Electronic Supplementary Material (ESI) for RSC Advances.


# $FeF_3$-catalyzed MCR in PEG-400: ultrasound assisted synthesis of *N*-substituted 2-aminopyridines

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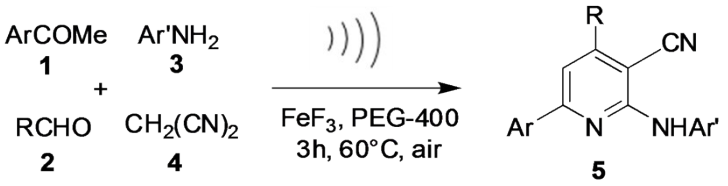
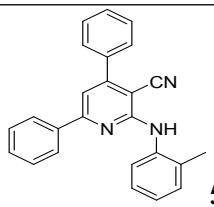
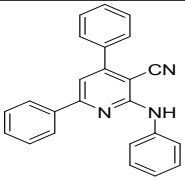
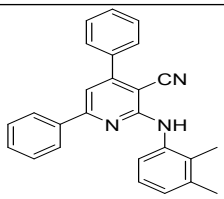
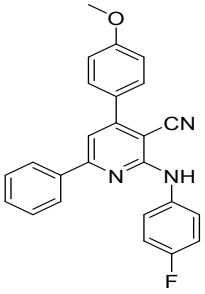
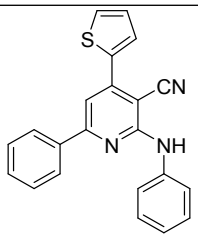
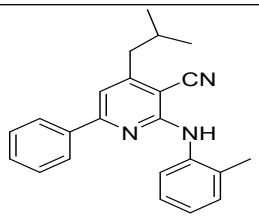
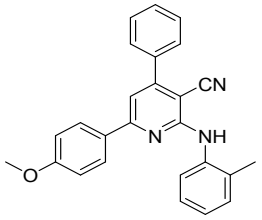
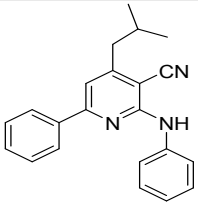
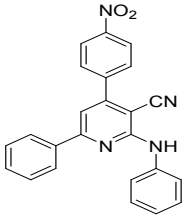
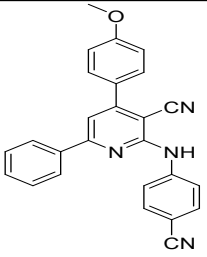
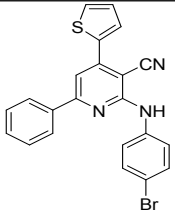
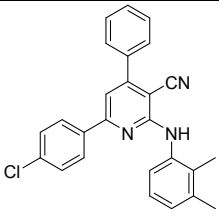
**General methods:** Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (100-200 mesh) using hexane and ethyl acetate. $^{1}H$ and $^{13}C$ NMR spectra were determined in $CDCl_3$ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point B-540 apparatus and are uncorrected. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus. Reactions were performed using a laboratory ultrasonic bath Bandelin SONOREX™ SUPER RK 514 BH model producing irradiation of 35 kHz.

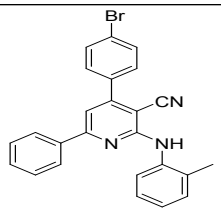
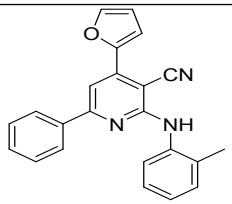
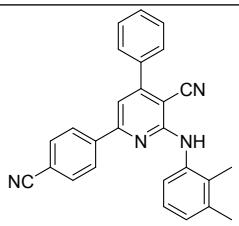
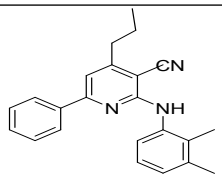
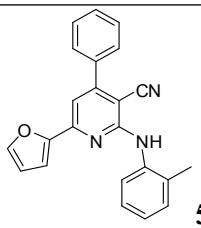
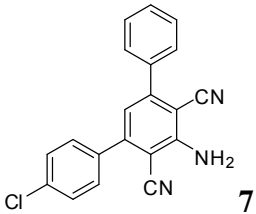
**Typical procedure for the synthesis of 5a:** To a mixture of acetophenone (**1a**, 150 mg, 1.25 mmol), benzaldehyde (**2a**, 130mg, 1.25 mmol), *o*-toluidine (**3a**, 134 mg, 1.25 mmol), and malononitrile (**4**, 82 mg, 1.25 mmol) in PEG-400 (0.3 mL) was added $FeF_3$ (14.1mg, 10 mol%) at room temperature. The mixture was then stirred at 60 ºC under ultrasound irradiation in open air for 3h (the reaction was monitored by TLC). After completion of the reaction the mixture was diluted with EtOAc (10 mL) and washed with cold water (2 x 5 mL). The organic layer was collected, dried over anhydrous $Na_2SO_4$, filtered and concentrated under low vacuum. The residue was purified by column chromatography over silica gel (100-200 mesh) using EtOAc-hexane to give the desired product.

**Table S-1**. Ultrasound assisted synthesis of *N*-substituted 2-aminopyridines (**5**) via $FeF_3$ catalyzed MCR.



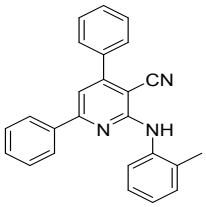

| Entry | Acetophenone (**1**) | Aldehyde (**2**) | Aniline (**3**) | Product (**5**) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Acetophenone **1a** | Bezaldehyde **2a** | *o*-Toludine **3a** |  **5a** | 92 |
| 2 | **1a** | **2a** | Aniline **3b** |  **5b** | 90 |
| 3 | **1a** | **2a** | 2,3-Dimethyl aniline **3c** |  **5c** | 92 |
| 4 | **1a** | 4-Methoxy bezaldehyde **2b** | 4-Flouro aniline **3d** |  **5d** | 89 |
| 5 | **1a** | Thiophene-2-aldehyde **2c** | **3b** |  **5e** | 90 |

| | | | | | |
|---|---|---|---|---|---|
| 6 | **1a** | Isovaleraldehyde **2d** | **3a** |  **5f** | 88 |
| 7 | 4-Methoxy acetophenone **1b** | **2a** | **3a** |  **5g** | 89 |
| 8 | **1a** | **2d** | **3b** |  **5h** | 90 |
| 9 | **1a** | 4-Nitro benzaldehyde **2e** | **3b** |  **5i** | 92 |
| 10 | **1a** | 4-Methoxy benzaldehyde **2b** | 4-Cyano aniline **3e** |  **5j** | 87 |
| 11 | **1a** | **2c** | 4-Bromo aniline **3f** |  **5k** | 89 |
| 12 | 4-Chloro acetophenone **1c** | **2a** | 2,3-Dimethyl aniline **3c** |  **5l** | 90 |

| | | | | | |
|---|---|---|---|---|---|
| 13 | **1a** | 4-Bromo bezaldehyde **2f** | **3a** |  **5m** | 86 |
| 14 | **1a** | Furan-2-aldehyde **2g** | **3a** |  **5n** | 85 |
| 15 | 4-Cyano acetophenone **1d** | **2a** | **3c** |  **5o** | 91 |
| 16 | **1a** | *Butyraldehyde* **2h** | **3c** |  **5p** | 85 |
| 17 | 1-(Furan-2-yl)ethanone **1e** | ***2a*** | **3a** |  **5q** | 51 |
| 18 | **1c** | ***2a*** | *n*-$BuNH_2$ **3g** |  **7** | 50 |

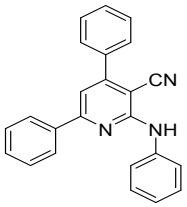
**Spectral data**

**4,6-Diphenyl-2-(o-tolylamino)nicotinonitrile (5a)**



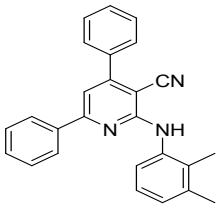

Off white solid, mp:194-196 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.6 Hz, 1H), 8.03-8.00 (m, 2H), 7.69-7.66 (m, 2H), 7.58-7.52 (m, 3H), 7.46-7.43 (m, 3H), 7.33-7.27 (m, 4H), 7.14 (t, *J* = 7.2 Hz, 1H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 159.6, 156.6, 153.1, 148.3, 143.1, 138.3, 137.4, 130.6, 130.2, 129.8, 129.0 (2C), 128.7 (2C), 128.2 (2C), 127.3 (2C), 126.5, 124.3 (2C), 122.7, 111.1, 89.5, 18.0; IR (KBr, $cm^{-1}$): 3334, 2963, 2214, 1601, 1582, 1491; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{25}H_{20}N_3O$: 362.1657, found: 362.1669.

**4,6-Diphenyl-2-(phenylamino)nicotinonitrile (5b)**




Pale yellow solid, mp: 213-215°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, $J_{1,2}$ = 2.4 Hz, $J_{1,3}$ = 8.0 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.67-7.65 (m, 2H), 7.57-7.47 (m, 6H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (s, 1H), 7.27-7.26 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.9, 156.5, 155.4, 138.9, 137.8, 136.9, 130.3, 129.9, 128.9 (2C), 128.9 (2C), 128.8(2C), 128.1 (2C), 127.4(2C), 123.5, 120.5 (2C), 117.0, 111.4, 90.0; IR (KBr, $cm^{-1}$): 3335, 2215, 1602, 1582, 1497; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{24}H_{18}N_3$: 348.1501, found: 348.1514.

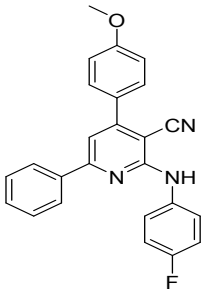
**2-((2,3-Dimethylphenyl)amino)-4,6-diphenylnicotinonitrile (5c)**




Off white solid, mp: 172-174°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.99 – 7.95 (m, 2H), 7.80 (d, *J* =

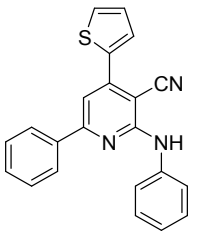
8.0Hz, 1H), 7.69-7.65 (m, 2H), 7.57-7.51 (m, 3H), 7.43-7.40 (m, 3H), 7.29 (s, 1H), 7.22 (t, $J$ = 8.0 Hz, 1H), 7.09-7.05 (m, 2H), 2.37 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.8, 157.4, 155.3, 137.8, 137.4, 137.1, 136.8, 130.1, 129.8, 129.6, 128.9 (2C), 128.7 (2C), 128.2 (2C), 127.3 (2C), 126.6, 125.5, 121.8, 117.2, 110.8, 89.5, 20.7, 14.0; IR (KBr, $cm^{-1}$) :3395, 2965, 2209, 1603, 1586, 1447; HRMS (ESI) ([M]$^+$1) calcd for $C_{26}H_{22}N_3$: 376.1814, found: 376.1801.

**2-((4-Fluorophenyl)amino)-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (5d)**




Yellow solid, mp: 169-172°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, $J$ = 8.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.65-7.61 (m, 2H), 7.52 (t, $J$ = 8.0 Hz, 3H), 7.39 (d, $J$ = 8.4 Hz, 3H), 7.03-6.94 (m, 4H), 3.85 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 161.5, 158.0, 159.1 & 157.1 (d,$^1J_{C,F}$ = 241.9 Hz), 155.1, 149.0, 144.5, 133.3,130.9, 130.8 (2C), 129.6 & 129.5 (d,$^3J_{C,F}$ =6.1 Hz) (2C), 128.9 (2C), 127.3 (2C), 127.1, 115.6, 115.3 (d,$^2J_{C,F}$ = 22.9 Hz) (2C), 114.7 (2C), 114.4, 113.6, 89.6, 55.5; IR (KBr, $cm^{-1}$): 3336, 2952, 2931, 2216, 1619, 1582, 1498,1210; HRMS (ESI) ([M] $^+$1) calcd for $C_{25}H_{19}N_3OF$: 396.1512, found: 396.1513.

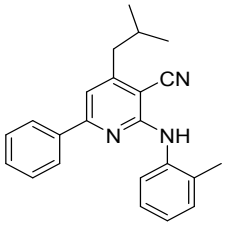
**6-Phenyl-2-(phenylamino)-4-(thiophen-2-yl)nicotinonitrile (5e)**




Pale yellow solid, mp:186-188 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, $J_{1,2}$ = 2.4 Hz, $J_{1,3}$= 7.6 Hz, 2H), 7.89 – 7.88 (m, 1H), 7.75 (d, $J$ = 7.6 Hz, 2H), 7.56 (d, $J$ = 5.2 Hz, 1H), 7.52 – 7.47 (m, 3 H), 7.43 – 7.41 (m, 3H), 7.28 – 7.26 (m, 1H), 7.24 – 7.22 (m, 1H), 7.16 (t, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 159.2, 156.9, 146.9, 138.8, 138.7, 137.8, 130.4, 130.3, 128.9,

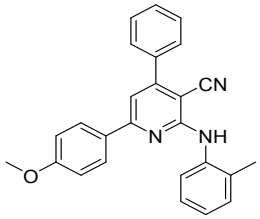
128.8 (2C), 128.7, 128.5 (2C), 127.4 (2C), 123.6, 120.7 (2C), 117.5, 110.4, 90.8; IR (KBr, $cm^{-1}$) :3328, 2216, 1603, 1549, 1497; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{22}H_{16}N_3S$: 354.1065, found: 354.1068.

**4-Isobutyl-6-phenyl-2-(o-tolylamino)nicotinonitrile (5f)**



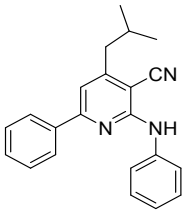

Off White color solid, mp:131-133 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, $J$ = 8.0 Hz, 1H), 7.98 (dd, $J_{1,2}$ =3.2 Hz, $J_{1,3}$ = 4.8 Hz, 2H), 7.58 – 7.49 (m, 3H), 7.44 (d, J = 3.2 Hz, 2H), 7.09 – 7.08 (m, 3H), 2.72 (d, $J$ = 7.6 Hz, 2H), 2.37 (s, 3H), 2.17-2.11 (m, 1H), 1.04 (d, $J$ = 6.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.5, 157.0, 156.0, 139.1, 139.0, 138.0, 130.6, 130.5, 128.7 (2C), 127.3 (2C), 126.4 (2C), 122.3, 116.7, 111.7, 91.4, 43.9, 29.6, 22.4 (2C), 18.0; IR (KBr, $cm^{-1}$) :3316, 2952, 2864, 2216, 1619, 1582, 1498; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{23}H_{24}N_3$: 342.1970, found: 342.1984.

**6-(4-Methoxyphenyl)-4-phenyl-2-(o-tolylamino)nicotinonitrile (5g)**



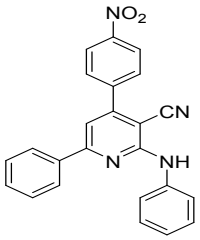

Brown color solid, mp: 199-201°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, $J$ = 8.0 Hz, 1H), 8.0 (d, $J$ = 8.8 Hz, 2H), 7.68 -7.65 (m, 2H), 7.57 – 7.50 (m, 3H), 7.33 – 7.27 (m, 2H), 7.25 (s, 1H), 7.14 – 7.10 (m, 2H), 6.97 (d, $J$ = 8.0 Hz, 2H), 3.87 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 160.0, 157.4, 156.4, 155.8, 141.8, 137.7, 136.6, 136.3, 130.6, 129.7, 128.9 (2C), 128.9 (2C), 128.2 (2C), 126.4 (2C), 124.3, 122.3, 114.1 (2C), 110.3, 90.8, 55.3, 18.0; IR (KBr, $cm^{-1}$) : 3423, 2962, 2923, 2200, 1598,1483, 1168; HRMS (ESI) ([M]$^{+}$1) calcd for $C_{26}H_{22}N_3O$: 392.1763, found: 392.1747.

**4-Isobutyl-6-phenyl-2-(phenylamino)nicotinonitrile (5h)**



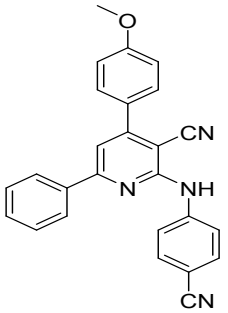

White solid, mp:124-126°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, $J_{1,2}$ = 2.0 Hz, $J_{1,3}$ = 8.0 Hz, 2H), 7.74 (d, $J$ = 8.0 Hz, 2H), 7.50 -7.43 (m, 3H), 7.41 (t, $J$ = 8.0 Hz, 2H), 7.12-7.09 (m, 3H), 2.71 (d, $J$ = 6.8 Hz, 2H), 2.13-2.06 (m, 1H), 1.03 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.4, 157.0, 156.1, 139.0, 138.0, 130.1, 128.9 (2C), 128.7 (2C), 127.3 (2C), 123.3, 120.3 (2C), 116.5, 112.0, 91.0, 44.0, 29.7, 22.3 (2C); IR (KBr, $cm^{-1}$): 3335, 2953, 2863, 2216, 1619, 1582, 1498; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{22}H_{22}N_3$: 328.1814, found: 328.1810.

**4-(4-Nitrophenyl)-6-phenyl-2-(phenylamino)nicotinonitrile (5i)**



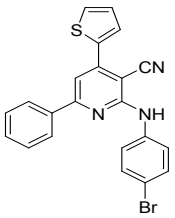

Orange solid, mp: 208-210 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, $J$ = 8.4 Hz, 2H), 8.07 (d, $J$ = 3.6 Hz, 2H), 7.84 (d, $J$ = 8.8 Hz, 2H), 7.75 (d, $J$ = 8.4 Hz, 2H), 7.51-7.42 (m, 5H), 7.31-7.26 (m, 2H), 7.21-7.18 (m, 1H); $^{1}$H NMR (400 MHz, $D_2O$ exchange): δ 8.43 (d, J = 8.0 Hz, 2H), 8.07 (d, $J$ = 4.0 Hz, 2H), 7.84 (d, $J$ = 8.8 Hz, 2H), 7.75 (d, $J$ = 8.0 Hz, 2H), 7.52-7.49 (m, 3H), 7.45-7.43 (m, 2H), 7.31 (s, 1H), 7.22-7.16 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 159.6, 156.6, 153.1, 148.3, 143.1, 138.5, 137.4, 130.7, 129.4 (2C), 129.0, 128.9 (2C), 127.4 (2C), 124.5 (2C), 124.0 (2C), 120.9 (2C),116.3, 110.9, 89.5; IR (KBr, $cm^{-1}$): 3335, 2217, 1607, 1579, 1514, 1498, 1352; HRMS (ESI) ([M]$^{+}$1) calcd for $C_{24}H_{17}N_4O_2$: 393.1352, found: 393.1349.

**2-((4-Cyanophenyl)amino)-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (5j)**



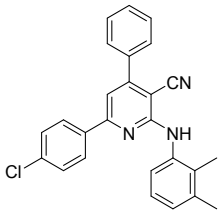

Off white color solid, mp:157-159 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.97-7.90 (m, 3H), 7.65-7.60 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 3H), 7.38 (d, *J* = 8.0 Hz, 3H), 7.02-6.93 (m, 4H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 161.7, 159.8, 158.7, 148.1, 137.4, 135.7, 134.1 (2C), 133.4, 129.1 (2C), 128.8 (2C), 128.6 (2C), 128.3, 128.0 (2C), 115.0, 114.5 (2C), 111.9, 111.7, 108.7, 89.6, 55.2; IR (KBr, $cm^{-1}$): 3394, 2913, 2254, 2223, 1606, 1572, 1449, 1178; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{26}H_{19}N_4O$: 403.1559, found: 403.1560.

**2-((4-Bromophenyl)amino)-6-phenyl-4-(thiophen-2-yl)nicotinonitrile (5k)**



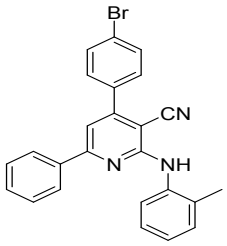

Brown color solid, mp: 196-198°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, $J_{1,2}$= 3.2 Hz, $J_{1,3}$= 8.0 Hz, 2H), 7.89 (dd, $J_{1,2}$= 2.8 Hz, $J_{1,3}$ = 8.0 Hz, 1H), 7.65-7.63 (m, 2H), 7.57-7.49 (m, 7H), 7.44 (s, 1H), 7.24-7.22 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 159.2, 156.9, 149.3, 146.9, 137.9, 137.6, 131.8 (2C), 130.5, 129.1, 128.9 (2C), 128.5 (2C), 127.3 (2C), 122.3 (2C), 117.9, 116.3, 110.7, 88.1; IR (KBr, $cm^{-1}$): 3343, 2218, 1620, 1573, 1490; HRMS (ESI) ([M] $^{+}$1) calcd for $C_{22}H_{15}N_3SBr$: 432.0170, found: 432.0199.

**6-(4-Chlorophenyl)-2-((2,3-dimethylphenyl)amino)-4-phenylnicotinonitrile (5l)**



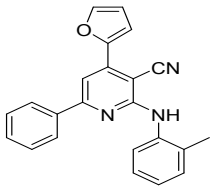

Off white solid, mp: 152-154°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, $J_{1,2}$= 2.0 Hz, $J_{1,3}$ = 8.8 Hz, 2H), 7.72 -7.65 (m, 3H), 7.57-7.51 (m, 3H), 7.40 (dd, $J_{1,2}$= 2.0 Hz, $J_{1,3}$ = 6.8 Hz, 2H), 7.24 (s, 1H), 7.21 (t, $J$ = 8.0 Hz, 1H), 7.09-7.06 (m, 2H), 2.37 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.5, 157.4, 155.5, 141.8, 137.5, 136.9, 136.7, 136.3, 136.2, 129.9, 129.0 (2C), 128.9 (2C), 128.5 (2C), 128.1 (2C), 126.8, 125.5, 121.9, 117.0, 110.5, 89.8, 20.7, 14.0; IR (KBr, cm$^{-1}$): 3307, 2916, 2218, 1583, 1569, 1487; HRMS (ESI) ([M]$^+$1) calcd for $C_{26}H_{21}N_3Cl$: 410.1424, found: 410.1431.

**4-(4-Bromophenyl)-6-phenyl-2-(*o*-tolylamino)nicotinonitrile (5m)**




Pale yellow color solid, mp:158-160 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, $J$ = 8.0 Hz, 1H), 8.02-7.98 (m, 2H), 7.70 (dd, $J_{1,2}$ = 1.6 Hz, $J_{1,2}$ = 8.4 Hz, 2H), 7.57-7.50 (m, 4H), 7.46 (t, $J$ = 4.0 Hz, 2H), 7.33 -7.27 (m, 3H), 7.15-7.12 (m, 1H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.2, 155.3, 153.4, 143.3, 137.2, 135.2, 132.3, 132.2 (2C), 130.5, 129.9 (2C), 129.1, 128.9 (2C), 127.3 (2C), 126.5, 124.5, 122.2, 122.0, 115.5, 112.9, 89.7,18.0; IR (KBr, cm$^{-1}$): 3446, 2956, 2235, 1658, 1608, 1486; HRMS (ESI) ([M]$^+$1) calcd for $C_{25}H_{19}N_3Br$: 440.0762, found: 440.0753.

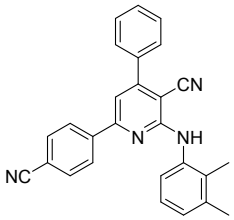
**4-(Furan-2-yl)-6-phenyl-2-(o-tolylamino)nicotinonitrile (5n)**




Brown color solid, mp:147-149 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, $J$ = 8.0 Hz, 1H), 8.04

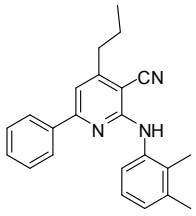
– 8.02 (m, 2H), 7.67 (d, $J$ = 7.2 Hz, 2H), 7.53 (d, $J$ = 4.0 Hz, 1H), 7.47-7.44 (m, 3H), 7.31-7.28 (m, 2H), 7.13 (t, $J$ = 7.6 Hz, 2H), 6.65 (dd, $J_{1,2}$ = 1.6 Hz, $J_{1,3}$= 3.6 Hz, 1H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.7, 155.6, 153.1, 146.6, 144.5, 138.8, 138.3, 130.6, 130.2, 128.7 (2C), 127.3 (2C), 126.5, 124.3, 124.2, 120.7, 116.5, 113.1, 112.6, 106.2, 86.0, 18.0; IR (KBr, $cm^{-1}$) :3434, 2953, 2198, 1602, 1556, 1487, 1032; HRMS (ESI) ([M]$^+$1) calcd for $C_{23}H_{18}N_3O$: 352.1450, found: 352.1458.

**6-(4-Cyanophenyl)-2-((2,3-dimethylphenyl)amino)-4-phenylnicotinonitrile (5o)**



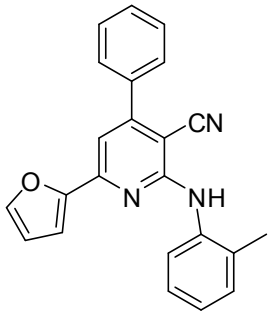

Brown color solid, mp:198-200 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, $J$ = 8.8 Hz, 2H), 7.69-7.64 (m, 4H), 7.58-7.55 (m, 2H), 7.39-7.29 (m, 3H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.12-6.92 (m, 2H), 2.37 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 157.4, 156.4, 155.8, 141.8, 137.7, 136.6, 136.3, 132.4 (2C), 130.1, 129.2, 129.0 (2C), 128.1 (2C), 127.4 (2C), 127.1, 125.6, 122.1, 118.5, 116.7, 113.3, 111.2, 90.8, 20.7, 14.0; IR (KBr, $cm^{-1}$): 3308, 2938, 2228, 2204, 1606, 1583, 1492; HRMS (ESI) ([M]$^+$1) calcd for $C_{27}H_{21}N_4$: 401.1766, found: 401.1749.

**2-((2,3-Dimethylphenyl)amino)-6-phenyl-4-propylnicotinonitrile (5p)**



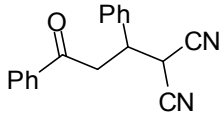

Brown gummy solid; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, $J$ = 4.0 Hz, 2H), 7.78 (d, $J$ = 8.0 Hz, 1H), 7.41-7.40 (m, 3H), 7.16-7.11 (m, 2H), 7.04-7.02 (m, 1H), 6.90 (s, 1H), 2.82 (t, $J$ = 7.6 Hz, 2H), 2.35 (s, 3H), 2.26 (s, 3H), 1.82-1.76 (m, 2H), 1.07 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 158.6, 157.0, 156.1, 139.0, 138.1, 130.6, 129.0 (2C), 128.9, 127.6 (2C), 126.6, 125.5, 123.3, 120.0, 115.3, 112.1, 89.5, 42.4, 29.6, 20.9, 13.8, 13.6; IR (KBr, $cm^{-1}$): 3316, 2916, 2864, 2218, 1620, 1582, 1498; HRMS (ESI) ([M]$^+$1) calcd for $C_{23}H_{24}N_3$: 342.1970, found: 342.1972.

**6-(Furan-2-yl)-4-phenyl-2-(o-tolylamino) nicotinonitrile (5q)**



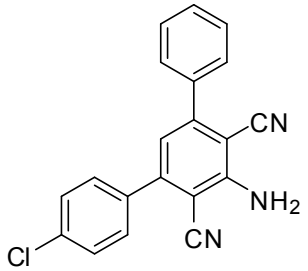

Pale yellow solid, mp: 166-168 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, $J$ = 8.0 Hz, 1H), 7.61 – 7.59 (m, 2H), 7.47 – 7.45 (m, 4H), 7.22 -7.18 (m, 2H), 7.02 – 6.95 (m, 3H), 6.66 (t, $J$ = 7.6 Hz, 1H), 6.47 (dd, $J_{1,2}$ = 2.0 Hz, $J_{1,3}$= 3.6 Hz, 1H), 2.31(s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$):δ 156.8, 155.2, 152.9, 150.1, 144.5, 137.1, 136.8, 130.5, 129.8, 129.3, 128.9(2C), 128.1(2C), 126.4, 124.2, 122.2, 117.1, 112.4, 112.1,109.1, 89.4, 18.0; IR (KBr, $cm^{-1}$) 3431, 2201, 1602, 1541,1478, 1012; ESI-MS (M+1); 352.1.

**2-(3-Oxo-1,3-diphenylpropyl)malononitrile (6)**



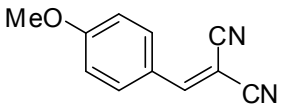

White solid, mp 122- 124 °C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, $J$ = 7.6 Hz, 2H), 7.64-7.51 (m, 1H), 7.49-7.39 (m, 7H), 4.65 (d, $J$ = 4.8 Hz, 1H), 3.98-3.93 (m, 1H), 3.70-3.61 (m, 2H); IR (KBr, $cm^{-1}$) 2901, 2255, 1682, 1449, 1186; MS (ESI) ($M+NH_3$); 292.10.

**3-(4-Chlorophenyl)-5-phenyl-2,6-dicyanoanilines (7)**




Off white solid; mp: 246-248°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, $J$ = 8.0 Hz, 2H), 7.53 – 7.47 (m, 7H), 6.86 (s, 1H), 5.39 (s, 2H); IR (KBr): 3466, 3365, 2214, 1499 cm-1

**2-(4-Methoxybenzylidene)malononitrile (8)**




Pale yellow solid, mp 114-116 °C; $^1$H NMR (400 MHz, $CDCl_3$): 7.92 (d, $J$ = 8.0 Hz, 2H), 7.65 (s, 1H), 7.03 (d, $J$ = 8.0 Hz, 2H), 3.91 (s, 3H); IR (KBr, cm$^{-1}$) 2984, 2222, 1605, 1456.

**Procedure for the scale up of compound 5i**

To a mixture of acetophenone (**1a**, 4.0 g, 0.033 mmol), 4-nitrobenzaldehyde (**2e**, 5.03 g, 0.033 mmol), aniline (**3b**, 3.1 g, 0.033 mmol), and malononitrile **4**, 2.2 g, 0.033 mmol) in PEG-400 (8 mL) was added $FeF_3$ (0.375 g, 10 mol%) at room temperature. The mixture was then stirred at 60 ºC under ultrasound irradiation in open air for 3h (the reaction was monitored by TLC). After completion of the reaction the mixture was diluted with EtOAc (60 mL) and filtered to separate the catalyst. The filtrate was collected, washed with cold water (2 x 30 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated under low vacuum. The residue was purified by column chromatography over silica gel (100-200 mesh) using EtOAc-hexane to give the desired product **5i** (11.75 g, 90%).

**Recovery of catalyst:** The filtered catalyst was collected, dried under vacuum below 50 ºC and reused for the next cycle.

**Pharmacology**

*Materials and Methods*

**Cells and Reagents:** HEK 293 and Sf9 cells were obtained from ATCC (Washington D.C., USA). HEK 293 cells were cultured in DMEM supplemented with 10% fetal bovine serum (Invitrogen Inc., San Diego, CA, USA). Sf9 cells were routinely maintained in Grace's supplemented medium (Invitrogen) with 10% FBS. RAW 264.7 cells (murine macrophage cell line) were obtained from ATCC and routinely cultured in RPMI 1640 medium with 10% fetal bovine serum (Invitrogen Inc.). cAMP was purchased from SISCO Research Laboratories (Mumbai, India). PDElight HTS cAMP phosphodiesterase assay kit was procured from Lonza (Basel, Switzerland).

*PDE4B protein production and purification*

PDE4B cDNA was sub-cloned into pFAST Bac HTB vector (Invitrogen) and transformed into

DH10Bac (Invitrogen) competent cells. Recombinant bacmids were tested for integration by PCR analysis. Sf9 cells were transfected with bacmid using Lipofectamine 2000 (Invitrogen) according to manufacturer's instructions. Subsequently, P3 viral titer was amplified, cells were infected and 48 h post infection cells were lysed in lysis buffer (50 mM Tris-HCl pH 8.5, 10 mM 2-Mercaptoethanol, 1 % protease inhibitor cocktail (Roche), 1 % NP40). Recombinant His-tagged PDE4B protein was purified as previously described elsewhere (Wang et al., 1997). Briefly, lysate was centrifuged at 10,000 rpm for 10 min at 4˚C and supernatant was collected. Supernatant was mixed with Ni-NTA resin (GE Life Sciences) in a ratio of 4:1 (v/v) and equilibrated with binding buffer (20 mM Tris-HCl pH 8.0, 500 mM-KCl, 5 mM imidazole, 10 mM 2-mercaptoethanol and 10 % glycerol) in a ratio of 2:1 (v/v) and mixed gently on rotary shaker for 1 hour at 4˚C. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4˚C and the supernatant was collected as the flow-through fraction. Resin was washed twice with wash buffer (20 mM Tris-HCl pH 8.5, 1 M KCl, 10 mM 2-Mercaptoethanol and 10% glycerol). Protein was eluted sequentially twice using elution buffers (Buffer I: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 250 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol, Buffer II: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 500 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol). Eluates were collected in four fractions and analyzed by SDS-PAGE. Eluates containing PDE4B protein were pooled and stored at -80˚C in 50% glycerol until further use.

*PDE4B enzymatic assay*

The inhibition of PDE4B enzyme was measured using PDElight HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer's recommendations. Briefly, 10 ng of PDE4B enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 μM) for 1 h. The reaction was halted with stop solution followed by incubation with detection reagent for 10 minutes in dark. Luminescence values (RLUs) were measured by a Multilabel plate reader (Perklin Elmer 1420 Multilabel counter). The percentage of inhibition was calculated using the following formula:

$$\%\ inhibition = \frac{(RLU\ of\ vehicle\ control - RLU\ of\ inhibitor)}{RLU\ of\ vehicle\ control} X\ 100$$

**Docking studies**

To understand the binding affinity and molecular interactions of compounds in the binding pocket of PDE4B the molecular docking simulations were carried out using GRIP method of docking in

Biopredicta module of Vlife MDS (Molecular Design Suite) 4.6.

**Docking Method:** The PDE4B protein in complex with rolipram obtained from Protein Data Bank (PDB ID: 1XMY) was used as the receptor for docking. The protein structure was visualized and pre-processed with Dock Prep tool of UCSF. Ligand geometries were optimized by energy minimization using Merck Molecular Force Field MMFF94 and Gasteiger-Marsili charges for the atoms till a gradient of 0.001 kcal/mol/A° was reached, maintaining the template structure rigid during the minimization. The active site pocket of the co-crystallized ligand was selected for docking. The GRIP batch docking and subsequent scoring were performed using the default parameters of the Biopredicta program. The following parameters were followed in the standard docking protocol, number of placements: 30, rotation angle: $30^{o}$, exhaustive docking method, scoring function: PLP score.

**Results:** The GRIP docking employs PLP (Piecewise Linear Pair wise Potential) scoring function for protein ligand interactions which includes hydrogen bonding, steric interactions, van der Waals interactions, hydrophobic interactions and electrostatic interactions.

Post docking analysis involved evaluation of interaction energies between each ligand and PDE4B protein for best ligand pose inside the receptor as PLP score. The PLP scores of compounds were compared with the reference Rolipram (Table S-2).

For consensus docking results and to validate the accuracy, molecular simulations were also done with **SWISSDOCK** web server and **ΔG** values were generated (Table S-2).

**Table S-2**. The PLP scores of compounds and the reference compound rolipram and **ΔG** values of compounds.

| **Vlife MDS** | |
|---|---|
| **Compound** | **PLP score** |
| Rolipram | -59.35 kcal/mol |
| **5d** | -89.26 kcal/mol |
| **5j** | -91.51 kcal/mol |
| **SWISSDOCK** | |
| **Compound** | **ΔG** |

| | |
|---|---|
| **5d** | -8.16 kcal/mol |
| **5j** | -8.40 kcal/mol |

**Molecular Interactions:** The H-bonds and hydrophobic interactions were analyzed post docking simulations and the results showed good binding modes in the active site of PDE4B. The molecular interactions summary of top-ranked docking poses of compounds **5d** and **5j** with PDE4B are listed in Table S-3.

**Table S-3.** H-bonds and hydrophobic interactions of compounds with PDE4B

| **Molecular interactions** | | |
|---|---|---|
| **Compounds** | **Hydrogen bonds** | **Hydrophobic bonds** |
| **5d** | CYS432 | SER429 , MET431 |
| **5j** | PRO430 | SER429, GLN284 |

The compound **5d** and **5j** showed good binding affinity as compared to standard drugs which revealed that the nature of the substituent and substitution pattern on the basic ring may have a considerable impact on the PDE4B activity of the synthesized compounds. Docking studies demonstrated that both the compounds were binding in the solvent filled side pocket residues in the active site of PDE4B. The **binding interactions of compounds with PDE4B are shown in Figure S-1 and S-2.** Dotted white bond showing H-bond interactions and yellow bonds shows hydrophobic interactions with binding site residues. Compounds and protein are represented by sticks and colored according to the atom type.

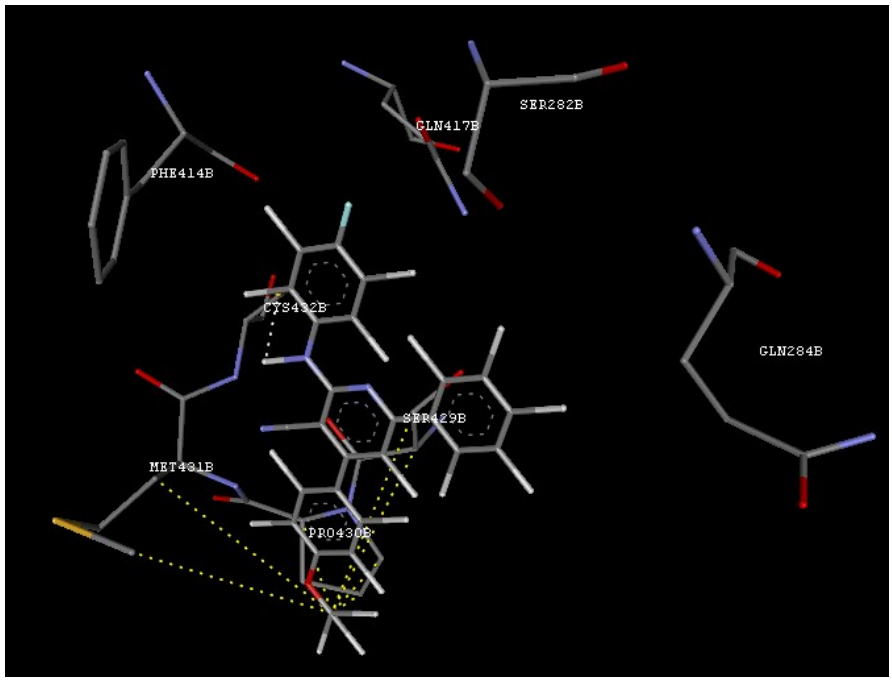



**Figure S-1. Binding interaction of compound 5d with PDE4B receptor**

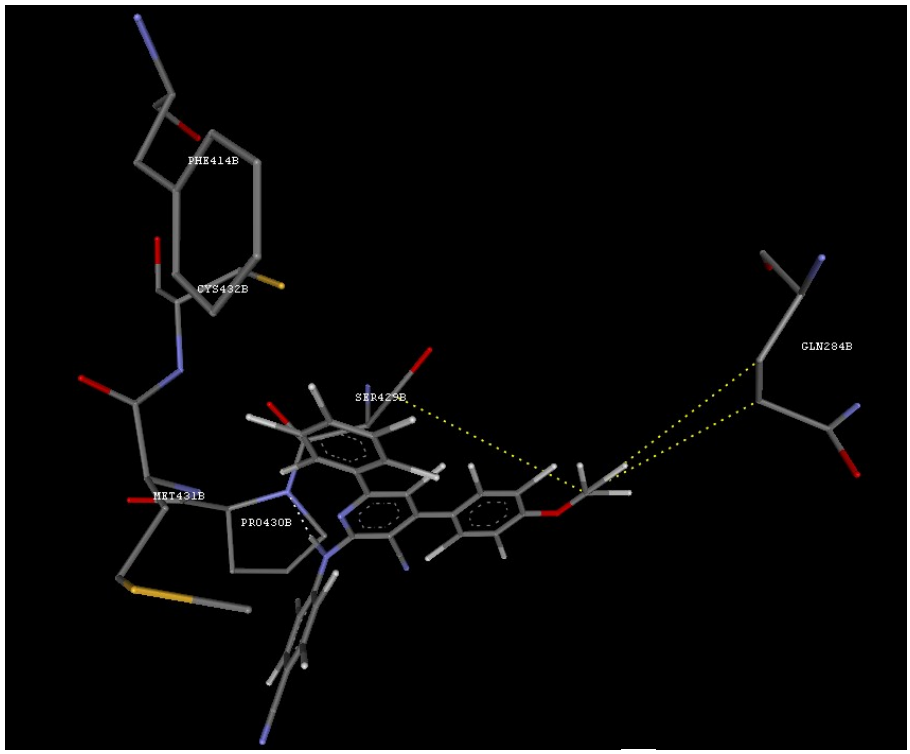
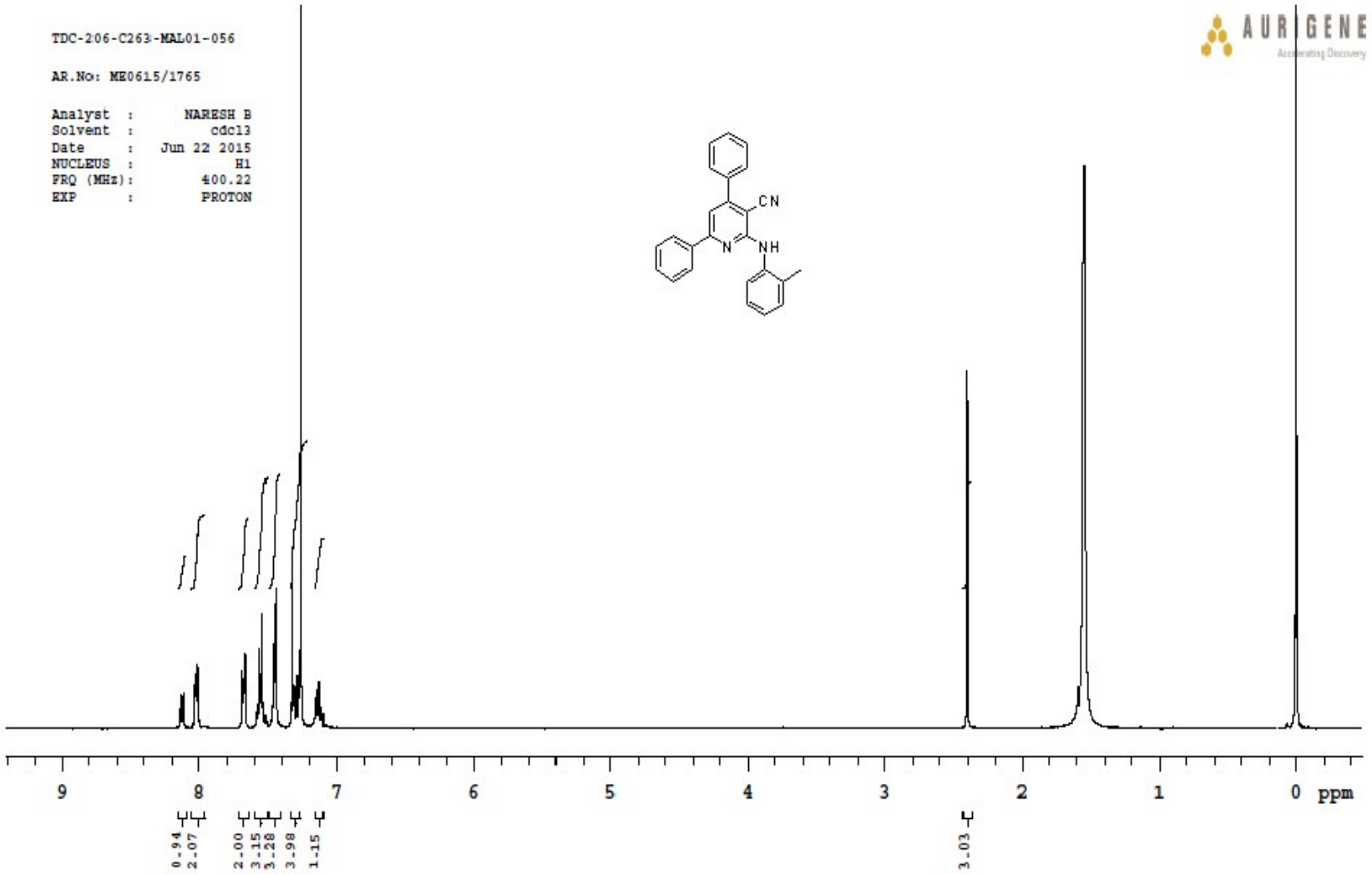



**Figure S-2. Binding interaction of compound 5j with PDE4B receptor**

## Copies of spectra

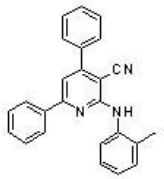
4,6-Diphenyl-2-(o-tolylamino)nicotinonitrile



**Elemental Composition Report** **Page 1**

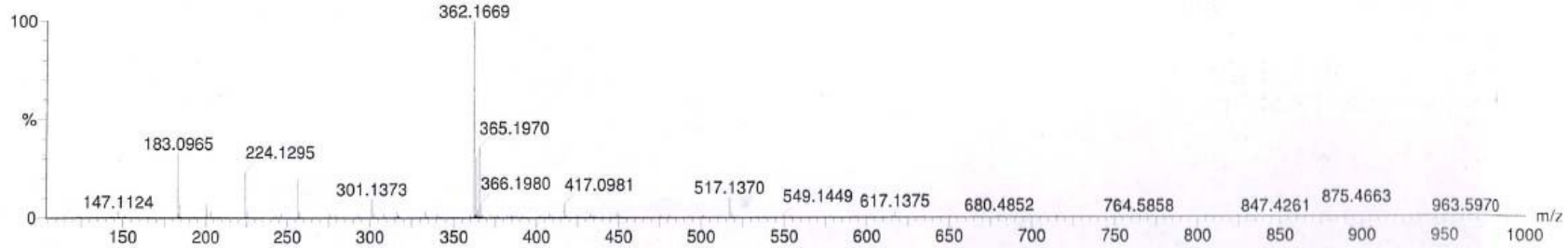
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
96 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-5 O: 0-2 Br: 0-1

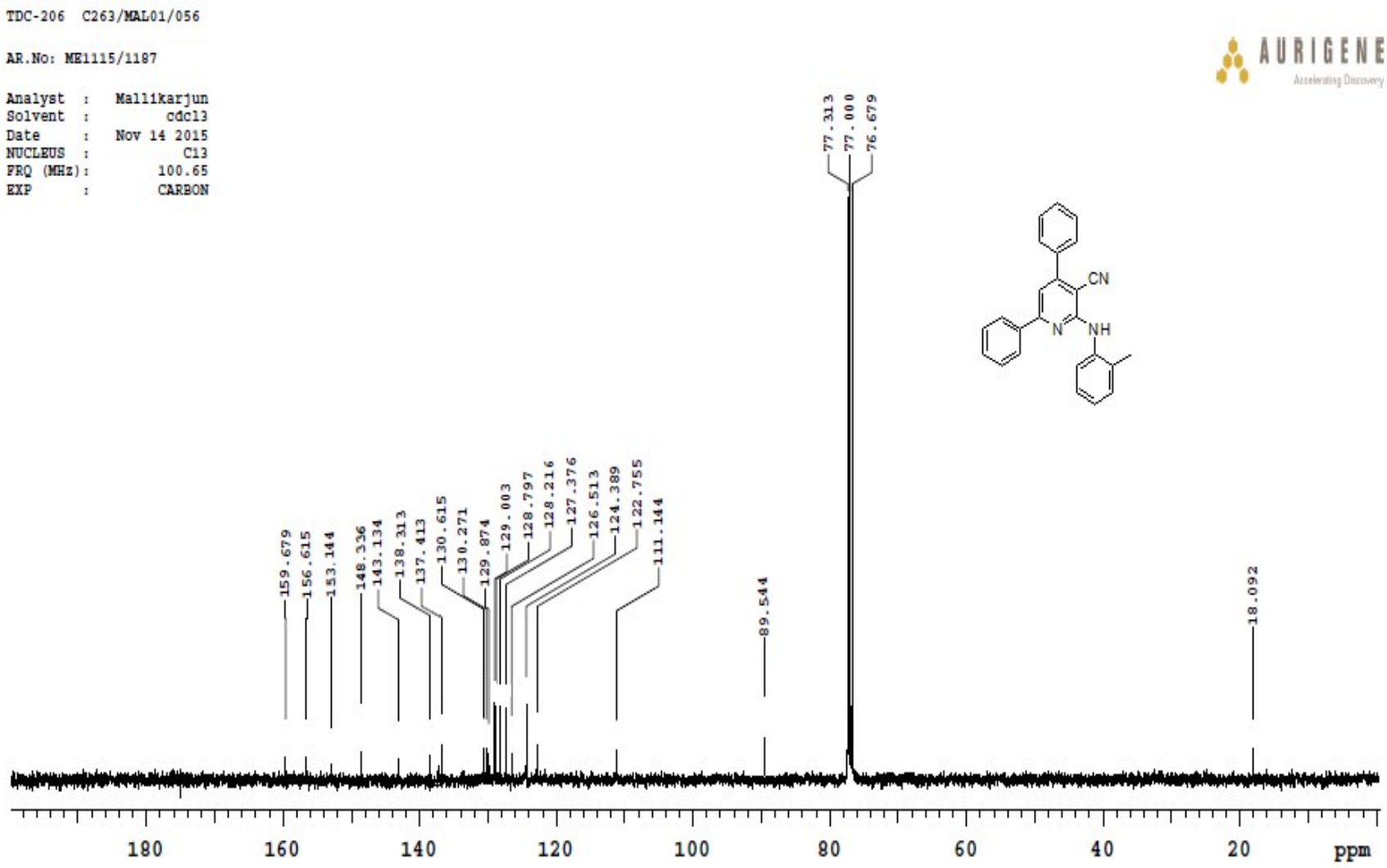



C263/MALO1/056
151016005 18 (0.339) Cm (17:18)

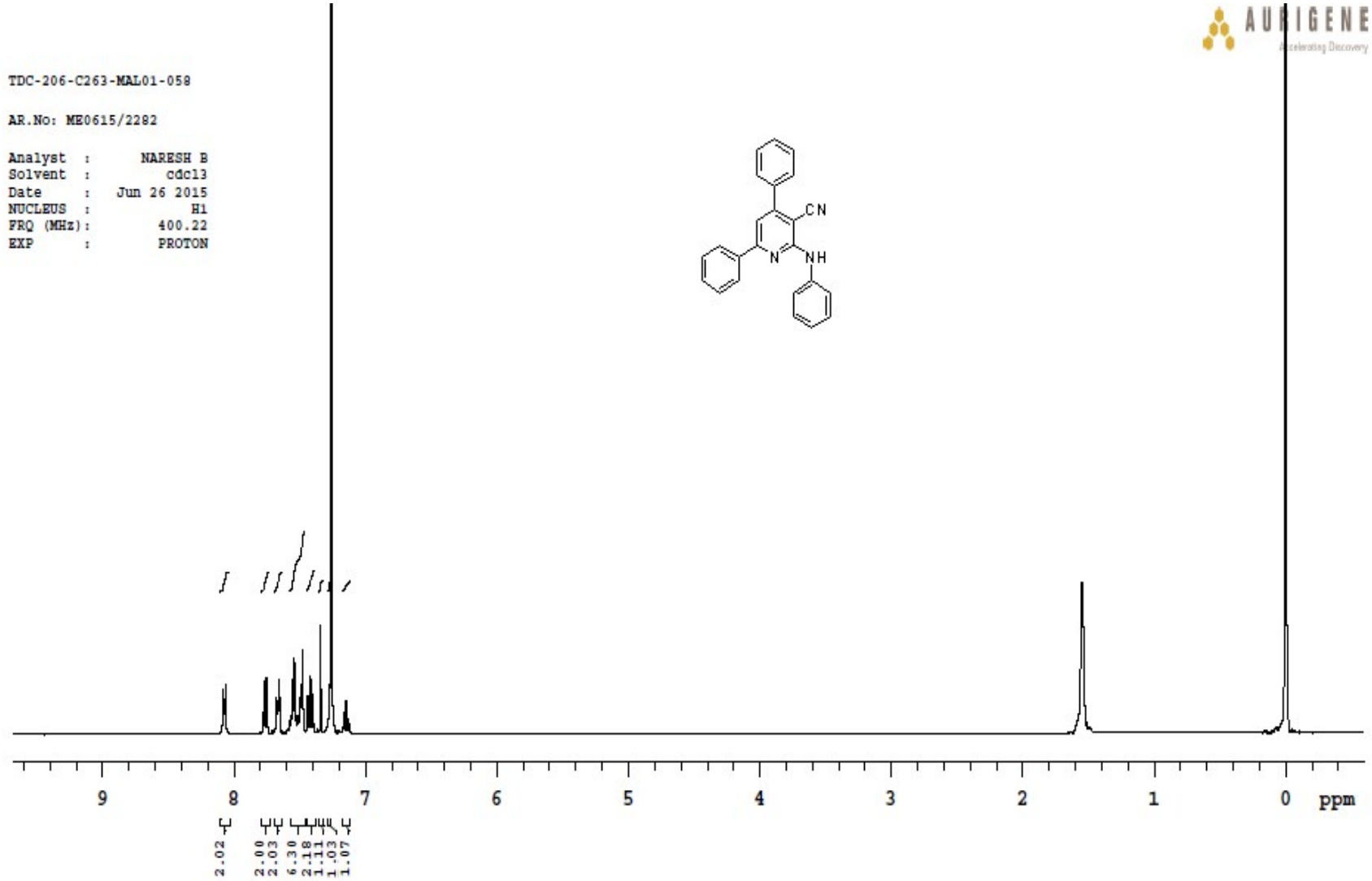
1: TOF MS ES+
3.28e+004




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 362.1669 | 362.1657 | 1.2 | 3.3 | 17.5 | 19.7 | C25 H20 N3 |


TDC-206 C263/MAL01/056
AR.No: ME1115/1187
Analyst : Mallikarjun
Solvent : cdcl3
Date : Nov 14 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.313
77.000
76.679
CN
N
NH
159.679
156.615
153.144
148.336
143.134
138.313
137.413
130.615
130.271
129.874
129.003
128.797
128.216
127.376
126.513
124.389
122.755
111.144
89.544
18.092
180
160
140
120
100
80
60
40
20
ppm

4,6-Diphenyl-2-(phenylamino)nicotinonitrile

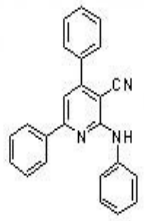


## Elemental Composition Report



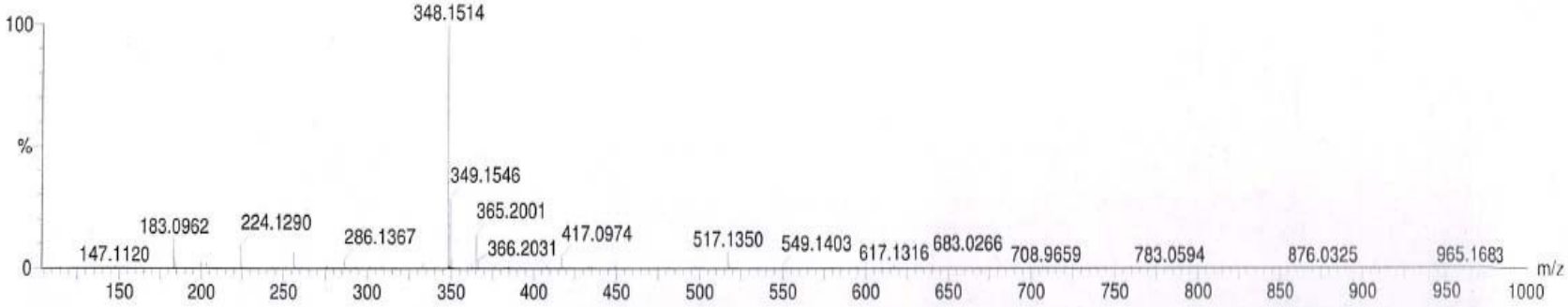
### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

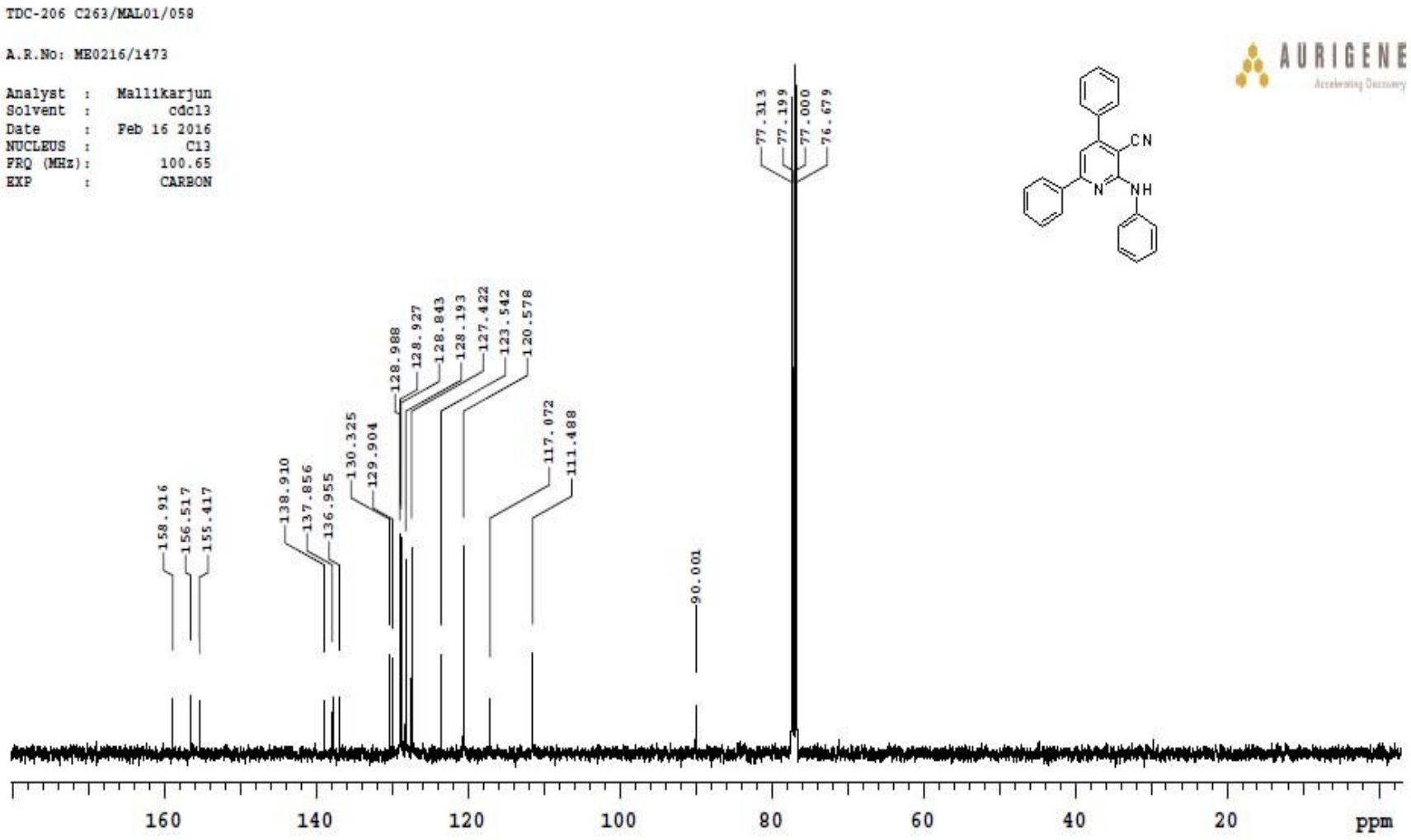



Monoisotopic Mass, Even Electron Ions
48 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-5 O: 0-2
C263/MALO1/058
151016006 19 (0.352) Cm (18:19)

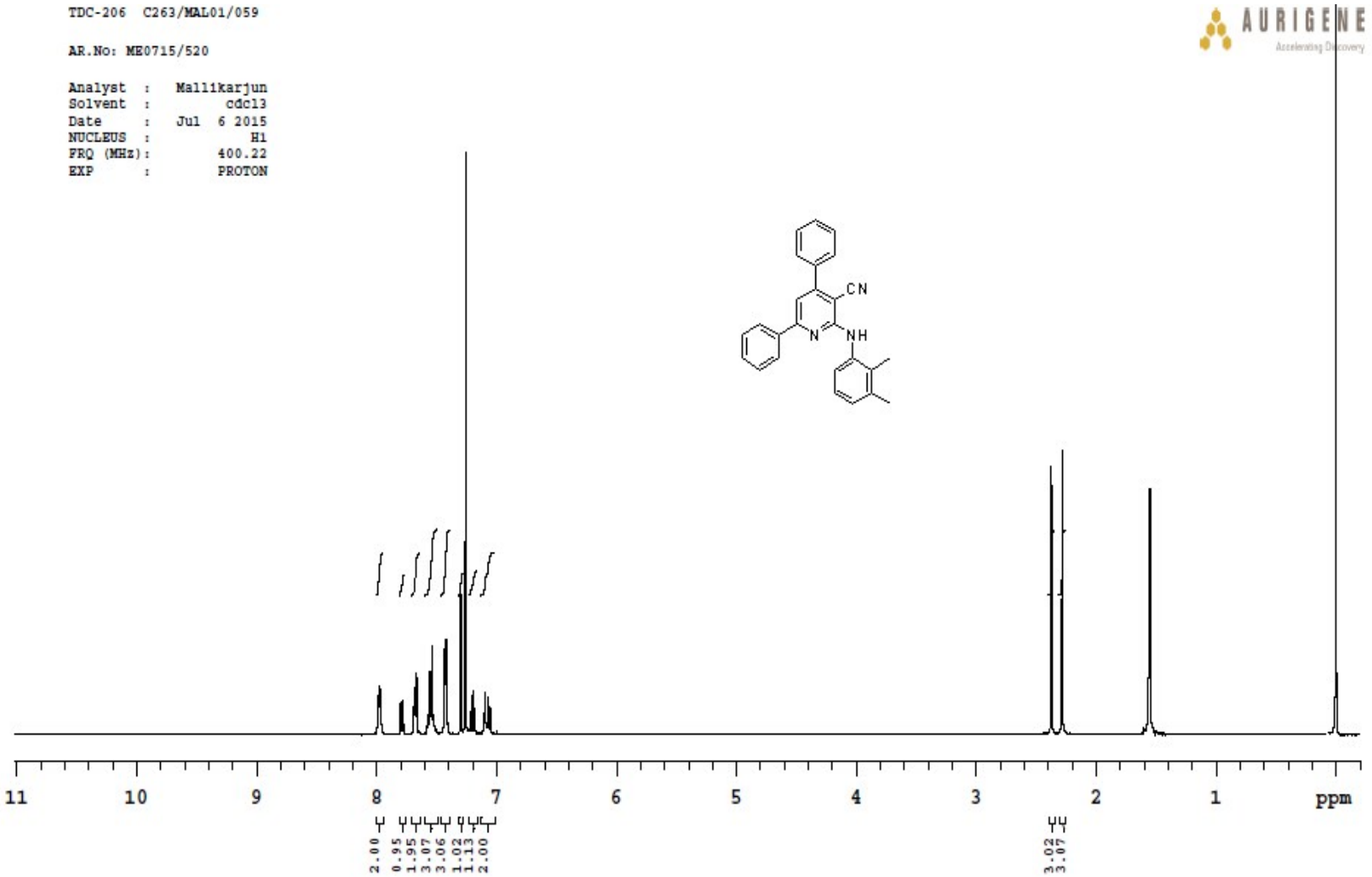
1: TOF MS ES+
8.93e+004




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 348.1514 | 348.1501 | 1.3 | 3.7 | 17.5 | 6.7 | C24 H18 N3 |


TDC-206 C263/MAL01/058
A.R.No: ME0216/1473
Analyst : Mallikarjun
Solvent : cdcl3
Date : Feb 16 2016
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
CN
N
NH
77.313
77.199
77.000
76.679
158.916
156.517
155.417
138.910
137.856
136.955
130.325
129.904
128.988
128.927
128.843
128.193
127.422
123.542
120.578
117.072
111.488
90.001
160
140
120
100
80
60
40
20
ppm

2-((2,3-Dimethylphenyl)amino)-4,6-diphenylnicotinonitrile

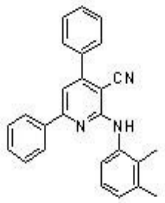


**Elemental Composition Report** **Page 1**

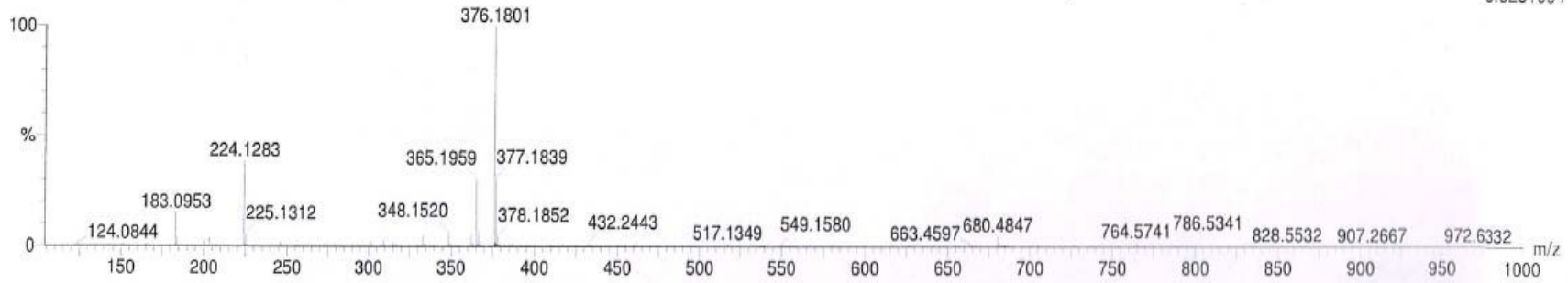
## Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

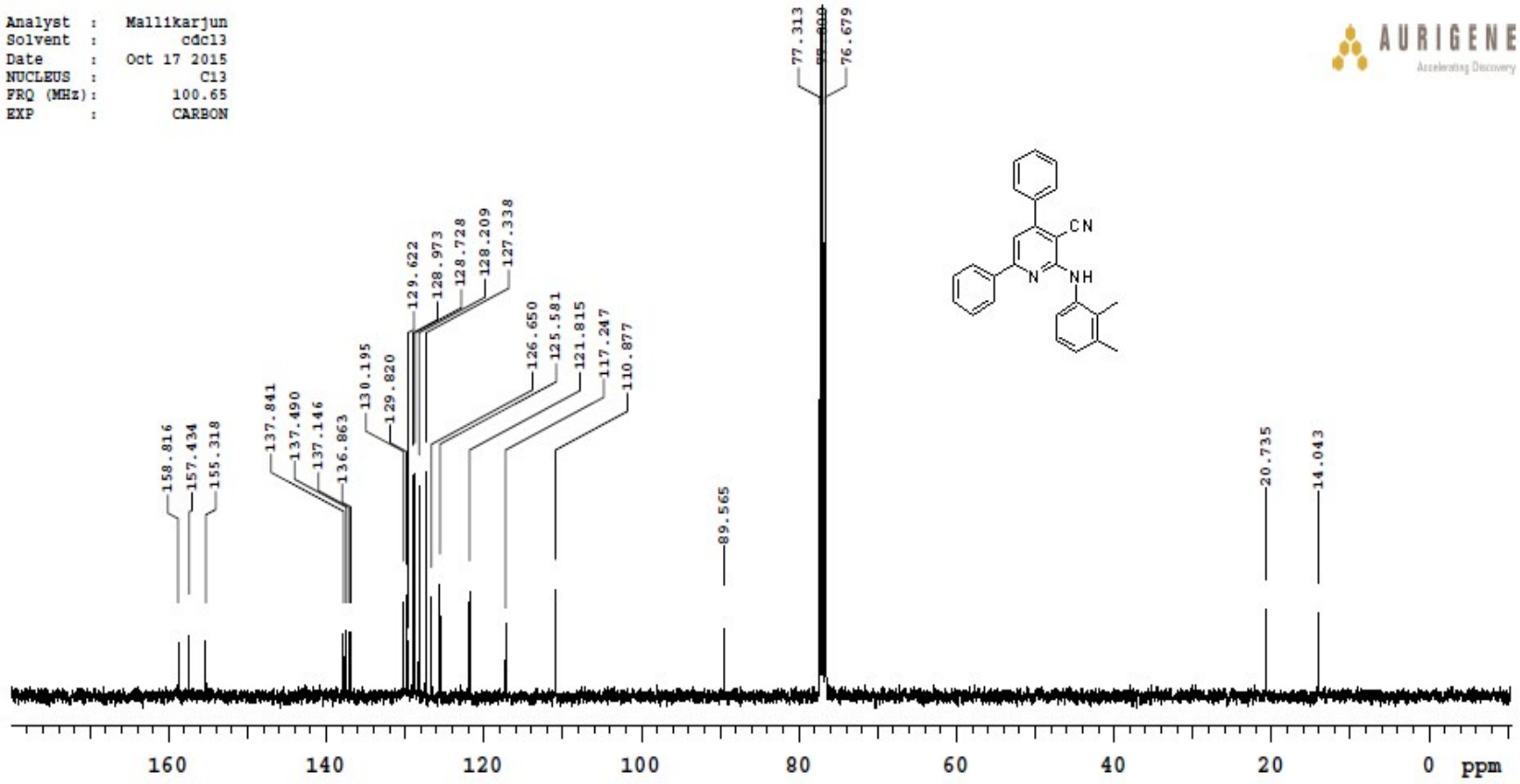
Monoisotopic Mass, Even Electron Ions
47 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-5 O: 0-2
C263/MALO1/059
151016007 37 (0.695) Cm (37)



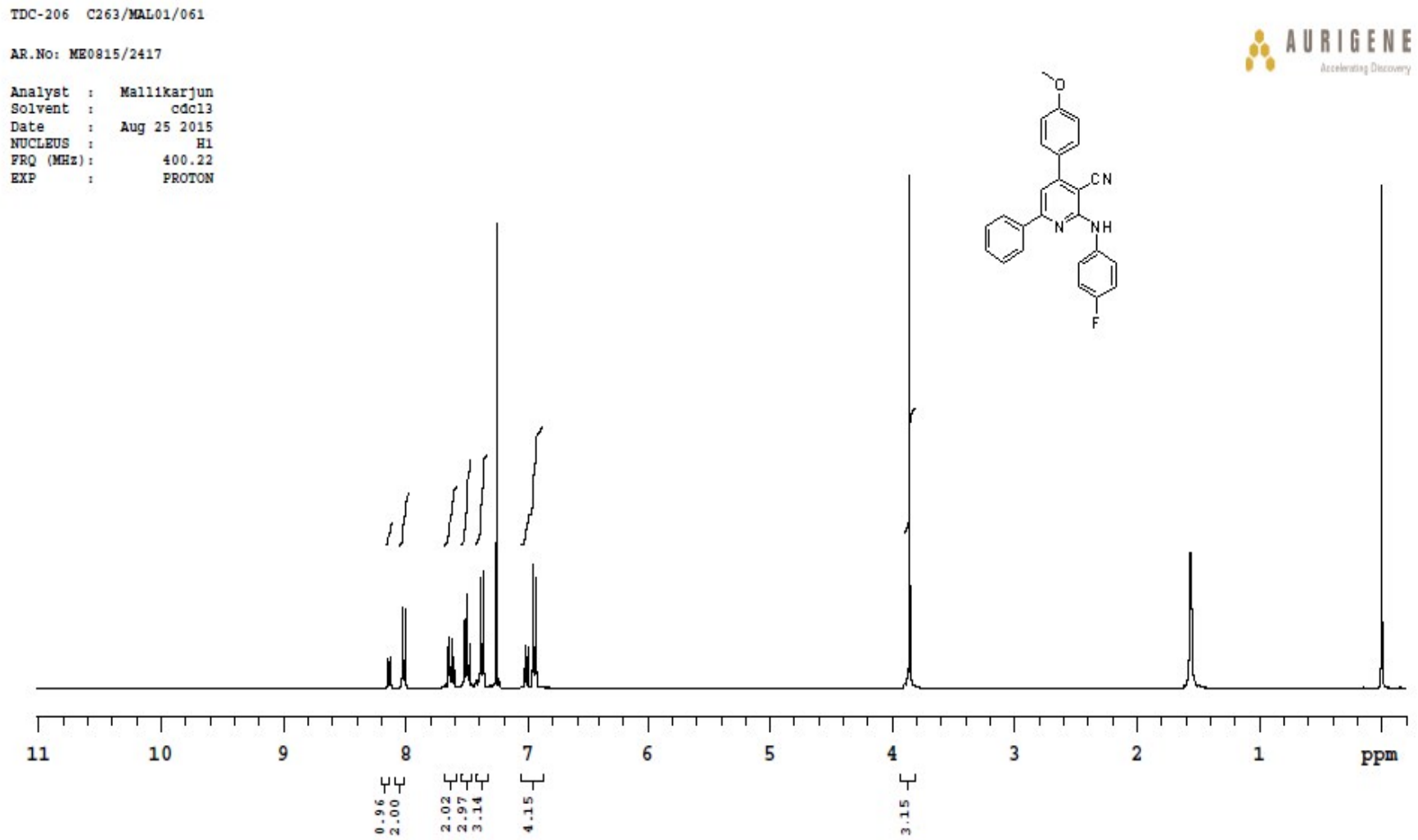

1: TOF MS ES+
3.62e+004




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 376.1801 | 376.1814 | -1.3 | -3.5 | 17.5 | 1.9 | C26 H22 N3 |

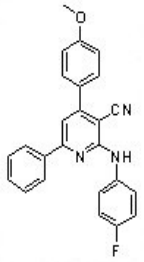

TDC-206 C263/MAL01/059
AR.No: ME1015/1393
Analyst : Mallikarjun
Solvent : cdcl3
Date : Oct 17 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.313
76.679
129.622
128.973
128.728
128.209
127.338
126.650
125.581
121.815
117.247
110.877
130.195
129.820
137.841
137.490
137.146
136.863
158.816
157.434
155.318
89.565
20.735
14.043
CN
N
NH
160
140
120
100
80
60
40
20
0
ppm

2-((4-Fluorophenyl)amino)-4-(4-methoxyphenyl)-6-phenylnicotinonitrile

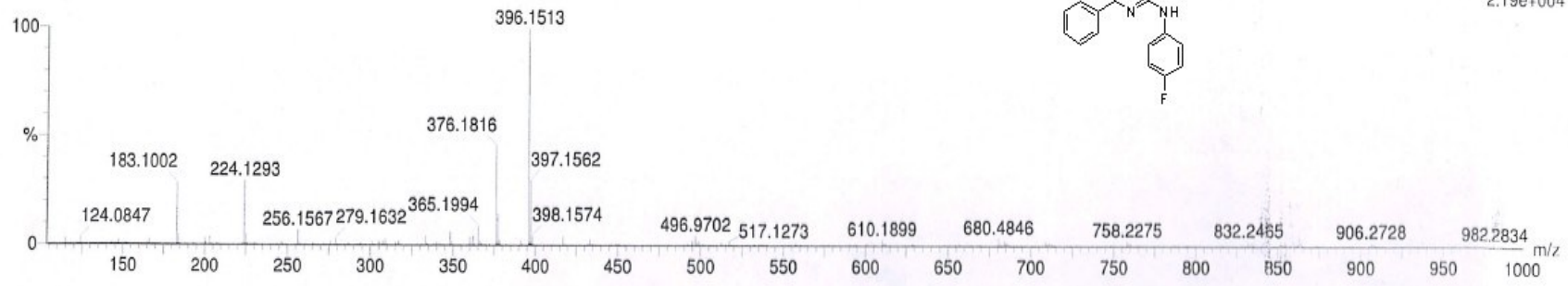


**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

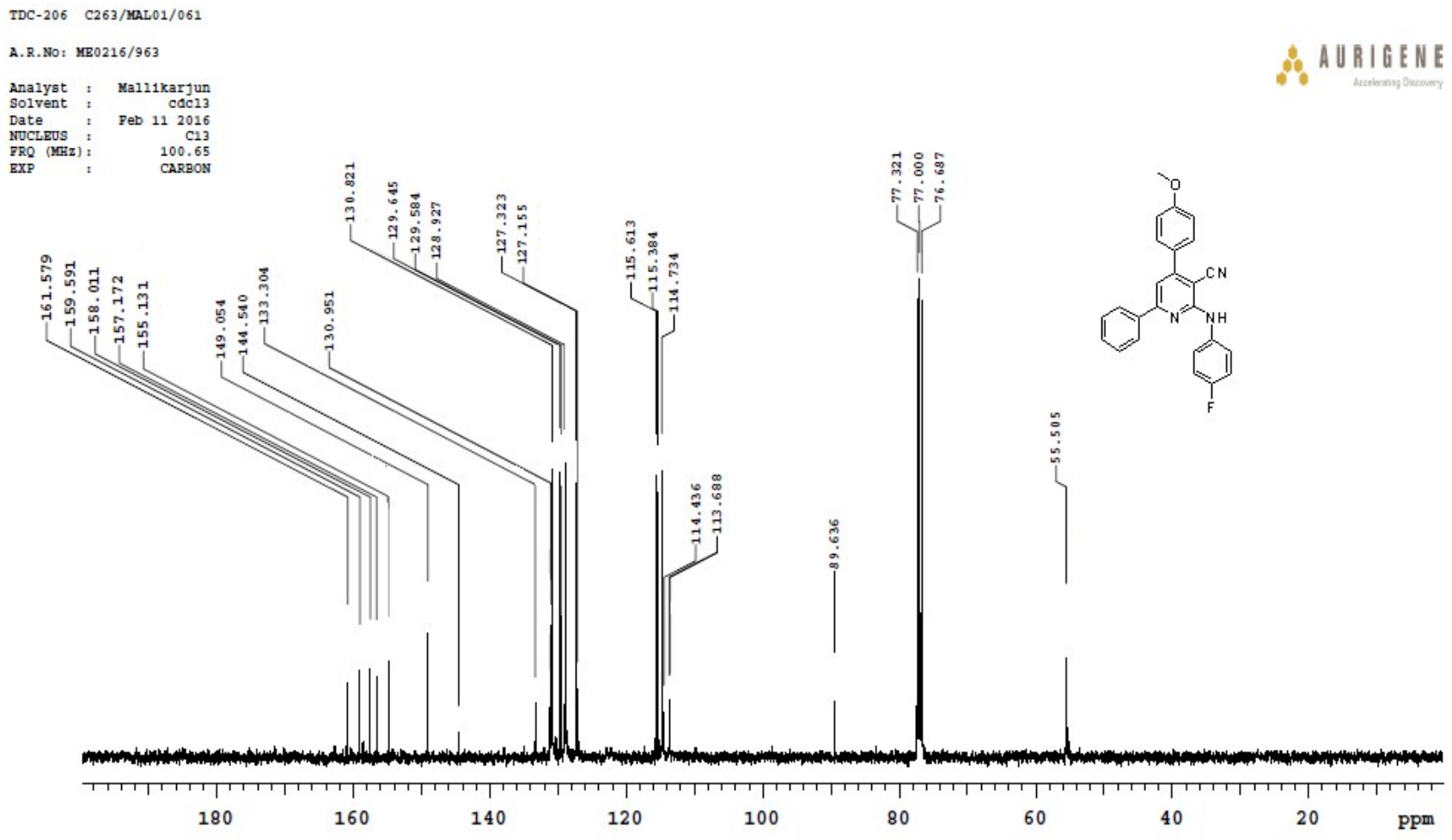
Monoisotopic Mass, Even Electron Ions
58 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-27 H: 0-30 N: 0-5 O: 0-2 F: 0-1
C263/MALO1/061
151016008 22 (0.412) Cm (21:22)



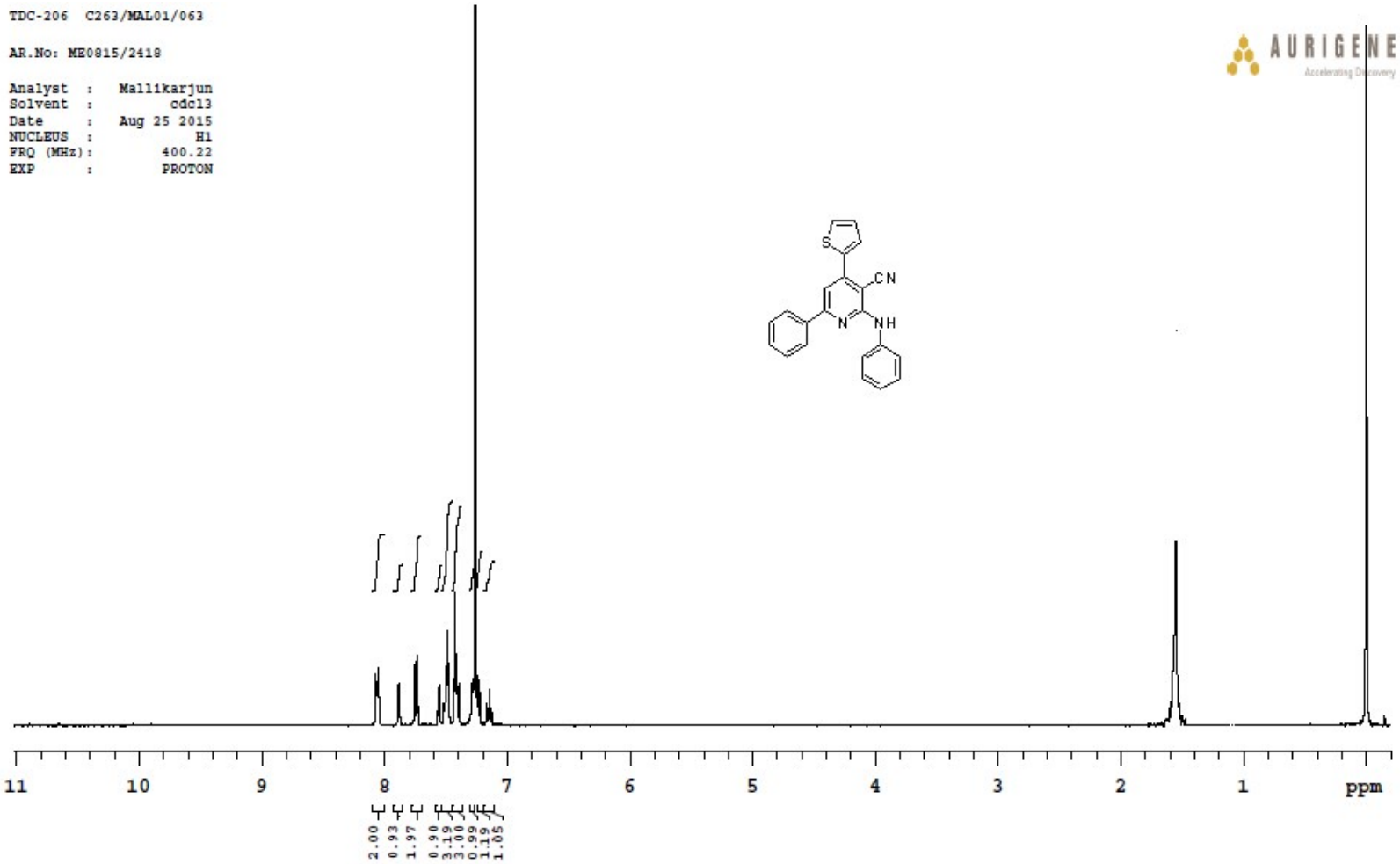

1: TOF MS ES+
2.19e+004

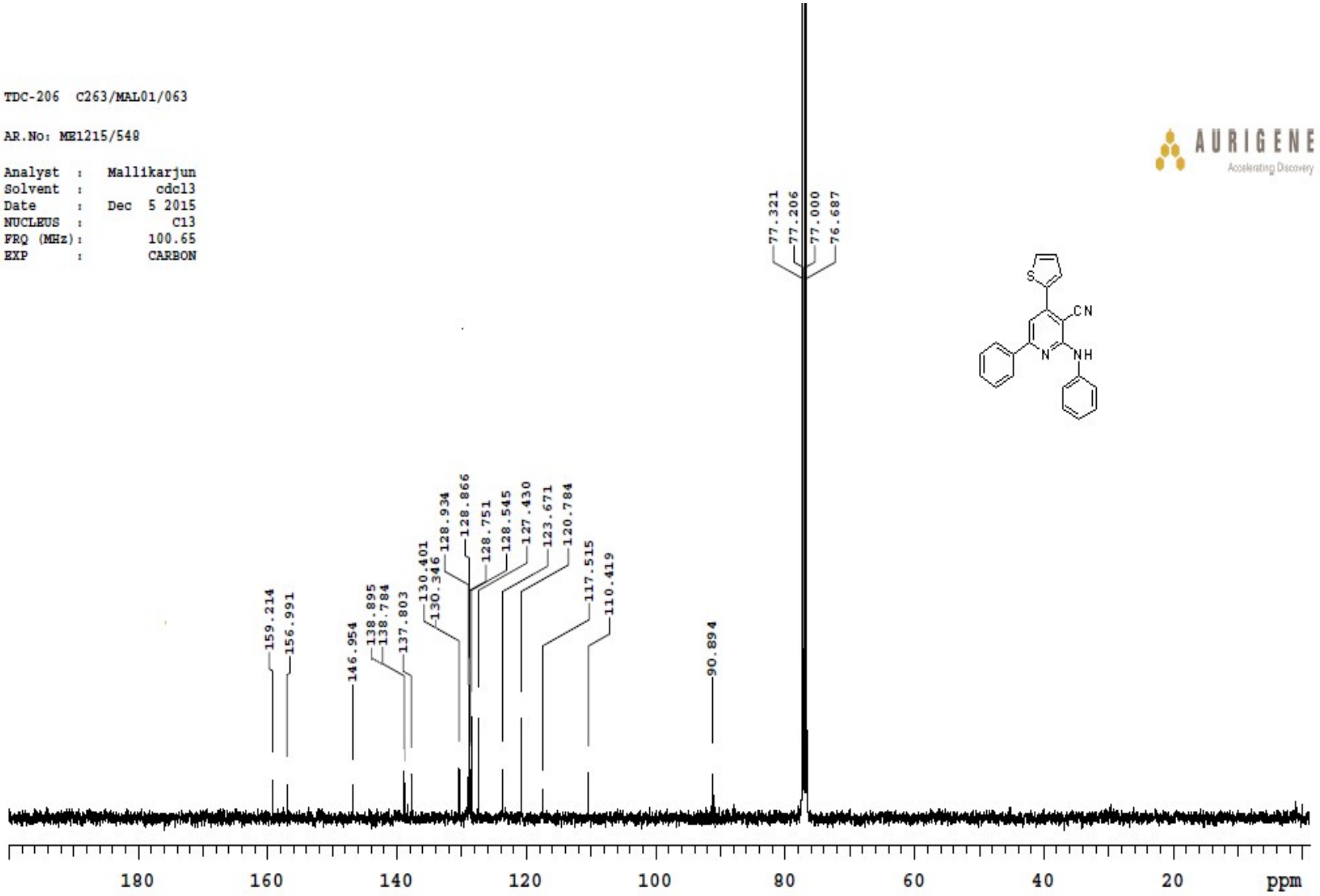



| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 396.1513 | 396.1512 | 0.1 | 0.3 | 17.5 | 1.6 | C25 H19 N3 O F |


TDC-206 C263/MAL01/061
A.R.No: ME0216/963
Analyst : Mallikarjun
Solvent : cdcl3
Date : Feb 11 2016
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
161.579
159.591
158.011
157.172
155.131
149.054
144.540
133.304
130.951
130.821
129.645
129.584
128.927
127.323
127.155
115.613
115.384
114.734
114.436
113.688
89.636
77.321
77.000
76.687
55.505
CN
N
NH
O
F
180
160
140
120
100
80
60
40
20
ppm

6-Phenyl-2-(phenylamino)-4-(thiophen-2-yl)nicotinonitrile



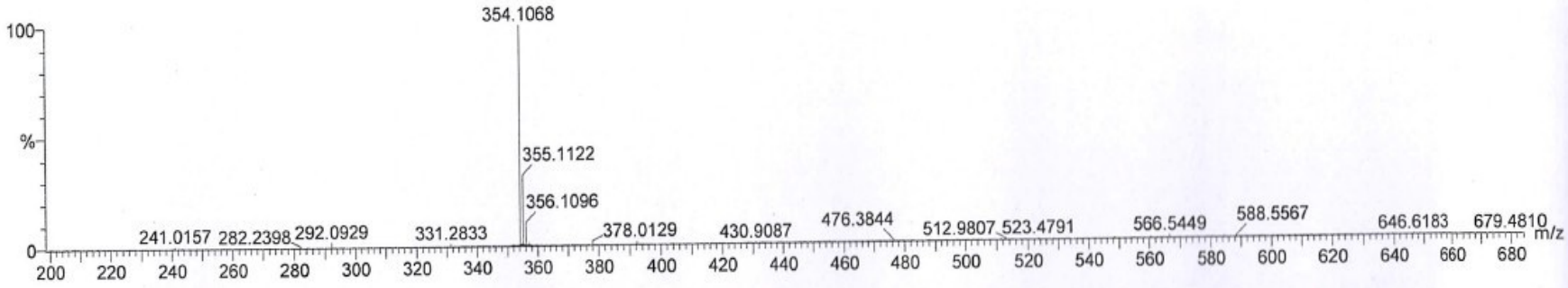

TDC-206 C263/MAL01/063
AR.No: ME1215/549
Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 5 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.321
77.206
77.000
76.687
159.214
156.991
146.954
138.895
138.784
137.803
130.401
130.346
128.934
128.866
128.751
128.545
127.430
123.671
120.784
117.515
110.419
90.894
S
CN
N
NH
180
160
140
120
100
80
60
40
20
ppm

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
20 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-25 H: 0-17 N: 0-5 S: 0-2

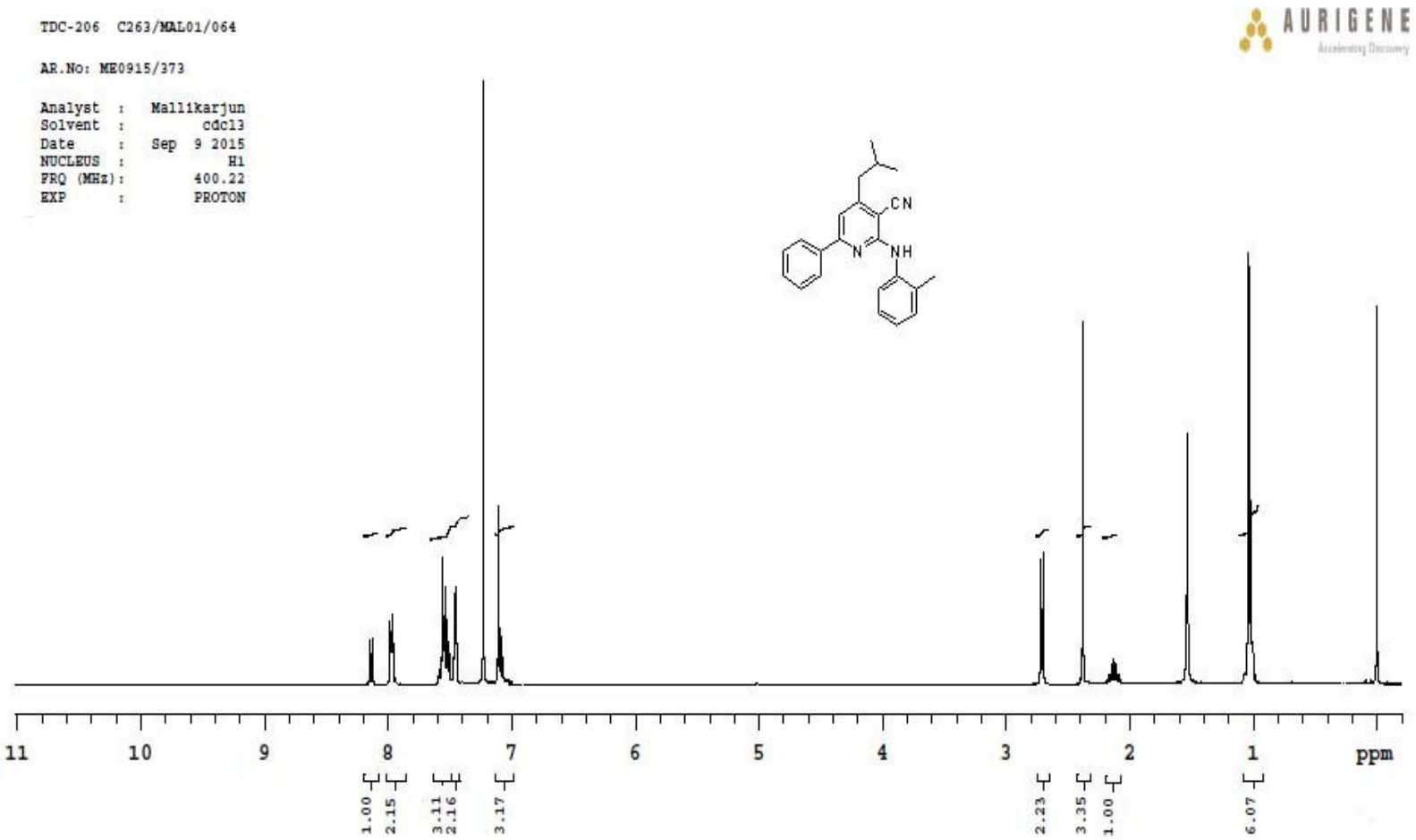
C263/MALO1/063
160122006 54 (1.003) Cm (51:54-79:87x0.500)

1: TOF MS ES+
1.75e+003



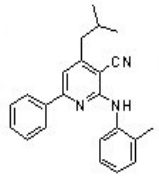

| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 354.1068 | 354.1065 | 0.3 | 0.8 | 16.5 | 6.4 | C22 H16 N3 S |

4-Isobutyl-6-phenyl-2-(o-tolylamino)nicotinonitrile



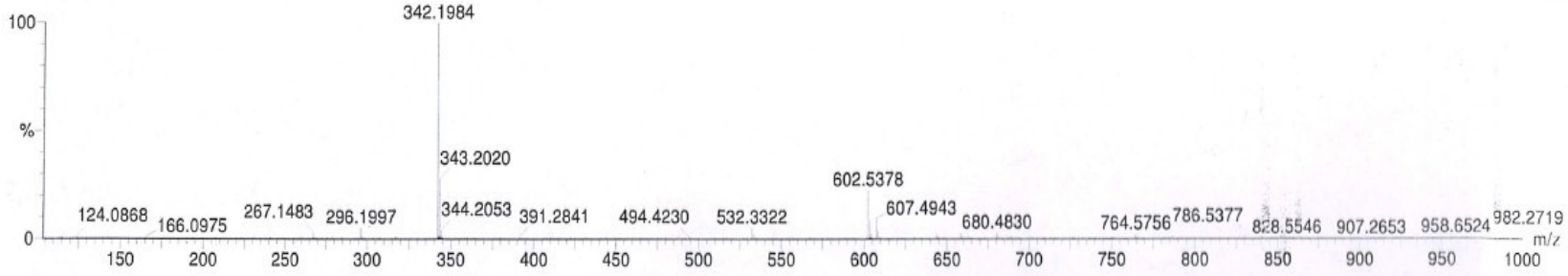
**Elemental Composition Report** 

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

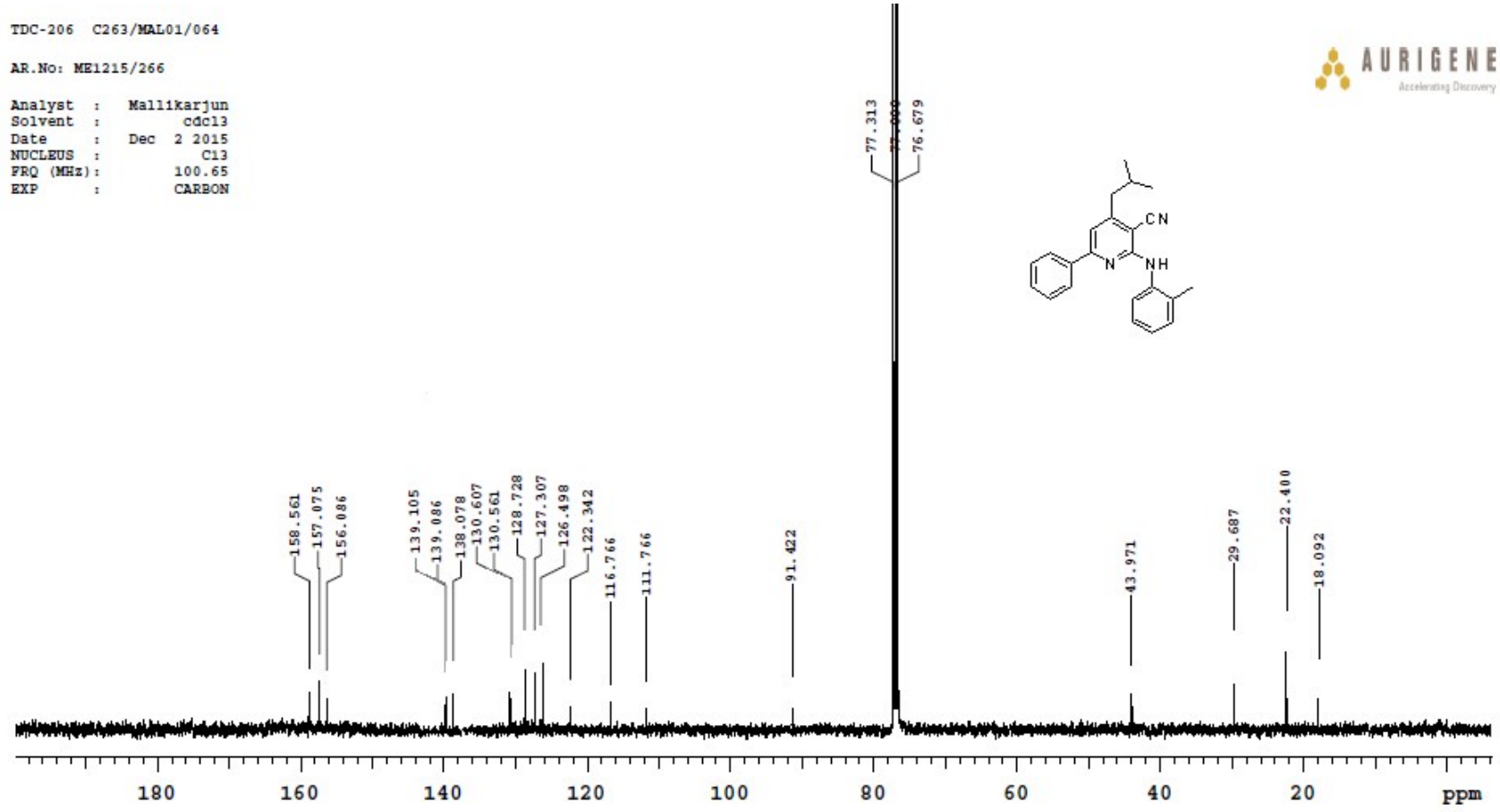



Monoisotopic Mass, Even Electron Ions
48 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-5 O: 0-2
C263/MALO1/064
151119005 21 (0.400) Cm (21:24)

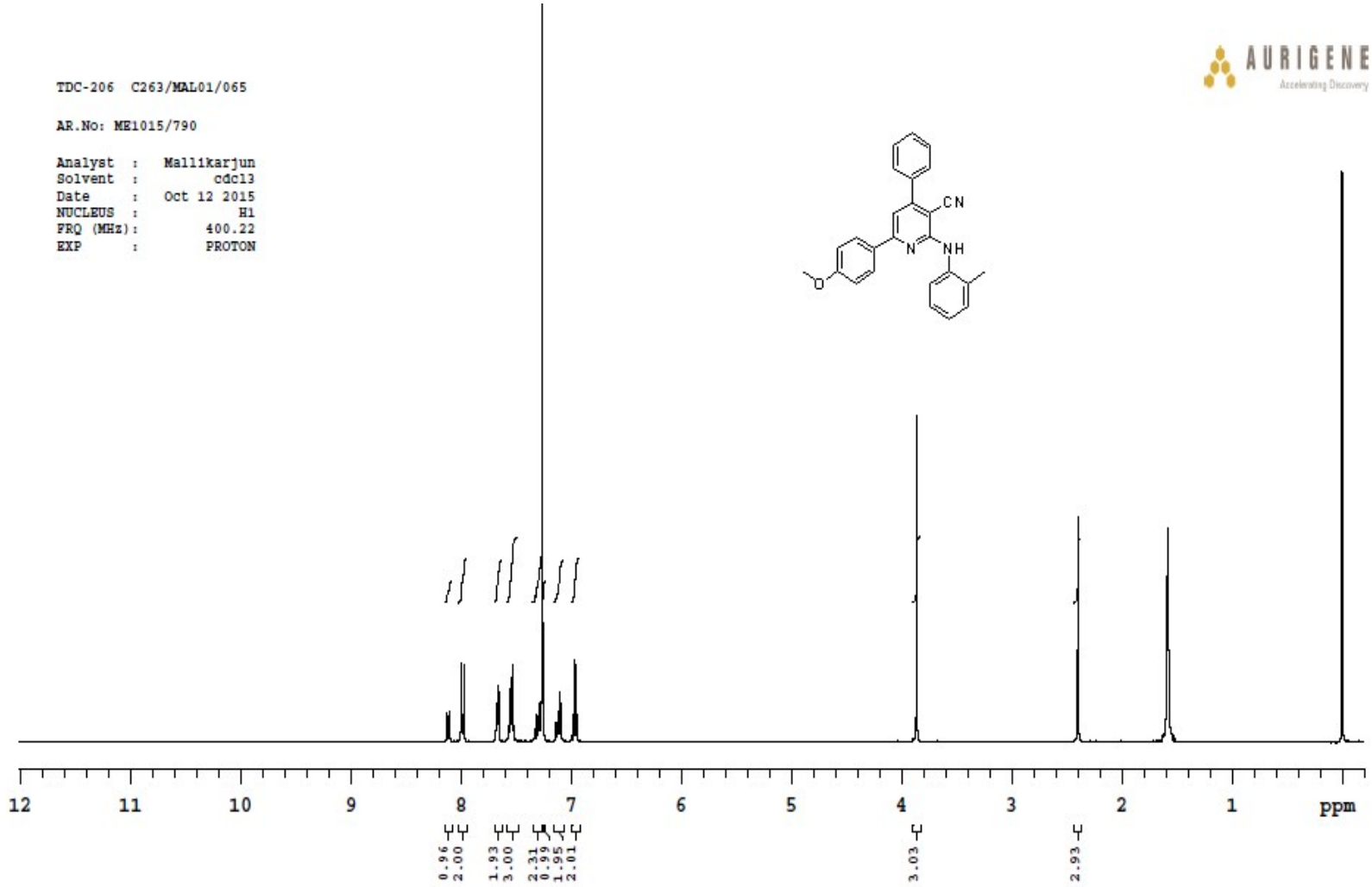
1: TOF MS ES+
1.87e+005




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 342.1984 | 342.1970 | 1.4 | 4.1 | 13.5 | 25.2 | C23 H24 N3 |

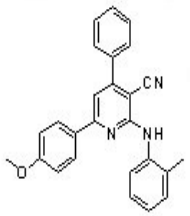

TDC-206 C263/MAL01/064
AR.No: ME1215/266
Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 2 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.313
77.000
76.679
158.561
157.075
156.086
139.105
139.086
138.078
130.607
130.561
128.728
127.307
126.498
122.342
116.766
111.766
91.422
43.971
29.687
22.400
18.092
CN
N
NH
180
160
140
120
100
80
60
40
20
ppm

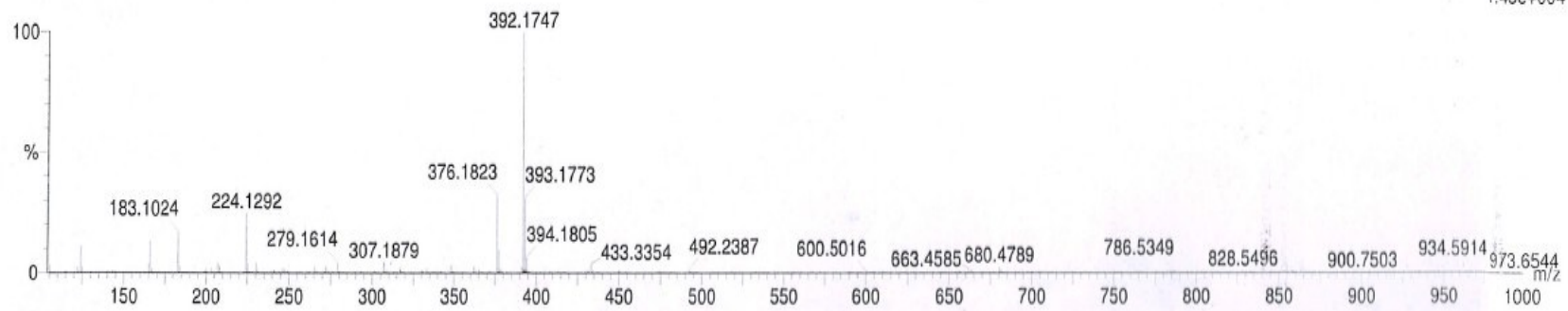
6-(4-Methoxyphenyl)-4-phenyl-2-(o-tolylamino)nicotinonitrile



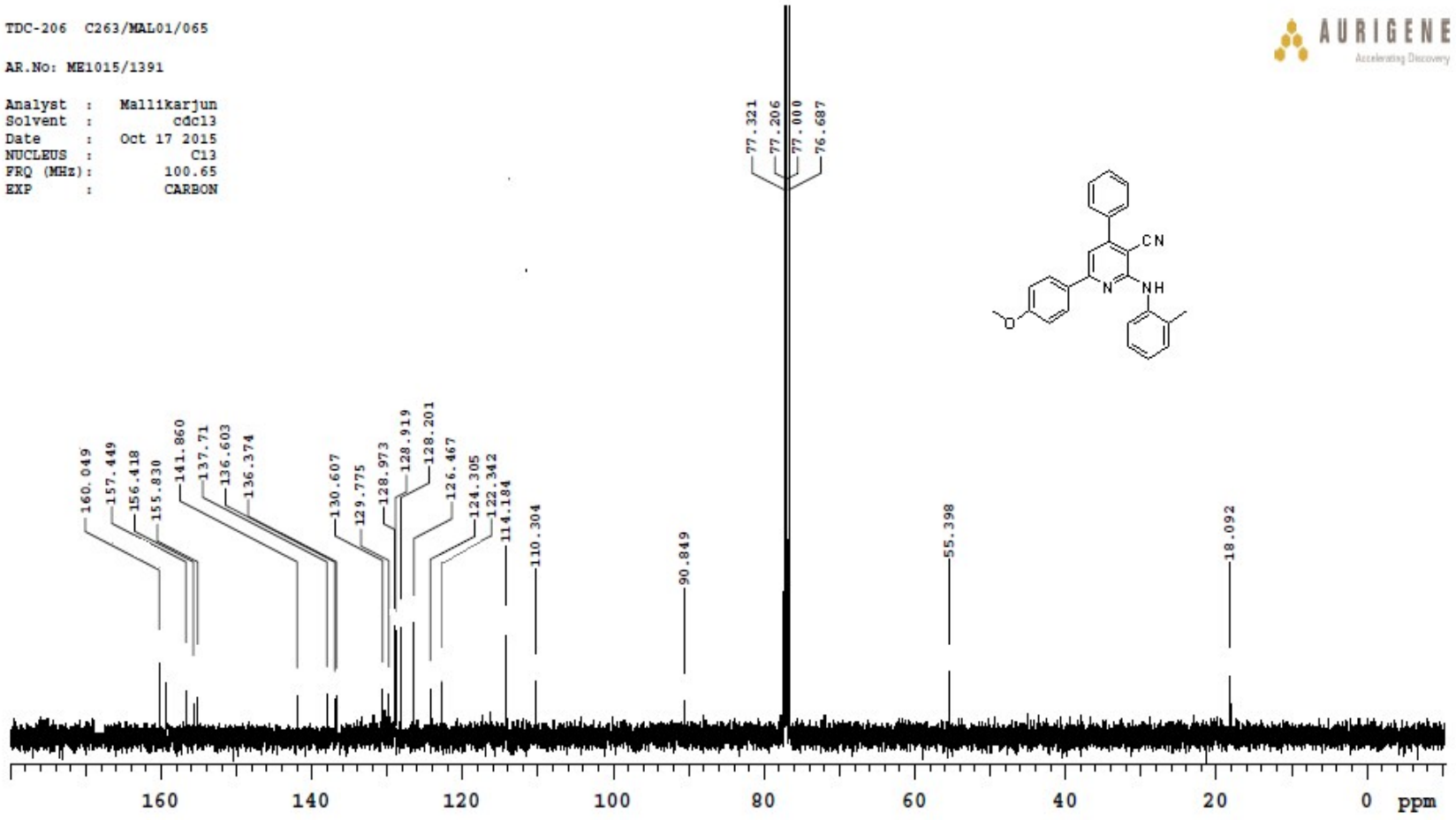
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
63 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-27 H: 0-30 N: 0-5 O: 0-2 F: 0-1
C263/MALO1/065
151016009 73 (1.358) Cm (73:74)

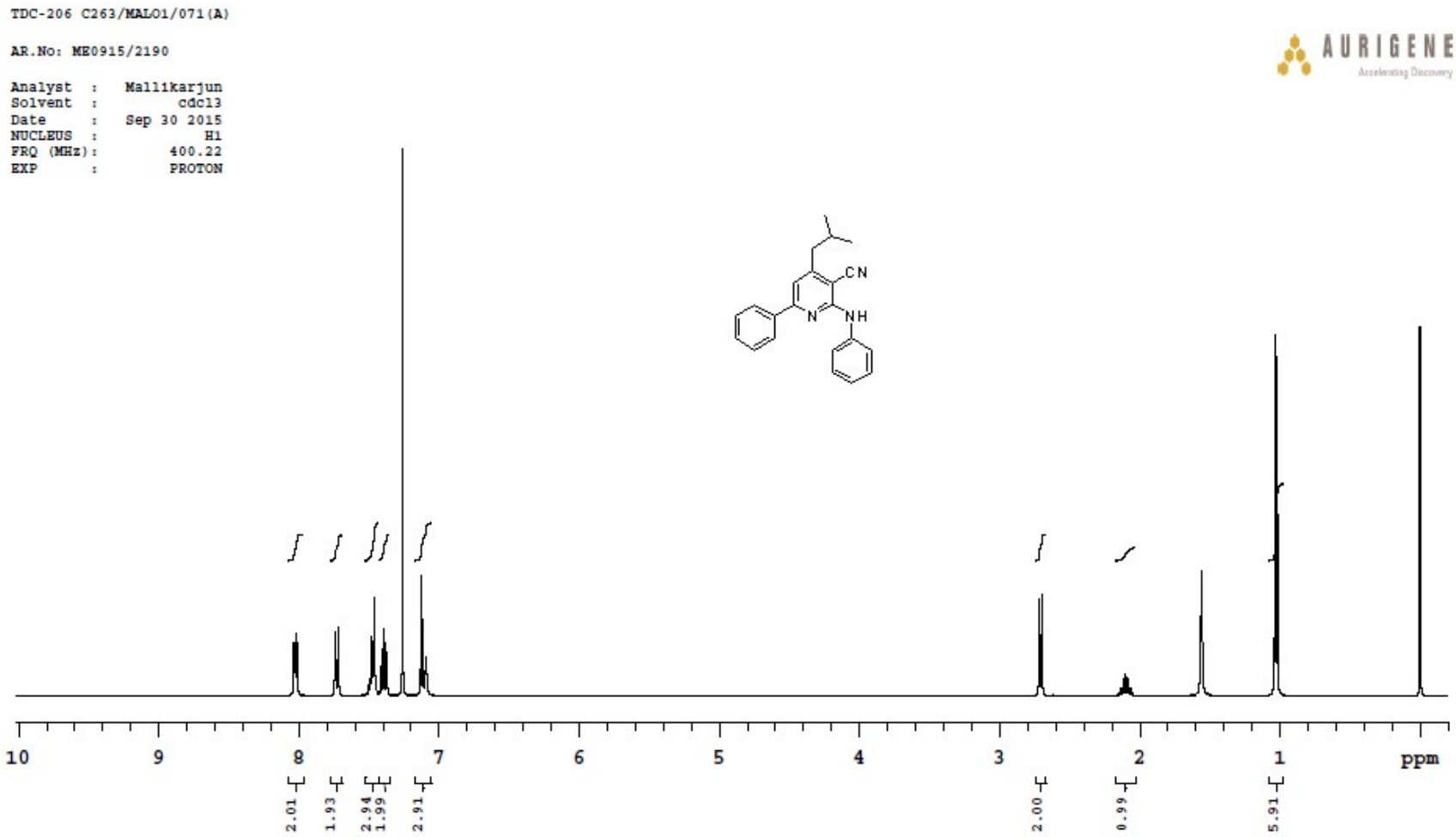



| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 392.1747 | 392.1763 | -1.6 | -4.1 | 17.5 | 1.6 | C26 H22 N3 O |

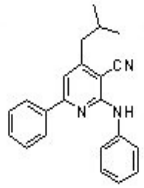

TDC-206 C263/MAL01/065
AR.No: ME1015/1391
Analyst : Mallikarjun
Solvent : cdcl3
Date : Oct 17 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.321
77.206
77.000
76.687
160.049
157.449
156.418
155.830
141.860
137.71
136.603
136.374
130.607
129.775
128.973
128.919
128.201
126.467
124.305
122.342
114.184
110.304
90.849
55.398
18.092
CN
N
NH
O
160
140
120
100
80
60
40
20
0
ppm

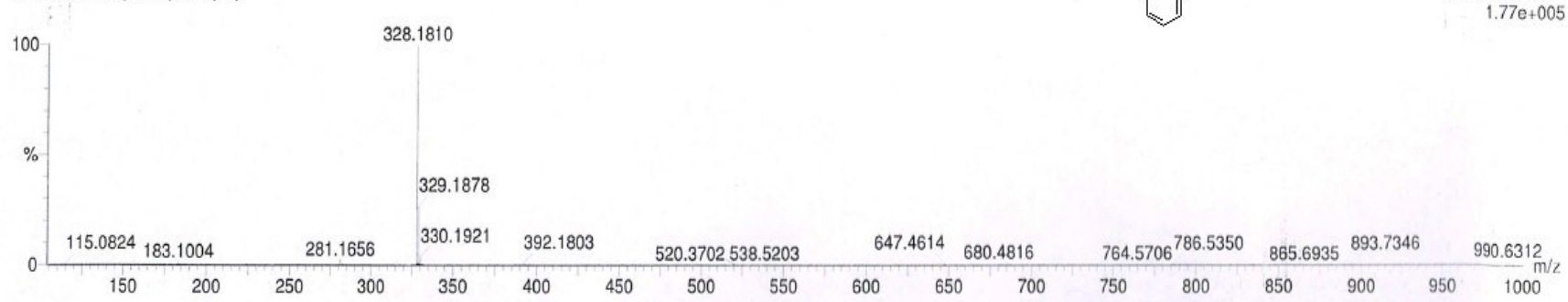
4-Isobutyl-6-phenyl-2-(phenylamino)nicotinonitrile



**Single Mass Analysis**
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
48 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-27 H: 0-30 N: 0-5 O: 0-2
C263/MALO1/071 A
151016011 20 (0.366) Cm (20)



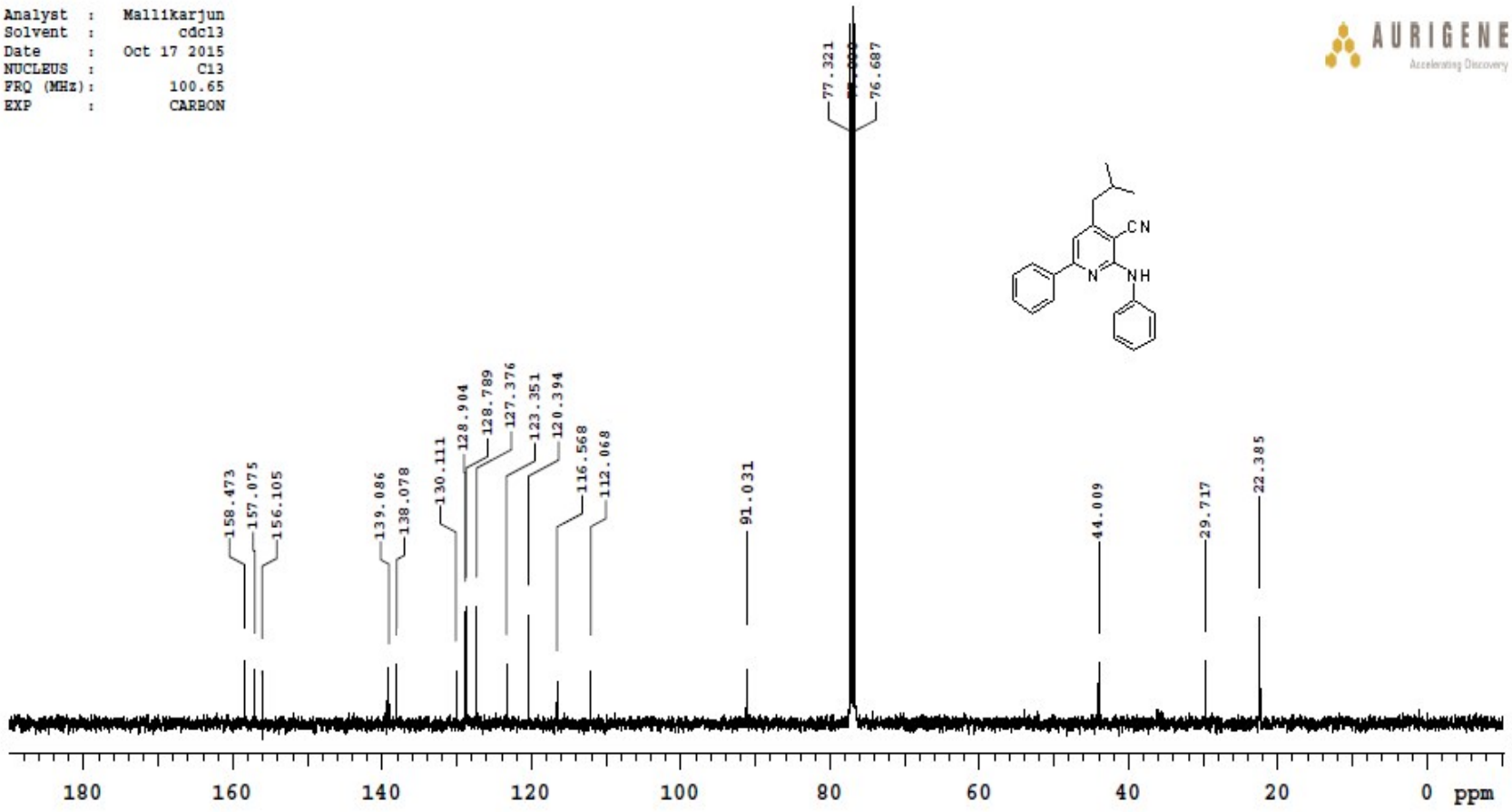




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 10.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 328.1810 | 328.1814 | -0.4 | -1.2 | 13.5 | 27.3 | C22 H22 N3 |

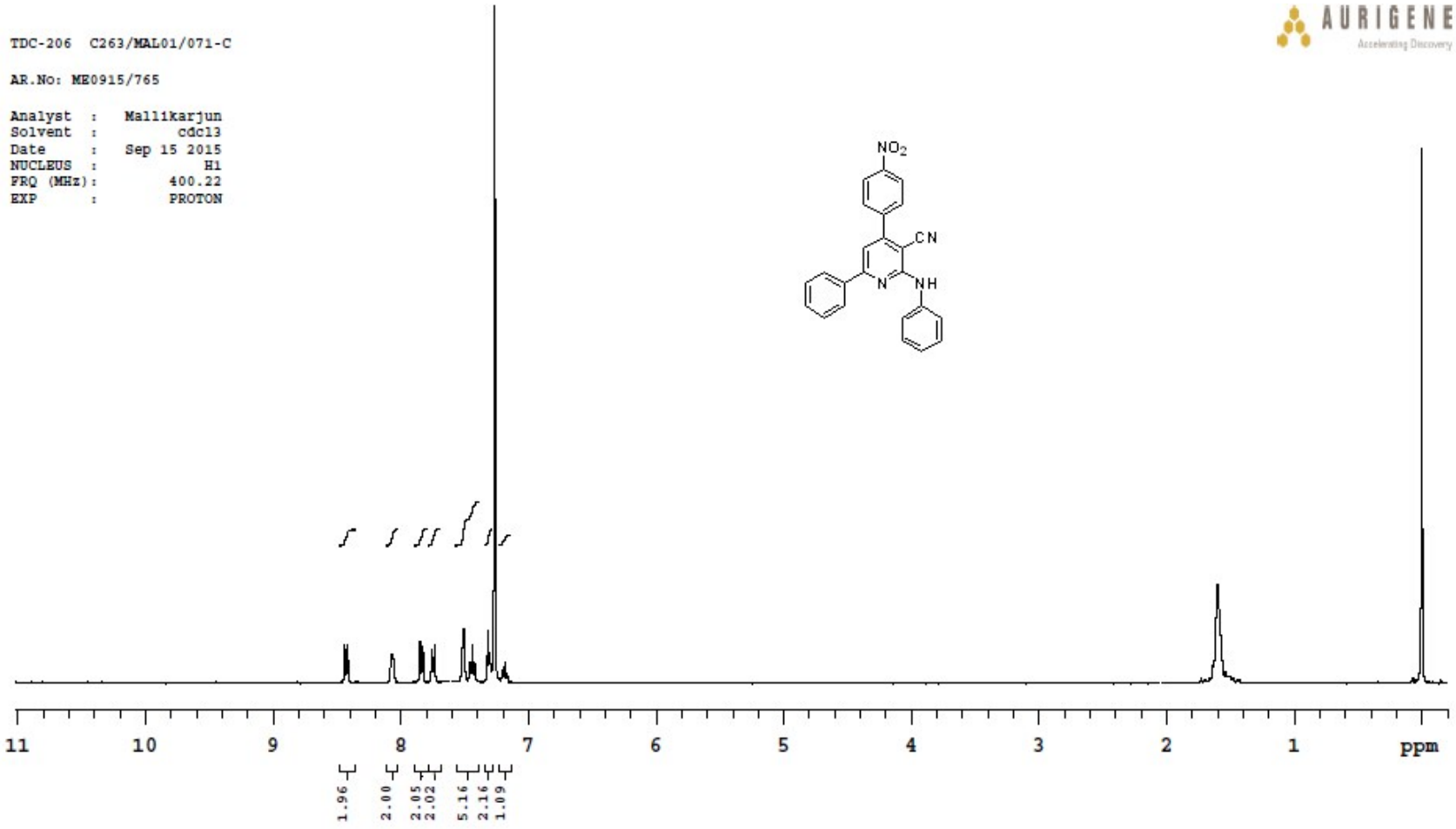
TDC-206 C263/MAL01/071-A

AR.No: ME1015/1394

Analyst : Mallikarjun
Solvent : cdcl3
Date : Oct 17 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON

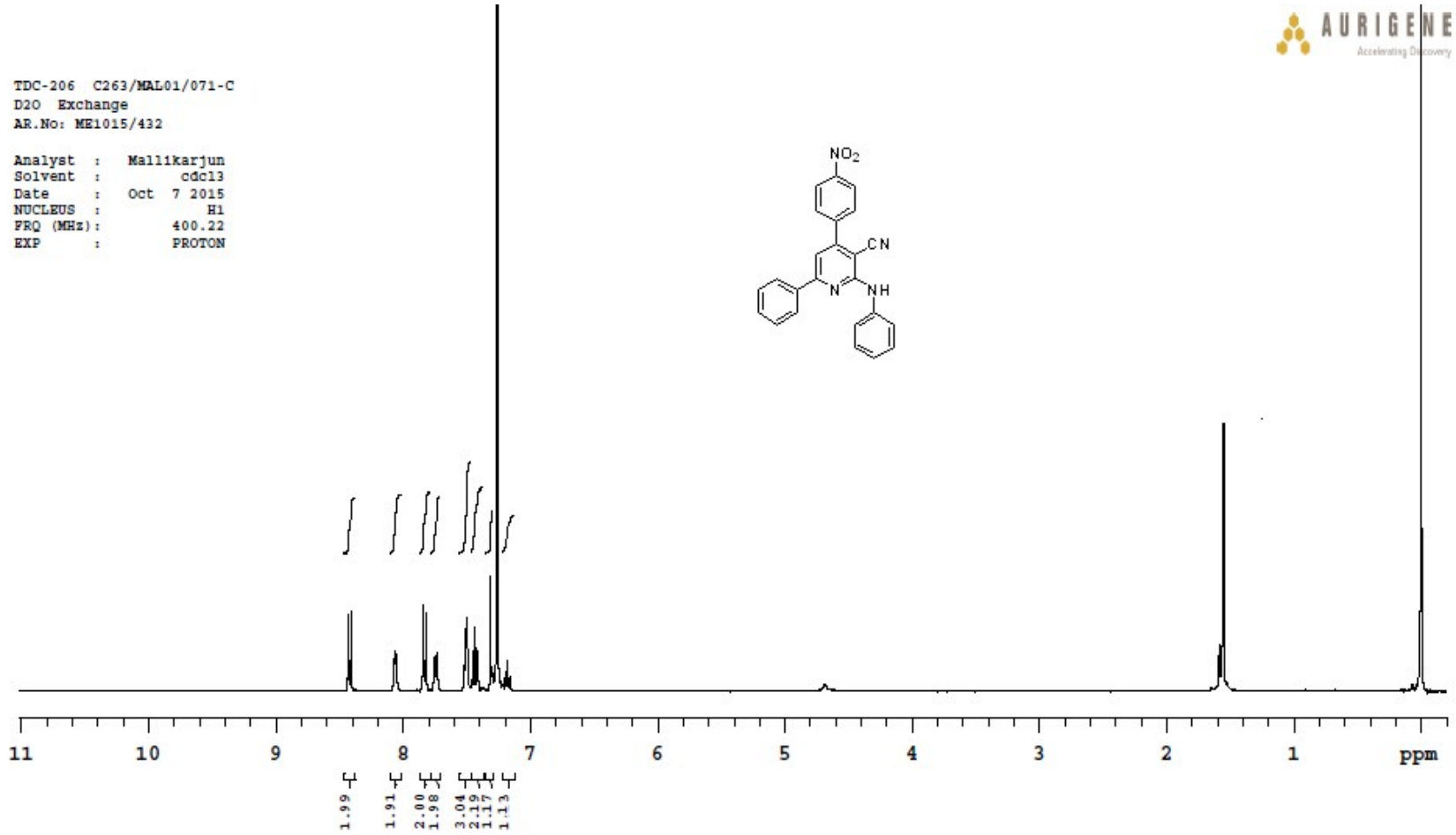


4-(4-Nitrophenyl)-6-phenyl-2-(phenylamino)nicotinonitrile



4-(4-Nitrophenyl)-6-phenyl-2-(phenylamino)nicotinonitrile

**$D_2O$ exchange**



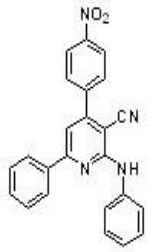
## Elemental Composition Report

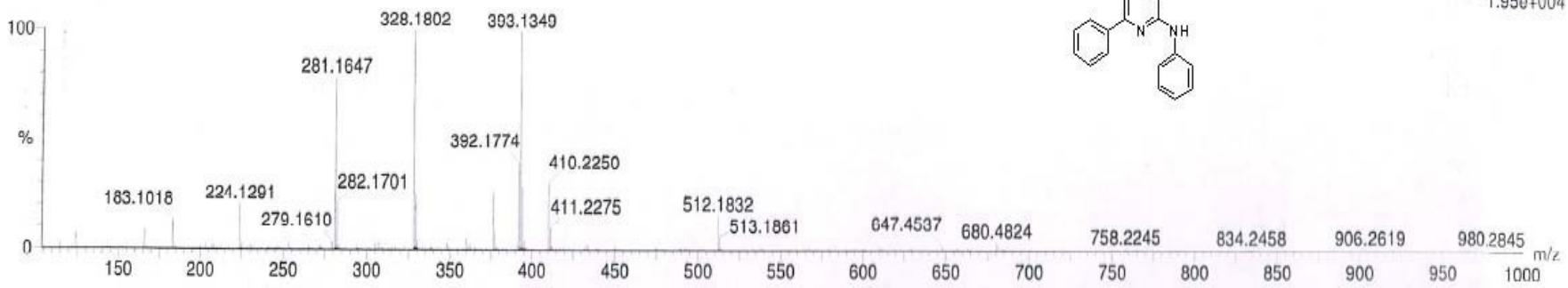


### Single Mass Analysis

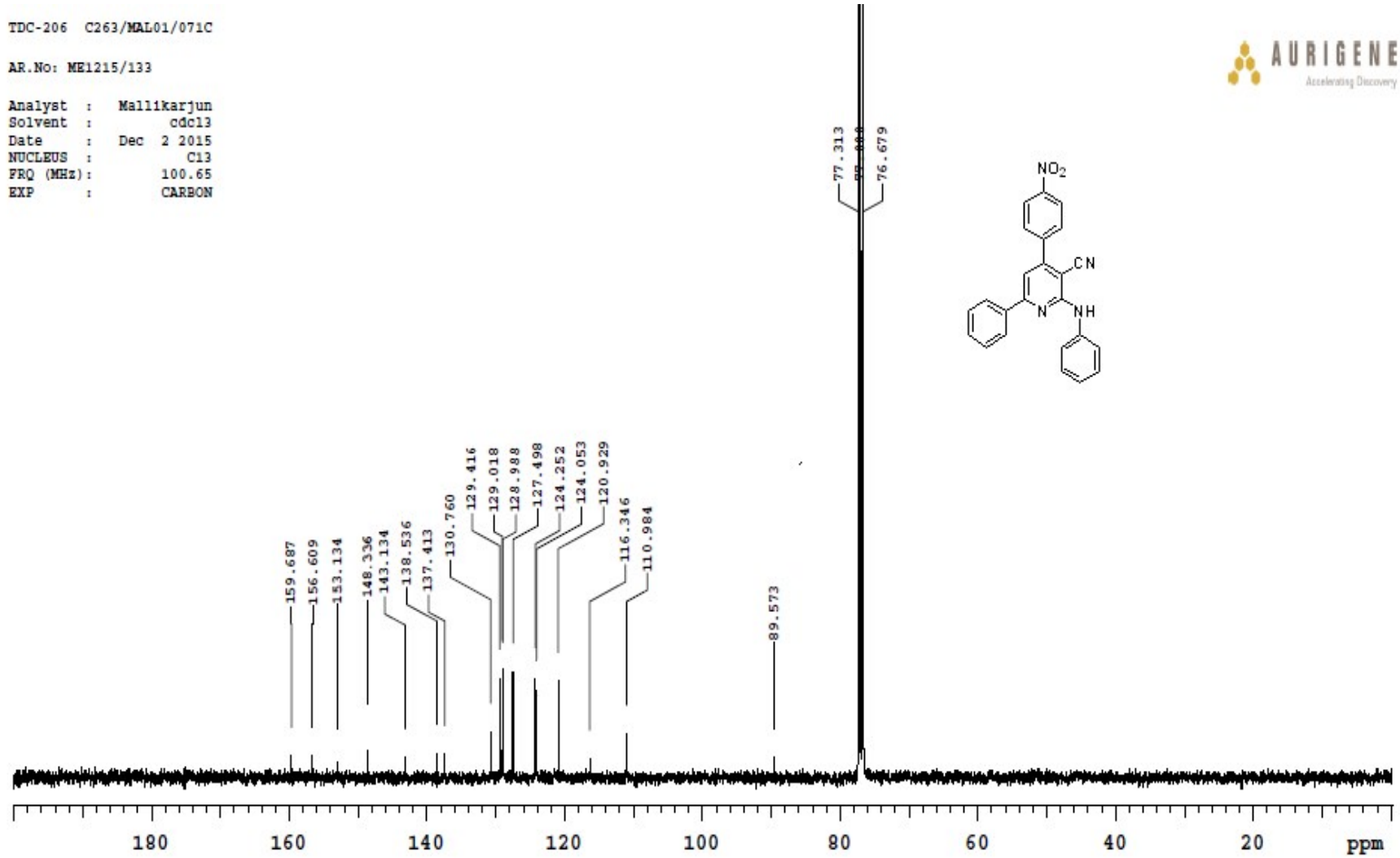
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
25 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-27 H: 0-30 N: 0-5 O: 0-2
C263/MALO1/071 C
151016012 22 (0.412) Cm (22:24-11:13x0.500)

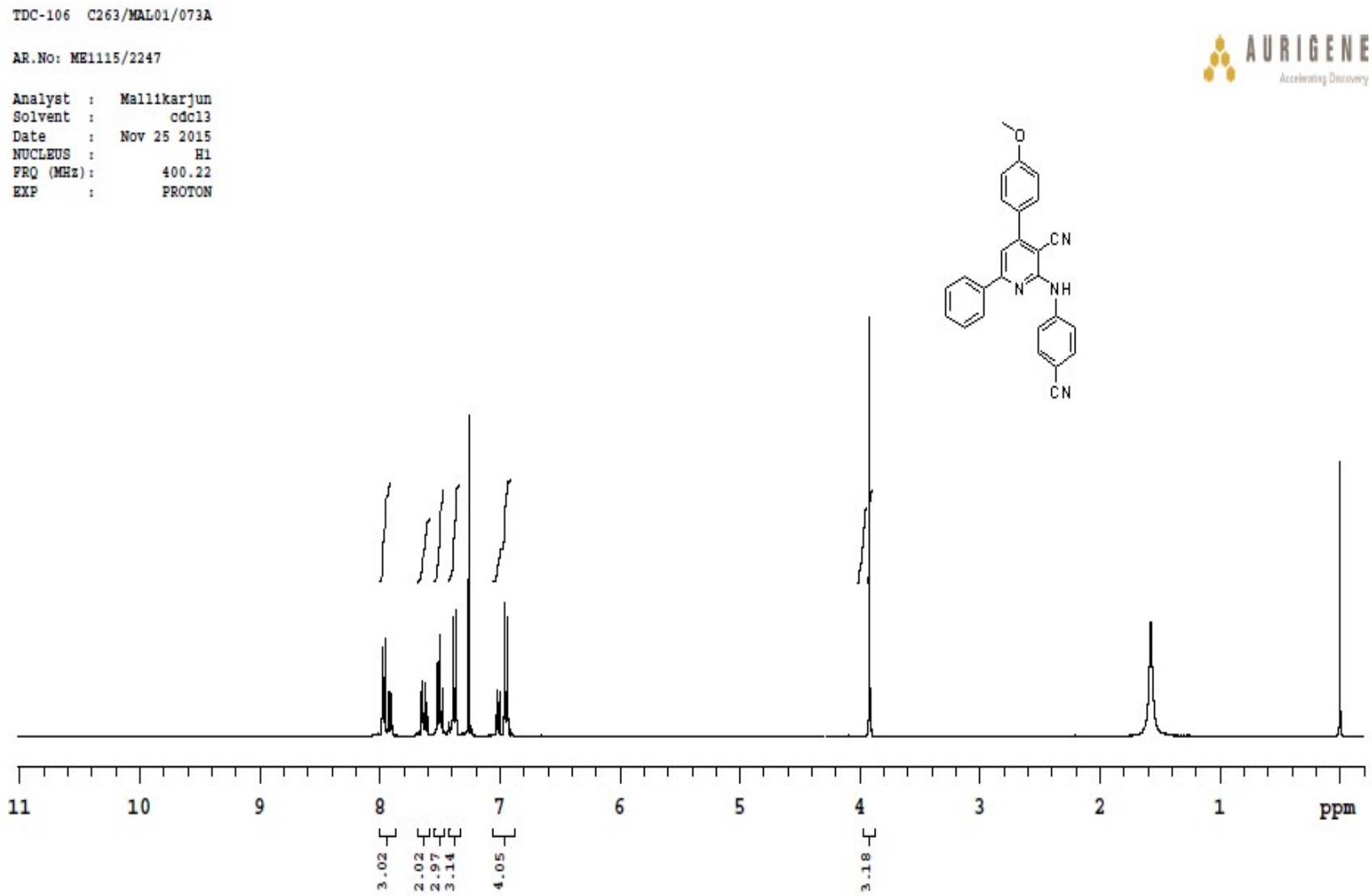



| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 10.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 393.1349 | 393.1352 | -0.3 | -0.8 | 18.5 | 0.1 | C24 H17 N4 O2 |

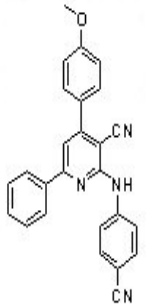

TDC-206 C263/MAL01/071C
AR.No: ME1215/133
Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 2 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
NO2
CN
N
NH
77.313
76.679
159.687
156.609
153.134
148.336
143.134
138.536
137.413
130.760
129.416
129.018
128.988
127.498
124.252
124.053
120.929
116.346
110.984
89.573
180
160
140
120
100
80
60
40
20
ppm

2-((4-Cyanophenyl)amino)-4-(4-methoxyphenyl)-6-phenylnicotinonitrile

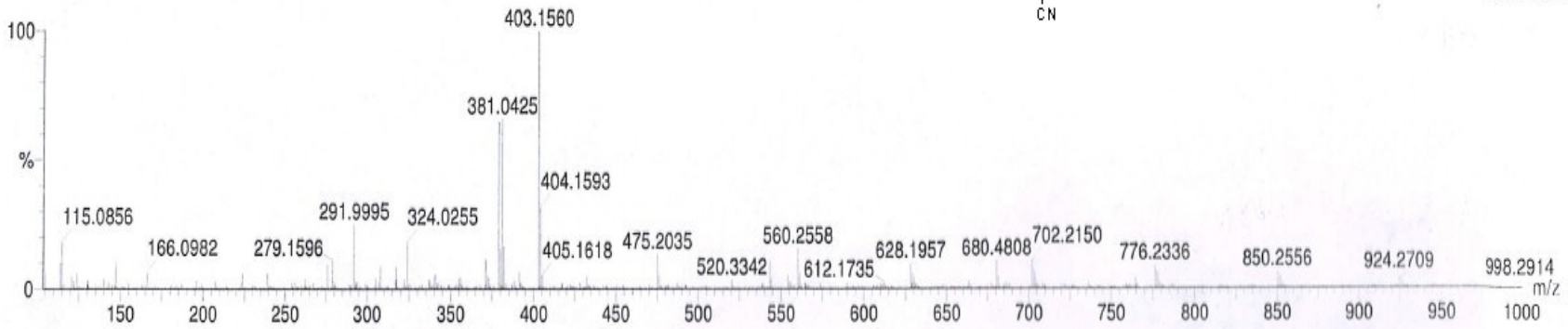


**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-30 H: 0-20 N: 0-5 O: 0-2
C263/MALO1/073 A
151119003 19 (0.352) Cm (17:20)




1: TOF MS ES+
1.54e+004

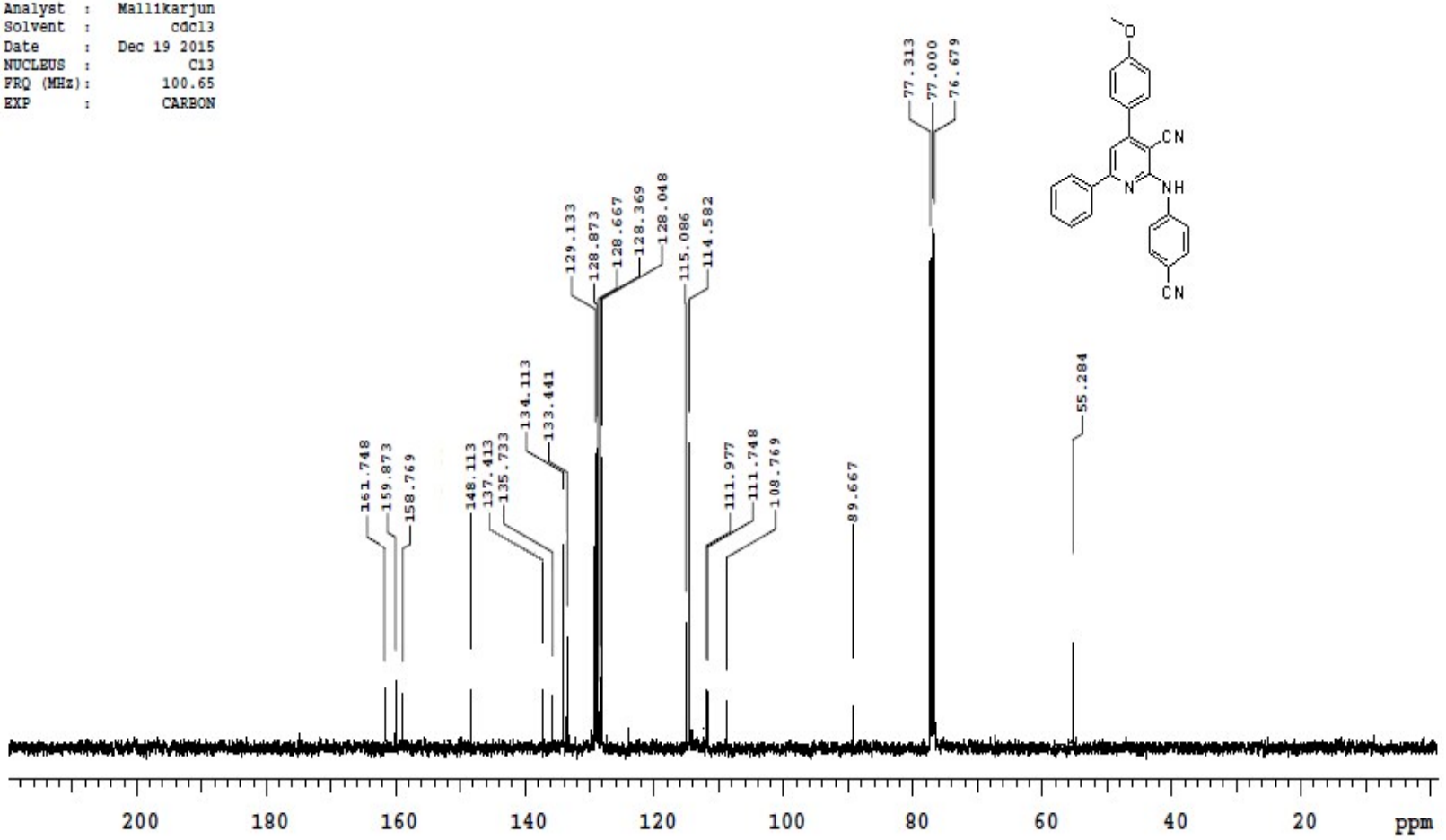



| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 403.1560 | 403.1559 | 0.1 | 0.2 | 19.5 | 3.0 | C26 H19 N4 O |

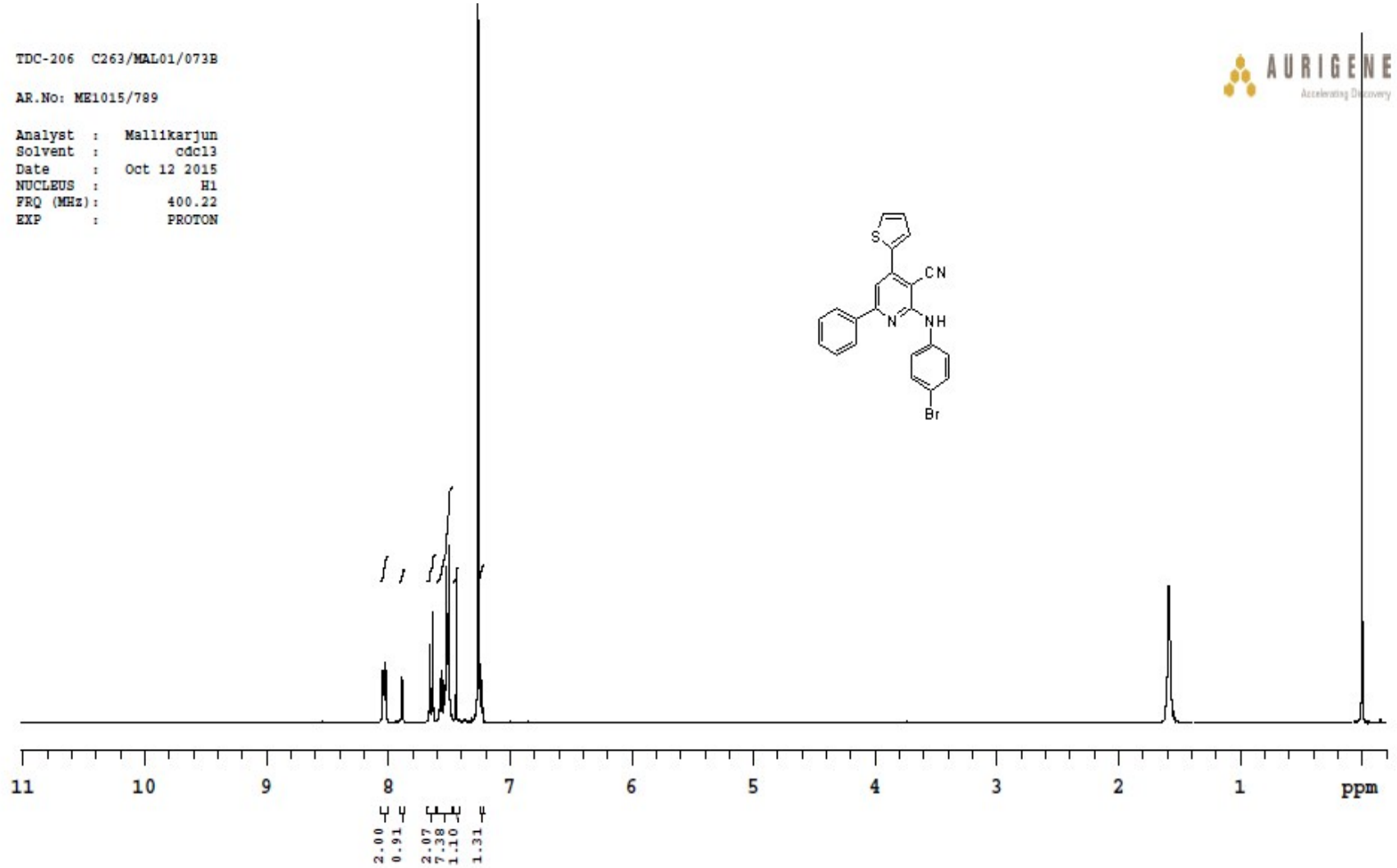
TDC-206 C263/MALO1/073(A)

AR.No: ME1215/1864

Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 19 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON



2-((4-Bromophenyl)amino)-6-phenyl-4-(thiophen-2-yl)nicotinonitrile



## Elemental Composition Report

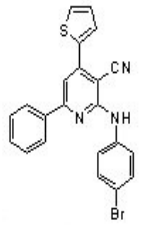


### Single Mass Analysis

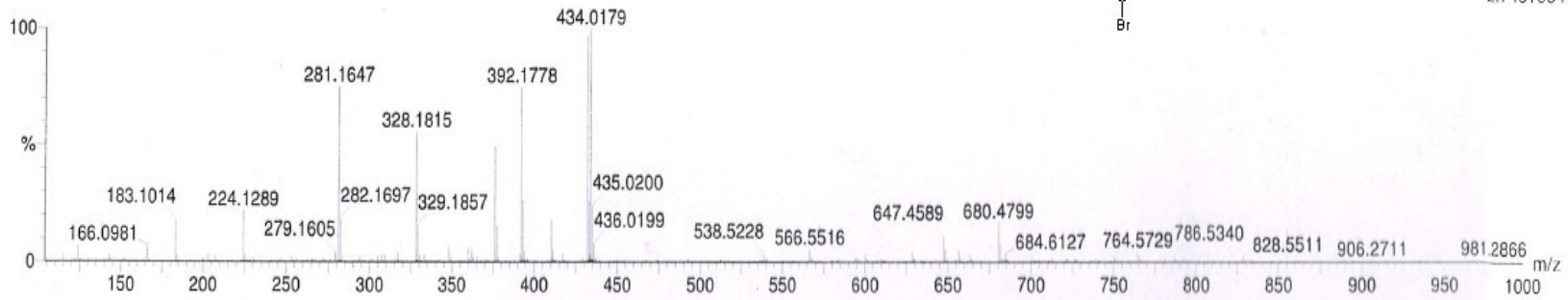
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
127 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-27 H: 0-30 N: 0-5 O: 0-2 S: 0-1 Br: 0-1

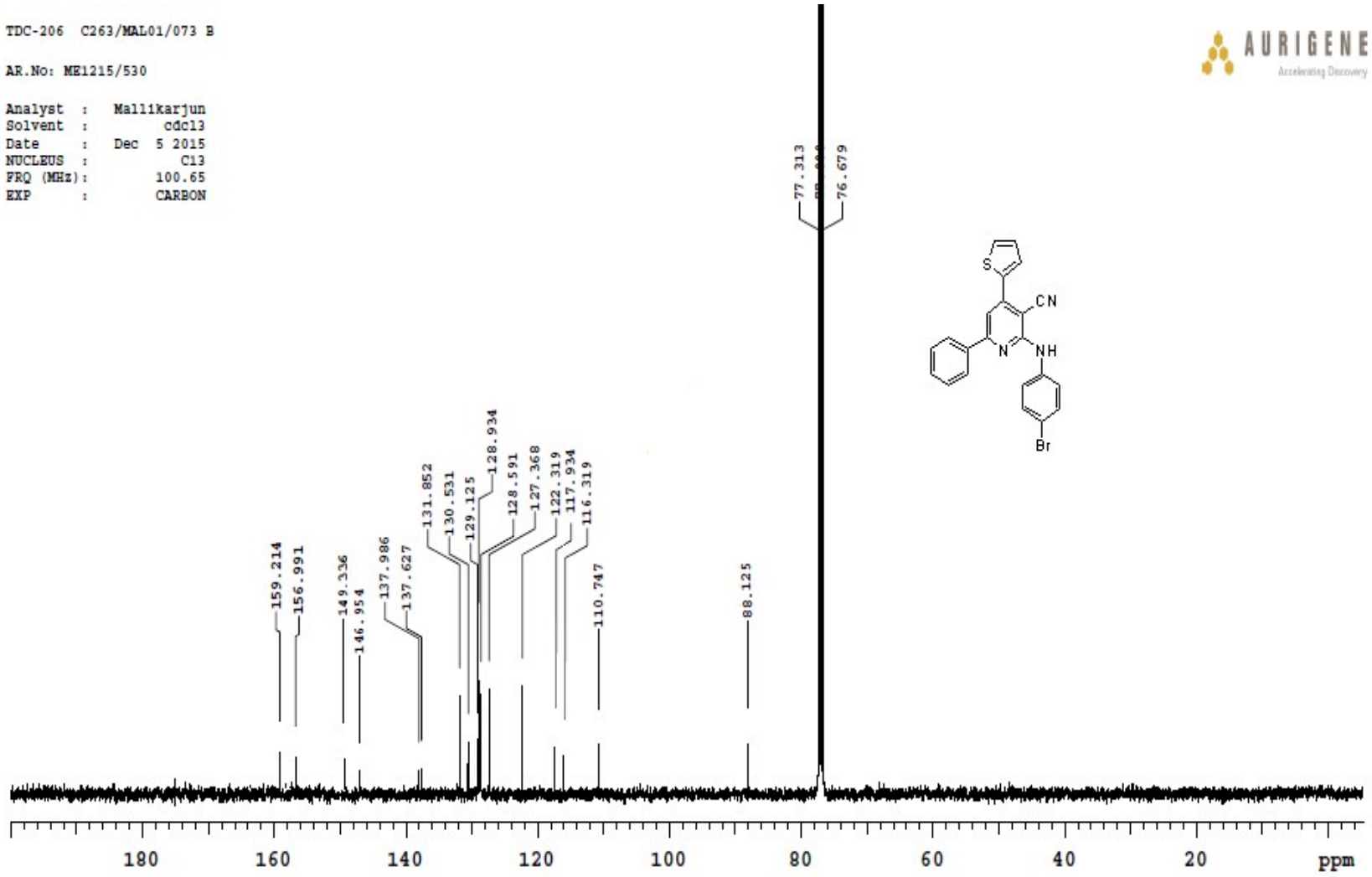
C263/MALO1/073 B
151016013 21 (0.399) Cm (21:26-5:11x0.500)



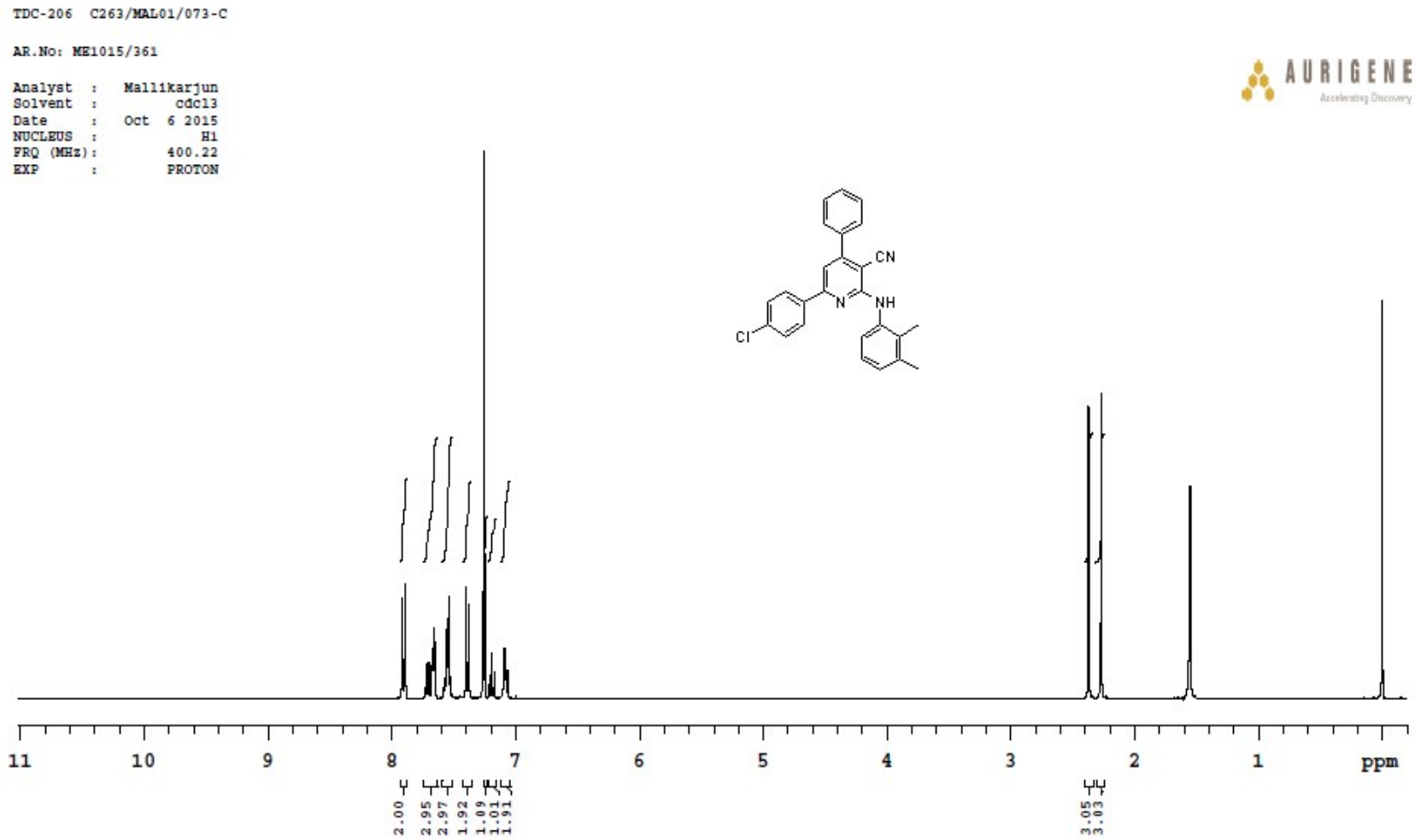

1: TOF MS ES+
2.74e+004




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 10.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 432.0199 | 432.0170 | 2.9 | 6.7 | 16.5 | 4.4 | C22 H15 N3 S Br |


TDC-206 C263/MAL01/073 B
AR.No: ME1215/530
Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 5 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.313
76.679
159.214
156.991
149.336
146.954
137.986
137.627
131.852
130.531
129.125
128.934
128.591
127.368
122.319
117.934
116.319
110.747
88.125
S
CN
N
NH
Br
180
160
140
120
100
80
60
40
20
ppm

6-(4-Chlorophenyl)-2-((2,3-dimethylphenyl)amino)-4-phenylnicotinonitrile

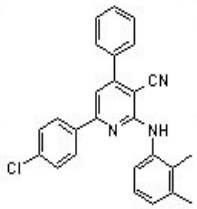


**Elemental Composition Report** **Page 1**

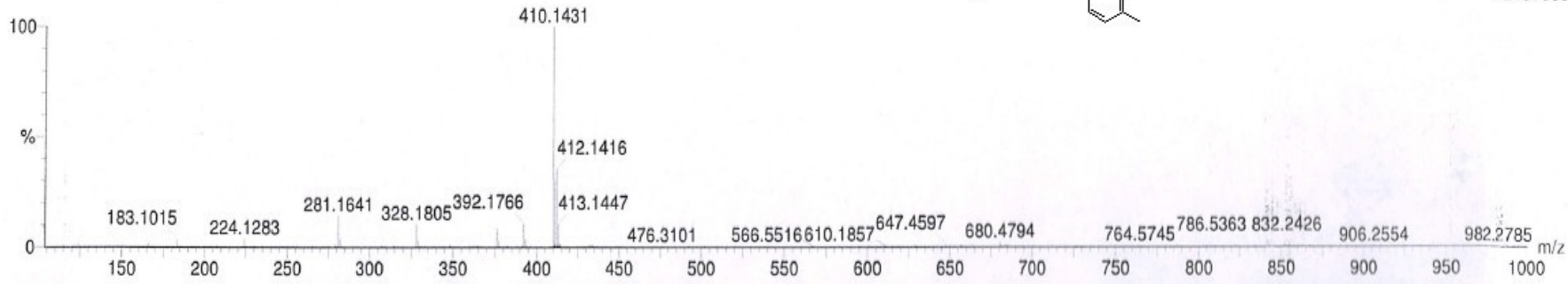
**Single Mass Analysis**

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
54 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-27 H: 0-30 N: 0-5 O: 0-2 Cl: 0-1
C263/MALO1/073 C
151016014 24 (0.440) Cm (23:26)




1: TOF MS ES+
1.24e+005

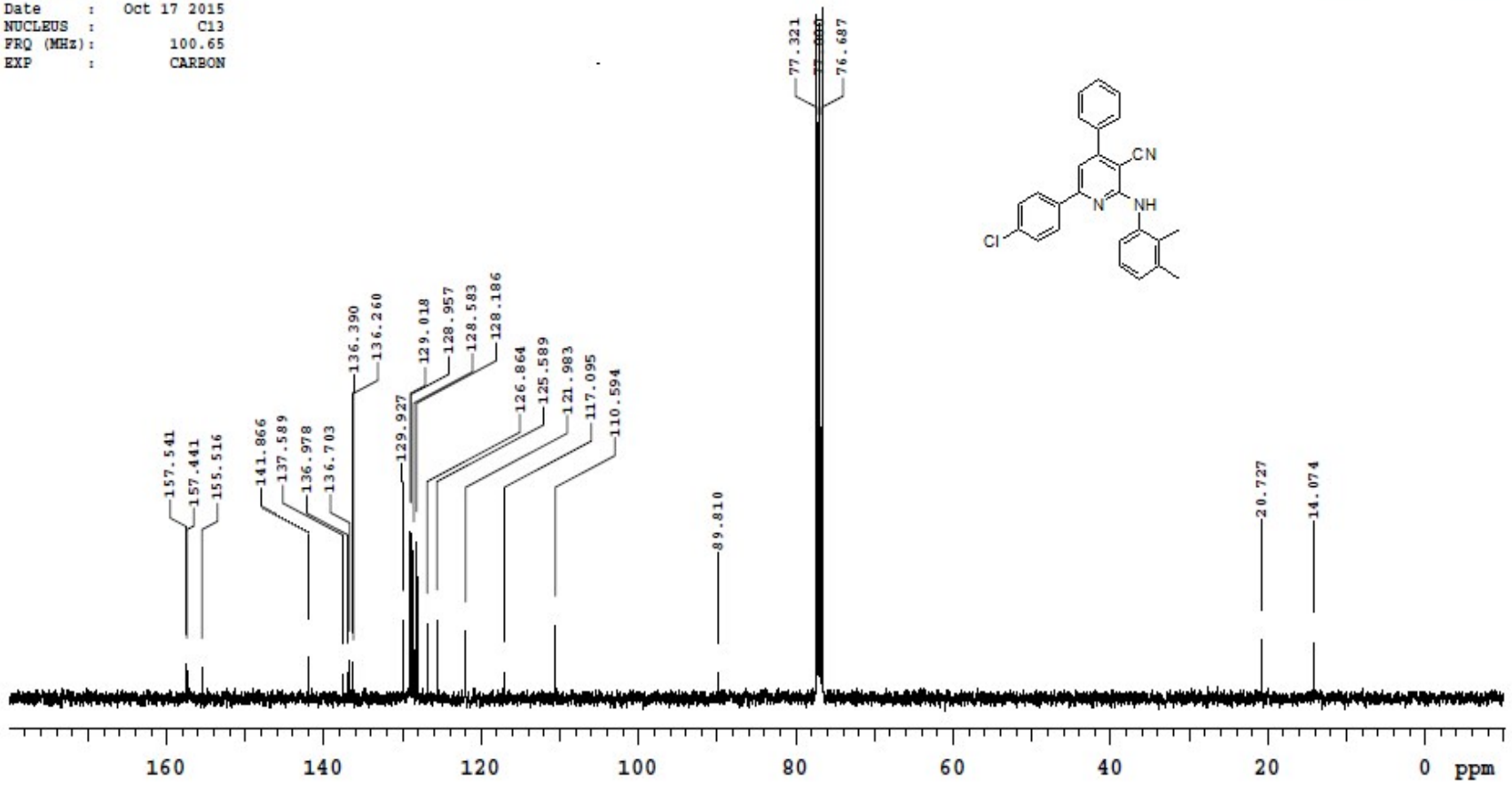



| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 410.1431 | 410.1424 | 0.7 | 1.7 | 17.5 | 4.5 | C26 H21 N3 Cl |

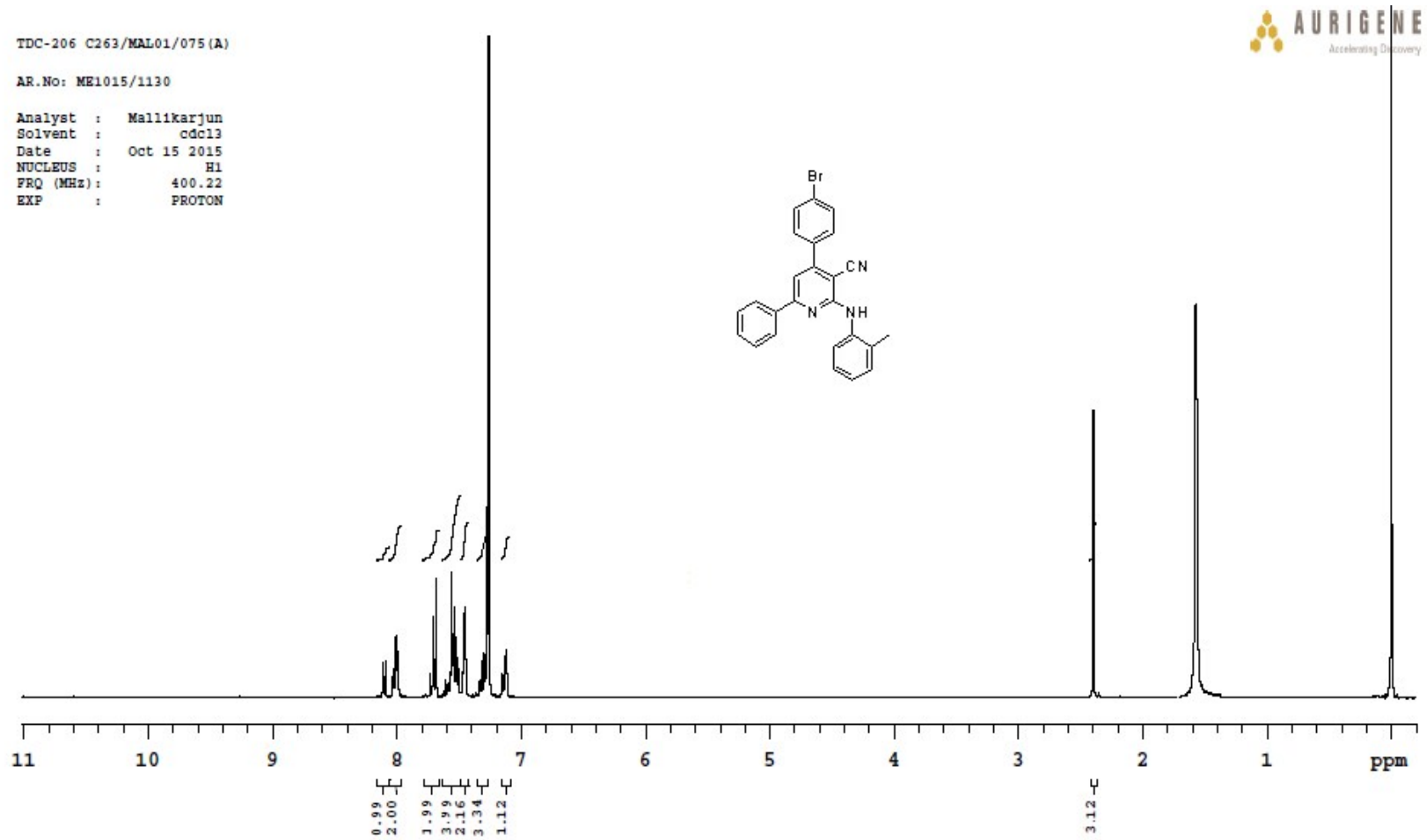
TDC-206 C263/MAL01/073-C

AR.No: ME1015/1392

Analyst : Mallikarjun
Solvent : cdcl3
Date : Oct 17 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON



4-(4-Bromophenyl)-6-phenyl-2-(o-tolylamino)nicotinonitrile

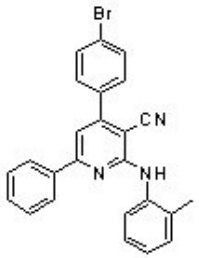


## Elemental Composition Report

### Single Mass Analysis

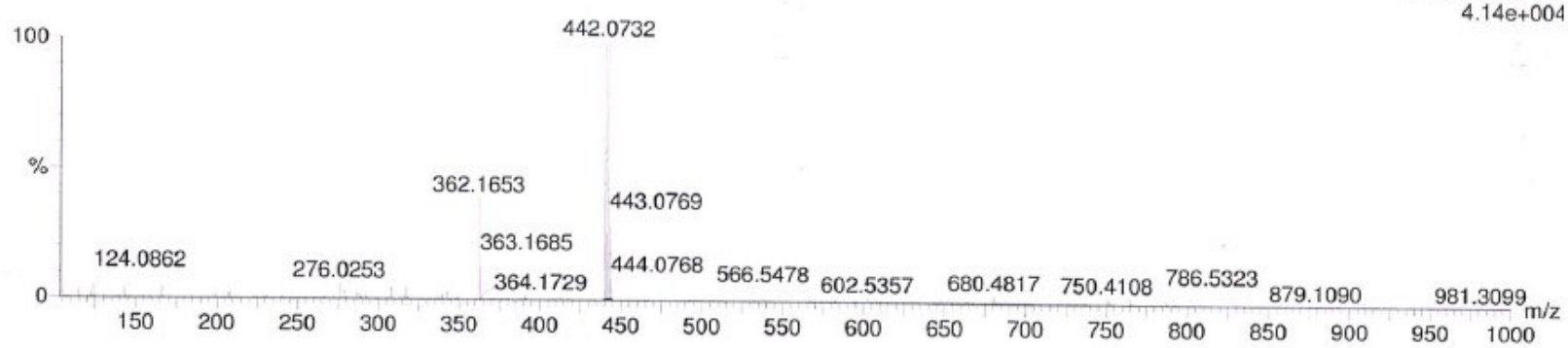
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
68 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-30 H: 0-30 N: 0-5 O: 0-2 Br: 0-1

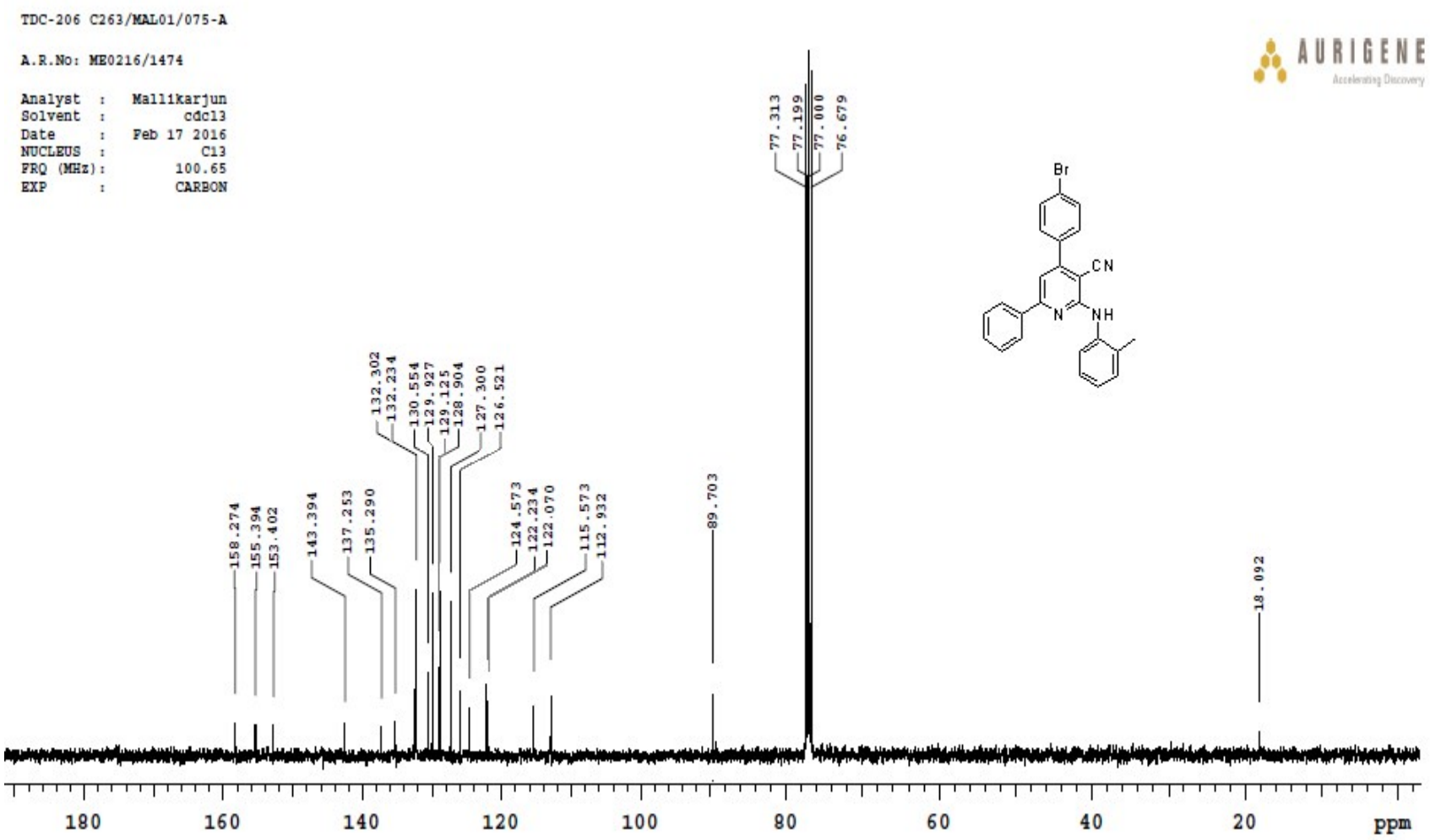



C263/MALO1/075 A
151119007 21 (0.400) Cm (21:23)

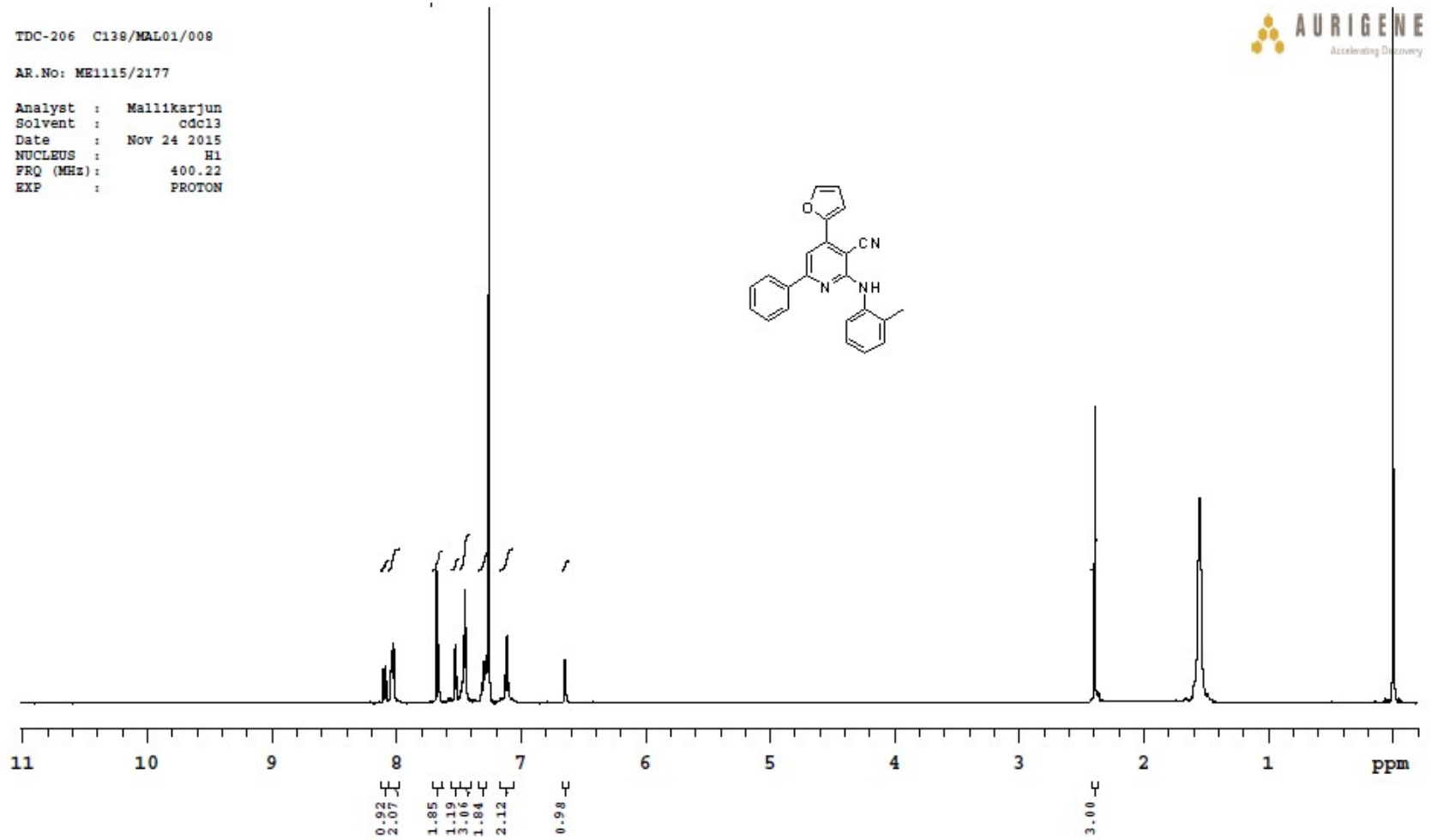
1: TOF MS ES+
4.14e+004



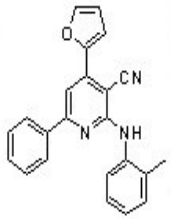

| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 440.0753 | 440.0762 | -0.9 | -2.0 | 17.5 | 39.2 | C25 H19 N3 Br |


TDC-206 C263/MAL01/075-A
A.R.No: ME0216/1474
Analyst : Mallikarjun
Solvent : cdcl3
Date : Feb 17 2016
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.313
77.199
77.000
76.679
158.274
155.394
153.402
143.394
137.253
135.290
132.302
132.234
130.554
129.927
129.125
128.904
127.300
126.521
124.573
122.234
122.070
115.573
112.932
89.703
18.092
Br
CN
N
NH
180
160
140
120
100
80
60
40
20
ppm

4-(Furan-2-yl)-6-phenyl-2-(o-tolylamino)nicotinonitrile

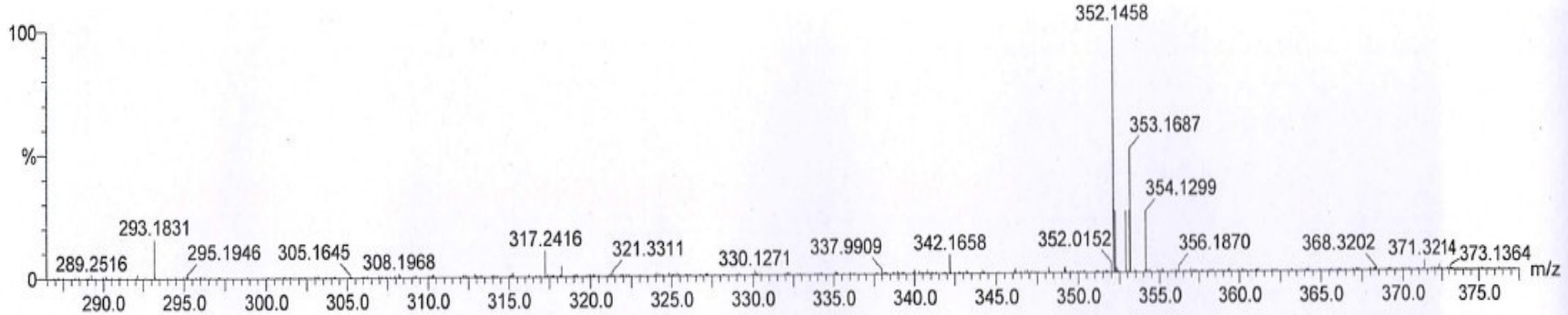


**Single Mass Analysis**
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

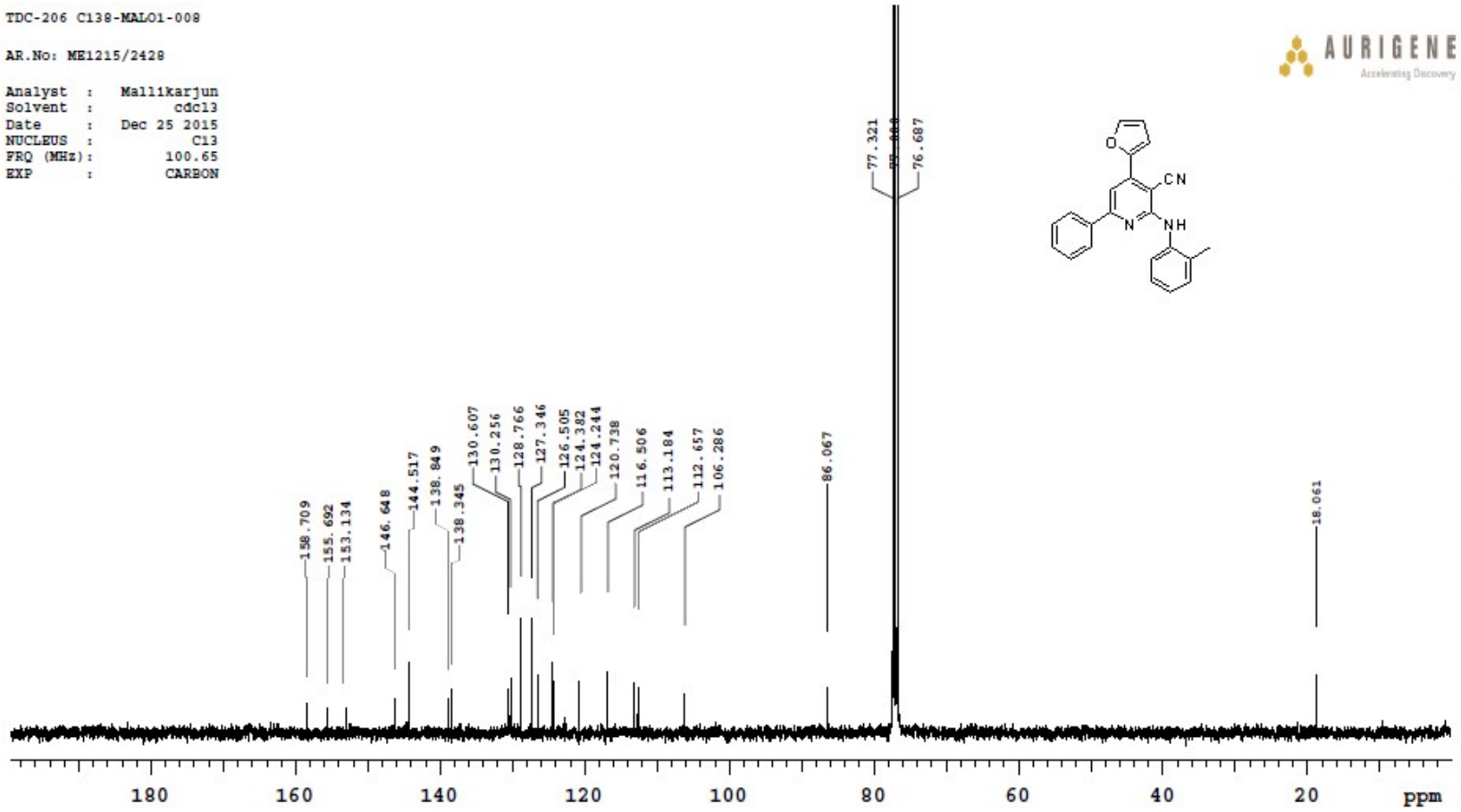



Monoisotopic Mass, Even Electron Ions
42 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-30 H: 0-23 N: 0-6 O: 0-2
C138/MALO1/008
160122004 28 (0.514) Cm (27:28-49:52x0.500)

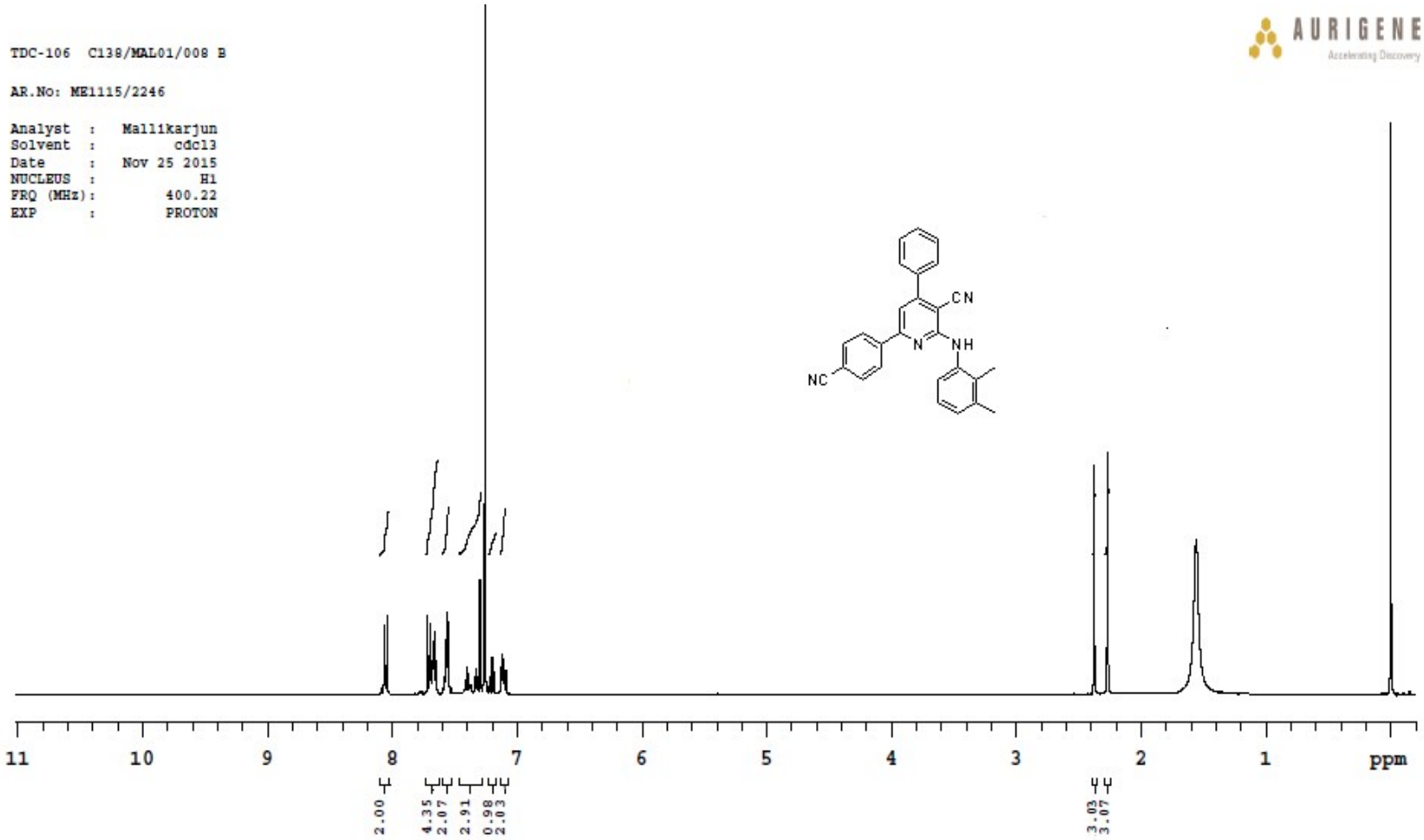
1: TOF MS ES+
2.94e+002




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 20.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 352.1458 | 352.1450 | 0.8 | 2.3 | 16.5 | 21.8 | C23 H18 N3 O |


TDC-206 C138-MALO1-008
AR.No: ME1215/2428
Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 25 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
158.709
155.692
153.134
146.648
144.517
138.849
138.345
130.607
130.256
128.766
127.346
126.505
124.382
124.244
120.738
116.506
113.184
112.657
106.286
86.067
77.321
76.687
18.061
CN
N
NH
O
180
160
140
120
100
80
60
40
20
ppm

6-(4-Cyanophenyl)-2-((2,3-dimethylphenyl)amino)-4-phenylnicotinonitrile

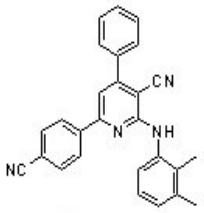


## Elemental Composition Report

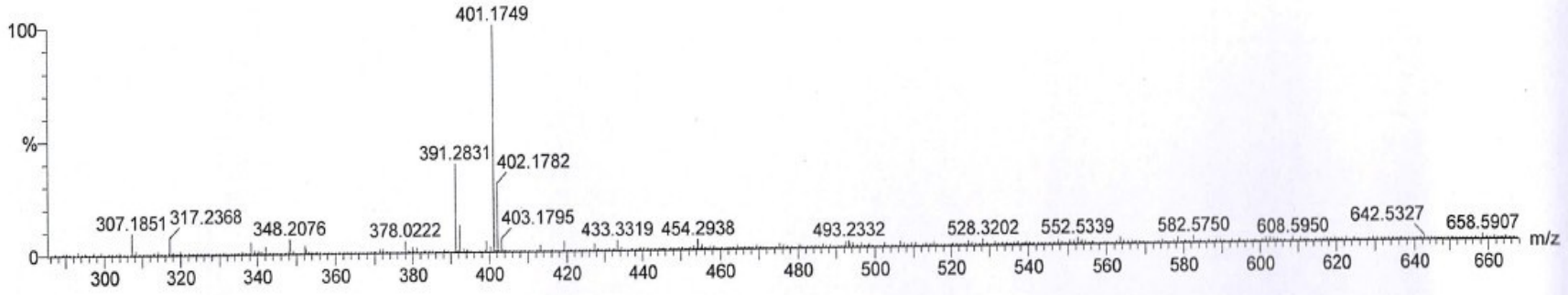


**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

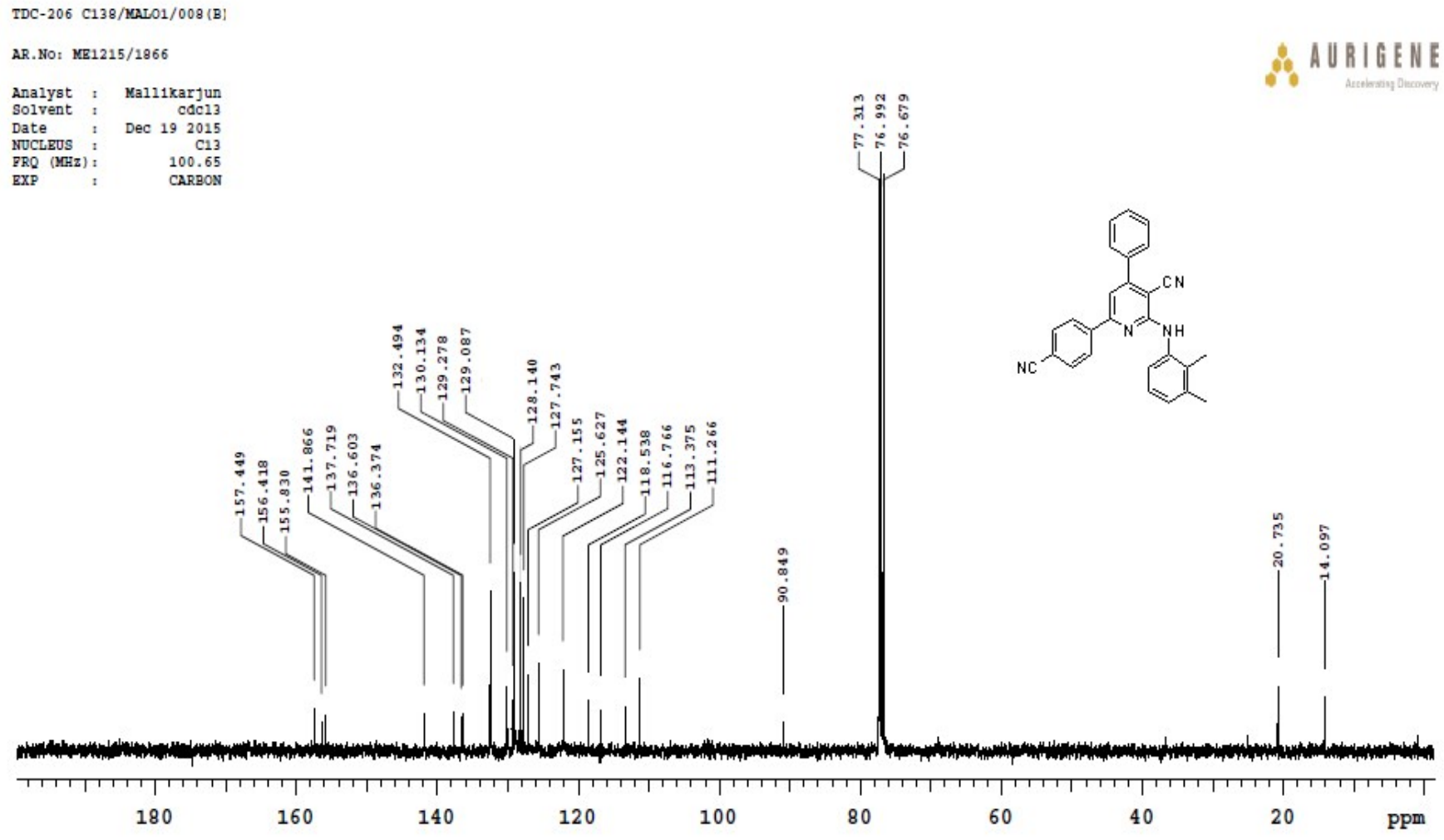
Monoisotopic Mass, Even Electron Ions
44 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-30 H: 0-25 N: 0-6 S: 0-2
C138/MALO1/008 B
160122005 43 (0.796) Cm (43:47-69:73x0.500)



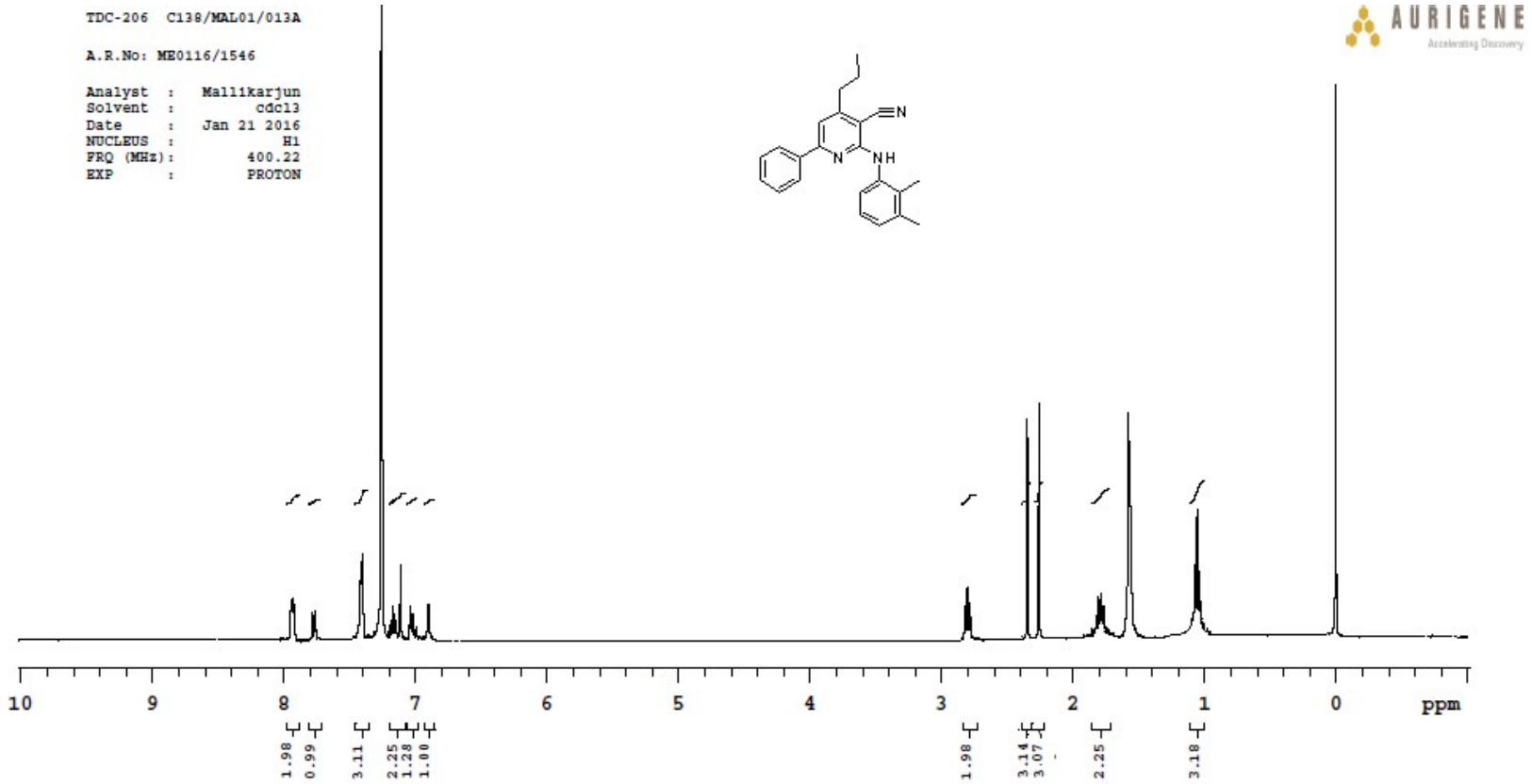

1: TOF MS ES+
8.45e+002




| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 401.1749 | 401.1766 | -1.7 | -4.2 | 19.5 | 0.3 | C27 H21 N4 |


TDC-206 C138/MALO1/008(B)
AR.No: ME1215/1866
Analyst : Mallikarjun
Solvent : cdcl3
Date : Dec 19 2015
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON
AURIGENE
Accelerating Discovery
77.313
76.992
76.679
132.494
130.134
129.278
129.087
128.140
127.743
127.155
125.627
122.144
118.538
116.766
113.375
111.266
157.449
156.418
155.830
141.866
137.719
136.603
136.374
90.849
20.735
14.097
CN
NC
N
NH
180
160
140
120
100
80
60
40
20
ppm

2-((2,3-Dimethylphenyl)amino)-6-phenyl-4-propylnicotinonitrile



## Elemental Composition Report

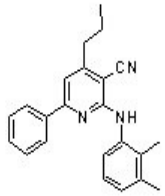


### Single Mass Analysis

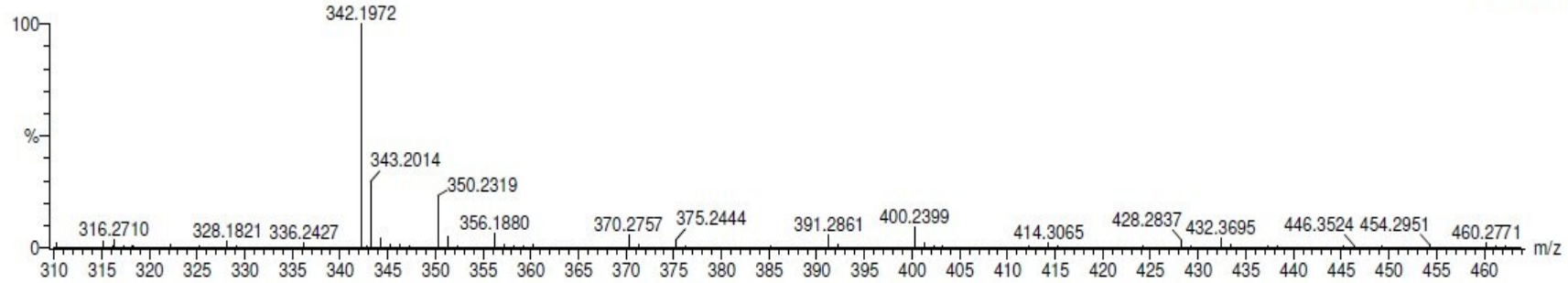
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
10 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-26 H: 0-25 N: 0-5

C138/MALO/013(A)
160324005 88 (1.617) Cm (87:93-101:104x0.500)




1: TOF MS ES+
2.25e+004

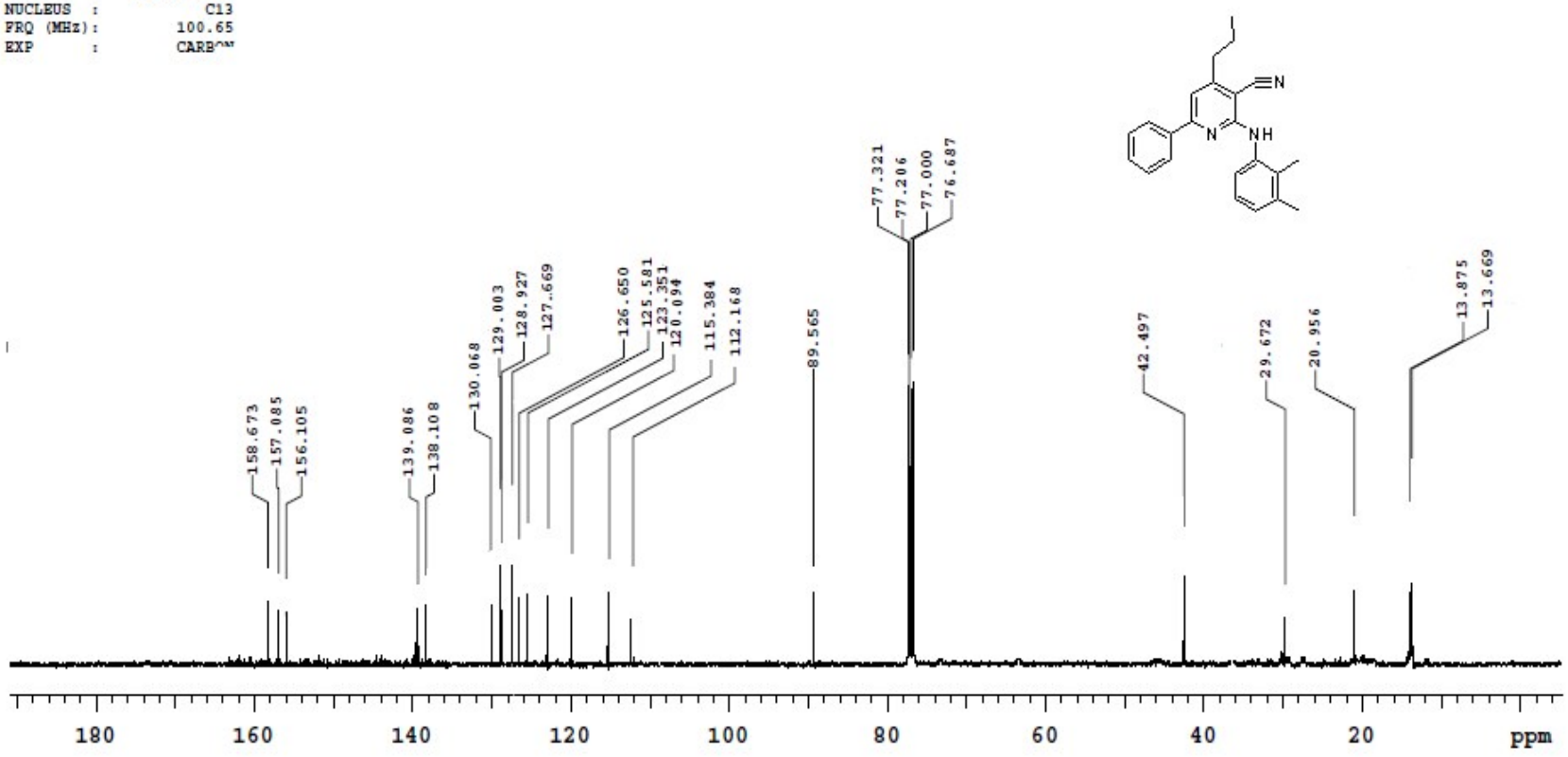



| | | | | | | |
|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Formula |
| 342.1972 | 342.1970 | 0.2 | 0.6 | 13.5 | 17.1 | C23 H24 N3 |

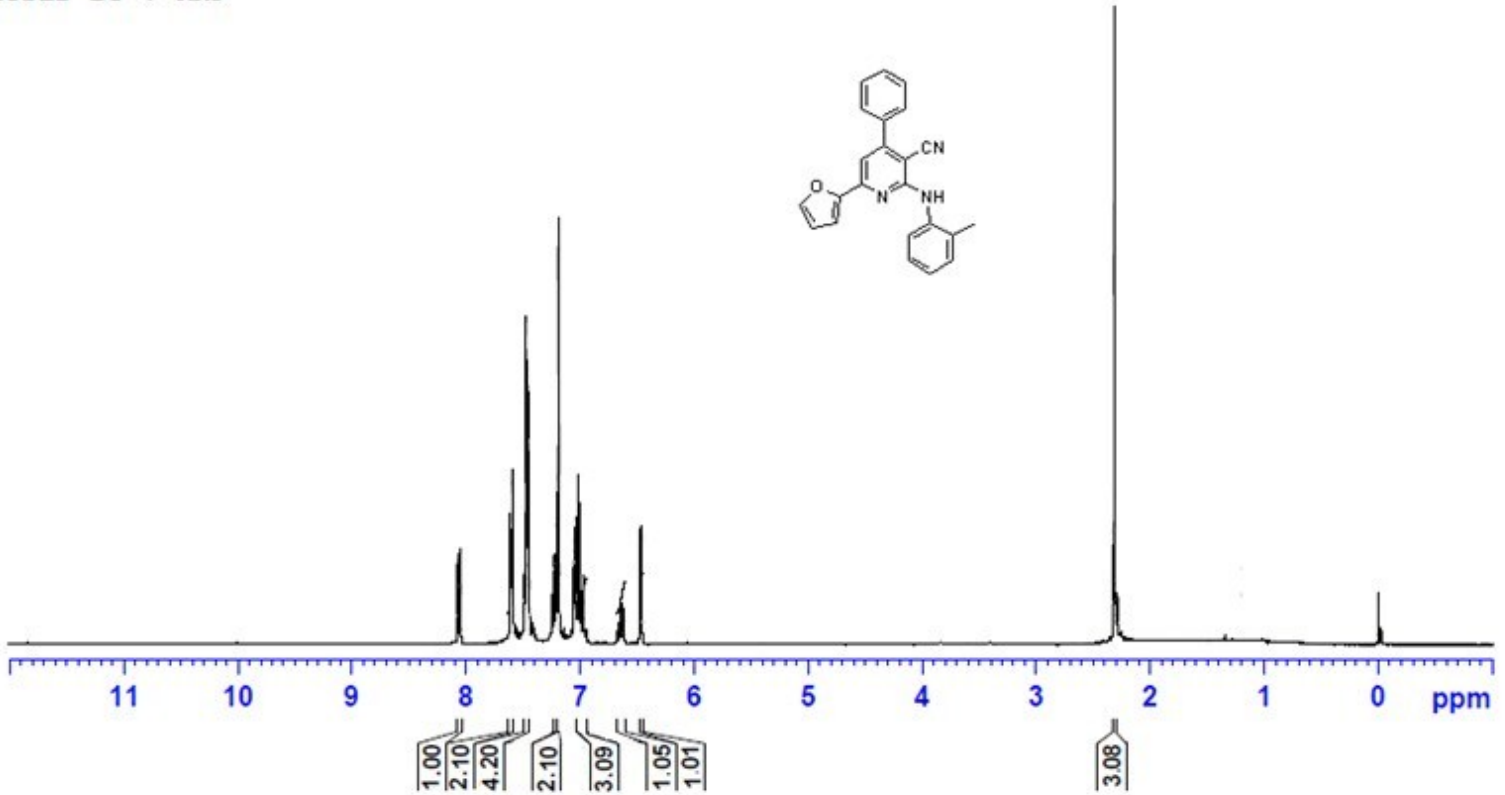
TDC-206 C138/MAL01/013A

A.R.No: ME0216/1202

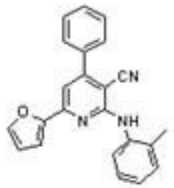
Analyst : Mallikarjun
Solvent : cdcl3
Date : Feb 13 2016
NUCLEUS : C13
FRQ (MHz): 100.65
EXP : CARBON



C138/MAL01/033(A)
1H-NMR\CDC13
01-07-2016
ANALYSED BY : KRP

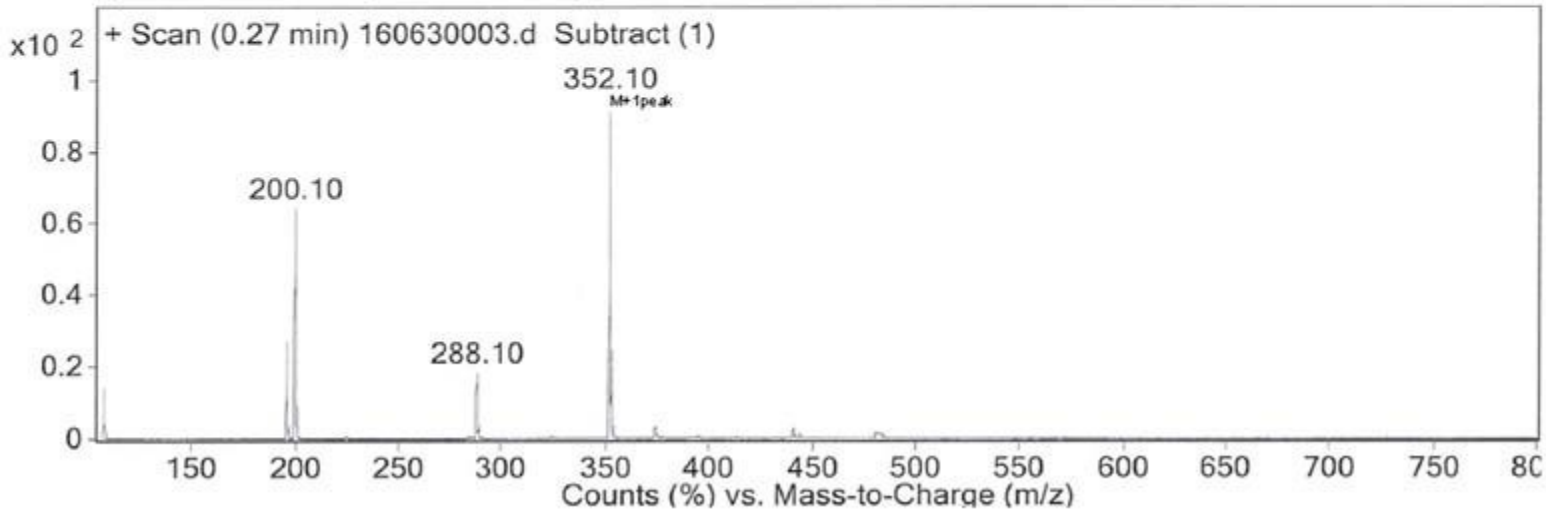


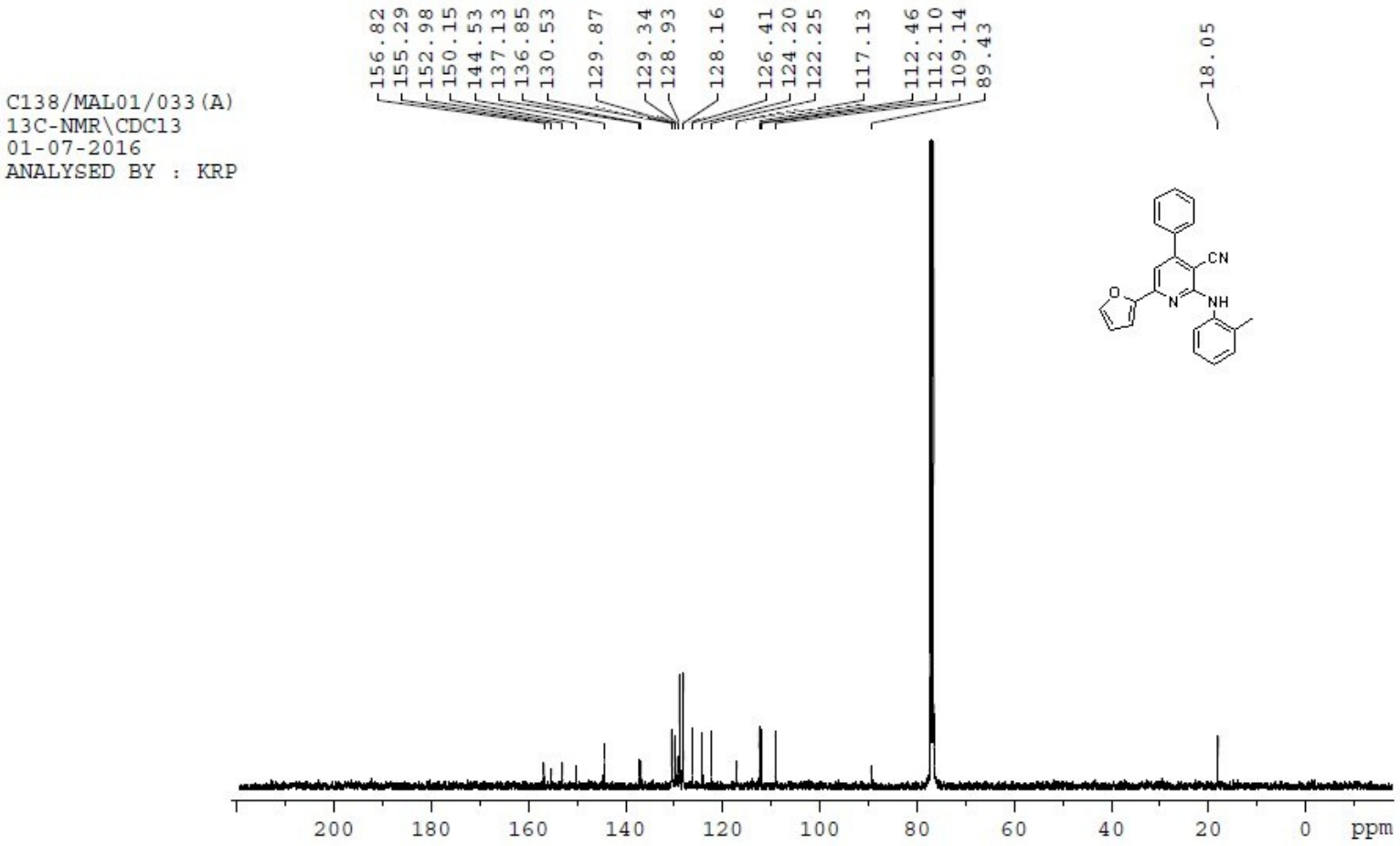
| | | | |
|---|---|---|---|
| **Data Filename** | 160630003.d | **Sample Name** | C138/MALO1/033 A |
| **Sample Type** | Sample | **Position** | Vial 65 |
| **Instrument Name** | Instrument 1 | **User Name** | |
| **Acq Method** | ESI.m | **IRM Calibration Status** | Success |
| **DA Method** | CACH8.m | **Comment** | |



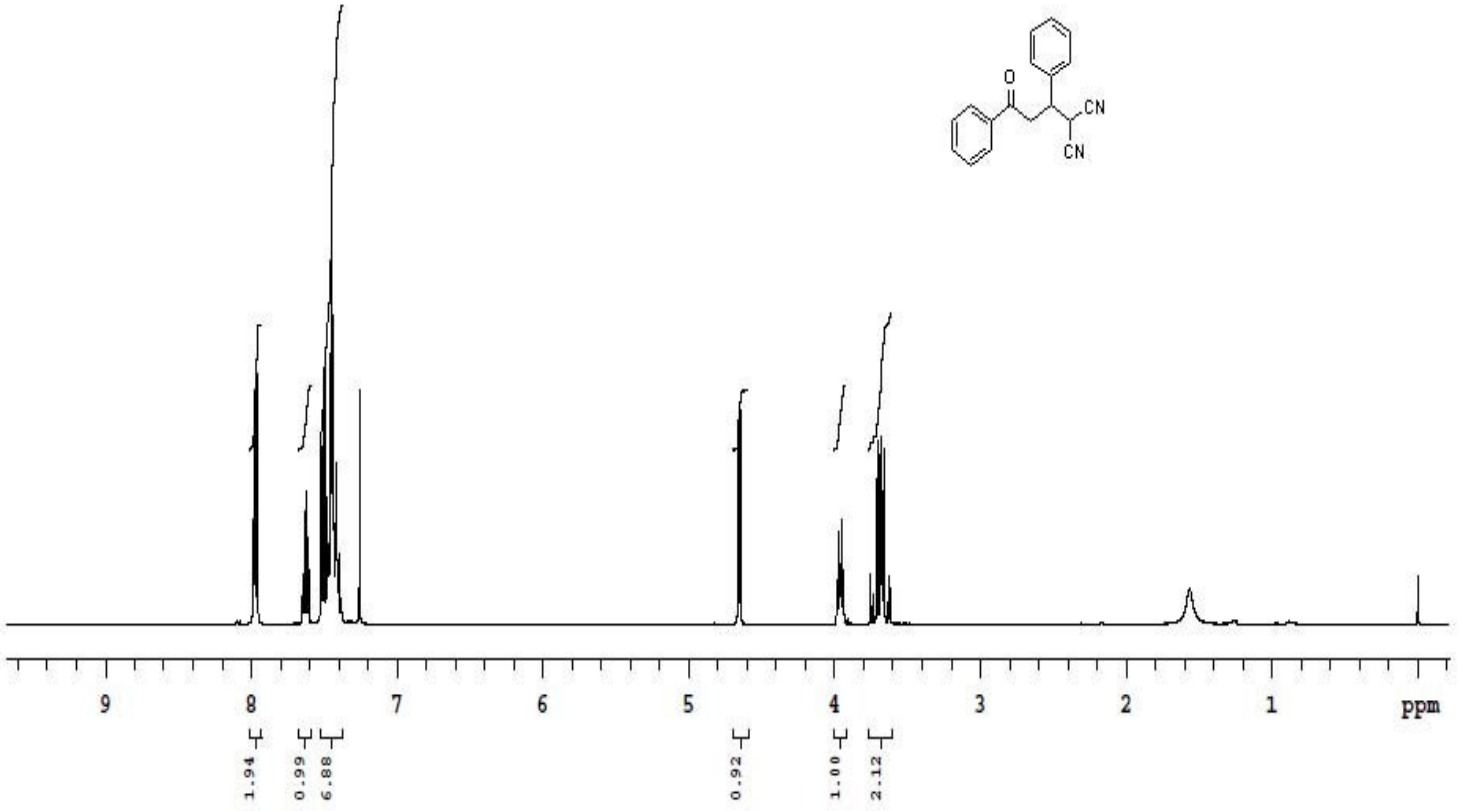

**User Spectra**

| Fragmentor Voltage | Collision Energy | Ionization Mode |
|---|---|---|
| 0 | 0 | Esi |




C138/MAL01/033(A)
13C-NMR\CDCl3
01-07-2016
ANALYSED BY : KRP
156.82
155.29
152.98
150.15
144.53
137.13
136.85
130.53
129.87
129.34
128.93
128.16
126.41
124.20
122.25
117.13
112.46
112.10
109.14
89.43
18.05
CN
NH
O
N
200
180
160
140
120
100
80
60
40
20
0
ppm

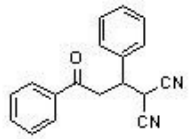
[1]HNMR spectra of compound **6** (Table 1) in $CDCl_3$



CPS,MIYAPUR

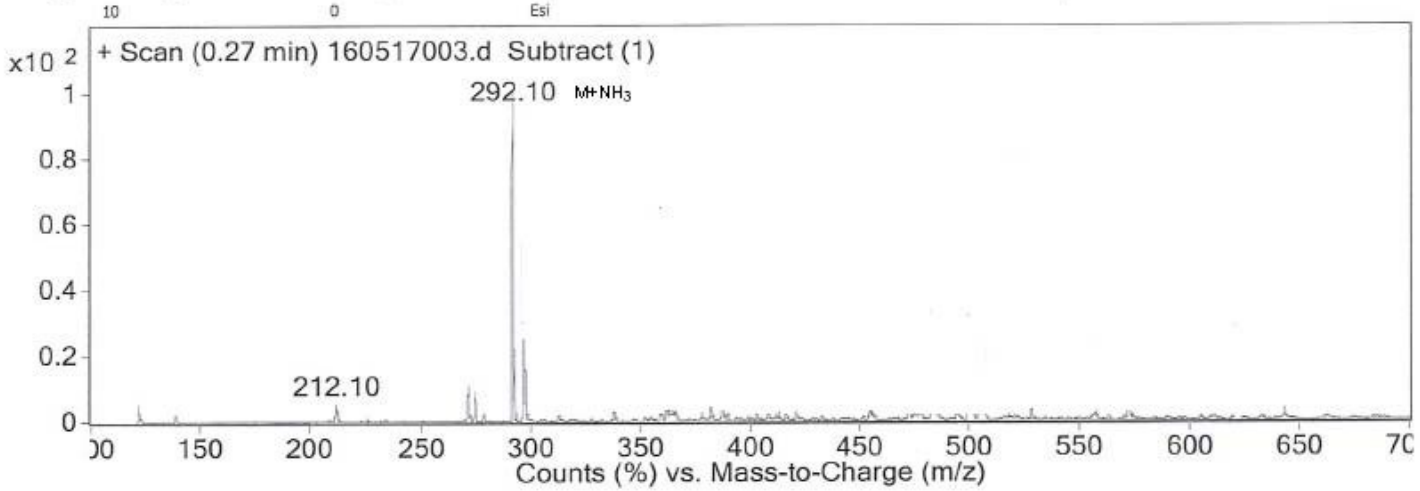
# Mass Analysis Report

| | | | |
|---|---|---|---|
| **Data Filename** | 160517003.d | **Sample Name** | C263/MALO1/056 Int |
| **Sample Type** | Sample | **Position** | Vial 43 |
| **Instrument Name** | Instrument 1 | **User Name** | |
| **Acq Method** | ESI.m | **IRM Calibration Status** | Success |
| **DA Method** | CACH8.m | **Comment** | |

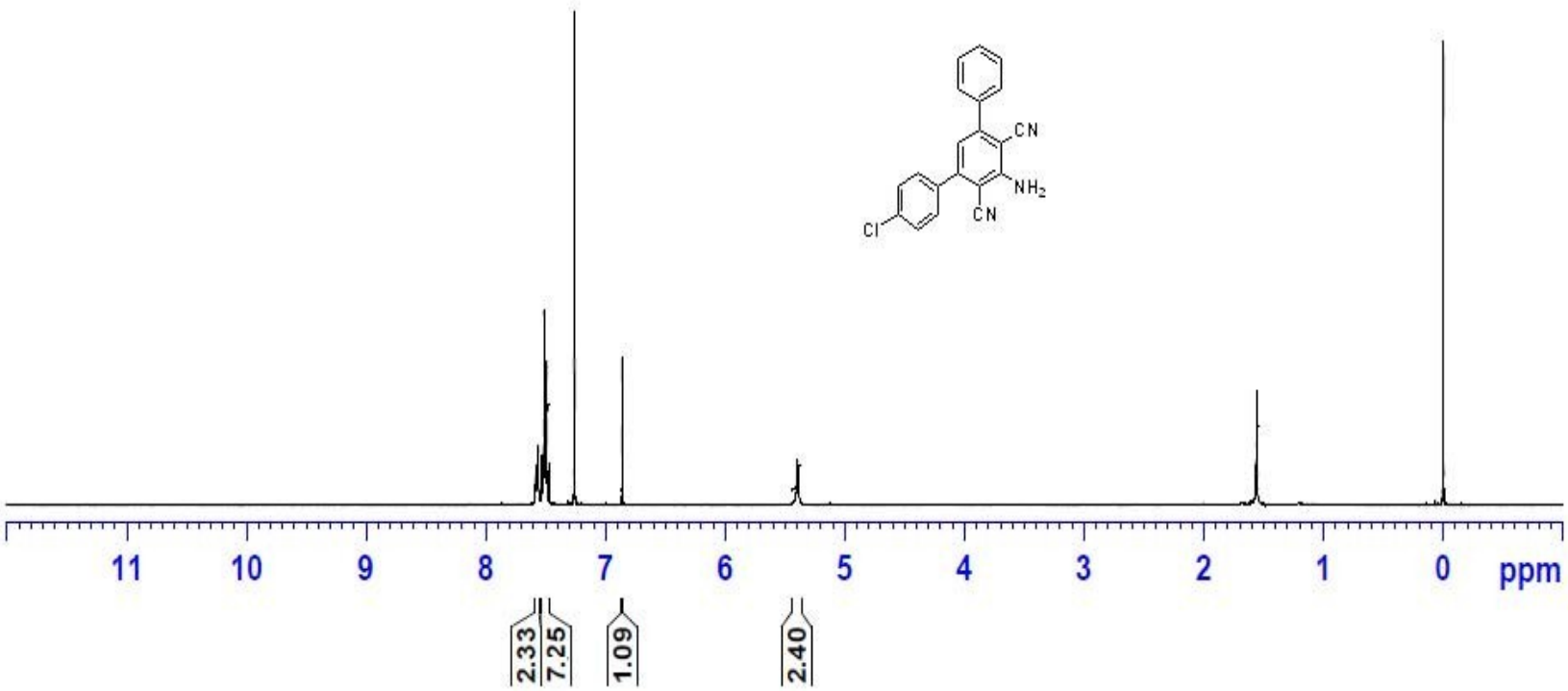



**User Spectra**

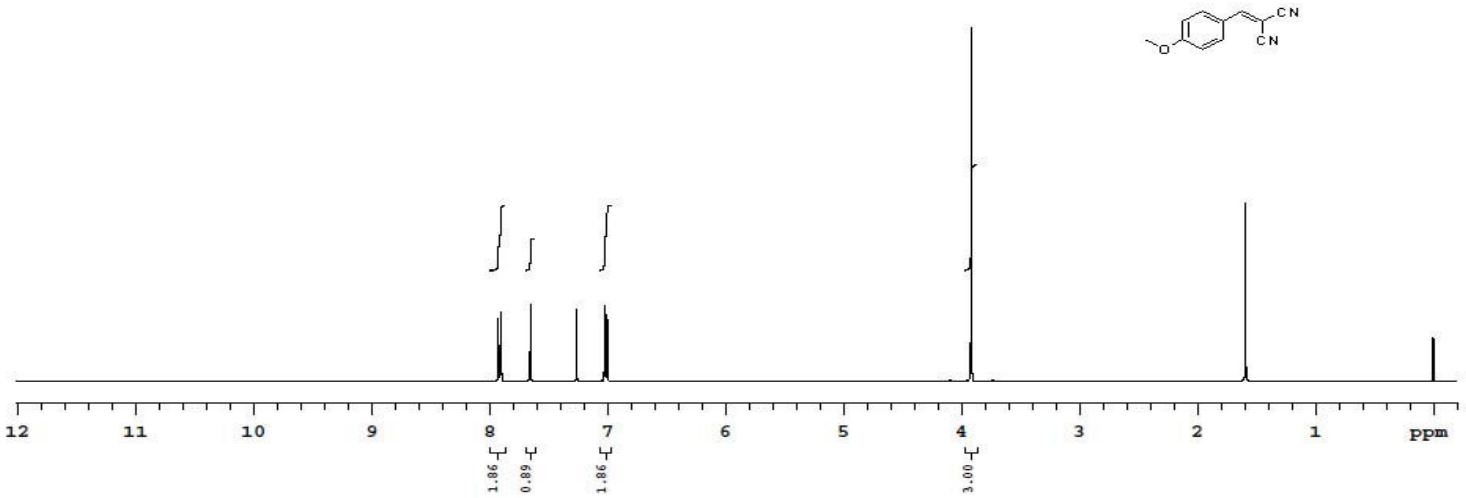
| Fragmentor Voltage | Collision Energy | Ionization Mode |
|---|---|---|
| 10 | 0 | Esi |



$^{1}$HNMR spectra of compound **7** in $CDCl_3$



$^{1}$HNMR spectra of compound **8** in $CDCl_3$



**IR spectra of recovered and fresh $FeF_3$ catalyst**