Supplementary Data

Synthesis and biological evaluation of coumarin-1, 2, 3-triazole-dithiocarbamate hybrids as potent LSD1 inhibitors

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1. General Experimental

The reaction process was monitored by TLC with silica gel plates (thickness 250μm, Indicator F-254). The target analogues were purified by column chromatography with silica gel (300 meshes). Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. The structures of intermediates and target analogues were characterized by NMR (400 and 100 MHz) in Acetone-d_6, DMSO-d_6 or $CDCl_3$ with TMS as an internal standard and HRMS. The purity of all biologically evaluated compounds was determined to be >95% by reverse phase high performance liquid chromatography (HPLC) analysis. HPLC measurement was performed with a Phenomenex column (C18, 5.0 μm, 4.60 mm × 250 mm) on Dionex UltiMate 3000 UHPLC instrument from Thermo-Fisher. The signal was monitored at 254 nm with a UV dector. A flow rate of 0.5 ml/min was used with mobile phase of MeOH in H_2O (70:30, v/v).

2. Experimental Procedures and Analytical Data

Preparation of intermediates **2**.

CS_2 (2.284 g, 30 mmol) was added drop wise to the solution of 1-Boc-piperazine (1.860 g, 10 mmol) and $Na_3PO_4{\cdot}12H_2O$ (2.281 g, 6 mmol) in acetone (40 mL). The reaction mixture was stirred at room temperature for 0.5 h. Then propargyl bromide (1.308 g, 11 mmol) was added to the mixture, the reaction mixture was stirred at room temperature for another 0.5 h. Upon completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure, the residue was dissolved in EtOAc (50 mL), washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compound **2** (2.78 g, yield: 92.2%). white solid. Mp: 87-88 ^oC. ^1H NMR (400 MHz, Acetone-d6, d, ppm): 4.28 (br, 2H), 4.14 (d, 2H, J = 2.7 Hz), 4.00 (br, 2H), 3.58 (br, 4H), 2.78 (t, 1H, J = 2.7 Hz), 1.46 (s, 9H); HRMS (ESI) calcd for $C_{13}H_{21}N_2O_2S_2$ $[M+H]^+$: 301.1044, found: 301.1046.

Preparation of intermediates **3a-k**.

To a well stirred solution of aqueous H_2SO_4 70% (20ml) cooled to -5 ^oC was slowly added substituted

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phenols (10mmol), followed by slowly adding 4-chloroacetoacetate ethyl ester (1.975g, 12mmol). After overnight reaction at -5 ^{o}C, the reaction mixture was poured into 100ml of ice cold water and stirred for 0.5 h. The resulting white precipitate was collected by filtration, washed with ice water until the filtrate was neutral and dried under reduced pressure to afford a solid, which was then subjected to recrystallization from ethanol to give **3a-k**.

7-chloro-4-(chloromethyl)-2*H*-chromen-2-one (3a)

White solid, yield: 60%, m.p.: 122-123 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 7.87 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H), 6.72 (s, 1H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 159.57, 154.28, 150.56, 137.07, 127.30, 125.17, 117.41, 116.57, 116.09, 41.61; HRMS (ESI) calcd for $C_{10}H_7Cl_2O_2$ $[M+H]^+$:228.9823, found: 228.9827.

6-chloro-4-(chloromethyl)-2*H*-chromen-2-one (3b)

White solid, yield: 42%, m.p.: 116-117 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.64 (d, J = 2.4 Hz, 1H), 7.53 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 6.62 (s, 1H), 4.64 (d, J = 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 159.52, 152.27, 148.51, 132.27, 130.05, 123.86, 118.88, 118.43, 116.96, 40.97; HRMS (ESI) calcd for $C_{10}H_7Cl_2O_2$ $[M+H]^+$:228.9823, found: 228.9821.

4-(chloromethyl)-7-fluoro-2*H*-chromen-2-one (3c)

White solid, yield: 65%, m.p.: 148-149 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.68 (dd, J_1 = 5.8 Hz, J_2 = 8.6 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.53 (s, 1H), 4.65 (d, J = 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 165.87, 163.34, 159.82, 155.26, 155.13, 149.09, 126.06, 125.96, 114.85, 114.82, 112.76, 112.53, 105.13, 104.88, 41.21; HRMS (ESI) calcd for $C_{10}H_7ClFO_2$ $[M+H]^+$: 213.0119, found: 213.0116; ^{19}F NMR (376 MHz, $CDCl_3$, δ , ppm): -104.39.

4-(chloromethyl)-2*H*-chromen-2-one (3d)

White solid, yield: 70%, m.p.: 144-145 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.68 (dd, J_1 = 1.3 Hz , J_2 = 8.0 Hz, 1H), 7.58 (td, J_1 = 1.4 Hz , J_2 = 7.8 Hz, 1H), 7.38 (dd, J_1 = 0.8 Hz , J_2 = 8.4 Hz, 1H), 7.35 (td, J_1 = 1.1 Hz , J_2 = 7.6 Hz, 1H), 6.59 (s, 1H), 4.69 (d, J = 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 160.23, 153.86, 149.48, 132.30, 124.53, 124.15, 117.50, 117.30, 115.96, 41.23; HRMS (ESI) calcd for $C_{10}H_8ClO_2$ $[M+H]^+$:195.0213, found: 195.0215.

7-amino-4-(chloromethyl)-2*H*-chromen-2-one (3e)

Yellow solid, yield: 68%, m.p.: 186-187 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 7.49 (d, J = 8.7 Hz, 1H), 6.61 (dd, J_1 = 8.7 HZ, J_2 = 2.1 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 6.19 (s, 1H), 5.78 – 5.07 (m, 2H), 4.88 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): δ 161.10, 156.39, 153.66, 151.70, 126.56, 111.86, 108.41, 106.67, 99.28, 41.90; HRMS (ESI) calcd for $C_{10}H_9ClNO_2$ $[M+H]^+$:210.0322, found: 210.0323.

4-(chloromethyl)-7-methyl-2*H*-chromen-2-one (3f)

White solid, yield: 78%, m.p.: 215-216 ^{o}C. Compound 3f was insoluble in DMSO, so the NMR data was not given and only characterized by HRMS. HRMS (ESI) calcd for $C_{11}H_{10}ClO_2$ $[M+H]^+$:209.0369, found: 209.0368.

4-(chloromethyl)-6-methyl-2*H*-chromen-2-one (3g)

White solid, yield: 56%, m.p.: 146-147 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.43 (s, 1H), 7.38 (dd, J_1 = 1.7 Hz, J_2 = 8.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.56 (s, 1H), 4.67 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 160.47, 151.97, 149.40, 134.29, 133.29, 123.90, 117.19, 116.99, 115.81, 41.28, 21.04; HRMS (ESI) calcd for $C_{11}H_{10}ClO_2$ $[M+H]^+$:209.0369, found: 209.0370.

4-(chloromethyl)-7-hydroxy-5-methyl-2*H*-chromen-2-one (3h)

White solid, yield: 80%; m.p.: 172-173 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 10.92 (s, 1H), 6.68 (s, 1H), 6.60 (s, 1H), 6.41 (s, 1H), 5.08 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 164.98,

160.87, 160.05, 156.94, 148.62, 117.34, 117.25, 113.11, 109.53, 50.22, 26.37; HRMS (ESI) calcd for $C_{11}H_{10}ClO_3$ $[M+H]^+$:225.0318, found: 225.0317.

4-(chloromethyl)-5,7-dihydroxy-2*H*-chromen-2-one (3i)

White solid, yield: 82%; m.p.: 245-246 ^oC. ^1H NMR (400 MHz, Acetone-d_6, δ , ppm): 9.84 (s, 1H), 9.33 (s, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 6.29 (s, 1H), 5.08 (d, *J* = 1.0 Hz, 2H); ^{13}C NMR (100 MHz, Acetone-d_6, δ , ppm): 161.36, 159.97, 157.10, 156.79, 151.74, 109.58, 100.53, 99.34, 99.24, 95.49, 44.89, 29.73, 29.56, 29.37, 29.18, 28.99, 28.79, 28.60, 28.41; HRMS (ESI) calcd for $C_{10}H_8ClO_4$ $[M+H]^+$:227.0111, found: 227.0112.

4-(chloromethyl)-7,8-dihydroxy-2*H*-chromen-2-one (3j)

White solid, yield: 85%; m.p.: 196-198 ^oC. ^1H NMR (400 MHz, Acetone-d_6, δ , ppm): 8.84 (s, 1H), 8.69 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.40 (s, 1H), 4.90 (s, 2H); ^{13}C NMR (100 MHz, Acetone-d_6, δ , ppm): 159.67, 151.14, 149.24, 143.59, 132.30, 115.68, 112.17, 111.44, 110.66, 41.37; HRMS (ESI) calcd for $C_{10}H_8ClO_4$ $[M+H]^+$:227.0111, found: 227.0108.

4-(chloromethyl)-7-hydroxy-2*H*-chromen-2-one (3k)

White solid, yield: 82%; m.p.: 184-185 ^oC. ^1H NMR (400 MHz, Acetone-d_6, δ , ppm): 9.52 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 6.91 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.40 (s, 1H), 4.91 (d, *J* = 0.7 Hz, 2H); ^{13}C NMR (100 MHz, Acetone-d_6, δ , ppm): 161.29, 159.95, 155.93, 150.56, 126.31, 112.89, 111.69, 110.11, 102.81, 41.28; HRMS (ESI) calcd for $C_{10}H_8ClO_3$ $[M+H]^+$:211.0162, found: 211.0164.

Preparation of intermediates **4a-k.**

4-(azidomethyl)-7-chloro-2*H*-chromen-2-one (4a)

To a magnetically stirred solution of compound **3a** (0.687 g, 3 mmol) in CH_3CN (15 mL), sodium azide (0.585 g, 9 mmol) was added carefully and the reaction mixture was refluxed for 10 h. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc (30 mL) and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compound **4a** which was purified with column chromatography. White solid, yield: 86%; m.p.: 133-133.7 ^oC. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.49 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.30 (dd, J_1 = 1.7 Hz, J_2 = 8.5 Hz, 1H), 6.52 (s, 1H), 4.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 159.43, 154.10, 148.03, 138.30, 125.11, 124.77, 117.71, 115.97, 114.67, 50.65; HRMS (ESI) calcd for $C_{10}H_7ClN_3O_2$ $[M+H]^+$:236.0227, found: 236.0225.

4-(azidomethyl)-6-chloro-2*H*-chromen-2-one (4b)

The method synthesizing compound **4b** was same to that of compound **4a**. White solid, yield: 89%; m.p.: 122 -123 ^oC. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.49-7.55 (m, 2H), 7.33 (d, *J* = 9.4 Hz, 1H), 6.58 (s, 1H), 4.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 159.47, 152.18, 147.57, 132.27, 130.06, 123.47, 118.87, 118.46, 115.74, 50.55; HRMS (ESI) calcd for $C_{10}H_7ClN_3O_2$ $[M+H]^+$:236.0227, found: 236.0225.

4-(azidomethyl)-7-fluoro-2*H*-chromen-2-one (4c)

To a magnetically stirred solution of compound **3c** (0.660 g, 3 mmol) in acetone (16 mL), aqueous solution (15ml) of sodium azide (0.585g, 9 mmol) was added and stirred at room temperature. Upon completion (monitored by TLC), the solvent was removed under reduced pressure, the residue was extracted with ethyl acetate and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford compound **4c** which was purified with column chromatography. White solid, yield: 86%; m.p.: 105-106 ^oC. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.55 (dd, J_1 = 5.8 Hz, J_2 = 8.7 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.49 (s, 1H), 4.56 (d, *J* = 1.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 165.88, 163.35, 159.75, 155.15, 155.02, 148.19, 125.65, 125.55, 113.62, 113.59, 112.77, 112.55, 105.09, 104.83, 50.77; HRMS

(ESI) calcd for $C_{10}H_7N_3FO_2$ $[M+H]^+$: 220.0522, found: 220.0522; ^{19}F NMR (376 MHz, $CDCl_3$, δ , ppm): -104.36.

4-(azidomethyl)-2*H*-chromen-2-one (4d)

The method synthesizing compound **4d** was same to that of compound **4c**. White solid, yield: 85%; m.p. 82.8-83.6 °C. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.61-7.53 (m, 2H), 7.38 (dd, J_1 = 0.6 Hz , J_2 = 8.3 Hz, 1H), 7.33 (td, J_1 = 1.0 Hz , J_2 = 7.6 Hz, 1H), 6.54 (s, 1H), 4.59 (d, J = 1.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 160.17, 153.78, 148.51, 132.34, 124.58, 123.71, 117.52, 117.34, 114.76, 50.72; HRMS (ESI) calcd for $C_{10}H_8N_3O_2$$[M+H]^+$: 202.0617, found: 202.0618.

7-amino-4-(azidomethyl)-2*H*-chromen-2-one (4e)

The method synthesizing compound **4e** was same to that of compound **4a**. the mixture was inseparate and used in the next step without further purification. HRMS (ESI) calcd for $C_{10}H_8N_4NaO_2$ $[M+H]^+$:239.0545, found: 239.0542.

4-(azidomethyl)-7-methyl-2*H*-chromen-2-one (4f)

The method synthesizing compound **4f** was same to that of compound **4a**. White solid, yield: 83%; m.p. 106.8-108 °C. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.43 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.48 (s, 1H), 4.56 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 160.50, 153.86, 148.56, 143.67, 125.73, 123.40, 117.60, 114.91, 113.58, 50.72, 21.69; HRMS (ESI) calcd for $C_{11}H_9N_3NaO_2$ $[M+Na]^+$:238.0592, found: 238.0596.

4-(azidomethyl)-6-methyl-2*H*-chromen-2-one (4g)

The method synthesizing compound **4g** was same to that of compound **4c**. White solid, yield: 80%; m.p. 107-108 °C. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm, δ , ppm): 7.38 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.51 (s, 1H), 4.56 (d, J = 1.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 160.39, 151.91, 148.39, 134.32, 133.30, 123.52, 117.19, 117.04, 114.64, 50.74, 21.01; HRMS (ESI) calcd for $C_{11}H_{10}N_3O_2$ $[M+H]^+$:216.0773, found: 216.0775.

4-(azidomethyl)-7-hydroxy-5-methyl-2*H*-chromen-2-one (4h)

The method synthesizing compound **4h** was same to that of compound **4a**. the mixture was inseparate and used in the next step without further purification.

4-(azidomethyl)-5,7-dihydroxy-2*H*-chromen-2-one (4i)

The method synthesizing compound **4i** was same to that of compound **4a**. yellow solid, yield: 76%; m.p. 220-221 °C. ^1H NMR (400 MHz, Acetone-d_6, δ , ppm): 9.62 (s, 1H), 6.38 (d, J = 2.3 Hz, 1H), 6.32 (d, J = 2.3 Hz, 1H), 6.14 (t, J = 1.4 Hz, 1H), 4.94 (d, J = 1.3 Hz, 2H); ^{13}C NMR (100 MHz, Acetone-d_6, δ , ppm): 161.34, 159.93, 157.11, 156.88, 151.36, 107.62, 100.66, 99.15, 95.42, 53.25; HRMS (ESI) calcd for $C_{10}H_8N_3O_4$ $[M+H]^+$:234.0515, found: 234.0512.

4-(azidomethyl)-7,8-dihydroxy-2*H*-chromen-2-one (4j)

The method synthesizing compound **4j** was same to that of compound **4a**. yellow solid, yield: 73%; m.p. 187-188 °C. ^1H NMR (400 MHz, DMSO-d_6, δ , ppm): 7.05 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.27 (d, J = 0.8 Hz, 1H), 4.77 (d, J = 0.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 160.49, 151.05, 150.55, 143.98, 133.00, 115.47, 112.85, 110.61, 109.68, 50.20; HRMS (ESI) calcd for $C_{10}H_8N_3O_4$ $[M+H]^+$:234.0515, found: 234.0514.

4-(azidomethyl)-7-hydroxy-2*H*-chromen-2-one (4k)

The method synthesizing compound **4k** was same to that of compound **4a**. yellow solid, yield: 75%; m.p. 166-167 °C. ^1H NMR (400 MHz, Acetone-d_6, δ , ppm): 9.49 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 6.88 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.30 (s, 1H), 4.78 (d, J = 1.0 Hz, 2H); ^{13}C NMR (100

MHz, Acetone-d_6, δ , ppm): 161.24, 159.91, 155.78, 149.67, 125.89, 112.88, 110.29, 110.20, 102.75, 50.23; HRMS (ESI) calcd for $C_{10}H_8N_3O_3$ $[M+H]^+$:218.0566, found: 218.0563.

Preparation of intermediates **5a-b**

3-methyl-2*H*-chromen-2-one (5a)

salicylaldehyde (2.000 g, 16.38 mmol), propionic anhydride (6.393 g, 49.13 mmol) and sodium propionate (3.146 g, 32.76mmol) were placed in a 50 mL round-bottom flask. Triethylamine (2.3 mL, 16.38 mmol) was then added, and the reaction mixture was heated to reflux for 6 h. After the reaction, water (30 ml) was poured and the resulting pink solid was collected by filtration and washed with cold water. Column chromatography (ethyl acetate: petroleum ether = 1:4) of the crude product over silica gel gave **5a** as a colorless powder. Yield: 45%, m.p. 89-90 ^oC. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.53 (s, 1H), 7.49 – 7.40 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.28 – 7.23 (m, 1H), 2.22 (d, *J* = 1.0 Hz, 3H).

7-hydroxy-3-methyl-2*H*-chromen-2-one (5b)

The method synthesizing compound **5b** was same to that of compound **5a**. White solid, yield: 46%; m.p.: 218-219 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.08 (s, 1H), 7.02 (dd, *J* = 8.4, 2.1 Hz, 1H), 2.20 (s, 3H).

Preparation of intermediates **6a-b**

3-(bromomethyl)-2*H*-chromen-2-one (6a): To a solution of compound **5a** (480mg, 3 mmol) in 10 mL of CCl_4 was added NBS (587 mg, 3.3 mmol) and a trace amount of AIBN, and the mixture was then refluxed. After the reaction, the solvent was removed under reduced pressure. Then the residue was purified by chromatography on silica gel to afford compound **6a** as colorless power. Yield 78%, m.p. 119-120 °C. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.87 (s, 1H), 7.56 (td, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.52 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.31 (td, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 159.93, 153.76, 141.99, 132.21, 128.07, 125.51, 124.76, 118.90, 116.76, 27.59; HRMS (ESI) calcd for $C_{10}H_8BrO_2$ $[M+H]^+$:238.9708, found: 238.9702.

3-(bromomethyl)-7-hydroxy-2*H*-chromen-2-one (6b): The method synthesizing compound **6b** was same to that of compound **6a**. White solid, yield: 78%, m.p. 154-155 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.43 (s, 2H).

Preparation of intermediates **7a-b**

3-(azidomethyl)-2*H*-chromen-2-one (7a): The method synthesizing compound **7a** was same to that of compound **4c**. Yellow solid, yield: 75%; m.p.: 95-97 °C. ^1H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.76 (s, 1H), 7.58 – 7.50 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 4.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 160.54, 153.43, 139.96, 131.86, 128.00, 124.75, 123.78, 118.76, 116.71, 49.97; HRMS (ESI) calcd for $C_{10}H_8N_3O_2$ $[M+H]^+$:224.0436, found: 224.0435.

3-(azidomethyl)-7-hydroxy-2*H*-chromen-2-one (7b): The method synthesizing compound **7b** was same to that of compound **4c**. the mixture was inseparate and used in the next step without further purification.

Preparation of **8a-l** and **9a-b**

Azide derivatives (3 mmol), **2** (901 mg, 3.3 mol), $CuSO_4 \cdot H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (40 mg, 0.2mmol) were placed in a 50 mL round-bottom flask. THF (10 mL) and H_2O (10 mL) were added. The mixture was stirred at room temperature. Upon completion (monitored by TLC), water (20 mL) was added and the reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was

washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by chromatography on silica gel to afford pure product.

tert-butyl 4-((((1-((7-chloro-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8a)

Yellow solid, yield: 82%, m.p.: 212-213 °C. purity: 98.1807 %. ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.30 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 5.98 (s, 1H), 5.65 (d, J = 1.0 Hz, 2H), 4.72 (s, 2H), 4.31 (br, 2H), 3.91 (br, 2H), 3.5 4(t, J = 5.1 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 196.02, 159.06, 154.40, 154.06, 147.45, 138.79, 125.44, 124.52, 117.88, 115.61, 115.10, 80.70, 50.04, 31.40, 28.35; HRMS (ESI) calcd for $C_{23}H_{27}ClN_5O_4S_2$ $[M+H]^+$:558.1012, found: 558.1010.

tert-butyl 4-((((1-((6-chloro-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl) thio) carbonothioyl)piperazine-1-carboxylate (8b)

White solid, yield: 85%, m.p.: 207.6-209 °C. purity: 98.2285 %. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.81 (s, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.55 (dd, J_1 = 2.3 Hz, J_2 = 8.8 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 5.93 (s, 1H), 5.66 (d, J = 0.9 Hz, 2H), 4.74 (s, 2H), 4.31 (br, 2H), 3.92 (br, 2H), 3.55 (t, J = 5.2Hz, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, DMSO, δ , ppm): 194.87, 159.38, 154.15, 152.24, 149.78, 143.38, 132.69, 129.09, 125.42, 124.85, 119.27, 119.00, 115.30, 79.87, 49.40, 31.77, 28.49; HRMS (ESI) calcd for $C_{23}H_{27}ClN_5O_4S_2$ $[M+H]^+$:558.1012, found: 558.1014.

tert-butyl 4-((((1-((7-fluoro-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8c)

Yellow solid, yield: 85%, m.p.: 187-188 °C. purity: 98.0904 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 8.25 (s, 1H), 7.93 (dd, J_1 = 6.1 Hz, J_2 = 8.9 Hz, 1H), 7.47 (dd, J_1 = 2.5 Hz, J_2 = 9.5 Hz, 1H), 7.34 (td, J_1 = 2.5 Hz, J_2 = 8.7 Hz, 1H), 5.95 (s, 2H), 5.79 (s, 1H), 4.63 (s, 2H), 4.23 (br, 2H), 3.92 (br, 2H), 3.45 (t, J = 4.8 Hz, 4H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 194.81, 165.69, 163.19, 159.65, 154.98, 154.84, 154.15, 150.25, 127.55, 127.44, 125.46, 114.67, 114.64, 113.24, 113.03, 112.81, 105.05, 104.79, 79.88, 49.65, 31.71, 28.49; ^{19}F NMR (376 MHz, $CDCl_3$, δ , ppm): -106.69. HRMS (ESI) calcd for $C_{23}H_{26}FN_5NaO_4S_2$ $[M+H]^+$: 542.1308, found: 542.1310.

tert-butyl 4-((((1-((2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio)carbonothioyl) piperazine-1-carboxylate (8d)

Yellow solid, yield: 79%, m.p.: 189-190 °C. purity: 99.1287 %.^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.80 (s, 1H), 7.65 – 7.57 (m, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.33 (td, J_1 = 0.9 Hz , J_2 = 7.6 Hz, 1H), 5.93 (s, 1H), 5.71 (d, J = 0.9 Hz, 2H), 4.72 (s, 2H), 4.30 (br, 2H), 3.91 (br, 2H), 3.54 (t, J = 5.2 Hz, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 196.08, 159.77, 154.41, 153.68, 148.06, 145.18, 132.73, 124.89, 123.72, 123.44, 117.63, 116.97, 115.01, 80.67, 50.03, 31.47, 28.35; HRMS (ESI) calcd for $C_{23}H_{28}N_5O_4S_2$ $[M+H]^+$:502.1583, found: 502.1581.

tert-butyl 4-((((1-((7-amino-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8e)

Yellow solid, yield: 78.3%, m.p.: 156-157.5 °C. purity: 96.1341 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 8.22 (s, 1H), 7.50 (d, J = 8.7 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.44 (s, 1H), 6.27 (s, 2H), 5.80 (s, 2H), 5.29 (s, 1H), 4.63 (s, 2H), 4.23 (br, 2H), 3.91 (br, 2H), 3.45 (s, 4H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 194.82, 160.90, 156.17, 154.13, 154.02, 151.25, 126.10, 111.82, 106.49, 106.25, 99.08, 79.87, 49.60, 31.74, 28.48; HRMS (ESI) calcd for $C_{23}H_{29}N_6O_4S_2$ $[M+H]^+$:539.1511, found: 539.1512.

tert-butyl 4-((((1-((7-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8f)

Pale yellow solid, yield: 82%, m.p.: 201-202 °C. purity: 95.7089 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 8.25 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.30 (s, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 5.93 (s, 2H), 5.74 (s, 1H), 4.62 (s, 2H), 4.22 (br, 2H), 3.91 (br, 2H), 3.45 (s, 4H), 2.42 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 194.82, 160.05, 154.13, 153.64, 150.67, 144.03, 126.12, 124.94, 117.31, 115.12, 113.06, 79.87, 49.60, 31.76, 28.48, 21.54; HRMS (ESI) calcd for $C_{24}H_{30}N_5O_4S_2$ $[M+H]^+$:516.1739, found: 516.1737.

tert-butyl 4-((((1-((6-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8g)

White solid, yield: 81%, m.p.: 194-195 °C. purity: 98.6344 %. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.80 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.39 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 1H), 5.68 (s, 2H), 4.73 (s, 2H), 4.31 (br, 2H), 3.92 (br, 2H), 3.54 (t, *J* = 5.2 Hz, 4H), 2.42 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, δ , ppm): 196.09, 173.28, 160.02, 154.41, 151.80, 148.01, 134.68, 133.71, 123.19, 117.32, 116.68, 114.77, 80.66, 50.00, 31.50, 28.35, 21.05; HRMS (ESI) calcd for $C_{24}H_{29}N_5NaO_4S_2$ $[M+Na]^+$:538.1559, found: 538.1557.

tert-butyl 4-((((1-((7-hydroxy-5-methyl-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl) thio)carbonothioyl)piperazine-1-carboxylate (8h)

Yellow solid, yield: 73%, m.p.: 144.3-146 °C. purity: 98.3841 %. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 9.74 (s, 1H), 7.89 (s, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 6.00 (s, 2H), 5.26 (s, 1H), 4.72 (s, 2H), 4.28 (br, 2H), 3.90 (br, 2H), 3.54 (t, *J* = 5.2 Hz, 4H), 2.30 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 195.80, 160.88, 154.99, 154.89, 154.62, 151.12, 144.48, 144.40, 124.80, 112.71, 110.06, 109.43, 104.69, 81.00, 52.97, 31.39, 28.37, 21.73. HRMS (ESI) calcd for $C_{24}H_{30}N_5O_5S_2$ $[M+H]^+$: 532.1688, found: 532.1686.

tert-butyl 4-((((1-((5,7-dihydroxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8i)

Yellow solid, yield: 79%, m.p.: 162-163 °C. purity: 96.7326 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 11.06 (s, 1H), 10.51 (s, 1H), 8.20 (s, 1H), 6.31 (d, *J* = 2.1 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 5.94 (s, 2H), 4.79 (s, 1H), 4.64 (s, 2H), 4.23 (br, 2H), 3.93 (br, 2H), 3.46 (s, 4H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 194.87, 162.27, 160.30, 157.98, 156.78, 154.14, 153.01, 142.85, 125.56, 106.11, 100.36, 99.60, 95.26, 79.86, 52.47, 31.90, 28.48; HRMS (ESI) calcd for $C_{23}H_{28}N_5O_6S_2$ $[M+H]^+$:534.1481, found: 534.1480.

tert-butyl 4-((((1-((7,8-dihydroxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8j)

Pale yellow solid, yield: 80.7%, m.p.: 173-174 °C. purity: 96.0708 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ , ppm): 10.27 (s, 1H), 9.47 (s, 1H), 8.24 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 5.86 (s, 2H), 5.50 (s, 1H), 4.62 (s, 2H), 4.23 (br, 2H), 3.91 (br, 2H), 3.45 (s, 4H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ , ppm): 194.83, 160.34, 154.13, 151.43, 150.46, 143.89, 143.08, 132.94, 125.41, 115.45, 112.87, 110.55, 109.46, 79.87, 49.72, 31.80, 28.48; HRMS (ESI) calcd for $C_{23}H_{28}N_5O_6S_2$ $[M+H]^+$:534.1481, found: 534.1485.

tert-butyl 4-(((1-((7-hydroxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)thio) carbonothioyl)piperazine-1-carboxylate (8k)

Yellow solid, yield: 83%, m.p.: 219-220 °C. purity: 97.4708 %. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.73 (s, 1H), 8.24 (s, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.77 (s, 1H), 5.88 (s, 2H), 5.54 (s, 1H), 4.63 (s, 2H), 4.23 (br, 2H), 3.92 (br, 2H), 3.45 (t, *J* = 5.2 Hz, 4H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 194.86, 162.14, 160.39, 155.57, 154.15, 150.99, 143.22, 126.54, 125.42,

113.65,109.84, 109.66, 103.01, 79.87, 67.48, 49.64, 31.77, 28.49, 25.59; HRMS:(ESI) calcd for $C_{23}H_{27}N_5NaO_2S_2$ $[M + Na]^+$: 540.1351, found: 540.1353.

tert-butyl 4-((((1-((7-methoxy-2-oxo-2H-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (8l)

To a magnetically stirred solution of compound **8k** (515 mg, 1 mmol) in DMF (10 ml), potassium carbonate (166 mg, 1.2 mmol) and iodomethane (213 mg, 1.5 mmol) were added and heated at 80 ℃ for 2h. Upon completion (monitored by TLC), water (20 ml) was added, and the mixture was extracted with dichloromethane and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product was purified by chromatography on silica gel to afford pure product. Yellow solid, yield: 81%, m.p.: 179-180 ℃. purity: 95.5043 %. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.77 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 6.84-6.90 (m, 2H), 5.81 (s, 1H), 5.65 (s, 2H), 4.72 (s, 2H), 4.32 (br, 2H), 3.89 (s, 5H), 3.54 (s, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 196.05, 163.30, 160.32, 155.65, 154.40, 148.14, 124.54, 112.99, 111.64, 110.46, 101.40, 80.66, 55.90, 50.19, 31.50, 28.35; HRMS (ESI) calcd for $C_{24}H_{30}N_5O_5S_2$ $[M+H]^+$:532.1688, found: 532.1687.

tert-butyl 4-((((1-((2-oxo-2H-chromen-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)carbonothioyl) piperazine-1-carboxylate (9a)

White solid, yield: 77%, m.p.: 127-128 °C. purity: 99.1512 %. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.90 (s, 1H), 7.63 (s, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 6.7 Hz, 1H), 7.36 – 7.29 (m, 2H), 5.44 (s, 2H), 4.71 (s, 2H), 4.31 (br, 2H), 3.92 (br, 2H), 3.54 (d, *J* = 5.1 Hz, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 196.26, 160.55, 154.41, 153.65, 144.05, 142.11, 132.44, 128.33, 124.92, 124.18, 122.82, 118.55, 116.73, 80.63, 49.05, 31.78, 28.36; HRMS (ESI) calcd for $C_{23}H_{28}N_5O_4S_2$ $[M+H]^+$:502.1583, found: 502.1575.

tert-butyl 4-((((1-((7-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio) carbonothioyl)piperazine-1-carboxylate (9b)

White solid, yield: 74%, m.p.: 130.3-132 °C. purity: 95.3827 %. ^{1}H NMR (400 MHz, $CDCl_3$, δ , ppm): 7.89 (s, 1H), 7.62 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.07 (dd, J_1 = 8.5 HZ, J_2 = 2.1 Hz, 1H), 5.42 (s, 2H), 4.71 (s, 2H), 4.31 (br, 2H), 3.91 (br, 2H), 3.55 (d, *J* = 5.0 Hz, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ , ppm): 196.02, 161.59, 161.37, 155.65, 154.64, 143.42, 129.68, 124.57, 117.63, 114.14, 111.58, 103.16, 80.99, 49.60, 31.50, 28.38. HRMS (ESI) calcd for $C_{23}H_{28}N_5O_5S_2$ $[M+H]^+$:518.1532, found: 518.1530.