Electronic supplementary Information

Discovery of a new class of Dithiocarbamates and Rhodanine Scaffolds as potent antifungal agent: Synthesis, Biology and molecular Docking

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Experimental Section

1. Chemistry

All reagents and solvents were commercially available and were used without further purification. IR spectra were recorded on a FTIR spectrophotometer Shimadzu 8201 PC and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Supercon Magnet Avance DRX-300 or DPX 200 FT spectrometers using TMS as an internal reference and the samples were dissolved in suitable deuterated solvents (Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in Hz). Electro Spray Ionisation Mass spectra (ESI-MS) were recorded by micromass quattro II instrument. HR-DART MS were recorded on JEOL, JMS T100LC Accu TOF. Purity of all tested compounds was ascertained on the basis of their elemental analysis and was carried out on Carlo-Erba-1108 instrument. Column chromatography purifications were performed in flash using 60-120 or 100-200 Mesh silica gel. Thin-layer chromatography (TLC) was carried out with silica gel plates (silica gel 60 F254), that were visualized by exposure to ultraviolet light. The melting points were recorded on an electrically heated melting point apparatus and are uncorrected.

General procedure for the preparation of Ethyl pyridin-4-ylmethylcarbamodithioate (4a):

A mixture of 4-aminomethylpyridine **(**0.36 mL, 3.54 mmol), carbon disulfide (0.21 mL, 3.54 mmol) and ethyl iodide (0.18 mL, 1.77 mmol) in acetonitrile (4 mL) was stirred magnetically at room temperature till the reaction mixture gets solidified. Reaction was completed (observed on TLC). Reaction mixture was concentrated under reduced pressure to provide crude product. The crude product was purified by column chromatography over silica-gel using 1% methanol/chloroform as eluent.Yield: 80%; Light brown solid; mp 92-94°C; HRMS: calc: 213.0520 (MH^+); Found: 213.0515 (MH^+); Anal. Calcd. For $C_9H_{12}N_2S_2$: C,

50.91; H, 5.70; N, 13.19. Found: C, 50.89; H, 5.69; N, 13.16; IR (KBr): ν 3450, 3174, 2921, 1603, 1261, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.54 (d, 2H, *J* = 4.4 Hz), 7.70 (s, 1H), 7.22 (d, 2H, *J* = 5.5 Hz), 4.98 (d, 2H, *J* = 5.1 Hz), 3.33-3.26 (m, 2H), 1.38 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.0, 149.8, 146.2, 122.5, 49.0, 30.0, 14.1; MS (m/z %): 213 (M^++H);

The following compounds **4b-f** were prepared using a procedure similar to that described for compound **4a** from the corresponding, 4-aminomethylpyridine, carbon disulfide and different halides.

Propyl pyridin-4-ylmethylcarbamodithioate (4b):

Compound **4b** was prepared by the reaction of 4-aminomethylpyridine**(**0.36 mL, 3.54 mmol), carbon disulfide (0.21 mL, 3.54 mmol) and propyl iodide (0.17 mL, 1.77 mmol), 76% Yield as White solid; mp 94-96°C; HRMS: calc.: 227.0677 (MH^+); Found: 227.0677 (MH^+); Anal. Calcd. For $C_{10}H_{14}N_2S_2$: C, 53.06; H, 6.23; N, 12.38. Found: C, 50.05; H, 6.21; N, 12.36. IR (KBr): ν 3420, 3162, 2925, 1657, 1257, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.55 (d, 2H, *J* = 3.8 Hz), 7.66 (s, 1H), 7.22 (d, 2H, *J* = 5.0 Hz), 4.99 (d, 2H, *J* = 4.6 Hz), 3.31 (t, 2H, *J* = 7.1 Hz), 1.80-1.68 (m, 2H), 1.05 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.3, 149.7, 146.3, 123.2, 49.1, 37.6, 29.7, 13.2; MS (m/z %) : 227 (M^++H);

Butyl pyridin-4-ylmethylcarbamodithioate (4c):

Compound **4c** was prepared by the reaction of 4-aminomethylpyridine**(**0.36 mL, 3.54 mmol), carbon disulfide (0.21 mL, 3.54 mmol) and butyl bromide (0.19 mL, 1.77 mmol), 78% Yield as Light brown solid; mp 91-93°C; HRMS: calc.: 241.0833 (MH^+); Found: 241.0828 (MH^+); Anal. Calcd. For $C_{11}H_{16}N_2S_2$: C, 54.96; H, 6.71; N, 11.65. Found: C, 54.93; H, 6.68; N, 11.66. IR (KBr): ν 3419, 3190, 2921, 1657, 1252, 1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.55 (d, 2H, *J* = 4.5 Hz), 7.61 (s, 1H), 7.22 (d, 2H, *J* = 5.3 Hz), 4.98 (d, 2H, *J* = 5.2 Hz), 3.32 (t, 2H, *J* = 7.3 Hz), 1.74-1.63 (m, 2H), 1.47-1.39 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ: 200.2, 149.6, 146.4, 122.6, 49.0, 35.4, 31.1, 22.0, 13.7; MS (m/z %) : 241 (M^++H);

Allyl pyridin-4-ylmethylcarbamodithioate (4d):

Compound **4d** was prepared by the reaction of 4-aminomethylpyridine**(**0.36 mL, 3.54 mmol), carbon disulfide (0.21 mL, 3.54 mmol) and allyl bromide (0.15 mL, 1.77 mmol), 70% Yield as brown solid; mp 95-97°C; HRMS: calc.: 225.0520 (MH^+); Found: 225.0523 (MH^+); Anal. Calcd. For $C_{10}H_{12}N_2S_2$: C, 53.54; H, 5.39; N, 12.49. Found: C, 53.55; H, 5.37; N, 12.48. IR (KBr): ν 3435, 3172, 2784, 1601, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.54 (s, 2H), 7.76 (s, 1H), 7.21 (s, 2H), 5.92-5.87 (m, 1H), 5.33 (d, 1H, *J* = 16.8 Hz), 5.18 (d, 1H, *J* = 9.5 Hz), 4.97 (s, 2H), 3.98 (d, 2H, *J* = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.0, 149.7, 146.2, 132.6, 122.6, 118.7, 49.2, 38.6; MS (m/z %) : 225 (M^++H);

Benzyl pyridin-4-ylmethylcarbamodithioate (4e):

Compound **4e** was prepared by the reaction of 4-aminomethylpyridine**(**0.36 mL, 3.54 mmol), carbon disulfide (0.21 mL, 3.54 mmol) and benzyl bromide (0.21 mL, 1.77 mmol), 80%Yield as light brown solid; mp 142-144°C; HRMS: calc.: 275.0677 (MH^+); Found: 275.0680 (MH^+); Anal. Calcd. For $C_{14}H_{14}N_2S_2$: C, 61.28; H, 5.14; N, 10.21. Found: C, 61.26; H, 5.13; N, 10.22. IR (KBr): ν 3444, 3127, 2886, 1662, 1253, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.54 (d, 2H, *J* = 4.8 Hz), 7.60 (s, 1H), 7.38-7.31 (m, 5H), 7.18 (d, 2H, *J* = 5.0 Hz), 4.97 (d, 2H, *J* = 5.0 Hz), 4.57 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO) δ: 203.3, 154.4, 151.3, 141.6, 133.8, 133.3 132.1, 127.3, 53.7, 45.6; MS (m/z %) : 275 (M^++H);

4-(Trifluoromethyl) benzyl pyridin-4-ylmethylcarbamodithioate (4f):

Compound **4f** was prepared by the reaction of 4-aminomethylpyridine**(**0.36 mL, 3.54 mmol), carbon disulfide (0.21 mL, 3.54 mmol) and 4-(Trifluoromethyl) benzyl bromide (0.27 mL, 1.77 mmol), 73% Yield as Light brown solid; mp 171-173°C; HRMS: calc.: 343.0550 (MH^+); Found: 343.0545 (MH^+); Anal. Calcd. For $C_{15}H_{13}F_3N_2S_2$: C, 52.62; H, 3.83; N, 8.18.

Found: C, 52.60; H, 3.82; N, 8.17. IR (KBr): ν 3466, 3177, 2819, 1662, 1260, 1215 cm-^{1}; ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD); δ: 8.56 (d, 2H, *J* = 4.9 Hz), 7.58-7.48 (m, 4H), 7.20 (d, 2H, *J* = 5.6 Hz), 4.98 (d, 2H, *J* = 4.9 Hz), 4.63 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO) δ: 197.3, 149.3, 146.0, 141.6, 129.1, 124.9, 122.2, 48.8, 40.5; MS (m/z %): 343.0 (M^++H);

General procedure for the preparation of compounds 3-(Pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (6):

Compound **6** was prepared by the reaction of 4-aminomethylpyridine(0.36 mL, 3.54 mmol), carbon disulphide (0.21 mL, 3.54 mmol) and ethylbromoacetate (0.20 mL, 1.77 mmol) in acetonitrile. The reaction mixture was stir at room temperature till the reaction mixture gets solidified. Reaction was completed (observed on TLC). Crude product was purified by column chromatography. Eluent 1% methanol-chloroform, 78% Yield as Brown solid; mp 130-132°C; HRMS: calc.: 225.0156 (MH^+); Found: 225.0152 (MH^+); Anal. Calcd. For $C_9H_8N_2OS_2$: C, 48.19; H, 3.59; N, 12.49. Found: C, 48.16; H, 3.57; N, 12.47. IR (KBr): ν 3153, 2927, 1738, 1637, 1224 cm^{-1}; 8.57 (d, 2H, *J* = 5.9 Hz), 7.27-7.25 (m, 2H), 5.17 (s, 2H), 4.05 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.7, 173.6, 150.1, 143.1, 123.2, 46.4, 35.5; MS (m/z %): 225.0 (M^++H);

General procedure for the preparation of compounds (Z)-5-Benzylidene-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7a):

Compound **7a** was prepared by the reaction of Compound **6**, (0.20 g, 0.892 mmol), benzaldehyde **(**0.90 mL, 0.892 mmol), ammonium acetate **(**0.14 g, 1.78 mmol), and 4-5 mL of acetic acid were taken in a round bottom flask equipped with a magnetic stirrer. The reaction mixture was reflux for an appropriate time and the progress of reaction was monitored by TLC. After completion of the reaction, reaction mixture was evaporated gave a crude product which was purified by column chromatography. Eluent 3% methanol-chloroform 76% Yield as Yellow solid; mp 165-167°C; HRMS: calc.: 313.0469 (MH^+);

Found: 313.0466 (MH^+); Anal. Calcd. For $C_{16}H_{12}N_2OS_2$: C, 61.51; H, 3.87; N, 8.97. Found: C, 61.50; H, 3.85; N, 8.98. IR (KBr): ν 3166, 2931, 1707, 1598, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.60 (d, 2H, *J* = 5.9 Hz), 7.80 (s, 1H), 7.52-7.49 (m, 5H), 7.32 (d, 2H, *J* = 5.8 Hz), 5.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 193.0, 167.6, 150.2, 143.3, 134.1, 133.1, 131.0, 130.7, 123.1, 122.5, 46.3; MS (m/z %): 313.0 (M^++H);

The following compounds **7b-o**, **9a** and **9b-e** were prepared using a procedure similar to that described for compound **7a** from the corresponding, compound **6**, appropriate aldehyde and ammonium acetate in acetic acid.

(Z)-5-(4-Fluorobenzylidene-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7b) :

Compound **7b** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4-fluorobenzaldehyde (0.94 mL, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 78% Yield as Yellow solid; mp 125-127°C; HRMS: calc.: 331.0375 (MH^+); Found: 331.0334 (MH^+); Anal. Calcd. For $C_{16}H_{11}FN_2OS_2$: C, 58.16; H, 3.36; N, 8.48. Found: C, 58.15; H, 3.34; N, 8.45. IR (KBr): ν 3392, 3005, 1699, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.60 (d, 2H, *J* = 4.6 Hz); 7.75 (s, 1H), 7.55-7.50 (m, 2H), 7.34-7.18 (m, 4H), 5.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.5, 167.5, 162.3, 150.0, 143.5, 132.9, 132.8, 123.2, 122.2, 117.0, 116.7, 46.3; MS(m/z %): 331.0 (M^++H);

(Z)-5-(2-Fluorobenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7c):

Compound **7c** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 2-fluorobenzaldehyde (0.94 mL, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 72% Yield as Yellow solid; mp 124-126°C; HRMS: calc.: 331.0375 (MH^+); Found: 331.0361 (MH^+); Anal. Calcd. For $C_{16}H_{11}FN_2OS_2$: C, 58.16; H, 3.36; N, 8.48. Found: C, 58.13; H, 3.31; N, 8.45. IR (KBr): ν 3353, 2991, 1684, 1245 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.58 (d, 2H, *J* = 4.5 Hz), 8.00 (s, 1H), 7.49-7.43 (m, 2H), 7.30-7.14 (m,

4H), 5.31 (s, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.6, 167.3, 163.3, 150.2, 143.2, 129.4, 125.8, 125.0, 124.9, 124.4, 123.2, 121.6 116.6, 116.3, 46.4; MS(m/z %): 331.0 (M^++H);

(Z)-5-(4-Chlorobenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7d):

Compound **7d** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4-chlorobenzaldehyde (1.0 mL, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid 75% Yield as Yellow solid; mp 125-127°C; HRMS: calc.: 347.0080 (MH^+); Found: 347.0073 (MH^+); Anal. Calcd. For $C_{16}H_{11}ClN_2OS_2$: C, 55.40; H, 3.20; N, 8.08. Found: C, 55.37; H, 3.19; N, 8.05. IR (KBr): ν 3312, 3050, 1701, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.58 (d, 2H, *J* = 4.6 Hz); 7.71(s, 1H), 7.45 (d, 4H, *J* = 3.2 Hz), 7.29 (d, 2H, *J* = 4.7 Hz), 5.30 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 192.3, 167.5, 150.1, 143.2, 137.3, 132.4, 131.7, 131.6, 129.8, 123.1, 46.4; MS(m/z %): 347.0 (M^++H);

(Z)-5-(2-Nitrobenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7e):

Compound **7e** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 2-nitrobenzaldehyde (0.13g, 0.892 mmol), and ammonium acetate (0.14g, 1.78 mmol), in 4-5 mL acetic acid, 75% Yield as Yellow solid; mp 125-127°C; HRMS: calc.: 358.0320 (MH^+); Found: 358.0299 (MH^+); Anal. Calcd. For $C_{16}H_{11}N_3O_3S_2$: C, 53.77; H, 3.10; N, 11.76. Found: C, 53.75; H, 3.07; N, 11.73. IR (KBr): ν 3381, 3015, 1696, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.53 (s, 2H); 8.14-8.08 (m, 2H), 7.71 (t, 1H, *J* = 7.0 Hz), 7.59-7.51 (m, 3H), 7.19 (s, 1H), 5.24 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.5, 166.4, 150.1, 148.1, 143.2, 134.1, 131.6, 131.1, 129.5, 127.9, 125.8, 123.3, 46.5; MS(m/z %): 358.0 (M^++H);

(Z)-5-(4-Nitrobenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7f):

Compound **7f** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4-nitrobenzaldehyde (0.13 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 75% Yield as Yellow solid; mp 125-127°C; HRMS: calc.: 358.0320 (MH^+); Found: 358.0309 (MH^+); Anal. Calcd. For $C_{16}H_{11}N_3O_3S_2$: C, 53.77; H, 3.10; N, 11.76.

Found: C, 53.72; H, 3.06; N, 11.73. IR (KBr): ν 3392, 3005, 1699, 1235 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.59 (d, 2H, *J* = 5.7 Hz), 8.35 (d, 2H, *J* = 8.7 Hz), 7.77 (s, 1H), 7.67 (d, 2H, *J* = 8.7 Hz), 7.30 (d, 2H, *J* = 5.4 Hz), 5.32 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 192.4, 166.0, 151.0, 144.0, 143.0, 140.0, 137.3, 129.8, 123.1, 121.0, 46.2; MS(m/z %): 358.0 (M^++H);

(Z)-5-(4-Ethylbenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7g):

Compound **7g** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4-ethylbenzaldehyde (1.2 mL, 0.892 mmol), and ammonium acetate (0.14g, 1.78 mmol), in 4-5 mL acetic acid, 75% Yield as Yellow solid; mp 125-127°C; HRMS: calc.: 341.0782 (MH^+); Found: 341.0776 (MH^+); Anal. Calcd. For $C_{18}H_{16}N_2OS_2$: C, 63.50; H, 4.74; N, 8.23. Found: C, 63.48; H, 4.70; N, 8.21. IR (KBr): ν 3392, 3005, 1699, 1235 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.57 (d, 2H, *J* = 4.5 Hz,); 7.76 (s, 1H), 7.45 (d, 2H, *J* = 8.1 Hz), 7.33-7.28 (m, 4H), 5.31 (s, 2H), 2.74-2.66 (m, 2H), 1.29 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 193.0, 167.6, 150.1, 143.4, 134.3, 131.0, 130.6, 129.0, 123.1, 121.2, 46.3, 28.9, 15.1; MS(m/z %): 341.0 (M^++H);

(Z)-5-(4-Methoxybenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7h):

Compound **7h** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4-methoxybenzaldehyde (1.1 mL, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 83% Yield as Yellow solid; mp 170-172°C; IR (KBr): ν 3449, 2924, 1706, 1262, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 8.48 (d, 2H, *J* = 4.5 Hz), 7.64 (s, 1H), 7.39 (d, 2H, *J* = 8.7 Hz), 7.21(d, 2H, *J* = 5.0 Hz), 6.93 (d, 2H, *J* = 8.7 Hz), 5.22 (s, 2H), 3.79 (s, 3H), ^{13}C NMR (50 MHz, $CDCl_3$) δ: 192.2, 167.4, 160.2, 150.1, 143.4, 125.7, 122.2, 111.1, 56.1, 46.3; MS(m/z %): 343.0 (M^++H);

(Z)-5-(3,4-Dimethoxybenzylidene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7i):

Compound **7i** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 3,4-

dimethoxybenzaldehyde (0.15 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 85% Yield as Yellow solid; mp 173-175°C; HRMS: calc.: 373.0681 (MH^+); Found: 373.0668 (MH^+); Anal. Calcd. For $C_{18}H_{16}N_2O_3S_2$: C, 58.04; H, 4.33; N, 7.52. Found: C, 58.02; H, 4.31; N, 7.50. IR (KBr): ν 3424, 3012, 1706, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.57 (d, 2H, *J* = 5.1 Hz), 7.72 (s, 1H), 7.29 (d, 2H, *J* = 4.7 Hz), 7.16 (d, 1H, *J* = 7.2 Hz), 6.98 (d, 2H, *J* = 8.7 Hz), 5.31 (s, 2H), 3.95 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.7, 167.6, 151.9, 150.0, 149.6, 143.5, 134.4, 126.1, 125.8, 123.2, 119.5, 112.5, 111.5, 56.1, 46.3; MS(m/z %): 373.0 (M^++H);

(Z)-3-(Pyridin-4-ylmethyl)-2-thioxo-5-(3, 4, 5-trimethoxybenzylidene) thiazolidin-4-one (7j):

Compound **7j** was prepared by the reaction of **6** (0.20 g, 0.892 mmol), 3,4,5-trimethoxybenzaldehyde (0.17 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 76% Yield as Yellow solid; mp 148-150°C; HRMS: calc.: 403.0786 (MH^+); Found: 403.0778 (MH^+); Anal. Calcd. For $C_{19}H_{18}N_2O_4S_2$: C, 56.70; H, 4.51; N, 6.96. Found: C, 56.67; H, 4.50; N, 6.94. IR (KBr): ν 3434, 2941, 1710, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.60 (s, 2H), 7.71(s, 1H), 7.32 (s, 2H), 6.74 (s, 2H), 5.33 (s, 2H), 3.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.7, 167.4, 153.7, 150.1, 143.4, 140.9, 128.4, 123.1, 121.2, 108.0, 61.1, 56.3, 46.3; MS(m/z %): 403.0 (M^++H);

(Z)-3-(pyridin-4-ylmethyl)-5-(pyridin-4-ylmethylene)-2-thioxothiazolidin-4-one (7k):

Compound **7k** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4-pyridinecarboxaldehyde (0.84 mL, 0.892 mmol), and ammonium acetate (0.14g, 1.78 mmol), in 4-5 mL acetic acid, 70% Yield as Brown solid; mp 148-150°C; HRMS: calc.: 314.0422 (MH^+); Found: 314.0410 (MH^+); Anal. Calcd. For $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.47; H, 3.53; N, 13.40. IR (KBr): ν 3450, 3043, 1716, 1208 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.79 (s, 2H), 8.62(s, 2H), 7.68 (s, 1H), 7.35 (s, 4H), 5.34 (s, 2H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ: 191.7, 167.2, 149.7, 142.6, 139.6, 130.5, 127.4, 46.7; MS (m/z %): 314.0 (M^++H);

(Z)-5-(pyridin-2-ylmethylene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7l):

Compound **7l** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 3-pyridinecarboxaldehyde (0.84 mL, 0.892 mmol), and ammonium acetate (0.14g, 1.78 mmol), in 4-5 mL acetic acid, 70% Yield as Brown solid; mp 148-150°C; HRMS: calc.: 314.0422 (MH^+); Found: 314.0414 (MH^+); Anal. Calcd. For $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.48; H, 3.52; N, 13.39. IR (KBr): ν 3450, 3043, 1716, 1208 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.79 (s, 1H), 8.66 (d, 1H, *J* = 4.2 Hz), 8.58 (d, 2H, *J* = 5.3 Hz), 7.79 (t, 3H, *J* = 8.1 Hz), 7.29 (d, 2H, *J* = 5.1 Hz), 5.31(s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 192.8, 166.1, 150.0, 149.0, 148.0, 142.6, 132.0, 124.0, 122.0, 46.0; MS (m/z %): 314.0 (M^++H);

(Z)-5-((5-nitrobenzo[d][1,3]dioxol-4-yl)methylene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7m):

Compound **7m** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 6-nitropiperonal (0.17 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 70% Yield as Brown solid; mp 168-170°C; HRMS: calc.: 402.0213 (MH^+); Found: 402.0214 (MH^+); Anal. Calcd. For $C_{17}H_{11}N_3O_5S_2$: C, 50.87; H, 2.76; N, 10.47. Found: C, 50.83; H, 2.74; N, 10.46. IR (KBr): ν 3450, 3043, 1716, 1208, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ: 8.59 (d, 2H, *J* = 5.7 Hz), 8.11(s, 1H), 7.67 (s, 1H), 7.31 (d, 2H, *J* = 4.7 Hz), 6.97 (s, 1H), 6.21(s, 2H), 5.29(s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 192.3, 166.5, 152.5, 150.2, 149.5, 143.1, 130.3, 125.4, 123.3, 107.5, 106.6, 103.9, 46.5; MS (m/z %): 402.0 (M^++H);

(Z)-5-(Furan-2-ylmethylene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7n):

Compound **7n** was prepared by the reaction of compound 6 (0.20 g, 0.892 mmol), 2-furfuraldehyde (0.74 mL, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5

mL acetic acid, 76% Yield as Yellow solid; mp 168-170°C; HRMS: calc.: 303.0256 (MH^+); Found: 303.0253 (MH^+); Anal. Calcd. For $C_{14}H_{10}N_2O_2S_2$: C, 55.61; H, 3.33; N, 9.26. Found: C, 55.60; H, 3.31; N, 9.23. IR (KBr): ν 3481, 3031, 1700, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 8.56 (d, 2H, *J* = 5.9 Hz), 7.72 (d, 1H, *J* = 1.2 Hz), 7.50 (s, 1H), 7.43 (s, 1H), 7.28 (s, 1H), 6.87(d, 1H, *J* = 3.5 Hz), 6.61-6.59 (m, 1H), 5.29 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.1, 167.3, 150.1, 150.0, 147.4, 143.5, 123.1, 120.3, 119.3, 119.1, 113.6, 46.2; MS(m/z %): 303.0 (M^++H);

(Z)-5-(Naphthalen-1-ylmethylene)-3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (7o):

Compound **7o** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), napthaldehyde (1.2 mL, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 82% Yield as Yellow solid; mp 172-174°C; HRMS: calc.: 363.0620 (MH^+); Found: 363.0609 (MH^+); Anal. Calcd. For $C_{20}H_{14}N_2OS_2$: C, 66.27; H, 3.89; N, 7.73. Found: C, 66.25; H, 3.84; N, 7.71. IR (KBr): ν 3471, 3065, 1707, 1190, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 8.52 (s, 2H), 8.17(d, 1H, *J* = 8.1 Hz), 7.98-7.86 (m, 2H), 7.68 (s, 1H), 7.61-7.32 (m, 4H), 7.34 (d, 2H, *J* = 5.9 Hz), 5.35 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 193.6, 167.1, 150.1, 143.4, 133.7, 131.8, 130.3, 129.1, 127.6, 127.2, 126.9, 124.9, 123.2, 46.3; MS(m/z %): 363.0 (M^++H);

(5Z, 5'Z)-5, 5'-(1, 4-Phenylenebis (methan-1-ylidene)) bis (3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one (9a)

Compound **9a** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), terepthaldehyde (0.12 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 65% Yield as Yellow solid; mp 165-167°C; Anal. Calcd. For $C_{26}H_{18}N_4O_2S_4$: C, 57.12; H, 3.32; N, 10.25. Found: C, 57.10, H, 3.28, N, 10.22. IR (KBr): ν 3489, 3048, 1713, 1660, 1181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + 1 drop of TFA): 8.92 (d, 4H, *J* = 5.3

Hz), 8.01 (d, 4H, *J* = 5.3 Hz), 7.86 (s, 2H), 7.67 (s, 4H), 5.59 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 191.5, 168.5, 156.7, 141.4, 135.3, 134.3, 131.7, 126.7, 124.1, 116.2, 112.4, 46.1; MS(m/z %): 547.0 (M^++H);

(5Z,5'Z)-5,5'-(4,4'-(ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one) (9b)

Compound **9b** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4,4'-(ethane-1,2-diylbis(oxy))dibenzaldehyde (0.24 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 68% Yield as Yellow solid; mp 215-217°C; Anal. Calcd. For $C_{34}H_{26}N_4O_4S_4$: C, 59.80; H, 3.84; N, 8.20. Found: C, 59.78, H, 3.83, N, 8.18; IR (KBr): ν 3418, 2925, 1697, 1188, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + 1 drop of TFA): 8.67 (d, 4H, *J* = 5.7 Hz), 7.88 (d, 4H, *J* = 5.4 Hz), 7.74 (s, 2H), 7.43 (d, 4H, *J* = 8.8 Hz), 6.99 (d, 4H, *J* = 8.7 Hz), 5.48 (s, 4H), 4.35 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$ + TFA) δ: 191.6, 167.3, 160.0, 156.7, 141.0, 135.2, 134.1, 130.8, 129.0, 126.4, 124.0, 118.0, 115.0, 70.0, 46.3; MS(m/z %): 683.0 (M^++H);

(5Z,5'Z)-5,5'-(4,4'-(propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one) (9c)

Compound **9c** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4,4'-(propane-1,3-diylbis(oxy))dibenzaldehyde (0.25g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 70% Yield as Yellow solid; mp 228-230°C; Anal. Calcd. for $C_{35}H_{28}N_4O_4S_4$: C, 60.32; H, 4.05; N, 8.04. Found: C, 60.29, H, 4.05, N, 8.03; IR (KBr): ν 3438, 2920, 1694, 1191 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA): 8.86 (d, 4H, *J* = 5.6 Hz), 8.00 (d, 4H, *J* = 5.1 Hz), 7.85 (s, 2H), 7.53 (d, 4H, *J* = 8.4 Hz), 7.07(d, 4H, *J* = 7.9 Hz), 5.59(s, 4H), 4.29 (m, 4H), 2.36 (s, 2H), ^{13}C NMR (50 MHz, $CDCl_3$+TFA) δ: 191.0, 168.4, 160.4, 156.4, 141.4, 136.0, 130.0, 126.7, 124.6, 119.0, 116.1, 60.0, 46.0, 26.0; MS(m/z %): 697.0 (M^++H);

(5Z,5'Z)-5,5'-(4,4'-(propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one) (9d)

Compound **9d** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4,4'-(butane-1,4-diylbis(oxy))dibenzaldehyde (0.26 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 62% Yield as yellow solid; mp 243-245°C; Anal. Calcd. For $C_{36}H_{30}N_4O_4S_4$: C, 60.82; H, 4.25; N, 7.88. Found: C, 60.80, H, 4.24, N, 7.86; IR (KBr): ν 3488, 2926, 1696, 1183, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA): 8.82 (d, 4H, *J* = 6.4 Hz), 8.02 (d, 4H, *J* = 6.2 Hz), 7.88 (s, 2H), 7.54 (d, 4H, *J* = 8.6 Hz), 7.06 (d, 4H, *J* = 8.6 Hz), 5.62 (s, 4H), 4.19 (m, 4H), 2.07 (m, 4H), ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 192.5, 168.2, 162.1, 160.7, 156.6, 141.5, 136.9, 133.5, 126.6, 117.9, 111.8, 106.1, 46.1, 25.6, 20.3; MS(m/z %): 711.0 (M^++H);

(5Z,5'Z)-5,5'-(4,4'-(pentane-1,5-diylbis(oxy))bis(4,1-phenylene))bis(methan-1-yl-1-ylidene)bis(3-(pyridin-4-ylmethyl)-2-thioxothiazolidin-4-one) (9e)

Compound **9e** was prepared by the reaction of compound **6** (0.20 g, 0.892 mmol), 4,4'-(pentane-1,5-diylbis(oxy))dibenzaldehyde (0.28 g, 0.892 mmol), and ammonium acetate (0.14 g, 1.78 mmol), in 4-5 mL acetic acid, 72% Yield as yellow solid; mp 208-210°C; Anal. Calcd. For $C_{37}H_{32}N_4O_4S_4$: C, 61.30; H, 4.45; N, 7.73. Found: C, 61.26, H, 4.44, N, 7.71; IR (KBr): ν 3476, 3476, 1696, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + TFA): 8.89 (d, 4H, *J* = 5.7 Hz), 7.98 (d, 4H, *J* = 5.6 Hz), 7.82 (s, 2H), 7.51 (d, 4H, *J* = 8.6 Hz), 7.03 (d, 4H, *J* = 8.6 Hz), 5.57 (s, 4H), 4.10 (m, 4H), 1.92 (m, 4H), 1.71 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 192.3, 169.4, 160.4, 156.9, 141.4, 137.6, 133.7, 126.7, 125.0, 122.7, 117.7, 111.4, 105.8, 68.4, 46.1, 22.4; MS(m/z %): 725.0 (M^++H);

2. Bioevaluation methods

***In vitro* antifungal assay**

The *in vitro* antifungal activity of synthesized compound dithiocarbamates (**4a-f**) and rhodanine (**6**), (**7a-o**), (**9a-e**) were evaluated against pathogenic fungi, *Candida albicans* (Ca), *Candida parapsilosis* (Cp, ATCC22019), *Sporothrix schenckii* (Ss), *Trichophyton mentagrophytes (Tm), Aspergillus fumigatus* (Af), *Cryptococcus neoformans* (Cn), *C. albicians* ATCC10231, *C. albicians* ATCC14053, *C. albicians* CDRI, *C. albicians* Patient, *C. albicians* Amphotericin B resistant,[1] *C. albicians* MTCC183, *C. tropicalis* ATCC750 and *C. glabrata* ATCC-MYA 2950, by broth micro-dilution technique as per guidelines of Clinical and laboratory Standard Institute (CLSI)[2] using RPMI 1640 Medium buffered with MOPS [3-(N-morpholino) propanesulphonic acid] in microtitre plates. The starting concentration of compound in first well was 50µg/ml and its 2 fold dilutions as follows 25, 12.5, 6.25, 3.12, 1.56, 0.78, 0.39 and so on. Inoculua of test culture were maintained using by McFarland standard and 1-5×10^3 cells were inoculated in each well. Microtitre plates were incubated for 24-48 h (yeasts) and 72-96 h (mycelial fungi) at 35ºC. After incubation minimal inhibitory concentrations (MIC) were determined by visual observation as well as on a spectrophotometer (Molecular Devices, USA) at 492nm. Clotrimazole and fluconazole were used as reference antifungal agents.[3]

3. *In vitro* Cytotoxicity evaluation assay

The cytotoxicity effect of the lead compounds dithiocarbamates and rhodanine analogues was evaluated against mammalian cells, mouse fibroblast cell line L929. Stock solutions (1 mg/ml) of the test compounds were prepared in DMSO. The cell line L929 was grown in RPMI 1640 medium supplemented with 10% FBS and 1 X antimycotic and antibacterial solution (sigma USA) at 37^{o}C in humidified atmosphere having 5% CO_2. One hundred ml (1X10^3 cells in RPMI 1640) of the confluent fibroblast stock suspension (1 X 10^5cells/ml) was dispensed in 96-well tissue culture plate. The original medium from the wells was replaced with 100 ml serum free RPMI 1640 when the cells reached 90% confluency after 5 h

incubation in a CO_2 incubator. Various concentrations of the test compounds (25, 12.5, 6.25, 3.12, 1.56, 0.78, 0.39 μg/ml) were added to the growing cells and incubated for 24 h. Response of L929 cells to the test compounds was determined spectrophotometrically at 570 and 630 nm. The difference between absorbance at 570 and 630 nm was used as an index of the cell viability.

$$\frac{(A570 - A630)\ sample}{(A570 - A630)\ control} \times 100$$

The morphology of the cells was observed under Phase contrast microscope as follows. After fixation of the cells in the wells of 96-well tissue culture plate, Giemsa stain was added to each well and incubated for 30 min at 37^{o}C. The culture plates were washed thoroughly with PBS, air dried and observed under a phase contrast microscope.

4. Molecular Docking

Materials and methods

Homology model was developed for Candida albicans Cyp51,[5] using crystal structure of Human cyp51 (3ld6) with the help of Modeller 9v9.[6] 3D structure of compounds were generated and minimized by Powell gradient method implemented in Sybyl7.1.[7] Autodock3[8] was used to get optimal docking solution of selected compounds. Grid box was centered on Heme group and Lamarckian genetic algorithm was used for calculation of 50 docking pose after 250000 evaluations. Docking protocol was validated by docking the Fluconazole (Extracted from Crystal structure of *Trypansoma cruzi* Cyp51; 3khm[9]) to modeled *Candida albicans* cyp51. For molecular visualization UCSF Chimera1.6[10] was used.

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