

Supporting Information

Rational Synthesis of Pyrazolopyrimidines via Cyclocondensation of Ynones Obtained from Sonogashira Reaction

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1. General considerations:

All the solvents were dried and distilled according to the literature. ¹H NMR, ¹³C NMR, and High resolution mass spectra (HRMS) were used to characterize all the isolated compounds. Nuclear magnetic resonance spectra were obtained using the Jeol or Bruker instrument operating at 400/100 MHz. Parts per million (ppm) is the unit of measurement for all ¹H NMR and ¹³C NMR experiments. The signals for residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) in the deuterated solvent were used for relative measurement. All ¹³C NMR spectra were acquired with ¹H decoupling and reported in ppm relative to deuteron dimethyl sulfoxide (40 ppm) and deuteron chloroform (77.23 ppm). An oil bath is a heat source for the reactions that need to be heated. Under UV light, TLC plates were observed. On silica gel 60-120 mesh, column chromatographic purifications were carried out. Unless otherwise specified, the beginning chemical reagents were used exactly as obtained after being purchased from commercial sources. The methods described in the literature were used to create starting compounds, and their spectroscopic characteristics agree well with those documented in the literature.

2. General Procedure for the synthesis of ynones (2, 4):

An oven dried round-bottom flask (100 mL) equipped with magnetic bar was charged with PdCl₂ (5.0 mol%), CuI, (2.0 mol%), PPh₃ (10.0 mol%), Et₃N (3.0 eq.) and ACN (5 mL) under inert atmosphere. Then, acyl chloride (1.0 eq) and alkyne (1.1 eq.) were added to the flask. The reaction mixture was allowed to stir at 70 °C for 2 hours. The completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool to room temperature and extracted with H₂O/EtOAc (10 mL/15 mL) 3 times. The organic layer

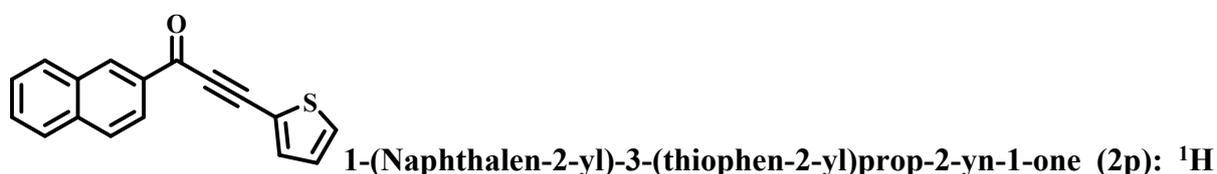
was dried over Na₂SO₄ and filtered. All the volatiles were removed under reduced pressure and the desired product was purified by silica gel chromatography.^[33-37]



(2m): ¹H NMR (400 MHz, CDCl₃) δ: 9.26(d, *J*=8.4 Hz, 1H), 8.63(d, *J*=7.6 Hz, 1H), 8.16(d, *J*=8.4 Hz, 1H), 7.96(d, *J*=8.0 Hz, 1H), 7.80(d, *J*=8.4 Hz, 2H), 7.74(d, *J*=8.4 Hz, 2H), 7.66-7.61(m, 2H), 7.28(s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 179.2, 135.6, 134.9, 133.9, 133.1, 132.5, 132.2, 131.9, 130.8, 129.2, 128.5, 126.9, 125.9, 125.6, 124.5, 118.2, 89.7, 89.2. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₂₀H₁₁NO: 282.0919; found: 282.0917.

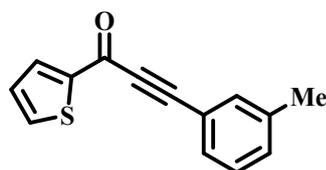


(2n): ¹H NMR (400 MHz, CDCl₃) δ: 9.15(d, *J*=8.8 Hz, 1H), 8.53(d, *J*=8.4 Hz, 1H), 8.00(d, *J*=8.0 Hz, 1H), 7.81(d, *J*=8.0 Hz, 1H), 7.67(d, *J*=8.0 Hz, 2H), 7.61-7.56(m, 3H), 7.52-7.46(m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ: 179.2, 135.6, 134.9, 133.9, 133.1, 132.5, 132.2, 131.9, 130.8, 129.2, 128.5, 126.9, 125.9, 125.6, 124.5, 124.2, 89.7, 89.2. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₂₀H₁₁F₃O: 325.0840; found: 325.0843.



(2p): ¹H NMR (400 MHz, CDCl₃) δ: 9.27(d, *J*=8.8 Hz, 1H), 8.62(d, *J*=7.2 Hz, 1H), 8.08(d, *J*=8.0 Hz, 1H), 7.90(d, *J*=8.4 Hz, 1H), 7.84(d, *J*=2.8 Hz, 1H), 7.70(t, *J*=6.8 Hz, 1H), 7.63-7.53(m, 3H), 7.38-7.33(m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 179.7, 135.6, 135.2, 134.6, 133.6, 132.9,

130.8, 130.3, 129.0, 128.7, 126.8, 126.3, 126.0, 124.5, 119.6, 88.8, 87.3. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₁₇H₁₀OS: 263.0531; found: 263.0525.



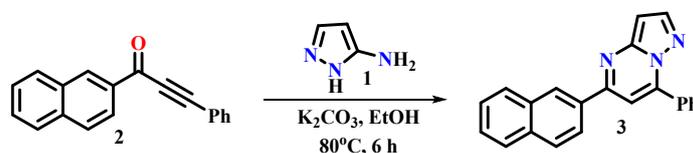
1-(Thiophen-2-yl)-3-(m-tolyl)prop-2-yn-1-one (4d): ¹H NMR

(400 MHz, CDCl₃) δ: 7.92(dd, *J*=4.0, 1.2 Hz, 1H), 7.63(dd, *J*=5.2, 1.2 Hz, 1 H), 7.40-7.38(m, 2H), 7.22-7.21(m, 2H), 7.11(t, *J*=4.8 Hz, 1H), 2.30 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 168.8, 143.9, 137.5, 134.2, 134.1, 129.2, 127.6, 127.3, 118.6, 91.1, 85.2, 20.2. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₁₄H₁₀OS: 227.0531; found: 227.0530.

3. General Procedure for the synthesis of Pyrazoles (3a-3p, 5a,5f):

An oven dried round-bottom flask (25 mL) equipped with stir bar was charged with ynone (2a-2p, 4a-4f) (0.5 mmol, 1.0 eq) and ethanol (0.5 mL) in the presence of K₂CO₃ (2.0 eq). 3-aminopyrazole (0.75 mmol, 2.0 eq) was added to the reaction mixture and stirred for 6 hrs at 80 °C. The completion of the reaction was monitored by TLC. After the completion, the reaction mixture was allowed to cool to room temperature and extracted with H₂O/EtOAc (10 mL/15 mL) 3 times. The organic layer was dried over Na₂SO₄ and filtered. All the volatiles were removed under reduced pressure and the desired product was purified by silica gel chromatography.

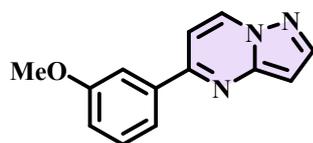
3.1 Optimization table for the synthesis of pyrazolo fused pyrimidies (3,5):



S. No	Base	Solvent	Temper - -ature (°C)	Tim e	Yiel d (%)
[1]	KOH (1.0 mmol)	DMSO	100	12 h	12
[2]	KOH (2.0	DMSO	100	12 h	18

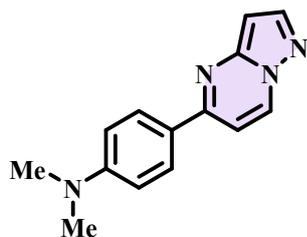
	mmol)				
[3]	K ₂ CO ₃ (1.0 mmol)	DMSO	100	12 h	10
[4]	K ₂ CO ₃ (1.0 mmol)	DMF	100	12 h	15
[5]	K ₂ CO ₃ (1.0 mmol)	H ₂ O	80	12 h	35
[6]	K ₂ CO ₃ (1.0 mmol)	EtOH	80	10 h	57
[7]	K ₂ CO ₃ (2.0 mmol)	EtOH	80	6 h	85
[8]	K ₂ CO ₃ (2.0 mmol)	EtOH	RT	24 h	68
[9]	K ₂ CO ₃ (2.0 mmol)	EtOH	0	24 h	-

Table S1: Optimization table for the synthesis of pyrazolo fused pyrimidies (3,5)



5-(3-Methoxyphenyl)pyrazolo[1,5-a]pyrimidine (3a): ¹H NMR

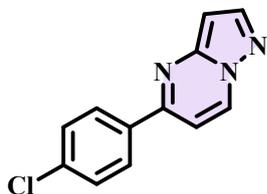
(400 MHz, CDCl₃) δ: 8.63(d, *J*=7.6 Hz, 1H), 8.05(d, *J*=2.4 Hz, 1H), 7.59(s, 1H), 7.53(d, *J*=7.6 Hz, 1H), 7.35-7.31(t, *J*=8.4 Hz, 1H), 7.17(m, 1H), 7.95(dd, *J*=2.0 Hz, 6.0 Hz, 1H), 6.63(d, *J*=1.6 Hz, 1H), 3.83(s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 159.1, 155.0, 147.4, 144.5, 137.5, 134.0, 128.9, 118.6, 115.6, 111.2, 104.6, 96.0, 54.4. HRMS (ESI) *m/z* (M+H)⁺: Calcd for C₁₃H₁₁ON₃: 226.0975; found: 226.0982.



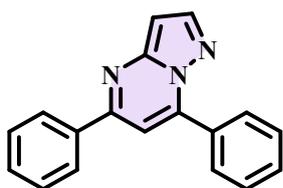
N,N-dimethyl-4-(pyrazolo[1,5-a]pyrimidin-5-yl)aniline (3b): ¹H

NMR (400 MHz, CDCl₃) δ: 8.98(d, *J*=7.6 Hz, 1H), 8.13-8.07(m, 3H), 7.50(d, *J*=7.6 Hz, 1H),

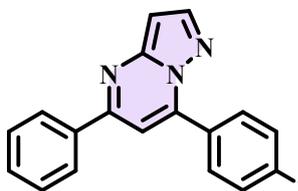
6.87-6.80(m, 2H), 6.58(d, $J=1.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ : 155.9, 152.30, 148.5, 145.4, 135.9, 128.7, 123.9, 112.2, 105.0, 95.6, 40.4. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4$: 239.1291; found:239.1301.



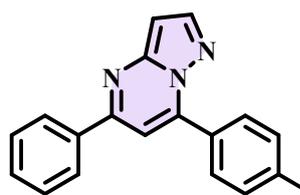
5-(4-Chlorophenyl)pyrazolo[1,5-a]pyrimidine (3c): ^1H NMR (400 MHz, CDCl_3) δ : 9.20(d, $J=7.6$ Hz, 1H), 8.25(m, 3H), 7.66(d, $J=7.2$ Hz, 1H), 7.61(d, $J=7.6$ Hz, 2H), 6.76(d, $J=2.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ : 154.5, 148.2, 146.0, 136.8, 135.9, 135.8, 129.4, 105.8, 96.9. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{12}\text{H}_8\text{ClN}_3$: 230.0480; found:230.0490.



5,7-Diphenylpyrazolo[1,5-a]pyrimidine (3d): ^1H NMR (400 MHz, CDCl_3) δ : 8.07, (d, $J=1.6$ Hz, 2H), 7.98(d, $J=6.4$ Hz, 3H), 7.92(m, 2H), 7.32(d, $J=6.8$ Hz, 2H), 7.10(d, $J=2.0$ Hz, 2H), 6.70(d, $J=2.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ : 155.2, 149.2, 145.9, 144.5, 136.8, 130.8, 130.3, 129.7, 128.7, 128.2, 127.9, 126.6, 104.4, 96.6. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_3$: 272.1182; found:272.1195.



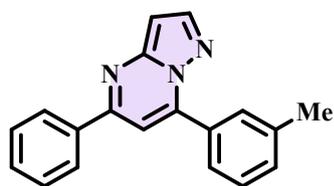
5-Phenyl-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine (3e): ^1H NMR (400 MHz, CDCl_3) δ : 8.07, (d, $J=2.4$ Hz, 2H), 7.97-7.93(m, 4H), 7.51-7.48(m, 3H), 7.24-7.22(m, 3H), 6.69(d, $J=2.4$ Hz, 1H), 2.34(s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 156.1, 149.8, 146.6, 145.0, 140.6, 134.6, 131.5, 130.8, 129.6, 129.2, 128.6, 127.1, 105.0, 96.9, 21.4. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_3$: 286.1344; found:286.1341.



7-(4-Methoxyphenyl)-5-phenylpyrazolo[1,5-a]pyrimidine (3f):

¹H NMR (400 MHz, CDCl₃) δ: 8.05, (d, *J*=2.4 Hz, 1H), 8.01(d, *J*=8.8 Hz, 2H), 7.97-7.95(m, 2H), 7.51-7.48(m, 3H), 7.20(s, 1H), 6.94(d, *J*=8.8 Hz, 2H), 6.66(d, *J*=2.4 Hz, 1H), 3.79(s, 3H).

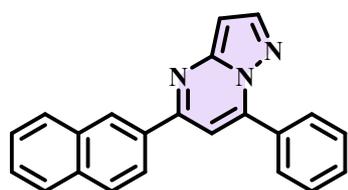
¹³C NMR (100 MHz, CDCl₃) δ: 161.5, 155.7, 149.8, 146.6, 145.0, 131.6, 130.8, 129.9, 129.2, 128.7, 128.6, 114.2, 104.7, 96.7, 55.4. **HRMS (ESI) *m/z* (M+H)⁺:** Calcd for C₁₉H₁₅N₃O: 302.1293; found:302.1290.



5-phenyl-7-(m-tolyl)pyrazolo[1,5-a]pyrimidine (3g):

¹H NMR (400 MHz, CDCl₃) δ: 8.08, (d, *J*=2.4 Hz, 1H), 7.98-7.96(m, 2H), 7.88(s, 1H), 7.80 (d, *J*=8 Hz, 1H), 7.50-7.48(m, 3H), 7.32 (t, *J*=7.6 Hz, 1H), 7.24-7.21(m, 2H), 6.72(d, *J*=2.4 Hz, 1H), 2.34(s, 3H).

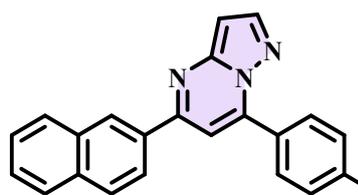
¹³C NMR (100 MHz, CDCl₃) δ: 155.4, 148.8, 145.7, 144.1, 137.7, 136.4, 130.5, 130.1, 129.9, 128.2, 127.9, 127.8, 127.7, 126.8, 126.2, 123.4, 104.3, 96.1, 20.5. **HRMS (ESI) *m/z* (M+H)⁺:** Calcd for C₁₈H₁₃N₃: 286.1344; found:286.1344.



5-(Naphthalen-2-yl)-7-phenylpyrazolo[1,5-a]pyrimidine (3h):

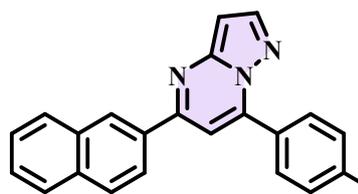
¹H NMR (400 MHz, CDCl₃) δ: 8.19-8.10, (m, 4H), 8.01(d, *J*=8.0 Hz, 1H), 7.81(d, *J*=6.8 Hz, 1H), 7.68 (t, *J*=8.0 Hz, 1H), 7.60-7.44(m, 7H), 6.89(d, *J*=2.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ: 155.9, 149.5, 146.6, 145.5, 137.4, 133.6, 131.1, 130.7, 130.4, 129.5, 129.0, 128.8, 127.9, 127.4, 127.2, 126.6, 125.3, 125.1, 107.4, 97.3. **HRMS (ESI) *m/z* (M+H)⁺:** Calcd for C₂₂H₁₅N₃: 322.1344; found: 322.1339.



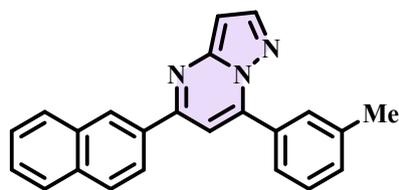
Me 5-(Naphthalen-2-yl)-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine

(3i): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.10, (t, $J=7.6$ Hz, 4H), 8.01(d, $J=8.0$ Hz, 1H), 7.79(d, $J=6.4$ Hz, 1H), 7.68 (t, $J=8.4$ Hz, 1H), 7.58(t, $J=6.4$ Hz, 1H), 7.52-7.45(m, 2H), 7.42 (s, 1H), 7.36(d, $J=8.0$ Hz, 2H), 6.86(d, $J=2.0$ Hz, 1H), 2.47(s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 156.0, 149.5, 146.5, 145.5, 140.8, 134.6, 133.6, 131.0, 130.7, 129.8, 129.6, 127.9, 128.8, 128.0, 127.3, 127.1, 126.6, 125.3, 125.1, 107.2, 97.0, 21.5. **HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$** : Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3$: 336.1501; found: 336.1502.



OMe 7-(4-methoxyphenyl)-5-(naphthalen-2-yl)pyrazolo[1,5-

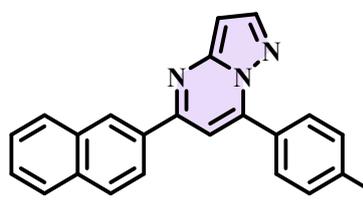
a]pyrimidine (3j): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.15, (d, $J=8.8$ Hz, 2H), 8.11-8.09(m, 2H), 8.00(d, $J=8.0$ Hz, 1H), 7.79(d, $J=7.2$ Hz, 1H), 7.67 (t, $J=8.0$ Hz, 1H), 7.57(t, $J=6.4$ Hz, 2H), 7.50-7.47(m, 1H), 7.38 (s, 1H), 7.06(d, $J=8.8$ Hz, 2H), 6.84(d, $J=2.4$ Hz, 1H), 3.91(s, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 161.5, 155.5, 149.4, 146.3, 145.3, 130.9, 129.7, 128.8, 127.8, 127.0, 126.5, 125.2, 125.0, 114.2, 106.8, 96.7, 55.3. **HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$** : Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}$: 352.1450; found: 352.1452.



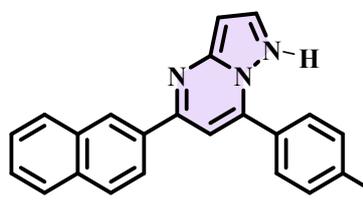
5-(Naphthalen-2-yl)-7-(m-tolyl)pyrazolo[1,5-a]pyrimidine

(3k): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.12, (m, 2H), 8.01(t, $J=6.8$ Hz, 2H), 7.94(d, $J=7.6$ Hz, 1H), 7.80 (d, $J=6.8$ Hz, 1H), 7.68(t, $J=8.0$ Hz, 1H), 7.58(t, $J=6.4$ Hz, 1H), 7.51-7.46(m, 2H), 7.43(t, $J=4.4$, 2H), 7.35(d, $J=7.6$ Hz, 1H), 6.88(d, $J=2.0$ Hz, 1H), 2.50(s, 3H). $^{13}\text{C NMR}$ (100

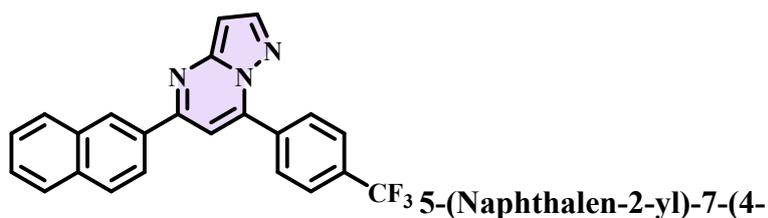
MHz, CDCl₃) δ : 156.1, 149.4, 146.4, 145.4, 138.7, 137.2, 133.5, 131.2, 131.0 130.6, 129.4, 128.8, 128.7, 127.9, 127.8, 127.1, 126.5, 125.2, 125.0, 124.5, 107.4, 97.1, 21.5. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₂₃H₁₇N₃: 336.1501; found: 336.1502.



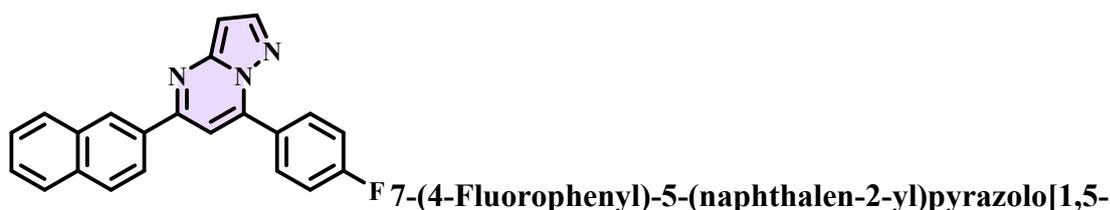
7-(4-Chlorophenyl)-5-(naphthalen-2-yl)pyrazolo[1,5-a]pyrimidine (3): **¹H NMR (400 MHz, CDCl₃)** δ : 8.01-8.79(m, 4H), 7.87(d, *J*=8.4 Hz, 1H), 7.65(dd, *J*=6.0 Hz, 1.2 Hz, 1H), 7.55(t, *J*=6.8 Hz, 1H), 7.47-7.43(m, 1H), 7.38(d, *J*=8.8 Hz, 2H), 7.35-7.33(m, 2H), 7.25(s, 1H), 6.75(d, *J*=2.4 Hz, 1H), 2.50(s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ : 153.5, 148.3, 145.8, 144.6, 135.6, 134.7, 132.5, 130.1, 129.6, 128.3, 128.2, 127.7, 127.6, 126.8, 126.1, 125.6, 124.2, 123.9, 105.8, 96.3. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₂₂H₁₄ClN₃: 356.0955; found: 356.0956.



4-(5-(Naphthalen-2-yl)pyrazolo[1,5-a]pyrimidin-7-yl)benzonitrile (3m): **¹H NMR (400 MHz, CDCl₃)** δ : 8.30(d, *J*=8.4 Hz, 2H), 8.17(d, *J*=2.4 Hz, 1H), 8.12(d, *J*=8.4 Hz, 1H), 8.01(d, *J*=8.0 Hz, 1H), 7.84(d, *J*=8.4 Hz, 2H), 7.79(d, *J*=6.0 Hz, 1H), 7.69(t, *J*=8.0 Hz, 1H), 7.61-7.57(m, 1H), 7.49-7.44(m, 3H), 6.93(d, *J*=2.4 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ : 153.4, 149.3, 147.2, 146.0, 141.4, 133.6, 132.7, 131.4, 130.5, 129.1, 128.9, 127.9, 127.3, 126.7, 125.3, 124.8, 118.5, 113.8, 107.0, 98.0. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₂₃H₁₄N₄: 347.1297; found: 347.1306.



(trifluoromethyl)phenyl)pyrazolo[1,5-a]pyrimidine (3n): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.29(d, $J=8.4$ Hz, 2H), 8.16(d, $J=2.4$ Hz, 1H), 8.11(d, $J=8.4$ Hz, 1H), 8.00(d, $J=8.0$ Hz, 1H), 7.81-7.76(m, 4H), 7.66(t, $J=8.0$ Hz, 1H), 7.60-7.56(m, 1H), 7.48(s, 1H), 7.43(s, 1H), 6.93 (d, $J=2.4$ Hz, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 154.1, 149.5, 147.0, 145.8, 140.6, 133.6, 131.3, 130.6, 129.3, 129.1, 128.6, 128.0, 127.7, 127.2, 126.7, 125.9, 125.1, 124.9, 107.1, 97.8. **HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$** : Calcd for $\text{C}_{23}\text{H}_{14}\text{F}_3\text{N}_4$: 390.1218; found: 390.1212.

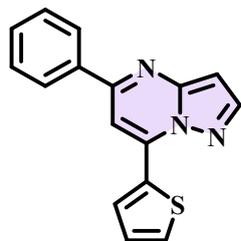


a]pyrimidine (3o): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.20-8.17(m, 2H), 8.12-8.10(m, 2H), 8.00(d, $J=8.0$ Hz, 1H), 7.79(dd, $J=4.0$ Hz, 1.2 Hz, 1H), 7.70-7.66(m, 1H), 7.60-7.56(m, 1H), 7.48(t, $J=6.0$ Hz, 2H), 7.67(t, $J=8.0$ Hz, 1H), 7.38(s, 1H), 7.23(t, $J=8.8$ Hz, 2H), 6.86(d, $J=2.4$ Hz, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 163.1, 154.8, 149.4, 146.8, 145.6, 133.6, 131.1, 130.7, 129.4, 128.8, 127.9, 127.2, 126.6, 126.2, 125.3, 125.0, 116.1, 115.9, 107.0, 97.2. **HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$** : Calcd for $\text{C}_{22}\text{H}_{14}\text{FN}_3$: 340.1250; found: 340.1277.



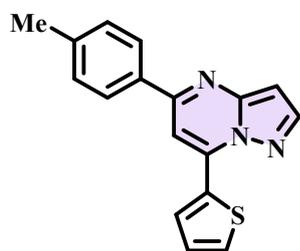
(3p): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.11-8.09(m, 2H), 8.05(dd, $J=4.0$ Hz, 1.2 Hz, 1H), 8.1(d, $J=8.0$ Hz, 1H), 7.86(dd, $J=4.0$ Hz, 1.2 Hz, 1H), 7.77(d, $J=6.0$ Hz, 1H), 7.67(t, $J=8.4$ Hz, 1H),

7.59-7.55(m, 1H), 7.50-7.44(m, 3H), 7.69(s, 1H), 6.83(d, $J=2.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ : 151.8, 149.4, 146.6, 145.5, 140.6, 133.6, 131.1, 130.7, 129.4, 128.8, 127.9, 127.2, 126.9, 126.6, 126.6, 126.1, 125.3, 125.0, 107.6, 97.0. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{S}$: 328.0908; found: 328.0924.



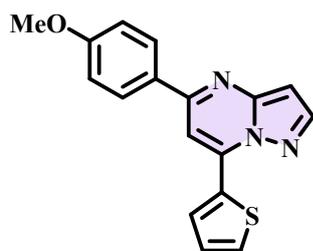
5-Phenyl-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (5a): ^1H NMR (400

MHz, CDCl_3) δ : 8.28(d, $J=4.0$ Hz, 1H), 8.15(d, $J=2.0$ Hz, 1H), 7.93(d, $J=8.0$ Hz, 2H), 7.62(dd, $J=4.0$ Hz, 1.2 Hz, 1H), 7.55(s, 1H), 7.24(d, $J=8.0$ Hz, 2H), 7.19-7.17(m, 1H), 6.69(d, $J=2.4$ Hz, 1H), 2.35(s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 155.7, 149.9, 144.8, 140.0, 137.7, 131.9, 131.3, 130.2, 128.9, 127.6, 127.3, 101.7, 97.2. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{16}\text{H}_{11}\text{N}_3\text{S}$: 278.0752; found: 278.0749.



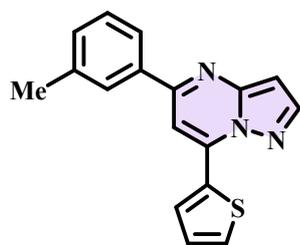
7-(Thiophen-2-yl)-5-(*p*-tolyl)pyrazolo[1,5-a]pyrimidine (5b): ^1H NMR

(400 MHz, CDCl_3) δ : 8.30 (dd, $J = 3.9, 1.2$ Hz, 1H), 8.17 (d, $J = 2.3$ Hz, 1H), 7.87 (s, 1H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.63 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.57 (s, 1H), 7.36-7.31 (m, 1H), 7.21-7.17 (m, 2H), 6.71 (d, $J = 2.3$ Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 155.6, 149.9, 144.7, 140.4, 139.9, 134.8, 131.9, 131.7, 129.6, 128.8, 128.5, 127.5, 127.1, 101.5, 96.9, 21.4. HRMS (ESI) m/z ($\text{M}+\text{H}$) $^+$: Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{S}$: 292.0908; found: 292.0907.



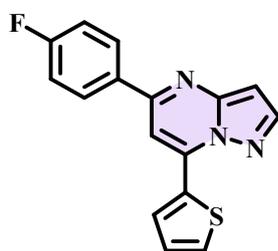
5-(4-Methoxyphenyl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (5c):

¹H NMR (400 MHz, CDCl₃) δ: 8.28-8.26(m, 1H), 8.14(d, *J*=3.2 Hz, 1H), 8.00(dd, *J*=6.8 Hz, 2.0 Hz, 2H), 7.62-7.60(m, 1H), 7.50(d, *J*=3.2 Hz, 1H), 7.19-7.16(m, 1H), 6.93(dd, *J*=6.8 Hz, 2.0 Hz, 1H), 6.66(d, *J*=2.4 Hz, 2H), 3.79(s, 3H). **¹³C NMR (100 MHz, CDCl₃) δ:** 161.3, 155.2, 149.9, 144.6, 139.8, 131.8, 131.7, 130.8, 128.6, 127.5, 114.2, 113.1, 101.2, 96.7, 55.4. **HRMS (ESI) *m/z* (M+H)⁺:** Calcd for C₁₇H₁₃N₃SO: 308.0858; found: 308.0862.



7-(Thiophen-2-yl)-5-(m-tolyl)pyrazolo[1,5-a]pyrimidine (5d):

¹H NMR (400 MHz, CDCl₃) δ: 8.28(dd, *J*=2.4 Hz, 1.2 Hz, 1H), 8.16(d, *J*=2.4 Hz, 1H), 7.87(s, 1H), 7.80(d, *J*=8.0 Hz, 1H), 7.62(dd, *J*=4.0 Hz, 1.2 Hz, 1H), 7.57(s, 1H), 7.36-7.31(m, 1H), 7.21-7.17(m, 2H), 6.71(d, *J*=2.4 Hz, 1H), 2.39(s, 3H). **¹³C NMR (100 MHz, CDCl₃) δ:** 155.6, 149.9, 144.7, 140.4, 139.9, 134.8, 131.9, 131.7, 129.6, 128.8, 128.5, 127.5, 127.1, 101.5, 96.9, 21.4. **HRMS (ESI) *m/z* (M+H)⁺:** Calcd for C₁₇H₁₃N₃S: 292.0908; found: 292.0909.

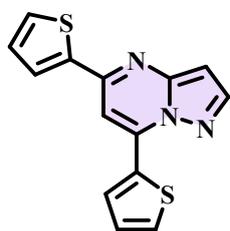


5-(4-Fluorophenyl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (5e):

¹H NMR (400 MHz, CDCl₃) δ: 8.30 (dd, *J* = 3.9, 1.2 Hz, 1H), 8.17 (d, *J* = 2.3 Hz, 1H), 7.87 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.63 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.57 (s, 1H), 7.36-7.31 (m, 1H), 7.21-7.17 (m, 2H), 6.71 (d, *J* = 2.3 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃) δ:** 154.6, 149.9,

144.9, 140.2, 133.9, 132.3, 131.9, 131.8, 131.4, 129.2, 127.7, 116.0, 101.3, 97.2. **HRMS (ESI)**

m/z (M+H)⁺: Calcd for C₁₆H₁₀FN₃S: 296.0658; found: 296.0662.



5,7-Di(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (5f) PPy64: ¹H NMR (400

MHz, CDCl₃) δ: 8.37(d, *J*=3.2 Hz, 1H), 8.24(d, *J*=2.4 Hz, 1H), 8.06(d, *J*=2.0 Hz, 1H), 7.82(d, *J*=4.4 Hz, 1H), 7.72(d, *J*=4.8 Hz, 1H), 7.54(s, 1H), 7.47-7.45(m, 1H), 7.29-7.27(m, 1H), 6.76(d, *J*=2.4 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃) δ**: 151.5, 149.8, 144.8, 140.8, 139.9, 131.8, 131.2, 127.6, 126.7, 126.5, 125.7, 101.8, 96.9. **HRMS (ESI) m/z (M+H)⁺**: Calcd for C₁₄H₉N₃S₂: 284.0316; found: 284.0342.

4. Calculation of green chemistry metrics for the scale-up reaction of the product (3):

Green chemistry matrix has been calculated based on the following parameters.

- 1) E-factor or environmental factor
- 2) Atom economy (AE)
- 3) Product mass intensity (PMI)
- 4) Reaction mass efficiency (RME)

E-factor: E-factor is defined as the ratio of the mass of waste per mass of the product.

E-Factor = Amount of waste/Amount of product

Amount of reactants: ynone (1) = 1.0 mmol and 3-aminopyrazole (2) = 1.5 mmol

Total amount of reactants (1h+2) = (256.30 mg/mmol × 1.0 mmol) + (83.09 mg/mmol × 1.5 mmol) = 256.30 mg + 124.64 mg = 380.94 mg = 0.381 g

Amount of product (3h) = 0.257 g

Amount of waste = 0.381 g – 0.257 g = 0.124g

E-factor = 0.124/ 0.257 = 0.48 (Ideal value of E-factor is considered zero)

Process mass index (PMI): PMI is defined as the total mass used in a chemical process divided by the mass of product.

PMI = Σ(mass of stoichiometric reactants + solvent)/mass of product (3h)

PMI = (256.30 mg × 1.0) + (83.09 mg × 1.5)/257 = 1.48

OR

PMI = E-factor +1= 0.32+1 =1.48

Atomic economy (AE): AE of a chemical reaction is a measure of the efficiency of that reaction with regard to how many atoms from the starting materials reside within the product. The ideal value of AE factor is 100% (i.e., all atoms from the starting materials reside in the product).

Atom economy (AE) = MW of product \div Σ (MW of stoichiometric reactants) \times 100

Molecular weight of product (3h) = 321.38 g/mol

Molecular weight of stoichiometric reactants (1h+2) = (256.30)(1.0) + (83.09)(1.5) = 380.94 g/mol

Atom economy (AE) = $321.38 \times 100 / 380.94 = 84.4\%$

Reaction mass efficiency (RME): Reaction mass efficiency is defined as the mass of product divided by the sum of total mass of stoichiometric reactants. The value of RME varies from 0-100%. The larger number of RME is considered as better as it is the measure of "cleanness" of the reaction.

Reaction mass efficiency = mass of product \div Σ (mass of stoichiometric reactants) \times 100

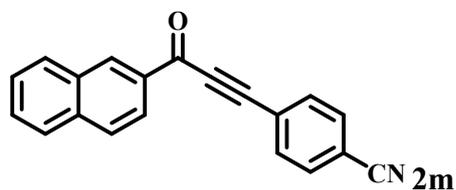
Mass of product (3h) = 0.257 g

Total mass of reactants (1h+2) = (256.30 mg/mmol \times 1.0 mmol) + (83.09 mg/mmol \times 1.5 mmol) = 256.30 mg + 124.64 mg = 380.94 mg = 0.381 g

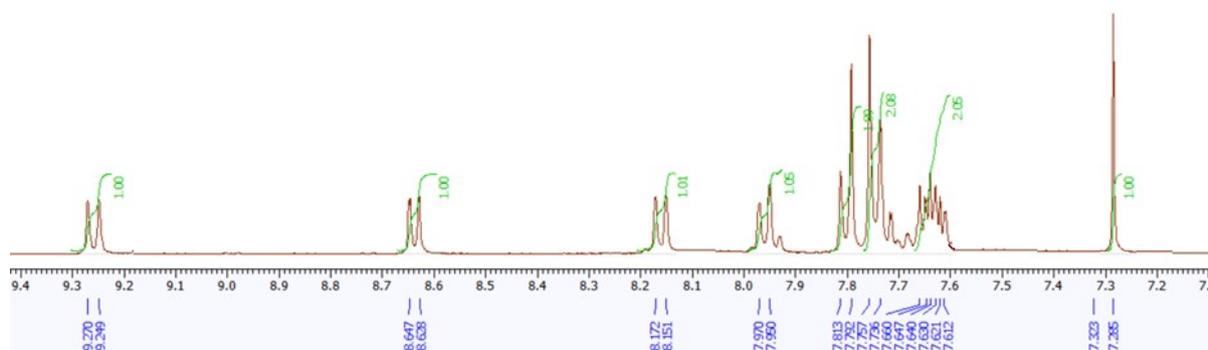
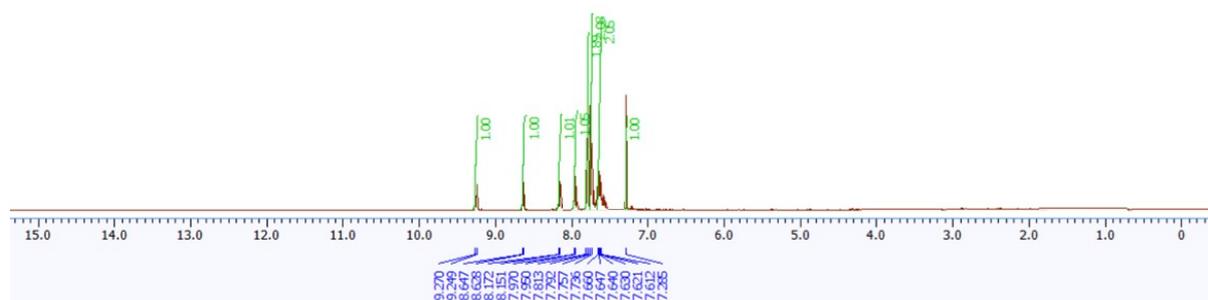
RME = $(0.257 \div 0.381) \times 100 = 67.4\%$

SPECTRAL DATA

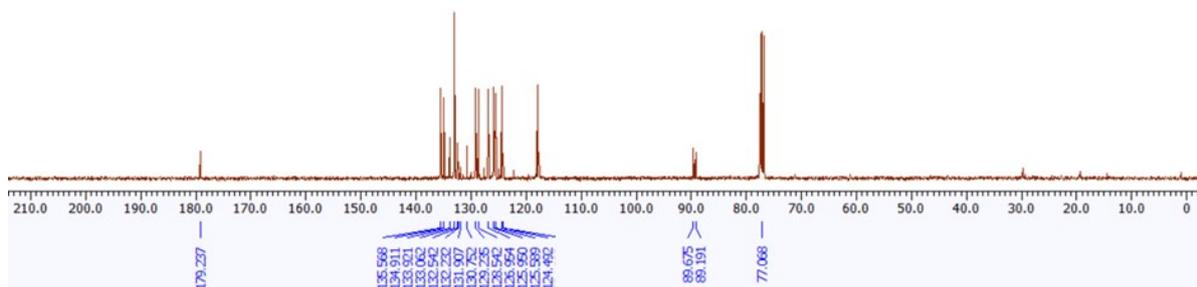
COPIES OF ^1H , ^{13}C NMR DATA & HRMS



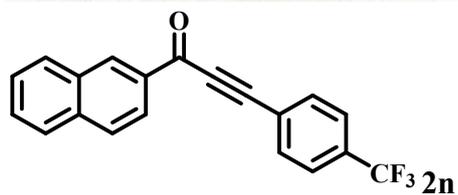
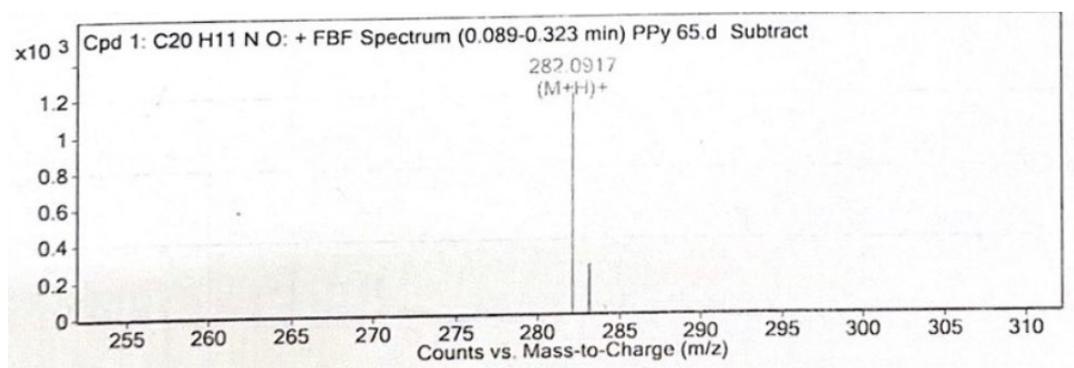
^1H NMR



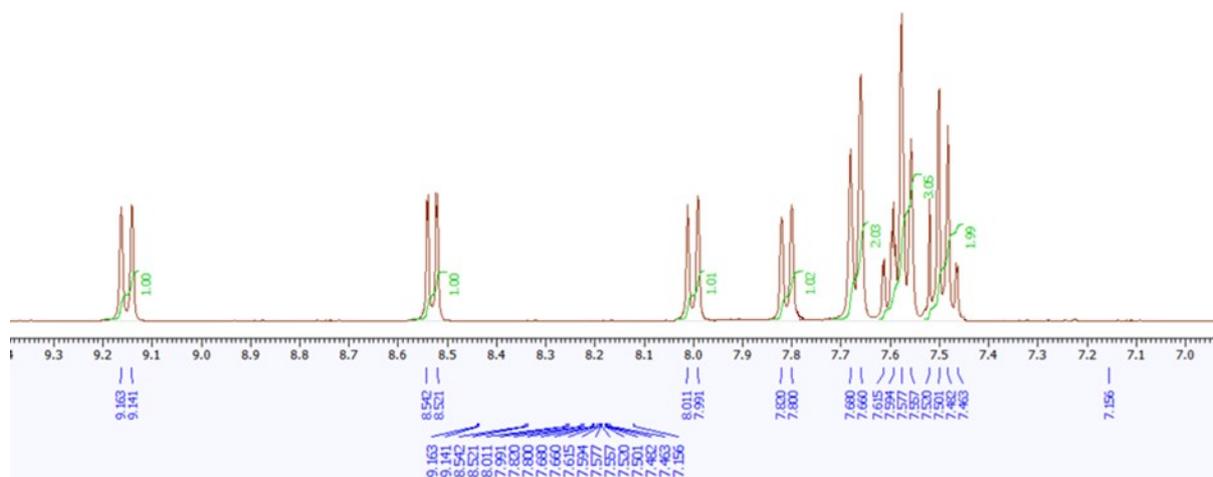
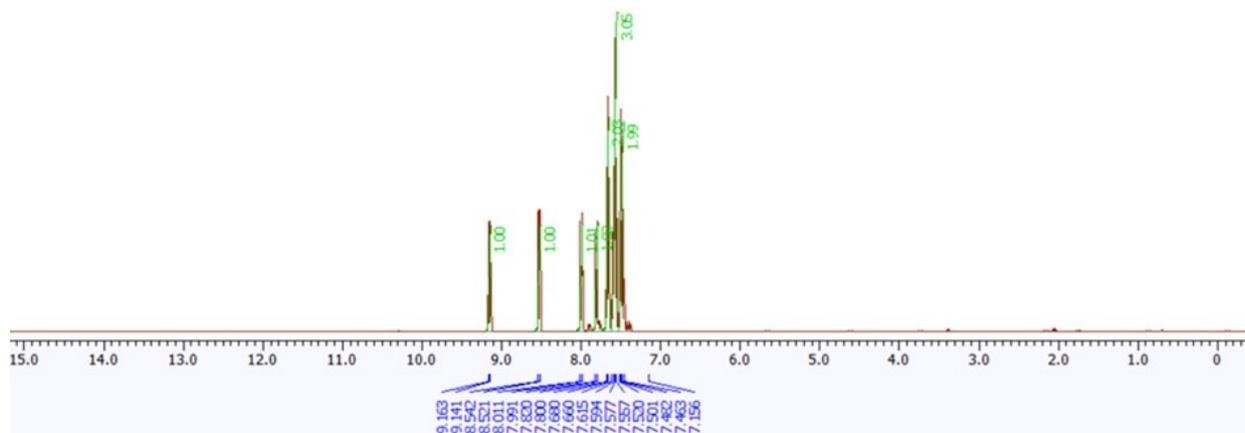
^{13}C NMR



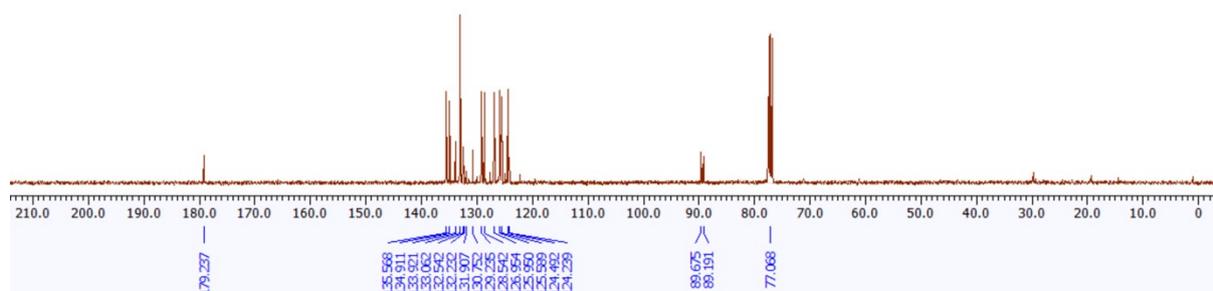
HRMS



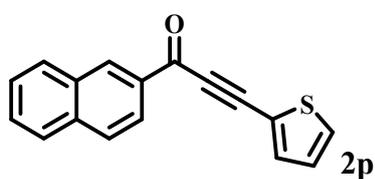
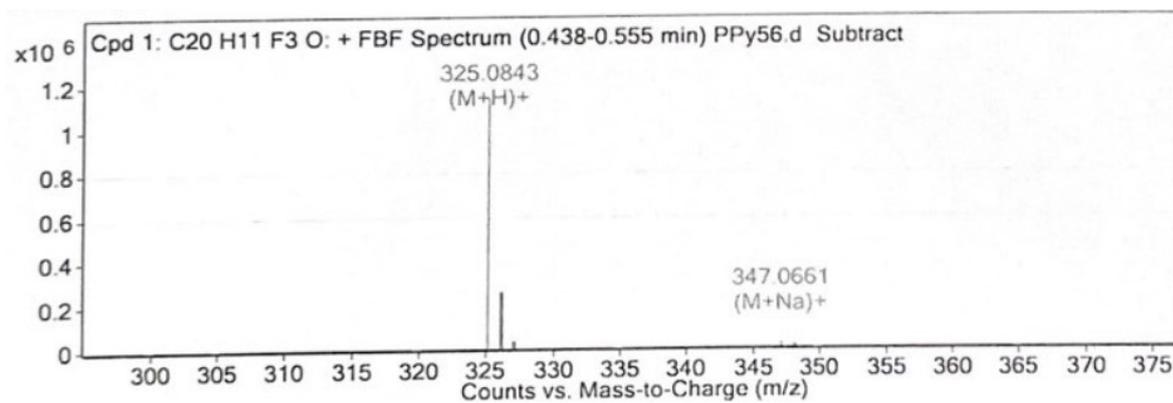
¹H NMR



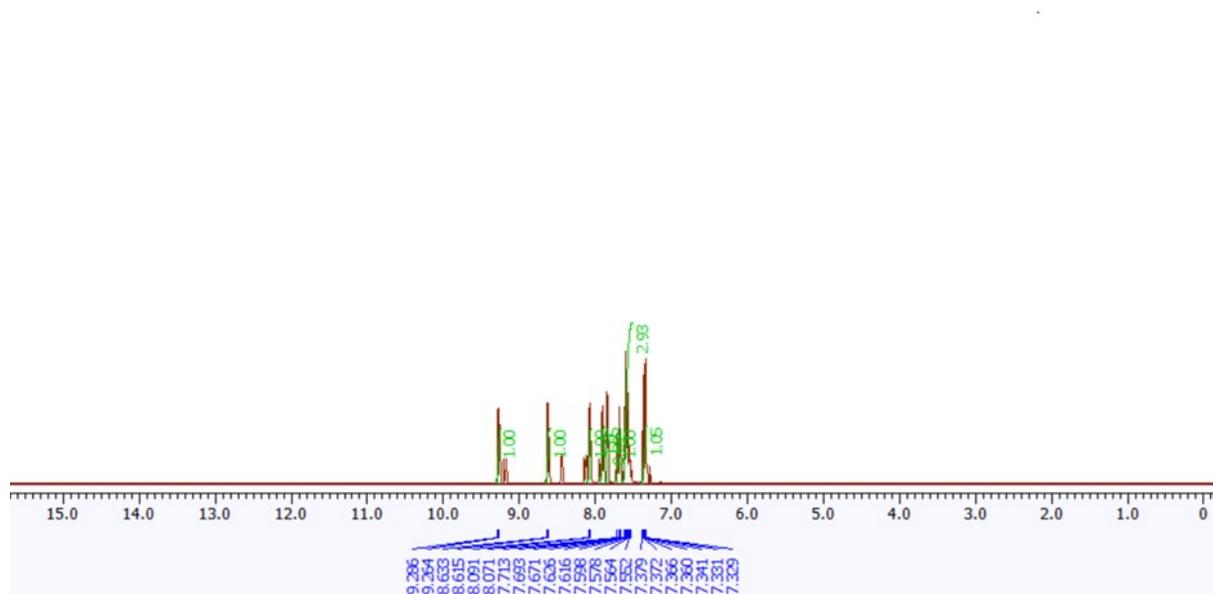
¹³C NMR

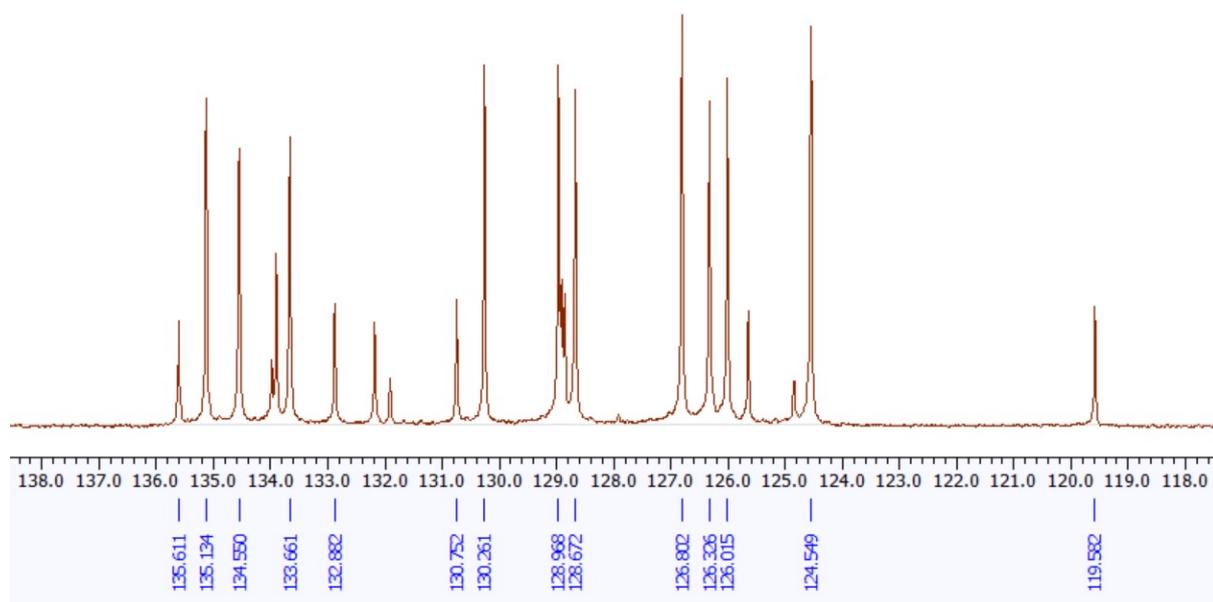


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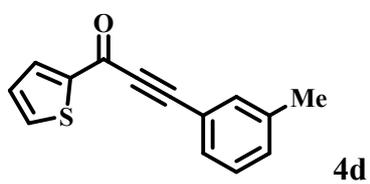
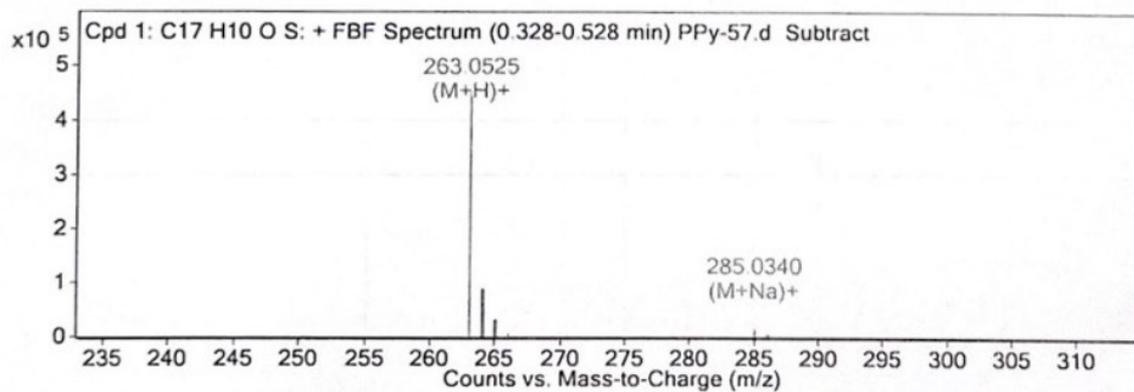


¹H NMR

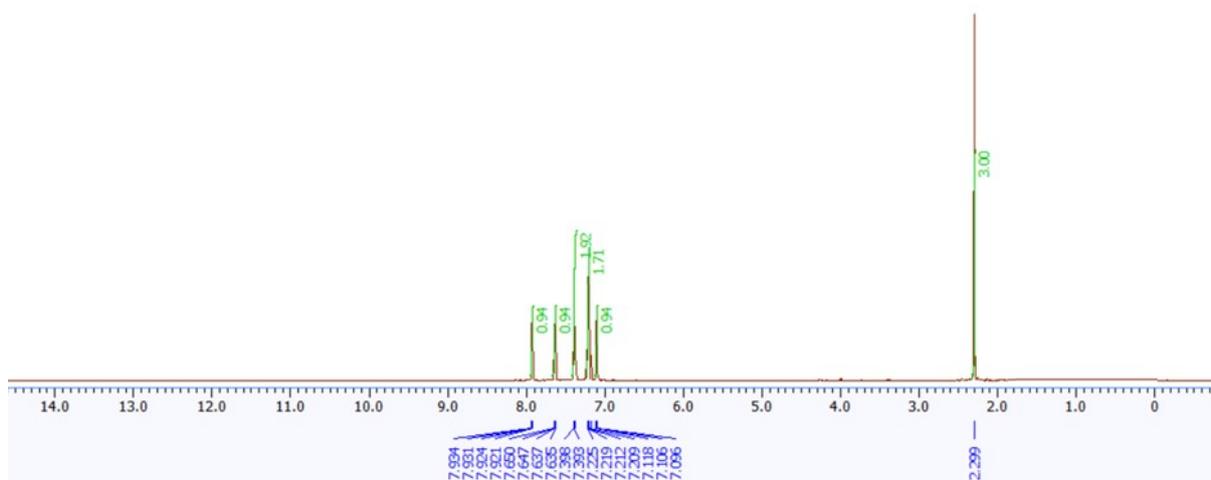




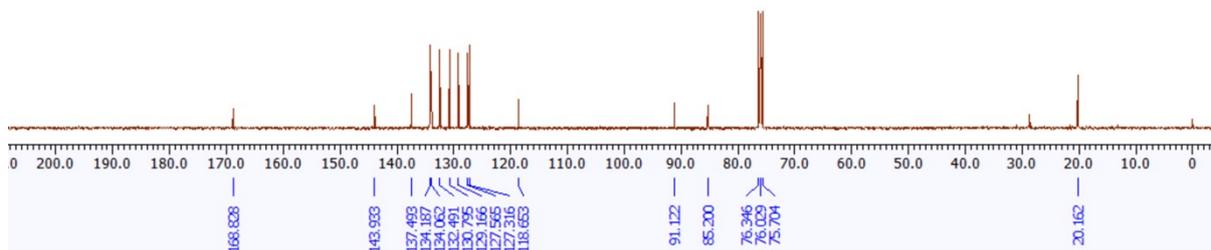
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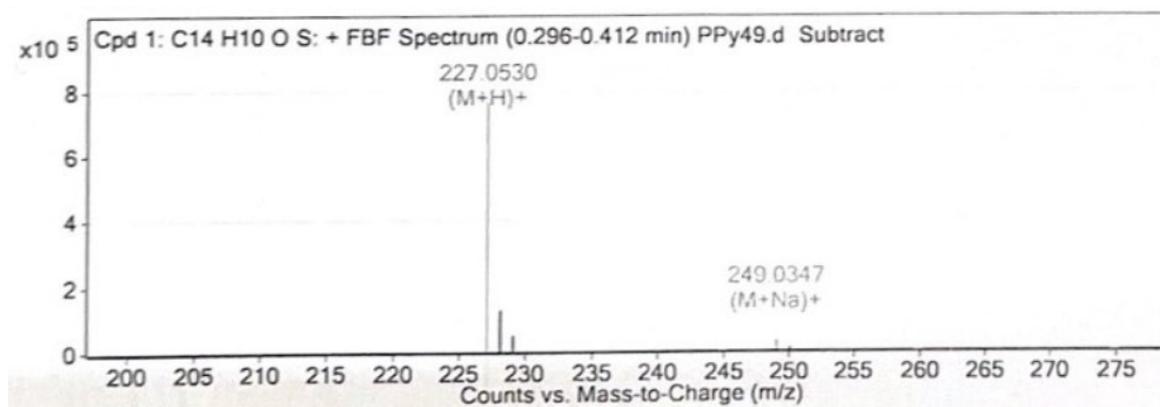
¹H NMR

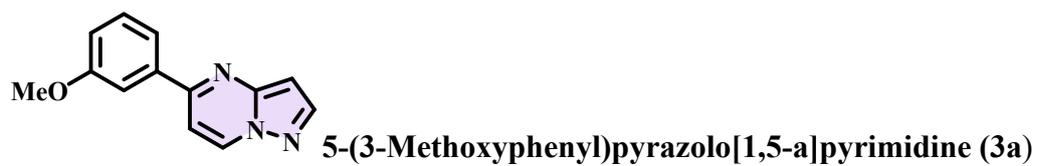


¹³C NMR

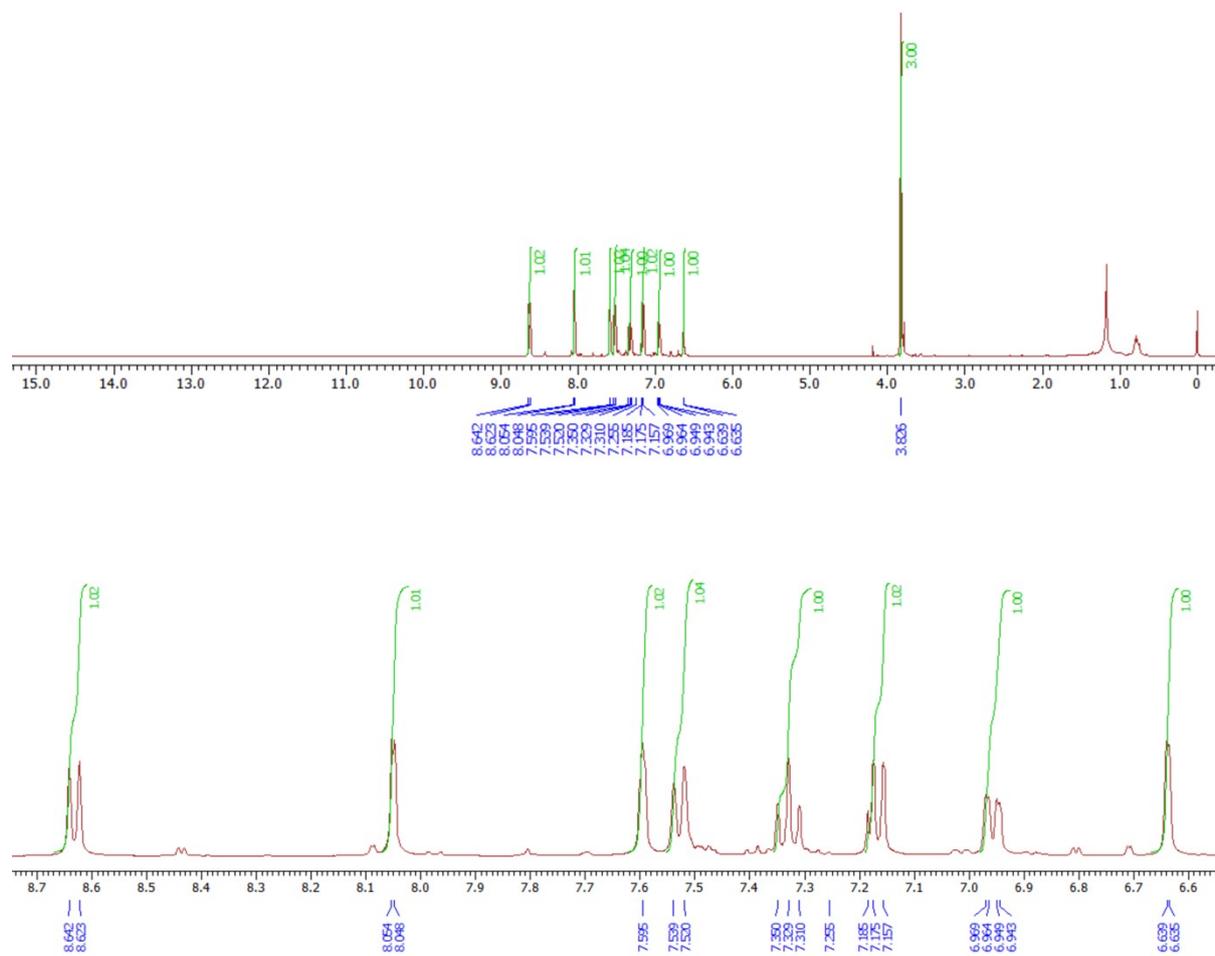


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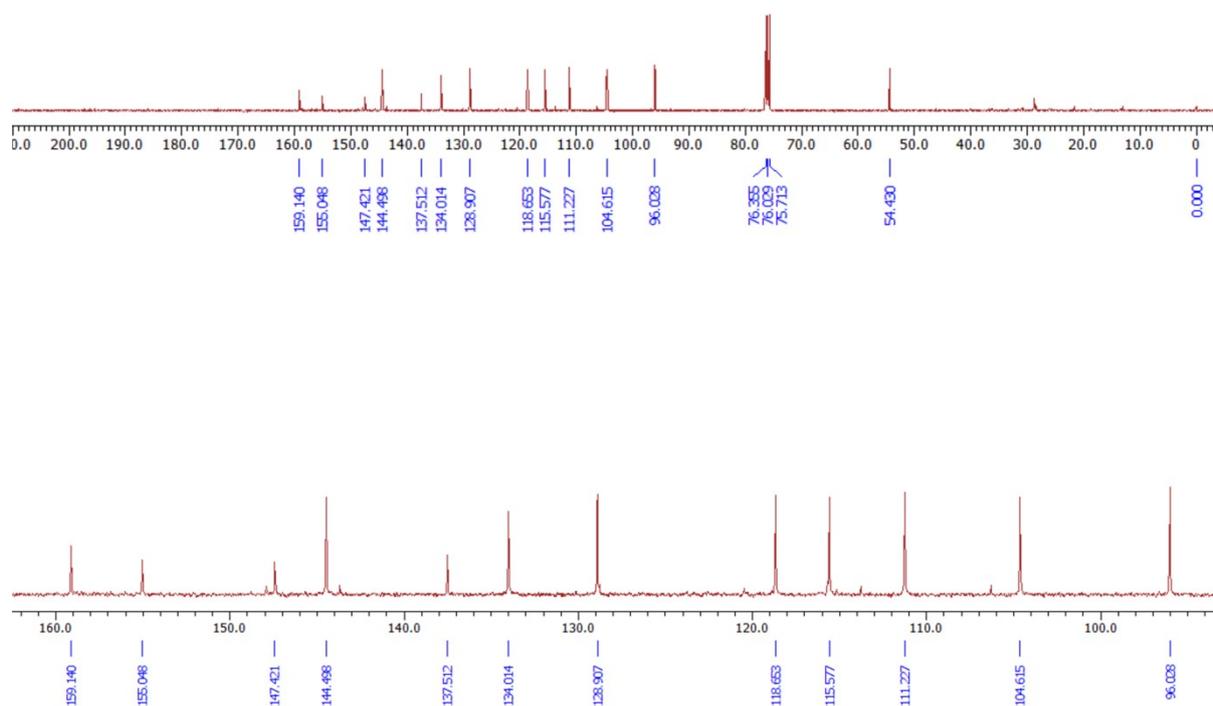




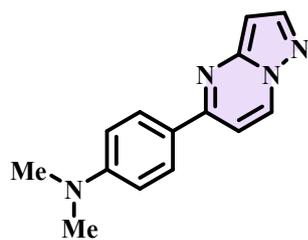
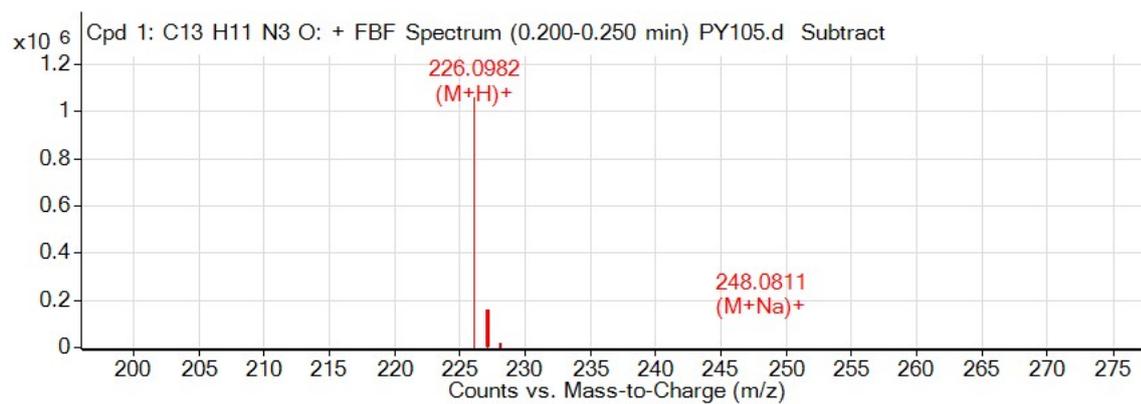
¹H NMR



^{13}C NMR

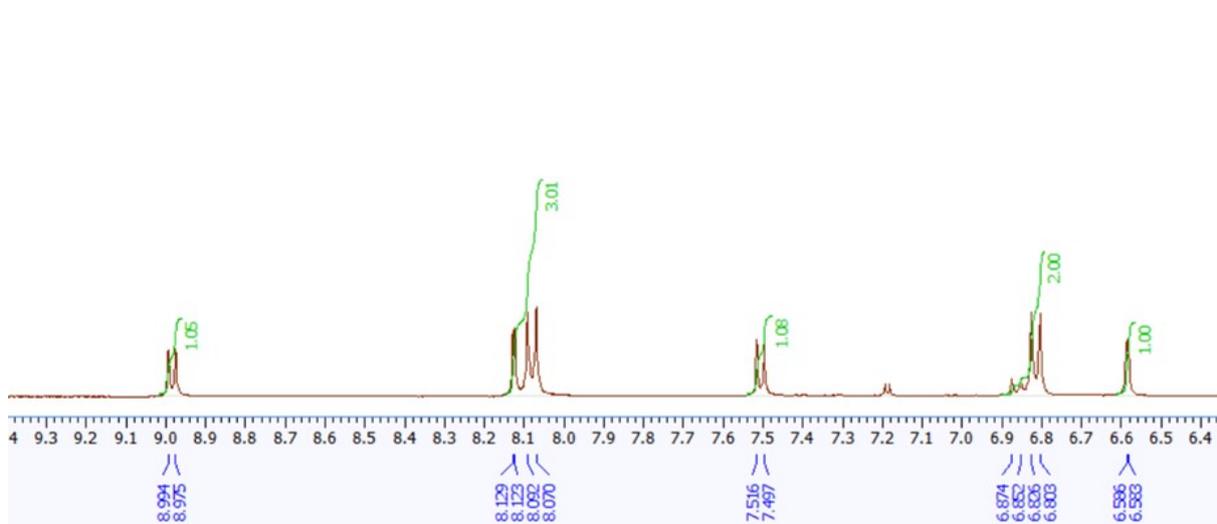
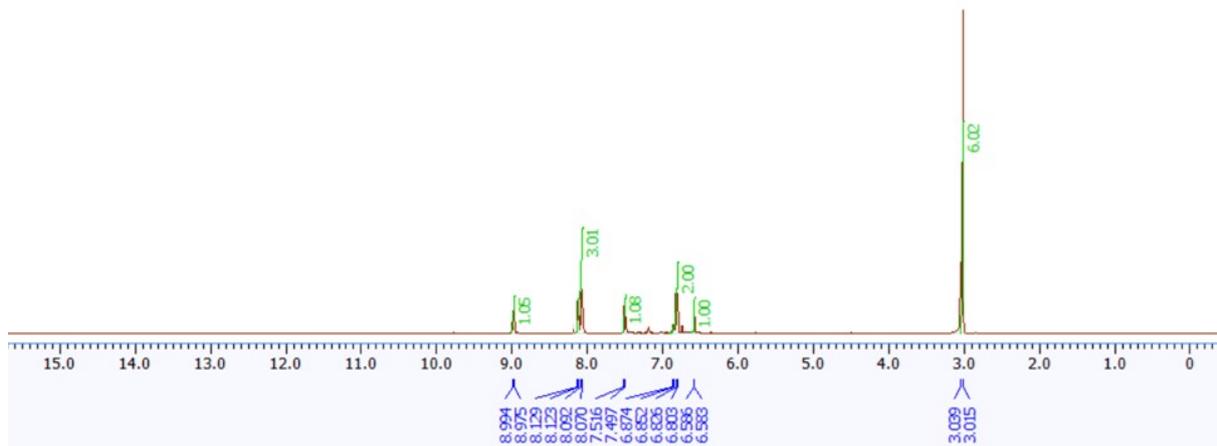


HRMS

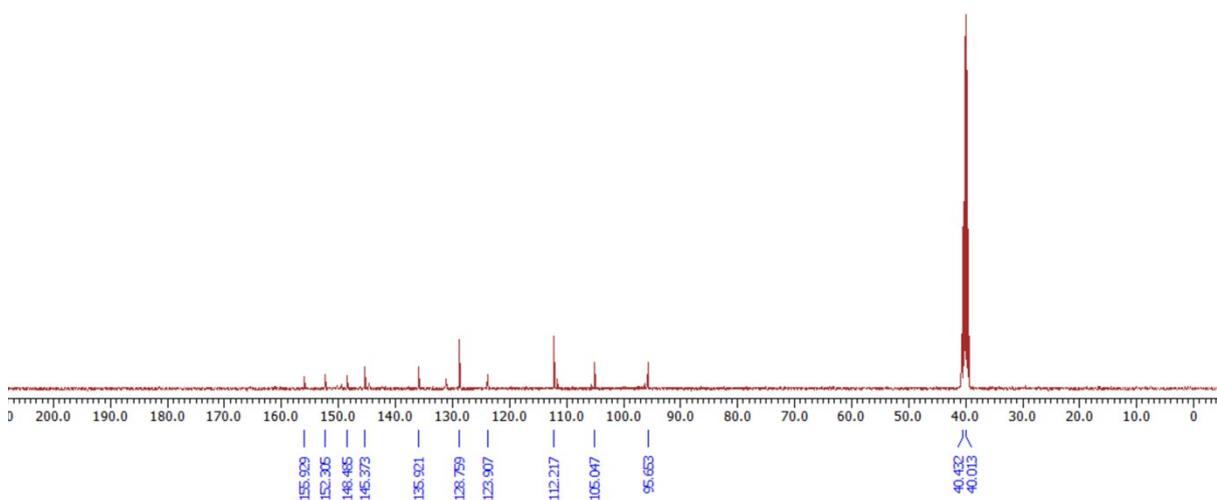


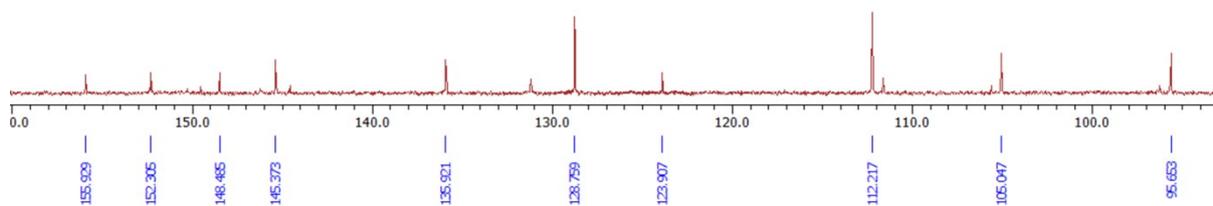
N,N-dimethyl-4-(pyrazolo[1,5-a]pyrimidin-5-yl)aniline (3b)

^1H NMR

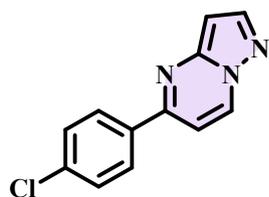
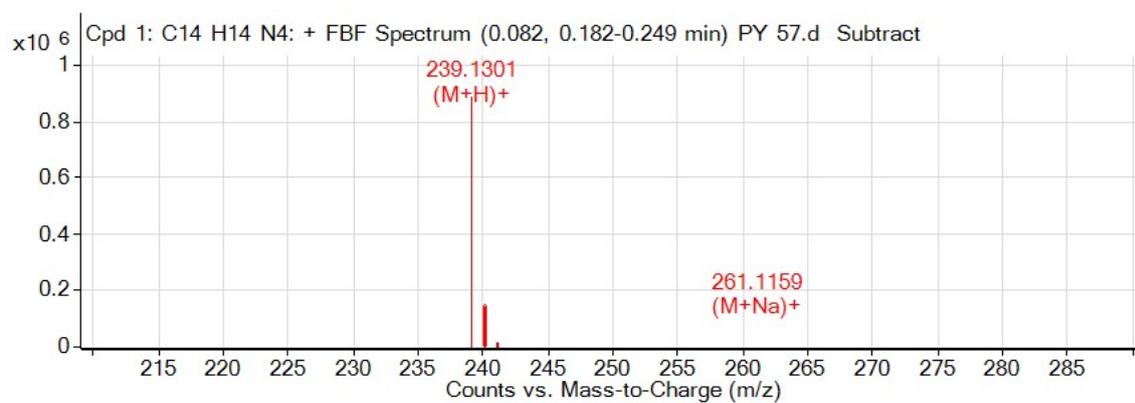


^{13}C NMR



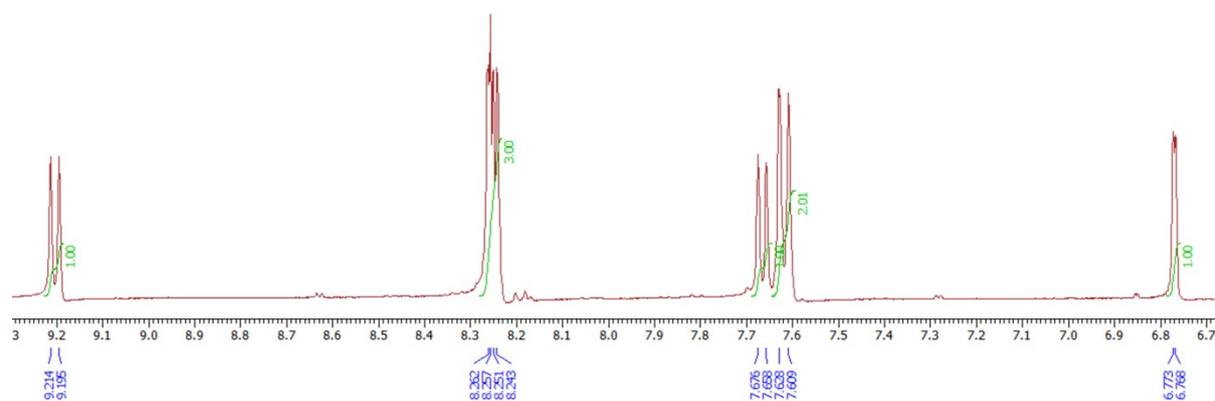
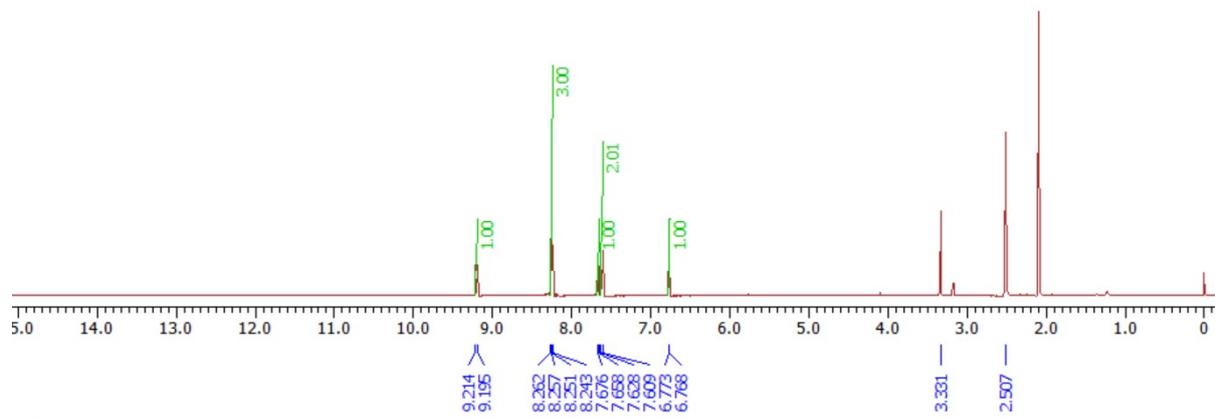


HRMS

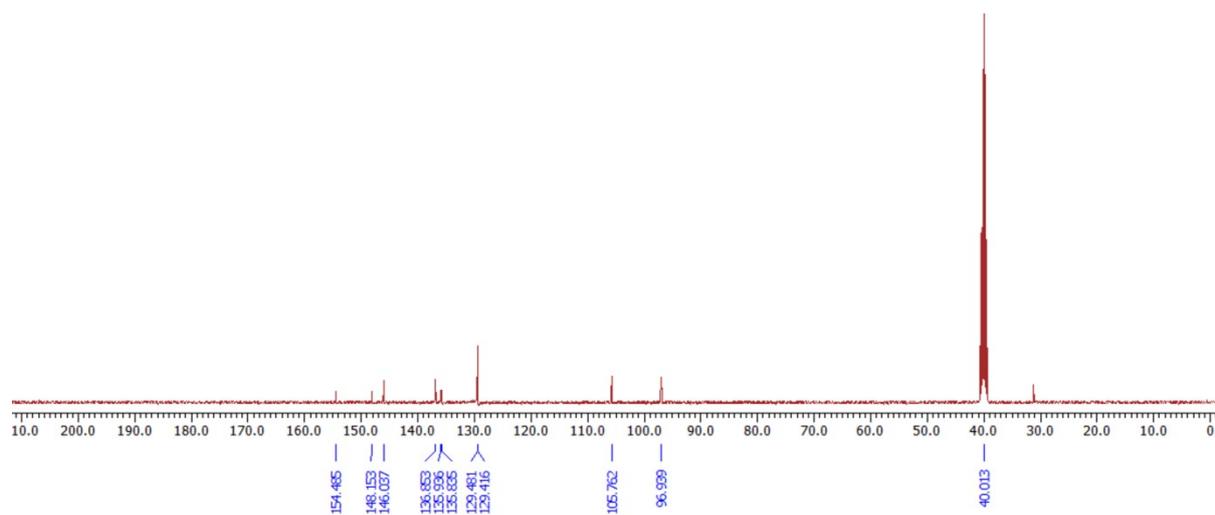


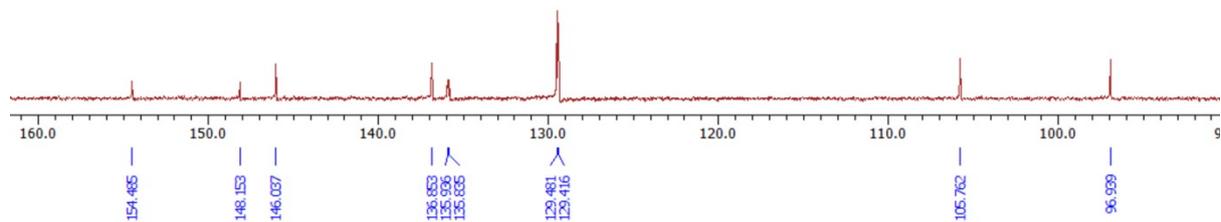
5-(4-Chlorophenyl)pyrazolo[1,5-a]pyrimidine (3c)

^1H NMR

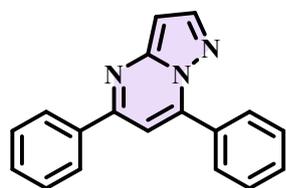
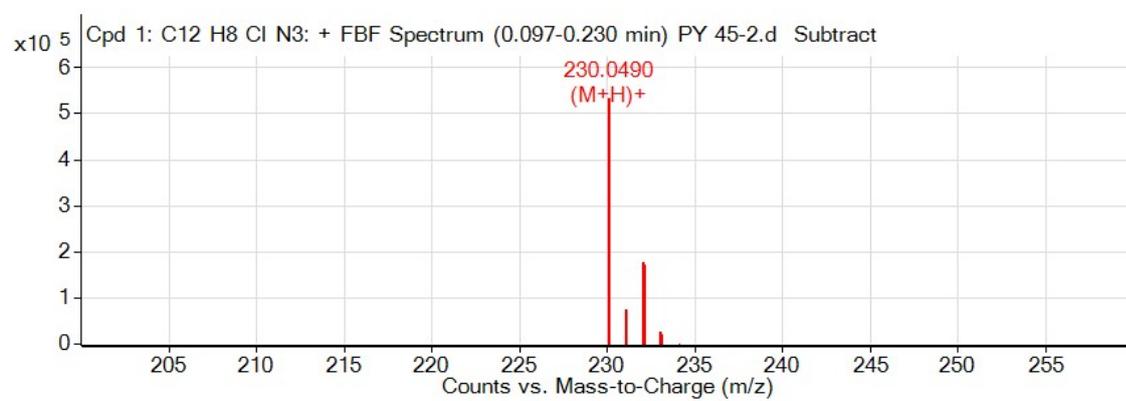


^{13}C NMR



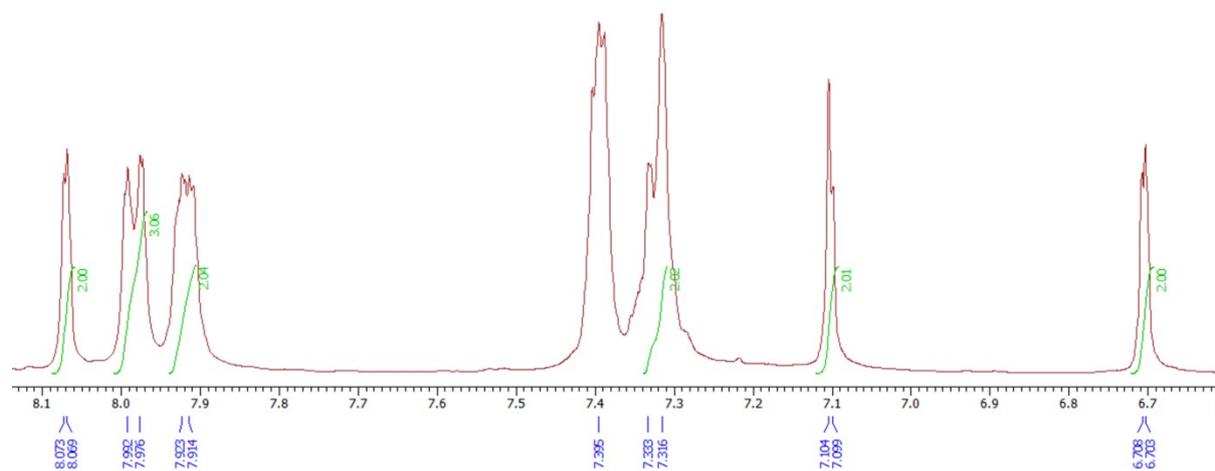
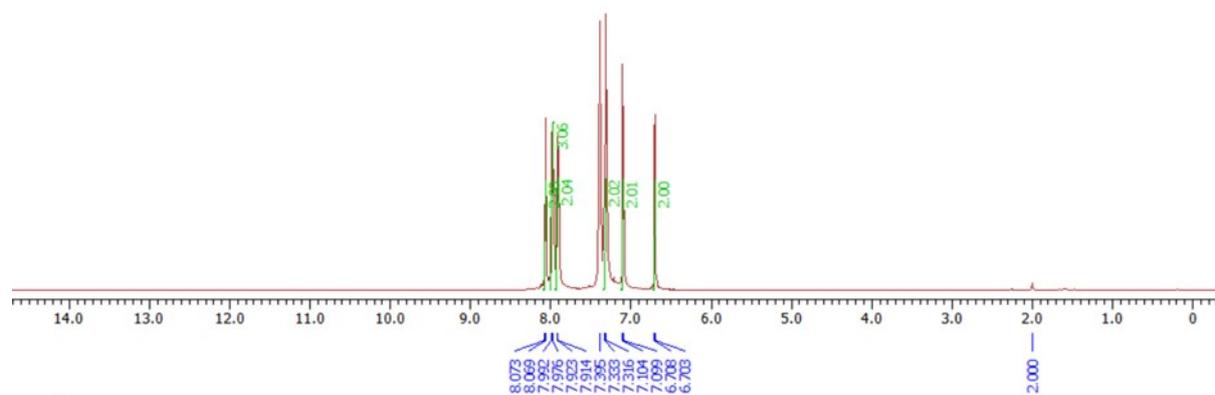


HRMS

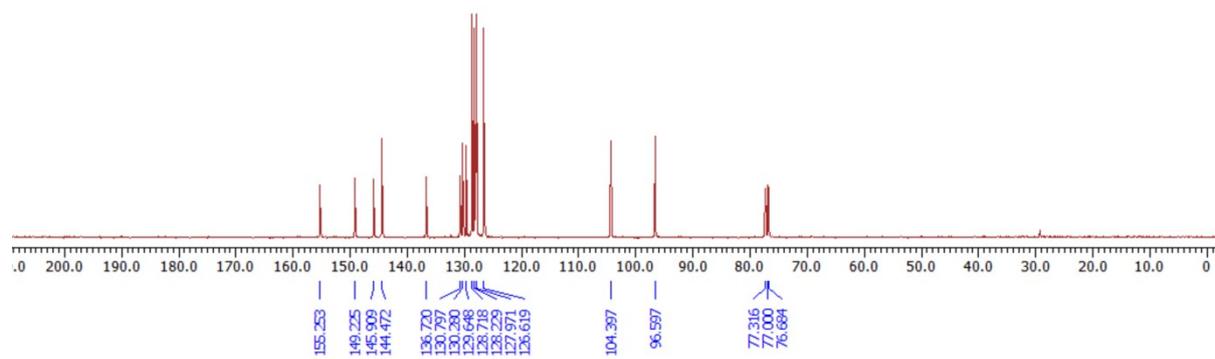


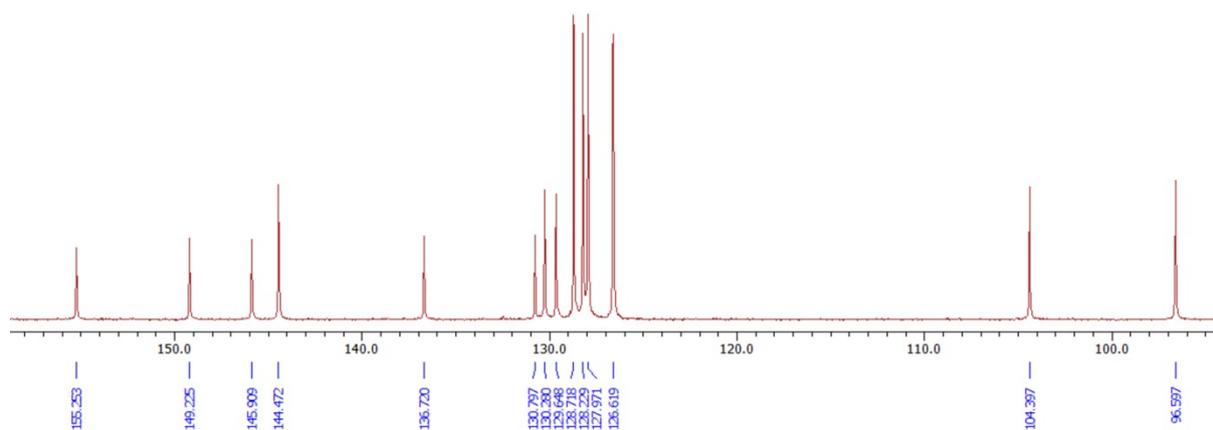
5,7-Diphenylpyrazolo[1,5-a]pyrimidine (3d)

^1H NMR

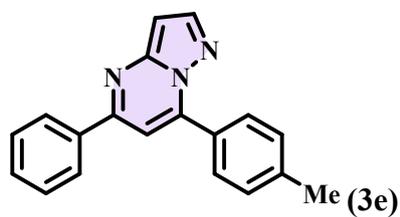
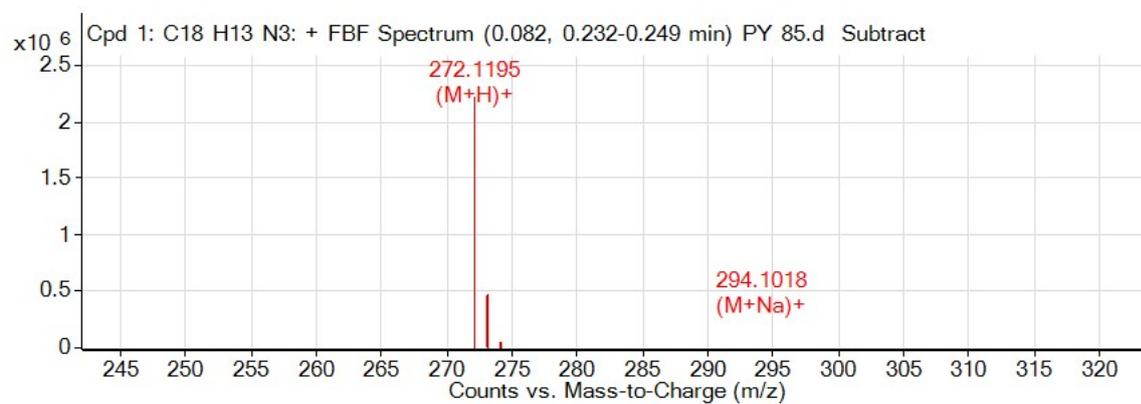


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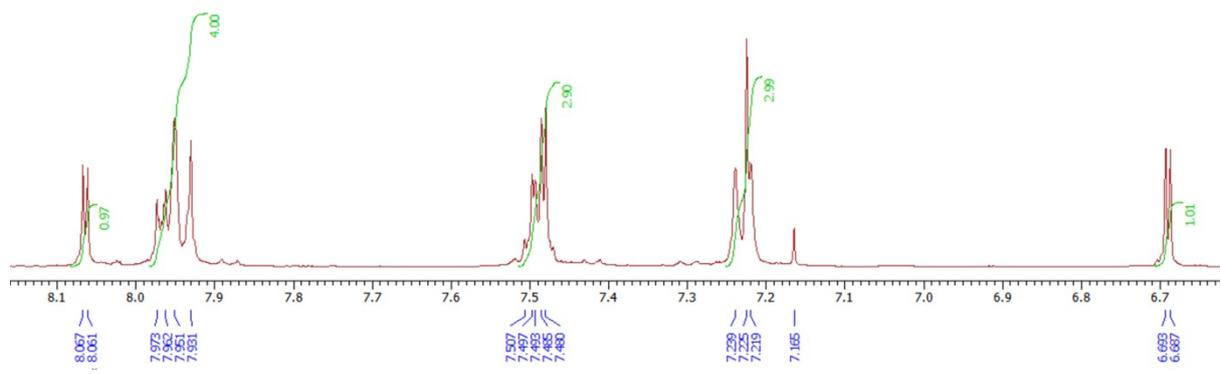
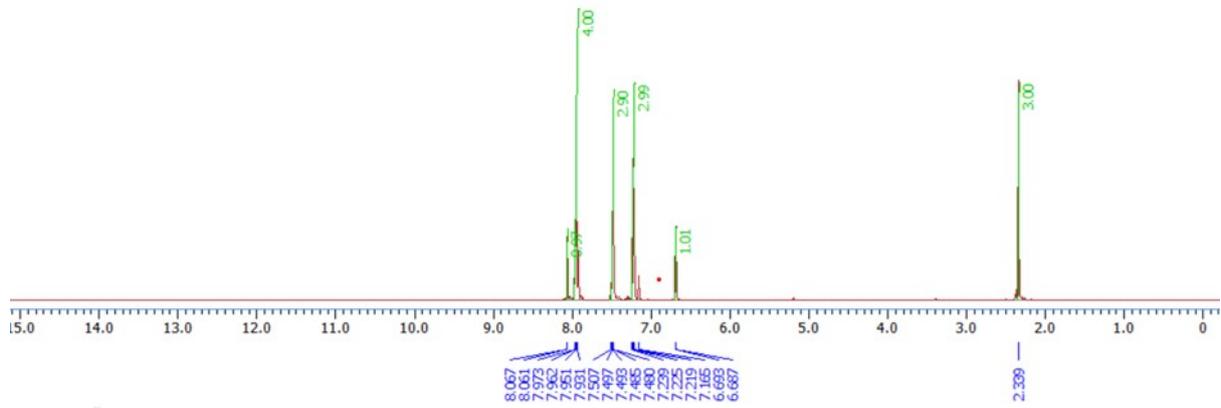




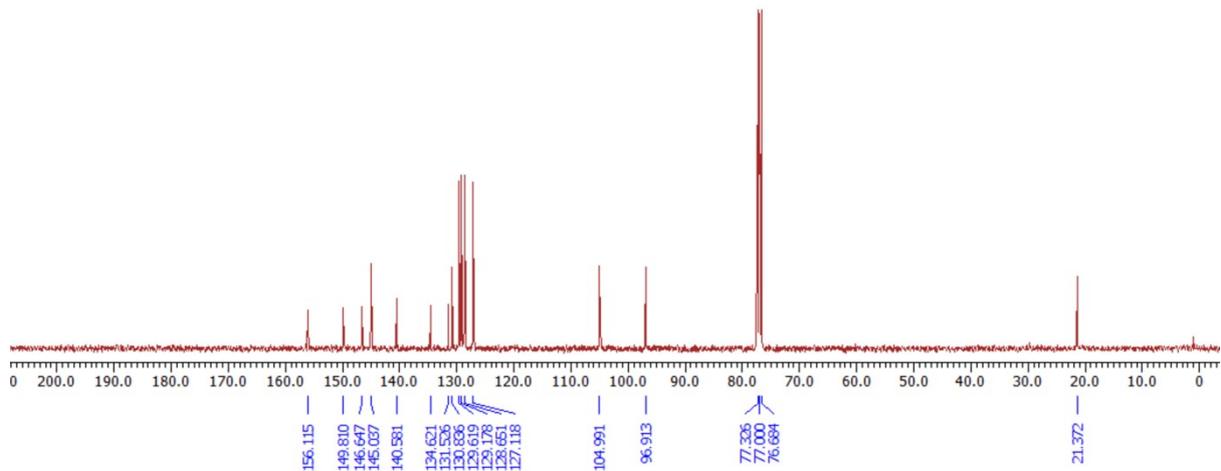
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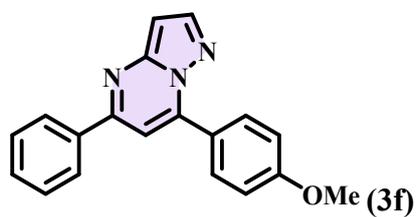
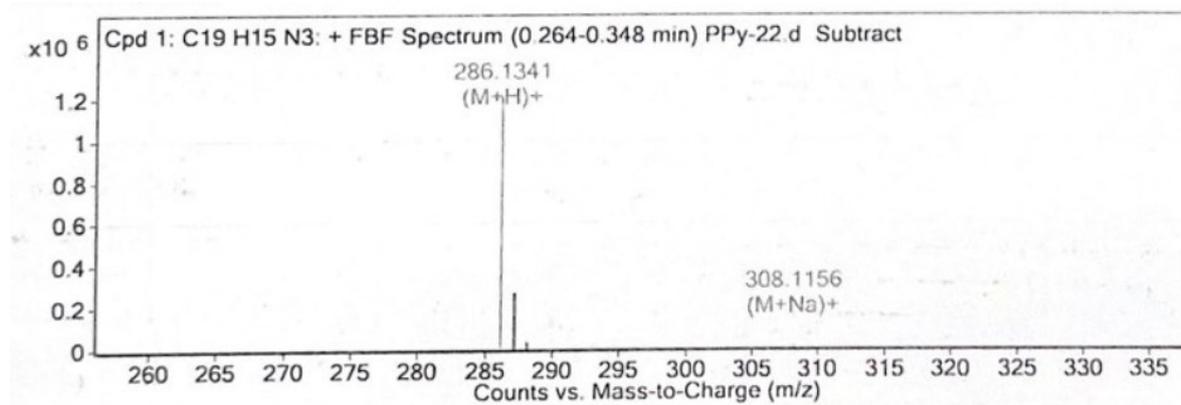
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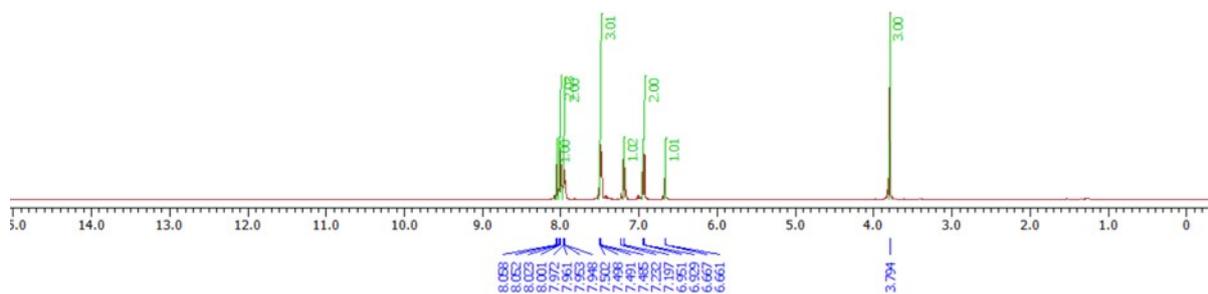
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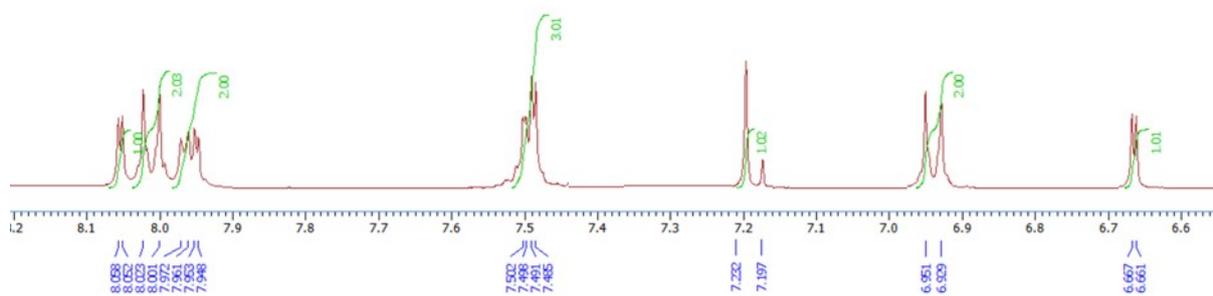


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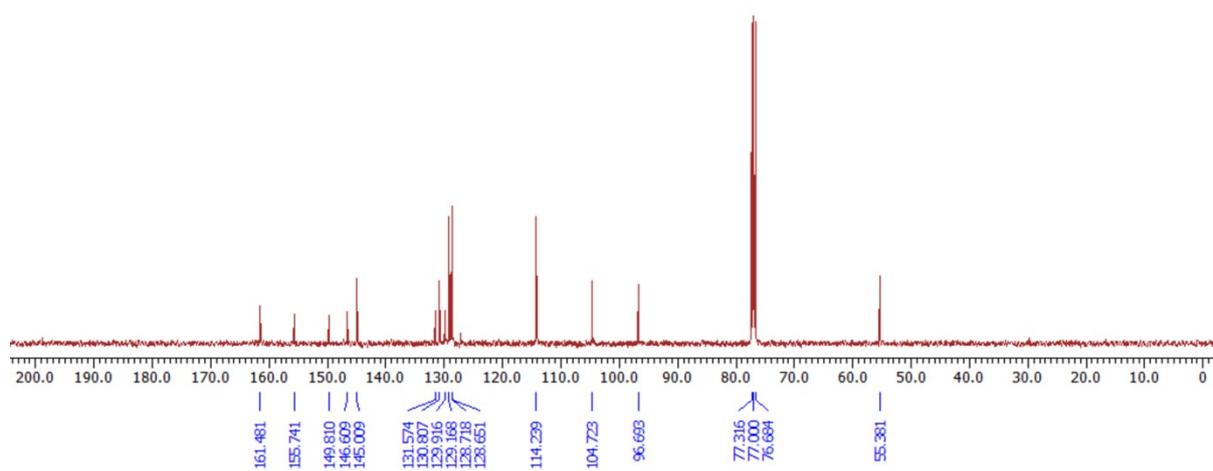


¹H NMR

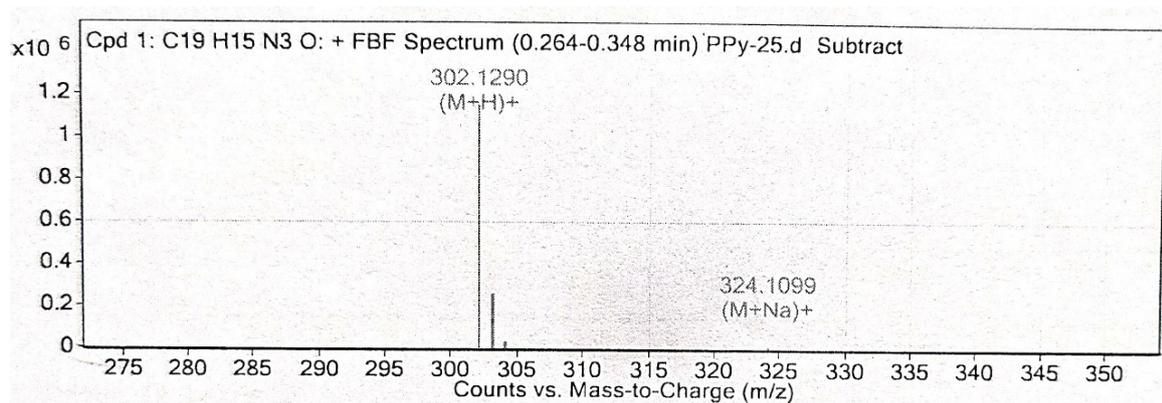


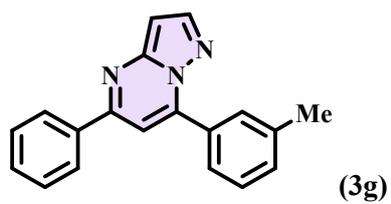


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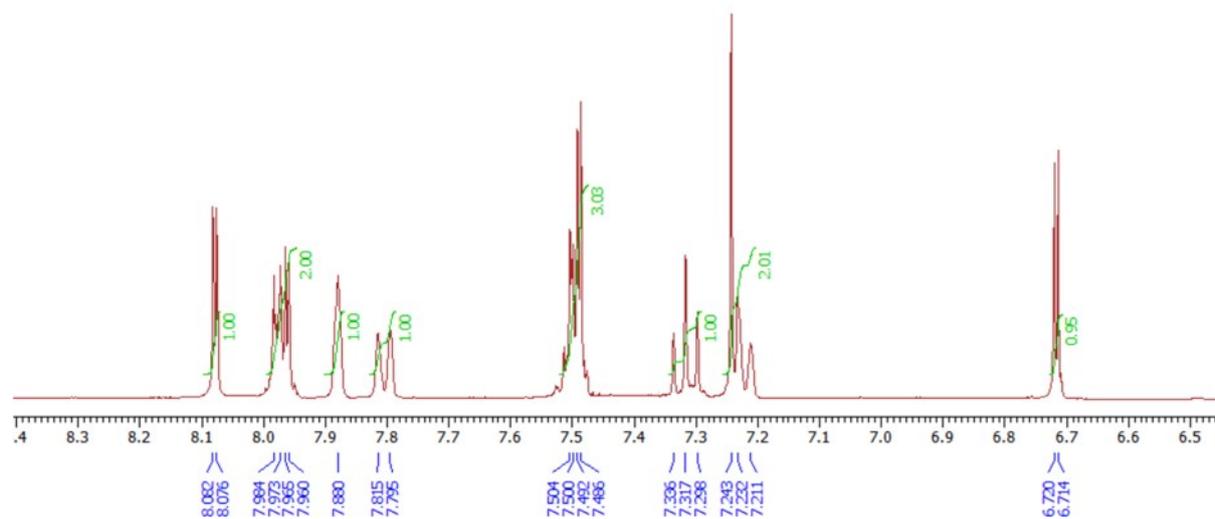
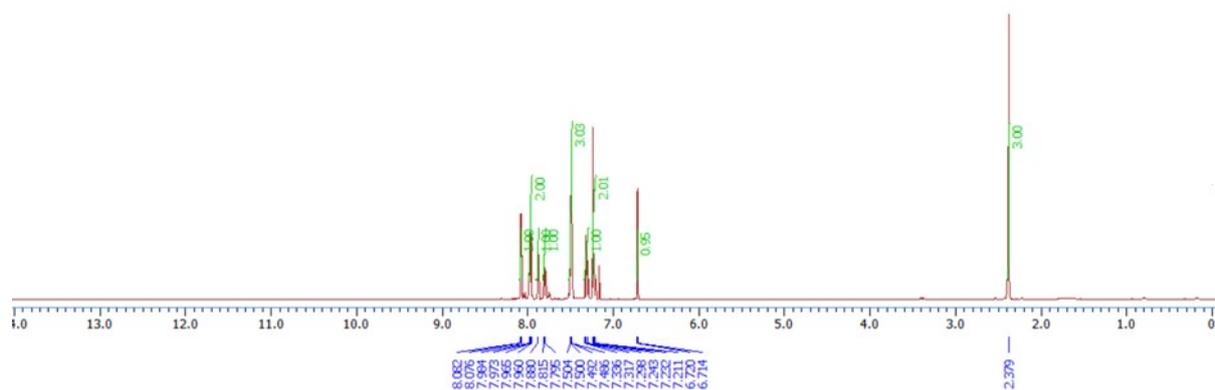


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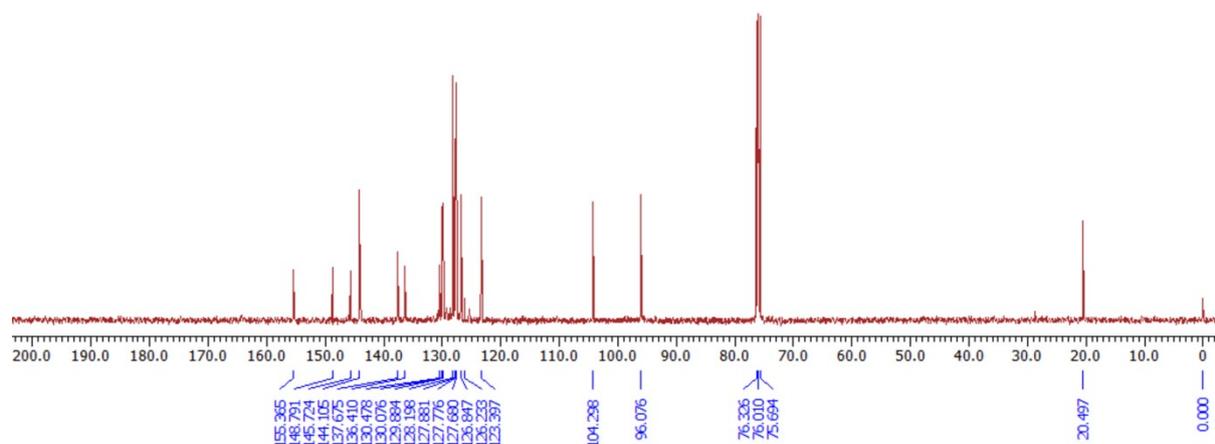




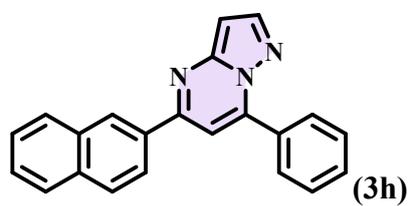
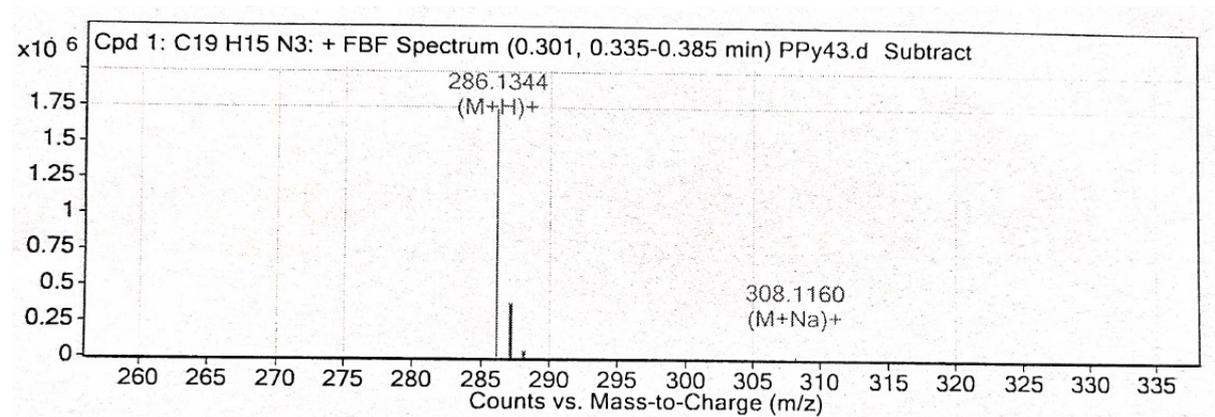
¹H NMR



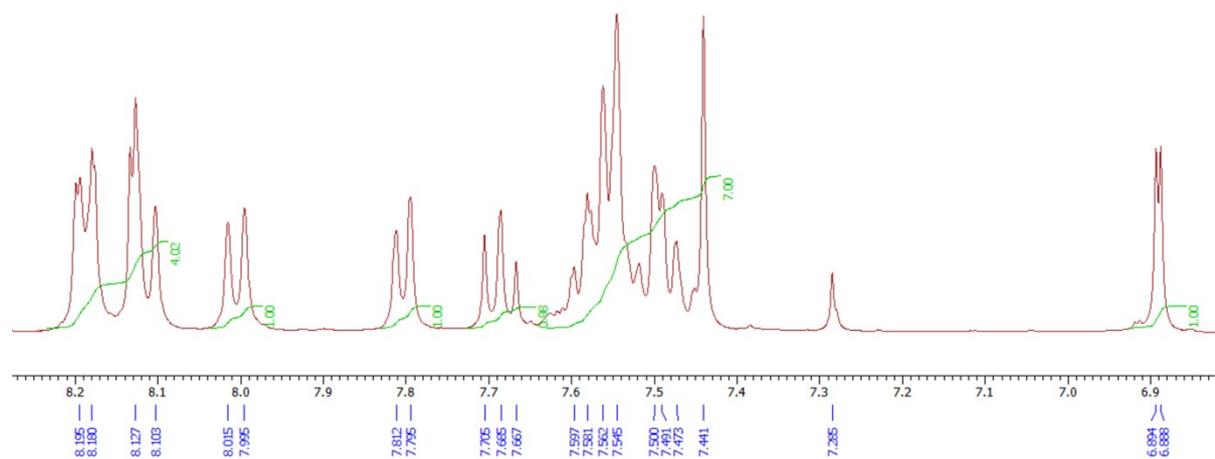
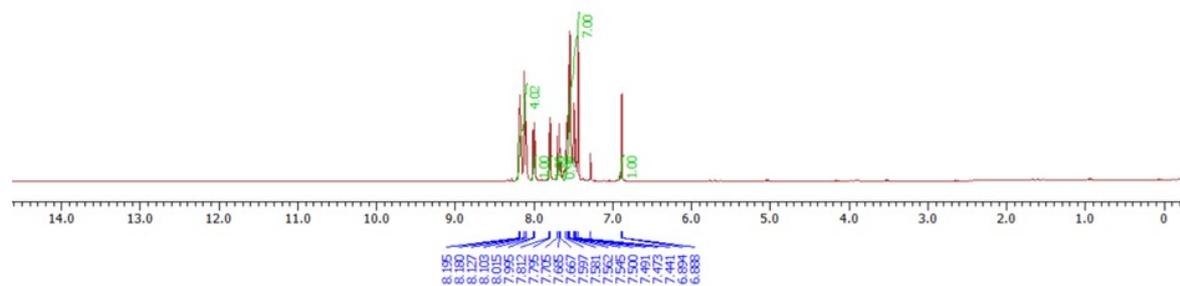
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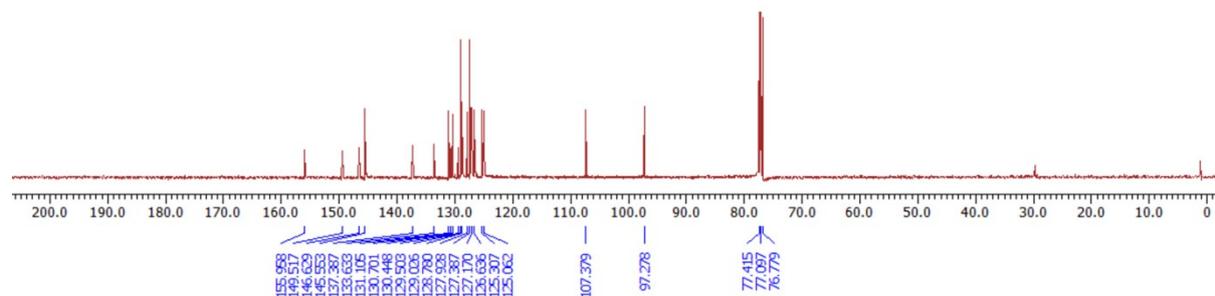
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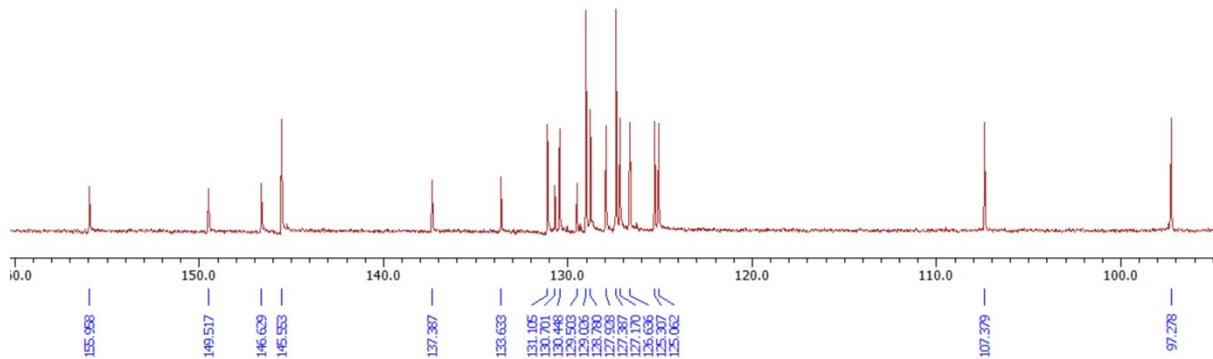


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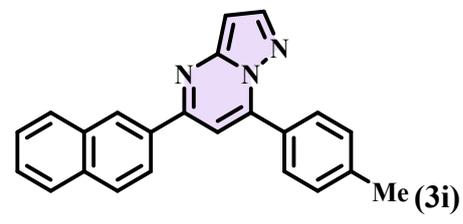
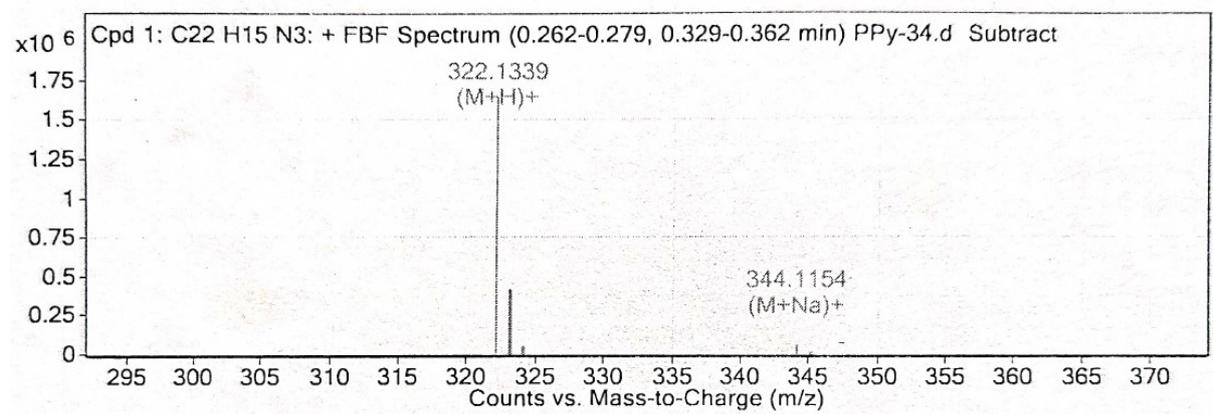


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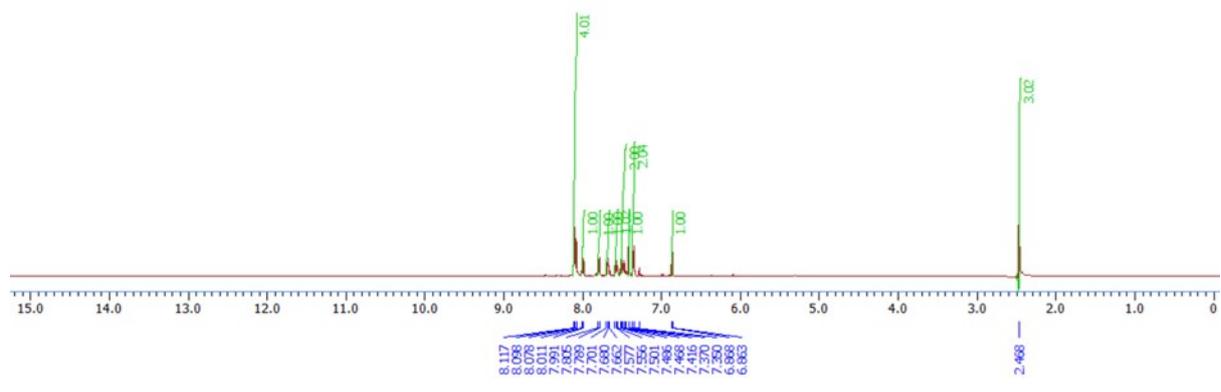


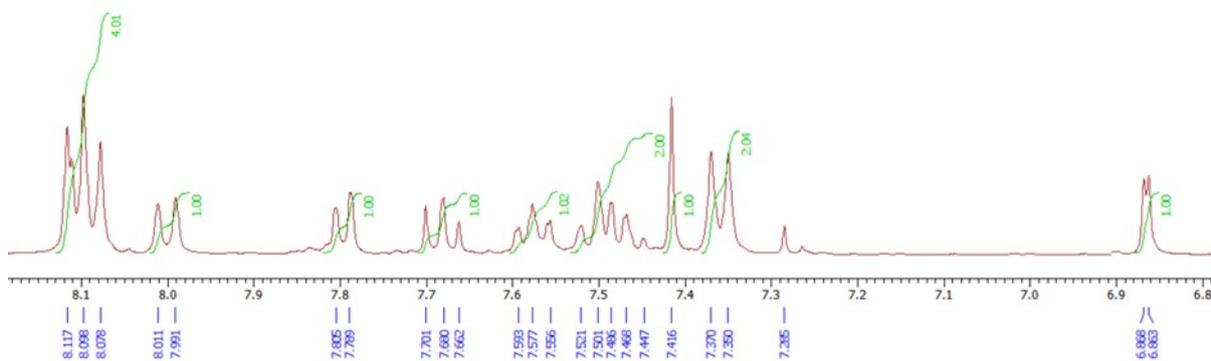


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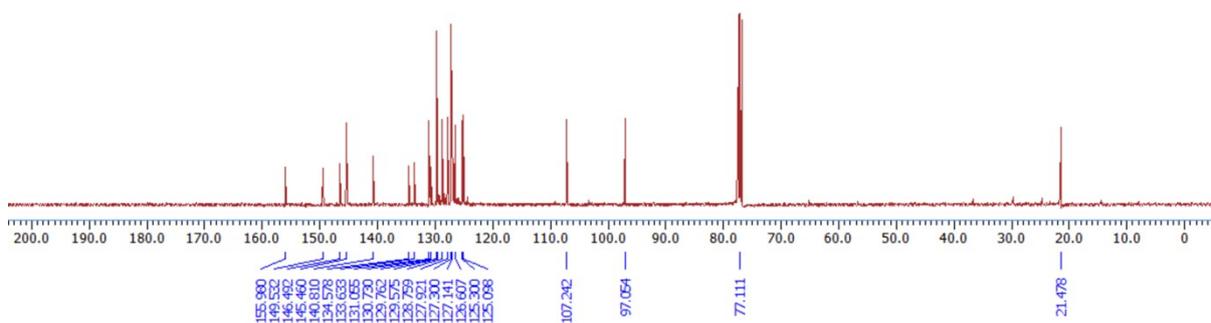


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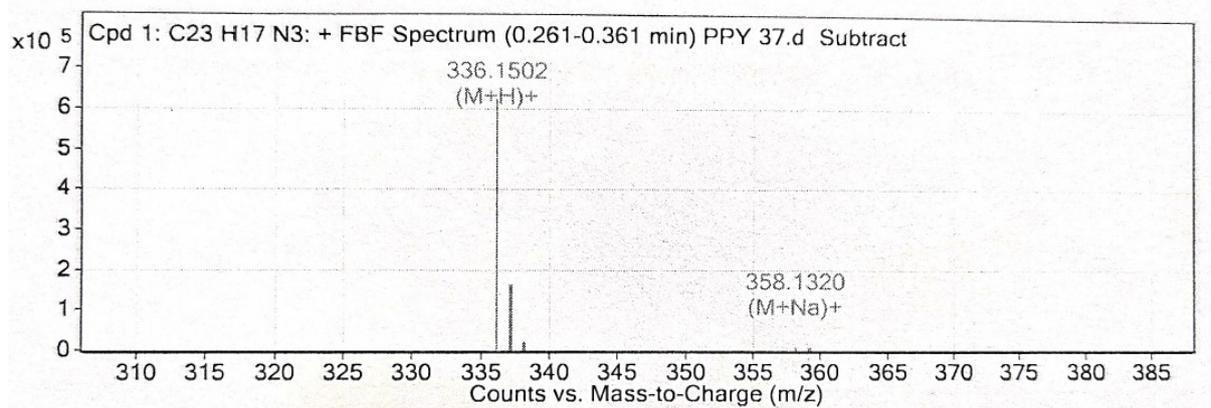


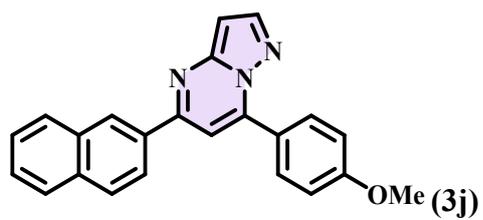


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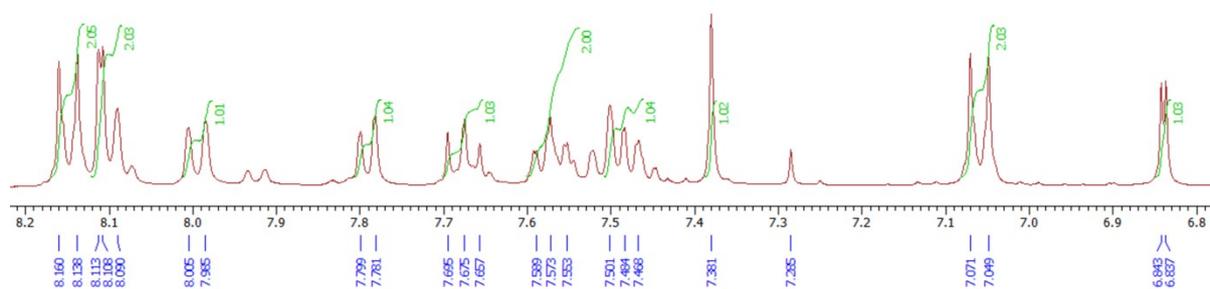
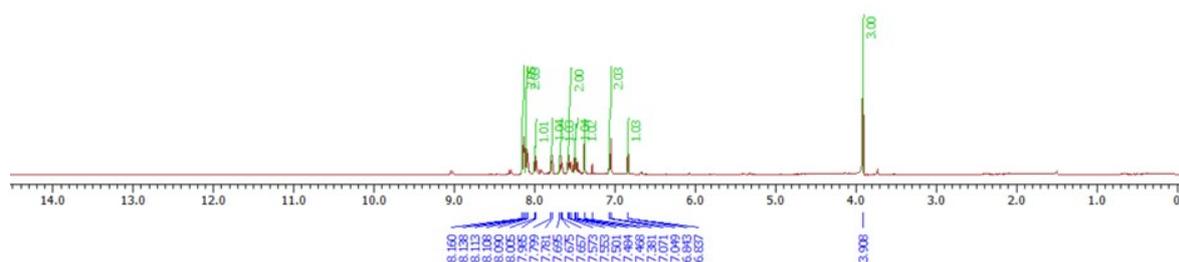


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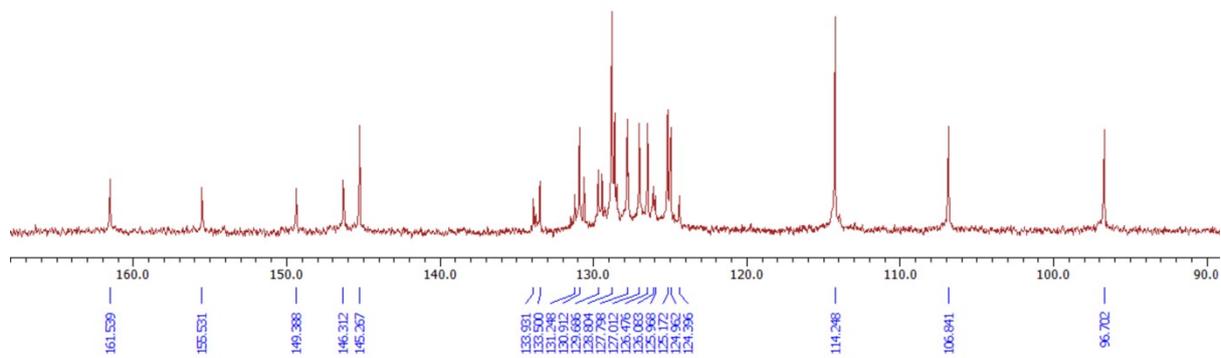
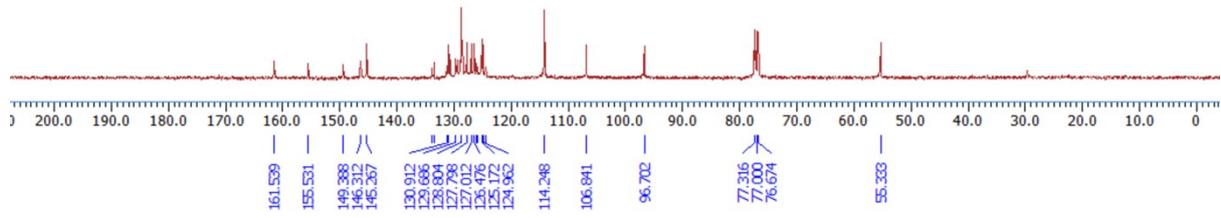




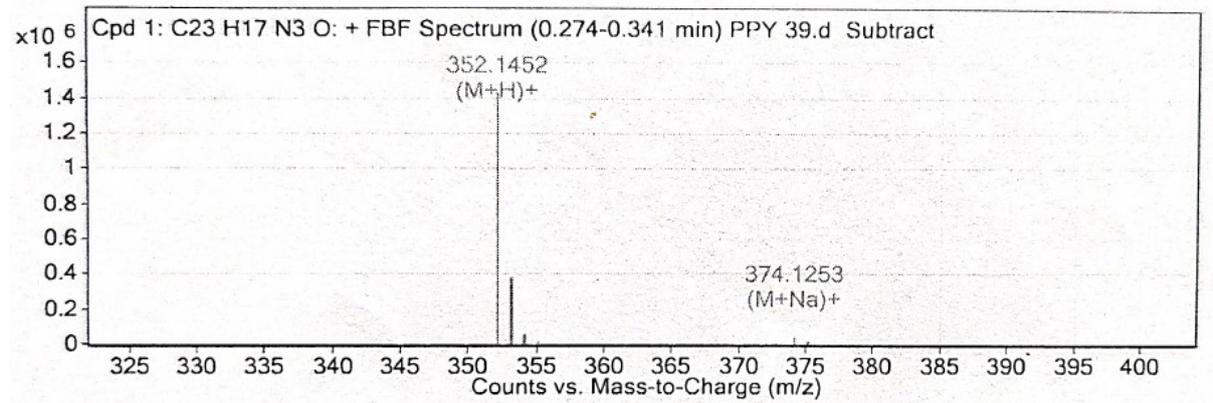
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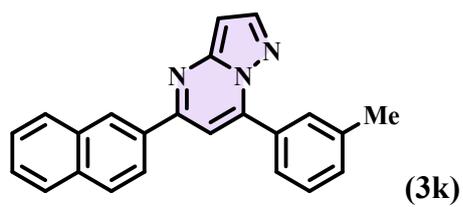


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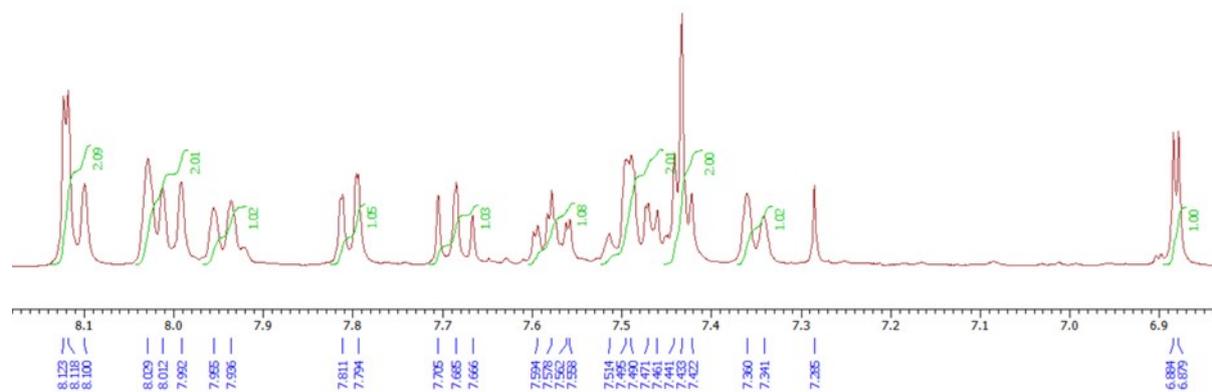
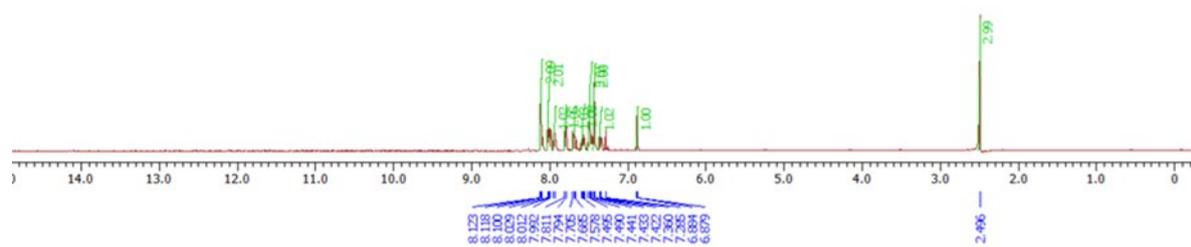


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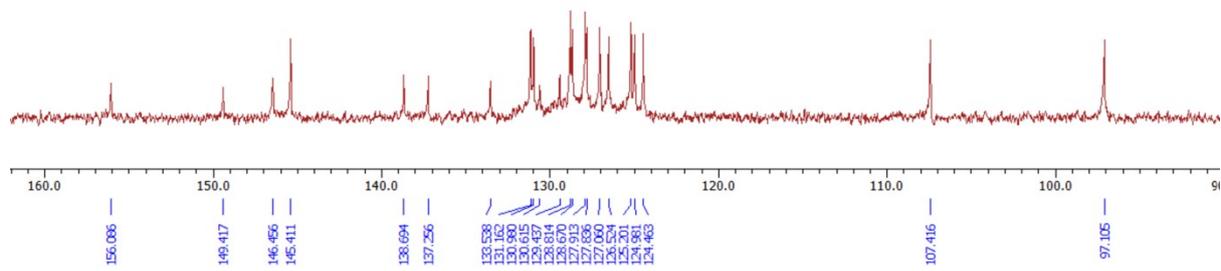
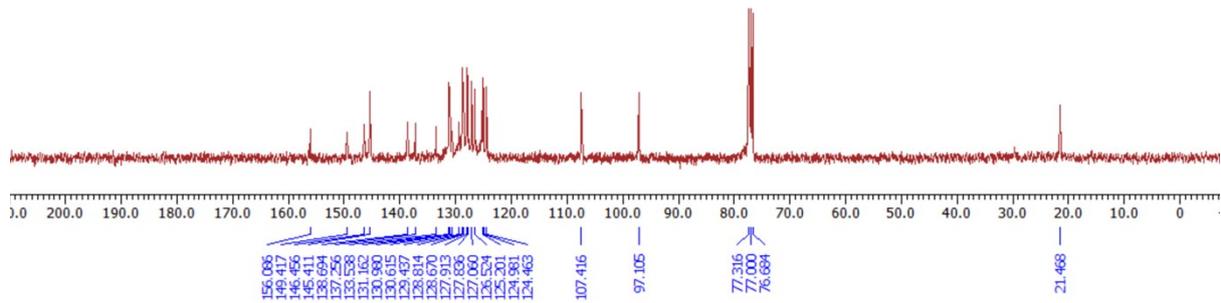




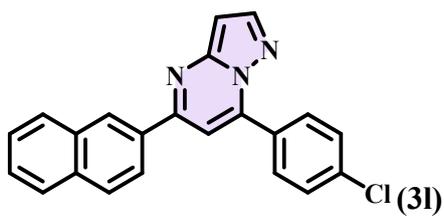
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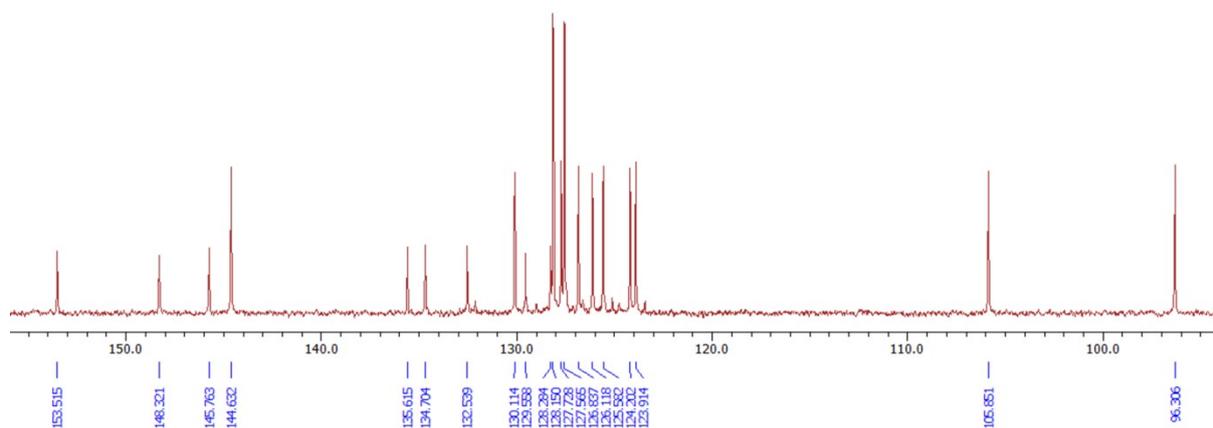
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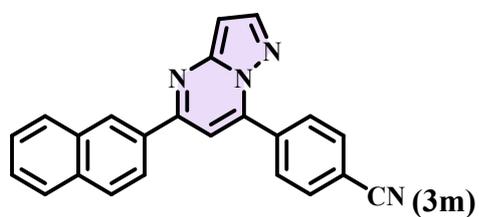
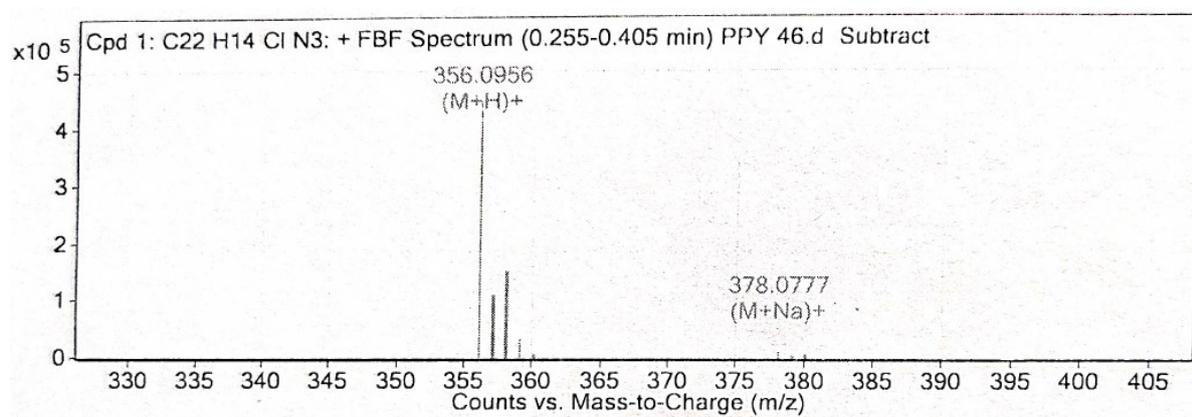
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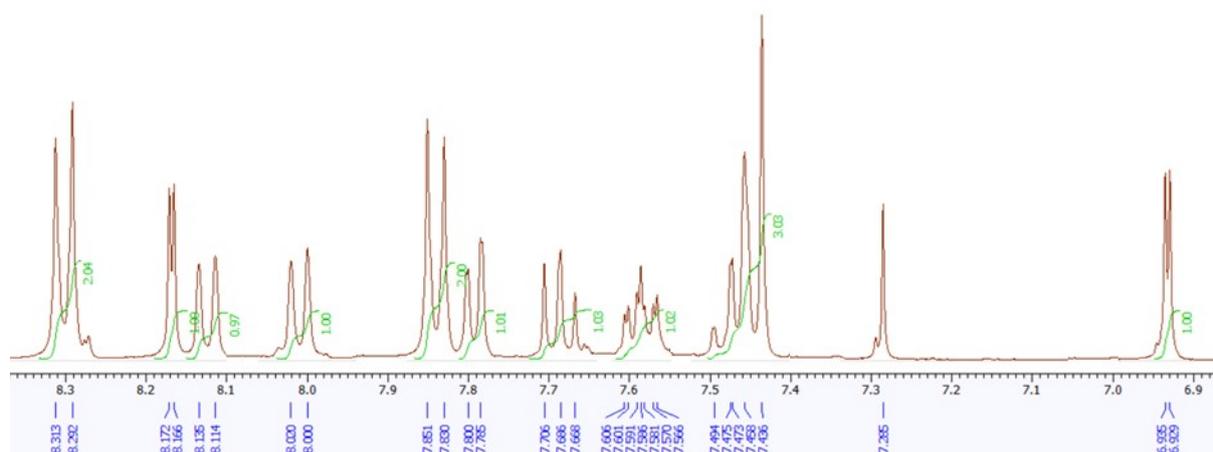
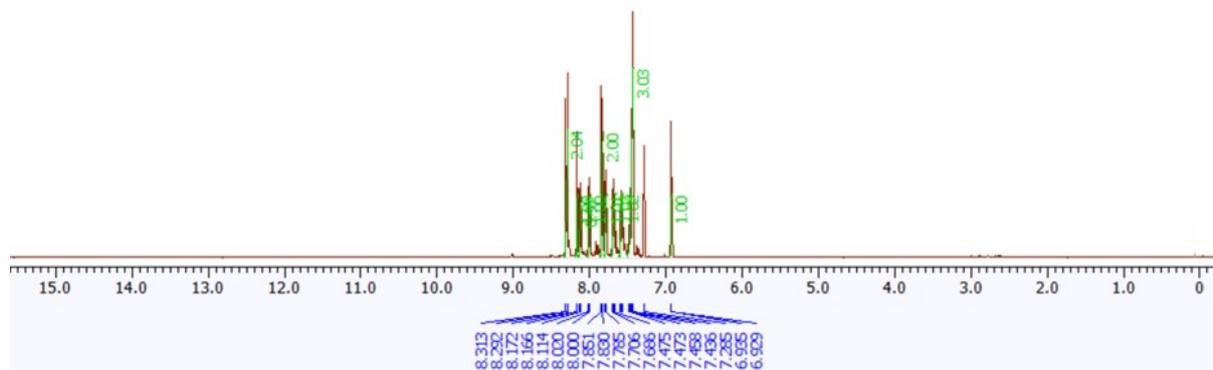
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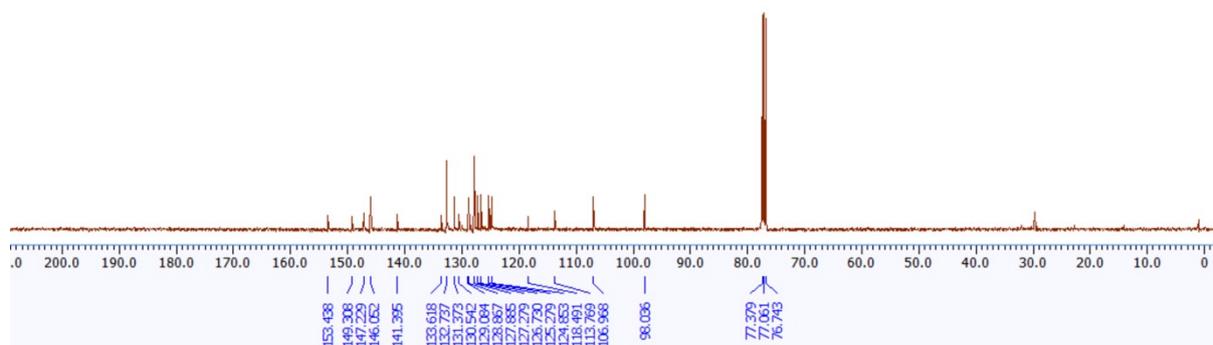
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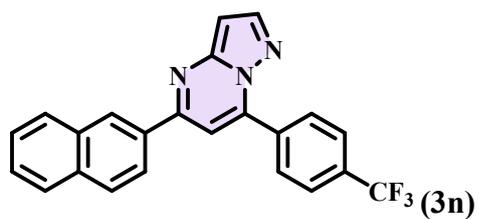
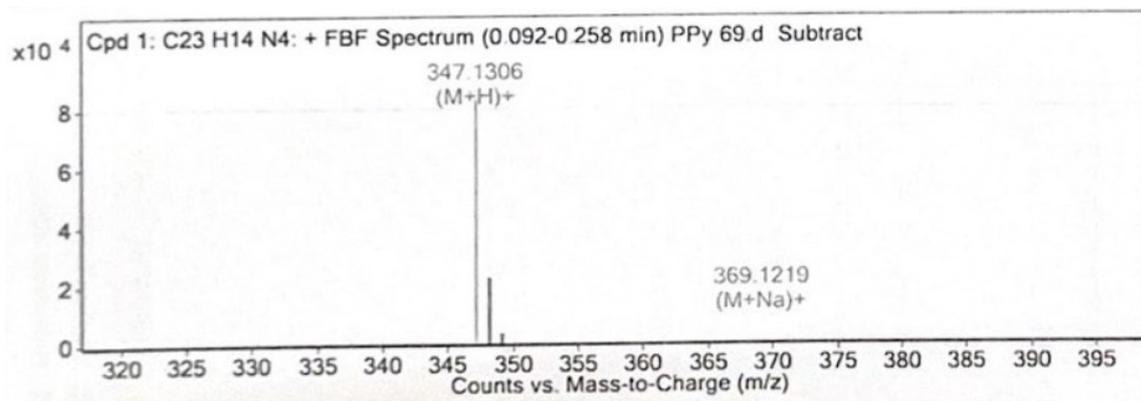
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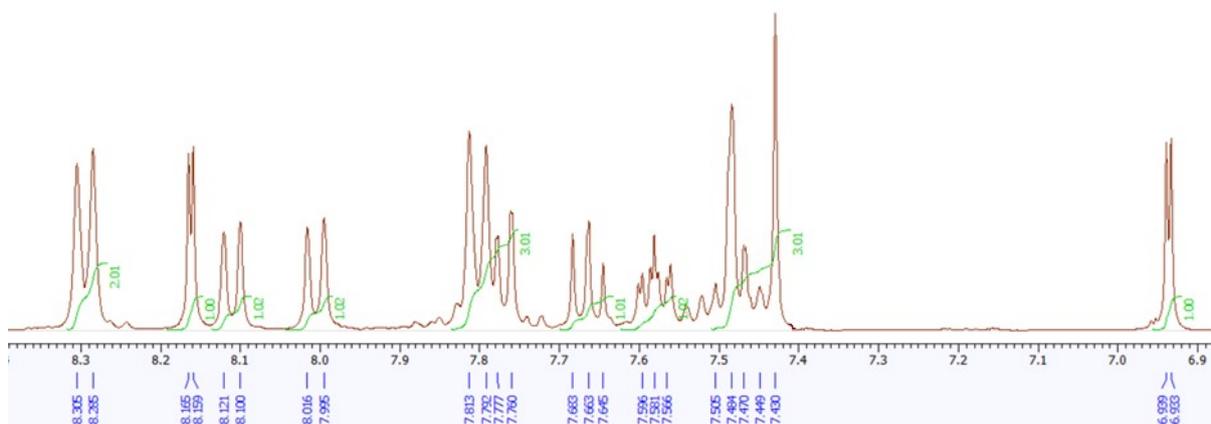
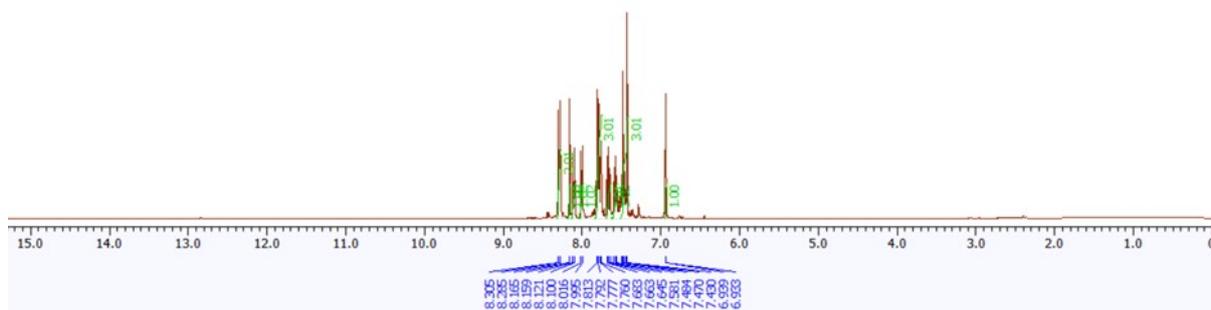
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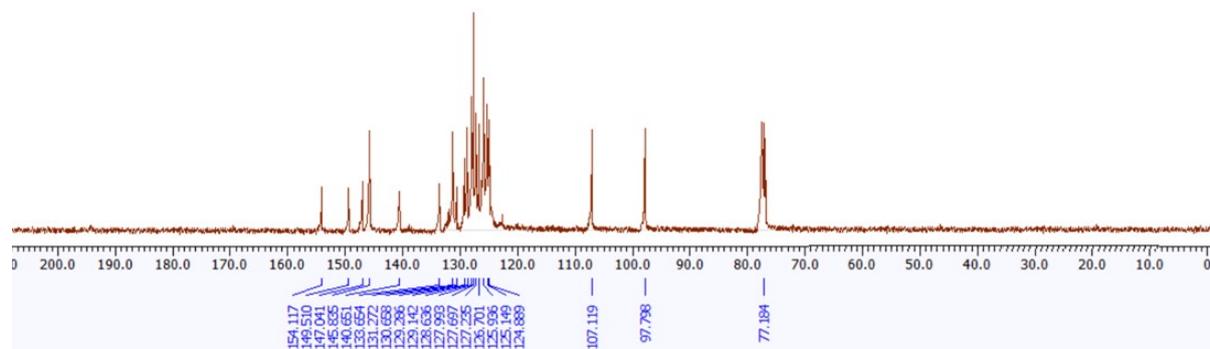
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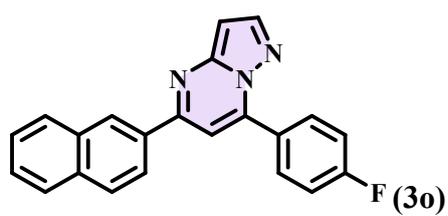
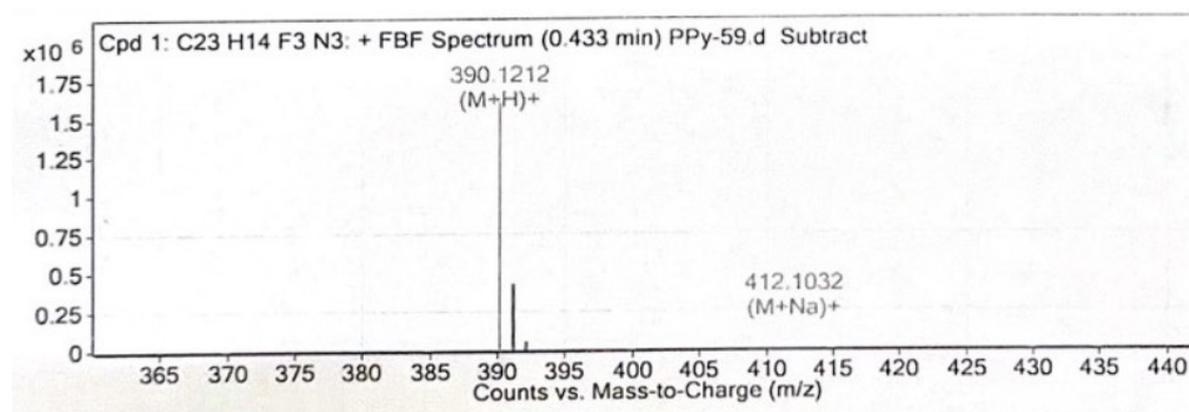
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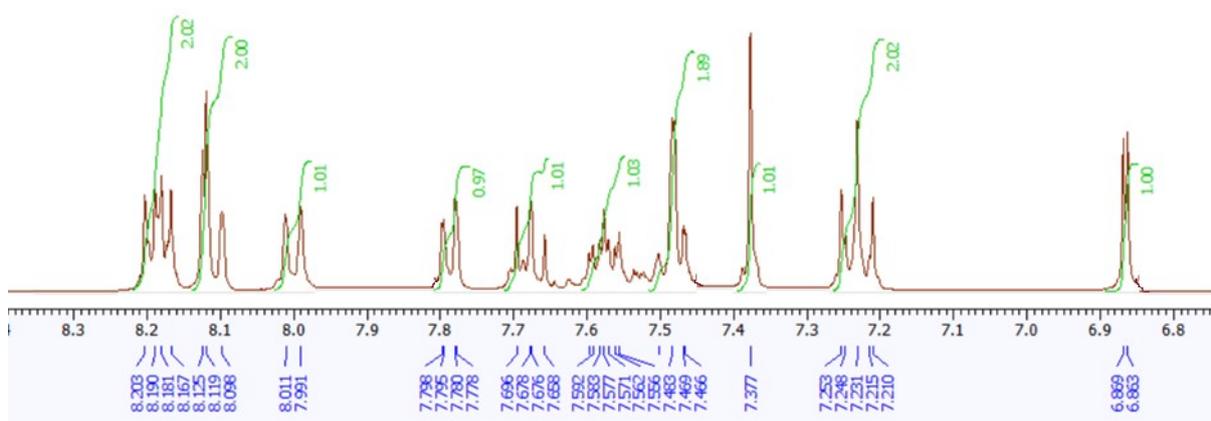
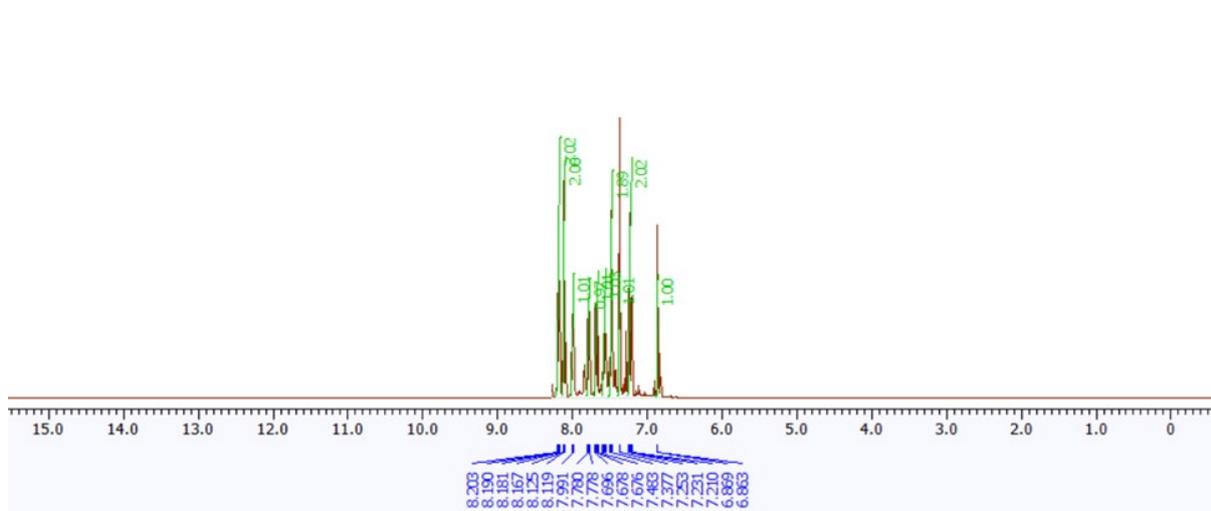
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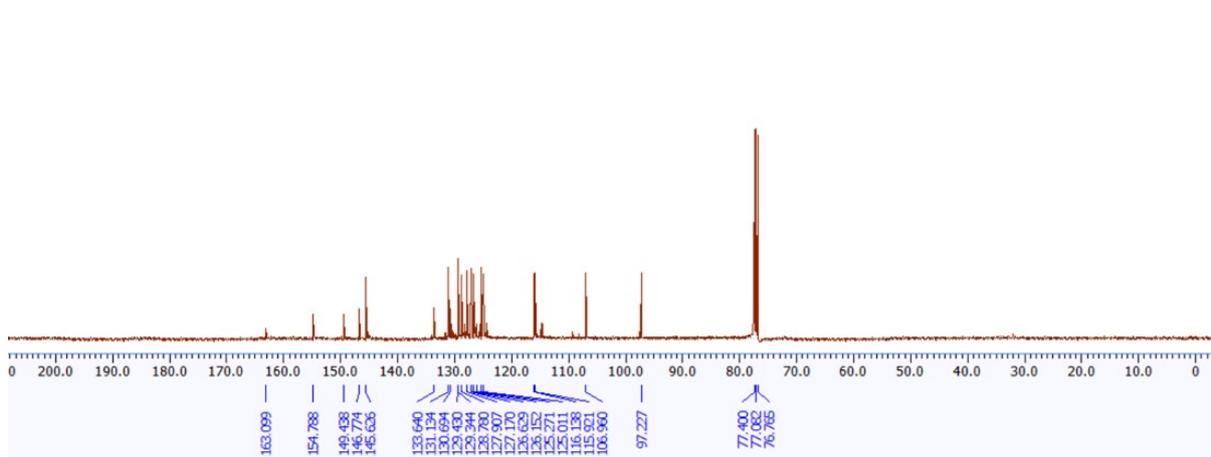
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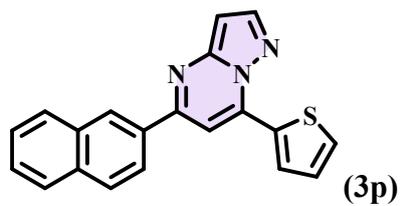
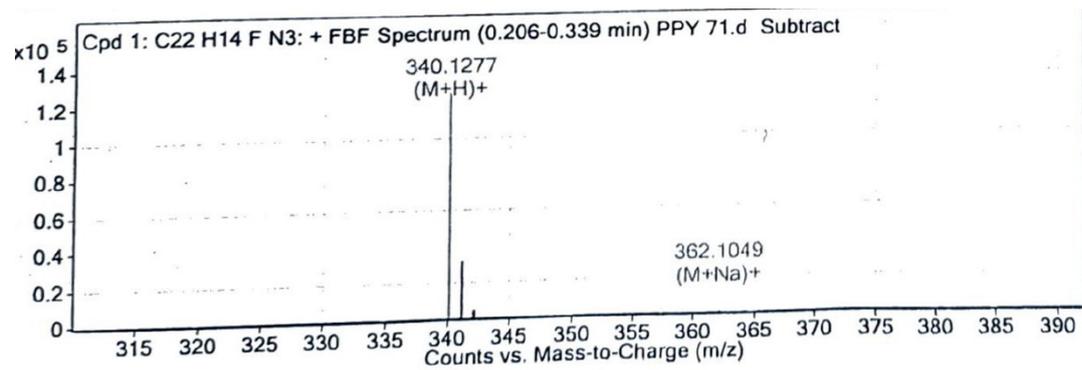
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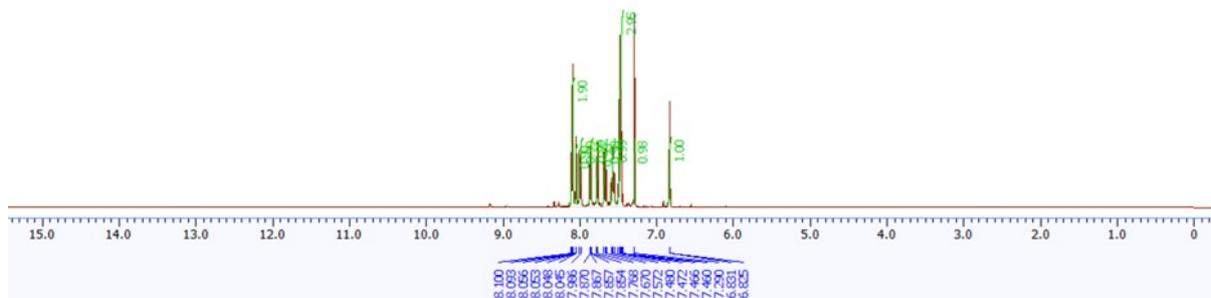
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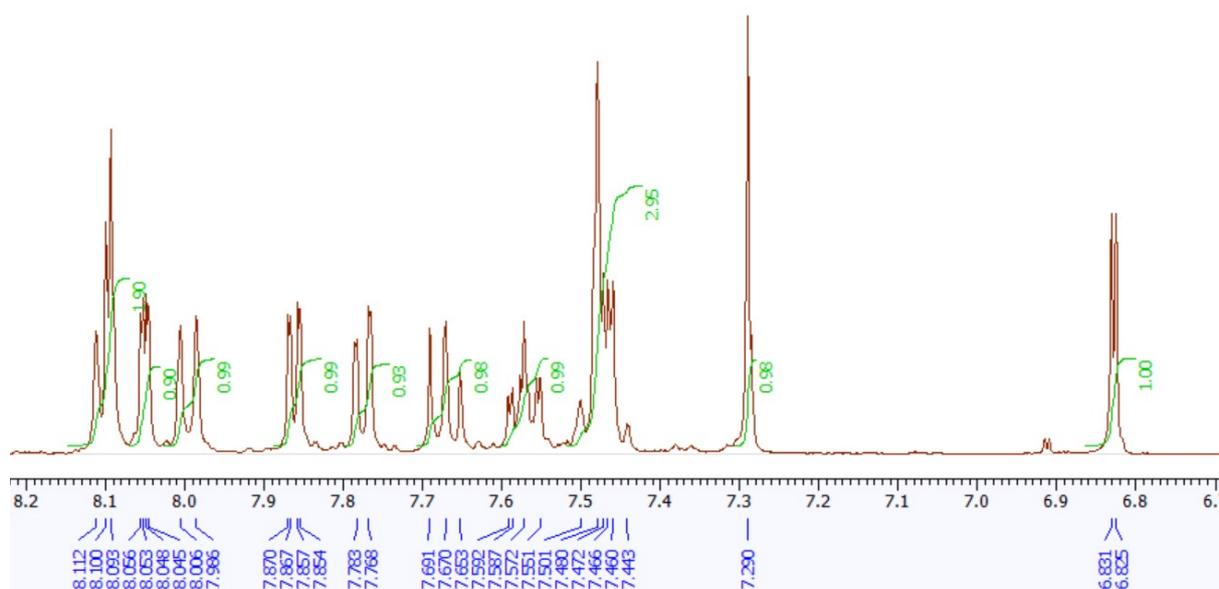


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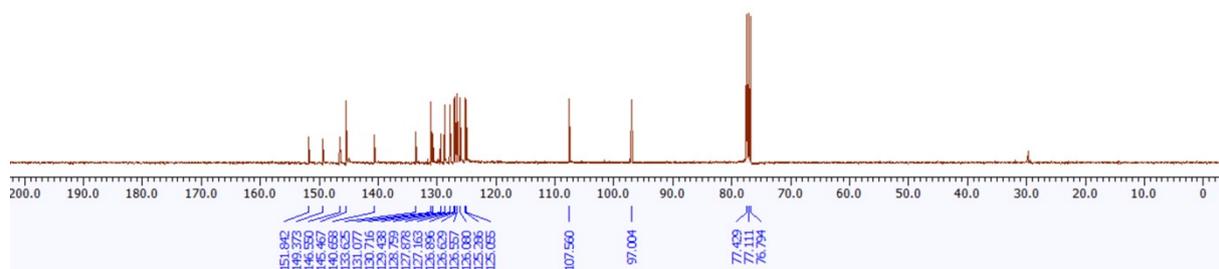


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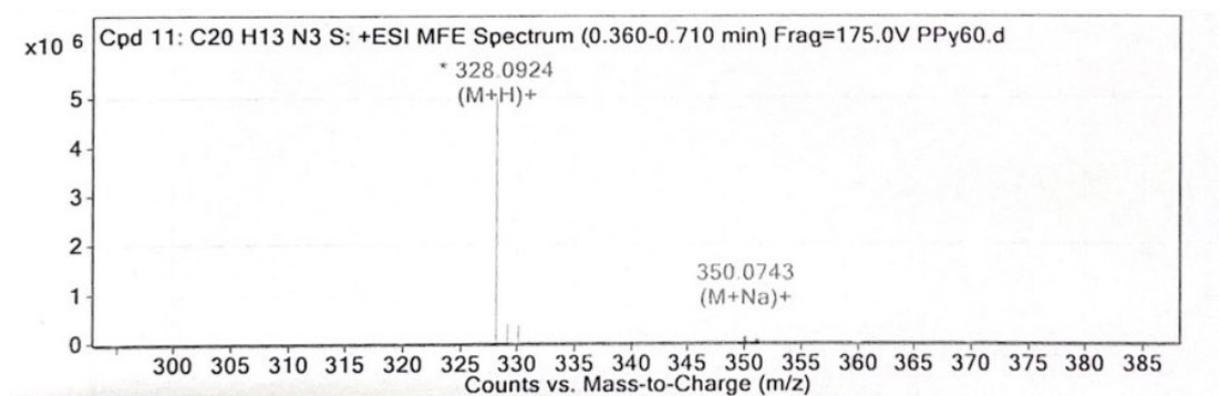


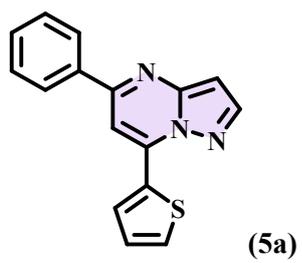


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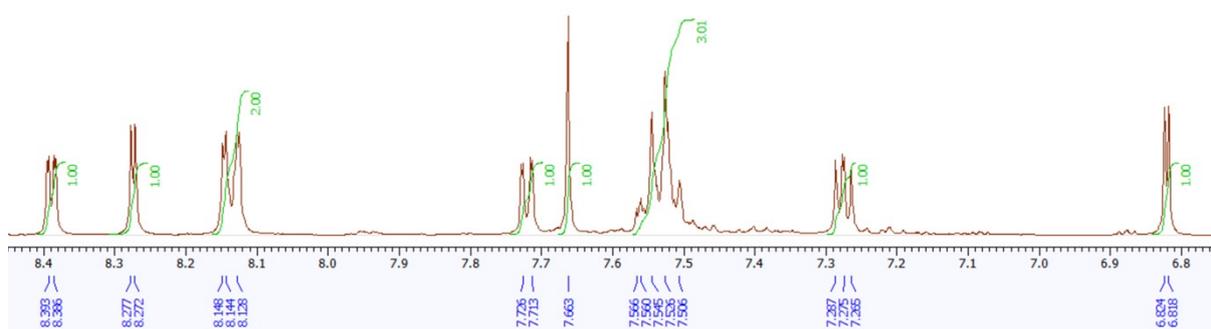
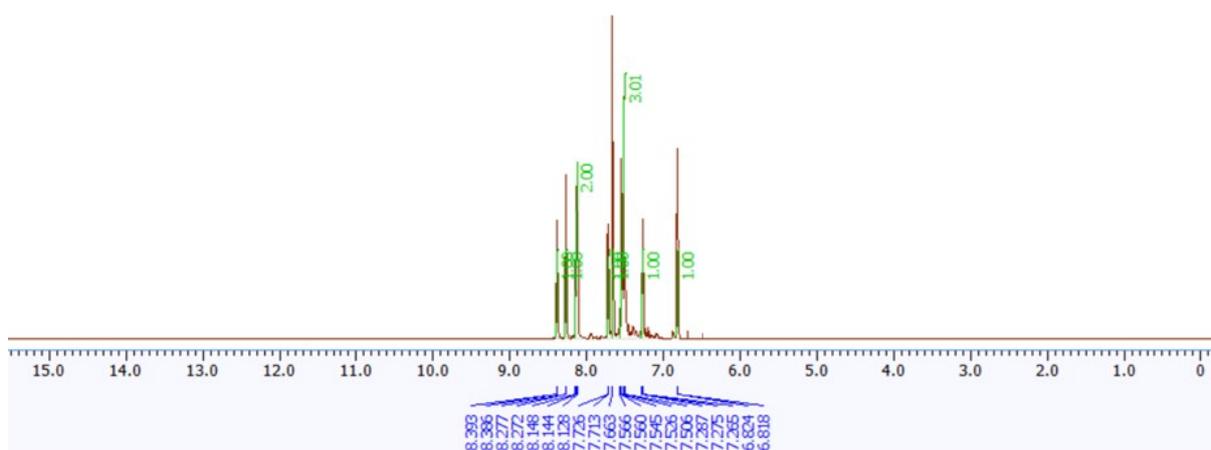


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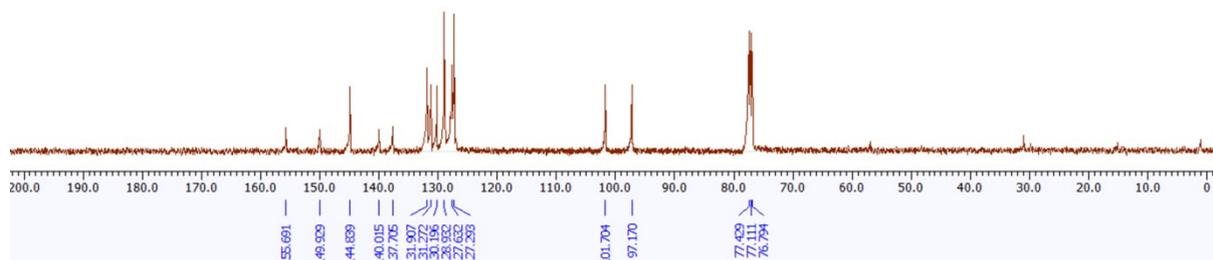




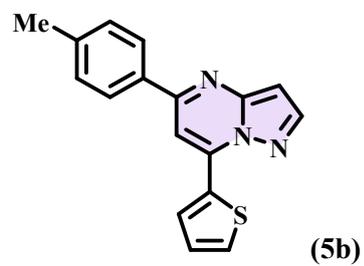
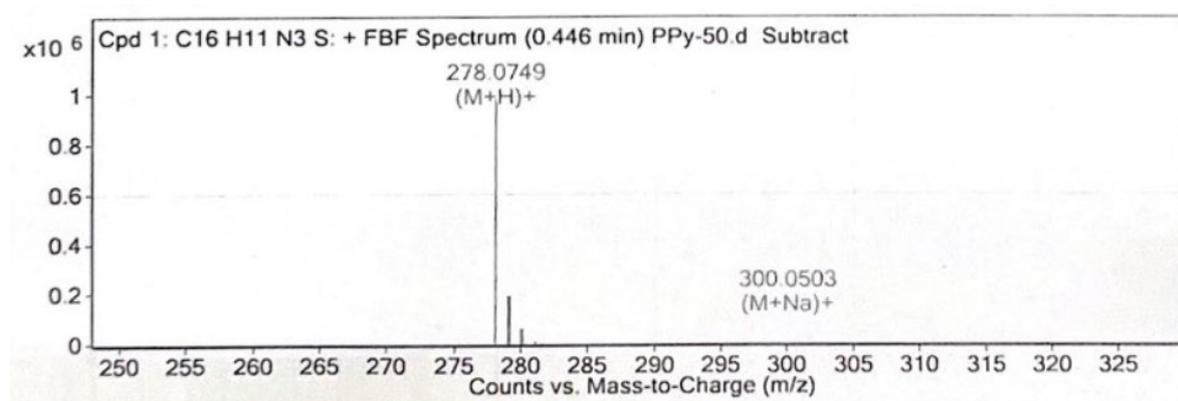
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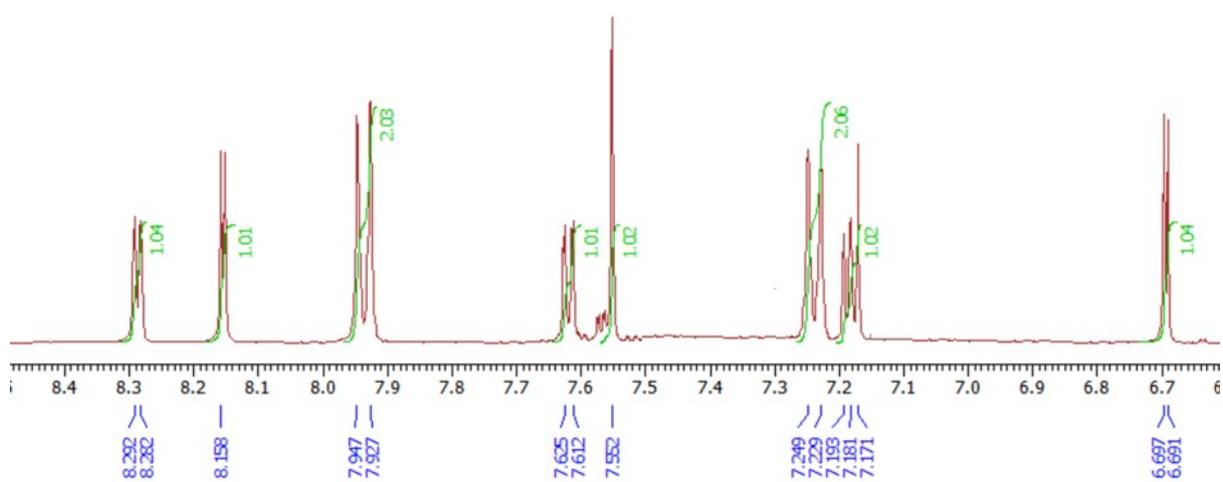
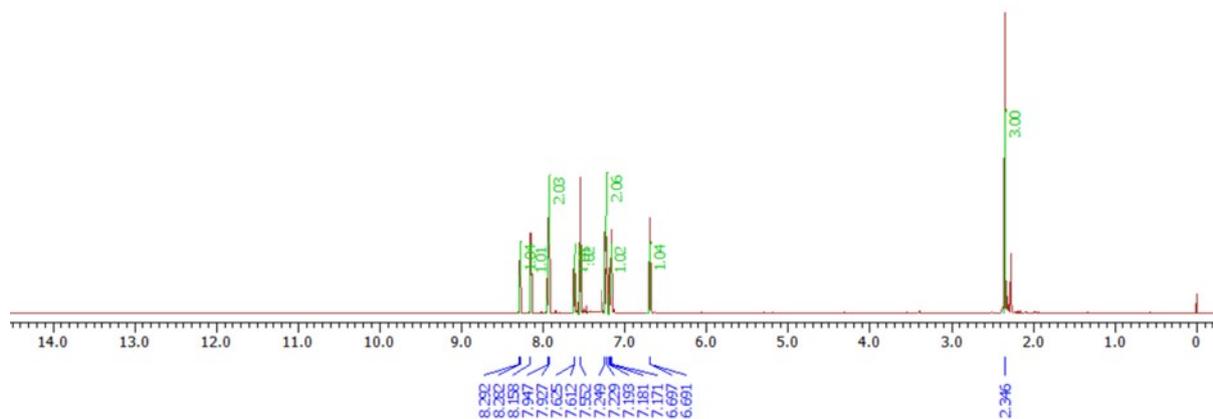
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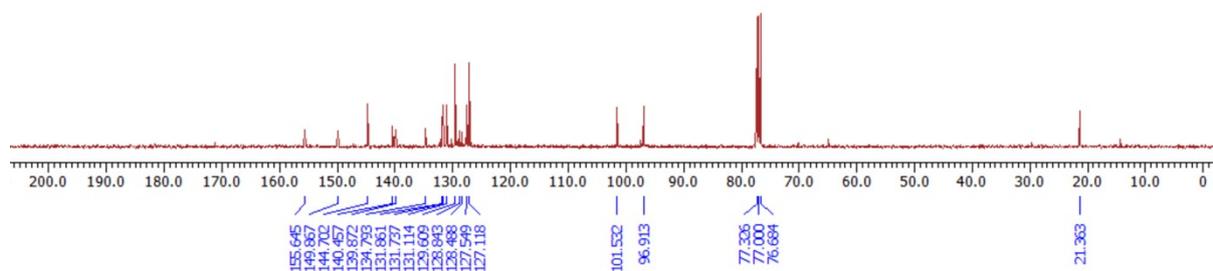
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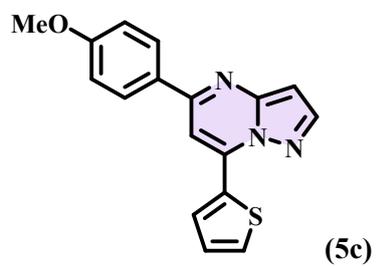
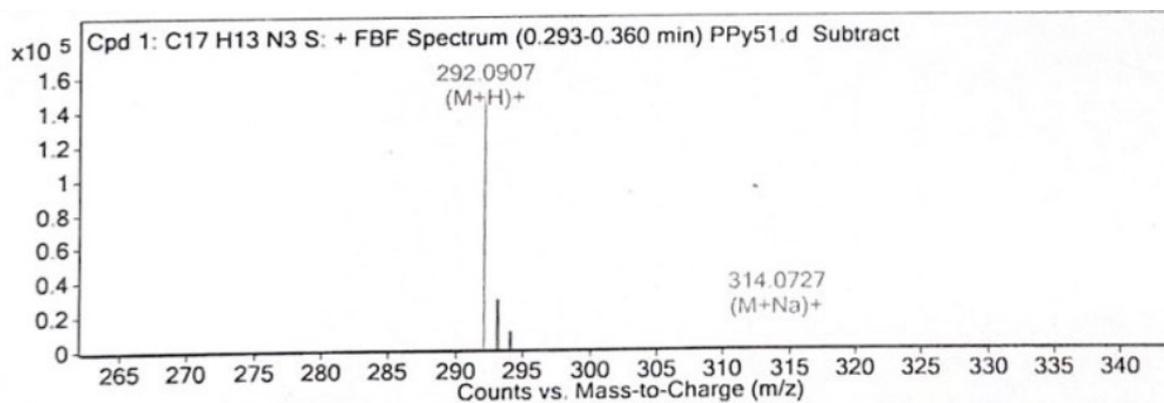
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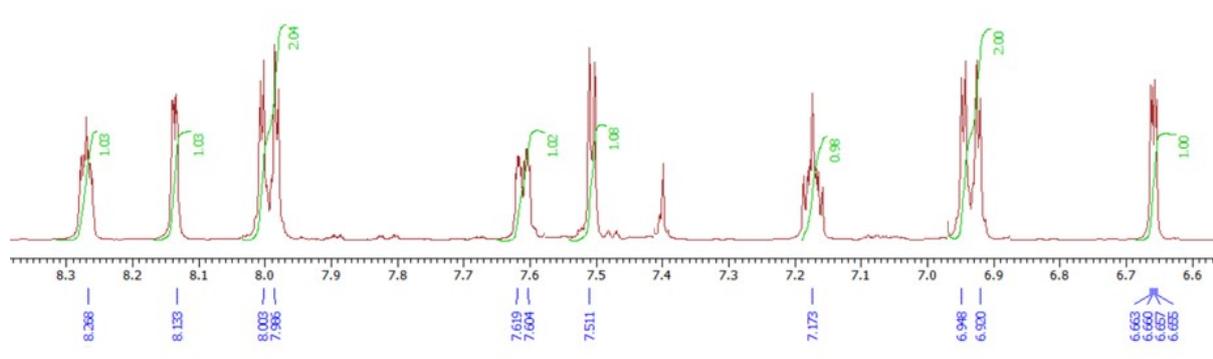
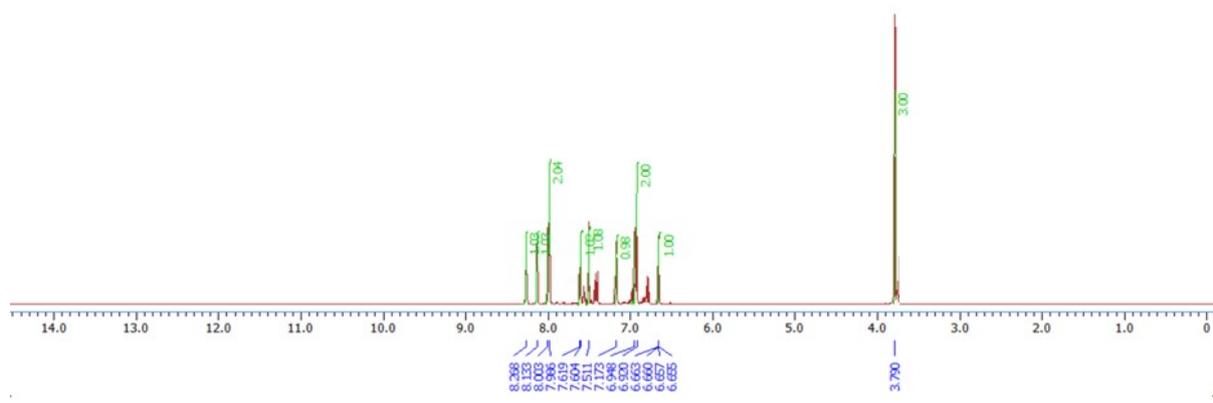
13C NMR



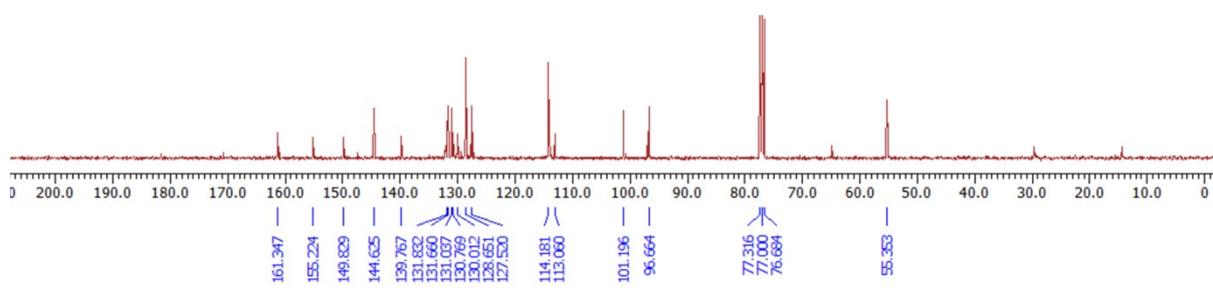
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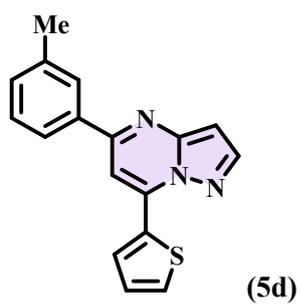
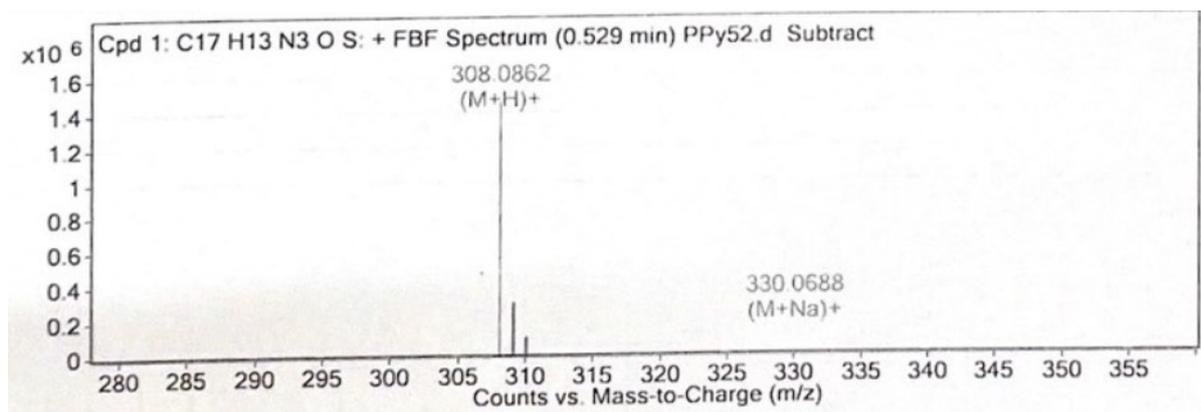
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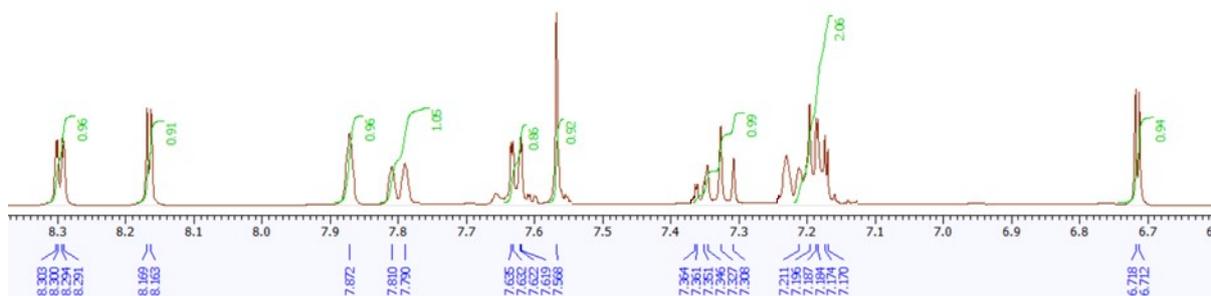
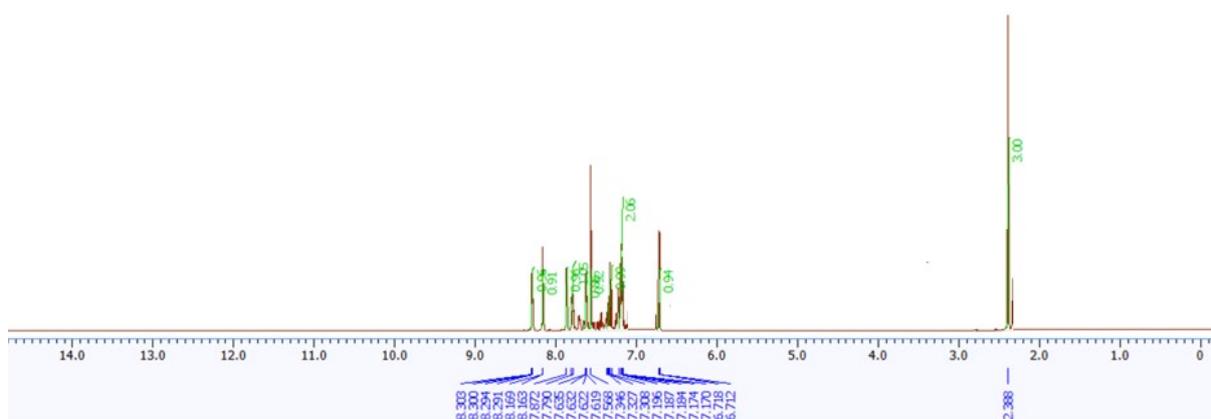
¹³C NMR



HRMS



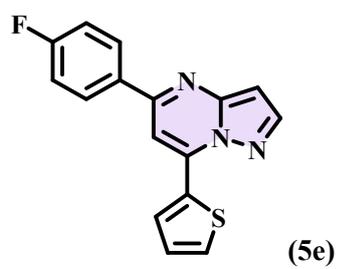
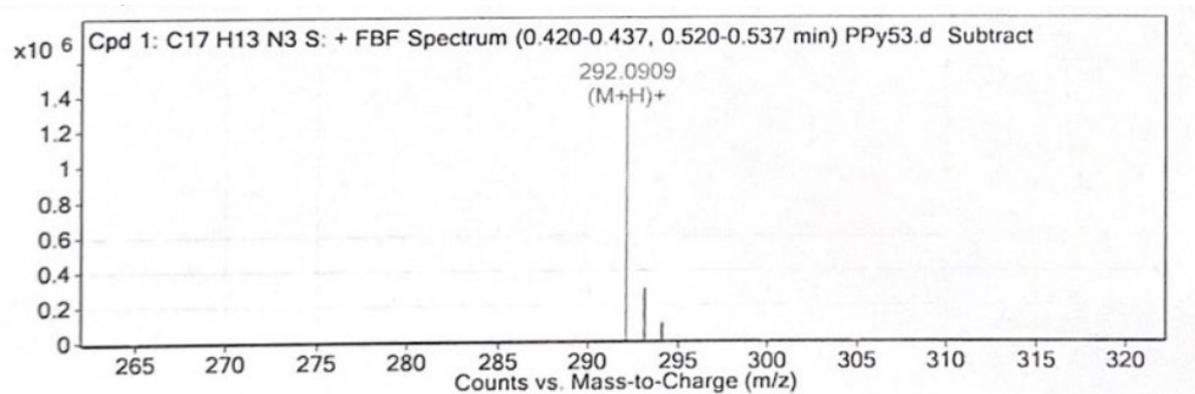
¹H NMR



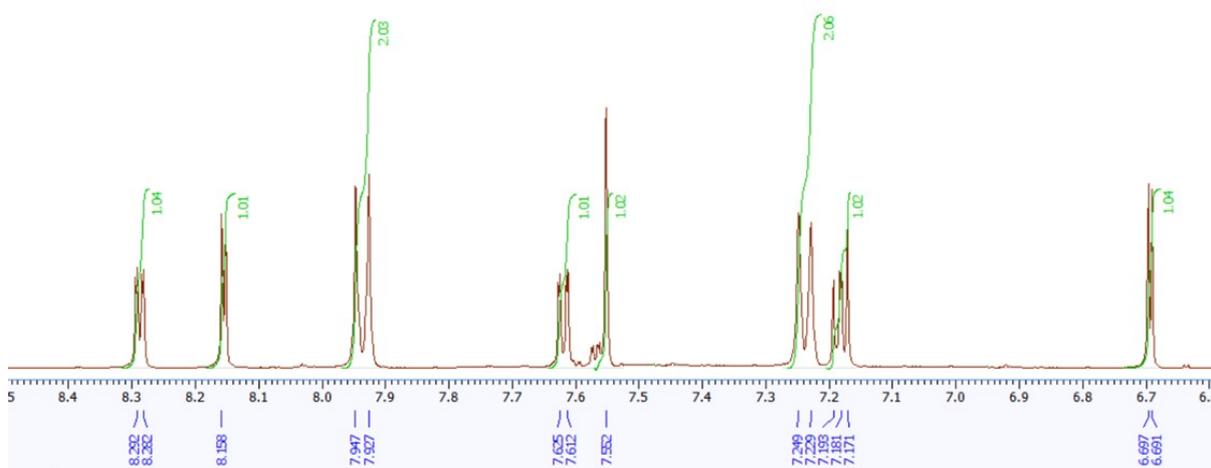
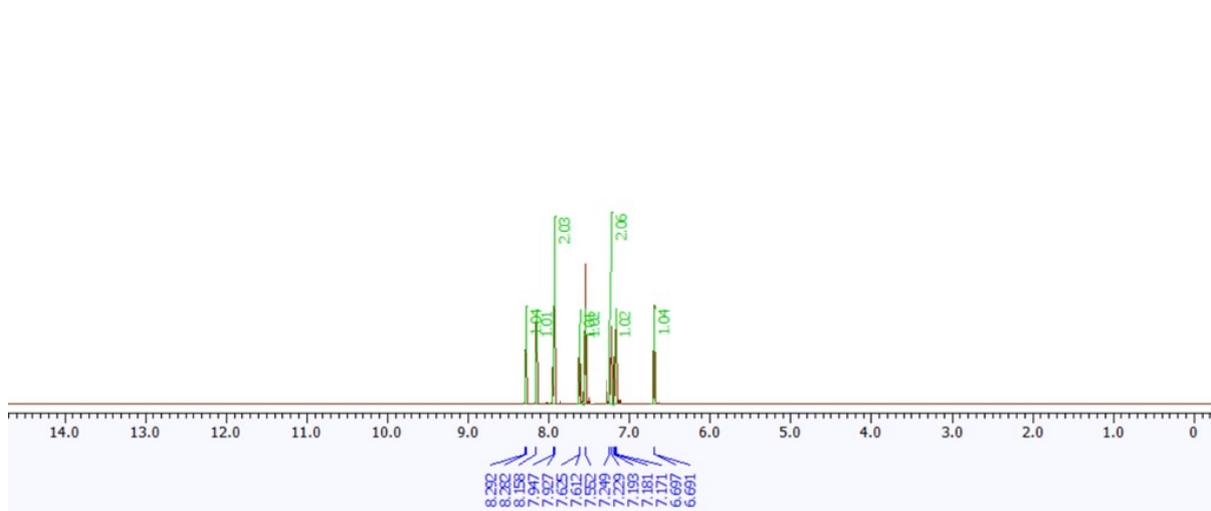
^{13}C NMR



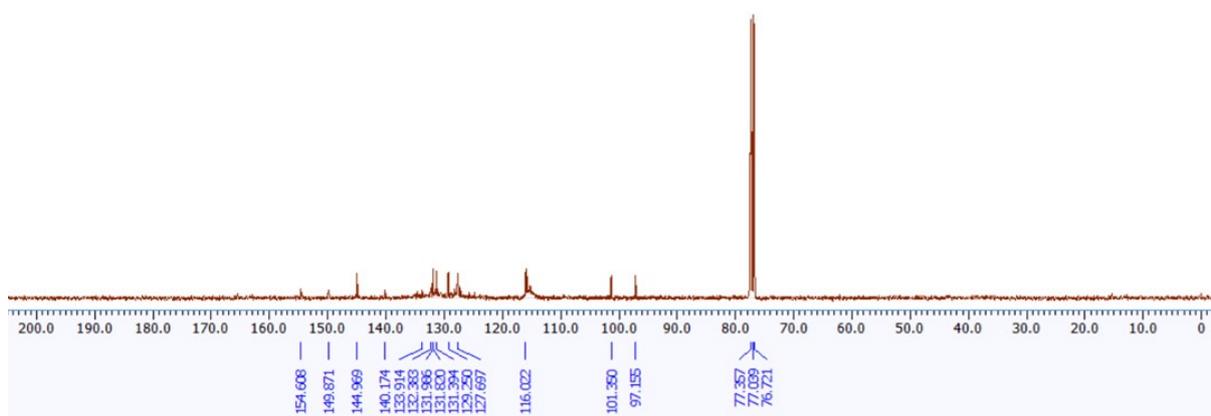
HRMS



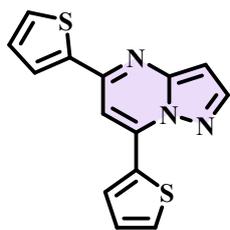
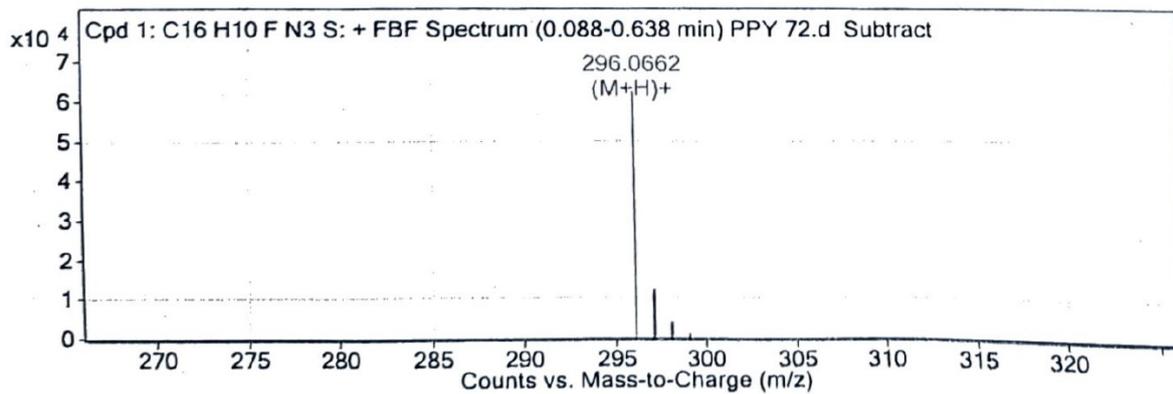
^1H NMR



¹³C NMR

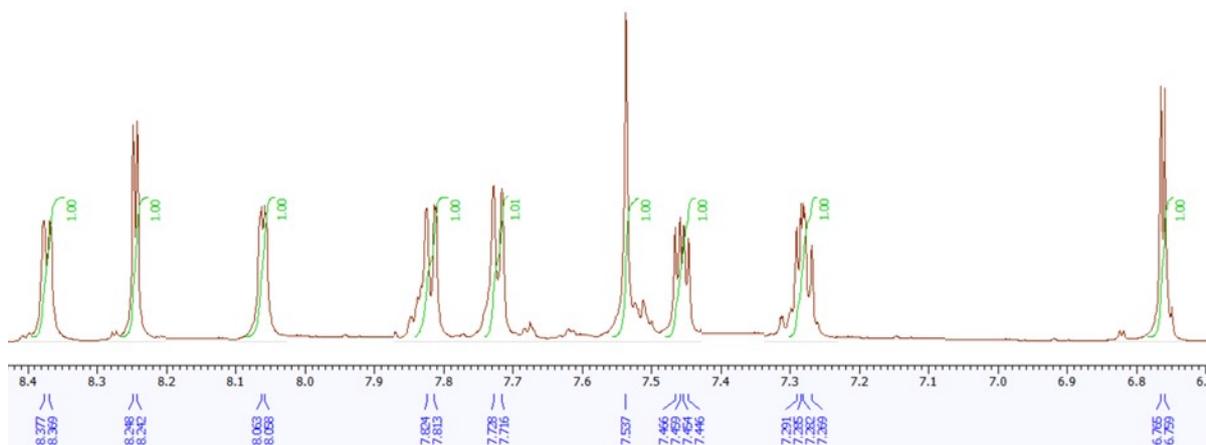
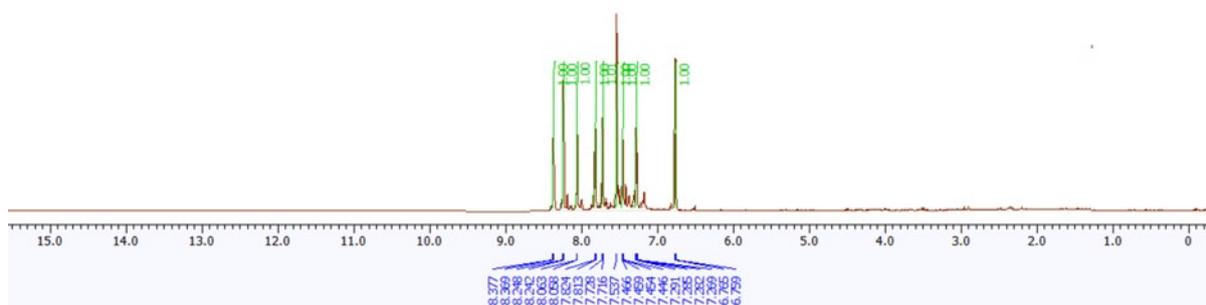


HRMS

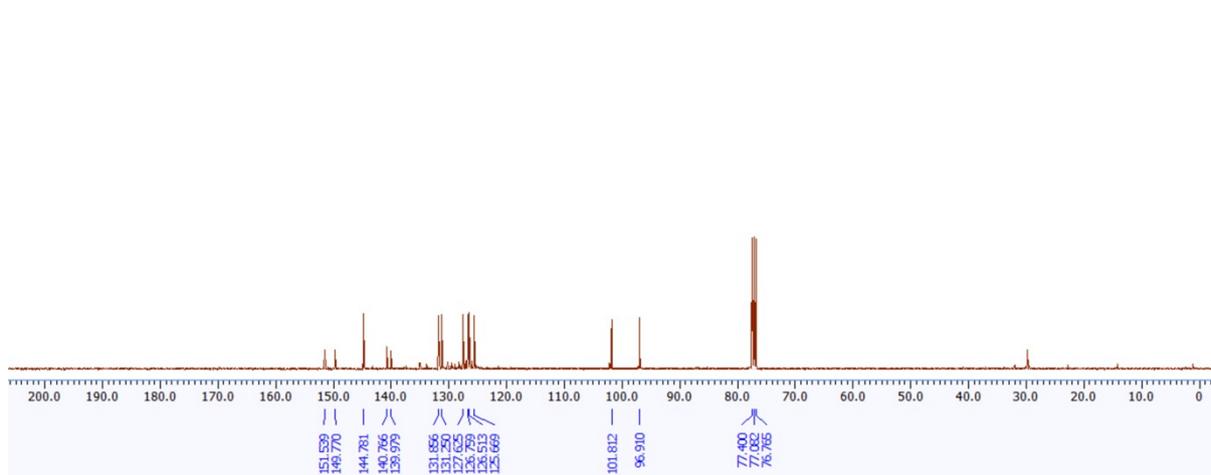


5,7-Di(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine (5f)

¹H NMR



¹³C NMR



HRMS

