

*Supporting Information*

**Lipase-Catalyzed One-Pot Four-Component Reaction in Water:  
Green Construction of Substituted 2,3-Dihydrothiophenes**

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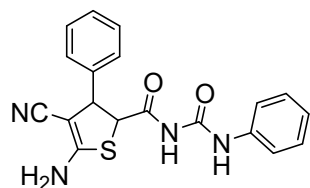
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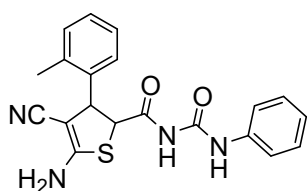
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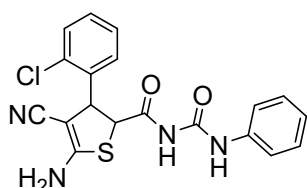
## Data of Products



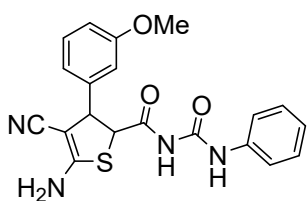
**5a: 5-amino-4-cyano-3-phenyl-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** White solid, 508.5 mg, 93% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.74 (s, 1H), 10.26 (s, 1H), 7.55 (d,  $J = 8.0$  Hz, 2H), 7.42 – 7.38 (m, 2H), 7.35 – 7.29 (m, 5H), 7.24 (s, 2H), 7.12 – 7.08 (m, 1H), 4.61 (d,  $J = 2.4$  Hz, 1H), 4.19 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.92, 162.29, 151.13, 142.06, 137.99, 129.50, 129.31, 128.09, 127.67, 124.38, 120.34, 118.78, 70.91, 55.86, 52.03. **MS** (ESI):  $m/z$  (%) = 363.40  $[\text{M-1}]^+$ .  $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$  (364.10): calcd. C 62.62, H 4.43, N 15.37%; found C 62.48, H 4.72, N 15.04%.



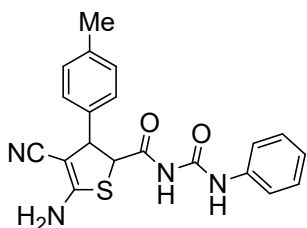
**5b: 5-amino-4-cyano-N-(phenylcarbamoyl)-3-(o-tolyl)-2,3-dihydrothiophene-2-carboxamide.** White solid, 499.5 mg, 88% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.78 (s, 1H), 10.23 (s, 1H), 7.56 (d,  $J = 8.0$  Hz, 2H), 7.36 – 7.32 (m, 2H), 7.27 – 7.20 (m, 6H), 7.13 – 7.08 (m, 1H), 4.85 (d,  $J = 2.1$  Hz, 1H), 4.06 (s, 1H), 2.29 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  173.05, 162.48, 151.05, 139.64, 137.90, 135.78, 131.34, 129.50, 127.97, 126.92, 124.46, 120.37, 118.73, 70.10, 54.90, 48.02, 19.56. **MS** (ESI):  $m/z$  (%) = 377.60  $[\text{M-1}]^+$ .  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$  (378.12): calcd. C, 63.47; H, 4.79; N, 14.80%. Found: C, 63.41; H, 4.89; N, 14.85%.



**5c: 5-amino-3-(2-chlorophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** Yellow solid, 514.5 mg, 86% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.87 (s, 1H), 10.23 (s, 1H), 7.58 – 7.55 (m, 3H), 7.48 – 7.39 (m, 4H), 7.38 – 7.32 (m, 3H), 7.13 – 7.09 (m, 1H), 4.98 (d,  $J = 1.6$  Hz, 1H), 4.06 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.72, 163.41, 151.06, 138.52, 137.90, 132.94, 130.49, 130.09, 129.48, 128.83, 128.34, 124.46, 120.42, 118.42, 68.19, 54.50, 48.56. **MS** (ESI):  $m/z$  (%) = 397.54  $[\text{M-H}]^+$ .  $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S}$  (398.06): calcd. C 57.21, H 3.79, N 14.05%; found C 57.48, H 4.07, N 13.65%.

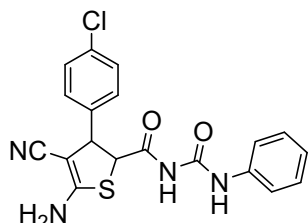


**5d: 5-amino-4-cyano-3-(3-methoxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** White solid, 532.5 mg, 90% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.75 (s, 1H), 10.27 (s, 1H), 7.55 (d,  $J = 7.9$  Hz, 2H), 7.34 – 7.29 (m, 3H), 7.24 (s, 2H), 7.12 – 7.08 (m, 1H), 6.92 – 6.86 (m, 3H), 4.58 (d,  $J = 2.4$  Hz, 1H), 4.18 (s, 1H), 3.76 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.93, 162.38, 160.07, 151.15, 143.62, 137.98, 130.39, 129.50, 124.39, 120.34, 119.69, 118.76, 113.69, 113.19, 70.73, 55.79, 55.60, 51.92. **MS** (ESI):  $m/z$  (%) = 393.40  $[\text{M-1}]^+$ .  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$  (394.11): calcd. C, 60.90; H, 4.60; N, 14.20%. Found: C, 60.81; H, 4.71; N, 14.26%.



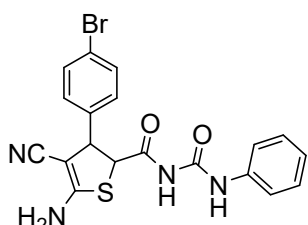
**5e: 5-amino-4-cyano-N-(phenylcarbamoyl)-3-(p-tolyl)-2,3-dihydrothiophene-2-carboxamide.** White solid, 511.0 mg, 90% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.78 (s, 1H), 10.28 (s, 1H), 7.55 (d,  $J = 7.9$  Hz,

2H), 7.35 – 7.32 (m, 2H), 7.25 – 7.18 (m, 6H), 7.12 – 7.08 (m, 1H), 4.57 (d,  $J = 2.6$  Hz, 1H), 4.15 (s, 1H), 2.30 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $D_6$ )  $\delta$  172.92, 162.09, 151.11, 138.96, 137.94, 137.31, 129.85, 129.51, 127.56, 120.34, 118.77, 71.03, 55.93, 51.78, 21.19. **MS** (ESI):  $m/z$  (%) = 377.57 [ $M-1$ ] $^+$ .  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$  (378.12): calcd. C, 63.47; H, 4.79; N, 14.80%. Found: C, 63.40; H, 4.90; N, 14.88%.



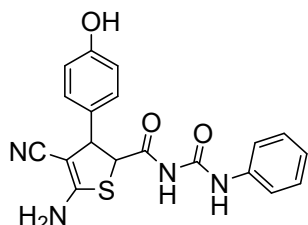
**5f: 5-amino-3-(4-chlorophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** Yellow solid, 556.5 mg, 93% yield.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.76 (s, 1H), 10.27 (s, 1H), 7.55 (d,  $J = 8.0$  Hz, 2H), 7.48 – 7.43 (m, 2H), 7.40 – 7.27 (m, 6H), 7.12 – 7.08 (m, 1H), 4.61 (d,  $J = 2.3$  Hz, 1H), 4.15 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $D_6$ )  $\delta$  172.77, 162.56, 151.14, 141.01, 137.97, 132.66, 129.61, 129.51, 129.26, 124.39, 120.32, 118.63, 70.53, 55.71, 51.31. **MS** (ESI):  $m/z$  (%) = 397.76 [ $M-1$ ] $^+$ .  $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S}$  (398.06): calcd. C 57.21, H 3.79, N 14.05%; found C 57.53, H 4.27, N 13.70%.



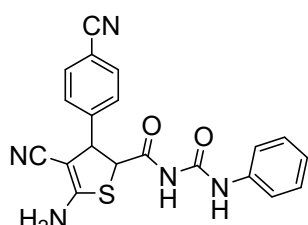
**5g: 5-amino-3-(4-bromophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** Yellow solid, 630.0 mg, 95% yield.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.78 (s, 1H), 10.27 (s, 1H), 7.61 – 7.59 (m, 2H), 7.55 (d,  $J = 8.0$  Hz, 2H), 7.36 – 7.29 (m, 6H), 7.12 – 7.08 (m, 1H), 4.59 (d,  $J = 2.2$  Hz, 1H), 4.15 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $D_6$ )  $\delta$  172.75, 162.58, 151.13, 141.42, 137.96, 132.19, 129.98, 129.51, 124.40, 121.18, 120.32, 118.62, 70.46, 55.64, 51.37. **MS** (ESI):  $m/z$  (%) = 441.61 [ $M-1$ ] $^+$ .  $\text{C}_{19}\text{H}_{15}\text{BrN}_4\text{O}_2\text{S}$  (443.01): calcd. C 51.48, H 3.41, N 12.64%; found C 51.33, H 3.79, N 12.42%.



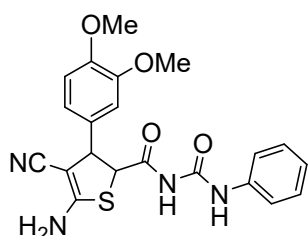
**5h: 5-amino-4-cyano-3-(4-hydroxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** White solid, 542.0 mg, 95% yield.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.75 (s, 1H), 10.27 (s, 1H), 9.42 (s, 1H), 7.55 (d,  $J = 7.9$  Hz, 2H), 7.36 – 7.32 (m, 2H), 7.18 (s, 2H), 7.14 – 7.08 (m, 3H), 6.80 – 6.73 (m, 2H), 4.51 (d,  $J = 2.7$  Hz, 1H), 4.12 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $D_6$ )  $\delta$  173.02, 161.80, 157.35, 151.11, 137.95, 132.10, 129.50, 128.73, 124.40, 120.34, 118.87, 115.98, 71.40, 56.16, 51.61. **MS** (ESI):  $m/z$  (%) = 379.44 [ $M-1$ ] $^+$ .  $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$  (380.09): calcd. C 59.99, H 4.24, N 14.73%; found C 60.13, H 4.20, N 14.68%.



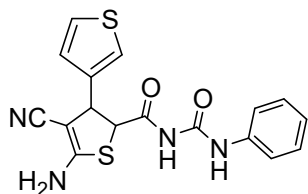
**5i: 5-amino-4-cyano-3-(4-cyanophenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** Yellow solid, 496.5 mg, 85% yield.

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.77 (s, 1H), 10.26 (s, 1H), 7.91 – 7.89 (m, 2H), 7.57 (dd,  $J = 7.7, 5.8$  Hz, 4H), 7.39 – 7.33 (m, 4H), 7.14 – 7.10 (m, 1H), 4.71 (d,  $J = 2.0$  Hz, 1H), 4.22 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $D_6$ )  $\delta$  172.61, 163.04, 151.15, 147.72, 137.96, 133.30, 129.51, 128.81, 124.40, 120.32, 119.29, 118.51, 110.90, 69.94, 55.34, 51.64. **MS** (ESI):  $m/z$  (%) = 388.64 [ $M-1$ ] $^+$ .  $\text{C}_{20}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$  (389.09): calcd. C 61.68, H 3.88, N 17.98%; found C 61.45, H 3.94, N 18.12%.



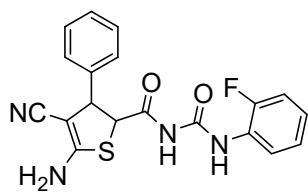
**5j: 5-amino-4-cyano-3-(3,4-dimethoxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** White solid, 541.0 mg, 85%

yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.77 (s, 1H), 10.30 (s, 1H), 7.56 (d,  $J = 7.9$  Hz, 2H), 7.36 – 7.32 (m, 2H), 7.23 (s, 2H), 7.13 – 7.08 (m, 1H), 6.98 – 6.95 (m, 2H), 6.82 (dd,  $J = 8.3, 2.1$  Hz, 1H), 4.57 (d,  $J = 2.6$  Hz, 1H), 4.16 (s, 1H), 3.76 (d,  $J = 3.8$  Hz, 6H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  173.04, 162.13, 151.15, 149.45, 148.80, 137.97, 134.12, 129.51, 124.40, 120.35, 119.38, 118.85, 112.41, 111.78, 70.96, 56.09, 51.78. **MS** (ESI):  $m/z$  (%) = 423.42 [ $\text{M-1}$ ] $^+$ .  $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$  (424.12): calcd. C 59.42, H 4.75, N 13.20%; Found: C 59.22, H 4.77, N 13.03%.



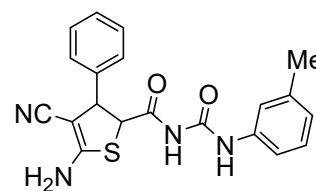
**5k: 5-amino-4-cyano-N-(phenylcarbamoyl)-2,3-dihydro-[3,3'-bithiophene]-2-carboxamide.** White solid, 500.0 mg, 90% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.80 (s, 1H), 10.24 (s, 1H), 7.55 (d,  $J = 8.0$  Hz, 2H), 7.44 (dd,  $J = 5.1, 1.3$  Hz, 1H), 7.37 – 7.30 (m, 4H), 7.12 – 7.07 (m, 2H), 7.02 (dd,  $J = 5.1, 3.5$  Hz, 1H), 4.91 (d,  $J = 2.0$  Hz, 1H), 4.25 (s, 1H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.60, 162.10, 151.12, 146.31, 137.97, 129.50, 127.64, 125.70, 125.53, 124.40, 120.35, 118.57, 71.84, 56.21, 47.47. **MS** (ESI):  $m/z$  (%) = 369.24 [ $\text{M-1}$ ] $^+$ .  $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2\text{S}_2$  (370.06): calcd. C 55.12, H 3.81, N 15.12%; Found: C 55.28, H 3.77, N 15.03%.

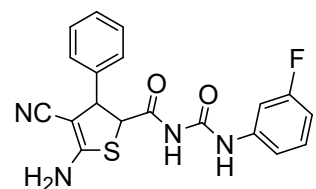


**5l: 5-amino-4-cyano-N-((2-fluorophenyl)carbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 493.5 mg, 86% yield.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.97 (s, 1H), 10.56 (s, 1H), 8.11 (td,  $J = 8.1, 1.9$  Hz, 1H), 7.42 – 7.29 (m, 6H), 7.26 (s, 2H), 7.22 – 7.12 (m, 2H), 4.62 (d,  $J = 2.4$  Hz, 1H), 4.19 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  173.36, 162.20, 154.18, 151.77, 151.04, 142.02, 129.30, 128.10, 127.66, 126.17 (126.06), 125.32 (125.39), 125.20 (125.12), 122.13, 118.75, 115.88, 115.69, 70.90, 55.81, 51.96. **MS** (ESI):  $m/z$  (%) = 381.85 [ $\text{M-1}$ ] $^+$ .  $\text{C}_{19}\text{H}_{15}\text{FN}_4\text{O}_2\text{S}$  (382.09): calcd. C 59.67, H 3.95, N 14.65%; Found: C 59.62, H 3.77, N 14.58%.

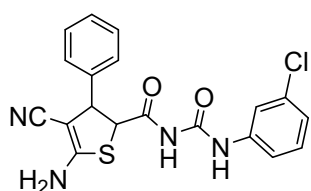


**5m: 5-amino-4-cyano-3-phenyl-N-(m-tolylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** Off-white solid, 499.5 mg, 88% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.77 (s, 1H), 10.26 (s, 1H), 7.42 – 7.26 (m, 7H), 7.26 – 7.20 (m, 3H), 6.92 (d,  $J = 7.5$  Hz, 1H), 4.61 (d,  $J = 2.5$  Hz, 1H), 4.19 (s, 1H), 2.29 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.94, 162.27, 151.06, 142.04, 138.86, 137.90, 129.31, 128.09, 127.66, 125.08, 120.76, 118.76, 117.39, 70.93, 55.86, 52.04, 21.61. **MS** (ESI):  $m/z$  (%) = 377.50 [ $\text{M-1}$ ] $^+$ .  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$  (378.12): calcd. C 63.47, H 4.79, N 14.80%; found C 63.42, H 5.04, N 14.53%.

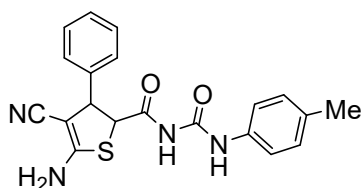


**5n: 5-amino-4-cyano-N-((3-fluorophenyl)carbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 487.5 mg, 85% yield.

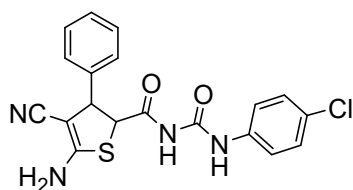
$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.83 (s, 1H), 10.38 (s, 1H), 7.57 (d,  $J = 11.7$  Hz, 1H), 7.42 – 7.29 (m, 7H), 7.26 (s, 2H), 6.96 – 6.91 (m, 1H), 4.61 (d,  $J = 2.3$  Hz, 1H), 4.19 (s, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.91, 163.94, 162.27, 161.53, 151.18, 142.01, 139.79 (d,  $J = 11.0$  Hz), 131.09 (d,  $J = 9.2$  Hz), 129.31, 128.10, 127.65, 118.75, 116.21, 110.84 (d,  $J = 21.1$  Hz), 107.27 (d,  $J = 26.5$  Hz), 70.89, 55.84, 51.98. **MS** (ESI):  $m/z$  (%) = 381.87 [ $\text{M-1}$ ] $^+$ .  $\text{C}_{19}\text{H}_{15}\text{FN}_4\text{O}_2\text{S}$  (382.09): calcd. C 59.67, H 3.95, N 14.65%; Found: C 59.60, H 3.80, N 14.56%.



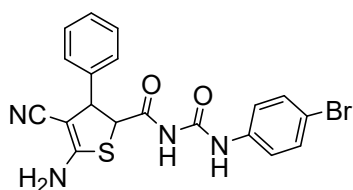
**5o: 5-amino-N-((3-chlorophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 520.5 mg, 87% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.83 (s, 1H), 10.35 (s, 1H), 7.80 (s, 1H), 7.46 – 7.41 (m, 1H), 7.39 (d,  $J = 7.2$  Hz, 2H), 7.36 – 7.29 (m, 4H), 7.25 (s, 2H), 7.16 (dd,  $J = 8.0, 2.1$  Hz, 1H), 4.60 (d,  $J = 2.4$  Hz, 1H), 4.19 (s, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.87, 162.27, 151.22, 142.00, 139.53, 133.76, 131.10, 129.31, 128.10, 127.65, 124.10, 119.89, 118.95, 118.76, 70.87, 55.84, 51.96. **MS** (ESI):  $m/z$  (%) = 397.48  $[\text{M}-1]^+$ .  $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S}$  (398.06): calcd. C, 57.21; H, 3.79; N, 14.05%. Found: C, 57.14; H, 4.02; N, 13.68%.



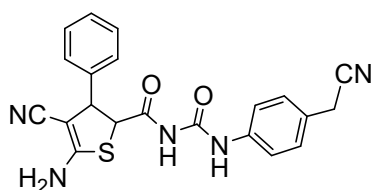
**5p: 5-amino-4-cyano-3-phenyl-N-(p-tolylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.** Off-white solid, 494.0 mg, 87% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.72 (s, 1H), 10.19 (s, 1H), 7.44 – 7.36 (m, 4H), 7.35 – 7.29 (m, 3H), 7.24 (s, 2H), 7.14 (d,  $J = 8.4$  Hz, 2H), 4.60 (d,  $J = 2.5$  Hz, 1H), 4.18 (s, 1H), 2.26 (s, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.86, 162.29, 151.07, 142.04, 135.40, 133.43, 129.89, 129.31, 128.09, 127.65, 120.33, 118.77, 70.87, 55.83, 52.02, 20.93. **MS** (ESI):  $m/z$  (%) = 378.00  $[\text{M}-1]^+$ .  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$  (378.12): calcd. C 63.47, H 4.79, N 14.80%; found C 63.45, H 5.08, N 14.51%.



**5q: 5-amino-N-((4-chlorophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 562.5 mg, 94% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.81 (s, 1H), 10.31 (s, 1H), 7.61 (d,  $J = 8.6$  Hz, 2H), 7.42 – 7.38 (m, 4H), 7.35 – 7.29 (m, 3H), 7.26 (s, 2H), 4.60 (d,  $J = 2.4$  Hz, 1H), 4.18 (s, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.84, 162.28, 151.16, 142.01, 137.00, 129.32, 128.10, 127.65, 122.04, 118.76, 70.87, 55.83, 51.99. **MS** (ESI):  $m/z$  (%) = 397.57  $[\text{M}-1]^+$ ,  $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S}$  (398.06): calcd. C 57.21, H 3.79, N 14.05%; found C 57.16, H 4.05, N 13.72%.

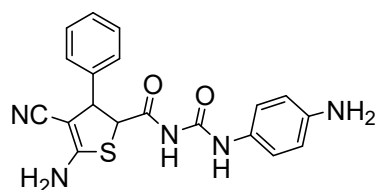


**5r: 5-amino-N-((4-bromophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 631.7 mg, 95% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.81 (s, 1H), 10.31 (s, 1H), 7.57 – 7.50 (m, 4H), 7.42 – 7.38 (m, 2H), 7.35 – 7.29 (m, 3H), 7.26 (s, 2H), 4.60 (d,  $J = 2.4$  Hz, 1H), 4.18 (s, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.84, 162.27, 151.14, 142.01, 137.43, 132.24, 129.31, 128.10, 127.65, 122.40, 118.76, 116.08, 70.87, 55.83, 51.98. **MS** (ESI):  $m/z$  (%) = 443.58  $[\text{M}-1]^+$ .  $\text{C}_{19}\text{H}_{15}\text{BrN}_4\text{O}_2\text{S}$  (444.01): calcd. C 51.48, H 3.41, N 12.64%; found C 51.35, H 3.78, N 12.46%.

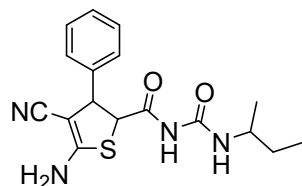


**5s: 5-amino-4-cyano-N-((4-(cyanomethyl)phenyl)carbamoyl)-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 575.2 mg, 95% yield.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.32 (s, 1H), 8.80 (s, 1H), 7.81 (d,  $J = 8.3$  Hz, 2H), 7.49 (d,  $J = 8.3$  Hz, 2H), 7.41 – 7.37 (m, 2H), 7.33 – 7.28 (m, 3H), 7.23 (s, 2H), 4.58 (d,  $J = 2.8$  Hz, 1H), 4.50 – 4.40 (m, 2H), 4.11 (s, 1H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}D_6$ )  $\delta$  172.11, 162.29,

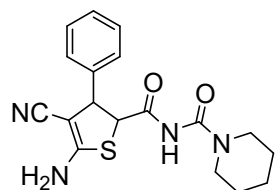
153.72, 145.76, 142.02, 132.85, 129.30, 128.59, 128.08, 127.66, 119.44, 118.76, 110.17, 70.84, 55.75, 52.10, 43.08. **MS** (ESI):  $m/z$  (%) = 402.10[M-1]<sup>+</sup>. C<sub>21</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S (403.11): calcd. C 62.52, H 4.25, N 17.36%; found C 62.67, H 4.14, N 17.46%.



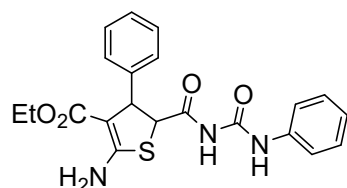
**5t: 5-amino-N-((4-aminophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** Off-white solid, 494.6 mg, 87% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.62 (s, 1H), 9.93 (s, 1H), 7.41 – 7.37 (m, 2H), 7.34 – 7.29 (m, 3H), 7.24 (s, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.53 (d, *J* = 8.7 Hz, 1H), 4.96 (s, 2H), 4.60 (d, *J* = 2.7 Hz, 1H), 4.16 (s, 1H). <sup>13</sup>C NMR (101 MHz, DMSO-*D*<sub>6</sub>) δ 172.66, 162.32, 151.05, 146.03, 142.07, 129.32, 128.09, 127.66, 126.61, 122.26, 118.79, 114.51, 70.88, 55.81, 52.10. **MS** (ESI):  $m/z$  (%) = 378.31 [M-1]<sup>+</sup>. C<sub>19</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S (379.11): calcd. C 60.14, H 4.52, N 18.46%; found C 60.18, H 4.54, N 18.40%.



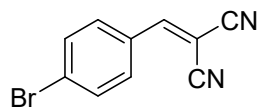
**5u: 5-amino-N-(sec-butylcarbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide.** White solid, 439.6 mg, 85% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.42 (s, 1H), 8.07 (s, 1H), 7.39 – 7.36 (m, 2H), 7.32 – 7.27 (m, 3H), 7.22 (s, 2H), 4.55 (s, 1H), 4.06 (s, 1H), 3.70 – 3.63 (m, 1H), 1.53 – 1.43 (m, 2H), 1.11 (dd, *J* = 6.6, 2.4 Hz, 3H), 0.88 – 0.84 (m, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*D*<sub>6</sub>) δ 172.48, 162.29, 152.85, 142.06, 129.29, 128.06, 127.64, 118.75, 70.92, 55.72, 52.08, 47.09, 29.37, 20.67, 20.63, 10.74. **MS** (ESI):  $m/z$  (%) = 343.28 [M-1]<sup>+</sup>. C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S (344.13): calcd. C 59.28, H 5.85, N 16.27%; found C 59.18, H 5.83, N 16.30%.



**5v: N-(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carbonyl)piperidine-1-carboxamide.** Yellow solid, 455.4 mg, 85% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.02 (s, 1H), 7.39 – 7.36 (m, 2H), 7.31 – 7.27 (m, 3H), 7.13 (s, 2H), 4.61 (d, *J* = 2.8 Hz, 1H), 4.41 (d, *J* = 2.9 Hz, 1H), 3.31 (t, *J* = 5.4 Hz, 4H), 1.53 (q, *J* = 4.8, 3.4 Hz, 2H), 1.44 (q, *J* = 5.7 Hz, 4H). <sup>13</sup>C NMR (101 MHz, DMSO-*D*<sub>6</sub>) δ 171.36, 162.35, 152.57, 142.80, 129.32, 127.97, 127.55, 118.96, 71.21, 56.24, 51.63, 45.68, 44.33, 25.94, 24.26, 22.74, 22.14, 19.07. **MS** (ESI):  $m/z$  (%) = 355.44 [M-1]<sup>+</sup>. C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S (356.13): calcd. C 60.65, H 5.66, N 15.72%; found C 60.35, H 5.78, N 15.70%.

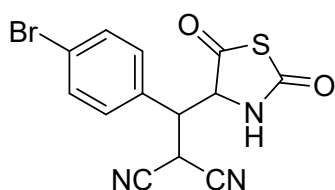


**5w: ethyl 2-amino-4-phenyl-5-((phenylcarbamoyl)carbamoyl)-4,5-dihydrothiophene-3-carboxylate.** White solid, 555.7 mg, 90% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.73 (s, 1H), 10.30 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.51 (s, 2H), 7.11 – 7.08 (m, 1H), 7.35 – 7.27 (m, 6H), 7.25 – 7.20 (m, 1H), 7.12 – 7.07 (m, 1H), 4.72 (d, *J* = 1.2 Hz, 1H), 3.98 (s, 1H), 3.90 (q, *J* = 7.0 Hz, 2H), 0.99 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-*D*<sub>6</sub>) δ 173.74, 165.39, 162.32, 151.28, 144.31, 138.06, 129.48, 128.82, 127.48, 127.24, 124.31, 120.32, 93.46, 58.55, 54.71, 50.80, 14.89. **MS** (ESI):  $m/z$  (%) = 410.23 [M-1]<sup>+</sup>. C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>S (411.13): calcd. C 61.30, H 5.14, N 10.21%; found C 61.41, H 5.10, N 10.17%.



**Intermediate I: 2-(4-bromobenzylidene)malononitrile.** White solid, 341.0 mg, 98% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.54 (s, 1H), 7.89-7.82 (m, 4H). <sup>13</sup>C NMR (101 MHz, DMSO-*D*<sub>6</sub>) δ 160.80, 133.21, 132.67, 130.90,

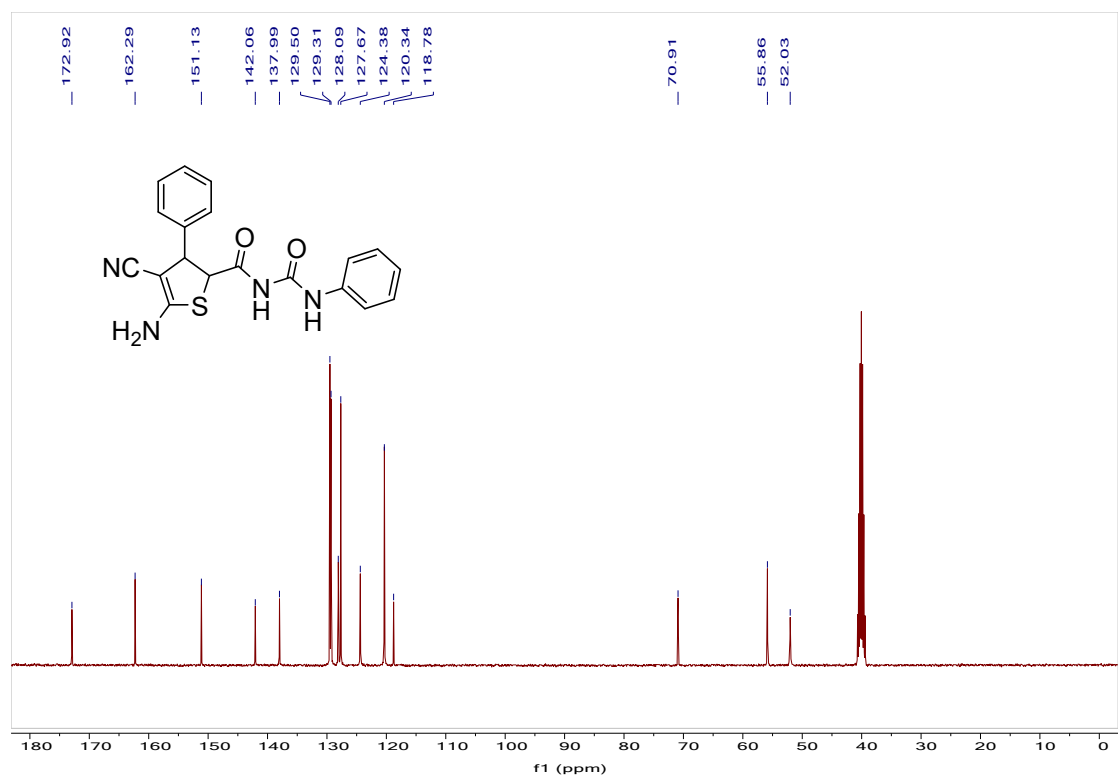
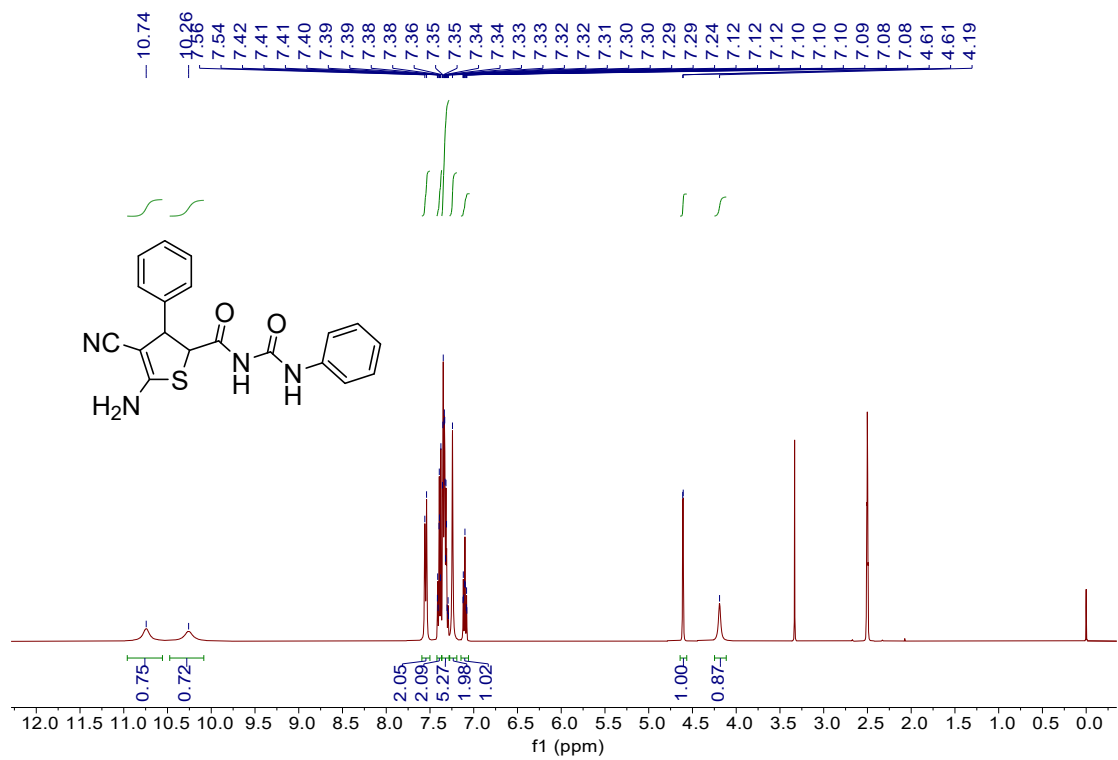
128.90, 114.60, 113.53, 82.81. **MS** (ESI):  $m/z$  (%) = 231.13 [M-1]<sup>+</sup>. C<sub>10</sub>H<sub>5</sub>BrN<sub>2</sub> (231.96): calcd. C 51.53, H 2.16, N 12.02%; found C 51.65, H 2.12, N 12.24%.



**Intermediate II: 2-((4-bromophenyl)(2,5-dioxothiazolidin-4-yl)methyl)malononitrile.** yellow solid, 501.1 mg, 96% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.96 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.99 (d, *J* = 7.2 Hz, 1H), 3.74 (d, *J* = 7.2 Hz, 1H), 3.26 (t, *J* = 7.2 Hz, 1H). <sup>13</sup>C NMR (101 MHz, DMSO-*D*<sub>6</sub>) δ 171.11, 170.24, 136.43, 131.93, 128.84, 127.20, 109.80, 54.05, 52.11, 27.73. **MS** (ESI):  $m/z$  (%) = 350.05 [M-1]<sup>+</sup>. C<sub>13</sub>H<sub>8</sub>BrN<sub>3</sub>O<sub>2</sub>S (350.95): calcd. C 44.59, H 2.30, N 12.00%; found C 44.75, H 2.24, N 12.18%.

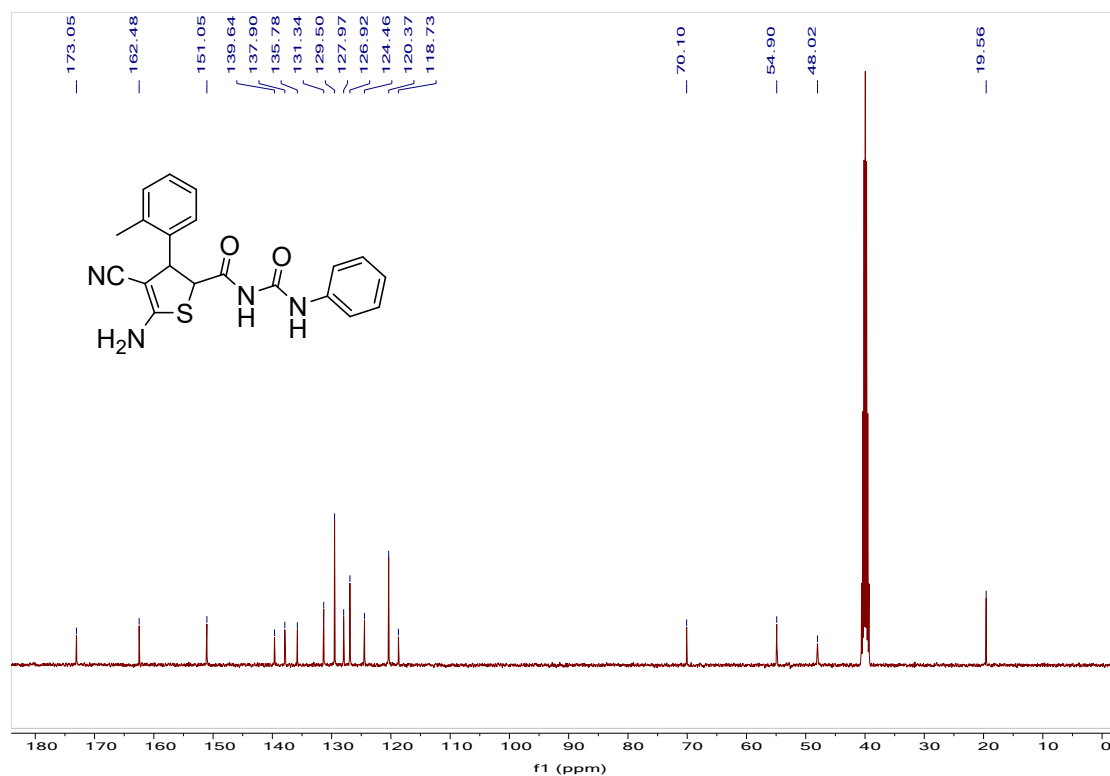
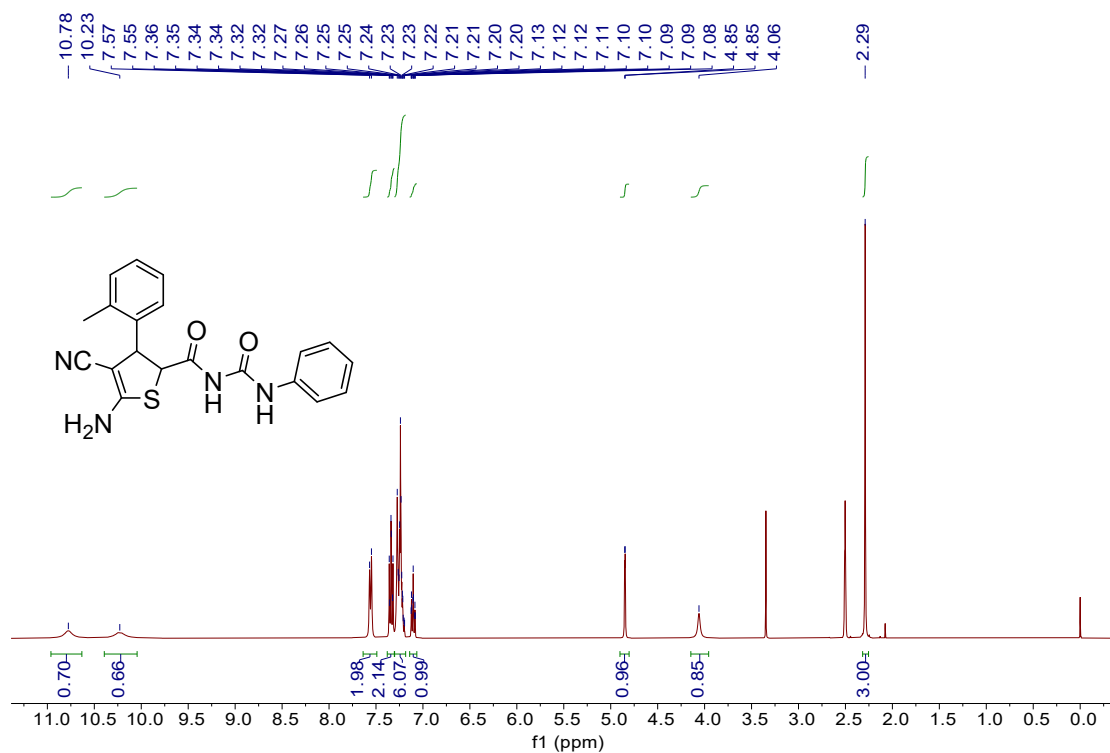
## Spectra of Products

**5a: 5-amino-4-cyano-3-phenyl-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.**

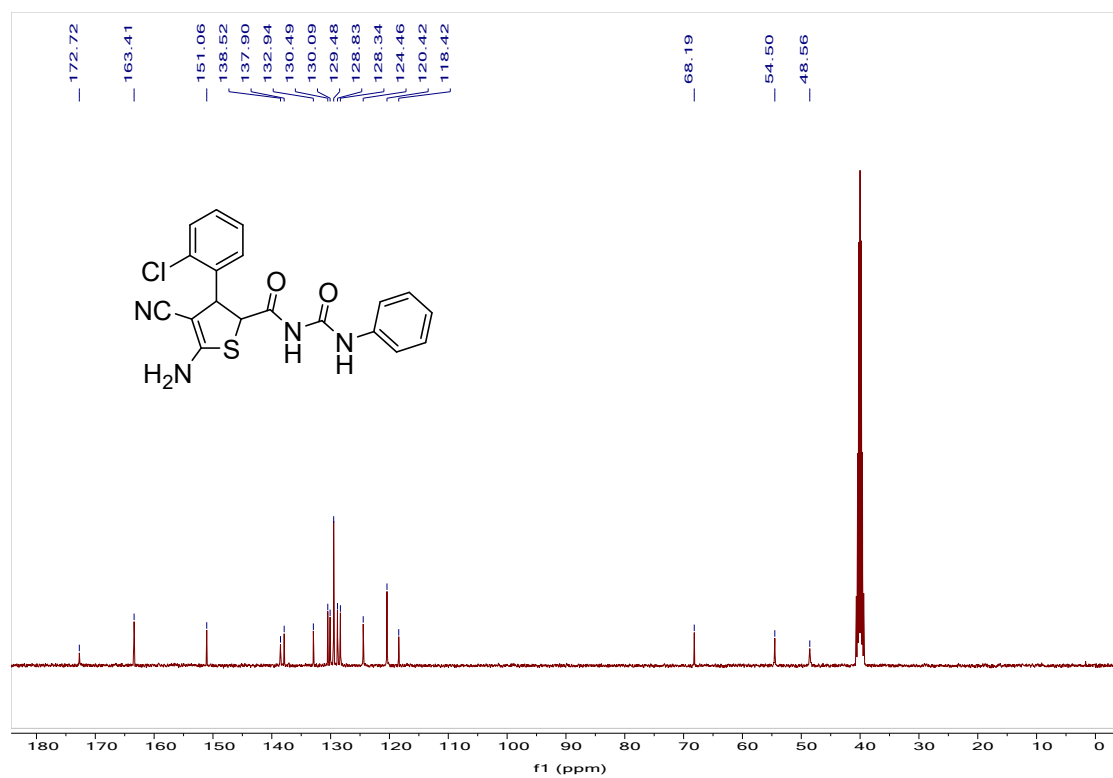
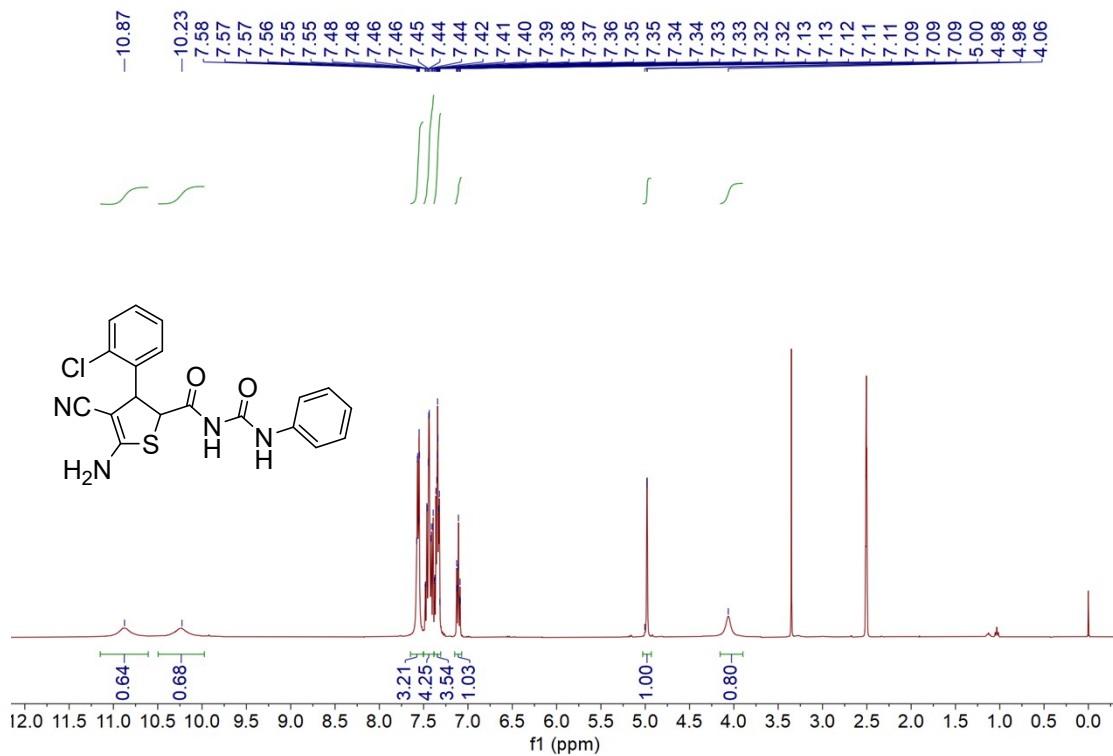


**5b: 5-amino-4-cyano-N-(phenylcarbamoyl)-3-(o-tolyl)-2,3-dihydrothiophene-2-carboxamide.**

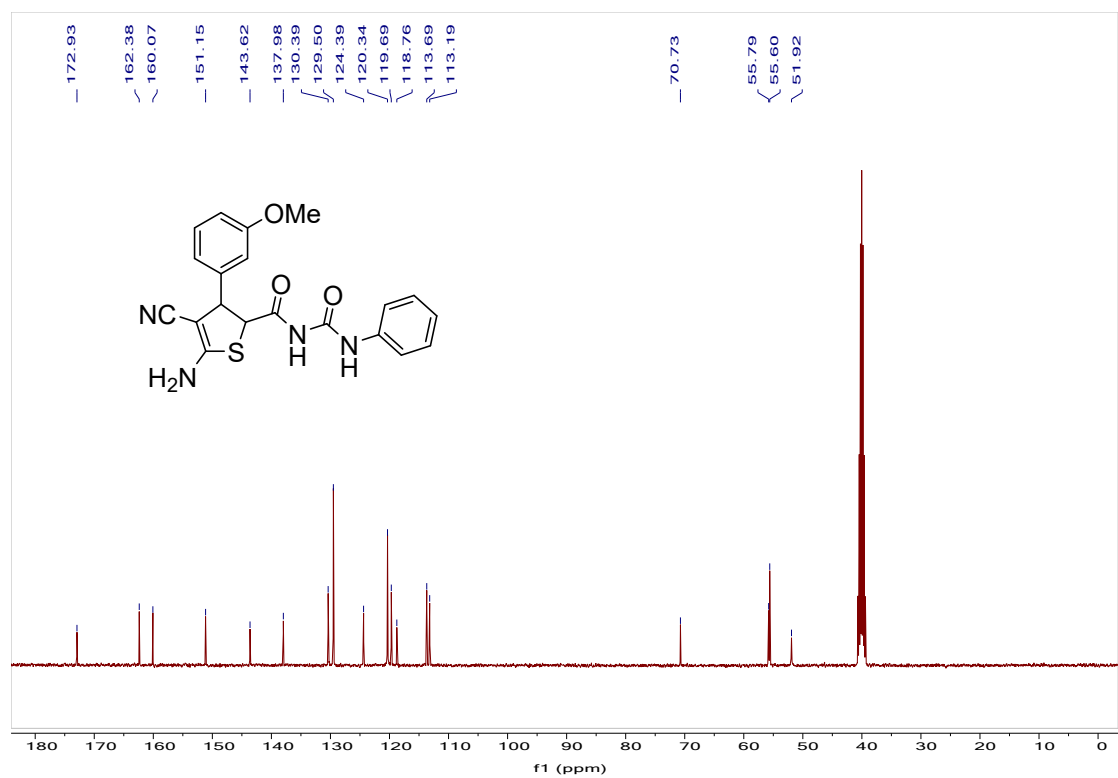
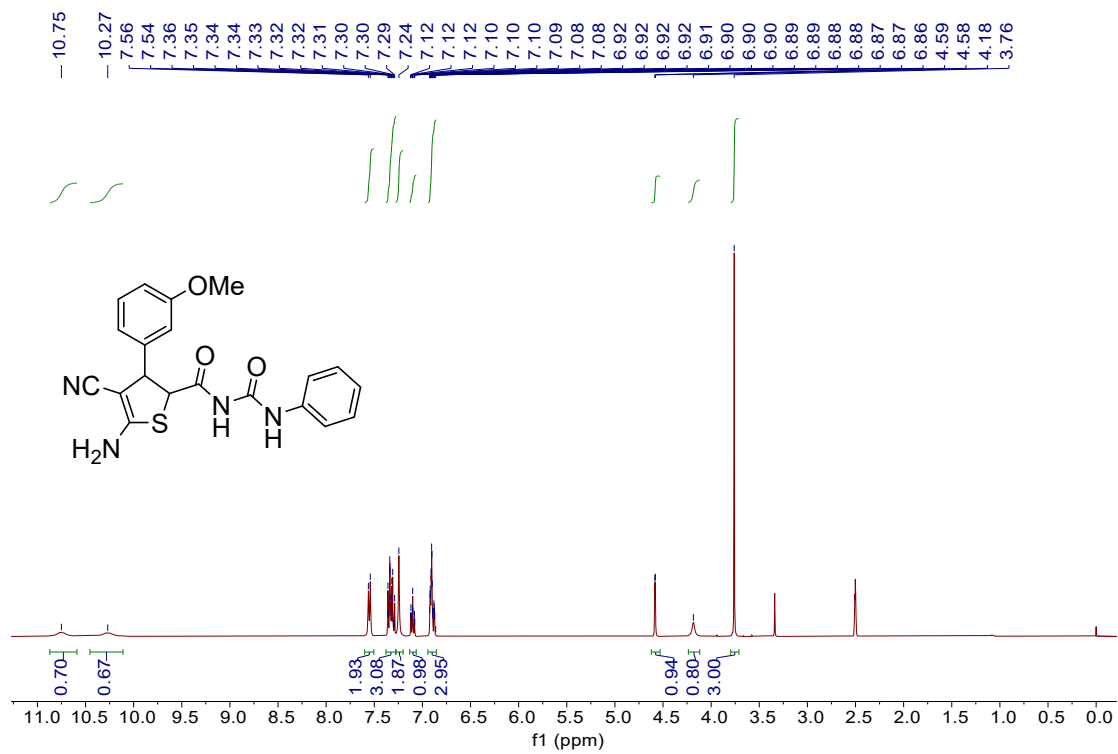




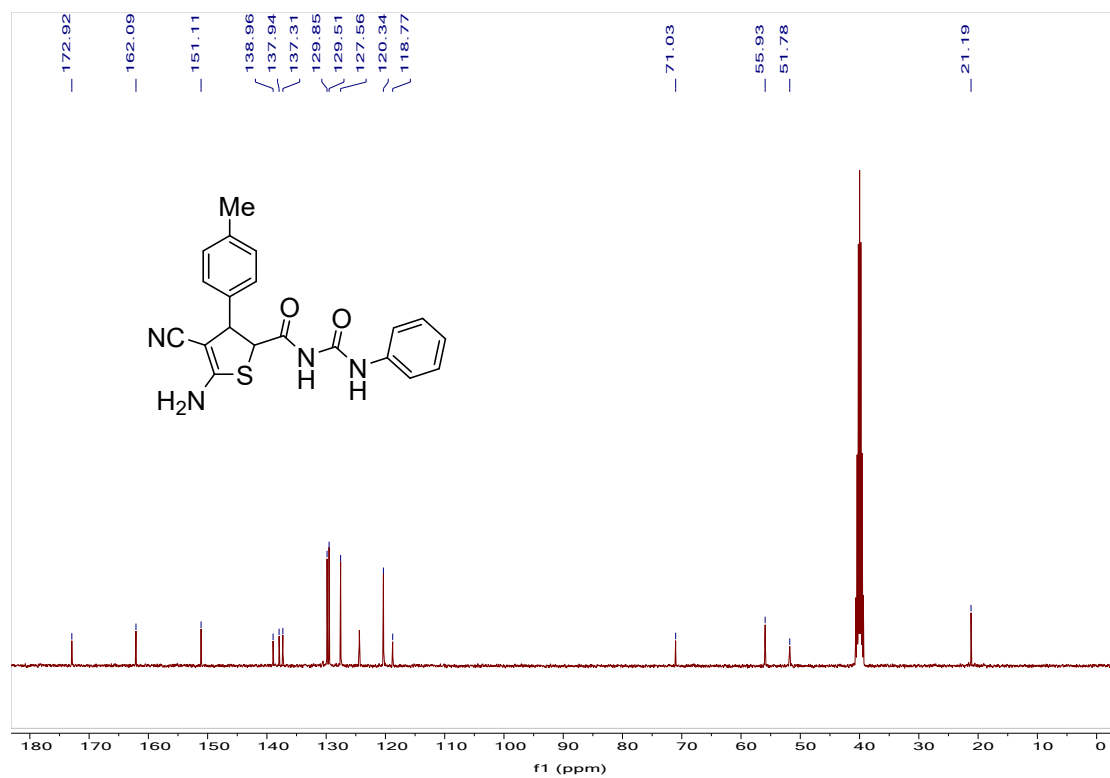
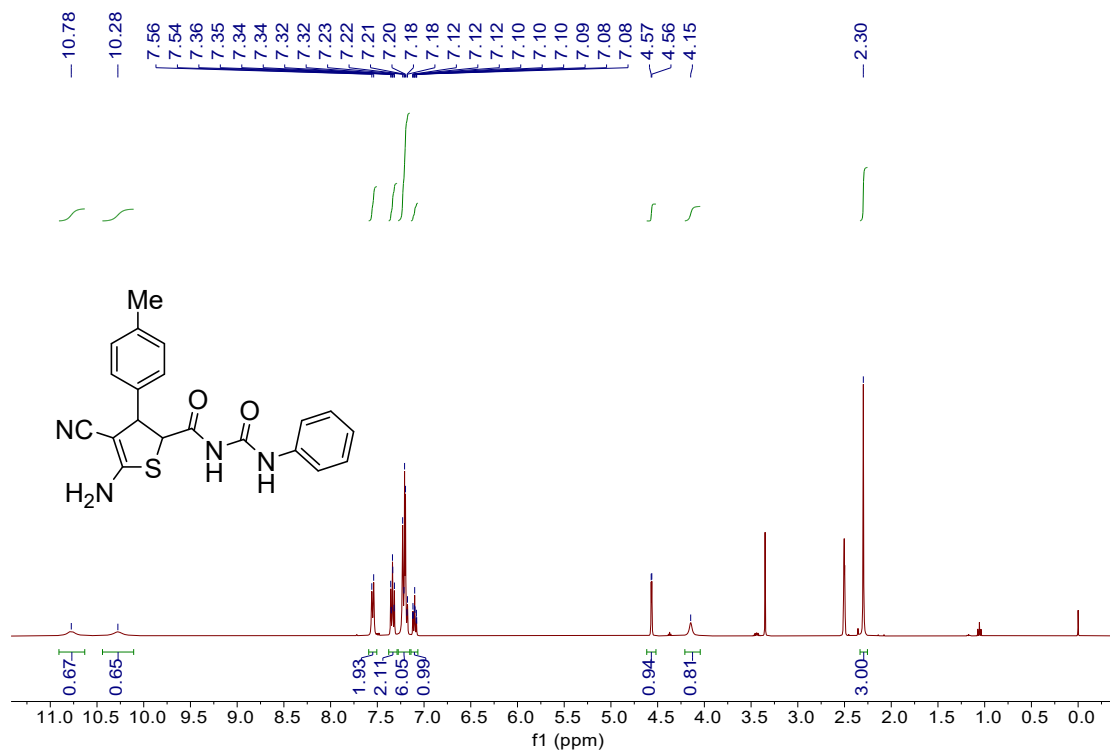
**5c:** 5-amino-3-(2-chlorophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.



**5d:** 5-amino-4-cyano-3-(3-methoxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.

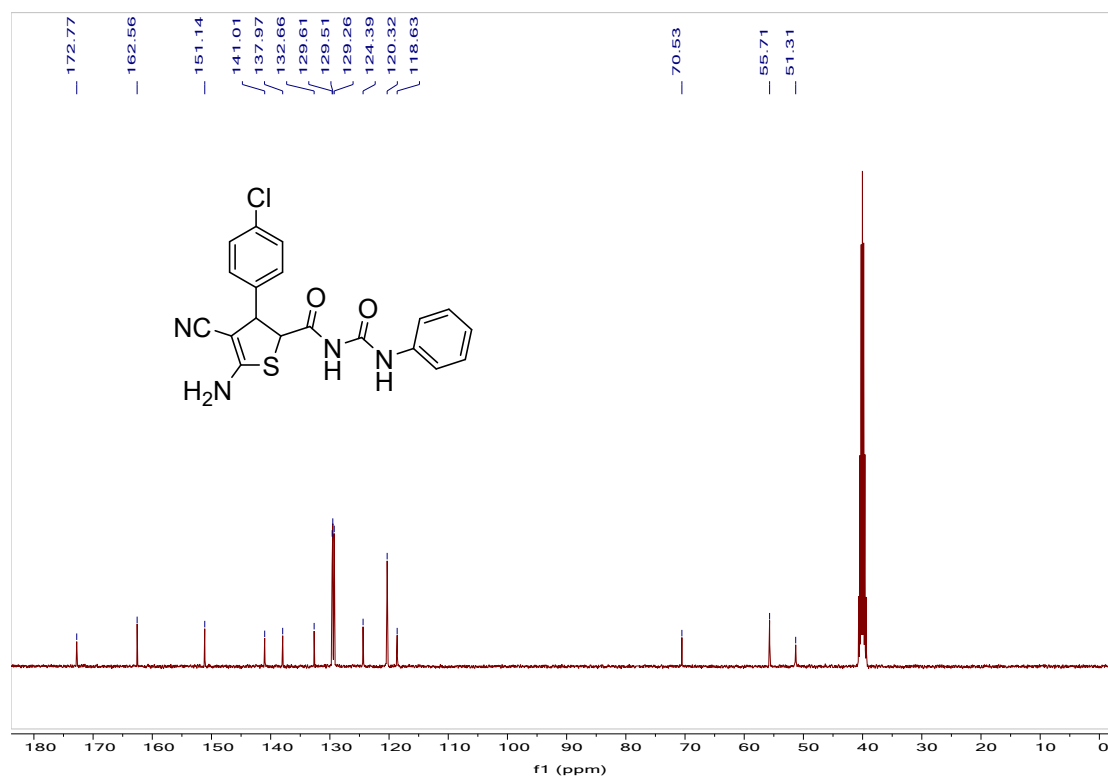
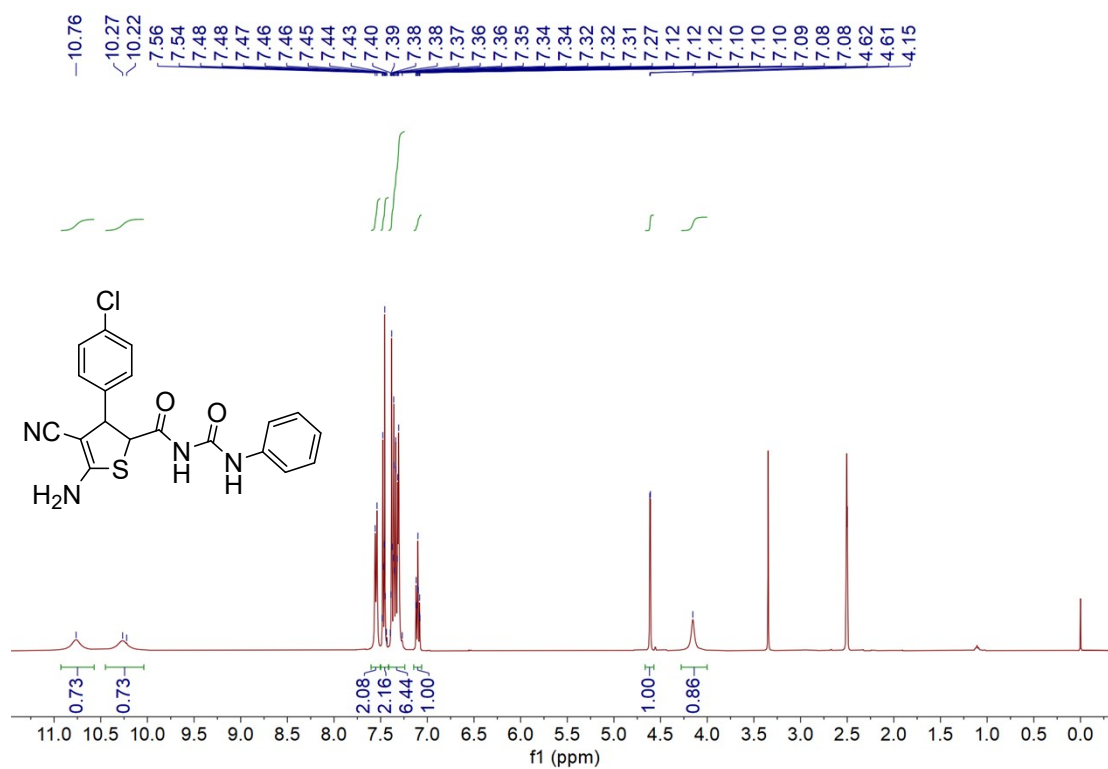


5e: 5-amino-4-cyano-N-(phenylcarbamoyl)-3-(ptolyl)-2,3-dihydrothiophene-2-carboxamide.



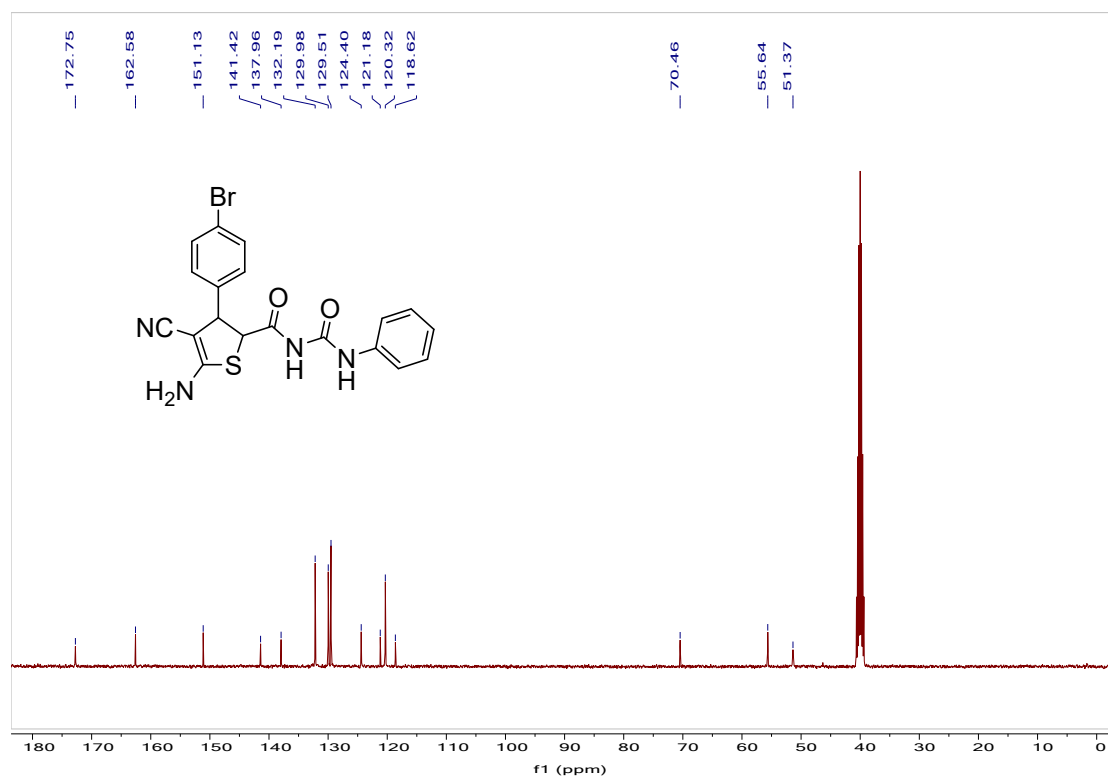
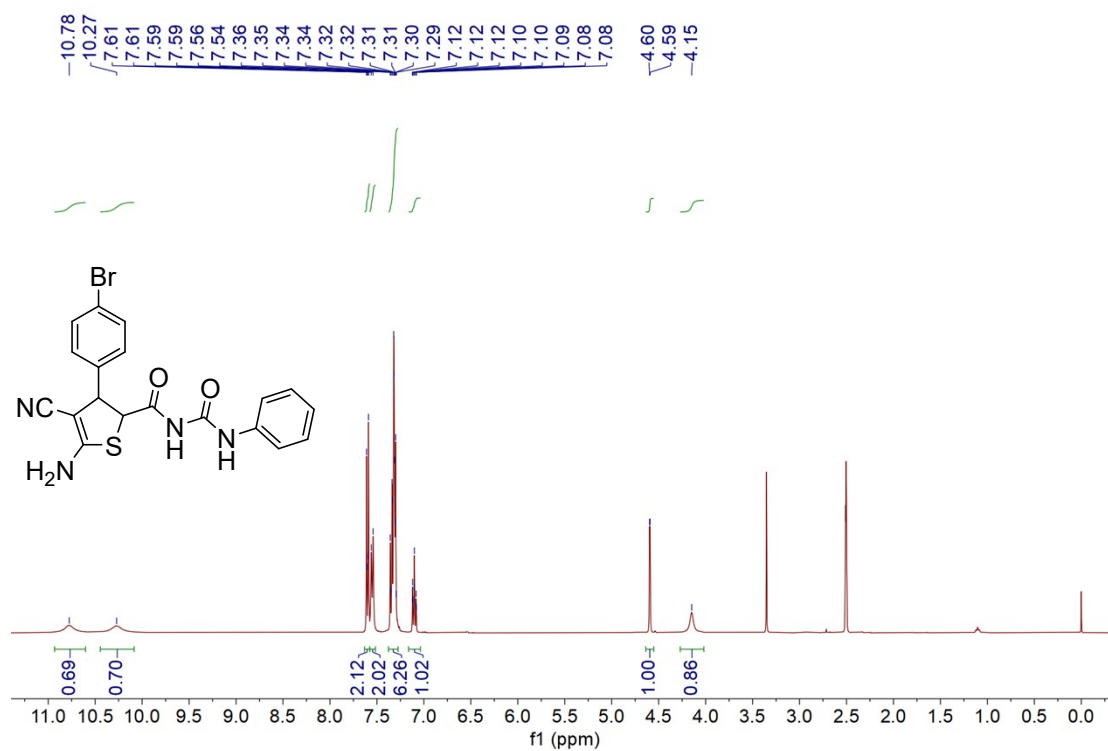
**5f:** 5-amino-3-(4-chlorophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-

carboxamide.



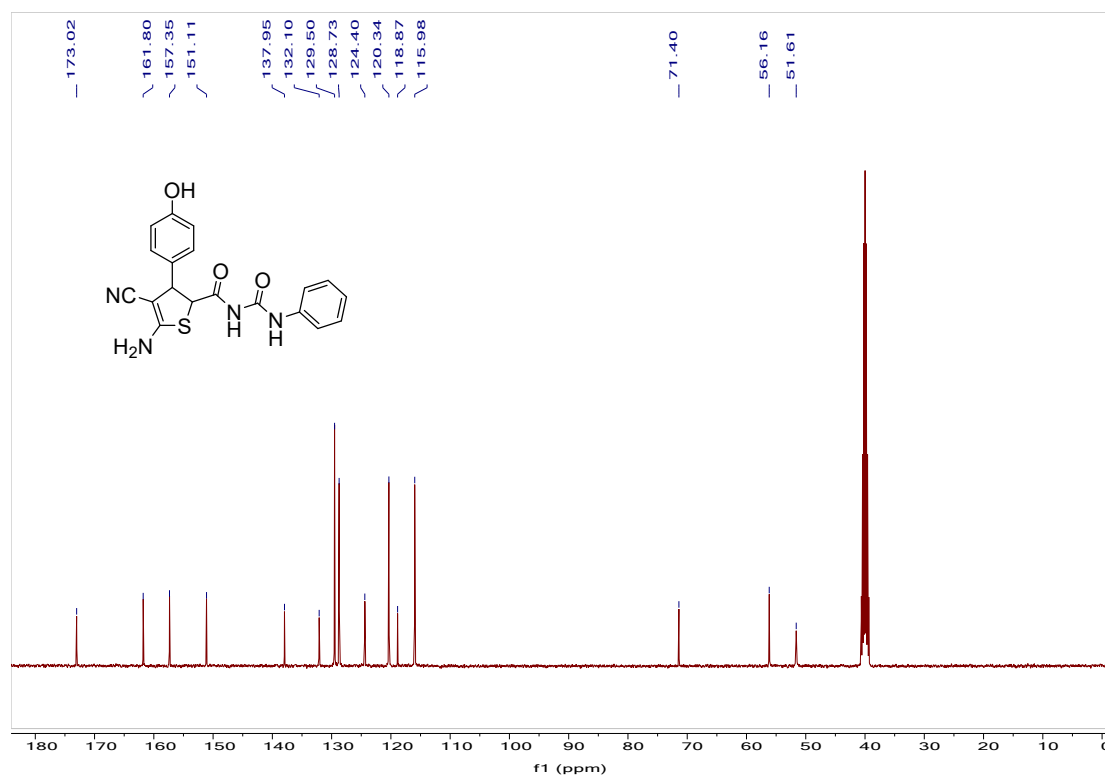
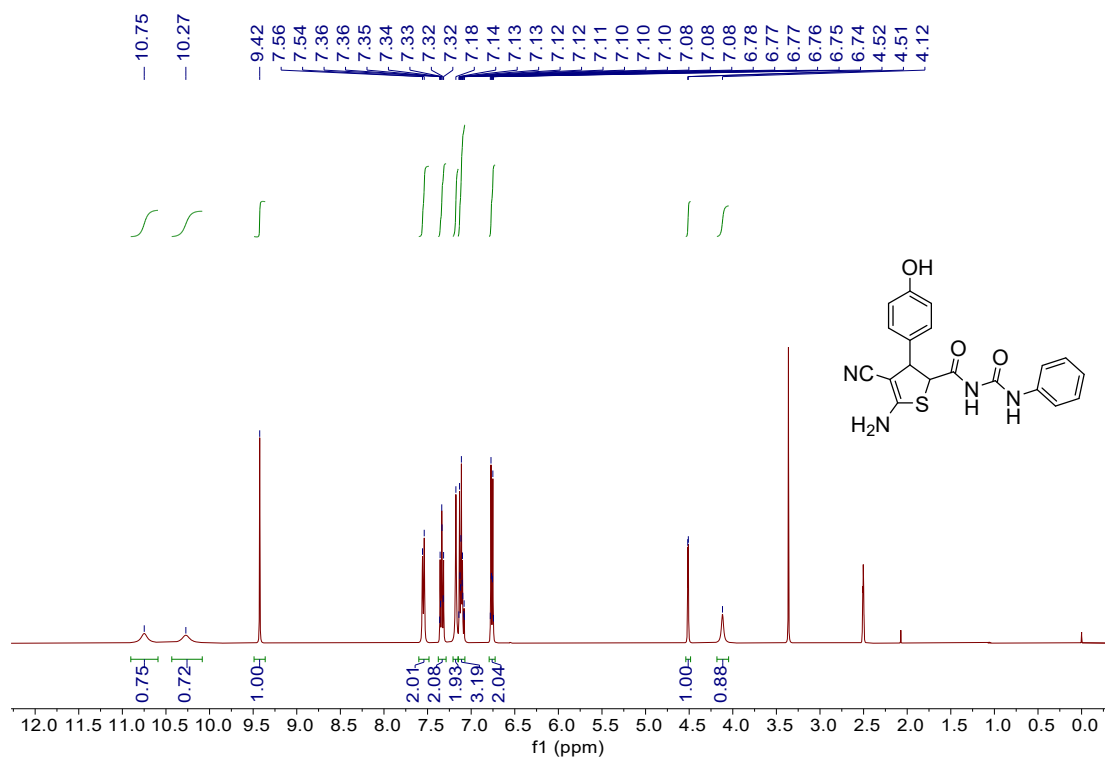
5g: 5-amino-3-(4-bromophenyl)-4-cyano-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-

carboxamide.



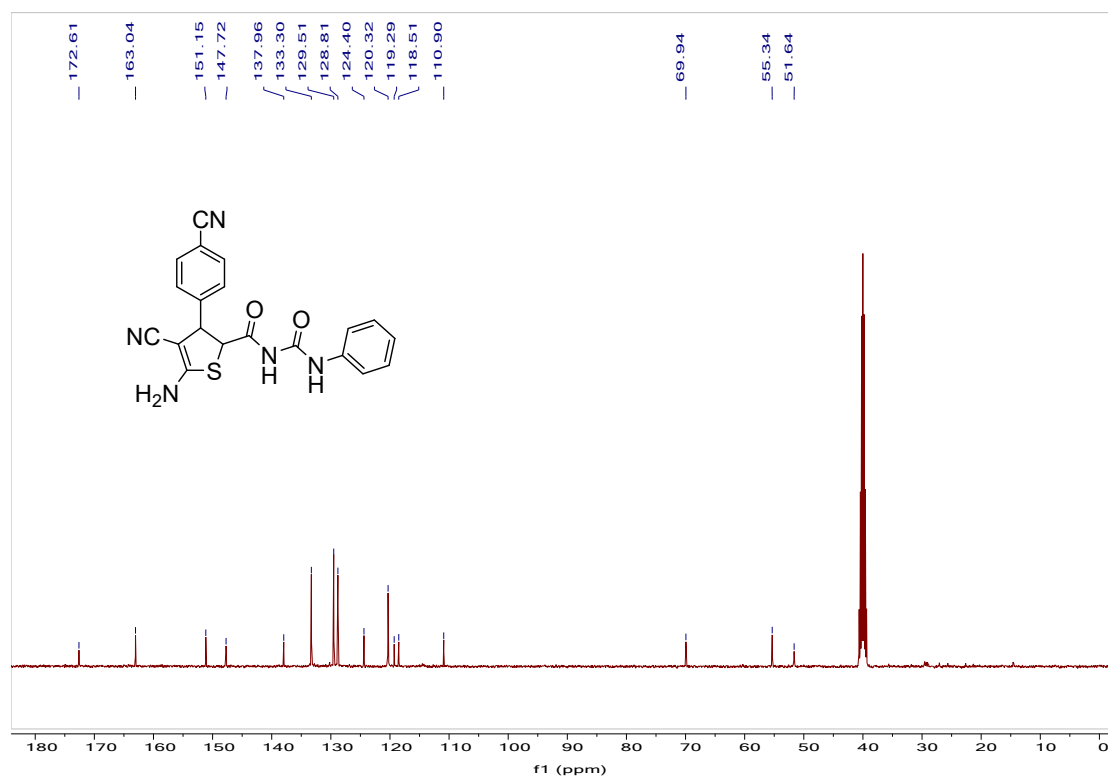
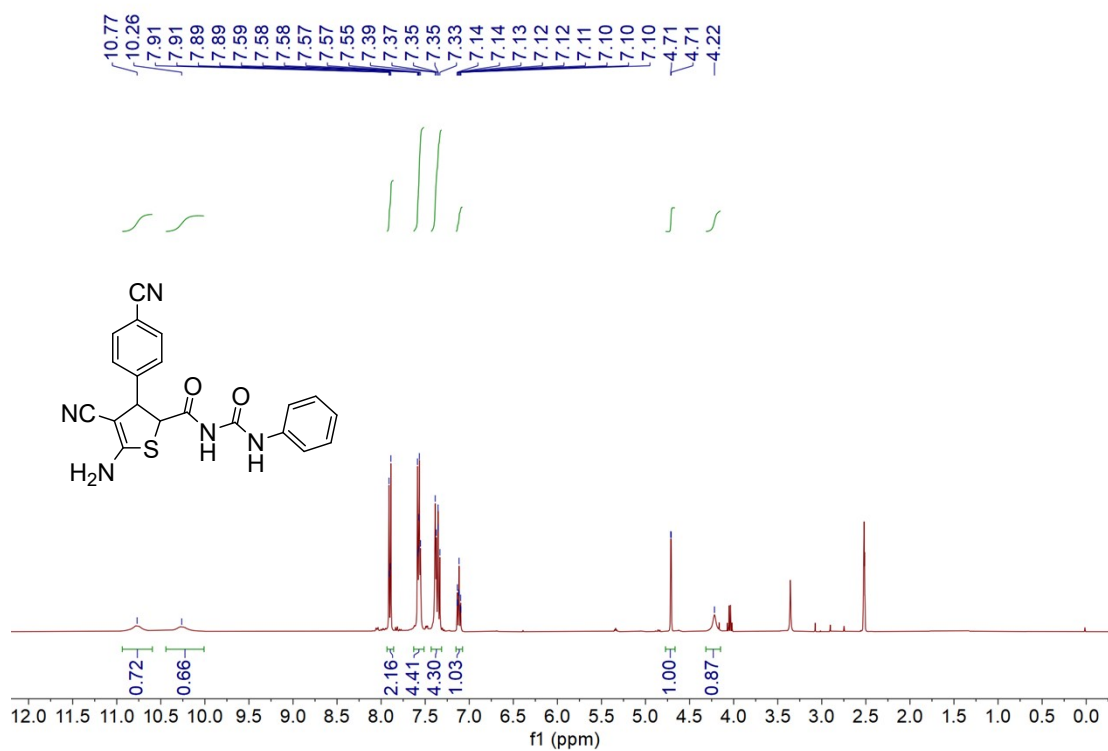
**5h:** 5-amino-4-cyano-3-(4-hydroxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-

carboxamide.



5i: 5-amino-4-cyano-3-(4-cyanophenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-

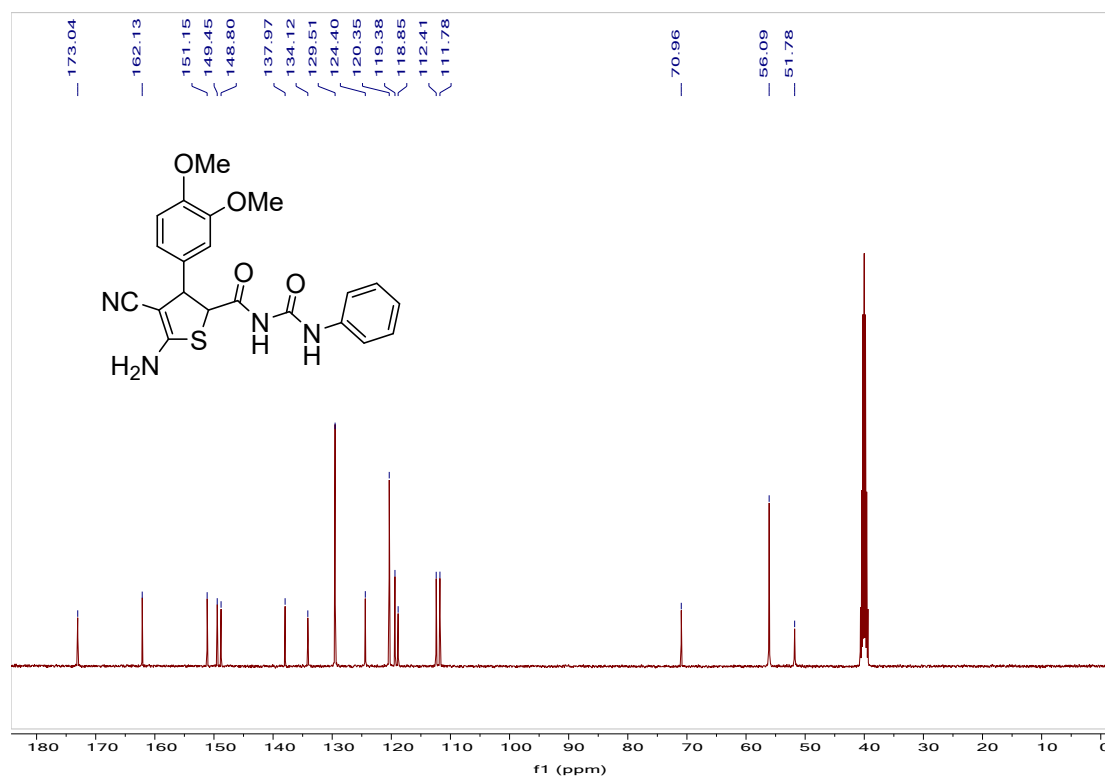
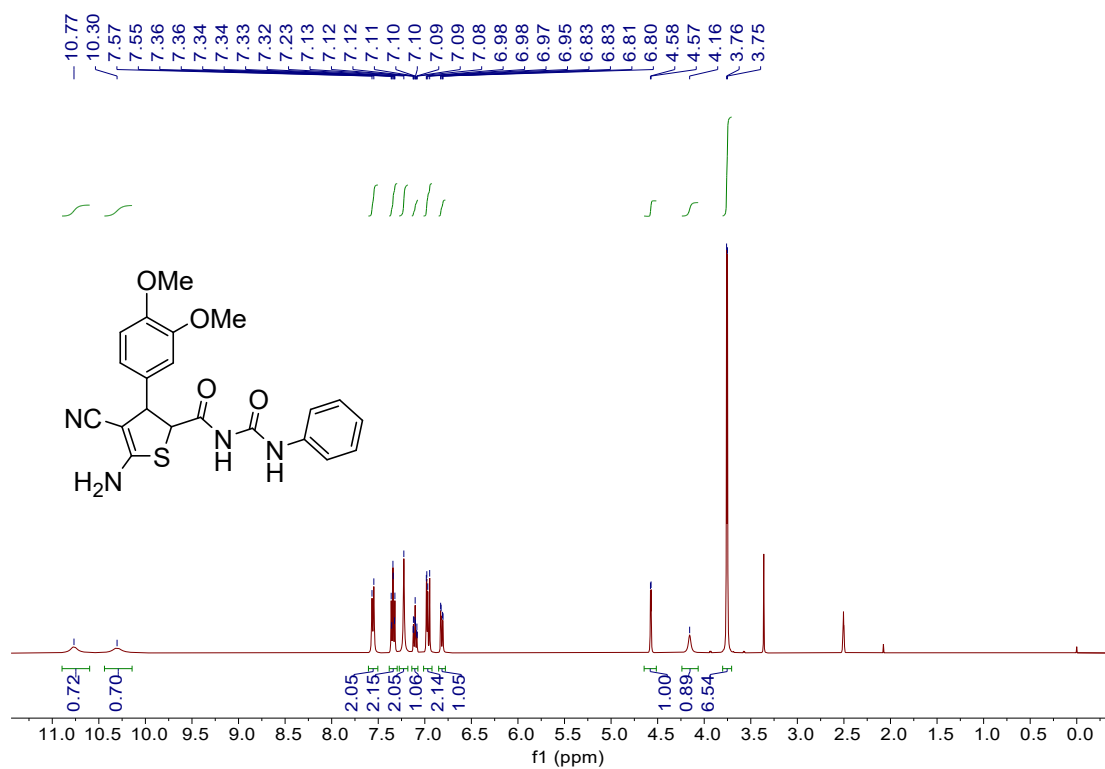
carboxamide.



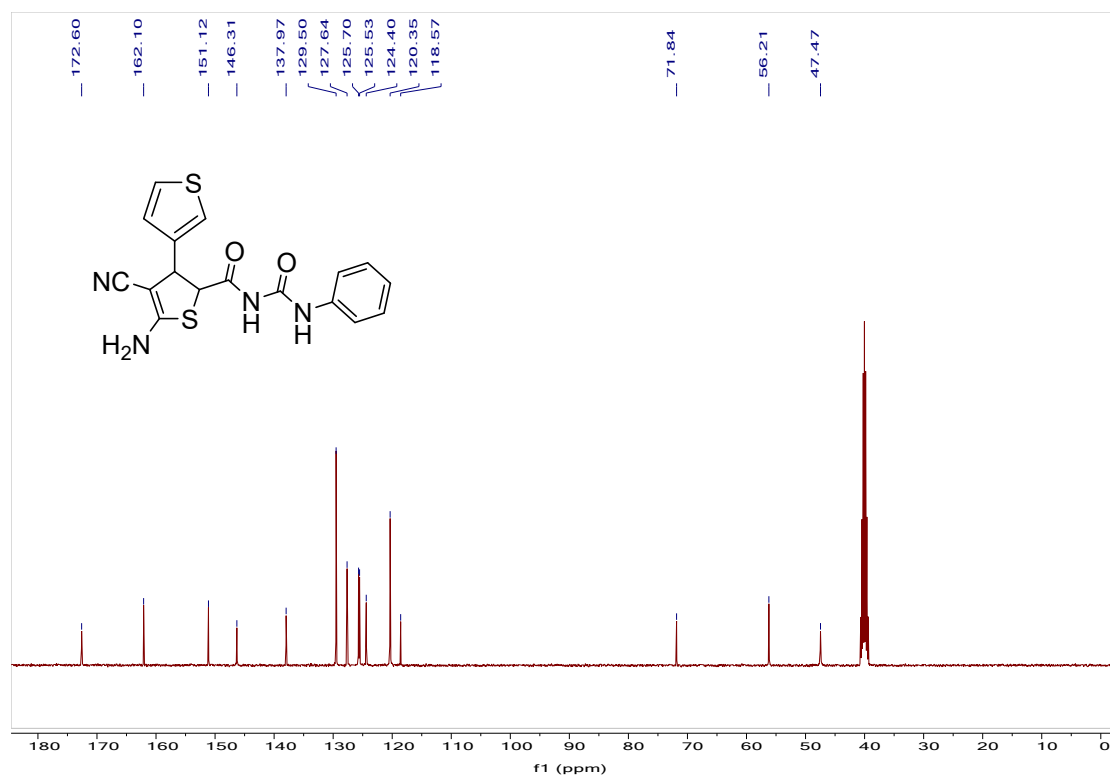
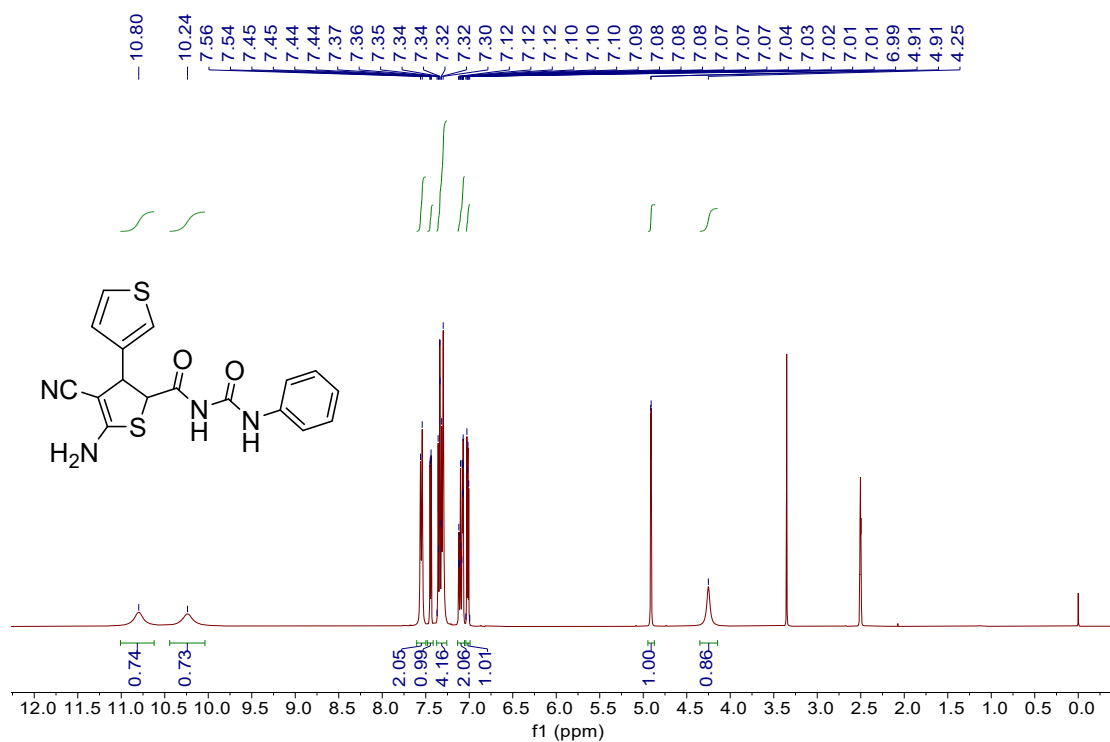
5j: 5-amino-4-cyano-3-(3,4-dimethoxyphenyl)-N-(phenylcarbamoyl)-2,3-dihydrothiophene-2-



carboxamide.

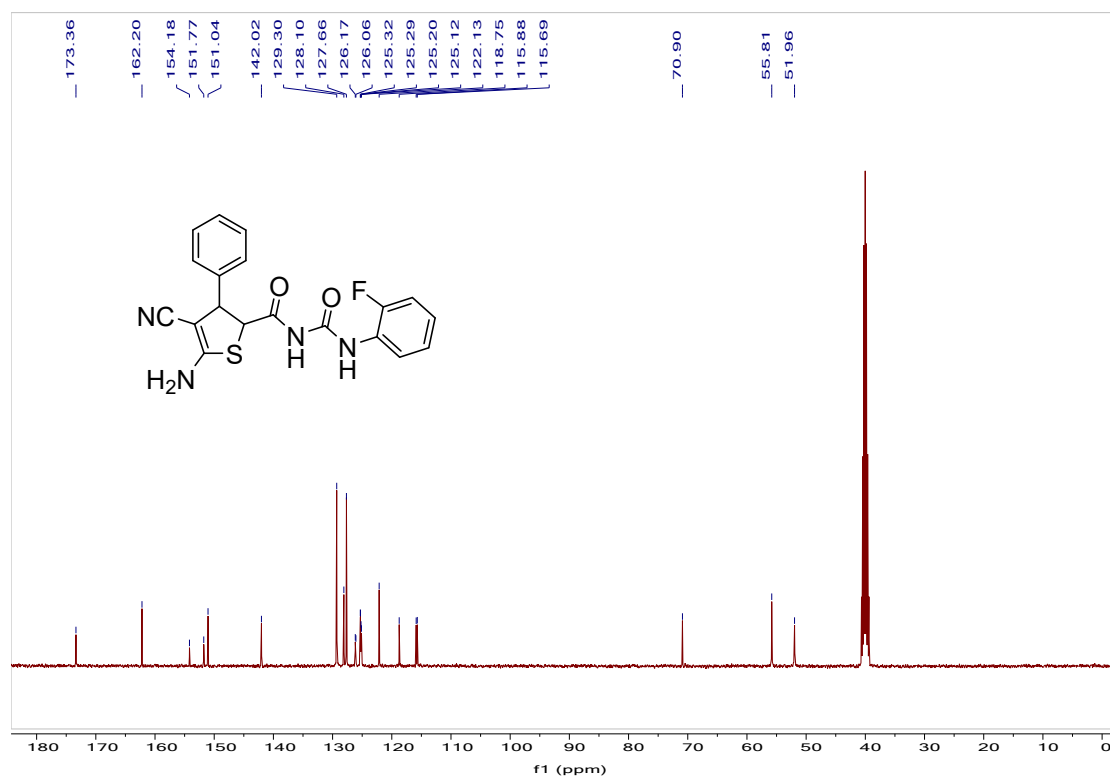
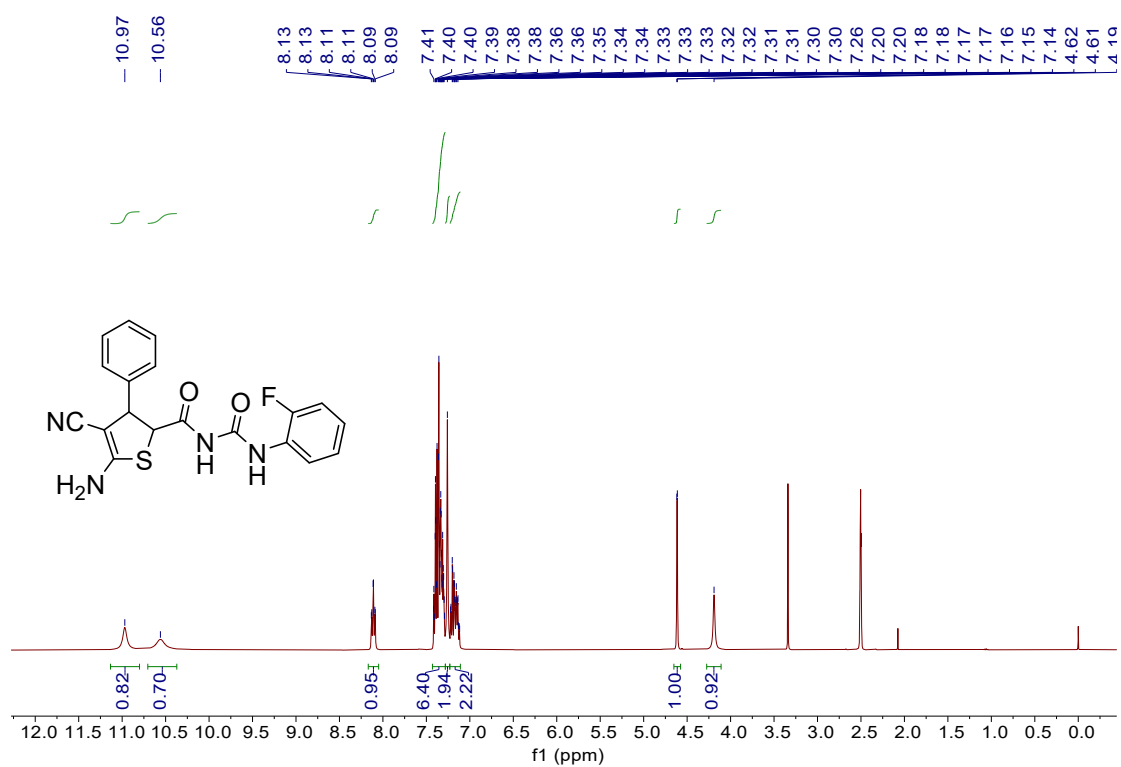


5k: 5-amino-4-cyano-N-(phenylcarbamoyl)-2,3-dihydro-[3,3'-bi-thiophene]-2-carboxamide.

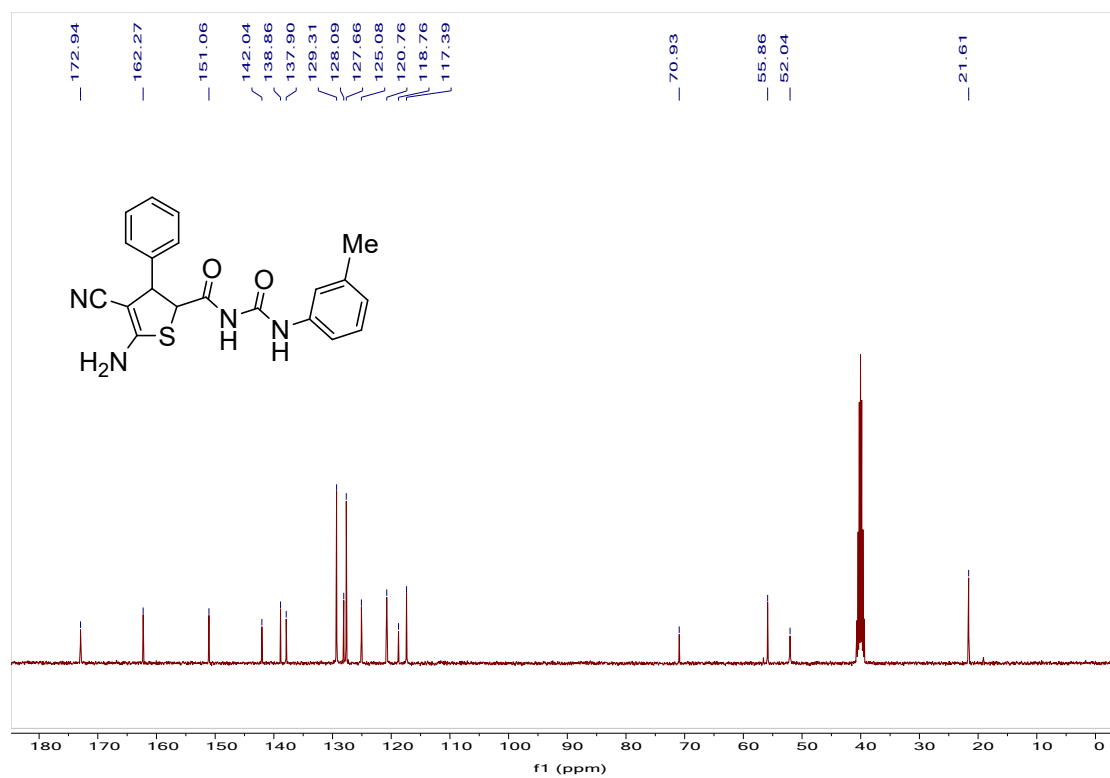
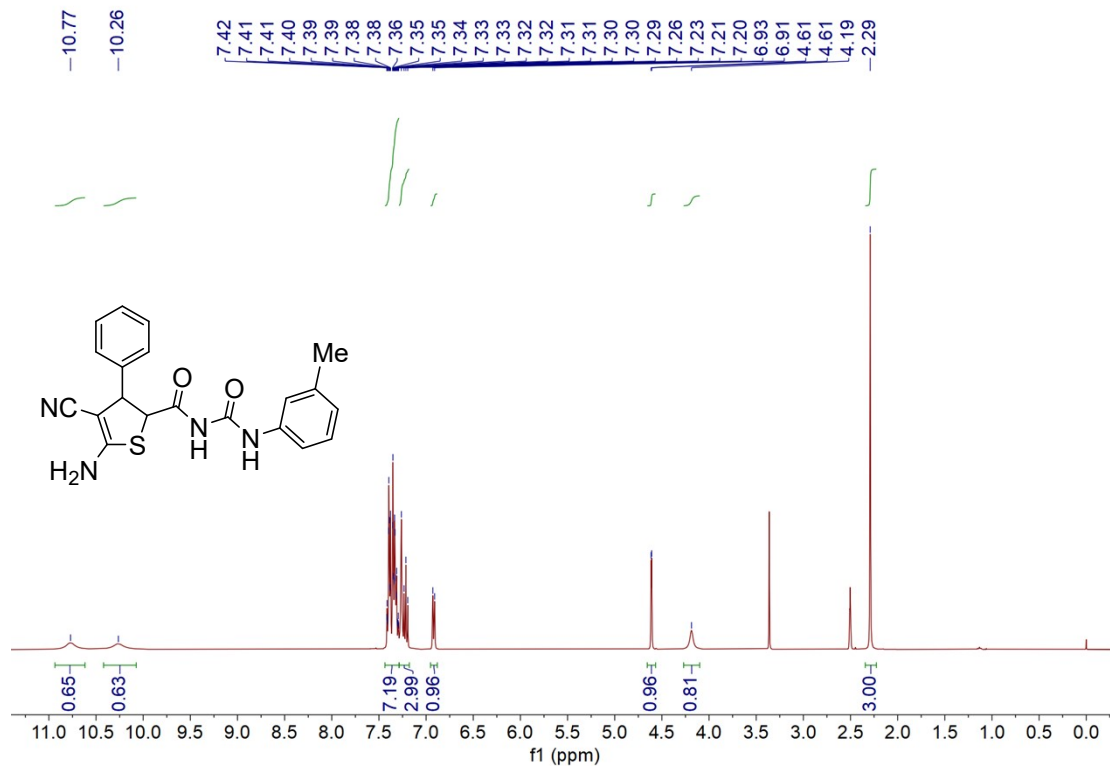


5l: 5-amino-4-cyano-N-((2-fluorophenyl)carbamoyl)-3-phenyl-2,3-dihydrothiophene-2-

carboxamide.

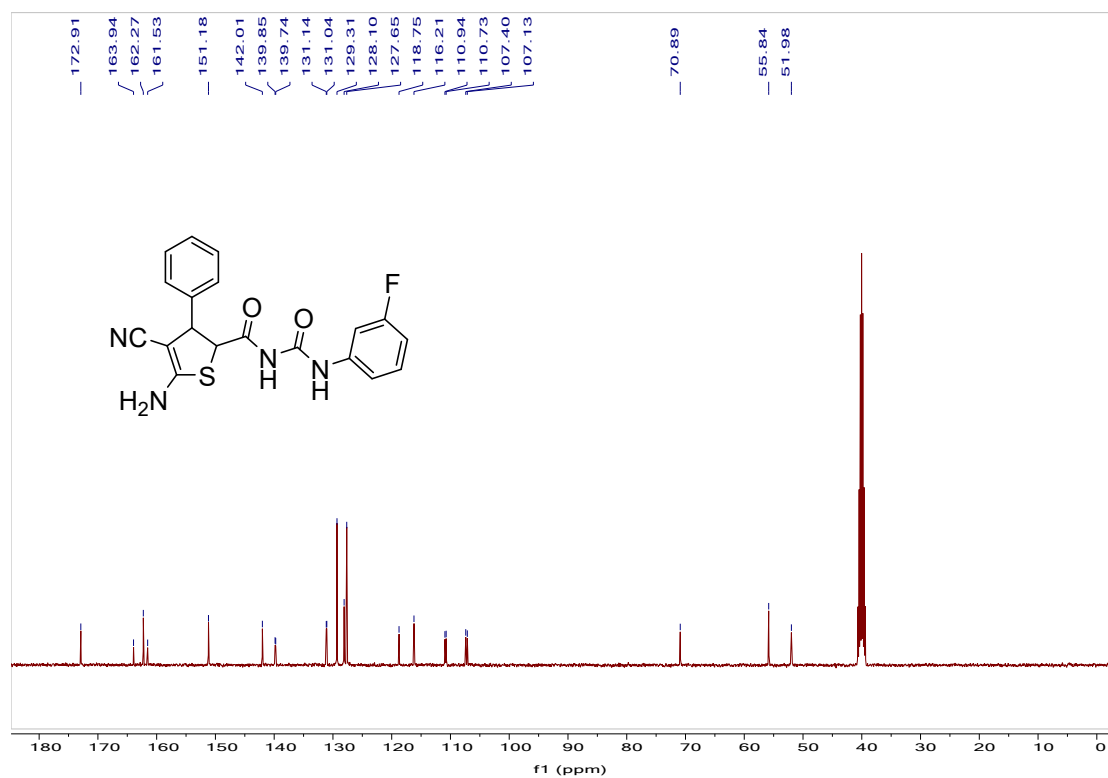
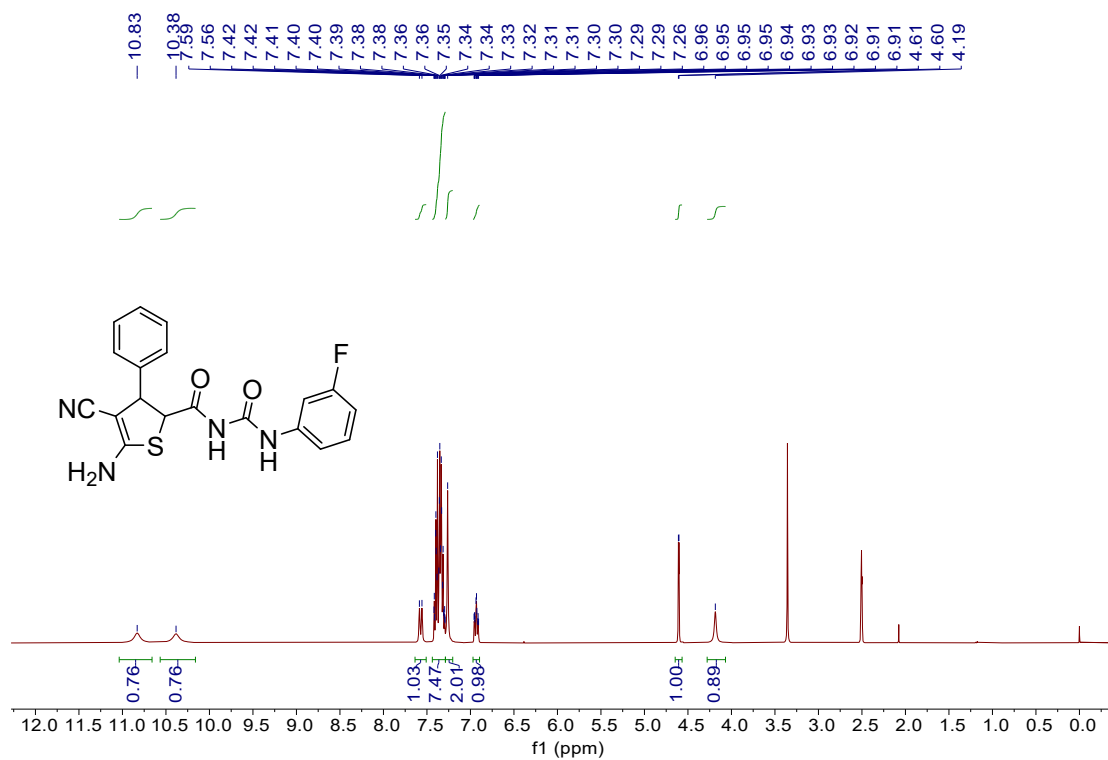


5m: 5-amino-4-cyano-3-phenyl-N-(m-tolylcarbamoyl)-2,3-dihydro-thiophene-2-carboxamide.



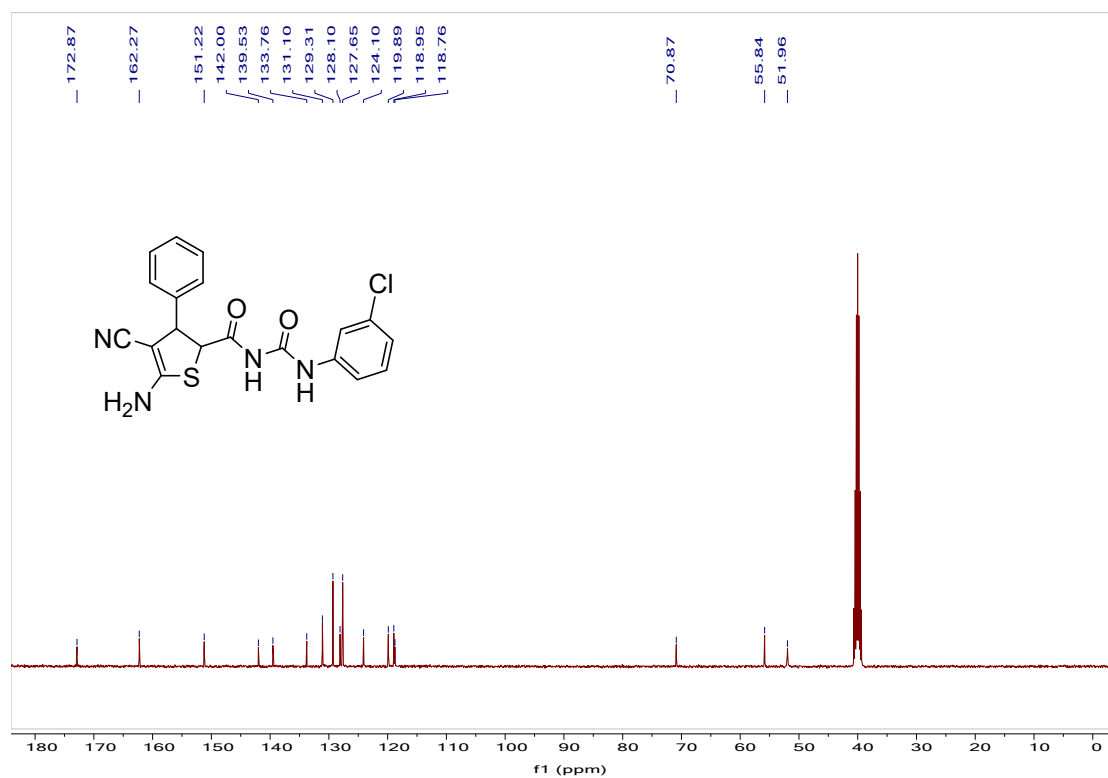
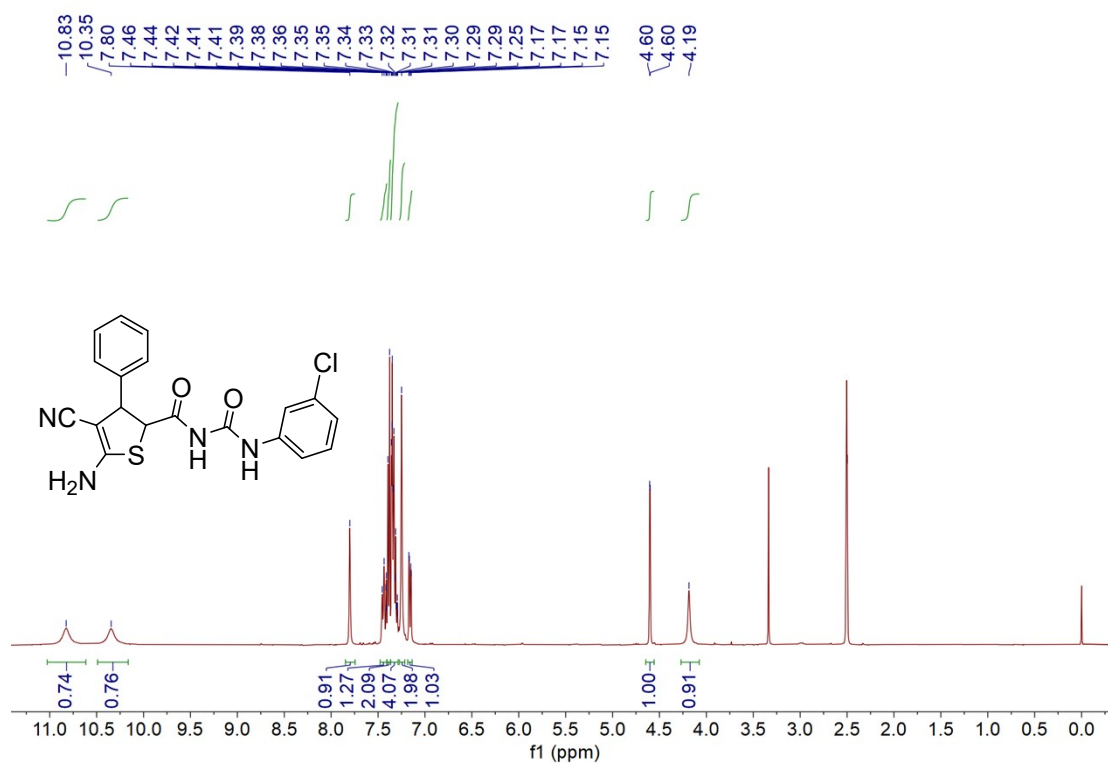
**5n:** 5-amino-4-cyano-N-((3-fluorophenyl)carbamoyl)-3-phenyl-2,3-dihydrothiophene-2-

carboxamide.

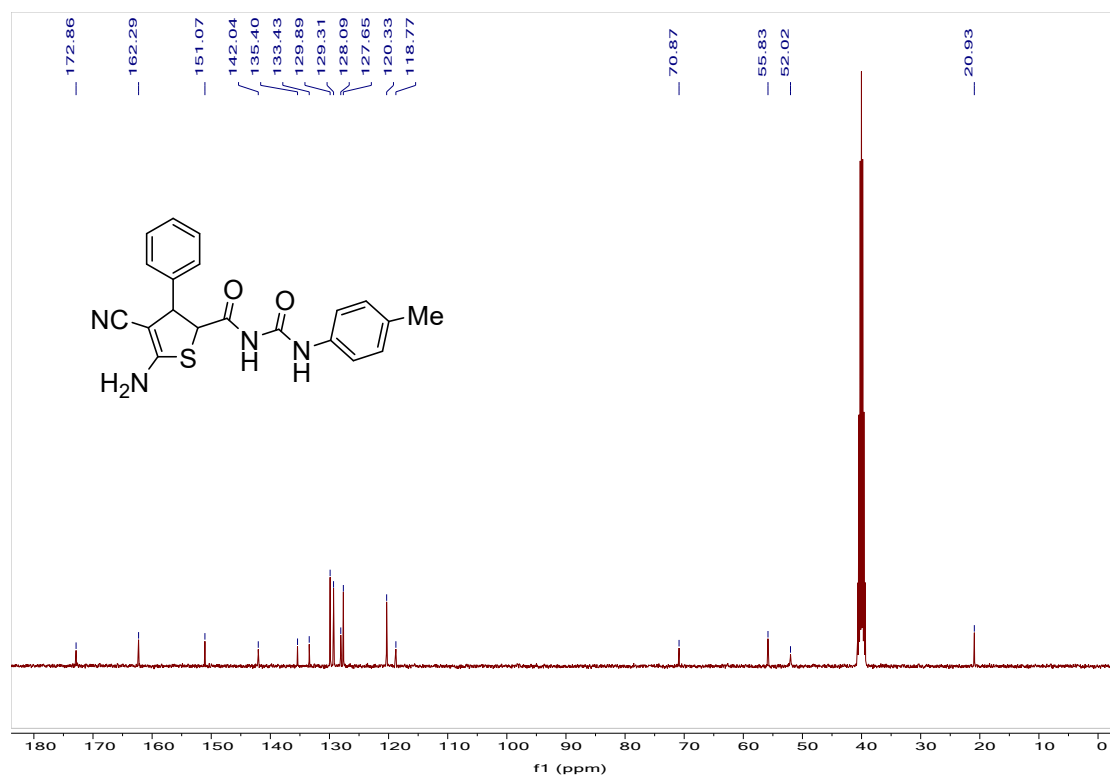
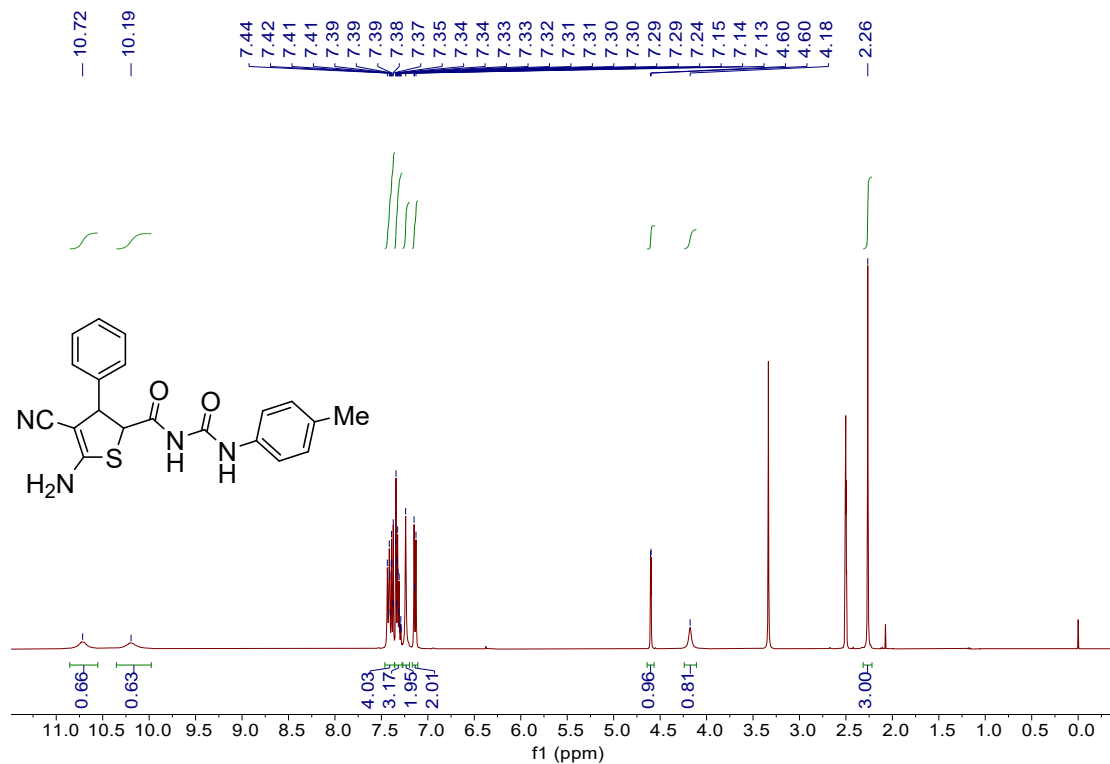


5o: 5-amino-N-((3-chlorophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-

carboxamide.

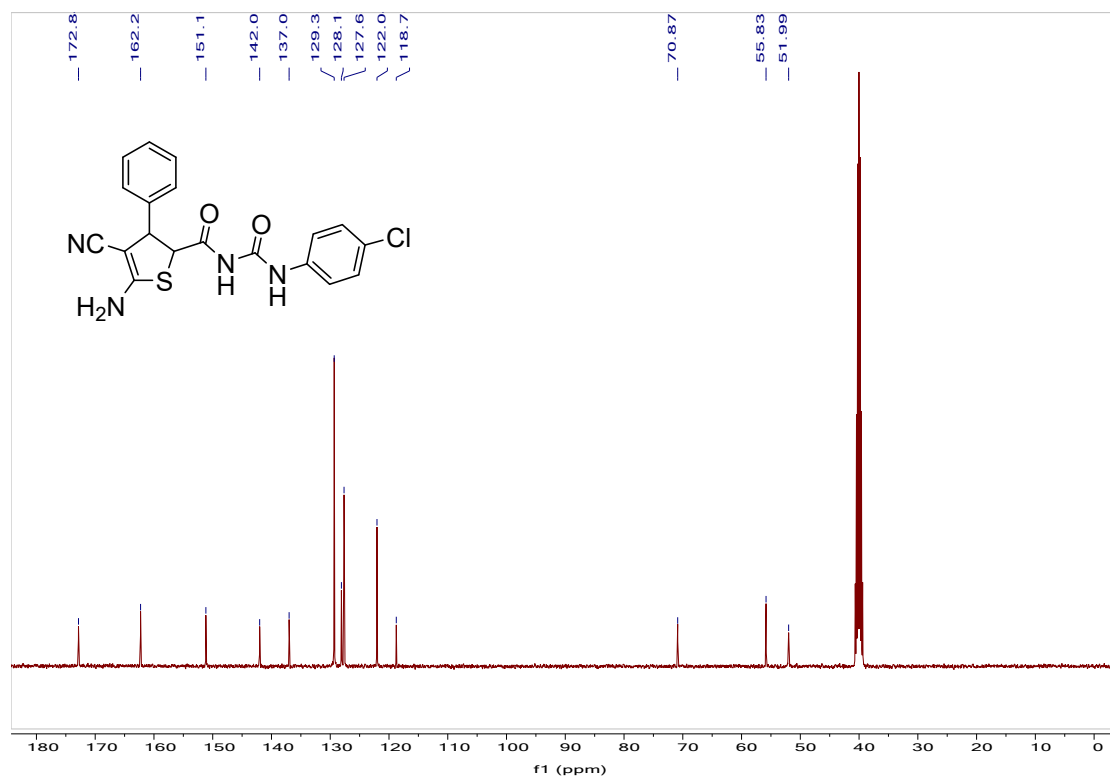
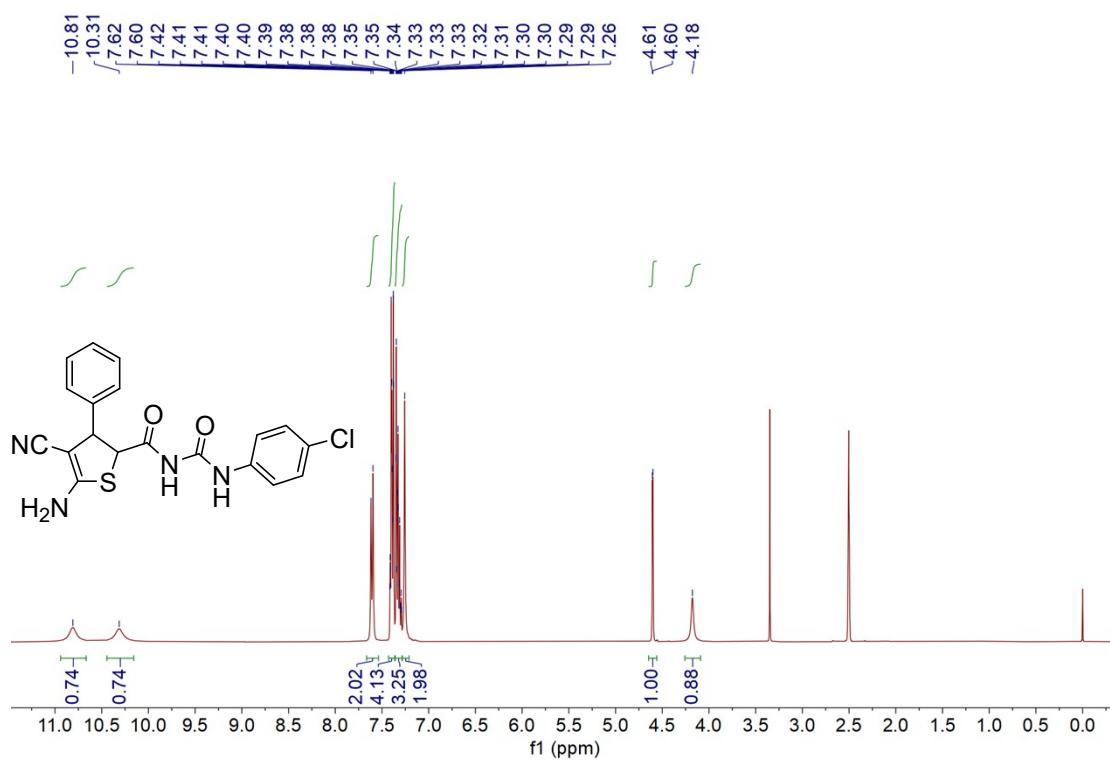


5p: 5-amino-4-cyano-3-phenyl-N-(p-tolylcarbamoyl)-2,3-dihydrothiophene-2-carboxamide.



5q: 5-amino-N-((4-chlorophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-

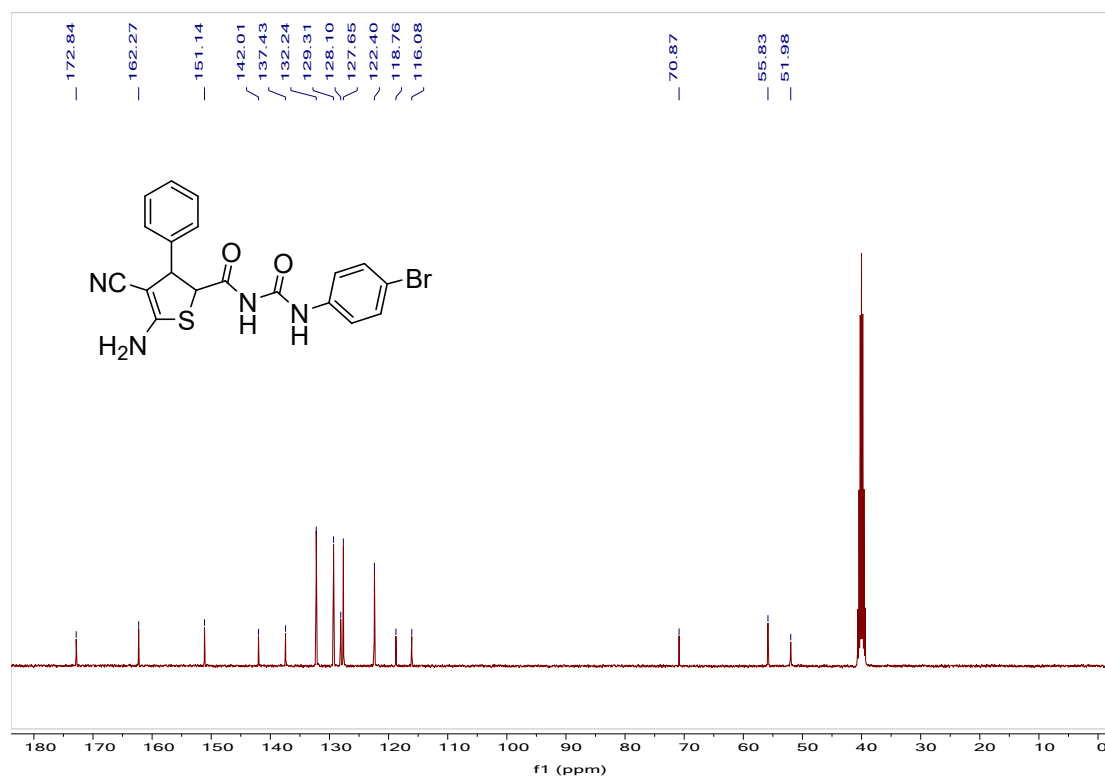
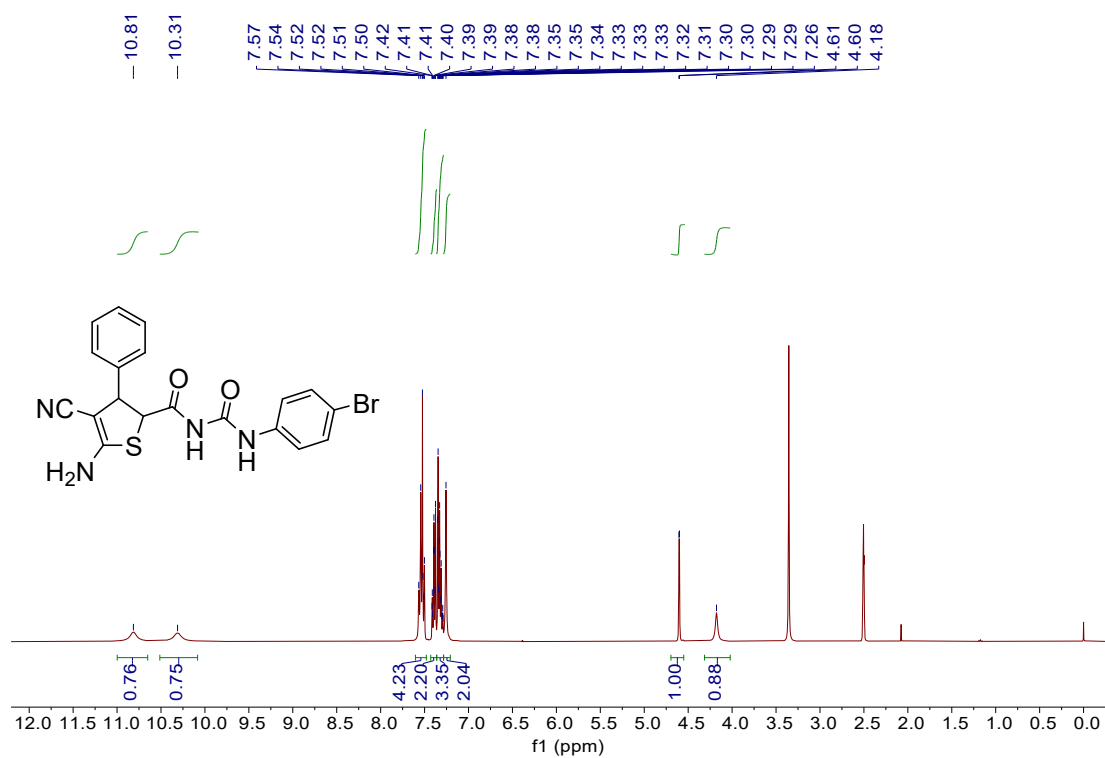
carboxamide.



5r: 5-amino-N-((4-bromophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-

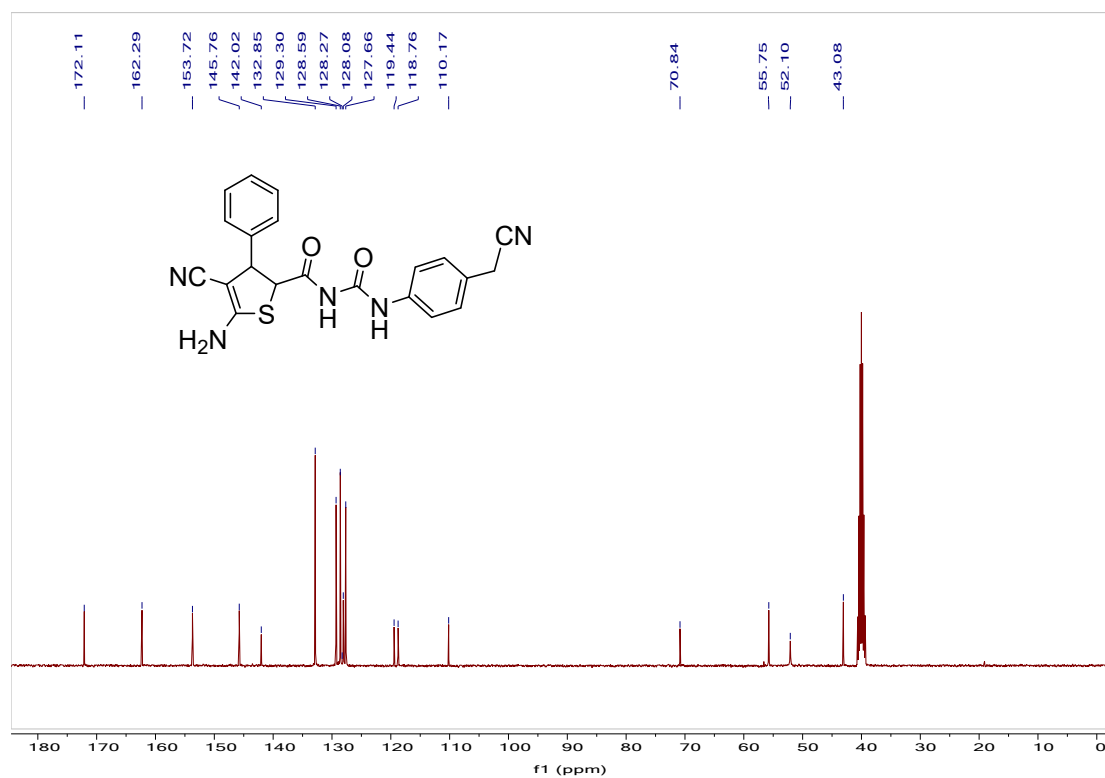
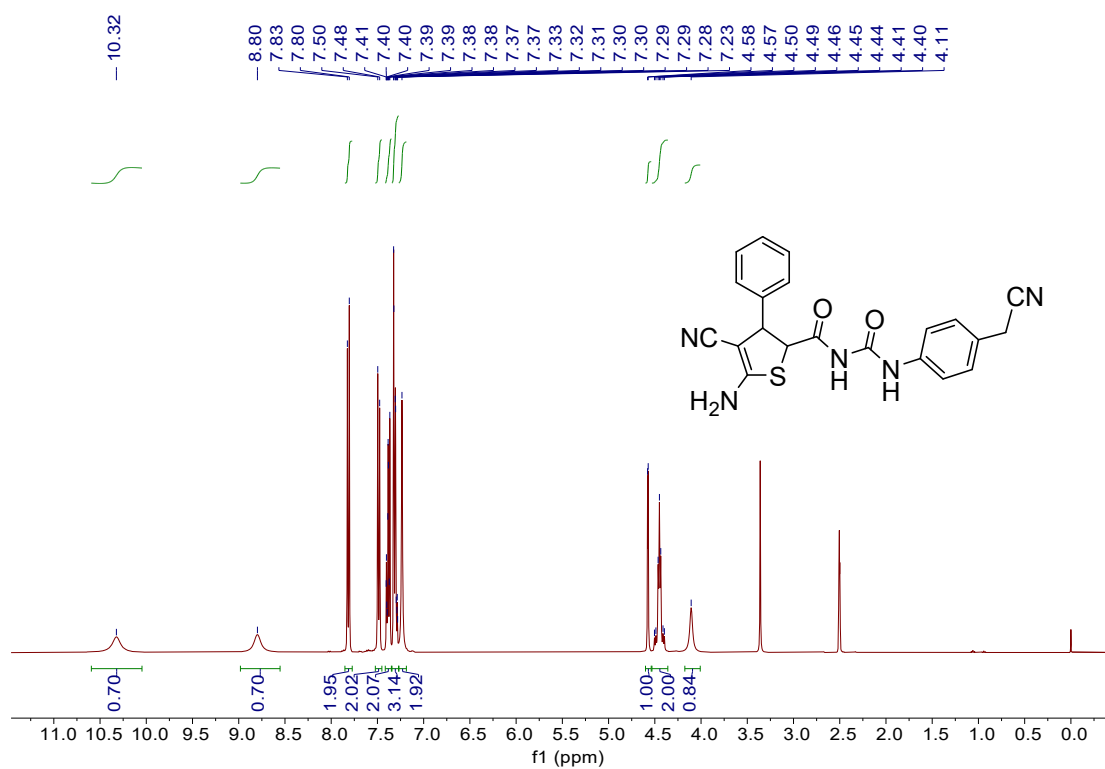


carboxamide.



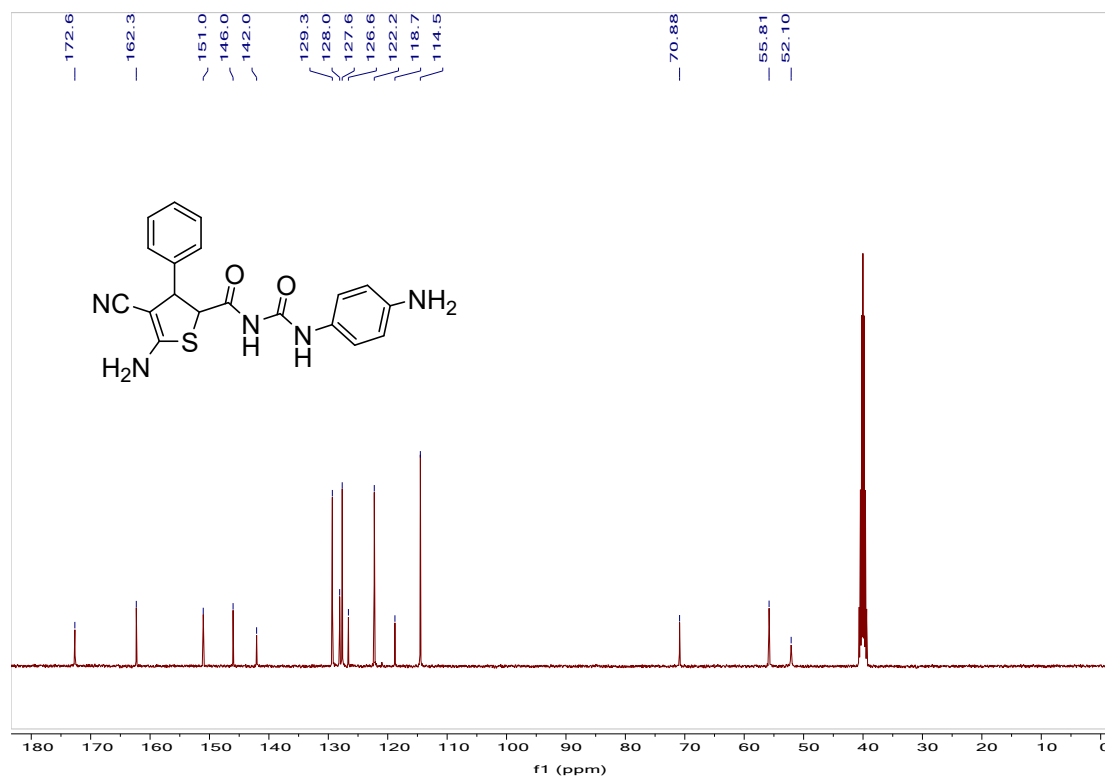
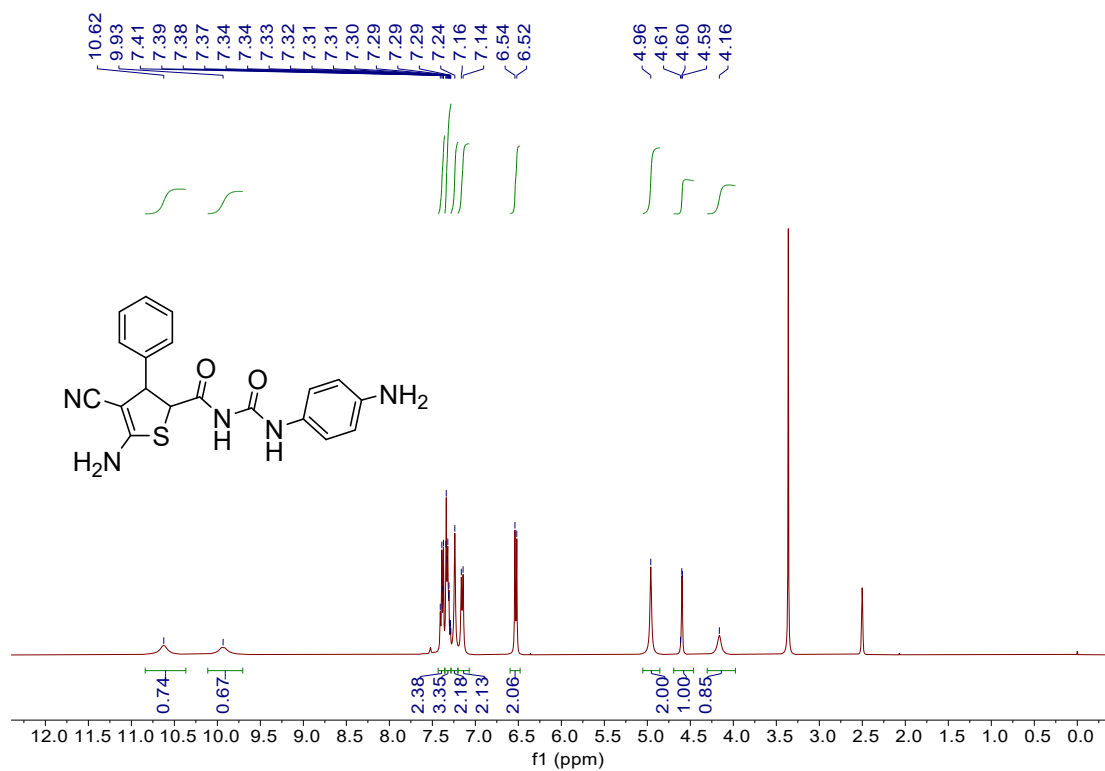
5s: 5-amino-4-cyano-N-((4-(cyanomethyl)phenyl)carbamoyl)-3-phenyl-2,3-dihydrothiophene-2-

carboxamide.

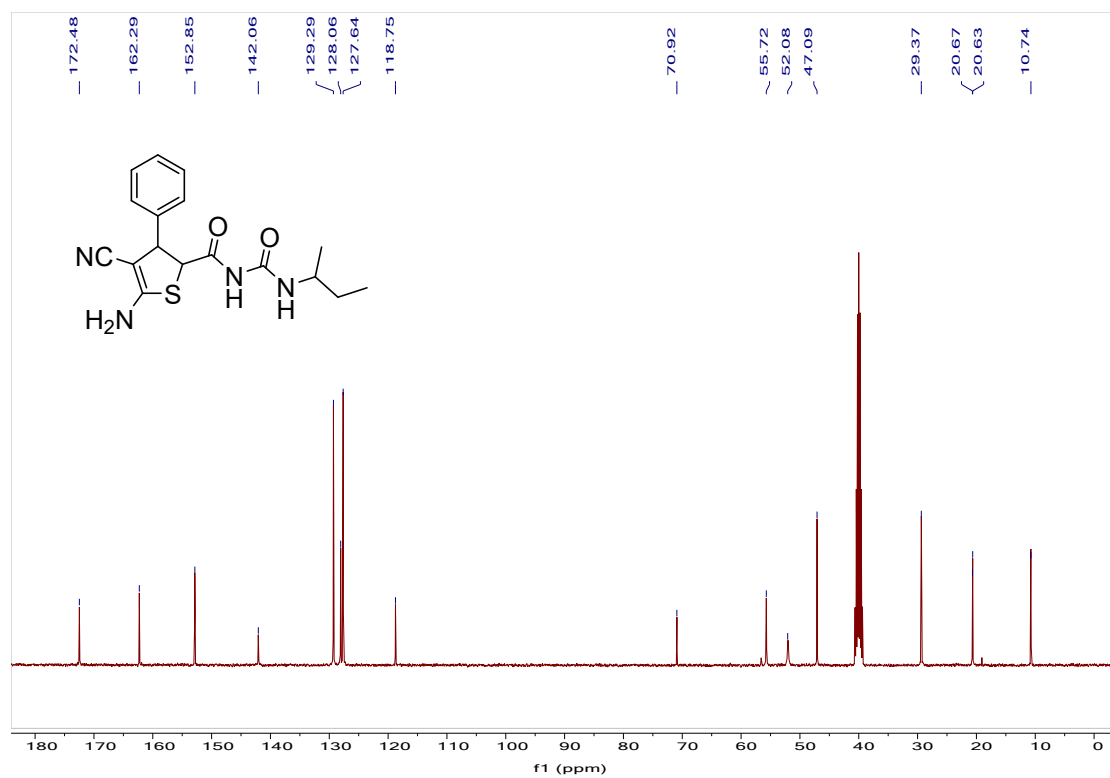
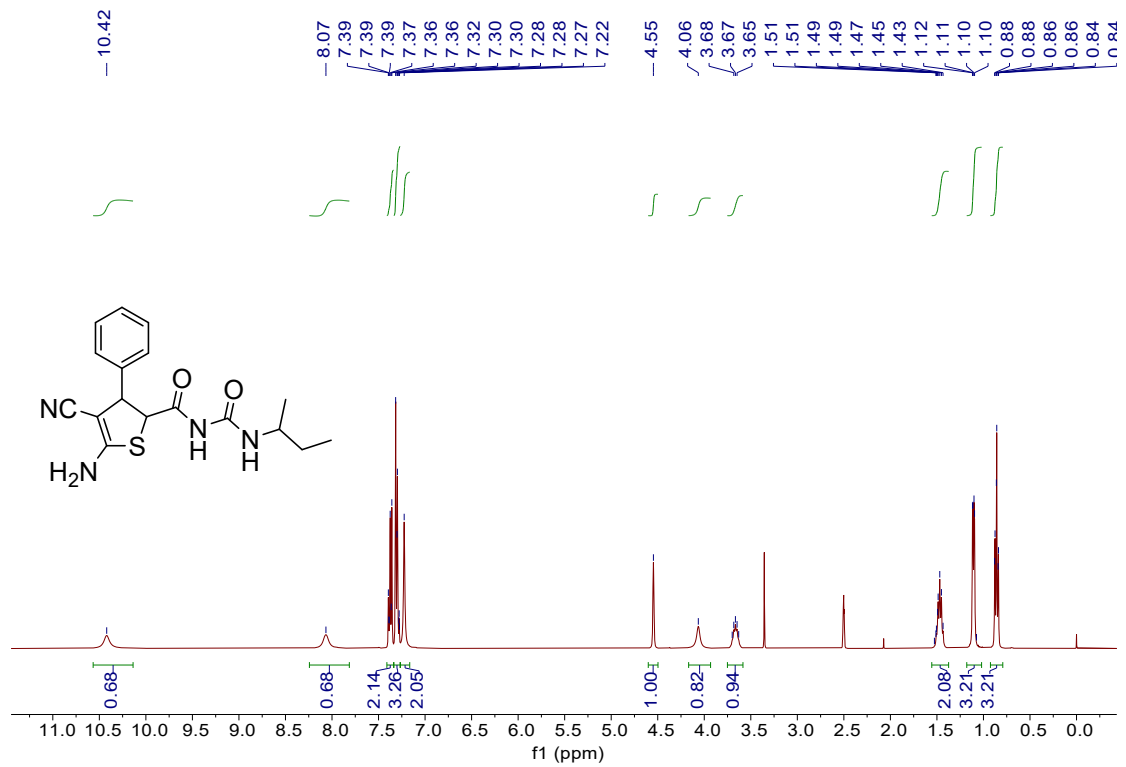


5t: 5-amino-N-((4-aminophenyl)carbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-

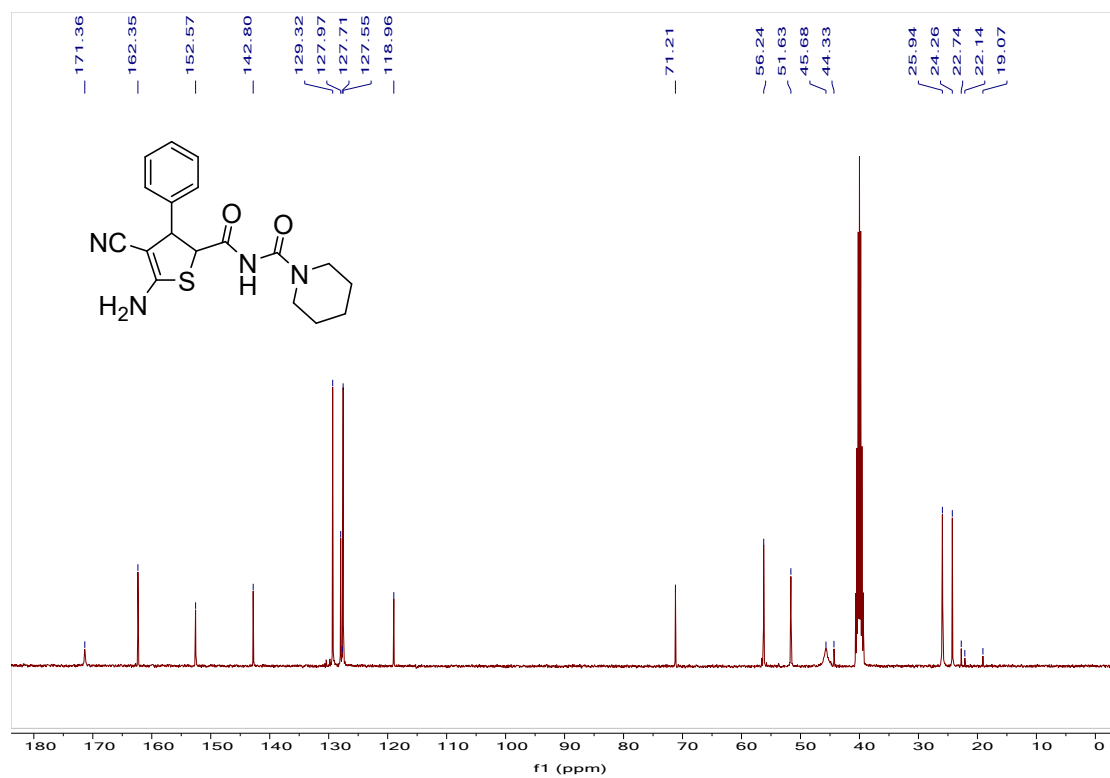
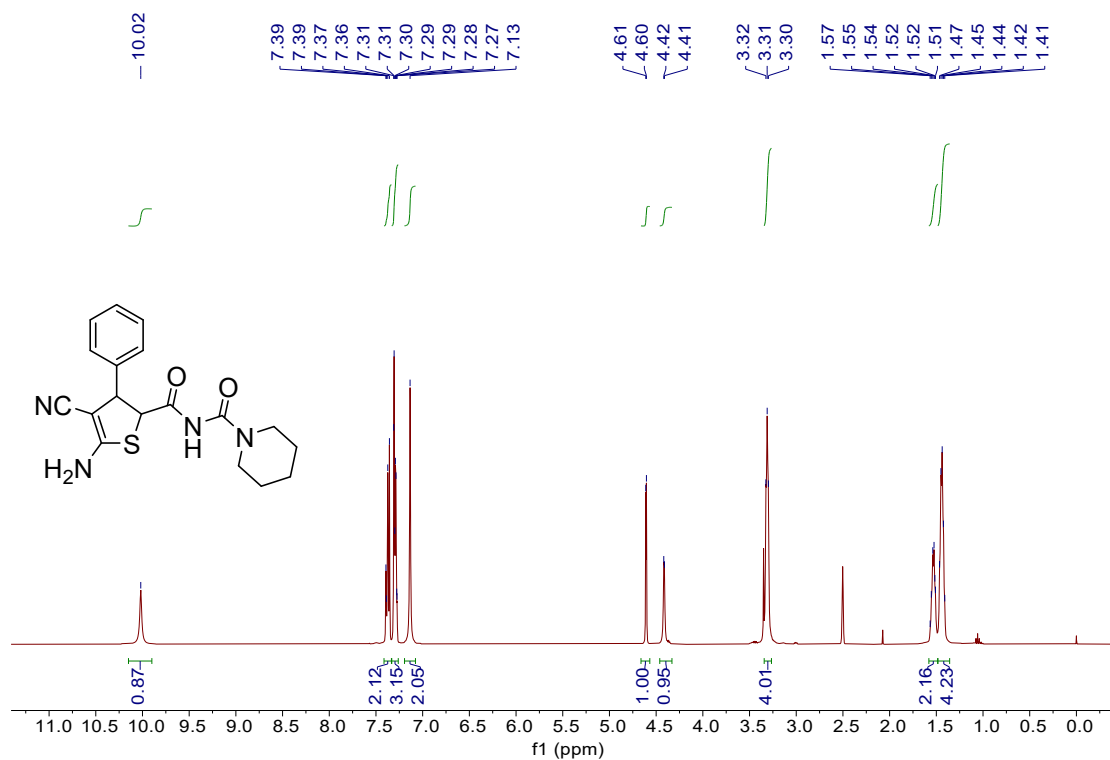
carboxamide.



**5u: 5-amino-N-(sec-butylcarbamoyl)-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carboxamide.**

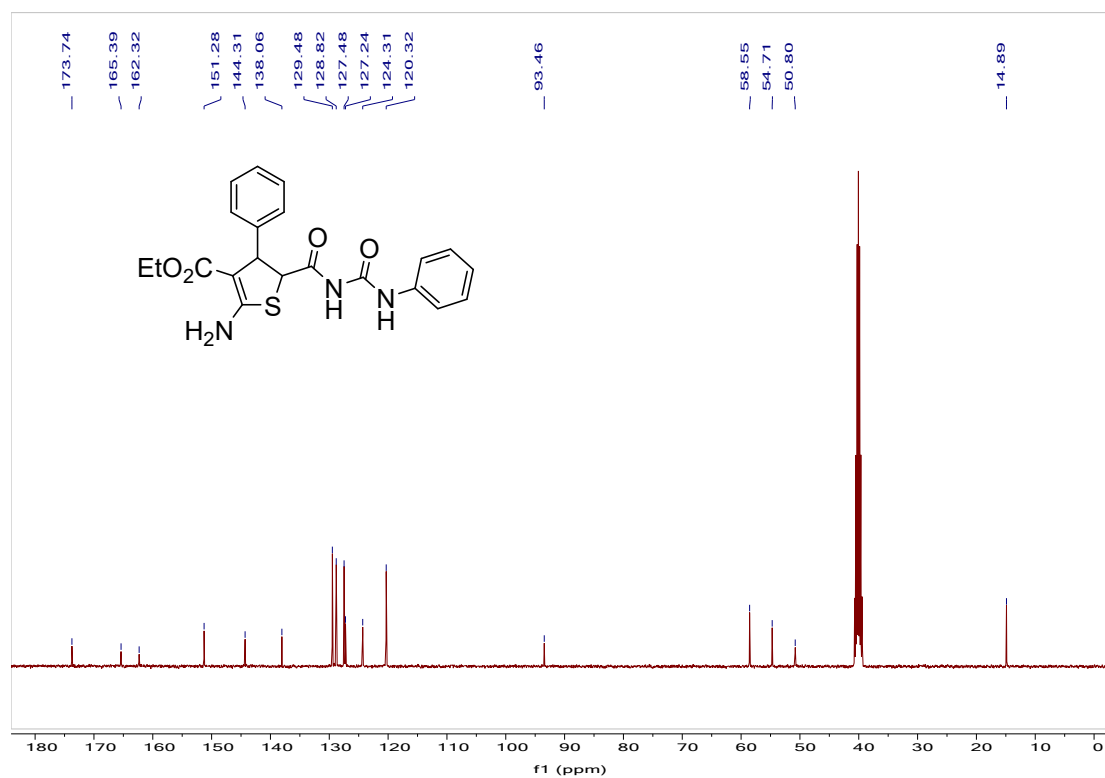
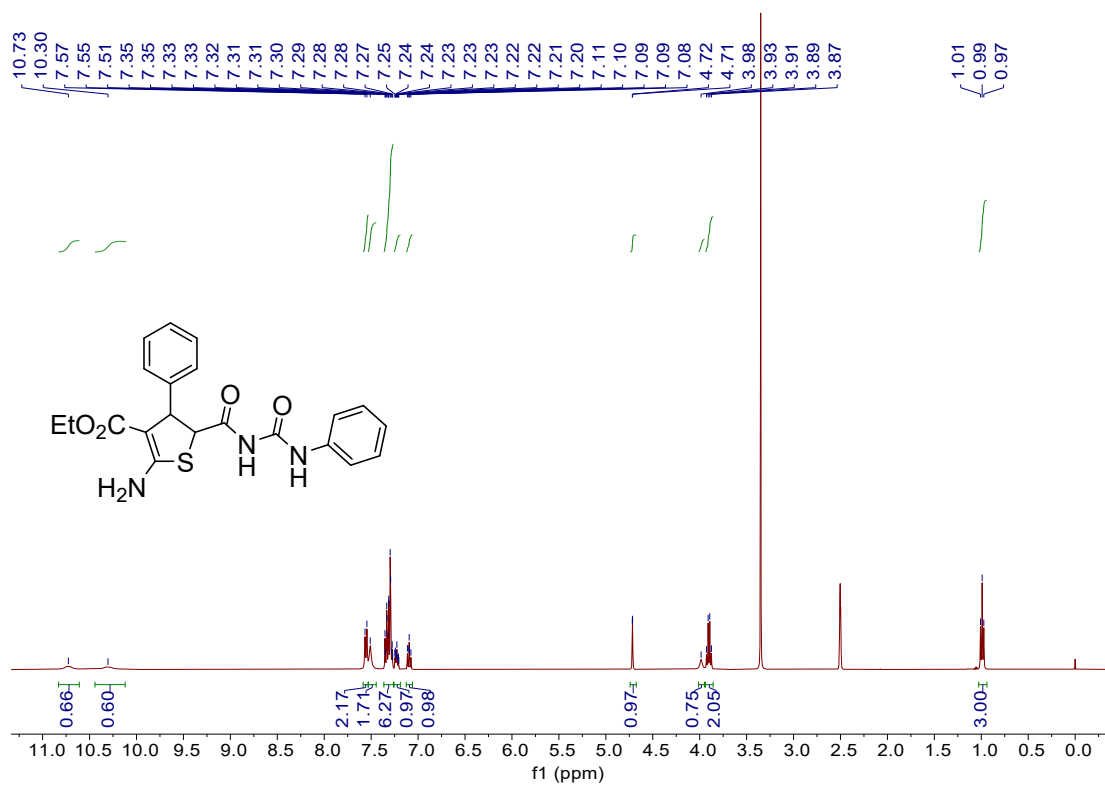


5v: N-(5-amino-4-cyano-3-phenyl-2,3-dihydrothiophene-2-carbonyl)piperidine-1-carboxamide.

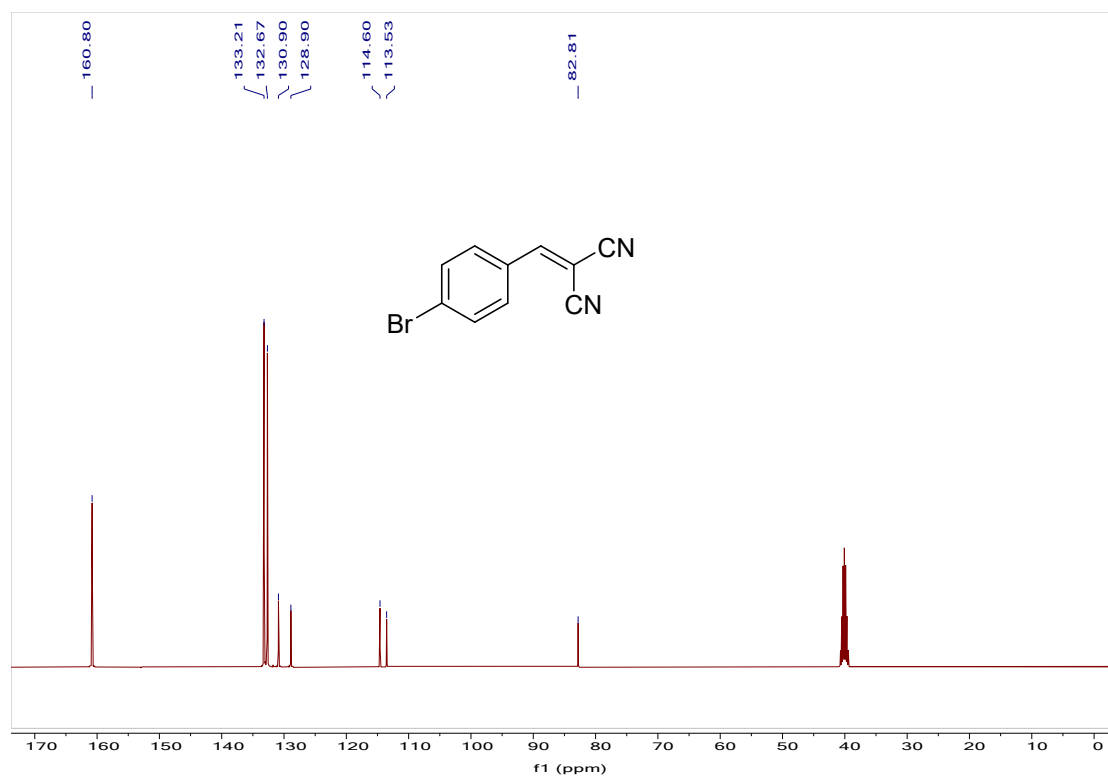
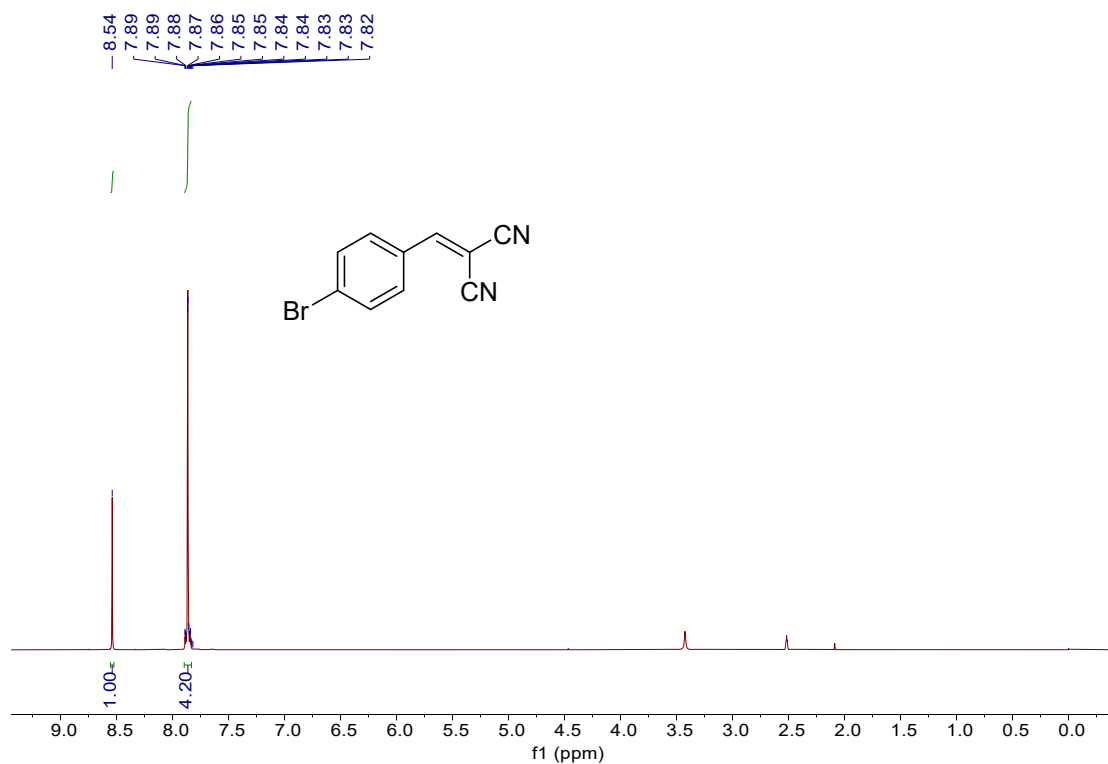


**5w:** Ethyl-2-amino-4-phenyl-5-((phenylcarbamoyl)carbamoyl)-4,5-dihydrothiophene-3-

carboxylate.



Intermediate I: 2-(4-bromobenzylidene)malononitrile.



**Intermediate II: 2-((4-bromophenyl)(2,5-dioxothiazolidin-4-yl)methyl)malononitrile.**

