1. Material and Method

General Procedures: reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized by heating up the plates sprayed with 10% of sulfuric acid in methanol. Melting points were determined on a Mel-TEMP II melting point apparatus without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance spectrometer at 300 MHz and 75 MHz, respectively. Chemical shifts (d) were reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR. Multiplicities were abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). IR spectra were recorded on a Nicolet iS10 Avatar FT-IR spectrometer using KBr film. MS spectra were recorded on a LC/MSD TOF HR-MS Spectrum. All chemicals purchased from commercial suppliers were used as received unless otherwise stated. All solvents were reagent grade and, when necessary, were purified and dried by standard methods.

1.1 Synthesis of compound I-1d

Limonin (500 mg, 1.06 mmol) and 3-methoxyphenethylamine (480 mg, 3.18 mmol) was dissolved in THF (10 ml), the reaction mixture was stirred at 80℃ for 3 hours, then diluted with CH_2Cl_2 (20 ml), washed successively with 1 M HCl (4 ml) and brine (4 ml). The organic layer was collected and dried over anhydrous $MgSO_4$, the volatile was removed under vacuum, the resulting crude product was purified by column chromatography (CH_2Cl_2 : CH_3OH = 40:1) to give compound **I-1d** (545 mg, 85% yield) as light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.41 (s, 1H), 7.39 (d, J = 1.6 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.75 (s, 1H), 6.61 (t, J = 5.4 Hz, 1H),6.35 (s, 1H), 5.43 (s, 1H), 4.10 (s, 2H), 3.80 (s, 1H), 3.77 (s, 3H), 3.67 (d, J = 9.0 Hz, 1H), 3.59 – 3.46 (m, 2H), 2.86 – 2.75 (m, 4H), 2.61 (dd, J_1 = 15.9 Hz, J_2= 9.4 Hz, 2H), 2.31 – 2.24 (m, 2H), 2.07 – 2.01 (m, 1H), 1.98 – 1.91 (m, 2H), 1.68 (dd, J_1 = 13.7 Hz, J_2 = 7.1 Hz, 1H), 1.44 – 1.36 (m, 1H), 1.30 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 207.77, 171.75, 167.12, 159.82, 143.11, 140.95, 140.42, 129.59, 121.06, 120.26, 114.84, 111.52, 109.68, 82.75, 78.68, 78.31, 65.50, 61.25, 60.79, 55.15, 53.15, 52.53, 51.02, 48.81, 40.30, 39.41, 37.65, 36.46, 35.42, 33.62, 29.60, 23.27, 22.34, 21.13, 15.89. HR-ESIMS *m/z* 622.3008 $[M+H]^+$ (calcd for $C_{35}H_{44}NO_9$, 622.3011).

1.2 Synthesis of compound I-2d

Compound **I-1d** (209 mg, 0.345 mmol) and 4-Dimethylaminopyridine (9 mg, 0.069 mmol) was dissolved in 5 ml CH_2Cl_2 and stirred for 30 minutes, the reaction mixture was cooled down to 0 ℃. Then di-tert-butyl decarbonate (83 mg, 0.380 mmol) was solubilized in 0.5 ml CH_2Cl_2 and added drop-wise to the reaction, then the reaction was warmed to 25 ℃ and stirred for 1 hour. The volatile was removed and resulting solid mass was purified by column chromatography (EtOAc : Hexane = 1:1) to afford compound **I-2d** (224 mg, 90 % yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.37 (m, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 6.76 (d, J = 9.3 Hz, 2H), 6.49 (brs, 1H), 6.35 (s, 1H), 5.44 (s,

1H), 4.45 (d, J = 12.1 Hz, 1H), 4.38 (d, J = 12.1 Hz, 1H), 3.78 (s, 3H), 3.77 – 3.69 (m, 2H), 3.63 – 3.53 (m, 1H), 3.52 – 3.45 (m, 1H), 2.88 – 2.66 (m, 4H), 2.46 – 2.29 (m, 3H), 2.01 – 1.94 (m, 2H), 1.79 – 1.71 (m, 1H), 1.62 (s, 2H), 1.48 (s, 9H), 1.09 – 1.06 (m, 9H), 1.02 (s, 3H). MS(ESI(+)70V) *m/z* 744.4 $[M+Na]^+$.

1.3 Synthesis of compound I-3d

To a solution of **I-2d** (106 mg, 0.147 mmol) in 4 ml toluene, Lawesson's reagent (30 mg, 0.074 mmol) was added, then the reaction mixture was stirred at 70 ℃ for 2 hours. The reaction was monitored by thin-layer chromatography until completion. The reaction solution was diluted with 8 ml CH_2Cl_2, washed with 4 ml brine, dried by Na_2SO_4. The solvent was evaporated in vacuo and the resulting crude product was purified by chromatography (EtOAc : Hexane = 1:2) to afford **I-3d** (94 mg, 87 % yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.38 (brs, 1H), 7.40 (d, J = 6.4 Hz, 2H), 7.24 – 7.20 (m, 1H), 6.83 – 6.74 (m, 3H), 6.34 (s, 1H), 5.44 (s, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.93 – 3.84 (m, 1H), 3.78 (s, 3H), 3.77 (s, 1H), 3.75 – 3.69 (m, 1H), 3.39 (d, J = 15.3 Hz, 1H), 3.00 - 2.74 (m, 2H), 2.85 – 2.78 (m, 2H), 2.36 – 2.29 (m, 2H), 2.10 – 2.02 (m, 1H), 2.00 – 1.93 (m, 2H), 1.91 - 1.77 (m, 1H), 1.49 (s, 9H), 1.45 – 1.41 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H). MS(ESI(+)70V) *m/z* 760.3 $[M+Na]^+$.

1.4 Synthesis of compound I-4d

Compound **I-3d** (106 mg, 0.144 mmol) was dissolved in 8 ml methanol, to which the freshly prepared Raney-Ni (300 mg) was added. The reaction was charged with hydrogen gas and stirred at room temperature for 2 hours. Raney-Ni was removed by celite assisted filtration, the solvent was evaporated and resulting crude product was purified by column chromatography (CH_2Cl_2 : CH_3OH = 25:1) to give compound **I-4d** (56 mg, 55% yield) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 2H), 7.23 (d, J = 7.8 Hz, 1H), 6.89 – 6.78 (m, 3H), 6.32 (s, 1H), 5.40 (s, 1H), 4.49 (d, J = 12.3 Hz, 1H), 4.28 (d, J = 12.1 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 1H), 3.64 (d, J = 10.3 Hz, 1H), 3.31 – 2.97 (m, 6H), 2.85 – 2.71 (m, 1H), 2.36 – 2.24 (m, 2H), 2.18 – 1.78 (m, 6H), 1.71 – 1.63 (m, 1H), 1.48 (s, 9H), 1.09 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.86 (s, 3H). MS(ESI(+)70V) *m/z* 708.3 $[M+H]^+$.

1.5 Synthesis of compound I-5d

To a solution of **I-4d** (53 mg, 0.075 mmol) in 5 ml methanol, 2 ml HCl saturated methanol was added dropwise, then the reaction mixture was stirred at 0 ℃ for 1 hours. The solvent was vaporated and the crude product was crystalized from 0.5 ml methanol and 2ml diethyl ether

to give compound **I-5d** (44 mg, 91 % yield) as white solid in hydrochloride salt format. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.73 (s, 1H), 7.66 (s, 1H), 7.24 (t, J = 7.8 Hz, 1H), 6.84 (s, 2H), 6.81 (s, 1H), 6.51 (s, 1H), 5.44 (s, 1H), 4.63 (s, 1H), 4.03 (d, J = 9.8 Hz, 1H), 3.85 - 3.83 (m, 2H), 3.74 (s, 3H), 3.54 (d, J = 10.8 Hz, 1H), 3.19 – 2.85 (m, 7H), 2.36 – 1.78 (m, 8H), 1.69 – 1.66 (m, 1H), 1.25 (s, 3H), 1.20 – 1.17 (m, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 209.20, 167.30, 159.39, 143.31, 141.63, 138.83, 129.63, 120.75, 120.21, 114.25, 112.15, 110.21, 83.67, 77.52, 65.80, 60.04, 59.34, 54.95, 52.70, 51.70, 50.07, 50.03, 47.58, 45.72, 37.09, 36.38, 32.40, 31.57, 29.55, 28.05, 23.42, 21.79, 21.77, 20.62, 15.42. HR-ESIMS m/z 608.3216 $[M+H]^+$ (calcd for $C_{35}H_{46}NO_8$, 608.3218).

1.6 Synthesis of compound I-5a

Compound **I-5a** was prepared from limonin and 4-fluorobenzyl amine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.44 (s, 2H), 7.36 (d, J = 10.2 Hz, 2H), 7.08 (t, J = 7.8 Hz, 2H), 6.32 (s, 1H), 5.38 (s, 1H), 4.20 (d, J = 10.9 Hz, 1H), 4.08 – 4.02 (m, 2H), 3.93 (d, J = 12.8 Hz, 1H), 3.77 (s, 1H), 3.46 (d, J = 9.7 Hz, 1H), 2.98 – 2.89 (m, 2H), 2.82 (t, J = 14.8 Hz, 1H), 2.38 (s, 1H), 2.34 – 2.19 (m, 3H), 2.08 – 1.87 (m, 3H), 1.67 – 1.58 (m, 1H), 1.41 – 1.29 (m, 2H), 1.28 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 207.70, 166.76, 163.49, 160.20, 142.53, 140.47, 129.86, 129.75, 119.81, 115.22, 114.94, 109.33, 86.02, 77.64, 65.01, 60.95, 60.28, 52.67, 52.05, 50.59, 48.31, 46.80, 37.16, 36.08, 33.16, 30.26, 29.40, 29.20, 27.30, 23.03, 21.95, 20.74, 15.43. HRMS (ESI): *m/z* $[M+H]^+$ (calcd for $C_{33}H_{41}FNO_7$: 582.2862; found: 582.2858).

1.7 Synthesis of compound I-5b

Compound **I-5b** was prepared from limonin and 4-methoxybenzyl amine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 8.0 Hz, 2H), 7.37 (s, 2H), 6.91 (d, J = 6.1 Hz, 2H), 6.33 (s, 1H), 5.40 (s, 1H), 4.22 – 3.88 (m, 4H), 3.78 (s, 3H), 3.77 (s, 1H), 3.53 – 3.39 (m, 1H), 3.20 – 2.95 (m, 2H), 2.91 – 2.46 (m, 5H), 2.40 - 2.25 (m, 2H), 2.11 – 1.98 (m, 1H), 1.92 – 1.86 (m, 1H), 1.71 – 1.59 (m, 1H), 1.29 (s, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 209.20, 167.28, 159.55, 143.31, 141.62, 131.53 (2C), 123.85, 120.20, 113.90 (2C), 110.21, 83.61, 77.49, 65.79, 59.99, 59.31, 55.13, 52.68, 51.70, 50.02, 49.19, 47.52, 44.81, 37.06, 36.37, 32.39, 29.56, 27.92, 23.44, 21.76, 20.60, 15.40. HR-ESIMS m/z 594.3064 $[M+H]^+$ (calcd for $C_{34}H_{44}NO_8$, 594.3061).

1.8 Synthesis of compound I-5c

Compound **I-5c** was prepared from limonin and 4-fluorophenethylamine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.64 (brs, 2H), 7.71 (s, 1H), 7.65 (s, 1H), 7.32 – 7.27 (m, 2H), 7.15 (t, J = 8.8 Hz, 2H), 6.50 (s, 1H), 5.44 (s, 1H), 4.58 (s, 1H), 4.03 (d, J = 11.5 Hz, 1H), 3.86 (d, J = 11.6 Hz, 1H), 3.84 (s, 1H), 3.54 (d, J = 10.2 Hz, 1H), 3.16 – 3.11 (m, 2H), 3.07 – 3.00 (m, 2H), 2.97 – 2.90 (m, 3H), 2.23 (dd, J = 9.3 Hz, 1H), 2.22 – 2.13 (m, 2H), 2.07 – 2.02 (m, 1H), 2.00 – 1.91 (m, 2H), 1.89 – 1.83 (m, 1H), 1.72 – 1.66 (m, 1H), 1.26 (s, 3H), 1.20 - 1.15 (m, 1H), 1.13 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 209.18, 167.28, 162.71, 159.50, 143.31, 141.62, 133.43, 130.57, 130.46, 120.21, 115.44, 115.16, 110.21, 83.59, 77.51, 65.80, 60.01, 59.32, 52.69, 51.69, 50.02, 47.65, 47.56, 45.69, 37.10, 36.37, 32.39, 30.67, 29.55, 28.05, 23.44, 21.78, 20.62, 15.42. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{43}FNO_7$: 596.3018; found: 596.3012.

1.9 Synthesis of compound I-5e

Compound **I-5e** was prepared from limonin and 3,4-dimethoxyphenethylamine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36 (s, 2H), 6.91 (s, 1H), 6.85 (s, 2H), 6.32 (s, 1H), 5.40 (s, 1H), 4.20 – 4.00 (m, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.77 (s, 1H), 3.55 – 3.48 (m, 1H), 3.42 – 3.31 (m, 2H), 3.15 – 3.05 (m, 2H), 2.99 – 2.89 (m, 1H), 2.81 (t, J = 14.5 Hz, 2H), 2.25 – 2.09 (m, 4H), 1.84 – 1.76 (m, 4H), 1.30 (s, 3H), 1.06 (s, 3H), 0.92 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 209.20, 167.27, 148.74, 147.59, 143.30, 141.62, 129.57, 120.46, 120.20, 112.41, 111.91, 110.20, 83.70, 77.49, 65.80, 60.02, 59.30, 55.46, 55.38, 52.68, 51.69, 50.02, 47.91, 47.57, 45.75, 37.09, 36.37, 32.39, 31.15, 29.53, 28.05, 23.41, 21.77, 20.61, 15.41. HR-ESIMS m/z 638.3321 $[M+H]^+$ (calcd for $C_{36}H_{48}NO_9$, 638.3324).

1.10 Synthesis of compound II-5a

Compound **II-5a** was prepared from deoxylimonin and 4-fluorobenzyl amine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.44 – 7.38 (m, 3H), 7.06 (t, J = 8.5 Hz, 2H), 6.62 (s, 1H), 6.39 (s, 1H), 5.01 (s, 1H), 4.21 (d, J = 12.5 Hz, 1H), 4.04 (d, J = 13.0 Hz, 1H), 3.91 – 3.82 (m, 2H), 3.61 (s1H), 3.03 – 2.91 (m, 2H), 2.68 – 2.25 (m, 6H), 2.12 – 2.00 (m, 2H), 1.77 – 1.68 (m, 1H), 1.63 (s, 3H), 1.59 – 1.49 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 210.37, 169.88, 164.81, 163.33, 160.11, 143.19, 141.71, 131.29, 131.18, 120.21, 115.22, 114.92, 113.63, 110.28, 83.22, 81.32, 77.68, 58.36, 56.90, 50.84, 50.22, 48.08, 46.05, 43.07, 38.06, 37.48,

29.85, 29.25, 26.06, 25.94, 23.99, 20.50, 17.95. HR-ESIMS m/z 566.2906 $[M+H]^+$ (calcd for $C_{33}H_{41}FNO_6$, 566.2912).

1.11 Synthesis of compound II-5b

Compound **II-5b** was prepared from deoxylimonin and 4-methoxybenzyl amine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.40 (m, 4H), 6.89 (d, J = 8.3 Hz, 2H), 6.57 (s, 1H), 6.36 (s, 1H), 4.98 (s, 1H), 4.25 – 4.13 (m, 2H), 3.95 (d, J = 10.3 Hz, 1H), 3.88 (s, 3H), 3.78 – 3.72 (m, 2H), 3.55 (d, J = 10.5 Hz, 1H), 3.17 – 3.05 (m, 1H), 3.04 – 2.93 (m, 1H), 2.70 – 2.60 (m, 2H), 2.58 – 2.51 (m, 1H), 2.45 – 2.38 (m, 1H), 2.36 – 2.28 (m, 1H), 2.23 – 2.16 (m, 1H), 2.07 – 1.98 (m, 1H), 1.75 – 1.67 (m, 1H), 1.64 (s, 3H), 1.55 – 1.48 (m, 1H), 1.35 – 1.22 (m, 2H), 1.19 (s, 3H),1.12 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.65, 168.43, 165.13, 159.88, 142.42, 140.86, 130.96(2C), 122.00, 119.53, 114.29, 114.01(2C), 109.55, 84.49, 81.98, 78.91, 58.63, 57.47, 54.81, 50.93, 50.05, 49.05, 45.33, 43.93, 38.24, 36.86, 29.78, 27.37, 26.20, 25.98, 23.46, 20.50, 18.52.HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{44}NO_7$: 578.3112; found: 578.3096.

1.12 Synthesis of compound II-5c

Compound **II-5c** was prepared from deoxylimonin and 4-fluorophenethylamine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.47 (s, 1H), 7.42 (s, 1H), 7.28 – 7.22 (m, 2H), 7.04 (t, J = 8.3 Hz, 2H), 6.63 (s, 1H), 6.39 (s, 1H), 5.00 (s, 1H), 4.22 (d, J = 11.6 Hz, 1H), 4.71 – 3.38 (brs, 3H), 3.88 (d, J = 11.5 Hz, 1H), 3.60 (d, J = 9.7 Hz, 1H), 3.27 – 2.87 (m, 6H), 2.65 (t, J = 12.1 Hz, 2H), 2.57 – 2.40 (m, 2H), 2.35 (dd, J_1 = 12.4 Hz, J_2 = 7.0 Hz, 1H), 2.23 – 1.98 (m, 2H), 1.79 – 1.68 (m, 1H), 1.63 (s, 3H), 1.21 (s, 3H), 1.07 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 208.01, 167.78, 164.87, 163.32, 160.04, 142.44, 140.90, 131.19, 130.11, 130.01, 119.54, 115.85, 115.57, 114.69, 109.52, 84.95, 81.99, 79.21, 58.72, 57.58, 50.88, 49.29, 47.72, 44.13, 38.27, 36.72, 31.07, 29.64, 27.25, 26.17, 23.15, 20.55, 18.70. HR-ESIMS *m/z* 580.3076 $[M+H]^+$ (calcd for $C_{34}H_{43}FNO_6$, 580.3069).

1.13 Synthesis of compound II-5d

Compound **II-5d** was prepared from deoxylimonin and 3-methoxyphenethylamine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.40 (s, 1H), 7.25 – 7.15 (m, 1H), 6.81 – 6.74 (m, 3H), 6.61 (s, 1H), 6.39 (s, 1H), 5.01 (s, 1H), 4.16 (d, J = 11.1 Hz, 1H), 3.84 (d, J = 11.4 Hz, 1H), 3.78 (s, 3H), 3.51 (s, 1H), 2.96 – 2.88 (m, 2H), 2.89-2.83 (m, 4H), 2.80 – 2.47 (m, 3H), 2.51 – 2.30 (m, 2H), 2.10-2.01 (m, 3H), 1.77 (s, 1H), 1.65 (s, 3H), 1.64 – 1.55 (m, 1H), 1.45 – 1.36 (m, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.98

(s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 208.95, 168.27, 165.00, 159.32, 142.39, 140.86, 139.99, 129.23, 120.49, 119.62, 114.36, 114.30, 110.96, 109.55, 85.18, 82.03, 78.00, 58.74, 57.95, 54.64, 50.95, 50.05, 48.95, 48.00, 44.17, 38.30, 37.07, 34.71, 30.33, 29.58, 26.17, 26.06, 23.36, 20.57, 18.53. HRMS (ESI): *m/z* [M+H] $^{+}$ calcd for $C_{36}H_{48}NO_8$: 592.3269; found: 592.3267.

1.14 Synthesis of compound II-5e

Compound **II-5e** was prepared from deoxylimonin and 3,4-dimethoxyphenethylamine by utilizing the same synthetic route described for compound **I-5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (brs, 1H), 7.44 (s, 2H), 7.39 (s, 1H), 6.87 (d, J = 15.4 Hz, 3H), 6.59 (s, 1H), 6.35 (s, 1H), 4.97 (s, 1H), 4.21 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H) (d, J = 11.5 Hz, 7H), 3.65-3.55 (m, 1H), 3.47-3.33 (m, 2H), 3.17 – 3.06 (m, 2H), 2.77 – 2.64 (m, 2H), 2.56 (s, , 1H), 2.40 (d, J = 11.2 Hz, 1H), 2.38 – 2.24 (m, 2H), 2.21 – 2.08 (m, 2H), 2.03 – 1.95 (m, 1H), 1.62 (s, 3H), 1.51 – 1.42 (m, 1H), 1.34 – 1.20 (m, 2H), 1.17 (s, 3H), 0.95 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 210.30, 169.81, 164.82, 148.72, 147.55, 143.22, 141.74, 129.84, 120.47, 120.22, 113.68, 112.42, 111.85, 110.29, 83.06, 81.30, 77.91, 58.38, 56.72, 55.47, 55.37, 50.82, 48.13, 46.19, 43.06, 38.62, 38.06, 37.40, 31.64, 29.83, 28.29, 26.08, 25.93, 23.93, 20.50, 17.98. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{48}NO_8$: 622.3374; found: 622.3364.

1.15 Synthesis of compound II-6a

Compound **II-5a** (50 mg, 0.086 mmol) was dissolved in 5 ml anhydrous toluene at 0 ℃, then sequentially added diethyl azodicarboxylate (30 mg, 0.17 mmol) and triphenylphosphine PPh_3 (45 mg, 0.17 mmol) to the reaction. The reaction was stirred and gradually warmed to room temperature over 4 hours. After completion, the solvent was evaporated in vacuo and the resulting solid mass was purified by column chromatography (EtOAc : Hexane = 1:1) to give **II-6a** (26 mg, 56% yield) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.43 (t, J = 1.6 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.25 (s, 1H), 7.01 (t, J = 8.6 Hz, 2H), 6.84 (s, 1H), 6.42 (d, J = 1.0 Hz, 1H), 4.95 (s, 1H), 3.68 – 3.54 (m, 2H), 3.16 (d, J = 11.6 Hz, 1H), 2.81 (d, J = 11.6 Hz, 2H), 2.70 (s, 1H), 2.55 – 2.35 (m, 2H), 2.32 – 2.17 (m, 2H), 2.06 – 1.92 (m, 3H), 1.85 – 1.72 (m, 1H), 1.58 (s, 1H), 1.45 – 1.33 (m, 2H), 1.30 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 209.35, 170.02, 164.98, 162.87, 159.65, 143.20, 141.72, 131.31, 131.21, 120.25, 114.94, 114.67, 113.86, 110.33, 81.36, 77.63, 77.20, 62.21, 56.85, 50.36, 50.26, 48.09, 45.28, 42.39, 38.19, 36.12, 30.80, 27.66, 25.94, 25.35, 24.22, 19.93, 18.84. HR-ESIMS m/z 548.2813 $[M+H]^+$ (calcd for $C_{33}H_{39}FNO_5$, 548.2807).

1.16 Synthesis of compound II-6b

Compound **II-6b** (30 mg, 60% yield) was prepared from **II-5b** (51 mg, 0.089 mmol) by utilizing the same procedure described for compound **II-6a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.68 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.58 (s, 1H), 6.53 (s, 1H), 5.10 (s, 1H), 3.70 (s, 3H), 3.62 (s, 1H), 3.48 – 3.39 (m, 1H), 3.18 – 3.10 (m, 1H), 2.88 – 2.80 (m, 1H), 2.73 – 2.63 (m, 1H), 2.54 (s, 2H), 2.31 – 2.20 (m, 3H), 2.15 – 2.11 (m, 1H), 2.11 – 2.06 (m, 1H), 1.74 – 1.62 (m, 2H), 1.22 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.21, 174.84, 169.73, 163.04, 147.96, 146.47, 135.26(2C), 134.99, 124.99, 118.54, 118.24 (2C), 115.08, 86.13, 82.45, 81.94, 67.24, 61.59, 59.78, 55.14, 55.02, 52.76, 50.03, 47.15, 45.03, 44.76, 44.48, 44.20, 43.92, 43.64, 43.37, 42.93, 40.91, 35.56, 32.41, 30.75, 30.13, 28.98, 24.69, 23.56. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{42}NO_6$: 560.3007; found: 560.2996.

1.17 Carrageenan-induced paw edema test in ICR mice

ICR male mice were housed in filtered capped polycarbonate cages and allowed food and water ad libitum. Animals were kept on a cycle of 12 h light/darkness at 22 ± 1 ℃ and acclimated for at least one week until use. All protocols of *in vivo* experiments and animals received human cares were operated according to National Institutes of Health Guidelines. The mice were randomly divided into groups, 8 mice/group. Doses (25 mg/kg, 50 mg/kg and 100 mg/kg) of compounds were administered by gavage administration to the test groups, respectively. The positive control group was given access to Indomethacin (22 mg/kg, i.g.) and the vehicle control group was given access to the same volume of olive oil (22 mg/kg, i.g.). Thirty minutes after the administration, acute paw edema was induced in the right hind paw by subplantar injection of 1% freshly prepared carrageenan suspension in normal saline, 50 mL per a mouse. The thickness of the paw was measured pre-injection and at intervals of 1, 2, 3, and 4 h post-oral administration, using a Dial Thickness Gage. The percent increase of paw thickness was calculated based on the pre-injection thickness of the paw.

1.18 *in vivo* anti-inflammatory tests by mice ear swelling model

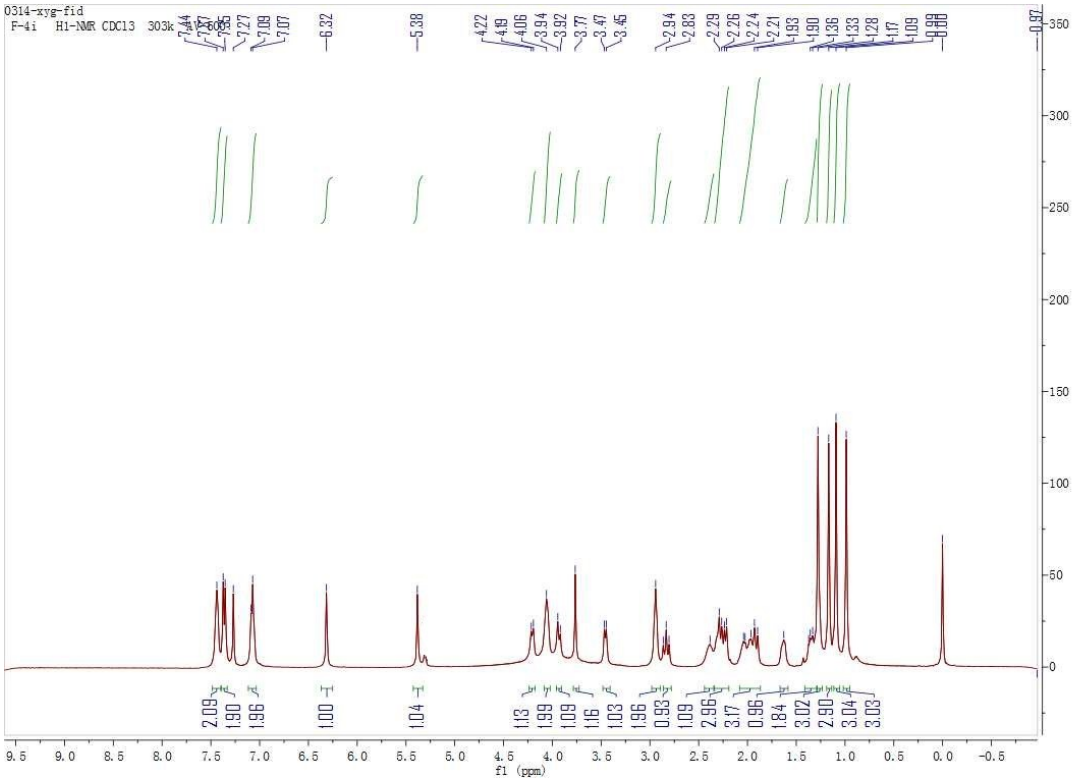
Ear swelling induced by xylene in mice was used to evaluate the anti-inflammatory activities of the target compounds. The limonin and their derivatives (100 mg/kg, i.g.) with naproxen (150 mg/kg, i.g.) as positive controls were suspended in 0.5 % CMC-Na. The vehicle control group treated with xylene was given 0.5 % CMC-Na with the same method. 90 minutes after administration of the corresponding drugs, 25 ul of xylene was applied to anterior and posterior surfaces of right ear lobe. Left ear was considered as control. 30 minutes after xylene application, the mice were sacrificed. Circular sections on both ears were taken using a cork borer with a diameter of 8 mm and weighed. Degree of swelling caused by the xylene was measured based on the weight of left ear without stimulus.

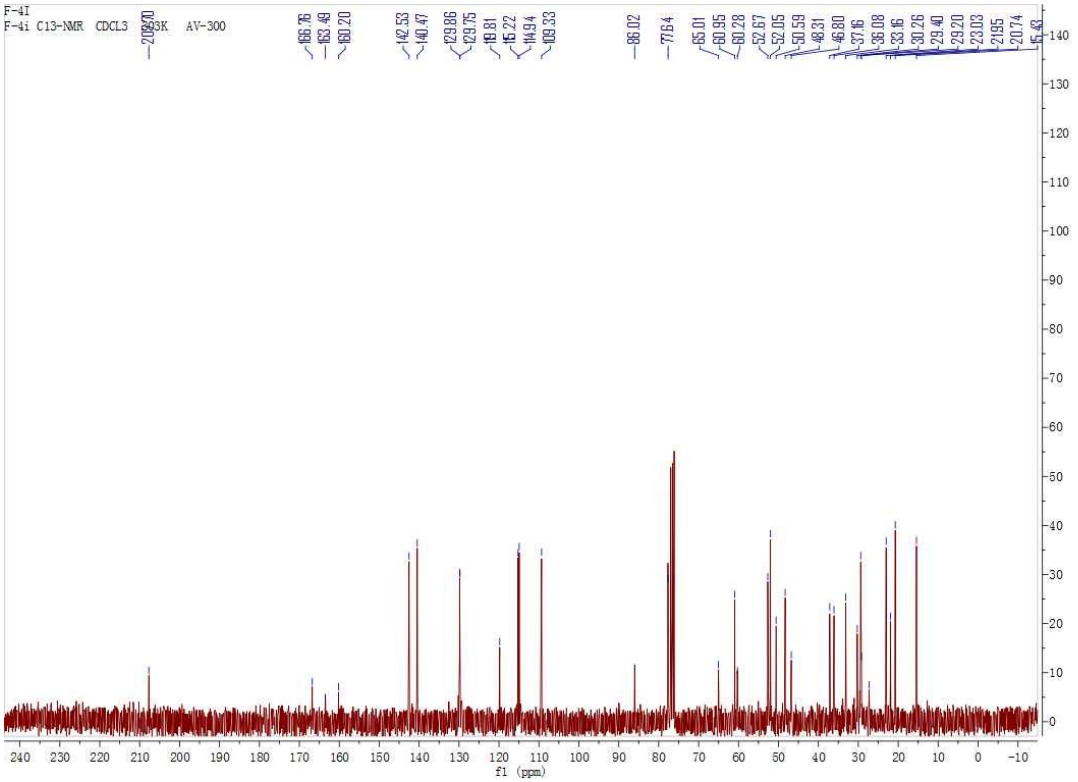
1.19 *in vivo* analgesic tests by acetic acid-induced abdominal writhing in mice

The test was performed as described by Collier et al. and Fontenele et al. Nociception was

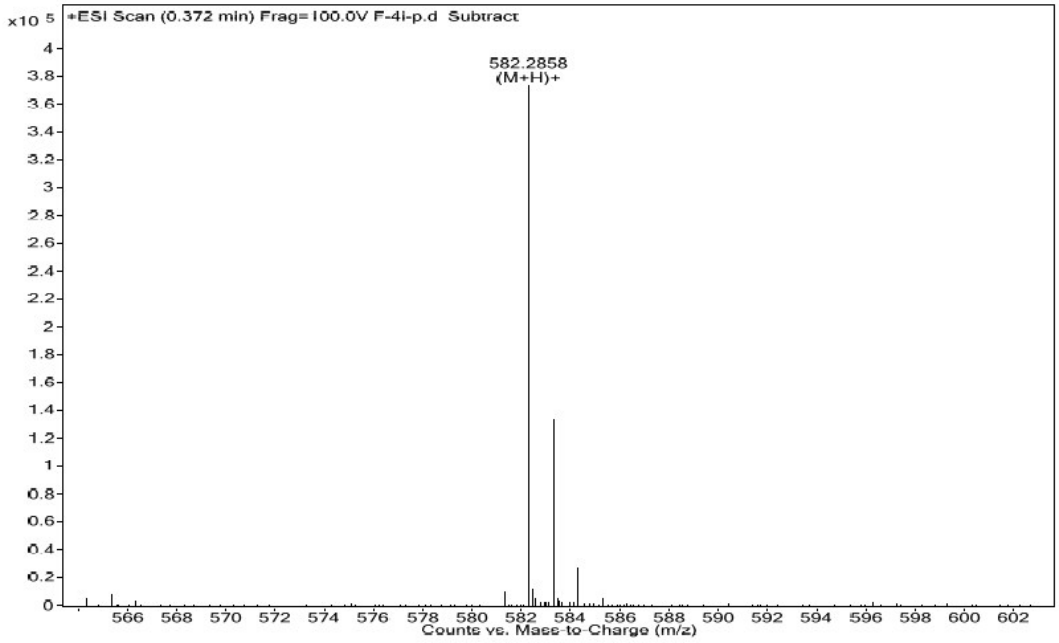
induced by an intraperitoneal (i.p.) injection of 0.6% acetic acid solution (10 ml/kg). Mice were orally treated with the tested compounds (70 mg/kg), limonin (70 mg/kg), and aspirin (200 mg/kg), 30 min later the acetic acid was injected. The control group received vehicle (0.5% CMC-Na). Immediately after the injection of acetic acid, each animal was isolated in an individual box (24 cm × 11 cm × 10 cm) to be observed during 15 min. The number of writhing and stretching was recorded and the anti-nociceptive activity was expressed as percentage change from writhing controls.

I-5a


0314-xyg-fid
F-4i H1-NMR CDCl3 303k AV-300
f1 (ppm)


F-4I
F-4i C13-NMR CDCL3 303K AV-300
f1 (ppm)

Sample Name		**Position**	P1-A6	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.03	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	F-4i-p.d	**ACQ Method**		**Comment**		**Acquired Time**	5/26/2015 4:44:46 PM

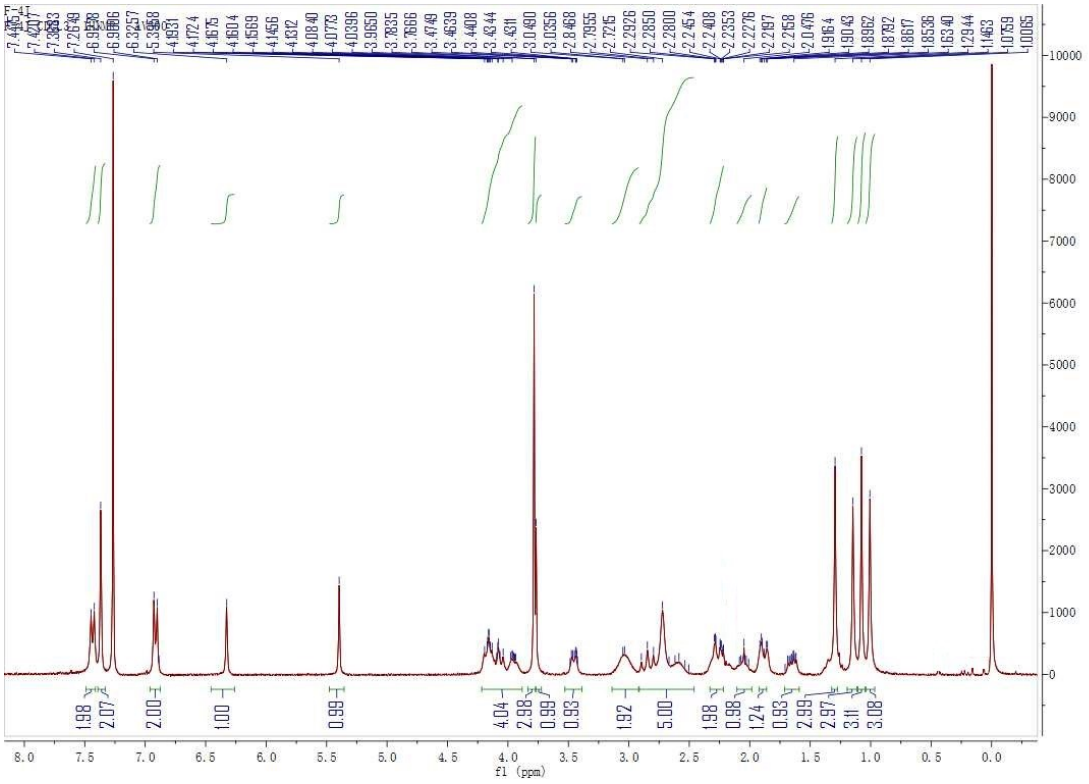


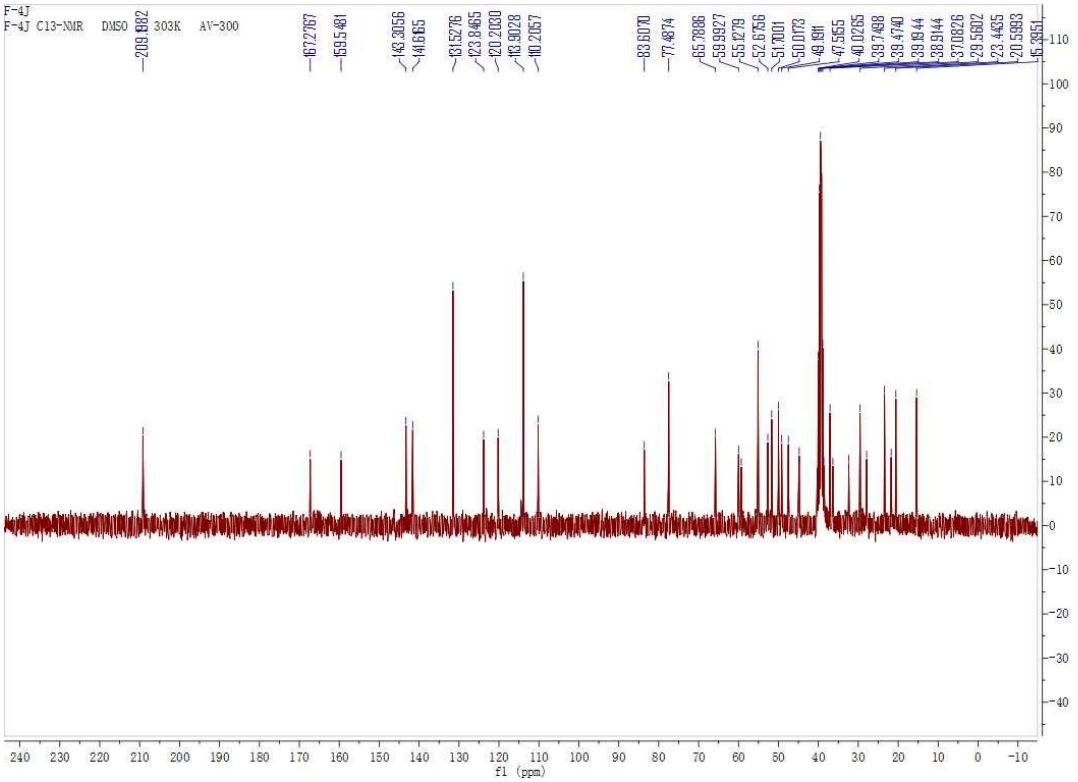
MS Formula Results: + Scan (0.372 min) Sub (F-4i-p.d)

m/z	Ion	Formula	Abundance
582.2858	(M+H)+	C33 H41 F N O7	373663.6

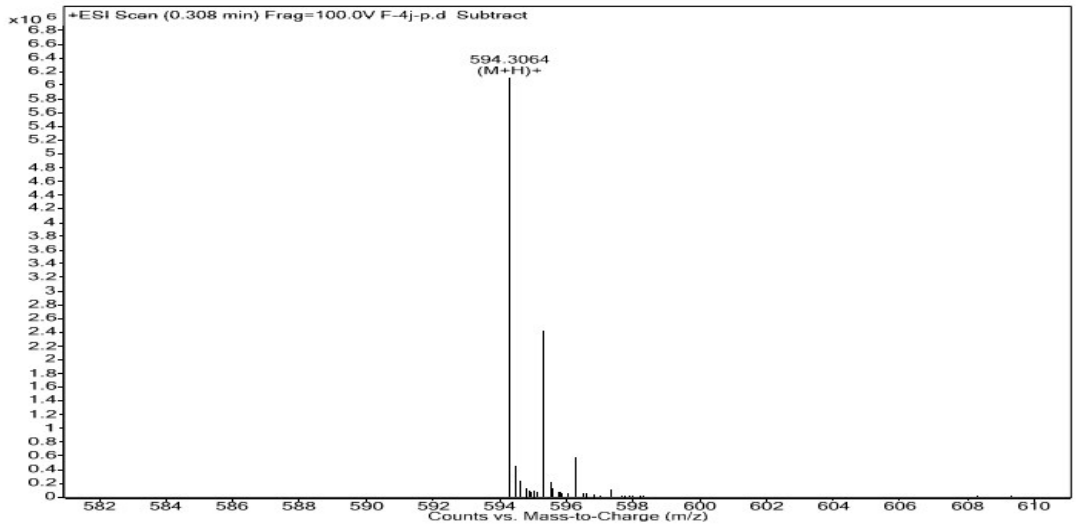
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C33 H40 F N O7	C33 H41 F N O7	582.2862	99.05		581.2785	581.2789	0.59	0.59	99.24	97.77	99.58	582.2858	14

I-5b





Sample Name		**Position**	P1-D7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.3	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	F-4j-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/22/2016 2:18:28 PM

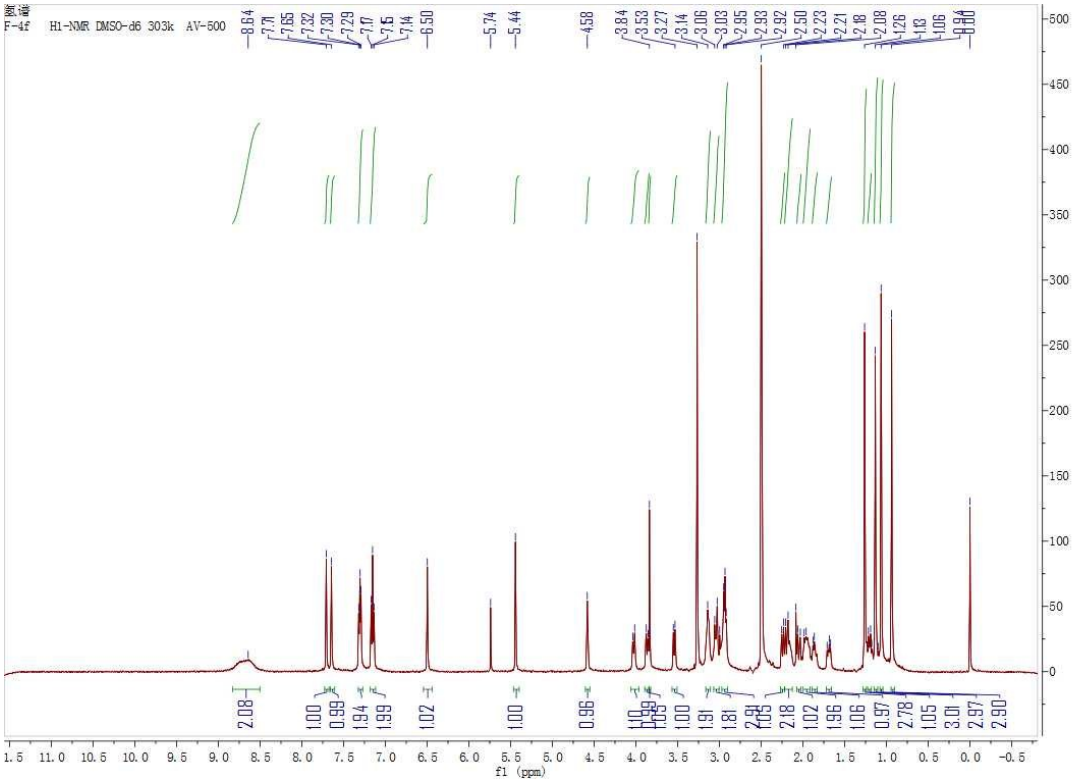


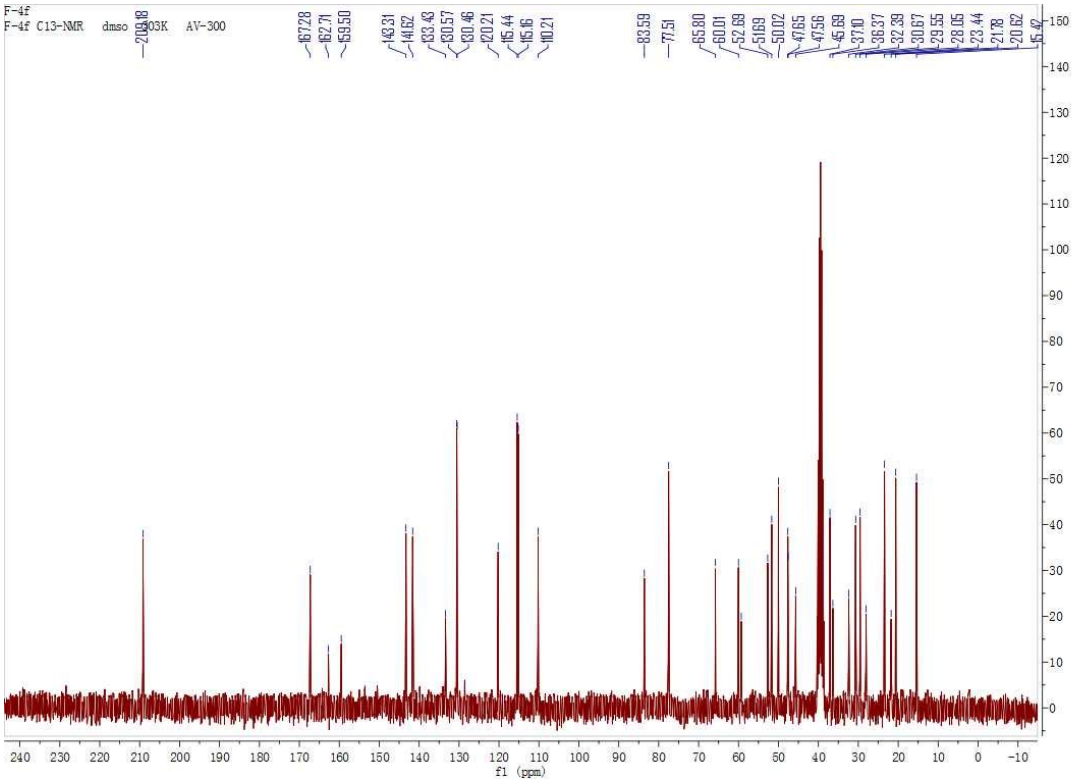
MS Formula Results: + Scan (0.308 min) Sub (F-4j-p.d)

m/z	Ion	Formula	Abundance
594.3064	(M+H)+	C34 H44 N O8	6103117.5

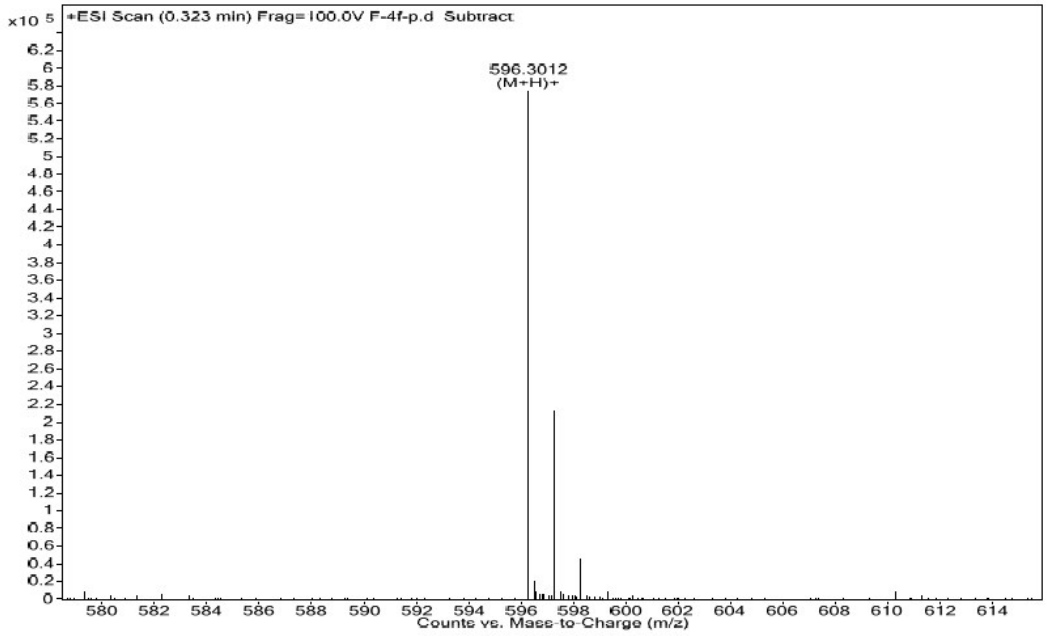
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C34 H43 N O8	C34 H44 N O8	594.3061	99.36		593.2991	593.2989	-0.36	0.36	98.96	98.88	99.84	594.3064	14

I-5c


F-4f H1-NMR DMSO-d6 303k AV-500
f1 (ppm)


F-4f
F-4f C13-NMR dmso 303K AV-300
f1 (ppm)

Sample Name		**Position**	P1-A7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.03	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	F-4f-p.d	**ACQ Method**		**Comment**		**Acquired Time**	5/26/2015 4:46:57 PM

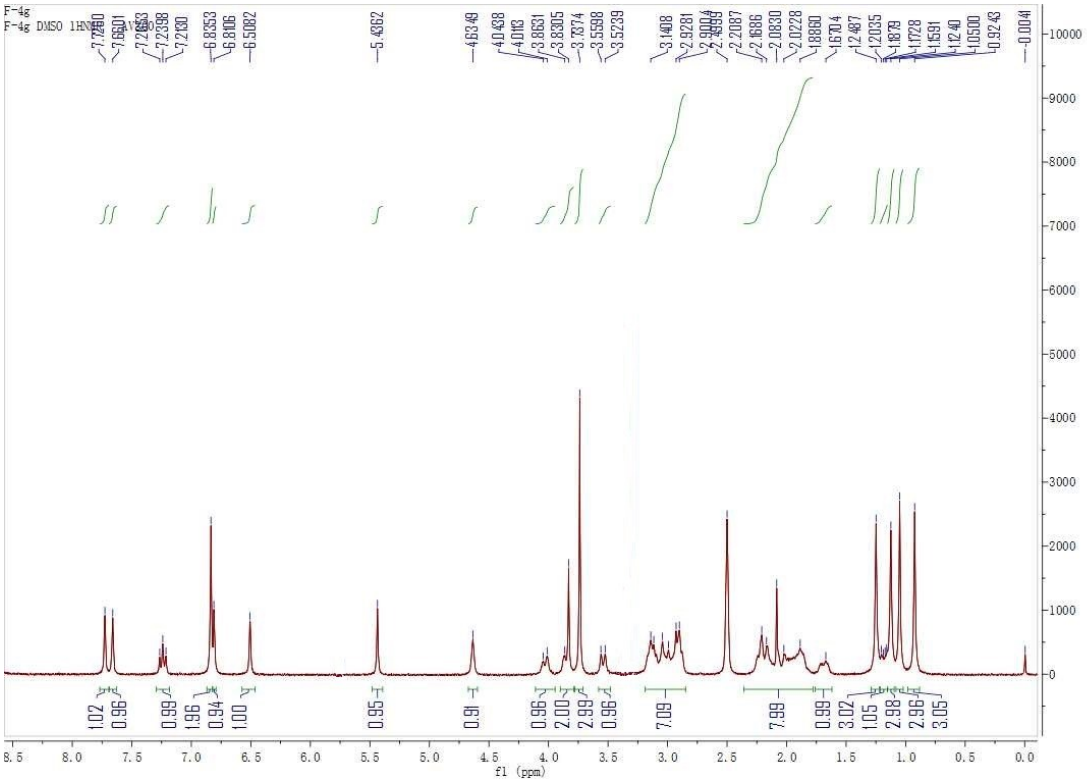


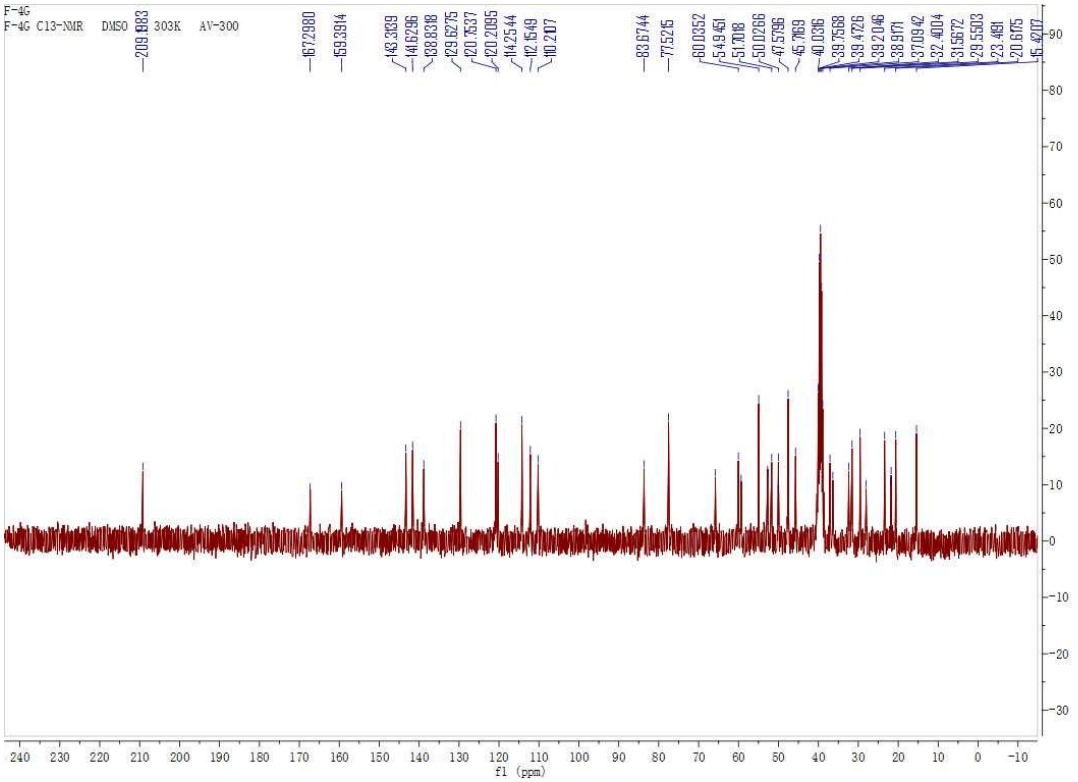
MS Formula Results: + Scan (0.323 min) Sub (F-4f-p.d)

m/z	Ion	Formula	Abundance
596.3012	(M+H)+	C34 H43 F N O7	573316.1

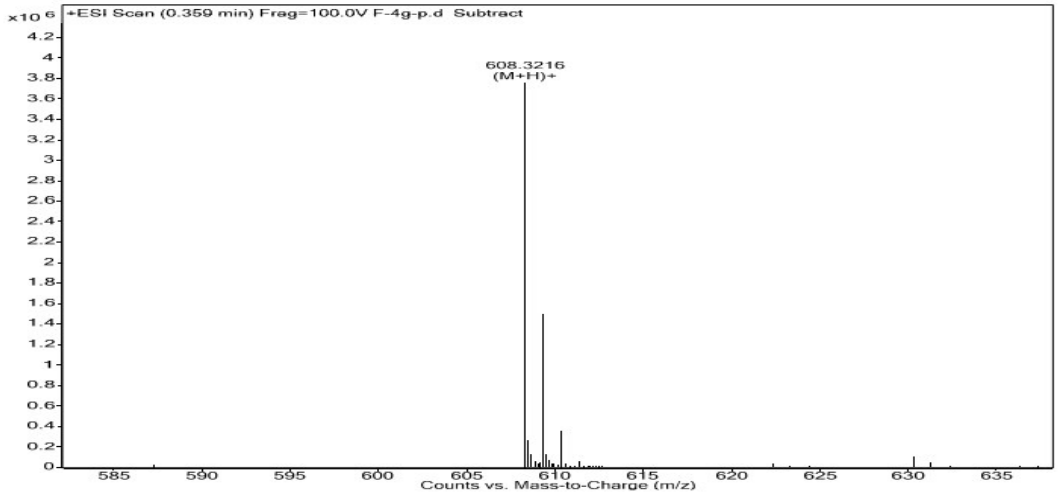
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C34 H42 F N O7	C34 H43 F N O7	596.3018	98.63		595.2939	595.2945	1.1	1.1	99.47	97.9	98.5	596.3012	14

I-5d


F-4g
F-4g DMSO 1HNMR
f1 (ppm)


F-4G
F-4G C13-NMR DMSO 303K AV-300
f1 (ppm)

Sample Name		**Position**	P1-D5	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.3	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	F-4g-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/22/2016 2:10:31 PM

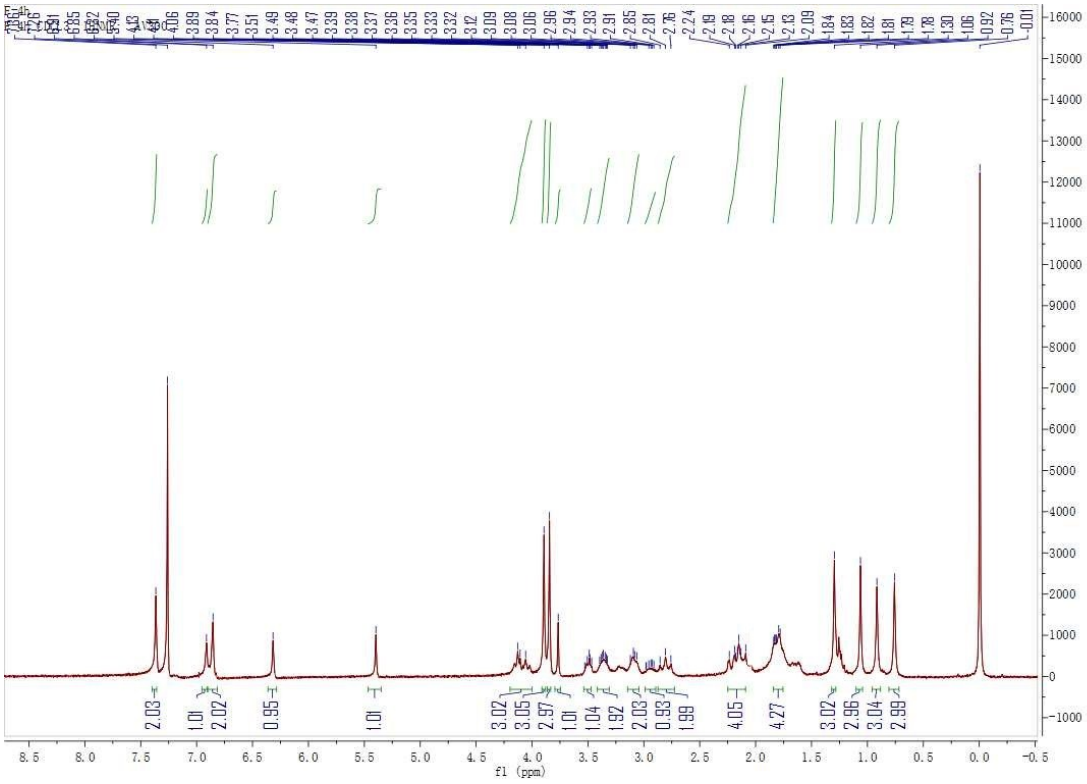


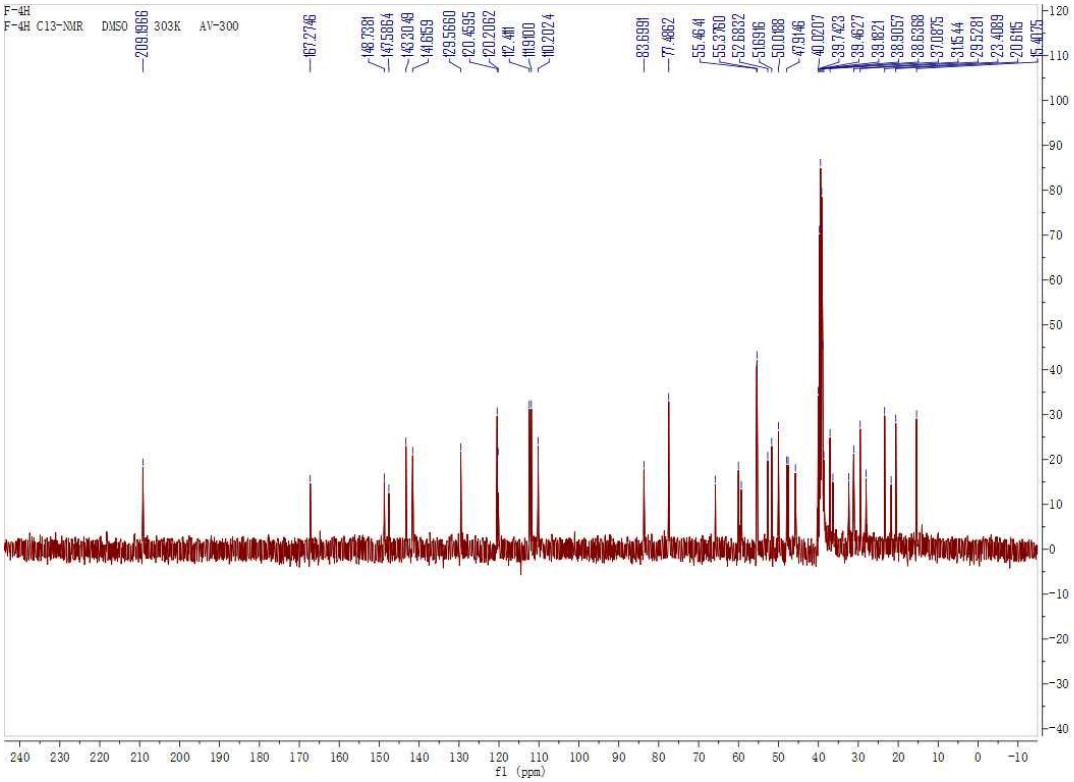
MS Formula Results: + Scan (0.359 min) Sub (F-4g-p.d)

m/z	Ion	Formula	Abundance
608.3216	(M+H)+	C35 H46 N O8	3757050.3

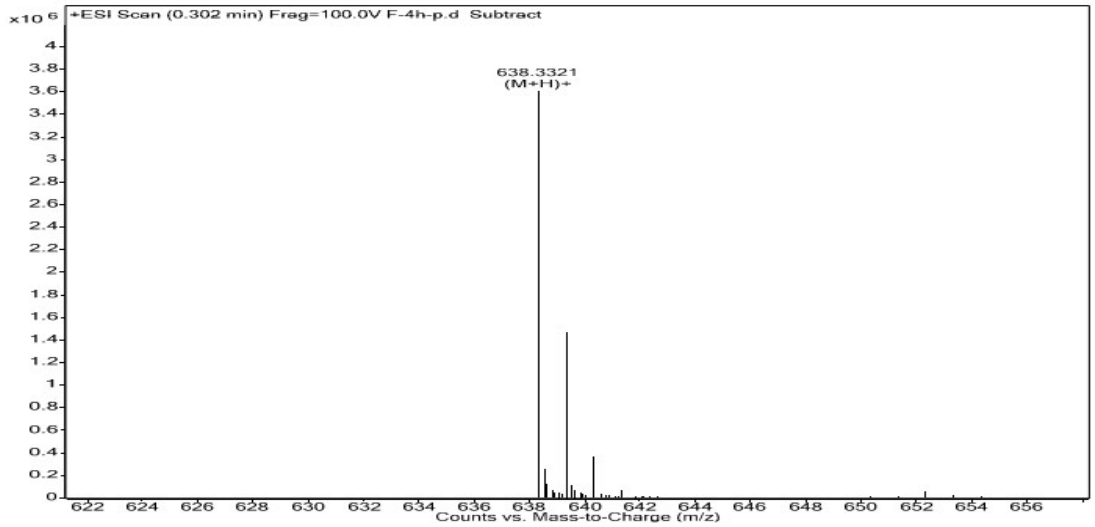
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C35 H45 N O8	C35 H46 N O8	608.3218	99.56		607.3143	607.3145	0.37	0.37	99.7	98.84	99.83	608.3216	14

I-5e





Sample Name		**Position**	P1-D6	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.3	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	F-4h-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/22/2016 2:13:43 PM

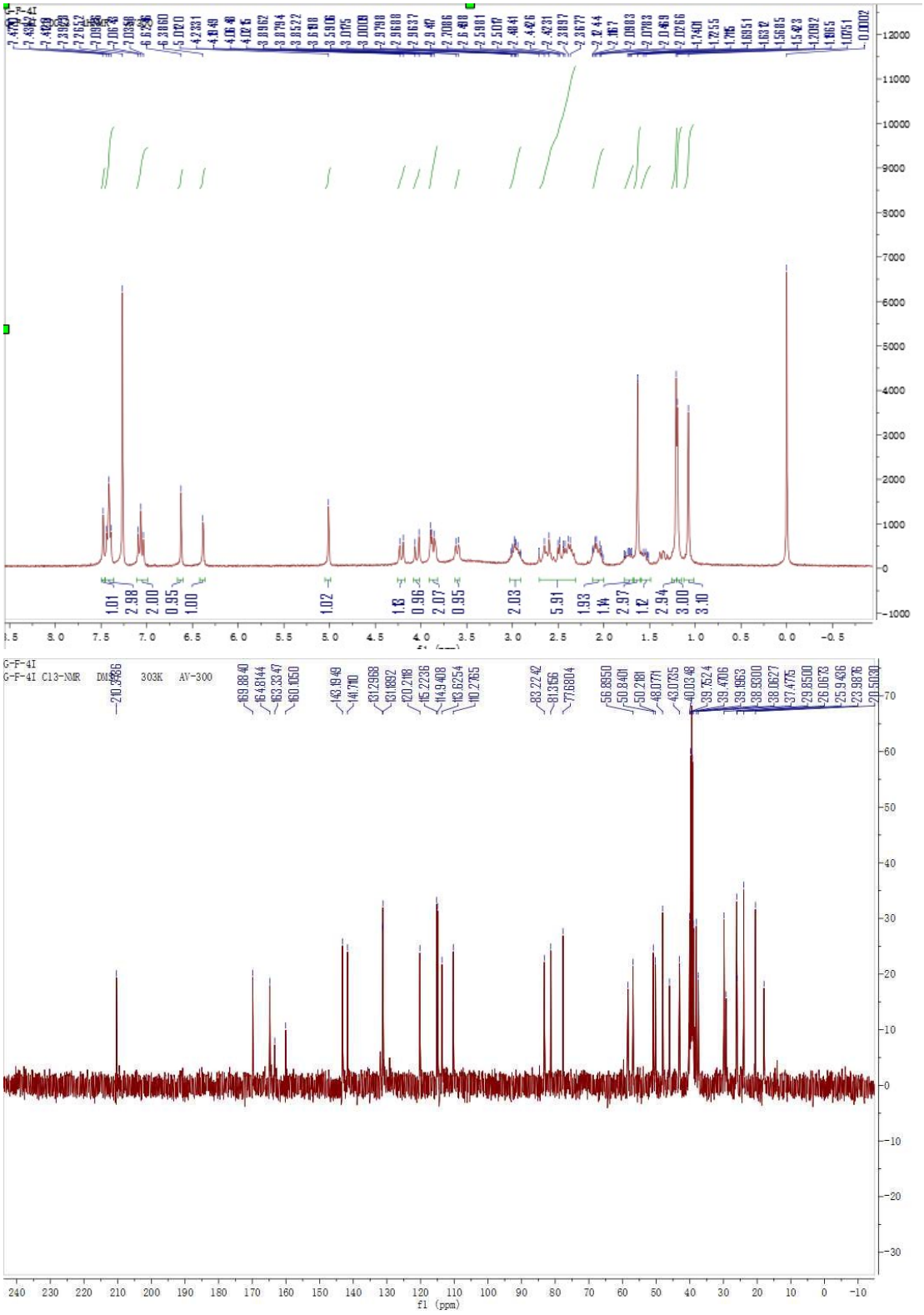


MS Formula Results: + Scan (0.302 min) Sub (F-4h-p.d)

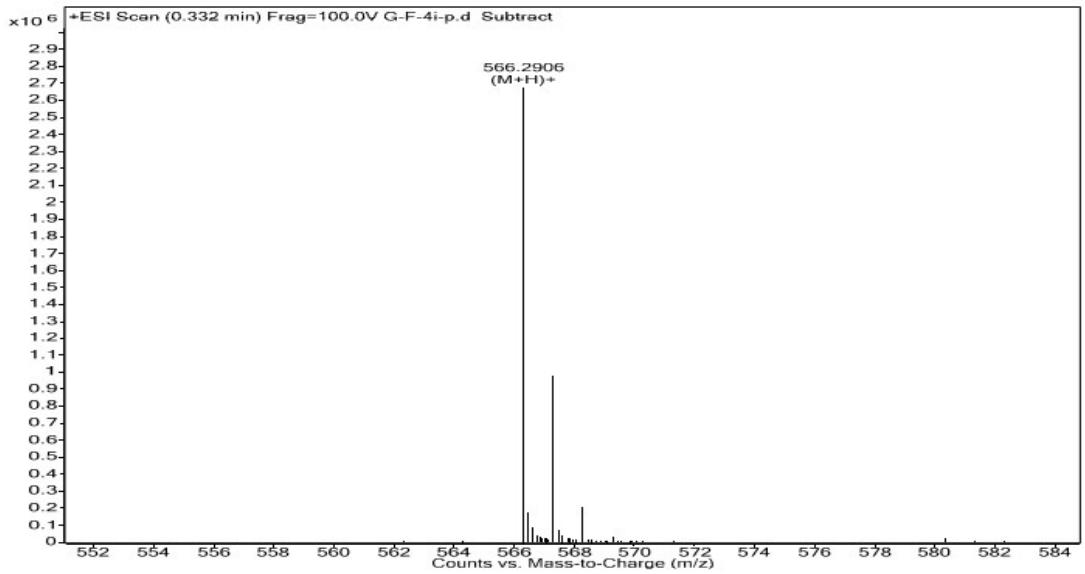
m/z	Ion	Formula	Abundance
638.3321	(M+H)+	C36 H48 N O9	3602683.8

Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C36 H47 N O9	C36 H48 N O9	638.3324	99.54		637.3248	637.3251	0.42	0.42	99.86	98.68	99.77	638.3321	14

II-5a



Sample Name		**Position**	P1-D9	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.5	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	G-F-4i-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/22/2016 2:27:18 PM

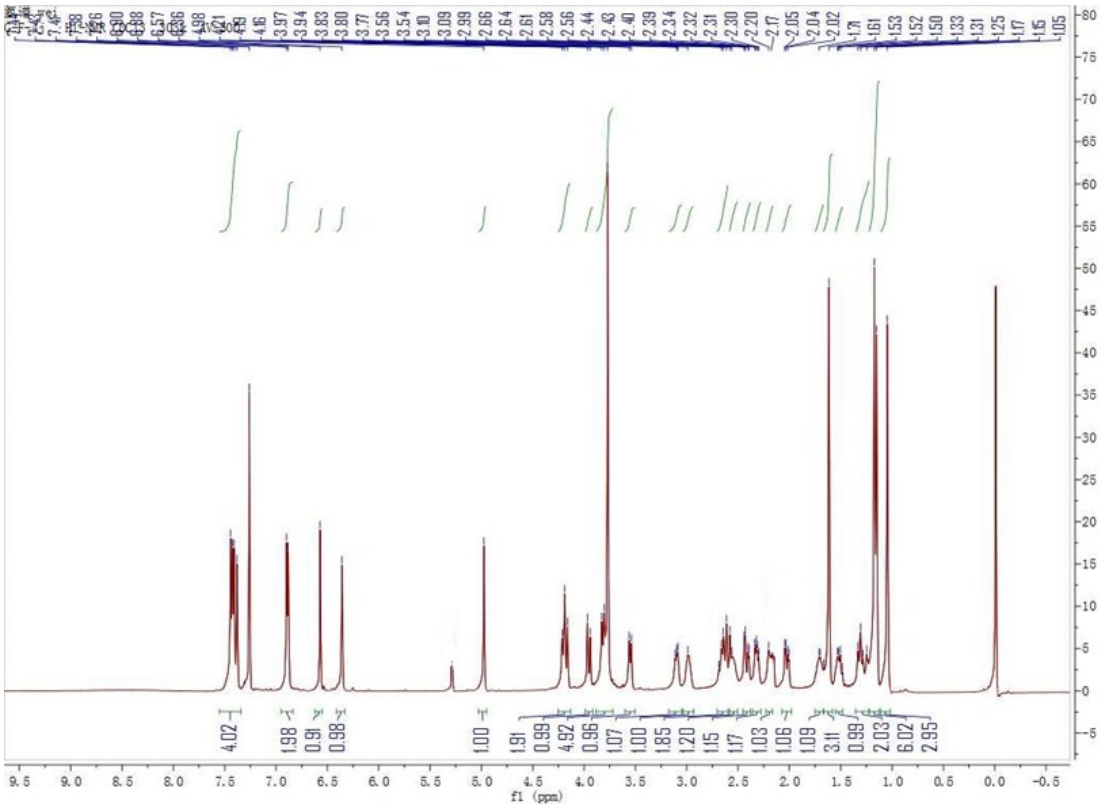


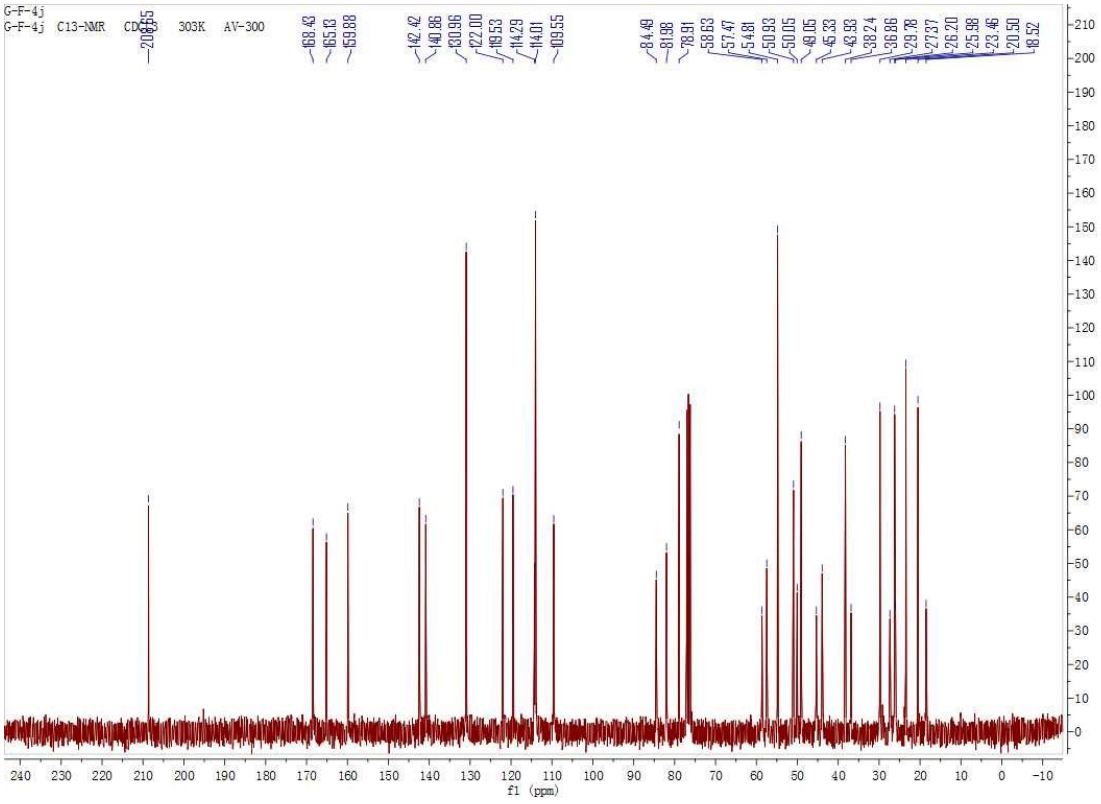
MS Formula Results: + Scan (0.332 min) Sub (G-F-4i-p.d)

m/z	Ion	Formula	Abundance
566.2906	(M+H)+	C33 H41 F N O6	2672381.8

Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C33 H40 F N O6	C33 H41 F N O6	566.2912	98.29		565.2833	565.284	1.12	1.12	99.96	95.85	98.51	566.2906	14

II-5b


4.02
1.98
0.91
0.98
1.00
1.91
0.99
4.92
0.96
1.07
1.00
1.85
1.20
1.15
1.17
1.03
1.06
1.09
3.11
0.99
2.03
6.02
2.95
f1 (ppm)


G-F-4j
G-F-4j C13-NMR CDCl3 303K AV-300
168.43
165.13
159.88
142.42
140.86
130.96
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119.53
114.29
114.01
109.55
84.49
81.98
78.91
58.63
57.47
54.81
50.93
50.05
46.05
45.33
43.93
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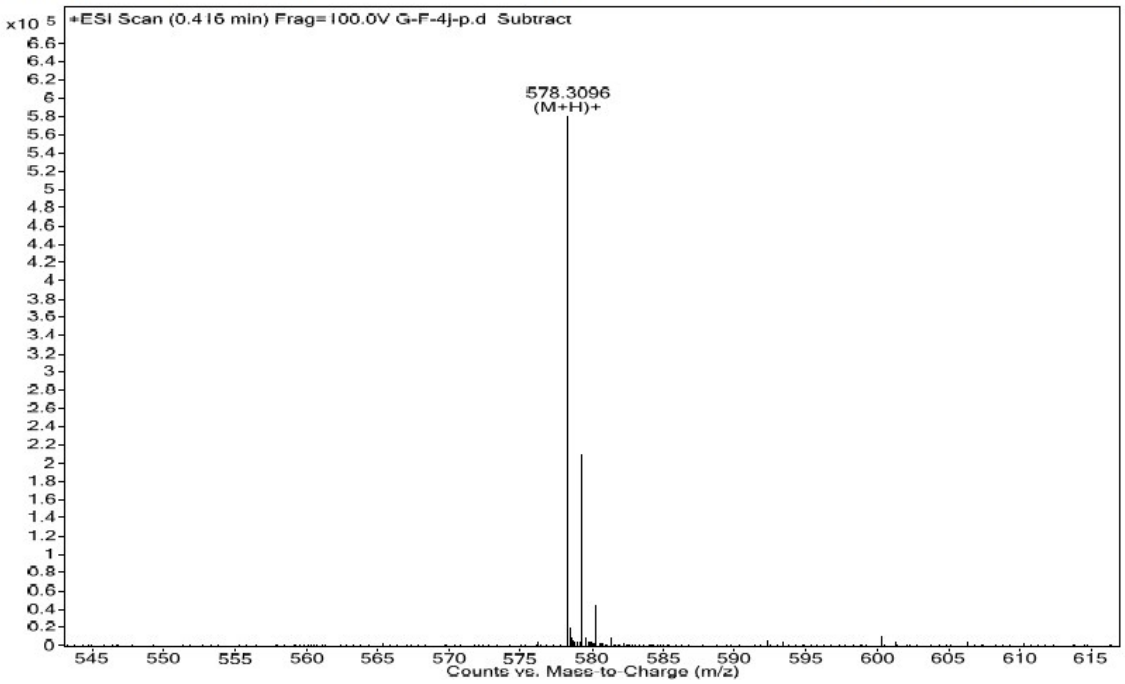
26.20
25.98
23.46
20.50
18.52
f1 (ppm)

Sample Name		**Position**	P1-A9	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.03	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	G-F-4j-p.d	**ACQ Method**		**Comment**		**Acquired Time**	5/26/2015 4:51:21 PM

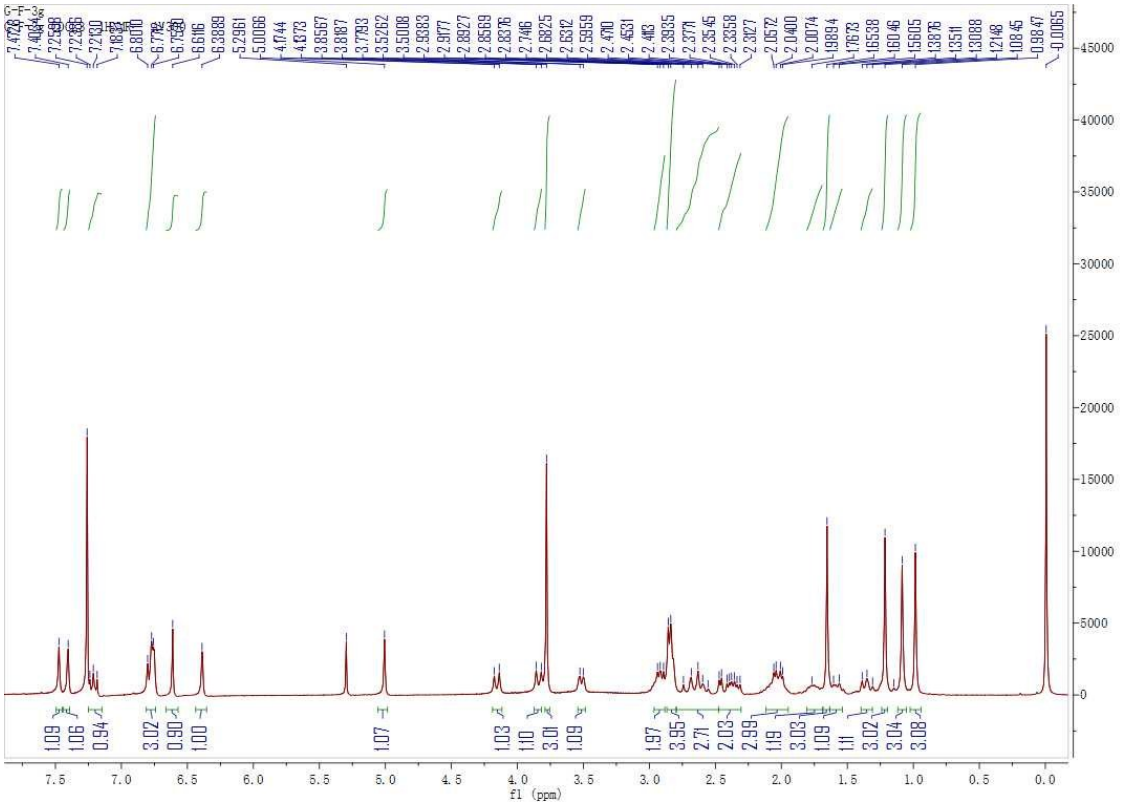


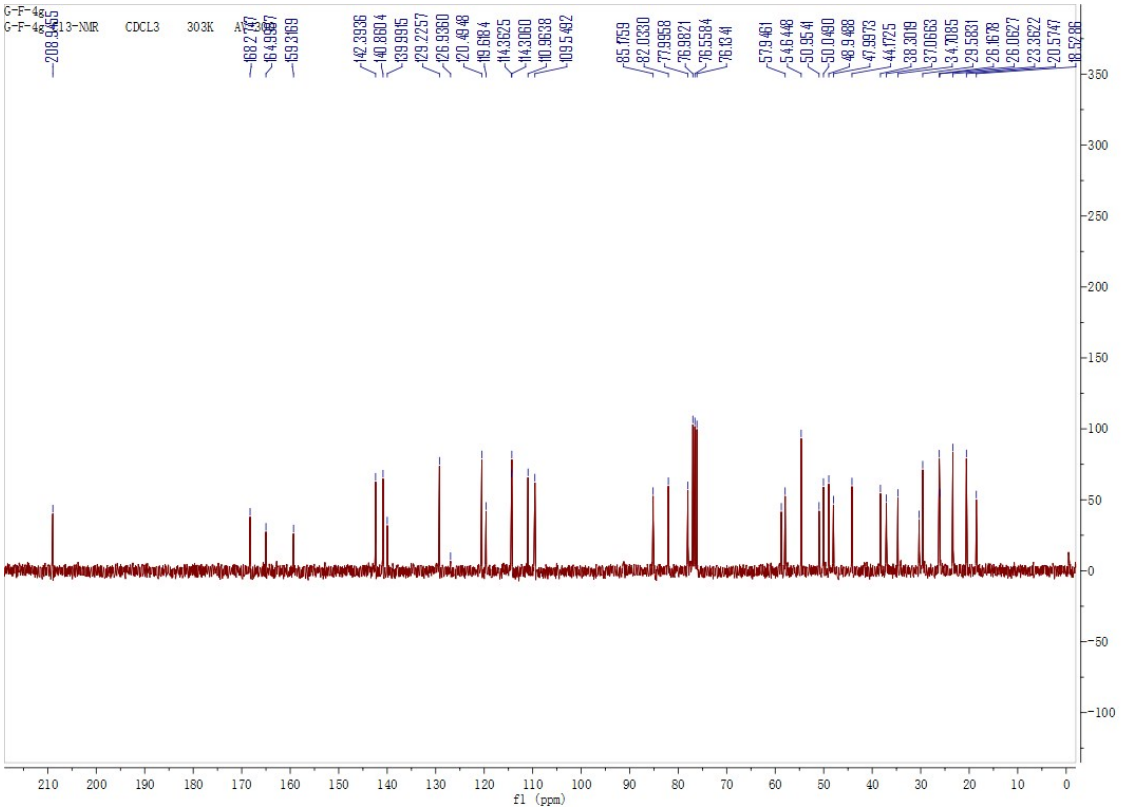
MS Formula Results: + Scan (0.416 min) Sub (G-F-4j-p.d)

m/z	Ion	Formula	Abundance
578.3096	(M+H)+	C34 H44 N O7	580220.6

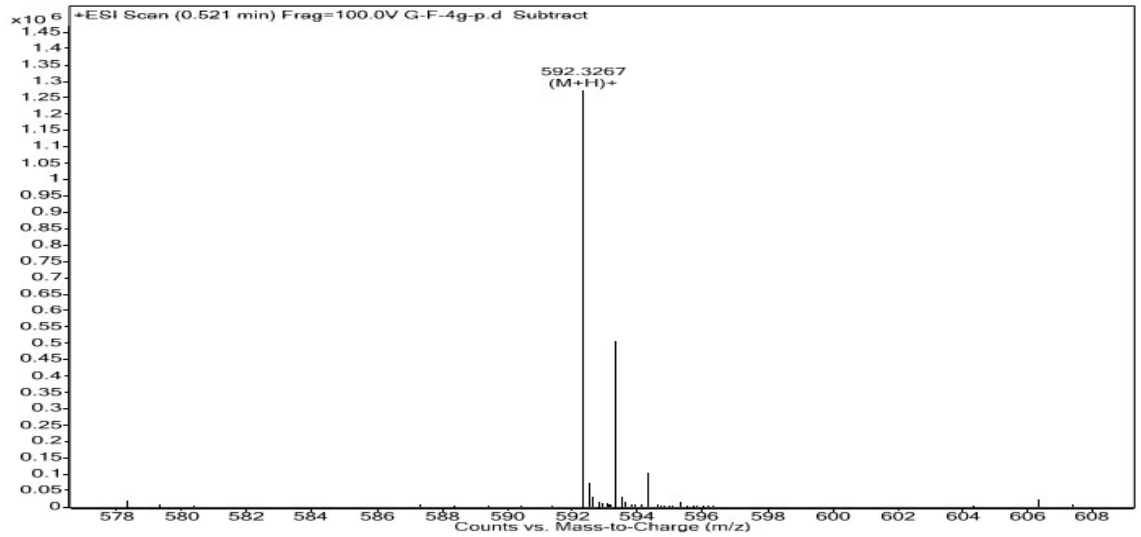
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
✓	C34 H43 N O7	C34 H44 N O7	578.3112	94.64		577.3023	577.304	2.92	2.92	98.41	99.05	90.17	578.3096	14

II-5d





Sample Name		**Position**	P1-D8	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.5	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	G-F-4g-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/22/2016 2:24:06 PM

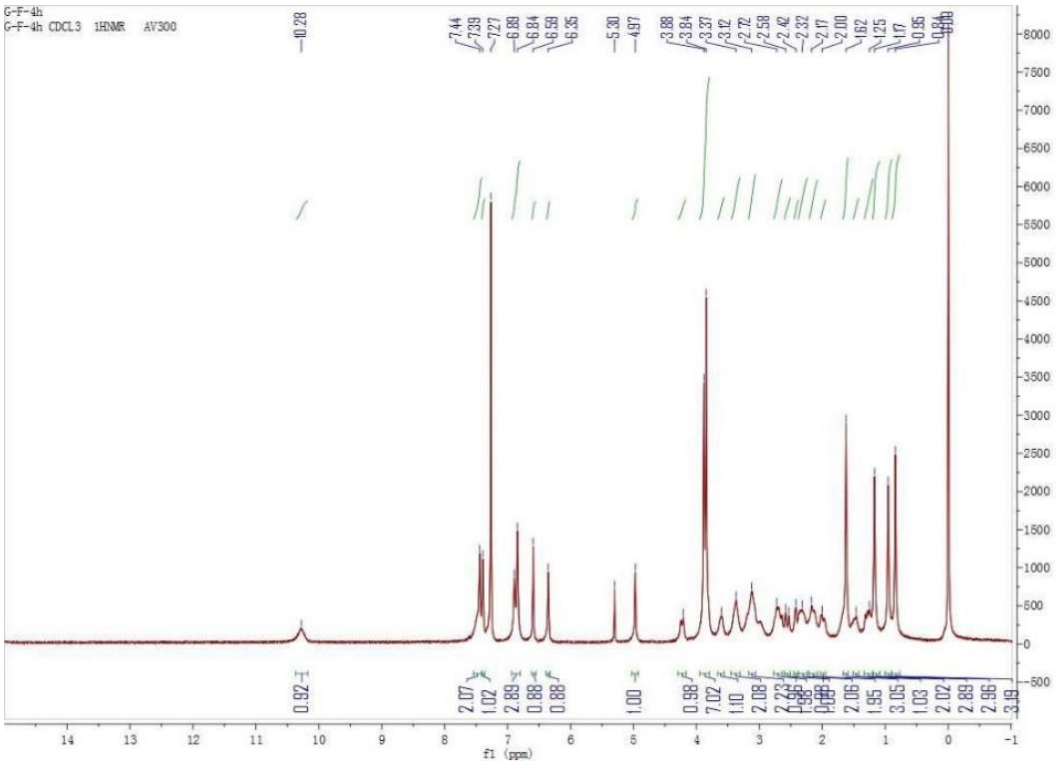


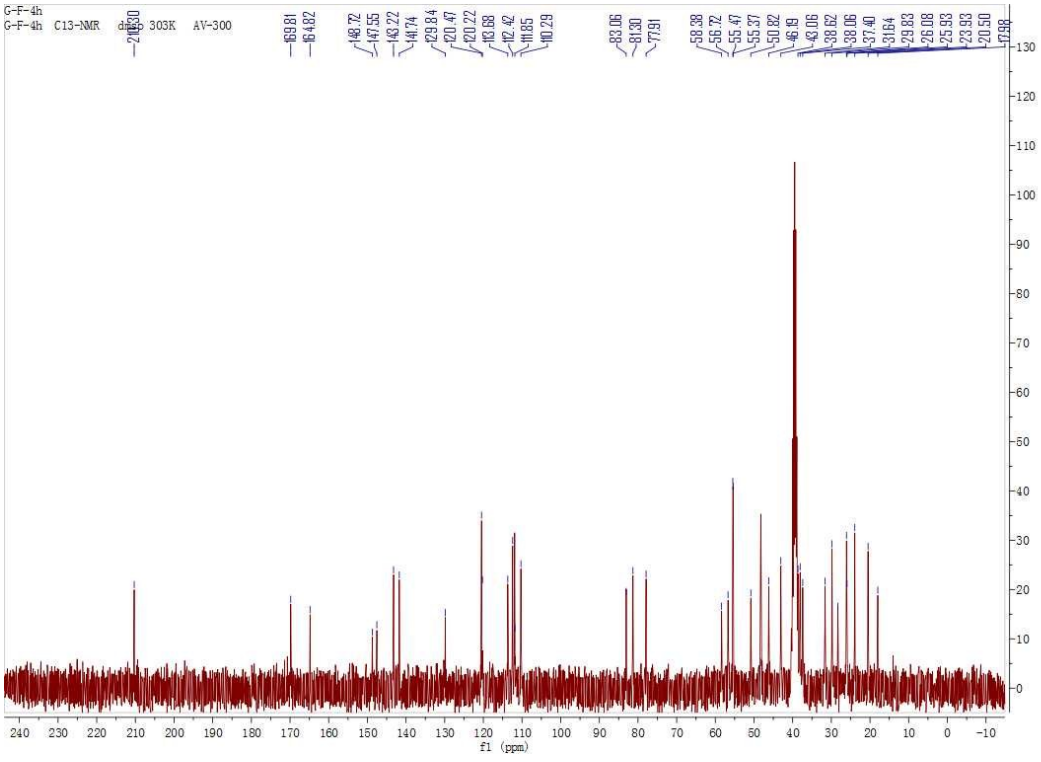
MS Formula Results: + Scan (0.521 min) Sub (G-F-4g-p.d)

m/z	Ion	Formula	Abundance
592.3267	(M+H)+	C35 H46 N O7	1270509.5

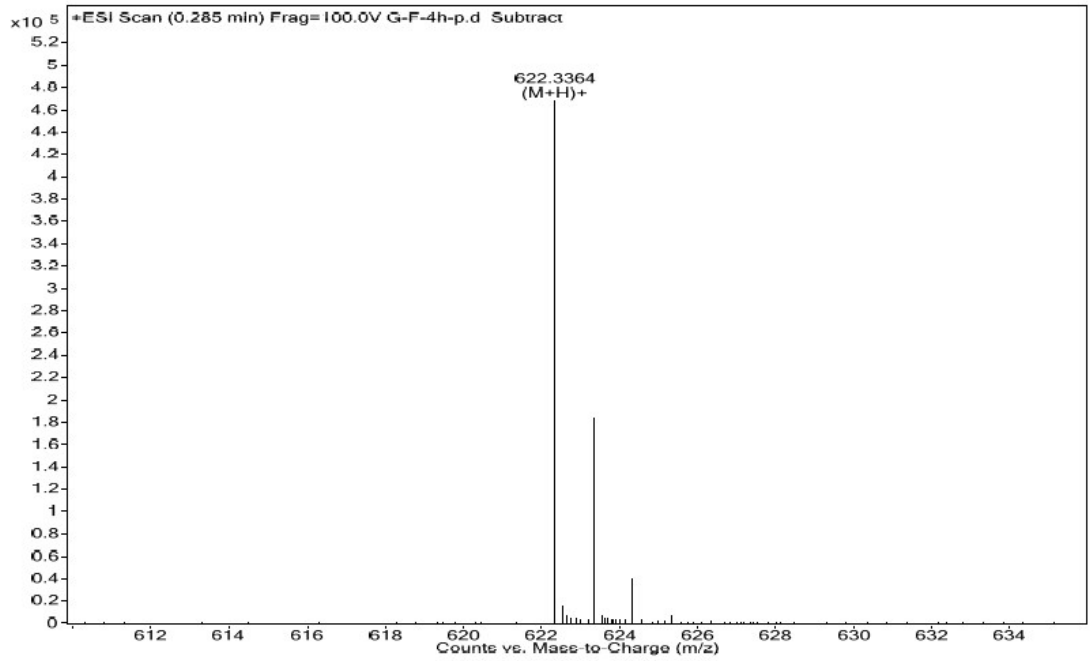
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C35 H45 N O7	C35 H46 N O7	592.3269	97.29		591.3194	591.3196	0.3	0.3	98.76	90.33	99.89	592.3267	14

II-5e





Sample Name		**Position**	P1-A8	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.03	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	G-F-4h-p.d	**ACQ Method**		**Comment**		**Acquired Time**	5/26/2015 4:48:55 PM

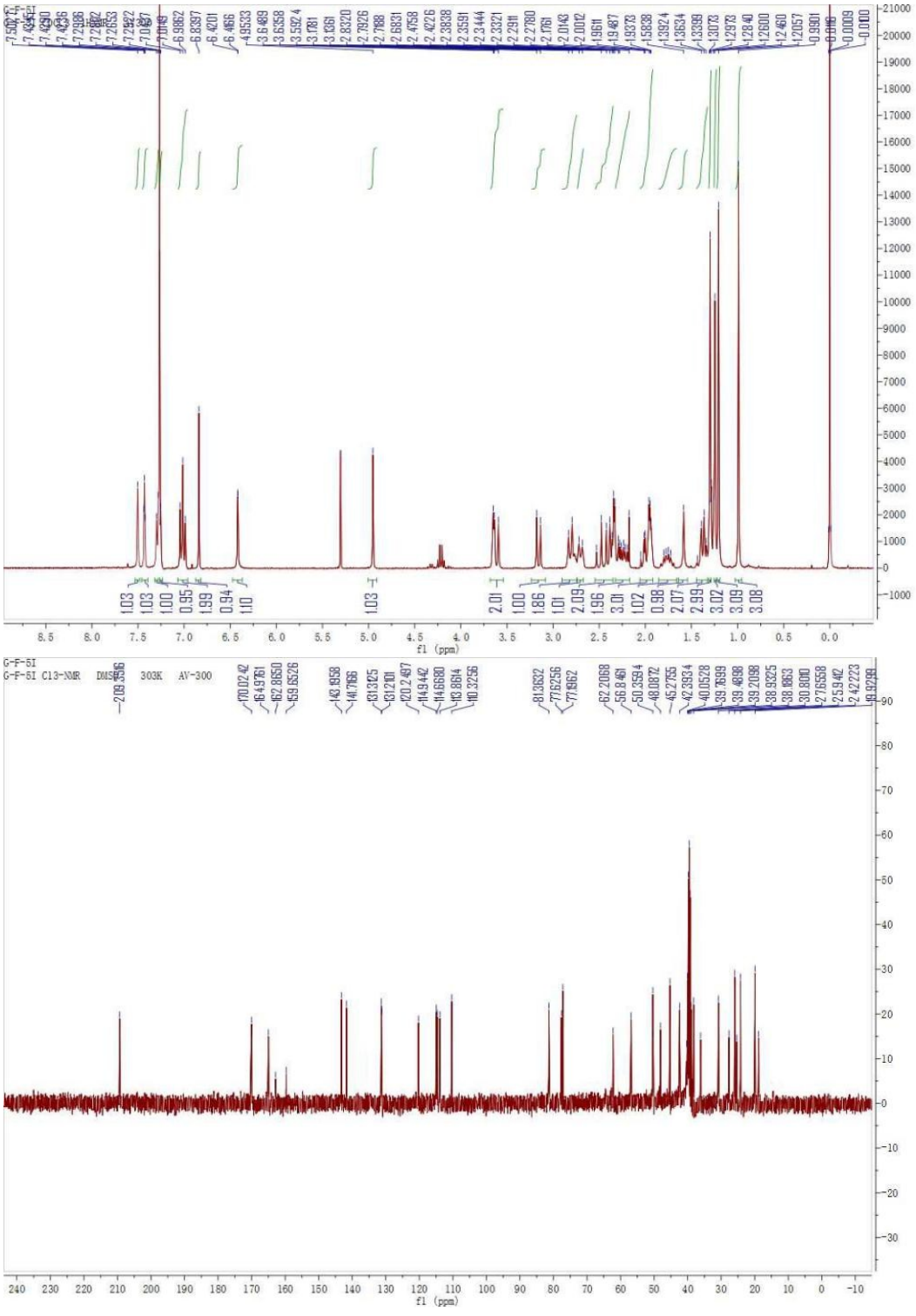


MS Formula Results: + Scan (0.285 min) Sub (G-F-4h-p.d)

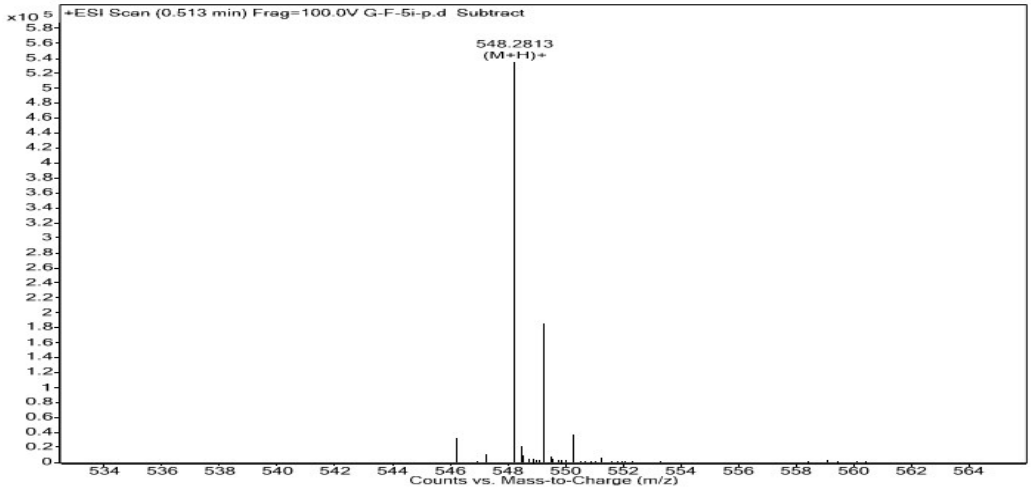
m/z	Ion	Formula	Abundance
622.3364	(M+H)+	C36 H48 N O8	467204.6

Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
✓	C36 H47 N O8	C36 H48 N O8	622.3374	97.71		621.3291	621.3302	1.67	1.67	99.12	98.47	96.48	622.3364	14

II-6a



Sample Name		**Position**	P1-E1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.5	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	G-F-5i-p.d	**ACQ Method**		**Comment**		**Acquired Time**	3/22/2016 2:30:12 PM

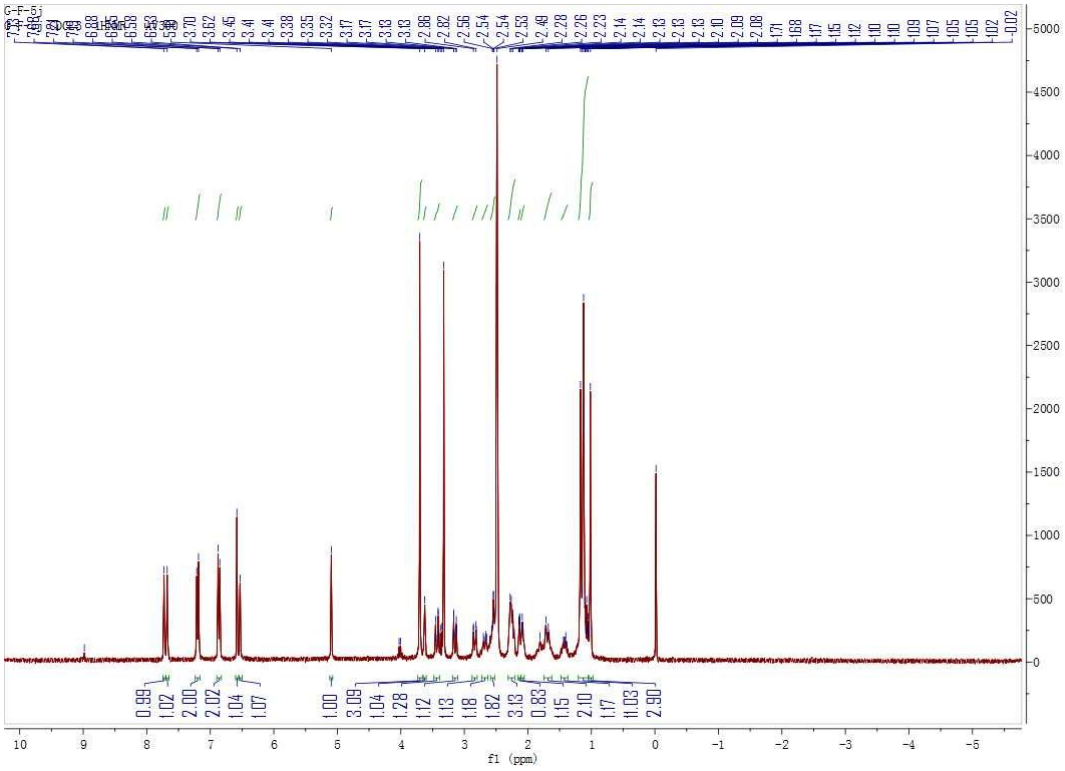


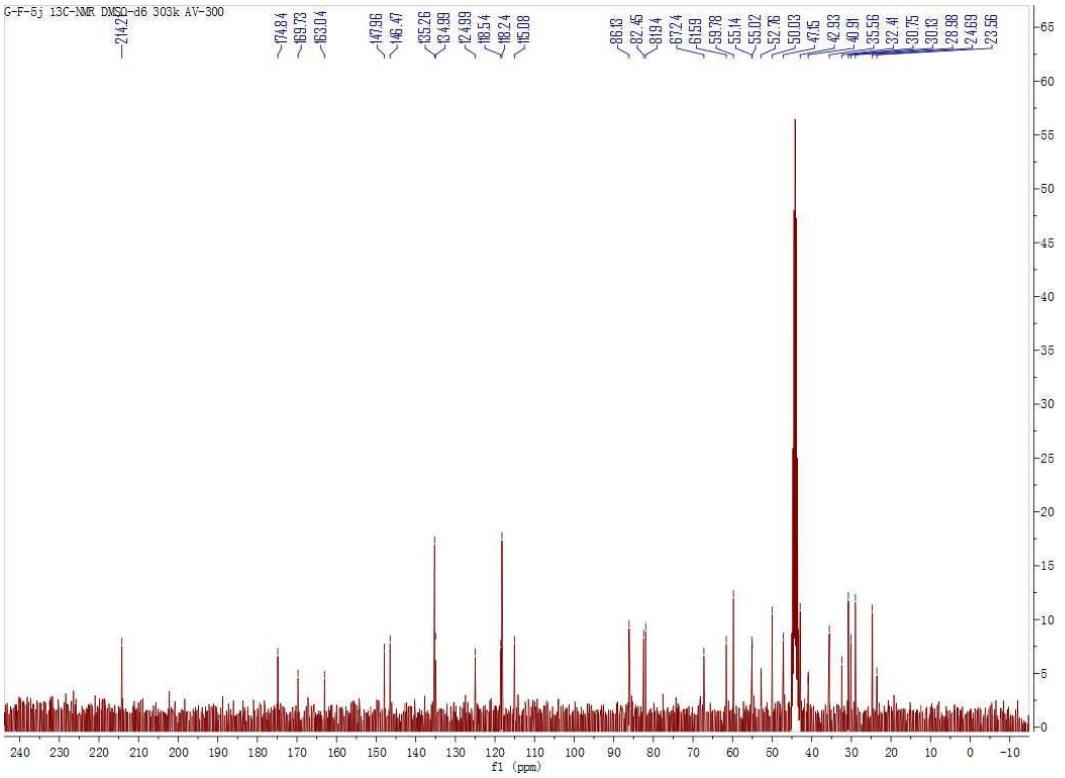
MS Formula Results: + Scan (0.513 min) Sub (G-F-5i-p.d)

m/z	Ion	Formula	Abundance
548.2813	(M+H)+	C33 H39 F N O5	535142.4

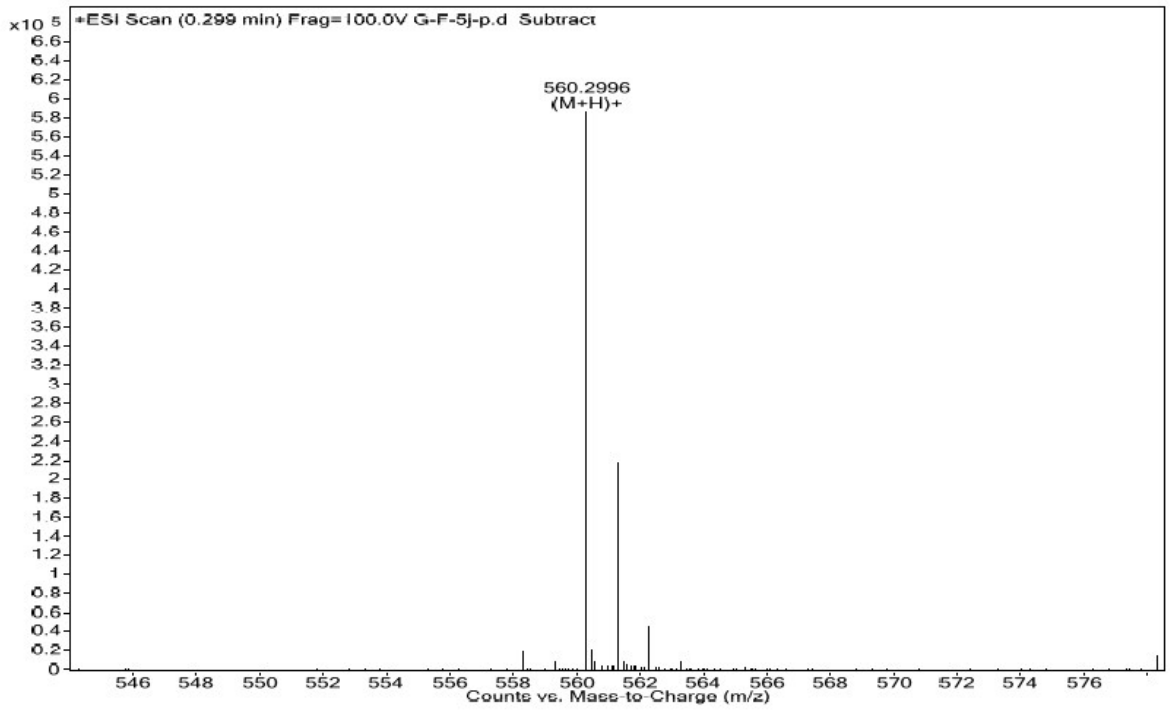
Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C33 H38 F N O5	C33 H39 F N O5	548.2807	98.1		547.274	547.2734	-1.04	1.04	98.49	96.33	98.75	548.2813	15

II-6b





Sample Name		**Position**	P1-B1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	0.03	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	G-F-5j-p.d	**ACQ Method**		**Comment**		**Acquired Time**	5/26/2015 4:55:00 PM



MS Formula Results: + Scan (0.299 min) Sub (G-F-5j-p.d)

m/z	Ion	Formula	Abundance
560.2996	(M+H)+	C34 H42 N O6	586167.4

Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
☑	C34 H41 N O6	C34 H42 N O6	560.3007	97.36		559.2923	559.2934	2	2	99.76	98.48	95.37	560.2996	15