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The first Catalytic Direct C-H arylation on C2 and C3 of thiophene ring applied to thieno-pyridines, -pyrimidines and –pyrazines

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Experimental Section

1. Materials and Methods

1.1. General Methods

All reagents were purchased from commercial suppliers and were used without further purification. THF was dried with a dry station GT S100 instantaneously prior to use. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230 - 400 mesh, 0.040 - 0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds were recorded on a Thermo Scientific Nicolet iS10. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker avance II spectrometer at 250 MHz (^{13}C, 62.9 MHz) and on a Bruker avance III HD nanobay 400 MHz (^{13}C 100.62 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) or deterred solvent (MeOH-d_4, Chloroform-d) as internal standard. The following abbreviations are used for the proton spectra multiplicities: b : broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HRMS (ESI)) were performed on a Maxis Bruker 4G by the "Federation de Recherche" ICOA/CBM (FR2708) platform.

1.2. General procedure for synthesis of thieno[3,2-d]pyrimidin-4-amines (7-13)

A solution of 4-chlorothieno[3,2-d]pyrimidine (**6**) (100 mg; 0.586 mmol) and amine derivative (1.172 mmol) was heated at 100 °C in dry toluene, for 20-30min. The reaction was followed by TLC. After completion, the mixture was concentrated under vacuum. The solid obtained was purified by column chromatography. The solvent polarity was increased via a gradient from neat petroleum ether to a mixture of AcOEt/petroleum ether.

4-(thieno[3,2-d]pyrimidin-4-yl)morpholine (7) [30]

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 50% AcOEt/petroleum ether, compound **7** was obtained as a white solid (111 mg, 86%), m.p. 141 – 143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 – 3.82 (m, 4H), 3.91 – 3.97 (m, 4H), 7.39 (d, *J* = 5.6 Hz, 1H), 7.69 (d, *J* = 5.6 Hz, 1H), 8.56 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.3 (2xCH), 66.7 (2xCH), 114.4 (C), 125.3 (CH), 131.5 (CH), 154.2 (CH), 158.2 (C), 161.6 (C) ppm.

N,N-dibutylthieno[3,2-d]pyrimidin-4-amine (8)

From compound **6** (100 mg; 0.586 mmol), di-n-butylamine (152 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 40% AcOEt/petroleum ether, compound **8** was obtained as a white solid (148 mg, 96%), m.p. 121 – 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.4 Hz, 6H), 1.32 – 1.40 (m, 4H), 1.64 (dd, *J* = 6.6, 16.9 Hz, 4H), 3.63 – 3.68 (m, 4H), 7.31 (d, *J* = 5.6 Hz, 1H), 7.62 (d, *J* = 5.6 Hz, 1H), 8.45 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (2xCH), 20.1 (2xCH), 30.8 (2xCH), 49.3 (2xCH), 113.3 (C), 124.9 (CH), 130.9 (CH), 154.3 (CH), 157.5 (C), 160.6 (C) ppm. HRMS: calcd. for $C_{14}H_{22}N_3S$ $[M+H]^+$ 264.1529, found 264.1532.

4-(piperidin-1-yl)thieno[3,2-d]pyrimidine (9)

From compound **6** (100 mg; 0.586 mmol), piperidine (100 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 40% AcOEt/petroleum ether, compound **9** was obtained as a white solid (105 mg, 82%), m.p. 154 – 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 – 1.61 (m, 6H), 3.87 – 3.90 (m, 4H), 7.33 (d, *J* = 5.6 Hz, 1H), 7.62 (d, *J* = 5.6 Hz, 1H), 8.49 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7 (CH), 26.1 (2xCH), 47.4 (2xCH),

114.2 (C), 125.1 (CH), 131.1 (CH), 154.2 (CH), 157.8 (C), 161.0 (C) ppm. CAS: 679394-37-7; SIA Enamine.

N-(2-(trifluoromethyl)phenyl)thieno[3,2-d]pyrimidin-4-amine (10)

From compound **6** (100 mg; 0.586 mmol), 2-trifluoromethylaniline (189 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 40% AcOEt/petroleum ether, compound **10** was obtained as a white solid (104 mg, 60%), m.p. 122 – 124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.70 – 7.76 (m, 2H), 7.99 (d, *J* = 8.1 Hz, 1H), 8.70 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 122.5 (C), 124.2 (C), 124.5 (C), 125.1 (CH), 126.0 (CH), 126.7 (CH), 127.8 (CH), 132.6 (CH), 132.9 (CH), 135.3 (C), 154.5 (CH), 155.9 (C), 161.5 (C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 ppm. HRMS: calcd. for $C_{13}H_9F_3N_3S$ $[M+H]^+$ 296.0464, found 296.0467.

N-(4-methoxyphenyl)thieno[3,2-d]pyrimidin-4-amine (11) [31]

From compound **6** (100 mg; 0.586 mmol), 4-methoxyaniline (144 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 45% AcOEt/petroleum ether, compound **11** was obtained as a white solid (130 mg, 86%), m.p. 154-156 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.92 – 6.96 (m, 2H), 7.36 (d, *J* = 5.4 Hz, 1H), 7.38 – 7.42 (m, 2H), 7.64 (d, *J* = 5.4 Hz, 1H), 7.93 (s, 1H), 8.60 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 55.5 (CH), 114.3 (2xCH), 114.4 (C), 124.6 (2xCH), 128.2 (CH), 129.7 (C), 133.2 (CH), 154.6 (CH), 157.3 (C), 158.6 (C), 161.2 (C) ppm.

methyl 4-(thieno[3,2-d]pyrimidin-4-ylamino)benzoate (12)

From compound **6** (100 mg; 0.586 mmol), methyl-4-aminobenzoate (177 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 45% AcOEt/petroleum ether, compound **12** was obtained as a white solid (111 mg, 67%), m.p. 227 – 229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.97 (d, *J* = 19.8 Hz, 1H), 7.51 (d, *J* = 5.4 Hz, 1H), 7.79 – 7.84 (m, 3H), 8.09 (d, *J* = 8.7 Hz, 2H), 8.82 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.7 (C), 52.1 (CH), 116.2 (C), 120.5 (2xCH), 125.6 (CH), 130.9 (2xCH), 132.1 (CH), 142.4 (C), 154.6 (CH), 154.9 (C), 161.2 (C), 166.6 (C) ppm. HRMS: calcd. for $C_{14}H_{12}N_3O_2S$ $[M+H]^+$ 286.0645, found 286.0646.

N-((3s,5s,7s)-adamantan-1-yl)thieno[3,2-d]pyrimidin-4-amine (13)

From compound **6** (100 mg; 0.586 mmol), adamantylamine (177 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 50% AcOEt/petroleum ether, compound **13** was obtained as a white solid (114 mg, 68%), m.p. 238 – 240 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 – 1.77 (m, 6H), 2.14 (s, 3H), 2.24 (d, *J* = 2.6 Hz, 6H), 4.52 (s, 1H), 7.36 (d, *J* = 5.4 Hz, 1H), 7.61 (d, *J* = 5.4 Hz, 1H), 8.57 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.6 (3xCH), 36.4 (3xCH), 41.9 (3xCH), 53.6 (C), 115.6 (C), 125.6 (CH), 129.7 (CH), 154.6 (CH), 156.9 (C), 159.5 (C) ppm. HRMS: calcd. for $C_{16}H_{20}N_3S$ $[M+H]^+$ 286.1372, found 286.1375**.**

General procedure for synthesis of 14-23 from 6 (one pot 2 steps "C-2" CH activation)

A solution of 4-chlorothieno[3,2-d]pyrimidine (**6**) (100 mg; 0.586 mmol) and morpholine (1.172 mmol) was heated at 100 °C in dry toluene, for 20 min. Then, $Pd(OAc)_2$ (0.059 mmol), $TTBP{\cdot}HBF_4$ (0.117 mmol), K_2CO_3 (1.172 mmol) and bromo derivative (1.172 mmol) were added. The reaction mixture was stirred at same temperature for 46h. The reaction was followed by TLC. After completion, the mixture was concentrated under vacuum. The solid obtained was purified by column chromatography. The solvent polarity was increased via a gradient from neat petroleum ether to a mixture of AcOEt/petroleum ether.

4-(6-phenylthieno[3,2-d]pyrimidin-4-yl)morpholine (14)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), bromobenzene (184 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 27% AcOEt/petroleum ether, compound **14** was obtained as a yellow solid (122 mg, 70%), m.p. 149 – 151 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 3.86 – 3.89 (m, 4H), 3.99 – 4.03 (m, 4H), 7.41 – 7.49 (m, 3H), 7.61 (s, 1H), 7.71 – 7.76 (m, 2H), 8.59 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.4 (2xCH), 66.8 (2xCH), 114.2 (C), 120.5 (CH), 126.6 (2xCH), 129.2 (2xCH), 129.6 (CH), 132.8 (C), 149.5 (C), 154.5 (CH), 157.9 (C), 162.3 (C) ppm. HRMS: calcd. for $C_{16}H_{16}N_3OS$ $[M+H]^+$ 298.1009, found 298.1008.

4-(6-(p-tolyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (16)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), 4-bromotoluene (200 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 40% AcOEt/petroleum ether, compound **17** was obtained as a white solid (106 mg, 58%), m.p. 144 – 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 6.98 – 6.93 (m, 3H), 3.71 – 3.69 (m, 4H), 3.58 – 3.55 (m, 4H), 2.11 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.4 (C), 157.9 (C), 154.5 (CH), 149.7 (C), 139.9 (C), 129.9 (2xCH), 126.5 (2xCH), 119.9 (CH), 113.9 (C), 100.0 (C), 66.8 (2xCH), 46.4 (2xCH), 21.4 (CH) ppm. HRMS: calcd. for $C_{17}H_{18}N_3OS$ $[M+H]^+$ 312.1165, found 312.1165.

4-(6-(3,4,5-trimethoxyphenyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (17)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), 5-bromo-1,2,3-trimethoxybenzene (290 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 35% AcOEt/petroleum ether, compound **18** was obtained as a white solid (143 mg, 63%), m.p. 191 – 193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 – 3.89 (m, 4H), 3.90 (s, 3H), 3.95 (s, 6H), 3.99 – 4.02 (m, 4H), 6.91 (s, 2H), 7.53 (s, 1H), 8.59 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.4 (2xCH), 56.3 (2xCH), 61.0 (CH), 66.8 (2xCH), 104.1 (2xCH), 114.0 (C), 120.4 (CH), 128.4 (C), 139.6 (C), 149.5 (C), 153.7 (2xC), 154.5 (CH), 157.8 (C), 162.3 (C) ppm. HRMS: calcd for $C_{19}H_{22}N_3O_4S$ $[M+H]^+$ 388.1326, found 388.1327.

methyl 4-(4-morpholinothieno[3,2-d]pyrimidin-6-yl)benzoate (18)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), methyl 4-bromobenzoate (252 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 40% AcOEt/petroleum ether, compound **19** was obtained as a yellow solid (127 mg, 61%), m.p. 195 – 197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (dd, *J* = 4.8, 3.1 Hz, 4H), 3.96 (s, 3H), 4.00 – 4.03 (m, 4H), 7.70 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.61 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.4 (2xCH), 52.3 (CH), 66.8 (2xCH), 122.0 (CH), 125.3 (C), 126.4 (2xCH), 130.4 (2xCH), 131.5 (C), 136.9 (C), 147.8 (C), 154.2 (C), 154.7 (CH), 157.9 (C), 166.4 (C) ppm. HRMS: calcd. for $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ 356.1063, found 356.1065.

4-(6-(4-ethylphenyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (19)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), 1-bromo-4-ethylbenzene (217 mg; 1.172 mmol) and after purification by column chromatography using

a solvent gradient from neat petroleum ether to 40% AcOEt/petroleum ether, compound **20** was obtained as a white solid (103 mg, 54%), m.p. 186 – 188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 7.6 Hz, 3H), 2.68 – 2.73 (m, 2H), 3.86 – 3.89 (m, 4H), 4.00 – 4.04 (m, 4H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.59 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 8.58 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.4 (CH), 28.7 (CH), 46.5 (2xCH), 66.8 (2xCH), 100.0 (C), 112.1 (C), 119.0 (C), 126.6 (2xCH), 127.6 (CH), 128.7 (2xCH), 130.0 (C), 155.3 (CH), 160.1 (C), 173.1 (C) ppm. HRMS: calcd. for $C_{18}H_{20}N_3OS$ $[M+H]^+$ 326.1322, found 326.1320.

4-(6-(benzo[b]thiophen-2-yl)thieno[3,2-d]pyrimidin-4-yl)morpholine (20)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), 2-bromobenzothiophene (250 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 55% AcOEt/petroleum ether, compound **21** was obtained as a yellow solid (89 mg, 43%), m.p. 209 – 211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 – 3.89 (m, 4H), 3.99 – 4.02 (m, 4H), 7.37 – 7.40 (m, 2H), 7.58 (s, 1H), 7.63 (s, 1H), 7.79 – 7.85 (m, 2H), 8.60 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.4 (2xCH), 66.8 (2xCH), 114.1 (C), 121.9 (CH), 122.3 (CH), 122.6 (CH), 124.2 (CH), 125.1 (CH), 125.7 (CH), 135.4 (C), 139.8 (C), 140.0 (C), 142.4 (C), 154.7 (CH), 157.8 (C), 161.9 (C) ppm. HRMS: calcd. for $C_{18}H_{16}N_3OS_2$ $[M+H]^+$ 354.0729, found 354.0731.

4-(6-(naphthalen-1-yl)thieno[3,2-d]pyrimidin-4-yl)morpholine (21)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), 1-bromonaphthalene (242 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 50% AcOEt/petroleum ether, compound **22** was obtained as a yellow solid (171 mg, 84%), m.p. 114 – 116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 – 3.88 (m, 4H), 4.01 – 4.04 (m, 4H), 7.50 – 7.57 (m, 3H), 7.59 (s, 1H), 7.63 – 7.66 (m, 1H), 7.94 (dd, *J* = 5.3, 8.4 Hz, 2H), 8.21 (dd, *J* = 2.8, 6.7 Hz, 1H), 8.66 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.43 (2xCH), 66.8 (2xCH), 115.0 (C), 125.1 (CH), 125.2 (CH), 125.2 (CH), 126.5 (CH), 127.1 (CH), 128.3 (CH), 128.5 (CH), 129.9 (CH), 130.8 (C), 131.3 (C), 133.8 (C), 147.8 (C), 154.5 (CH), 157.9 (C), 161.8 (C) ppm. HRMS: calcd. for $C_{20}H_{18}N_3OS$ $[M+H]^+$ 348.1165, found 348.1166.

4-(4-morpholinothieno[3,2-d]pyrimidin-6-yl)benzonitrile (22)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), 4-bromobenzonitrile (213 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 60% AcOEt/petroleum ether, compound **23** was obtained as a yellow solid (104 mg, 55%), m.p. 255 – 257 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.70 (s, 1H), 4.01 (d, *J* = 5.1 Hz, 4H), 3.89 – 3.86 (m, 4H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.0 (C), 157.9 (C), 154.8 (CH), 146.6 (C), 137.1 (C), 132.9 (2xCH), 127.0 (2xCH), 122.8 (CH), 118.2 (C), 114.9 (C), 112.9 (C), 66.7 (2xCH), 46.4 (2xCH) ppm. HRMS: calcd. for $C_{17}H_{15}N_4OS$ $[M+H]^+$ 323.0961, found 323.0957.

N-((3s,5s,7s)-adamantan-1-yl)-6-phenylthieno[3,2-d]pyrimidin-4-amine (23)

From compound **6** (100 mg; 0.586 mmol), adamantylamine (177 mg; 1.172 mmol) followed by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), bromobenzene (184 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 25% AcOEt/petroleum ether, compound **24** was obtained as a yellow solid (142 mg, 67%), m.p. 201 – 203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 – 1.79 (m, 6H), 2.22 (d, *J* = 40.6 Hz, 9H), 4.47 (s, 1H), 7.37 – 7.48 (m, 3H), 7.55 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H),

8.57 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.7 (3xCH), 36.4 (3xCH), 42.0 (3xCH), 53.6 (C), 115.3 (C), 121.0 (CH), 126.6 (2xCH), 129.1 (2xCH), 129.3 (CH), 133.3 (C), 148.2 (C), 154.8 (CH), 156.5 (C), 160.2 (C) ppm. HRMS: calcd. for $C_{22}H_{24}N_3S$ $[M+H]^+$ 362.1685, found 362.1684.

General procedure for synthesis of 15 and 24 from 6 (one pot 3 steps "C-2" and "C-3" CH activation)

A solution of 4-chlorothieno[3,2-d]pyrimidine (**6**) (100 mg; 0.586 mmol) and morpholine (1.172 mmol) was heated at 100 °C in dry toluene, for 20 min. Then, $Pd(OAc)_2$ (0.059 mmol), $TTBP{\cdot}HBF_4$ (0.117 mmol), K_2CO_3 (1.172 mmol) and bromo derivative (1.172 mmol) were added. The reaction mixture was stirred at same temperature for 46h. Then, $Pd(OAc)_2$ (0.059 mmol), $TTBP{\cdot}HBF_4$ (0.117 mmol), K_2CO_3 (1.172 mmol) and bromo derivative (1.172 mmol) were added. The reaction mixture was stirred at 130 °C for 46h. The reaction was followed by TLC. After completion, the mixture was concentrated under vacuum. The solid obtained was purified by column chromatography. The solvent polarity was increased via a gradient from neat petroleum ether to a mixture of AcOEt/petroleum ether.

4-(6,7-diphenylthieno[3,2-d]pyrimidin-4-yl)morpholine (15)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed 2 times by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), bromobenzene (184 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 3% AcOEt/petroleum ether, compound **15** was obtained as a yellow solid (105 mg, 48 %), m.p. 182 – 184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 – 3.85 (m, 4H), 3.97 – 4.00 (m, 4H), 7.23 – 7.37 (m, 10H), 8.64 (s, 1H)ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.5 (2xCH), 66.8 (2xCH), 114.4 (C), 127.7 (CH), 128.5 (2xCH), 128.7 (2xCH), 128.8 (CH), 129.5 (2xCH), 130.7 (2xCH), 133.1 (C), 133.6 (2xC), 145.0 (C), 154.7 (CH), 158.0 (C), 161.0 (C) ppm. HRMS: calcd. for $C_{22}H_{20}N_3OS$ $[M+H]^+$ 374.1322, found 374.1320.

4-(4-morpholino-6-phenylthieno[3,2-d]pyrimidin-7-yl)benzonitrile (24)

From compound **6** (100 mg; 0.586 mmol), morpholine (102 mg; 1.172 mmol) followed 2 times by $Pd(OAc)_2$ (13 mg; 0.059 mmol), TTBP · HBF_4 (34 mg; 0.117 mmol), K_2CO_3 (162 mg; 1.172 mmol), bromobenzene (184 mg; 1.172 mmol) or 4-bromobenzonitrile (213 mg; 1.172 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 9% AcOEt/petroleum ether, compound **25** was obtained as a yellow solid (84 mg, 36%), m.p. 227 – 229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 – 3.90 (m, 4H), 4.02 – 4.05 (m, 4H), 7.28 – 7.40 (m, 5H), 7.53 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 8.63 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 46.5 (2xCH), 66.8 (2xCH), 111.3 (C), 114.5 (C), 118.9 (C), 129.0 (2xCH), 129.4 (CH), 129.5 (2xCH), 131.6 (2xCH), 160.3 (C), 132.1 (2xCH), 132.3 (C), 138.6 (C), 146.6 (C), 154.8 (CH), 158.0 (C) ppm. HRMS: calcd. for $C_{23}H_{19}N_4OS$ $[M+H]^+$ 399.1274, found 399.1271.

General procedure for synthesis of 25-29 from 2

A solution of **2** (50 mg; 0.237 mmol), $Pd(OAc)_2$ (0.024 mmol), TTBP · HBF_4 (0.047 mmol), K_2CO_3 (0.473 mmol) and bromo derivative (0.473 mmol) was heated at 130 °C in dry toluene, for 46h. The reaction was followed by TLC. After completion, the mixture was concentrated under vacuum. The solid obtained was purified by column chromatography. The solvent polarity was increased via a gradient from neat petroleum ether to a mixture of AcOEt/petroleum ether.

2,3-diphenylthieno[3,2-b]pyridine (25) [11]

From compound **2** (50 mg; 0.237 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.473 mmol), bromobenzene (74 mg; 0.473 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 4% AcOEt/petroleum ether, compound **26** was obtained as a white solid (62 mg, 91%), m.p. 139 – 141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.45 (m, 11H), 8.21 (dd, *J* = 1.6, 8.1Hz, 1H), 8.73 (dd, J = 1.6, 4.6Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 118.9 (CH), 127.6 (CH), 128.4 (CH), 128.4 (2xCH), 128.5 (2xCH), 128.6 (2xCH), 129.9 (CH), 130.8 (2xCH), 133.2 (C), 133.6 (C), 134.1 (C), 134.2 (C), 143.7 (C), 147.6 (CH), 155.5 (C) ppm.

2-phenyl-3-(p-tolyl)thieno[3,2-b]pyridine (26) [11]

From compound **2** (50 mg; 0.237 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.473 mmol), 4-bromotoluene (81 mg; 0.473 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 3% AcOEt/petroleum ether, compound **28** was obtained as a white solid (46 mg, 65%), m.p. 138 – 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.20-7.41 (m, 10H), 8.18 (dd, J = 1.6, 8.1 Hz, 1H), 8.71 (dd, J = 1.6, 4.6 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4 (CH), 118.8 (CH), 128.3 (CH), 128.5 (2xCH), 129.2 (2xCH), 129.5 (2xCH), 129.8 (CH), 130.6 (2xCH), 131.2 (C), 133.1 (C), 133.6 (C), 134.3 (C), 137.2 (C), 143.2 (C), 147.5 (CH), 155.7 (C) ppm.

methyl 4-(2-phenylthieno[3,2-b]pyridin-3-yl)benzoate (27)

From compound **2** (50 mg; 0.237 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.473 mmol), methyl 4-bromobenzoate (102 mg; 0.473 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 3% AcOEt/petroleum ether, compound **29** was obtained as a white solid (73 mg, 89%), m.p. 173 – 175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.32 (ddt, *J* = 4.4, 8.1, 12.3 Hz, 6H), 7.53 – 7.57 (m, 2H), 8.04 – 8.08 (m, 2H), 8.20 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.72 (dd, *J* = 1.5, 4.6 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 52.1 (CH), 119.1 (CH), 128.7 (CH), 128.7 (2xCH), 129.0 (C), 129.6 (2xCH), 129.7 (2xCH), 130.0 (CH), 130.9 (2xCH), 132.4 (C), 133.3 (C), 133.7 (C), 139.2 (C), 144.8 (C), 147.7 (CH), 155.0 (C), 167.1 (C) ppm. HRMS: calcd. for $C_{21}H_{16}NO_2S$ $[M+H]^+$ 346.0896, found 346.0903.

3-(4-ethylphenyl)-2-phenylthieno[3,2-b]pyridine (28)

From compound **2** (50 mg; 0.237 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.473 mmol), 1-bromo-4-ethylbenzene (87 mg; 0.473 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 2% AcOEt/petroleum ether, compound **30** was obtained as a white solid (31 mg, 41%), m.p. 118 – 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.6 Hz, 3H), 2.68 (q, *J* = 7.6 Hz, 2H), 7.21 – 7.24 (m, 2H), 7.26 – 7.32 (m, 4H), 7.34 – 7.41 (m, 4H), 8.18 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.72 (dd, *J* = 1.5, 4.6 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.3 (CH), 28.7 (CH), 118.8 (CH), 128.0 (2xCH), 128.3 (CH), 128.5 (2xCH), 129.6 (2xCH), 129.9 (CH), 130.6 (2xCH), 131.4 (C), 133.2 (C), 133.6 (C), 134.3 (C), 143.3 (C), 143.4 (C), 147.5 (CH), 155.6 (C) ppm. HRMS: calcd. for $C_{21}H_{18}NS$ $[M+H]^+$ 316.1154, found 316.1156.

4-(2-phenylthieno[3,2-b]pyridin-3-yl)benzonitrile (29) [11]

From compound **2** (50 mg; 0.237 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.473 mmol), 4-bromobenzonitrile (86 mg; 0.473 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 10% AcOEt/petroleum ether, compound **31** was obtained as a white solid (62 mg, 84%), m.p. 182-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.36 (m, 6H), 7.59 (d, J = 8.7 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 8.22 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.72 (dd, *J* = 1.5, 4.6 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 111.1 (C),

119.0 (C), 119.3 (CH), 128.9 (2xCH), 129.0 (CH), 129.6 (2xCH), 130.2 (CH), 131.3 (C), 131.6 (2xCH), 132.1 (2xCH), 133.3 (C), 139.2 (C), 145.5 (C), 147.7 (CH), 154.6 (C) ppm.

General procedure for synthesis of 30-32 from 4

A solution of **4** (50 mg; 0.235 mmol), $Pd(OAc)_2$ (0.024 mmol), TTBP · HBF_4 (0.047 mmol), K_2CO_3 (0.470 mmol) and bromo derivative (0.470 mmol) was heated at 130 °C in dry toluene, for 46h. The reaction was followed by TLC. After completion, the mixture was concentrated under vacuum. The solid obtained was purified by column chromatography. The solvent polarity was increased via a gradient from neat petroleum ether to a mixture of AcOEt/petroleum ether.

6,7-diphenylthieno[2,3-b]pyrazine (30) [11]

From compound **4** (50 mg; 0.235 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.470 mmol), bromobenzene (74 mg; 0.470 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 9% AcOEt/petroleum ether, compound **32** was obtained as a white solid (32 mg, 47%), m.p. 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.45 (m, 10H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 127.9 (CH), 128.6 (2xCH), 128.7 (2xCH), 128.9 (CH), 129.7 (2xCH), 130.6 (2xCH), 131.2 (C), 133.2 (C), 133.5 (C), 140.3 (CH), 142.0 (CH), 144.6 (C), 149.8 (C), 155.6 (C) ppm.

6-phenyl-7-(p-tolyl)thieno[2,3-b]pyrazine (31) [11]

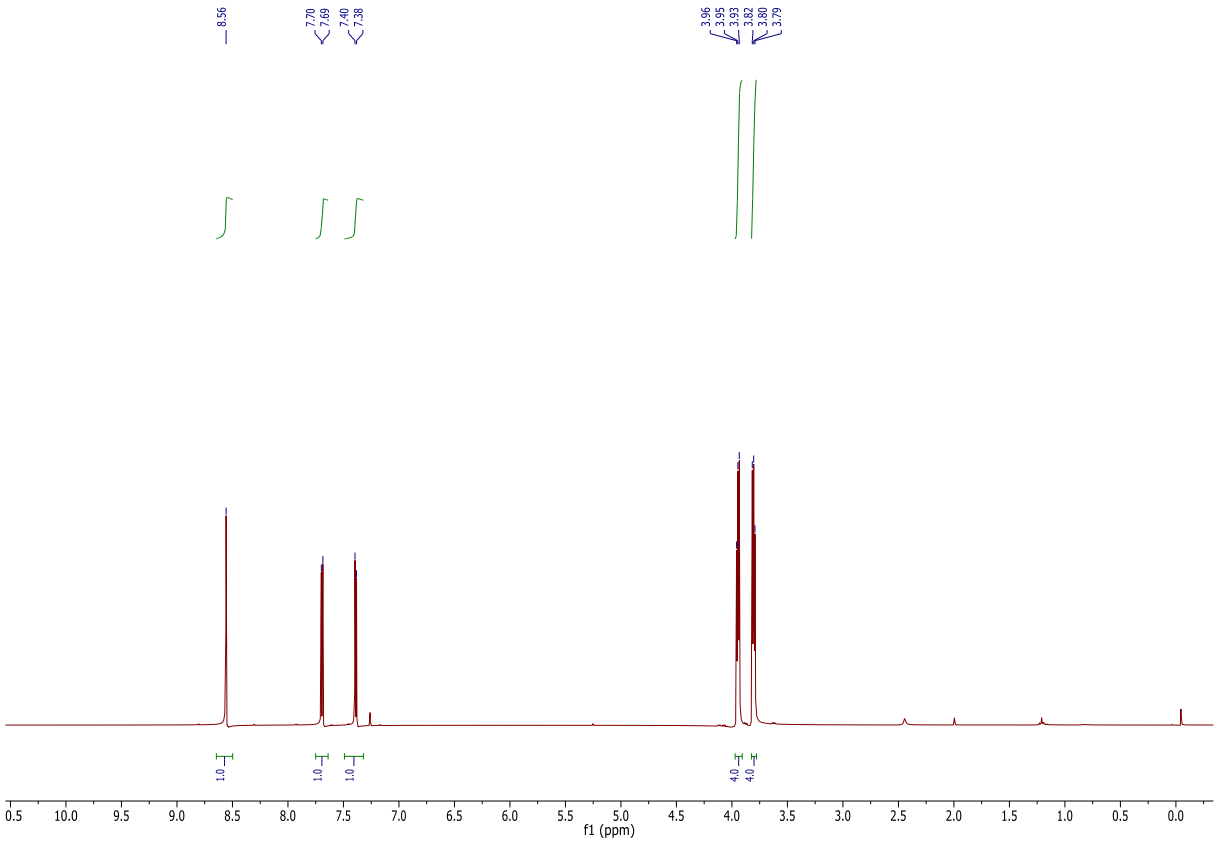
From compound 4 (50 mg; 0.235 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.470 mmol), 4-bromotoluene (80 mg; 0.470 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 3% AcOEt/petroleum ether, compound **33** was obtained as a white solid (22 mg, 31%), m.p. 172-174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.31-7.34 (m, 5H), 7.42-7.44 (m, 2H), 8.49 (d, *J* = 2.4 Hz, 1H), 8.65 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4 (CH), 128.7 (2xCH), 128.8 (CH), 129.3 (2xCH), 129.6 (2xCH), 130.2 (C), 130.4 (2xCH), 131.2 (C), 133.6 (C), 137.7 (C), 140.2 (CH), 142.0 (CH), 144.1 (C), 150.0 (C), 155.6 (C) ppm.

4-(6-phenylthieno[2,3-b]pyrazin-7-yl)benzonitrile (32) [11]

From compound **4** (50 mg; 0.235 mmol), $Pd(OAc)_2$ (5 mg; 0.024 mmol), TTBP · HBF_4 (14 mg; 0.047 mmol), K_2CO_3 (65 mg; 0.470 mmol), 4-bromobenzonitrile (86 mg; 0.470 mmol) and after purification by column chromatography using a solvent gradient from neat petroleum ether to 5% AcOEt/petroleum ether, compound **34** was obtained as a white solid (28 mg, 38%), m.p. 219-221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.40 (m, 5H), 7.57 (d, *J* = 8 Hz, 2H), 7.70 (d, *J* = 8 Hz, 2H), 8.54 (d, *J* = 2.4 Hz, 1H), 8.66 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 111.5 (C), 118.8 (C), 128.9 (C), 129.1 (2xCH), 129.5 (CH), 129.7 (2xCH), 131.4 (2xCH), 132.2 (2xCH), 132.7 (C), 138.0 (C), 140.8 (CH), 142.1 (CH), 146.4 (C), 149.0 (C), 155.6 (C) ppm.

1.3. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR Spectra of all Products

332 **4-(thieno[3,2-d]pyrimidin-4-yl)morpholine (7)**



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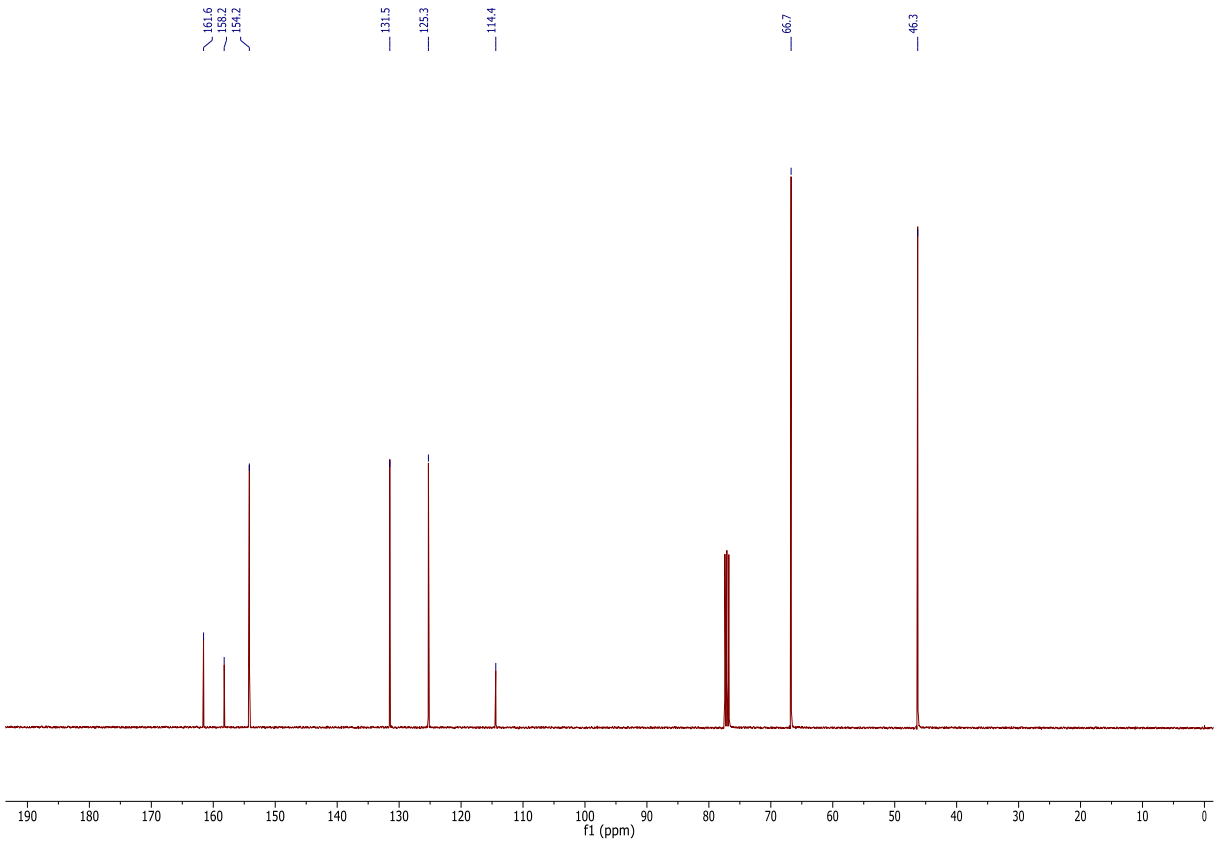
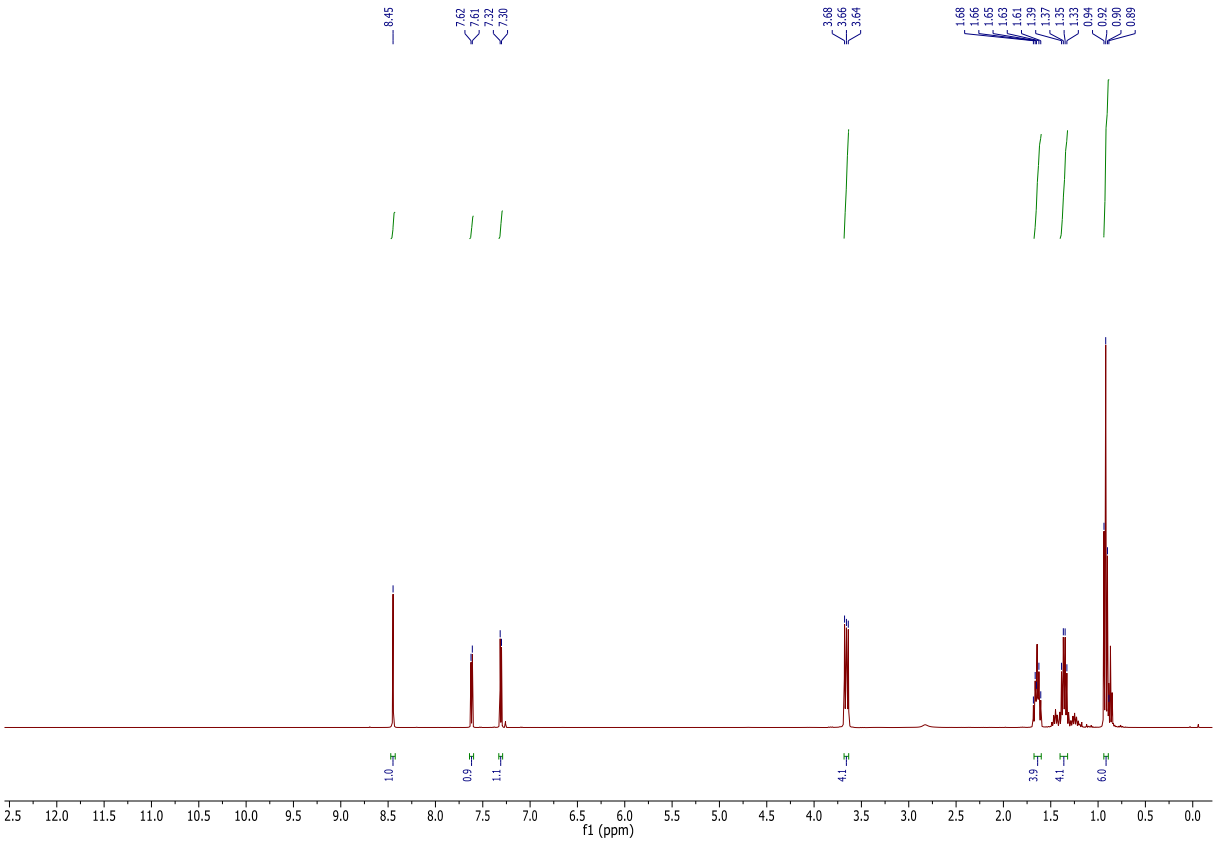


334

335 **N,N-dibutylthieno[3,2-d]pyrimidin-4-amine (8)**



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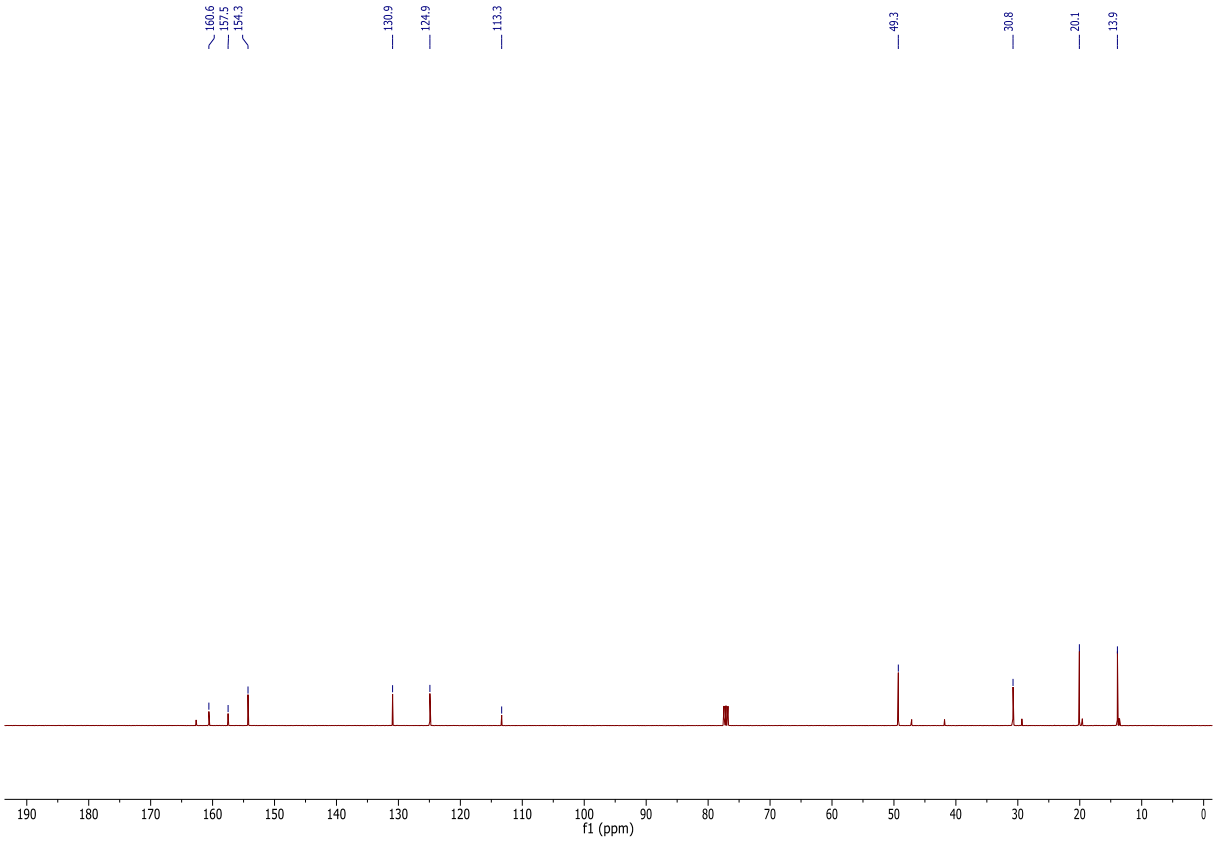
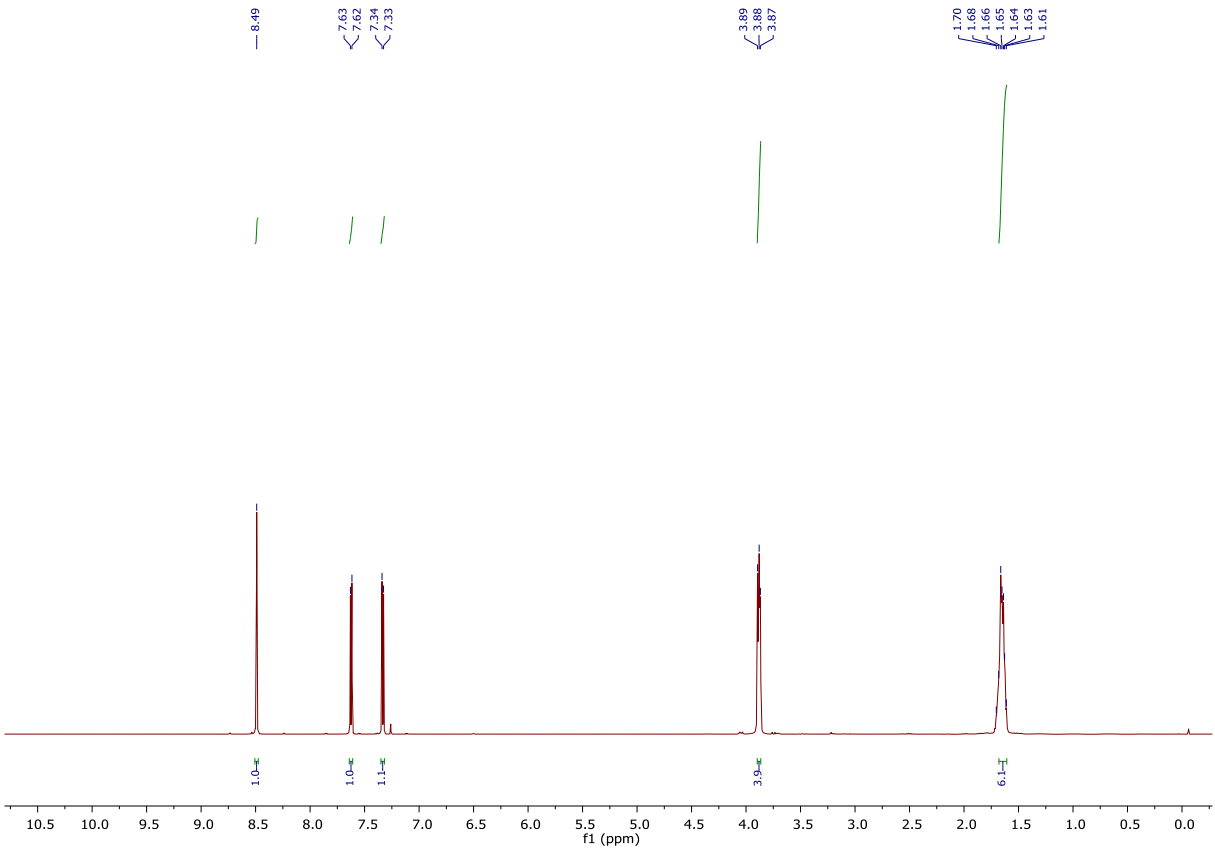


337

338 **4-(piperidin-1-yl)thieno[3,2-d]pyrimidine (9)**



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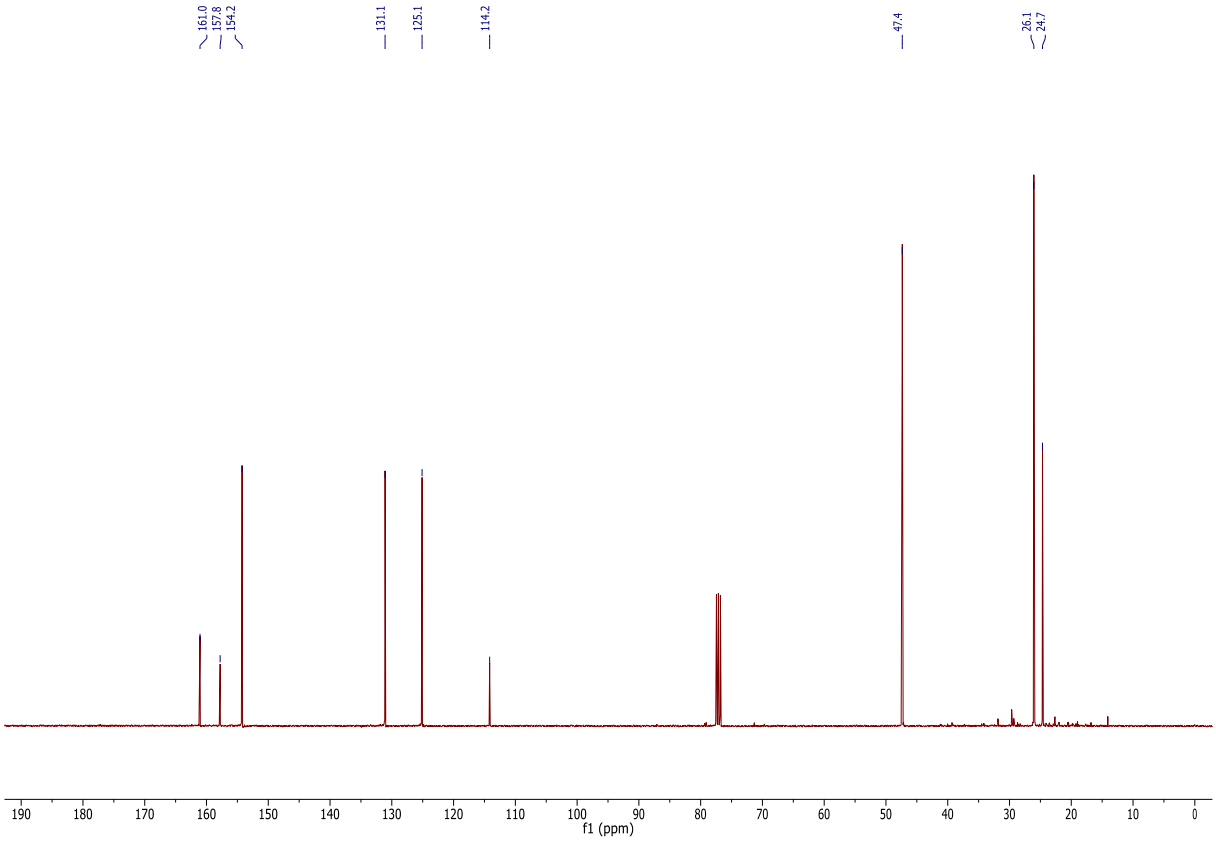

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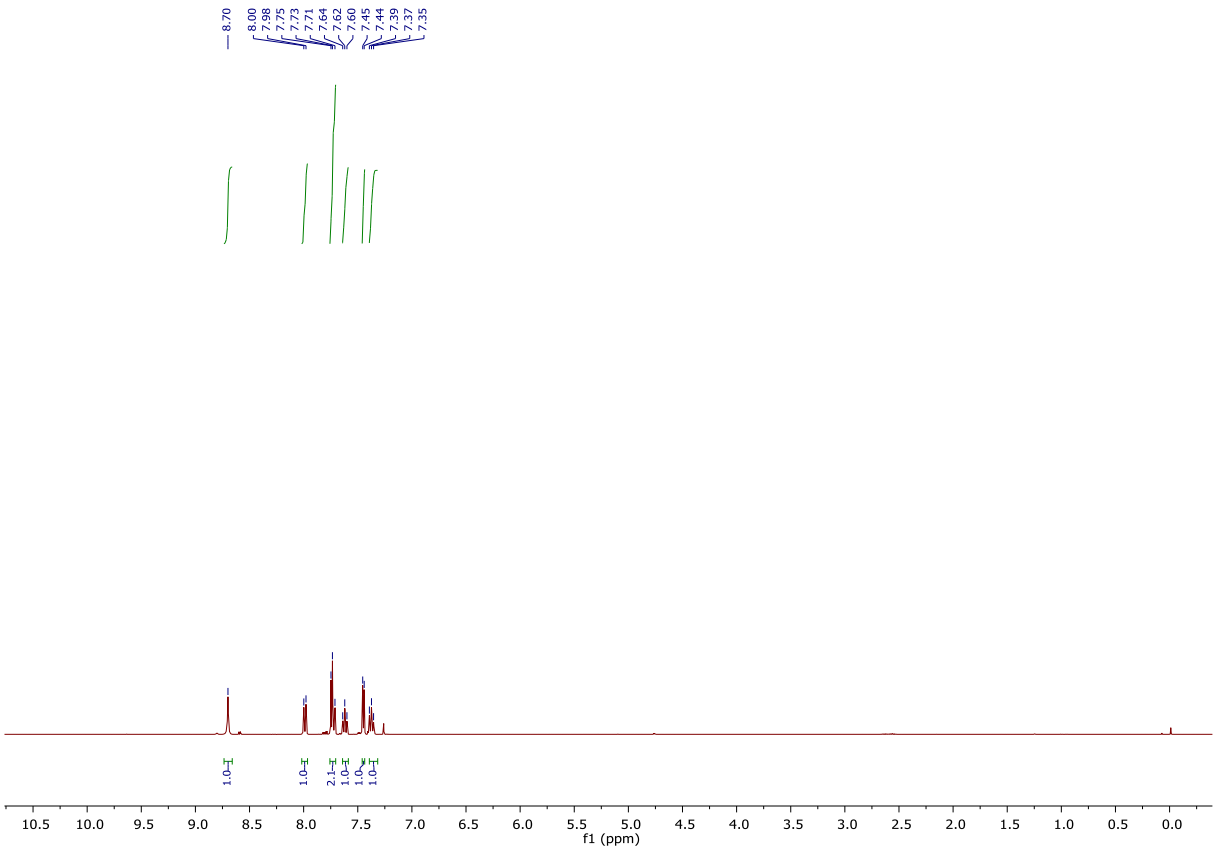
341

342 **N-(2-(trifluoromethyl)phenyl)thieno[3,2-d]pyrimidin-4-amine (10)**



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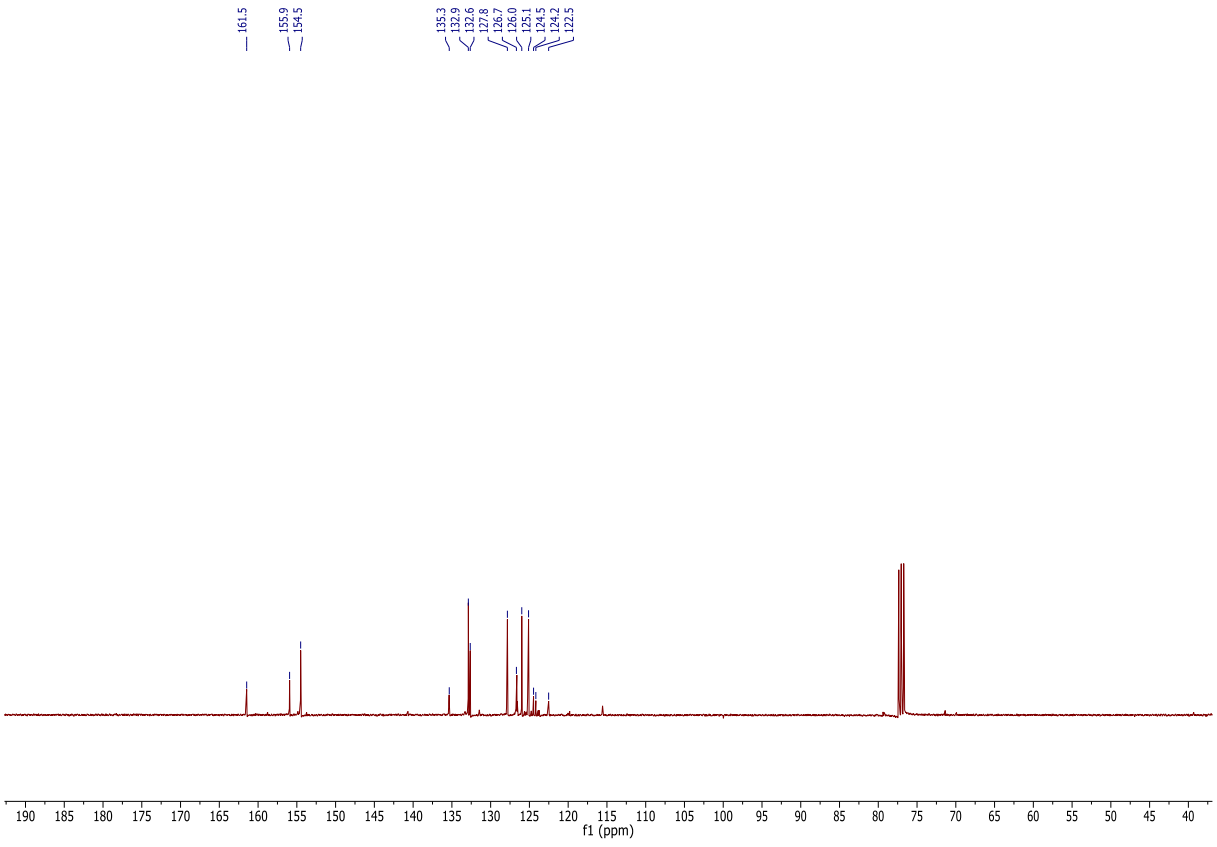

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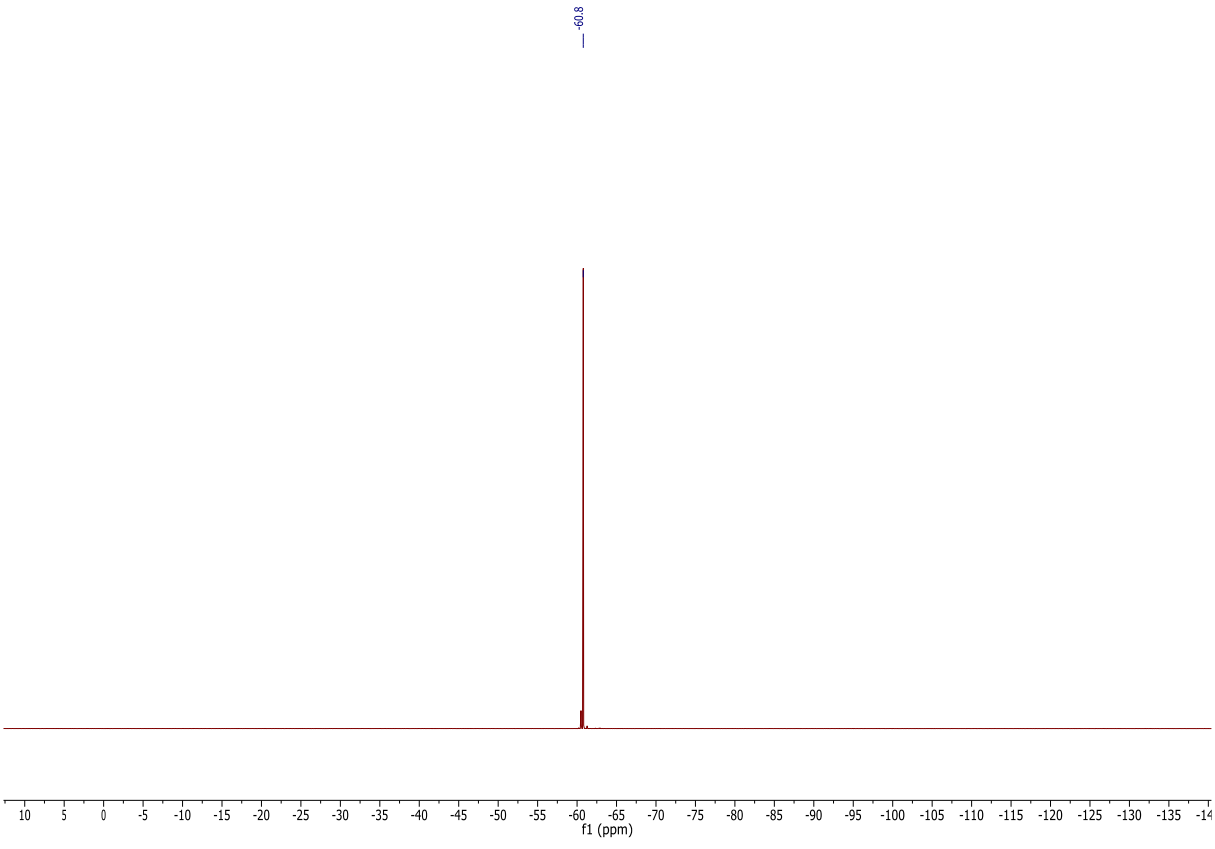
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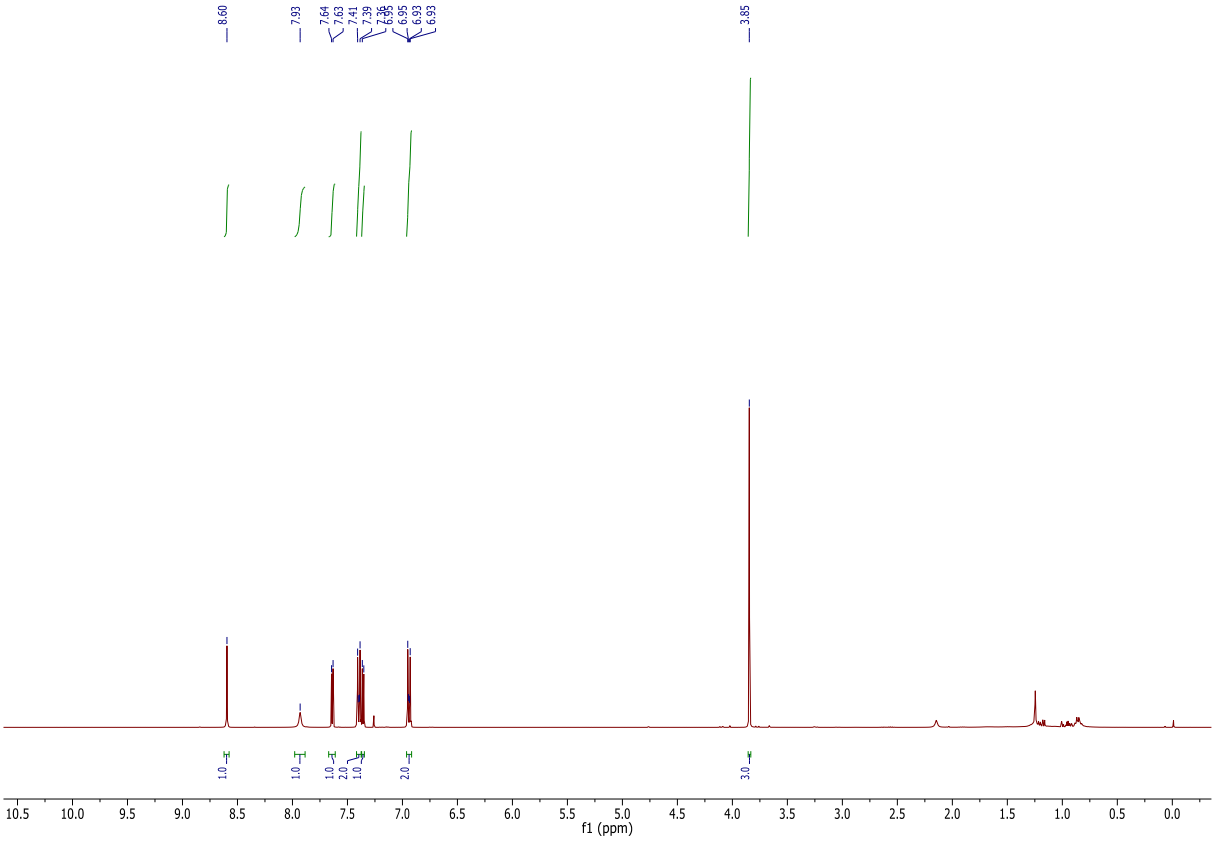
f1 (ppm)

360 **N-(4-methoxyphenyl)thieno[3,2-d]pyrimidin-4-amine (11)**



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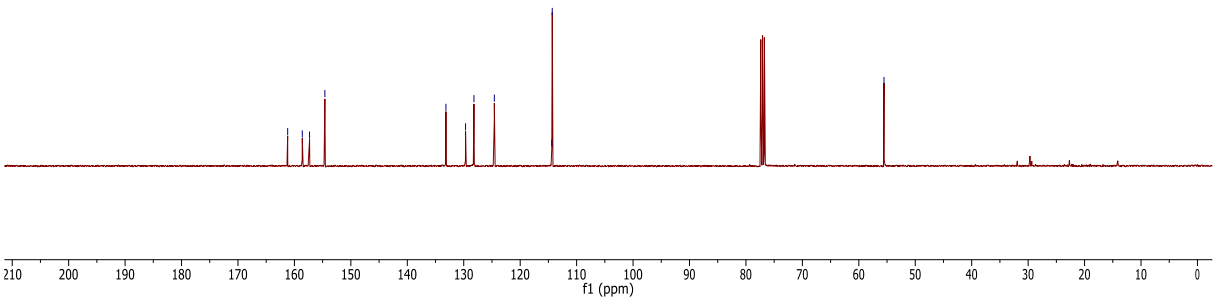
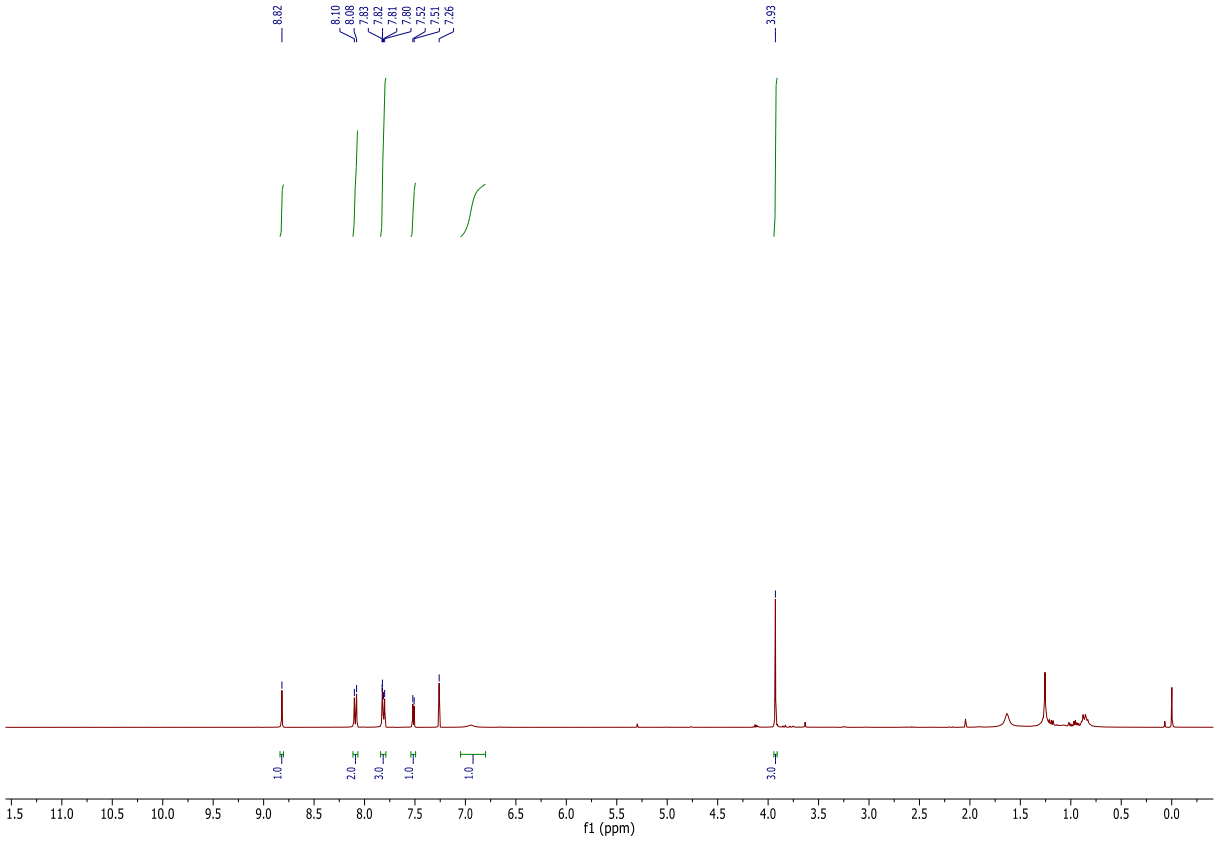


364 **methyl 4-(thieno[3,2-d]pyrimidin-4-ylamino)benzoate (12)**



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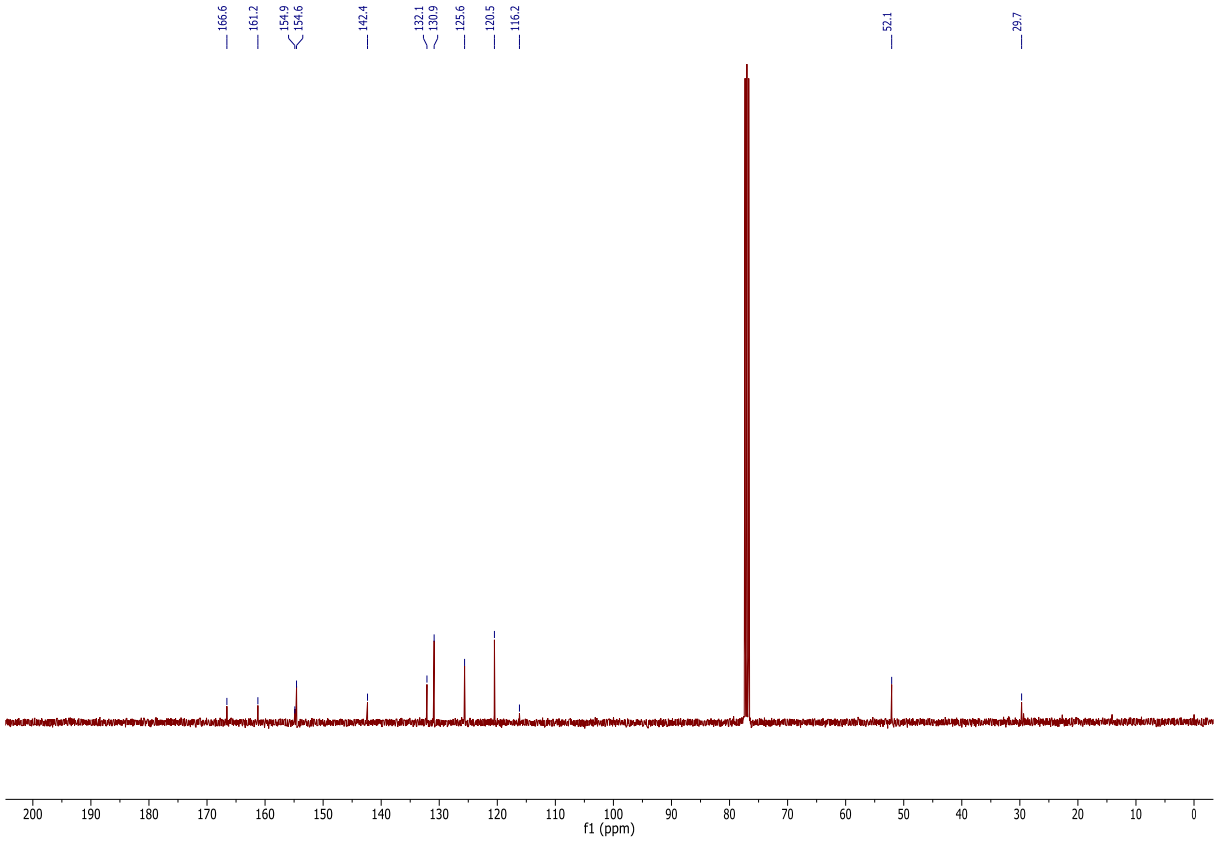

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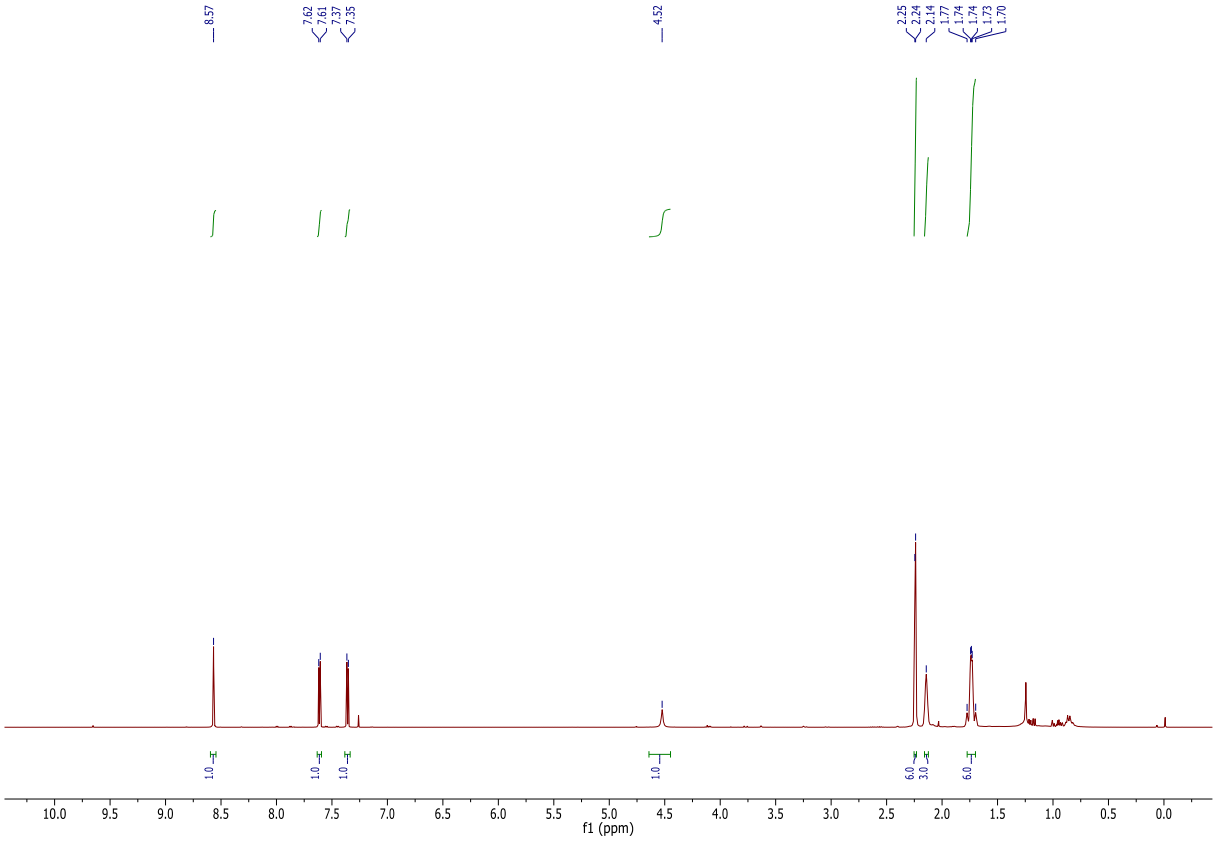
367

368 **N-((3s,5s,7s)-adamantan-1-yl)thieno[3,2-d]pyrimidin-4-amine (13)**



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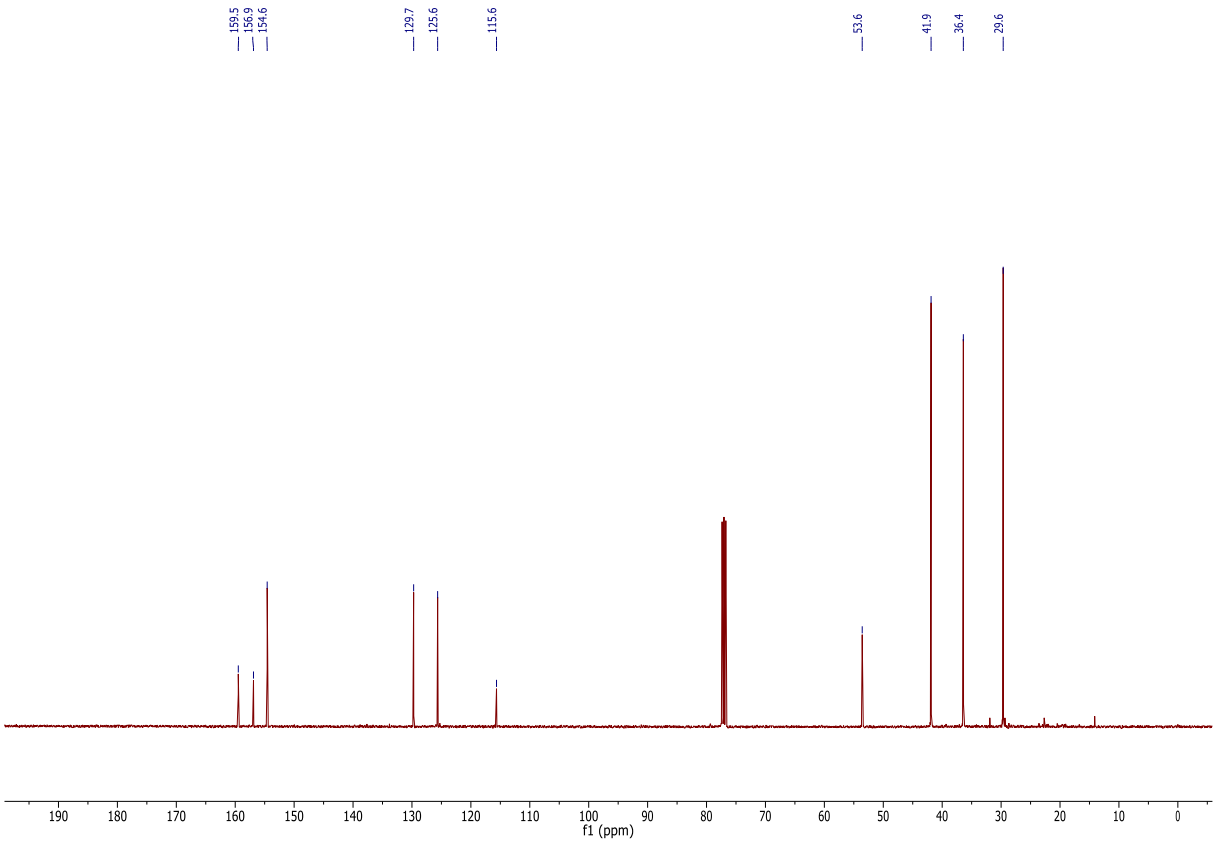
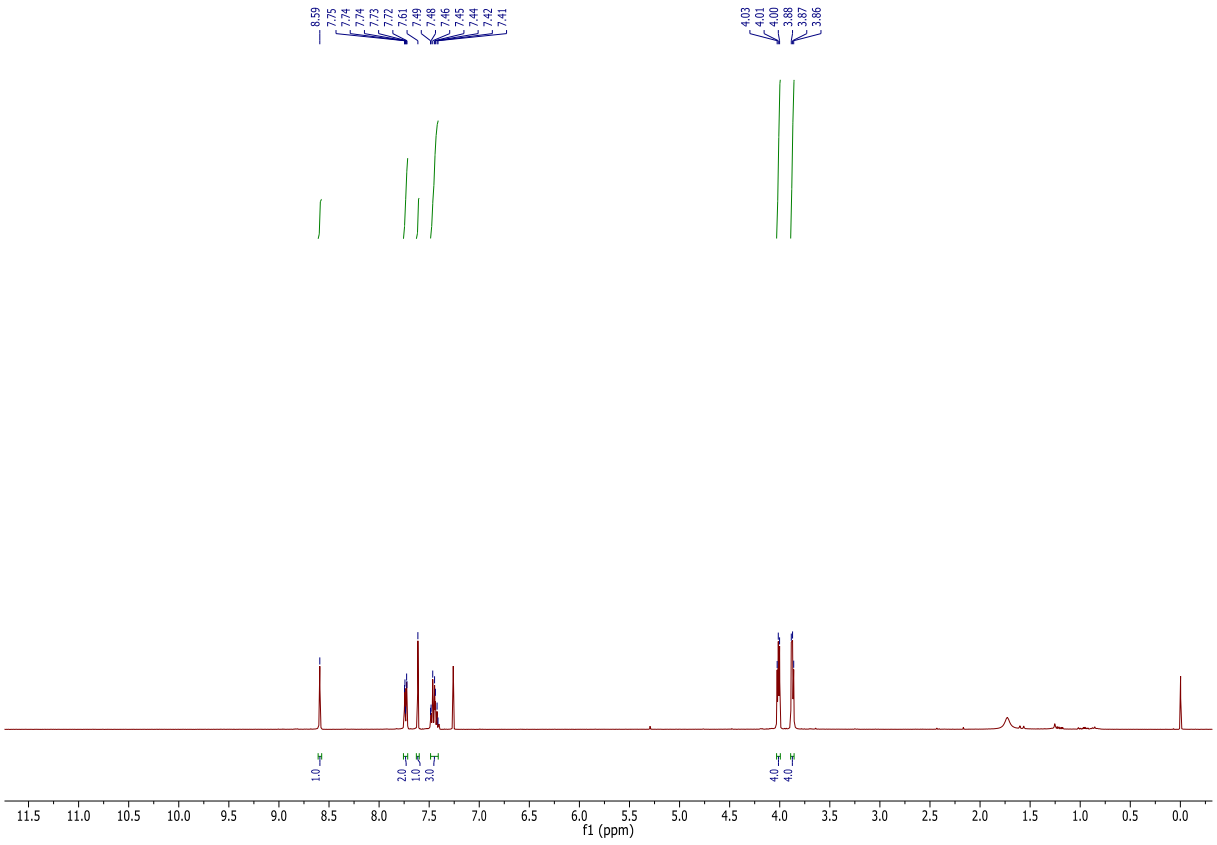


370

371 **4-(6-phenylthieno[3,2-d]pyrimidin-4-yl)morpholine (14)**



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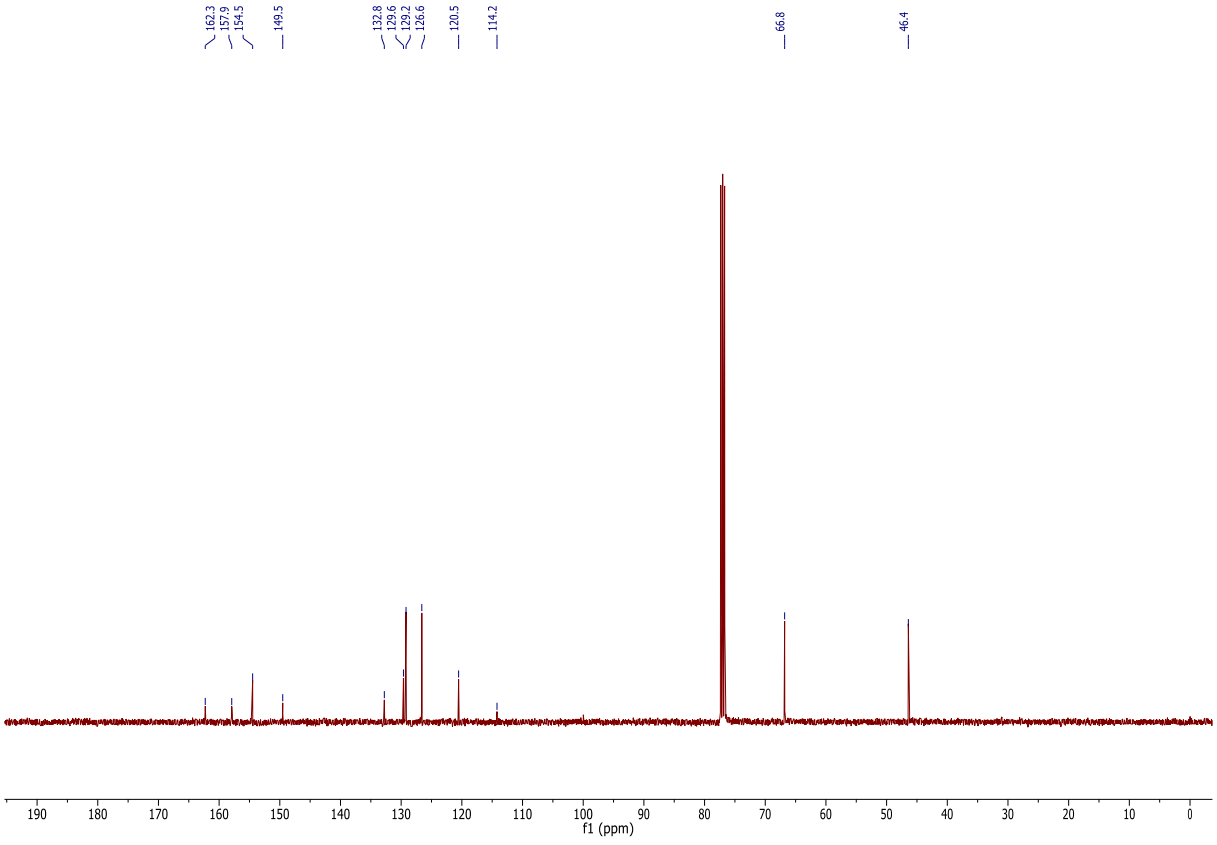

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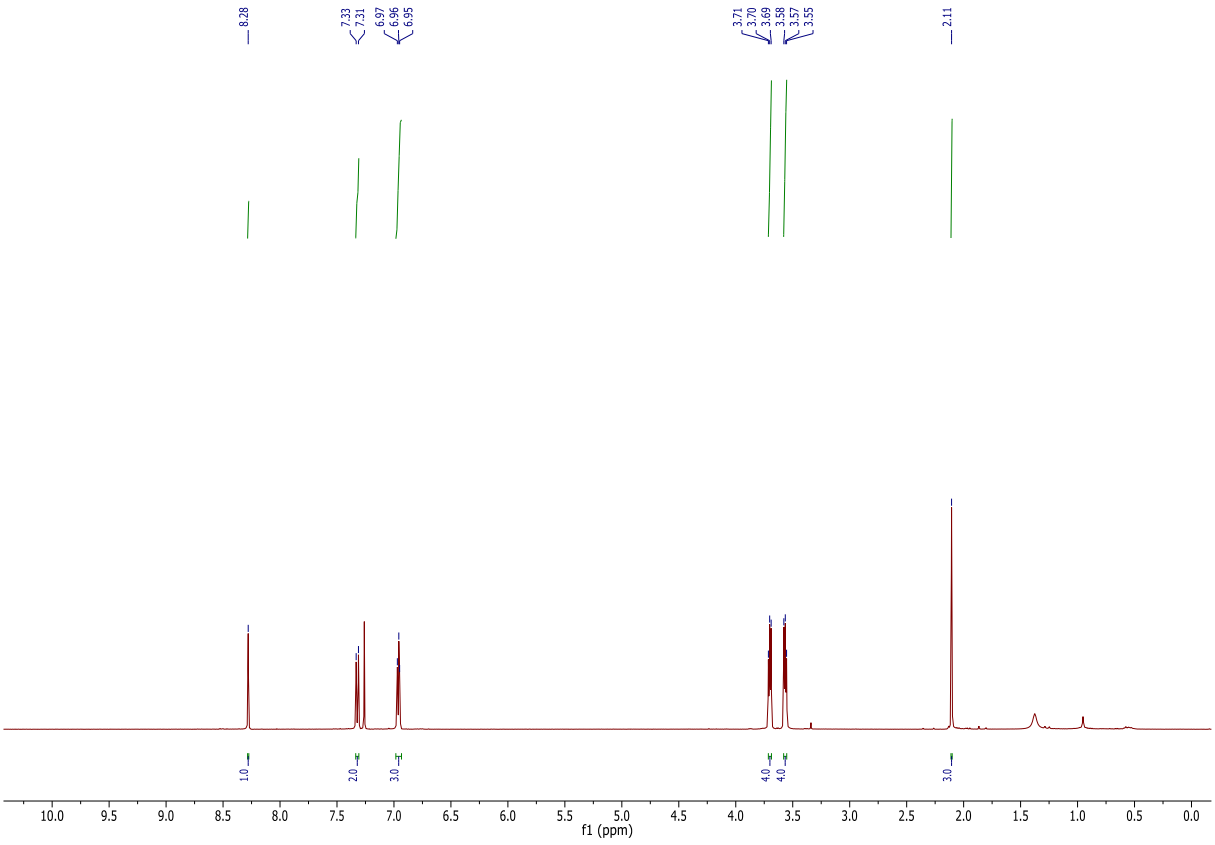
374 **4-(6-(p-tolyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (16)**



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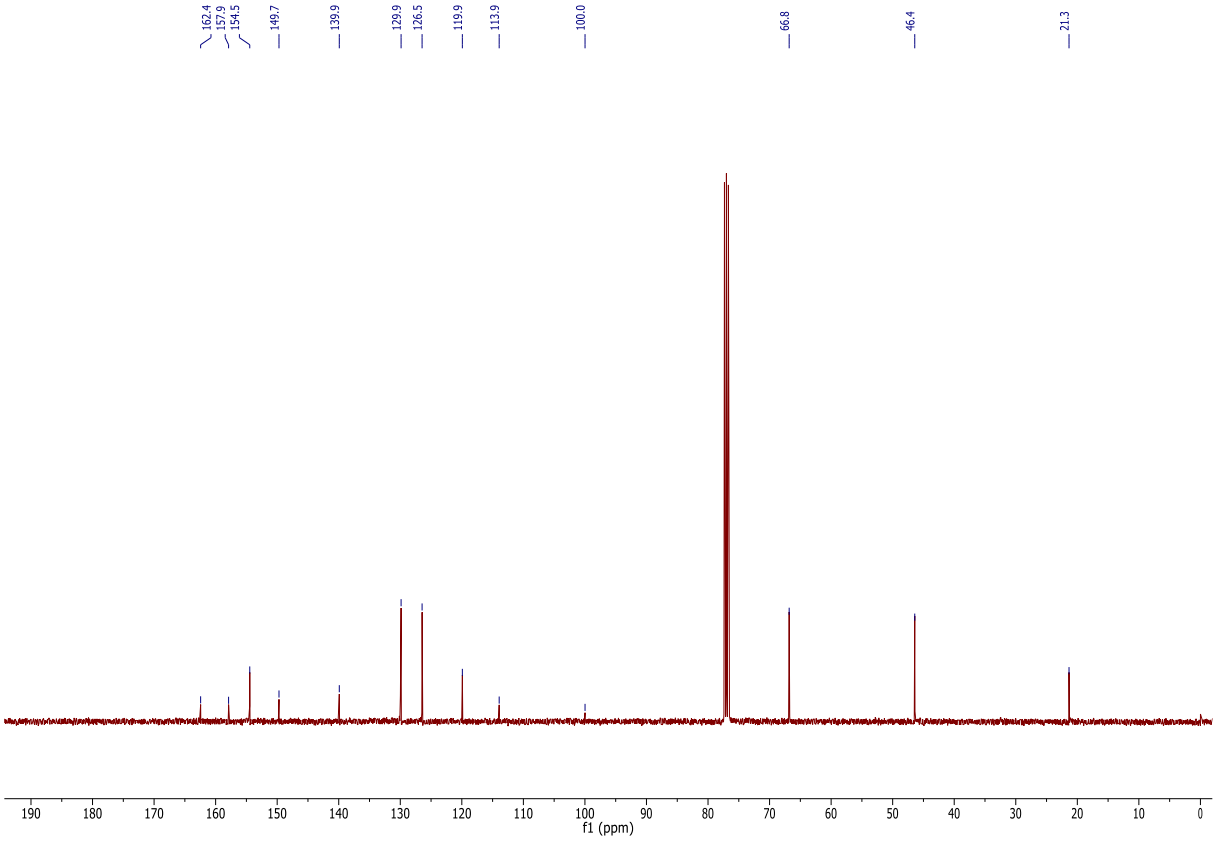
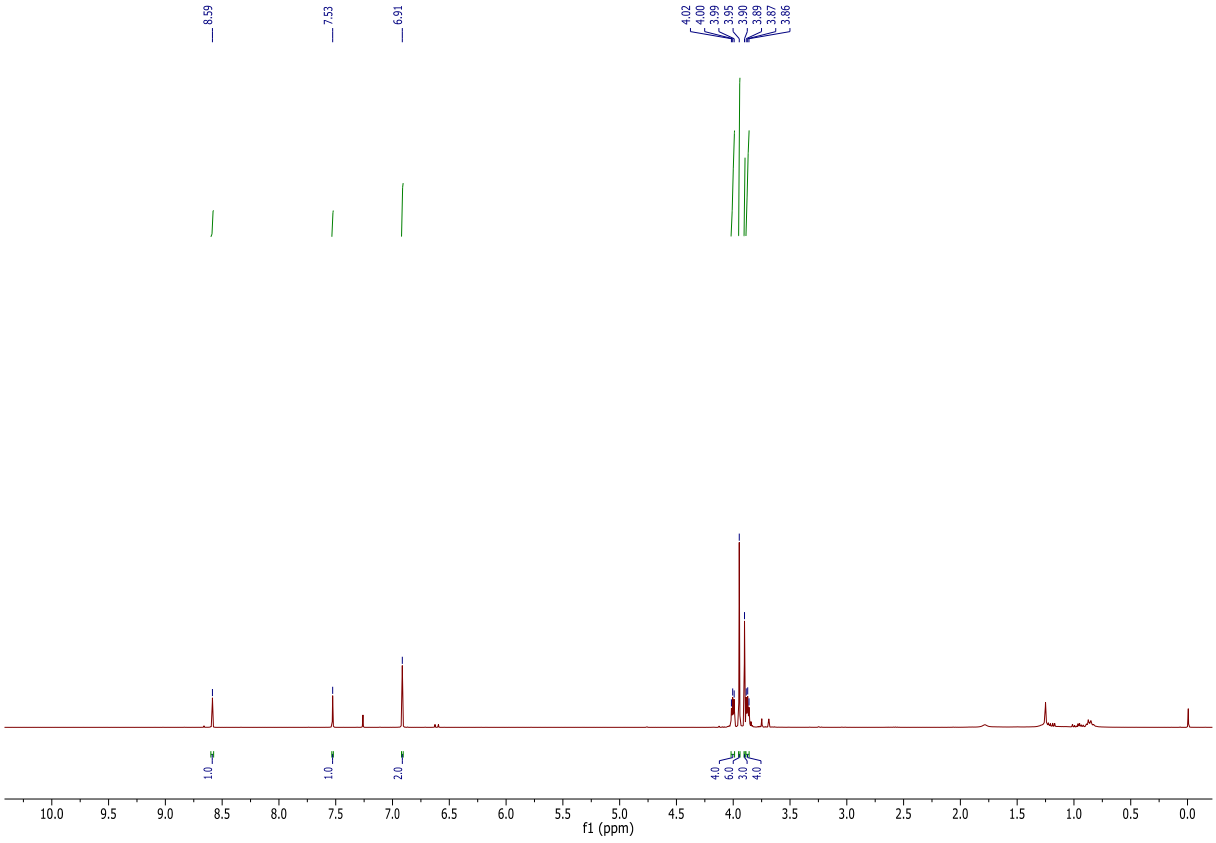
377



378 **4-(6-(3,4,5-trimethoxyphenyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (17)**



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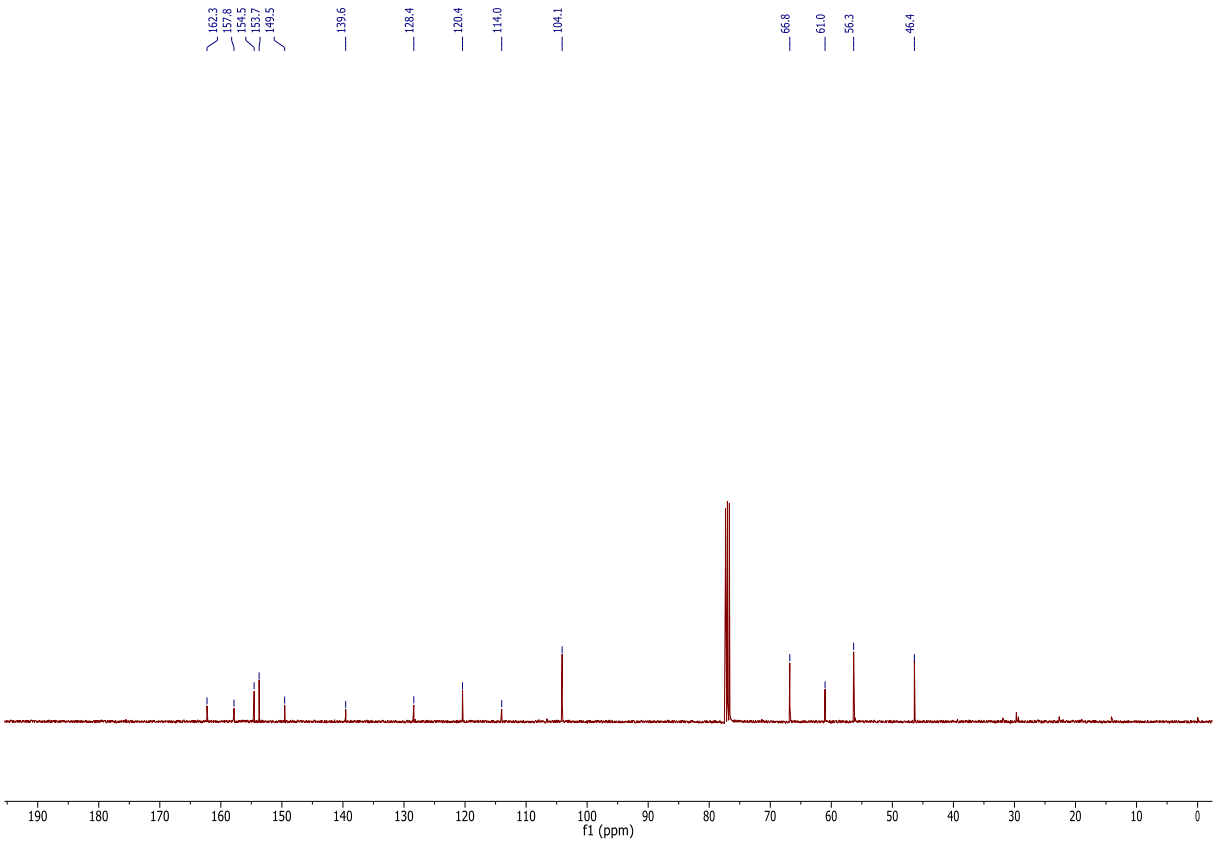

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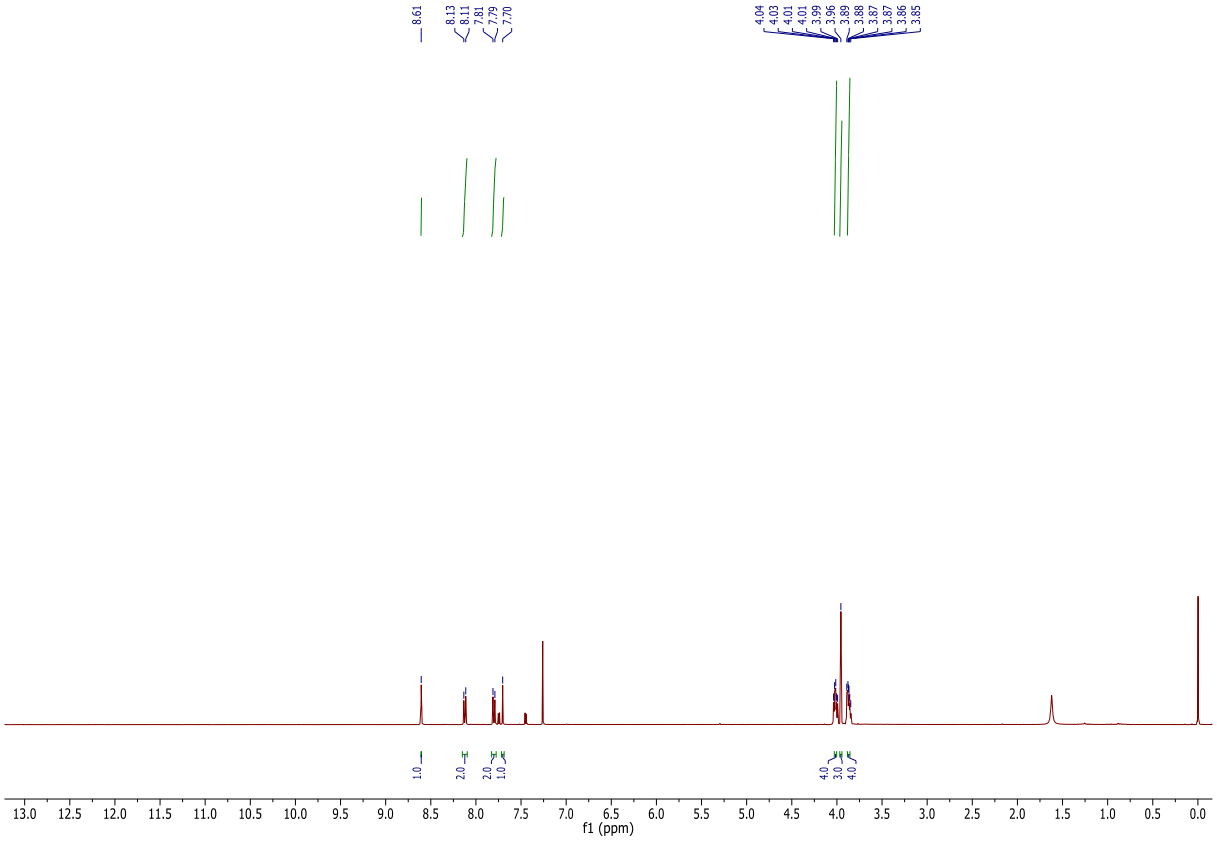
methyl 4-(4-morpholinothieno[3,2-d]pyrimidin-6-yl)benzoate (18)



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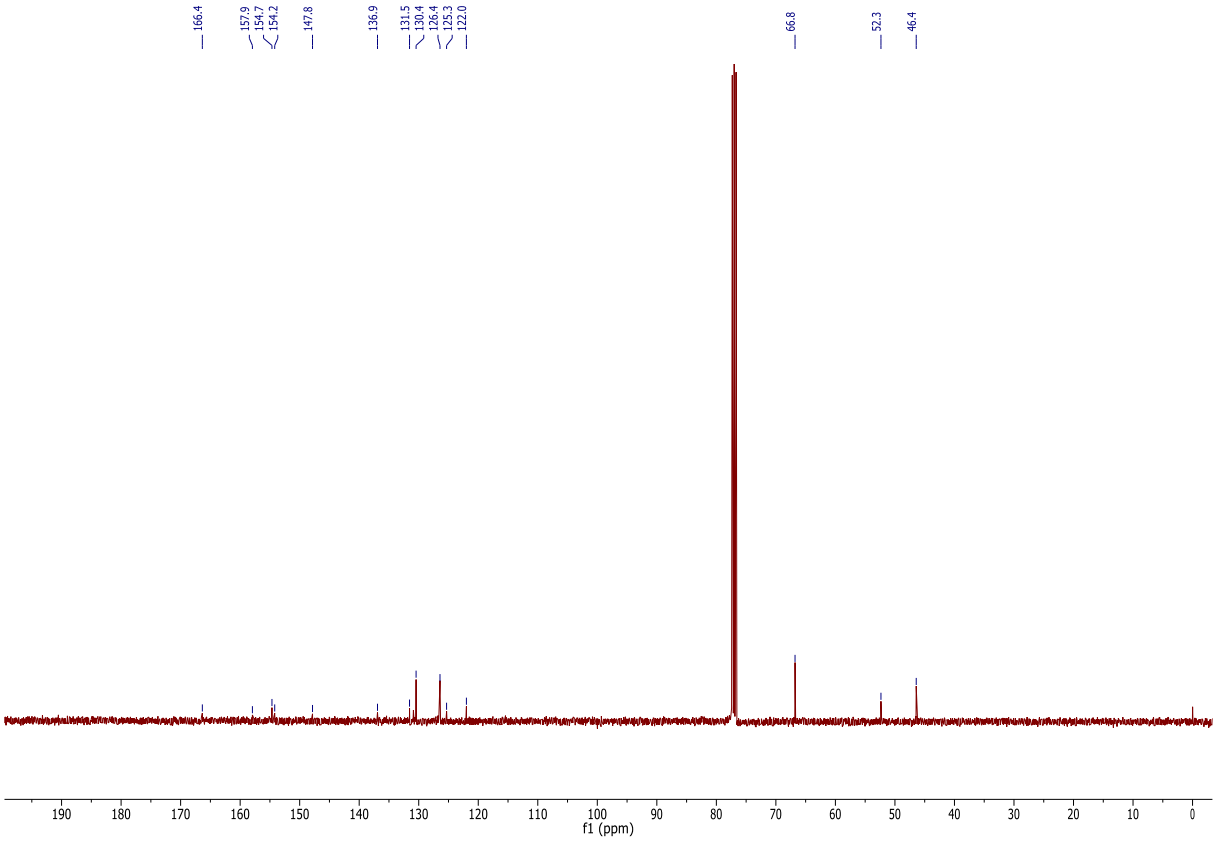
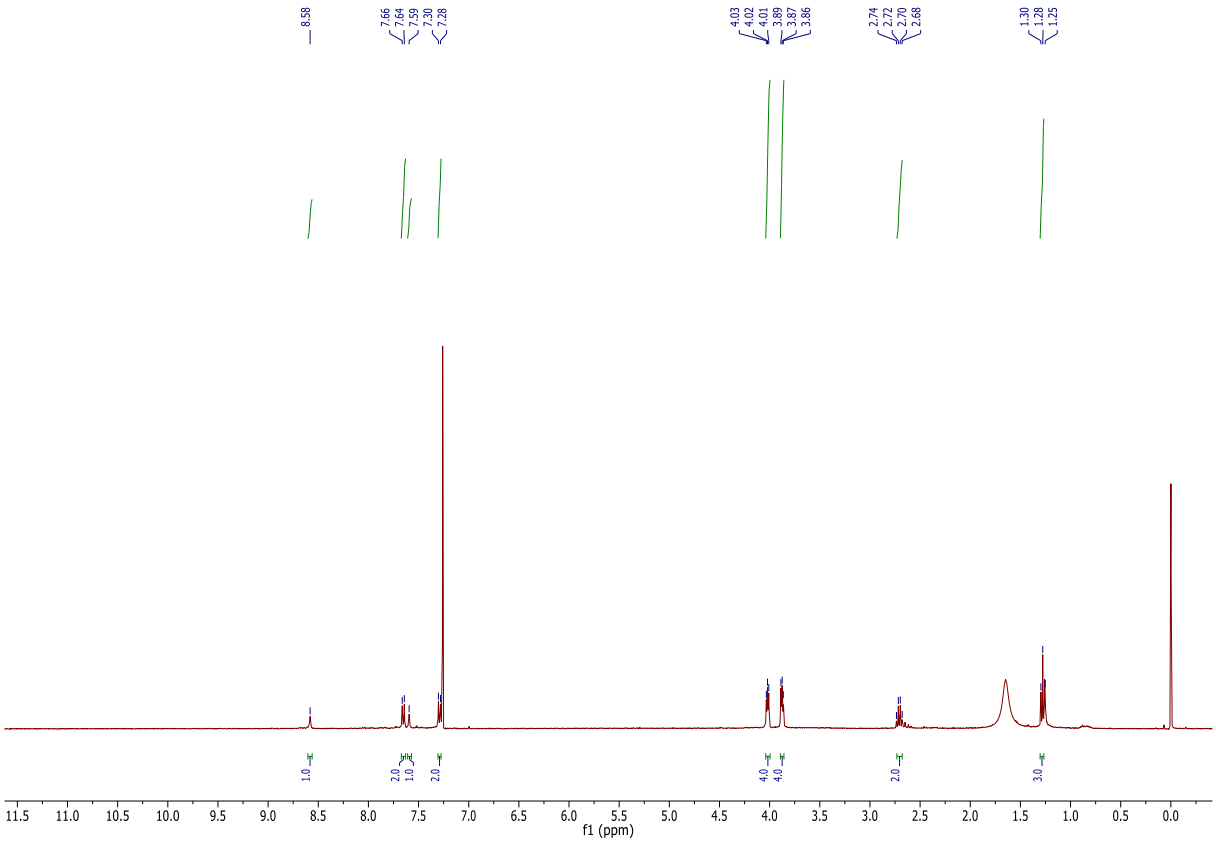


383

384 **4-(6-(4-ethylphenyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (19)**



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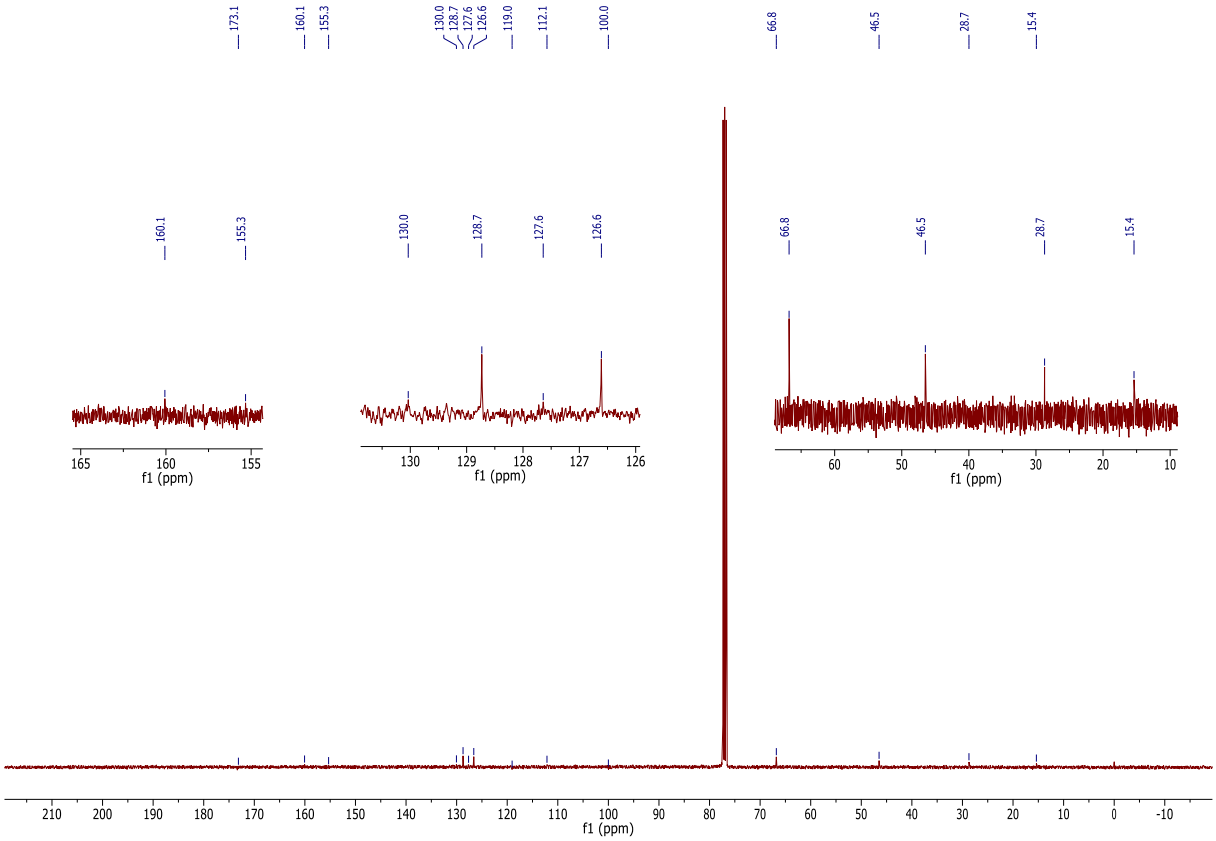

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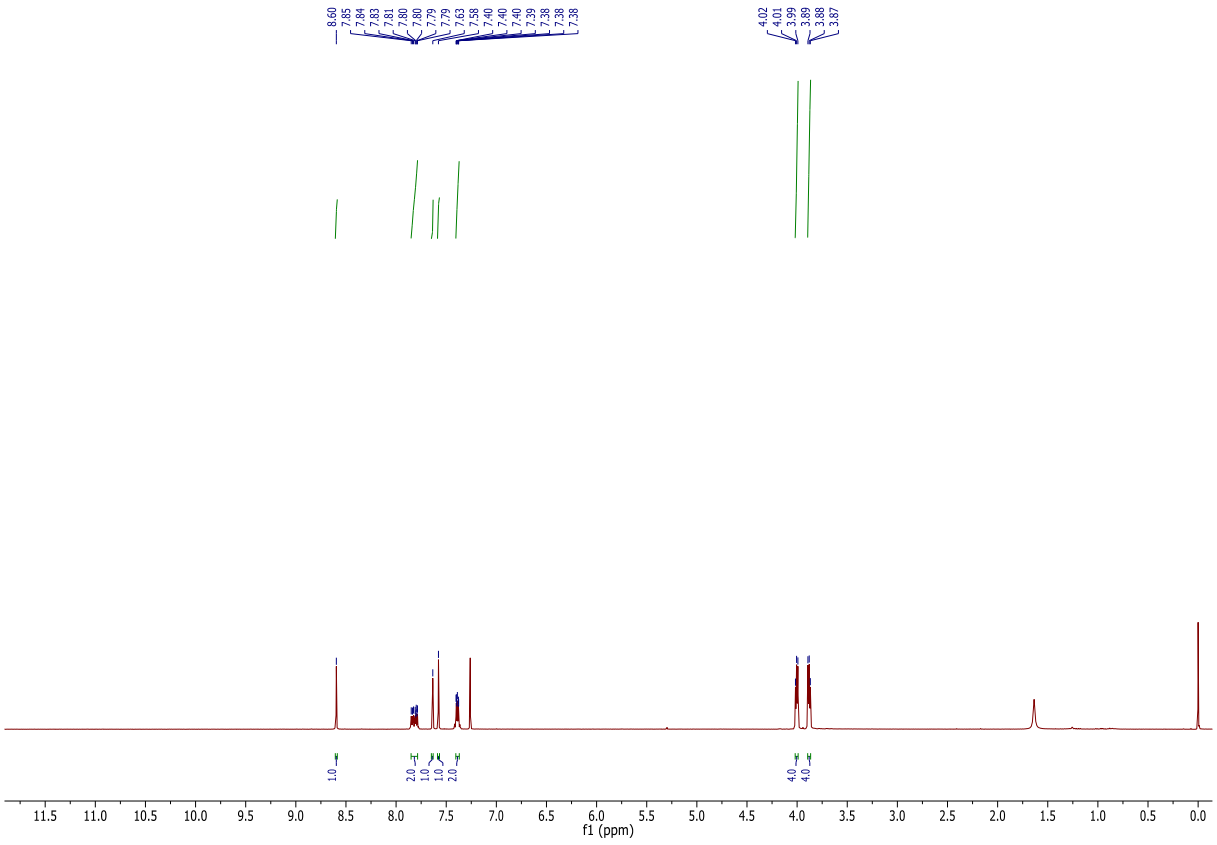
388 **4-(6-(benzo[b]thiophen-2-yl)thieno[3,2-d]pyrimidin-4-yl)morpholine (20)**



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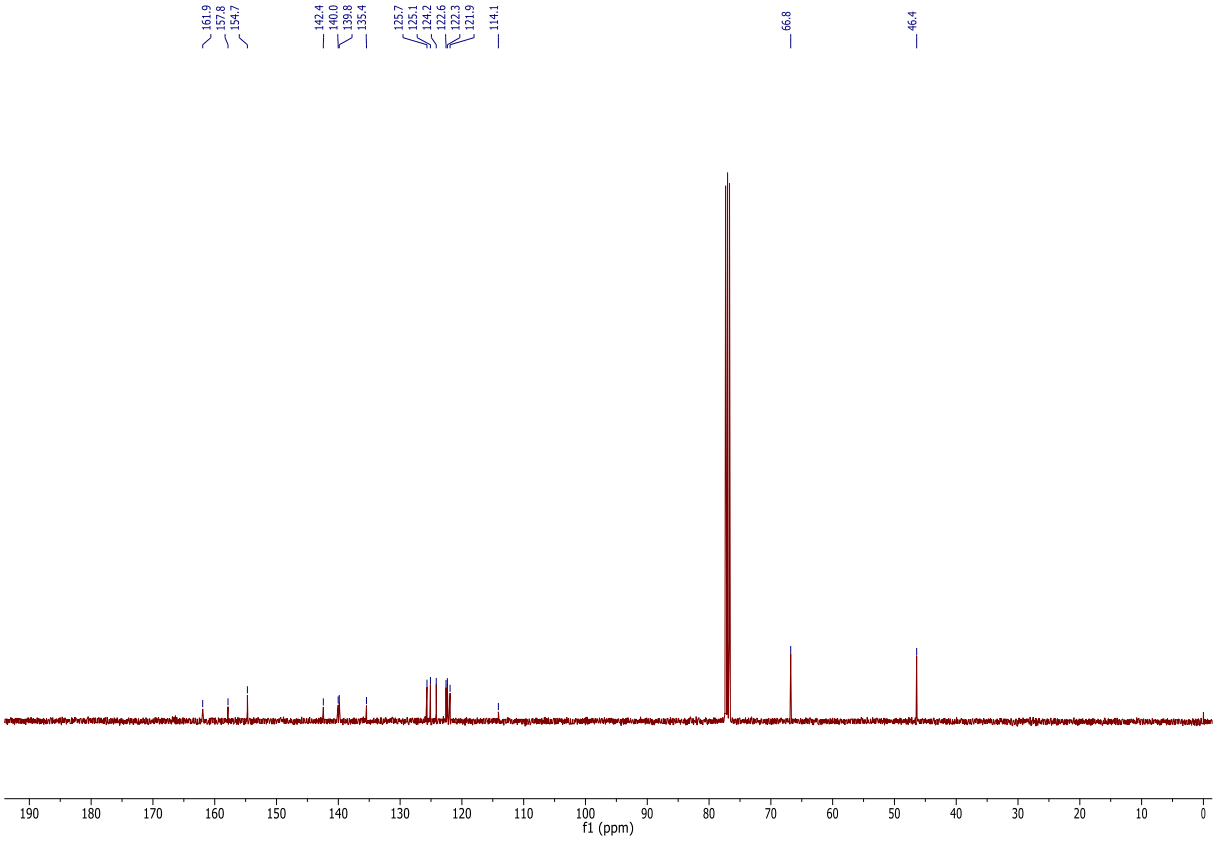
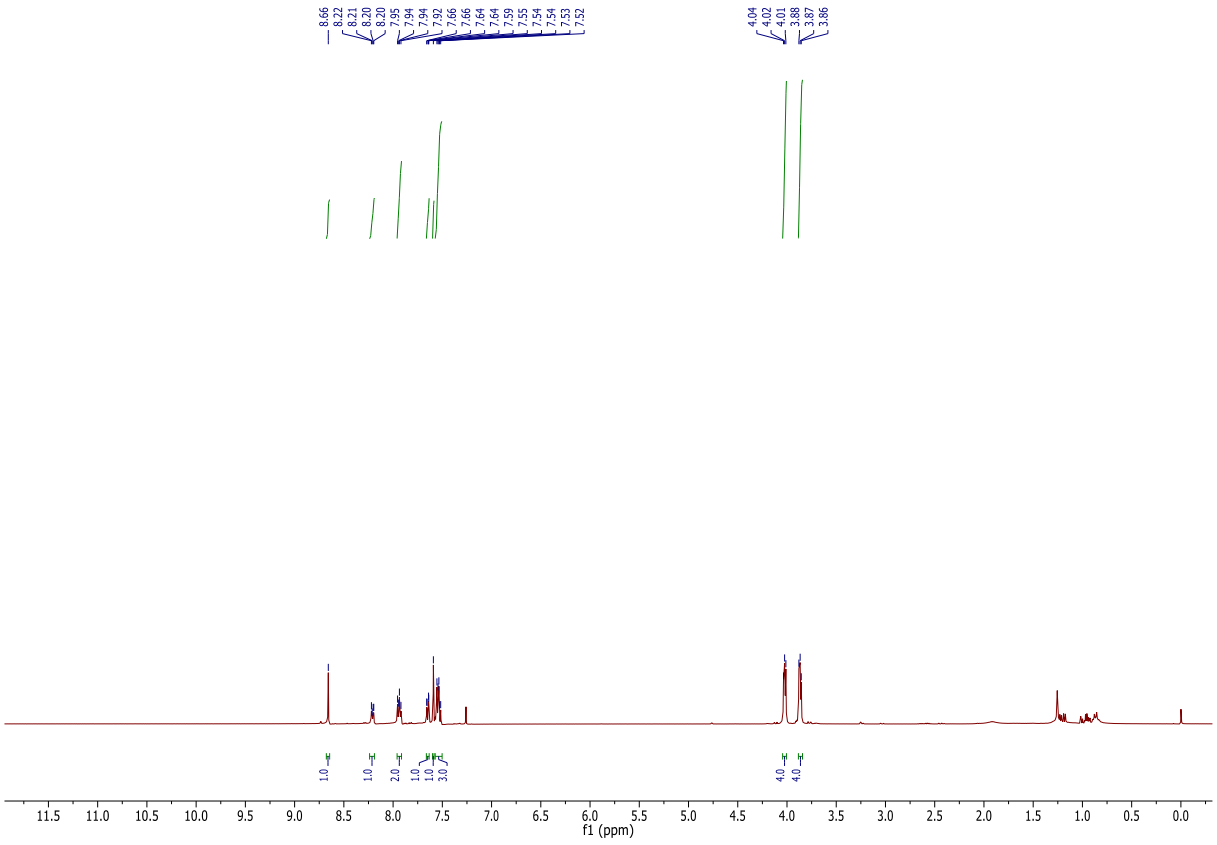


391 **4-(6-(naphthalen-1-yl)thieno[3,2-d]pyrimidin-4-yl)morpholine (21)**



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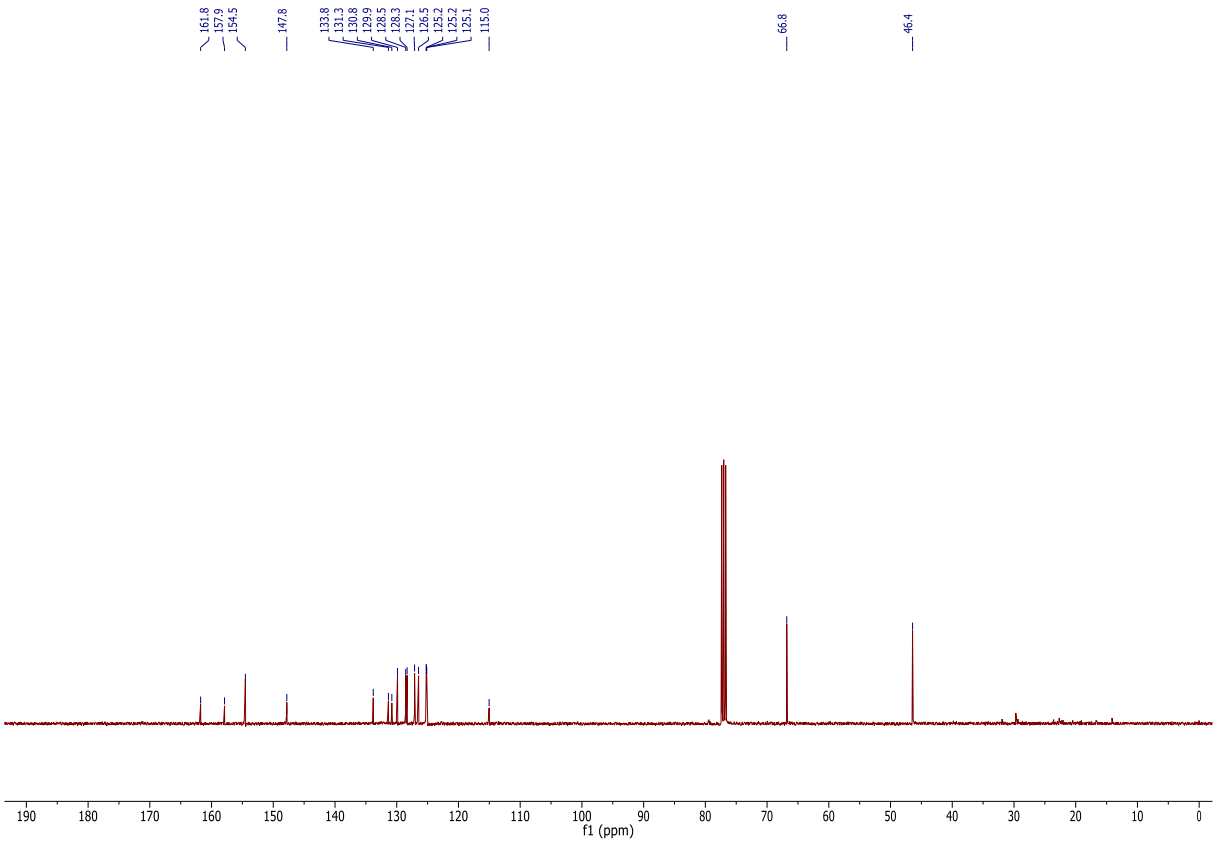
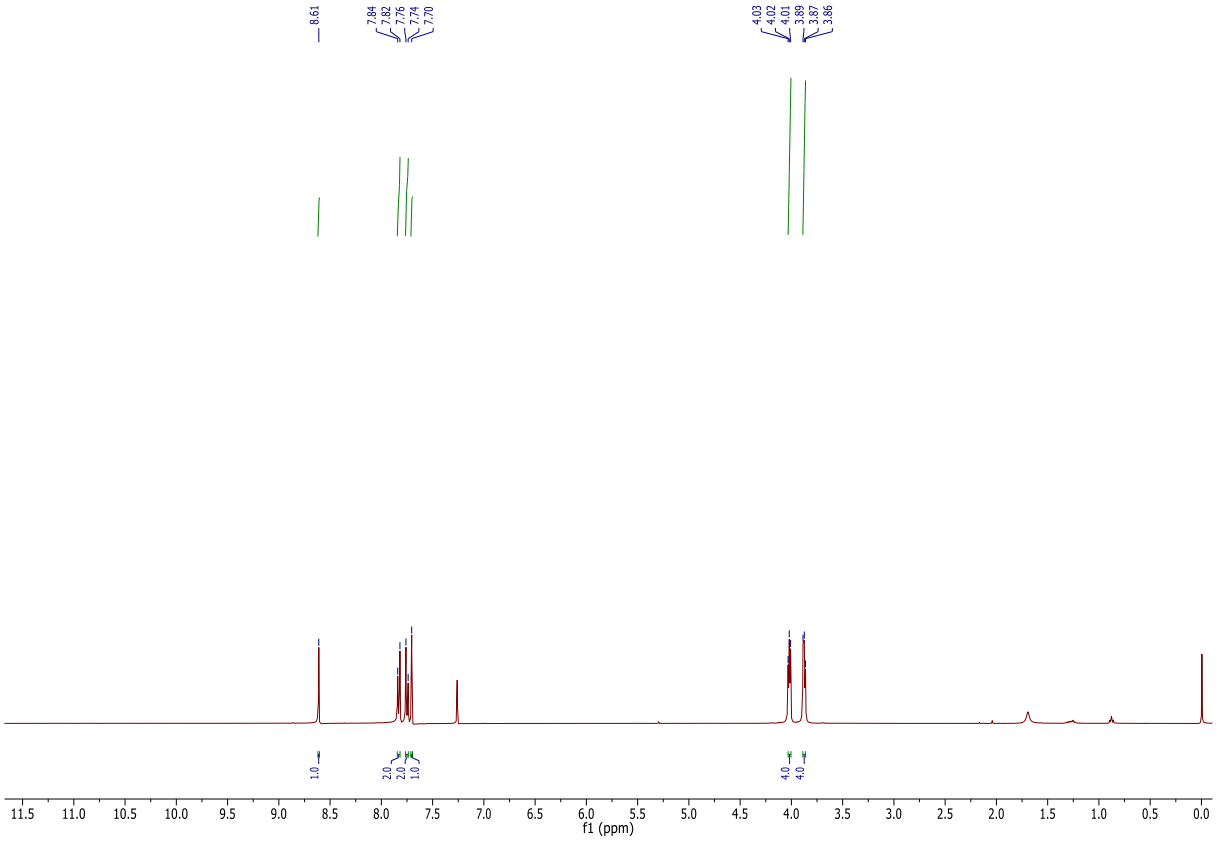


393

394 **4-(4-morpholinothieno[3,2-d]pyrimidin-6-yl)benzonitrile (22)**



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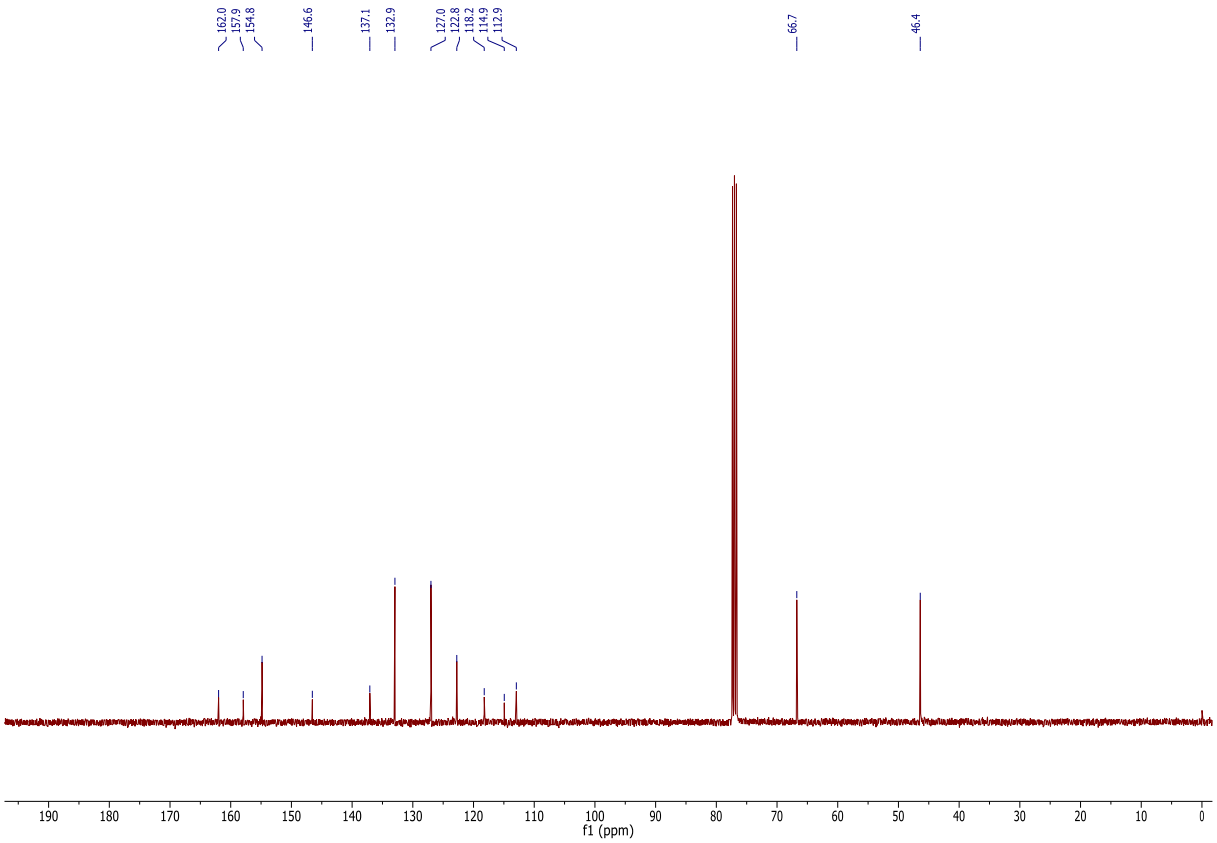

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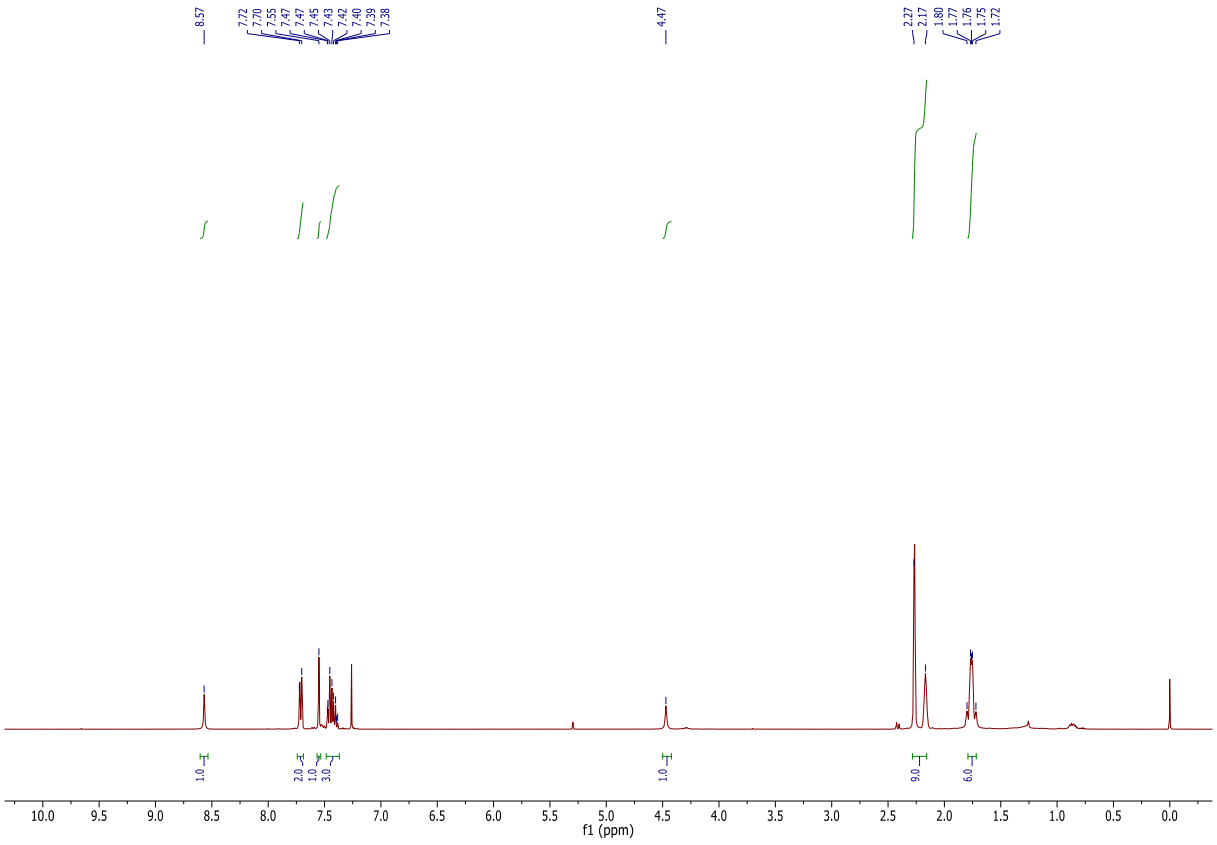
397 **N-((3s,5s,7s)-adamantan-1-yl)-6-phenylthieno[3,2-d]pyrimidin-4-amine (23)**



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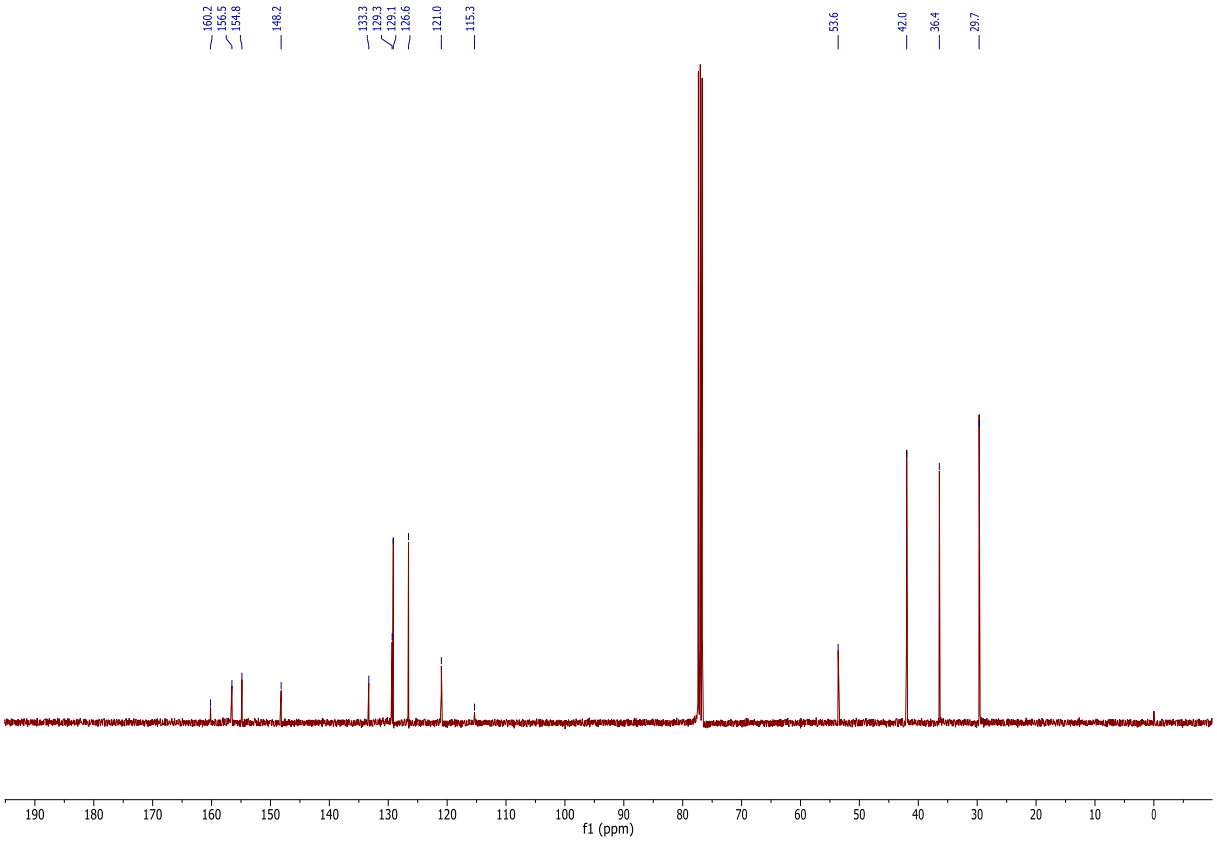
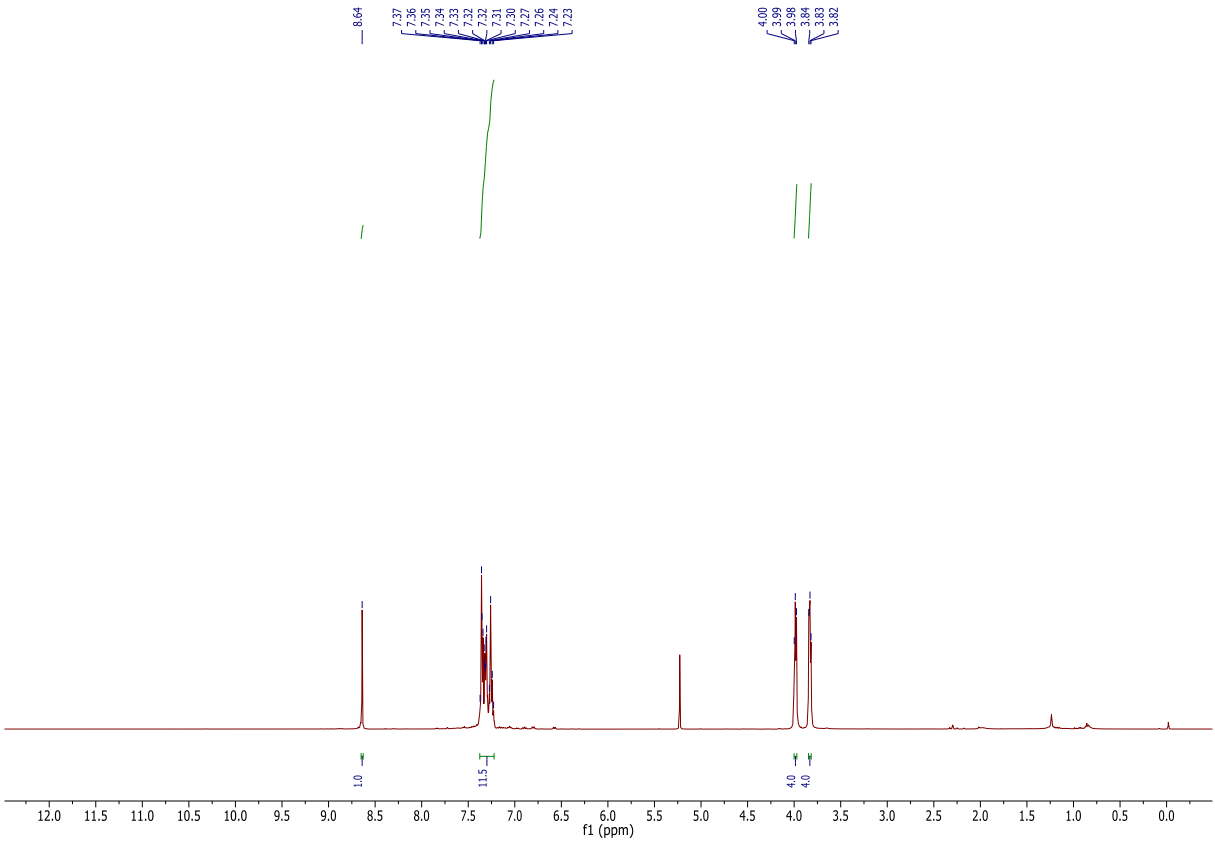


399

400 **4-(6,7-diphenylthieno[3,2-d]pyrimidin-4-yl)morpholine (15)**



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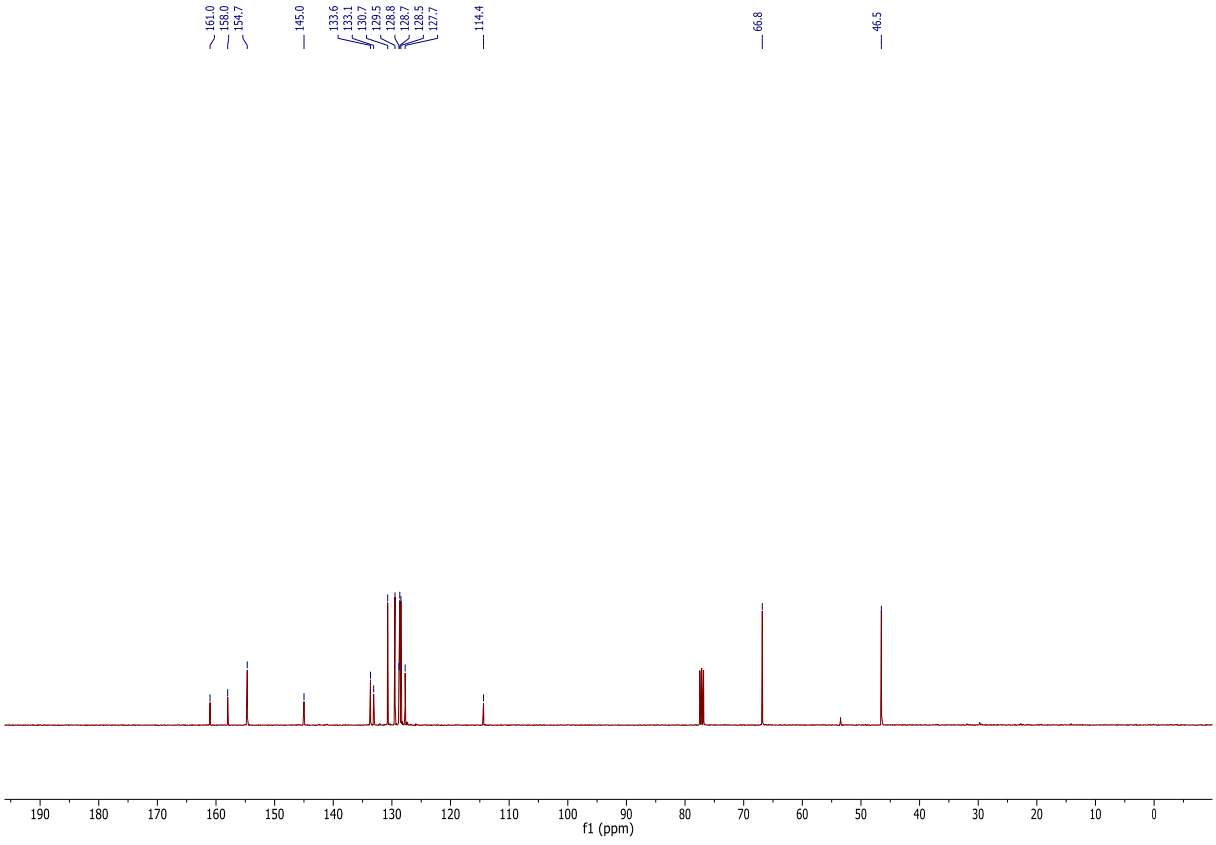

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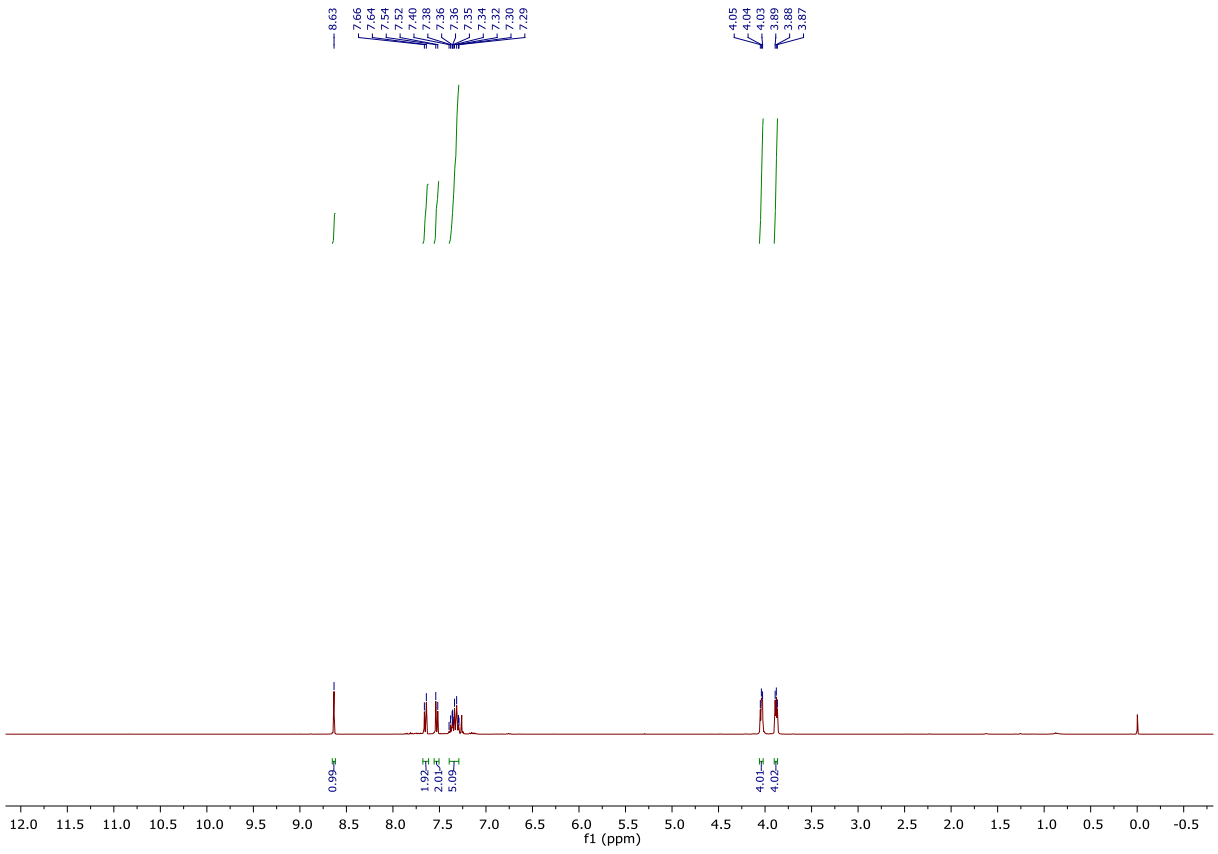
403

404 **4-(4-morpholino-6-phenylthieno[3,2-d]pyrimidin-7-yl)benzonitrile (24)**



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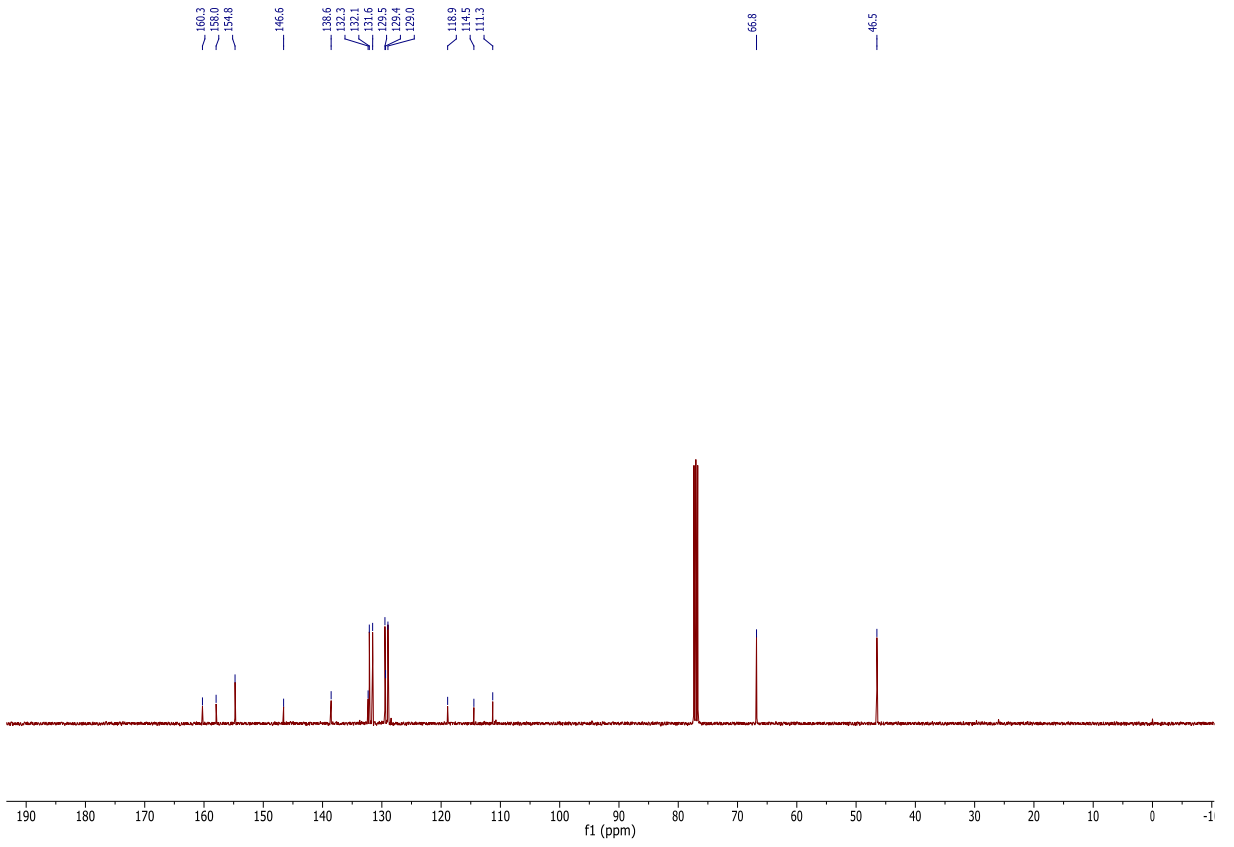
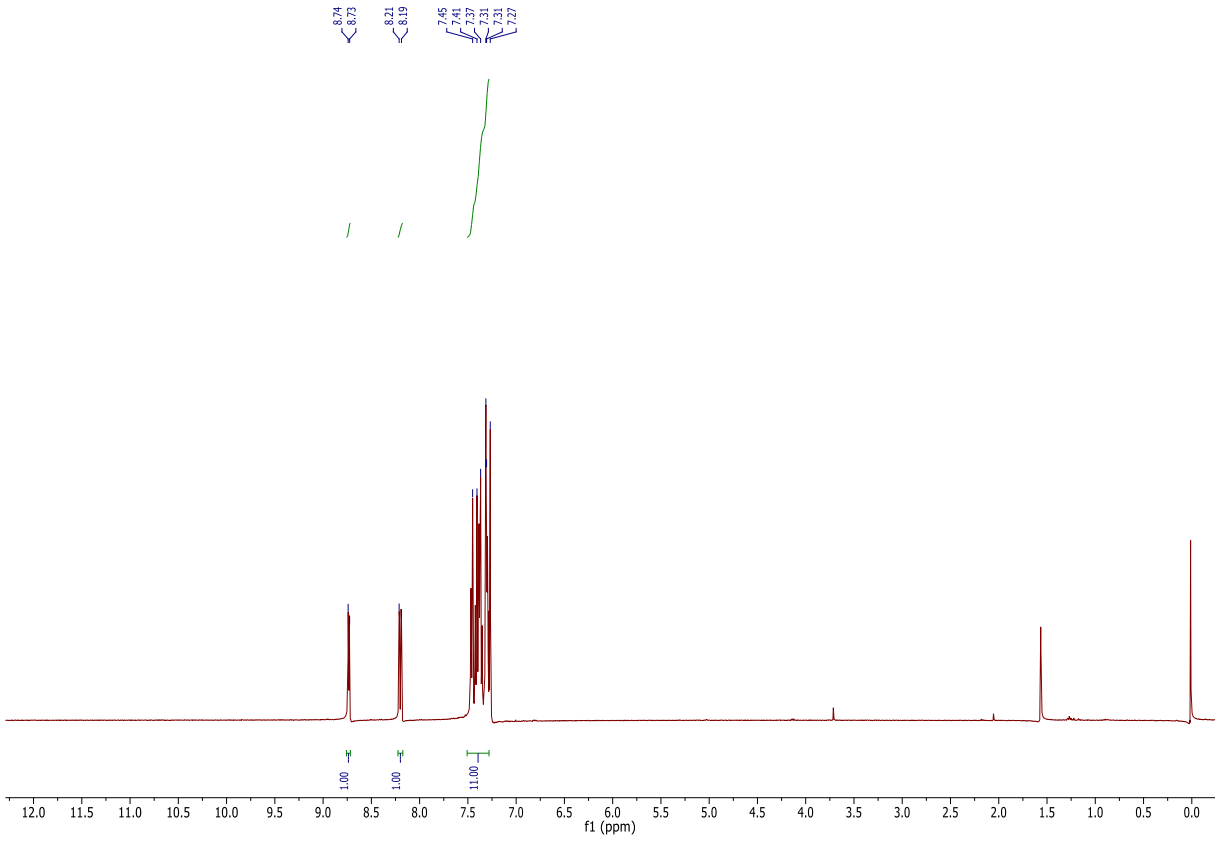


406

407 **2,3-diphenylthieno[3,2-b]pyridine (25)**



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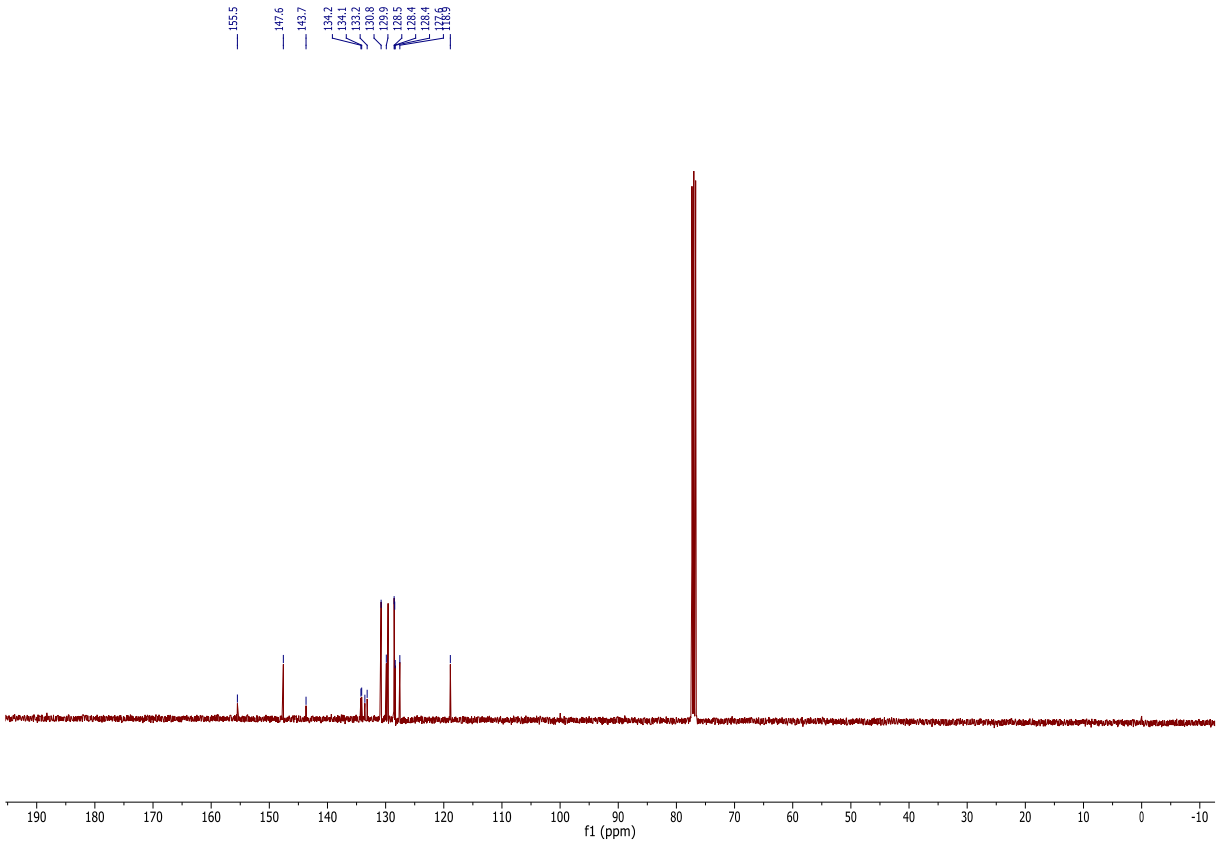
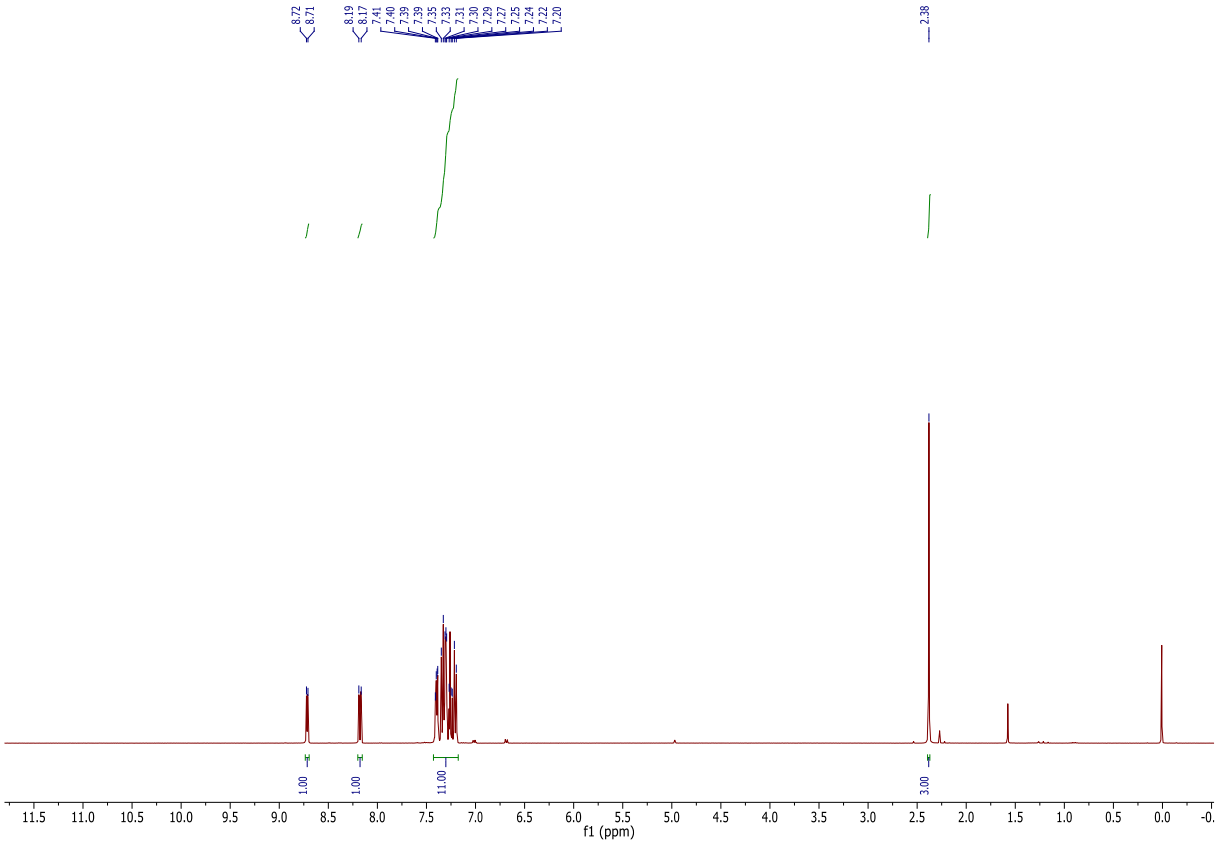


409

410 **2-phenyl-3-(p-tolyl)thieno[3,2-b]pyridine (26)**



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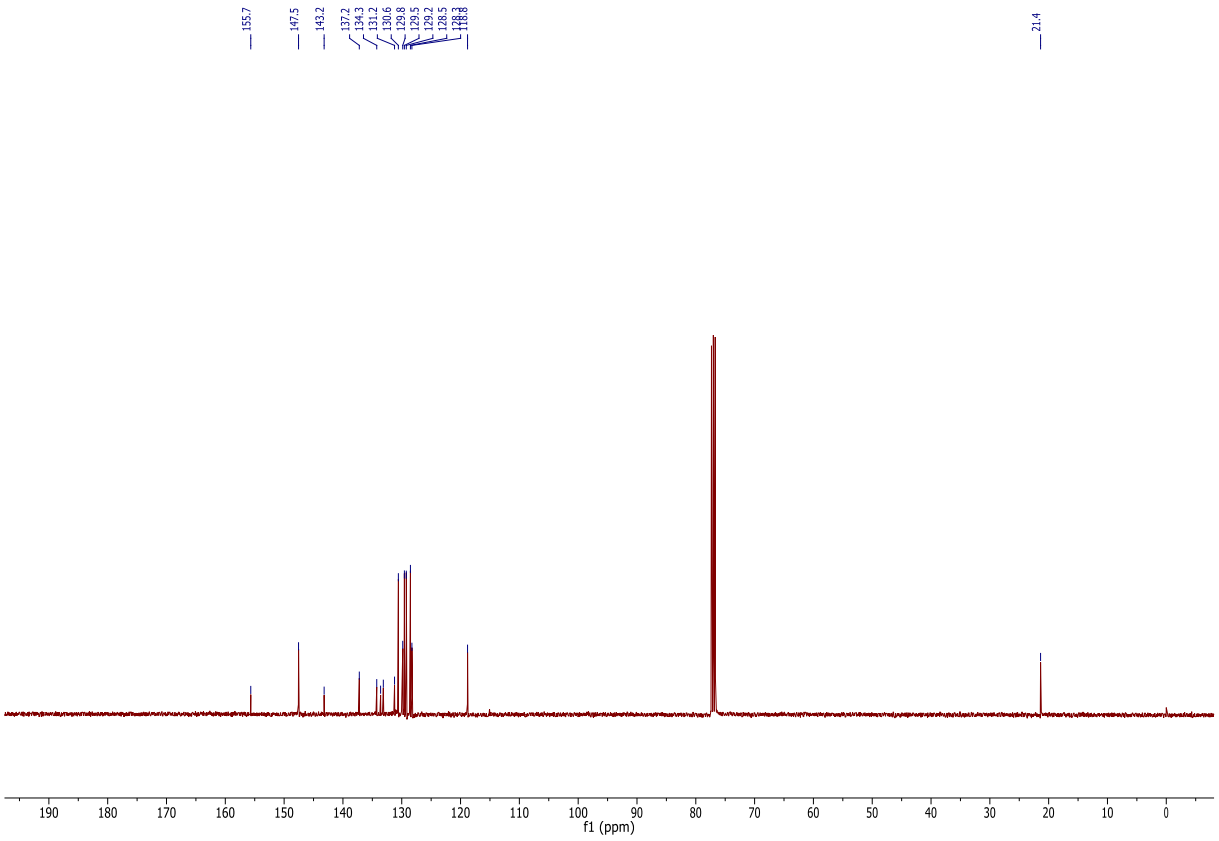

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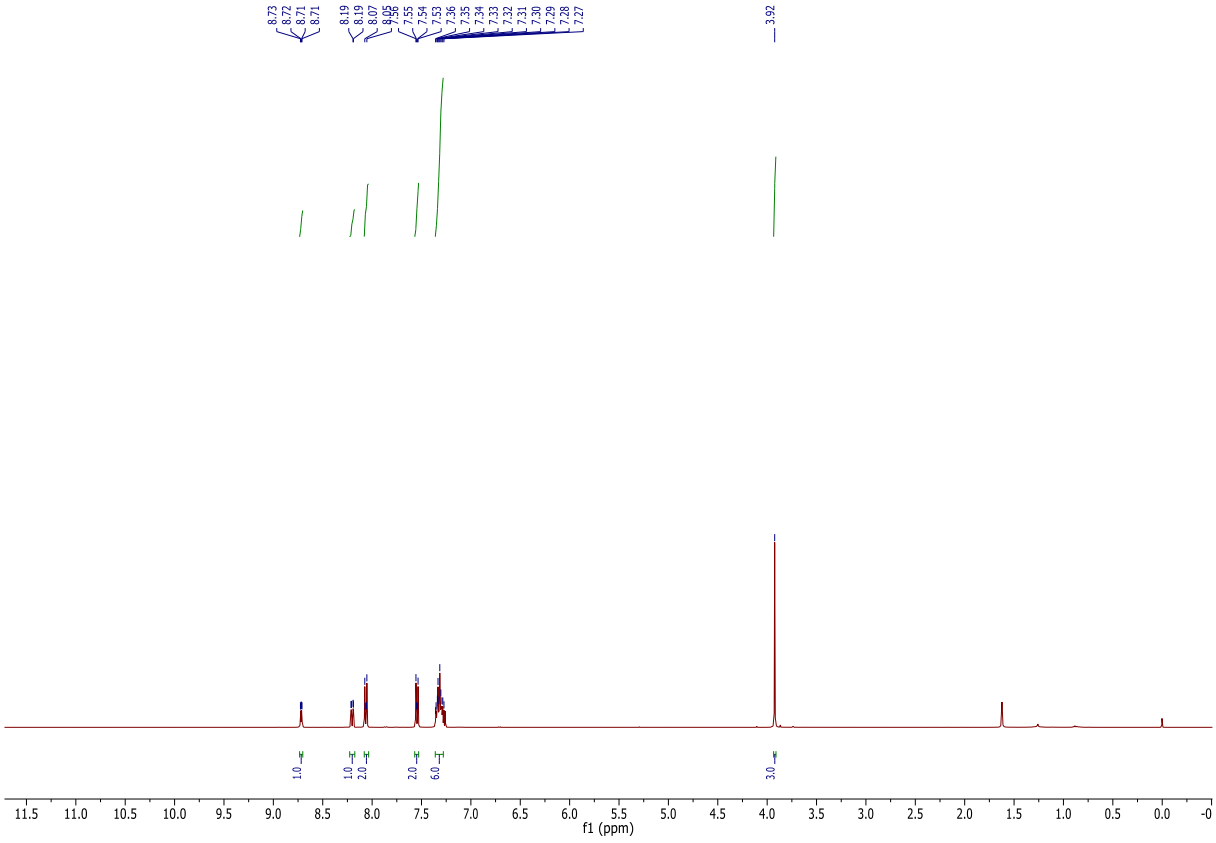
413

414 **methyl 4-(2-phenylthieno[3,2-b]pyridin-3-yl)benzoate (27)**



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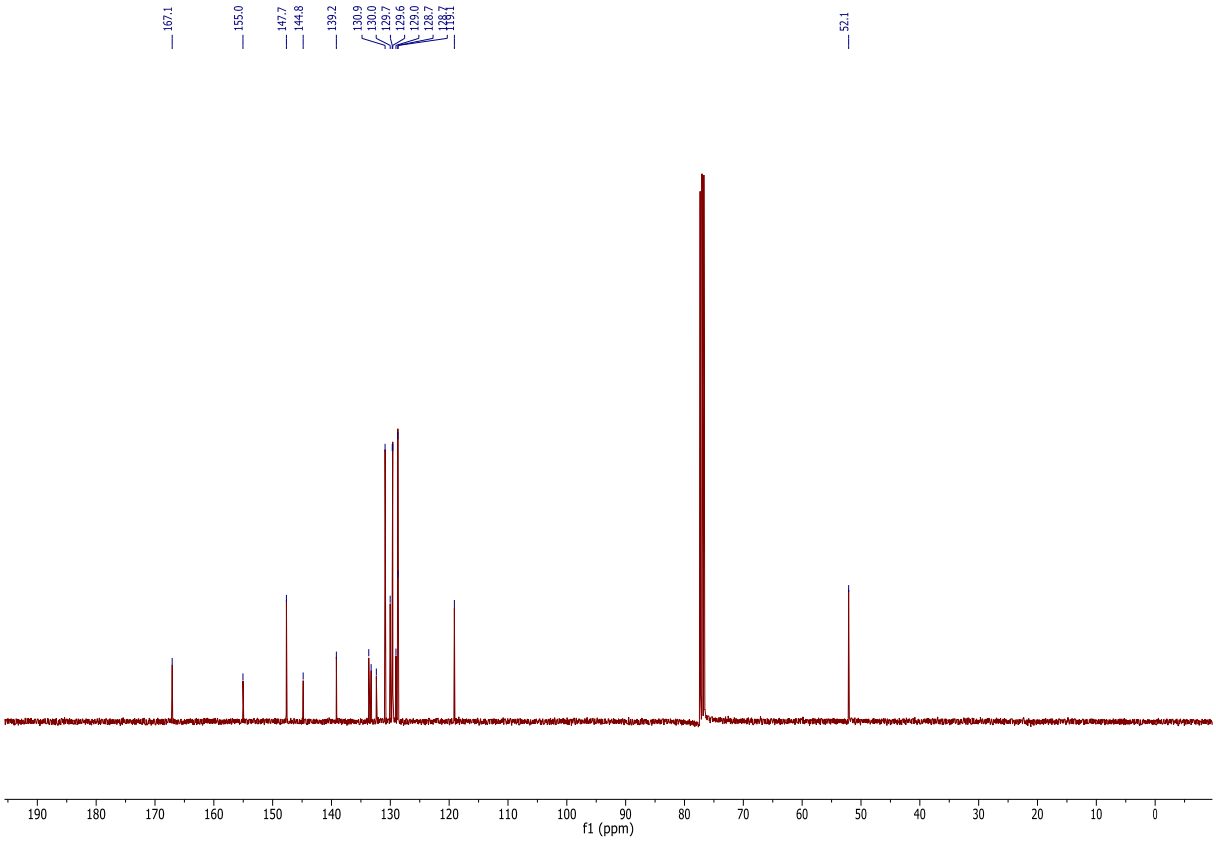
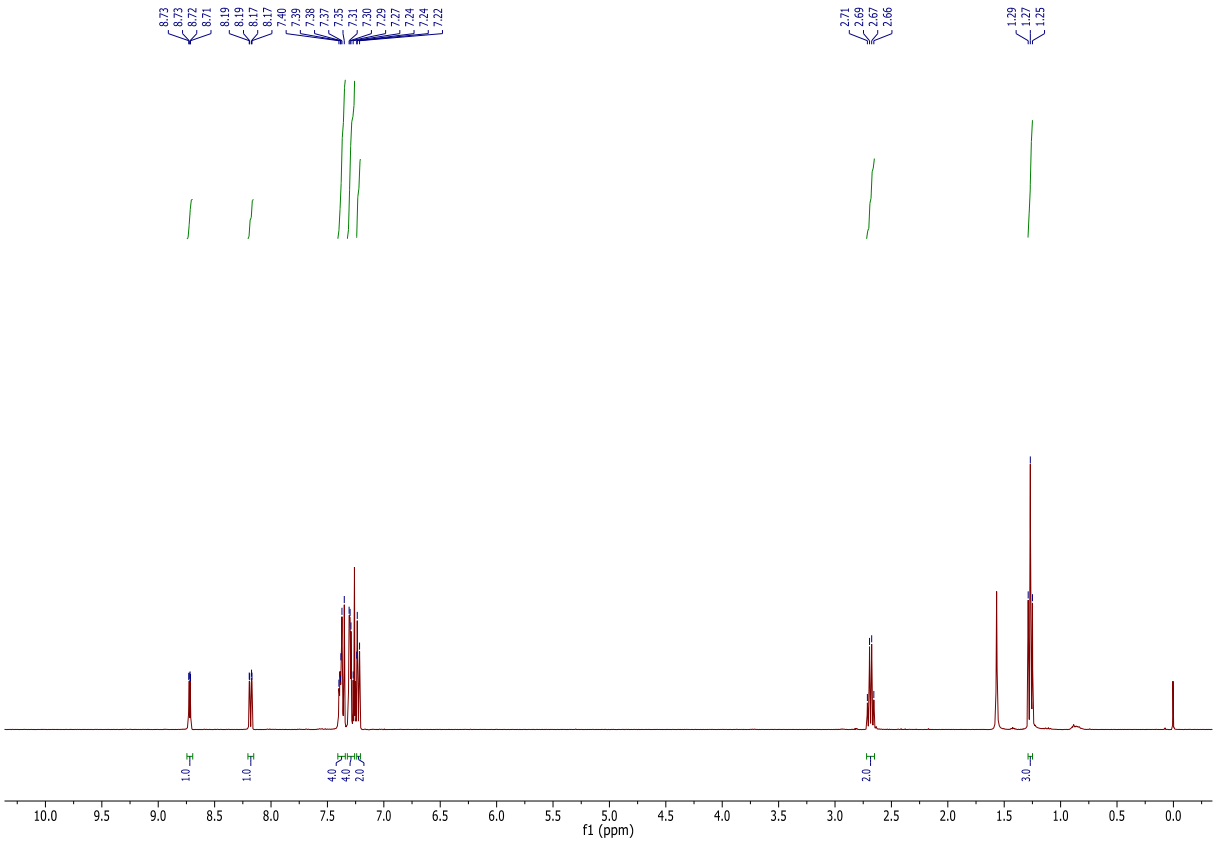


416

417 **3-(4-ethylphenyl)-2-phenylthieno[3,2-b]pyridine (28)**



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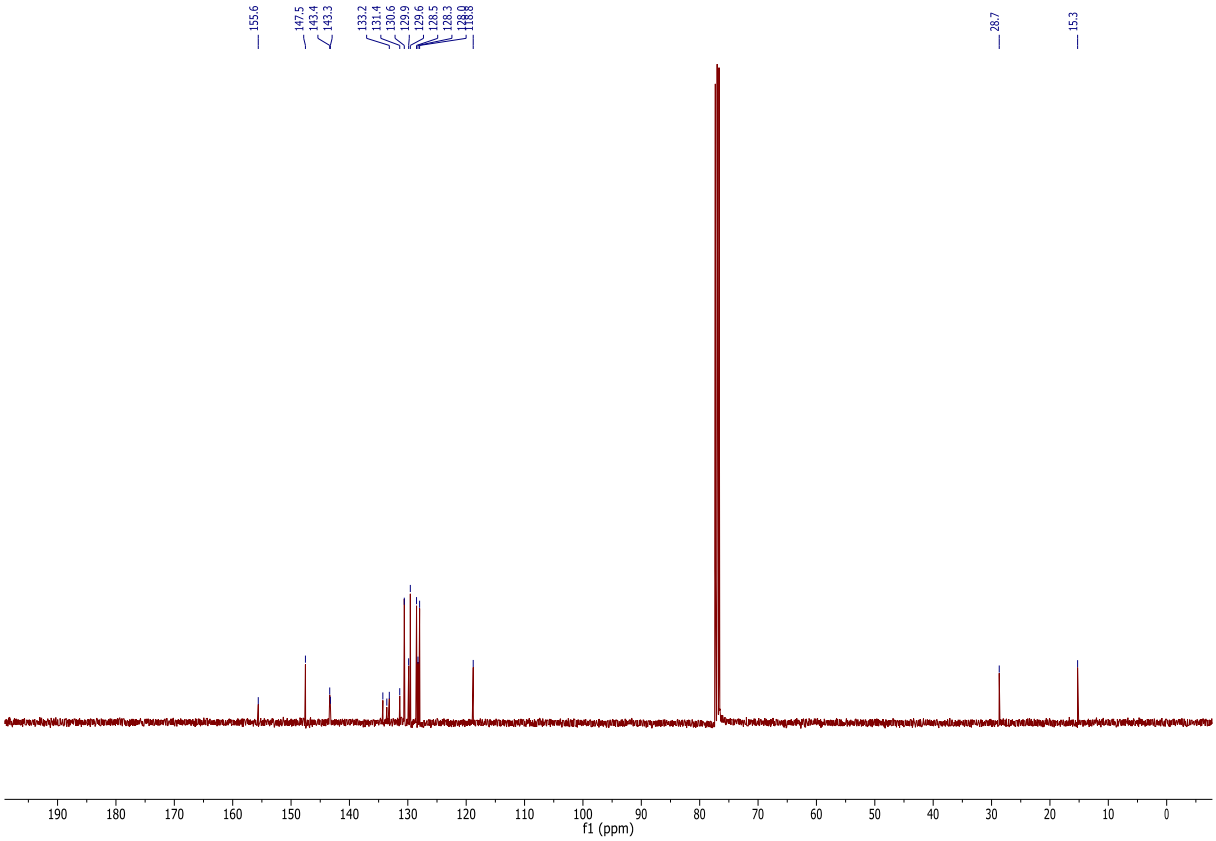

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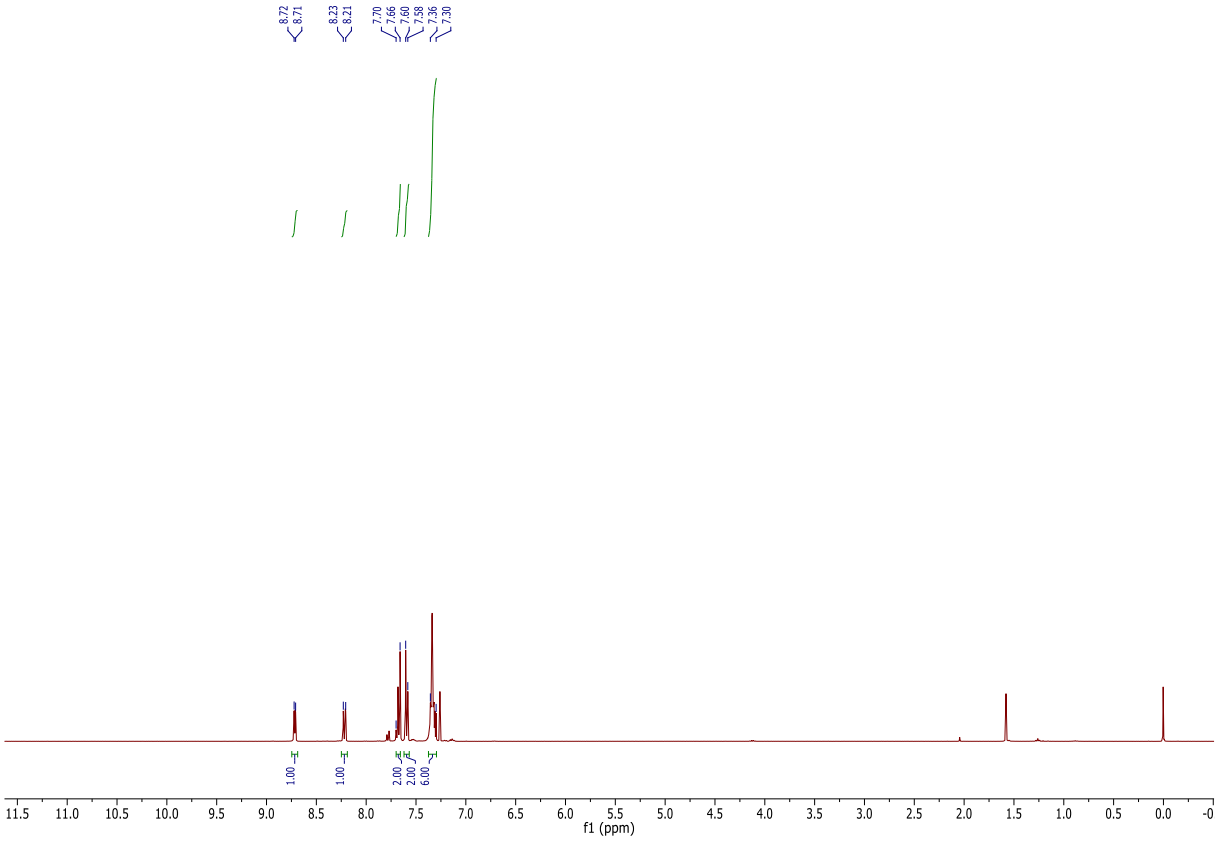
420 **4-(2-phenylthieno[3,2-b]pyridin-3-yl)benzonitrile (29)**



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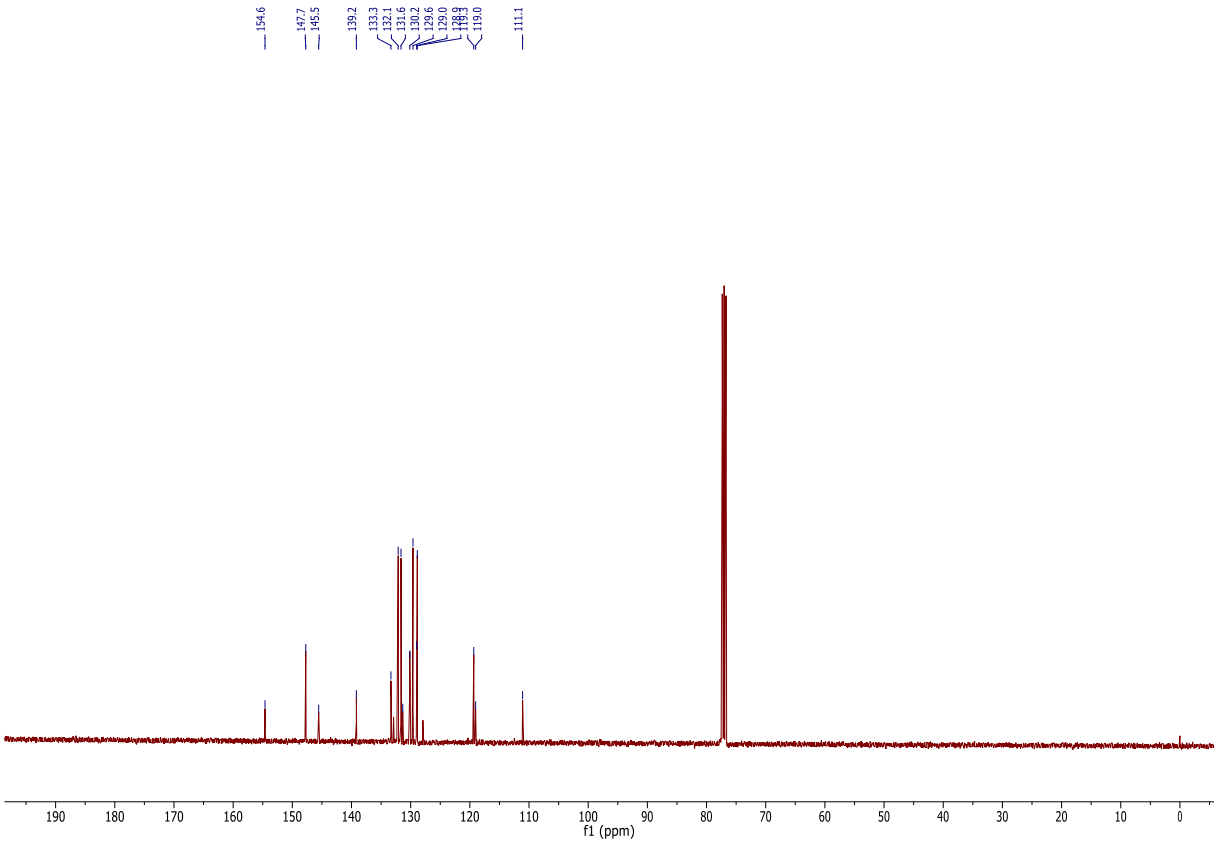
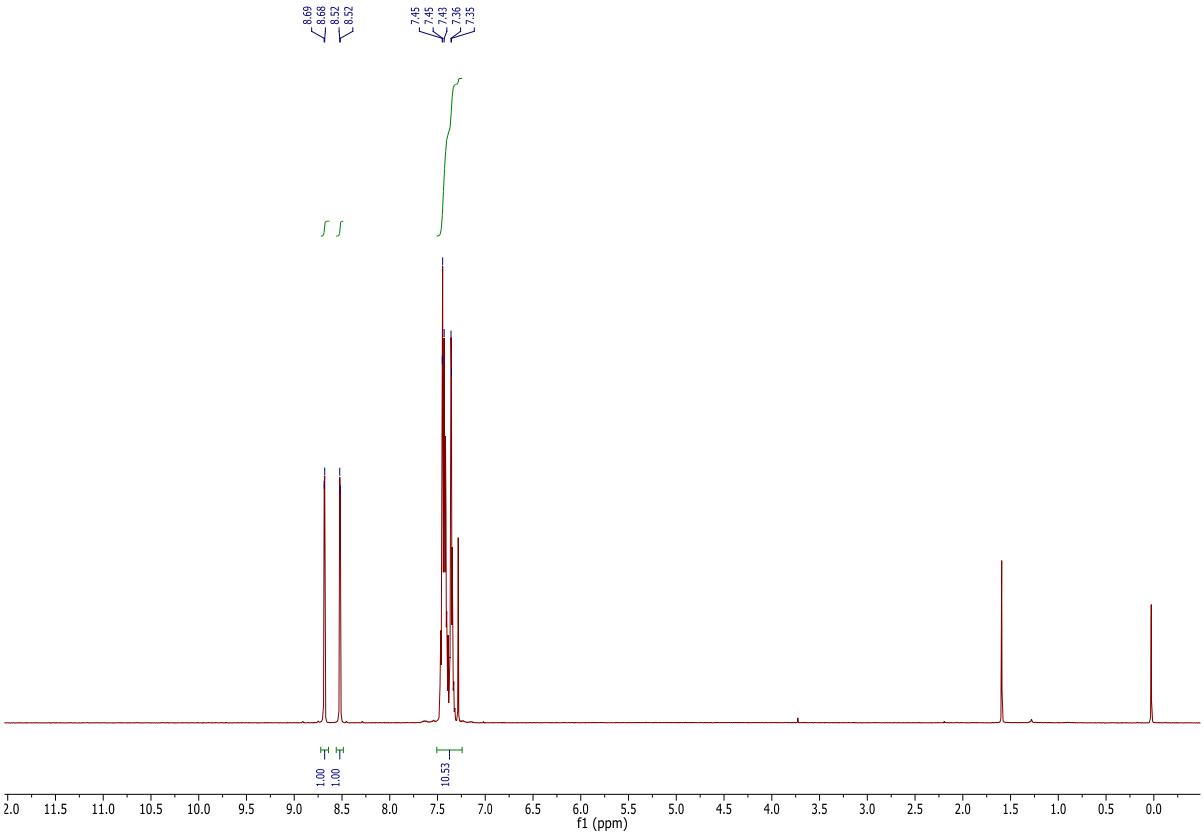


422

423 **6,7-diphenylthieno[2,3-b]pyrazine (30)**



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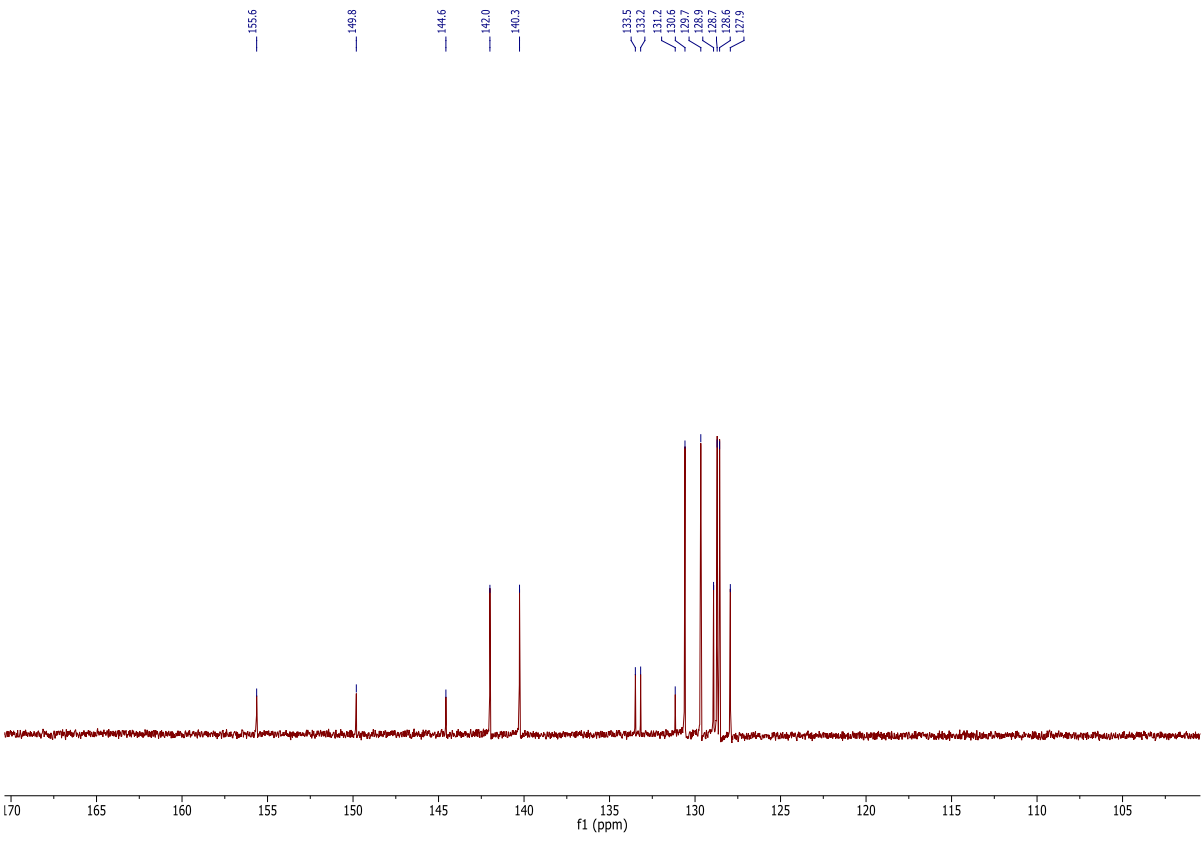
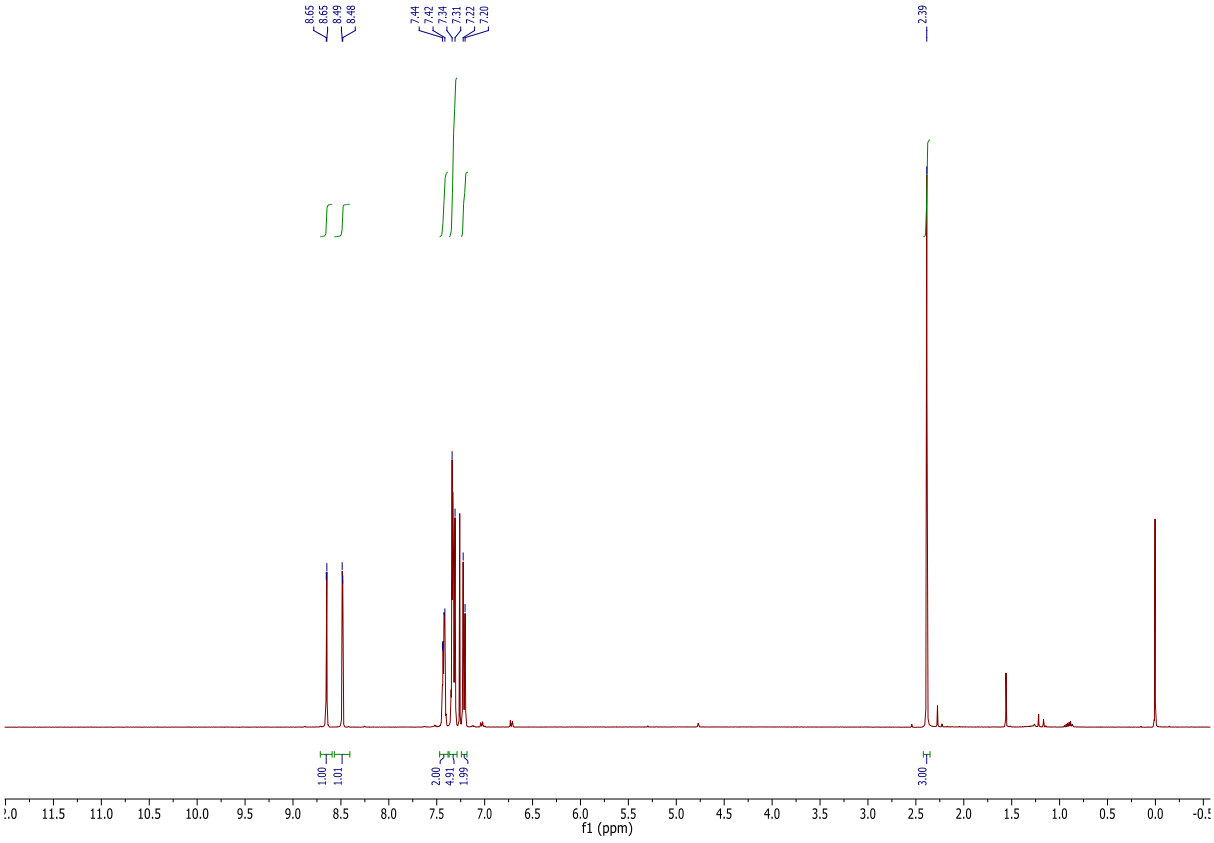


425

426

427 **6-phenyl-7-(p-tolyl)thieno[2,3-b]pyrazine (31)**



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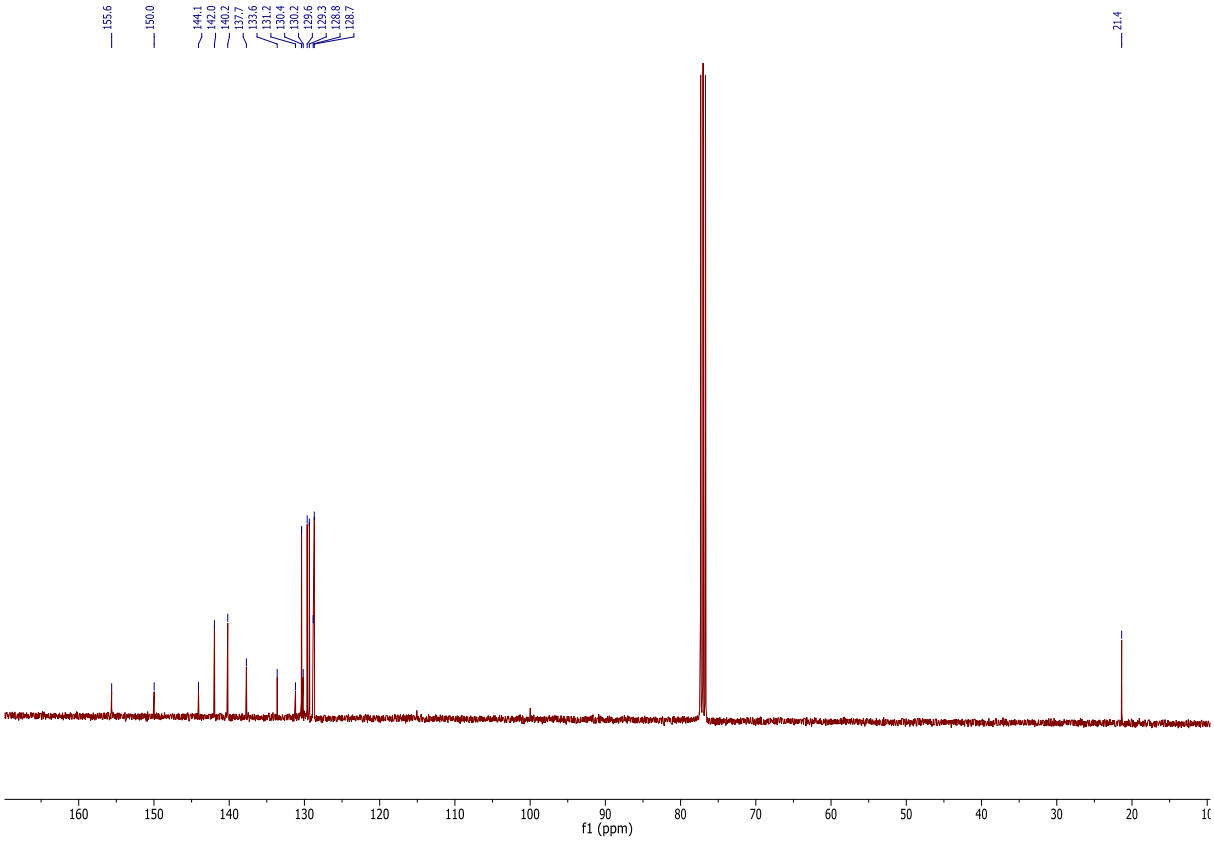
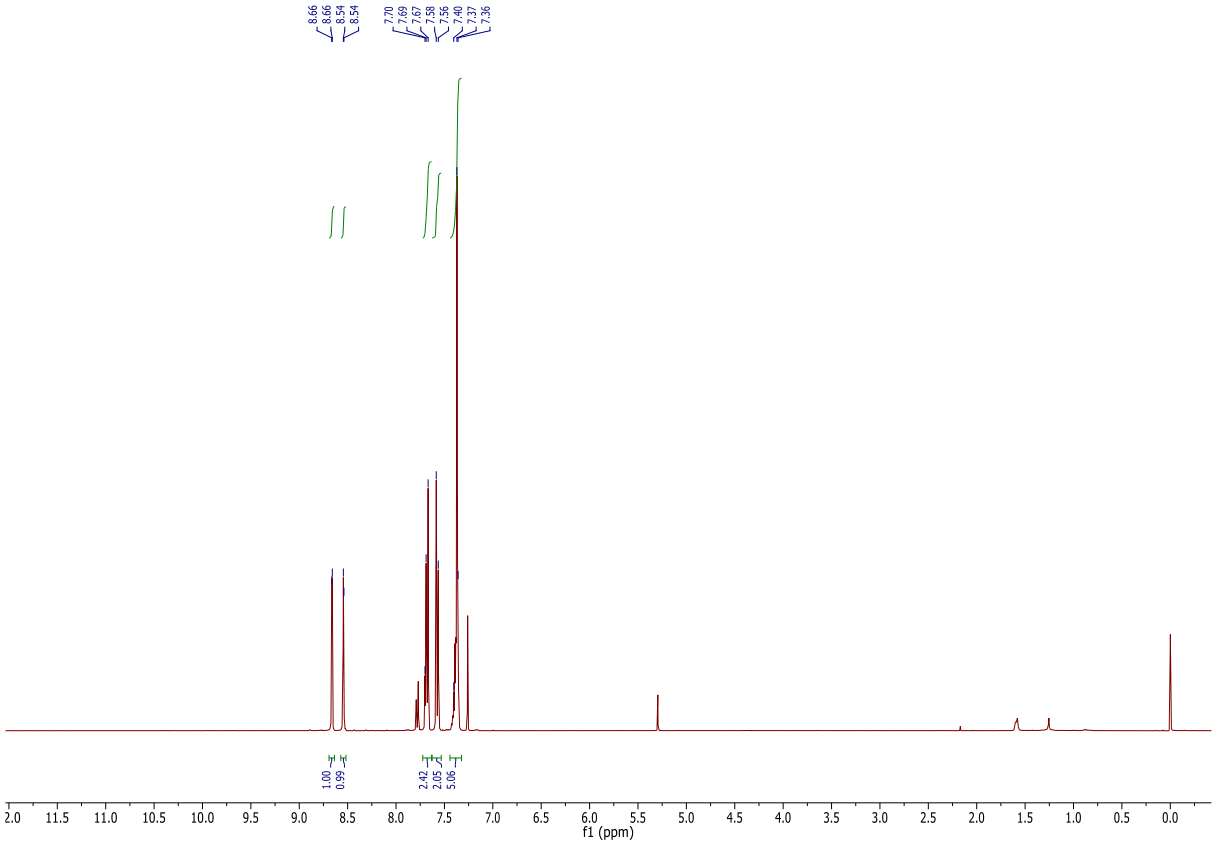


429

430 **4-(6-phenylthieno[2,3-b]pyrazin-7-yl)benzonitrile (32)**



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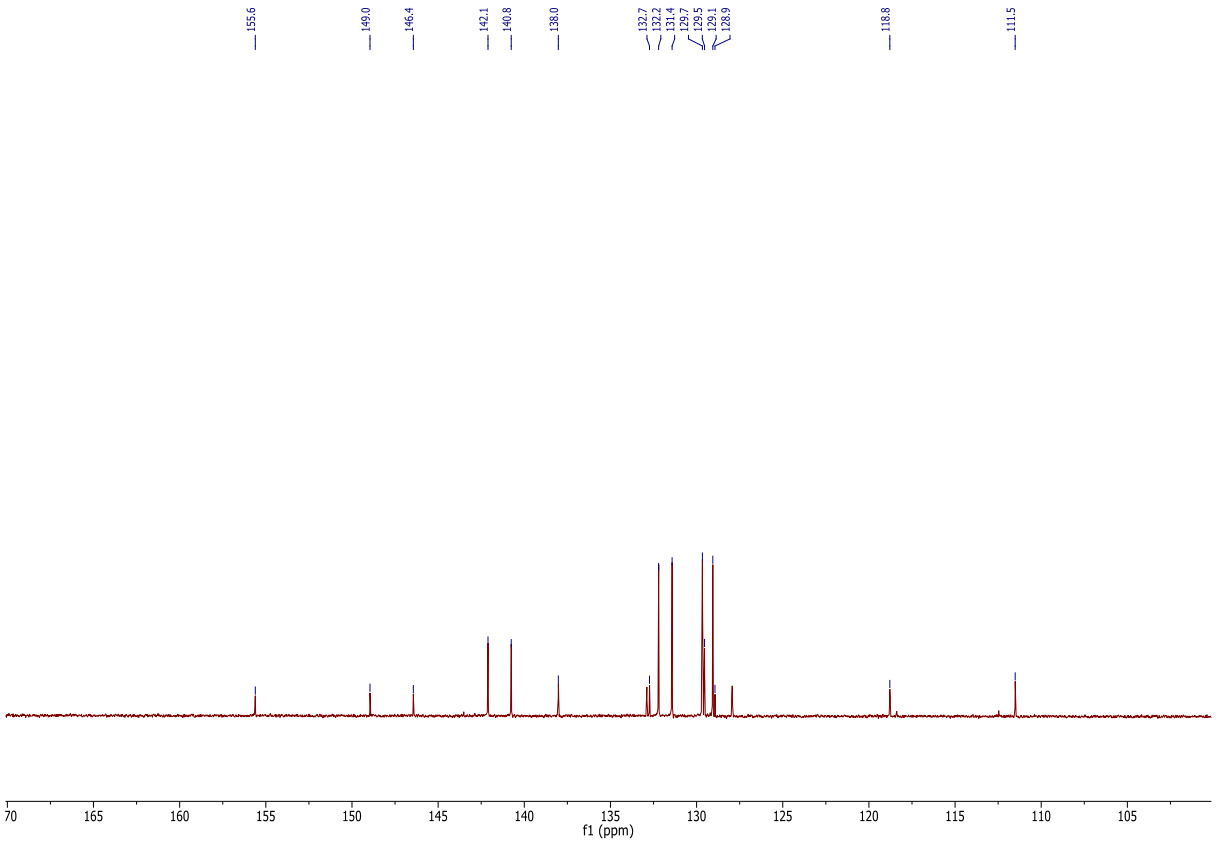

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433 *1.4. References*

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