Transition-metal-free cross dehydrogenative alkylation of pyridine under neutral conditions

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Supporting Information

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General information

All reactions were performed under an N_2 atmosphere. Unless otherwise stated, commercially available reagents and solvents were used without further purification. Chromatography was generally performed on silica gel (200-300 mesh) and TLC inspections were on silica gel GF254 plates. NMR spectra were recorded at 400 MHz/100 MHz (^{1}H NMR/^{13}C NMR) in $CDCl_3$. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplet, b = broad).

Typical procedure for the dehydrogenative cross-coupling of pyridine derivatives

In a 25 mL Teflon cap-sealed tube, the substrate (0.2 mmol, 1 equiv) and $K_2S_2O_8$ (162 mg, 0.6 mmol, 3 equiv) were dissolved in a mixture of 1 mL of 1,4-dioxane (or other solvents such as THF, cyclohexane or toluene) and 1 mL of water under atmospheric air. The tube was sealed with a Teflon-lined cap, degassed and refilled with N_2 for three times. Then, the reaction mixture was stirred at 80°C for 12 h. After that, the mixture was extracted with 10 mL of ether and concentrated under vacuum. The residue was then purified by column chromatography on silica gel with n-hexane/ethyl acetate.

Characterization data of the substituted pyridine derivatives 3

*2,6-di(1,4-dioxan-2-yl)isonicotinonitrile (**3aa**).* 65% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.36-3.44 (m, 2H), 3.66-3.73 (m, 2H), 3.81-3.84 (m, 2H), 3.92-4.00 (m, 4H), 4.18 (dt, *J* = 2.8, 11.6 Hz, 2H), 4.73 (dt, *J* = 2.4, 10.0 Hz, 2H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.3, 66.8, 70.7, 70.8, 76.7, 116.6, 121.1, 121.2, 121.8, 159.1 (a mixture of diastereomers); MS m/e (relative intensity) 276 (M^+, 15), 217 (100), 173 (28), 159 (40), 73 (69).

*2-(tetrahydrofuran-2-yl)isonicotinonitrile (**3ab**).* 24% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.95-2.05 (m, 3H), 2.46-2.50 (m, 1H), 3.98-4.04 (m, 1H), 4.09-4.13 (m, 1H),

5.04-5.07 (m, 1H), 7.39 (dd, *J* = 1.2, 4.8 Hz, 1H), 7.72 (s, 1H), 8.72 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.7, 33.0, 69.3, 80.7, 116.7, 120.9, 121.6, 123.4, 149.9, 165.2; MS m/e (relative intensity) 174 (M^+, 1), 143 (17), 131 (100), 118 (69), 103 (19), 71 (30).

2-cyclohexylisonicotinonitrile ***(3ac).*** 22% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34-1.49 (m, 5H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.81 (d, *J* = 12.8 Hz, 2H), 1.88 (d, *J* = 12.8 Hz, 2H), 2.69 (t, *J* = 11.2 Hz, 1H), 7.19 (s, 1H), 7.26 (d, *J* = 4.8 Hz, 1H), 8.63 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.3, 29.7, 32.6, 46.4, 116.9, 120.6, 122.4, 122.9, 150.1, 186.4; MS m/e (relative intensity) 186 (M^+, 75), 157 (100), 131 (100), 118 (57).

2-benzylisonicotinonitrile ***(3ad).*** 51% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.21 (s, 2H), 7.24-7.28 (m, 3H), 7.31-7.36 (m, 4H), 8.72 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 44.5, 116.6, 120.8, 122.6, 124.6, 127.0, 128.9, 129.1, 137.8, 150.3, 162.8; MS m/e (relative intensity) 194 (M^+, 35), 193 (100), 91 (13), 65 (10).

2-(3-methylbenzyl)isonicotinonitrile ***(3ae).*** 19% yield; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 4.18 (s, 2H), 7.21-7.23 (m, 1H), 7.03-7.09 (m, 3H), 7.21-7.23 (m, 1H), 7.32-7.35 (m, 2H), 8.73 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.4, 44.4, 116.6, 120.9, 122.6, 124.7, 126.1, 127.8, 128.8, 129.9, 137.7, 138.6, 150.2, 163.0; MS m/e (relative intensity) 208 (M^+, 39), 207 (100), 192 (33), 183 (22), 127 (19).

2-(1,2-dimethoxyethyl)isonicotinonitrile ***(3af)***. 46% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.37 (s, 3H), 3.44 (s, 3H), 3.64-3.74 (m, 2H), 4.52-4.58 (m, 1H), 7.45 (dd, J = 1.2, 4.8 Hz, 1H), 7.72 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 58.0, 59.4, 74.9, 83.4, 116.6, 121.0, 123.1, 124.0, 150.1, 161.4; MS m/e (relative intensity) 192 (M^+, 6), 177 (15), 161 (21), 147 (100), 131 (27), 119 (28).

2-methylcyclopentylisonicotinonitrile ***(3ag)***. 21% yield; colorless oil; a mixture of regio-isomers.

2,4,6-tri(1,4-dioxan-2-yl)pyridine ***(3ba).*** 49% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.38-3.49 (m, 3H), 3.71-3.75 (m, 3H), 3.79-3.82 (m, 3H), 3.90-3.99 (m, 7H), 4.15 (dd, *J* = 2.8, 11.6 Hz, 2H), 4.65 (dd, *J* = 2.4, 10.0 Hz, 1H), 4.72-4.75 (m, 2H), 7.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.26, 66.31, 66.8, 66.9, 71.1, 71.7, 76.6, 77.6, 77.7, 77.8, 116.5, 116.8, 116.9, 148.9, 157.44, 157.49, 157.5, 157.6 (a mixture of diastereomers); MS m/e (relative intensity) 337 (M^+, 22), 278 (100), 234 (16), 220 (24), 206 (18), 73 (28).

4-(1,4-dioxan-2-yl)picolinonitrile and 6-(1,4-dioxan-2-yl)picolinonitrile (1:2) ***(3ca).*** 45% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.33-3.43 (m, 1H), 3.68-3.75 (m, 1H), 3.83-3.86 (m, 1H), 3.89-4.00 (m, 3H), 4.67-4.76 (m, 1H), 7.46-7.48 (m, 0.6H), 7.69-7,72 (m, 1 H), 7.84-7.86 (m, 0.3H), 8.68-8.69 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.3, 66.8, 66.9, 71.5, 71.8, 74.9, 75.3, 117.1, 123.9, 125.7, 128.2, 134.3, 134.6, 148.8, 149.1, 151.1 (a 1:2 mixture of regio-isomers); MS m/e (relative intensity) 190 (M^+, 25), 131 (100), 107 (25), 76 (20), 51 (20).

2,4,6-tri(1,4-dioxan-2-yl)nicotinonitrile ***(3da).*** 61% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.30-3.44 (m, 2H), 3.64-3.86 (m, 7H), 3.90-4.06 (m, 9H), 4.22 (ddd, *J* = 2.8, 11.6, 17.6 Hz, 1H), 4.74-4.79 (m, 1H), 4.95-5.03 (m, 2H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.2, 66.29, 66.32, 66.9, 67.21, 67.24, 67.3, 67.4, 68.9, 69.0, 70.68, 70.74, 75.2, 76.7, 77.0, 77.3 105.7, 105.8, 114.08, 114.11, 117.34, 117.38, 117.4, 117.5, 152.7, 152.8, 158.4, 159.0,

161.74, 161.77, 162.1 (a mixture of diastereomers); MS m/e (relative intensity) 362 (M^+, 33), 303 (100), 243 (24), 73 (89).

3,6-di(1,4-dioxan-2-yl)-2-phenylpyridine ***(3ea).*** 45% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.42-3.47 (m, 1H), 3.53-3.59 (m, 1H), 3.73-3.77 (m, 2H), 3.81-3.84 (m, 2H) , 3.94-3.99 (m, 4H), 4.31-4.34 (m, 1H), 4.68-4.72 (m, 1H), 4.81-4.83 (m, 1H), 7.39-7.42 (m, 2H), 7.44-7.48 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.3, 66.4, 66.86, 66.94, 71.3, 71.9, 77.98, 78.05, 115.8, 116.0, 116.4, 126.9, 128.6, 129.1, 138.9, 148.5, 156.66, 156.69, 158.25, 158.33 (a mixture of diastereomers); MS m/e (relative intensity) 327 (M^+, 5), 268 (100), 210 (13), 183 (11), 154 (20), 127 (14).

2,6-di(1,4-dioxan-2-yl)-4-phenylpyridine ***(3fa).*** 68% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.40-3.48 (m, 2H), 3.65-3.76 (m, 4H), 3.87-3.92 (m, 4H), 4.12 (dd, *J* = 3.2, 7.6 Hz, 2H), 4.69 (dd, *J* = 2.8, 10.0 Hz, 2H), 7.34-7.40 (m, 3H), 7.55 (s, 2H), 7.60-7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.4, 66.9, 71.2, 71.3, 77.9, 78.1, 117.4, 117.6, 118.6, 120.7, 127.0, 127.1, 128.9, 129.0, 138.1, 138.3, 149.2, 149.4, 149.9, 157.8, 158.4 (a mixture of diastereomers); MS m/e (relative intensity) 327 (M^+, 26), 268 (100), 224 (18), 210 (30), 196 (24), 154 (22).

4-benzyl-2,6-di(1,4-dioxan-2-yl)pyridine ***(3ga).*** 53% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.41-3.55 (m, 2H), 3.70-3.73 (m, 2H), 3.70-3.73 (m, 2H), 3.77-3.80 (m, 2H), 3.90-3.95 (m, 4H), 3.97 (s, 2H), 4.11-4.15 (m, 2H), 4.66-4.73 (m, 2H), 7.17-7.19 (m, 2H), 7.29 (s, 2H), 7.29-7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 41.4, 66.3, 67.0, 71.2, 77.9, 119.9, 120.2, 126.6, 126.7, 128.69, 128.72, 128.98, 129.0, 139.0, 149.1, 157.4 (a mixture of diastereomers); MS m/e (relative intensity) 341 (M^+, 46), 282 (100), 224 (46), 210 (35), 73 (42), 57 (45).

1-(2,6-di(1,4-dioxan-2-yl)pyridin-4-yl)ethanone ***(3ha).*** 29% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.65 (s, 3H), 3.42-3.50 (m, 2H), 3.70-3.76 (m, 2H), 3.81-3.84 (m, 2H), 3.94-3.99 (m, 4H), 4.18 (dd, *J* = 2.8, 7.6 Hz, 2H), 4.77 (dd, *J* = 2.8, 10.0 Hz, 2H), 7.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 26.9, 66.3, 66.9, 71.00, 71.05, 77.5, 77.6, 117.2, 117.3, 144.5, 158.9, 197.5 (a mixture of diastereomers); MS m/e (relative intensity) 293 (M^+, 18), 234 (100), 190 (31), 176 (41), 162 (26), 73 (69).

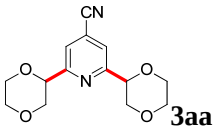
3-chloro-2-(1,4-dioxan-2-yl)-6-phenylpyridine ***(3ia).*** 85% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.83-3.87 (m, 2H), 3.98-4.01 (m, 2H), 4.03-4.07 (m, 1H), 4.21-4.26 (m, 1H), 5.15 (dd, *J* = 2.8, 10.0 Hz, 2H), 7.42-7.49 (m, 3H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.4, 67.5, 69.1, 74.7, 120.8, 127.0, 128.7, 128.8, 129.4, 130.1, 138.1, 148.8, 153.0, 155.1; MS m/e (relative intensity) 275 (M^+, 35), 216 (100), 189 (21), 154 (55), 127 (23).

4-(1,4-dioxan-2-yl)-2-methoxy-6-phenylpyridine ***(3ja).*** 32% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.41-3.47 (m, 1H), 3.70-3.77 (m, 1H), 3.80-3.83 (m, 1H), 3.90-3.97 (m, 3H), 4.03 (s, 3H), 4.64 (dd, *J* = 2.8, 10.0 Hz, 1H), 6.66 (s, 1H), 7.33 (s, 1H), 7.37-7.41 (m, 1H), 7.43-7.47 (m, 2H), 8.04-8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 53.4, 66.4, 66.9, 71.9, 76.7, 106.3, 110.4, 126.8, 128.6, 128,9, 138.9, 150.4, 155.0, 164.1; MS m/e (relative intensity) 271 (M^+, 55), 242 (36), 212 (100), 184 (31), 154 (28).

*4-(1,4-dioxan-2-yl)-2-methyl-6-phenylpyridine (**3ka**).* 76% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.62 (s, 3H), 3.41-3.46 (m, 1H), 3.70-3.76 (m, 1H), 3.80-3.84 (m, 1H), 3.88-3.99 (m, 3H), 4.65 (dd, *J* = 2.8, 10.4 Hz, 1H), 7.07 (s, 1H), 7.37-7.49 (m, 4H), 7.97-7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.7, 66.3, 66.9, 71.9, 76.7, 114.9, 118.7, 127.0, 128.6, 128.8, 139.5, 147.8, 157.3, 158.6; MS m/e (relative intensity) 255 (M^+, 39), 196 (100), 170 (22), 111 (15).

*4-(1,4-dioxan-2-yl)-2,6-diphenylpyridine (**3la**).* 78% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.45-3.50 (m, 1H), 3.71-3.84 (m, 2H), 3.90-4.01 (m, 3H), 4.74 (dd, *J* = 2.8, 10.0 Hz, 1H), 7.40-7.43 (m, 2H), 7.47-7.50 (m, 4H), 7.65 (s, 2H), 8.14-8.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 66.3, 66.9, 72.0, 76.8, 115.9, 127.0, 128.6, 129.0, 139.2, 148.5, 157.1; MS m/e (relative intensity) 317 (M^+, 31), 288 (20), 258 (25), 231 (100).

*4-(1,4-dioxan-2-yl)-2-methyl-6-phenylpyridine (**3ma**).* 73% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.47 (t, J = 7.2 Hz, 3H) 3.42-3.47 (m, 1H), 3.72-3.79 (m, 1H), 3.82-3.87 (m, 1H), 3.92-4.04 (m, 3H), 4.49 (q, J = 7.2 Hz, 2H), 4.77 (dd, J = 2.8, 10.0 Hz, 1H), 7.44-7.51 (m, 3H), 7.91 (s, 1H), 7.99 (s, 1H), 8.07-8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 61.9, 66.3, 66.9, 71.8, 76.3, 120.6, 127.3, 128.8, 129.5, 138.3, 148.6, 149.0, 158.1, 165.4; MS m/e (relative intensity) 313 (M^+, 6), 241 (100), 183 (27), 154 (16), 127(15).



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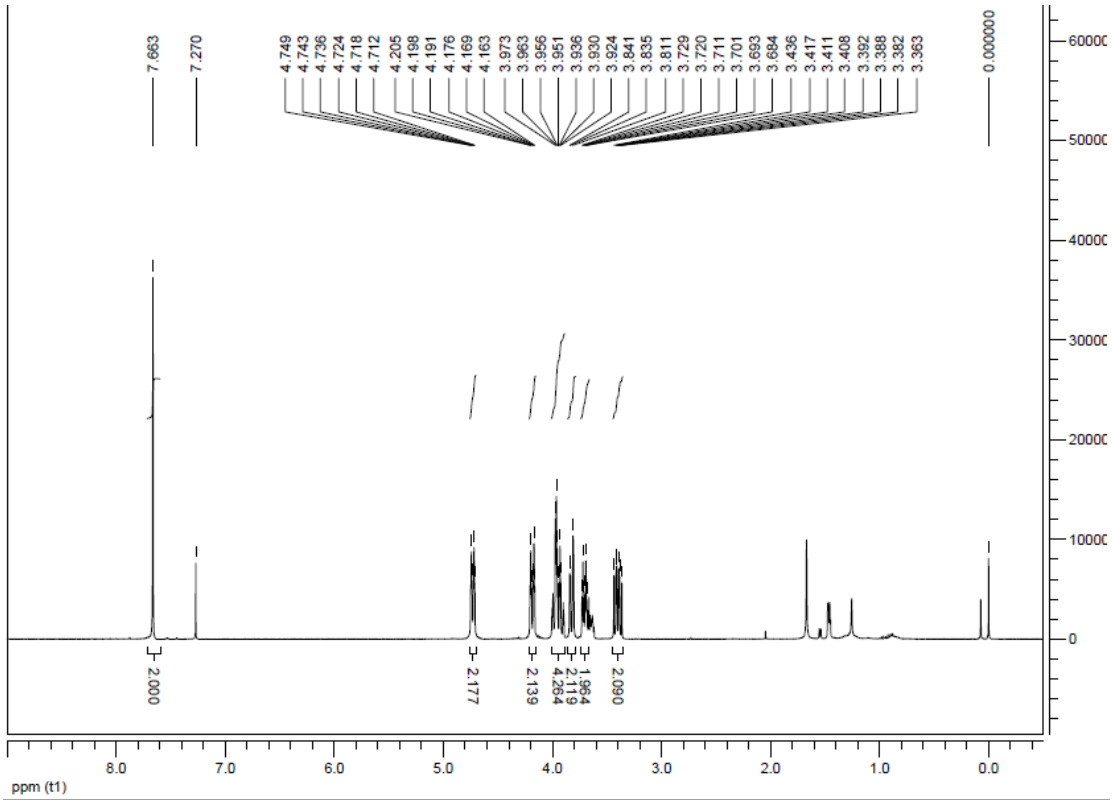

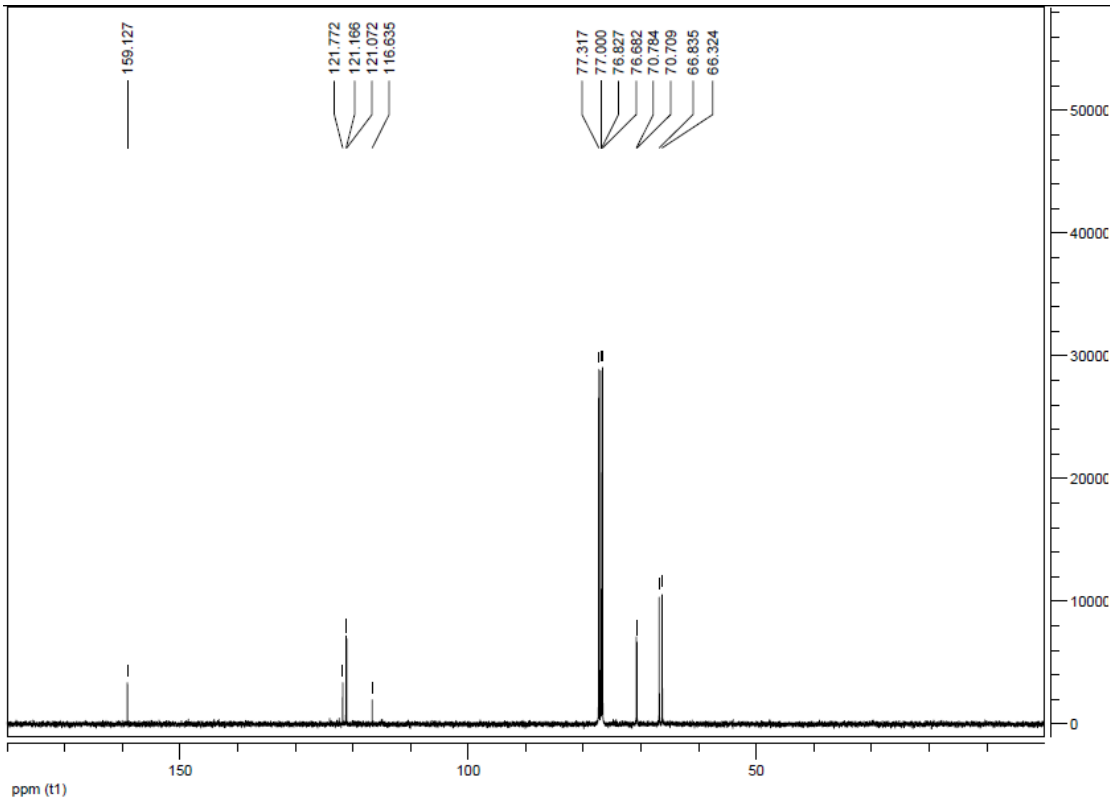

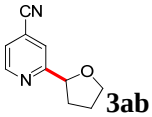

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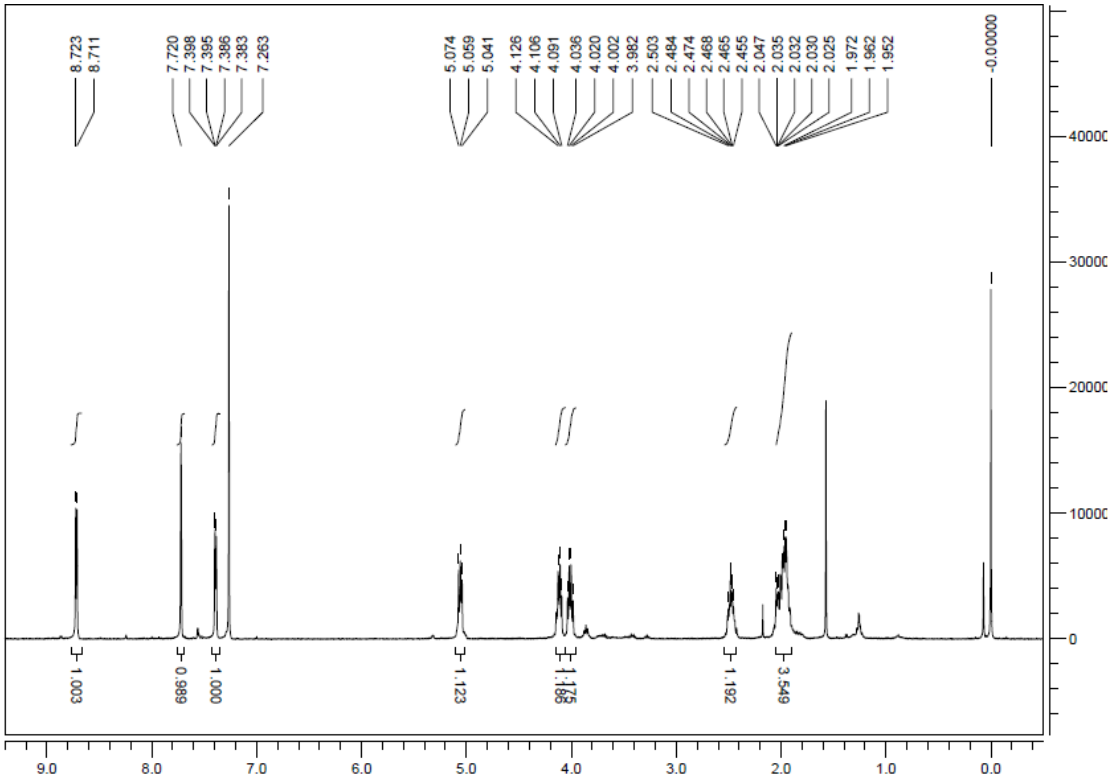

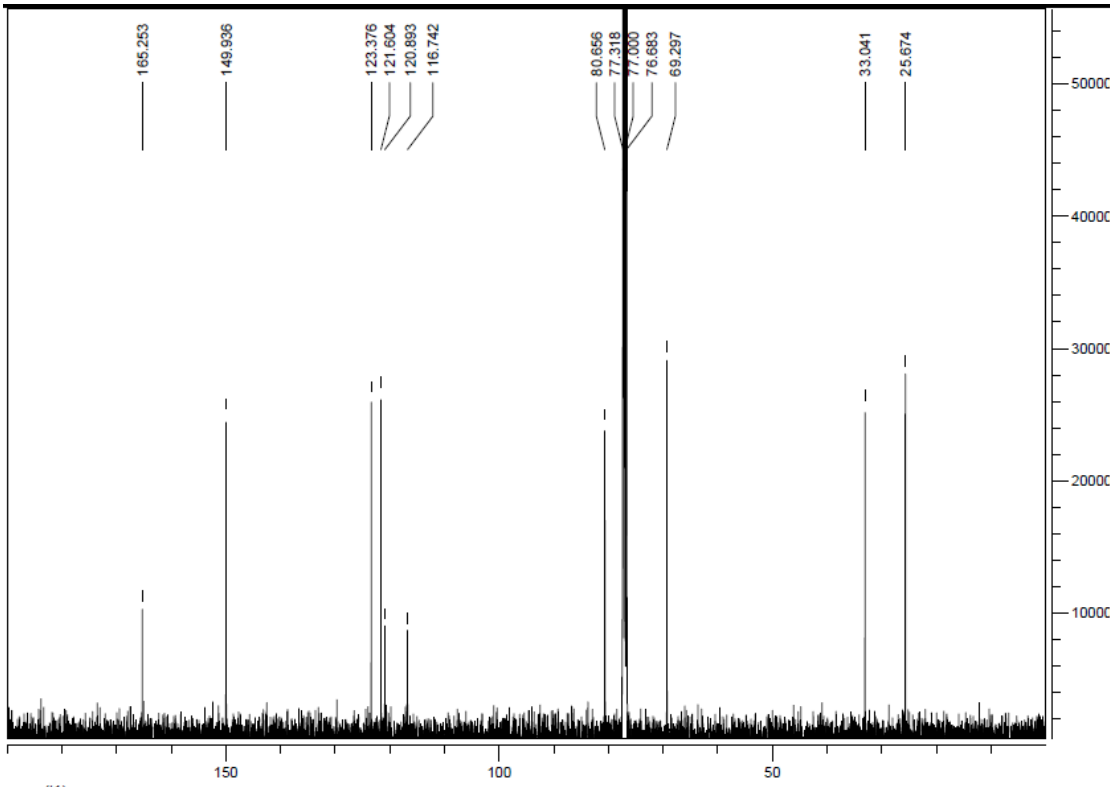

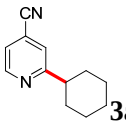

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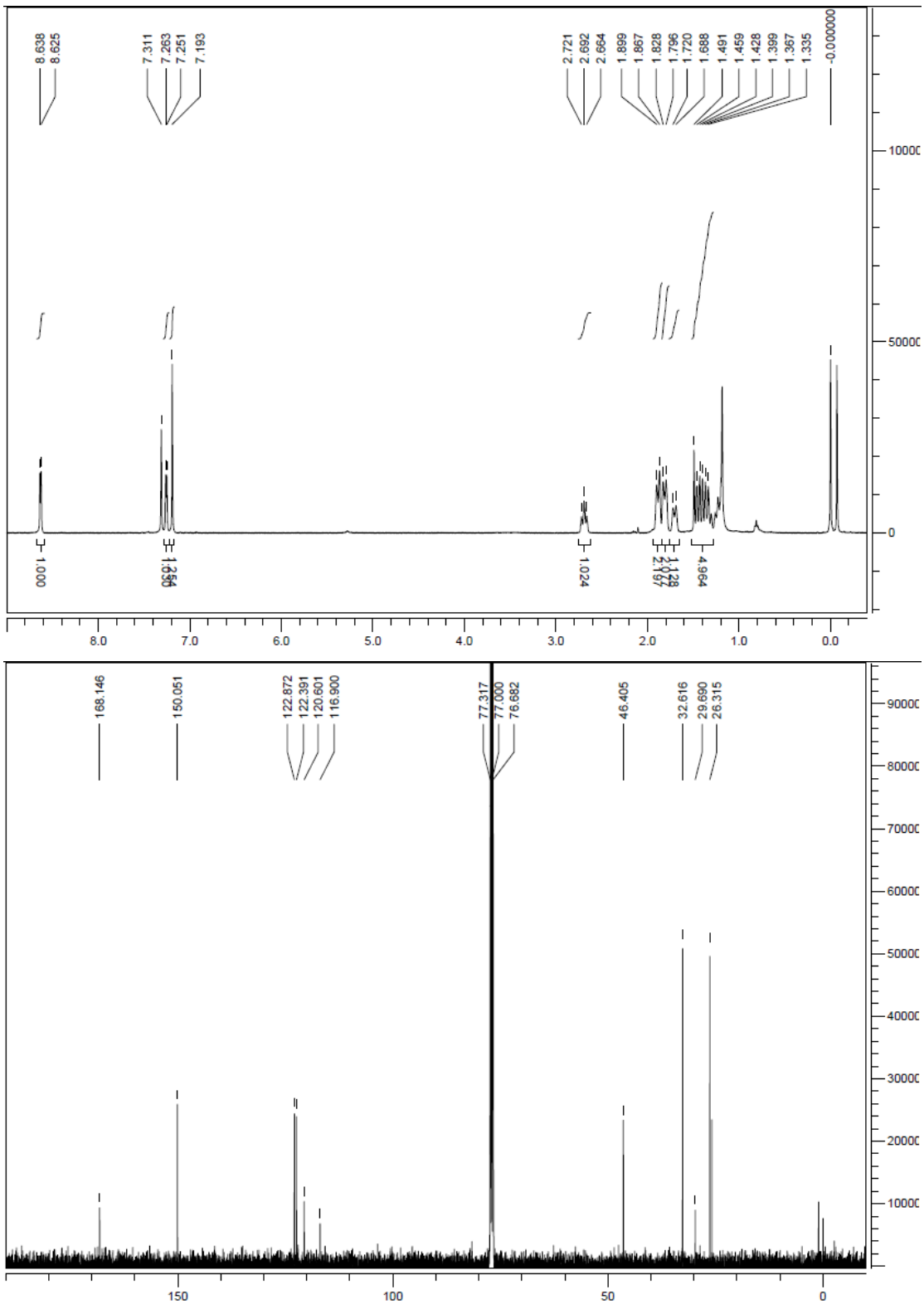

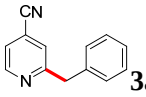

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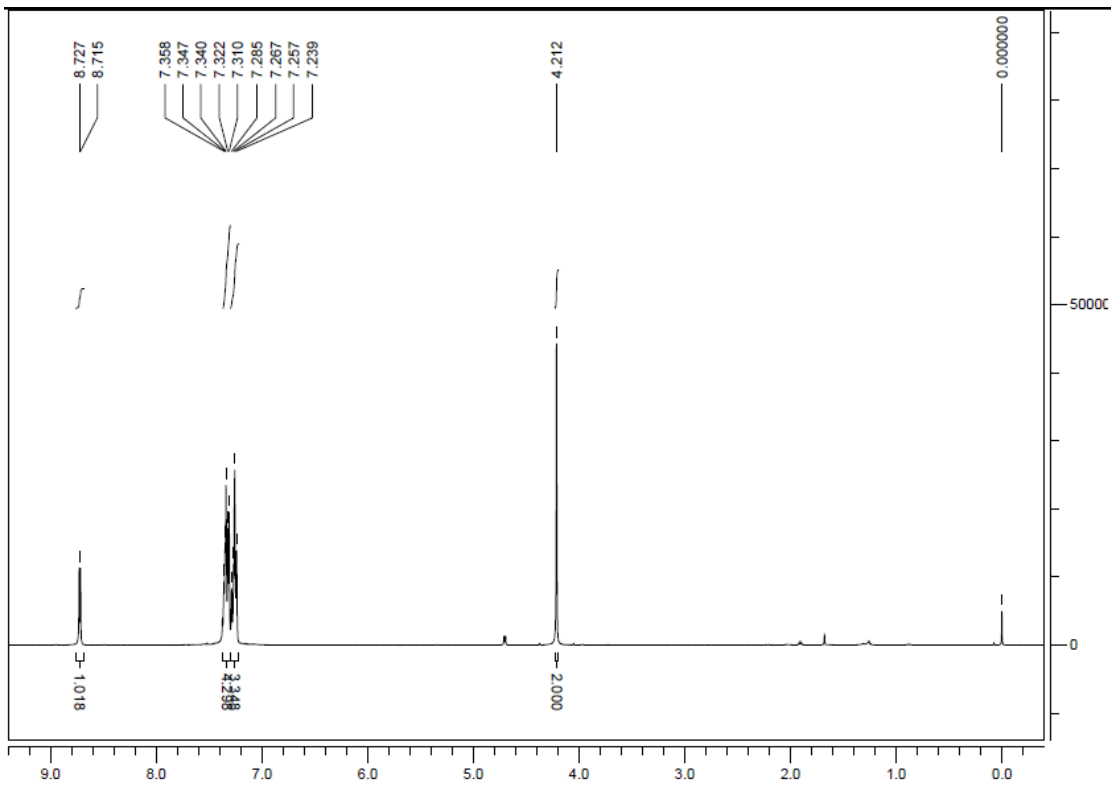

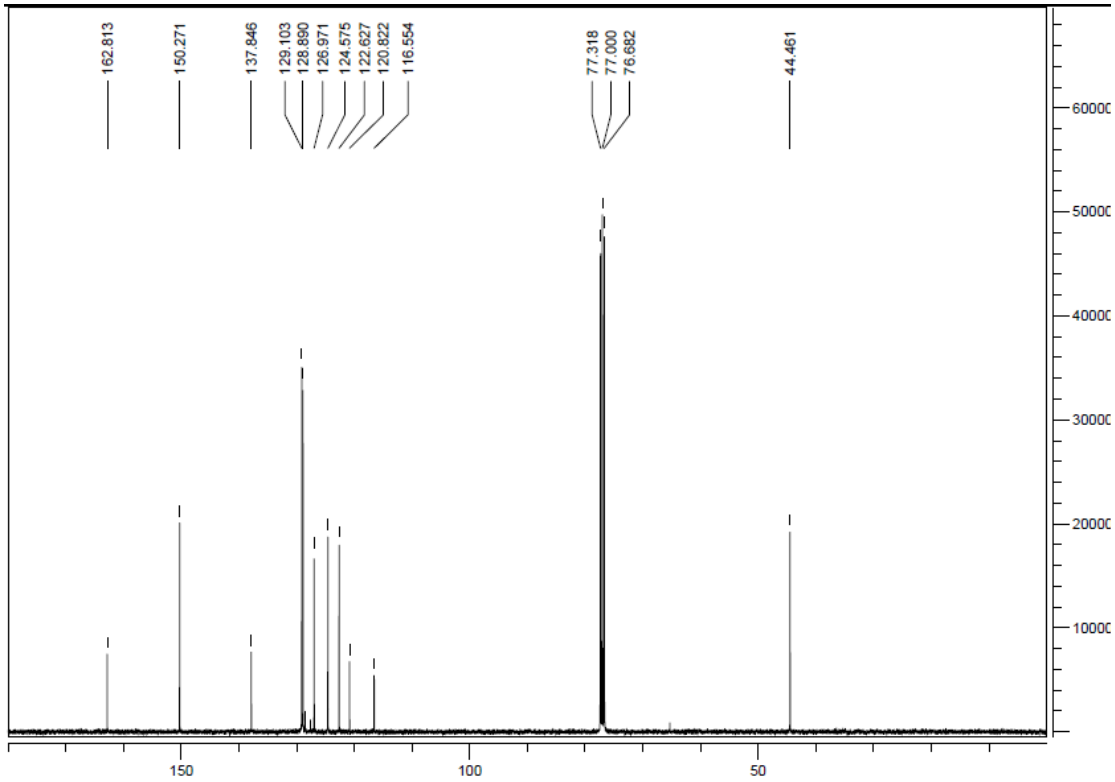

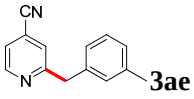

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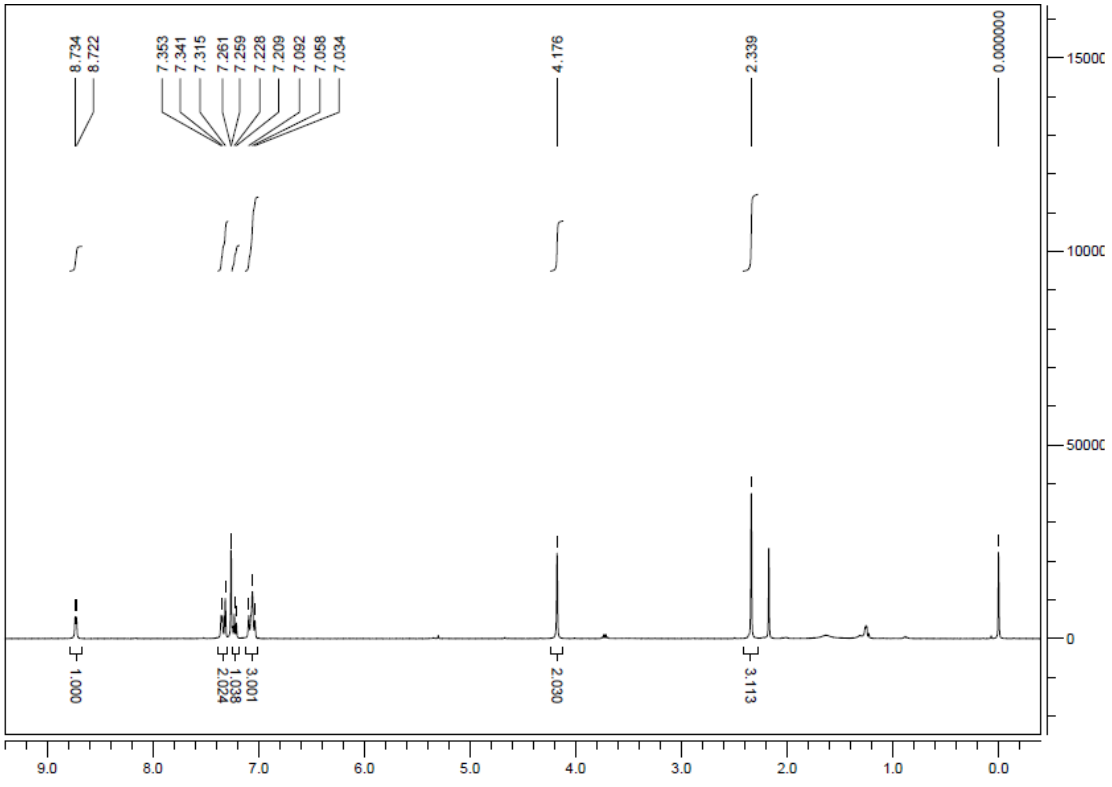

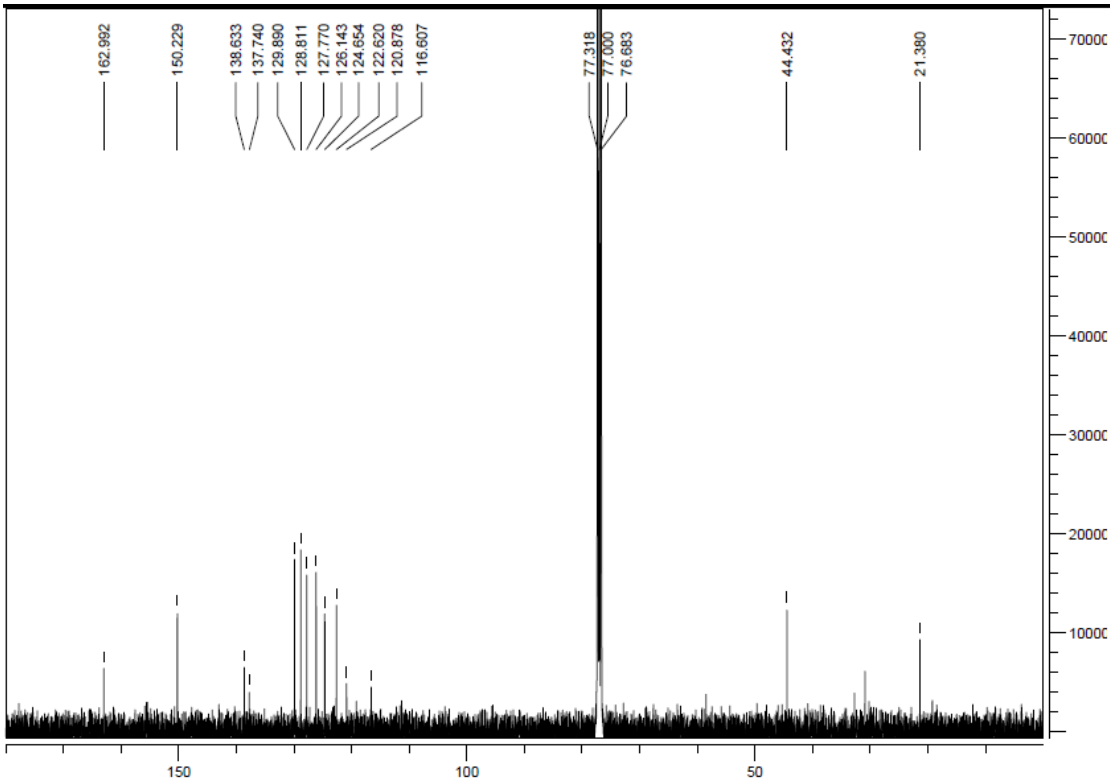

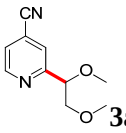

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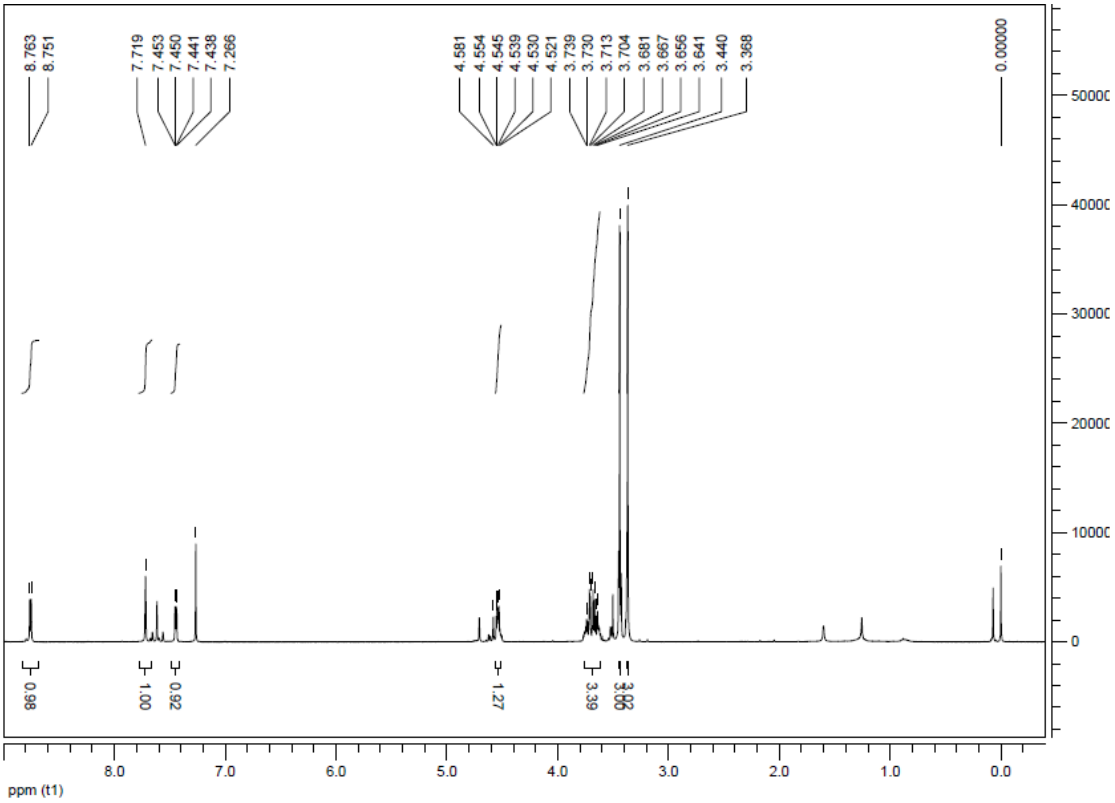

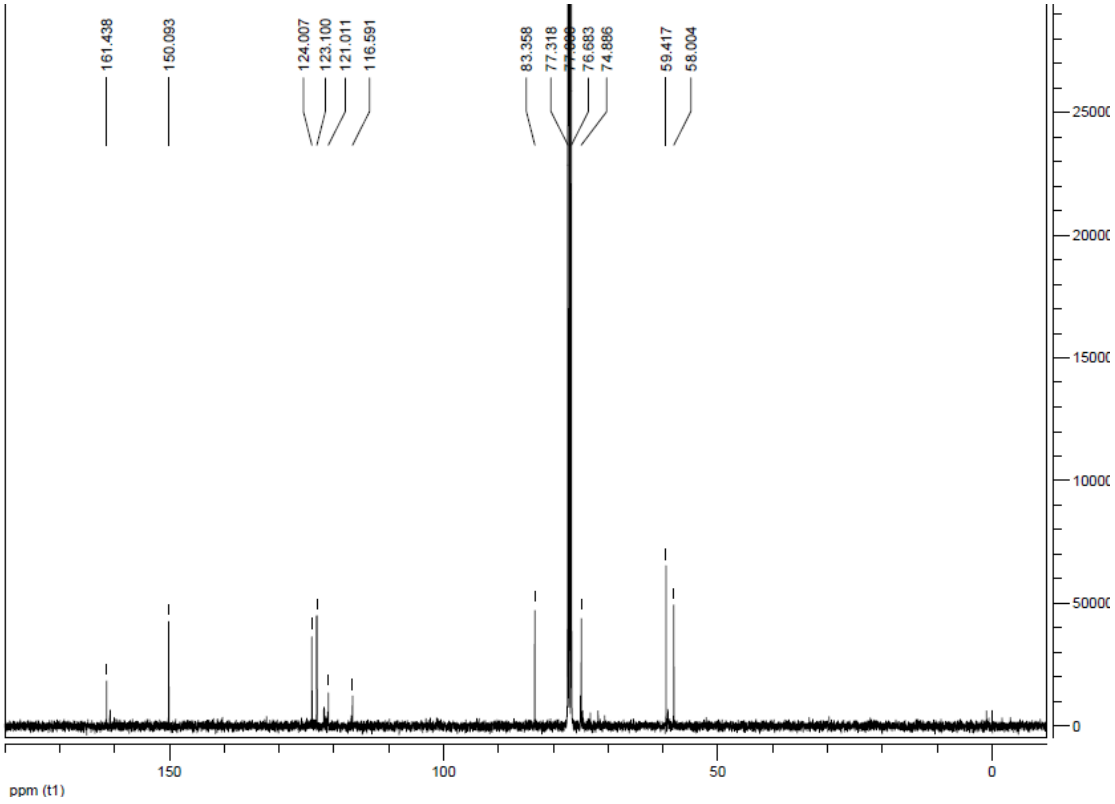

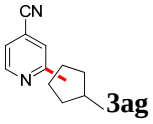

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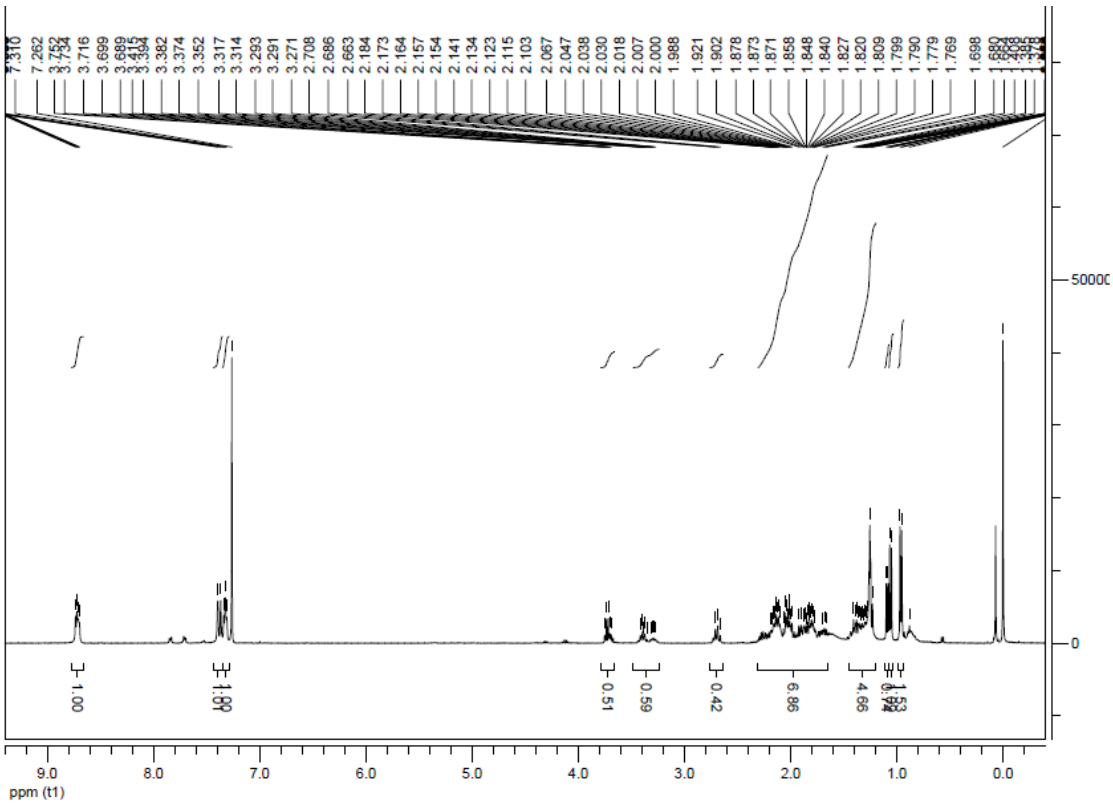

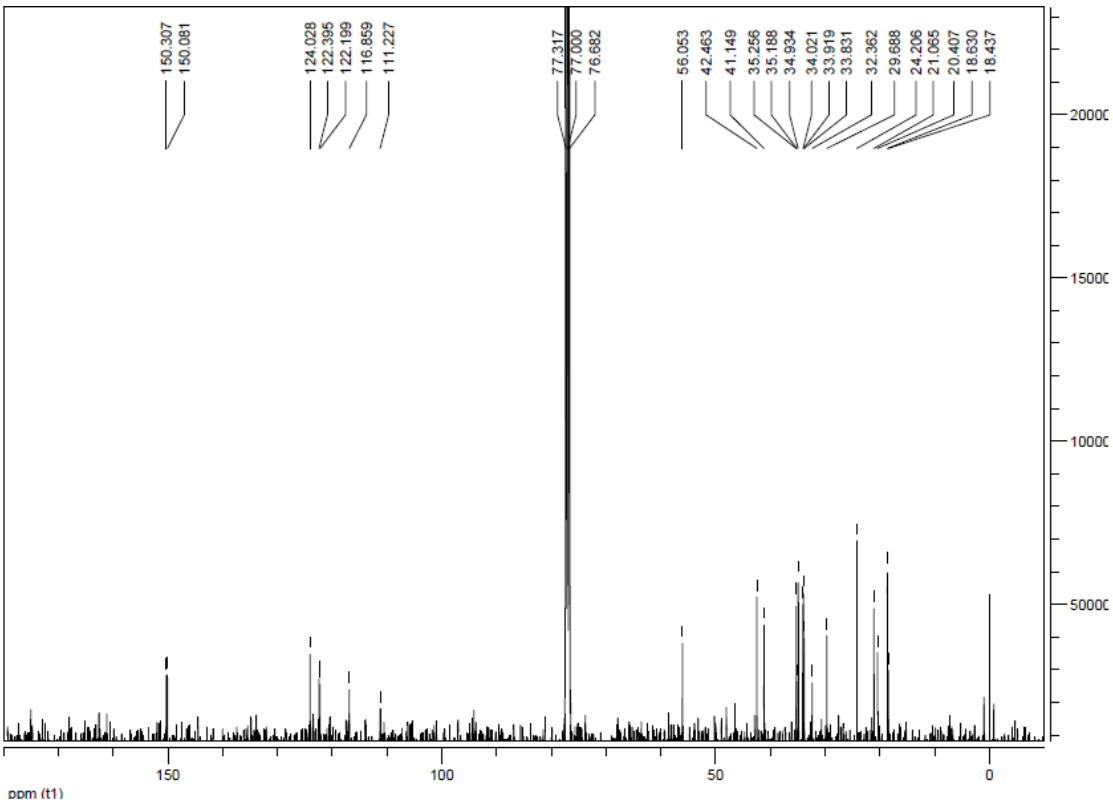

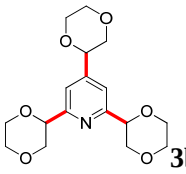

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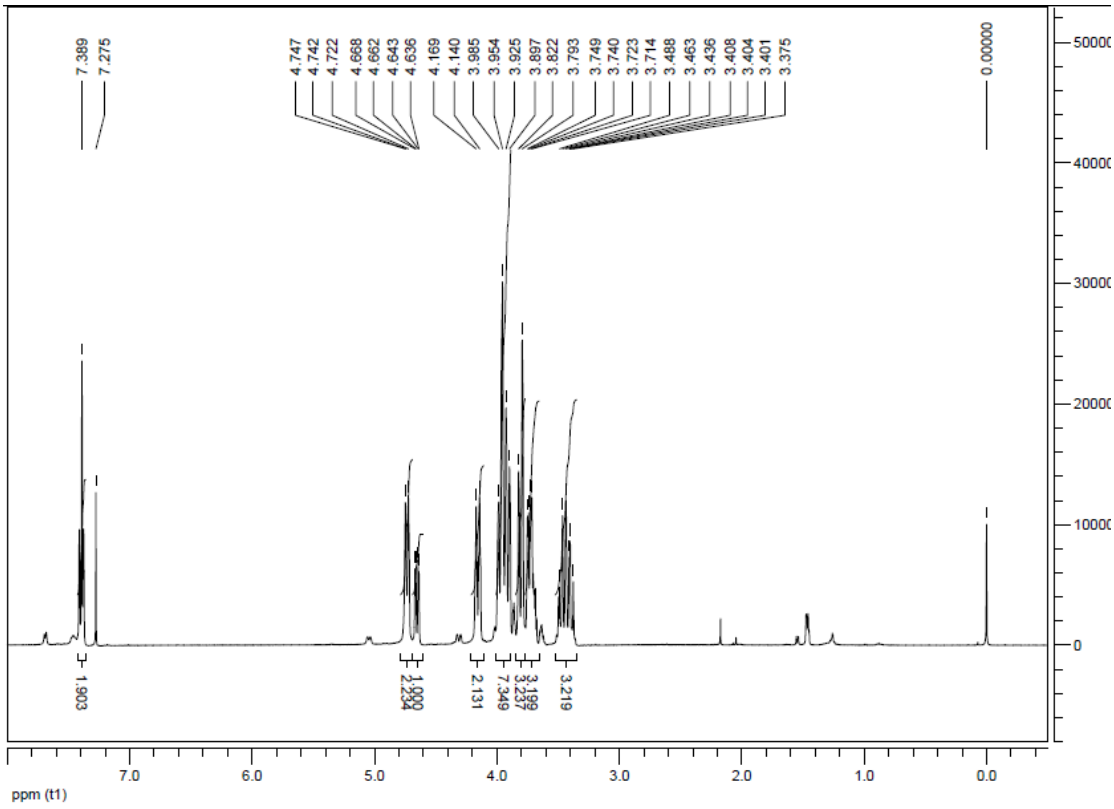

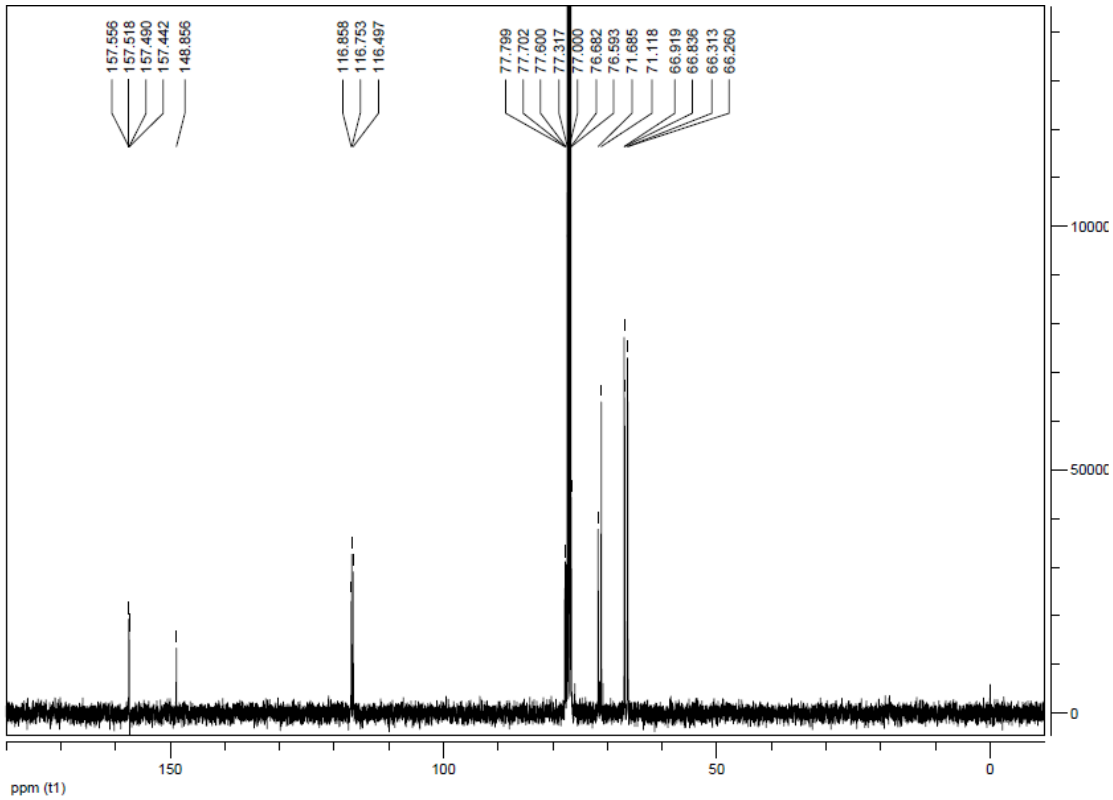

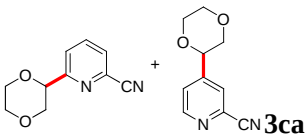

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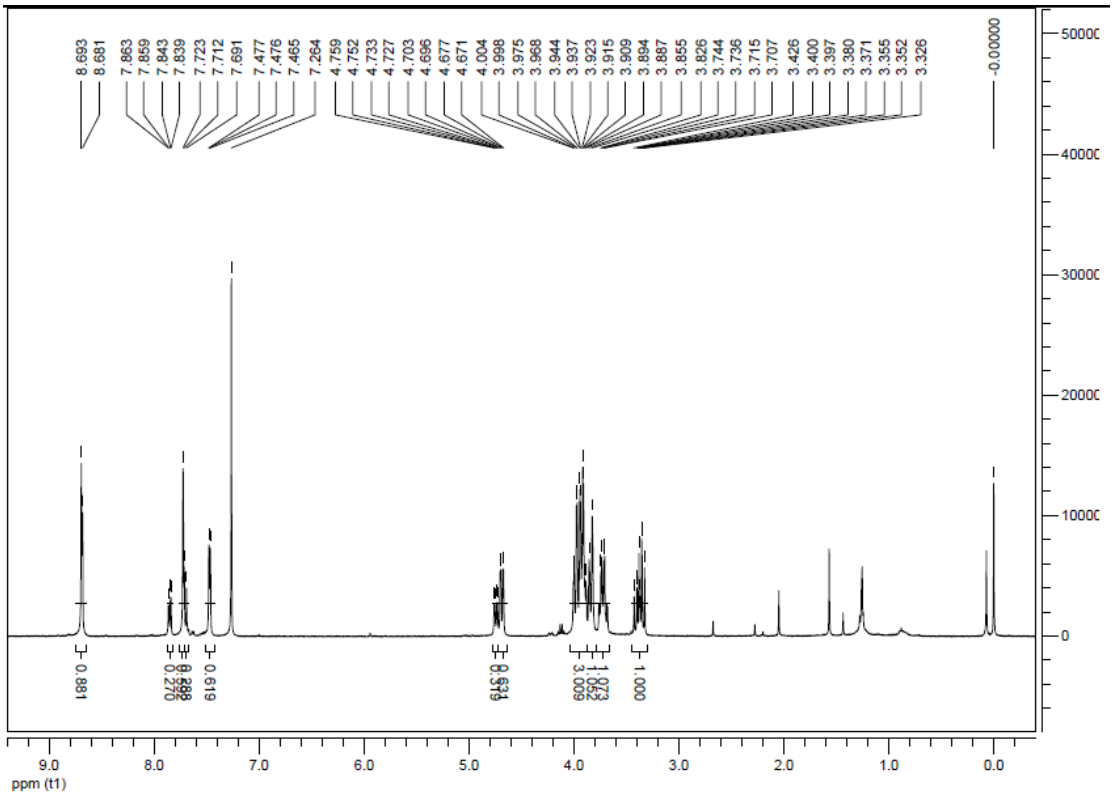

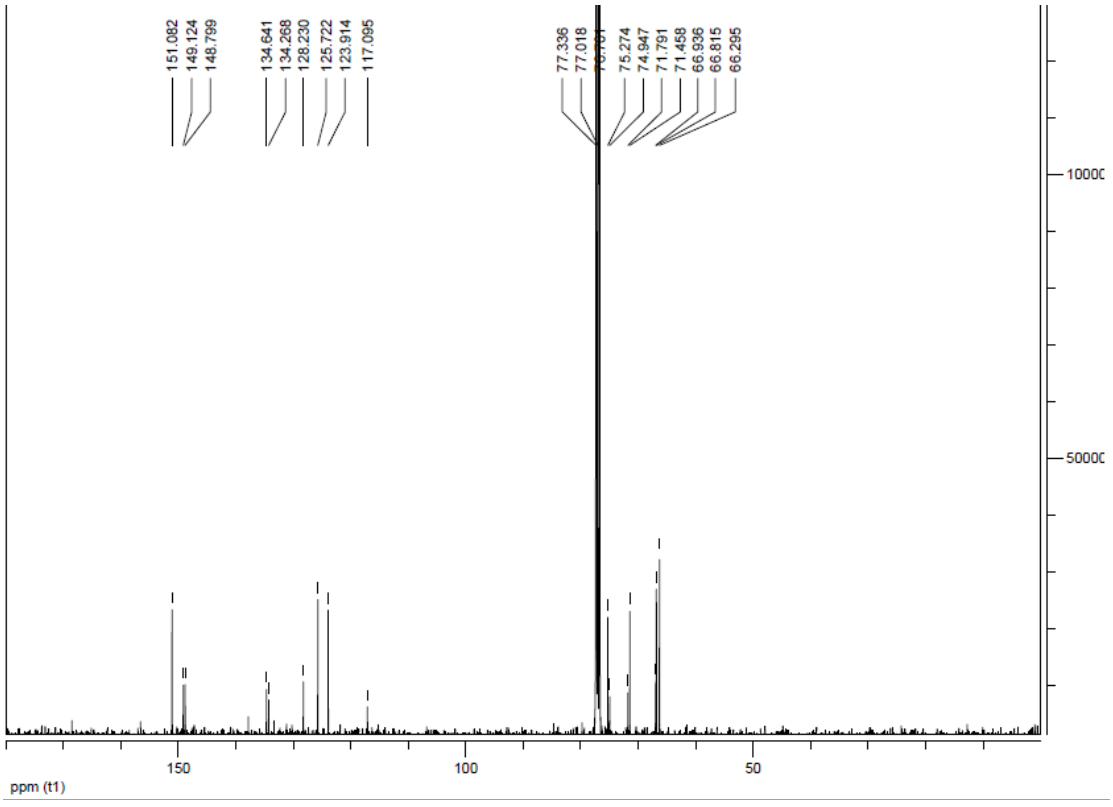

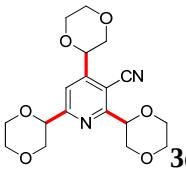

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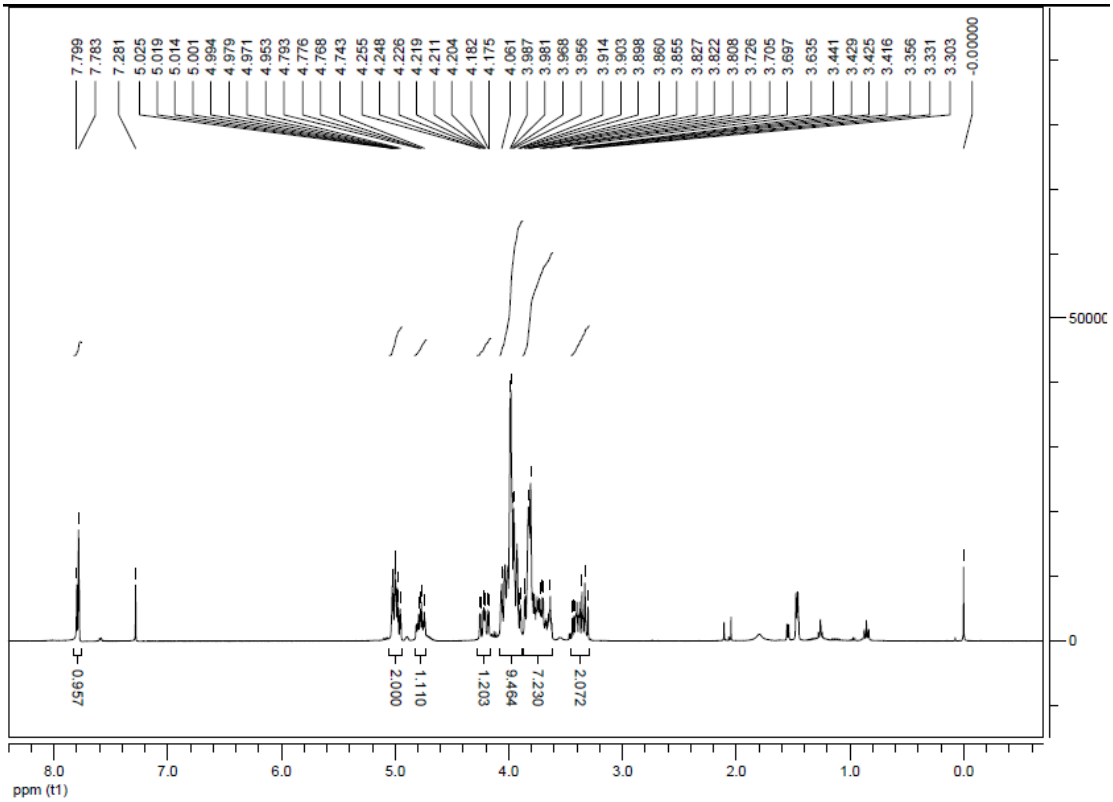

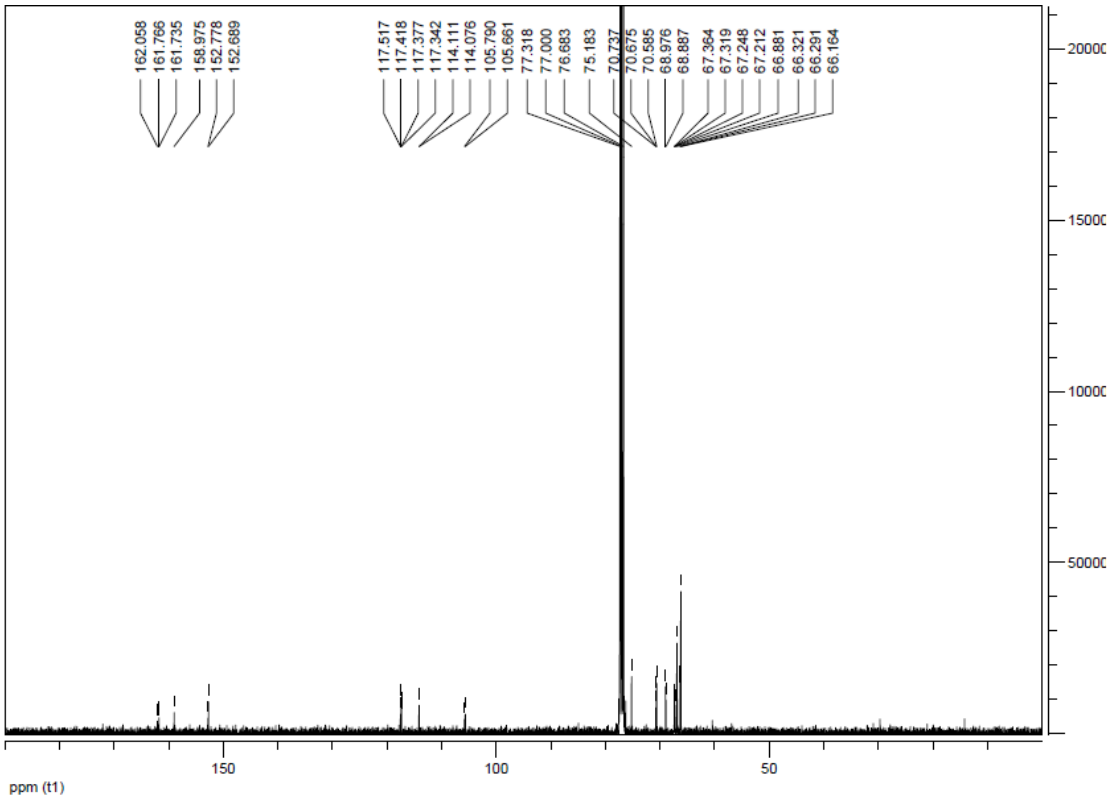

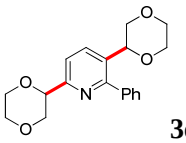

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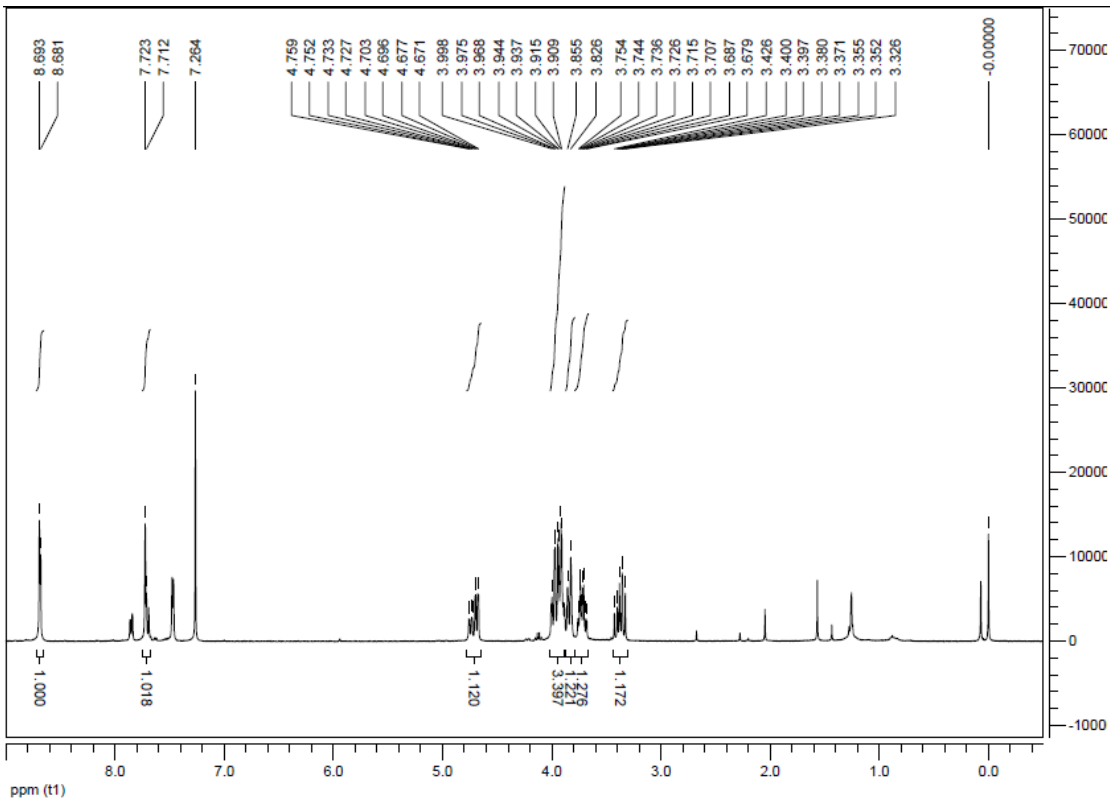

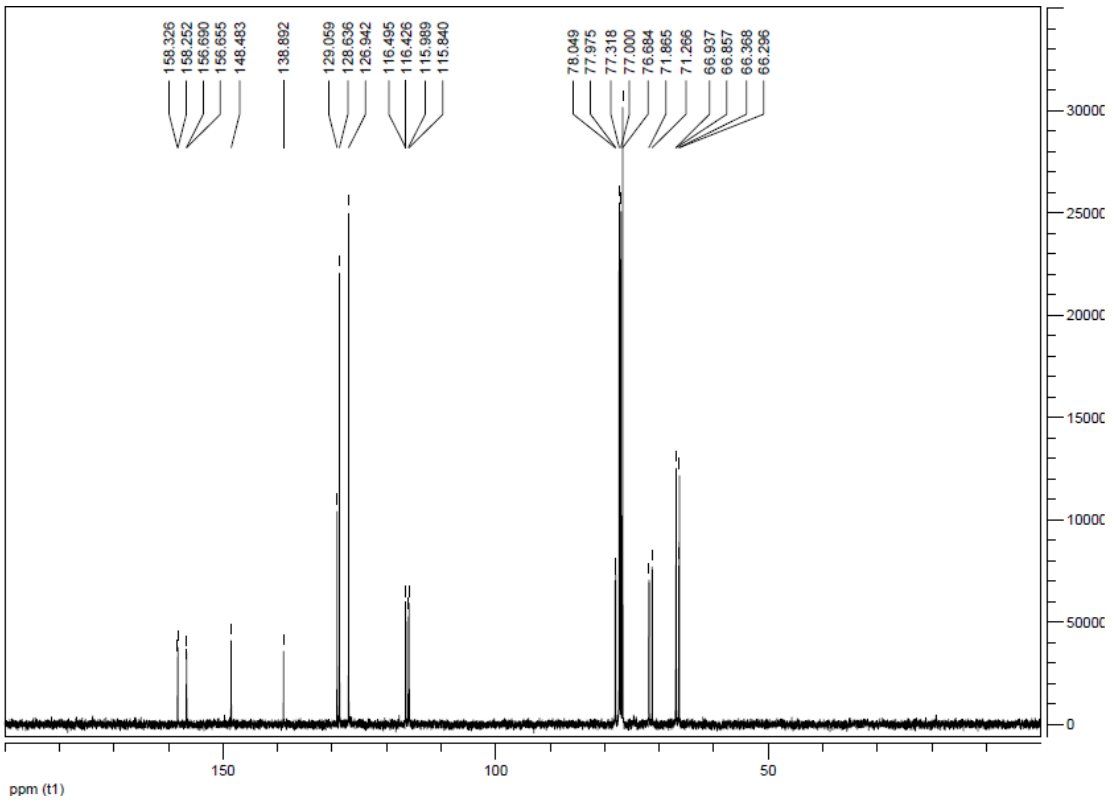

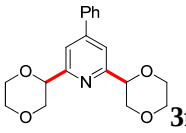

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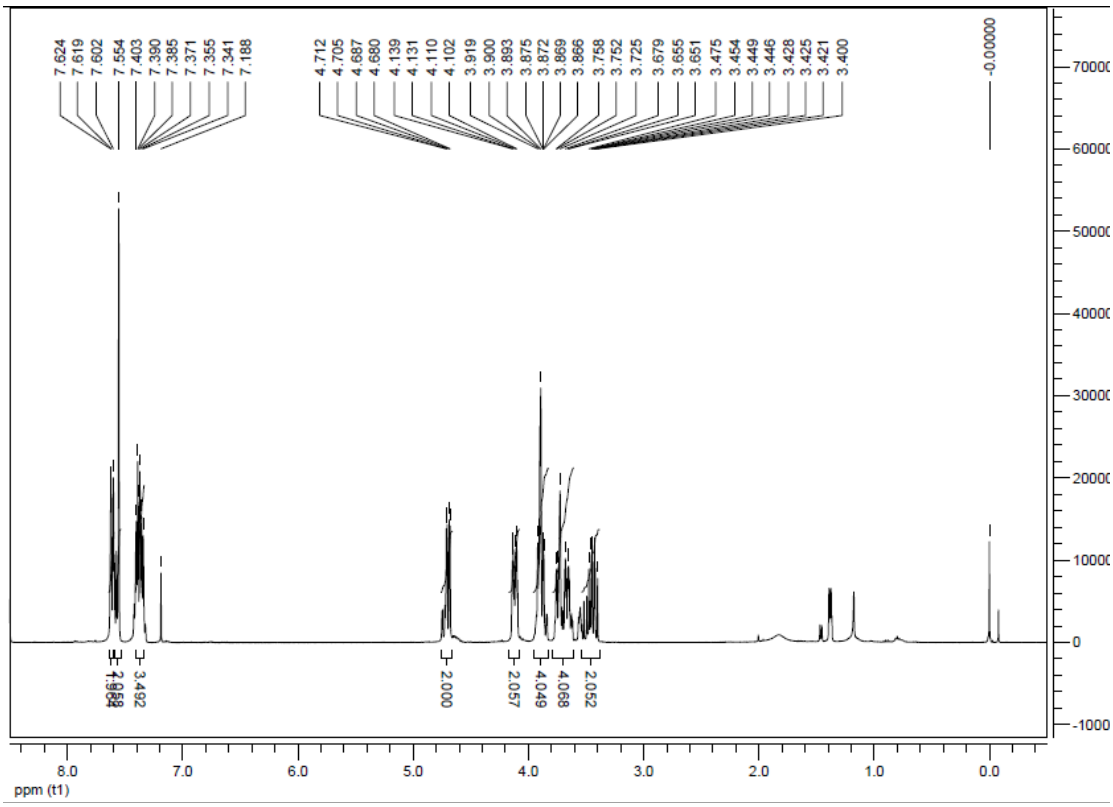

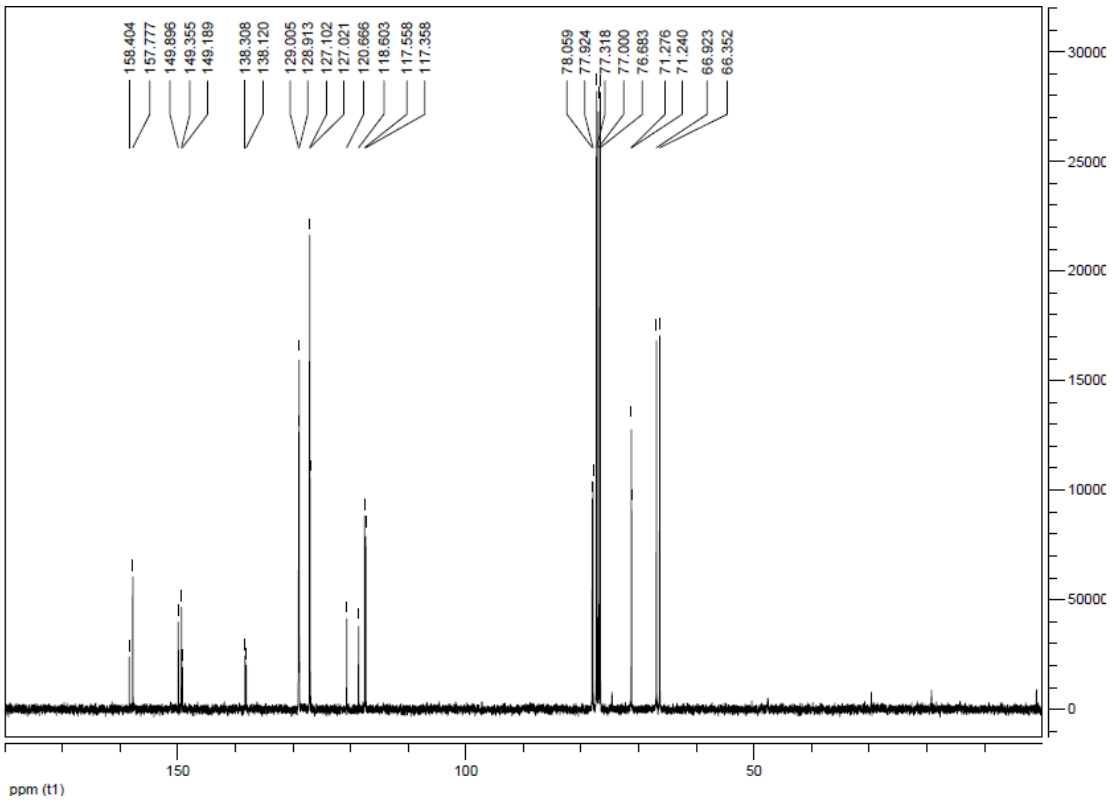

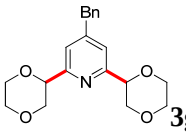

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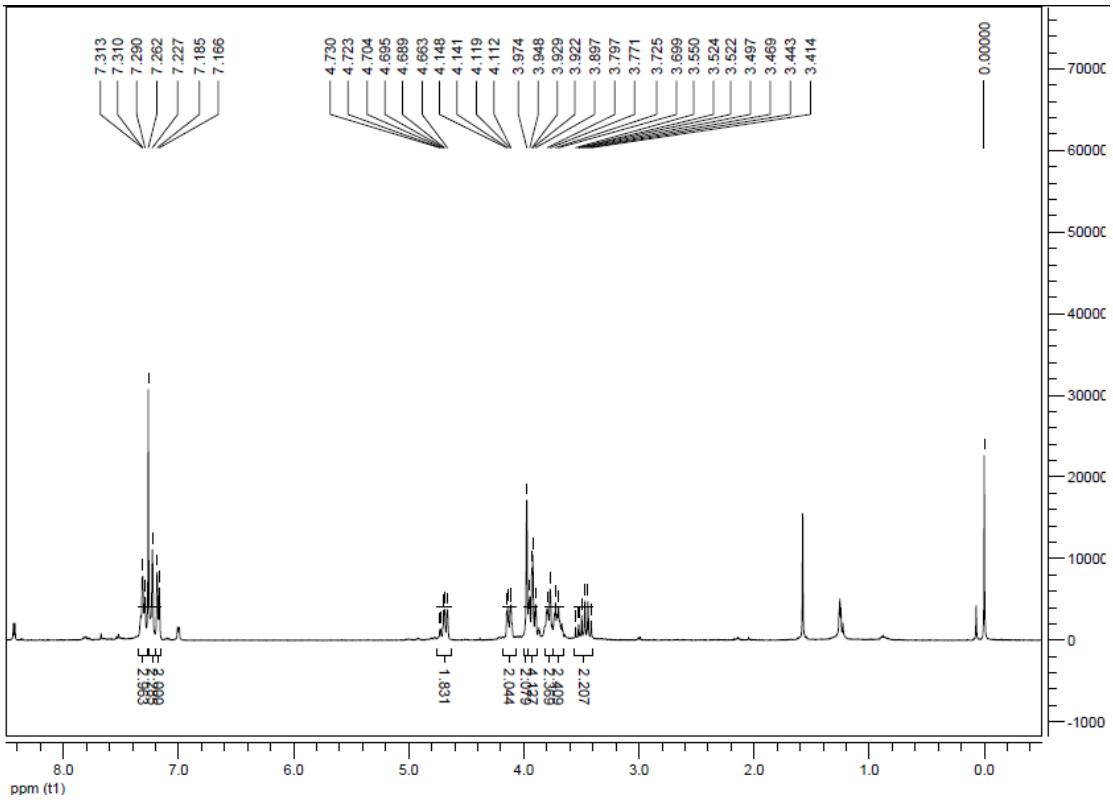

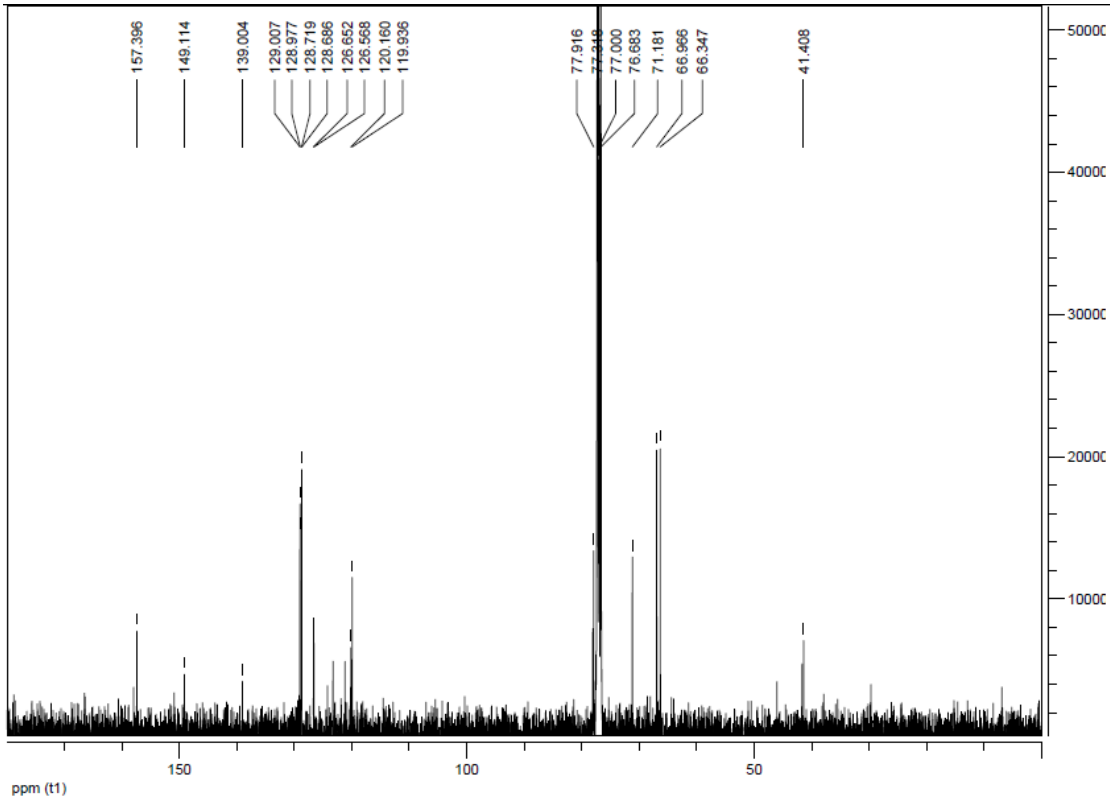

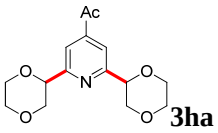

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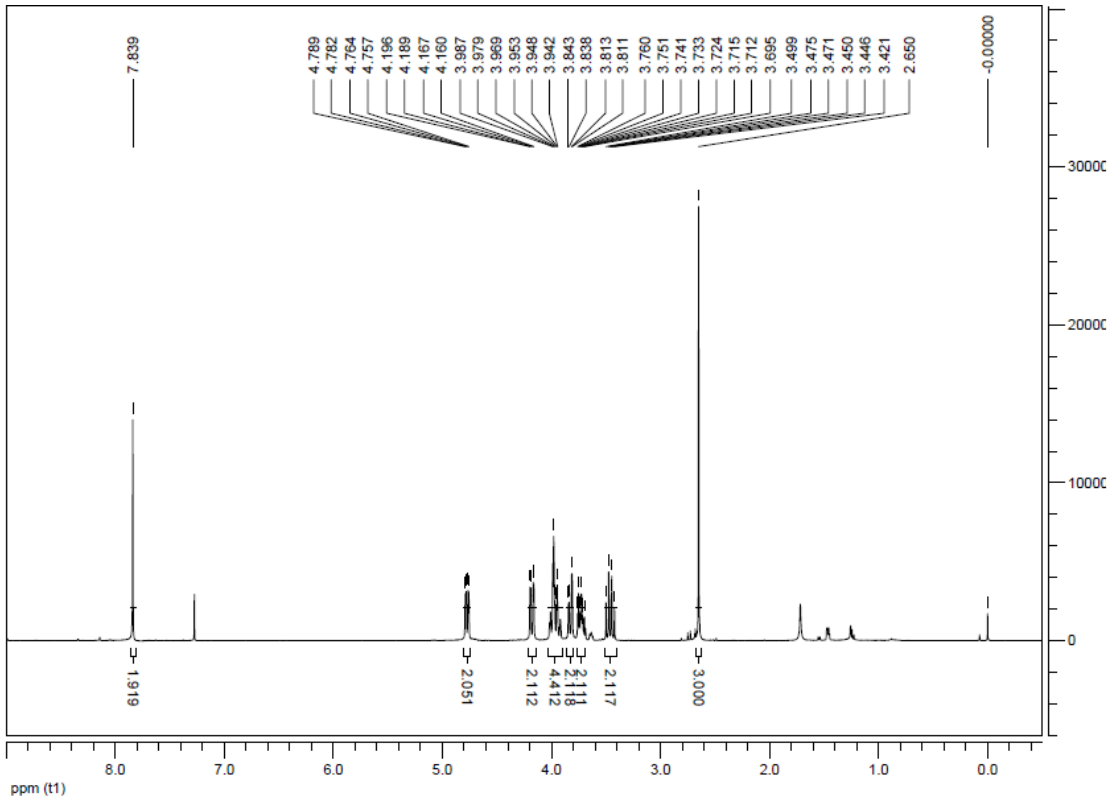

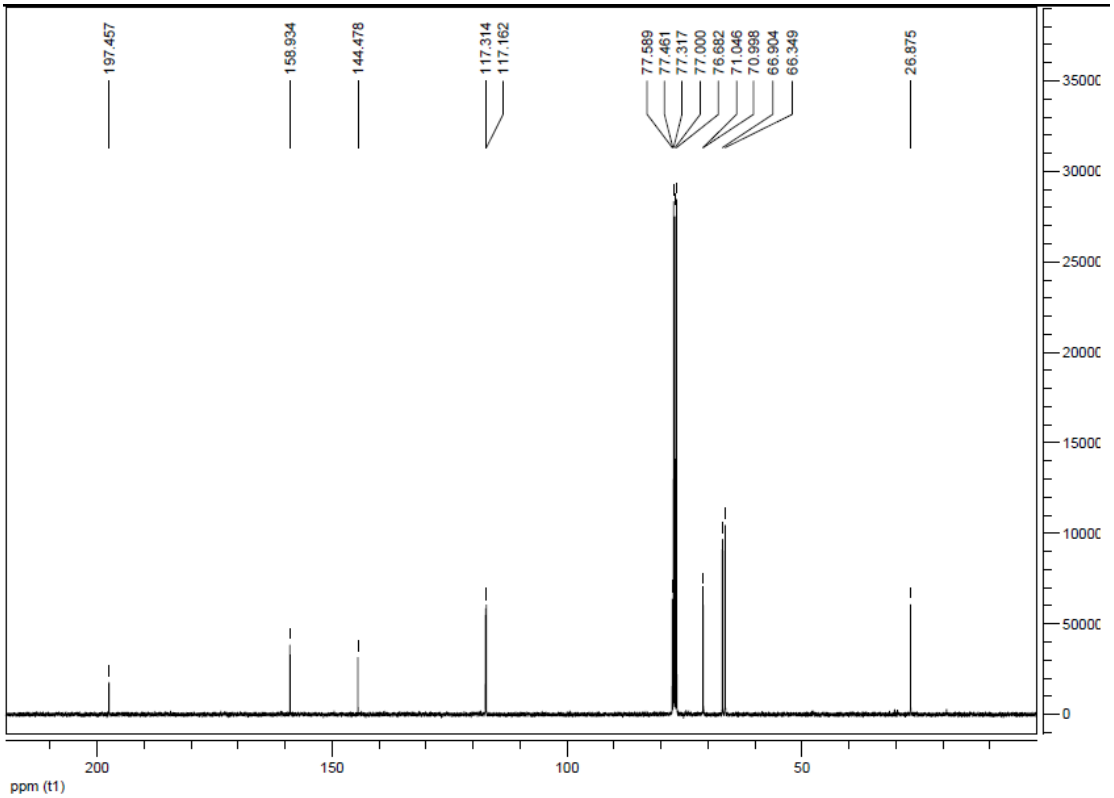

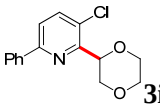

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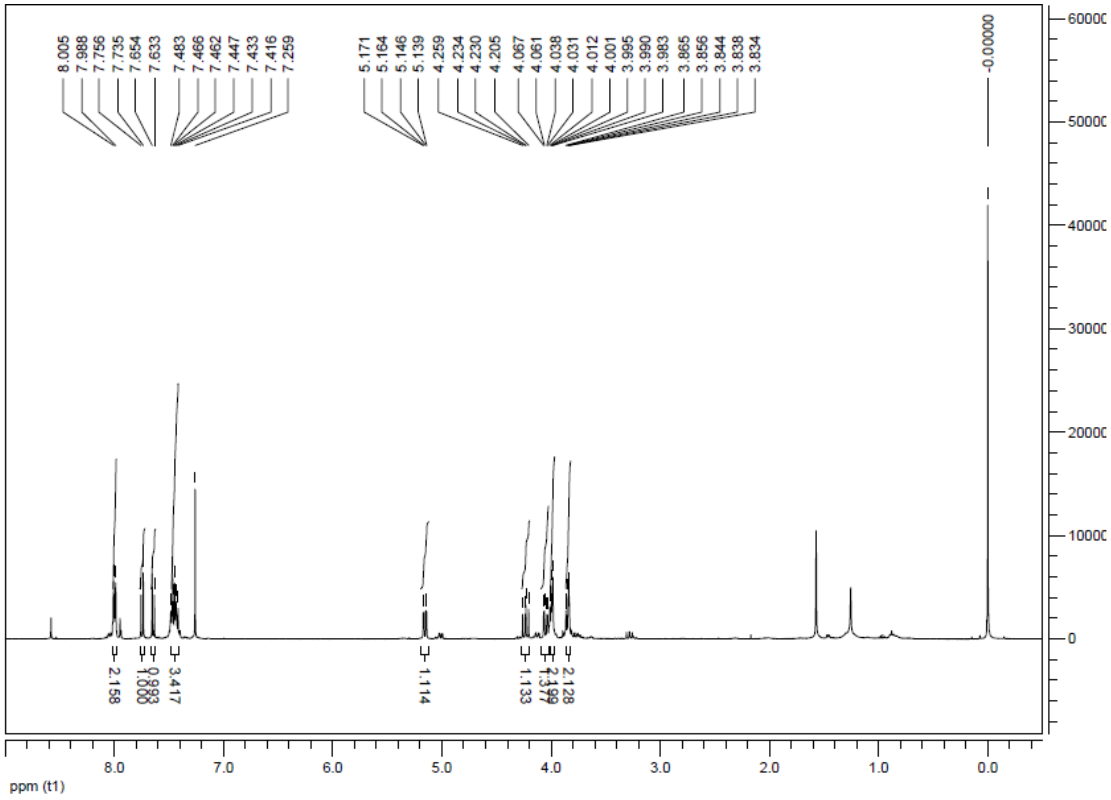

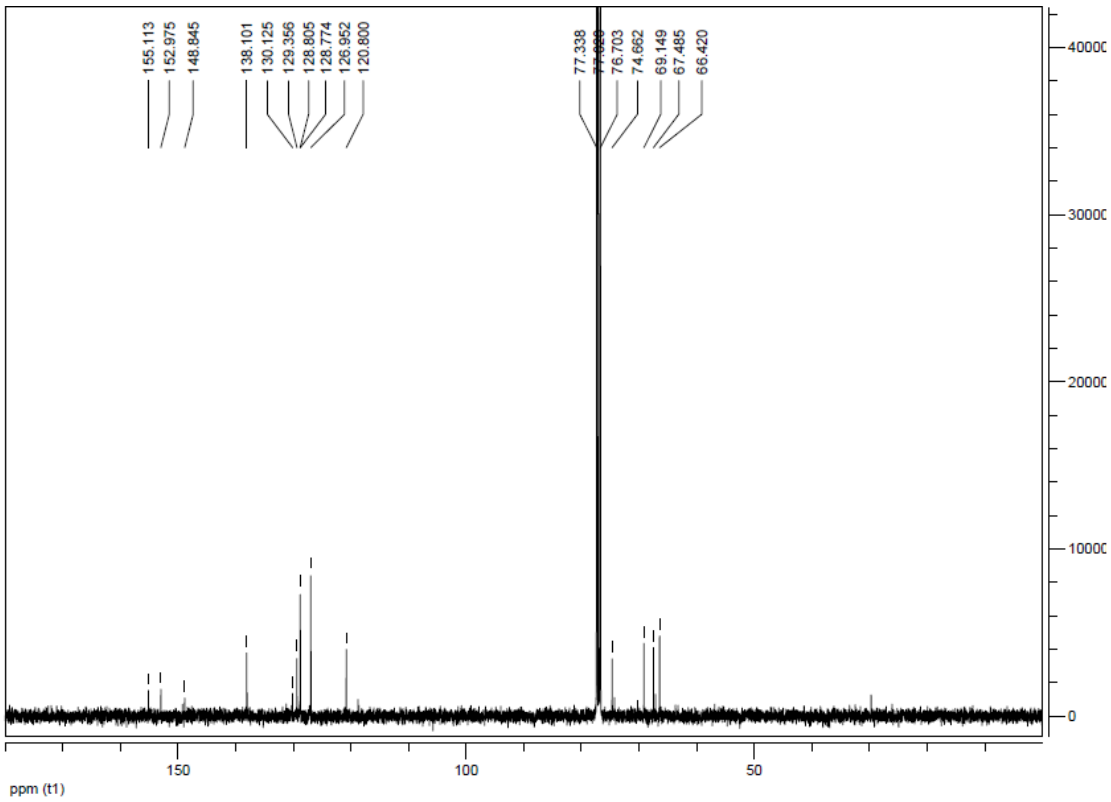

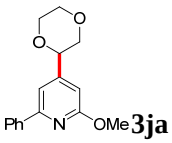

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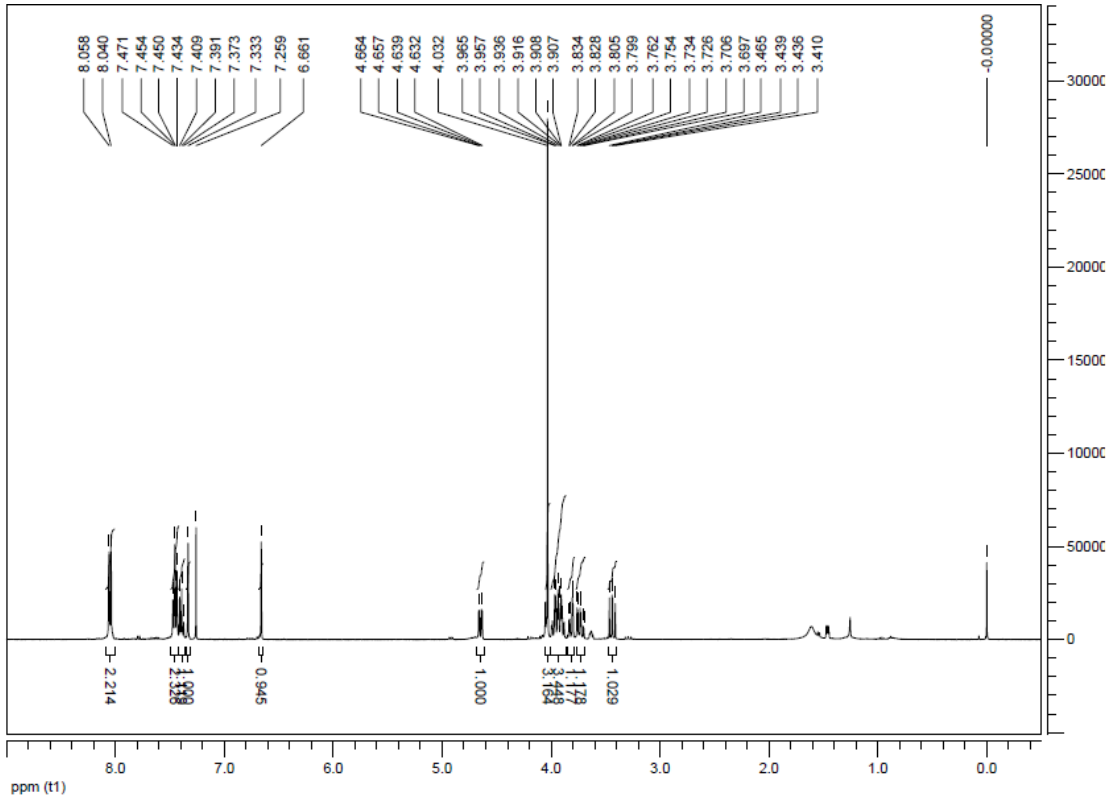

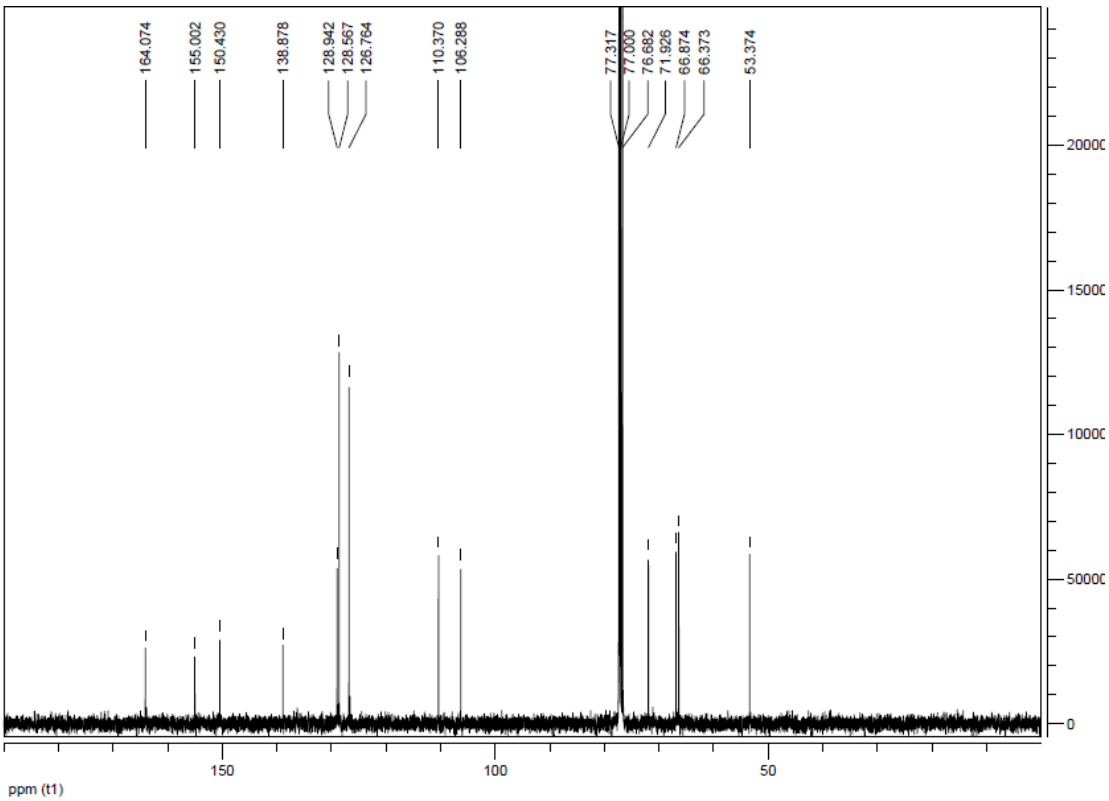

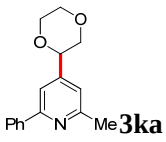

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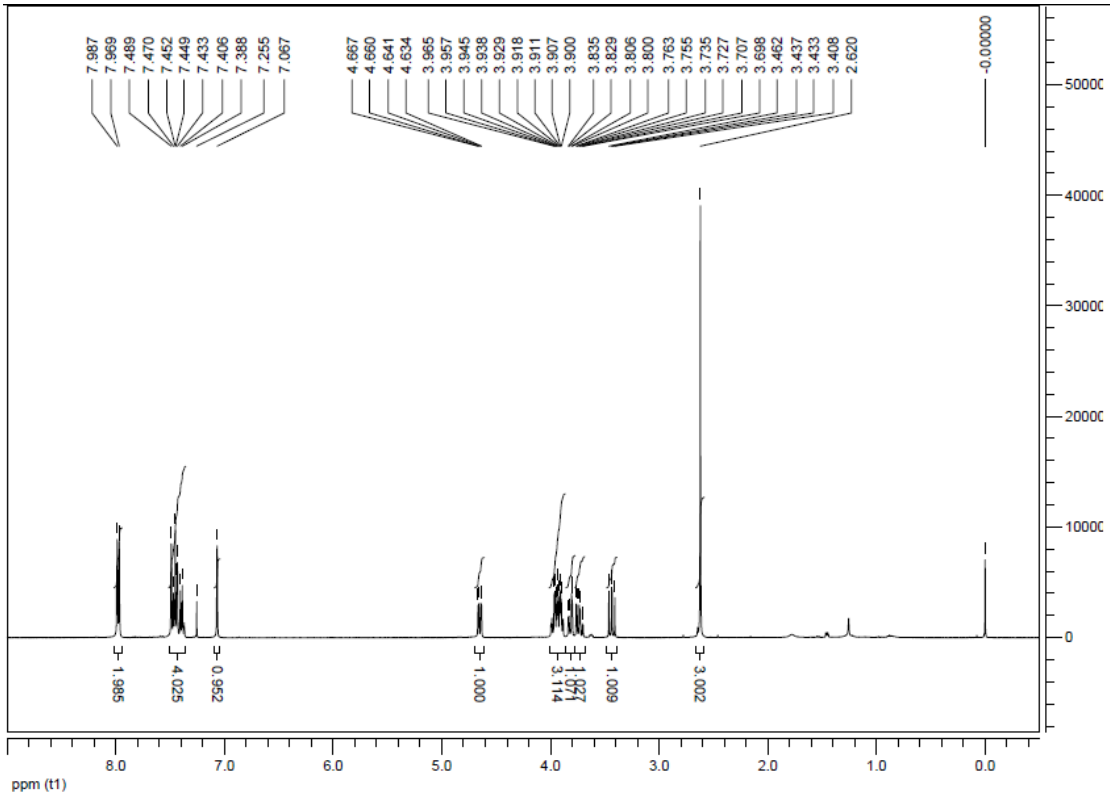

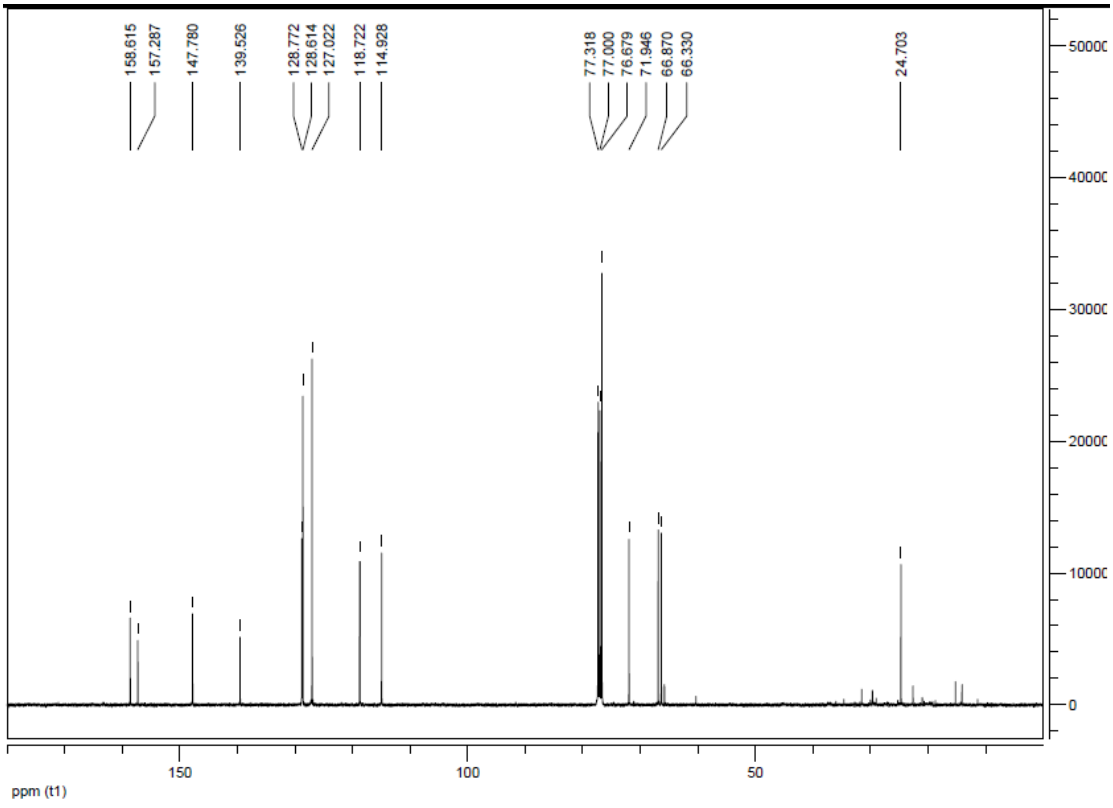

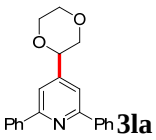

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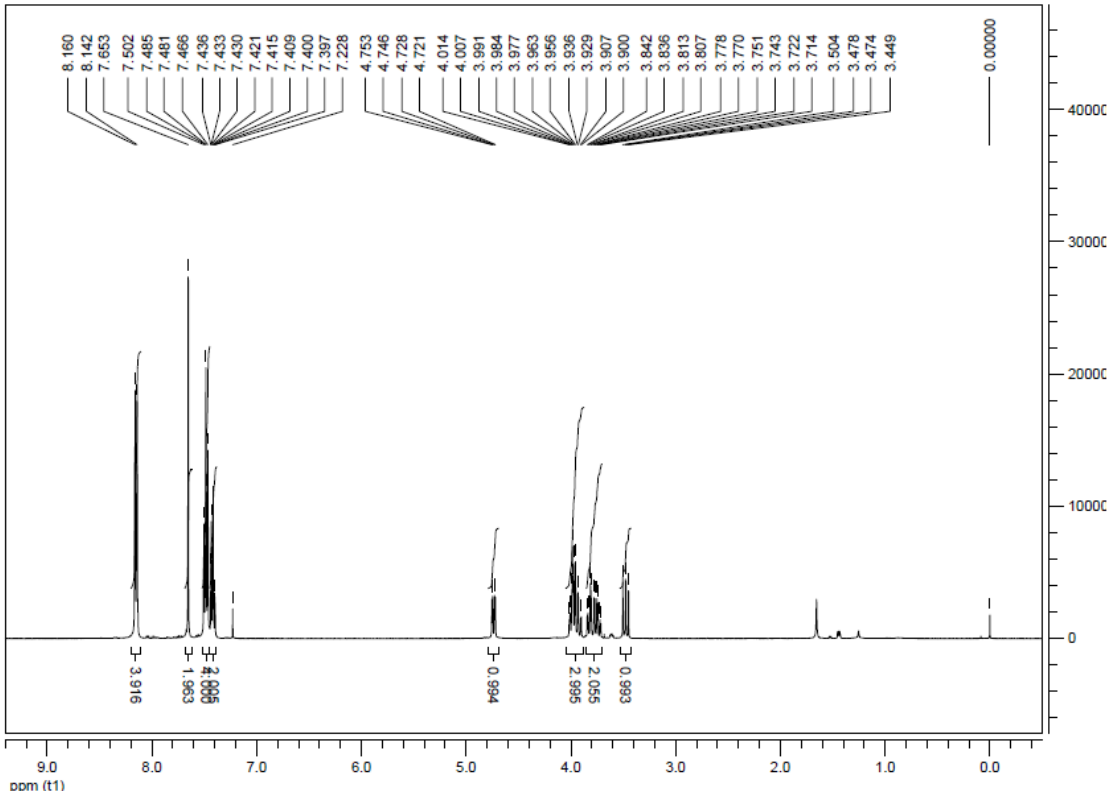

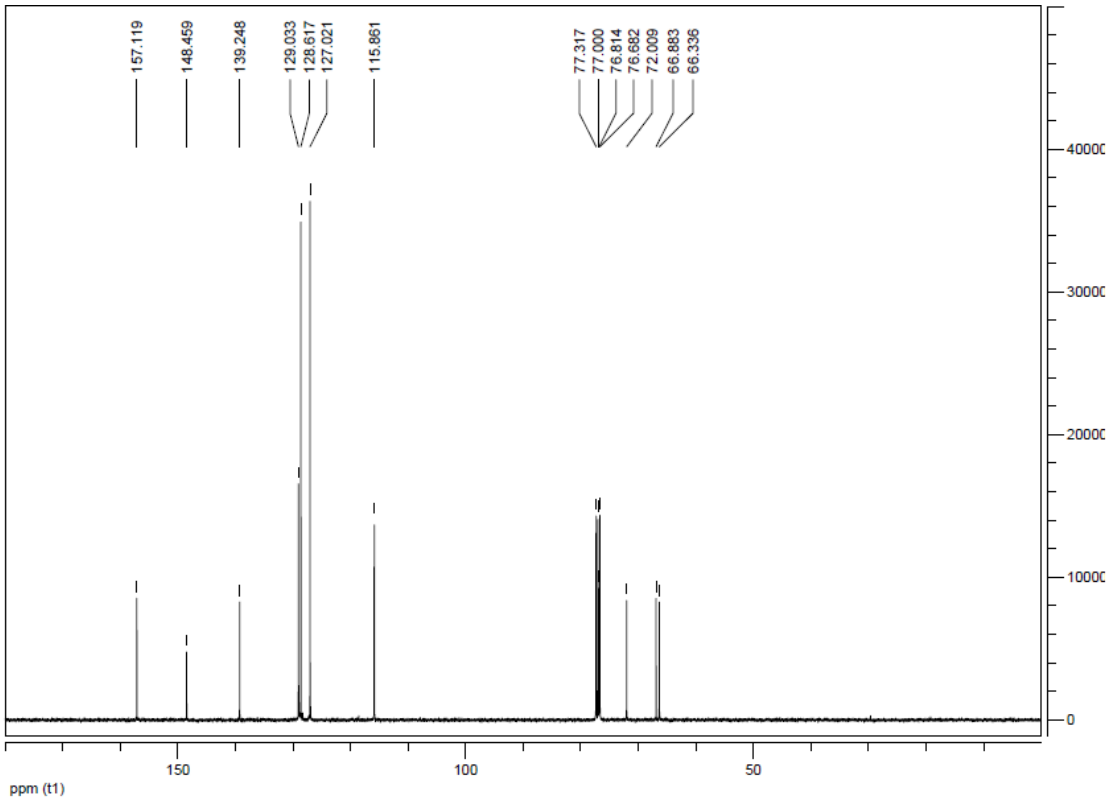

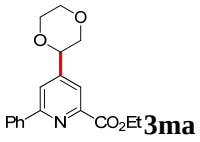

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