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Design, Synthesis and Characterization of Pyrimidine based Thiazolidinedione Derivatives

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Novel thiazolidine-2,4-dione (TZD) based pyrimidine derivatives have been synthesized by Knoevenagel condensation reaction between thiazolidine-2,4-dione and amino pyrimidinyl aliphatic aldehydes followed by heterogeneous metal reduction. Synthetic strategy involved nucleophillic substitution of hydroxyl protected six membered aliphatic chain on 4,6-dichloropyrimidine followed by Suzuki coupling. This approach is regioselective, efficient and versatile for synthesis of such analogs.

Keywords: Thiazolidine-2,4-dione, Suzuki coupling, Knoevenagel condensation.

INTRODUCTION

Design and synthesis of molecules possessing value as human therapeutic agents is one of the main objectives of drug discovery. Compounds containing heterocyclic ring systems have being receiving great attention as they belong to a class of compounds with proven beneficial in medicinal chemistry [1]. Thiazolidine-2,4-dione (TZD) is a derivative from thiazolidine which belongs to an important heterocyclic group. Thiazolidinedione possesses different types of biological activities like anticonvulsant activity, hypnotic activity, antitubercular activity, antibacterial activity antimicrobial, antidiabetic, anticancer and anti-inflammatory, *etc*. [2-5]. Antidiabetic activity of this moiety is very well established and numbers of drugs are available in market based on this moiety (Fig. 1). In 1980's, antihyper glycaemia activity of thiazolidine-2,4-diones were studied extensively. Ciglitazone was the first active compound of this class, whereas other derivatives *viz*. pioglitazone, troglitazone, englitazone and rosiglitazone (Fig. 1) were reported soon after this. Various derivatives of thiazolidinedione have been reported for their diverse biological activities apart from synthetic interests [6-8]. Biological/therapeutically activities such as hypoglycaemic, cardiovascular, antibacterial, anti-inflammatory, antilipidimic and various other activities have been reported [9]. Thiazolidine-2,4-dione derivatives have been studied extensively and found to have diverse chemical reactivities along with broad spectrum of biological activities [10-14]. Literature provides ample indications that varying the substitutions on the thiazolidine ring results in modulation of the biological activities [15].

2,4-Thiazolidinedione derivatives with aliphatic chain up to five carbon chain was reported as insulin sensitizers with antidiabetic activities [16]. Keeping in mind further scope for thiazolidinedione, a series of pyrimidine based thiazolidinedione with C-linked aromatic substituents and amine substituted six membered aliphatic chain with terminal thiazolidine-2,4-dione group were designed. Suzuki partners for C-C bond formation are chosen based on their potential to influence the SAR.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz instruments, respectively and spectral data were reported in ppm relative to tetramethylsilane (TMS) as the internal standard. UPLC-LCMS were recorded in UPLC coupled with Single quadruple mass spectrometer using electrospray ionization (ESI).

Step-1: Synthesis of compound 3: To a solution of 6-aminohexanol **(1)** (1 eq.) in DCM (500 mL) was added DMAP (0.1 eq.) at ambient temperature and reaction mixture was cooled to 0 °C. Triethyl amine (1.5 eq.) and *tert*-butyldimethyl-

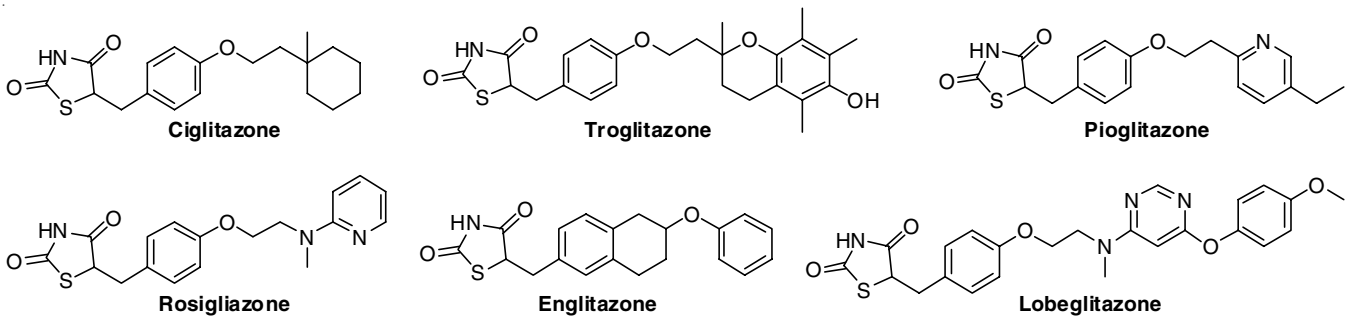


Fig. 1. Structures of some commercial drugs containing 1,3-thiazolidine-2,4-dione moiety

silyl chloride (1.2 eq) were added sequentially. Reaction mixture was allowed to come to ambient temperature and stirred at same temperature for 18 h. TLC (10 % methanol in DCM, stain visualization-ninhydrin) showed that starting material was consumed. After completion, reaction mixture was concentrated under vacuum and suspension was filtered off. Filterate was concentrated under reduced pressure to afford 6-((*tert*-butyldimethylsilyl)oxy)hexan-1-amine **(3)**. Yield: 99.3 %; colourless oil which was used as such for further reactions LC-MS (ESI) *m/z* calculated for $C_{16}H_{30}N_{30}SiCl$ $(M + H)^+$: 231.20. ^1H NMR (400 MHz, chloroform-d_1): δ 5.80-5.60 (s, b, 2H), 3.60 (s, 2H), 2.83-2.88 (m, 2H), 1.66 (m, 2H), 1.28-1.54 (m, 6H), 0.83 (br, s, 9H), 0.00 (s, 6 H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 63.0, 41.5, 32.7, 32.5, 25.9, 25.9, 25.5, 18.2, 18.2, 18.2, 5.4, 5.4; Anal. calcd. (%) for $C_{12}H_{29}NOSi$: C, 62.27; H, 12.63; N, 6.05; found (%): C, 62.39; H, 12.56; N, 6.07.

Step-2: Synthesis of compound 5: To a solution of 6-((*tert*-butyldimethylsilyl)oxy)hexan-1-amine (**3**) (1 eq.) was charged in ethanol (50 mL). Reaction mixture was cooled to 0 °C. DIPEA (1 eq.) was added drop-wise into it. 2,4-Dichloropyrimidine (**4**) (1 eq.) was added portion wise at same temperature. Reaction mixture was allowed to room temperature and stirred at ambient temperature for 18 h. TLC (40 % ethyl acetate:hexane, stain visualization–UV active) showed that starting material was consumed. After completion, reaction mixture was concentrated under reduced pressure and ice water (100 mL) was added in to this. Organic phase was extracted with ethyl acetate (2 × 250 mL). Combined organic layers were washed with water (2 × 50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude product. Crude product was purified by Combi-Flash {(Teledyne Isco) using Hi-Purit flash column silica (NP) 80 g, 60 Å, max pressure: 350 psi (24 bar)-using 0-70 % ethyl acetate: hexane to afford N-(6-((*tert*-butyldimethylsilyl)oxy)hexyl)-6-chloropyrimidin-4-amine (**5**). Yield: 70.3 %; transparent liquid which solidifies on freezing; LC-MS (ESI) *m/z* calculated for $C_{16}H_{30}N_3OSiCl$ $(M + H)^+$: 344.18; found (%): 344.30, ^1H NMR (400 MHz, chloroform-d_1): δ 8.32 (s, 1H), 6.32 (s, 1H), 5.16 (br, s, 1H), 3.60 (t, J = 6.36 Hz, 2H), 3.28 (br, m, 2H), 1.32-1.70 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6 H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.1, 163.9, 154.1, 104.1, 64.2, 51.5, 34.1, 32.2, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{16}H_{30}N_{30}SiCl$: C, 55.87; H, 8.79; Cl, 10.31; N, 12.22; found (%): C, 55.80; H, 8.79; Cl, 10.36; N, 12.24.

Step-3: Synthesis of compounds (6a-i): In a sealed tube, a mixture of N-(6-((*tert*-butyldimethylsilyl)oxy)hexyl)-6-chloropyrimidin-4-amine (**5**) (1 eq.), boronic acid/ester (1.5 eq.) and Cs_2CO_3 (3 eq.) were charged in dioxane:water (3:1) (20 vol.) and nitrogen was purged for 10 min. [1,1'-*Bis*(diphenyl phosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.15 eq.) was added and nitrogen was again purged for 5 min. Reaction mixture was allowed to stir at 100 °C for 3 h. TLC (40 % ethyl acetate/hexane, stain visualization-UV active) showed that starting material was consumed. The reaction mixture was allowed to come at ambient temperature and concentrated under reduced pressure. Water was added into reaction mixture and organic phase was extracted in DCM (2 times). Combined organic layers were washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude product. Crude product was purified by Combi-Flash {(Teledyne Isco) using Hi-Purit flash column silica (NP), 60 Å, max pressure: 350 psi (24 bar)} using 0-30 % ethyl acetate:hexane) to afford the desired compound.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-6-phenylpyrimidin-4-amine (6a): Yield: 87.0 %; transparent oil which solidifies on freezing; LC-MS (ESI) *m/z* calculated for $C_{22}H_{35}N_3OSi$ $(M + H)^+$: 386.25; found (%): 386.90; ^1H NMR (400 MHz, chloroform-d_1): δ 8.64 (s, 1H), 7.97 (m, 2H), 7.46 (m, 3H), 6.68 (s, 1H), 4.97 (br, s, 1H), 3.60 (m, 2H), 3.35 (br, m, 2H), 1.31-1.73 (m, 8H), 0.89 (s, 9H), 0.05 (s, 6 H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.2, 163.8, 154.2, 134.2, 129.1, 129.1, 128.2, 128.2, 126.1, 104.1, 64.1, 51.6, 34.1, 32.2, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{22}H_{35}N_3OSi$: C, 68.52; H, 9.15; N, 10.90; found (%): C, 68.50; H, 9.17; N, 10.92.

***tert*-Butyl 4-(6-(((6-((*tert*-butyldimethylsilyl)oxy)hexyl)-amino)pyrimidin-4-yl)benzoate (6b):** Yield: 68.6 %; transparent oil which solidifies on freezing; LC-MS (ESI) *m/z* calculated for $C_{27}H_{43}N_3O_3Si$ $(M + H)^+$: 486.31; found (%): 486.40; ^1H NMR (400 MHz, chloroform-d_1): δ 8.65 (s, 1H), 7.91-8.13 (m, 4H), 6.71 (s, 1H), 5.01 (br, s, 1H), 3.60 (m, 2H), 3.38 (m, 2H), 1.33-1.73 (m, 26H), 0.05 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.2, 163.8, 161.9, 157.9, 157.9, 156.1, 150.2, 150.2, 134.3, 128.2, 104.1, 64.1, 62.1, 51.6, 34.1, 32.2, 28.3, 28.3, 28.3, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{27}H_{43}N_3O_3Si$: C, 66.76; H, 8.92; N, 8.65; found (%): C, 66.70; H, 8.96; N, 8.62.

6-(2-(*tert*-Butyl)pyridin-4-yl)-N-(6-((*tert*-butyldimethylsilyl)oxy)hexyl)pyrimidin-4-amine (6c): Yield: 67.1 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{25}H_{42}N_4OSi$ $(M + H)^+$: 443.31; found (%): 443.40; ^1H NMR (400 MHz, chloroform-d_1): δ 8.67 (m, 2H), 7.91 (s, 1H), 7.56 (dd, J = 1.53, 5.04 Hz,

1H), 6.70 (s, 1H), 5.05 (br, s, 1H), 3.61 (t, *J* = 6.36 Hz, 2H), 3.39 (br, m, 2H), 1.33-1.73 (m, 17H), 0.89 (s, 9H), 0.04 (s, 6 H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.4, 162.3, 159.1, 157.7, 149.2, 145.1, 117.4, 115.6, 102.0, 64.2, 51.5, 37.4, 34.1, 32.2, 29.9, 29.9, 29.9, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{25}H_{42}N_4OSi$: C, 67.82; H, 9.56; N, 12.66; found (%): C, 67.80; H, 9.58; N, 12.65.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-6-(*o*-tolyl)-pyrimidin-4-amine (6d): Yield: 62.0 %; transparent oil; LC-MS (ESI) *m/z* calculated for $C_{23}H_{37}N_3OSi$ (M + H)$^+$: 400.27; found (%): 400.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.61 (s, 1H), 7.33 (m, 4H), 6.37 (s, 1H), 4.97 (br, s, 1H), 3.61 (t, *J* = 6.36 Hz, 2H), 3.32 (br, m, 2H), 2.38 (m, 3H), 1.28-1.73 (m, 8H), 0.89 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.8, 158.3, 158.2, 135.9, 133.1, 129.9, 129.5, 128.7, 126.5, 102.1, 64.2, 51.6, 34.1, 32.2, 25.9, 25.9, 24.1, 20.0, 18.6, 18.6, 18.6, 5.4, 5.4; Anal. calcd. (%) for $C_{23}H_{37}N_3OSi$: C, 69.12; H, 9.33; N, 10.51; found (%): C, 69.15; H, 9.34; N, 10.53.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-6-(quinolin-4-yl)pyrimidin-4-amine (6e): Yield: 78.1 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{25}H_{36}N_4OSi$ (M + H)$^+$: 437.27; found (%): 437.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.00 (d, *J* = 4.38 Hz, 1H), 8.73 (s, 1H), 8.17 (m, 2H), 7.70-7.84 (t, 1H), 7.57 (t, *J* = 7.45 Hz, 1H), 7.49 (d, 1H), 6.58 (s, 1H), 5.12 (br, s, 1H), 3.61 (t, *J* = 6.36 Hz, 2H), 3.36 (br, s, 2H), 1.32-1.76 (m, 8H), 0.88 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.5, 160.4, 158.2, 150.9, 147.9, 144.3, 129.5, 129.3, 127.4, 127.1, 126.1, 121.2, 104.1, 64.2, 51.5, 34.1, 32.2, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{25}H_{36}N_4OSi$: C, 68.76; H, 8.31; N, 12.83; found (%): C, 68.74; H, 8.31; N, 12.84.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-6-(3-methoxyphenyl)pyrimidin-4-amine (6f): Yield: 73.8 %; transparent oil which solidifies on freezing; LC-MS (ESI) *m/z* calculated for $C_{23}H_{37}N_3O_2Si$ (M + H)$^+$: 416.27; found (%): 416.70 and 417.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.47 (s, 1H), 7.54 (br, s, 2H), 7.40 (t, *J* = 7.89 Hz, 2H), 7.03 (m, 1H), 6.90 (s, 1H), 3.82 (s, 3H), 3.55 (m, 2H), 3.32 (br, m, 2H) 1.28-1.61 (m, 8H), 0.85 (s, 9H) 0.00 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.4, 159.9, 159.7, 157.9, 138.5, 129.6, 118.4, 115.5, 111.1, 100.1, 64.2, 56.0, 51.4, 34.1, 32.2, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{23}H_{37}N_3O_2Si$: C, 66.46; H, 8.97; N, 10.11; found (%): C, 66.42; H, 8.95; N, 10.10.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-[4,5'-bipyrimidin]-6-amine (6g): Yield: 84.1 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{20}H_{33}N_5OSi$ (M + H)$^+$: 387.25; found (%): 388.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.29 (s, 3H), 8.66 (s, 1H), 6.69 (s, 1H), 5.07 (br, s, 1H), 3.60 (m, 2H), 3.40 (br, s, 2H), 1.30-1.76 (m, 8H), 0.89 (s, 9H), 0.00 (s, 6H); Anal. calcd. (%) for $C_{20}H_{33}N_5OSi$: C, 61.98; H, 8.58; N, 18.07; found (%): C, 61.99; H, 8.60; N, 18.05.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-6-(2-methylpyridin-4-yl)pyrimidin-4-amine (6h): Yield: 86.2 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{22}H_{36}N_4OSi$ (M + H)$^+$: 401.27; found (%): 401.7 and 402.4; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.64 (d, *J* = 14.91 Hz, 1H), 8.61 (s, 1H), 7.74 (s, 1H), 7.60 (d, *J* = 5.26 Hz, 1H), 6.71 (d, *J* = 0.88 Hz, 1H), 5.03-5.16 (br, s, 1H), 3.61 (t, *J* = 6.36 Hz, 2H), 3.40 (br, m, 2H), 2.65 (s, 3H), 1.35-1.71 (m, 8H), 0.89 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.5, 162.4, 159.2, 157.6, 149.3, 145.2, 117.5, 115.7, 102.1, 64.2, 51.5, 34.1, 32.3, 28.1, 25.9, 25.9, 24.1, 18.5, 18.5, 18.5, 5.4, 5.4; Anal. calcd. (%) for $C_{22}H_{36}N_4OSi$: C, 65.95; H, 9.06; N, 13.98; found (%): C, 65.98; H, 9.076; N, 13.95.

N-(6-((*tert*-Butyldimethylsilyl)oxy)hexyl)-6-(2,6-dimethylphenylpyrimidin-4-amine (6i): Yield: 62.0 %; transparent oil; LC-MS (ESI) *m/z* calculated for $C_{24}H_{39}N_3OSi$ (M + H)$^+$: 414.29; found (%): 414.80 and 415.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.63 (s, 1H), 7.17 (m, 1H), 7.08 (d, *J* = 7.45 Hz, 2H), 6.24 (s, 1H), 4.91-5.10 (br, s, 1H), 3.60 (t, *J* = 6.58 Hz, 2H), 3.30 (br, s, 2H), 2.12 (s, 6H), 1.25-1.70 (m, 8H), 0.89 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.8, 158.3, 136.3, 136.3, 133.5, 129.8, 129.8, 128.9, 104.2, 64.2, 51. 5, 34.1, 34.1, 32.1, 25.8, 25.8, 24.1, 20.1, 20.1, 18.5, 18.5, 18.5, 5.3, 5.3; Anal. calcd. (%) for $C_{24}H_{39}N_3OSi$: C, 69.68; H, 9.50; N, 10.16; found (%): C, 69.69; H, 9.51; N, 10.15.

Step-4: Synthesis of compounds (7a-i): In a round bottom flask, Suzuki product (**6a-i**) (1 eq.) was charged in THF (10 vol.). Solution was cooled to 0 °C and 1 M TBAF in THF (3 eq.) was added in to this drop-wise with constant stirring. Reaction mixture was allowed to come to ambient temperature and stirred at same temperature for 16 h. TLC (40 % ethyl acetate/hexane, stain visualization-UV active) showed that starting material was consumed. Reaction mixture was concentrated under reduced pressure and water was added into reaction mixture. Organic phase was extracted in DCM (2 times). Combined organic layers were washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford desired compound **(7a-i)** which was used as such for further reaction.

6-((6-Phenylpyrimidin-4-yl)amino)hexan-1-ol (7a): Yield: 100 %; transparent oil; LC-MS (ESI) *m/z* calculated for $C_{16}H_{21}N_3O$ (M + H)$^+$: 272.17; found (%): 272.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.66 (s, 1H), 7.97 (m, 2H), 7.46 (m, 3H), 6.70 (s, 1H), 5.15 (br, s, 1H), 3.66 (t, *J* = 6.58 Hz, 2H), 3.33 (t, 2H), 1.33-1.86 (m, 8H).

***tert*-Butyl 4-(6-((6-hydroxyhexyl)amino)pyrimidin-4-yl)benzoate (7b):** Yield: 63.8 %; brown oil; LC-MS(ESI): *m/z* calculated for $C_{16}H_{21}N_3O$ (M + H)$^+$: 372.22; found (%): 372.30.

6-((6-(2-(*tert*-Butyl)pyridin-4-yl)pyrimidin-4-yl)-amino)hexan-1-ol (7c): Yield: 69.2 %; light yellow oil; LC-MS (ESI) *m/z* calculated for $C_{19}H_{28}N_4O$ (M + H)$^+$: 329.23; found (%): 329.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.67 (m, 2H), 7.91 (s, 1H), 7.56 (dd, *J* = 1.32, 5.26 Hz, 1H), 6.71 (s, 1H), 5.06 (br, s, 1H), 3.67 (t, *J* = 6.36 Hz, 2H), 3.20-3.48 (m, 2H), 1.17-1.77 (m, 17H).

6-((6-(*o*-Tolyl)pyrimidin-4-yl)amino)hexan-1-ol (7d): Yield: 77.8 %; transparent oil; LC-MS (ESI) *m/z* calculated for $C_{17}H_{23}N_3O$ (M + H)$^+$: 286.18; found (%): 286.30.; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.62 (s, 1H), 7.20-7.45 (m, 4H), 6.38 (s, 1H), 5.03 (br, s, 1H), 3.65 (t, *J* = 6.36 Hz, 2H), 3.34 (br, s, 2H), 2.40 (s, 3H), 1.23-1.77 (m, 8H).

6-((6-(Quinolin-4-yl)pyrimidin-4-yl)amino)hexan-1-ol (7e): Yield: 73.7 %; transparent oil; LC-MS (ESI) *m/z* calcu-

lated for $C_{19}H_{22}N_4O$ (M + H)$^+$: 323.18; found (%): 323.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.99 (d, *J* = 3.95 Hz, 1H), 8.59 (br, s, 1H), 8.20 (d, *J* = 8.33 Hz, 1H), 8.10 (m, 1H), 7.81 (t, *J* = 7.45 Hz, 1H), 7.54-7.68 (m, 2H), 6.75 (s, 1H), 5.45 (br, s, 1H), 3.38 (br, m, 4H), 1.16-1.64 (m, 8H).

6-((6-(3-Methoxyphenyl)pyrimidin-4-yl)amino)hexan-1-ol (7f): Yield: 99%; Brown oil; LC-MS (ESI) *m/z* calculated for $C_{17}H_{23}N_3O_2$ (M + H)$^+$: 302.3; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.62 (s, 1H), 7.45-7.61 (m, 2H), 7.37 (t, *J* = 7.89 Hz, 1H), 7.00 (dd, *J* = 1.75, 7.89 Hz, 1H), 6.67 (s, 1H), 5.09 (br, s, 1H), 3.89 (s, 3H), 3.66 (t, *J* = 6.58 Hz, 2H), 3.37 (m, 2H), 1.49-1.44 (m, 8H).

6-([4,5'-Bipyrimidin]-6-ylamino)hexan-1-ol (7g): Yield: 99%; Yellow oil; LC-MS (ESI) *m/z* calculated for $C_{14}H_{19}N_5O$ (M + H)$^+$: 274.16; found (%): 274.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.30 (s, 3H), 8.64 (s, 1H), 6.70 (s, 1H), 3.67 (t, *J* = 6.36 Hz, 2H), 3.40 (br, m, 2H), 1.32-1.83 (m, 8H).

6-((6-(2-Methylpyridin-4-yl)pyrimidin-4-yl)amino)-hexan-1-ol (7h): Yield: 99%; Yellow oil; LC-MS (ESI) *m/z* calculated for $C_{16}H_{22}N_4O$ (M + H)$^+$: 287.18; found (%): 287.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.53-8.69 (m, 2H), 7.74 (s, 1H), 7.60 (d, *J* = 4.82 Hz, 1H), 6.73 (s, 1H), 5.19 (br, s, 1H), 3.66 (t, *J* = 6.36 Hz, 2H), 3.40 (br, s, 2H), 2.64 (s, 3H), 1.33-1.76 (m, 8H).

6-((6-(2,6-Dimethylphenyl)pyrimidin-4-yl)amino)-hexan-1-ol (7i): Yield: 99%; brown oil; LC-MS (ESI) *m/z* calculated for $C_{18}H_{25}N_3O$ (M + H)$^+$: 300.20; found (%): 300.40.

Step-5: Synthesis of compounds (8a-d,8f): To a solution of alchol (**7a-d,f**) (1 eq.) in DCM (50 vol.), added triethylamine (7 eq.). Resultant mixture was stirred at 0 °C for 15 min. DMSO (7 eq.) and sulfur trioxide-pyridine complex (5 eq.) were added in to the suspension at same temperature. Resultant mixture was allowed to stir at room temperature for 3 h. TLC (40 % ethyl acetate/hexane, stain visualization-UV active) showed that starting material was consumed. Water was added in to this and organic phase was extracted. Aqueous layer was extracted with DCM (2 times). Combined organic layers were washed with water (3 times), dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. Crude product was purified by Combi-Flash {(Teledyne Isco) using Hi-Purit flash column silica (NP) 40 g, 60 Å, max pressure: 350 psi (24 bar)} using 0-40 % ethyl acetate:hexane) to afford desired aldehyde **(8a-d,8f)**.

6-((6-Phenylpyrimidin-4-yl)amino)hexanal (8a): Yield: 36.4 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{16}H_{19}N_3O$ (M + H)$^+$: 270.15; found (%): 270.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.79 (s, 1H), 8.64 (s, 1H), 7.96 (m, 2H), 7.44 (m, 3H), 6.69 (s, 1H), 4.93 (br, s, 1H), 3.40 (br, s, 2H), 2.48 (s, 2H), 1.20-1.73 (m, 6 H).

***tert*-Butyl-4-(6-((6-oxohexyl)amino)pyrimidin-4-yl)-benzoate (8b):** Yield: 11.2 %; yellow solid; LC-MS (ESI) *m/z* calculated for $C_{21}H_{27}N_3O_3$ (M + H)$^+$: 370.21; found (%): 370.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.79 (s, 1H), 8.66 (s, 1H), 7.96-8.12 (m, 4H), 6.72 (s, 1H), 5.04 (br, s, 1H), 3.42 (m, 2H), 2.47 (m, 2H), 1.38-1.79 (m, 15H).

6-((6-(2-(*tert*-Butyl)pyridin-4-yl)pyrimidin-4-yl)amino)-hexanal (8c): Yield: 90.5 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{19}H_{26}N_4O$ (M + H)$^+$: 327.21; found (%): 327.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.79 (s, 1H), 8.68 (m, 2H), 7.91 (s, 1H), 7.56 (dd, *J* = 1.53, 5.04 Hz, 2H), 6.71 (s, 1H), 5.04 (br, s, 1H), 3.43 (br, m, 2H), 2.43-2.55 (m, 2H), 1.29-1.82 (m, 15 H).

6-((6-(*o*-Tolyl)pyrimidin-4-yl)amino)hexanal (8d): Yield: 50.0 %; transparent oil which solidifies on freezing; LC-MS (ESI) *m/z* calculated for $C_{17}H_{21}N_3O$ (M + H)$^+$: 284.17; found (%): 284.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.78 (d, *J* = 1.32 Hz, 1H), 8.62 (s, 1H), 7.33-7.27 (m, 4H), 6.38 (s, 1H), 4.91-5.17 (br, s, 1H), 3.33 (br, m, 2H), 2.48 (m, 2H), 2.40 (s, 3H), 1.23-1.77 (m, 8H).

6-((6-(3-Methoxyphenyl)pyrimidin-4-yl)amino)hexanal (8f): Yield 22.8 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{17}H_{21}N_3O_2$ (M + H)$^+$: 300.16; found (%): 300.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.78 (s, 1H), 8.63 (s, 1H), 7.43-7.60 (m, 3H), 7.37 (t, 1H), 7.01 (dd, *J* = 1.97, 8.11 Hz, 1H), 6.63 (s, 1H), 5.02 (br, s, 2H), 3.39 (br, m, 2H), 2.48 (t, *J* = 7.02 Hz, 2H), 1.58-1.80 (m, 4H), 1.36-1.51 (m, 2H), 1.20-1.32 (m, 2H).

Step-6: Synthesis of compounds (8e,8g-i): To an alcoholic solution of (**7e,g-i**) (1 eq.) in DCM (50 vol) and the resulting solution was cooled to 0 °C. Dess martin (3 eq.) was added into this and resultant mixture was stirred for 0.5 h at 0 °C. Resultant mixture was allowed to stir at room temperature for 3 h. TLC (60 % ethyl acetate/hexane, stain visualization-UV active) showed that starting material was consumed. Water was added in to this and organic phase was extracted. Aqueous layer was extracted with DCM (2 times). Combined organic layers were washed with water (3 times), dried over anhydrous sodium sulphate and evaporated under reduced pressure to get crude product. Crude product was purified by Combi-Flash {(Teledyne Isco) using Hi-Purit flash column silica (NP) 40 g, 60 Å, max pressure: 350 psi (24 bar)} using 0-70 % ethyl acetate:hexane) to afford the desired aldehyde **(8e,8g-i)**.

6-((6-(Quinolin-4-yl)pyrimidin-4-yl)amino)hexanal (8e): Yield: 27.9 %; yellow solid; LC-MS (ESI) *m/z* calculated for $C_{19}H_{20}N_4O$ (M + H)$^+$: 321.16; found (%): 321.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.79 (s, 1H), 8.99 (d, 1H), 8.74 (s, 1H), 8.17 (t, *J* = 7.24 Hz, 2H), 7.74-7.80 (m, 1H), 7.57 (t, *J* = 8.11 Hz, 1H), 7.48 (d, 1H), 6.59 (s, 1H), 5.17 (br, s, 1H) 3.40 (br, m, 2H), 2.49 (t, *J* = 6.58 Hz, 2H), 1.41-1.74 (m, 6H).

6-([4,5'-Bipyrimidin]-6-ylamino)hexanal (8g): Yield: 11.3 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{14}H_{17}N_5O$ (M + H)$^+$: 272.14; found (%): 272.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.79 (s, 1H), 9.29 (s, 3H), 8.67 (s, 1H), 6.70 (s, 1H), 5.14 (br, s, 1H), 3.36-3.52 (br, m, 2H), 2.46-2.56 (m, 2H), 1.39-1.74 (m, 8H).

6-((6-(2-Methylpyridin-4-yl)pyrimidin-4-yl)amino)-hexanal (8h): Yield: 25.2 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{16}H_{20}N_4O$ (M + H)$^+$: 285.16; found (%): 285.30 ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 8.41-8.62 (m, 3H), 7.56 (m, 1H), 7.00 (m, 1H), 3.32 (br, m, 2H), 2.36-2.49 (m, 2H), 1.16-1.61 (m, 8H).

6-((6-(2,6-Dimethylphenyl)pyrimidin-4-yl)amino)-hexanal (8i): Yield: 59.5 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{18}H_{23}N_3O$ (M + H)$^+$ 298.18; found (%): 298.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.78 (d, *J* = 1.32 Hz, 1H), 8.64 (s, 1H), 6.94-7.23 (m, 4H), 6.25 (s, 1H), 5.04-5.27

(br, s, 1H), 3.33 (br, m, 2H), 2.47 (m, 2H), 2.18 (m, 6H), 1.61-1.70 (m, 4H), 1.35-1.51 (m, 2H), 1.16-1.32 (m, 2H).

Step-6: A mixture of aldehyde (**8a-i**) (1 eq.), 2,4-thiazolidinedione (1.5 eq.), piperidine (0.15 eq.) were charged in acetic acid for 2 h. TLC (60 % ethyl acetate/hexane, stain visualization-UV active) and LCMS showed that starting material was consumed. After completion, reaction mixture was concentrated under reduced pressure. Residue was diluted with DCM and washed with saturated aqueous sodium bicarbonate (2 times) and water (1 time). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get the crude product. Crude product was purified by Combi-Flash {(Teledyne Isco) using Hi-Purit flash column silica (NP) 12 g, 60 Å, max pressure: 350 psi (24 bar)} using 0-70 % ethyl acetate:hexane) to afford desired product **(9a-i)**.

5-(6-((6-Phenylpyrimidin-4-yl)amino)hexylidene)-thiazolidine-2,4-dione (9a): Yield: 50.6 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{19}H_{20}N_4O_2S$ $(M + H)^+$: 369.13; found (%): 369.30; ^{1}H NMR (400 MHz, chloroform-d_1), 3.40 (br, s, 2H), 2.19-2.31 (m, 2H), 2.10 (br, s, 2H), 1.32-1.76 (m, 6 H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (br, s, 1H), 8.47 (m, 2H), 7.98 (m, 2H), 7.47 (m, 3H), 6.84-6.88 (m, 2H), 2.13-2.25 (m, 2H), 1.29-1.63 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.9, 169.8, 163.8, 158.3, 158.2, 147.9, 133.1, 131.6, 129.9, 129.5, 128.7, 126.5, 126.4, 98.1, 42.5, 32.1, 28.7, 26.7, 26.6; Anal. calcd. (%) for $C_{19}H_{20}N_4O_2S$: C, 61.94; H, 5.47; N, 15.21; found (%): C, 61.87; H, 5.45; N, 15.24.

4-(6-((6-(2,4-Dioxothiazolidin-5-ylidene)hexyl)amino)-pyrimidin-4-yl)benzoate (9b): Yield: 39.4 %; white solid; LC-MS(ESI) *m/z* calculated for $C_{24}H_{28}N_4O_4S$ $(M + H)^+$: 469.18; found (%): 469.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.65 (s, 1H), 7.94-8.12 (m, 4H), 7.03 (m, 1H), 6.70 (s, 1H), 3.38 (m, 2H), 1.99-2.15 (m, 2H), 1.33-1.82 (m, 15H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.0, 169.7, 162.9, 160.0, 158.9, 158.8, 158.7, 155.4, 155.3, 145.1, 133.5, 130.2, 128.1, 101.6, 55.4, 51.5, 32.1, 28.7,28.7, 28.7, 28.6, 26.7, 26.6, 26.0; Anal. calcd. (%) for $C_{24}H_{28}N_4O_4S$: C, 61.52; H, 6.02; N, 11.96; found (%): C, 61.56; H, 6.01; N, 11.98.

5-(6-((6-(2-(*tert*-Butyl)pyridin-4-yl)pyrimidin-4-yl)-amino)hexylidene)thiazolidine-2,4-dione (9c): Yield: 28.5 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{22}H_{27}N_5O_2S$ $(M + H)^+$: 426.19; found (%): 426.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.68 (m, 2H), 7.92 (s, 1H), 7.57 (d, J = 5.26 Hz, 1H), 7.03 (t, J = 7.89 Hz, 1H), 6.71 (s, 1H), 5.22 (br, s, 1H), 3.43 (br, m, 2H), 2.26 (q, J = 7.31 Hz, 2H), 1.38-1.74 (m, 15H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.2, 170.9, 169.4, 162.5, 159.1, 157.7, 149.1, 146.4, 145.0, 130.0, 117.4, 115.5, 101.8, 40.2, 38.0, 32.2, 30.4, 30.4, 30.4, 28.3, 26.5, 26.4; Anal. calcd. (%) for $C_{22}H_{27}N_5O_2S$: C, 62.09; H, 6.40; N, 16.46; found (%): C, 62.12; H, 6.41; N, 16.42.

5-(6-((6-(*o*-Tolyl)pyrimidin-4-yl)amino)hexylidene)-thiazolidine-2,4-dione (9d): Yield: 22.2 %; light orange solid; LC-MS (ESI) *m/z* calculated for $C_{20}H_{22}N_4O_2S$ $(M + H)^+$: 383.15; found (%): 384.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.61 (s, 1H), 7.24-7.46 (m, 4H), 7.02 (t, J = 7.67 Hz, 1H), 6.38 (s, 1H), 4.02 (s, 2H), 3.35 (br, s, 2H), 2.39 (s, 3H), 1.30-1.86 (m, 8H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.2, 170.9, 169.4, 155.9, 145.0, 135.9, 133.1, 130.0, 129.9, 129.5, 128.7, 126.5, 104.2, 40.2, 38.0, 32.2, 28.3, 26.4, 26.4, 22.1; Anal. calcd. (%) for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.80; N, 14.65; found (%): C, 62.79; H, 5.81; N, 14.63.

5-(6-((6-(Quinolin-4-yl)pyrimidin-4-yl)amino)hexylidene)thiazolidine-2,4-dione (9e): Yield: 24.8 %; light yellow solid; LC-MS (ESI) *m/z* calculated for $C_{22}H_{21}N_5O_2S$ $(M + H)^+$: 420.14; found (%): 420.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 12.37 (br, s, 1H), 8.99 (d, J = 4.38 Hz, 1H), 8.59 (br, s, 1H), 8.19 (d, J = 8.77 Hz, 1H), 8.10 (d, J = 8.33 Hz, 1H), 7.81 (t, J = 7.02 Hz, 1H), 7.55-7.70 (m, 3H), 6.91 (m, 1H), 6.74 (s, 1H), 3.38 (br, m, 2H), 2.20 (d, J = 7.45 Hz, 2H), 1.57-1.38 (br, m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.2, 167.9, 161.9, 159.8, 157.7, 149.8, 147.6, 146.6, 143.9, 129.2, 128.9, 127.8, 127.3, 124.8, 120.2,116.2, 106.3, 40.2, 32.5, 29.4,26.7, 26.6; Anal. calcd. (%) for $C_{22}H_{21}N_5O_2S$: C, 62.99; H, 5.05; N; found (%): C, 62.95; H, 5.07; N, 16.70.

5-(6-((6-(3-Methoxyphenyl)pyrimidin-4-yl)amino)-hexylidene)thiazolidine-2,4-dione (9f): Yield: 60.2 %; off white solid; LC-MS (ESI) *m/z* calculated for $C_{20}H_{22}N_4O_3S$ $(M + H)^+$: 399.15; found (%): 399.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.64 (s, 1H), 7.49-7.59 (m, 2H), 7.37 (t, 1H), 7.01 (m, 2H), 6.63 (s, 1H), 3.89 (s, 3H), 3.33-3.49 (m, 2H), 2.24 (m, 2H), 1.17-1.74 (m, 8 H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.6, 172.1, 163.2, 159.8, 159.7, 157.9, 145.0 138.7, 129.8, 126.5 118.6, 115.7, 111.3, 100.7, 55.1, 40.1 32.2, 29.2, 26.6, 26.4; Anal. calcd. (%) for $C_{20}H_{22}N_4O_3S$: C, 60.28; H, 5.57; N, 14.06; found (%): C, 60.30; H, 5.55; N, 14.07.

5-(6-([4,5'-Bipyrimidin]-6-ylamino)hexylidene)thiazolidine-2,4-dione (9g): Yield: 58.4 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{17}H_{18}N_6O_2S$ $(M + H)^+$: 371.12; found (%): 371.20; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.30 (s, 3H), 8.67 (s, 1H), 6.96 (m, 1H), 6.70 (s, 1H), 3.40 (br, m, 2H), 2.24 (m, 2H), 1.36-1.73 (m, 6H).^{1}H NMR (400 MHz, methanol-d_4): δ 9.30 (br, s, 2H), 9.23 (s, 1H), 8.51 (s, 1H), 6.93 (m, 2H), 3.45 (br, m, 2H), 2.29 (m, 2H), 1.13-1.72 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.9, 173.0, 159.4, 159.1, 155.5, 155.3, 145.7, 134.0, 130.7, 127.2 101.9, 98.2, 59.3, 31.9, 28.5, 26.0, 25.6; Anal. calcd. (%) for $C_{17}H_{18}N_6O_2S$: C, 55.12; H, 4.90; N, 22.69; found (%): C, 55.15; H, 4.91; N, 22.64;

5-(6-((6-(2-Methylpyridin-4-yl)pyrimidin-4-yl)amino)-hexylidene)thiazolidine-2,4-dione (9h): Yield: 22.3 %; beige solid; LC-MS (ESI) *m/z* calculated for $C_{19}H_{21}N_5O_2S$ $(M + H)^+$: 384.14; found (%): 384.30; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30-12.45 (m, 1H), 8.43-8.61 (m, 3H), 7.53-7.60 (m, 1H), 6.95-7.06 (m, 1H), 6.81-6.94 (m, 1H), 3.32 (m, 2H), 2.55 (m, 2H), 2.20-2.22 (m, 2H), 1.24-1.62 (m, 4H);); ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.1, 172.7, 171.3, 164.5, 160.7, 159.2, 158.8, 146.0, 139.8, 130.9, 127.4 117.1, 111.2, 52.2, 50.7, 32.4, 29.8, 29.4, 27.0; Anal. calcd. (%) for $C_{19}H_{21}N_5O_2S$: C, 59.51; H, 5.52; N, 18.26; found (%): C, 59.50; H, 5.54; N, 18.25.

5-(6-((6-(2,6-Dimethylphenyl)pyrimidin-4-yl)amino)-hexylidene)thiazolidine-2,4-dione (9i): Yield: 28.9 %; light yellow solid; LC-MS (ESI) *m/z* calculated for $C_{21}H_{24}N_4O_2S$ $(M + H)^+$: 397.16; found (%): 397.30; ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.65 (s, 1H), 6.97-7.21 (m, 4H), 6.26 (s, 1H), 3.29 (br, m, 2H), 2.15 (m, 6H), 1.39-1.74 (m, 8H) ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.8, 158.3, 136.3, 136.3, 133.5,

129.8, 129.8, 128.9, 104.2, 64.2, 51. 5, 34.1, 34.1, 32.1, 25.8, 25.8, 24.1, 20.1, 20.1, 18.5, 18.5, 18.5, 5.3, 5.3; Anal. calcd. (%) for $C_{21}H_{24}N_4O_2S$: C, 63.61; H, 6.10; N; S, 8.09; found (%): C, 63.63; H, 6.11; N, 14.10.

Step-7: Synthesis of compounds (10a-i): In an autoclave, Knoevenagel product (**9a-i**) (1 eq.) was charged in methanol: water (10:1) (50 vol). 10 % Pd/C (0.1 mol %) was added at room temperature. The reaction mixture was stirred at 80 °C under hydrogen at 40 psi for 2h. ^{1}H NMR showed that starting material was consumed. After completion, reaction mixture was cooled to room temperature and passed through a celite bed. Celite bed was washed with methanol (20 mL × 2) and filtrate was concentrated under reduced pressure. Crude product was purified by Combi-Flash {(Teledyne Isco) using Hi-Purit flash column silica (NP) 4 g, 60 Å, max pressure: 350 psi (24 bar)} using 0-100 % ethyl acetate:hexane) to afford desired compound.

5-(6-((6-Phenylpyrimidin-4-yl)amino)hexyl)thiazolidine-2,4-dione (10a): Yield: 38.2 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{19}H_{22}N_4O_2S$ (M + H)$^+$: 370.15; found (%): 371.30;. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (br, s, 1H), 8.45 (s, 1H), 7.98 (m, 2H), 7.36-7.53 (m, 4H), 6.90 (s, 1H), 4.55 (dd, J=8.33, 3.95 Hz, 1H), 3.30 (m, 2H) 1.98 (m, 1H), 1.77 (m, 1H), 1.18-1.59 (m, 8H). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ 8.40 (s, 1H), 7.92 (m, 2H), 7.46 (m, 3H), 6.88 (s, 1H), 4.45 (m, 1H), 3.28 (m, 2H), 1.98 (m, 1H), 1.72 (m, 1H), 1.07-1.56 (m, 8 H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.4, 171.9, 163.8, 158.3, 158.2, 133.1, 129.9, 129.5, 128.7, 126.5, 126.4, 98.1, 52.0, 40.2, 31.7, 28.3, 28.0, 26.3, 26.2; Anal. calcd. (%) for $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12; found (%): C, 61.62; H, 5.95; N, 15.15.

***tert*-Butyl 4-(6-((6-(2,4-dioxothiazolidin-5-yl)hexyl)-amino)pyrimidin-4-yl)benzoate (10b):** Yield: 30 %; transparent oil which was further lyophilized to get white solid; LC-MS (ESI) *m/z* calculated for $C_{24}H_{30}N_4O_4S$ (M + H)+: 471.20; found (%): 471.40; ^{1}H NMR (400 MHz, chloroform-d_1): δ 9.36 (br, s, 1H), 8.65 (s, 1H), 7.95-8.16 (m, 4H), 6.72 (s, 1H), 4.33 (m, 1H), 3.38 (m, 2H), 1.87-2.21 (m, 2H), 1.12-1.82 (m, 17H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.1, 172.3, 162.9, 158.4, 158.3, 158.2, 158.1, 154.8, 154.7,133.5, 130.2, 101.6, 60.4, 55.4, 51.5, 31.7, 28.4,28.4, 28.4, 28.3, 28.0, 26.3, 26.2, 25.9; Anal. calcd. (%) for $C_{24}H_{30}N_4O_4S$: C, 61.26; H, 6.43; N, 11.91; found (%): C, 61.24; H, 6.44; N, 11.93.

5-(6-((6-(2-(*tert*-Butyl)pyridin-4-yl)pyrimidin-4-yl)-amino)hexylidene)thiazolidine-2,4-dione (10c): Yield: 40%; white solid; LC-MS (ESI) *m/z* calculated for $C_{22}H_{29}N_5O_2S$ (M + H)$^+$: 428.20; found (%): 428.40; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (br, s, 1H), 8.48-8.67 (m, 2H), 7.94 (br, s, 1H), 7.63-7.72 (m, 1H), 7.56 (br, m, 1H), 7.02 (s, 1H), 4.56 (dd, *J* = 4.38, 8.77 Hz, 1H), 1.74-2.07 (m, 4H), 1.21-1.62 (m, 15H); ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ 8.42-8.68 (m, 2H), 7.86-8.01 (br, m, 1H), 7.66 (br, m, 1H), 6.93 (s, 1H), 4.46-4.58 (dd, *J* = 4.38, 8.77 Hz, 1H), 3.32 (br, m, 2H), 1.91-2.04 (m, 2H), 1.72-1.35 (m, 17H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.4, 171.9, 169.3, 162.6, 159.0, 157.8, 149.1, 145.0, 117.4, 115.5, 101.8, 51.4, 40.2, 37.4, 31.8, 30.0, 30.0, 30.0, 28.3, 28.1, 26.2, 26.1; Anal. calcd. (%) for $C_{22}H_{29}N_5O_2S$: C, 61.80; H, 6.84; N, 16.38; found (%): C, 61.82; H, 6.85; N, 16.38.

5-(6-((6-(*o*-Tolyl)pyrimidin-4-yl)amino)hexyl)thiazolidine-2,4-dione (10d): Yield: 45.1 %; transparent oil which was further lyophilized to get white solid; LC-MS (ESI) *m/z* calculated for $C_{20}H_{24}N_4O_2S$ (M + H)$^+$ = 385.16; found (%): 386.30; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (br. s), 8.45 (s, 1H), 7.20-7.44 (m, 5H), 6.49 (s, 1H), 4.48-4.61 (m, 1H), 2.32 (s, 3H), 2.01 (m, 1H), 1.76 (m, 1H), 1.24-1.63 (m, 8H); ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ 8.43 (br, s, 1H), 7.19-7.38 (m, 4H), 6.48 (s, 1H), 4.48-4.56 (m, 1H), 3.32 (br, m, 2H), 2.31 (s, 3H), 1.97 (m, 1H), 1.76 (m, 1H), 1.19-1.56 (m, 8H); ^{1}H NMR (400 MHz, chloroform-d_1): δ 8.62 (s, 1H), 7.27-7.40 (m, 4H), 6.38 (s, 1H), 4.28 (dd, *J* = 4.38, 8.77 Hz, 1H), 3.32 (m, 2H), 2.38 (s, 3H), 2.09 (m, 1H), 1.94 (m, 1H), 1.29-1.80 (m, 8H); ^{13}C (101 MHz, DMSO-d_6): δ 176.4, 171.9, 163.8, 158.3, 158.2, 135.9, 133.1, 129.9, 129.5, 128.7, 126.5, 98.1, 52.0, 40.2, 31.7, 28.3, 28.0, 26.3, 26.2,20.0; Anal. calcd. (%) for $C_{20}H_{24}N_4O_2S$: C, 62.48; H, 6.29; N, 14.57; found (%): C, 62.47; H, 6.29; N, 14.56.

5-(6-((6-(Quinolin-4-yl)pyrimidin-4-yl)amino)hexyl)-thiazolidine-2,4-dione (10e): Yield: 41.5 %, off white solid; LC-MS (ESI) *m/z* calculated for $C_{22}H_{23}N_5O_2S$ (M + H)$^+$: 422.16; found (%): 422.20; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (br, s, 1H), 8.98 (br, m, 1H), 8.59 (br, m, 1H), 8.00-8.27 (m, 2H), 7.54-7.89 (m, 4H), 6.75 (s, 1H), 4.56 (m, 1H), 3.17 (m, 2H), 1.12-2.07 (m, 10H); ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ 8.97 (br, s, 1H), 8.56 (br, m, 1H), 8.05-8.22 (m, 2H), 7.80 (br, m, 1H), 7.59 (m, 3H), 6.74 (m, 2H), 4.46 (m, 1H), 3.30 (br, m, 2H), 1.15-2.04 (m, 10H); ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.94 (s, 1H), 8.55 (br, s, 1H), 8.07-8.15 (m, 1H), 7.83 (t, *J* = 7.02 Hz, 1H), 7.56-7.69 (m, 2H), 6.75 (s, 1H), 4.42 (m, 1H), 3.45 (br, m, 2H), 2.15 (br, m, 1H), 1.86 (br, m, 1H), 1.24-1.70 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.12, 177.1, 173.0, 162.6, 160.5, 158.4, 151.1, 147.8, 144.4, 129.5, 129.4, 127.3, 127.2, 126.0, 126.5, 121.2, 106.3, 51.4, 40.2, 31.8, 28.8, 28.7,26.0, 25.9; Anal. calcd. (%) for $C_{22}H_{23}N_5O_2S$: C, 62.69; H, 5.50; N; found (%): C, 62.67; H, 5.52; N, 16.65.

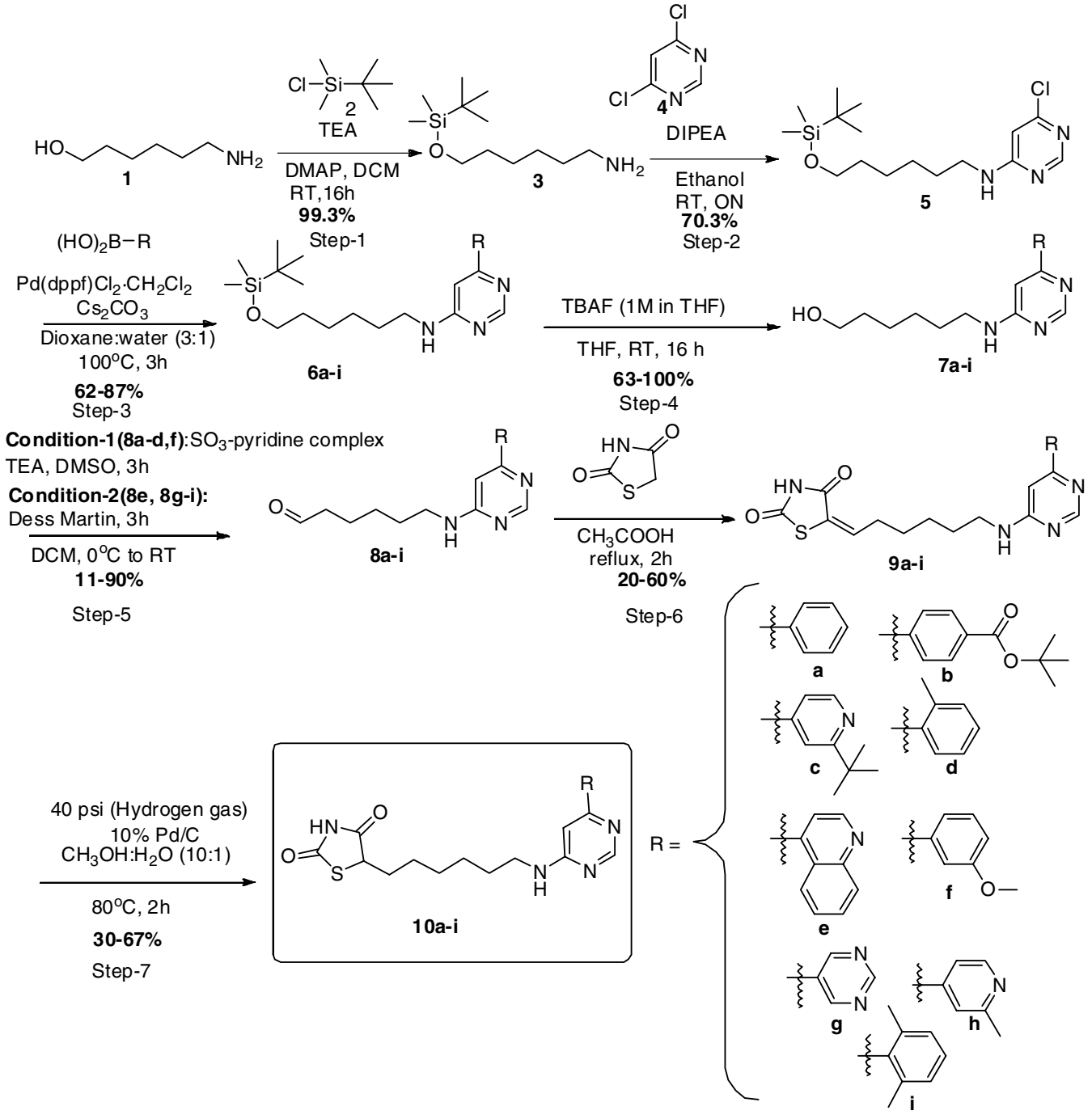
5-(6-((6-(3-Methoxyphenyl)pyrimidin-4-yl)amino)-hexyl)thiazolidine-2,4-dione (10f): Yield: 37.3 %; white solid; LC-MS (ESI) *m/z* calculated for $C_{20}H_{24}N_4O_3S$ (M + H)$^+$: 401.16; found (%): 401.30; ^{1}H NMR (400 MHz, methanol-d_4): δ 8.43 (s, 1H), 7.35-7.48 (m, 3H), 7.04 (d, *J* = 6.14 Hz, 1H), 6.84 (s, 1H), 4.43 (dd, *J* = 4.39, 8.77 Hz, 1H), 3.86 (s, 2H), 2.13 (br, s, 1H), 1.93 (br, s, 1H), 1.21-1.70 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.6, 172.1, 163.2, 159.8, 159.7, 157.9, 138.7, 129.8, 118.6, 115.7, 111.3, 100.7, 55.1, 51.4, 40.1 31.8, 28.8, 28.4, 26.2, 26.1; Anal. calcd. (%) for $C_{20}H_{24}N_4O_3$: C, 59.98; H, 6.04; N, 13.99; found (%): C, 59.99; H, 6.05; N, 14.02.

5-(6-([4,5'-Bipyrimidin]-6-ylamino)hexyl)thiazolidine-2,4-dione (10g): Yield: 33.3 %; transparent oil which was further lyophilized to get white solid; LC-MS (ESI) *m/z* calculated for $C_{17}H_{20}N_6O_2S$ (M + H)$^+$: 373.14; found (%): 373.20; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (br, s, 1H), 9.13-9.54 (m, 4H), 8.43-8.57 (m, 1H), 7.62 (br, m, 1H), 7.01 (br, m, 1H), 4.49-4.53 (m, 1H), 1.98 (br, m, 1H), 1.77 (br, m, 1H), 1.19-1.60 (m, 8H). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O): δ 9.25 (m, 3H), 8.40-8.57 (s, 1H), 6.92-7.14 (s, 1H), 4.41-4.55 (m, 1H), 3.12-3.39 (m, 2H), 1.89-2.07 (m, 1H), 1.66-1.88 (m,

1H), 1.10-1.61 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.1, 172.3, 158.7, 158.4, 154.8, 154.6 134.0, 130.7, 101.9, 98.2, 59.3, 51.7, 31.9, 28.5, 28.4, 26.0, 25.6; Anal. calcd. (%) for $C_{17}H_{20}N_6O_2S$: C, 54.82; H, 5.41; N, 22.56; found (%): C, 54.85; H, 5.40; N, 22.55.

5-(6-((6-(2-Methylpyridin-4-yl)pyrimidin-4-yl)amino)-hexyl)thiazolidine-2,4-dione (10h): Yield: 66.7 %, off white solid; LC-MS (ESI) *m/z* calculated for $C_{19}H_{23}N_5O_2S$ $(M + H)^+$: 386.16; found (%): 386.30; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.98-12.08 (br, s, 1H), 8.62-8.71 (m, 1H), 8.51-8.61 (m, 1H), 7.73-7.99 (m, 2H), 7.01-7.16 (m, 1H), 4.51-4.64 (m, 1H), 2.61 (br, m, 2H), 1.92-2.09 (m, 1H), 1.68-1.87 (m, 1H), 1.34 (br, s, 8H). ^{1}H NMR (400 MHz, DMSO-d_6 +D_2O): δ 8.48-8.67 (m, 1H), 8.45-8.57 (m, 1H), 7.73-7.99 (m, 2H), 6.97-7.11 (m, 1H), 4.48-4.59 (m, 1H), 3.32 (br, m, 2H), 2.64 (m, 3H), 1.94-2.06 (m, 1H), 1.70-1.85 (m, 1H), 1.16-1.56 (m, 8H) ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.8, 172.1, 171.1, 164.1, 160.0, 158.9, 158.6, 139.7, 130.3, 116.7, 111.2, 55.8, 52.2, 51.7, 31.8, 29.5, 28.9, 28.7, 27.0; Anal. calcd. (%) for $C_{19}H_{23}N_5O_2S$: C, 59.20; H, 6.01; N, 18.17; found (%): C, 59.21; H, 6.03; N, 18.14.

5-(6-((6-(2-Methylpyridin-4-yl)pyrimidin-4-yl)amino)-hexyl)thiazolidine-2,4-dione (10i): Yield: 32.9 %; transparent oil which was further lyophilized to get white solid; LC-MS (ESI) *m/z* calculated for $C_{21}H_{26}N_4O_2S$ $(M + H)^+$: 399.18; found (%): 399.6 and 400.3; ^{1}H NMR (400 MHz, methanol-d_4): δ 8.45 (s, 1H), 7.02-7.24 (m, 3H), 6.38 (s, 1H), 4.43 (m, 1H), 3.43 (m, 2H), 2.10 (s, 6H), 1.22-1.92 (m, 10H); ^{13}C NMR (101



Scheme-I: General scheme for synthesis of compounds

MHz, DMSO-d_6): δ 176.4, 171.9, 163.8, 158.3, 158.2, 136.1, 136.1, 133.1, 129.9, 129.5, 128.7, 98.1, 52.0, 40.2, 31.7, 28.3, 28.0, 26.3, 26.2, 19.1, 19.1; Anal. calcd. (%) for $C_{21}H_{26}N_4O_2S$: C, 63.29; H, 6.58; N, 14.06; found (%): C, 63.28; H, 6.59; N, 14.07.

RESULTS AND DISCUSSION

Novel compounds of six membered aliphatic chain with terminal thiazolidone and pyrimidine based nucleus have been synthesized. We optimized synthesis (**Scheme-I**) based on the literature available for different steps. Some of the steps needed optimization and the details of the optimization have been discussed. Aliphatic amine chain (6-aminohexan-1-ol) is substituted on 4,6-dichloro pyrimidine. Hydroxyl group is protected with TBDMS [17] to exclusively get the amine substitution. Displacement was optimized in DIPEA-ethanol at 0 °C to room temperature [18]. Suzuki coupling was done with Pd(dppf)Cl_2·CH_2Cl_2/Cs_2CO_3 [19]. TBDMS de-protection (Step-4) was done in usual TBAF method [20]. Parikh-Doering oxidation [21] worked fine for (**8a-d,8i**) but product formation was not observed for others in this condition. Dess martin oxidation was optimized for (**8f, 8h-I**) [22].

Step-6 was optimized by slight modification of reported Knoevenagel condensation conditions and product formation was observed in piperidine/acetic acid at 100 °C (entry-3 in Table-1) [16].

TABLE-1
SCREENING OF REACTION CONDITIONS FOR STEP-6

Entry	Reagent (0.015 eq.)	Solvent	Time (h)	Temp. (°C)	Yield[a] (%)
1	Urea	DMF	16	25-100	0[b]
2	Thio-urea	DMF	16	50-100	< 5[b]
3	Piperidine	Acetic acid	3	100	40-70

[a]Conversions by UPLC-LCMS; [b]Starting material remained unreacted.

Alkene reduction with Pd/C did not work at ambient temperature and product formation was observed in methanol:water under hydrogen atmosphere at 40 psi at reflux [23] to render all the target compounds. Nine examples of this scaffold have been synthesized using different boronic acid/esters.

Conclusion

Novel class of TZD based pyrimidine analogs have been designed and synthesized. The synthesis strategy is based on hydroxyl protection of 6-aminohexan-1-ol to obtain exclusively the amino substituted pyrimidine under mild conditions. Suzuki coupling at this stage is very facile and gave good yield with all boronic acids. Steps involved in this synthesis are reproducible with high level of regio-selectivity. Further scope of coupling with other Suzuki partners and alterations in the length of the aliphatic chain as well as the composition of the linker substitution cannot be undermined.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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