Supporting Information

Two cycles with one catch: hydrazine in Ugi 4-CR and its post-cyclizations

Yuanze Wang[†], Pravin Patil[†], Katarzyna Kurpiewska[‡], Justyna Kalinowska-Tluscik[‡], Alexander Dömling[†]*

[†]University of Groningen, Department of Drug Design, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands.

[‡]Jagiellonian University, Faculty of Chemistry, Department of Crystal Chemistry and Crystal Physics, Biocrystallography Group, Ingardena 3, 30-060 Krakow, Poland.

Fax: (+31)503637582.

E-mail: a.s.s.domling@rug.nl, www.drugdesign.nl

Contents

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: One pot synthesis of 6 and 7 in acidic conditions: To the stirred solution of oxo-component (**2**) (2 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added *tert*-butyl carbazate (**1**) (2 mmol, 1.0 equiv.), $(CF_3SO_3)_2Mg$ (10 mol%), isocyanide (2.1 mmol, 1.05 equiv.) and trimethylsilyl azide (2 mmol, 1.0 equiv.). The resulting mixture was stirred at same temperature for 18h. Then 2M HCl in methanol (2 mL) was added to the reaction mixture and stirred for 4h at same temperature. Solvents were removed under vacuum. The crude product dissolved in dichloromethane (10 mL) and pH of solution was adjusted to basic (pH~8) by ammonium hydroxide solution. The solvents were removed under vacuum. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 1:1) to give pure product (**6 and 7**).

General procedure B: Synthesis of Ugi-tetrazole adduct 5: To the stirred solution of oxo-component (**2**) (1 mmol, 1.0 equiv.) in methanol (1M) at room temperature, was added *tert*-butyl carbazate (**1**) (1 mmol, 1.0 equiv.), $(CF_3SO_3)_2Mg$ (10 mol%), isocyanide (1.05 mmol, 1.05 equiv.) and trimethylsilyl azide (1 mmol, 1.0 equiv.). The resulting mixture was stirred at same temperature for 18 hr. Solvents were removed under vacuum. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 7:3) to give pure product (**5**).

General procedure C: Synthesis of 8: To the stirred solution of ugi-tetrazole adduct (**5**) (0.5 mmol, 1.0 equiv.) in methanol (0.5M) at room temperature, was added sodium methoxide (0.5 mmol, 1.0 equiv.). The resulting mixture was stirred at same temperature for 1hr. Solvents were removed under vacuum. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 6:4) to give pure product (**8**).

General procedure D: Synthesis of 9: The 6-membered cyclized product (**8**) (0.3 mmol) was dissolved in 1 mL 2M HCl/methanol and stirred at room temperature for 18 hr. Solvents were removed under vacuum and the pure product was obtained as hydrochloric salts (**9**).

6a: 7-amino-5-isobutyl-8,8-dimethyl-7,8-dihydrotetrazolo [1,5-a]pyrazin-6 (5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (305 mg, 64% yield), M.P.= 195–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (dd, *J* = 7.4, 4.8 Hz, 1H), 4.21 (s, 2H), 2.20 – 2.12 (m, 1H), 2.00 1.93 (m, 1H), 1.92 – 1.86 (m, 1H), 1.85 (s, 3H), 1.78 (s, 3H), 0.94 (dd, *J* = 6.6, 2.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 154.5, 58.5, 57.9, 43.1, 27.6, 26.6, 24.6, 23.0, 21.7; HRMS calcd for $C_{10}H_{19}N_6O$ $[M+H]^+$: 239.16149; found $[M+H]^+$: 239.16124.

7a: 5-isobutyl-9,9-dimethyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5]triazepin-6(7*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as semi-solid (30 mg, 6% yield), M.P.= 181–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 5.46 (s, 1H), 4.22 (s, 1H), 2.23 (d, *J* = 7.8 Hz, 2H), 1.64 (d, *J* = 6.7 Hz, 6H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 5.3 Hz, 3H), 0.96-0.90 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.6, 159.4, 64.8, 57.9, 42.0, 27.1, 25.4, 25.3, 22.4, 22.2; HRMS calcd for $C_{10}H_{19}N_6O$ $[M+H]^+$: 239.16149; found $[M+H]^+$: 239.16144.

6b: 7-amino-8,8-dimethyl-7,8-dihydrotetrazolo[1,5-a] pyrazine-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (120 mg, 33% yield), M.P.= 111–113 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.29 (s, 2H), 4.86 (s, 2H), 1.68 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.5, 155.3, 57.8, 47.8, 26.7; HRMS calcd for $C_6H_{11}N_6O$ $[M+H]^+$:183.09889; found $[M+H]^+$: 183.09904.

6c: 7'-amino-5'H-spiro[cyclohexane-1,8'-tetrazolo[1,5-a] pyrazin]-6'(7'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (30 mg, 7% yield), M.P.= 193–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (s, 2H), 4.22 (s, 2H), 2.55 – 2.41 (m, 2H), 2.25 – 2.07 (m, 2H), 1.86 – 1.79 (m, 1H), 1.78 – 1.71 (m, 2H), 1.71 – 1.64 (m, 2H), 1.34 – 1.22 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 153.7, 62.3, 47.3, 33.4, 24.2, 21.6; HRMS calcd for $C_9H_{15}N_6O$ $[M+H]^+$: 223.13019; found $[M+H]^+$:223.13025.

7c: 7',8'-dihydrospiro[cyclohexane-1,9'-tetrazolo[5,1-d] [1,2,5]triazepin]-6'(5'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (150 mg, 34% yield), M.P.=162–164 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 6.10

(s, 1H), 5.67 (s, 1H), 4.91 (s, 1H), 1.95 – 1.78 (m, 3H), 1.73 – 1.61 (m, 4H), 1.54 (s, 2H), 1.40 – 1.29 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.0, 160.1, 58.4, 51.6, 32.3, 24.8, 20.1; HRMS calcd for $C_9H_{15}N_6O$ $[M+H]^+$: 223.13019; found $[M+H]^+$: 223.13019.

7d: 9-isobutyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5] triazepin-6(7*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as semi-solid (120 mg, 29% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.62 (s, 1H), 6.14 (s, 1H), 5.28 (s, 2H), 4.50 – 4.35 (m, 1H), 2.06 – 1.93 (m, 1H), 1.75 – 1.57 (m, 2H), 0.95 (dd, *J* = 13.5, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.6, 156.9, 51.6, 40.5, 23.5, 23.1, 21.4; HRMS calcd for $C_8H_{15}N_6O$ $[M+H]^+$: 211.13019; found $[M+H]^+$: 211.13019.

6e: 7-amino-8-phenethyl-7,8-dihydrotetrazolo[1,5-a] pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (140 mg, 27% yield), M.P.= 133–135°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 – 7.09 (m, 5H), 5.36 – 5.21 (m, 2H), 5.13 (s, 2H), 5.06 (s, 1H), 2.72 – 2.58 (m, 1H), 2.45 – 2.37 (m, 2H), 2.36 – 2.28 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.4, 150.5, 140.5, 128.4, 126.0, 55.5, 47.5, 33.2, 29.2; HRMS calcd for $C_{12}H_{15}N_6O$ $[M+H]^+$: 259.13019; found $[M+H]^+$: 259.12990.

7e: 9-phenethyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5] triazepin-6(7*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as semi-solid (50 mg, 10% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.46 – 7.09 (m, 5H), 6.29 (s, 1H), 5.43 – 5.13 (m, 2H), 4.42 – 4.29 (m, 1H), 2.91 – 2.74 (m, 2H), 2.18 – 2.07 (m, 1H), 2.11 – 1.95 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.6, 156.4, 141.2, 128.5, 126.0, 55.4, 51.7, 33.5, 30.9; HRMS calcd for $C_{12}H_{15}N_6O$ $[M+H]^+$: 259.13019; found $[M+H]^+$: 259.13008.

6f: 7-amino-8-isopropyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (90 mg, 24% yield), M.P.= 141–143 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.42 (dd, *J* = 17.5, 1.6 Hz, 1H), 5.30 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.14 (s, 2H), 4.95 – 4.89 (m, 1H), 2.74 – 2.60 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), 0.50 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.2, 148.7, 61.5, 47.4, 29.9, 18.3, 15.3; HRMS calcd for $C_7H_{13}N_6O$ $[M+H]^+$: 197.11454; found $[M+H]^+$: 197.11462.

7f: 9-isopropyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5] triazepin-6(7*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (40 mg, 10% yield), M.P.= 147–149 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.62 (s, 1H), 6.08 (s, 1H), 5.49 (d, *J* = 14.3 Hz, 1H), 5.07 (d, *J* = 14.3 Hz, 1H), 4.26 (t, *J* = 4.1 Hz, 1H), 2.43 – 2.22 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.4, 155.5, 61.9, 51.8, 31.0, 18.5, 18.1; HRMS calcd for $C_7H_{13}N_6O$ $[M+H]^+$: 197.11454; found $[M+H]^+$: 197.11462.

6g: 7-amino-8-cyclopropyl-7,8-dihydrotetrazolo[1,5-a] pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as semi-solid (90 mg, 23% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.41 – 5.22 (m, 2H), 5.13 (s, 2H), 4.60 (dd, *J* = 8.2, 1.6 Hz, 1H), 1.37 – 1.28 (m, 1H), 0.85 – 0.69 (m, 2H), 0.57 – 0.34 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.6, 150.1, 59.4, 47.5, 14.7, 4.9, 1.2; HRMS calcd for $C_7H_{11}N_6O$ $[M+H]^+$: 195.09889; found $[M+H]^+$: 195.09900.

6h: 7-amino-5-benzyl-8,8-dimethyl-7,8-dihydrotetrazolo [1,5-a]pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (160 mg, 30% yield), M.P.= 198–200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.22 – 7.11 (m, 3H), 6.71 – 6.65 (m, 2H), 5.80 (dd, *J* = 4.9, 3.0 Hz, 1H), 4.80 (s, 2H), 3.61 (dd, *J* = 14.0, 3.1 Hz, 1H), 3.49 (dd, *J* = 14.0, 4.9 Hz, 1H), 1.56 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4, 155.0, 133.8, 129.3, 128.6, 127.4, 59.2, 57.1, 38.1, 26.4, 26.2; HRMS calcd for $C_{13}H_{17}N_6O$ $[M+H]^+$:273.14584; found $[M+H]^+$: 273.14580.

6i: 7'-amino-5'-benzyl-5'*H*-spiro[cyclohexane-1,8'-tetrazolo [1,5-a] pyrazin]-6'(7'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (100 mg, 16% yield), M.P.= 136–138 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 – 7.04 (m, 3H), 6.73 – 6.59 (m, 2H), 5.82 (dd, *J* = 4.8, 3.1 Hz, 1H), 4.75 (s, 2H), 3.66 – 3.43 (m, 2H), 2.36 – 2.22 (m, 1H), 2.18 – 2.04 (m, 1H), 1.91 – 1.76 (m, 1H), 1.69 – 1.46 (m, 4H), 1.33 – 1.22 (m, 1H), 1.13 – 0.93 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 153.4, 133.8, 129.3, 128.5, 127.3, 60.4, 59.0, 38.2, 32.3, 24.0, 21.0; HRMS calcd for $C_{16}H_{21}N_6O$ $[M+H]^+$: 313.17714; found $[M+H]^+$: 313.17697.

7i: 5'-benzyl-7',8'-dihydrospiro[cyclohexane-1,9'-tetrazolo [5,1-d][1,2,5]triazepin] -6'(5'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded **7i** as white solid (160 mg, 26% yield), M.P.= 229–231 °C; ^{1}H NMR (500 MHz, DMSO-d_6)(major isomer) δ 9.88 (s, 1H), 9.70 (s, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.34 – 7.18 (m, 8H), 6.30 (t, *J* = 6.9 Hz, 1H), 6.17 (d, *J* = 15.1 Hz, 2H), 5.31 (d, *J* = 9.8 Hz, 1H), 3.81 – 3.69 (m, 2H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.60 – 3.52 (m, 1H), 2.08 (d, *J* = 11.1 Hz, 1H), 1.98 – 1.77 (m, 7H), 1.75 – 1.53 (m, 11H), 1.42 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) 126.4, 132.3, 131.6, 72.4, 64.7, 64.2, 64.1, 43.7, 40.2, 39.6, 37.5, 37.3, 37.1, 29.9, 25.5, 25.3, 25.2, 25.0; HRMS calcd for $C_{16}H_{21}N_6O$ $[M+H]^+$: 313.17714; found $[M+H]^+$: 313.17703.

6j: 7'-amino-5'-benzyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazine]-6'(7'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (200 mg, 34% yield), M.P.= 214– 216 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 – 7.07 (m, 3H), 6.72 – 6.61 (m, 2H), 5.82 (dd, *J* = 5.0, 2.9 Hz, 1H), 4.90 (s, 2H), 3.57 (dd, *J* = 13.9, 3.0 Hz, 1H), 3.44 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.39 – 2.30 (m, 1H), 1.94 – 1.86 (m, 1H), 1.84 – 1.72 (m, 2H), 1.65 – 1.51 (m, 2H), 1.51 – 1.41 (m, 1H), 0.43 – 0.27 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 157.0, 134.2, 129.8, 129.7, 129.0, 127.8, 66.4, 59.5, 38.8, 38.3, 26.3, 26.1; HRMS calcd for $C_{15}H_{19}N_6O$ $[M+H]^+$: 299.16149; found $[M+H]^+$: 299.16132.

6k: 7-amino-5-benzyl-8-phenethyl-7,8-dihydrotetrazolo [1,5-a]pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as semi-solid (100 mg, 15% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 – 7.19 (m, 2H), 7.19 – 7.05 (m, 3H), 7.03 – 6.93 (m, 3H), 6.81 – 6.71 (m, 2H), 5.86 – 5.70 (m, 1H), 5.09 (s, 2H), 4.83 – 4.72 (m, 1H), 3.67 – 3.51 (m, 2H), 2.11 – 2.01 (m, 1H), 2.01 – 1.89 (m, 1H), 1.81 – 1.63 (m, 1H), 0.97 – 0.82 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.7, 150.5, 140.6, 133.9, 129.6, 129.5, 128.6, 128.2, 128.2, 127.5, 125.8, 59.6, 55.3, 37.5, 33.0, 28.7; HRMS calcd for $C_{19}H_{21}N_6O$ $[M+H]^+$: 349.17714; found $[M+H]^+$: 349.17700.

6l: 7-amino-5-benzyl-8-isopropyl-7,8-dihydrotetrazolo[1,5-a] pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as a semi-solid (200 mg, 35% yield); ^{1}H NMR (500 MHz, DMSO-d_6) (major isomer) δ 7.19 – 7.09 (m, 3H), 6.87 – 6.77 (m, 2H), 6.01 – 5.93 (m, 1H), 5.16 (s, 2H), 4.44 (dd, *J* = 3.1, 1.5 Hz, 1H), 3.71 – 3.53 (m, 2H), 2.72 – 2.60 (m, 1H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.41 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) (major isomer) δ 162.5, 149.1, 134.3, 129.7, 128.8, 127.7, 61.2,

59.4, 37.6, 30.1, 18.6, 15.4.; HRMS calcd for $C_{14}H_{19}N_6O$ $[M+H]^+$: 287.16149; found $[M+H]^+$: 287.16134.

6m: 7-amino-5-isopropyl-8,8-dimethyl-7,8-dihydrotetrazolo [1,5-a]pyrazin-6(5*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as colorless oil (170 mg, 38% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.31 (s, 1H), 4.89 (s, 2H), 2.74 – 2.62 (m, 1H), 1.68 (d, J = 10.0 Hz, 6H), 1.08 (d, J = 7.1 Hz, 3H), 0.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.4, 155.6, 64.1, 57.5, 33.0, 27.9, 27.2, 19.2, 17.3; HRMS calcd for $C_9H_{17}N_6O$ $[M+H]^+$: 225.14584; found $[M+H]^+$: 225.14578.

7n: 5'-isopropyl-7',8'-dihydrospiro[cyclohexane-1,9'-tetrazolo[5,1-d][1,2,5] triazepin]-6'(5'*H*)–one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded **7n** as white solid (210 mg, 40% yield), M.P.= 233–234 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.79 (s, 1H), 6.00 (s, 1H), 4.66 (d, J = 10.5 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.04 – 1.95 (m, 1H), 1.90 (d, J = 13.5 Hz, 1H), 1.72 – 1.53 (m, 7H), 1.42 – 1.28 (m, 1H), 1.07 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.6, 160.8, 73.0, 59.4, 35.1, 32.2, 31.5, 25.1, 20.5, 20.4, 20.1, 19.6; HRMS calcd for $C_{12}H_{21}N_6O$ $[M+H]^+$: 265.17714; found $[M+H]^+$: 265.17694.

6o: 7'-amino-5'-isopropyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a] pyrazin]-6'(7'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded as white solid (190 mg, 38% yield), M.P.= 105–107 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.33 (d, J = 2.7 Hz, 1H), 4.98 (s, 2H), 2.67 – 2.58 (m, 1H), 2.42 – 2.33 (m, 1H), 2.09 – 2.01 (m, 1H), 2.01 – 1.82 (m, 6H), 1.07 (d, J = 7.1 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 156.9, 66.1, 63.6 (J = 4.2 Hz), 38.5, 32.7, 32.7, 26.2, 26.1, 18.8, 16.8; HRMS calcd for $C_{11}H_{19}N_6O$ $[M+H]^+$: 251.16149; found $[M+H]^+$: 251.16142.

7o: 5'-isopropyl-7',8'-dihydrospiro[cyclopentane-1,9'-tetrazolo[5,1-d][1,2,5] triazepin]-6'(5'*H*)-one

The product was synthesized according to procedure **A** in 2 mmol scale**,** afforded **7o** as semi-solid (30 mg, 6% yield); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (s, 1H), 5.87 (s, 1H), 4.68 (d, J = 10.5 Hz, 1H), 3.16 (d, J = 5.3 Hz, 1H), 3.01 – 2.87 (m, 1H), 2.30 – 2.18 (m, 1H), 2.17 –

2.07 (m, 1H), 1.87 – 1.67 (m, 5H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.3, 161.1, 73.1, 67.6, 38.8, 37.2, 31.5, 24.2, 24.2, 20.1, 19.5; HRMS calcd for $C_{11}H_{19}N_6O$ $[M+H]^+$: 251.16149; found $[M+H]^+$: 251.16147.

5a: *tert*-butyl 2-(2-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5-yl)propan-2-yl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as semi-solid (270 mg, 73% yield), M.P.= 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, *J* = 5.5 Hz, 1H), 5.90 (dd, *J* = 9.9, 5.2 Hz, 1H), 4.21 (d, *J* = 6.1 Hz, 1H), 3.78 (s, 3H), 2.51 – 2.38 (m, 1H), 2.27 – 2.16 (m, 1H), 1.70 (s, 3H), 1.55 – 1.59 (m,1H), 1.54 (s, 3H), 1.42 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 165.5, 158.5, 60.4, 57.8, 53.5, 40.1, 28.4, 25.7, 25.1, 24.4, 22.8, 21.9; HRMS calcd for $C_{16}H_{31}N_6O_4$ $[M+H]^+$: 371.24019; found $[M+H]^+$: 371.23999.

8a: *tert*-butyl(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8*H*)-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as semi-solid (140 mg, 83% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.28 (s, 1H), 2.20 – 2.08 (m, 1H), 2.05 – 1.91 (m, 2H), 1.79 (s, 6H), 1.49 (s, 9H), 0.96 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 155.5, 154.4, 83.0, 59.8, 58.2, 43.4, 43.0, 28.1, 24.6, 23.0, 21.6; HRMS calcd for $C_{15}H_{27}N_6O_3$ $[M+H]^+$: 339.21392; found $[M+H]^+$: 339.21374.

5b: *tert*-butyl 2-(1-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5-yl) cyclohexyl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as white solid (330 mg, 90% yield), M.P.= 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dd, *J* = 9.8, 5.3 Hz, 1H), 5.82 (d, *J* = 6.5 Hz, 1H), 4.40 (d, *J* = 6.2 Hz, 1H), 3.75 (s, 3H), 2.46 – 2.35 (m, 2H), 2.23 – 2.16 (m, 1H), 2.08 – 1.99 (m, 1H), 1.88 – 1.72 (m, 4H), 1.69 – 1.61 (m, 1H), 1.57 – 1.48 (m, 2H), 1.47 – 1.41 (m, 1H), 1.39 (s, 9H), 0.93 (dd, *J* = 11.7, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 157.6, 157.1, 80.1, 60.4, 60.2, 53.4, 40.2, 34.4, 32.6, 28.3, 25.3, 25.1, 22.8, 22.3, 22.0, 21.9; HRMS calcd for $C_{19}H_{35}N_6O_4$ $[M+H]^+$: 411.27143; found $[M+H]^+$: 411.27133.

8b: *tert*-butyl (5'-isobutyl-6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclohexane-1,8'-tetrazolo[1,5-a] pyrazin]-7'-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (150 mg, 78% yield), M.P.= 150–152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (major rotamer) δ 6.42 (s, 1H), 5.38 – 5.16 (m, 1H), 2.61 – 2.40 (m, 1H), 2.36 – 2.19 (m, 1H), 2.18 – 1.89 (m, 6H), 1.89 – 1.77 (m, 2H), 1.75 – 1.67 (m, 2H), 1.49 (s, 9H), 1.32 – 1.22 (m, 1H), 1.00 – 0.90 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 153.0, 83.0, 63.4, 57.8, 43.4, 36.1, 35.0, 34.2, 33.3, 28.2, 24.5, 24.4, 23.0, 21.8; HRMS calcd for $C_{18}H_{31}N_6O_3$ $[M+H]^+$: 379.24522; found $[M+H]^+$: 379.24522.

5c: *tert*-butyl 2-(1-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5 yl)cyclopentyl) hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as colorless oil (230 mg, 58% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 6.6 Hz, 1H), 5.66 (dd, *J* = 10.4, 4.7 Hz, 1H), 4.32 (d, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 2.58 – 2.45 (m, 2H), 2.25 – 2.10 (m, 2H), 2.04 – 1.88 (m, 4H), 1.88 – 1.81 (m, 1H), 1.80 – 1.71 (m, 1H), 1.59 – 1.47 (m, 1H), 1.40 (s, 9H), 0.95 (dd, *J* = 7.9, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 158.5, 157,4, 81.0, 67.9, 60.0, 53.3, 39.7, 36.1, 33.8, 28.2, 24.9, 24.4, 23.6, 22.8, 21.6; HRMS calcd for $C_{18}H_{33}N_6O_4$ $[M+H]^+$: 397.25578; found $[M+H]^+$: 397.25516.

8c: *tert*-butyl (5'-isobutyl-6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (140 mg, 77% yield), M.P.= 134–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$)(major rotamer) δ 6.46 (d, *J* = 12.4 Hz, 1H), 5.37 – 5.20 (m, 1H), 2.61 – 2.45 (m, 1H), 2.44 – 2.27 (m, 2H), 2.23 – 1.92 (m, 8H), 1.49 (s, 9H), 0.95 (dd, *J* = 16.6, 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 155.9, 155.6, 83.0, 68.6, 58.1, 42.9, 40.3, 39.3, 38.2, 37.3, 28.1, 25.5, 24.4, 23.0, 21.5; HRMS calcd for $C_{17}H_{29}N_6O_3$ $[M+H]^+$: 365.22957; found $[M+H]^+$: 365.22952.

5d: *tert*-butyl 2-(1-(1-(2-methoxy-2-oxoethyl)-1*H*-tetrazol-5-yl)cyclohe-xyl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as colorless oil (76%, 0.27g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (d, *J* = 5.2 Hz, 1H), 5.55 (s, 2H), 4.36 – 4.23 (m, 1H), 3.81 (s, 3H), 2.24 – 2.15 (m, 2H), 1.85 – 1.74 (m, 2H), 1.73 – 1.67 (m, 2H), 1.65 – 1.57 (m, 2H), 1.54 – 1.42 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 157.4,

156.9, 81.0, 59.7, 53.3, 50.0, 33.3, 28.3, 25.2, 22.0; HRMS calcd for $C_{15}H_{27}N_6O_4$ $[M+H]^+$: 355.20883; found $[M+H]^+$: 355.20875.

8d: *tert*-butyl(6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclohexane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (60 mg, 38% yield), M.P.= 123–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (s, 1H), 5.28 (d, *J* = 18.2 Hz, 1H), 5.16 (d, *J* = 18.1 Hz, 1H), 2.37 – 2.24 (m, 1H), 2.20 – 2.09 (m, 3H), 2.03 (d, *J* = 7.7 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.82 – 1.68 (m, 3H), 1.50 (s, 9H), 1.33 – 1.23 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 155.7, 153.6, 83.0, 63.6, 47.7, 34.7, 33.7, 28.1, 24.3, 21.8, 21.7; HRMS calcd for $C_{14}H_{23}N_6O_3$ $[M+H]^+$: 323.18262; found $[M+H]^+$: 323.18259.

5e: *tert*-butyl 2-(2-(1-(1-methoxy-1-oxo-3-phenylpropan-2-yl) -1*H*-tetrazol-5-yl)propan-2-yl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as colorless oil (250 mg, 63% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 3H), 7.06 – 6.98 (m, 2H), 6.35 – 6.31 (m, 1H), 4.75 (d, *J* = 6.1 Hz, 1H), 3.90 (d, *J* = 6.2 Hz, 1H), 3.83 (s, 3H), 3.82 – 3.78 (m, 1H), 3.73 – 3.69 (m, 1H), 1.43 (s, 3H), 1.38 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 158.9, 157.4, 136.0, 129.5, 129.1, 127.9, 80.9, 63.3, 57.8, 53.7, 37.5, 28.3, 25.1, 24.5; HRMS calcd for $C_{19}H_{29}N_6O_4$ $[M+H]^+$: 405.22448; found $[M+H]^+$: 405.22415.

8e: *tert*-butyl (5-benzyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a] pyrazin-7(8*H*)-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as colorless oil (150 mg, 83% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.06 (m, 3H), 6.70 (s, 2H), 6.31 – 6.12 (m, 1H), 5.63 (s, 1H), 3.79 – 3.63 (m, 2H), 1.67 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 155.4, 155.1, 133.1, 129.8, 129.1, 128.1, 83.0, 60.2, 59.8, 38.9, 28.1, 27.1, 26.8; HRMS calcd for $C_{18}H_{25}N_6O_3$ $[M+H]^+$: 373.19827; found $[M+H]^+$: 373.19826.

5f: *tert*-butyl 2-(1-(1-(1-methoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-tetrazol-5-yl)cyclopentyl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as colorless oil (240 mg, 56%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 3H), 7.09 – 7.00 (m, 2H), 6.15 (dd, *J* = 12.0, 3.6 Hz, 1H), 4.69 – 4.57 (m, 1H), 4.08 (d, *J* = 6.4 Hz, 1H), 3.83 (s, 3H), 3.71 (dd, *J* = 14.1, 3.6 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.90 – 1.83 (m, 1H), 1.82 – 1.63 (m, 5H), 1.60

– 1.52 (m, 1H), 1.47 – 1.40 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 158.8, 157.6, 136.0, 129.5, 129.0, 127.8, 80.9, 68.1, 63.0, 53.6, 37.3, 35.1, 34.5, 28.3, 23.8, 23.8; HRMS calcd for $C_{22}H_{33}N_6O_4$ $[M+H]^+$: 431.24013; found $[M+H]^+$: 431.23991.

8f: *tert*-butyl (5'-benzyl-6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl)carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as semi-solid (150 mg, 74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 3H), 6.67 (d, *J* = 7.1 Hz, 2H), 6.19 (s, 1H), 5.65 (s, 1H), 3.72 (dd, *J* = 14.2, 3.0 Hz, 1H), 3.65 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.36 – 2.32 (m, 1H), 2.20 – 2.13 (m, 1H), 2.04 – 1.95 (m, 1H), 1.80 – 1.71 (m, 2H), 1.66 – 1.61 (m, 1H), 1.5 (s, 9H), 1.07 – 1.03 (m, 1H), 0.57 – 0.53 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 156.5, 155.7,133.2, 129.8, 129.1, 128.2, 83.2, 68.5, 60.1, 39.1, 39.0, 38.0, 28.1, 25.7, 25.4; HRMS calcd for $C_{20}H_{27}N_6O_3$ $[M+H]^+$: 399.21392; found $[M+H]^+$: 399.21372.

5g: *tert*-butyl 2-(2-(1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1*H*-tetrazol-5-yl)propan-2-yl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as white solid (270 mg, 76% yield), M.P.= 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (d, *J* = 5.4 Hz, 1H), 5.73 (d, *J* = 8.3 Hz, 1H), 4.24 – 4.14 (m, 1H), 3.78 (s, 3H), 2.96 – 2.88 (m, 1H), 1.66 (s, 3H), 1.55 (s, 3H), 1.42 (s, 9H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 158.7, 157.3, 81.2, 67.1, 57.9, 53.2, 31.0, 28.3, 25.9, 24.8, 19.8, 19.7; HRMS calcd for $C_{15}H_{29}N_6O_4$ $[M+H]^+$: 357.22448; found $[M+H]^+$: 357.22435.

8g: *tert*-butyl (5-isopropyl-8,8-dimethyl-6-oxo-5,6-dihydro-tetrazolo[1,5-a]pyrazin-7(8*H*)-yl)carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (140 mg, 87% yield), M.P.= 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (s, 1H), 5.15 (s, 1H), 2.94 – 2.78 (m, 1H), 1.82 (s, 6H), 1.49 (s, 9H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 155.5, 154.9, 82.9, 64.7, 59.7, 34.2, 28.0, 27.6, 19.0, 17.2; HRMS calcd for $C_{14}H_{25}N_6O_3$ $[M+H]^+$: 325.19827; found $[M+H]^+$: 325.19815.

5h: *tert*-butyl 2-(1-(1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1*H*-tetrazol-5-yl)cyclohexyl) hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale, afforded as semi-solid (220 mg, 56% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (d, *J* = 5.9 Hz, 1H), 5.73 (d, *J* = 8.0

Hz, 1H), 4.39 (s, 1H), 3.78 (s, 3H), 2.98 – 2.86 (m, 1H), 2.45 – 2.32 (m, 1H), 2.16 – 2.06 (m, 1H), 1.88 – 1.66 (m, 5H), 1.57 – 1.49 (m, 1H), 1.46 (t, *J* = 4.8 Hz, 2H), 1.42 (s, 9H), 1.14 (dd, *J* = 6.8, 2.2 Hz, 3H), 1.02 (dd, *J* = 6.9, 1.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 157.2, 157.1, 81.1, 66.9, 60.2, 53.2, 33.0, 31.1, 28.3, 25.3, 22.2, 22.0, 19.9, 19.7; HRMS calcd for $C_{18}H_{33}N_6O_4$ $[M+H]^+$: 397.25578; found $[M+H]^+$: 397.25568.

8h: *tert*-butyl (5'-isopropyl-6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclohexane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (150 mg, 81% yield), M.P.= 185–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$)(major rotamer) δ 6.33 (s, 1H), 5.10 (s, 1H), 2.88 – 2.73 (m, 1H), 2.57 – 2.34 (m, 1H), 2.29 – 2.04 (m, 3H), 2.00 – 1.83 (m, 2H), 1.80 – 1.68 (m, 2H), 1.60 – 1.54 (m, 1H), 1.47 (s, 9H), 1.33 – 1.23 (m, 1H), 1.18 (d, *J* = 8.1 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 155.9, 153.4, 82.9, 64.5, 63.3, 35.8, 34.8, 34.4, 34.0, 28.2, 24.4, 21.6, 19.1, 17.4; HRMS calcd for $C_{17}H_{29}N_6O_3$ $[M+H]^+$: 365.22957; found $[M+H]^+$: 365.22940.

5i: *tert*-butyl 2-(1-(1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1*H*-tetrazol-5-yl)cyclopentyl) hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as white solid (280 mg, 73% yield), M.P.= 100–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 5.8 Hz, 1H), 5.53 (d, *J* = 7.9 Hz, 1H), 4.38 – 4.21 (m, 1H), 3.77 (s, 3H), 2.98 – 2.84 (m, *J* = 6.8 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.22 – 2.14 (m, 1H), 2.05 – 1.99 (m, 2H), 1.98 – 1.87 (m, 2H), 1.86 – 1.73 (m, 2H), 1.40 (s, 9H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 158.7, 157.4, 81.2, 68.0, 66.9, 53.2, 36.2, 34.4, 30.9, 28.3, 23.7, 24.4, 19.9, 19.6; HRMS calcd for $C_{17}H_{31}N_6O_4$ $[M+H]^+$: 383.24013; found $[M+H]^+$: 383.24019.

8i: *tert*-butyl (5'-isopropyl-6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (150 mg, 87% yield), M.P.= 146–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$)(major rotamer) δ 6.41 (s, 1H), 5.16 (d, *J* = 49.8 Hz, 1H), 2.84 – 2.67 (m, 1H), 2.61 – 2.46 (m, 1H), 2.34 – 2.24 (m, 1H), 2.19 – 2.05 (m, 3H), 2.01 – 1.90 (m, 2H), 1.51 (s, 9H), 1.18 (s, 3H), 0.95 (s, 3H), 0.88 – 0.79 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 156.5, 155.8, 83.0, 68.6, 64.7, 40.9, 39.4,

38.3, 34.2, 28.2, 25.8, 19.1, 17.2; HRMS calcd for $C_{16}H_{27}N_6O_3$ $[M+H]^+$: 351.21392; found $[M+H]^+$: 351.21375.

5j: benzyl 4-(2-(tert-butoxycarbonyl)hydrazineyl)-4-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5-yl) piperidine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as white solid (440 mg, 81% yield), M.P.= 78–80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.98 – 5.76 (m, 2H), 5.12 (d, *J* = 3.5 Hz, 2H), 4.39 (s, 1H), 4.05 – 3.95 (m, 1H), 3.96 – 3.86 (m, 1H), 3.79 (s, 3H), 3.71 – 3.41 (m, 1H), 3.31 – 3.06 (m, 1H), 2.55 – 2.36 (m, 2H), 2.29 – 2.17 (m, 1H), 2.15 – 2.02 (m, 1H), 2.01 – 1.92 (m, 1H), 1.91 – 1.82 (m, 1H), 1.57 – 1.46 (m, 1H), 1.41 (s, 9H), 0.94 (dd, *J* = 11.2, 6.6 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 157.3, 156.4, 155.2, 136.7, 128.7, 128.2, 128.1, 81.5, 67.4, 60.5, 59.1, 53.6, 40.9, 40.1, 33.6, 32.4, 28.3, 25.1, 24.7, 22.8, 21.9; HRMS calcd for $C_{26}H_{40}N_7O_6$ $[M+H]^+$: 546.30346; found $[M+H]^+$: 546.30341.

8j: benzyl 7'-((tert-butoxycarbonyl)amino)-5'-isobutyl-6'-oxo-6',7'-dihydro-5'*H*-spiro [piperidine-4,8'-tetrazolo [1,5-a]pyrazine]-1-carboxylate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (200 mg, 79% yield), M.P.= 172–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$)(major rotamer) δ 7.41 – 7.30 (m, 5H), 6.37 (s, 1H), 5.38 – 5.25 (m, 1H), 5.17 (d, *J* = 3.4 Hz, 2H), 4.34 – 4.12 (m, 2H), 4.12 – 3.92 (m, 1H), 3.66 – 3.40 (m, 1H), 2.53 – 2.24 (m, 2H), 2.18 – 2.08 (m, 1H), 2.04 – 1.92 (m, 2H), 1.91 (s, 9H), 1.68 – 1.57 (m, 2H), 0.97 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 155.4, 155.2, 151.9, 136.5, 128.6, 128.2, 127.9, 83.3, 67.4, 61.2, 57.8, 43.5, 43.2, 39.9, 39.6, 33.5, 28.0, 24.4, 22.9, 21.4; HRMS calcd for $C_{25}H_{36}N_7O_5$ $[M+H]^+$: 514.27724; found $[M+H]^+$: 514.27716.

5k: *tert*-butyl 2-(1-(1-(1-methoxy-2-methyl-1-oxopropan-2-yl)-1*H*-tetra-zol-5-yl) cyclohexyl)hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as a white solid (220 mg, 57% yield), M.P.= 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (d, *J* = 7.3 Hz, 1H), 4.56 (d, *J* = 5.7 Hz, 1H), 3.73 (s, 3H), 2.12 – 2.08 (m, 1H), 2.05 (s, 6H), 2.01 – 1.95 (m, 2H), 1.91 – 1.88 (m, 1H), 1.71 – 1.59 (m, 5H), 1.52 – 1.48 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 159.7, 156.7, 81.1, 66.2, 60.6, 53.2, 34.1, 28.4, 27.0, 25.1, 24.4, 21.3; HRMS calcd for $C_{17}H_{31}N_6O_4$ $[M+H]^+$: 383.24013; found $[M+H]^+$: 383.24036.

8k: *tert*-butyl (5',5'-dimethyl-6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclohexane-1,8'-tetrazolo[1,5-a] pyrazin]-7'-yl) carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as white solid (140 mg, 80% yield), M.P.= 166–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 1H), 2.39 – 2.06 (m, 4H), 1.94 (s, 1H), 1.90 (s, 6H), 1.88 – 1.83 (m, 1H), 1.79 – 1.70 (m, 2H), 1.67 – 1.59 (m, 1H), 1.50 (s, 9H), 1.32 – 1.22 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 155.7, 151.7, 82.8, 63.1, 62.2, 35.1, 34.1, 28.3, 26.9, 24.34, 21.7, 21.6; HRMS calcd for $C_{16}H_{27}N_6O_3$ $[M+H]^+$: 351.21392; found $[M+H]^+$: 351.21381.

5l: *tert*-butyl 2-(2-(1-(3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-1*H*-tetrazol-5-yl) propan-2-yl) hydrazine-1-carboxylate

The product was synthesized according to procedure **B** in 1 mmol scale**,** afforded as colorless oil (360 mg, 82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.18 – 7.08 (m, 2H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.48 (dd, *J* = 11.0, 4.6 Hz, 1H), 4.57 (d, *J* = 5.7 Hz, 1H), 3.96 – 3.88 (m, 2H), 3.85 (s, 3H), 3.76 (d, *J* = 5.7 Hz, 1H), 1.36 (s, 3H), 1.32 (s, 9H), 1.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 159.0, 157.4, 135.9, 126.2, 124.1, 122.6, 120.1, 117.9, 111.9, 109.2, 80.7, 62.1, 57.6, 53.5, 28.2, 27.6, 25.1, 24.3; HRMS calcd for $C_{21}H_{30}N_7O_4$ $[M+H]^+$: 444.23538; found $[M+H]^+$: 444.23529.

8l: *tert*-butyl (5-((1*H*-indol-3-yl)methyl)-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo [1,5-a] pyrazine-7(8*H*)-yl)carbamate

The product was synthesized according to procedure **C** in 0.5 mmol scale**,** afforded as semi-solid (140 mg, 69% yield); ^{1}H NMR (500 MHz, $CDCl_3$)(major rotamer) δ 8.08 (s, 1H), 7.34 (s, 1H), 7.29 (s, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.43 (s, 1H), 5.69 (s, 2H), 3.98 (d, *J* = 15.0 Hz, 1H), 3.85 – 3.75 (m, 1H), 1.60 (s, 3H), 1.50 (s, 9H), 0.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 156.8, 155.3, 135.7, 126.8, 124.3, 123.9, 122.7, 120.2, 118.5, 111.4, 82.8, 61.0, 59.6, 29.7, 28.0, 26.9, 26.2; HRMS calcd for $C_{20}H_{26}N_7O_3$ $[M+H]^+$: 412.20916; found $[M+H]^+$: 412.20911.

9a: 7'-amino-5'-isobutyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'*H*)-one hydrochloride

The product was synthesized according to procedure **D** in 0.3 mmol scale, afforded as white solid (80 mg, 89% yield), M.P= 159-161 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.44 (dd, *J* = 6.8, 4.8 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.42 – 2.35 (m, 1H), 2.10 – 1.82 (m, 8H), 1.76 – 1.66 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.2,

156.1, 66.2, 57.3, 41.7, 38.7, 37.6, 25.8, 24.1, 22.9, 21.7, 21.2. HRMS calcd for $C_{12}H_{21}N_6O$ $[M+H]^+$: 265.17714; found $[M+H]^+$: 265.17703.

9b: 7'-amino-5'-benzyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'*H*)-one hydrochloride

The product was synthesized according to procedure **D** in 0.3 mmol scale**,** afforded as white solid (90 mg, 89% yield), M.P.= 165–167 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.19 – 7.07 (m, 3H), 6.70 – 6.59 (m, 2H), 5.81 (dd, *J* = 4.9, 2.9 Hz, 1H), 3.61 – 3.36 (m, 2H), 2.41 – 2.30 (m, 1H), 1.96 – 1.83 (m, 1H), 1.83 – 1.68 (m, 2H), 1.65 – 1.42 (m, 3H), 0.40 – 0.29 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) 161.8, 156.6, 133.8, 129.3, 128.6, 127.4, 66.0, 59.1, 38.4, 37.9, 25.9, 25.6; HRMS calcd for $C_{15}H_{19}N_6O$ $[M+H]^+$: 299,16149; found $[M+H]^+$: 299,16129.

9c: 7'-amino-5'-isopropyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'*H*)-one hydrochloride

The product was synthesized according to procedure **D** in 0.3 mmol scale**,** afforded as white solid (80 mg, 93% yield), M.P= 166–168 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.33 (d, *J* = 2.6 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.43 – 2.34 (m, 1H), 2.10 – 2.01 (m, 1H), 1.99 – 1.82 (m, 6H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 156.9, 66.1, 63.6, 32.8, 26.1, 26.0, 18.8, 16.8; HRMS calcd for $C_{11}H_{19}N_6O$ $[M+H]^+$: 251.16149; found $[M+H]^+$: 251.16138

9d: 7'-amino-5',5'-dimethyl-5'*H*-spiro[cyclohexane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'*H*)-one hydrochloride

The product was synthesized according to procedure **D** in 0.3 mmol scale**,** afforded as white solid (80 mg, 93% yield), M.P.= 160–162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.48 – 2.39 (m, 2H), 2.13 – 2.01 (m, 2H), 1.77 (s, 6H), 1.74– 1.63 (m, 5H), 1.28 – 1.16 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) 166.8, 152.0, 61.2, 60.7, 32.9, 27.4, 24.0, 21.3; HRMS calcd for $C_{11}H_{19}N_6O$ $[M+H]^+$: 251,16149; found $[M+H]^+$: 251,16129.

10: N-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo [1,5-a] pyrazine-7(8*H*)-yl) acrylamide

The product was obtained as colorless oil (230 mg, 78% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 6.49 (dd, *J* = 17.1, 1.2 Hz, 1H), 6.31 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.86 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.26 (dd, *J* = 7.9, 5.0 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.04 – 1.98 (m, 1H), 1.97

– 1.90 (m, 1H), 1.82 (s, 3H), 1.71 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 163.6, 154.2, 130.6, 127.4, 60.1, 58.5, 43.3, 28.3, 26.6, 24.6, 23.0, 21.5; HRMS calcd for $C_{13}H_{21}N_6O_2$ $[M+H]^+$: 293.17205; found $[M+H]^+$: 293.17191.

11: 2-(4-chlorophenyl)-N-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo [1,5-a]pyrazin-7(8*H*)-yl)acetamide

The product was obtained as semi-solid (290 mg, 75% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.07 (s, 1H), 5.30 – 5.23 (m, 1H), 3.74 (s, 2H), 2.19 – 2.10 (m, 1H), 2.07 – 1.94 (m, 2H), 1.76 (s, 3H), 1.68 (s, 3H), 0.97 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 167.5, 163.2, 131.7, 130.9, 129.5, 60.0, 58.4, 43.4, 41.1, 28.3, 26.8, 24.6, 23.0, 21.6; HRMS calcd for $C_{18}H_{24}ClN_6O_2$ $[M+H]^+$: 391.16304; found $[M+H]^+$: 391.16296.

12: N-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo [1,5-a]pyrazin-7(8*H*)-yl)-4 methylbenzenesulfonamide

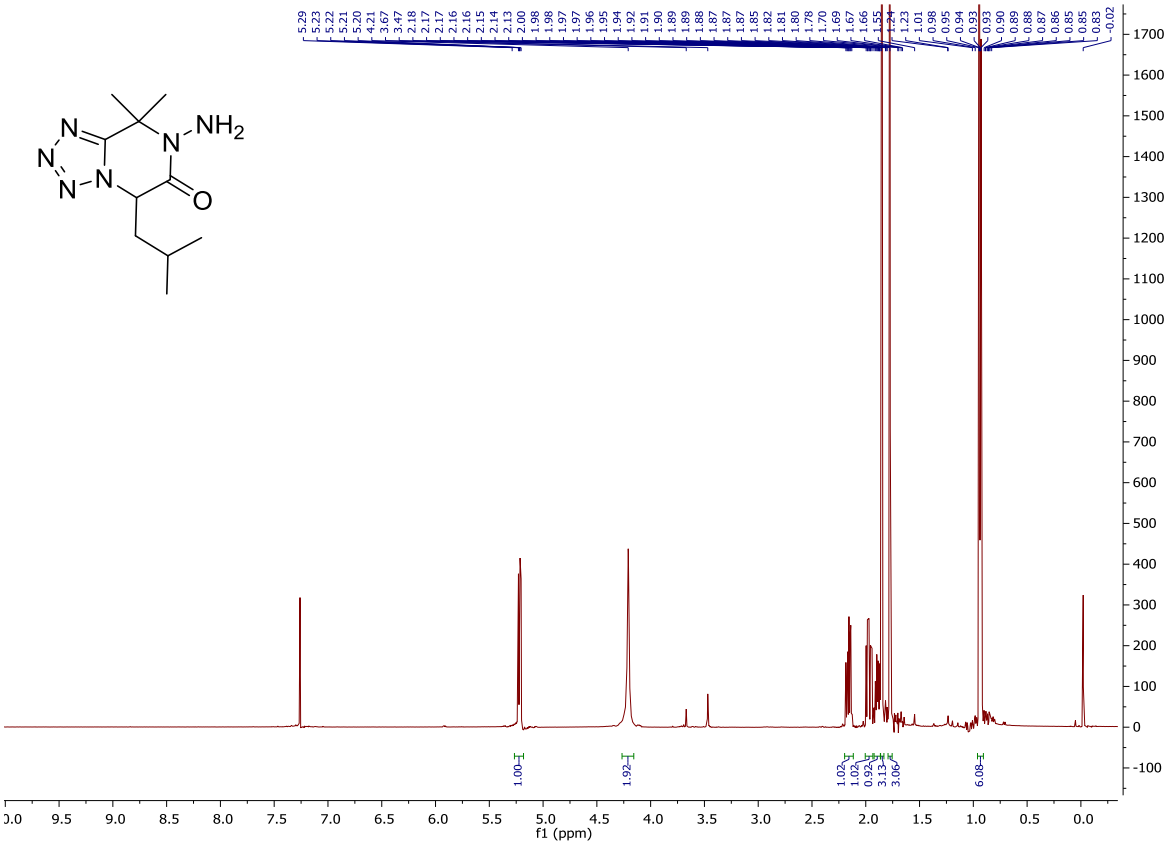
The product was obtained as white solid (260 mg, 66% yield), M.P.= 175–177 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.37 (s, 1H), 2.39 (s, 3H), 1.94 – 1.83 (m, 1H), 1.69 (s, 6H), 1.54 (s, 2H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.0, 154.5, 143.5, 129.3, 127.8, 57.9, 41.9, 27.2, 26.7, 24.1, 22.6, 21.3, 21.0; HRMS calcd for $C_{17}H_{25}N_6O_3S$ $[M+H]^+$: 393.17034; found $[M+H]^+$: 393.17029.

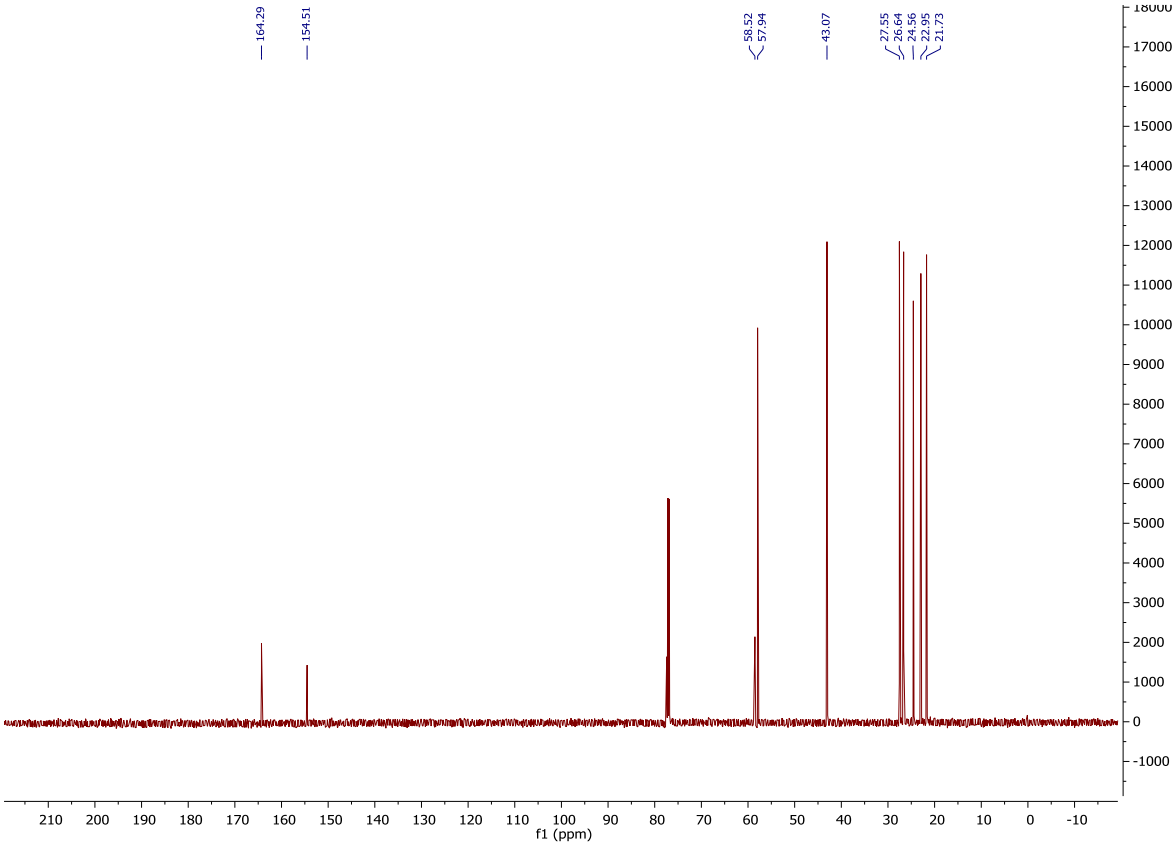
13: 1-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo [1,5-a]pyrazin-7(8*H*)-yl)-3-phenylthiourea

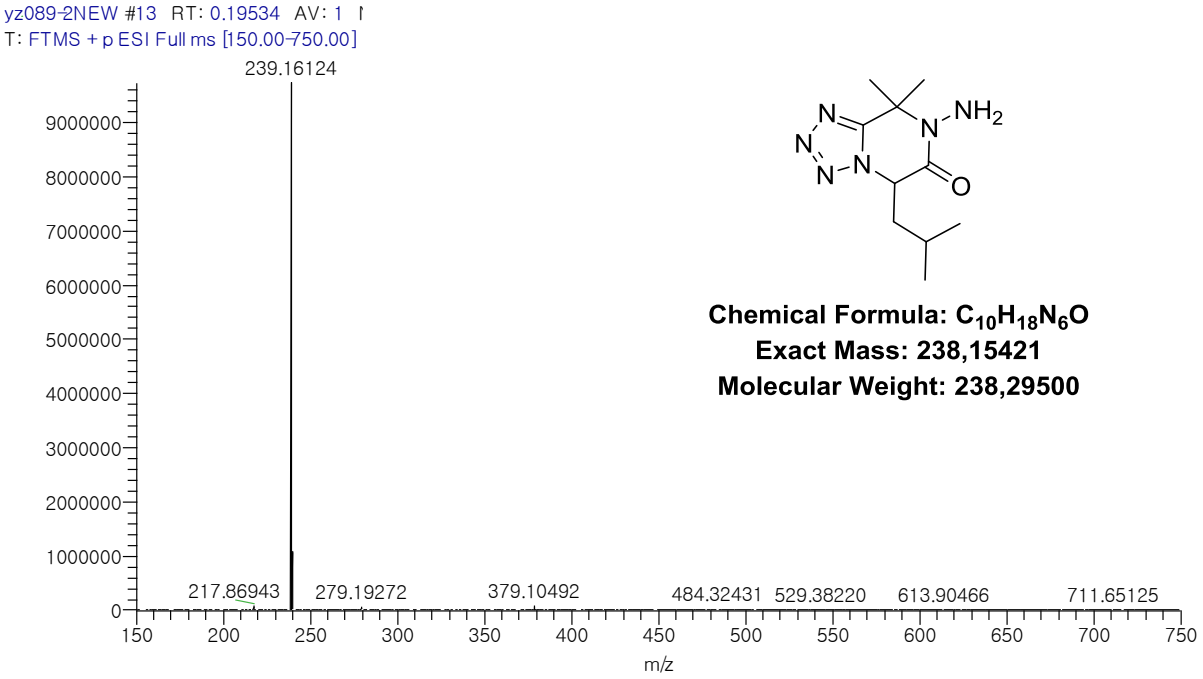
The product was obtained as white solid (210 mg, 56% yield), M.P.= 233–235 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.74 (s, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 5.39 (t, *J* = 6.5 Hz, 1H), 1.99 (t, *J* = 6.8 Hz, 2H), 1.82 (s, 3H), 1.64 (s, 3H), 1.08 – 1.02 (m, 1H), 0.94 (dd, *J* = 11.4, 6.5 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 182.1, 164.3, 154.6, 138.5, 128.2, 126.5, 126.0, 58.9, 58.1, 41.9, 29.0, 24.1, 23.7, 22.9, 21.4; HRMS calcd for $C_{17}H_{24}N_7OS$ $[M+H]^+$: 374.17576; found $[M+H]^+$: 374.17572.

^{1}H, ^{13}C NMR and mass spectra of the novel synthesized compounds :

6a: 7-amino-5-isobutyl-8,8-dimethyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6 (5*H*)-one

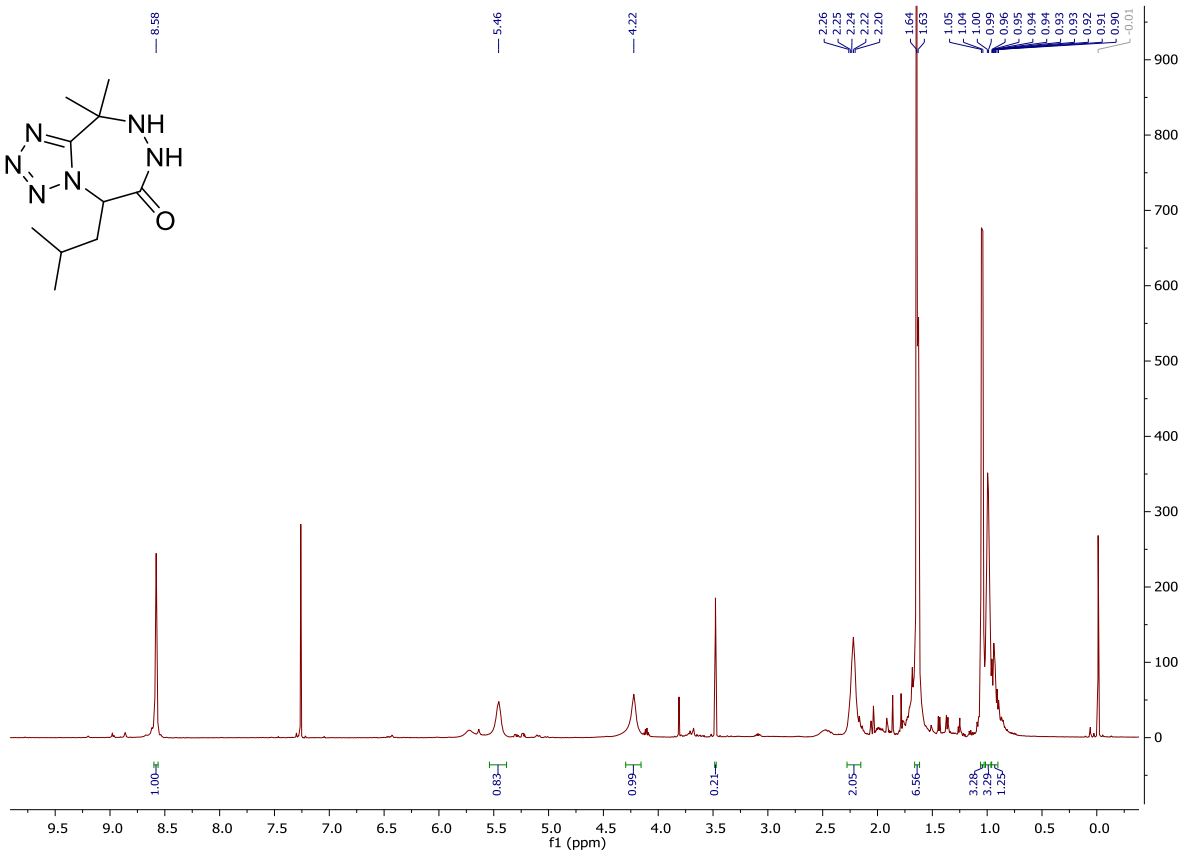


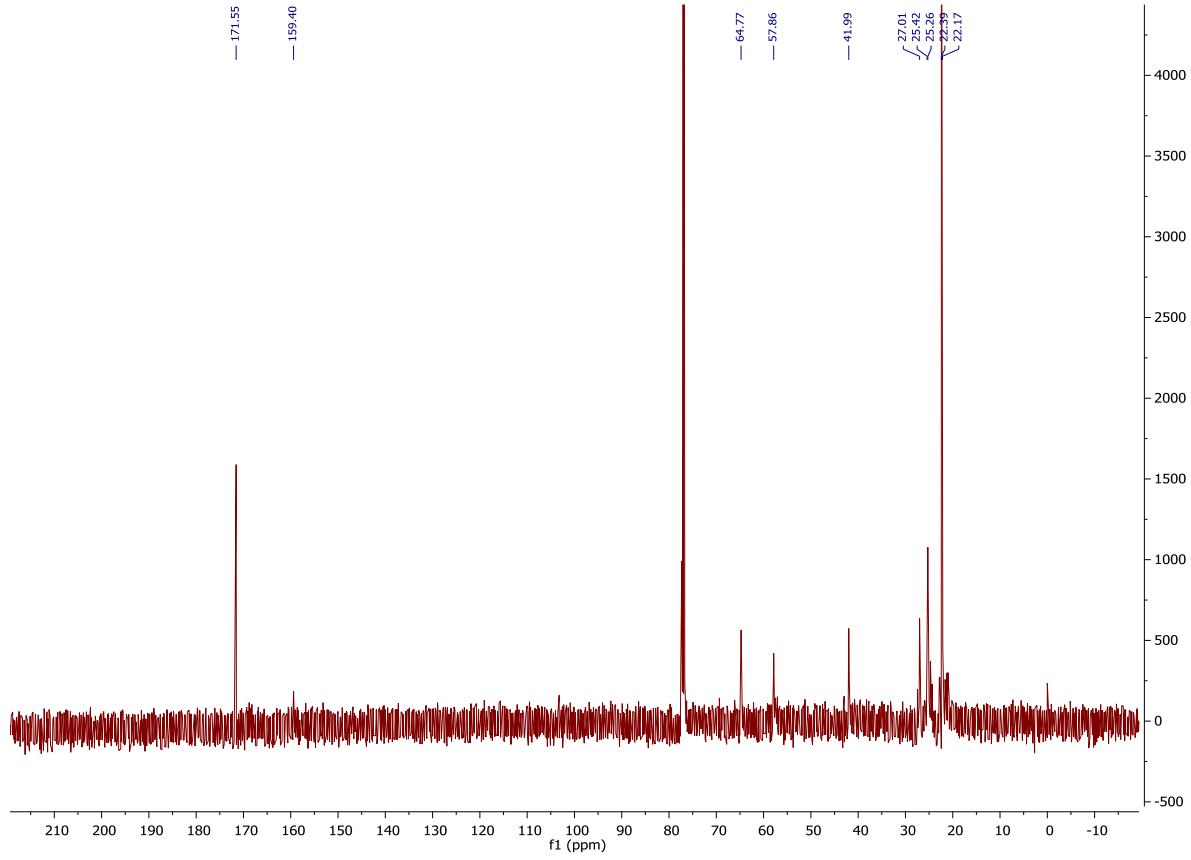




Chemical Formula: $C_{10}H_{18}N_6O$
Exact Mass: 238,15421
Molecular Weight: 238,29500

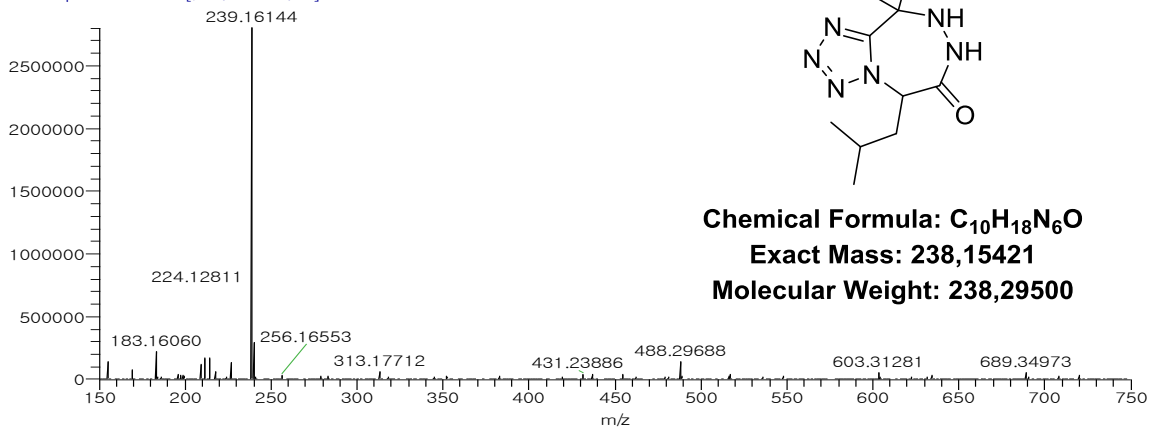
7a: 5-isobutyl-9,9-dimethyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5]triazepin-6(7*H*)-one





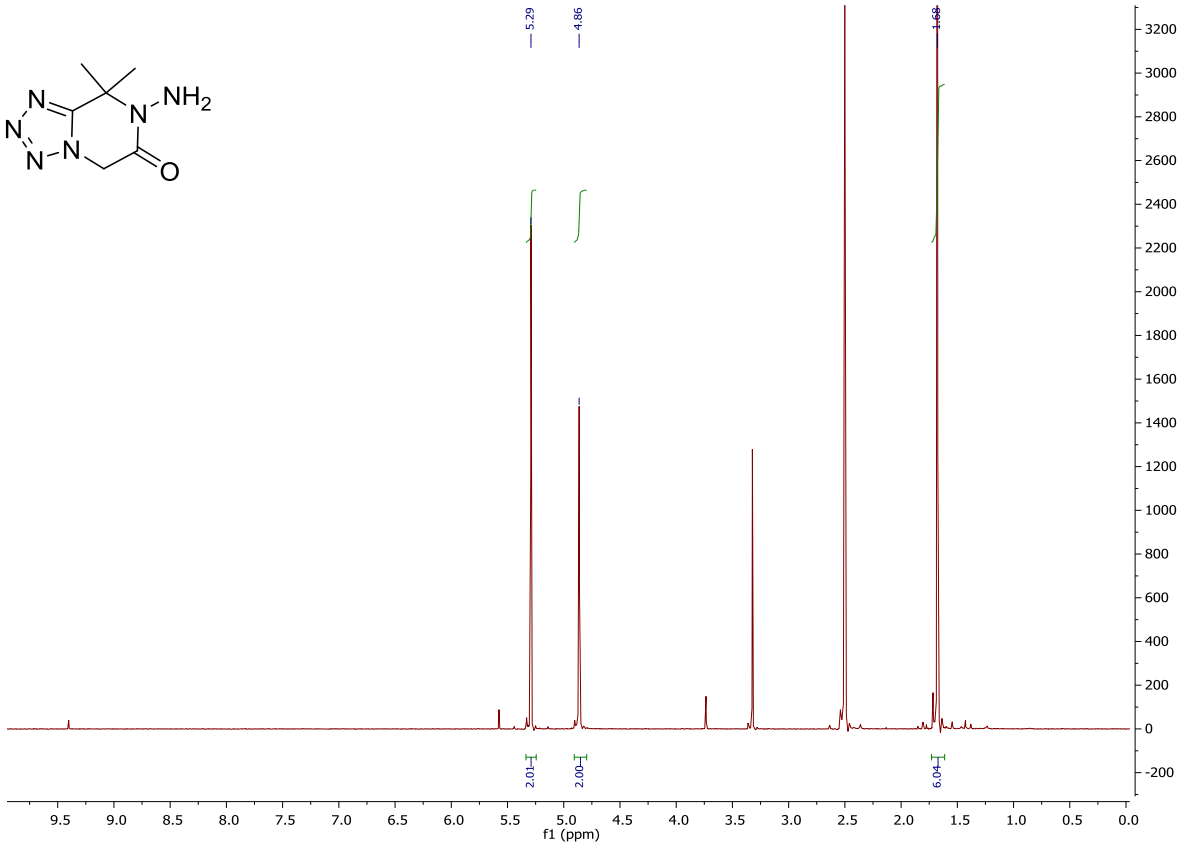
J:\20161130_ FIA-AccMass50\090-3 11/30/16 13:00:35

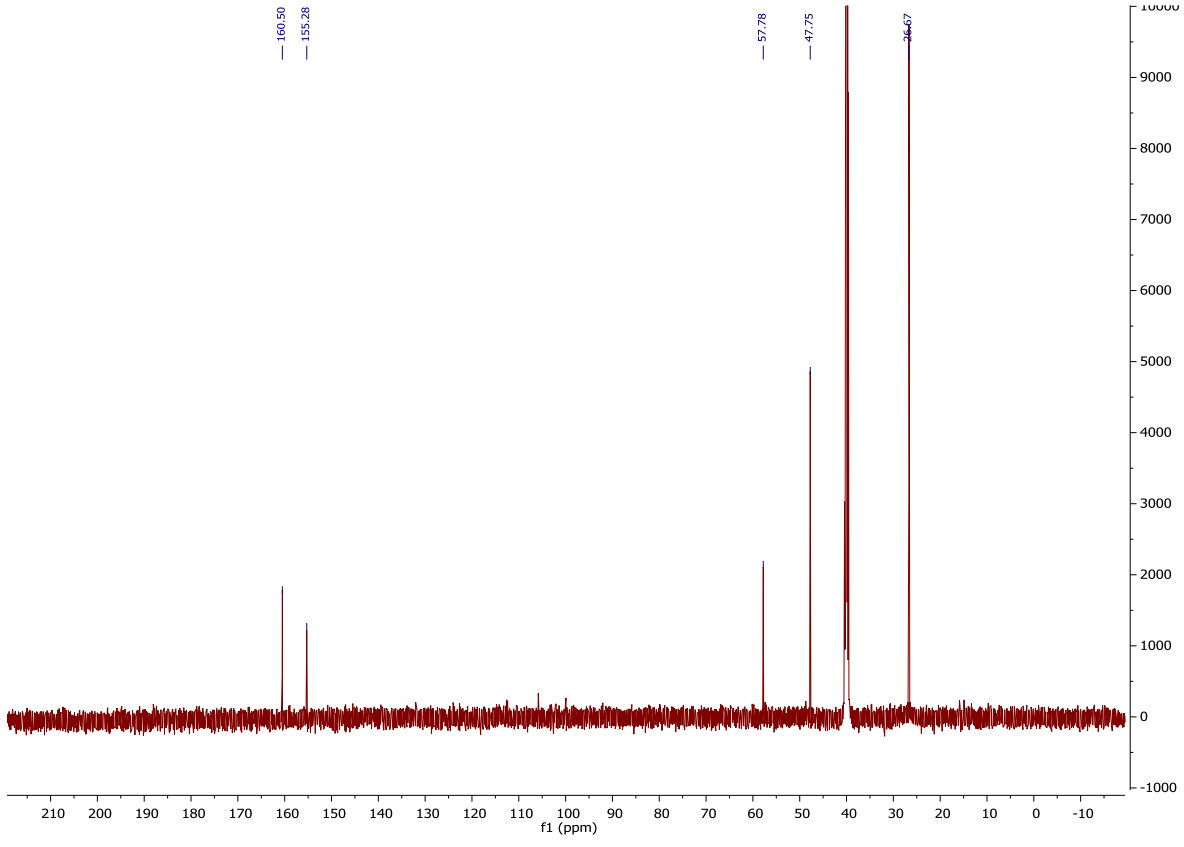
090-3 #20 RT: 0.34739 AV: 1 NL: 2.80E6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_{10}H_{18}N_6O$
Exact Mass: 238,15421
Molecular Weight: 238,29500

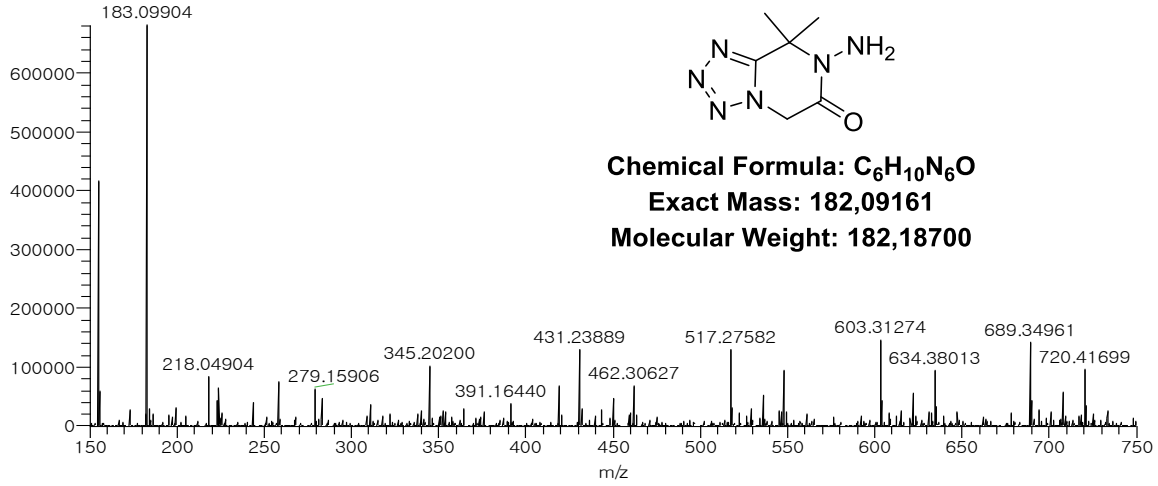
6b: 7-amino-8,8-dimethyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one





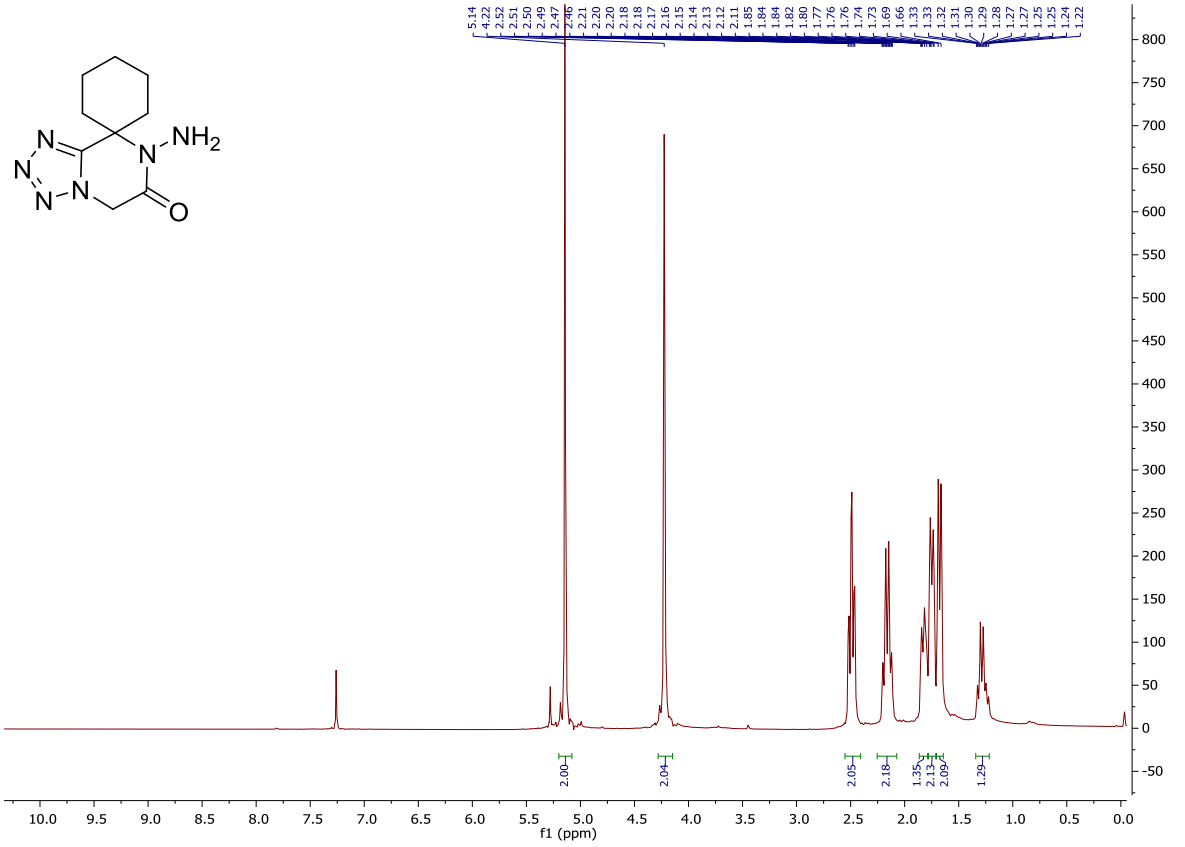
J:₩20161130_ FIA-AccMass50₩02a 11/30/16 12:55:50

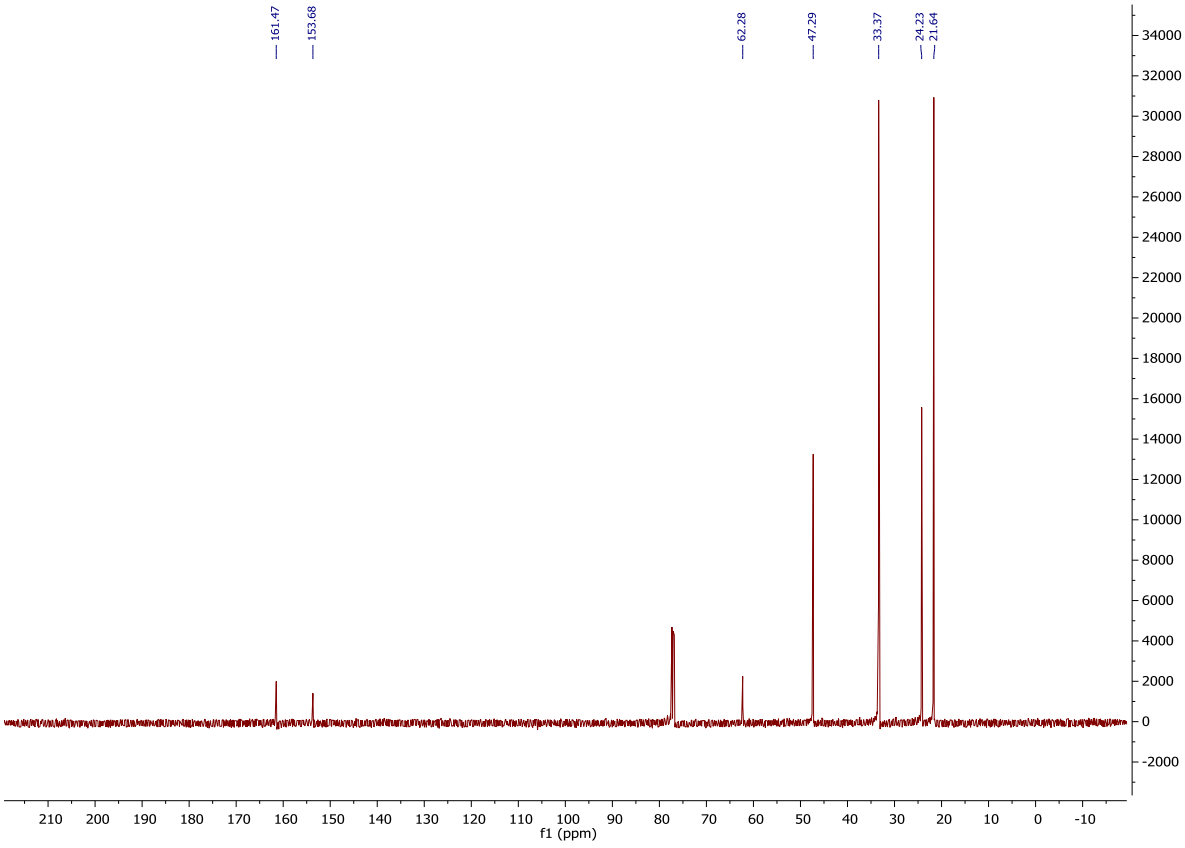
102a #17 RT: 0.28609 AV: 1 NL: 6.81E6
T: FTMS + p ESI Full ms [150.00-750.00]

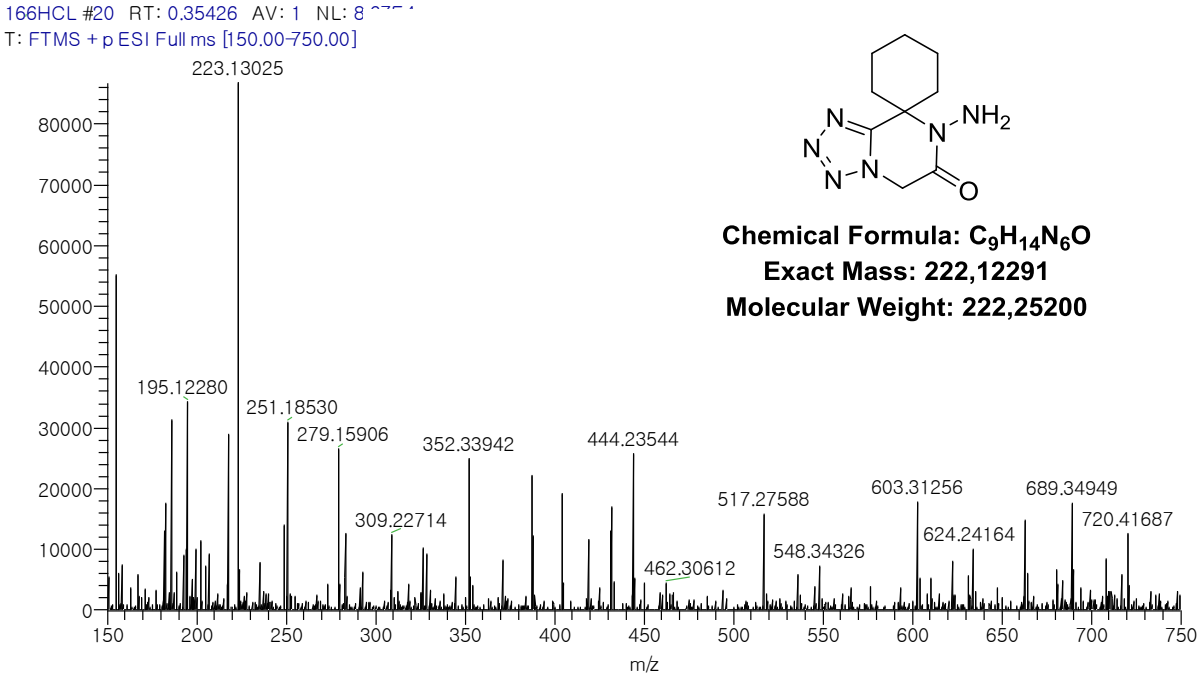


Chemical Formula: $C_6H_{10}N_6O$
Exact Mass: 182,09161
Molecular Weight: 182,18700

6c: 7'-amino-5'*H*-spiro[cyclohexane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'*H*)-one

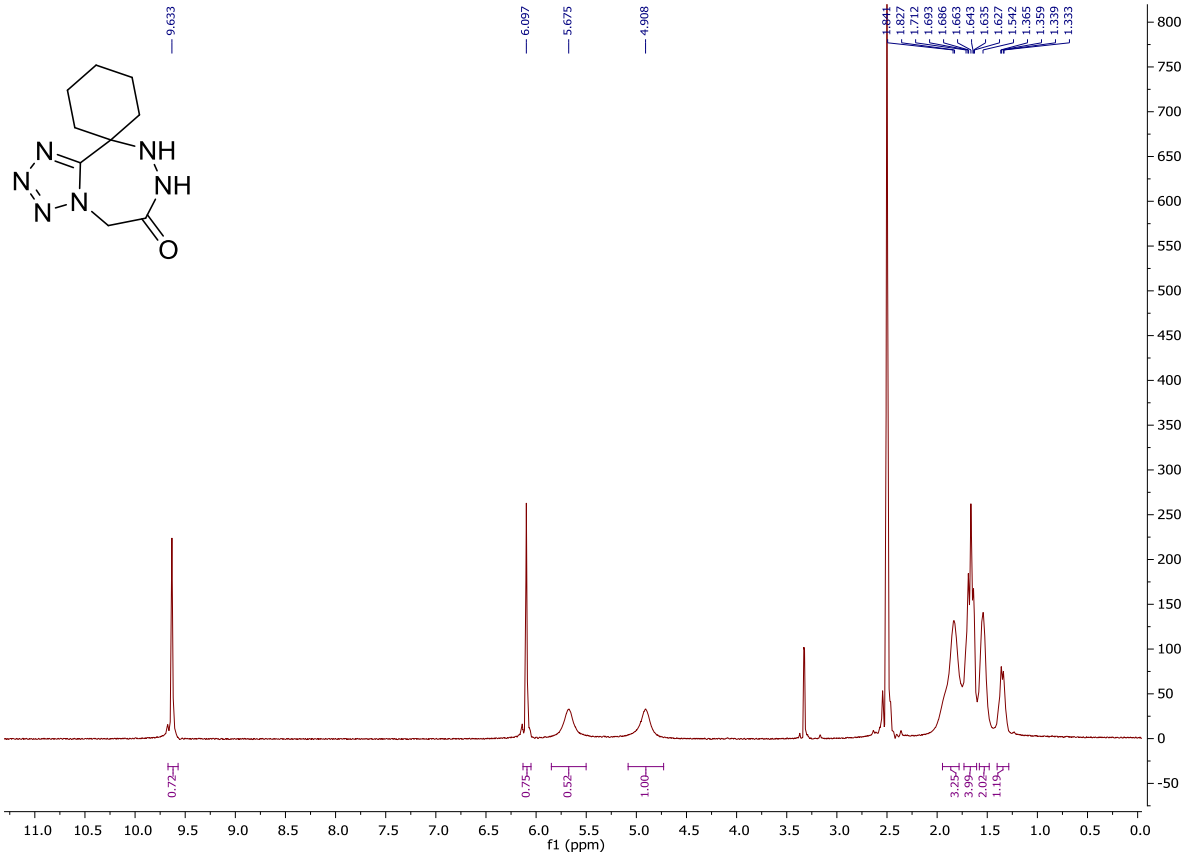


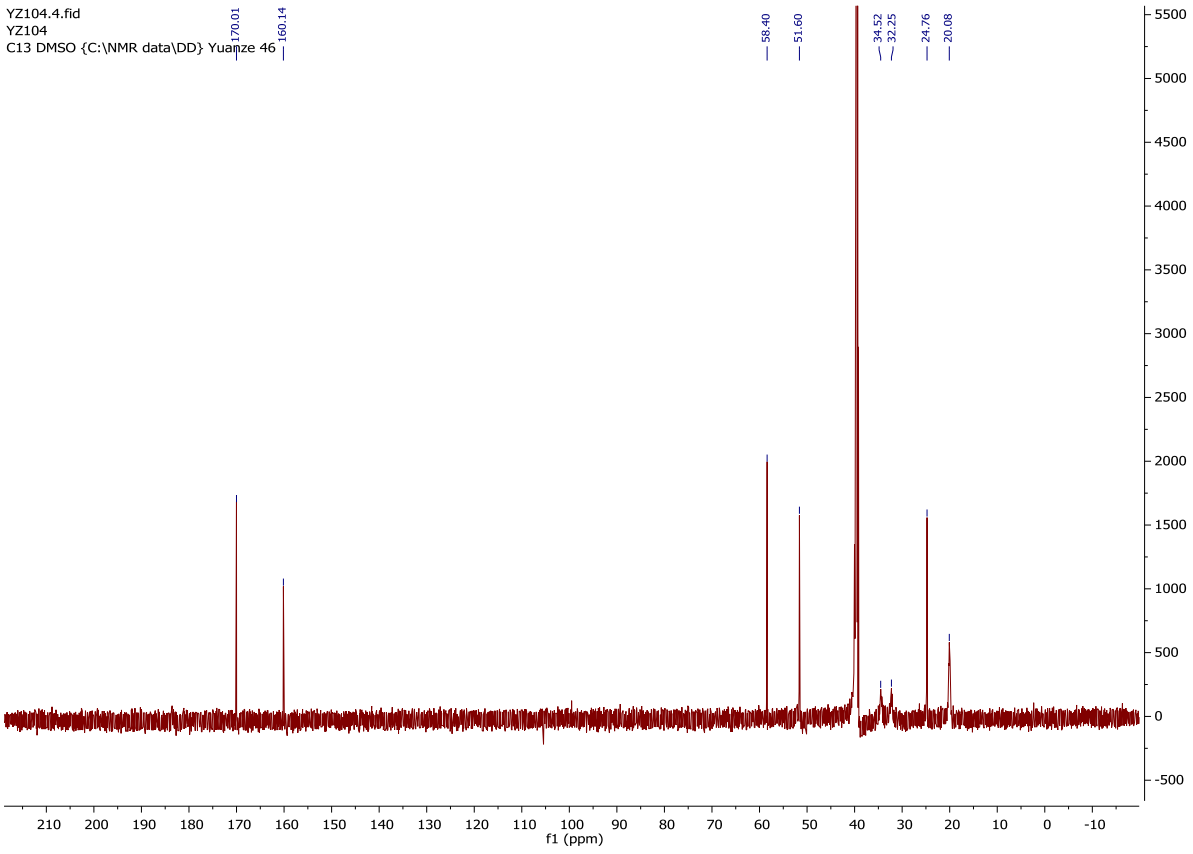




Chemical Formula: $C_9H_{14}N_6O$
Exact Mass: 222,12291
Molecular Weight: 222,25200

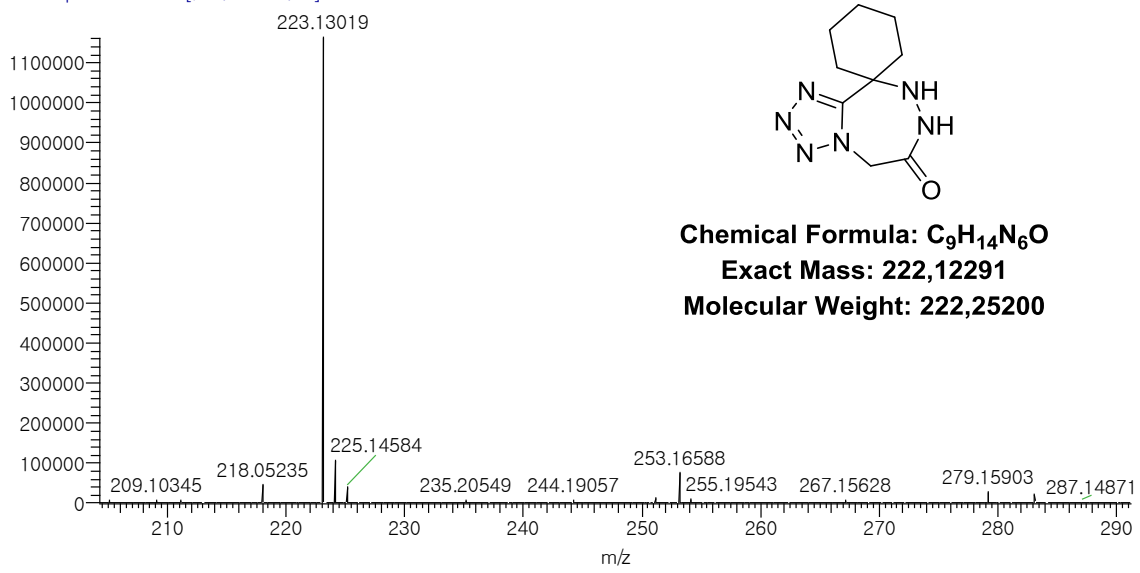
7c: 7',8'-dihydrospiro[cyclohexane-1,9'-tetrazolo[5,1-d][1,2,5]triazepin]-6'(5'*H*)-one





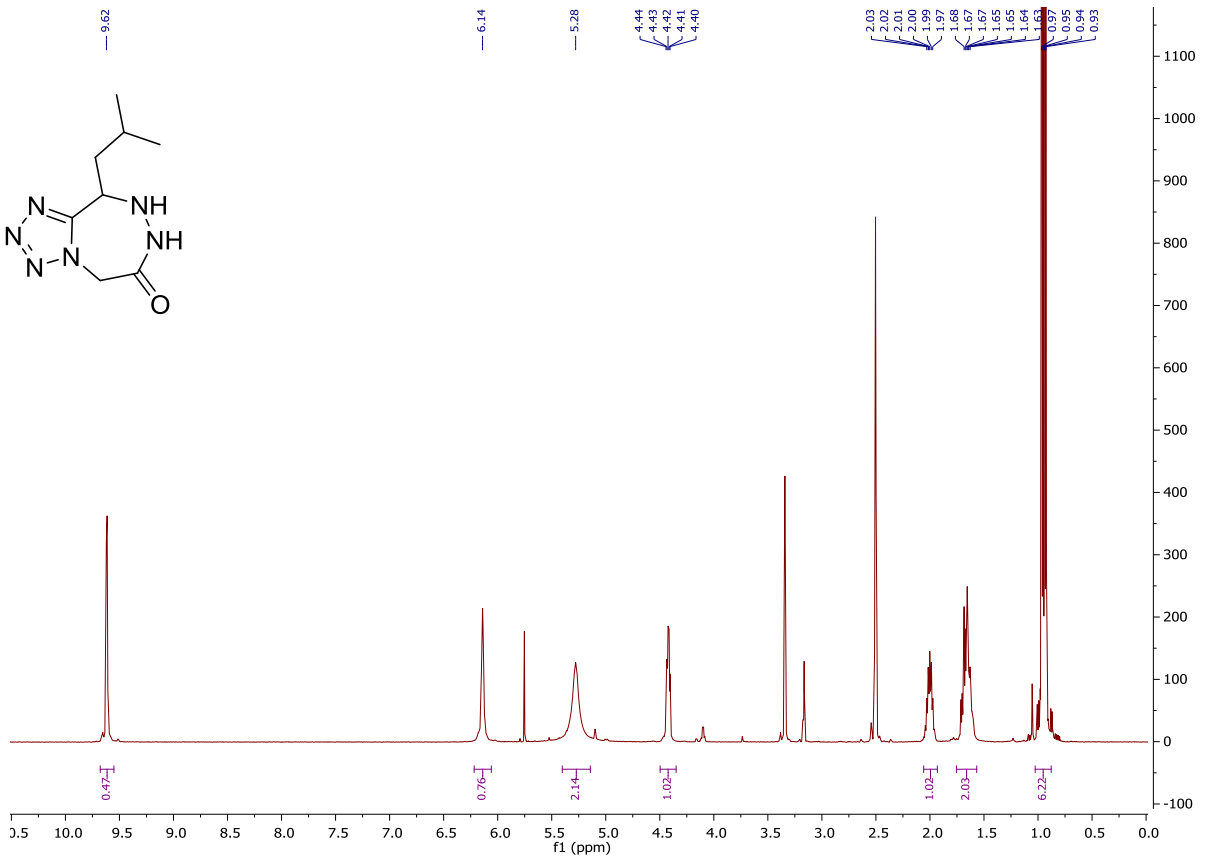
J:₩20161130_ FIA-AccMass50₩04b 11/30/16 12:47:35

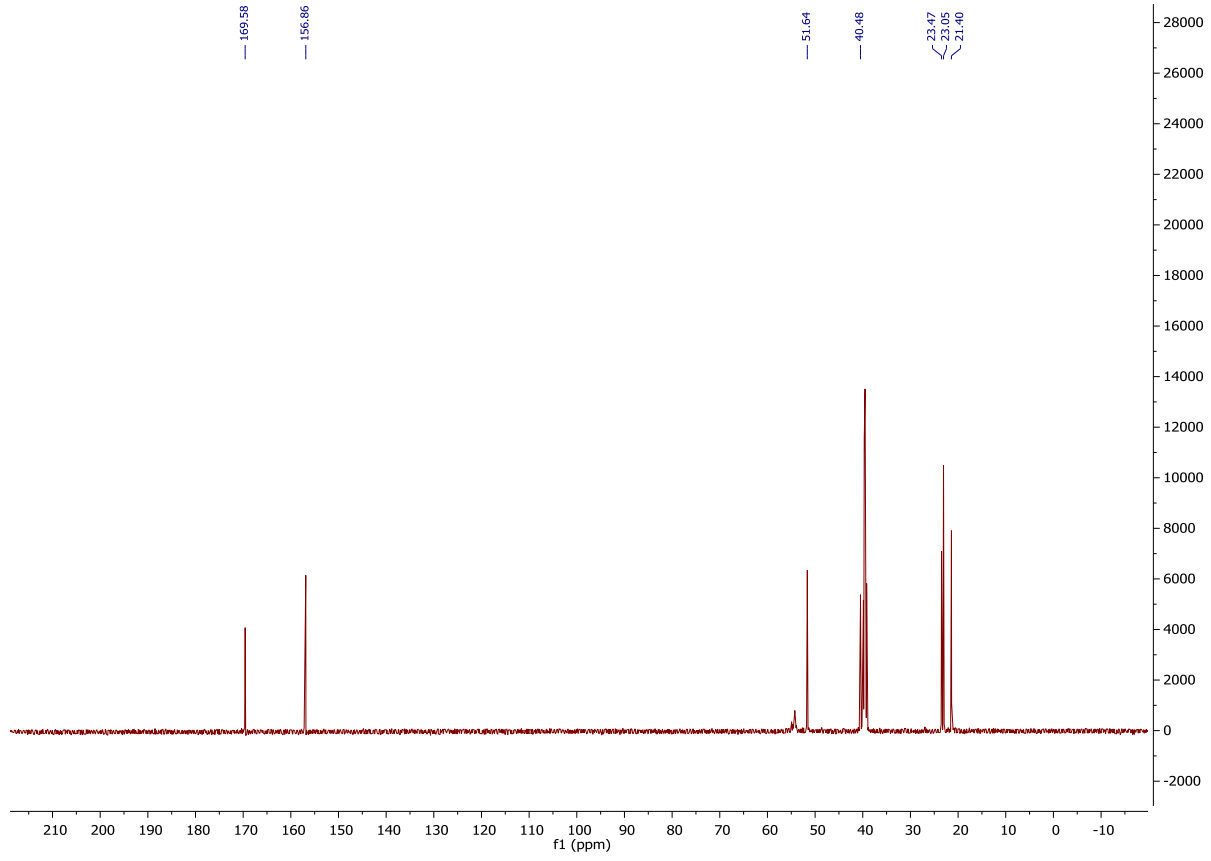
104b #21 RT: 0.35390 AV: 1 NL: 1.16E6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_9H_{14}N_6O$
Exact Mass: 222,12291
Molecular Weight: 222,25200

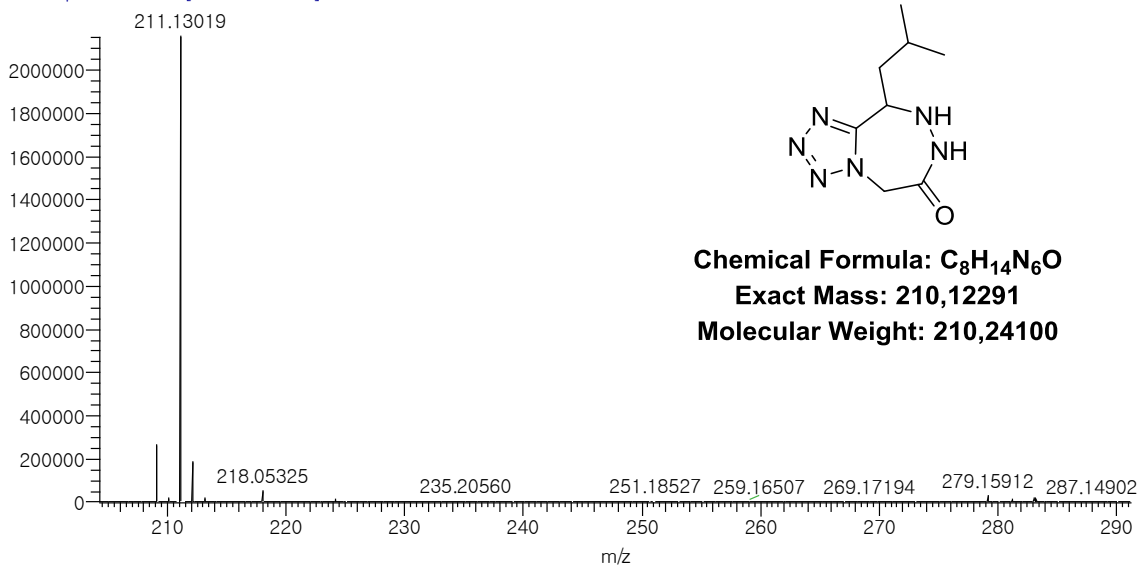
7d: 9-isobutyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5]triazepin-6(7*H*)-one





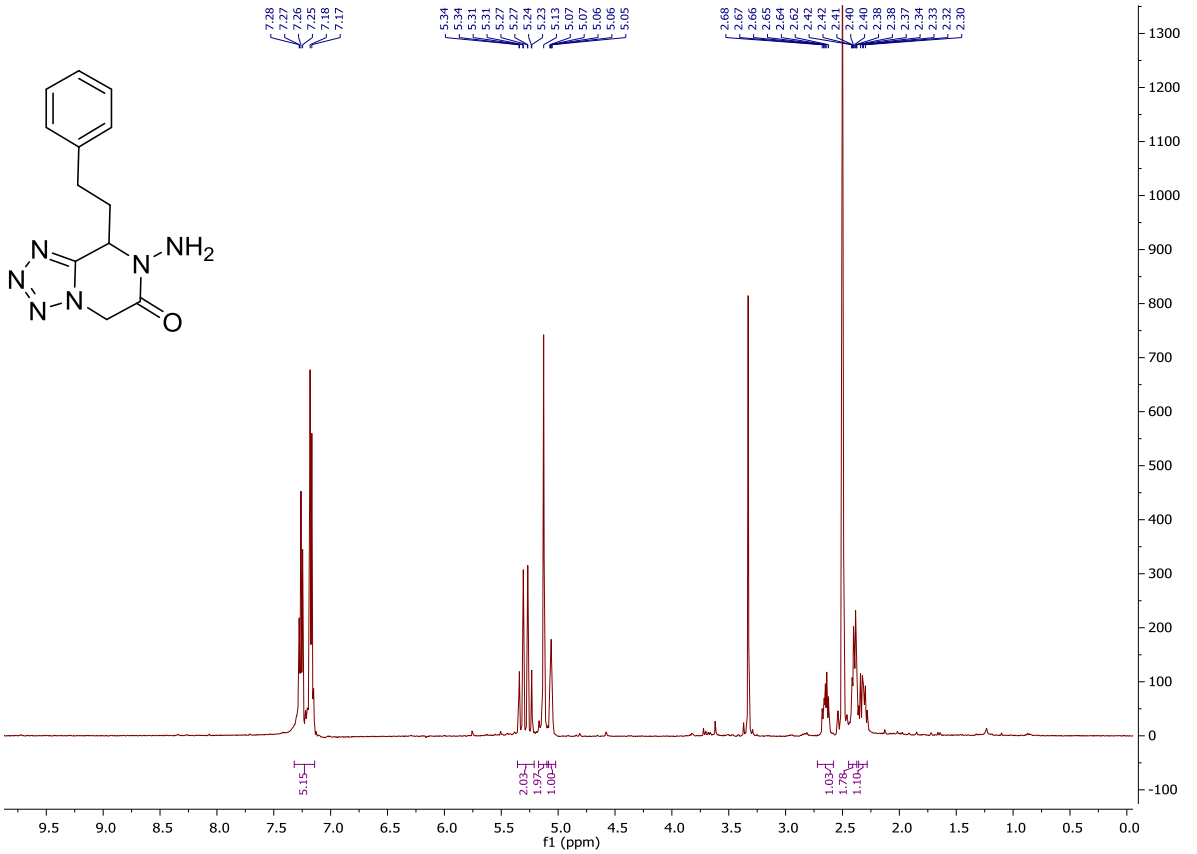
J:₩20161130_ FIA-AccMass50₩08b 11/30/16 12:33:31

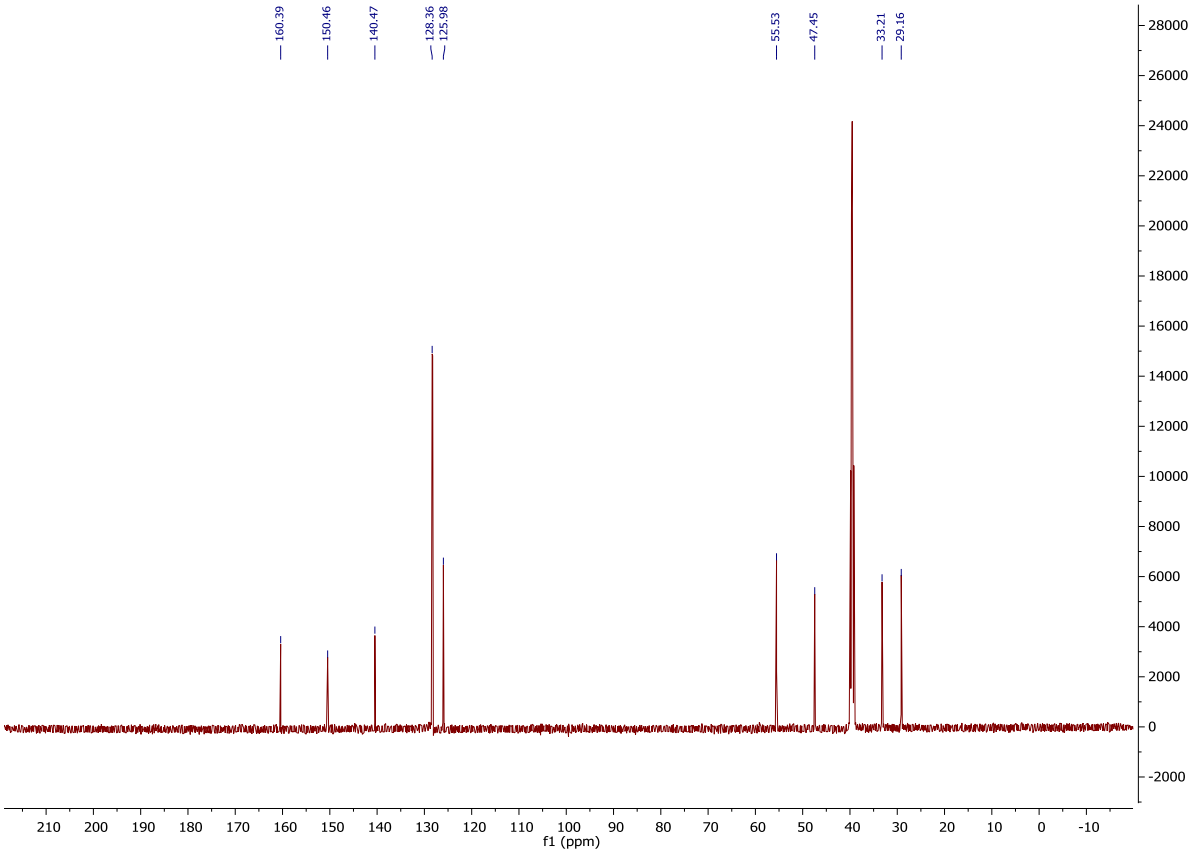
108b #20 RT: 0.34934 AV: 1 NL: 2.16E6
T: FTMS + p ESI Full ms [150.00-750.00]



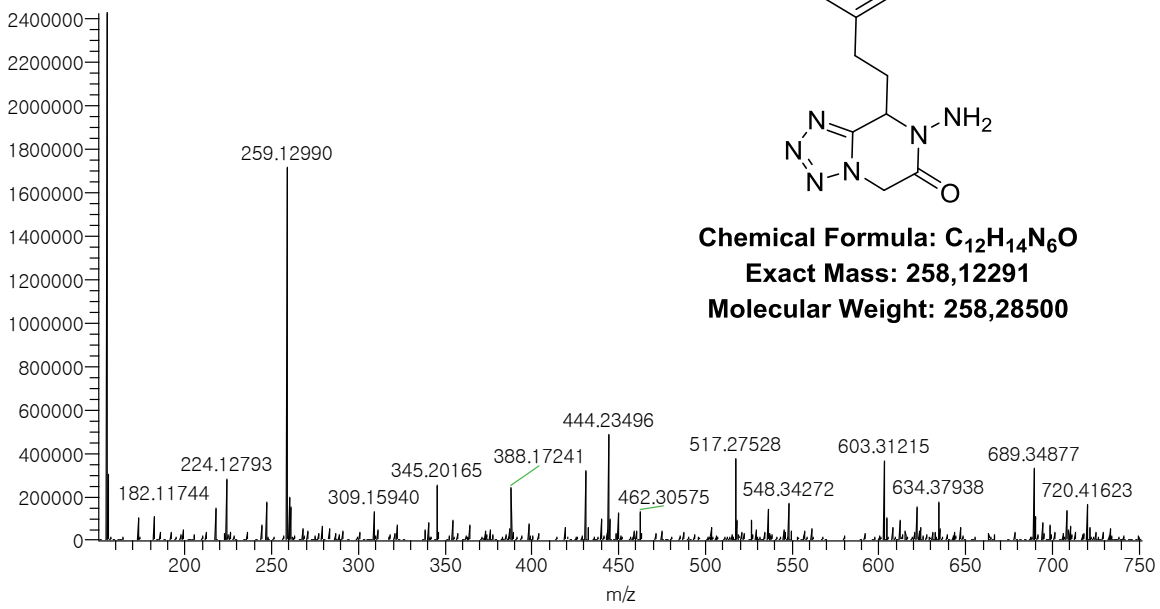
Chemical Formula: $C_8H_{14}N_6O$
Exact Mass: 210,12291
Molecular Weight: 210,24100

6e: 7-amino-8-phenethyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one



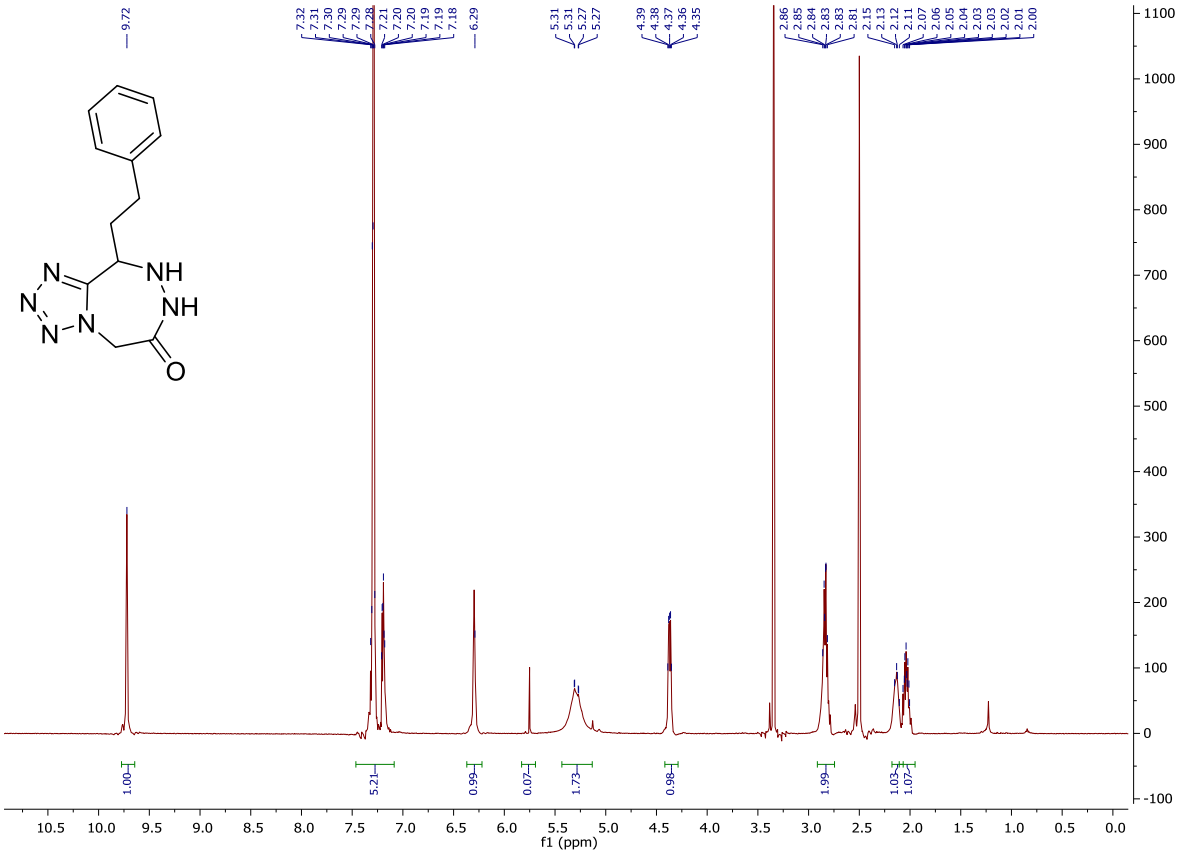


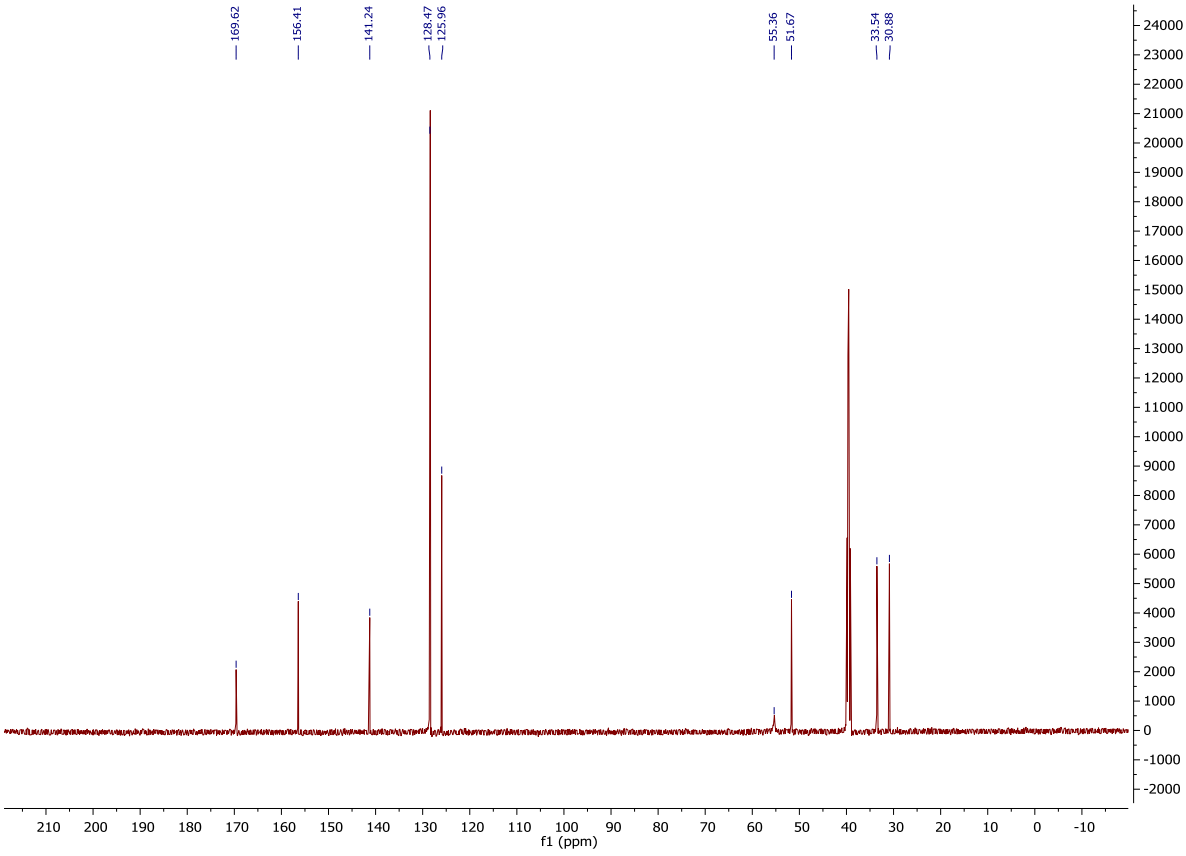
112A #10-14 RT: 0.18034-0.24604 AV:
T: FTMS + p ESI Full ms [150.00-750.00]

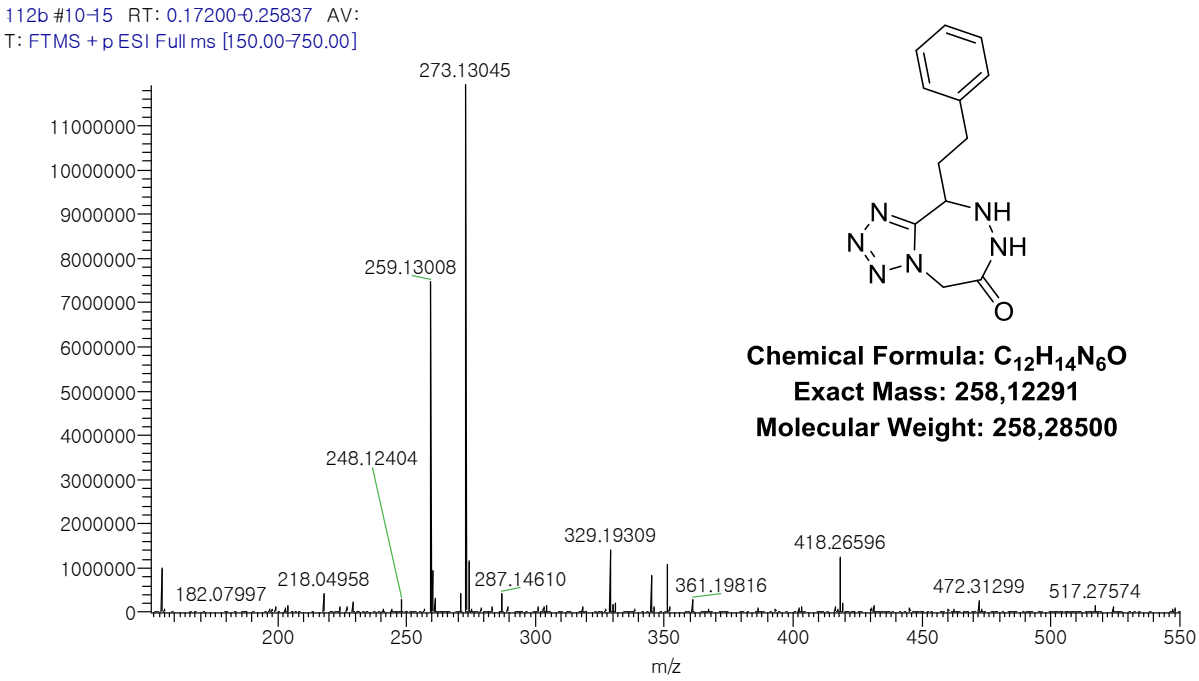


Chemical Formula: $C_{12}H_{14}N_6O$
Exact Mass: 258,12291
Molecular Weight: 258,28500

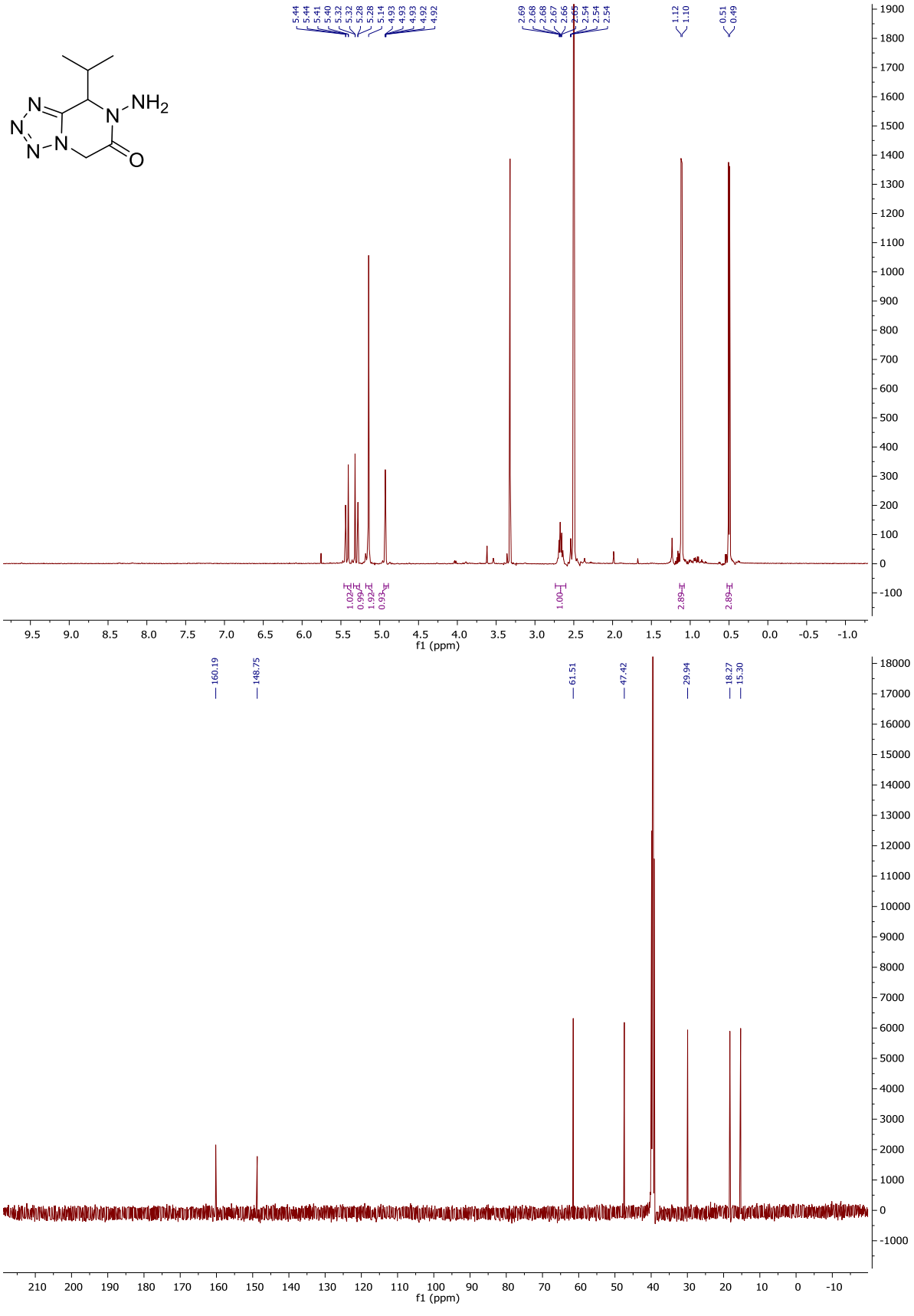
7e: 9-phenethyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5]triazepin-6(7*H*)-one





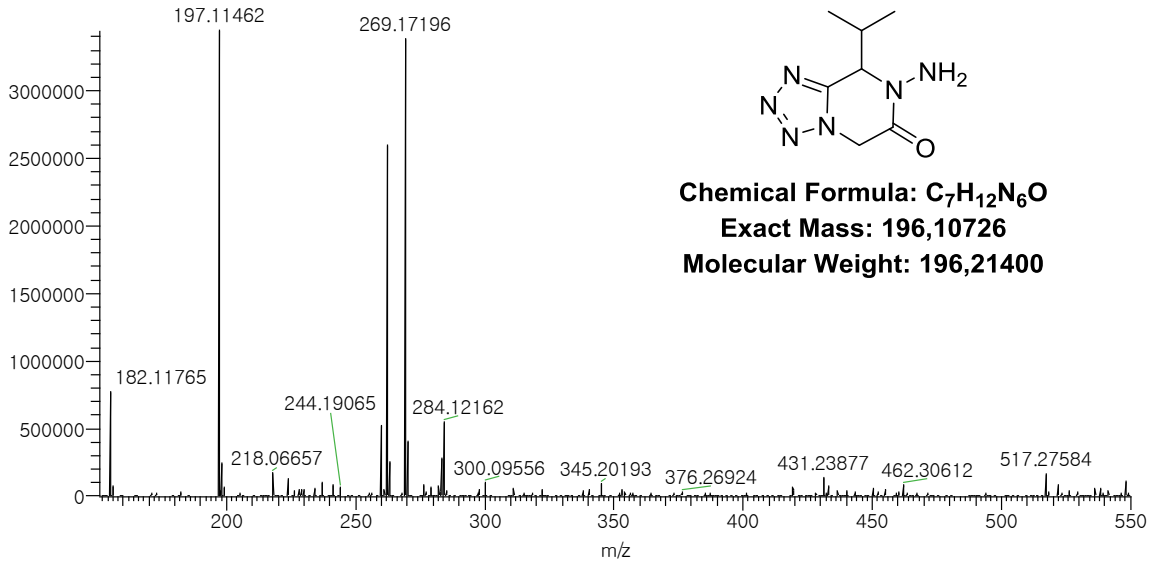

112b #10-15 RT: 0.17200-0.25837 AV:
T: FTMS + p ESI Full ms [150.00-750.00]
273.13045
259.13008
248.12404
329.19309
418.26596
182.07997
218.04958
287.14610
361.19816
472.31299
517.27574
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
200
250
300
350
400
450
500
550
m/z
N
NH
N
NH
N
N
O
Chemical Formula: C12H14N6O
Exact Mass: 258,12291
Molecular Weight: 258,28500

6f: 7-amino-8-isopropyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one



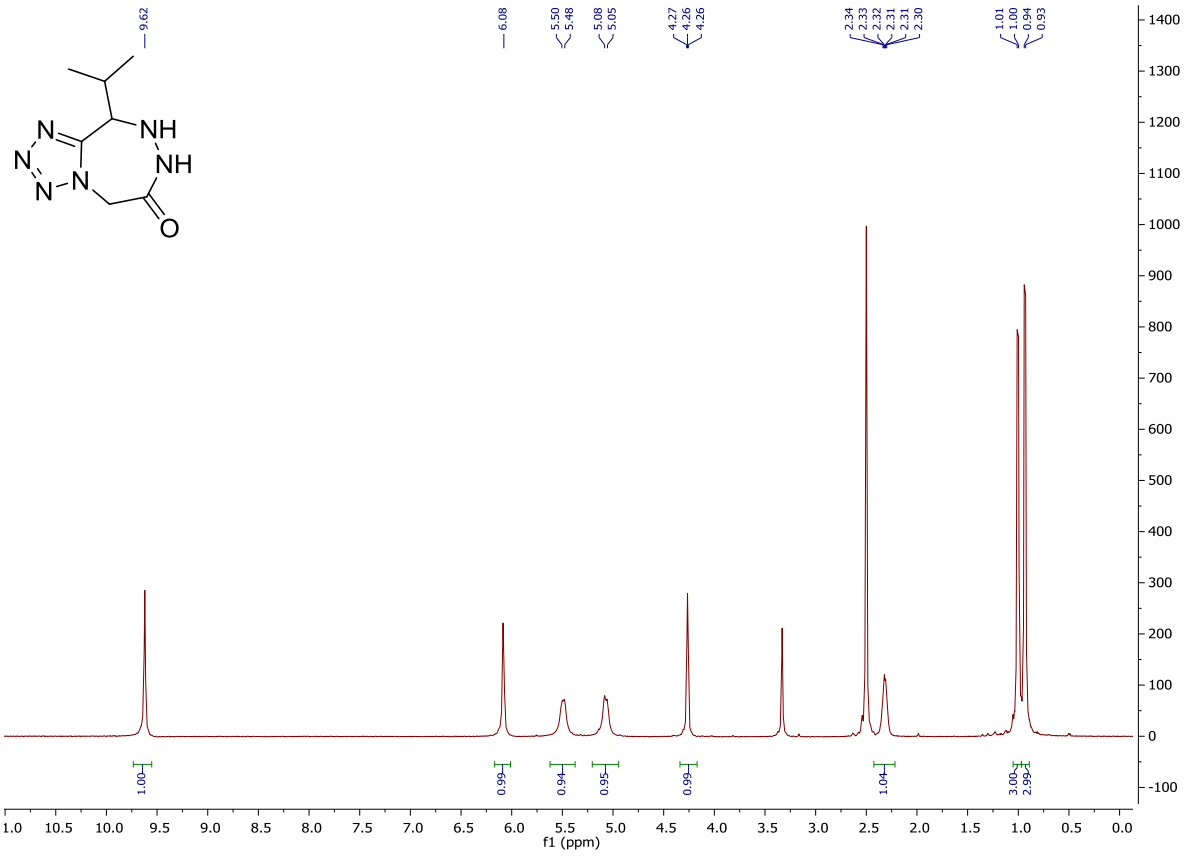
J:₩20161130_ FIA-AccMass50₩14a 11/30/16 12:14:36

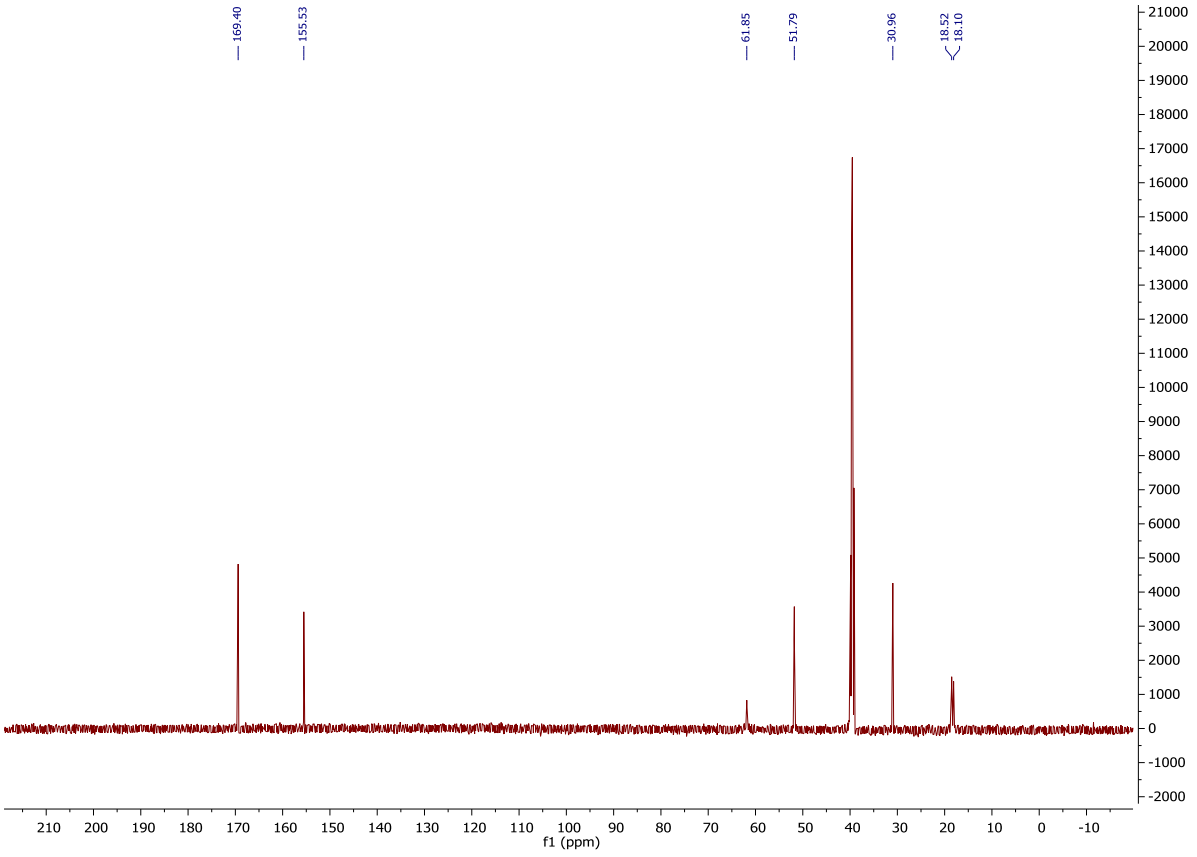
114a #9-14 RT: 0.16763-0.25226 AV: 6 NL: 3.44E6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_7H_{12}N_6O$
Exact Mass: 196,10726
Molecular Weight: 196,21400

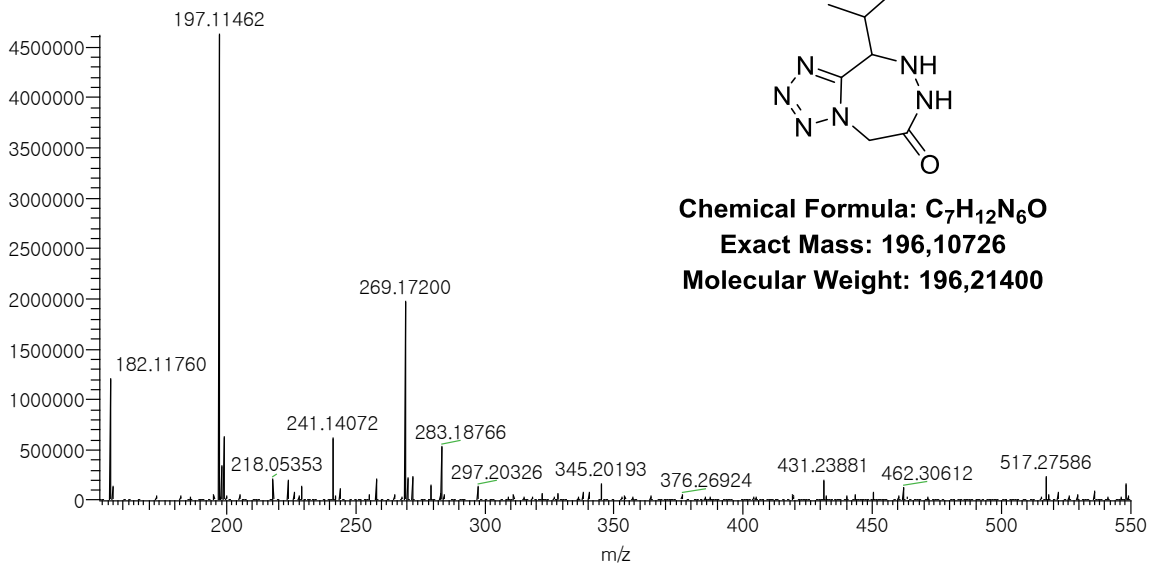
7f: 9-isopropyl-8,9-dihydro-5*H*-tetrazolo[5,1-d][1,2,5]triazepin-6(7*H*)-one





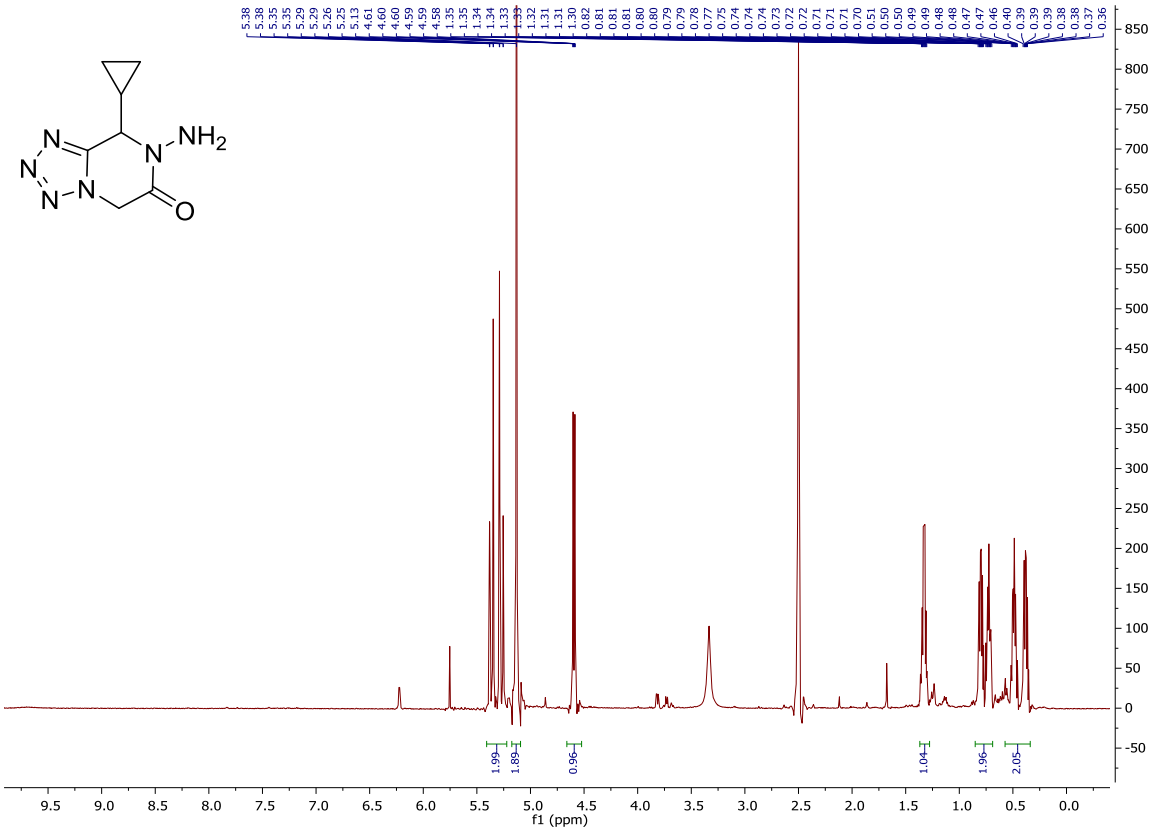
J:₩20161130_ FIA-AccMass50₩14b 11/30/16 12:22:53

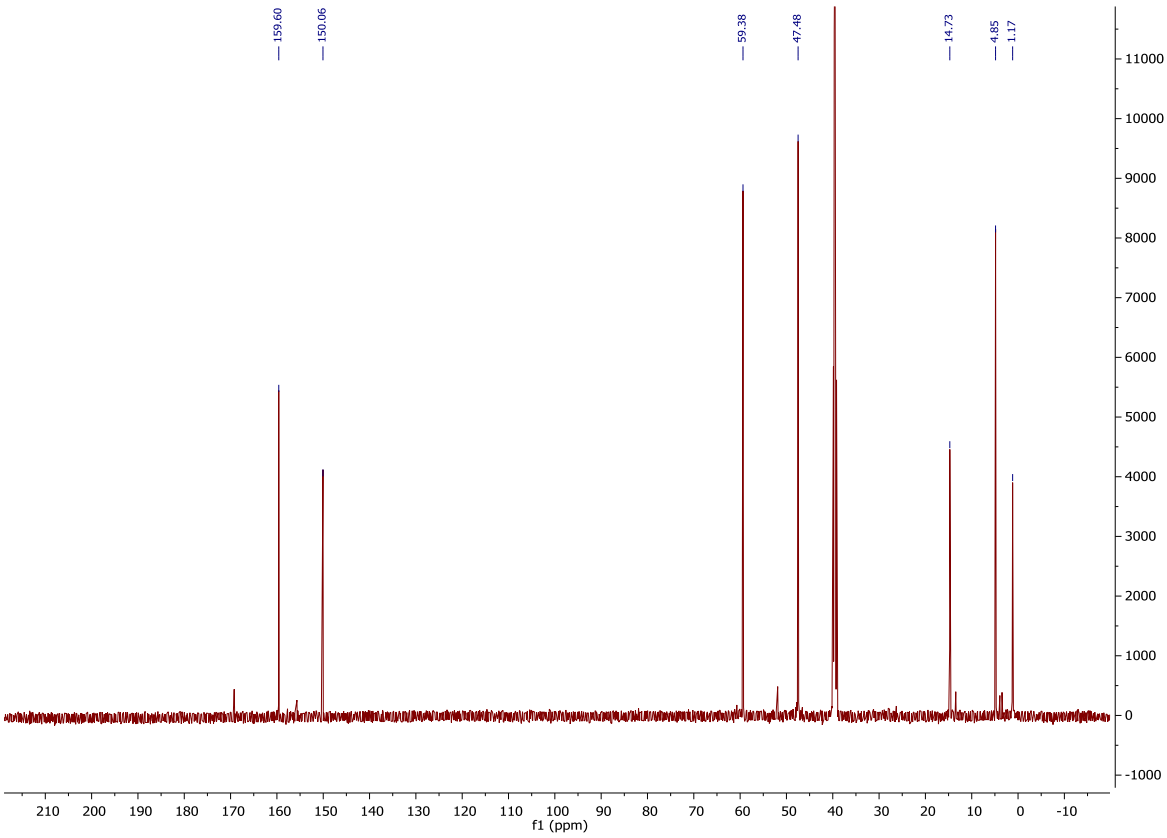
114b #9-14 RT: 0.17497-0.25395 AV: 6 NL: 4.82E6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_7H_{12}N_6O$
Exact Mass: 196,10726
Molecular Weight: 196,21400

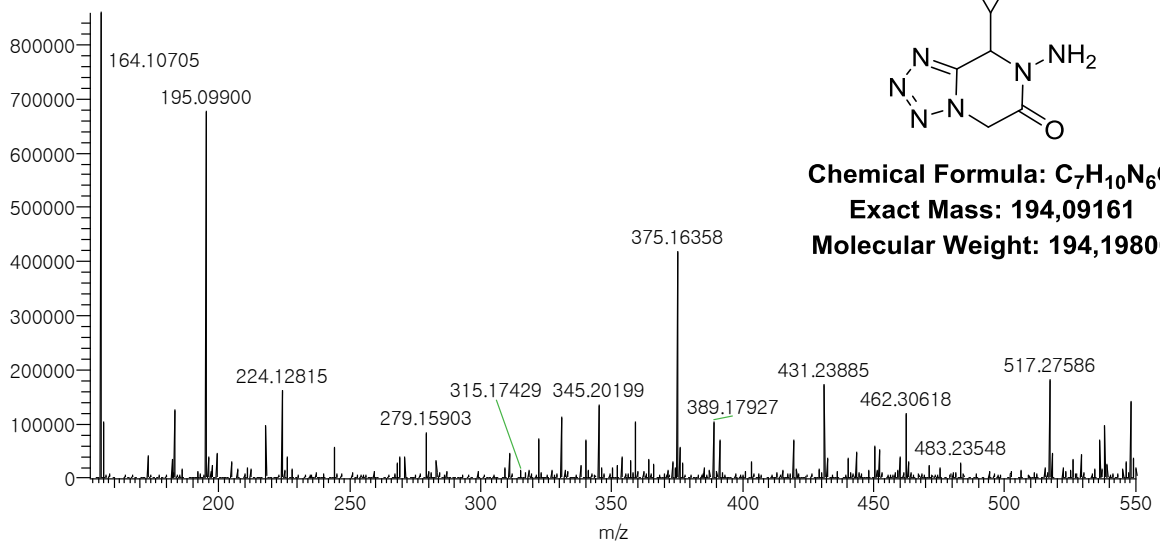
6g: 7-amino-8-cyclopropyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one





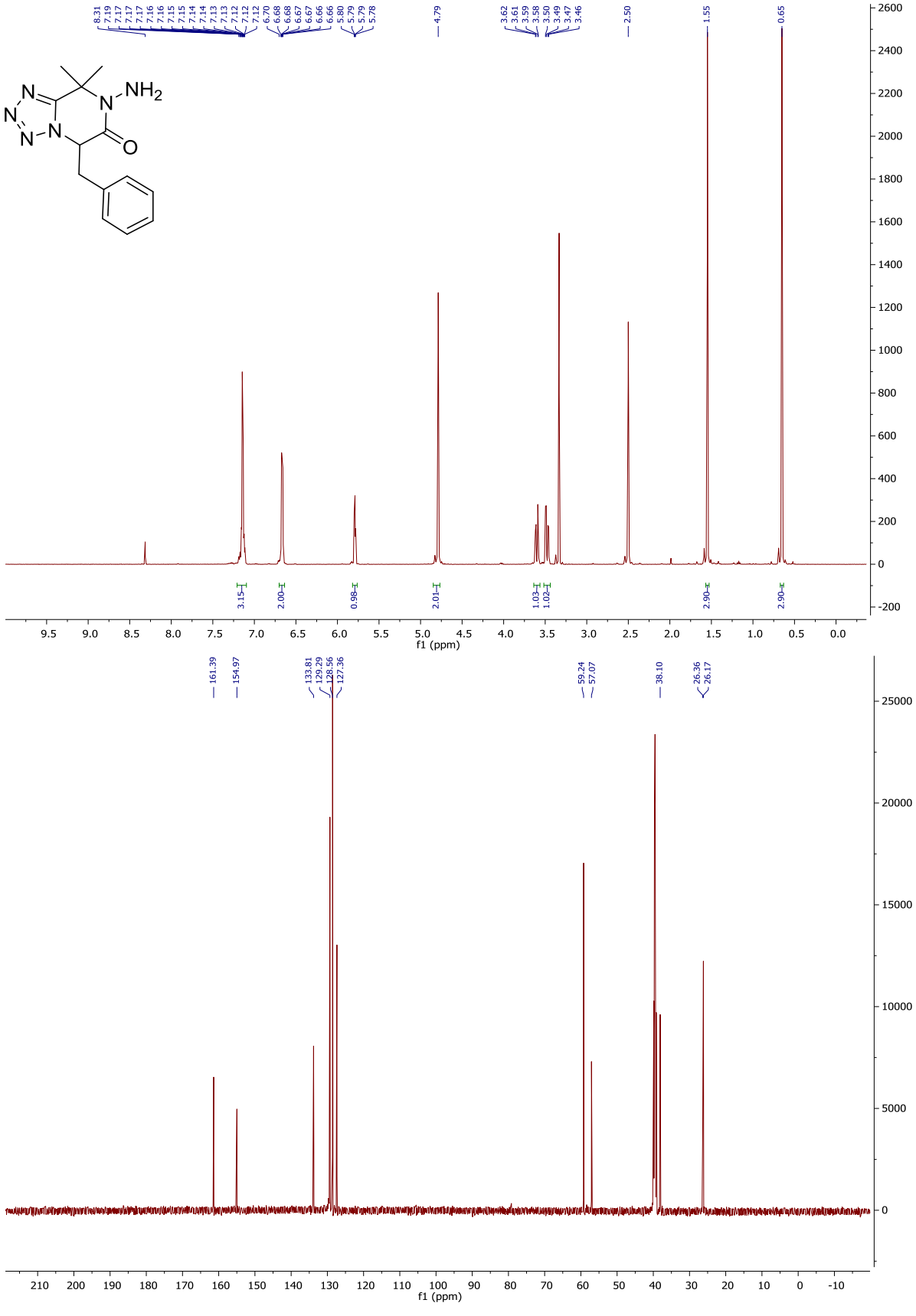
J:₩20161130_ FIA-AccMass50₩16a 11/30/16 12:15:46

116a #9-14 RT: 0.16811-0.25293 AV: 6 NL: 0.55E5
T: FTMS + p ESI Full ms [150.00-750.00]



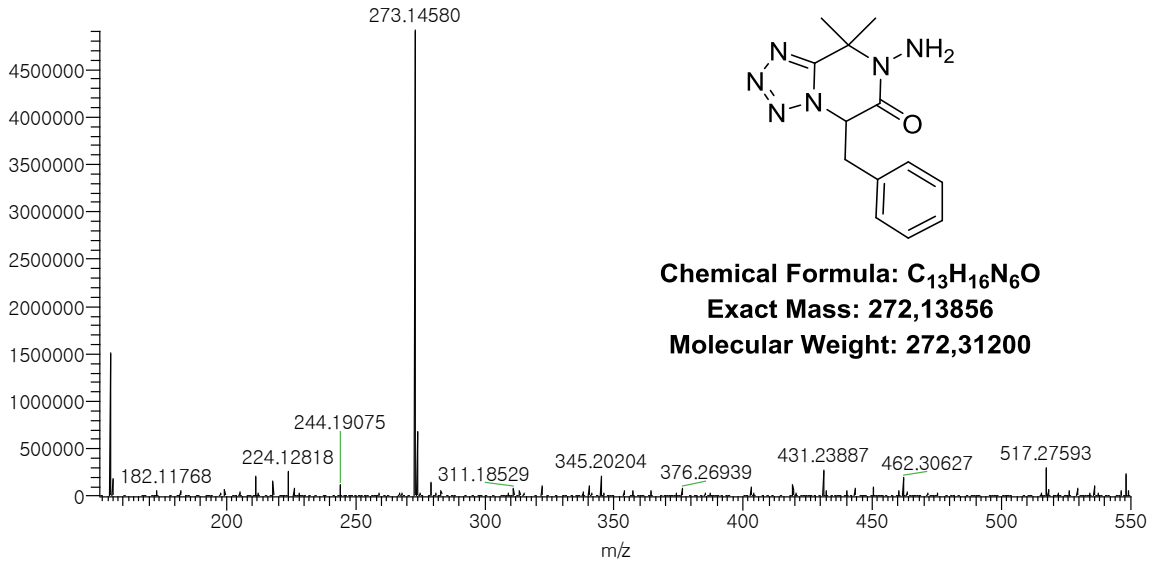
Chemical Formula: $C_7H_{10}N_6O$
Exact Mass: 194,09161
Molecular Weight: 194,19800

6h: 7-amino-5-benzyl-8,8-dimethyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one



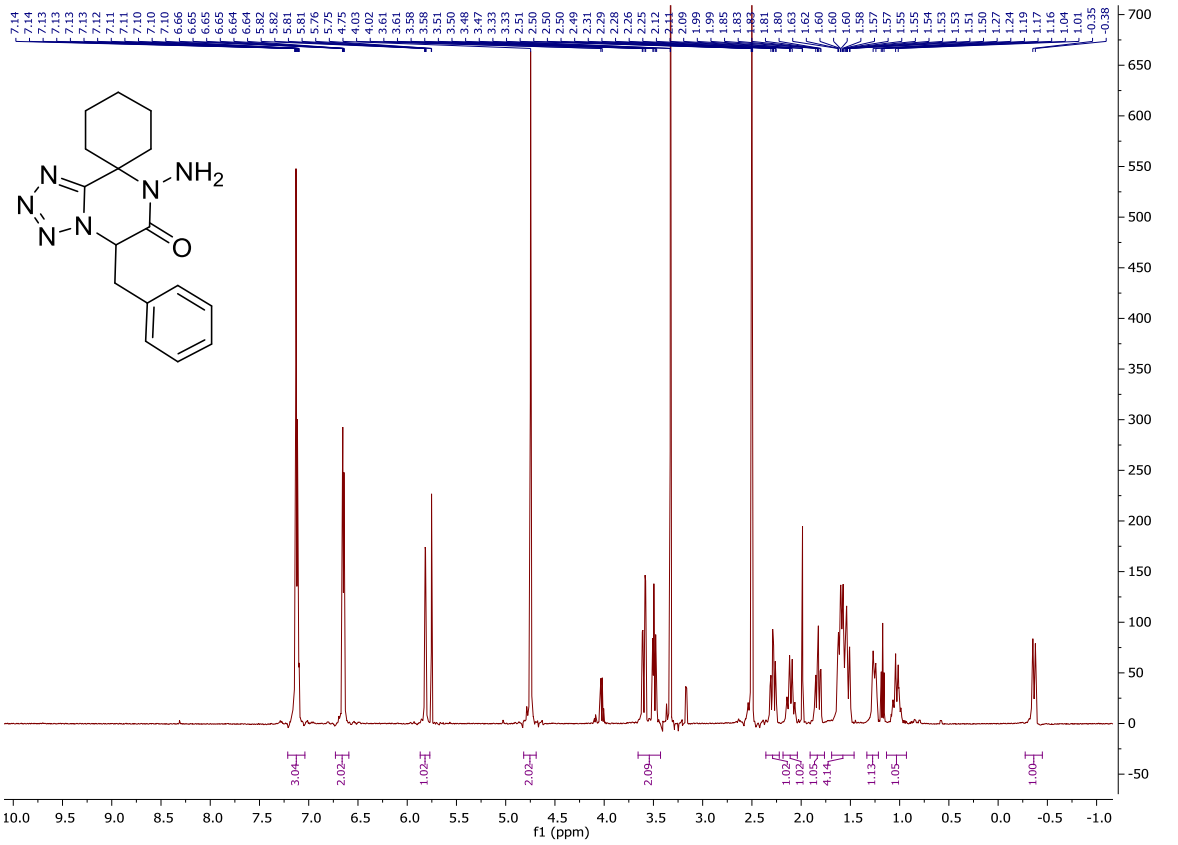
J:₩20161130_ FIA-AccMass50₩18 11/30/16 12:34:40

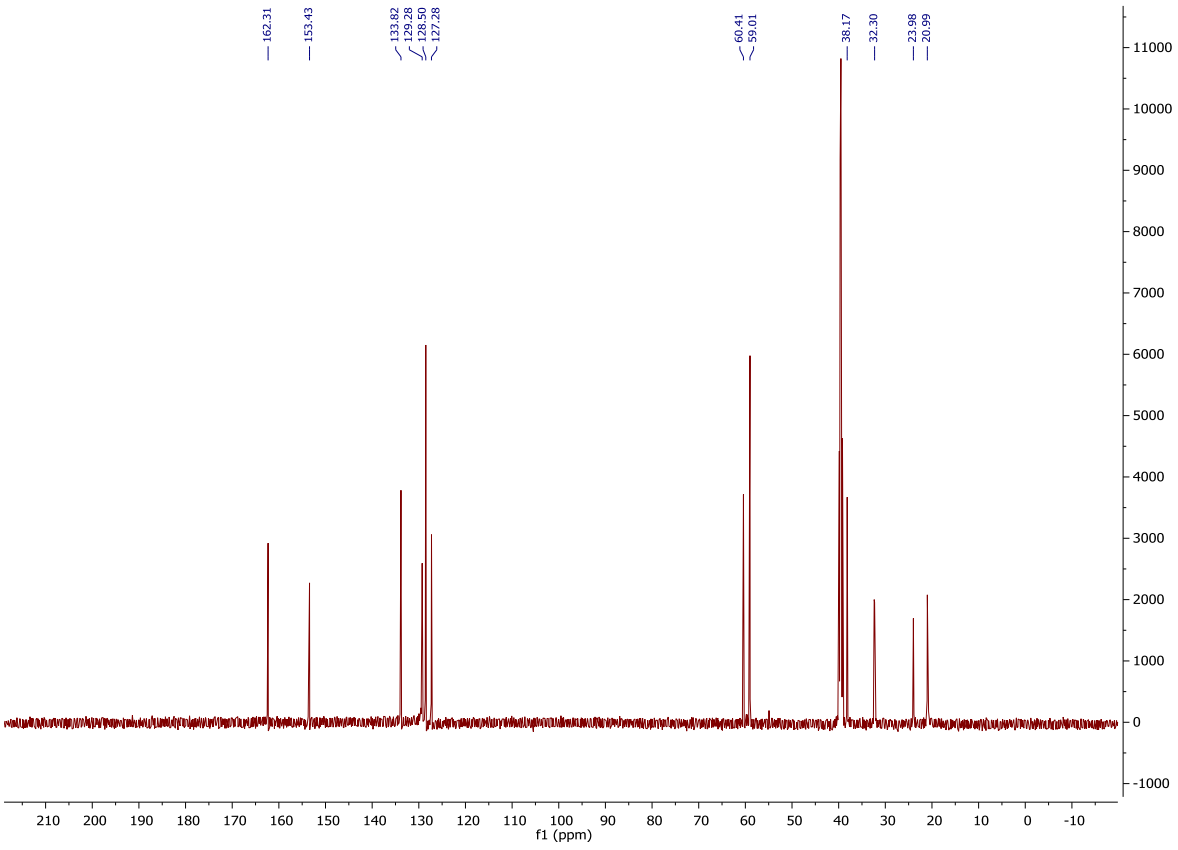
118 #10-15 RT: 0.17473-0.25155 AV: 6 NL: 4.91E6
T: FTMS + p ESI Full ms [150.00-750.00]

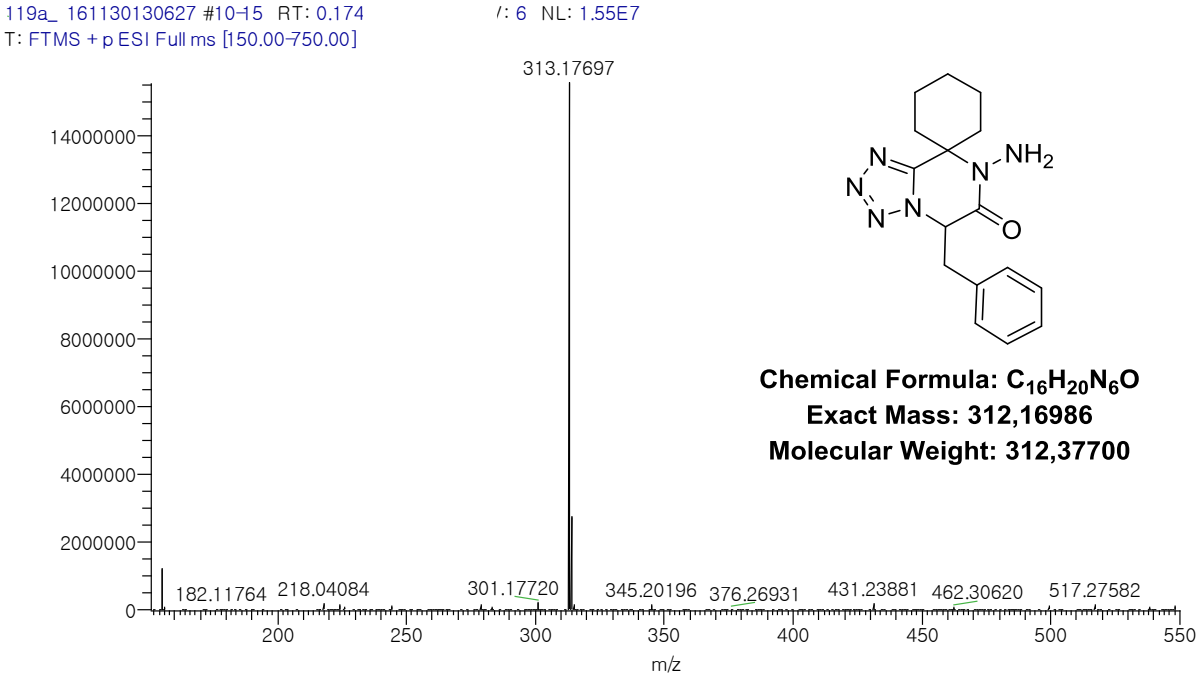


Chemical Formula: $C_{13}H_{16}N_6O$
Exact Mass: 272,13856
Molecular Weight: 272,31200

6i:7'-amino-5'-benzyl-5'*H*-spiro[cyclohexane-1,8'-tetrazolo[1,5-a] pyrazin] -6'(7'*H*)-one

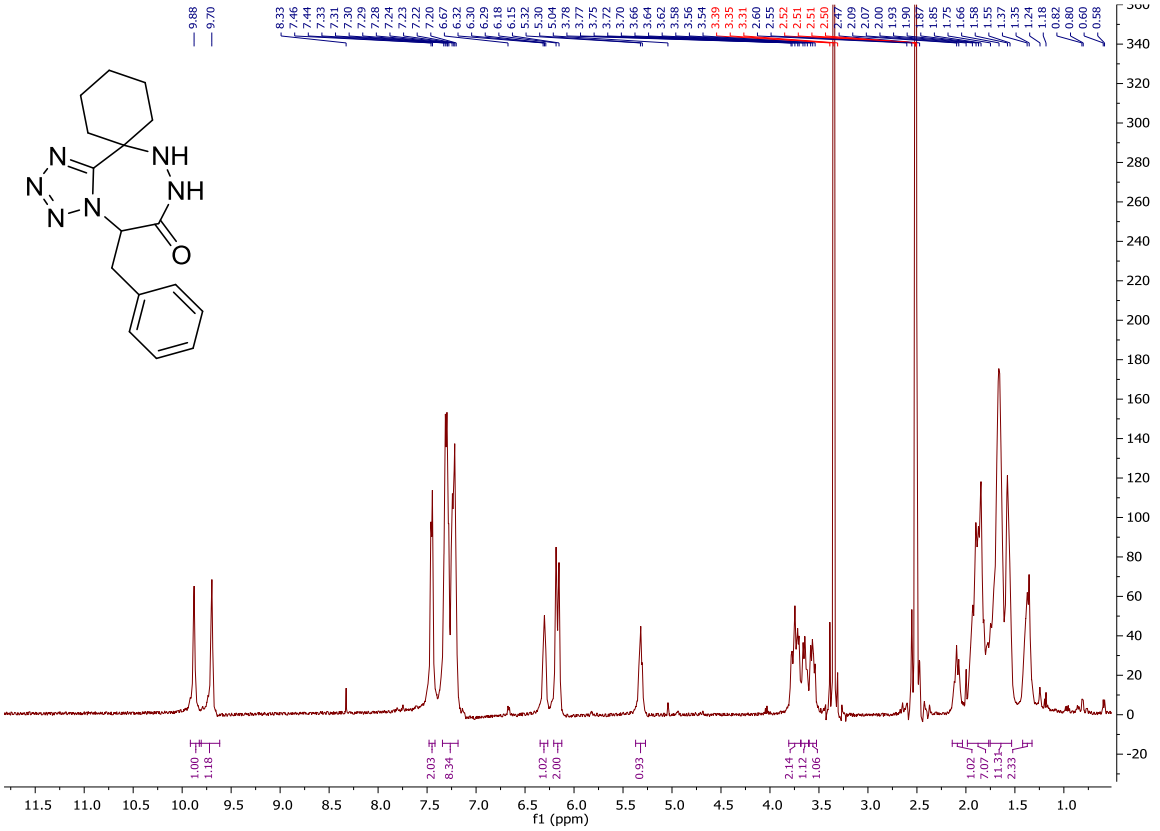


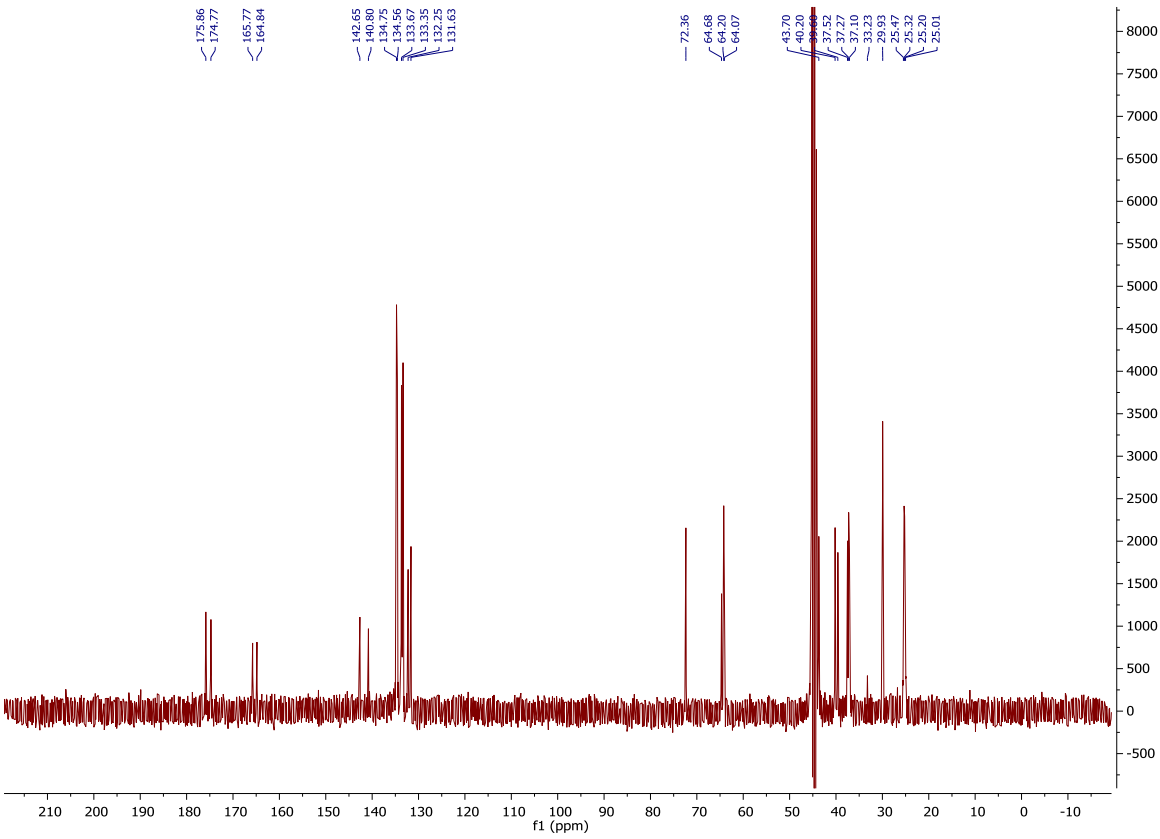




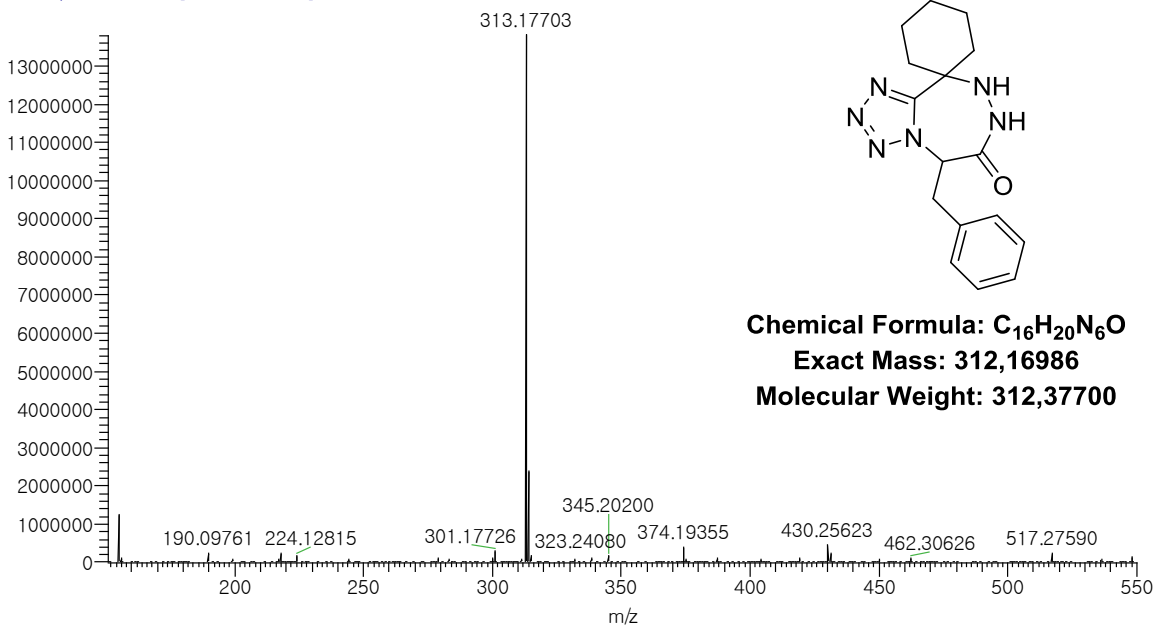
Chemical Formula: $C_{16}H_{20}N_6O$
Exact Mass: 312,16986
Molecular Weight: 312,37700

7i: 5'-benzyl-7',8'-dihydrospiro[cyclohexane-1,9'-tetrazolo[5,1-d][1,2,5] triazepin]-6'(5'H)-one



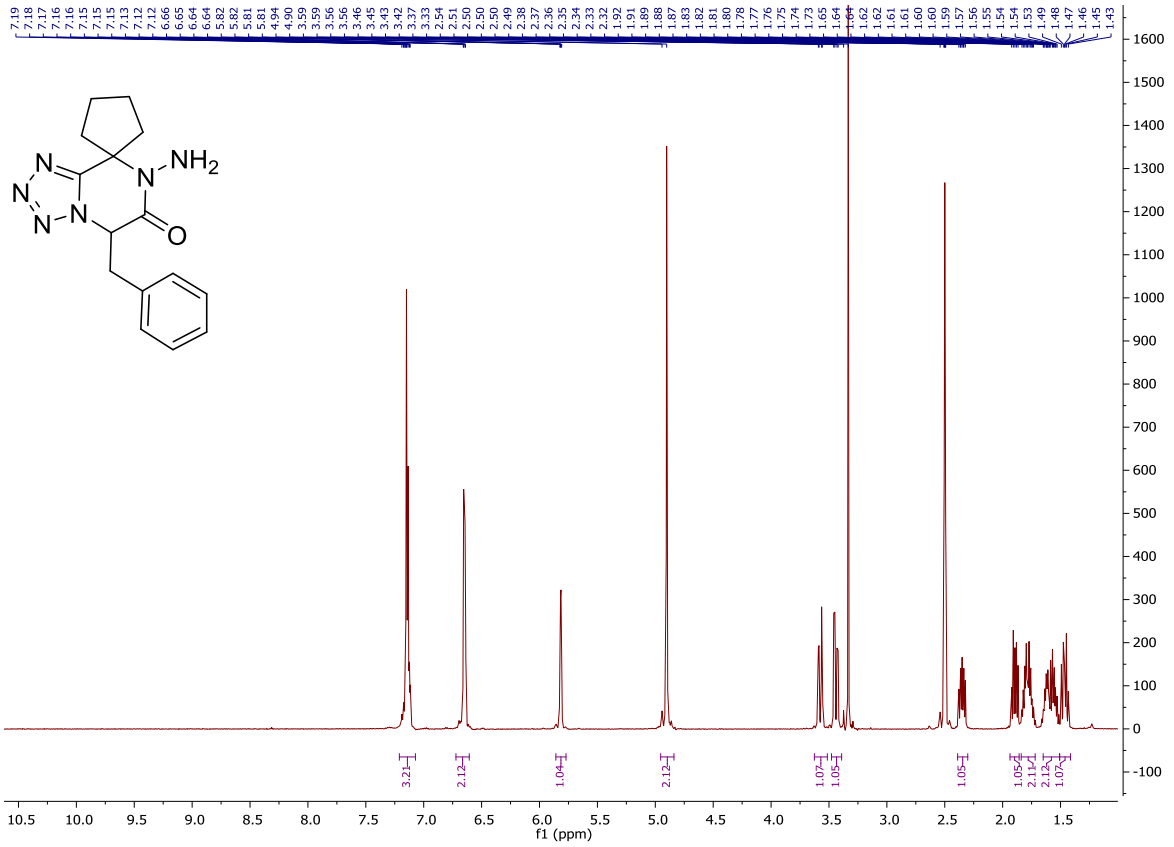


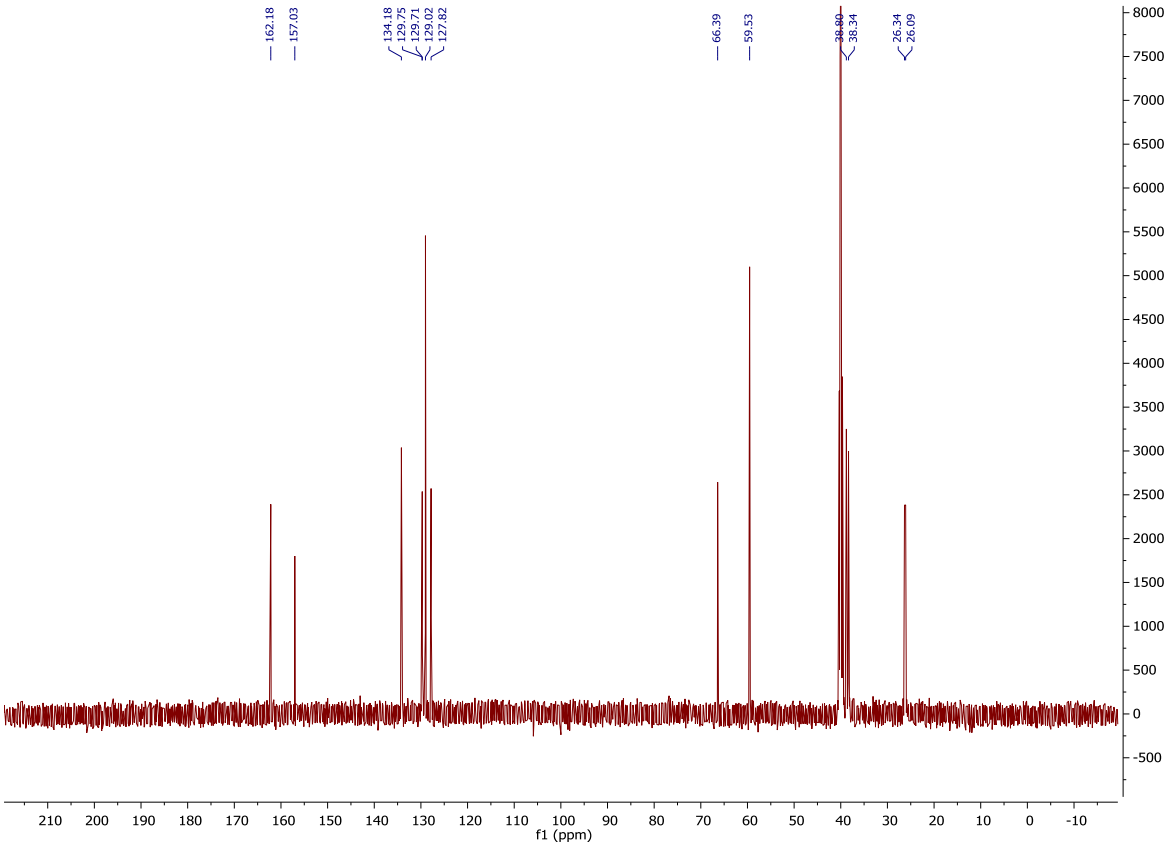
119b #10-15 RT: 0.17457-0.25068 AV:
T: FTMS + p ESI Full ms [150.00-750.00]



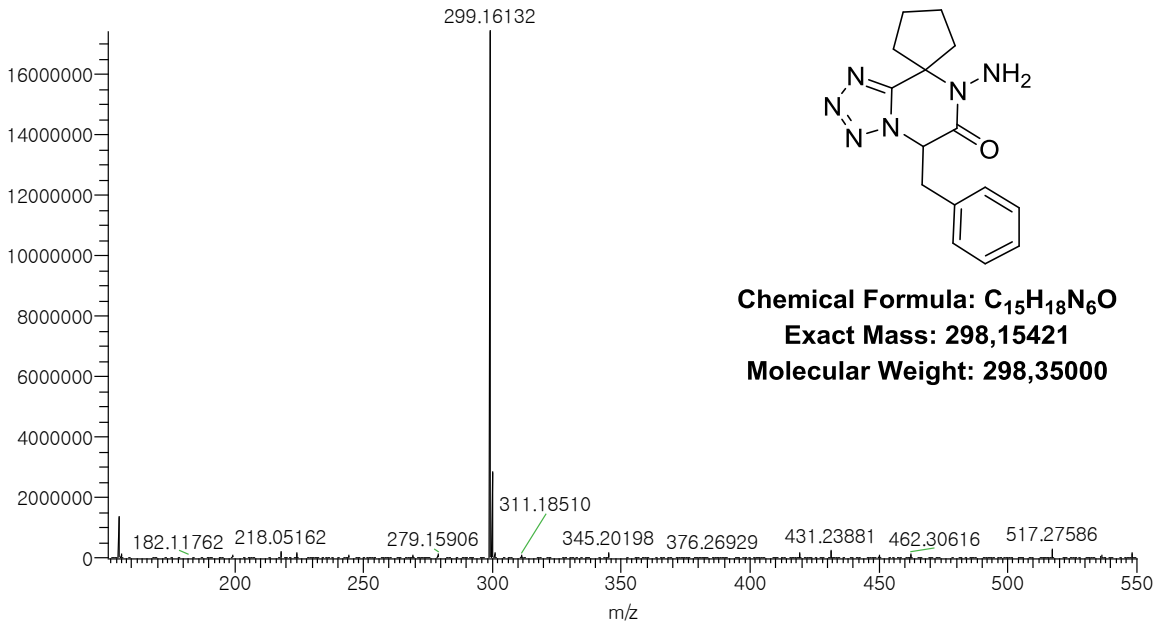
Chemical Formula: $C_{16}H_{20}N_6O$
Exact Mass: 312,16986
Molecular Weight: 312,37700

6j: 7'-amino-5'-benzyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a] pyrazine]-6'(7'*H*)-one



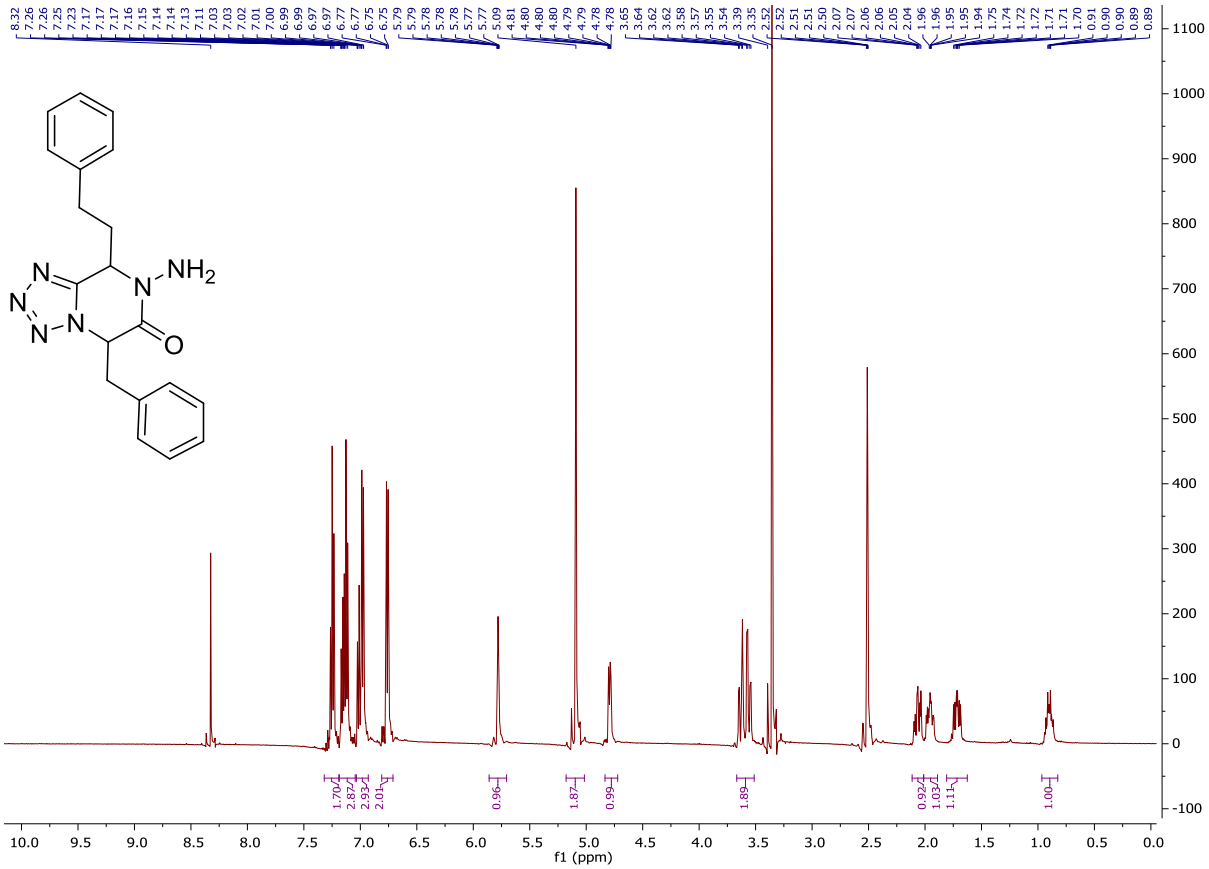


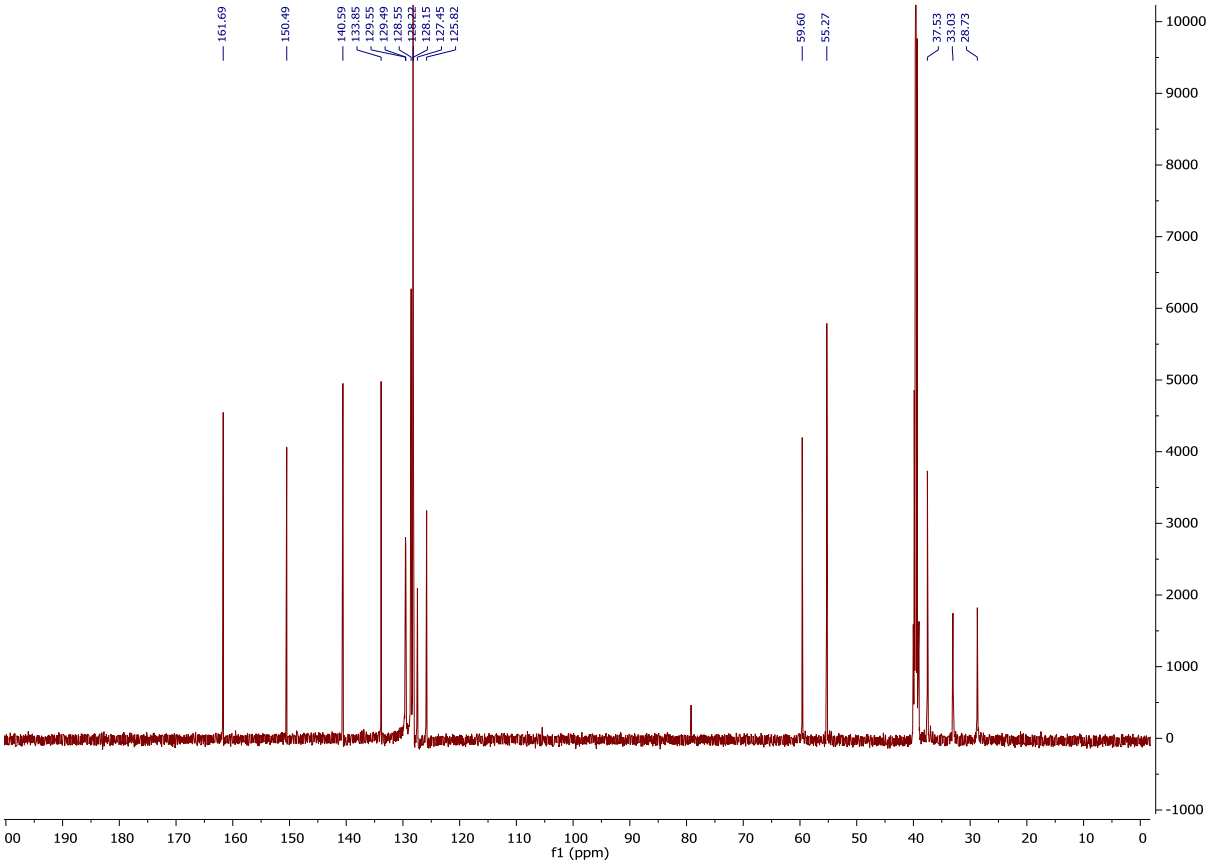
124a #10-15 RT: 0.17475-0.25571 AV:
T: FTMS + p ESI Full ms [150.00-750.00]

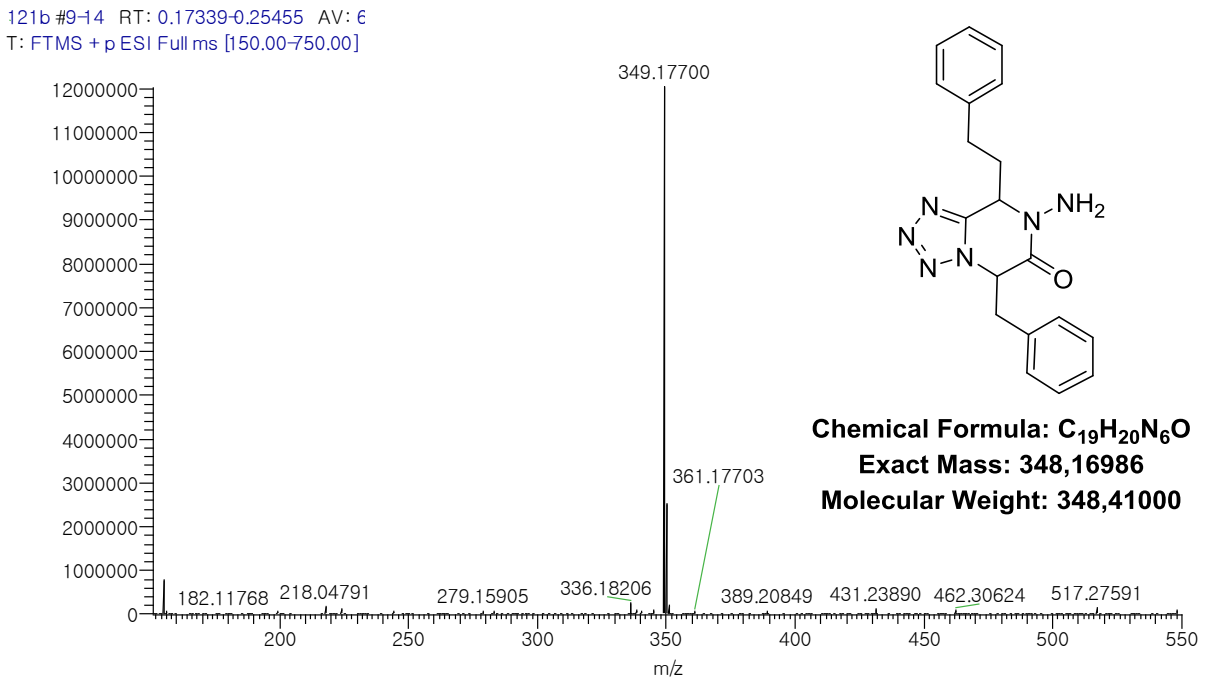


Chemical Formula: $C_{15}H_{18}N_6O$
Exact Mass: 298,15421
Molecular Weight: 298,35000

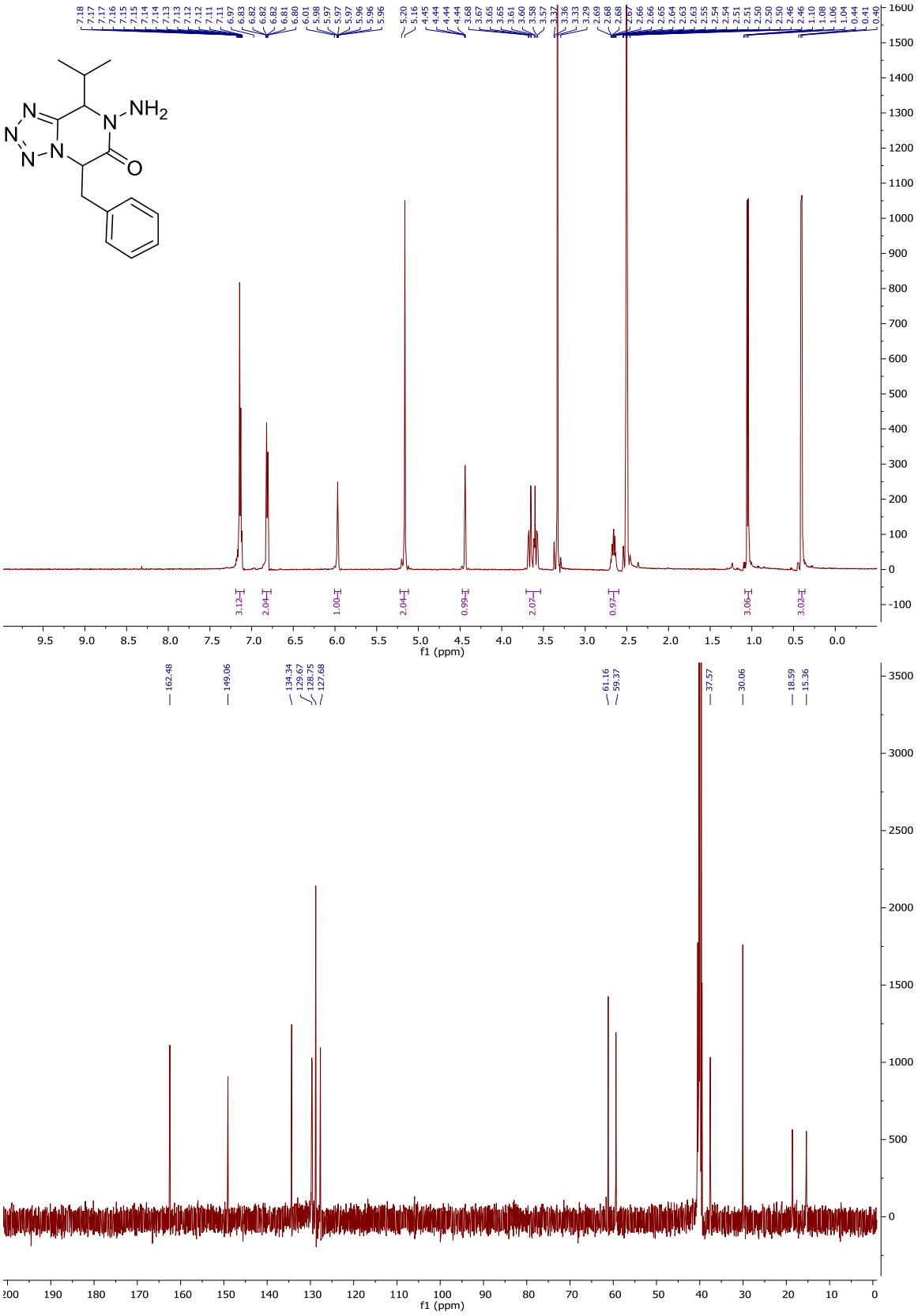
6k: 7-amino-5-benzyl-8-phenethyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one



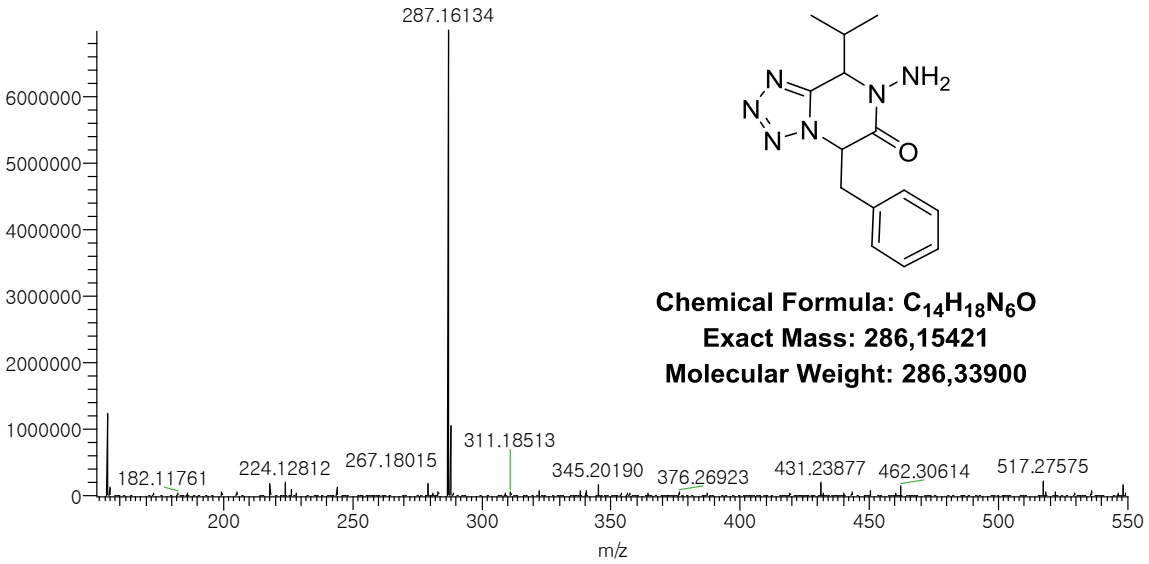



121b #9-14 RT: 0.17339-0.25455 AV: 6
T: FTMS + p ESI Full ms [150.00-750.00]
349.17700
361.17703
182.11768
218.04791
279.15905
336.18206
389.20849
431.23890
462.30624
517.27591
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
200
250
300
350
400
450
500
550
m/z
NH2
N
O
Chemical Formula: C19H20N6O
Exact Mass: 348,16986
Molecular Weight: 348,41000

6l: 7-amino-5-benzyl-8-isopropyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*) -one

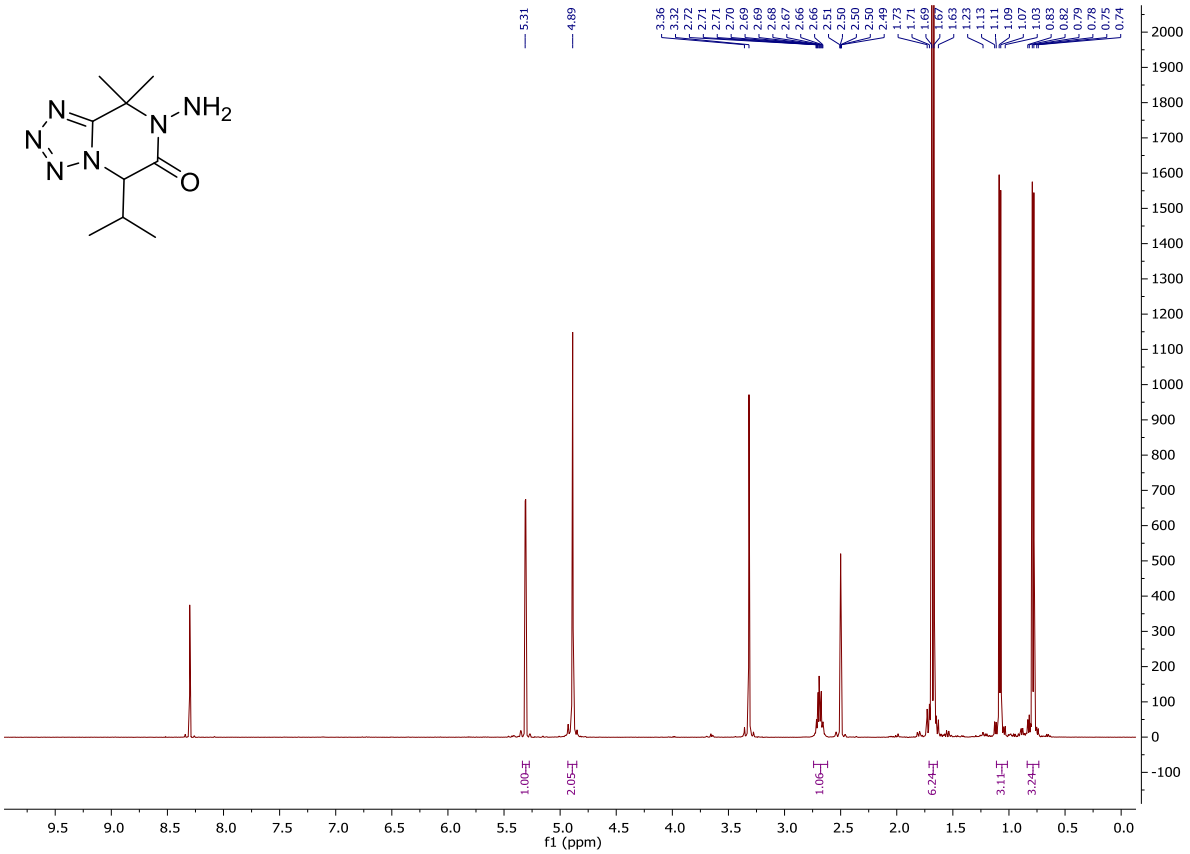


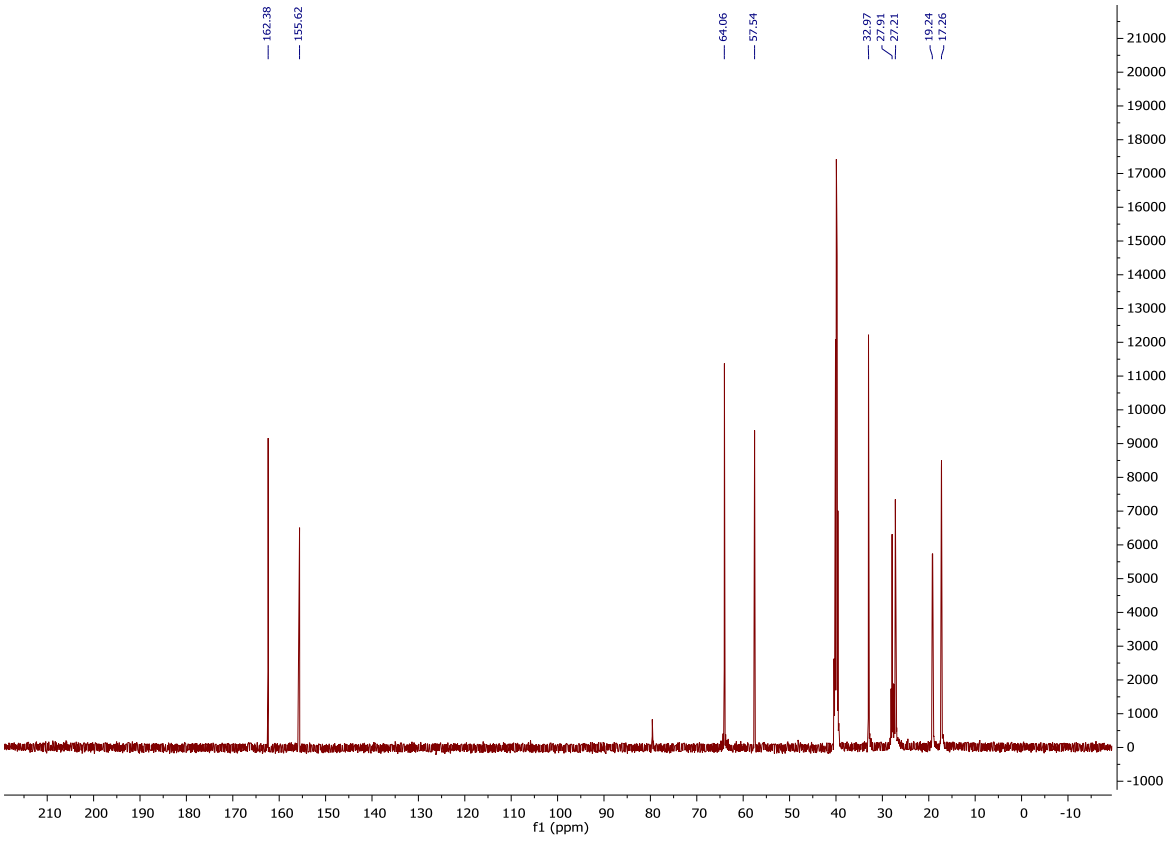
122a #10-15 RT: 0.17562-0.25247 AV: 6 NL: 8.99E6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_{14}H_{18}N_6O$
Exact Mass: 286,15421
Molecular Weight: 286,33900

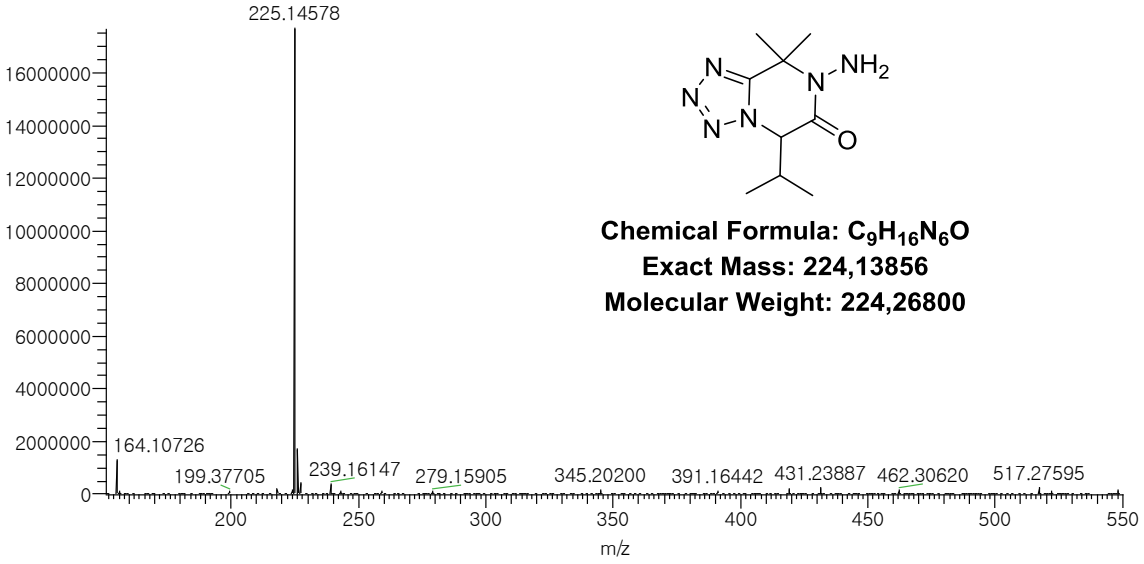
6m: 7-amino-5-isopropyl-8,8-dimethyl-7,8-dihydrotetrazolo[1,5-a]pyrazin-6(5*H*)-one





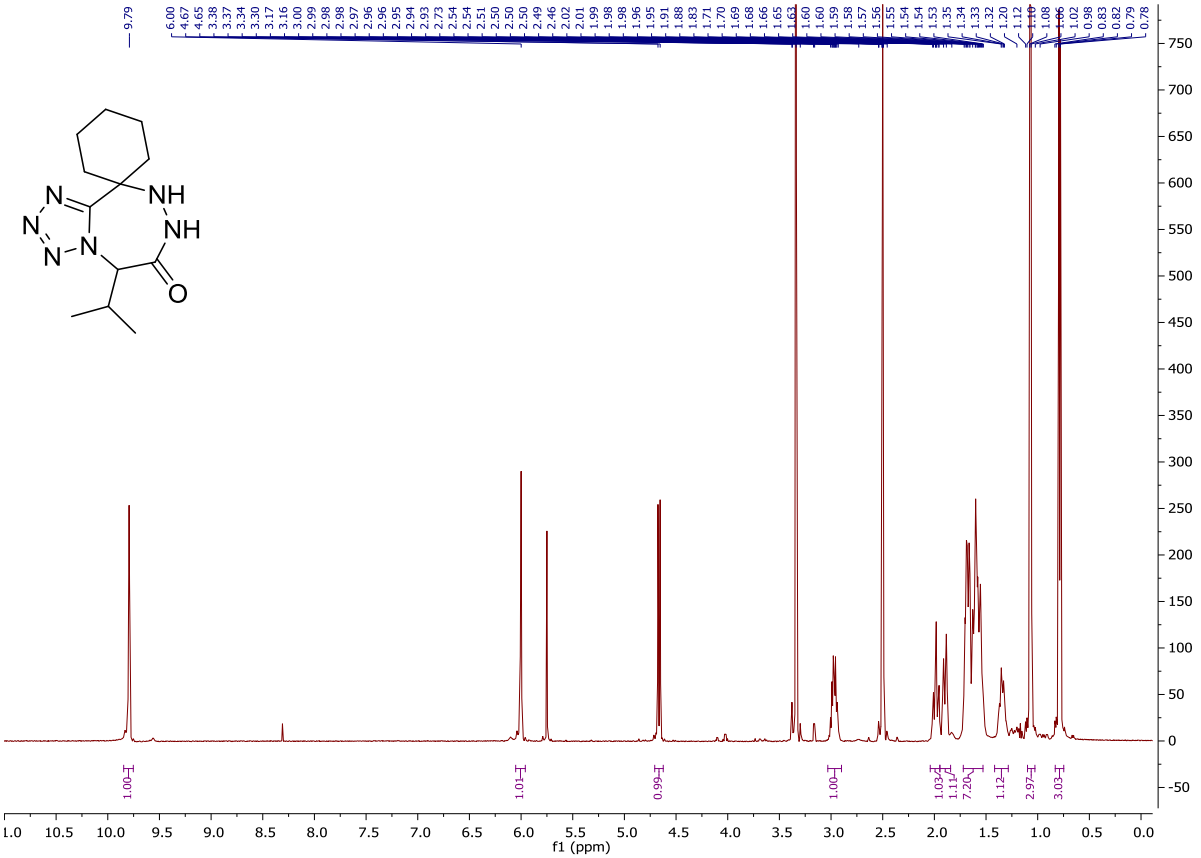
J:₩20161130_ FIA-AccMass50₩28 11/30/16 12:44:04

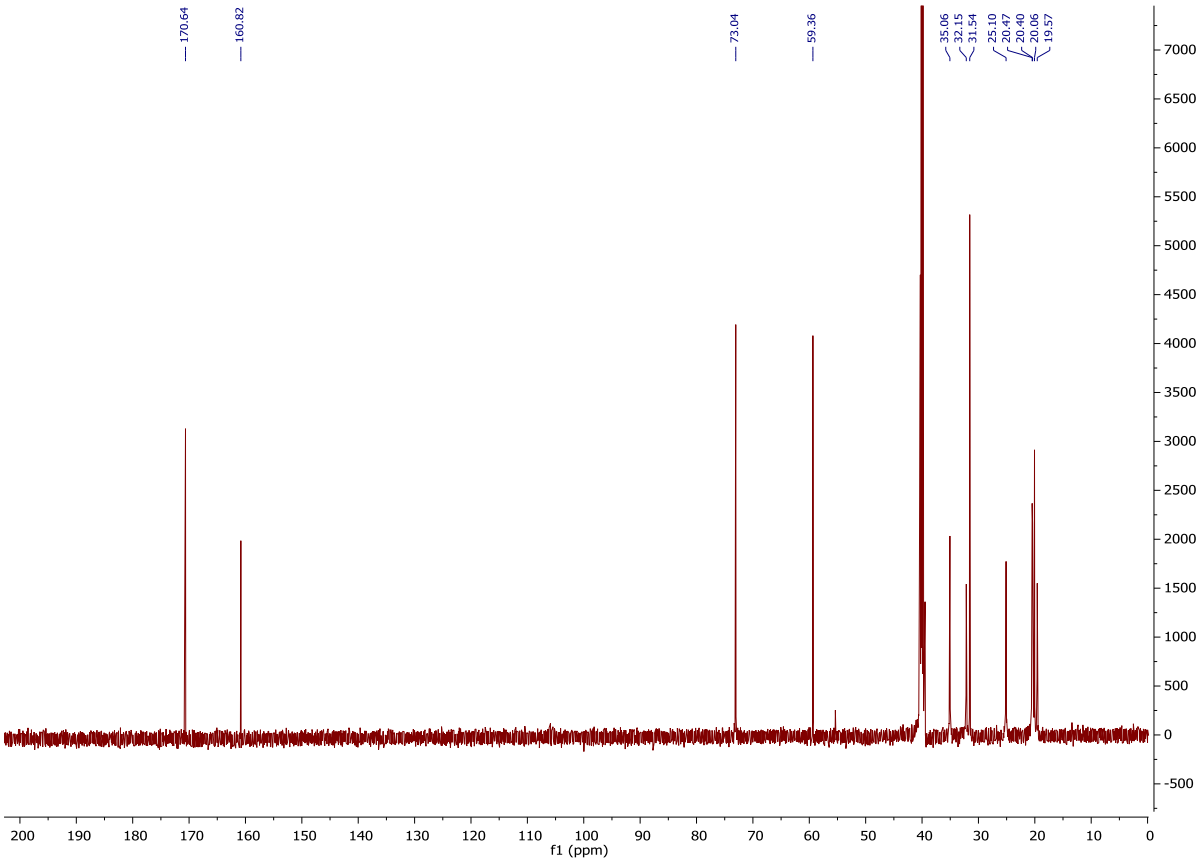
128 #10-15 RT: 0.17486-0.25062 AV: 6 NL: 1.77E7
T: FTMS + p ESI Full ms [150.00-750.00]

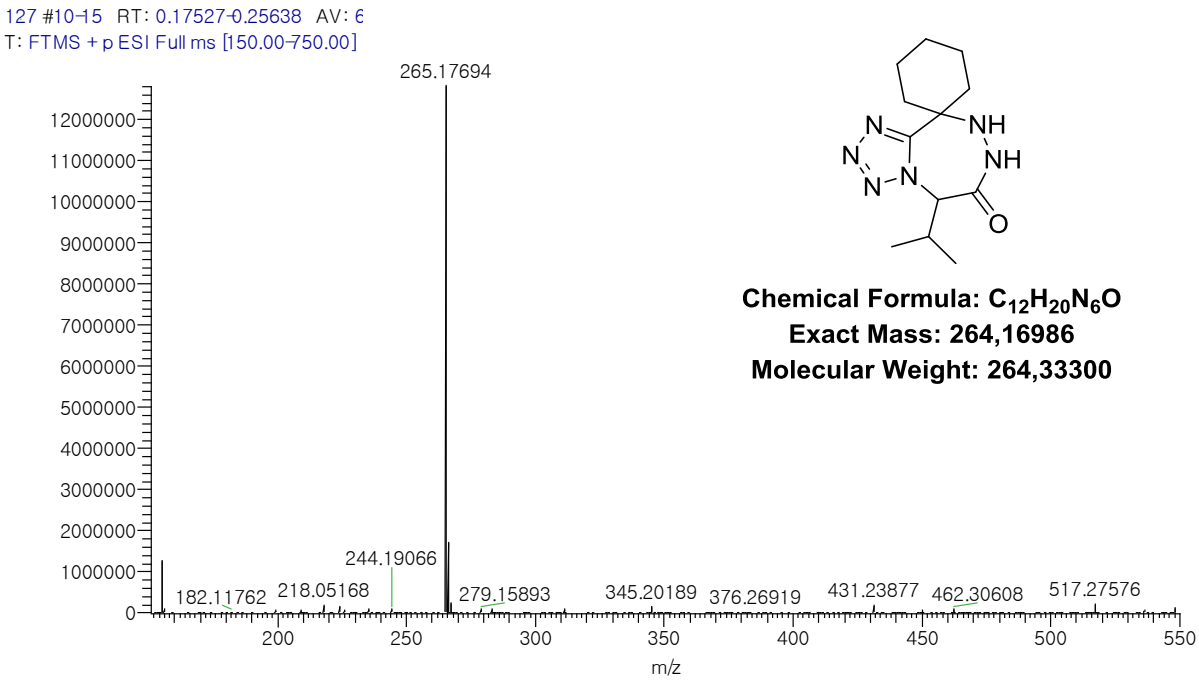


Chemical Formula: $C_9H_{16}N_6O$
Exact Mass: 224,13856
Molecular Weight: 224,26800

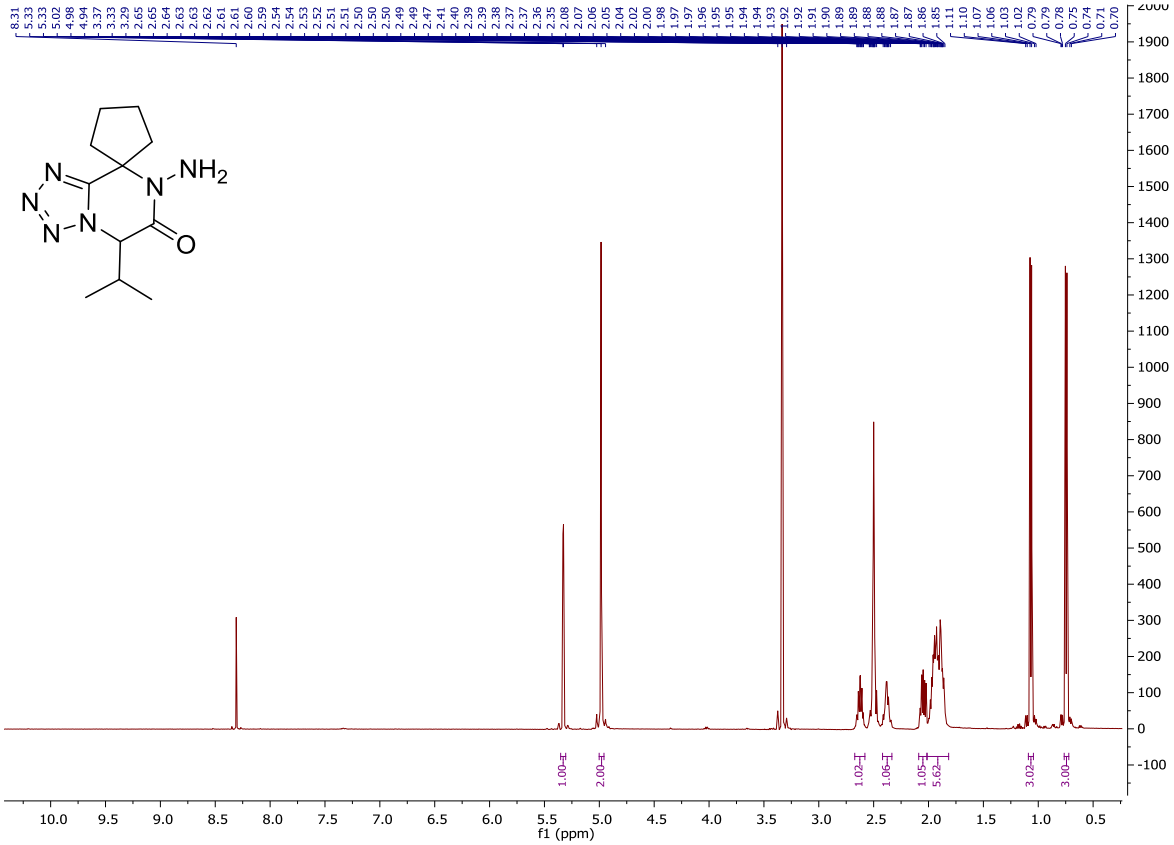
7n: 5'-isopropyl-7',8'-dihydrospiro[cyclohexane-1,9'-tetrazolo[5,1-d][1,2,5] triazepin]-6'(5'*H*) –one

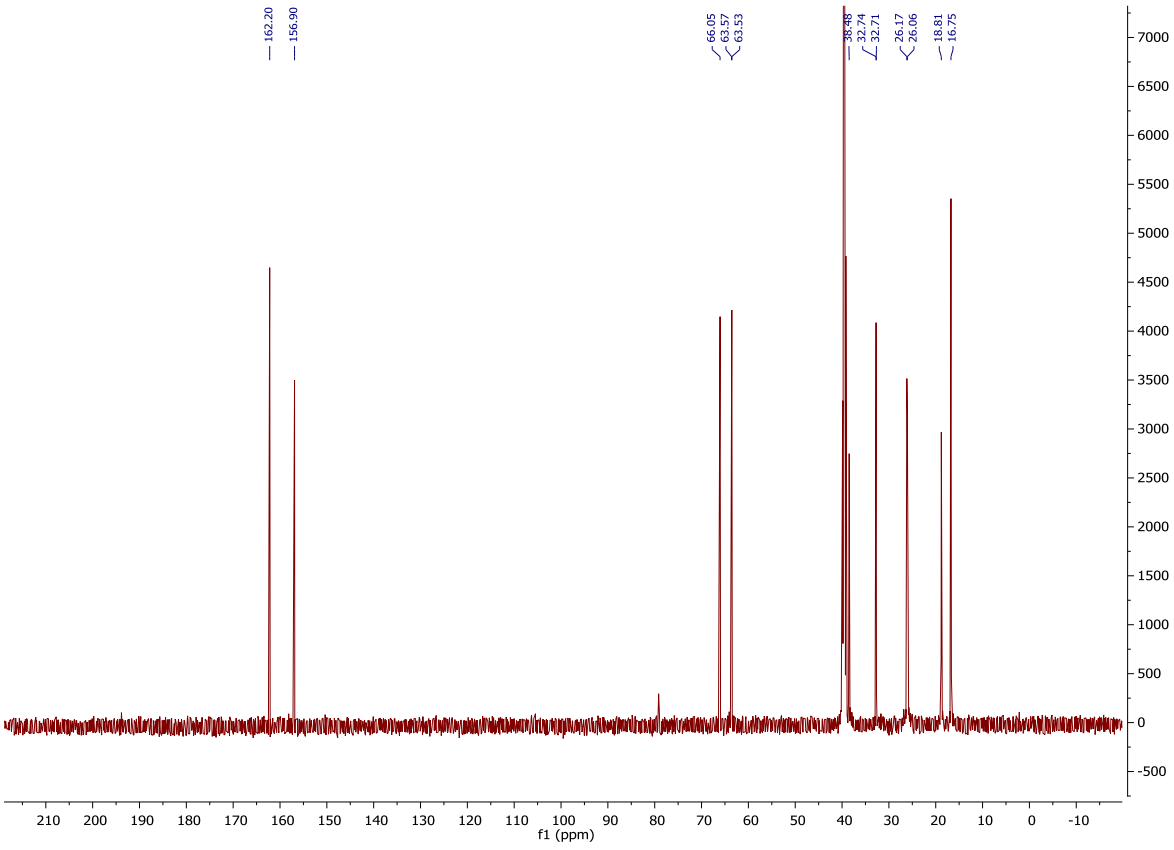


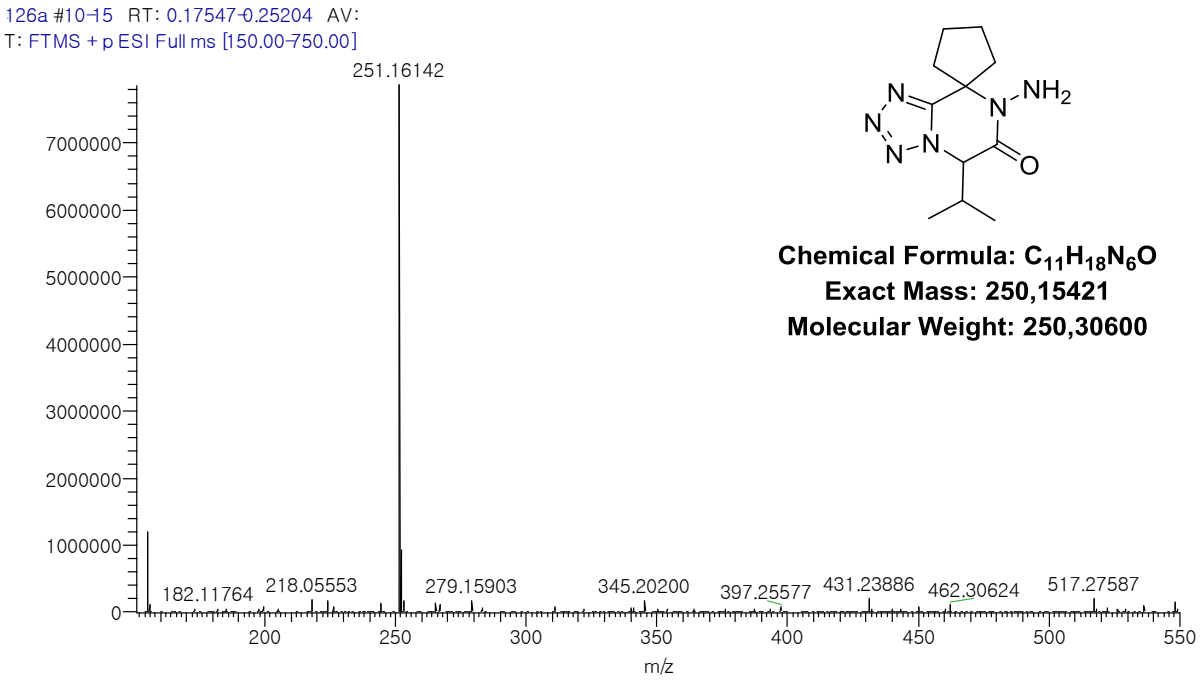



127 #10-15 RT: 0.17527-0.25638 AV: 6
T: FTMS + p ESI Full ms [150.00-750.00]
265.17694
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
244.19066
182.11762
218.05168
279.15893
345.20189
376.26919
431.23877
462.30608
517.27576
200
250
300
350
400
450
500
550
m/z
N
NH
N
NH
N
N
O
Chemical Formula: C12H20N6O
Exact Mass: 264,16986
Molecular Weight: 264,33300

6o: 7'-amino-5'-isopropyl-5'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a] pyrazin]-6'(7'*H*)-one

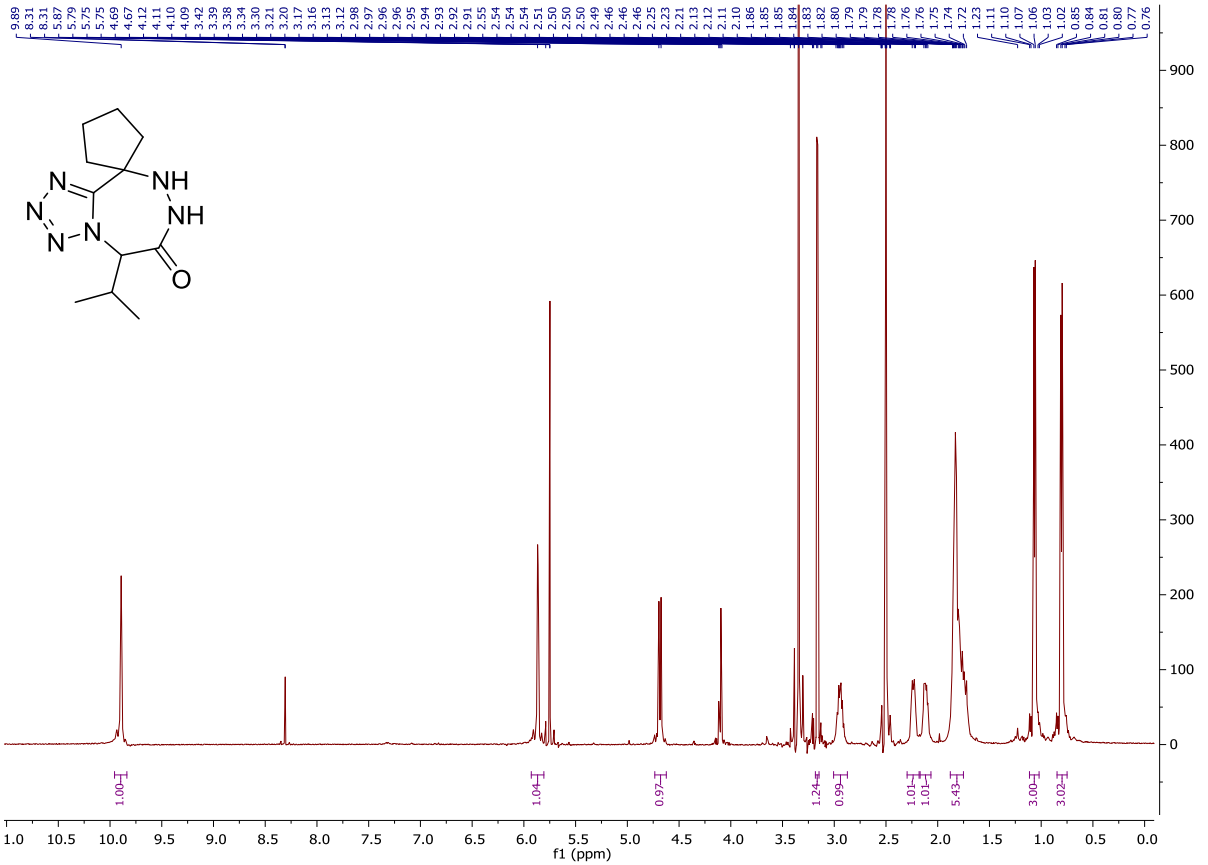


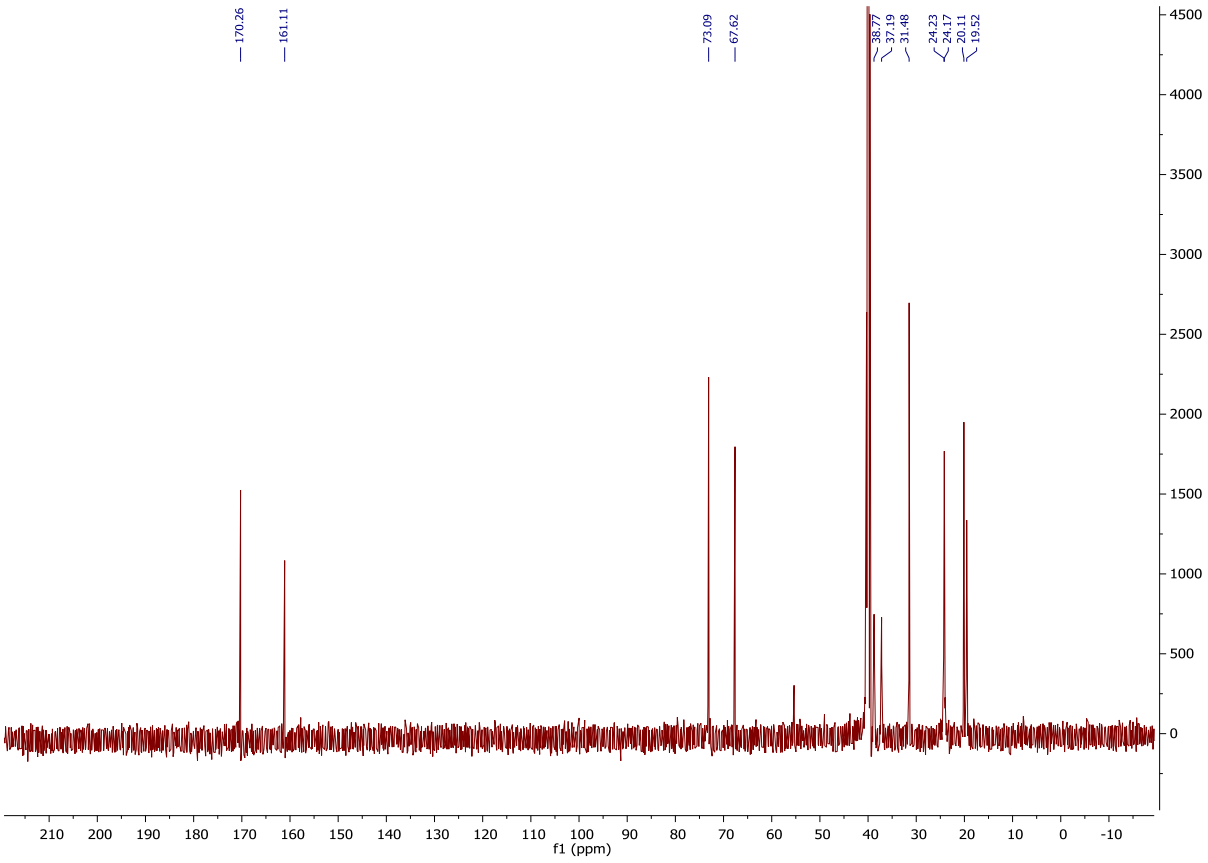




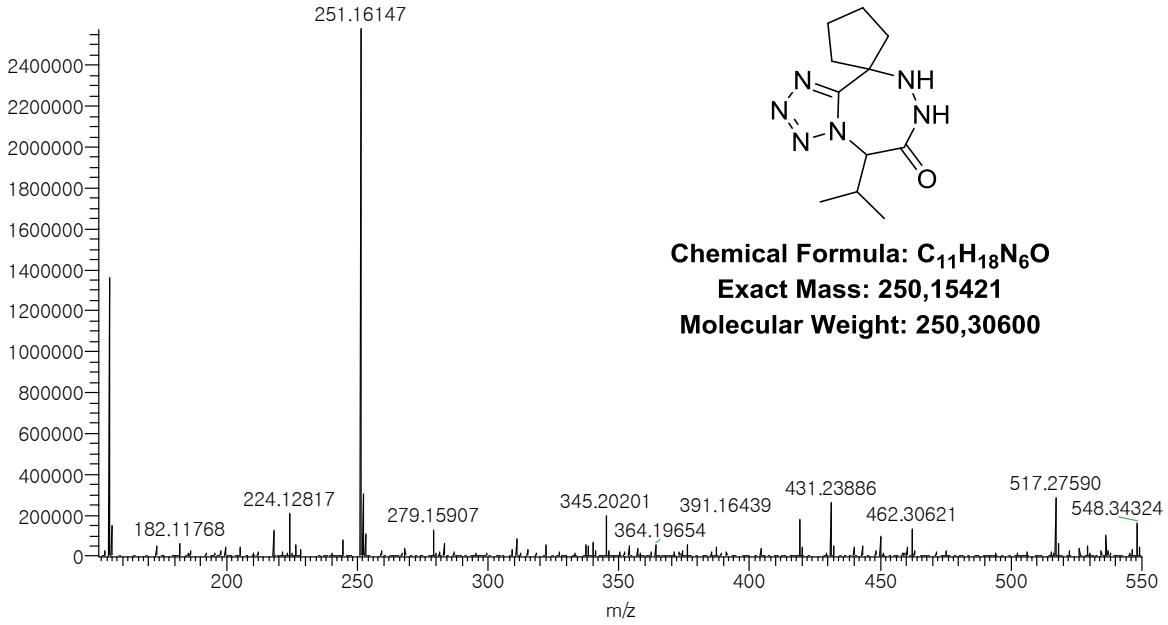
Chemical Formula: $C_{11}H_{18}N_6O$
Exact Mass: 250,15421
Molecular Weight: 250,30600

7o: 5'-isopropyl-7',8'-dihydrospiro[cyclopentane-1,9'-tetrazolo[5,1-d][1,2,5] triazepin]-6'(5' *H*)-one



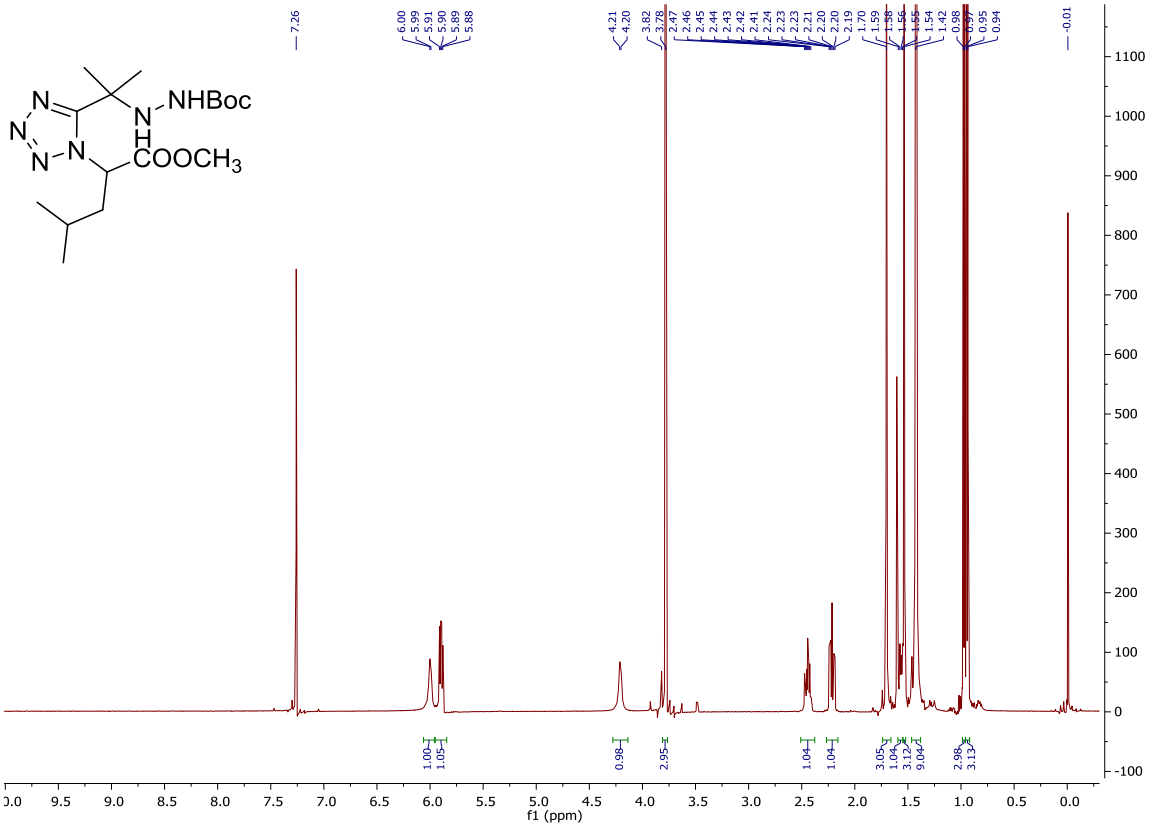


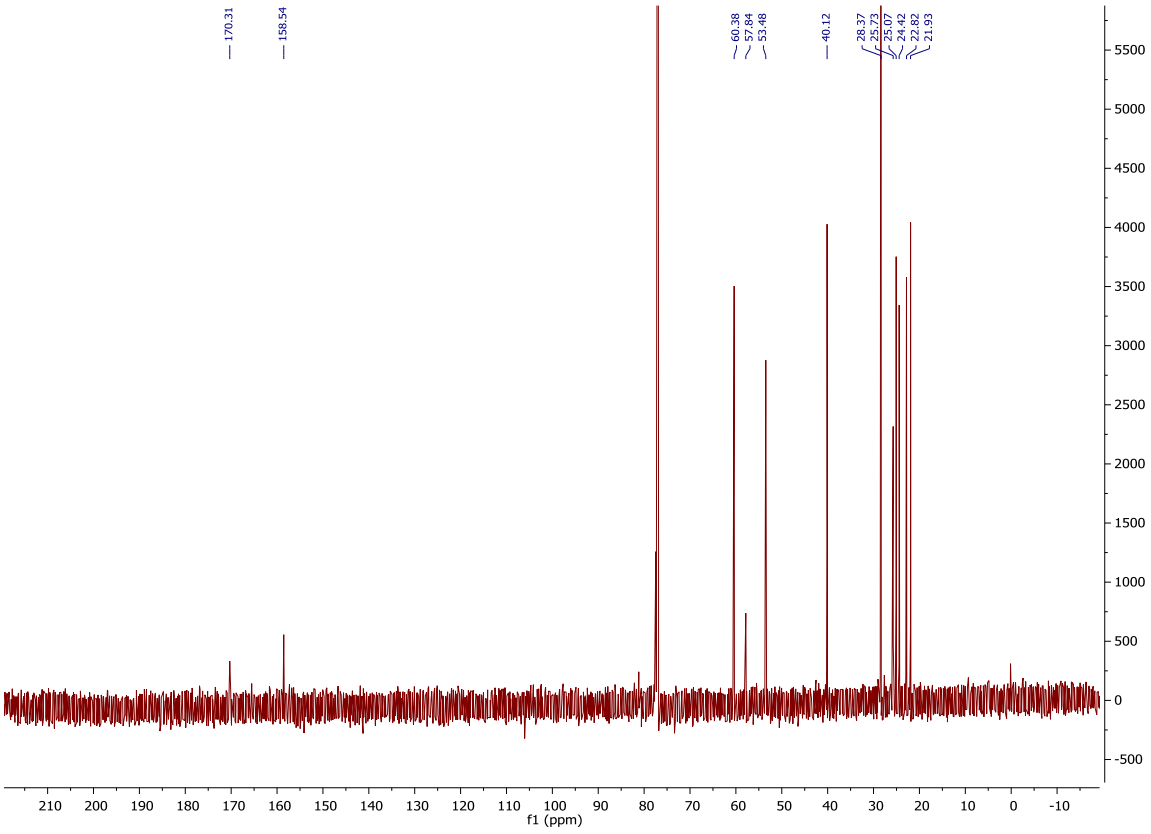
126b #10-15 RT: 0.17654-0.25426 AV:
T: FTMS + p ESI Full ms [150.00-750.00]

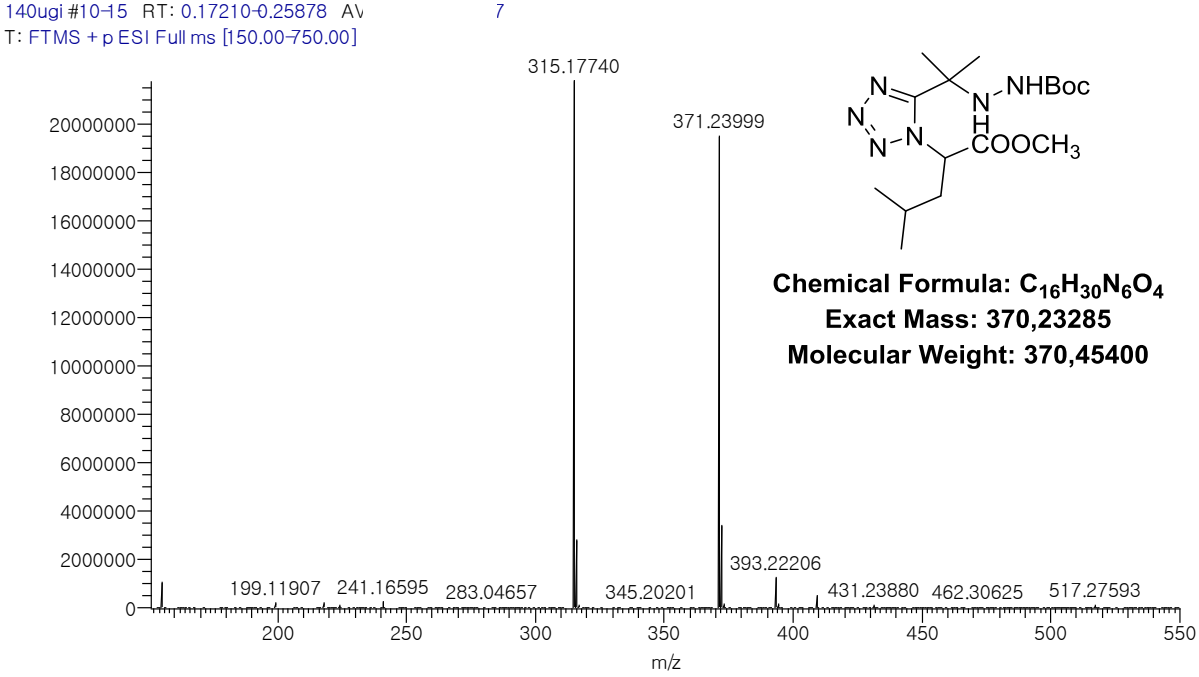


Chemical Formula: $C_{11}H_{18}N_6O$
Exact Mass: 250,15421
Molecular Weight: 250,30600

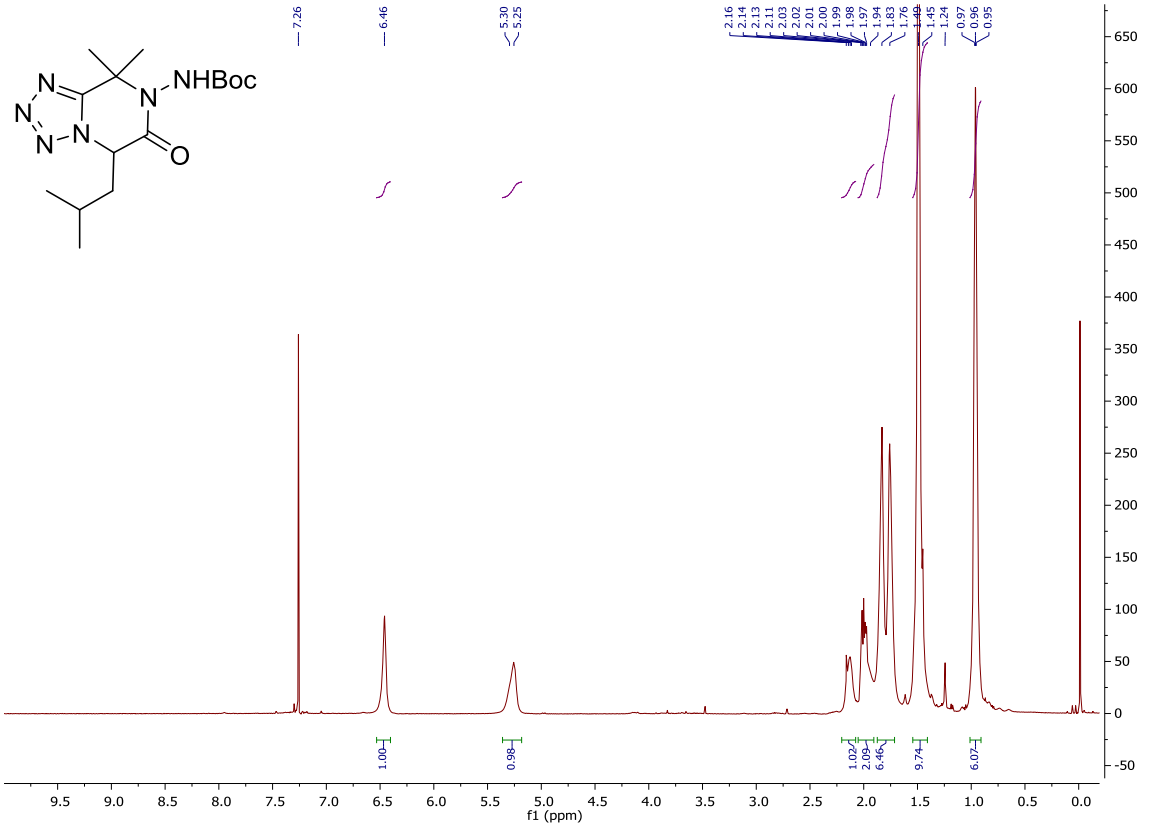
5a: *tert*-butyl 2-(2-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5-yl)propan-2-yl) hydrazine-1-carboxylate

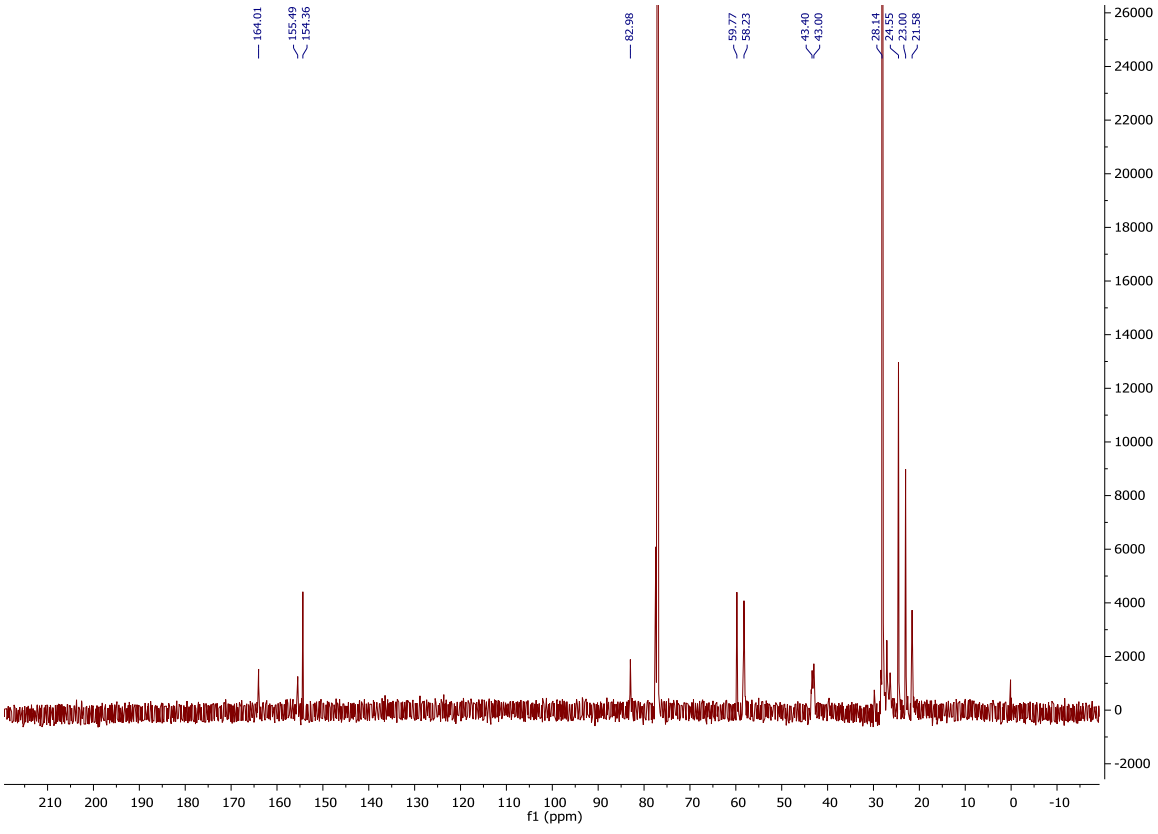


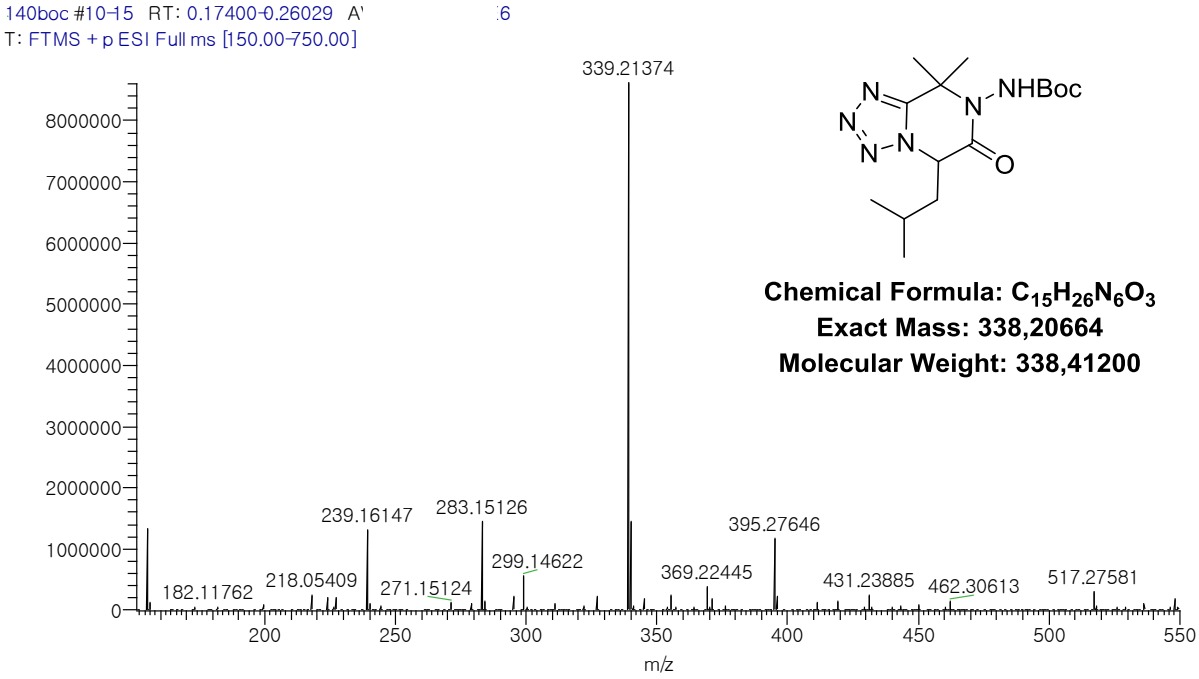



140ugi #10-15 RT: 0.17210-0.25878 AV 7
T: FTMS + p ESI Full ms [150.00-750.00]
315.17740
371.23999
393.22206
199.11907
241.16595
283.04657
345.20201
431.23880
462.30625
517.27593
20000000
18000000
16000000
14000000
12000000
10000000
8000000
6000000
4000000
2000000
0
200
250
300
350
400
450
500
550
m/z
NHBoc
N
H
COOCH3
Chemical Formula: C16H30N6O4
Exact Mass: 370,23285
Molecular Weight: 370,45400

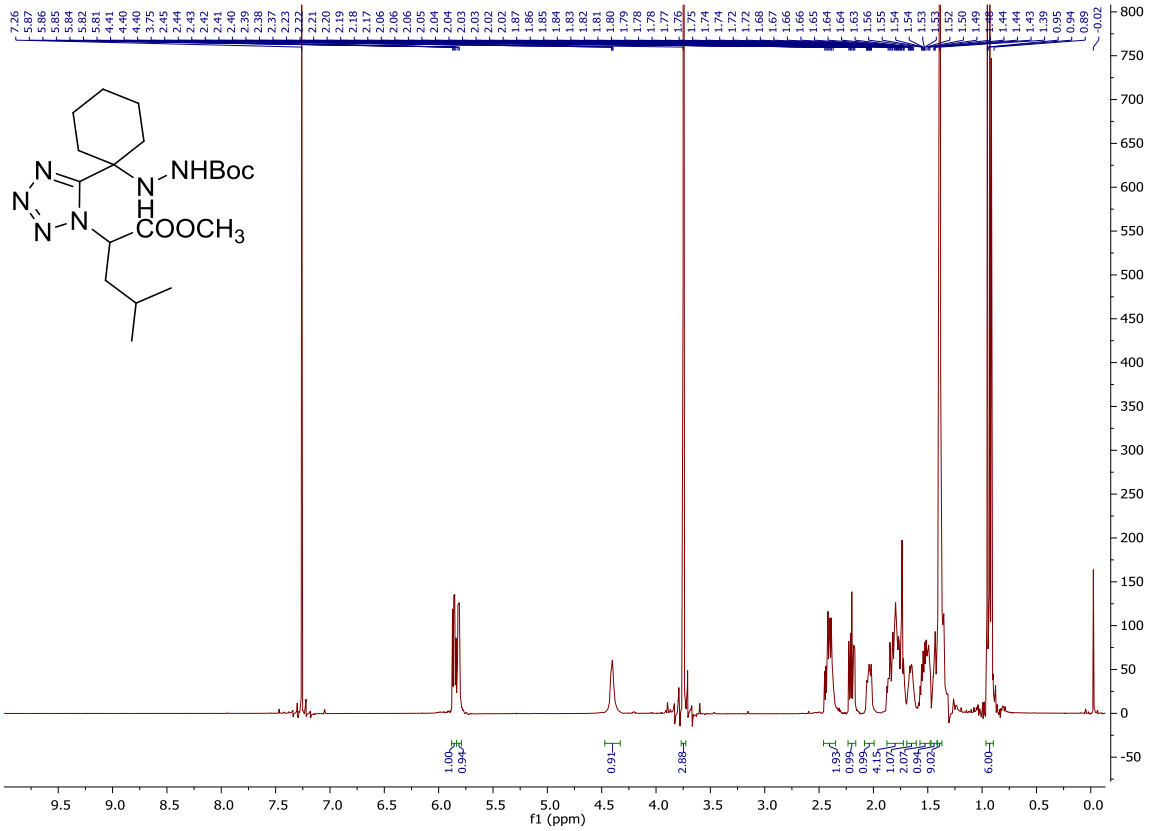
8a: *tert*-butyl (5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8*H*)-yl) carbamate

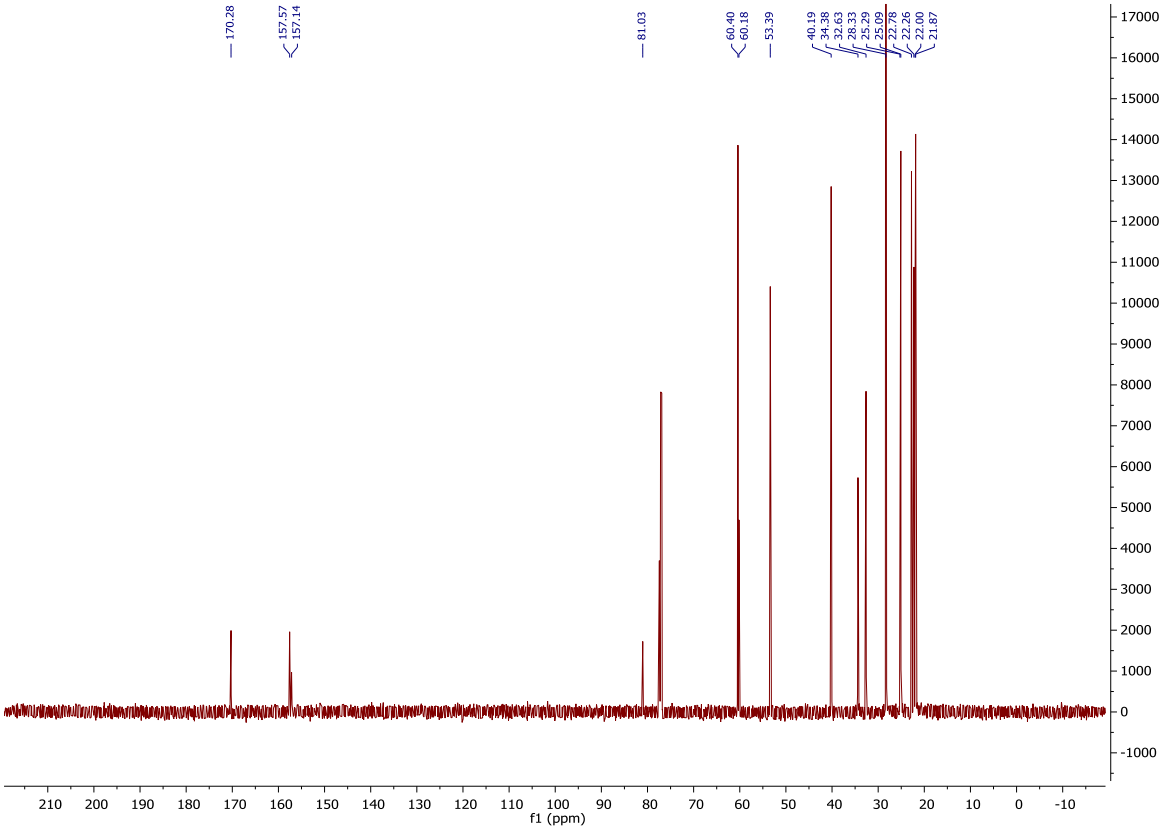




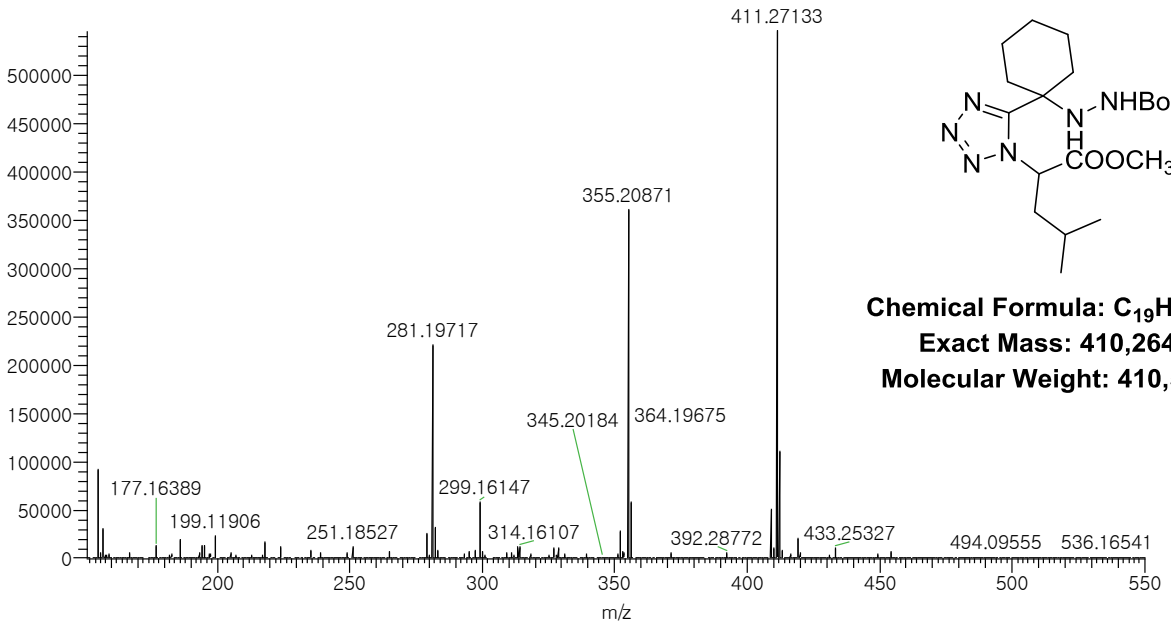

140boc #10-15 RT: 0.17400-0.26029 A
T: FTMS + p ESI Full ms [150.00-750.00]
339.21374
NHBoc
N
N
N
N
O
Chemical Formula: C15H26N6O3
Exact Mass: 338,20664
Molecular Weight: 338,41200
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
239.16147
283.15126
395.27646
299.14622
182.11762
218.05409
271.15124
369.22445
431.23885
462.30613
517.27581
200
250
300
350
400
450
500
550
m/z

5b: *tert*-butyl 2-(1-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5-yl)cyclohexyl) hydrazine-1-carboxylate



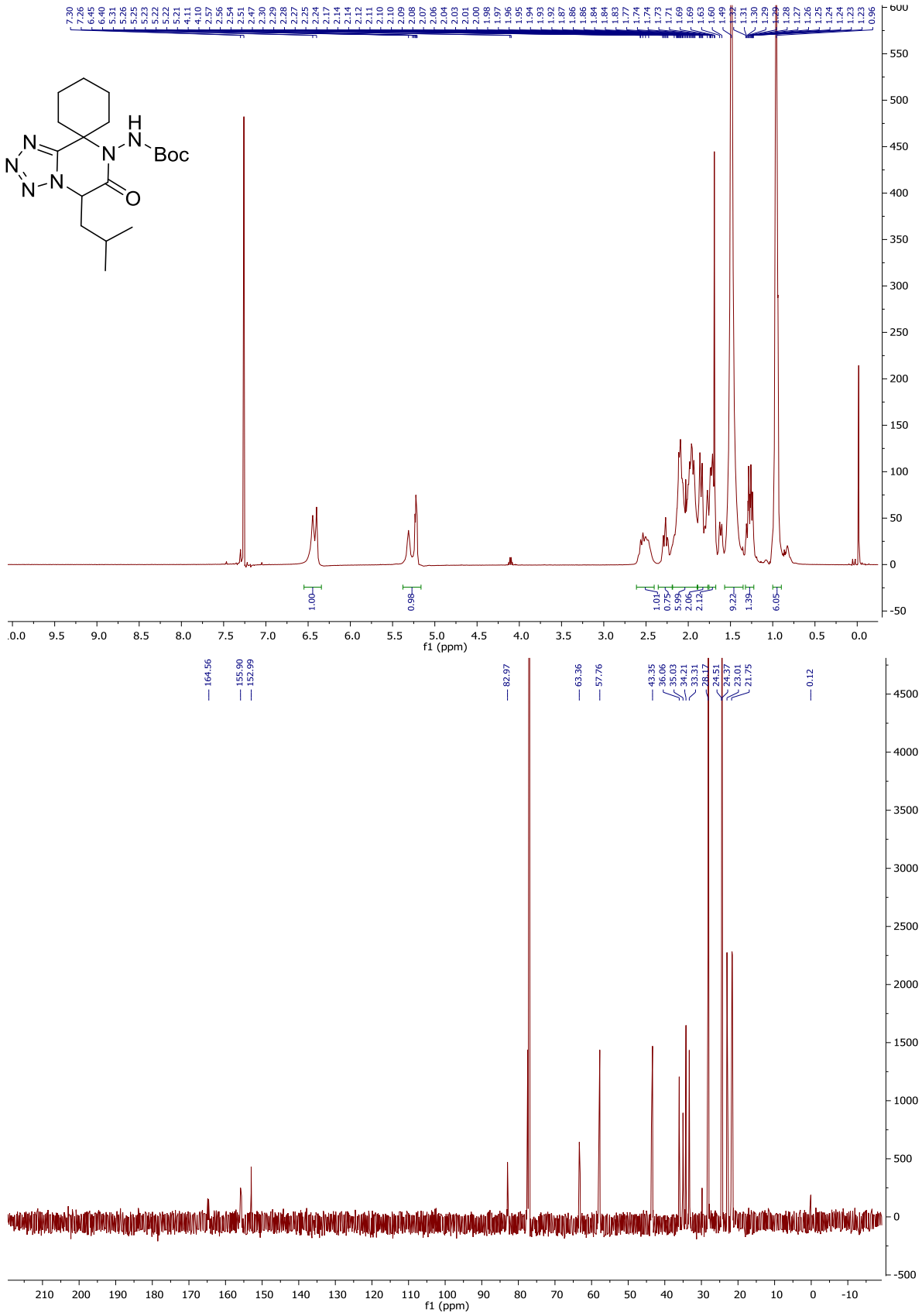


157ugi #26 RT: 0.44883 AV: 1 NL: 5.4
T: FTMS + p ESI Full ms [150.00-750.00]

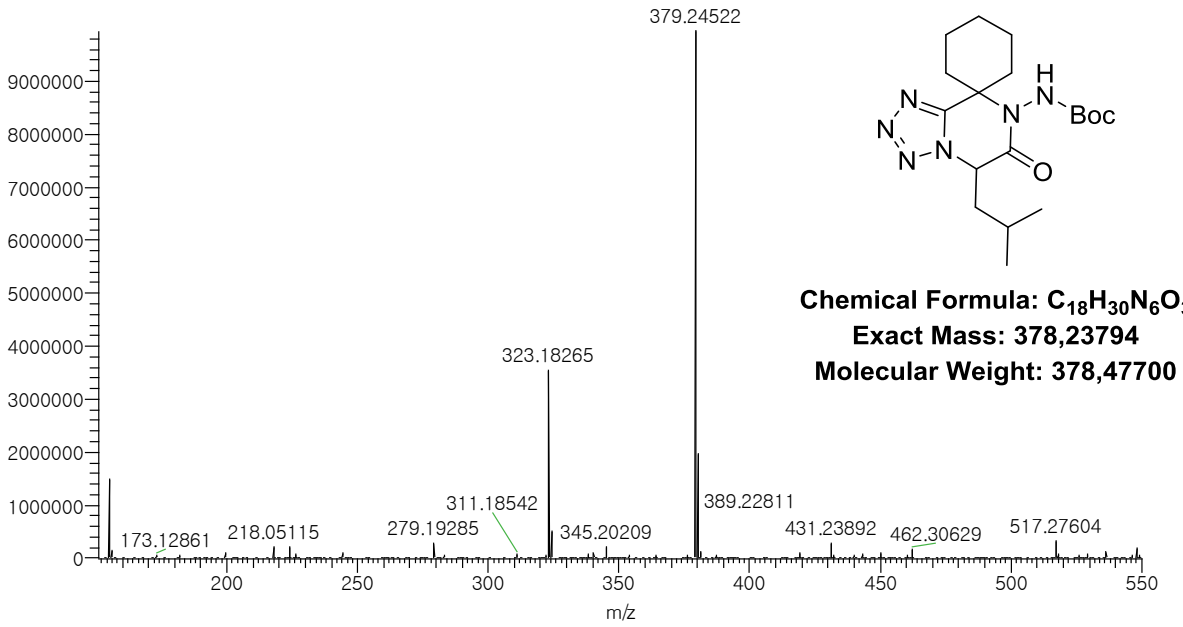


Chemical Formula: $C_{19}H_{34}N_6O_4$
Exact Mass: 410,26415
Molecular Weight: 410,51900

8b: *tert*-butyl (5'-isobutyl-6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclohexane-1,8'-tetrazolo[1,5-a] pyrazin]-7'-yl)carbamate

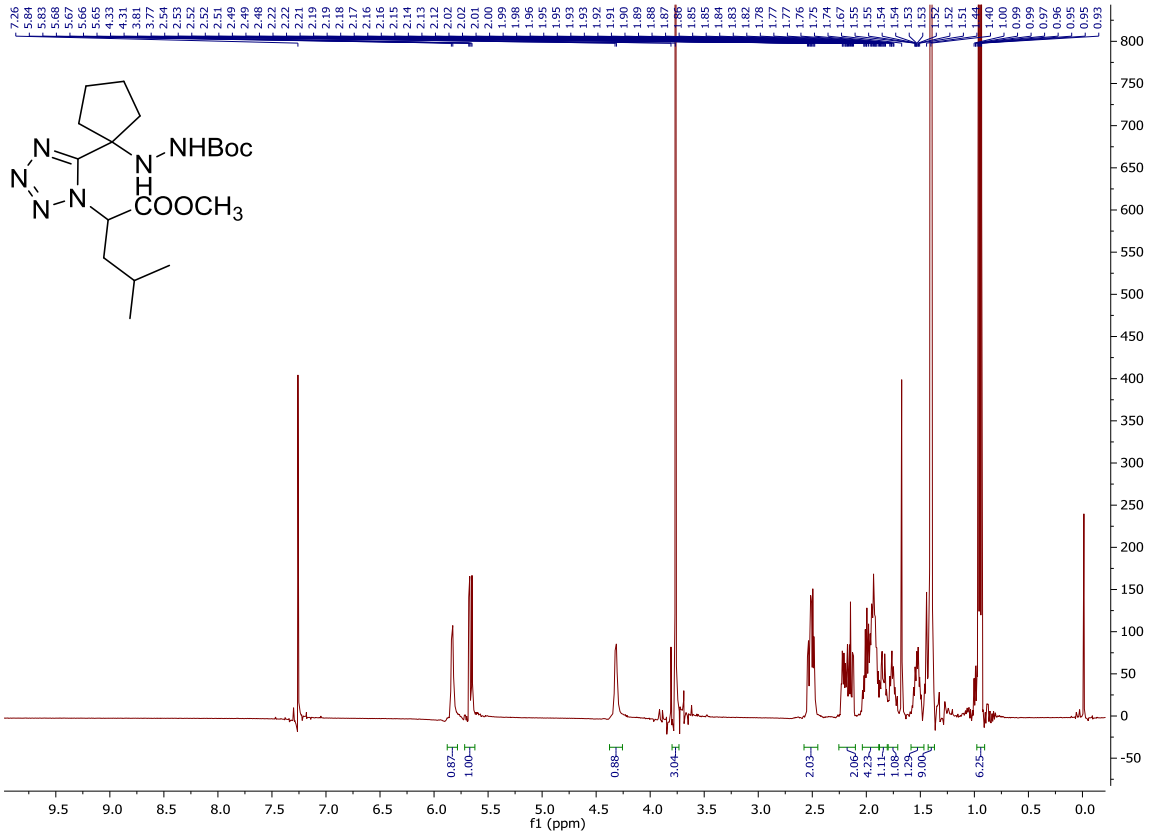


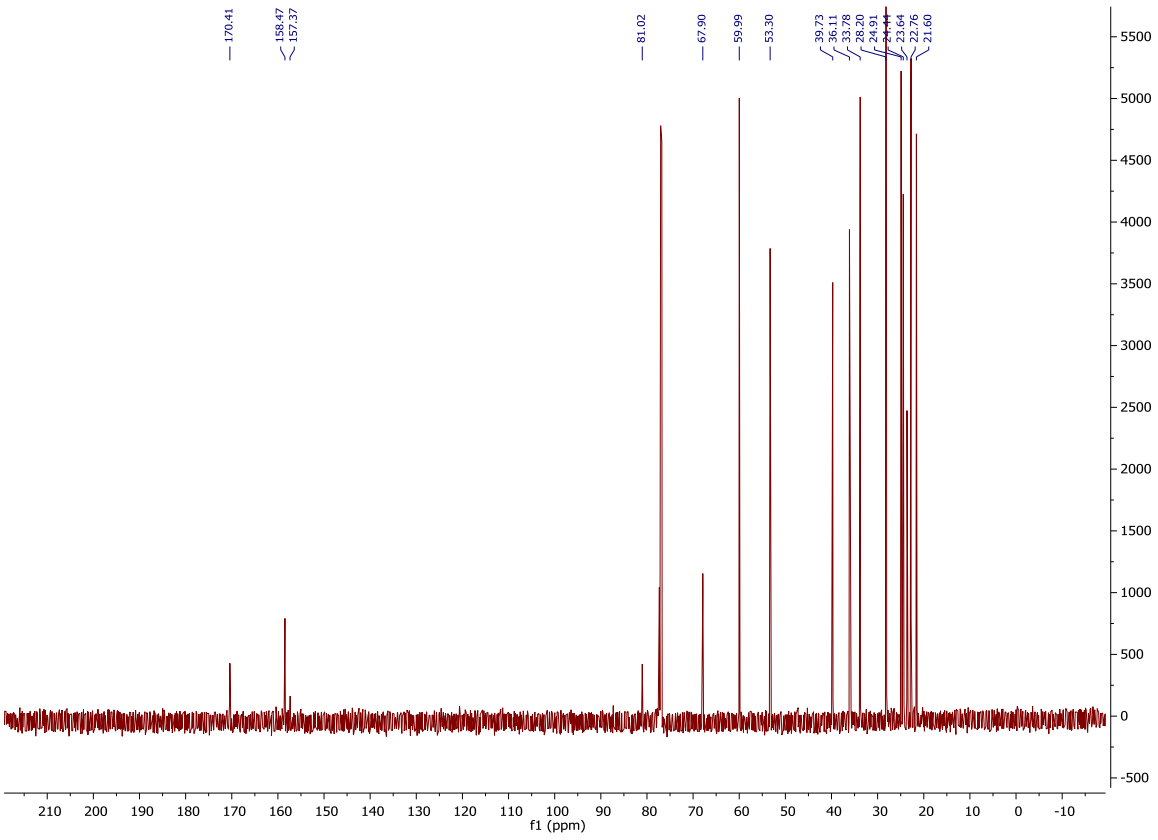
157boc #10-15 RT: 0.17503-0.25181 A\ :6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_{18}H_{30}N_6O_3$
Exact Mass: 378,23794
Molecular Weight: 378,47700

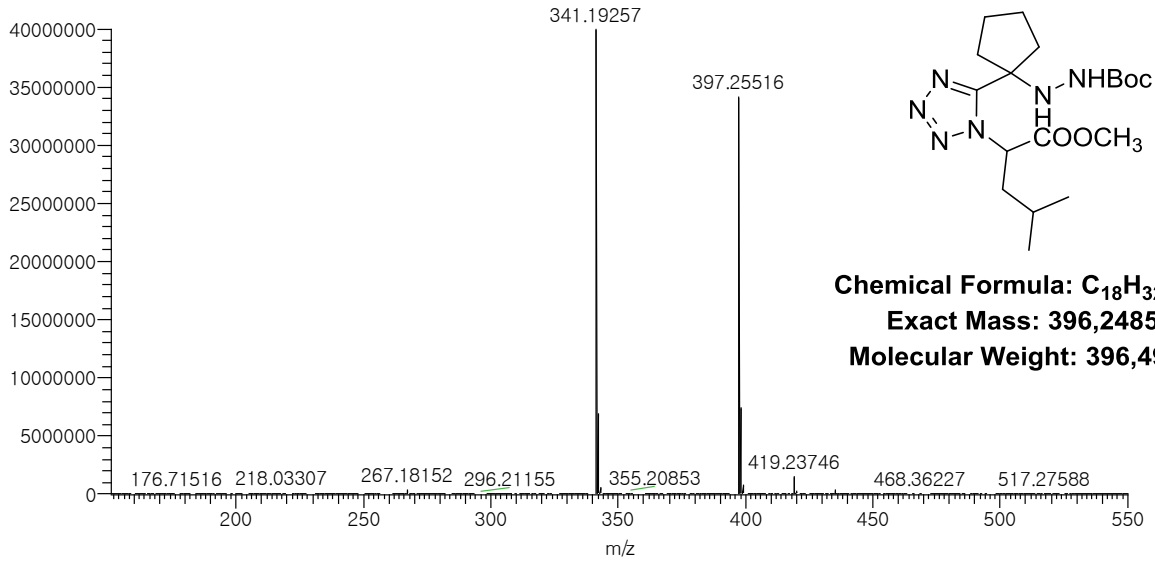
5c: *tert*-butyl 2-(1-(1-(1-methoxy-4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5 yl)cyclopentyl) hydrazine-1-carboxylate





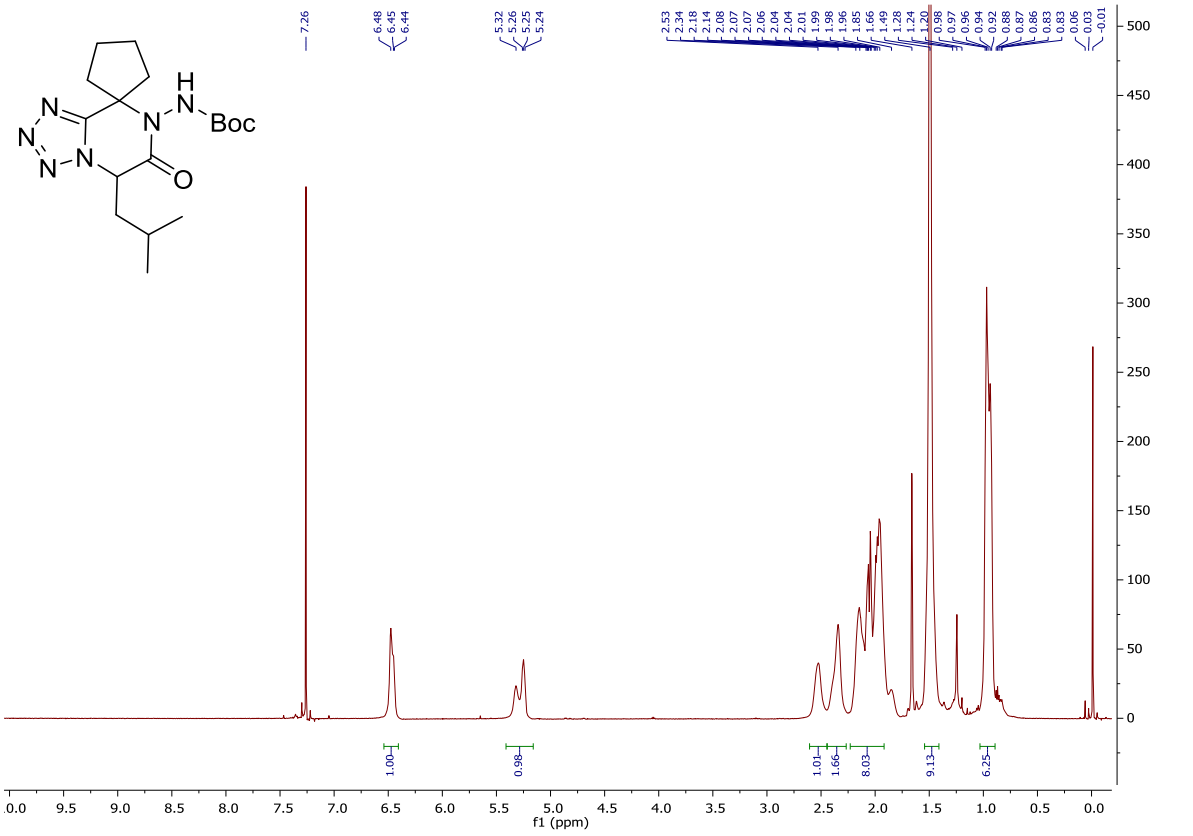
J:₩20161130_ FIA-AccMass50₩56ugi 11/30/16 13:02:56

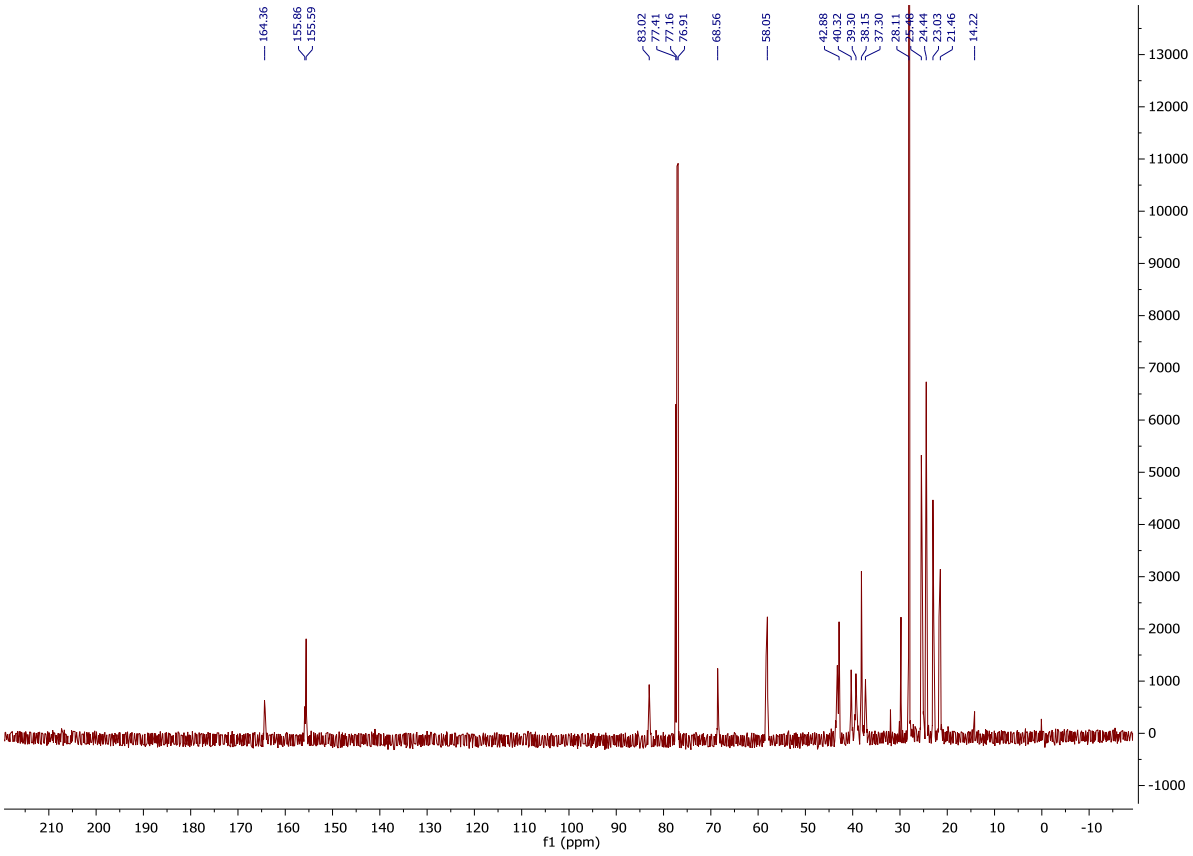
156ugi #6 RT: 0.10566 AV: 1 NL: 4.00E7
T: FTMS + p ESI Full ms [150.00-750.00]



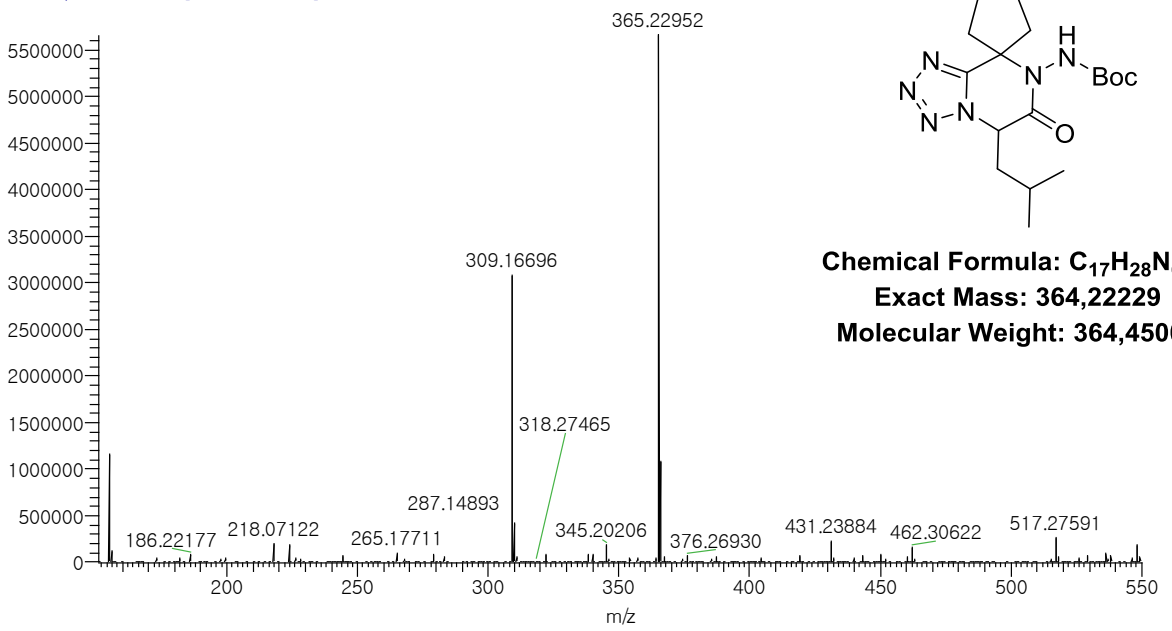
Chemical Formula: $C_{18}H_{32}N_6O_4$
Exact Mass: 396,24850
Molecular Weight: 396,49200

8c: *tert*-butyl (5'-isobutyl-6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl)carbamate



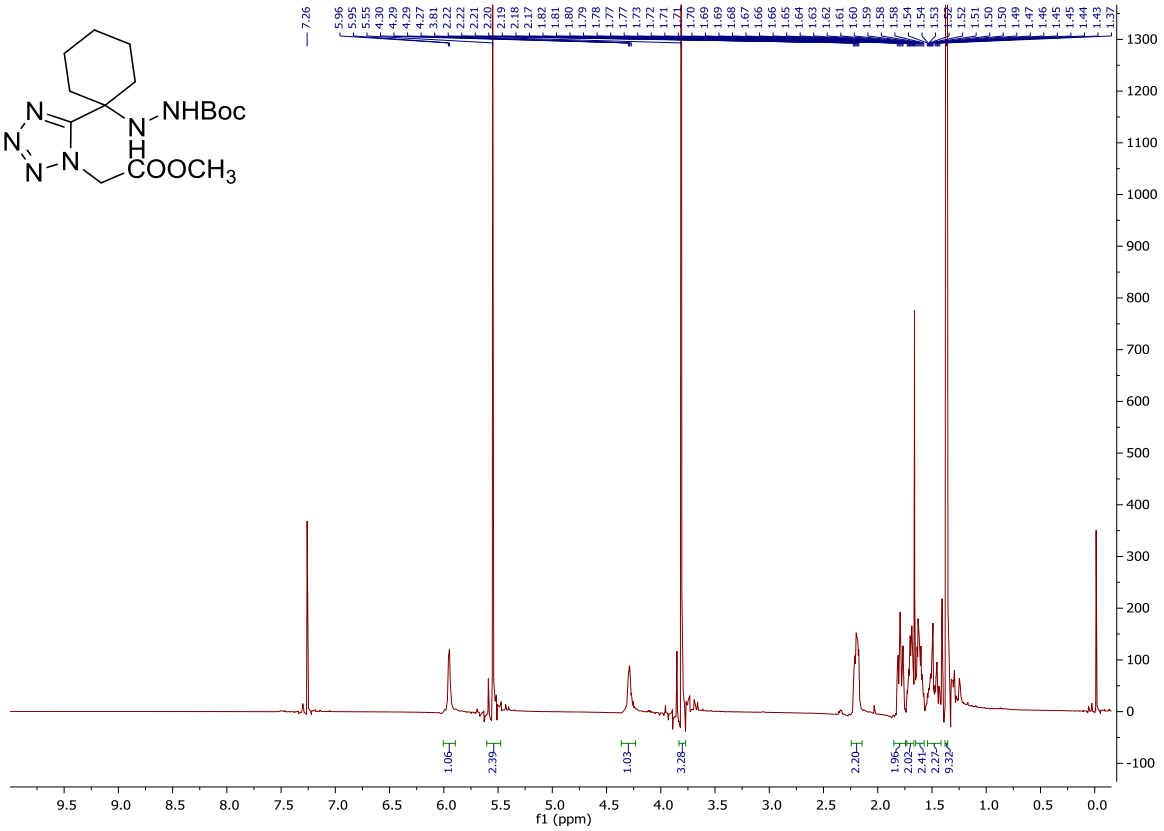


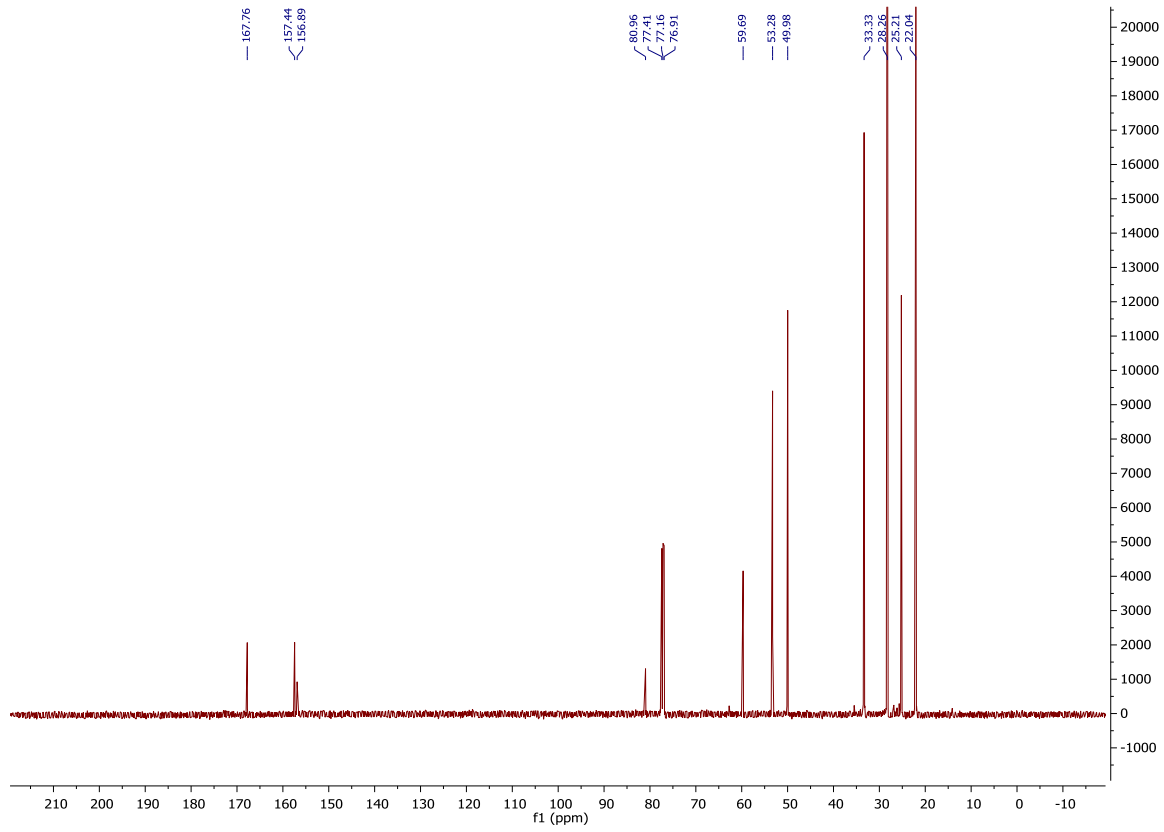
156boc #10-14 RT: 0.18579-0.24793 A\ :6
T: FTMS + p ESI Full ms [150.00-750.00]

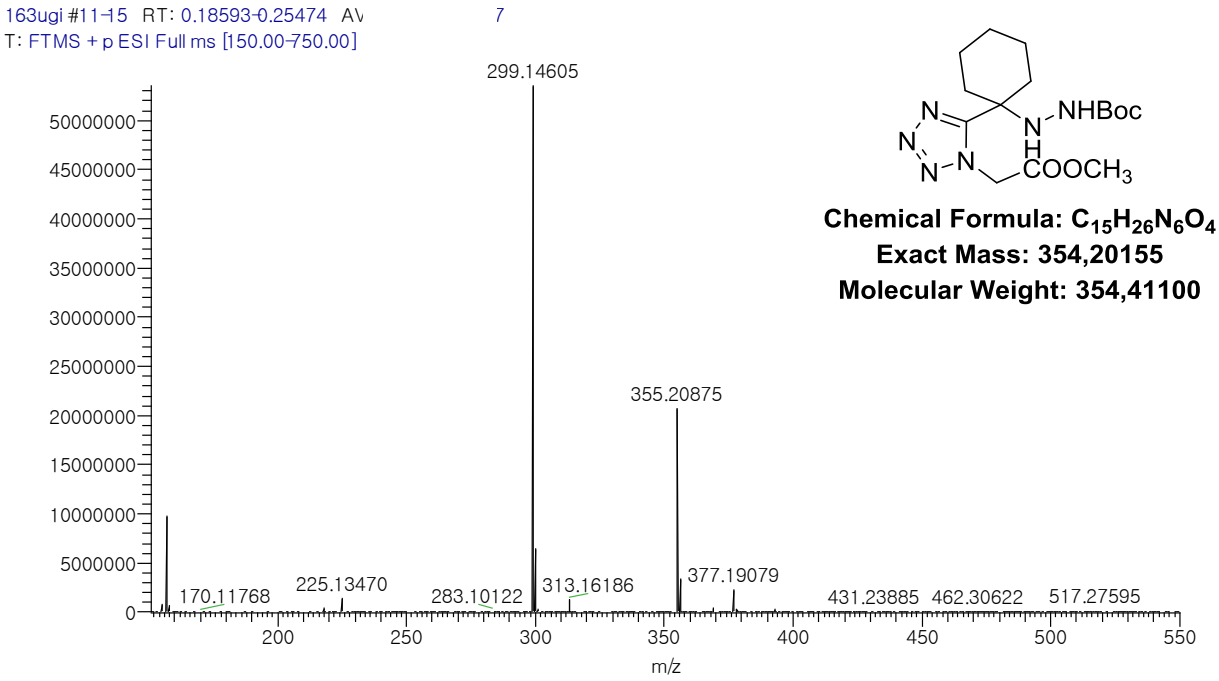


Chemical Formula: $C_{17}H_{28}N_6O_3$
Exact Mass: 364,22229
Molecular Weight: 364,45000

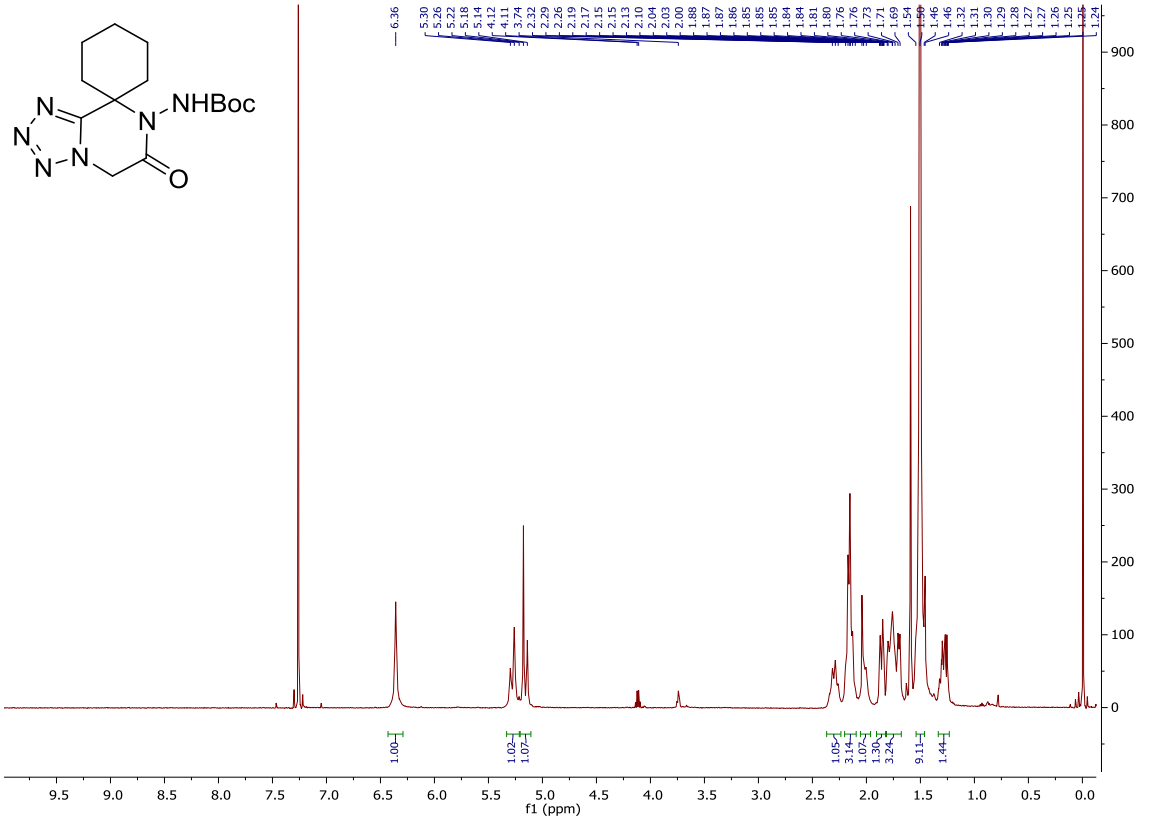
5d: *tert*-butyl 2-(1-(1-(2-methoxy-2-oxoethyl)-1*H*-tetrazol-5-yl)cyclohe-xyl)hydrazine-1-carboxylate

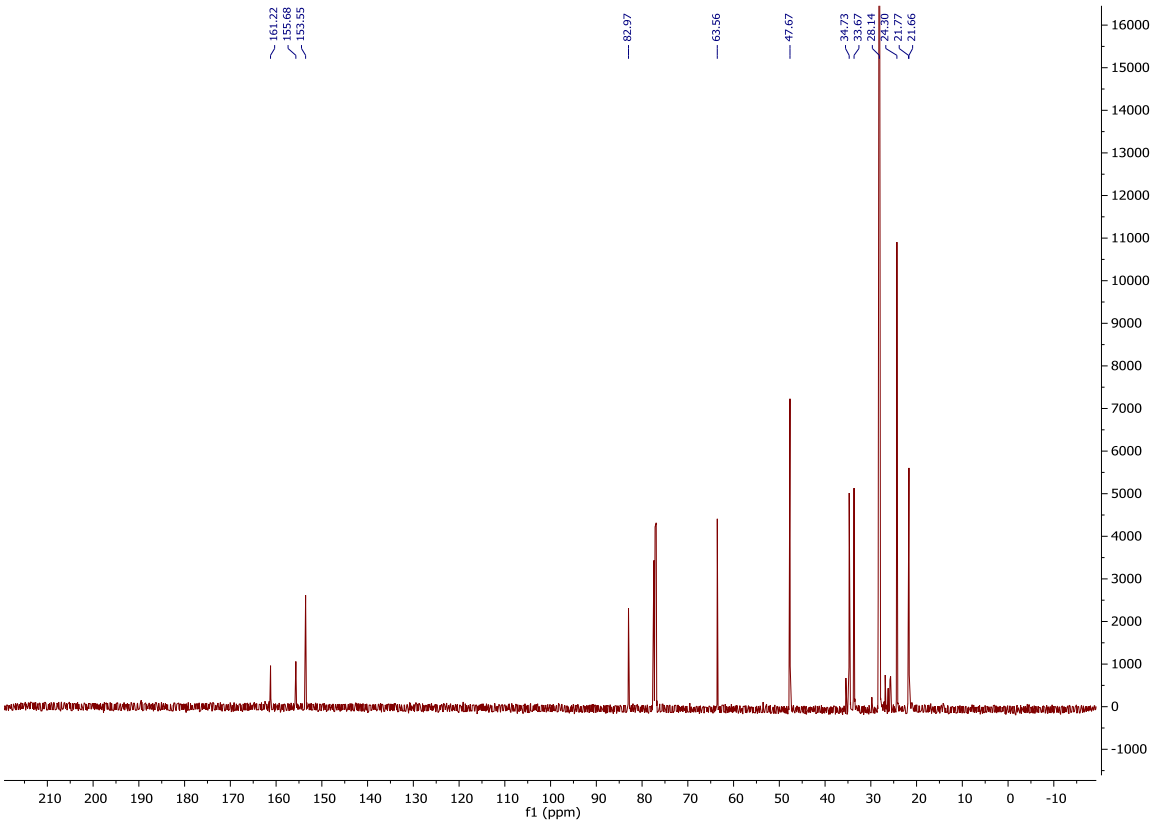


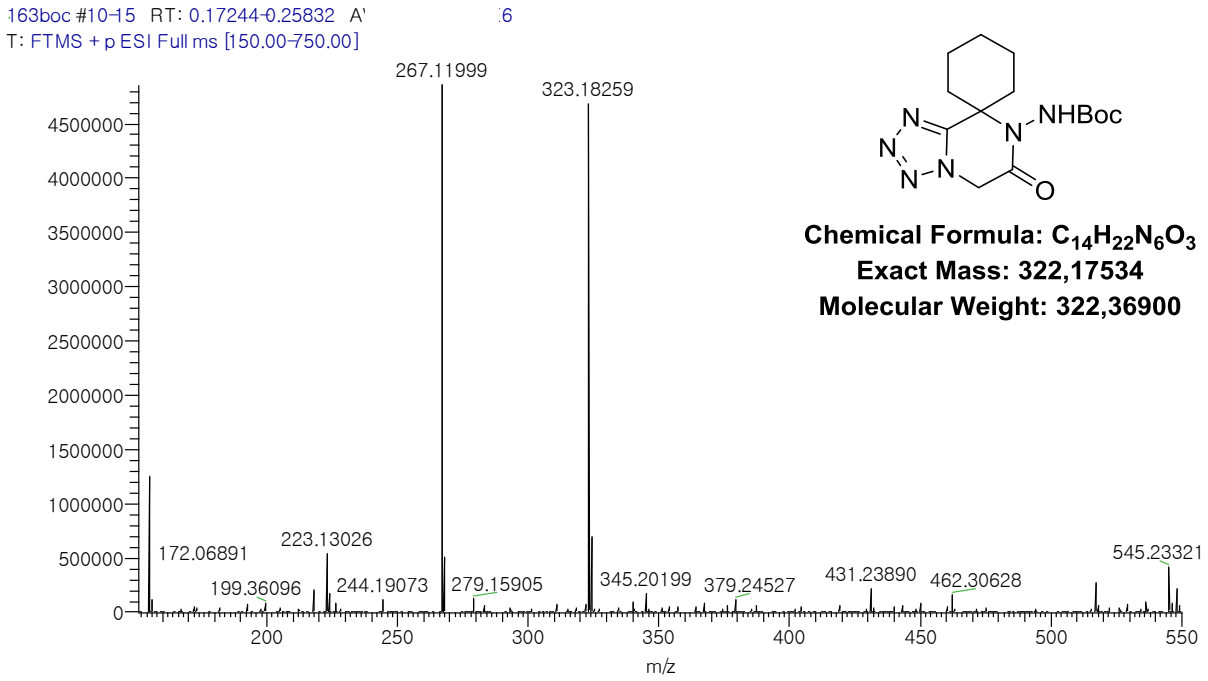



163ugi #11-15 RT: 0.18593-0.25474 AV 7
T: FTMS + p ESI Full ms [150.00-750.00]
299.14605
355.20875
170.11768
225.13470
283.10122
313.16186
377.19079
431.23885
462.30622
517.27595
m/z
NHBoc
COOCH3
Chemical Formula: C15H26N6O4
Exact Mass: 354,20155
Molecular Weight: 354,41100

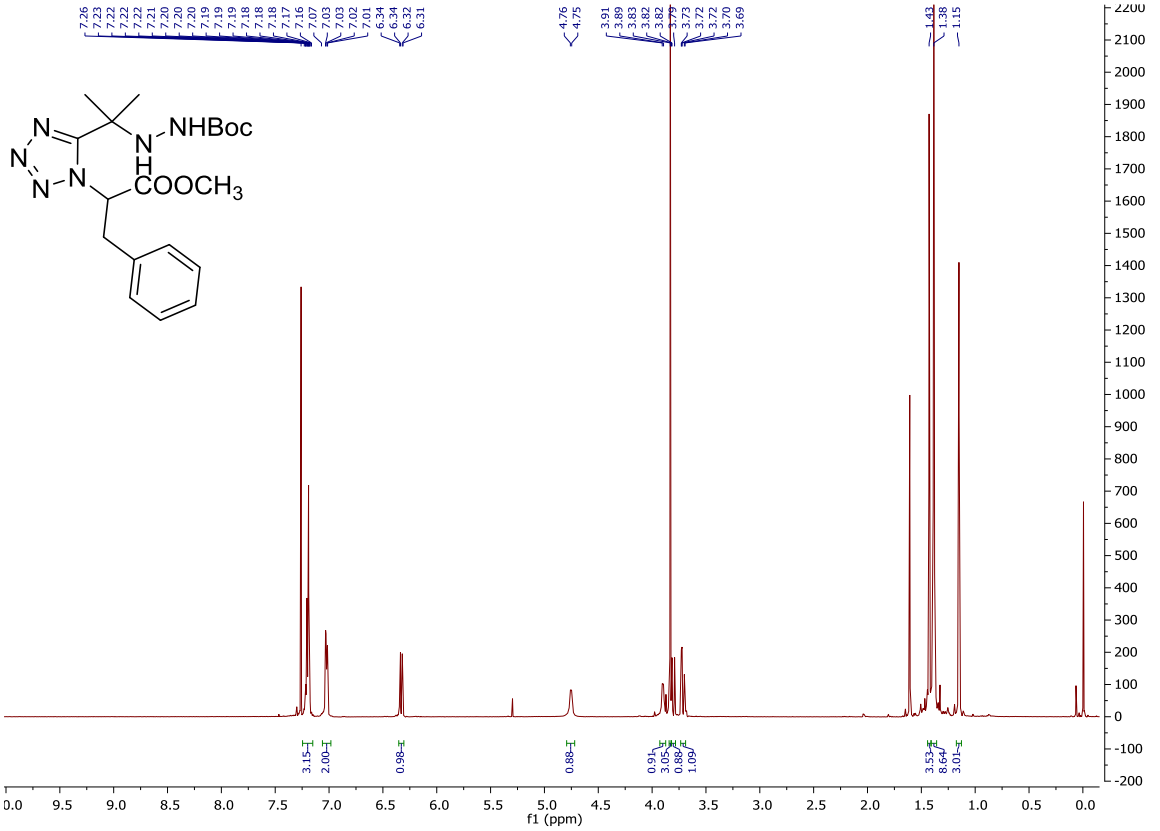
8d: *tert*-butyl(6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclohexane-1,8'-tetrazolo [1,5-a]pyrazin]-7'-yl)carbamate

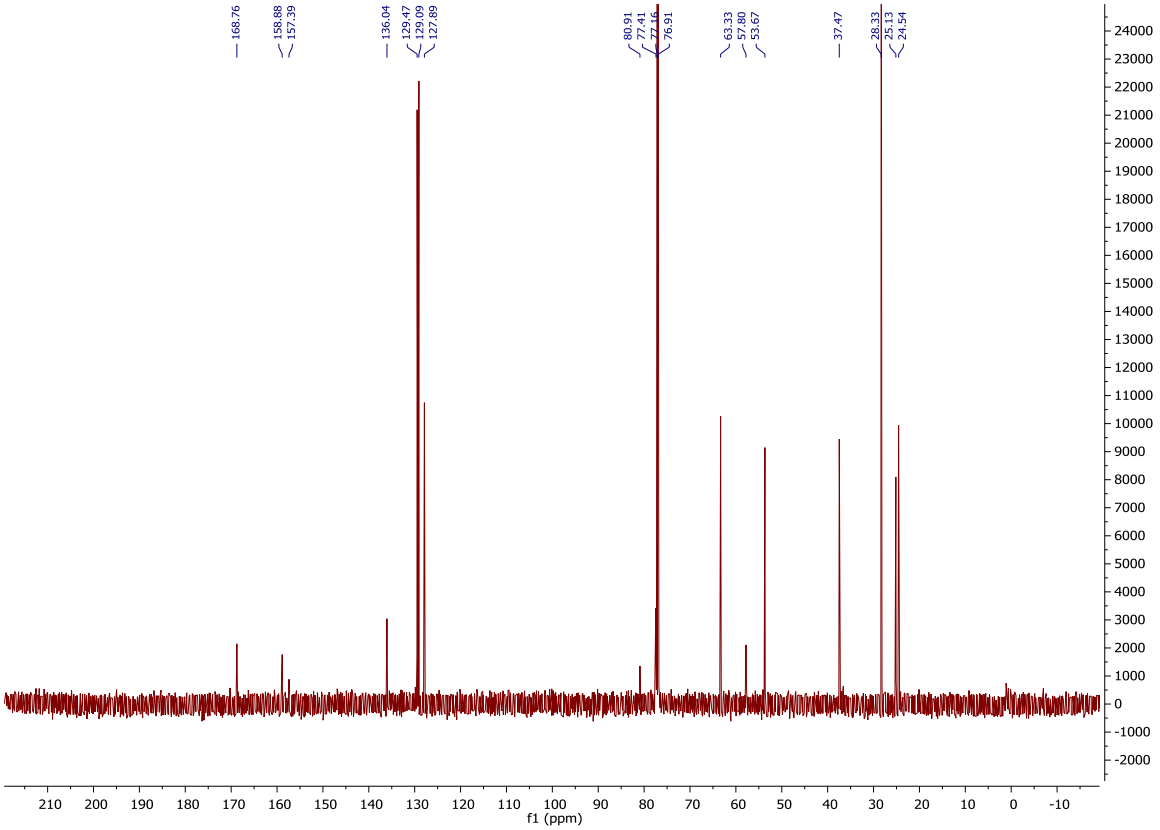




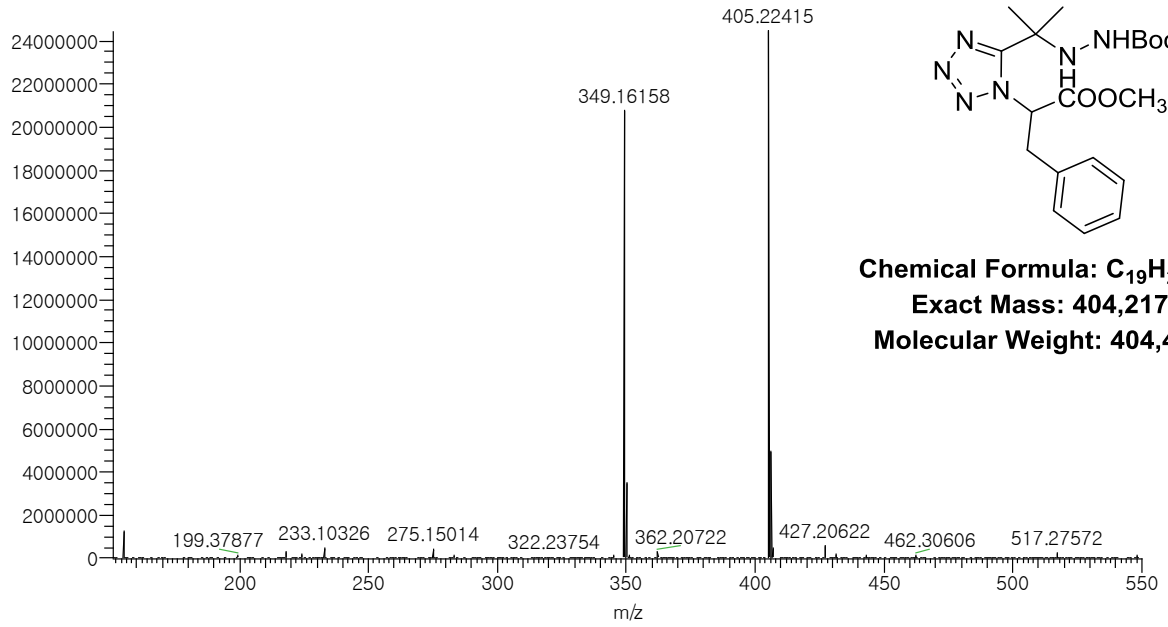

163boc #10-15 RT: 0.17244-0.25832 A
T: FTMS + p ESI Full ms [150.00-750.00]
267.11999
323.18259
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
172.06891
223.13026
199.36096
244.19073
279.15905
345.20199
379.24527
431.23890
462.30628
545.23321
200
250
300
350
400
450
500
550
m/z
NHBoc
O
Chemical Formula: C14H22N6O3
Exact Mass: 322,17534
Molecular Weight: 322,36900

5e: *tert*-butyl 2-(2-(1-(1-methoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-tetra-zol-5-yl)propan-2-yl)hydrazine-1-carboxylate



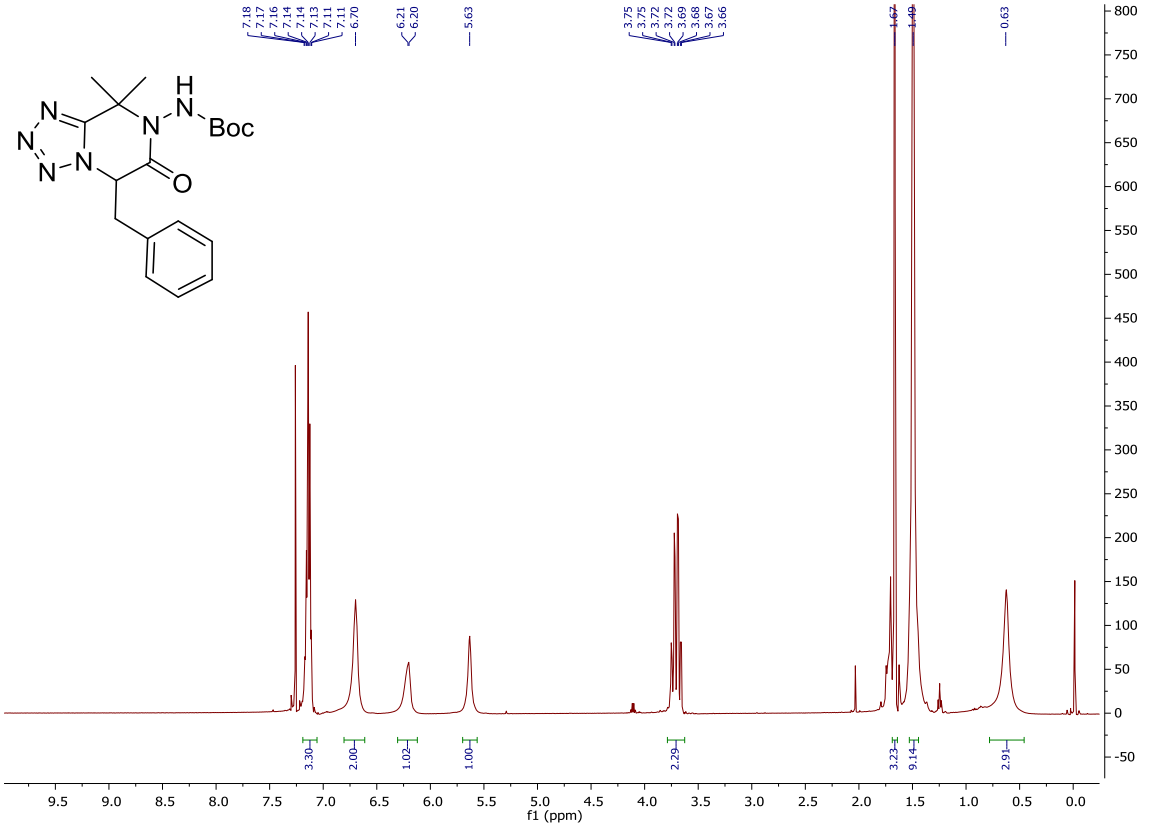


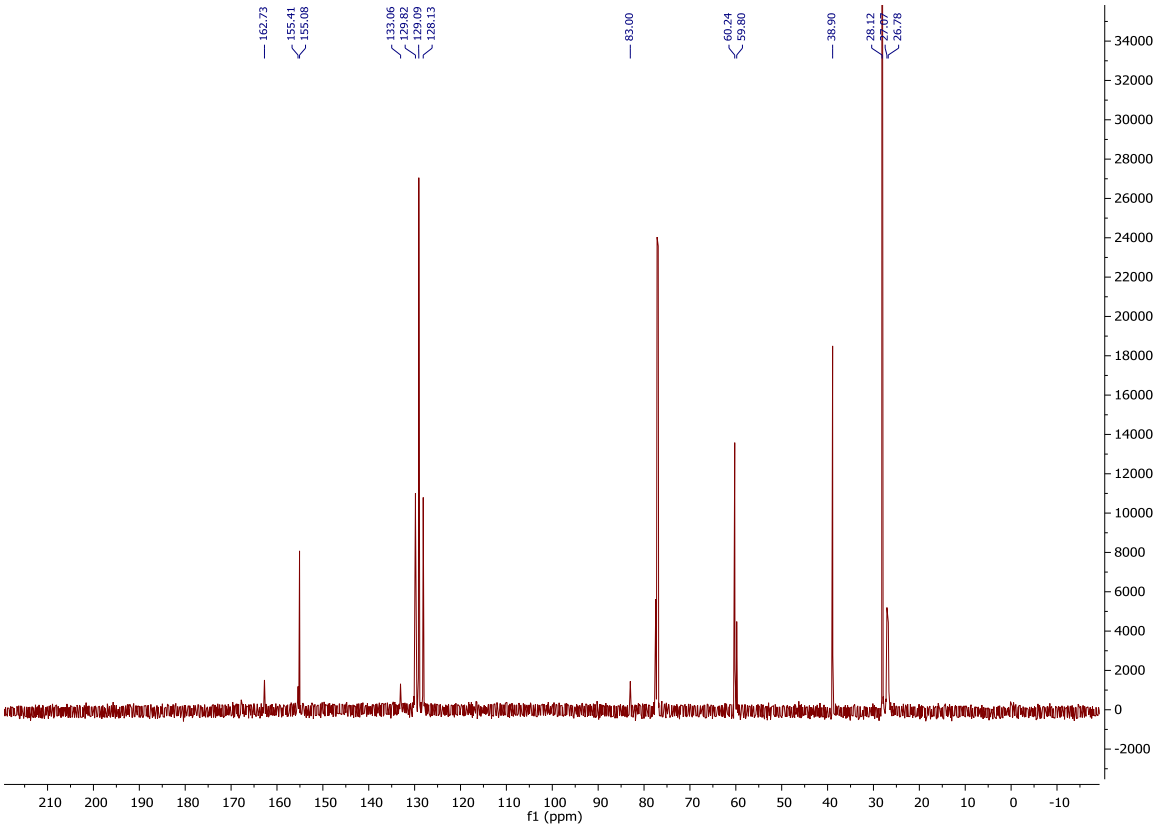
173ugi #10-15 RT: 0.17105-0.25569 AV 7
T: FTMS + p ESI Full ms [150.00-750.00]

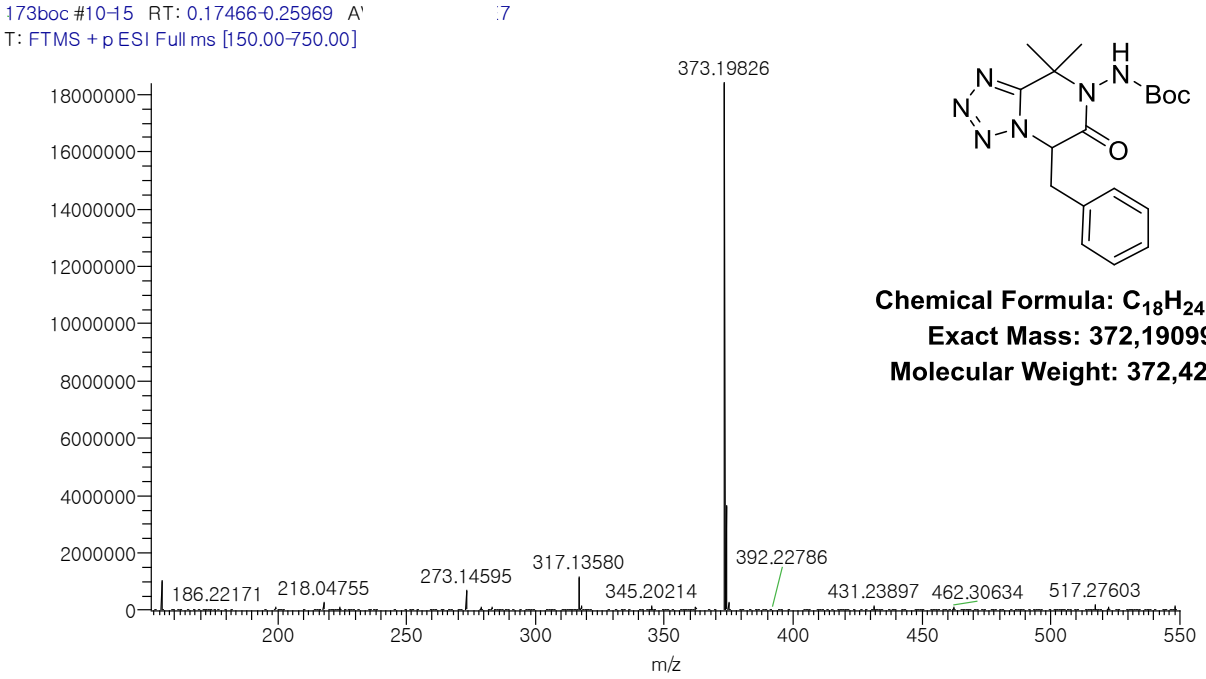


Chemical Formula: $C_{19}H_{28}N_6O_4$
Exact Mass: 404,21720
Molecular Weight: 404,47100

8e: *tert*-butyl (5-benzyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a] pyrazin-7(8*H*)-yl) carbamate

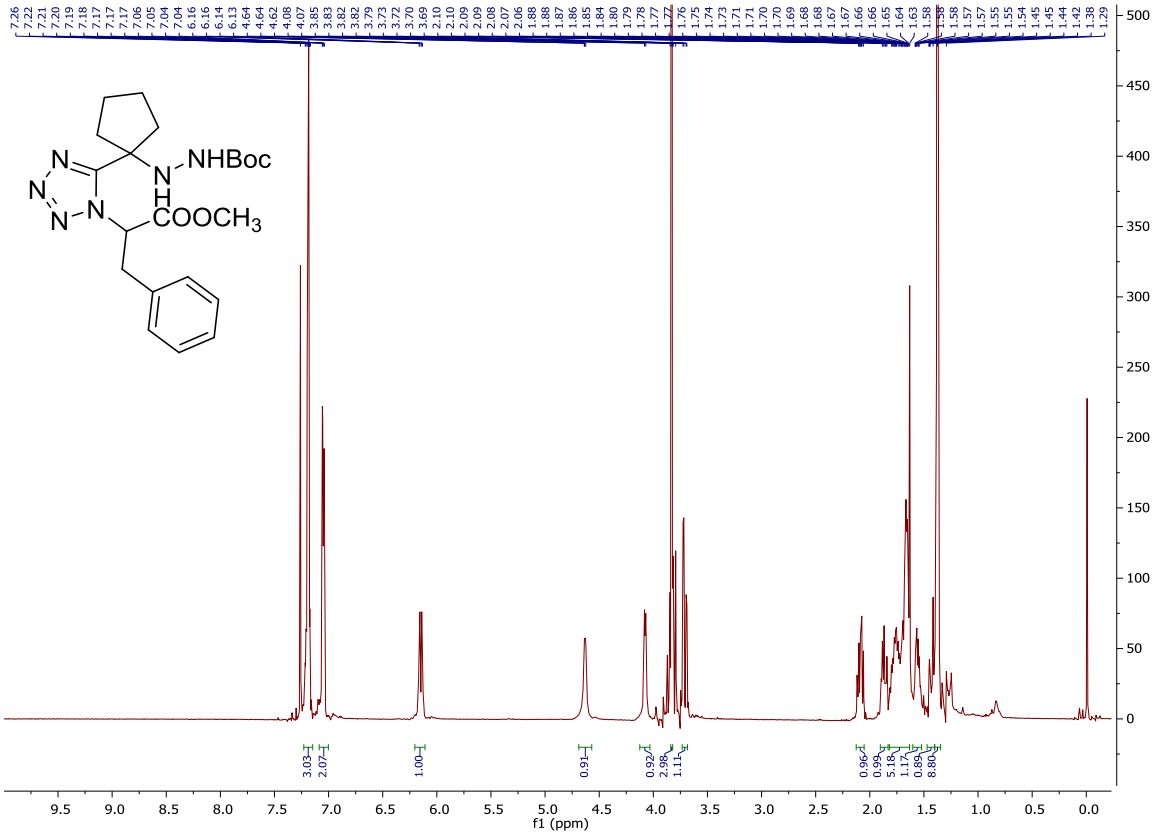


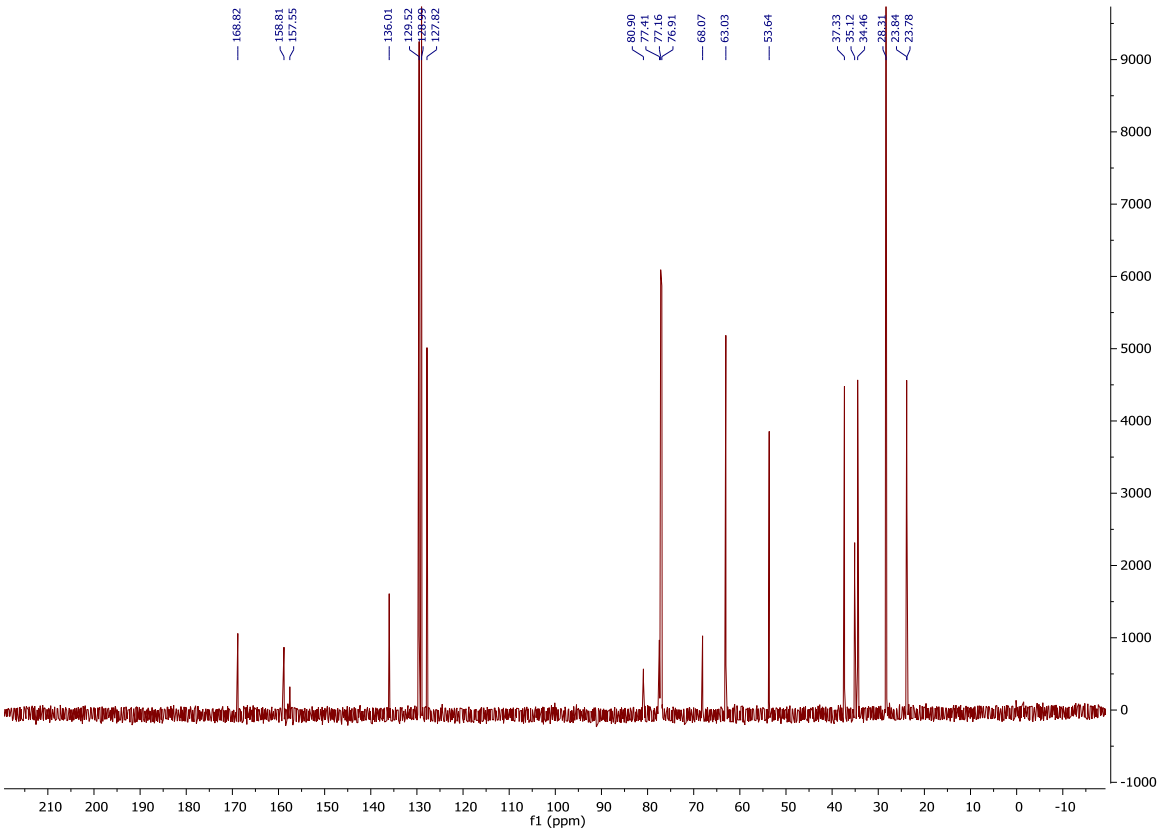


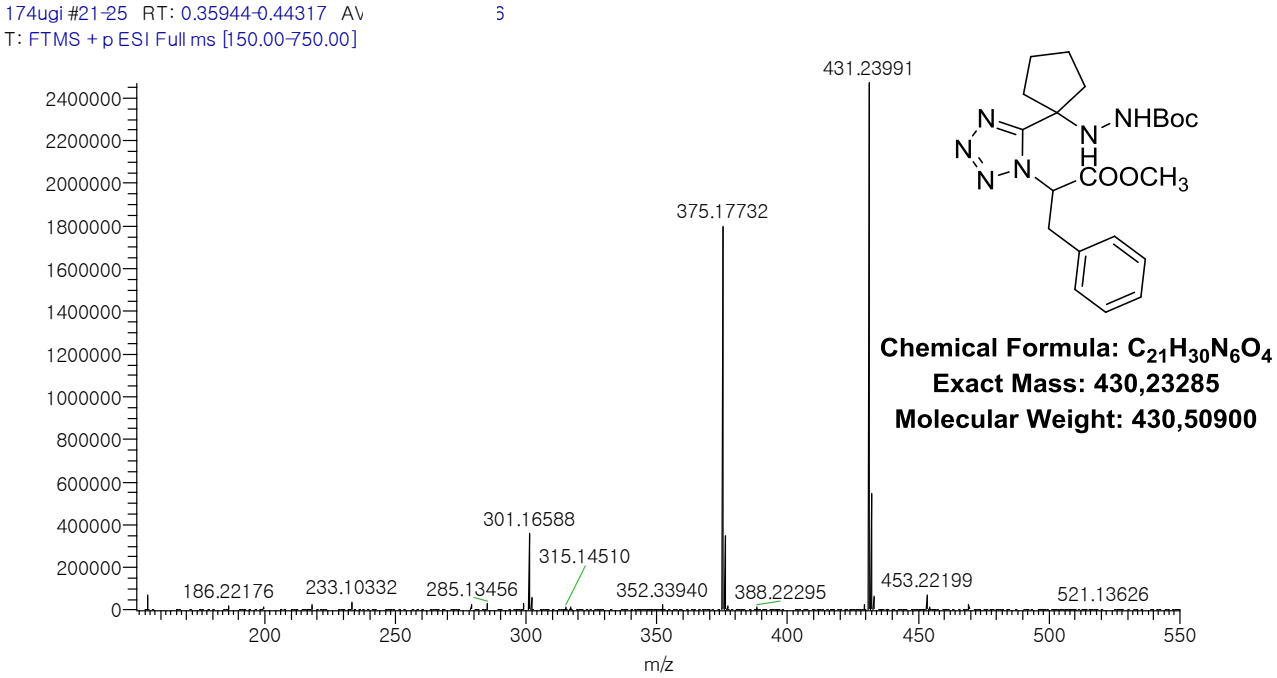


Chemical Formula: $C_{18}H_{24}N_6O_3$
Exact Mass: 372,19099
Molecular Weight: 372,42900

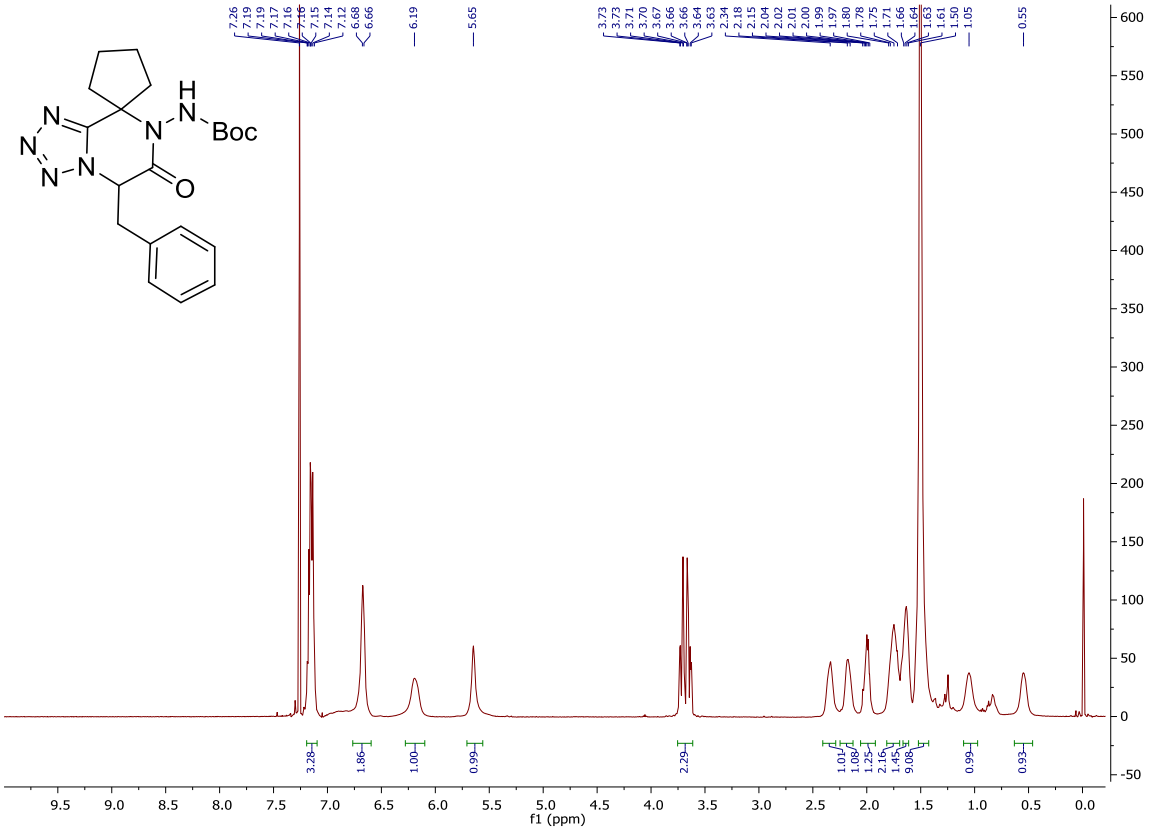
5f: *tert*-butyl 2-(1-(1-(1-methoxy-1-oxo-3-phenylpropan-2-yl)-1*H*-tetrazol-5-yl)cyclopentyl)hydrazine-1-carboxylate

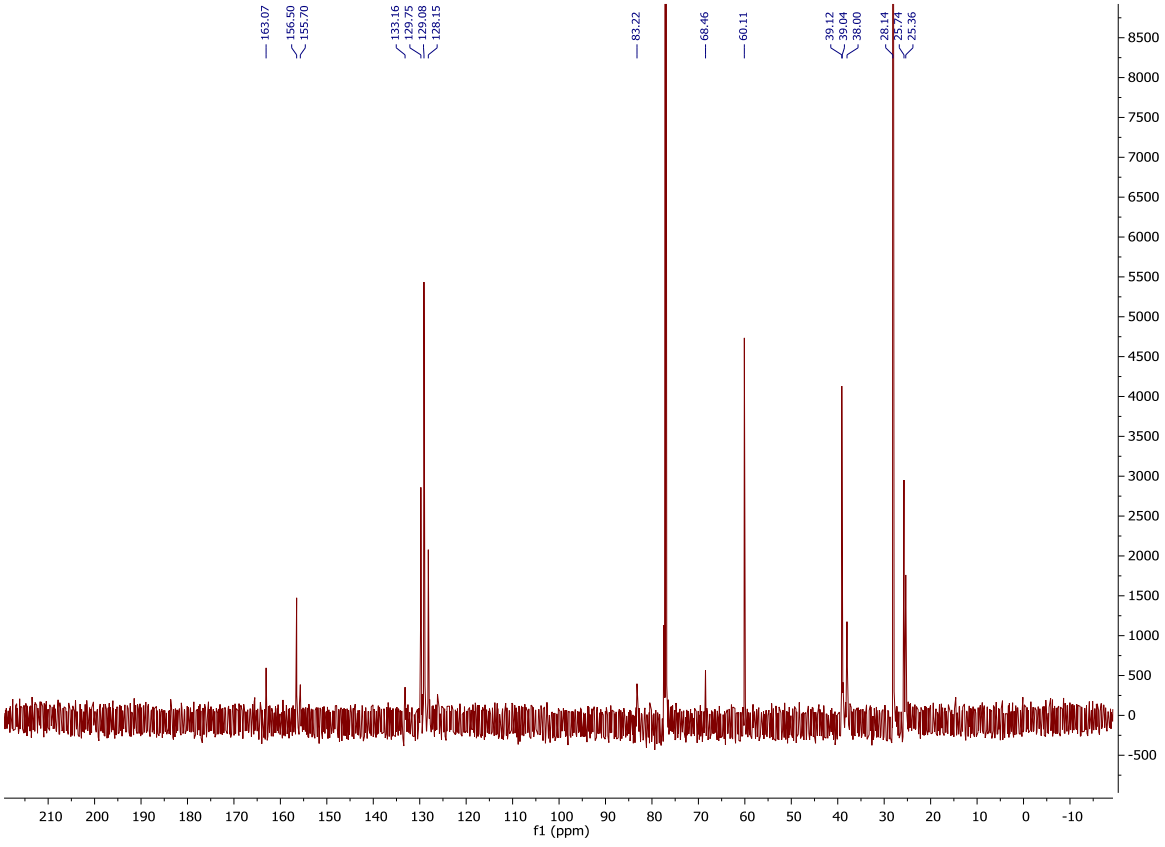


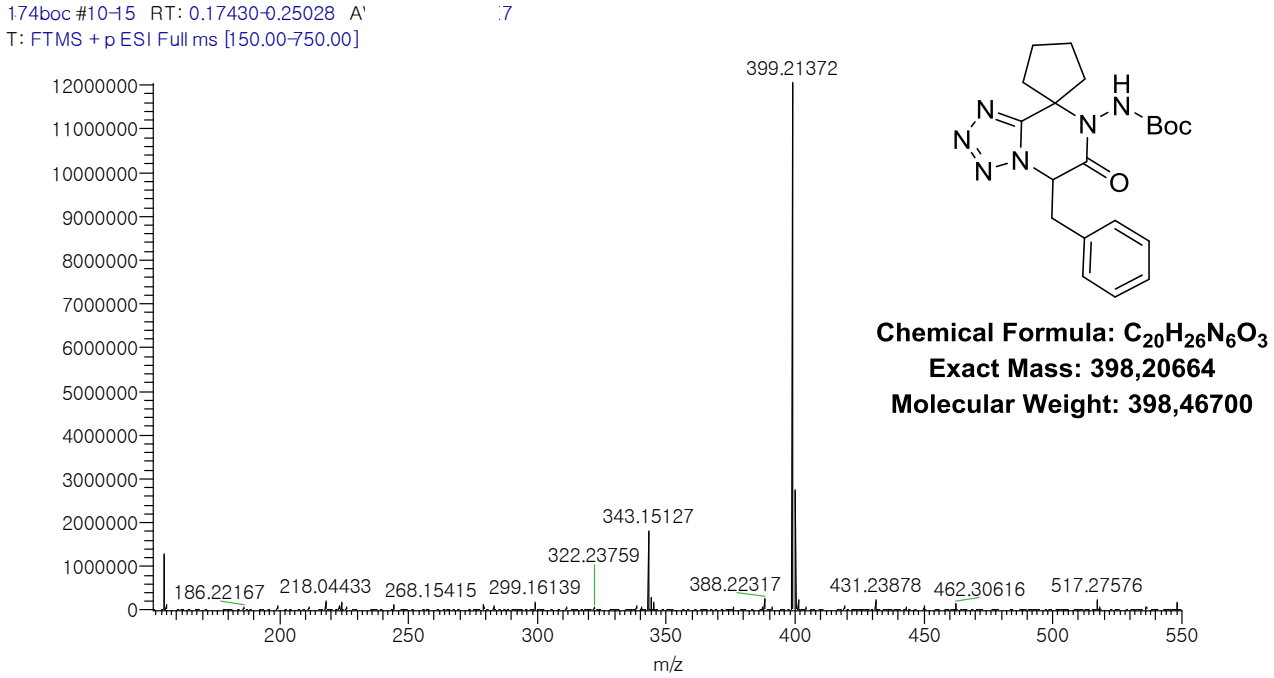



174ugi #21-25 RT: 0.35944-0.44317 AV
T: FTMS + p ESI Full ms [150.00-750.00]
431.23991
375.17732
301.16588
315.14510
186.22176
233.10332
285.13456
352.33940
388.22295
453.22199
521.13626
m/z
NHBoc
COOCH3
Chemical Formula: C21H30N6O4
Exact Mass: 430,23285
Molecular Weight: 430,50900

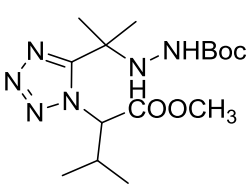
8f: *tert*-butyl (5'-benzyl-6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclohexane-1,8'-tetrazolo[1,5-a] pyrazin]-7'-yl)carbamate

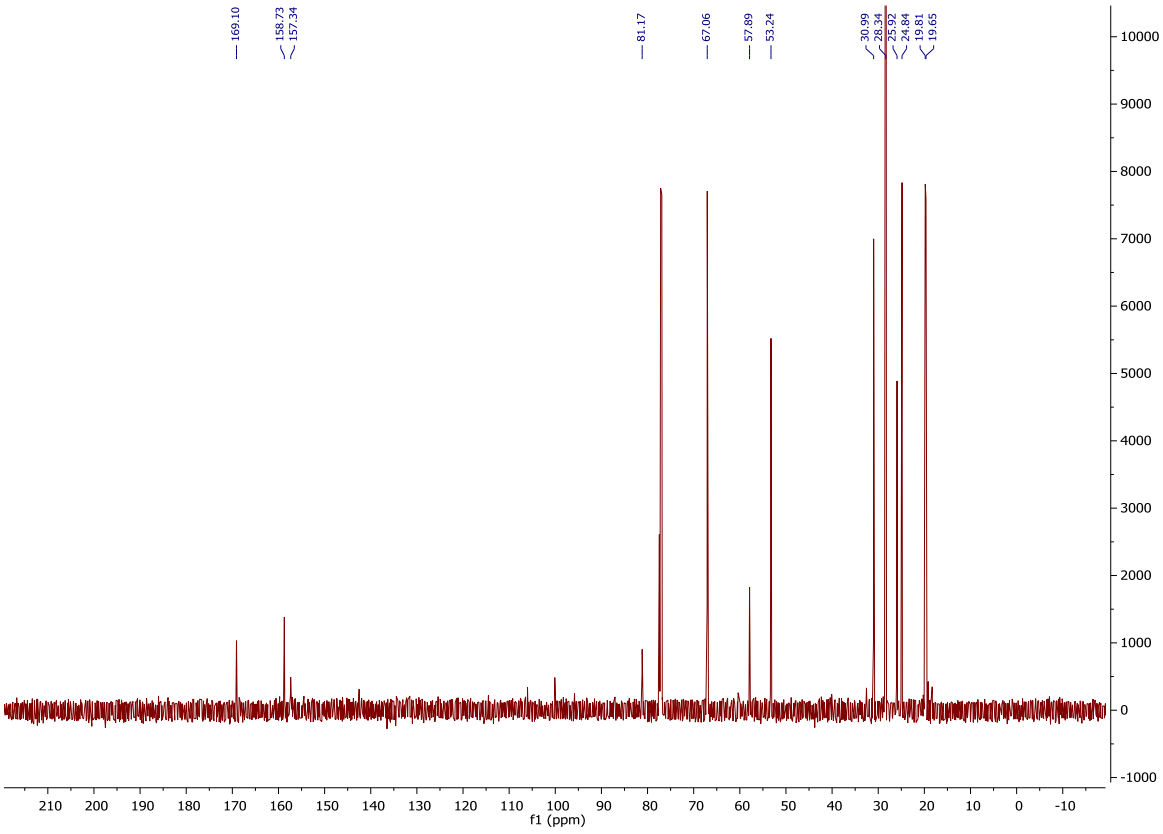


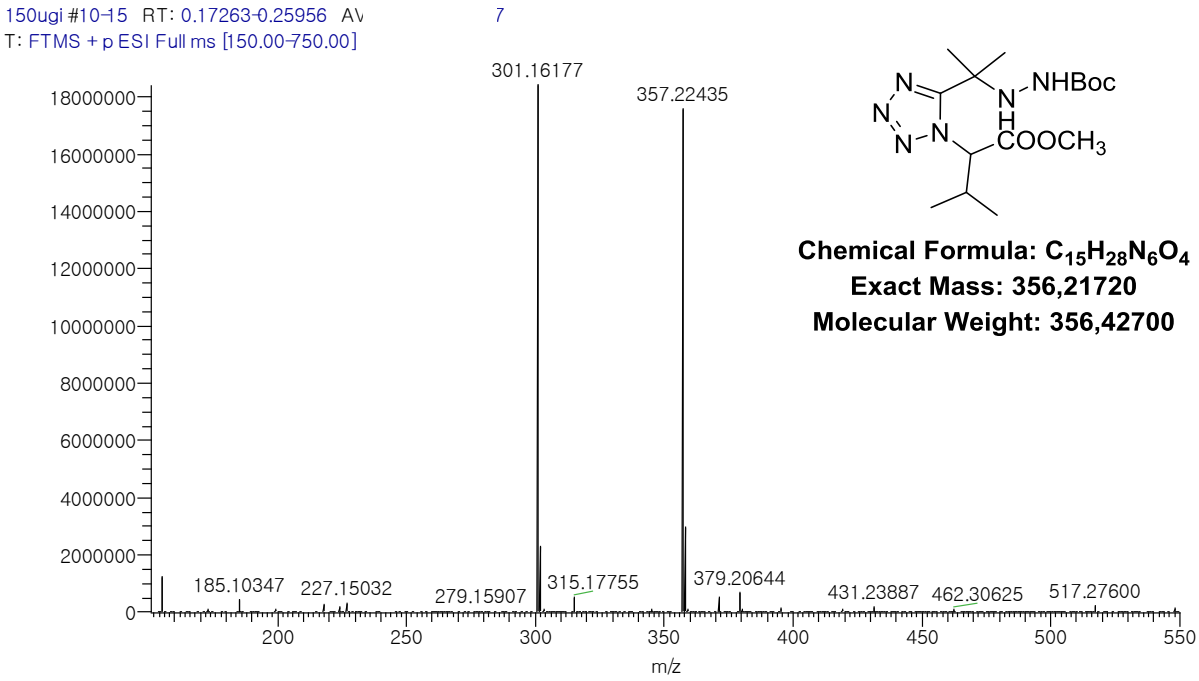



174boc #10-15 RT: 0.17430-0.25028 A
T: FTMS + p ESI Full ms [150.00-750.00]
399.21372
343.15127
322.23759
186.22167
218.04433
268.15415
299.16139
388.22317
431.23878
462.30616
517.27576
m/z
Boc
Chemical Formula: C20H26N6O3
Exact Mass: 398,20664
Molecular Weight: 398,46700

5g: *tert*-butyl 2-(2-(1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1*H*-tetra-zol-5-yl)propan-2-yl)hydrazine-1-carboxylate

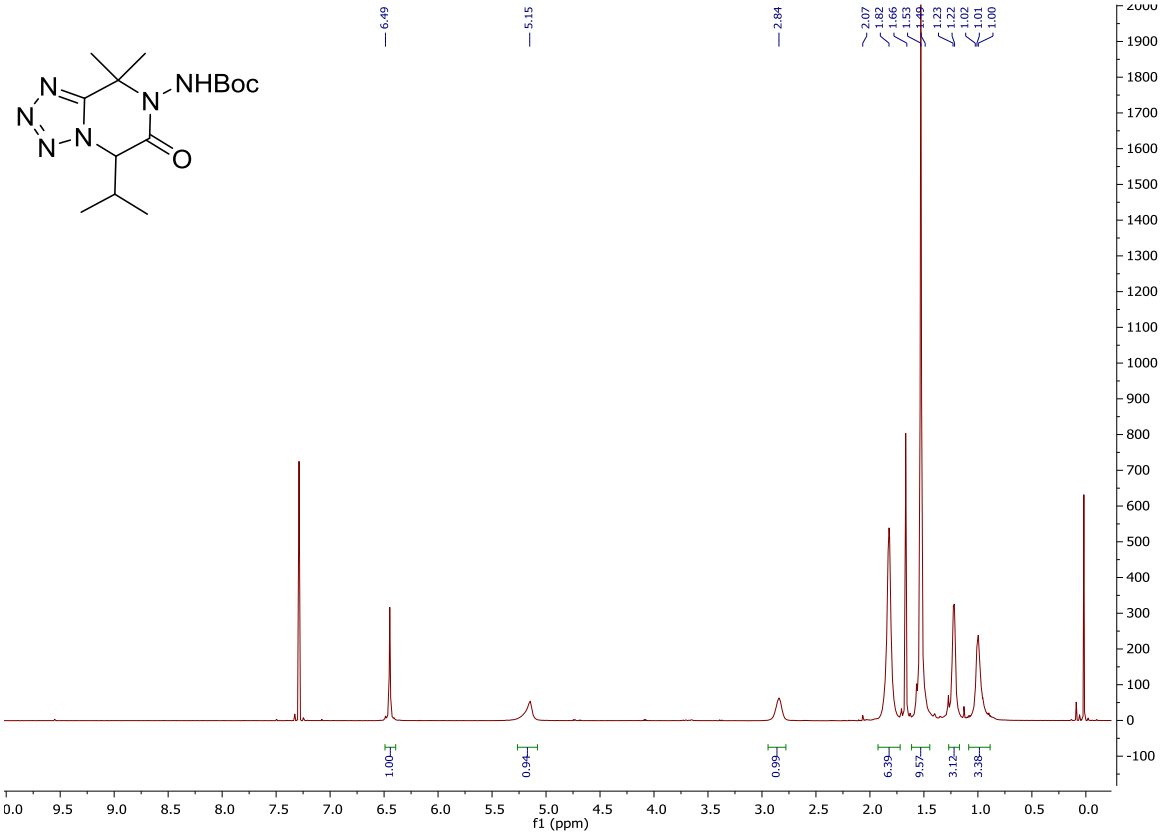


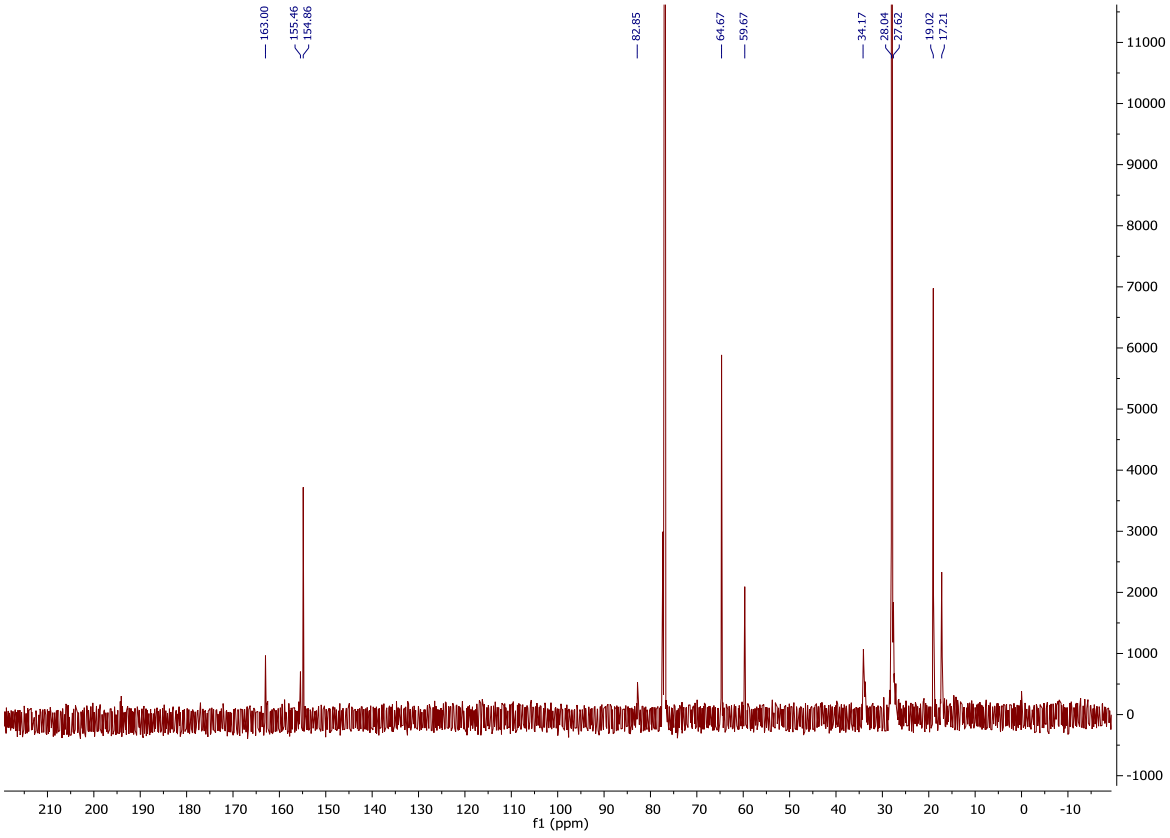




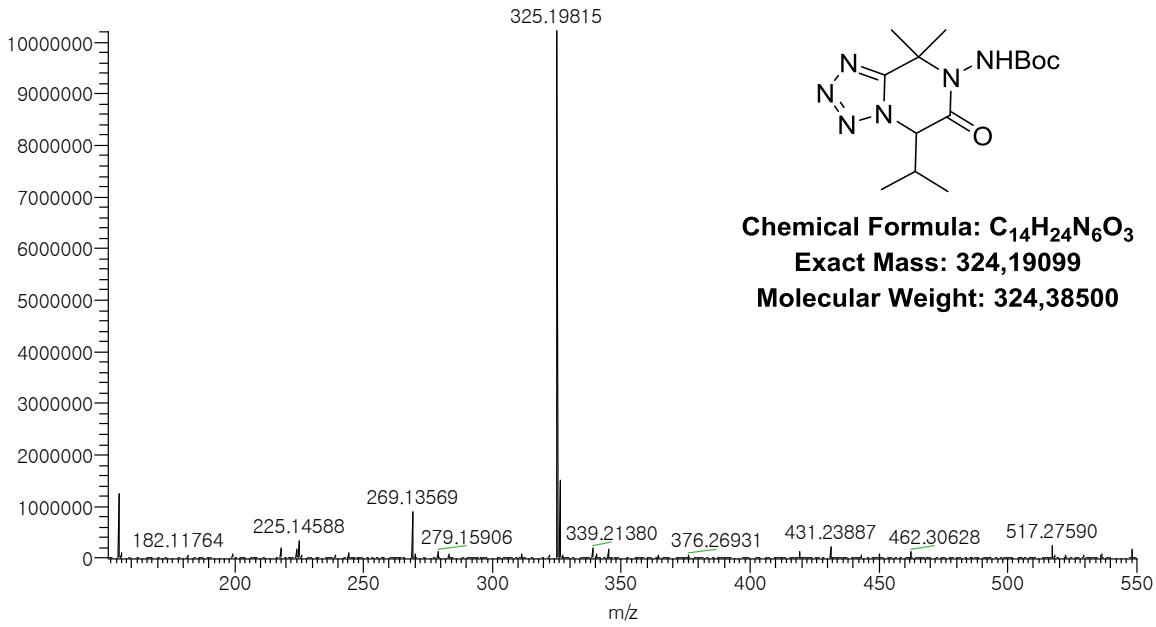
Chemical Formula: $C_{15}H_{28}N_6O_4$
Exact Mass: 356,21720
Molecular Weight: 356,42700

8g: *tert*-butyl (5-isopropyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8*H*)-yl)carbamate



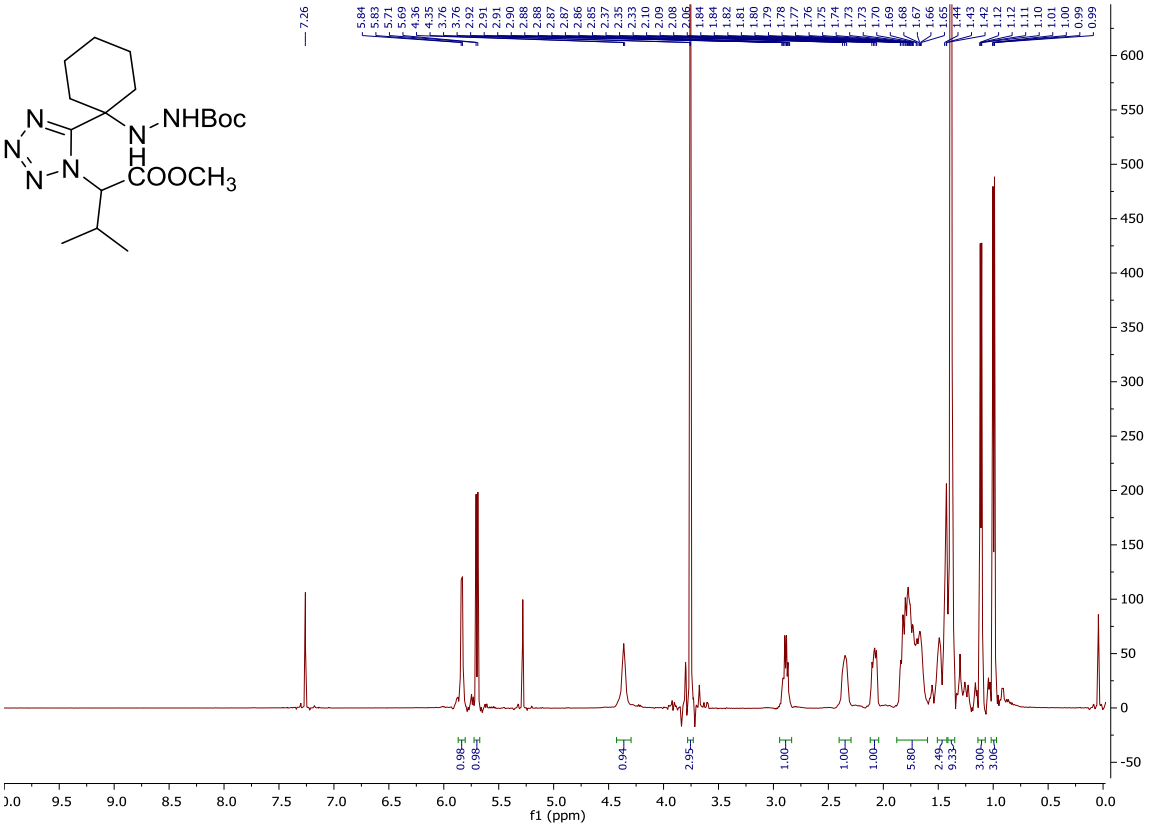


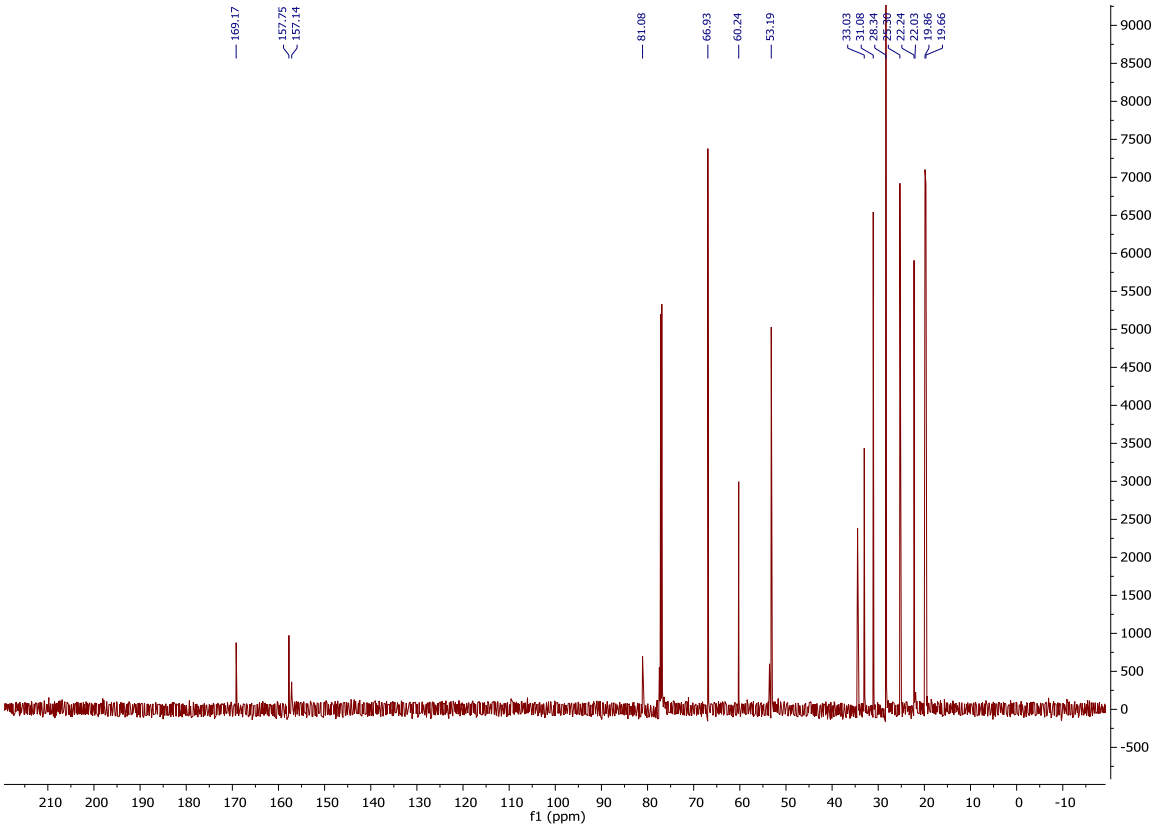
150boc #10-15 RT: 0.17554-0.25221 A\ :7
T: FTMS + p ESI Full ms [150.00-750.00]



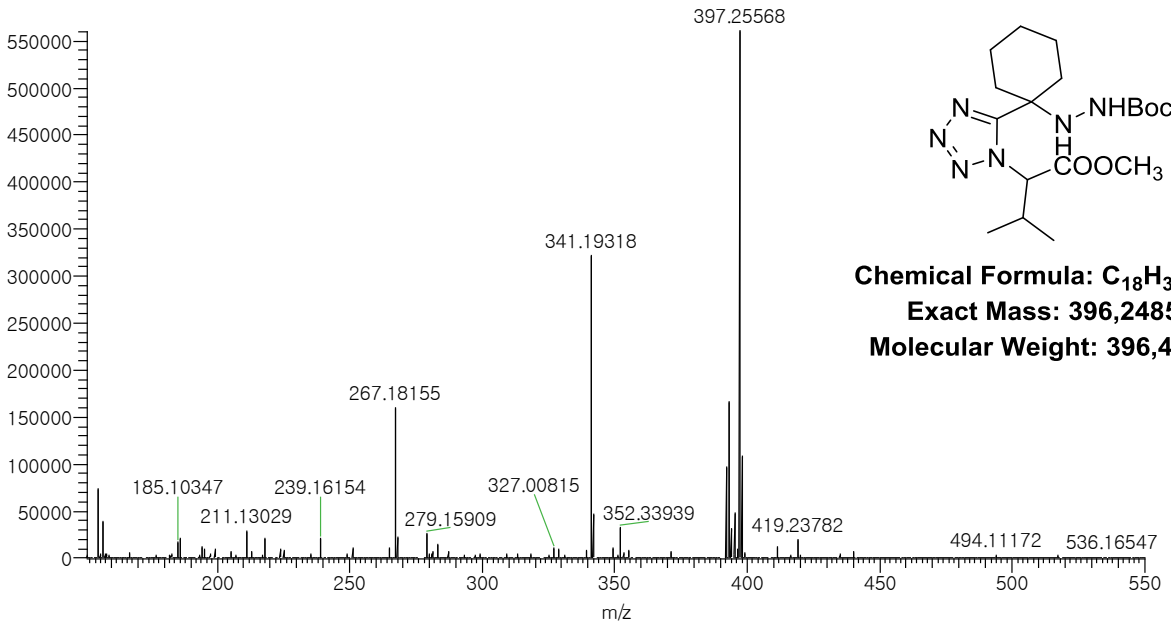
Chemical Formula: $C_{14}H_{24}N_6O_3$
Exact Mass: 324,19099
Molecular Weight: 324,38500

5h: *tert*-butyl 2-(1-(1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1*H*-tetrazol-5-yl)cyclohexyl) hydrazine-1-carboxylate



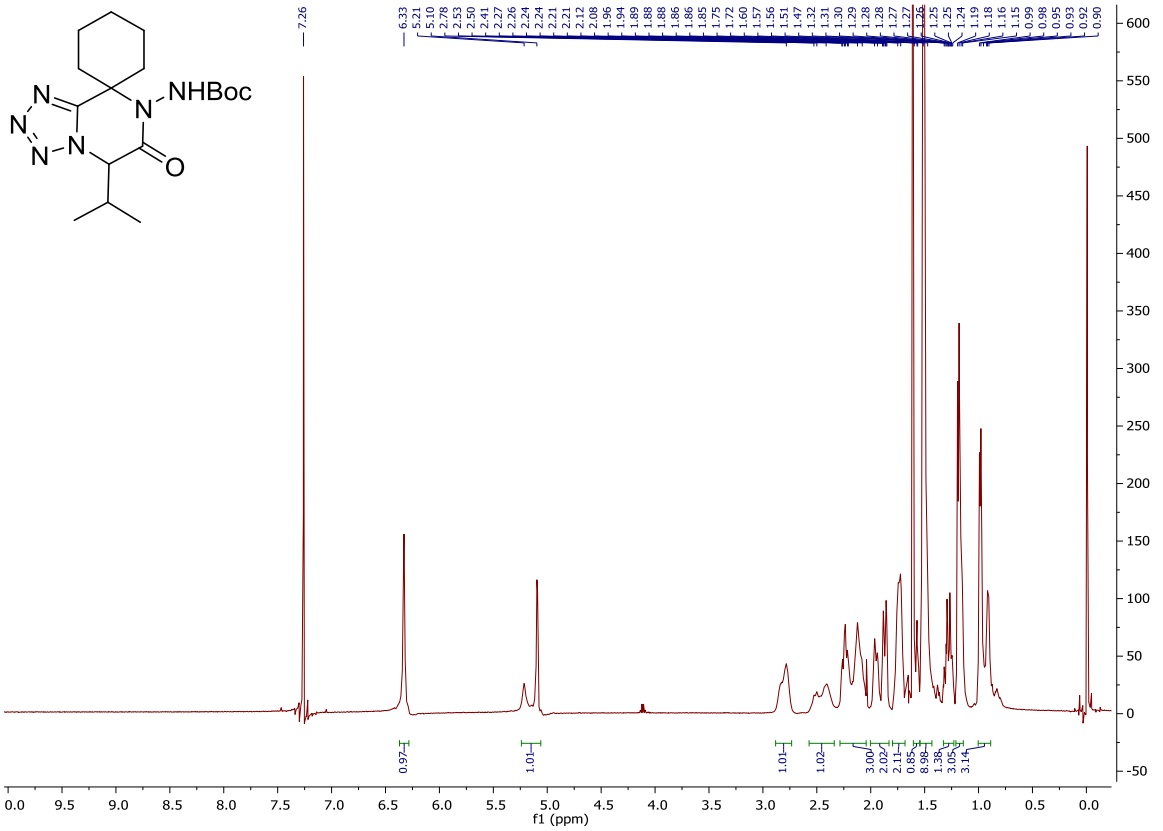


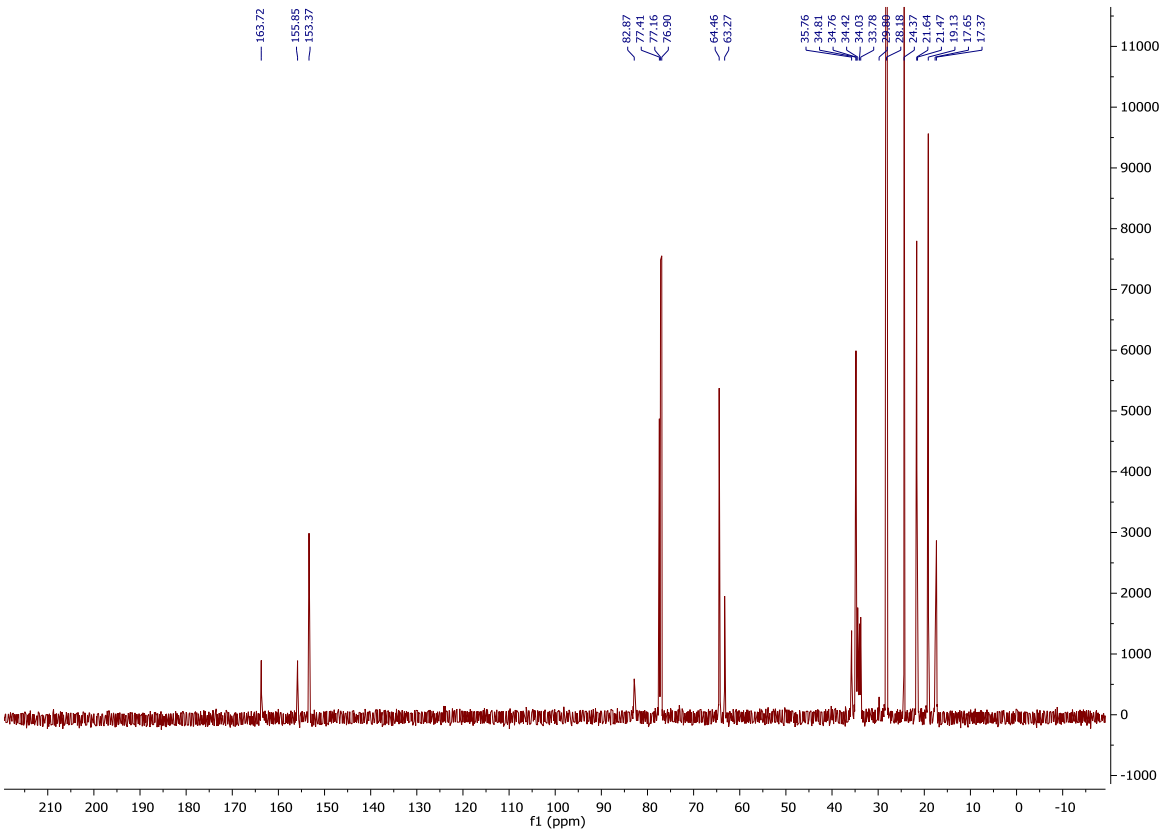
149ugi #25 RT: 0.44661 AV: 1 NL: 5.6
T: FTMS + p ESI Full ms [150.00-750.00]



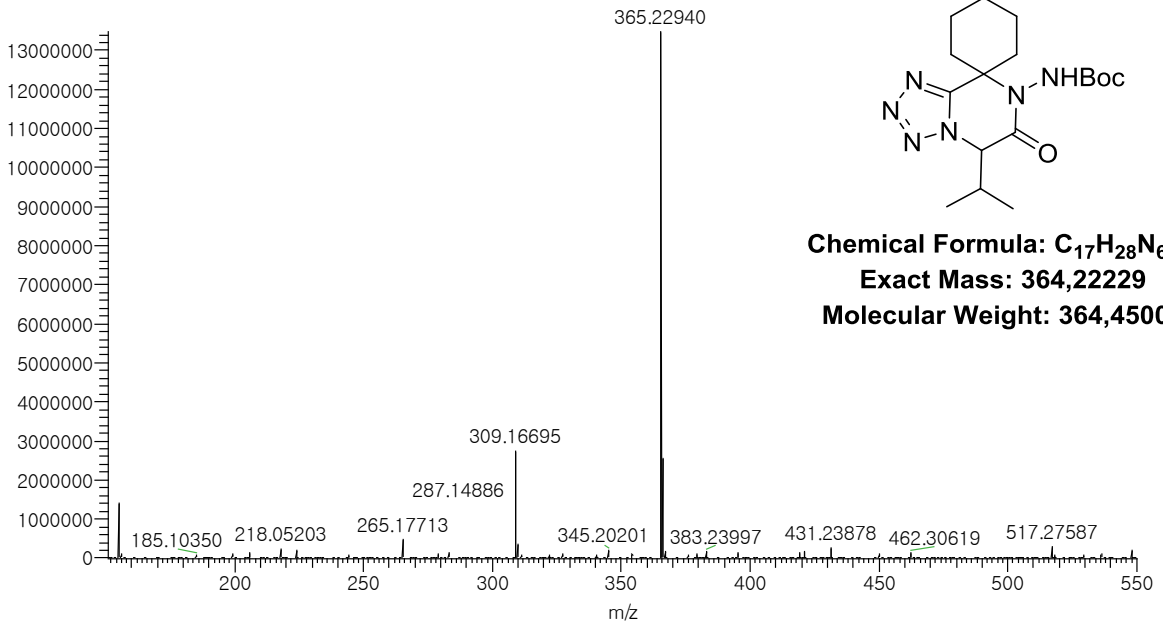
Chemical Formula: $C_{18}H_{32}N_6O_4$
Exact Mass: 396,24850
Molecular Weight: 396,49200

8h: *tert*-butyl (5'-isopropyl-6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclohexane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl)carbamate



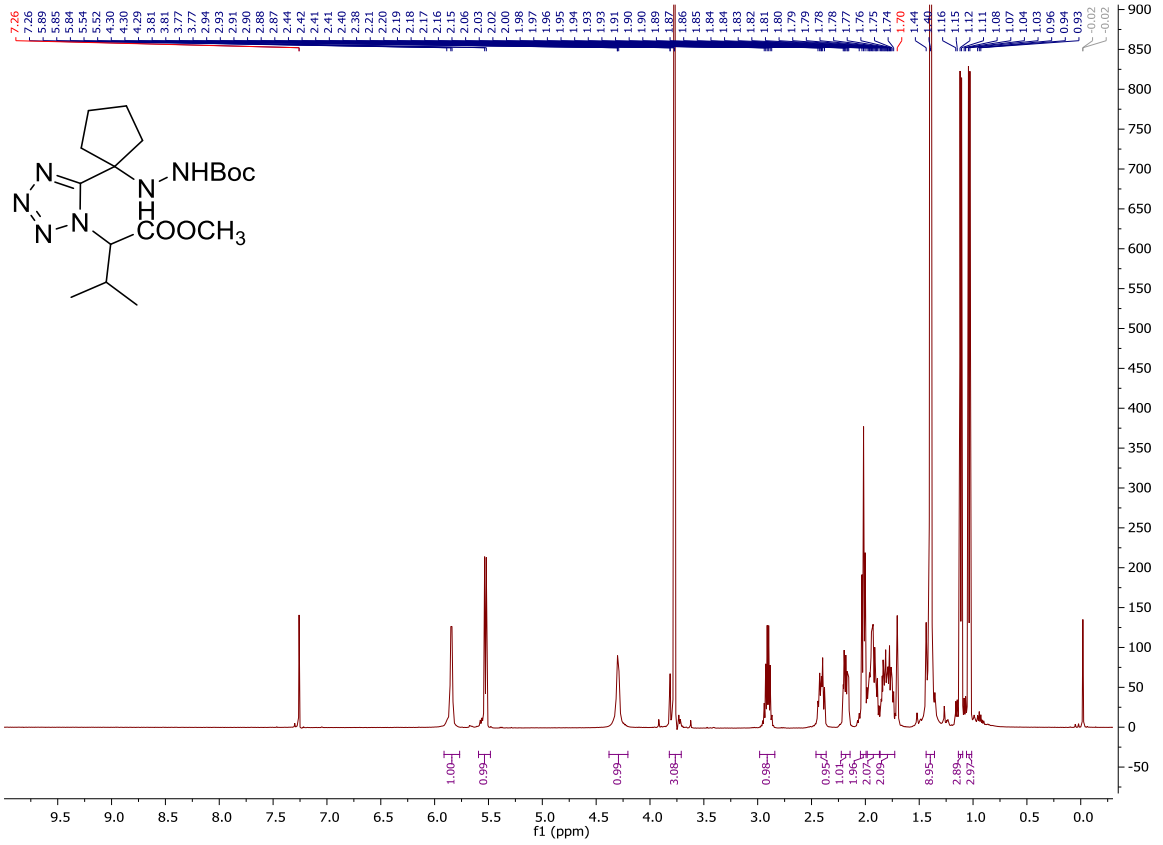


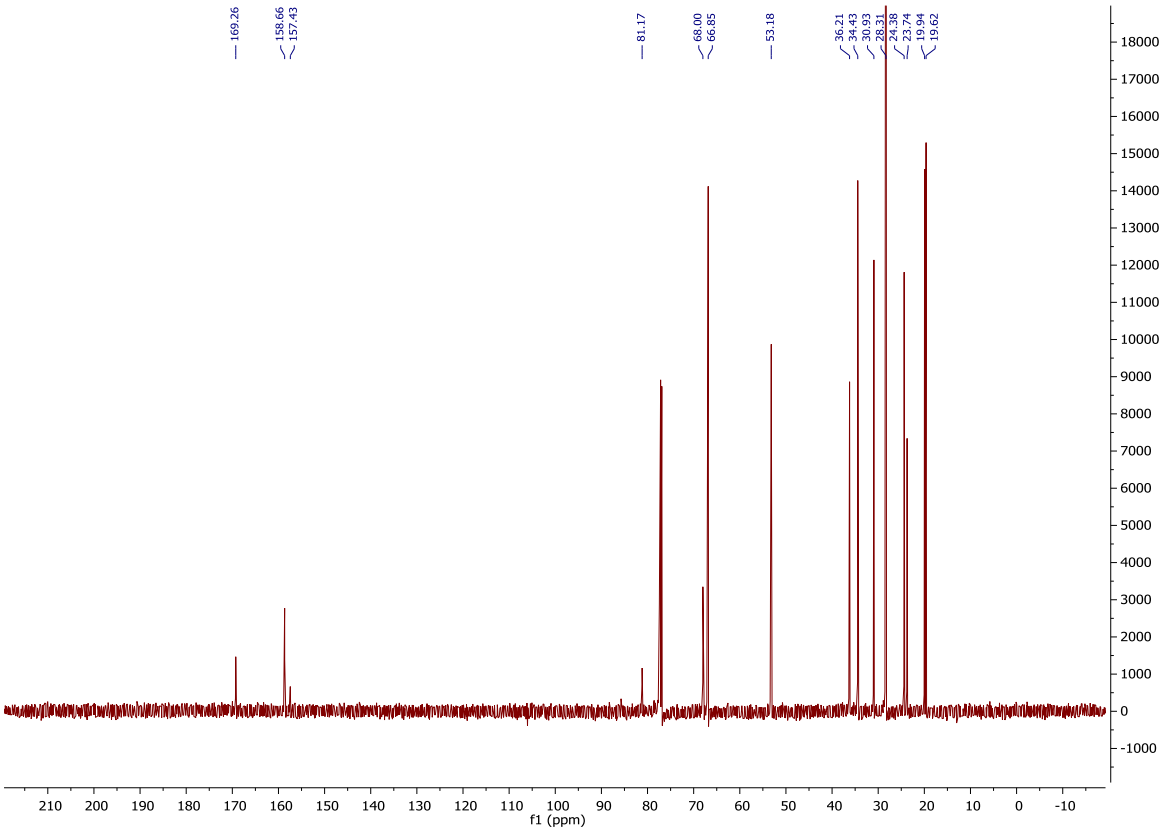
149boc #10-15 RT: 0.17454-0.25011 A' :7
T: FTMS + p ESI Full ms [150.00-750.00]



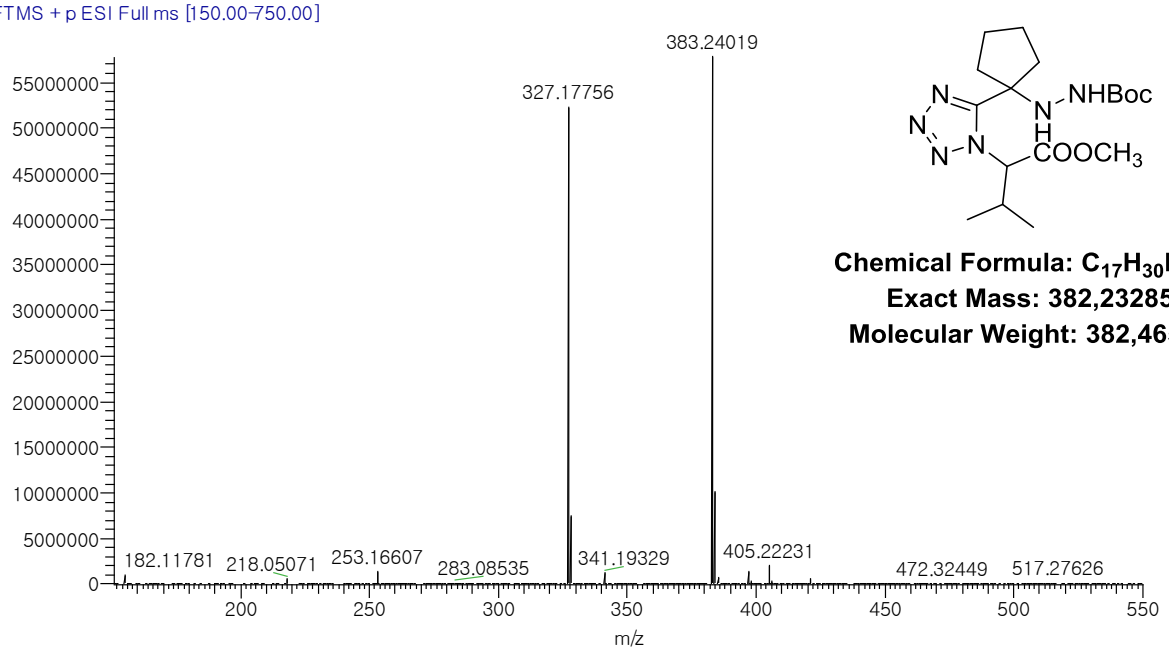
Chemical Formula: $C_{17}H_{28}N_6O_3$
Exact Mass: 364,22229
Molecular Weight: 364,45000

5i: *tert*-butyl 2-(1-(1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1*H*-tetra-zol-5-yl)cyclopentyl) hydrazine-1-carboxylate



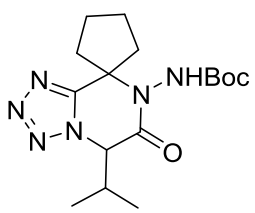


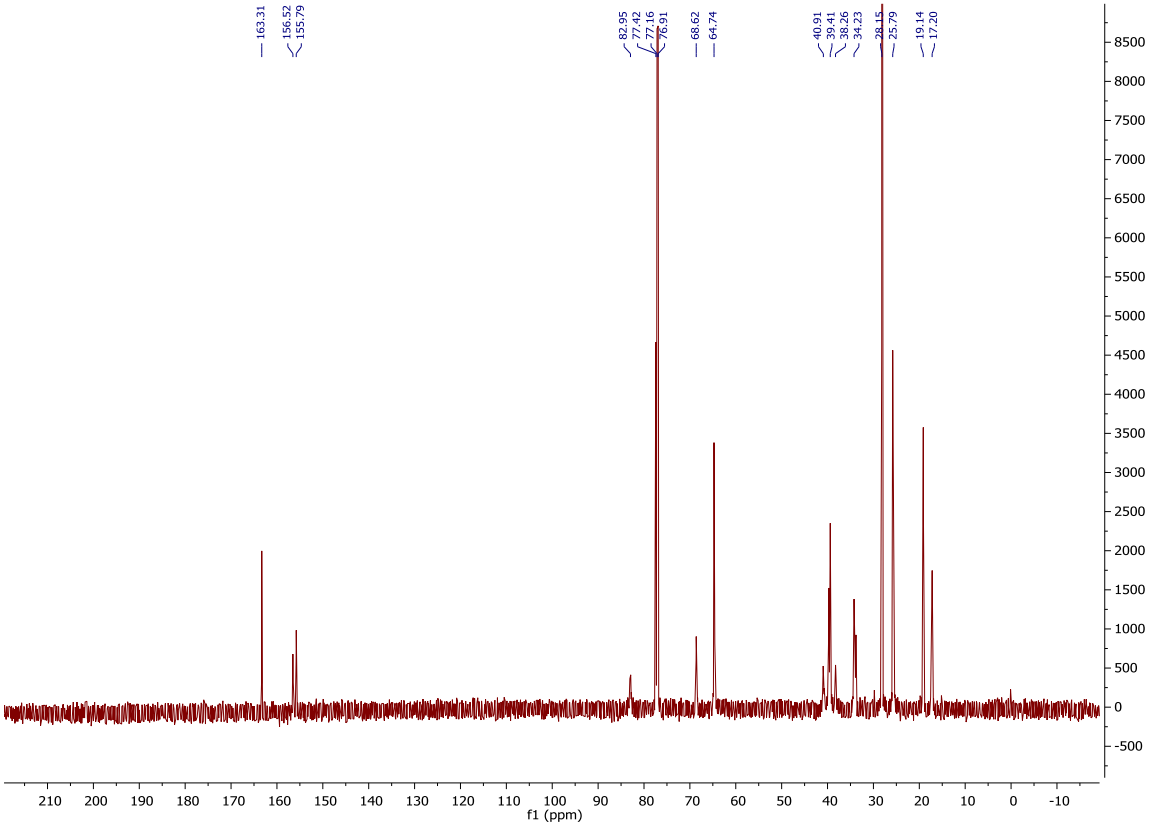
155ugi #11-15 RT: 0.18605-0.25467 AV 7
T: FTMS + p ESI Full ms [150.00-750.00]



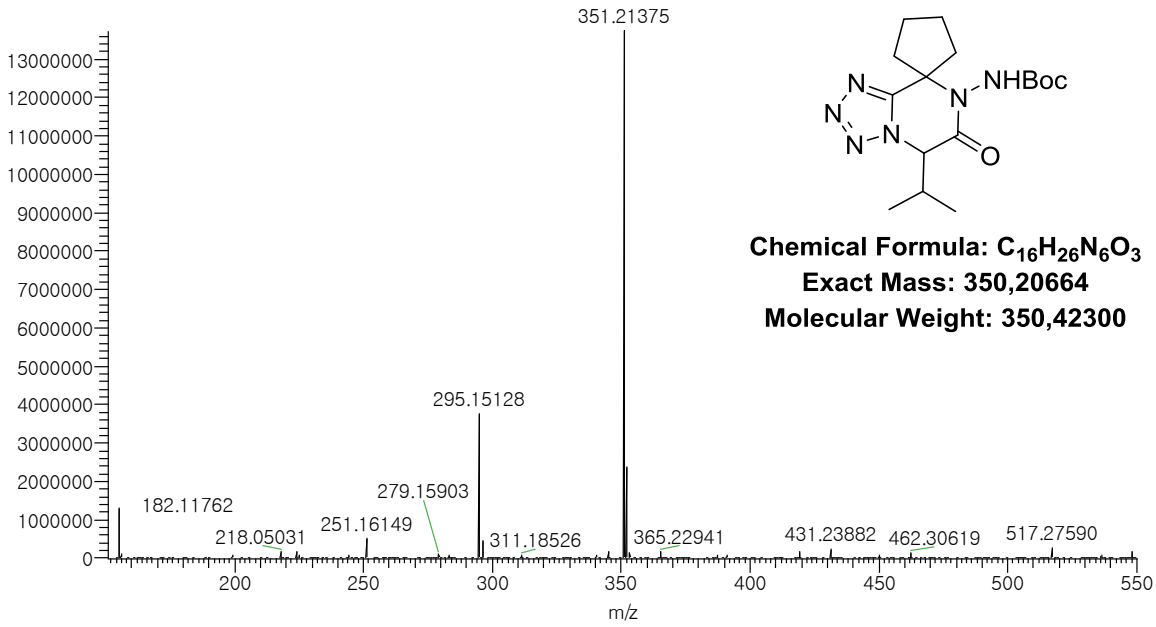
Chemical Formula: $C_{17}H_{30}N_6O_4$
Exact Mass: 382,23285
Molecular Weight: 382,46500

8i: *tert*-butyl (5'-isopropyl-6'-oxo-5',6'-dihydro-7'*H*-spiro [cyclopen-tane-1,8'-tetrazolo[1,5-a]pyrazin]-7'-yl)carbamate



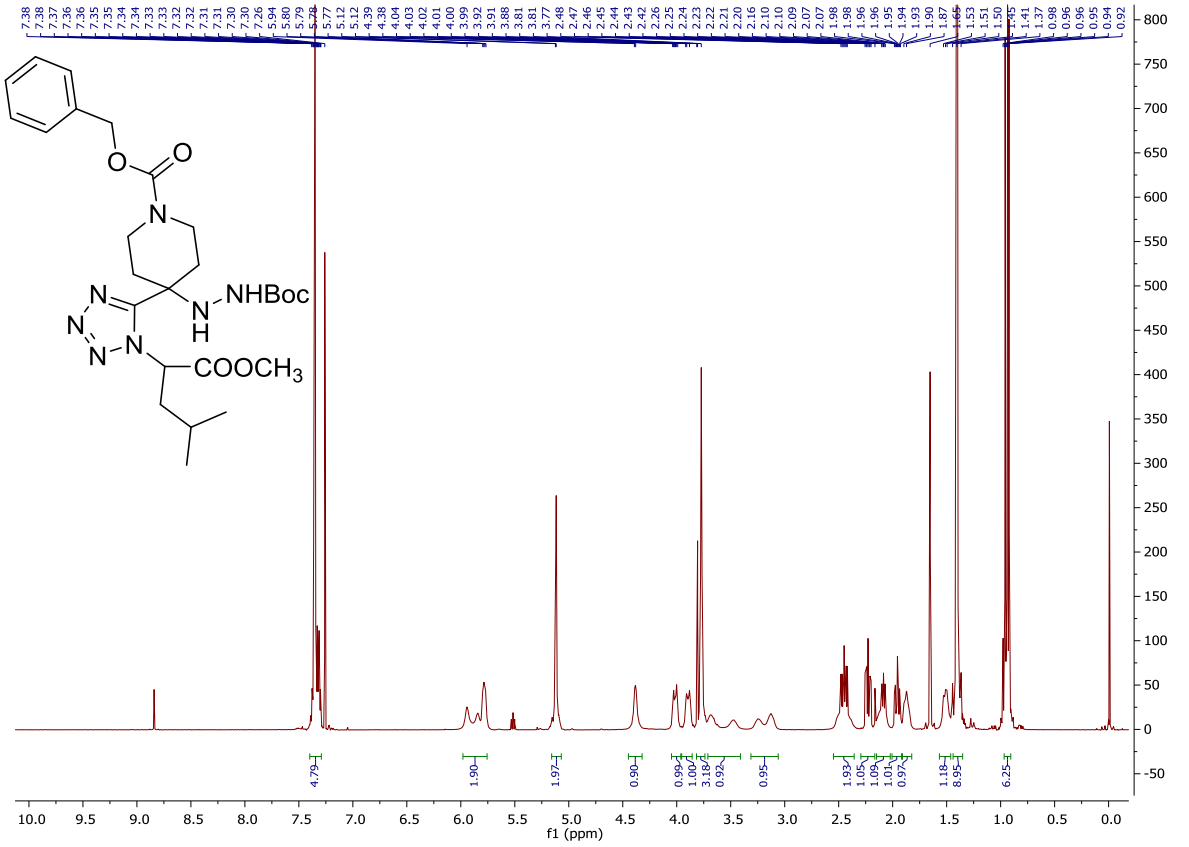


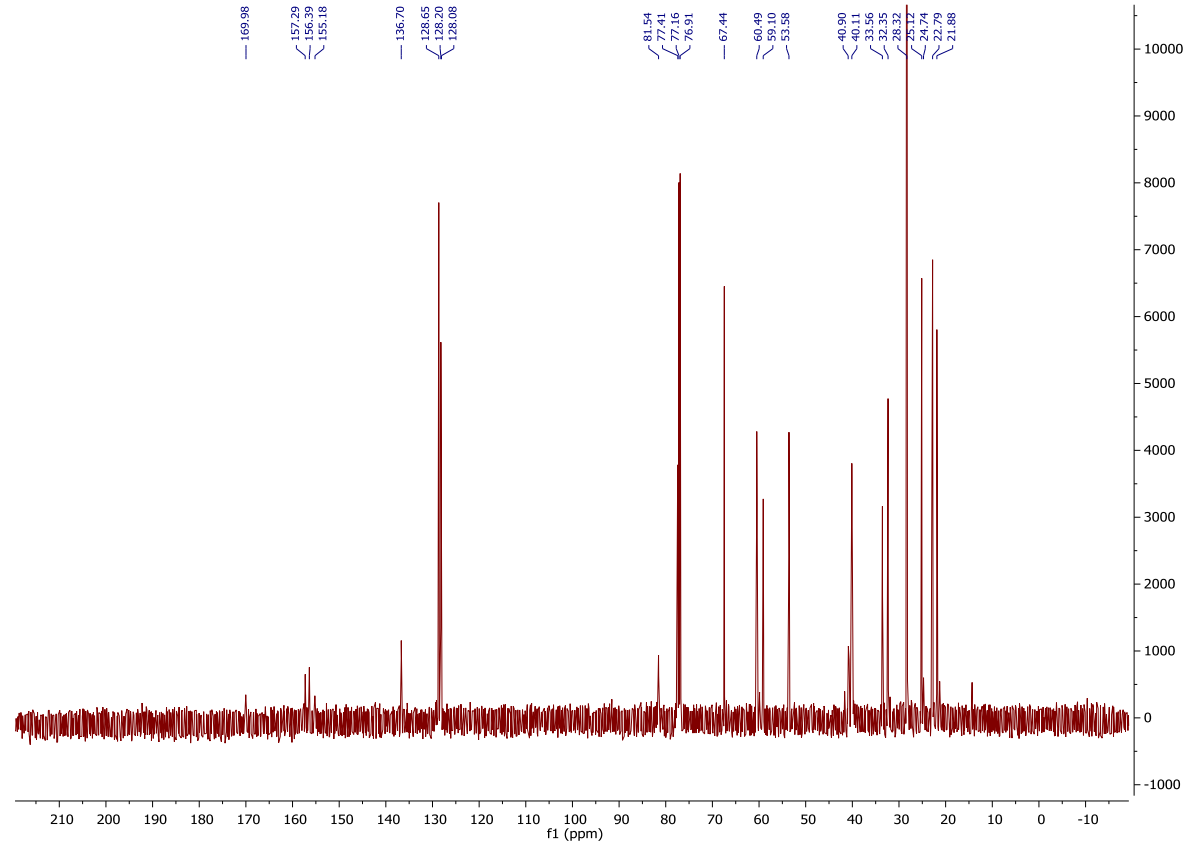
155boc #10-15 RT: 0.17489-0.25078 A :7
T: FTMS + p ESI Full ms [150.00-750.00]

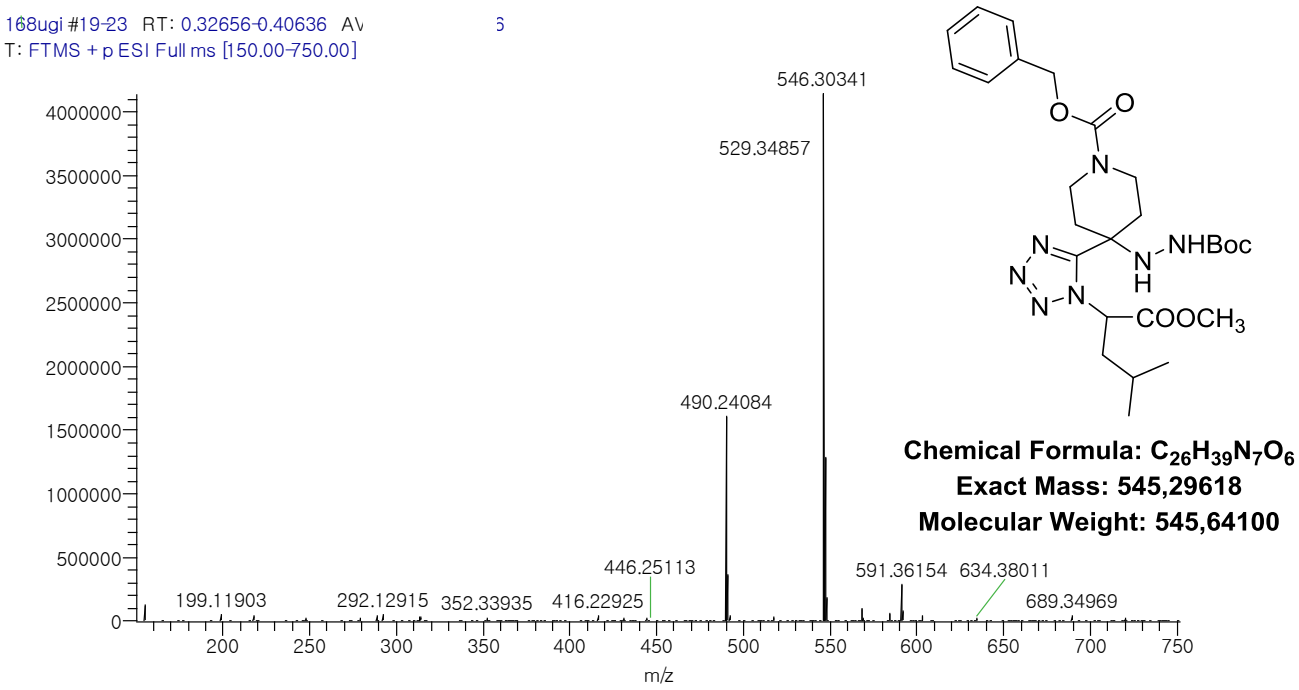


Chemical Formula: $C_{16}H_{26}N_6O_3$
Exact Mass: 350,20664
Molecular Weight: 350,42300

5j: benzyl 4-(2-(*tert*-butoxycarbonyl)hydrazineyl)-4-(1-(1-methoxy -4-methyl-1-oxopentan-2-yl)-1*H*-tetrazol-5-yl)piperidine-1-carboxylate

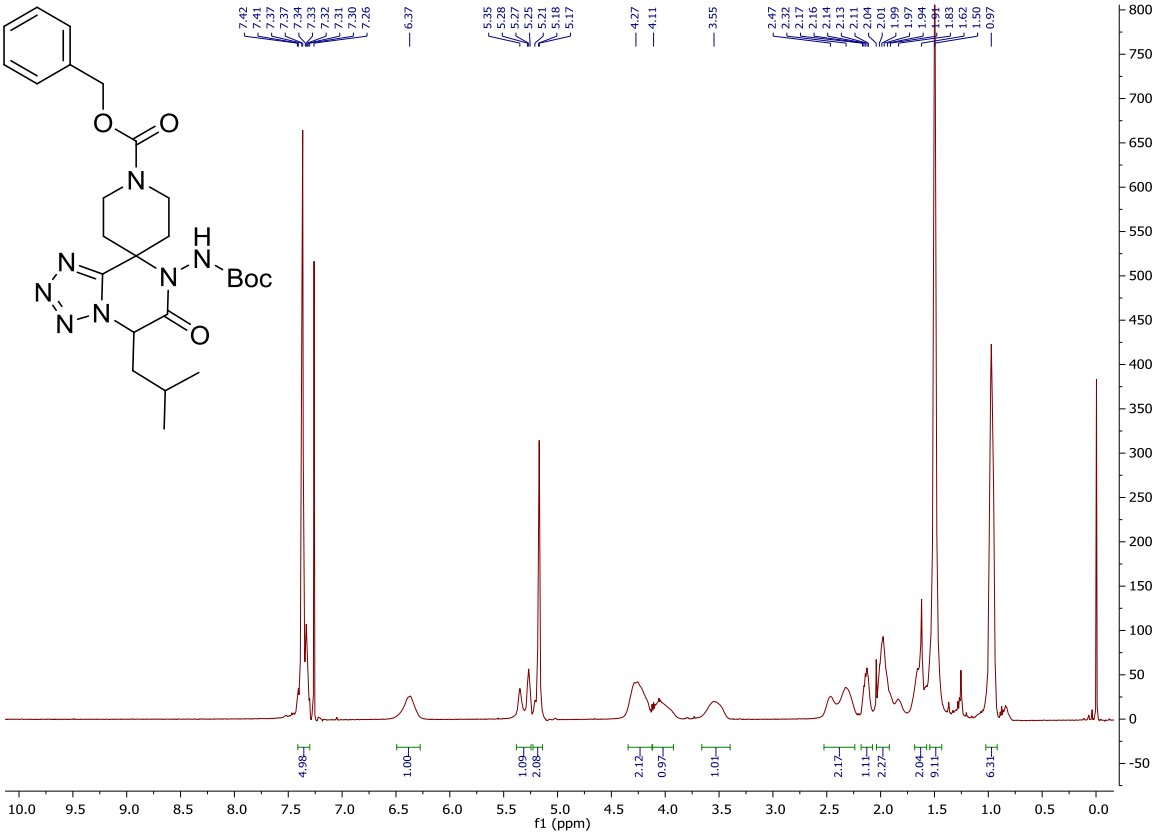


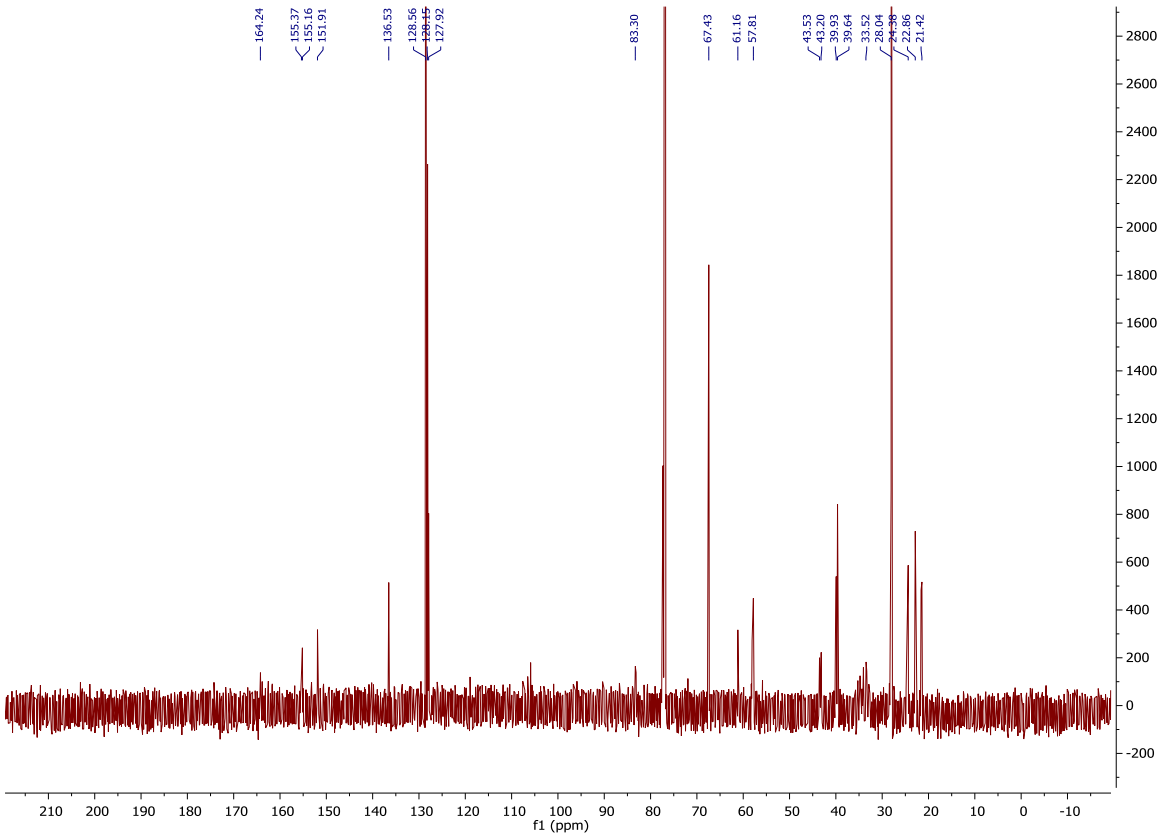


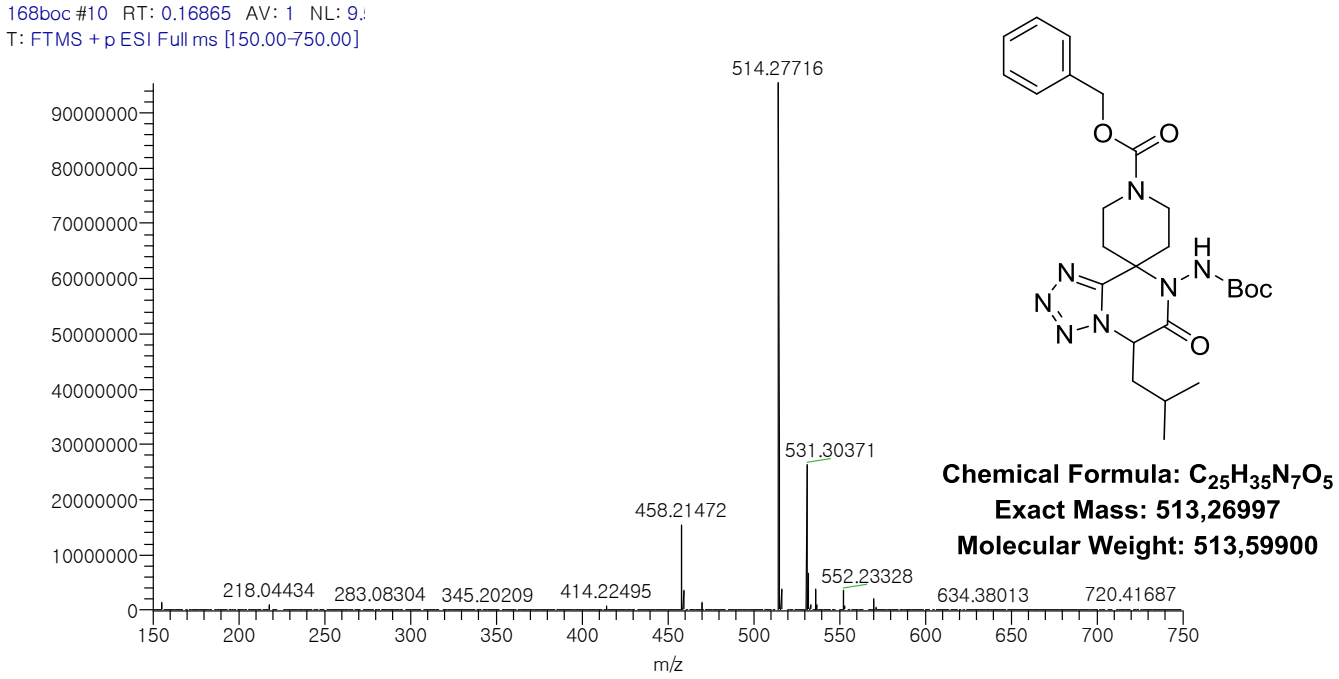


Chemical Formula: $C_{26}H_{39}N_7O_6$
Exact Mass: 545,29618
Molecular Weight: 545,64100

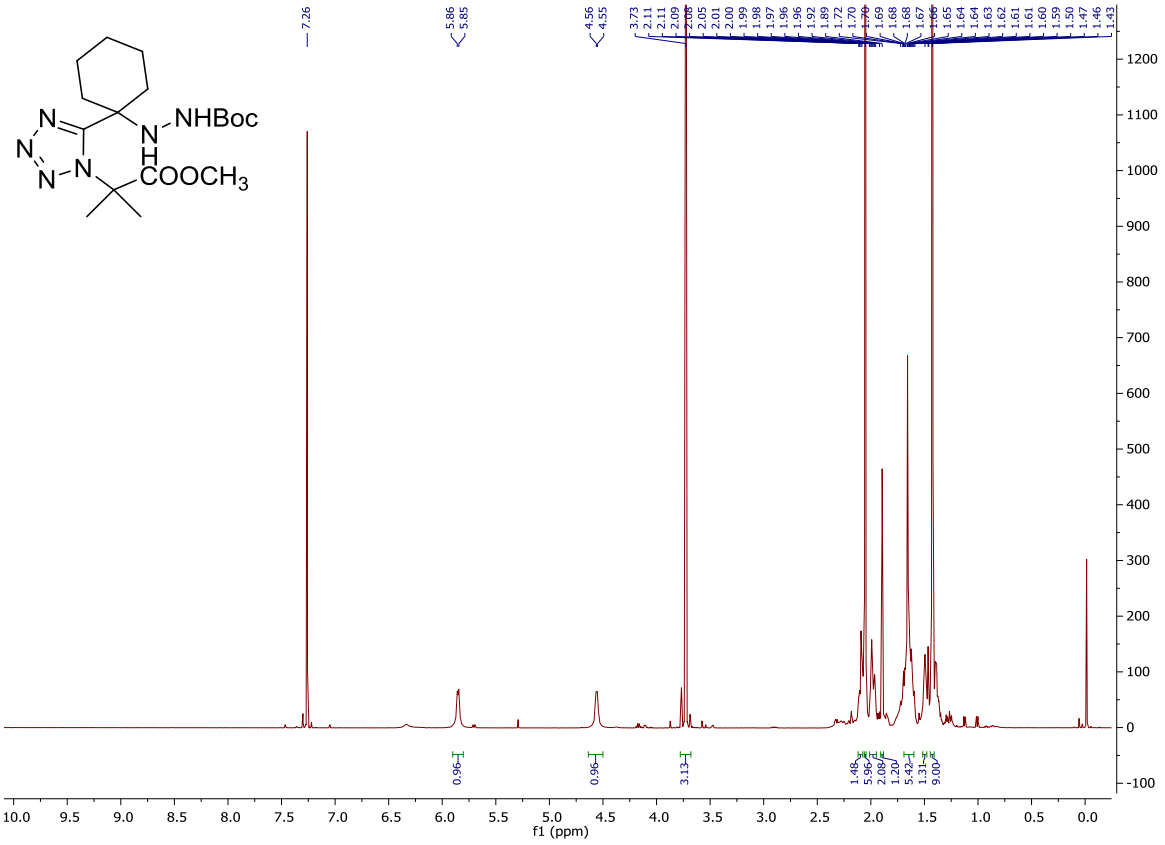
8j: benzyl 7'-((*tert*-butoxycarbonyl)amino)-5'-isobutyl-6'-oxo-6',7'-dihydro-5'*H*-spiro [piperidine-4,8'-tetrazolo[1,5-a]pyrazine]-1-carboxylate

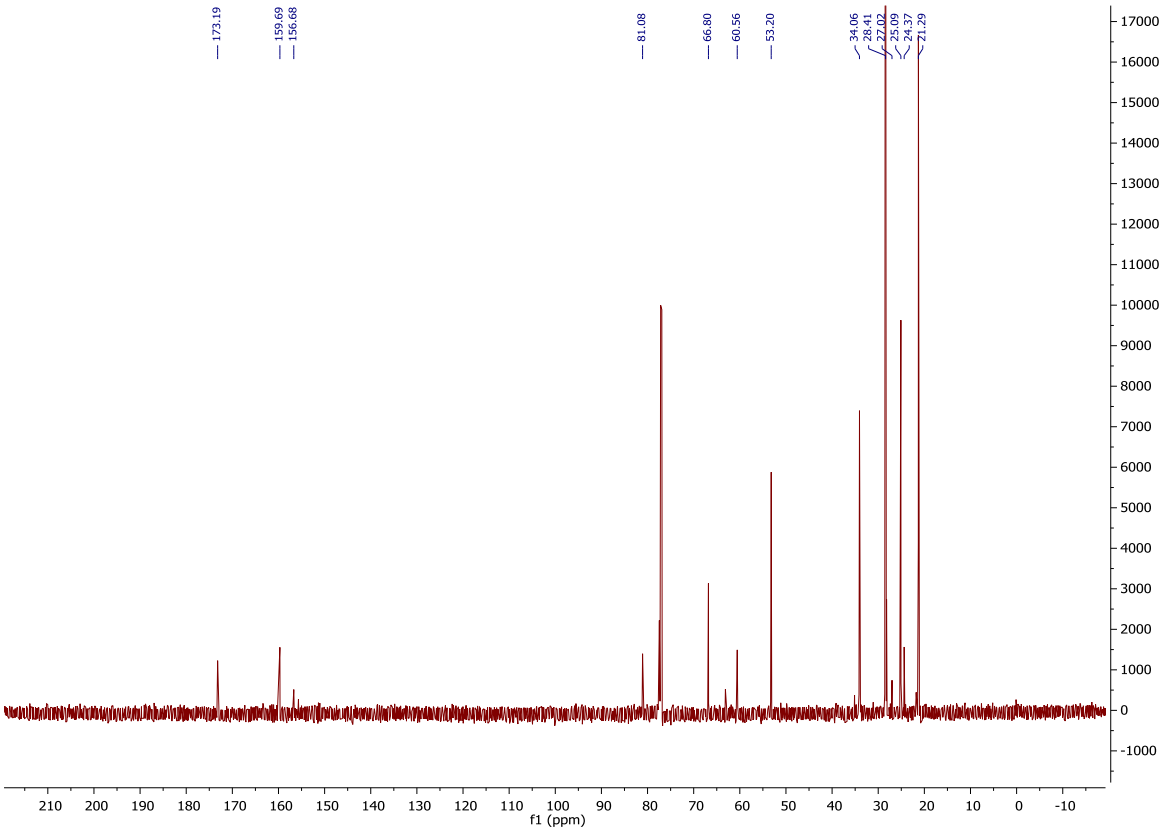




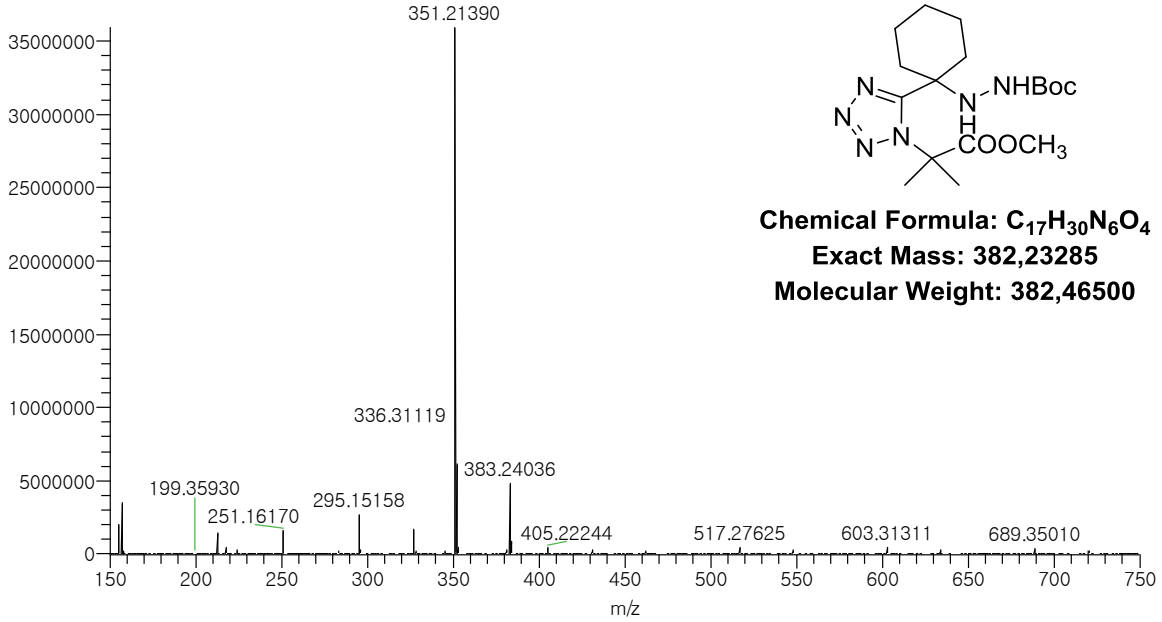

168boc #10 RT: 0.16865 AV: 1 NL: 9.
T: FTMS + p ESI Full ms [150.00-750.00]
514.27716
531.30371
458.21472
552.23328
218.04434
283.08304
345.20209
414.22495
634.38013
720.41687
m/z
Boc
Chemical Formula: C25H35N7O5
Exact Mass: 513,26997
Molecular Weight: 513,59900

5k: *tert*-butyl 2-(1-(1-(1-methoxy-2-methyl-1-oxopropan-2-yl)-1*H*-tetrazol-5-yl)cyclohexyl) hydrazine-1-carboxylate



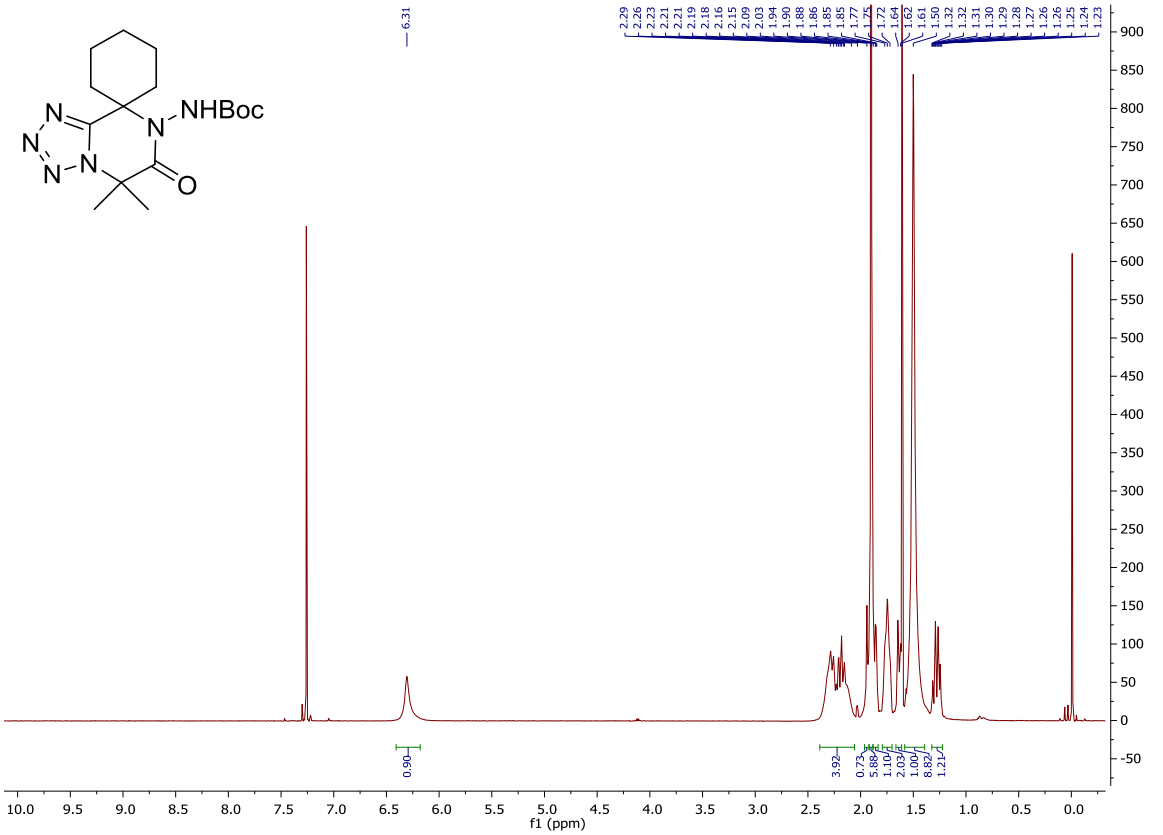


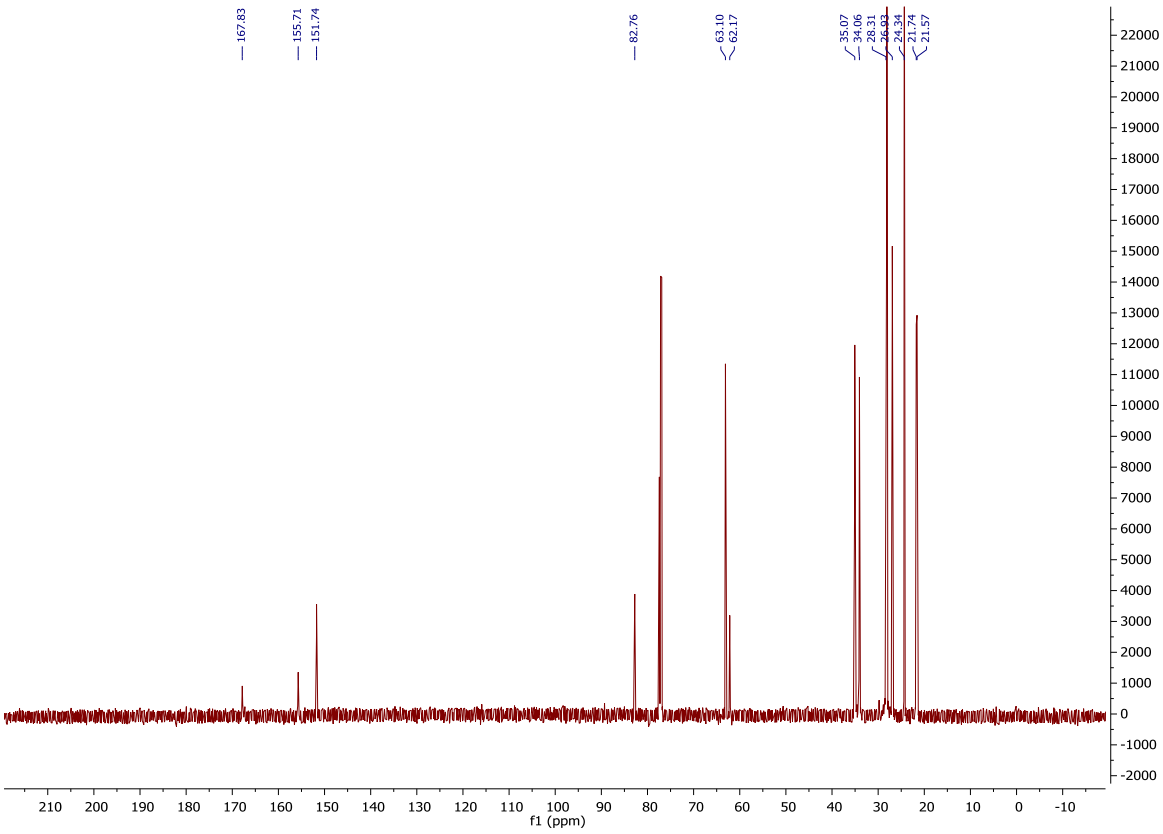
160ugi #10 RT: 0.17034 AV: 1 NL: 3.6
T: FTMS + p ESI Full ms [150.00-750.00]



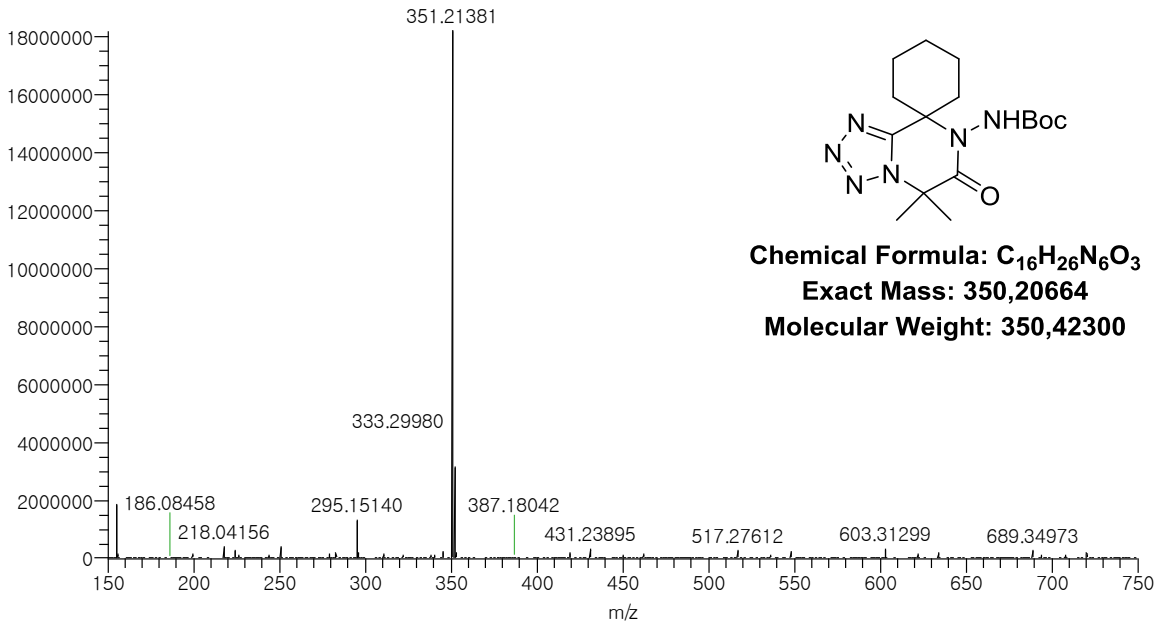
Chemical Formula: $C_{17}H_{30}N_6O_4$
Exact Mass: 382,23285
Molecular Weight: 382,46500

8k: *tert*-butyl (5',5'-dimethyl-6'-oxo-5',6'-dihydro-7'*H*-spiro[cyclo-hex-ane-1,8'-tetrazolo[1,5-a] pyrazin]-7'-yl)carbamate



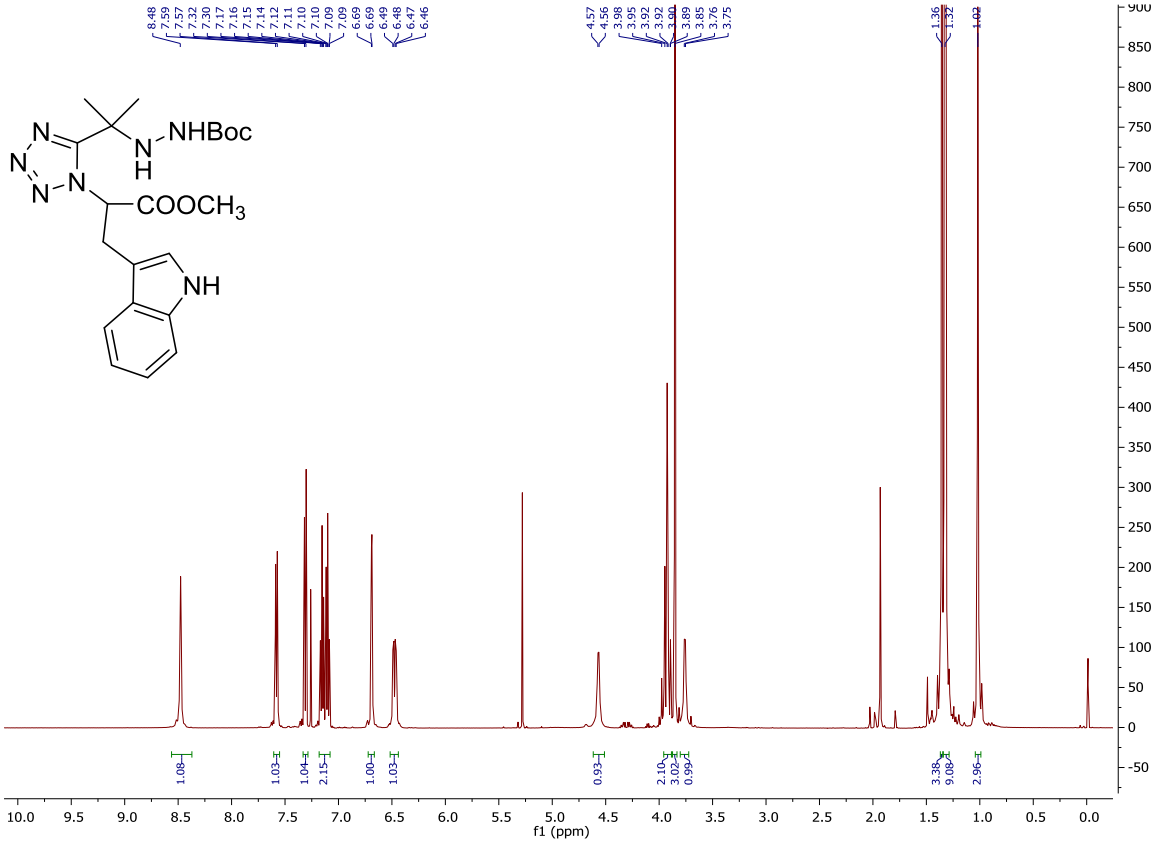


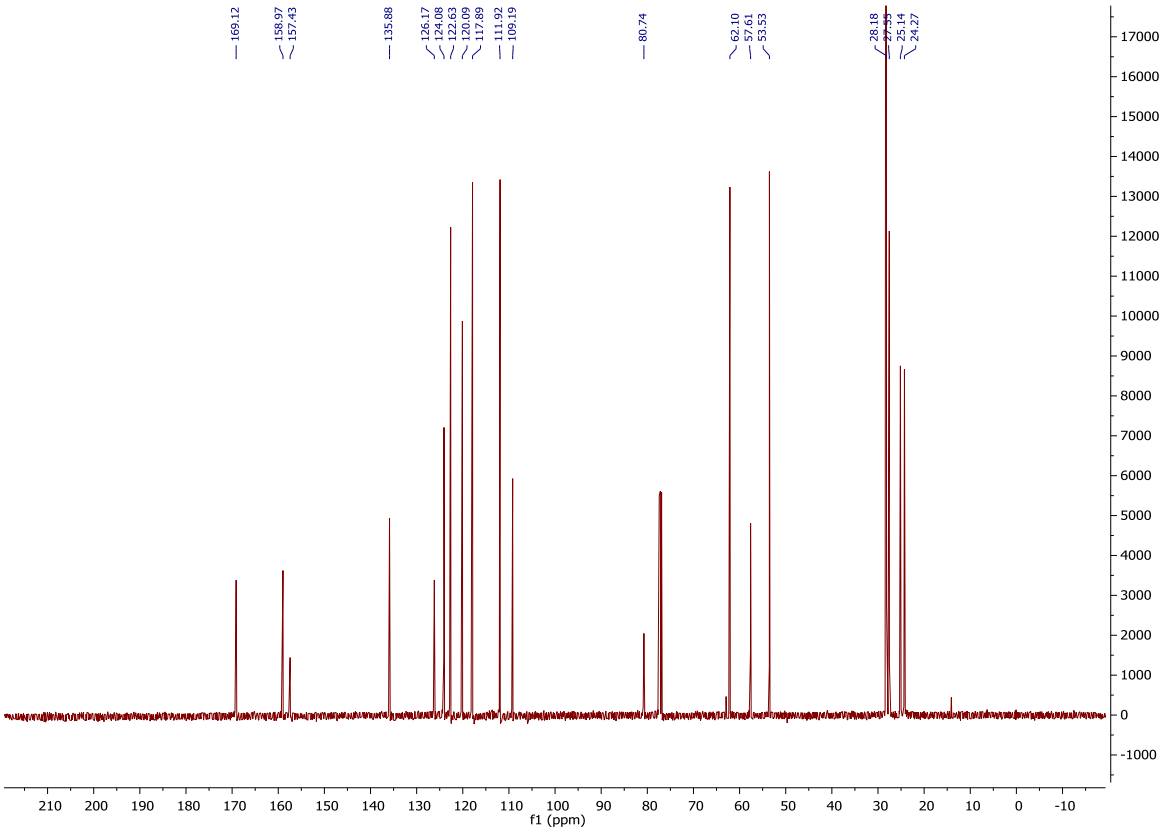
160boc #9 RT: 0.15964 AV: 1 NL: 1.8
T: FTMS + p ESI Full ms [150.00-750.00]

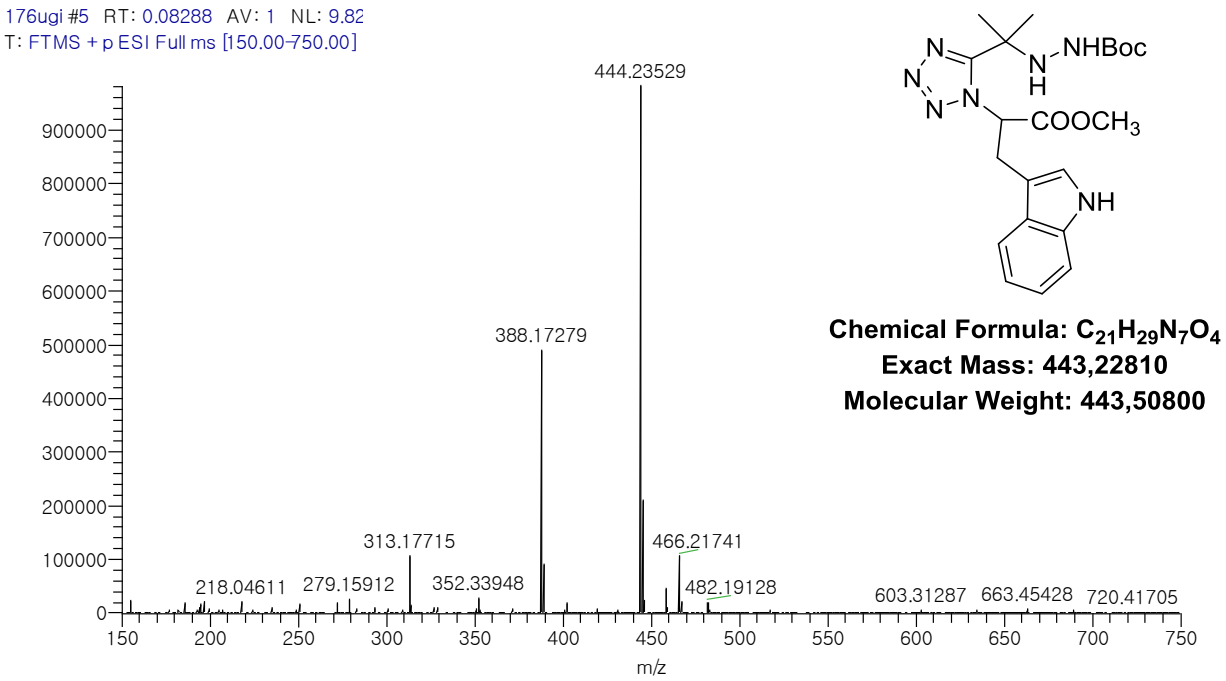


Chemical Formula: $C_{16}H_{26}N_6O_3$
Exact Mass: 350,20664
Molecular Weight: 350,42300

5l: *tert*-butyl 2-(2-(1-(3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-1*H*-tetrazol-5-yl) propan-2-yl)hydrazine-1-carboxylate

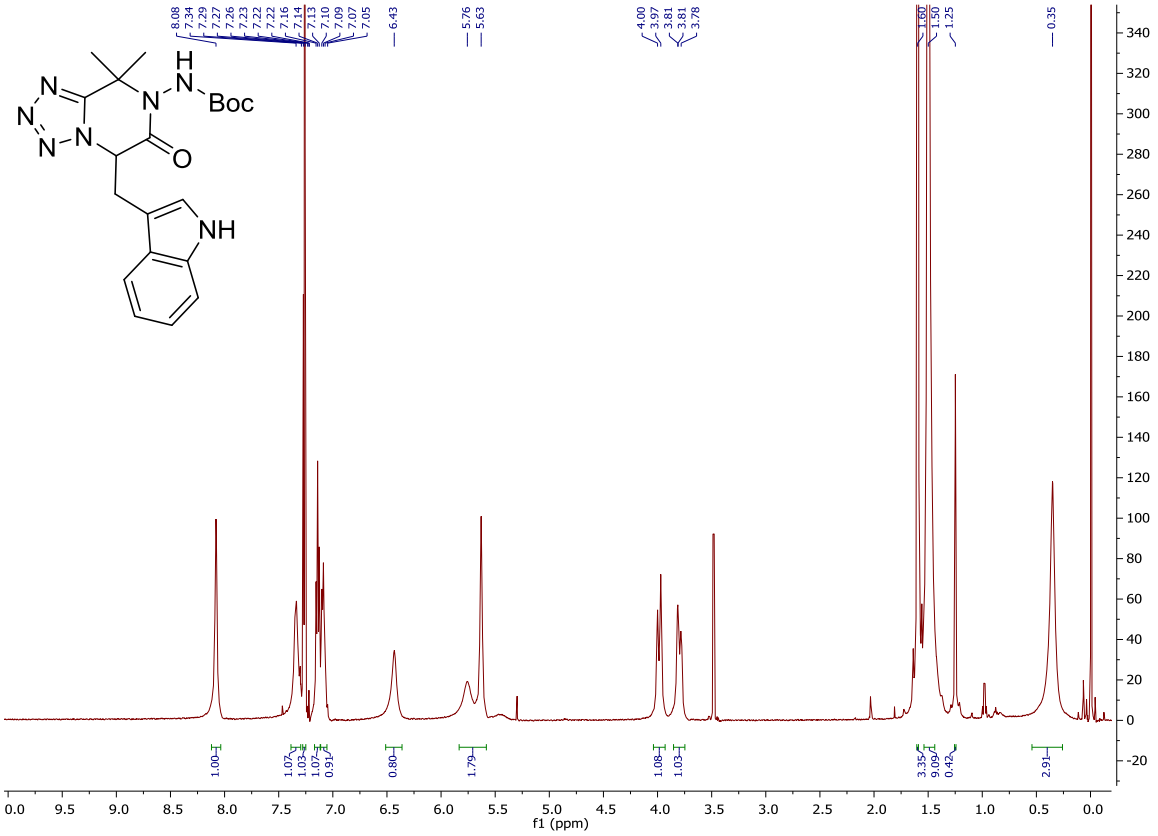


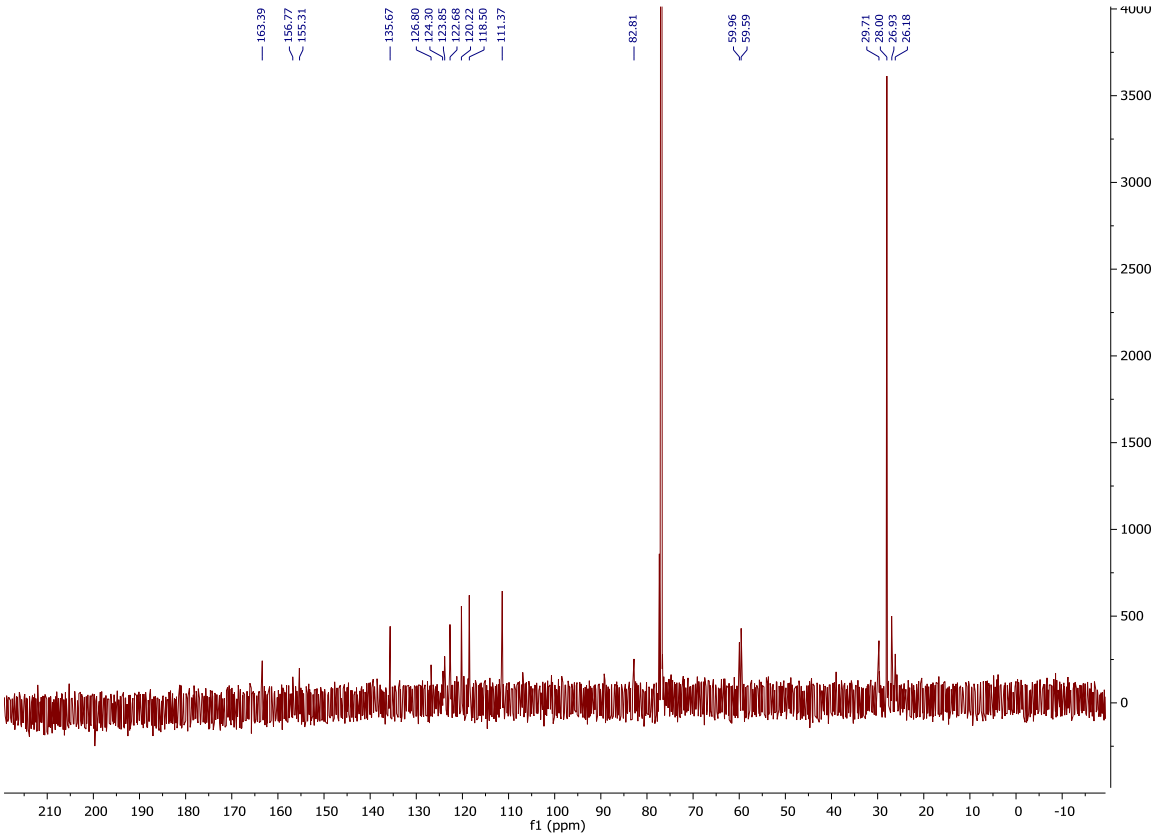




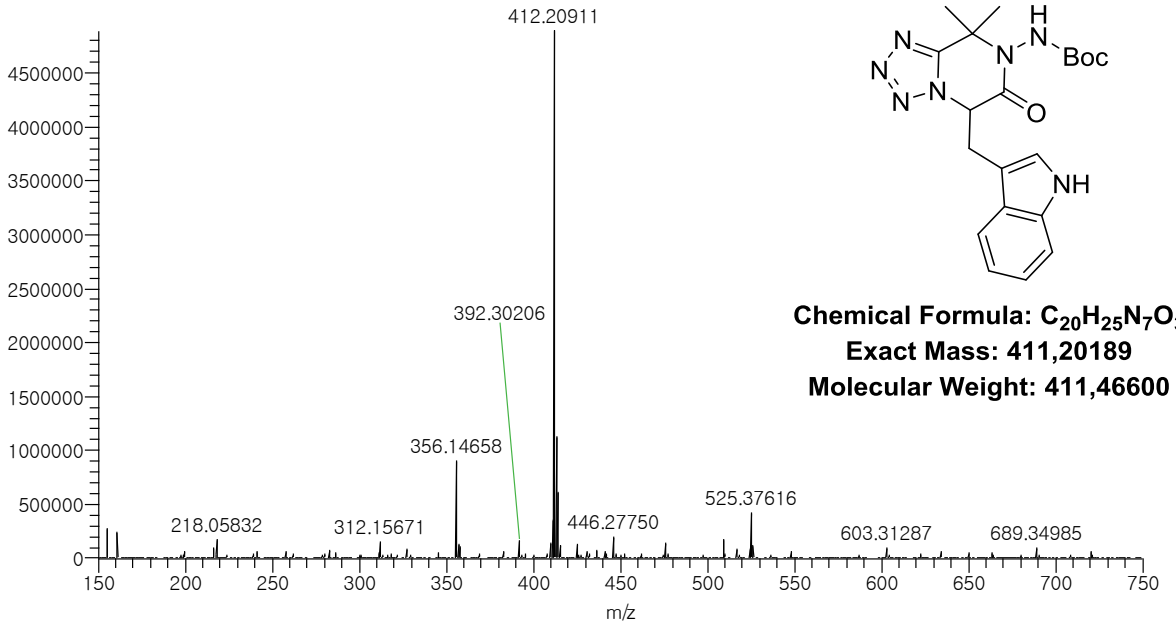
Chemical Formula: $C_{21}H_{29}N_7O_4$
Exact Mass: 443,22810
Molecular Weight: 443,50800

8l: *tert*-butyl (5-((1*H*-indol-3-yl)methyl)-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a] pyrazine-7(8*H*)-yl)carbamate



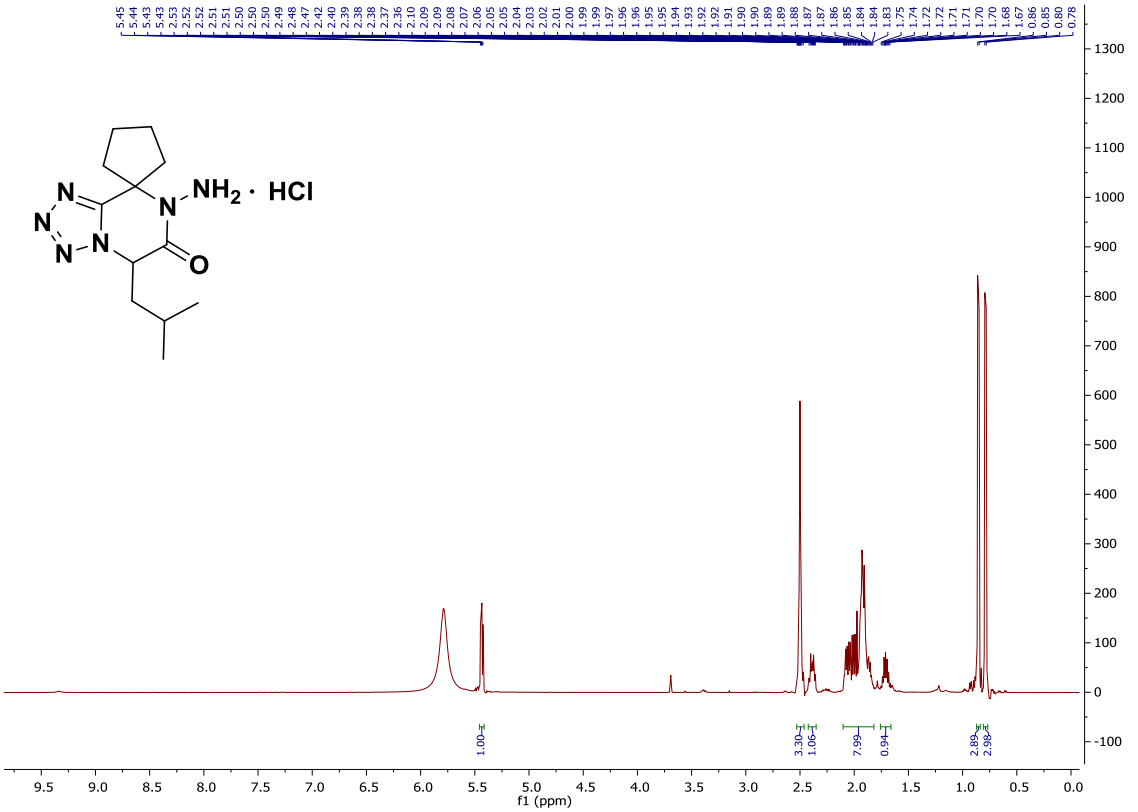


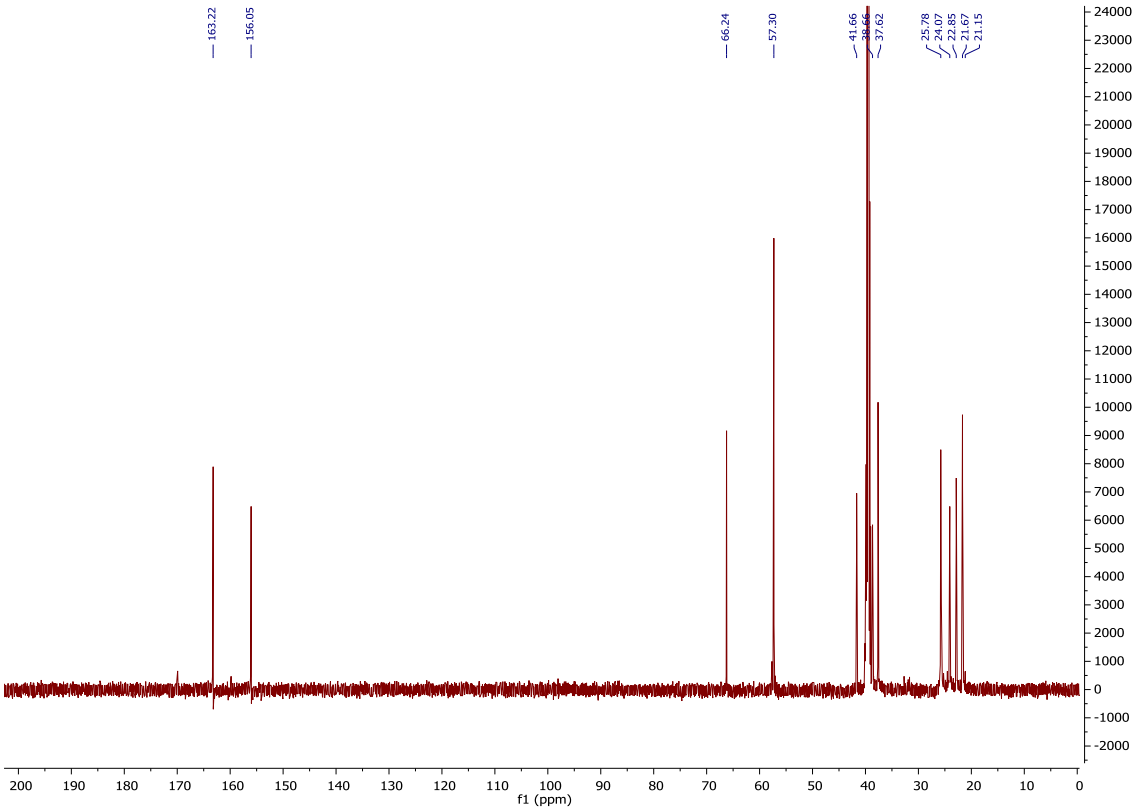
176boc #17 RT: 0.29393 AV: 1 NL: 4.
T: FTMS + p ESI Full ms [150.00-750.00]

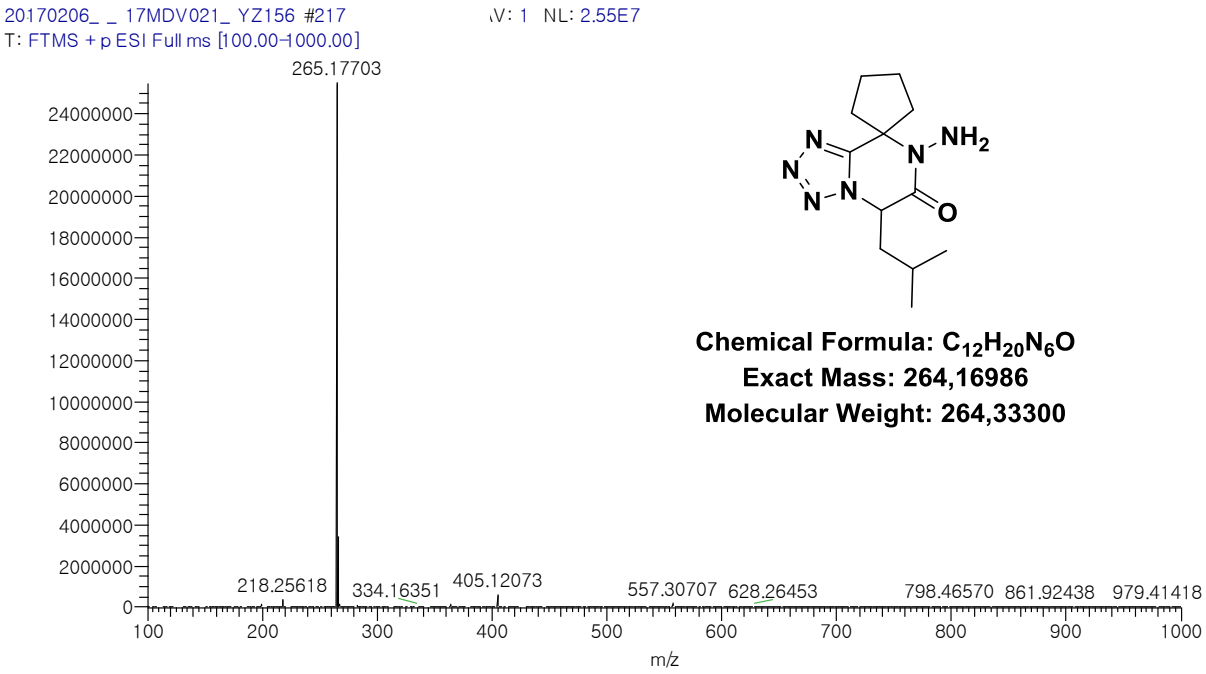


Chemical Formula: $C_{20}H_{25}N_7O_3$
Exact Mass: 411,20189
Molecular Weight: 411,46600

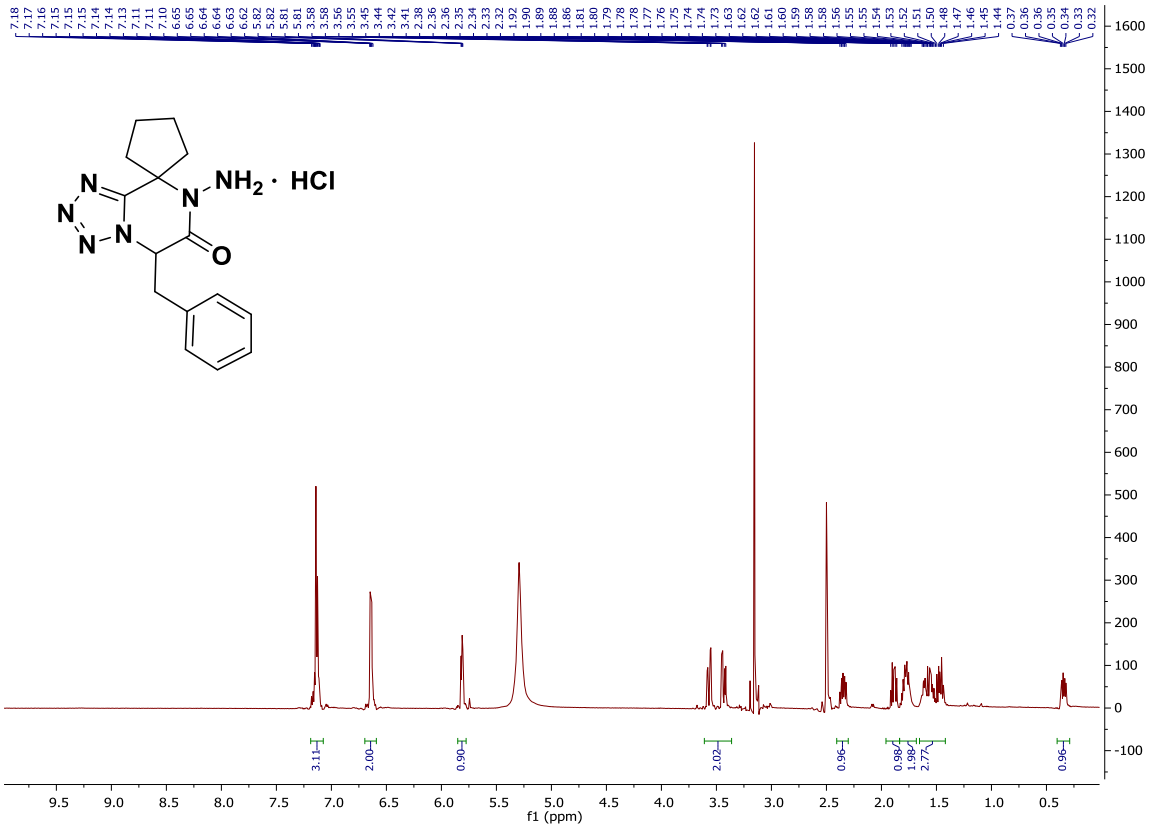
9a: 7'-amino-5'-isobutyl-5'H-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'H)-one hydrochloride

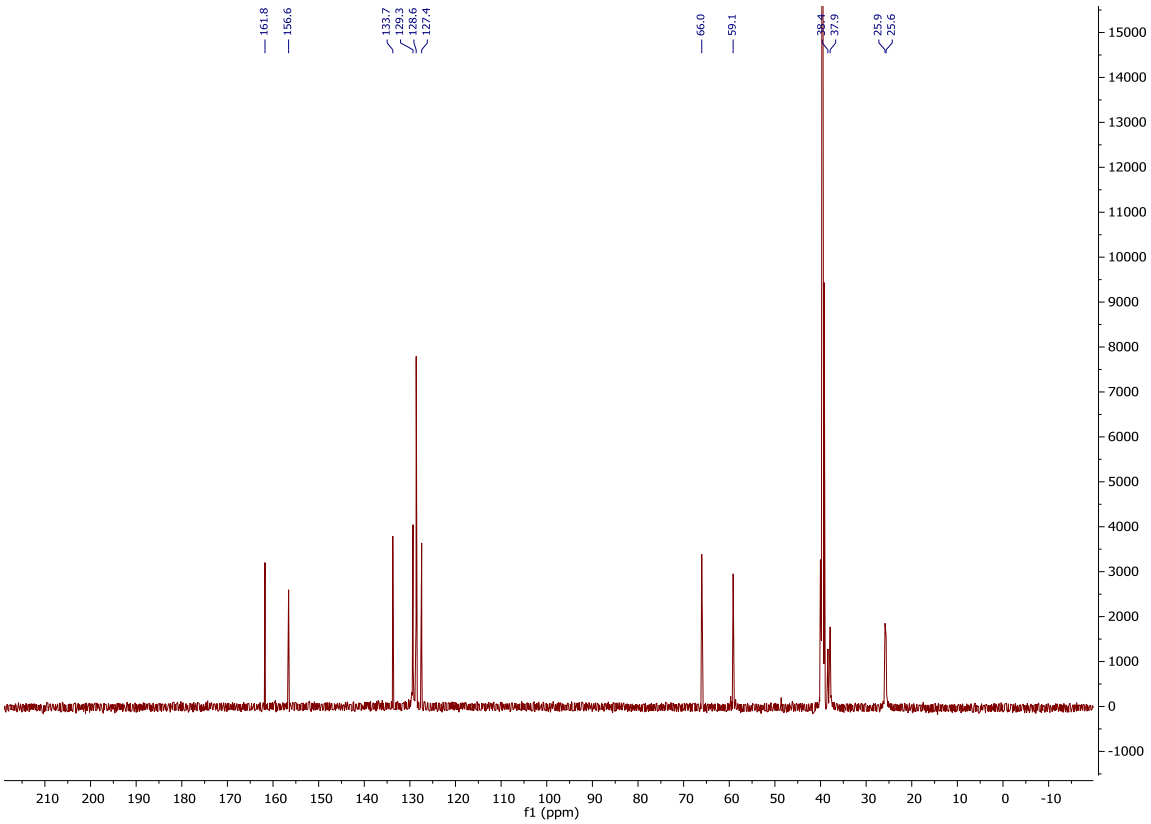


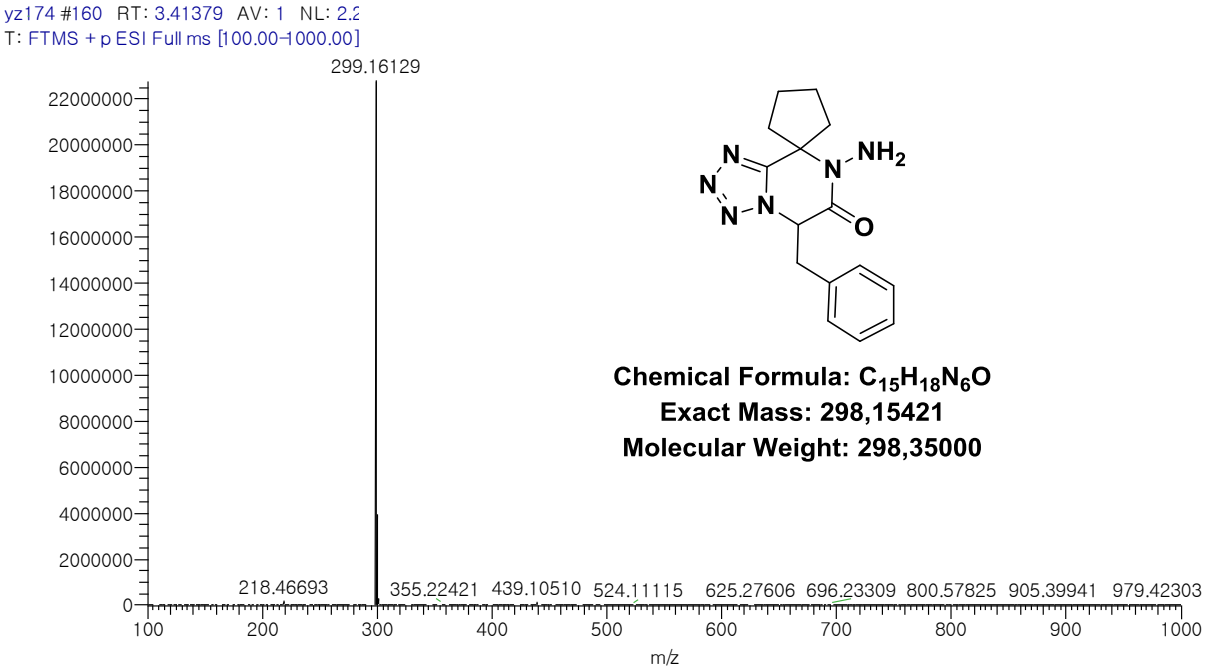



20170206_ _ 17MDV021_ YZ156 #217
V: 1 NL: 2.55E7
T: FTMS + p ESI Full ms [100.00-1000.00]
265.17703
218.25618
334.16351
405.12073
557.30707
628.26453
798.46570
861.92438
979.41418
m/z
Chemical Formula: C12H20N6O
Exact Mass: 264,16986
Molecular Weight: 264,33300

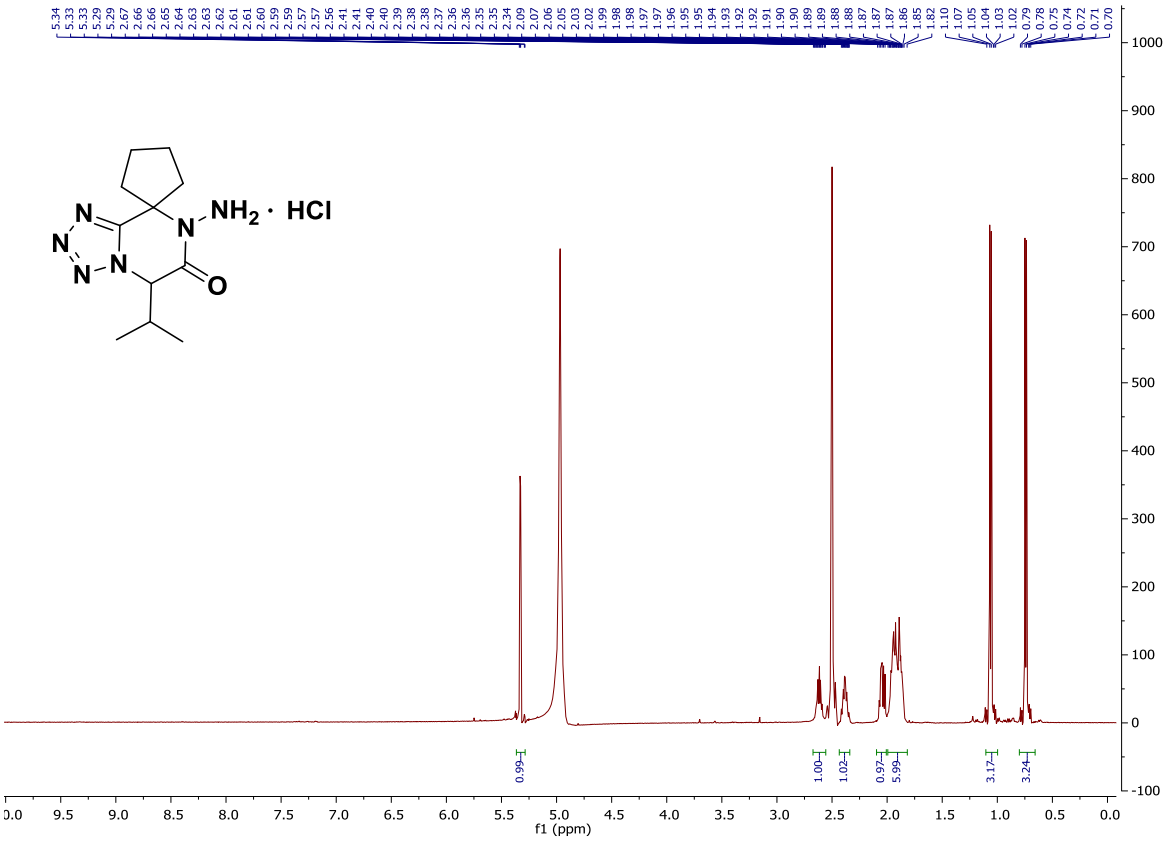
9b: 7'-amino-5'-benzyl-5'H-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'H)-one hydrochloride

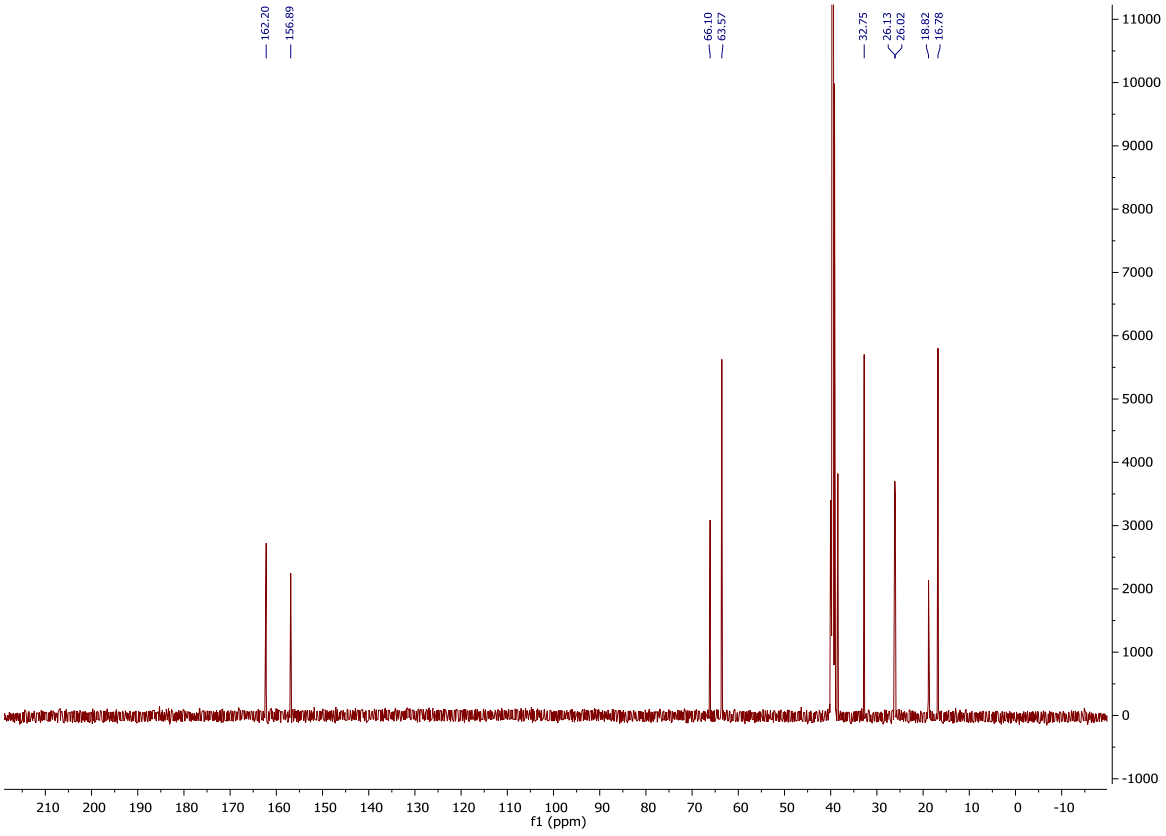


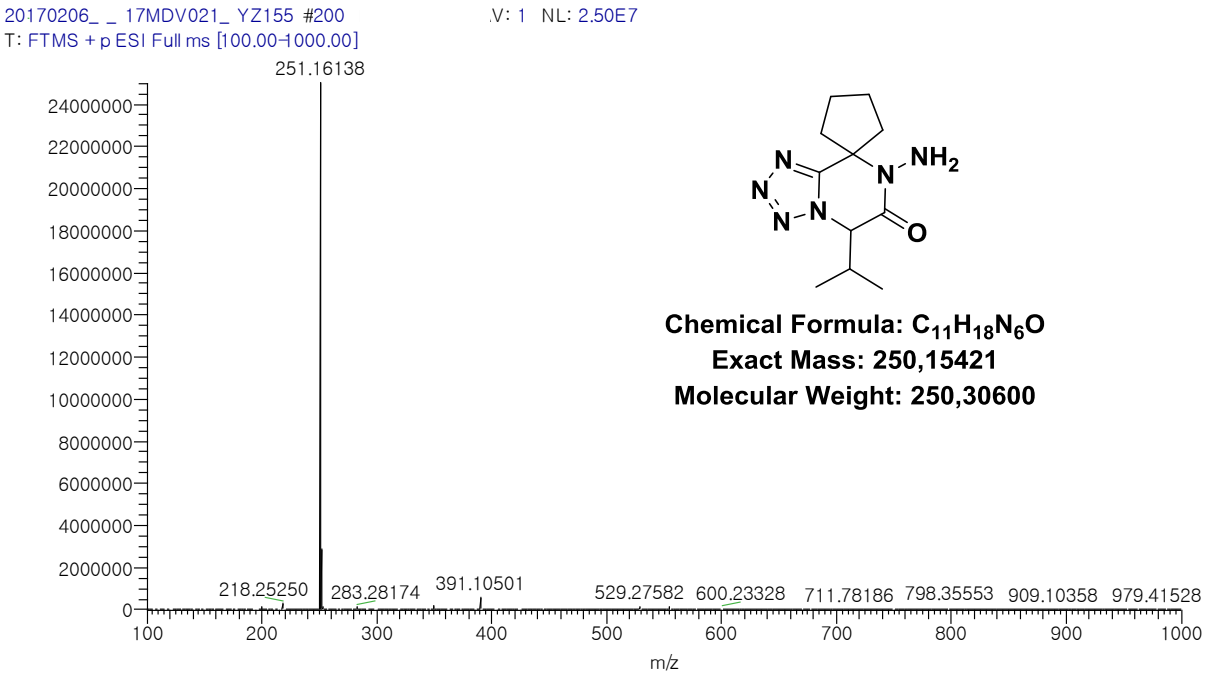



yz174 #160 RT: 3.41379 AV: 1 NL: 2.2
T: FTMS + p ESI Full ms [100.00-1000.00]
299.16129
218.46693
355.22421
439.10510
524.11115
625.27606
696.23309
800.57825
905.39941
979.42303
m/z
Chemical Formula: C15H18N6O
Exact Mass: 298,15421
Molecular Weight: 298,35000

9c: 7'-amino-5'-isopropyl-5'H-spiro[cyclopentane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'H)-one hydrochloride

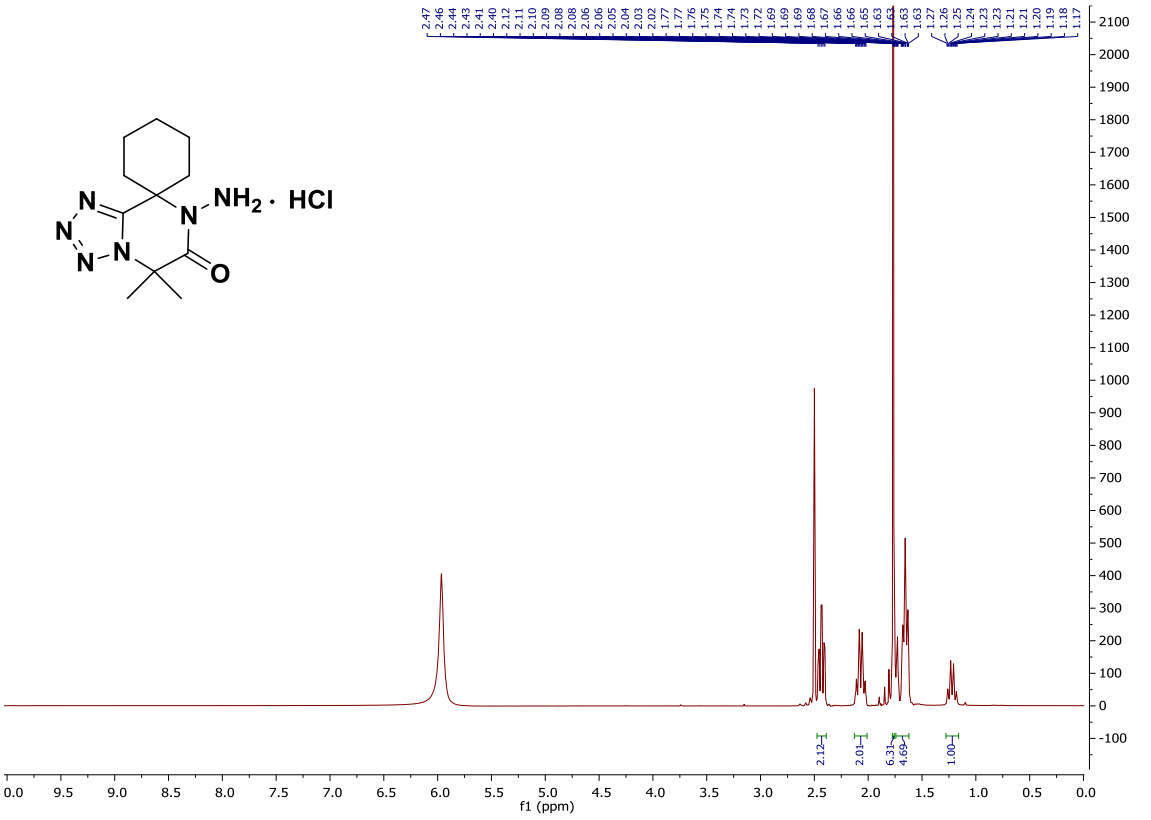


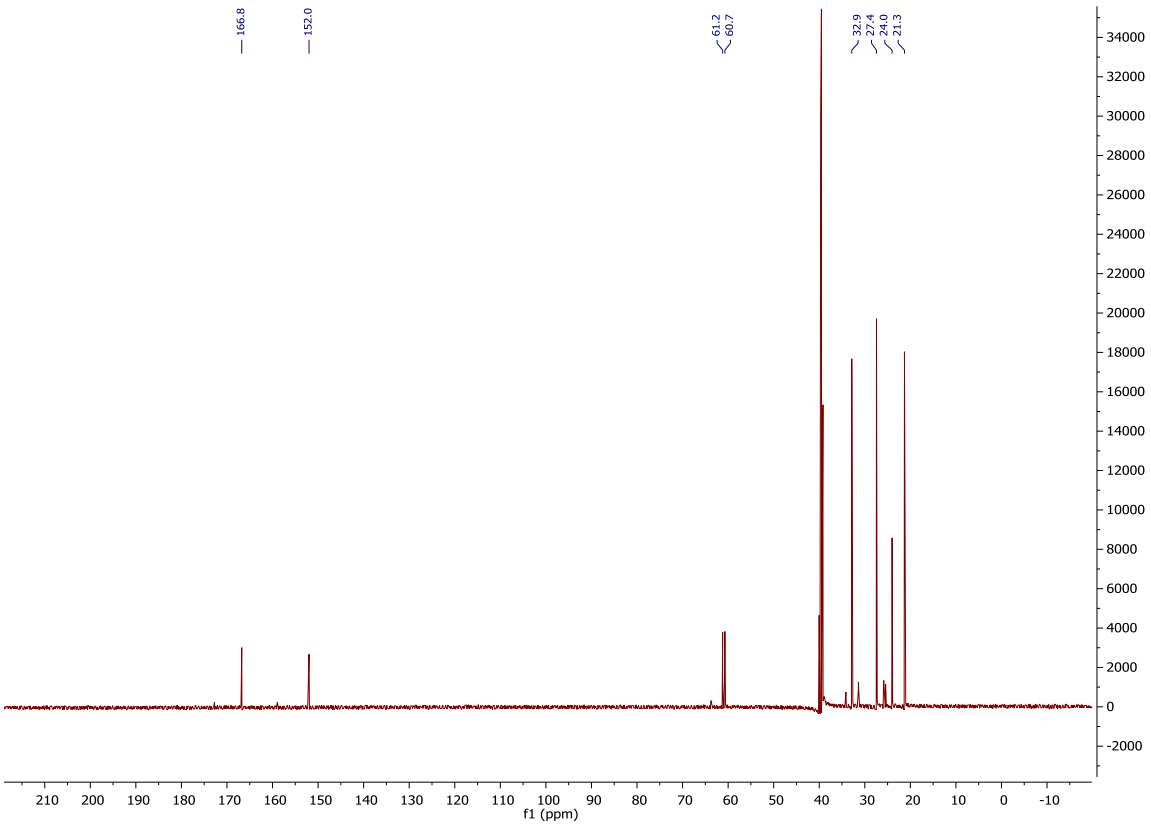


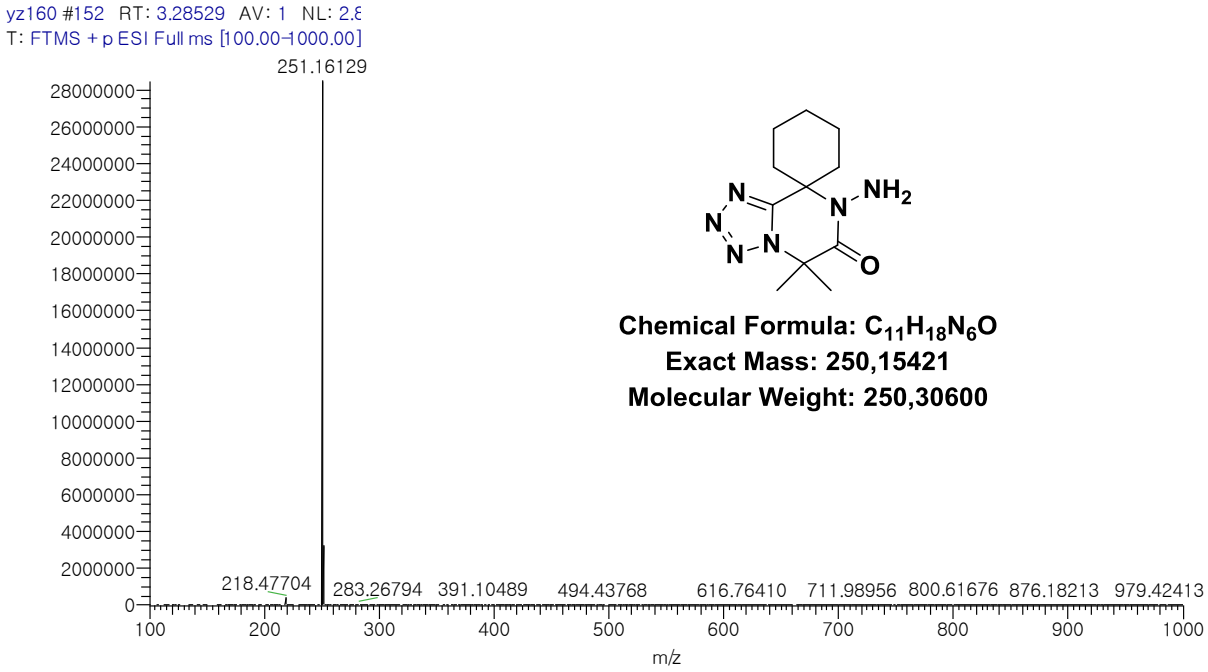


Chemical Formula: $C_{11}H_{18}N_6O$
Exact Mass: 250,15421
Molecular Weight: 250,30600

9d: 7'-amino-5',5'-dimethyl-5'H-spiro[cyclohexane-1,8'-tetrazolo[1,5-a]pyrazin]-6'(7'H)-one hydrochloride

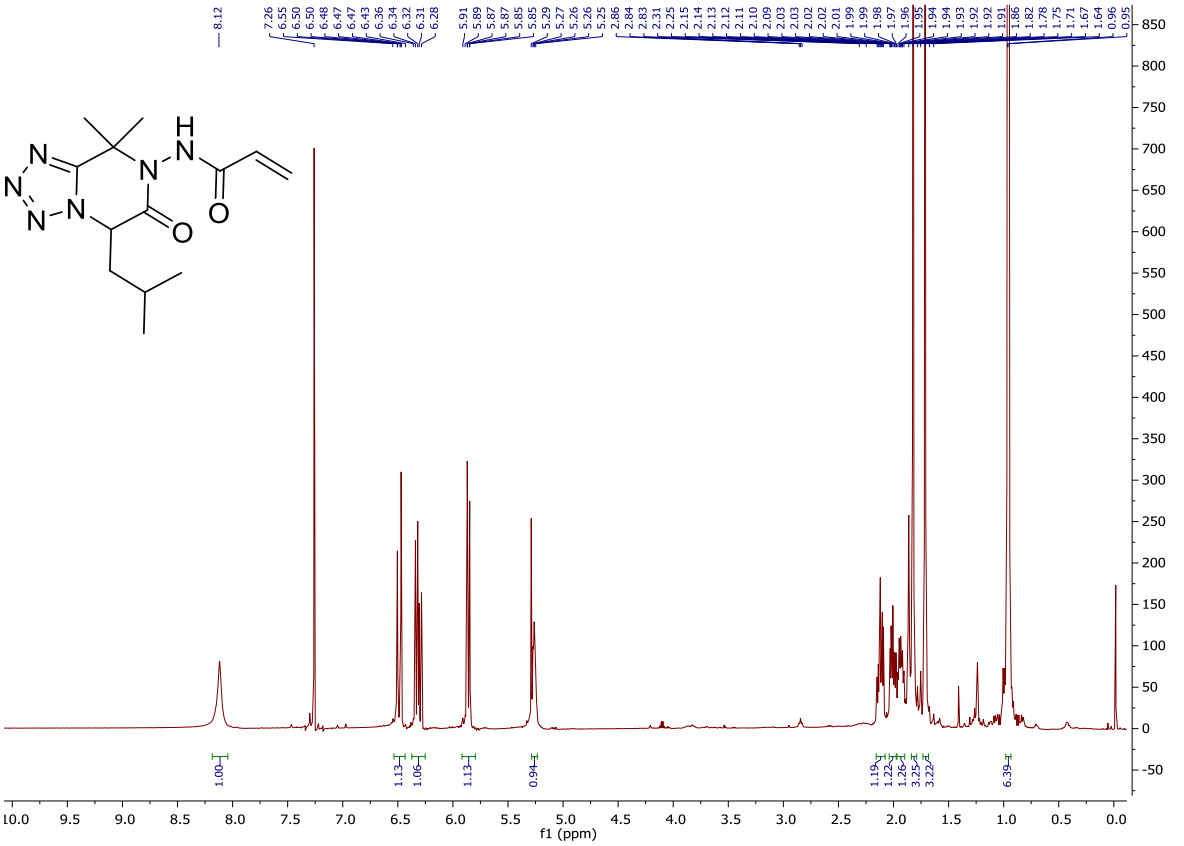


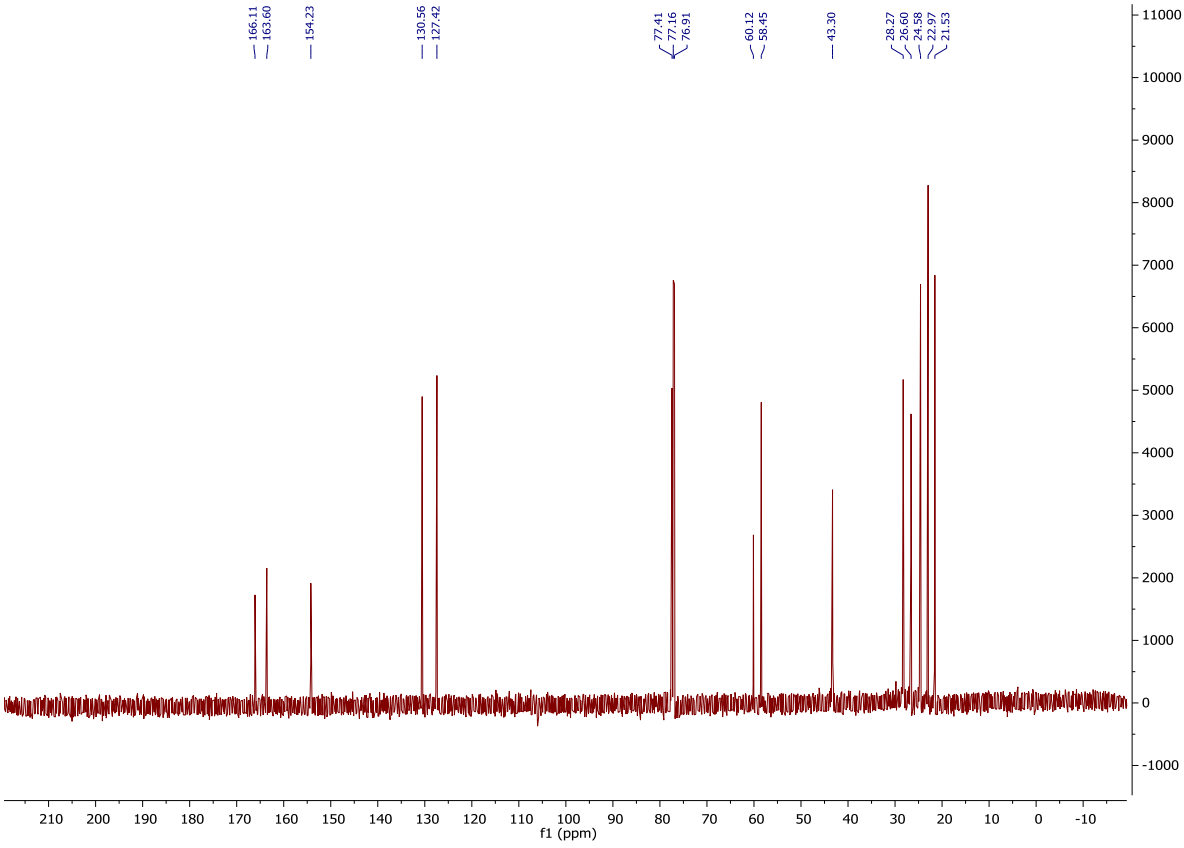




Chemical Formula: $C_{11}H_{18}N_6O$
Exact Mass: 250,15421
Molecular Weight: 250,30600

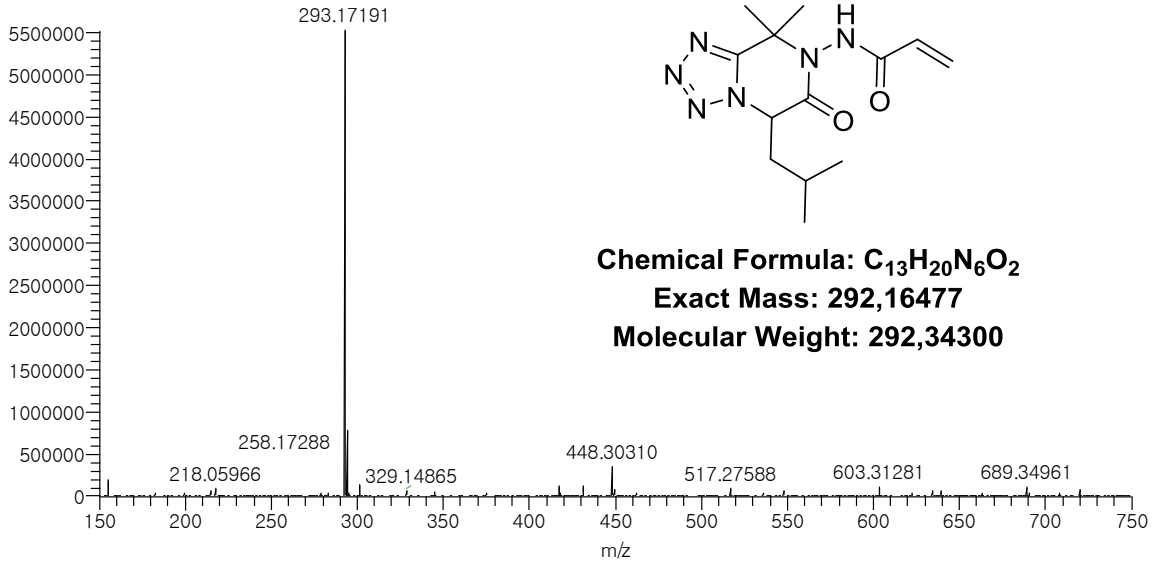
10: N-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a] pyrazine-7(8*H*)-yl) acrylamide





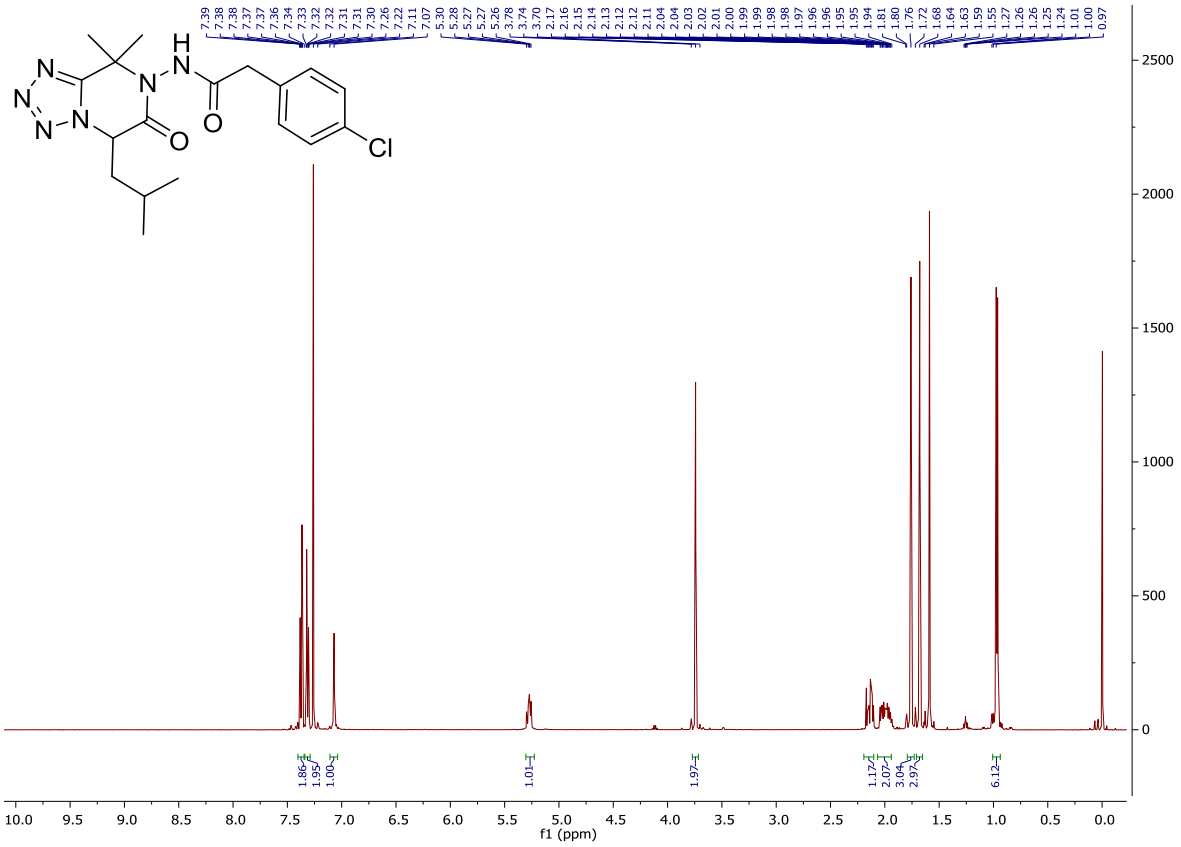
J:₩20161130_ FIA-AccMass50₩79 11/30/16 12:19:22

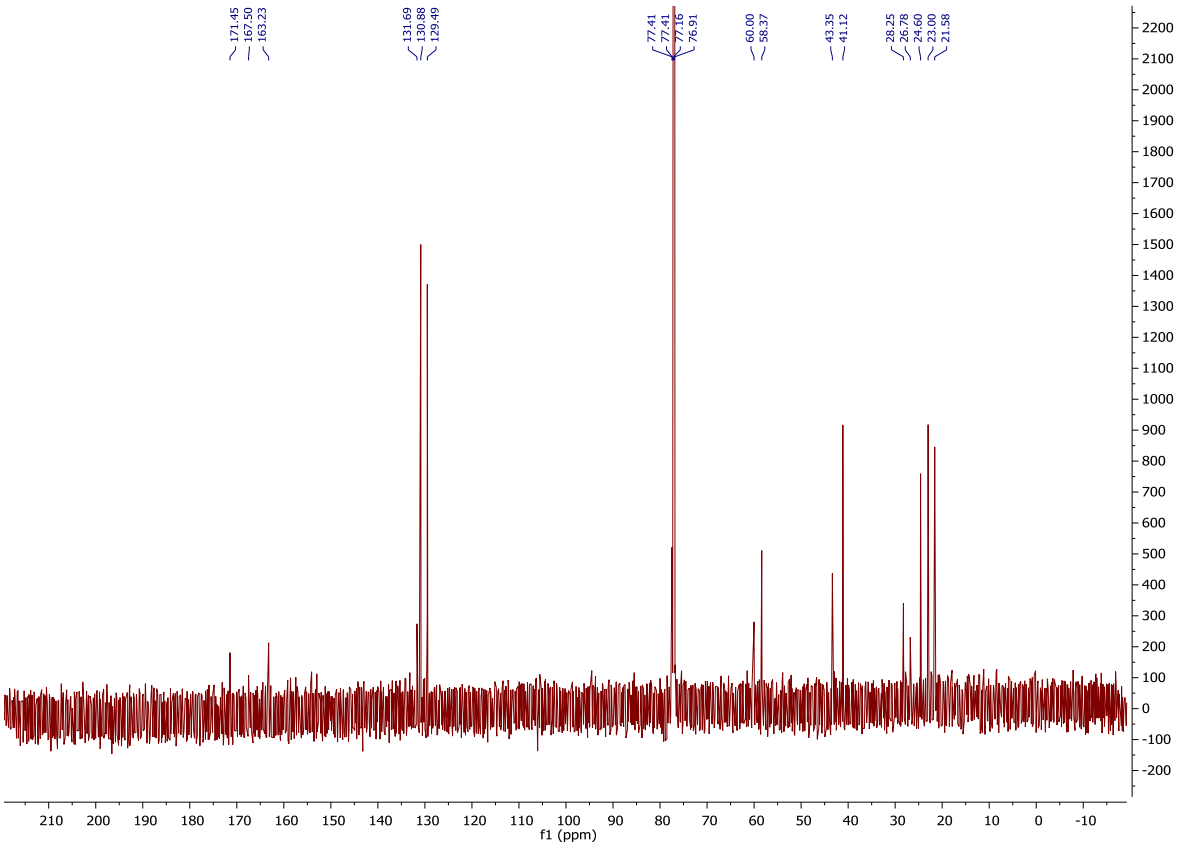
179 #17 RT: 0.29101 AV: 1 NL: 5.52E6
T: FTMS + p ESI Full ms [150.00-750.00]

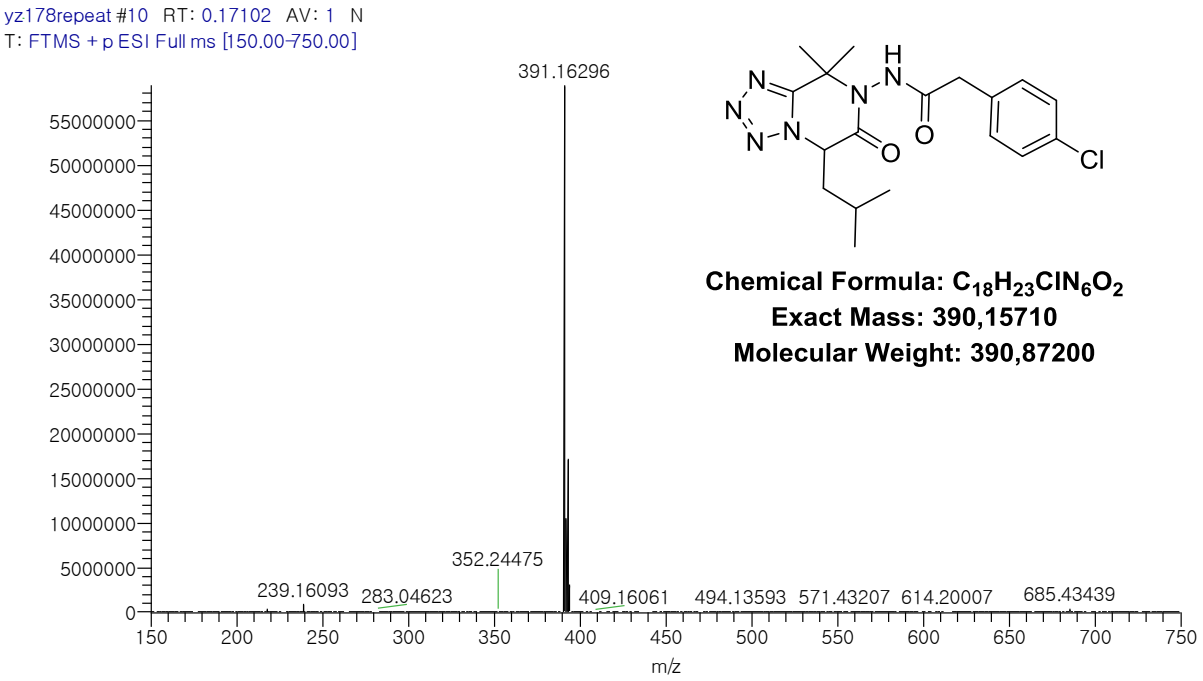


Chemical Formula: $C_{13}H_{20}N_6O_2$
Exact Mass: 292,16477
Molecular Weight: 292,34300

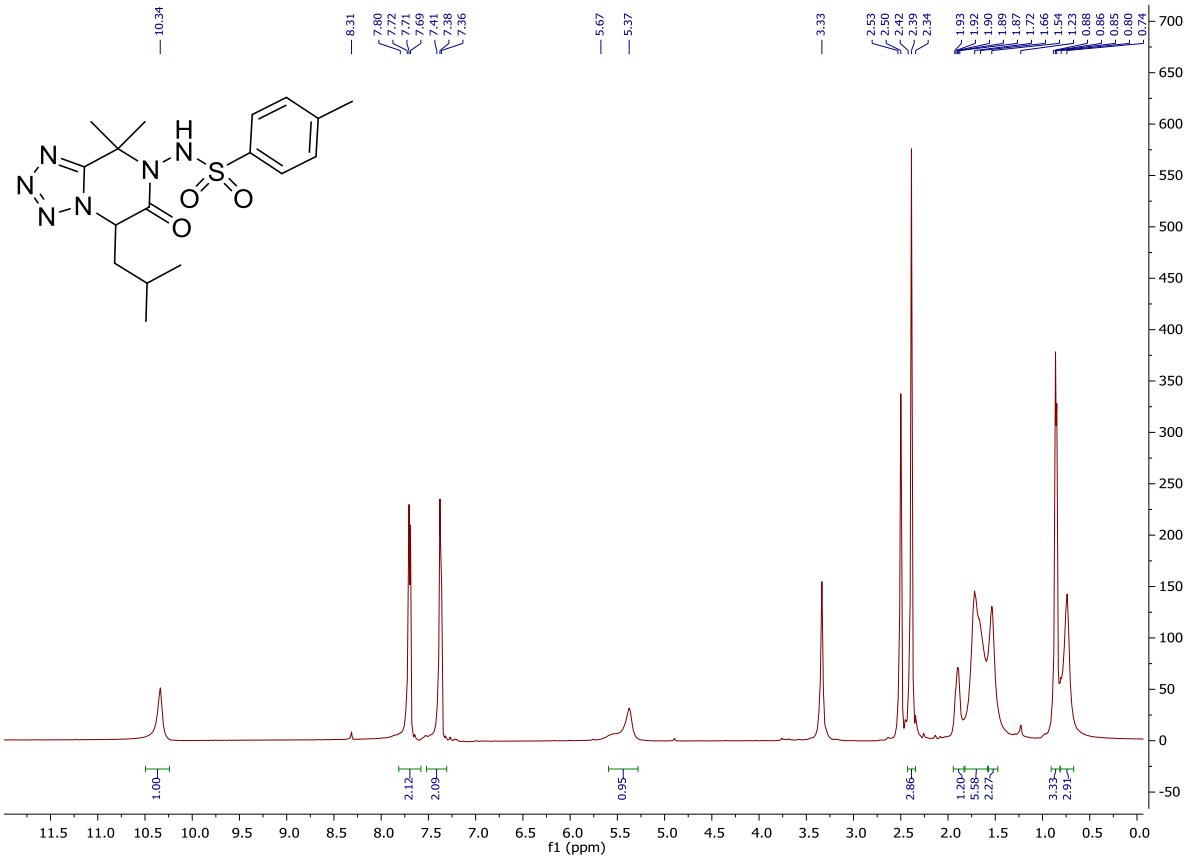
11: 2-(4-chlorophenyl)-N-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7 (8*H*)-yl)acetamide

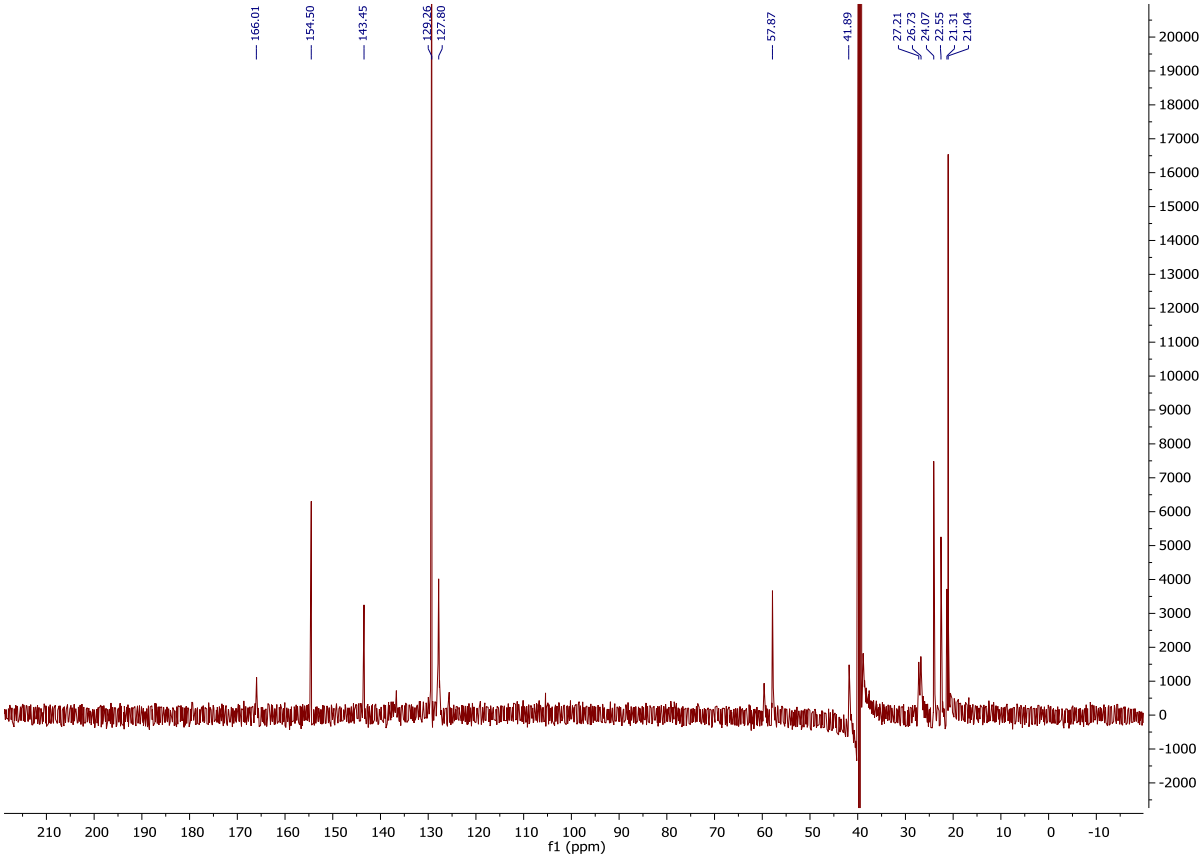




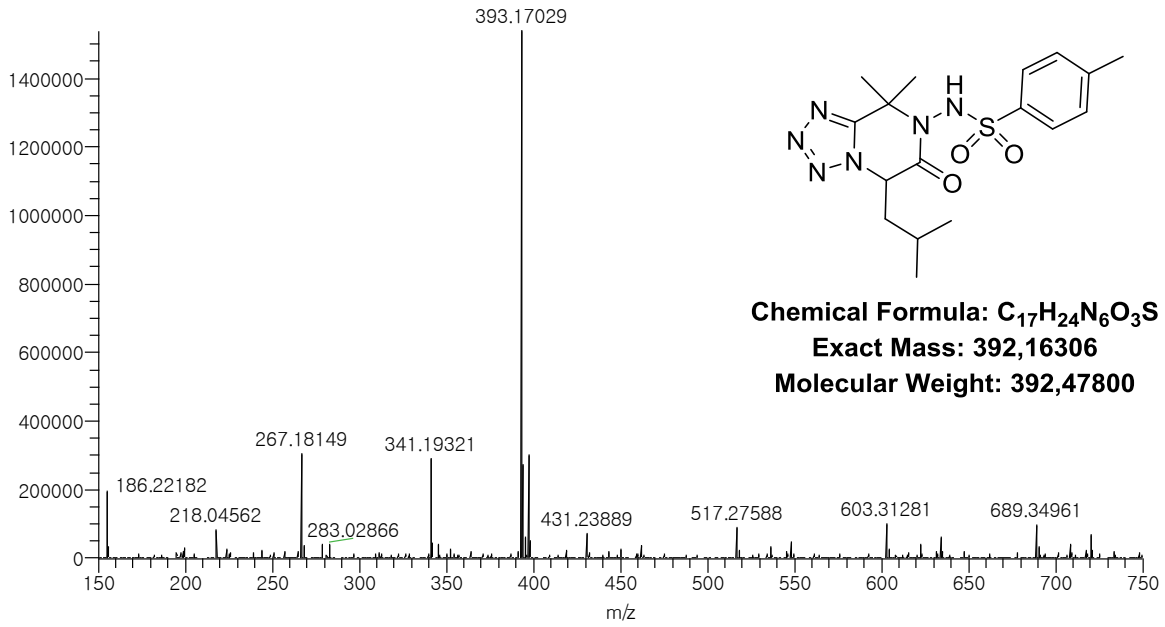

yz178repeat #10 RT: 0.17102 AV: 1 N
T: FTMS + p ESI Full ms [150.00-750.00]
391.16296
352.24475
239.16093
283.04623
409.16061
494.13593
571.43207
614.20007
685.43439
m/z
Chemical Formula: C18H23ClN6O2
Exact Mass: 390,15710
Molecular Weight: 390,87200

12: N-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8*H*)-yl)-4 methyl-benzenesulfonamide



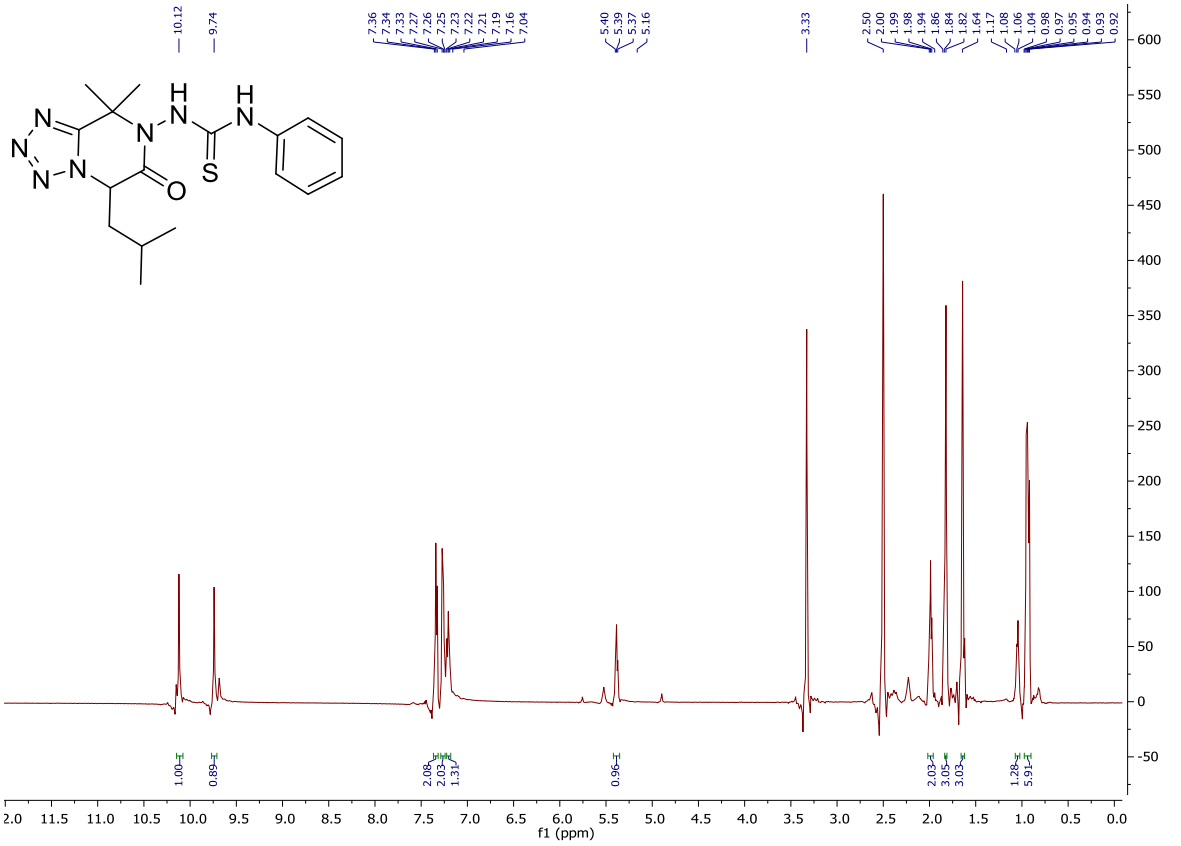


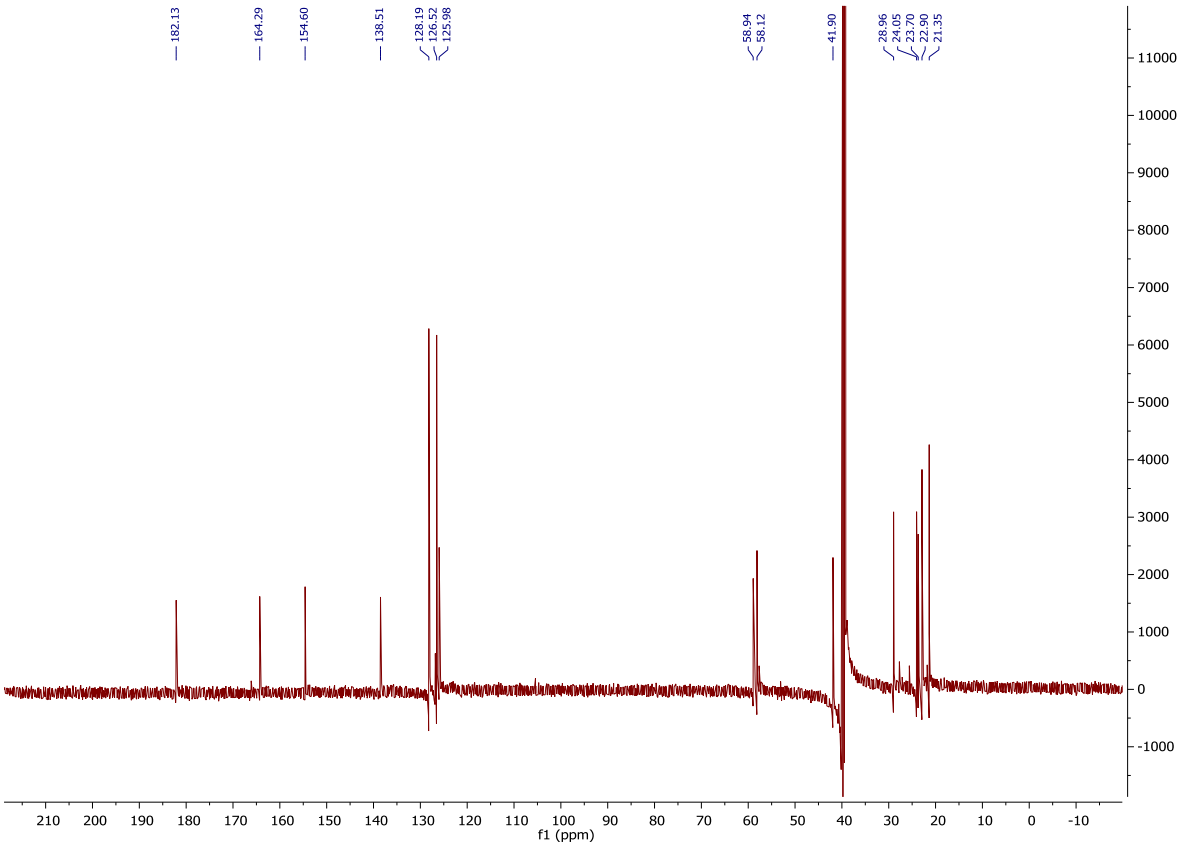
202 #19 RT: 0.31481 AV: 1 NL: 1.54E
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_{17}H_{24}N_6O_3S$
Exact Mass: 392,16306
Molecular Weight: 392,47800

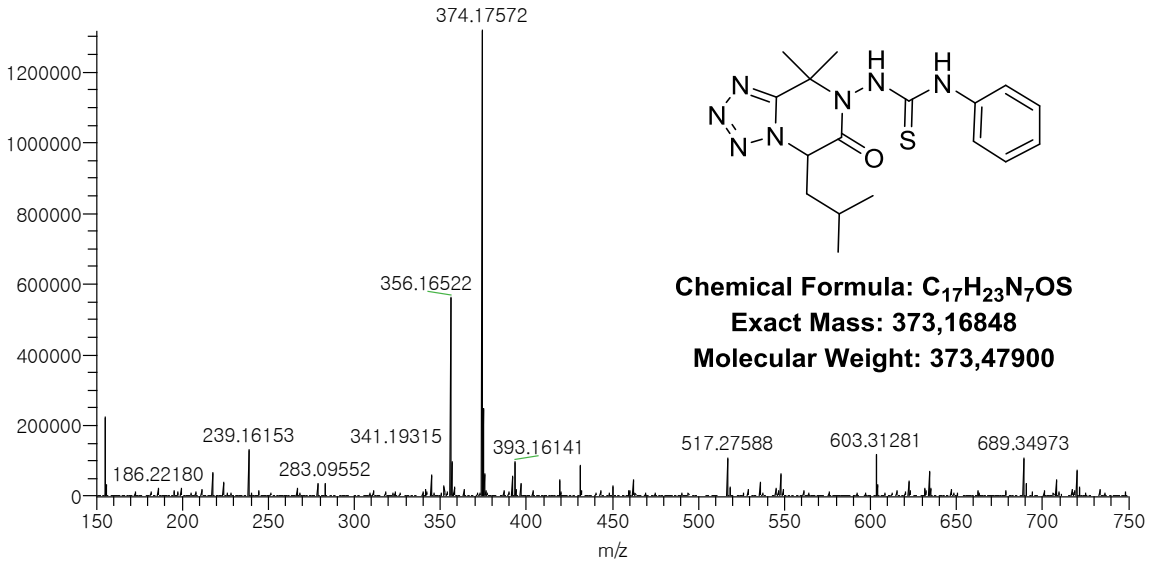
13: 1-(5-isobutyl-8,8-dimethyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8*H*)-yl)-3-phenylthiourea





J:₩20161130_ FIA-AccMass50₩90 11/30/16 12:41:43

190 #18 RT: 0.31437 AV: 1 NL: 1.32E6
T: FTMS + p ESI Full ms [150.00-750.00]



Chemical Formula: $C_{17}H_{23}N_7OS$
Exact Mass: 373,16848
Molecular Weight: 373,47900

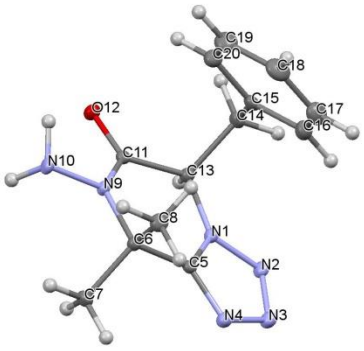
Crystal structure determination

X-ray diffraction data for single crystals of compounds **5a, 5d, 6h, 6j and 7e** were collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.7107 Å). Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments. Single crystals were mounted on MicroMounts™ and measured at temperature close to 130 K. The obtained data sets were processed with CrysAlisPro software [S1]. The phase problem was solved by direct methods using SHELXS [S2], SIR2002 [S3] or SUPERFLIP [S4]. Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6 [S2]. Calculations were performed using WinGX integrated system (ver. 2013.2) [S5]. Figures were prepared with Mercury 3.5 software [S6].

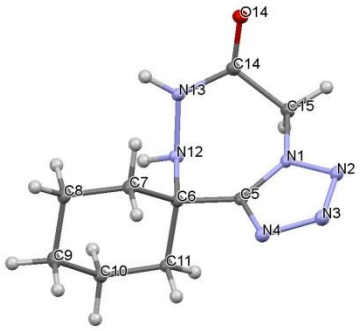
All non-hydrogen atoms in the crystal structures of **5a, 5d, 6h, 6j and 7e** were refined anisotropically to ensure the convergence of the refinement process. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter U_{iso}[H] = 1.2 (or 1.5) U_{eq}[C]. The position of hydrogen atoms linked to the N atoms were found on the difference Fourier map and refined with no restrains on the isotropic displacement parameter. Crystal data and structure refinement results for compounds **5a, 5d, 6h, 6j and 7e** are shown in Table S1.

In the crystal structure of compound **6j** a conformational disorder is observed for the cyclopentane fragment. The two alternative conformations were modelled with 88% and 12% refined site occupancies.

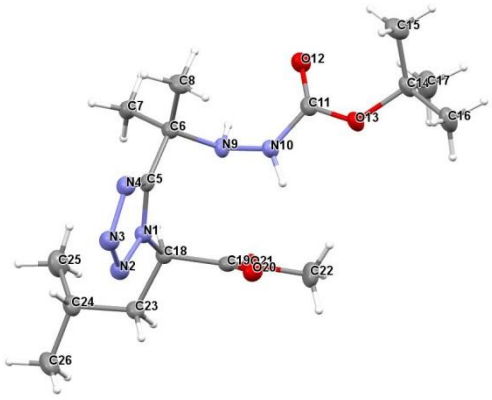
Crystallographic data for structures presented in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1507439 (**6h**), CCDC 1507441 (**7e**), CCDC 1507084 (**5a**), CCDC 1507110 (**5d**), CCDC 1507440 (**6j**). Copies of the data can 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).



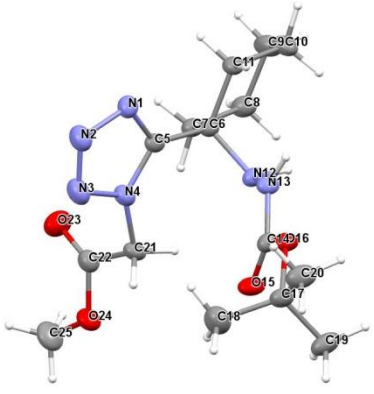
6h



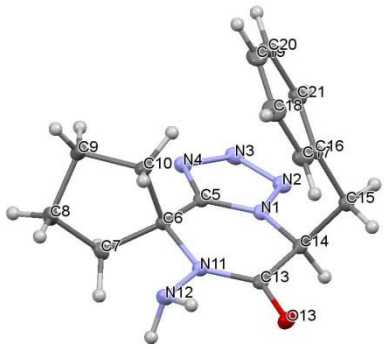
7e



5a



5d



6j

Figure 1. Molecular geometry observed in the crystal structures of compounds **1**-**5**, showing the atom labelling scheme. In case of partially disordered molecule of compound **5** only the more abundant conformation is shown, with the site occupancy 88%. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

Table S1. Crystal data and structure refinement results for compounds **1**-**5**.

	1 **6h**	**2** **7e**	**3** **5a**	**4** **5d**	**5** **6j**
Empirical moiety formula	C_{13} H_{16} N_6 O	C_9 H_{14} N_6 O	C_{16} H_{30} N_6 O_4	C_{15} H_{26} N_6 O_4	C_{15} H_{18} N_6 O
Formula weight [g/mol]	544.63	222.26	370.46	354.42	298.35
Temperature [K]	130(2)	130(2)	130(10)	134(5)	130(2)
Wavelength [Å]	0.7107	0.7107	0.7107	0.7107	0.7107
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	I2/*a*	$P2_1/c$	$P2_1/c$	C2/*c*	$P2_1/c$
Unite cell dimensions	a = 14.3819(6) Å b = 8.1017(3) Å c = 23.2784(9) Å α=90° β=91.397(4)° γ=90°	a = 10.7348(5) Å b = 9.1446(3) Å c = 11.7753(6) Å α=90° β=116.418(6)° γ=90°	a=22.7944(8) Å b=7.5374(2) Å c=12.1001(4) Å α=90.0° β=102.072(4)° γ=90.0°	a=15.8975(6) Å b=12.9679(3) Å c=19.3594(9) Å α=90° β=115.611(5)° γ=90°	a=11.5427(4) Å b=8.6359(3) Å c=14.61473(5) Å α=90° β=93.932(3)° γ=90°
Volume [$Å^3$]	2711.54(18)	1035.22(9)	2032.94(13)	3599.0(3)	1453.39(9)
Z	4	4	4	8	4
D_{calc} [Mg/m^3]	1.334	1.426	1.210	1.308	1.364
μ [mm^{-1}]	0.091	0.101	0.089	0.097	0.092
F(000)	1152	472	800	1520	632
Crystal size [mm^3]	0.6 x 0.6 x 0.3	0.6 x 0.6 x 0.4	0.6 x 0.6 x 0.4	0.4 x 0.4 x 0.2	0.5 x 0.4 x 0.3
Θ range	2.89° to 28.53°	2.95° to 29.41°	2.91° to 28.62°	3.14° to 28.51°	2.95° to 30.32°
Index ranges	$-18 \le h \le 15$, $-10 \le k \le 10$, $-30 \le l \le 29$	$-14 \le h \le 14$, $-12 \le k \le 12$, $-16 \le l \le 15$	$-30 \le h \le 30$, $-10 \le k \le 9$, $-9 \le l \le 16$	$-20 \le h \le 21$, $-16 \le k \le 17$, $-25 \le l \le 25$	$-16 \le h \le 15$, $-11 \le k \le 11$, $-20 \le l \le 20$
Refl. collected	11596	14724	16329	12175	22705
Independent reflections	3188 [R(int) = 0.0289]	2711 [R(int) = 0.0519]	4756 [R(int) = 0.0347]	4562 [R(int) = 0.0433]	4117 [R(int) = 0.0696]
Completeness [%] to Θ	99.9 (Θ 25.24°)	99.9 (Θ 25.24°)	99.8 (Θ 26.31°)	99.9 (Θ 26.31°)	99.9 (Θ 25.24°)

Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan	Multi-scan
Max. and min. transmission	0.588 and 1.000	0.662 and 1.000	0.791 and 1.000	0.710 and 1.000	0.538 and 1.000
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/ restraints/parameters	3188 / 0 / 192	2711 / 0 / 154	4756 / 0 / 252	4139 / 0 / 238	4117 / 2 / 226
GooF on F2	1.047	1.051	1.048	0.998	1.092
Final R indices [I>2sigma(I)]	R1= 0.0365, wR2= 0.0876	R1= 0.0436, wR2= 0.0933	R1= 0.0414, wR2= 0.1003	R1= 0.0427, wR2= 0.0984	R1= 0.0502, wR2= 0.1189
R indices (all data)	R1= 0.0450, wR2= 0.0945	R1= 0.0624, wR2= 0.1052	R1= 0.0585, wR2= 0.1003	R1= 0.0629, wR2= 0.1104	R1= 0.0723, wR2= 0.1346
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e·Å^{-3}]	0.35 and -0.21	0.34 and -0.24	0.26 and -0.18	0.28 and -0.19	0.33 and -0.28

References:

[S1] Oxford Diffraction (**2006**). CrysAlis^{Pro} Oxford Diffraction Ltd, Abingdon, England, Version 1.171.36.20 (release 27-06-2012 CrysAlis171.NET)

[S2] Sheldrick, G. M. A short history of SHELX *ActaCryst.* **2008**, *A64*, 112-122.

[S3] Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Polidori, G.; Spagna, R. SIR2002: the program. *J. Appl. Cryst*., **2003**, *36*, 1103.

[S4] Palatinus, L. Chapuis, G., SUPERFLIP - a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. *J. Appl. Cryst*. **2007**, *40*, 786-790.

[S5] Farrugia, L., J. WinGX suite for small- molecule single-crystal crystallography. *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.; van de Streek, J.; Mercury: visualization and analysis of crystal structures. *J. Appl. Cryst*. **2006**, *39*, 453-457.