Supporting Information

Trisodium citrate dihydrate catalyzed one-pot pseudo four-component synthesis of fully functionalized pyridine derivatives

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Experimental

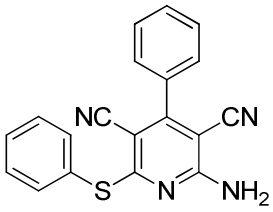
General.

Melting points were recorded on a Digital Melting Point Apparatus (Model No. MT-934) and are uncorrected. TLC was performed on silica gel 60 F254 (Merck) plates. ^{1}H and ^{13}C NMR spectra were obtained at 500 MHz Jeol (JNM ECX-500) NMR machines with DMSO-d_6 as the solvent. Mass spectra (TOF-MS ES^{+}) were measured on a Bruker Impact HD QTOF Micro mass spectrometer.

General procedure for the synthesis of 2-amino-4-aryl-6-(arylthio)pyridine-3,5-dicarbonitrile (4a-4i)

In a dry screw-cap test tube a magnetic stir bar, substitute benzaldehydes (**1a**; 0.5 mmol), malononitrile (**2**; 1 mmol), thiophenol (**3**; 0.5 mmol), 4 ml aqueous ethanol and a catalytic amount of tri-sodium citrate dihydrate (20 mol%) were taken sequentially. The whole reaction mixture was then refluxed for 30-45 minutes. The reaction was monitored by TLC. After completion of the reaction, corresponding products (**4a-4d** were isolated pure just by simple filtration and subsequent washing with aqueous ethanol (H_2O:EtOH = 1:2). Under the same optimized reaction conditions, 2-amino-4-aryl-6-(naphthalen-2-ylthio)pyridine-3,5-dicarbonitriles (**4e-4i**) were also synthesized from the reactions of substitute benzaldehydes (**1a**; 0.5 mmol), malononitrile (**2**; 1 mmol), 2-naphthalenethiol (**3**; 0.5 mmol).

Characterization data along with scanned spectra of all the synthesized compounds are given below:



4a

2-Amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (**4a**). White solid; yield 91%; mp 240-245 °C (lit. 220-221°C)[1]; FTIR (cm^{-1}): 3444, 2924, 2855, 2174, 1547, 1264, 1035, 740, 698; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm: 7.80 (s, 2H, -N*H*$_2$); 7.58-7.50 (m, 6H, aromatic H), 7.47-7.45 (m, 4H aromatic H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm: 166.26, 160.20, 159.20, 135.41 (2C), 134.44, 130.96, 130.29, 130.04 (2C), 129.28 (2C), 128.97 (2C), 127.57, 115.88, 115.58, 93.82, 87.60; HRMS (ESI-TOF) m/z: For $C_{19}H_{10}N_4S$ Calcd. $[M]^+$ 328.0783; Found $[M-H]^-$ 327.1804.

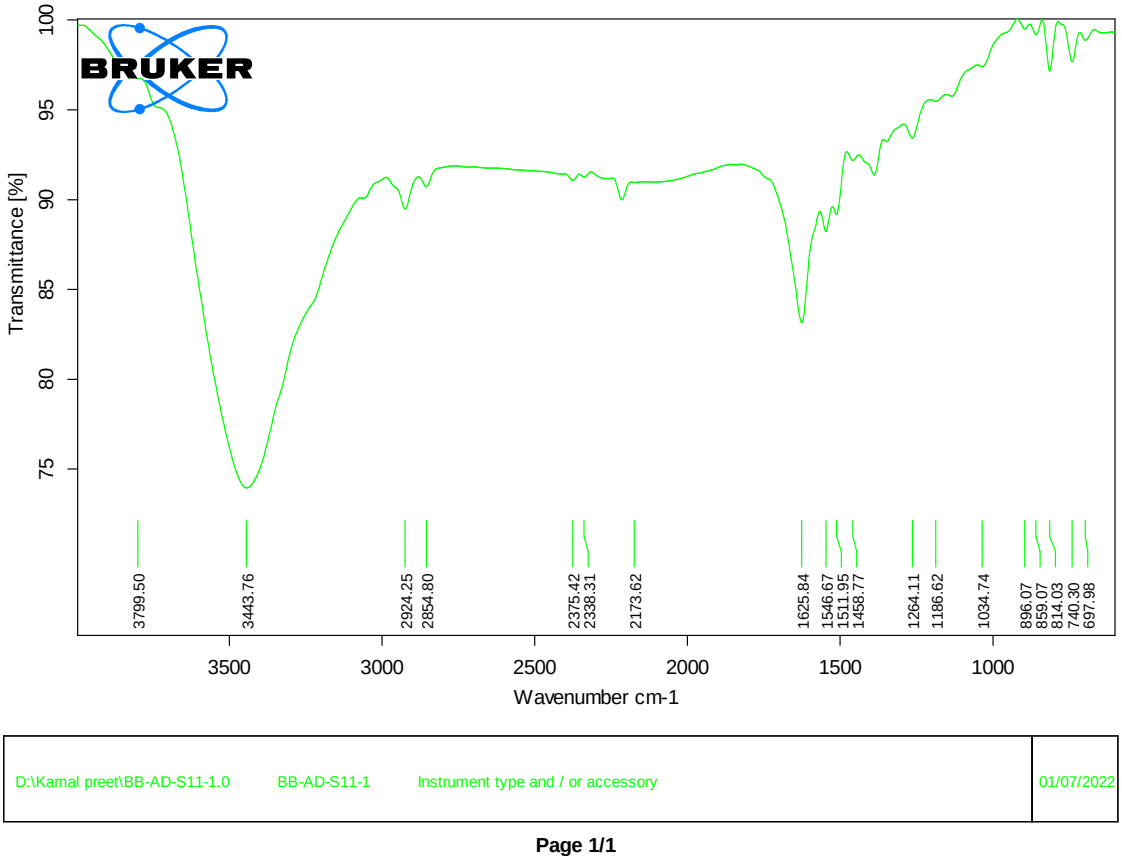


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Figure S1. FTIR spectrum of **4a**

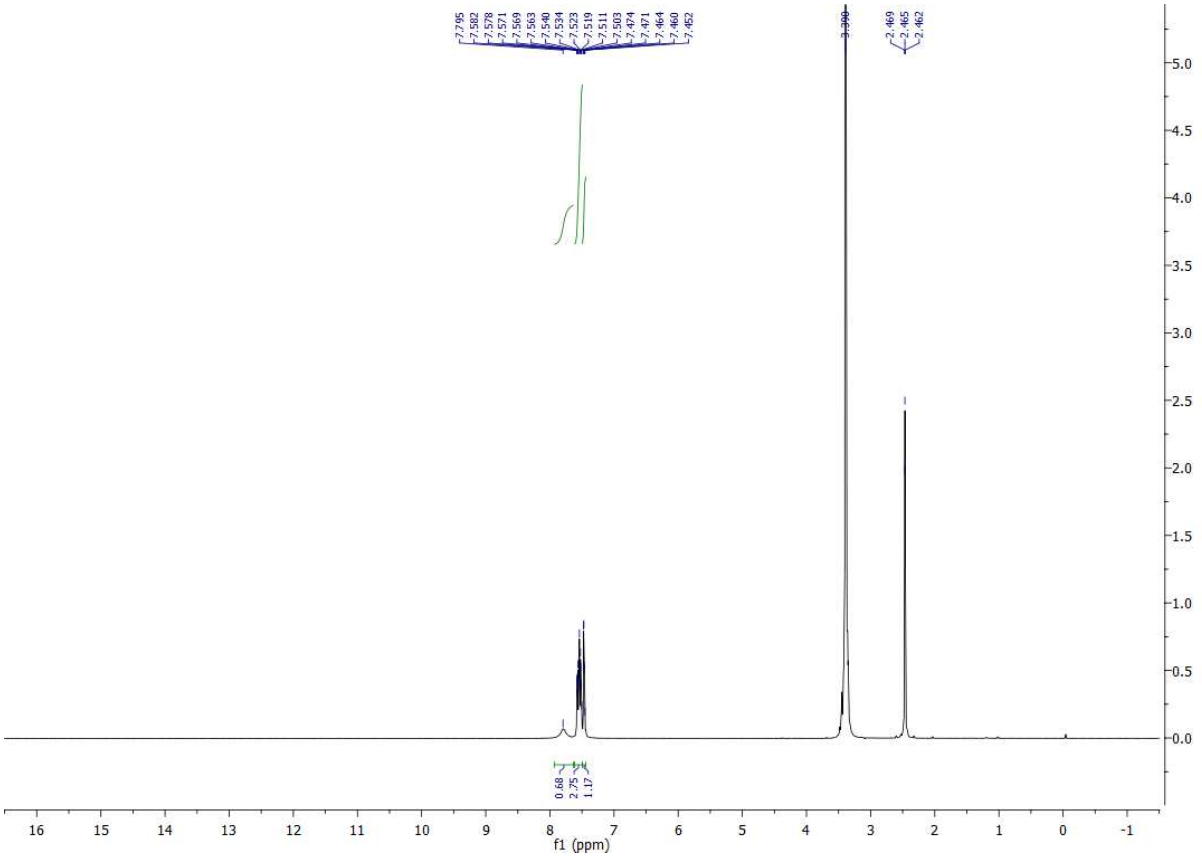

Figure S2. ^{1}H NMR spectrum of **4a**

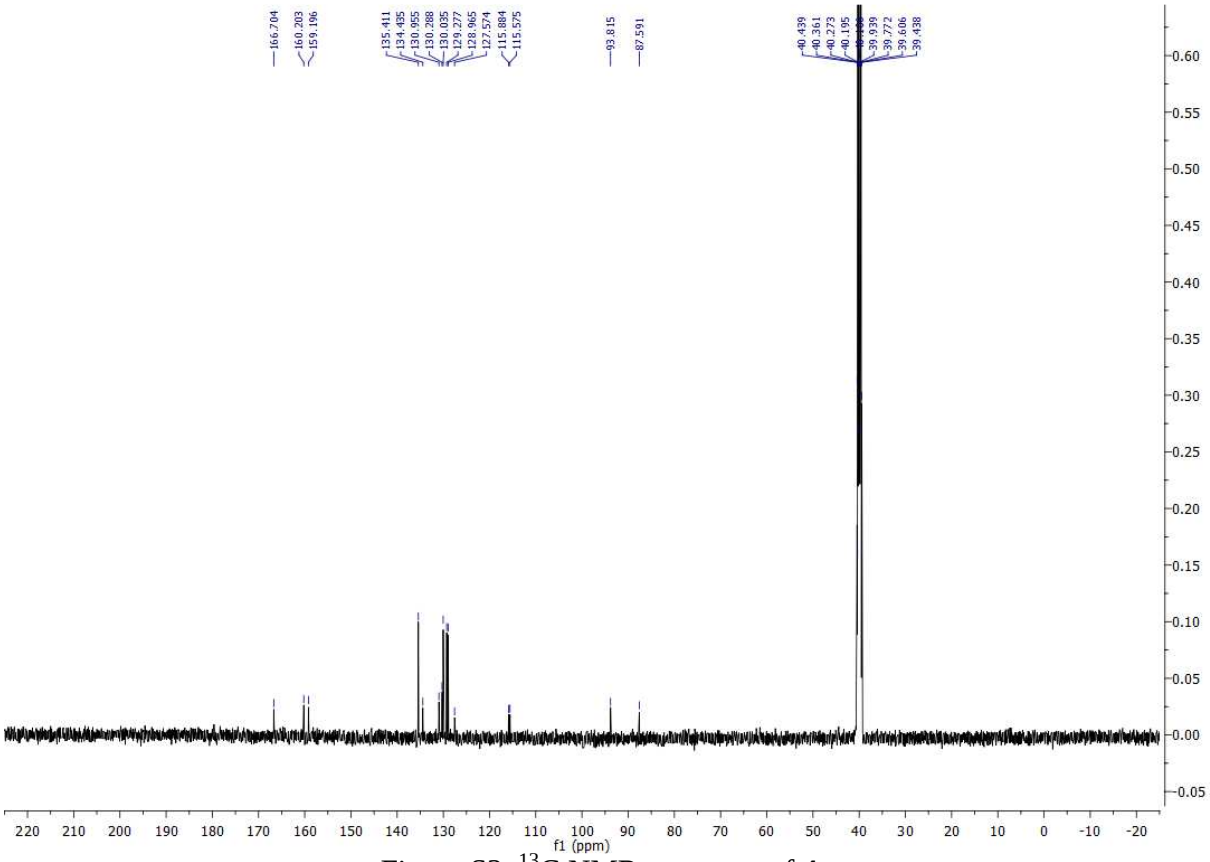

Figure S3. ^{13}C NMR spectrum of **4a**

Display Report

Analysis Info

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Method	Tune_neg_Standard.m	Operator	HRMS
Sample Name		Instrument	maXis impact 1819696.00160
Comment			

Acquisition Parameter

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Scan End	3000 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C

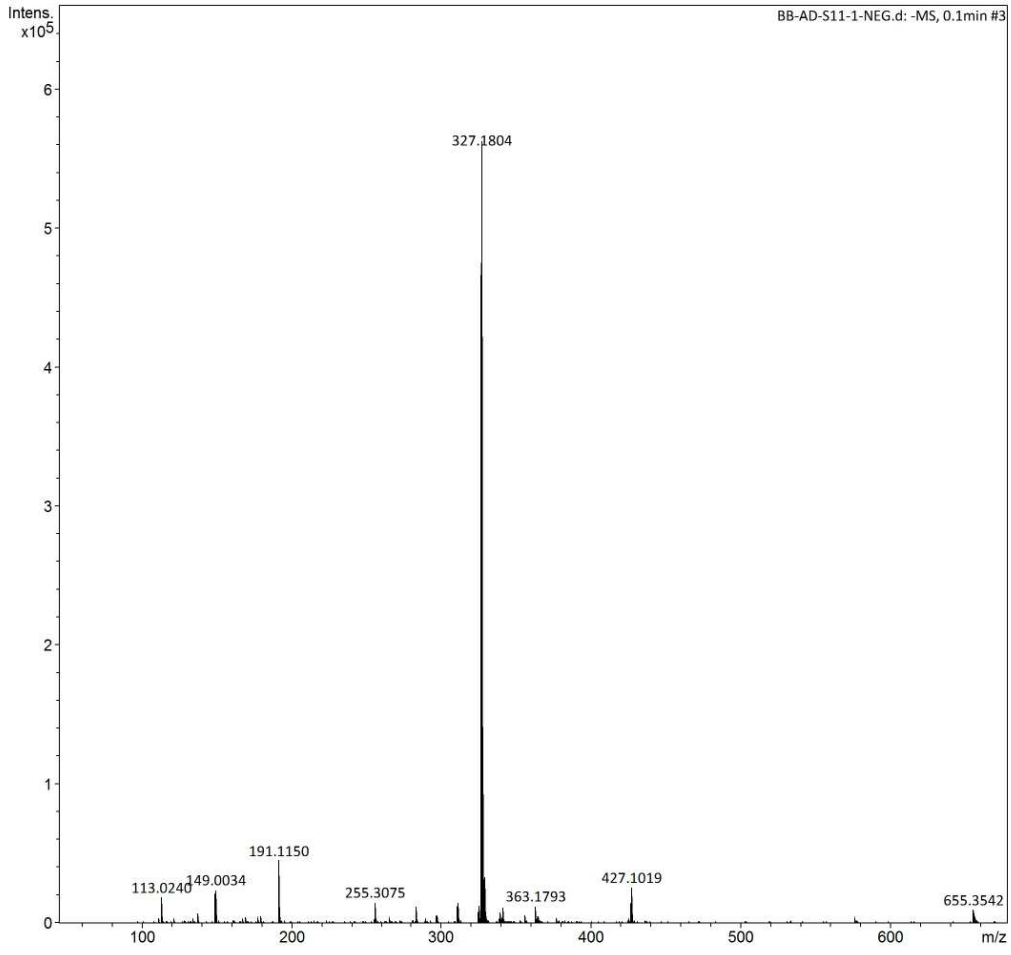

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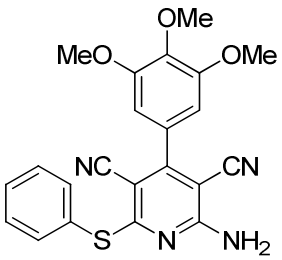
Figure S4. HRMS spectrum of **4a**



4b

2-Amino-6-(phenylthio)-4-(3,4,5-trimethoxyphenyl)pyridine-3,5-dicarbonitrile (**4b**). White solid, yield 93%; mp 258-262 °C (lit. 238-239 °C)[2]; FTIR (cm^{-1}): 3322, 3222, 2753, 2211, 1623, 1503, 1415, 1253, 1128, 841, 744, 703; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.76 (br s, 2H, -N*H*$_2$), 7.56 (t, *J* = 4 Hz, 2H, aromatic H), 7.51-7.40 (m, 3H, aromatic H), 6.89 (s, 2H, aromatic H), 3.78 (s, 6H, 2X -OC*H*$_3$), 3.71 (s, 3H, -OC*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 166.64, 160.20, 158.89, 153.31 (2C), 139.29, 135.41 (2C), 130.28, 130.04 (2C), 129.49, 127.60, 116.04, 115.75, 106.86 (2C), 93.89, 87.60, 60.68, 56.70 (2C); HRMS (ESI-TOF) m/z: For $C_{22}H_{18}N_4O_3S$ Calcd. $[M]^+$ 418.1100; Found $[M\text{-}H]^-$ 417.0281.

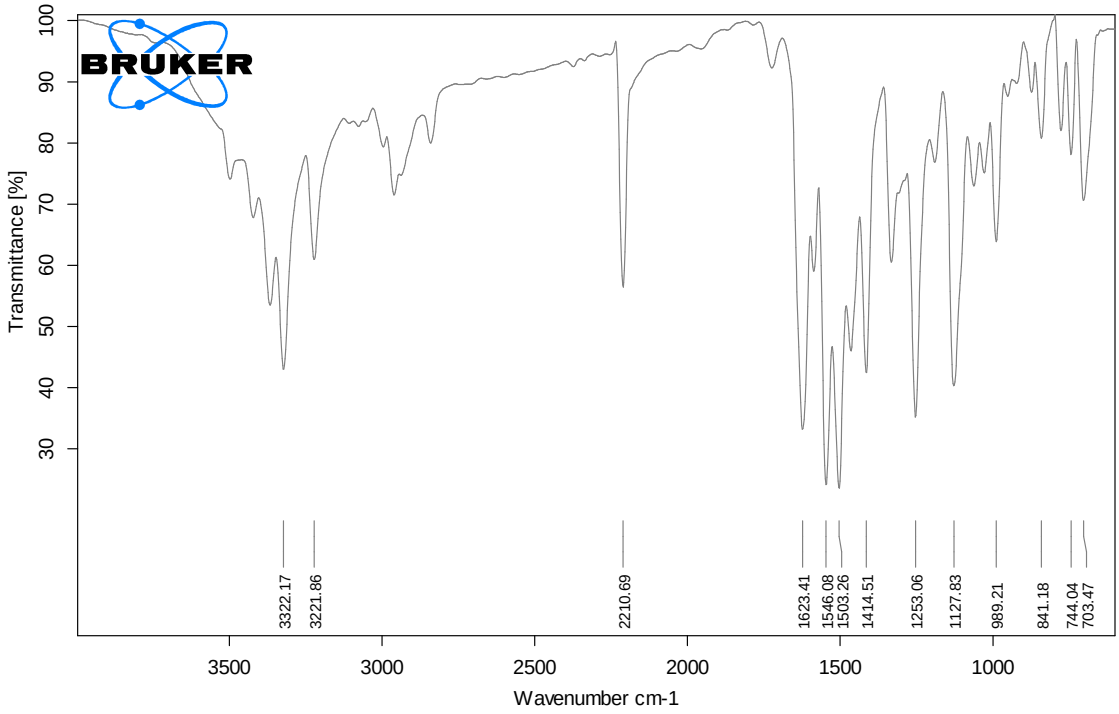


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Figure S5. FTIR spectrum of **4b**

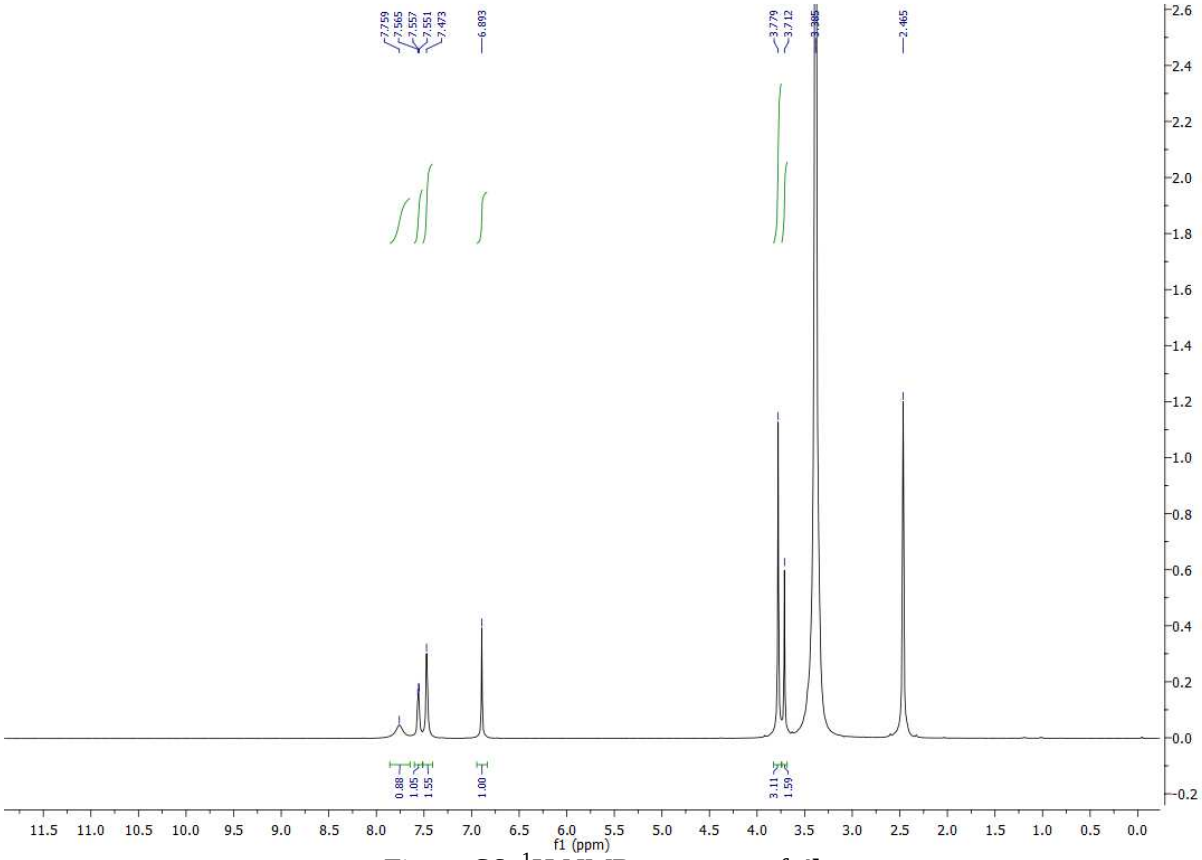


Figure S6. ^{1}H NMR spectrum of **4b**

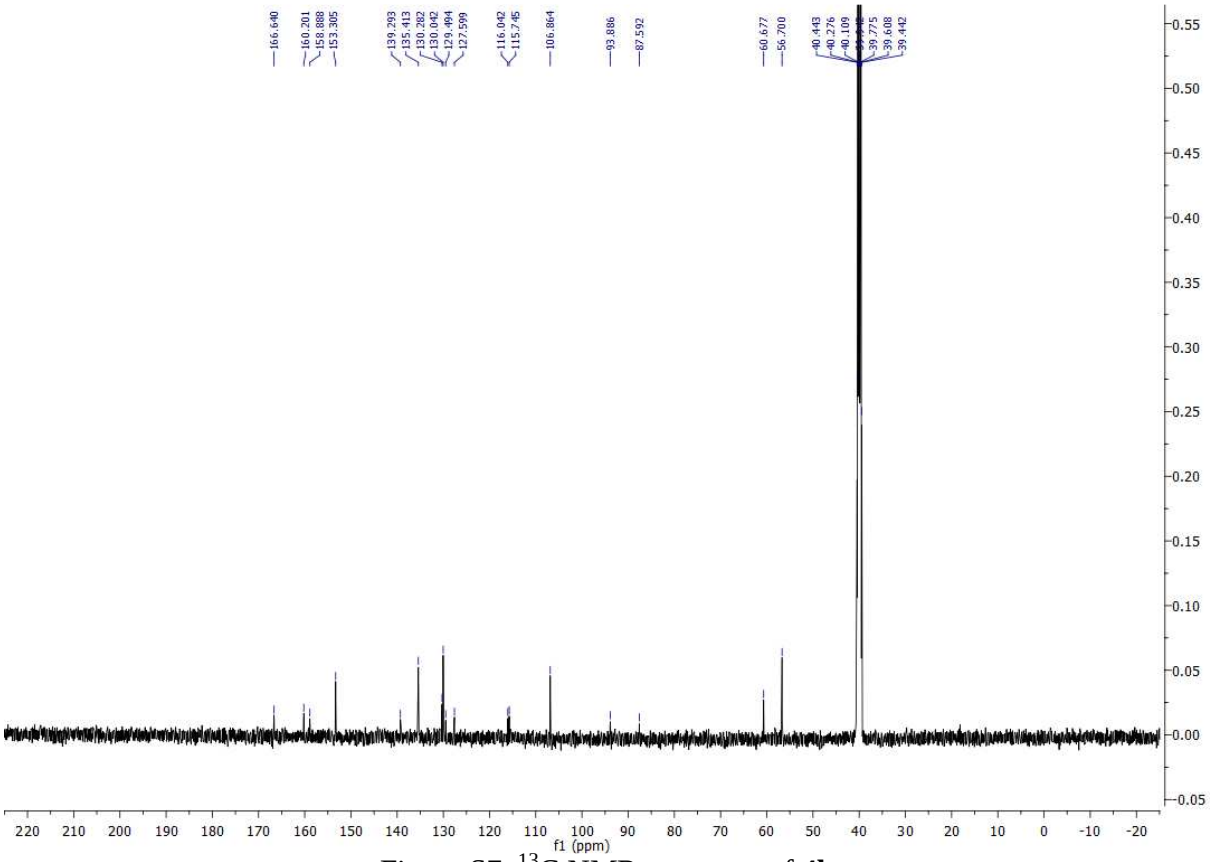


Figure S7. ^{13}C NMR spectrum of **4b**

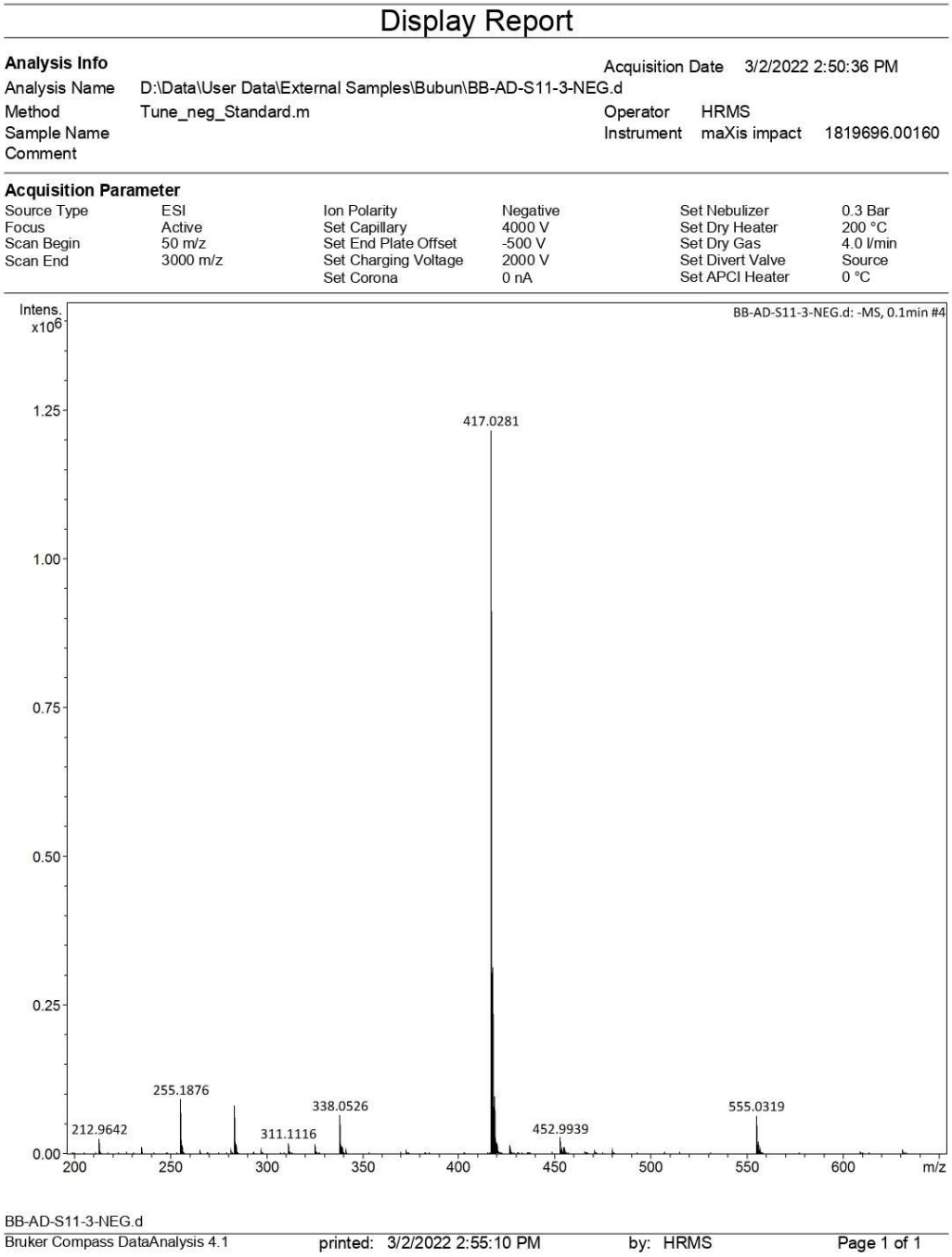
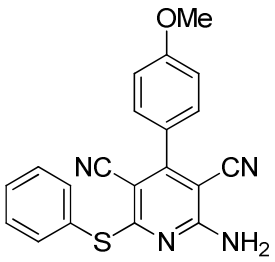


Figure S8. HRMS spectrum of **4b**



4c

2-Amino-4-(4-methoxyphenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile (**4c**). White solid, yield 92%; mp 274-277 °C (lit. 251-253 °C)[3]; FTIR (cm^{-1}): 3329, 3226, 2927, 2847, 2217, 1641, 1512, 1254, 1021, 755, 688; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.73 (br s, 2H, -NH_2), 7.57-7.55 (m, 2H, aromatic H), 7.49-7.44 (m, 5H, aromatic H), 7.09 (d, J = 8.5 Hz, 2H, aromatic H), 3.81 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 166.22, 161.38, 160.32, 158.88, 135.38 (2C), 130.80 (2C), 130.23, 130.01 (2C), 127.70, 126.32, 116.12, 115.84, 114.64, 105.32, 93.87, 87.50, 55.90; HRMS (ESI-TOF) m/z: For $C_{20}H_{14}N_4OS$ Calcd. $[M + Na]^+$ 381.0786; Found $[M + Na]^+$ 381.2312.

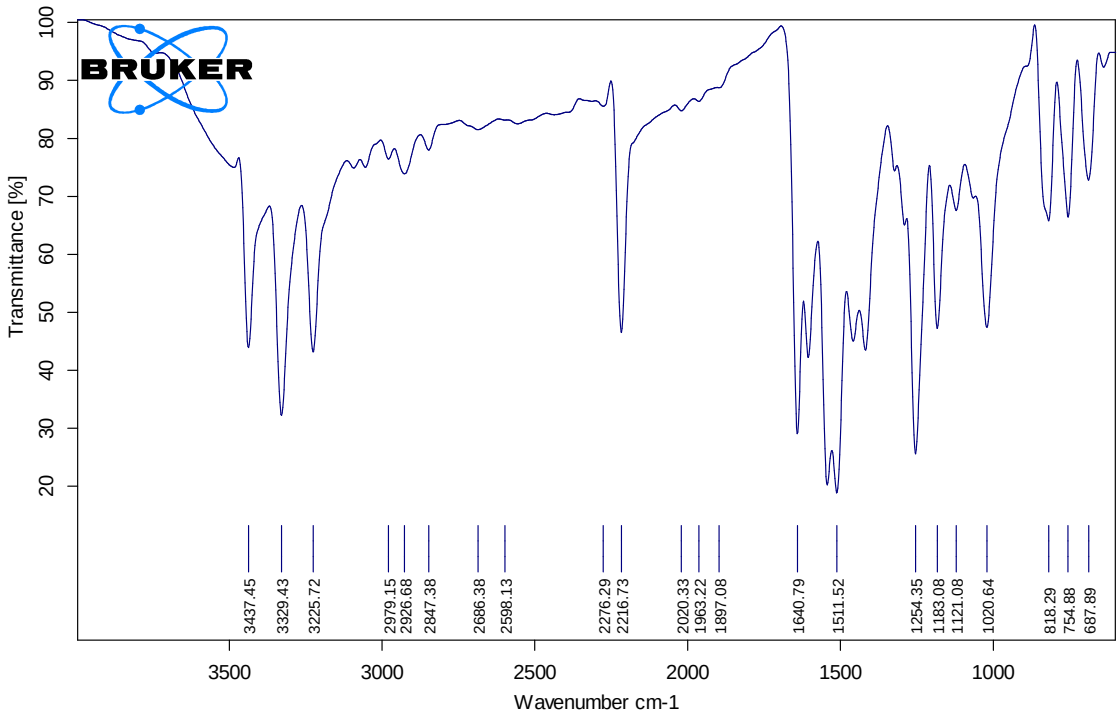


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Figure S9. FTIR spectrum of **4c**

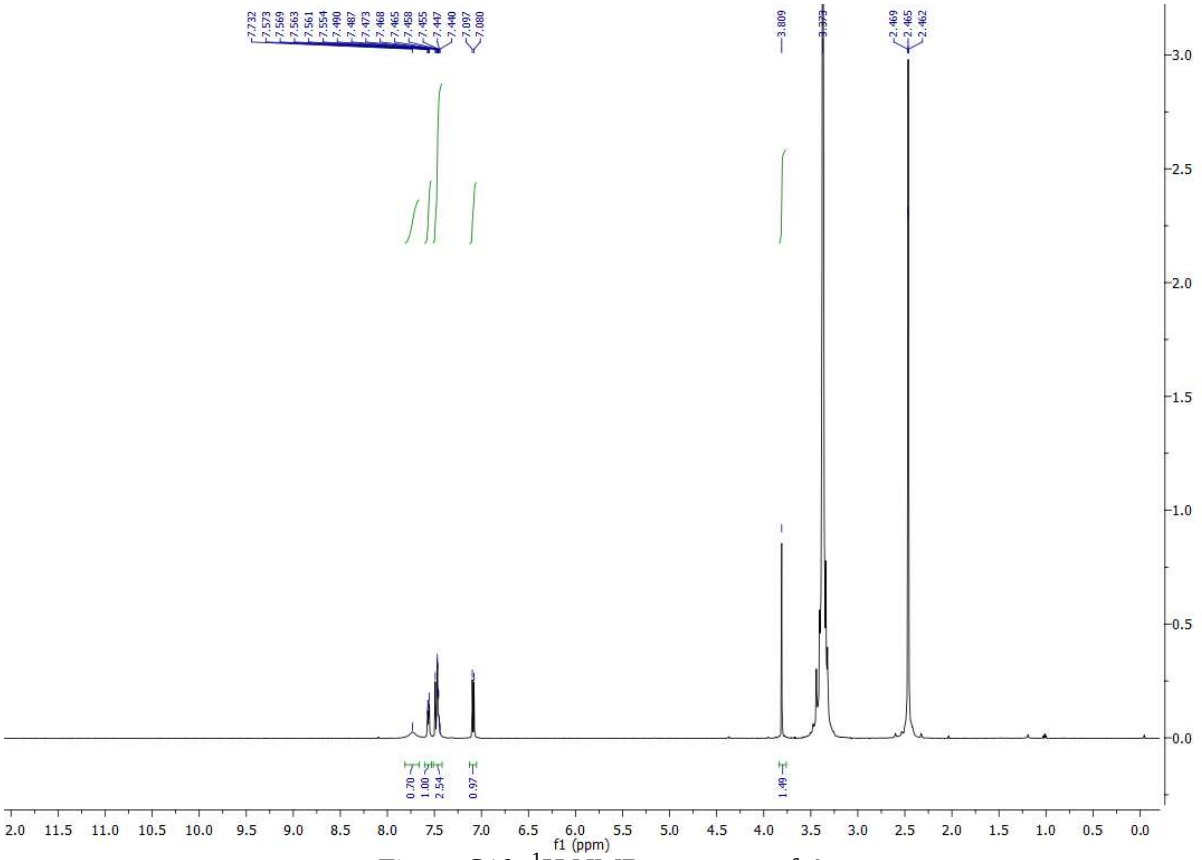


Figure S10. ^{1}H NMR spectrum of **4c**

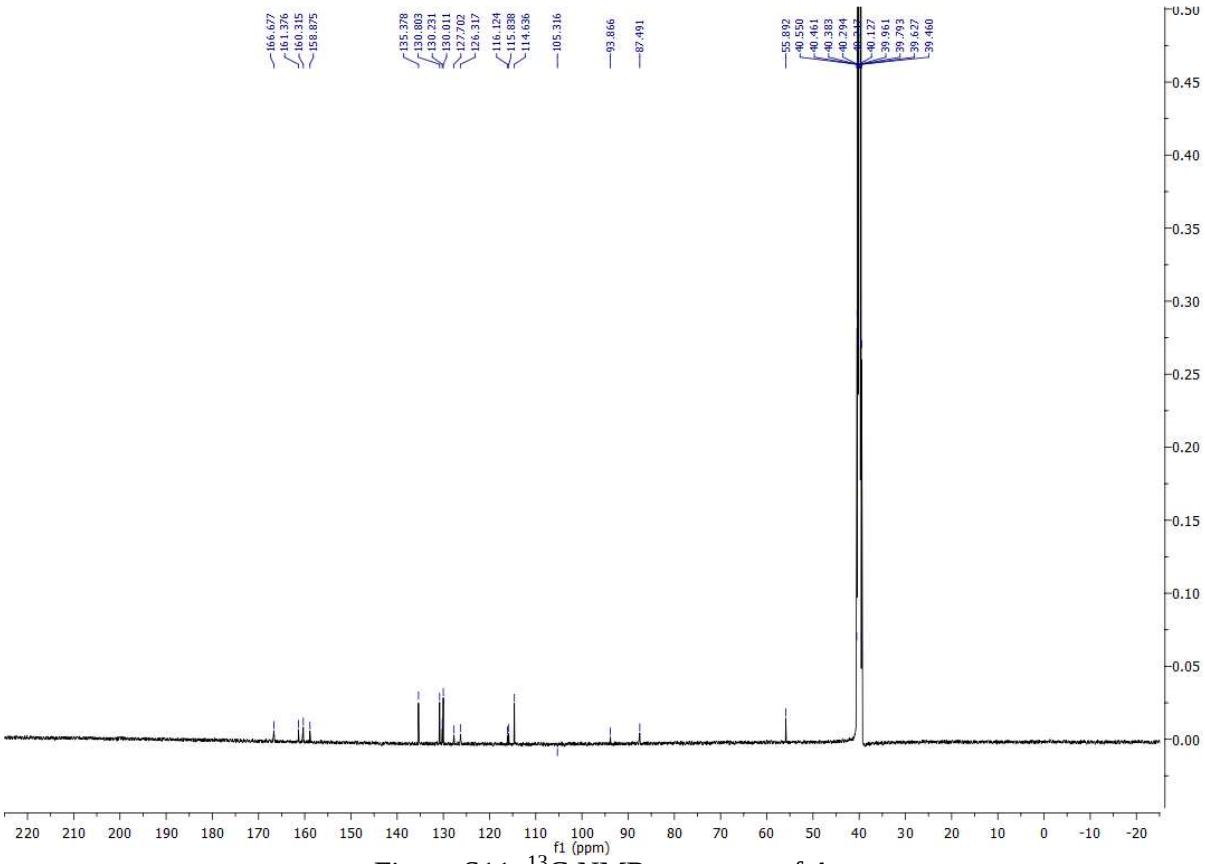


Figure S11. ^{13}C NMR spectrum of **4c**

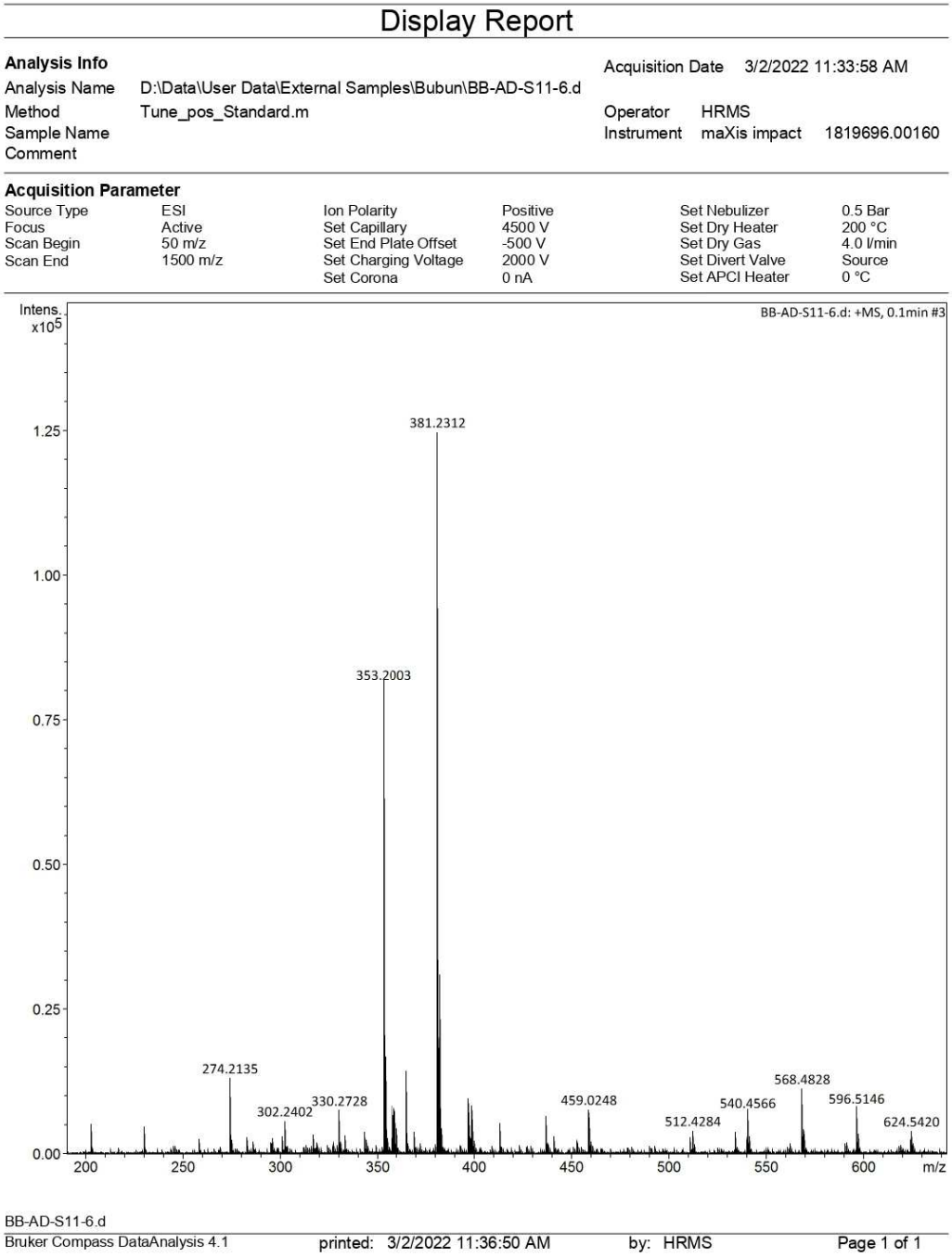
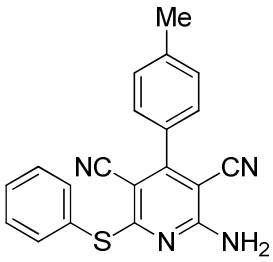


Figure S12. HRMS spectrum of **4c**



4d

2-Amino-6-(phenylthio)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (**4d**). White solid, yield 90%; mp 222-224 °C (lit. 206-210 °C)[4]; FTIR (cm^{-1}): 3348, 3213, 3070, 2214, 1617, 1538, 1257, 1020, 685, 639 ; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 7.74 (br s, 2H, -NH_2), 7.56 (t, J = 7 Hz, 2H, aromatic H), 7.46 (d, J = 4.5 Hz, 3H aromatic H), 7.40 (d, J = 8 Hz, 2H, aromatic H), 7.35 (d, J = 8 Hz, 2H, aromatic H), 2.37 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 181.06, 171.58, 167.06, 166.57, 146.01, 139.47, 136.65, 135.39, 130.02 (2C), 129.82, 128.93, 127.63, 127.60, 118.82, 115.68, 113.86, 76.35, 75.34, 19.07; HRMS (ESI-TOF) m/z: For $C_{20}H_{14}N_4S$ Calcd. $[M]^+$ 342.0939; Found $[M-H]^-$ 341.1014.

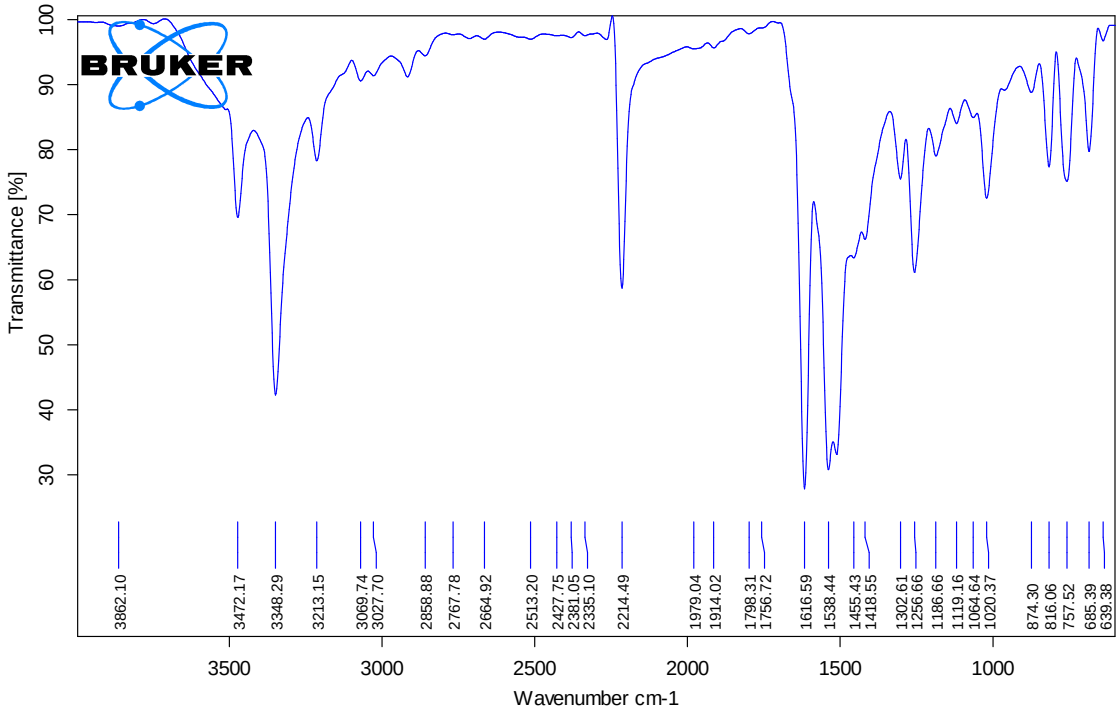


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Figure S13. FTIR spectrum of **4d**

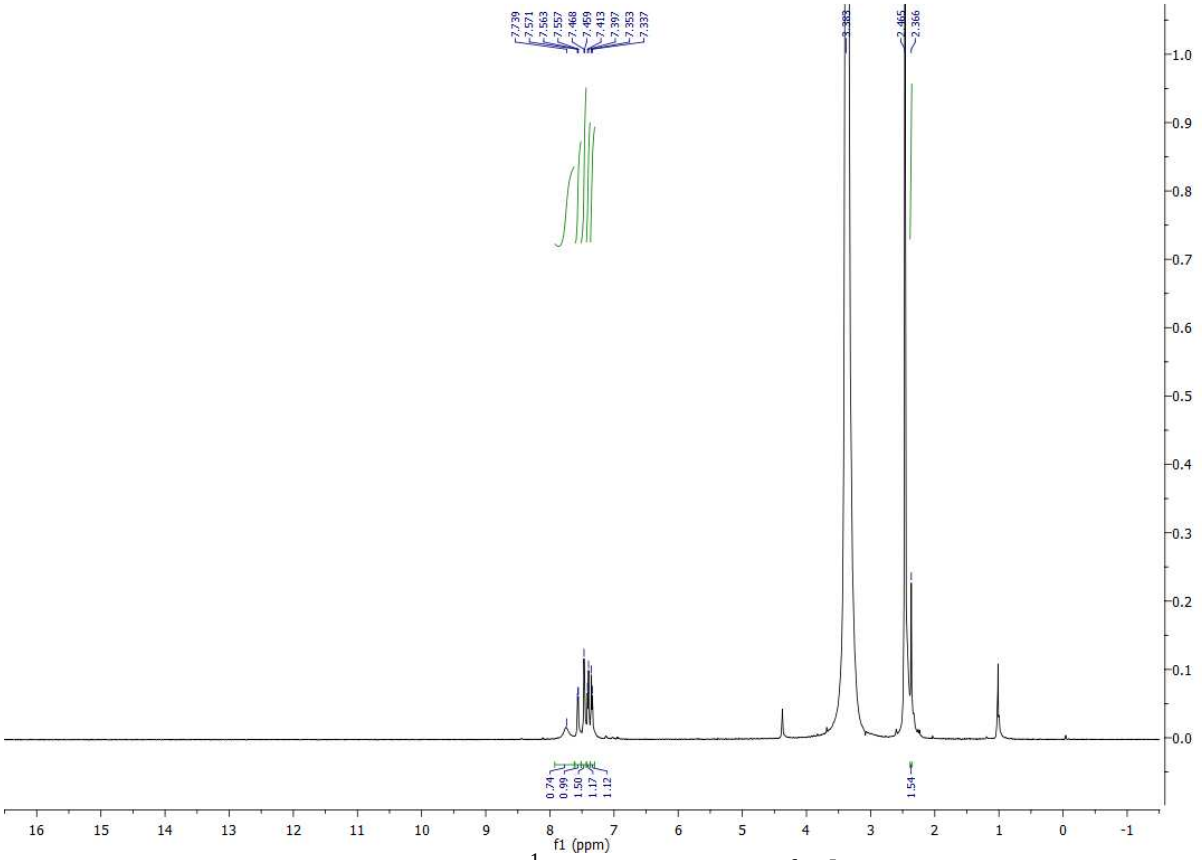


Figure S14. ^{1}H NMR spectrum of **4d**

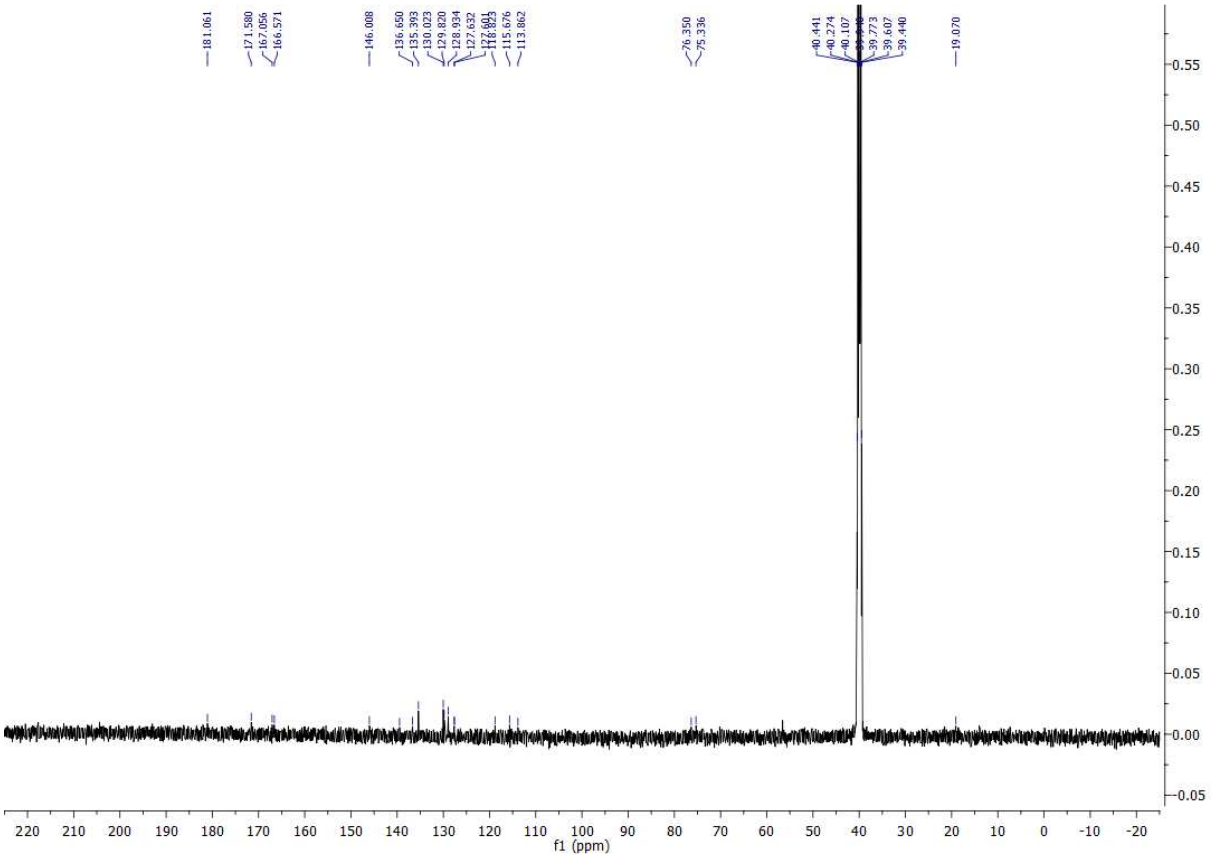


Figure S15. ^{13}C NMR spectrum of **4d**

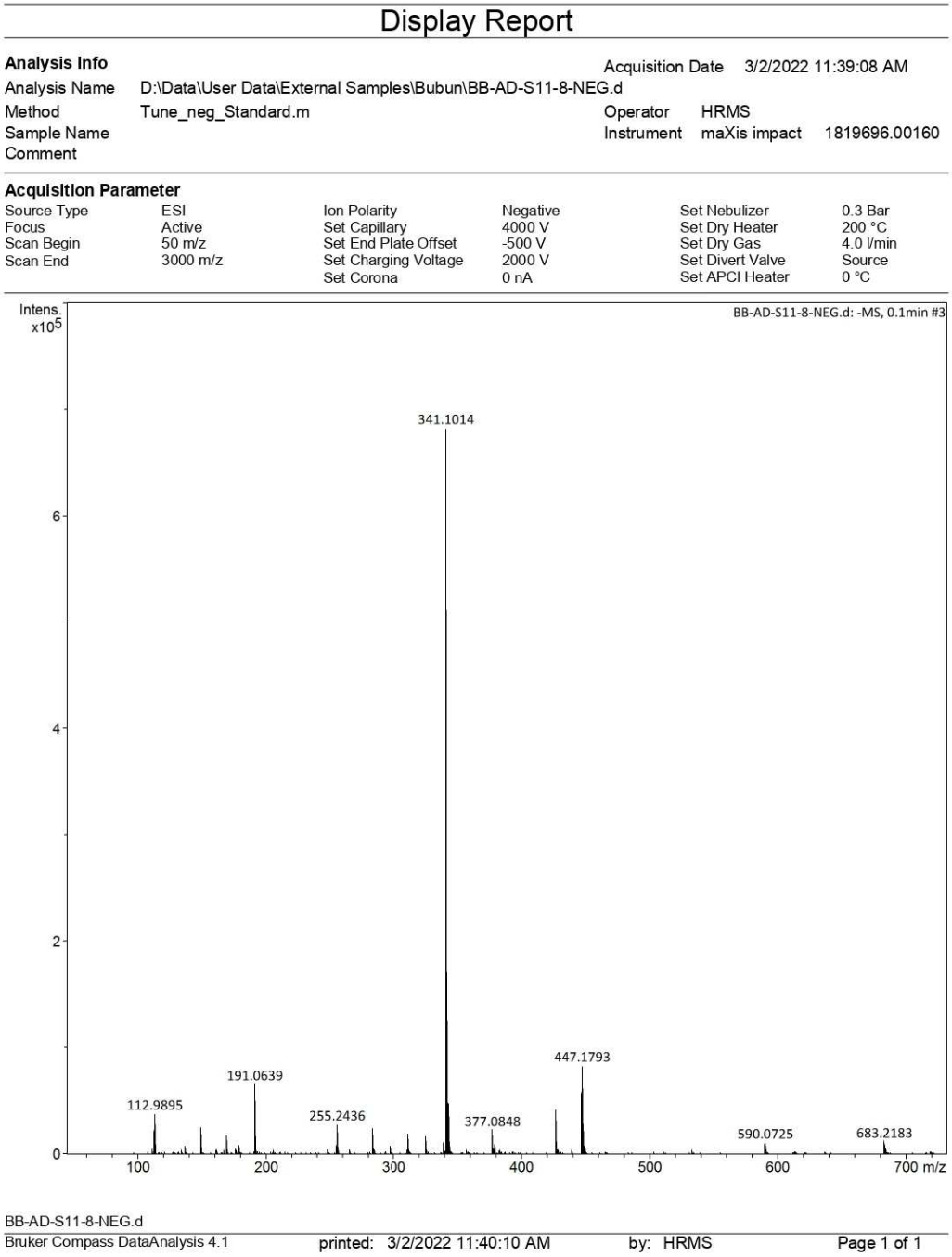
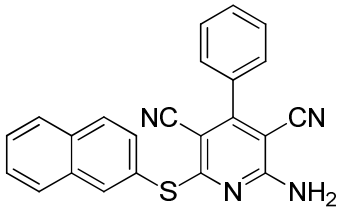


Figure S16. HRMS spectrum of **4d**



4e

2-Amino-6-(naphthalen-2-ylthio)-4-phenylpyridine-3,5-dicarbonitrile (**4e**). White solid, yield 94%; mp 159-161 °C; FTIR (cm^{-1}): 3360, 3213, 3057, 2215, 1620, 1544, 1260, 1076, 751, 701; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 8.10 (d, *J* = 2 Hz, 2H, aromatic H), 7.91 (d, *J* = 9 Hz, 2H, aromatic H), 7.85 (q, *J* = 7.5 Hz, 4H aromatic H), 7.63 (dd, *J* = 8.75, 2 Hz, 2H, aromatic H), 7.50-7.47 (m, 2H, aromatic H), 7.49 (s, 2H, -N*H*$_2$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 173.63, 163.91, 162.13, 146.97, 141.93, 140.33, 133.61 (2C), 133.53 (2C), 129.87 (2C), 128.28 (2C), 127.92 (2C), 127.66 (2C), 127.18, 126.71, 125.79, 107.53, 80.05; HRMS (ESI-TOF) m/z: For $C_{23}H_{14}N_4S$ Calcd. $[M]^+$ 378.0939; Found $[M\text{-}H]^-$ 377.0448.

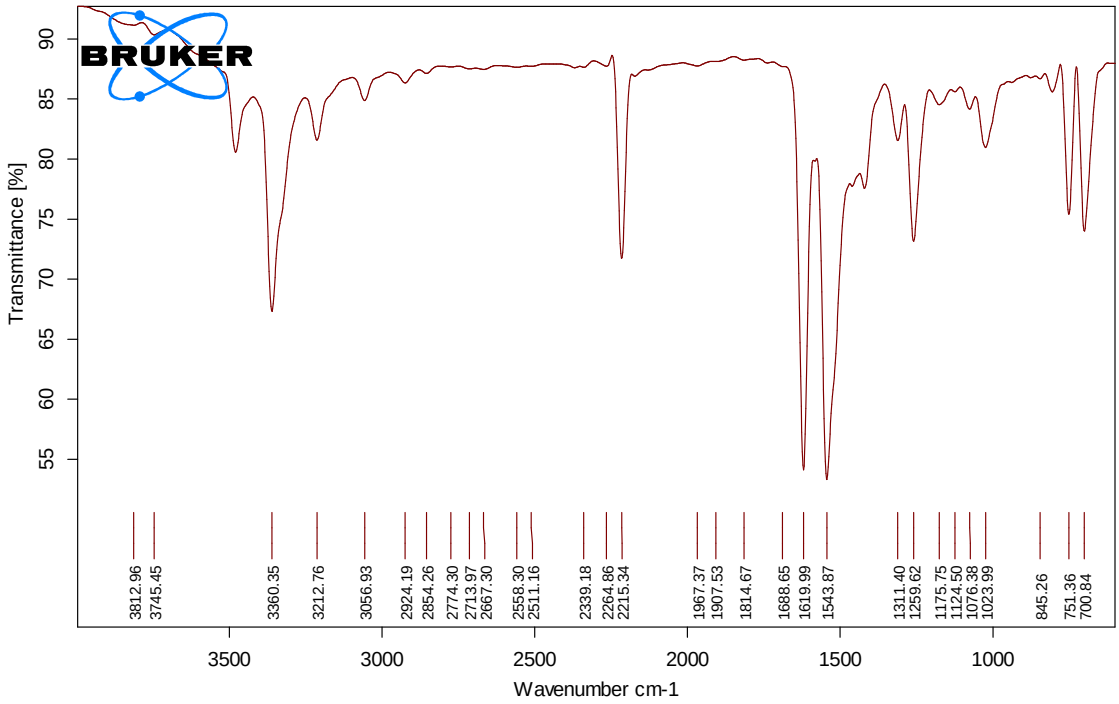


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Figure S17. FTIR spectrum of **4e**

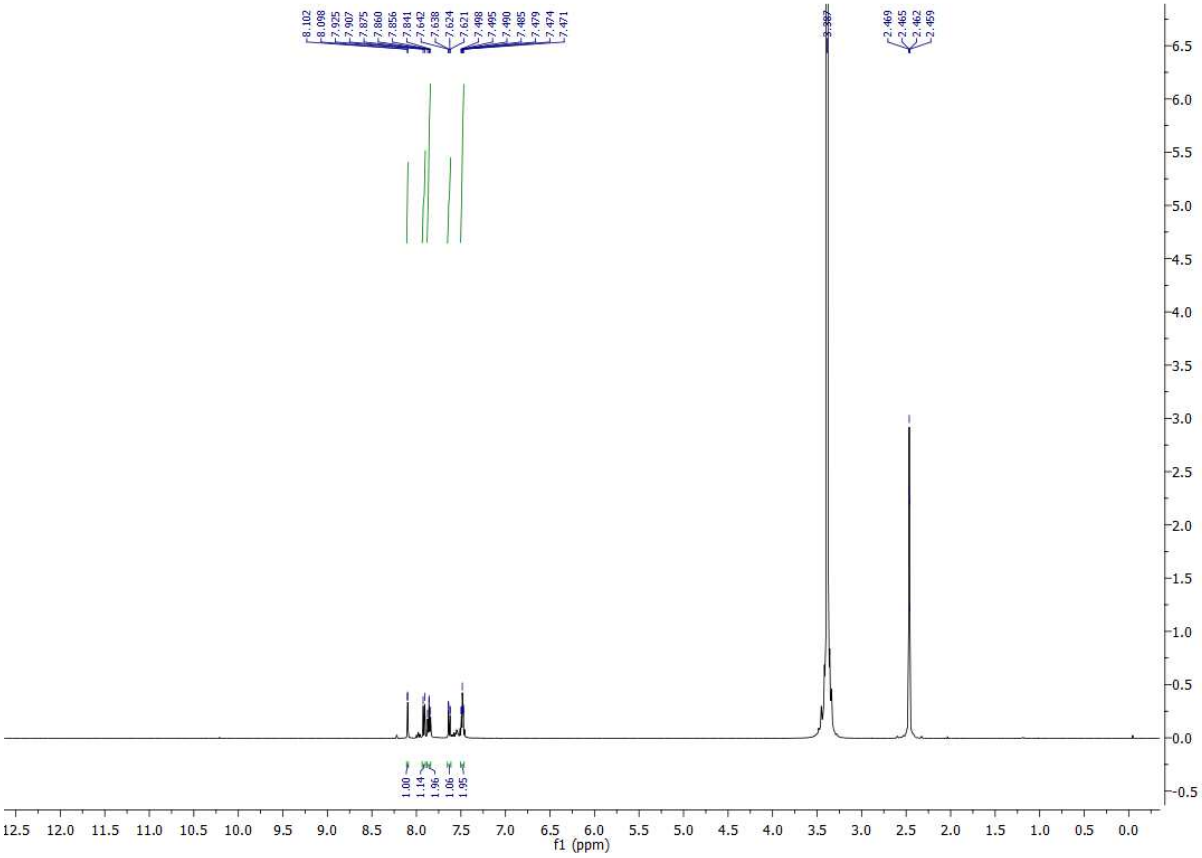


Figure S18. ^{1}H NMR spectrum of **4e**

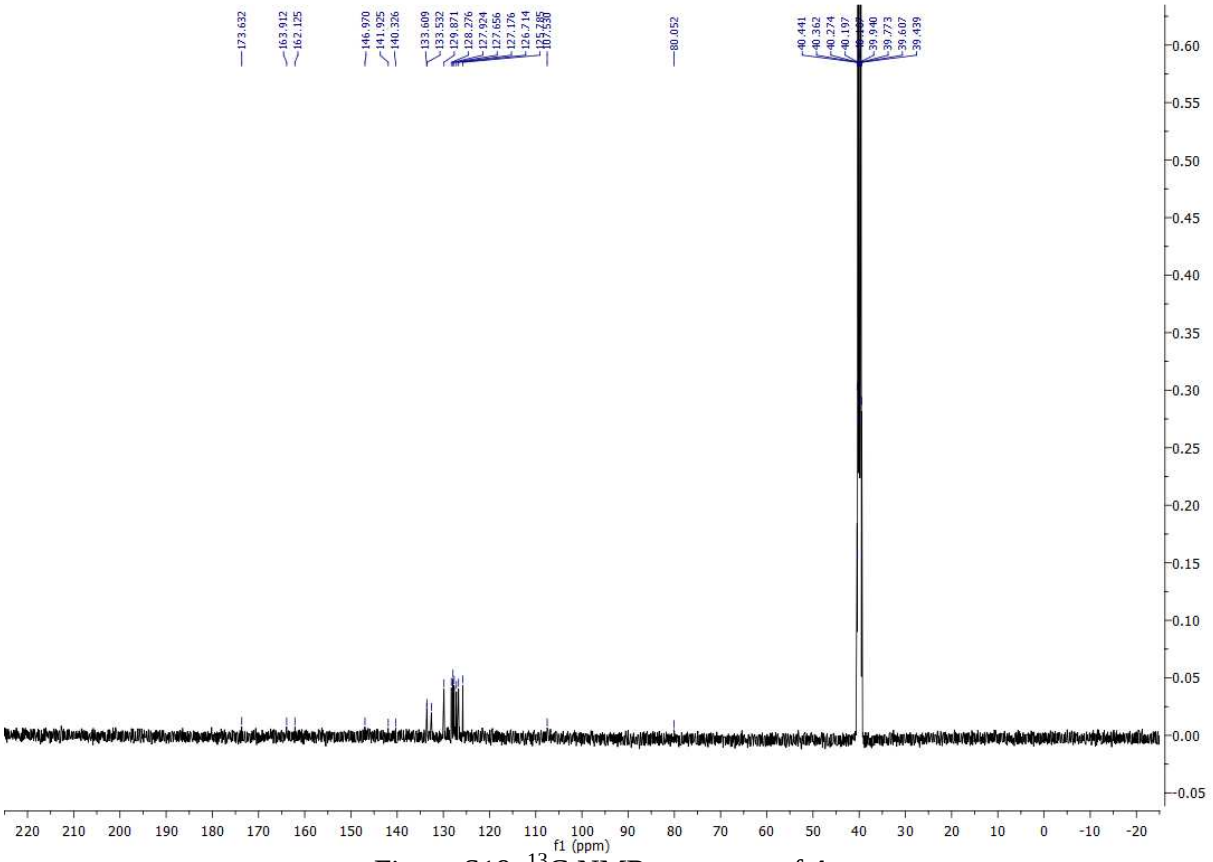


Figure S19. ^{13}C NMR spectrum of **4e**

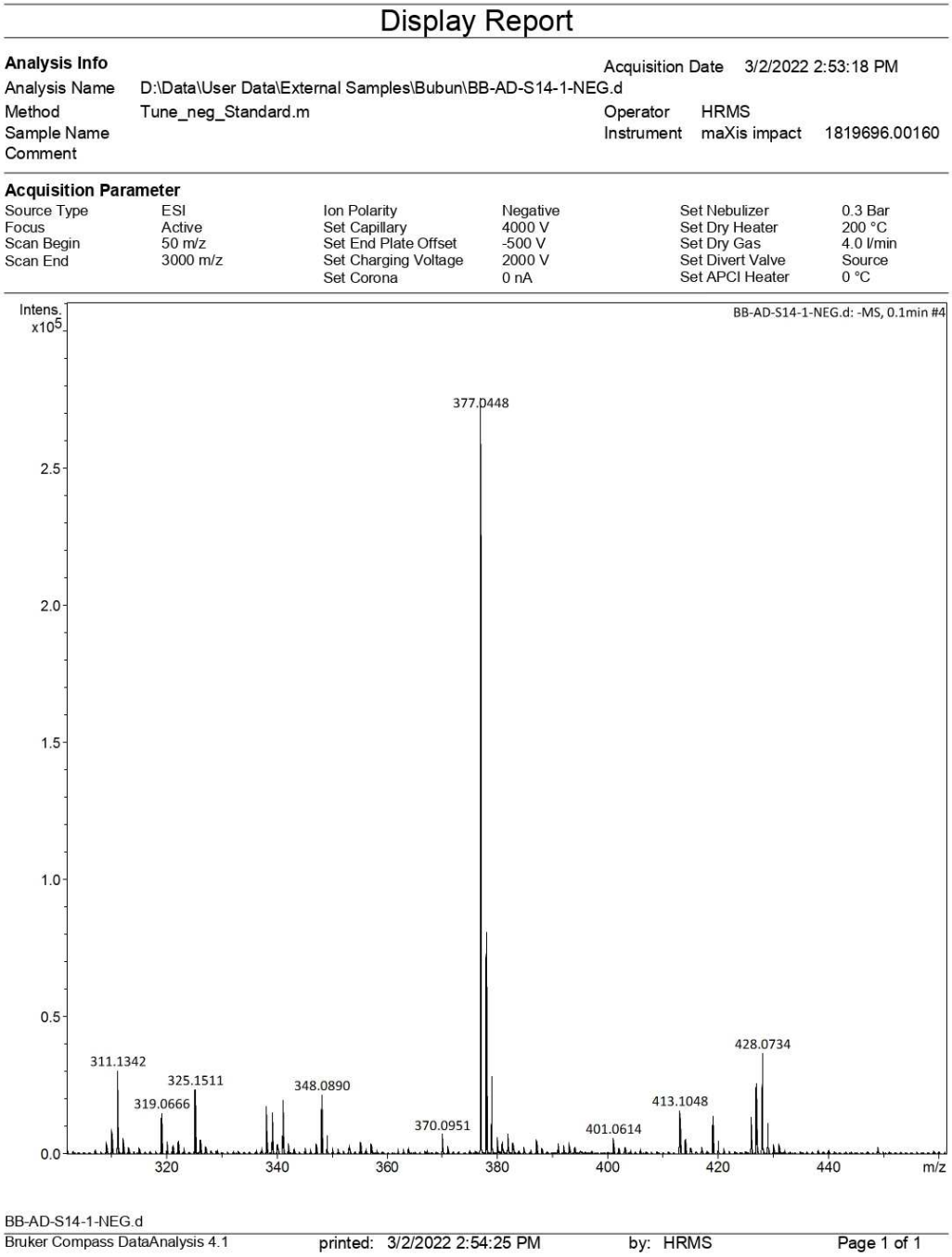
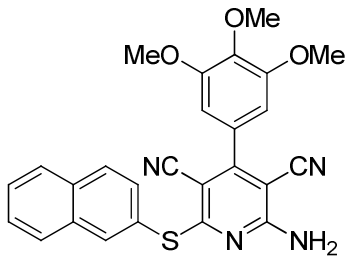


Figure S20. HRMS spectrum of **4e**



4f

2-Amino-6-(naphthalen-2-ylthio)-4-(3,4,5-trimethoxyphenyl)pyridine-3,5-dicarbonitrile (**4f**). White solid, yield 93%; mp 236-240 °C; FTIR (cm^{-1}): 3391, 3200, 3054, 2210, 1545, 1417, 1132, 779, 744, 702; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 8.21 (s, 1H aromatic H), 7.60-7.59 (t, *J* = 8 Hz, 3H, aromatic H), 7.91 (t, 1H, *J* = 7.5 Hz, aromatic H), 7.68 (s, 2H, -N*H*$_2$), 7.58 (d, 3H, *J* = 6 Hz, aromatic H), 7.52-7.45 (m, 1H, aromatic H) 3.80 (s, 6H, 2X -OC*H*$_3$), 3.74 (s, 3H, -OC*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 166.87, 160.28, 158.88, 153.37 (2C), 150.87, 139.58, 134.81, 133.82, 133.57, 131.98, 129.43, 128.52, 128.23, 127.97, 127.27, 125.43, 117.44, 115.69, 107.10, 106.11, 94.22, 87.76, 60.71, 56.81; HRMS (ESI-TOF) m/z: For $C_{26}H_{20}N_4O_3S$ Calcd. $[M]^+$ 468.1256; Found $[M\text{-}H]^-$ 467.4878.

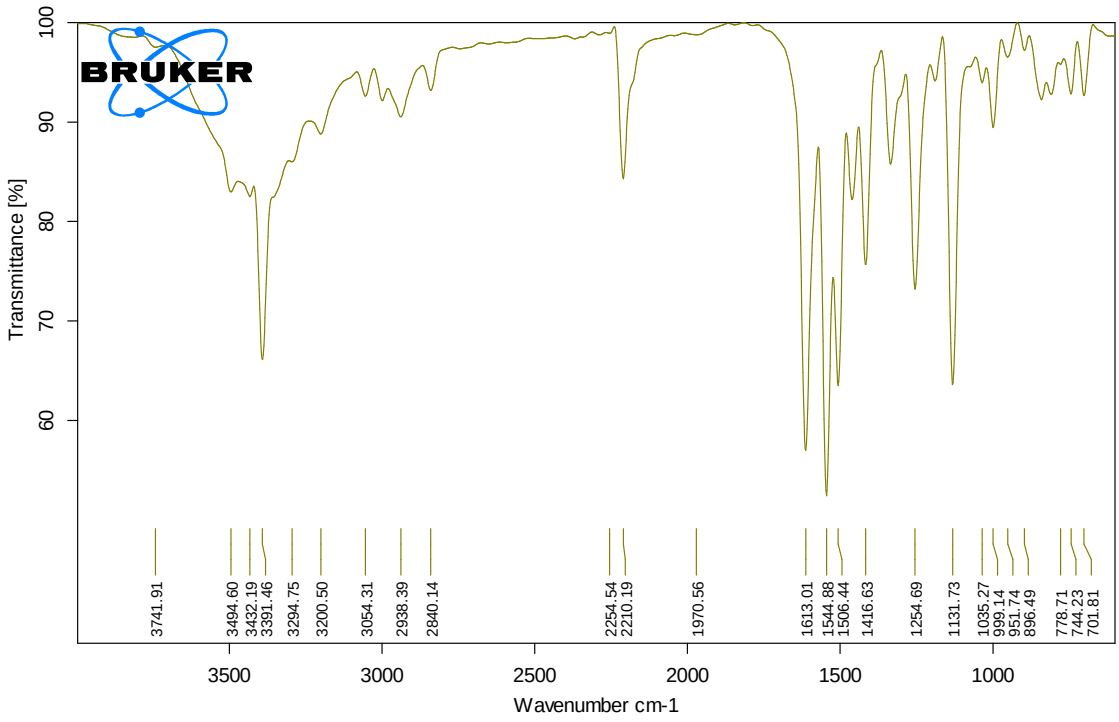


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Figure S21. FTIR spectrum of **4f**

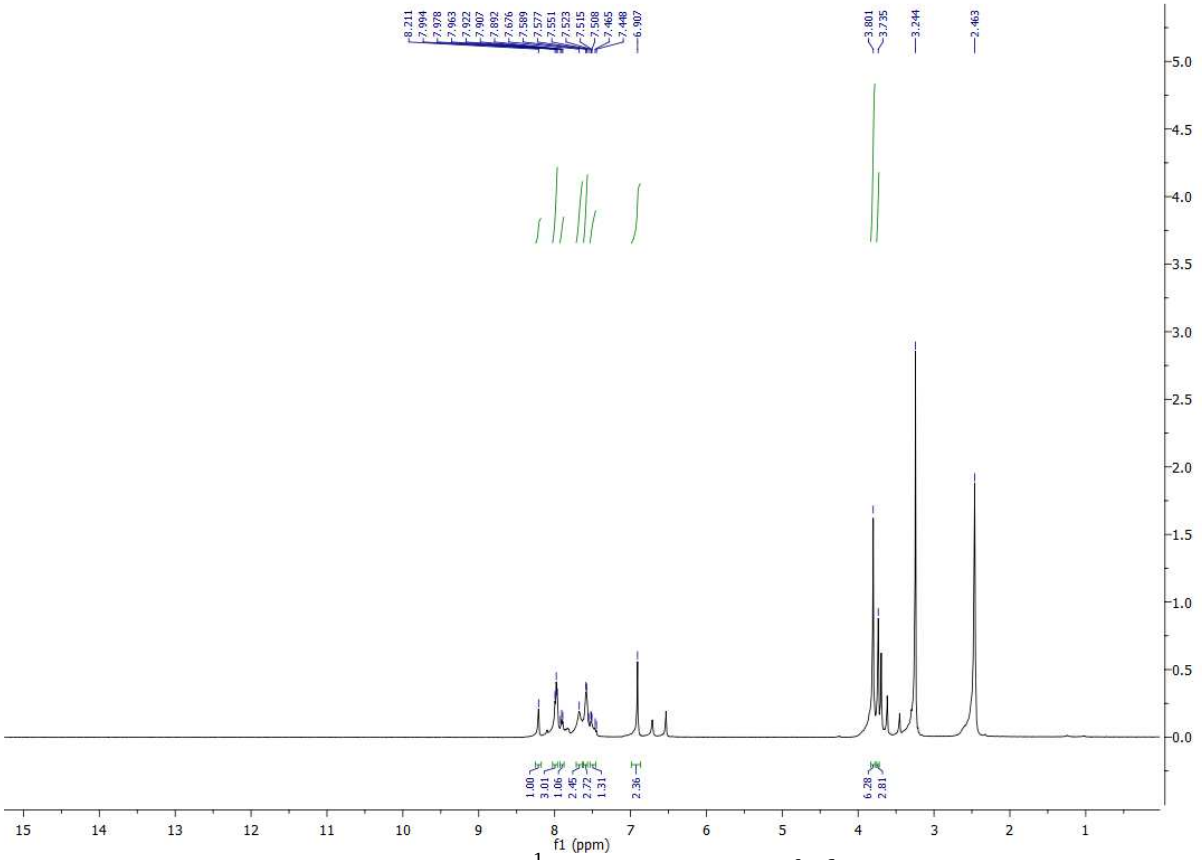


Figure S22. ^{1}H NMR spectrum of **4f**

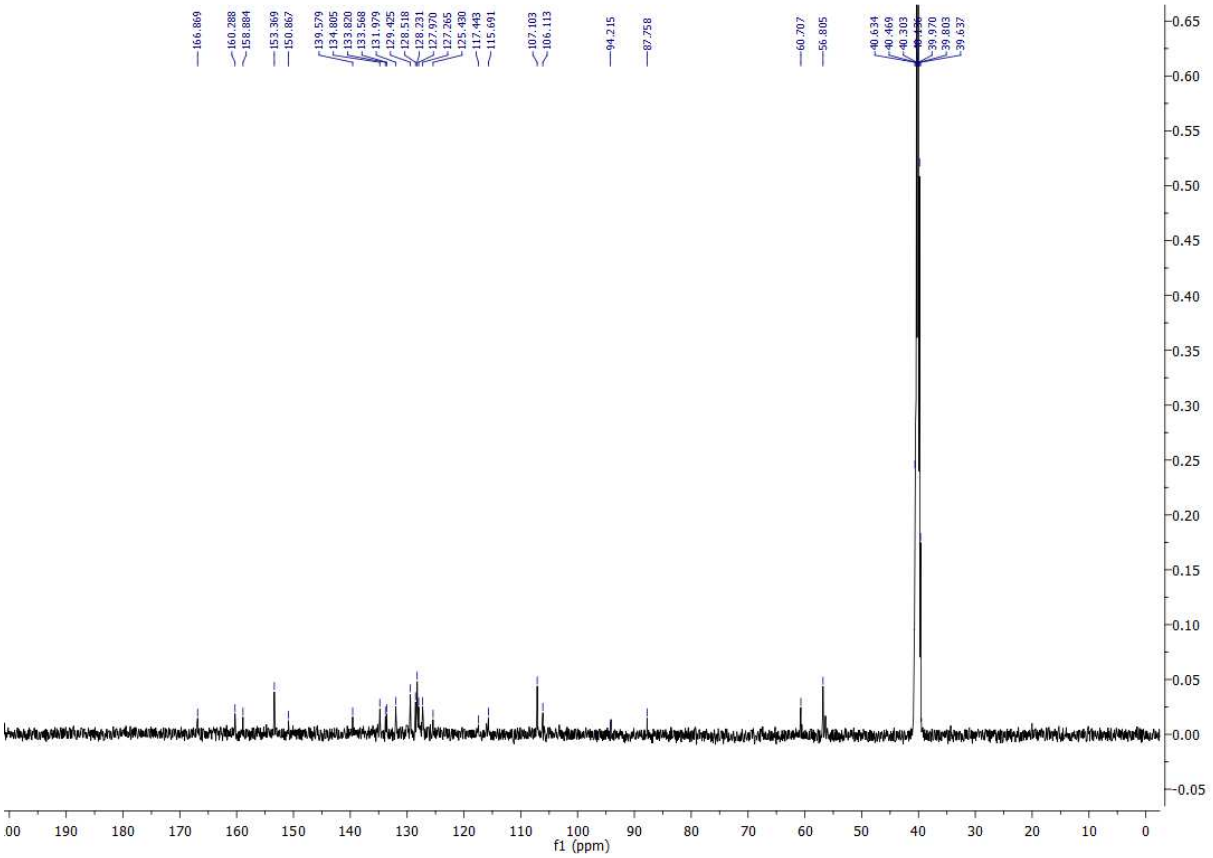


Figure S23. ^{13}C NMR spectrum of **4f**

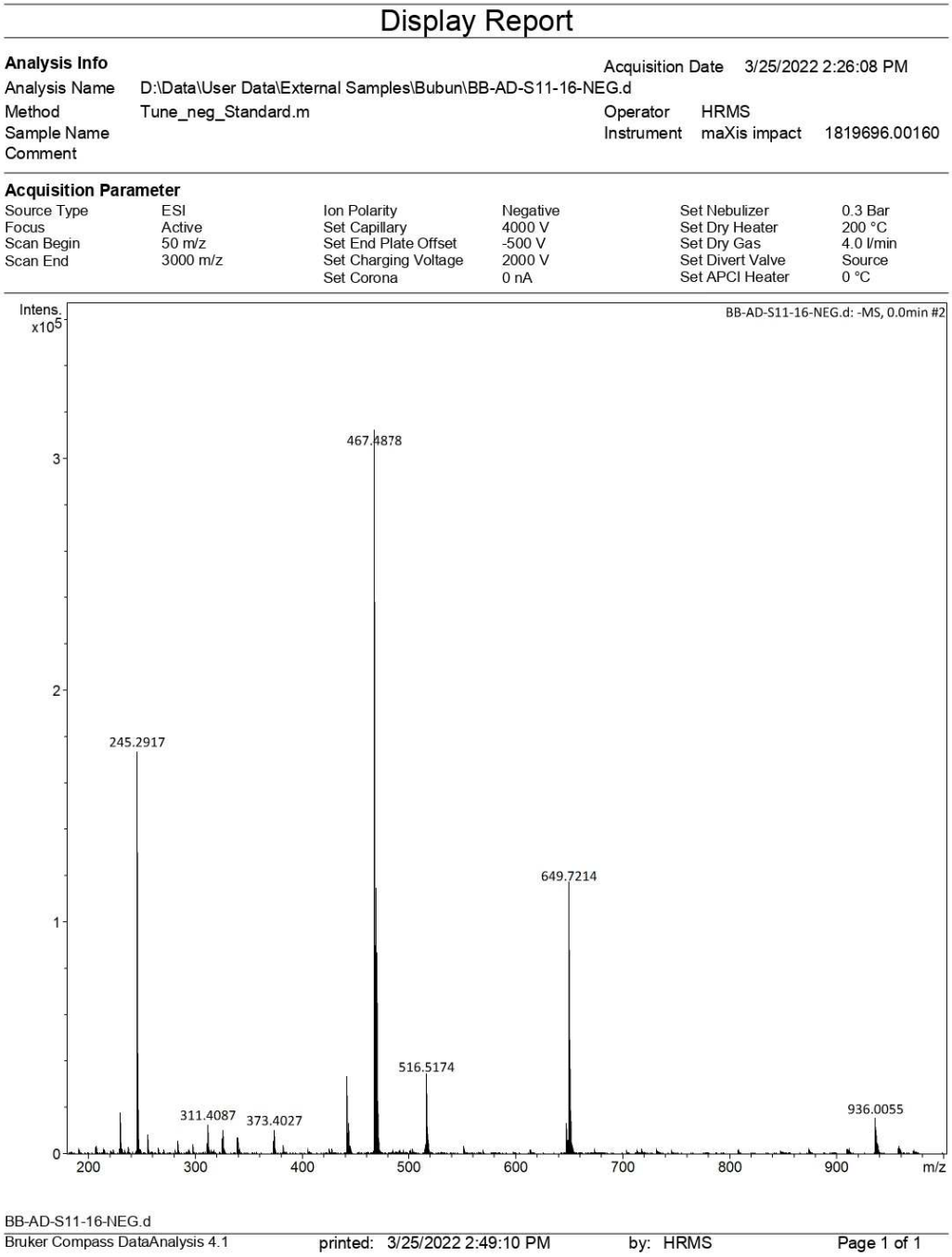
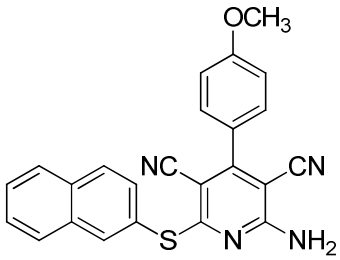


Figure S24. HRMS spectrum of **4f**



4g

2-Amino-4-(4-methoxyphenyl)-6-(naphthalen-2-ylthio)pyridine-3,5-dicarbonitrile (**4g**). White solid, yield 91%; mp 208-211 °C; FTIR (cm^{-1}): 3297, 2212, 1617, 1511, 1262, 1180, 813; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 8.22 (d, 1H aromatic H), 7.98 (t, *J* = 8.5 Hz, 3H, aromatic H), 7.71 (br s, 2H, -N*H*$_2$), 7.59-7.56 (m, 3H, aromatic H), 7.51 (d, *J* = 8.5 Hz, 2H, aromatic H), 7.10 (d, 2H, *J* = 8.5 Hz, aromatic H), 3.82 (s, 3H, -OC*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 166.95, 161.39, 160.38, 158.86, 134.85, 133.79, 133.54, 132.06, 130.85, 130.81, 129.41, 128.51, 128.24, 127.98, 127.26, 126.33, 125.39, 116.20, 115.84, 114.68, 114.62, 93.91, 87.55, 55.86; HRMS (ESI-TOF) m/z: For $C_{22}H_{16}N_4O_3S$ Calcd. $[M]^+$ 408.1045; Found $[M-H]^-$ 407.2195.

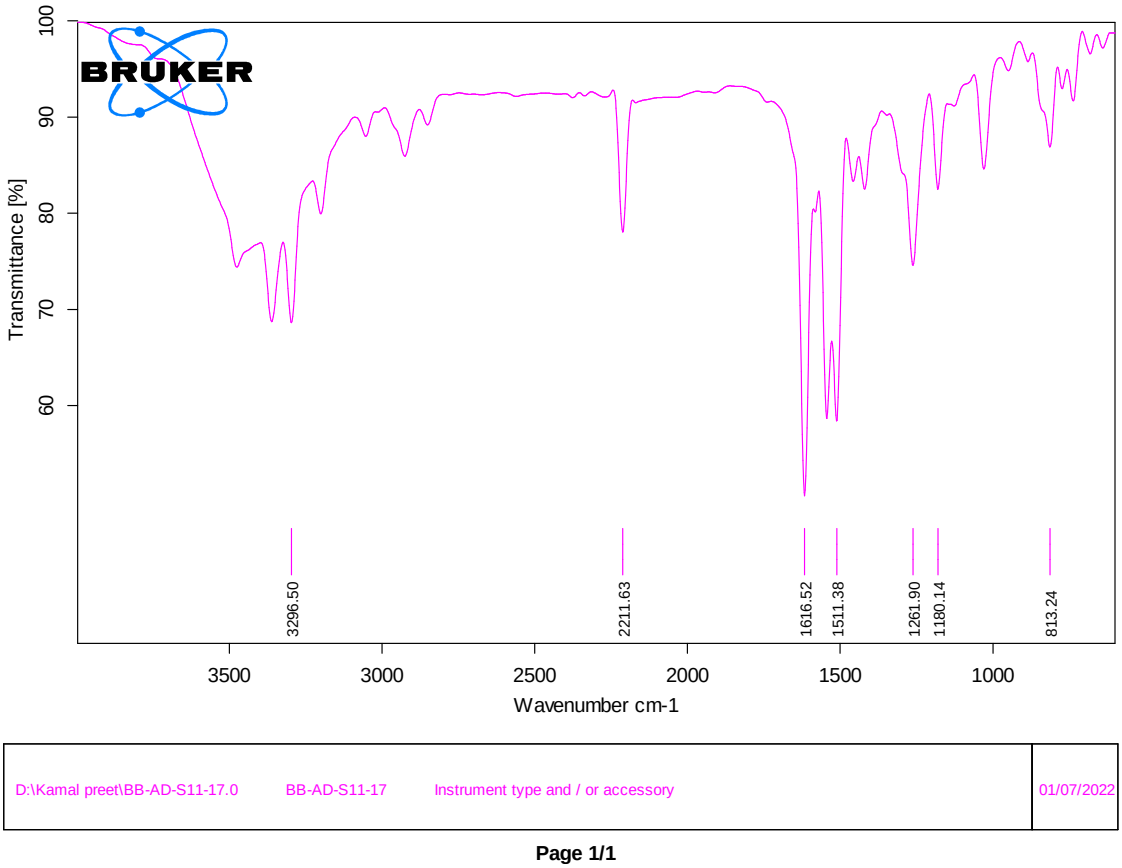


Figure S25. FTIR spectrum of **4g**

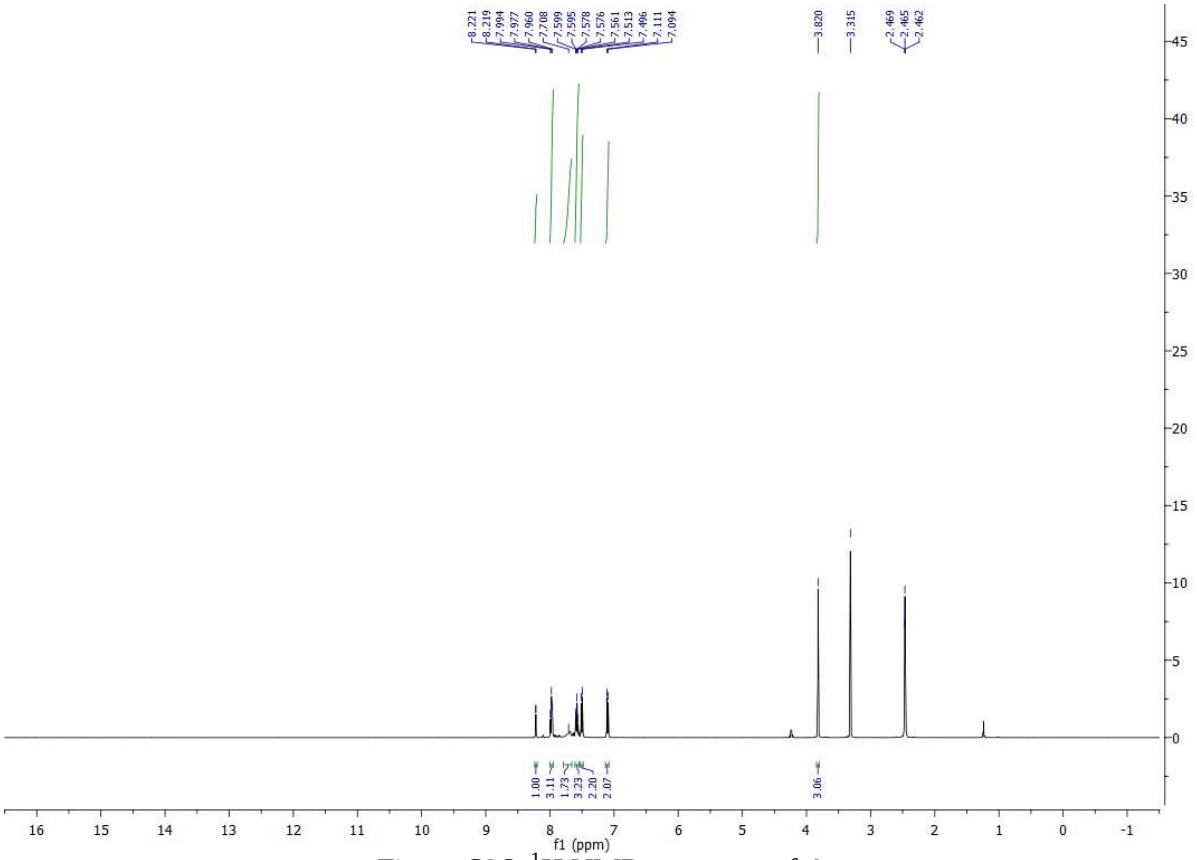


Figure S26. ^{1}H NMR spectrum of **4g**

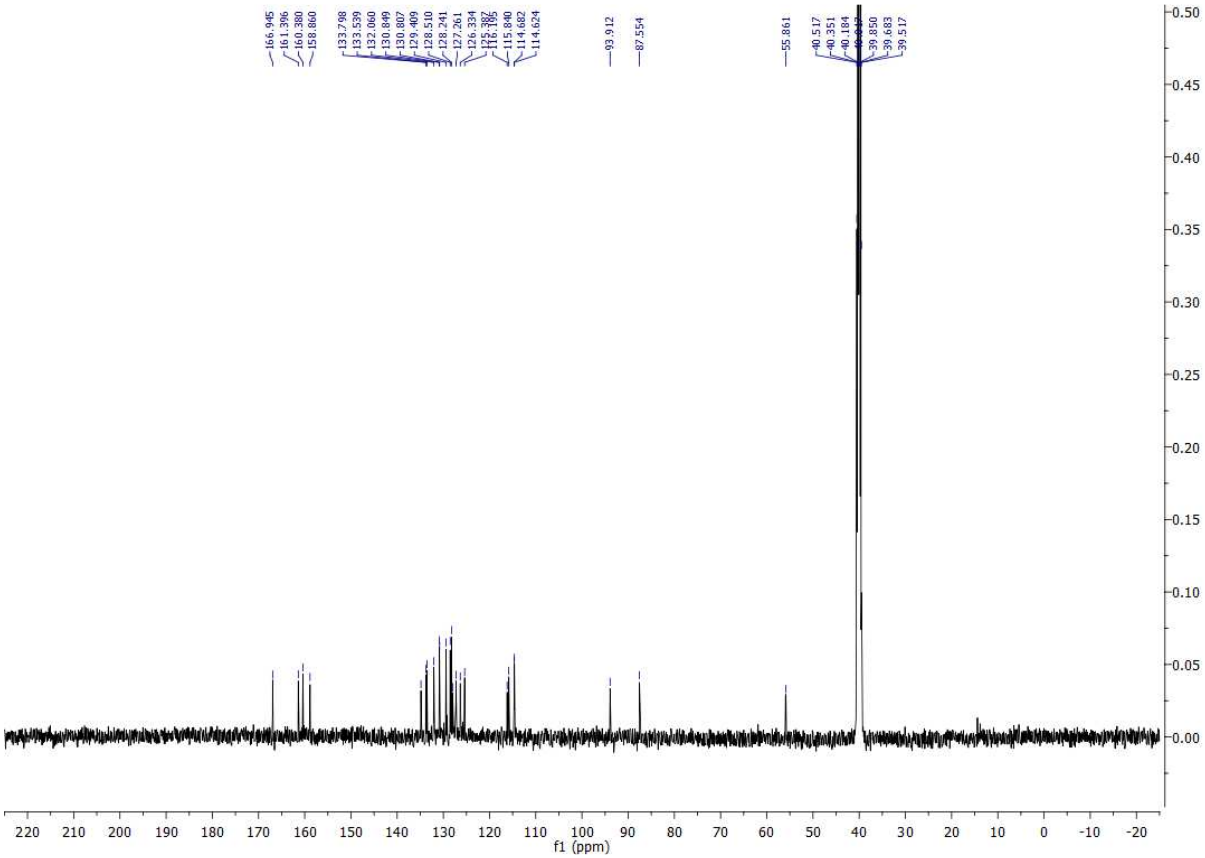


Figure S27. ^{13}C NMR spectrum of **4g**

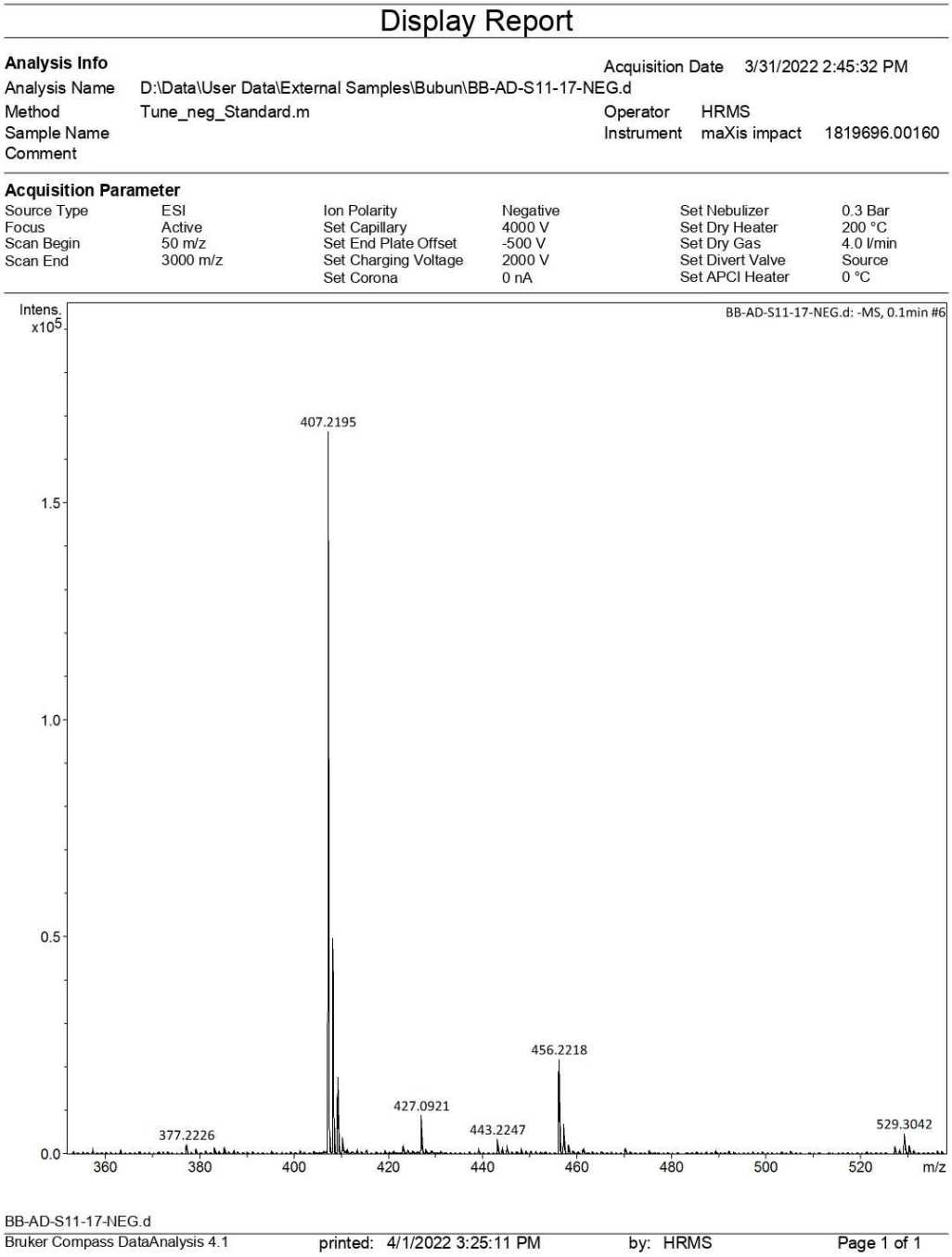
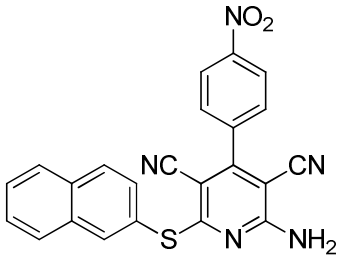


Figure S28. HRMS spectrum of **4g**



4h

2-amino-6-(naphthalen-2-ylthio)-4-(4-nitrophenyl)pyridine-3,5-dicarbonitrile (**4h**). Yellow solid, yield 95%; mp 154-157 °C; FTIR (cm^{-1}): 3331, 3233, 3051, 2218, 1637, 1552, 1344, 1023, 813, 740; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 8.09 (s, 2H, aromatic H), 7.91 (d, J = 8.5 Hz, 2H, aromatic H), 7.87-7.83 (m, 4H aromatic H), 7.64 (dd, J = 8.5, 1.5 Hz, 2H, aromatic H), 7.51 (s, 2H, -NH_2), 7.49-7.46 (m, 1H aromatic H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 175.12, 164.51, 155.35, 133.79 (2C), 133.62, 132.71, 129.80 (2C), 128.24 (2C), 127.92 (2C), 127.57 (2C), 127.13, 127.04 (2C), 125.96 (2C), 122.81, 117.20, 77.56; HRMS (ESI-TOF) m/z: For $C_{23}H_{13}N_4S$ Calcd. $[M]^+$ 423.0790; Found $[M\text{-}H]^-$ 422.2160.

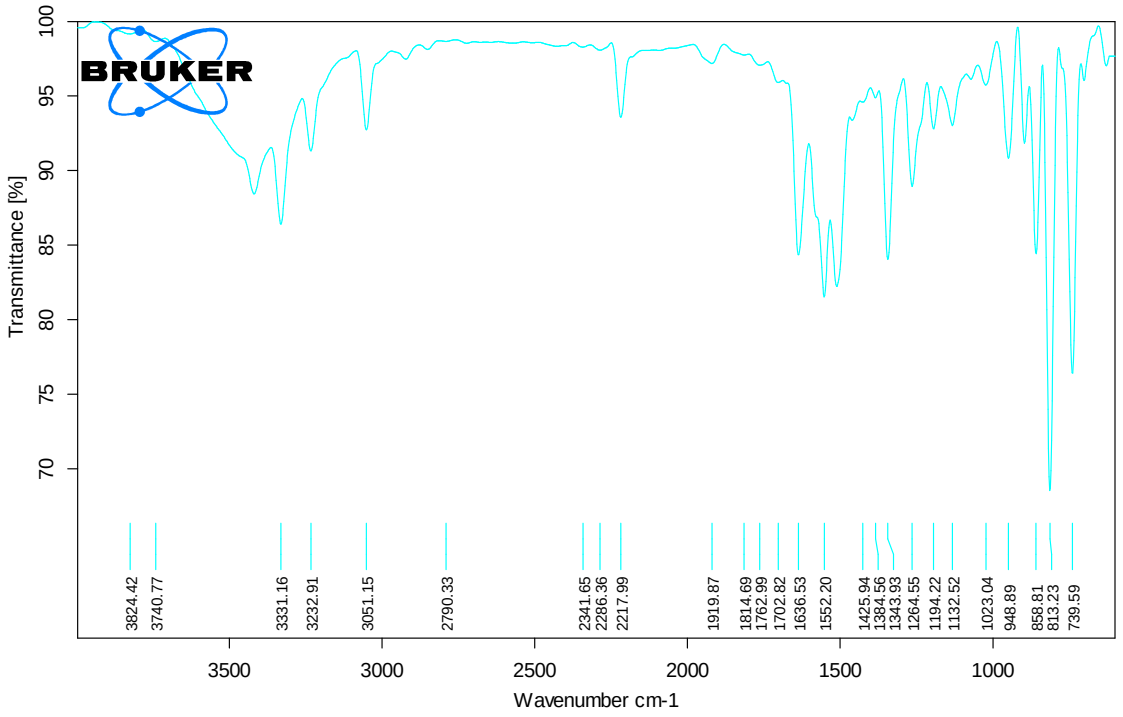


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Figure S29. FTIR spectrum of **4h**

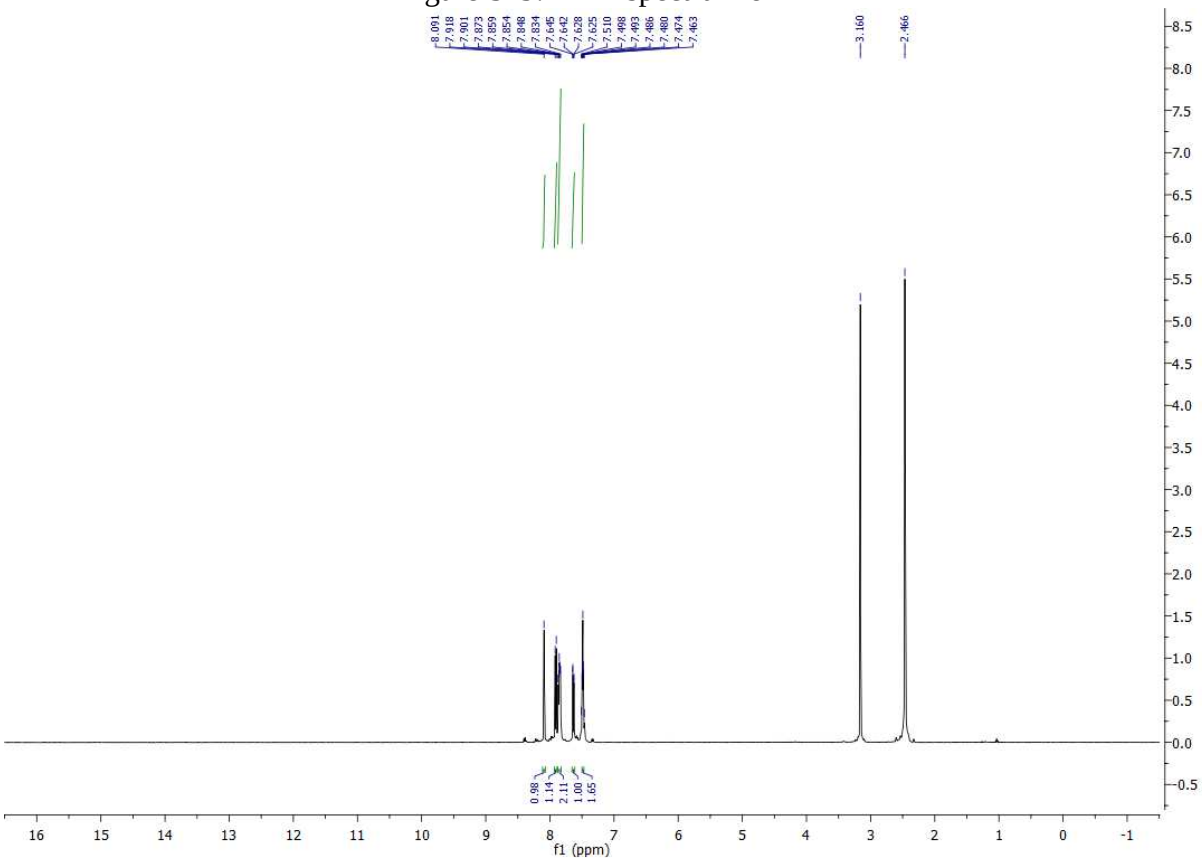


Figure S30. ^{1}H NMR spectrum of **4h**

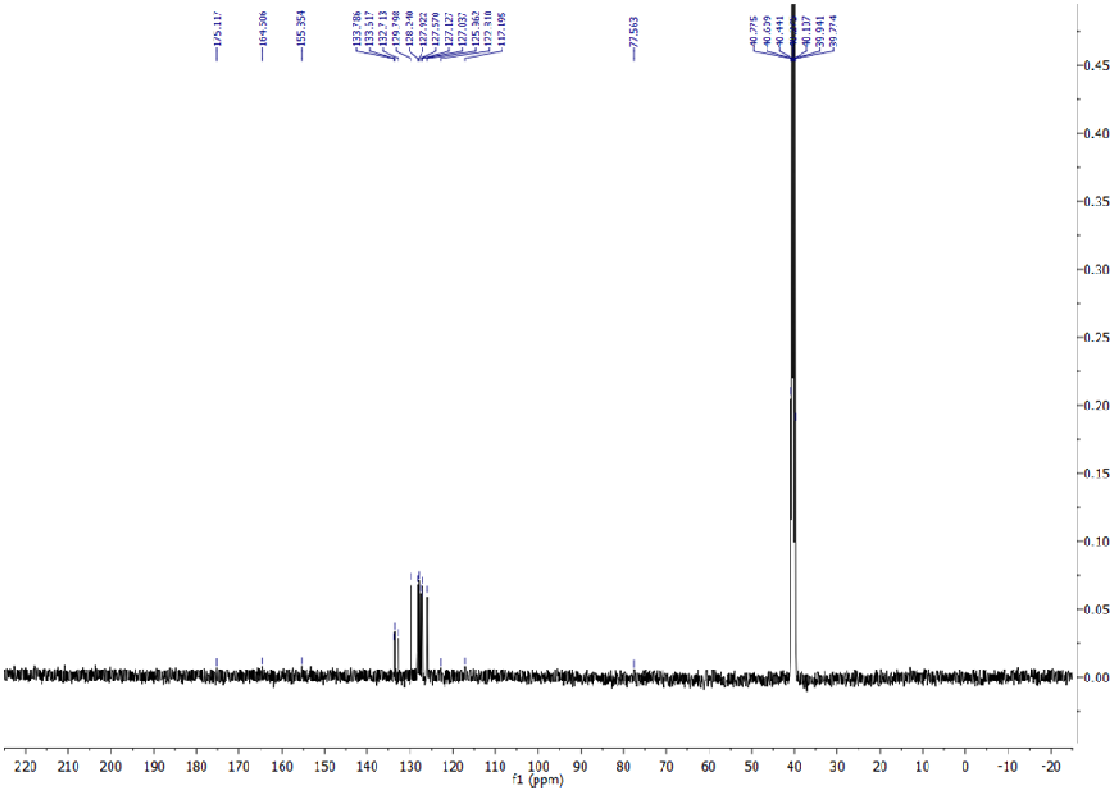


Figure S31. ^{13}C NMR spectrum of **4h**

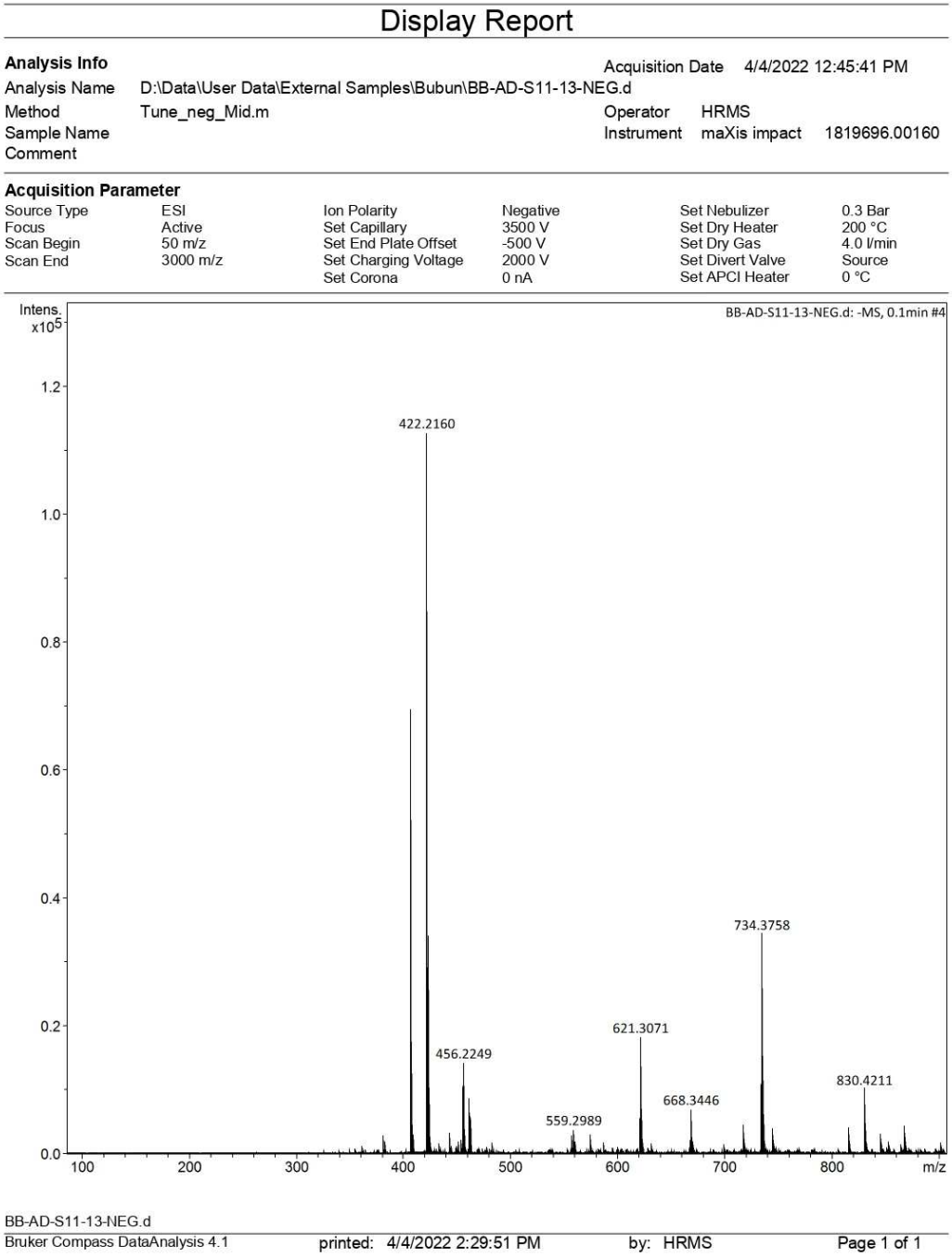
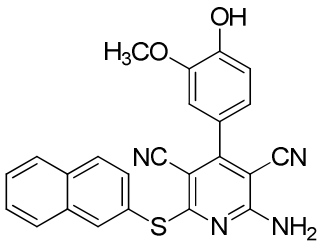


Figure S32. HRMS spectrum of **4h**



4i

2-amino-4-(4-hydroxy-3-methoxyphenyl)-6-(naphthalen-2-ylthio)pyridine-3,5-dicarbonitrile (**4i**). White solid, yield 94%; mp 205-209 °C; FTIR (cm^{-1}): 3362, 3056, 2786, 2215, 1617, 1512, 1277, 1023, 816, 752; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H/ppm 9.49 (s, 1H, O*H*), 8.20 (s, 1H, aromatic H), 7.98-7.95 (m, 3H aromatic H), 7.58 (m, 2H, aromatic H), 7.51 (s, 2H, -NH_2), 7.50-7.48 (m, 1H aromatic H), 7.15(d, J = 2 Hz, 1H, aromatic H), 6.99 (dd, J = 8, 2 Hz, 1H, aromatic H), 6.95 (d, 1H, aromatic H), 3.80 (s, 3H, -OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C/ppm 169.03, 166.83, 161.29, 160.46, 159.08, 149.48, 148.02, 134.69 (2C), 131.91 (2C), 129.34, 128.50 (2C), 128.20 (2C), 127.89, 127.20, 122.50, 116.19, 113.86, 94.34, 87.70, 56.53; HRMS (ESI-TOF) m/z: For $C_{24}H_{16}N_4O_2S$ Calcd. $[M]^+$ 424.0994; Found $[M\text{-}H]^-$ 423.4188.

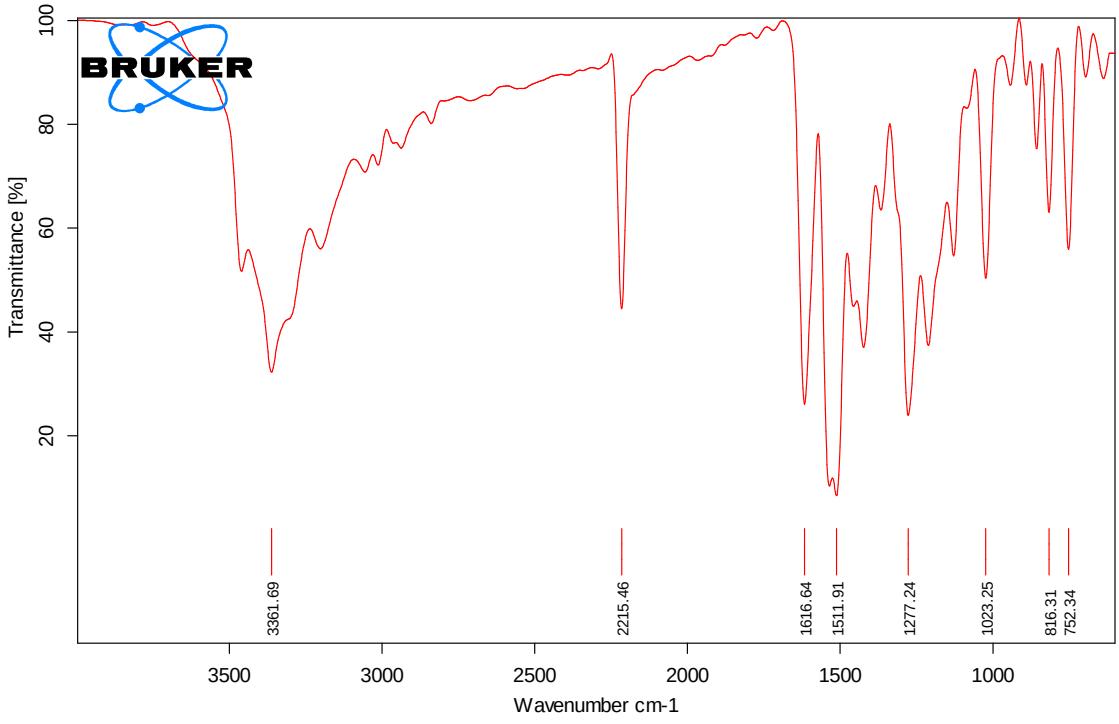


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Figure S33. FTIR spectrum of **4i**

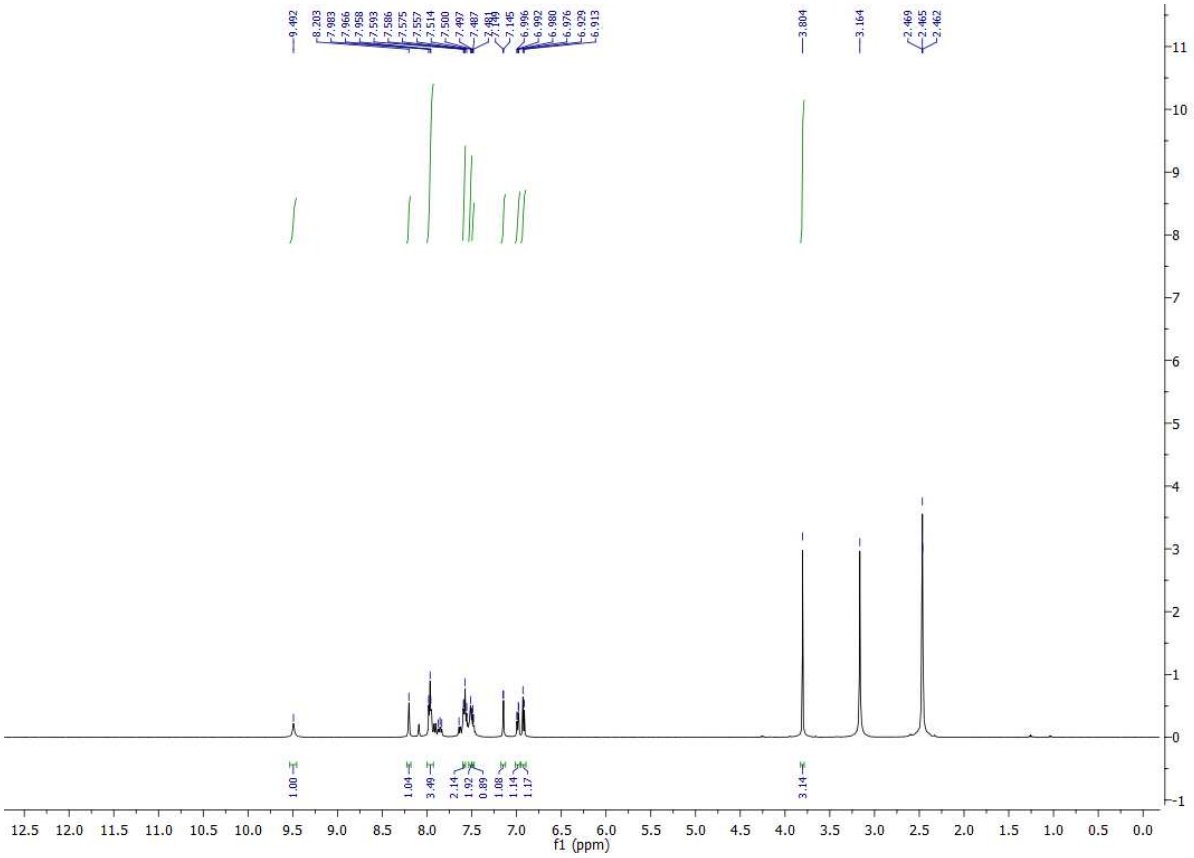

Figure S34. ^{1}H NMR spectrum of **4i**

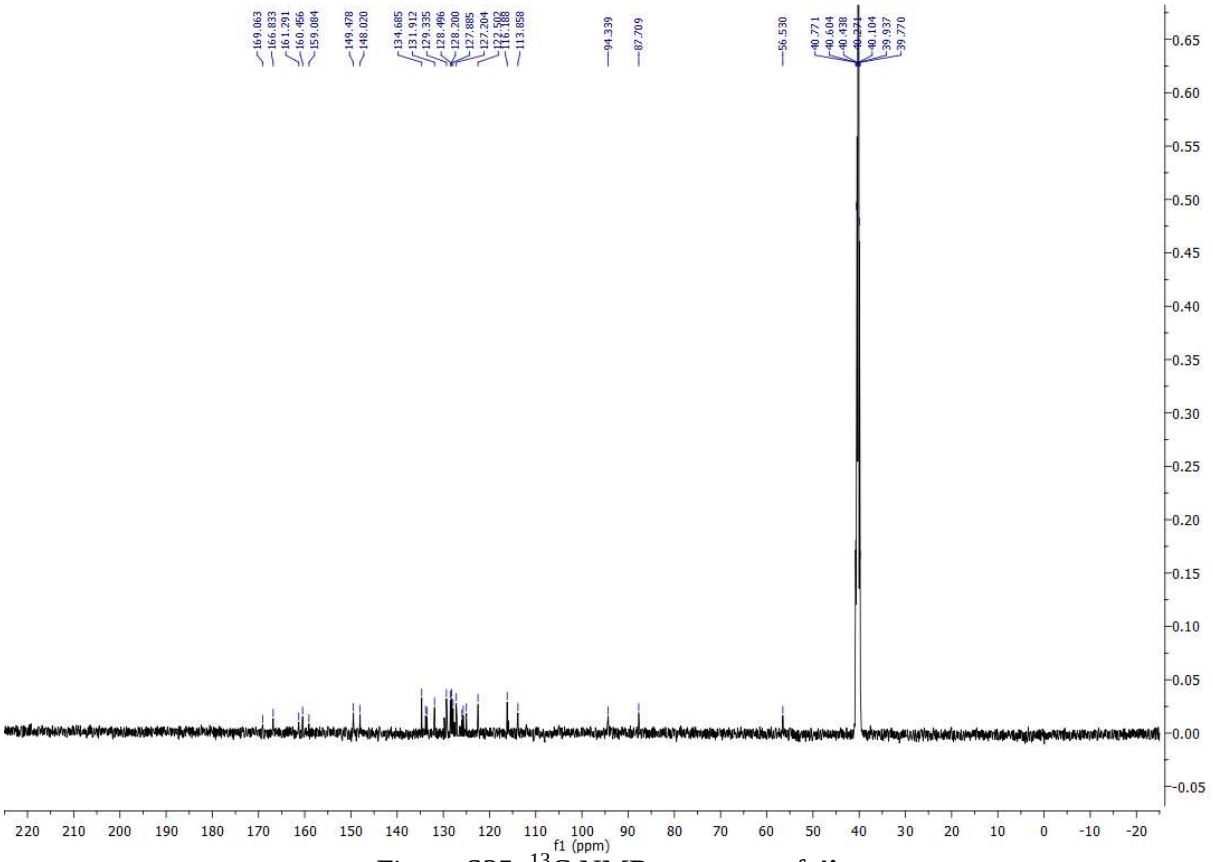

Figure S35. ^{13}C NMR spectrum of **4i**

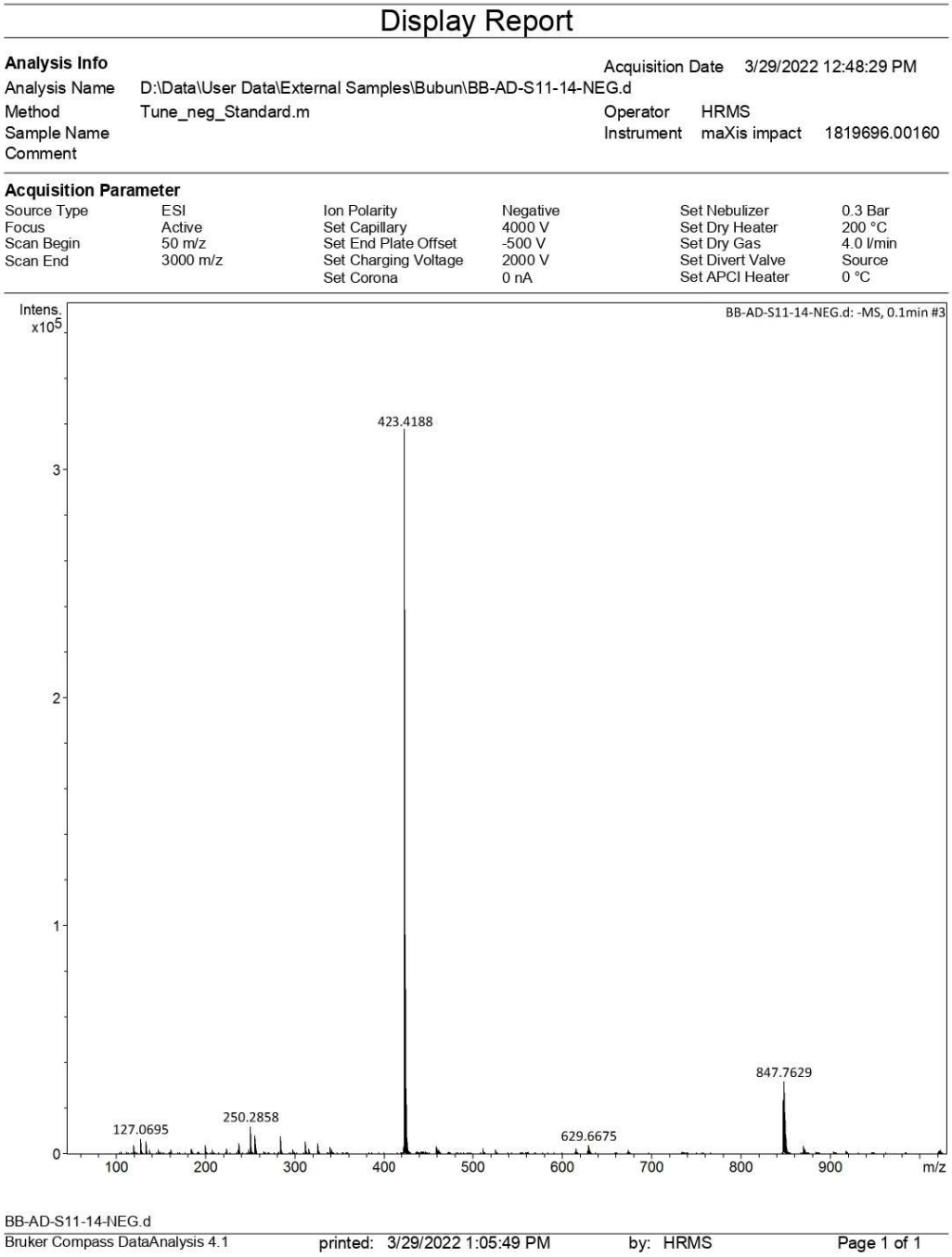

Figure S36. HRMS spectrum of **4i**

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[4] Ranu, B. C.; Jana, R.; Sowmiah, S. An Improved Procedure for the Three-Component Synthesis of Highly Substituted Pyridines Using Ionic Liquid. *J. Org. Chem.* **2007**, *72*, 3152-3154.