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Research Article

DESIGN, SYNTHESIS, BIOLOGICAL EVALUATION, AND COMPUTATIONAL INSIGHTS OF 1,2,4-TRIAZOLE-BASED SCHIFF AND MANNICH BASE DERIVATIVES INCORPORATING 3,4,5-TRIHYDROXYBENZOIC ACID

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SUPPLEMENTARY

S1. Synthesis and analytical data of target compounds

Synthesis of 3,4,5-trihydroxybenzoate (1)

A mixture of 3,4,5-trihydroxybenzoic acid monohydrate (18.813 g, 0.10 mol), anhydrous methanol (100 mL), and concentrated sulfuric acid (25 mL) was refluxed with stirring for 6 h. After removing two-thirds of the methanol, the residue was cooled to 10 °C, poured into distilled water (75 mL), and kept overnight. The resulting precipitate was collected by filtration, washed with water and a small amount of cold methanol, and dried. Yield: 76.9%, White solid, m.p.: 195-198 ^{o}C, Rf: 0.76 (ethyl acetate: *n*-hexane, 8:2).

Synthesis of 3,4,5-trihydroxybenzohydrazide (2)

Hydrazine monohydrate (0.8 mL, 0.024 mol) was added dropwise to a stirred solution of 3,4,5-trihydroxybenzoate **(1)** (1.841 g, 0.01 mol) in absolute ethanol (40 mL). The mixture was refluxed for 8 h, concentrated to half its volume on a water bath, and cooled to afford crystals. The crystals were collected by filtration, washed with cold ethanol, recrystallized from absolute ethanol, and dried. Yield: 84%, Off-white solid, m.p.: Above 250 ^{o}C, Rf: 0.66 (ethyl acetate: *n*-hexane, 8:2).

Synthesis of Potassium 2-(3,4,5-trihydroxybenzoyl) hydrazinecarbodithioate (3)

A cold solution of potassium hydroxide (0.84 g, 0.015 mol) in absolute ethanol (20 mL) was treated with 3,4,5-trihydroxybenzohydrazide **(2)** (1.841 g, 0.01 mol). Carbon disulfide (1.14 g) was added dropwise with stirring, maintaining the temperature below 30 °C. The mixture was stirred at room temperature for 21 h, treated with anhydrous diethyl ether (50 mL), and the precipitate was filtered, washed with diethyl ether, and dried. Yield: 81.7%, Off-white solid, m.p.: Above 265 ^{o}C, Rf: 0.75 (ethyl acetate: *n*-hexane, 8:2).

Synthesis of 4-amino-3-(3,4,5-trihydroxyphenyl)-1*H*-1,2,4-triazole -5(4*H*)-thione (04T)

Potassium salt **(3)** (2.983 g, 0.01 mol) in distilled water (10 mL) was refluxed with hydrazine hydrate (1.1 mL, 0.0227 mol) for 5 h until hydrogen sulfide evolution ceased. The mixture was cooled, poured into ice–water (50 mL), acidified with concentrated HCl, filtered, washed with cold water (3 × 30 mL), and recrystallized from ethanol. Yield: 79.89%, Yellow solid, m.p.: 210 ^{o}C, Rf: 0.68 (ethyl acetate: *n*-hexane, 8:2). UV-Vis (ethanol, 0.1 mg/mL, λ_{max} nm): 328, 344; FT-IR (KBr, ν, cm^{-1}): 3267 (s), 3064 (m), 1698 (m), 1613 (s), 1539 (m), 1373 (m), 1340 (m), 1242 (s), 1204 (m), 1047 (m); ^{1}H NMR (400 MHz, DMSO-d6), **δ (ppm):** 6.913 (2H, s, H-7 & 11)**;** ^{13}C NMR (100 MHz, DMSO-d6), **δ (ppm):** 167.49 (C-3), 189.89 (C-5), 120.46 (C-6), 108.74 (C-7 & C-11), 145.43 (C-8 & C-10), 138.01 (C-9).

General procedure for synthesis of Schiff's bases (5)

Triazole thione **(04T)** (2.4 g, 0.01 mol) in hot absolute ethanol (5 mL) containing concentrated sulfuric acid (0.5 mL) was treated with a hot ethanolic solution of desired aromatic aldehyde (0.01 mol) over 1 h with stirring. The mixture was refluxed for 5 h, cooled, and the precipitate was filtered, washed with cold ethanol, and recrystallized from hot ethanol.

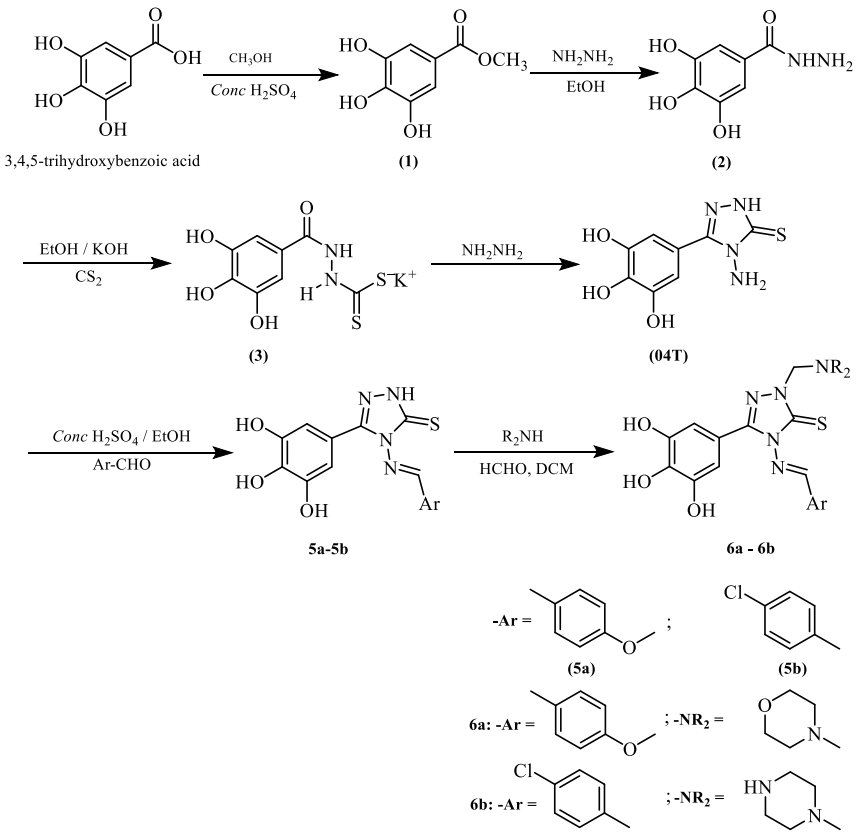

Figure S1. Schematic representation of synthesis of 1,2,4-triazole derivatives

Synthesis of 4-((4-methoxybenzylidene)amino)-3-(3,4,5-trihydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (5a)

Yield: 74.21%, Yellow solid, m.p.: 154 ºC, Rf: 0.84 (ethyl acetate: *n*-hexane, 8:2). UV-Vis (ethanol, 0.1 mg/mL, λ_{max} nm): 328, 344; FT-IR (KBr, ν, cm^{-1}): 3428 (s), 3200 (s), 2975 (m), 1706 (m), 1512 (m), 1476 (m), 1307 (m), 1218 (s), 1178 (m), 1116 (m); ^{1}H NMR (400 MHz, DMSO-d6), **δ (ppm):** 6.883, 6.770 (1H, s, H-1, *E & Z* geometrical isomers), 6.934, 6.905 (2H,s, H-7 & 11, *E* & *Z* geometrical isomers), 9.864 (1H, s, H-13), 7.855, 7.475 (2H, d, *J* = 8.4 Hz, H-15 & 19, *E* & *Z* geometrical isomers), 7.104, 6.994, (2H, d, *J* = 8.4 Hz, H-16 & 18, *E* & *Z* geometrical isomers), 3.859, 3.773, (3H, br s, CH_3, *E* & *Z* geometrical isomers), 4.363 (3H, br s, OH, *E* & *Z* geometrical isomers); ^{13}C NMR (100 MHz, DMSO-d6), **δ (ppm):** 145.36 (C-3), 191.27 (C-5), 114.49, 113.80 (C-6, *E* & *Z* geometrical isomers), 108.70, 101.47 (C- 7 & 11, *E* & *Z* geometrical isomers), 145.51, 140.29 (C-8 & 10, *E* & *Z* geometrical isomers), 139.76, 138.29 (C-9, *E* & *Z* geometrical isomers), 159.49, 147.72 (C-13, *E* & *Z* geometrical isomers), 131.78, 129.64 (C-14, *E* & *Z* geometrical isomers), 128.84, 128.67 (C-15 & 19, *E* & *Z* geometrical isomers), 115.53, 113.80 (C-16 & 18, *E* & *Z* geometrical isomers), 170.36, 164.19 (C-17, *E* & *Z* geometrical isomers), 55.12, 80.00 (CH_3, *E* & *Z* geometrical isomers).

Synthesis of 4-((4-chlorobenzylidene)amino)-3-(3,4,5-trihydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (5b)

Yield: 76%, Yellow solid, m.p.: 162 ºC, Rf: 0.88 (ethyl acetate: *n*-hexane, 8:2). UV-Vis (ethanol, 0.1 mg/mL, λ_{max} nm): 328, 344; FT-IR (KBr, ν, cm^{-1}): 3493 (s), 3416 (s), 3211 (s), 2988 (w), 1692 (s), 1621 (m), 1476 (s), 1286 (s), 1187 (m), 1116 (m), 1091 (m), 765 (s), 720 (m); ^{1}H NMR (400 MHz, DMSO-d6), **δ (ppm):** 6.936, 6.795 (2H, s, H-7 & 11, *E* & *Z* geometrical isomers), 8.695, 8.662 (1H, s, H-13 *E* & *Z* geometrical isomers), 7.875, 7.398 (2H, d, *J* = 8.0 Hz, H-15 & 19, *E* & *Z* geometrical isomers), 7.933, 7.552 (2H, d, *J* = 7.2 Hz, H-16 & 18, *E* & *Z* geometrical isomers), 5.371 (3H, br s, OH, *E* & *Z* geometrical isomers); ^{13}C NMR (100 MHz, DMSO-d6), **δ (ppm):** 148.03 (C-3), 190.18 (C-5), 129.42, 128.34 (C-6, E & Z geometrical isomers), 108.56, 101.77 (C-7 & 11, *E* & *Z* geometrical isomers), 145.62, 141.07 (C-8 & 10, *E* & *Z* geometrical isomers), 140.37 (C-9), 170.37, 165.92 (C-13, *E* & *Z* geometrical isomers), 138.40, 133.34 (C-14, *E* & *Z* geometrical isomers), 129.67, 128.61 (C-15 & 19, *E*

& *Z* geometrical isomers), 119.67, 115.21 (C-16 & 18, *E* & *Z* geometrical isomers), 140.05, 136.19 (C-17, *E* & *Z* geometrical isomers).

General Procedure for synthesis of Mannich's bases (6)

A solution of Schiff base **(5)** (0.007 mol) in dichloromethane (10 mL) was treated with formaldehyde (37%, 1.00 mL) and the desired amine (0.007 mol). The mixture was stirred at room temperature for 3 h, concentrated under reduced pressure, and the residue was treated with water, filtered, and recrystallized from ethyl acetate :petroleum ether (1 : 2).

Synthesis of 4-((4-methoxybenzylidene)amino)-1-(morpholinomethyl)-3-(3,4,5-trihydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (6a)

Yield: 78.24%, Brown solid, m.p.: 103 ^{o}C, Rf: 0.80 (ethyl acetate: *n*-hexane, 8:2). UV-Vis (ethanol, 0.1 mg/mL, λ_{max} nm): 326, 342; FT-IR (KBr, ν, cm^{-1}): 2968 (m), 2836 (m), 1608 (s), 1512 (s), 1454 (m), 1334 (m), 1289 (s), 1244 (s), 1154 (m), 1108 (s); ^{1}H NMR (400 MHz, DMSO-d6), **δ (ppm):** 6.420, 6.380 (2H, s, H-7 & 11, *E* & *Z* geometrical isomers), 9.868 (1H, s, H-13), 7.860, 7.157, (2H, d, *J* = 8.4 Hz, H-15 & 19, *E* & *Z* geometrical isomers), 7.107, 6.920 (2H, d, *J* = 8.0 Hz, H-16 & 18, *E* & *Z g*eometrical isomers), 5.413, 5.106 (2H, s, H-20, *E* & *Z* geometrical isomers), 3.106, 2.695 (2H, s, H-22 & 26, *E* & *Z* geometrical isomers), 3.741, 3.546 (2H, br s, H-23 & 25, *E* & *Z* geometrical isomers), 3.382, 3.206 (2H, s, CH_3, *E* & *Z* geometrical isomers), 4.773, 4.549 (3H, s, OH, *E* & *Z* geometrical isomers)**;** ^{13}C NMR (100 MHz, DMSO-d6), **δ (ppm):** 146.67 (C-3), 191.27, 186.72 (C-5, *E* & *Z* geometrical isomers), 114.49 (C-6), 113.88, 113.60 (C-7 & 11, *E* & *Z* geometrical isomers), 140.29, 140.03 (C-8 & 10, *E* & *Z* geometrical isomers), 141.11, 140.13 (C-9, *E* & *Z* geometrical isomers), 159.70, 148.32 (C-13, *E* & *Z* geometrical isomers), 131.77, 129.80 (C-14, *E* & *Z* geometrical isomers), 129.24, 128.92 (C-15 & 19, *E* & *Z* geometrical isomers), 115.38, 112.39 (C-16 & 18, *E* & *Z* geometrical isomers), 170.39, 169.87 (C-17, *E* & *Z* geometrical isomers, 79.36, 70.24 (C-20, *E* & *Z* geometrical isomers), 50.23,42.89 (C-22 & 26, *E* & *Z* geometrical isomers), 66.01, 63.27 (C-23 & 25, *E* & *Z* geometrical isomers), 55.14, 79.82 (CH_3, *E* & *Z* geometrical isomers).

Synthesis of 4-((4-chlorobenzylidene)amino)-1-(piperazin-1-ylmethyl)-3-(3,4,5-trihydroxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (6b)

Yield: 72.97%, Yellow solid, m.p.: 178 ^{o}C, Rf: 0.77 (ethyl acetate: *n*-hexane, 8:2) UV-Vis (ethanol, 0.1 mg/mL, λ_{max} nm): 342; FT-IR (KBr, ν, cm^{-1}): 2944 (m), 1599 (s), 1452 (m), 1369 (m), 1294 (m), 1202 (m), 1156 (s), 1054 (m), 791 (m), 722 (m); ^{1}H NMR (400 MHz, DMSO-d6), **δ (ppm):** 7.441, 7.287 (2H, d, *J* = 8.0 Hz, H-7 & 11,*E* & *Z* geometrical isomers), 10.005, 8.552, (1H, br s, H-13, *E* & *Z* geometrical isomers), 7.944, 7.697, (2H, d, *J* = 8.0 Hz, H-15 & 19, *E* & *Z* geometrical isomers), 7.917 - 7.846, 7.601 - 7.530 (2H, m, H-16 & 18, *E* & *Z* geometrical isomers), 5.228, 5.118 (2H, br s, H-20, *E* & *Z* geometrical isomers), 2.941, 2.792 (2H, br s, H-22 & 26, *E* & *Z* geometrical isomers), 3.427, 3.085 (2H, br s, H-23 & 25, *E* & *Z* geometrical isomers), 1.985 (1H, br s), 5.751, 5.463 (3H, s, OH, *E* & *Z* geometrical isomers); ^{13}C NMR (100 MHz, DMSO-d6), **δ (ppm):** 148.29 (C-3), 192.15, 187.41 (C-5, *E* & *Z* geometrical isomers), 131.18, 129.37 (C-6, *E* & *Z* geometrical isomers), 108.87, 101.34 (C-7 & 11, *E* & *Z* geometrical isomers), 144.93, 137.25 (H-8 & 10, *E* & *Z* geometrical isomers), 140.09 (C-9), 170.32, 168.86 (C-13, *E* & *Z* geometrical isomers), 134.84, 132.51 (C-14, *E* & *Z* geometrical isomers), 129.21, 128.27 (C-15 & 19, *E* & *Z* geometrical isomers), 119.42, 110.51 (C-16 & 18, *E* & *Z* geometrical isomers), 139.36, 135.08 (C-17, *E* & *Z* geometrical isomers), 71.90, 69.07 (C-20, *E* & *Z* geometrical isomers), 59.74, 54.90 (C-22 & 26, *E* & *Z* geometrical isomers), 46.74, 42.96 (C-23 & 25, *E* & *Z* geometrical isomers).

^{1}H and ^{13}C-NMR spectra of target compounds

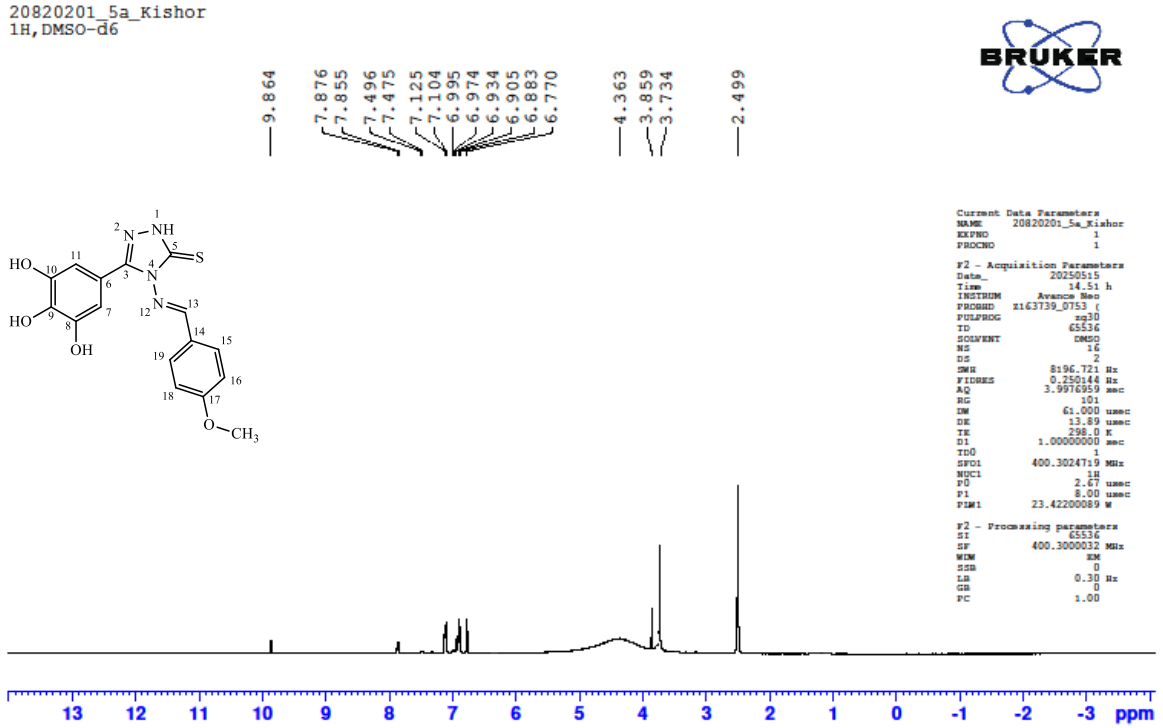

Figure S2. ^{1}H-NMR of 5a

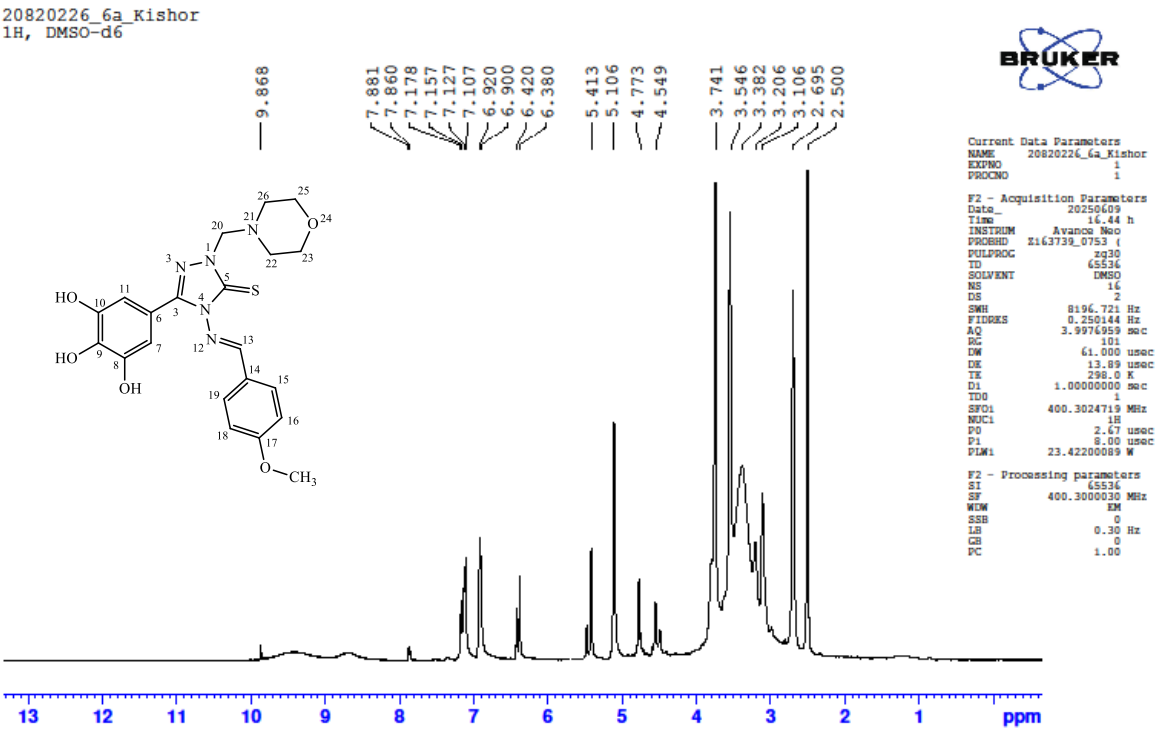

Figure S3. ^{1}H-NMR of 6a

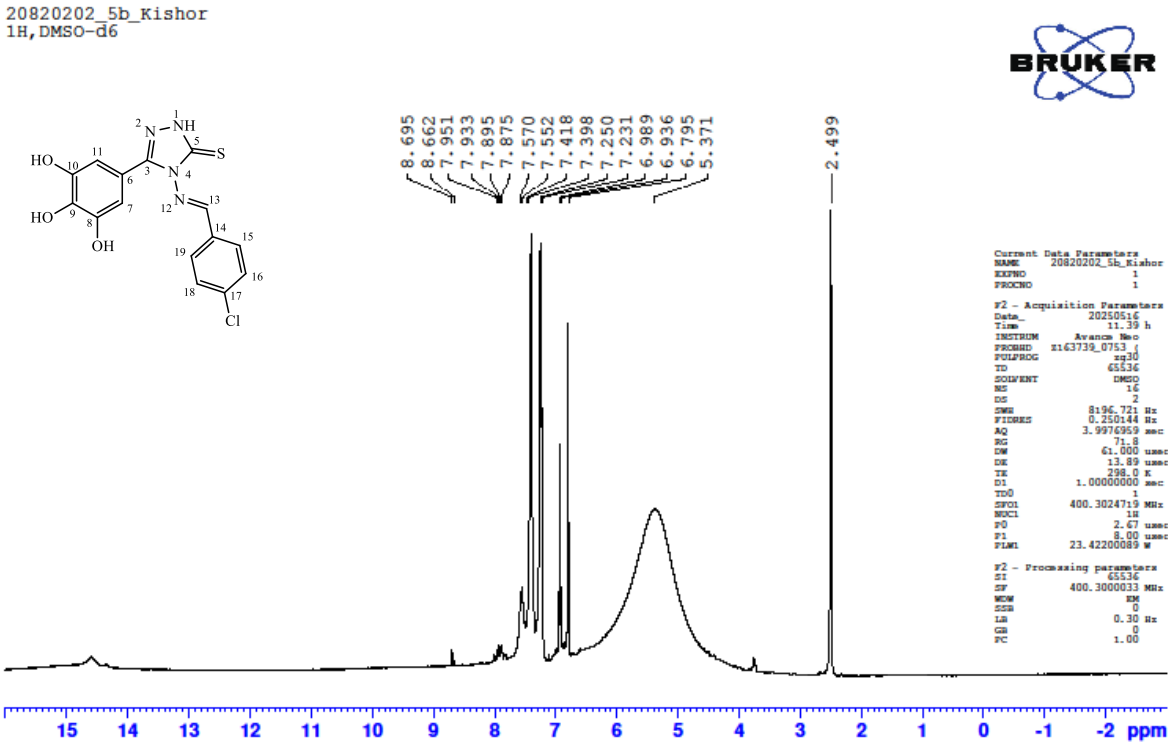

Figure S4. ^{1}H-NMR of 5b

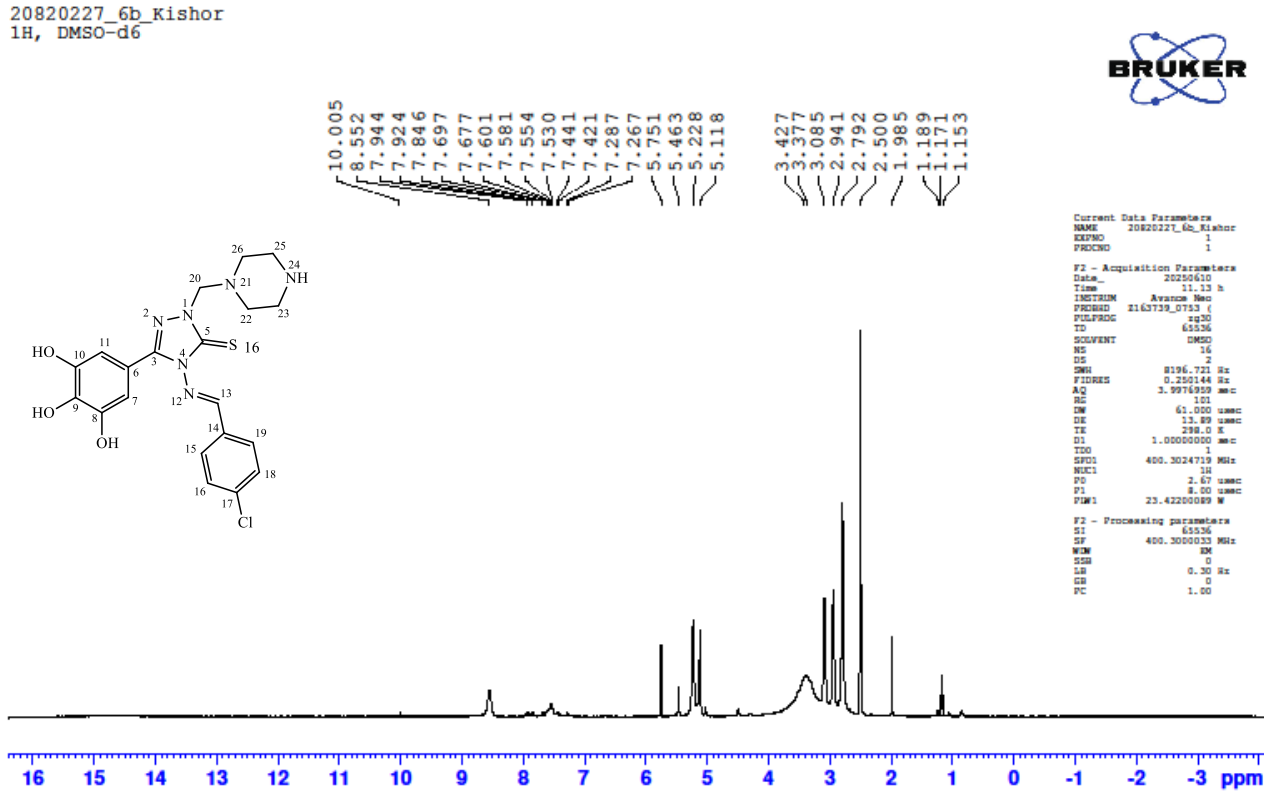

Figure S5. ^{1}H-NMR of 6b

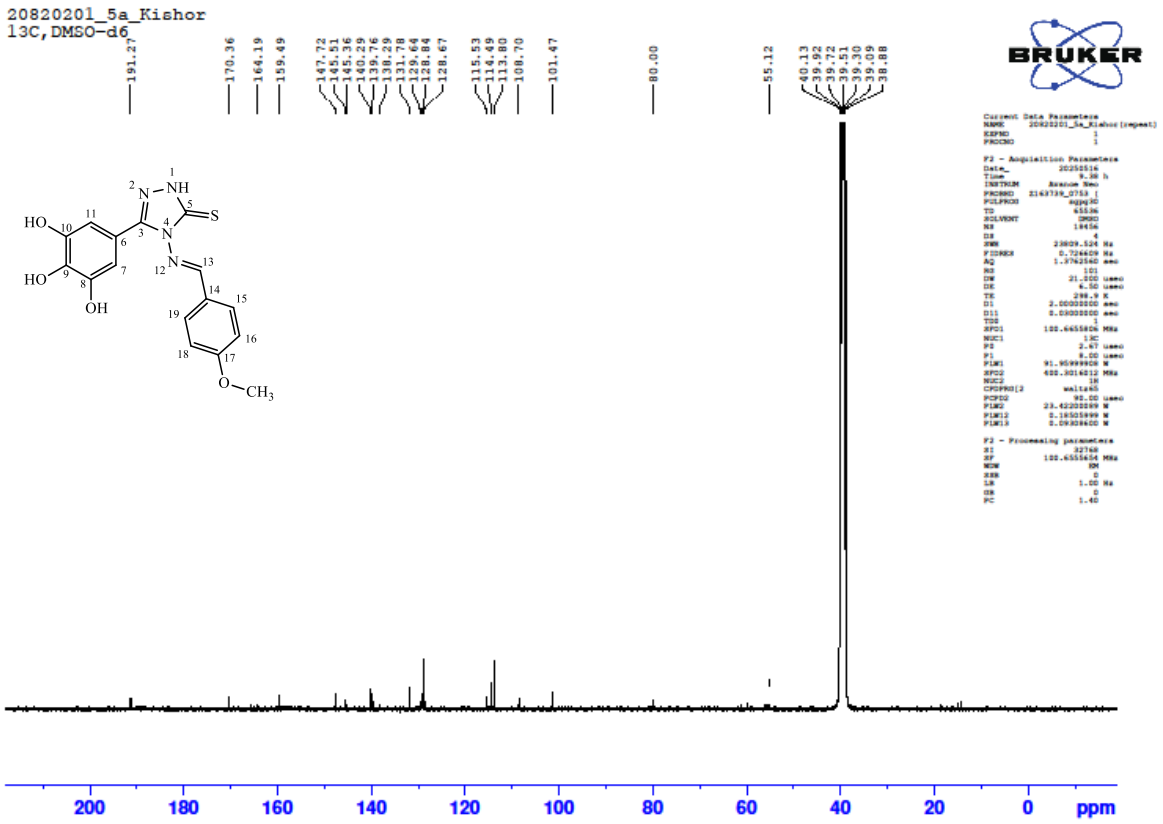

Figure S6. ^{13}C-NMR of 5a

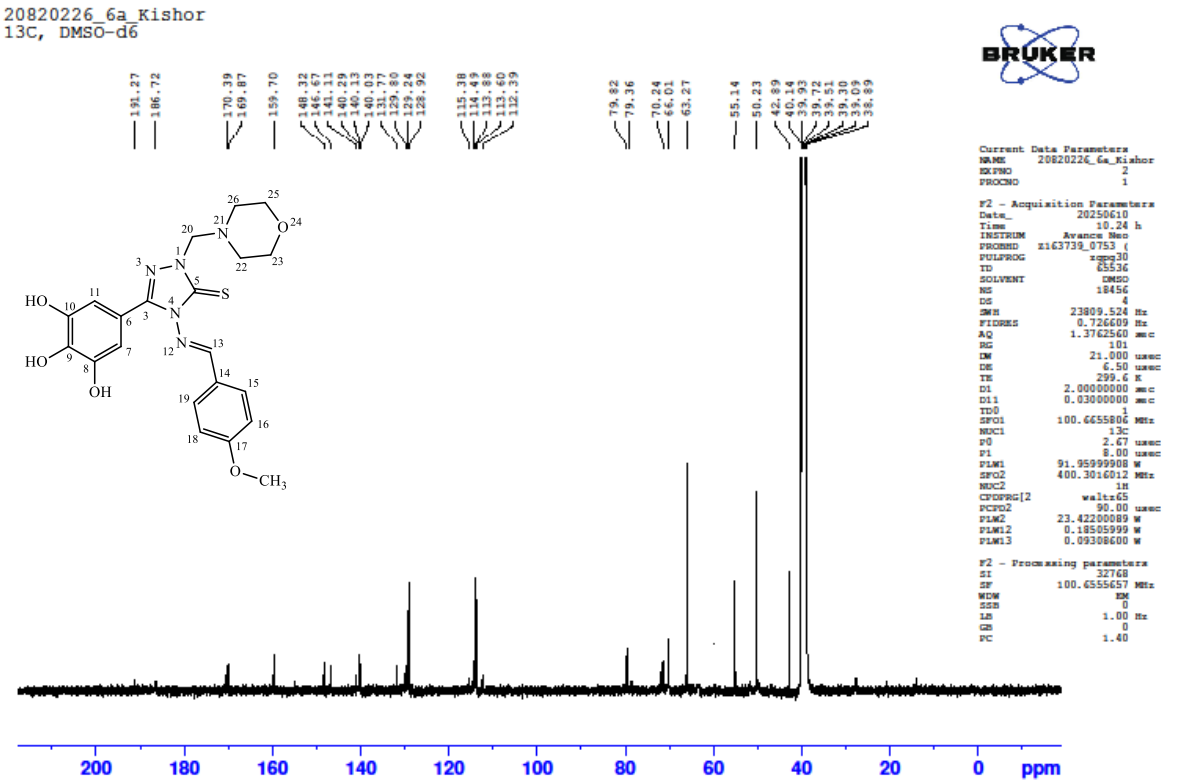

Figure S7. ^{13}C-NMR of 6a

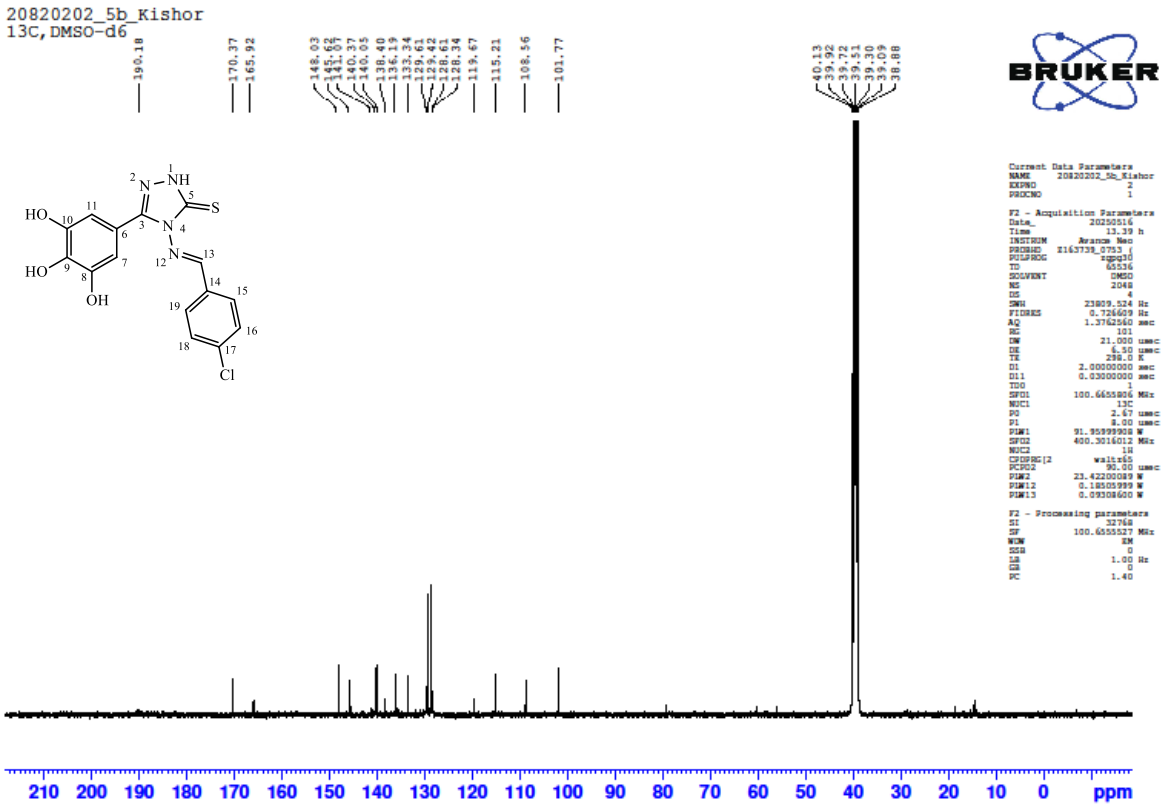

Figure S8. ^{13}C-NMR of 5b

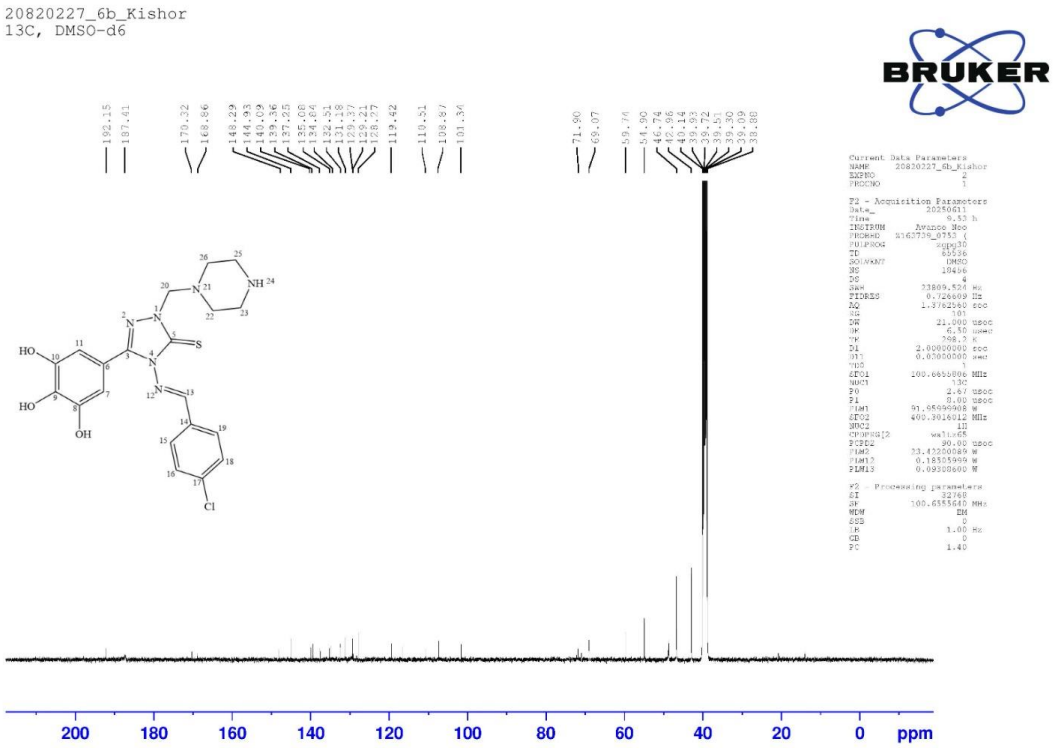

Figure S9. ^{13}C-NMR of 6b