

Domino Synthesis of Functionalized 1, 6-Naphthyridines and their *in vitro* Anti-inflammatory and Anti-oxidant Efficacies

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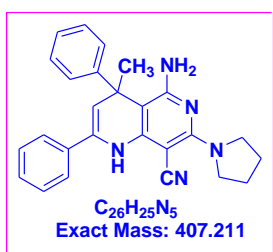
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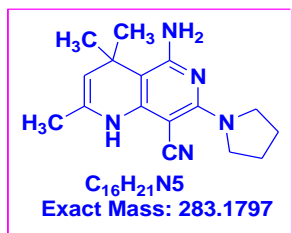
Spectral data of 1, 6-naphthyridines:

5-amino-1, 4-dihydro-4-methyl-2, 4-diphenyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-carbonitrile



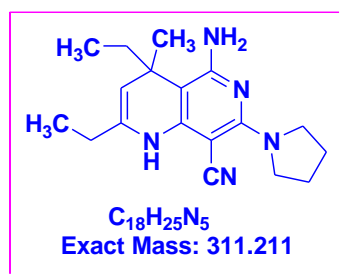
(3a): Pale yellow solid, mp: 184-186 °C. FT-IR (KBr, cm^{-1}): 3493, 3356, 3311, 3230, 2177. 1H -NMR: ($CDCl_3$, 400 MHz): δ 1.66 (3H, s), 1.86-1.84 (4H, m), 3.67-3.62 (4H, m), 3.98 (2H, bs, exchangeable with D_2O), 5.28 (1H, bs, exchangeable with D_2O), 5.35 (1H, s), 7.19-7.15 (2H, m) 7.29-7.25 (6H, m), 7.38 (2H, d, J 8.5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.5, 30.3, 48.5, 57.0, 66.8, 89.7, 124.9, 125.3, 125.6, 127.0, 127.3, 127.9, 128.2, 128.5, 129.6, 132.8, 139.5, 147.7, 154.8, 155.1. ^{13}C NMR (DEPT-135): δ 25.5 (\downarrow), 48.5 (\downarrow). HRMS [EI^+]: Calcd for $C_{26}H_{25}N_5$ m/z 407.211 [M^+], found m/z 407.2110 [M^+].

5-amino-1, 4-dihydro-2, 4, 4-trimethyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-carbonitrile



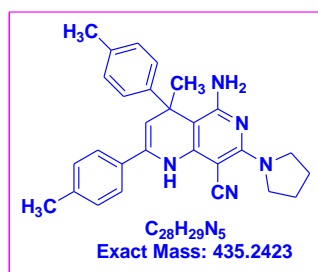
(3b): Orange crystalline solid, mp: 186-188°C, FT-IR (KBr, cm^{-1}): 3493, 3344, 3207, 2179. 1H -NMR: ($CDCl_3$, 400 MHz): δ 1.36 (6H, s), 1.79 (3H, s) 1.91-1.88 (4H, m), 3.66 (4H, t, J 6.5), 4.20 (1H, s), 4.70 (2H, bs), 5.89 (1H, bs). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.1, 25.5, 26.4, 31.0, 31.9, 48.4, 66.6, 94.1, 110.3, 119.9, 126.9, 149.2, 156.0, 157.8. HRMS [EI^+]: Calcd for $C_{16}H_{21}N_5$ m/z 283.1797 [M^+] found m/z 283.1790 [M^+].

5-amino-2, 4-diethyl-1, 4-dihydro-4-methyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-dicarbonitrile



(3c): Orange crystalline solid, mp: 134-136 °C. FT-IR (KBr, cm⁻¹): 3493, 3352, 3207, 2177. ¹H-NMR: (CDCl₃, 400 MHz): δ 0.76 (3H, t, J 7.2), 1.12 (3H, t, J 7.5), 1.36 (3H, s), 1.69-1.54 (1H, m), 1.94-1.85 (5H, m), 2.13, 2.12 (2H, q, J 14.7, J 7.3), 3.67 (4H, bs), 3.99 (1H, bs), 4.65 (2H, bs), 5.88 (1H, bs). ¹³C NMR (CDCl₃, 100 MHz): δ 10.4, 11.7, 25.5, 25.9, 30.6, 35.0, 36.7, 48.4, 66.5, 91.4, 106.8, 120.1, 134.3, 150.4, 156.0, 157.8. HRMS [EI⁺]: Calcd for C₁₈H₂₅N₅ m/z 311.211 [M⁺], found m/z 311.2100 [M⁺].

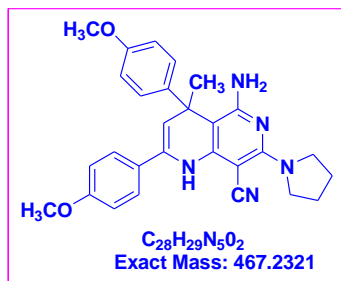
5-amino-1, 4-dihydro-4-methyl-7-(pyrrolidin-1-yl)-2, 4-dip-tolyl-1, 6-naphthyridine-8-dicarbonitrile



(3d): Pale yellow solid, mp: 152-154 °C. FT-IR (KBr, cm⁻¹): 3485, 3298, 3232, 2189. ¹H-NMR: (CDCl₃, 400 MHz): δ 1.71 (3H, s), 1.92 (4H, bs), 2.32 (3H, s), 2.36 (3H, s), 3.71 (4H, bs), 4.09 (2H, bs), 5.32 (1H, bs), 5.38 (1H, s), 7.15, 7.14 (4H, d d J 7.5, J 3.1), 7.20 (2H, d, J 7.5), 7.32 (2H, d J 7.9). ¹³C NMR (CDCl₃, 100 MHz): δ 20.9, 21.2, 25.5, 30.3, 48.5, 56.8, 66.8, 89.7, 120.1, 124.9, 125.5, 128.1, 129.1, 132.5, 136.6, 137.7, 144.9, 154.8, 155.1, 156.8. HRMS [EI⁺]: Calcd for C₂₈H₂₉N₅ m/z 435.2423[M⁺], found m/z 435.2420

[M⁺].

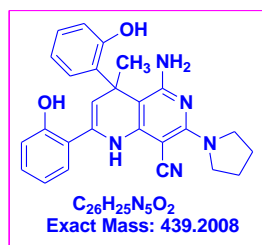
5-amino-1, 4-dihydro-2, 4-bis (4-methoxyphenyl)-4-methyl-7-(pyrrolidin-1-yl) 1, 6-naphthyridinepyridine-8-carbonitrile



(3e): Pale yellow solid, mp: 120-122 °C. FT-IR (KBr, cm⁻¹): 3491, 3400, 3296, 2189. ¹H-NMR: (CDCl₃, 400 MHz): δ 1.70 (3H, s), 1.91 (4H, bs), 3.70 (4H, bs), 3.79 (3H, s), 3.82 (3H, s), 4.11 (2H, bs), 5.28 (1H, bs), 5.33 (1H, s), 6.87 (4H, t, J 7.8), 7.23 (2H, m), 7.35 (2H, d, J 8.2). ¹³C NMR (CDCl₃, 100 MHz): δ 23.2, 25.4, 30.1, 35.5, 48.5, 56.5, 66.7, 89.7, 113.7, 113.8, 120.1, 125.3, 126.2, 129.4, 131.7, 132.0, 139.9, 154.9, 155.0, 156.8, 158.4, 159.3.

HRMS [EI⁺]: Calcd for C₂₈H₂₉N₅O₂ m/z 467.2321 [M⁺], found m/z 467.2320 [M⁺].

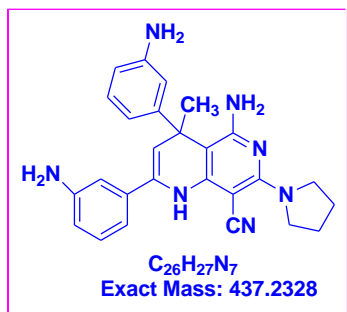
5-amino-1, 4-dihydro-2, 4-bis (2-hydroxyphenyl)-4-methyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-dicarbonitrile



(3f): Pale yellow solid, mp: 172-174 °C. FT-IR (KBr, cm⁻¹): 3491, 3300, 3230, 2191. ¹H-NMR: (CDCl₃, 400 MHz): δ 1.71 (3H, s), 1.93 (4H, bs), 3.71 (4H, bs), 4.04 (2H, bs), 5.31 (1H, bs), 5.38 (1H, s), 7.24 (2H, d, J

8.1), 7.29 (2H, d, J 8.5), 7.35-7.32 (4H, m). ^{13}C NMR (CDCl_3 , 100 MHz): δ 25.4, 30.2, 31.6, 48.5, 56.6, 66.9, 89.4, 119.8, 125.3, 126.3, 126.6, 128.6, 128.7, 129.5, 129.7, 132.3, 132.9, 134.0, 137.6, 146.1, 154.6, 155.1, 156.7. HRMS $[\text{EI}^+]$: Calcd for $\text{C}_{26}\text{H}_{25}\text{N}_5\text{O}_2$ m/z 439.2008 $[\text{M}^+]$, found m/z 439.2005 $[\text{M}^+]$.

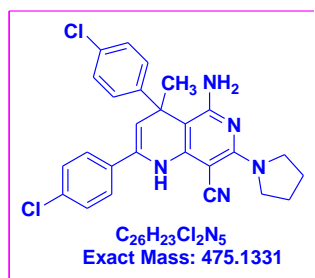
5-amino-2, 4-bis (3-aminophenyl)-1, 4-dihydro-4-methyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-carbonitrile



(3g): Dark red solid, mp: 200-202 °C. FT-IR (KBr, cm^{-1}): 3471, 3460, 3441, 3367, 3321, 2185. ^1H -NMR: (CDCl_3 , 400 MHz): δ = 1.69 (3H, s), 1.93 (5H, bs), 3.74 (8H, bs), 4.30-4.09 (2H, m), 5.38 (1H, s), 6.58-6.55 (2H, m), 6.68-6.62 (2H, d d, J 7.9, J 1.7), 6.72 (1H, s), 6.79 (1H, d, J 7.6), 7.12 (2H, t, J 7.7). ^{13}C NMR (CDCl_3 , 100 MHz): δ 25.5, 26.1, 30.3, 48.7, 57.1, 66.7, 89.5, 111.9, 113.8, 114.7, 115.1, 118.3, 120.0, 125.2, 129.4, 129.6, 132.3, 140.7, 146.5,

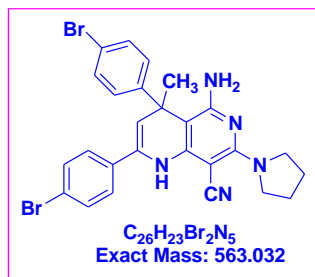
146.6, 149.0, 155.0, 156.6. HRMS $[\text{EI}^+]$: Calcd for $\text{C}_{26}\text{H}_{27}\text{N}_7$ m/z 437.2328 $[\text{M}^+]$, found m/z 437.2327 $[\text{M}^+]$.

5-amino-2, 4-bis (4-chlorophenyl)-1, 4-dihydro-4-methyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-carbonitrile



(3h): Pale yellow solid, mp: 174-176 °C. FT-IR (KBr, cm^{-1}): 3506, 3300, 3230, 2191. ^1H -NMR: (CDCl_3 , 400 MHz): δ 1.71 (3H, s), 1.93 (4H, bs), 3.71 (4H, s), 4.04 (2H, bs), 5.31 (1H, bs), 5.38 (1H, s), 7.33 (8H, m). ^{13}C NMR (CDCl_3 , 100 MHz): δ 25.4, 30.2, 48.5, 56.7, 66.9, 89.4, 119.8, 125.3, 126.3, 126.6, 128.7, 129.5, 132.3, 132.9, 134.0, 137.7, 146.0, 155.1, 156.8. HRMS $[\text{EI}^+]$: Calcd for $\text{C}_{26}\text{H}_{23}\text{Cl}_2\text{N}_5$ m/z 475.1331 $[\text{M}^+]$, found m/z 475.1330 $[\text{M}^+]$.

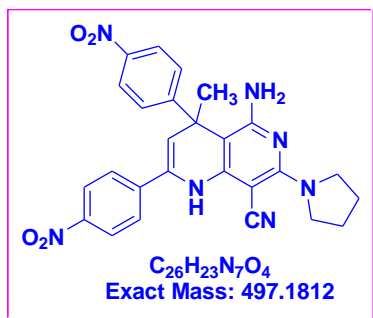
5-amino-2, 4-bis (4-bromophenyl)-1, 4-dihydro-4-methyl-7-(pyrrolidin-1-yl)-1, 6-naphthyridine-8-carbonitrile



(3i): Pale yellow solid, mp: 148-150 °C. FT-IR (KBr, cm^{-1}): 3491, 3298, 3232, 2187. ^1H -NMR: (CDCl_3 , 400 MHz): δ 1.58, (3H, s), 1.93 (4H, bs), 3.70 (4H, bs), 4.03 (2H, bs), 5.31 (1H, bs), 5.38 (1H, s), 7.18 (2H, d, J 7.1), 7.28 (2H, s), 7.51-7.44 (4H, m). ^{13}C NMR (CDCl_3 , 100 MHz): δ 25.5, 29.7, 30.2, 48.6, 56.8, 66.8, 89.2, 121.2, 122.3, 125.4, 126.4, 126.7, 126.9, 129.8, 131.7, 137.9, 146.5, 154.7, 155.1, 156.7. HRMS $[\text{EI}^+]$: Calcd for $\text{C}_{26}\text{H}_{23}\text{Br}_2\text{N}_5$ m/z 563.032

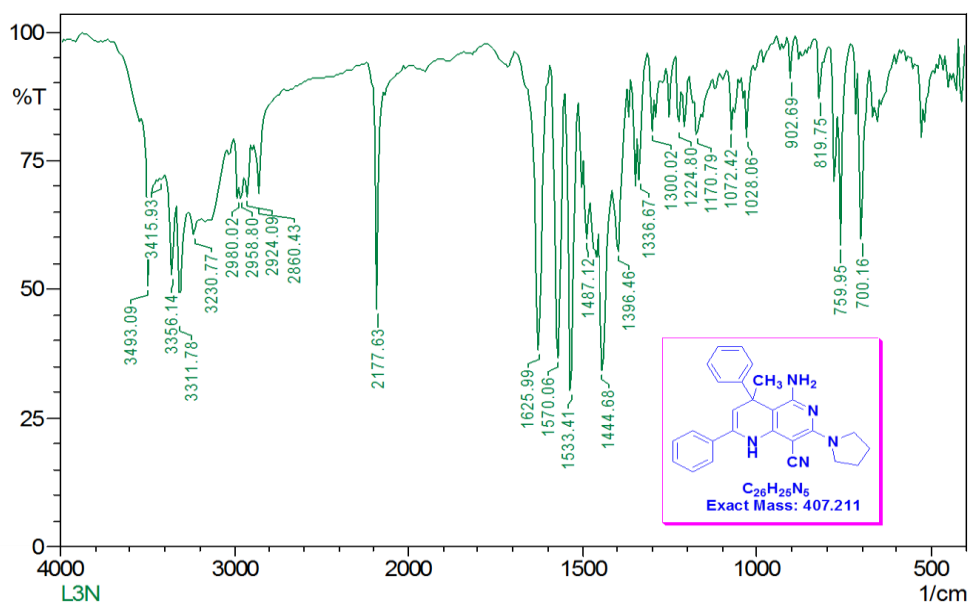
$[\text{M}^+]$, found m/z 563.0310 $[\text{M}^+]$.

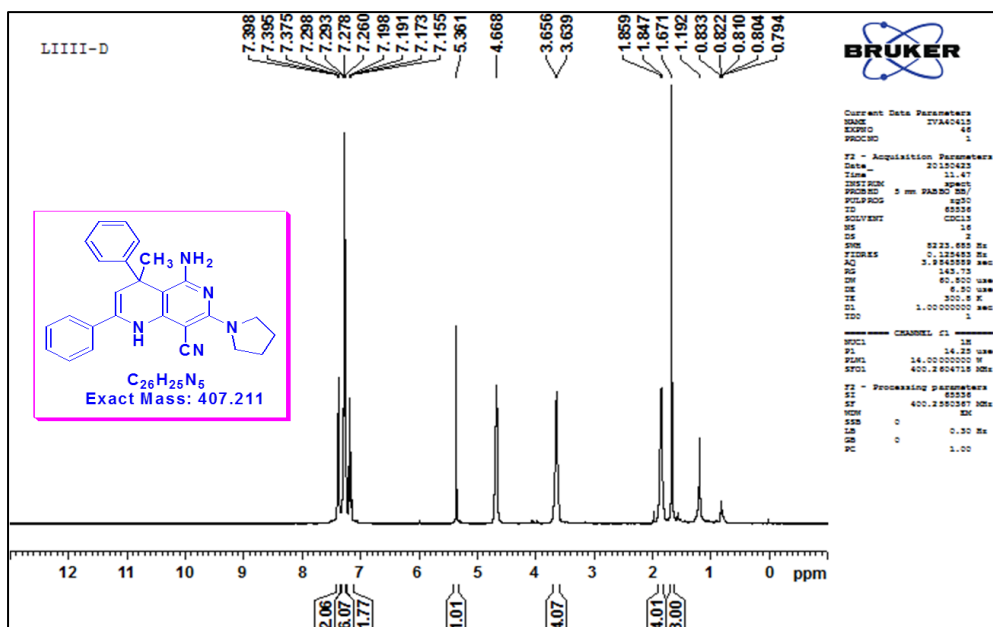
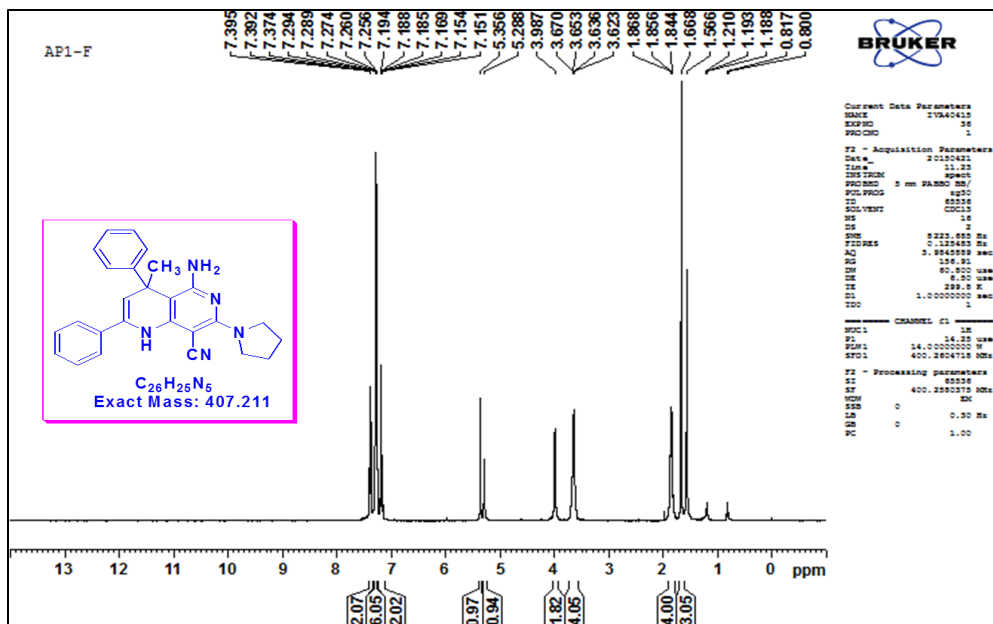
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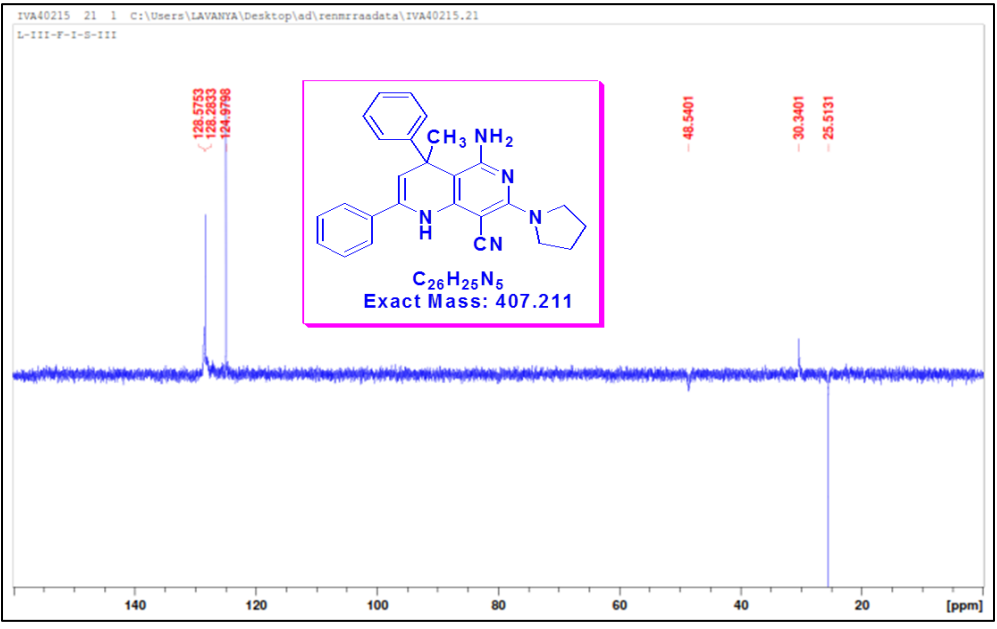
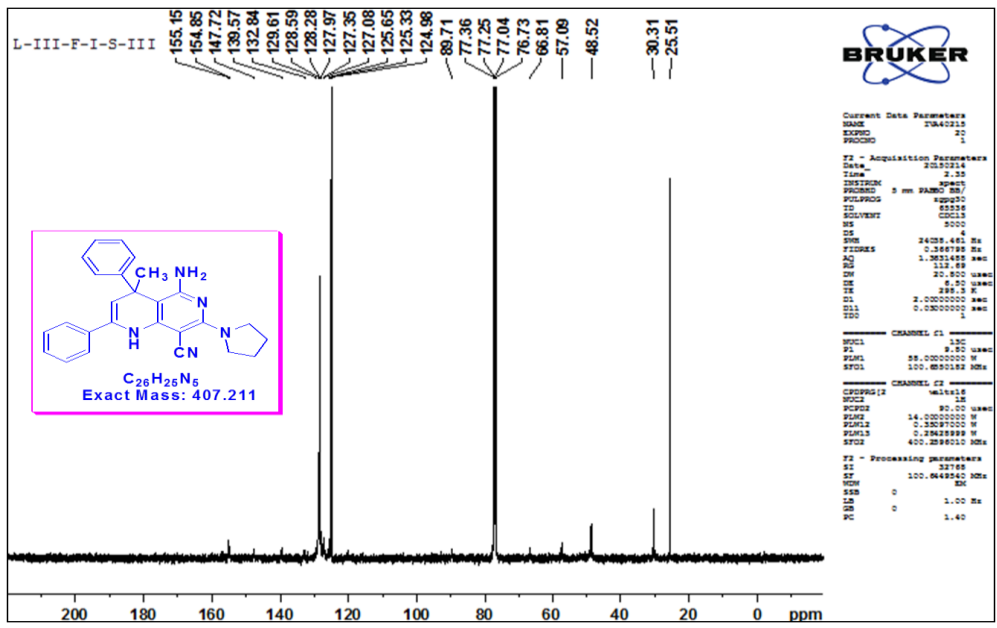


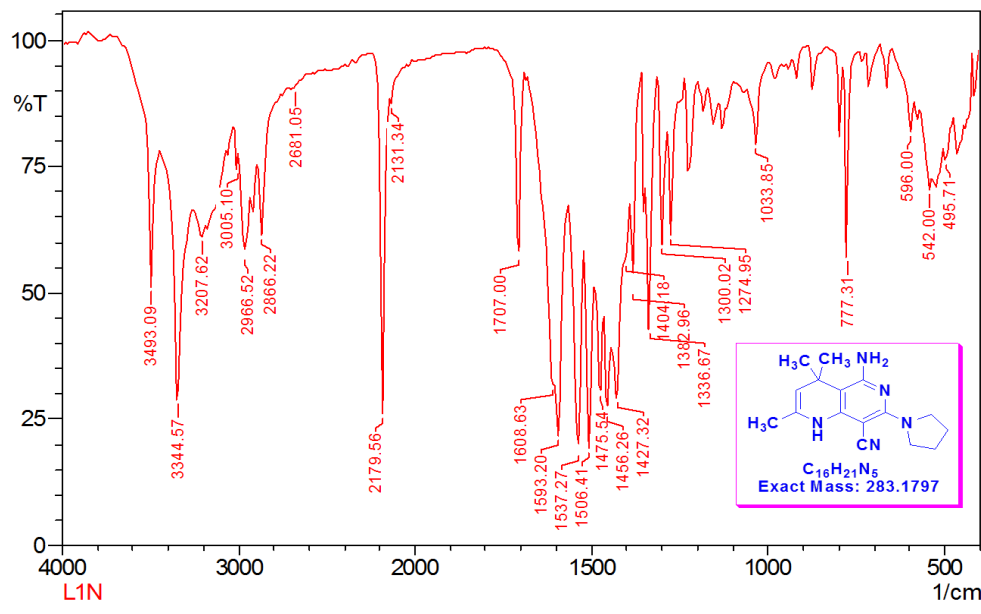
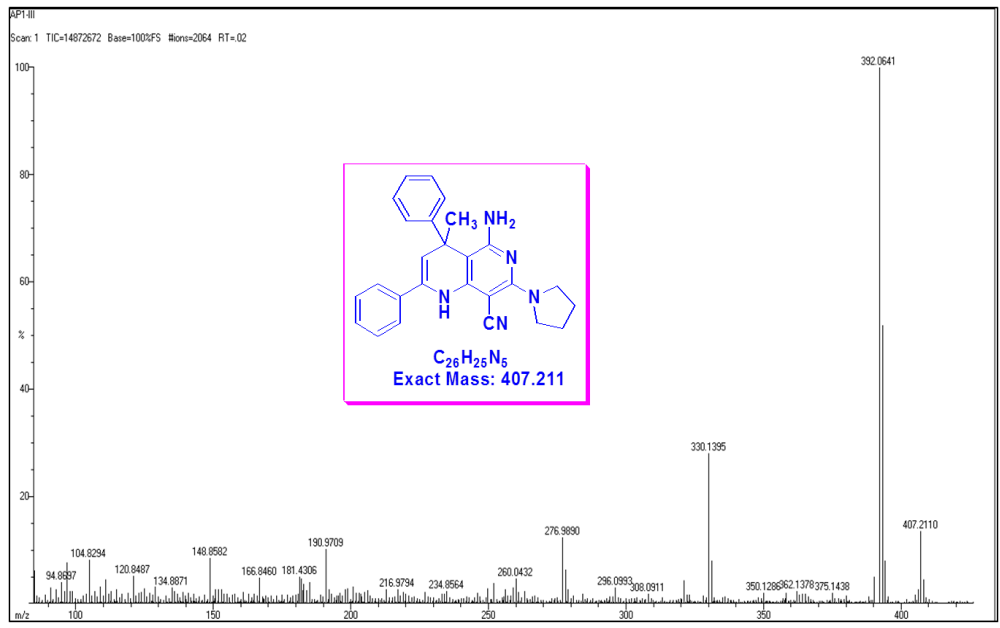
(3j): Dark red solid, mp: 202-204 °C. FT-IR (KBr, cm⁻¹): 3491, 3388, 3300, 2191. ¹H-NMR: (CDCl₃, 400 MHz): δ 1.80 (3H, s), 1.97 (4H, bs), 3.74 (4H, bs), 3.95 (2H, bs), 5.43 (1H, bs), 5.56 (1H, s), 7.47 (2H, d, J 8.1), 7.56 (2H, d, J 8.6), 8.22 (4H, t, J 7.4). ¹³C NMR (CDCl₃, 100 MHz): δ 25.4, 29.7, 30.3, 48.7, 57.0, 67.1, 89.1, 113.7, 123.8, 123.9, 124.3, 125.7, 125.9, 129.0, 130.8, 133.0, 145.4, 147.0, 147.7, 154.4, 155.2. HRMS [EI⁺]: Calcd for C₂₆H₂₃N₇O₄ m/z 497.1812 [M⁺], found m/z 497.1810

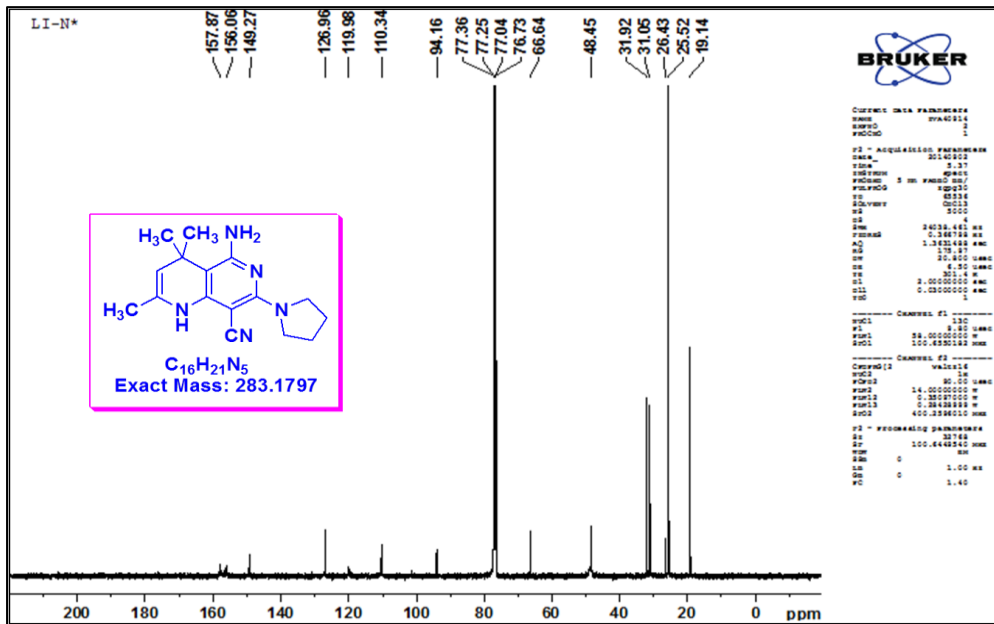
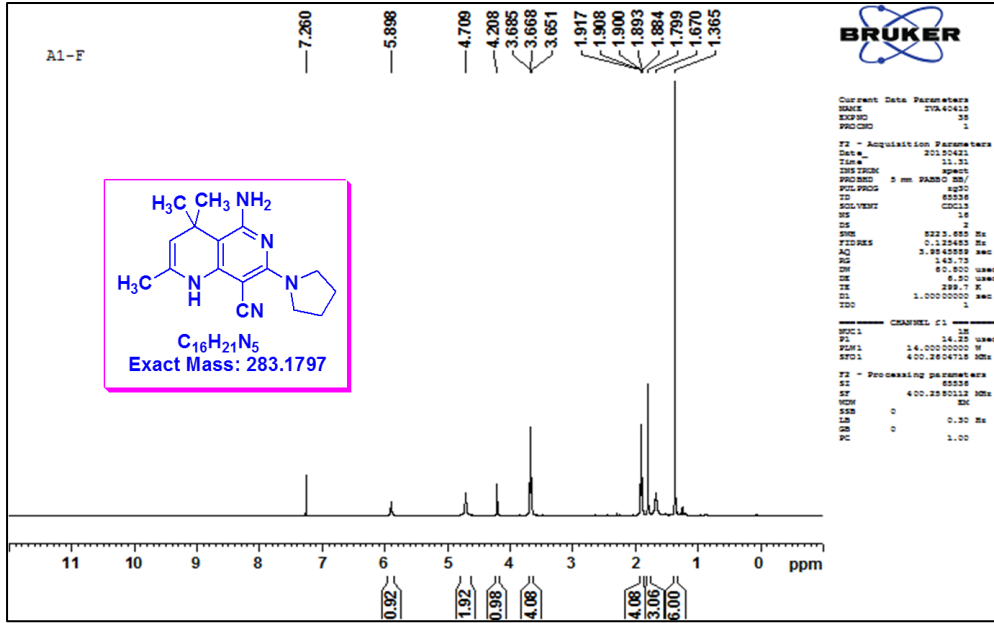
[M⁺].

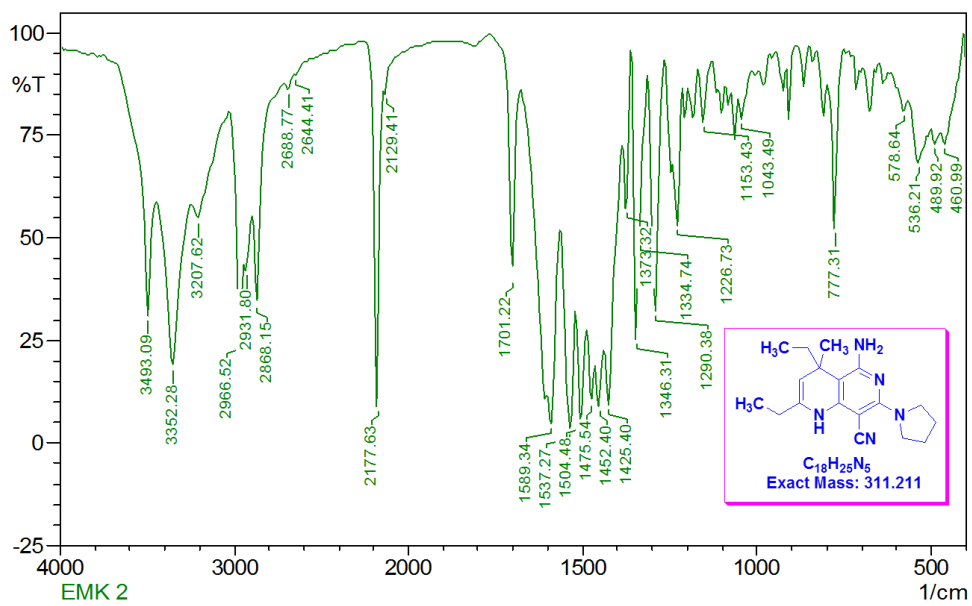
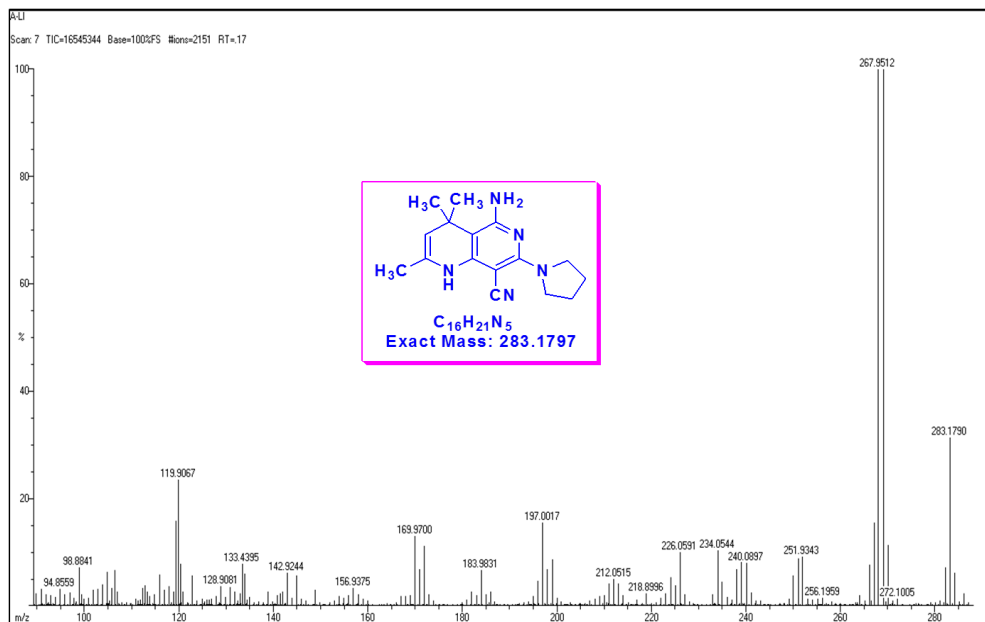


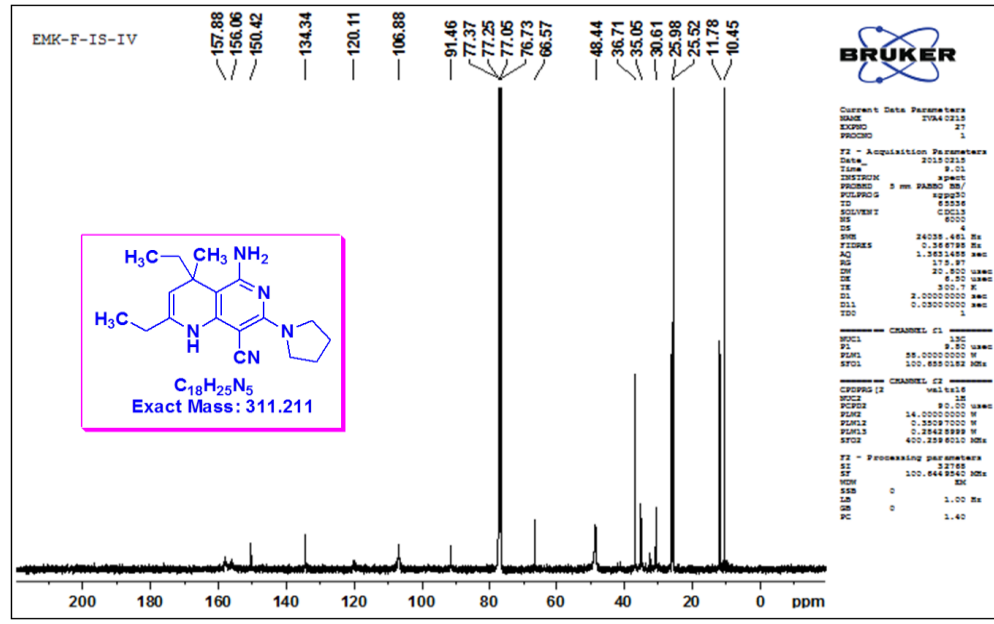
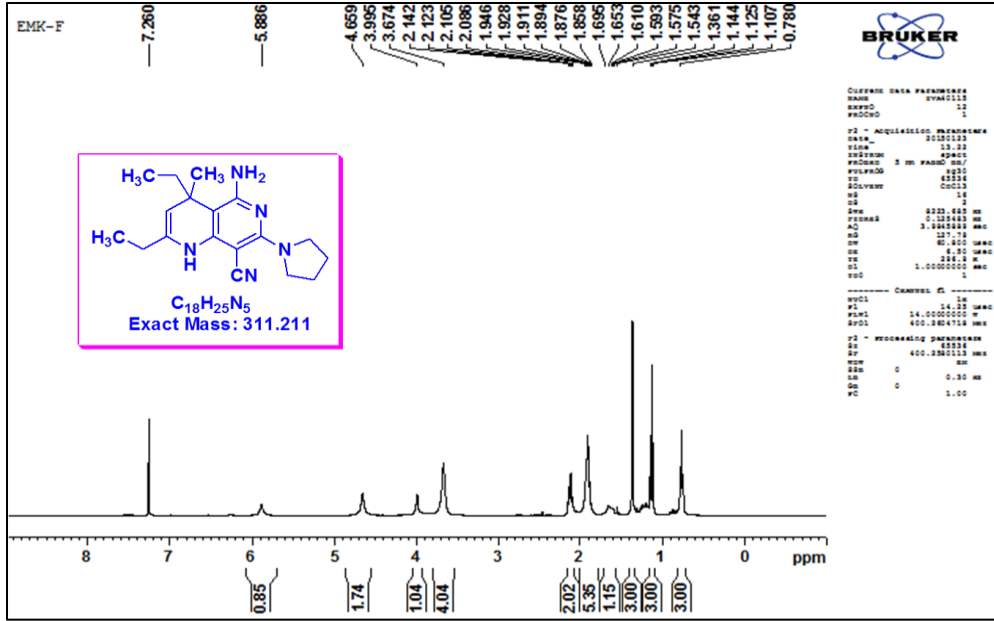


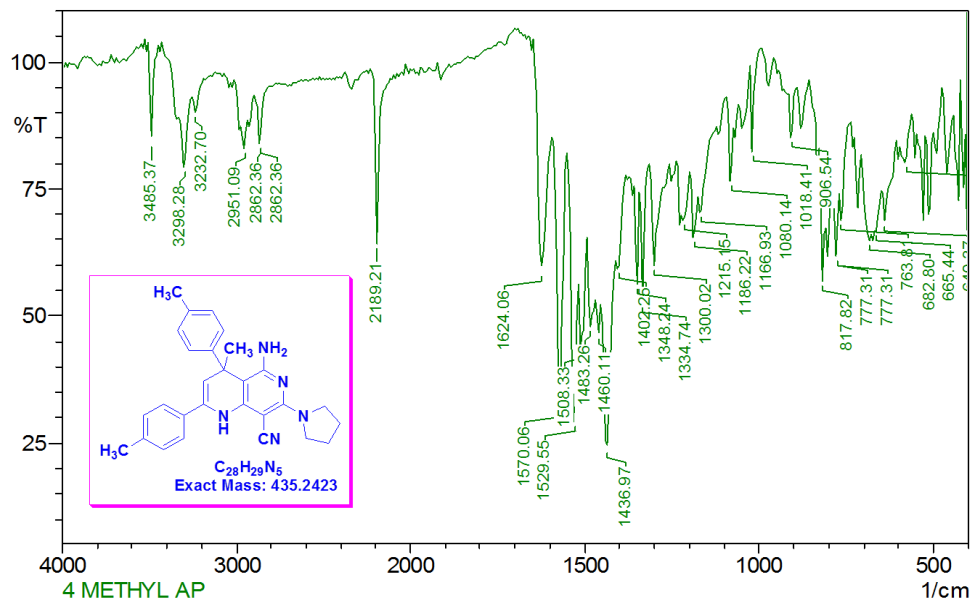
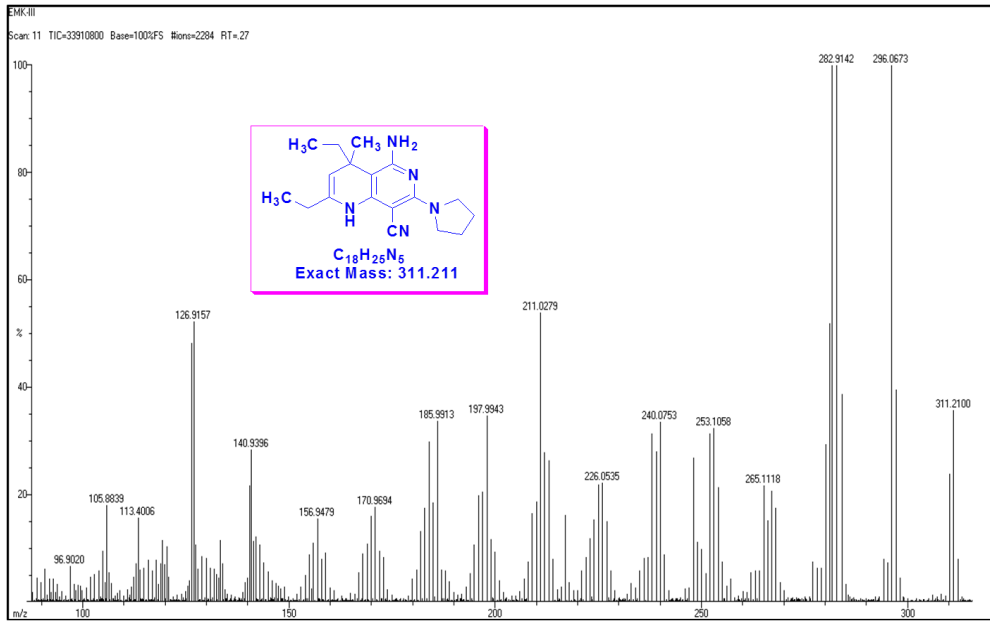


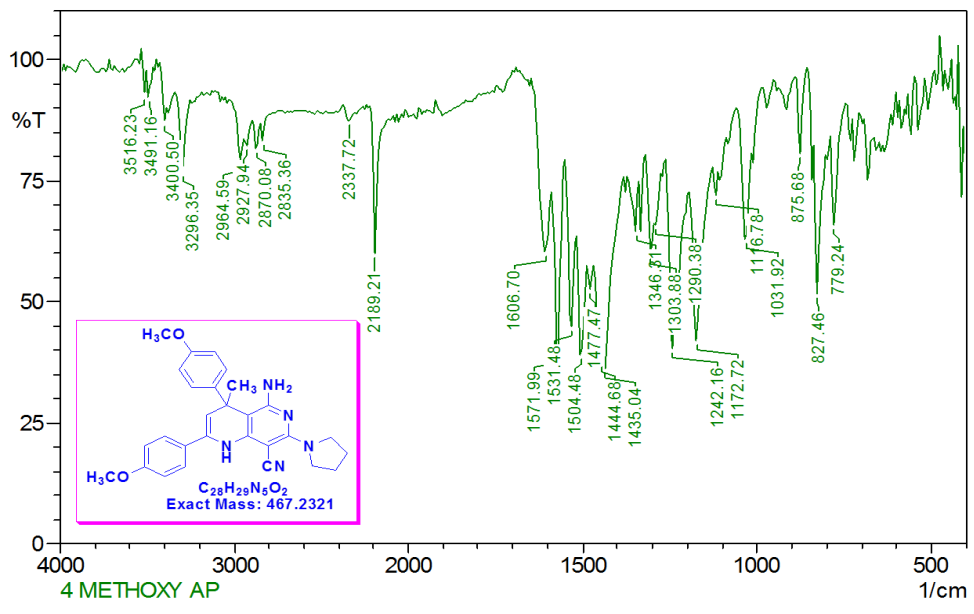
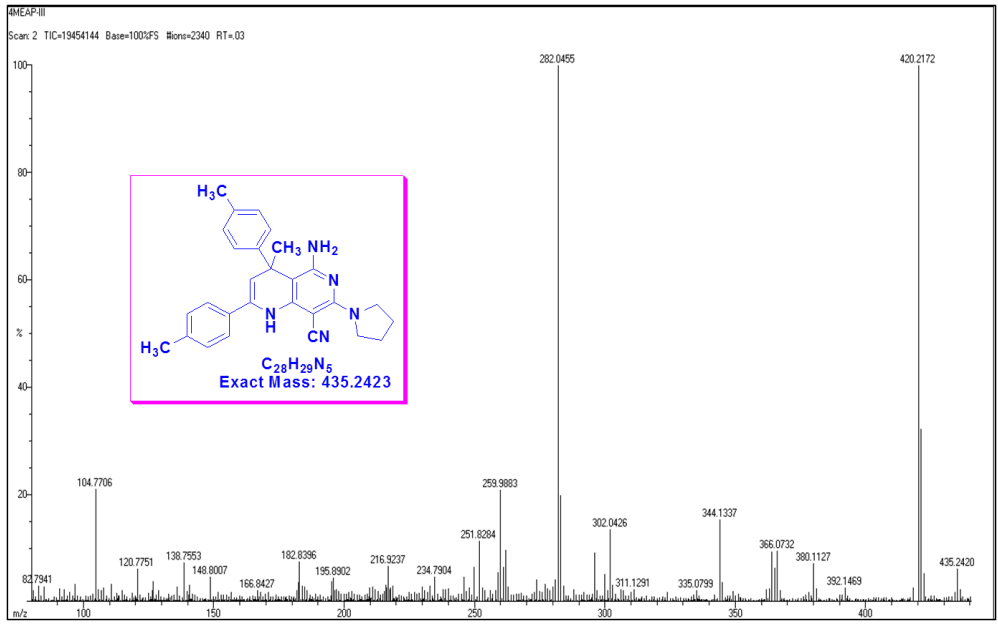


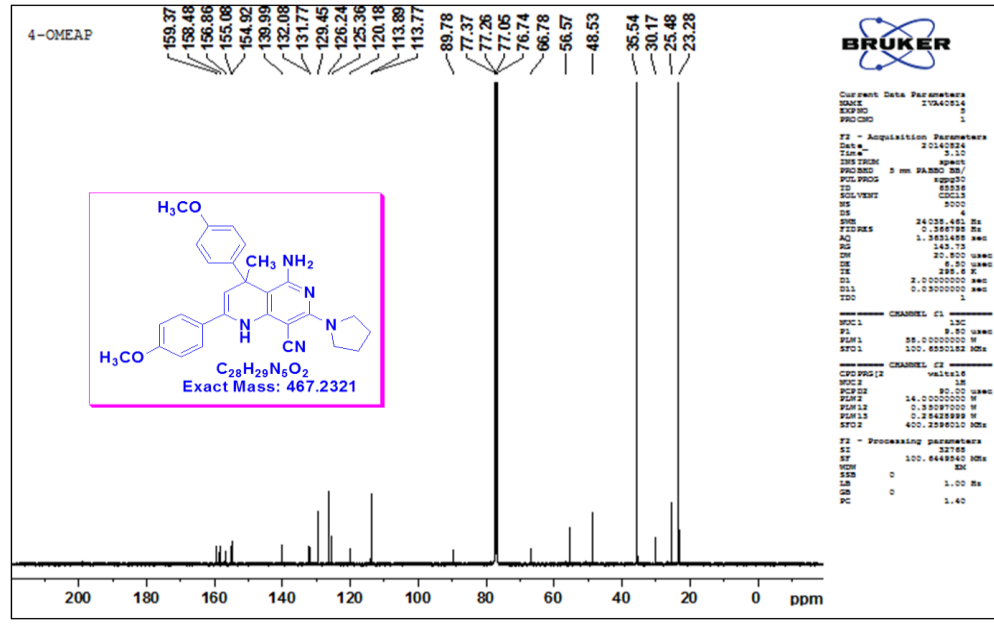
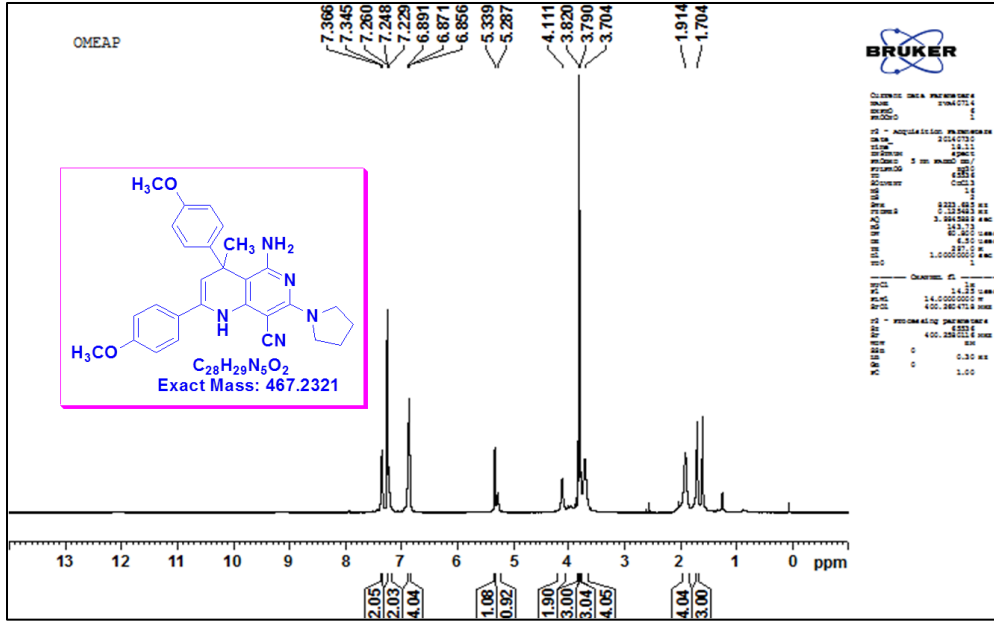


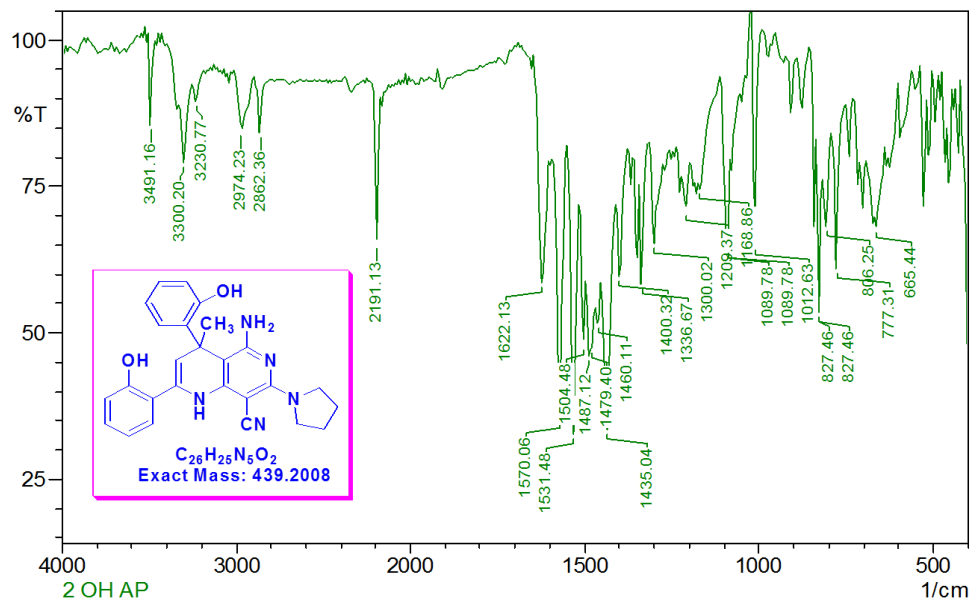
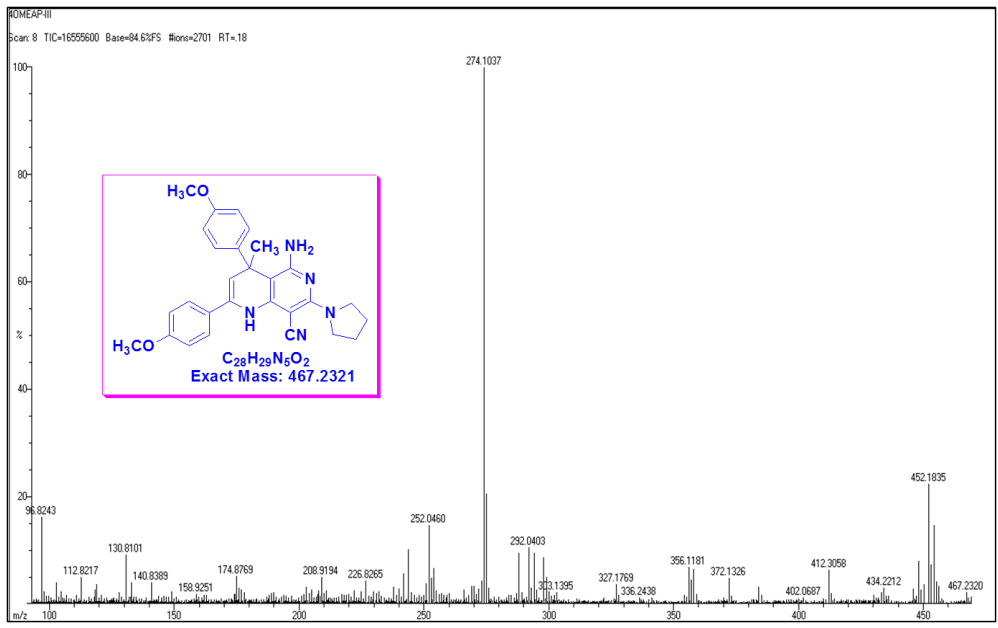


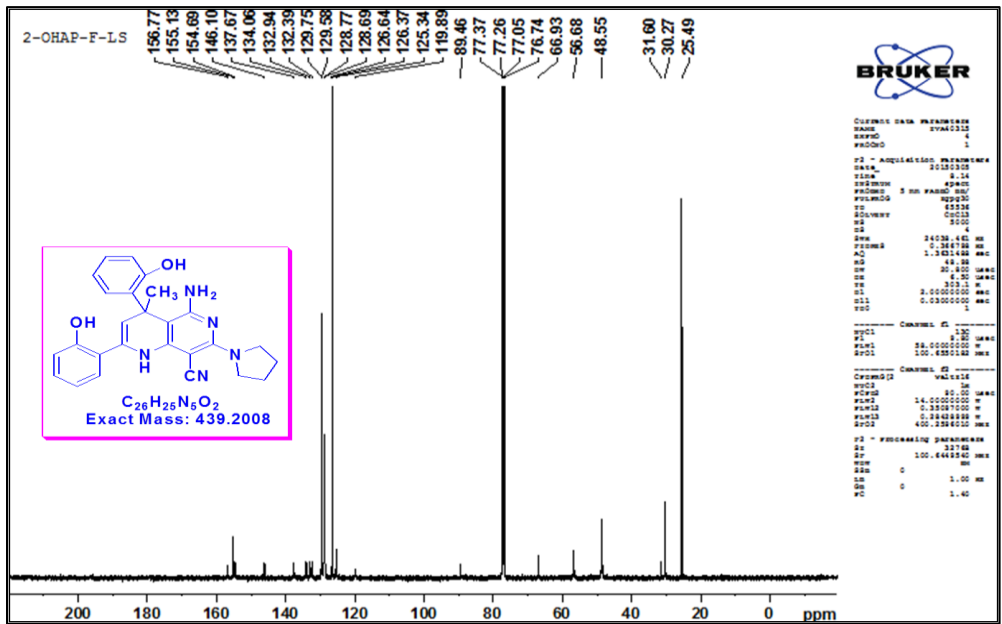
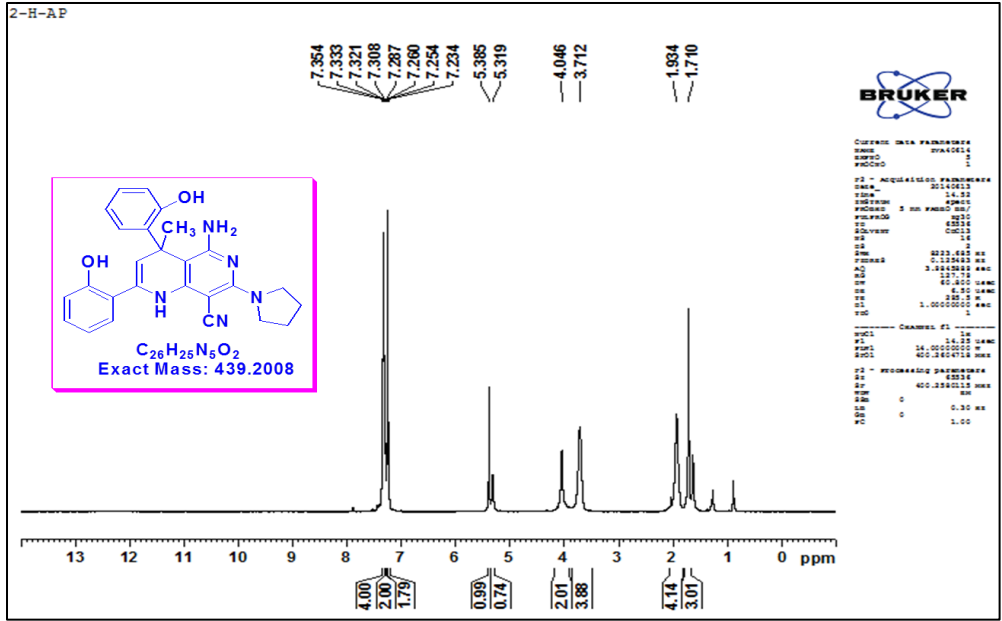


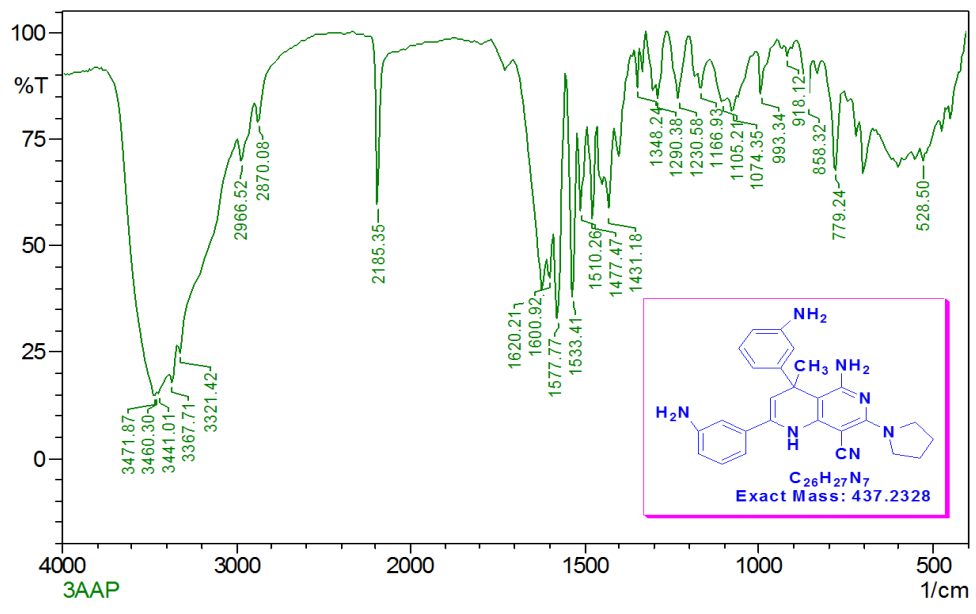
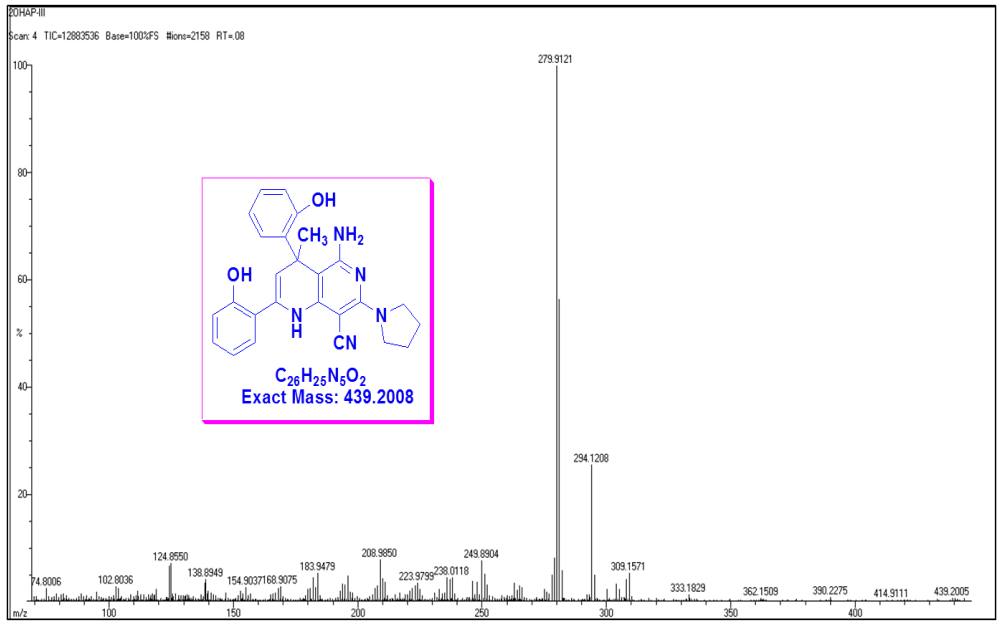


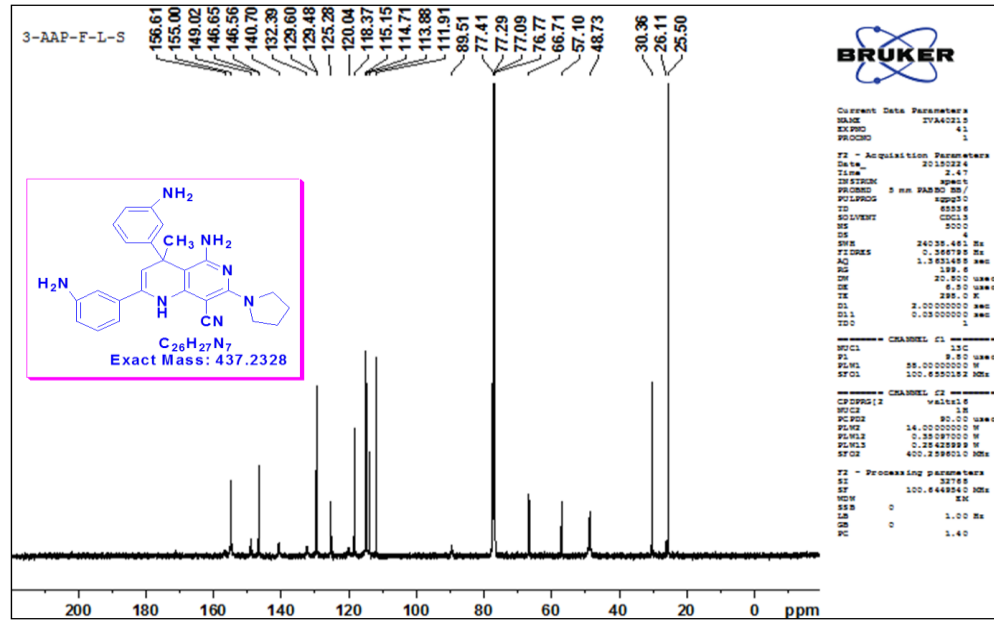
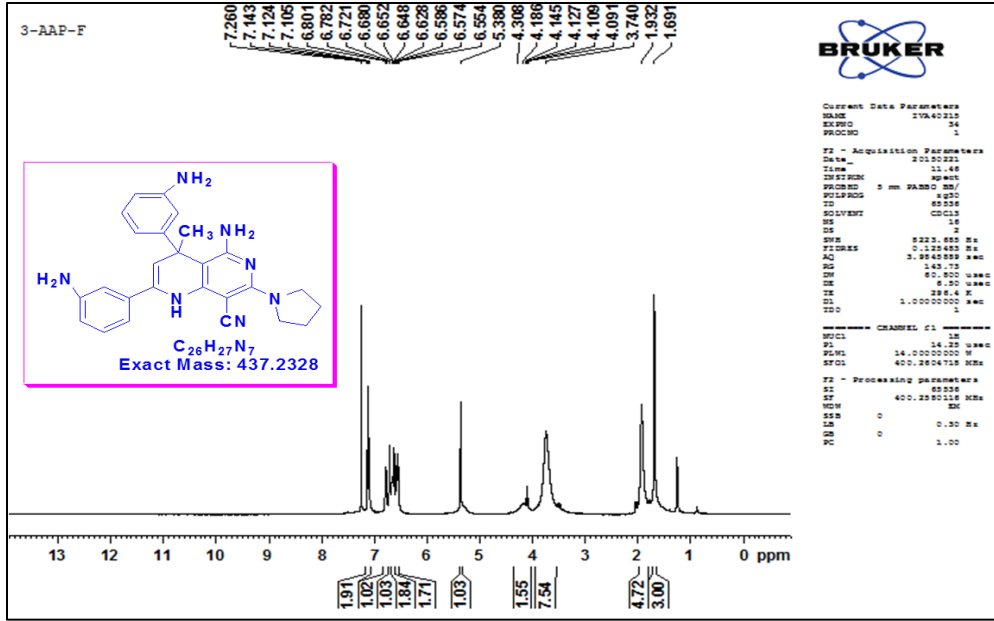


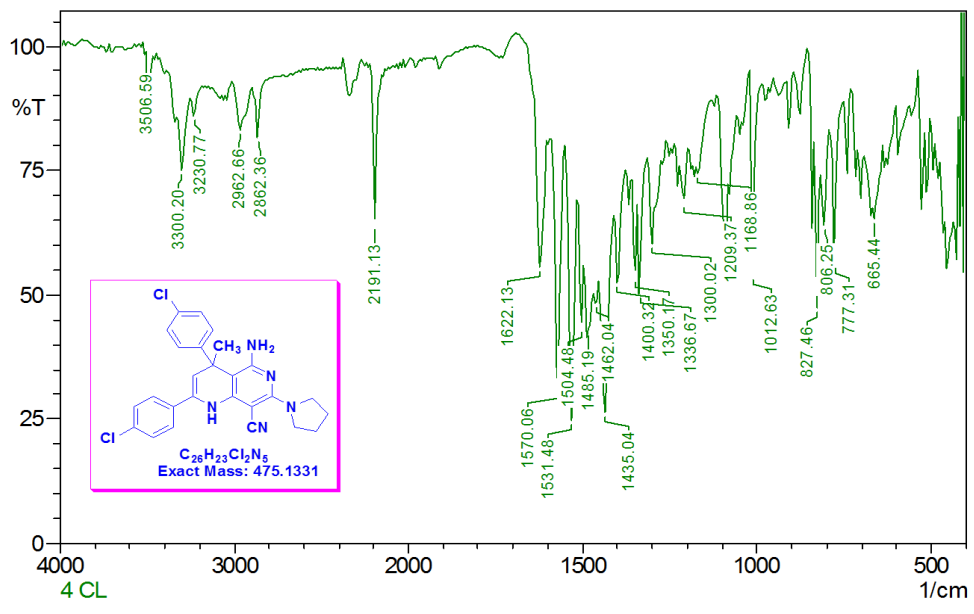
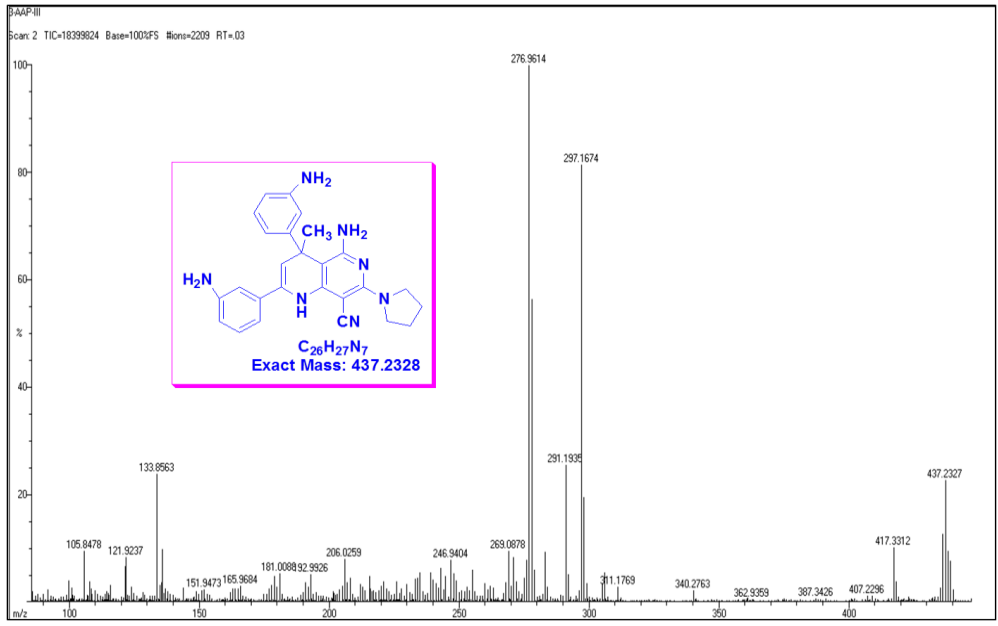


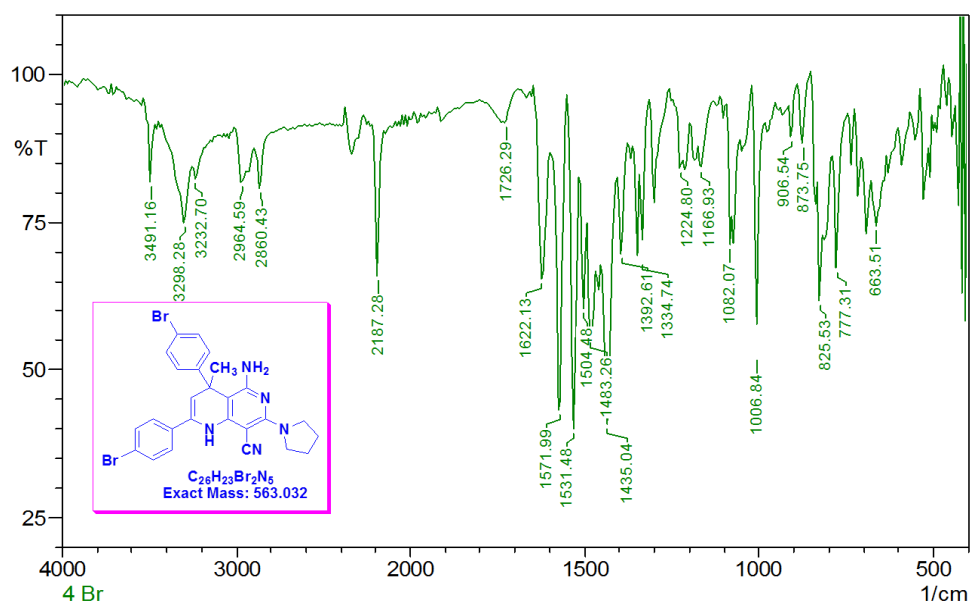
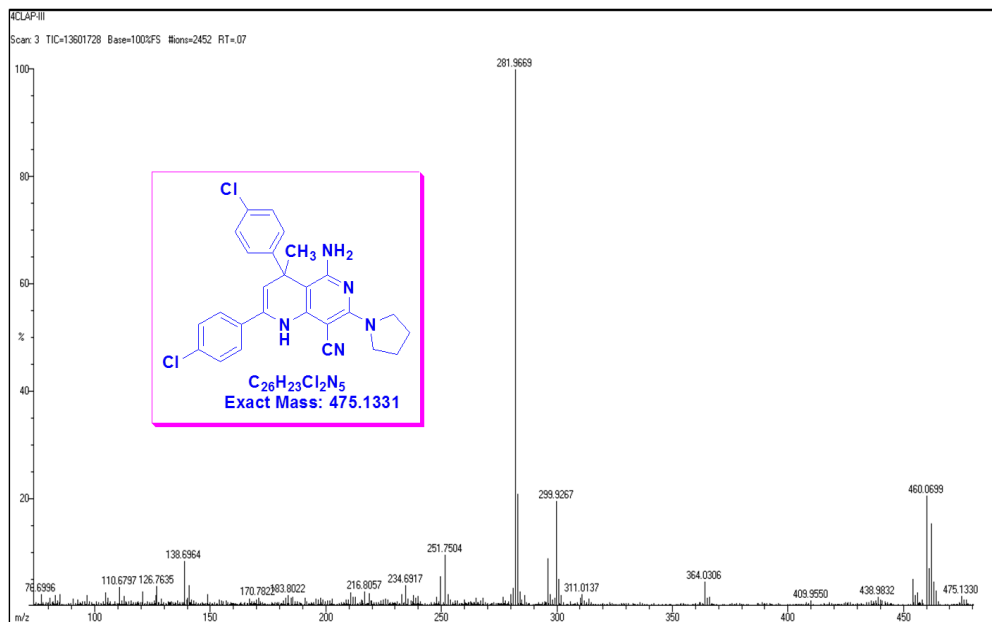


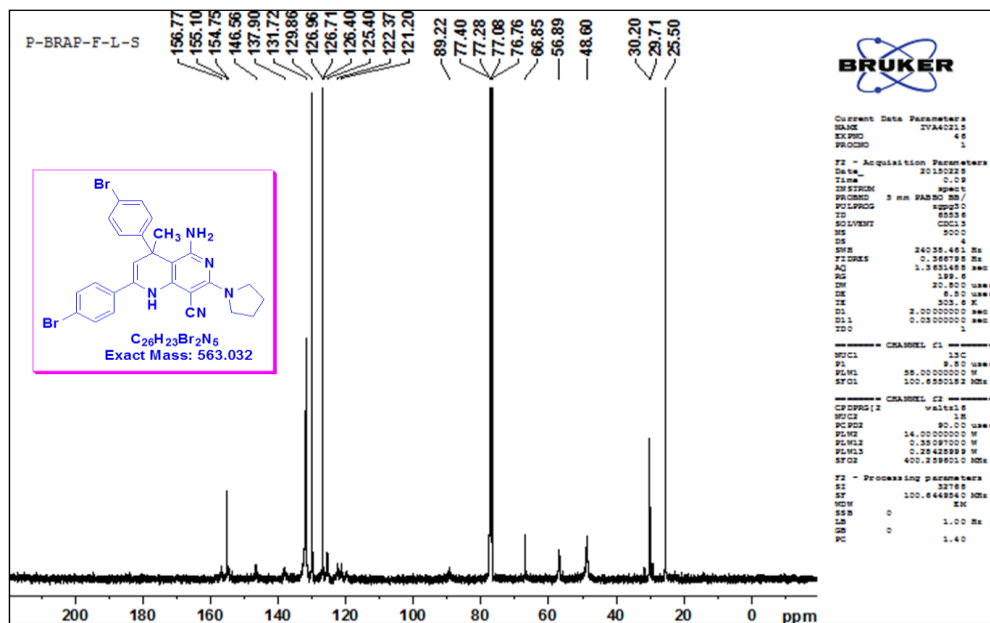
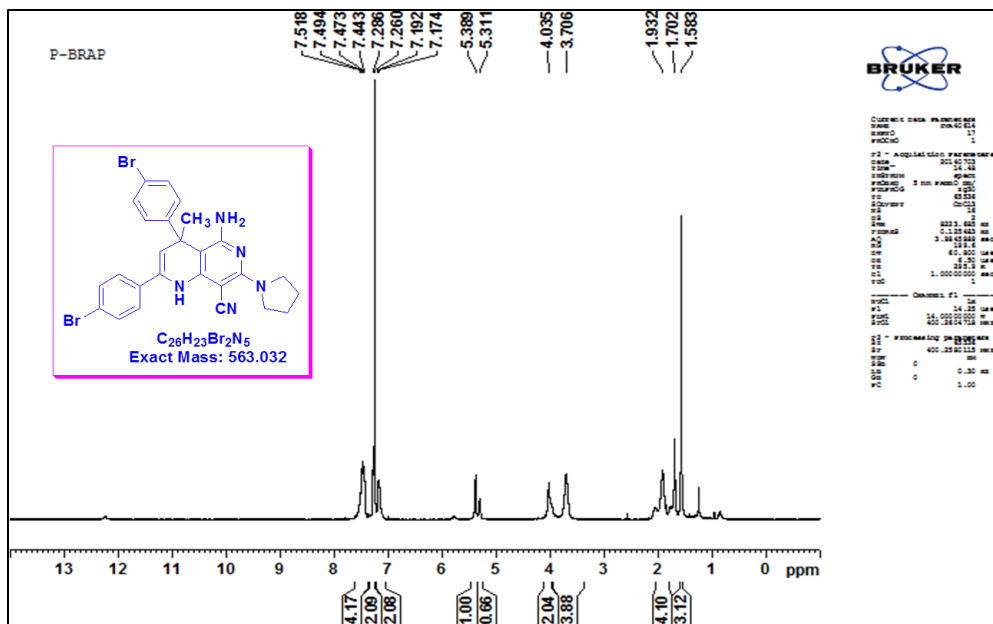


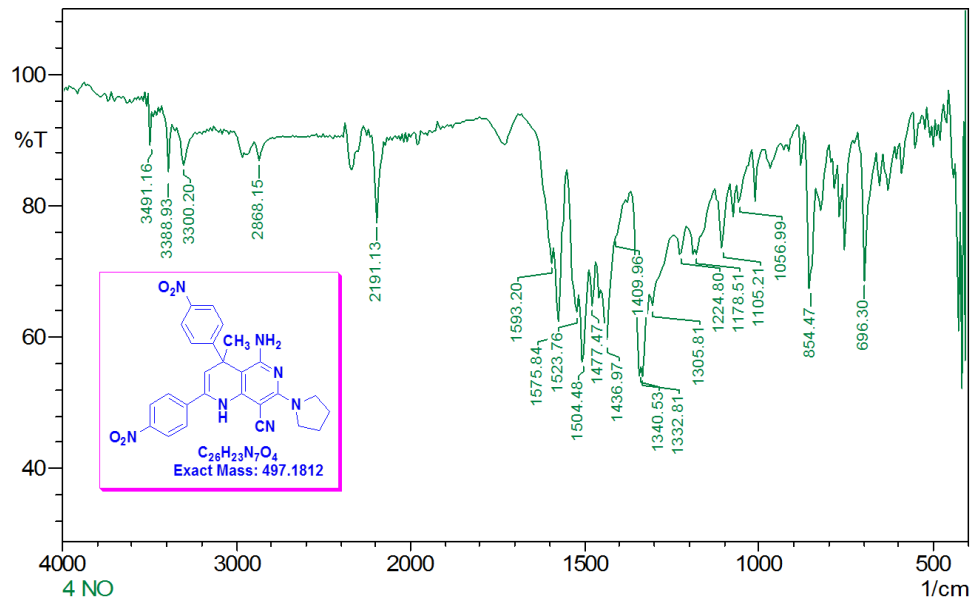
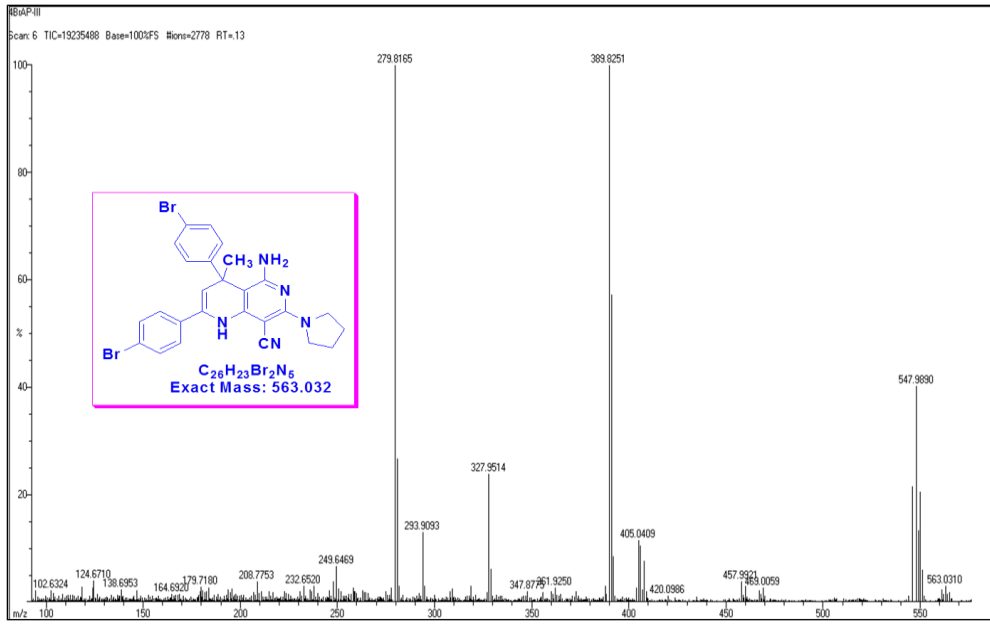












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