# Electronic Supporting Information

# *N*-Arylalkylbenzo[*d*]thiazole-2-carboxamides as anti-mycobacterial agents: Design, new methods of synthesis and biological evaluation

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## 1. General Information about Synthesis

**Materials and Instrumentation:** Chemicals and all solvents were commercially available (Aldrich Chemical, Merck AG, Fluka, Alfa Aesar and S-D Fine Chemiscals) and used without further purification. Reactions at lower temperature were performed in Julabo Cool bath. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance DX spectrometer at 400 and 100 MHz, respectively, with TMS as an internal standard and using $CDCl_3$ as solvent. The $^{1}$H NMR spectra were referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. Coupling constants were reported in hertz (Hz). $^{13}$C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent at 77.00 ppm. The abbreviations used to characterize the signals are as follows: s = singlet, m = multiplet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet,

br s = broad singlet. Mass spectra were measured in the APCI mode at an ionization potential of 70 eV with LCMS MSD (Hewlett Packard) and on a GCMS-QP 5000 (Shimadzu) (for EI) mass spectrometers; Infra-red spectra were recorded on Perkin Elmer FT-IR spectrometer in the range of 4000-600 $cm^{-1}$ either as neat samples or using KBr for preparing pellets for solid samples. Compounds were routinely checked for their purity on the silica gel GF-254 and visualized under UV at wavelength 254 nm. Melting points were measured with Gupta Scientific melting point apparatus. Evaporation of solvent was performed at reduced pressure, using a Buchi rotary evaporator.

## 2. Experimental procedure for synthesis.

### 2.1. Synthesis of ethyl benzo[*d*]thiazole-2-carboxlate (2a), ethyl 5-chlorobenzo[*d*]thiazole-2-carboxylate (2b) and ethyl 5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxylate (2c).

**Ethyl benzo[*d*]thiazole-2-carboxlate (2a).** To a magnetically stirred miceller solution of SDOSS (44 mg, 10 mol %) in demineralised water (2 mL), was added 2-aminothiophenol **1a** (0.12 mL, 1 mmol, 1 equiv) and ethyl glyoxalate (0.118 mL, 1 mmol, 1.2 equiv) and the mixture was stirred at room temperature. After completion of the reaction (5 h, TLC), the reaction mixture was extracted with EtOAc (4 × 15 mL). The combined EtOAc extracts were washed with satd brine (15 mL), dried (anhydrous $Na_2SO_4$), filtered and concentrated under vacuum rotary evaporation. The crude product was purified by passing through a column of silica gel (60-120 mesh) and eluted with hexane-EtOAc to afford the pure **2a**.[6] Following this general procedure **2b** and **2c** were prepared by the cyclocondensation of ethyl glyoxalate with 5-chloro-2-aminothiophenol **1b** and 5-trifluoromethyl-2-aminothiophenol **1c**, respectively.

**Ethyl benzo[*d*]thiazole-2-carboxylate** (**2a**): Yield: 172 mg, 83% (yellow solid), mp 68-72°C. IR (KBr) ν: 1750 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.25 (d, $J$ = 8.16 Hz, 1H), 7.97 (d, $J$ = 7.92 Hz, 1H), 7.60-7.52 (m, 2H), 4.56 (q, $J$ = 7.12 Hz, 2H), 1.49 (t, $J$ = 7.12, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 160.68, 158.57, 153.22, 136.78, 127.54, 127.09, 125.52, 122.08, 63.13, 14.29. MS (APCI) *m/z* 208.21 $(M + H)^+$.

**Ethyl 5-chlorobenzo[*d*]thiazole-2-carboxylate** (**2b**): Yield: 176 mg, 73% (yellowish solid), mp 91-93°C. IR (KBr) ν: 1743 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.24 (d, $J$ = 1.88 Hz, 1H), 7.91 (d, $J$ = 8.68 Hz, 1H), 7.53 (dd, $J$ = 8.64, 1.96 Hz), 4.57 (q, $J$ = 7.16 Hz, 2H),

1.50 (t, *J* = 7.12 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 160.33, 160.31, 153.95, 134.98, 133.28, 128.26, 125.05, 122.89, 63.37, 14.27. MS (ESI) (*m/z*) 242.23 $(M)^+$.

**Ethyl 5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxylate** (**2c**): Yield: 193 mg, 70% (white solid), mp 73-75 °C. IR (KBr) ν: 1736 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.53 (s, 1H), 8.13 (d, *J* = 8.52 Hz, 1H), 7.79 (dd, *J* = 8.52, 1.32 Hz, 1H), 4.60 (q, *J* = 7.12 Hz, 2H), 1.52 (t, *J* = 7.12 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 160.80, 160.01, 152.87, 139.93, 130.22, 129.89, 123.62, 123.59, 122.77, 122.49, 63.22, 14.05. MS (APCI) (*m/z*) 275.97 $(M+H)^+$.

## 3. Synthesis of benzothiazole-2-carboxylic acid (3a)[7]

**Route b:** Ethyl benzo[*d*]thiazole-2-carboxylate **2a** (207 mg, 1 mmol) was dissolved in minimum amount of THF and cooled at 10°C. To it solution of $LiOH{\cdot}H_2O$ (40 mg, 1 mmol, 1 equiv) in water (2 mL) was added and allowed to stir for 30 min. The reaction mixture was then filtered while cool and to the filtrate was added dil. HCl slowly untill precipitation occurred. The precipitate was filtered and dried *in vacuo* to afford **3a**. Yield: 161 mg, 90%.(white solid), mp 104-108°C (Literature report[7c]: 105 °C). IR (KBr) ν: 1708 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$D_6$): $\delta$ (ppm): 9.43 (s, 1H), 8.19 (d, *J* = 8.52 Hz, 1H), 8.12 (d, *J* = 8.44 Hz, 1H), 7.57 (dt, *J* = 1.16, 8.2 Hz, 1H), 7.51 (dt, *J* = 1.2, 8.08 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$D_6$): $\delta$ (ppm): 161.43, 159.98, 152.97, 136.26, 127.47, 127.15, 124.68, 122.99; MS (APCI) *m/z* 180 $(M + H)^+$.

**Route c:** 2-Aminothiophenol **1a** (107 mg, 1 mmol) was reacted with oxalic acid dihydrate (126 mg, 1.4 mmol, 1.4 equiv) under magnetic stirring at 100°C for 4 h. The crude product diluted with aq. HCl (6 N) and the precipitate was filtered and dried under vacuo to afford **3a** as white solid. Yield: 107 mg, 60%.

## 4. General procedure for the synthesis of compounds

**Method A**: To the two neck round bottom flask was added benzothiazole-2-carboxylic acid (179 mg, 1 mmol) and to it under inert conditions DCM (2 mL), DCC (247 mg, 1.2 mmol, 1.2 equiv) and amine (1.3 equiv), followed by drop wise addition of $Et_3N$ (0.58 mL, 4 mmol, 4 equiv) were added. The reaction mixture was stirred for 12 h under inert conditions at rt. After completion of reaction, the reaction mixture was washed with brine water to remove triethylamine. The DCM layer was then dried over anhydrous sodium sulphate followed by

concentration *in vacuo* to give crude product which was purified by column chromatography, eluting with hexane/ethyl acetate to afford pure compound (**5aa-az**).

**Method B:** To a solution of ester **2a** (207 mg, 1 mmol) in MeCN (2 mL) was added benzylamine substrates (1.2 equiv) and reaction was irradiated to microwaves in sealed vessel at 100$^{o}$C, 50 watt, 15 min. After completion of reaction, mixture was diluted with EtOAc (10 mL) and adsorbed on silica (120-240 mesh). The crude product was purified by column chromatography on silica gel using Hexane-EtOAc (95:5) as eluent to give final product (**5aa-5az**).

## Synthesis of the additional *N*-arylmethyl benzo[*d*]thiazole-2-carboxamides with chloro/trifluoromethyl substitution in the benzene ring of the benzothiazole scaffold:

**Method C:** The 5-substituted benzo[*d*]thiazole-2-carboxylate **2b**/**2c** (1 mmol) was taken in a round bottom flask (10 mL). To it the amine (1 equiv) was added along with catalytic amount (20 mol%) of $NH_4Cl$ and reaction mixture was heated at 100 ºC for 1-2 h under magnetic stirring. After completion of reaction (TLC), ice-cold water (2 mL) was added to the reaction mixture and the mixture was allowed to stir for 10 min. The solid precipitate was filtered and air dried to furnish the final product that did not require any further purification.

***N*-Benzylbenzo[*d*]thiazole-2-carboxamide (5aa)[8]:** Yield: 228 mg, 85% (white crystalline solid), mp 108-112°C. IR (KBr) ν: 3445, 1737, 1649 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.02 (d, $J$ = 7.72 Hz, 1H), 7.96 (d, $J$ = 7.48, 1H), 7.81 (br s, 1H), 7.55-7.45 (m, 2H), 7.40-7.28 (m, 5H), 4.69 (d, $J$ = 6.08, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.78, 159.82, 152.86, 137.40, 137.14, 128.83, 128.02, 127.81, 126.82, 126.74, 124.27, 122.41, 43.90. MS (APCI) *m/z* 269.03 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{12}N_2OSNa^+$ $[M + Na]^+$, calc.:291.0568; observed 291.0560.

***N*-(2-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ab**)**:** Yield: 238 mg, 83% (white crystalline solid), mp 103-105°C. IR (KBr) ν: 3445, 1737, 1646 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.06 (d, $J$ = 7.96 Hz, 1H), 7.98 (d, $J$ = 7.2 Hz, 1H), 7.80 (br s, 1H), 7.57-7.43 (m, 4H), 7.16-7.07 (m, 2H), 4.75 (d, $J$ = 6.28 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.78, 159.82, 152.86, 135.94, 129.36, 128.99, 126.91, 126.85, 124.30, 122.46, 117.66, 43.17. MS (APCI) *m/z* 287.01 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{11}FN_2OSNa^+$ $[M + Na]^+$ calc.: 309.0474; observed: 309.0469.

***N*-(3-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ac**)**:** Yield: 137 mg, 48% (light brown crystalline solid), mp 84-86°C. IR (KBr) ν: 3400, 1669, 1530 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.05 (d, *J* = 8 Hz, 1H), 7.98 (d, *J* = 7.96 Hz, 1H), 7.82 (br s, 1H), 7.57-7.48 (m, 2H), 7.35-7.30 (m, 1H), 7.16 (d, *J* = 7.52 Hz, 1H), 7.10 (d, *J* = 9.48 Hz, 1H), 7.02 (s, *J* = 7.24 Hz, 1H), 4.69 (d, *J* = 6.16 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.46, 159.95, 152.82, 139.98, 137.16, 130.43, 130.34, 126.91, 126.85, 124.32, 123.44, 122.46, 114.95, 114.84, 114.73, 114.63, 43.29. MS (APCI) *m/z* 286.96 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{12}FN_2OSNa^+$ $[M + Na]^+$, calc.: 309.0474; observed: 309.0474.

***N*-(4-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ad**)[9]**:** Yield: 249 mg, 87% (brown crystalline solid), mp 96-98°C. IR (KBr) ν: 3435, 1659, 1529 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.06 (d, *J* = 8.08 Hz, 1H), 8.08 (d, *J* = 7.76 Hz, 1H), 7.8 (br s, 1H), 7.59-7.50 (m, 2H), 7.38 (t, *J* = 7Hz, 2H), 7.07 (td, *J* = 8.52 Hz, 1.36 Hz, 2H), 4.68 (d, *J* = 5.92 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.61, 161.16, 159.85, 152.83, 137.14, 133.25, 133.22, 129.80, 129.72, 126.89, 126.82, 124.28, 122.45, 115.82, 115.60, 43.16. MS (APCI) *m/z* 287.01 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{11}FN_2OSNa^+$ $[M + Na]^+$, calc.: 309.0474; observed: 309.0470.

***N*-(2,4-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ae**)**:** Yield: 289 mg, 95% (dark brown powder), mp 119-121°C. IR (KBr) ν: 3403, 1669, 1530 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.05 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.84 Hz, 1H), 7.79 (s, 1H), 7.55-7.49 (m, 3H), 6.86 (q, 16.52, 7.84 Hz, 2H), 4.70 (d, *J* = 6.16 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.83, 159.75, 152.87, 150.90, 137.13, 134.31, 127.92, 126.82, 126.73, 125.80, 124.28, 122.44, 43.62. MS (APCI) *m/z* 327.13 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{15}H_{10}F_2N_2OSNa^+$ $[M + Na]^+$, calc.: 327.0380; observed: 327.0375.

***N*-(2,5-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5af**)**:** Yield: 292 mg, 96% (light brown powder), mp 119-121°C. IR (KBr) ν: 3407, 1673, 1527 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.06 (d, *J* = 8.16 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.56-7.26 (m, 3H), 6.88-6.85 (m, 2H), 4.71 (d, *J* = 6.16 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 159.95, 152.84, 137.15, 131.41, 126.89, 126.83, 124.33, 122.43, 111.67, 104.05, 37.24. MS (APCI) *m/z* 327.11 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{15}H_{10}F_2N_2OSNa^+$ $[M + Na]^+$, calc.: 327.0380; observed 327.0372.

***N*-(3,4-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ag**)**:** Yield: 295 mg, 97% (light brown powder), mp 129-131°C. IR (KBr) ν: 3329, 1668, 1521 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.05 (d, *J* = 8.16 Hz, 1H), 7.98 (d, *J* = 7.88 Hz, 1H), 7.83 (s, 1H), 7.58-7.49

(m, 2H), 7.24-7.12 (m, 3H), 4.65 (d, *J* = 6.16 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 163.31, 159.98, 152.79, 151.61, 149.26, 137.15, 134.55, 126.97, 124.32, 123.94, 122.49, 117.50, 116.89, 42.83. MS (APCI) *m/z* 326.77 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{15}H_{10}F_2N_2OSNa^+$ $[M + Na]^+$, calc.: 327.0380; observed: 327.0372.

***N*-(2-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ah**)**:** Yield: 205 mg, 68% (white flakes), mp 117-120°C. IR (KBr) ν: 3449, 1654, 1528 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.07 (d, *J* = 8.04 Hz, 1H), 8.01 (d, *J* = 7.88, 1H), 7.79 (s, 1H), 7.60-7.53 (m, 2H), 7.36 (s, 4H), 4.70 (d, *J* = 6.28 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm): 164.24, 159.64, 157.69, 152.95, 137.12, 129.97, 129.46, 126.72, 126.60, 125.44, 124.25, 122.39, 120.72, 110.44, 55.45. MS (APCI) *m/z* 302.95 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{11}ClN_2OSNa^+$ $[M + Na]^+$, calc.: 325.0178; observed: 325.0176.

***N*-(3-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ai**)**:** Yield: 257 mg, 85% (brown amorphous powder), mp 106-108°C. IR (KBr) ν: 3429, 1736, 1645 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.04 (d, *J* = 8.04 Hz, 1H), 7.98 (d, *J* = 7.76 Hz, 1H), 7.83 (s, 1H), 7.55-7.48 (m, 2H), 7.37 (s, 1H), 7.28 (s, 2H), 4.66 (d, *J* = 5.72 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm): 159.94, 152.81, 139.49, 130.11, 128.02, 126.90, 126.07, 124.31, 122.44, 43.26. MS (APCI) *m/z* 302.97 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{11}ClN_2OSNa^+$ $[M + Na]^+$, calc.: 325.0178; observed: 325.0174.

***N*-(4-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5aj**)**:** Yield: 254 mg, 84% (light brown crystalline solid), mp 134-136 °C. IR (KBr) ν: 3398, 1672, 1527 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.06 (d, *J* = 8.04 Hz, 1H), 7.97 (d, *J* = 7.88, 1H), 7.88 (br s, 1H), 7.56-7.47 (m, 3H), 7.41 (t, *J* = 5.04 Hz, 1H) 7.56-7.39(m, 4H), 7.26 (t, *J* = 5.32 Hz, 2H), 4.79 (d, *J* = 6.28 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.55, 159.92, 152.87, 137.15, 134.87, 133.83, 130.36, 129.68, 129.28, 127.23, 126.86, 126.79, 124.36, 122.42, 41.76. MS (APCI) *m/z* 302.92 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{11}ClN_2OSNa^+$ $[M + Na]^+$, calc.:325.0178; observed 325.0171.

***N*-(2,4-Dichlorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ak**)**:** Yield: 212 mg, 63% (pale brown solid), mp 109-113°C. IR (KBr) ν: 3358, 1673, 1525 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.79 (s, 1H), 8.05 (d, *J* = 8.53 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.35 (s, 1H), 7.31-7.24 (m, 2H), 4.88 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 158.90, 137.34, 135.84, 135.27, 133.99, 133.46, 131.50, 130.46, 129.64, 129.32, 129.18, 127.61, 127.22, 61.56. MS (APCI) *m/z* 358.07 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{15}H_{10}Cl_2N_2OSNa^+$ $[M + Na]^+$, calc.: 358.9789; observed 358.9786.

***N*-(2-Methylbenzyl)benzo[*d*]thiazole-2-carboxamide** (**5al**)**:** Yield: 212 mg, 75% (white solid powder), mp 141-143 $^{o}$C. IR (KBr) ν: 3419, 1736, 1668, 1531 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.03 (d, *J* = 8.28 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 1H), 7.58 (br s, 1H), 7.56-7.46 (m, 2H), 7.36-7.34 (m, 1H), 7.25-7.15 (m, 3H), 4.69 (d, *J* = 5.64 Hz, 2H), 2.40 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.73, 159.65, 152.87, 137.15, 136.65, 135.03, 130.69, 128.91, 127.02, 128.13, 126.74, 126.20, 128.38, 124.27, 122.43 42.08, 19.15. MS (APCI) *m/z* 282.90 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{14}N_2OSNa^+$ $[M + Na]^+$, calc.:305.0725; observed 305.0717.

***N*-(4-Methylbenzyl)benzo[*d*]thiazole-2-carboxamide** (**5am**)**:** Yield: 223 mg, 79% (brown solid flakes), mp 111-113$^{o}$C. IR (KBr) ν: 3445, 1661, 1529 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.05 (d, *J* = 7.64 Hz, 1H), 7.98 (d, *J* = 8.4, 1H), 7.74 (s, 1H), 7.58-7.49 (m, 2H), 7.30 (t, *J* = 7.92 Hz, 2H), 7.20 (d, *J* = 7.84 Hz, 2H), 4.68 (d, *J* = 5.96 Hz, 2H), 2.38 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.85, 159.75, 152.87, 137.59, 137.14, 134.33, 129.51, 128.07, 126.81, 126.72, 124.27, 122.42, 43.70, 21.14. MS (APCI) *m/z* 282.90 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{14}N_2OSNa^+$ $[M + Na]^+$, calc.: 305.0725; observed 305.0724.

***N*-(4-Methoxybenzyl)benzo[*d*]thiazole-2-carboxamide** (**5an**)**:** Yield: 253 mg, 85% (off white solid), mp 122-124$^{o}$C. IR (KBr) ν: 3394, 1668, 1530 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.02 (d, *J* = 8.04 Hz, 1H), 7.97 (d, *J* = 8.52 Hz, 1H), 7.71 (br s, 1H), 7.55-7.46 (m, 2H), 7.31 (d, *J* = 8.48 Hz, 1H), 6.89 (d, *J* = 8.52 Hz, 1H), 4.62 (d, *J* = 5.96 Hz, 2H), 3.80 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.90, 159.70, 159.29, 152.88, 137.14, 129.45, 126.80, 126.71, 124.26, 122.41, 114.23, 55.33, 43.41. MS (APCI) *m/z* 298.85 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{14}N_2O_2SNa^+$ $[M + Na]^+$, calc.: 321.0674; observed 321.0674.

***N*-(2-Methoxybenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ao**)[10]: Yield: 239 mg, 80% (brown crystalline solid). mp 134-136$^{o}$C. IR (KBr) ν: 3408, 1673, 1527 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.07 (d, *J* = 8.12 Hz, 1H), 7.98 (d, *J* = 7.92 Hz, 1H), 7.93 (br s, 1H), 7.57-7.47 (m, 2H), 7.40 (d, *J* = 7.28 Hz, 1H), 7.34-7.29 (m, 1H), 6.99-6.92 (m, 2H), 4.72 (d, *J* = 6.04 Hz, 2H), 3.93 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 164.24, 159.64, 157.69, 152.95, 137.11, 129.96, 129.22, 126.71, 125.44, 124.25, 122.39, 120.72, 110.44, 55.44, 39.63. MS (APCI) *m/z* 298.90 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{14}N_2O_2SNa^+$ $[M + Na]^+$, calc.: 321.0674; observed 321.0669.

***N*-(3,4-Dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ap**): Yield: 210 mg, 64% (white crystalline solid), mp 109-111$^{o}$C. IR (KBr) ν: 3399, 1666, 1516 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.03 (d, *J* = 8.16 Hz, 1H), 7.98 (d, *J* = 7.84 Hz, 1H), 7.70 (s, 1H),

7.47-7.56 (m, 2H), 6.91-6.95 (m, 2H), 6.85 (d, *J* = 8.08 Hz, 1H), 4.63 (d, *J* = 5.84 Hz, 2H), 3.88 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm): 163.83, 159.72, 152.87, 149.30, 148.79, 137.15, 129.92, 126.84, 124.27, 122.43, 120.49, 111.45, 55.98, 43.80. MS (APCI) *m/z* 351.04 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{17}H_{16}N_2O_3SNa^+$ $[M + Na]^+$, calc.: 351.0779; observed: 351.0783.

***N*-(2, 4-Dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide** (**5aq**)[11]: Yield: 243 mg, 74% (green crystalline solid), mp 124-126$^0$C. IR (KBr) ν: 3403, 1668, 1529 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.04 (d, *J* = 7.96 Hz, 1H), 7.95 (d, *J* = 7.48 Hz, 1H), 7.81 (s, 1H), 7.53-7.47 (m, 2H), 6.48-6.44 (m, 2H), 4.61 (d, *J* = 5.88 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 164.36, 160.80, 159.54, 158.74, 152.96, 137.11, 130.79, 126.70, 124.23, 122.40, 118.0, 104, 98.6, 55.48, 55.46, 39.23. MS (APCI) *m/z* 351.15 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{17}H_{16}N_2O_3SNa^+$ $[M + Na]^+$, calc.: 351.0779; observed 351.0779.

***N*-(3-Hydroxy-4-methoxybenzyl)benzo[*d*]thiazole-2-carboxamide** (**5ar**): Yield: 182 mg, 58% (white flakes), mp 117-119$^0$C. IR (KBr) ν: 3390, 1662, 1529 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.03 (d, *J* = 8 Hz, 1H), 7.97 (d, *J* = 8Hz, 1H), 7.72 (s, 1H), 7.57-7.54 (m, 2H), 6.96 (s, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.83 (d, 8.24 Hz, 1H), 5.69 (s, 1H), 4.60 (d, *J* = 6.28 Hz, 2H), 3.90 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.83, 159.67, 152.84, 146.23, 145.85, 137.10, 130.51, 126.82, 126.71, 124.26, 122.42, 119.81, 114.33, 110.78, 56.02, 43.54. MS (APCI) *m/z* 314.78 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{14}N_2O_3SNa^+$ $[M + Na]^+$, calc.: 337.0623; observed 337.0623.

***N*-(4-*tert*-butylbenzyl)benzo[*d*]thiazole-2-carboxamide** (**5as**): Yield: 194 mg, 60% (brown solid powder), mp 127-129$^\circ$C. IR (KBr) ν: 3407, 1668, 1530 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.04 (d, *J* = 8.24 Hz, 1H), 8.00 (d, *J* = 7.68 Hz, 1H), 7.97 (s, 1H), 7.54-7.49 (m, 2H), 7.40 (d, *J* = 8.32 Hz, 1H), 7.34 (d, *J* = 8.28 Hz, 1H), 4.66 (d, *J* = 5.96 Hz, 2H), 1.32 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.83, 159.75, 152.87, 150.90, 137.13, 134.31, 127.92, 126.82, 126.73, 125.80, 122.44, 43.62, 34.59, 31.34. MS (APCI) *m/z* 347.23 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{19}H_{20}N_2OSNa^+$ $[M + Na]^+$, calc.: 347.1194; observed 347.1196.

***N*-(4-(Trifluoromethyl)benzyl)benzo[*d*]thiazole-2-carboxamide** (**5at**): Yield: 215 mg, 64% (off white powder), mp 102-104 $^o$C. IR (KBr) ν: 3401, 1668, 1531 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.04 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 9.16 Hz, 1H), 7.98 (s, 1H), 7.62 (d, *J* = 8.12 Hz, 2H), 7.56-7.51 (m, 4H), 4.76 (d, *J* = 6.28 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$

(ppm): 163.29, 160.06, 152.80, 141.49, 137.17, 130.24, 129.92, 128.15, 126.97, 125.78, 124.33, 122.49, 43.31. MS (APCI) *m/z* 359.32 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{16}H_{11}F_3N_2OSNa^+$ $[M + Na]^+$, calc.: 359.0442; observed 359.0433.

***N*-(4-Cyanobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5au**): Yield: 188 mg, 64% (light brown powder), mp 143-146°C. IR (KBr) ν: 3334, 1669, 1531 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.05 (d, *J* = 8.16 Hz, 1H), 8.01 (d, *J* = 7.88 Hz, 1H), 7.97 (s, 1H), 7.65 (d, *J* = 8.24 Hz, 2H), 7.57-7.49 (m, 3H), 4.76 (d, *J* = 6.32 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.06, 160.18, 152.76, 142.92, 137.17, 132.64, 128.40, 127.03, 124.35, 122.51, 118.63, 111.67, 43.31. MS (APCI) *m/z* 316.13 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{16}H_{11}N_3OSNa^+$ $[M + Na]^+$, calc.: 316.0521; observed 316.0521.

***N*-(4-Nitrobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5av**): Yield: 160 mg, 51% (yellow solid). mp 151-153°C. IR (KBr) ν: 1670, 1553, 1368 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.21 (d, *J* = 8.53 Hz, 2H), 8.07 - 7.98 (m, 3H), 7.57 – 7.52 (m, 4H), 4.80 (d, *J* = 6.53 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.02, 160.22, 152.72, 147.49, 144.91, 137.13, 128.47, 127.04, 124.32, 122.49, 43.06. MS (APCI) *m/z* 314.13 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{15}H_{11}N_3O_3SNa^+$ $[M + Na]^+$, calc.: 336.0419; observed: 336.0422.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)benzo[*d*]thiazole-2-carboxamide** (**5aw**): Yield: 172 mg, 55% (light brown powder), mp 116-117°C. IR (KBr) ν: 3420, 1668, 1532 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.07 - 8.02 (m, 1H), 8.01-7.97 (m, 1H), 7.72 (br s, 1H), 7.58 - 7.48 (m, 2H), 6.90 - 6.79 (m, 2H), 6.77 - 6.83 (m, 1H), 5.97 (s, 2H), 4.61 (d, *J* = 6.09 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.73, 159.71, 152.83, 148.02, 147.25, 137.12, 131.15, 126.85, 126.76, 124.26, 122.44, 121.47, 108.65, 101.16, 43.73. MS (APCI) *m/z* 313.05 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{12}N_2O_3SNa^+$ $[M + Na]^+$, calc.: 335.0466; observed: 335.0462.

***N*-Phenethylbenzo[*d*]thiazole-2-carboxamide** (**5ax**)[12] **:**Yield: 152 mg, 54% (white solid), mp 68-72°C. IR (neat) ν: 3328, 1670, 1532 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.99 (dd, *J* = 7.4, 7.28 Hz, 2H), 7.53 – 7.25 (m, 8H), 3.76 (d, *J* = 6.04, 2H), 2.98 (s, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.94, 159.93, 152.90, 138.51, 137.13, 128.81, 128.76, 126.79, 126.79, 126.70, 124.30, 122.43, 41.15, 35.81. MS (EI) (*m/z*) 281.97 $(M)^+$.

***N*-(4-Aminophenethyl)benzo[*d*]thiazole-2-carboxamide (5ay):** Yield: 193 mg, 65% (light brown solid). mp 131-134°C. IR (KBr) ν: 3421, 1647, 1511 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.01 - 8.09 (m, 1H), 7.93 - 8.01 (m, 1H), 7.45 - 7.59 (m, 3H), 7.00 - 7.10 (m, 2H), 6.63 - 6.71 (m, 2H), 3.68 - 3.77 (m, 1H), 3.64 (br s, 2H), 2.88 (t, *J* = 7.15 Hz, 2H). $^{13}C$

NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 159.84, 152.69, 144.97, 137.09, 129.63, 126.74, 126.64, 124.27, 122.41, 115.48, 41.40, 39.41. MS (APCI) *m/z* 298 $(M + H)^+$. HRMS (ESI) *m/z* for $C_{16}H_{12}N_2O_3SNa^+$ $[M + Na]^+$, calc.: 320.0834; observed: 320.0831.

***N*-(3,4-dimethoxyphenethyl)benzo[*d*]thiazole-2-carboxamide** (**5az**): Yield: 240 mg, 70% (dark brown solid). mp 127-129°C. IR (KBr) ν: 3313, 1659, 1514 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 8.01 - 8.08 (m, 1H), 7.95 - 8.00 (m, 1H), 7.46 - 7.57 (m, 3H), 6.78 - 6.86 (m, 3H), 3.88 (d, *J* = 3.26 Hz, 6H), 3.70 - 3.78 (m, 2H), 2.89 - 2.98 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 163.06, 160.17, 152.76, 142.92, 137.16, 132.63, 128.40, 127.02, 124.34, 122.51, 118.62, 111.67, 55.92, 43.30. MS (APCI) *m/z* 316.13 $(M + Na)^+$. HRMS (ESI) *m/z* for $C_{16}H_{12}N_2O_3SNa^+$ $[M + Na]^+$, calc.: 365.0936; observed 365.0947.

***N*-Benzyl-5-chlorobenzo[*d*]thiazole-2-carboxamide** (**5ba**)**:** Yield: 239 mg, 79% (brown solid), mp 106–107 ºC. IR (KBr) ν: 3398, 1668, 1532 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.04 (d, *J* = 1.92 Hz, 1H), 7.91 (d, *J* = 8.64 Hz, 1H), 7.74 (br s, 1H), 7.49 (dd, *J* = 1.96, 8.68 Hz, 1H), 7.41-7.32 (m, 5H), 4.72 (d, *J* = 6.04 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.61, 159.44, 153.62, 137.21, 135.37, 132.95, 128.90, 128. 04, 127.91, 127.41, 123.96, 123.21, 43.95. HRMS (ESI): *m/z* for $C_{15}H_{11}ClN_2OSNa^+$ $[M + Na]^+$, calc.: 325.0178; observed: 325.0179.

**5-Chloro-*N*-(4-fluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5bd**)**:** Yield: 241 mg, 75% (yellowish solid), mp 109-110 ºC. IR (KBr) ν: 3391, 1670, 1510 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.04 (d, *J* = 1.96 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.75 (br s, 1H), 7.50 (dd, *J* = 2, 8.64 Hz, 1H), 7.30-7.40 (m, 2H), 7.10-7.03 (m, 2H), 4.68 (d, *J* = 6.16 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.45, 163.63, 159.46, 153.59, 135.36, 133.01, 129.81, 129.73, 129.61, 127.48, 123.97, 123.24, 115.88, 115.67, 43.21.

**5-Chloro-*N*-(2,5-difluorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5bf**)**:** Yield: 176 mg, 52% (yellowish solid), mp 118-119 ºC. IR (KBr) ν: 3303, 1675, 1532 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.05 (d, *J* = 2 Hz, 1H), 7.91 (d, *J* = 8.72 Hz, 1H), 7.80 (br s, 1H), 7.48 (dd, *J* = 8.68, 2 Hz, 1H), 7.17-7.13 (m, 1H), 7.08-7.02 (m, 1H) 7.00-6.95 (m, 1H), 4.72 (d, *J* = 6.36 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.09, 159.65, 158.10, 158.07, 155.69, 155.66, 153.57, 135.38, 133.05, 127.54, 124.04, 123.22, 116.79, 116.75, 116.70, 116.55, 116.51, 116.46, 116.14, 116.06, 115.90, 115.82, 37.59, 37.55. HRMS (ESI): *m/z* for $C_{15}H_9ClF_2N_2OSNa^+$ $[M + Na]^+$, calc.: 360.9990; observed: 360.9990.

**5-Chloro-*N*-(2-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bh):** Yield: 209 mg, 62% (white solid), mp 106-108ºC. IR (KBr) ν: 1672, 1531 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$

(ppm): 8.04 (d, *J* = 1.96 Hz, 1H), 7.86 (m, 2H), 7.51-7.45 (m, 2H), 7.42-7.39 (m, 1H), 7.28-7.24 (m, 2H), 4.79 (d, *J* = 6.28 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.42, 159.50, 153.62, 135.36, 134.73, 133.84, 132.96, 130.36, 129.70, 129.35, 127.41, 127.24, 124.03, 123.16, 41.83. HRMS (ESI): *m/z* for $C_{15}H_{10}Cl_2N_2OSNa^+$ $[M + Na]^+$, calc.: 358.9789; observed: 358.9789.

**5-Chloro-*N*-(3-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5bi**)**:** Yield: 199 mg, 59% (yellowish solid), mp 123-124 ºC. IR (KBr) ν: 3318, 1670, 1534 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.04 (d, *J* = 1.88 Hz, 1H), 7.92 (d, *J* = 8.64 Hz, 1H), 7.81 (br s, 1H), 7.50 (dd, *J* = 8.64, 1.96 Hz, 1H), 7.40 (s, 1H), 7.33-7.29 (m, 3H), 4.70 (d, *J* = 6.24, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.29, 159.55, 153.57, 139.30, 135.38, 134.71, 133.03, 130.15, 128.07, 128.02, 127.50, 126.06, 123.99, 123.22, 43.29. MS (EI) (*m/z*) 337 $(M)^+$.

**5-Chloro-*N*-(4-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide** (**5bj**): Yield: 189 mg, 56% (yellowish solid), mp 130-132ºC. IR (KBr): $\tilde{\nu}$ 3403, 1665, 1536 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.01 (s, 1H), 7.89 (d, *J* = 8.04 Hz, 1H), 7.76 (br s, 1H), 7.46 (d, *J* = 7.48 Hz, 1H), 7.33 (s, 4H), 4.66 (d, *J* = 4.68 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.40, 159.54, 153.60, 135.81, 135.37, 133.77, 133.04, 129.35, 129.03, 127.50, 123.98, 123.23, 43.23. HRMS (ESI): *m/z* for $C_{15}H_{10}Cl_2N_2OSNa^+$ $[M + Na]^+$, calc.: 358.9789; observed: 358.9786.

**5-Chloro-*N*-(2-methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5bo):** Yield: 210 mg, 63% (White solid), mp 131-133ºC. IR (KBr) ν: 3407, 1673, 1532 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.06 (d, *J* = 1.88 Hz, 1H), 7.89 (m, 2H), 7.47 (dd, *J* = 2, 8.64 Hz, 1H), 7.39 (dd, *J* = 7.36, 1.44, Hz, 1H), 7.35-7.31 (m, 1H),6.99-6.94 (m, 2H), 4.71 (d, *J* = 6.16 Hz, 2H), 3.95 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 166.12, 159.20, 157.70, 153.72, 135.36, 132.80, 129.99, 129.30, 127.21, 125.30, 123.95, 123.15, 120.75, 110.47, 55.46, 39.77. MS (EI) (*m/z*) 331.87 $(M)^+$. HRMS (ESI): *m/z* for $C_{16}H_{13}ClN_2O_2SNa^+$ $[M + Na]^+$, calc.: 355.0284; observed: 355.0284.

**5-Chloro-*N*-(3,4-dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide** (**5bp**)**:** Yield: 229 mg, 63% (yellowish solid), mp 118-119 ºC. IR (KBr) ν: 3399, 1667, 1516 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 8.64 Hz, 1H), 7.70 (br s, 1H), 7.49 (dd, *J* = 1.96, 8.64 Hz, 1H), 6.98–6.86 (m, 3H), 4.65 (d, *J* = 6 Hz, 2H), 3.92-3.90 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.67, 159.32, 153.63, 149.27, 148.79, 135.35, 132.95, 129.72, 127.40, 123.95, 123.20, 120.48, 111.37, 111.28, 55.97, 55.84, 43.85.

***N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5-chlorobenzo[*d*]thiazole-2-carboxamide (5bw):** (**5bw**)**:** 225 mg, 65% (yellowish solid), mp 124-127 ºC. IR (KBr) ν: 3304, 1660, 1535 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.02 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.66 (br s, 1H), 7.47 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.88-6.78 (m, 3H), 5.96 (s, 2H), 4.59 (d, *J* = 5.96 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.61, 159.33, 153.62, 148.07, 147.33, 135.37, 132.96, 131.01, 127.41, 123.96, 123.20, 121.48, 108.62, 108.46, 101.19, 43.79. HRMS (ESI): *m/z* for $C_{16}H_{11}ClN_2O_3SNa^+$ $[M + Na]^+$, calc.: 369.0077; observed: 369.0077.

***N*-(4-Aminophenethyl)-5-chlorobenzo[*d*]thiazole-2-carboxamide** (**5by**)**:** Yield: 242 mg, 73% (white solid), mp 130-132ºC. IR (KBr) ν: 3352, 1668, 1517 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.01 (d, *J* = 1.88 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.55 (br s, 1H), 7.45 (dd, *J* = 8.64, 2, Hz, 1H), 7.05 (d, *J* = 8.28 Hz, 2H), 6.68 (d, *J* = 8.32 Hz, 2H), 3.74-3.69 (m, 4H), 2.87 (t, *J* = 7.12 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.99, 159.45, 153.68, 145.12, 135.33, 132.81, 129.58, 128.16, 127.21, 123.95, 123.13, 115.49, 41.43, 34.82. MS (EI) (*m/z*) 332 $(M)^+$. HRMS (ESI): *m/z* for Chemical Formula: $C_{16}H_{14}ClN_3OSNa^+$ $[M + Na]^+$, calc.: 354.0444; observed: 354.0449.

**5-Chloro-*N*-(3,4-dimethoxyphenethyl)benzo[*d*]thiazole-2-carboxamide (5bz):** Yield: 245 mg, 65% (yellowish solid), mp 155-157ºC. IR (KBr) ν: 3393, 1671, 1516 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.99 (d, *J* = 1.88 Hz, 1H), 7.87 (d, *J* = 8.64 Hz, 1H), 7.54 (br s, 1H), 7.45 (dd, *J* = 8.64, 1.96 Hz, 1H), 6.86-6.79 (m, 3H), 3.88 (d, *J* = 2.72 Hz, 6H), 3.75 (q, *J* = 6.88 Hz, 2H), 2.93 (t, *J* = 7.08 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.80, 159.46, 153.60, 149.06, 147.81, 135.28, 132.87, 130.87, 127.30, 123.89, 123.19, 120.69, 111.91, 111.45, 55.92, 55.85, 41.25, 35.29. HRMS (ESI): *m/z* for $C_{18}H_{17}ClN_2NaO_3S$ $[M + Na]^+$, calc.: 399.0546; observed: 399.0546.

***N*-Benzyl-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5ca) :** Yield: 279 mg, 83% (white solid), mp 76-79ºC. IR (KBr) ν: 3318, 1669, 1533 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.30 (s, 1H), 8.10 (d, *J* = 8.44 Hz, 1H), 7.88 (br s, 1H), 7.72 (d, *J* = 8.36 Hz, 1H), 7.41-7.34 (m, 5H), 4.74 (d, *J* = 6 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 166.09, 159.29, 152.35, 140.32, 137.18, 129.69, 129.37, 128.89, 128.00, 127.92, 125.29, 123.24, 123.05, 123.02, 122.99, 122.95, 122.58, 121.63, 121.59, 121.55, 121.51, 44.0. HRMS (ESI): *m/z* for $C_{16}H_{11}F_3N_2OSNa^+$ $[M + Na]^+$, calc.: 359.0442; observed: 359.0445.

***N*-(4-Fluorobenzyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cd) :** Yield: 276 mg, 78% (white solid), mp 70-73ºC. IR (KBr) ν: 3327, 1670, 1537 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.32 (s, 1H), 8.13 (d, *J* = 8.36 Hz, 1H), 7.82 (br s, 1H), 7.75 (d, *J* =

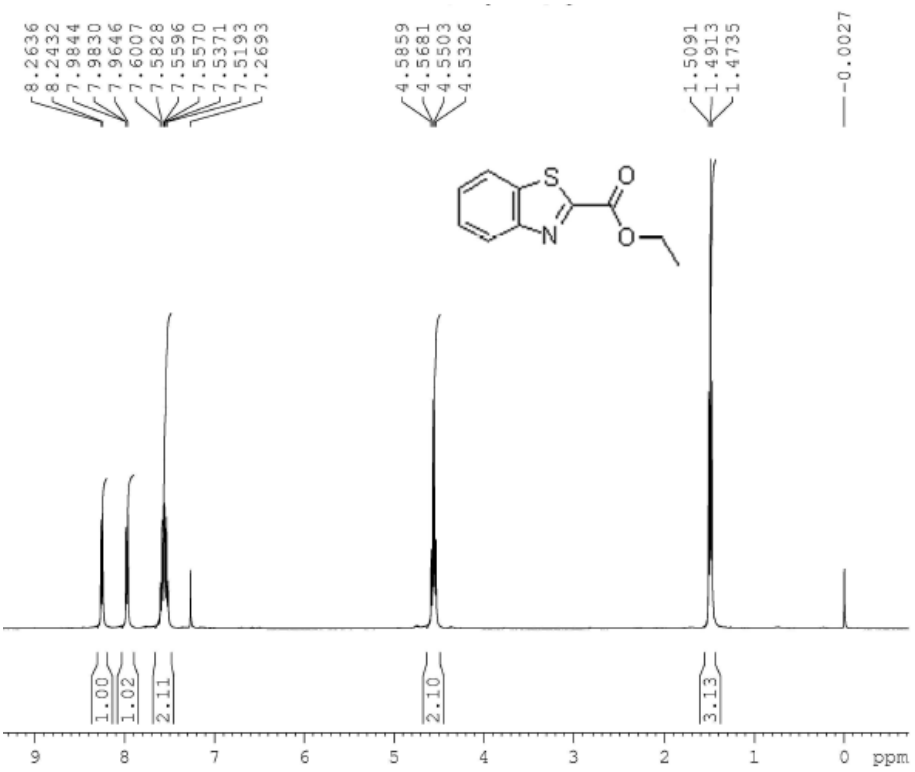
8.28 Hz, 1H), 7.41-7.38 (m, 2H), 7.08 (t, *J* = 8.32 Hz, 2H) 4.71 (d, *J* = 5.72 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 165.88, 163.65, 161.20, 159.29, 152.33, 140.32, 133.00, 132.97, 129.79, 129.71, 123.27, 123.14, 123.11, 123.08, 123.04, 121.66, 121.62, 121.58, 121.54, 115.89, 115.68, 43.26. HRMS (ESI): *m/z* for $C_{16}H_{10}F_4N_2OSNa^+$ $[M + Na]^+$ calc.: 377.0348; observed: 377.0343.

***N*-(4-Aminophenethyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cy):** Yield: 197 mg, 54% (yellowish solid), mp 123-126 ºC. IR (KBr) ν: 1668, 1520 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): $\delta$ 8.32 (s, 1H), 8.10 (d, *J* = 8.08 Hz, 1H), 7.72 (d, *J* = 8.00 Hz, 1H), 7.55 (br s, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.69 (d, *J* = 6.92, 2H), 3.75-3.58 (m, 4H), 2.90 (d, *J* = 6.52 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 166.33, 159.28, 152.42, 145.10, 140.32, 129.62, 129.29, 128.12, 125.34, 123.21, 122.94, 122.91, 122.89, 122.84, 121.68, 121.63, 121.59, 121.56, 115.54, 41.46, 34.79. HRMS (ESI): *m/z* for $C_{17}H_{15}F_3N_3OS$ $[M + H]^+$, calc.: 366.0888; observed: 366.0887.

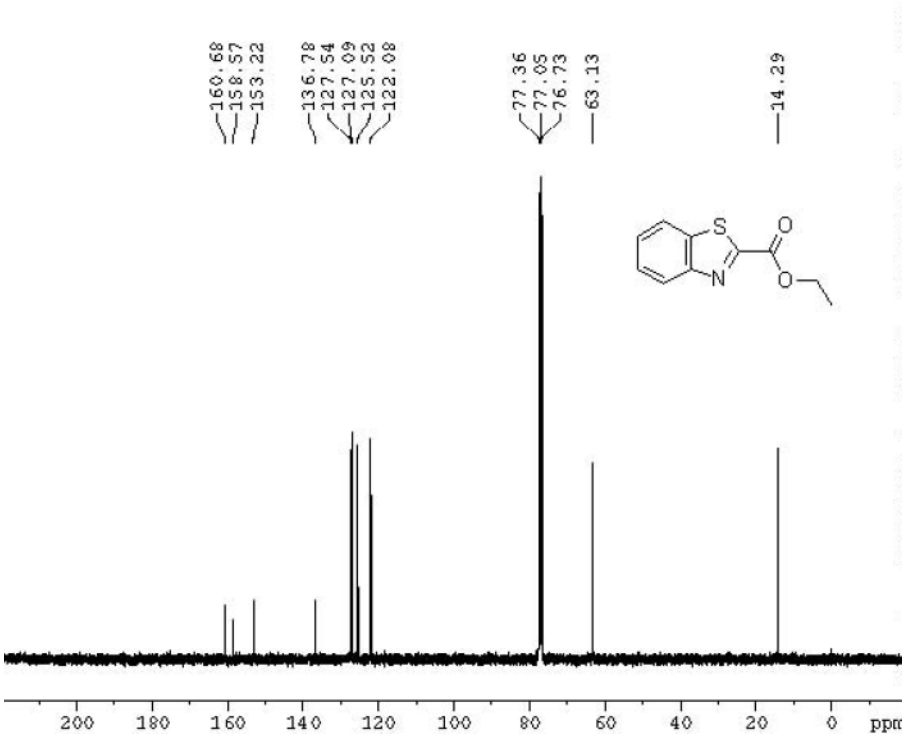
***N*-(3,4-Dimethoxyphenethyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cz):** Yield: 287 mg, 70% (white solid), mp 110-113 ºC. IR (KBr) ν: 3402, 1672, 1519 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 8.33 (s, 1H), 8.12 (d, *J* = 8.28 Hz, 1H), 7.75 (d, *J* = 8.12 Hz, 1H), 7.53 (br s, 1H), 6.89-6.81 (m, 3H), 3.91 (s, 6H)3.79 (q, *J* = 6.24 Hz, 2H), 2.96 (t, *J* = 6.68 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 166.21, 159.28, 152.40, 149.14, 147.90, 140.32, 130.79, 129.73, 123.24, 123.03, 123.00, 122.96, 122.93, 121.64, 121.61, 121.57, 121.53, 120.71, 111.93, 111.52, 55.95, 55.88, 41.27, 35.29. HRMS (ESI): *m/z* for $C_{19}H_{18}F_3N_2O_3S$ $[M + H]^+$ calc.: 411.0990; observed: 411.0993.

# 5. Scanned NMR spectral data of unknown compounds

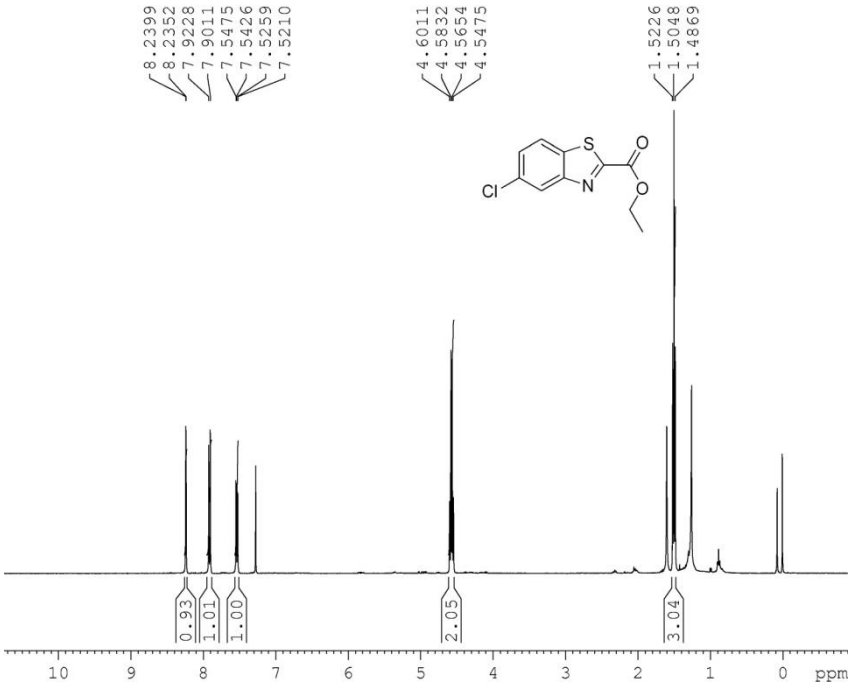
## 5.1. $^{1}$H NMR of Ethyl benzo[*d*]thiazole-2-carboxlate (2a):



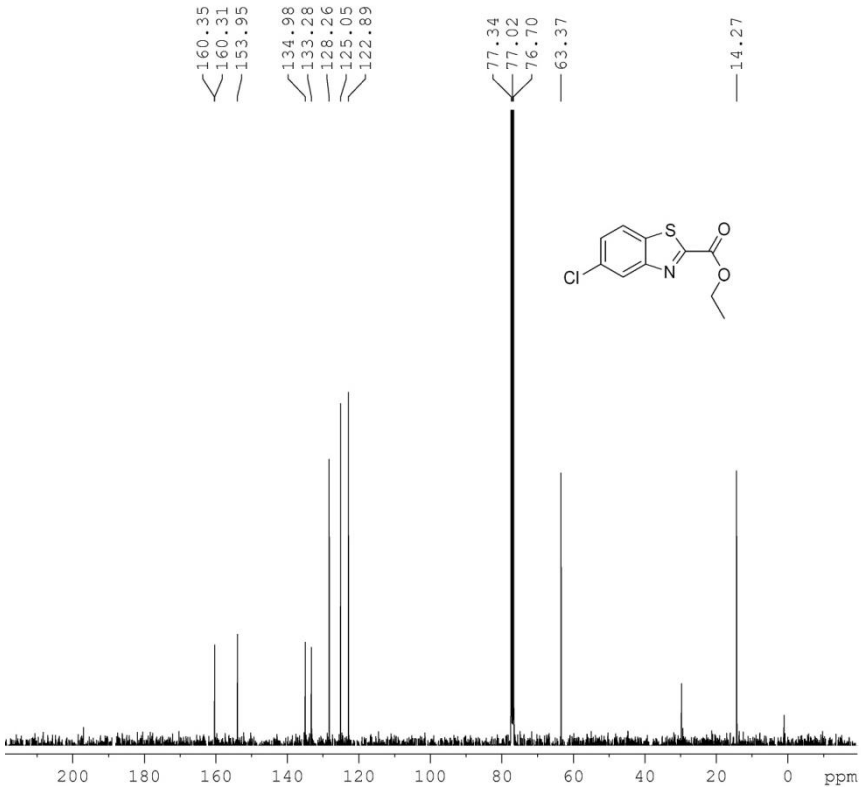

## 5.2. $^{13}$C NMR of Ethyl benzo[*d*]thiazole-2-carboxlate (2a):



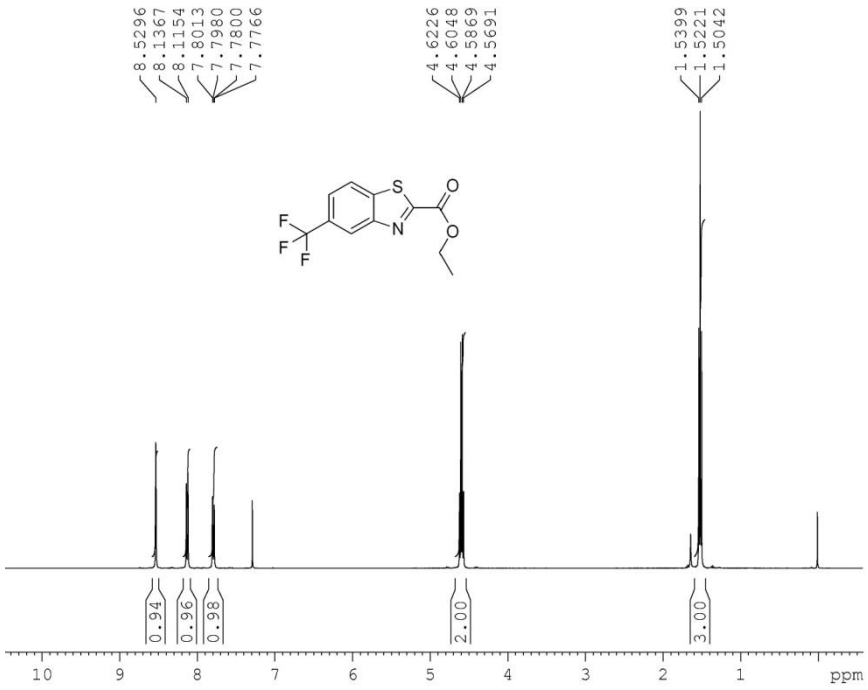
**5.3. $^{1}$H NMR of Ethyl 5-chlorobenzo[*d*]thiazole-2-carboxylate (2b):**



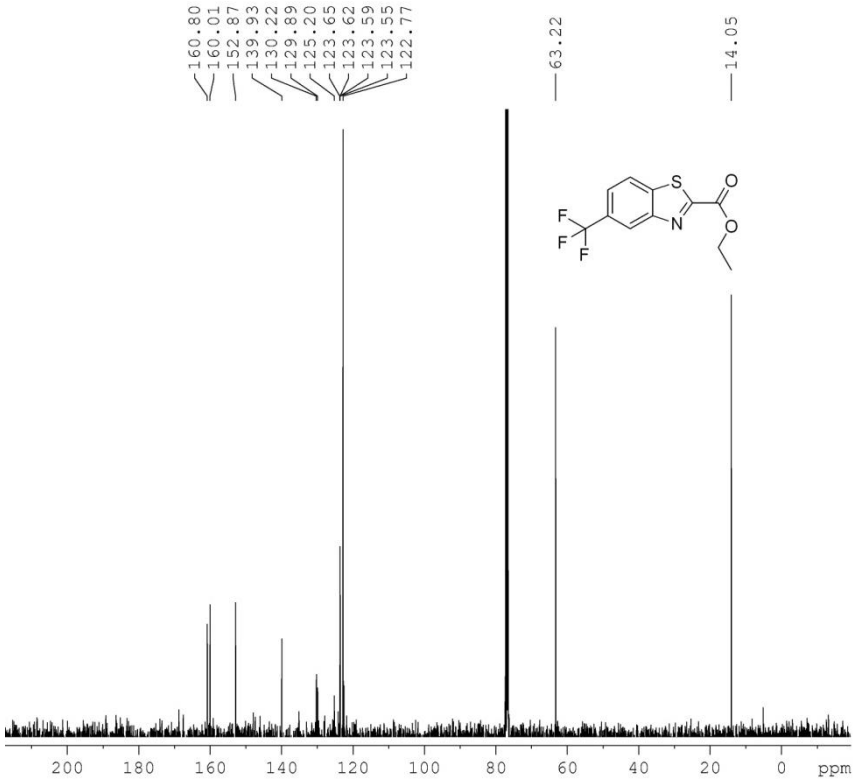

**5.4. $^{13}$C NMR of Ethyl 5-chlorobenzo[*d*]thiazole-2-carboxylate (2b):**



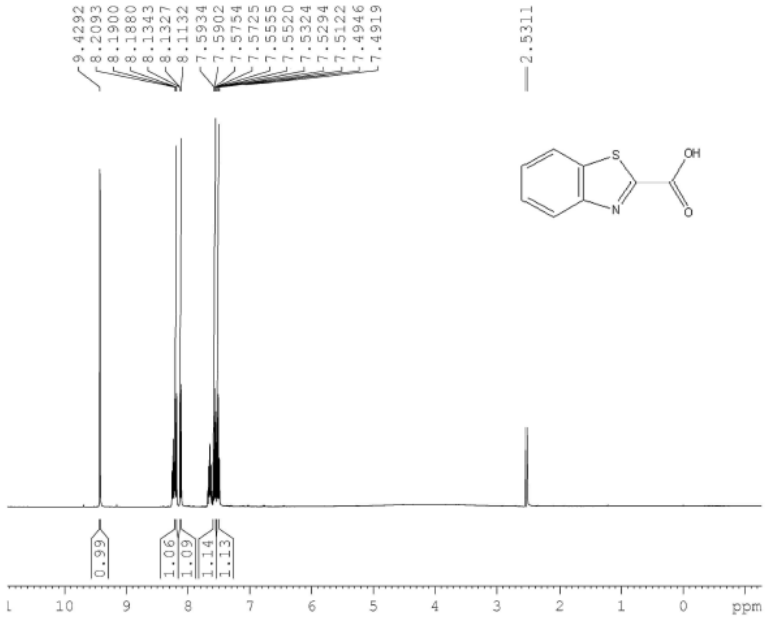
**5.5. $^{1}$H NMR of Ethyl 5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxylate (2c):**



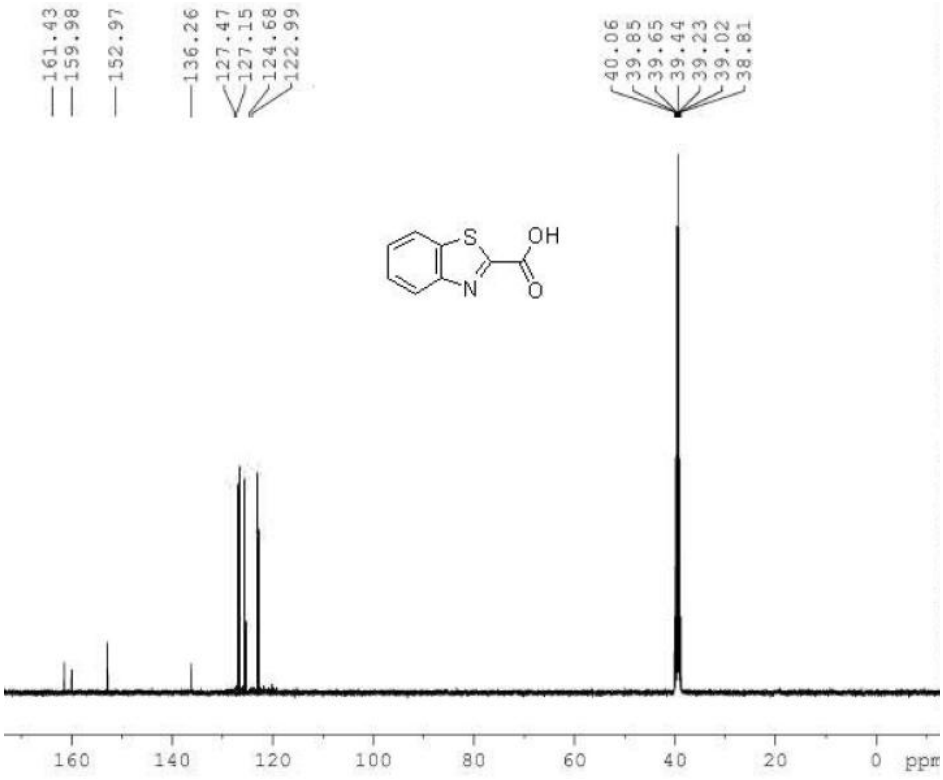

**5.6. $^{13}$C NMR of Ethyl 5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxylate (2c):**



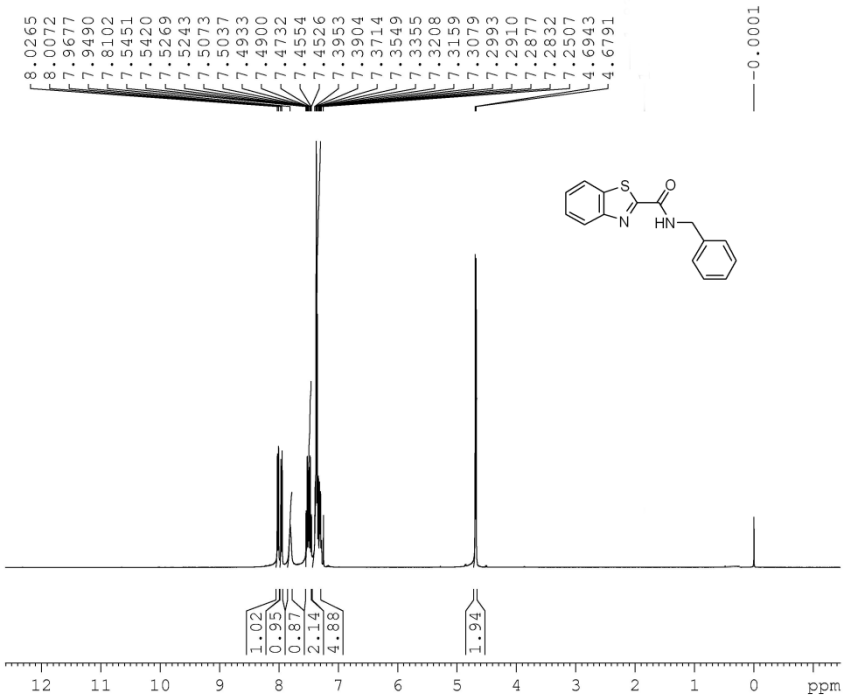
**5.7. $^{1}$H NMR of <u>benzothiazole-2-carboxylic acid</u> (3a):**



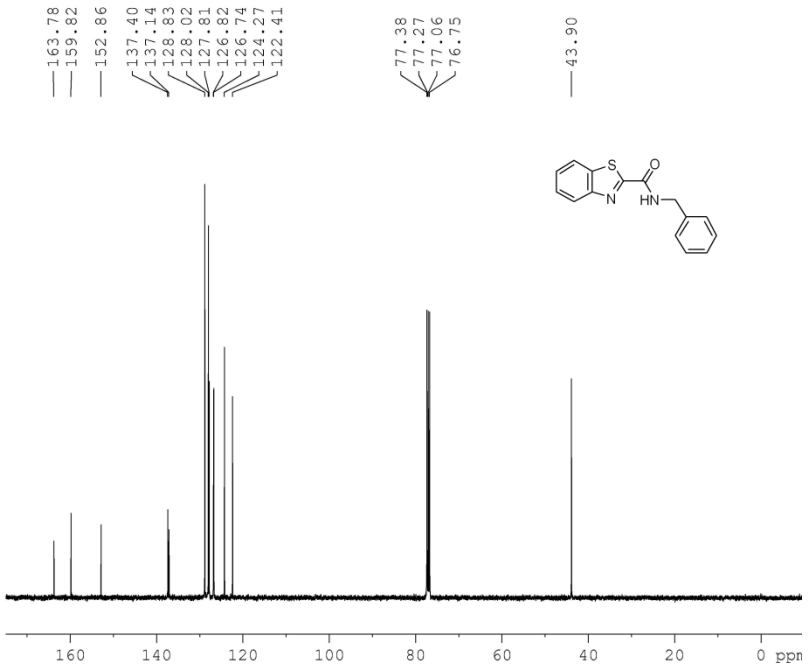

**5.8 $^{13}$C NMR of <u>benzothiazole-2-carboxylic acid</u> (3a):**



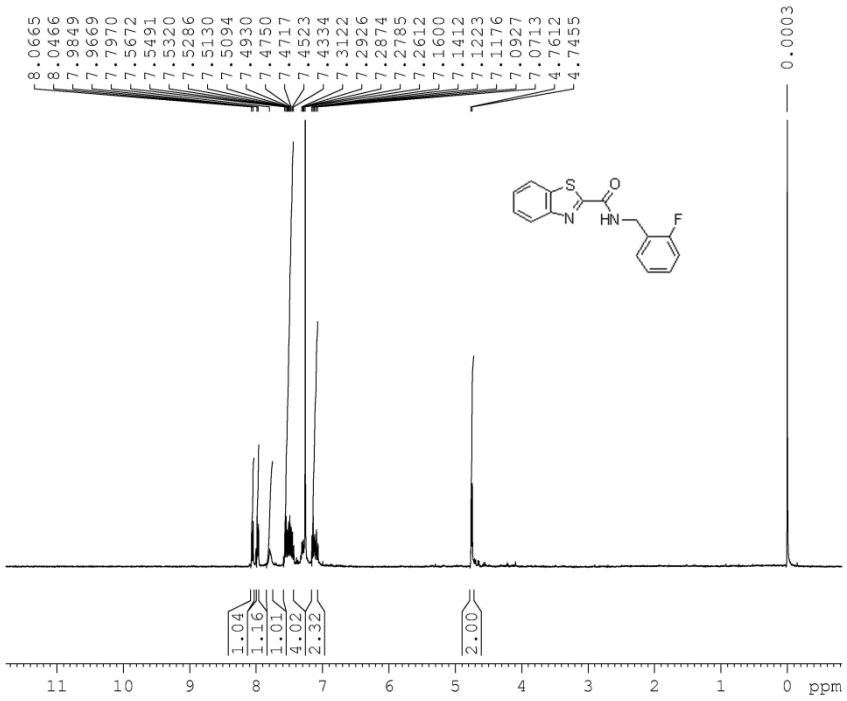
## 5.9. $^{1}$H NMR of *N*-Benzylbenzo[*d*]thiazole-2-carboxamide (5aa)[8]



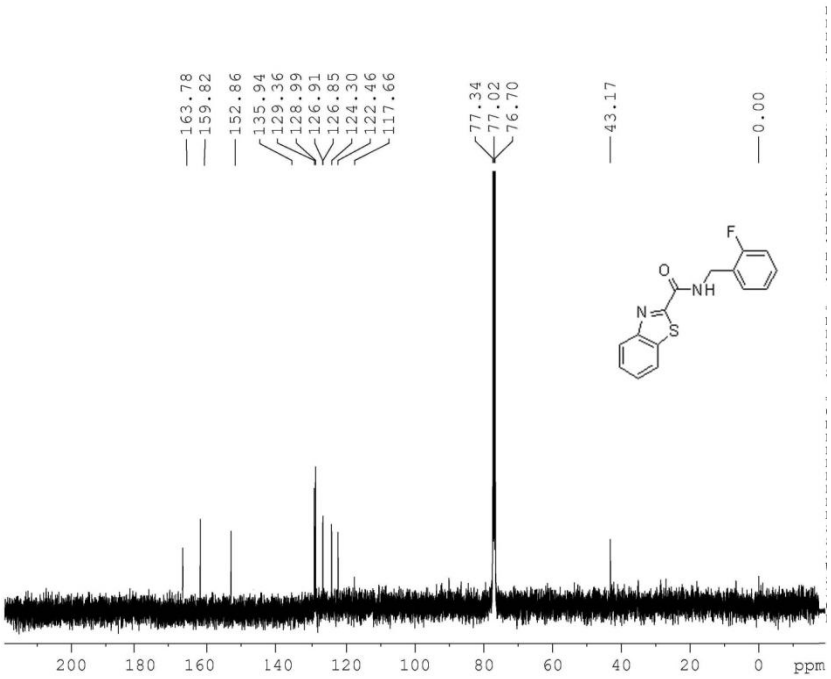

## 5.10. $^{13}$C NMR of *N*-Benzylbenzo[*d*]thiazole-2-carboxamide (5aa)[8]



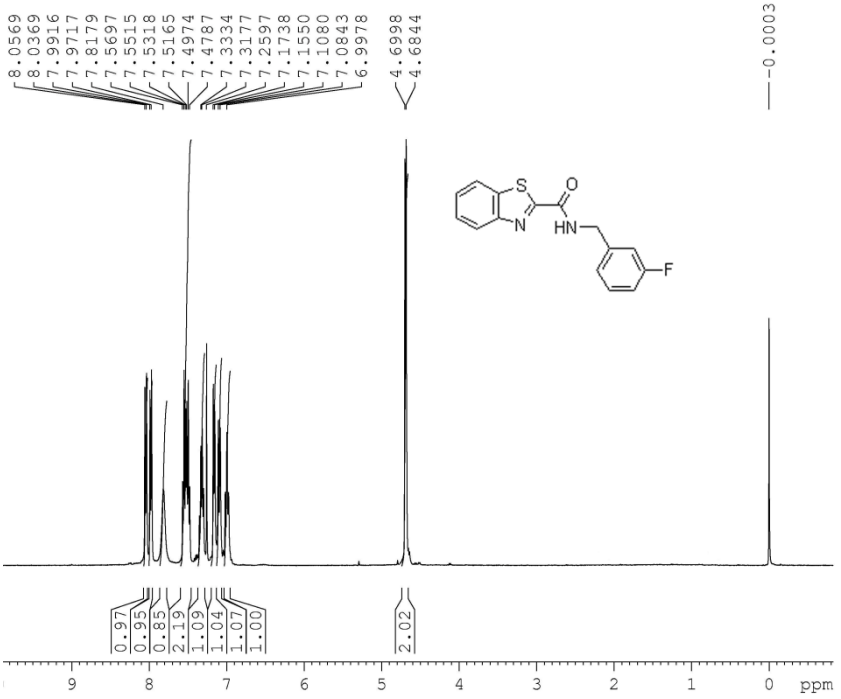
**5.11. $^{1}$H NMR of *N*-(2-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ab):**



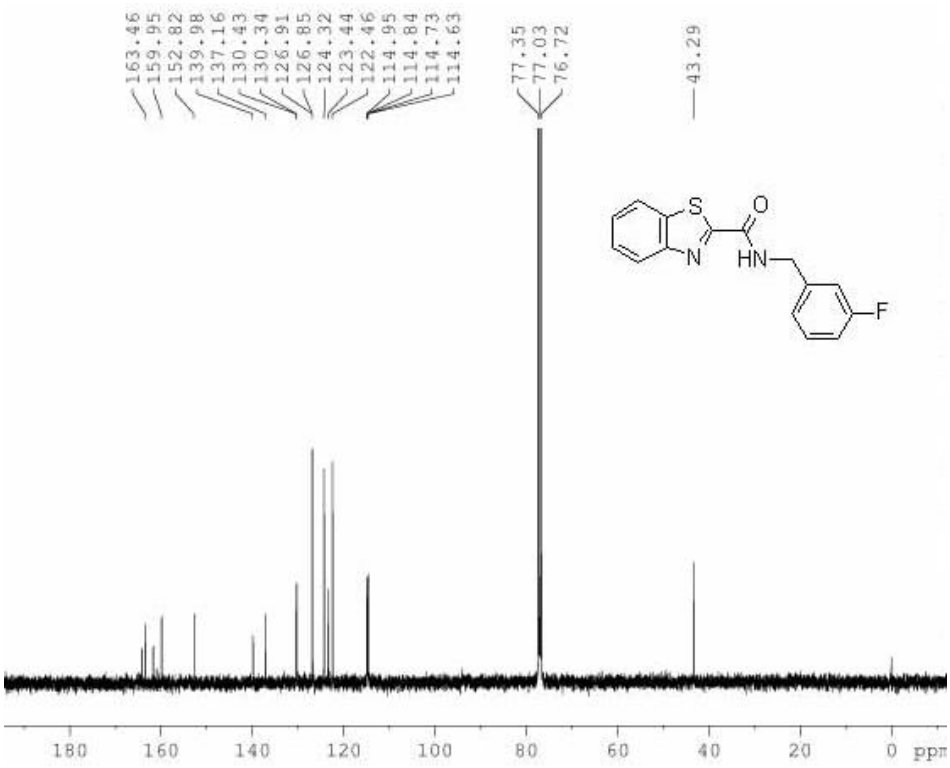

**5.12. $^{13}$C NMR of *N*-(2-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ab):**



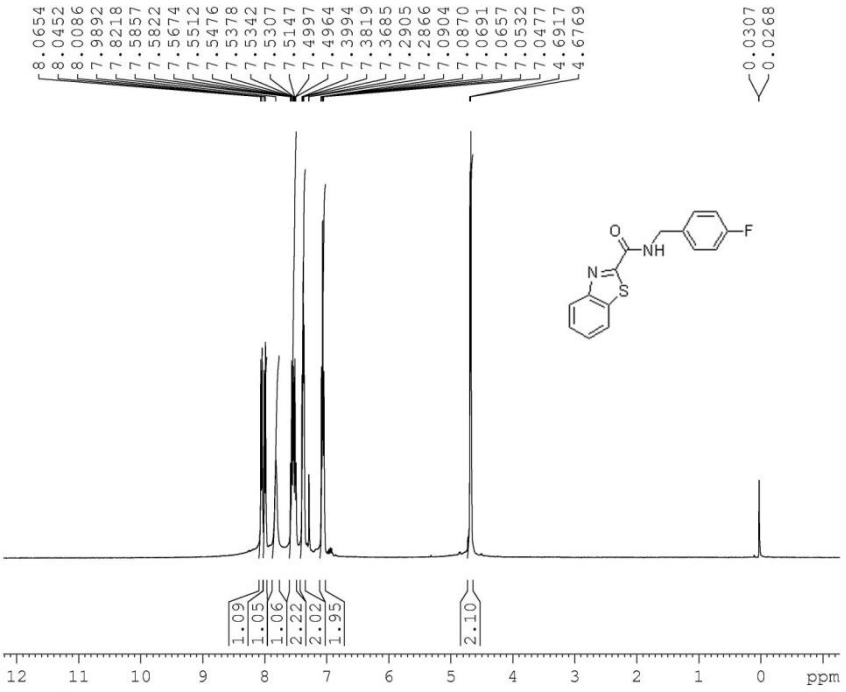
**5.13. $^{1}$H NMR of *N*-(3-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ac):**



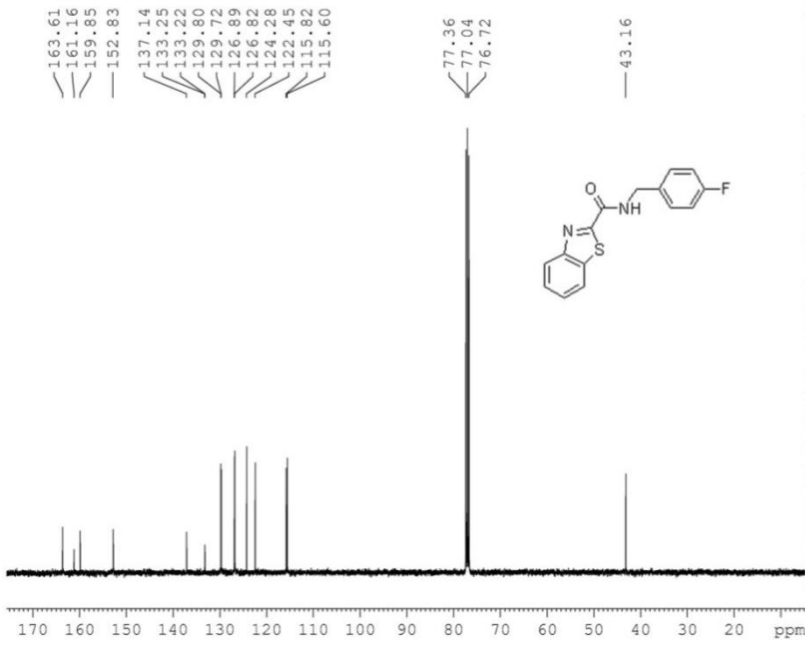

**5.14. $^{13}$C NMR of *N*-(3-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ac):**



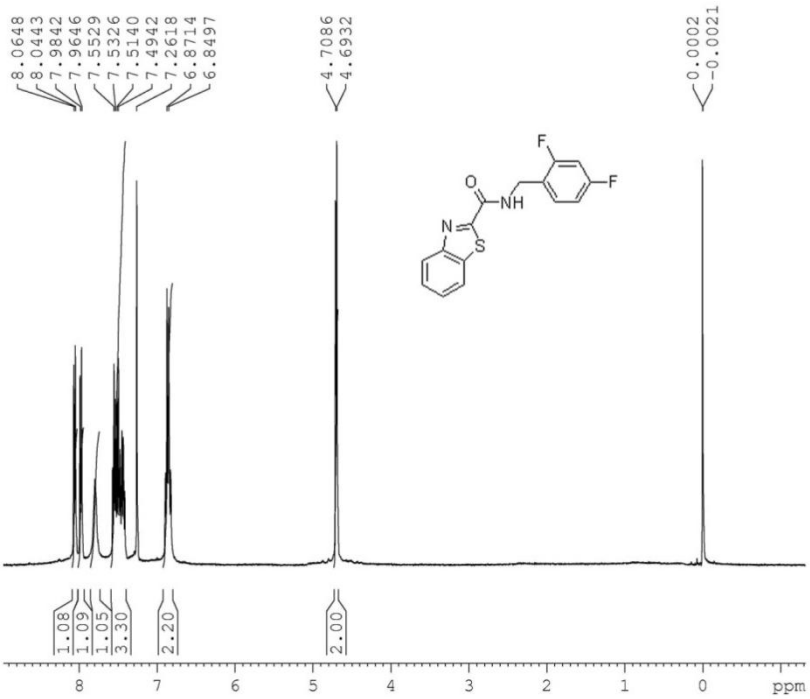
**5.15. $^{1}$H NMR of *N*-(4-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ad)[9]:**



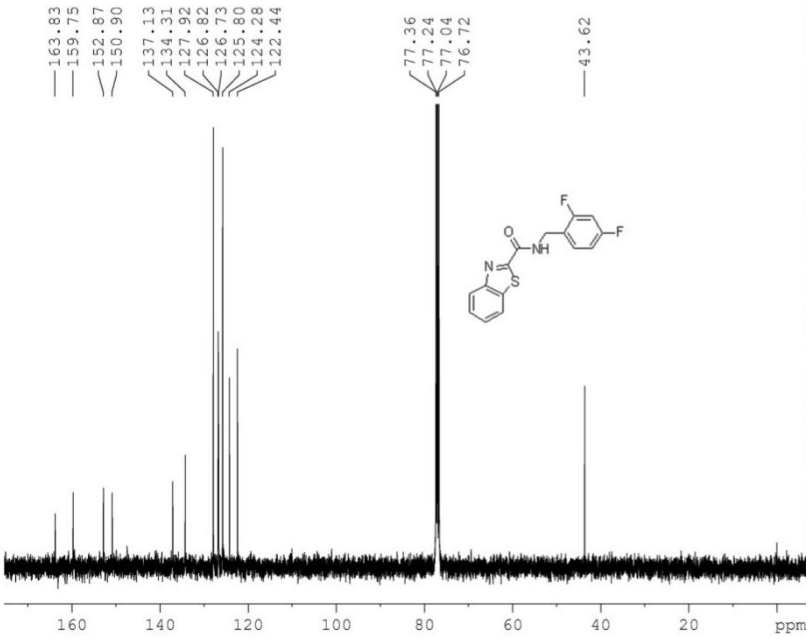

**5.16. $^{13}$C NMR of *N*-(4-Fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ad)[9]:**



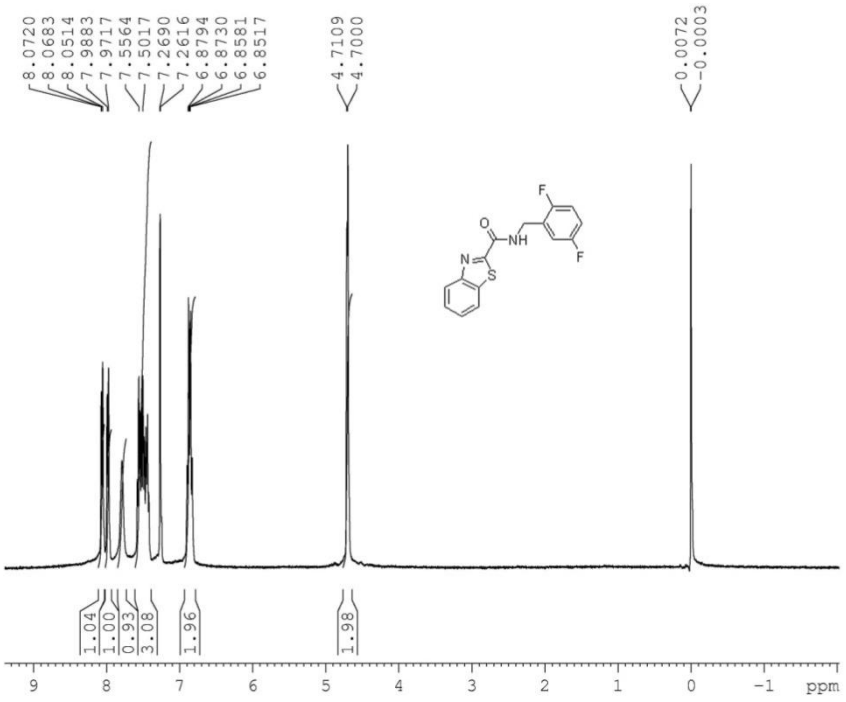
**5.17. $^{1}$H NMR of *N*-(2,4-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ae):**



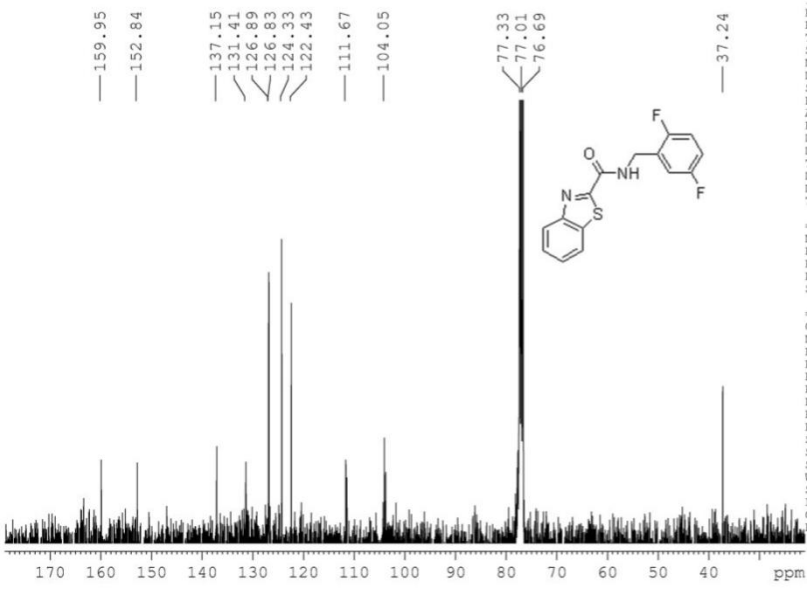

**5.18. $^{13}$C NMR of *N*-(2,4-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ae):**



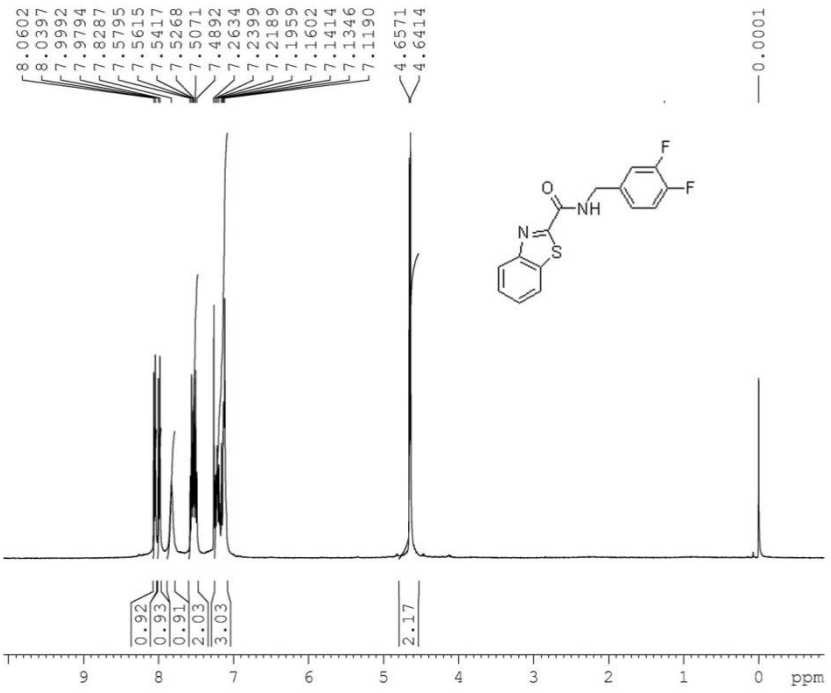
**5.19. $^{1}$H NMR of *N*-(2,5-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5af):**



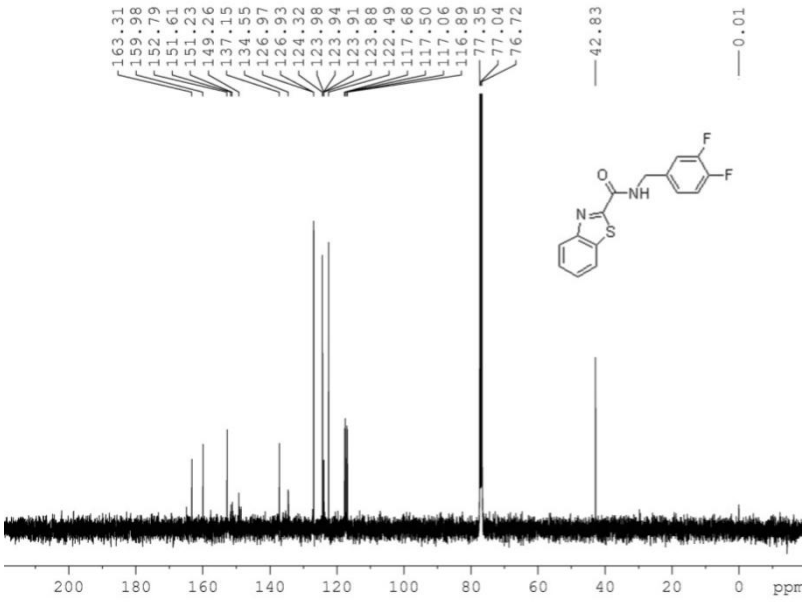

**5.20. $^{13}$C NMR of *N*-(2,5-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5af):**



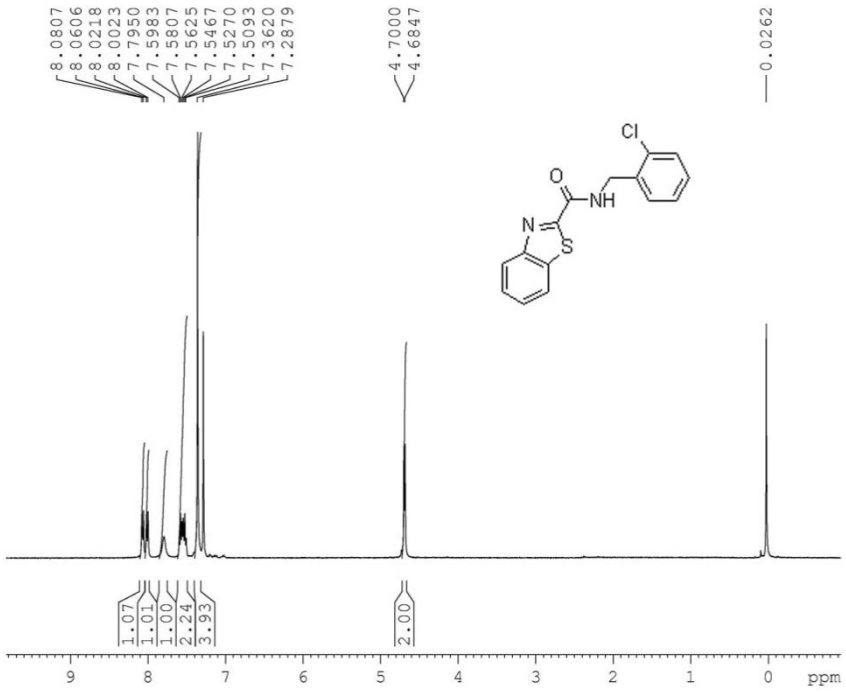
**5.21. $^{1}$H NMR of *N*-(3,4-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ag):**



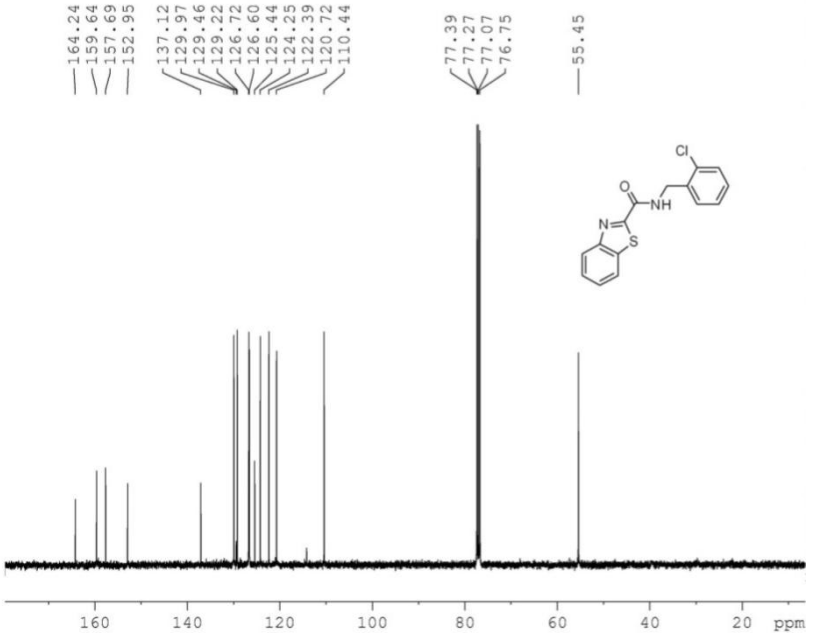

**5.22. $^{1}$H NMR of *N*-(3,4-Difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ag):**



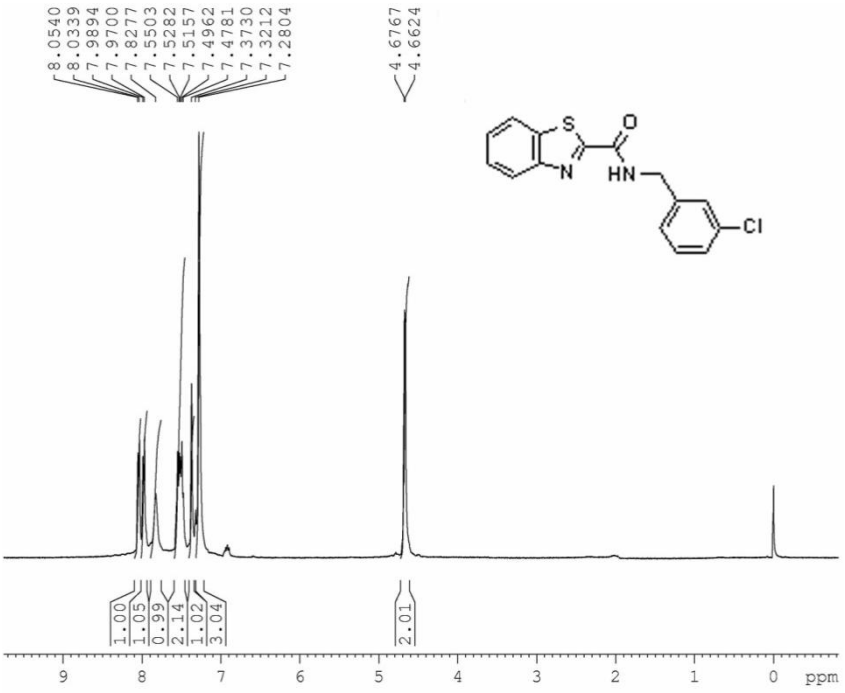
**5.23. $^{1}$H NMR of *N*-(2-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ah):**



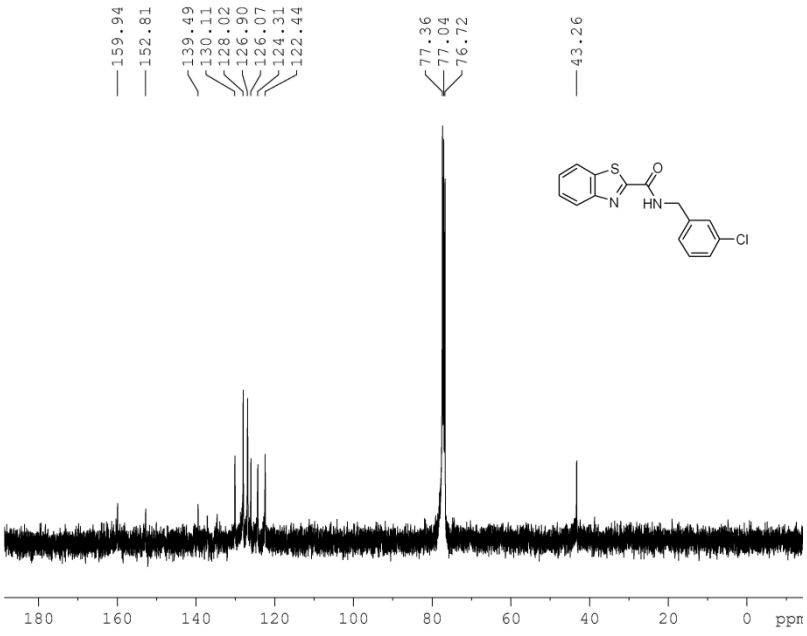

**5.24. $^{13}$C NMR of *N*-(2-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ah):**



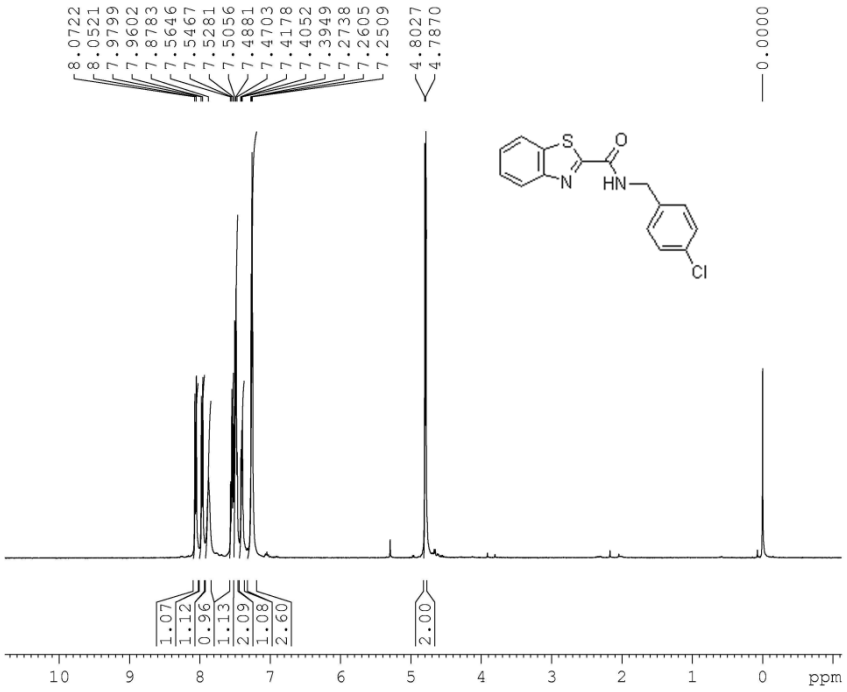
**5.25. $^{1}$H NMR of *N*-(3-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ai):**



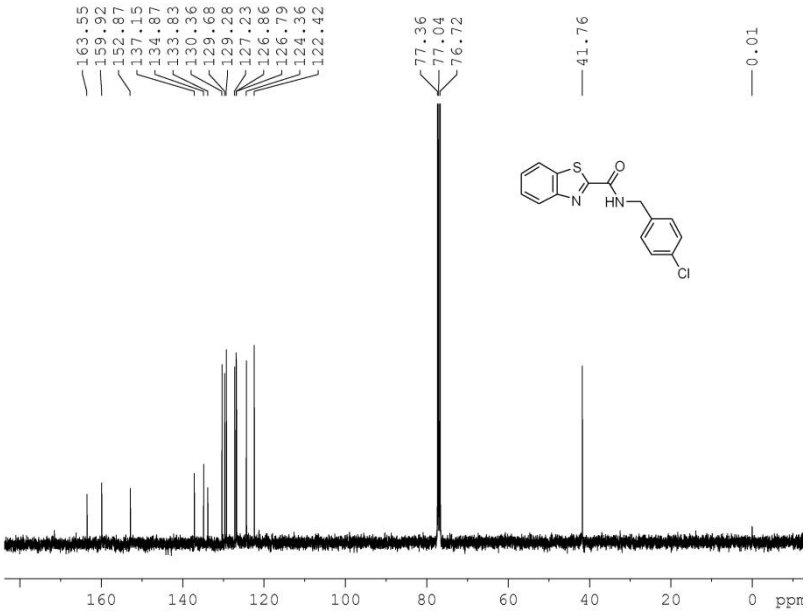

**5.26. $^{13}$C NMR of *N*-(3-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ai):**



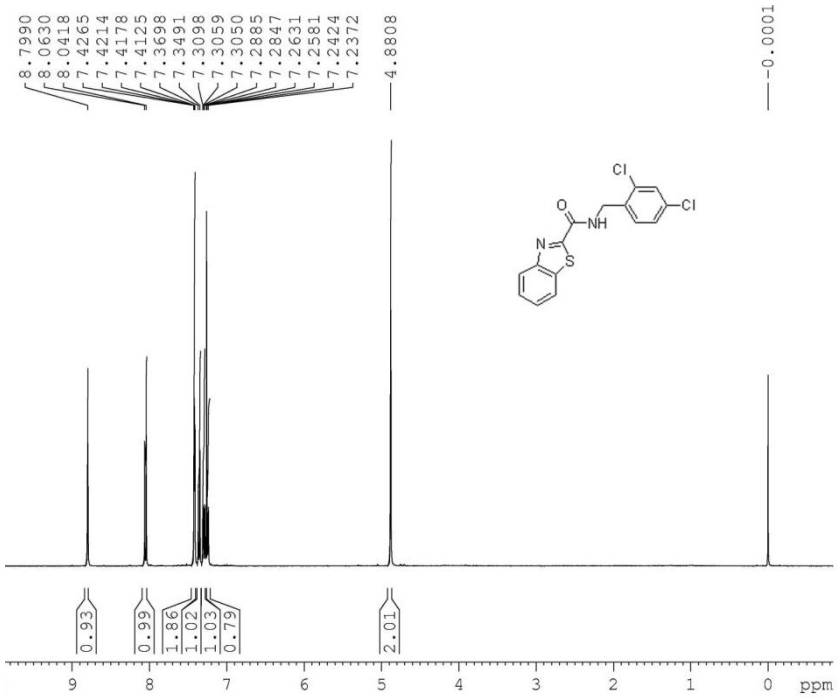
**5.27. $^{1}$H NMR of *N*-(4-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5aj):**



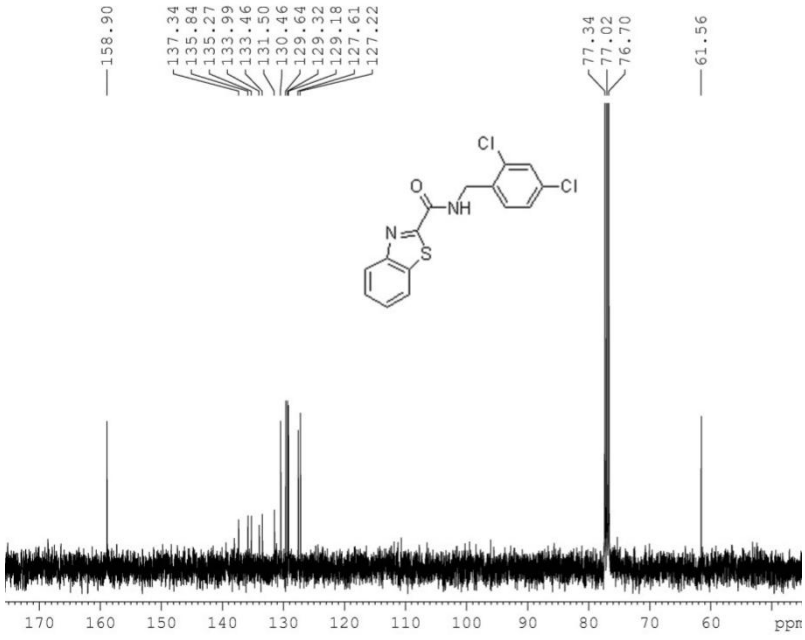

**5.28. $^{13}$C NMR of *N*-(4-Chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5aj):**



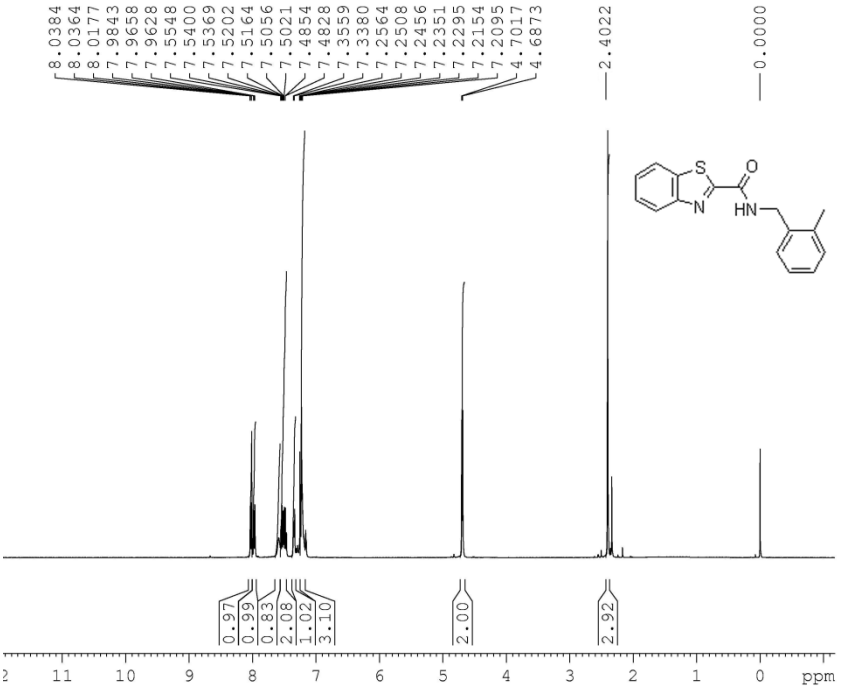
**5.29. $^{1}$H NMR of *N*-(2,4-Dichlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ak):**



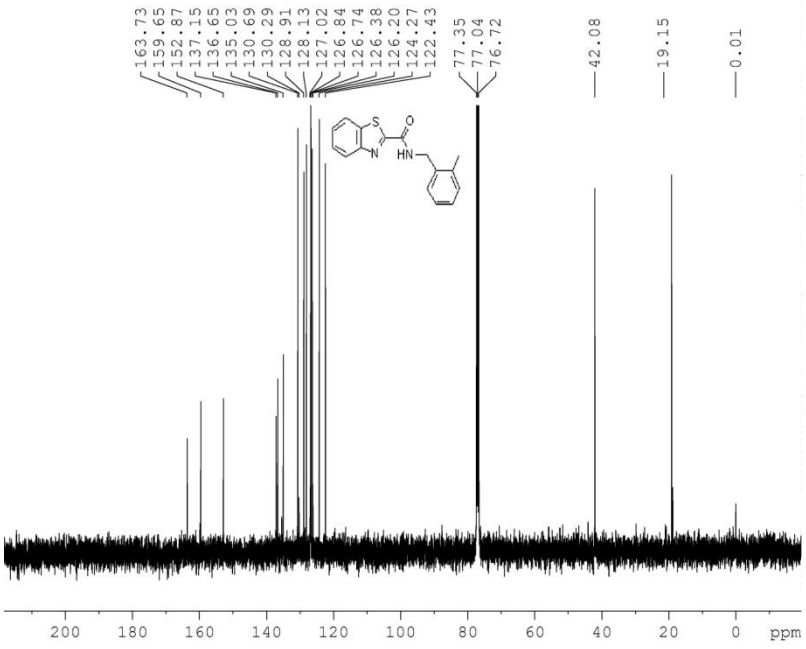

**5.30. $^{13}$C NMR of *N*-(2,4-Dichlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5ak):**



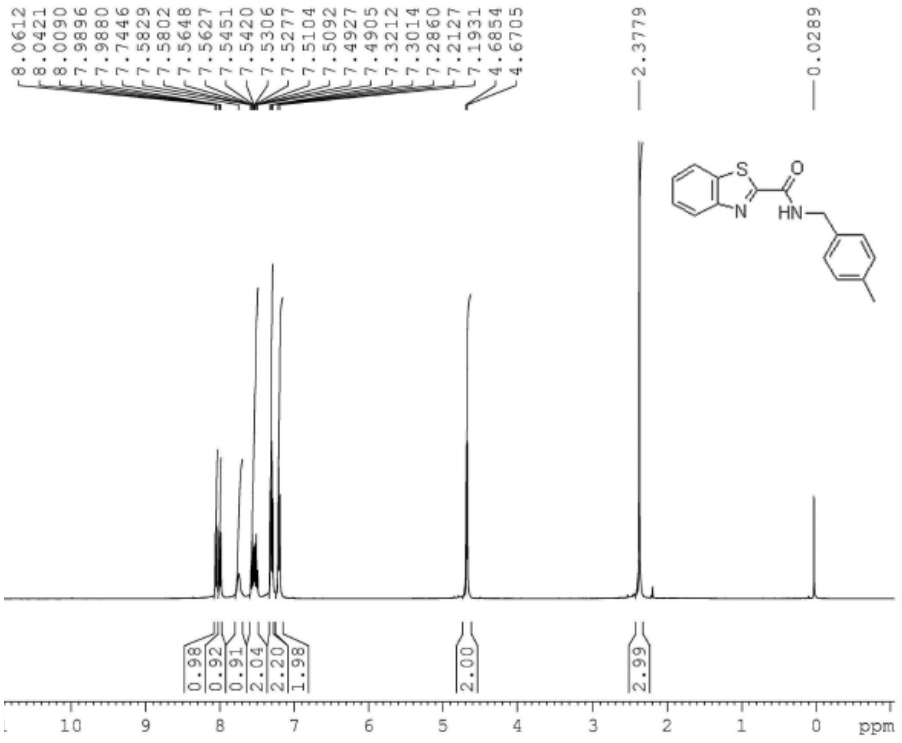
**5.31. $^{1}$H NMR of *N*-(2-Methylbenzyl)benzo[*d*]thiazole-2-carboxamide (5al):**



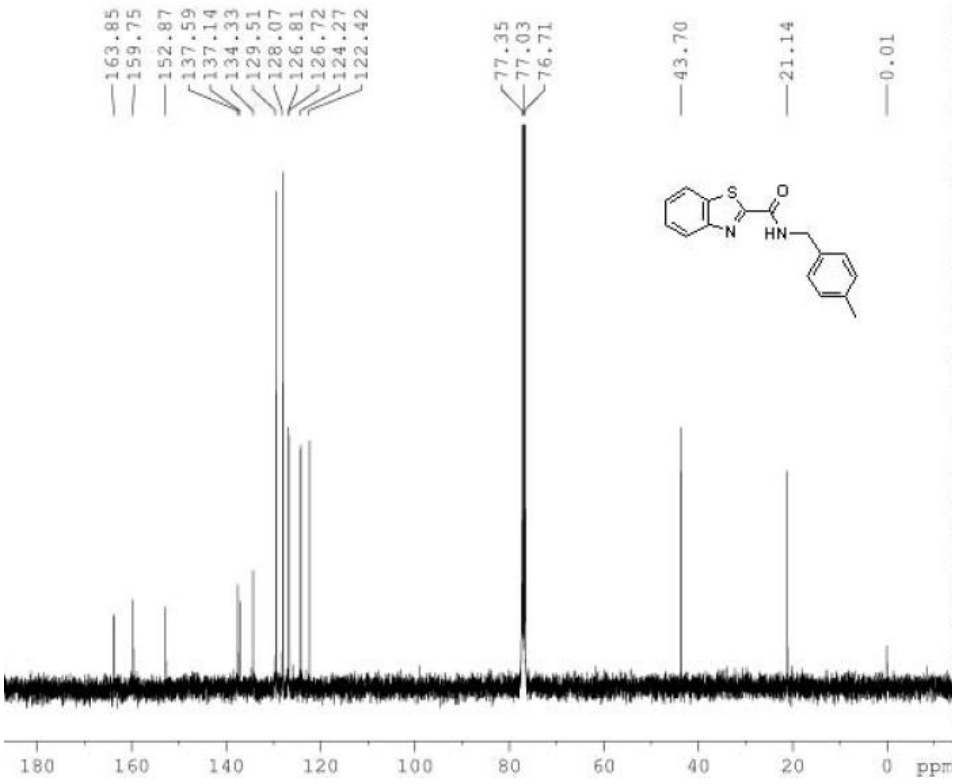

**5.32. $^{13}$C NMR of *N*-(2-Methylbenzyl)benzo[*d*]thiazole-2-carboxamide (5al):**



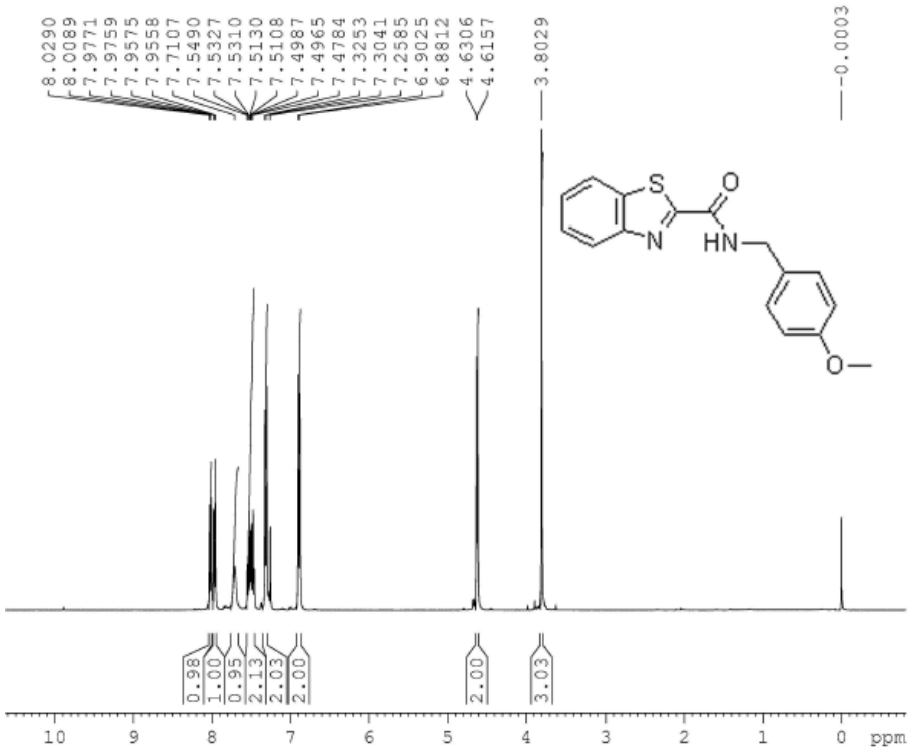
**5.33. $^{1}$H NMR of *N*-(4-Methylbenzyl)benzo[*d*]thiazole-2-carboxamide (5am):**



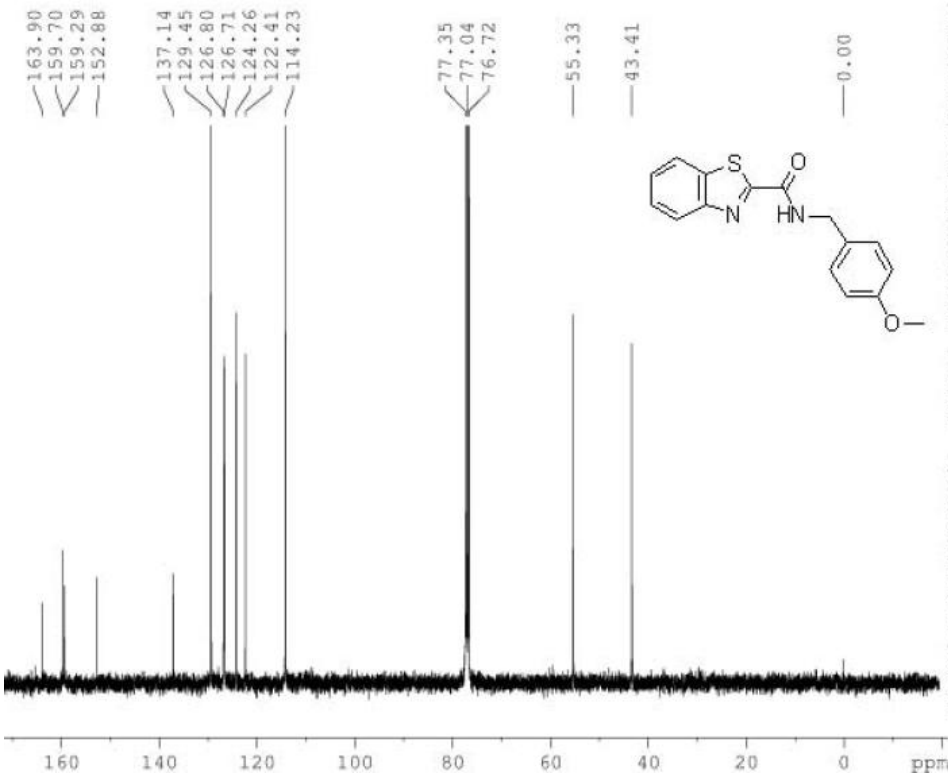

**5.34. $^{13}$C NMR of *N*-(4-Methylbenzyl)benzo[*d*]thiazole-2-carboxamide (5am):**



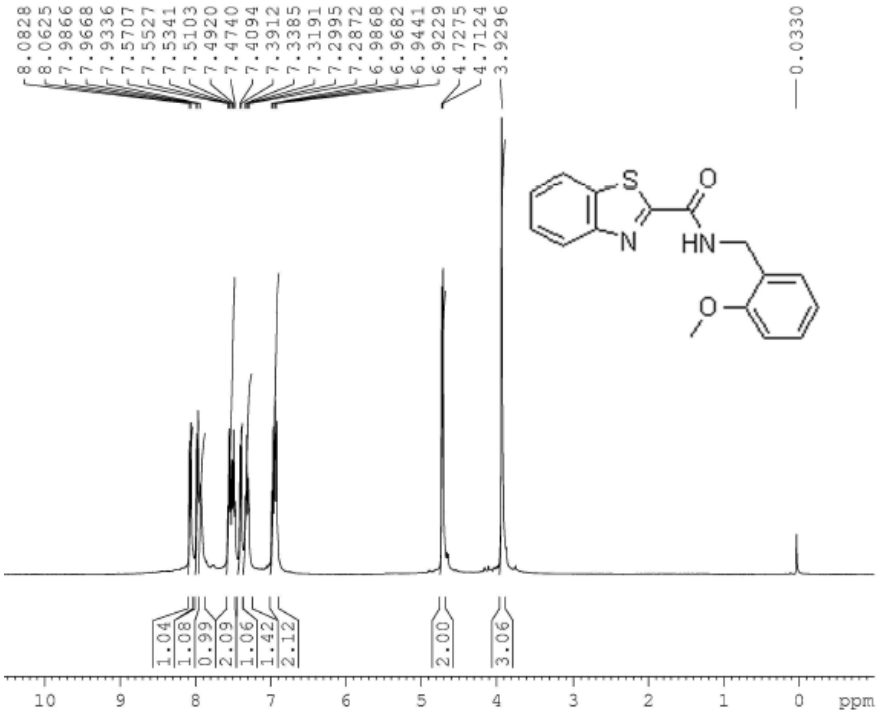
**5.35. $^{1}$H NMR of *N*-(4-Methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5an):**



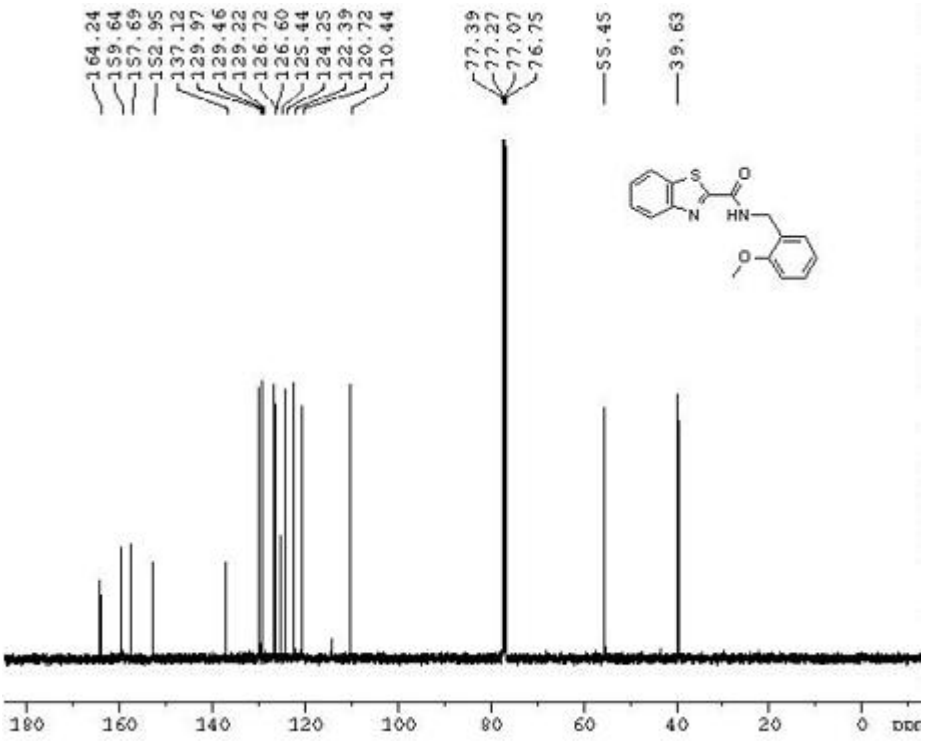

**5.36. $^{13}$C NMR of *N*-(4-Methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5an):**



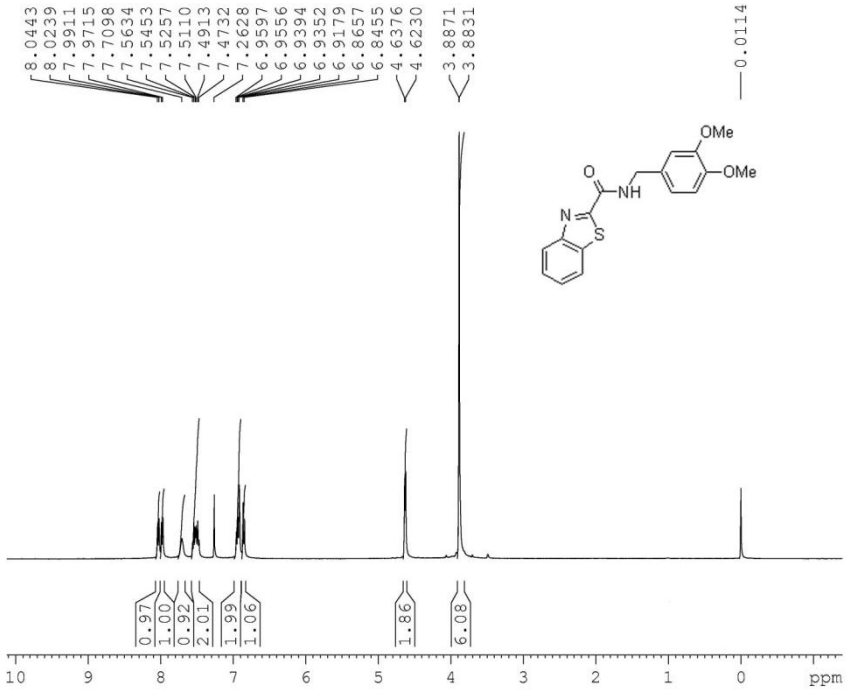
**5.37. $^{1}$H NMR of *N*-(2-Methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5ao)[10]:**



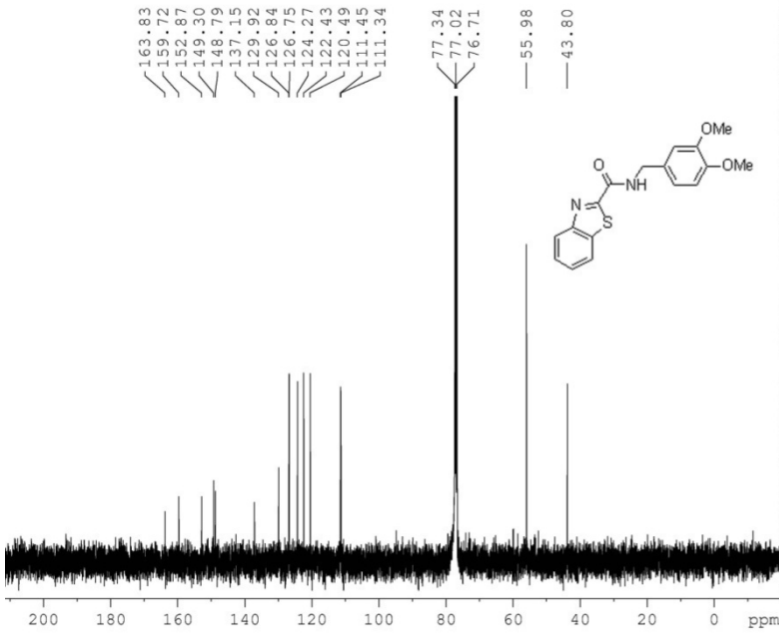

**5.38. $^{13}$C NMR of *N*-(2-Methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5ao)[10]:**



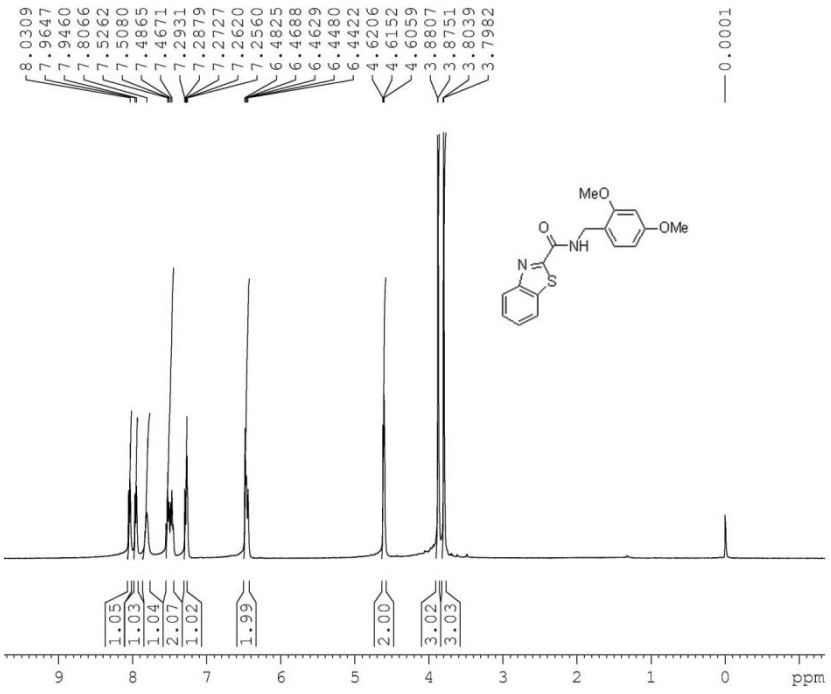
**5.39. $^{1}$H NMR of *N*-(3,4-Dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5ap):**



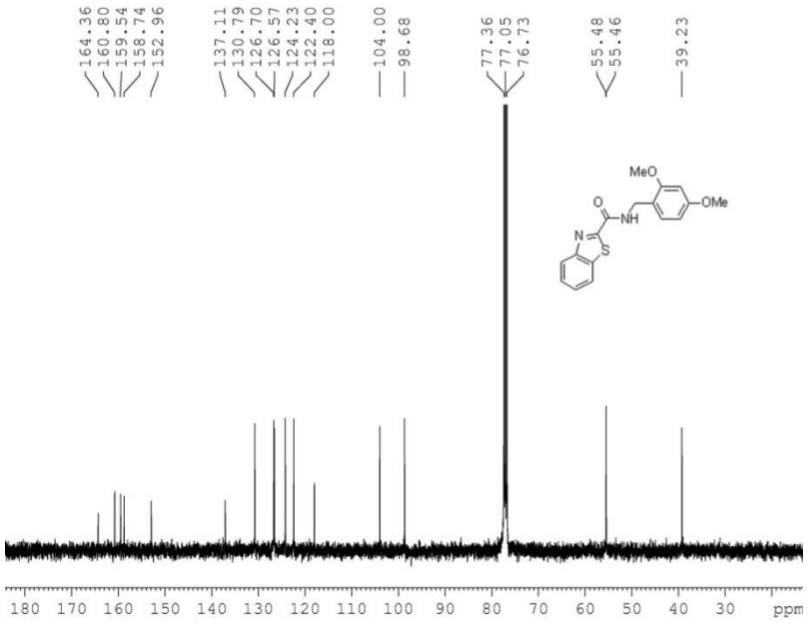

**5.40. $^{13}$C NMR of *N*-(3,4-Dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5ap):**



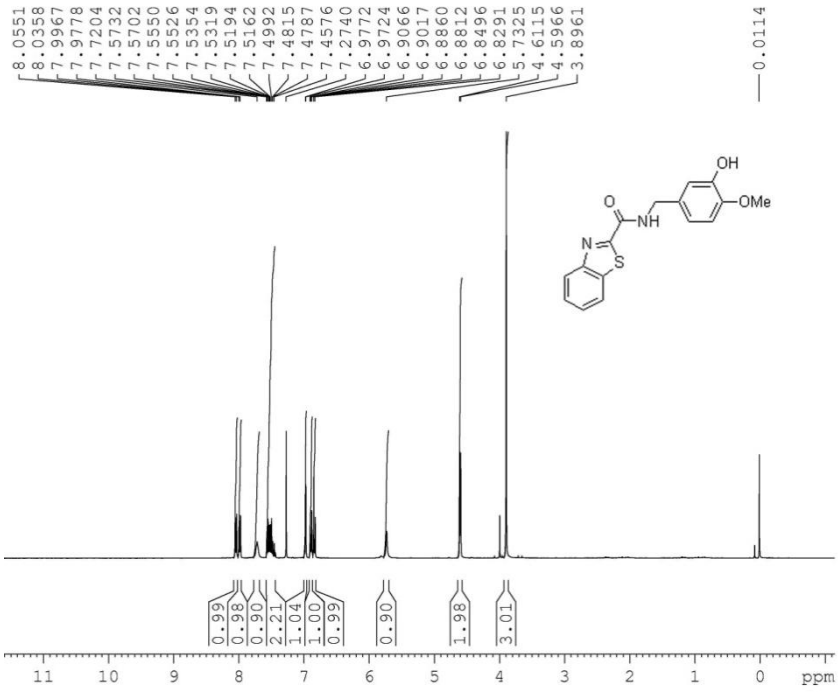
**5.41. $^{1}$H NMR of *N*-(2, 4-Dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5aq)[11]:**



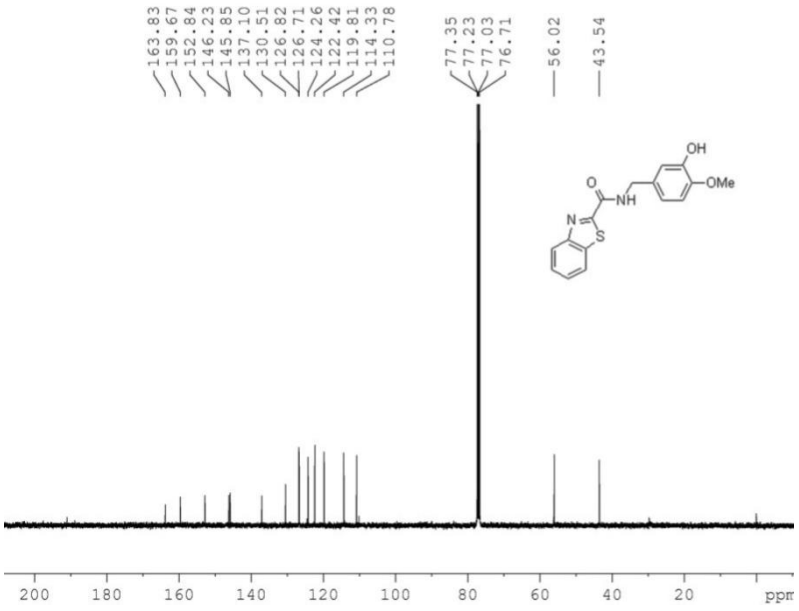

**5.42. $^{13}$C NMR of *N*-(2, 4-Dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5aq)[11]:**



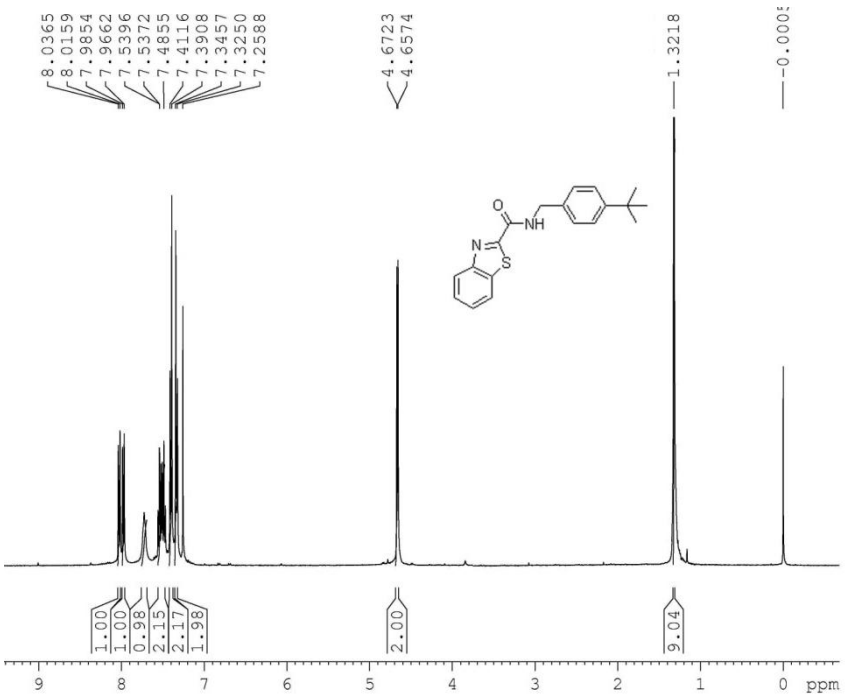
**5.43. $^{1}$H NMR of *N*-(3-Hydroxy-4-methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5ar):**



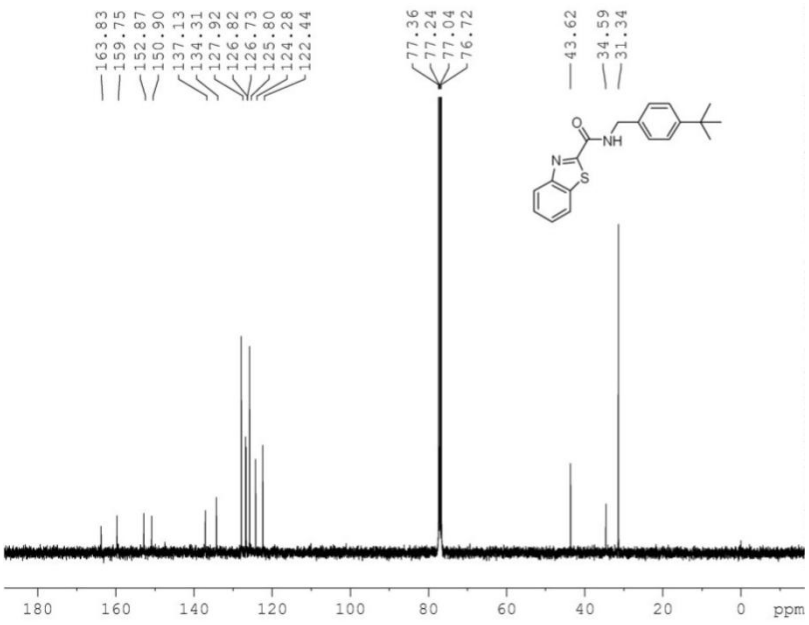

**5.44. $^{13}$C NMR of *N*-(3-Hydroxy-4-methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5ar):**



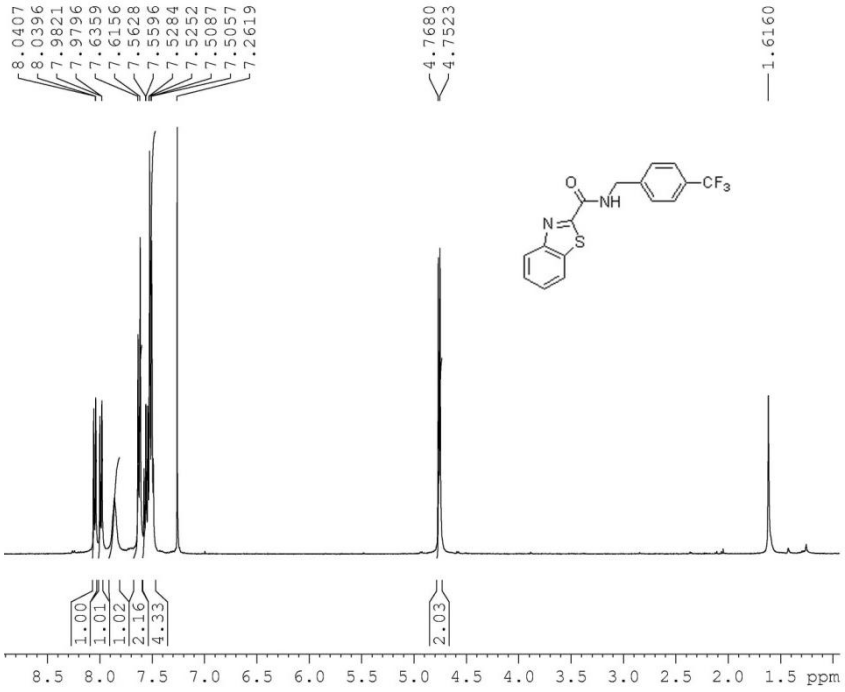
**5.45. $^{1}$H NMR of *N*-(4-*tert*-butylbenzyl)benzo[*d*]thiazole-2-carboxamide (5as):**



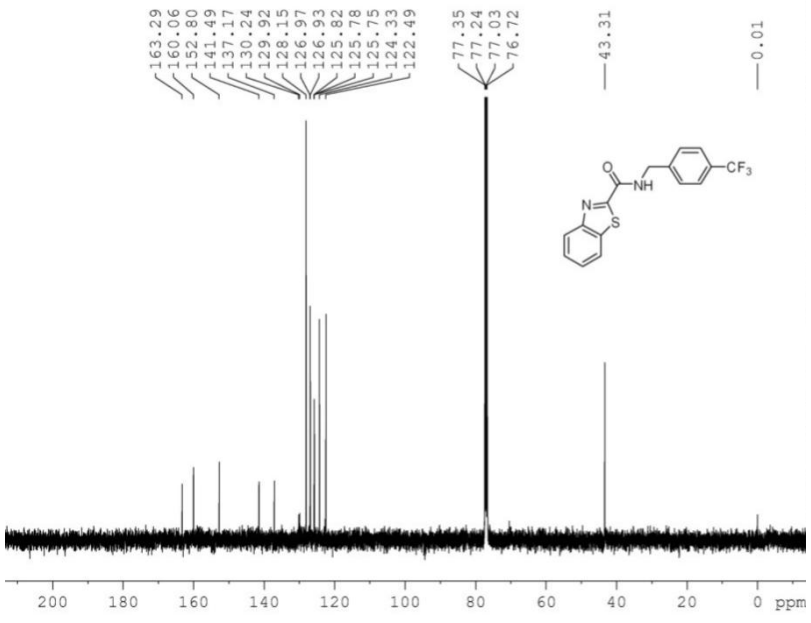

**5.46. $^{13}$C NMR of *N*-(4-*tert*-butylbenzyl)benzo[*d*]thiazole-2-carboxamide (5as):**



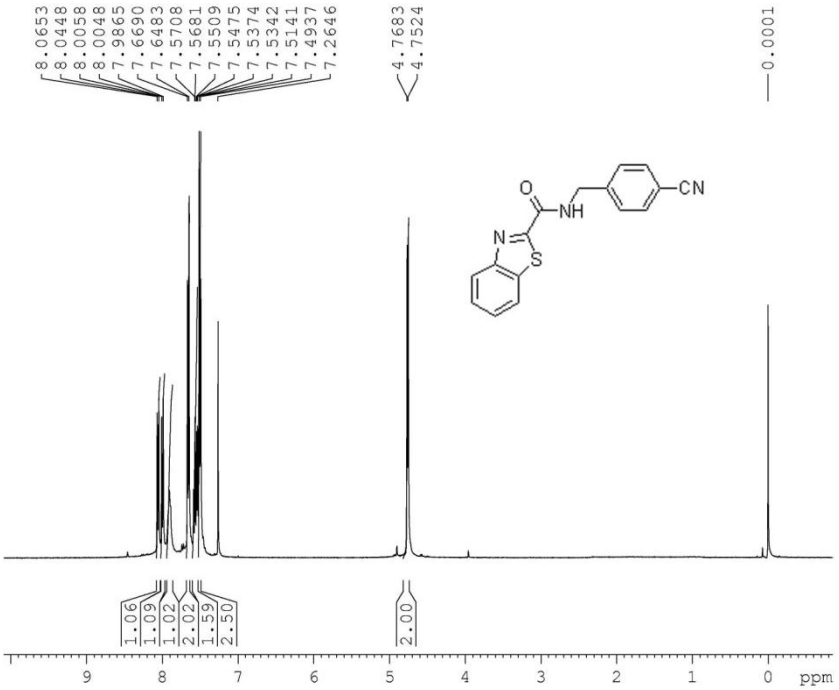
**5.47. $^{1}$H NMR of *N*-(4-(Trifluoromethyl)benzyl)benzo[*d*]thiazole-2-carboxamide (5at):**



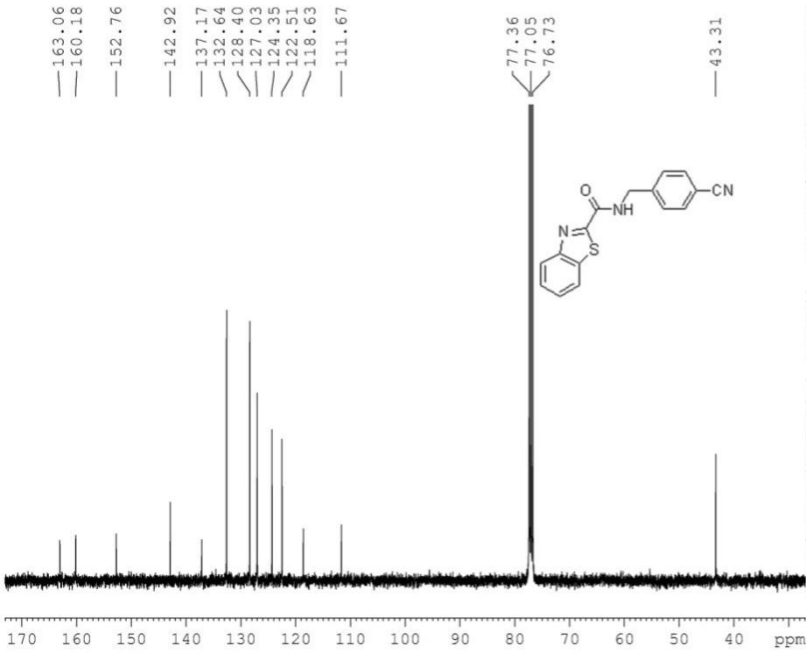

**5.48. $^{13}$C NMR of *N*-(4-(Trifluoromethyl)benzyl)benzo[*d*]thiazole-2-carboxamide (5at):**



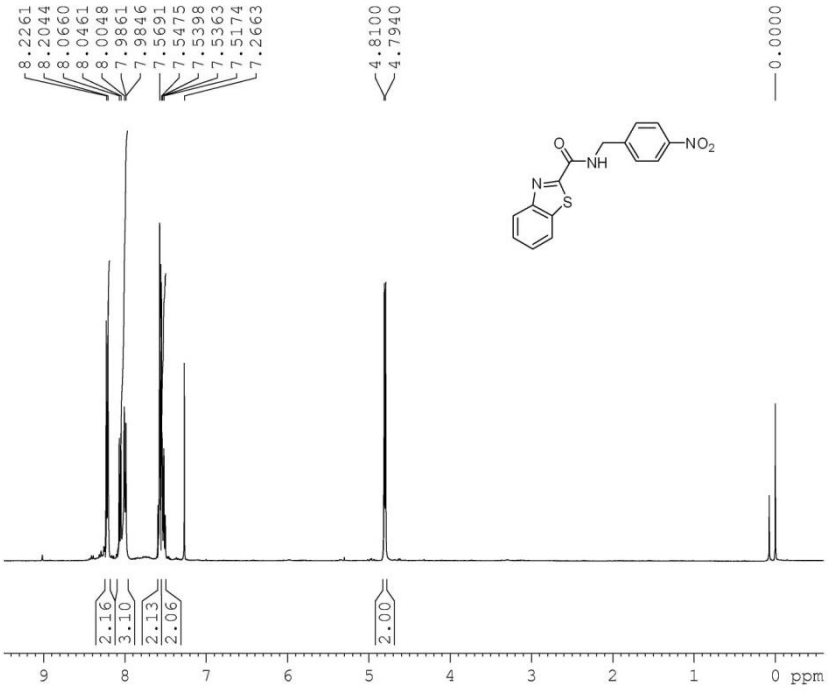
**5.49. $^{1}$H NMR of *N*-(4-Cyanobenzyl)benzo[*d*]thiazole-2-carboxamide (5au):**



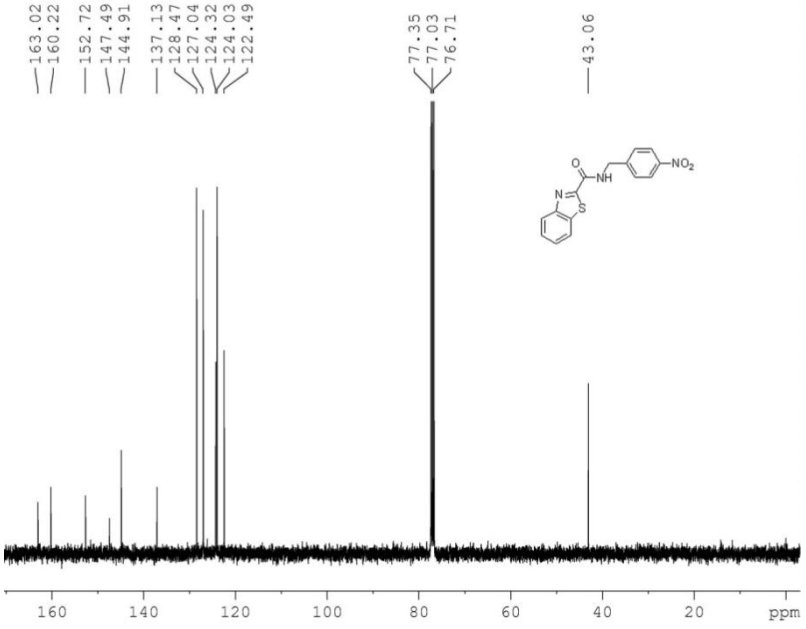

**5.50. $^{13}$C NMR of *N*-(4-Cyanobenzyl)benzo[*d*]thiazole-2-carboxamide (5au):**



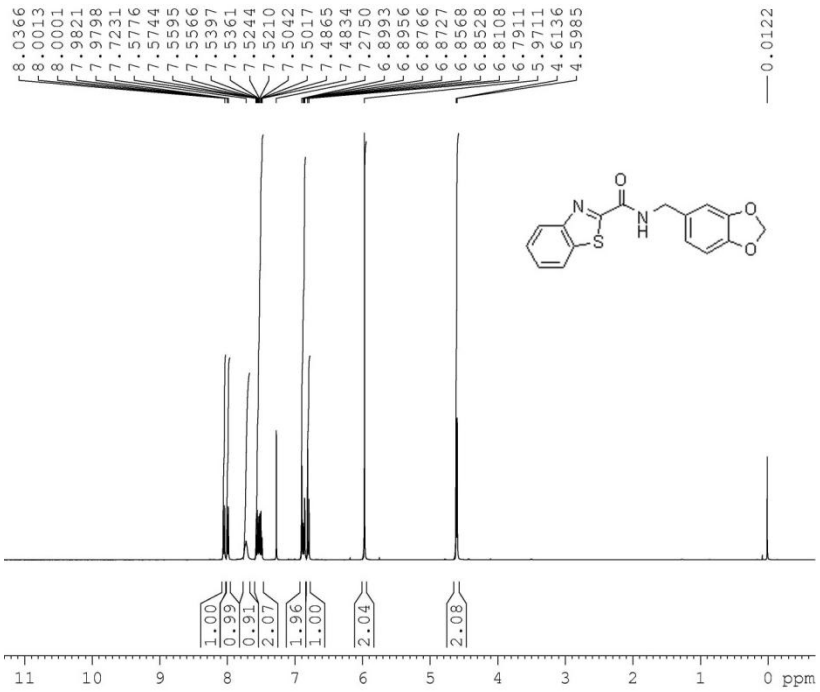
**5.51. $^{1}$H NMR of *N*-(4-Nitrobenzyl)benzo[*d*]thiazole-2-carboxamide (5av):**



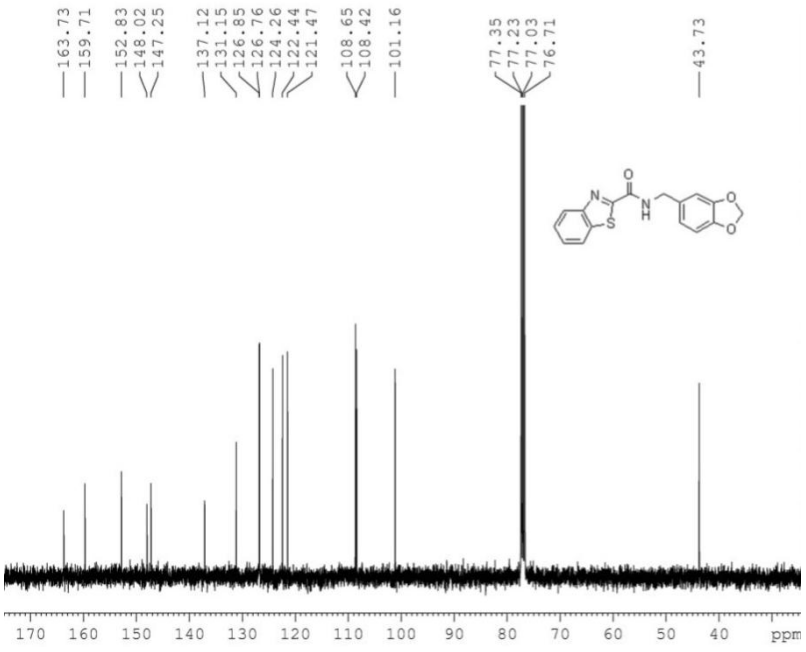

**5.52. $^{13}$C NMR of *N*-(4-Nitrobenzyl)benzo[*d*]thiazole-2-carboxamide (5av):**



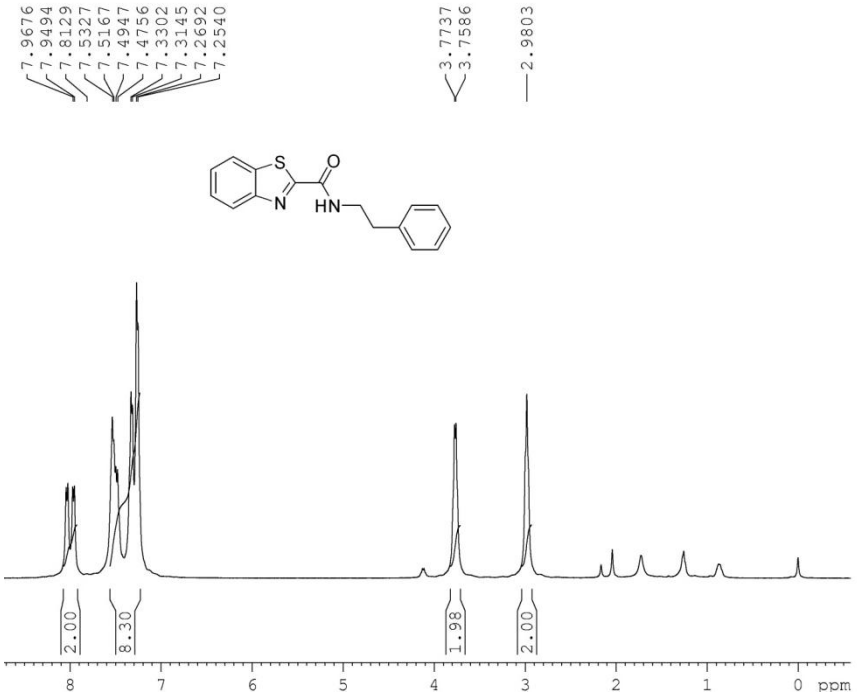
**5.53. $^{1}$H NMR of *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)benzo[*d*]thiazole-2-carboxamide (5aw):**



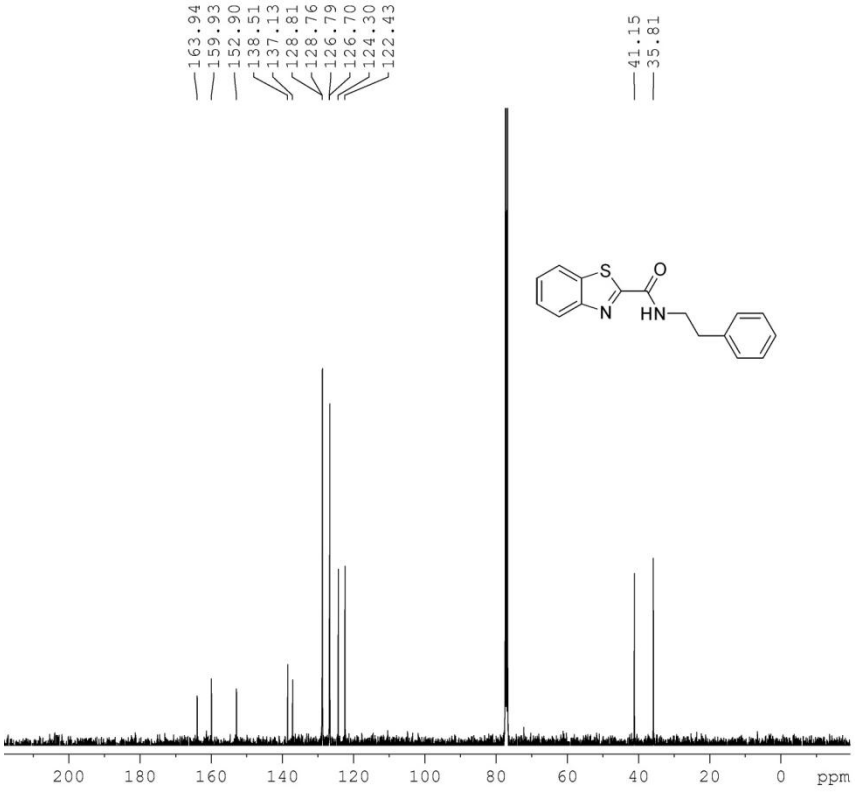

**5.54. $^{13}$C NMR of *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)benzo[*d*]thiazole-2-carboxamide (5aw):**



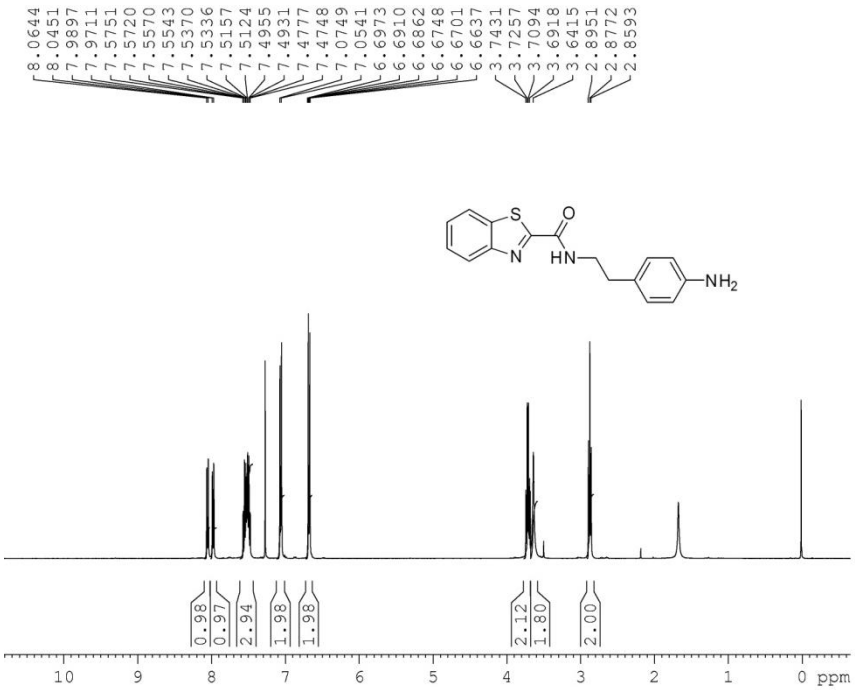
## 5.55. $^{1}$H NMR of *N*-Phenethylbenzo[*d*]thiazole-2-carboxamide (5ax)[12]



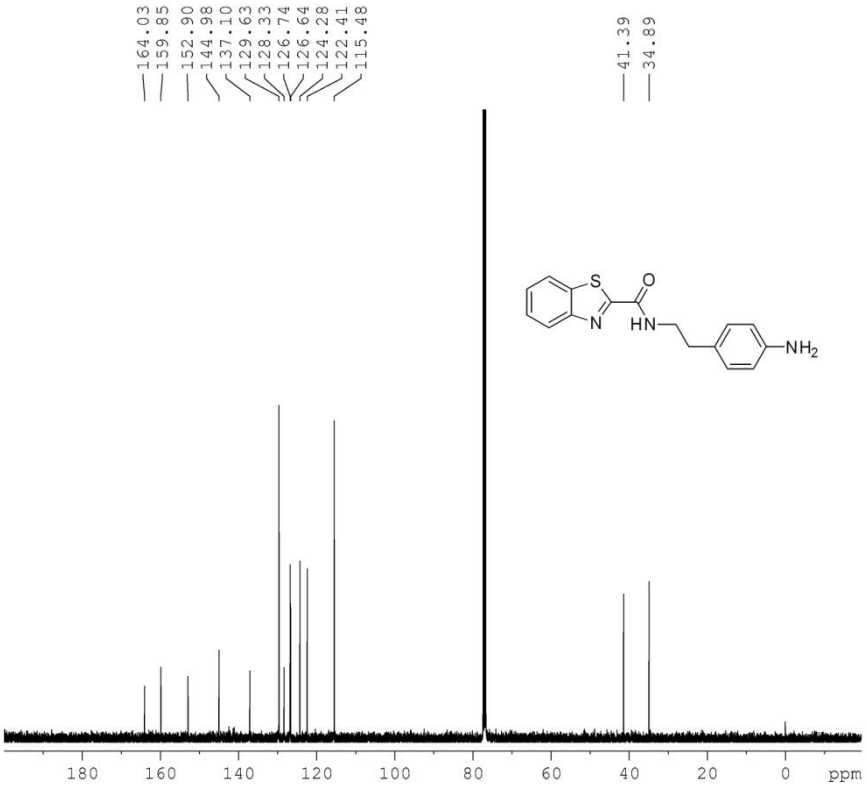

## 5.56. $^{13}$C NMR of *N*-Phenethylbenzo[*d*]thiazole-2-carboxamide (5ax)[12]



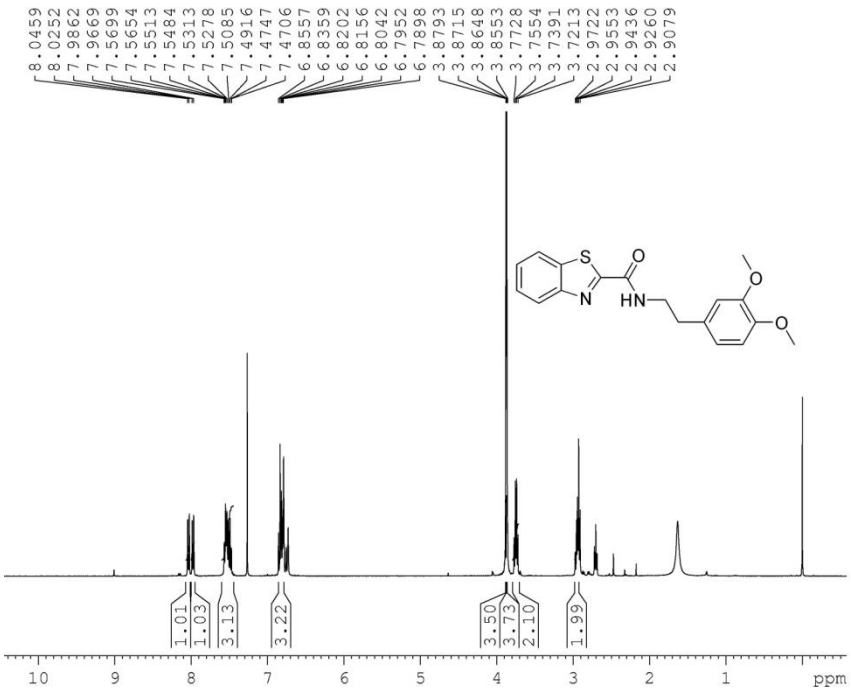
**5.57. $^{1}$H NMR of *N*-(4-Aminophenethyl)benzo[*d*]thiazole-2-carboxamide (5ay):**



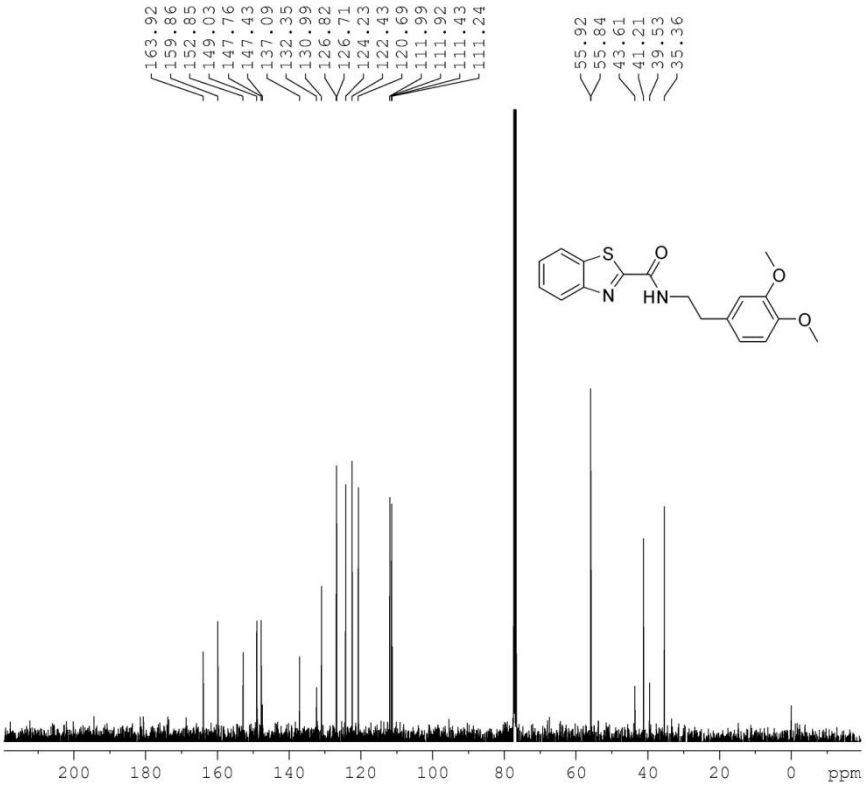

**5.58. $^{13}$C NMR of *N*-(4-Aminophenethyl)benzo[*d*]thiazole-2-carboxamide (5ay):**



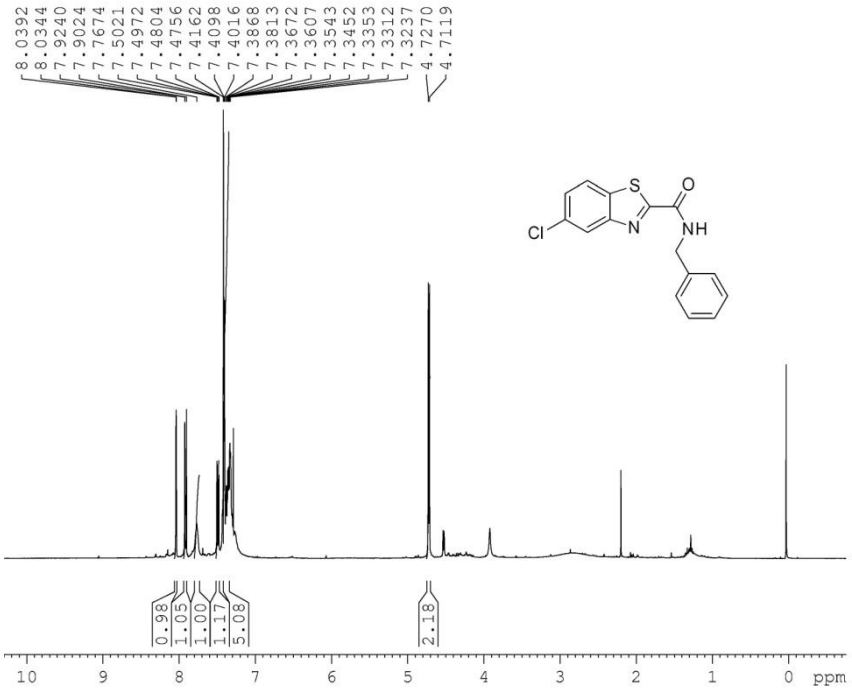
**5.59. $^{1}$H NMR of *N*-(3,4-dimethoxyphenethyl)benzo[*d*]thiazole-2-carboxamide (5az):**



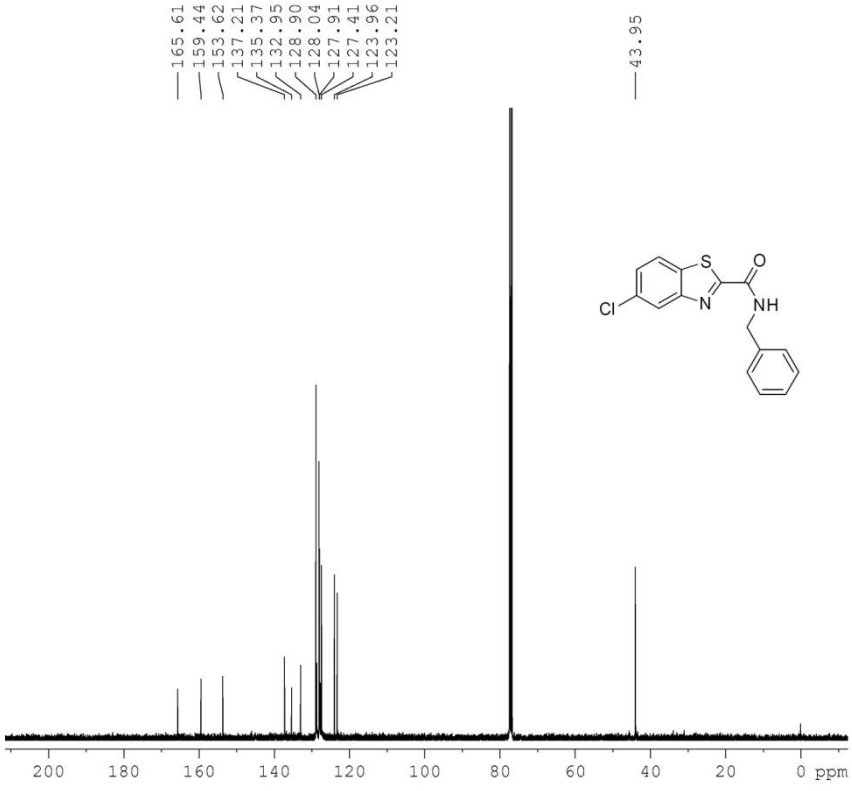

**5.60. $^{13}$C NMR of *N*-(3,4-dimethoxyphenethyl)benzo[*d*]thiazole-2-carboxamide (5az):**



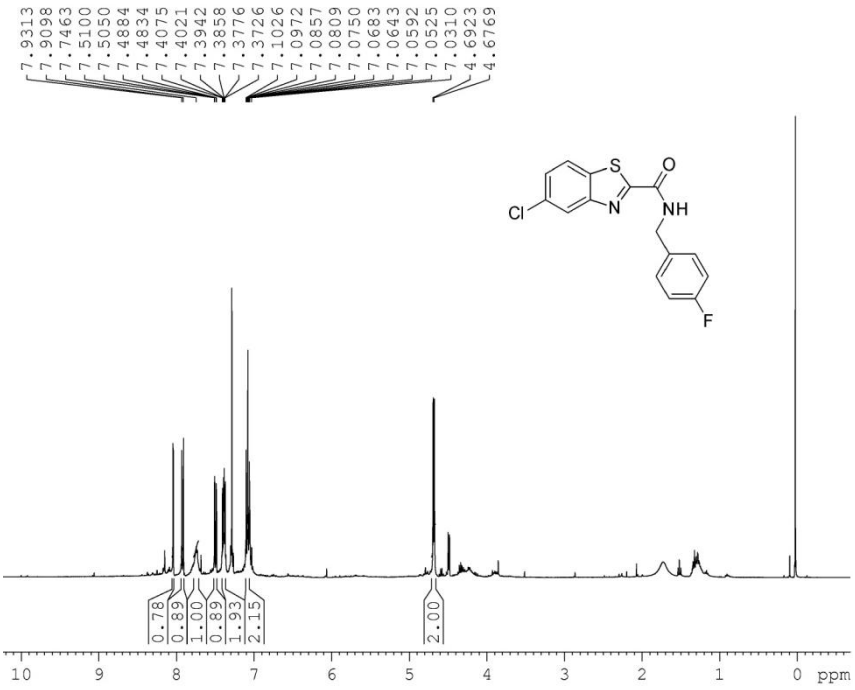
**5.61. $^{1}$H NMR of *N*-Benzyl-5-chlorobenzo[*d*]thiazole-2-carboxamide (5ba):**



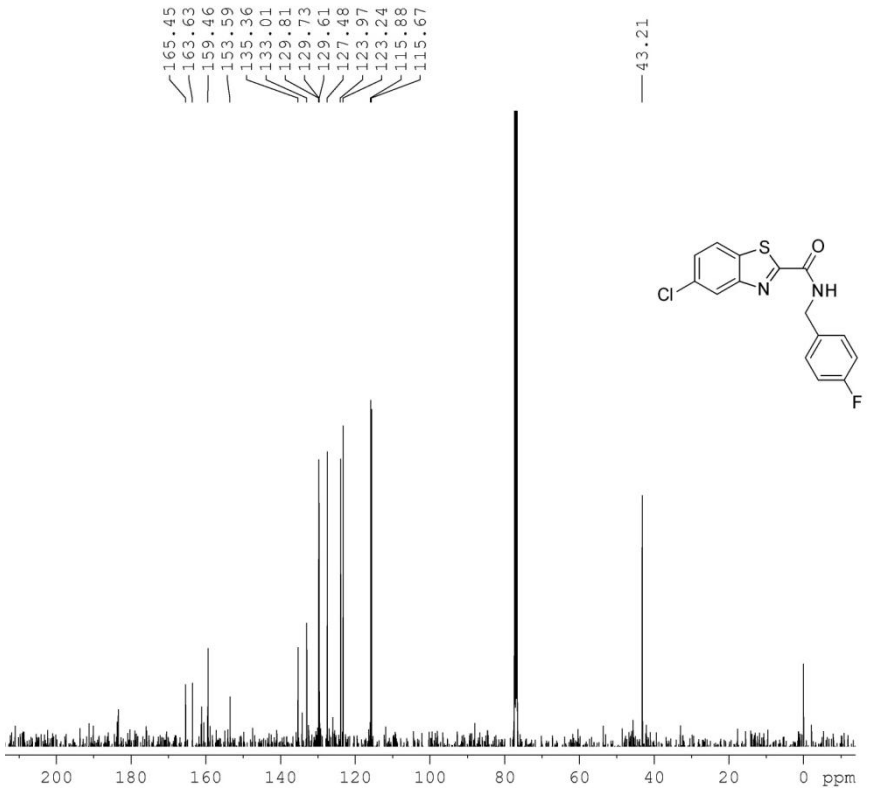

**5.62. $^{13}$C NMR of *N*-Benzyl-5-chlorobenzo[*d*]thiazole-2-carboxamide (5ba):**



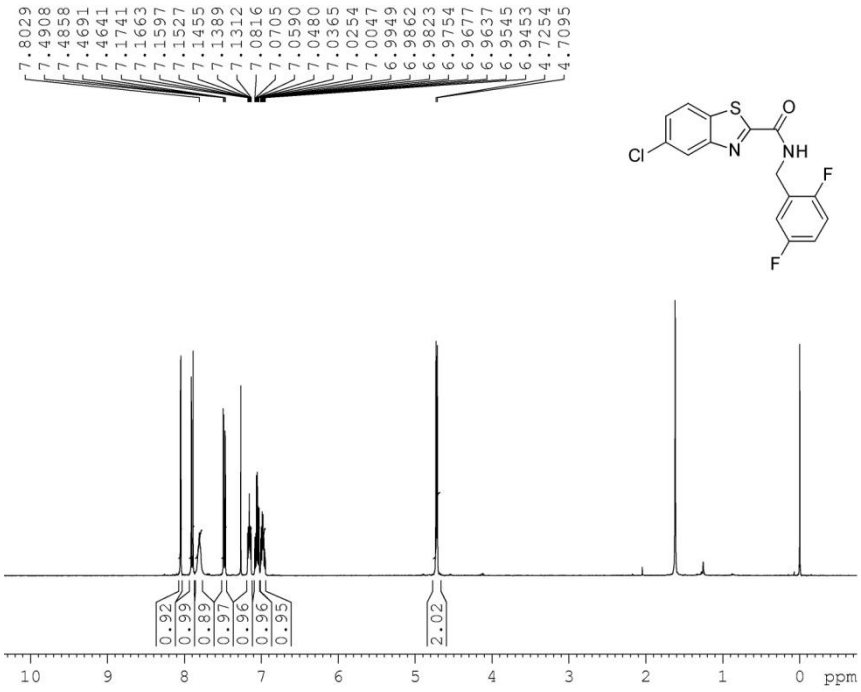
**5.63. $^{1}$H NMR of 5-Chloro-*N*-(4-fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bd):**



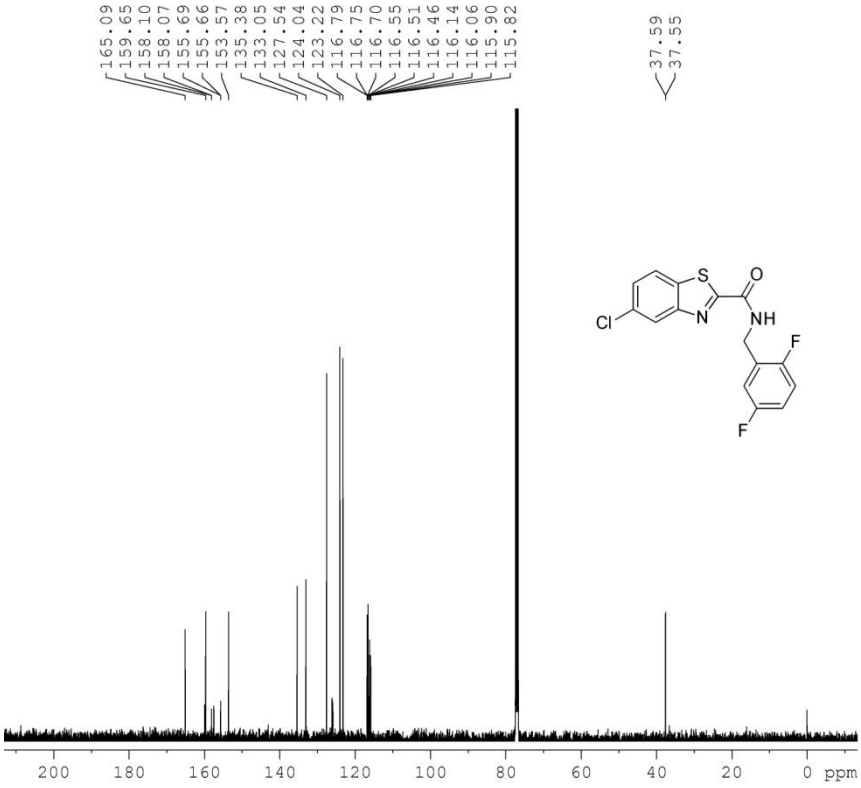

**5.64. $^{13}$C NMR of 5-Chloro-*N*-(4-fluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bd):**



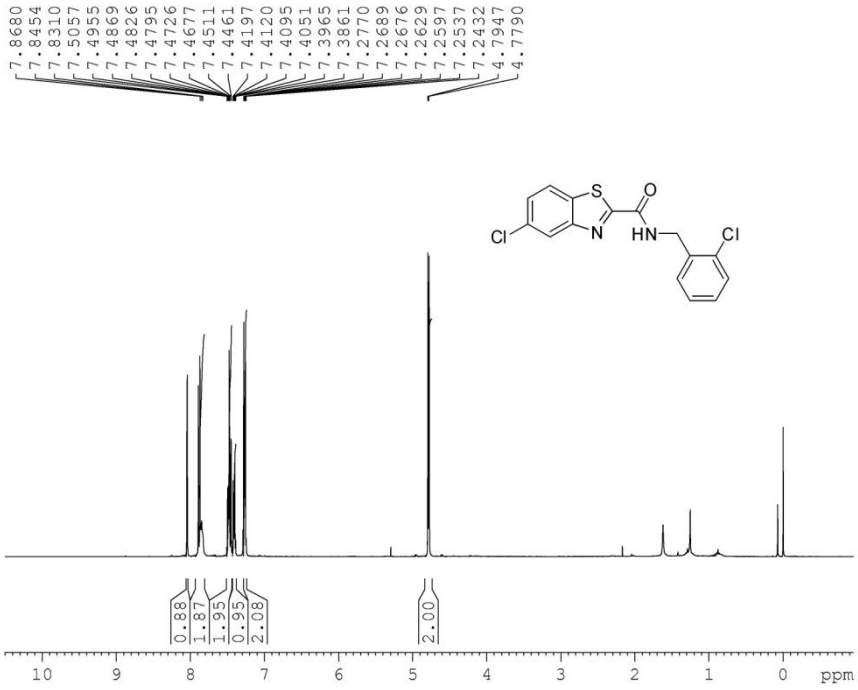
**5.65. $^{1}$H NMR of 5-Chloro-*N*-(2,5-difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bf):**



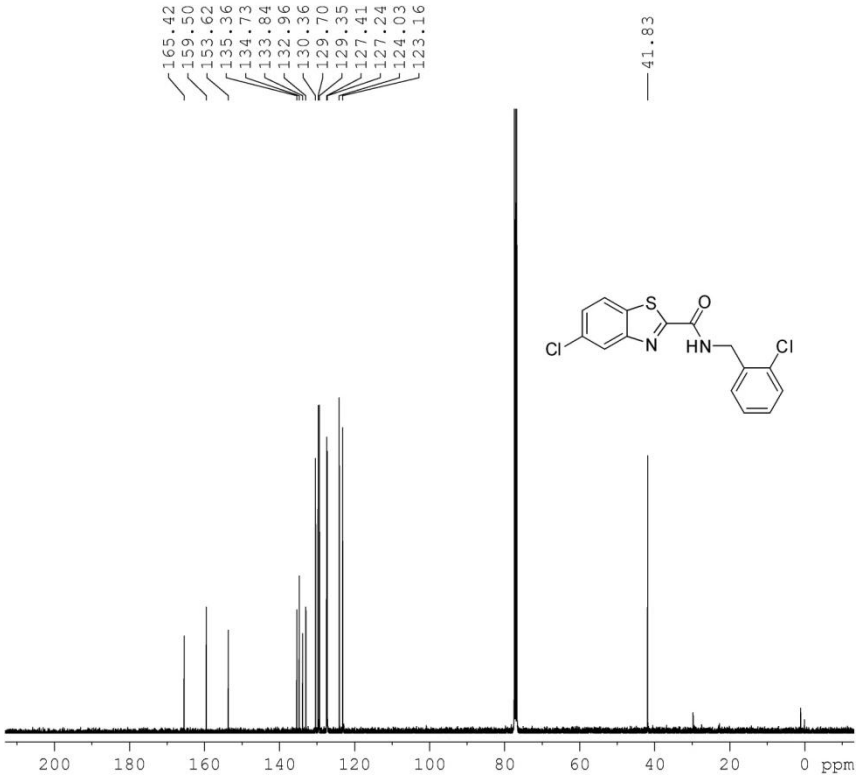

**5.66. $^{13}$C NMR of5-Chloro-*N*-(2,5-difluorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bf):**



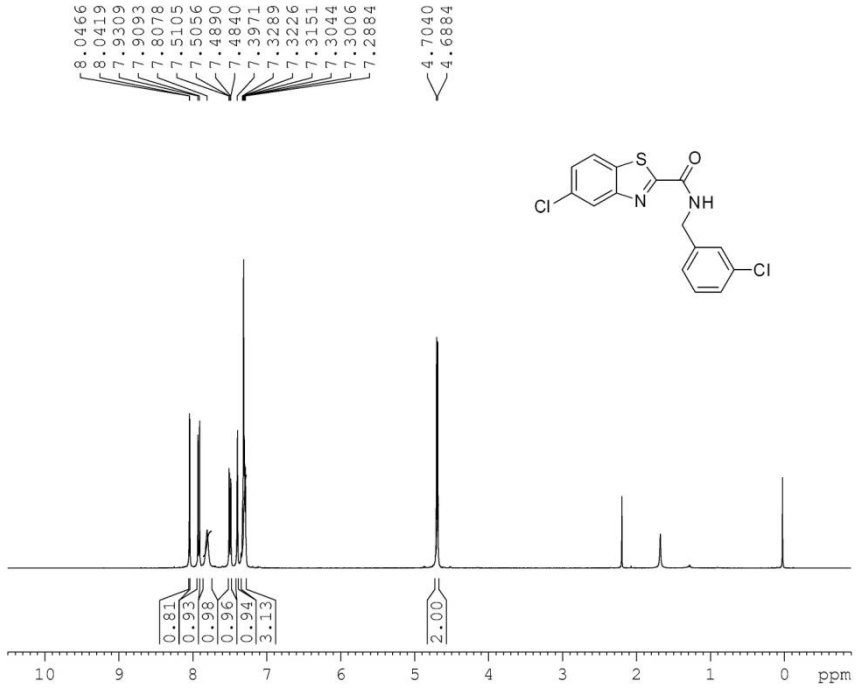
**5.67. $^{13}$C NMR of 5-Chloro-*N*-(2-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bh):**



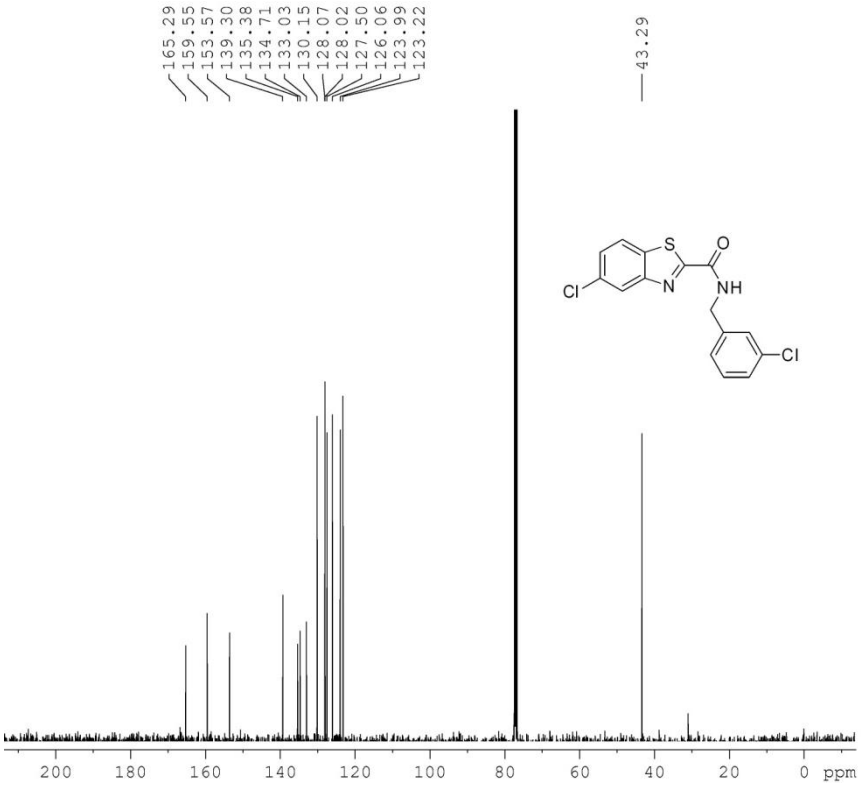

**5.68. $^{1}$H NMR of 5-Chloro-*N*-(2-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bh):**



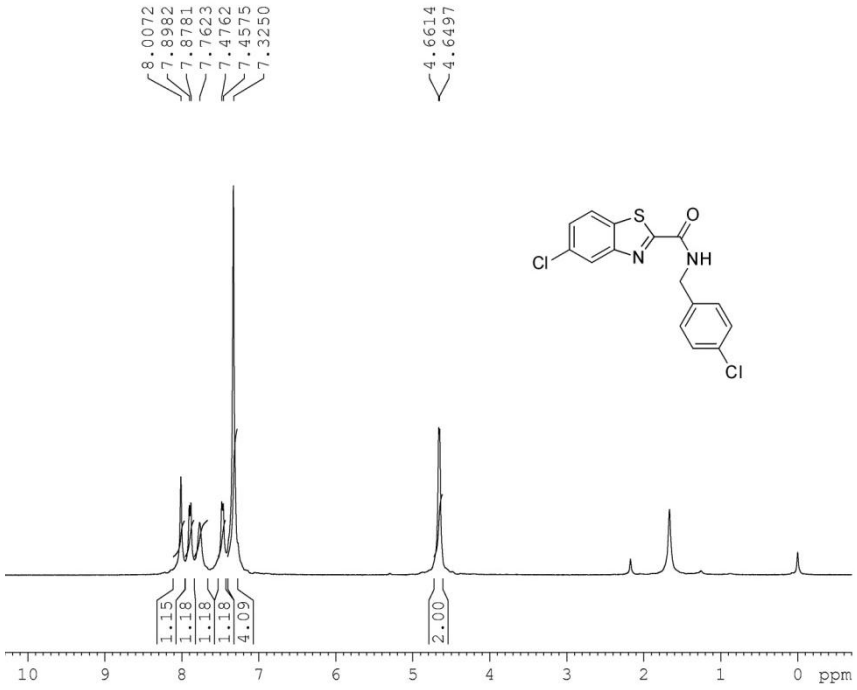
**5.69. $^{13}$C NMR of 5-Chloro-*N*-(3-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bi):**



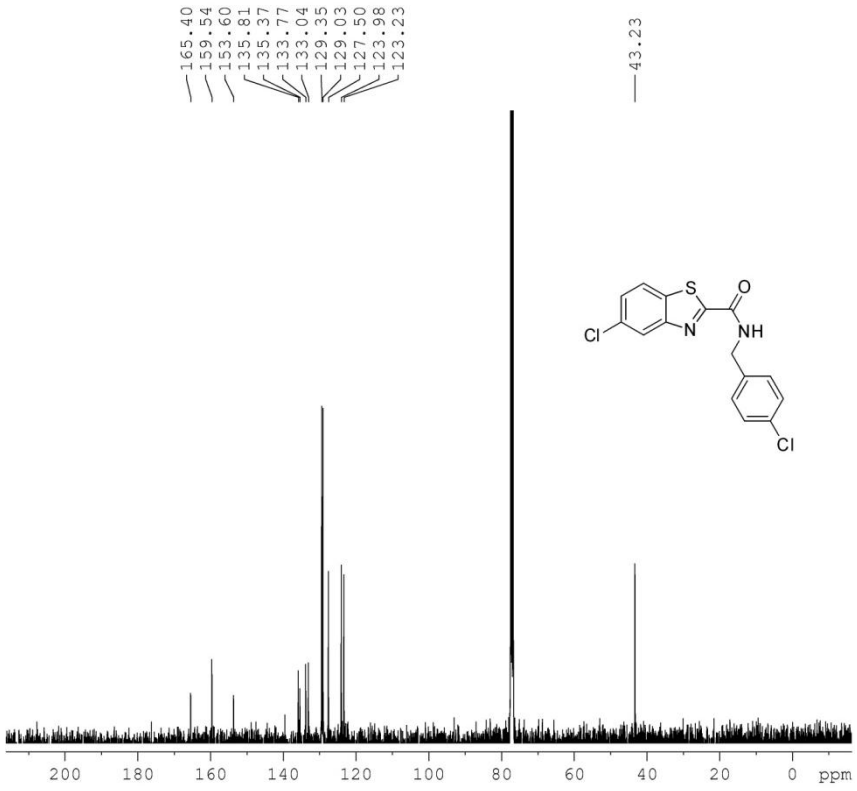

**5.70. $^{1}$H NMR of 5-Chloro-*N*-(3-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bi):**



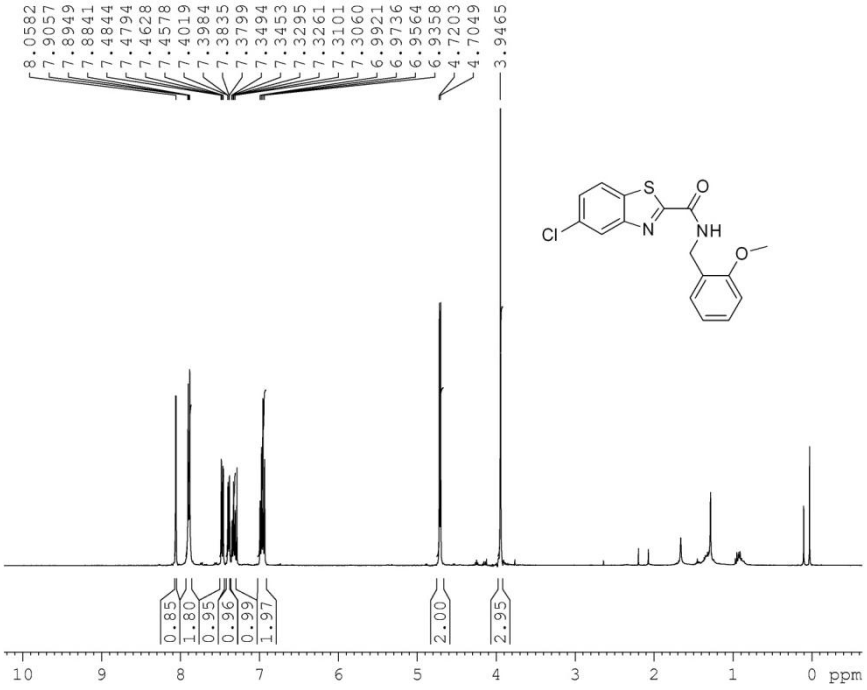
**5.71. $^{13}$C NMR of 5-Chloro-*N*-(4-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bj):**



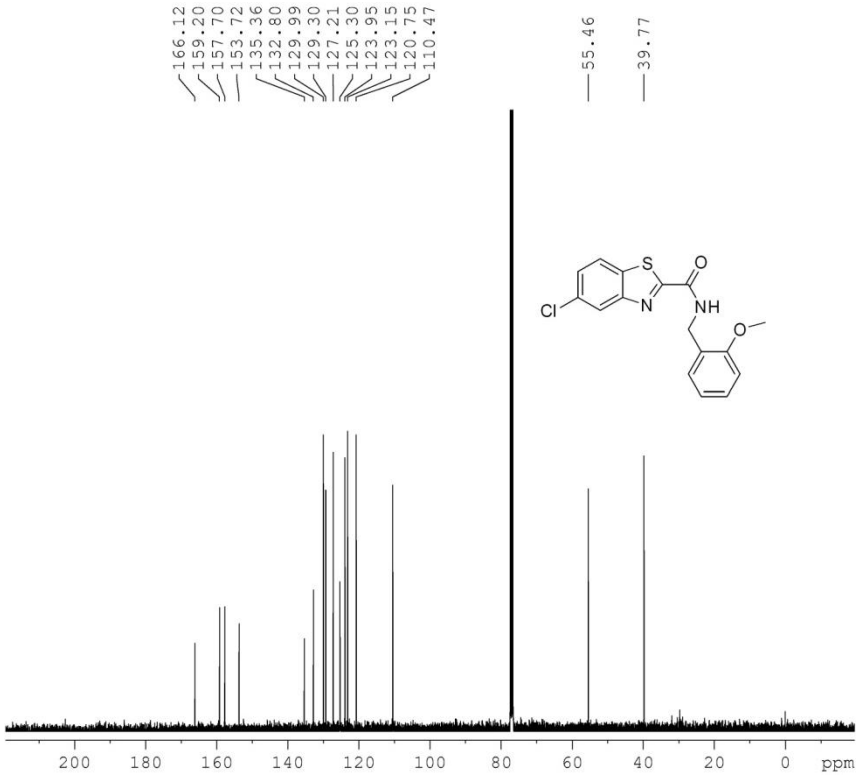

**5.72. $^{1}$H NMR of 5-Chloro-*N*-(4-chlorobenzyl)benzo[*d*]thiazole-2-carboxamide (5bj):**



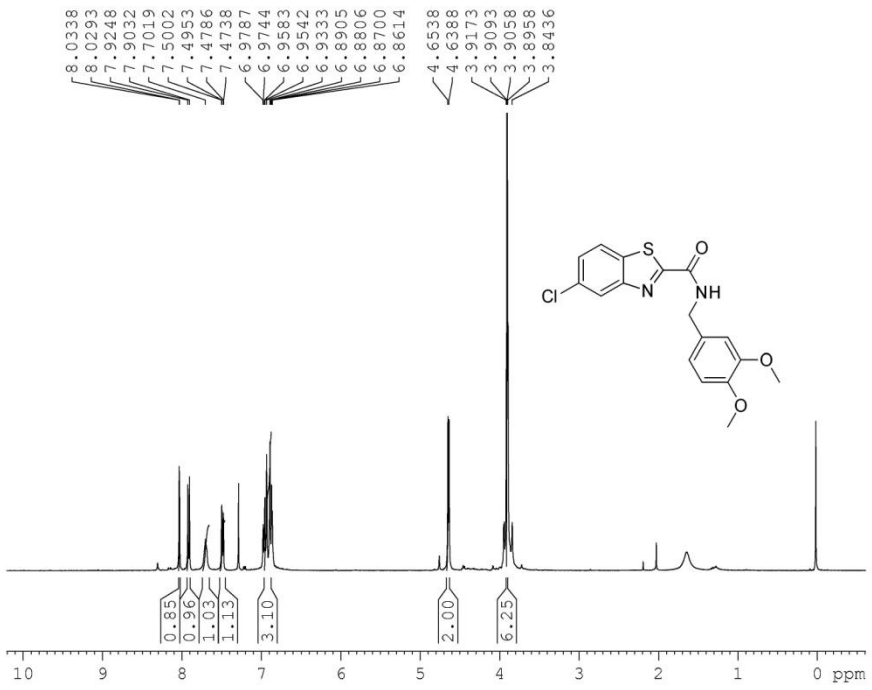
**5.73. $^{13}$C NMR of 5-Chloro-*N*-(2-methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5bo):**



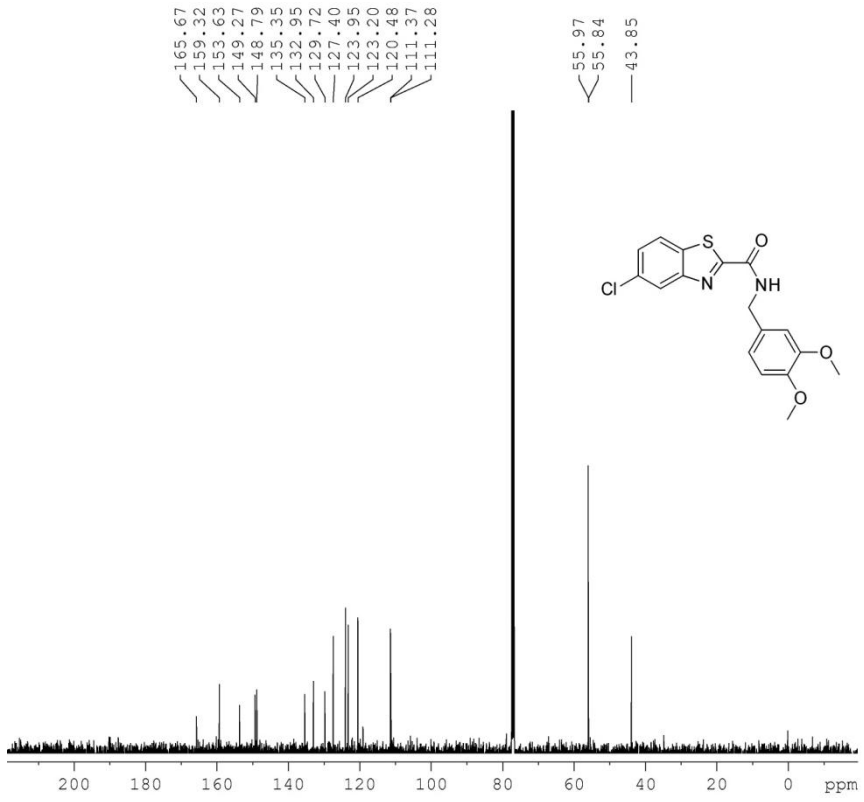

**5.74. $^{1}$H NMR of 5-Chloro-*N*-(2-methoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5bo):**



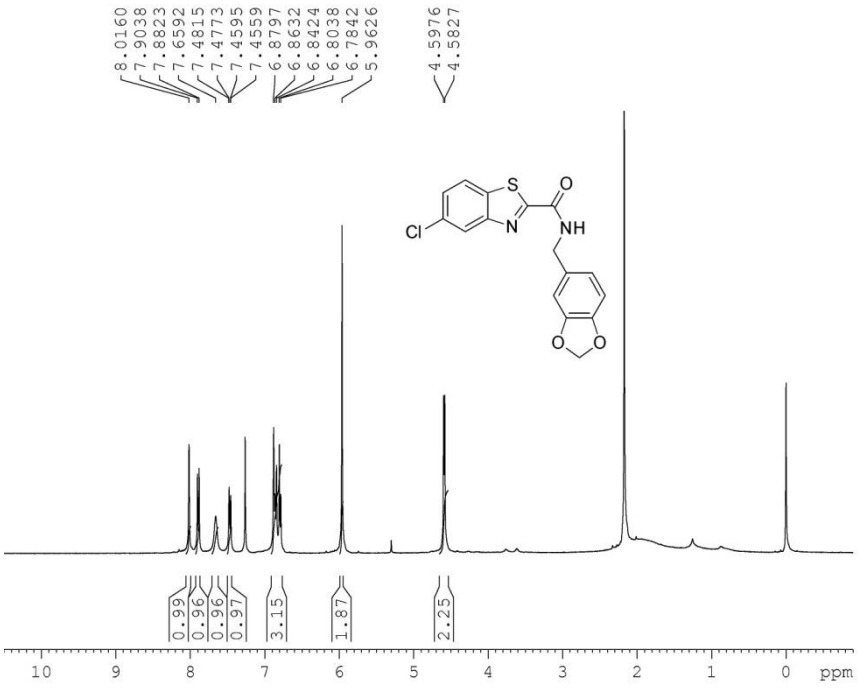
**5.75. $^{13}$C NMR of 5-Chloro-*N*-(3,4-dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5bp):**



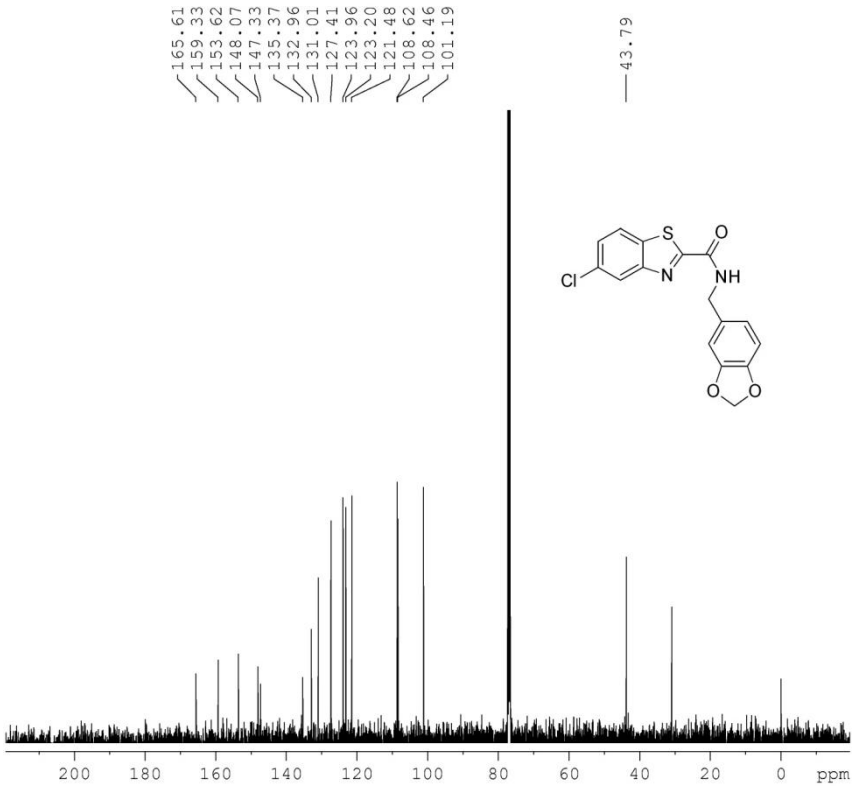

**5.76. $^{1}$H NMR of 5-Chloro-*N*-(3,4-dimethoxybenzyl)benzo[*d*]thiazole-2-carboxamide (5bp):**



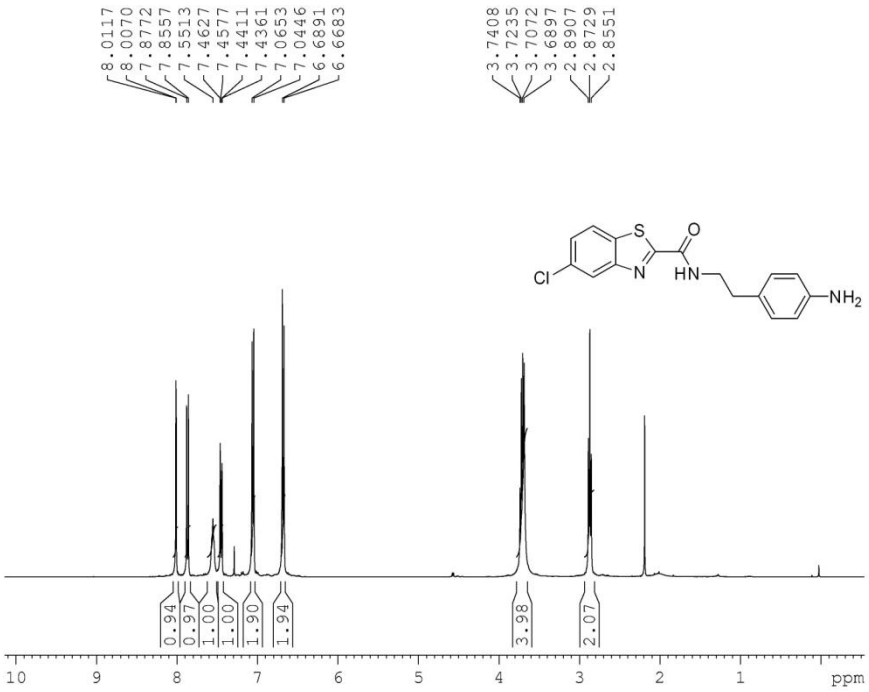
**5.77. $^{1}$H NMR of *N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5-chlorobenzo[*d*]thiazole-2-carboxamide (5bw):**



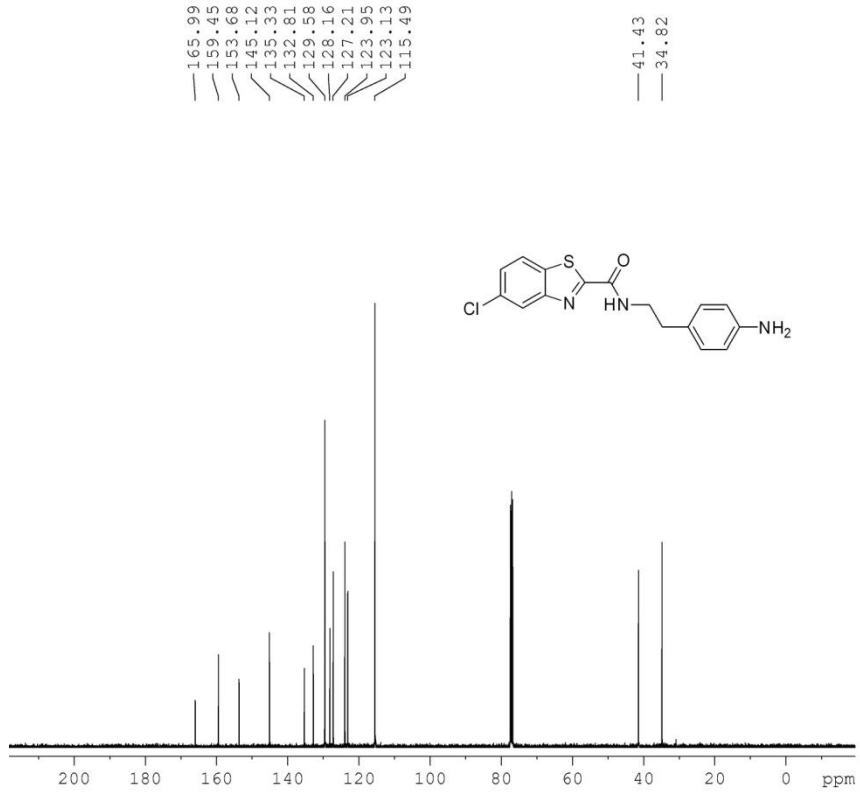

**5.78. $^{13}$C NMR of *N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5-chlorobenzo[*d*]thiazole-2-carboxamide (5bw):**



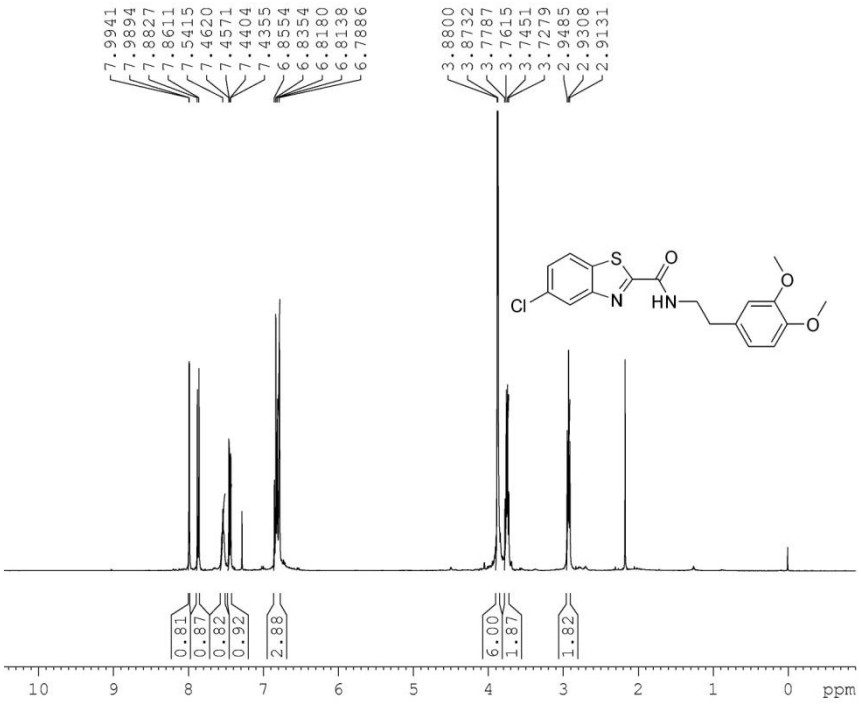
**5.79. $^{1}$H NMR of *N*-(4-Aminophenethyl)-5-chlorobenzo[*d*]thiazole-2-carboxamide (5by):**



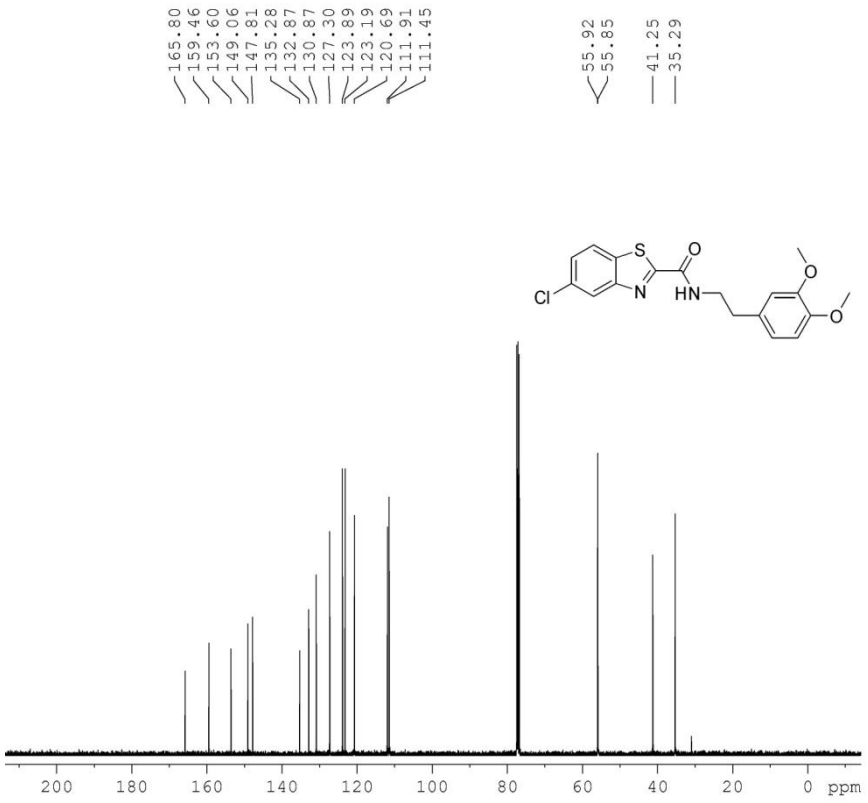

**5.80. $^{13}$C NMR of *N*-(4-Aminophenethyl)-5-chlorobenzo[*d*]thiazole-2-carboxamide (5by):**



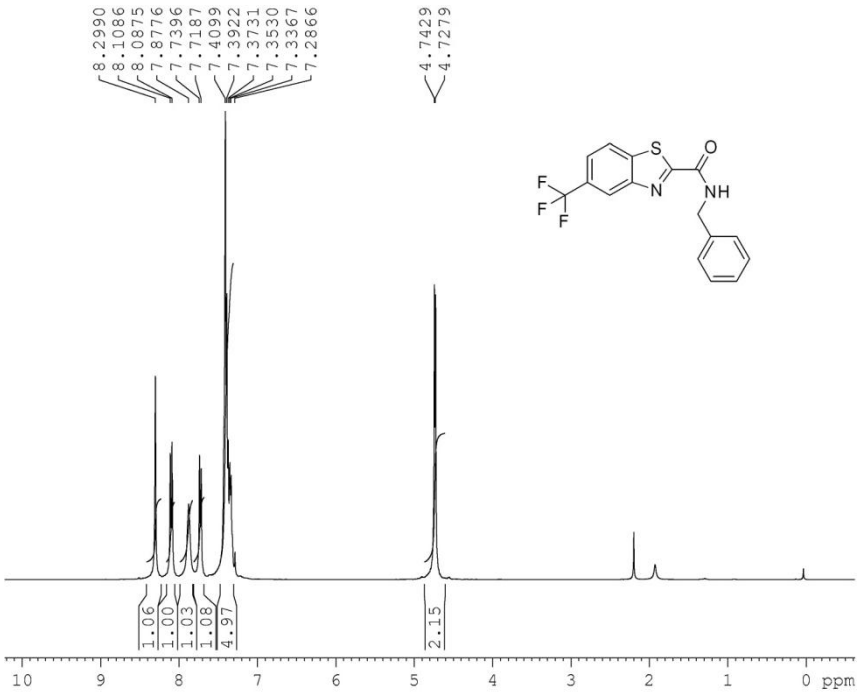
**5.81. $^{1}$H NMR of 5-Chloro-*N*-(3,4-dimethoxyphenethyl)benzo[*d*]thiazole-2-carboxamide (5bz):**



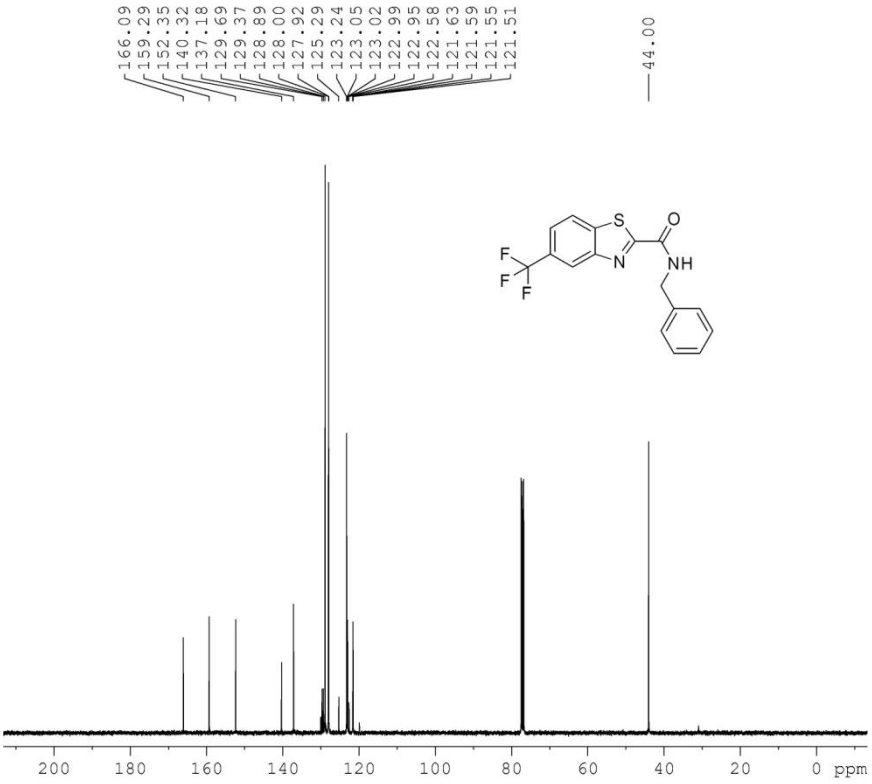

**5.82. $^{13}$C NMR of 5-Chloro-*N*-(3,4-dimethoxyphenethyl)benzo[*d*]thiazole-2-carboxamide (5bz):**



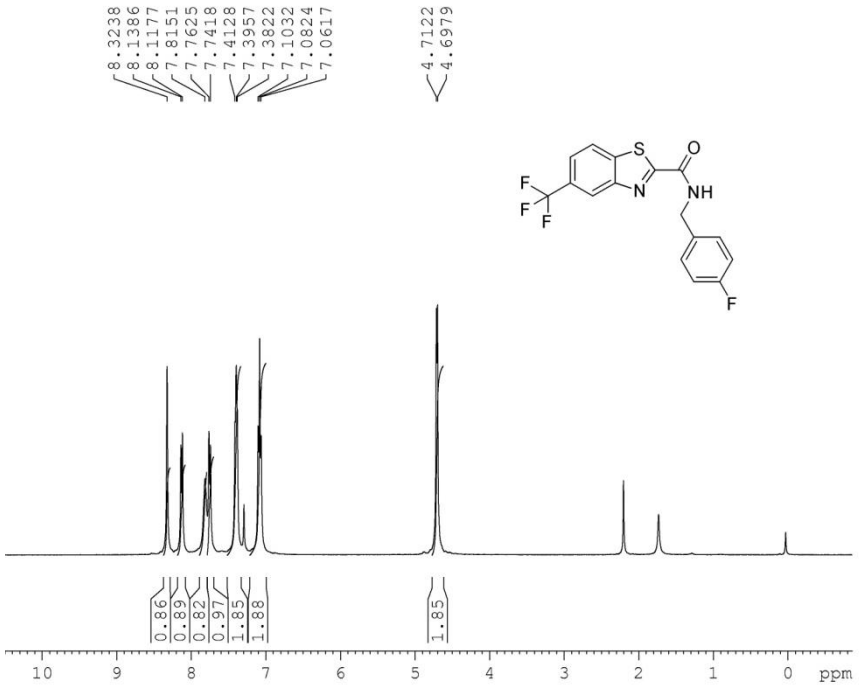
**5.82. $^{1}$H NMR of *N*-Benzyl-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5ca) :**



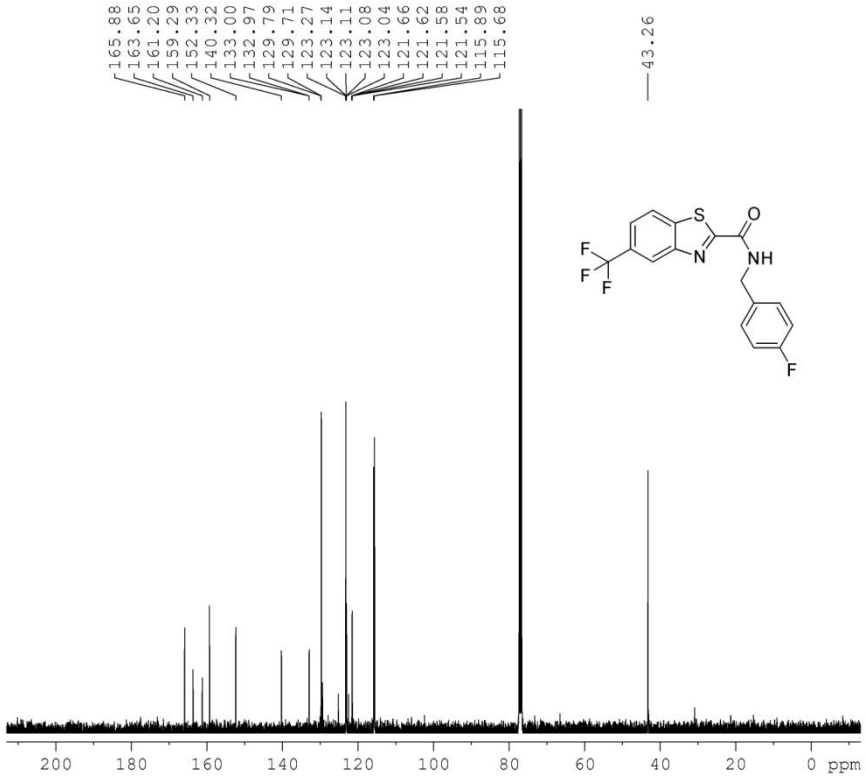

**5.84. $^{13}$C NMR of *N*-Benzyl-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5ca) :**



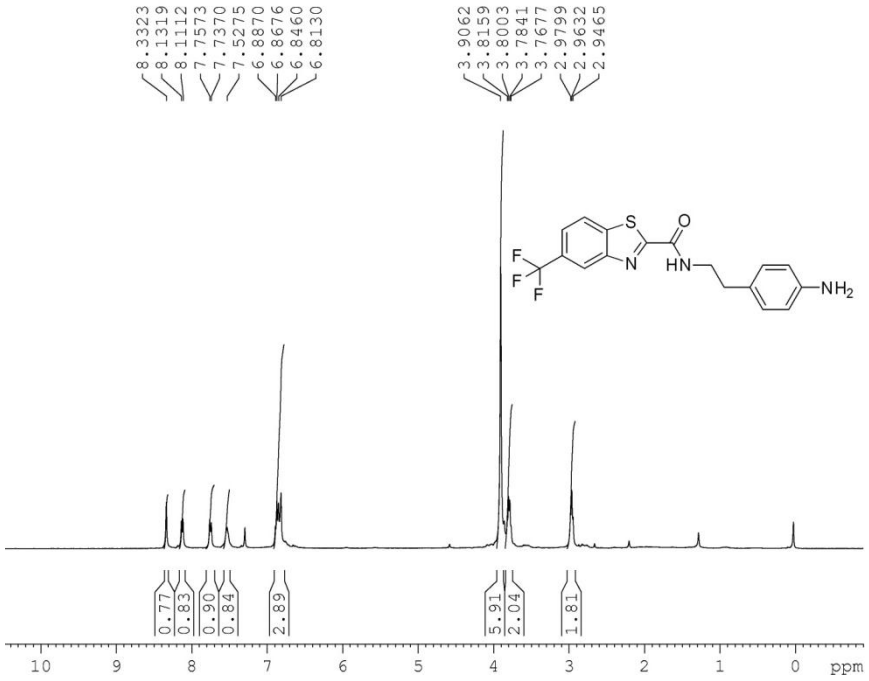
**5.85. $^{1}$H NMR of *N*-(4-Fluorobenzyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cd) :**



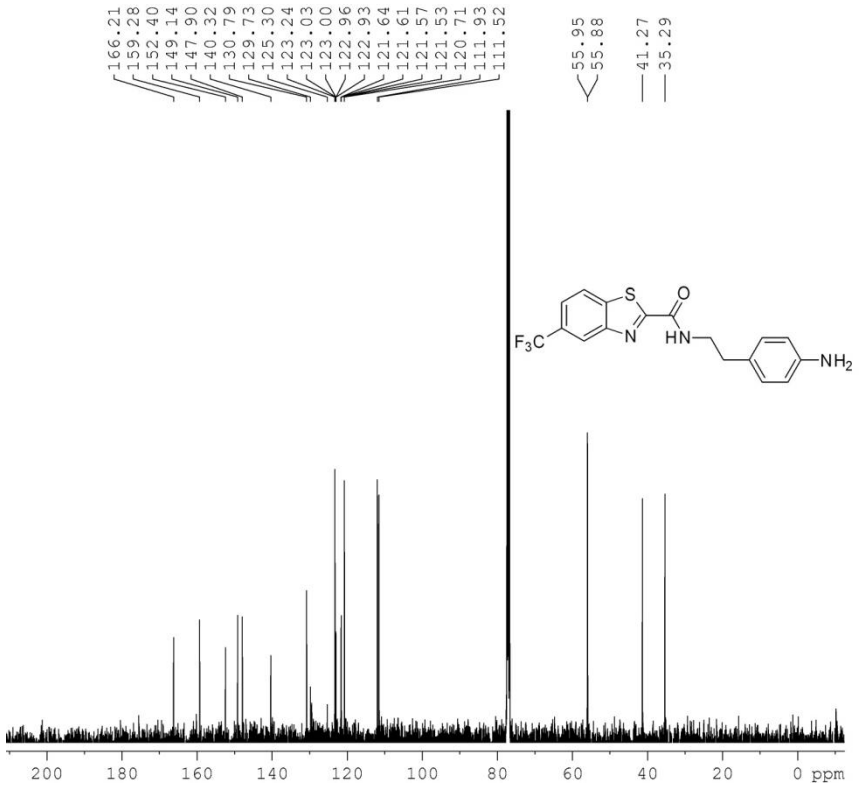

**5.86. $^{13}$C NMR of *N*-(4-Fluorobenzyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cd) :**



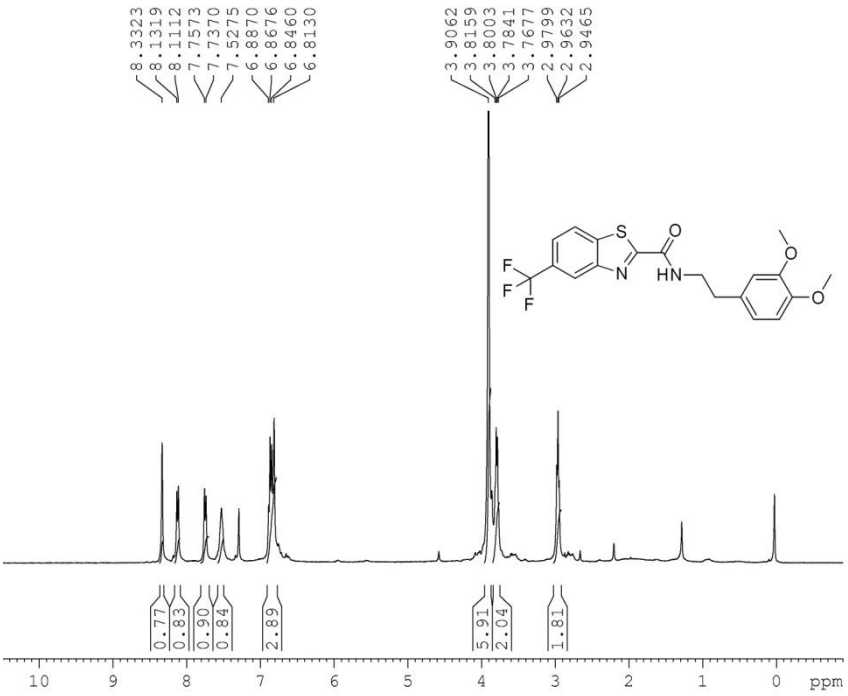
**5.87. $^{1}$H NMR of *N*-(4-Aminophenethyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cy):**



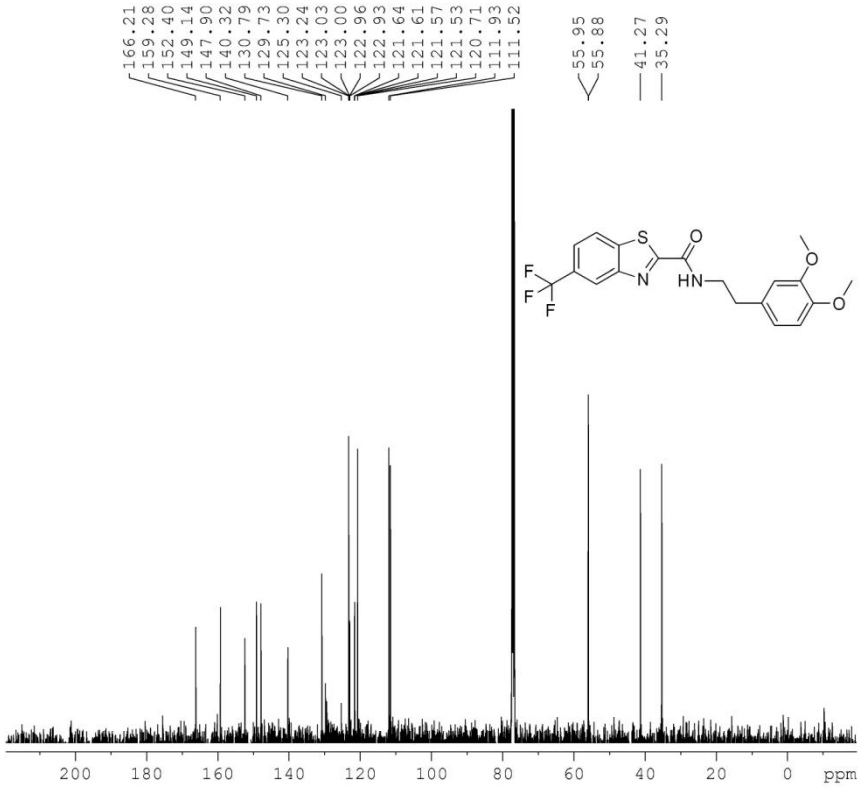

**5.88 $^{13}$C NMR of *N*-(4-Aminophenethyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cy):**



**5.89. $^{1}$H NMR of *N*-(3,4-Dimethoxyphenethyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cz):**




**5.90. $^{13}$C NMR of *N*-(3,4-Dimethoxyphenethyl)-5-(trifluoromethyl)benzo[*d*]thiazole-2-carboxamide (5cz):**



## 6. Biological evaluation

### 6.1. Determination of the minimal inhibitory concentration (MIC) of 2 and *N*-arylmethyl benzo[*d*]thiazole-2-carboxamides:

The drug susceptibility of *Mycobacterium tuberculosis* strain $H_{37}Rv$ was determined using the method recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate. Two-fold serial dilutions (50.0, 25.0, 12.5, 6.25, 3.13, 1.56, 0.78 and 0.4 µg/mL) of each test compounds and drugs were prepared and incorporated into Middlebrook 7H11 agarmedium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H37Rv ATCC 27294 was prepared from fresh Middlebrook 7H11 agar slants with OADC (oleic acid, albumin, dextrose and catalase; Difco) Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to $10^{-2}$ to give a concentration of ~ 107 cfu/mL. A 5 µL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 ºC, and final readings were recorded after 28 days.

### 6.2. Cytotoxicity Evaluation:

Anti-TB active compounds with MIC ≤ 12.5µg/mL were further examined for toxicity in HEK-293T (human embryonic kidney) cell lines by using MTT assay at the concentration of 50 µg/mL. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.

## 7. Docking studies

**7.1.** AutoDock Vina 4.2,[1] a grid-based docking program was used for docking study. The crystal structure of protein HisG (PDB code: 1NH8), which is an ATP-phosphoribosyl transferase (ATP-PRTase), was used. The 3D structure of 1NH8 was reported by Cho et al.[2] using X-ray diffraction technique with a resolution of 1.8 A ˚. The 1NH8 was retrieved from the RCSB protein data bank: URL* http://www.rcsb.org/pdb/explore/explore.do?structureId=1nh8 accessed on December 5, 2013, as a complex bound with the inhibitor adenosine monophosphate (AMP), histidine, sulfate ion. For the docking study, water molecules, AMP ligand, Histidine and sulfate ion were removed from the protein. Protein was prepared using Ligprep model of Schrödinger GLIDE,[3] then the polar hydrogens and united atom *Kollman* charges were assigned for the protein. Then, various inhibitors **5a-x** were docked within the prepared protein (1NH8). The mode of interaction of AMP ligand against HisG 1NH8 was used as standard docked model,

the one used for the calculation of the root mean square deviation (RMSD) of the docked inhibitors.

**7.2. Docking parameters:**

Prior to the AutoDock, AutoGrid was carried out for the preparation of the grid map using a grid box with an npts (number of points in xyz) of 60–60–60 A˚ box, which encloses the original ligand AMP. The box spacing was 0.3 A˚ and grid center was designated at dimensions (x, y, z): 40, 40 and 48. A scoring grid was calculated from the original ligand structure (AMP) to minimize the computation time. Finally AutoDock was run using maximum number of retries and generations of 27,000. The genetic algorithm with local search (GALS) was used for calculation of the docking possibilities. The complexes obtained by AutoDock were minimized using a maximum 300 iterations and the hybrid GALS runs with max of 250 cycles using different random number seeds to obtain score convergence.

**7.3. Preparation of small molecules:**

All the molecular modeling calculations were performed using SYBYL 7.1 (Tripos Inc., USA) molecular modeling package installed on a Silicon Graphics Fuel Workstation running IRIX 6.5.[3] Structures of all monophosphonate derivatives were generated using sketch molecule module. Geometry-optimization was carried out by applying Tripos molecular mechanics force field with conJugate gradient method. No constraints were applied on the internal geometries of the molecules. The minimization was terminated when the energy gradient convergence criterion of 0.001kcal/mol was reached or when the 10,000 steps minimization cycle was exceeded.

**7.4. Evaluation of docked results:**

Pymol [The PyMOL Molecular Graphics System, Version 1.3 Schrödinger, LLC.][4] was utilized for molecular modeling for the evaluation of hydrogen bonds in ligand–receptor interaction. The correct hydrogen bonds were considered if their geometry angle within 110–180° according to Murray-Rust et al.[5] Also Pymol was used for measurement of RMSD, which was computed and expressed in A ˚ as a structural comparison of two molecules in terms of distance. That is, it was measured as distance between the centroid of the docked inhibitor and the original AMP ligand. Initially model was validated with RMSD of docked AMP to that of original AMP ligand, about 0.91 A°.

# 8. References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