Electronic Supplementary Information

Transition metal mediated construction of pyrrole ring on 2,3-dihydroquinolin-4(1*H*)-one: Synthesis and pharmacological evaluation of novel tricyclic heteroarenes

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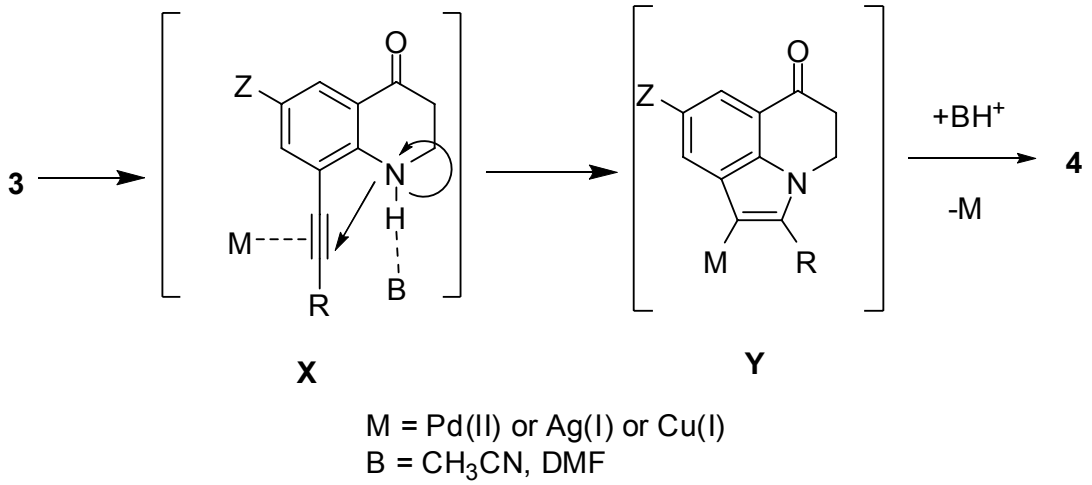
Scheme 4. Probable mechanism for the metal-mediated intramolecular cyclization of alkyne **3**.



Preparation of 6-substituted 8-iodo-2,3-dihydroquinolin-4(1*H*)-one (1)

6-Methyl-2,3-dihydroquinolin-4(1*H*)-one (7a): Methyl acrylate (8.0 g, 93.3 mmol) was added to a solution of 4-methylaniline (10.0 g) in acetic acid (20 mL). The mixture was heated to 70 ºC for 4.0 h. The mixture was allowed to cool to room temperature and partitioned between dicholoromethane (200 mL) and H_2O (100 mL). The combined organic layers were washed with brine, treated with Na_2SO_4, filtered and concentrated to give the crude methyl 3-(*p*-tolylamino)propanoate (**6a**) in quantitative yield. This was used in the next step without further purification.

Phosphorus pentoxide (18.0 g) in methane sulfonic acid (180.0 mL) was stirred at 130 ^{0}C until a clear solution is obtained. The mixture was allowed to cool to room temperature for 15 min, and the compound **6a** was added. The mixture was heated to 90 ^{0}C for 12.0 h. The reaction mass was cooled to 30 ^{0}C and poured into ice. A solution of 50% NaOH was added, until the pH was 7-8. The mixture was extracted with dicholoromethane (2 x 500 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using 10% ethyl acetate /n-hexane to afford the title compound as an off yellow solid (5.0 g, 33.3 %); mp 65 ºC; R_f 0.25 (25% E.A / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.11 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.27 (bs, 1H), 3.53 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 20.1, 38.1, 42.3, 115.8, 118.3, 126.8, 126.9, 136.3, 150.1, 193.9; IR (cm^{-1}, KBr) cm^{-1} 3370, 3020, 2920, 1660, 1245 Mass (ES) m/z 162 (M+1, 100 %); HRMS (ESI): calcd for $C_{10}H_{12}No$ $(M+H)^+$ 162.0920, found 162.0923

6-Chloro-2,3-dihydroquinolin-4(1*H*)-one (7b): This compound was prepared from 4-chloroaniline according to the procedure described above. This compound was isolated as yellow solid (4.5 g, 29.0 %); mp 78 ºC; R_f 0.25 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.8 (d, *J* = 2.1 Hz, 1H), 7.21 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 4.40 (bs, 1H), 3.58 (m, 2H), 2.70 (t, *J* = 6.8 Hz, 1H),; ^{13}C NMR ($CDCl_3$, 200 MHz) δ 37.7, 42.1, 117.5, 120.0, 123.3, 126.9, 134.6, 135.3, 150.3, 192.5; IR (cm^{-1}, KBr) cm^{-1} 3375, 3075, 2930, 1668, 1248 Mass (ES) m/z 182 (M+1, 100 %); HRMS (ESI): calcd for C_9H_9ClNo $(M+H)^+$ 182.0402, found 182.0413

8-Iodo-6-methyl-2,3-dihydroquinolin-4(1*H*)-one (1a)

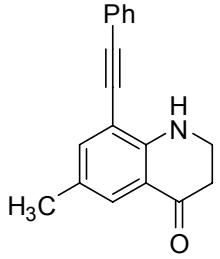
A solution of iodine monochloride (34.1 mmol) in methanol (50 mL) was added dropwise to a stirred suspension of 6-methyl-2,3-dihydro-quinolin-4(1*H*)-one **7a** (5.0 g, 31.0 mmol) and calcium carbonate (34.1 mmol) in 4:1 methanol-water (160 mL) at 0 ^{0}C. The mixture was allowed to warm to room temperature, stirred for 2 h and filtered through a celite bed. The filtrate was extracted with dicholoromethane (2 x 50 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuo. The residue was purified by column chromatography on silica gel, eluting with 15% ethyl acetate / n-hexane to give the title compound as yellow solid (3.5 g, 39.3%) ; mp 70 -72 ºC; R_f (25% ethylacetate-n-hexane) 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (m, 2H), 4.70 (bs, 1H), 3.60 (m, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.7, 37.3, 42.0, 85.0, 119.5, 128.1, 128.6, 145.5, 149.0, 193.1 ; IR (cm^{-1}, KBr) cm^{-1} 3378, 2917, 1666, 1241, 871; Mass (ES) m/z 288 (M+1, 100 %); HRMS (ESI): calcd for $C_{10}H_{11}INO$ $(M+H)^+$ 287.9885, found 287.9815

6-Chloro-8-iodo-2,3-dihydroquinolin-4(1H)-one (1b): This compound was prepared according to the procedure described above and was isolated as yellow solid (2.5 g, 30%); mp 131 -133 ºC; R_f (25% ethyl acetate/n-hexane) 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 4.85 (bs, 1H), 3.63 (m, 2H), 2.68 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 36.7, 41.7, 85.0, 119.6, 123.3, 127.5, 143.4, 149.4, 191.7; IR (cm^{-1}, KBr) cm^{-1} 3370, 2923, 1670, 1245, 873; Mass (ES) m/z 308 (M+1, 100 %); HRMS (ESI): calcd for C_9H_8ClIN $O(M+H)^+$ 307.9338, found 307.9325

Preparation of 6-substituted-8-alkynyl-2,3-dihydroquinolin-4(1*H*)-one (3)

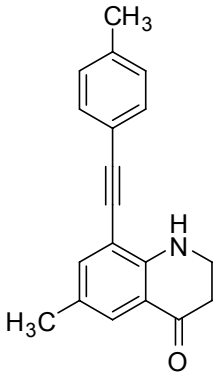
Typical procedure: A mixture of compound **1a** (300 mg, 1.04 mmol), 10% Pd/C (11.12 mg, 0.01 mmol), PPh_3 (10.91 mg, 0.04 mmol), CuI (19.8 mg, 0.10 mmol) and TEA (2.60 mmol) in ethanol (8 mL) was stirred at 25 °C for 1 h under nitrogen. The acetylenic compound **2** (1.56 mmol) was added and the mixture was stirred at 80 ºC for the time mentioned in Table 1. After completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (120 mL) and filtered through a celite bed. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate to afford the desired product**.**

6-Methyl-8-(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3a)



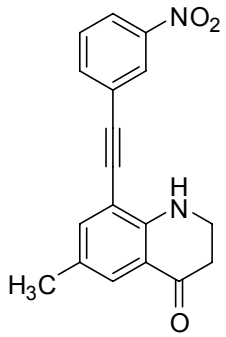
Yield 88%; light yellow solid; mp 146-148 ºC; R_f 0.45 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (s, 1H), 7.54-7.52 (m, 2H), 7.38-7.36 (m, 4H), 5.12 (bs, 1H), 3.67-3.63 (m, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H); IR (cm^{-1}, KBr) ν : 3567, 3343, 2919, 2343, 1667,1511; Mass (ES): m/z 262 (M+1, 100 %); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 20.1, 37.9, 42.0, 84.3, 95.7, 109.3, 118.8, 122.7, 126.3, 128.0, 128.4, 128.6 (2C), 131.5 (2C), 138.7, 150.3, 193.4.

6-Methyl-8-(*p*-tolylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3b)



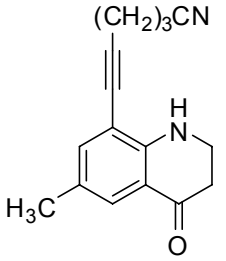
Yield 70%; yellow solid; mp 173-175 ºC; R_f 0.40 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.12 (bs, 1H), 3.67-3.63 (m, 2H) , 2.70 (t, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 20.1, 21.5, 37.9, 42.0, 83.6, 95.9, 109.5, 118.8, 119.5, 126.3, 127.8, 129.2 (2C), 131.4 (2C), 138.6, 138.9, 150.3, 193.5; IR (cm^{-1}, KBr) ν : 3375, 2918, 2855, 1661; Mass (ES) : m/z 276.1 (M+1, 100 %).

6-Methyl-8-((3-nitrophenyl)ethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3c)



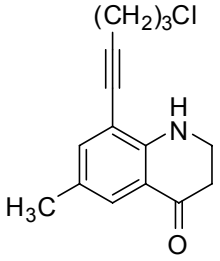
Yield 60%; light red solid; mp 151-158 ºC; R_f (20% ethyl acetate/ n-hexane) 0.45; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19 (dd, *J* = 8.4, 1.2 Hz, 1H) 7.75-7.47 (m, 4H), 7.4 (d, *J* = 2.0 Hz, 1H), 5.87 (bs, 1H), 3.77-3.72 (m, 2H), 2.72 (t, *J* = 6.8 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz): 20.5, 37.7, 41.6, 91.8, 93.6, 107.9, 118.7, 125.1, 125.8, 128.5, 129.5, 133.0, 133.4, 134.3, 138.9, 148.3, 151.6, 193.4; IR (cm^{-1}, KBr) ν : 3397, 2922, 2184, 1549, 1682, 1513; Mass (ES) m/z: 307.2 (M+1, 100 %).

6-(6-Methyl-4-oxo-1,2,3,4-tetrahydroquinolin-8-yl)hex-5-ynenitrile (3d)



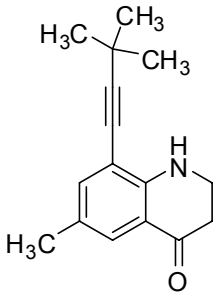
Yield 90%; yellow solid; mp 85-88 ºC; R_f 0.3 (40% ethyl acetate/ n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (d, *J* = 1.6 Hz, 1H), 7.25 (d, *J* = 1.6 Hz, 1H), 5.04 (bs, 1H), 3.63-3.59 (m, 2H), 2.71-2.55 (m, 6H), 2.21 (s, 3H), 2.02-1.97(m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ : 16.3, 18.7, 20.0, 24.4, 29.6, 37.8, 41.9, 93.3, 109.2, 118.7, 119.0, 126.2, 127.6, 138.8, 150.4, 193.4 ; IR (cm^{-1}, KBr) ν : 3363, 2924, 2859, 2244, 1677; Mass (ES) m/z : 253.2 (M+1, 100 %); HRMS (ESI): calcd for $C_{16}H_{16}N_2O$ (M+H) 253.1341, found 253.1351

8-(5-Chloropent-1-yn-1-yl)-6-methyl-2,3-dihydroquinolin-4(1*H*)-one (3e)



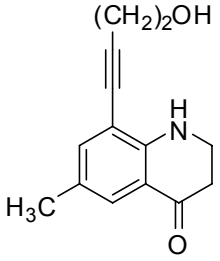
Yield 90%; brown low melting solid; R_f 0.3 (40% ethyl acetate/ n-hexane)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 5.03 (bs, 1H), 3.74-3.59 (m, 4H), 2.71-2.63 (m, 4H), 2.20 (s, 3H), 2.12-2.0 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 17.0, 20.0, 31.2 (2C), 37.9, 41.9, 43.6, 94.5, 109.6, 118.7, 126.2, 127.4, 138.6, 150.4, 193.5; IR (cm^{-1}, KBr) ν : 3354, 2957, 2923, 1672; Mass (E/Z) m/z : 262.2 (M+1, 100 %); HRMS (ESI): calcd for $C_{15}H_{17}ClNO$ (M+H) 262.0999, found 262.1008

8-(3,3-Dimethylbut-1-yn-1-yl)-6-methyl-2,3-dihydroquinolin-4(1*H*)-one (3f)



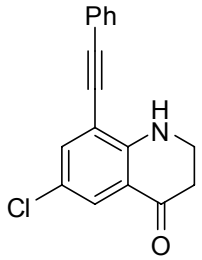
Yield 55%; light yellow solid; mp 120-123 ºC; R*f* 0.35 (25% ethyl acetate hexane)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (d, *J* = 1.2 Hz, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 5.3 (bs, 1H), 3.63-3.59 (m, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.21 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 20.0, 28.6, 31.1, 37.9, 42.1, 74.0, 105.3, 110.0, 118.0, 126.1, 126.9, 138.5, 150.1, 193.6; IR (cm^{-1}, KBr) ν : 3360, 3051, 2968, 2215, 1669; Mass (ES) m/z : 242.20 (M+1, 100 %).

8-(4-Hydroxybut-1-yn-1-yl)-6-methyl-2,3-dihydroquinolin-4(1*H*)-one (3g)



Yield 85%; yellow solid, mp 110-113 ºC; R*f* 0.20 (50% ethyl acetate/ n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (s, 1H), 7.26 (s, 1H), 5.13 (bs, 1H), 3.84 (t, *J* = 6.0 Hz, 2H), 3.59 (t, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ : 19.9, 23.8, 37.7, 41.7, 60.9, 93.5, 109.6, 118.3, 126.0, 127.2, 138.6 (2C), 150.4, 193.8; IR (cm^{-1}, KBr); 3340, 2924, 1646, 1052; Mass (ES) m/z: 230.1 (M+1, 100 %).

6-Chloro-8-(phenylethynyl) 2,3-dihydroquinolin-4(1*H*)-one (3h);



Yield 76%; yellow solid, mp 163-165 ºC; R_f 0.4 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79 (s, 1H), 7.54-7.38 (m, 6H), 5.25 (bs, 1H), 3.69-3.66 (m, 2H), 2.72 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 37.4, 41.6, 82.8, 97.0, 111.1, 119.4, 122.0, 122.2, 127.4, 128.5 (2C), 129.0, 131.6 (2C), 137.0, 150.4, 192.0; IR (cm^{-1}, KBr) ν : 3565, 3345, 2924, 1670; Mass (ES): m/z 282 (M+1, 100 %) ; HRMS (ESI): calcd for $C_{17}H_{13}ClNO$ (M+H) 282.0686, found 282.0698

Preparation of 5,8-disubstituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4)

Typical procedure for the preparation of 4a

Using $AgNO_3$: To a clear solution of **3a** (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added $AgNO_3$ (32.5 mg, 0.191 mmol) at room temperature under N_2 condition. The reaction mixture was heated at 80 °C for 12 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated

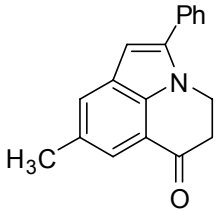
under vacuum. The crude residue was purified by flash silica gel chromatography (n-hexane/EtOAc) to yield the desired product (75 mg).

Using $AgSbF_6$: To a clear solution of **3a** (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added $AgSbF_6$ (65.8 mg, 0.191 mmol) at room temperature under N_2 condition. The reaction mixture was heated at 80 °C for 10 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (n-hexane/EtOAc) to yield the desired product (80 mg).

Using CuI: To a clear solution of **3a** (100.0 mg, 0.382 mmol) in dry DMF (10 mL) was added CuI (36.47 mg, 0.191 mmol) at room temperature under N_2 condition. The reaction mixture was heated at 100 °C for 12 h. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (n-hexane/EtOAc) to yield the desired product (75 mg).

Using $PdCl_2$: To a clear solution of **3a** (150.0 mg, 0.574 mmol) in CH_3CN (15 mL) was added $PdCl_2$ (5.0 mg, 0.028 mmol) at room temperature. The reaction mixture was heated at 70-80 °C for the time mentioned in Table 3. After completion, the reaction mixture was cooled to room temperature and the solvent was concentrated under vacuum. The crude residue was purified by flash silica gel chromatography (hexane/EtOAc) to yield the desired product**.**

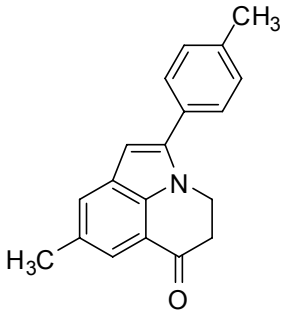
8-Methyl-5-phenyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4a)



Yield 88%; white solid, mp 127-130 ºC; R_f 0.50 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63-7.42 (m, 6H), 7.37 (s, 1H), 6.58 (s, 1H), 4.44 (t, *J* = 6.8 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 21.5, 38.2, 42.8, 102.2, 117.6, 119.5, 126.7, 128.1, 128.2 (2C), 128.6 (2C), 128.8, 129.9, 131.7, 139.8, 141.9, 192.9; IR (cm^{-1}, KBr) ν : 2917, 1682, 747; Mass (ES) :

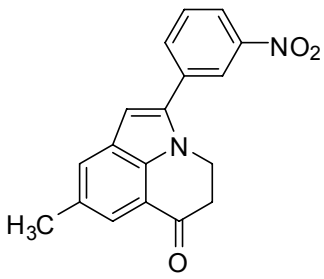
m/z 262 (M+1, 100 %); HRMS (ESI): calcd for $C_{18}H_{16}NO$ (M+H) 262.1232, found 262.1235

8-Methyl-5-p-tolyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4b)



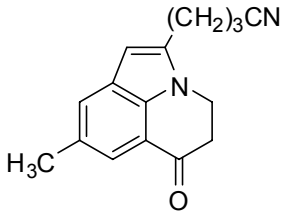
Yield 70%; yellow solid; mp 118-121 ºC; R_f 0.45 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62-7.43 (m, 4H), 7.30-7.25 (m, 2H), 6.54 (s, 1H), 4.39 (t, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 6.8 Hz, 2H), 2.49 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 22.7, 29.7, 38.3, 42.8, 101.8, 117.6, 119.3, 126.6, 128.2, 128.5 (2C), 128.8, 129.4 (2C), 129.9, 138.3, 139.8, 142.1, 192.9; IR (cm^{-1}, KBr) ν : 3360, 3051, 2967, 2856, 1669; Mass (ES) : m/z 276.2 (M+1, 100 %); HRMS (ESI): calcd for $C_{19}H_{18}NO$ (M+H) 276.1388, found 276.1400

8-Methyl-5-(3-nitrophenyl)-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4c)



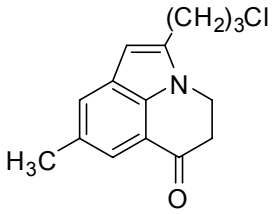
Yield 60%; light red solid; mp 161-163 ºC; R_f 0.5 (20% ethyl acetate/ n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.36 (d, *J* = 1.6 Hz, 1H) 8.02 (d, *J* = 8.8, 2H), 7.73 (d, *J* = 9.2, 1H) 7.44-7.40 (m, 1H), 7.24(m, 2H), 3.77-3.71 (m, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz): 20.2, 36.9, 40.6, 115.8, 118.6, 120.4, 121.5, 124.7, 127.9, 131.3 (2C), 135.6, 140.4, 152.6, 157.1, 161.2, 181.9, 192.6; IR (cm^{-1}, KBr) ν : 3284, 2956, 2853, 1663, 1568; Mass (ES) m/z: 307.2 (M+1, 100 %); HRMS (ESI): calcd for $C_{18}H_{15}N_2O_3$ (M+H) 307.1082, found 307.1091

4-(8-Methyl-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-5-yl)butanenitrile (4d)



Yield 90%; brown solid, mp 95-97 ºC; R_f 0.35 (50% ethyl acetate/n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (s, 1H), 7.50 (s, 1H), 6.28 (s, 1H), 4.30 (t, *J* = 6.8 Hz, 2H), 3.05 (t, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.50-2.46 (m, 5H), 2.09 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 16.5, 21.4, 24.3, 24.8, 29.6, 37.9, 41.3, 100.3, 117.0, 118.8, 126.3, 127.7, 129.7, 138.8, 139.0, 192.5; IR (cm^{-1}, KBr) ν : 3102, 3026, 2924, 2246, 1669; Mass (ES) m/z : 253.2 (M+1, 100 %); HRMS (ESI): calcd for $C_{16}H_{16}N_2O$ (M+H) 253.1341, found 253.1330.

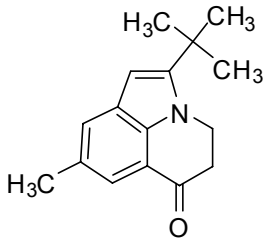
5-(3-Chloropropyl)-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4e)



Yield 90%; brown low melting solid; 79-82 ºC; R_f 0.35 (40% ethyl acetate/ n-hexane)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (s, 1H), 7.48 (s, 1H), 6.27 (s, 1H), 4.31 (t, *J* =6.8 Hz, 2H), 3.63 (t, *J* =6.4 Hz, 2H), 3.08-2.93 (m, 4H), 2.46 (s, 3H), 2.23-2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 21.5, 23.3, 31.4, 37.9, 41.4, 44.0, 99.9, 117.0, 118.5, 126.2, 127.9, 129.5, 138.8, 140.2, 192.7; IR (cm^{-1}, KBr) ν : 3326, 3015, 2922, 2851, 1672

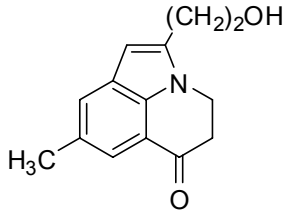
Mass (E/Z) m/z : 262.1 (M+1, 100 %); HRMS (ESI): calcd for $C_{16}H_{17}ClNO$ (M+H) 262.0999, found 262.1004.

5-*tert*-Butyl-8-methyl- 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4f)



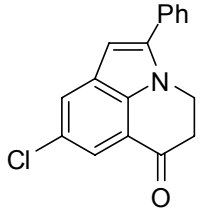
Yield 65%; light yellow solid; mp 96-98 ºC; R_f 0.35 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (s, 1H), 7.49(s, 1H), 6.27(s, 1H), 4.51 (t, *J* = 6.8 Hz, 2H), 3.03 (t, *J* = 6.8 Hz, 2H), 1.46 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 21.3, 29.9, 32.4, 38.5, 44.8, 98.6, 117.4, 118.6, 126.4, 127.7, 129.3, 140.0, 150.8, 192.9; IR (cm^{-1}, KBr) ν : 2966, 2872, 1683; Mass (ES) m/z : 242.20 (M+1, 100 %); HRMS (ESI): calcd for $C_{16}H_{20}NO$ (M+H) 242.1545, found 242.1557.

5-(2-Hydroxyethyl)-8-methyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4g)



Yield 85%; yellow solid, mp 91-93 ºC; R_f 0.25 (50% ethyl acetate hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 1H), 7.82 (s, 1H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.64-3.61 (m, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H); IR (cm^{-1}, KBr); 3343, 2921, 1668; Mass (ES) m/z: 230.1 (M+1, 100 %); ^{13}C NMR ($CDCl_3$, 200 MHz) δ : 20.1, 27.3, 36.9 , 40.3, 62.0, 119.2, 120.3, 123.6, 134.3, 138.5 (2C), 151.4, 193.1; IR (cm^{-1}, KBr); 3343, 2921, 1668; Mass (ES) m/z: 230.1 (M+1, 100 %); HRMS (ESI): calcd for $C_{14}H_{16}NO_2$ (M+H) 230.1180, found 230.1169.

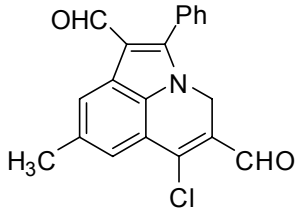
8-Chloro-5-phenyl-2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-one (4h)



Yield 76%; white solid, mp 127-130 ºC; R_f 0.45 (25% ethyl acetate / n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J* = 1.6 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.56 –

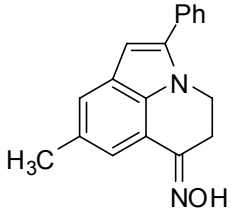
7.45 (m, 6H), 6.61 (s, 1H), 4.43 (t, *J* = 6.8 Hz, 2H), 3.08 (t, *J* = 6.8 Hz, 2H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 38.0, 42.7, 102.2, 118.4, 125.7, 126.7, 128.7(3C), 128.9 (3C), 129.0, 131.0, 139.4, 143.3, 191.7 ; IR (cm^{-1}, KBr) ν : 2925, 2854, 1672; Mass (ES) : m/z 282.3 (M+1, 100 %); HRMS (ESI): calcd for $C_{17}H_{13}ClNO$ (M+H) 282.0686, found 282.0698.

Preparation of 6-chloro-8-methyl-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,5-dicarbaldehyde (8)



To a cooled (0 ºC) solution of **4a** (148 mg) in dry DMF (1.0 mL) was added $POCl_3$ (1.25 mL) dropwise and the temperature was raised to 25 ^{0}C. The reaction mixture was stirred for 3 h and then poured into ice water (100 mL). The yellow solid separated was filtered, triturated with n-hexane, filtered and dried to give the pure product (180.4 mg, 95%); mp 276 -279 ºC; R_f 0.45 (15% ethyl acetate/n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.29 (s,1H), 9.77 (s,1H), 8.17 (s, 1H), 7.44-759 (m, 6H), 5.0 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 29.0, 45.0, 116.2, 116.6, 122.3, 123.2, 124.9, 127.2, 127.6 (2C), 129.2 (2C), 130.0 (2C), 130.3, 134.0, 144.5, 149.5, 186.4, 186.3; IR (cm^{-1}, KBr) cm^{-1} 3434, 2919, 1655, 1577, 1417; Mass (ES) m/z 336 (M+1, 100 %); HRMS (ESI): calcd for $C_{20}H_{15}ClNO_2$ $(M+H)^+$ 336.0801, found 336.0855.

Preparation of 8-methyl-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5H)-one oxime (9)



To a solution of **4a** (150 mg) in pyridine (6 mL) was added $NH_2OH.HCl$ (4.59 mmol, 321.7 mg) at room temperature and the mixture was stirred for 2 h. The solvent was removed to give a gummy mass, which was poured into ice water (10 mL). The solid

was precipitated and filtered. The crud product was triturated with n-hexane, filtered and dried to get the title compound as yellow solid (119.0 mg, 75%); mp 229-232 ºC; R_f 0.40 (15% E.A / n-hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.28 (s, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.53-7.35 (m, 5H), 6.54 (s, 1H), 4.17 (t, J = 6.8 Hz, 2H), 3.13 (t, J = 6.4 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ: 21.5, 22.5, 42.8, 100.9, 115.3, 116.5, 120.3, 126.9, 127.8, 128.3 (2C), 128.7(2C), 128.8, 131.7, 134.9, 140.7, 147.5 ; IR (cm^{-1}, KBr) 3232, 2922, 1603, 956; Mass (ES) : m/z 277 (M+1, 100 %); HRMS (ESI): calcd for $C_{18}H_{17}N_2O$ (M+H) 277.1341, found 277.1350.

In Vitro assay for measuring SIRT1 activation[1]

The activity of small molecules on Sirt1 was determined using SIRT1 fluorescence activity assay kit from Cyclex Inc. according to manufacturer's protocol. Briefly, bacterially purified hSIRT1 enzyme was incubated with the fluorophore labeled substrate peptide (25 uM) and cofactor, NAD^+ (25 uM) in presence or absence of 10 μM compounds (suramin, an inhibitor of Sirt1 along with compounds **4a**, **4b**, **4e, 4f** and **4c**) for 15 min at 37 ºC. Then 50 uL of stock solution was added and incubated for 45 min at room temperature. Fluorescence was read at Ex: 360 nm and Em: 450 nm. Blank consists of all components of the reaction mixture except enzyme. The difference between the blank and control reading gives the enzyme activity. Blank value is subtracted from all the sample readings. The compound control contains all the components of reaction mixture including the compound but no enzyme. So the reading obtained in the compound control indicates the autofluorescence of the compound and this is also subtracted from the reading. Finally a graph is plotted against the samples on X-axis and absorbance value after subtracting blank and autofluorescence values from the sample. Absorbance/Fluorescence is directly proportional to the enzyme activity.

Docking studies: Materials and Methods

Homology Model of hSIRT1 (144-217)

The three dimensional model of hSIRT1 (uniprot code: Q96EB6, 144-217 amino acid residues) was developed by threading method using PRIME homology modeling program (Schrödinger L.L.C., USA). The multi step Schrödinger's Protein preparation tool (PPrep) has been used for final preparation of receptor model. Hydrogen's were

added to the model automatically *via* the Maestro interface.[2] PPrep neutralizes side chains and residues which are not involving in salt bridges.[3] This step is then followed by restrained minimization using the OPLS 2005 force field to RMSD of 0.3A$^{0.}$

Docking Procedure: The synthesized compounds were sketched by using chemdraw and converted them to their 3D representation. All the compounds and protein (homology model of hSIRT1) were prepared for docking (i.e. adding hydrogen's, gasteiger charge addition, and energy minimization) by using Chimera program. Autodock 4.0 program was used for docking.

Results and discussion: The best model of activator domain of hSIRT1 was developed and validated. The receptor grid was generated with co ordinates X: 43.804; Y: 47.333; Z: 29.948.The best 5 poses and corresponding scores have been evaluated by autodock 4.0 program. The best score and interacting amino acid residues are shown in the following tables.

Binding Energy:

Ligand	Binding Energy (Kcal/mol)
4a	-5.83
4b	-5.57
4f	-6.09

Interacting amino acids:

4a	**4b**	**4f**
Pro2	Pro2	Pro2
Leu3	Leu3	Leu3
Glu20	Glu20	-
Asp5	Asp5	Asp5
ILE27	ILE27	ILE27
Ala24	Ala24	Ala24
Asp37	Asp37	Asp37
His45	His45	His45
-	Ala23	-
-	-	Glu38

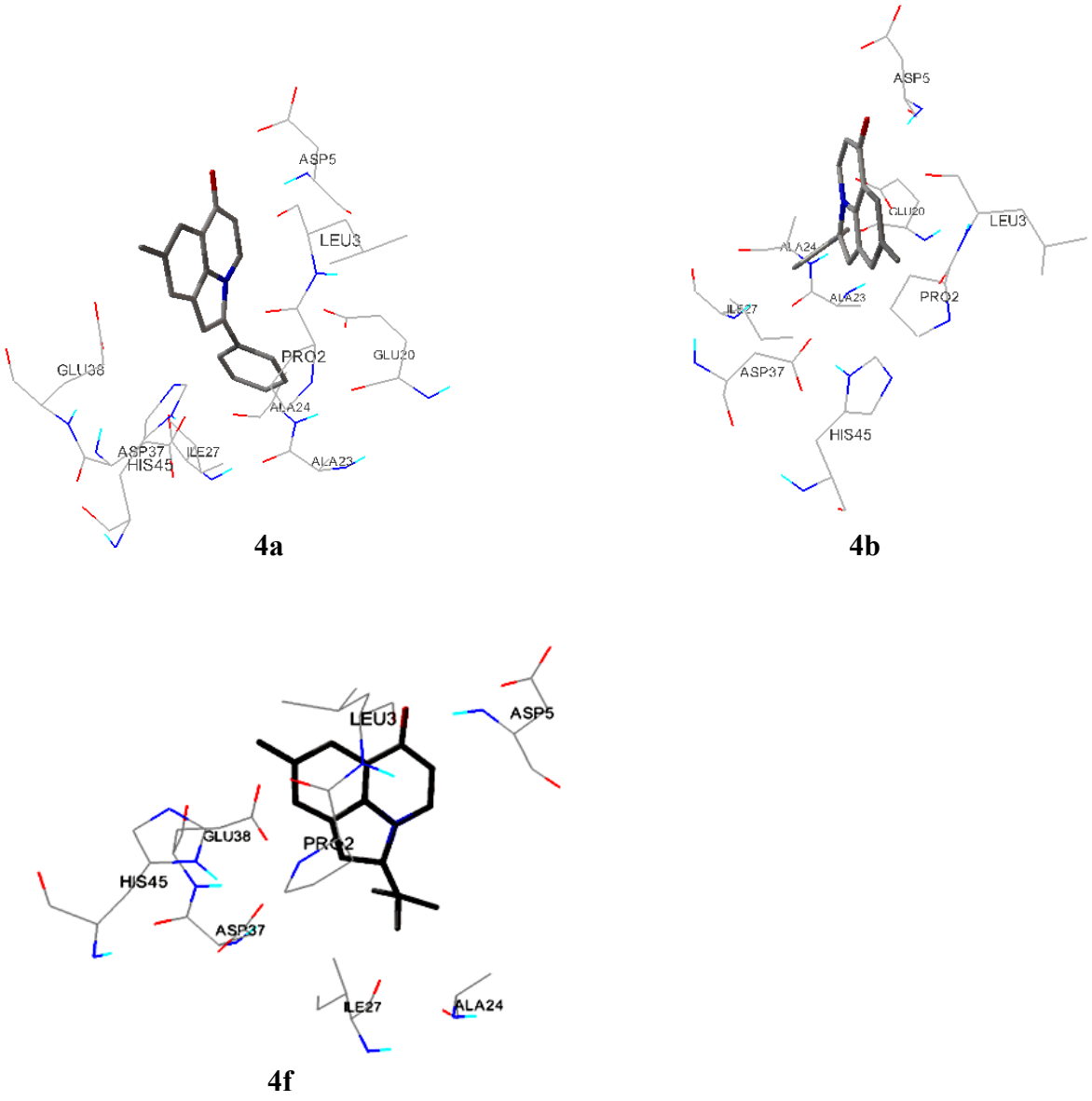


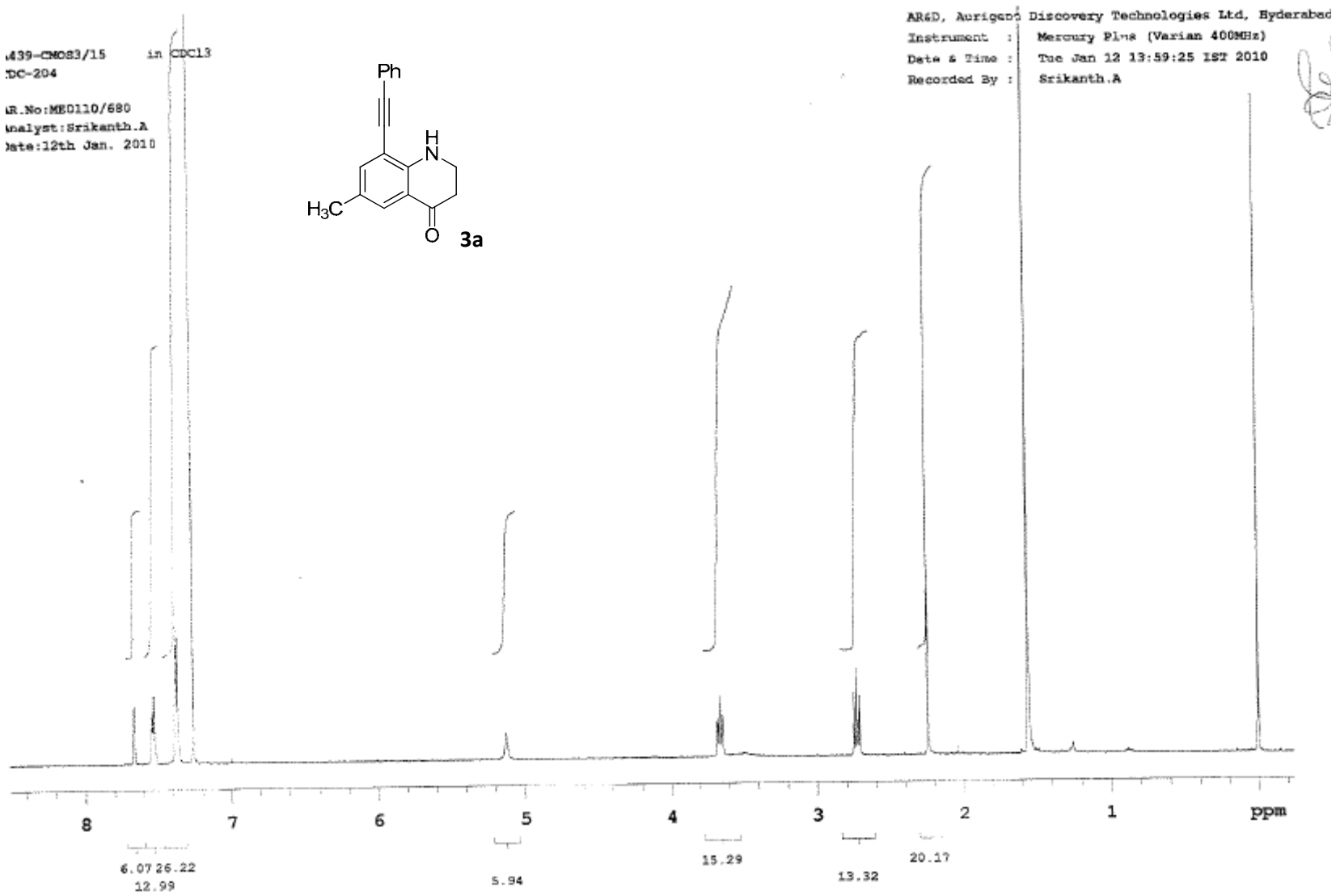
Fig. 1. Docking of compounds **4a**, **4b** and **4f** into the active site of SIRT1

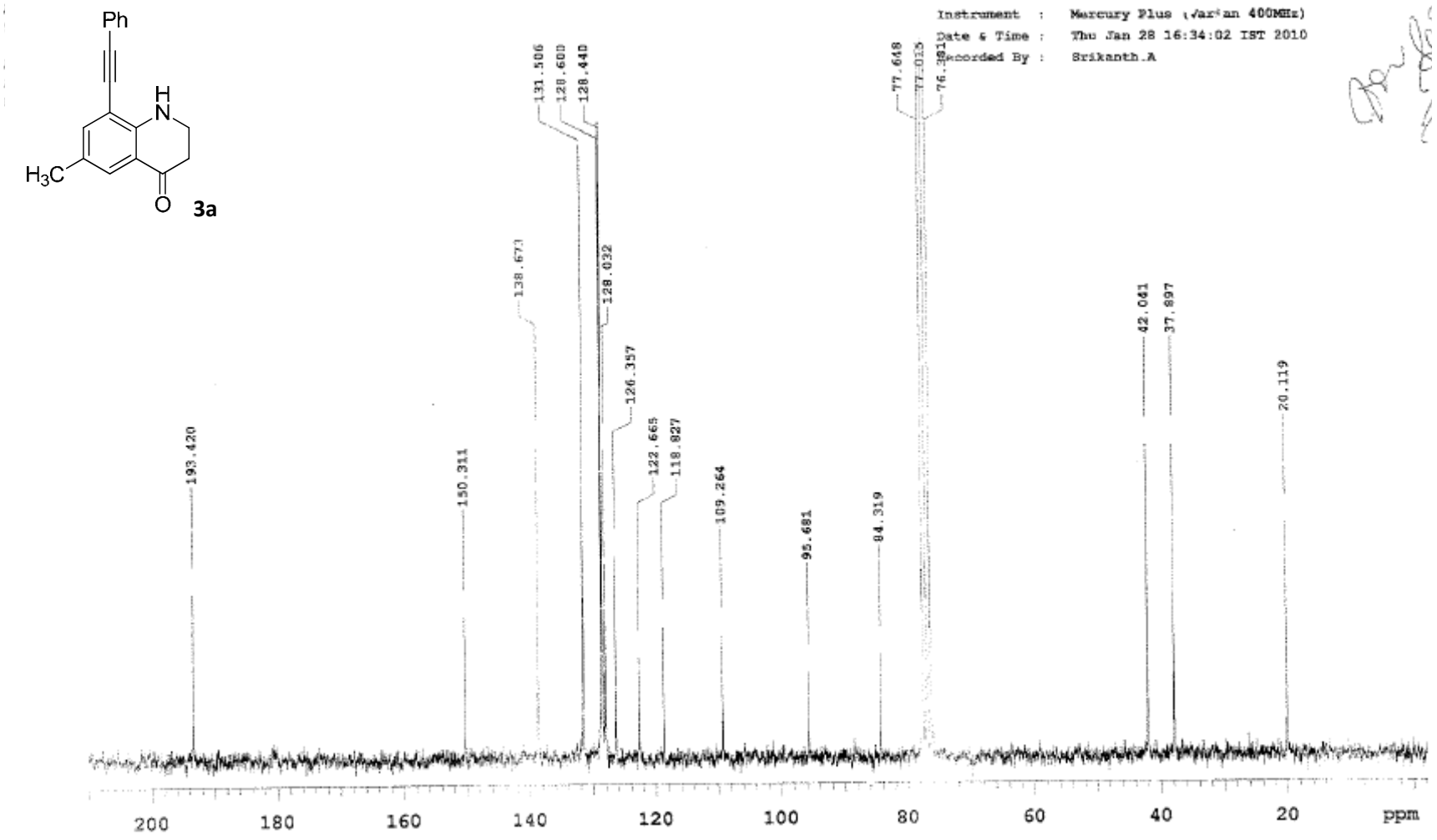
References

1. J. C. Milne, P. D. Lambert, S. Schenk, D. P. Carney, J. J. Smith, D. J. Gagne, L. Jin, O. Boss, R. B. Perni, C. B. Vu, J. E. Bemis, R. Xie, J. S. Disch, P. Y. Ng, J. J. Nunes, A. V. Lynch, H. Yang, H. Galonek, K. Israelian, W. Choy, A. Iffland, S. Lavu, O. Medvedik, D. A. Sinclair, J. M. Olefsky, M. R. Jirousek and P. J. Elliott, *Nature* 2007, **450**, 712.
2. Schrodinger L. L. C., http://www. Schrödinger. Com, (accessed: 24. 04. 2007)
3. Michel F, Sanner.Python: A programming language for software integration

and development. J. Mol. Graphics Mod., 1999, Vol17, February.PP57-61.

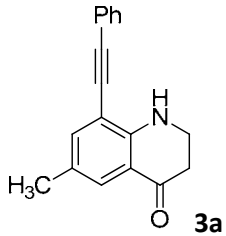
Copies of spectra





CPS,MIYAPUR

Mass Analysis Report



3a

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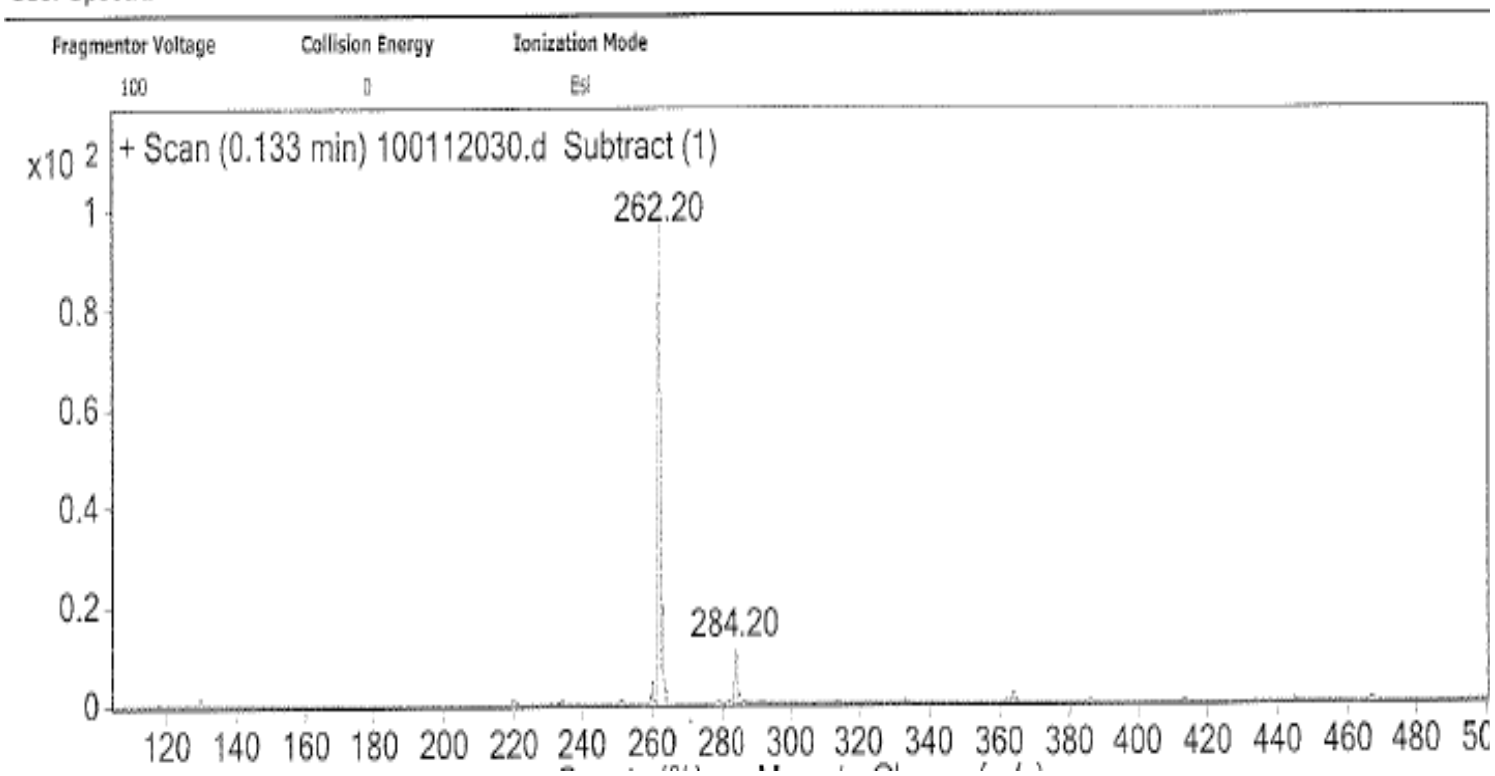

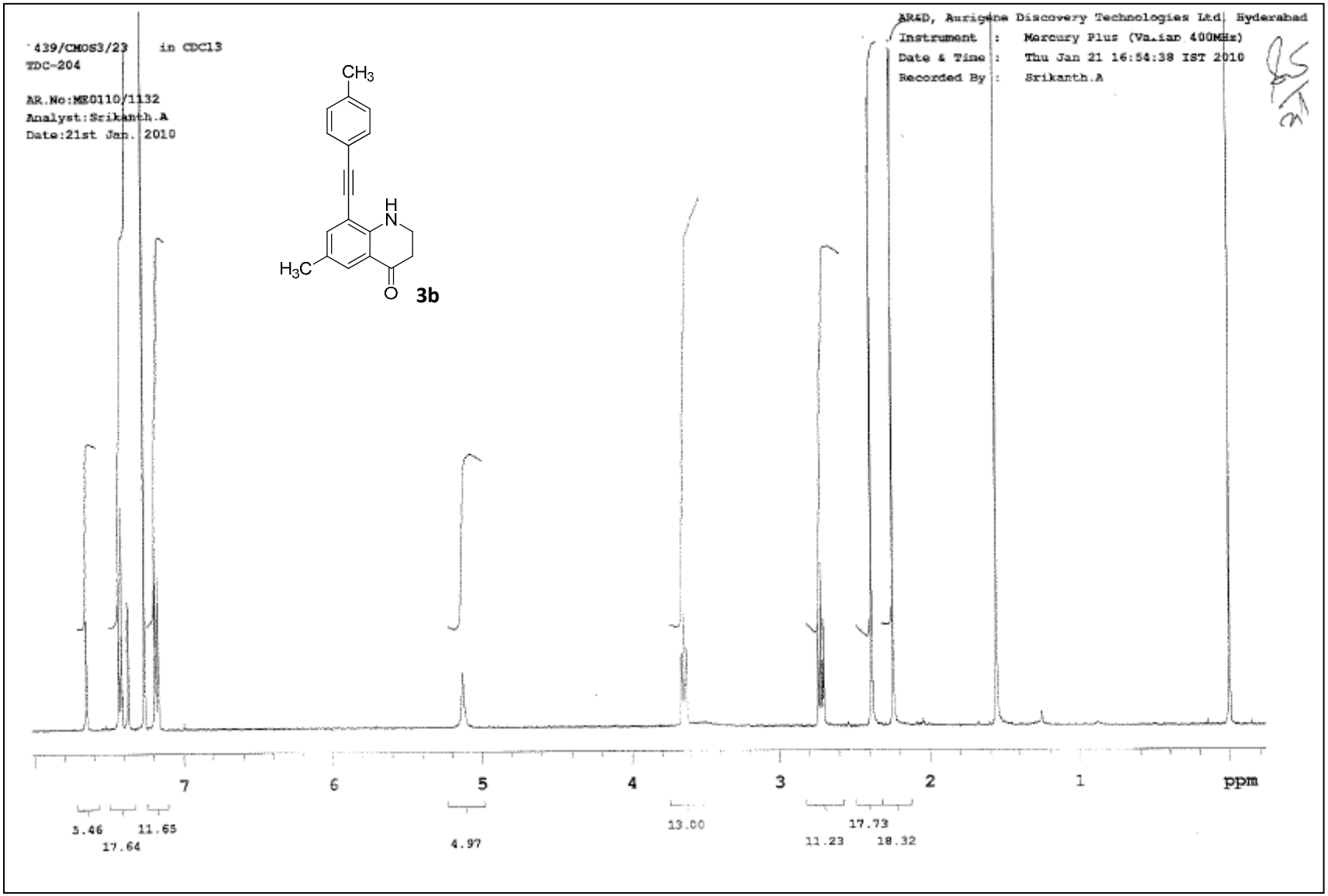

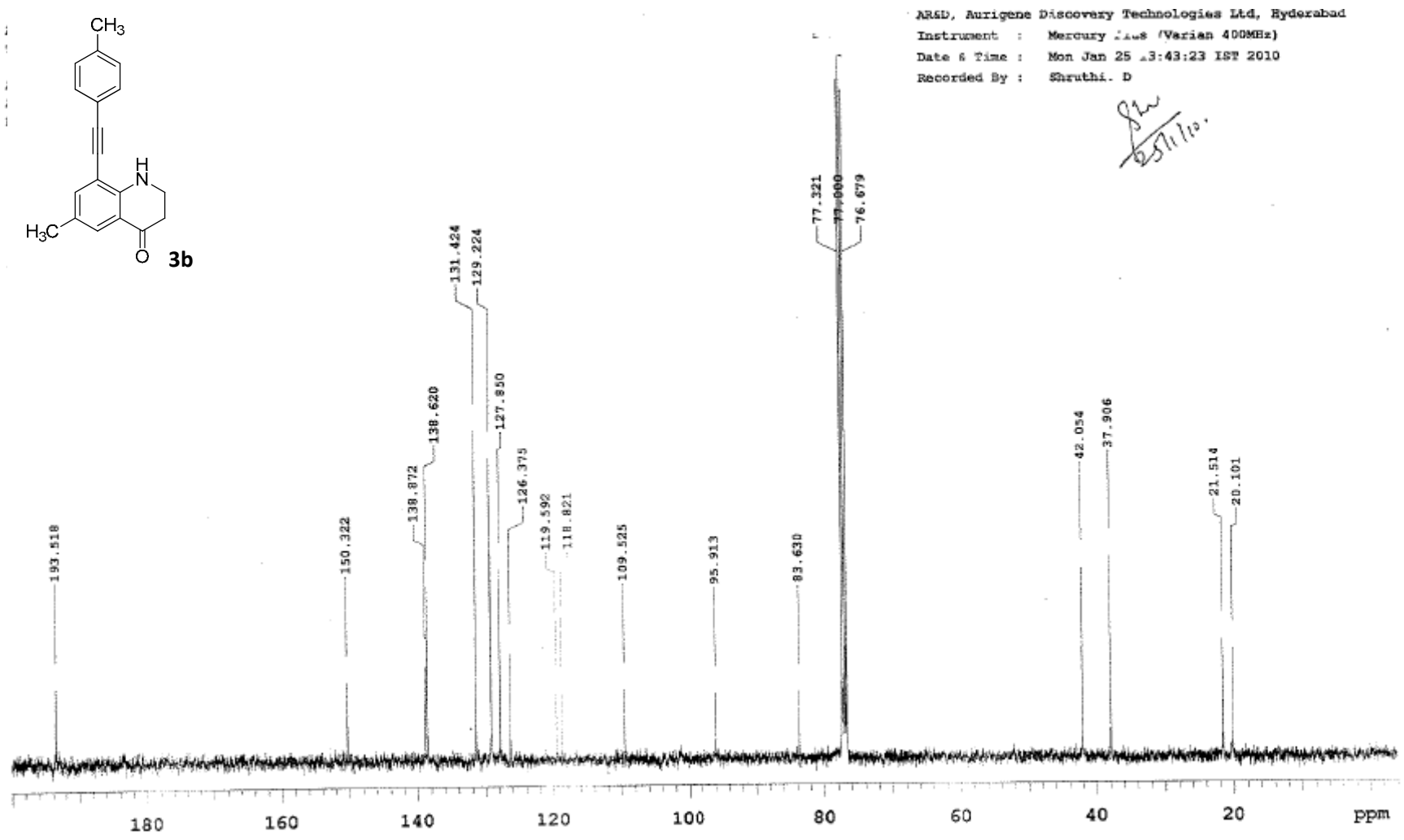

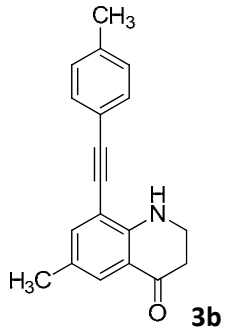

3b

Mass Analysis Report

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User Name	
IRM Calibration Status	Success
Comment	

User Spectra

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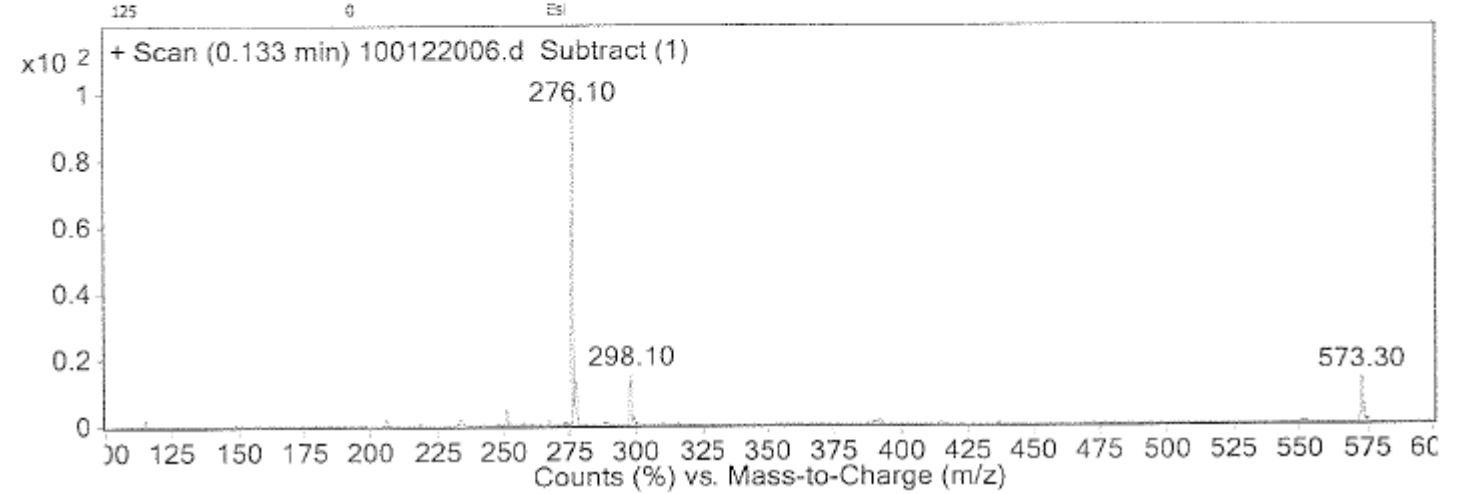

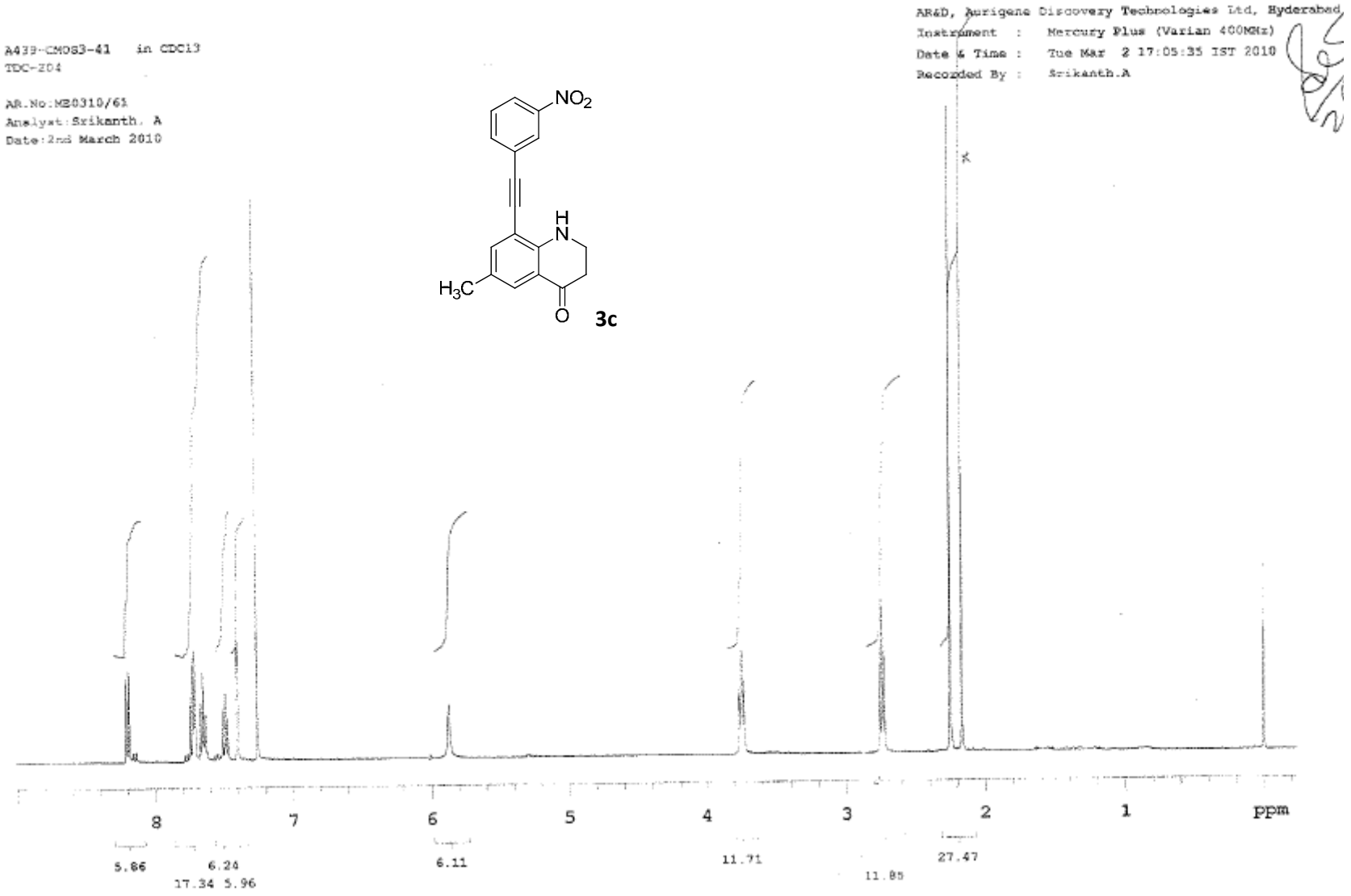

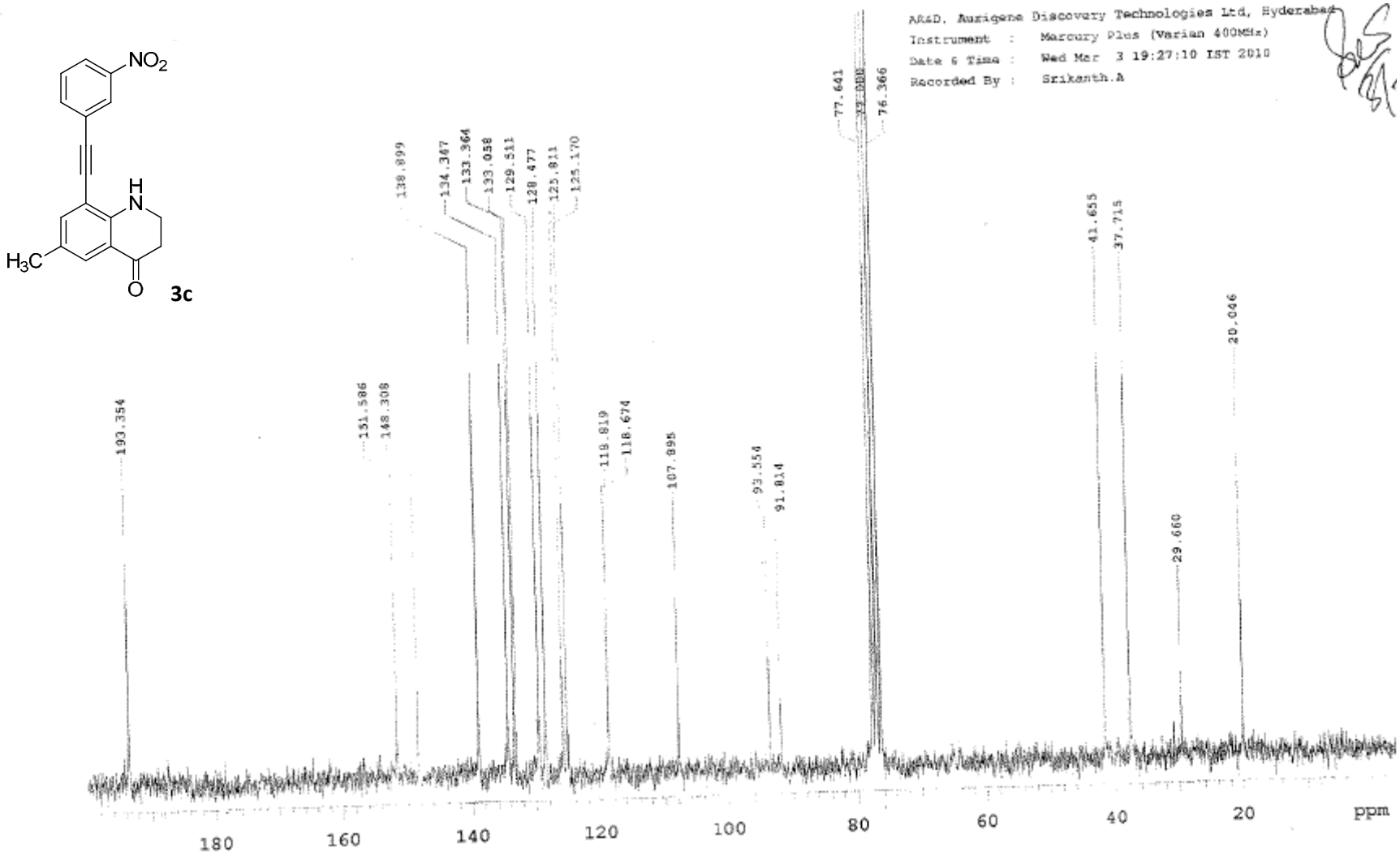

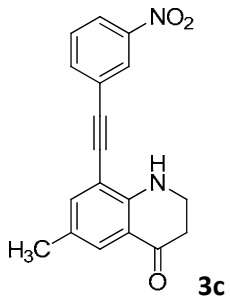

3c

Mass Analysis Report

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User Name	
IRM Calibration Status	Success
Comment	

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
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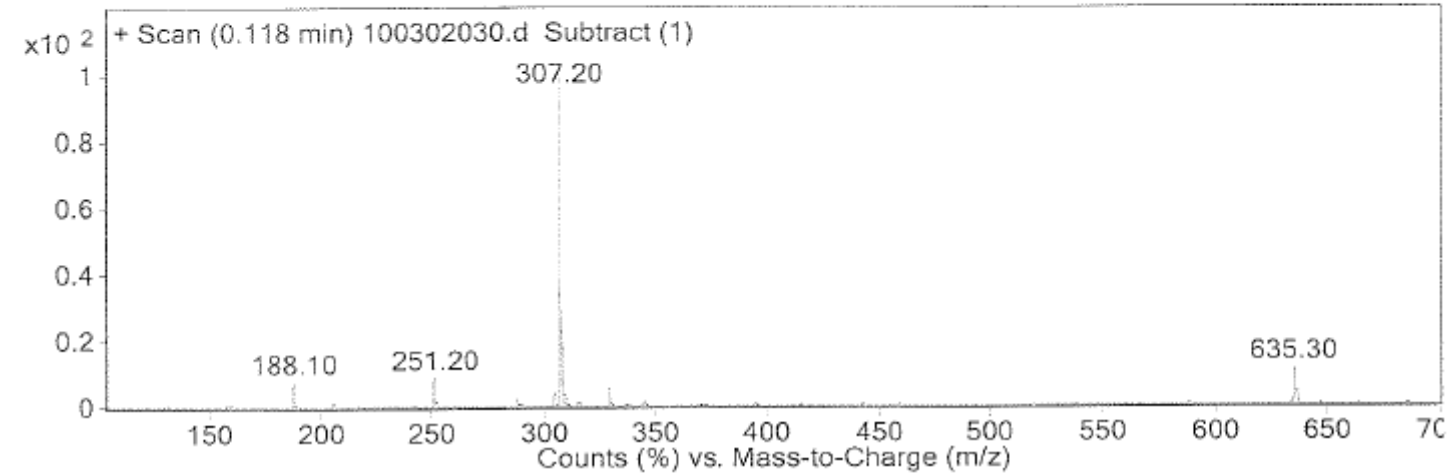

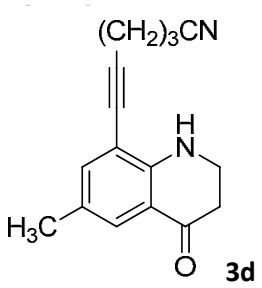

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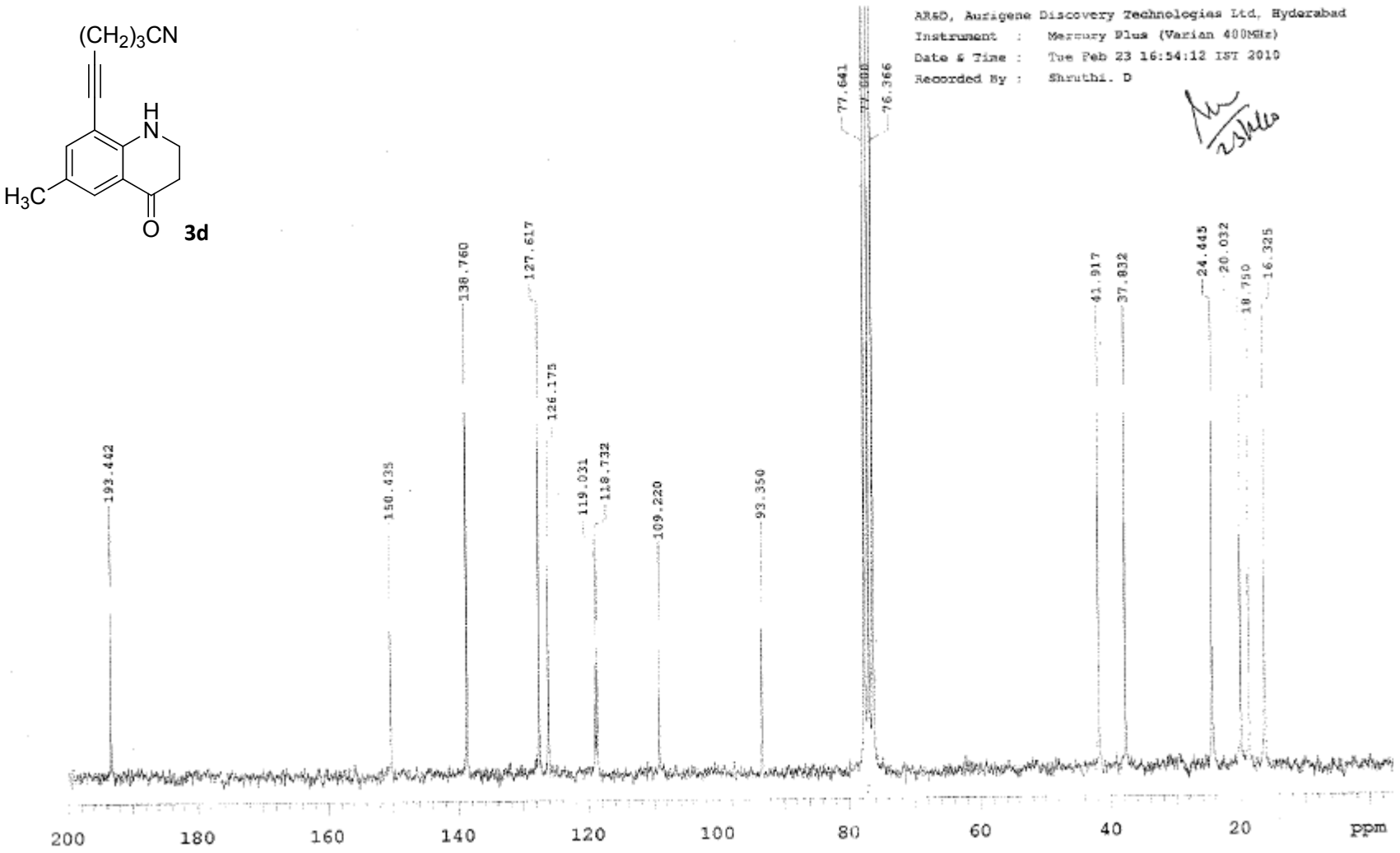

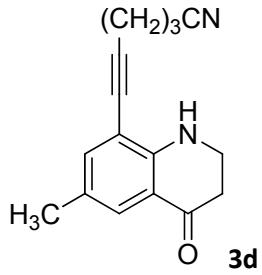

3d

Mass Analysis Report

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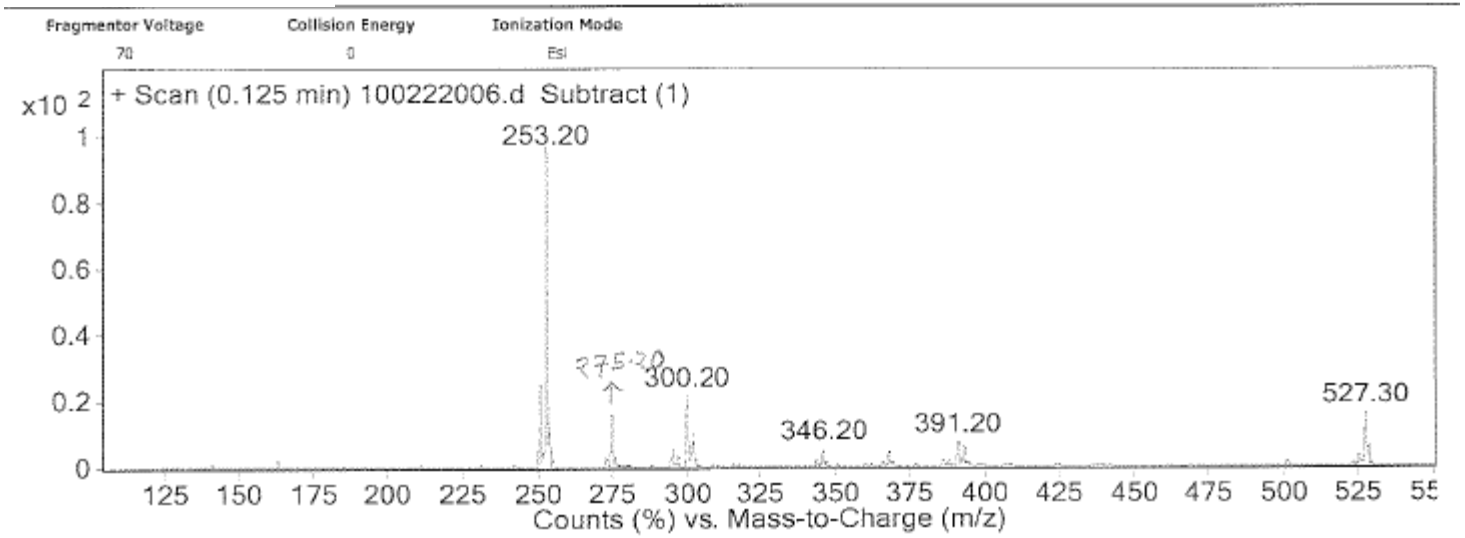
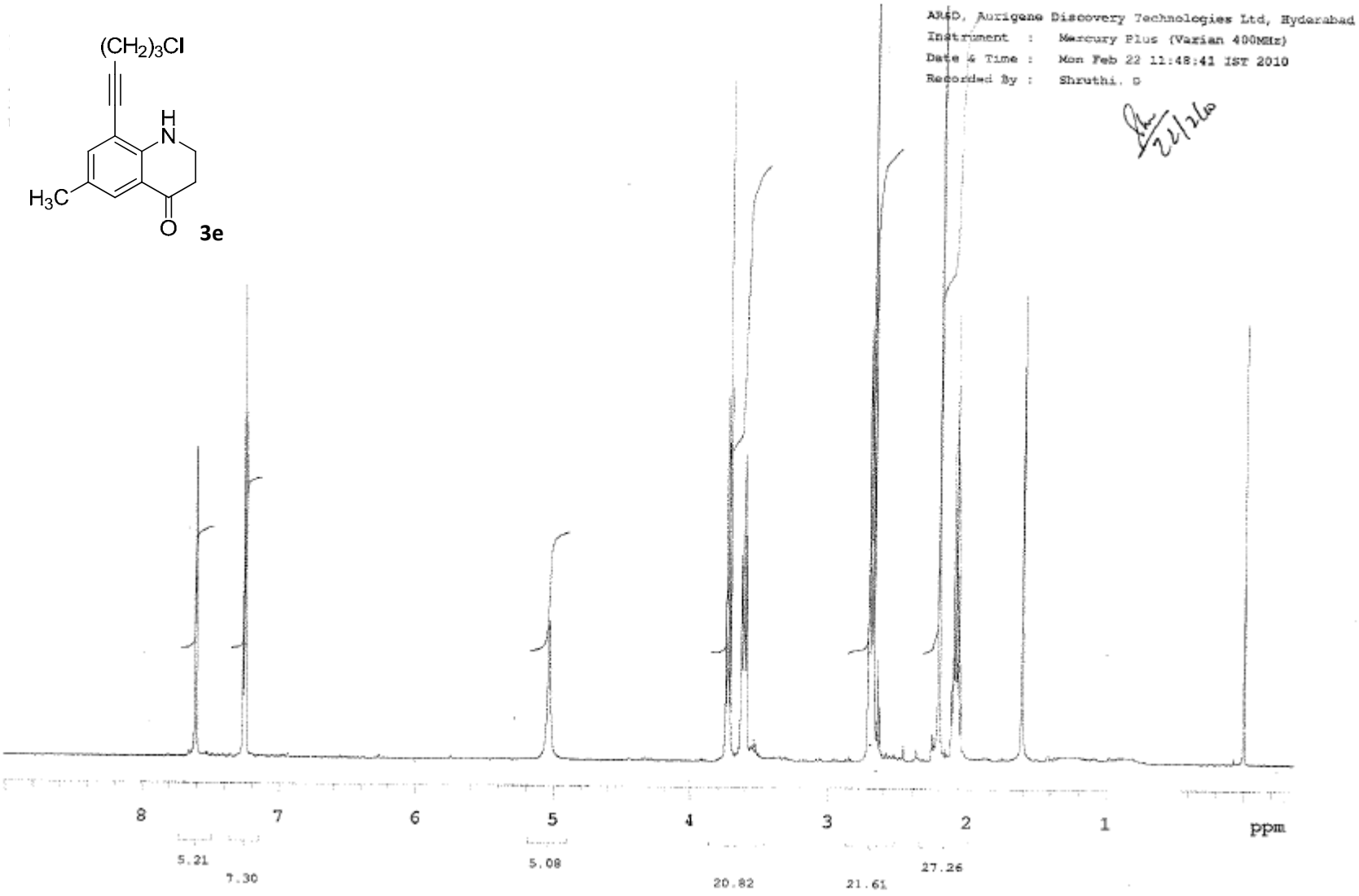
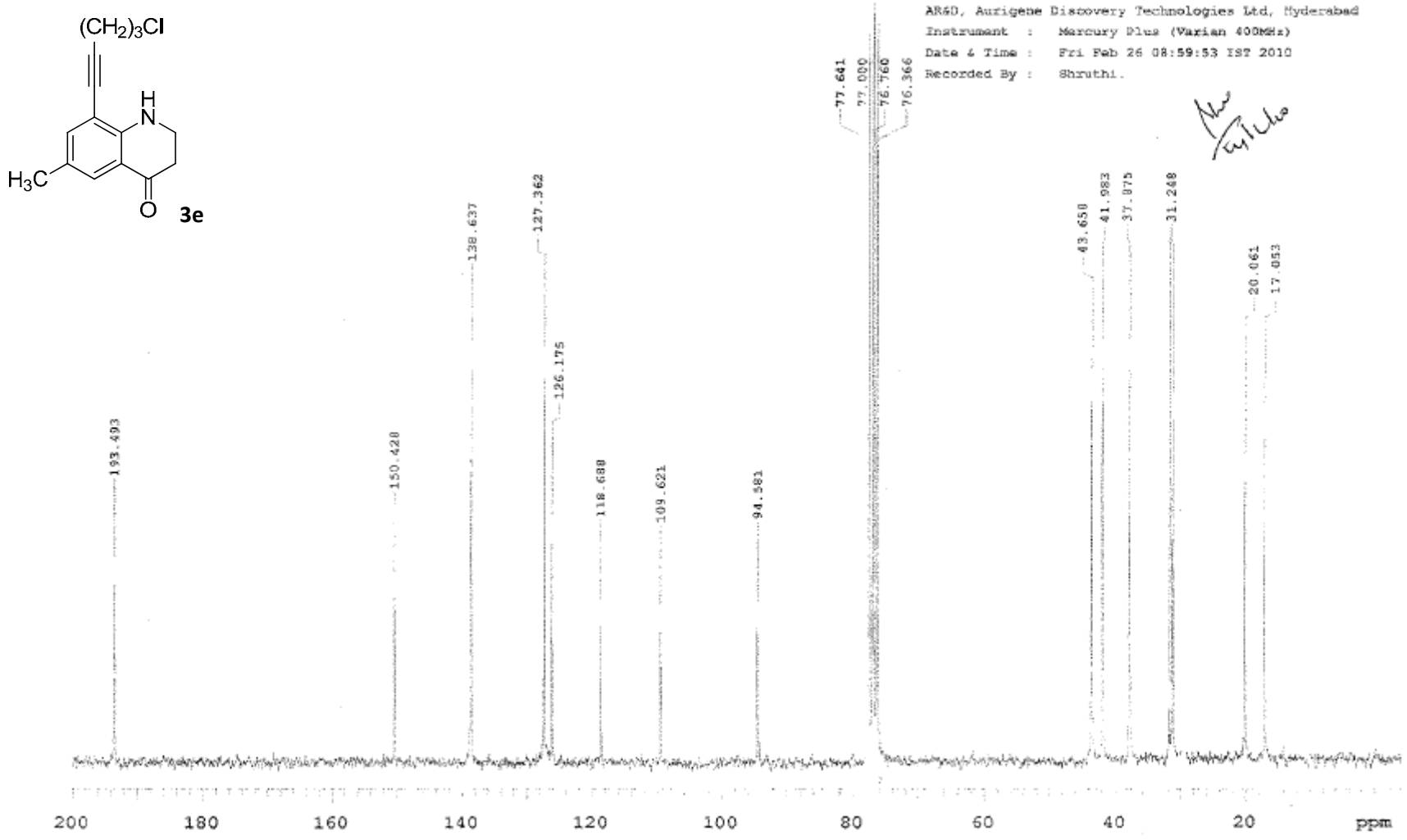
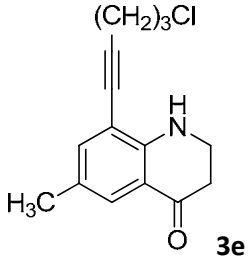
User Name	
IRM Calibration Status	Success
Comment	









3e

Mass Analysis Report

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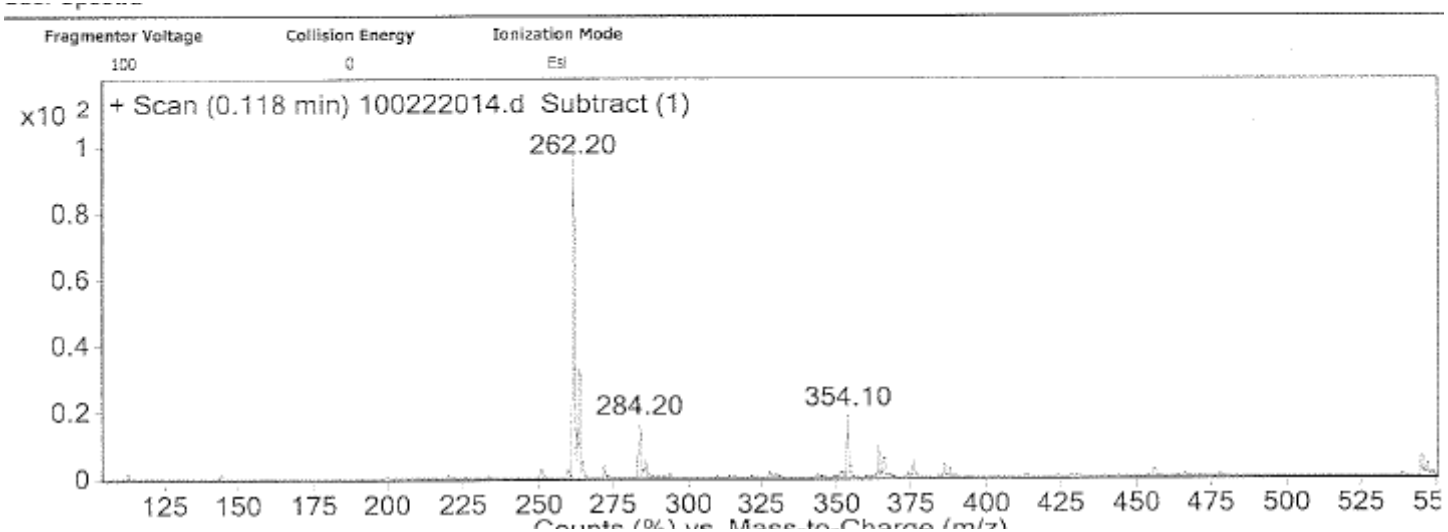
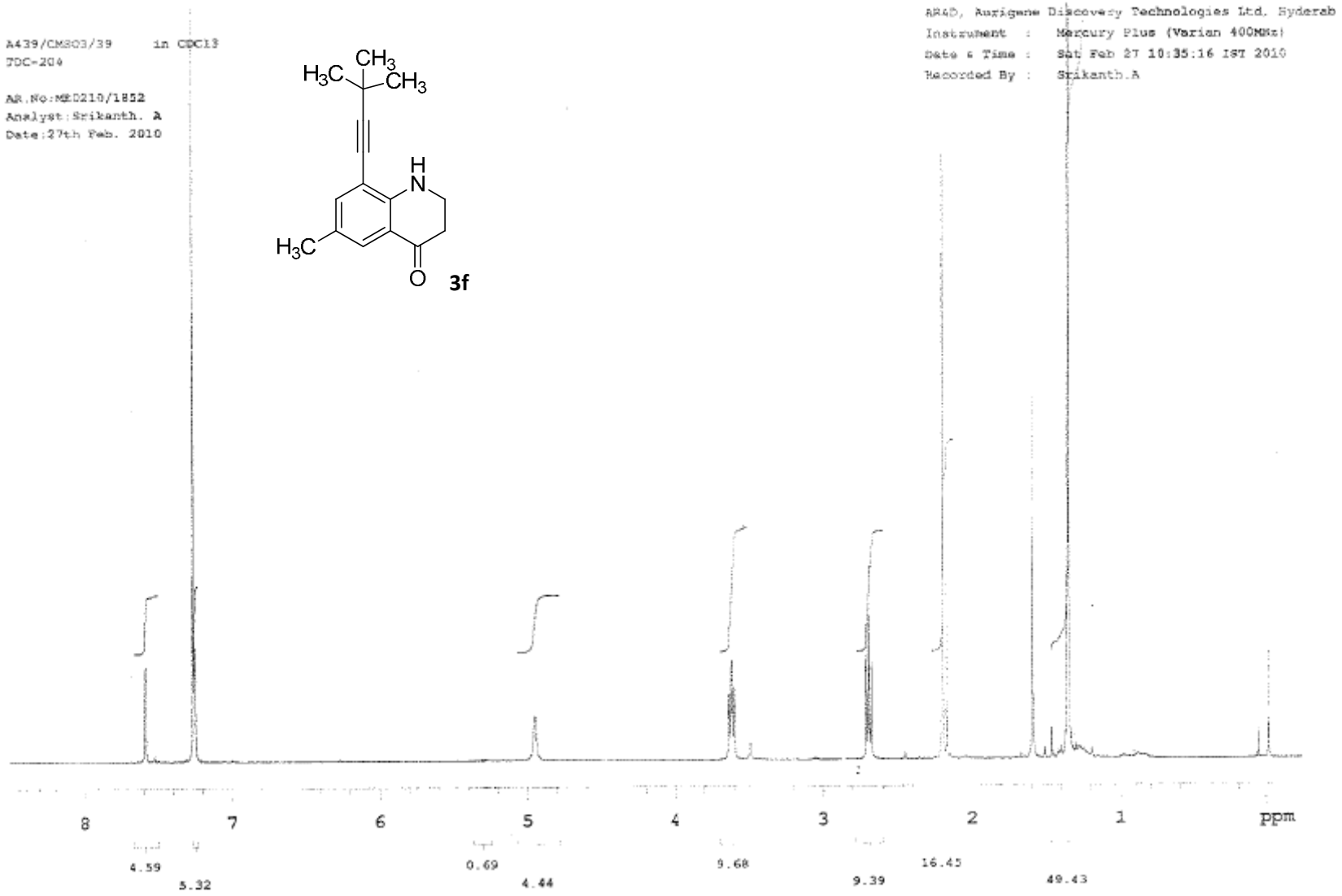
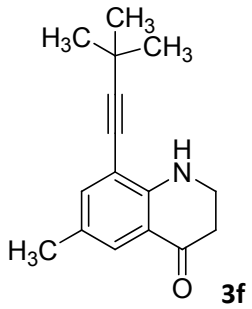
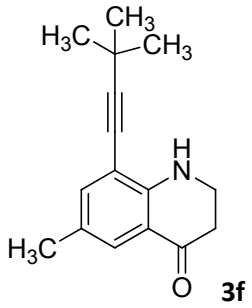
User Name	
IRM Calibration Status	Success
Comment	







3f



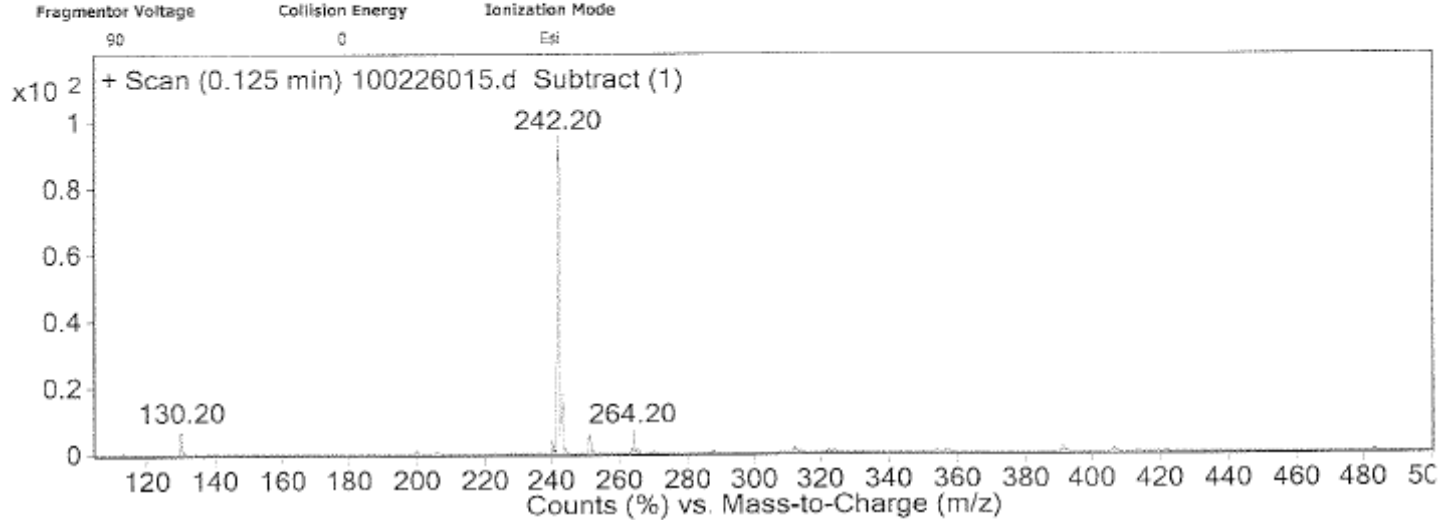
3f

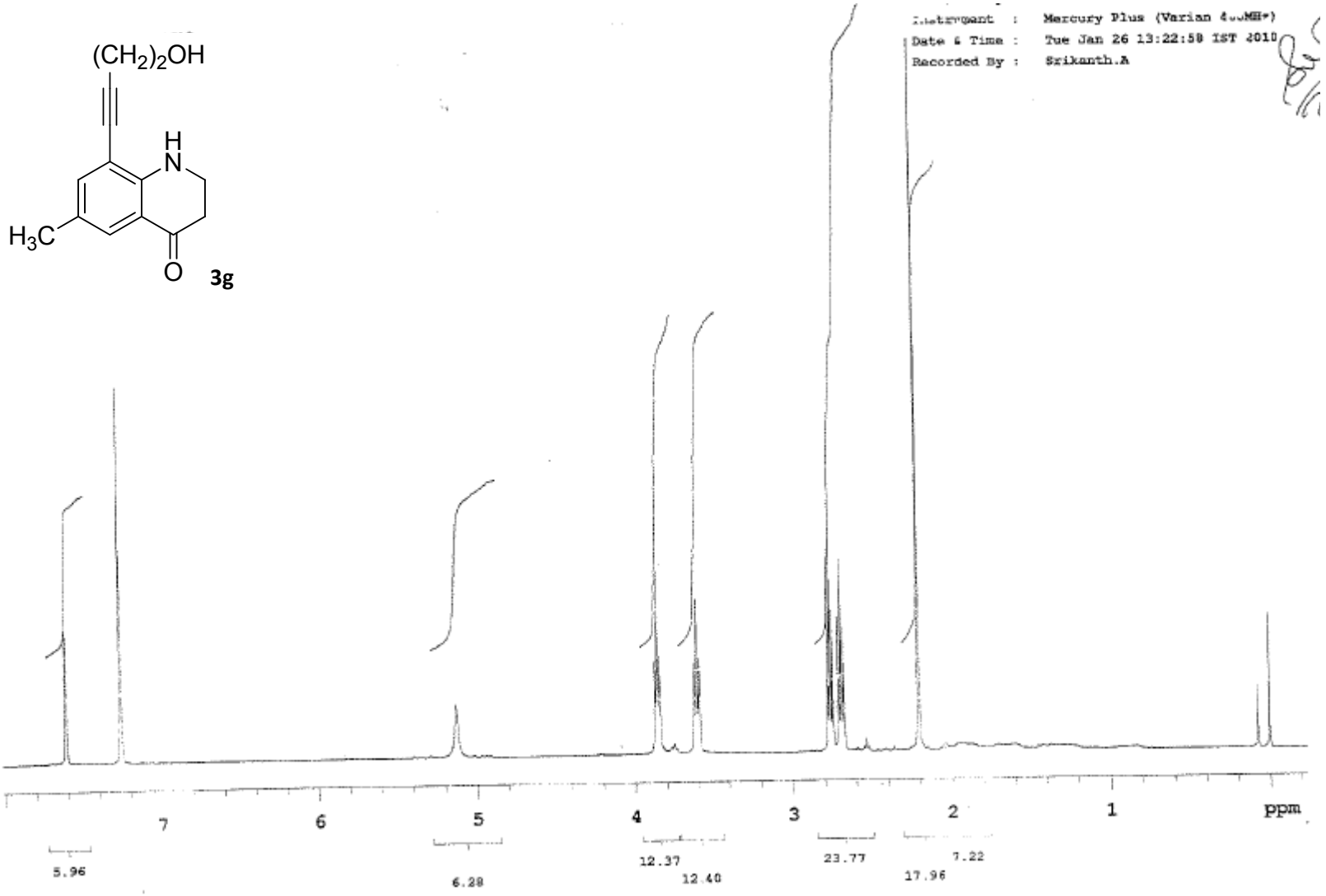
Mass Analysis Report

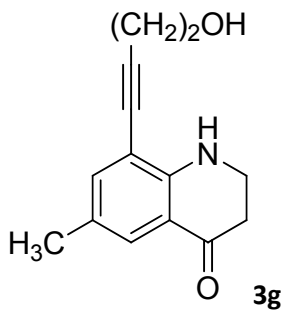
Sample Name	A439/Cmos3/39
Position	Val 44
User Name	
IRM Calibration Status	Success
Comment	

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
90	0	Esi



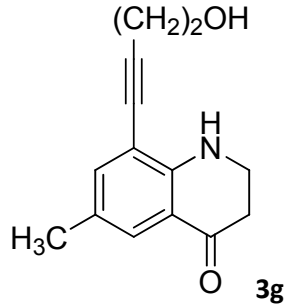




3g

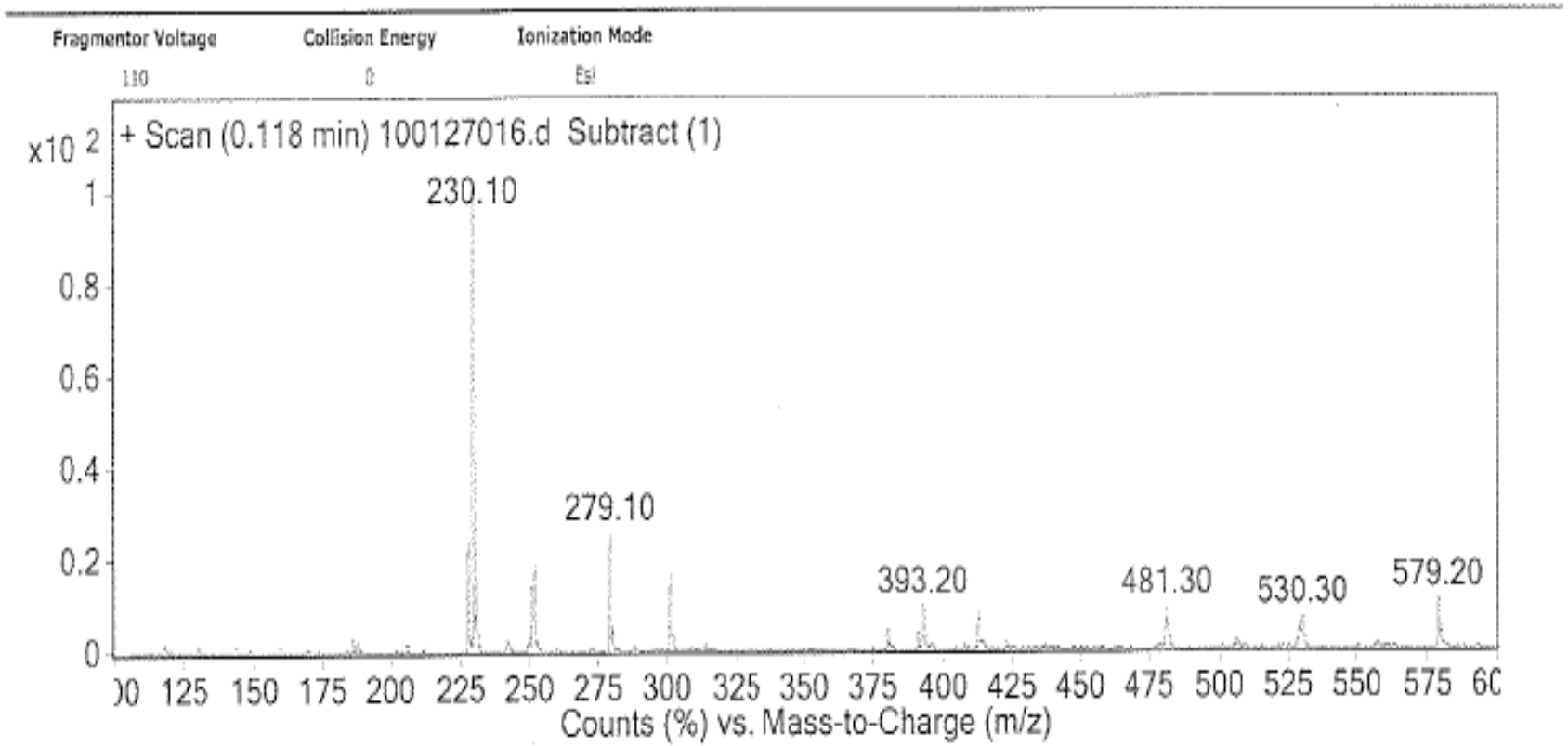
CPS,MIYAPUR

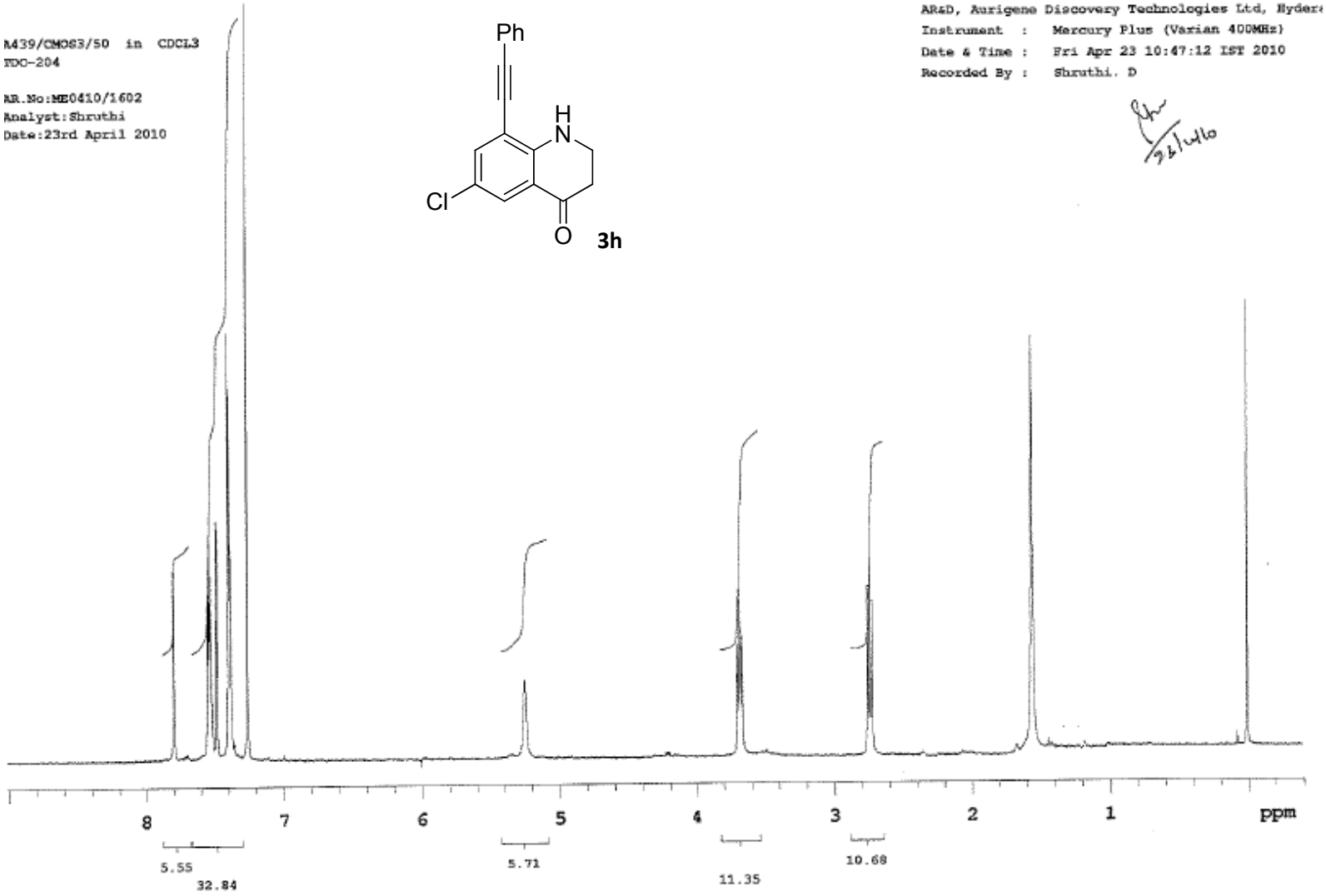
Mass Analysis Report

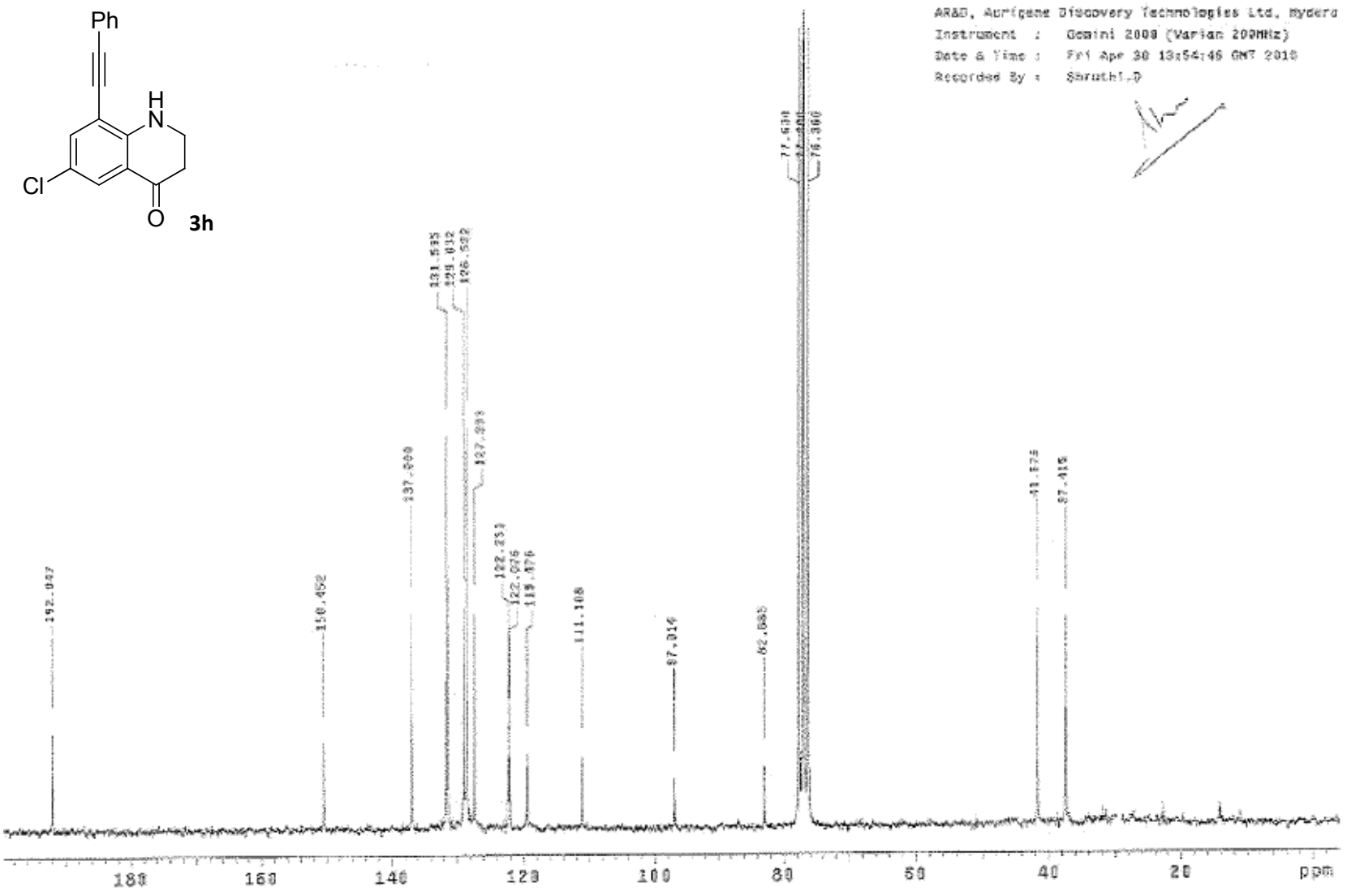


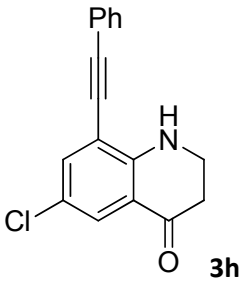
3g

Sample Name	A439/Cmos3/26
Position	Vial 46
User Name	
IRM Calibration Status	Success
Comment	







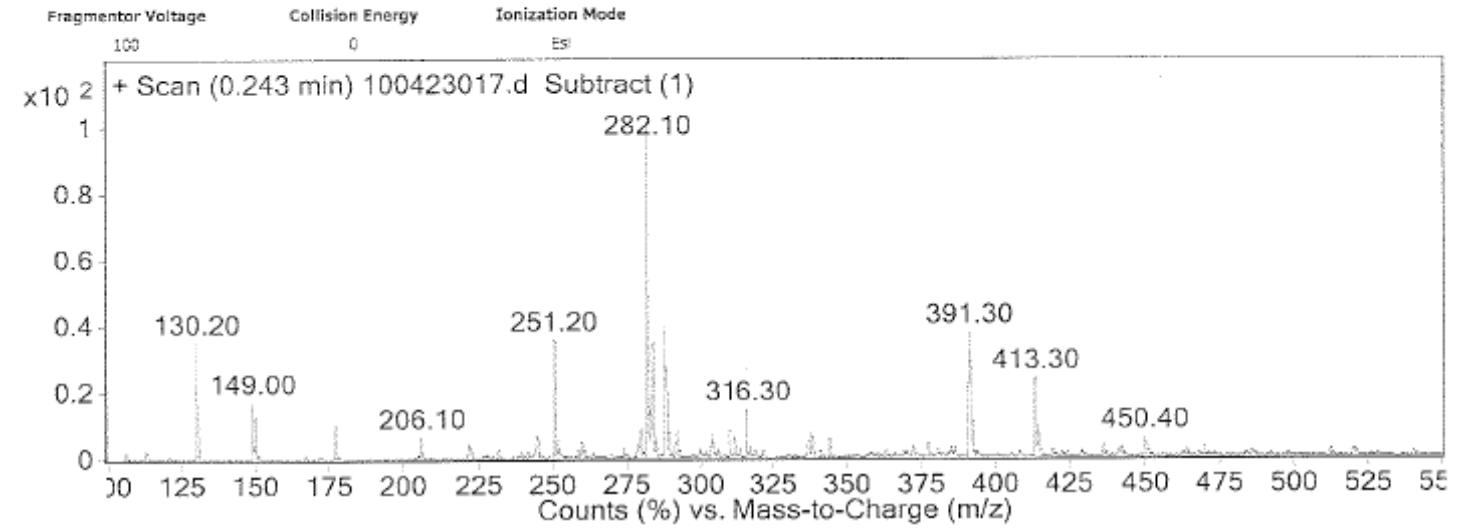


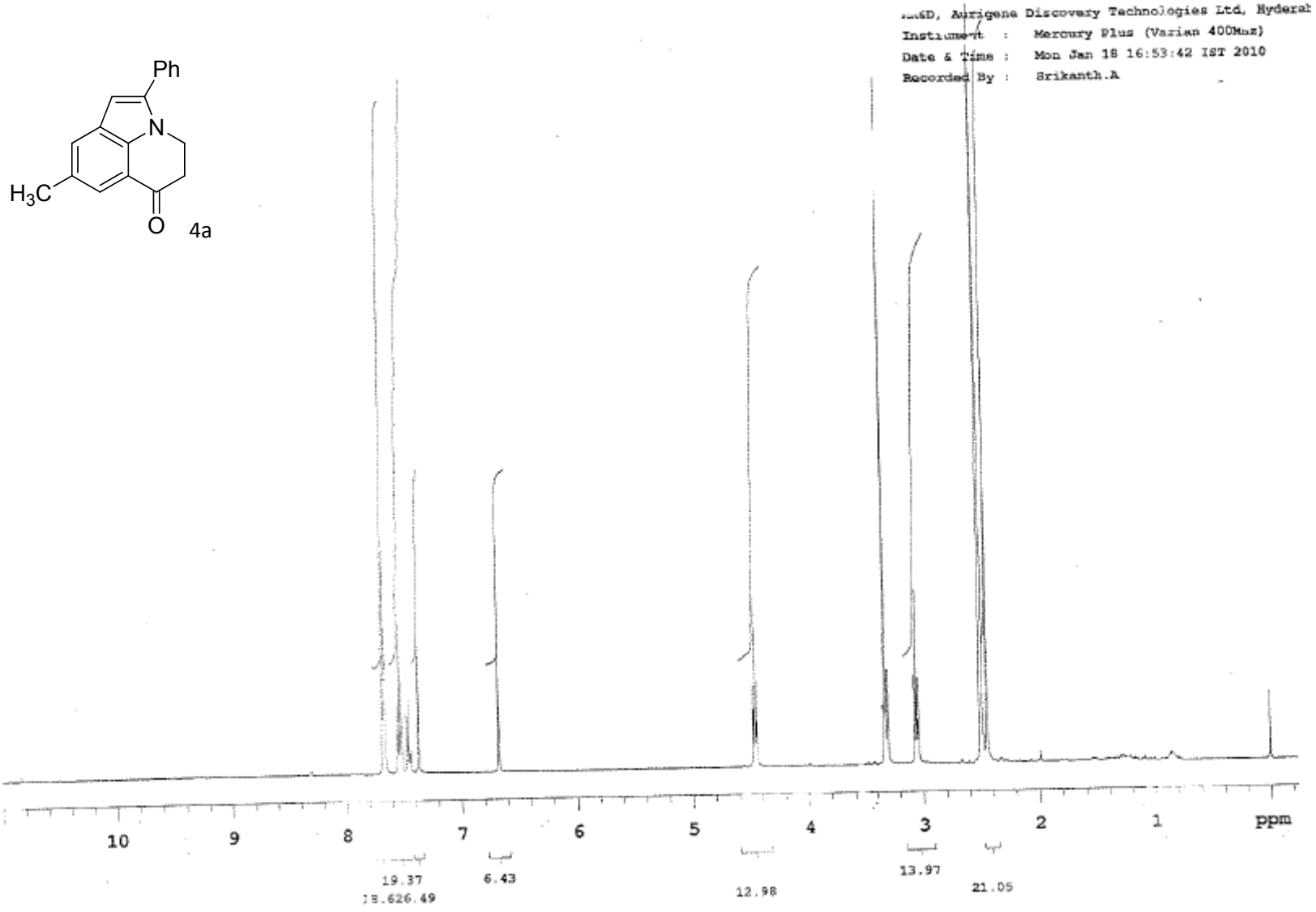
3h

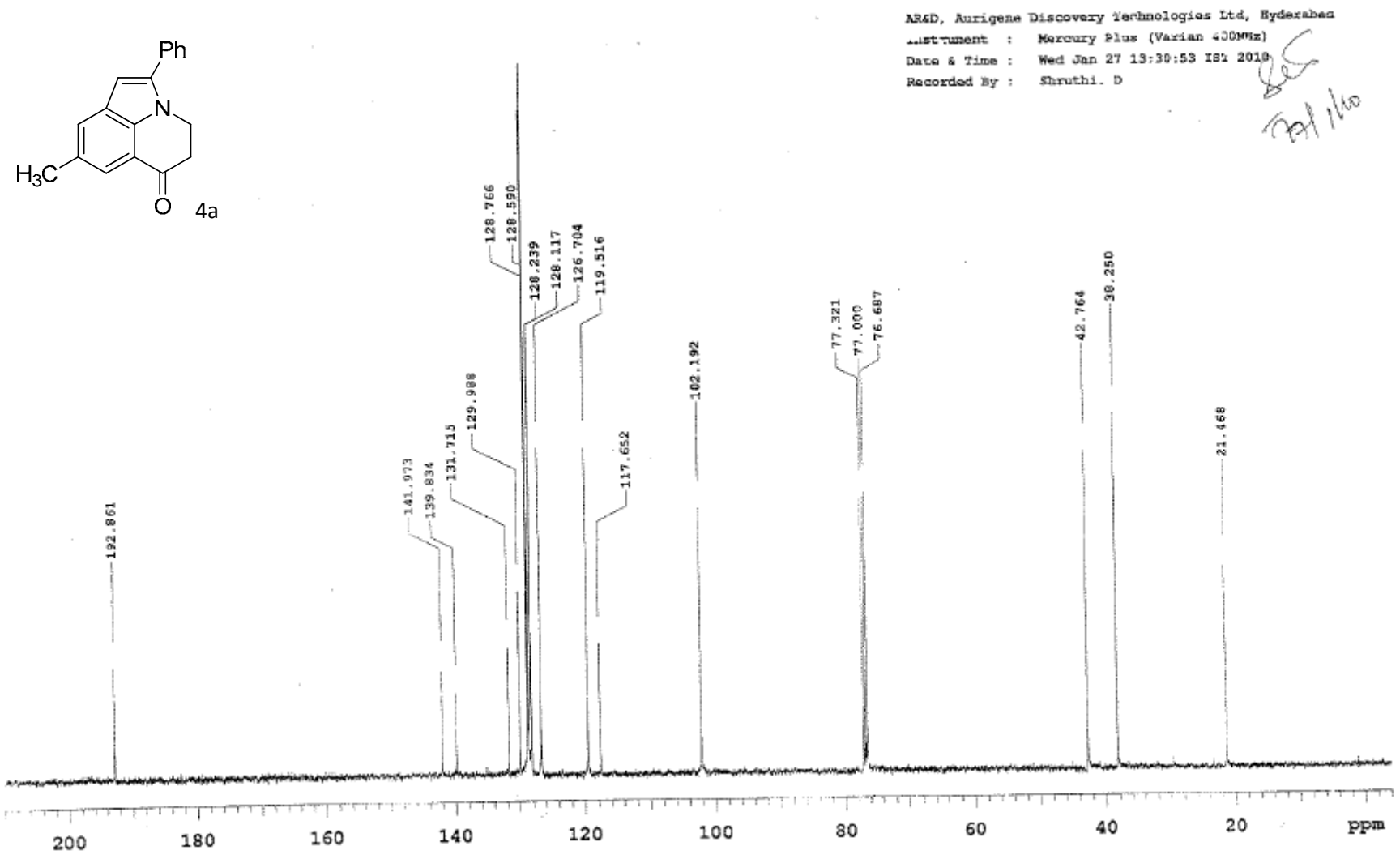
Mass Analysis Report

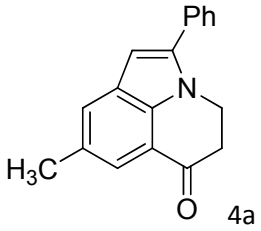
Sample Name	A439/CMOS3/50
Position	Vial 17
User Name	
IRM Calibration Status	Success
Comment	

User Spectra





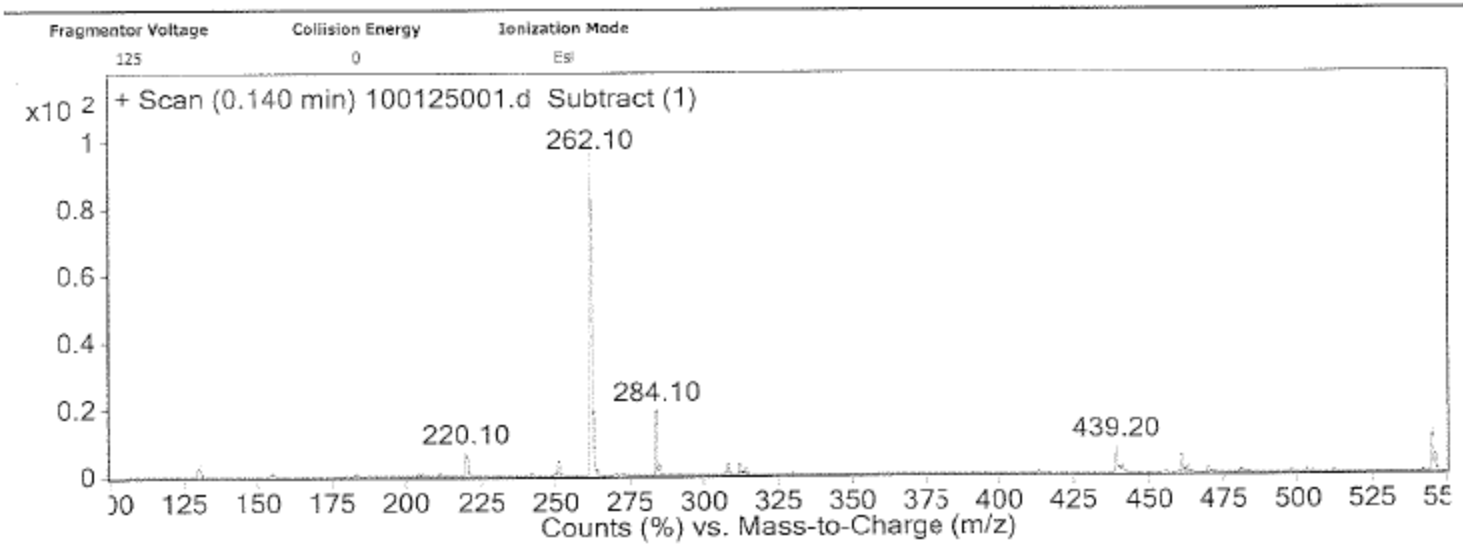




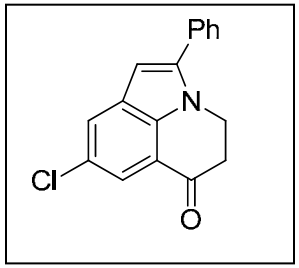
4a

Mass Analysis Report

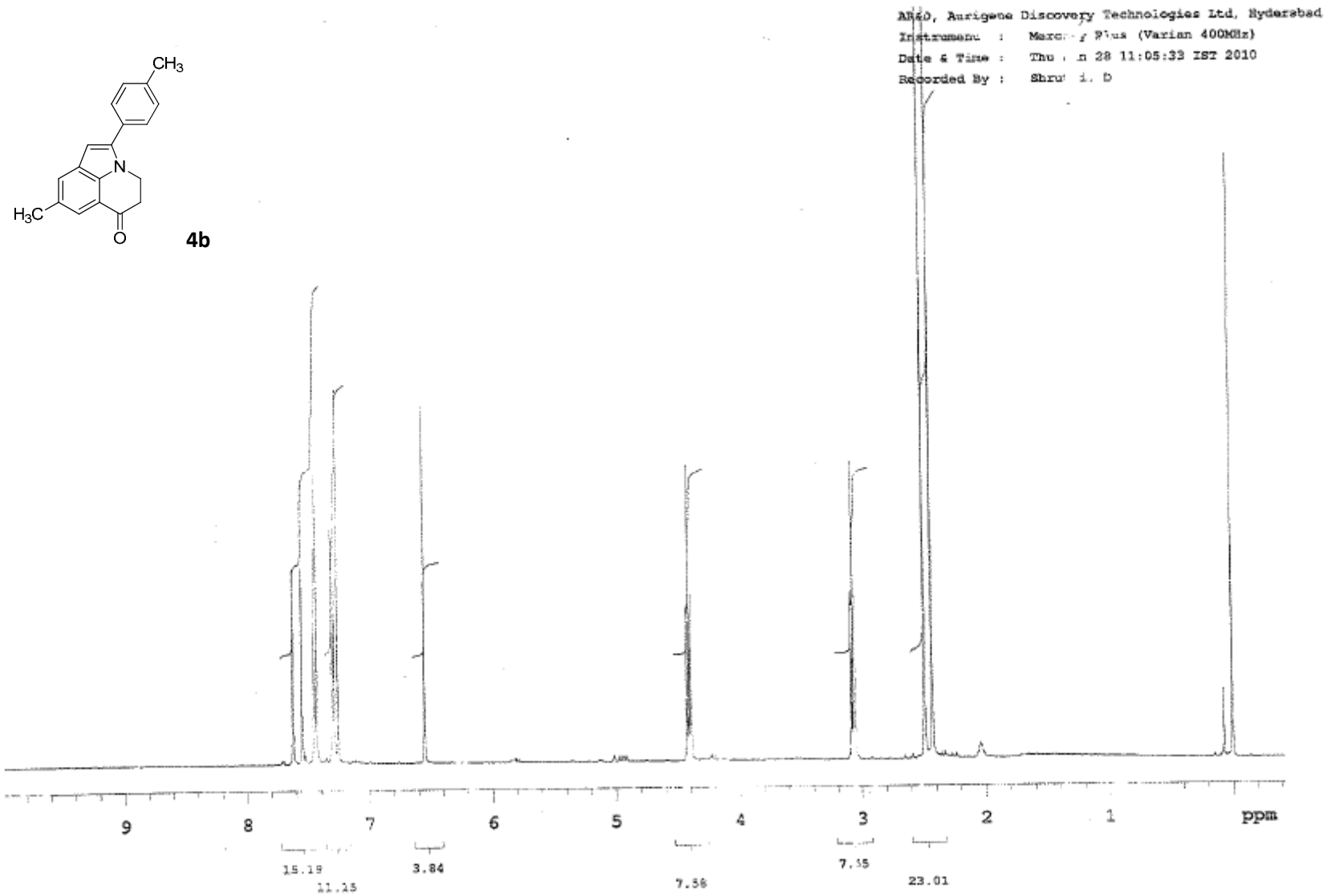
Sample Name	A439/Cmos3/25
Position	Vial 1
User Name	
IRM Calibration Status	Success
Comment	

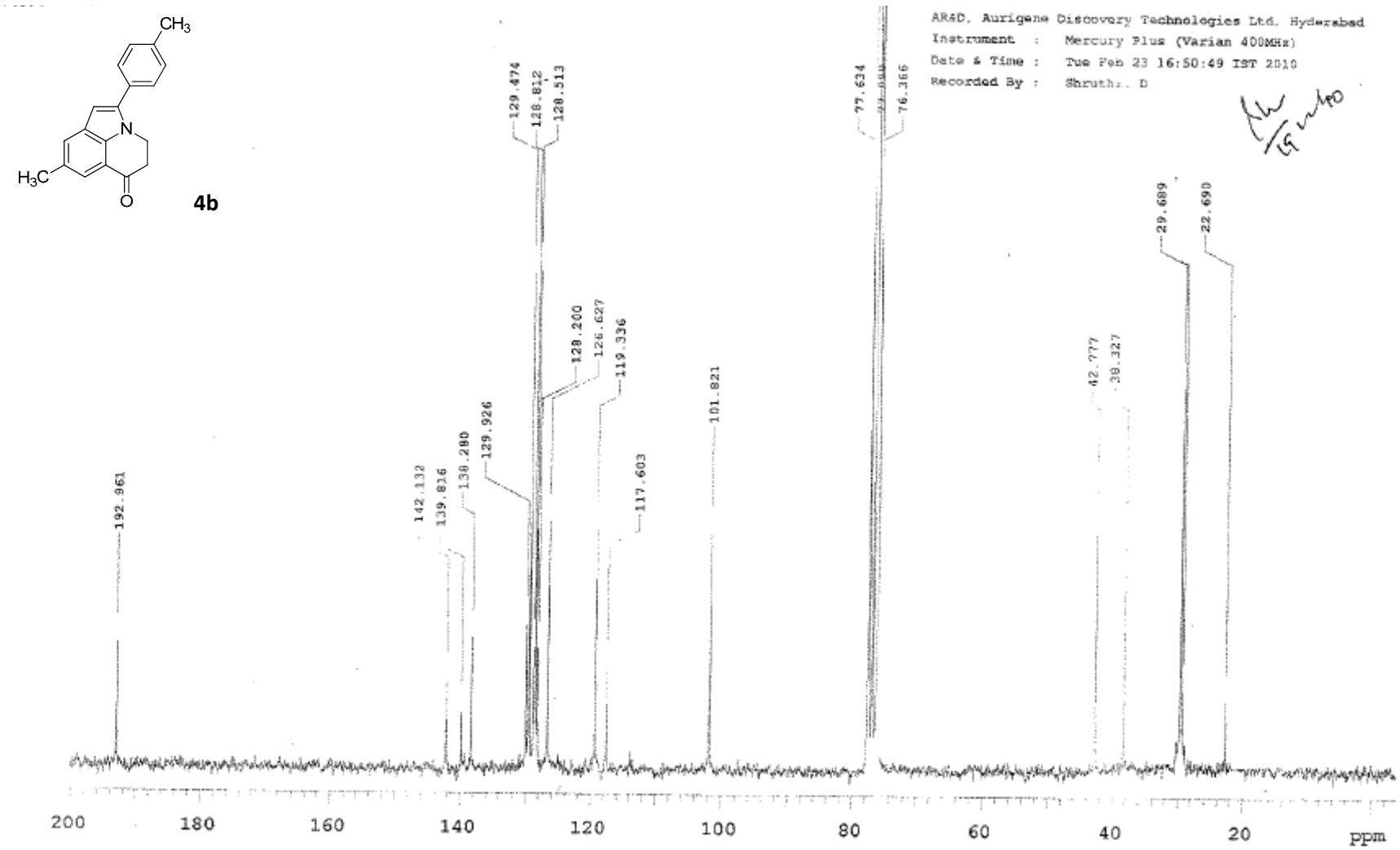


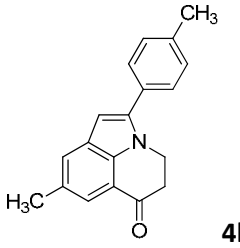
X



X



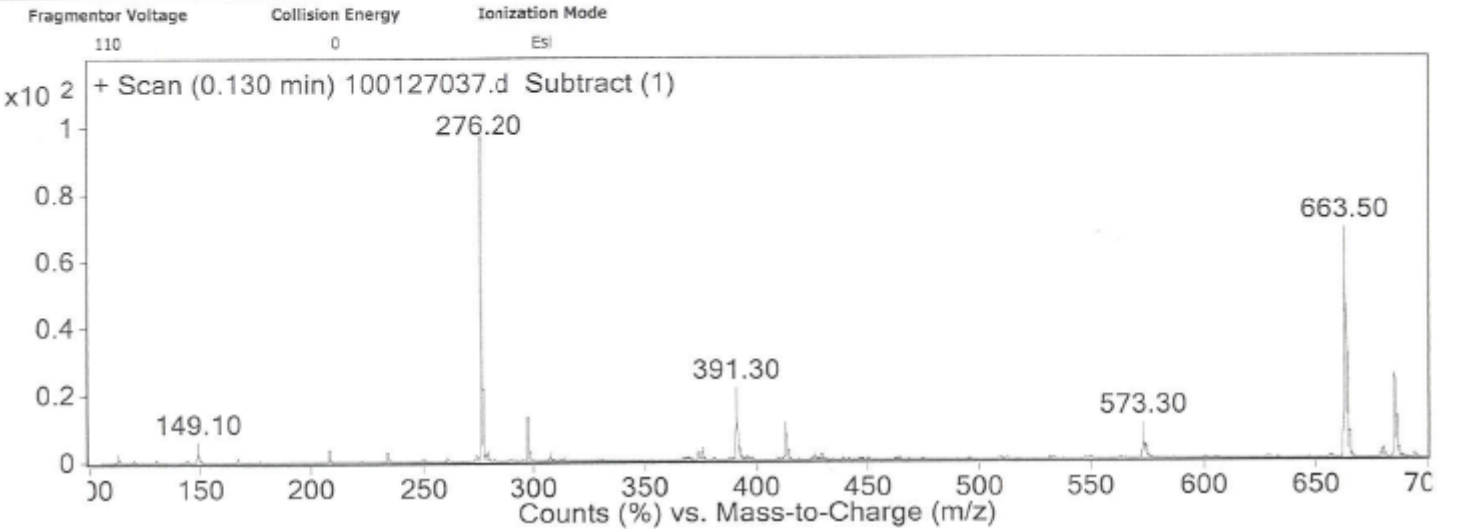


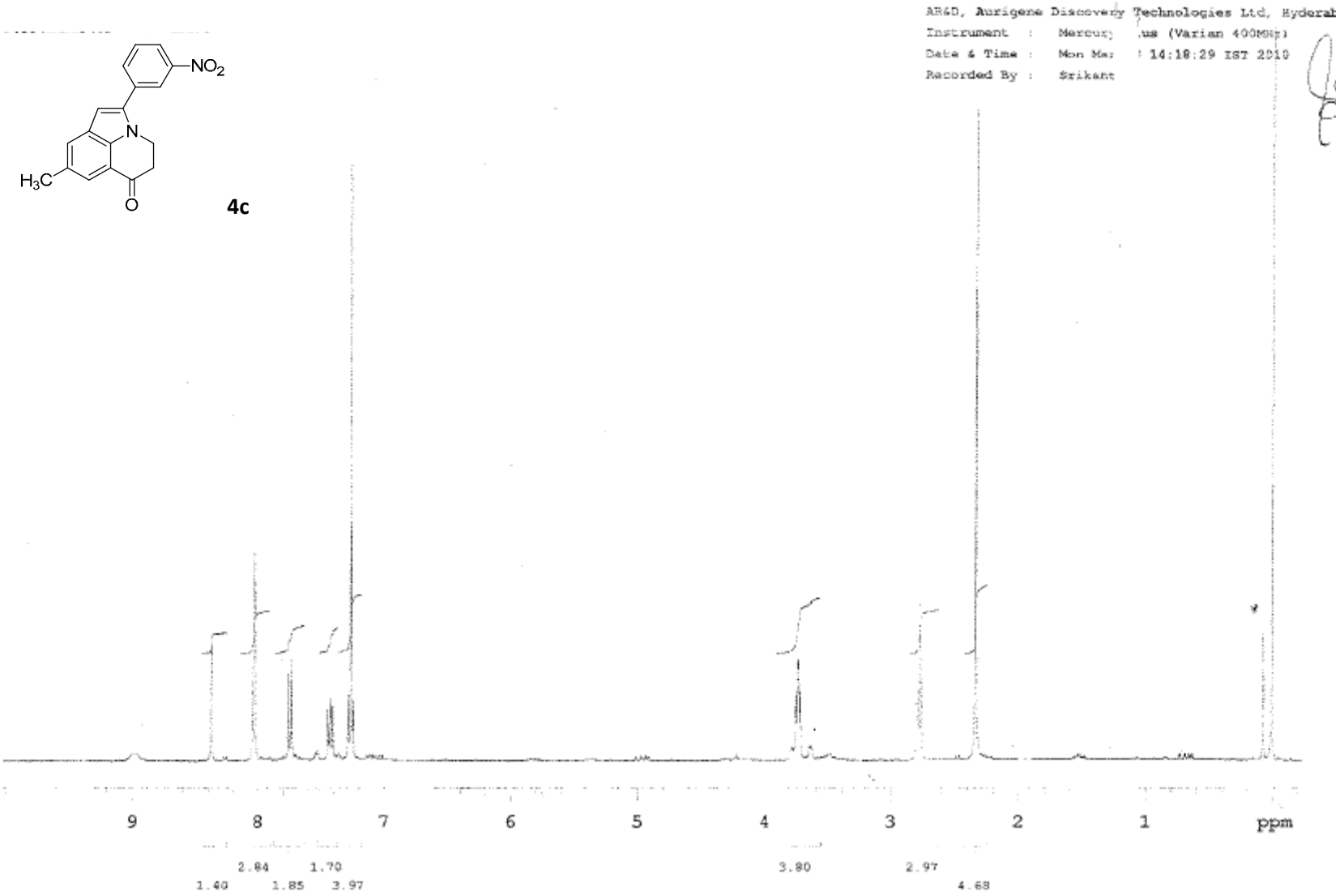


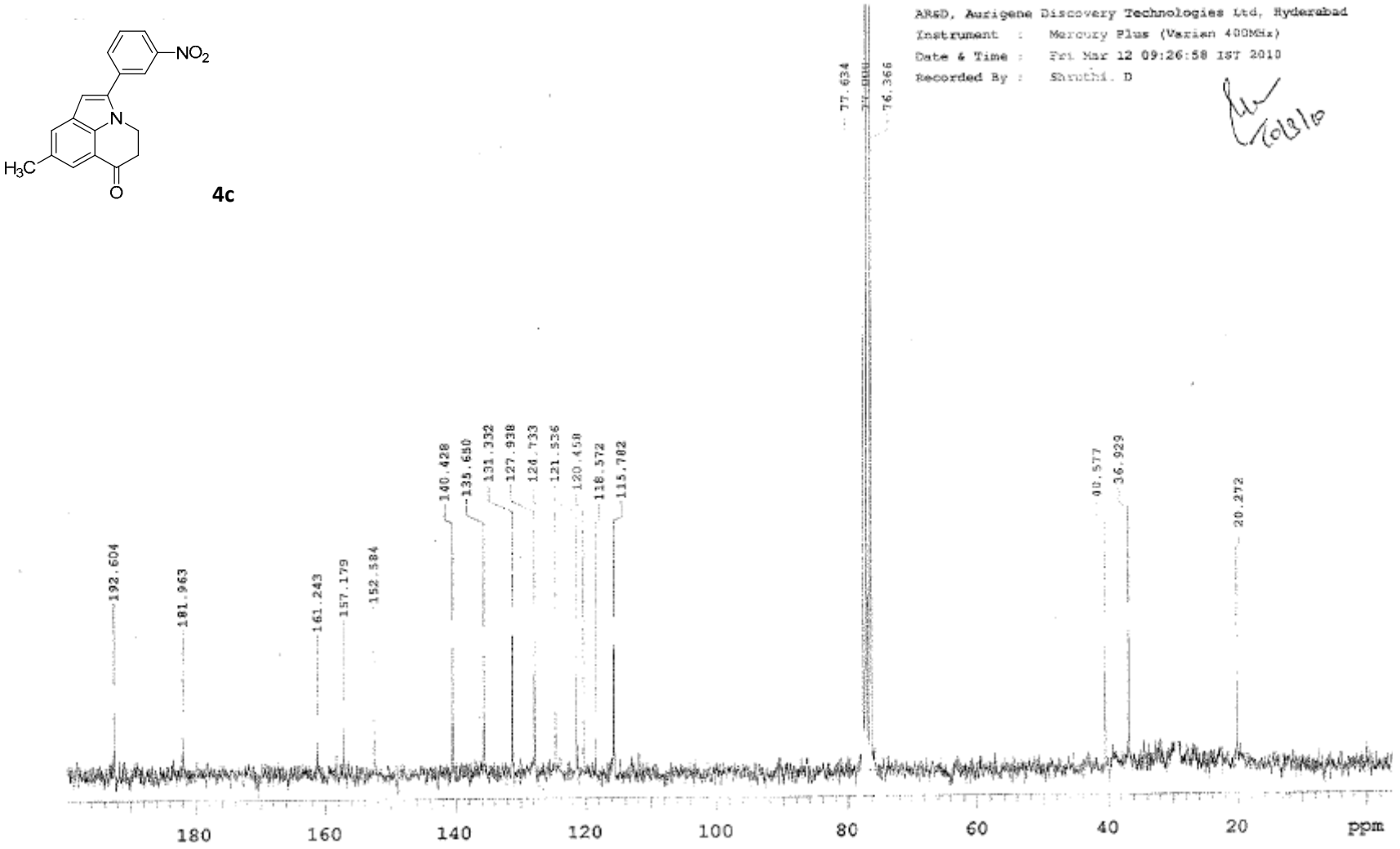
4b

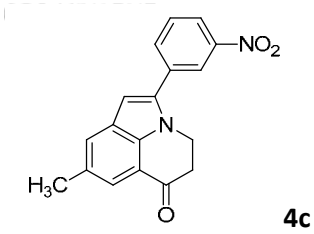
Mass Analysis Report

Sample Name	A439/Cmos-3/29
Position	Vial 4
User Name	
IRM Calibration Status	Success
Comment	





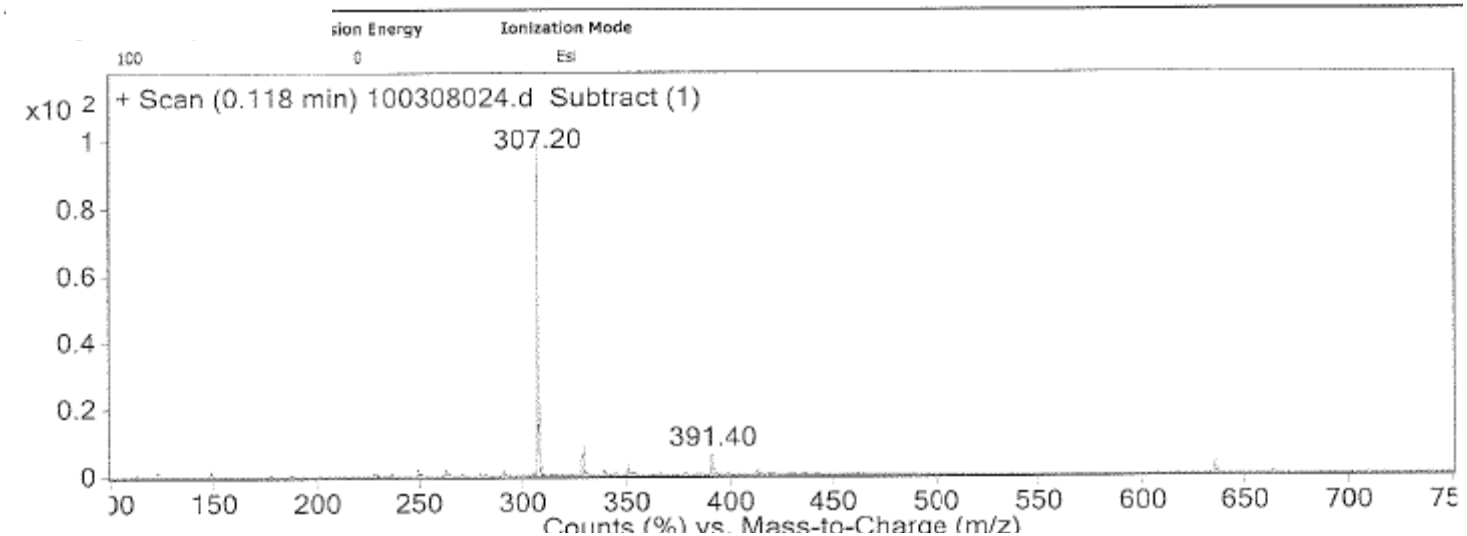


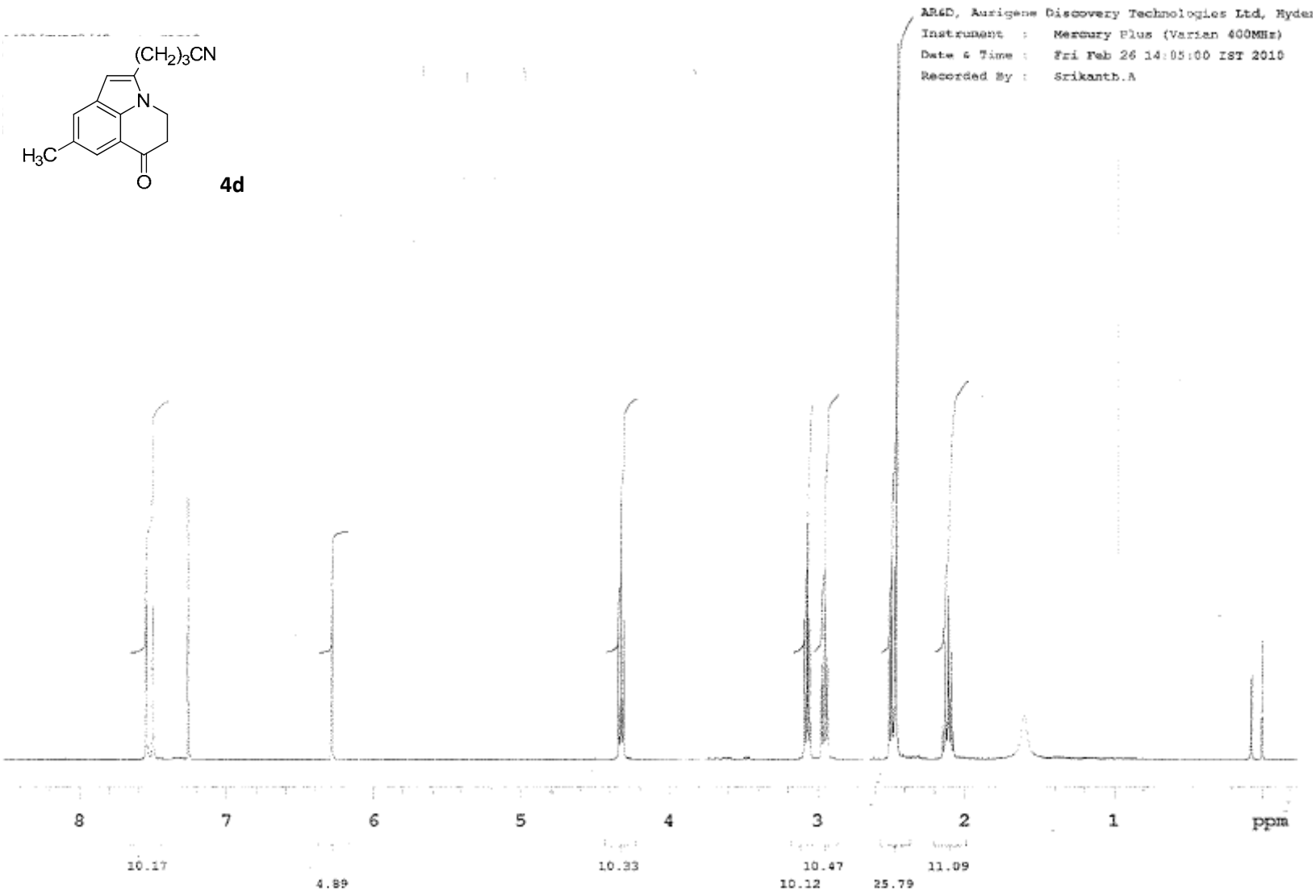


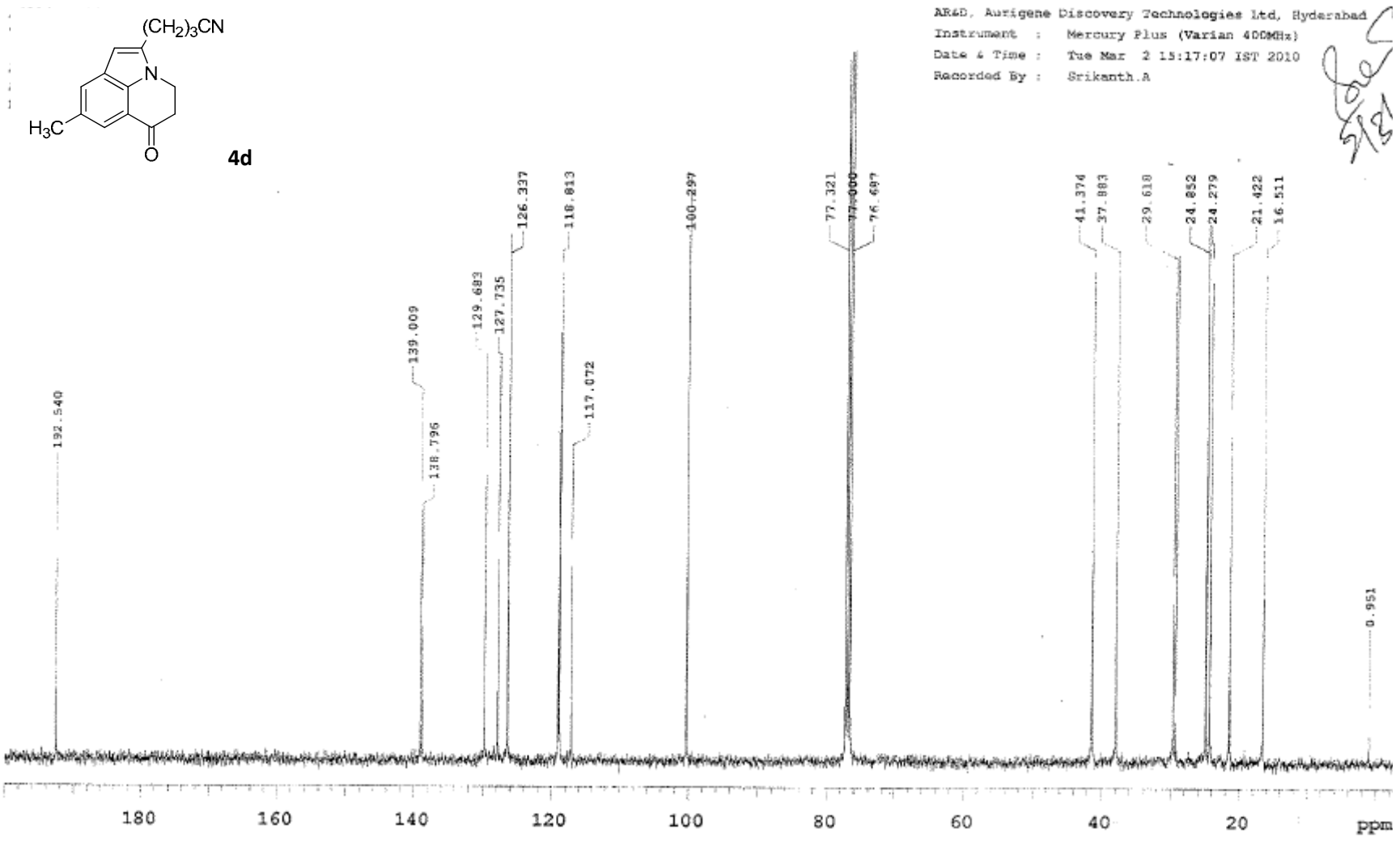
4c

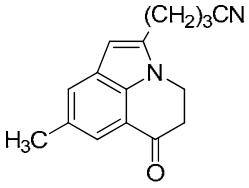
Mass Analysis Report

Sample Name	A439/CMOS3/45
Position	Vial 64
User Name	
IRM Calibration Status	Success
Comment	





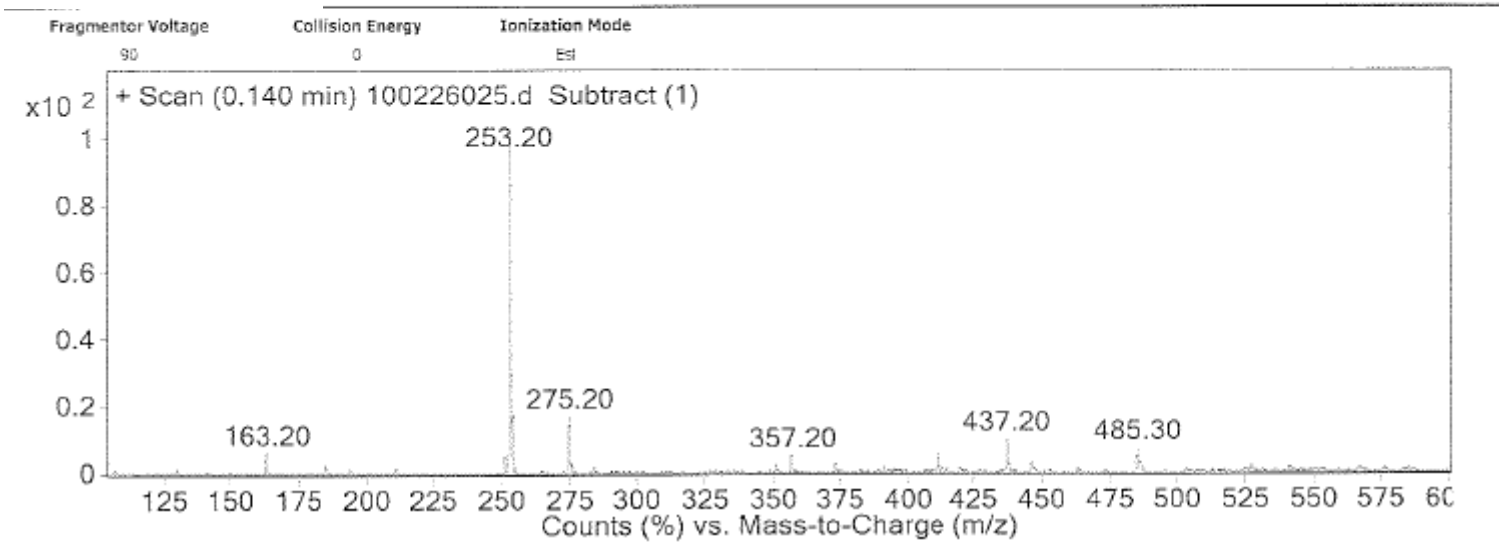


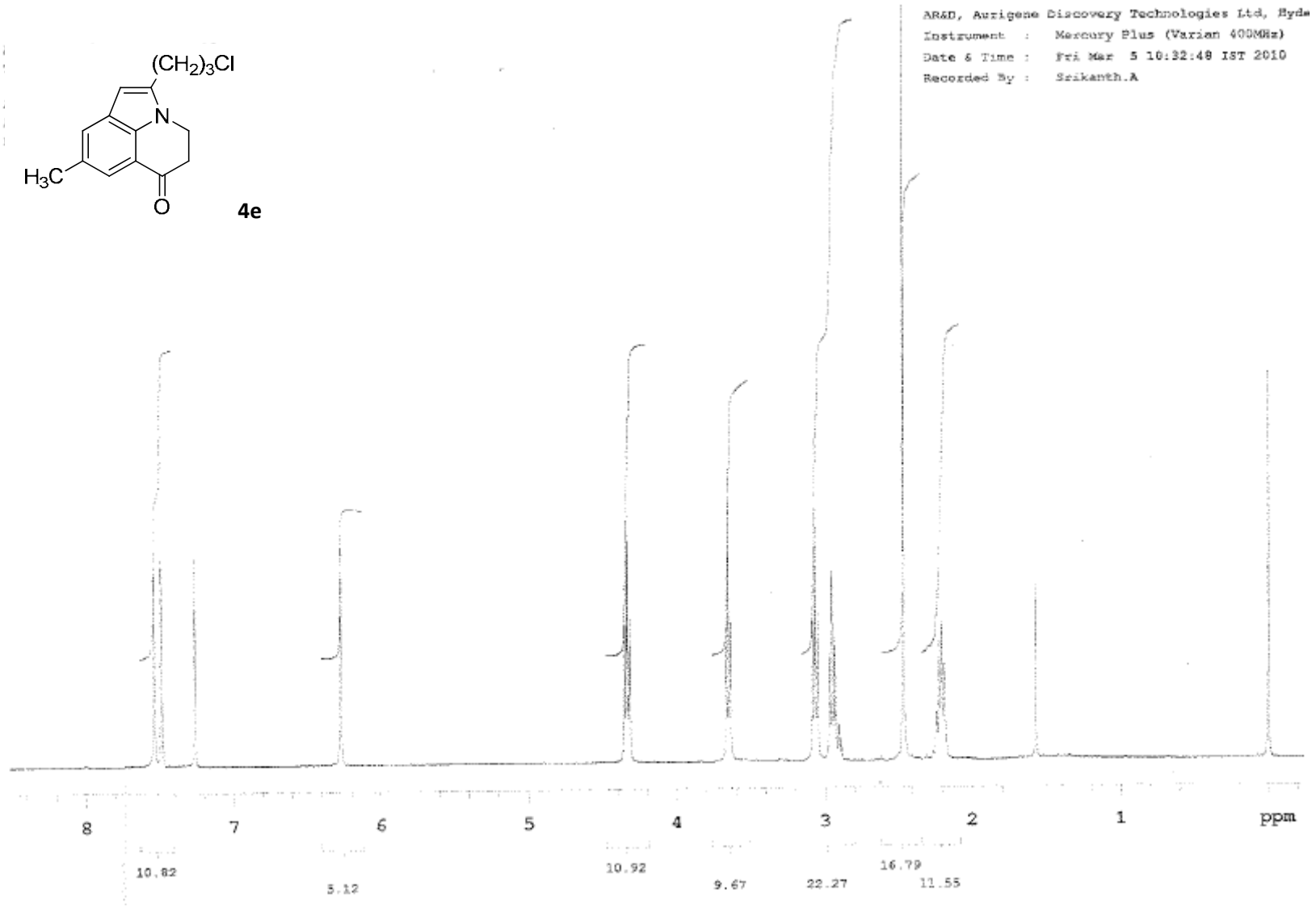


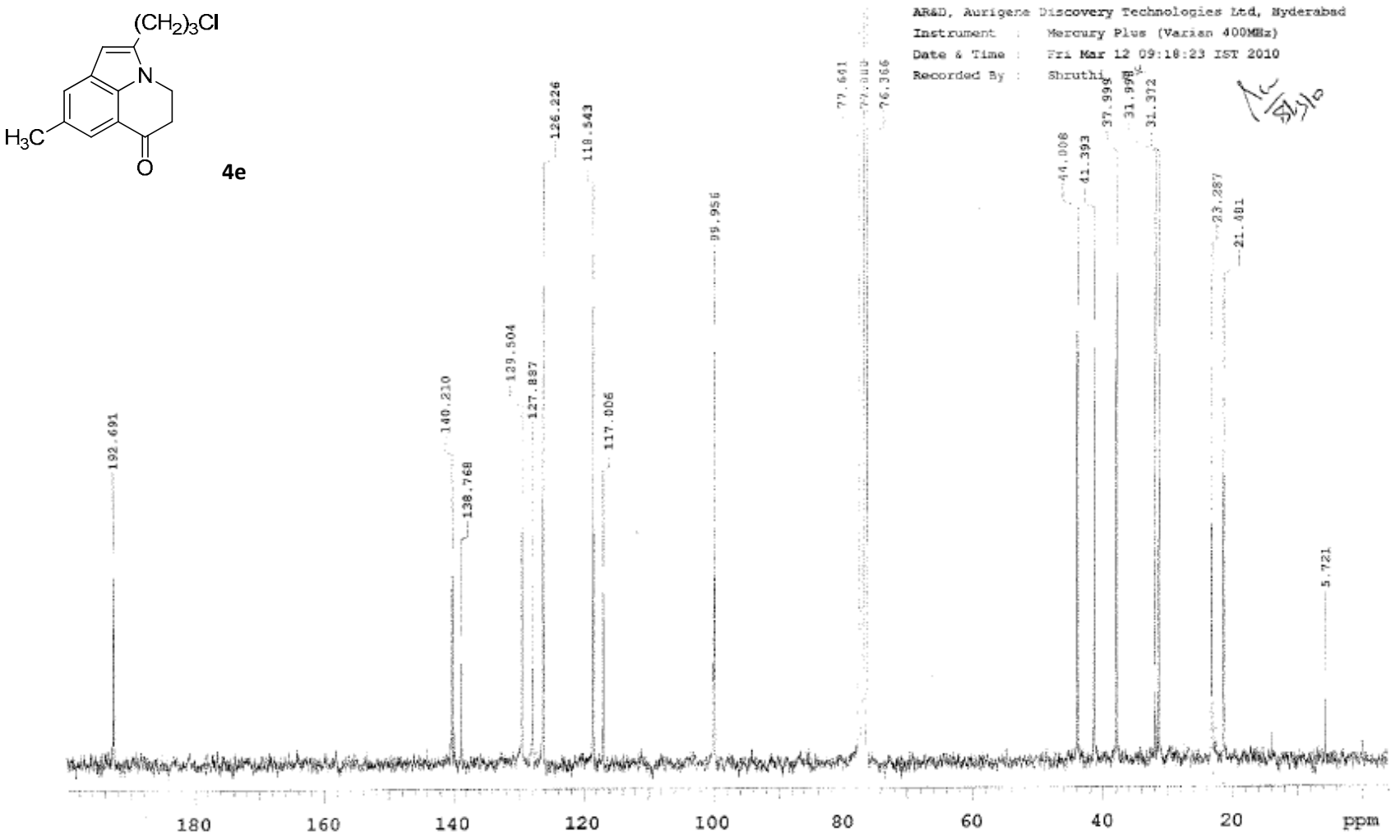
4d

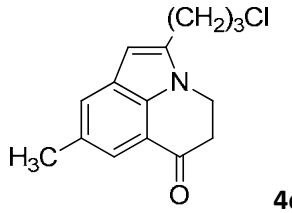
Mass Analysis Report

Sample Name	A439/CMOS3/42
Position	Vial 57
User Name	
IRM Calibration Status	Success
Comment	





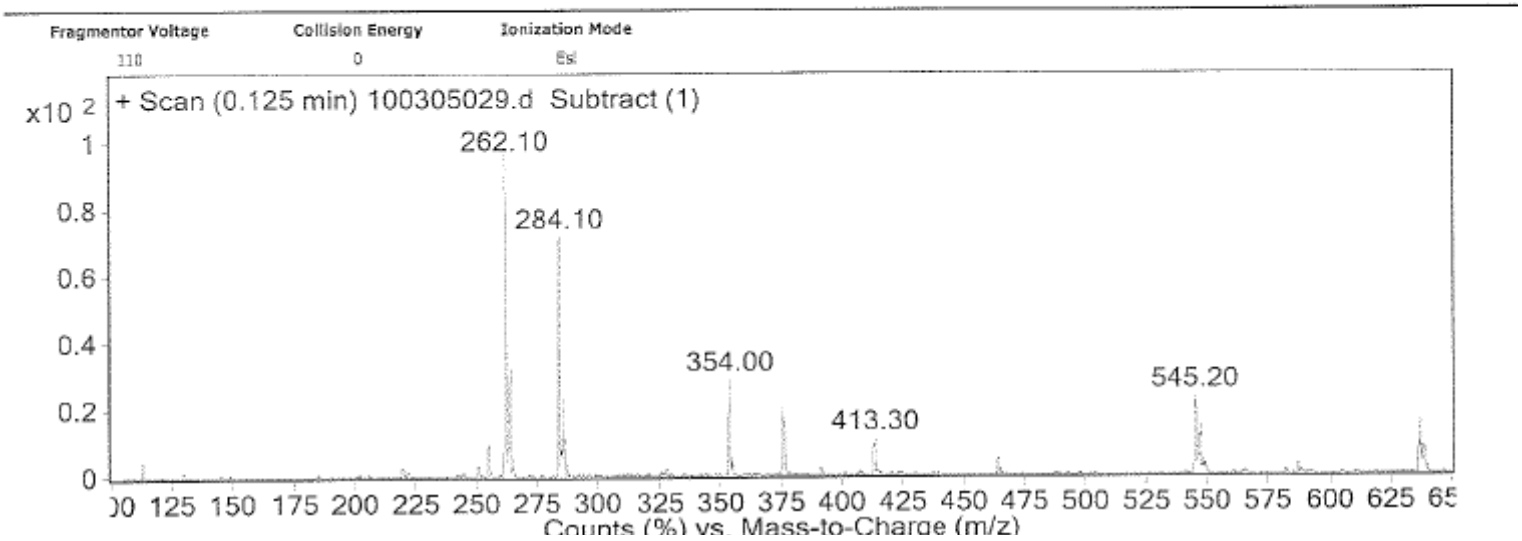


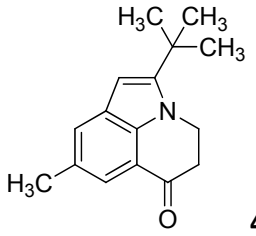


4e

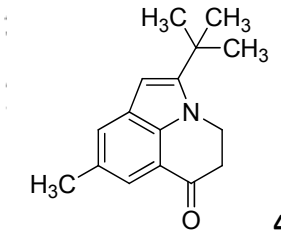
Mass Analysis Report

Sample Name	A439/CMOS3/44
Position	Vial 38
User Name	
IRM Calibration Status	Success
Comment	

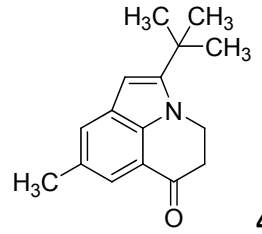




4f



4f



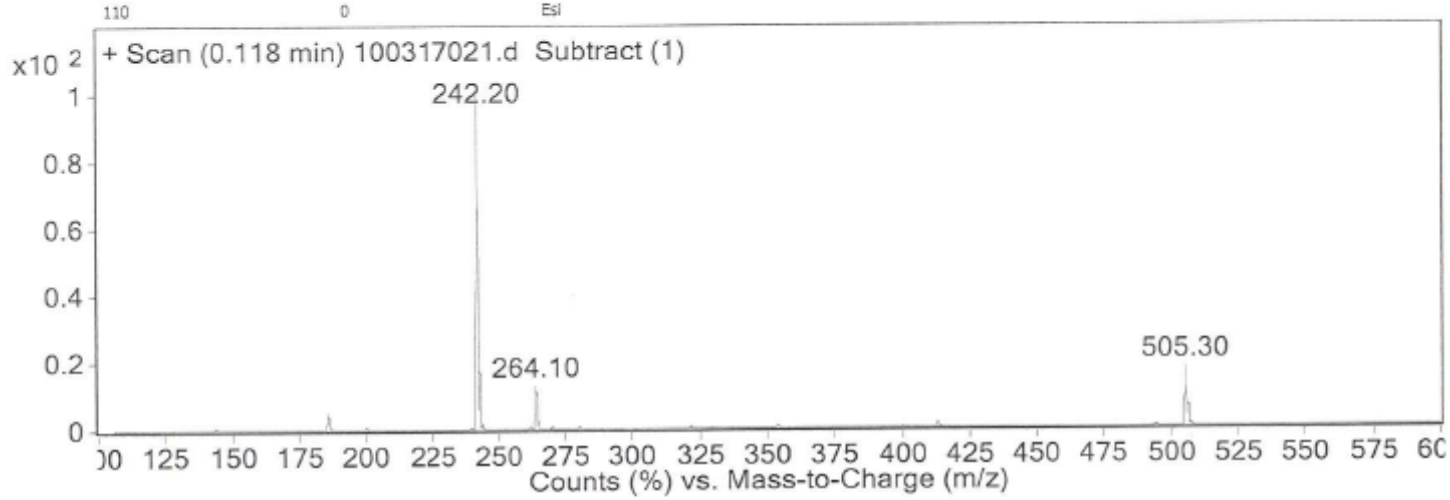
4f

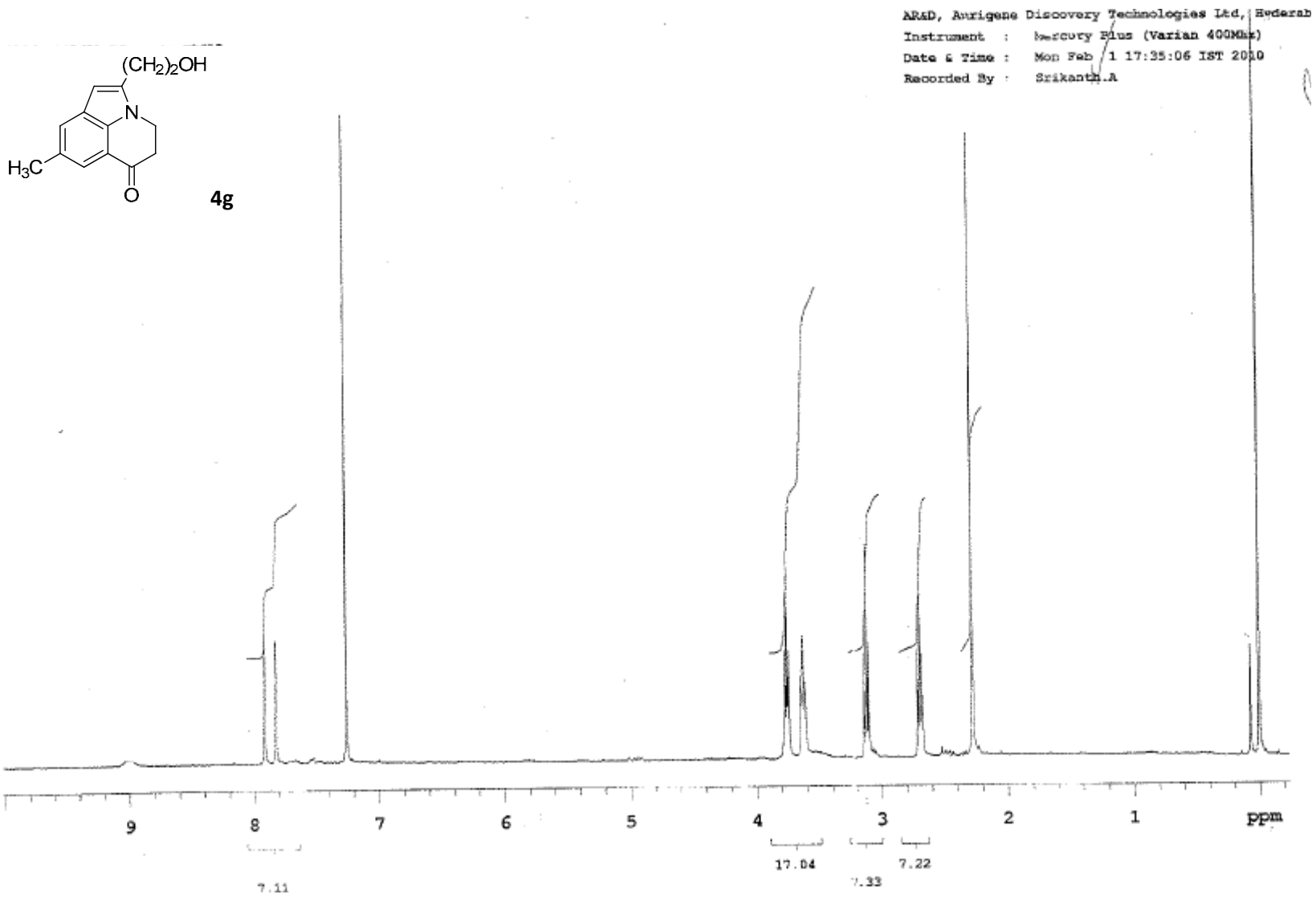
Mass Analysis Report

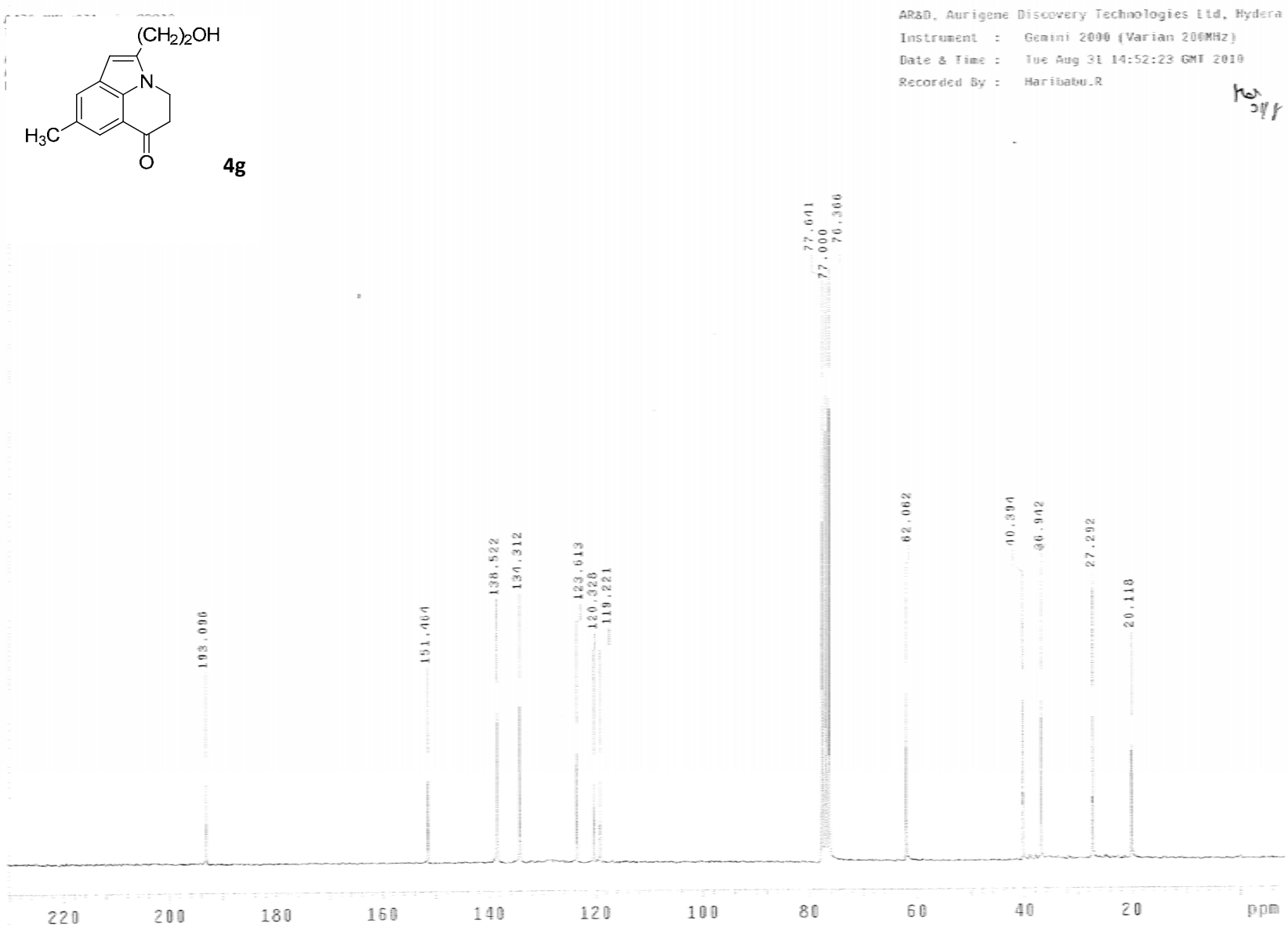
Sample Name	A439/Cmos3/48
Position	Vial 47
User Name	
IRM Calibration Status	Success
Comment	

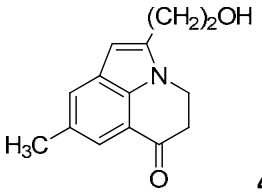
User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
110	0	Esi







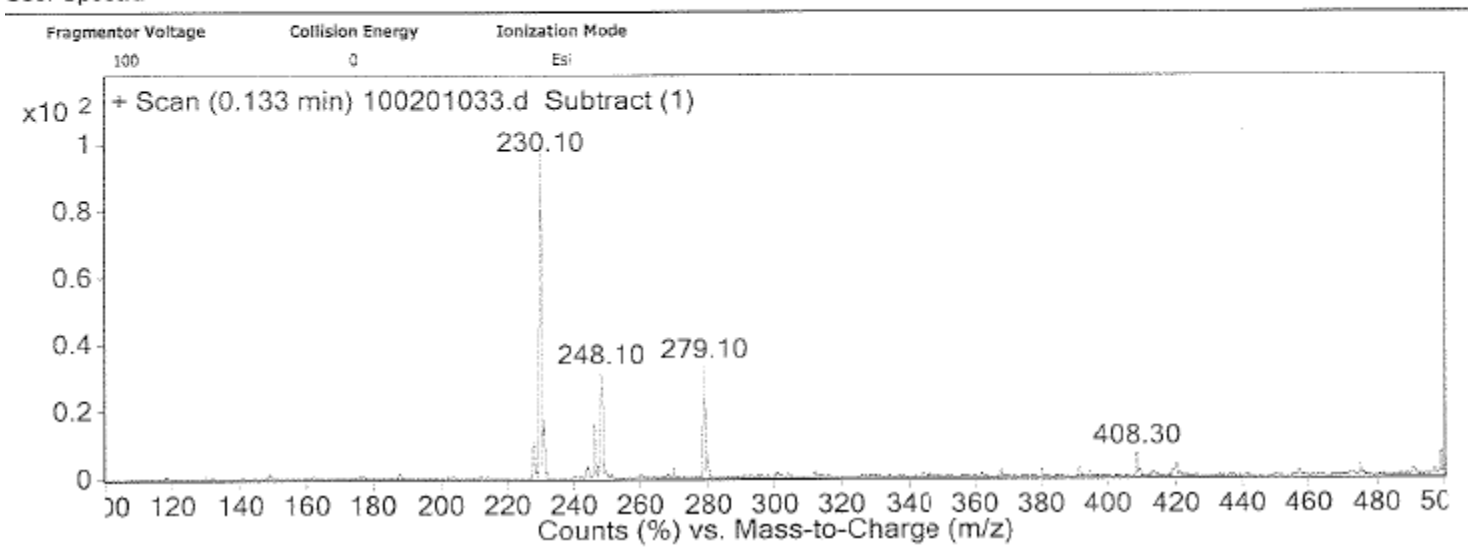


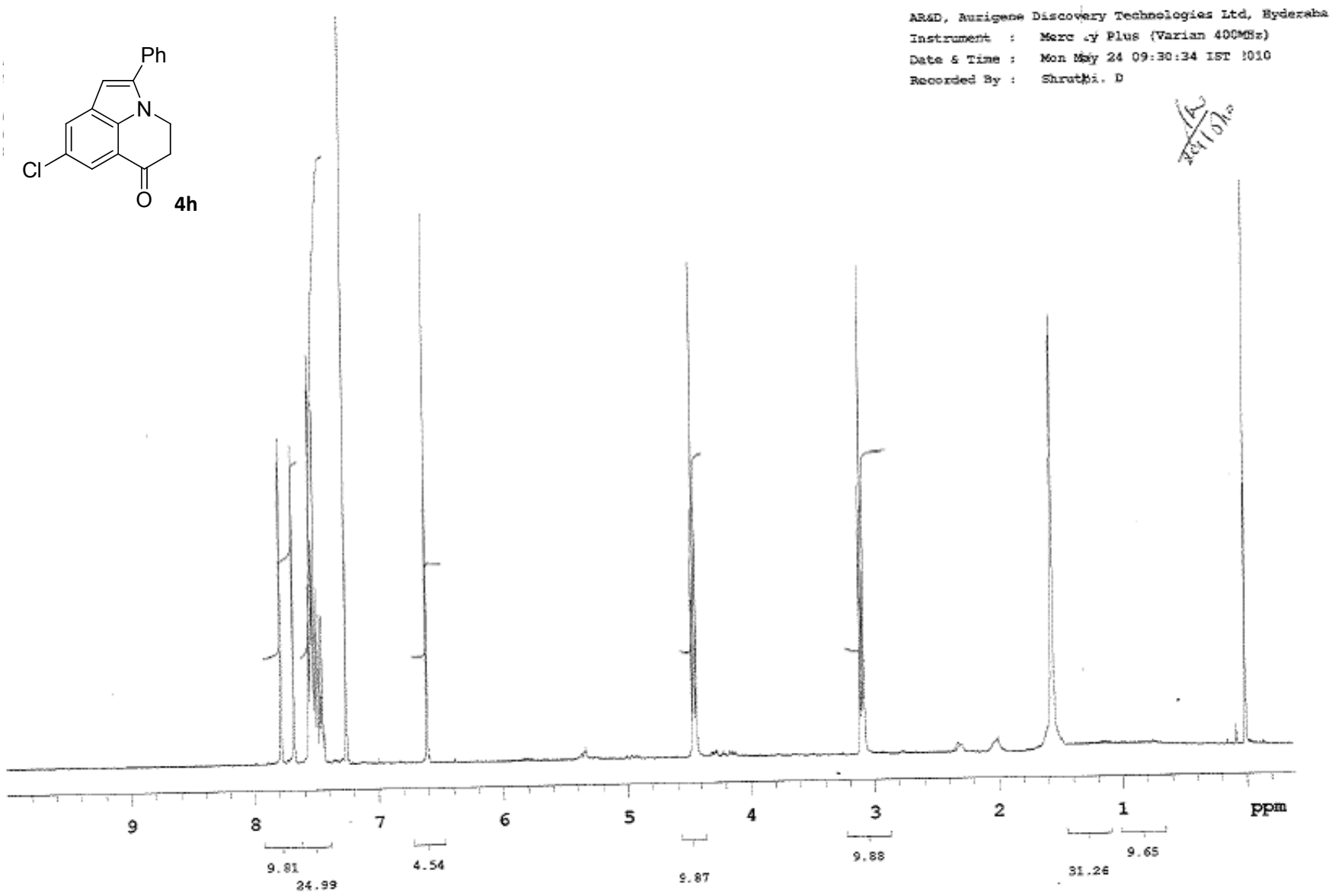
4g

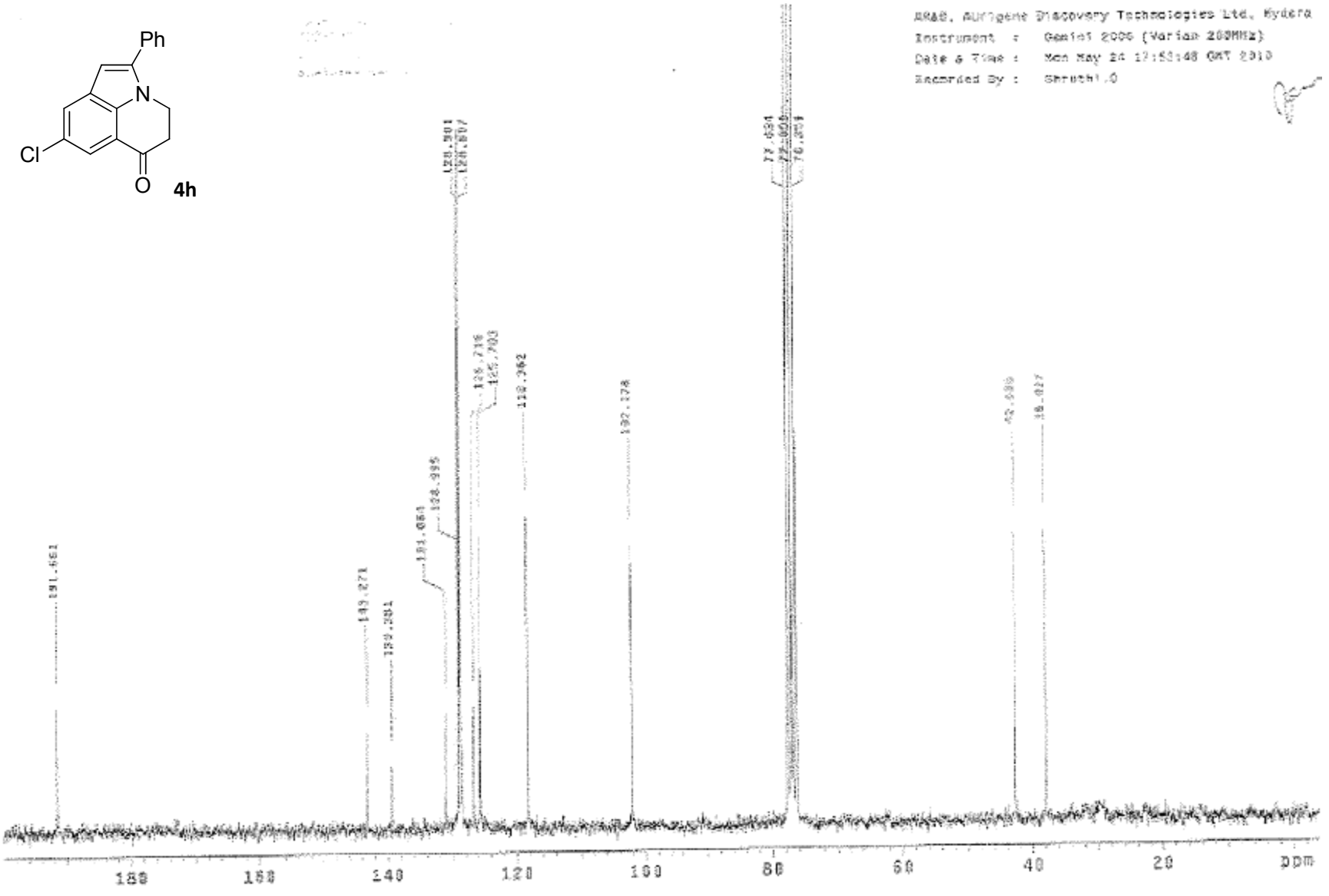
Mass Analysis Report

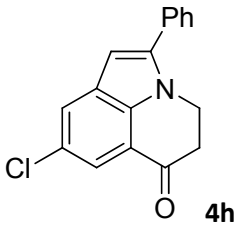
Sample Name	A439/CMOS3/31-PS
Position	Vial 48
User Name	
IRM Calibration Status	Success
Comment	

User Spectra









4h

Mass Analysis Report

Sample Name	A439/CMOS3/51
Position	Vial 61
User Name	
IRM Calibration Status	Success
Comment