10.1071/CH13266_AC

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SUPPLEMENTARY MATERIAL

Development of inhibitors of *Plasmodium falciparum* apical membrane antigen 1 based on fragment screening

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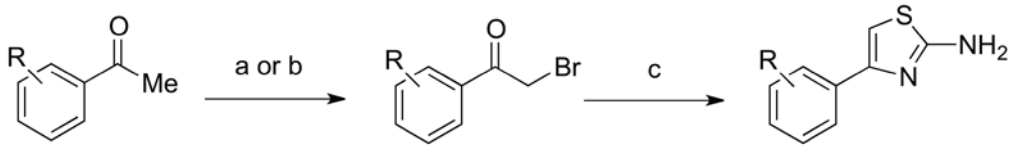
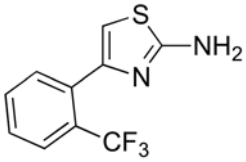


Synthesis of the 2-aminothiazoles. (a) For **10**, **11**, **12**, **13**, **14**, **16**, **17**, **18**: Br_2, MeCN, 100 ^oC, 2 h; (b) For **15**, **19**, **20**, **21**: Br_2, $CHCl_3$, 50 ^oC, 2 h; (c) thiourea, MeCN, 100 ^oC, 2 h.

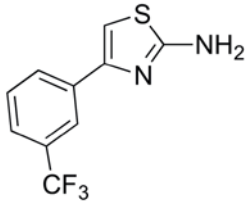
General methods: Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. All NMR spectra were recorded on a Bruker Avance III 400-MHz Ultrashield Plus spectrometer and ^1H, ^{19}F and ^{13}C NMR spectra were recorded at 400, 376 and 101 MHz, respectively. Thin-layer chromatography was conducted on 0.2 mm plates using Merck silica gel 60 F254. Column chromatography was achieved using Merck silica gel 60 (article size 0.063–0.200μm, 70–230 mesh). High resolution mass spectra were obtained on a Waters 2795 Alliance Separations Module. LCMS were routinely run to verify reaction outcome using an Agilent 6100 Series Single Quad couple to an Agilent 1200 Series HPLC. All compounds were of > 95% purity.

4-(2-(Trifluoromethyl)phenyl)thiazol-2-amine (10)



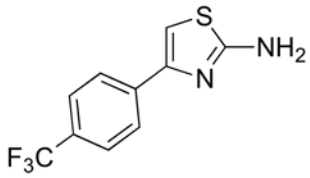
2'-(Trifluoromethyl)acetophenone (200 mg, 1.06 mmol, 159 µL) was added to MeCN (3 mL). Br_2 (93 mg, 1.17 mmol, 30 µL) was added dropwise to the mixture at room temperature. The mixture was then heated for 2 h at 100 °C. At this time, thiourea (89 mg, 1.17 mmol) was added to the cooled reaction mixture, which was then heated for a further 2 h at 100 °C. The reaction was cooled on ice and the precipitate that formed was filtered. This solid was dissolved in EtOAc (20 mL) and washed twice with Na_2CO_3 (1M) (20 mL). The organic fraction was dried over $MgSO_4$ and the filtrate reduced *in vacuo* to yield a white compound. The compound was purified using column chromatography using a step gradient from Hexane: EtOAc (1:1) to EtOAc 100 % to yield a crystalline white solid (48 mg, 20 %). m.p: 116-118 ^oC. Analytical HPLC indicates greater than 97 % purity at 254 nm; ^1H NMR (400 MHz; DMSO): δ 7.76 (d, *J* = 7.9 Hz, 1H, ArH), 7.70-7.64 (m, 1H, ArH), 7.63-7.58 (m, 1H, ArH), 7.55 (dd, *J* = 11.2, 3.9 Hz, 1H, ArH), 7.02 (br s, 2H, NH_2), 6.58 (s, 1H, ArH); ^{19}F NMR (376 MHz; DMSO) δ -56.3 (s, CF_3); ^{13}C NMR (101 MHz, DMSO): δ 167.7 (C), 147.5 (C), 135.2 (q, *J* = 3.0 Hz, C), 132.1 (CH), 131.8 (CH), 128.1 (CH), 126.6 (q, *J* = 32.0 Hz, *C*CF_3), 126.2 (q, *J* = 5.5 Hz, CH), 124.2 (q, *J* = 273.6 Hz, C*C*F_3), 104.9 (q, *J* = 3.0 Hz, CH). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 245.0355; Observed $[M+H]^+$ = 245.0353.

4-(3-(Trifluoromethyl)phenyl)thiazol-2-amine (11)



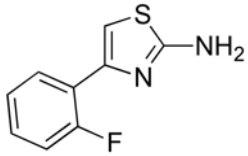
Same procedure as for **10**, from 3'-(trifluoromethyl)acetophenone gave a golden yellow solid (59 mg, 23 %). m.p: 78-80 ^{o}C. Analytical HPLC indicates greater than 95 % purity at 254 nm; ^{1}H NMR (400 MHz; MeOD): δ 8.05 (s, 1H, ArH), 7.95 (d, *J* = 7.1 Hz, 1H, ArH), 7.54-7.48 (m, 2H, ArH), 6.94 (s, 1H, ArH); ^{19}F NMR (376 MHz; MeOD) δ -64.1 (s, CF_3); ^{13}C NMR (101 MHz, MeOD): δ 171.4 (d, *J* = 6.8 Hz, C), 149.6 (d, *J* = 13.1 Hz, C), 136.8 (d, *J* = 2.2 Hz, C), 131.9 (q, *J* = 32.1 Hz, *C*CF_3), 130.3 (CH), 130.2 (d, *J* = 1.0 Hz, CH), 125.8 (q, *J* = 271.1 Hz, C*C*F_3), 124.9 (q, *J* = 3.9 Hz, CH), 123.5 (q, *J* = 3.9 Hz, CH), 104.5 (CH). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 245.0355; Observed $[M+H]^+$ = 245.0355.

4-(4-(Trifluoromethyl)phenyl)thiazol-2-amine (12)



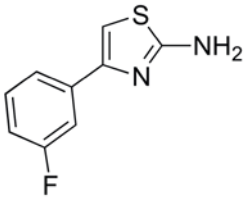
Same procedure as for **10**, from 4'-(trifluoromethyl)acetophenone gave a light orange solid (39 mg, 15 %). m.p: 158-160 ^{o}C. Analytical HPLC indicates greater than 97 % purity at 254 nm; ^{1}H NMR (400 MHz; DMSO): 8.00 (d, *J* = 8.0 Hz, 2H, ArH), 7.72 (d, *J* = 8.1 Hz, 2H, ArH), 7.25 (s, 1H, ArH), 7.21 (br s, 2H, NH_2); ^{19}F NMR (376 MHz; DMSO) δ -60.8 (s, CF_3); ^{13}C NMR (101 MHz, DMSO): δ 168.5 (C), 148.1 (C), 138.4 (C), 127.2 (q, *J* = 31.7 Hz, *C*CF_3), 126.0 (2 × CH), 125.5 (q, *J* = 3.7 Hz, 2 × CH), 124.4 (q, *J* = 272.0 Hz, C*C*F_3), 104.4 (CH). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 245.0355; Observed $[M+H]^+$ = 245.0353.

4-(2-Fluorophenyl)thiazol-2-amine (13)



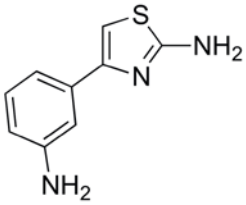
Same procedure as for **10**, from 2'-fluoroacetophenone gave a pink solid (31 mg, 11 %). m.p: 76-80 ^{o}C. Analytical HPLC indicates greater than 97 % purity at 254 nm; R_f: 0.3 (DCM: MeOH: NH_4 OH; 96: 2: 2); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.01 (td, *J* = 7.8, 1.9 Hz, 1H, ArH), 7.25 (dtd, *J* = 7.1, 5.4, 1.9 Hz, 1H, ArH), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H, ArH), 7.10 (ddd, *J* = 11.8, 8.0, 1.3 Hz, 1H, ArH), 7.02 (d, *J* = 2.2 Hz, 1H, ArH), 5.17 (br s, 2H, NH_2); ^{19}F NMR (376 MHz; $CDCl_3$) δ -114.2 (s, F); ^{13}C NMR (101 MHz; $CDCl_3$): 166.6 (C), 160.3 (d, *J* = 250.0 Hz, CF), 144.8 (d, *J* = 3.5 Hz, C), 129.8 (d, *J* = 3.3 Hz, CH), 128.9 (d, *J* = 8.6 Hz, CH), 124.4 (d, *J* = 3.5 Hz, CH), 122.4 (d, *J* = 11.3 Hz, C), 116.0 (d, *J* = 22.6 Hz, CH), 108.0 (d, *J* = 15.0 Hz, CH). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 195.0387; Observed $[M+H]^+$ = 195.0390.

4-(3-Fluorophenyl)thiazol-2-amine (14)



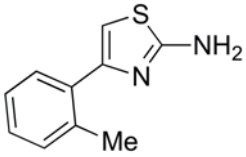
Same procedure as for **10**, from 3'-fluoroacetophenone gave a yellow powder (44 mg, 16 %) m.p: 75-78 ^{o}C. Analytical HPLC indicates greater than 97 % purity at 254 nm; R_f: 0.2, (DCM; 100); ^{1}H NMR (400 MHz; DMSO): δ 7.66-7.61 (m, 1H, ArH), 7.57 (ddd, *J* = 10.9, 2.6, 1.5 Hz, 1H, ArH), 7.39 (td, *J* = 8.0, 6.2 Hz, 1H, ArH), 7.14 (s, 1H, ArH), 7.13-7.02 (m, 3H, ArH, NH_2); ^{19}F NMR (376 MHz; DMSO) δ -113.4 (s, F); ^{13}C NMR (101 MHz, DMSO): δ 168.3 (C), 162.5 (d, *J* = 242.1 Hz, CF), 148.5 (d, *J* = 2.8 Hz, C), 137.3 (d, *J* = 8.2 Hz, C), 130.4 (d, *J* = 8.5 Hz, CH), 121.5 (d, *J* = 2.6 Hz, CH), 113.8 (d, *J* = 21.2 Hz, CH), 112.0 (d, *J* = 22.8 Hz, CH), 103.0 (CH). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 195.0387; Observed $[M+H]^+$ = 195.0389.

4-(3-Aminophenyl)thiazol-2-amine (15)



3'-Aminoacetophenone (500 mg, 3.70 mmol) was dissolved in $CHCl_3$ (3 mL). Br_2 (698 mg, 3.88 mmol, 225 µL) was added dropwise over 10 min whilst stirring at 0 ^{o}C. The mixture was then heated at 50 ^{o}C for 2 h, at which time the reaction mixture was cooled and quenched using Na_2CO_3 (1M). The biphasic mixture was added to $CHCl_3$ (20 mL) and washed twice with Na_2CO_3 (1M) (20 mL). The organic fraction was dried over $MgSO_4$ and the filtrate reduced *in vacuo* to yield a cream-coloured powder. The crude powder was dissolved in MeCN (4 mL), thiourea (187 mg, 2.45 mmol) was added and the mixture heated at 100 ^{o}C for 2 h. The reaction was cooled on ice and the precipitate that formed was filtered. This solid was dissolved in EtOAc (20 mL) and washed twice with Na_2CO_3 (1M) (20 mL). The organic fraction was dried over $MgSO_4$ and the filtrate reduced *in vacuo* to yield a white powder. The compound was purified using column chromatography using a step gradient from Hexane: EtOAc (1:1) to EtOAc 100 % to yield a light brown solid (36 mg, 5 %). m.p: 160-163 ^{o}C; Analytical HPLC indicates greater than 97 % purity at 254 nm; ^{1}H NMR (400 MHz; DMSO): δ 7.03-6.90 (m, 5H, 3 × ArH, NH_2), 6.77 (s, 1H, ArH), 6.45 (ddd, J = 7.7, 2.3, 1.2 Hz, 1H, ArH), 5.04 (br s, 2H, NH_2); ^{13}C NMR (101 MHz, DMSO): δ 167.8 (C), 150.7 (C), 148.6 (C), 135.5 (C), 128.8 (CH), 113.5 (CH), 113.0 (CH), 111.5 (CH), 100.5 (CH). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 192.0590; Observed $[M+H]^+$ = 192.0589.

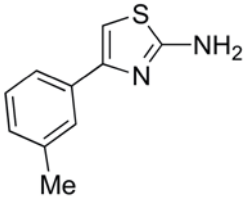
4-(o-Tolyl)thiazol-2-amine (16)



Same procedure as for **10**, from 2'-methylacetophenone gave a pink solid (84.5 mg, 30 %). m.p: 73-75 ^{o}C. Analytical HPLC indicates greater than 97 % purity at 254 nm; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.52 (ddd, J = 5.1, 3.7, 1.9 Hz, 1H, ArH), 7.39-7.11 (m, 3H, 3 × ArH), 6.45 (s, 1H, ArH), 5.28 (br s, 2H, NH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7 (C), 151.4 (C), 136.2 (C), 135.1 (C),

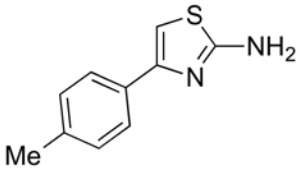
130.8 (CH), 129.7 (CH), 127.9 (CH), 125.9 (CH), 105.8 (CH), 21.1 (CH_3). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 191.0637; Observed $[M+H]^+$ = 191.0632.

4-(*m*-Tolyl)thiazol-2-amine (17)



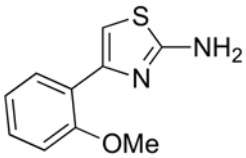
Same procedure as for **10**, from 3'-methylacetophenone gave a bright yellow solid (63.3 mg, 22 %). m.p: 56-58 ^oC. Analytical HPLC indicates greater than 97 % purity at 254 nm; ^1H NMR (400 MHz; DMSO): δ 7.62 (s, 1H, ArH), 7.57 (d, *J* = 7.8 Hz, 1H, ArH), 7.23 (t, *J* = 7.6 Hz, 1H, ArH), 7.06 (dd, *J* = 8.1, 0.6 Hz, 1H, ArH), 7.02 (br s, 2H, NH_2), 6.96 (s, 1H, ArH), 2.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO): δ 168.1 (C), 149.9 (C), 137.4 (C), 134.8 (C), 128.3 (CH), 127.8 (CH), 126.2 (CH), 122.7 (CH), 101.3 (CH), 21.1 (CH_3). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 191.0637; Observed $[M+H]^+$ = 191.0637.

4-(*p*-Tolyl)thiazol-2-amine (18)



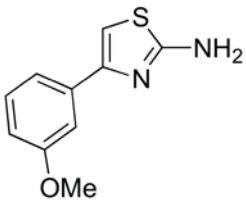
Same procedure as for **10**, from 4'-methylacetophenone gave a light yellow powder (40 mg, 14 %). m.p: 100-102 ^oC. Analytical HPLC indicates greater than 97 % purity at 254 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H, 2 × ArH), 7.18 (d, *J* = 7.9 Hz, 2H**,** 2 × ArH), 6.67 (s, 1H, ArH), 5.03 (br s, 2H, NH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): 167.2 (C), 151.5 (C), 137.7 (C), 132.1 (C), 129.4 (2 × CH), 126.0 (2 × CH), 102.2 (CH), 21.4 (CH_3). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 191.0637; Observed $[M+H]^+$ = 191.0639.

4-(2-Methoxyphenyl)thiazol-2-amine (19)



Same procedure as for **15**, from 2'-methoxyacetophenone gave a white powder (262 mg, 38%). m.p: 83-85^oC. Analytical HPLC indicates greater than 98 % purity at 254 nm; ^1H NMR (400 MHz; DMSO): δ 8.02 (dd, *J* = 7.7, 1.8 Hz, 1H, ArH), 7.23 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H, ArH), 7.11 (s, 1H, ArH), 7.05 (dd, *J* = 8.3, 0.9 Hz, 1H, ArH), 7.01-6.90 (m, 3H, ArH, NH_2), 3.87 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO): δ 166.3 (C), 156.5 (C), 145.8 (C), 129.3 (CH), 128.0 (CH), 123.1 (C), 120.3 (CH), 111.4 (CH), 105.7 (CH), 55.3 (OCH_3). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 207.0587 ; Observed $[M+H]^+$ = 207.0593.

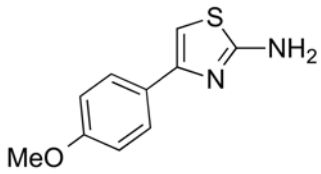
4-(3-Methoxyphenyl)thiazol-2-amine (20)



Same procedure as for **15**, from 3'-methoxyacetophenone gave a yellow solid (95 mg, 14 %). m.p: 98-100 ^oC. Analytical HPLC indicates greater than 97 % purity at 254 nm; ^1H NMR (400 MHz; DMSO): δ 7.38-7.35 (m, 2H, ArH), 7.26 (t, *J* = 7.9 Hz, 1H, ArH), 7.05 (br s, 2H, NH_2), 7.02 (s, 1H, ArH), 6.82 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H, ArH), 3.77 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO): δ 168.0 (C), 159.4 (C), 149.7 (C), 136.3 (C), 129.5 (CH), 117.9 (CH), 113.0 (CH),

110.8 (CH), 101.9 (CH), 55.0 (OCH_3). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 207.0587; Observed $[M+H]^+$ = 207.0585

4-(4-Methoxyphenyl)thiazol-2-amine (21)

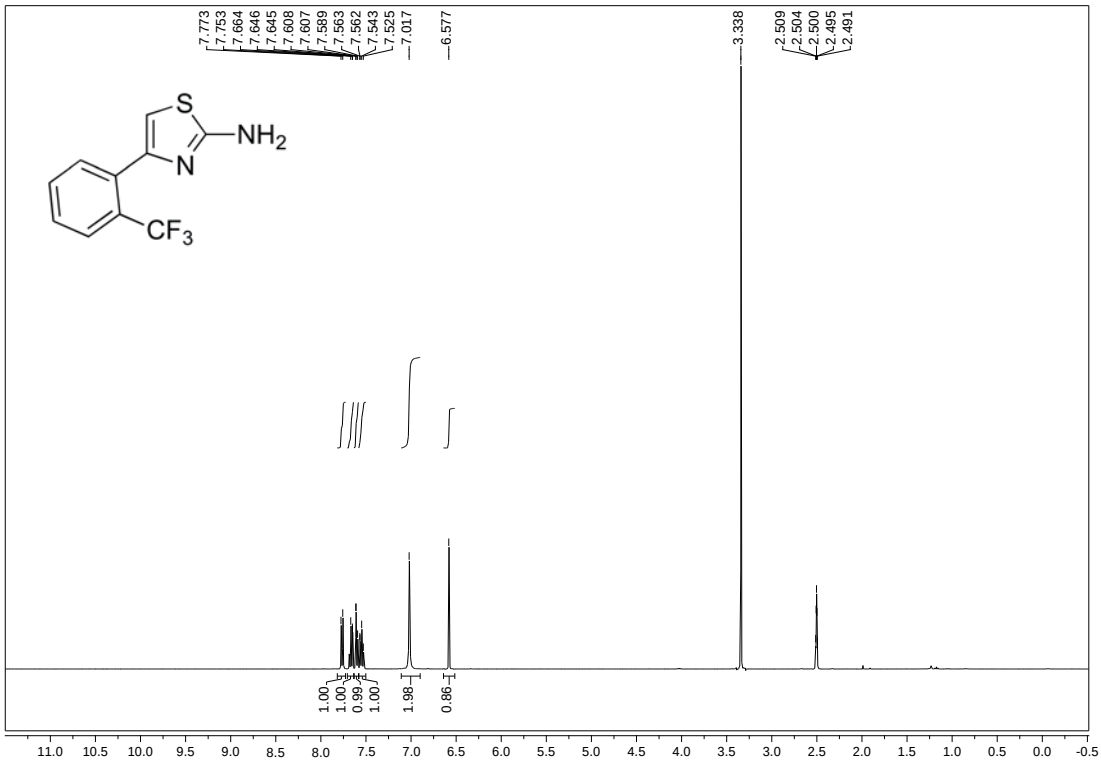


Same procedure as for **15**, from 4'-methoxyacetophenone gave a beige solid (96 mg, 14 %). m.p: 185-187^{o}C**.** Analytical HPLC indicates greater than 98 % purity at 254 nm; ^{1}H NMR (400 MHz; DMSO): δ 7.72 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 6.99 (br s, 2H, NH_2), 6.92 (d, *J* = 8.9 Hz, 2H, 2 × ArH), 6.82 (s, 1H, ArH), 3.76 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO): δ 168.1 (C), 158.5 (C), 149.7 (C), 127.9 (C), 126.8 (2 × CH), 113.8 (2 × CH), 99.3 (CH), 55.1 (OCH_3). *m/z* (ESI-HRMS) Calc $[M+H]^+$ = 207.0587 ; Observed $[M+H]^+$ = 207.0593.

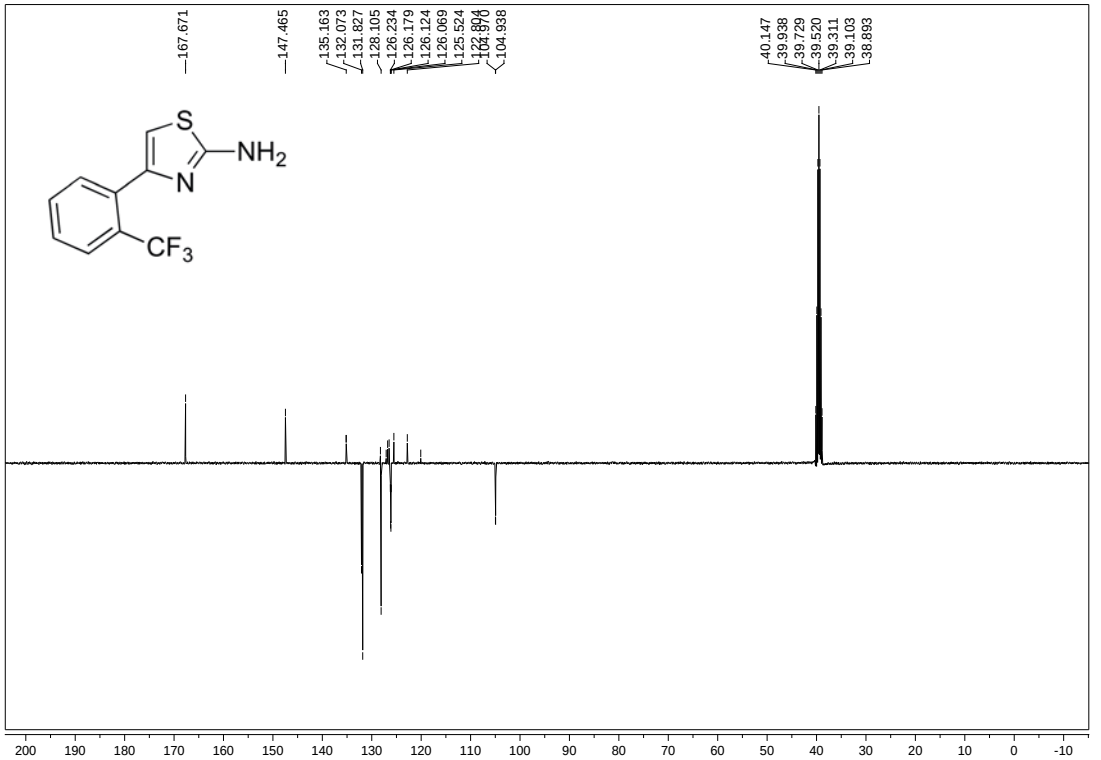
NMR Spectra

4-(2-(Trifluoromethyl)phenyl)thiazol-2-amine (10)

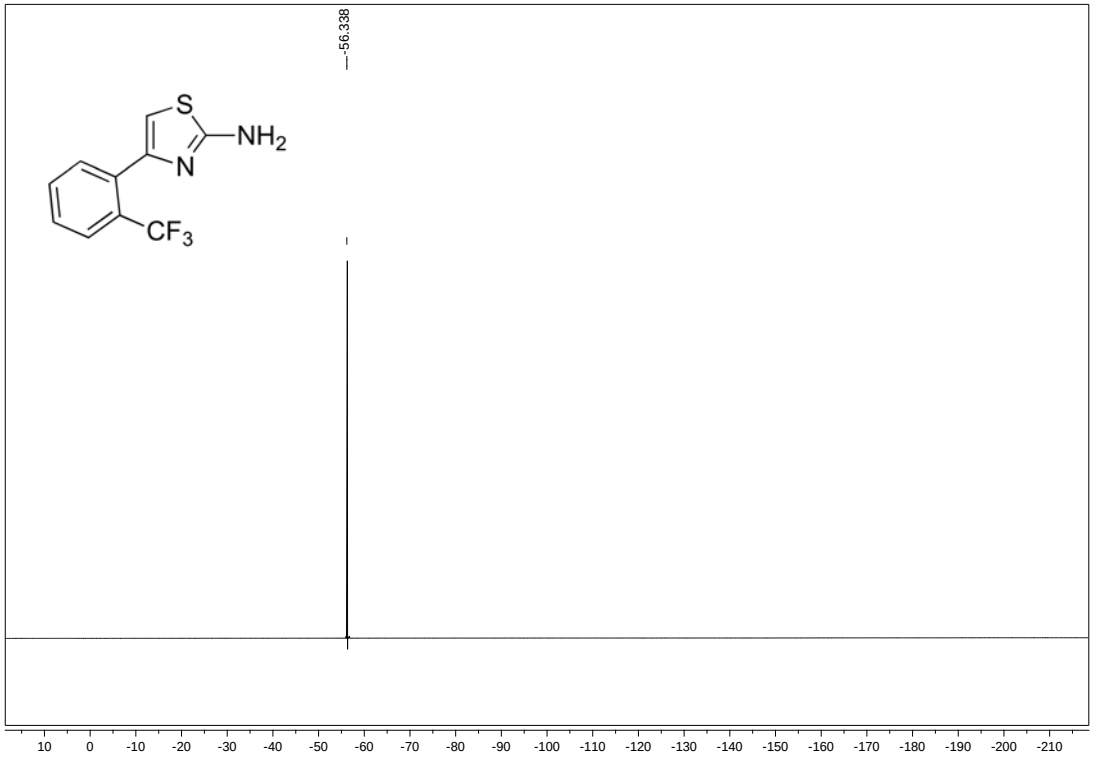
^{1}H NMR Spectrum (400 MHz, DMSO)



^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

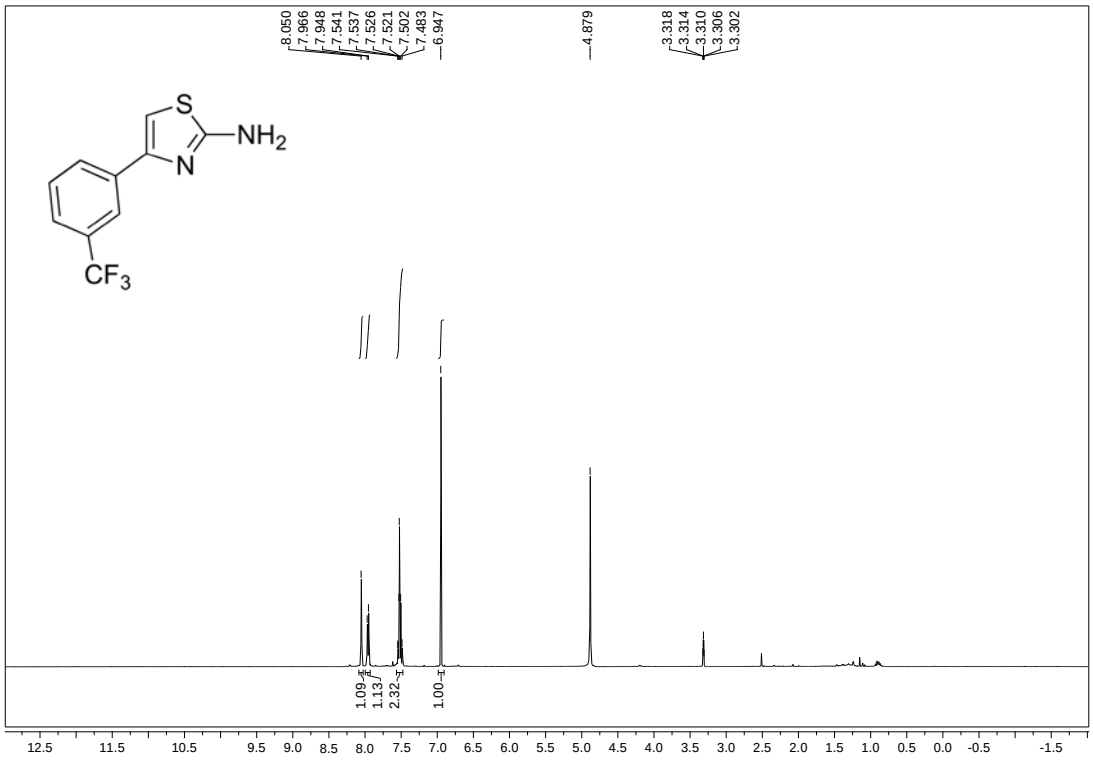


^{19}F NMR Spectrum (376 MHz, DMSO)

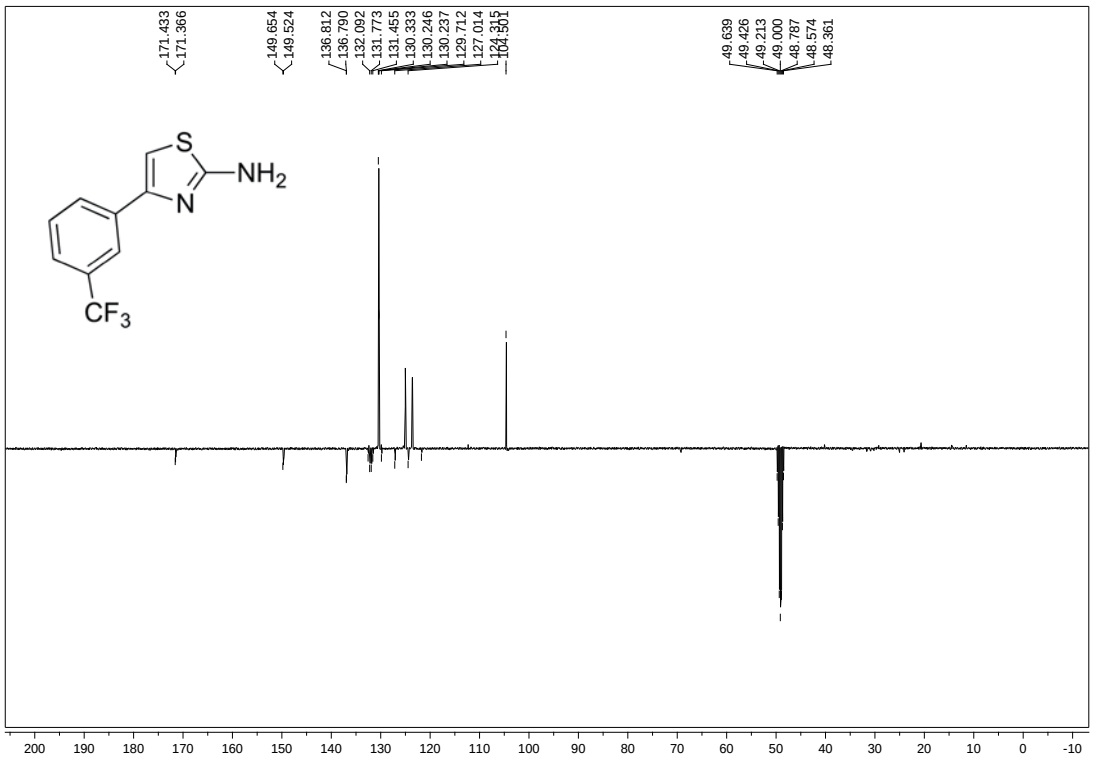


4-(3-(Trifluoromethyl)phenyl)thiazol-2-amine (11)

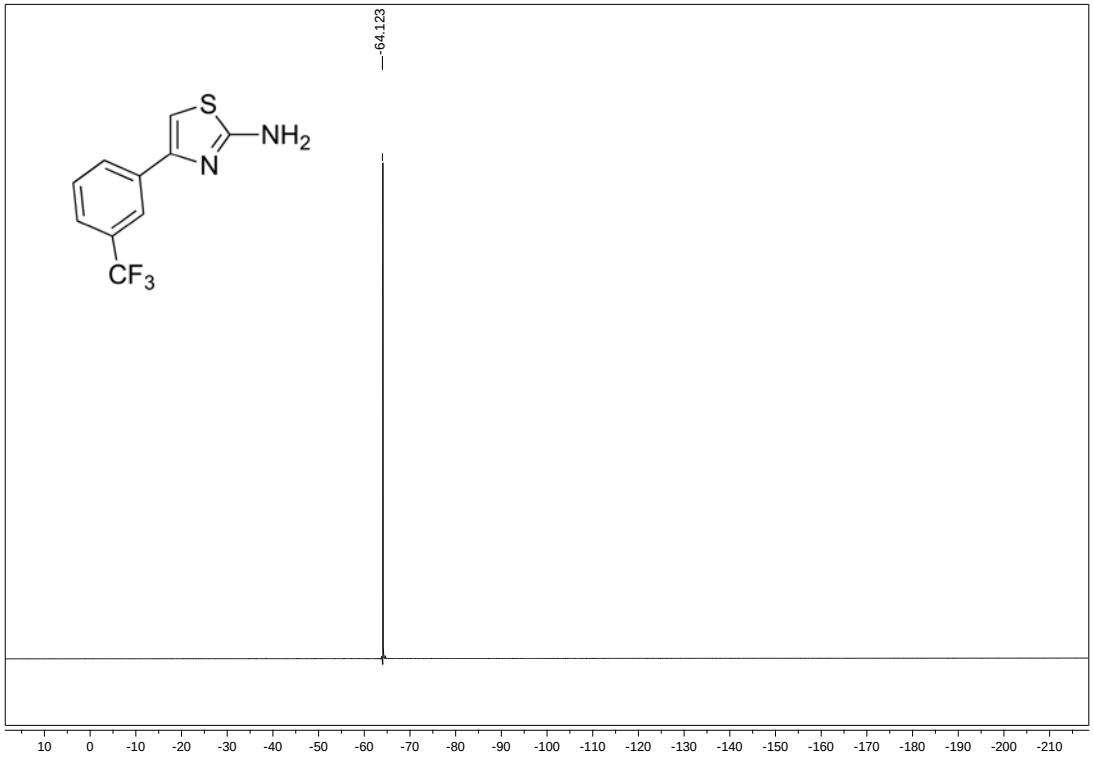
^{1}H NMR Spectrum (400 MHz, MeOD)



^{13}C DEPTQ NMR Spectrum (101 MHz, MeOD)

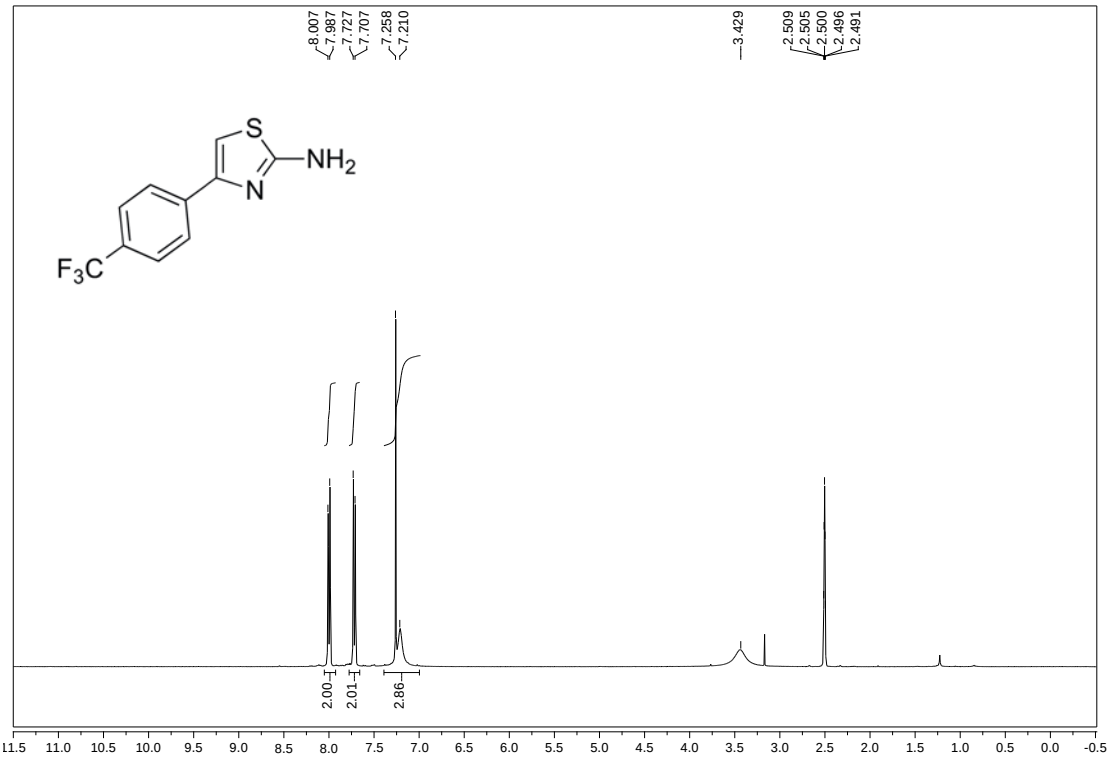


^{19}F NMR Spectrum (376 MHz, MeOD)

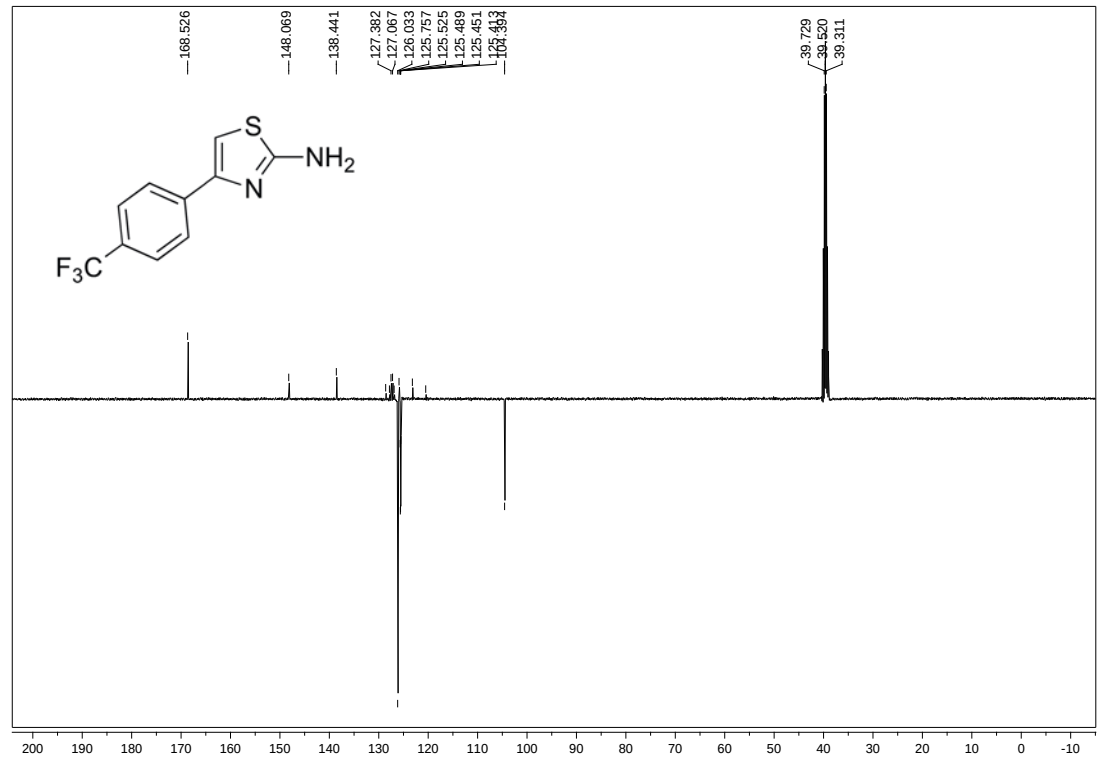


4-(4-(Trifluoromethyl)phenyl)thiazol-2-amine (12)

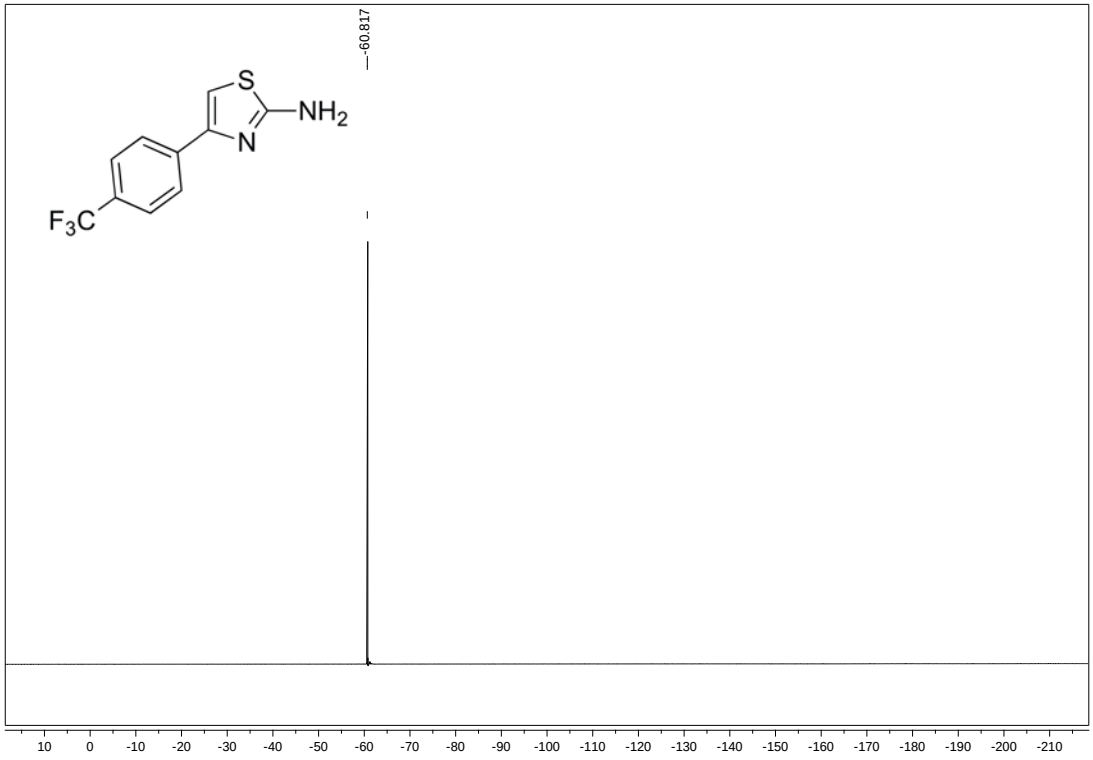
^{1}H NMR Spectrum (400 MHz, DMSO)



^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

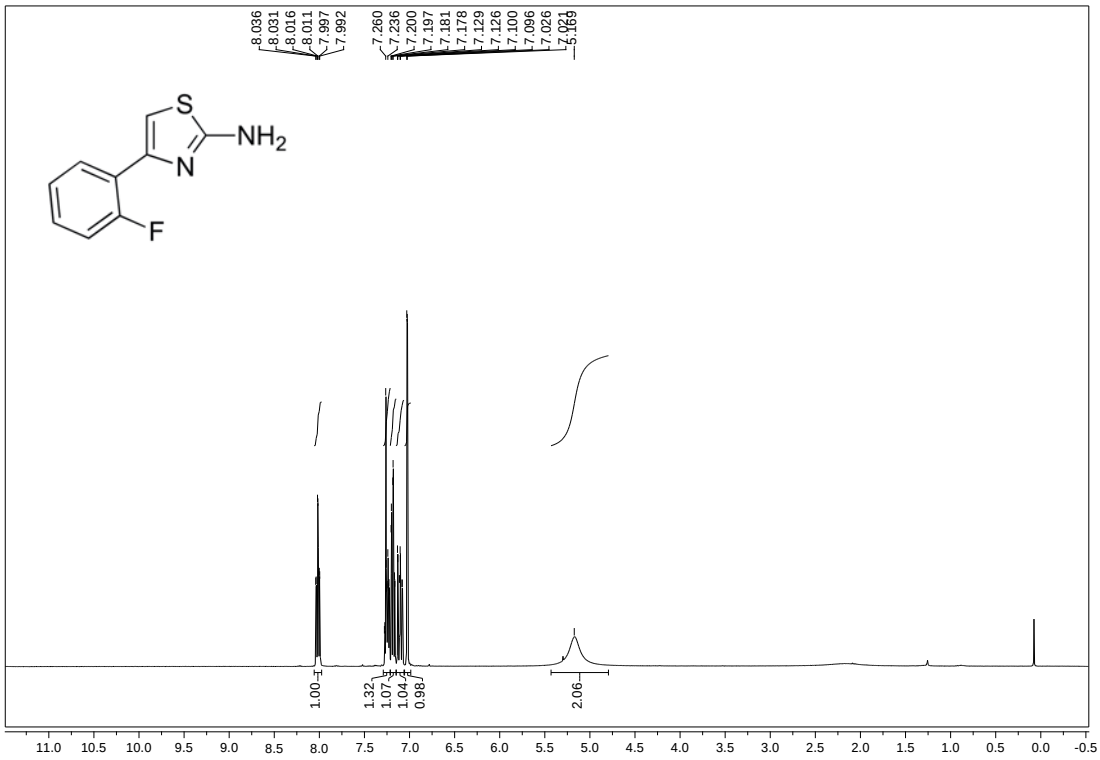


^{19}F NMR Spectrum (376 MHz, DMSO)

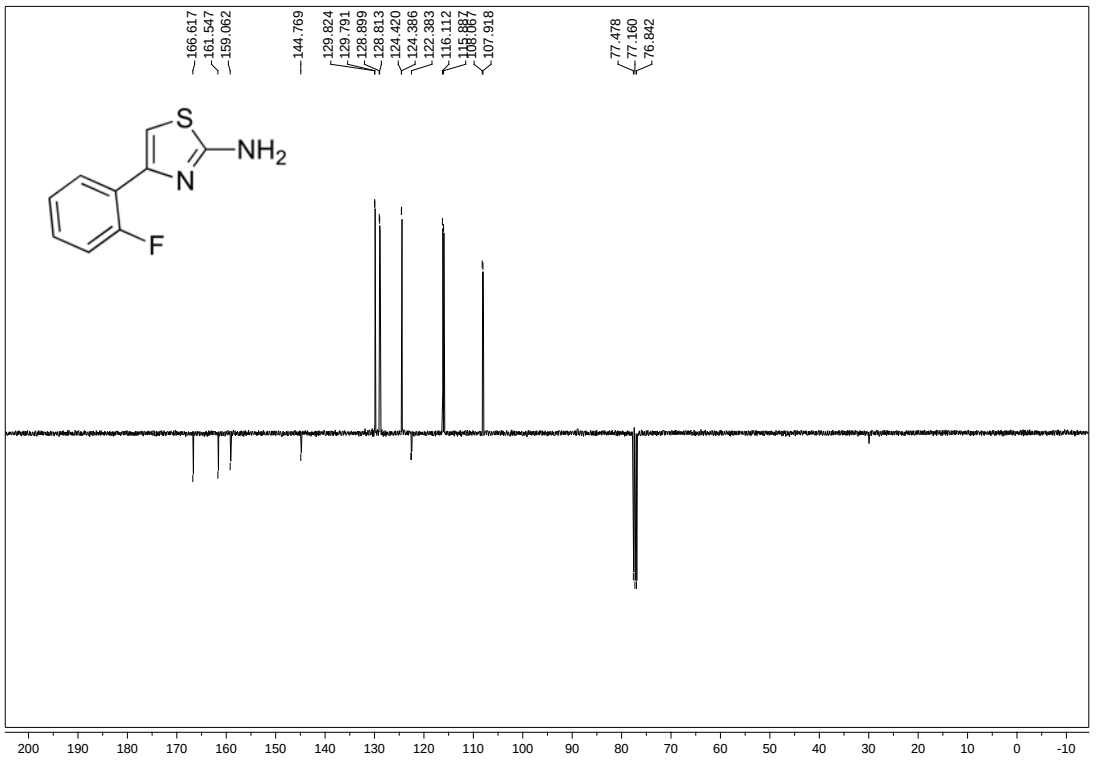


4-(2-Fluorophenyl)thiazol-2-amine (13)

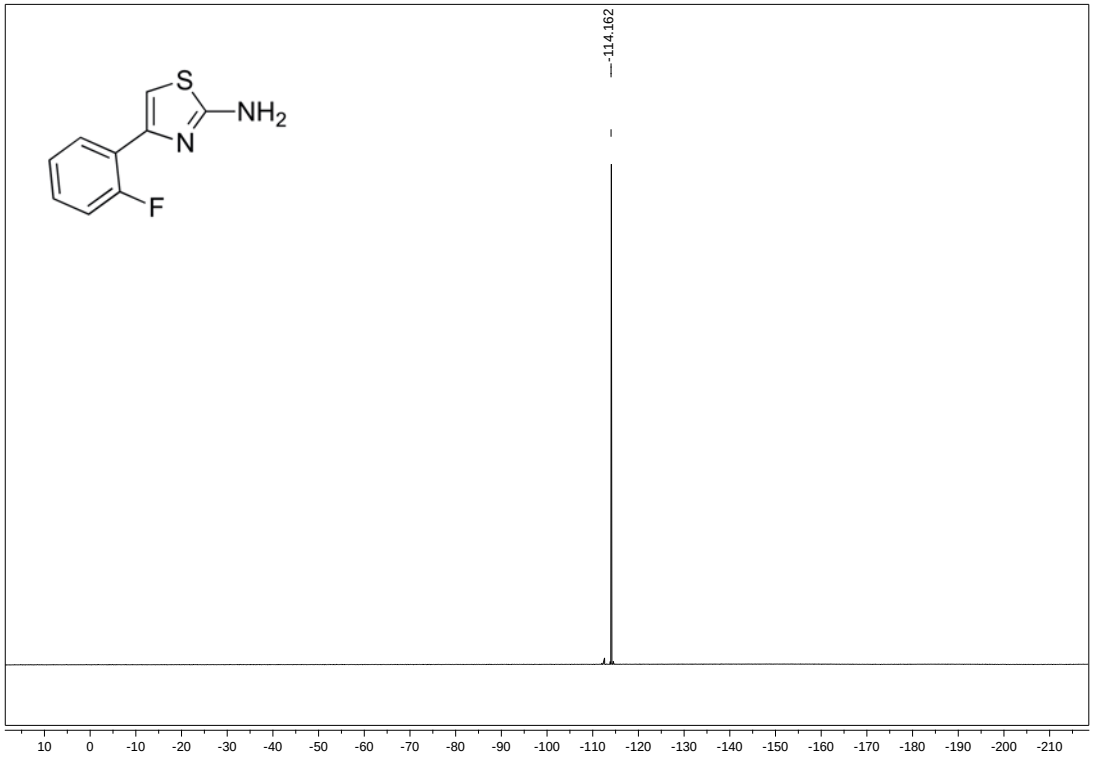
^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



^{13}C DEPTQ NMR Spectrum (101 MHz, $CDCl_3$)

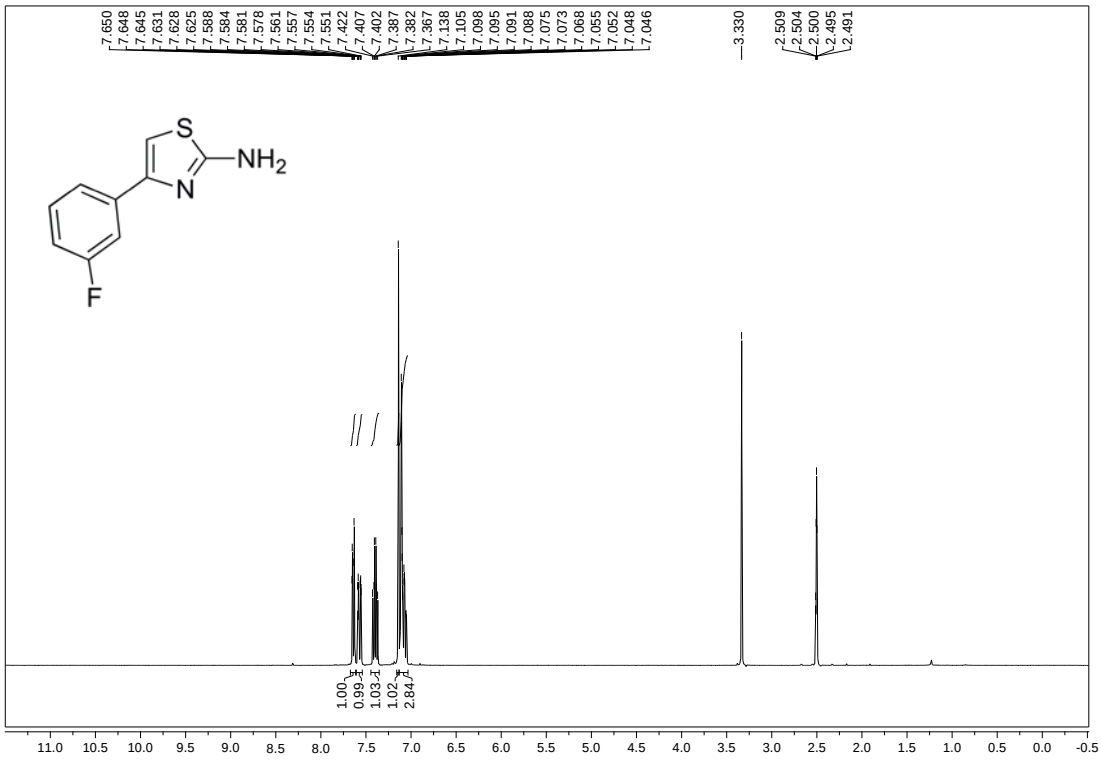


^{19}F NMR Spectrum (376 MHz, $CDCl_3$)

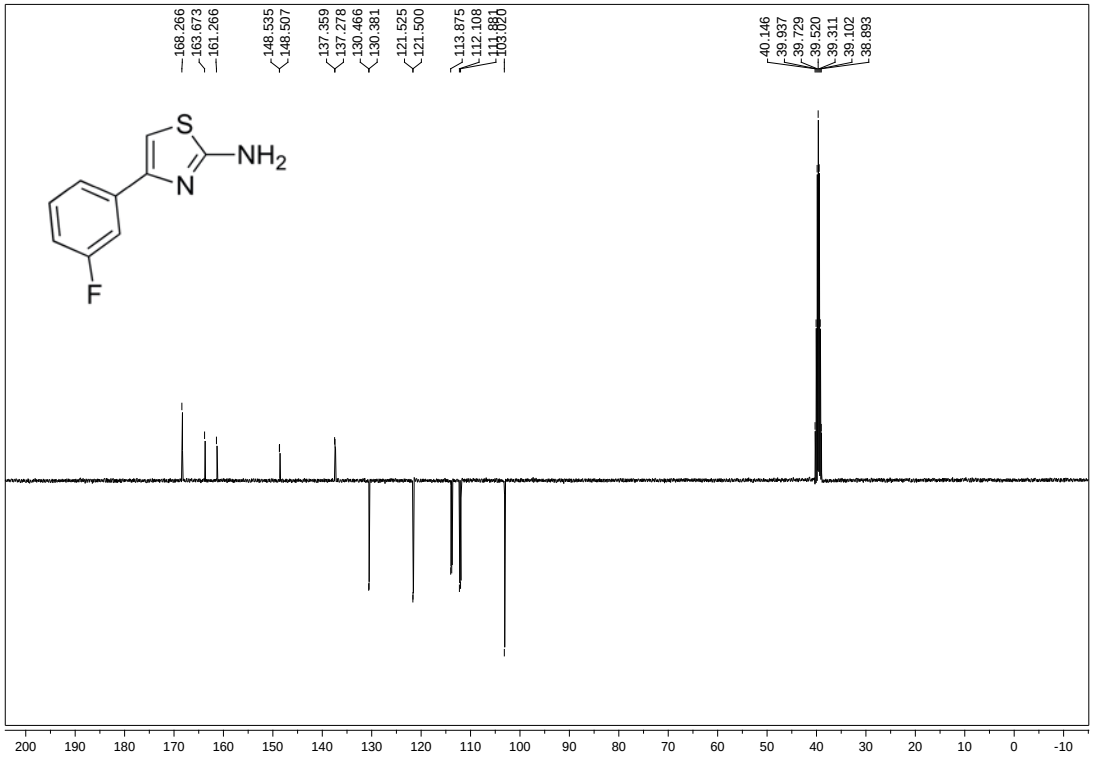


4-(3-Fluorophenyl)thiazol-2-amine (14)

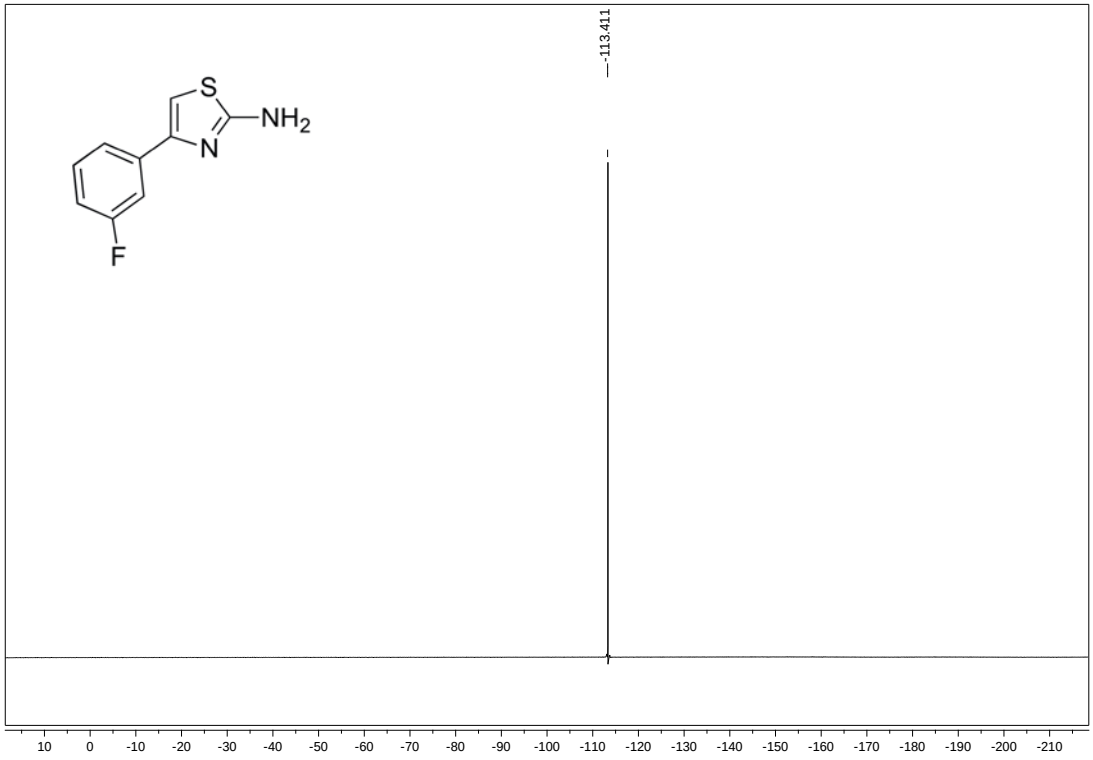
^{1}H NMR Spectrum (400 MHz, DMSO)



^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

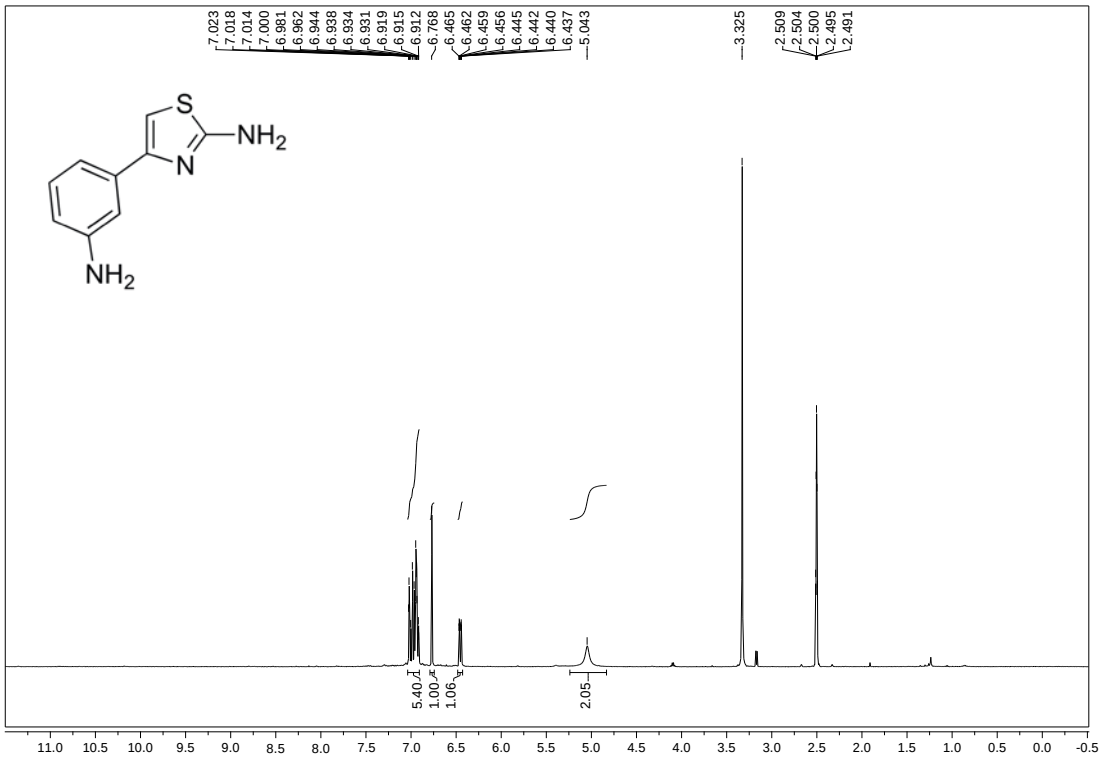


^{19}F NMR Spectrum (376 MHz, DMSO)

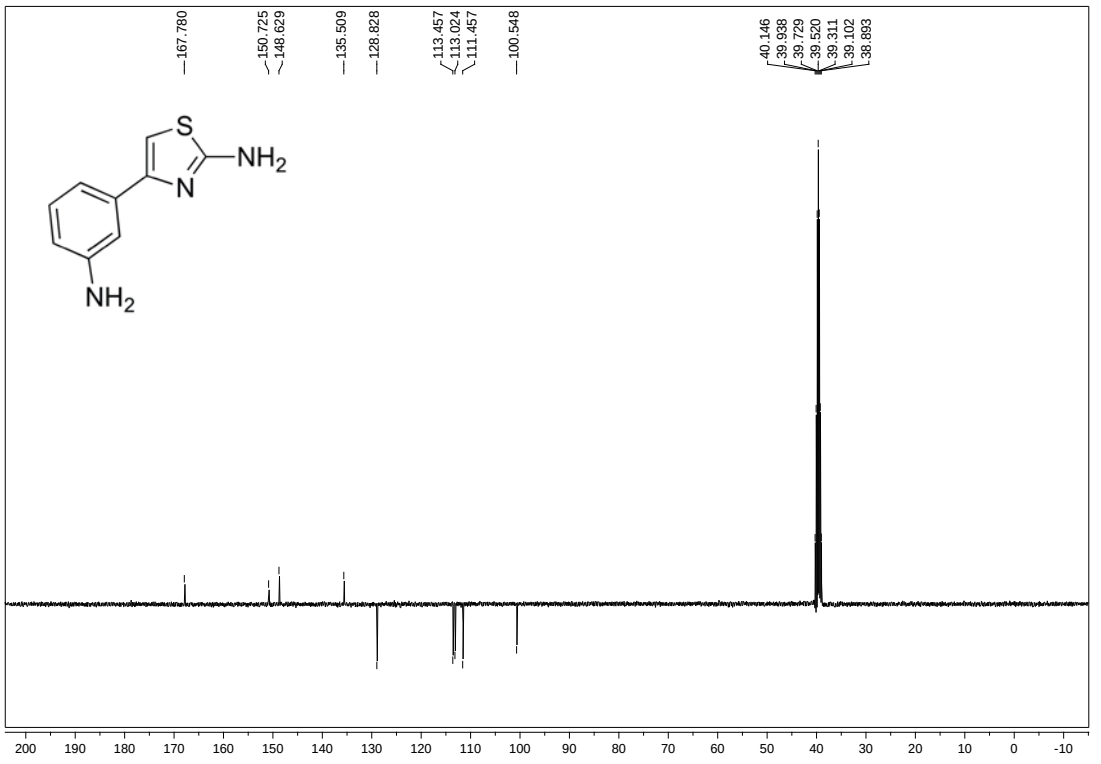


4-(3-Aminophenyl)thiazol-2-amine (15)

^{1}H NMR Spectrum (400 MHz, DMSO)

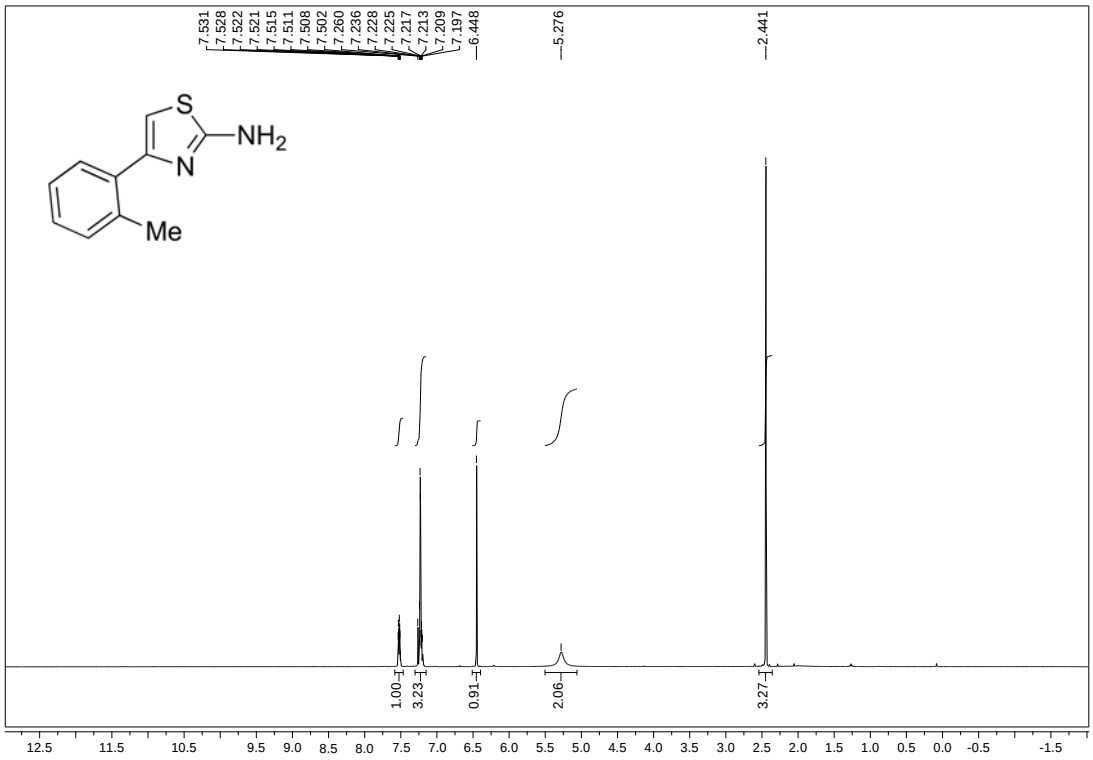


^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

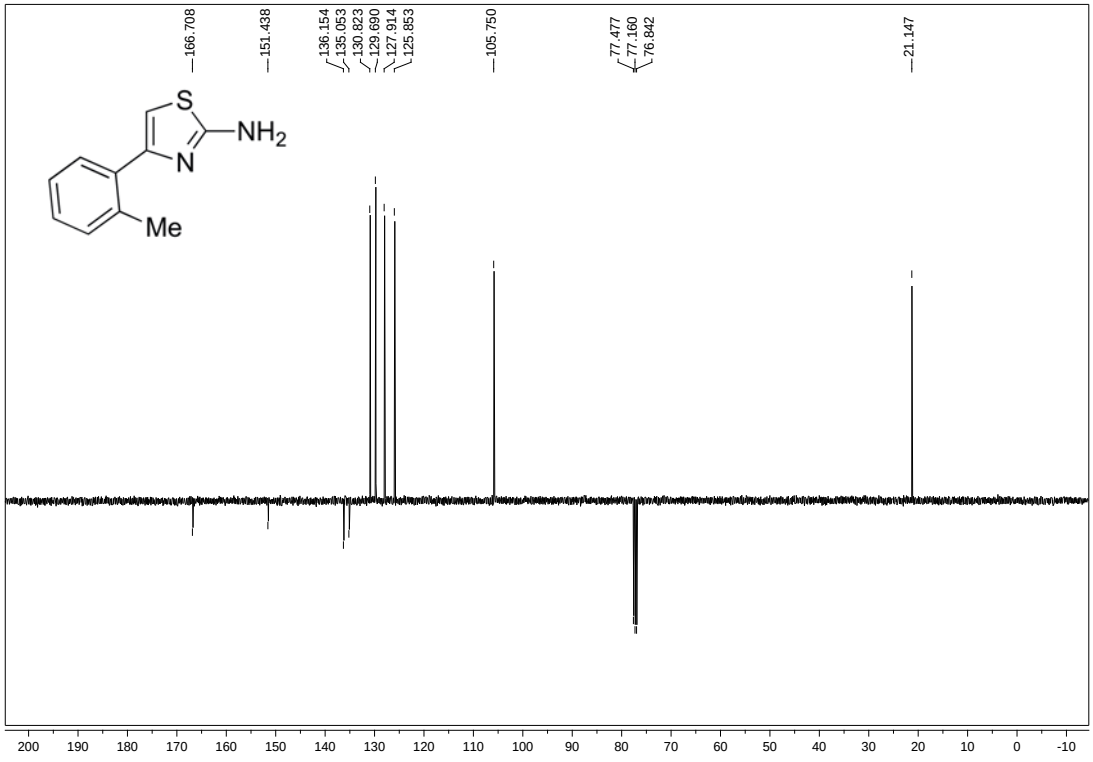


4-(o-Tolyl)thiazol-2-amine (16)

^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

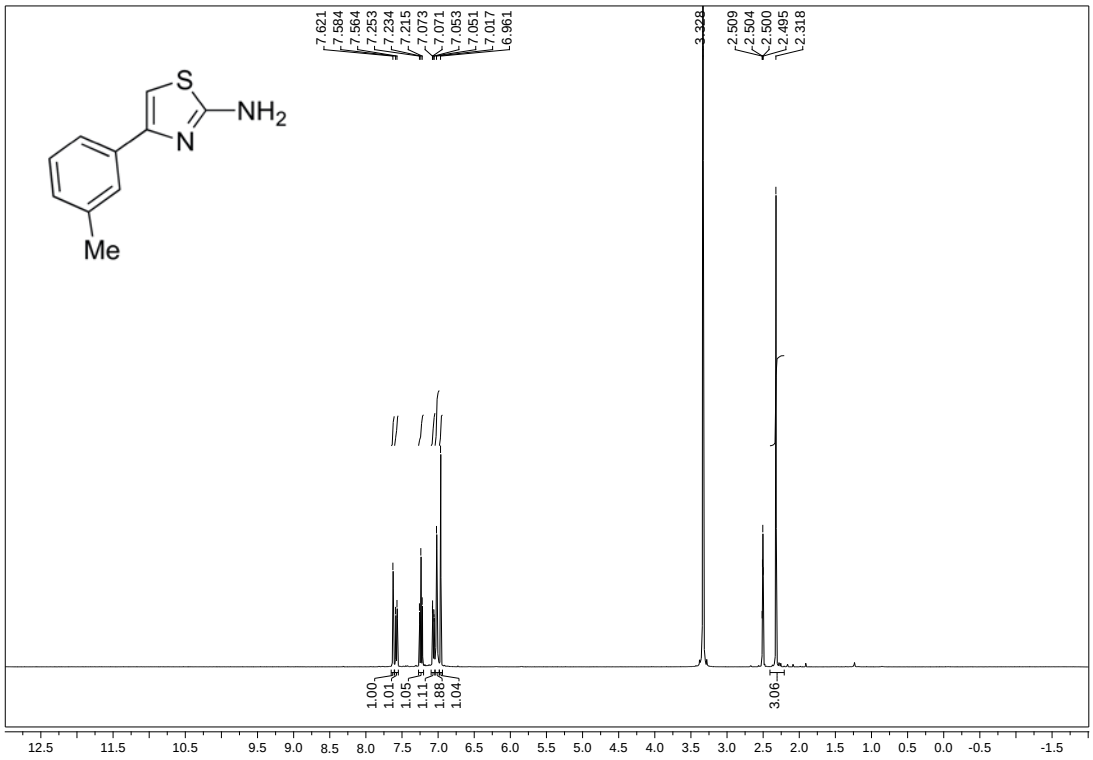


^{13}C DEPTQ NMR Spectrum (101 MHz, $CDCl_3$)

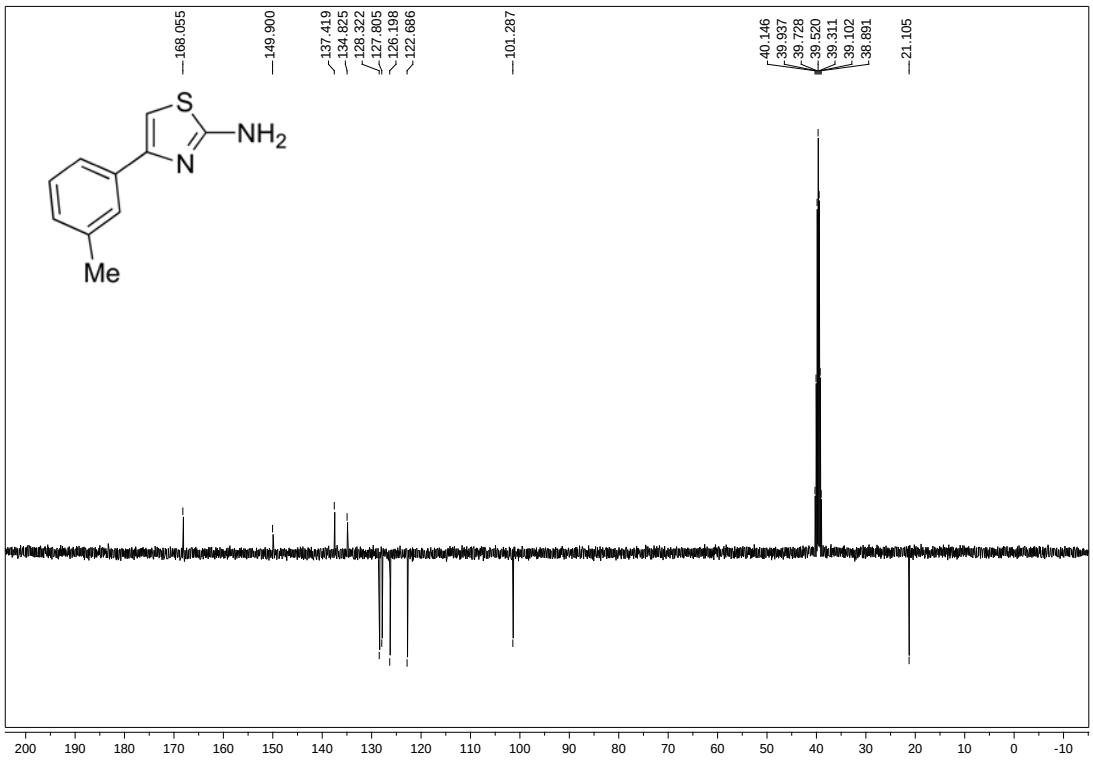


4-(*m*-Tolyl)thiazol-2-amine (17)

^{1}H NMR Spectrum (400 MHz, DMSO)

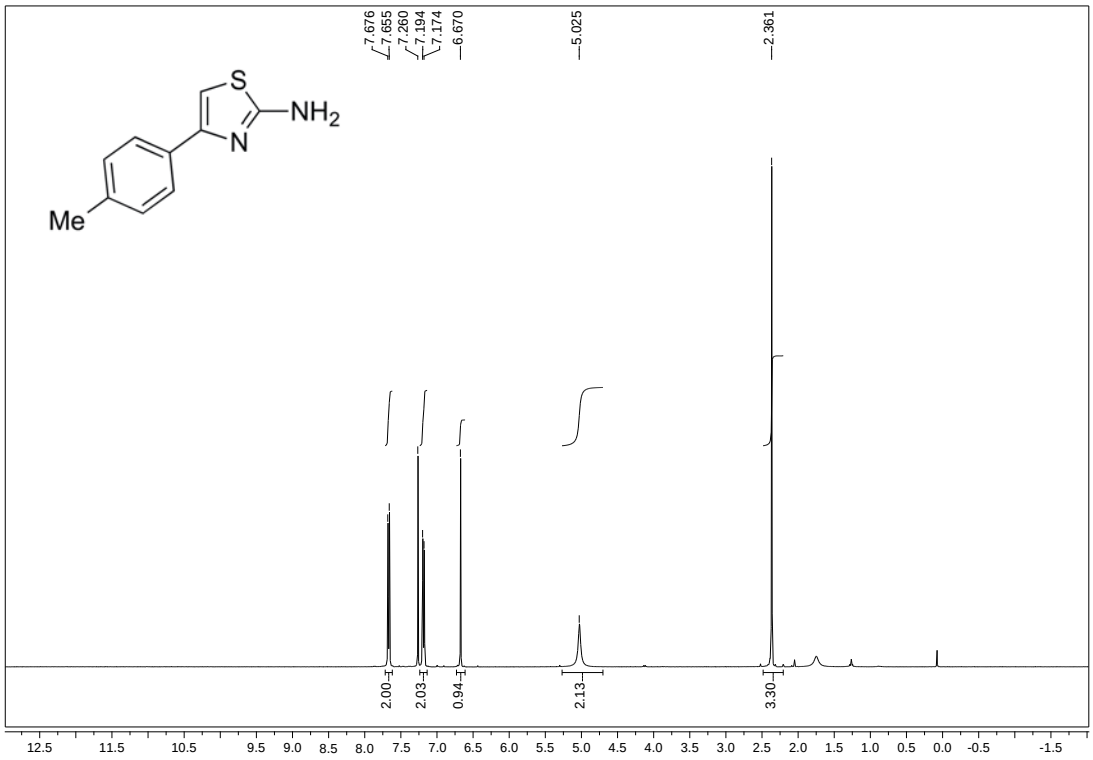


^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

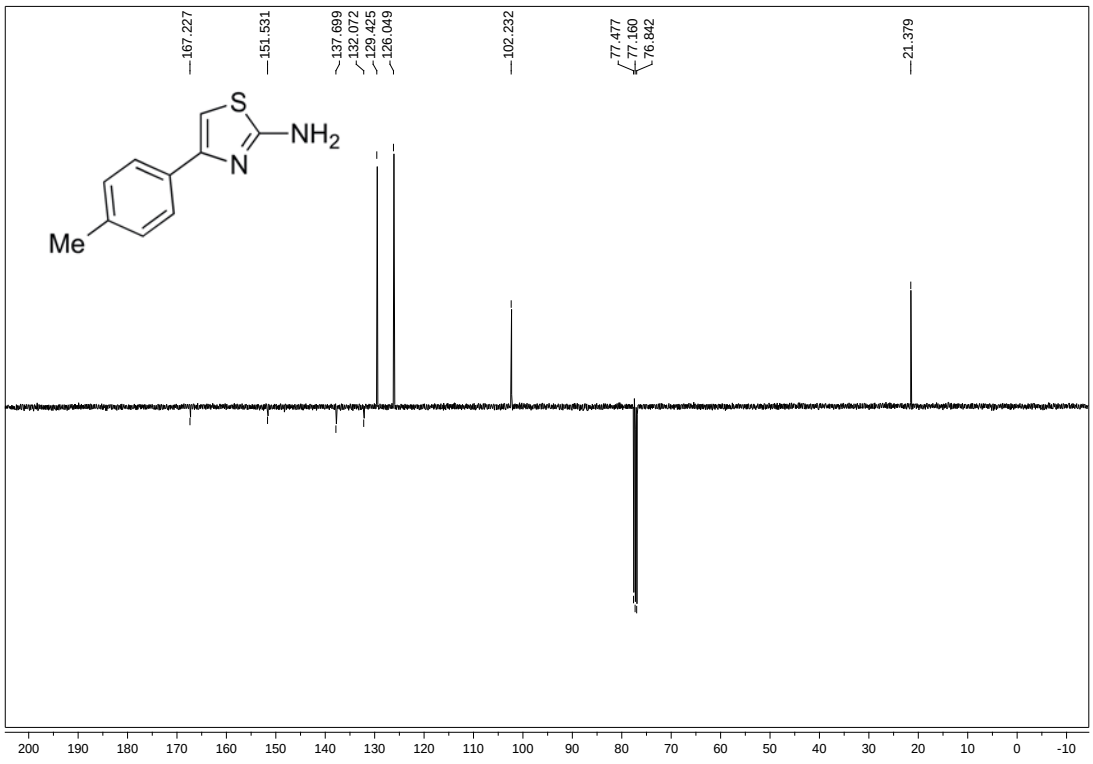


4-(*p*-Tolyl)thiazol-2-amine (18)

^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

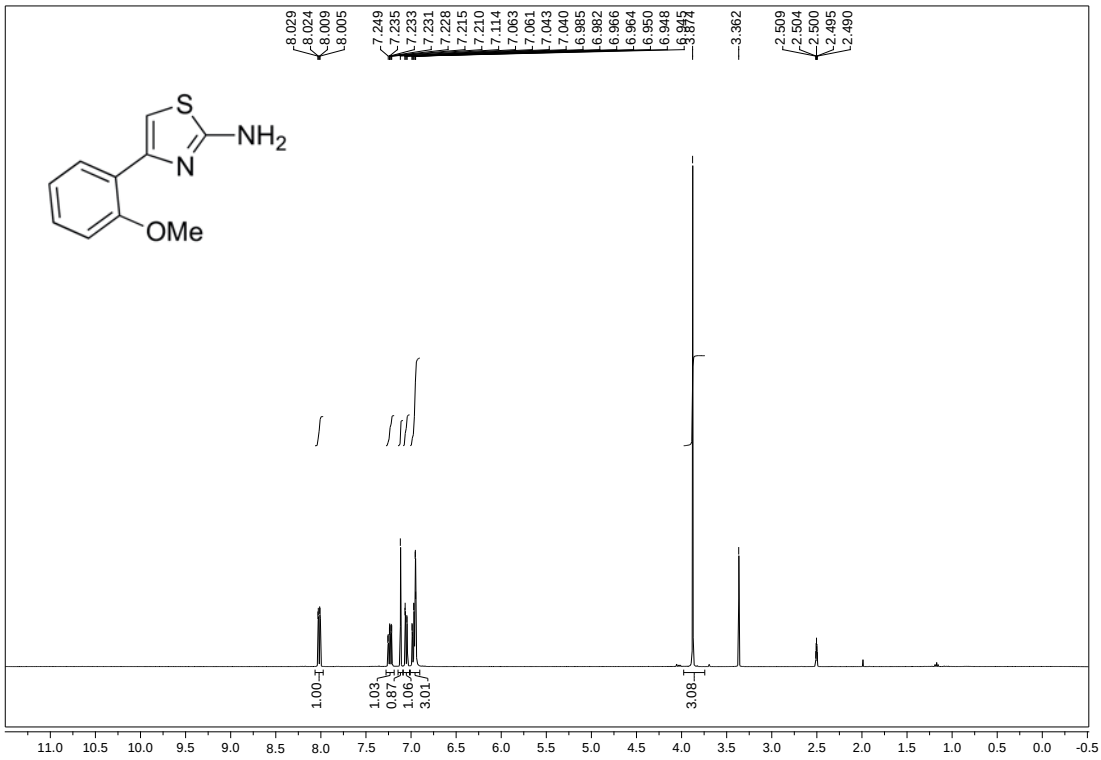


^{13}C DEPTQ NMR Spectrum (101 MHz, $CDCl_3$)

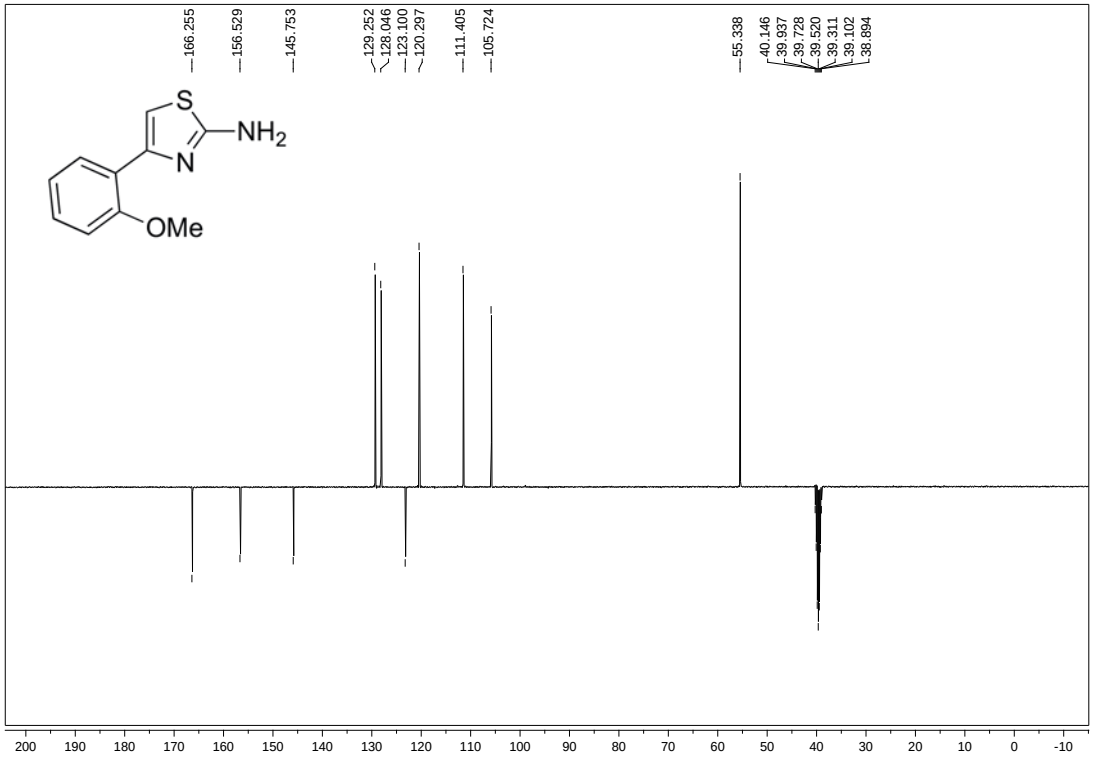


4-(2-Methoxyphenyl)thiazol-2-amine (19)

^{1}H NMR Spectrum (400 MHz, DMSO)

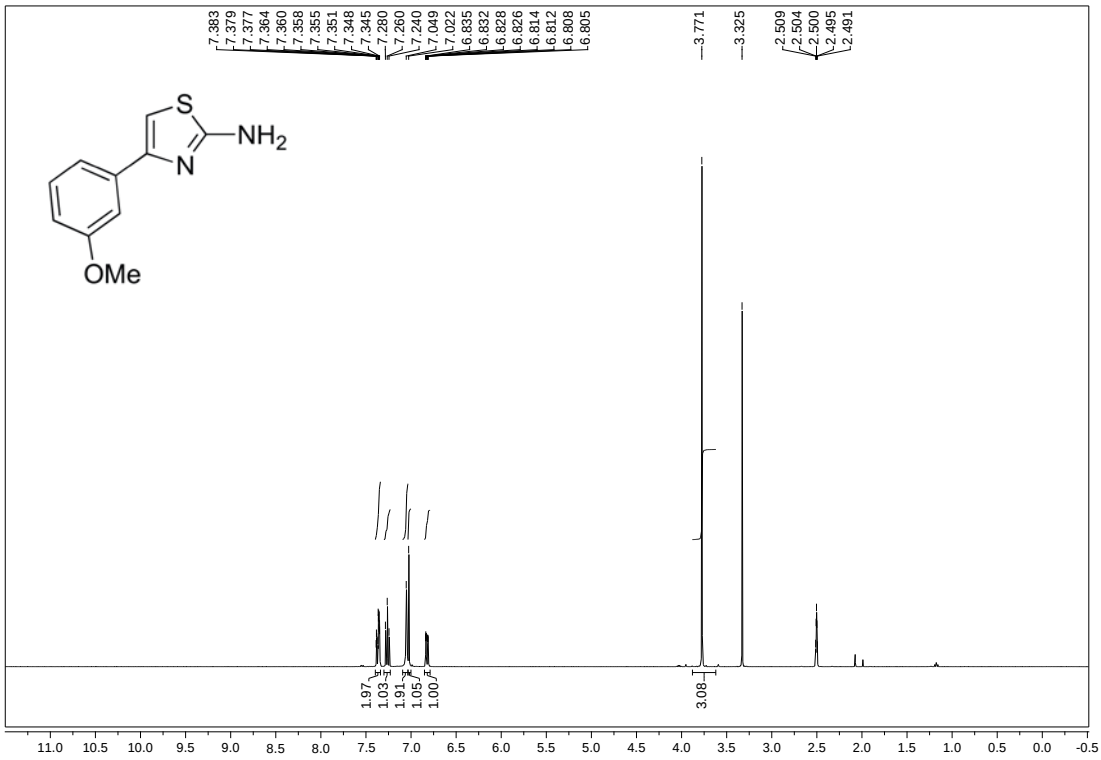


^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

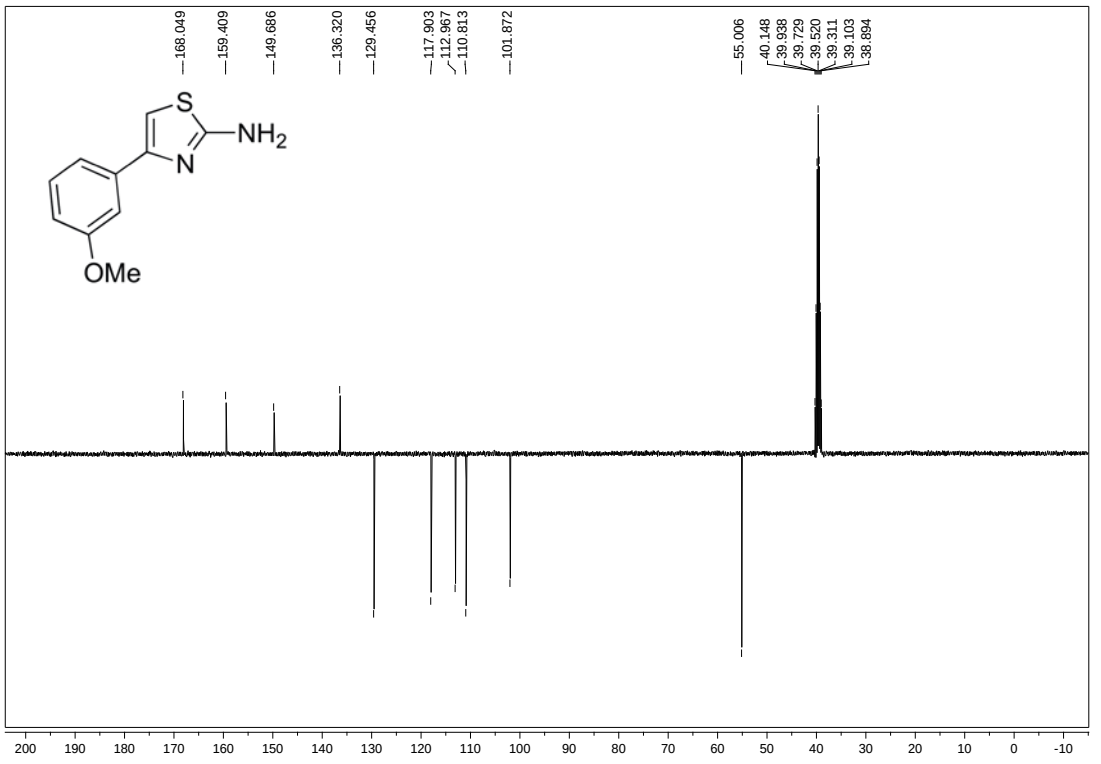


4-(3-Methoxyphenyl)thiazol-2-amine (20)

^{1}H NMR Spectrum (400 MHz, DMSO)

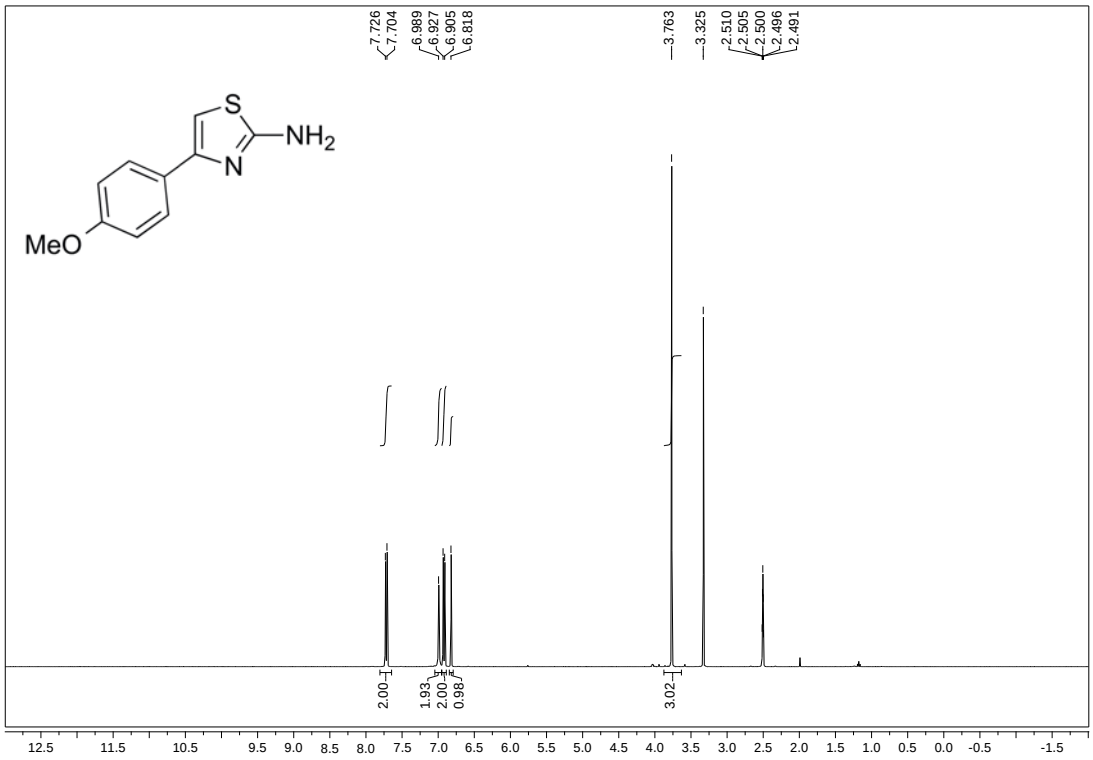


^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

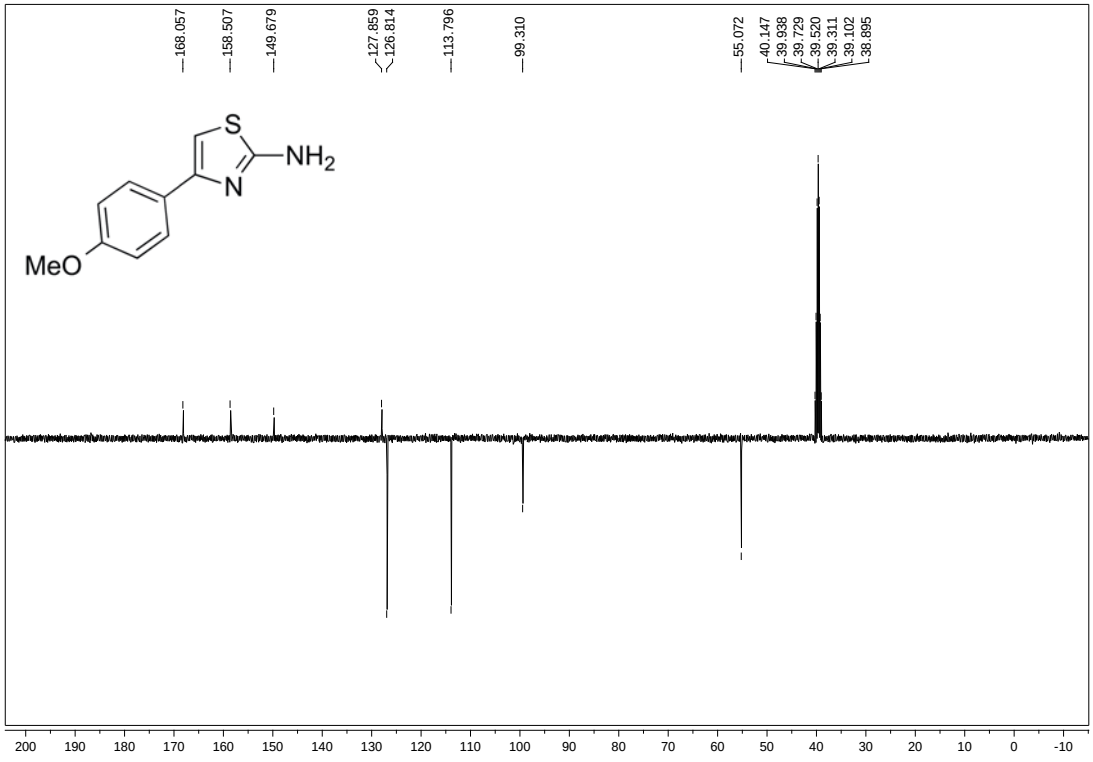


4-(4-Methoxyphenyl)thiazol-2-amine (21)

^{1}H NMR Spectrum (400 MHz, DMSO)

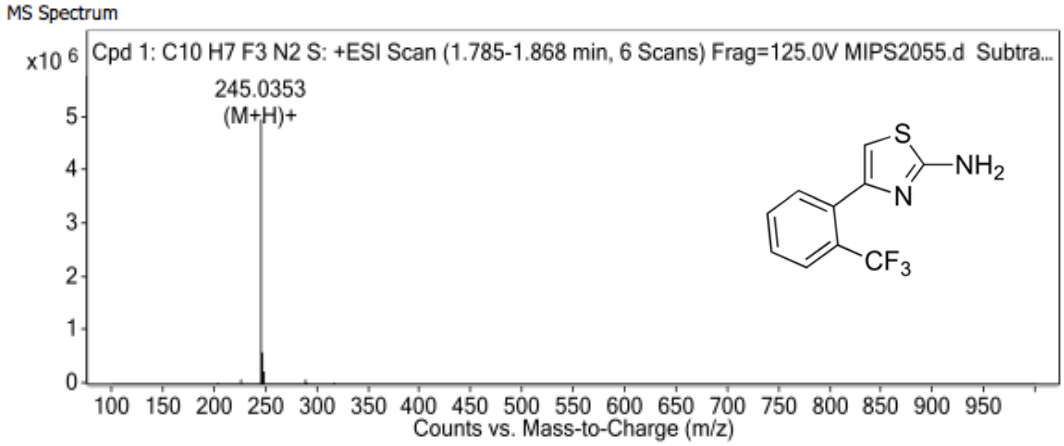


^{13}C DEPTQ NMR Spectrum (101 MHz, DMSO)

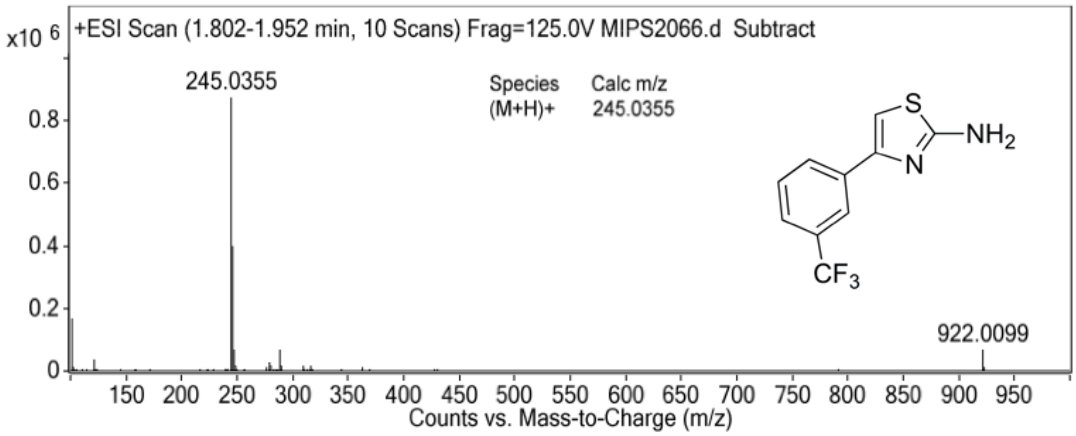


High-Resolution Mass Spectra

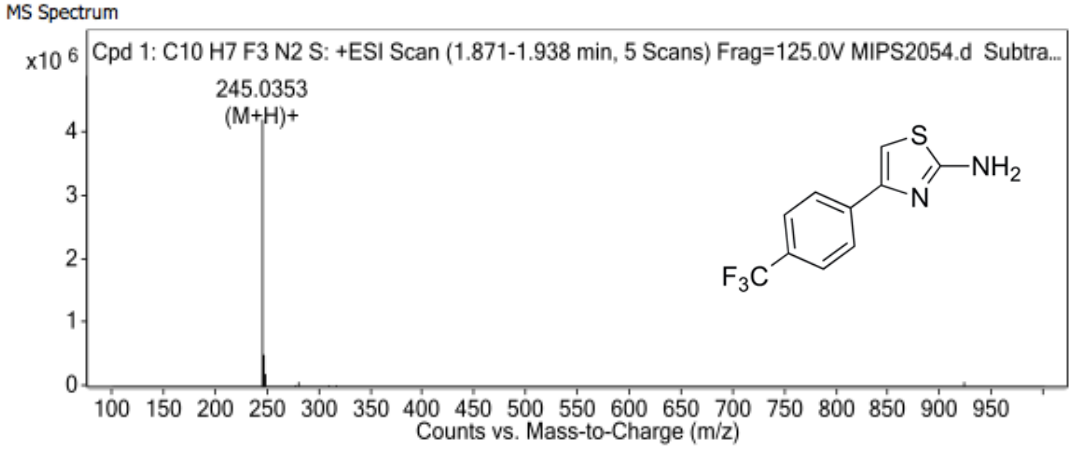
4-(2-(Trifluoromethyl)phenyl)thiazol-2-amine (10)



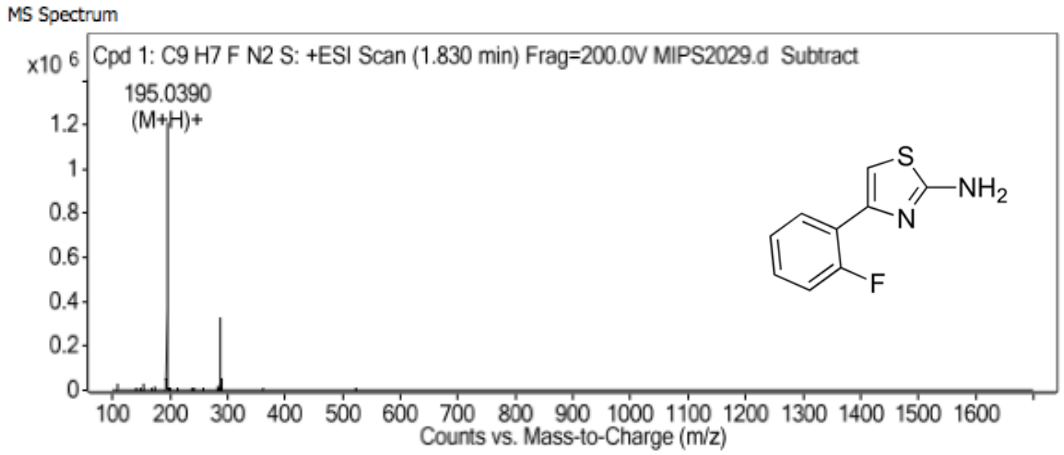
4-(3-(Trifluoromethyl)phenyl)thiazol-2-amine (11)



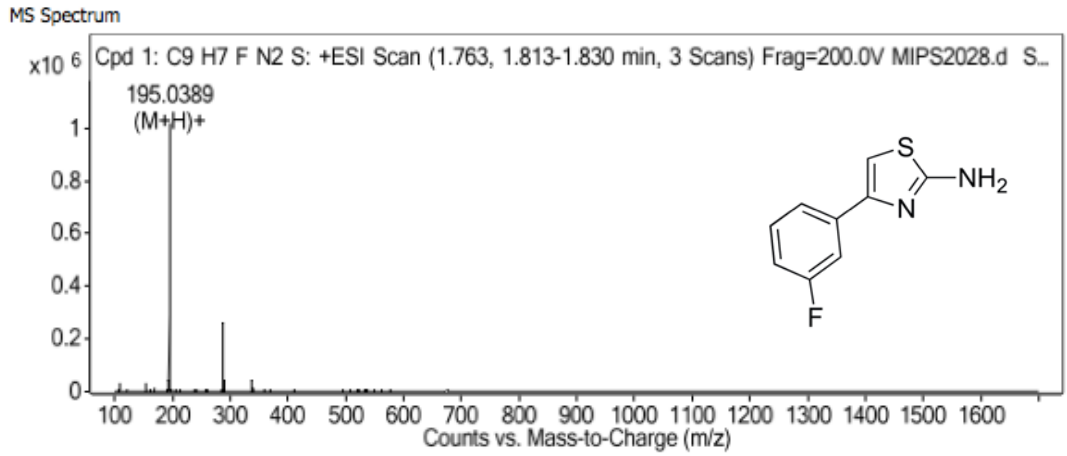
4-(4-(Trifluoromethyl)phenyl)thiazol-2-amine (12)



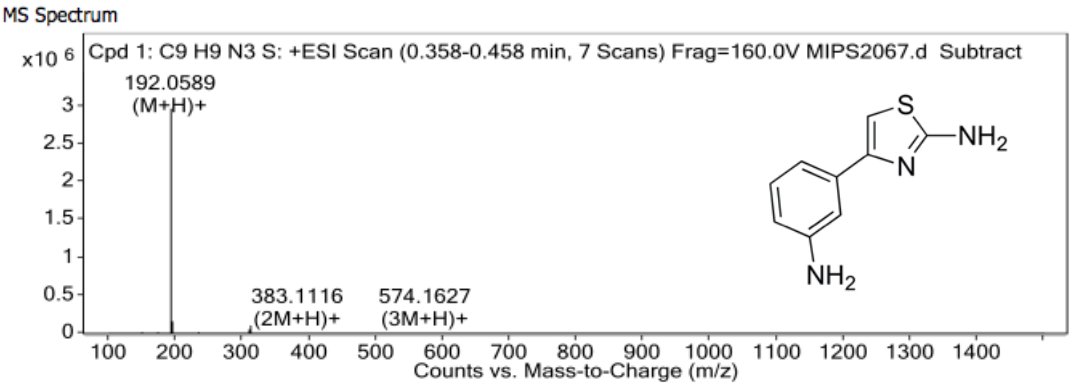
4-(2-Fluorophenyl)thiazol-2-amine (13)



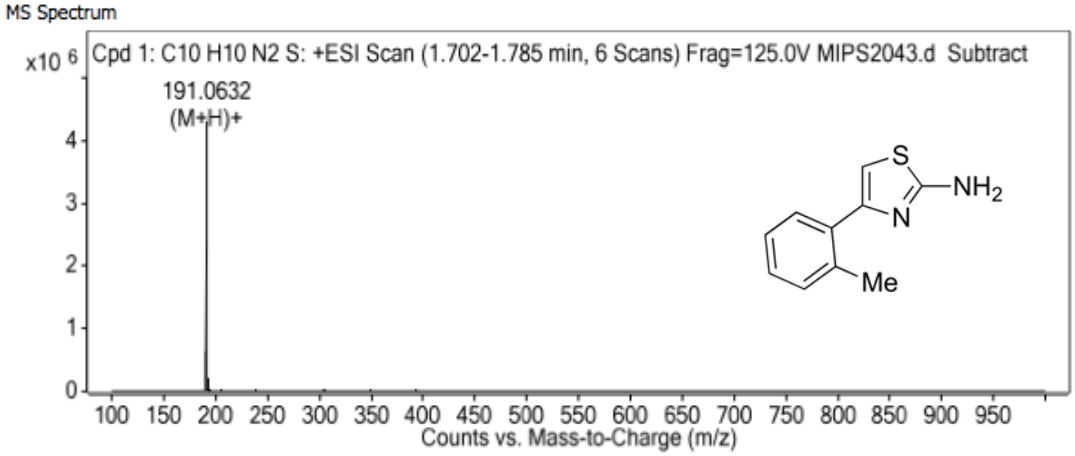
4-(3-Fluorophenyl)thiazol-2-amine (14)



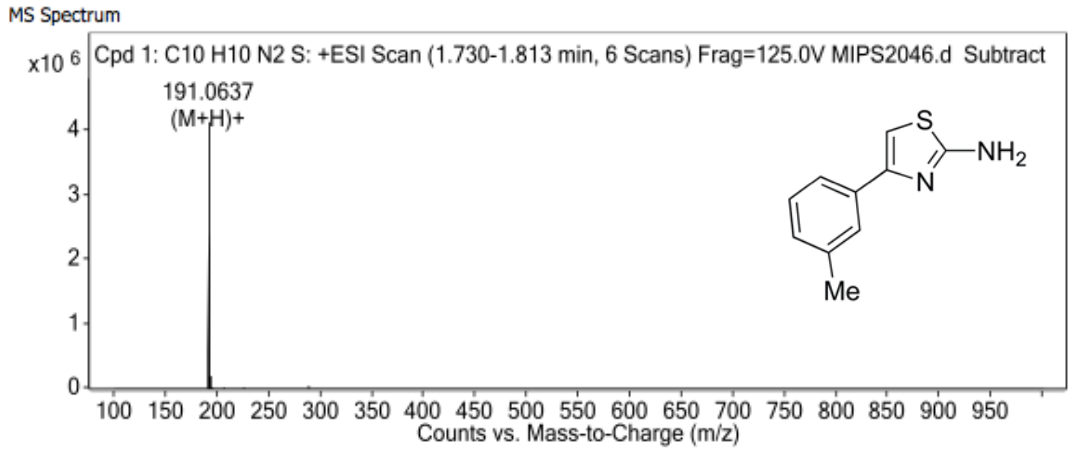
4-(3-Aminophenyl)thiazol-2-amine (15)



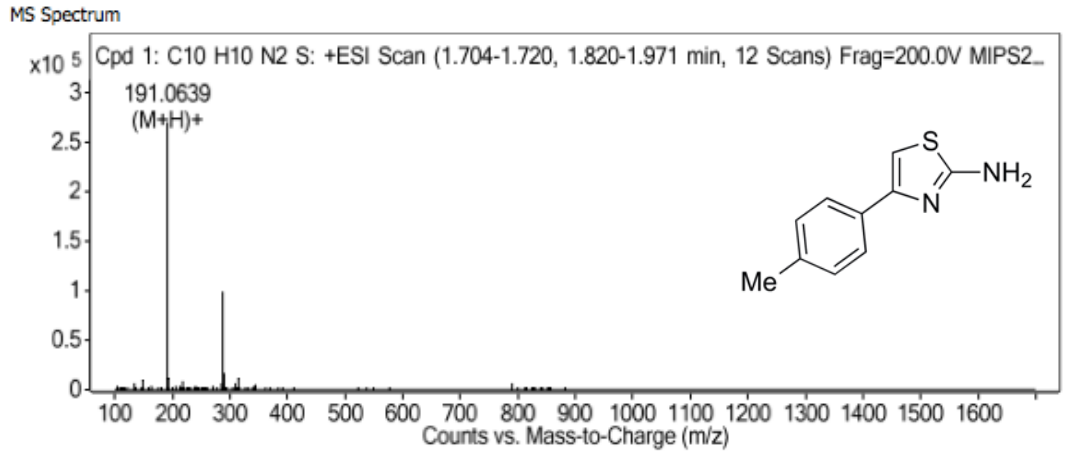
4-(o-Tolyl)thiazol-2-amine (16)



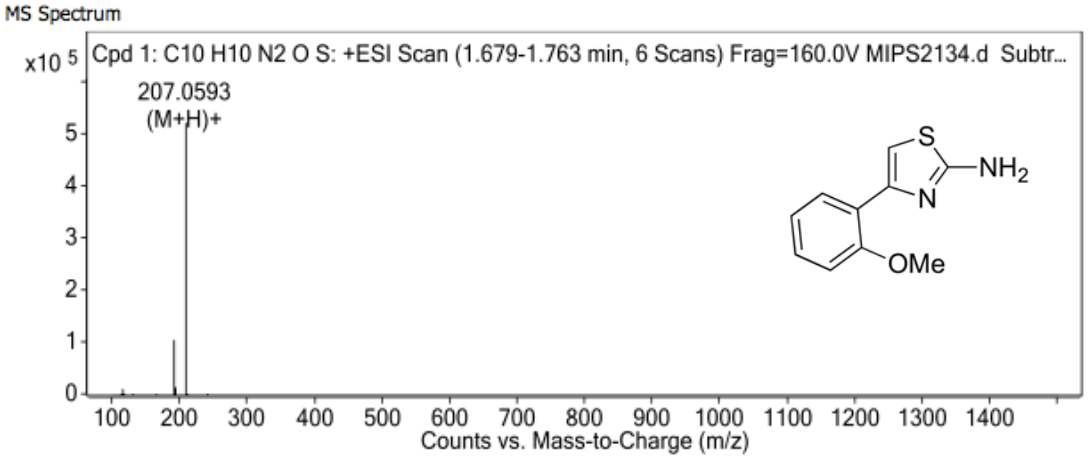
4-(*m*-Tolyl)thiazol-2-amine (17)



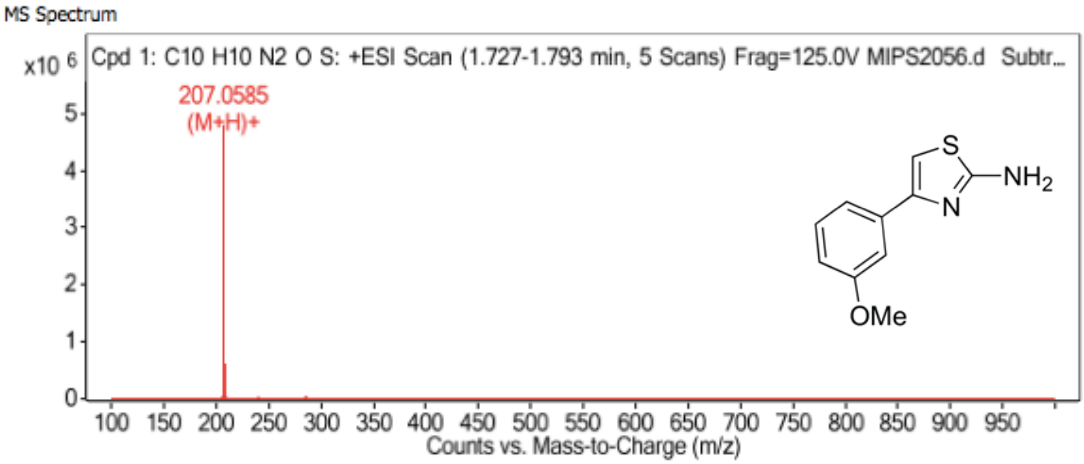
4-(*p*-Tolyl)thiazol-2-amine (18)



4-(2-Methoxyphenyl)thiazol-2-amine (19



4-(3-Methoxyphenyl)thiazol-2-amine (20)



4-(4-Methoxyphenyl)thiazol-2-amine (21)