Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting information

Towards a facile and convenient synthesis of highly functionalized indole derivatives based on Multi-Component Reactions

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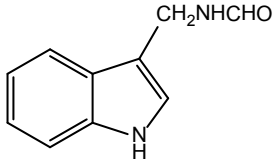
General methods

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)}. 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, brs= broad singlet, d= doublet, t= triplet, 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 Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230 - 400 mesh). Reagents were available from commercial suppliers (Sigma Aldrich, ABCR, Acros and AK Scientific) and used without any purification unless otherwise noted. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument.

Synthetic procedure and the characterization data of indole formamide **1** and isocyanides **2**,**8**

Synthesis of *N*-((1*H*-indol-3-yl)methyl)formamide (**1**)



A solution of indole-3-carboxaldehyde (2 mmol) in formamide (100 mmol) and formic acid (50 mmol) was irradiated in a microwave oven at 180°C for 3 min *(attention: during irradiation, pressure develops)*. After cooling down, extractions with dichloromethane (3x30 ml) followed. The organic layer was separated, washed with water, dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with hexane-ethyl acetate (1:2) afforded **1** as white solid in 71% yield.

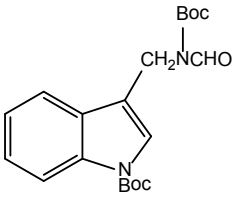
Alternative procedure

To a solution of indole-3-carboxaldehyde (0.5 mmol) in MeOH (10mL), formamide (0.5 mmol) and $NaBH_4$ (0,5 mmol) were added. The reaction mixture stirred at rt for 1.5h. The solvent was evaporated and extractions with dichloromethane (3x30 ml) followed. The organic layer was separated, washed with water, dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with hexane-ethyl acetate (3:1) first afforded (1*H*-indol-3-yl)methanol[13] in 30% yield and then compound **1** as white solid in 49% yield.

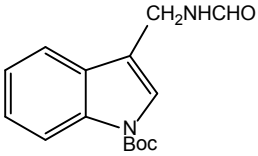
^{1}H NMR (500 MHz, $CDCl_3$), *major isomer*, δ 4.66 (d, *J* = 5.0 Hz, 2H), 5.72 (brs, 1H), 7.15 (t, *J* = 5.0 Hz, 1H), 7.17 (s, 1H), 7.23 (t, *J* = 5.0 Hz, 1H), 7.39 (d, *J* = 10.0 Hz, 1H), 7.63 (d, *J* = 10.0 Hz, 1H), 8.21 (s, 1H), 8.22 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), *major isomer*, δ 33.9, 111.6, 118.9, 120.2, 122.8, 123.5, 126.5, 136.6, 161.2. MS (SFC): t_R = 3.95 min; *m/z* = 173.02 $[M-H]^+$, 197.17 $[M+Na]^+$

Synthesis of tert-butyl 3-(formamidomethyl)-1*H*-indole-1-carboxylate and tert-butyl 3-((*N*-(tert-butoxycarbonyl)formamido)methyl)-1*H*-indole-1-carboxylate

To a solution of indole-formamide **1** (5.0 mmol) in THF (15mL) at 0°C, di-tert-butyl dicarbonate (7.5 mmol) was added in portions, followed by catalytic addition of DMAP and the reaction mixture stirred at rt overnight. After the completion of the reaction, dichloromethane was added and the organic layer was separated, washed with water, dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with hexane-ethyl acetate (1:1) first afforded tert-butyl 3-((*N*-(tert-butoxycarbonyl)formamido) methyl)-1*H*-indole-1-carboxylate in 20% yield and then tert-butyl 3-(formamidomethyl)-1*H*-indole-1-carboxylate as orange solid in 70% yield.

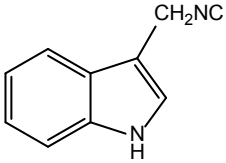


White solid, 20% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, (9H), 1.65 (s, 9H), 4.87 (s, 2H), 7.24 (t, *J* = 5.0 Hz, 1H), 7.30 (t, *J* = 5.0 Hz, 1H), 7.61 (s, 1H), 7.75 (d, *J* = 10.0 Hz, 1H), 8.12 (d, *J* = 10.0 Hz, 1H), 9.24 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.3, 28.4, 35.1, 115.3, 119.9, 122.9, 124.7, 126.2, 163.1. MS (SFC): t_R = 1.66 min; *m/z* = 397.21 $[M+Na]^+$



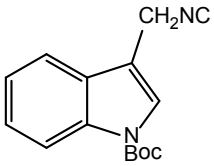
Orange solid, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$), *major isomer*, δ 1.65 (s, 9H), 4.53 (d, *J* = 5.0 Hz, 2H), 7.21 (t, *J* = 5.0 Hz, 1H), 7.30 (t, *J* = 5.0 Hz, 1H), 7.50 (s, 1H), 7.52 (d, *J* = 10.0 Hz, 1H), 8.10 (d, *J* = 5.0 Hz, 1H), 8.16 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), *major isomer,* δ 28.3, 33.3, 115.5, 119.2, 123.0, 124.4, 125.2, 161.2. MS (SFC): t_R = 2.87 min; *m/z* = 273.27 $[M-H]^+$

Synthesis of 1*H*-indole-methyl-isocyanide (**2**)



To a solution of indole-formamide **1** (3.0 mmol) in dichloromethane (15mL), Et_3N (15 mmol) was added. The reaction mixture was stirred at 0°C where $POCl_3$ (3.3 mmol) was added dropwise in about 15 minutes. The solution was stirred at rt for 3h and then was quenched with saturated solution of Na_2CO_3. The organic layer was separated, washed with water, dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with dichloromethane afforded **2** as brown liquid in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (s, 2H), 7.08 (s, 1H), 7.16 (t, *J* = 5.0 Hz, 1H), 7.22 (t, *J* = 5.0 Hz, 1H), 7.33 (d, *J* = 10.0 Hz, 1H), 7.60 (d, *J* = 10.0 Hz, 1H), 8.30 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.0 (t, *J* = 6.3Hz), 111.8, 118.4, 120,4, 122.9, 123.3, 125.6, 136.4, 155.6 (t, *J* = 6.3Hz).

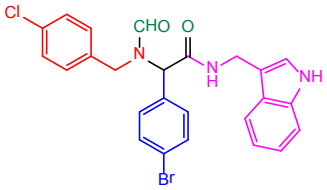
Synthesis of tert-butyl 3-(isocyanomethyl)-1*H*-indole-1-carboxylate (**8**)



To a solution of tert-butyl 3-(formamidomethyl)-1*H*-indole-1-carboxylate (3.0 mmol) in dichloromethane (15mL), Et_3N (15 mmol) was added. The reaction mixture was stirred at 0°C where $POCl_3$ (3.3 mmol) was added dropwise in about 15 minutes. The solution was stirred at rt for 3h and then was quenched with saturated solution of Na_2CO_3. The organic layer was separated, washed with water, dried with magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography on silica gel eluted with dichloromethane afforded **8** as orange solid in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 9H), 4.72 (s, 2H), 7.30 (t, J = 5.0 Hz, 1H), 7.38 (t, J = 5.0 Hz, 1H), 7.56 (d, J = 10.0 Hz, 1H), 7.65 (s, 1H), 8.17 (d, J = 10.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4, 38.0 (t, J = 6.3Hz), 112.7, 115.8, 118.7, 123.3, 124.5, 125.4, 128.1, 155.7 (t, J = 6.3Hz). MS (SFC): t_R = 2.86 min; m/z = 297.21 $[M+K]^+$

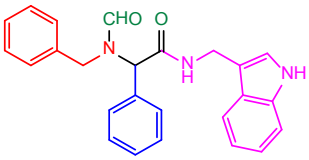
General information and general procedure for Ugi-4C reaction and the characterization data for the indole derivatives **4a-c**, **9**.

To a solution of benzylamine (0.5 mmol) in MeOH (1mL), aldehyde (0.5 mmol), isocyanide (0.5 mmol) and formic acid (0.5 mmol) were added. The reaction mixture stirred at rt for 24-48h. The solvent was evaporated and reaction mixture purified with flash chromatography on silica gel eluted with hexane-ethyl acetate (1:2).



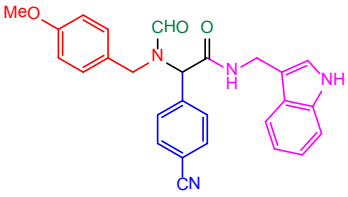
N-((1*H*-indol-3-yl)methyl)-2-(4-bromophenyl)-2-(*N*-(4-chloro benzyl)formamido)acetamide (**4a**), yellow solid, 85% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 4.40 (d, J = 15Hz, 1H), 4.49-4.52 (m, 1H), 4.58-4.62 (m, 1H), 4.74 (d, J = 15Hz, 1H), 5.09 (s, 1H), 6.89 (d, J = 10Hz, 1H), 7.04-7.10 (m, 10H), 7.13-7.20 (m, 4H), 7.30 (s, 1H), 7.30-7.37 (m, 4H), 7.50 (d, J = 15Hz, 2H), 7.87 (s, 1H), 8.28 (d, J = 10Hz, 2H), 9.71 (brs, 1H), 9.81 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, DMSO), *mixture of rotamers*, δ 35.1, 35.2, 46.5, 49.1, 58.9, 63.1, 111.4, 111.5, 118.6, 118.6, 119.1, 119.2, 121.7, 121.8, 123.5, 123.7, 126.4, 128.3, 128.7, 129.7, 131.2, 132.9, 134.5, 135.4, 163.7, 163.9, 167.9, 168.0. MS (SFC): t_R = 4.26 min; m/z = 508.02 $[M-H]^+$



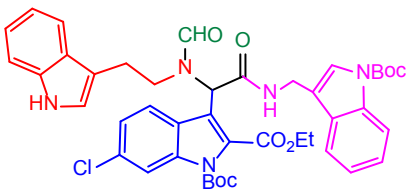
N-((1*H*-indol-3-yl)methyl)-2-(*N*-benzylformamido)-2-phenyl acetamide (**4b**), yellow oil, 82% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 4.28-4.34 (m, 2H), 4.50-4.58 (m, 5H), 4.74 (d, *J* = 15Hz, 1H), 4.88 (s, 1H), 5.67 (s, 1H), 6.18 (s, 1H), 6.92 (s, 2H), 6.97 (s, 2H), 7.03-7.11 (m, 2H), 7.13-7.17 (m, 8H), 7.18-7.21 (m, 8H), 7.24-7.26 (m, 7H), 7.30-7.32 (m, 3H), 7.46-7.53 (m, 1H), 8.18 (s, 1H), 8.53 (brs, 1H), 8.61 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, DMSO), *mixture of rotamers*, δ 35.6, 35.7, 47.5, 50.5, 61.1, 64.9, 111.6, 111.7, 118.8, 118.9, 119.8, 120.0, 122.4, 122.6, 123.5, 123.8, 126.5, 127.8, 127.8, 128.7, 128.8, 128.9, 129.3, 134.1, 134.6, 136.5, 136.6, 136.7, 164.2, 164.3, 168.9. MS (SFC): t_R = 4.25 min; *m/z* = 396.35 $[M-H]^+$, 420.27 $[M+Na]^+$



N-((1*H*-indol-3-yl)methyl)-2-(4-cyanophenyl)-2-(*N*-(4-methoxy benzyl)formamido)acetamide (**4c**), yellow oil, 74% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 3.71 (s, 6H), 4.26-4.31 (m, 2H), 4.42-4.58 (m, 6H), 5.61 (s, 1H), 6.60-6.62 (m, 2H), 6.67 (d, *J* = 10Hz, 1H), 6.81 (d, *J* = 5Hz, 1H), 6.99 (s, 3H), 7.05-7.08 (m, 2H), 7.12-7.16 (m, 4H), 7.23-7.24 (m, 3H), 7.25-7.28 (m, 2H), 7.30-7.34 (m, 3H), 7.47-7.50 (m, 2H), 8.09 (s, 1H), 8.17 (s, 1H), 8.55 (brs, 1H), 8.63 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, DMSO), *mixture of rotamers*, δ 35.6, 35.7, 47.0, 50.6, 55.4, 60.5, 63.8, 111.6, 111.8, 111.9, 112.1, 114.1, 114.2, 114.3, 118.3, 118.4, 118.7, 119.9, 120.0, 122.5, 122.6, 123.6, 123.9, 126.5, 127.8, 129.2, 129.4, 130.0, 132.2, 132.6, 136.5, 139.7, 159.5, 163.9, 164.0, 167.8. MS (SFC): t_R = 4.40 min; *m/z* = 451.38 $[M-H]^+$

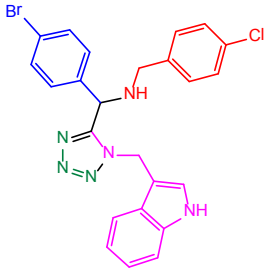


1-tert-butyl 2-ethyl 3-(1-(*N*-(2-(1*H*-indol-3-yl)ethyl) formamido)-2-(((1-(tert-butoxycarbonyl)-1*H*-indol 3-yl)methyl)amino)-2-oxoethyl)-6-chloro-1*H*-indole-1,2-dicarboxylate (**4d**), yellow oil, 70% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 1.24 (t, *J* = 10Hz, 3H), 1.32 (t, *J* = 10Hz, 3H), 1.62-1.65 (m, 27H), 2.50-2.55 (m, 1H), 2.61-2.62 (m, 1H), 3.59-3.62 (m, 1H), 3.72-3.75 (m, 1H), 4.30-4.38 (m, 2H), 4.43-4.46 (m, 3H), 4.47-4.54 (m, 2H), 6.38 (s, 1H), 6.66 (s, 1H), 6.96 (d, *J* = 10Hz, 2H), 7.05-7.07 (m, 5H), 7.23-7.28 (m, 6H), 7.40-7.43 (m, 3H), 7.50-7.58 (m, 1H), 7.84 (s, 1H), 8.10 (s, 1H), 8.16 (s, 1H), 8.29 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, DMSO), *mixture of rotamers*, δ 14.0, 14.1, 14.3, 21.1, 26.7, 28.2, 33.3, 35.1, 35.2, 45.1, 51.5, 57.3, 60.5, 62.5, 62.6, 83.9, 86.2, 111.2, 111.3, 111.5, 115.3, 118.2, 119.3, 122.8, 123.2, 124.6, 124.9, 136.4, 148.5, 149.6, 161.3, 161.9, 163.9, 167.9. MS (SFC): t_R = 4.01 min; *m/z* = 794.26 $[M-H]^+$

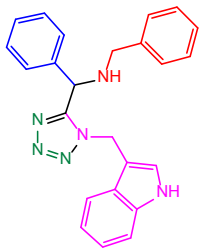
General information and general procedure for Ugi-tetrazole reaction and the characterization data for the indole derivatives **5a-c**.

To a solution of benzylamine (0.5 mmol) in MeOH (1mL), aldehyde (0.5 mmol), isocyanide (0.5 mmol) and $TMSN_3$ (0.5 mmol) were added. The reaction mixture stirred at rt for 24-48h. The solvent was evaporated and reaction mixture purified with flash chromatography on silica gel eluted with hexane-ethyl acetate (2:1).



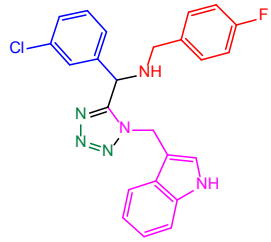
1-(1-((1*H*-indol-3-yl)methyl)-1*H*-tetrazol-5-yl)-1-(4-bromophenyl)-*N*-(4-chlorobenzyl) methanamine (**5a**), white solid, 88% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54 (dd, J_{AB} = 10Hz, 2H), 4.90 (s, 1H), 5.51 (dd, J_{AB} = 15Hz, 2H), 6.78 (d, J = 5Hz, 1H), 6.93 (d, J = 10Hz, 2H), 6.97 (d, J = 10Hz, 2H), 7.10 (t, J = 10Hz, 1H), 7.18 (d, J = 5Hz, 2H), 7.22 (d, J = 10Hz, 1H), 7.29 (d, J = 10Hz, 1H), 7.35 (d, J = 10Hz, 1H), 7.37 (d, J = 10Hz, 2H), 8.09 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.1, 50.5, 55.1, 108.2, 111.8, 118.6, 121.0, 123.5, 128.8, 129.7, 136.7, 137.3, 155.2. MS (SFC): t_R = 3.42 min; *m/z* = 507.15 $[M+H]^+$



1-(1-((1*H*-indol-3-yl)methyl)-1*H*-tetrazol-5-yl)-*N*-benzyl-1-phenyl methanamine (**5b**), yellow oil, 80% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (brs, 1H), 3.61 (dd, J_{AB} = 10Hz, 2H), 5.08 (s, 1H), 5.49 (dd, J_{AB} = 15Hz, 2H), 6.71 (d, J = 5Hz, 1H), 7.06 (t, J = 10Hz, 1H), 7.10-7.16 (m, 5H), 7.18-7.29 (m, 7H), 7.33 (d, J = 10Hz, 1H), 7.37 (J = 10Hz, 1H), 8.45 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 43.9, 51.3, 56.0, 111.8, 118.7, 120.7, 123.1, 124.2, 125.9, 127.5, 128.7, 137.7, 139.0, 155.7. MS (SFC): t_R = 3.74 min; *m/z* = 395.30 $[M+H]^+$, 393.19 $[M-H]^+$

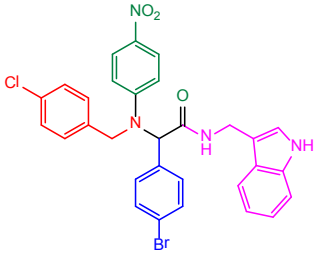


1-(1-((1*H*-indol-3-yl)methyl)-1*H*-tetrazol-5-yl)-1-(3-chlorophenyl)-*N*-(4-fluorobenzyl)methanamine (**5c**), yellow oil, 71% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (d, J_{AB} = 10Hz, 1H), 3.52 (d, J_{AB} = 10Hz, 1H), 4.97 (s, 1H), 5.53 (dd, J_{AB} = 15Hz, 2H), 6.82 (s, 1H), 6.89 (t, J = 10Hz, 2H), 6.95 (d, J = 5Hz, 1H), 6.99-7.00 (m, 3H), 7.04-7.07 (m, 3H), 7.12-7.21 (m, 4H), 7.29-7.33 (m, 2H), 8.61 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.3, 50.5, 55.3, 107.8, 111.9, 115.4, 118.4, 123.2, 125.7, 127.9, 134.4, 139.6, 155.3, 161.2, 163.2. MS (SFC): t_R = 3.52 min; *m/z* = 447.21 $[M+H]^+$

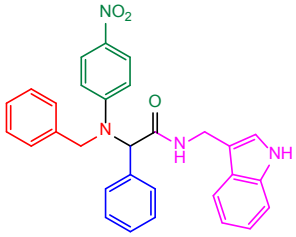
General information and general procedure for Ugi-Smiles reaction and the characterization data for the indole derivatives **6a-c**.

To a solution of benzylamine (0.5 mmol) in MeOH (1mL), aldehyde (0.5 mmol), isocyanide (0.5 mmol) and *p*-nitro-phenol (0.5 mmol) were added. The reaction mixture stirred at rt for 24-48h. The solvent was evaporated and reaction mixture purified with flash chromatography on silica gel eluted with hexane-ethyl acetate (2:1).



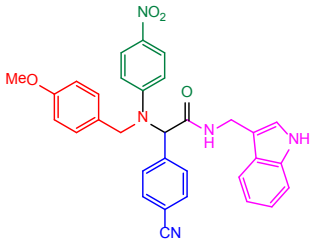
N-((1*H*-indol-3-yl)methyl)-2-(4-bromophenyl)-2-((4-chlorobenzyl)(4-nitrophenyl)amino)acetamide (**6a**), yellow oil, 35% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 4.58 (d, J_{AB} = 15Hz, 2H), 4.63(s, 2H), 5.46 (s, 1H), 6.03 (brs, 1H), 6.67 (d, *J* = 10Hz, 2H), 6.92 (d, *J* = 5Hz, 2H), 7.05 (s, 2H), 7.08 (d, *J* = 5Hz, 4H), 7.13 (d, *J* = 10Hz, 4H), 7.19-7.29 (m, 10H), 7.36-7.40 (m, 1H), 7.97 (d, *J* = 10Hz, 2H), 8.10 (brs, 2H). ^{13}C NMR (126 MHz, $CDCl_3$), *mixture of rotamers*, δ 35.7, 52.3, 53.0, 61.1, 67.4, 111.7, 113.3, 115.7, 118.7, 120.3, 123.0, 123.6, 126.0, 127.8, 128.5, 129.0, 130.6, 131.1, 132.3, 133.4, 135.8, 168.8. MS (SFC): t_R = 4.34 min; *m/z* = 601.03 $[M-H]^+$



N-((1*H*-indol-3-yl)methyl)-2-(benzyl(4-nitrophenyl)amino)-2-phenyl acetamide (**6b**), yellow solid, 41% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 4.61(d, *J* = 5Hz, 2H), 4.73 (d, J_{AB} = 15Hz, 2H), 5.78 (s, 1H), 6.77 (d, *J* = 10Hz, 2H), 7.01-7.05 (m, 4H), 7.08-7.14 (m, 8H), 7.32-7.33 (m, 2H), 7.34 (d, *J* = 15Hz, 2H), 7.43 (t, *J* = 5Hz, 1H), 7.48 (d, *J* = 10Hz, 1H), 7.96 (d, *J* = 5Hz, 2H), 9.46 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), *mixture of rotamers*, δ 35.2, 52.4, 66.7, 111.5, 111.7, 112.8, 115.7, 118.7, 123.7, 126.5, 128.5, 135.0, 136.5, 137.8, 138.3, 154.2, 169.6. MS (SFC): t_R = 4.37 min; *m/z* = 491.36 $[M+H]^+$, 489.31 $[M-H]^+$

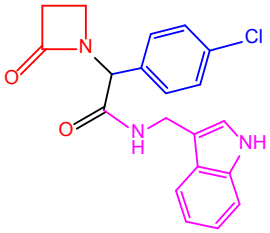


N-((1*H*-indol-3-yl)methyl)-2-(4-cyanophenyl)-2-((4-methoxy benzyl)(4-nitrophenyl)amino)acetamide (**6c**), yellow oil, 45% yield

^{1}H NMR (500 MHz, $CDCl_3$), *mixture of rotamers*, δ 3.88 (s, 3H), 4.54 (d, *J* = 5Hz, 2H), 4.55 (d, J_{AB} = 20Hz, 2H), 5.43 (s, 1H), 6.64 (d, *J* = 10Hz, 3H), 6.68 (*J* = 5Hz, 3H), 6.83-6.89 (m, 11H), 6.97 (d, *J* = 10Hz, 4H), 6.99-7.07 (m, 5H), 7.13-7.18 (m, 8H), 7.23-7.35 (m, 15H), 7.52 (d, d, *J* = 5Hz, 2H), 7.58 (d, *J* = 5Hz, 2H), 7.66 (d, *J* = 15Hz, 3H), 7.78 (d, *J* = 10Hz, 2H), 7.84 (d, *J* = 10Hz, 2H), 7.91 (d, *J* = 10Hz, 2H), 8.06 (brs, 1H), 8.40 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$), *mixture of rotamers*, δ 35.6, 35.7, 49.9, 49.3, 51.9, 53.3, 55.5, 67.2, 111.1, 111.6, 111.6, 112.4, 113.1, 113.4, 113.7, 114.2, 114.2, 118.5, 120.2, 123.6, 128.0, 132.8, 136.7, 139.6, 146.4, 153.1, 159.3, 163.1, 168.0, 172.2. MS (SFC): t_R = 4.41 min; *m/z* = 544.11 $[M-H]^+$

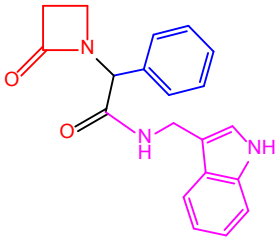
General information and general procedure for Ugi-lactam reaction and the characterization data for the indole derivatives **10a-c**.

A solution of aldehyde (0.5 mmol) and β-alanine (0.5 mmol) in MeOH (1mL) was irradiated in a microwave oven at 100°C for 15 min. The solvent was evaporated and reaction mixture purified with flash chromatography on silica gel eluted with hexane-ethyl acetate (1:2).



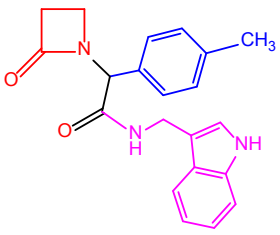
N-((1*H*-indol-3-yl)methyl)-2-(4-chlorophenyl)-2-(2-oxoazetidin-1-yl) acetamide (**10a**), yellow oil, 59% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 (ddd, *J* = 2Hz, 5Hz, 10Hz, 2H), 3.36 (dq, *J* = 2Hz, 5Hz, 10Hz, 2H), 4.56 (t, *J* = 5Hz, 2H), 5.43 (s, 1H), 7.03 (t, *J* = 5Hz, 1H), 7.06 (d, *J* = 2Hz, 1H), 7.14 (t, *J* = 10Hz, 1H), 7.26-7.28 (s, 4H), 7.33 (d, *J* = 10Hz, 2H), 7.38 (brs, 1H), 7.50 (d, *J* = 5Hz, 1H), 9.38 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.2, 36.1, 39.0, 58.3, 111.5, 111.7, 118.7, 119.4, 122.0, 123.6, 126.5, 129.0, 129.6, 133.6, 134.3, 136.5, 167.8, 168.2. MS (SFC): t_R = 3.96 min; *m/z* = 366.31 $[M-H]^+$, 390.23 $[M+Na]^+$



N-((1*H*-indol-3-yl)methyl)-2-(2-oxoazetidin-1-yl)-2-phenylacetamide (**10b**), yellow oil, 45% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 10Hz, 2H), 3.35 (dd, *J* = 15Hz, 2H), 4.59 (s, 2H), 5.35 (s, 1H), 7.03-7.08 (m, 2H), 7.17 (t, *J* = 15Hz, 2H), 7.26-7.32 (s, 6H), 7.50 (d, *J* = 5Hz, 1H), 8.27 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.6, 36.3, 39.2, 60.1, 111.5, 118.9, 120.0, 122.6, 123.5, 128.5, 128.9, 129.3, 168.3, 168.7. MS (SFC): t_R = 4.04 min; *m/z* = 332.24 $[M-H]^+$

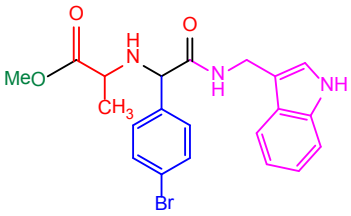


N-((1*H*-indol-3-yl)methyl)-2-(2-oxoazetidin-1-yl)-2-(*p*-tolyl)acetamide (**10c**), yellow oil, 39% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.79 (dd, *J* = 10Hz, 2H), 3.33 (dd, *J* = 15Hz, 2H), 4.57 (dd, J_{AB} = 5Hz, 2H), 5.32 (s, 1H), 7.00-7.06 (m, 3H), 7.07-7.18 (m, 5H), 7.30 (d, *J* = 10Hz, 1H), 7.49 (d, *J* = 10Hz, 1H), 8.40 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3, 35.6, 36.2, 39.1, 59.8, 110.0, 111.5, 118.9, 119.9, 123.5, 126.6, 128.4, 136.5, 138.7, 168.3, 168.4. MS (SFC): t_R = 4.02 min; *m/z* = 346.18 $[M-H]^+$

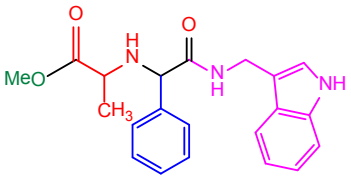
General information and general procedure for Ugi-4C-5 center reaction and the characterization data for the indole derivatives **11a-c**.

To a solution of aldehyde (0.5 mmol) in MeOH (1mL), isocyanide (0.5 mmol) and the aminoacid (0.5 mmol) were added. The reaction mixture stirred at rt for 24-48h. The solvent was evaporated and reaction mixture purified with flash chromatography on silica gel eluted with hexane-ethyl acetate (2:1).



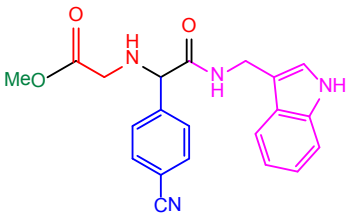
methyl 2-((2-(((1*H*-indol-3-yl)methyl)amino)-1-(4-bromophenyl)-2-oxoethyl)amino)propanoate (**11a**), yellow oil, 70% yield

^{1}H NMR (500 MHz, $CDCl_3$), *major rotamer*, δ 1.24 (t, J = 5Hz, 3H), 3.19 (q, J = 5Hz, 1H), 3.58 (s, 3H), 3.67 (s, 3H), 4.29 (s, 1H), 4.57 (ddd, J = 5Hz, 10Hz, 25Hz, 2H), 7.04-7.10 (m, 6H), 7.18 (t, J = 10Hz, 6H), 7.31-7.39 (m, 4H), 7.44-7.51 (m, 4H), 8.50 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.9, 35.3, 52.1, 52.3, 54.2, 55.8, 111.5, 111.6, 118.8, 123.4, 126.6, 132.2, 136.6, 137.7, 171.4, 175.2, 175.7. MS (SFC): t_R = 3.69 min; m/z = 444.12 $[M+H]^+$



methyl 2-((2-(((1*H*-indol-3-yl)methyl)amino)-2-oxo-1-phenylethyl) amino)propanoate (**11b**), yellow oil, 55% yield

^{1}H NMR (500 MHz, $CDCl_3$), *major rotamer*, δ 1.24 (t, J = 5Hz, 3H), 3.23 (q, J = 5Hz, 1H), 3.57 (s, 3H), 4.33 (s, 3H), 4.59 (ddd, J = 5Hz, 15Hz, 2H), 7.01-7.08 (m, 4H), 7.17 (t, J = 10Hz, 2H), 7.27-7.33 (m, 8H), 7.48 (d, J = 10Hz, 1H), 8.48 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.9, 35.2, 52.2, 54.4, 55.9, 65.6, 66.6, 111.5, 118.9, 119.9, 122.5, 126.7, 127.9, 129.1, 136.6, 138.8, 171.9, 175.3. MS (SFC): t_R = 3.67 min; m/z = 366.31 $[M+H]^+$, 364.23 $[M-H]^+$

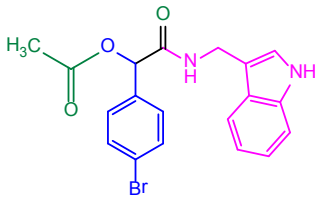


methyl 2-((2-(((1*H*-indol-3-yl)methyl)amino)-1-(4-cyanophenyl)-2-oxoethyl)amino)acetate (**11c**), yellow oil, 71% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (dd, J_{AB} = 40Hz, 2H), 3.67 (s, 3H), 4.32 (s, 1H), 5.62 (ddd, J = 5Hz, 10Hz, 25Hz, 2H), 7.07 (t, J = 5Hz, 1H), 7.10 (s, 1H), 7.21 (t, J = 10Hz, 1H), 7.29 (s, 1H), 7.36 (d, J = 5Hz, 1H), 7.45 (t, J = 15Hz, 3H), 7.55 (d, J = 10Hz, 2H), 8.33 (brs, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 35.3, 49.0, 52.3, 66.9, 111.6, 112.4, 112.5, 118.7, 120.1, 126.5, 132.8, 136.6, 143.8, 170.4, 172.2. MS (SFC): t_R = 4.09 min; m/z = 377.26 $[M+H]^+$, 375.18 $[M-H]^+$

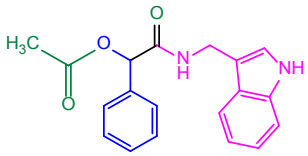
General information and general procedure for Passerini reaction and the characterization data for the indole derivatives **12a-c**.

To a solution of aldehyde (0.5 mmol) in dichloromethane (1mL), isocyanide (0.5 mmol) and the acid (0.5 mmol) were added. The reaction mixture stirred at rt for 24-48h. The solvent was evaporated and reaction mixture purified with flash chromatography on silica gel eluted with hexane-ethyl acetate (2:1). *(The reaction also proceeds in MeOH with lower yields).*



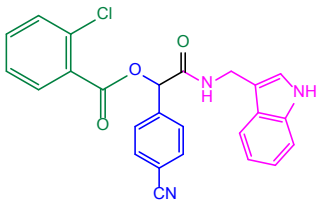
2-(((1*H*-indol-3-yl)methyl)amino)-1-(4-bromophenyl)-2-oxoethyl acetate (**12a**), yellow oil, 67% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 4.60 (dd, *J* = 10Hz, 2H), 5.99 (s, 1H), 7.12 (t, *J* = 10Hz, 1H), 7.14 (s, 1H), 7.22 (t, *J* = 10Hz, 1H), 7.29 (d, *J* = 10Hz, 2H), 7.39 (d, *J* = 5Hz, 1H), 7.47 (d, *J* = 10Hz, 2H), 7.50 (d, *J* = 10Hz, 1H), 8.20 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1, 35.5, 75.1, 111.7, 111.9, 118.8, 120.1, 122.7, 123.3, 123.7, 126.5, 129.2, 132.0, 134.8, 136.6, 168.0, 169.3. MS (SFC): t_R = 3.81 min; *m/z* = 401.03 $[M-H]^+$, 423.05 $[M+Na]^+$



2-(((1*H*-indol-3-yl)methyl)amino)-2-oxo-1-phenylethyl acetate (**12b**), yellow oil, 55% yield

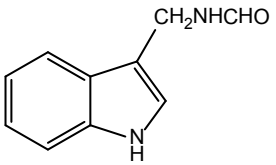
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H), 4.61 (dd, *J* = 10Hz, 2H), 6.07 (s, 1H), 6.41 (brs, 1H), 7.02 (s, 1H), 7.07 (t, *J* = 10Hz, 1H), 7.20 (t, *J* = 10Hz, 1H), 7.30-7.32 (s, 5H), 7.39-7.40 (m, 2H), 7.48 (d, *J* = 5Hz, 1H), 8.44 (brs, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1, 35.5, 75.8, 111.6, 118.9, 120.0, 122.6, 123.6, 126.5, 128.9, 135.8, 136.6, 168.5, 169.5. MS (SFC): t_R = 3.76 min; *m/z* = 345.21 $[M+Na]^+$

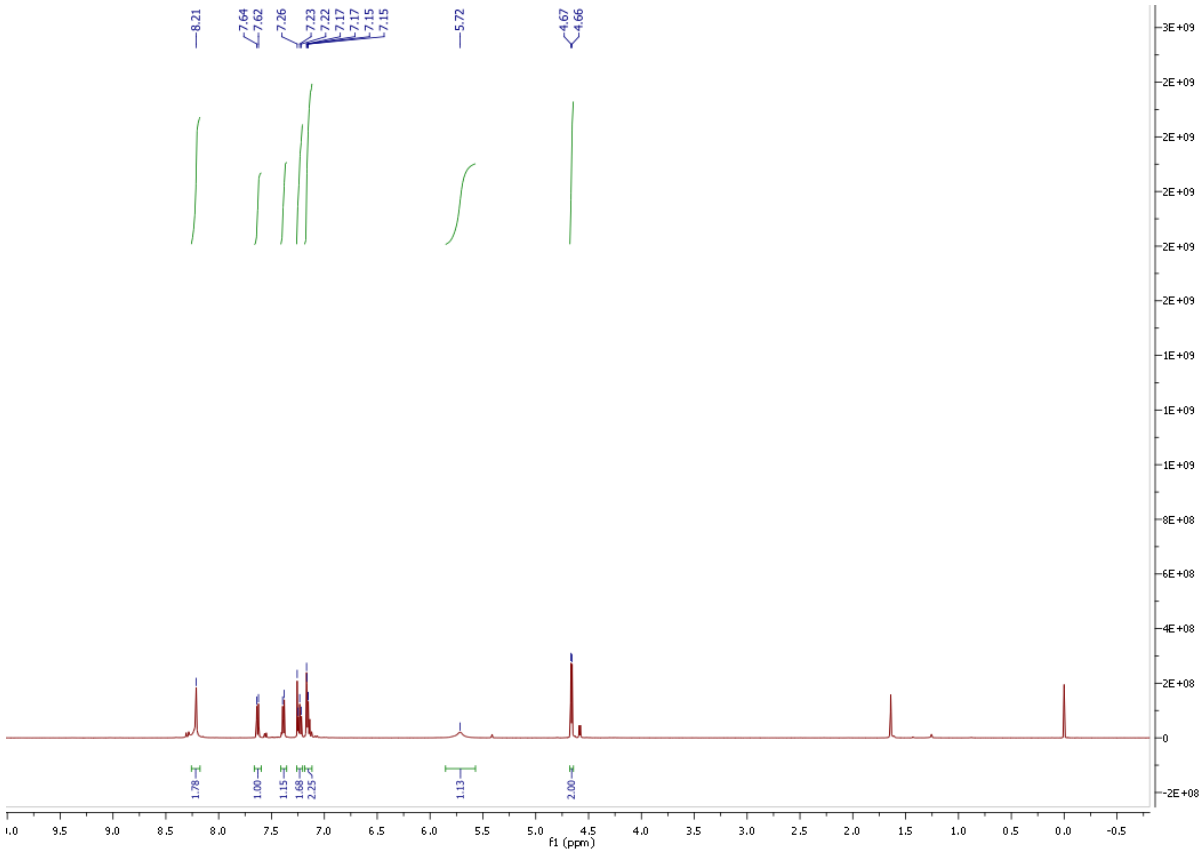


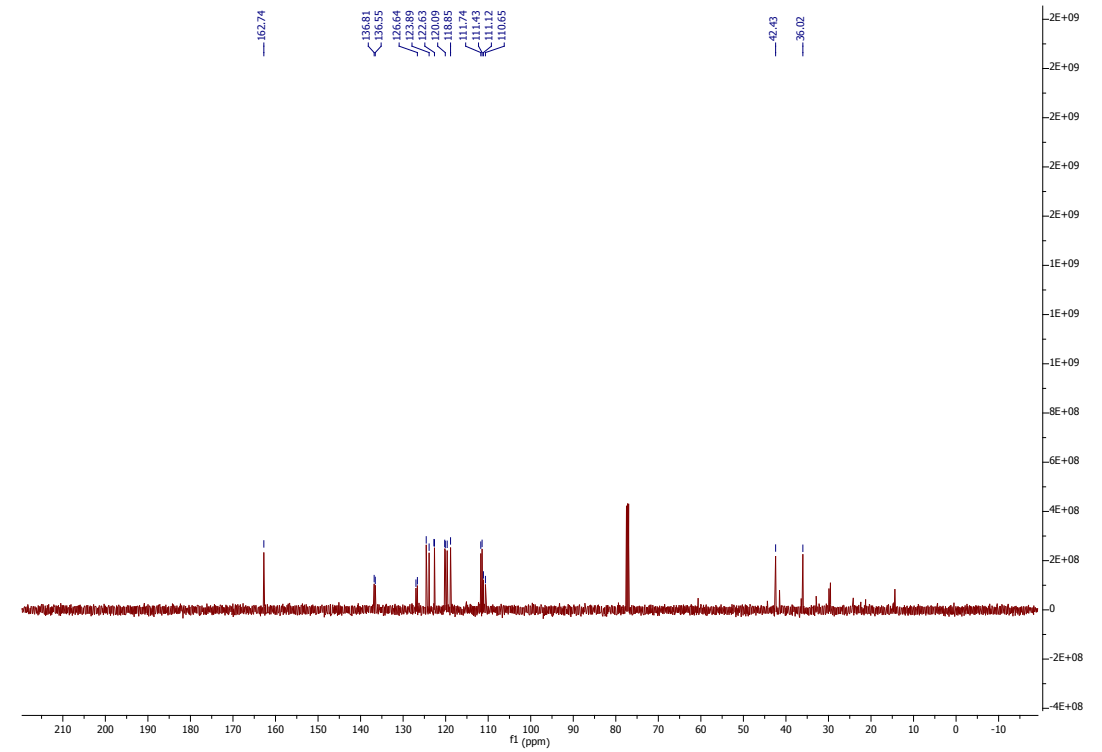
2-(((1*H*-indol-3-yl)methyl)amino)-1-(4-cyanophenyl)-2-oxoethyl 2-chlorobenzoate (**12c**), yellow oil, 69% yield

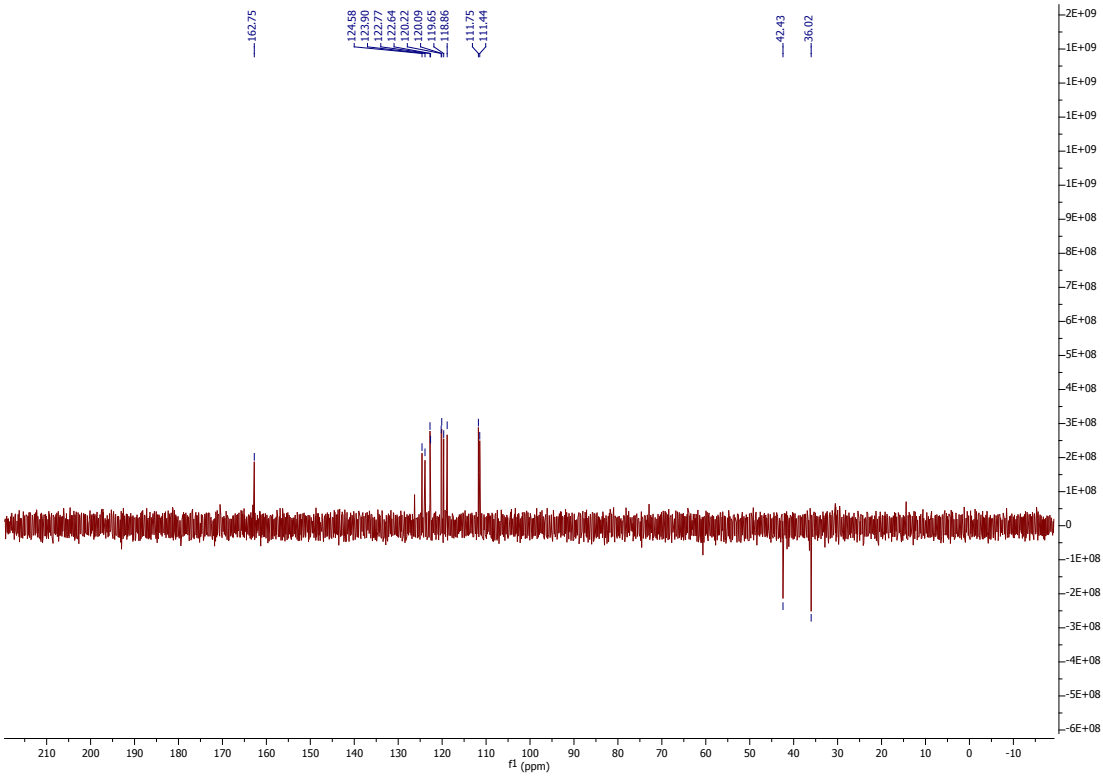
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (dd, *J* = 10Hz, 2H), 6.36 (s, 1H), 6.92 (brs, 1H), 7.09 (t, *J* = 10Hz, 1H), 7.16 (s, 1H), 7.22 (t, *J* = 10Hz, 1H), 7.30 (t, *J* = 10Hz, 1H), 7.33-7.51 (m, 6H), 7.64 (s, 4H), 7.80 (d, *J* = 10Hz, 1H), 7.97 (d, *J* = 10Hz, 1H), 8.18 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.6, 76.2, 111.6, 118.6, 122.9, 123.6, 126.9, 128.9, 132.5, 133.5, 140.7, 164.0, 167.0. MS (SFC): t_R = 4.06 min; *m/z* = 442.14 $[M-H]^+$

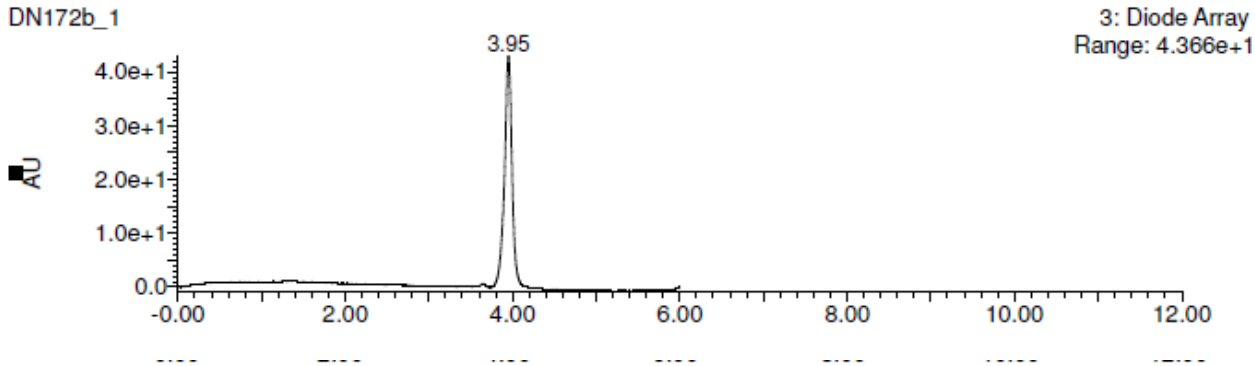
^{1}H, ^{13}C NMR, DEPT-135 and mass spectra of the synthesized compounds

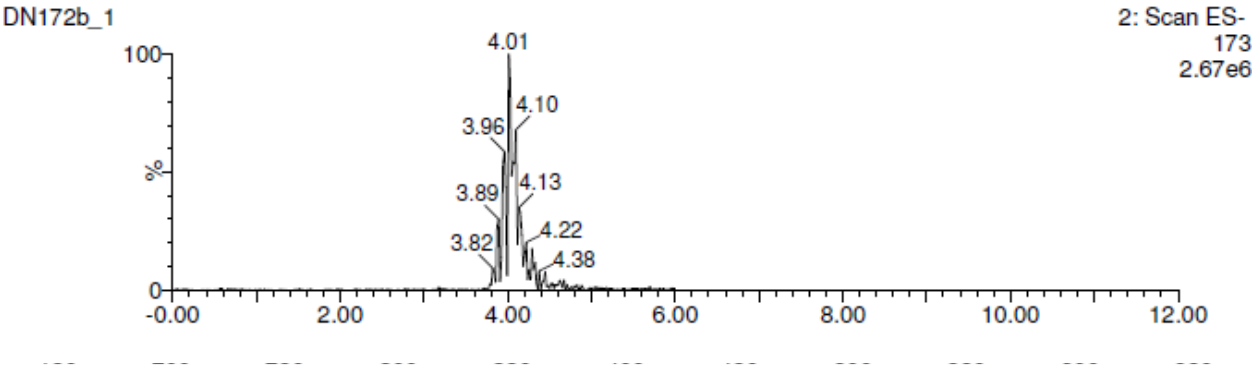


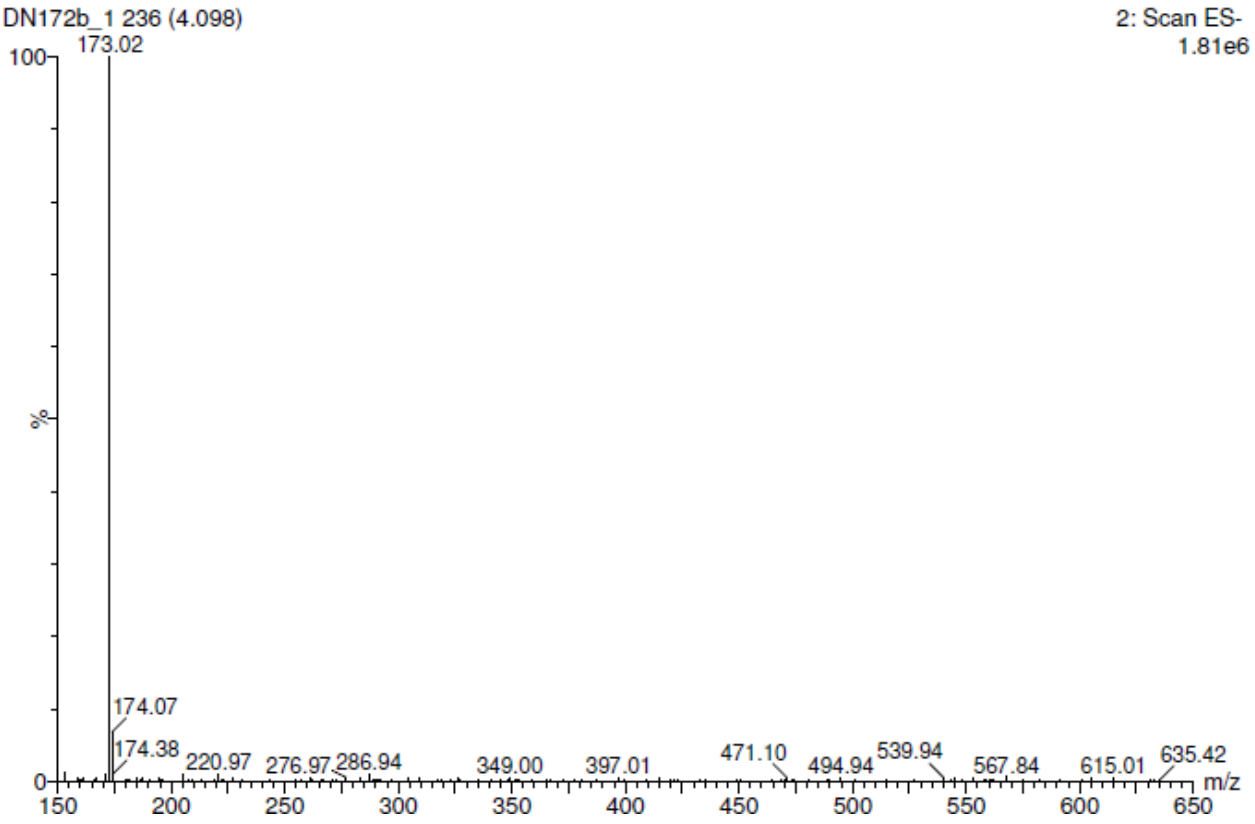


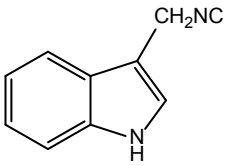


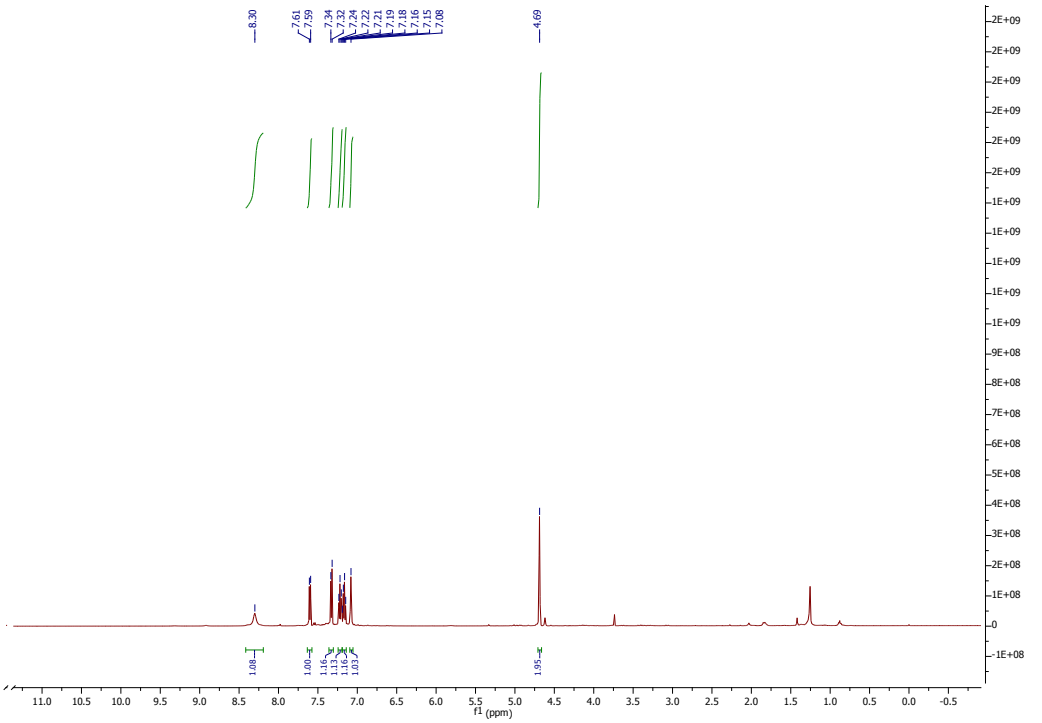


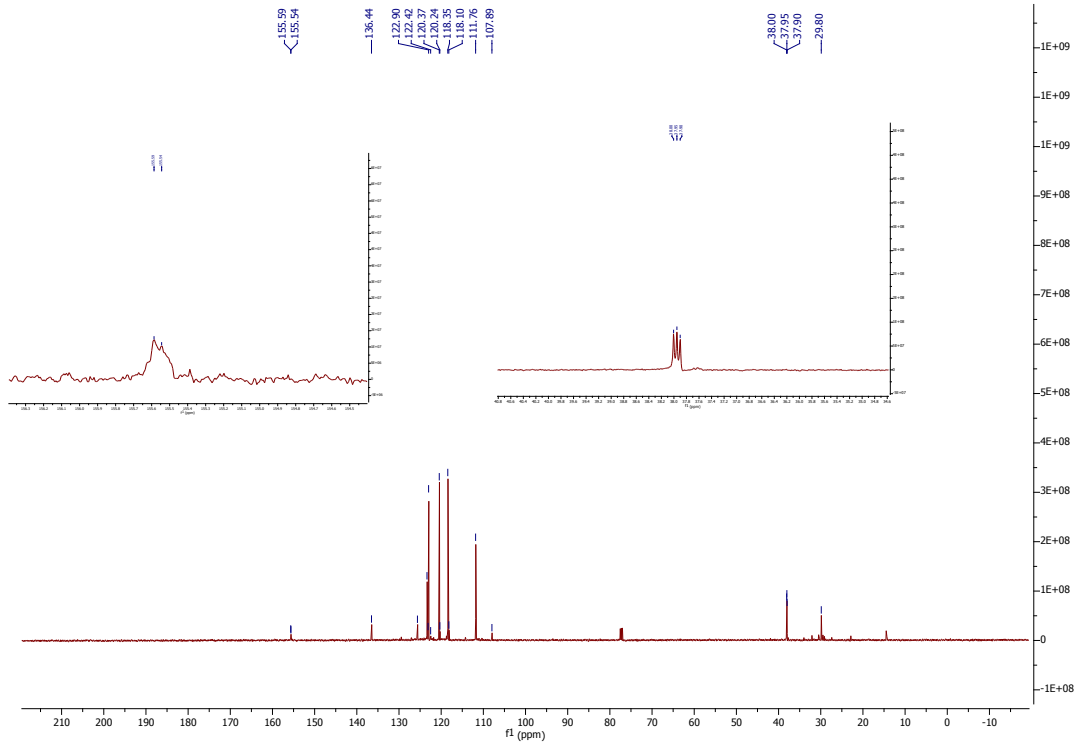


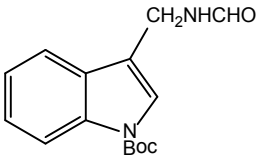


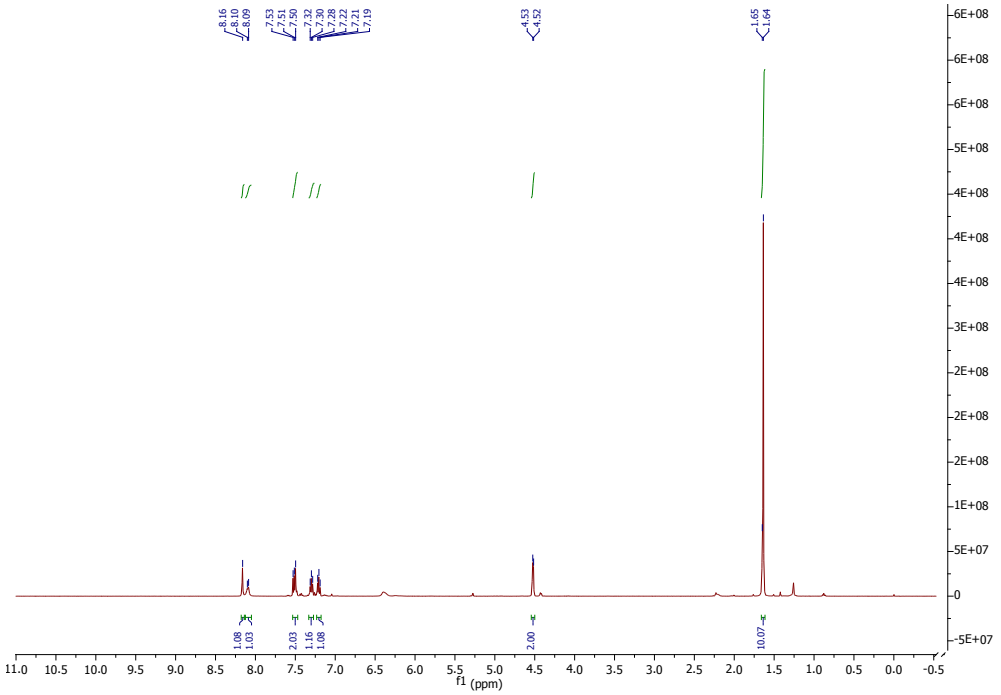


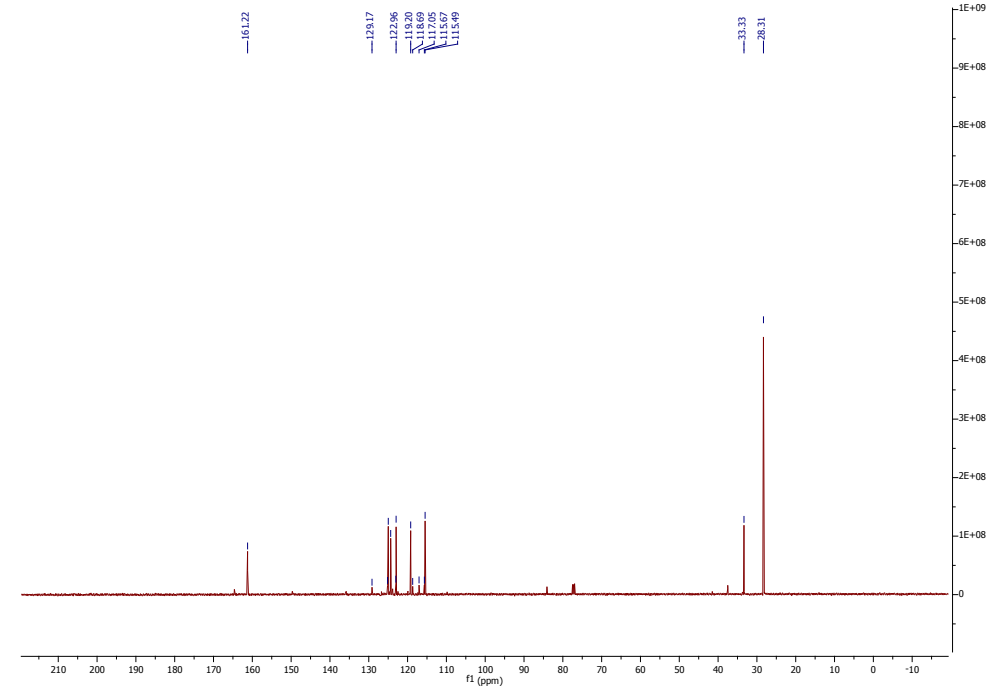


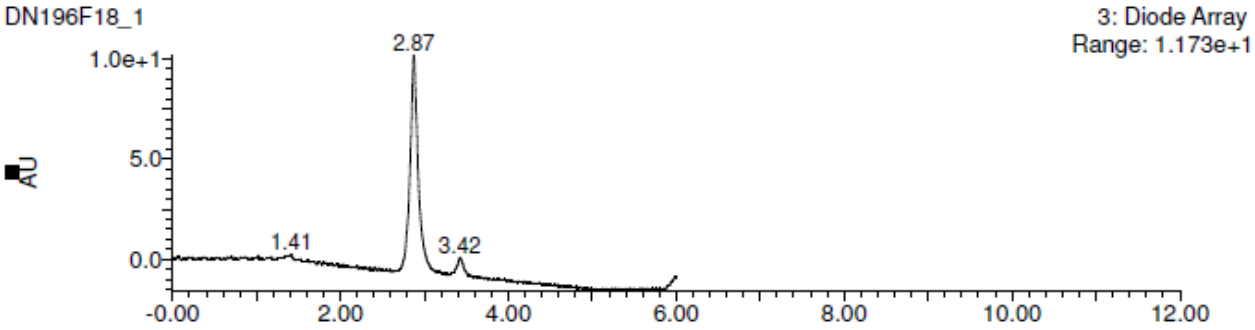


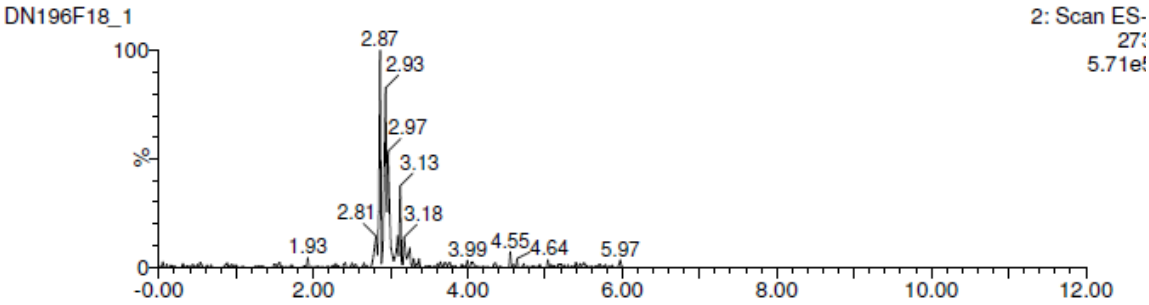


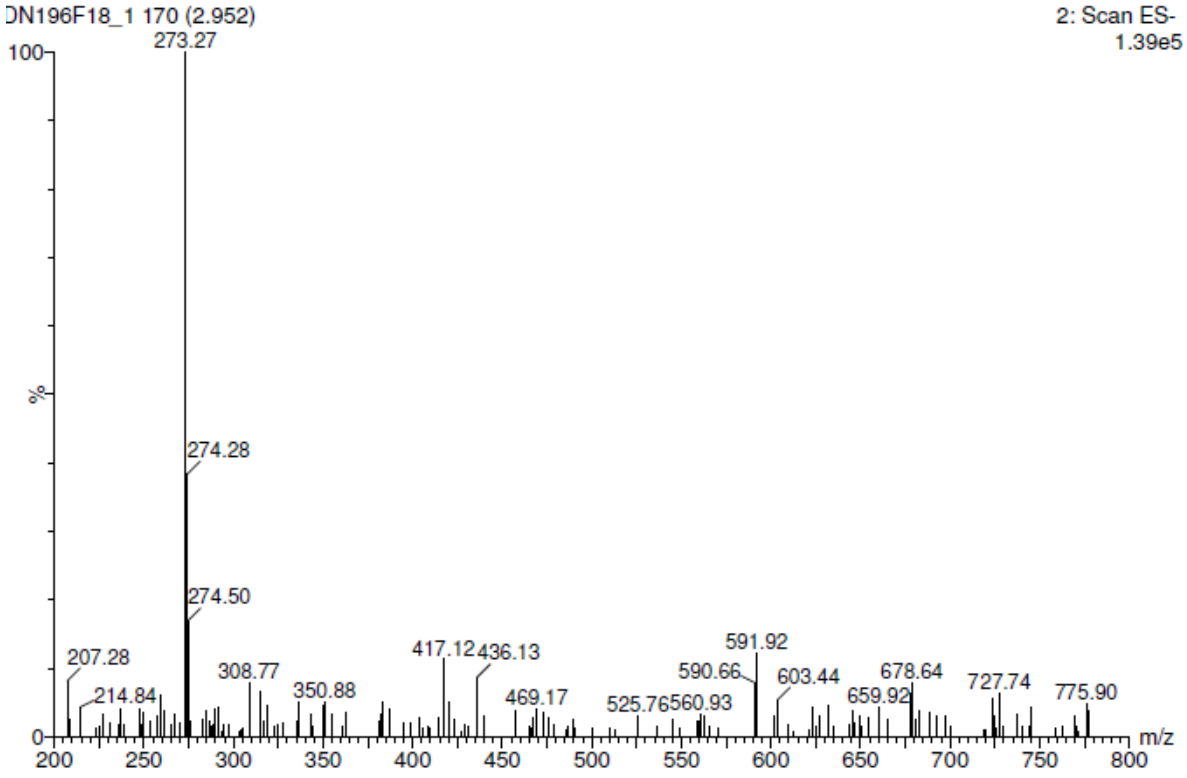


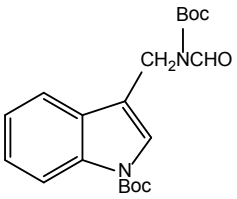


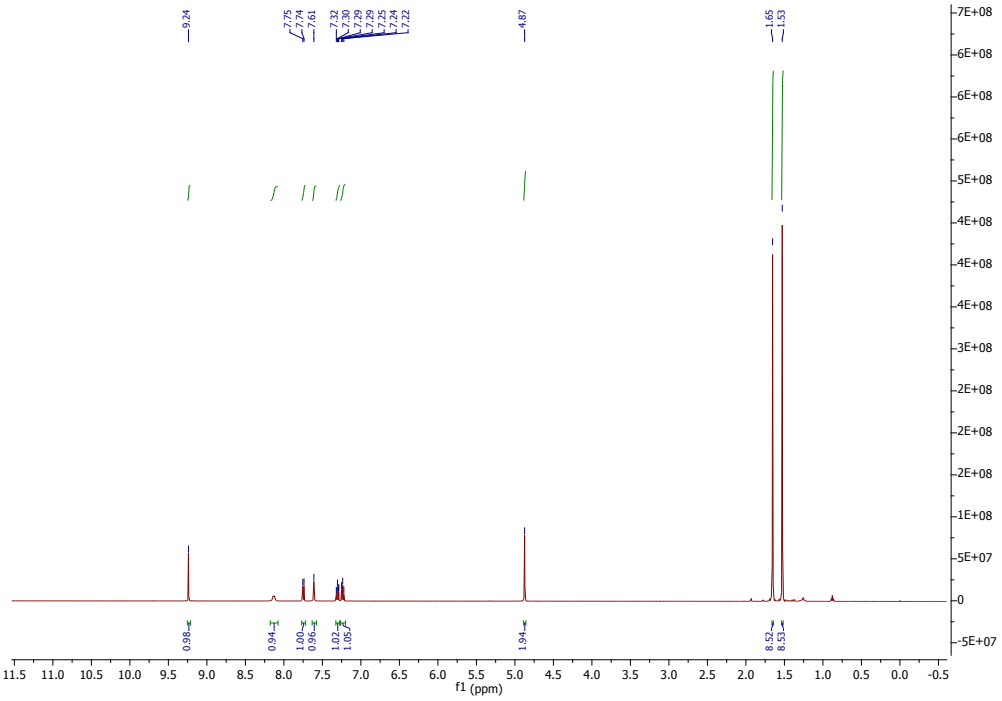


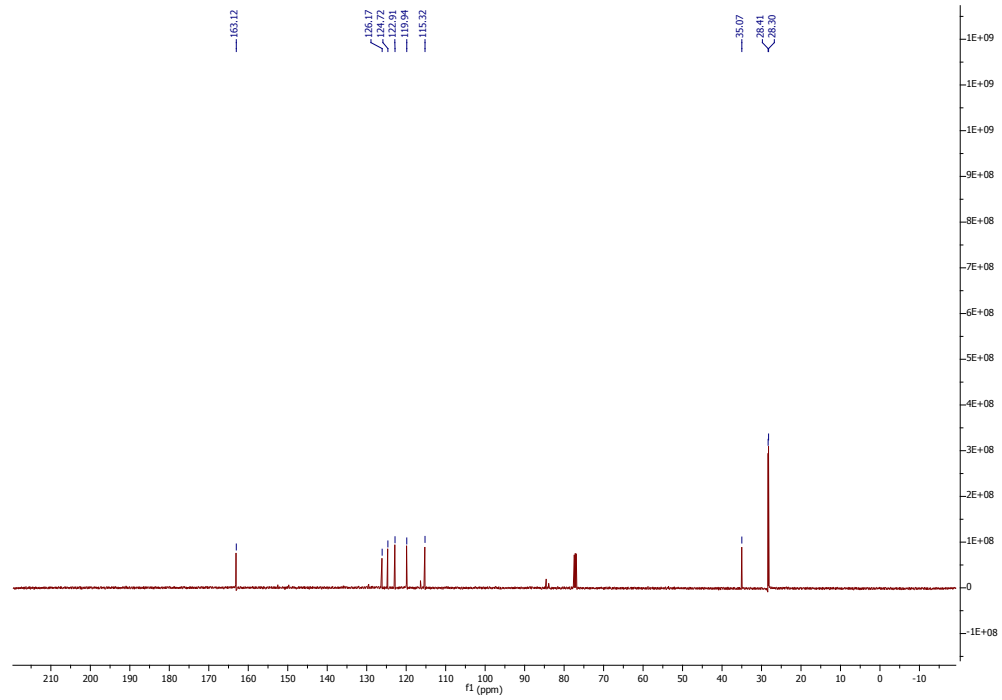


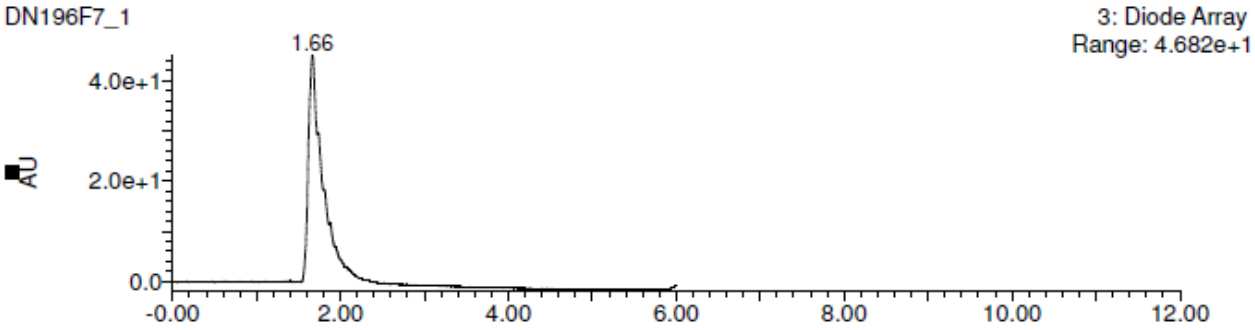


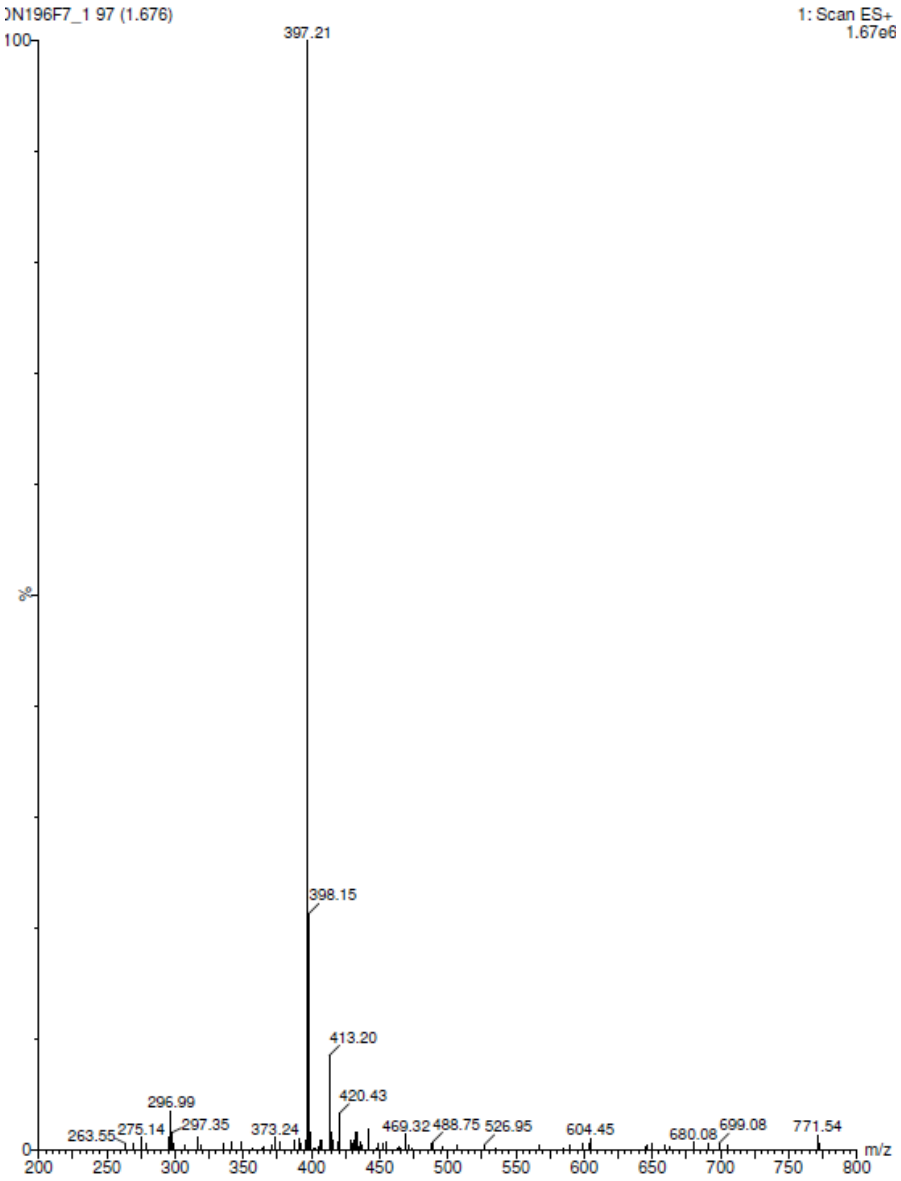


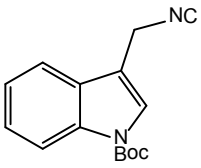


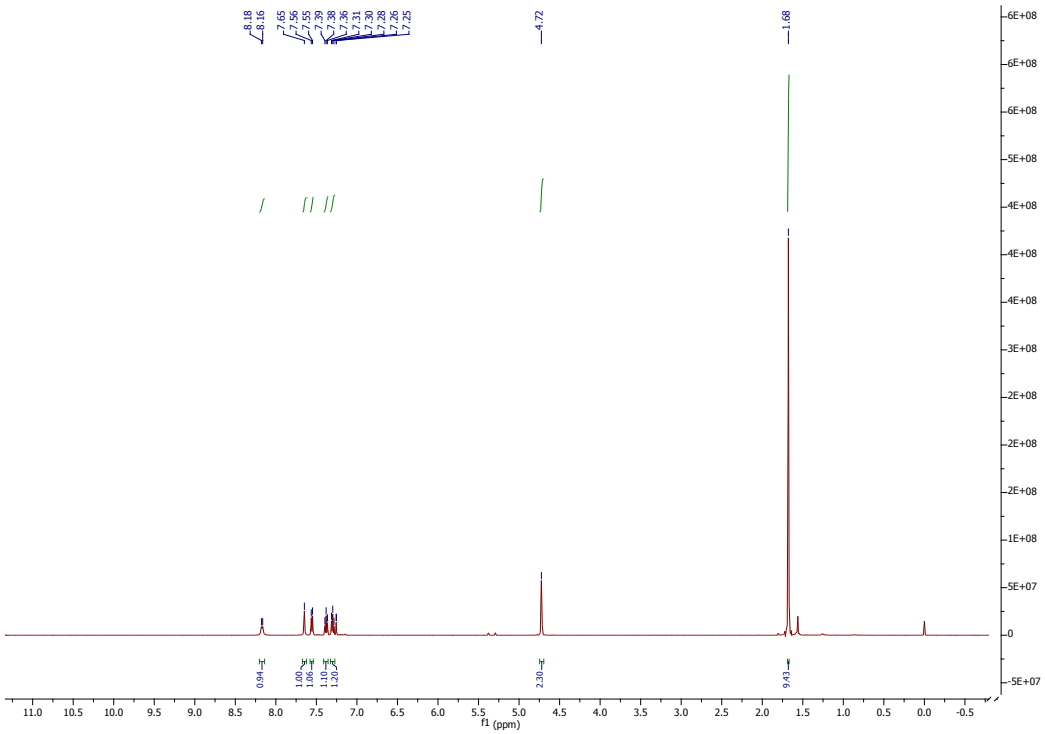


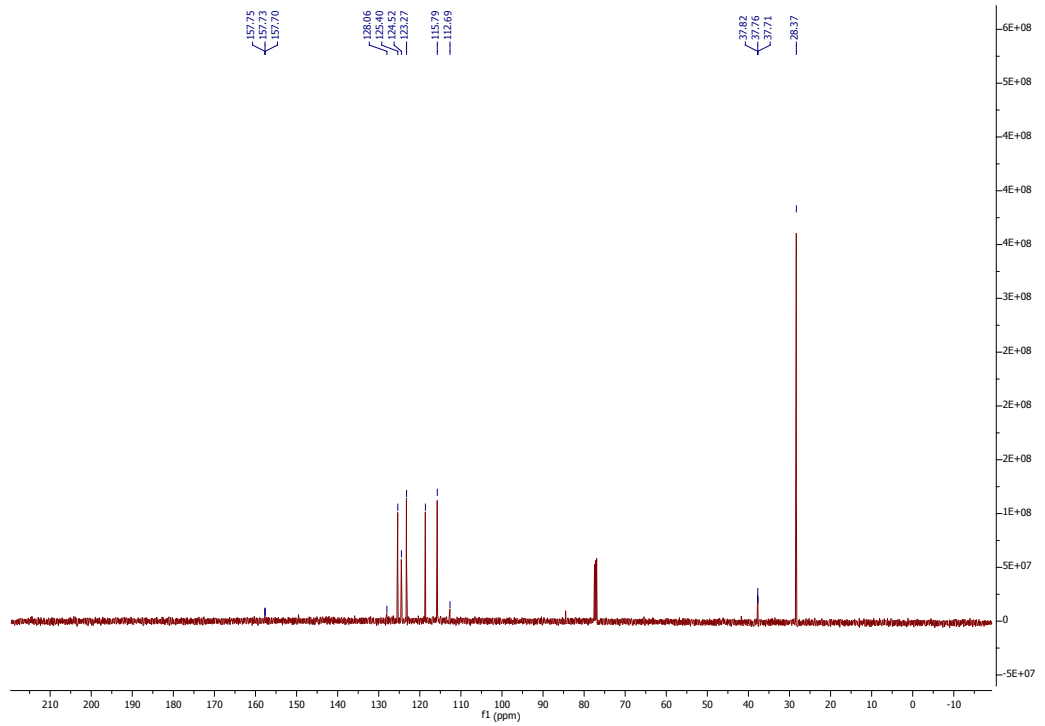


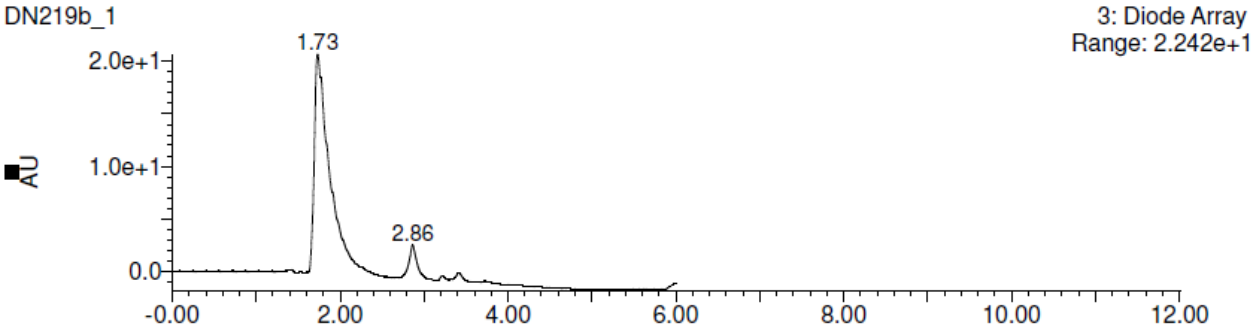


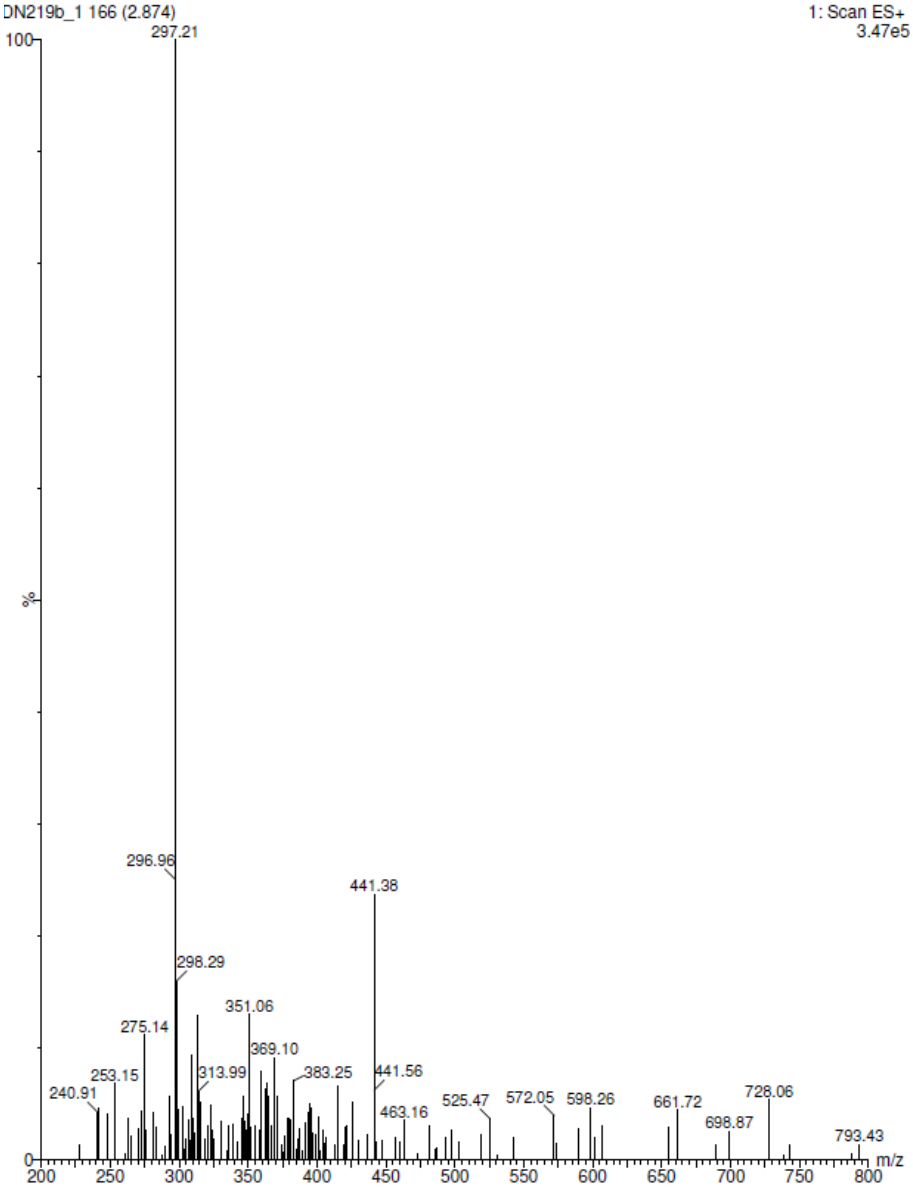


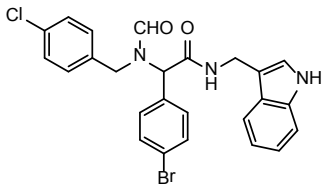


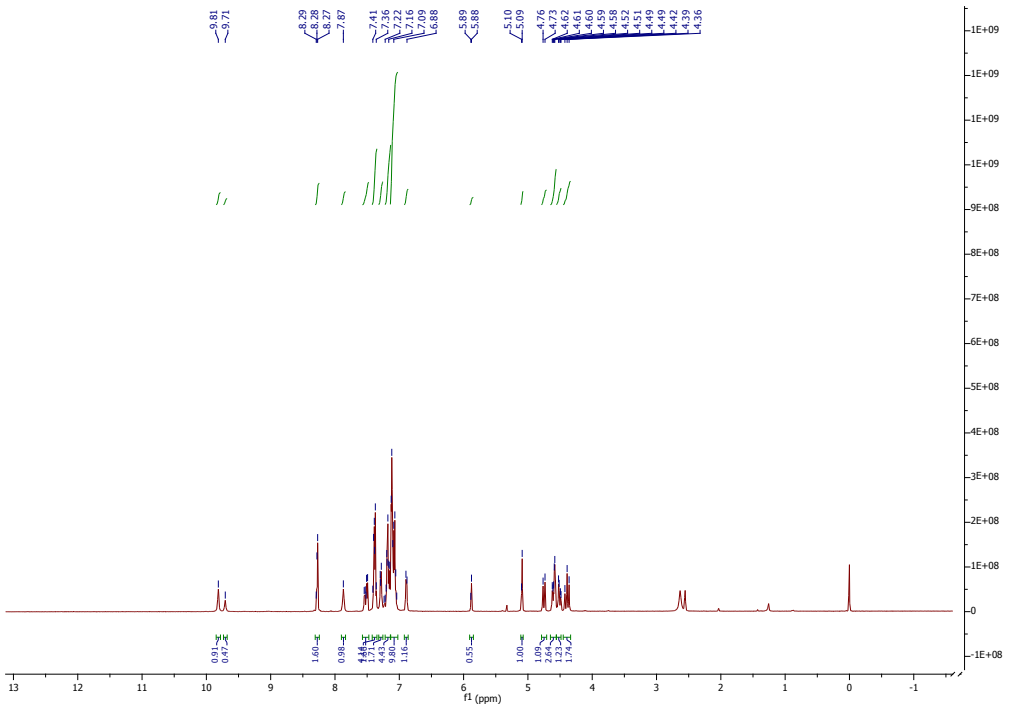


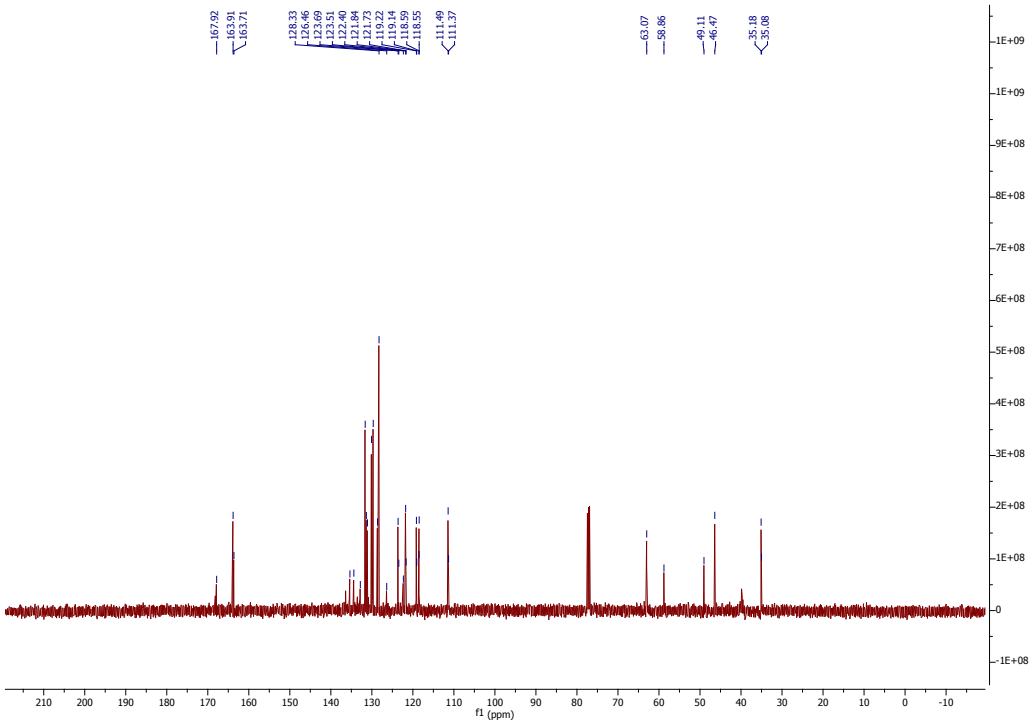


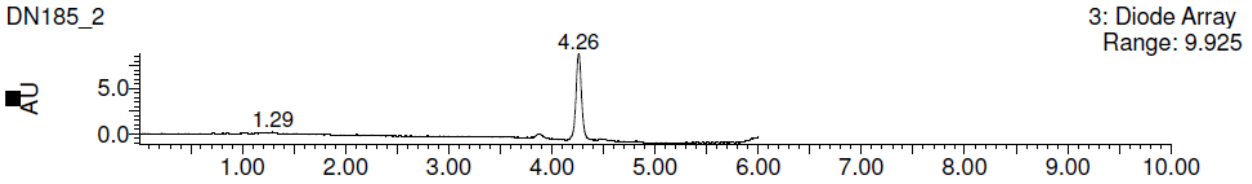


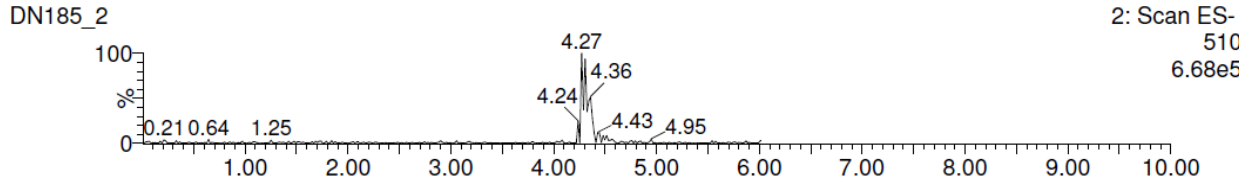


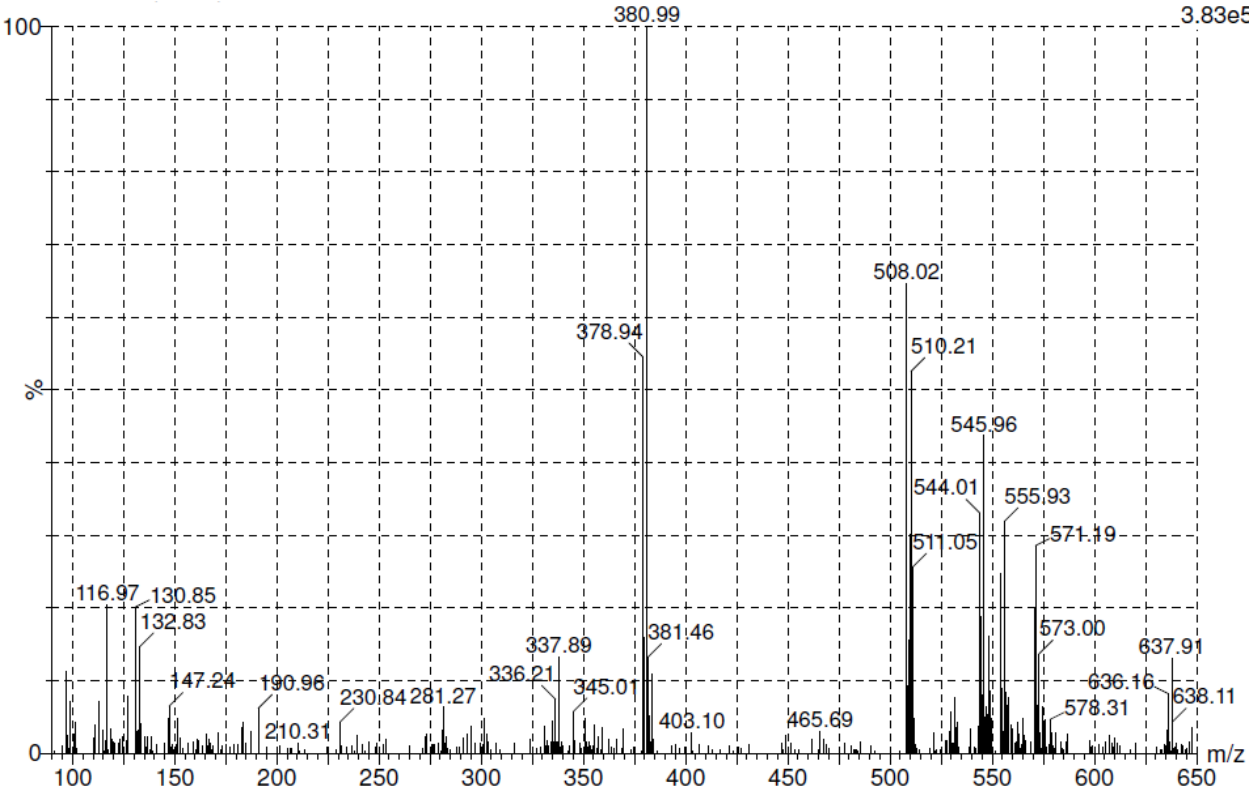


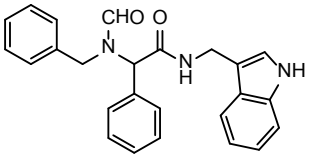


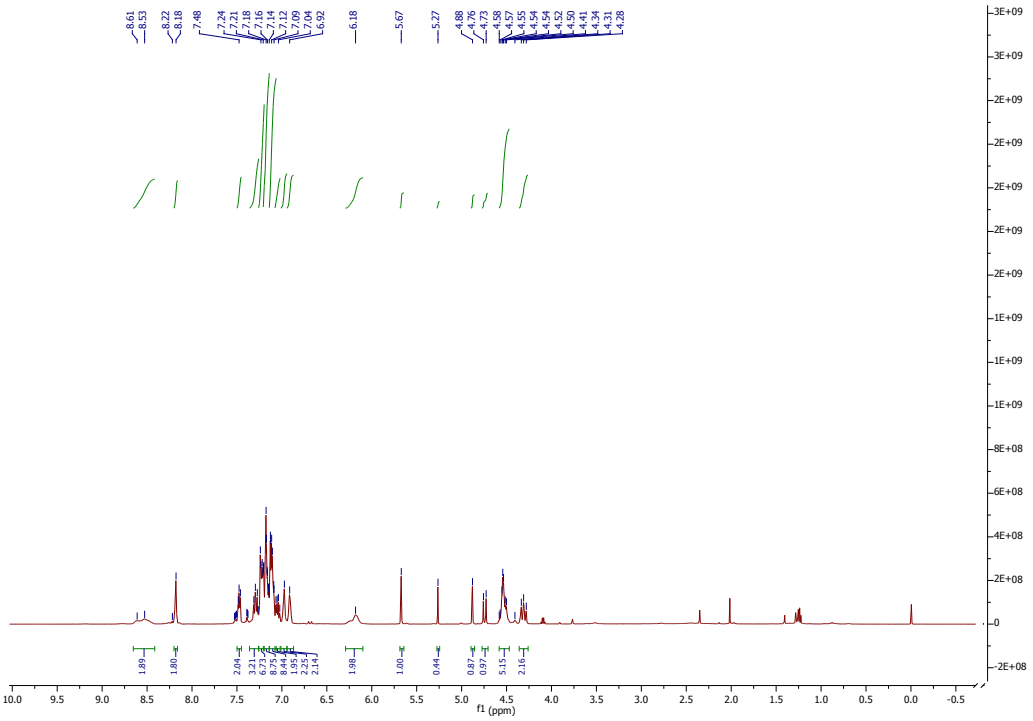


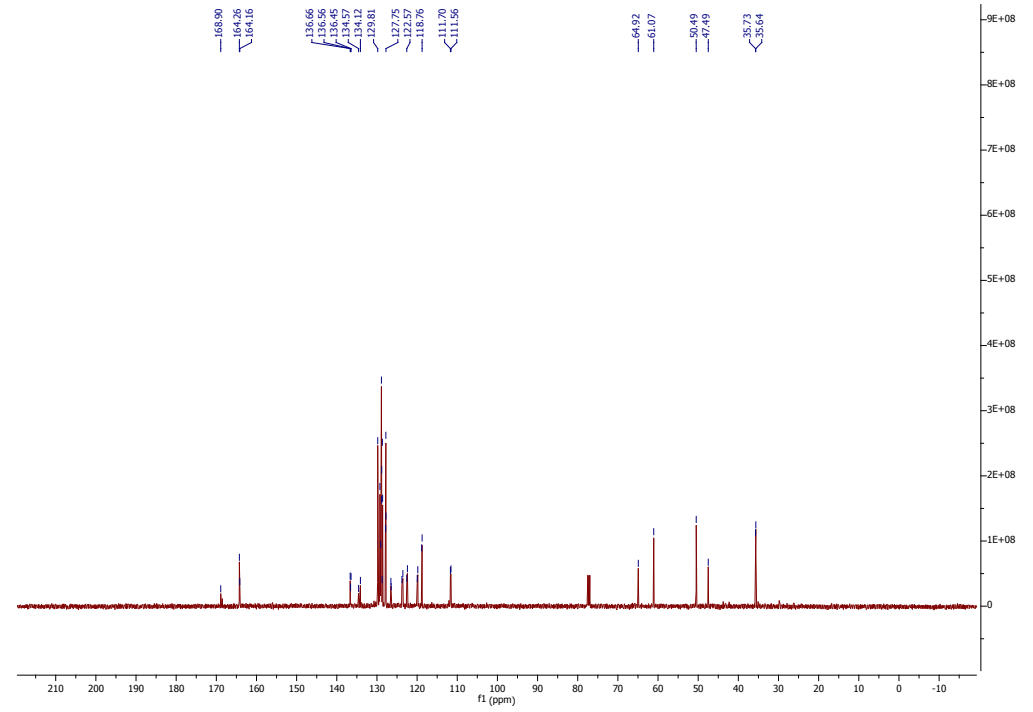


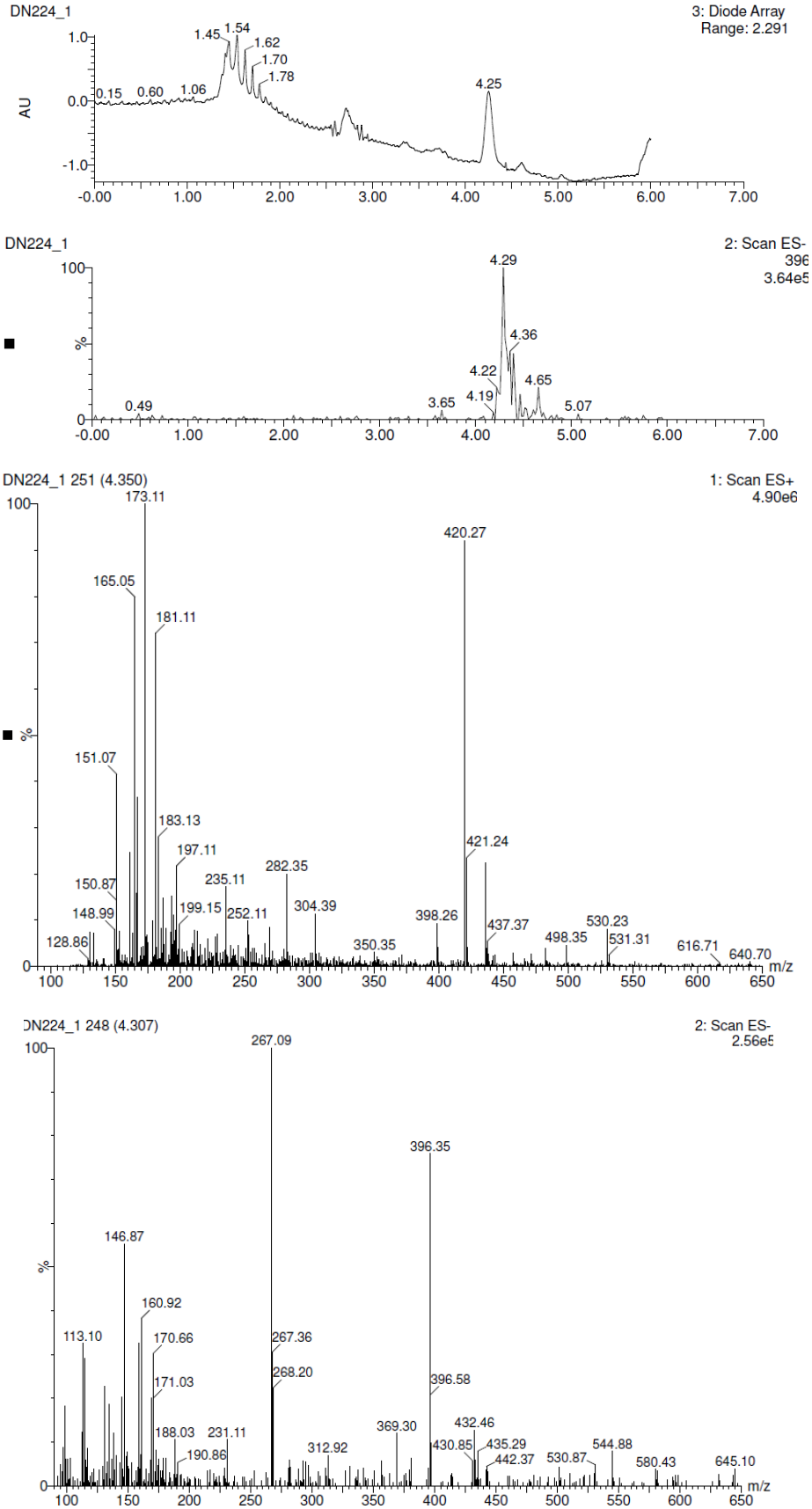


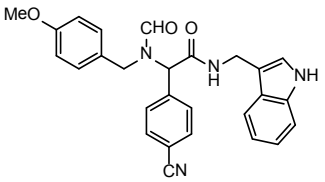


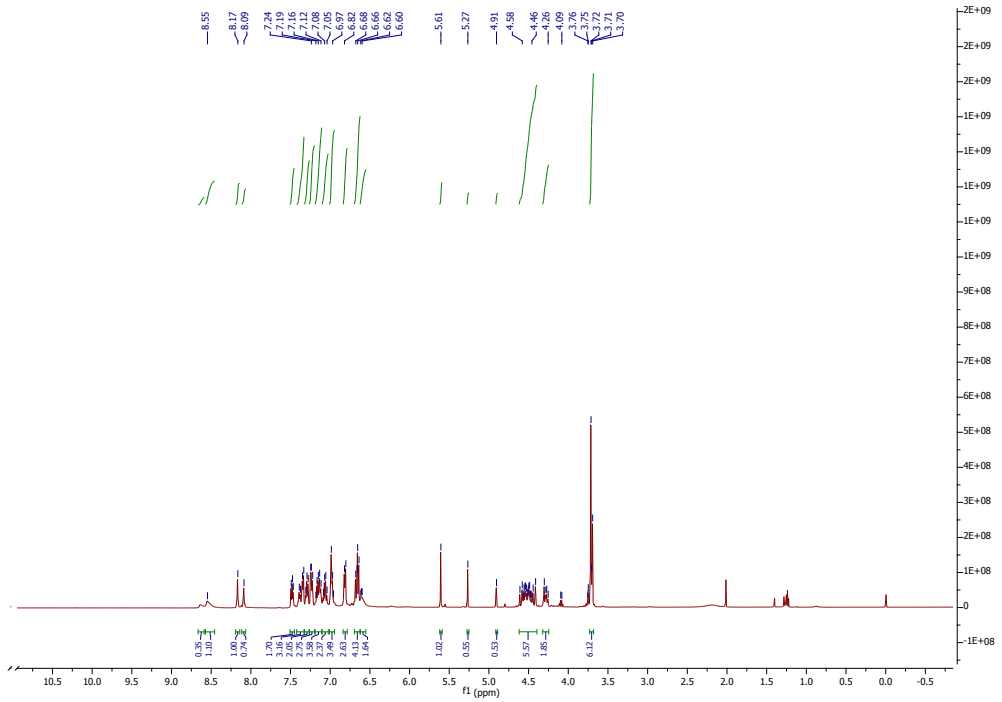


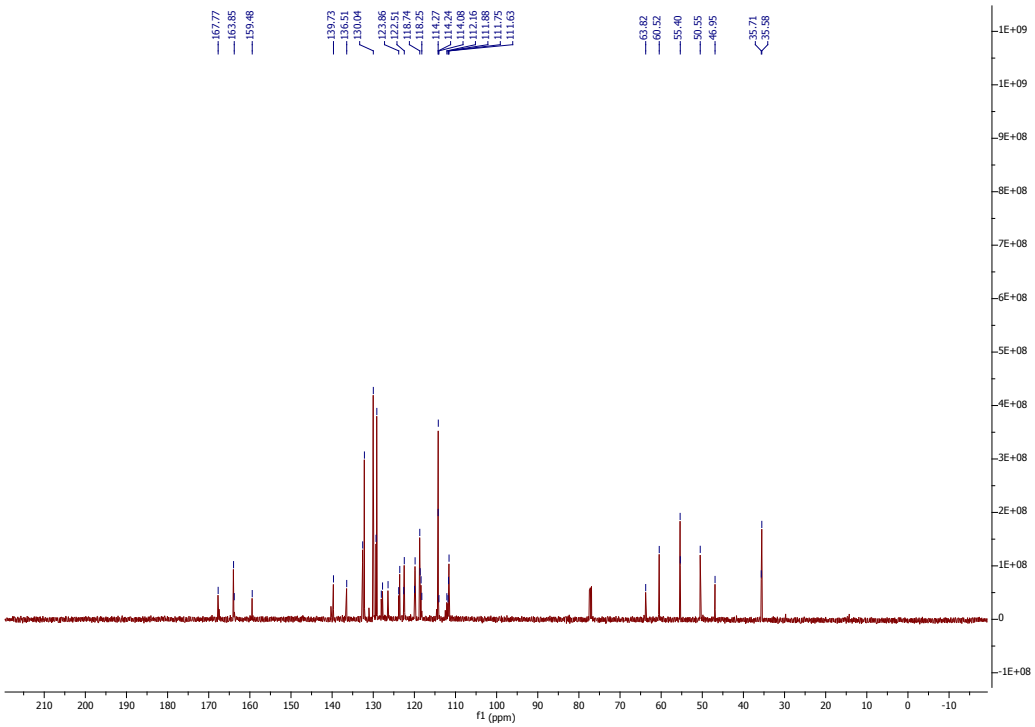


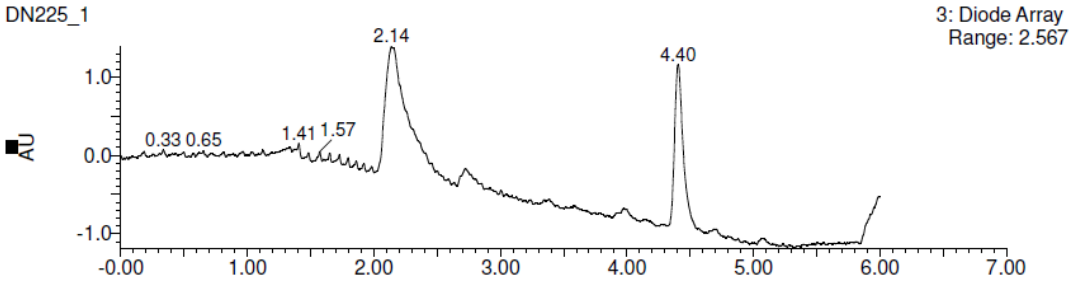


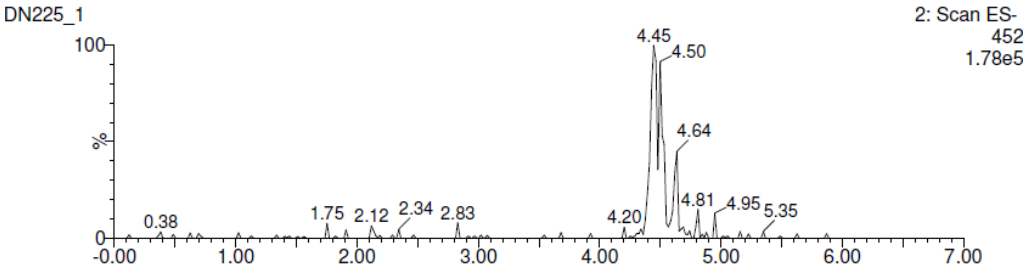


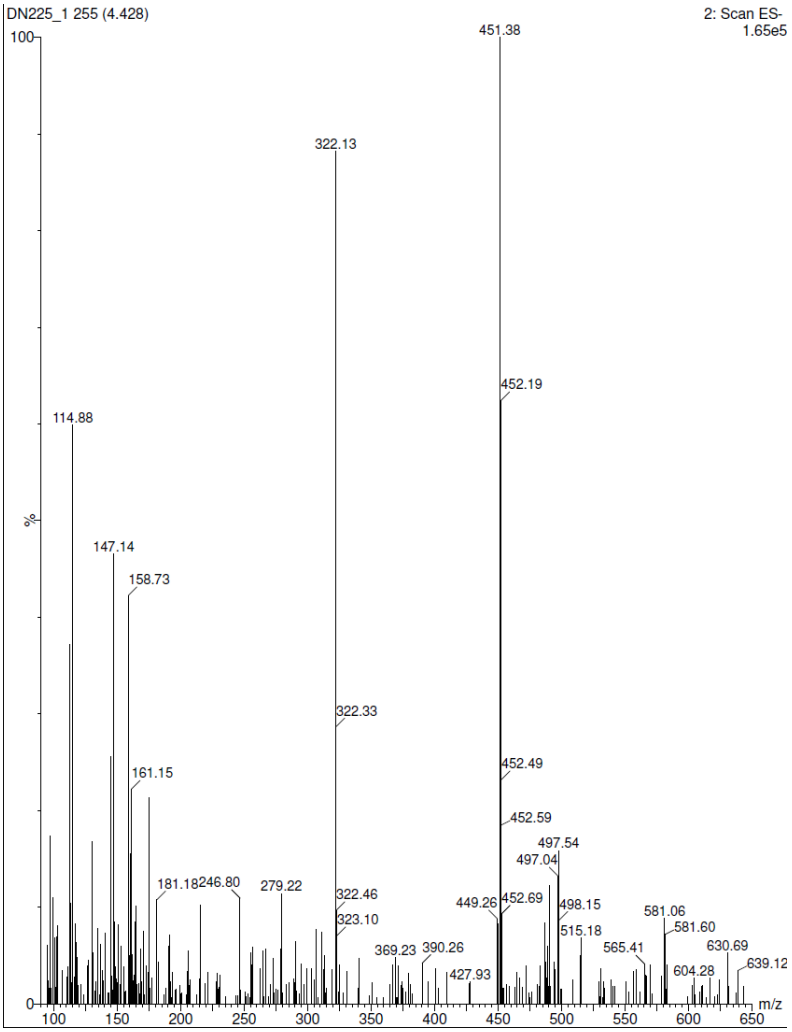


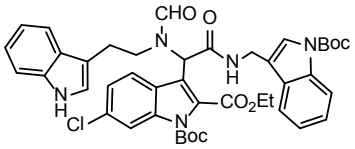








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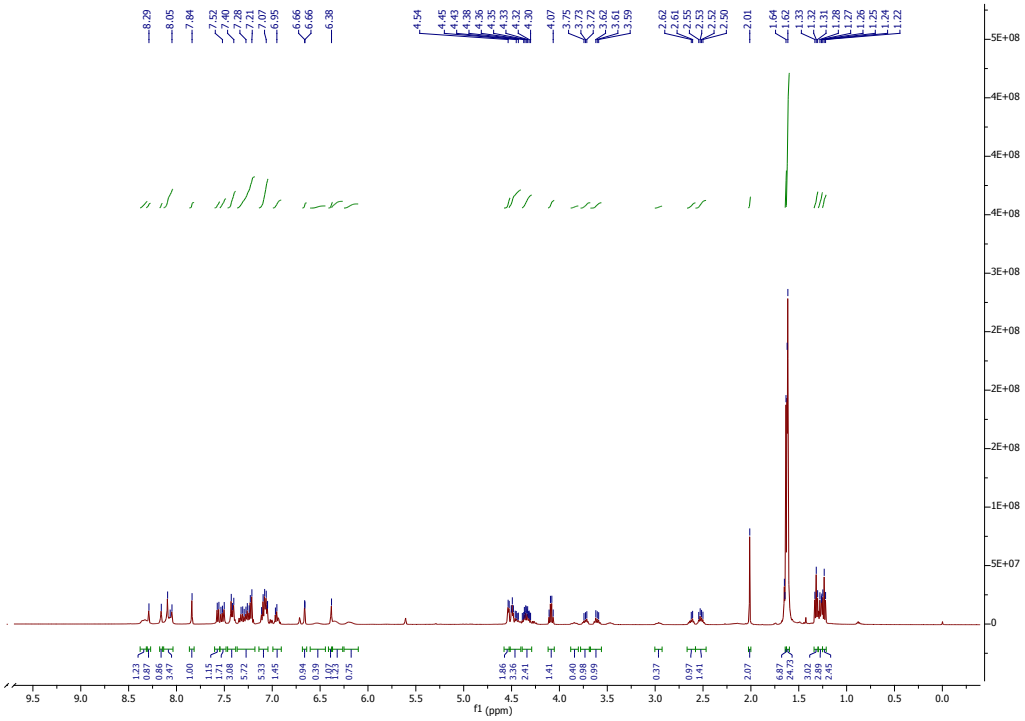
Boc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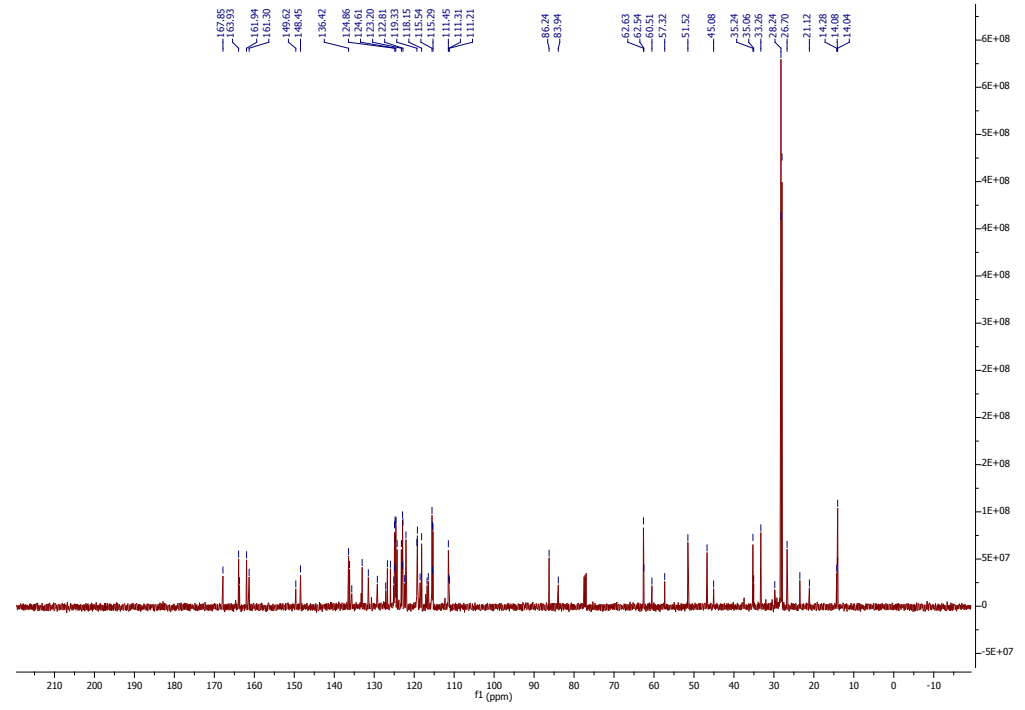
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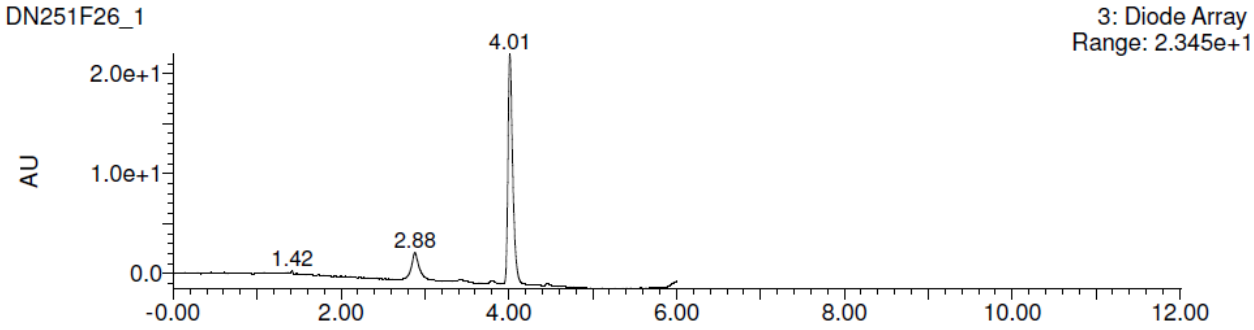

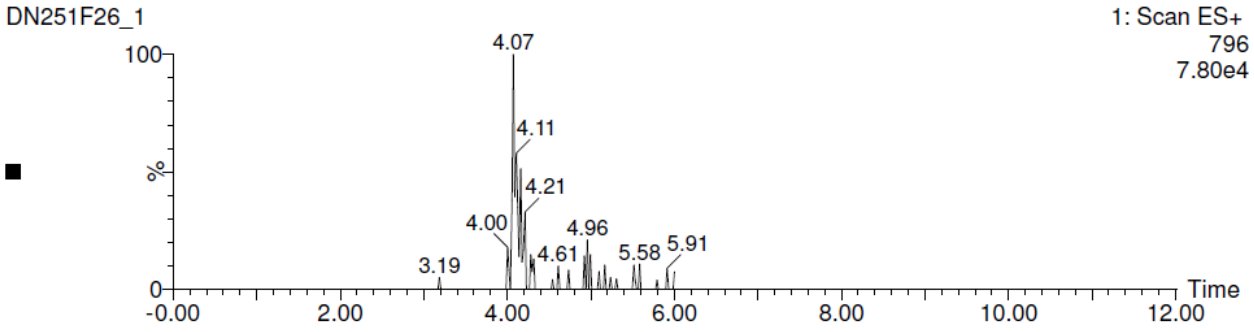

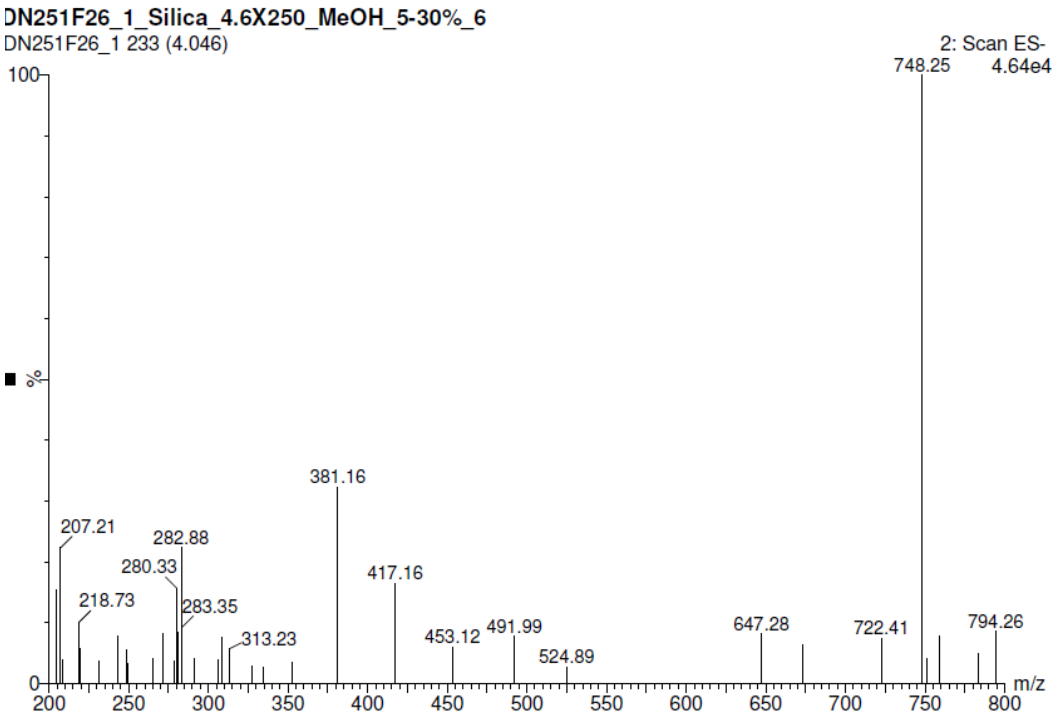

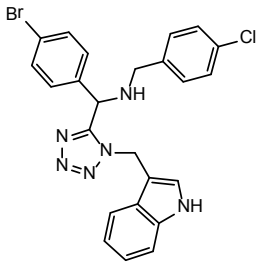
Br
Cl
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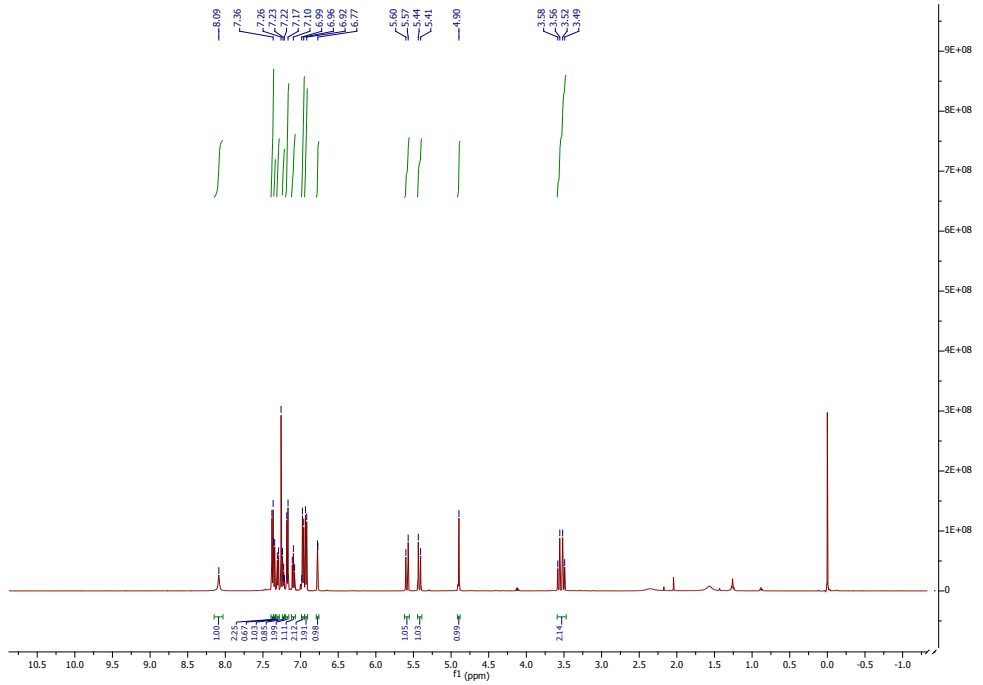
N
N
N
NH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3.52
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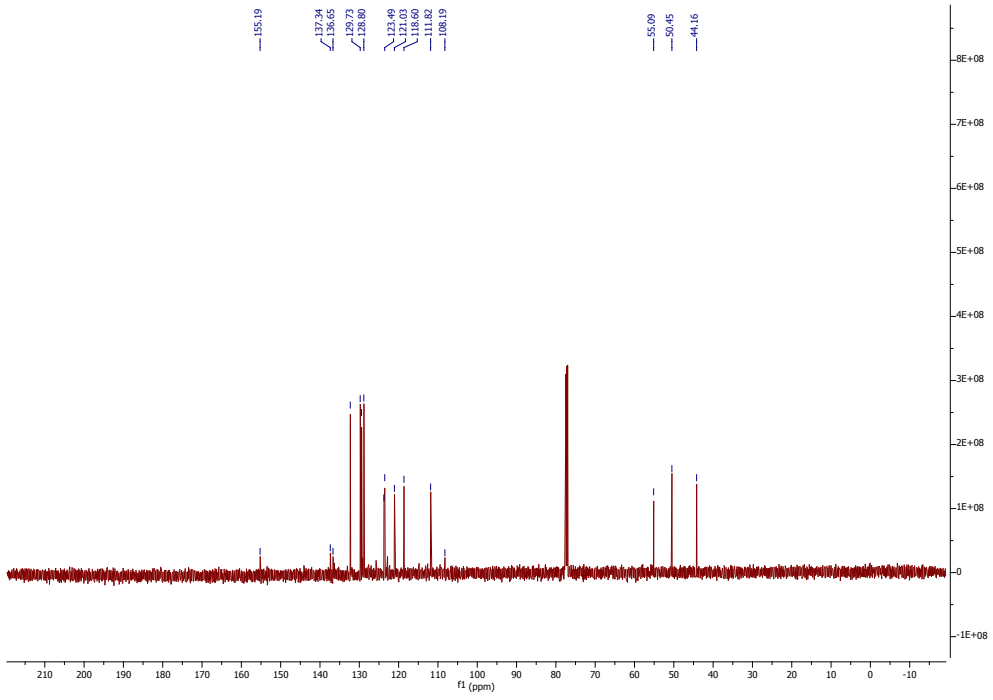
f1 (ppm)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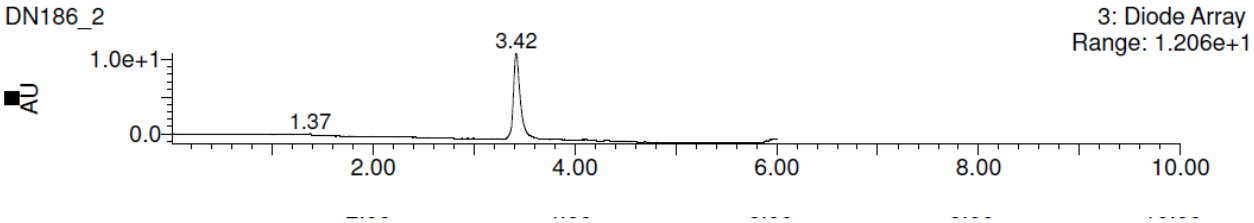
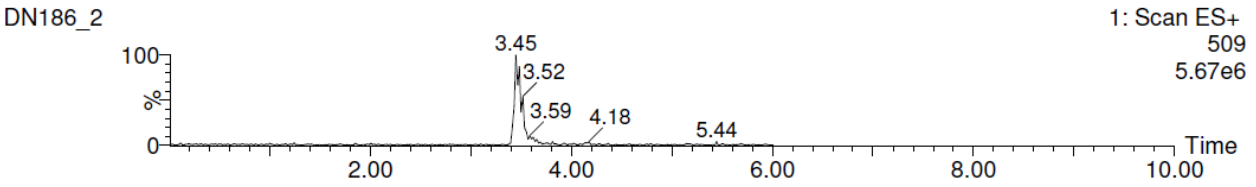
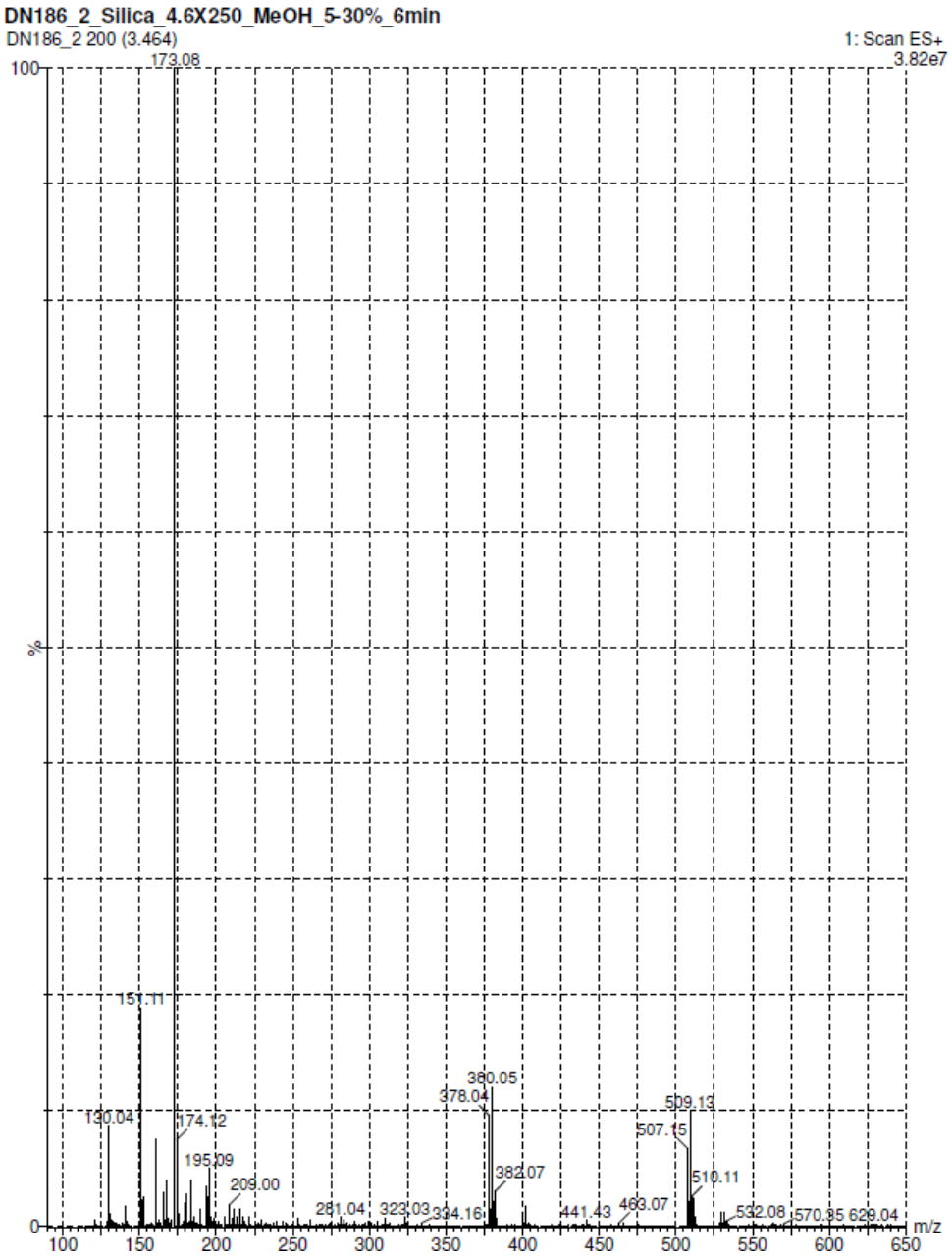
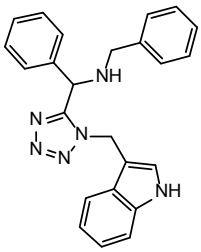
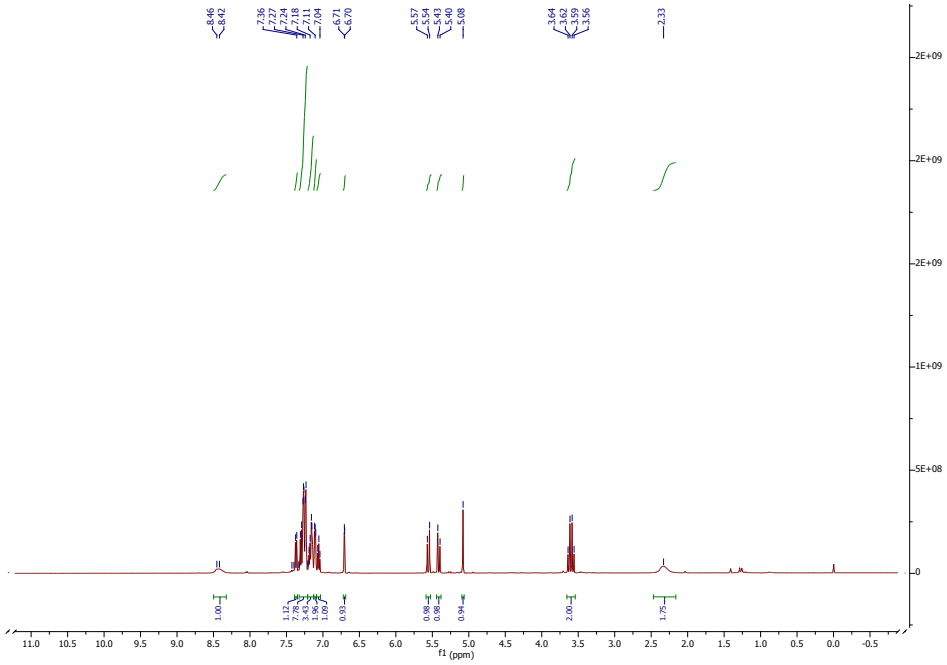
f1 (ppm)

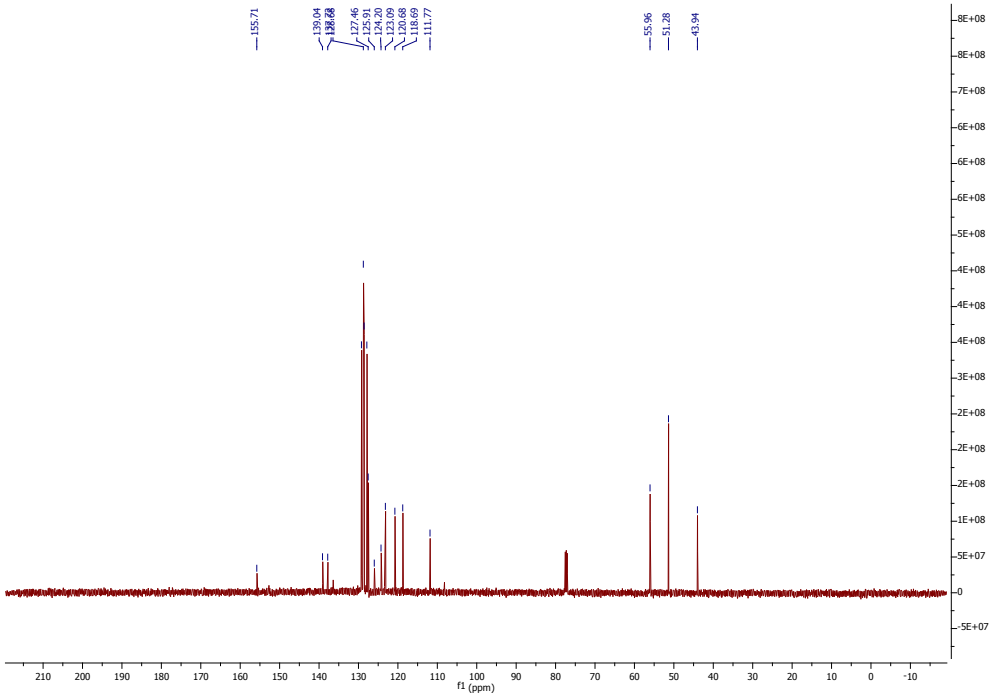


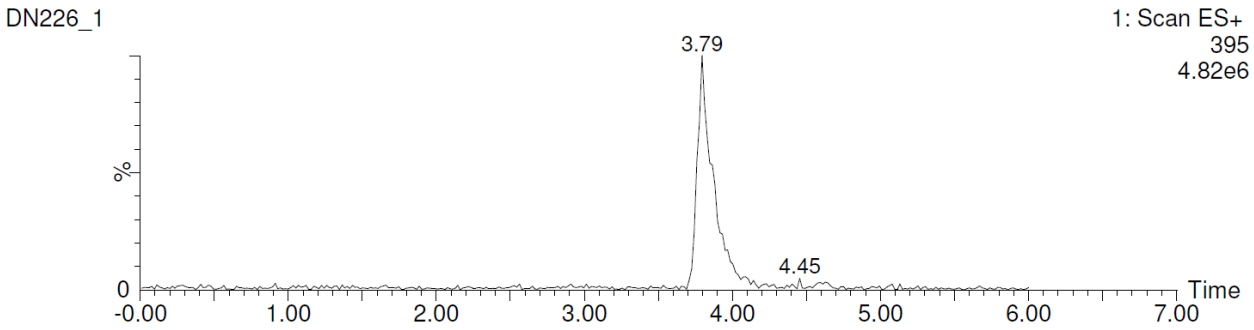








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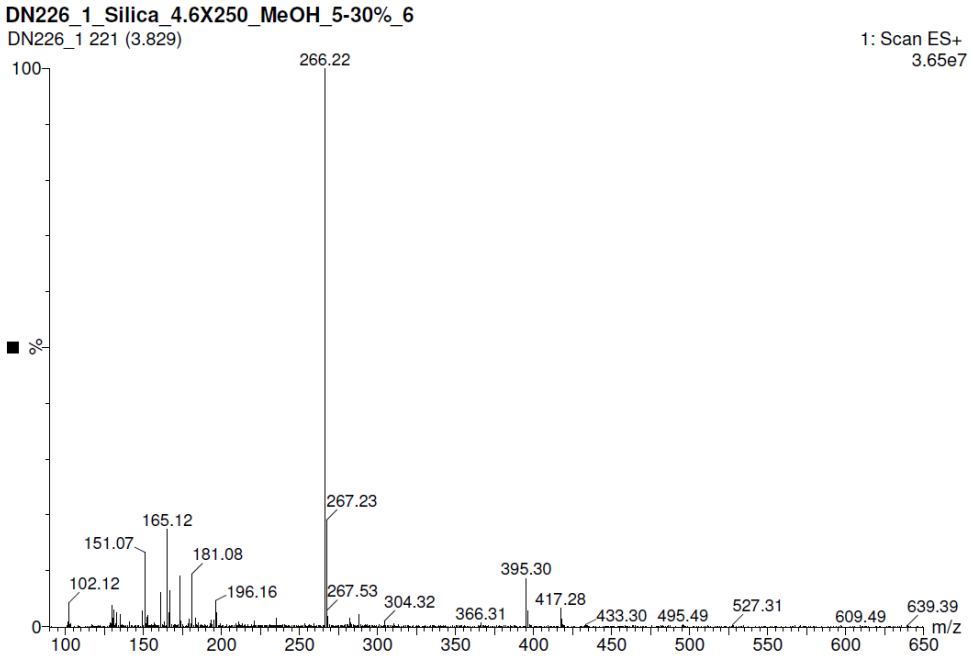
395
4.82e6
3.79
4.45
%
0
Time
-0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00


DN226_1_Silica_4.6X250_MeOH_5-30%_6
DN226_1 221 (3.829)
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3.65e7
100
%
0
266.22
267.23
165.12
151.07
181.08
102.12
196.16
267.53
304.32
366.31
395.30
417.28
433.30
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639.39
m/z
100
150
200
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300
350
400
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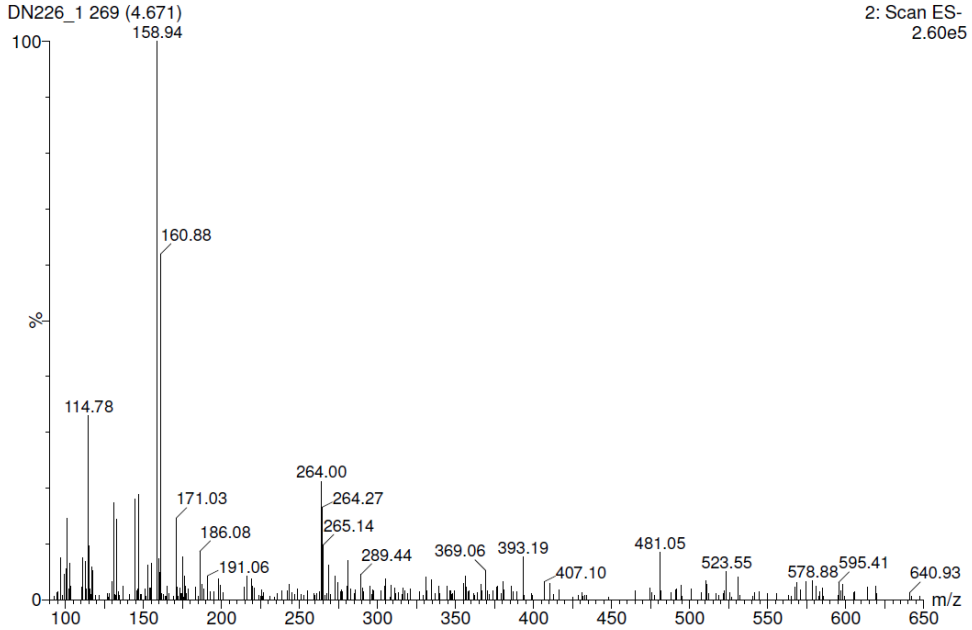
500
550
600
650


DN226_1 269 (4.671)
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%
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114.78
264.00
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265.14
186.08
289.44
191.06
369.06
393.19
407.10
481.05
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m/z
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300
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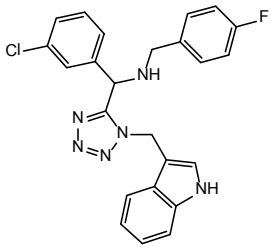
650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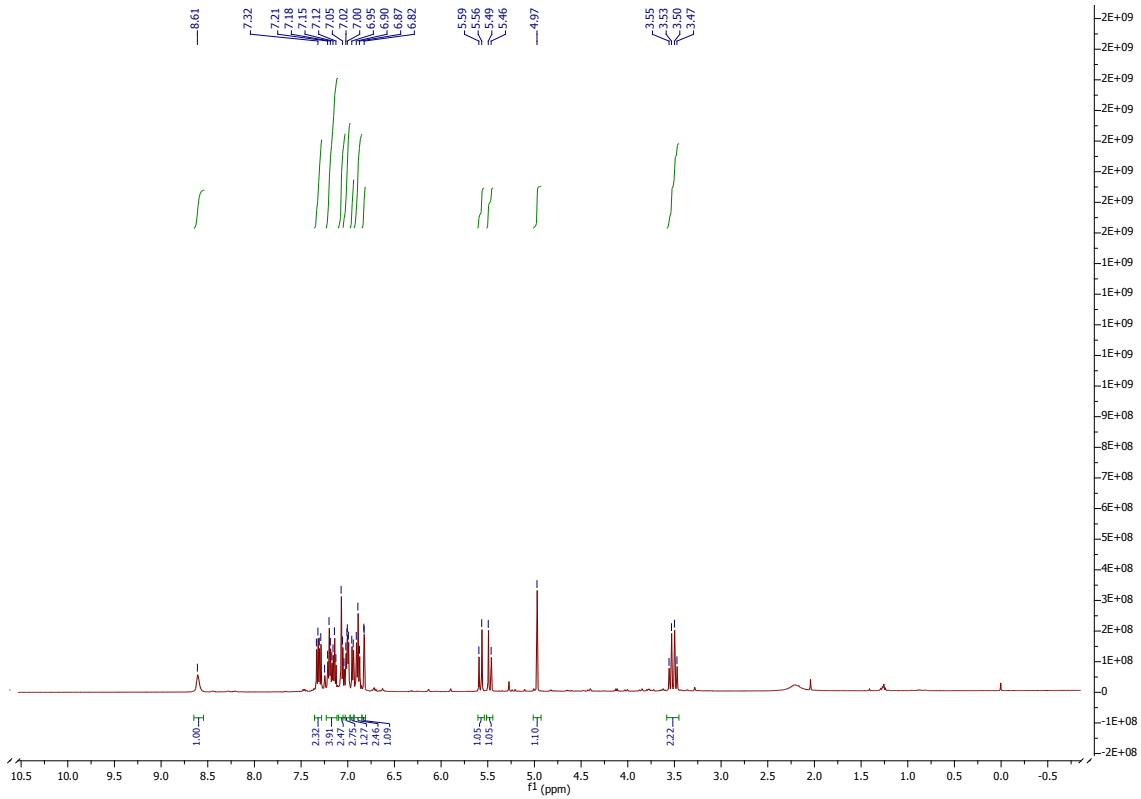
NH
F
N
N
N
N
NH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4.97
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3.53
3.50
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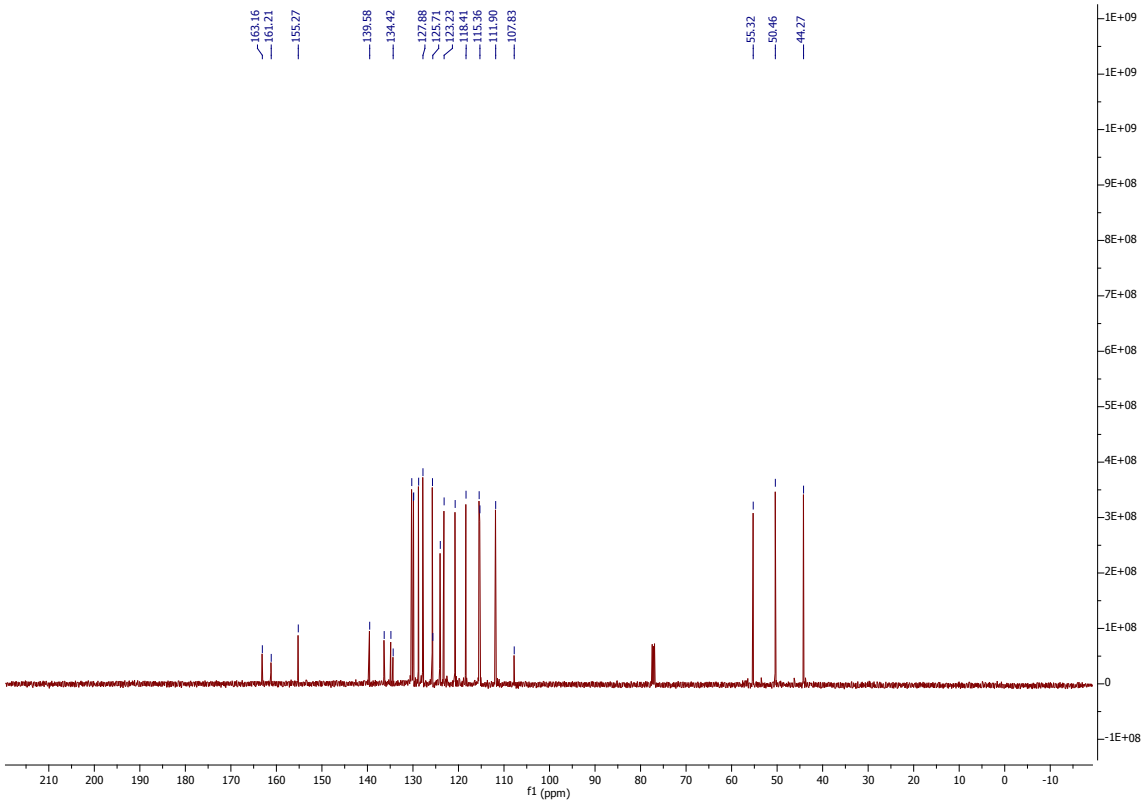
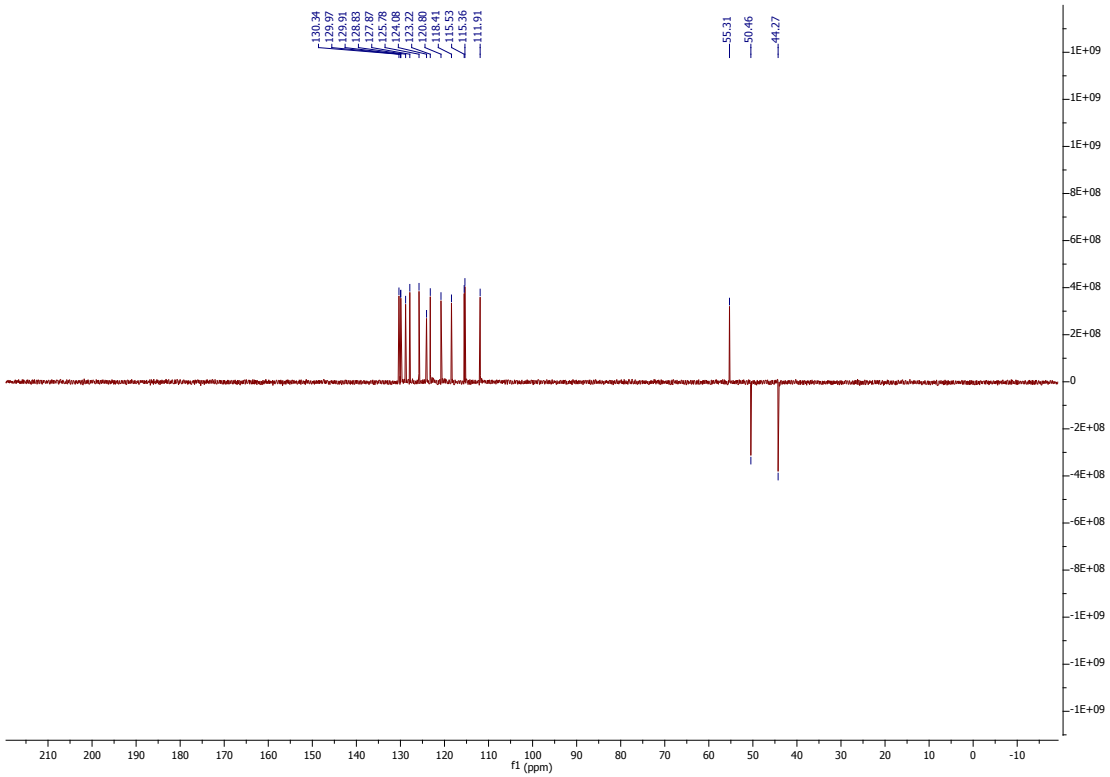
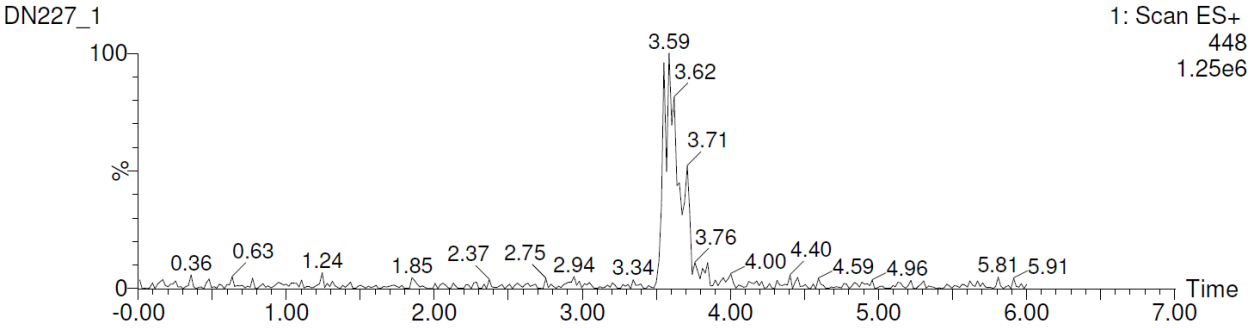
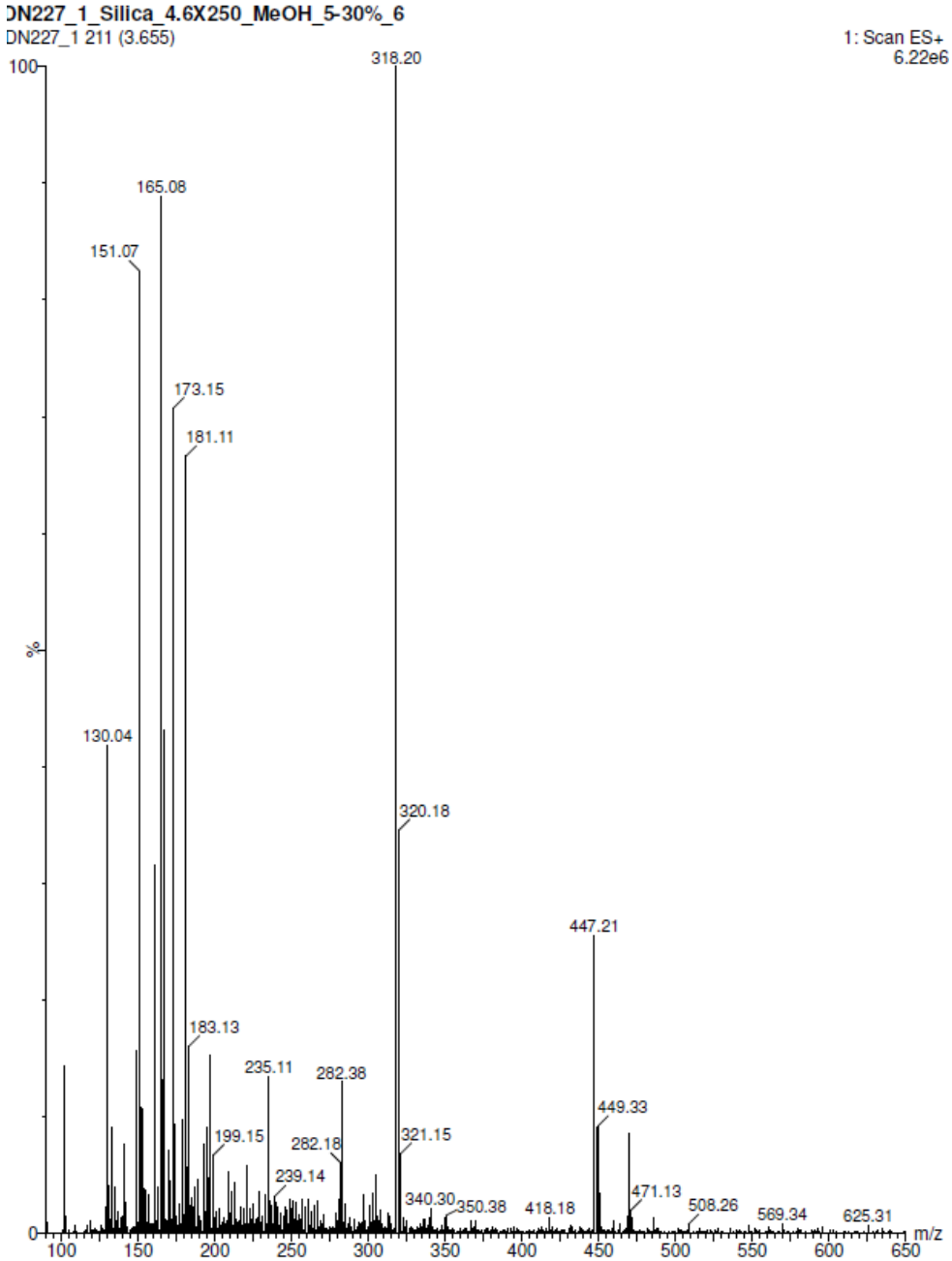
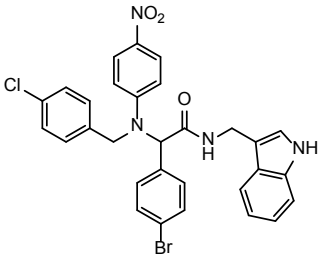
2.22
f1 (ppm)

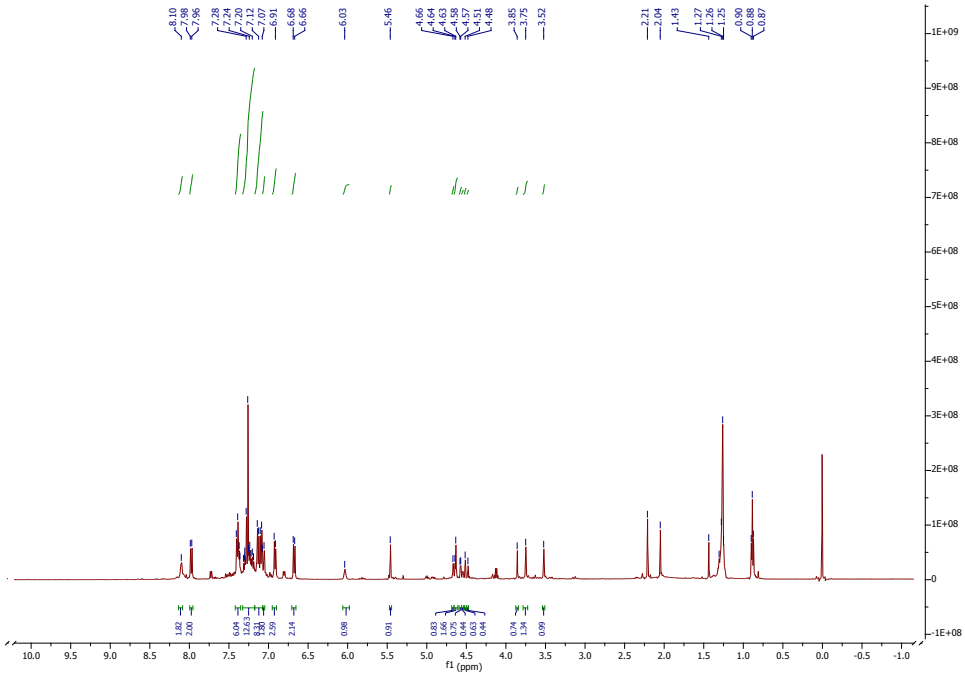


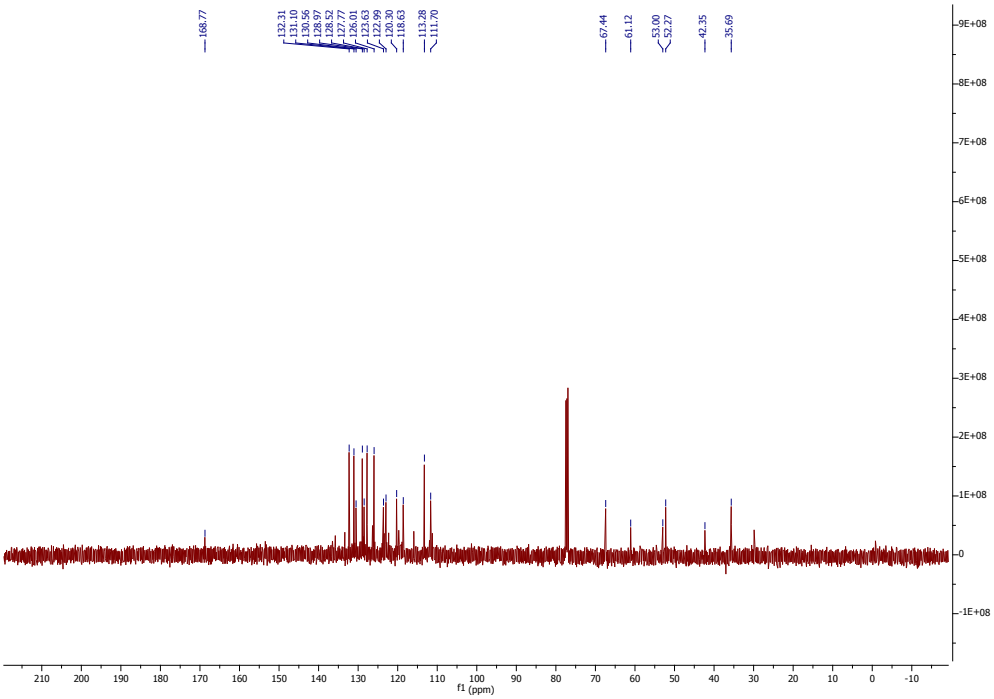


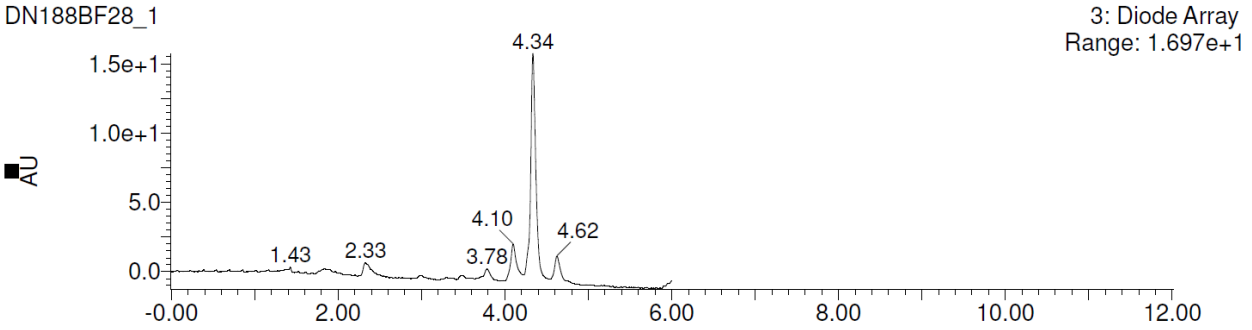


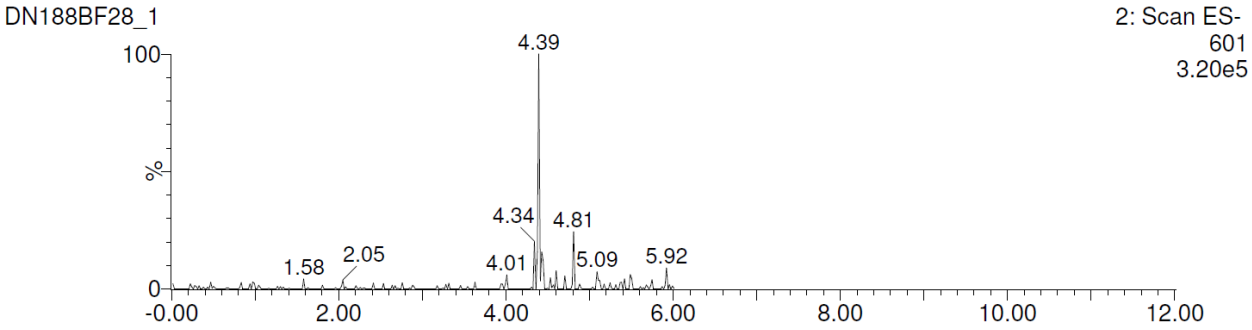


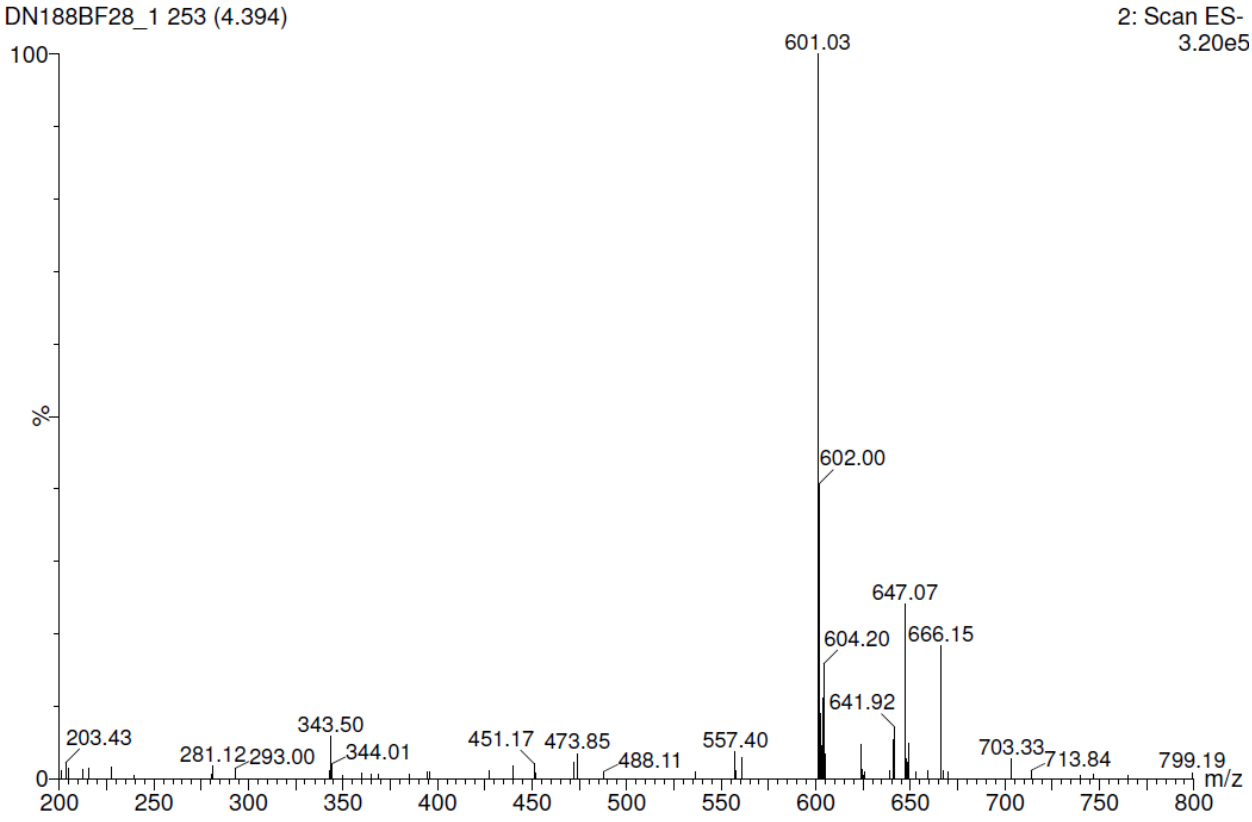


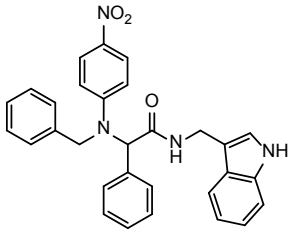


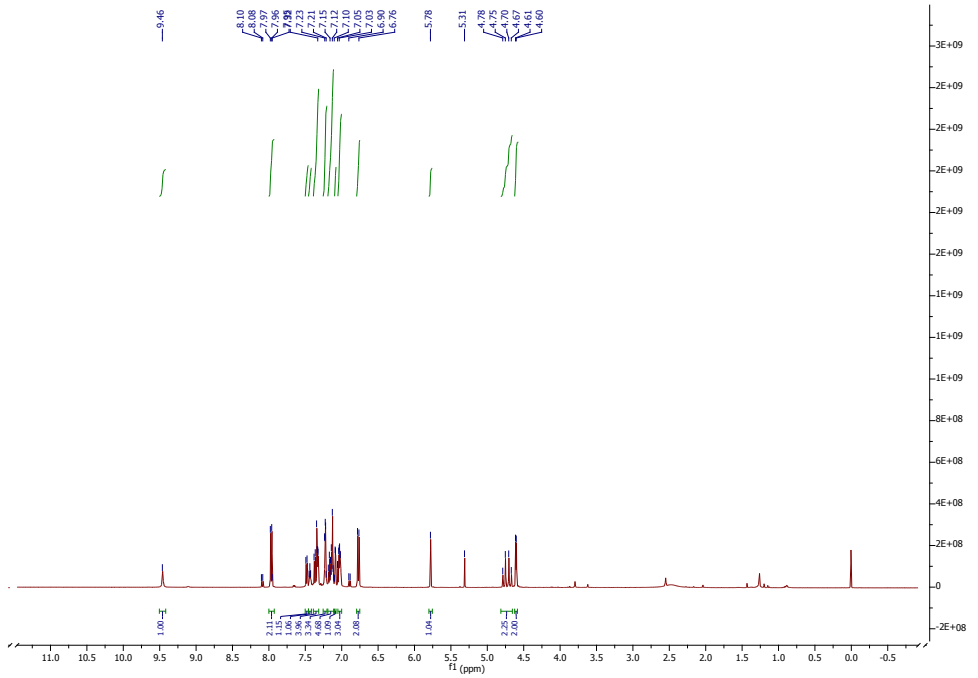


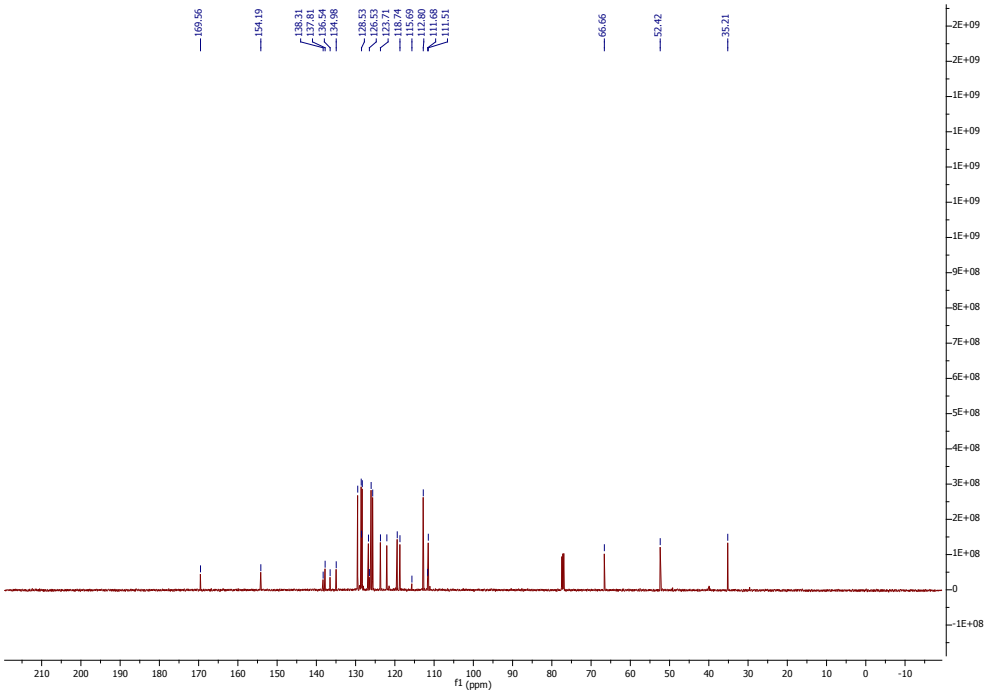


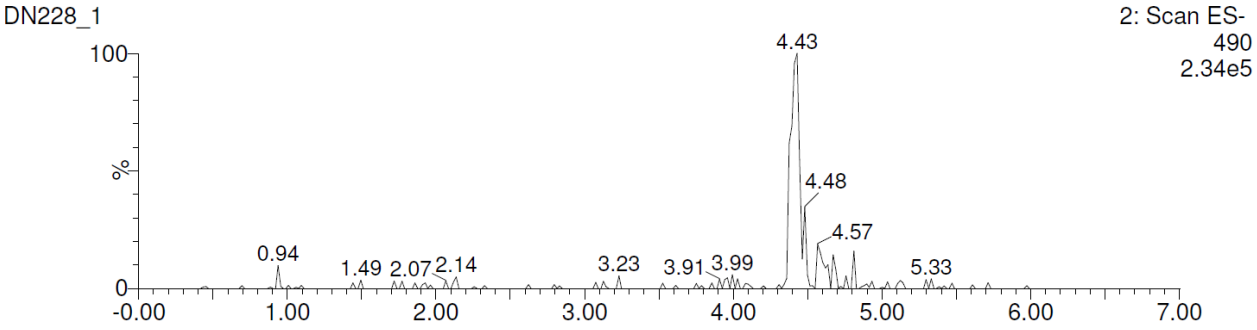


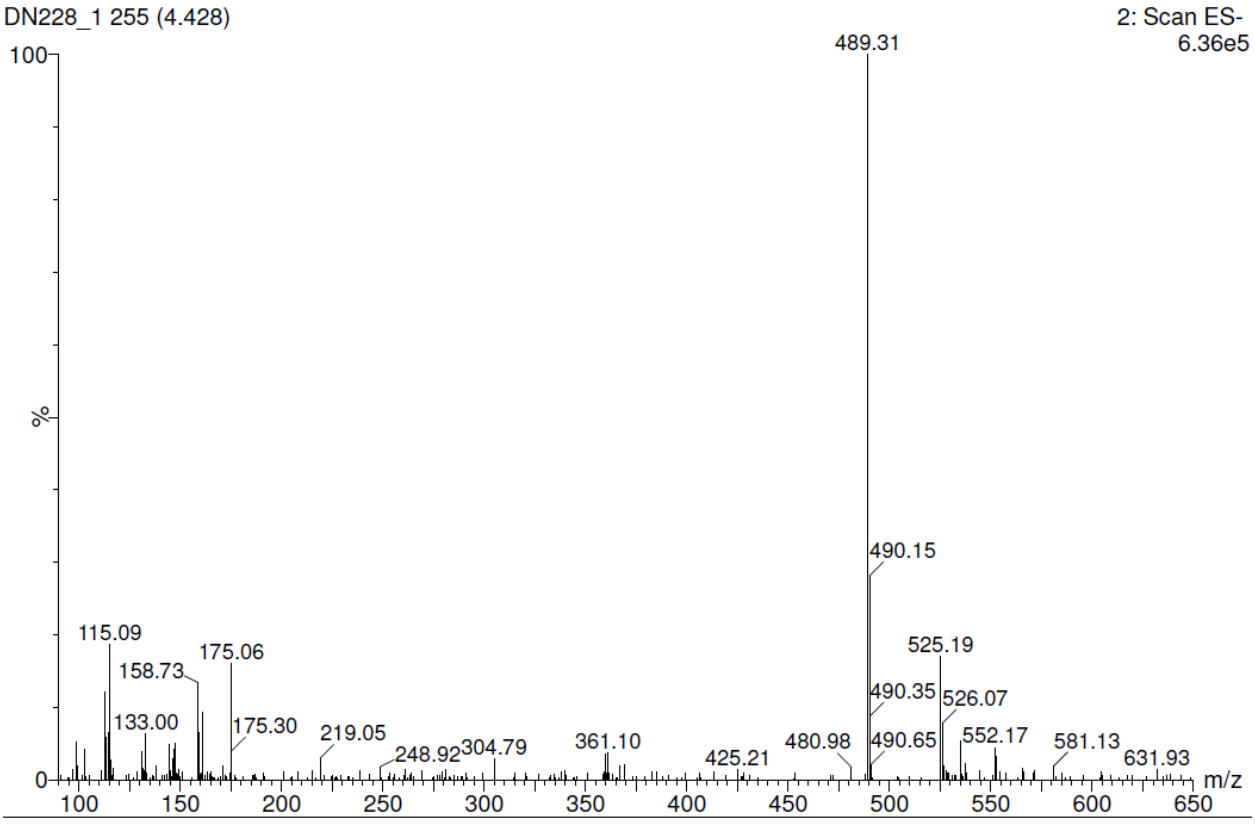


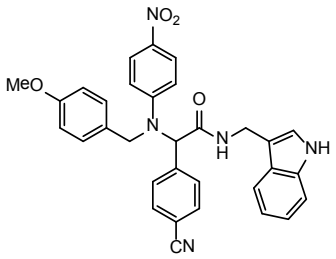


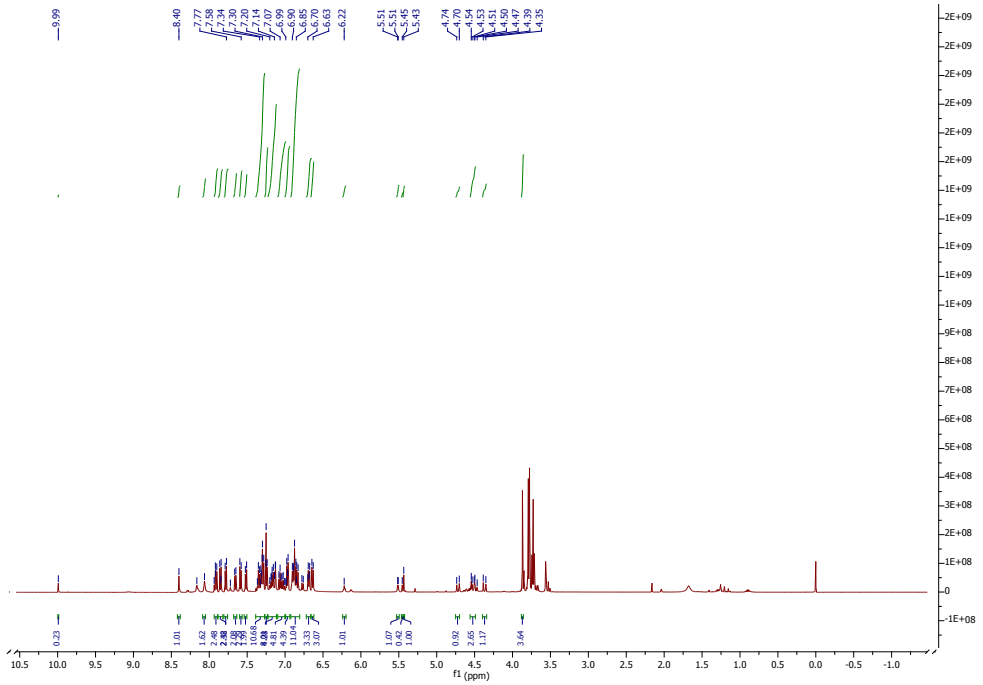


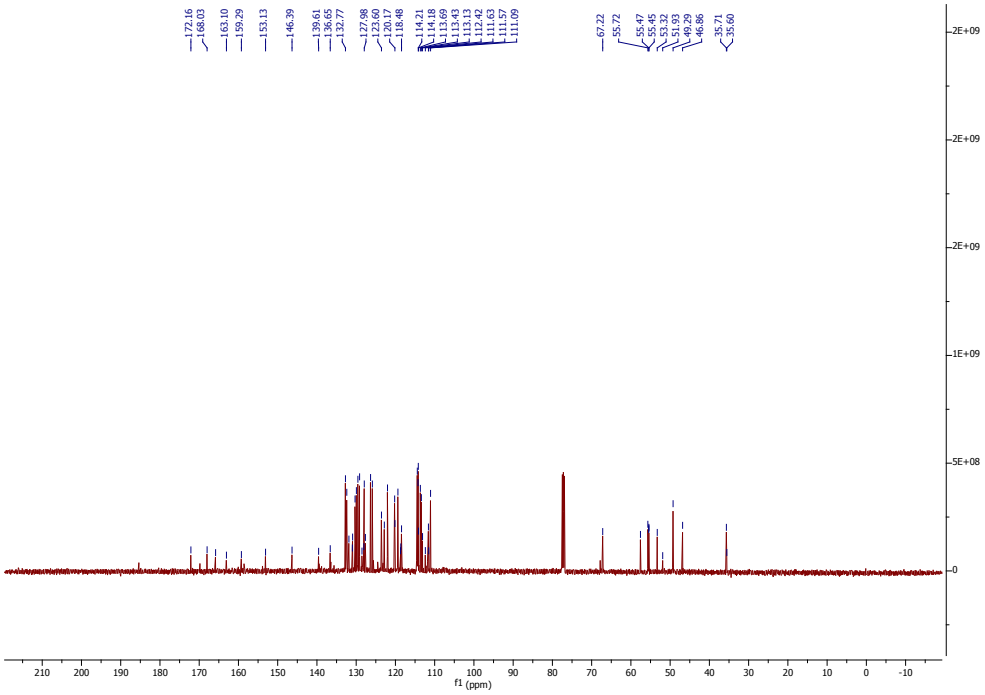


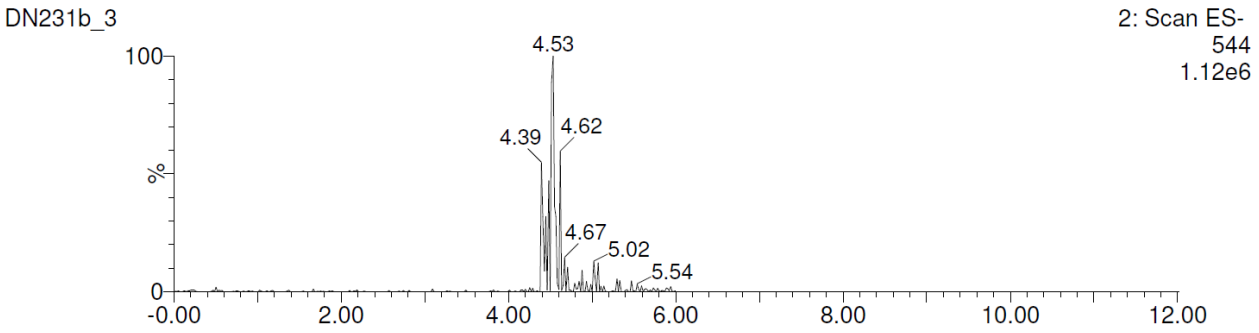


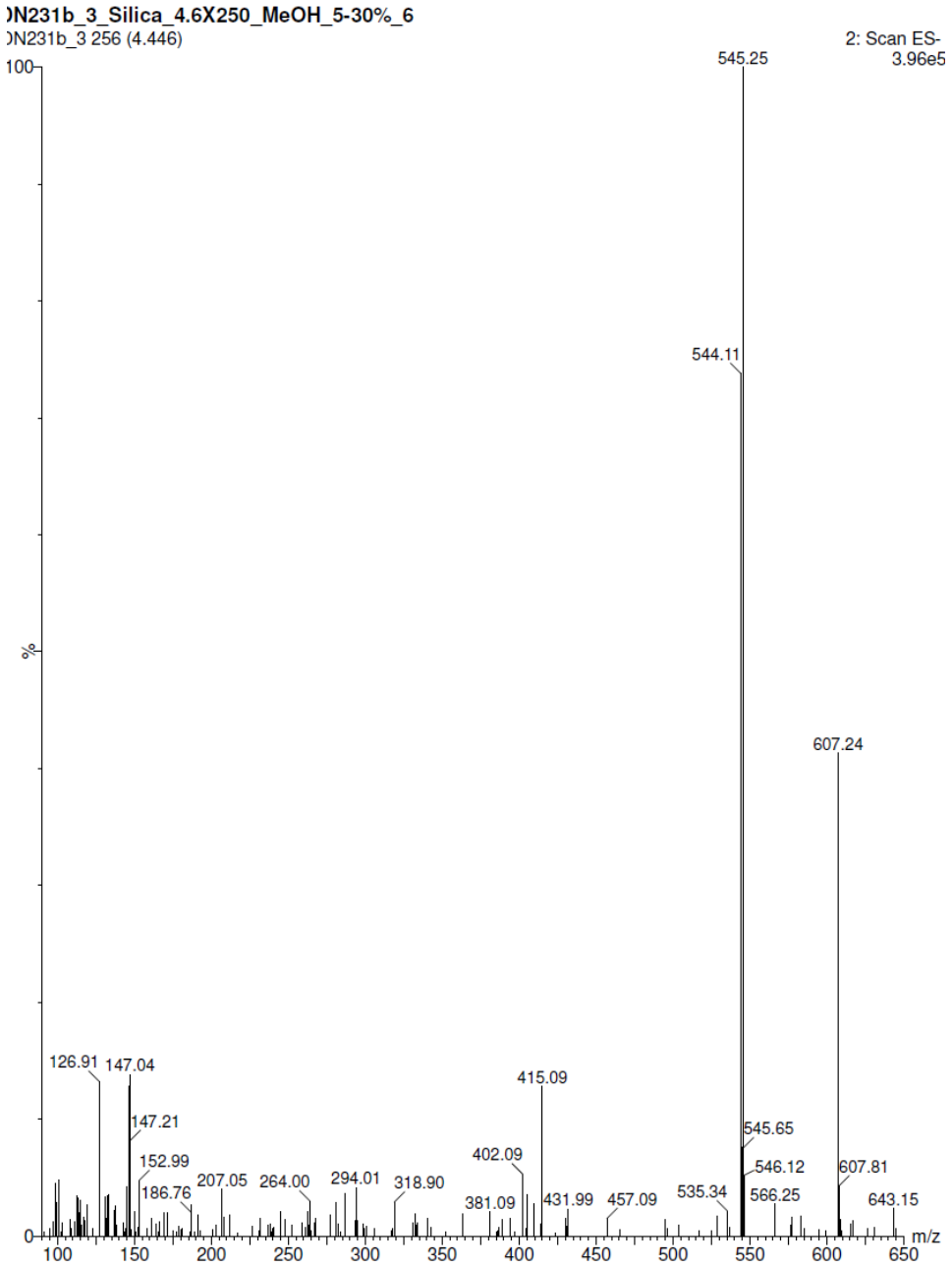


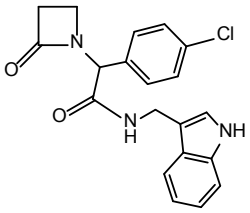

NO2
MeO
O
N
N
H
NH
CN

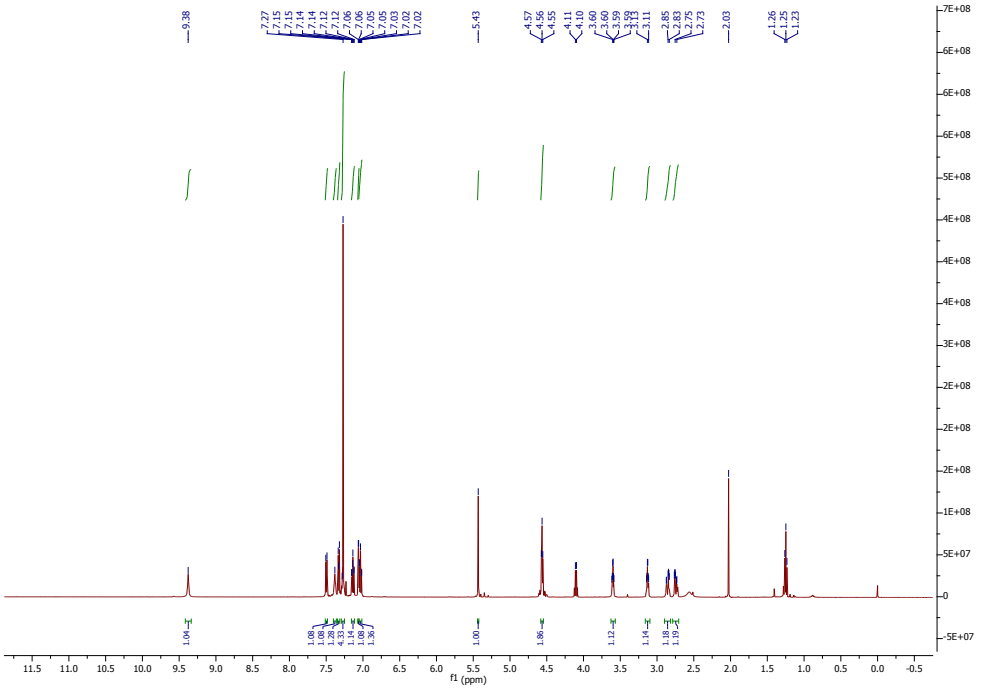

9.99
8.40
7.77
7.58
7.34
7.30
7.20
7.14
7.07
7.00
6.99
6.90
6.85
6.70
6.63
6.22
5.51
5.51
5.45
5.43
4.74
4.70
4.54
4.53
4.51
4.50
4.47
4.39
4.35
f1 (ppm)

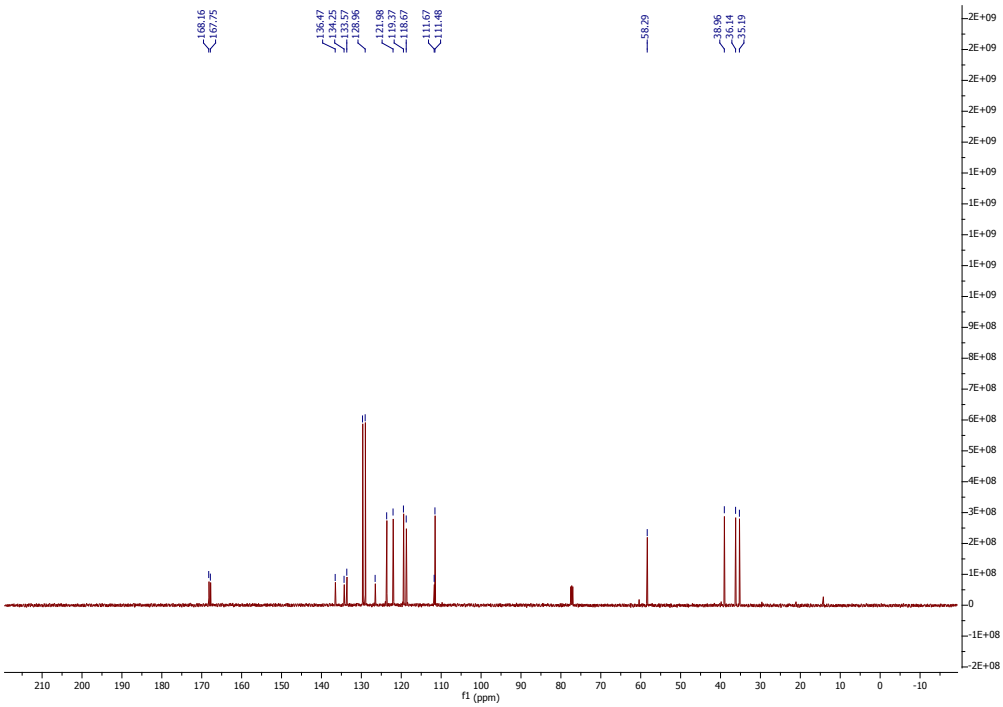

172.16
168.03
163.10
159.29
153.13
146.39
139.61
136.65
132.77
127.98
123.60
120.17
118.48
114.21
114.18
113.69
113.43
113.13
112.42
111.63
111.57
111.09
67.22
55.72
55.47
55.45
53.23
51.93
49.29
46.86
35.71
35.60
f1 (ppm)

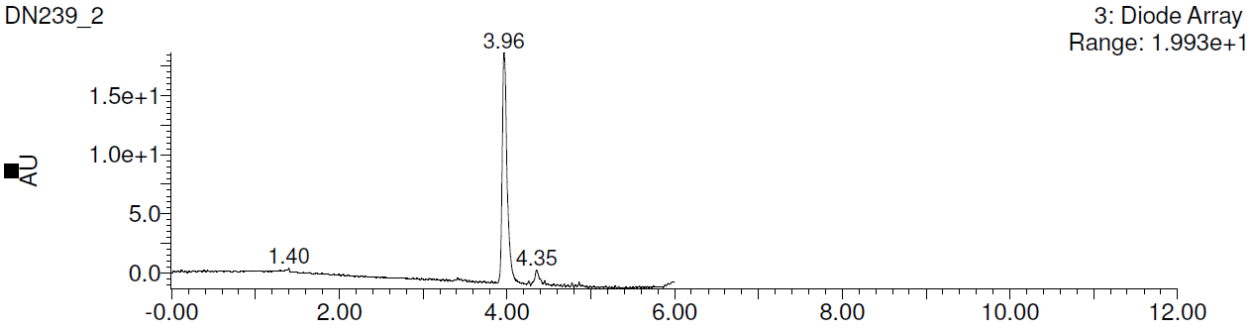


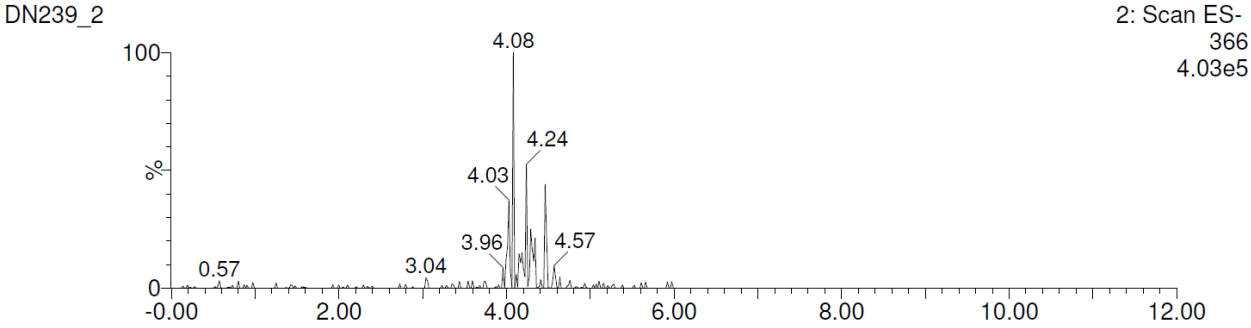


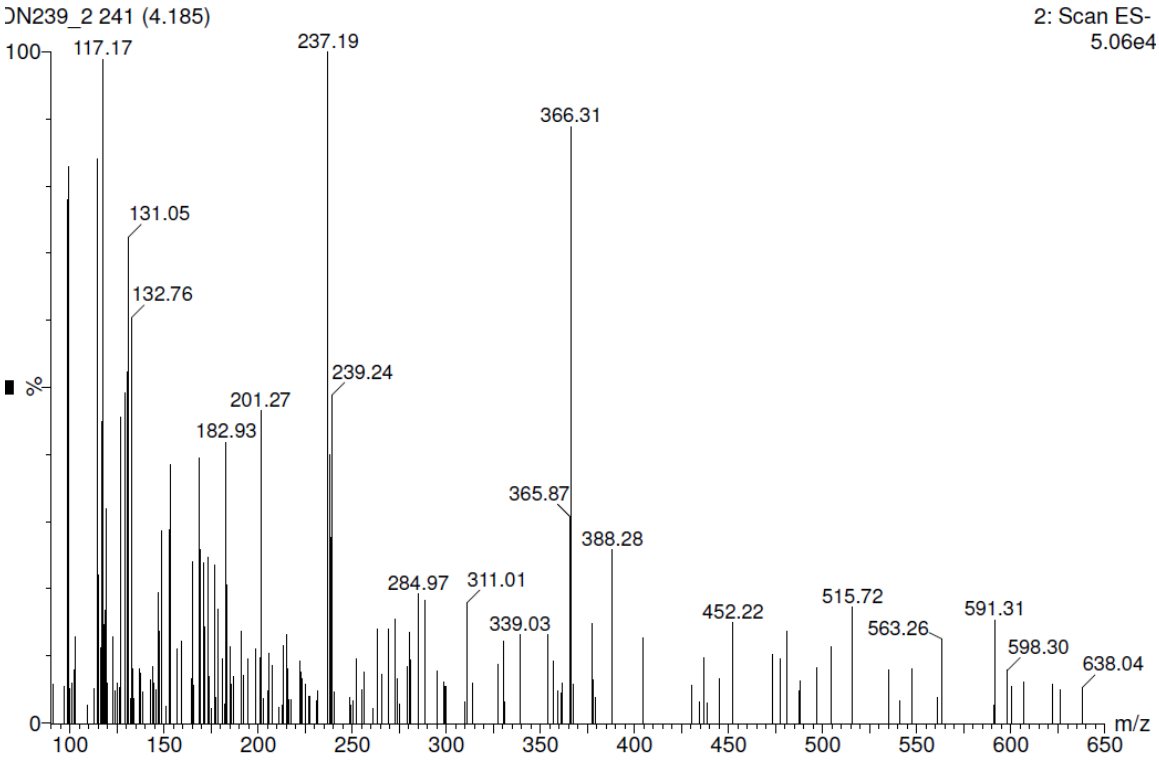


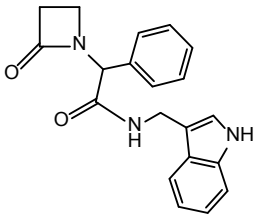


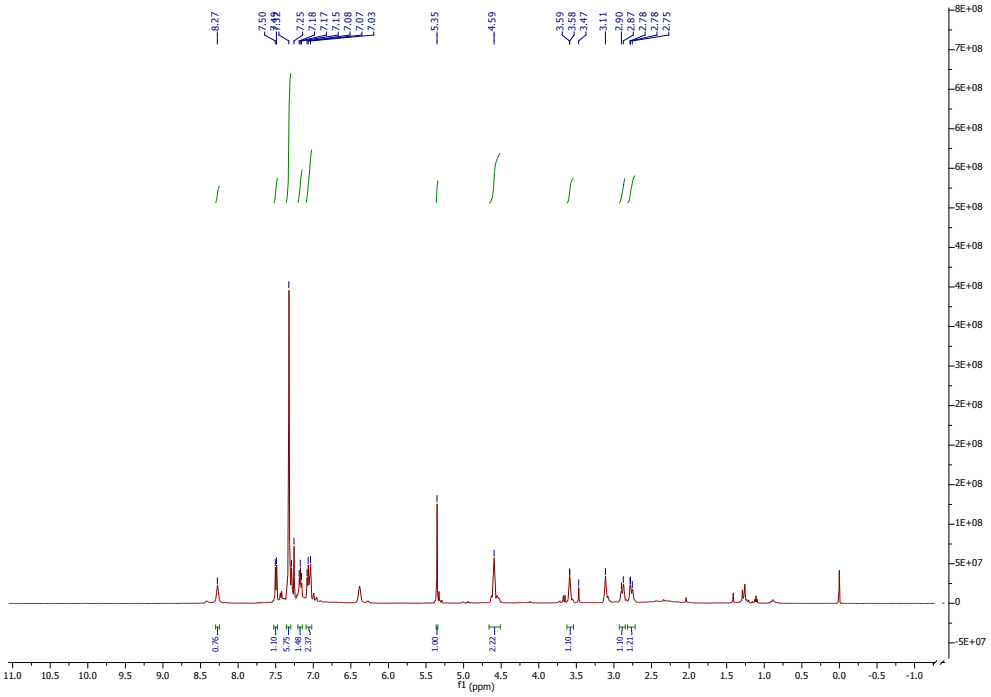


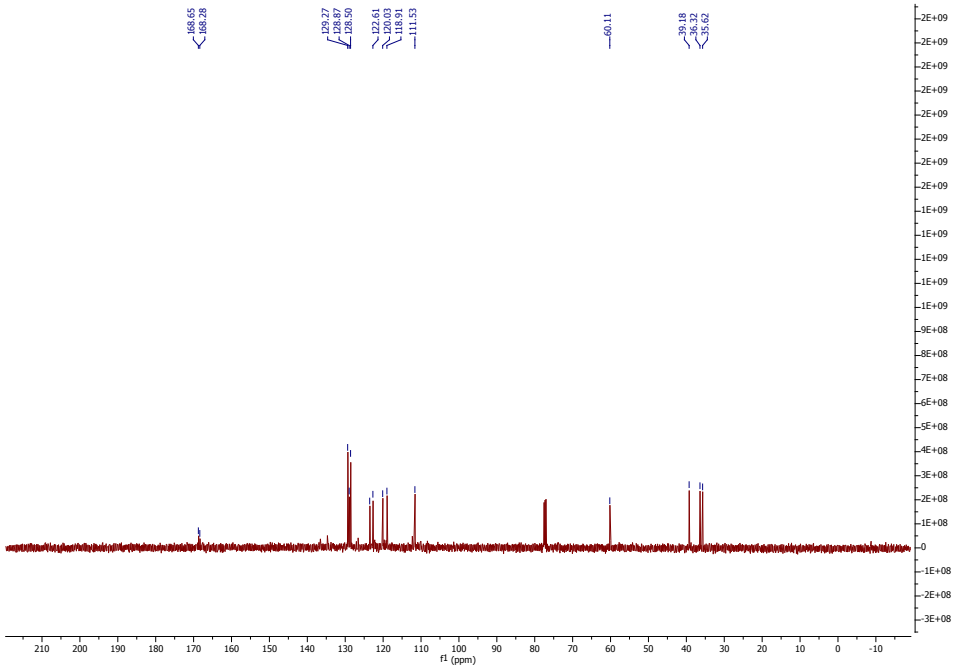


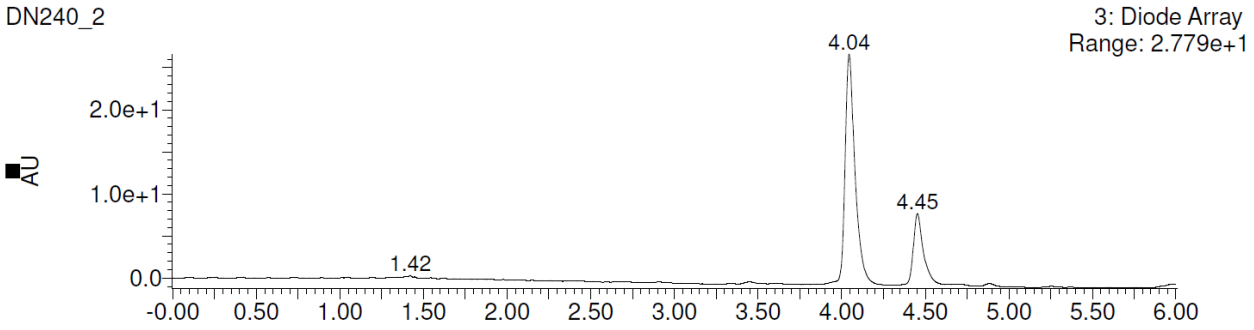


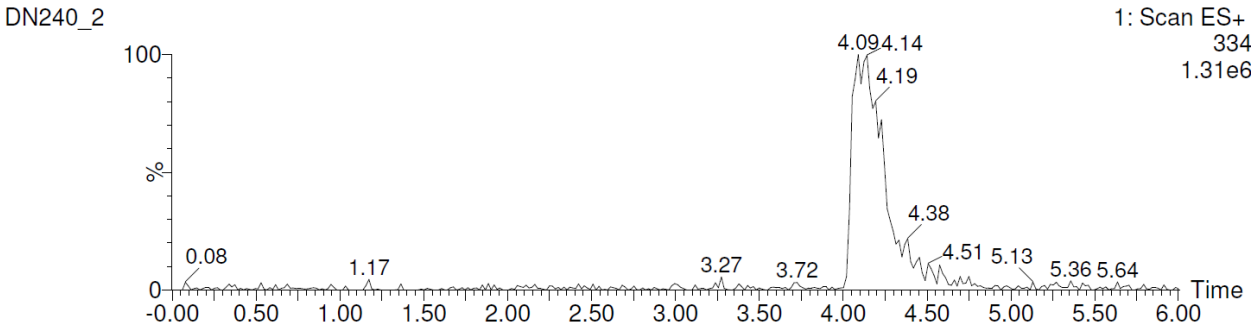


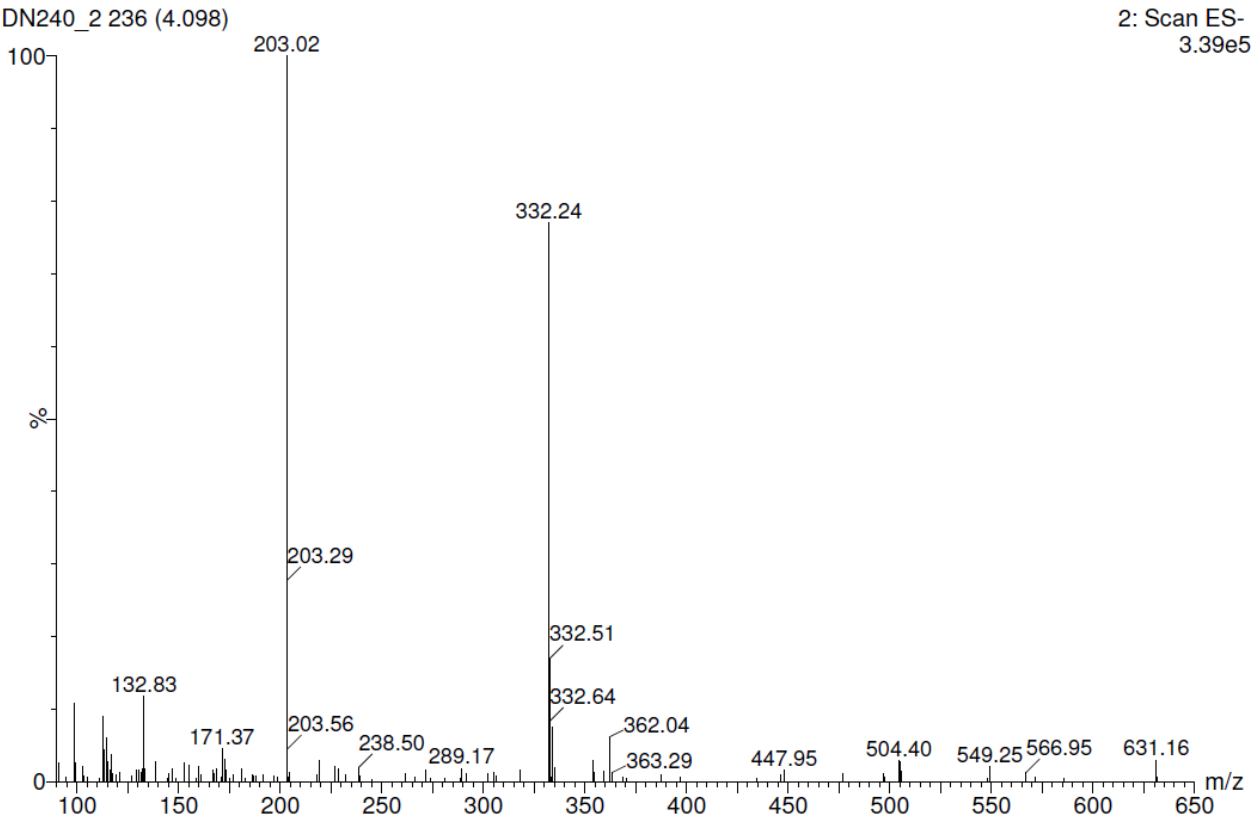


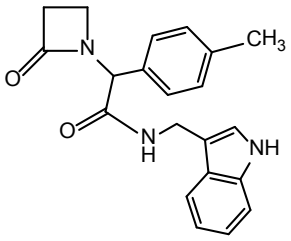


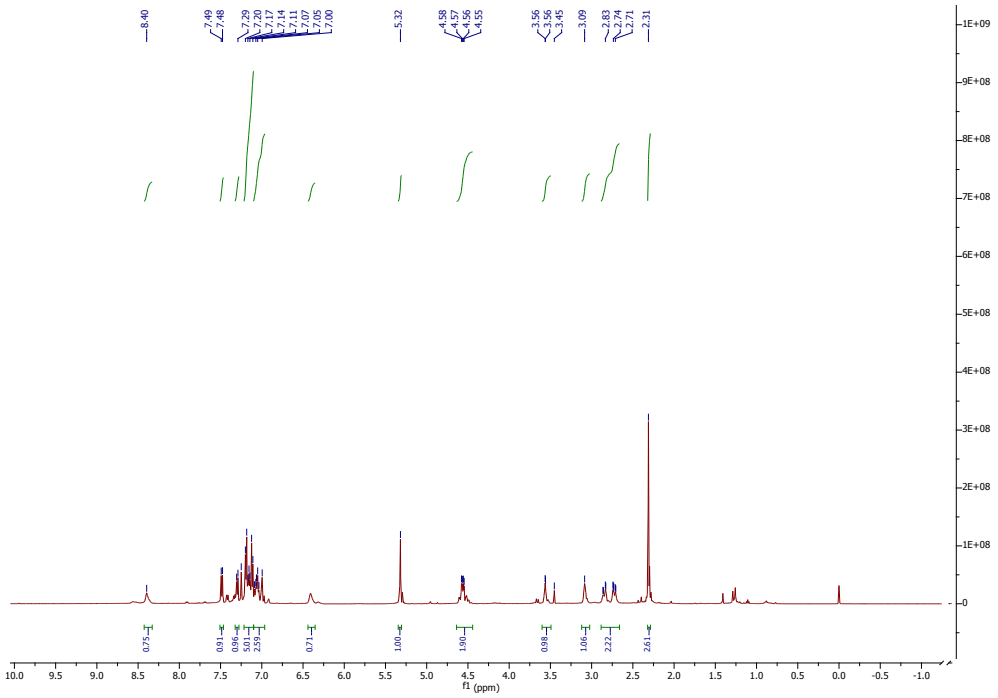


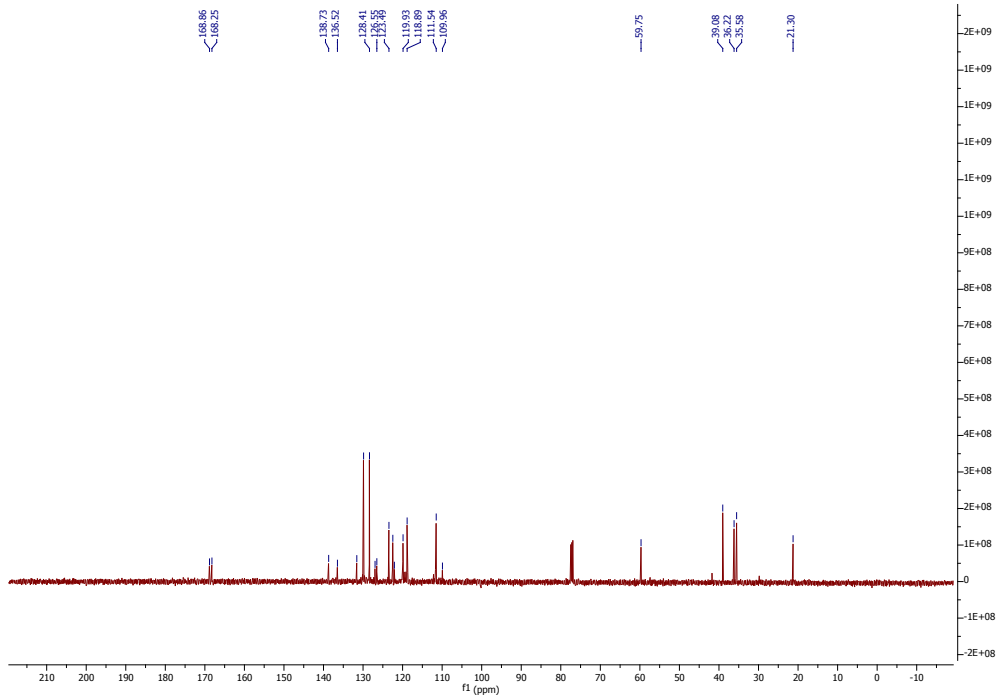

DN240_2
3: Diode Array
Range: 2.779e+1
AU
2.0e+1
1.0e+1
0.0
4.04
4.45
1.42
-0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00

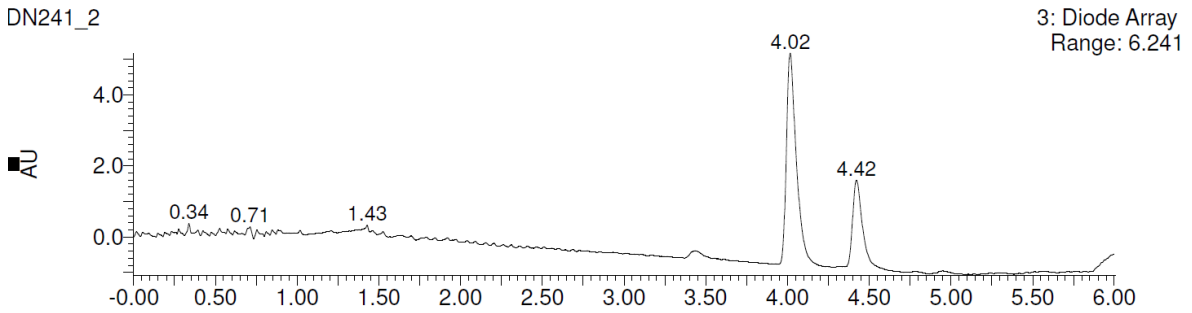

DN240_2
1: Scan ES+
334
1.31e6
100
%
0
4.09 4.14
4.19
4.38
4.51
5.13
5.36 5.64
0.08
1.17
3.27
3.72
Time
-0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00

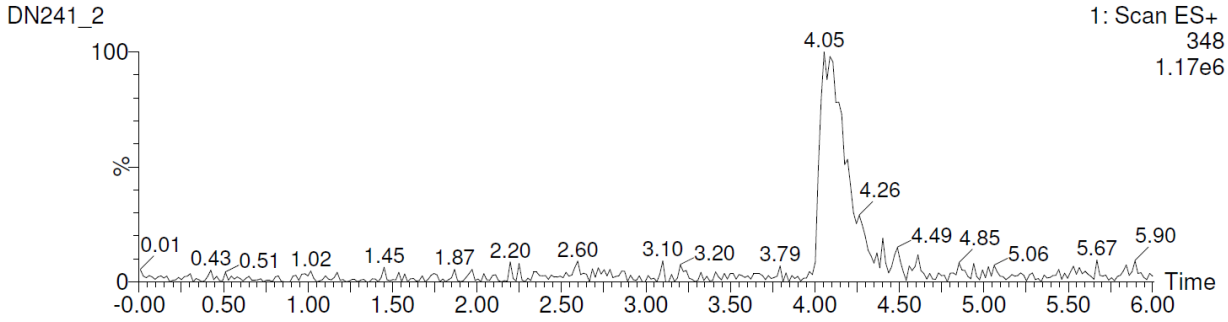

DN240_2 236 (4.098)
2: Scan ES-
3.39e5
100
%
0
203.02
332.24
203.29
332.51
132.83
332.64
362.04
171.37
203.56
238.50
289.17
363.29
447.95
504.40
549.25
566.95
631.16
m/z
100 150 200 250 300 350 400 450 500 550 600 650

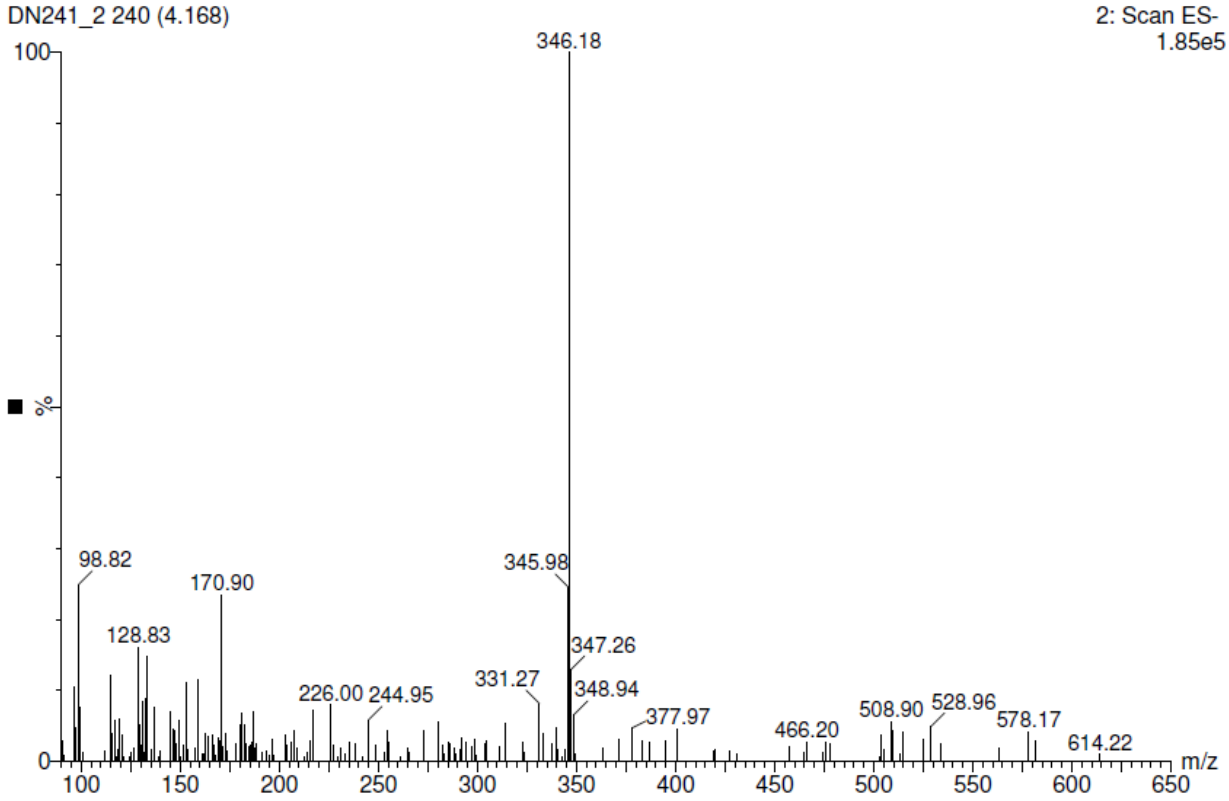


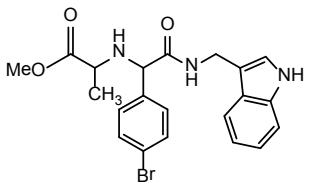


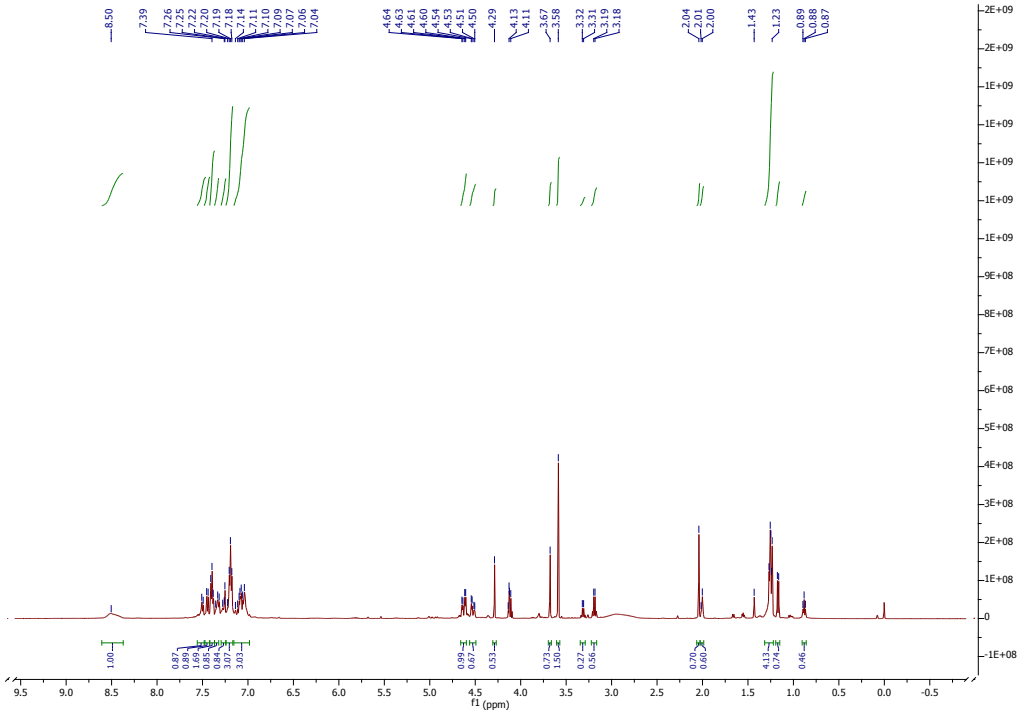


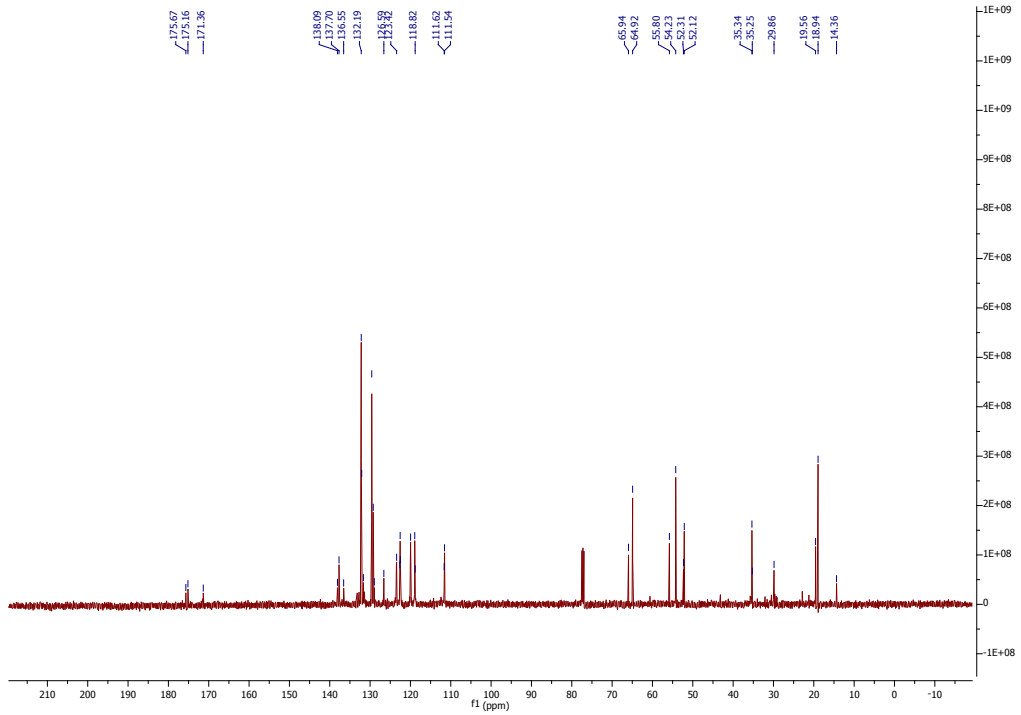


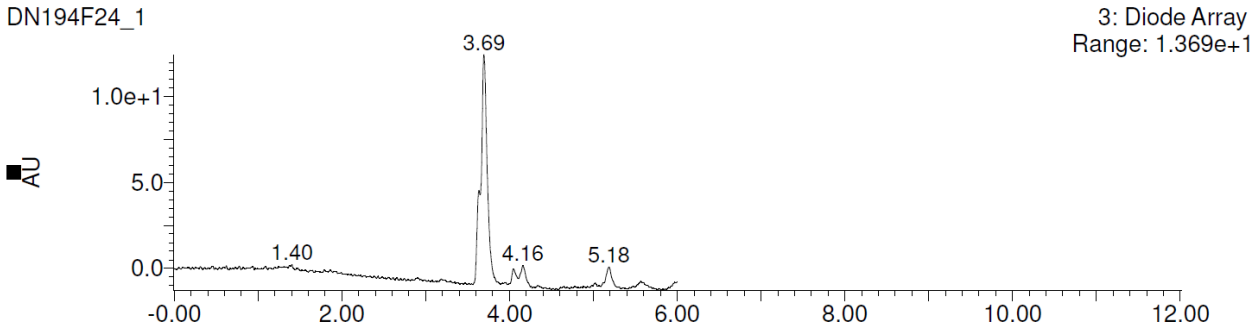


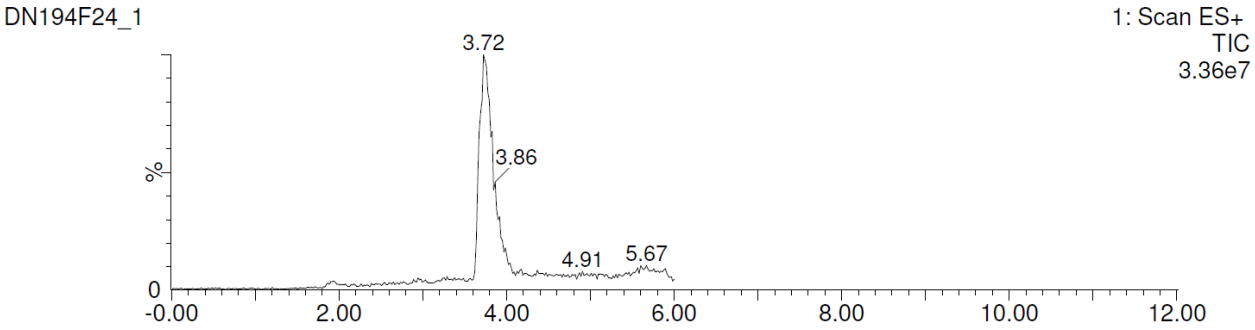


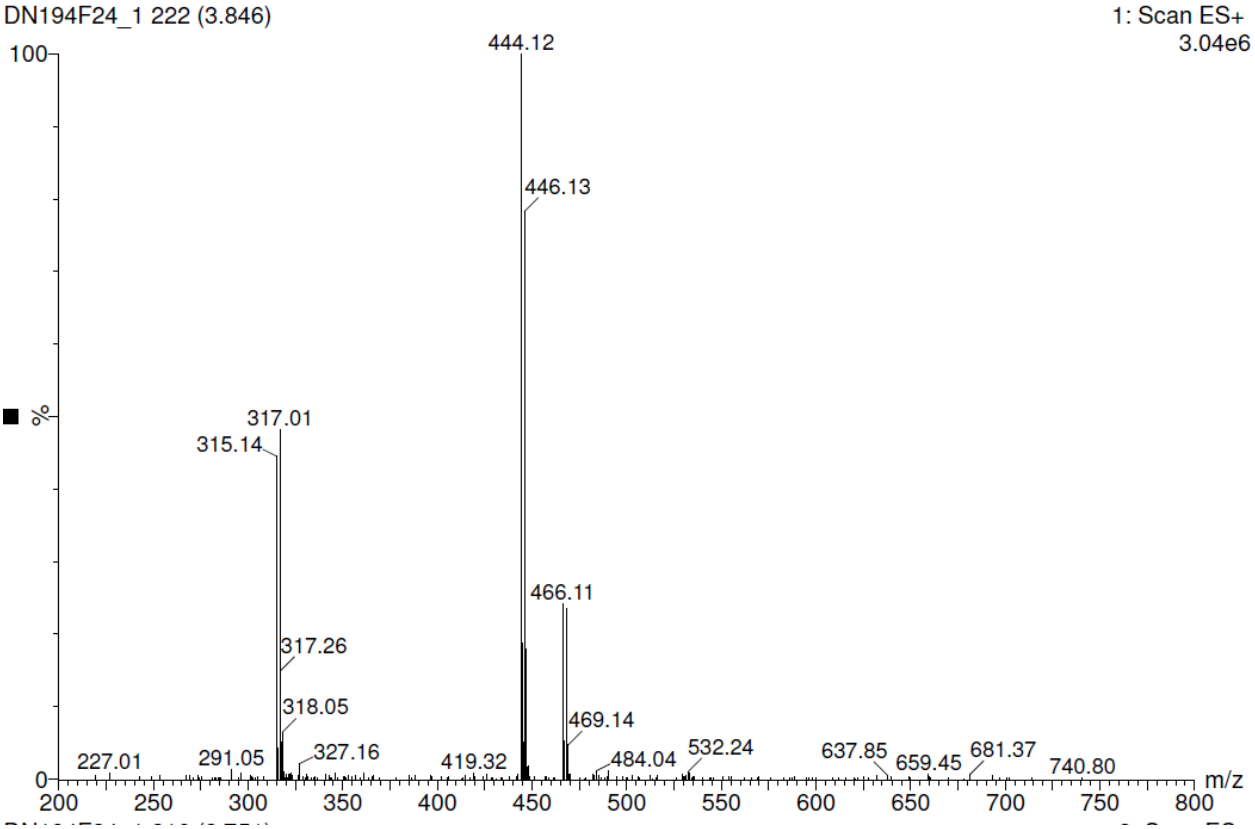


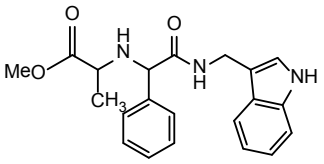


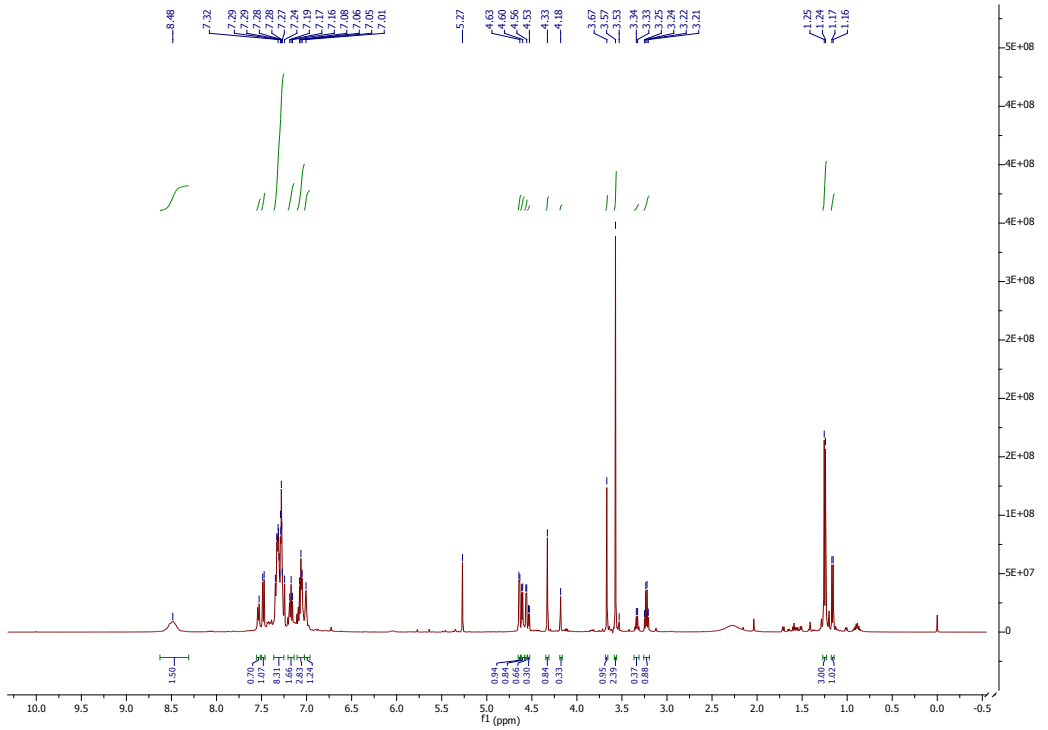


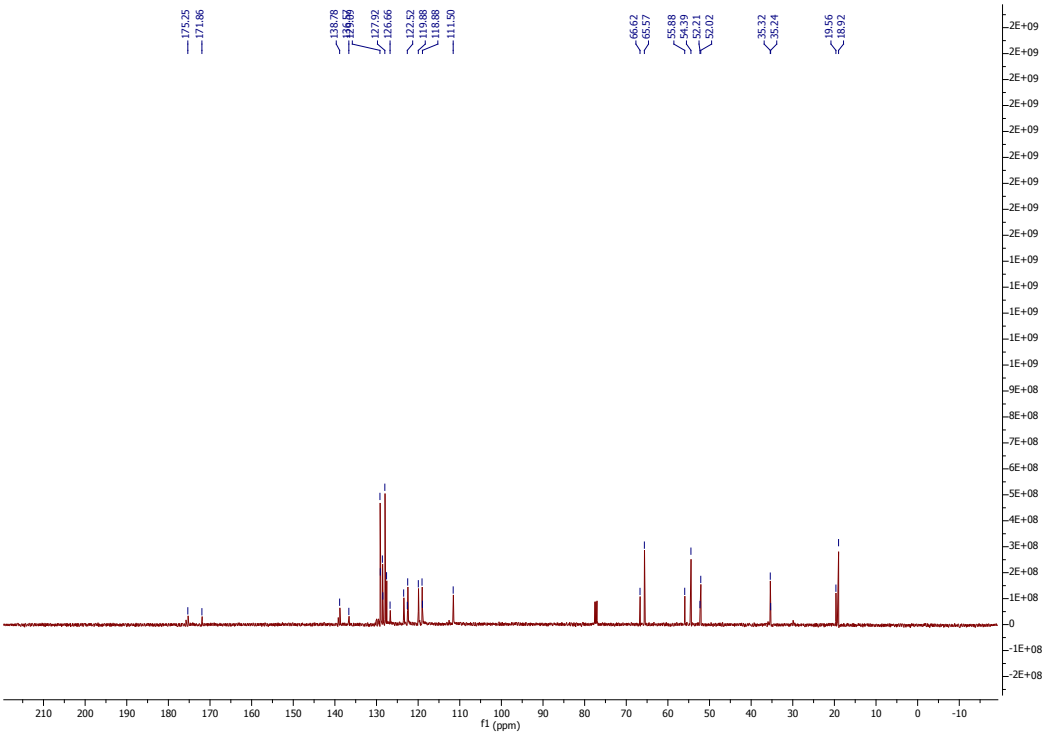


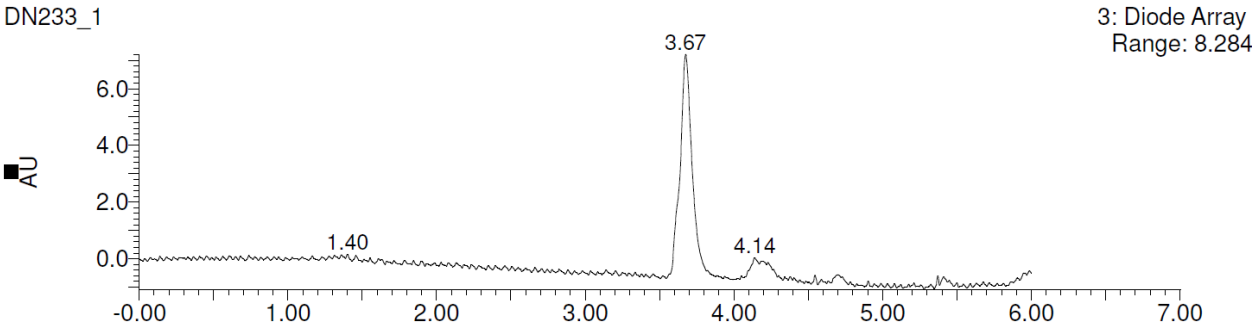


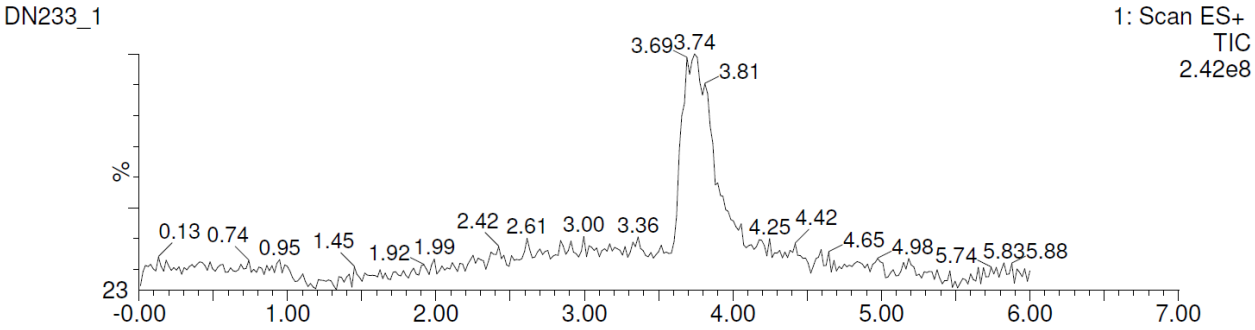


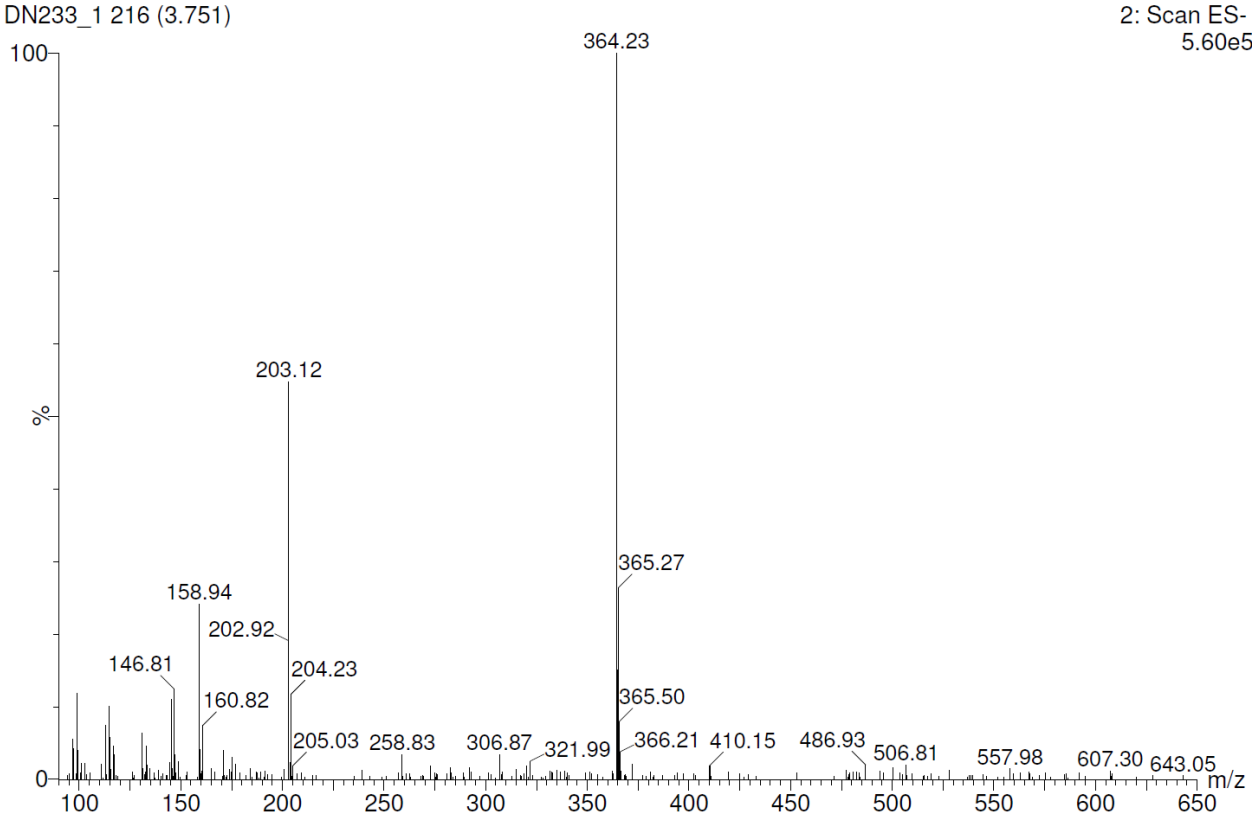


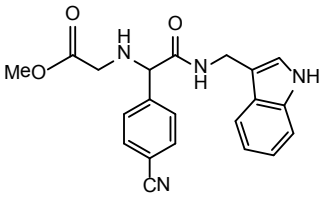


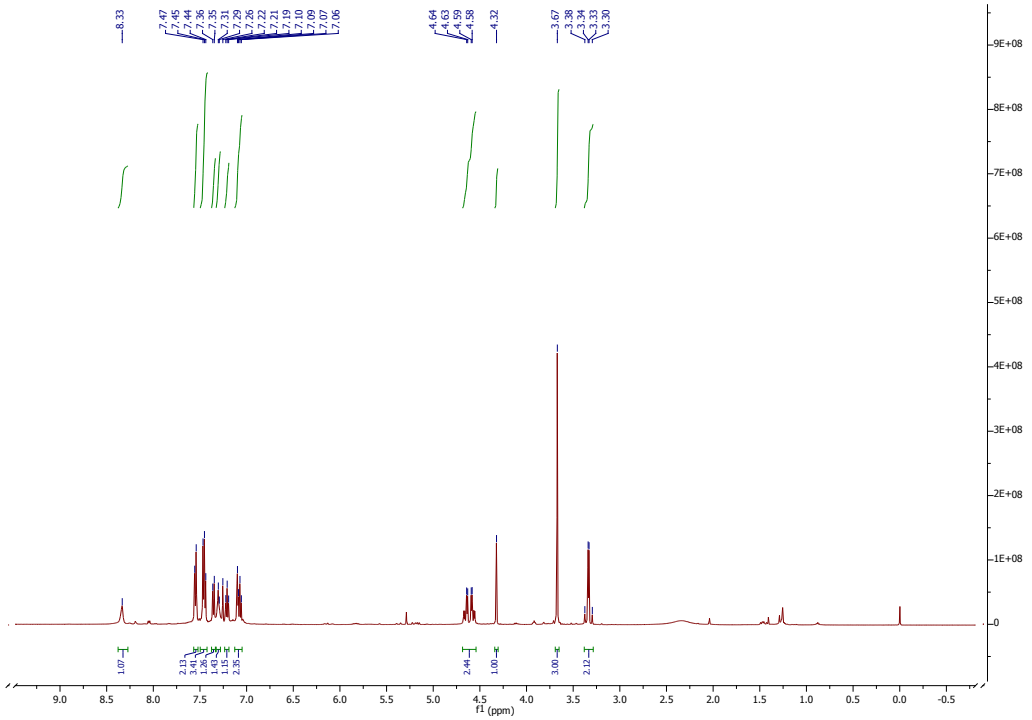


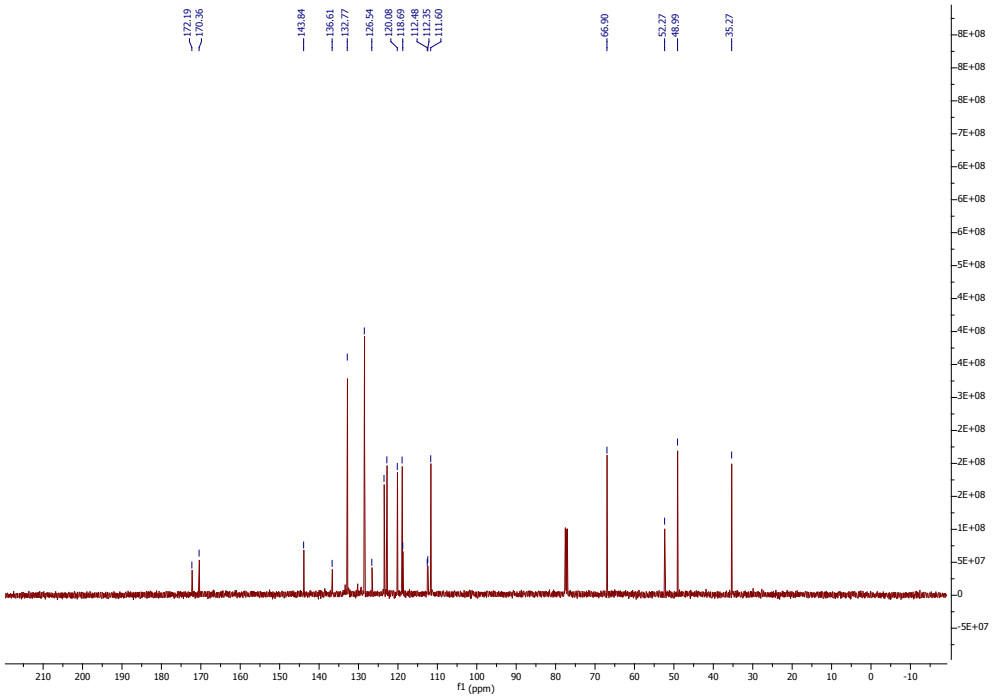


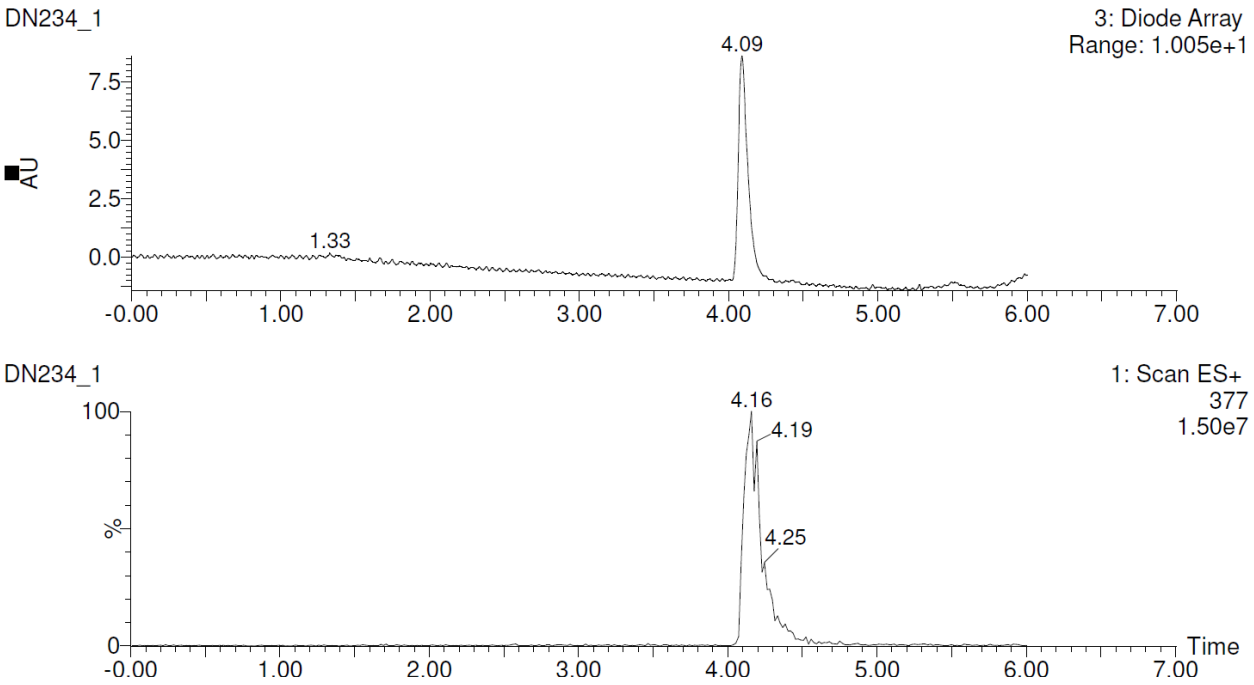


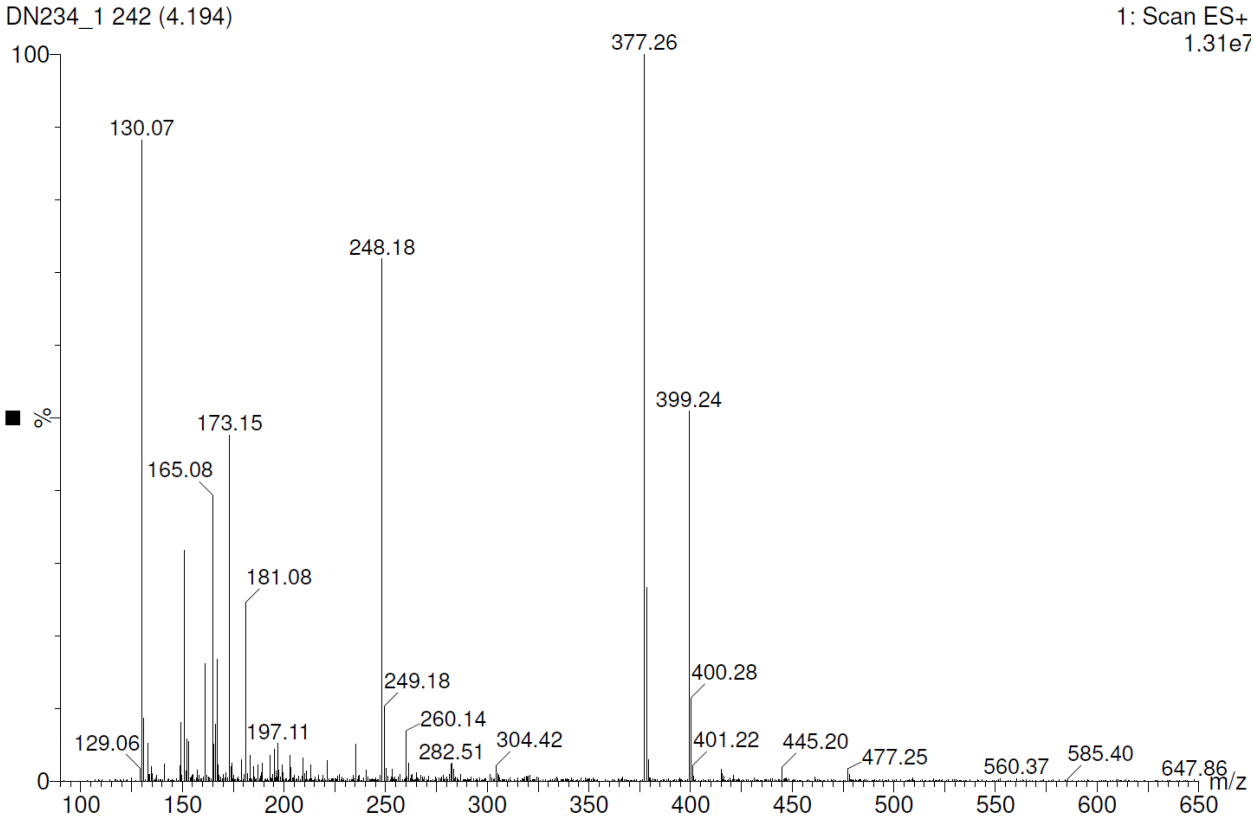


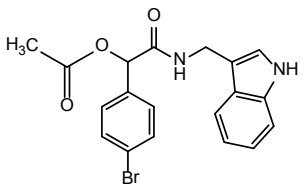


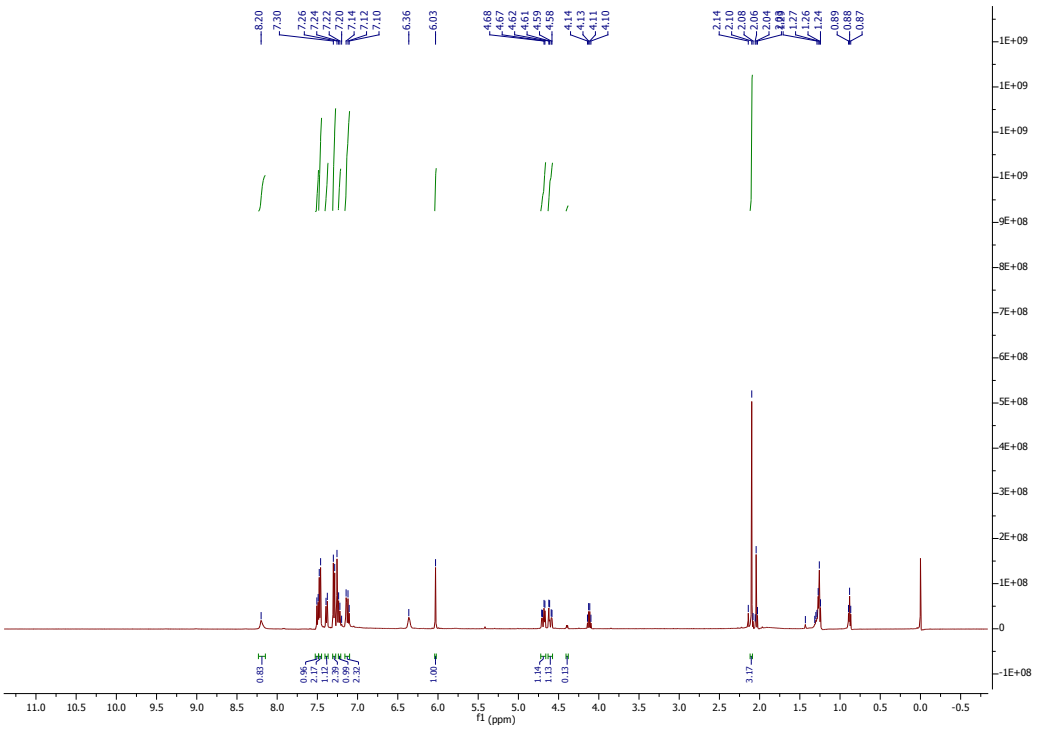


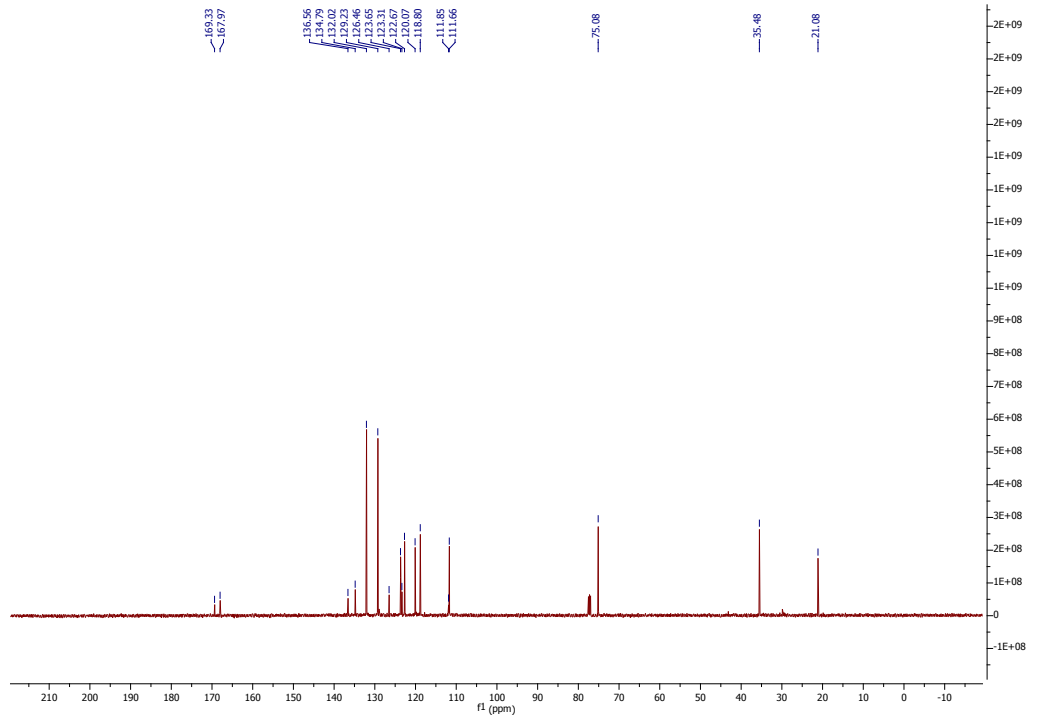



DN234_1
3: Diode Array
Range: 1.005e+1
4.09
1.33
AU
7.5
5.0
2.5
0.0
-0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
DN234_1
1: Scan ES+
377
1.50e7
4.16
4.19
4.25
100
%
0
Time


DN234_1 242 (4.194)
1: Scan ES+
1.31e7
377.26
130.07
248.18
399.24
173.15
165.08
181.08
249.18
400.28
260.14
129.06
197.11
282.51
304.42
401.22
445.20
477.25
560.37
585.40
647.86
100
%
0
100
150
200
250
300
350
400
450
500
550
600
650
m/z


H3C
O
O
O
N
H
NH
Br


8.20
7.30
7.26
7.24
7.22
7.20
7.14
7.12
7.10
6.36
6.03
4.68
4.67
4.62
4.61
4.59
4.58
4.14
4.13
4.11
4.10
2.14
2.10
2.08
2.06
2.04
1.27
1.26
1.24
0.89
0.88
0.87
0.83
0.96
2.17
1.39
0.99
2.32
1.00
1.14
1.13
0.13
3.17
f1 (ppm)


169.33
167.97
136.56
134.79
132.02
129.23
126.46
123.65
123.31
122.67
120.07
118.80
111.85
111.66
75.08
35.48
21.08
f1 (ppm)