Supporting Information

An Efficient Synthesis of Mono-, Di-, and Tri-substituted 1,3-Thiazoles Employing Functionalized Thioamides as Thiocarbonyl Precursors

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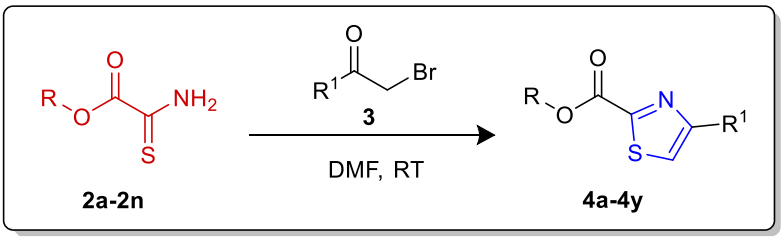
General procedure for the synthesis of alkyl 4-phenylthiazole-2-carboxylate 4a-4y



Equimolar ratios of alkyl 2-amino-2-thioxoacetates **2** (1 mmol) and α-bromoketones **3** (1 mmol) were dissolved in 2 mL of DMF and stirred at room temperature for 3 hours. The progress of the reactions was monitored by thin layer chromatography. After completion, the reaction mixture was quenched in brine solution, and crude product was extracted into ethyl acetate (2 × 25 mL). The organic extract was subjected to dehydration using anhydrous sodium sulphite, followed by concentration under reduced pressure. Further, the crude product was subjected to purification through column chromatography on silica gel, using ethyl acetate and hexane, yielding alkyl 4-phenylthiazole-2-carboxylate **4a-4y**.

X-Ray Crystallographic Information of Product (4a)

Single crystal of product **4a** with approximate dimensions 0.190 mm × 0.260 mm × 0.320 mm was obtained through slow evaporation (at room temperature) of a solution in hexane/ethyl acetate. The X-ray intensity data were collected on a Bruker Kappa Apex-II diffractometer having an X-rays tube containing Mo and Cu as a target. The graphite monochromator and CCD were used for recording the intensity peaks. APEX-II and SAINT software were used to carry- out for data collection and data reduction [1]. SHELXS97 was employed for structure solution [2] and SHELXL2018/3 was used for the structure refinement [3]. Anisotropic refinement was done for all the non-hydrogen atoms.

References

1. Bruker APEX2 (Version 1.22) and SAINT-Plus (Version 7.06a), 2009.
2. Sheldrick, G. M. A short history of SHELX. Acta Crystallogr., Sect. A: Found. Crystallogr.2008, 64, 112−122.
3. Sheldrick, G. M. Crystal structure refinement with SHELXL. Acta Crystallogr., Sect. C:Struct. Chem. 2015, 71, 3−8.
4. Spek, A. L. Single-crystal structure validation with the program PLATON. J. Appl. Crystallogr. 2003, 36, 7−13.
5. Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M. Mercury 4.0: from visualization to analysis, design and prediction. J. Appl. Crystallogr 2020, 53, 226

Table S1: Crystal data and structure refinement details. **(4a)**

Empirical formula	$C_{17}H_{13}NO_2S$
Formula weight	295.34
Temperature	150
Wavelength	0.71073 Å
Reflections for cell determination	9533
θ range for above	2.92° to 27.34°
Crystal system	Monoclinic
Space group	*P* 21/c
Cell dimensions	*a* = 14.0054(11) Å
	b = 13.9608(11) Å
	c = 7.3675(6) Å
	α = 90°
	β = 97.698(2) °
	γ = 90°
	1427.6(2) Å3
Volume	4
Z	1.374 Mg m-3
Density(calculated)	0.230 mm-1
Absorption coefficient	616
F_{000}	0.190 mm × 0.260 mm × 0.320 mm
Crystal size	2.92° to 27.53°
θ range for data collection	-18 ≤ h ≤ 18
Index ranges	-18 ≤ h ≤ 18
	-9 ≤ l ≤ 8
Reflections collected	33795
Independent reflections	3296 [Rint = 0.061]
Absorption correction	Multi-scan
Refinement method	full matrix least-squares on F^2
Data / restraints / parameters	3296 / 0 / 190
Goodness-of-fit on F^2	1.134
Final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0650, wR2 = 0.1363
R indices (all data)	R1 = 0.0776, wR2 = 0.1420
Largest diff. peak and hole	0.635; -0.307 e $Å^{-3}$

The single crystal of the product **4a** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of hexane/ ethyl acetate mixture. The crystal data of product **4a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is 2263782.

ORTEP of the product 4a

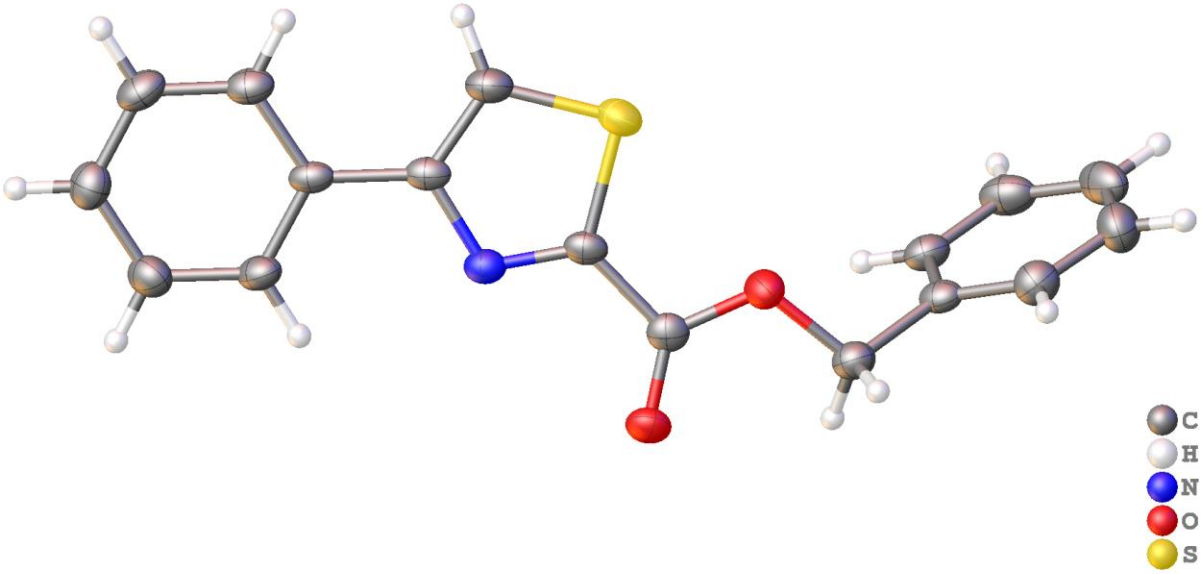
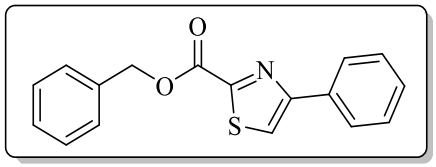


Figure S1. ORTEP (thermal ellipsoid plot) of Product **4a** (drawn at 50% probability level)

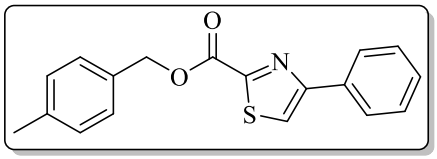
Characterization details of alkyl 4-phenylthiazole-2-carboxylate 4a-4y

Benzyl 4-phenylthiazole-2-carboxylate (4a): White solid; Yield 0.283 g (96%); mp 88-90 °C; IR:



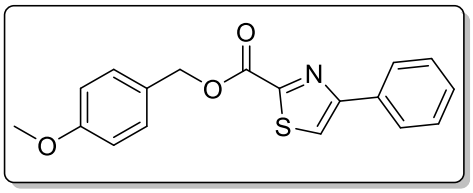
$\upsilon_{max}(cm^{-1})$ 692, 746, 949, 1086, 1232, 1444, 1728, 2924; ^1H NMR (600 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.73 (s, 1H, Het-H), 7.49 (d, *J* = 7.5 Hz, 3H, Ar-H), 7.45 – 7.33 (m, 5H, Ar-H), 5.46 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 158.0, 157.7, 135.2, 133.5, 128.9, 128.8, 128.7, 128.7, 127.0, 126.8, 119.0, 68.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}NO_2S$ 296.0745; found 296.0740.

4-methylbenzyl 4-phenylthiazole-2-carboxylate (4b): White solid; Yield 0.274 g (89%); mp



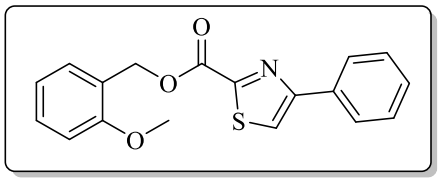
93-94 °C; IR: $\upsilon_{max}(cm^{-1})$ 743, 950, 1080, 1230, 1450, 1729, 2930; ^1H NMR (600 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.71 (s, 1H, Het-H), 7.49 – 7.29 (m, 5H, Ar-H), 7.20 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.43 (s, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 157.9, 157.8, 138.7, 133.6, 132.2, 129.6, 129.5, 128.9, 128.9, 126.8, 119.0, 68.1, 21.4; HRMS (ESI) m/z: [M + H]+ calcd for $C_{18}H_{16}NO_2S$ 310.0902; found 310.0893.

4-methoxybenzyl 5-phenylthiazole-2-carboxylate (4c): White solid; Yield 0.286 g (88%); mp



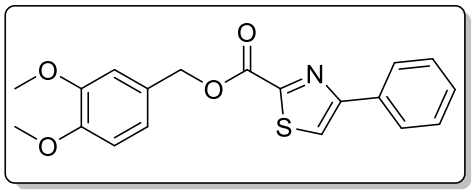
98-100 °C; IR: $\upsilon_{max}(cm^{-1})$ 751, 1100, 1239, 1445, 1723, 2921; ^1H NMR (600 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.71 (s, 1H, Het-H), 7.49 – 7.29 (m, 5H, Ar-H), 7.20 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.43 (s, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.1, 160.0, 157.9, 157.9, 133.6, 130.8, 128.9, 127.3, 126.9, 126.8, 118.9, 114.1, 68.0, 55.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}NO_3S$ 326.0851; found 326.0843.

2-methoxybenzyl 4-phenylthiazole-2-carboxylate (4d): White solid; Yield 0.282 g (87%); mp



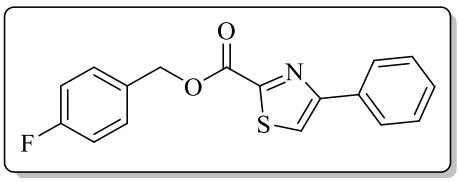
97-98 °C; IR: $\upsilon_{max}(cm^{-1})$ 745, 1090, 1225, 1440, 1715, 2118; ^1H NMR (600 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 8.3, 1.3 Hz, 2H, Ar-H), 7.73 (s, 1H, Het-H), 7.45 – 7.39 (m, 3H, Ar-H), 7.39 – 7.30 (m, 2H, Ar-H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.91 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar-H), 5.53 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.0, 157.9, 157.9, 157.7, 133.6, 130.0, 130.0, 128.9, 128.9, 126.8, 123.6, 120.6, 118.8, 110.6, 63.6, 55.6; HRMS (ESI) m/z: [M + H]+ calcd for $C_{18}H_{16}NO_3S$ 326.0851; found 326.0847

3,4-dimethoxybenzyl 4-phenylthiazole-2-carboxylate (4e): White solid; Yield 0.287 g (81%);



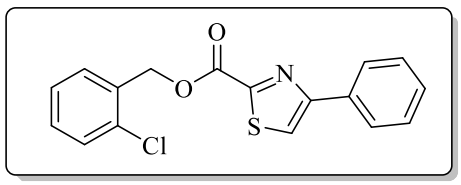
mp 110-112 °C; IR: $\upsilon_{max}(cm^{-1})$ 690, 755, 1120, 1235, 1449, 1720, 2910; ^1H NMR (600 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.3, 1.3 Hz, 2H, Ar-H), 7.73 (s, 1H, Het-H), 7.45 – 7.33 (m, 3H, Ar-H), 7.06 (dd, *J* = 8.2, 2.0 Hz, 1H, Ar-H), 7.03 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.86 (d, *J* = 8.2 Hz, 1H, Ar-H), 5.40 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3).^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 158.0, 157.9, 149.6, 149.2, 133.6, 128.9, 127.7, 126.8, 122.0, 118.8, 115.85, 112.4, 111.3, 68.2, 56.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4S$ 356.0957; found 356.0943

4-fluorobenzyl 4-phenylthiazole-2-carboxylate (4f): White solid; Yield 0.269 g (86%); mp 91-



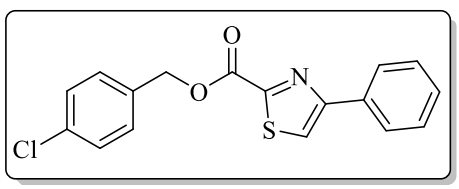
93 °C; IR: $\upsilon_{max}(cm^{-1})$ 695, 758, 830, 950, 1099, 1238, 1453, 1515, 1737, 2945; ^1H NMR (600 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.3, 1.3 Hz, 2H, Ar-H), 7.74 (s, 1H, Het-H), 7.47 (dd, *J* = 8.6, 5.4 Hz, 2H, Ar-H), 7.43 – 7.39 (m, 5H, Ar-H), 5.42 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.0, 160.0, 158.0, 134.7, 133.5, 130.9, 130.8 (d, *J* = 9.6 Hz), 128.8, 128.7 (d, *J* = 21.4 Hz), 126.8, 119.1, 115.7, 68.1. ^{19}F NMR (151 MHz, $CDCl_3$): δ = –112.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}FNO_2S$ 314.0651; found 314.0653.

2-chlorobenzyl 4-phenylthiazole-2-carboxylate (4g): White solid; Yield 0.280 g (85%); mp 99-



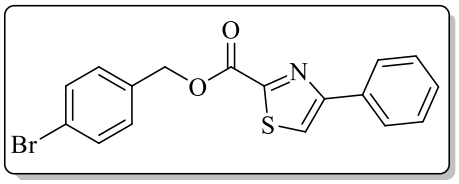
100 °C; IR: $\upsilon_{max}(cm^{-1})$ 682, 747, 823, 952, 1096, 1229, 1439, 1513, 1726, 2941; ^1H NMR (600 MHz, $CDCl_3$): δ 7.98 – 7.92 (m, 2H, Ar-H), 7.75 (s, 1H, Het-H), 7.58 – 7.52 (m, 1H, Ar-H), 7.46 – 7.39 (m, 3H, Ar-H), 7.39 – 7.33 (m, 1H, Ar-H), 7.30 (dd, J = 5.8, 3.4 Hz, 2H, Ar-H), 5.57 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.7, 158.1, 157.3, 133.9, 133.5, 132.9, 130.1, 130.0, 129.8, 129.0, 128.9, 127.1, 126.8, 119.1, 77.4, 77.2, 76.9, 65.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}ClNO_2S$ 330.0356; found 330.0343.

4-chlorobenzyl 4-phenylthiazole-2-carboxylate (4h): White solid; Yield 0.291 g (89%); mp 95-

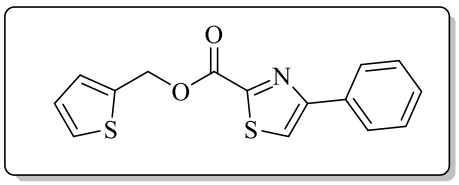


96 °C; IR: $\upsilon_{max}(cm^{-1})$ 689, 755, 828, 948, 1096, 1234, 1446, 1506, 1729, 2938; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.66 (s, 1H, Het-H), 7.35 (dt, *J* = 7.9, 3.2 Hz, 4H, Ar-H), 7.28 (dd, *J* = 8.6, 2.4 Hz, 3H, Ar-H), 5.34 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.84, 157.99, 157.43, 134.62, 133.58, 133.40, 130.05, 128.91, 128.86, 126.72, 122.9, 119.00, 67.13; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}ClNO_2S$ 330.0356; found 330.0343.

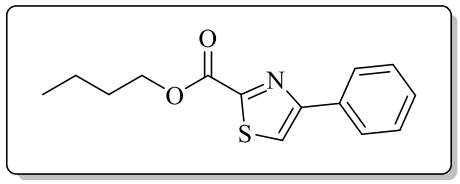
4-bromobenzyl 4-phenylthiazole-2-carboxylate (4i): White solid; Yield 0.322 g (87%); mp 103-105 °C; IR: $\upsilon_{max}(cm^{-1})$ 687, 752, 825, 945, 1092, 1230, 1440, 1504, 1725, 2935; ^1H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.74 (s, 1H, Het-H), 7.51 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.45 – 7.39 (m, 2H, Ar-H), 7.39 – 7.31 (m, 3H, Ar-H), 5.39 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.9, 158.1, 157.5, 134.2, 133.5, 132.0, 130.4, 129.0, 129.0, 126.8, 122.9, 119.1, 67.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_2S$ 373.9850; found 373.9843.



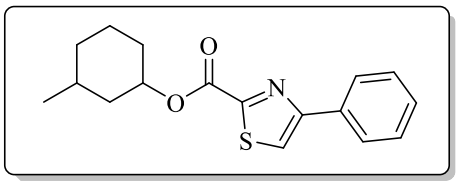
Thiophen-2-ylmethyl 4-phenylthiazole-2-carboxylate (4j): White solid; Yield 0.236 g (79%); mp 82-83 °C; IR: $\upsilon_{max}(cm^{-1})$ 704, 760, 847, 935, 1079, 1232, 1435, 1733, 2921; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.83 (m, 2H, Ar-H), 7.66 (s, 1H, Het-H), 7.41 – 7.30 (m, 3H, Ar-H), 7.28 (dd, *J* = 4.0, 1.1 Hz, 1H, Het-H), 7.17 (dd, *J* = 3.5, 1.1 Hz, 1H, Het-H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H, Het-H), 5.54 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8, 158.0, 157.5, 136.7, 133.4, 129.4, 128.8, 128.3, 127.5, 127.0, 126.7, 119.0, 62.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}NO_2S_2$ 302.0309; found 302.030



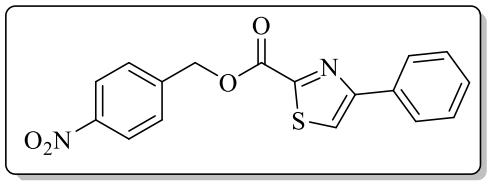
Butyl 4-phenylthiazole-2-carboxylate (4k): White solid; Yield 0.232 g (89%); mp 86-87 °C; IR: $\upsilon_{max}(cm^{-1})$ 763, 1091, 1221, 1361, 1430, 1714, 3002; ^1H NMR (600 MHz, $CDCl_3$): δ 7.97 – 7.90 (m, 2H, Ar-H), 7.72 (s, 1H, Het-H), 7.53 – 7.32 (m, 3H, Ar-H), 4.42 (t, *J* = 6.8 Hz, 2H, CH_2), 1.83 – 1.75 (m, 2H, CH_2), 1.47 (h, *J* = 7.4 Hz, 2H, CH_2), 0.97 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.2, 158.1, 157.8, 133.6, 128.9, 128.9, 126.8, 118.7, 66.5, 30.7, 19.2, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}NO_2S$ 262.0902; found 262.0890



3-methylcyclohexyl 4-phenylthiazole-2-carboxylate (4l): White solid; Yield 0.264 g (88%); mp 87-90 °C; IR: $\upsilon_{max}(cm^{-1})$ 693, 754, 893, 1091, 1244, 1440, 1735, 2900; ^1H NMR (600 MHz, $CDCl_3$): δ 7.95 (ddd, *J* = 10.8, 8.4, 1.3 Hz, 2H, Ar-H), 7.71 (s, 1H, Het-H), 7.44 – 7.30 (m, 3H, Ar-H), 5.06 – 4.97 (m, 1H, CH), 2.18 – 1.93 (m, 2H, CH_2), 1.92 – 1.80 (m, 1H, CH), 1.79 – 1.59 (m, 2H, CH_2), 1.58 – 1.33 (m, 2H, CH_2), 1.32 – 1.16 (m, 2H, CH_2), 0.91 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 158.4, 157.8, 133.7, 128.9, 126.8, 118.6, 118.4, 73.2, 40.3, 38.4, 29.9, 27.3, 24.0, 20.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}NO_2S$ 302.1215; found 302.1210

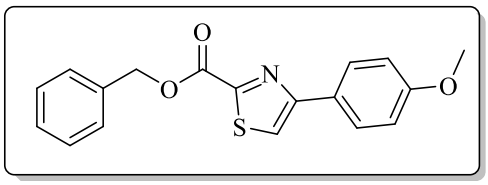


4-nitrobenzyl 4-phenylthiazole-2-carboxylate (4m): White solid; Yield 0.286 g (84%); mp 109-111 °C; IR: $\upsilon_{max}(cm^{-1})$ 761, 844, 999, 1100, 1245, 1338, 1443, 1739, 2925; ^1H NMR (600 MHz,



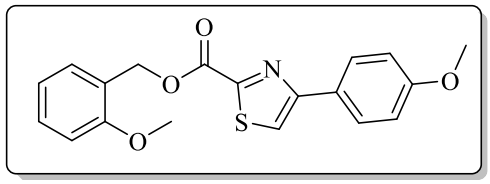
$CDCl_3$): δ 8.26 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.97 – 7.90 (m, 2H, Ar-H), 7.79 (s, 1H, Het-H), 7.66 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.51 – 7.33 (m, 3H, Ar-H), 5.55 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.8, 158.3, 157.0, 148.0, 142.3, 133.4, 129.1, 129.0, 128.9, 126.8, 124.1, 119.4, 66.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_4S$ 341.0596; found 341.0589

Benzyl 4-(4-methoxyphenyl)thiazole-2-carboxylate (4n): White solid; Yield 0.269 g (83%);



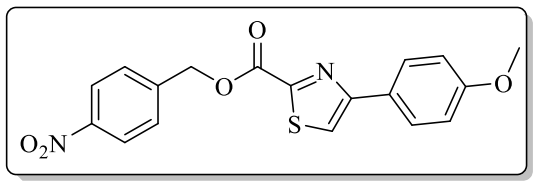
mp 90-91 °C; IR: $\upsilon_{max}(cm^{-1})$ 835, 1029, 1120, 1246, 1345, 1449, 1719, 2923; ^1H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.60 (s, 1H, Het-H), 7.51 – 7.46 (m, 2H, Ar-H), 7.39 – 7.34 (m, 3H, Ar-H), 6.94 (d, *J* = 8.8 Hz, 2H, Ar-H), 5.46 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.2, 160.0, 157.9, 157.5, 135.2, 128.8, 128.7, 128.7, 128.2, 126.5, 117.3, 114.2, 68.0, 55.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}NO_3S$ 326.0851; found 326.0845

2-methoxybenzyl 4-(4-methoxyphenyl)thiazole-2-carboxylate (4o): White solid; Yield 0.305



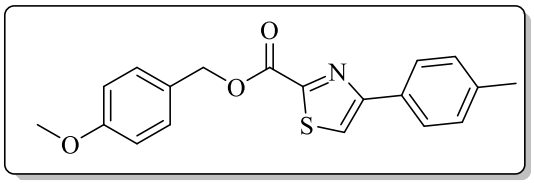
g (86%); mp 95-96 °C; IR: $\upsilon_{max}(cm^{-1})$ 839, 1032, 1093, 1235, 1349, 1437, 1512, 1723, 2917; ^1H NMR (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.59 (s, 1H, Het-H), 7.45 (dd, *J* = 7.5, 1.8 Hz, 1H, Ar-H), 7.32 (td, *J* = 7.7, 1.7 Hz, 1H, Ar-H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.94 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.90 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar-H), 5.51 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.2, 160.1, 157.7, 157.7, 157.7, 130.0, 128.2, 126.5, 123.6, 120.6, 117.2, 117.2, 114.2, 110.6, 63.6, 55.6, 55.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4S$ 356.0957; found 356.0953

4-nitrobenzyl 4-(4-methoxyphenyl)thiazole-2-carboxylate (4p): White solid; Yield 0.307 g



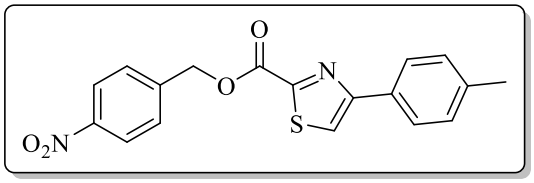
(83%); mp 97-98 °C; IR: $\upsilon_{max}(cm^{-1})$ 831, 1024, 1099, 1240, 1343, 1440, 1518, 1726, 2925; ^1H NMR (600 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.87 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.65 (s, 1H, Het-H), 7.64 (d, *J* = 0.7 Hz, 2H, Ar-H), 6.96 (d, *J* = 8.9 Hz, 2H, Ar-H), 5.54 (s, 2H, CH_2), 3.84 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.4, 159.8, 158.2, 156.7, 142.3, 130.1, 128.8, 128.2, 126.3, 124.0, 117.8, 114.3, 66.4, 55.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_5S$ 371.0702; found 371.0690.

4-methoxybenzyl 4-(p-tolyl)thiazole-2-carboxylate (4q): White solid; Yield 0.289 g (85%); mp 93-95 °C; IR: $\upsilon_{max}(cm^{-1})$ 829, 1016, 1093, 1236, 1350, 1438, 1500, 1711, 2900; ^1H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.66 (s, 1H, Het-H), 7.43 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.22 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.91 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.40 (s, 2H, CH_2), 3.80 (s, 3H,

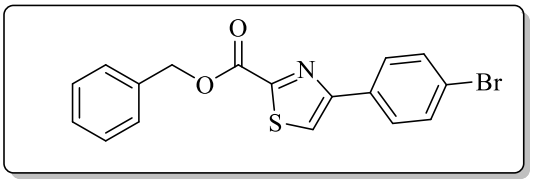


OCH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.1, 160.0, 158.0, 157.8, 138.9, 130.9, 130.7, 129.6, 127.3, 126.7, 118.2, 114.1, 68.0, 55.4, 21.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_3S$ 340.1007; found 340.10010

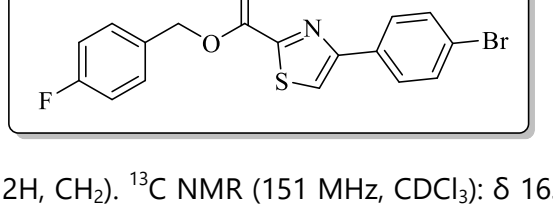
4-nitrobenzyl 4-(p-tolyl)thiazole-2-carboxylate (4r): White solid; Yield 0.293 g (83%); mp 111-114 °C; IR: $\upsilon_{max}(cm^{-1})$ 830, 1016, 1084, 1238, 1340, 1431, 1500, 1718, 2920; ^1H NMR (600 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.83 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.73 (s, 1H, Het-H), 7.64 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.8 Hz, 2H, Ar-H), 5.54 (s, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.8, 158.4, 156.8, 148.0, 142.3, 139.1, 130.7, 129.7, 128.8, 126.7, 124.0, 118.7, 66.4, 21.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_4S$ 355.0753; found 355.0750



Benzyl 4-(4-bromophenyl)thiazole-2-carboxylate (4s): White solid; Yield 0.293 g (79%); mp 105-107 °C; IR: $\upsilon_{max}(cm^{-1})$ 698, 760, 837, 916, 1087, 1236, 1446, 1730, 2922; ^1H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.72 (s, 1H, Het-H), 7.54 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.50 – 7.44 (m, 2H, Ar-H), 7.42 – 7.32 (m, 3H, Ar-H), 5.46 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.8, 158.0, 156.7, 135.1, 132.4, 132.1, 128.8, 128.7, 128.3, 123.1, 119.3, 117.8, 68.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_2S$ 373.9850; found 373.9843



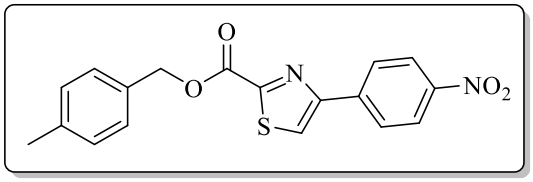
4-fluorobenzyl 4-(4-bromophenyl)thiazole-2-carboxylate (4t): White solid; Yield 0.319 g (82%); mp 125-127 °C; IR: $\upsilon_{max}(cm^{-1})$ 691, 765, 843, 917, 1074, 1238, 1451, 1728, 2929; ^1H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.74 (s, 1H, Het-H), 7.55 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.51 – 7.42 (m, 2H, Ar-H), 7.07 (t, *J* = 8.7 Hz, 2H, Ar-H), 5.42 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.8, 159.8, 157.9, 156.8, 132.4, 132.1, 130.9, 130.8 (d, *J* = 8.3 Hz), 128.3, 123.2, 119.3, 115.8, 115.7 (d, *J* = 21.7 Hz), 67.5. ^{19}F NMR (151 MHz, $CDCl_3$): δ = −112.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}BrFNO_2S$ 391.9756; found 391.9750



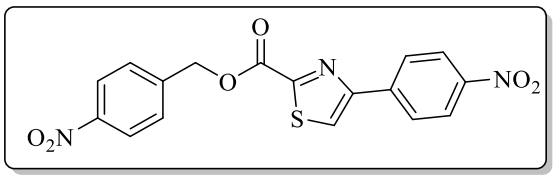
Benzyl 4-(4-nitrophenyl)thiazole-2-carboxylate (4u): White solid; Yield 0.271 g (80%); mp 115-117 °C; IR: $\upsilon_{max}(cm^{-1})$ 793, 937, 1075, 1238, 1333, 1437, 1731, 2928; ^1H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.12 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.94 (s, 1H, Het-H), 7.51 – 7.46 (m, 2H, Ar-H),

7.42 – 7.38 (m, 3H, Ar-H), 5.48 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.6, 158.7, 155.3, 147.9, 139.2, 134.9, 128.9, 128.8, 128.8, 127.5, 124.3, 121.8, 68.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_4S$ 341.0596; found 341.0585

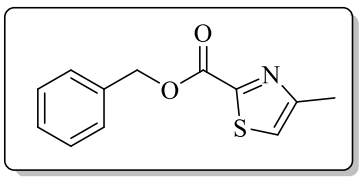
4-methylbenzyl 4-(4-nitrophenyl)thiazole-2-carboxylate (4v): White solid; Yield 0.289 g (82%); mp 117-118 °C; IR: $\upsilon_{max}(cm^{-1})$ 798, 931, 1089, 1233, 1338, 1440, 1728, 2930; ^1H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.11 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.93 (s, 1H, Het-H), 7.38 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.20 (d, *J* = 7.6 Hz, 2H, Ar-H), 5.43 (s, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.6, 158.8, 155.2, 147.9, 139.3, 138.9, 131.9, 129.5, 129.0, 127.5, 124.3, 121.8, 68.4, 21.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_4S$ 355.0753; found 355.0748



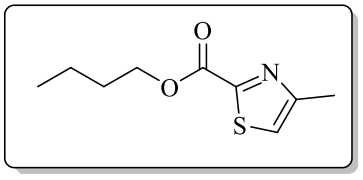
4-nitrobenzyl 4-(4-nitrophenyl)thiazole-2-carboxylate (4w): White solid; Yield 0.288 g (75%); mp 120-122 °C; IR: $\upsilon_{max}(cm^{-1})$ 791, 925, 1081, 1238, 1329, 1449, 1726, 2939; ^1H NMR (600 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.9 Hz, 2H, Ar-H), 8.27 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.13 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.99 (s, 1H, Het-H), 7.66 (d, *J* = 8.9 Hz, 2H, Ar-H), 5.57 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.4, 158.0, 155.6, 148.1, 148.0, 141.9, 139.0, 129.0, 127.5, 124.4, 124.1, 122.2, 66.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}N_3O_6S$ 386.0447; found 386.0444



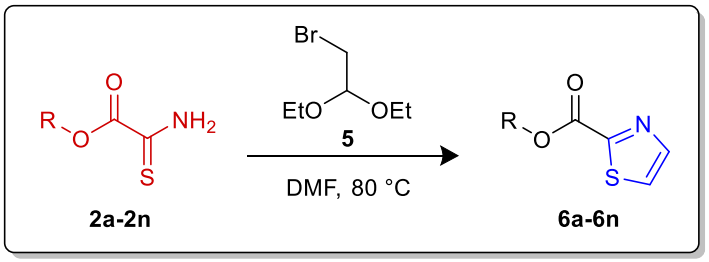
Benzyl 4-methylthiazole-2-carboxylate (4x): Brown liquid; Yield 0.167 g (72%); IR: $\upsilon_{max}(cm^{-1})$ 890, 1120, 1253, 1342, 1470, 1725, 2947; ^1H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.44 (m, 2H, Ar-H), 7.37 – 7.32 (m, 3H, Ar-H), 7.17 (s, 1H, Het-H), 5.42 (s, 2H, CH_2), 2.52 (s, 3H, CH_3).^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 157.1, 155.7, 135.2, 128.8, 128.7, 128.7, 120.5, 68.0, 17.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NO_2S$ 234.0589; found 234.0582



Butyl 4-methylthiazole-2-carboxylate (4y): Brown liquid; Yield 0.157 g (79%); IR: $\upsilon_{max}(cm^{-1})$ 837, 953, 1123, 1252, 1345, 1465, 1723, 2946; ^1H NMR (600 MHz, $CDCl_3$): δ 7.15 (s, 1H, Het-H), 4.37 (t, J = 6.8 Hz, 2H, CH_2), 2.50 (s, 3H, CH_3), 1.78 – 1.71 (m, 2H, CH_2), 1.41 (h, J = 7.5 Hz, 2H, CH_2), 0.92 (t, J = 7.3 Hz, 3H, CH_3).^{13}C NMR (151 MHz, $CDCl_3$): δ 160.2, 157.5, 155.5, 120.2, 66.3, 30.7, 19.1, 17.3, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{14}NO_2S$ 200.0745; found 200.0737



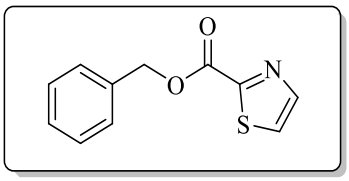
General procedure for the synthesis of alkyl thiazole-2-carboxylate 6a-6n



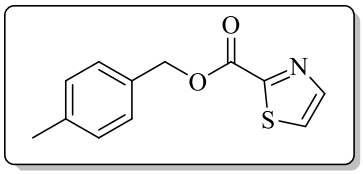
Alkyl 2-amino-2-thioxoacetates **2** (1 mmol) and bromoacetal **5** (1 mmol) were dissolved in DMF (2 mL) and stirred for 1 hour at 80 °C. The reaction was monitored using thin layer chromatography. After the reaction was completed, 25 mL of brine was added to the reaction mixture. It was then subjected to multiple extractions using ethyl acetate. The combined ethyl acetate layer was dried over anhydrous sodium sulphite and concentrated under reduced pressure. Further, crude product was purified by column chromatography on silica gel with an ethyl acetate/hexane mixture to yield alkyl thiazole-2-carboxylate **6a-6n**.

Characterization details of alkyl 4-phenylthiazole-2-carboxylate 6a-6n

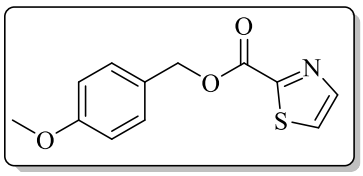
Benzyl thiazole-2-carboxylate (6a): Brown gummy solid; Yield 0.175 g (80%); IR: $\upsilon_{max}(cm^{-1})$ 756, 1089, 1223, 1361, 1435, 1713, 2900; ^1H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 3.1 Hz, 1H, Het-H), 7.63 (d, *J* = 3.1 Hz, 1H, Het-H), 7.50 – 7.42 (m, 2H, Ar-H), 7.41 – 7.34 (m, 3H, Ar-H), 5.44 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.9, 158.3, 145.1, 135.0, 128.8, 128.8, 128.8, 125.5, 68.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{10}NO_2S$ 220.0432; found 220.0422



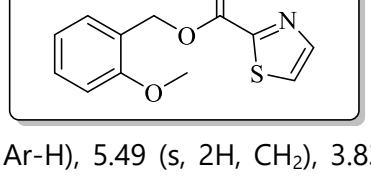
4-methylbenzyl thiazole-2-carboxylate (6b): Brown gummy solid; Yield 0.174 g (75%); IR: $\upsilon_{max}(cm^{-1})$ 751, 1077, 1232, 1369, 1428, 1717, 2910; ^1H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 3.0 Hz, 1H, Het-H), 7.60 (d, *J* = 3.0 Hz, 1H, Het-H), 7.36 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.17 (d, *J* = 7.9 Hz, 2H, Ar-H), 5.39 (s, 2H, CH_2), 2.34 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 158.4, 145.1, 138.7, 132.1, 129.4, 129.0, 125.4, 68.1, 21.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NO_2S$ 234.0589; found 234.0580



4-methoxybenzyl thiazole-2-carboxylate (6c): Brown gummy solid; Yield 0.179 g (72%); IR: $\upsilon_{max}(cm^{-1})$ 758, 1037, 1248, 1477, 1716, 2929; ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 3.0 Hz, 1H, Het-H), 7.61 (d, *J* = 3.1 Hz, 1H, Het-H), 7.41 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.89 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.37 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.1, 158.5, 145.1, 130.8, 128.8, 127.2, 125.4, 114.1, 68.0, 55.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NO_3S$ 250.0538; found 250.0533



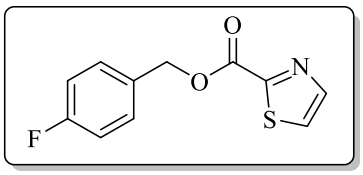
2-methoxybenzyl thiazole-2-carboxylate (6d): Brown gummy solid; Yield 0.186 g (75%); IR: $\upsilon_{max}(cm^{-1})$ 753, 1029, 1243, 1481, 1707, 2934; ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 3.1 Hz, 1H, Het-H), 7.61 (d, *J* = 3.0 Hz, 1H, Het-H), 7.42 (dd, *J* = 7.4, 1.8 Hz, 1H, Ar-H), 7.35 – 7.28 (m, 1H, Ar-H), 6.95 (dd, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.89 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar-H), 5.49 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 158.5, 157.8, 145.1, 130.1, 130.1, 125.3, 123.4, 120.6, 110.6, 63.7, 55.6; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NO_3S$ 250.0538; found 250.0530



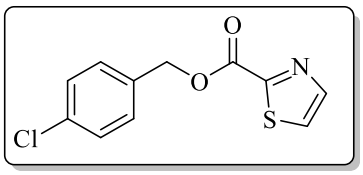
4-nitrobenzyl thiazole-2-carboxylate (6e): Brown gummy solid; Yield 0.191 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 768, 1020, 1230,1298, 1400, 1713, 2922; ^1H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.03 (d, *J* = 3.0 Hz, 1H, Het-H), 7.69 (d, *J* = 3.0 Hz, 1H, Het-H), 7.54 – 7.48 (m, 2H, Ar-H), 5.51 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.7, 157.5,

145.3, 128.9, 127.1, 126.1, 124.0, 123.8, 66.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_9N_2O_4S$ 265.0283; found 265.0277

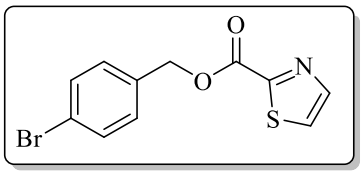
4-fluorobenzyl thiazole-2-carboxylate (6f): Brown gummy solid; Yield 0.163 g (69%); IR: $\upsilon_{max}(cm^{-1})$ 761, 1082, 1152, 1264, 1395, 1727, 2930; ^1H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 3.0 Hz, 1H, Het-H), 7.61 (d, *J* = 3.0 Hz, 1H, Het-H), 7.43 (dd, *J* = 8.6, 5.4 Hz, 2H, Ar-H), 7.03 (t, *J* = 8.7 Hz, 2H, Ar-H), 5.37 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.8, 162.2, 159.9, 158.1, 145.2, 130.9, 130.8 (d, *J* = 8.2 Hz), 125.6, 115.8, 115.7 (d, *J* = 21.6 Hz) 67.4. ^{19}F NMR (151 MHz, $CDCl_3$): δ = –104.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_9FNO_2S$ 238.0338; found 238.0333



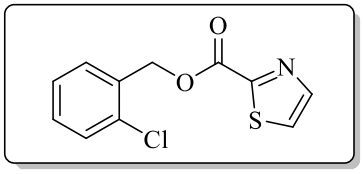
4-chlorobenzyl thiazole-2-carboxylate (6g): Brown gummy solid; Yield 0.185 g (74%); IR: $\upsilon_{max}(cm^{-1})$ 758, 1079, 1149, 1260, 1392, 1723, 2929; ^1H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 3.0 Hz, 1H, Het-H), 7.63 (d, *J* = 3.0 Hz, 1H, Het-H), 7.39 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.33 (d, *J* = 8.5 Hz, 2H, Ar-H), 5.38 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.9, 158.0, 145.2, 130.2, 129.0, 128.7, 128.3, 125.7, 67.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_9ClNO_2S$ 254.0043; found 254.0037



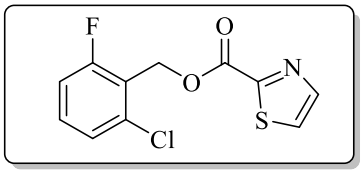
4-bromobenzyl thiazole-2-carboxylate (6h): Brown gummy solid; Yield 0.215 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 755, 1073, 1146, 1259, 1388, 1720, 2926; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 3.0 Hz, 1H, Het-H), 7.64 (d, *J* = 3.0 Hz, 1H, Het-H), 7.34 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.5 Hz, 2H, Ar-H), 5.39 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.8, 157.9, 145.1, 130.1, 128.9, 128.6, 128.3, 125.6, 67.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_9BrNO_2S$ 297.9537; found 297.9529



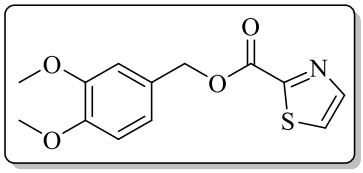
2-chlorobenzyl thiazole-2-carboxylate (6i): Brown gummy solid; Yield 0.194 g (77%); IR: $\upsilon_{max}(cm^{-1})$ 779, 1092, 1173, 1292, 1401, 1726, 2932; ^1H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, J = 3.0 Hz, 1H, Het-H), 7.64 (d, J = 3.1 Hz, 1H, Het-H), 7.54 – 7.48 (m, 1H, Ar-H), 7.42 – 7.36 (m, 1H, Ar-H), 7.31 – 7.24 (m, 2H, Ar-H), 5.53 (s, 2H, CH_2).^{13}C NMR (151 MHz, $CDCl_3$): δ 159.7, 157.9, 145.3, 134.0, 132.8, 130.3, 130.0, 129.8, 127.1, 125.6, 65.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_9ClNO_2S$ 254.0043; found 254.0031



2-chloro-6-fluorobenzyl thiazole-2-carboxylate (6j): Brown gummy solid; Yield 0.193 g (72%); IR: $\upsilon_{max}(cm^{-1})$ 765, 1086, 1157, 1269, 1399, 1730, 2938; ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 3.0 Hz, 1H, Het-H), 7.62 (d, *J* = 3.0 Hz, 1H, Het-H), 7.31 (td, *J* = 8.2, 5.9 Hz, 2H, Ar-H), 7.04 (ddd, *J* = 9.2, 8.3, 1.2 Hz, 1H, Ar-H), 5.60 (s, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.1, 161.5, 159.8, 157.9, 145.2, 136.8, 131.3, 131.2 (d, *J* = 9.7 Hz), 125.7, 125.6 (d, *J* = 3.5 Hz), 125.5, 114.6, 114.4 (d, *J* = 22.5 Hz), 59.0. ^{19}F NMR (151 MHz, $CDCl_3$): δ = –103.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_8ClFNO_2S$ 271.9948; found 271.9939

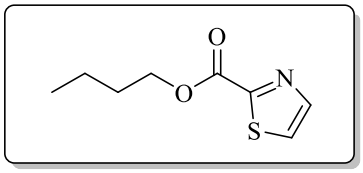


3,4-dimethoxybenzyl thiazole-2-carboxylate (6k): Brown gummy solid; Yield 0.190 g (66%);



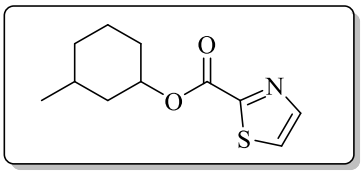
IR: $\upsilon_{max}(cm^{-1})$ 779, 1047, 1257, 1489, 1723, 2918; ^1H NMR (600 MHz, $CDCl_3$): δ 7.79 (d, *J* = 3.1 Hz, 1H, Het-H), 7.48 (d, *J* = 3.1 Hz, 1H, Het-H), 6.97– 6.93 (m, 2H, Ar-H), 6.84 (d, *J* = 4.4 Hz, 2H, Ar-H), 5.26 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.5, 157.2, 152.9, 148.2, 147.2, 130.4, 127.3, 125.7, 122.1, 121.1, 66.4, 60.5, 55.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}NO_4S$ 280.0644; found 280.0639

Butyl thiazole-2-carboxylate (6l): Brown gummy solid; Yield 0.142 g (77%); IR: $\upsilon_{max}(cm^{-1})$ 749,



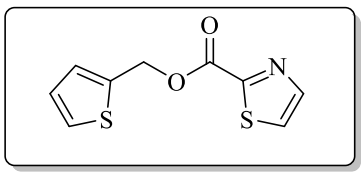
1070, 1147, 1259, 1381, 1719, 2923; ^1H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 3.1 Hz, 1H, Het-H), 7.62 (d, *J* = 3.0 Hz, 1H, Het-H), 4.41 (t, *J* = 6.8 Hz, 2H, CH_2), 1.83 – 1.75 (m, 2H, CH_2), 1.46 (h, *J* = 7.5 Hz, 2H, CH_2), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.2, 158.7, 145.1, 125.2, 66.5, 30.7, 19.2, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_8H_{12}NO_2S$ 186.0589; found 186.0580

3-methylcyclohexyl thiazole-2-carboxylate (6m): Brown gummy solid; Yield 0.163 g (73%); IR:



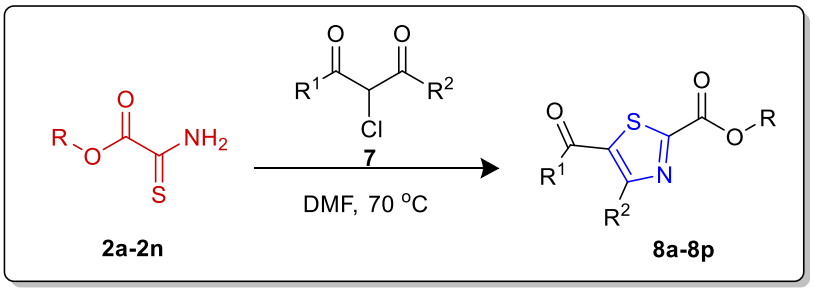
$\upsilon_{max}(cm^{-1})$ 723, 872, 988, 1012, 1112, 1233, 1365, 1722, 2910; ^1H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 3.1 Hz, 1H, Het-H), 7.59 (d, *J* = 2.9 Hz, 1H, Het-H), 5.03 – 4.95 (m, 1H, CH), 2.15 – 1.92 (m, 2H, CH_2), 1.91 – 1.80 (m, 1H, CH), 1.75 – 1.47 (m, 2H, CH_2), 1.47 – 1.31 (m, 2H, CH_2), 1.30 – 1.14 (m, 2H, CH_2), 0.93 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.6, 159.2, 145.0, 125.1, 76.0, 40.3, 33.9, 31.5, 31.4, 24.0, 22.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{16}NO_2S$ 226.0902; found 226.0899

Thiophen-2-ylmethyl thiazole-2-carboxylate (6n): Brown gummy solid; Yield 0.162 g (73%);



IR: $\upsilon_{max}(cm^{-1})$ 717, 866, 977, 1023, 1123, 1246, 1378, 1725, 2923; ^1H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, *J* = 3.0 Hz, 1H, Het-H), 7.79– 7.78 (m, 1H, Ar-H), 7.70 – 7.70 (d, *J* = 3.0 Hz, 1H, Het-H), 7.20 – 7.21 (m, 1H, Het-H), 5.53 (s, 2H, CH_2) ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.9, 156.4, 144.8, 132.9, 130.0, 129.9, 126.42, 124.2, 65; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_7NO_2S_2$ 224.9916; found 224.9909

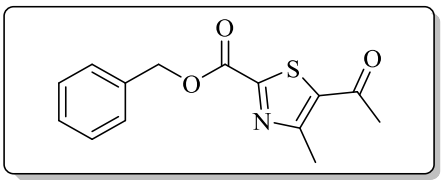
General procedure for the synthesis of alkyl 5-acetyl-4-methylthiazole-2-carboxylate 8a-8p



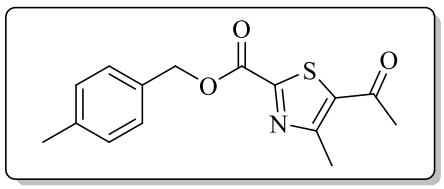
Alkyl 2-amino-2-thioxoacetates **2** (1 mmol) and 3-chloropentane-2,4-dione **7** (1 mmol) were dissolved in 2 mL DMF and stirred at 70 °C for 1 hour. The progress of the reaction was monitored using thin layer chromatography. After the reaction completion, 25 mL of brine solution was added, and then the reaction mixture was extracted into ethyl acetate (25 mL). The organic extract was then dehydrated using anhydrous sodium sulphite and concentrated under reduced pressure. The crude product was purified via column chromatography on silica gel, employing an ethyl acetate/hexane mixture as the eluent, yielding alkyl 5-acetyl-4-methylthiazole-2-carboxylate **8a-8p**.

Characterization details of alkyl 5-acetyl-4-methylthiazole-2-carboxylate 8a-8p

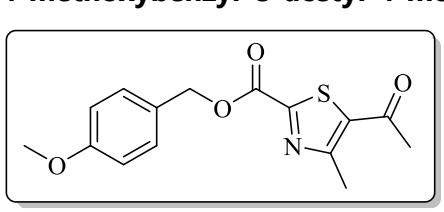
Benzyl 5-acetyl-4-methylthiazole-2-carboxylate (8a): Pale yellow gummy solid; Yield 0.214 g (78%); IR: $\upsilon_{max}(cm^{-1})$ 644, 756, 1018, 1107, 1225, 1470, 1678, 1735, 2923; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar-H), 7.42 – 7.32 (m, 3H, Ar-H), 5.45 (s, 2H, CH_2), 2.80 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.5, 159.9, 159.5, 157.8, 138.9, 135.9, 134.7, 128.9, 128.8, 68.6, 30.9, 18.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{14}NO_3S$ 276.0694; found 276.0688



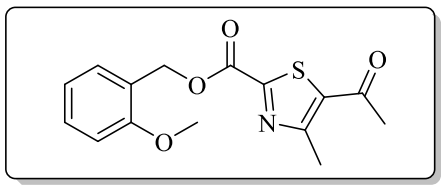
4-methylbenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8b): Pale yellow gummy solid; Yield 0.210 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 641, 749, 1012, 1104, 1220, 1467, 1673, 1730, 2920; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.18 (d, *J* = 7.8 Hz, 2H, Ar-H), 5.40 (s, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.35 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.5, 159.9, 159.5, 157.9, 138.9, 131.7, 129.5, 129.1, 127.2, 68.6, 30.9, 21.3, 18.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}NO_3S$ 290.0851; found 290.0843



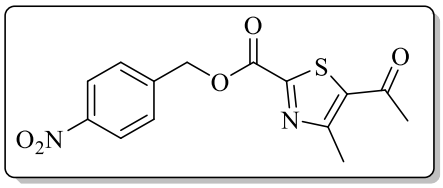
4-methoxybenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8c): Pale yellow gummy solid; Yield 0.216 g (71%); IR υ (cm^{-1}): 645, 759, 1015, 1113, 1231, 1478, 1684, 1732, 2922; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.90 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.38 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.5, 159.5, 157.9, 135.7, 130.2, 123.2, 120.6, 110.7, 96.2, 64.1, 55.6, 30.9, 18.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}NO_4S$ 306.0800; found 306.0794



2-methoxybenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8d): Pale yellow gummy solid; Yield 0.213 g (70%); IR: $\upsilon_{max}(cm^{-1})$ 643, 756, 1018, 1107, 1225, 1470, 1678, 1735, 2923; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.5, 1.8 Hz, 1H, Ar-H), 7.36 – 7.29 (m, 1H, Ar-H), 6.95 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.89 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar-H), 5.49 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.6, 159.9, 159.5, 158.0, 157.8, 135.7, 130.3, 130.2, 123.1, 120.6, 110.7, 64.2, 55.6, 30.9, 18.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}NO_4S$ 306.0800; found 306.079

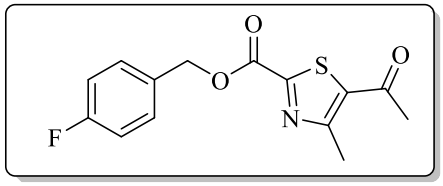


4-nitrobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8e): Pale yellow gummy solid; Yield 0.214 g (67%); IR: $\upsilon_{max}(cm^{-1})$ 651, 762, 937, 1023, 1116, 1237, 1475, 1683, 1731, 2327; ^{1}H NMR



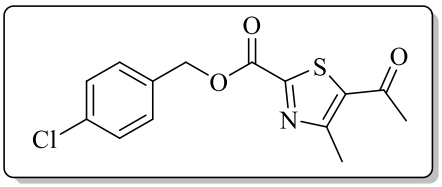
(600 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.62 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.52 (s, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.4, 160.0, 159.3, 148.3, 147.4, 129.0, 127.1, 124.1, 123.8, 66.8, 30.9, 18.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_5S$ 321.0545; found 321.0537

4-fluorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8f): Pale yellow gummy solid; Yield



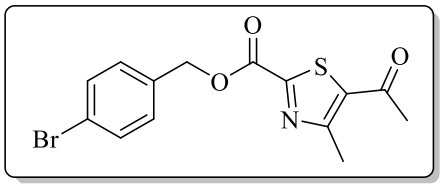
0.202 g (69%); IR: $\upsilon_{max}(cm^{-1})$ 664, 767, 948, 1025, 1127, 1238, 1489, 1692, 1729, 2935; ^1H NMR (600 MHz, $CDCl_3$): δ 7.44 (ddt, *J* = 8.0, 4.9, 2.5 Hz, 2H, Ar-H), 7.06 (td, *J* = 8.7, 3.3 Hz, 2H, Ar-H), 5.40 (s, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.5, 162.4, 162.2, 159.9, 159.5, 157.7, 136.0, 131.1, 131.0 (d, *J* = 8.3 Hz), 115.9, 115.7 (d, *J* = 21.5 Hz), 77.3, 30.9, 18.5. ^{19}F NMR (151 MHz, $CDCl_3$): δ = −118.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}FNO_3S$ 294.0600; found 294.0597

4-chlorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8g): Pale yellow gummy solid;



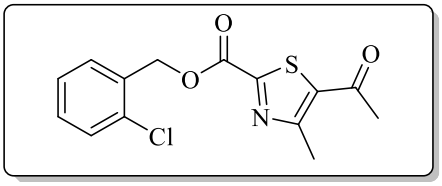
Yield 0.217 g (71%); IR: $\upsilon_{max}(cm^{-1})$ 660, 762, 944, 1021, 1120, 1231, 1483, 1690, 1725, 2929; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.30 (d, *J* = 9.1 Hz, 2H, Ar-H), 5.40 (s, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.58 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.5, 160.0, 159.4, 157.6, 135.0, 130.3, 129.1, 128.8, 128.4, 67.7, 30.9, 18.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_3S$ 310.0305; found 310.0300

4-bromobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8h): Pale yellow gummy solid;



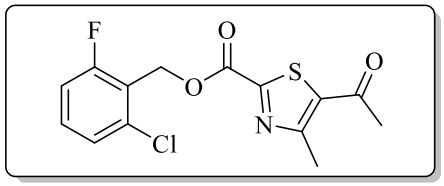
Yield 0.252 g (72%); IR υ (cm^{-1}): 654, 760, 939, 1017, 1116, 1227, 1480, 1688, 1719, 2923; ^1H NMR (600 MHz, $CDCl_3$ δ 7.32 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.97 (d, *J* = 7.5 Hz, 2H, Ar-H), 5.50 (s, 2H, CH_2), 2.79 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.6, 159.5, 157.8, 135.7, 130.3, 123.1, 120.5, 110.7, 96.2, 64.2, 30.9, 18.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}BrNO_3S$ 353.9800; found 353.9797

2-chlorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8i): Pale yellow gummy solid; Yield

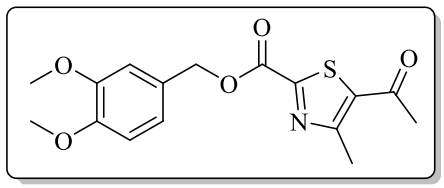


0.217 g (71%); IR: $\upsilon_{max}(cm^{-1})$ 660, 762, 944, 1021, 1120, 1231, 1483, 1690, 1725, 2929; ^1H NMR (600 MHz, $CDCl_3$): δ 7.57–7.45 (m, 1H, Ar-H), 7.41 (ddd, *J* = 15.2 Hz, 1H, Ar-H), 7.36–7.24 (m, 2H), 5.58 (s, 2H, CH_2), 2.79 (s, 3H, CH_3), 2.58 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.6, 180.1, 165.5, 158.1, 130.9, 130.6, 130.4, 130.1, 130.0, 129.8, 127.2, 66.5, 29.8, 18.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_3S$ 310.0305; found 310.0297

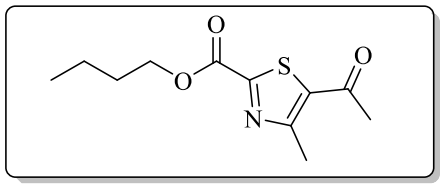
2-chloro-6-fluorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8j): Pale yellow gummy solid; Yield 0.227 g (70%); IR: $\upsilon_{max}(cm^{-1})$ 669, 769, 955, 1030, 1134, 1245, 1496, 1699, 1738, 2936; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (td, *J* = 8.2, 6.0 Hz, 2H, Ar-H), 7.08 – 7.02 (m, 1H, Ar-H), 5.60 (s, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.4, 163.1, 161.4, 160.0, 159.2, 157.2, 136.8, 135.9, 131.5, 131.4 (d, *J* = 10.0 Hz), 125.7, 125.6, (d, *J* = 3.9 Hz) 114.6, 114.5 (d, *J* = 22.1 Hz), 59.4, 30.9, 18.4. ^{19}F NMR (151 MHz, $CDCl_3$): δ = −118.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}ClFNO_3S$ 328.0210; found 328.0210



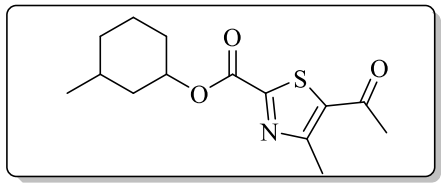
3,4-dimethoxybenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8k): Pale yellow gummy solid; Yield 0.227 g (70%); IR: $\upsilon_{max}(cm^{-1})$ 697, 756, 976, 1056, 1176, 1297, 1506, 1687, 1729, 2941; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43– 7.41 (m, 1H, Ar-H), 7.07 – 7.03 (m, 1H, Ar-H), 6.86 (d, J=9.2 Hz, 1H, Ar-H), 5.37 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3), 2.49 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.0, 161.8, 161.6, 144.8, 135.6, 132.9, 130.8, 128.9, 126.8, 122.4, 121.3, 66.4, 54.2, 30.6, 18.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}NO_5S$ 335.0827; found 335.0819



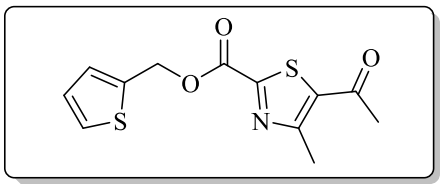
Butyl 5-acetyl-4-methylthiazole-2-carboxylate (8l): Pale yellow gummy solid; Yield 0.180 g (75%); IR: $\upsilon_{max}(cm^{-1})$ 627, 738, 929, 998, 1087, 1209, 1436, 1629, 1732, 2907; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.41 (t, *J* = 6.8 Hz, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 1.81 – 1.73 (m, 2H, CH_2), 1.49 – 1.40 (m, 2H, CH_2), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.6, 159.9, 159.7, 158.2, 135.7, 67.0, 30.6, 29.8, 19.1, 18.5, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{16}NO_3S$ 242.0851; found 242.0846



3-methylcyclohexyl 5-acetyl-4-methylthiazole-2-carboxylate (8m): Pale yellow gummy solid; Yield 0.205 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 613, 738, 895, 927, 1002, 1089, 1203, 1322, 1474, 1628, 1729, 2308; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.04 – 4.96 (m, 1H, CH), 2.78 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.13 – 1.92 (m, 2H, CH_2), 1.86 – 1.78 (m, 1H, CH), 1.70 – 1.59 (m, 2H, CH_2), 1.47 – 1.32 (m, 2H, CH_2), 1.32 – 1.15 (m, 2H, CH_2), 0.94 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.5, 159.8, 159.0, 158.6, 135.4, 73.9, 40.1, 33.8, 31.4, 31.3, 30.9, 23.9, 22.2, 18.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1164; found 282.1159

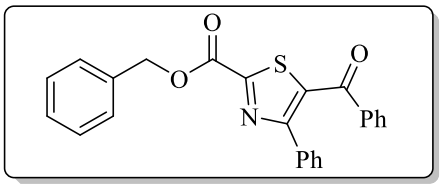


Thiophen-2-ylmethyl 5-acetyl-4-methylthiazole-2-carboxylate (8n): Pale yellow gummy solid; Yield 0.205 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 723, 779, 902, 967, 1056, 1112, 1203, 1354, 1491, 1625, 1731, 2296; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 – 7.81 (m, 1H, Het-H), 7.23–7.22 (m, 1H, Het-H),

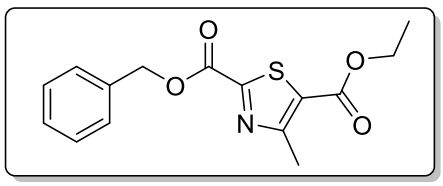


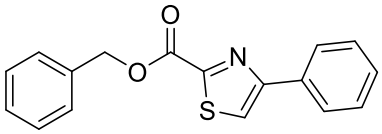
7.11–7.10 (m, 1H, Het-H), 5.26 (s, 2H, CH_2), 2.83 (s, 3H, CH_3), 2.61 (s, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 190.9, 163.7, 156.4, 155.0, 129.6, 127.6, 127.2, 125.6, 118.85, 65.4, 31.2, 18.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NO_3S_2$ 282.0259; found 282.0248

Benzyl 5-benzoyl-4-phenylthiazole-2-carboxylate (8o): Pale yellow gummy solid; Yield 0.205 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 697, 771, 912, 998, 1076, 1123, 1278, 1357, 1498, 1674, 1727, 2334; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (t, J = 7.7 Hz, 2H, Ar-H), 7.36 (m, 7H, Ar-H), 7.00 (m, 3H, Ar-H), 6.77 (d, J = 7.5 Hz, 2H, Ar-H), 5.53 (s, 1H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.4, 170.8, 160.6, 155.6, 150.0, 146.4, 141.8, 136.9, 129.8, 129.3, 129.2, 128.7, 126.0, 124.1, 114.7, 65.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{18}NO_3S$ 400.1007; found 400.9998

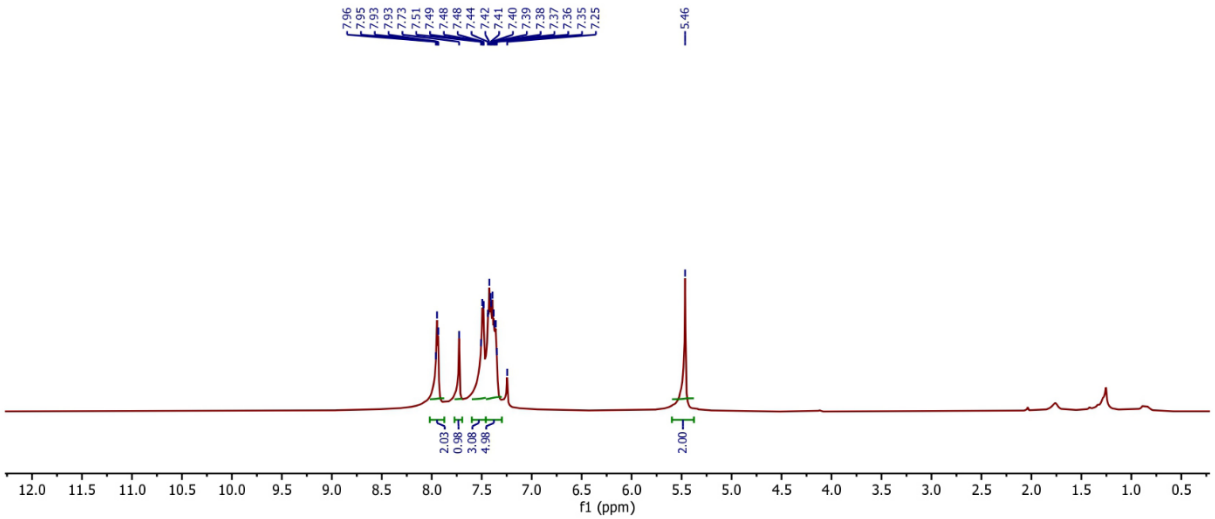


2-benzyl 5-ethyl 4-methylthiazole-2,5-dicarboxylate (8p): Pale yellow gummy solid; Yield 0.205 g (73%); IR: $\upsilon_{max}(cm^{-1})$ 823, 978, 1023, 1067, 1223, 1356, 1463, 1632, 1731, 2323; ^1H NMR (600 MHz, $CDCl_3$): δ 7.44 – 7.37 (m, 5H, Ar-H), 5.53 (s, 2H, CH_2), 4.40– 4.34 (q, *J* = 5.2 Hz, 2H, CH_2), 2.75 (s, 3H, CH_3), 1.36– 1.33 (t, *J* = 5.0 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5, 168.0, 163.8, 150.2, 143.6, 131.8, 130.1, 129.3, 128.7, 65.1, 62.1, 62.4, 15.2, 13.8; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}NO_4S$ 306.0800; found 306.0793

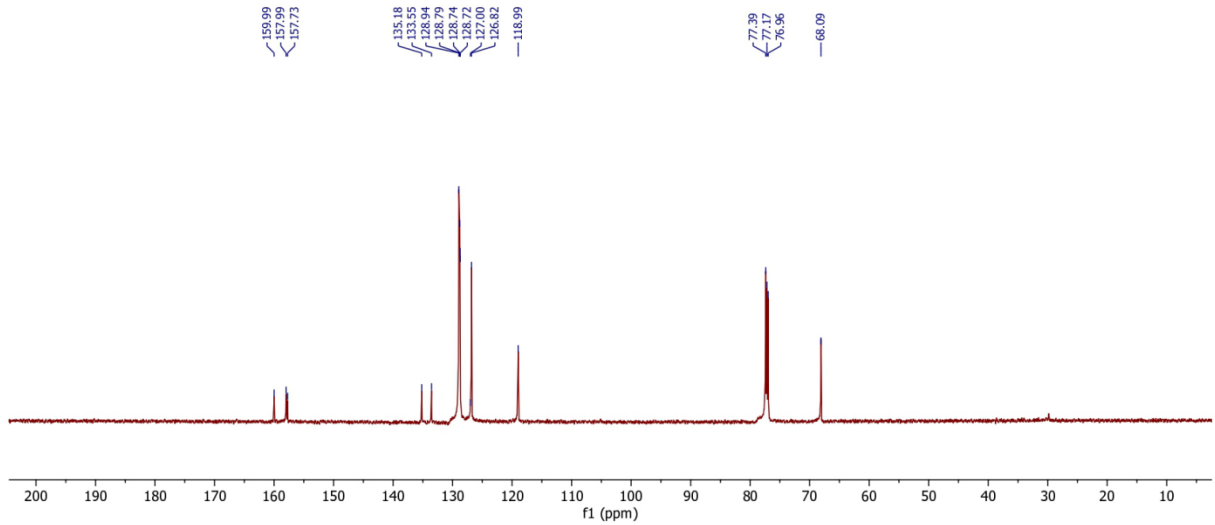




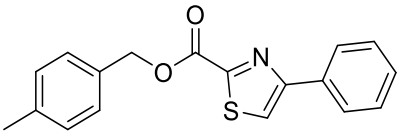
Benzyl 4-phenylthiazole-2-carboxylate (4a)



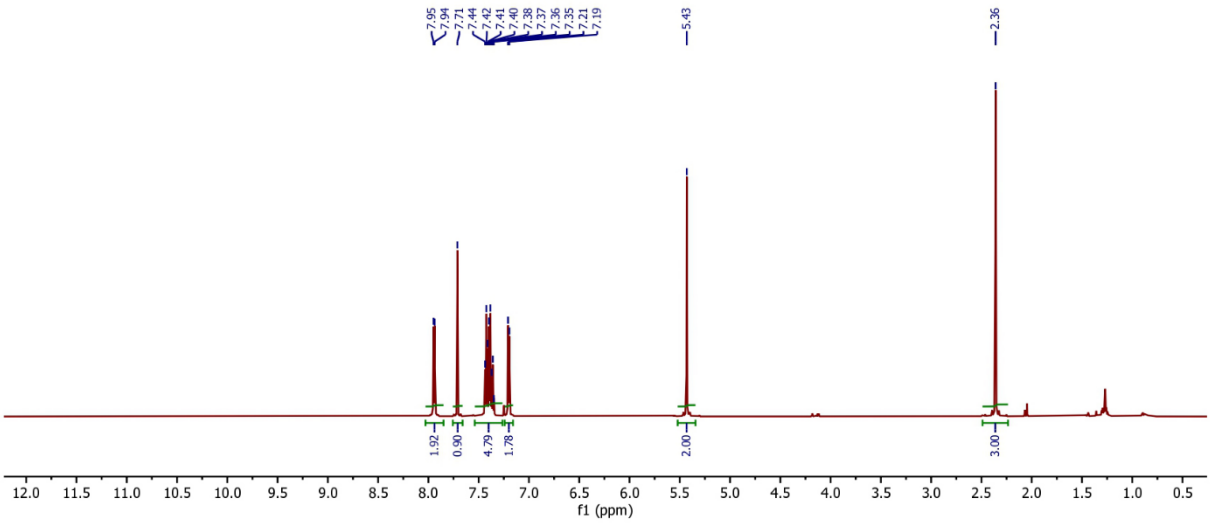
^{1}H NMR Spectrum of 4a (600 MHz, $CDCl_3$)



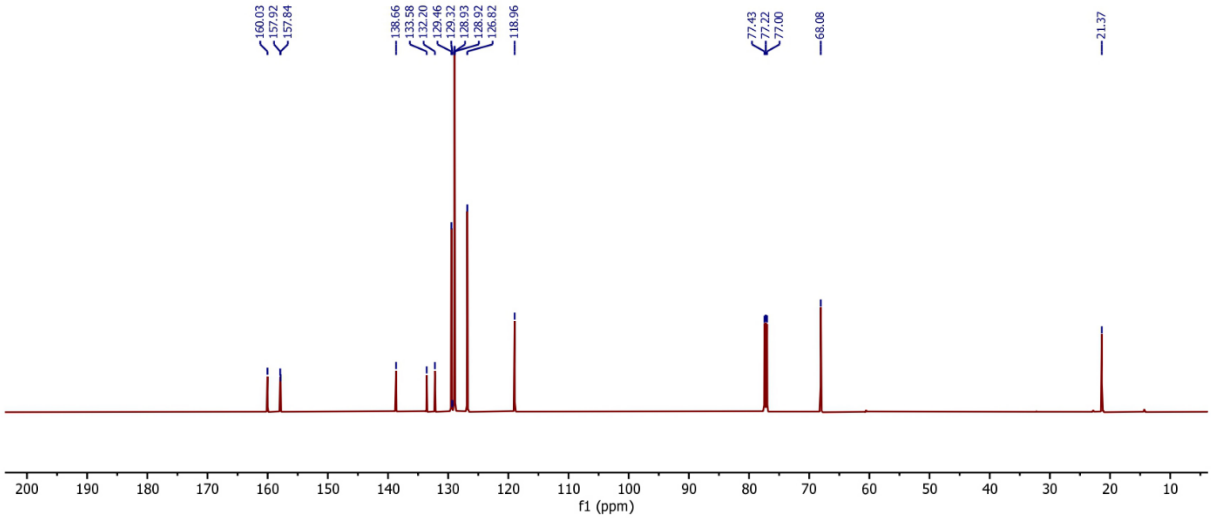
^{13}C NMR Spectrum of 4a (151 MHz, $CDCl_3$)



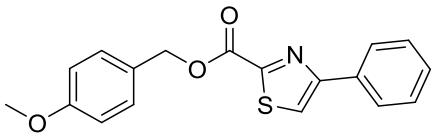
4-methylbenzyl 4-phenylthiazole-2-carboxylate (4b)



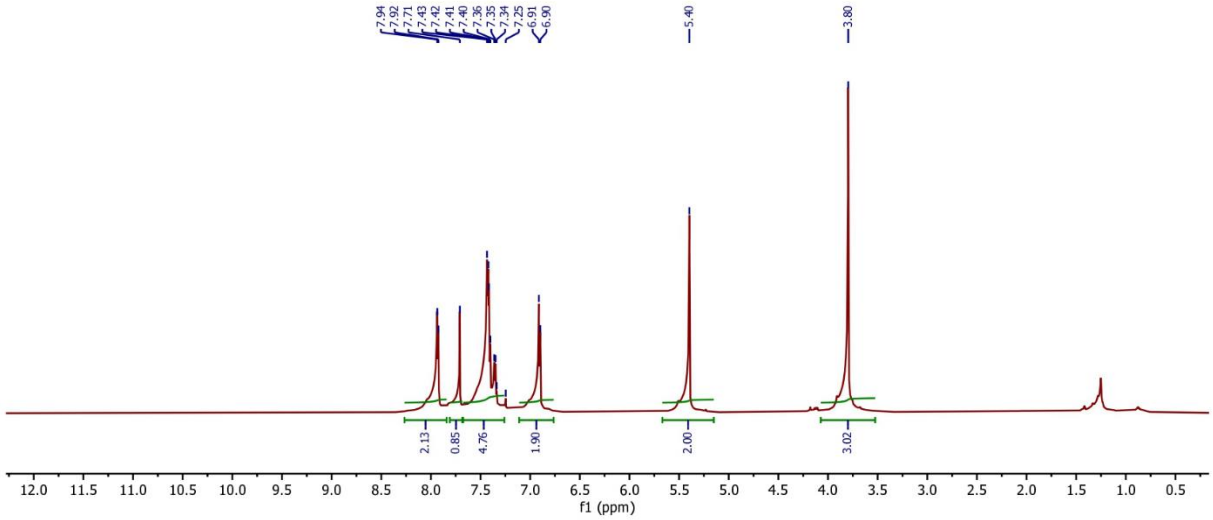
^{1}H NMR Spectrum of 4b (600 MHz, $CDCl_3$)



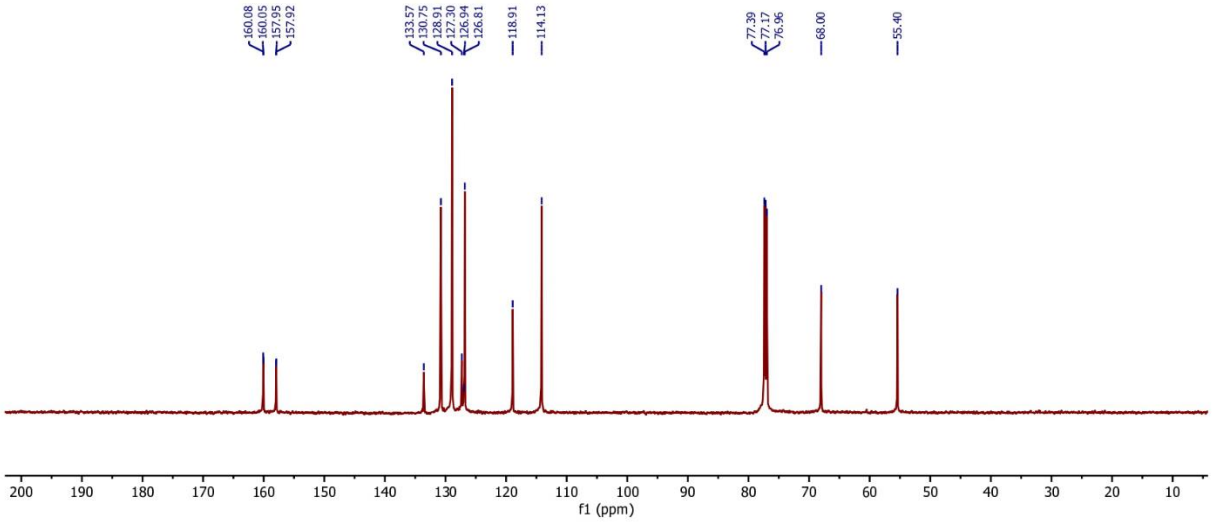
^{13}C NMR Spectrum of 4b (151 MHz, $CDCl_3$)



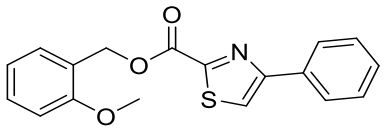
4-methoxybenzyl 4-phenylthiazole-2-carboxylate (4c)



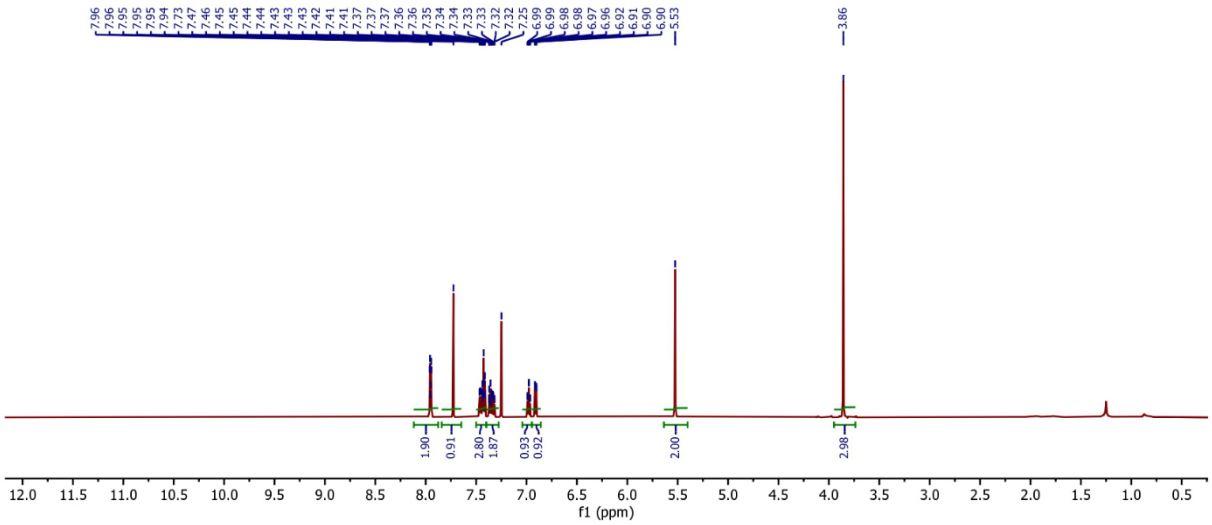
^{1}H NMR Spectrum of 4c (600 MHz, $CDCl_3$)



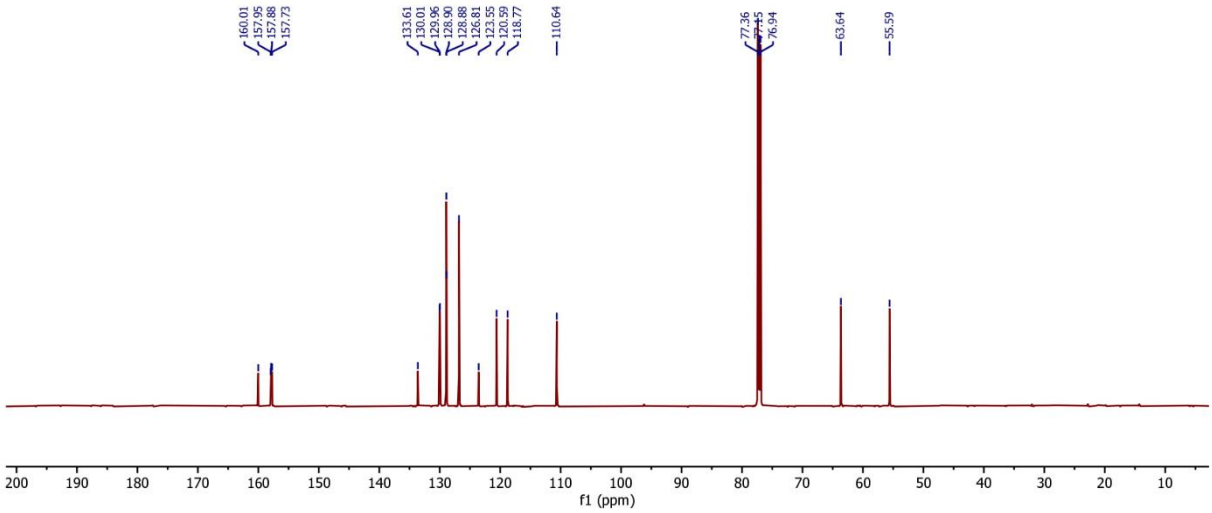
^{13}C NMR Spectrum of 4c (151 MHz, $CDCl_3$)



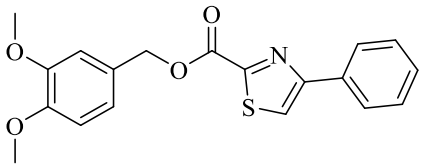
2-methoxybenzyl 4-phenylthiazole-2-carboxylate (4d)



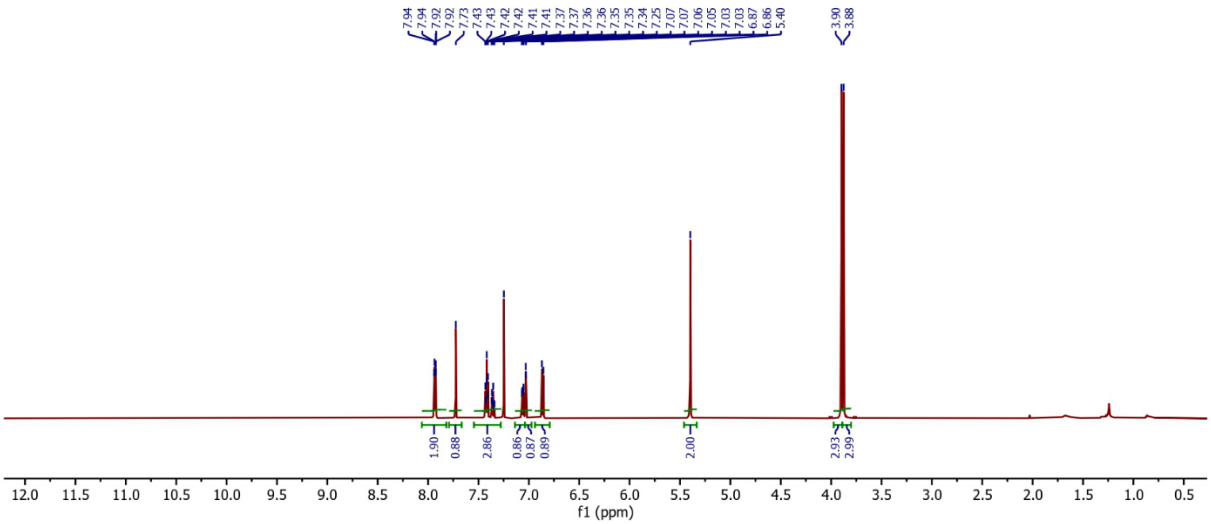
^{1}H NMR Spectrum of 4d (600 MHz, $CDCl_3$)



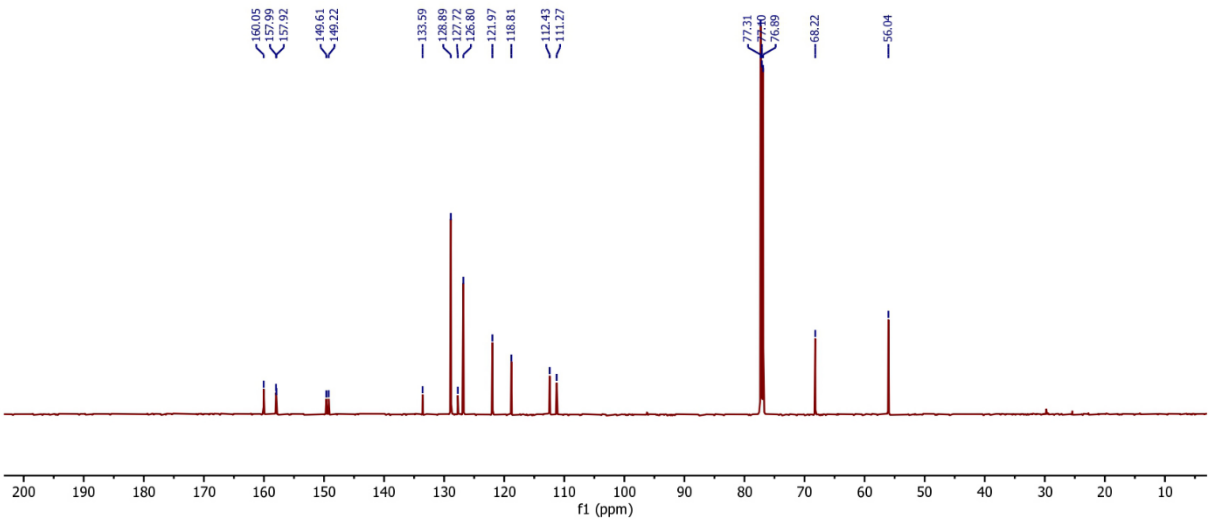
^{13}C NMR Spectrum of 4d (151 MHz, $CDCl_3$)



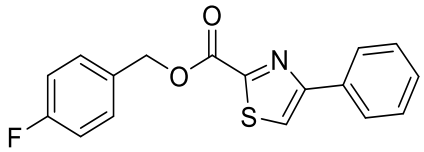
3,4-dimethoxybenzyl 4-phenylthiazole-2-carboxylate (4e)



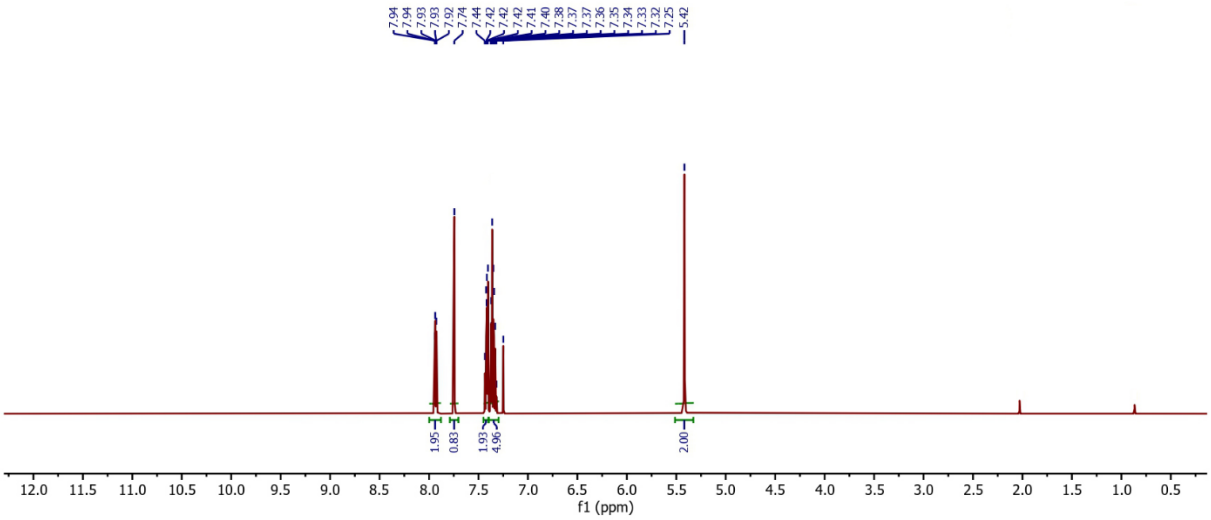
^{1}H NMR Spectrum of 4e (600 MHz, $CDCl_3$)



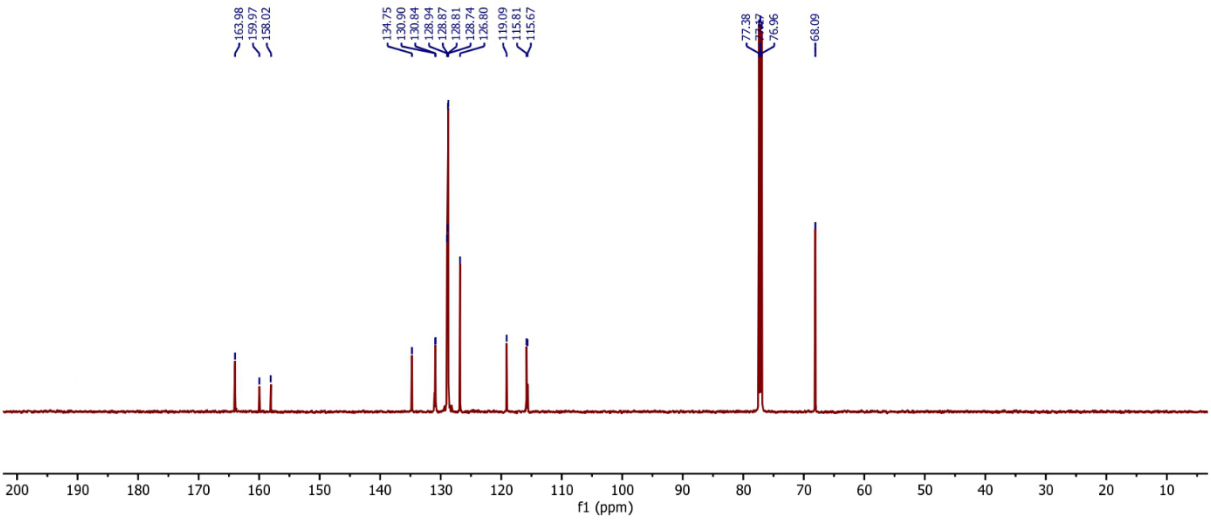
^{13}C NMR Spectrum of 4e (151 MHz, $CDCl_3$)



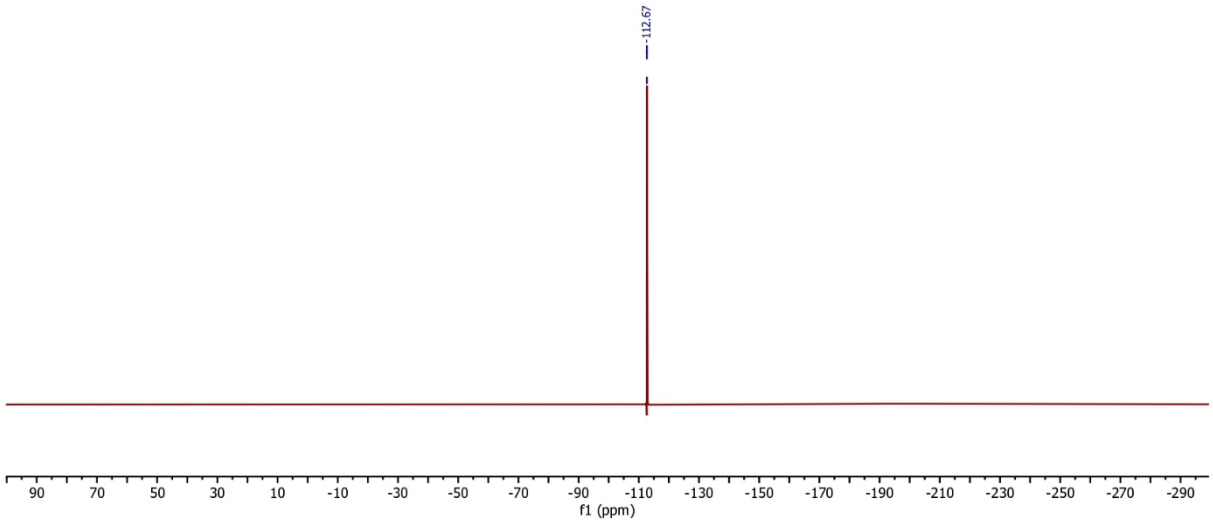
4-fluorobenzyl 4-phenylthiazole-2-carboxylate (4f)



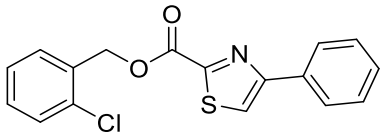
^{1}H NMR Spectrum of 4f (600 MHz, $CDCl_3$)



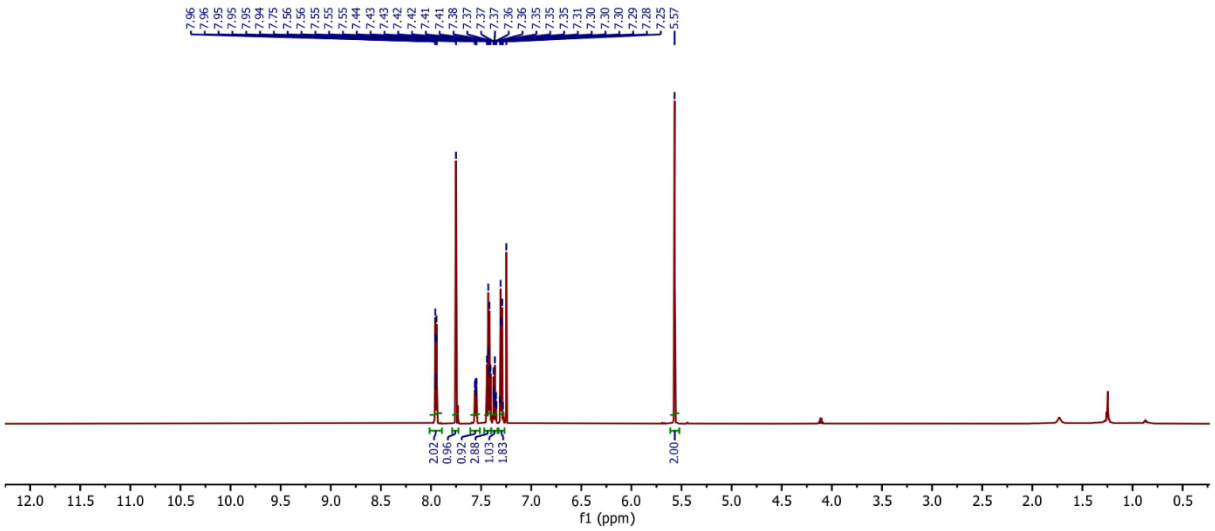
^{13}C NMR Spectrum of 4f (151 MHz, $CDCl_3$)



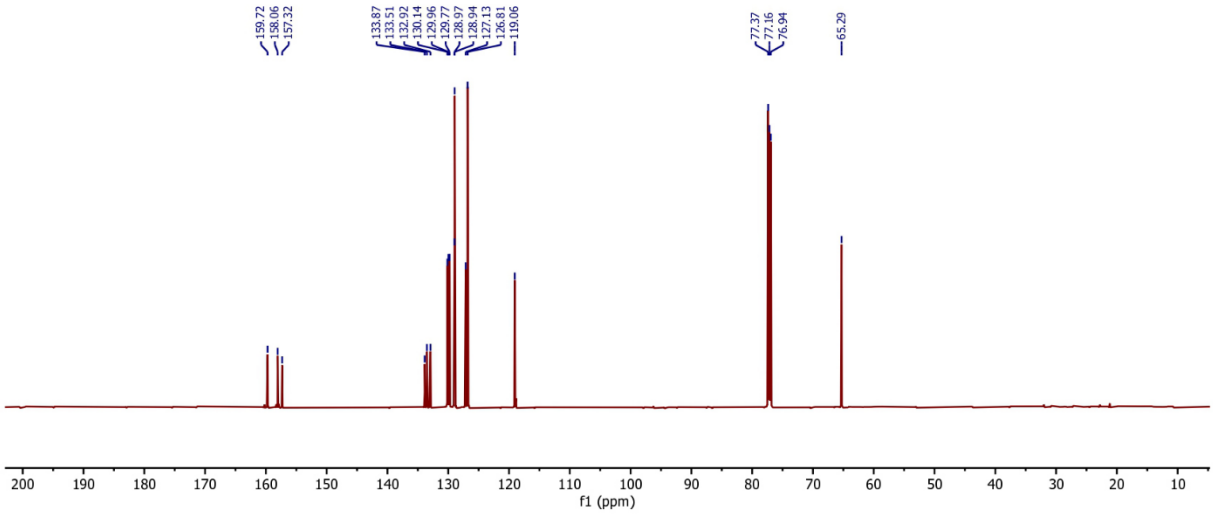
^{19}F NMR Spectrum of 4-fluorobenzyl 4-phenylthiazole-2-carboxylate (4f)



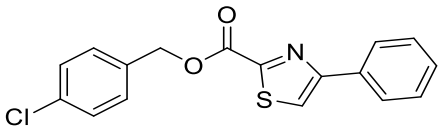
2-chlorobenzyl 4-phenylthiazole-2-carboxylate (4g)



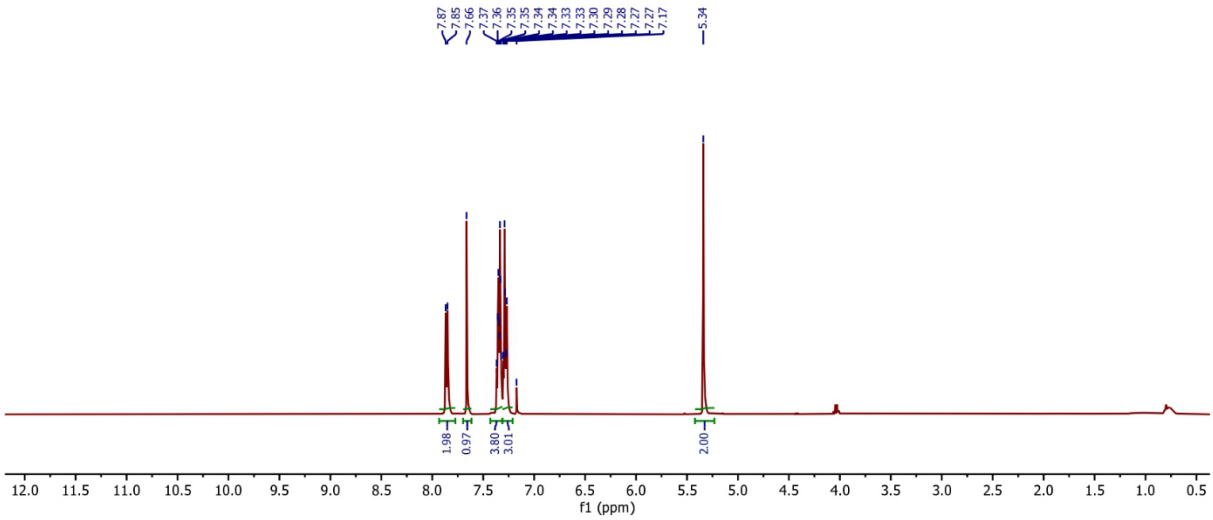
^{1}H NMR Spectrum of 4g (600 MHz, $CDCl_3$)



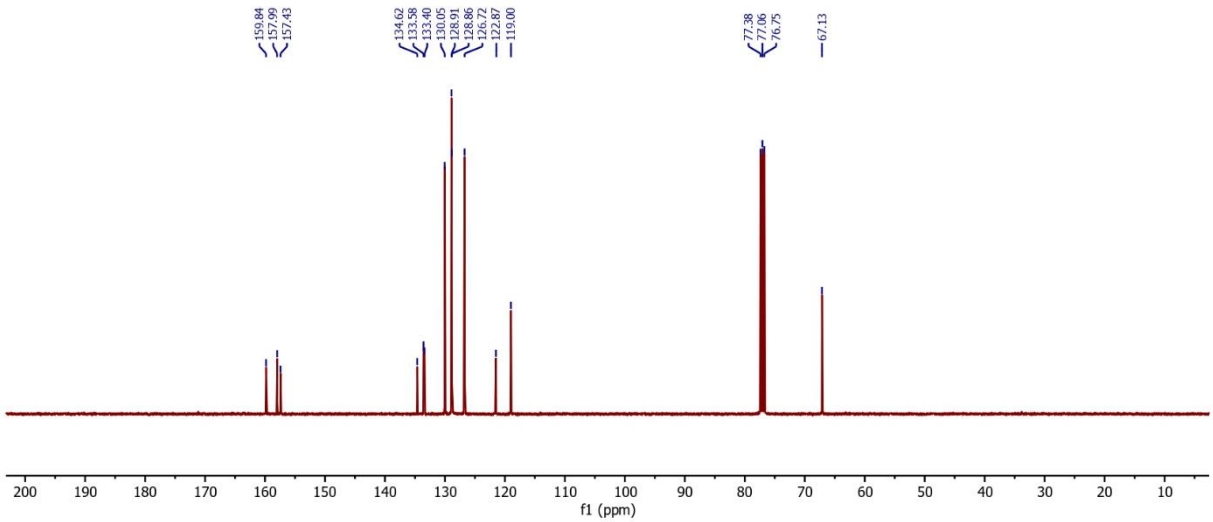
^{13}C NMR Spectrum of 4g (151 MHz, $CDCl_3$)



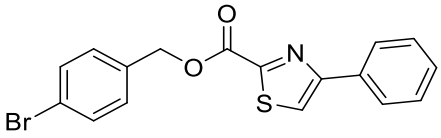
4-chlorobenzyl 4-phenylthiazole-2-carboxylate (4h)



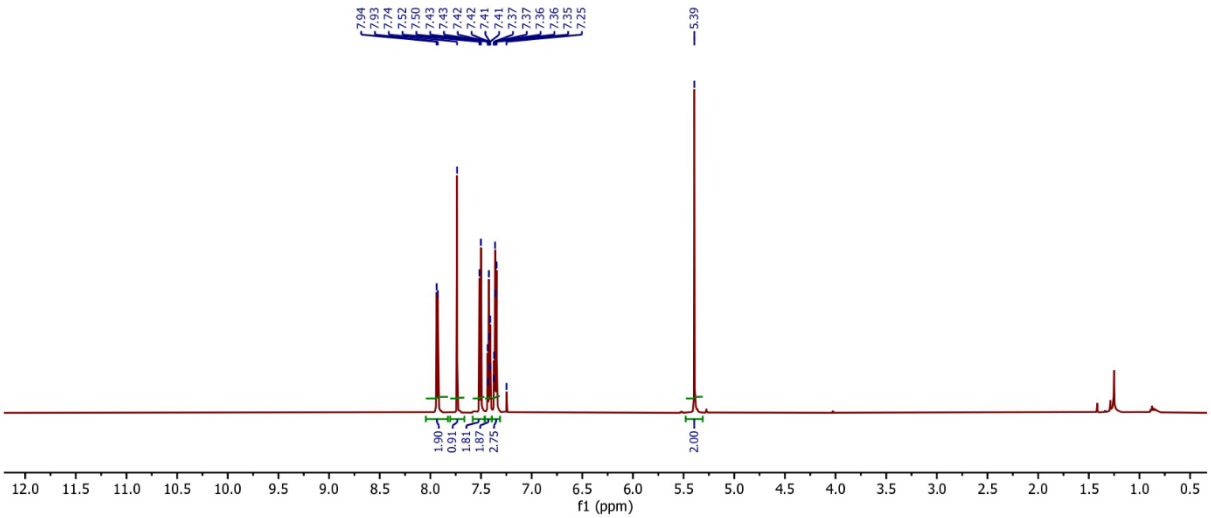
^{1}H NMR Spectrum of 4h (400 MHz, $CDCl_3$)



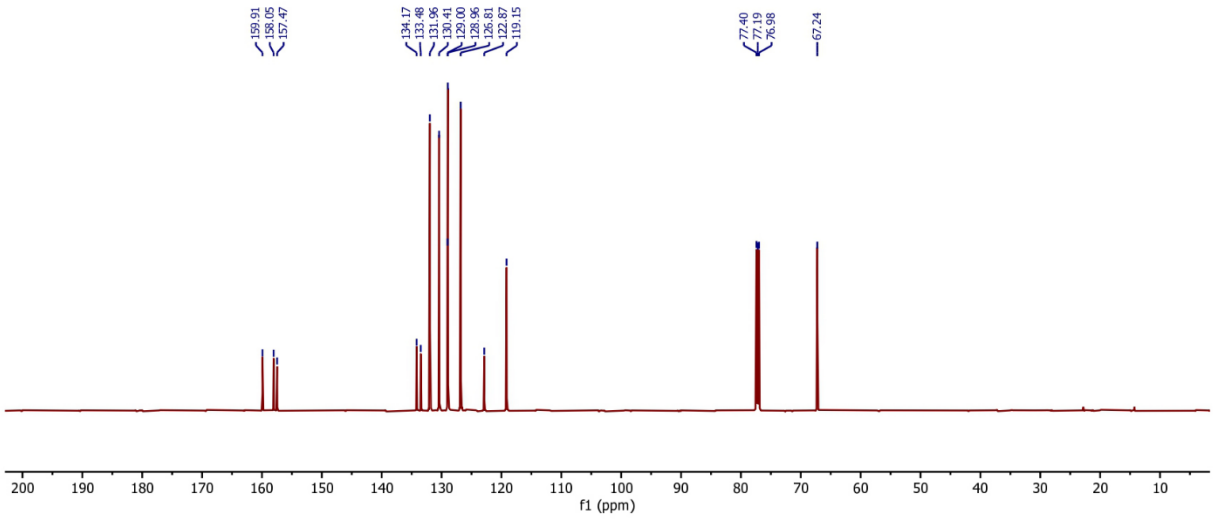
^{13}C NMR Spectrum of 4h (151 MHz, $CDCl_3$)



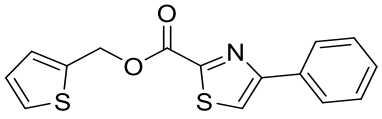
4-bromobenzyl 4-phenylthiazole-2-carboxylate (4i)



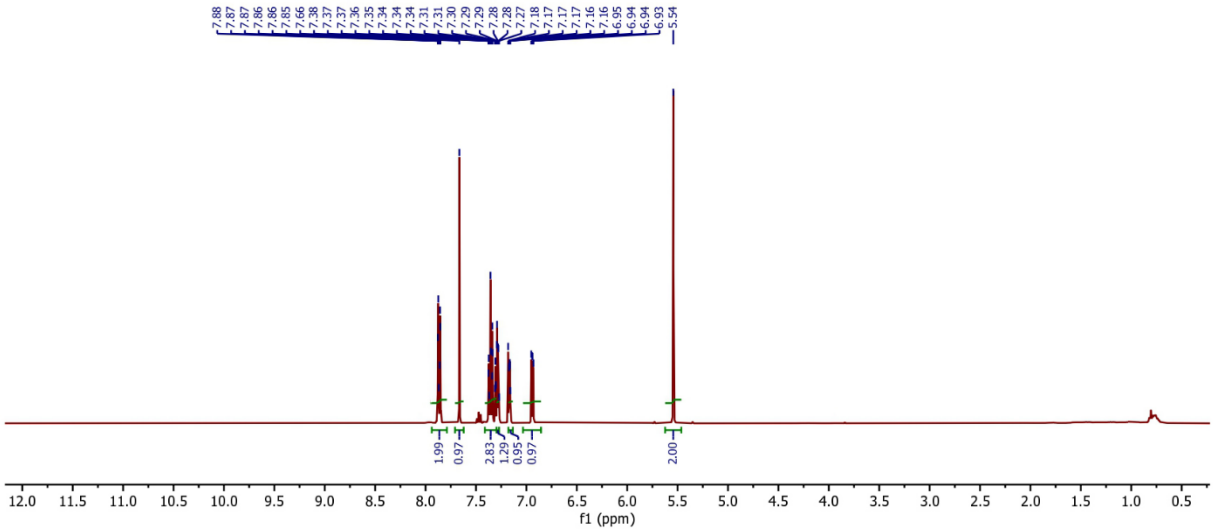
^{1}H NMR Spectrum of 4i (600 MHz, $CDCl_3$)



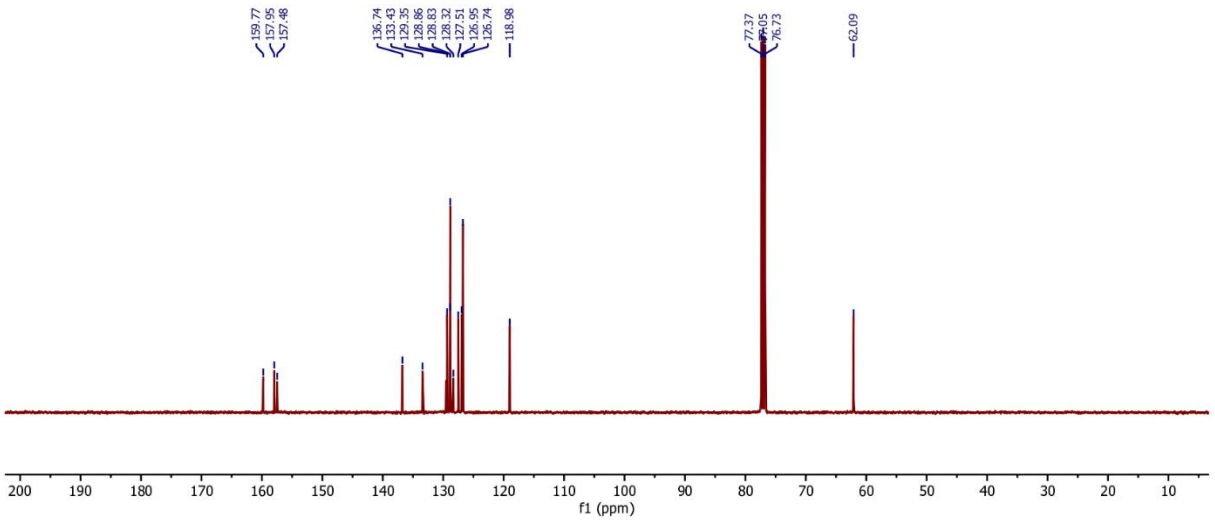
^{13}C NMR Spectrum of 4i (151 MHz, $CDCl_3$)



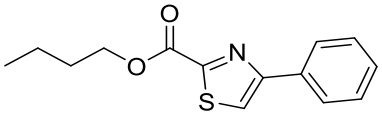
Thiophen-2-ylmethyl 4-phenylthiazole-2-carboxylate (4j)



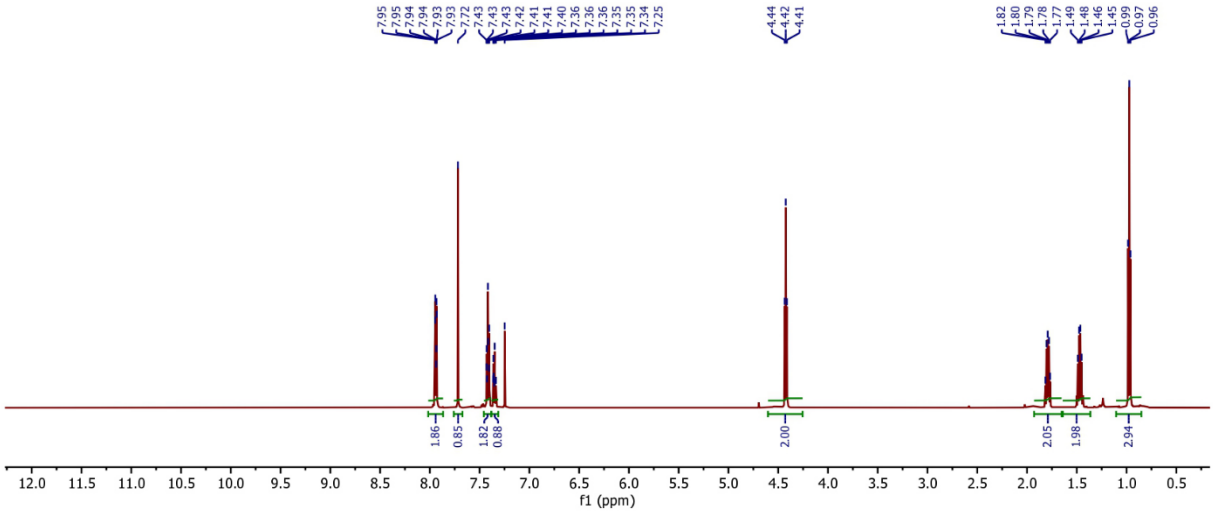
^{1}H NMR Spectrum of 4j (400 MHz, $CDCl_3$)



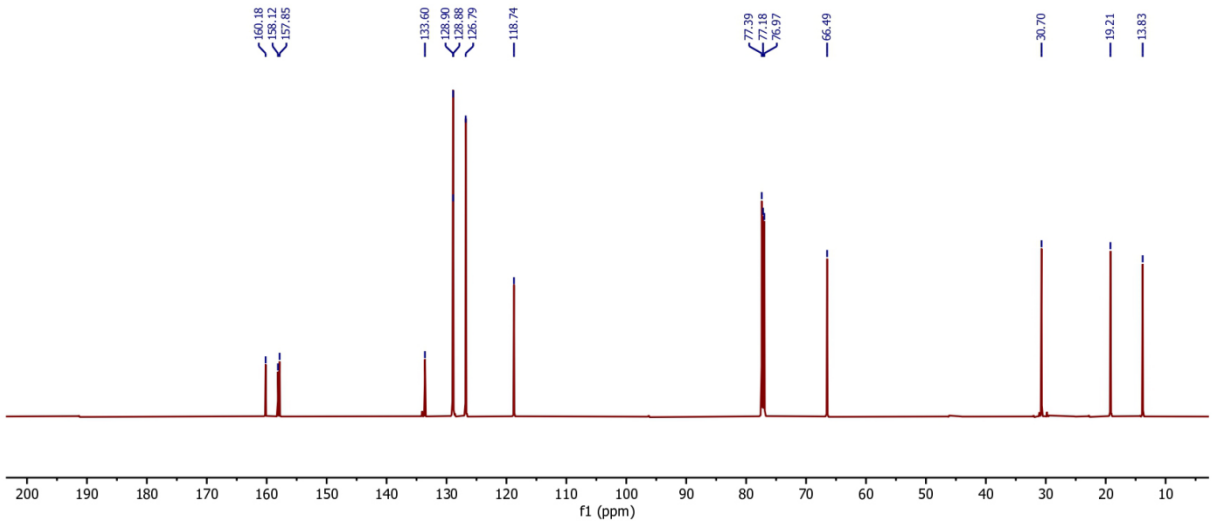
^{13}C NMR Spectrum of 4j (151 MHz, $CDCl_3$)



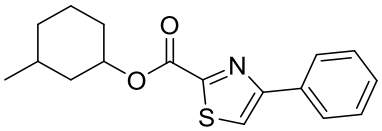
Butyl 4-phenylthiazole-2-carboxylate (4k)



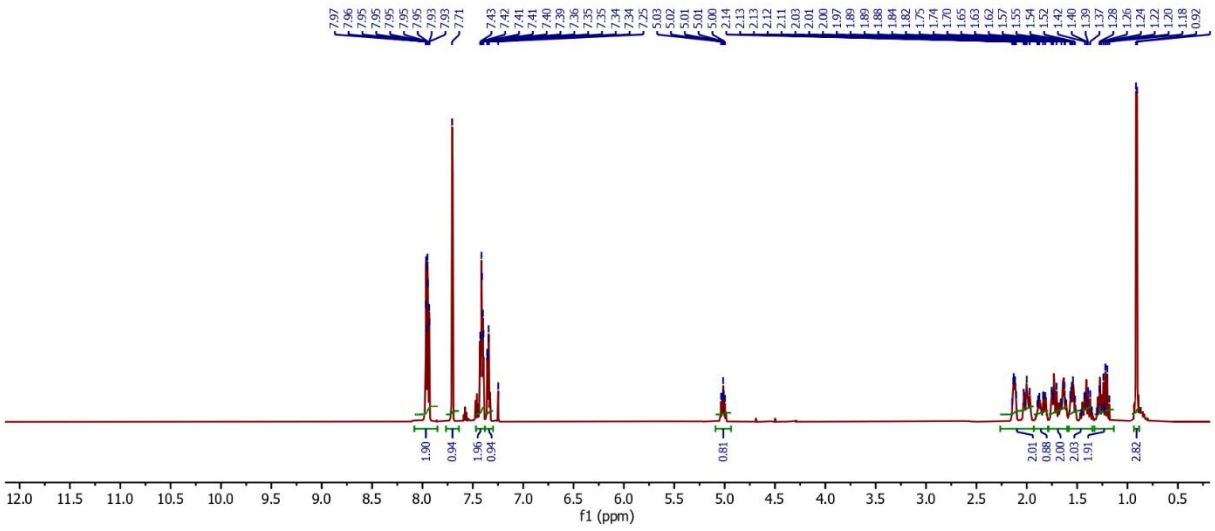
^{1}H NMR Spectrum of 4k (600 MHz, $CDCl_3$)



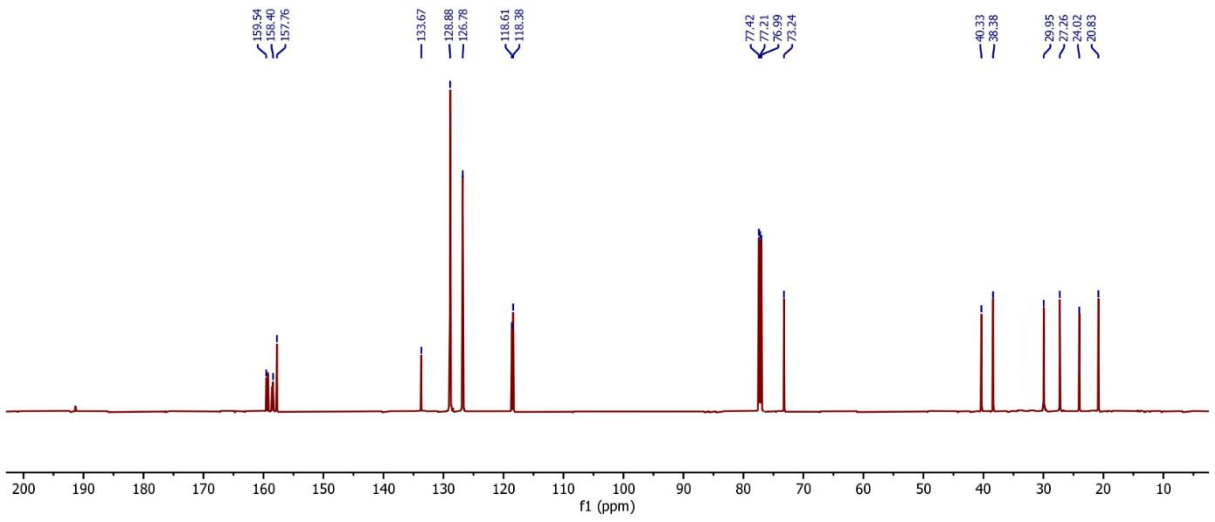
^{13}C NMR Spectrum of 4k (151 MHz, $CDCl_3$)



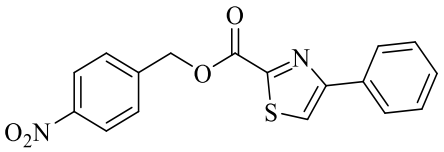
3-methylcyclohexyl 4-phenylthiazole-2-carboxylate (4l)



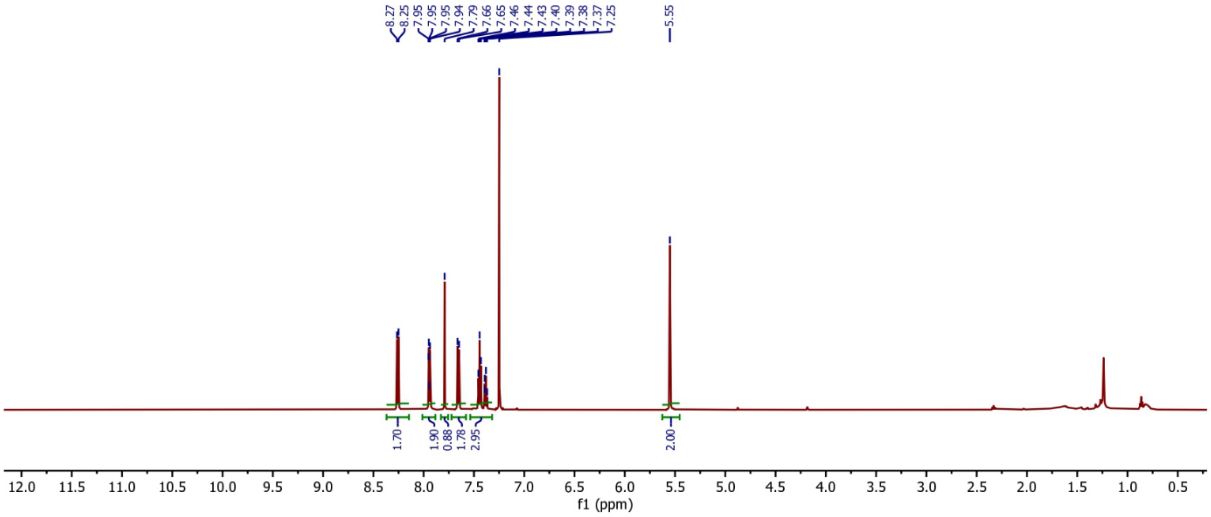
^{1}H NMR Spectrum of 4l (600 MHz, $CDCl_3$)



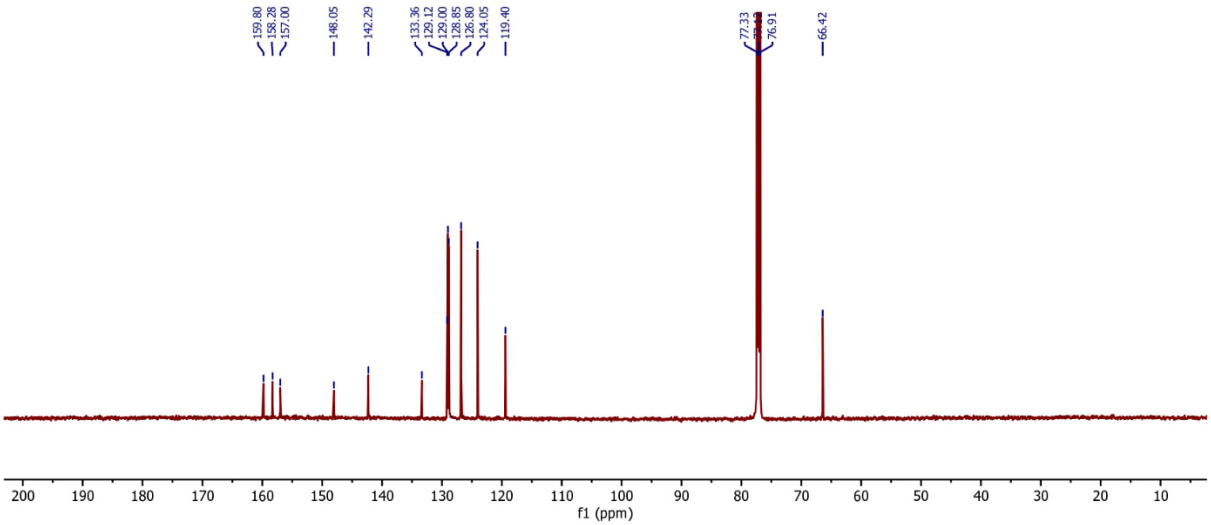
^{13}C NMR Spectrum of 4l (151 MHz, $CDCl_3$)



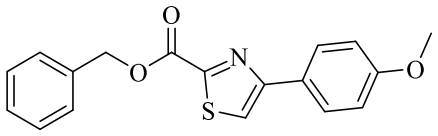
4-nitrobenzyl 4-phenylthiazole-2-carboxylate (4m)



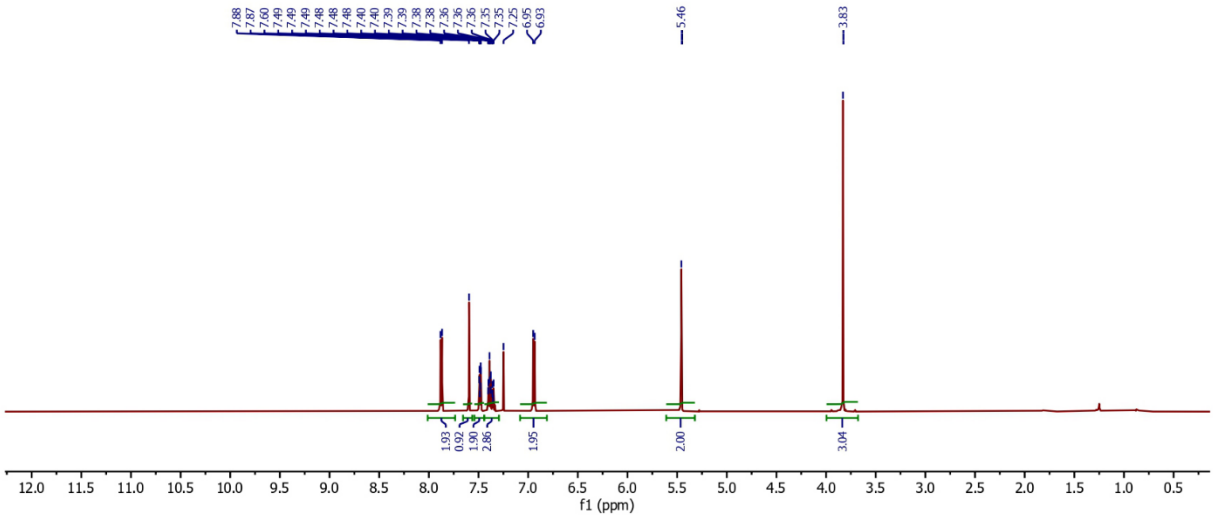
^{1}H NMR Spectrum of 4m (600 MHz, $CDCl_3$)



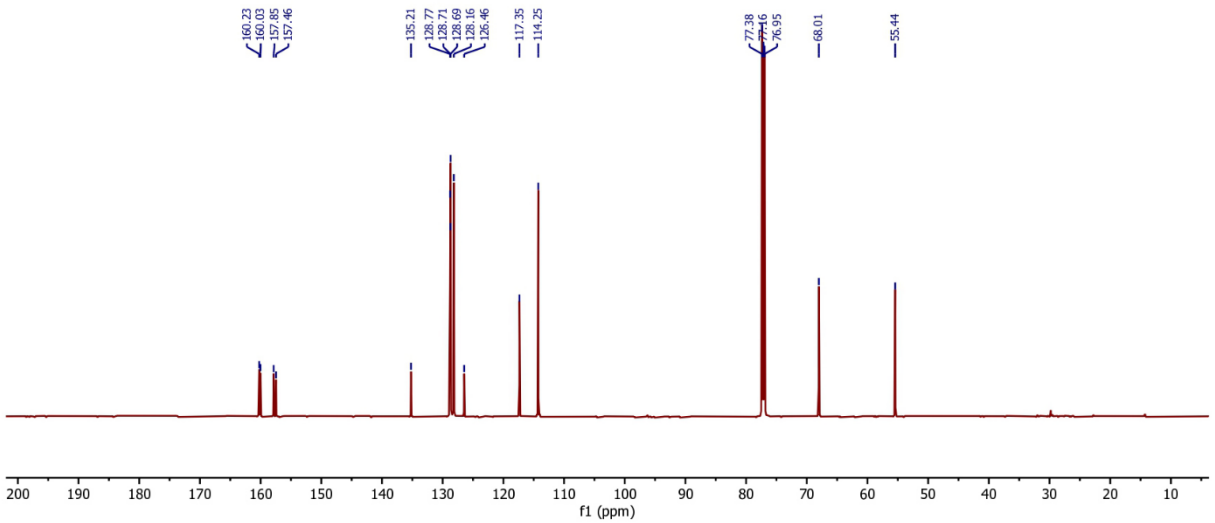
^{13}C NMR Spectrum of 4m (151 MHz, $CDCl_3$)



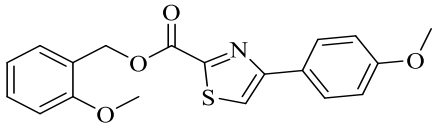
Benzyl 4-(4-methoxyphenyl)thiazole-2-carboxylate (4n)



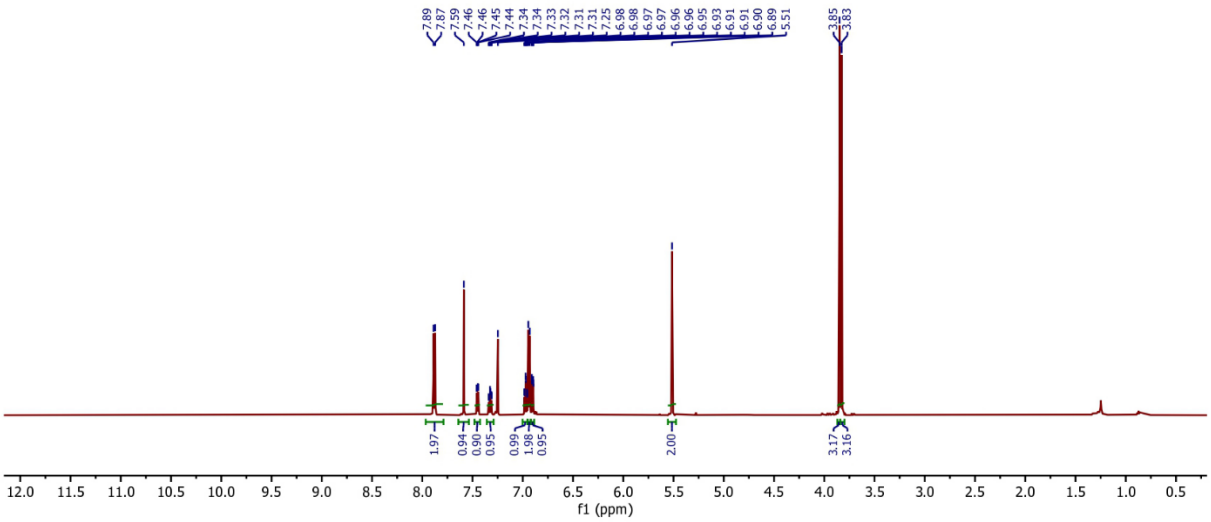
^{1}H NMR Spectrum of 4n (600 MHz, $CDCl_3$)



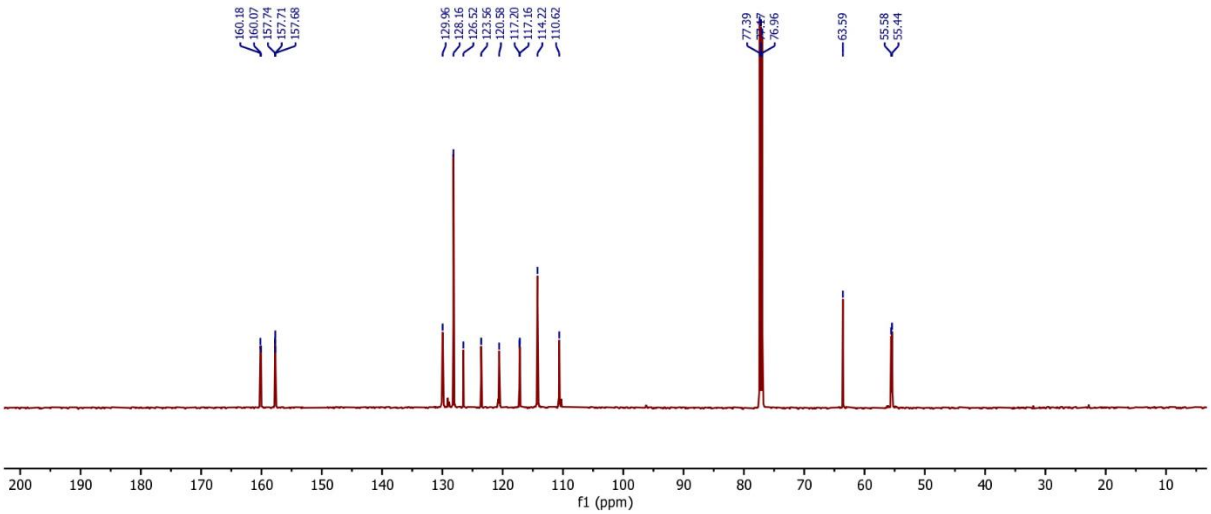
^{13}C NMR Spectrum of 4n (151 MHz, $CDCl_3$)



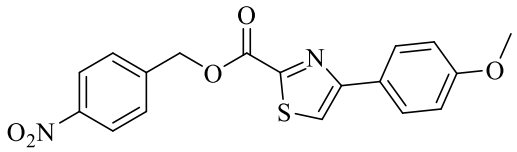
2-methoxybenzyl 4-(4-methoxyphenyl)thiazole-2-carboxylate (4o)



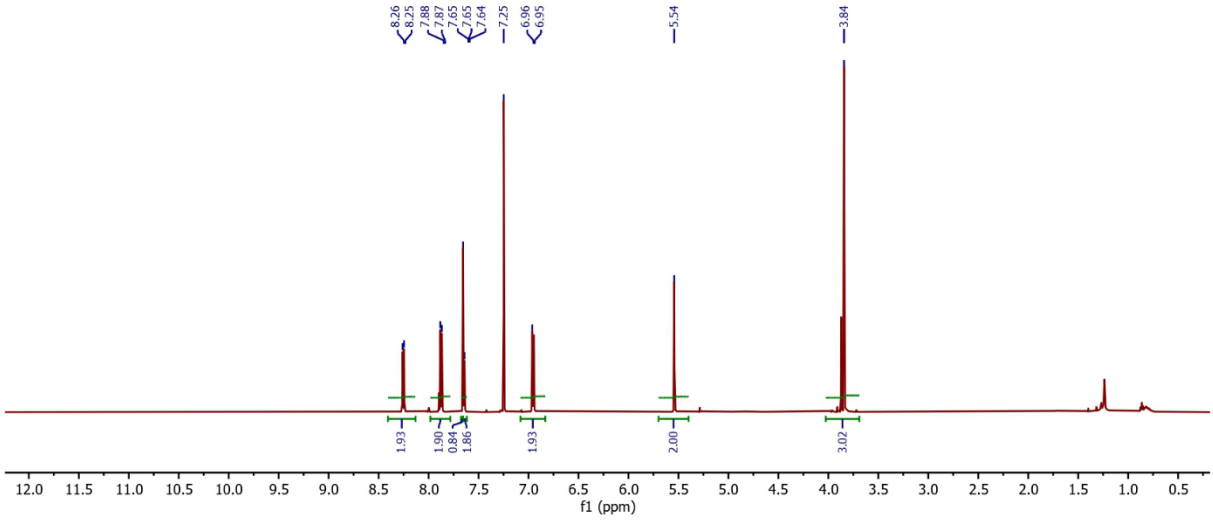
^{1}H NMR Spectrum of 4o (600 MHz, $CDCl_3$)



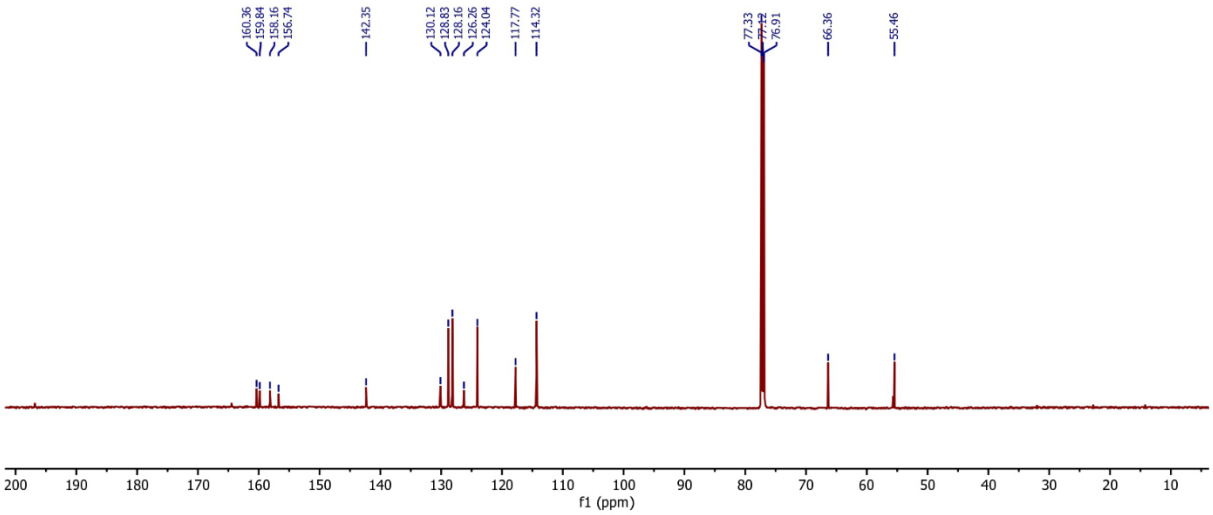
^{13}C NMR Spectrum of 4o (151 MHz, $CDCl_3$)



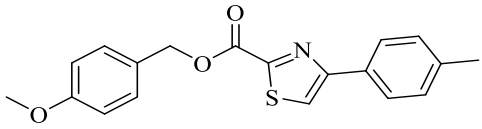
4-nitrobenzyl 4-(4-methoxyphenyl)thiazole-2-carboxylate (4p)



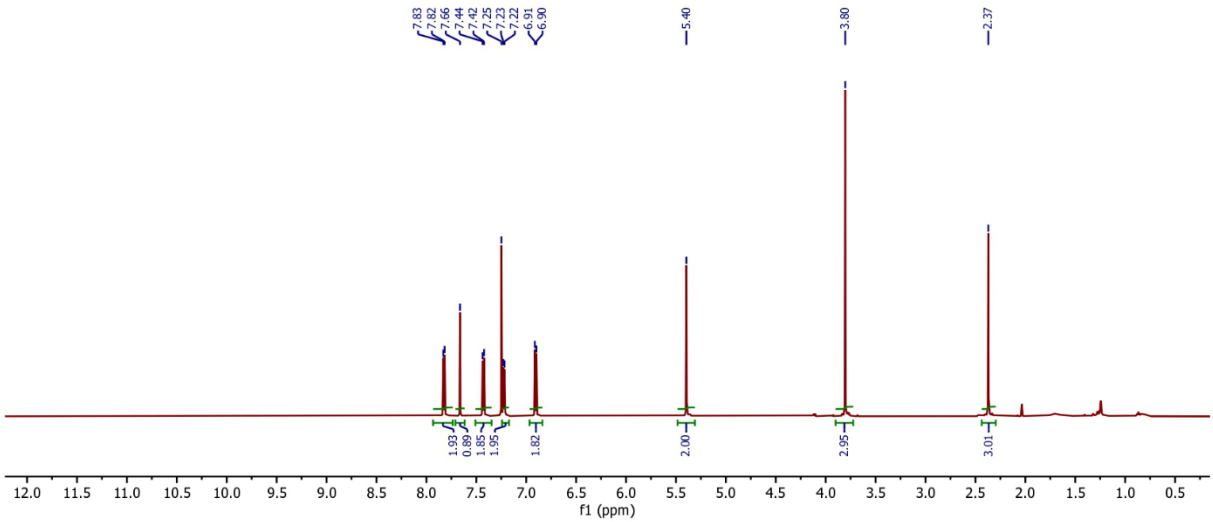
^{1}H NMR Spectrum of 4p (600 MHz, $CDCl_3$)



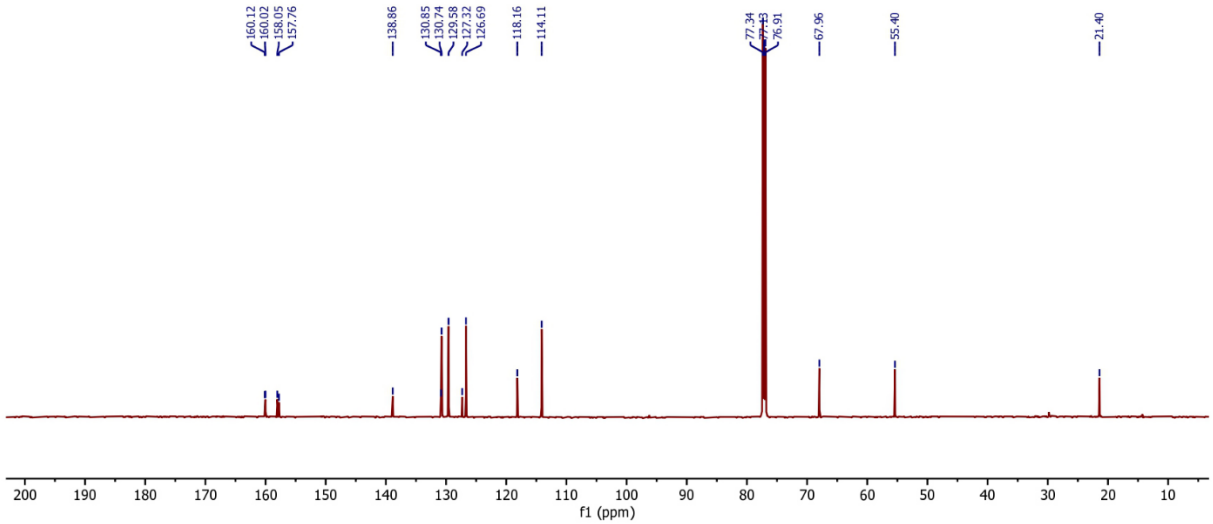
^{13}C NMR Spectrum of 4p (151 MHz, $CDCl_3$)



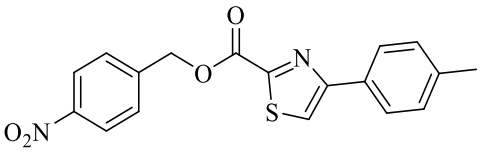
4-methoxybenzyl 4-(p-tolyl)thiazole-2-carboxylate (4q)



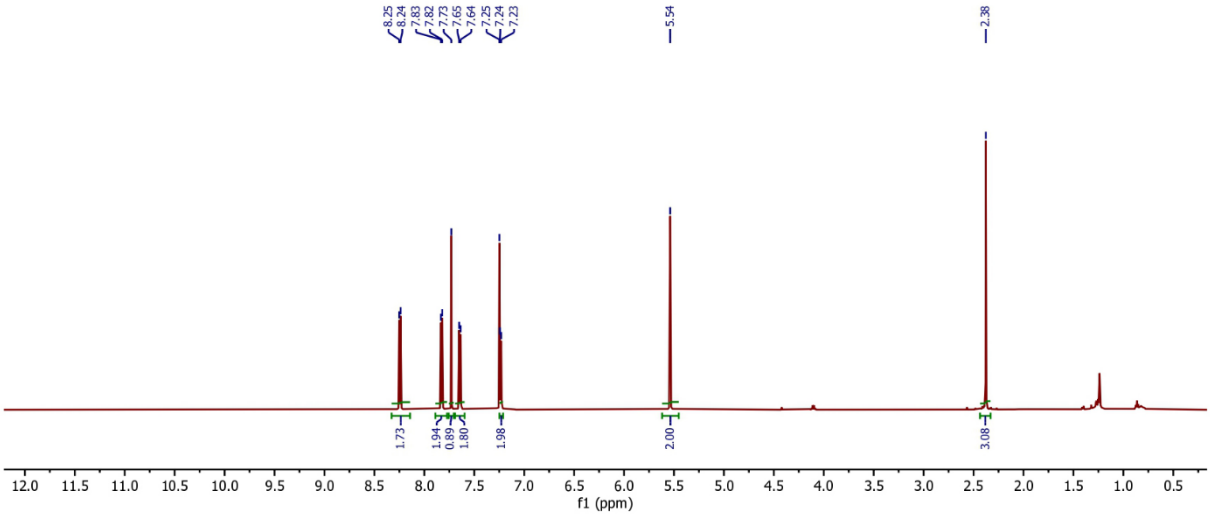
^{1}H NMR Spectrum of 4q (600 MHz, $CDCl_3$)



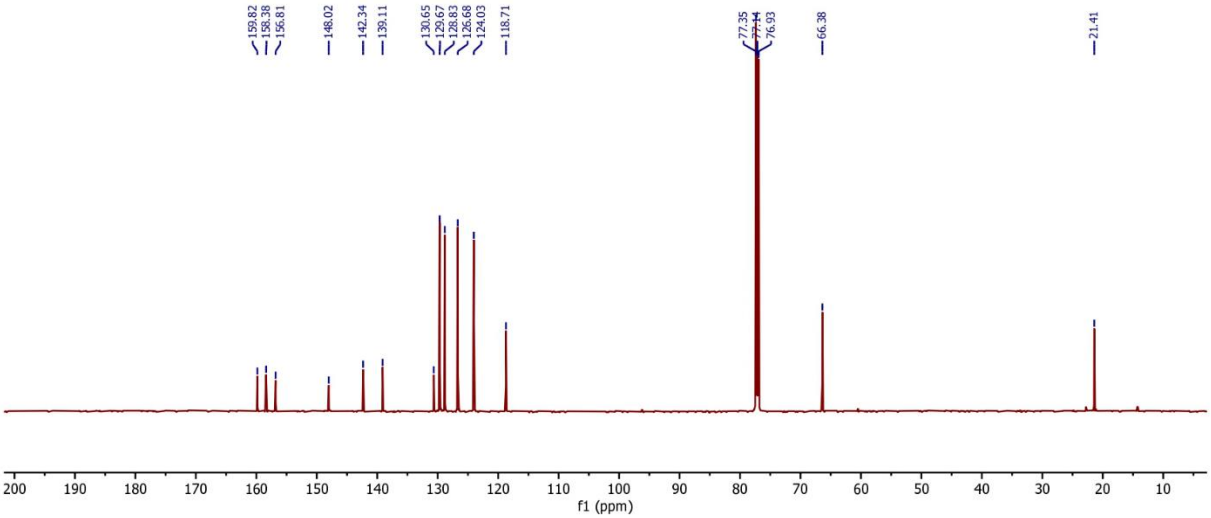
^{13}C NMR Spectrum of 4q (151 MHz, $CDCl_3$)



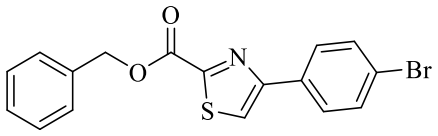
4-nitrobenzyl 4-(p-tolyl)thiazole-2-carboxylate (4r)



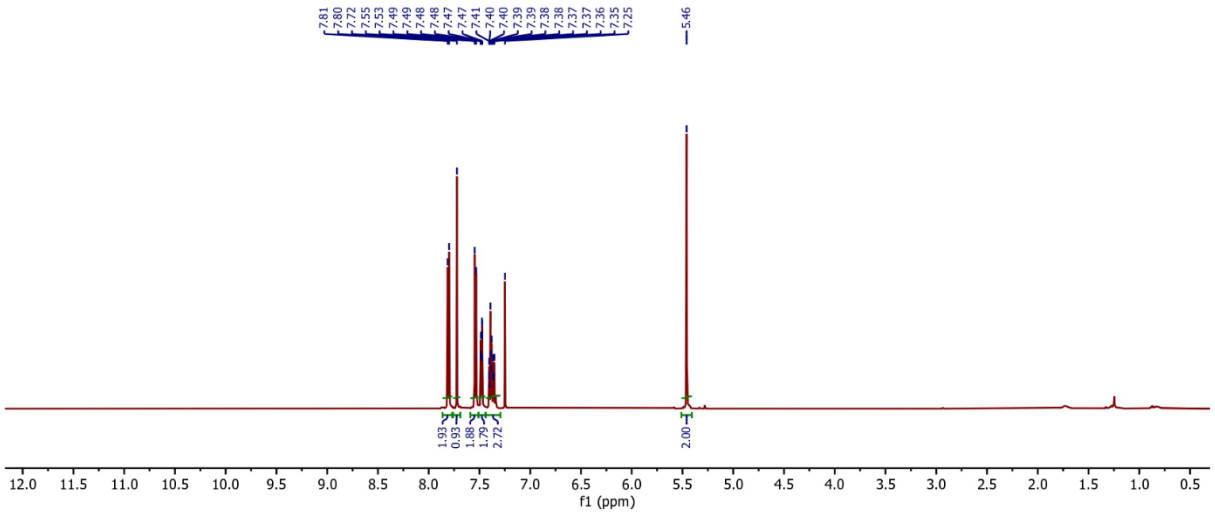
^{1}H NMR Spectrum of 4r (600 MHz, $CDCl_3$)



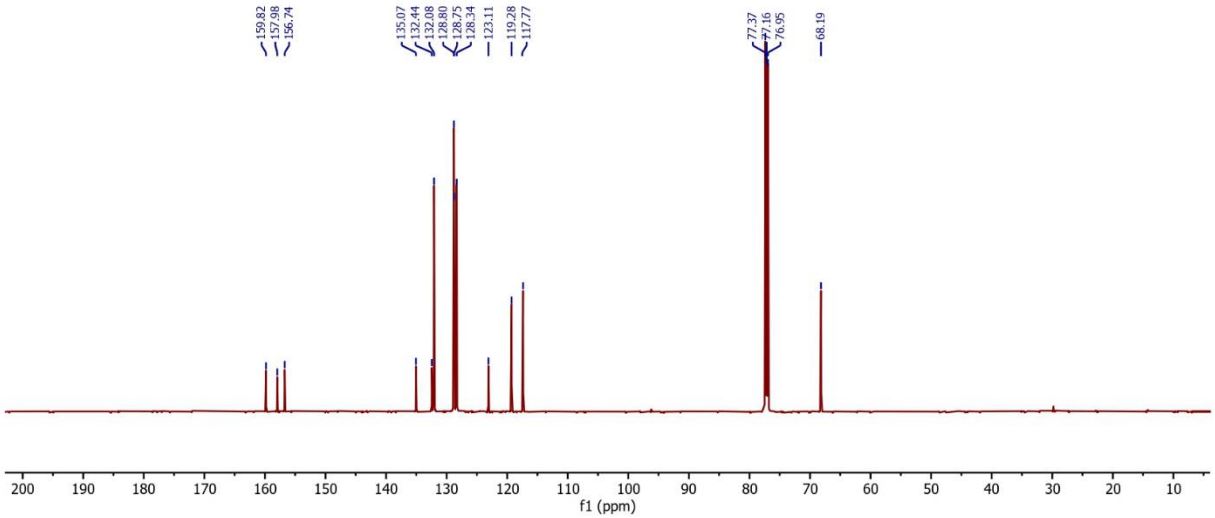
^{13}C NMR Spectrum of 4r (151 MHz, $CDCl_3$)



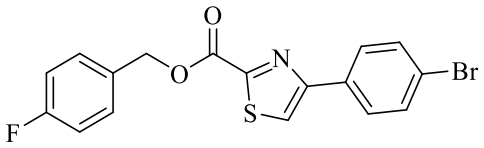
Benzyl 4-(4-bromophenyl)thiazole-2-carboxylate (4s)



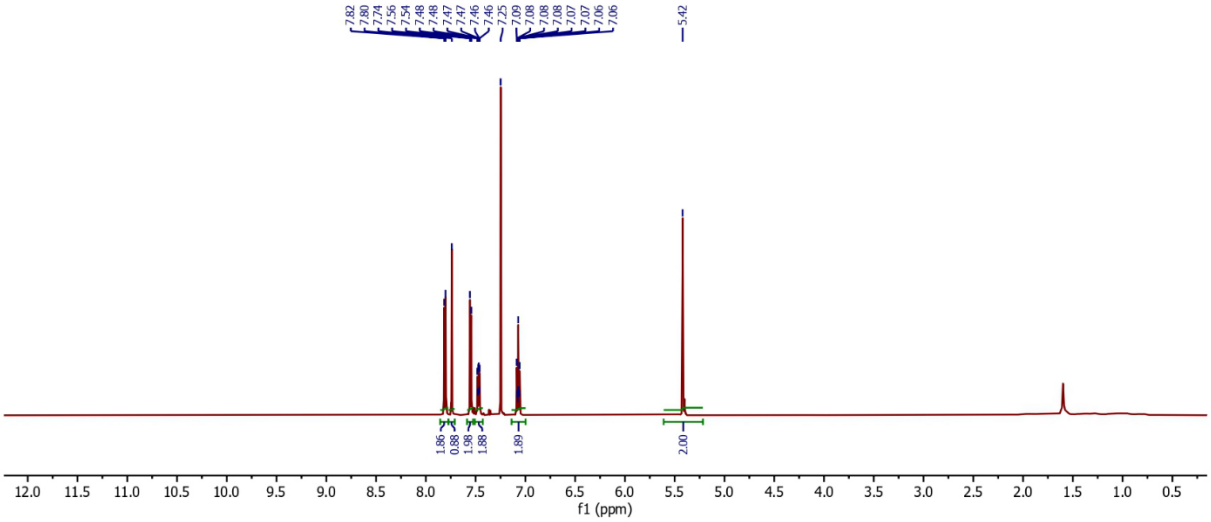
^{1}H NMR Spectrum of 4s (600 MHz, $CDCl_3$)



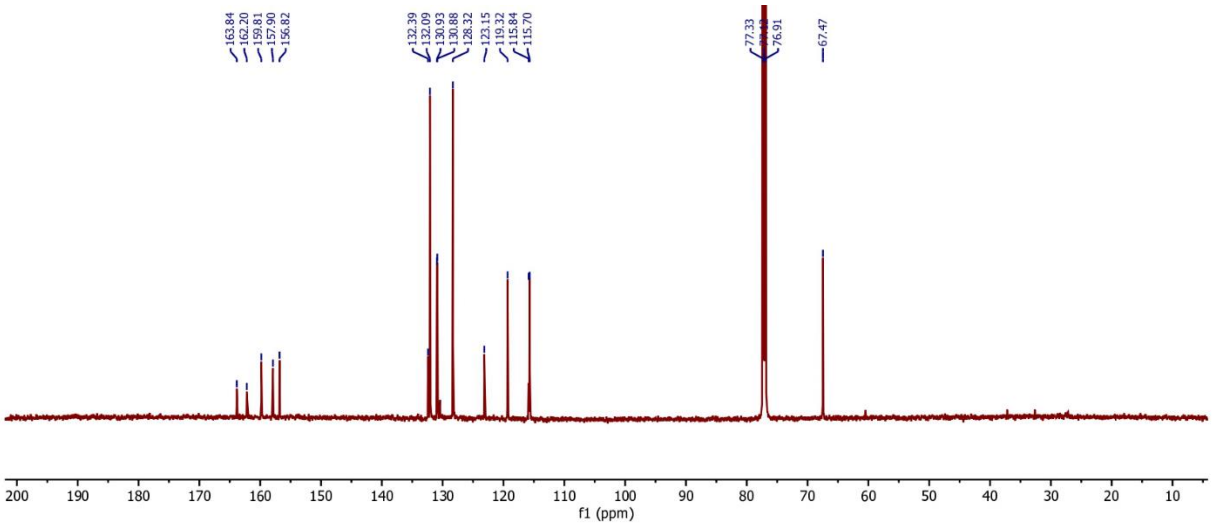
^{13}C NMR Spectrum of 4s (151 MHz, $CDCl_3$)



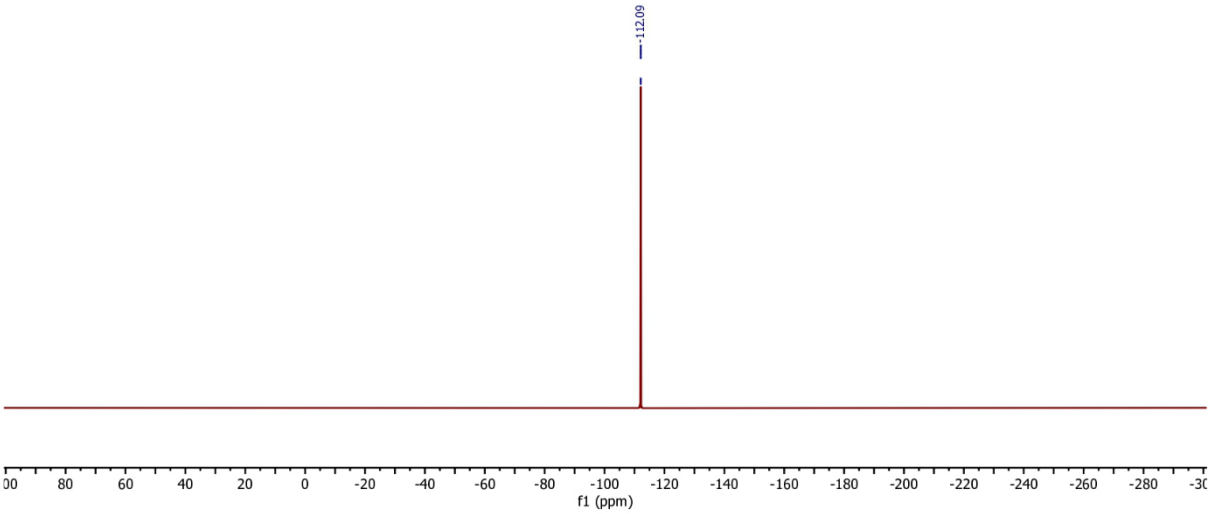
4-fluorobenzyl 4-(4-bromophenyl)thiazole-2-carboxylate (4t)



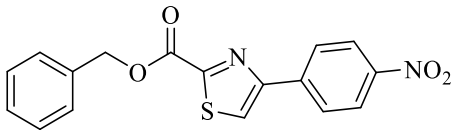
^{1}H NMR Spectrum of 4t (600 MHz, $CDCl_3$)



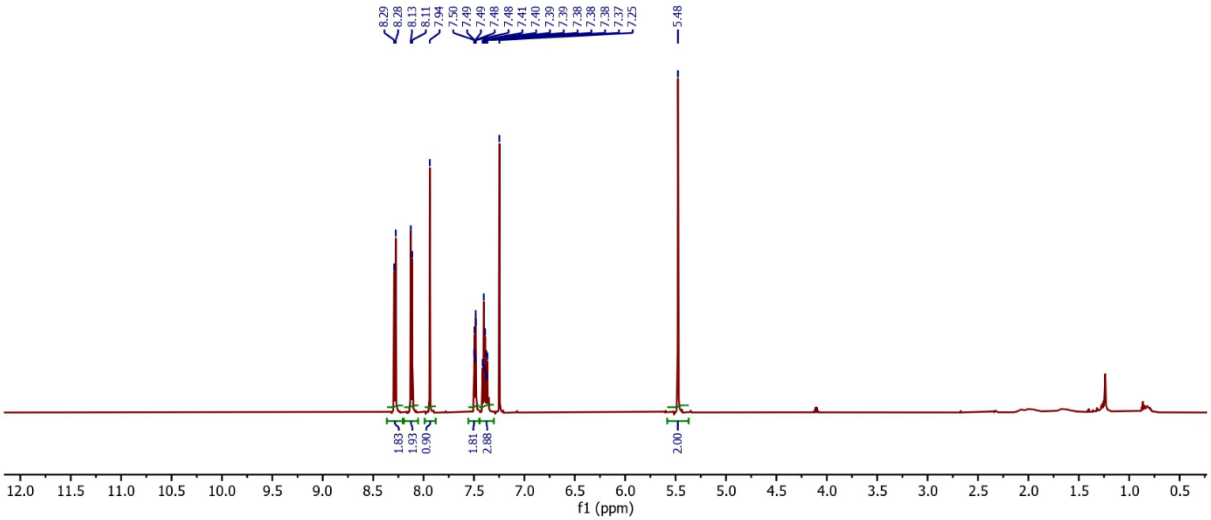
^{13}C NMR Spectrum of 4t (151 MHz, $CDCl_3$)



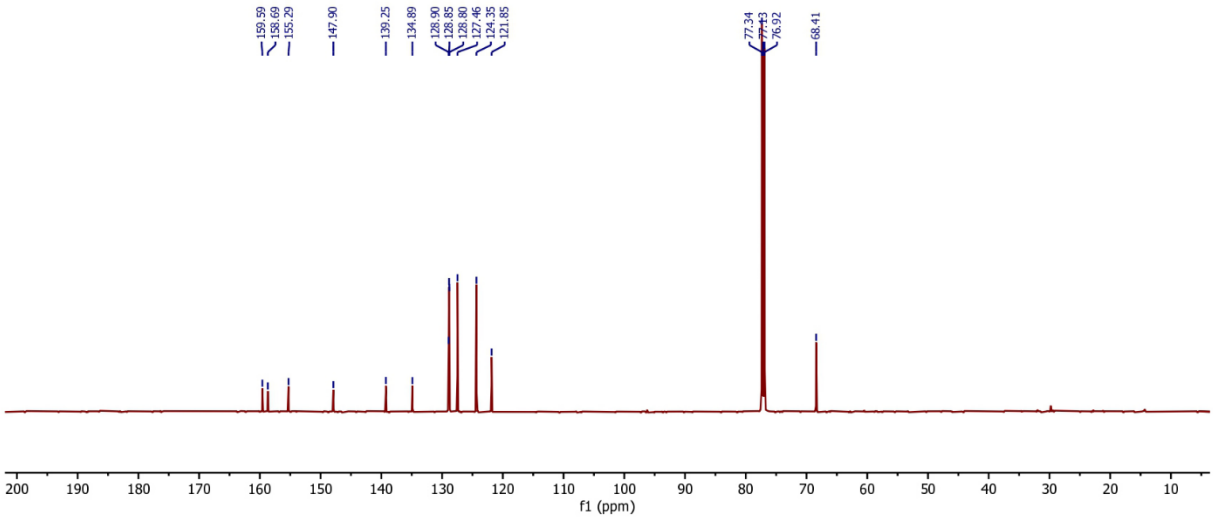
^{19}F NMR Spectrum of 4-fluorobenzyl 4-(4-bromophenyl)thiazole-2-carboxylate (4t)



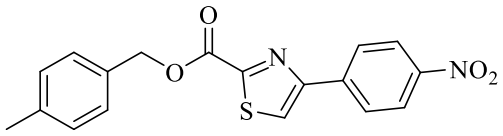
Benzyl 4-(4-nitrophenyl)thiazole-2-carboxylate (4u)



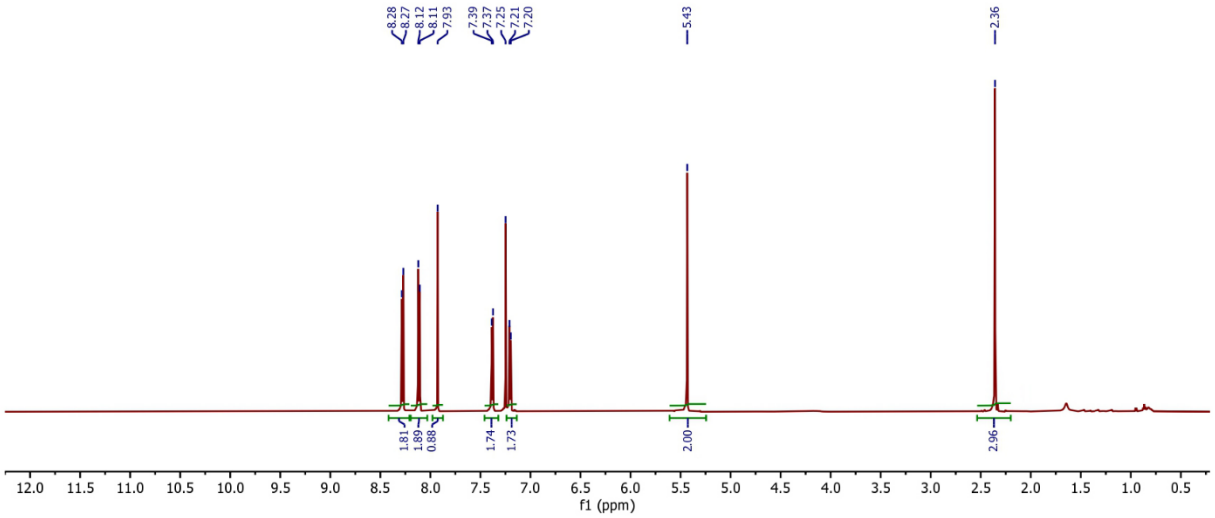
^{1}H NMR Spectrum of 4u (600 MHz, $CDCl_3$)



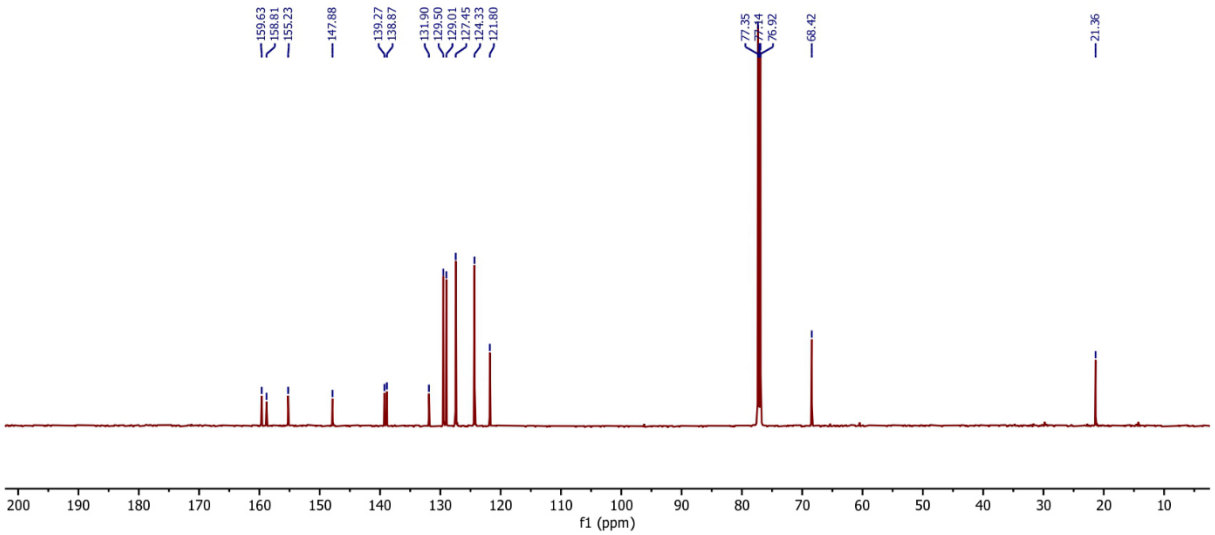
^{13}C NMR Spectrum of 4u (151 MHz, $CDCl_3$)



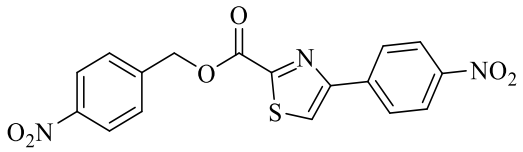
4-methylbenzyl 4-(4-nitrophenyl)thiazole-2-carboxylate (4v)



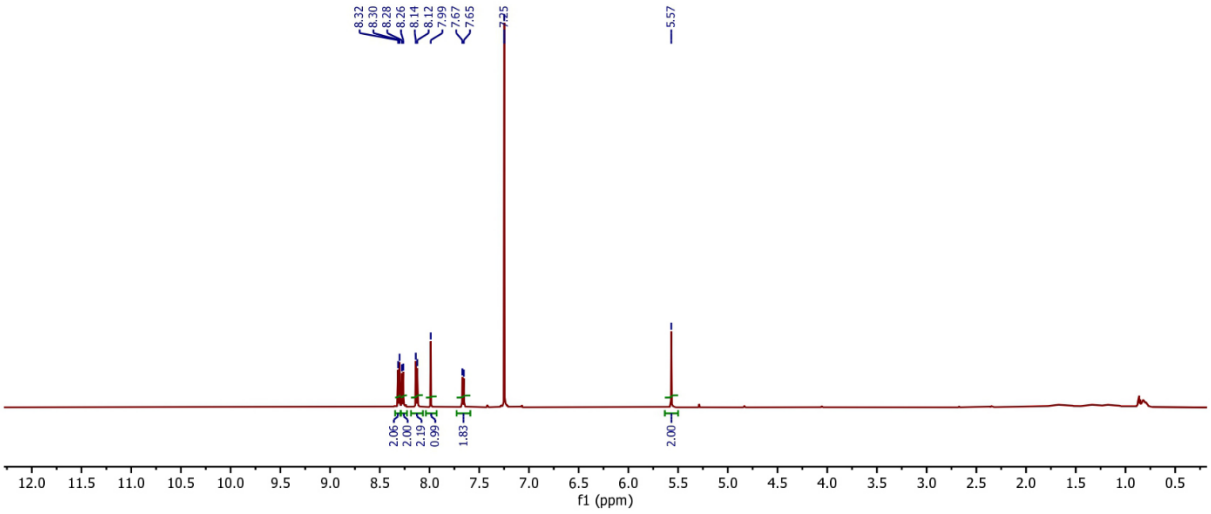
^{1}H NMR Spectrum of 4v (600 MHz, $CDCl_3$)



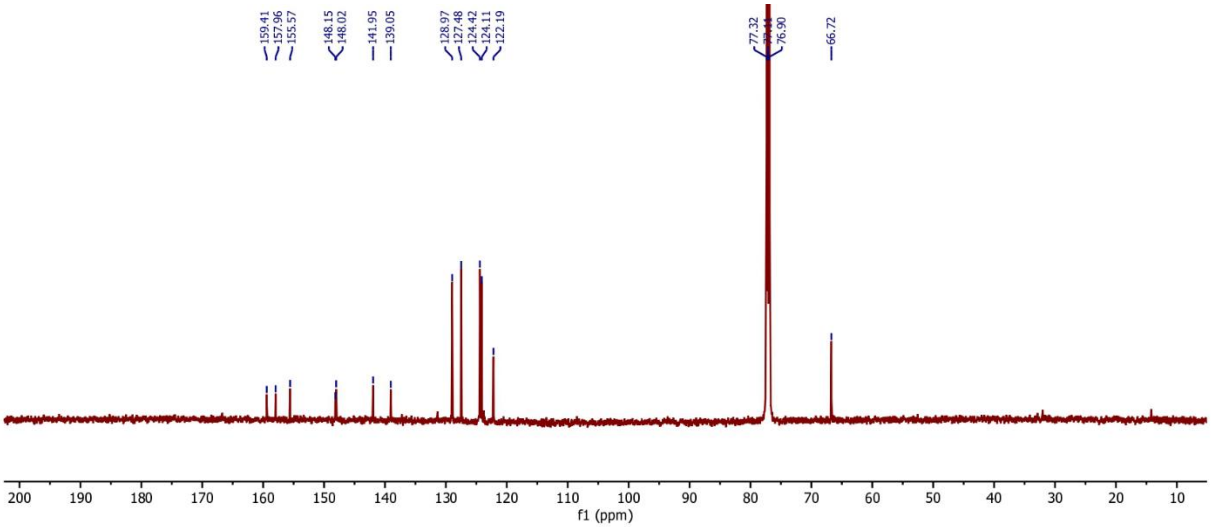
^{13}C NMR Spectrum of 4v (151 MHz, $CDCl_3$)



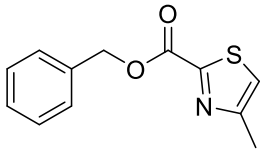
4-nitrobenzyl 4-(4-nitrophenyl)thiazole-2-carboxylate (4w)



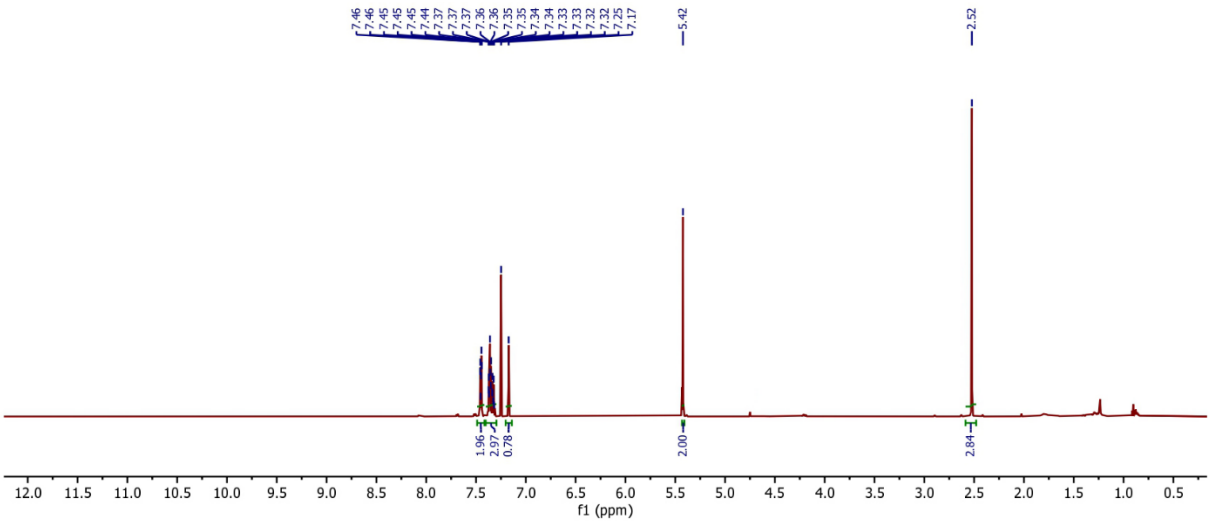
^{1}H NMR Spectrum of 4w (600 MHz, $CDCl_3$)



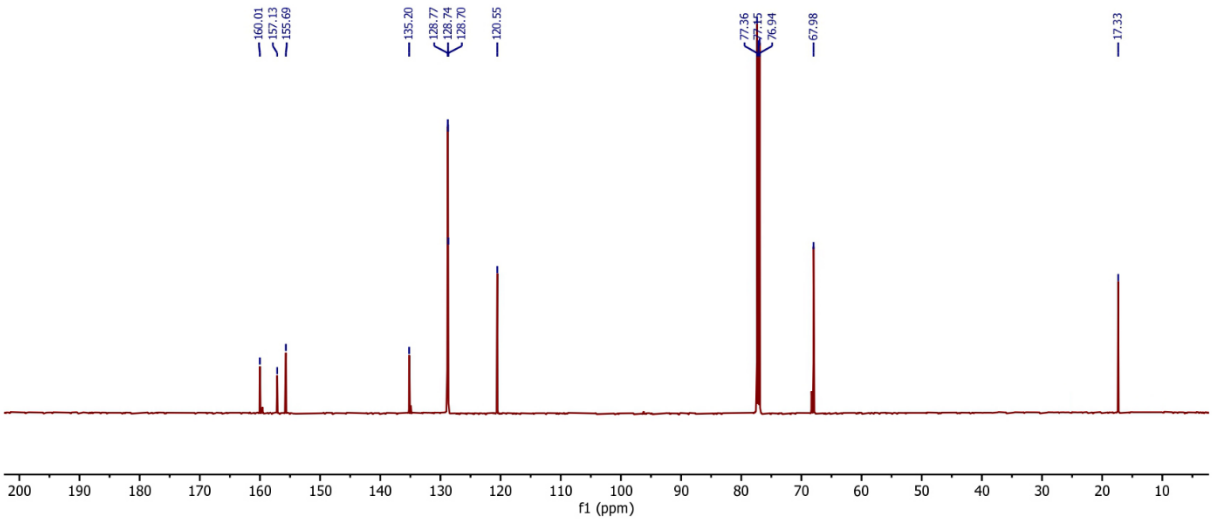
^{13}C NMR Spectrum of 4w (151 MHz, $CDCl_3$)



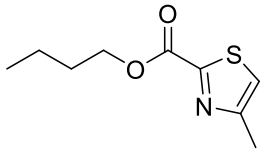
Benzyl 4-methylthiazole-2-carboxylate (4x)



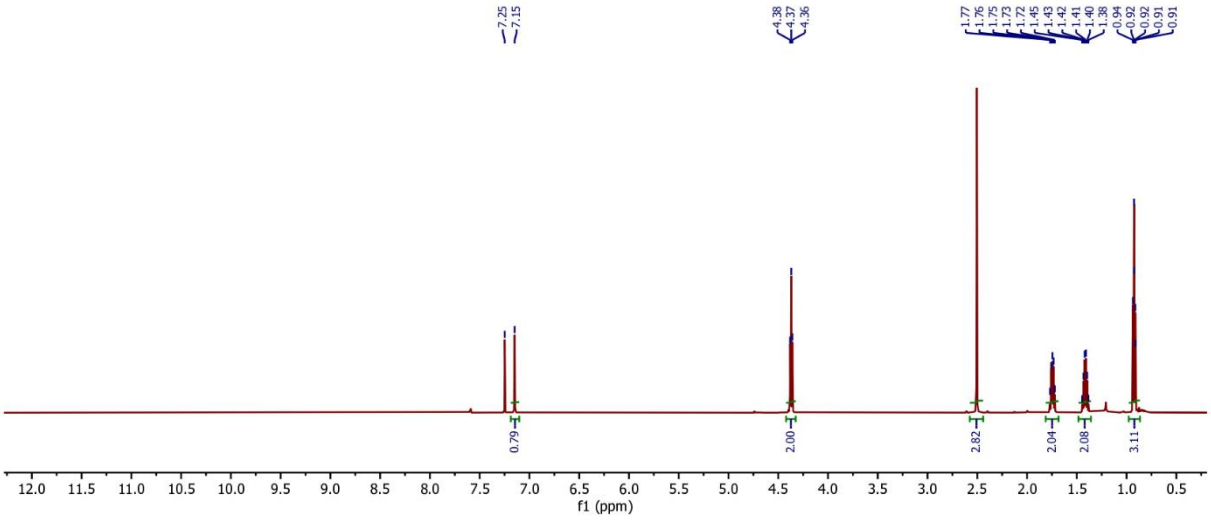
^{1}H NMR Spectrum of 4x (600 MHz, $CDCl_3$)



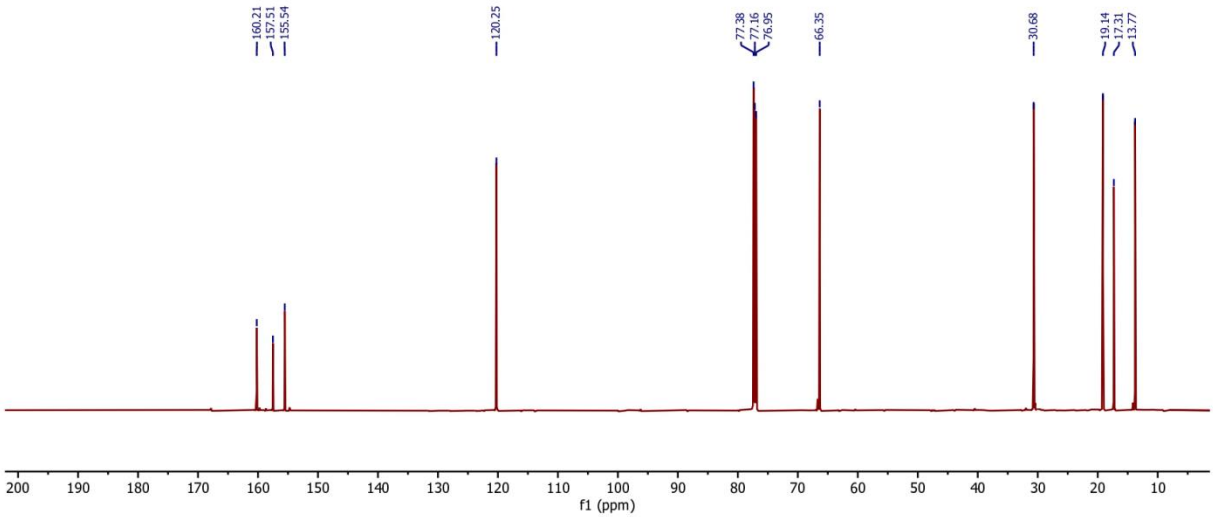
^{13}C NMR Spectrum of 4x (151 MHz, $CDCl_3$)



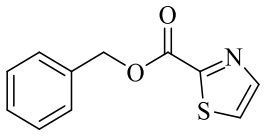
Butyl 4-methylthiazole-2-carboxylate (4y)



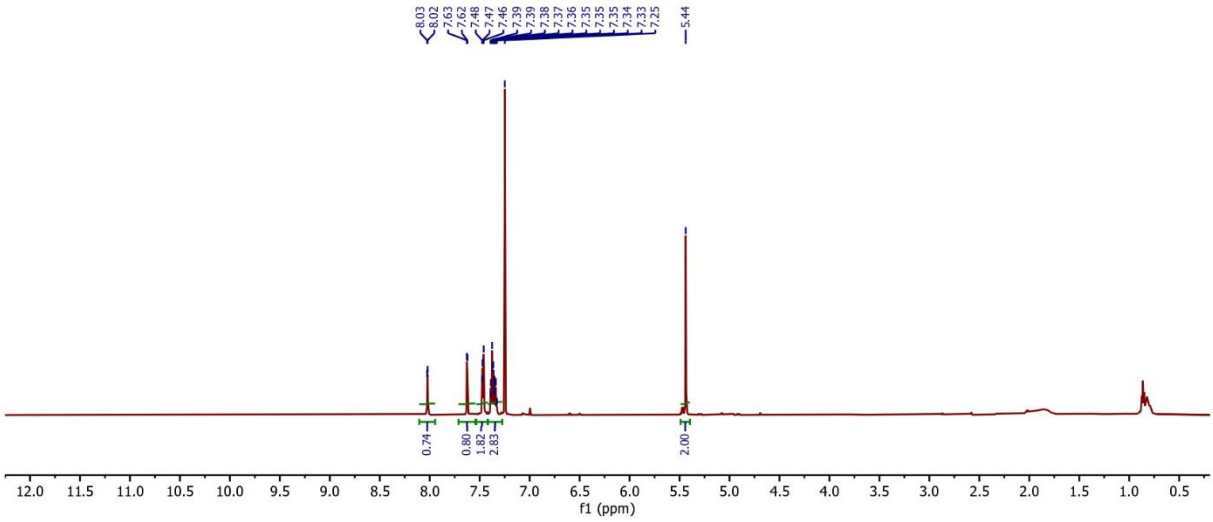
^{1}H NMR Spectrum of 4y (600 MHz, $CDCl_3$)



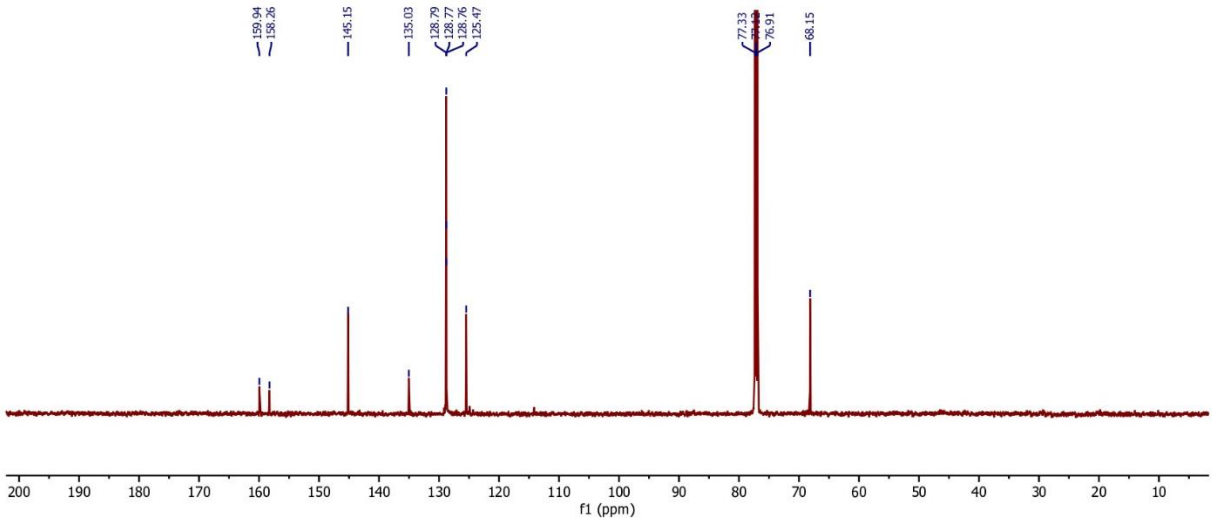
^{13}C NMR Spectrum of 4y (151 MHz, $CDCl_3$)



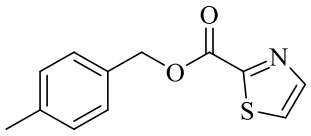
Benzyl thiazole-2-carboxylate (6a)



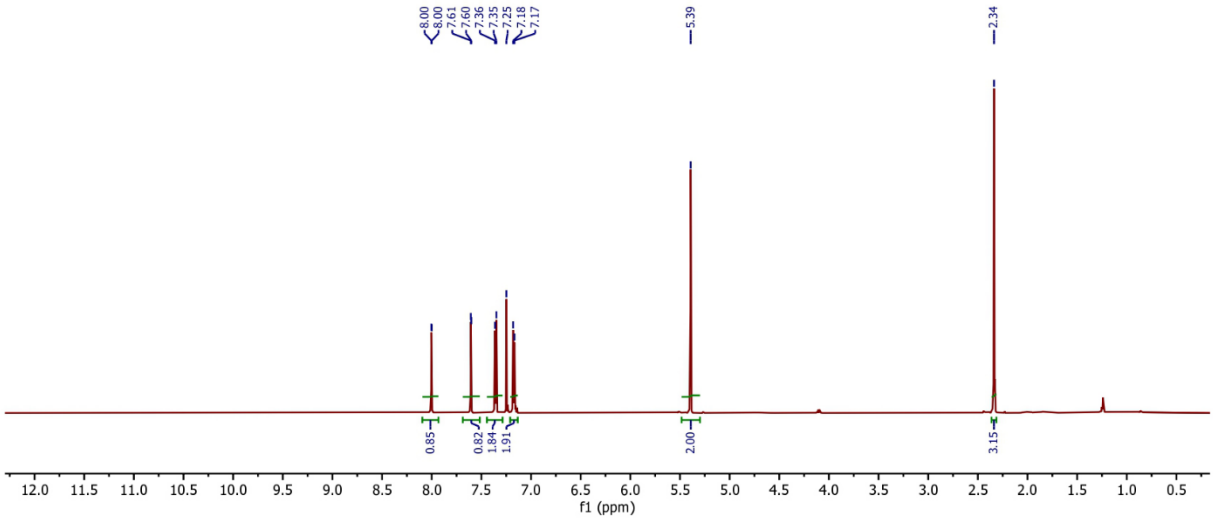
^{1}H NMR Spectrum of 6a (600 MHz, $CDCl_3$)



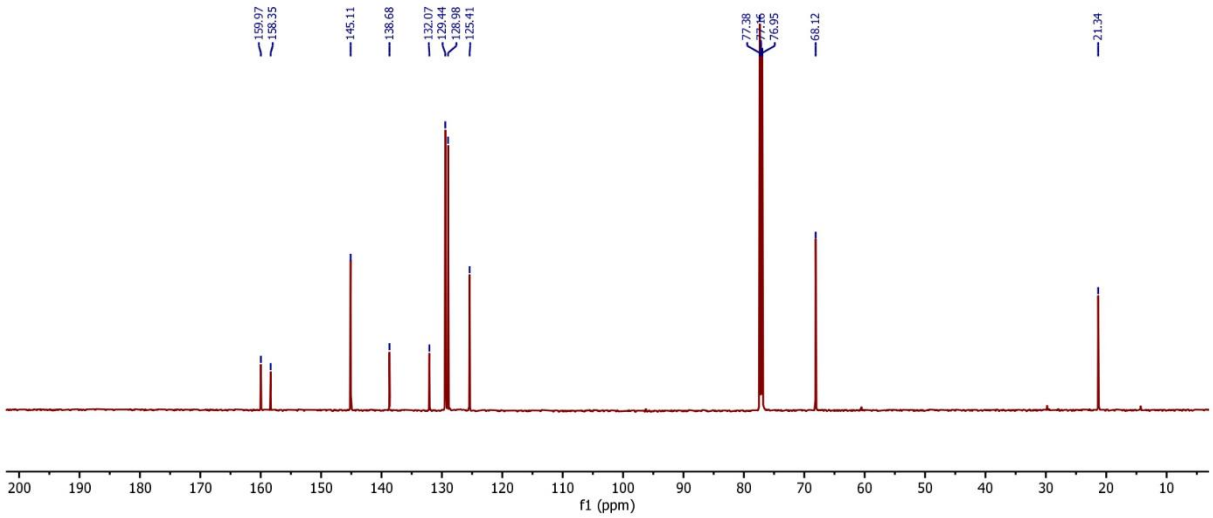
^{13}C NMR Spectrum of 6a (151 MHz, $CDCl_3$)



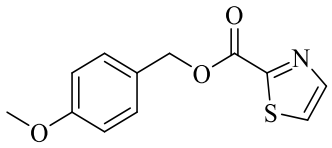
4-methylbenzyl thiazole-2-carboxylate (6b)



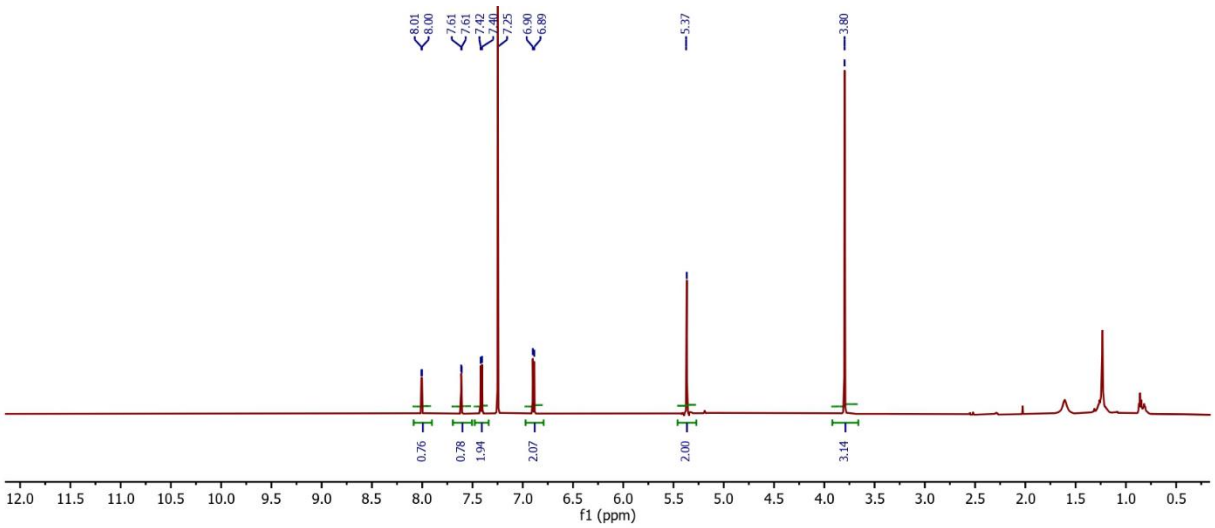
^{1}H NMR Spectrum of 6b (600 MHz, $CDCl_3$)



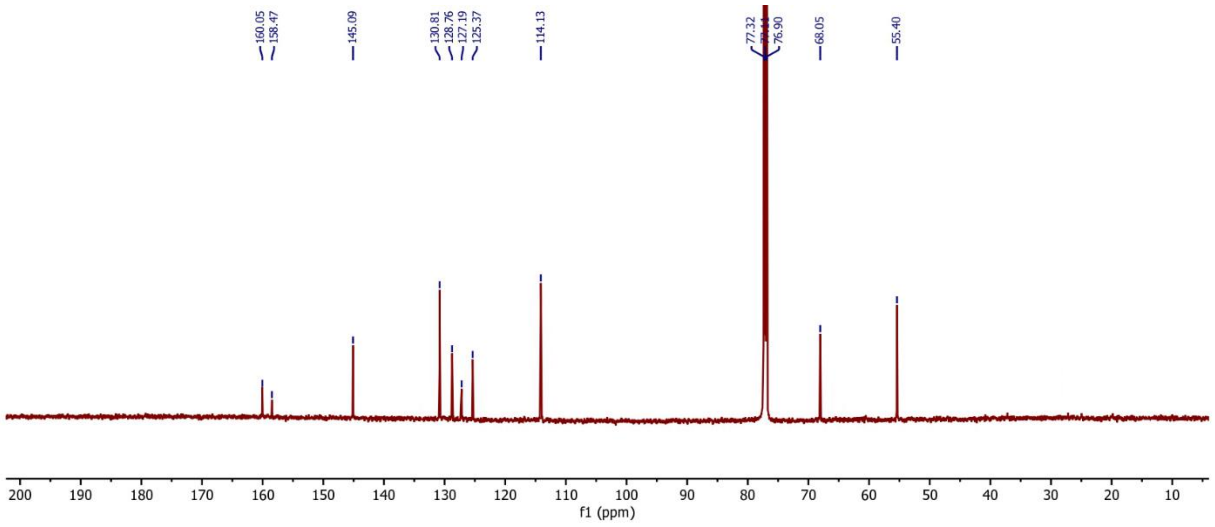
^{13}C NMR Spectrum of 6b (151 MHz, $CDCl_3$)



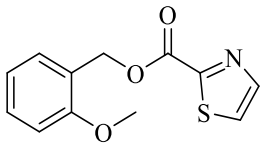
4-methoxybenzyl thiazole-2-carboxylate (6c)



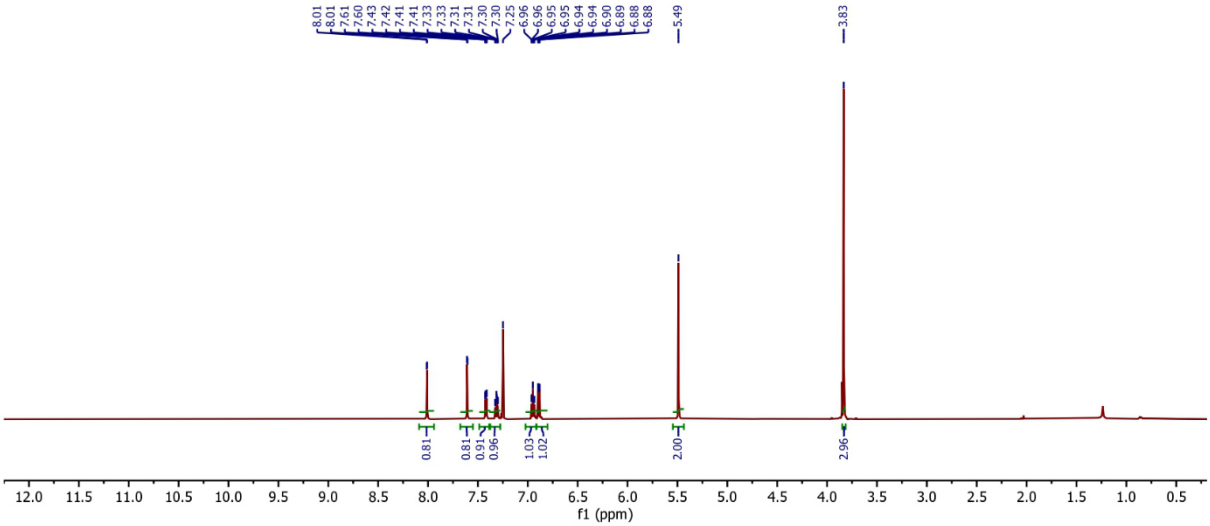
^{1}H NMR Spectrum of 6c (600 MHz, $CDCl_3$)



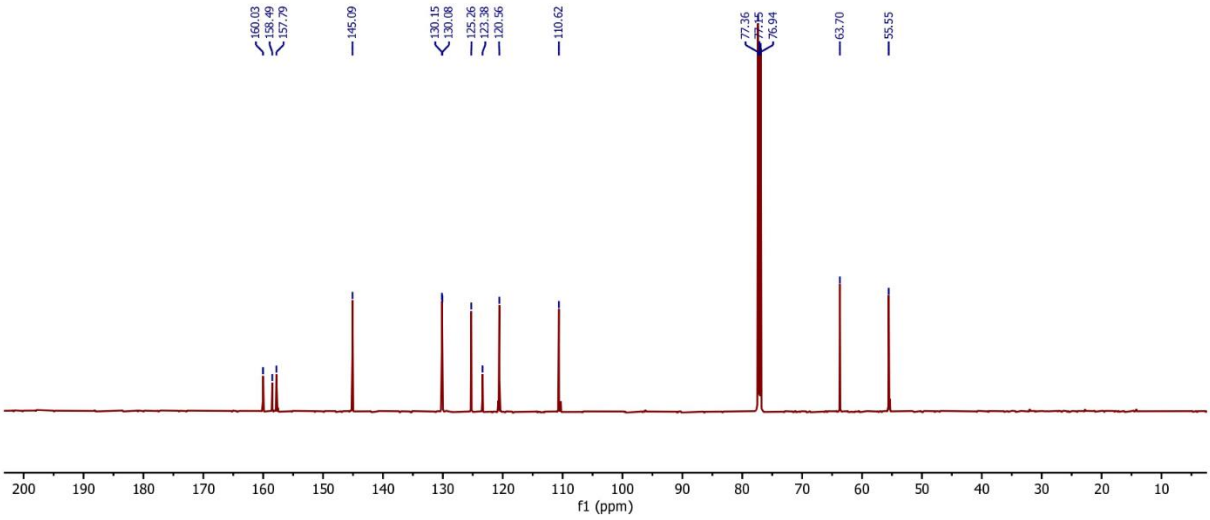
^{13}C NMR Spectrum of 6c (151 MHz, $CDCl_3$)



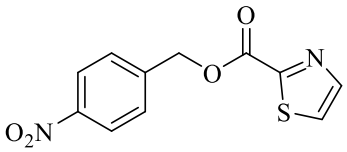
2-methoxybenzyl thiazole-2-carboxylate (6d)



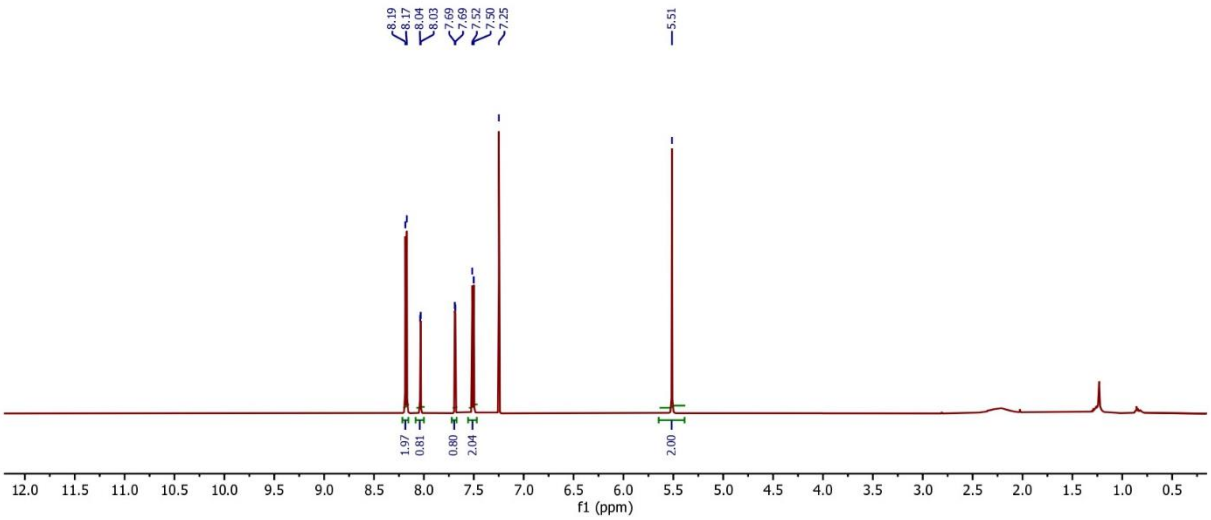
^{1}H NMR Spectrum of 6d (600 MHz, $CDCl_3$)



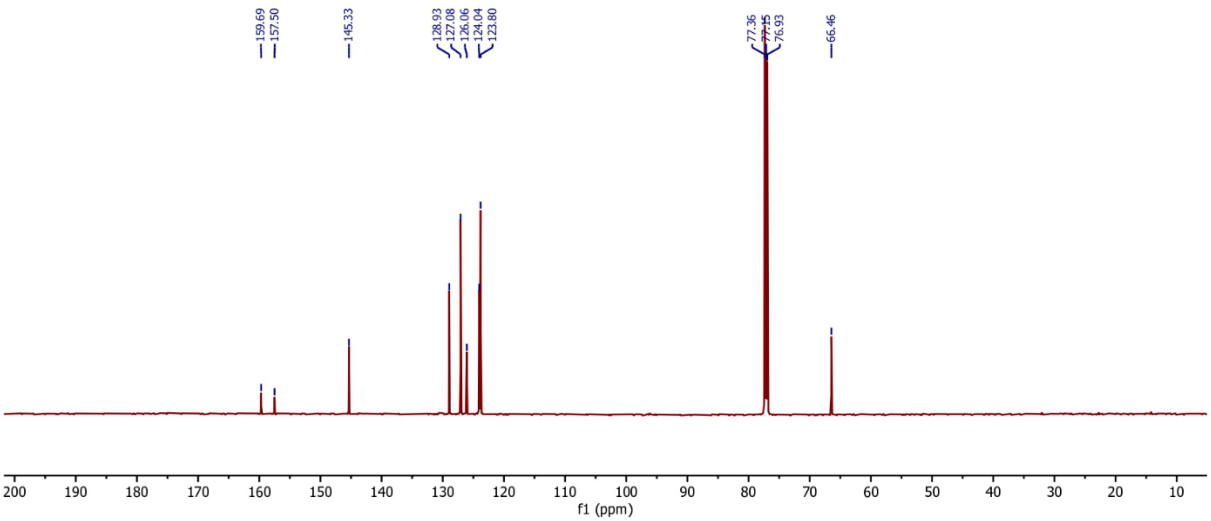
^{13}C NMR Spectrum of 6d (151 MHz, $CDCl_3$)



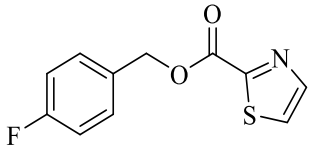
4-nitrobenzyl thiazole-2-carboxylate (6e)



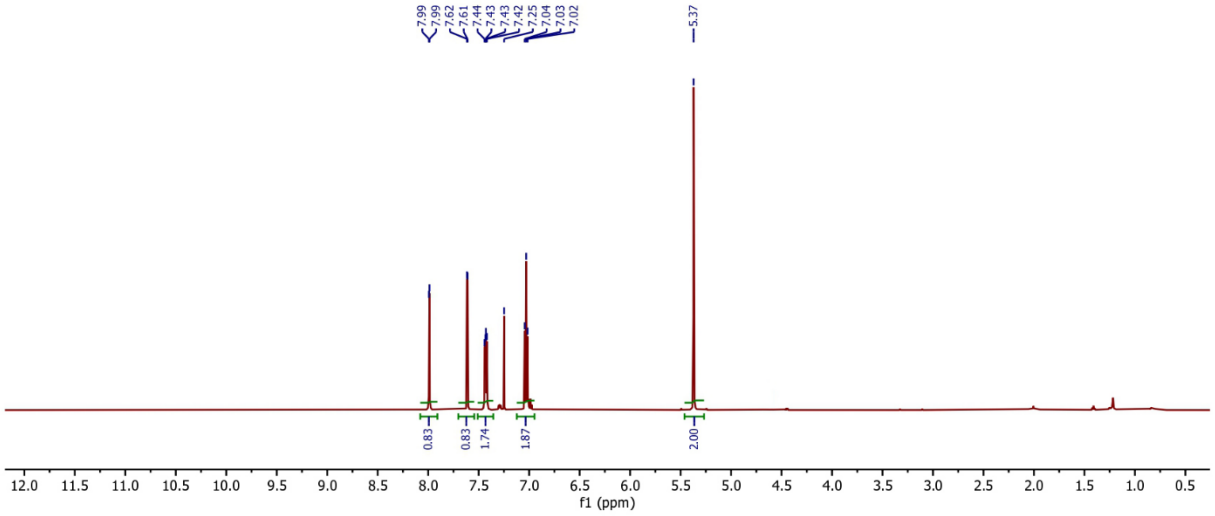
^{1}H NMR Spectrum of 6e (600 MHz, $CDCl_3$)



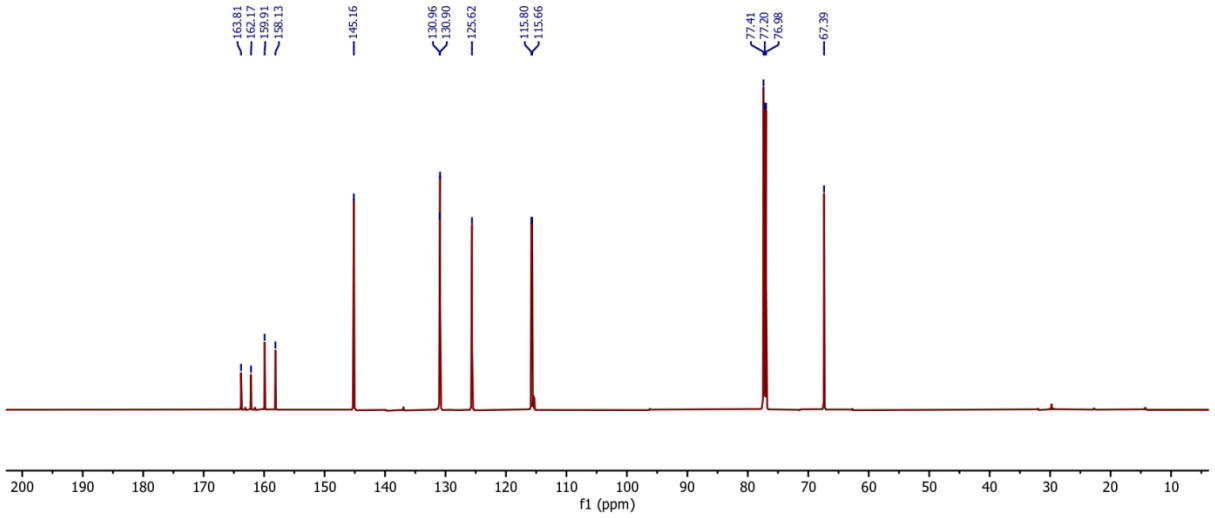
^{13}C NMR Spectrum of 6e (151 MHz, $CDCl_3$)



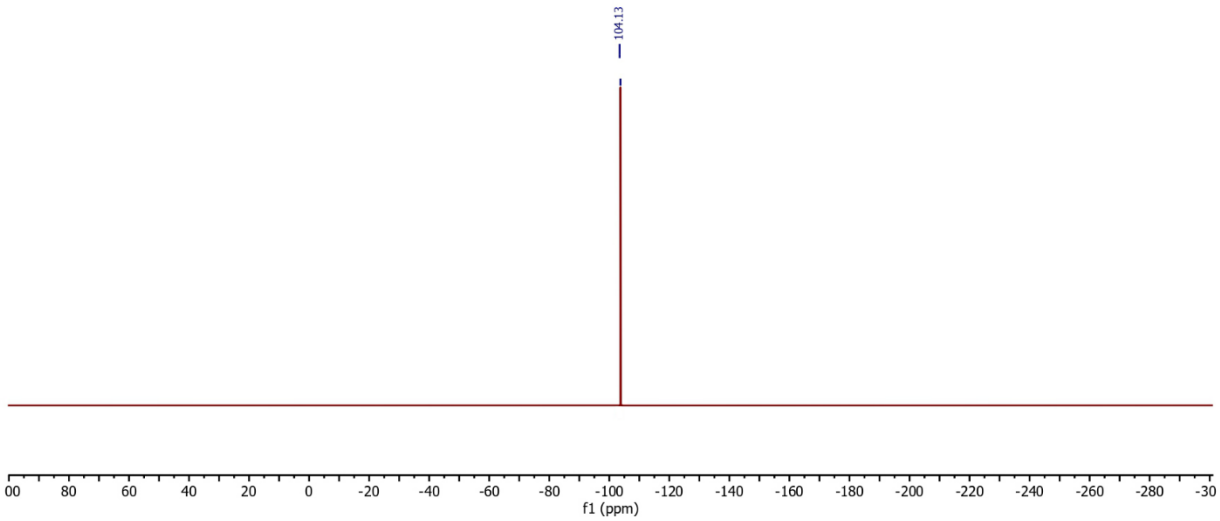
4-fluorobenzyl thiazole-2-carboxylate (6f)



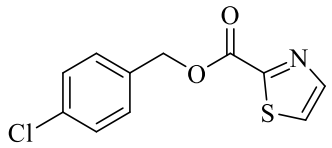
^{1}H NMR Spectrum of 6f (600 MHz, $CDCl_3$)



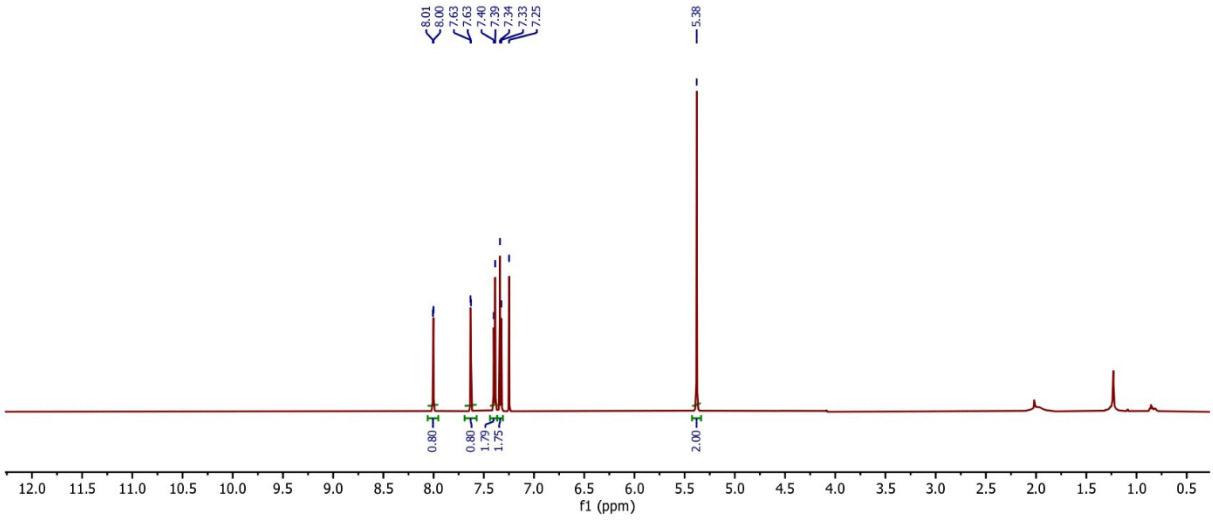
^{13}C NMR Spectrum of 6f (151 MHz, $CDCl_3$)



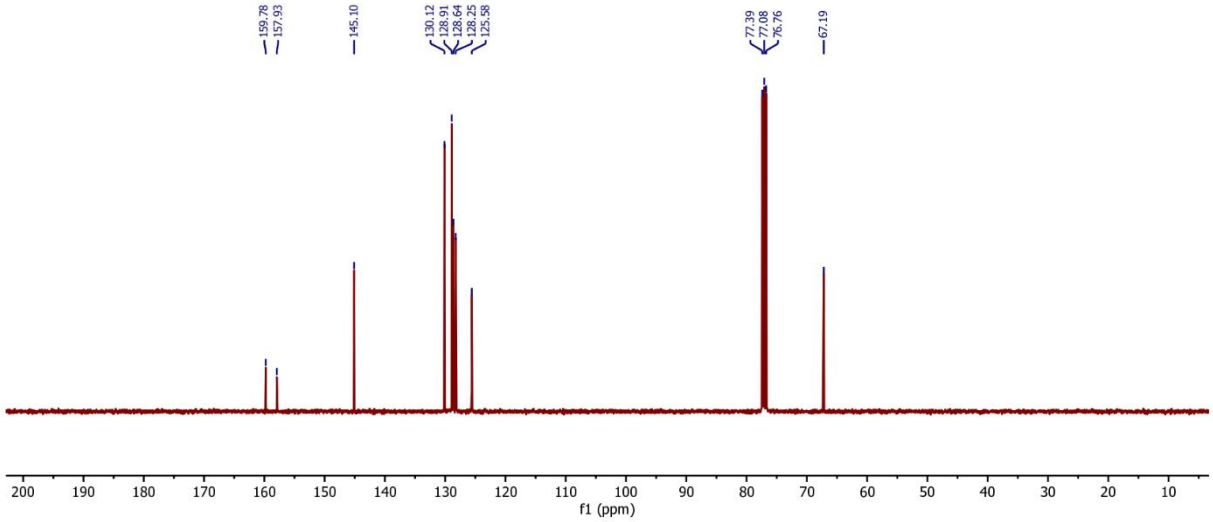
^{19}F NMR Spectrum of 4-fluorobenzyl thiazole-2-carboxylate (6f)



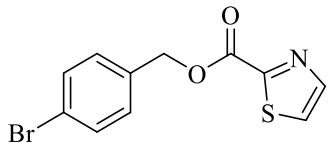
4-chlorobenzyl thiazole-2-carboxylate (6g)



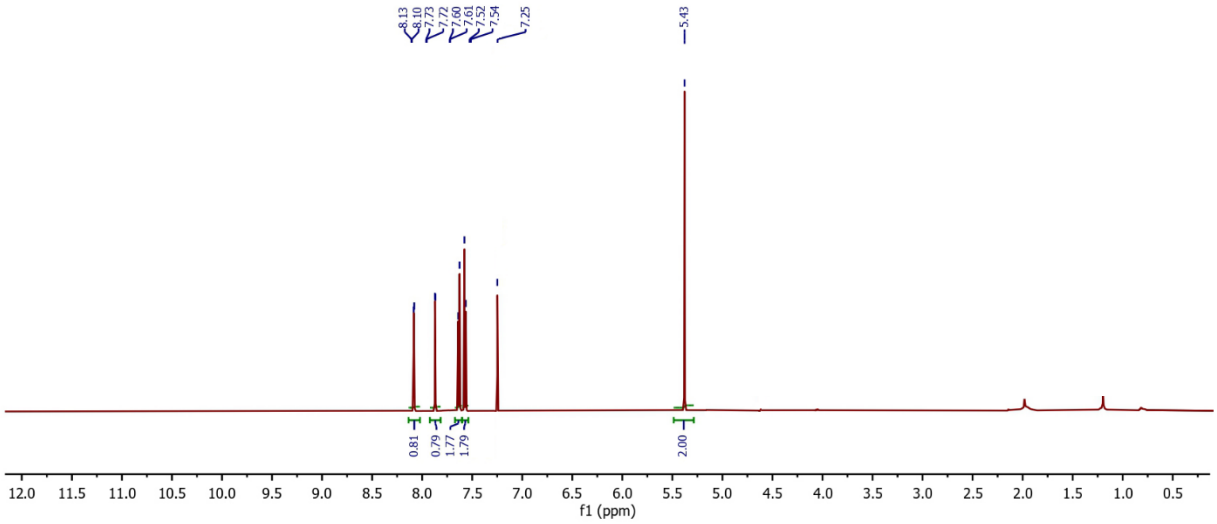
^{1}H NMR Spectrum of 6g (600 MHz, $CDCl_3$)



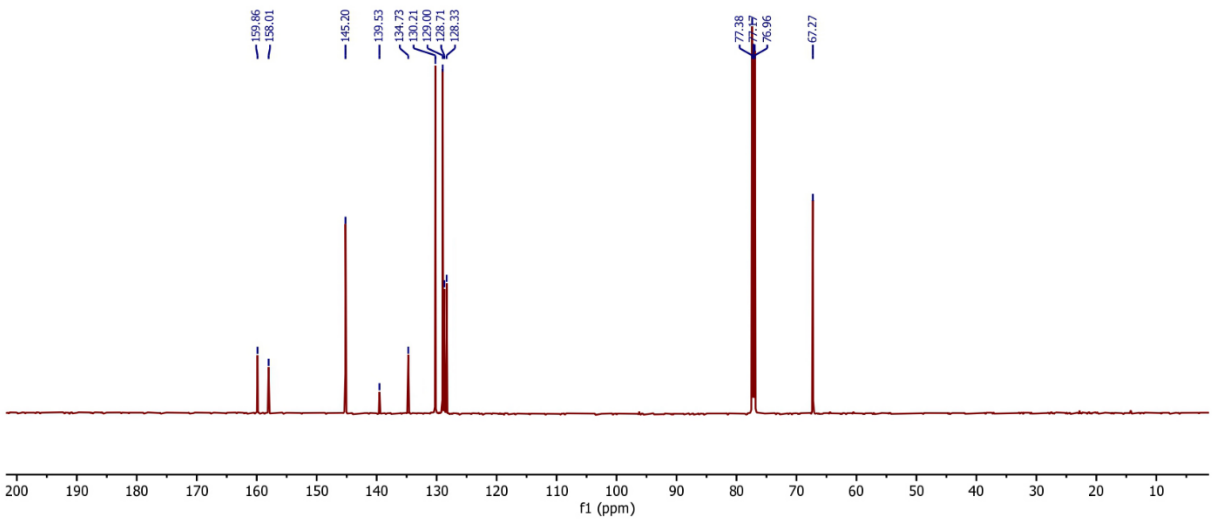
^{13}C NMR Spectrum of 6g (151 MHz, $CDCl_3$)



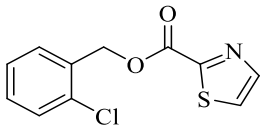
4-bromobenzyl thiazole-2-carboxylate (6h)



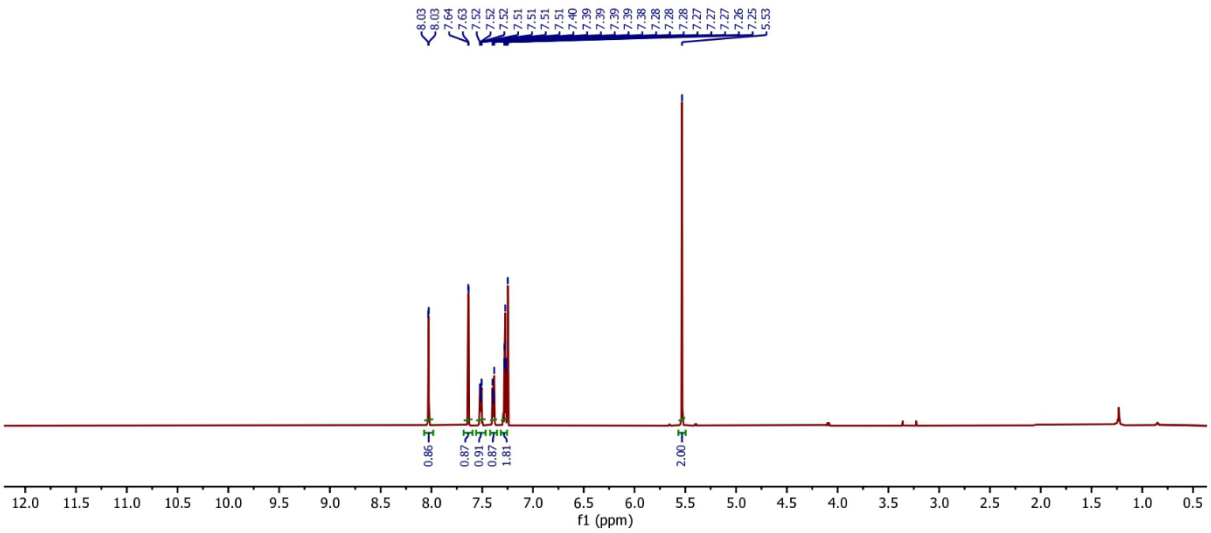
^{1}H NMR Spectrum of 6h (400 MHz, $CDCl_3$)



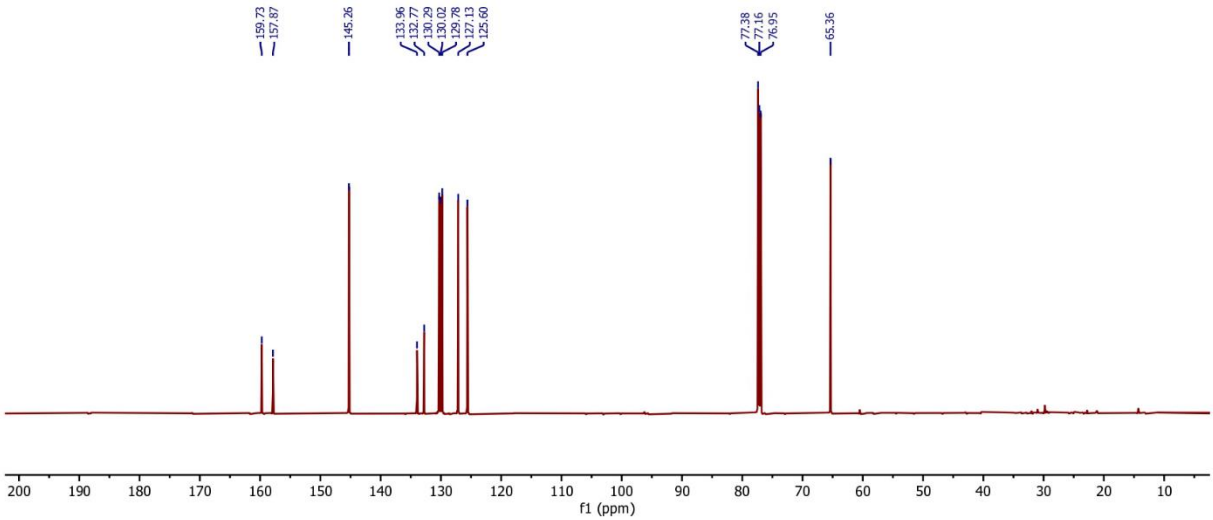
^{13}C NMR Spectrum of 6h (101 MHz, $CDCl_3$)



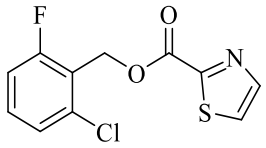
2-chlorobenzyl thiazole-2-carboxylate (6i)



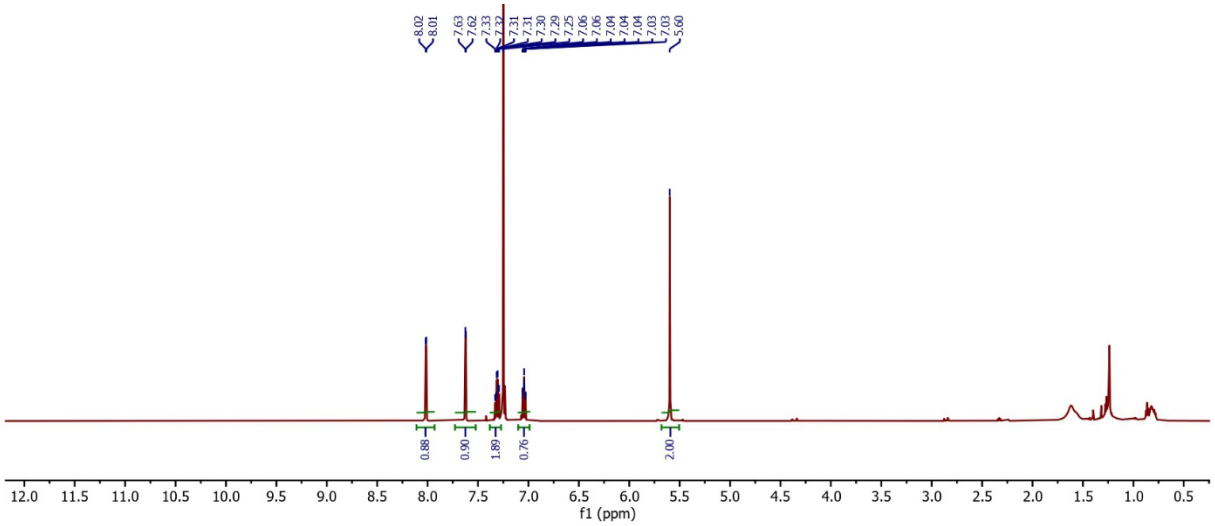
^{1}H NMR Spectrum of 6i (600 MHz, $CDCl_3$)



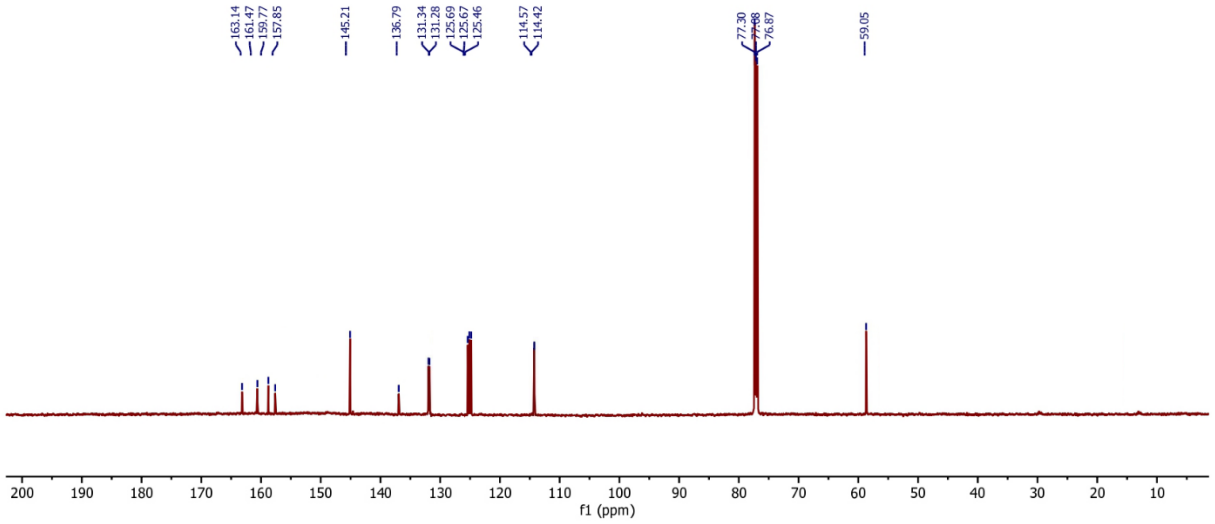
^{13}C NMR Spectrum of 6i (151 MHz, $CDCl_3$)



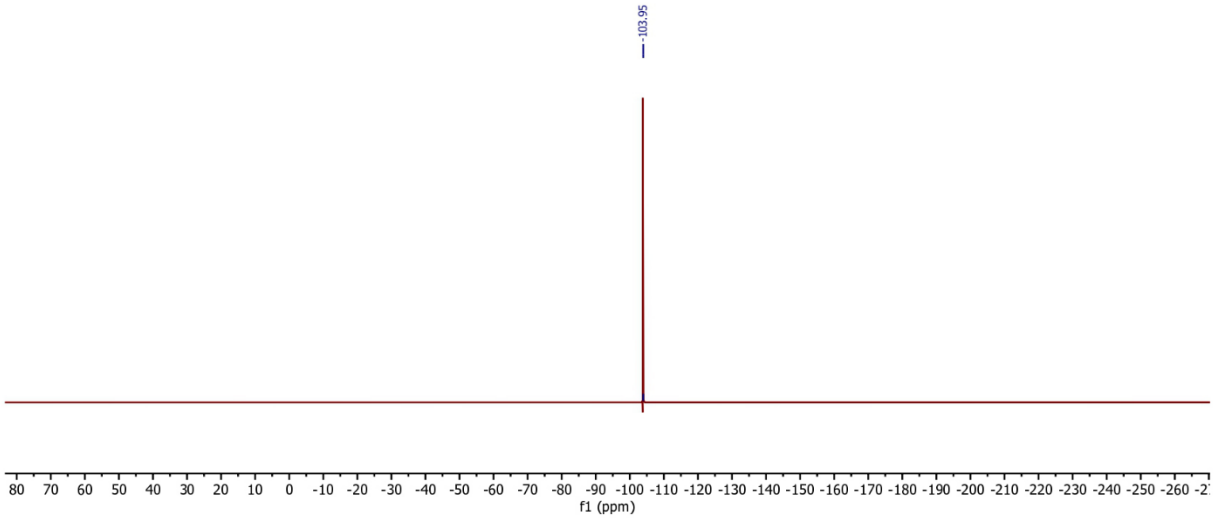
2-chloro-6-fluorobenzyl thiazole-2-carboxylate (6j)



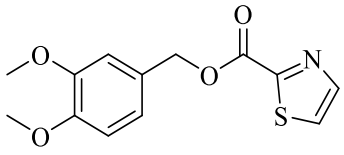
^{1}H NMR Spectrum of 6j (600 MHz, $CDCl_3$)



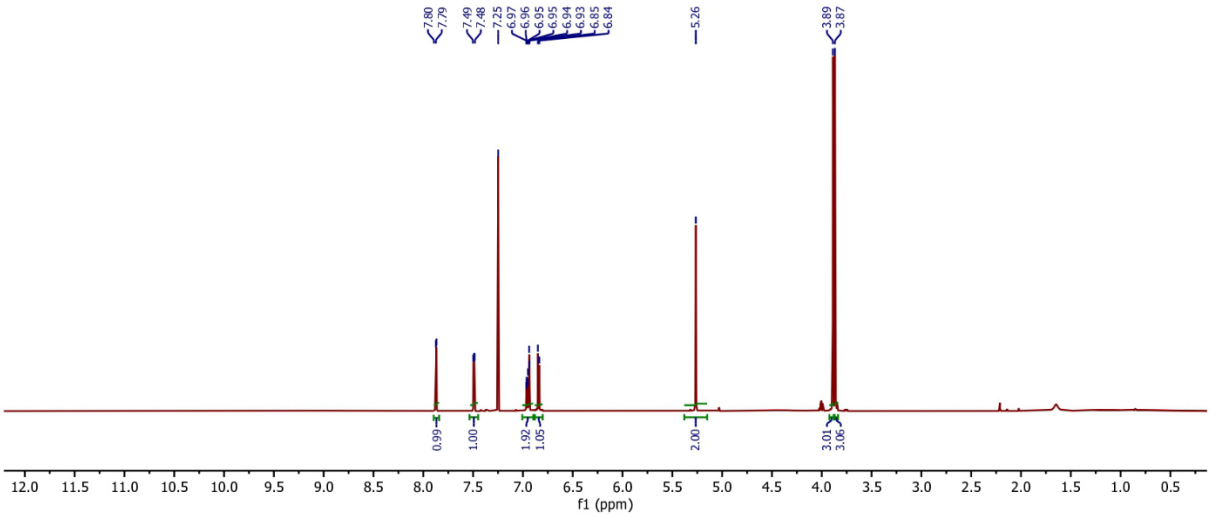
^{13}C NMR Spectrum of 6j (151 MHz, $CDCl_3$)



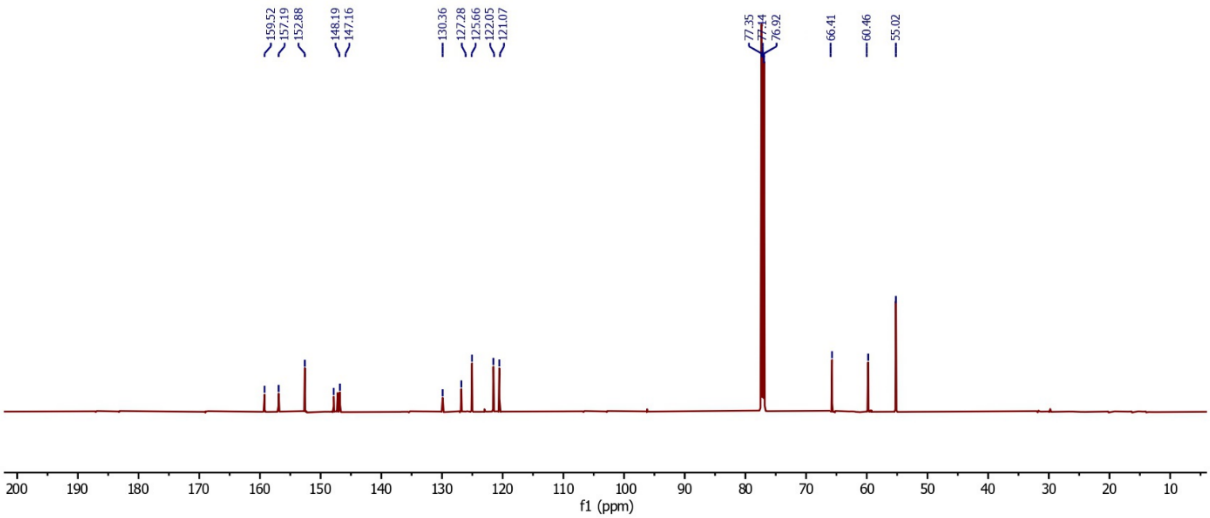
^{19}F NMR Spectrum of 2-chloro-6-fluorobenzyl thiazole-2-carboxylate (6j)



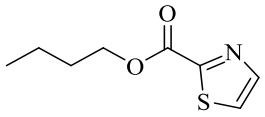
3,4-dimethoxybenzyl thiazole-2-carboxylate (6k)



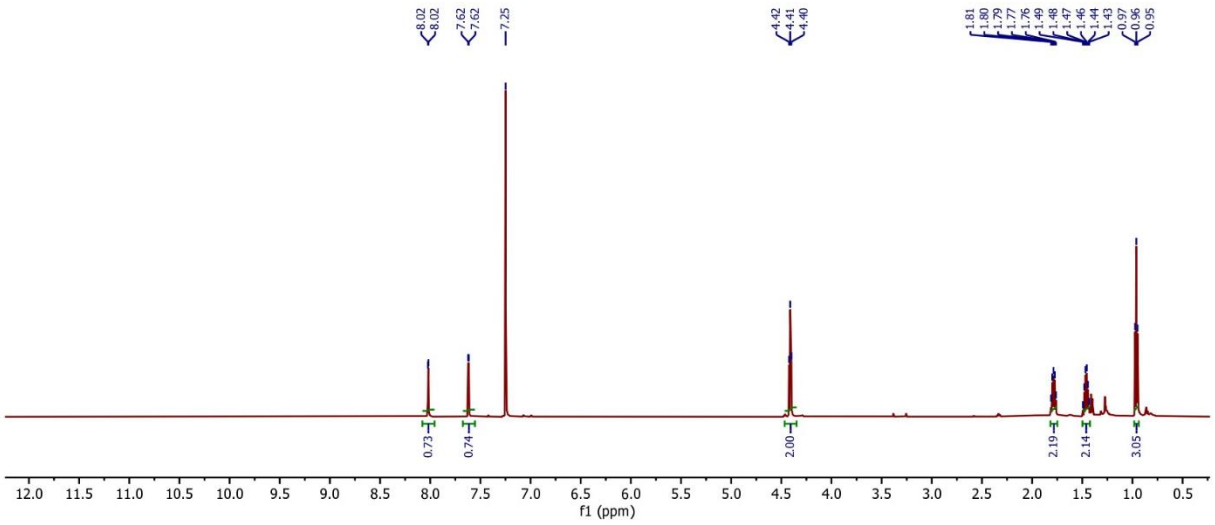
^{1}H NMR Spectrum of 6k (600 MHz, $CDCl_3$)



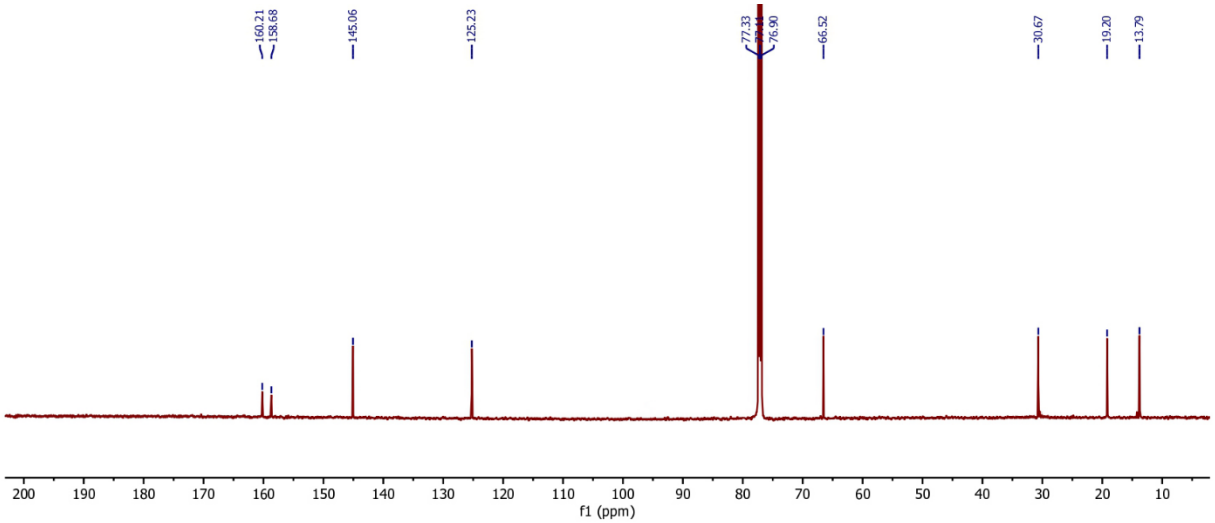
^{13}C NMR Spectrum of 6k (151 MHz, $CDCl_3$)



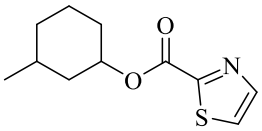
Butyl thiazole-2-carboxylate (6l)



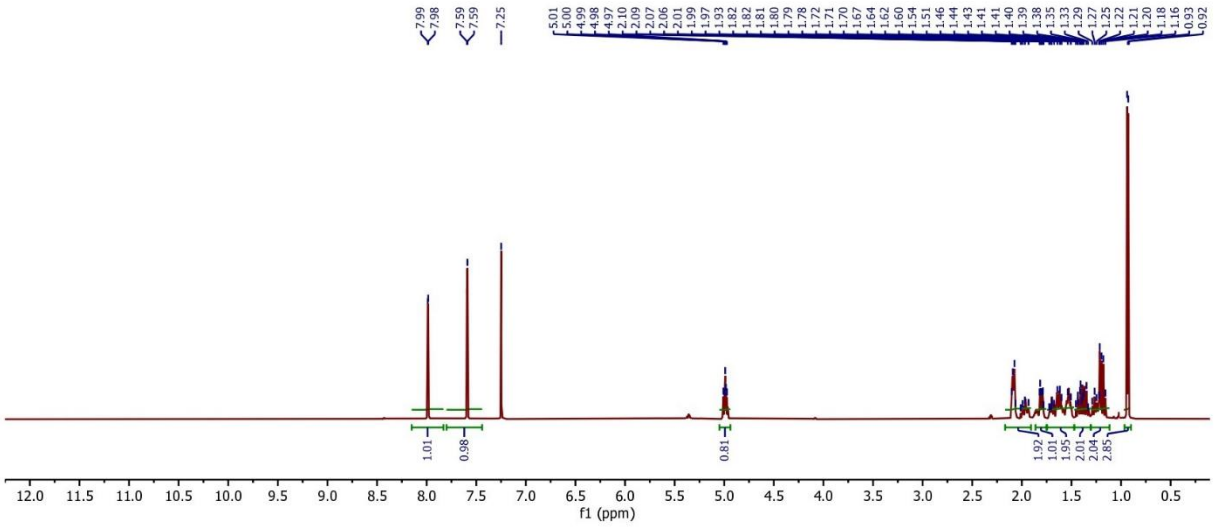
^{1}H NMR Spectrum of 6l (600 MHz, $CDCl_3$)



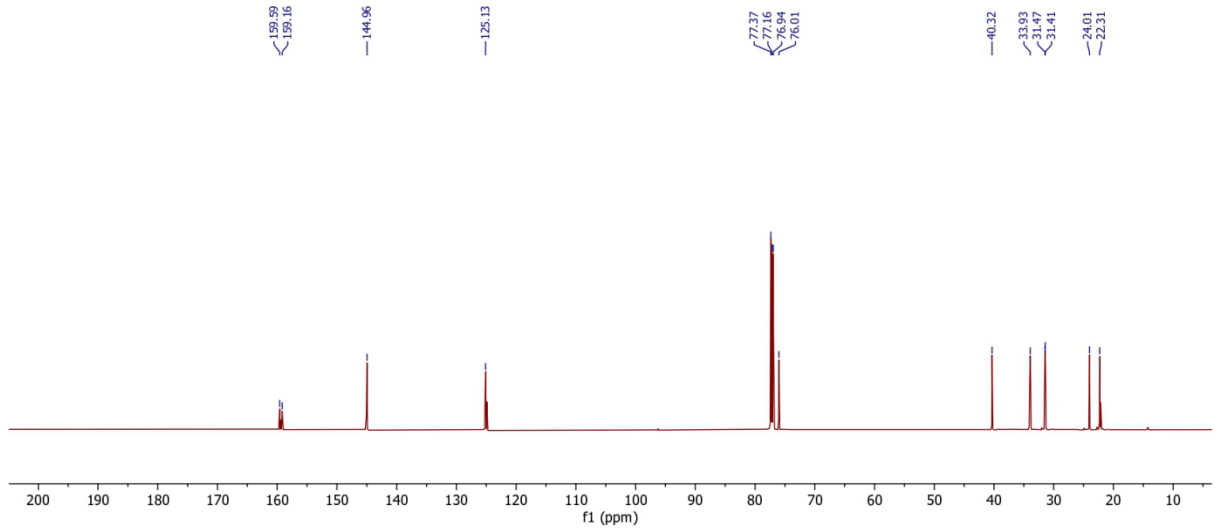
^{13}C NMR Spectrum of 6l (151 MHz, $CDCl_3$)



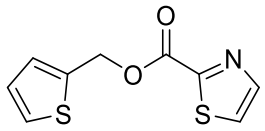
3-methylcyclohexyl thiazole-2-carboxylate (6m)



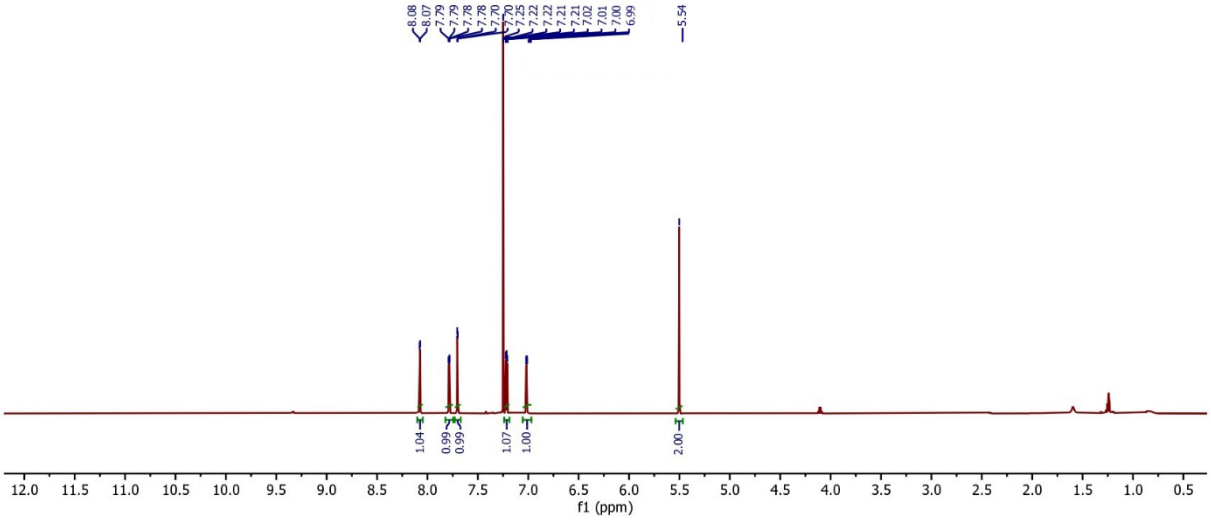
^{1}H NMR Spectrum of 6m (600 MHz, $CDCl_3$)



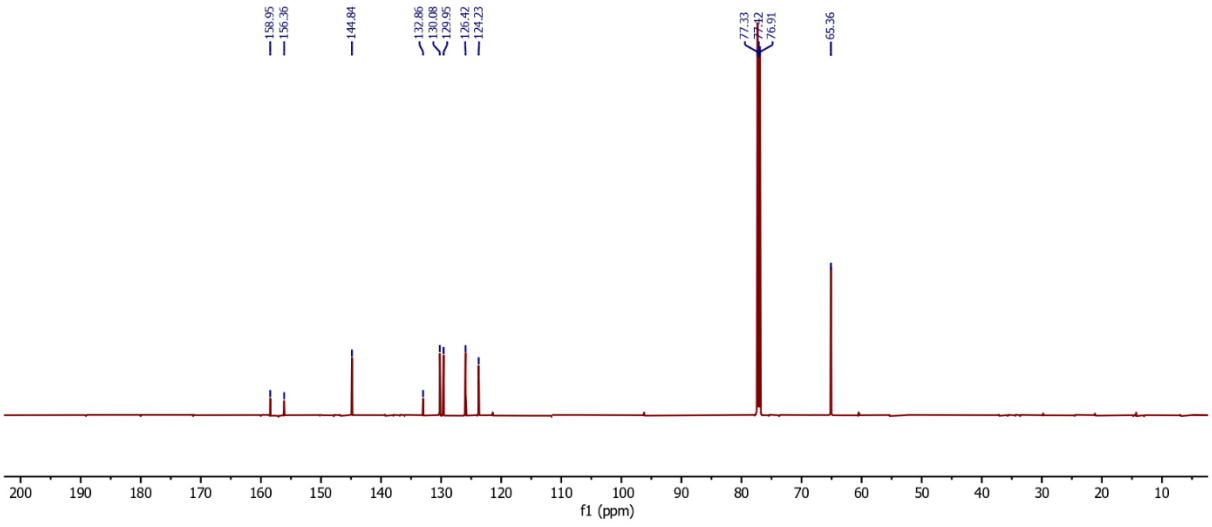
^{13}C NMR Spectrum of 6m (151 MHz, $CDCl_3$)



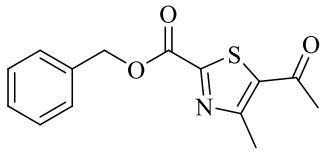
Thiophen-2-ylmethyl thiazole-2-carboxylate (6n)



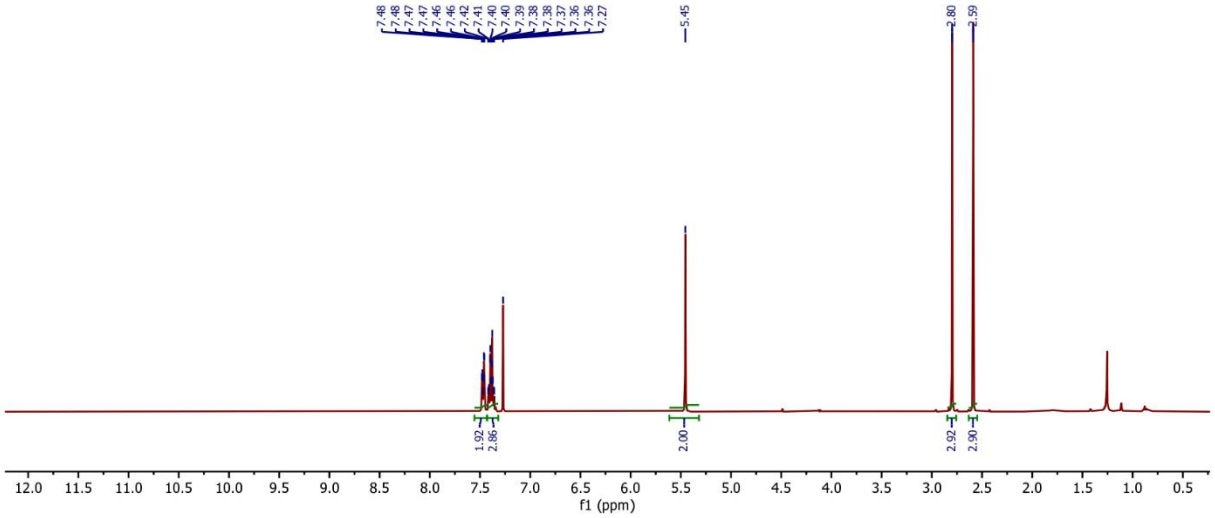
^{1}H NMR Spectrum of 6n (600 MHz, $CDCl_3$)



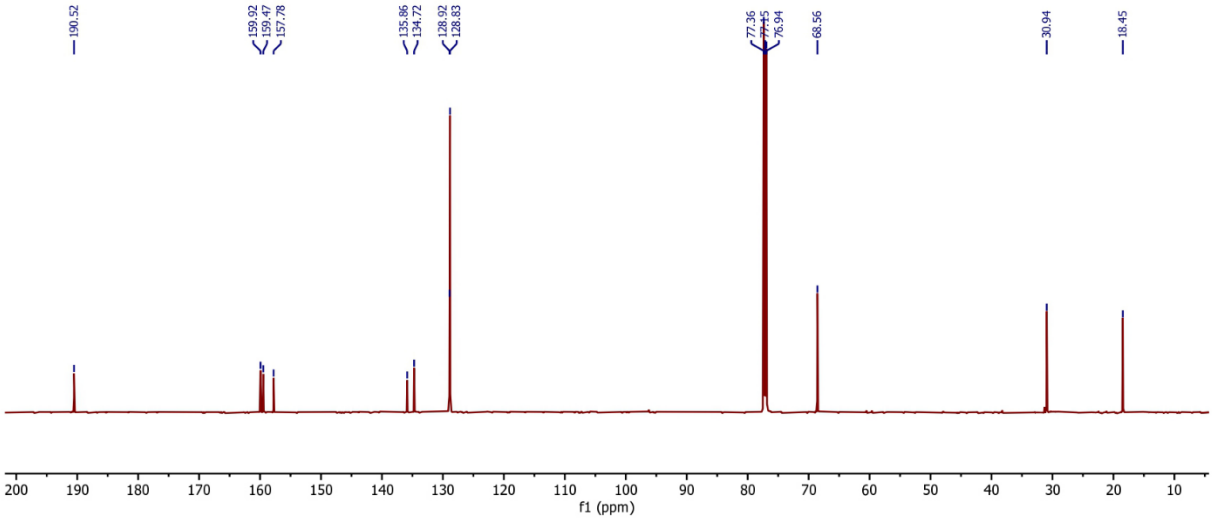
^{13}C NMR Spectrum of 6n (151 MHz, $CDCl_3$)



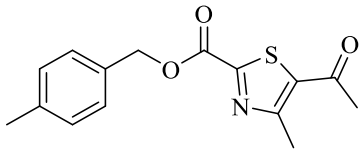
Benzyl 5-acetyl-4-methylthiazole-2-carboxylate (8a)



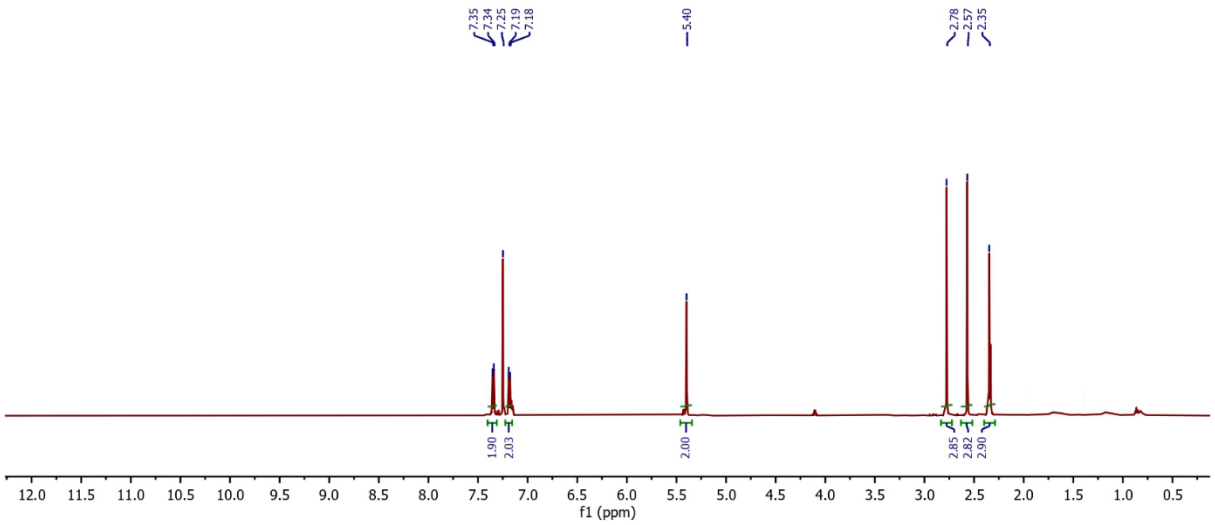
^{1}H NMR Spectrum of 8a (400 MHz, $CDCl_3$)



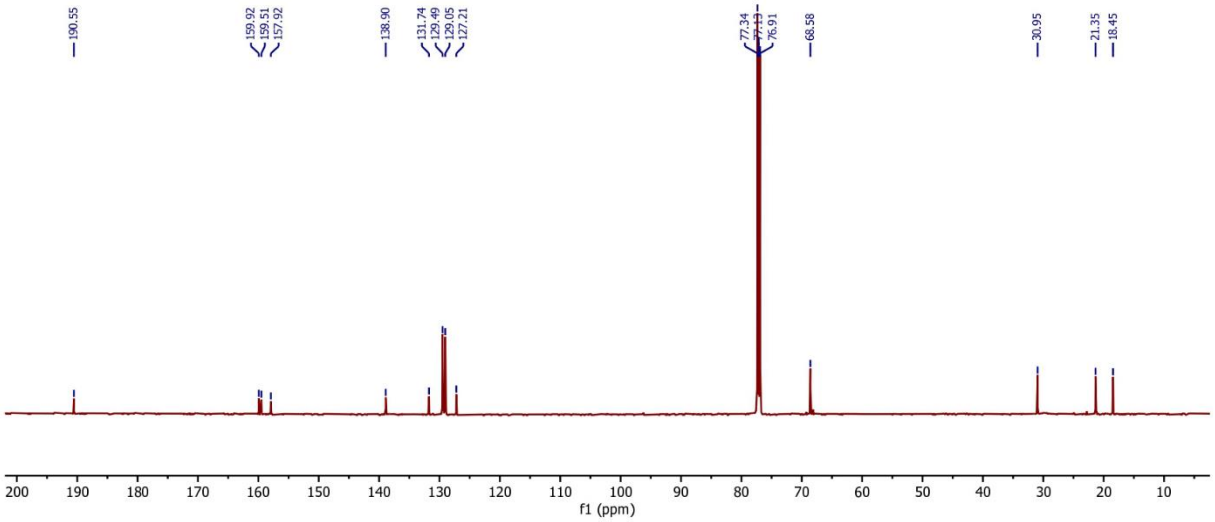
^{13}C NMR Spectrum of 8a (151 MHz, $CDCl_3$)



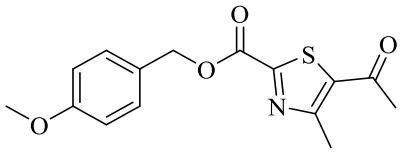
4-methylbenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8b)



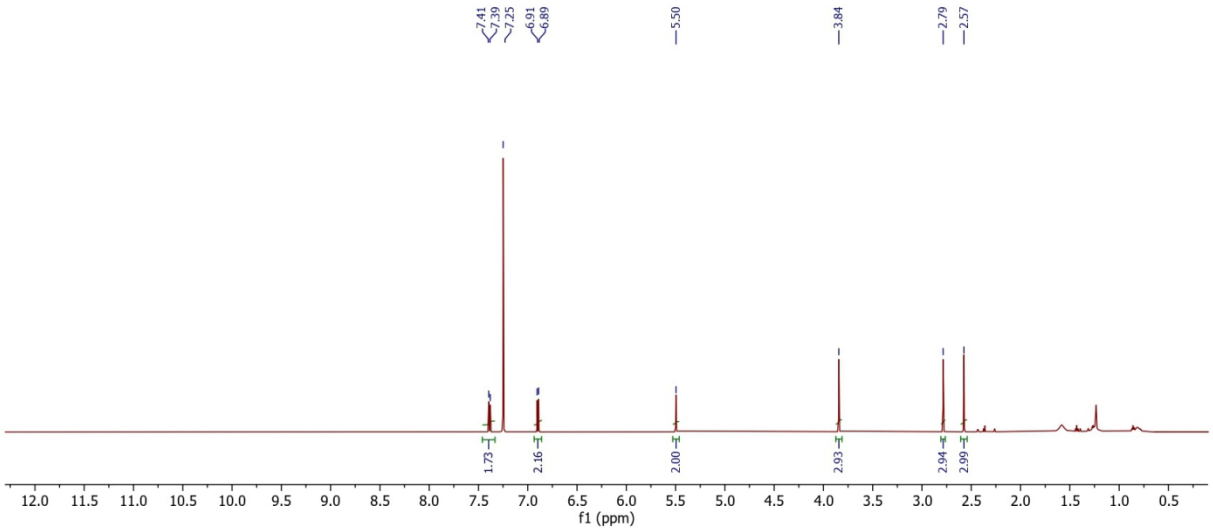
^{1}H NMR Spectrum of 8b (600 MHz, $CDCl_3$)



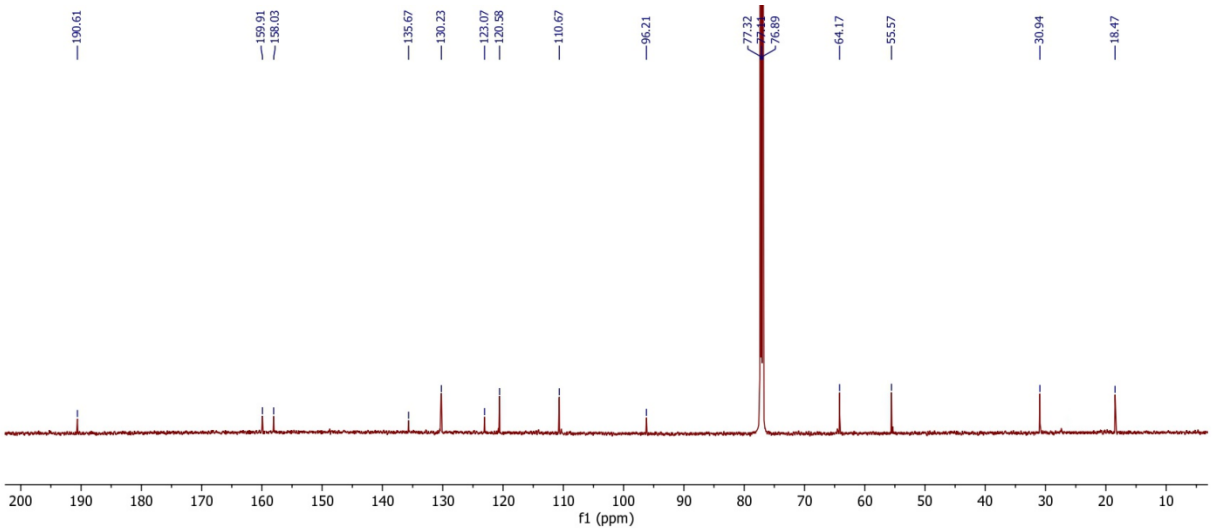
^{13}C NMR Spectrum of 8b (151 MHz, $CDCl_3$)



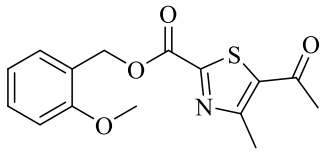
4-methoxybenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8c)



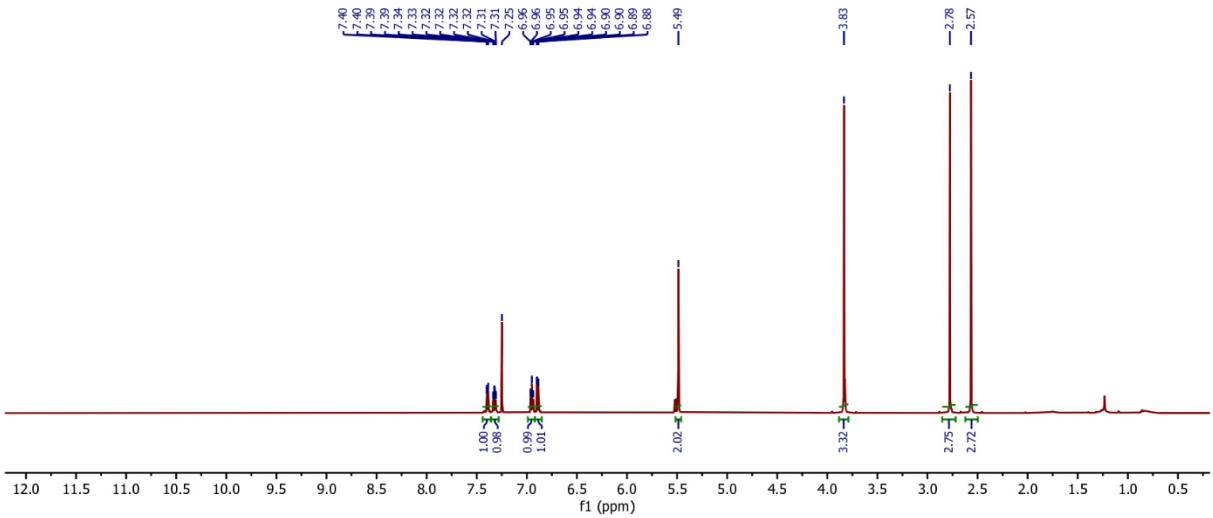
^{1}H NMR Spectrum of 8c (600 MHz, $CDCl_3$)



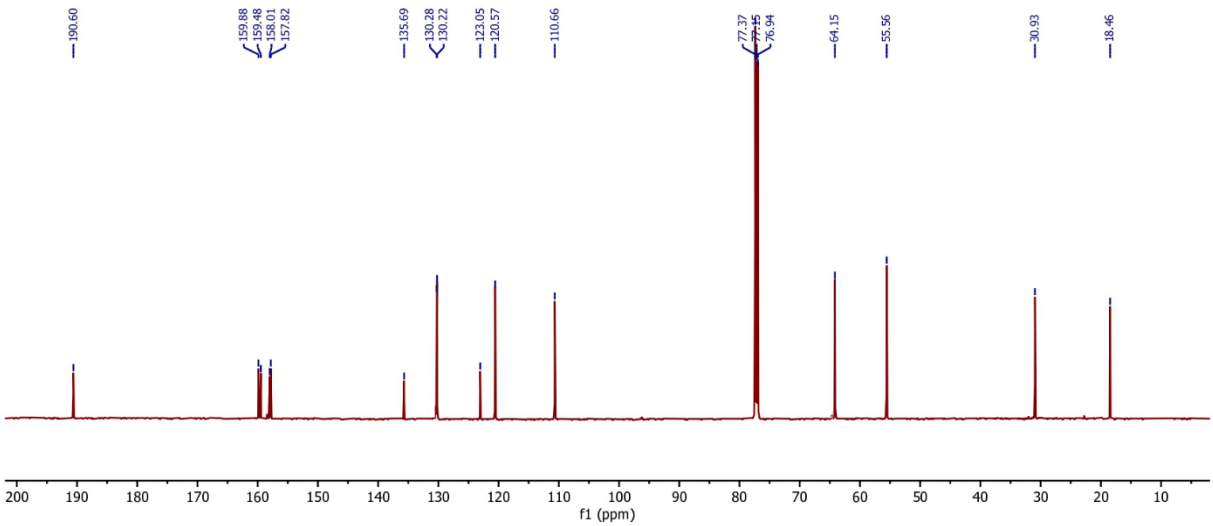
^{13}C NMR Spectrum of 8c (151 MHz, $CDCl_3$)



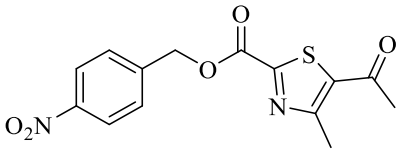
2-methoxybenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8d)



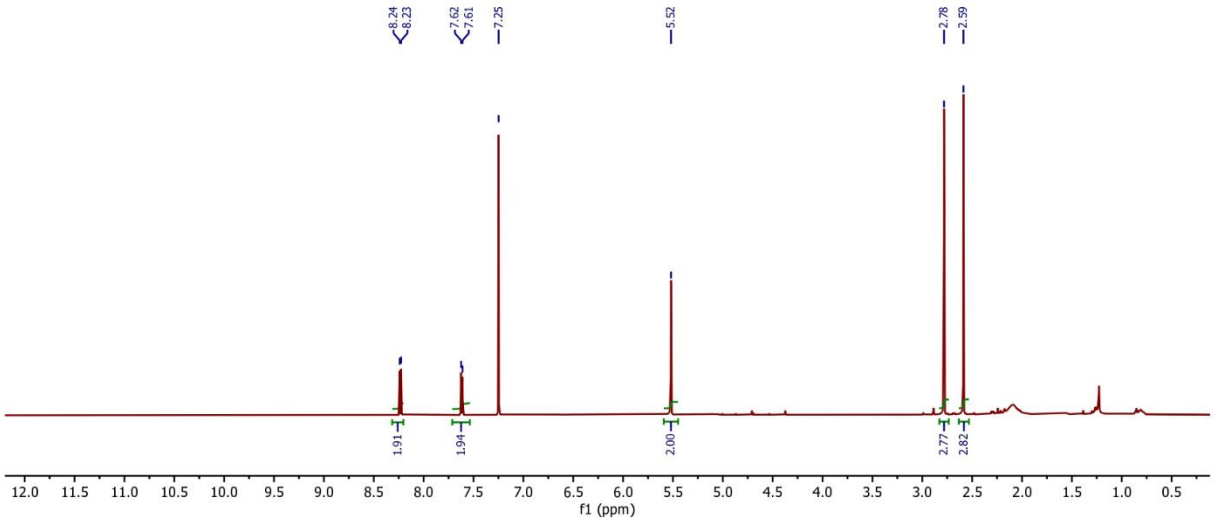
^{1}H NMR Spectrum of 8d (600 MHz, $CDCl_3$)



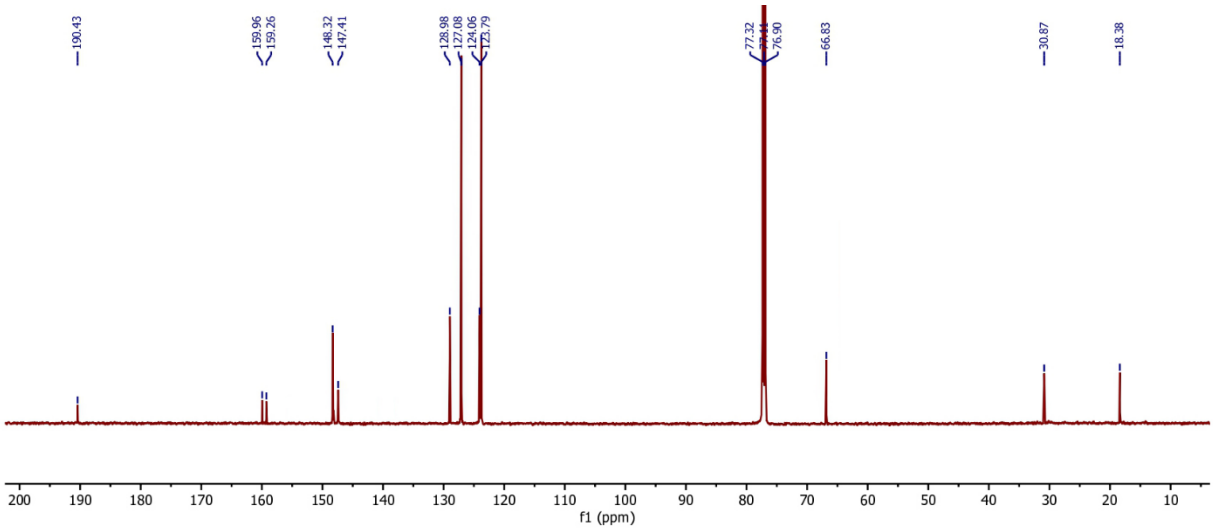
^{13}C NMR Spectrum of 8d (151 MHz, $CDCl_3$)



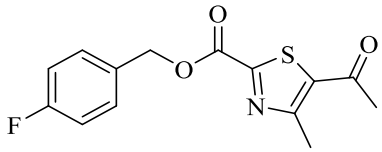
4-nitrobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8e)



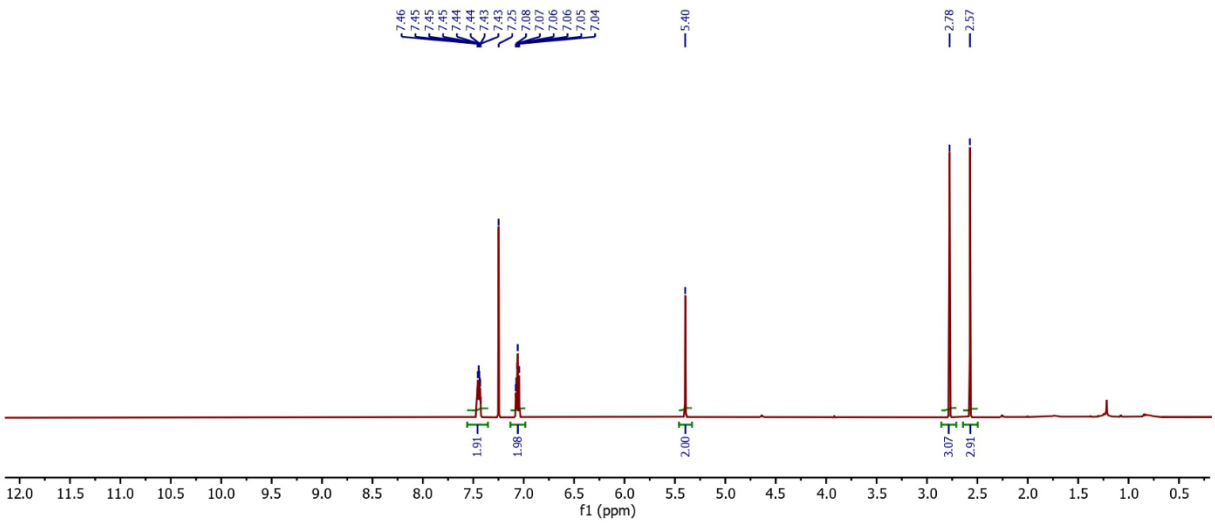
^{1}H NMR Spectrum of 8e (600 MHz, $CDCl_3$)



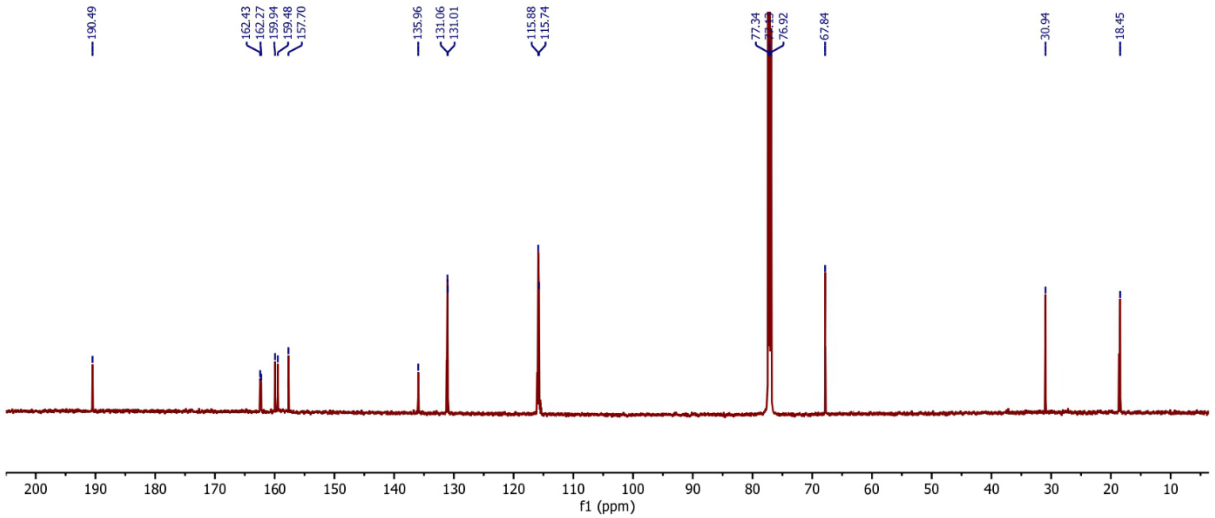
^{13}C NMR Spectrum of 8e (151 MHz, $CDCl_3$)



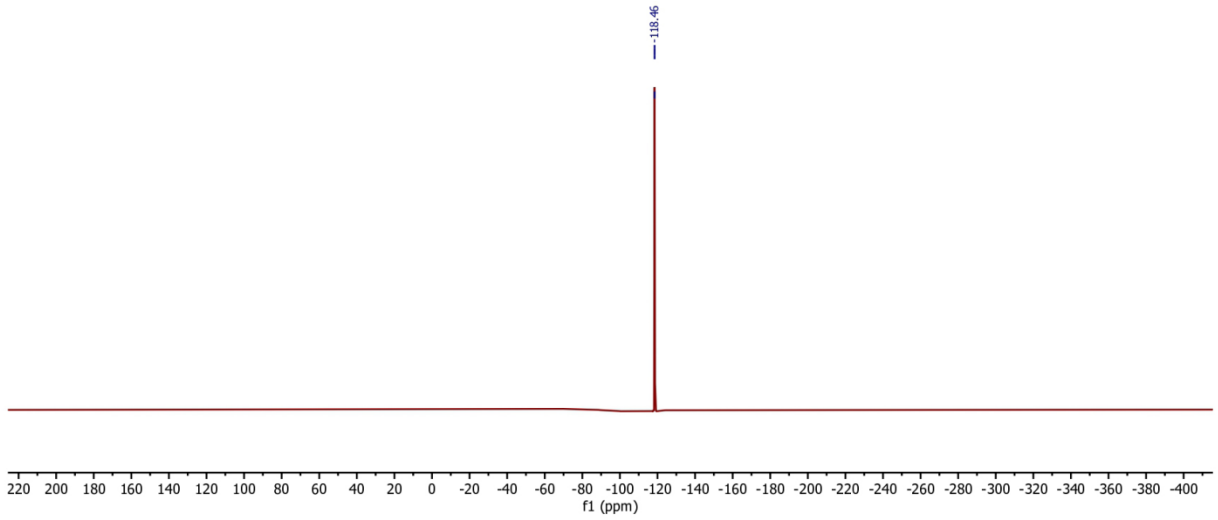
4-fluorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8f)



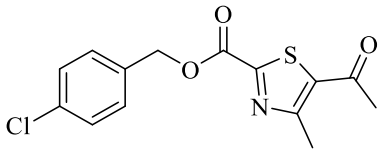
^{1}H NMR Spectrum of 8f (600 MHz, $CDCl_3$)



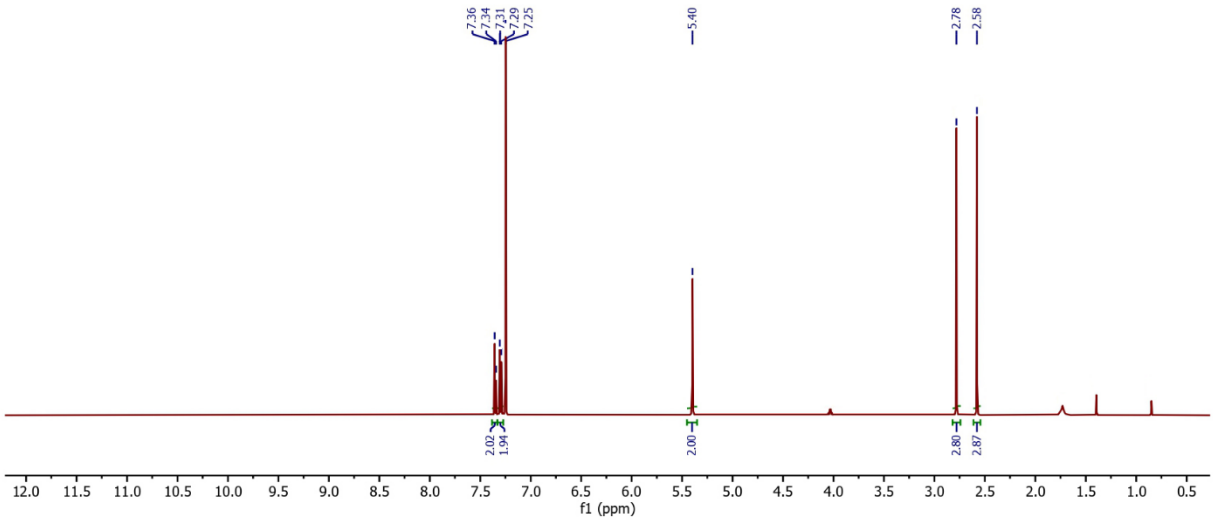
^{13}C NMR Spectrum of 8f (151 MHz, $CDCl_3$)



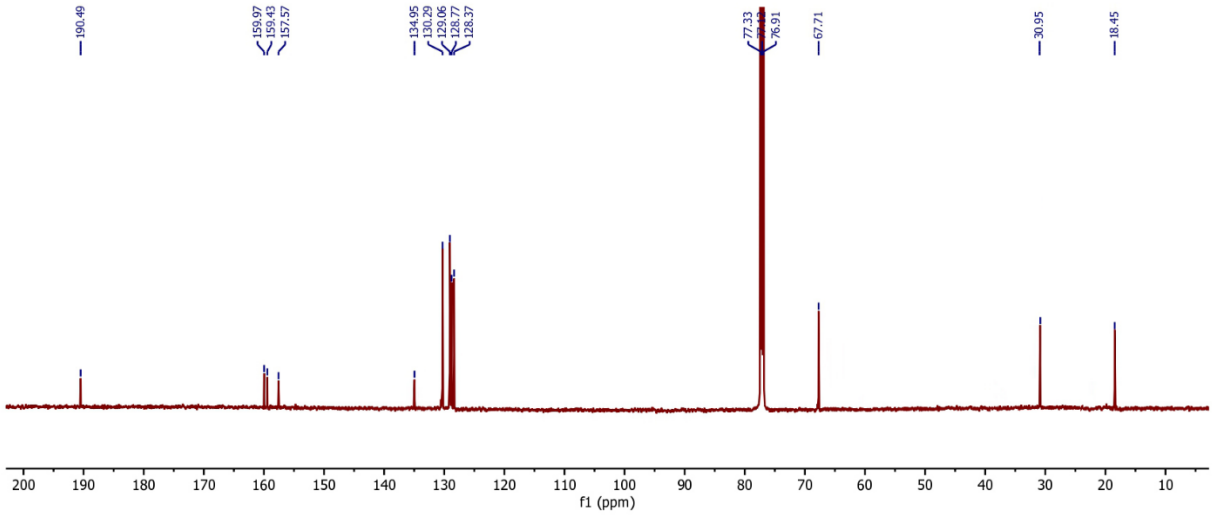
^{19}F NMR Spectrum of 4-fluorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8f)



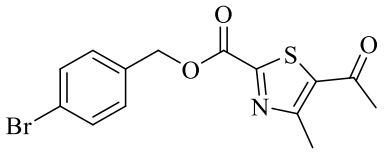
4-chlorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8g)



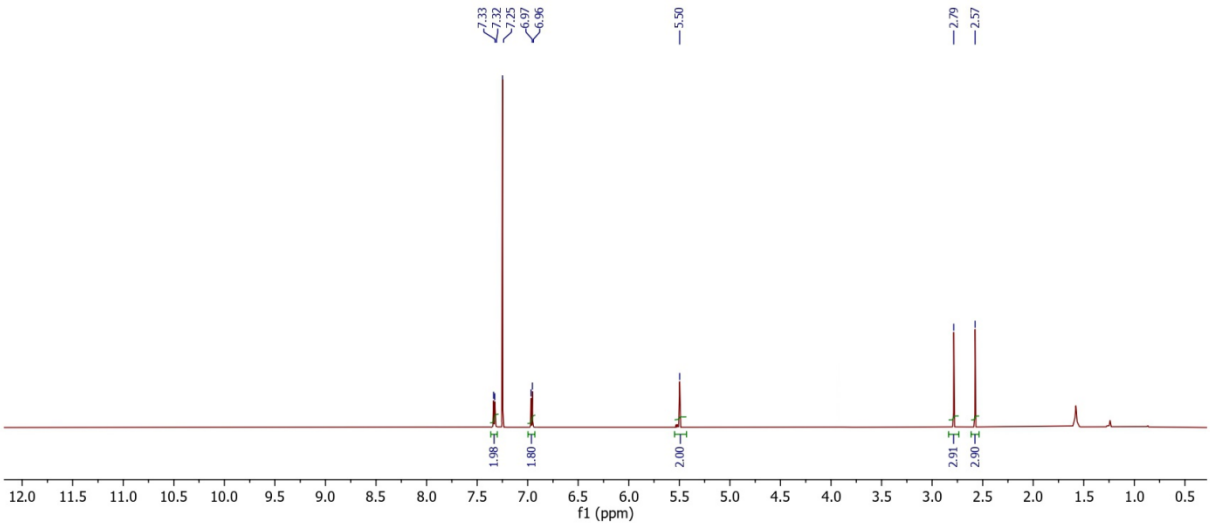
^{1}H NMR Spectrum of 8g (600 MHz, $CDCl_3$)



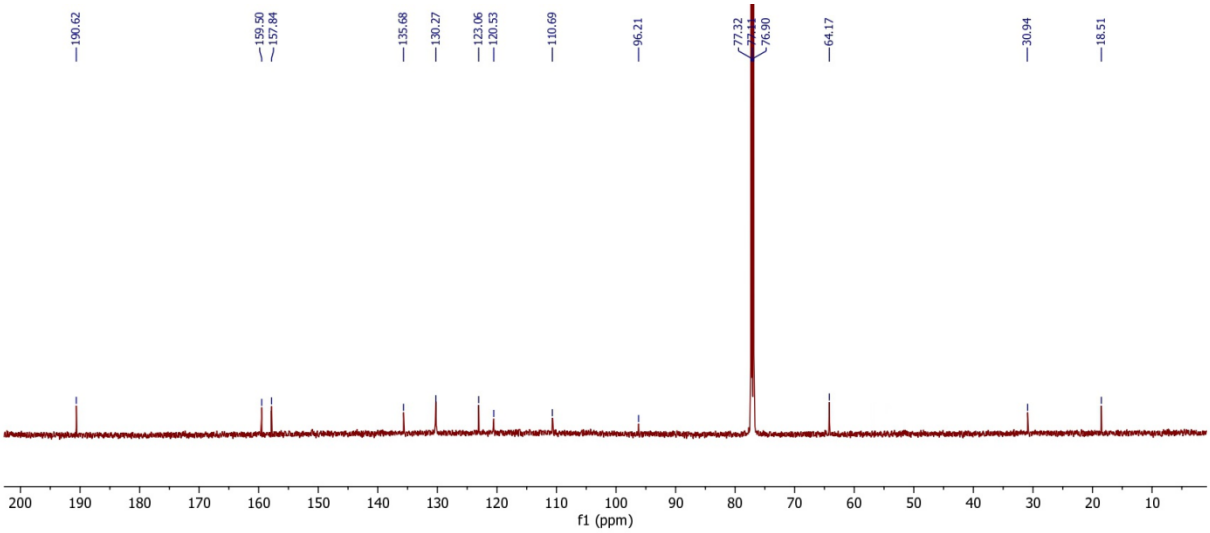
^{13}C NMR Spectrum of 8g (151 MHz, $CDCl_3$)



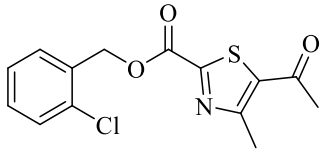
4-bromobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8h)



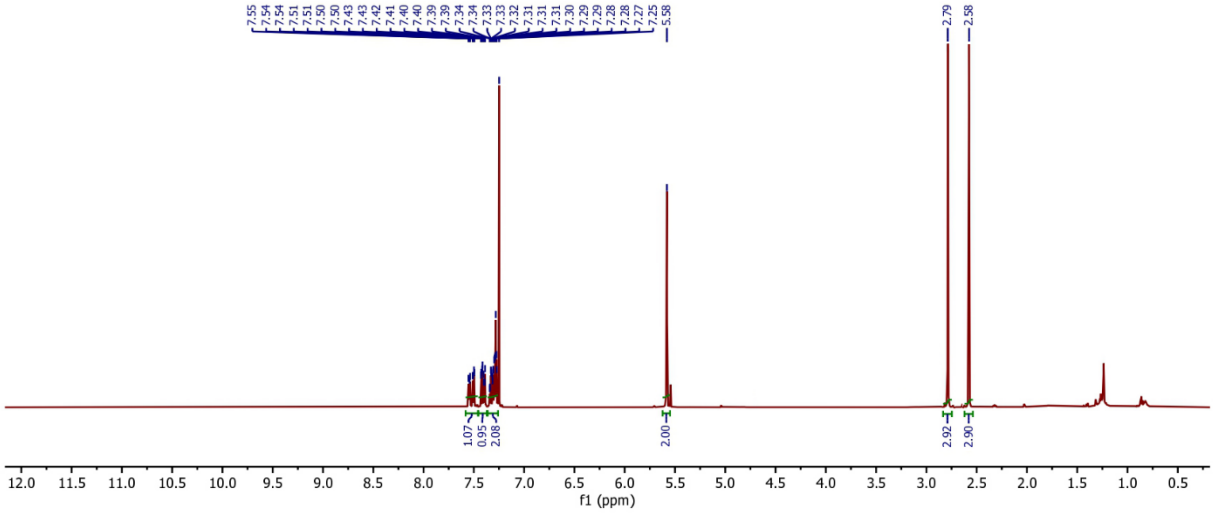
^{1}H NMR Spectrum of 8h (600 MHz, $CDCl_3$)



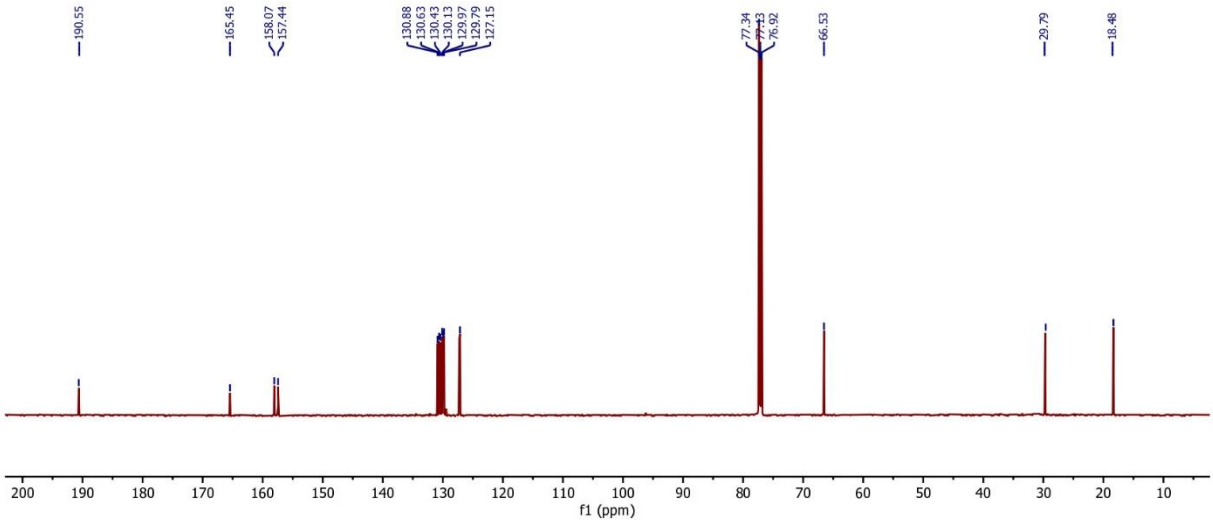
^{13}C NMR Spectrum of 8h (151 MHz, $CDCl_3$)



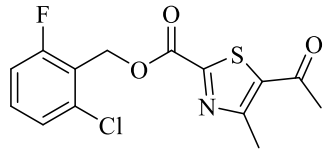
2-chlorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8i)



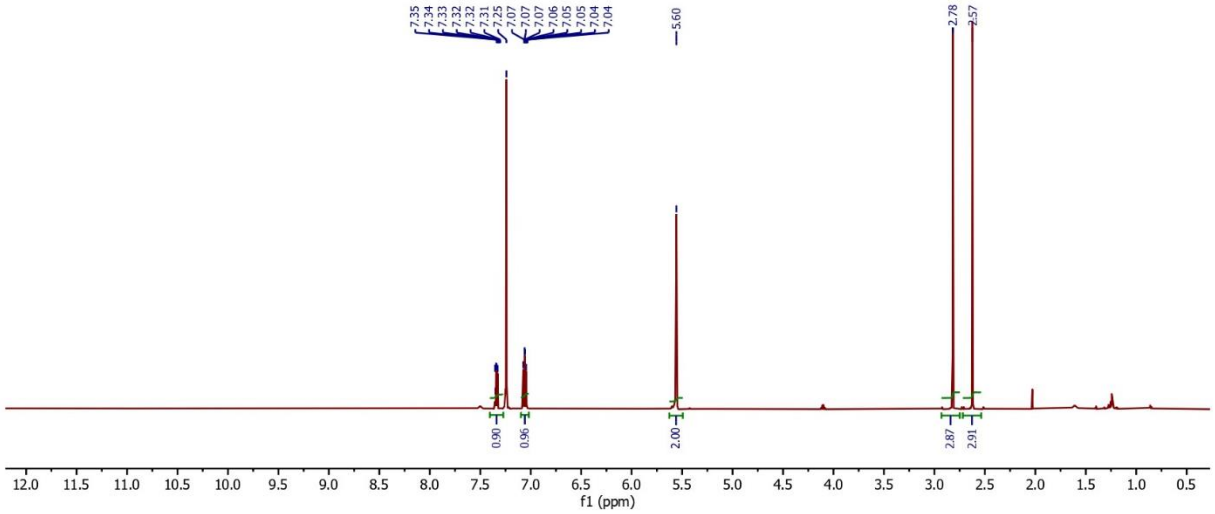
^{1}H NMR Spectrum of 8i (600 MHz, $CDCl_3$)



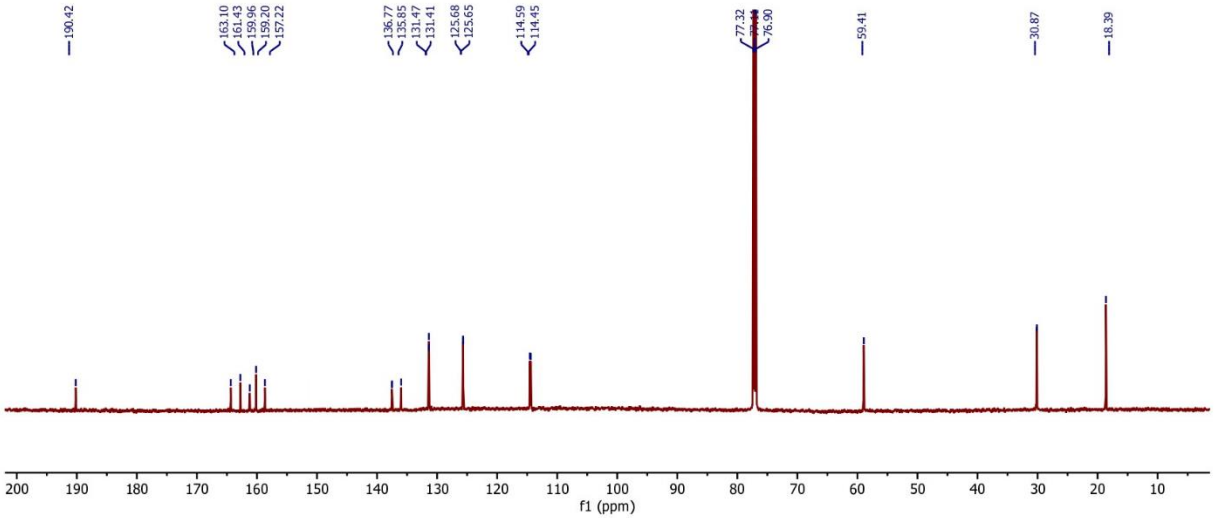
^{13}C NMR Spectrum of 8i (151 MHz, $CDCl_3$)



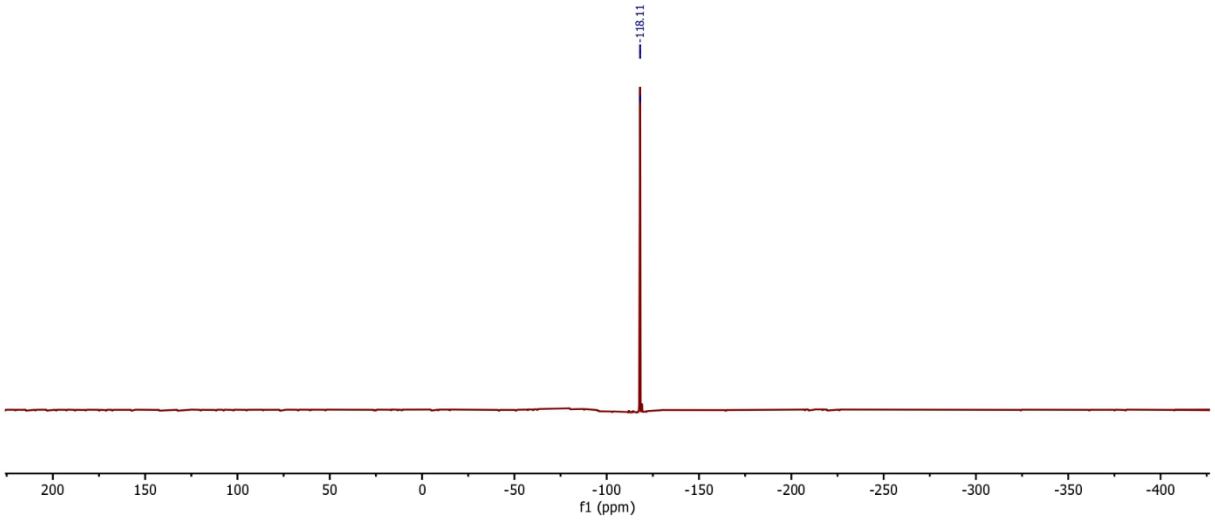
2-chloro-6-fluorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8j)



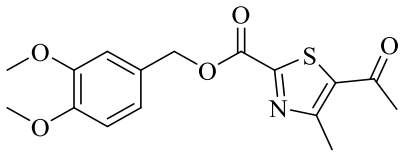
^{1}H NMR Spectrum of 8j (600 MHz, $CDCl_3$)



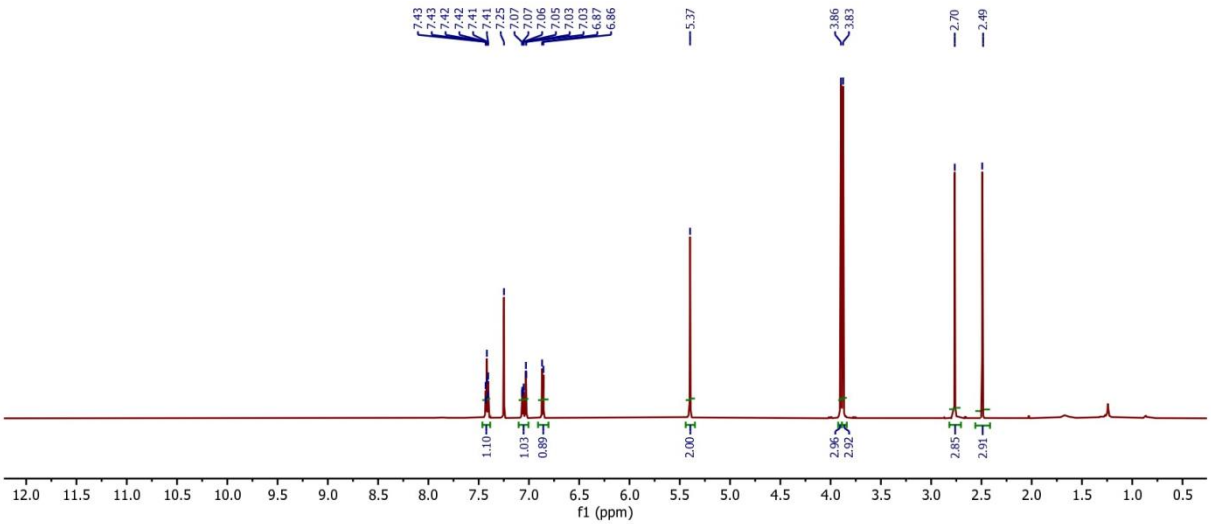
^{13}C NMR Spectrum of 8j (151 MHz, $CDCl_3$)



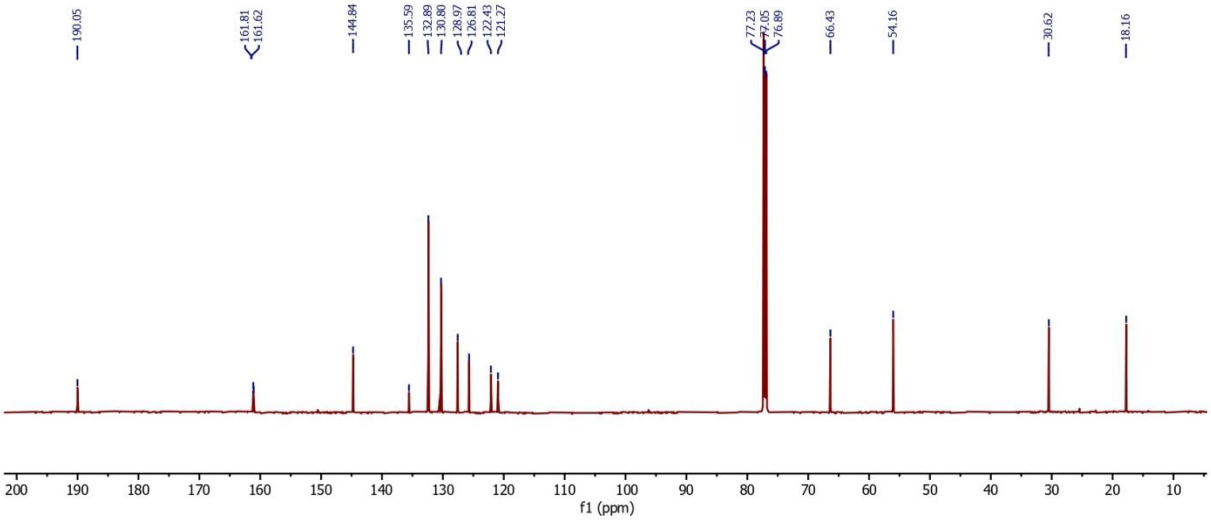
^{19}F NMR Spectrum of 2-chloro-6-fluorobenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8j)



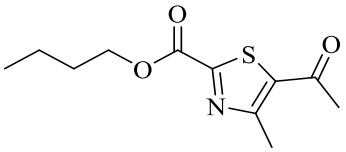
3,4-dimethoxybenzyl 5-acetyl-4-methylthiazole-2-carboxylate (8k)



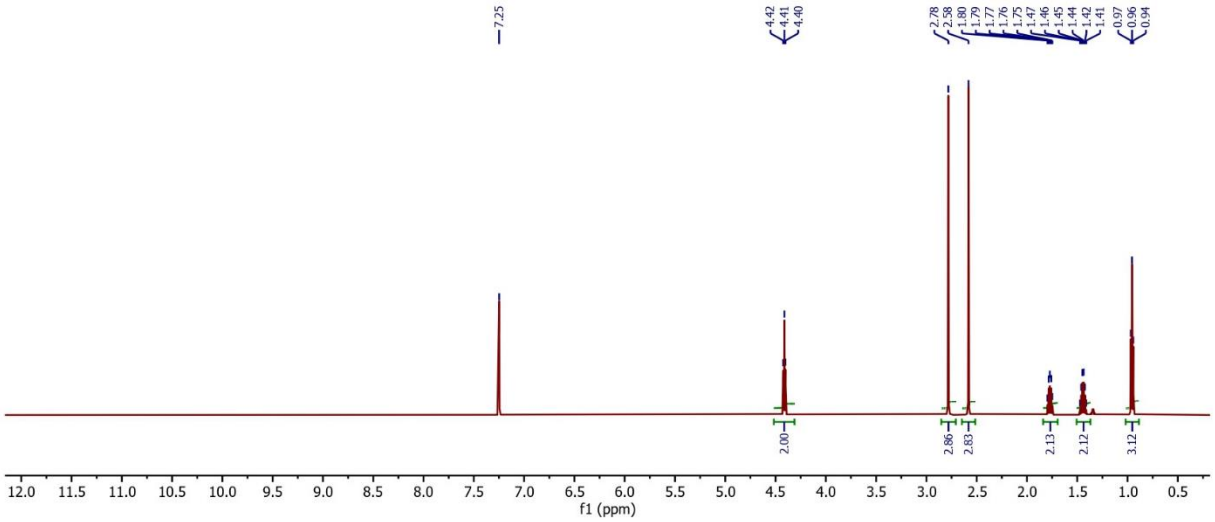
^{1}H NMR Spectrum of 8k (600 MHz, $CDCl_3$)



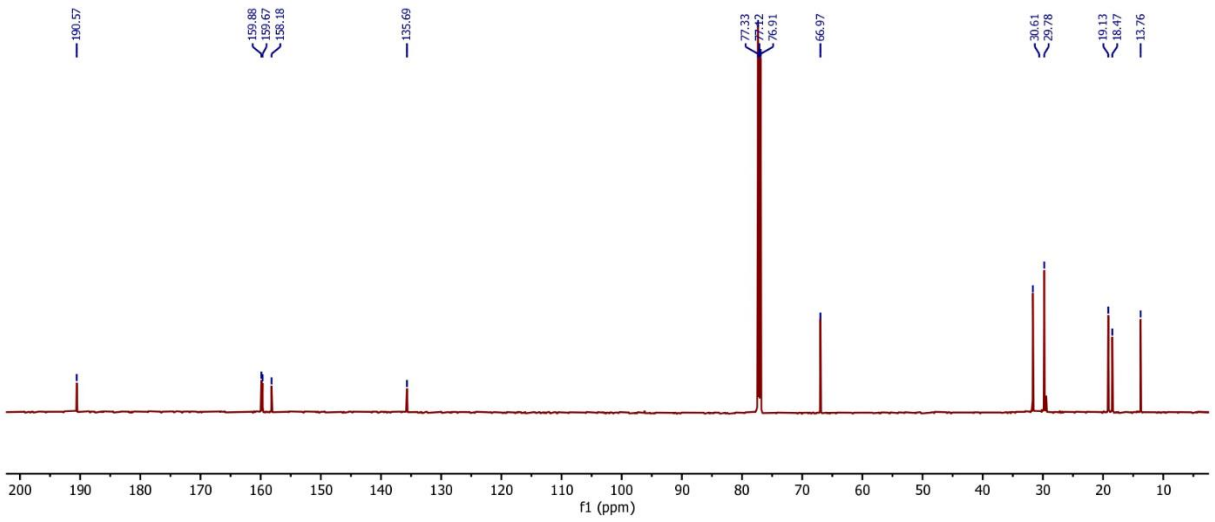
^{13}C NMR Spectrum of 8k (151 MHz, $CDCl_3$)



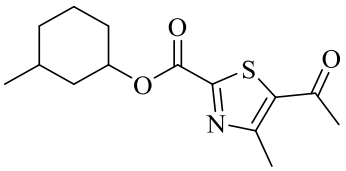
Butyl 5-acetyl-4-methylthiazole-2-carboxylate (8l)



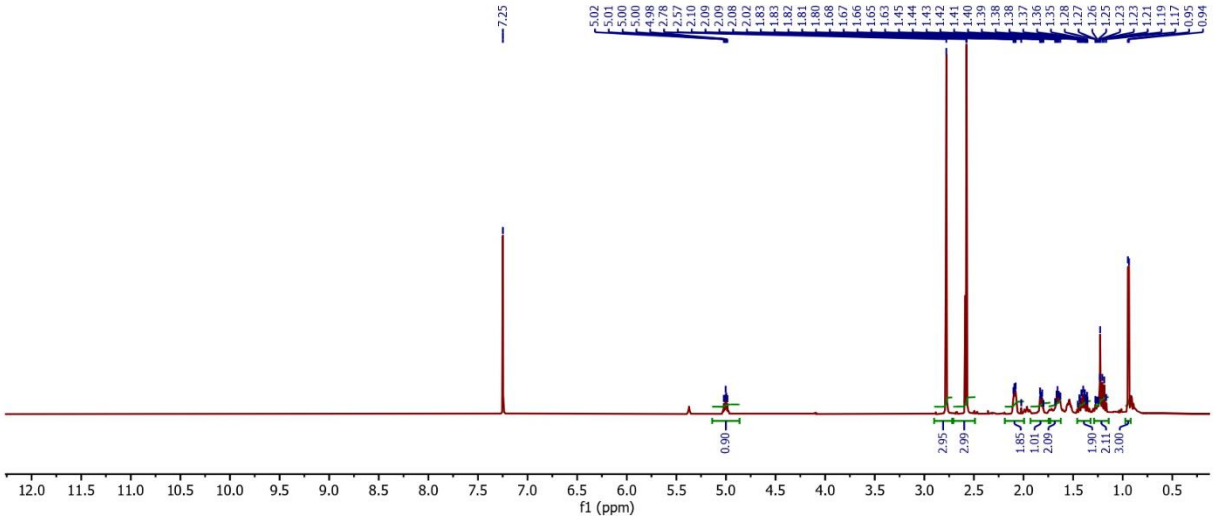
^{1}H NMR Spectrum of 8l (600 MHz, $CDCl_3$)



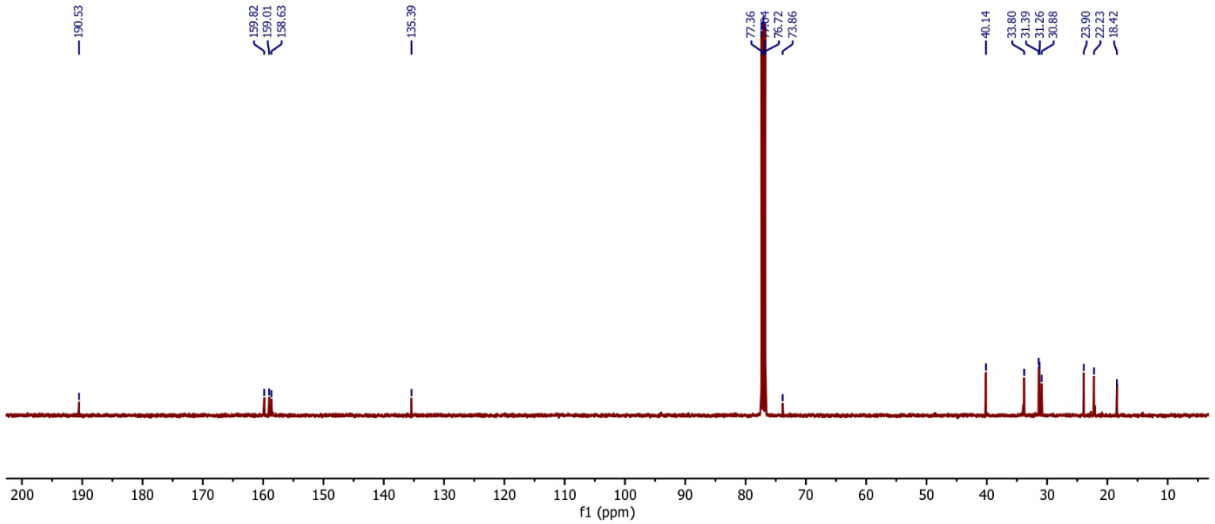
^{13}C NMR Spectrum of 8l (151 MHz, $CDCl_3$)



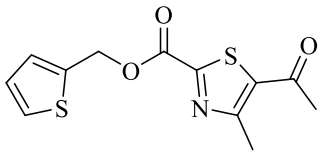
3-methylcyclohexyl 5-acetyl-4-methylthiazole-2-carboxylate (8m)



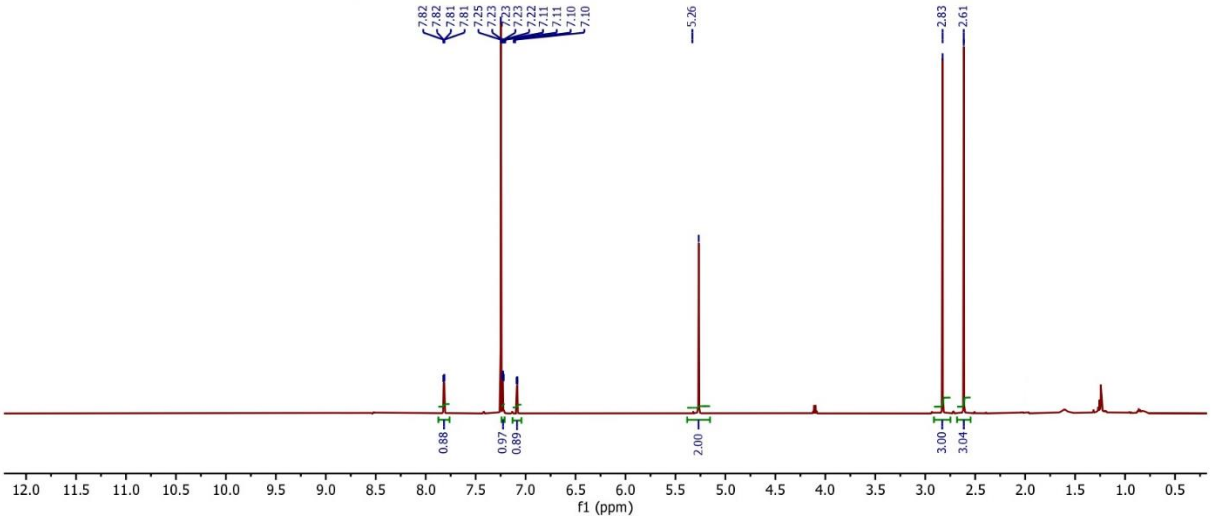
^{1}H NMR Spectrum of 8m (600 MHz, $CDCl_3$)



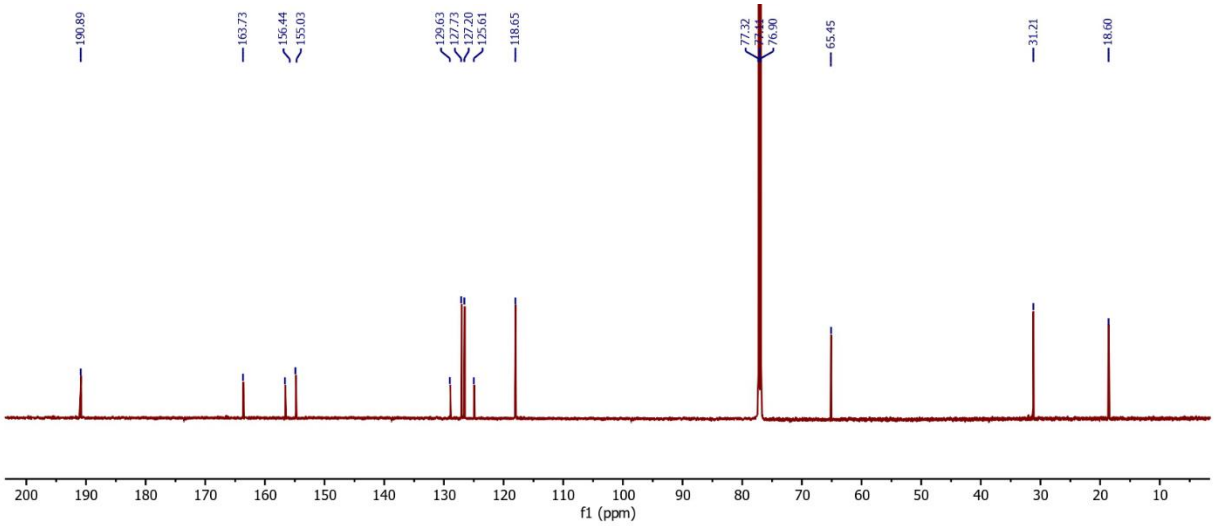
^{13}C NMR Spectrum of 8m (151 MHz, $CDCl_3$)



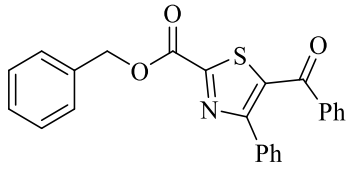
Thiophen-2-ylmethyl 5-acetyl-4-methylthiazole-2-carboxylate (8n)



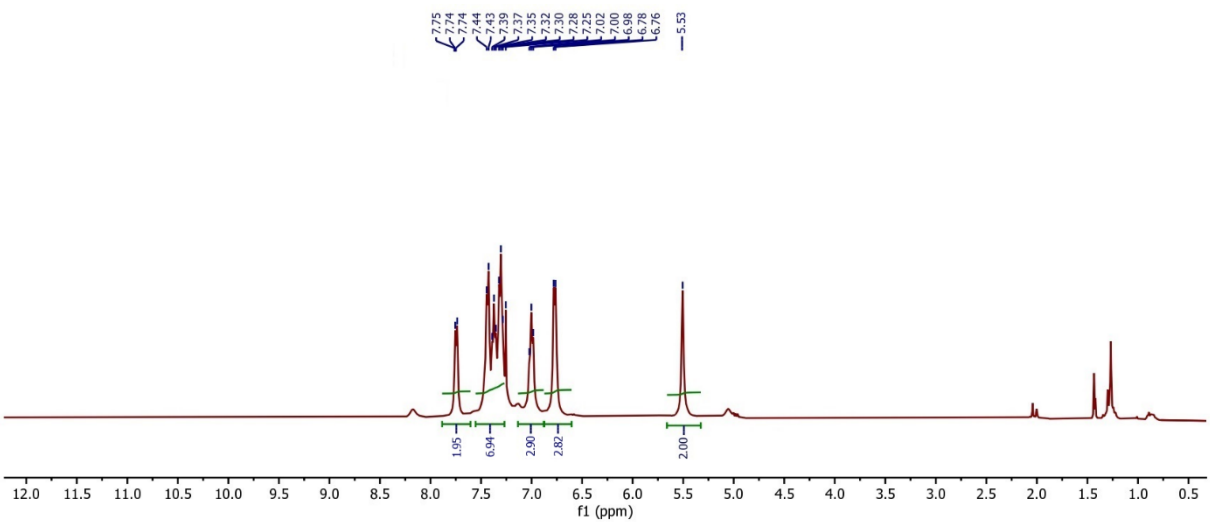
^{1}H NMR Spectrum of 8n (600 MHz, $CDCl_3$)



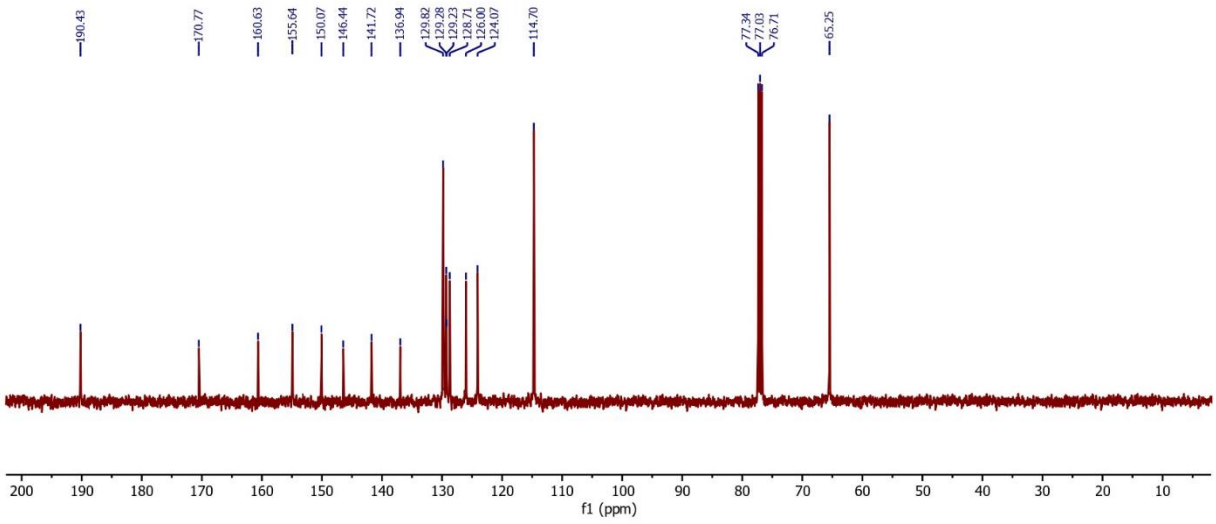
^{13}C NMR Spectrum of 8n (151 MHz, $CDCl_3$)



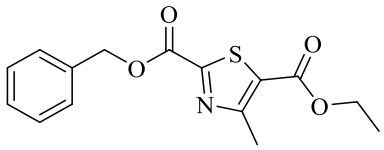
Benzyl 5-benzoyl-4-phenylthiazole-2-carboxylate (8o)



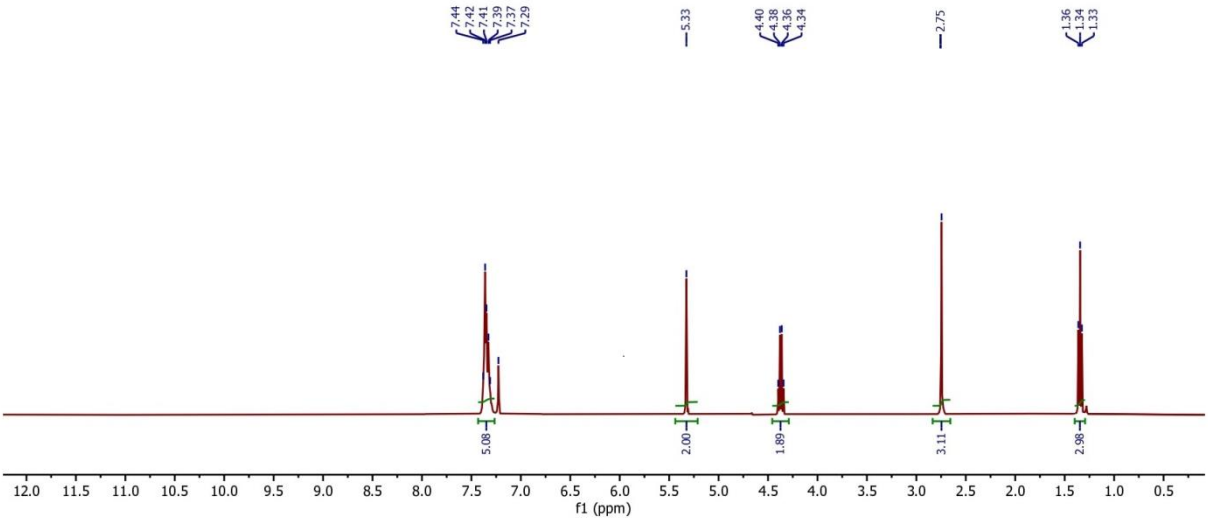
^{1}H NMR Spectrum of 8o (400 MHz, $CDCl_3$)



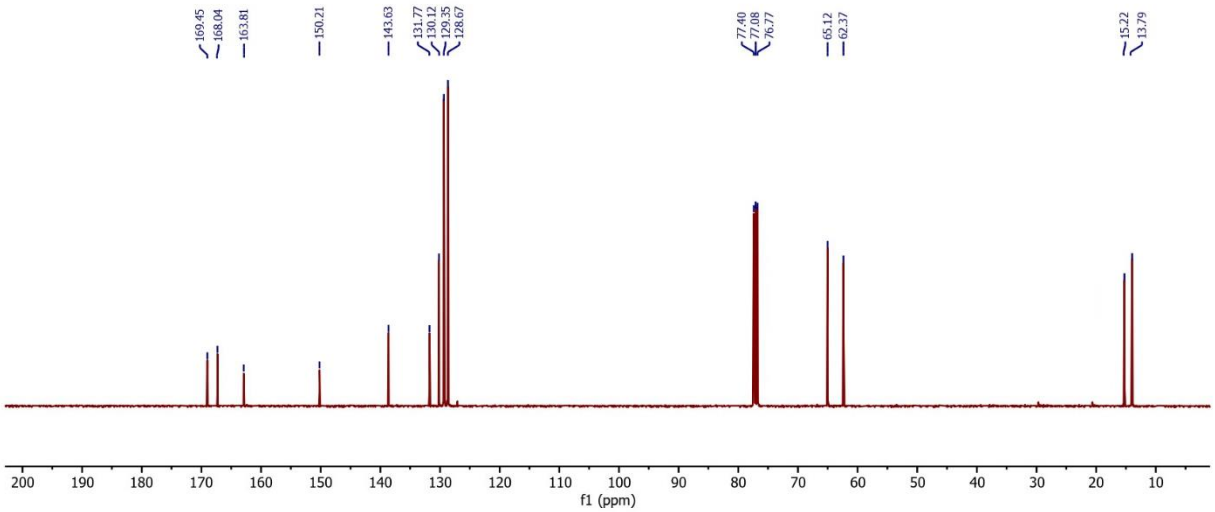
^{13}C NMR Spectrum of 8o (101 MHz, $CDCl_3$)



2-benzyl 5-ethyl 4-methylthiazole-2,5-dicarboxylate (8p)



^{1}H NMR Spectrum of 8p (600 MHz, $CDCl_3$)



^{13}C NMR Spectrum of 8p (151 MHz, $CDCl_3$)

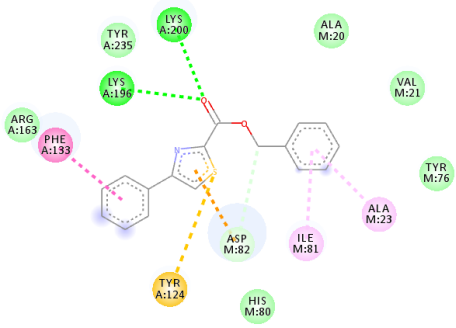
Molecular docking

It is a widely used computer simulation procedure to predict the conformation of a receptor ligand complex, where the receptor is usually a protein or a nucleic acid molecule and the ligand is either a small molecule or another protein. The prediction of accurate binding modes between the ligand and protein is of fundamental importance in modern structure-based drug design. The most important application of docking software is virtual screening, in which the most interesting and promising molecules are selected from an derived and existing database for further research, this places demands on the used computational method; it must be fast and reliable. Another application is the research of molecular complexes, there are many interesting docking suites and algorithms that have shown significant progress in predicting near-native binding poses by making use of biophysical and biochemical information combination with bioinformatics (i.e., Auto Dock.,).

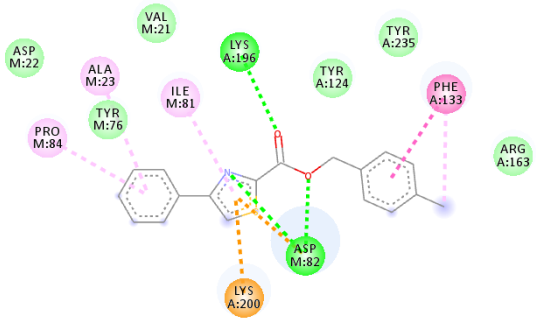
Table 1 Predicted docking scores and detailed interactions of the compounds **4a-4y**

Code	Docking score (kcal mol^{-1})	Interacting residues	
		H-Bond	**Other Interactions (Hydrophobic, Amide–π, π-σ.,)**
4a	-7.5	LYS-196, LYS-200	ALA-20, VAL-21, ALA-23, TYR-76, HIS-80, ILE-81, ASP-82, TYR-124, PHE-133, ARG-163, TYR-235
4b	-7.4	ASP-82, LYS-196	VAL-21, ASP-22, ALA-23, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, ARG-163, LYS-200, TYR-235
4c	-7.7	ALA-23, LYS-196, LYS-200	ALA-20, VAL-21, ASP-22, ALA-24, TYR-76, HIS-80, ILE-81, ASP-82, PRO-84, TYR-124, PHE-133, ARG-163, TYR-235
4d	-7.6	ASP-82, LYS-200	ALA-20, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, LYS-196, TYR-235
4e	-7.5	ASP-82, LYS-196, LYS-200	ALA-18, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, HIS-80, ILE-81, , TYR-124, PHE-133, ARG-163, TYR-235
4f	-7.3	LYS-200, TYR-235	VAL-21, ALA-23, TYR-76, HIS-80, ILE-81, ASP-82, TYR-124, THR-131, PHE-133, LYS-196, THR-219
4g	-7.1	LYS-200, TYR-235	VAL-21, ALA-23, TYR-76, HIS-80, ILE-81, ASP-82 , TYR-124, PHE-133, LYS-196 TYR197, THR-219
4h	-7.1	LYS-200, TYR-235	VAL-21, ALA-23, TYR-76, HIS-80, ILE-81, ASP-82, TYR-124, THR-131, PHE-133, LYS-196, THR-219
4i	-7.6	ASP-82, LYS-196, LYS-200	ALA-18, ALA-23, TYR-76, HIS-80, ILE-81, PRO-84, TYR-124, PHE-133, ARG-163, TYR-235
4j	-6.4	LYS-200, TYR-235	VAL-21, ASP-22, ALA-23, TYR-76, HIS-80, ILE-81, ASP-82, TYR-124, PHE-133, LYS-196, TYR-219
4k	-6.2	LYS-200, TYR-235	VAL-21, ALA-23, TYR-76, ILE-81, ASP-82, TYR-124, PHE-133, ARG-163, LYS-196, THR-219
4l	-7.3	LYS-200, TYR-235	VAL-21, ALA-23, TYR-76, HIS-80, ILE-81, ASP-82, TYR-124, PHE-133, LYS-196, THR-219
4m	-7.6	ASP-82, LYS-196, LYS-200	ALA-18, ALA-23, TYR-76, HIS-80, ILE-81, PRO-84, TYR-124, PHE-133, ARG-163, TYR-235
4n	-7.2	ASP-82, LYS-196	ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, ARG-163, LYS-200, TYR-235
4o	-7.5	ASP-82, LYS-196, LYS-200	ALA-18, ALA-23, TYR-76, HIS-80, ILE-81, TYR-124, PHE-133, ASN-160, ARG-163, TYR-235
4p	-8.0	ALA-23, ASP-82, LYS-196, LYS-200	VAL-21, ASP-22, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, ARG-163, LYS-200, TYR-235
4q	-7.6	LYS-196, LYS-200	ALA-18, ALA-23, TYR-76, HIS-80, ILE-81, HIS-80, PRO-84, TYR-124, PHE-133, ASN-160, ARG-163, TYR-235
4r	-7.5	ASP-82, ARG-163, LYS-196	VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, ASN-160, LYS-200, TYR-235
4s	-7.1	ASP-82	ALA-20, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, TYR-124, PHF-133, LYS-196, LYS-200, TYR-235
4t	-7.8	ALA-23, LYS-196, LYS-200	ALA-20, VAL-21, ASP-22, ALA-24, TYR-76, HIS-80, ILE-81, ASP-82, TYR-124, PHE-133, ASN-160, ARG-163, TYR-235
4u	-7.8	ALA-23, ALA-24, ASP-82, LYS-196	VAL-21, ASP-22, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, LYS-200
4v	-8.1	ALA-23, ASP-82, LYS-196, LYS-200	ASP-22, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, ARG-163, LYS-200, TYR-235
4w	-8.2	ALA-23, ALA-24, ASP-82, LYS-196	ALA-18, VAL-21, ASP-22, ALA-24, TYR-76, HIS-80, ILE-81, HIS-80, PRO-84, TYR-124, PHE-133, ASN-160,
4x	-6.2	ASP-82, LYS-196, LYS-200	ALA-23, TYR-76, ILE-81, TYR-124, PHE-133, TYR-235
4y	-5.2	ASP-82, LYS-196, LYS-200	VAL-21, ALA-23,TYR-76, HIS-80, ILE-81, TYR-124, THR-131,PHE-133,TYR-235

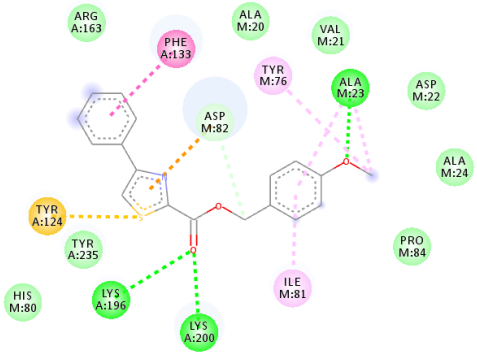
Compound 4a

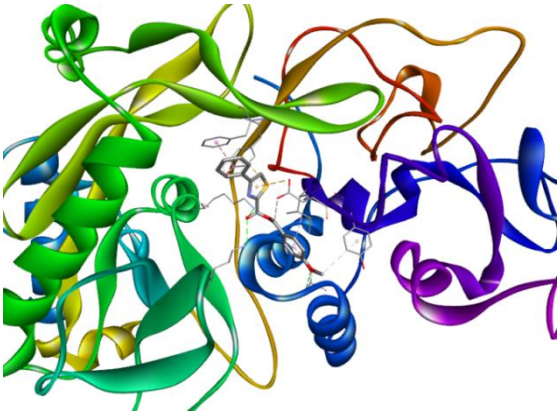


Compound 4b

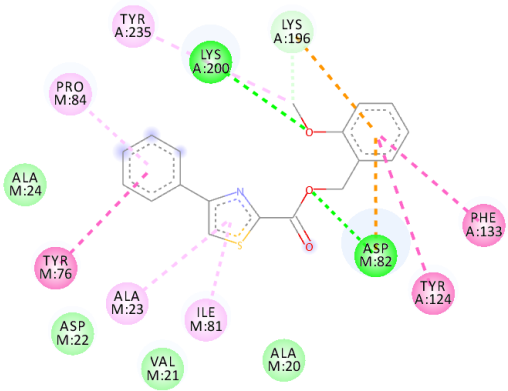


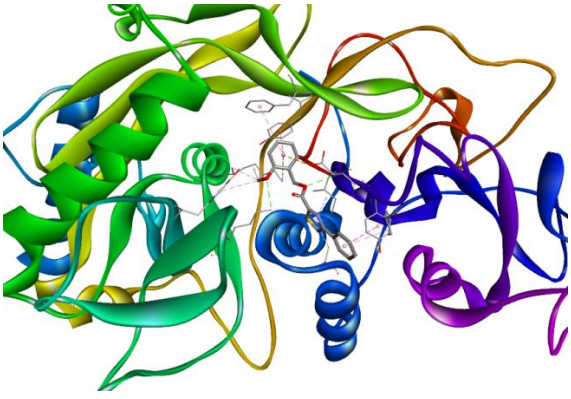
Compound 4c



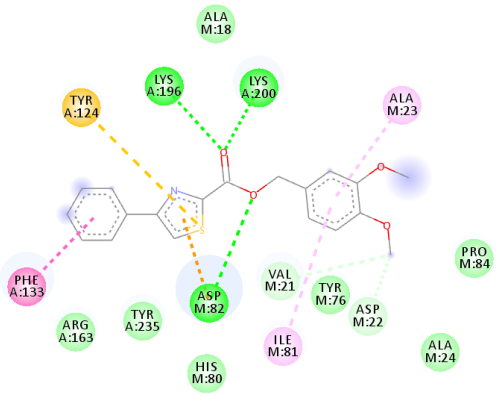


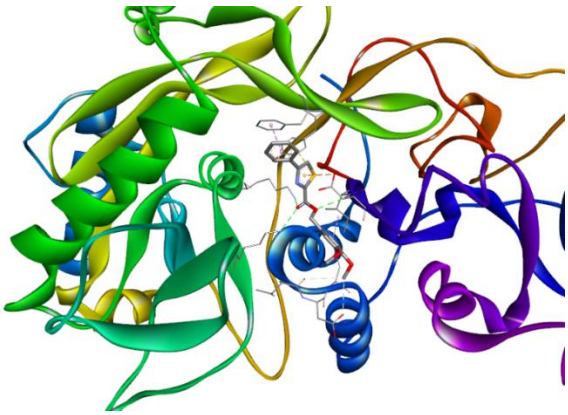
Compound 4d



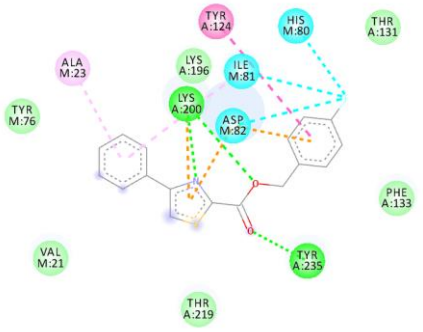


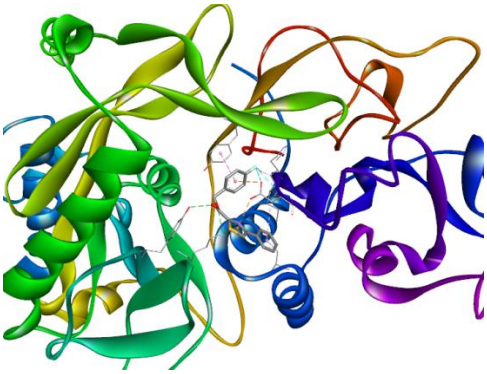
Compound 4e



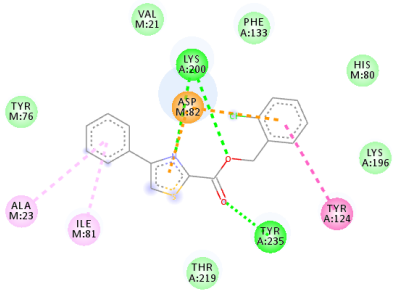


Compound 4f

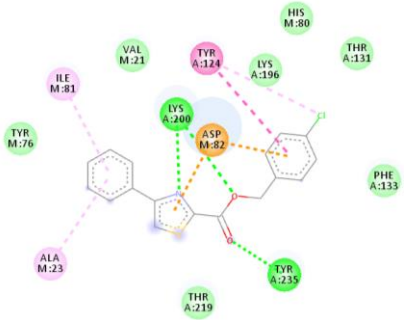




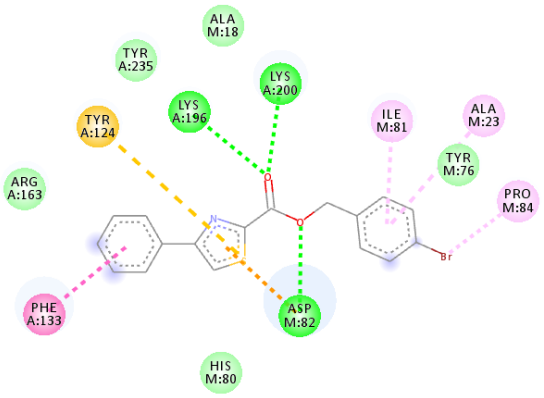
Compound 4g



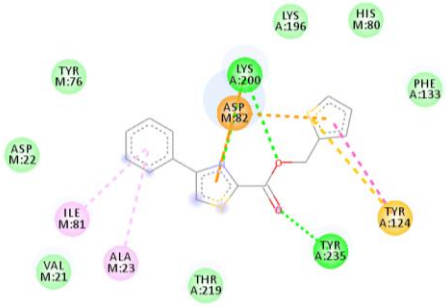
Compound 4h



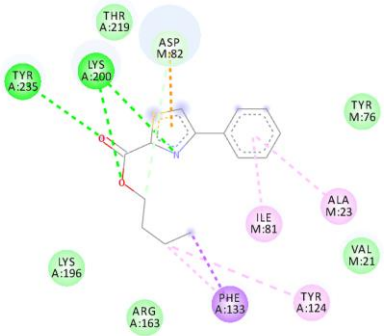
Compound 4i

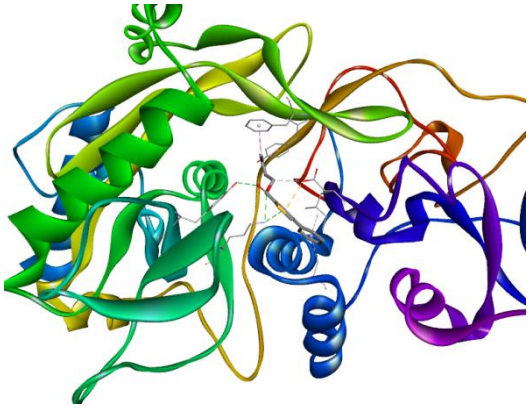


Compound 4j

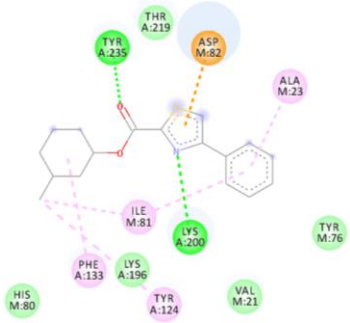


Compound 4k

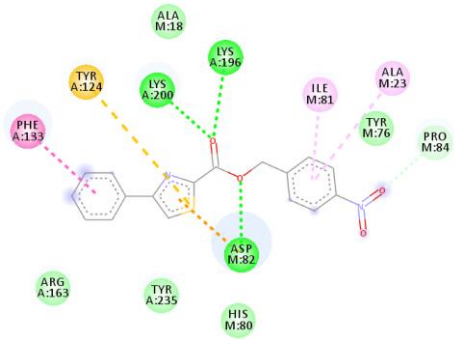


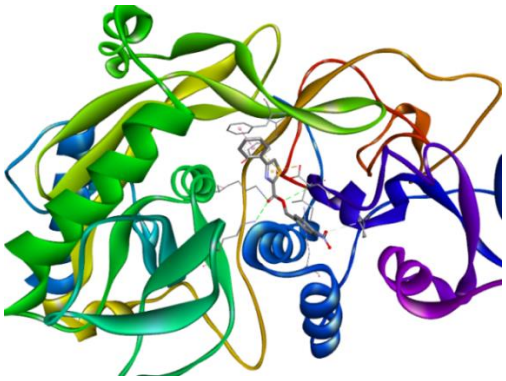


Compound 4l

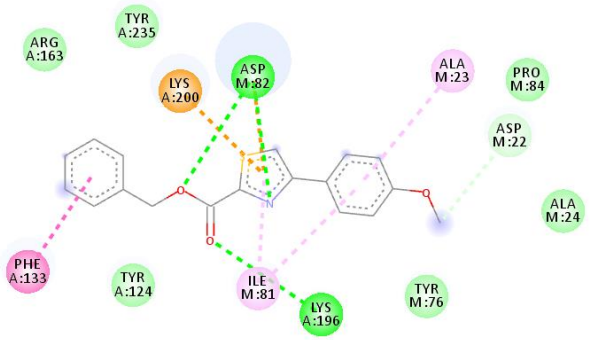


Compound 4m

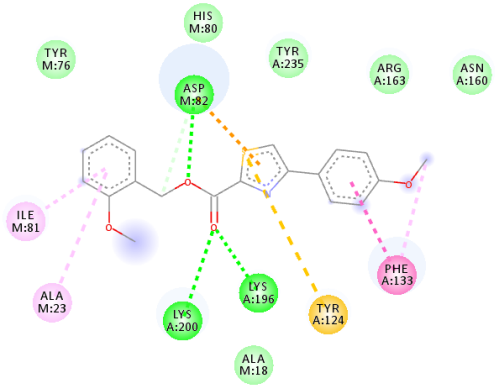




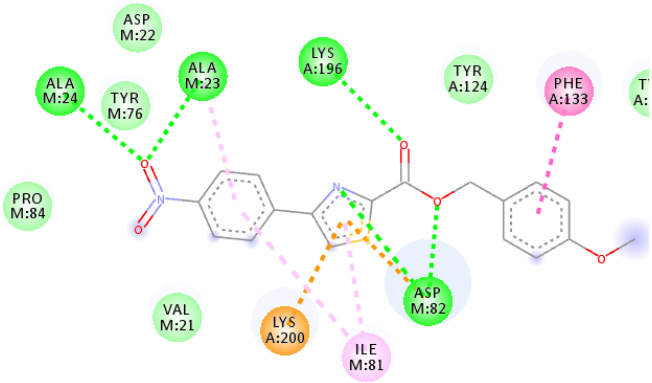
Compound 4n

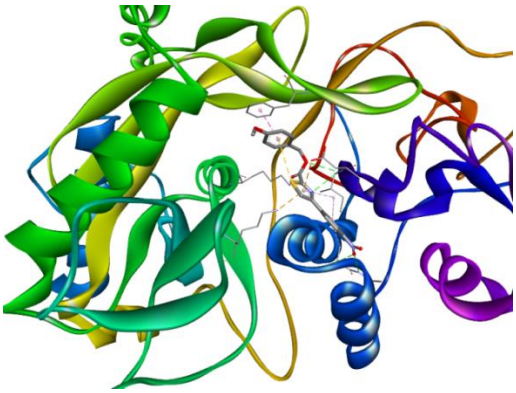


Compound 4o

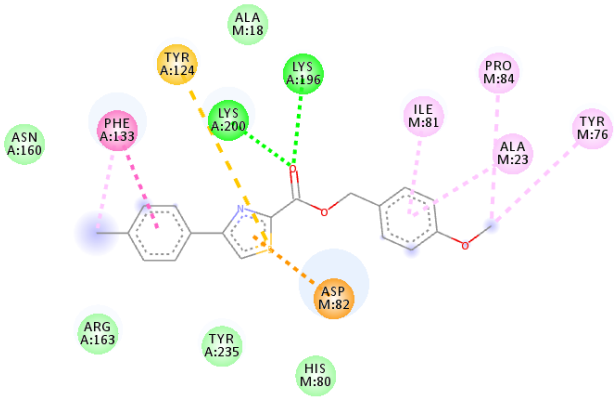


Compound 4p

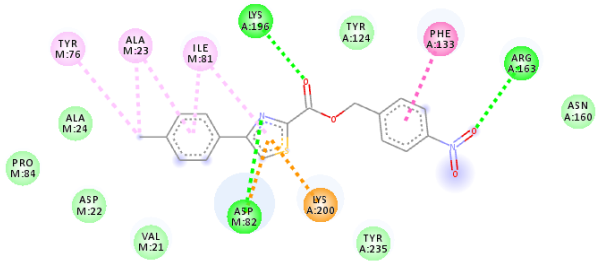


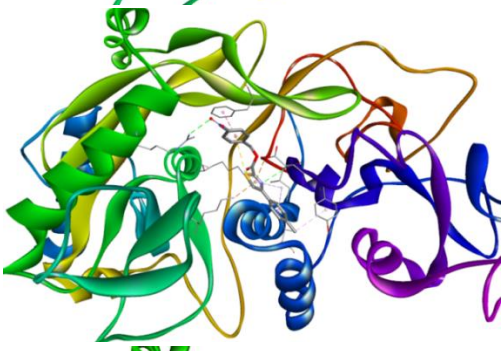


Compound 4q

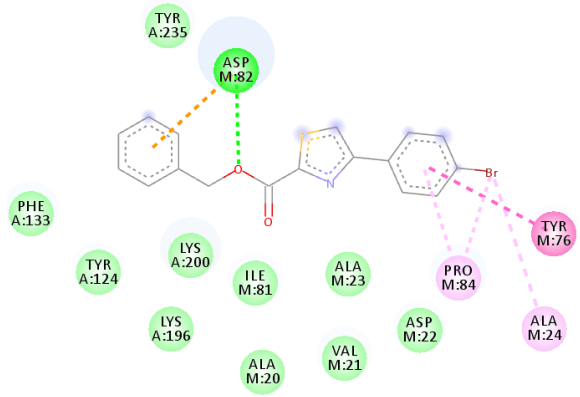


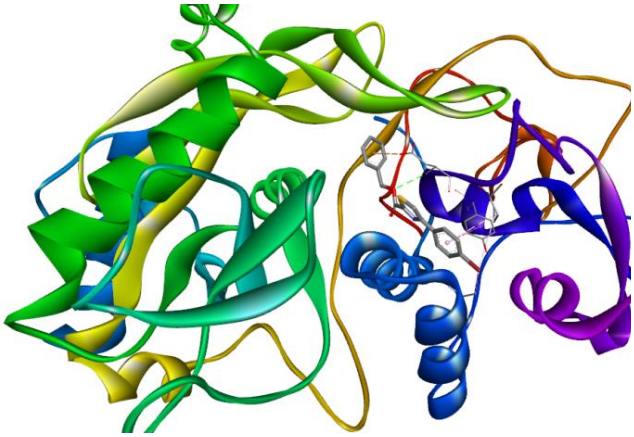
Compound 4r



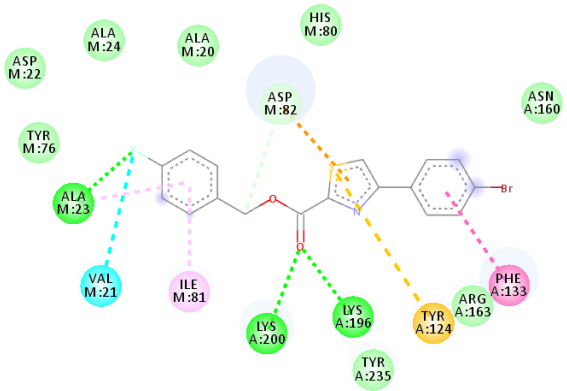


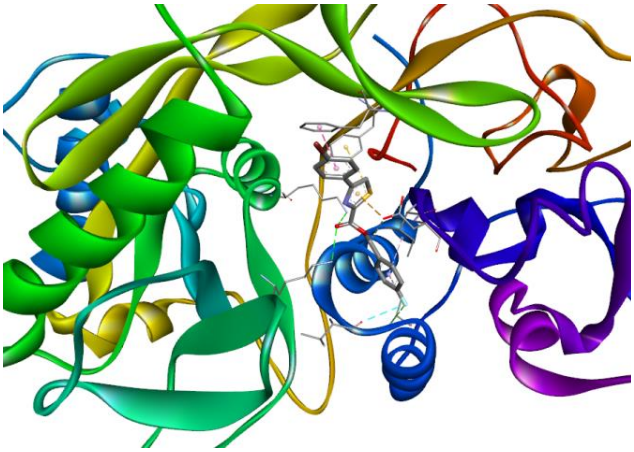
Compound 4s



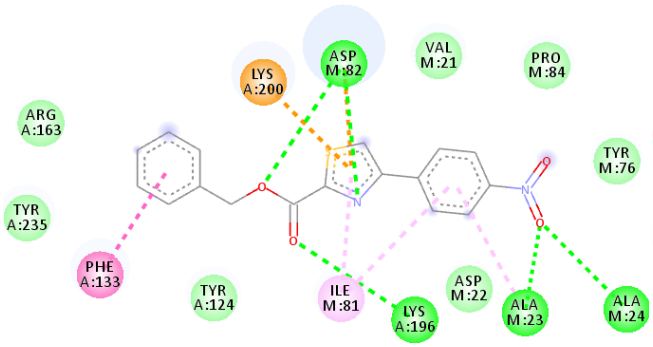


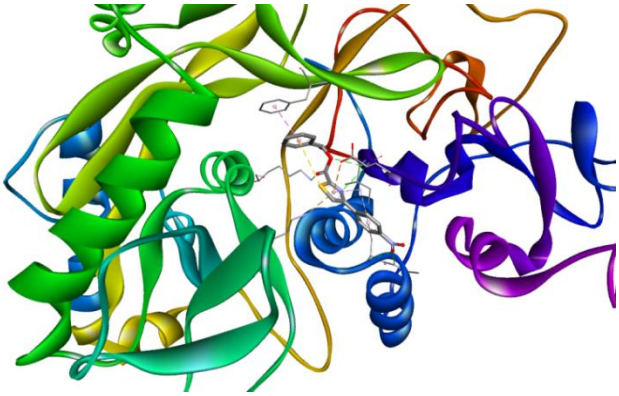
Compound 4t



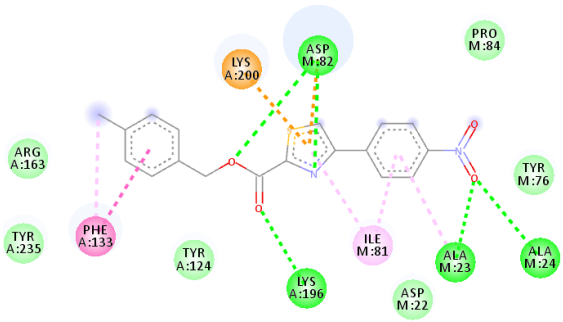


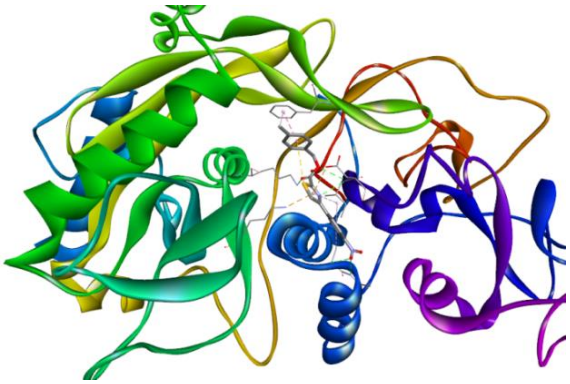
Compound 4u



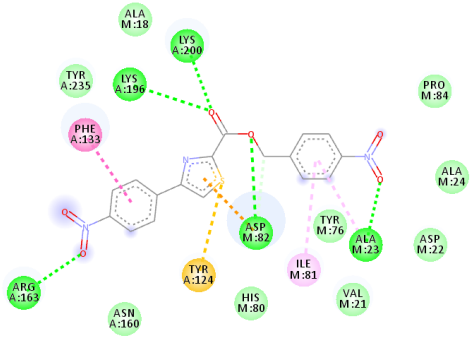


Compound 4v

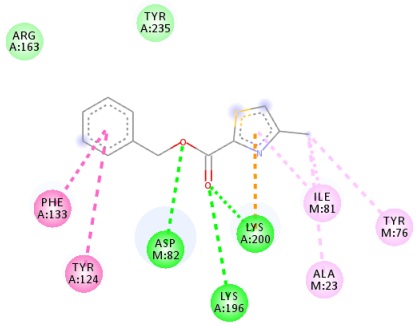


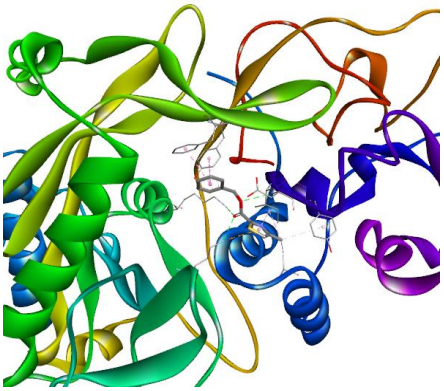


Compound 4w

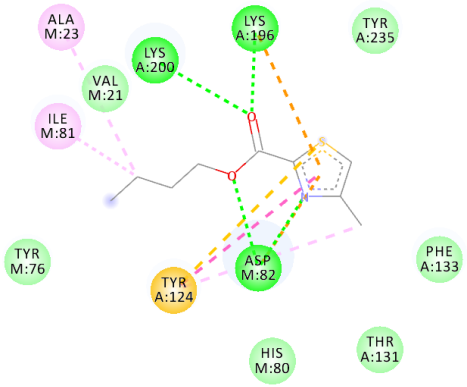


Compound 4x





Compound 4y


ALA
M:23
LYS
A:196
TYR
A:235
LYS
A:200
VAL
M:21
ILE
M:81
TYR
M:76
ASP
M:82
PHE
A:133
TYR
A:124
HIS
M:80
THR
A:131

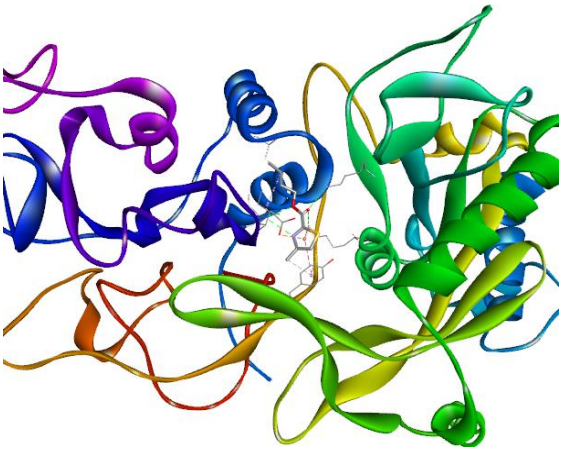
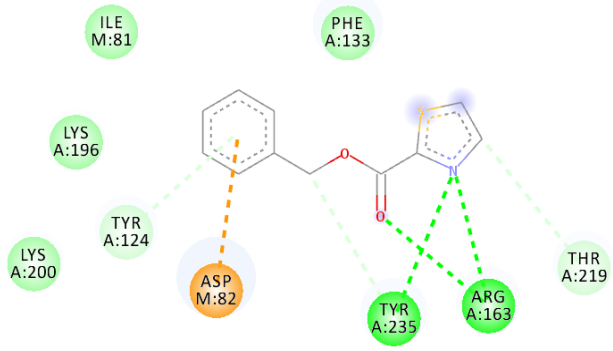
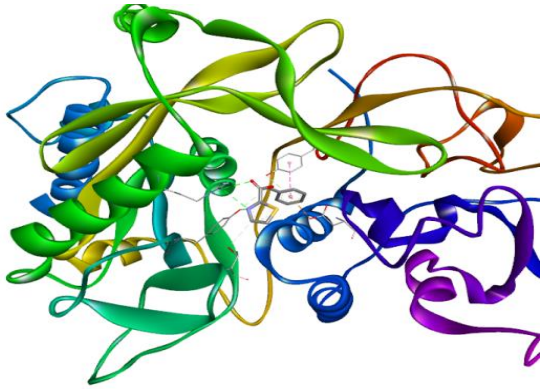


Table 2 Predicted docking scores and detailed interactions of the compounds **6a-6n**

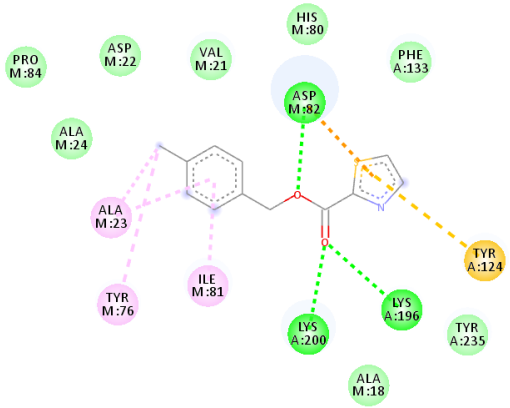
Compound	Docking score (kcal mol^{-1})	Interacting residues	
		H-Bond	**Other Interactions (Hydrophobic, Amide–π, π-σ.,)**
6a	-5.6	ARG-163, TYR-235	ILE-81, ASP-82, TYR-124, PHE-133, LYS-196, LYS-200, THR-219
6b	-6.1	ASP-82, LYS-196, LYS-200	ALA-18, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, HIS-80, ILE-81, PRO-84, TYR-124, PHE-133, TYR-235
6c	-6.3	ALA-23, ASP-82 LYS-196, LYS-200	ALA-20, VAL-21, ASP-22, ALA-24, TYR-76, ILE-81, TYR-124, PHE-133, TYR-235
6d	-6.2	ARG-163, TYR-235	ILE-81, ASP-82, TYR-124, PHE-133, LYS-196, LYS-200, THR-219, ASP-234
6e	-6.4	ALA-23, ASP-82, LYS-196, LYS-200	ALA-18, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, PRO-84, TYR-124, PHE-133, TYR-235
6f	-6.2	ALA-23, ASP-82, LYS-196, LYS-200, TYR-235	ALA-18, ALA-20, VAL-21, ASP-22, ALA-24, TYR-76, ILE-81, TYR-124, PHE-133
6g	-5.9	LYS-196	VAL-21, ILE-81, ASP-82, TYR-124, PHE-133, ARG-163, LYS-200, TYR-235
6h	-6.1	ASP-82, LYS-196, LYS-200	ALA-18, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, TYR-124, PHE-133, TYR-235
6i	-6.0	ASP-82, LYS-196, LYS-200	ALA-18, ALA-23, TYR-76, HIS-80 ILE-81, ASP-82 TYR-124, PHE-133, TYR-235
6j	-5.5	ALA-23, ALA-24, TYR-76	VAL-21, ASP-22, ILE-81, ASP-82, PRO-84, LYS-200
6k	-5.8	ASP-82, LYS-196, LYS-200	ALA-18, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, HIS-83, PRO-84, TYR-124, PHE-133
6l	-4.3	ARG-163, TYR-235	ILE-81, ASP-82, TYR-124, PHE-133, LYS-196, LYS-200
6m	-5.6	ASP-82, LYS-196, LYS-200	ALA-18, VAL-21, ALA-23, TYR-76, ILE-81, TYR-124, PHE-133, TYR-235
6n	-4.8	ARG-163, TYR-235	ILE-81, ASP-82, TYR-124, PHE-133, LYS-196, LYS-200, THR-219, ASP-234

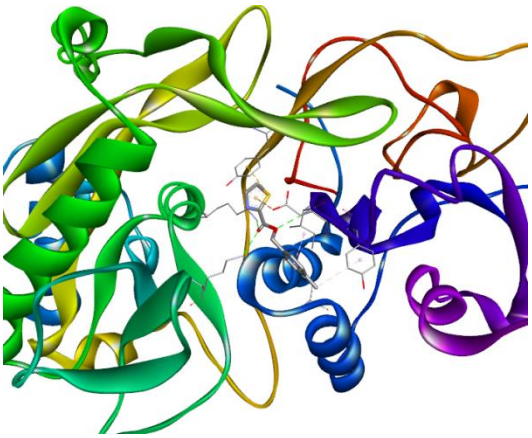
Compound 6a



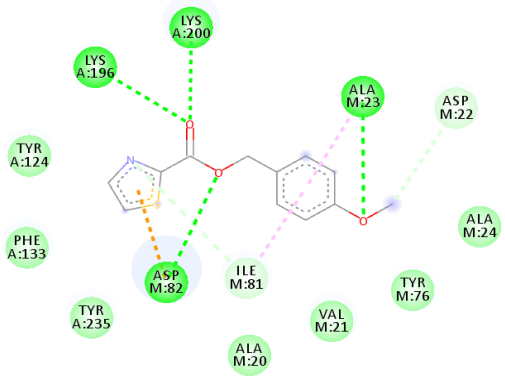


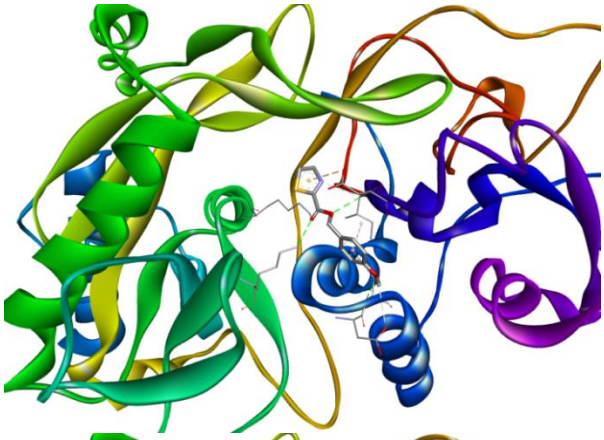
Compound 6b



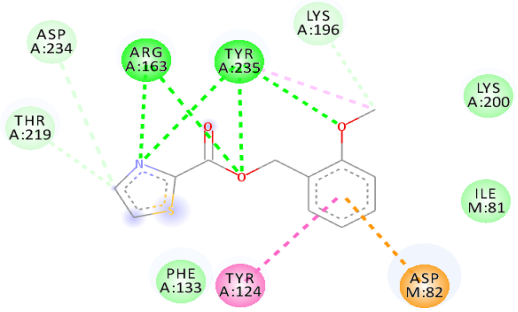


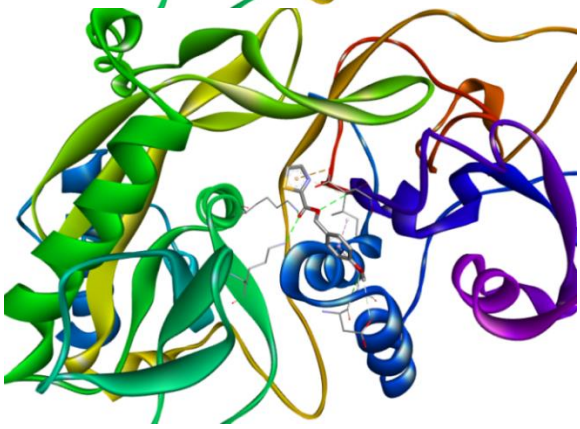
Compound 6c



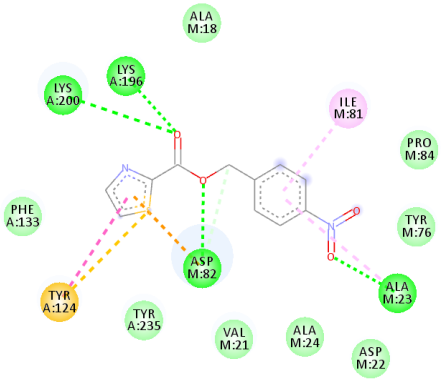


Compound 6d

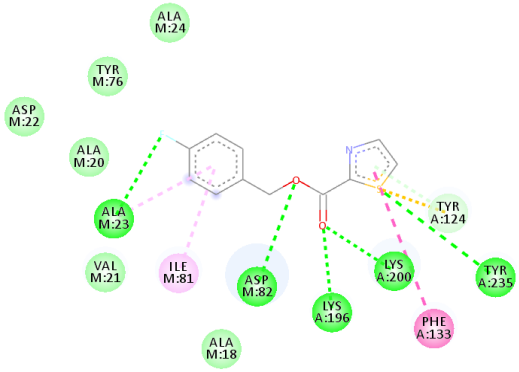




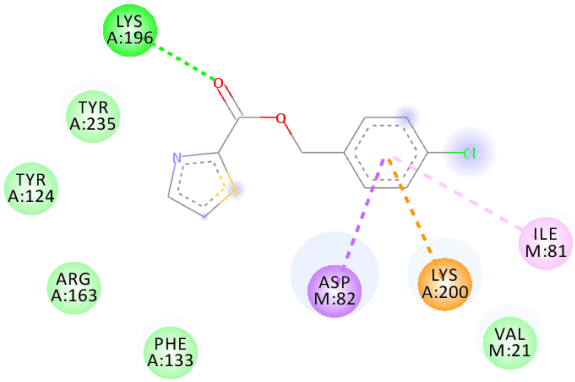
Compound 6e

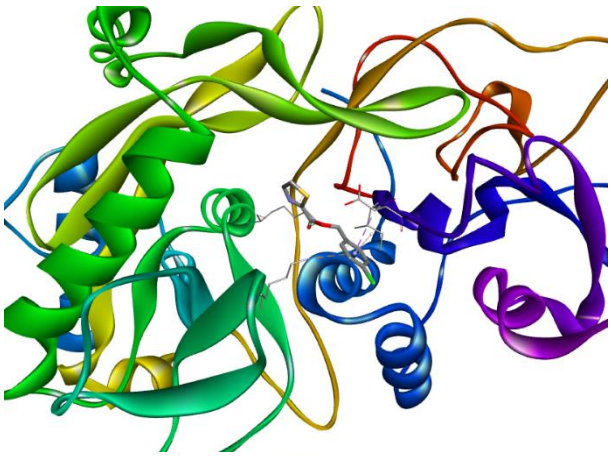


Compound 6f

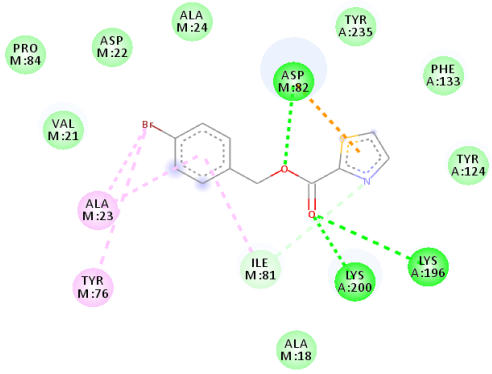


Compound 6g

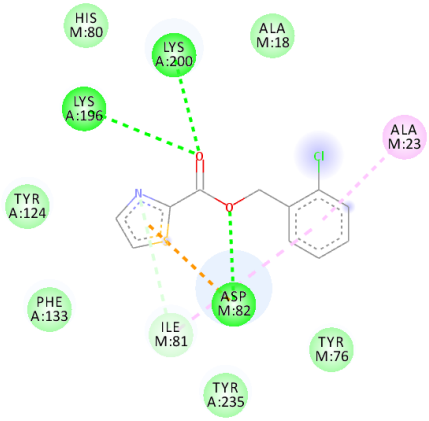




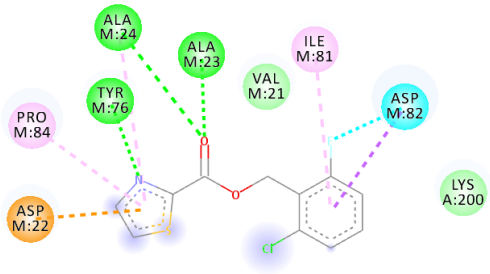
Compound 6h

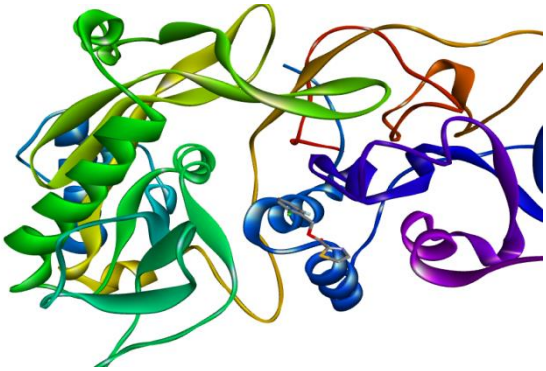


Compound 6i

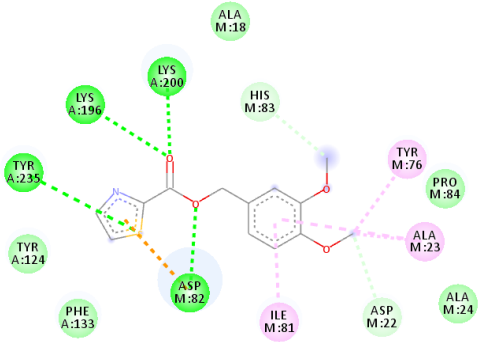


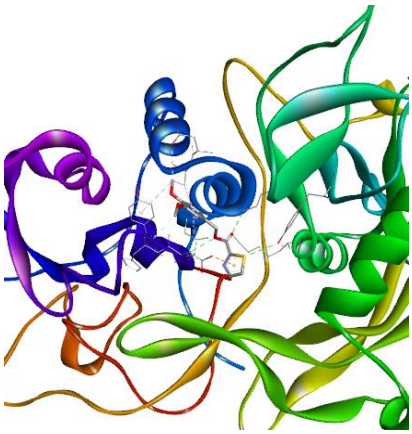
Compound 6j





Compound 6k





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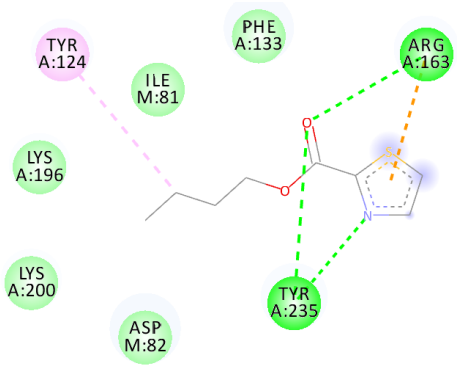
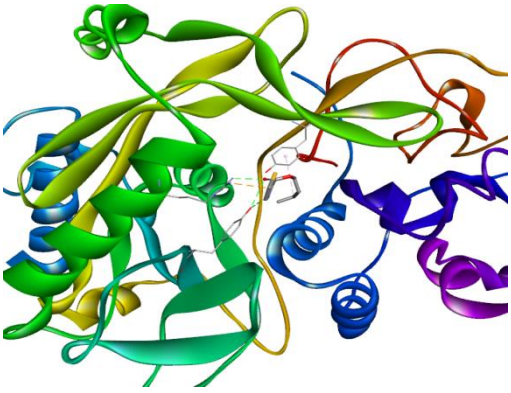
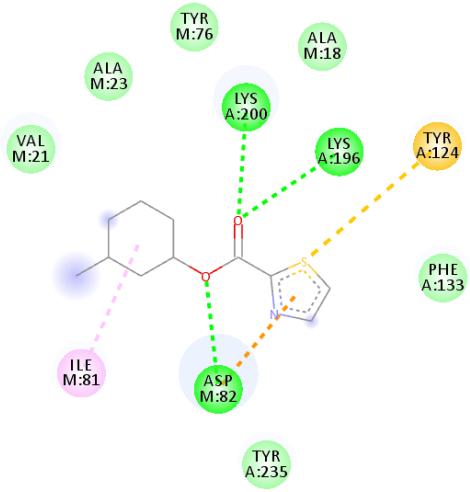
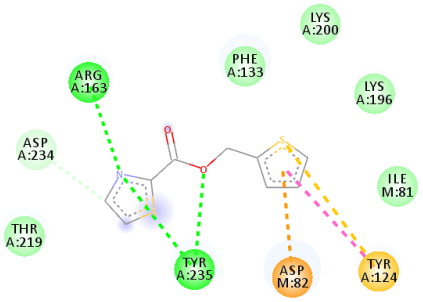




Compound 6m



Compound 6n



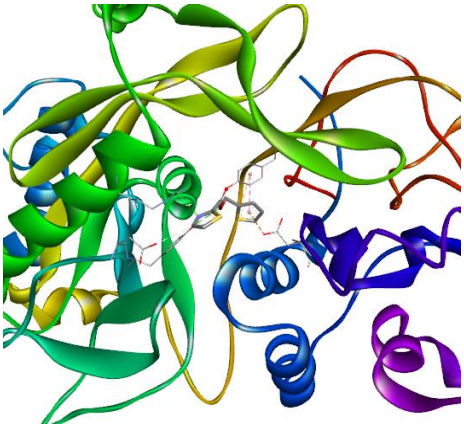
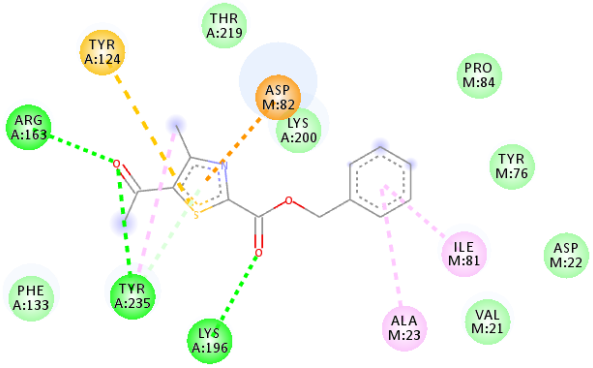
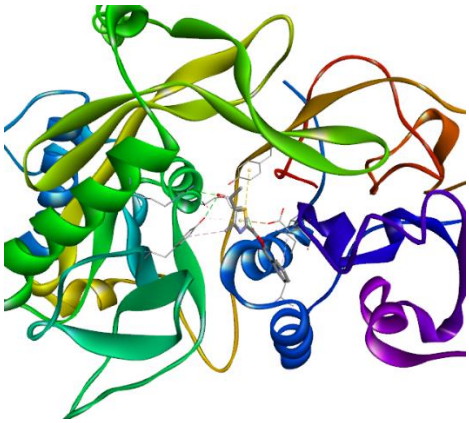


Table 3 Predicted docking scores and detailed interactions of the compounds **8a-8k**

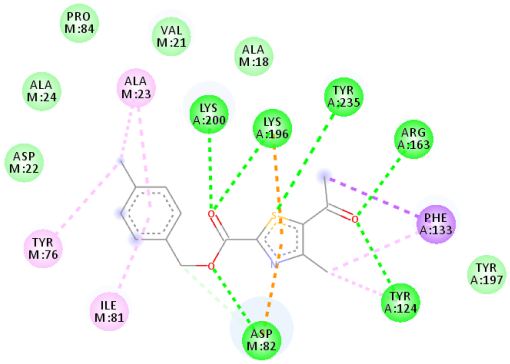
Compound	Docking score (kcal mol^{-1})	Interacting residues	
		H-Bond	**Other Interactions (Hydrophobic, Amide–π, π-σ.,)**
8a	-6.3	ARG-163, LYS-196, LYS-235	VAL-21, ASP-22, ALA-23, TYR-76, ILE-81, ASP-82, PRO-84, TYR-124, PHE-133, LYS-200, THR-219
8b	-7.4	ASP-82, TYR-124, ARG-163, LYS-196, TYR-235	ALA-18, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, PHE-133
8c	-7.2	ALA-23, ASP-82, TYR-124, ARG-163, LYS-200, TYR-235	ALA-18, VAL-21, ASP-22, ALA-24, TYR-76, ILE-81, PRO-84, PHE-133, LYS-196, TYR-197
8d	-7.2	ASP-82, TYR-124, ARG-163, LYS-196, LYS-200, TYR-235	ALA-18, ALA-23, TYR-76, ILA-81, PRO-84, PHE-133, TYR-197
8e	-6.8	ARG-163, LYS-196, LYS-200	ALA-18, VAL-21, ASP-22, ALA-23, TYR-76, ILE-81, ASP-82, PRO-84, TYR-124, PHE-133, LYS-200
8f	-6.8	ASP-82, ARG-163, LYS-196, LYS-200	VAL-21, ALA-23, TYR-76, ILE-81, TYR-124, PHE-133, TYR-235
8g	-6.3	ALA-23, ALA-24, TYR-76, ASP-82, LYS-200	VAL-21, ASP-22, ILE-81, PRO-84, PHE-217, THR-219, ASP-222
8h	-7.4	ASP-82, TYR-124, ARG-163, LYS-200, TYR-235	ALA-18, VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, ILE-81, PRO-84, PHE-133, LYS-196, TYR-197
8i	-6.9	ASP-82, LYS-200, TYR-235	ALA-20, VAL-21, ALA-23, TYR-76, PRO-84, PHE-133, ARG-163, LYS-196, TYR-197
8j	-6.6	ASP-82, LYS-200, TYR-235	VAL-21, ASP-22, ALA-23, ALA-24, TYR-76, HIS-80, ILE-81, PRO-84, TYR-124, THR-131, PHE-133, LYS-196
8k	-7.1	ASP-82, TYR-124 ARG-163, LYS-196, LYS-200	ALA-18, ASP-22, ALA-23, TYR-76, ILE-81, PRO-84 PHE-133, TYR-197, TYR-235
8l	-5.2	ASP-82, LYS-200	VAL-21, ALA-23, TYR-76, HIS-80, ILE-81, PRO-84, TYR-124, PHE-133, LYS-196, TYR-235
8m	-6.2	TYR-124, TYR-235	VAL-21, ASP-22, ALA-23, TYR-76, ILE-81, ASP-82, PRO-84, PHE-133, ARG-163, LYS-196, TYR-197, LYS-200, THR-219
8n	-5.5	ASP-82, LYS-200	ALA-18, VAL-21, ASP-22, TYR-76, ILE-81, HIS-83, PRO-84, TYR-124, PHE-133, LYS-196, ASP-234
8o	-8.0	ASP-82, LYS-196, LYS-200	VAL-21, ASP-22, ALA-23, TYR-76, ILE-81, HIS-83, PRO-84, TYR-124, PHE-133, ARG-163, PHE-217, THR-219, TYR-235
8p	-6.4	ASP-82, LYS-196, LYS-200	ALA-18, VAL-21, ASP-22, ALA-23, TYR-76, HIS-83, PRO-84, TYR-124, PHE-133, ARG-163, TYR235

Compound 8a

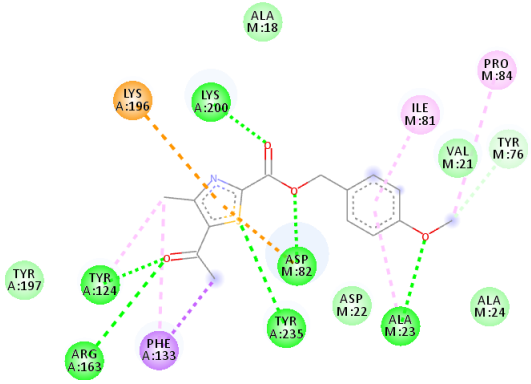


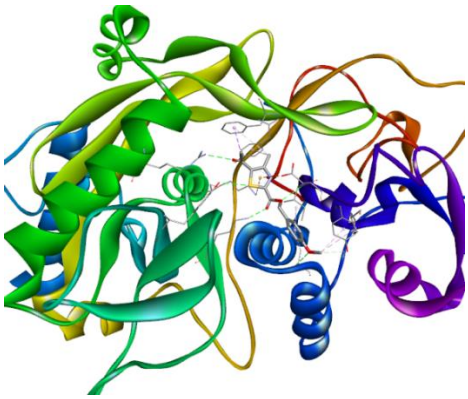


Compound 8b



Compound 8c





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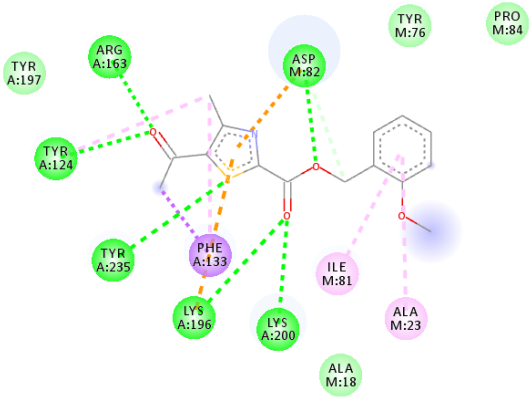
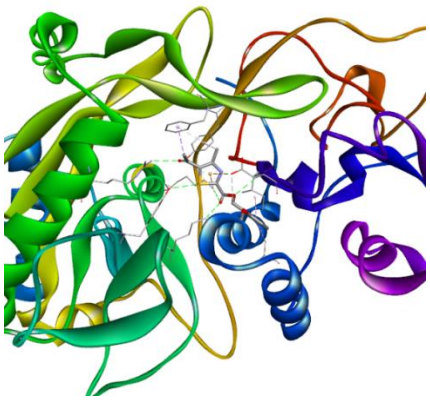
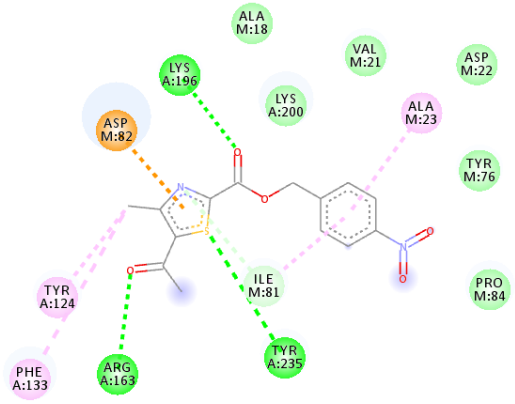
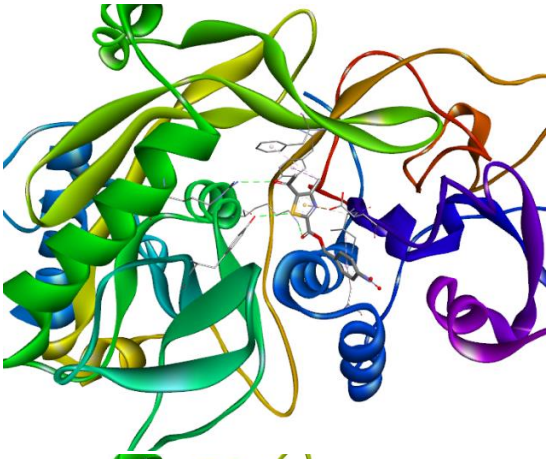


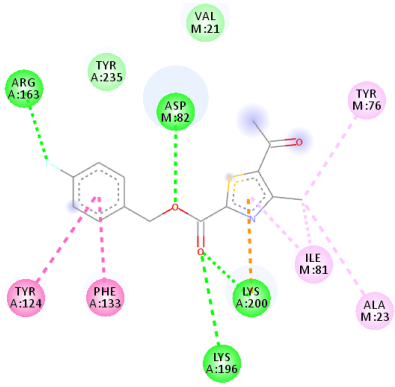


Compound 8e

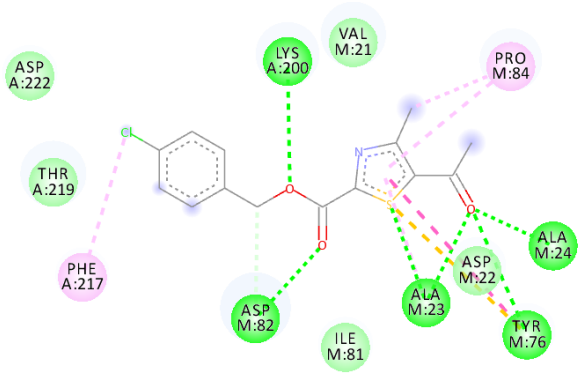




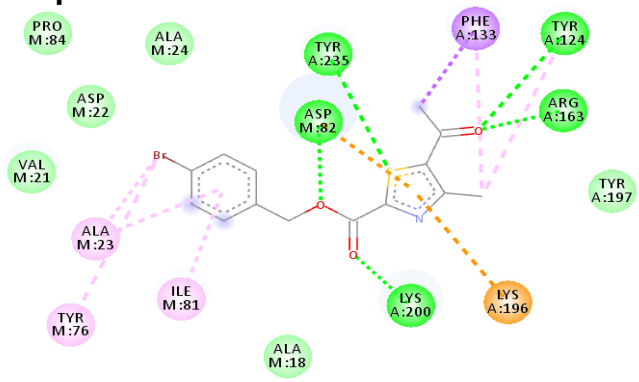
Compound 8f

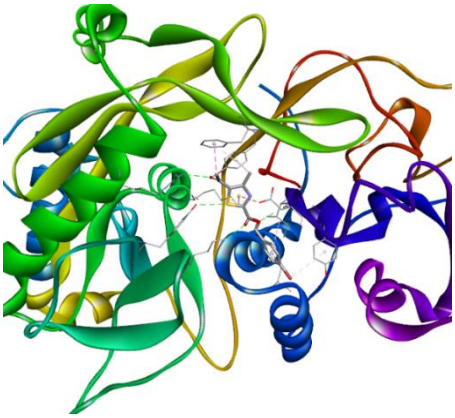


Compound 8g

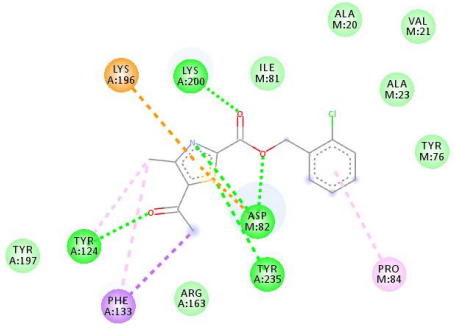


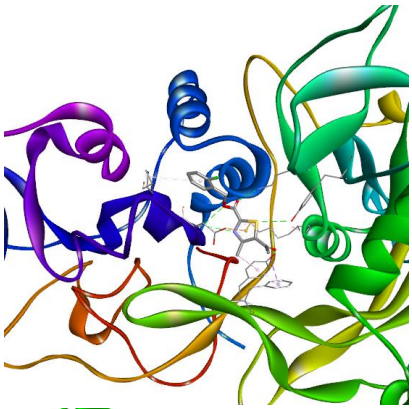
Compound 8h





Compound 8i





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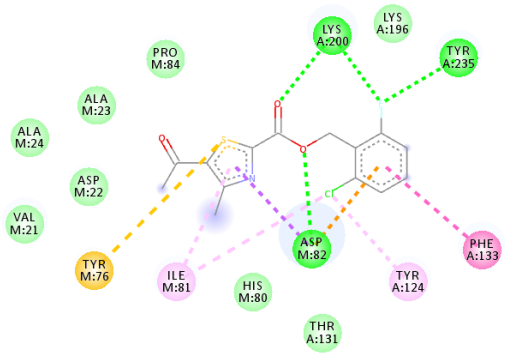
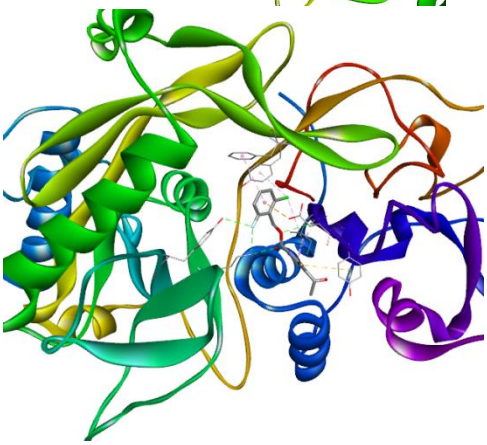
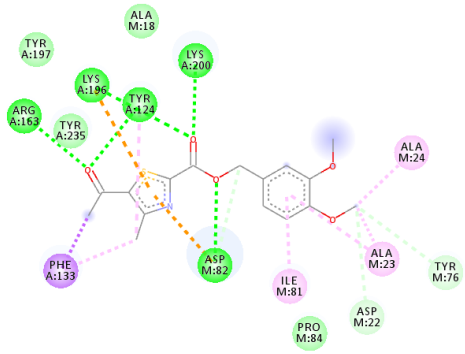
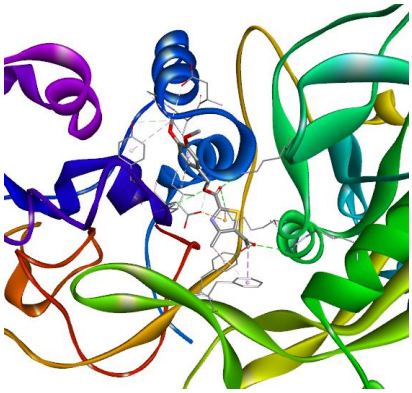




Compound 8k





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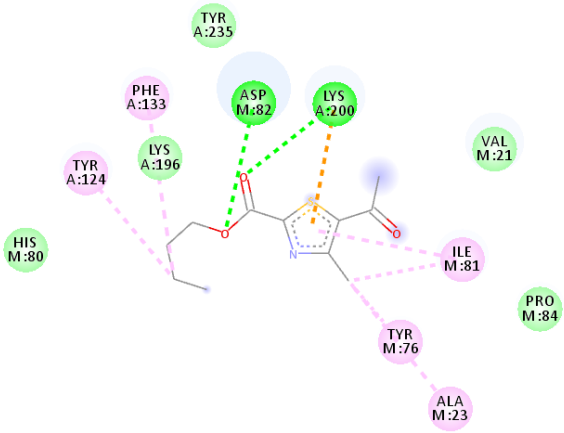
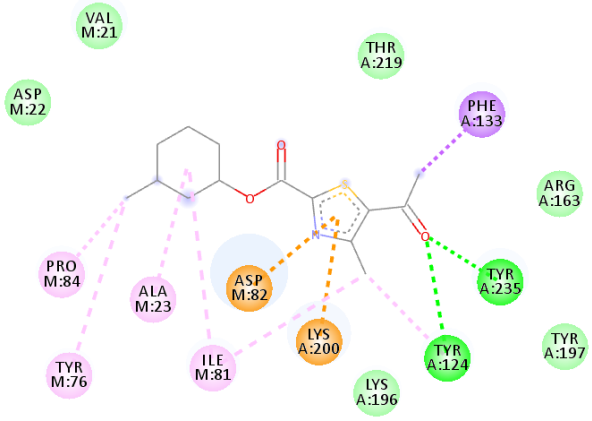
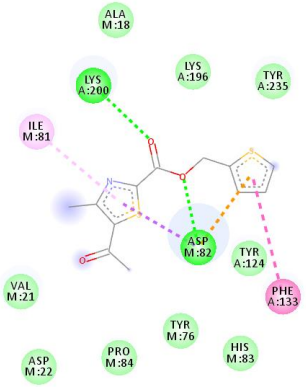
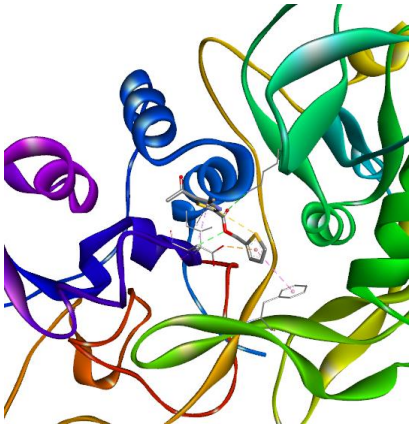


Compound 8m

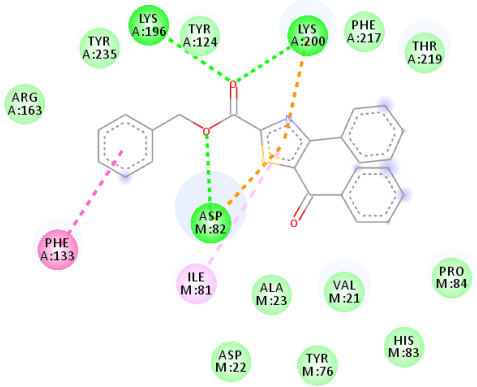


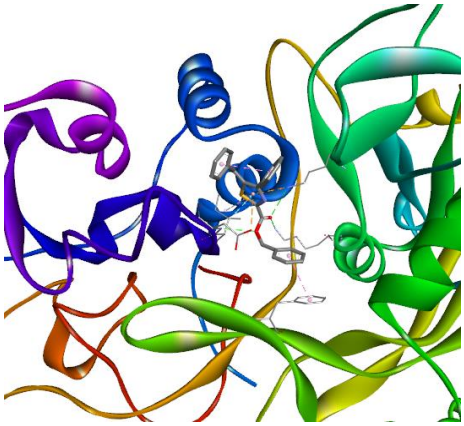
Compound 8n



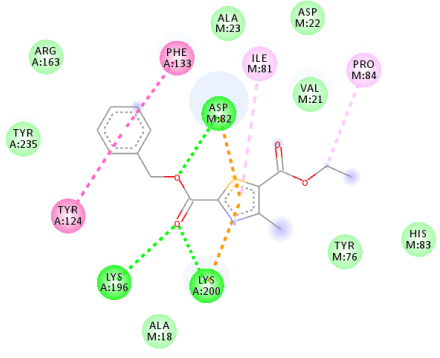


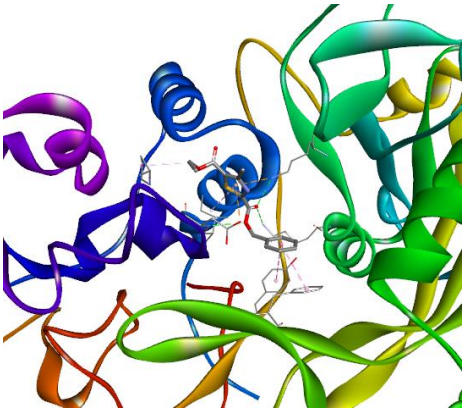
Compound 8o





Compound 8p





ADME analysis

In drug design and drug discovery, the main objective is to get hit compounds that have the desired drug properties. ADME studies are used to determine the physicochemical and pharmacokinetics parameters such as absorption, distribution, metabolism, and excretion (sometimes toxicity predictions are made to assess how likely the compound is to harm some organs-leading to ADMET). The Lipinski's rule of five was utilized to evaluate the desired drug-likeness properties and the main properties are defined as follows.

1. The Molecular weight < 500 Daltons (Da)
2. Number of hydrogen bond acceptor (HBA) < 10
3. Number of hydrogen bond donors (HBD) < 5
4. Calculated lipophilicity (Log P) in the range of -6.5 to 0.5

Table 4, Table 5 and **Table 6** provides strong evidence that the compounds **4a-4y, 6a-6n** and **8a-8p** does not violate Lipinski's rule. The calculated MW is less than 500 and both the HBA and HBD rules are within the thresholds. Closer analysis of the data in **Table 4, Table 5** and **Table 6** confirms the drug-likeness of synthesized compounds **4a-4y, 6a-6n** and **8a-8p** as the estimated parameters fall within the recommended ranges. Bioavailability score values were found to be in perfect agreement with the most important drug-likeness rules. Therefore, the pharmacological parameters of derivatives suggest that they may be excellent candidates for drug development.

Table 4 ADME predictions of compounds **4a-4y**

Compound	Molecular weight	Rotatable bonds	HBA[a]	HBD[b]	log P	Molar refractivity	log Kp (cm/s)	Bioavailability score
4a	295.36	5	3	0	2.7	83.32	-5.06	0.55
4b	309.38	5	3	0	2.94	88.28	-4.88	0.55
4c	325.38	6	4	0	2.35	89.81	-5.25	0.55
4d	325.38	6	4	0	2.35	89.81	-5.25	0.55
4e	355.41	7	5	0	2.02	96.3	-5.46	0.55
4f	313.35	5	4	0	3.09	83.27	-5.09	0.55
4g	329.41	5	3	0	3.34	88.33	-4.82	0.55
4h	329.41	5	3	0	3.2	88.33	-4.82	0.55
4i	374.25	5	3	0	3.32	91.02	-5.04	0.55
4j	301.4	4	3	0	2.18	73.25	-5.02	0.55
4k	261.34	5	3	0	2.24	81.19	-5.29	0.55
4l	301.38	5	3	0	2.93	85.56	-4.55	0.55
4m	340.35	6	5	0	2.5	92.14	-5.45	0.55
4n	325.38	6	4	0	2.35	89.81	-5.25	0.55
4o	355.41	7	5	0	2.02	96.3	-5.46	0.55
4p	370.38	7	6	0	1.39	98.63	-5.65	0.55
4q	339.41	6	4	0	2.59	94.77	-5.08	0.55
4r	354.38	6	5	0	1.92	97.1	-5.27	0.55
4s	374.25	5	3	0	3.32	91.02	-5.04	0.55
4t	392.24	5	4	0	3.71	90.97	-5.08	0.55
4u	340.35	6	5	0	2.5	92.14	-5.45	0.55
4v	354.38	6	5	0	1.92	97.1	-5.27	0.55
4w	385.35	5	3	0	2.7	83.32	-5.85	0.55
4x	233.29	4	3	0	2.65	62.85	-5.57	0.55
4y	199.27	5	3	0	2.69	52.78	-5.53	0.55
Lipinski rule	≤ 500	-	< 10	< 10	< 10	40-130	-	-

[a] Hydrogen bond acceptor. [b] Hydrogen bond donor.

Table 5 ADME predictions of compounds **6a-6n**

Compound	Molecular weight	Rotatable bonds	HBA[a]	HBD[b]	log P	Molar refractivity	log Kp (cm/s)	Bioavailability score
6a	219.26	4	3	0	2.32	57.88	-5.77	0.55
6b	233.29	4	3	0	2.58	62.85	-5.59	0.55
6c	249.29	5	4	0	2.64	64.37	-5.97	0.55
6d	249.29	5	4	0	2.58	64.37	-5.97	0.55
6e	264.26	5	5	0	2.12	66.7	-6.17	0.55
6f	237.25	4	4	0	2.46	57.84	-5.81	0.55
6g	253.7	4	3	0	2.64	62.89	-5.53	0.55
6h	298.16	4	3	0	2.73	65.58	-5.76	0.55
6i	252.9964	4	3	0	2.55	62.89	-5.53	0.55
6j	271.7	4	4	0	2.65	62.85	-5.57	0.55
6k	279.31	6	5	0	2.81	70.86	-6.17	0.55
6l	185.24	5	3	0	2.46	47.81	-5.73	0.55
6m	225.31	3	3	0	2.73	60.12	-5.27	0.55
6n	225.29	4	3	0	2.29	55.76	-6.01	0.55
Lipinski rule	≤ 500	-	< 10	< 10	< 10	40-130	-	-

[a] Hydrogen bond acceptor. [b] Hydrogen bond donor.

Table 6 ADME predictions of compounds **8a-8p**

Compound	Molecular weight	Rotatable bonds	HBA[a]	HBD[b]	log P	Molar refractivity	log Kp (cm/s)	Bioavailability score
8a	275.32	5	4	0	2.69	73.04	-5.81	0.55
8b	289.35	5	4	0	3.05	78.01	-5.64	0.55
8c	305.35	6	5	0	3.01	79.53	-6.02	0.55
8d	305.35	6	5	0	2.98	79.53	-6.02	0.55
8e	320.32	6	6	0	2.36	81.86	-6.21	0.55
8f	293.31	5	5	0	2.87	73.00	-5.85	0.55
8g	309.77	5	4	0	2.99	78.05	-5.58	0.55
8h	354.22	5	4	0	3.13	80.74	-5.81	0.55
8i	309.77	5	4	0	2.91	78.05	-5.58	0.55
8j	327.76	5	5	0	3	78.01	-5.62	0.55
8k	335.37	7	6	0	3.16	86.03	-6.22	0.55
8l	241.31	6	4	0	2.85	62.97	-5.78	0.55
8m	281.37	4	4	0	3.03	75.28	-5.32	0.55
8n	281.37	5	4	0	3.16	86.03	-6.05	0.55
8o	399.46	7	4	0	3.6	113.19	-4.5	0.55
8p	305.35	7	5	0	3.42	78.93	-5.61	0.55
Lipinski rule	≤ 500	-	< 10	< 10	< 10	40-130	-	-

[a] Hydrogen bond acceptor. [b] Hydrogen bond donor.