 Hz, 1H), 6.09 (d, *J* = 9.0 Hz, 1H), 4.99 (d, *J* = 6.2 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.56 – 3.44 (m, 1H), 2.81 – 2.72 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.7, 165.8, 162.1, 157.5, 138.1, 137.0, 128.9, 128.5, 126.5, 114.9, 114.4, 106.0, 98.3, 97.5, 55.7, 55.4, 54.3, 49.9, 39.1, 34.6, 27.7; HRMS (ESI) m/z calculated for $C_{25}H_{31}N_2O_4$ $[M+H]^+$: 423.2278; found $[M+H]^+$: 423.2279.

8d: *N*-(6-oxo-7-phenethyl-6,7-dihydro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*] azepin-5-yl)pivalamide



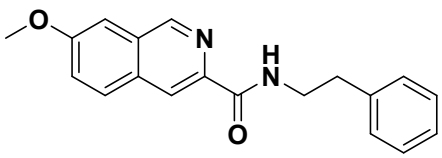
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (159 mg, 39% yield), M.P.= 142 – 143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 3H), 7.12 – 7.07 (m, 2H), 6.79 (d, *J* = 1.3 Hz, 1H), 6.73 (s, 2H), 6.39 (s, 1H), 6.09 (s, 1H), 5.95 – 5.90 (m, 2H), 5.29 (d, *J* = 5.9 Hz, 1H), 3.86 – 3.71 (m, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 164.7, 148.0, 147.5, 138.1, 129.1, 128.7, 126.8, 119.9, 113.6, 110.3, 108.4, 107.3, 101.2, 59.1, 48.1, 39.7, 34.7, 28.0, 27.9; HRMS (ESI) m/z calculated for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.1965; found $[M+H]^+$: 407.1968.

8e: *N*-(3-benzyl-6,8-dimethoxy-2-oxo-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide



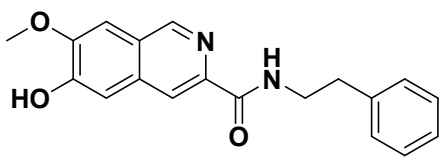
The product was synthesized according to procedure **B** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (176 mg, 41% yield), M.P.= 139 – 141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 6.3 Hz, 1H), 7.29 – 7.21 (m, 3H), 7.12 – 7.08 (m, 2H), 6.75 (d, *J* = 9.0 Hz, 1H), 6.40 – 6.37 (m, 2H), 6.21 (d, *J* = 9.0 Hz, 1H), 5.12 (d, *J* = 6.2 Hz, 1H), 4.85 – 4.65 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 166.3, 162.1, 157.6, 137.0, 136.1, 128.8, 127.7, 127.5, 126.0, 115.0, 114.4, 98.5, 97.7, 55.9, 55.3, 54.3, 51.0, 39.1, 27.8; HRMS (ESI) m/z calculated for $C_{24}H_{28}N_2O_4Na$ $[M+Na]^+$: 431.1941; found $[M+Na]^+$: 431.1941.

10a: 5-methoxy-*N*-phenethylisoquinoline-3-carboxamide



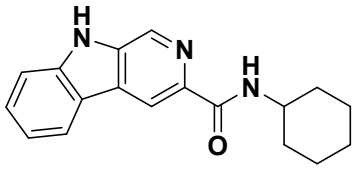
The product was synthesized according to procedure **C** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as grey solid (104 mg, 34% yield), M.P.= 147–149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.54 (s, 1H), 8.27 (t, *J* = 6.1 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.36 – 7.21 (m, 6H), 3.97 (s, 3H), 3.83 – 3.76 (m, 2H), 2.99 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 159.8, 149.6, 142.3, 139.3, 131.6, 131.3, 129.8, 129.0, 128.7, 126.5, 124.2, 120.2, 105.1, 55.7, 41.0, 36.2; HRMS (ESI) m/z calculated for $C_{19}H_{19}N_2O_2$ $[M+H]^+$: 307.1441; found $[M+H]^+$: 307.1441.

10b: 6-hydroxy-7-methoxy-*N*-phenethylisoquinoline-3-carboxamide



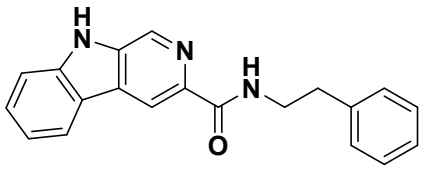
The product was synthesized according to procedure **C** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (125 mg, 39% yield), M.P.= 202–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.42 (s, 1H), 9.03 (s, 1H), 8.80 (t, *J* = 6.1 Hz, 1H), 8.25 (s, 1H), 7.58 (s, 1H), 7.33 (s, 1H), 7.32 – 7.24 (m, 4H), 7.22 – 7.16 (m, 1H), 3.96 (s, 3H), 3.62 – 3.54 (m, 2H), 2.89 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 151.7, 151.0, 148.6, 142.3, 139.5, 132.3, 128.6, 128.4, 126.1, 125.2, 117.7, 109.2, 106.2, 55.8, 40.3, 35.3; HRMS (ESI) m/z calculated for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1390; found $[M+H]^+$: 323.1391.

10c: *N*-cyclohexyl-9*H*-pyrido[3,4-*b*]indole-3-carboxamide



The product was synthesized according to procedure **C** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as light yellow solid (102 mg, 35% yield), M.P.= 253–254 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.93 (s, 1H), 8.88 (s, 1H), 8.83 (s, 1H), 8.39 (d, *J* = 7.9 Hz, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.32 – 7.26 (m, 1H), 3.90 – 3.78 (m, 1H), 1.89 – 1.82 (m, 2H), 1.76 – 1.70 (m, 2H), 1.64 – 1.57 (m, 1H), 1.46 – 1.31 (m, 4H), 1.24 – 1.13 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 141.0, 139.7, 137.1, 132.1, 128.5, 128.2, 122.2, 120.9, 119.9, 113.8, 112.2, 47.6, 32.4, 25.1, 24.7; HRMS (ESI) m/z calculated for $C_{18}H_{20}N_3O$ $[M+H]^+$: 294.1601; found $[M+H]^+$: 294.1600.

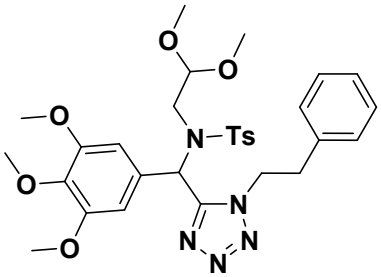
10d: *N*-phenethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxamide



The product was synthesized according to procedure **C** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (116 mg, 37% yield), M.P.= 196–198 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.95 (s, 1H), 8.88 (s, 1H), 8.84 (s, 1H), 8.74 (t, *J* = 6.0 Hz, 1H), 8.39 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.34 – 7.25 (m, 5H), 7.24 – 7.18 (m, 1H), 3.65 – 3.57 (m, 2H), 2.91 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.6, 141.0, 139.7, 139.5, 137.1, 132.3, 128.6, 128.4, 128.2, 126.1,

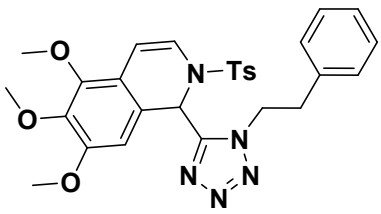
122.3, 121.0, 120.0, 113.9, 112.3, 40.3, 35.4; HRMS (ESI) m/z calculated for $C_{20}H_{18}N_3O$ $[M+H]^+$: 316.1444; found $[M+H]^+$: 316.1444.

12a: *N*-(2,2-dimethoxyethyl)-4-methyl-*N*-((1-phenethyl-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methyl)benzenesulfonamide



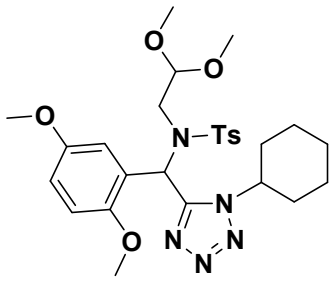
The product was synthesized according to procedure **D** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as semi-solid (830 mg, 68% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.12 (m, 6H), 7.09 – 7.05 (m, 1H), 6.11 (s, 1H), 5.96 (s, 2H), 4.61 (dd, *J* = 8.0, 6.0 Hz, 2H), 4.22 (dd, *J* = 6.4, 4.0 Hz, 1H), 3.78 (s, 3H), 3.60 (s, 6H), 3.58 – 3.53 (m, 1H), 3.47 – 3.41 (m, 1H), 3.21 (s, 3H), 3.27 – 3.15 (m, 2H), 3.08 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 152.7, 144.3, 138.4, 136.2, 135.6, 129.6, 128.9, 128.7, 127.6, 127.4, 105.8, 105.7, 103.2, 103.1, 60.9, 60.9, 56.1, 55.0, 54.9, 54.5, 53.9, 48.8, 47.7, 35.8, 21.6; HRMS (ESI) m/z calculated for $C_{30}H_{37}N_5O_7SNa$ $[M+Na]^+$: 634.2306; found $[M+Na]^+$: 634.2306.

13a: 5,6,7-trimethoxy-1-(1-phenethyl-1*H*-tetrazol-5-yl)-2-tosyl-1,2-dihydro-isoquinoline



The product was synthesized according to procedure **E** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (172 mg, 63% yield), M.P.= 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.30 (m, 1H), 7.23 – 7.19 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.48 (d, *J* = 7.3 Hz, 1H), 6.29 – 6.25 (m, 1H), 5.80 (s, 1H), 5.69 (s, 1H), 5.03 – 4.94 (m, 1H), 4.91 – 4.83 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.35 – 3.18 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 153.1, 149.0, 144.6, 142.2, 136.9, 133.5, 129.7, 129.1, 128.9, 127.3, 127.1, 121.4, 121.1, 116.9, 114.5, 105.9, 61.3, 61.0, 56.4, 50.9, 48.9, 36.6, 21.6. HRMS (ESI) m/z calculated for $C_{28}H_{30}N_5O_5S$ $[M+H]^+$: 548.1962; found $[M+H]^+$: 548.1973.

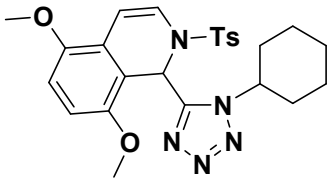
12b: *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(2,5-dimethoxyphenyl)methyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide



The product was synthesized according to procedure **D** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (658 mg, 59% yield), M.P.= 146 – 148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.75 – 6.72 (m, 2H), 6.25 (d, *J* = 2.5 Hz, 1H), 4.36 – 4.28 (m, 2H), 3.72 – 3.64 (m, 1H), 3.60 – 3.56 (m, 4H), 3.53 (s, 3H), 3.09 (s, 3H), 3.04 (s, 3H), 2.36 (s, 3H), 2.23 – 2.16 (m, 1H), 2.13 – 2.04 (m, 1H), 2.01 – 1.95 (m, 1H), 1.91 – 1.82 (m, 3H), 1.77 – 1.69 (m, 1H), 1.51 – 1.42 (m, 1H), 1.41 – 1.27 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 152.8, 150.8, 143.9, 136.2, 129.4, 127.7, 123.6, 114.9, 111.9, 103.4, 57.9, 56.0, 55.6,

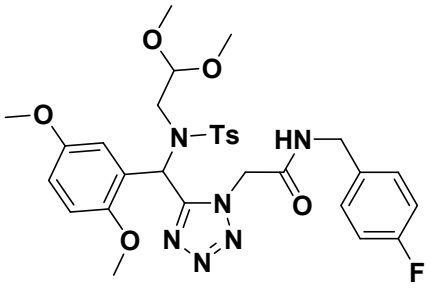
54.5, 53.4, 50.6, 48.3, 33.0, 32.3, 25.4, 21.6; HRMS (ESI) m/z calculated for $C_{27}H_{37}N_5O_6SNa$ $[M+Na]^+$: 582.2357; found $[M+Na]^+$: 582.2354.

13b: 1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-5,8-dimethoxy-2-tosyl-1,2-dihydro-isoquinoline



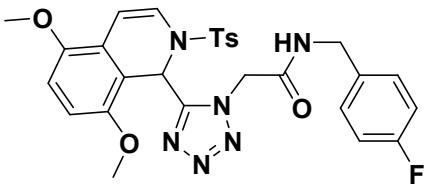
The product was synthesized according to procedure **E** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (213 mg, 86% yield), M.P.= 141 – 143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ7.52 – 7.49 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H), 6.66 – 6.59 (m, 3H), 6.49 – 6.46 (m, 1H), 4.99 – 4.90 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.28 (s, 3H), 2.23 – 2.16 (m, 1H), 2.10 – 1.95 (m, 5H), 1.85 – 1.77 (m, 1H), 1.65 – 1.53 (m, 2H), 1.42 – 1.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 148.7, 148.5, 144.3, 134.8, 129.4, 126.9, 123.0, 120.1, 116.0, 112.5, 111.3, 110.4, 58.1, 56.2, 55.9, 45.1, 33.3, 33.2, 25.7, 25.4, 25.1, 21.6; HRMS (ESI) m/z calculated for $C_{25}H_{29}N_5O_4SNa$ $[M+Na]^+$: 518.1833; found $[M+Na]^+$: 518.1835.

12c: 2-(5-(((*N*-(2,2-dimethoxyethyl)-4-methylphenyl)sulfonamido)(2,5-dimethoxy phenyl)methyl)-1*H*-tetrazol-1-yl)-*N*-(4-fluorobenzyl)acetamide



The product was synthesized according to procedure **D** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (786 mg, 46% yield), M.P.= 148 – 150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.23 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.99 – 6.92 (m, 2H), 6.76 – 6.71 (m, 2H), 6.70 – 6.66 (m, 2H), 6.17 (d, *J* = 2.9 Hz, 1H), 5.17 (d, *J* = 16.6 Hz, 1H), 5.07 (d, *J* = 16.6 Hz, 1H), 4.53 – 4.38 (m, 2H), 4.31 (m, 1H), 3.59 – 3.55 (m, 2H), 3.53 (s, 3H), 3.42 (s, 3H), 3.09 (s, 3H), 2.98 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 163.3, 161.4, 154.5, 153.4, 150.6, 144.3, 135.8, 133.4, 129.8, 129.6, 127.6, 122.3, 115.7, 114.7, 111.9, 103.2, 55.9, 55.5, 54.5, 53.7, 50.9, 50.8, 49.9, 48.1, 43.3, 21.6; HRMS (ESI) m/z calculated for $C_{30}H_{35}FN_6O_7SNa$ $[M+Na]^+$: 665.2164; found $[M+Na]^+$: 665.2164.

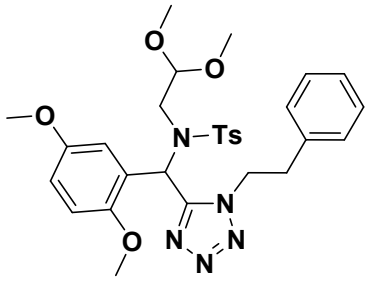
13c: 2-(5-(5,8-dimethoxy-2-tosyl-1,2-dihydroisoquinolin-1-yl)-1*H*-tetrazol-1-yl)-*N*-(4-fluorobenzyl)acetamide



The product was synthesized according to procedure **E** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as yellow solid (208 mg, 72% yield), M.P.= 106 – 108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.00 (t, *J* = 8.4 Hz, 2H), 6.76 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.61 – 6.54 (m, 2H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.44 (t, *J* = 5.8 Hz, 1H), 5.40 (s, 2H), 4.60 – 4.52 (m, 1H), 4.45 – 4.38 (m, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.1, 163.4, 161.4, 153.8, 148.7, 148.6, 144.7, 134.4, 133.3, 129.9,

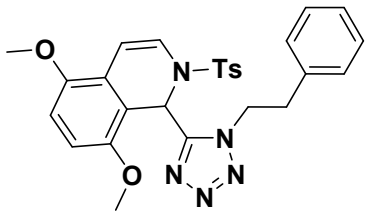
129.6, 126.9, 123.0, 119.7, 115.8, 115.6, 115.2, 111.6, 111.3, 110.7, 56.1, 50.2, 45.4, 43.4; HRMS (ESI) m/z calculated for $C_{28}H_{27}FN_6O_5SNa$ $[M+Na]^+$: 601.1639; found $[M+Na]^+$: 601.1637.

12d: *N*-(2,2-dimethoxyethyl)-*N*-((2,5-dimethoxyphenyl)(1-phenethyl-1*H*-tetrazol-5-yl)methyl)-4-methylbenzenesulfonamide



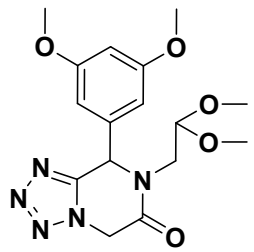
The product was synthesized according to procedure **D** in 2 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as light yellow solid (732 mg, 63% yield), M.P.= 143 – 144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.31 – 7.19 (m, 5H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.85 (s, 1H), 6.78 – 6.71 (m, 2H), 6.28 (d, *J* = 2.7 Hz, 1H), 4.65 – 4.52 (m, 2H), 4.31 (t, *J* = 5.2 Hz, 1H), 3.60 (d, *J* = 5.3 Hz, 2H), 3.57 (s, 3H), 3.54 (s, 3H), 3.26 – 3.18 (m, 2H), 3.09 (s, 3H), 3.07 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 153.4, 150.8, 143.9, 136.5, 136.1, 129.4, 128.9, 127.7, 127.3, 123.0, 115.0, 114.7, 111.8, 103.5, 56.0, 55.6, 54.9, 53.5, 50.3, 50.2, 48.6, 48.2, 35.7, 21.6; HRMS (ESI) m/z calculated for $C_{29}H_{36}N_5O_6S$ $[M+H]^+$: 582.2381; found $[M+H]^+$: 582.2387.

13d: 5,8-dimethoxy-1-(1-phenethyl-1*H*-tetrazol-5-yl)-2-tosyl-1,2-dihydro-isoquinoline



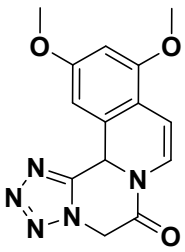
The product was synthesized according to procedure **E** in 0.5 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (219 mg, 85% yield), M.P.= 155 – 157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.34 (m, 4H), 7.32 – 7.27 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 1.2 Hz, 1H), 6.67 – 6.57 (m, 3H), 6.44 (m, 1H), 4.99 – 4.79 (m, 2H), 3.71 (s, 3H), 3.65 (s, 3H), 3.37 (t, *J* = 8.1 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 148.7, 148.6, 144.4, 136.8, 134.6, 129.4, 129.2, 129.0, 127.2, 126.9, 122.9, 119.9, 115.7, 112.9, 111.3, 110.5, 56.1, 55.9, 49.0, 45.2, 36.1, 21.6; HRMS (ESI) m/z calculated for $C_{27}H_{27}N_5O_4SNa$ $[M+Na]^+$: 540.1676; found $[M+Na]^+$: 540.1677.

14: 7-(2,2-dimethoxyethyl)-8-(3,5-dimethoxyphenyl)-7,8-dihydrotetrazolo [1,5-*a*] pyrazin-6(5*H*)-one



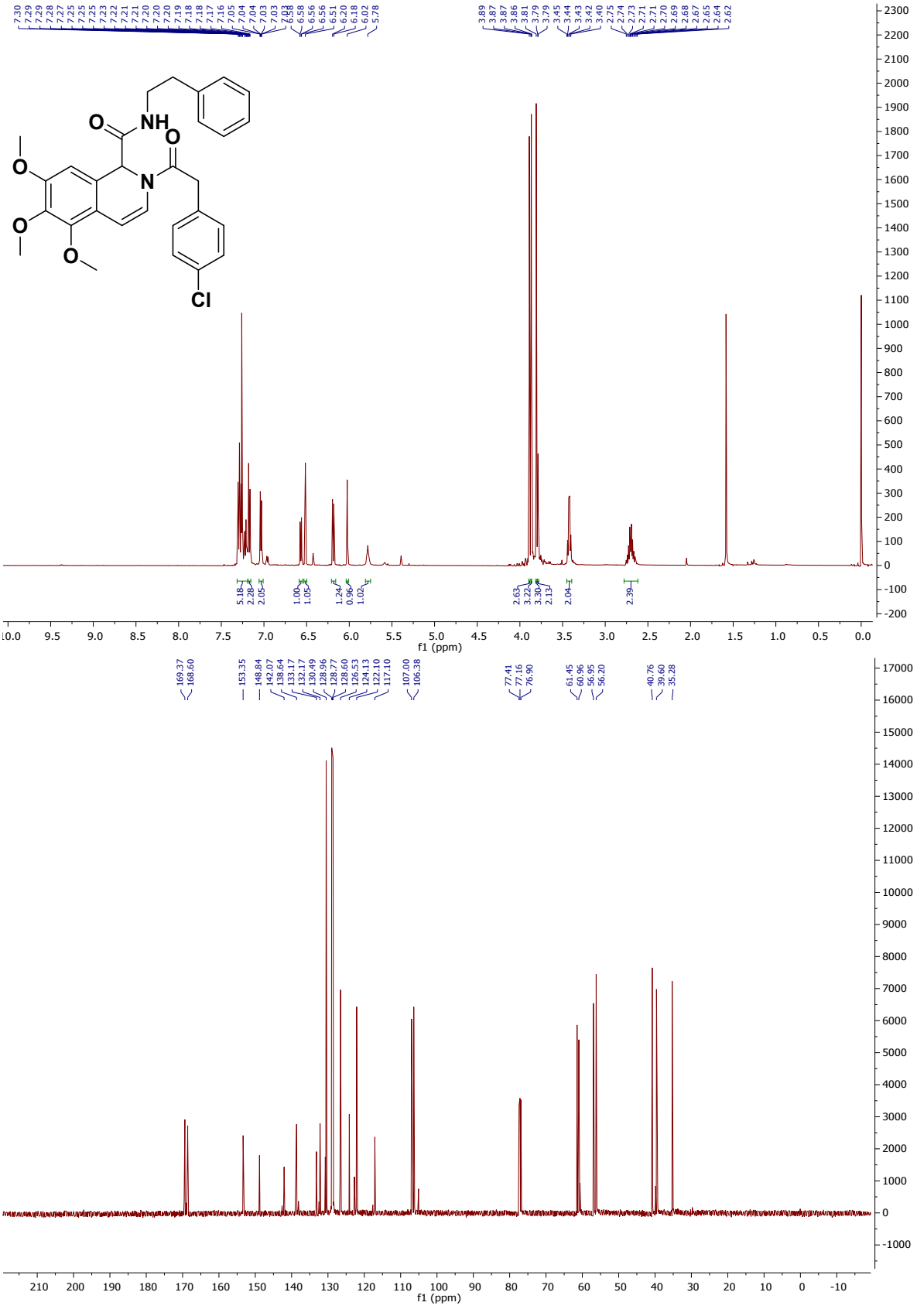
The product was synthesized according to procedure **F** in 3 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as colorless oil (675 mg, 62% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 – 6.39 (m, 3H), 6.33 (s, 1H), 5.37 – 5.27 (m, 1H), 5.17 – 5.07 (m, 1H), 4.54 – 4.49 (m, 1H), 4.31 – 4.26 (m, 1H), 3.77 (s, 6H), 3.40 (s, 3H), 3.38 (s, 3H), 2.93 – 2.85 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 161.5, 137.4, 104.9, 103.1, 100.9, 57.8, 55.8, 55.7, 55.6, 55.0, 48.0, 47.0; HRMS (ESI) m/z calculated for $C_{16}H_{22}N_5O_5$ $[M+H]^+$: 364,1616; found $[M+H]^+$: 364,1617.

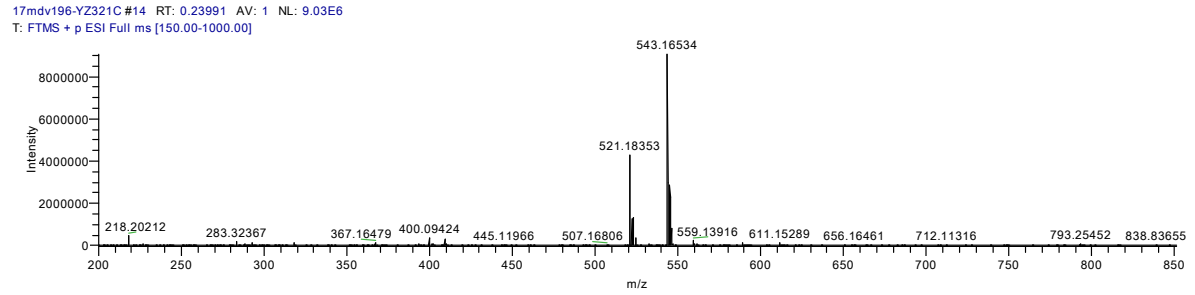
15: 10,12-dimethoxy-13*bH*-tetrazolo[5',1':3,4]pyrazino[2,1-*a*]isoquinolin-6(5*H*)-one

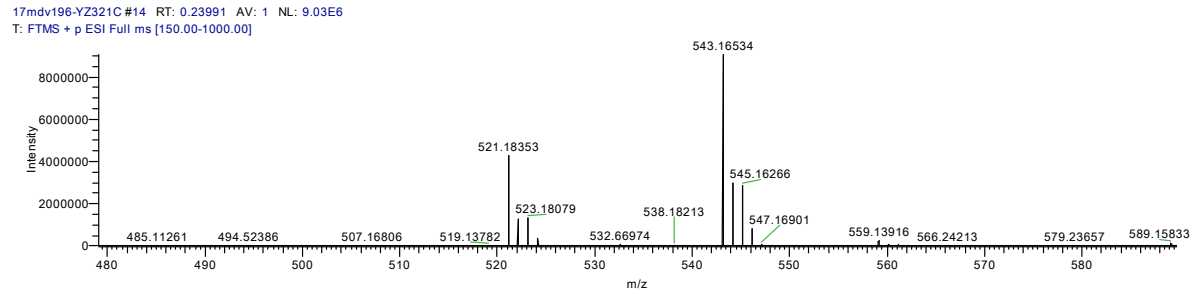


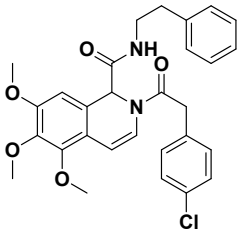
The product was synthesized according to procedure **G** in 1 mmol scale and purified by column chromatography using petroleum ether: ethyl acetate, afforded as white solid (276 mg, 92% yield), M.P.= 185 – 186 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.08 – 6.05 (m, 1H), 5.31 – 5.18 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 157.8, 156.1, 146.8, 129.1, 121.7, 113.3, 112.2, 101.5, 99.1, 55.9, 55.8, 53.4, 47.7; HRMS (ESI) m/z calculated for $C_{14}H_{14}N_5O_3$ $[M+H]^+$: 300.1091; found $[M+H]^+$: 300.1095.

6a: 2-(2-(4-chlorophenyl)acetyl)-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydro-isoquinoline-1-carboxamide



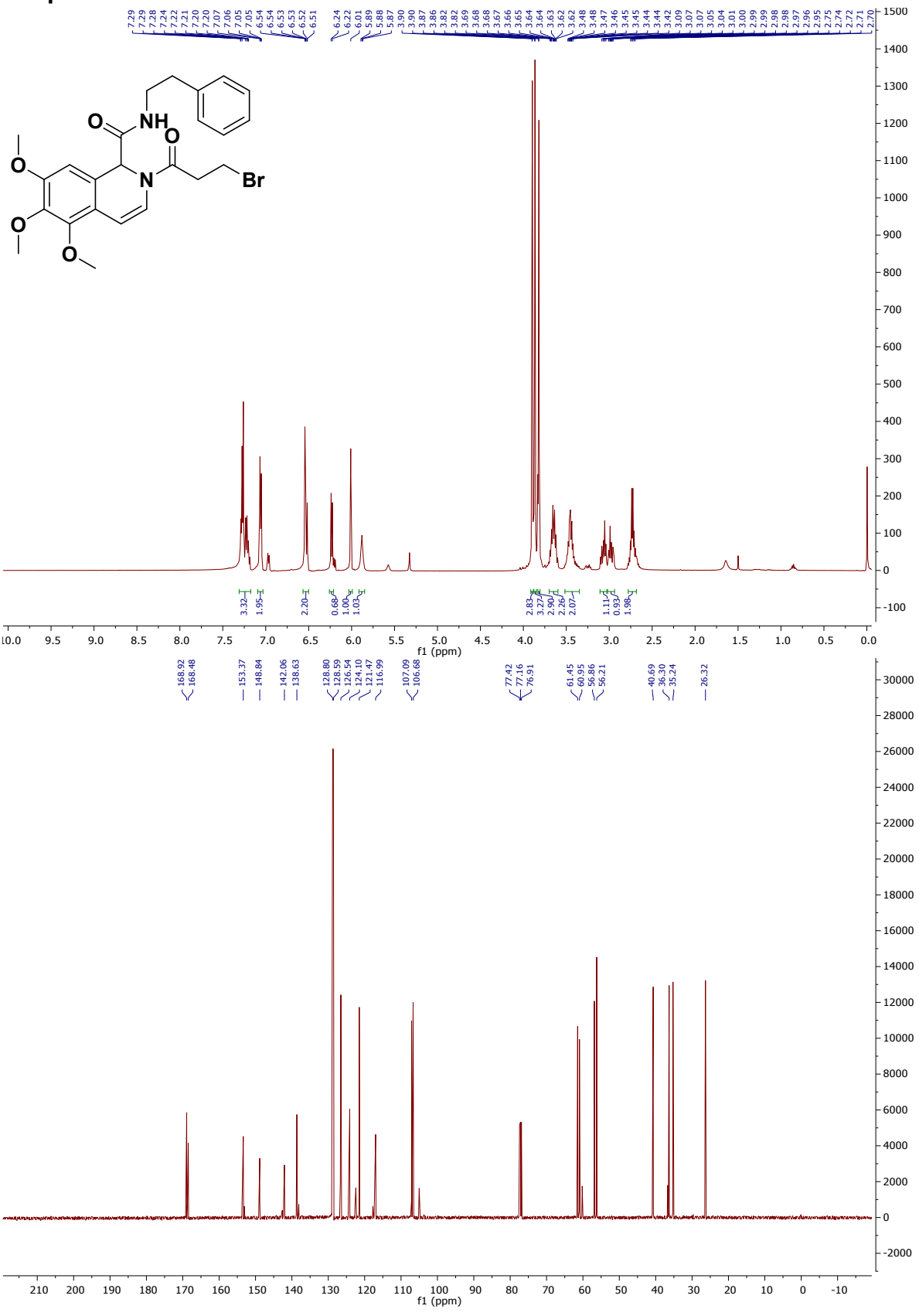


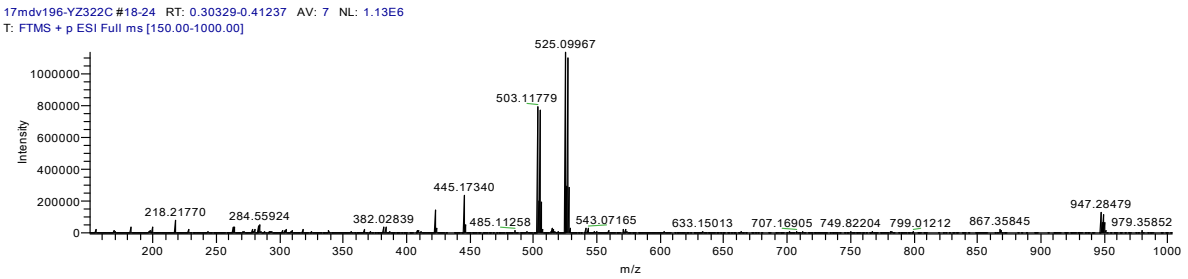


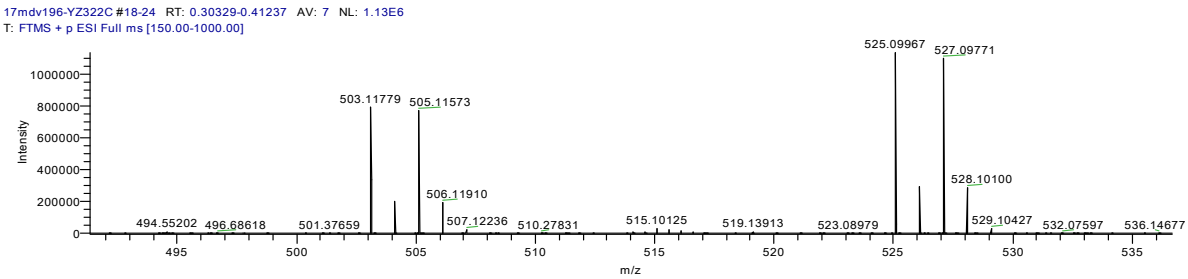


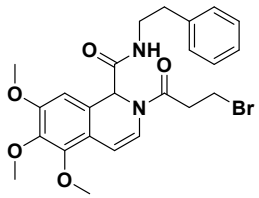
Chemical Formula: $C_{29}H_{29}ClN_2O_5$
Exact Mass: 520.1765
Molecular Weight: 521.0100

6b: 2-(3-bromopropanoyl)-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydro-isoquinoline-1-carboxamide



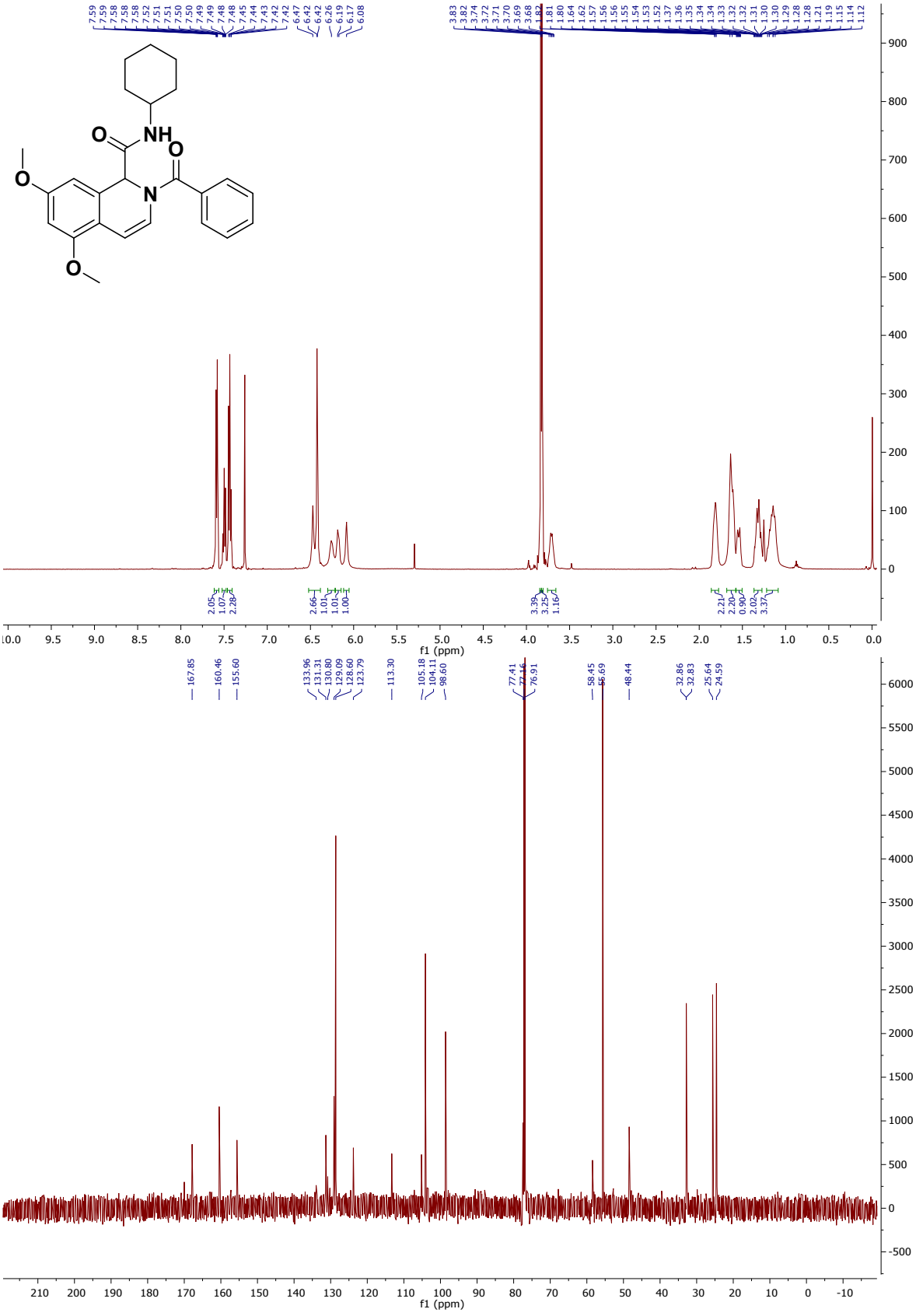


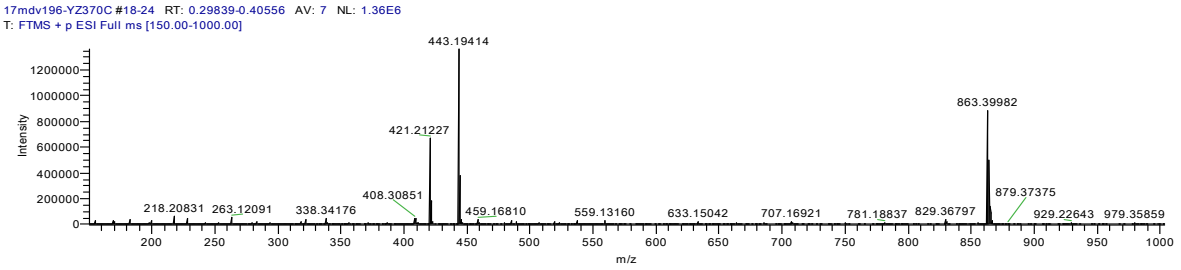


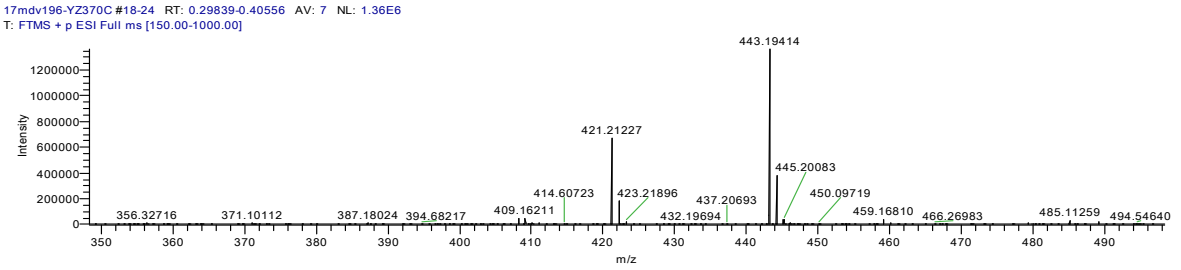


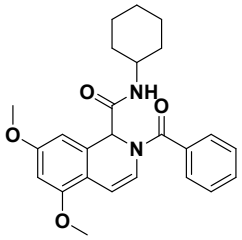
Chemical Formula: $C_{24}H_{27}BrN_2O_5$
Exact Mass: 502.1103
Molecular Weight: 503.3930

6c: 2-benzoyl-*N*-cyclohexyl-5,7-dimethoxy-1,2-dihydroisoquinoline-1-carboxamide



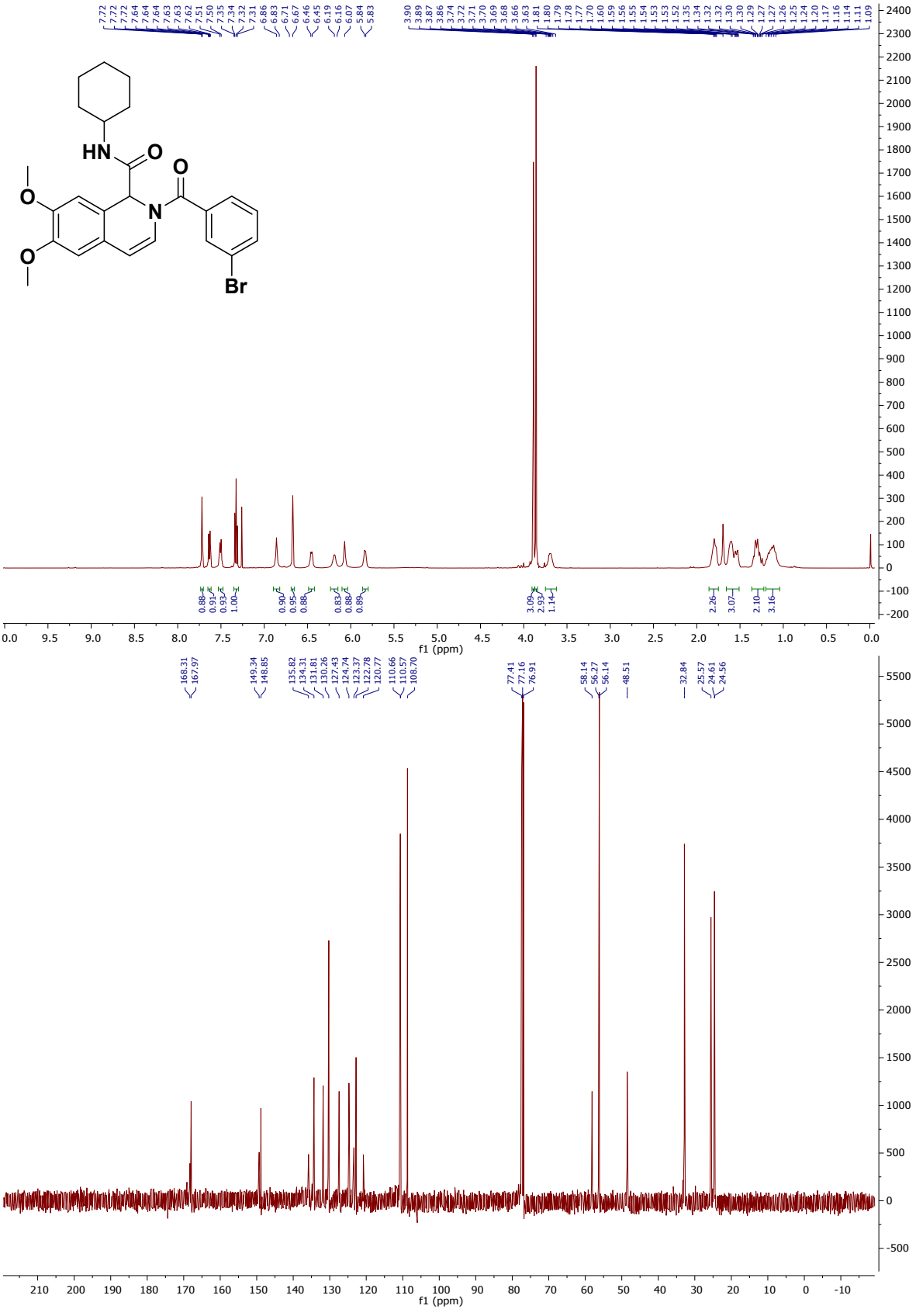


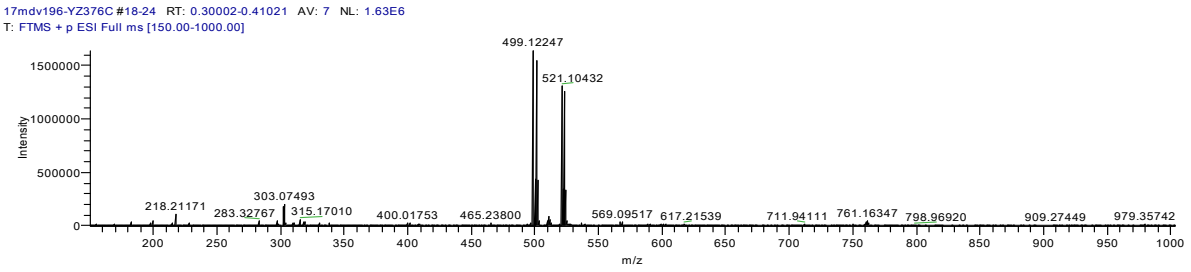


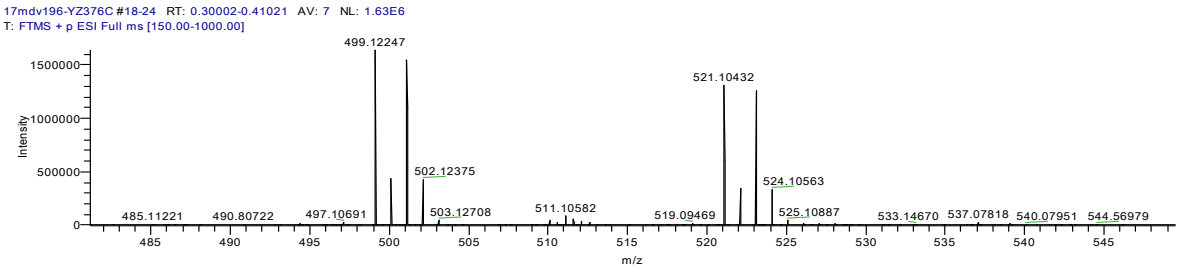


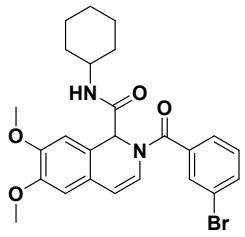
Chemical Formula: $C_{25}H_{28}N_2O_4$
Exact Mass: 420.2049
Molecular Weight: 420.5090

6d: 2-(3-bromobenzoyl)-*N*-cyclohexyl-6,7-dimethoxy-1,2-dihydroisoquinoline-1-carboxamide



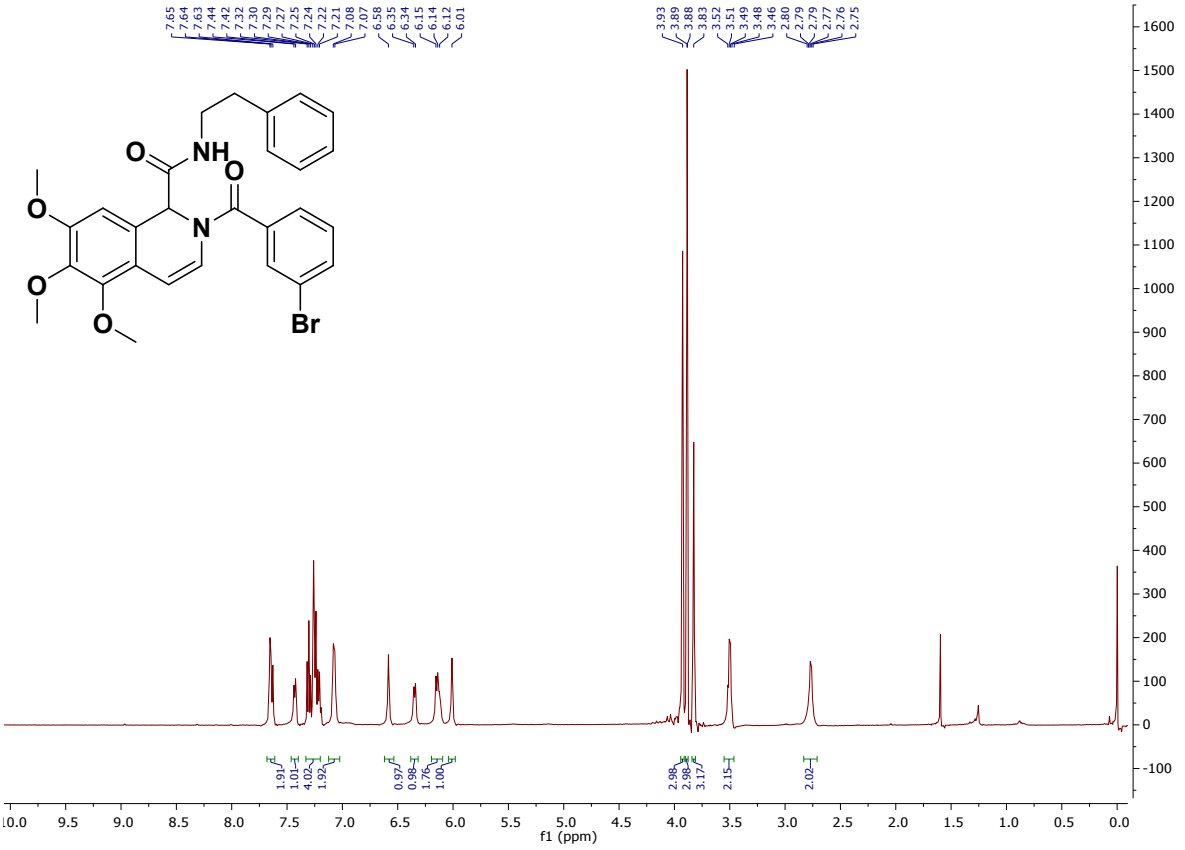


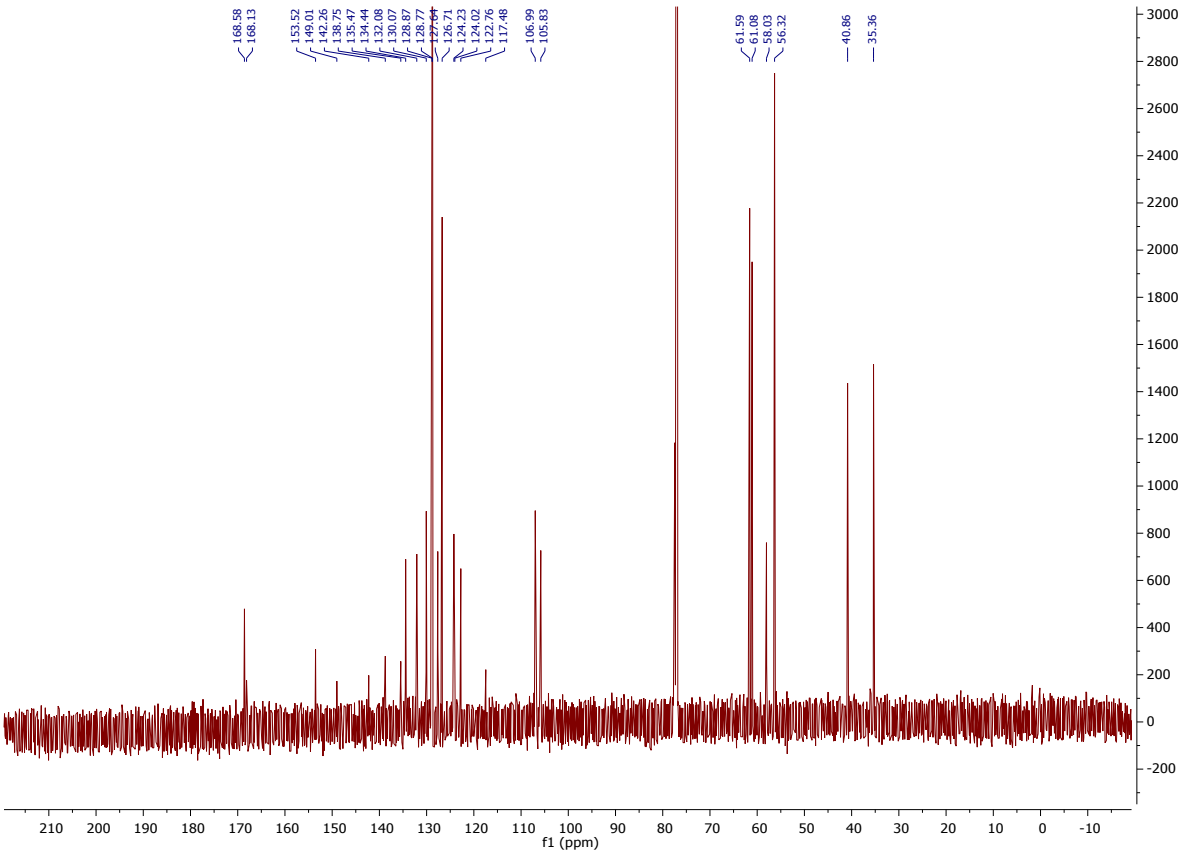


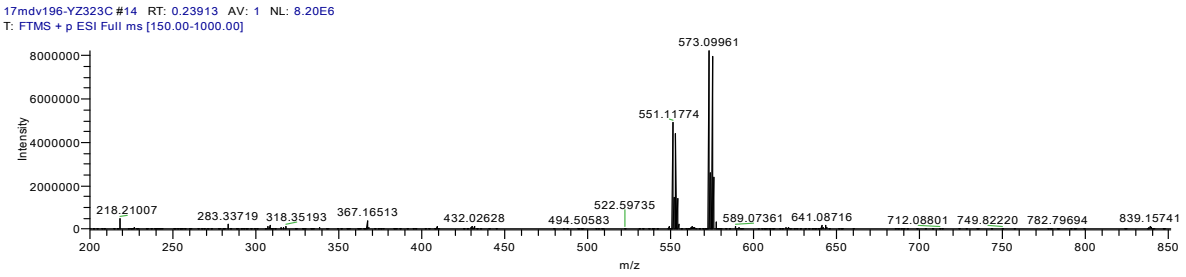


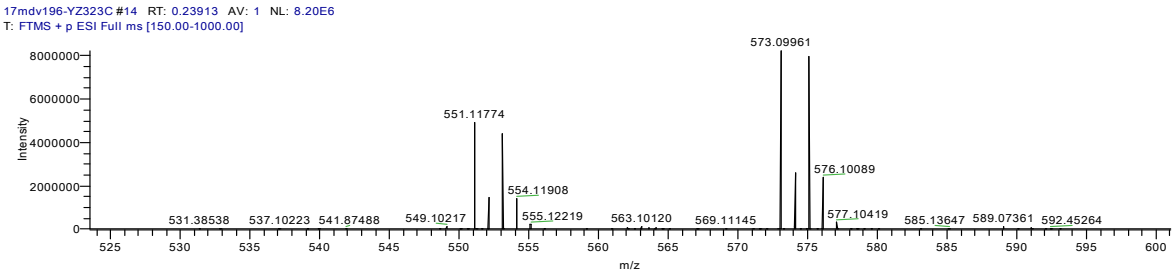
Chemical Formula: $C_{25}H_{27}BrN_2O_4$
Exact Mass: 498.1154
Molecular Weight: 499.4050

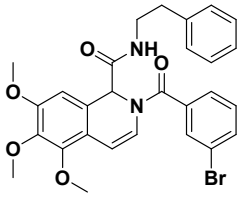
6e: *N*-benzyl-2-(3-bromopropanoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide





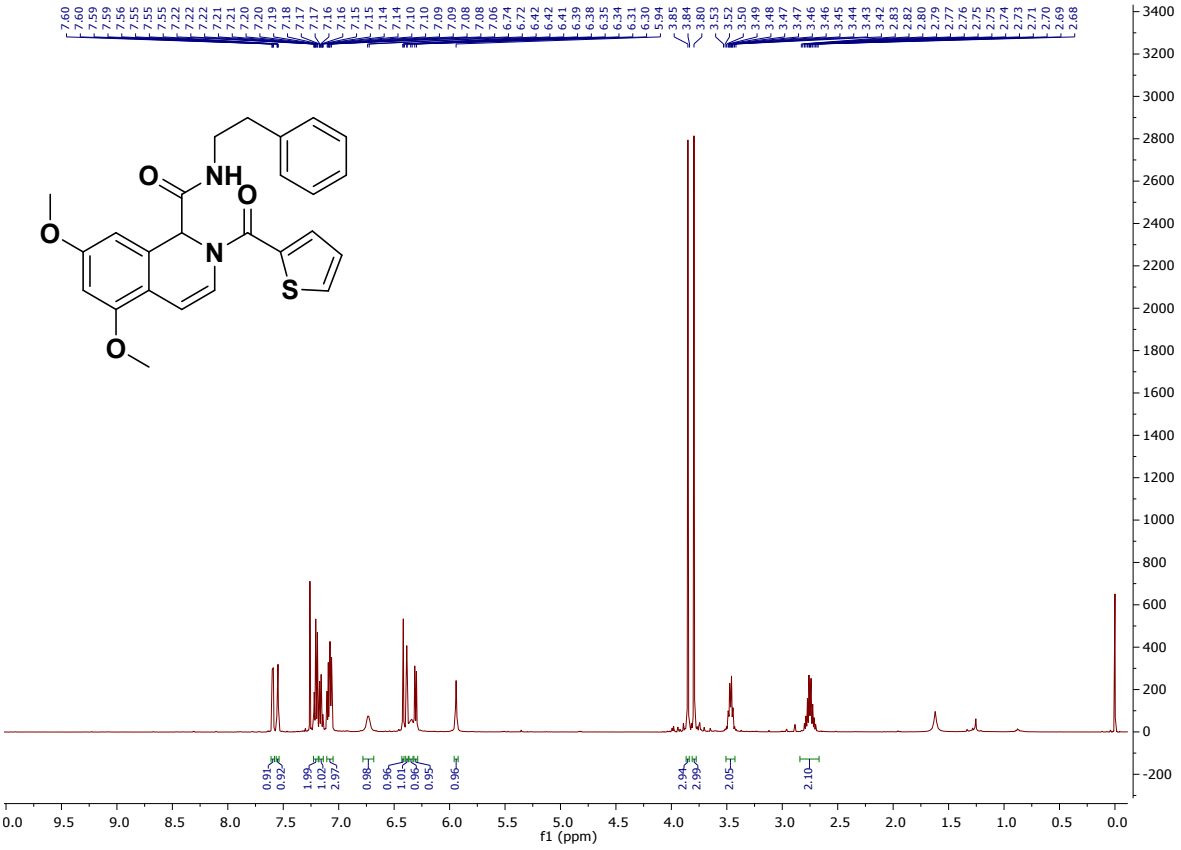


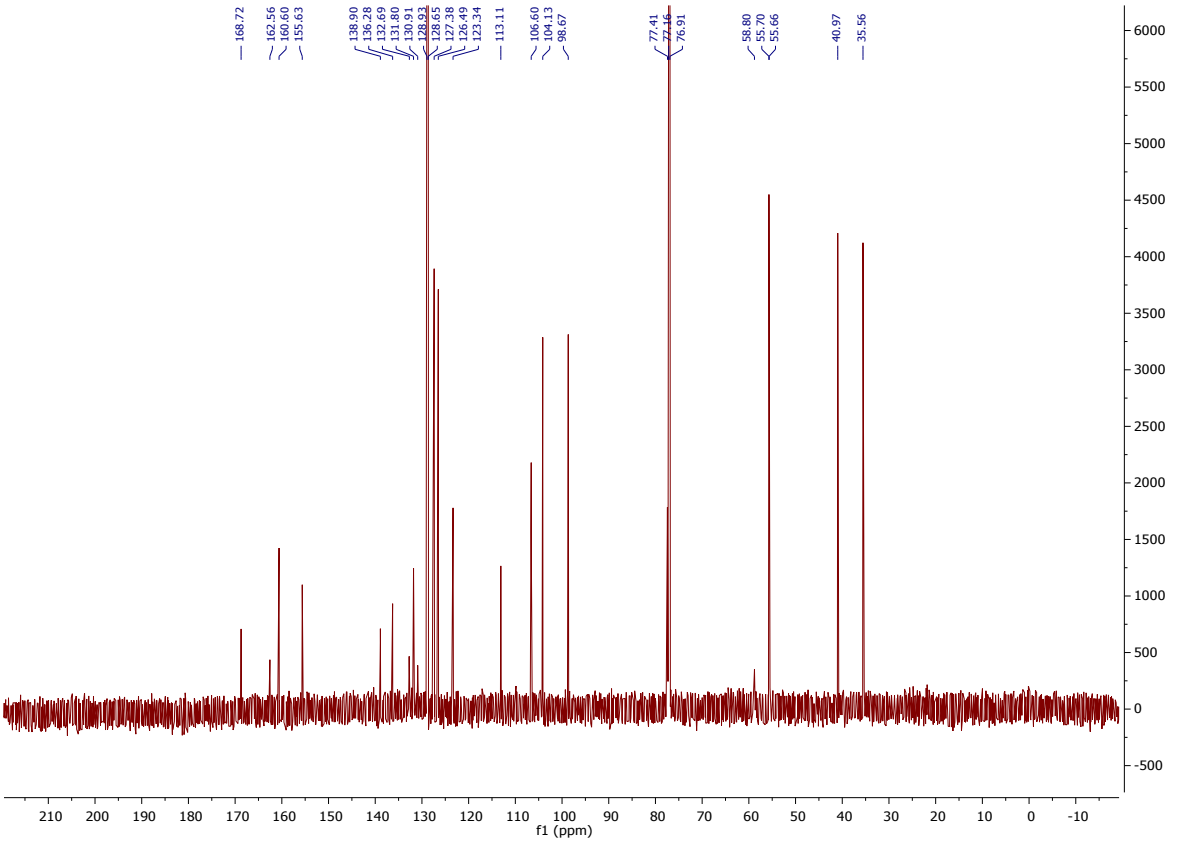


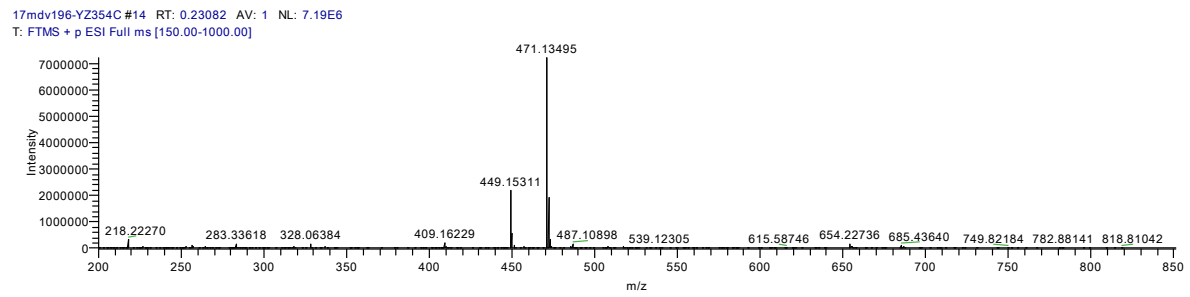


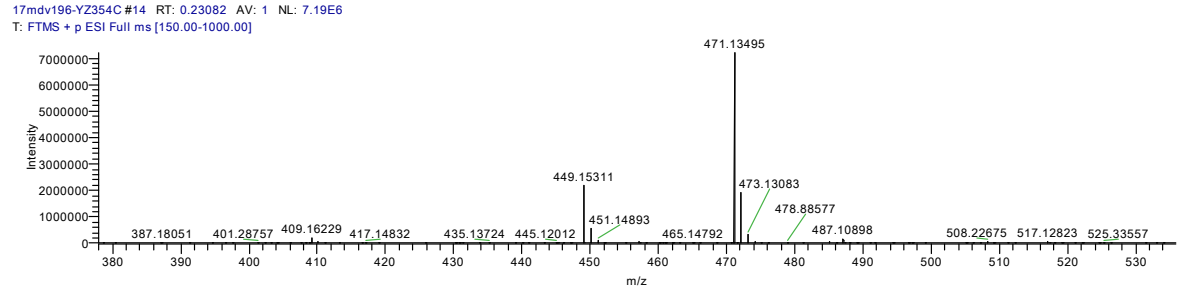
Chemical Formula: $C_{28}H_{27}BrN_2O_5$
Exact Mass: 550.1103
Molecular Weight: 551.4370

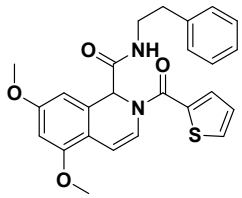
6f: 5,7-dimethoxy-*N*-phenethyl-2-(thiophene-2-carbonyl)-1,2-dihydro-isoquinoline-1-carboxamide





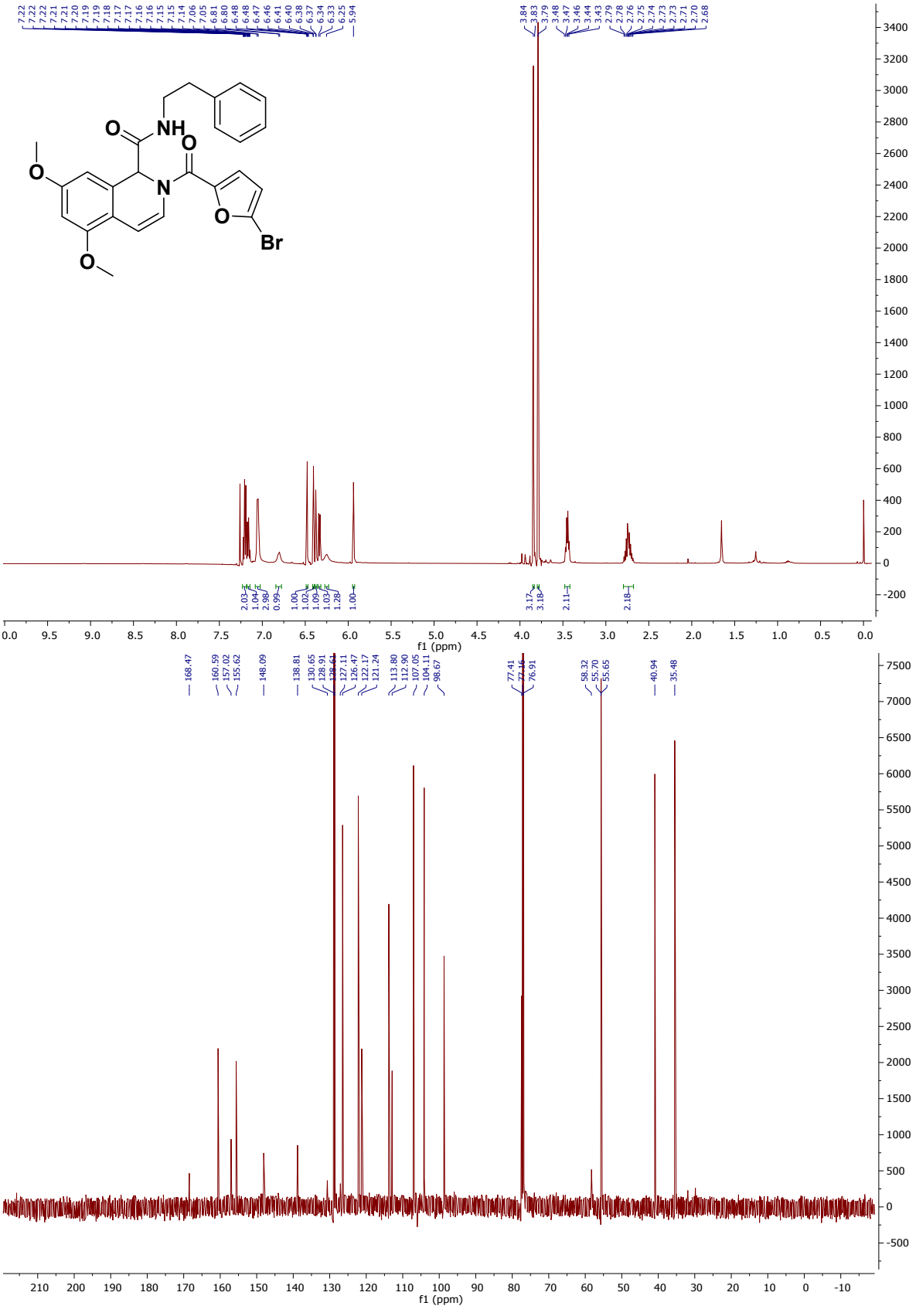


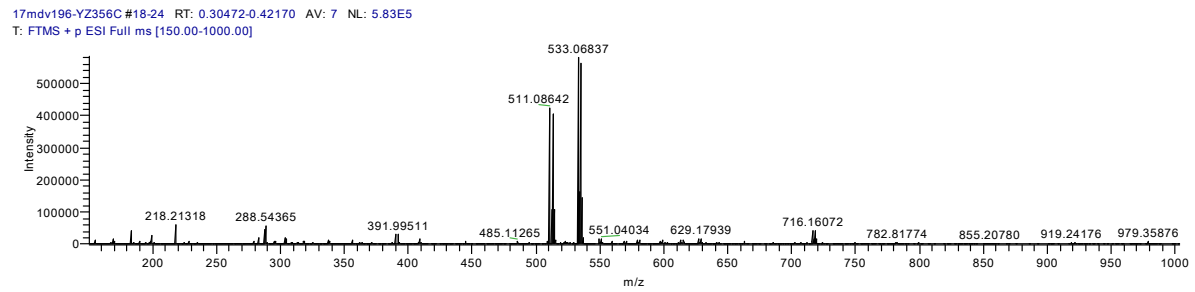


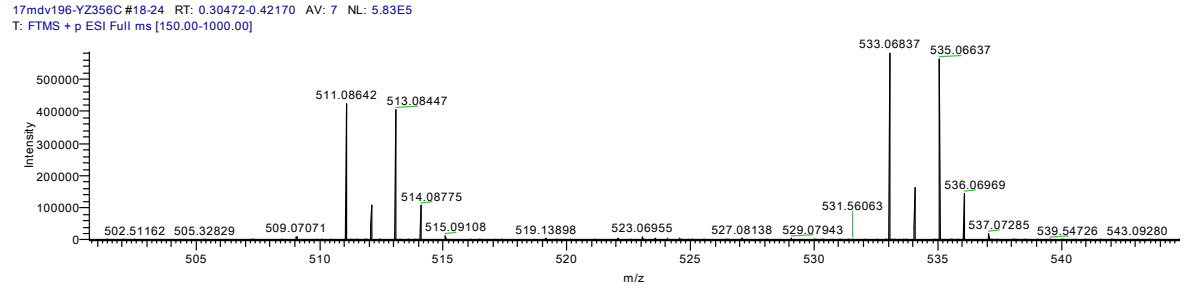


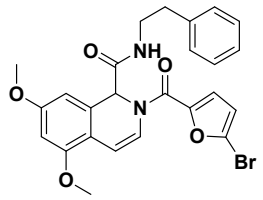
Chemical Formula: $C_{25}H_{24}N_2O_4S$
Exact Mass: 448.1457
Molecular Weight: 448.5370

6g: 2-(5-bromofuran-2-carbonyl)-5,7-dimethoxy-*N*-phenethyl-1,2-dihydroisoquinoline-1-carboxamide



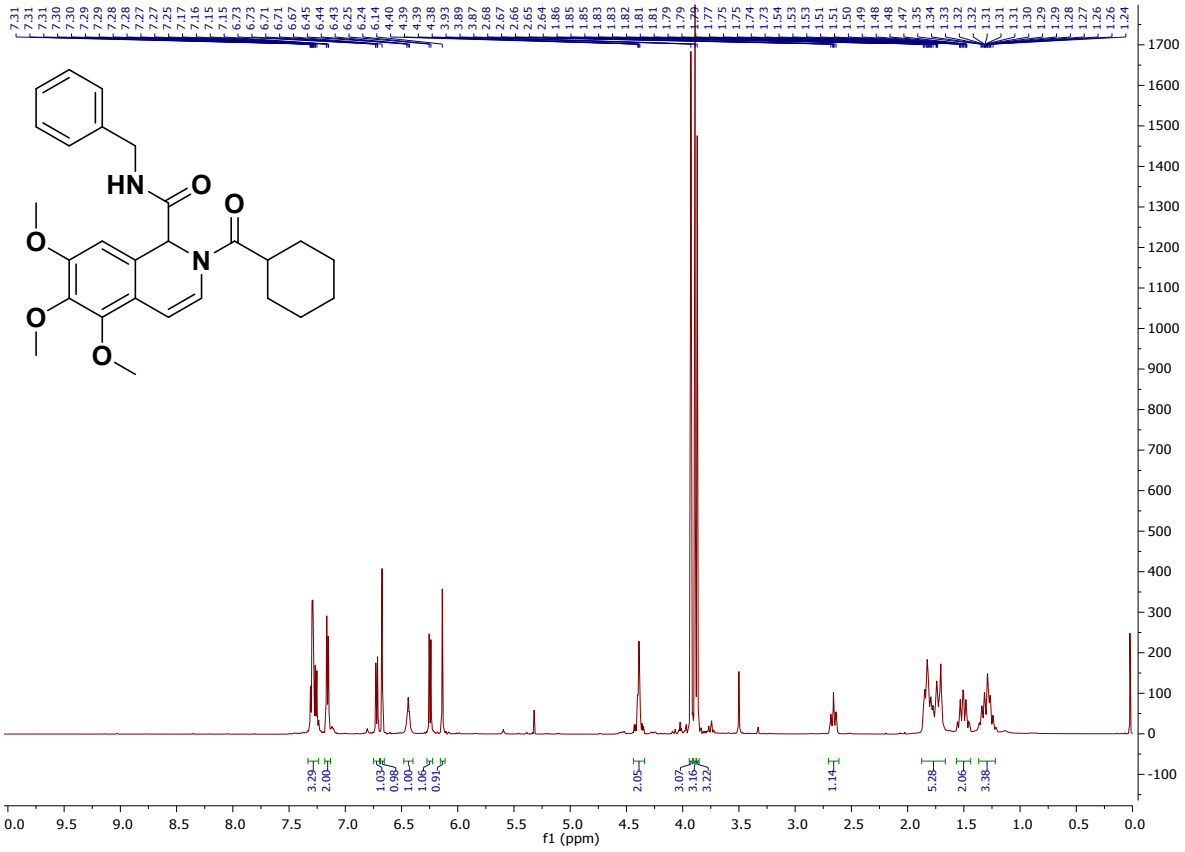


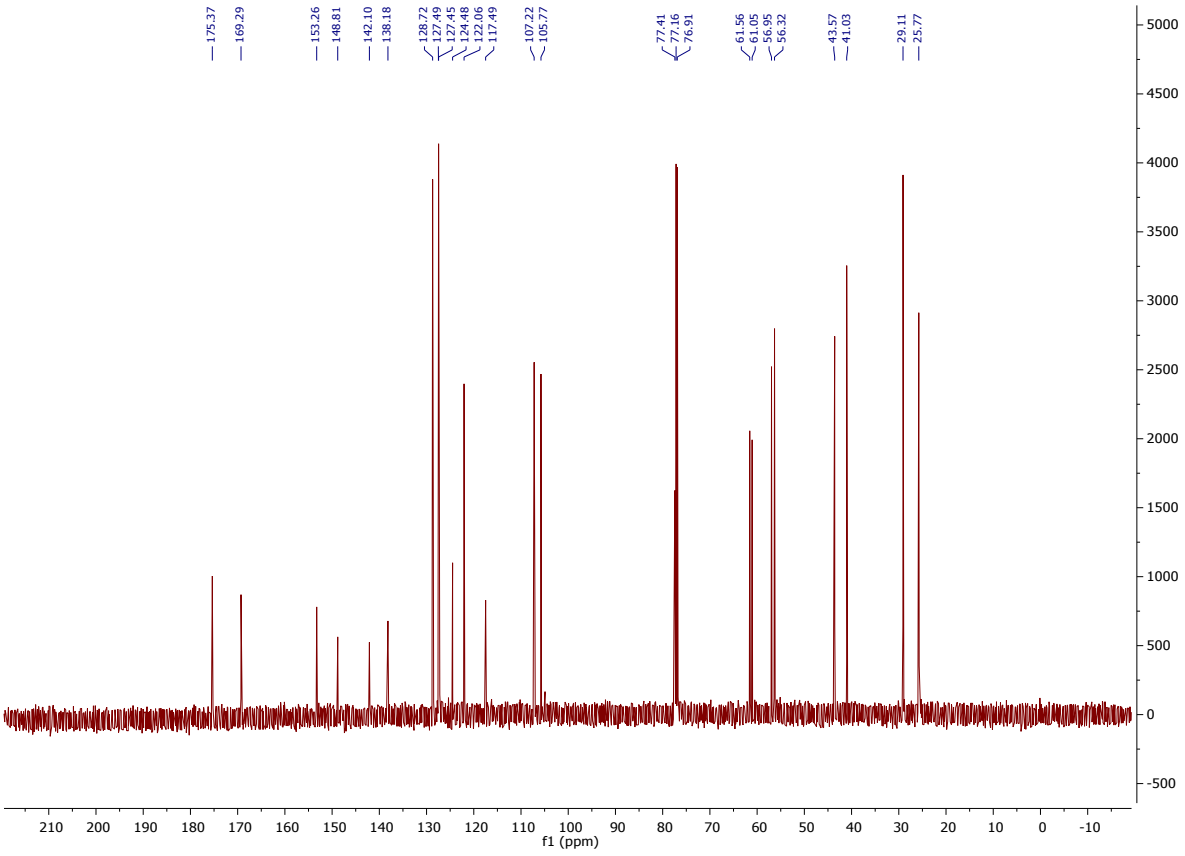


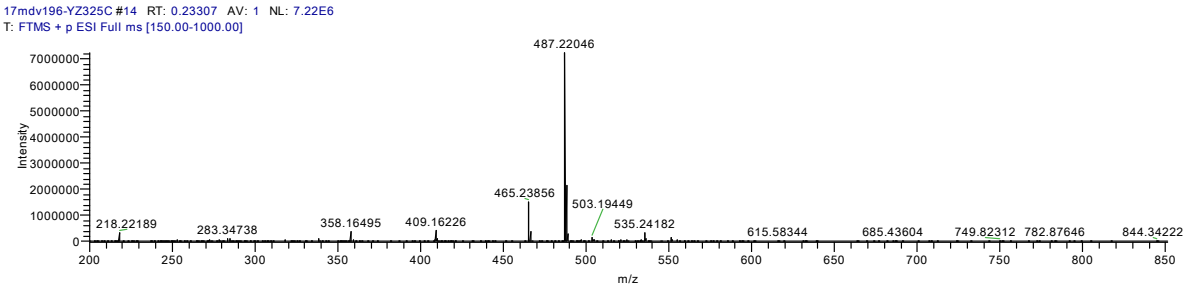


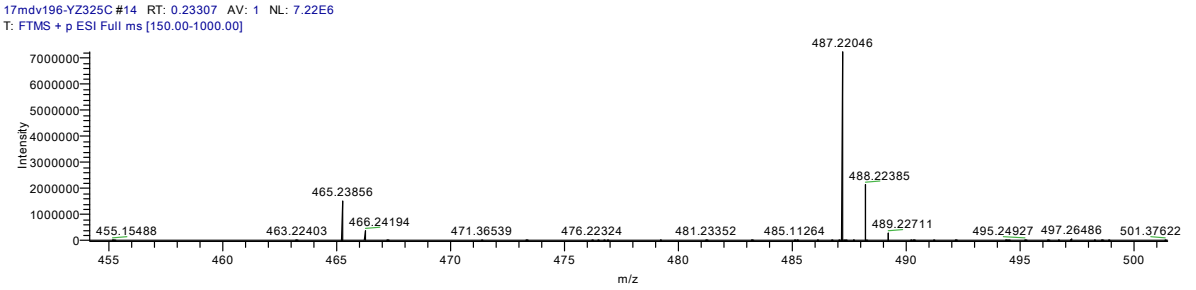
Chemical Formula: $C_{25}H_{23}BrN_2O_5$
Exact Mass: 510.0790
Molecular Weight: 511.3720

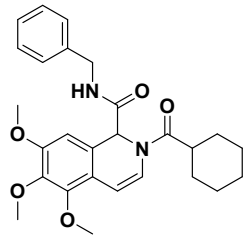
6h: *N*-benzyl-2-(cyclohexanecarbonyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide





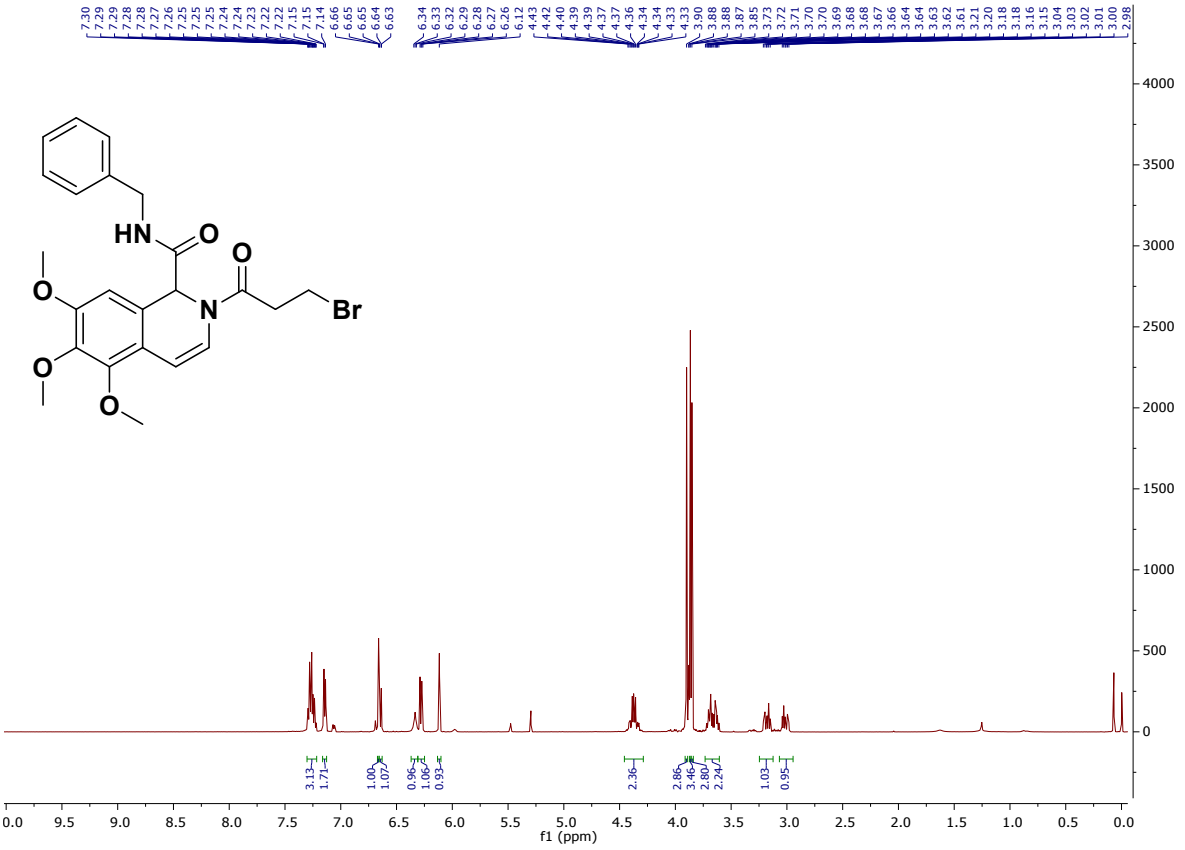


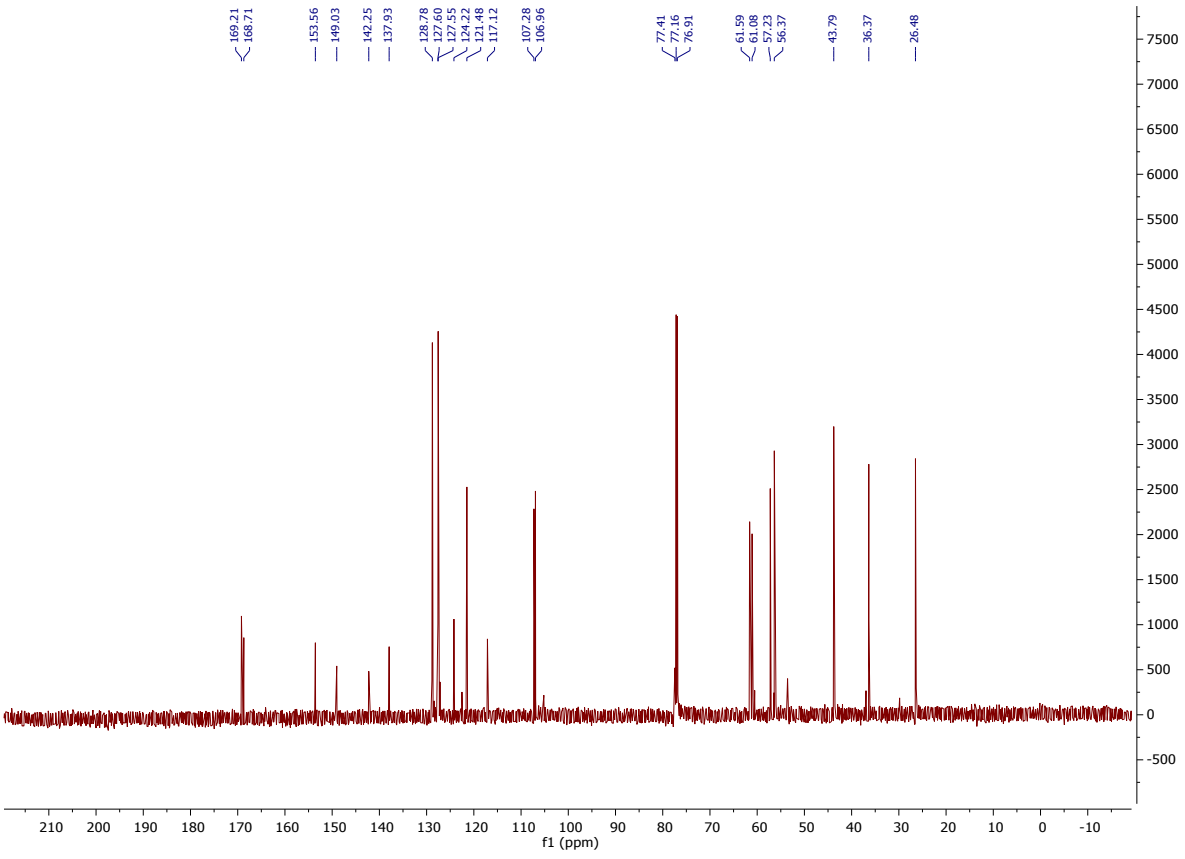


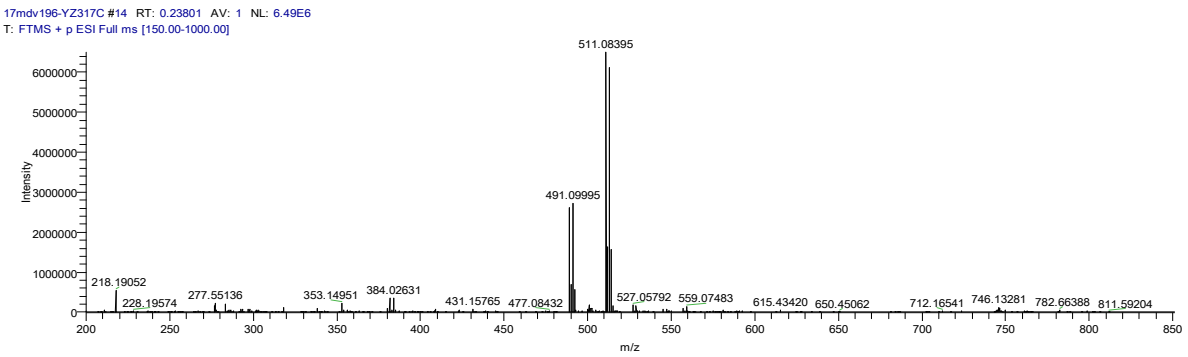


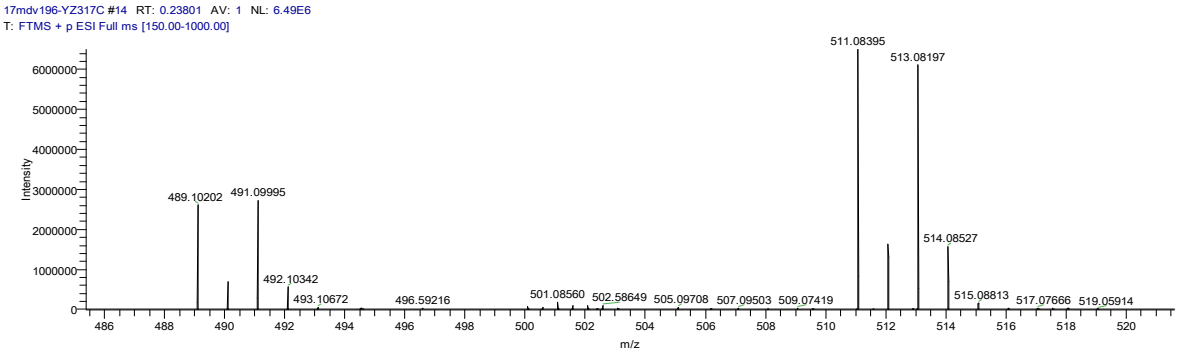
Chemical Formula: $C_{27}H_{32}N_2O_5$
Exact Mass: 464.2311
Molecular Weight: 464.5620

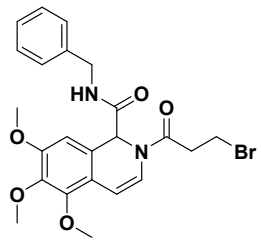
6i: *N*-benzyl-2-(3-bromopropanoyl)-5,6,7-trimethoxy-1,2-dihydroisoquinoline-1-carboxamide





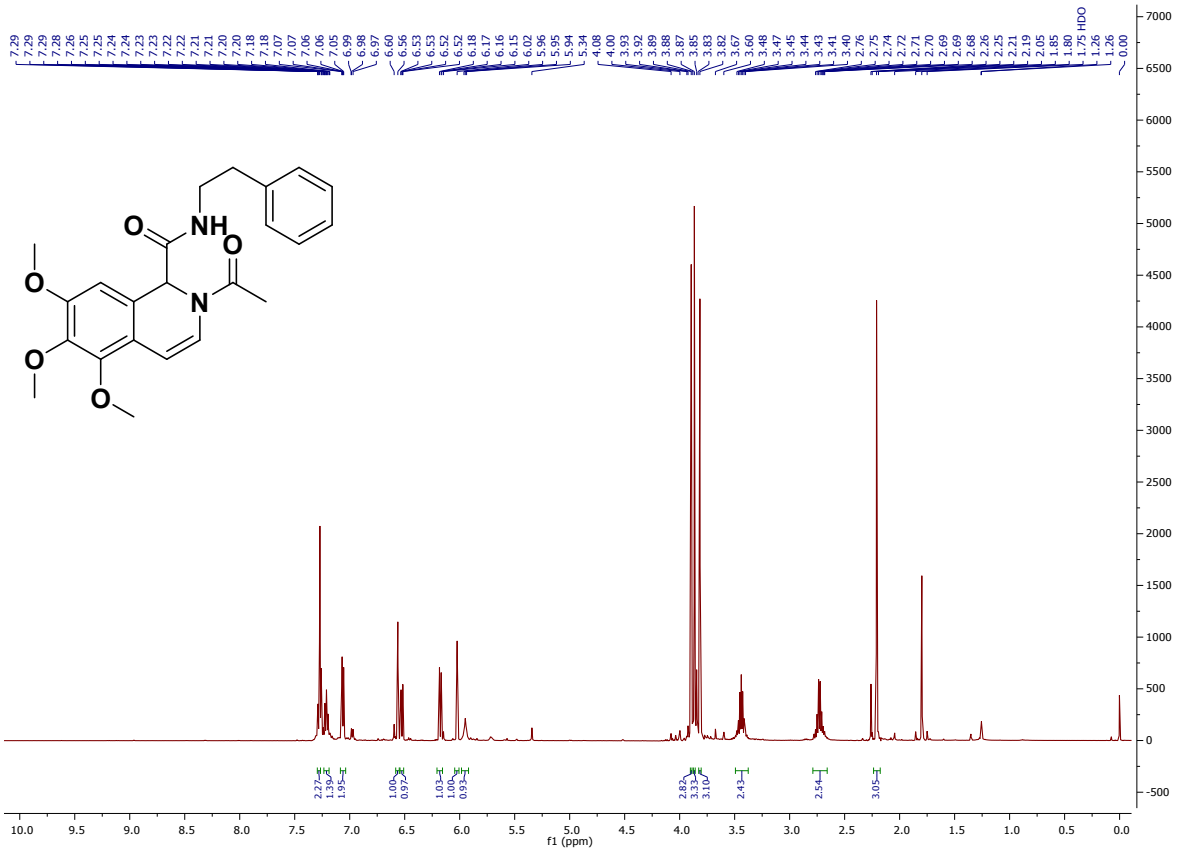


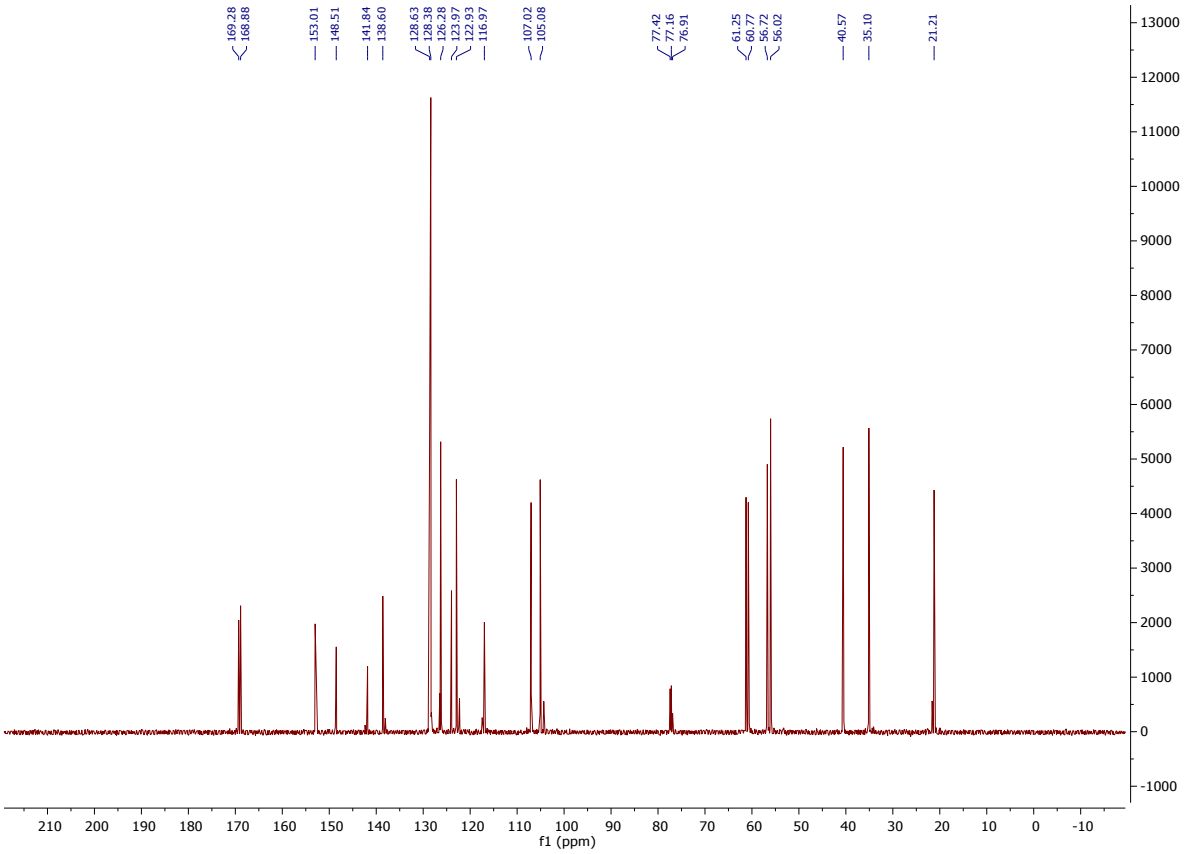


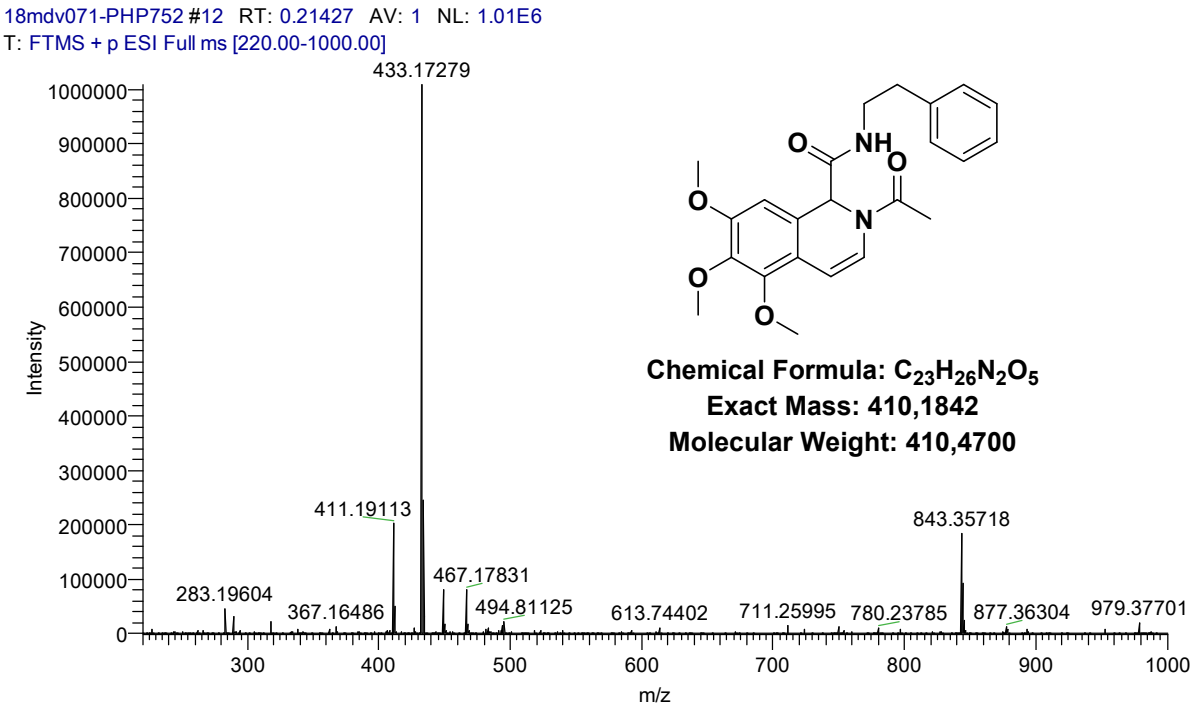


Chemical Formula: $C_{23}H_{25}BrN_2O_5$
Exact Mass: 488.0947
Molecular Weight: 489.3660

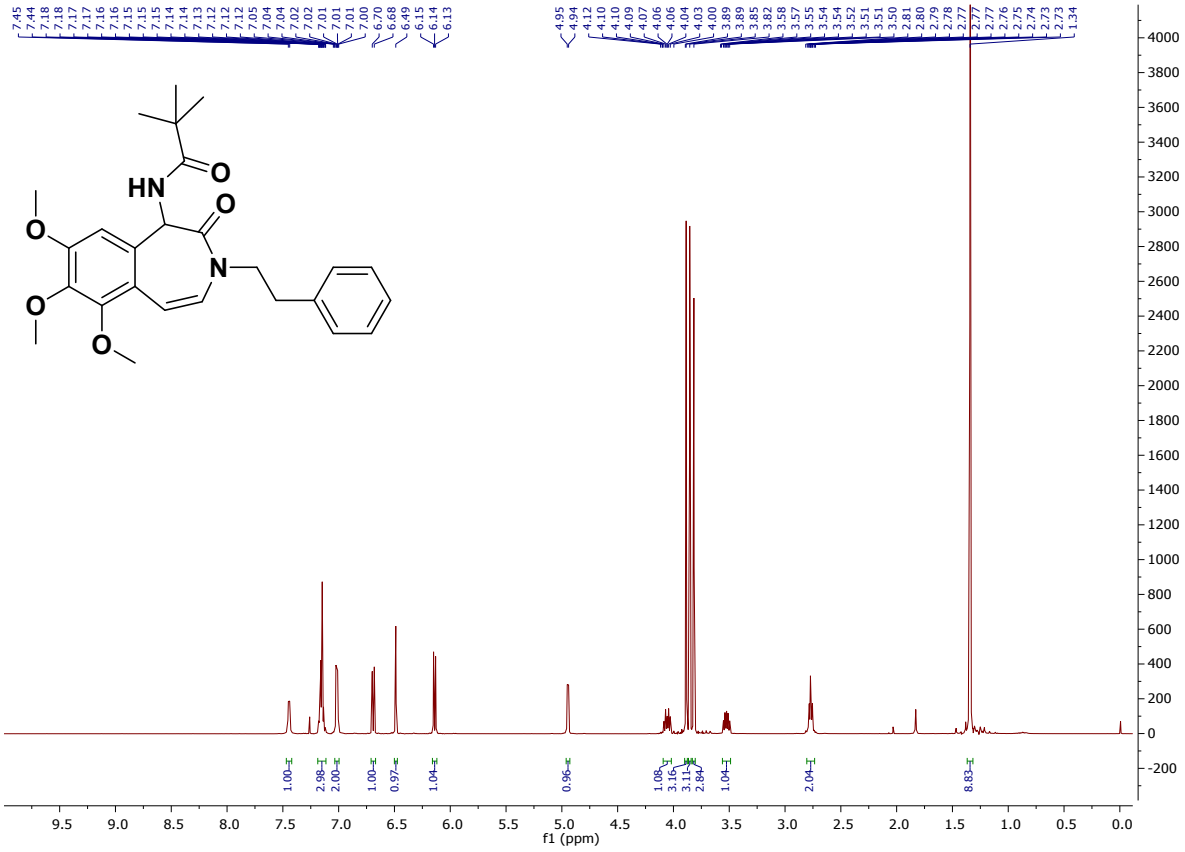
6j: 2-acetyl-5,6,7-trimethoxy-*N*-phenethyl-1,2-dihydroisoquinoline-1-carboxamide

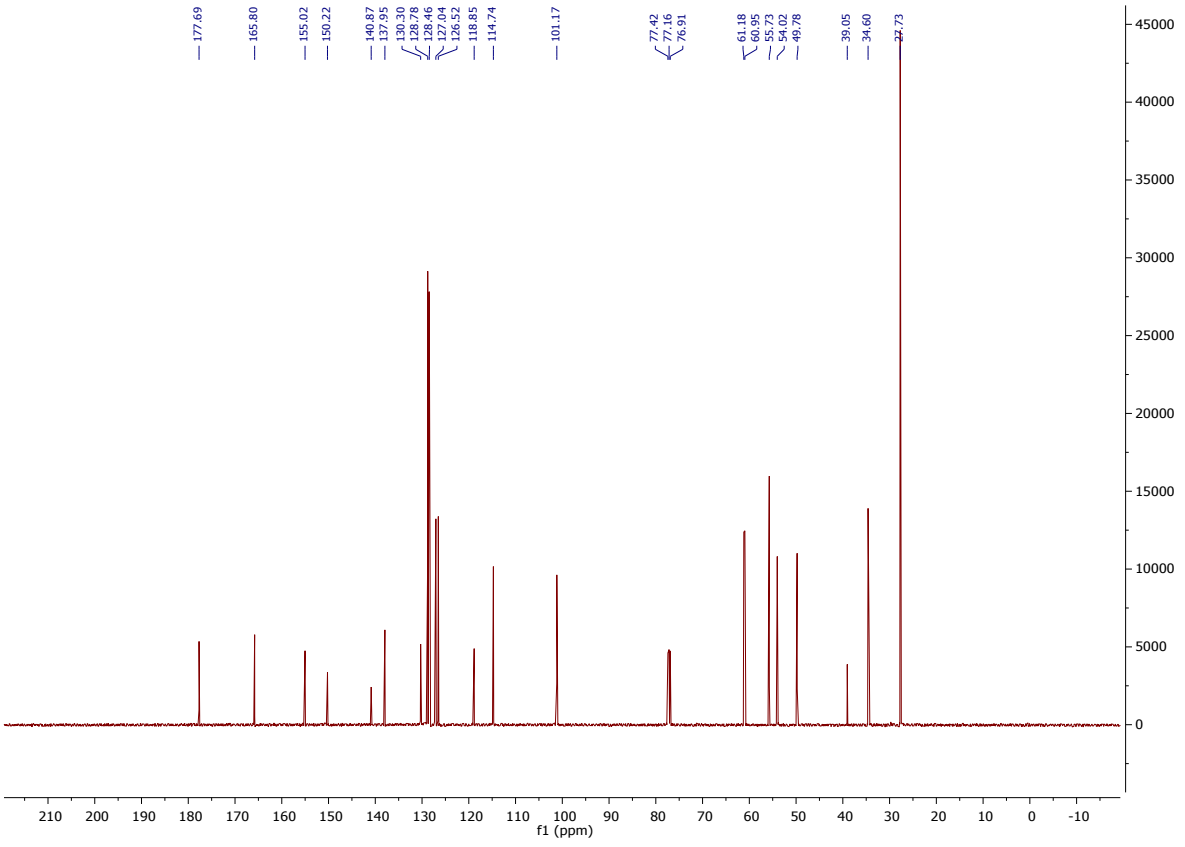


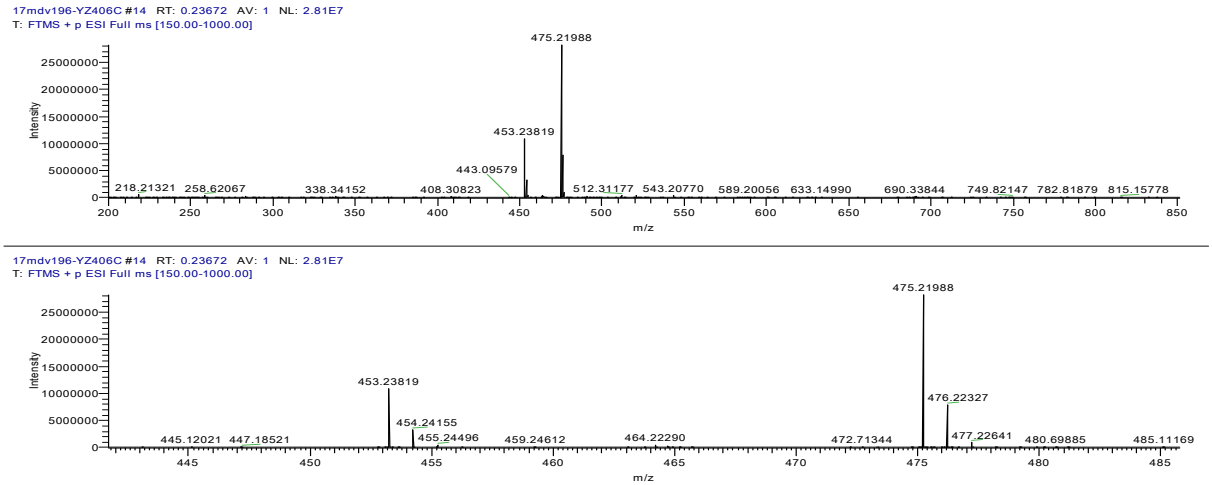


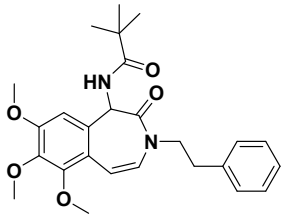

18mdv071-PHP752 #12 RT: 0.21427 AV: 1 NL: 1.01E6
T: FTMS + p ESI Full ms [220.00-1000.00]
433.17279
411.19113
843.35718
467.17831
283.19604
367.16486
494.81125
613.74402
711.25995
780.23785
877.36304
979.37701
Intensity
m/z
Chemical Formula: C23H26N2O5
Exact Mass: 410,1842
Molecular Weight: 410,4700

8a: *N*-(6,7,8-trimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl)pivalamide



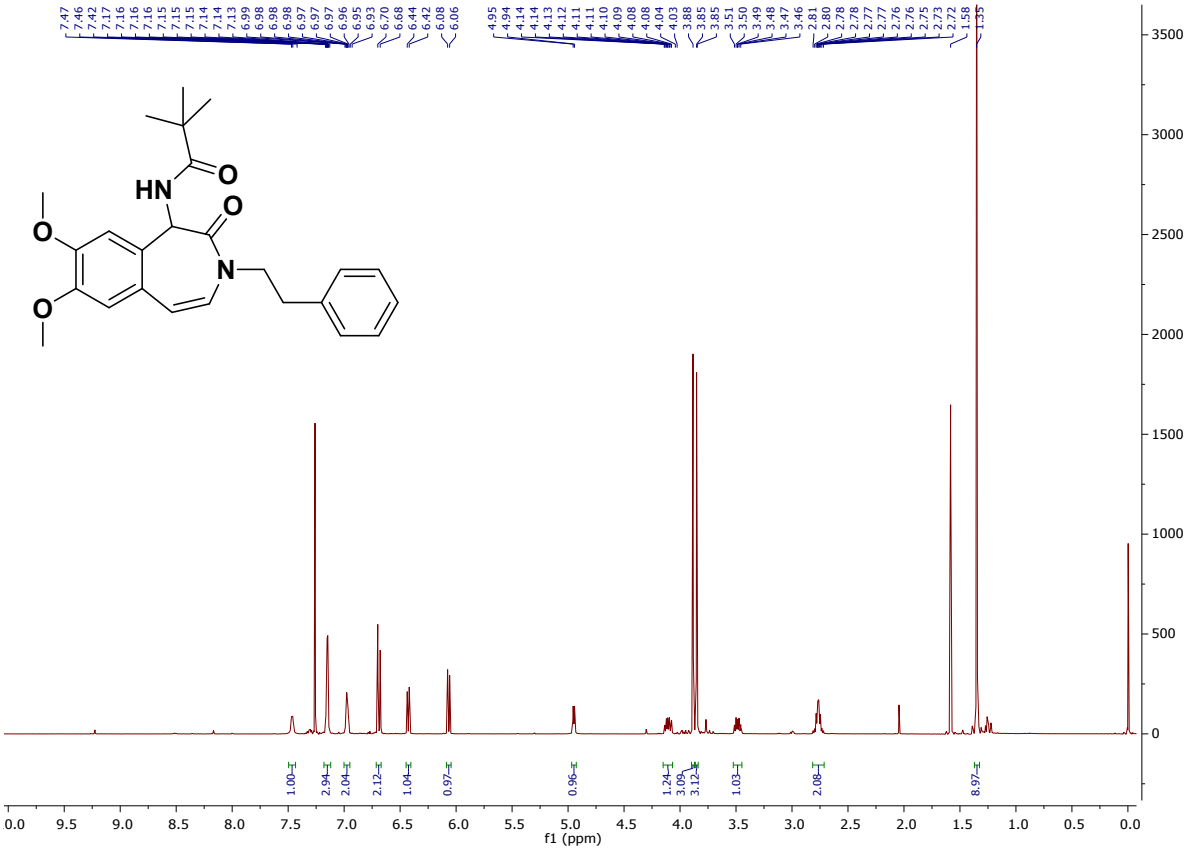


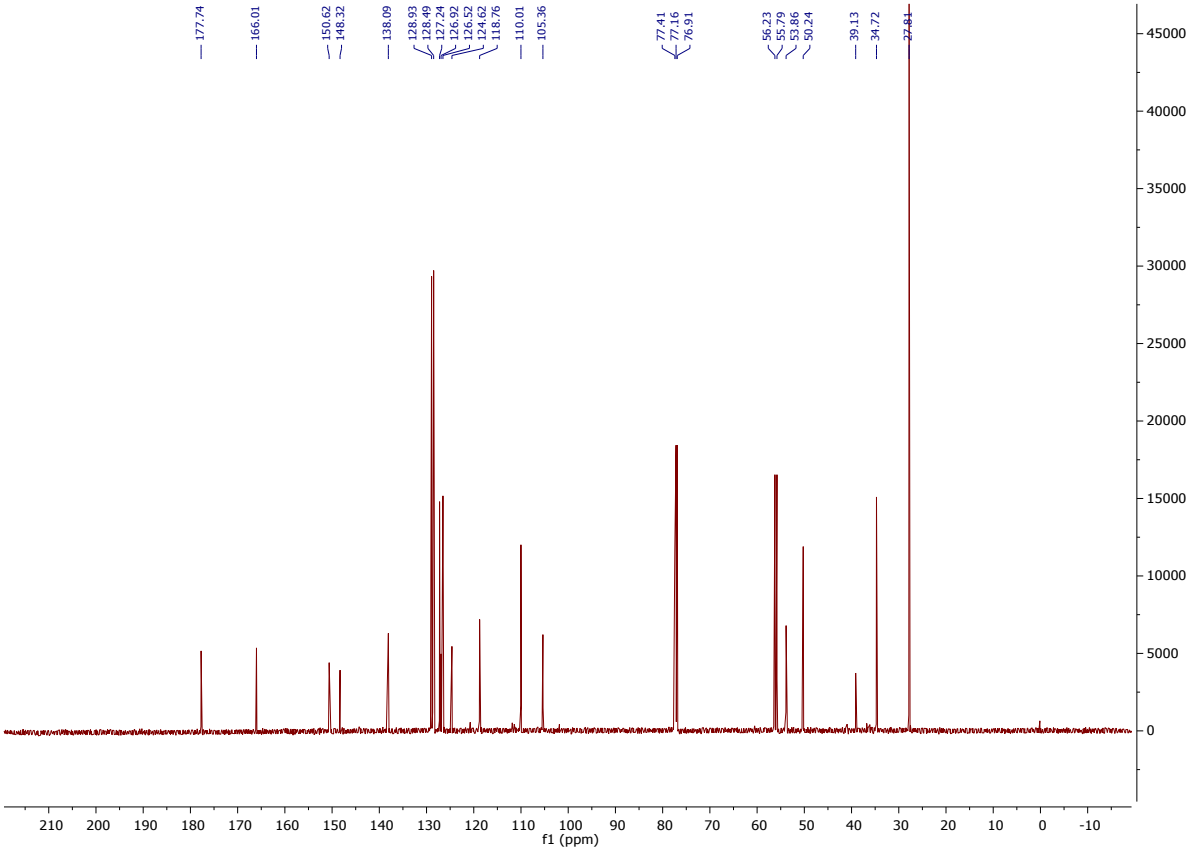


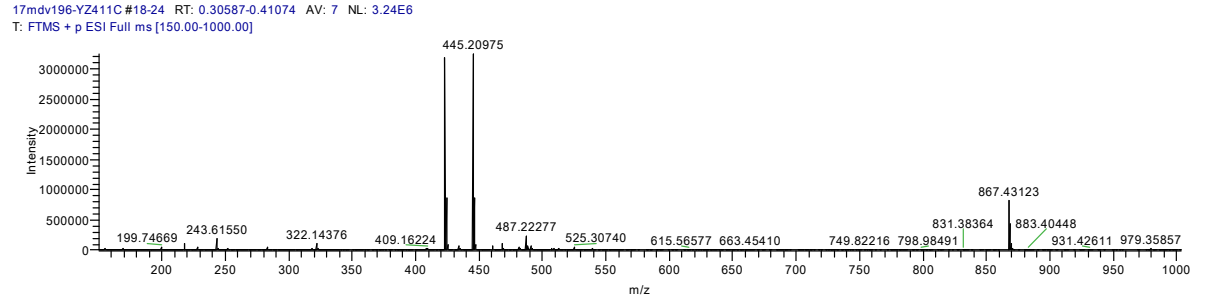


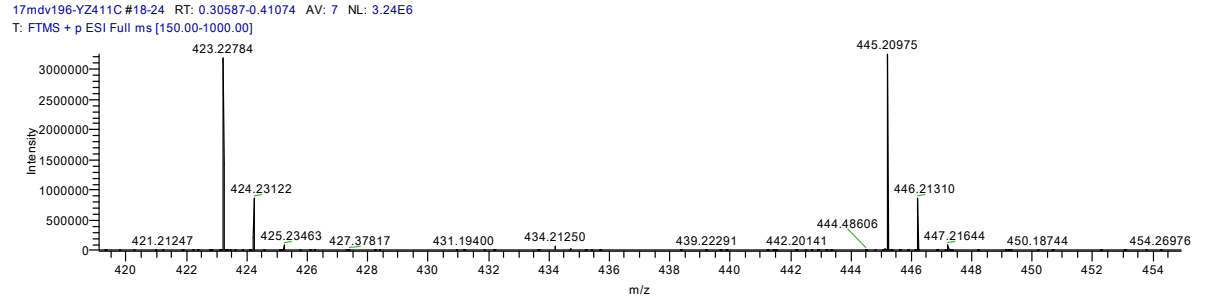
Chemical Formula: $C_{26}H_{32}N_2O_5$
Exact Mass: 452.2311
Molecular Weight: 452.5510

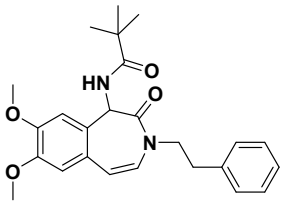
8b: *N*-(7,8-dimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl) pivalamide





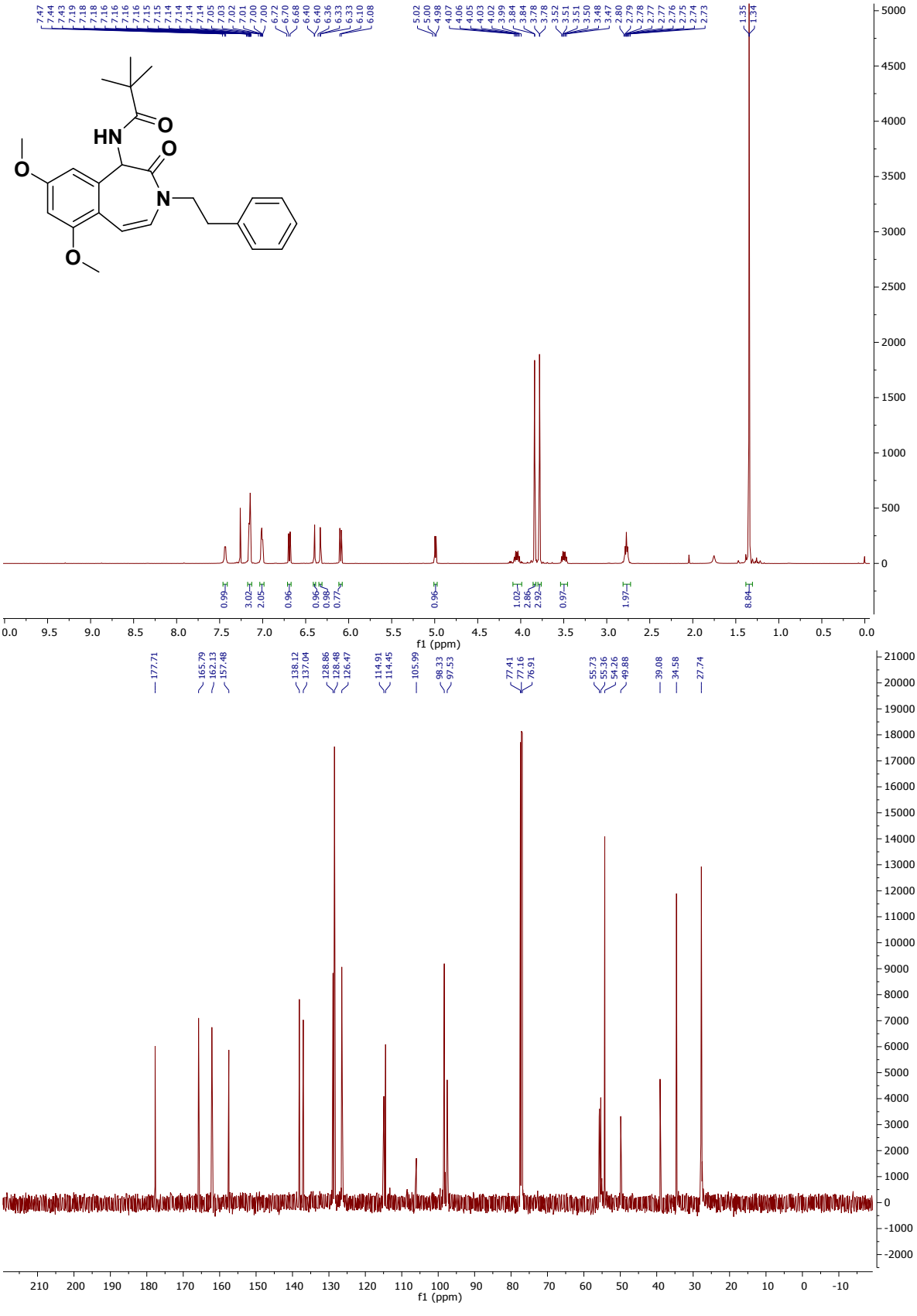


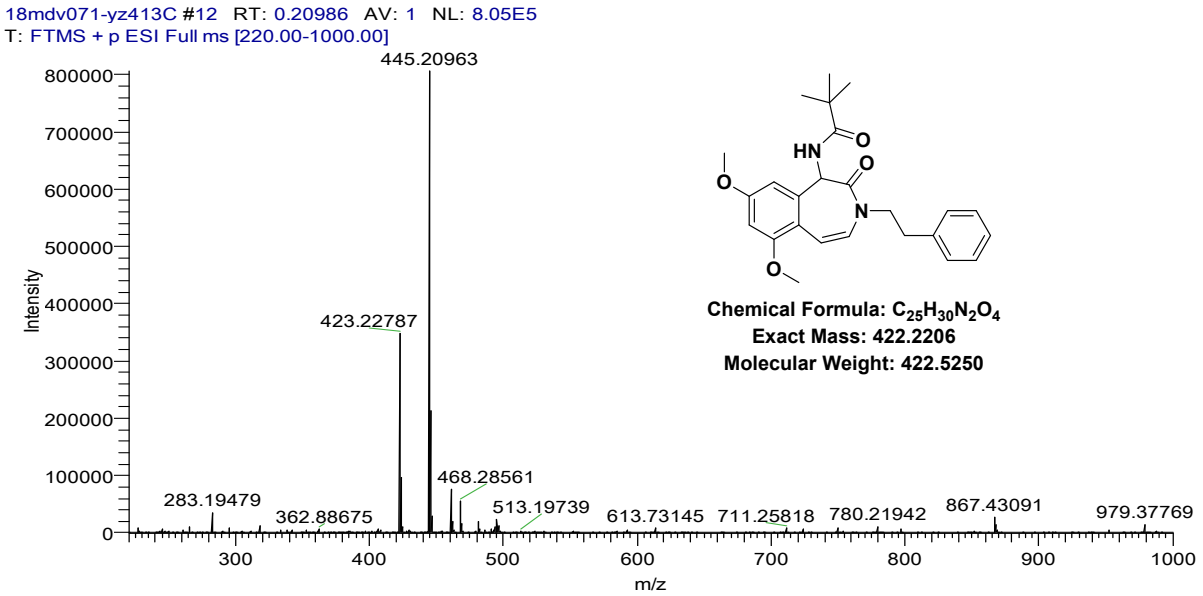




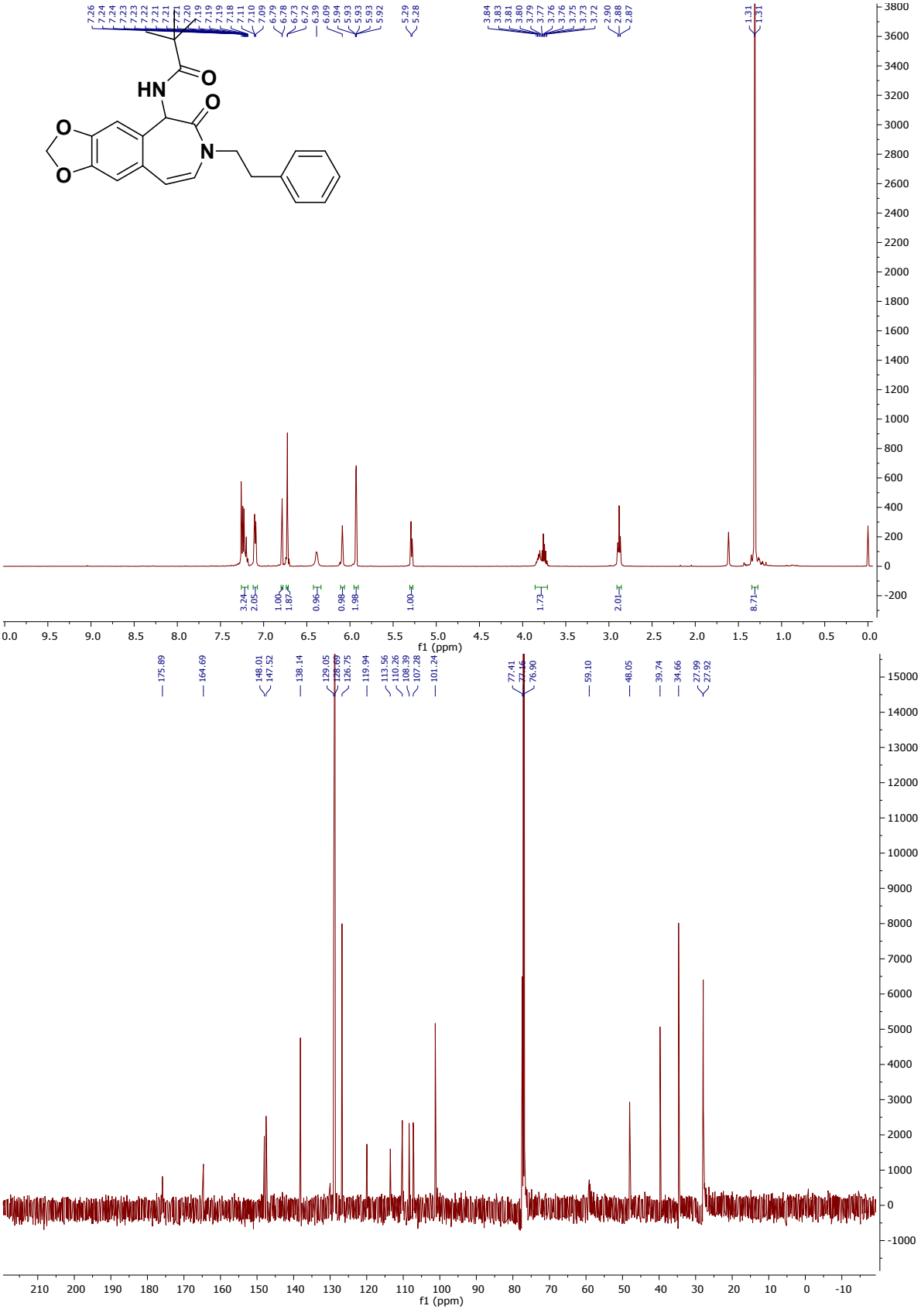
Chemical Formula: $C_{25}H_{30}N_2O_4$
Exact Mass: 422.2206
Molecular Weight: 422.5250

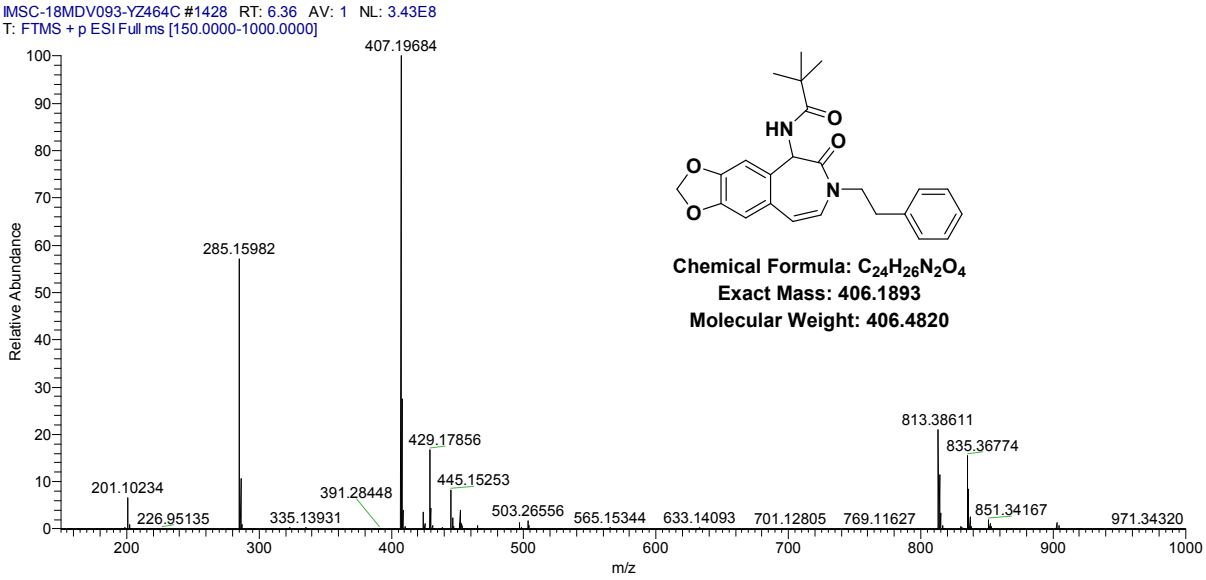
8c: *N*-(6,8-dimethoxy-2-oxo-3-phenethyl-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl)pivalamide



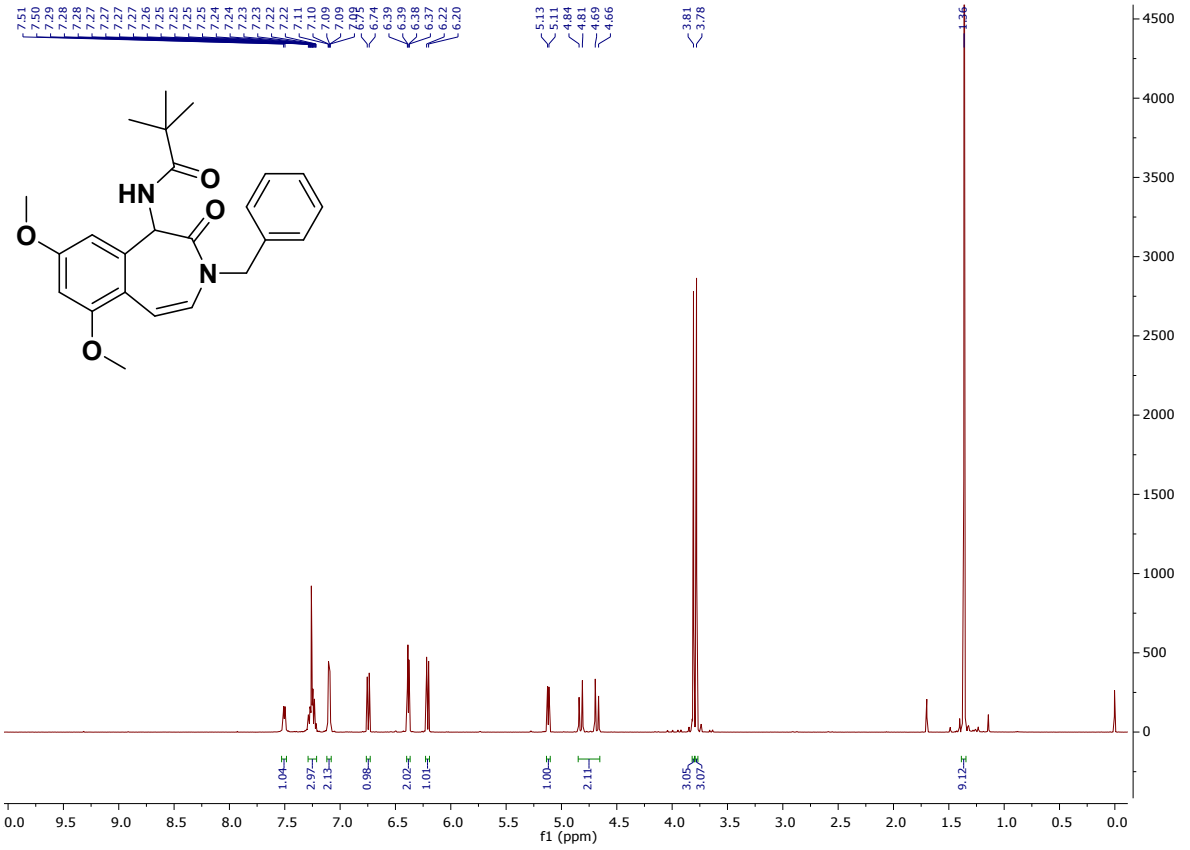

18mdv071-yz413C #12 RT: 0.20986 AV: 1 NL: 8.05E5
T: FTMS + p ESI Full ms [220.00-1000.00]
445.20963
423.22787
468.28561
283.19479
362.88675
513.19739
613.73145
711.25818
780.21942
867.43091
979.37769
Intensity
m/z
HN
O
O
O
N
O
Chemical Formula: C25H30N2O4
Exact Mass: 422.2206
Molecular Weight: 422.5250

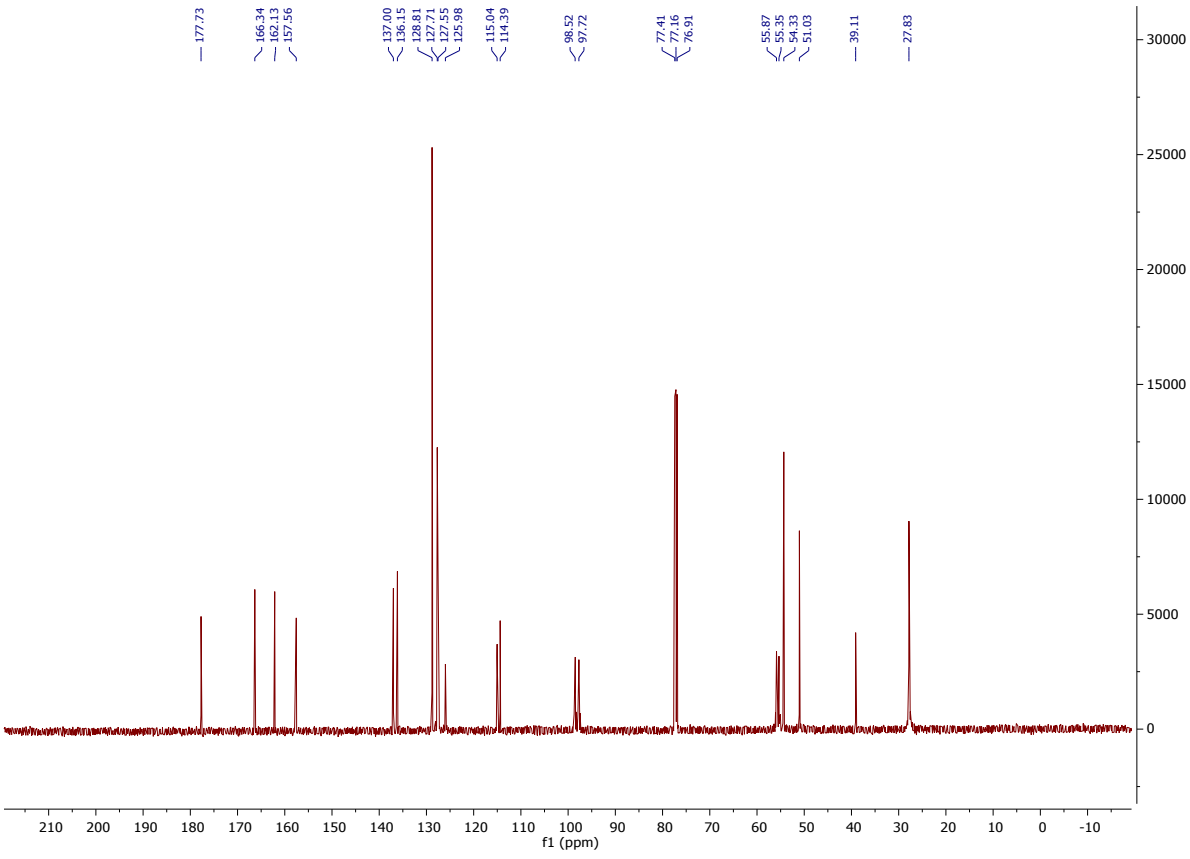
8d: *N*-(6-oxo-7-phenethyl-6,7-dihydro-5*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*]azepin-5-yl)pivalamide

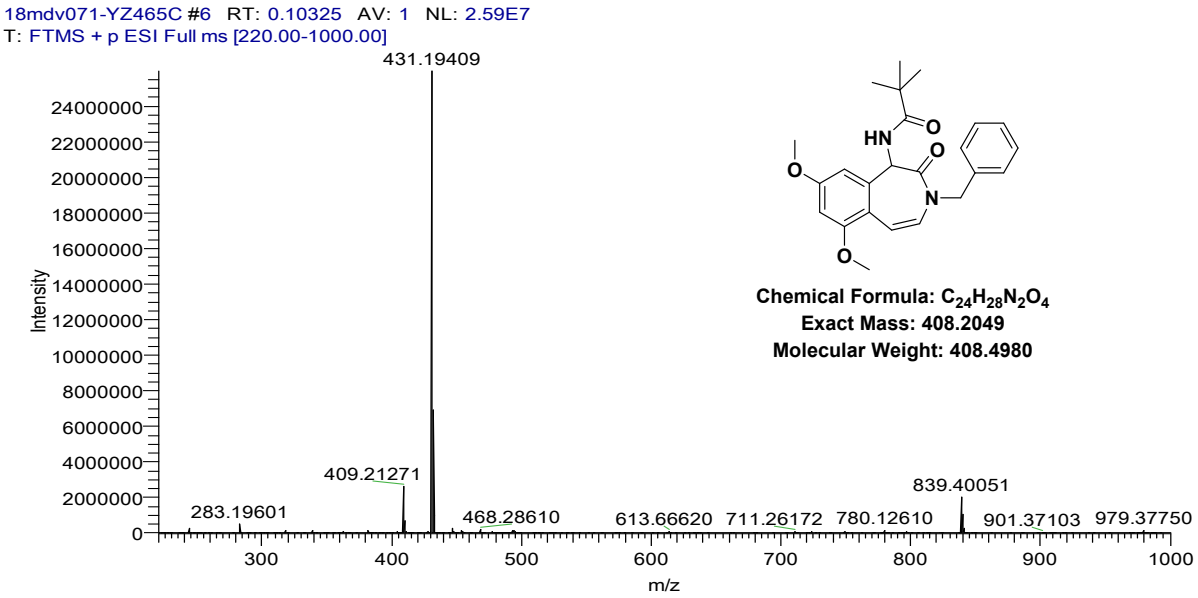



IMSC-18MDV093-YZ464C #1428 RT: 6.36 AV: 1 NL: 3.43E8
T: FTMS + p ESI Full ms [150.0000-1000.0000]
Relative Abundance
m/z
407.19684
285.15982
429.17856
445.15253
391.28448
201.10234
226.95135
335.13931
503.26556
565.15344
633.14093
701.12805
769.11627
813.38611
835.36774
851.34167
971.34320
HN
O
O
O
O
N
Chemical Formula: C24H26N2O4
Exact Mass: 406.1893
Molecular Weight: 406.4820

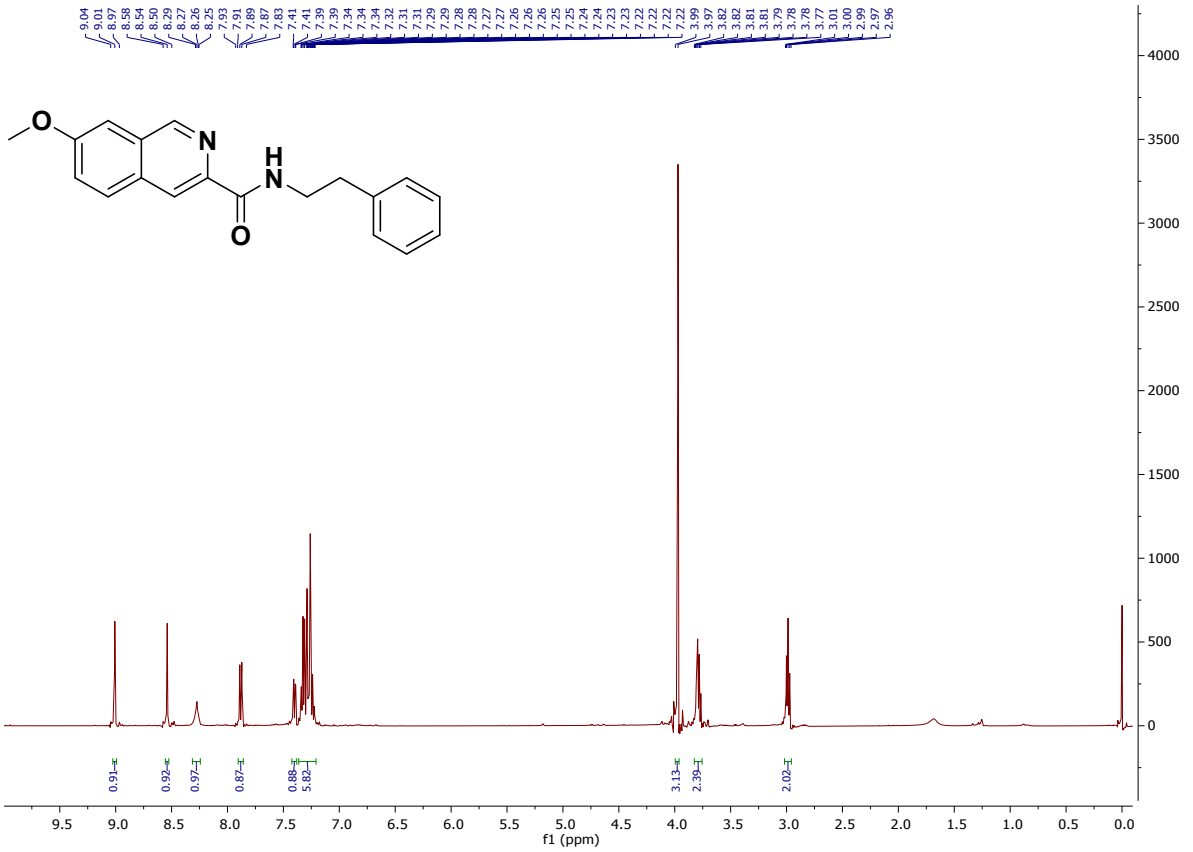
8e: *N*-(3-benzyl-6,8-dimethoxy-2-oxo-2,3-dihydro-1*H*-benzo[*d*]azepin-1-yl)pivalamide

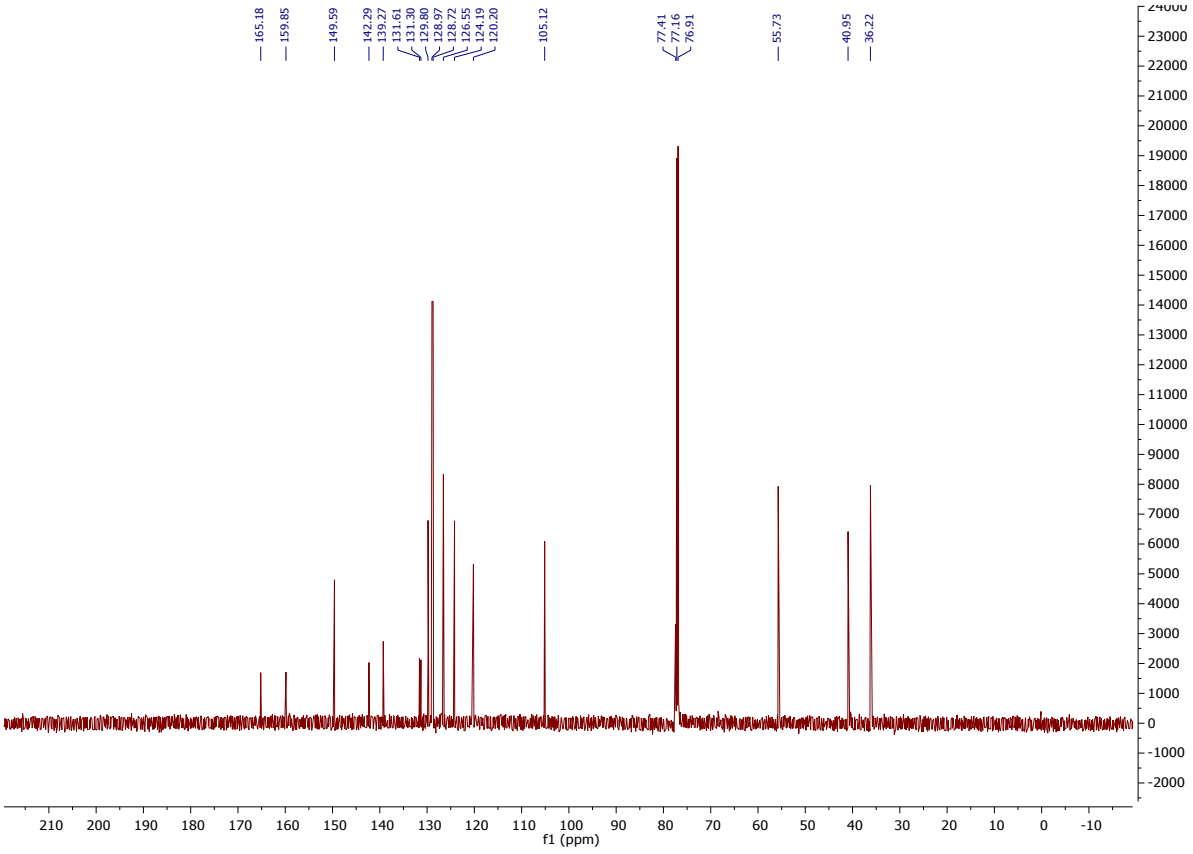


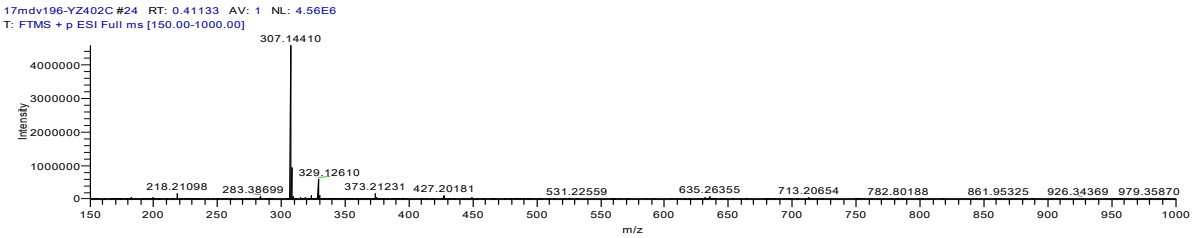


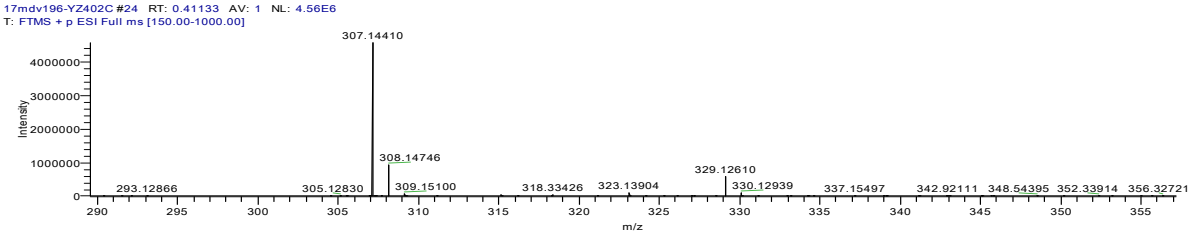

18mdv071-YZ465C #6 RT: 0.10325 AV: 1 NL: 2.59E7
T: FTMS + p ESI Full ms [220.00-1000.00]
431.19409
409.21271
283.19601
468.28610
613.66620
711.26172
780.12610
839.40051
901.37103
979.37750
Intensity
m/z
HN
O
O
O
N
O
Chemical Formula: C24H28N2O4
Exact Mass: 408.2049
Molecular Weight: 408.4980

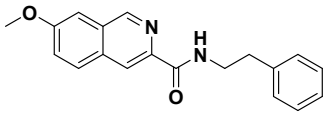
10a: 5-methoxy-*N*-phenethylisoquinoline-3-carboxamide





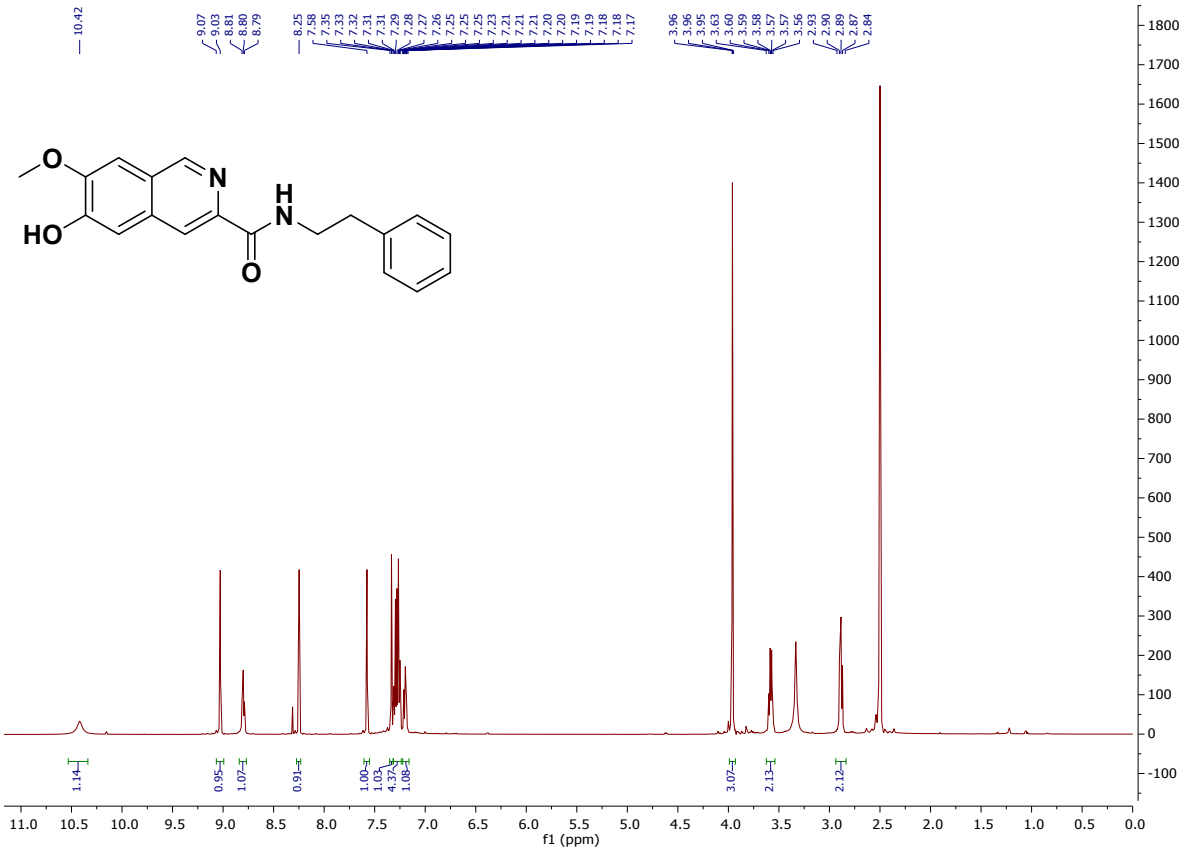


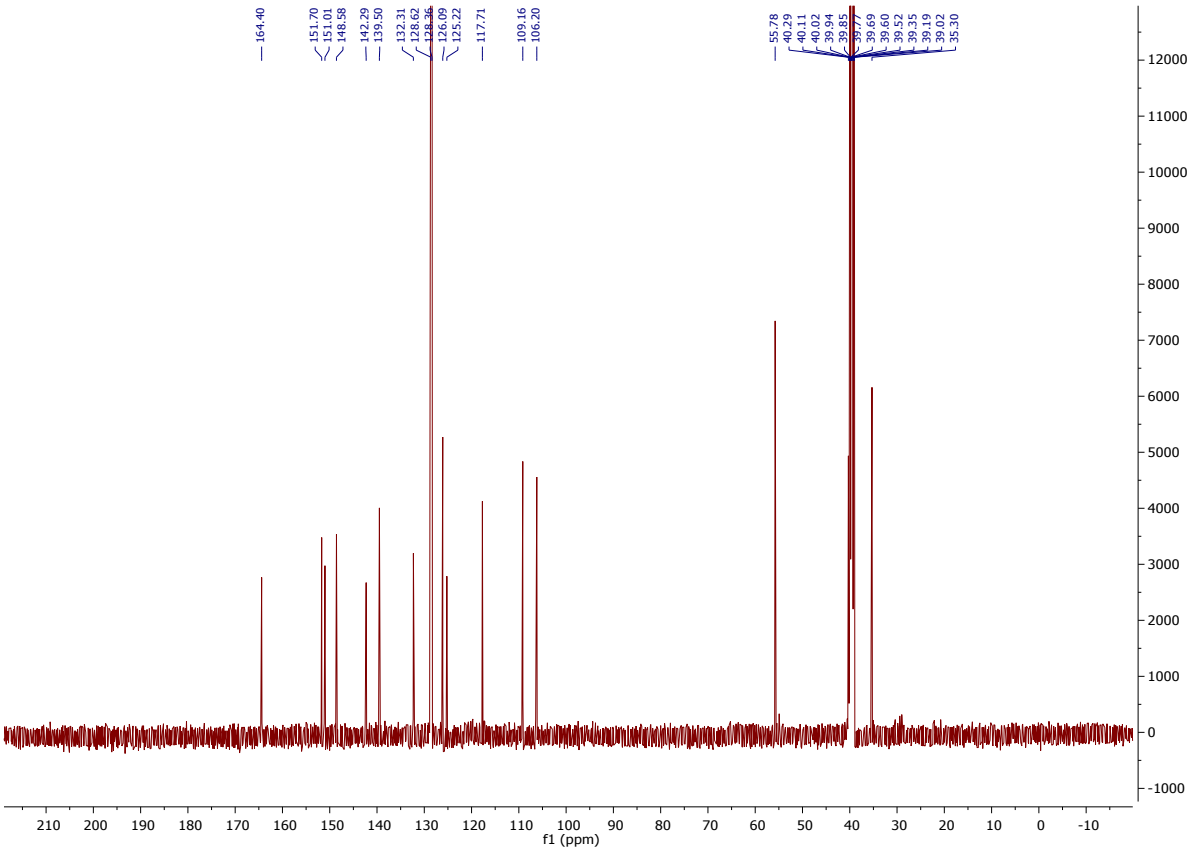


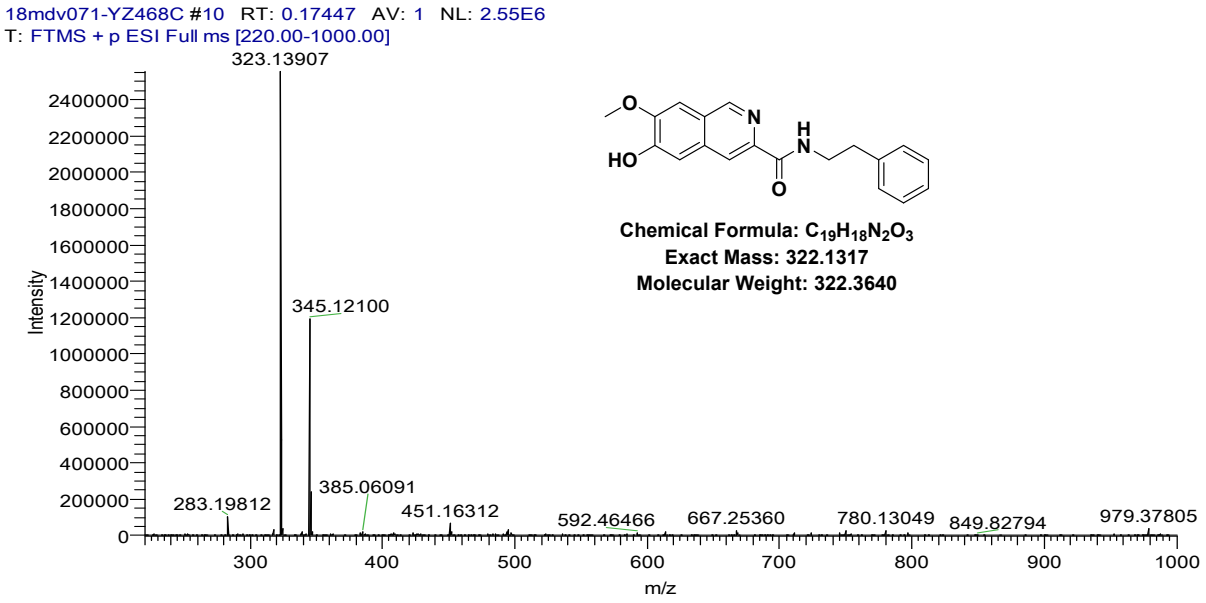


Chemical Formula: $C_{19}H_{18}N_2O_2$
Exact Mass: 306,14
Molecular Weight: 306,37

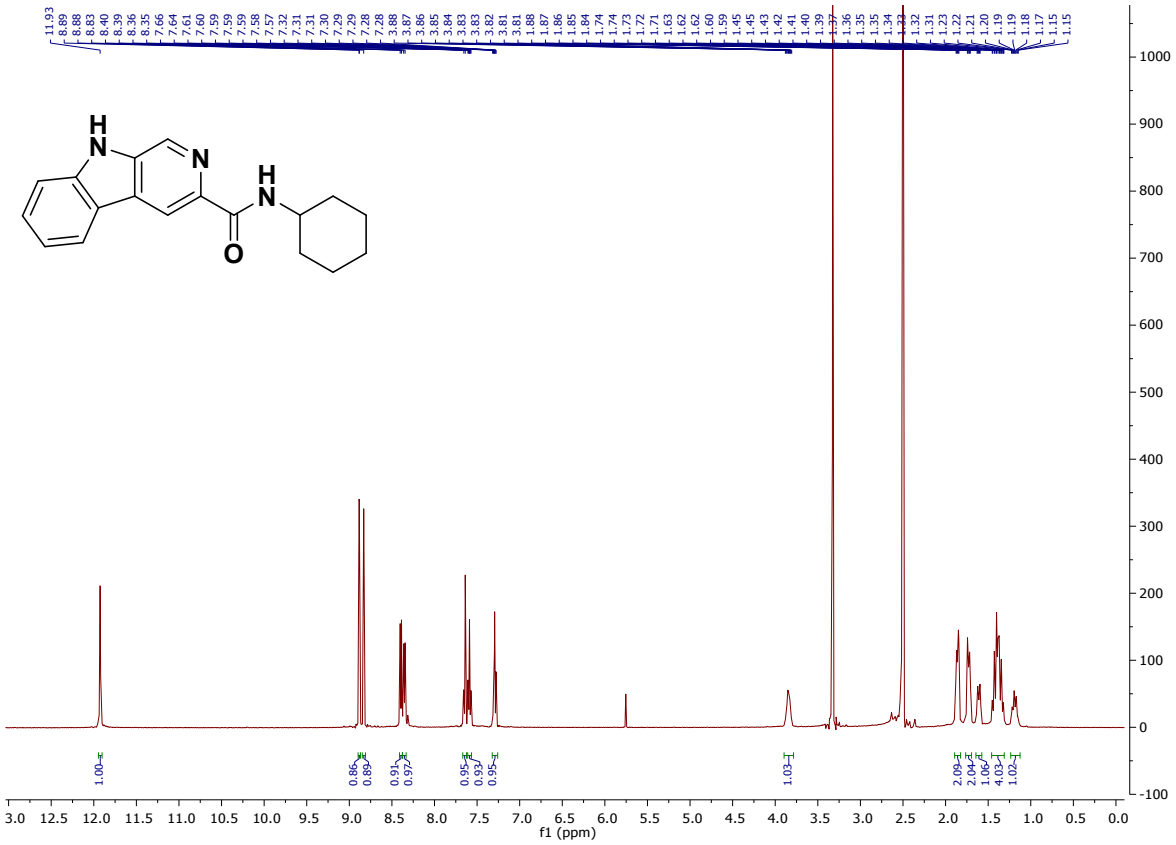
10b: 6-hydroxy-7-methoxy-*N*-phenethylisoquinoline-3-carboxamide

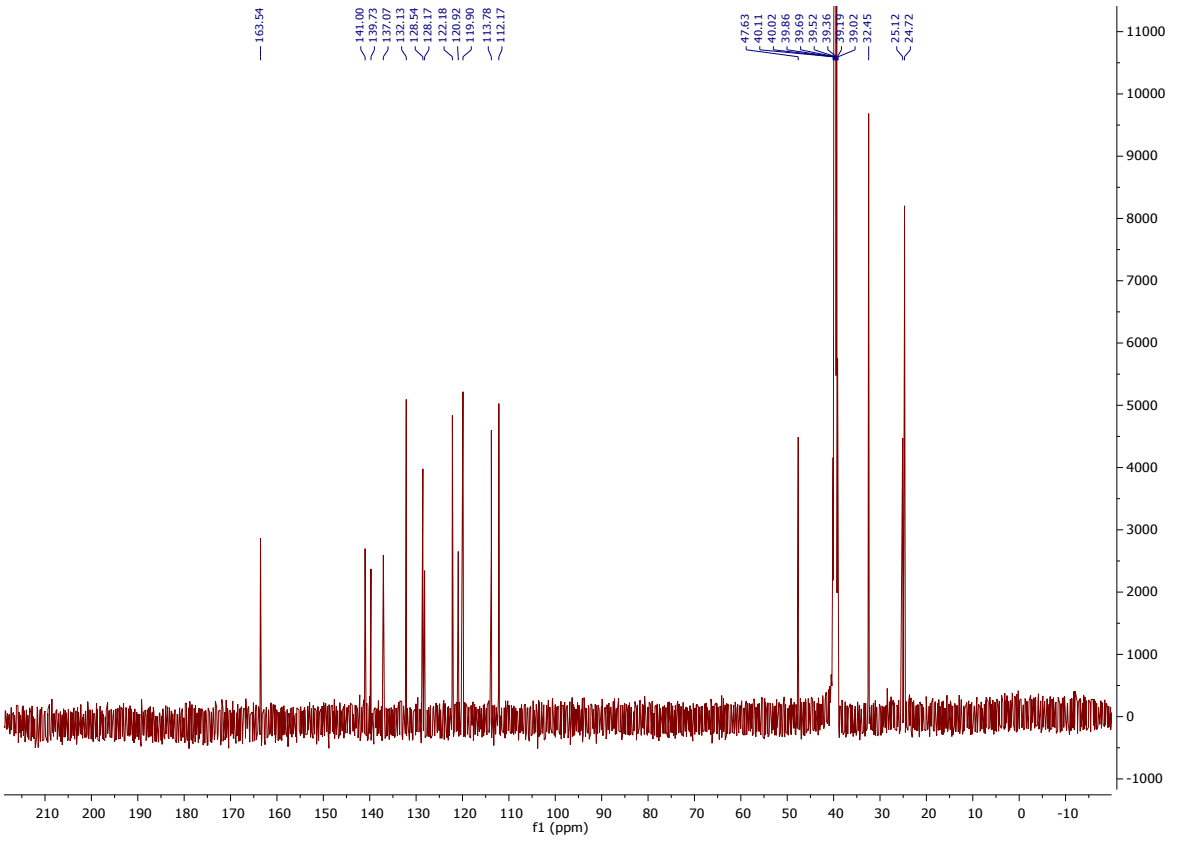


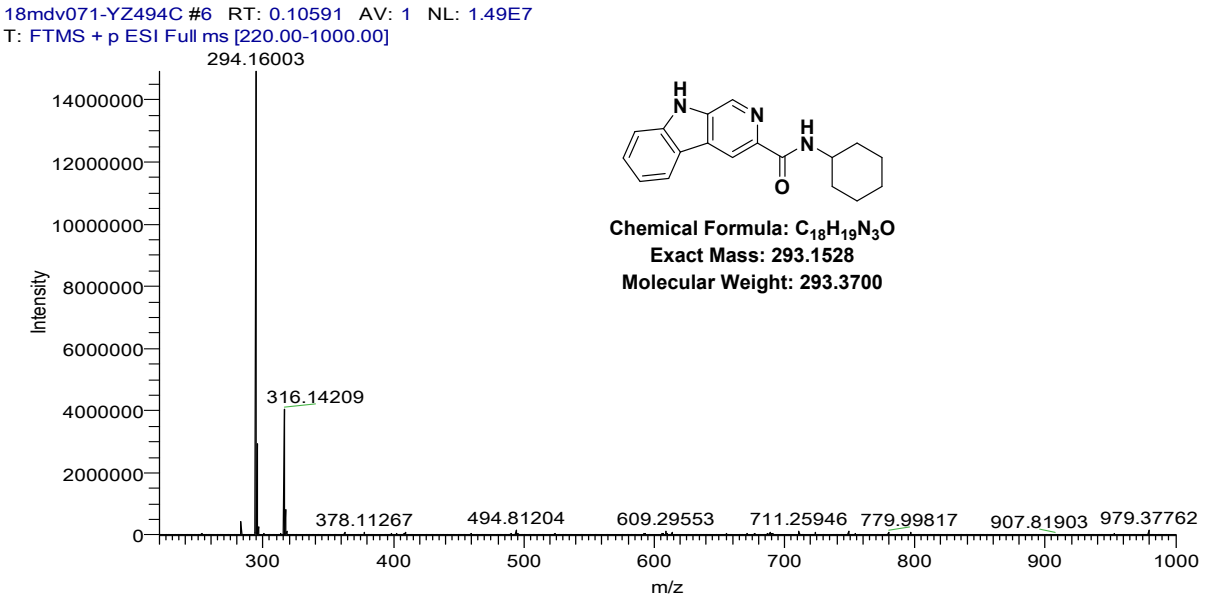



18mdv071-YZ468C #10 RT: 0.17447 AV: 1 NL: 2.55E6
T: FTMS + p ESI Full ms [220.00-1000.00]
323.13907
345.12100
385.06091
283.19812
451.16312
592.46466
667.25360
780.13049
849.82794
979.37805
Intensity
m/z
Chemical Formula: C19H18N2O3
Exact Mass: 322.1317
Molecular Weight: 322.3640

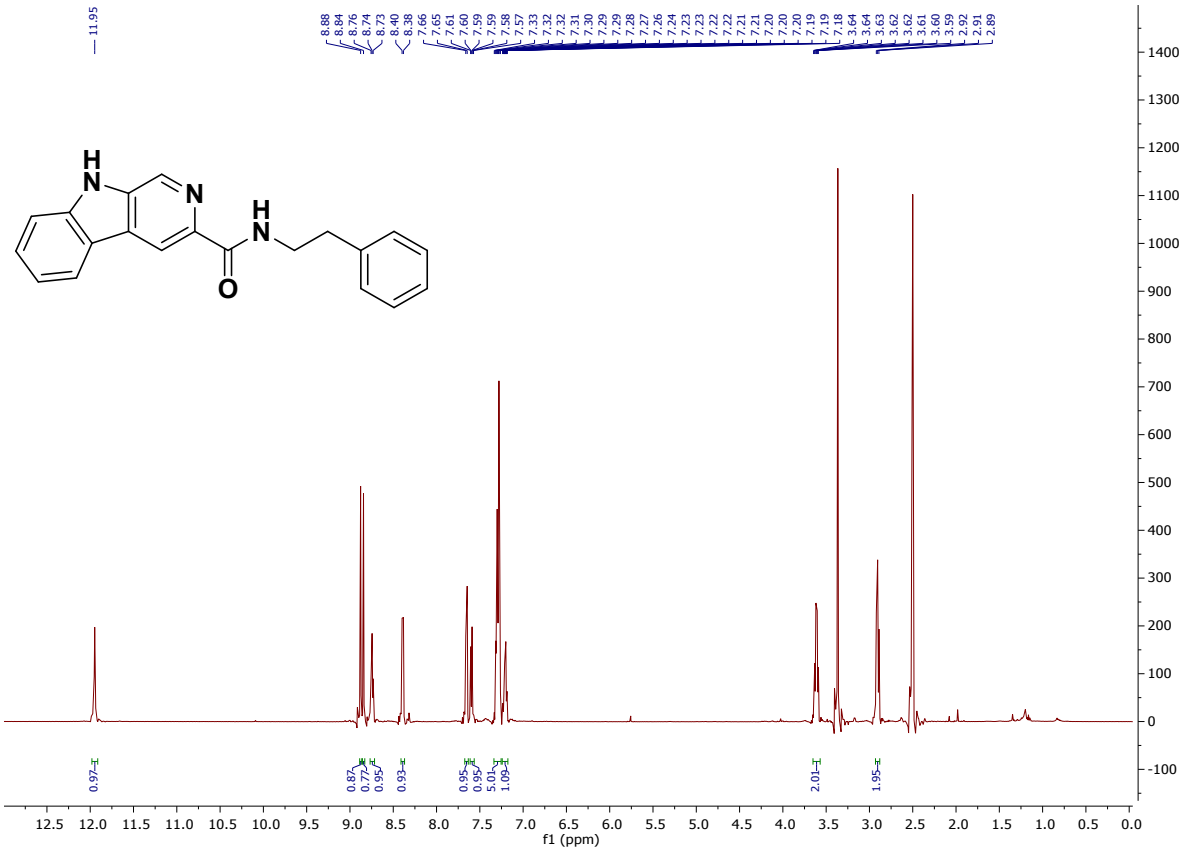
10c: *N*-cyclohexyl-9*H*-pyrido[3,4-*b*]indole-3-carboxamide

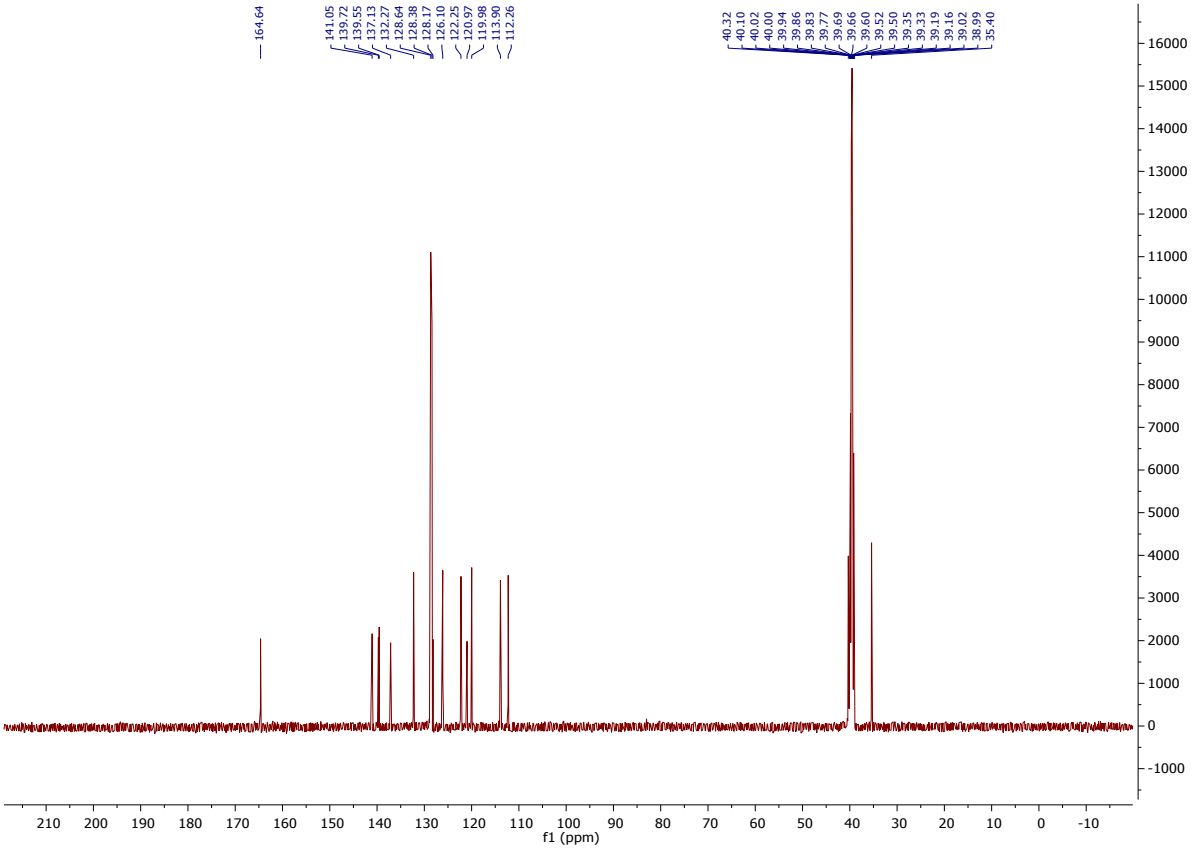


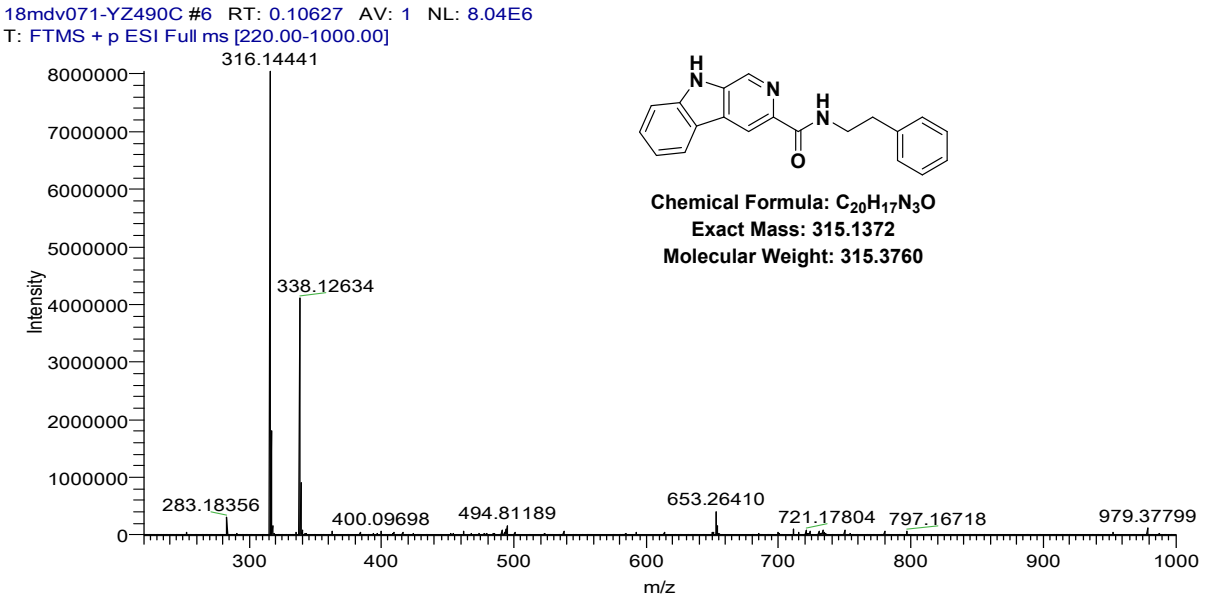



18mdv071-YZ494C #6 RT: 0.10591 AV: 1 NL: 1.49E7
T: FTMS + p ESI Full ms [220.00-1000.00]
294.16003
316.14209
378.11267
494.81204
609.29553
711.25946
779.99817
907.81903
979.37762
Intensity
m/z
Chemical Formula: C18H19N3O
Exact Mass: 293.1528
Molecular Weight: 293.3700

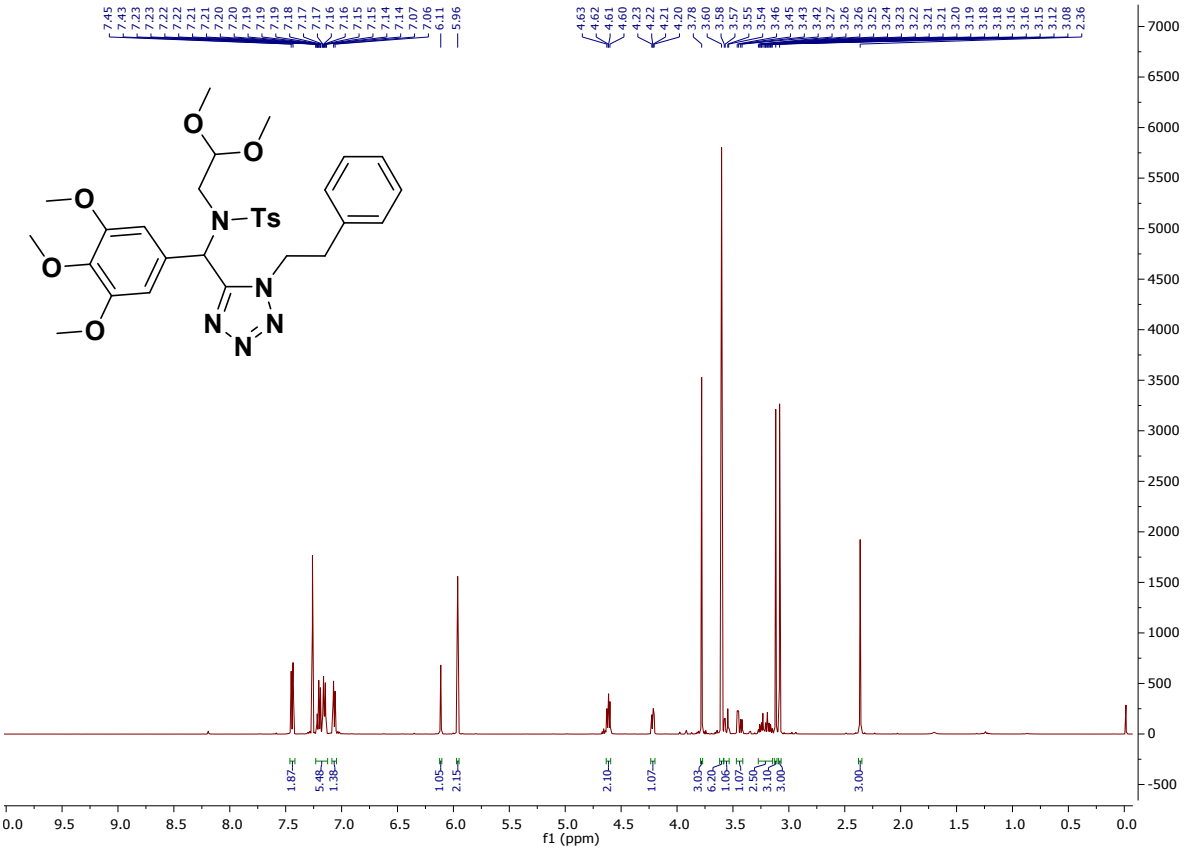
10d: *N*-phenethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxamide

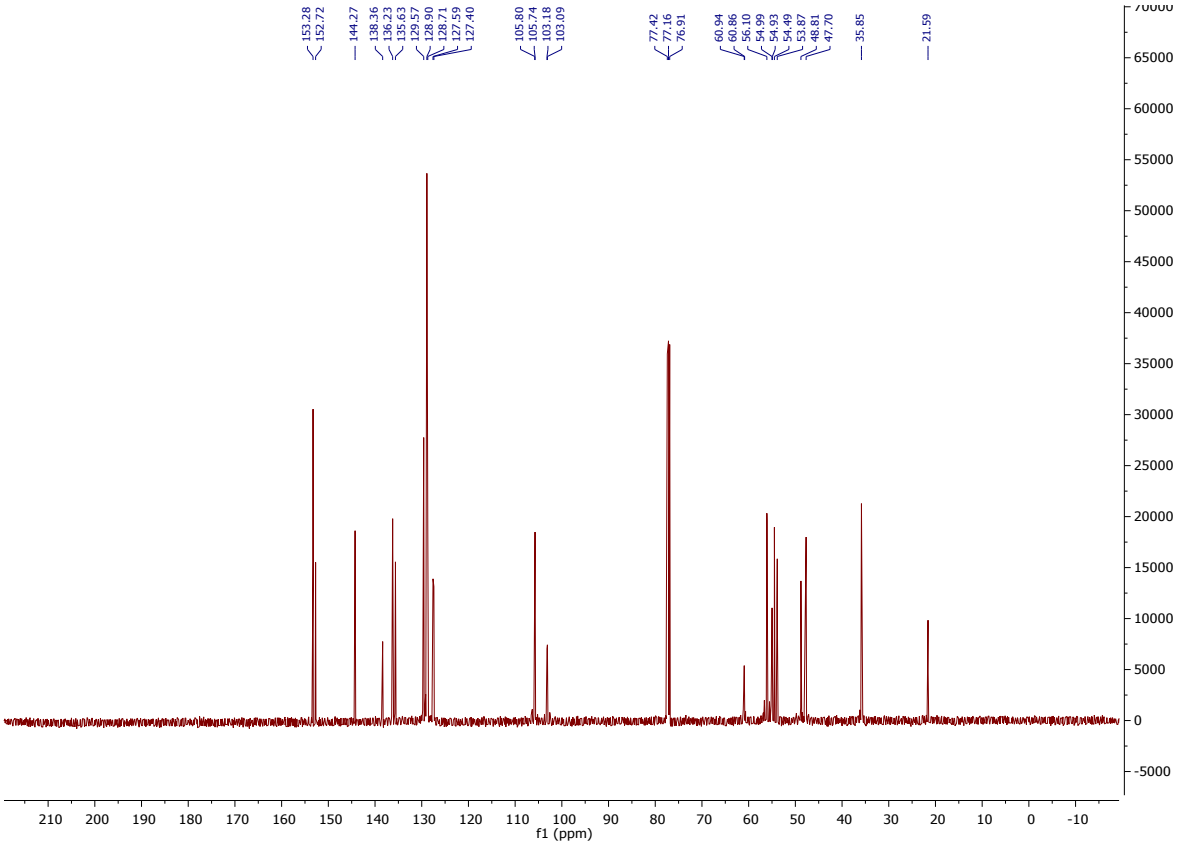


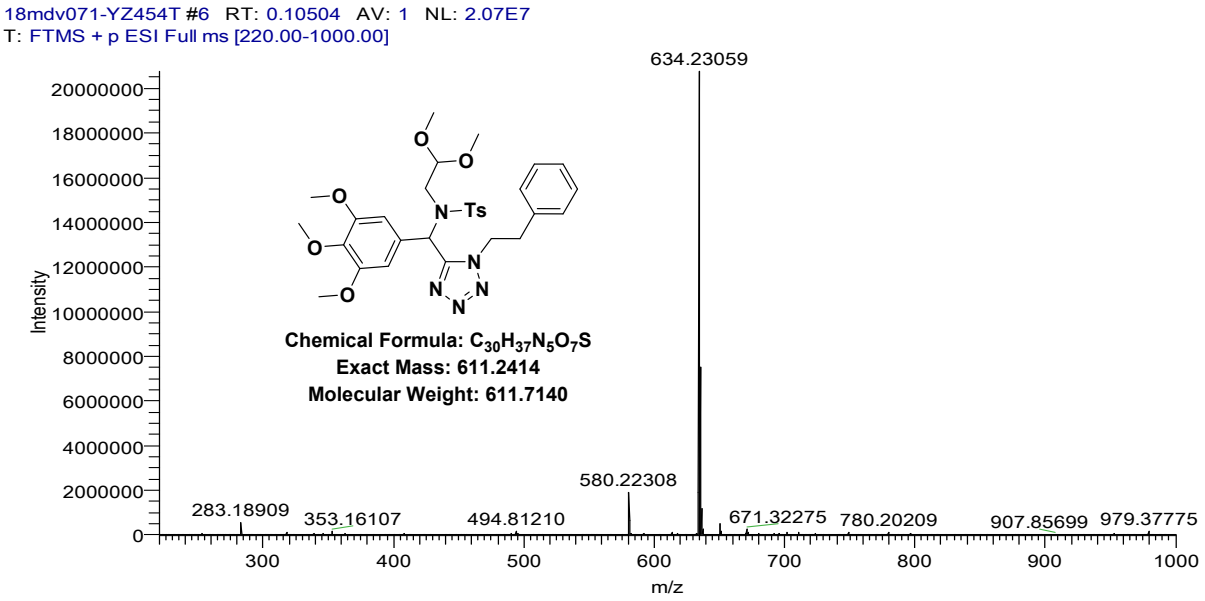



18mdv071-YZ490C #6 RT: 0.10627 AV: 1 NL: 8.04E6
T: FTMS + p ESI Full ms [220.00-1000.00]
316.14441
338.12634
283.18356
400.09698
494.81189
653.26410
721.17804
797.16718
979.37799
Intensity
m/z
Chemical Formula: C20H17N3O
Exact Mass: 315.1372
Molecular Weight: 315.3760

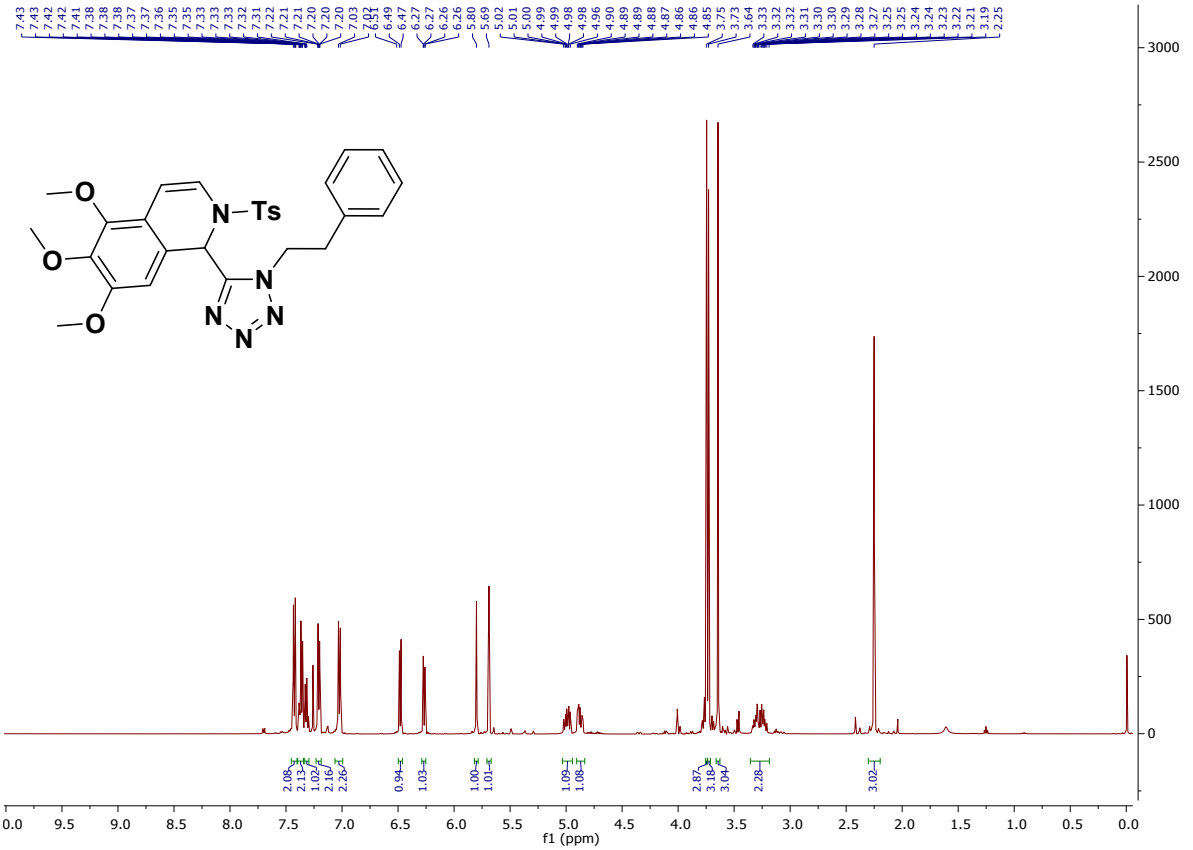
12a: *N*-(2,2-dimethoxyethyl)-4-methyl-*N*-((1-phenethyl-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methyl)benzenesulfonamide

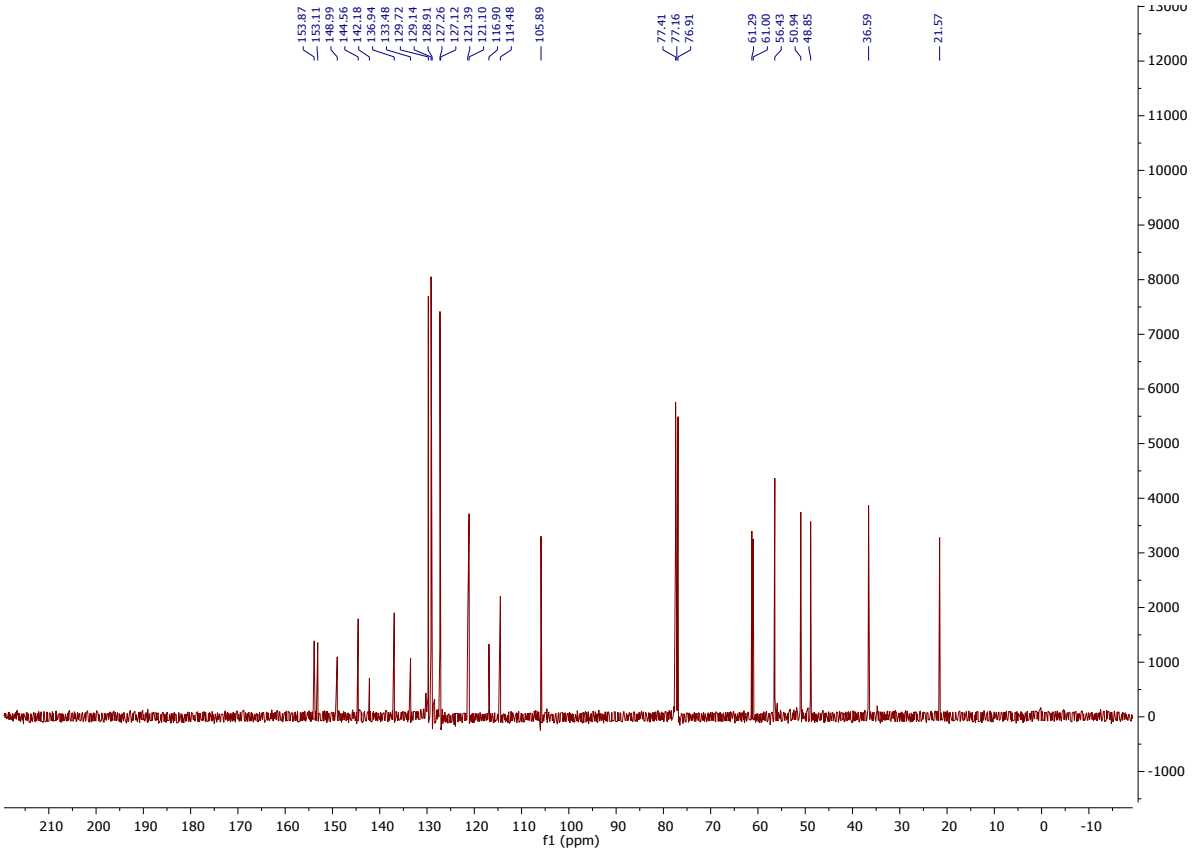


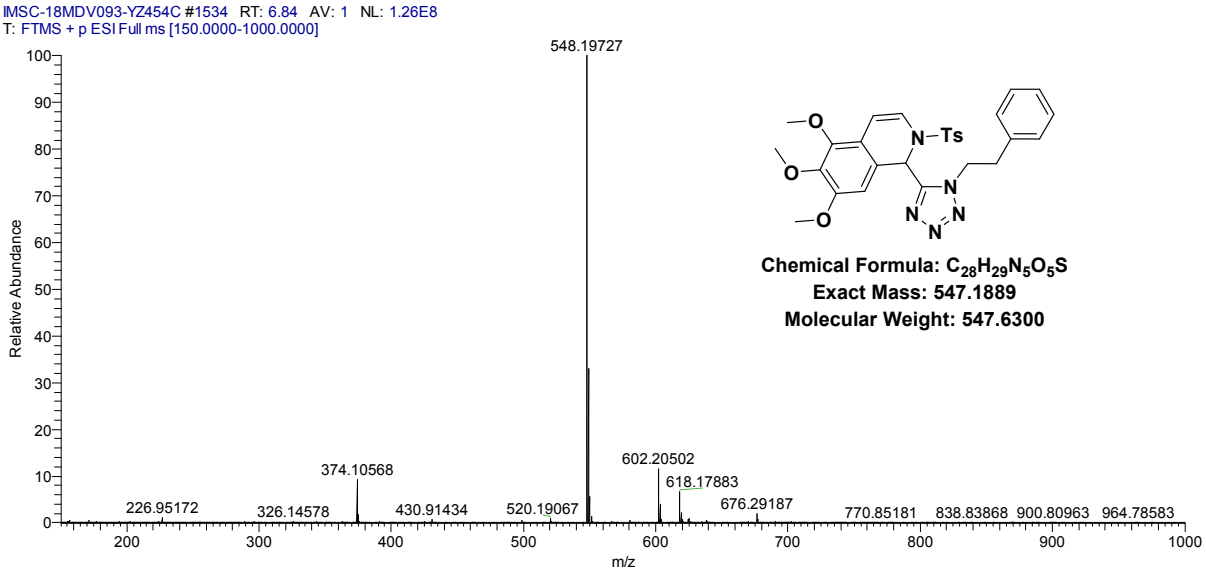



18mdv071-YZ454T #6 RT: 0.10504 AV: 1 NL: 2.07E7
T: FTMS + p ESI Full ms [220.00-1000.00]
634.23059
Intensity
20000000
18000000
16000000
14000000
12000000
10000000
8000000
6000000
4000000
2000000
0
Chemical Formula: C30H37N5O7S
Exact Mass: 611.2414
Molecular Weight: 611.7140
580.22308
283.18909
353.16107
494.81210
671.32275
780.20209
907.85699
979.37775
300
400
500
600
700
800
900
1000
m/z

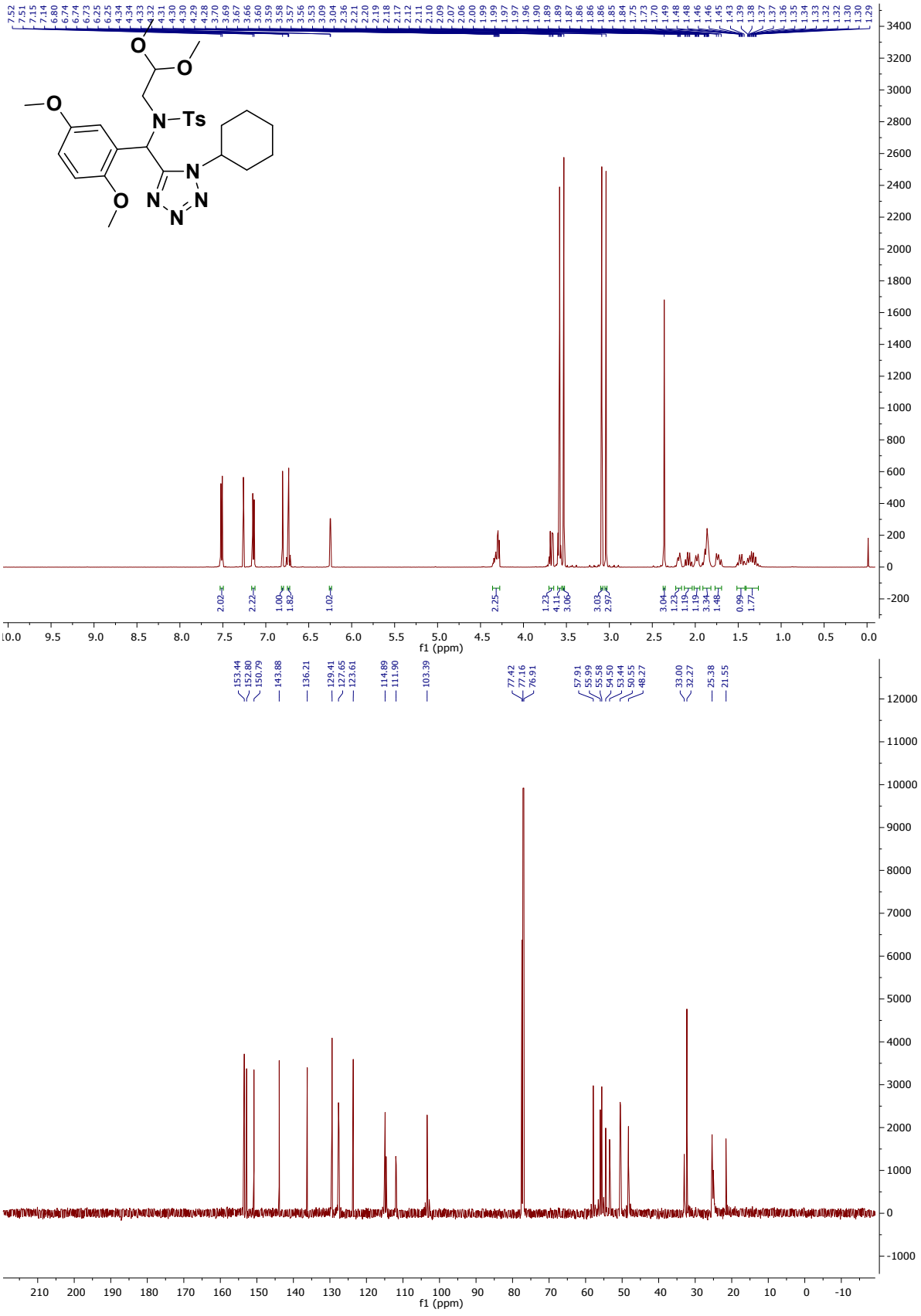
13a: 5,6,7-trimethoxy-1-(1-phenethyl-1*H*-tetrazol-5-yl)-2-tosyl-1,2-dihydroisoquinoline



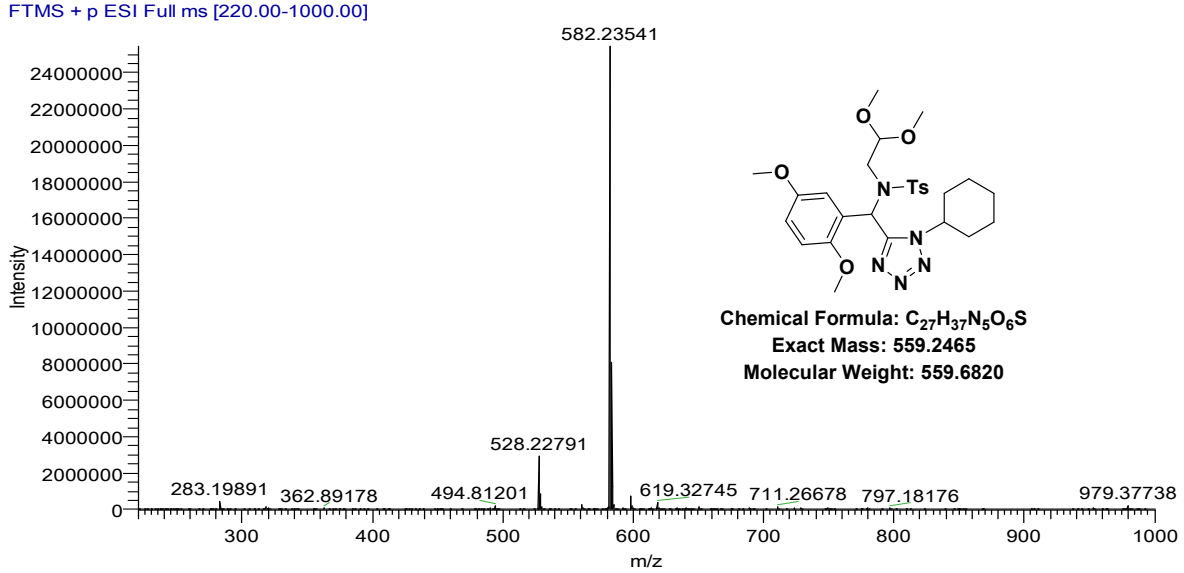



IMSC-18MDV093-YZ454C #1534 RT: 6.84 AV: 1 NL: 1.26E8
T: FTMS + p ESI Full ms [150.0000-1000.0000]
548.19727
Relative Abundance
m/z
374.10568
602.20502
618.17883
226.95172
326.14578
430.91434
520.19067
676.29187
770.85181
838.83868
900.80963
964.78583
N–Ts
Chemical Formula: C28H29N5O5S
Exact Mass: 547.1889
Molecular Weight: 547.6300

12b: *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(2,5-dimethoxyphenyl)methyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide

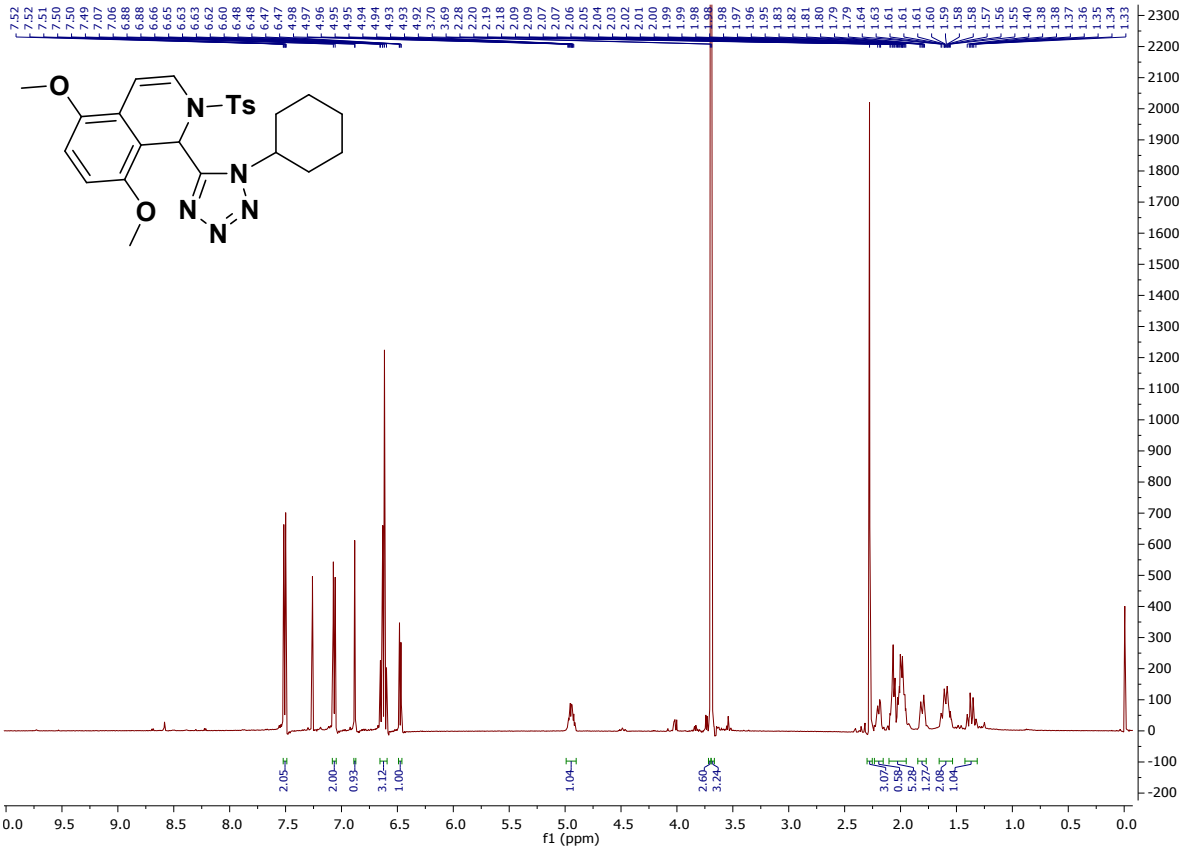


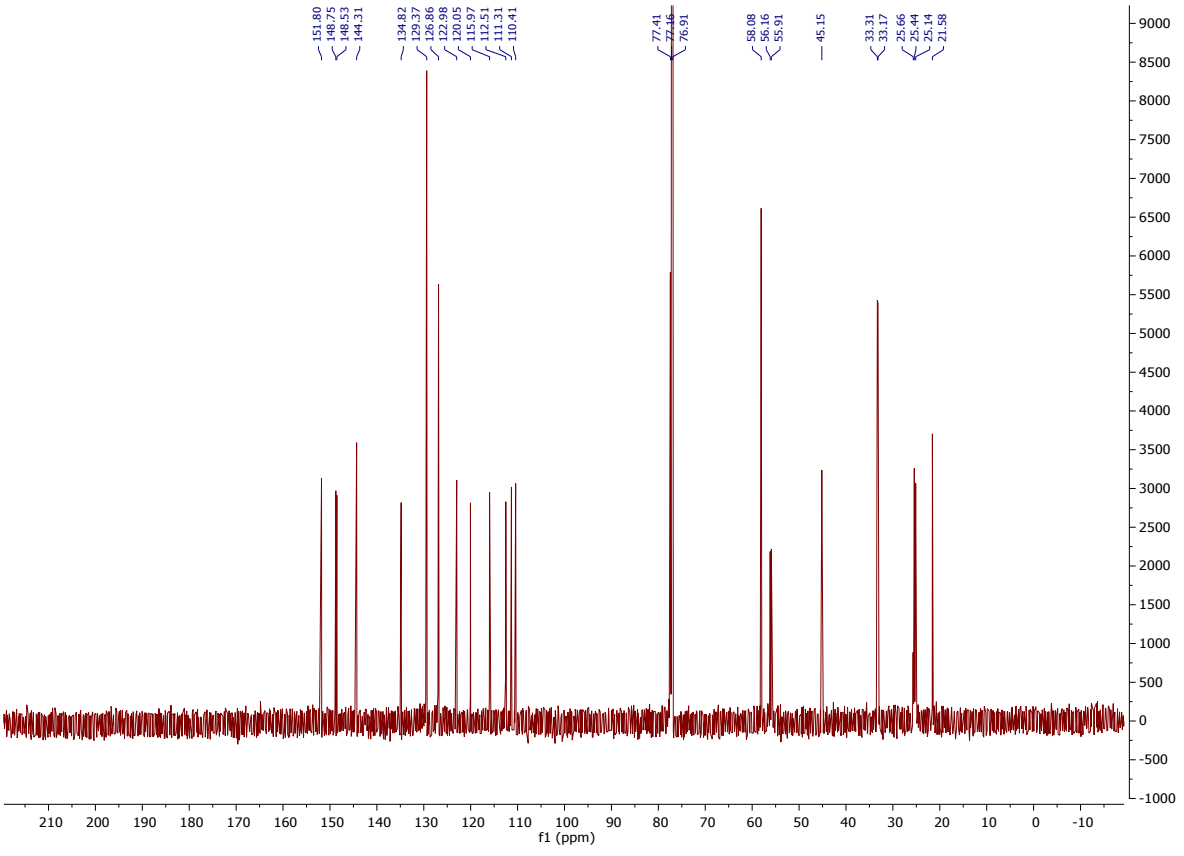
18mdv071-YZ381T #6 RT: 0.10197 AV: 1 NL: 2.54E7
T: FTMS + p ESI Full ms [220.00-1000.00]

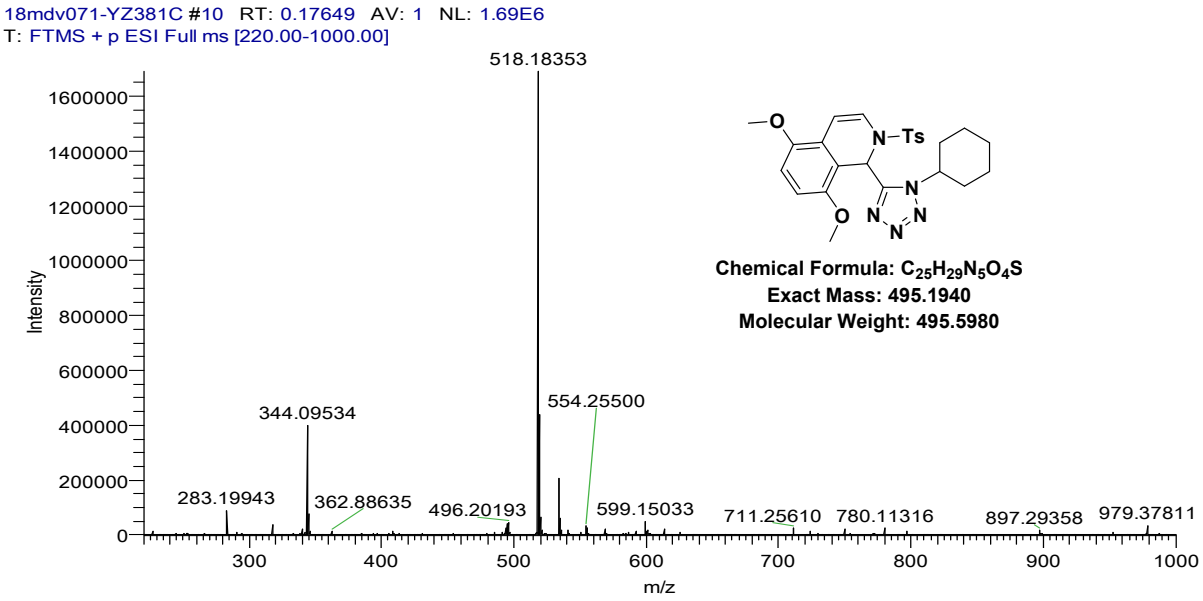


Chemical Formula: $C_{27}H_{37}N_5O_6S$
Exact Mass: 559.2465
Molecular Weight: 559.6820

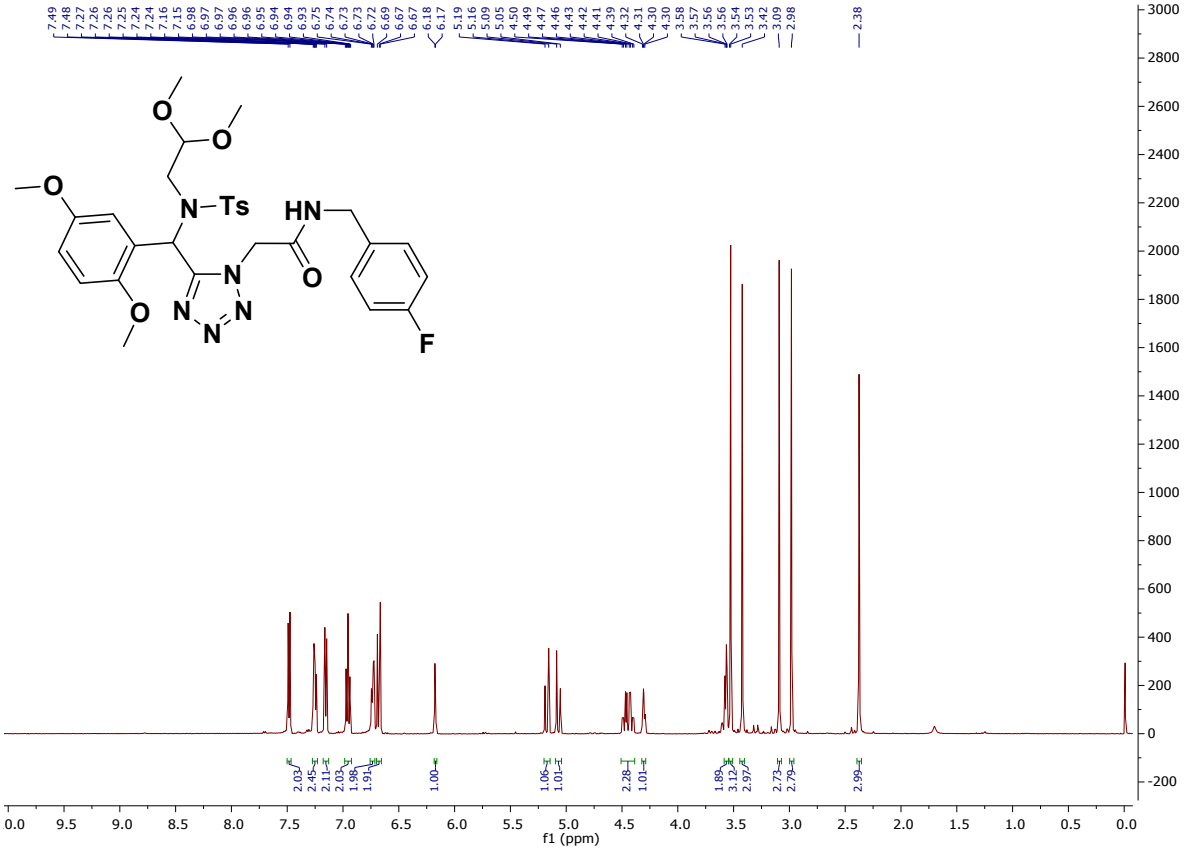
13b: 1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-5,8-dimethoxy-2-tosyl-1,2-dihydroisoquinoline

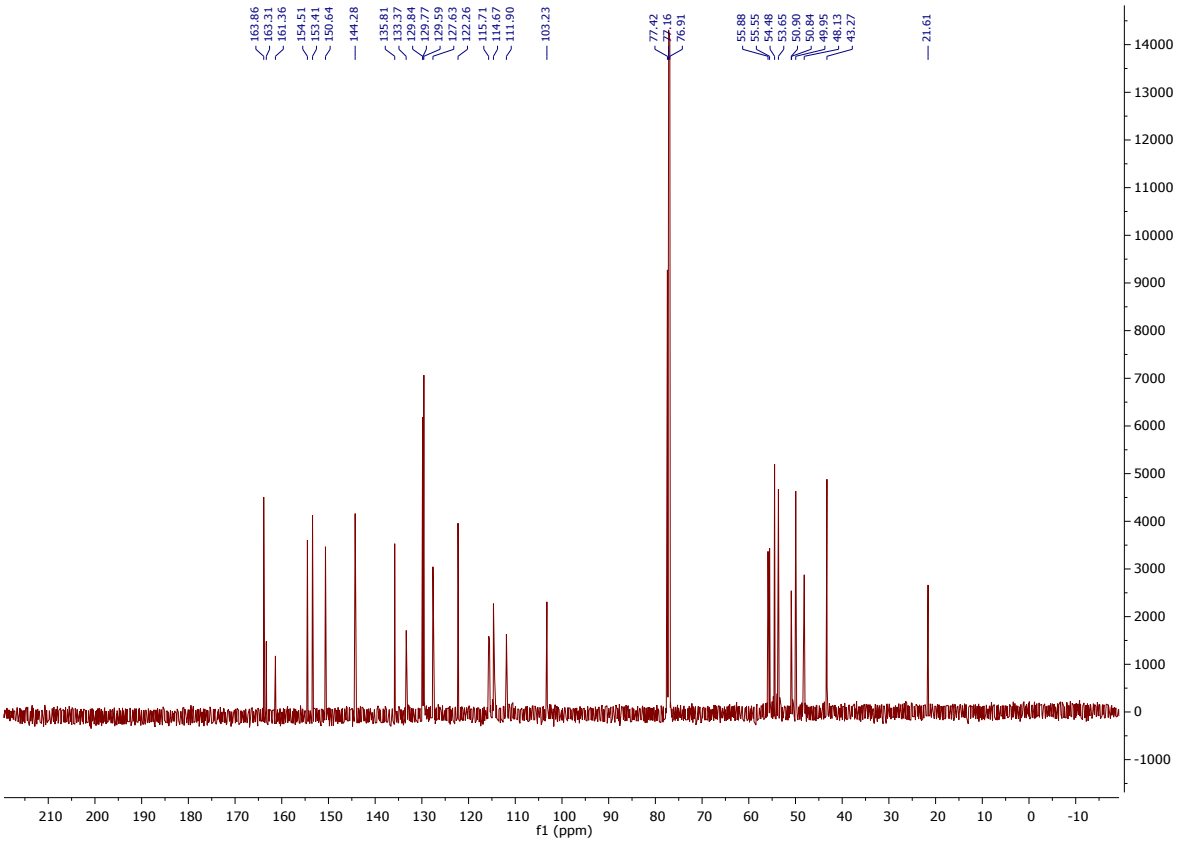


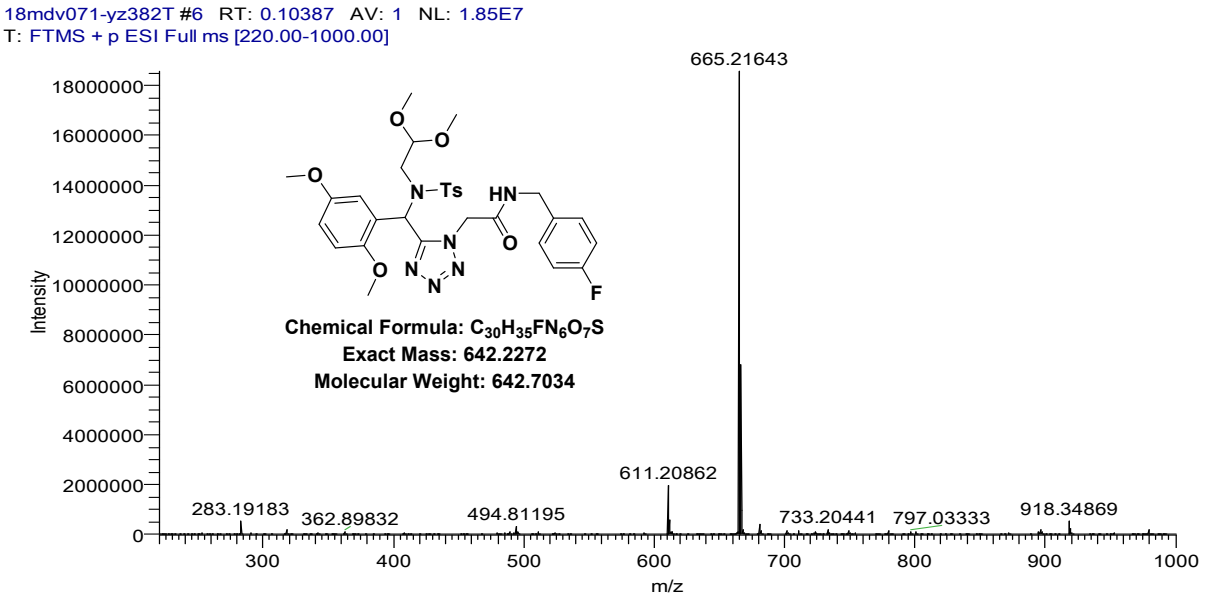



18mdv071-YZ381C #10 RT: 0.17649 AV: 1 NL: 1.69E6
T: FTMS + p ESI Full ms [220.00-1000.00]
518.18353
554.25500
344.09534
283.19943
362.88635
496.20193
599.15033
711.25610
780.11316
897.29358
979.37811
Intensity
m/z
Chemical Formula: C25H29N5O4S
Exact Mass: 495.1940
Molecular Weight: 495.5980

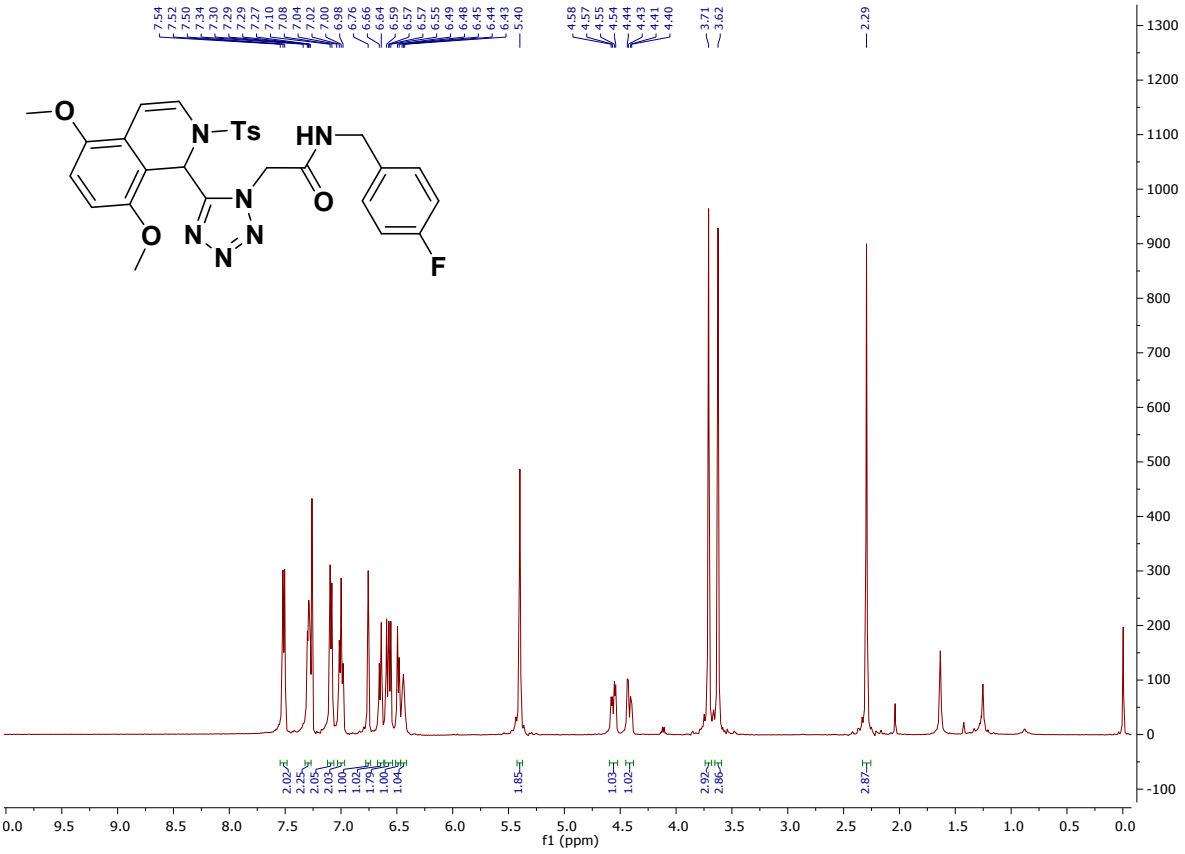
12c: 2-(5-(((*N*-(2,2-dimethoxyethyl)-4-methylphenyl)sulfonamido)(2,5-dimethoxyphenyl)methyl)-1H-tetrazol-1-yl)-*N*-(4-fluorobenzyl)acetamide

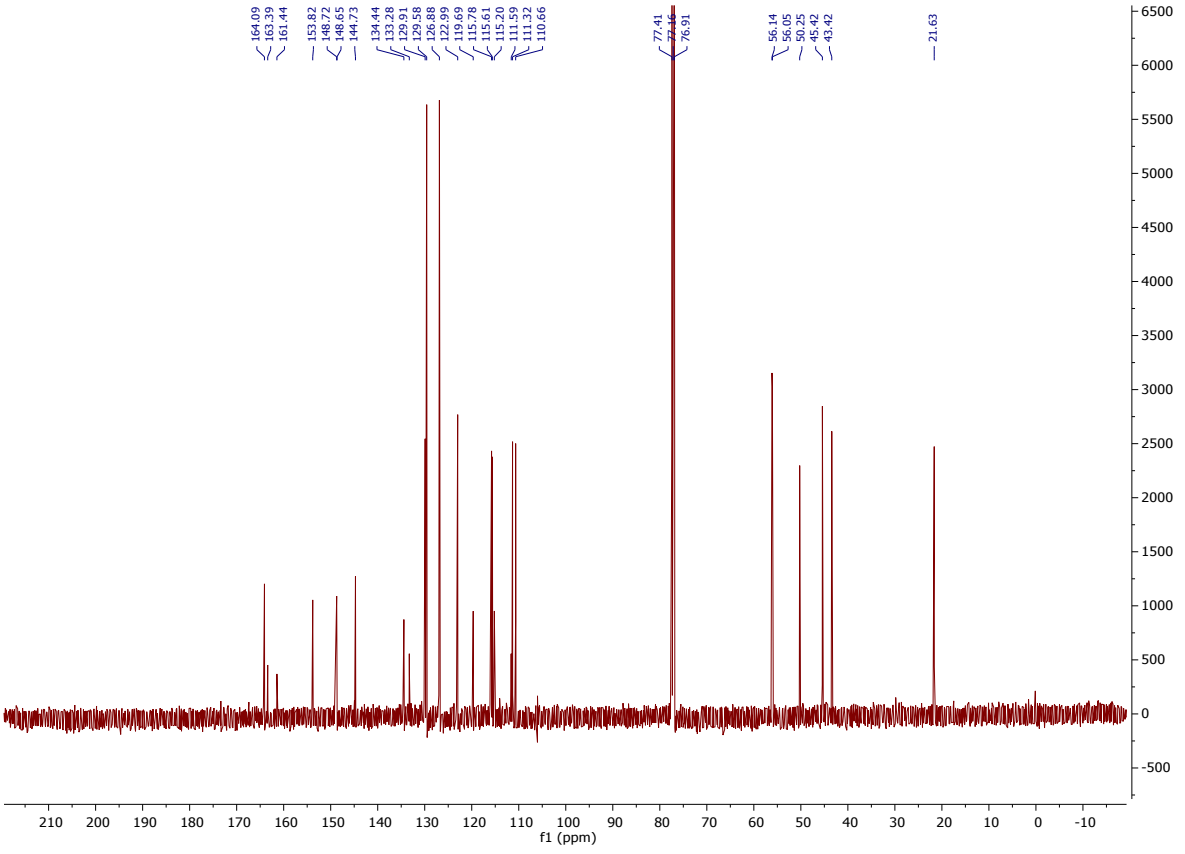


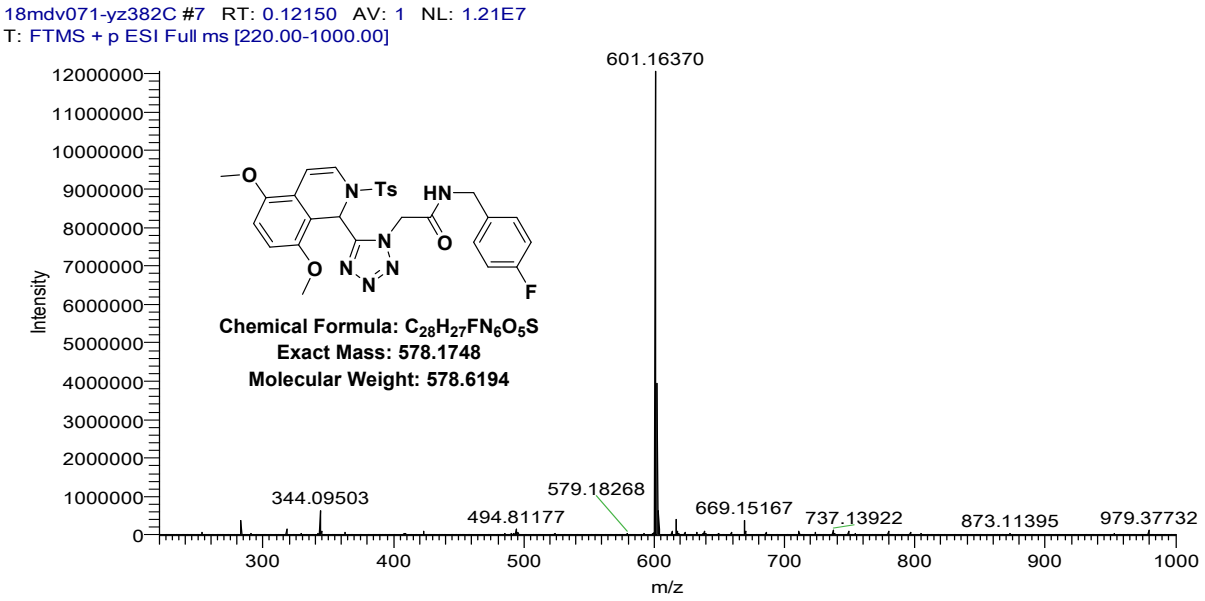



18mdv071-yz382T #6 RT: 0.10387 AV: 1 NL: 1.85E7
T: FTMS + p ESI Full ms [220.00-1000.00]
665.21643
611.20862
283.19183
362.89832
494.81195
733.20441
797.03333
918.34869
Intensity
m/z
Chemical Formula: C30H35FN6O7S
Exact Mass: 642.2272
Molecular Weight: 642.7034

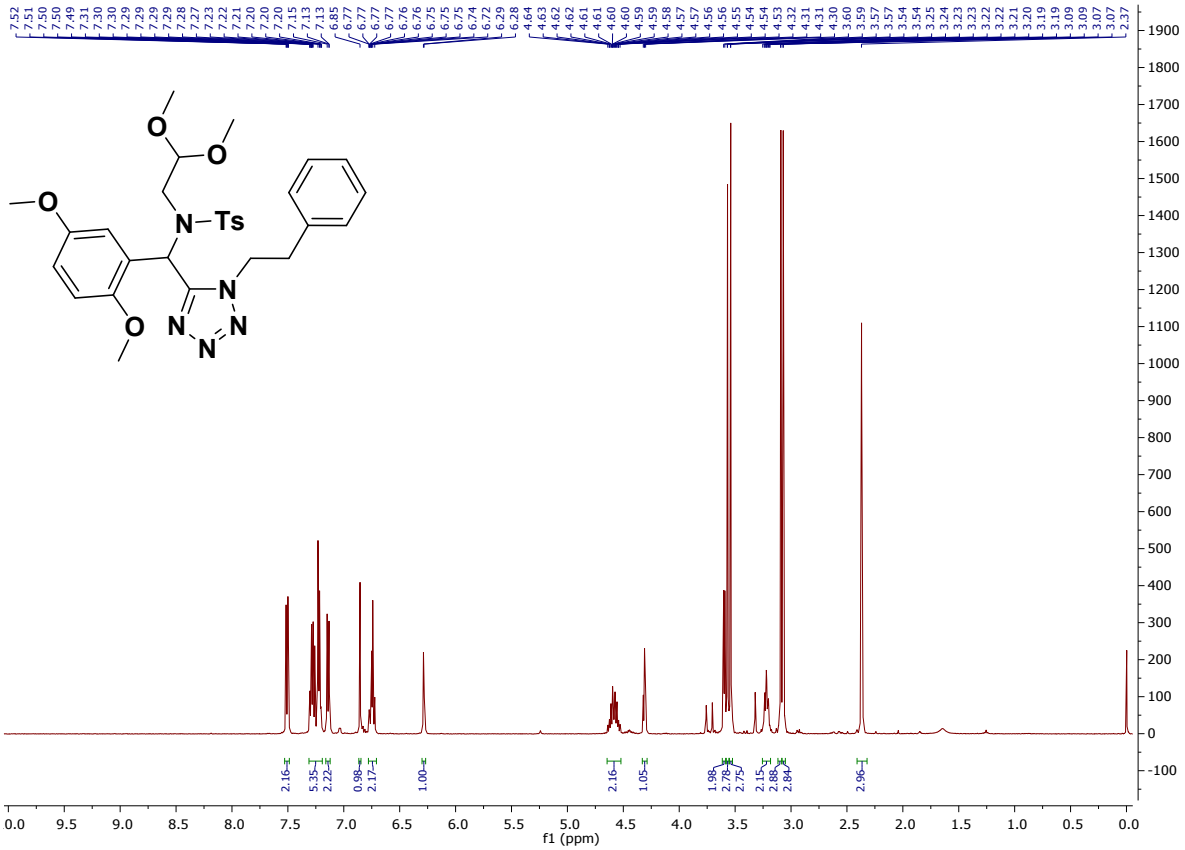
13c: 2-(5-(5,8-dimethoxy-2-tosyl-1,2-dihydroisoquinolin-1-yl)-1*H*-tetrazol-1-yl)-*N*-(4-fluorobenzyl)acetamide

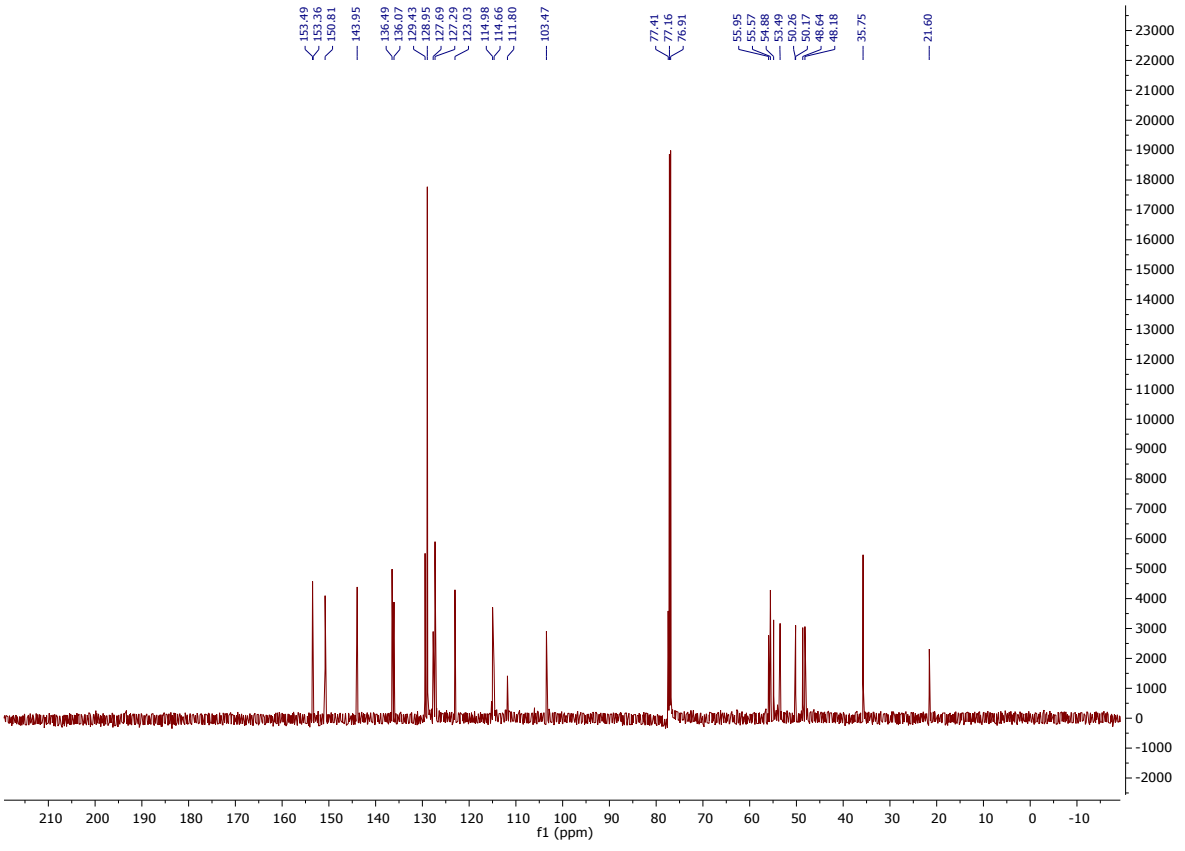


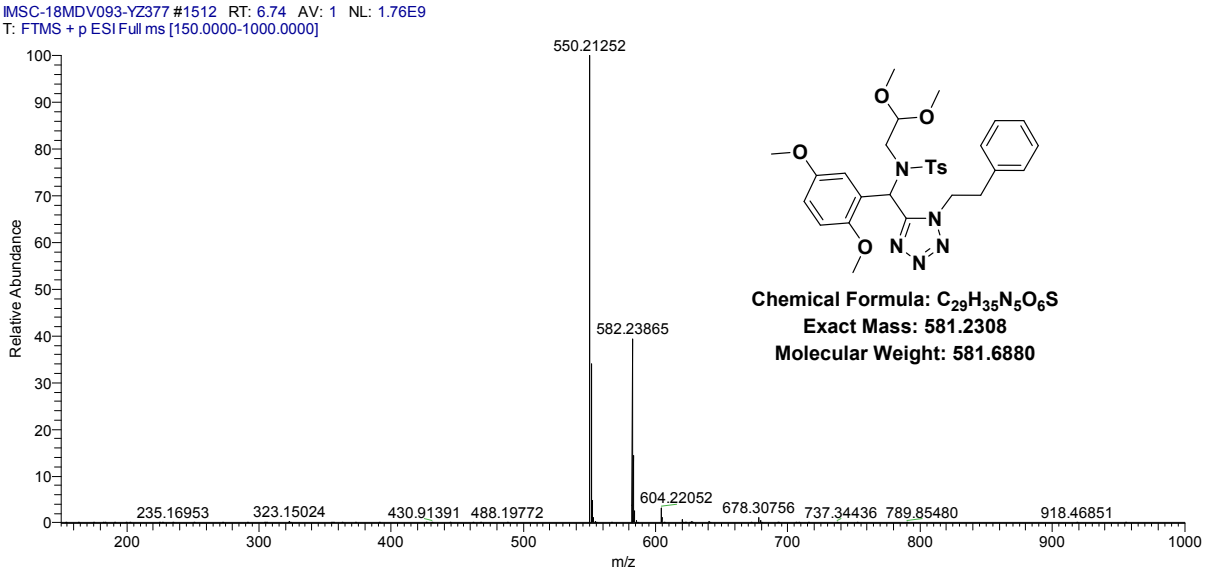



18mdv071-yz382C #7 RT: 0.12150 AV: 1 NL: 1.21E7
T: FTMS + p ESI Full ms [220.00-1000.00]
601.16370
Intensity
m/z
Chemical Formula: C28H27FN6O5S
Exact Mass: 578.1748
Molecular Weight: 578.6194
344.09503
494.81177
579.18268
669.15167
737.13922
873.11395
979.37732

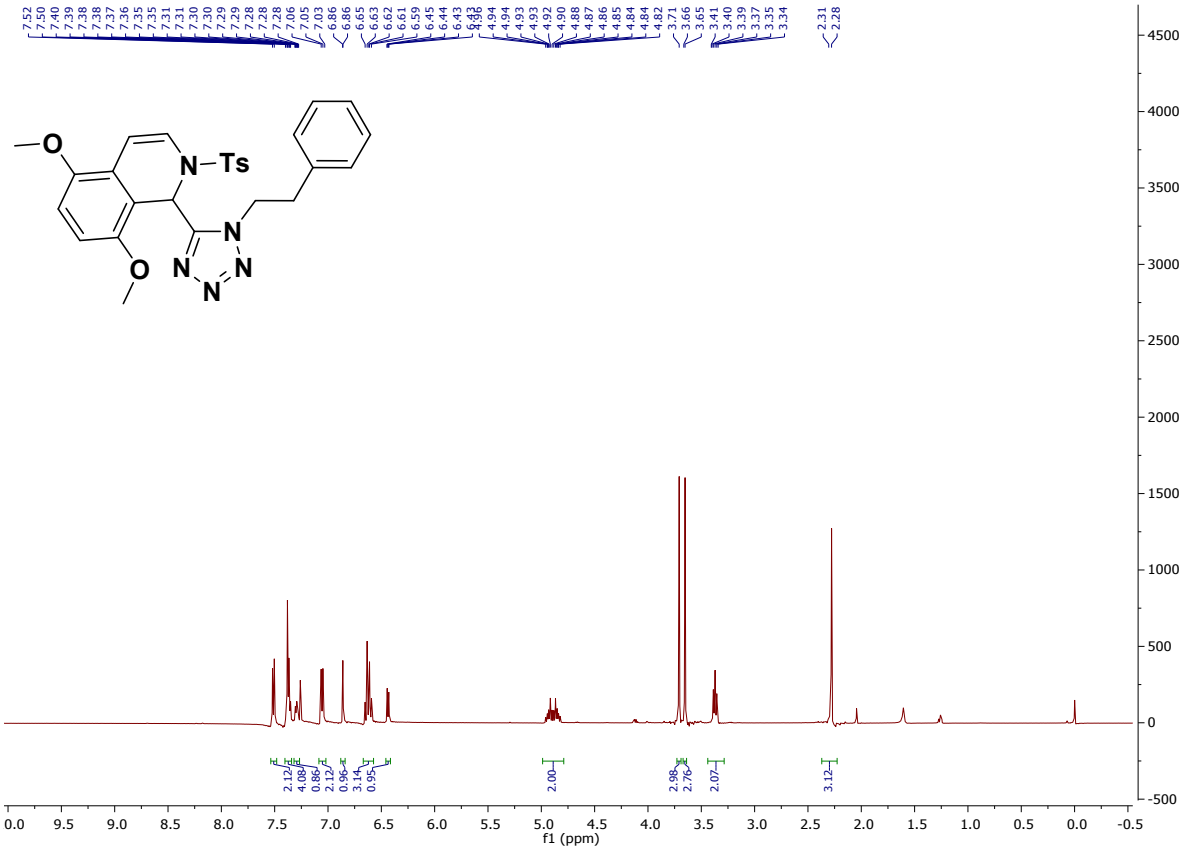
12d: *N*-(2,2-dimethoxyethyl)-*N*-((2,5-dimethoxyphenyl)(1-phenethyl-1*H*-tetrazol-5-yl)methyl)-4-methylbenzenesulfonamide

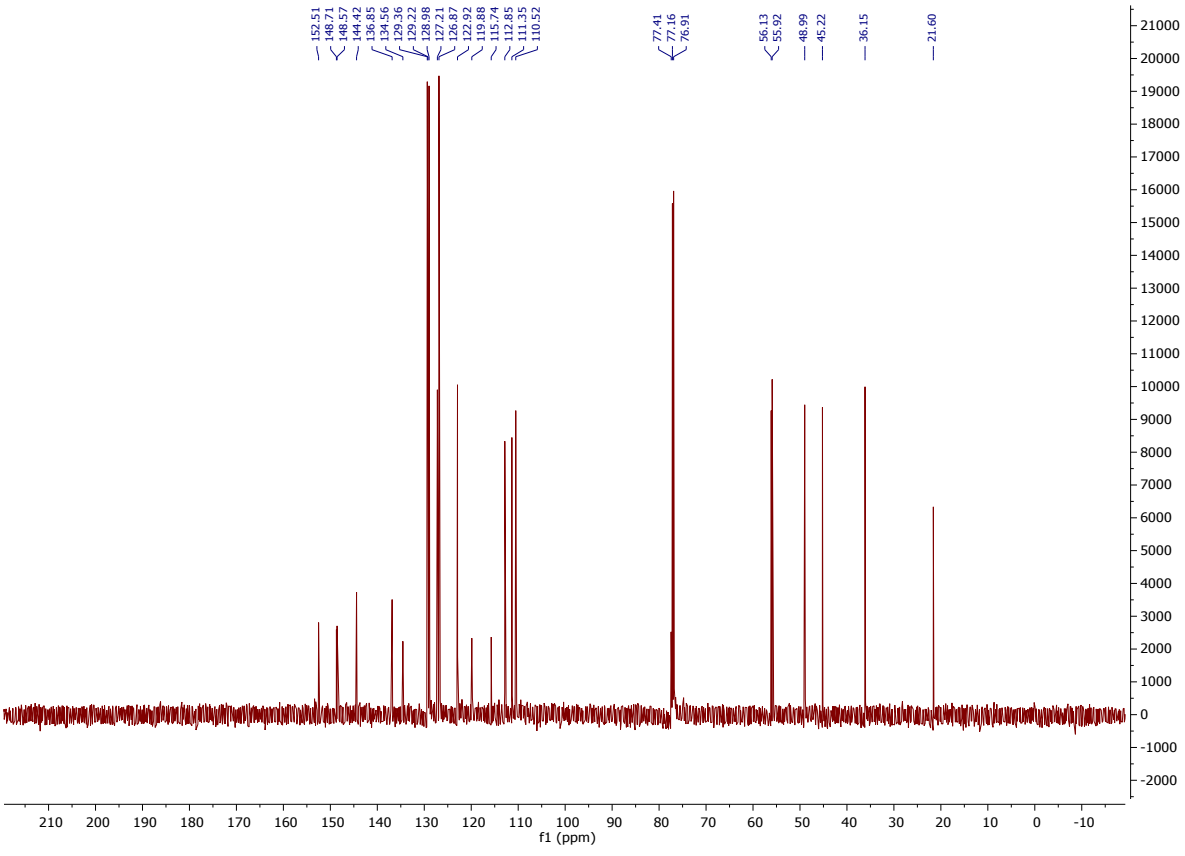




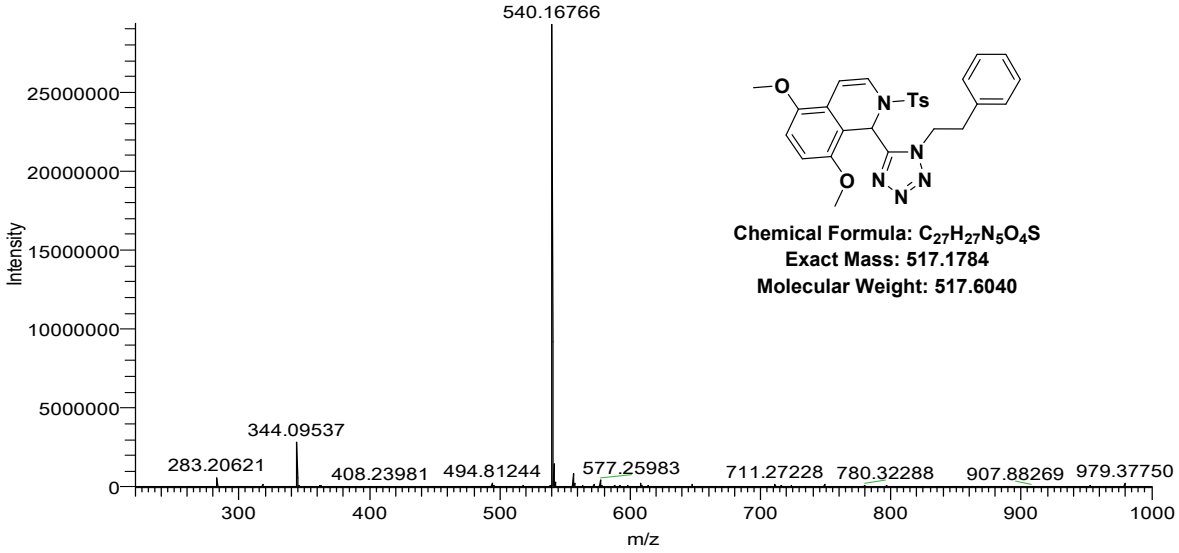

IMSC-18MDV093-YZ377 #1512 RT: 6.74 AV: 1 NL: 1.76E9
T: FTMS + p ESI Full ms [150.0000-1000.0000]
550.21252
582.23865
604.22052
235.16953
323.15024
430.91391
488.19772
678.30756
737.34436
789.85480
918.46851
Relative Abundance
m/z
N–Ts
Chemical Formula: C29H35N5O6S
Exact Mass: 581.2308
Molecular Weight: 581.6880

13d: 5,8-dimethoxy-1-(1-phenethyl-1*H*-tetrazol-5-yl)-2-tosyl-1,2-dihydroisoquinoline



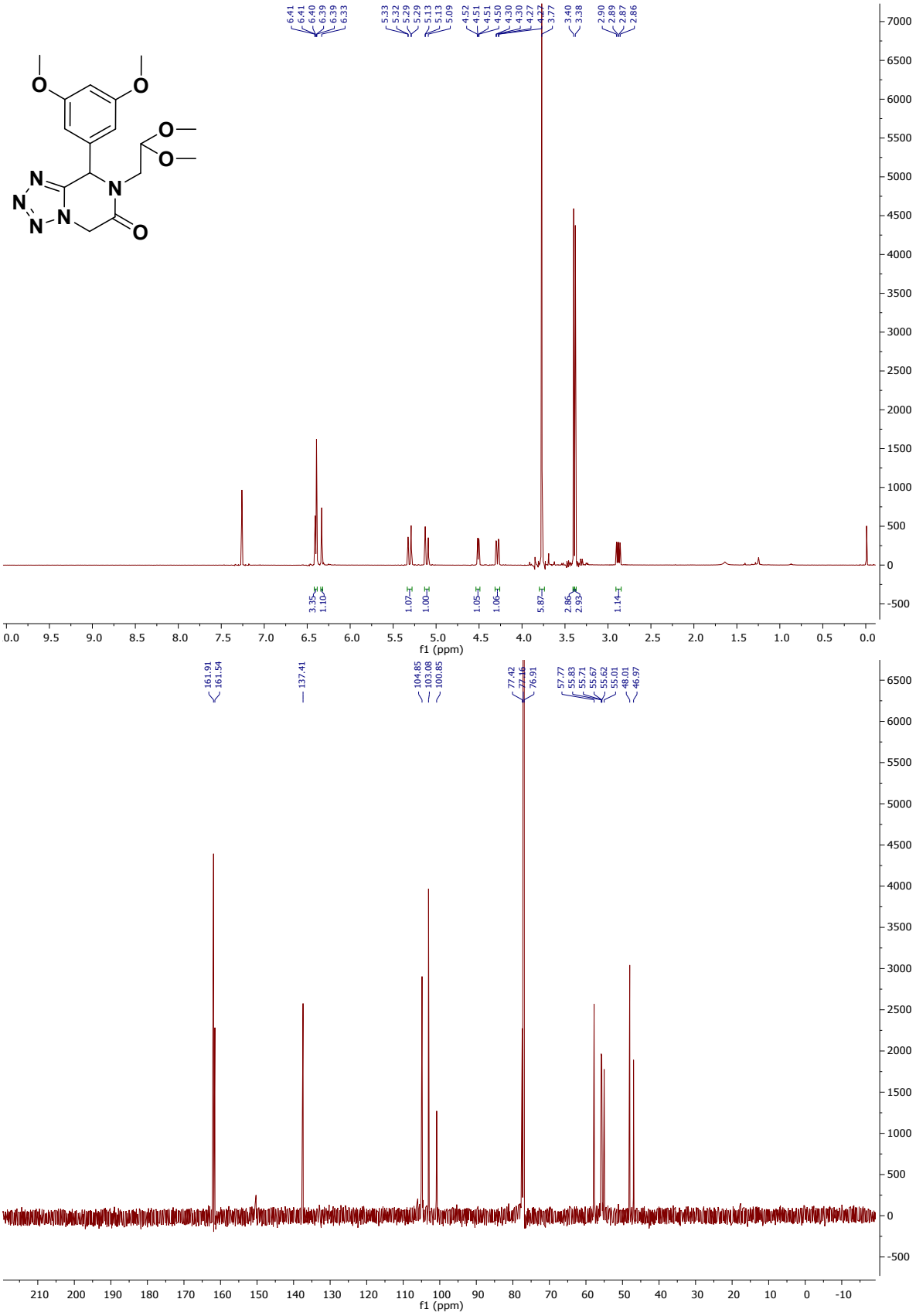


18mdv071-yz377C #6 RT: 0.10229 AV: 1 NL: 2.93E7
T: FTMS + p ESI Full ms [220.00-1000.00]

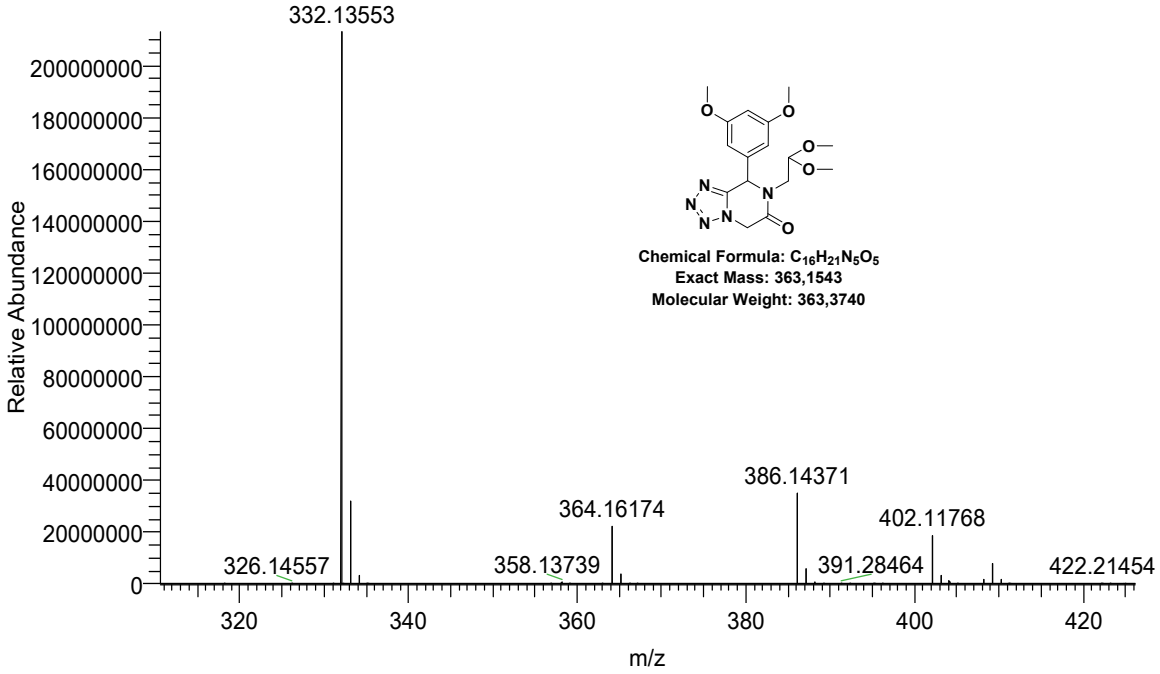


Chemical Formula: $C_{27}H_{27}N_5O_4S$
Exact Mass: 517.1784
Molecular Weight: 517.6040

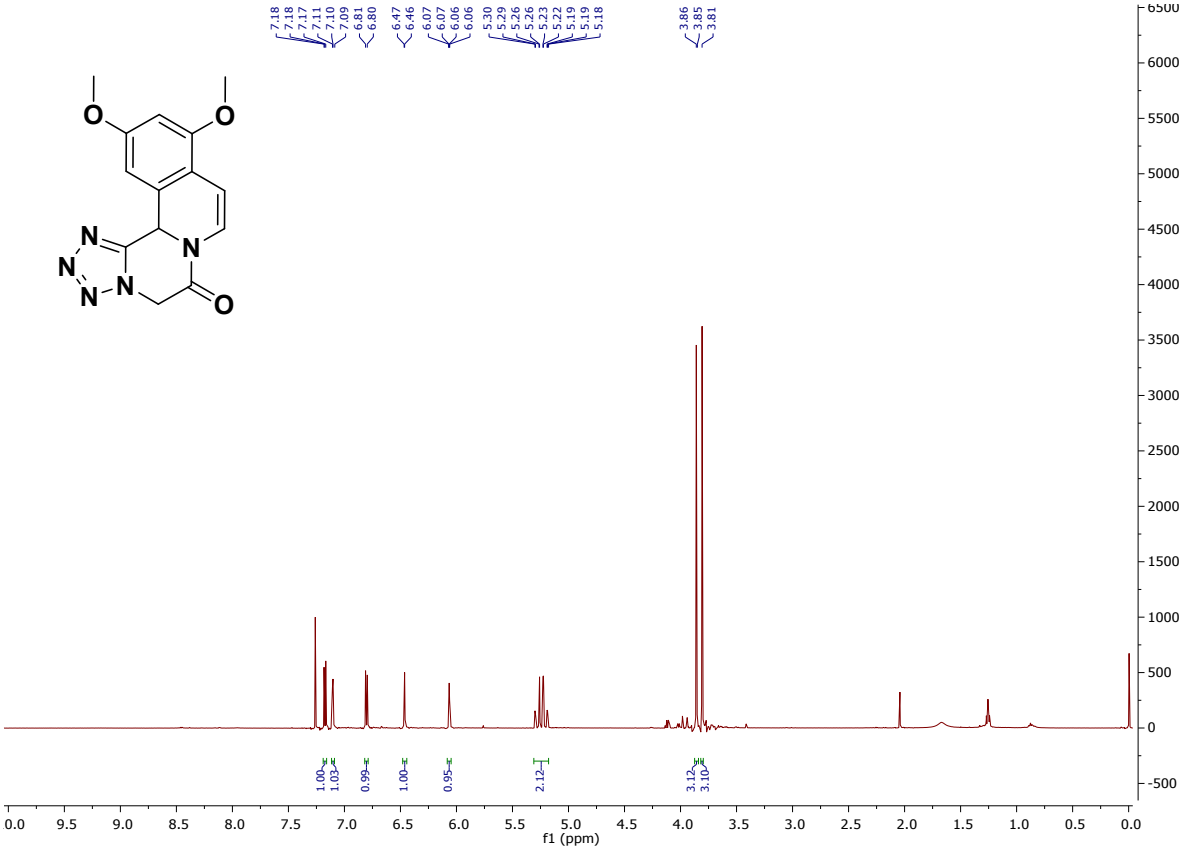
14: 7-(2,2-dimethoxyethyl)-8-(3,5-dimethoxyphenyl)-7,8-dihydrotetrazolo [1,5-*a*]pyrazin-6(5*H*)-one

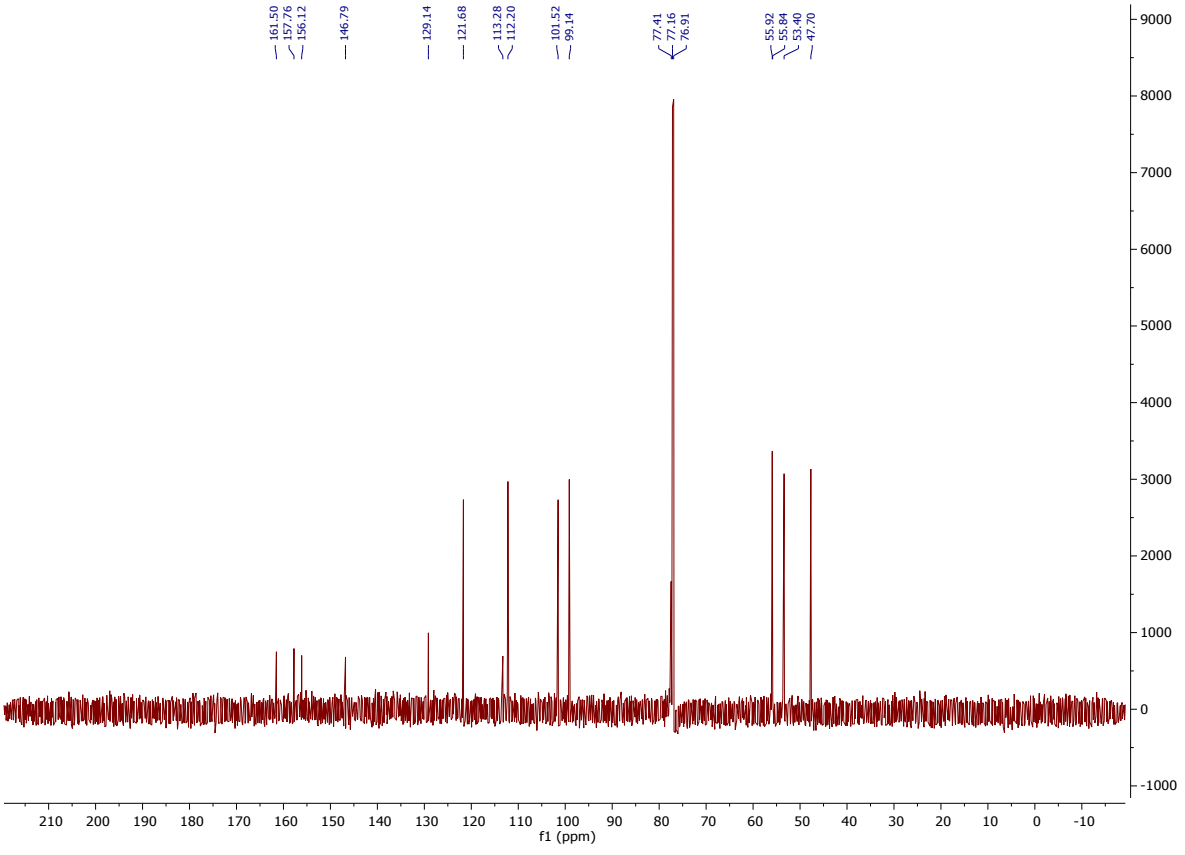


IMSC-18MDV093-YZ261 #935 RT: 4.16558 AV: 1 NL: 2.13E8
T: FTMS + p ESI Full ms [150.0000-1000.0000]

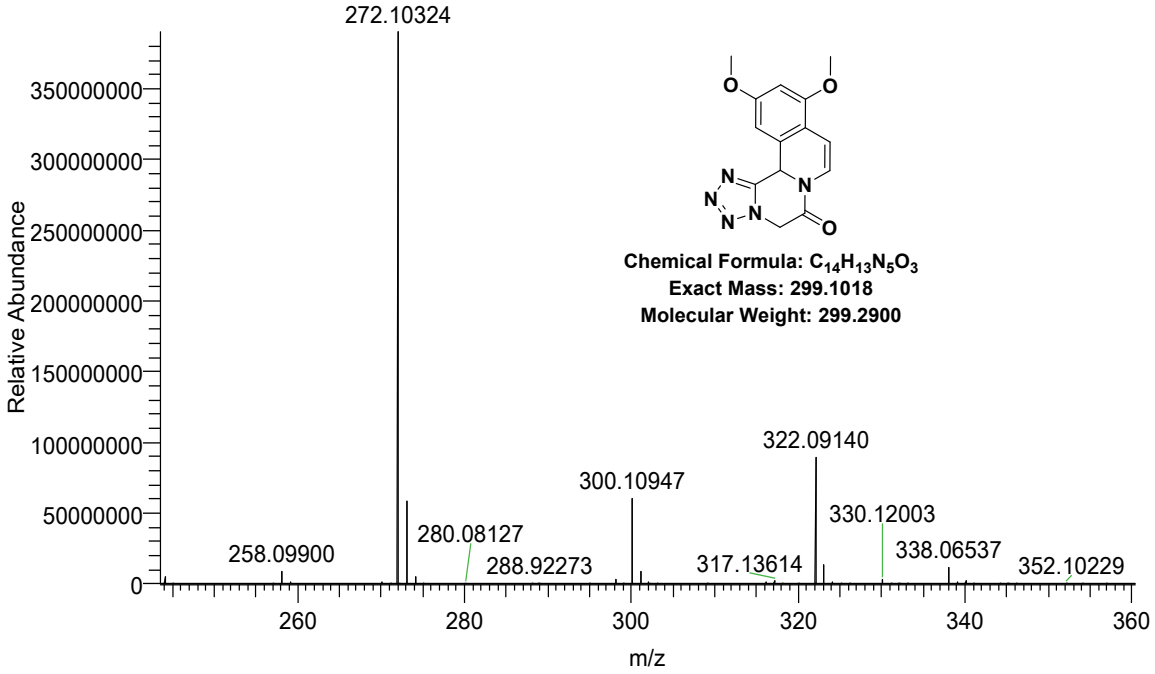


15: 10,12-dimethoxy-13*bH*-tetrazolo[5',1':3,4]pyrazino[2,1-*a*]isoquinolin-6(5*H*)-one





IMSC-18MDV093-YZ337C #953 RT: 4.24576 AV: 1 NL: 3.90E8
T: FTMS + p ESI Full ms [150.0000-1000.0000]



Crystal structure determination

X-ray diffraction data for single crystals of compounds **6j, 8a, 10b, 10d and 13d** was collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å) which was used for monocrystals of **6j, 8a** and **13d**, and CuKα radiation source (λ = 1.5418 Å) used for **10b** and **10d**. Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments performed at 130(2) K for all but **6j**, for which the experiment temperature was set at 120(2) K. The obtained data sets were processed with CrysAlisPro software [S1]. The phase problem was solved with direct methods using SIR2004 [S2] or SUPERFLIP [S3]. Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6 [S4]. Calculations were performed using WinGX integrated system (ver. 2014.1) [S5]. Figure was prepared with Mercury 3.7 software [S6].

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter U_{iso}[H] = 1.2 (or 1.5 (methyl groups only)) U_{eq}[C]. Hydrogen atoms bound to nitrogen atoms were positioned on the difference Fourier map and were refined with no restrains on the isotropic displacement parameters. Crystal data and structure refinement results for presented crystal structures are shown in Table S1. The molecular geometry observed in crystal structures are shown in Figure S1.

In the asymmetric unit of **8a** two independent molecules are observed with slightly different conformation of the phenethyl group. In the case of structure **6j**, a conformational disorder within the phenyl ring of the phenethyl group is observed, with refined site occupancies being equal for both alternative conformers.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos.: CCDC 1573261 (**6j**), CCDC1827938 (**8a**), CCDC 1856636 (**10b**) CCDC 1827865 (**10d**) and CCDC1828772 (**13d**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

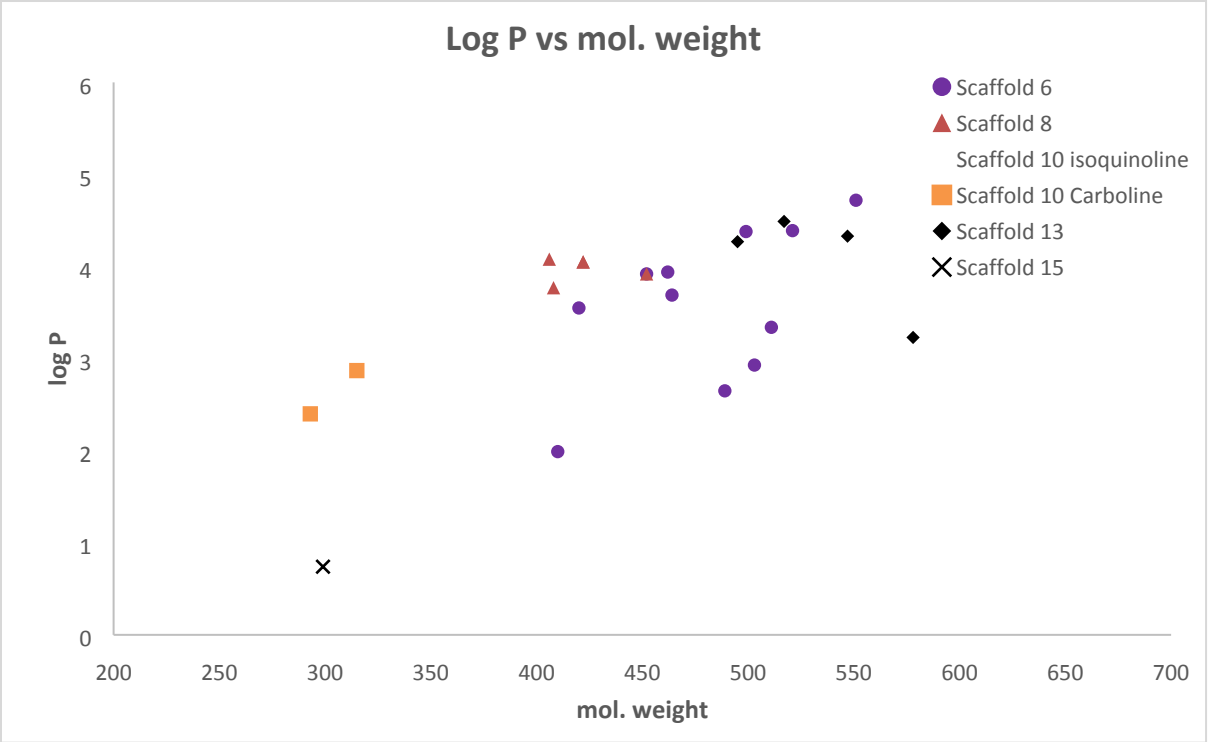


Figure. SI-1a: All synthesized molecules reported in this manuscript in a single plot of log P vs mol. weight.

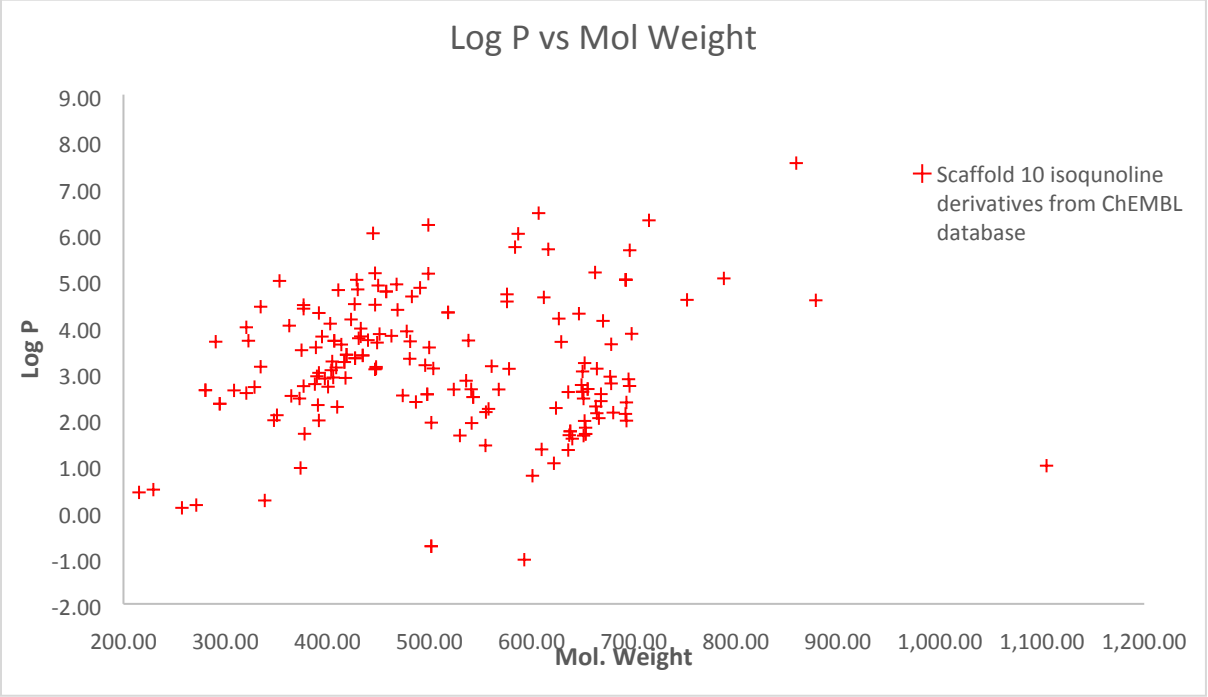


Figure. SI-1b: Lipophilicity vs molecular weight of 100 randomly selected of ChEMBL database of scaffold **10**-isoquinoline.

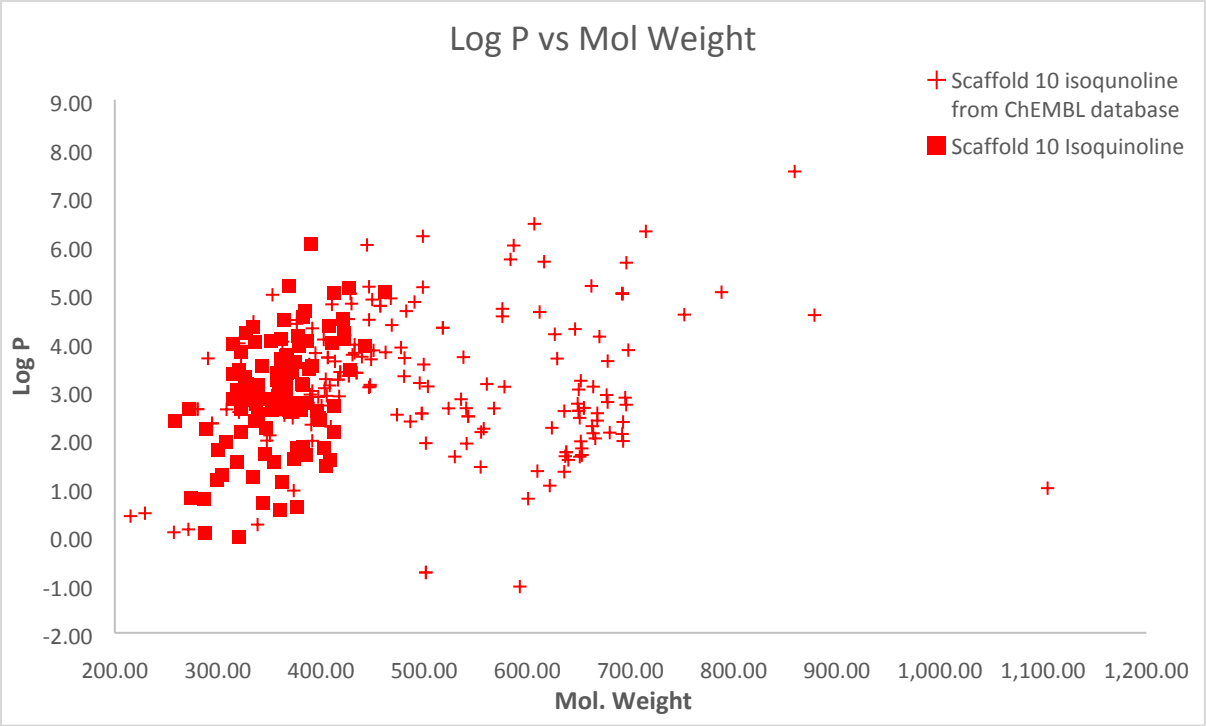


Figure. SI-1c: Comparison of 176 random molecules from the ChEMBL database and 100 virtually generated molecules of scaffold **10**-isoquinoline. Most of our randomly generate molecules fullfil the Lipinski's rule of 5.

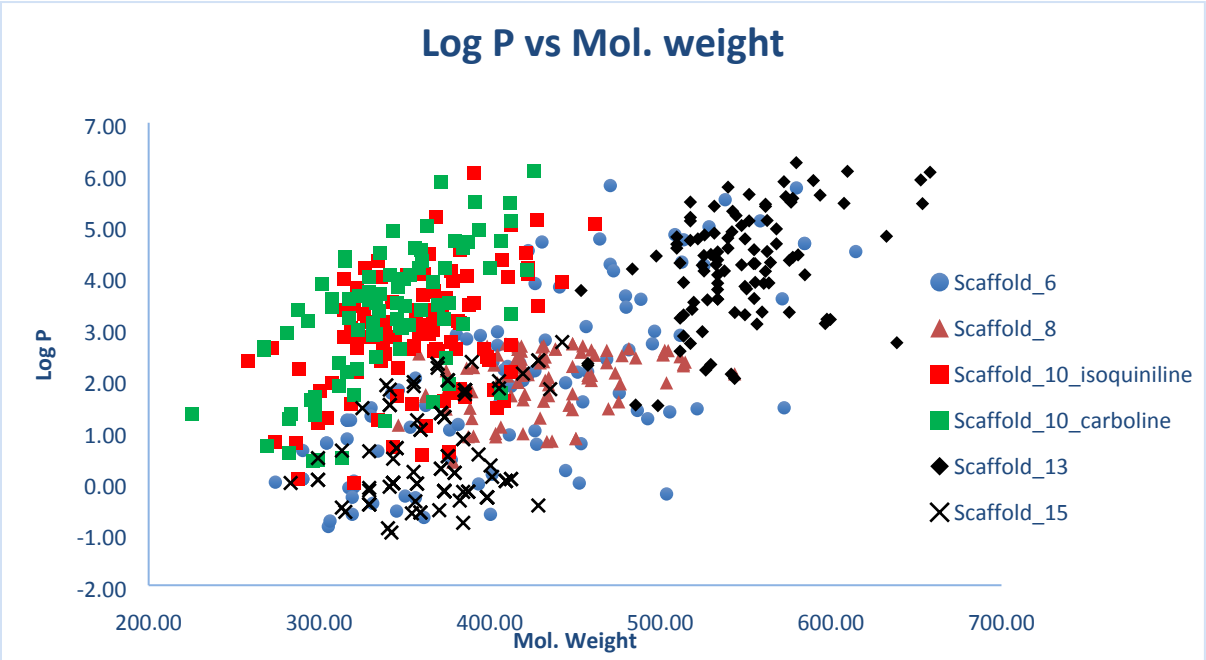


Figure. SI-1d: Lipophilicity vs molecular weight plotof virtual libraries of 100 randomly generated molecules of scaffolds of scaffold_**6** (blue, circle), scaffold_**8** (orange, tringle), scaffold_**10**-isoquinoline (red, square), scaffold_**10**-carboline (green, square), scaffold_**13** (black, square), and scaffold_**15** (black, cross).

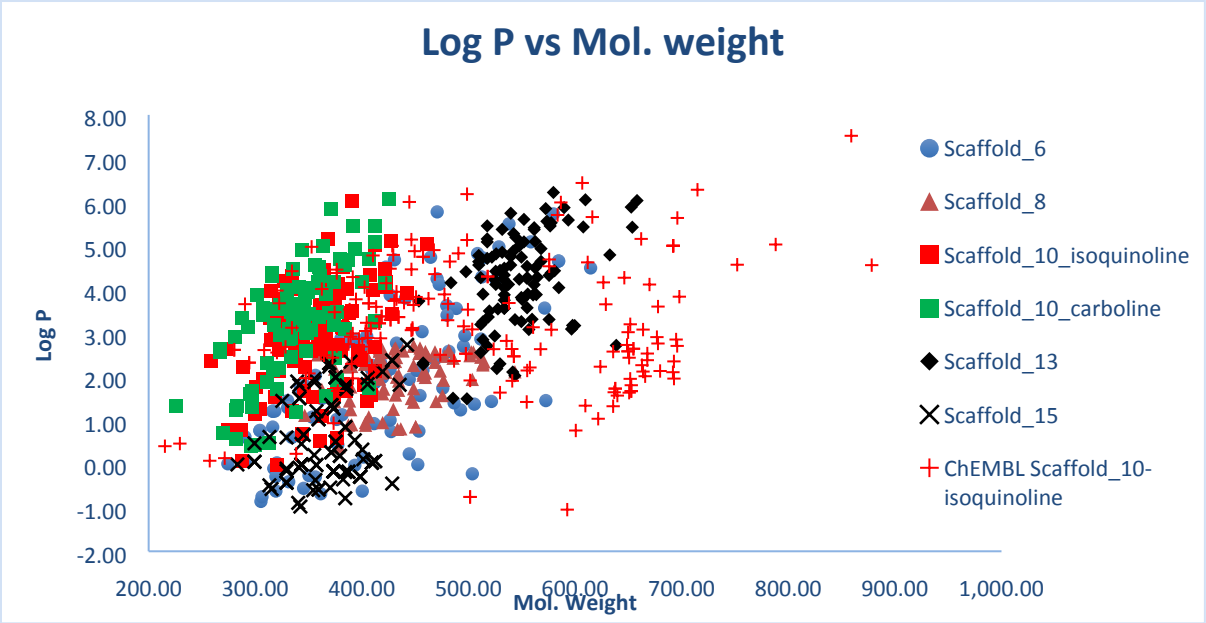


Figure. SI-1e: log P vs Mol. Weight of virtual libraries of 100 randomly generated molecules of scaffolds of scaffold_**6** (blue, circle), scaffold_**8** (orange, tringle), scaffold_**10**-isoquinoline (red, square), scaffold_**10**-carboline (green, square), scaffold_**13** (black, square), and scaffold_**15** (black, cross) comparing with the ChEMBL database of scaffold_**10**-isoquinoline molecules (yellow-red, square-plus).

References:

[S1] Rigaku-Oxford Diffraction; CrysAlisPro Oxford Diffraction Ltd, Abingdon, England V 1. 171. 36. 2. (release 27-06-2012 CN) 2006.

[S2] Burla M.C., Caliandro R., Camalli M., Carrozzini B., Cascarano G.L., De Caro L., Giacovazzo C., Polidori G. and Spagna R., J. Appl.Cryst. 2005, 38(2), 381–388.

[S3] Palatinus L., Chapuis G., J. App. Cryst. 2007, 40, 786-790.

[S4] Sheldrick G. M., ActaCryst. 2008, A64, 112-122.

[S5] Farrugia L.J., J. Appl. Cryst. 1999, 32, 837-838.

[S6] Macrae C. F., Edgington P.R., McCabe P., Pidcock E., Shields G.P., Taylor R., Towler M. and van de Streek J., J. Appl. Cryst. 2006, 39,