

Supporting Information

Design, Synthesis, in Silico Testing, and in Vitro Evaluation of Thiazolidinone-Based Benzothiazole Derivatives as Inhibitors of α -Amylase and α -Glucosidase

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5.2. Spectral analysis

5.2.1. (2Z,5Z)-5-((5-nitrobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (1)

Yield 82%, m.p. 235–236 °C, Light yellow. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.69 (s, 1H, NH), 9.37 (s, 1H, Benzo-thiazole-H), 8.34 (s, 1H, Benzo-thiazole-H), 8.26 (s, 1H, Benzo-thiazole-H), 7.33 (s, 1H, C-H), 7.13 (d, *J* = 8.0Hz, 1H, Thiazole-H), 6.84 (d, *J* = 7.8Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 162.2, 149.3, 148.4, 148.8, 127.4, 125.0, 123.4, 122.2, 121.1, 119.7, 118.8, 115.6, 109.0, 100.5. HR EI-MS: *m/z*calcd for C₁₄H₇N₅O₃S₃ [M]⁺ 388.8162; Found: 388.3820.

5.2.2. (2Z,5Z)-5-((4-nitrobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (2)

Yield 80%, m.p. 233–234°C, Yellow. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.70 (s, 1H, NH), 9.38 (s, 1H, Benzo-thiazole-H), 8.35 (s, 1H, Benzo-thiazole-H), 8.27 (s, 1H, Benzo-thiazole-H), 7.34 (s, 1H, C-H), 7.14 (d, *J* = 8.2Hz, 1H, Thiazole-H), 6.85 (d, *J* = 7.4Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 162.3, 149.4, 148.5, 148.9, 127.6, 125.3, 123.2, 122.7, 121.3, 119.8, 118.6, 115.3, 109.9, 100.6. HR EI-MS: *m/z*calcd for C₁₄H₇N₅O₃S₃ [M]⁺ 388.8159; Found: 388.3816.

5.2.3. (2Z,5Z)-5-((4-chloro-5-nitrobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (3)

Yield 81%, m.p. 233–234°C, Light yellow. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.62 (s, 1H, NH), 9.39 (s, 1H, Benzo-thiazole-H), 8.36 (s, 1H, Benzo-thiazole-H), 7.33 (s, 1H, C-H), 7.10 (d, *J* = 8.1Hz, 1H, Thiazole-H), 6.86 (d, *J* = 8.0Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 162.5, 149.6, 148.9, 148.0, 127.6, 125.9, 123.5, 122.8, 121.5, 119.4, 118.6, 115.5, 109.4, 100.9. HR EI-MS: *m/z*calcd for C₁₄H₆ClN₅O₃S₃ [M]⁺ 422.9130; Found: 422.8980.

5.2.4. (2Z,5Z)-5-((4-fluorobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (4)

Yield 86%, m.p. 237–238 °C, Light green. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.92 (s, 1H, NH), 10.45 (s, 1H, Benzo-thiazole-H), 8.88 (s, 1H, Benzo-thiazole-H), 8.81 (s, 1H, Benzo-thiazole-H), 8.57 (s, 1H, C-H), 7.59 (d, *J* = 6.7Hz, 1H, Thiazole-H), 6.96 (d, *J* = 7.4Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 159.6, 149.6, 147.3, 142.7, 135.8, 129.8, 127.6, 121.2, 119.9, 118.7, 116.0, 114.6, 111.3, 100.9. HR EI-MS: *m/z*calcd for C₁₄H₇FN₄OS₃ [M]⁺ 361.9629; Found: 361.9254.

5.2.5. (2Z,5Z)-5-((5-fluorobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (5)

Yield 82%, m.p. 233–234 °C, Light green. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.90 (s, 1H, NH), 10.41 (s, 1H, Benzo-thiazole-H), 8.84 (s, 1H, Benzo-thiazole-H), 8.79 (s, 1H, Benzo-thiazole-H), 8.55 (s, 1H, C-H), 7.56 (d, *J* = 7.0Hz, 1H, Thiazole-H), 6.94 (d, *J* = 7.1Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 159.5, 149.5, 147.2, 142.6, 135.7, 129.7, 127.5, 121.1, 119.8, 118.6, 116.1, 114.5, 111.2, 100.8. HR EI-MS: *m/z* calcd for C₁₄H₇FN₄OS₃ [M]⁺ 361.9521; Found: 3651.9134.

5.2.6. (2Z,5Z)-5-((7-hydroxy-4-(trifluoromethyl)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (6)

Yield 85%, m.p. 232–233°C, Light yellow. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.70 (s, 1H, NH), 11.33 (s, 1H, OH), 9.70 (s, 1H, Benzo-thiazole-H), 8.42 (s, 1H, Benzo-thiazole-H), 7.88 (s, 1H, C-H), 7.60 (d, *J* = 6.7Hz, 1H, Thiazole-H), 6.85 (d, *J* = 8.3Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 168.4, 167.1, 148.7, 137.6, 136.4, 132.9, 130.1, 129.6, 127.5, 126.7, 125.0, 120.6, 118.5, 116.0, 112.1. HR EI-MS: *m/z* calcd for C₁₅H₇F₃N₄O₂S₃ [M]⁺ 427.8691; Found: 427.8630.

5.2.7. (2Z,5Z)-5-((4,7-dihydroxybenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (7)

Yield 92%, m.p. 232–233°C, Light brown. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.73 (s, 1H, NH), 11.38 (s, 1H, OH), 11.32 (s, 1H, OH), 9.73 (s, 1H, Benzo-thiazole-H), 8.49 (s, 1H, Benzo-thiazole-H), 7.70 (s, 1H, C-H), 7.63 (d, *J* = 7.7Hz, 1H, Thiazole-H), 6.89 (d, *J* = 7.3Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 160.9, 148.1, 129.6, 129.3, 128.2, 126.7, 125.5, 124.8, 122.4, 119.5, 116.1, 115.0, 112.2, 101.8. HR EI-MS: *m/z* calcd for C₁₄H₈N₄O₃S₃ [M]⁺ 375.9429; Found: 375.9380.

5.2.8. (2Z,5Z)-5-((7-hydroxy-5-methoxybenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (8)

Yield 84%, m.p. 227–228°C, Light gray. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.69 (s, 1H, NH), 11.26 (s, 1H, OH), 9.66 (s, 1H, Benzo-thiazole-H), 8.38 (s, 1H, Benzo-thiazole-H), 7.61 (s, 1H, C-H), 7.58 (d, *J* = 7.6Hz, 1H, Thiazole-H), 6.77 (d, *J* = 7.8Hz, 1H, Thiazole-H), 2.41 (s, 3H, CH₃), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 160.7, 148.9, 129.2, 129.8, 128.3, 126.4, 125.0, 124.2, 122.1, 119.7, 116.6, 115.5, 112.9, 101.4, 43.6. HR EI-MS: *m/z* calcd for C₁₅H₁₀N₄O₃S₃ [M]⁺ 389.4511; Found: 389.4480.

5.2.9. (2Z,5Z)-5-((7-(2-chloro-3-nitrophenyl)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (9)

Yield 81%, m.p. 241–242 °C, Light brown. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.38 (s, 1H, NH), 8.66 (s, 1H, Benzo-thiazole-H), 8.45 (d, *J* = 7.9Hz, 1H, Benzo-thiazole-H), 8.26 (s, 1H, C-H), 8.17 (t, *J* = 8.1Hz, 1H, Ar-H), 7.80 (d, *J* = 7.9Hz, 1H, Benzo-thiazole-H), 7.65 (d, *J* = 7.9Hz, 1H, Ar-H), 7.57 (d, *J* = 7.9Hz, 1H, Ar-H), 7.05 (d, *J* = 8.2Hz, 1H, Thiazole-H), 7.00 (d, *J* = 8.6Hz, 1H, Thiazole-H), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 165.5, 163.6, 162.4, 149.0, 147.6, 142.4, 140.1, 138.0, 134.8, 131.7, 130.0, 128.2, 127.5, 126.9, 124.0, 123.7, 120.1, 117.7, 115.0. HR EI-MS: *m/z* calcd for C₂₀H₁₀ClN₅O₃S₃ [M]⁺ 498.0937; Found: 498.0830.

5.2.10. (2Z,5Z)-5-((4-(dimethylamino)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (10)

Yield 84%, m.p. 227–228 °C, Light gray. ¹H-NMR (600 MHz, DMSO-*d*₆): δ 11.36 (s, 1H, NH), 8.18 (d, *J* = 2.2Hz, 1H, Benzo-thiazole-H), 8.12 (d, *J* = 2.4Hz, 1H, Benzo-thiazole-H), 7.87 (s, 1H, Benzo-thiazole-H), 7.24 (s, 1H, C-H), 7.58 (d, *J* = 7.7Hz, 1H, Thiazole-H), 7.20 (d, *J* = 7.5Hz, 1H, Thiazole-H), 2.38 (s, 6H, -NCH₃), ¹³C-NMR (150 MHz, DMSO-*d*₆): δ 160.4, 159.3, 149.9, 147.7,

142.8, 135.3, 129.1, 127.4, 121.6, 119.7, 118.0, 116.8, 114.6, 111.7, 39.6, 39.5. HR EI-MS: m/z calcd for $C_{16}H_{13}N_5OS_3$ $[M]^+$ 387.0630; Found: 387.0518.

5.2.11. (2Z,5Z)-5-((7-chloro-5-hydroxybenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (11)

Yield 90%, m.p. 236–237°C, Light yellow. 1H -NMR (600 MHz, DMSO- d_6): δ 11.86 (s, 1H, NH), 11.59 (s, 1H, OH), 9.80 (s, 1H, Benzo-thiazole-H), 8.36 (s, 1H, Benzo-thiazole-H), 7.51 (s, 1H, C-H), 7.56 (d, J = 6.9Hz, 1H, Thiazole-H), 6.85 (d, J = 8.0Hz, 1H, Thiazole-H), ^{13}C -NMR (150 MHz, DMSO- d_6): δ 159.3, 147.8, 128.7, 128.6, 127.5, 125.4, 124.6, 123.9, 121.5, 118.6, 115.7, 114.7, 111.4, 100.9. HR EI-MS: m/z calcd for $C_{14}H_7ClN_4O_2S_3$ $[M]^+$ 393.9155; Found: 393.9060.

5.2.12. (2Z,5Z)-5-((7-chloro-4-hydroxybenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (12)

Yield 83%, m.p. 234–235°C, Yellowish white. 1H -NMR (600 MHz, DMSO- d_6): δ 11.88 (s, 1H, NH), 11.61 (s, 1H, OH), 9.82 (s, 1H, Benzo-thiazole-H), 8.38 (s, 1H, Benzo-thiazole-H), 7.54 (s, 1H, C-H), 7.59 (d, J = 7.9Hz, 1H, Thiazole-H), 6.87 (d, J = 7.0Hz, 1H, Thiazole-H), ^{13}C -NMR (150 MHz, DMSO- d_6): δ 159.2, 147.7, 128.6, 128.5, 127.4, 125.3, 124.5, 123.8, 121.4, 118.5, 115.6, 114.6, 111.3, 100.8. HR EI-MS: m/z calcd for $C_{14}H_7ClN_4O_2S_3$ $[M]^+$ 393.9130; Found: 393.9003.

5.2.13. (2Z,5Z)-5-((7-chlorobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (13)

Yield 89%, m.p. 226–227°C, Light yellow. 1H -NMR (600 MHz, DMSO- d_6): δ 11.70 (s, 1H, NH), 9.22 (s, 1H, Benzo-thiazole-H), 8.55 (s, 1H, Benzo-thiazole-H), 8.44 (s, 1H, Benzo-thiazole-H), 8.37 (s, 1H, C-H), 7.50 (d, J = 7.2Hz, 1H, Thiazole-H), 6.80 (d, J = 7.8Hz, 1H, Thiazole-H), ^{13}C -NMR (150 MHz, DMSO- d_6): δ 159.6, 149.6, 147.3, 142.7, 135.8, 129.8, 127.6, 121.2, 119.9, 118.7,

116.0, 114.6, 111.3, 101.9. HR EI-MS: m/z calcd for $C_{14}H_7ClN_4OS_3$ $[M]^+$ 377.7210; Found: 377.7180.

5.2.14. (2Z,5Z)-5-((4,5-dichlorobenzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (14)

Yield 84%, m.p. 235–236°C, Light yellow. 1H -NMR (600 MHz, DMSO- d_6): δ 11.66 (s, 1H, NH), 9.17 (s, 1H, Benzo-thiazole-H), 8.48 (s, 1H, Benzo-thiazole-H), 8.33 (s, 1H, C-H), 7.45 (d, J = 7.1Hz, 1H, Thiazole-H), 6.77 (d, J = 6.8Hz, 1H, Thiazole-H), ^{13}C -NMR (150 MHz, DMSO- d_6): δ 159.8, 149.4, 147.0, 142.3, 135.2, 129.7, 127.5, 121.1, 119.8, 118.6, 116.7, 114.4, 111.2, 101.9. HR EI-MS: m/z calcd for $C_{14}H_6Cl_2N_4OS_3$ $[M]^+$ 411.8238; Found: 411.8028.

5.2.15. 3-(6-((Z)-((Z)-4-oxo-2-(thiazol-2-ylimino)thiazolidin-5-ylidene)methyl)benzo[d]thiazol-7-yl)benzonitrile (15)

Yield 88%, m.p. 243–244 °C, Light brown. 1H -NMR (600 MHz, DMSO- d_6): δ 11.33 (s, 1H, NH), 9.68 (s, 1H, Benzo-thiazole-H), 8.33 (d, J = 6.7Hz, 1H, Benzo-thiazole-H), 8.14 (d, J = 6.7Hz, 1H, Benzo-thiazole-H), 8.19-8.15 (m, 1H, Ar-H), 7.88 (s, 1H, C-H), 7.26 (d, J = 7.2Hz, 1H, Thiazole-H), 7.17 (dd, J = 8.2, 1.3Hz, 1H, Ar-H), 7.06 (d, J = 8.6Hz, 1H, Thiazole-H), 6.97 (t, J = 1.9Hz, 1H, Ar-H), ^{13}C -NMR (150 MHz, DMSO- d_6): δ 168.9, 148.2, 148.1, 146.1, 145.9, 141.5, 135.6, 135.0, 126.0, 124.8, 121.5, 121.0, 120.8, 119.0, 117.8, 114.9, 114.1, 112.3, 111.6, 109.8, 43.3. HR EI-MS: m/z calcd for $C_{21}H_{11}N_5OS_3$ $[M]^+$ 445.0113; Found: 445.0104.

5.3 α -amylase inhibitory assay protocol

20 μ L of α -amylase solution (0.5 mg/ml) was added to phosphate buffer (pH 6.9, 0.02 M, 200 μ L). 250 μ L of test samples (10-50 μ g/mL) was added, to all the above solutions and kept for incubation for 10 min. 1% starch solution (200 μ L) was further added and again kept for incubation for 10 min at a temperature of 25°C. Termination of the reaction was affected by the addition of 400 μ L of 3, 5-dinitrosalicylic acid (DNS) reagent. Lastly, it was incubated in water (at 70°C, 5 min). The

absorbance was recorded using an ELISA microplate reader at 540 nm. Acarbose was served as the standard. All the reactions were carried out in triplicates. The reaction mixture, devoid of the test sample, served as control. The following formula was employed to calculate percentage inhibition. The IC₅₀ values are tabulated in table-7 [1].

$$\% \text{ Inhibition} = [(Ac - As) / Ac] \times 100 \text{ Ac-Control absorbance, As-Standard absorbance}$$

5.4 α -glucosidase inhibitory assay protocol

10 μ l of the α -glucosidase enzyme, 20 μ l of test samples (10-50 μ g/ml) and 50 μ l, of 0.1M phosphate buffer (pH=6.8), were incubated at 37°C for 15 min in a 96-well plate. 20 μ l of p-nitrophenyl—D-glucopyranoside solution was further added as a substrate and again incubated for 20 min at 37 oC. Sodium carbonate (50 μ l of 0.1M) was added to terminate the reaction. P-nitrophenol was liberated, during the reaction which was measured at 405nm using an ELISA microplate reader. Acarbose served as the standard. A control was prepared under similar conditions by omitting test samples. All the experiments were carried out in triplicates. The percentage inhibition was calculated by the formula. The IC₅₀ values are tabulated in table-7 [1].

$$\% \text{ Inhibition} = [(Ac - As) / Ac] \times 100 \text{ Ac-absorbance for control, As-absorbance for standard.}$$

5.5 Molecular docking assay

In this study the synthesized compounds were analyzed against α -amylase and α -glucosidase enzyme. In the first step protein was prepared by using DSV by removing water molecules and already present ligand were removed save both the target protein as well as prepared ligand in PDB format. The process was further carried out in auto dock in which polar hydrogen and Kollman and Gasteiger charges were added to protein. Selected ligand was also prepared done by using torsion tree to detect root. Moreover, configuration file was generated along with X, Y and Z axis save both ligand and protein in PDBQT format in the same docking folder. At the end command prompt was used to generate varied poses of ligand thus, 9 different poses were obtained in PDBQT format. The dock protein and ligand were then open in DSV to identify the binding interaction of ligand with active sites of enzyme [2].

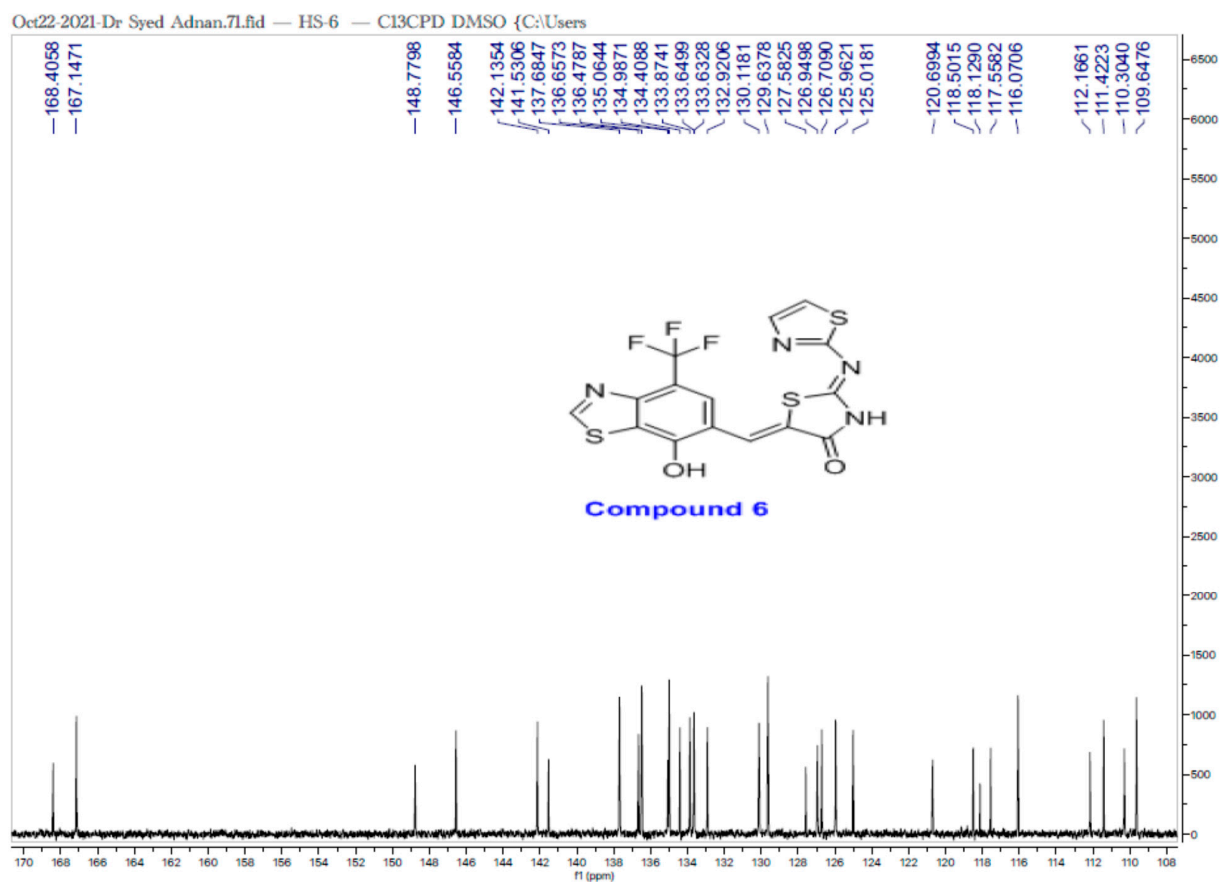


Figure S1. High resolution ^{13}C NMR spectra of (2*Z*,5*Z*)-5-((7-hydroxy-4-(trifluoromethyl)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (6)

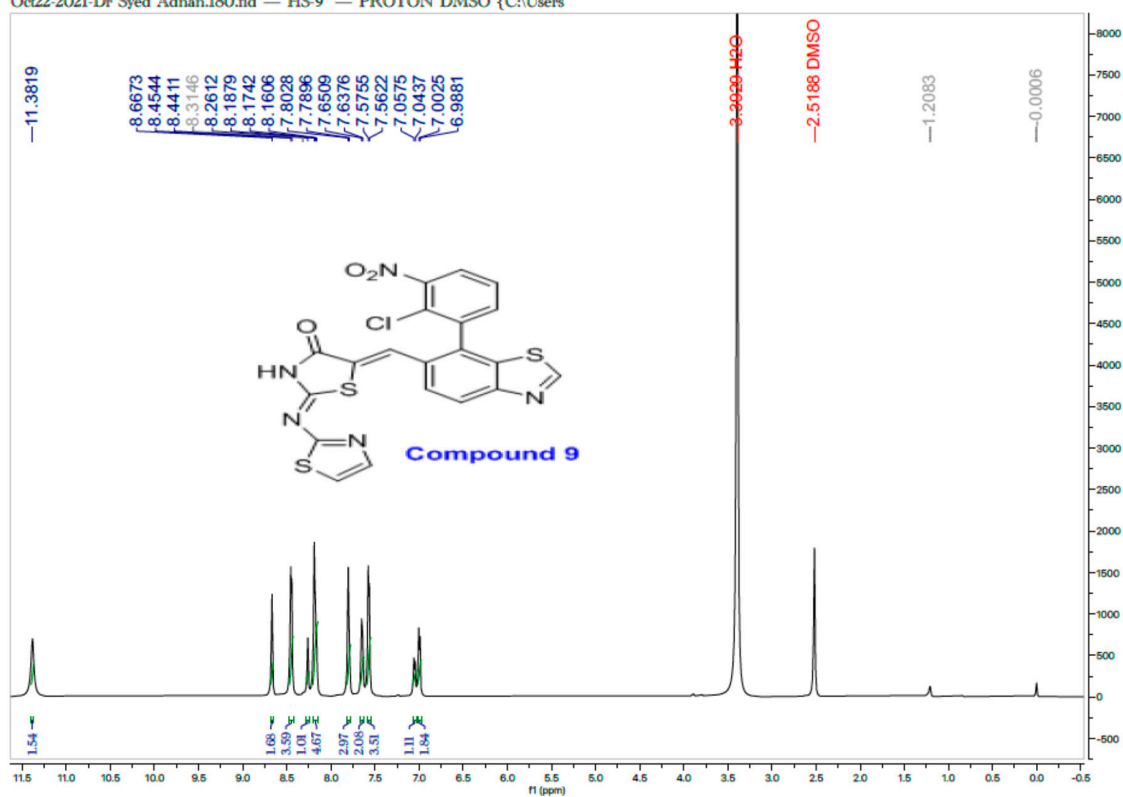
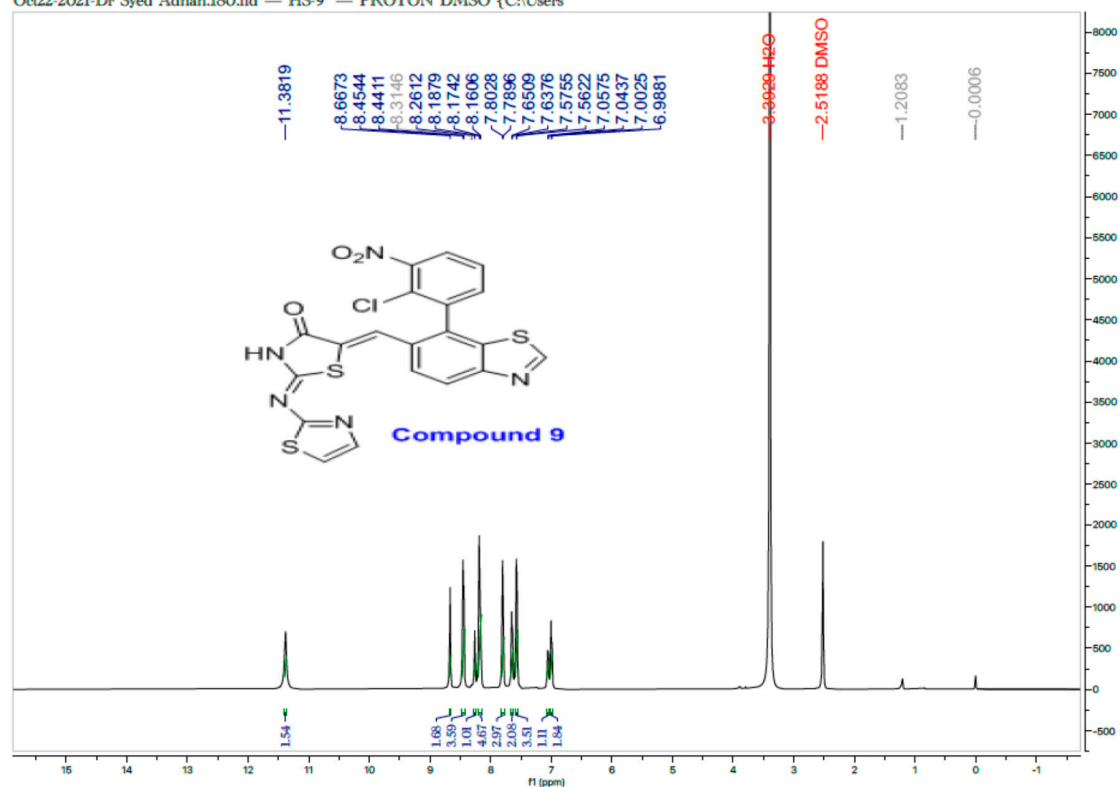


Figure S2. Low resolution Proton NMR Spectra of (2Z,5Z)-5-((7-(2-chloro-3-nitrophenyl)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (9)

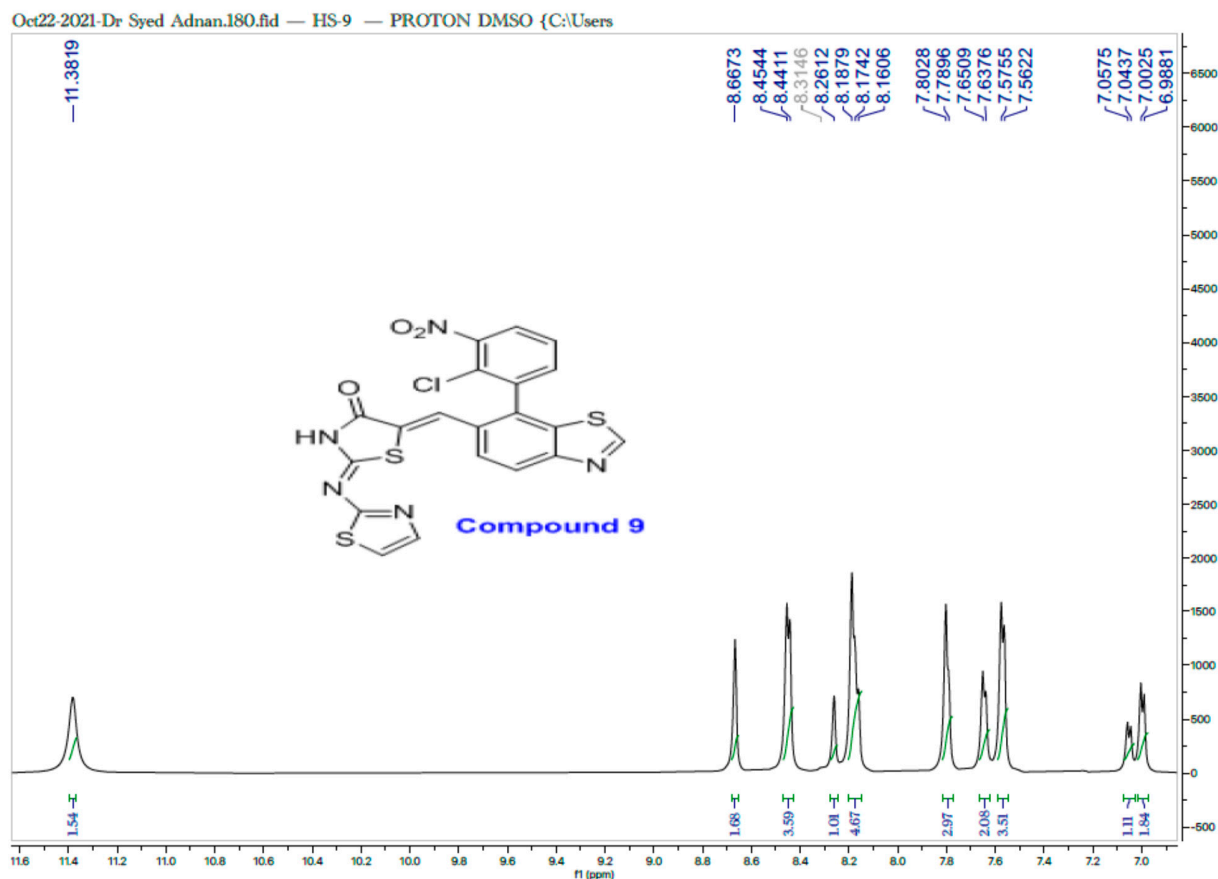


Figure S3. High resolution Proton NMR Spectra of (2Z,5Z)-5-((7-(2-chloro-3-nitrophenyl)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (9)

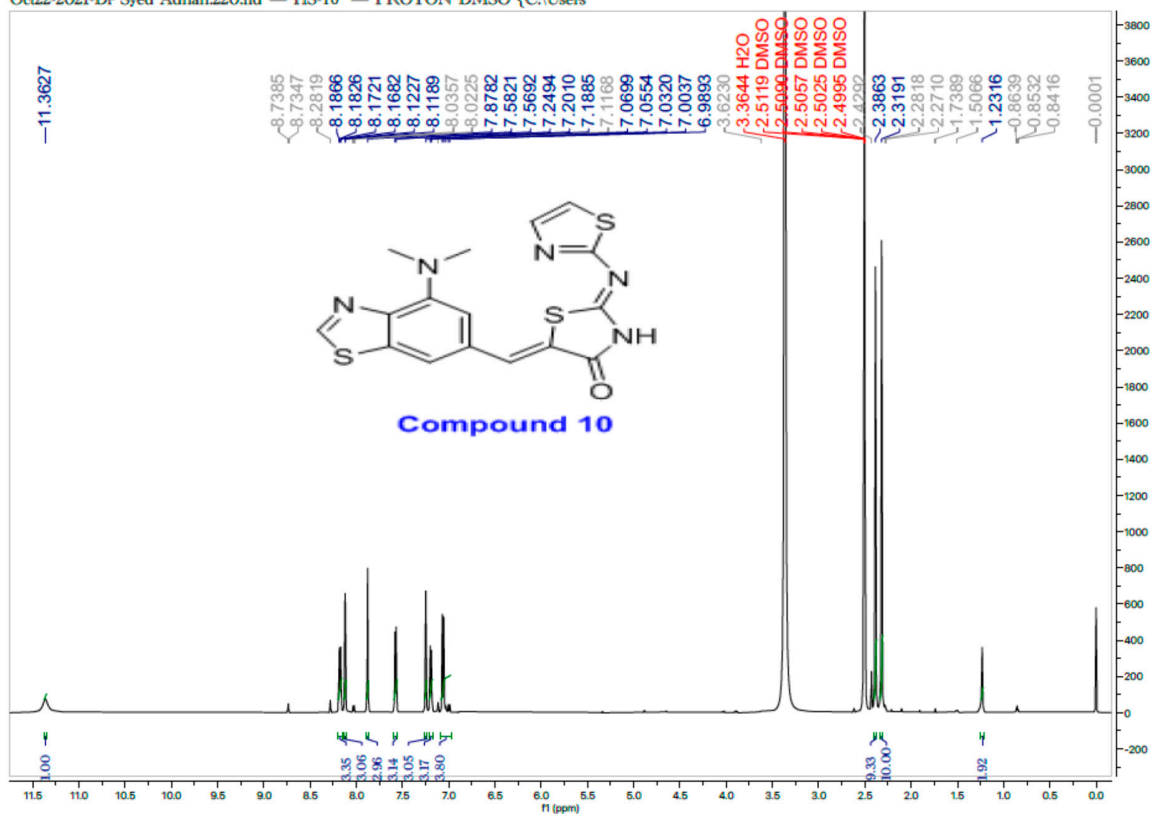
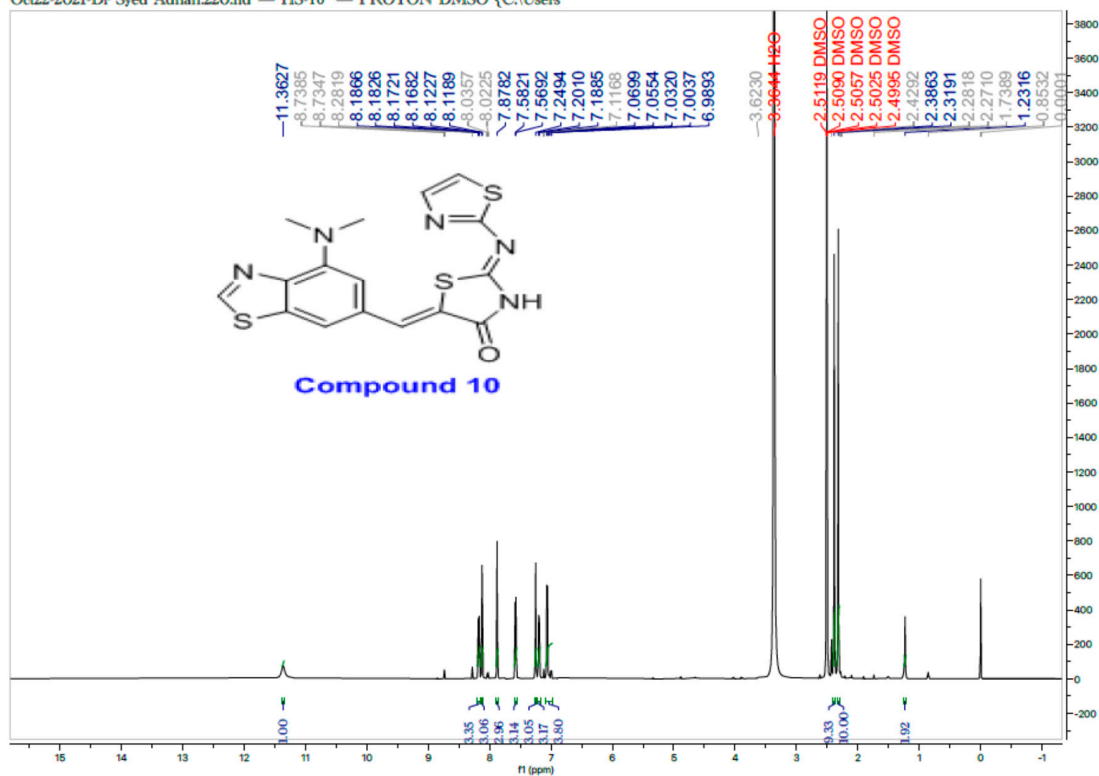


Figure S4. Low resolution Proton NMR Spectra of (2Z,5Z)-5-((4-(dimethylamino)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (10)

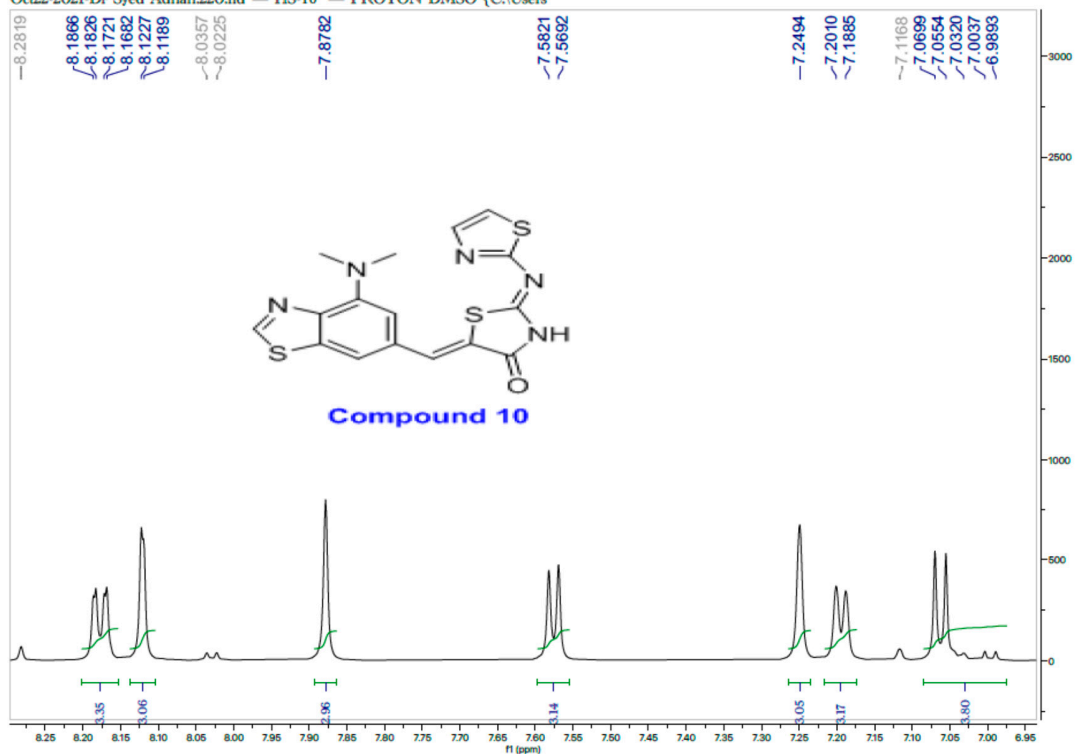
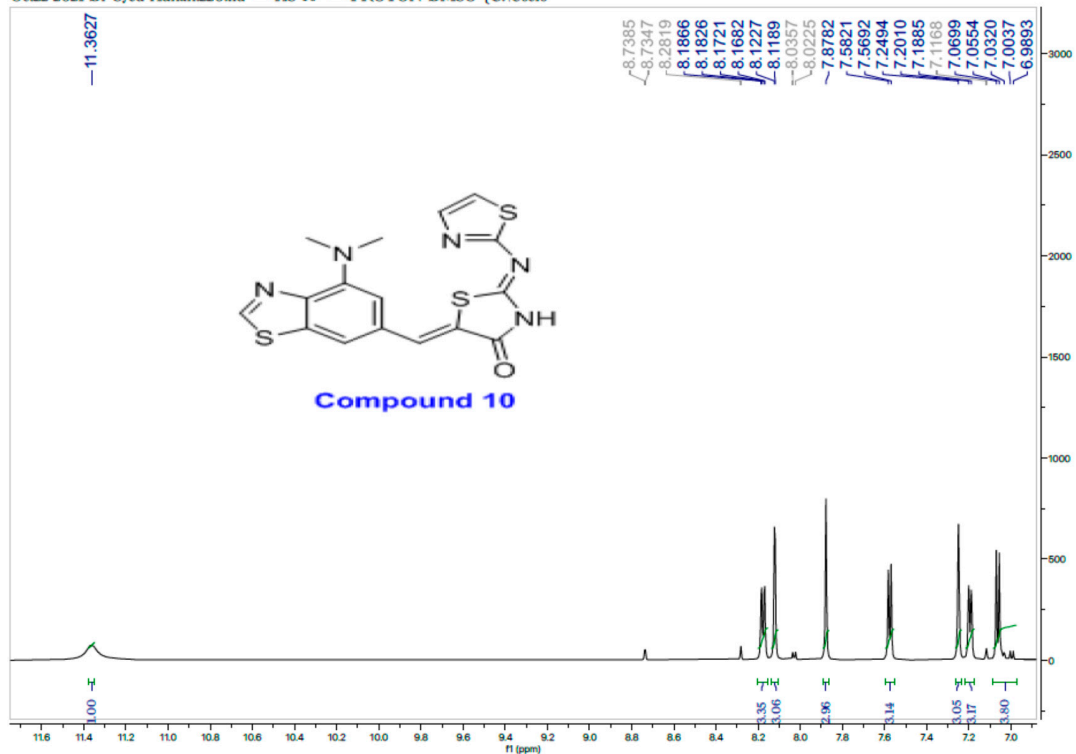


Figure S5. High resolution Proton NMR Spectra of (2Z,5Z)-5-((4-(dimethylamino)benzo[d]thiazol-6-yl)methylene)-2-(thiazol-2-ylimino)thiazolidin-4-one (10)

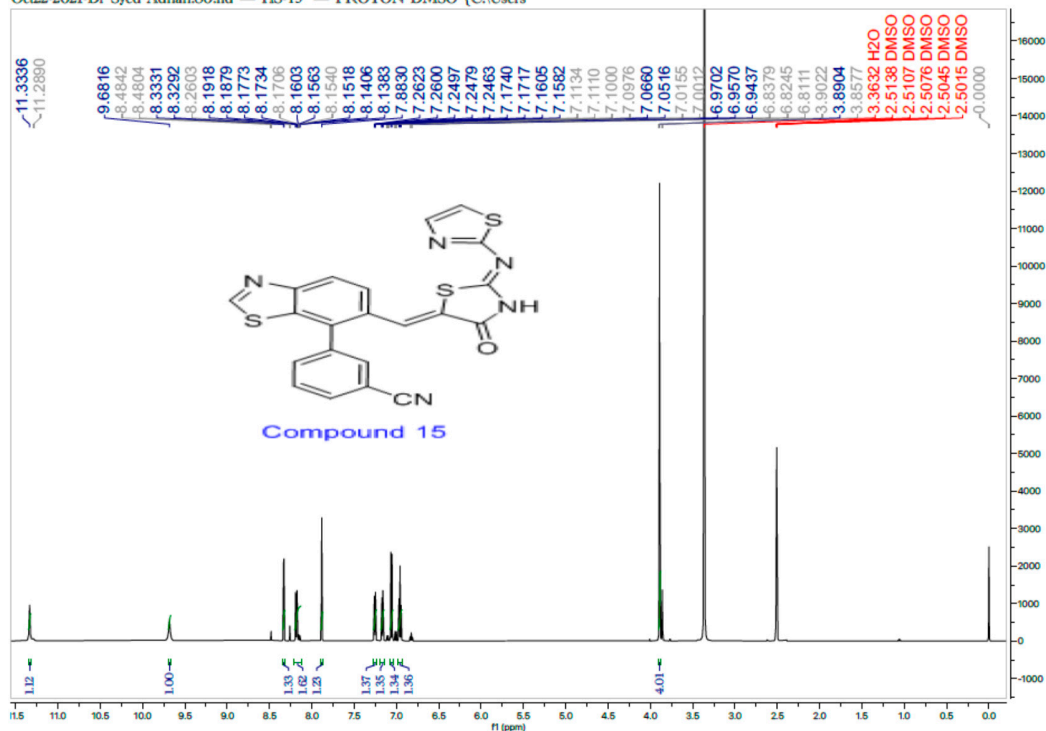
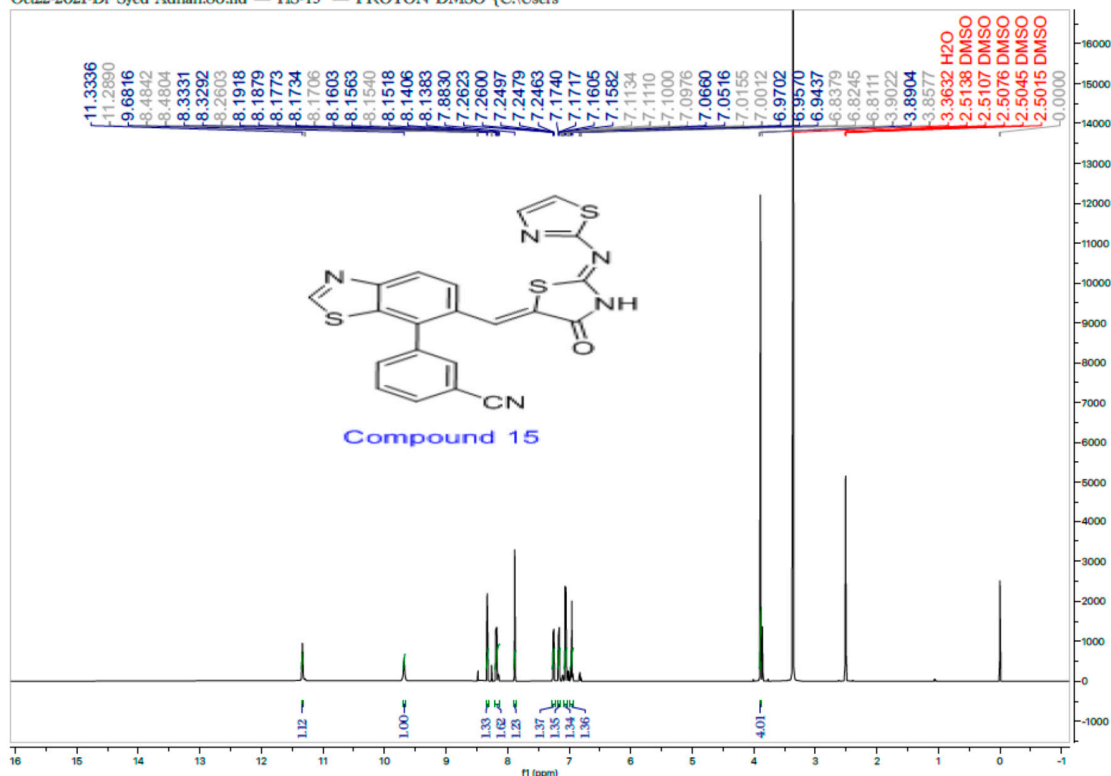


Figure S6. Low resolution Proton NMR Spectra of 3-(6-((Z)-((Z)-4-oxo-2-(thiazol-2-ylimino)thiazolidin-5-ylidene)methyl)benzo[d]thiazol-7-yl)benzonitrile (15)

Figure S7. High resolution Proton NMR Spectra of 3-(6-((Z)-((Z)-4-oxo-2-(thiazol-2-ylimino)thiazolidin-5-ylidene)methyl)benzo[d]thiazol-7-yl)benzonitrile (15)

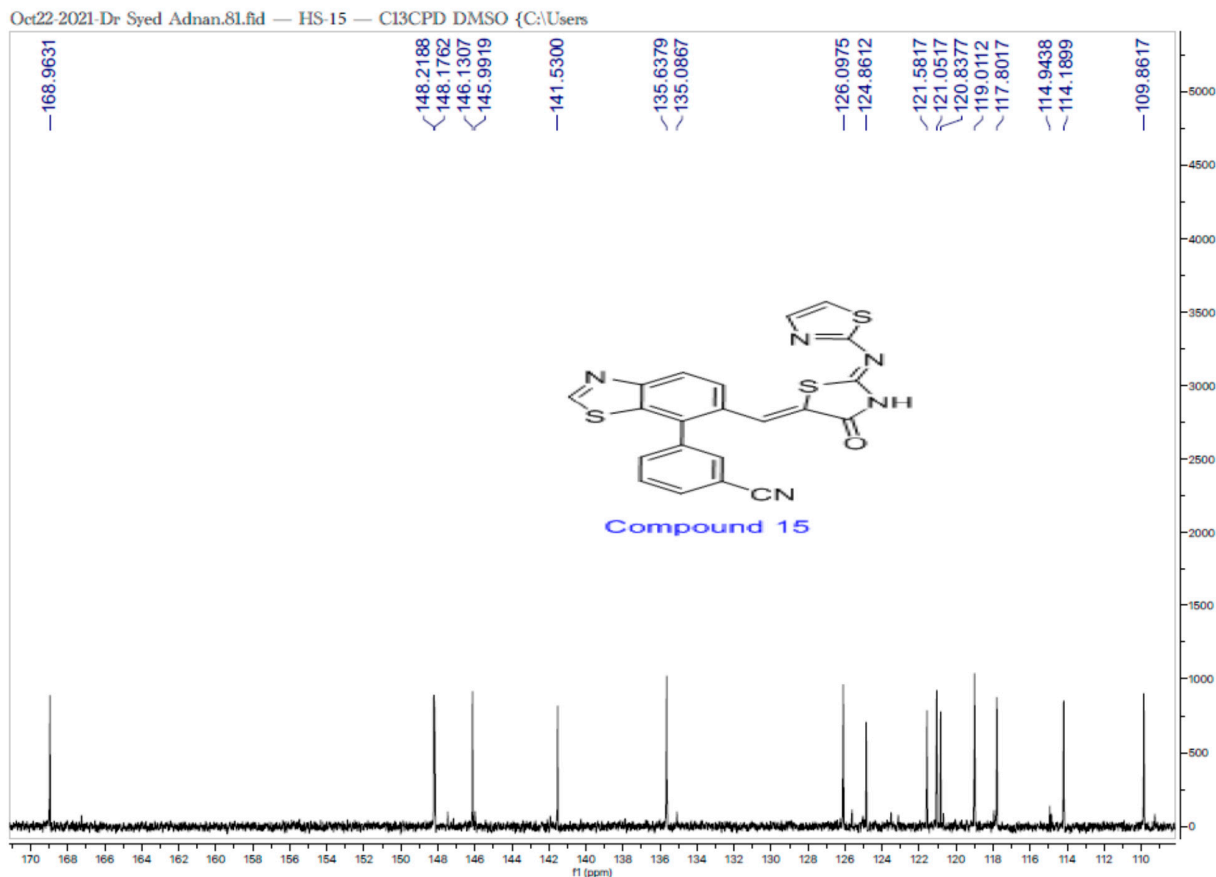


Figure S8. High resolution ^{13}C -NMR Spectra of 3-(6-((Z)-((Z)-4-oxo-2-(thiazol-2-ylimino)thiazolidin-5-ylidene)methyl)benzo[d]thiazol-7-yl)benzonitrile (15)

References

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