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Synthesis of biologically active 2-thio-5-arylbenzo[4,5]thiazolopyrimido [5,4-d]pyrimidin-4-one derivatives catalyzed by metal proline in water

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A facile and highly efficient one pot multi-component reaction for the synthesis of 2-thio-5-arylbenzo [4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one derivatives **4** under aqueous medium has been developed. The reaction takes place by condensation of thiobarbituric acids **1**, 2-aminobenzothiazole **2** and aldehydes **3** using metal-proline catalyzed domino Knoevenagel, Michael and intramolecular cyclization approach.

Keywords: Synthesis, arylbenzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, metal-proline, aqueous medium

Drugs and pharmaceuticals are mainly derived from heterocyclic compounds containing nitrogen and sulphur atoms. It has been found that incorporation of various fused heterocycles pyrimidine with nucleus enhances the biological activities. The structural diversity and biological importance of fused pyrimidines have made them attractive targets for synthesis over many years. Synthesis of heterocycles with a pyrimidopyrimidine or a thiazolopyrimidine framework is of particular importance as they exhibit a broad spectrum of biological properties and widely found for application in drug discovery. Pyrimidopyrimidines and its derivatives are important class of annulated uracils which have biological significance because of their connection with purine system[1]. Derivatives of pyrimidopyrimidines are used as anti-microbial[2,3], antifungal[4]. No generally useful procedures for the preparation of thiazolo[4,5-d]pyrimidines have been reported. It has been briefly mentioned that the reaction of 4-amino-5-amidothiazoles with orthoformates in the presence of acetic anhydride leads to the desired thiazolo[4,5d]pyrimidines[5]. When carbodiimides which were derived from iminophosphoranes and aromatic isocyanates, were heated at temperatures slightly above their melting points, they underwent electrocyclic ring closure to give thiazolo[4,5-d]pyrimidines[6]. Thiazolo[3,2-*a*]pyrimidine derivatives were also synthesized by the treatment of 2-aminothiazole with the corresponding ketene S,S-acetals[7]. The synthesis proceeded successfully in ethanol containing a catalytic amount of triethylamine. Pyrimidobenzothiazole derivative was also synthesized by reacting ketene S,S-acetal with 2-aminobenzothiazole in absolute ethanol and triethylamine[7]. Goldman[8] has utilized 6-amino-1,3-dimethyl uracils for the synthesis thiadiazolopyrimidines upon treatment with thionyl chloride-pyridine.

We observe that it would be of interest to combine these two heterocyclic compounds – benzothiazolo pyrimidines and pyrimidopyrimidines – in a molecular framework. A survey of literature reveals that a very few work was done on the synthesis and biological activities of heterocyclic compounds containing benzothiazolopyrimidines fused with pyrimidine ring. Although various methods have been developed for the synthesis of thiazolo-pyrimidopyrimidines, most of these procedures offer several disadvantages, such as longer reaction times, unsatisfactory yields, drastic reaction conditions and use of costly or toxic catalysts.

Multi-component reactions (MCRs) have been developed as an efficient and powerful tool in the synthetic organic chemistry for the synthesis of fused compounds in a one-pot reaction. These reactions enable the formation of compounds in an efficient way giving higher yields, saving time and energy, more economical and easier to isolate as compared to sequential synthesis of the same compound. Moreover, the synthesis of biologically active compounds in water, environmentally benign solvent, through multi-component reaction is one of the most widely developed methods[9-13]. It is planned to synthesize these heterocyclic compounds using dabco-based ionic liquids. Recently, we have reported the use of Dabco-based basic ionic liquids as highly

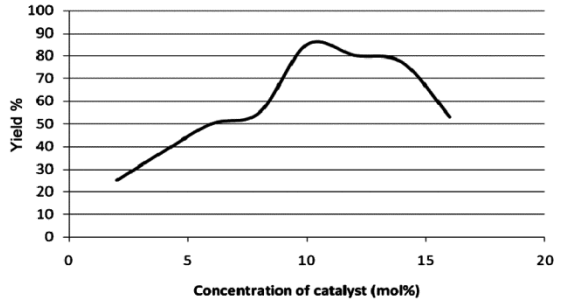
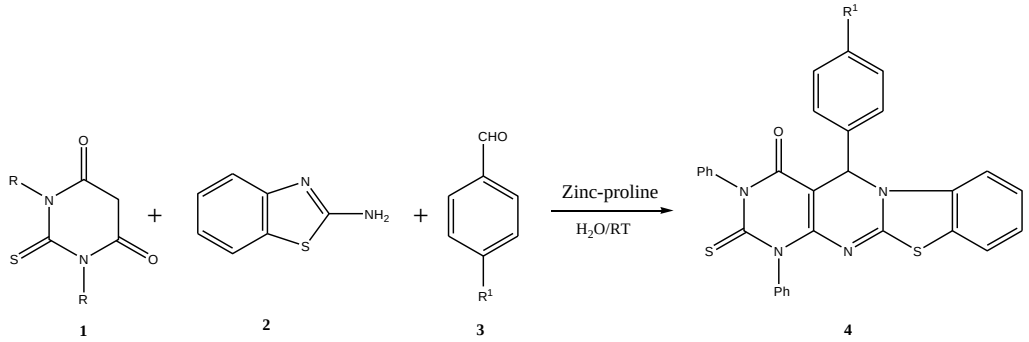


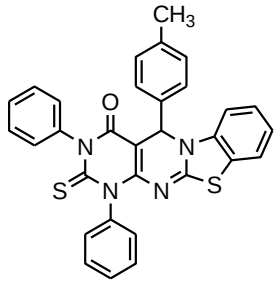
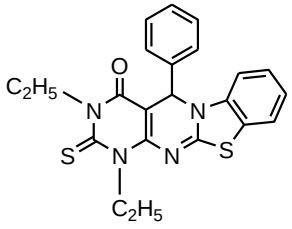
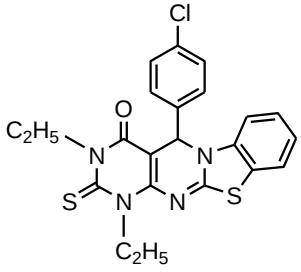
Figure 4 — Effect of concentration of catalyst on yield

of KBr discs using a Shimadzu FT-IR spectrophotometer in the range of 200 cm^{-1} to 4000 cm^{-1}. ^1H NMR spectra were recorded on Brucker–ACF-400 (400 MHz) and ^{13}C NMR spectra were recorded on Brucker–ACF-400 (100 MHz) in dimethylsulfoxide (DMSO-d_6) and TMS as an internal standard. The FAB mass spectra were recorded at 6000 Mass Spectrometer data systems using Argon/Xenon (6KV, 10mA) as the FAB gas. The CHN analyses were performed on Perkin-Elmer CHN

Table III — Synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, **4** [a]

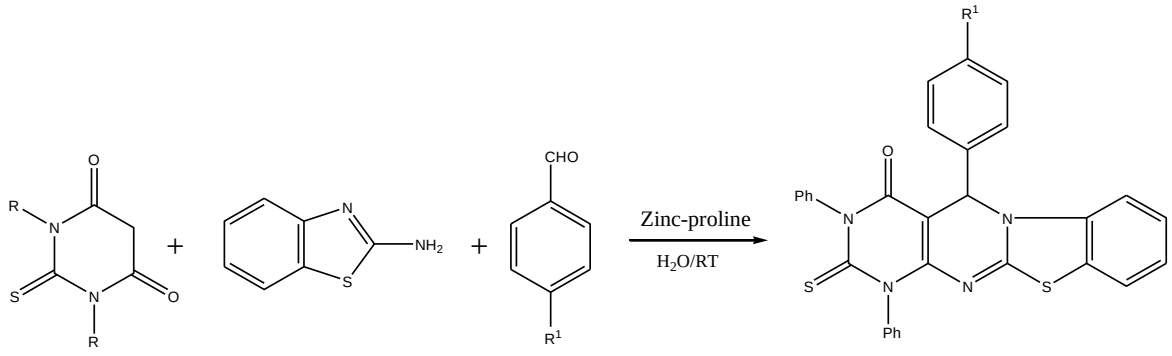


1 **2** **3** **4**

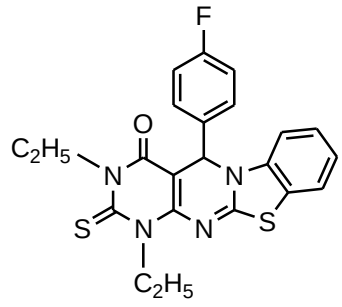
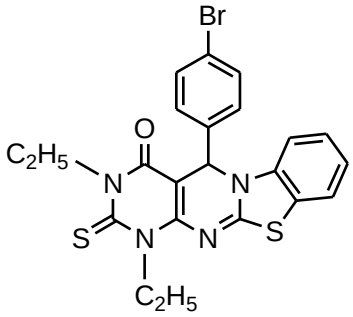
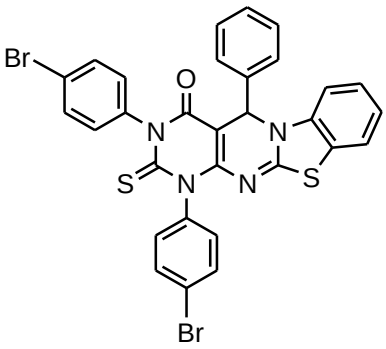
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
1	R=Ph	R^1=CH_3	 **4a**	15	92
2	R=Et	R^1=H	 **4b**	20	82
3	R=Et	R^1=4-Cl	 **4c**	30	88

(*Contd*.)

Table III — Synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, **4** [a] — (*Contd*.)

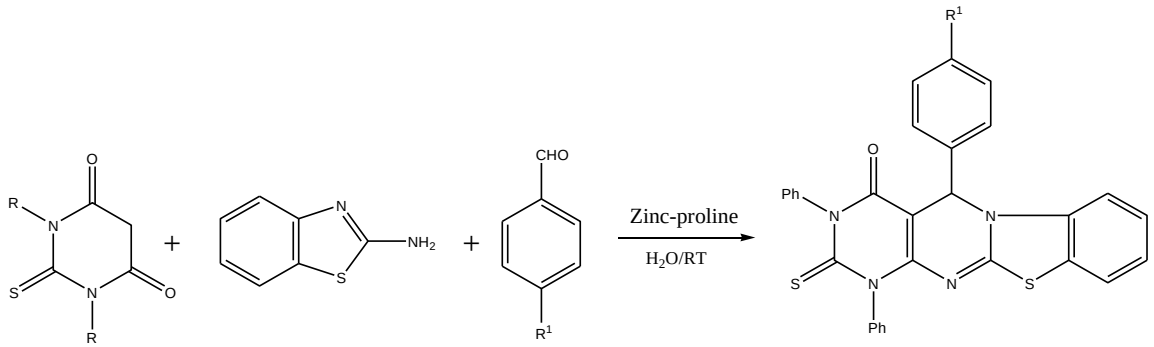


1 **2** **3** **4**

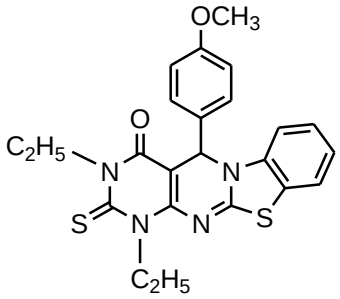
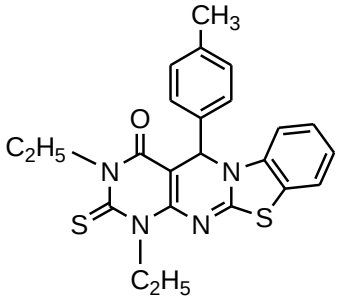
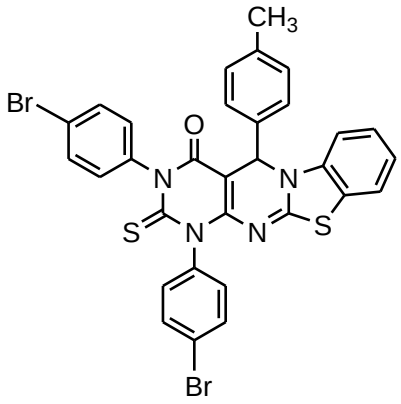
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
4	R=Et	R^1=F	 **4d**	25	78
5	R=Et	R^1=Br	 **4e**	28	88
6	R=4-BrC_6H_4	R^1=H	 **4f**	30	86

(*Contd*.)

Table III — Synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, **4** [a] — (*Contd*.)

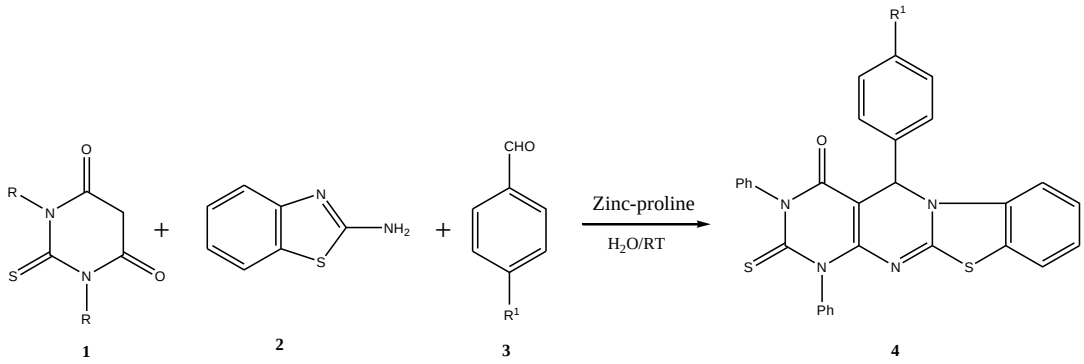


1 **2** **3** **4**

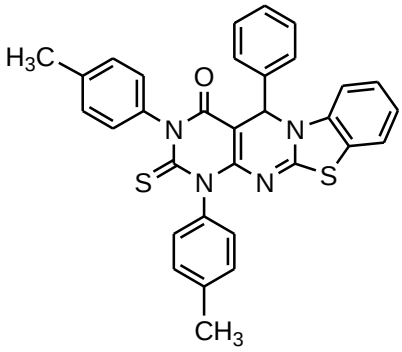
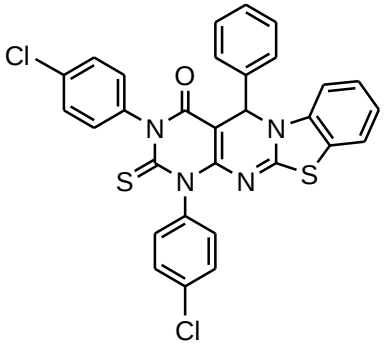
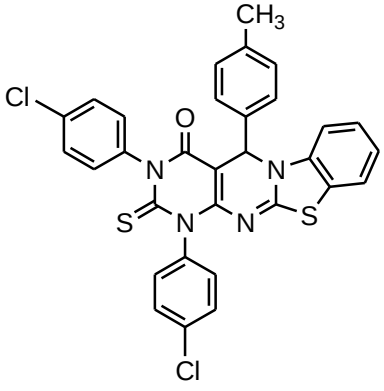
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
7	R=Et	R^1=OCH_3	 **4g**	25	83
8	R=Et	R^1=CH_3	 **4h**	20	85
9	R=4-BrC_6H_4	R^1=CH_3	 4i	55	74

(*Contd*.)

Table III — Synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, **4** [a] — (*Contd*.)

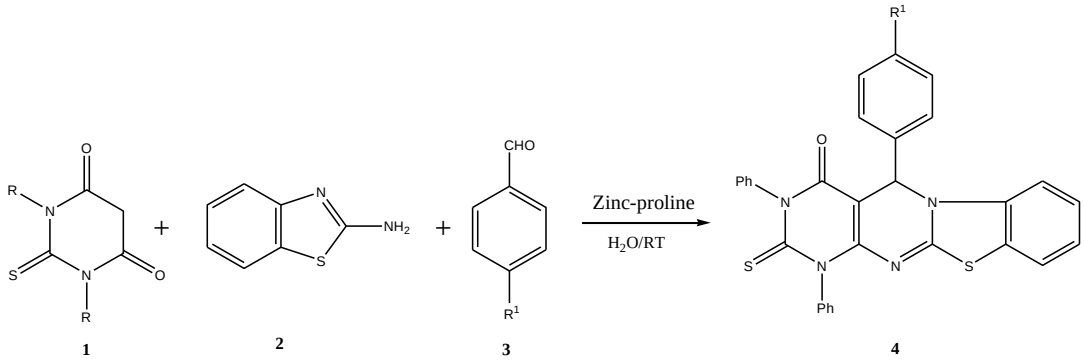


1 **2** **3** **4**

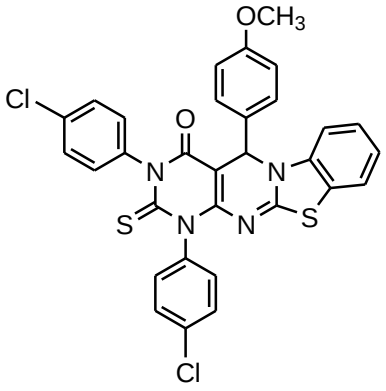
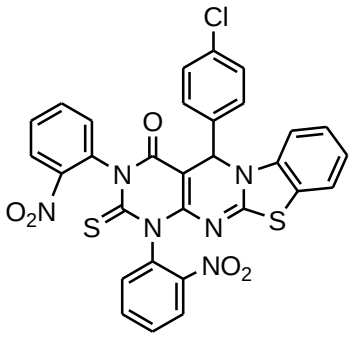
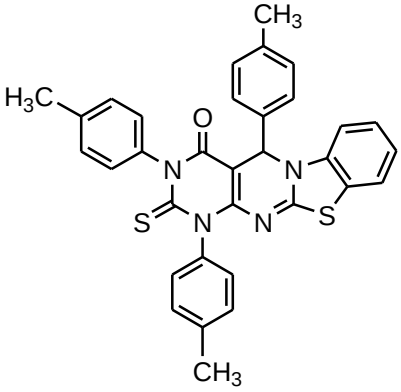
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
10	R=4-$CH_3C_6H_4$	R^1=H	 **4j**	45	78
11	R=4-ClC_6H_4	R^1=H	 **4k**	35	75
12	R=4-ClC_6H_4	R^1=CH_3	 **4l**	40	72

(*Contd*.)

Table III — Synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, **4** [a] — (*Contd*.)

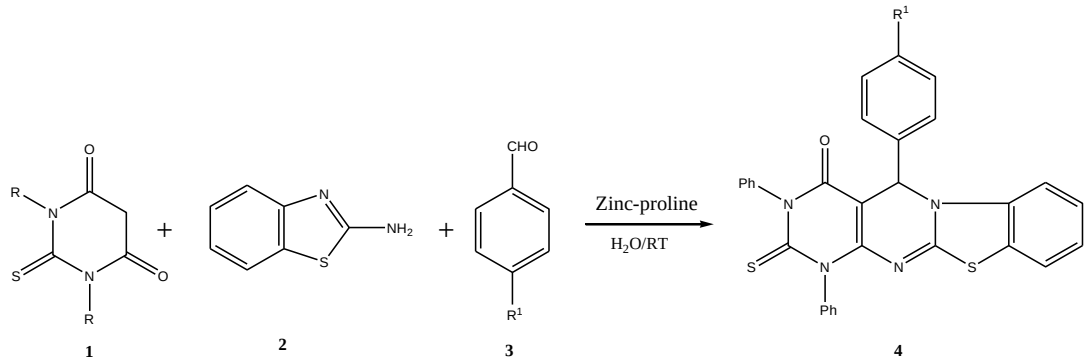


1 **2** **3** **4**

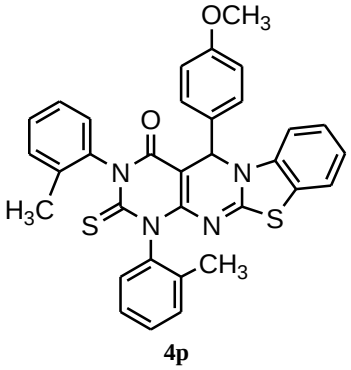
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
13	R=4-ClC_6H_4	R^1=OCH_3	 **4m**	30	80
14	R=2-$NO_2C_6H_4$	R^1=Cl	 **4n**	20	82
15	R=4-$CH_3C_6H_4$	R^1=CH_3	 **4o**	40	74

(*Contd*.)

Table III — Synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, **4** [a] — (*Contd*.)



1 **2** **3** **4**

Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
16	R=2-$CH_3C_6H_4$	R^1=OCH_3		45	72

4p

[a] Zinc-proline complex (10 mol%), thiobarbituric acid, **1** (1.0 mmol), 2-aminobenzothiazole, **2** (1.0 mmol) and aldehyde, **3** (1.0 mmol) in 5.0 mL water at room temperature; [b] Isolated yield.

analyzer. The accelerating voltage was 10 KV and the spectra were recorded at room temperature. All the commercial chemicals were distilled before use.

Procedure for the synthesis of Metal-proline complexes

Metal-proline complexes were prepared by adding Et_3N (0.7 mL) to a mixture of L-proline (5.0 mmol) in MeOH (10.0 mL); after 10 min, metal acetate (2.5 mmol) was added. After stirring for 45 minutes, a white precipitate was collected by filtration. Complexes were characterized by NMR, IR, and ESI-MS.

Zinc-proline complex: White amorphous solid; Yield=100%; m.p.= decomposed at 220°C; IR (KBr, Cm^{-1}): 3217, 2962, 1605, 1447, 1335; ^{1}H NMR(300MHz, D_2O): 1.81 (m br, 3H), 2.22 (m br, 1H), 2.96 (s br, 1H), 3.14 (m br, 1H), 3.82 (m br, 1H); ^{13}CNMR (75 MHz, D_2O): δ 24.9 (CH_2-C), 31.4 (CH_2-NH), 47.2 (CH_2-C), 59.8 (CH-CO); MS (D_2O) *m/z:* 291 $[M]^+$; Anal Cald for $C_{10}H_{16}ZnN_2O_4$: C, 35.26; H, 4.73; N, 8.22. Found: C, 35.19; H, 4.69; N, 8.20.

Cadmium-proline complex: White amorphous solid; Yield=100%; m.p.= decomposed at 240°C; IR (KBr, Cm^{-1}): 3269, 3202, 2964, 1575, 1389; ^{1}H NMR(300MHz, D_2O): δ1.66 (m, br, 3H), 2.12 (m, br, 1H), 2.76 (s, br, 1H), 3.03 (m, br, 1H), 3.70 (m, br, 1H); ^{13}CNMR (75 MHz, D_2O): δ 25.7(CH_2-C), 30.1(CH_2-NH), 47.8 (CH_2-C), 60.7(CH-CO); MS (D_2O) *m/z:*358[M+H_2O];Anal Cald for $C_{10}H_{16}CdN_2O_4$: C, 35.26; H, 4.73; N, 8.22. Found: C, 35.19; H, 4.69; N, 8.20.

Mercury-proline complex: White amorphous solid ; Yield=100%; m.p.= decomposed at 250°C; IR (KBr, Cm^{-1}): 3543, 3231, 2974, 1615, 1424, 1070; ^{1}H NMR (300MHz, D_2O): δ1.56 (m, br, 3H), 1.96 (m, br, 1H), 2.79 (m, br, 1H), 3.06 (s, br, 1H), 3.72 (m, br, 1H); ^{13}C NMR (75 MHz,D_2O): δ 24.7(-CH_2-C), 29.2(-CH_2-NH), 51.7(-CH_2-C), 61.9(-CH-CO), 178.6(-CO); MS (D_2O) *m/z*: 428$[M^+]$,429[M+H],447[M+H_2O], 467[M+K]; Anal Cald for $C_{10}H_{16}HgN_2O_4$: C, 28.01; H, 3.76; N, 6.53. Found: C, 27.95; H, 3.70; N, 6.48.

Lead-proline complex: White amorphous solid; Yield=100%; m.p.= decomposed at 210°C; IR (KBr,Cm^{-1}): 3236, 2981, 2868, 1653, 1571, 1377; ^{1}HNMR(300MHz,D_2O): 1.93 (m, br, 3H), 2.23 (m, br, 1H), 3.14(m, br, 1H), 3.23 (m, br, 1H), 3.91(m, br,

1H); ^{13}CNMR (75 MHz, D_2O): δ 178.3(-CO), 62.4 (-CH-C), 49.1(-CH_2-C), 47.1(-CH_2-NH), 30.6(-CH_2-C); Anal Cald for $C_{10}H_{16}N_2O_4Pb$: C, 27.58, H, 3.70; N, 6.43. Found: C, 27.53, H, 3.62; N, 6.39.

General procedure for the synthesis of 2-thio-5-aryl-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-ones, 4a-p

Zinc-proline complex (0.1 mmol,10 mol%) was added to a mixture of aldehyde (1.0 mmol), 2-aminobenzothiazole (1.0 mmol), and thiobarbituric acid (1.0 mmol) in 5.0 mL of water, then the reaction mixture was stirred at room temperature until the TLC indicate the complete reaction. After completion of the reaction, the organic part was removed by adding ethyl acetate and the aqueous phase was collected for further reaction. The organic part was washed once with water (10.0 mL), dried with anhydrous $NaSO_4$ and then filtered. The crude mixture was concentrated on rotary evaporator under reduced pressure (Buchi Rotavapor) and was purified using flash chromatography.

2-Thio-1,3-diphenyl-5-(4-methylphenyl)-benzo [4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4a: Yellowish solid; anal. cal. for $C_{31}H_{22}N_4OS_2$: C, 70.17; H, 4.18; N, 10.56; S, 12.08%; found: C, 69.45; H, 4.23; N, 10.16%. IR (KBr, cm^{-1}): 1512, 1600, 1668, 2924, 3032. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 2.3 (3H, s, CH_3) 5.2 (1H, s, CH), 7.1-8.3 (18H, m, Ar-H), ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.96, 43.2, 124, 126, 128, 134, 165.8, 177.8. Mass (m/z): 530.12 (100%), 531.13 (1.5%).

2-Thio-1,3-diethyl-5-phenyl-benzo[4,5]thiazolop yrimido[5,4-d]pyrimidin-4-one, 4b: Yellowish solid; anal. cal. for $C_{22}H_{20}N_4OS_2$: C, 62.83; H, 4.79; N, 13.32; S, 15.25%; found: C, 63.07; H, 5.04; N, 13.61%. IR (KBr, cm^{-1}): 1540, 1683, 2930, 3085. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 0.8 (3H, t, CH_3), 1.2 (3H, t, CH_3), 4.0 (2H, q, CH_2), 4.2 (2H, q, CH_2), 5.1 (1H, s, CH), 7.2-7.4 (9H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.62, 11.96, 43.21, 43.87, 55.68, 63.16, 127.22, 129.16, 130.21, 132.91, 151.46, 165.86, 176.48. Mass (m/z): 420.11 (100%), 421.11 (1.6%).

2-Thio-1,3-diethyl-5-(4-chlorophenyl)-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4c: Light yellow solid; anal. cal. for $C_{22}H_{19}ClN_4OS_2$: C, 58.08; H, 4.21; N, 12.31, S, 14.09%; found: C, 58.17; H, 4.13; N, 12.11%. IR (KBr, cm^{-1}): 1558, 1674, 2917, 3040, 3067. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 0.8 (3H, t, CH_3), 1.2 (3H, t, CH_3), 4.0 (2H, q, CH_2), 4.2 (2H, q, CH_2), 5.3 (1H, s, CH), 7.1-7.4 (8H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.62, 11.96, 43.21, 43.86, 56.34, 63.22, 128.34, 129.16, 132.76, 151.4, 165.86, 177.91. Mass (m/z): 454.07 (100%), 456.08 (2.7%).

2-Thio-1,3-diethyl-5-(4-fluorophenyl)-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4d: White solid; anal. cal. for $C_{22}H_{19}FN_4OS_2$: C, 60.26; H, 4.37; N, 12.78; S, 14.62%; found: C, 60.11; H, 4.17; N, 12.67%. IR (KBr, cm^{-1}): 1407, 1669, 2907, 2910, 3021. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 1.0 (3H, t, CH_3), 1.4 (3H, t, CH_3), 4.1 (2H, q, CH_2), 4.3 (2H, q, CH_2), 5.1 (1H, s, CH), 7.1-7.4 (8H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.56, 11.91, 43.50, 44.22, 51.02, 63.14, 127.21, 128.54, 132.25, 166.08, 178.01. Mass (m/z): 438.10 (100%), 439.10 (2.2%).

2-Thio-1,3-diethyl-5-(4-bromophenyl)-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4e: Light yellow solid; anal. cal. for $C_{22}H_{19}BrN_4OS_2$: C, 52.91; H, 3.83; N, 11.22; S, 12.84%; found: C, 52.39; H, 4.02; N, 11.04%. IR (KBr, cm^{-1}): 1413, 1566, 1661, 2916, 2928, 3056. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 1.1 (3H, t, CH_3), 1.4 (3H, t, CH_3), 4.0 (2H, q, CH_2), 4.3 (2H, q, CH_2), 5.5 (1H, s, CH), 7.3-7.5 (8H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.14, 11.66, 43.21, 55.6, 128.63, 132.01, 165.76, 177.03. Mass (m/z): 498.02 (100%), 499.05 (1.4%).

2-Thio-1,3-di(4-bromophenyl)-5-phenyl-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4f: Yellowish solid; anal. cal. for $C_{30}H_{18}Br_2N_4OS_2$: C, 53.43; H, 2.69; N, 8.31; S, 9.51%; found: C, 53.49; H, 2.50; N, 8.17%. IR (KBr, cm^{-1}): 1413, 1566, 1641, 2963, 3056. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 1.0 (3H, t, CH_3), 1.2 (3H, t, CH_3), 3.9 (2H, q, CH_2), 4.1(2H, q, CH_2), 5.2 (1H, s, CH), 6.8-7.8 (17H, m, Ar-H).^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm):11.9, 43.8, 63.2, 129.1, 131.4, 135.6, 168.5, 178.4. Mass (m/z): 673.93 (100%).

2-Thio-1,3-diethyl-5-(4-methoxyphenyl)-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4g: White solid; anal. cal. for $C_{23}H_{22}N_4O_2S_2$: C, 61.31; H, 4.92; N, 12.43; S, 14.23%; found C, 61.55; H, 4.58, N, 12.66%. IR (KBr, cm^{-1}): 1402, 1554, 1639, 2964, 3066, 3109. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 0.8 (3H, t, CH_3), 1.2 (3H, t, CH_3), 3.8 (3H, s, OCH_3), 4.1 (2H, q, CH_2), 4.2 (2H, q, CH_2), 5.0 (1H, s, CH), 7.2-7.7 (8H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.6, 43.2, 55.2, 121.2, 129.2, 138.3, 167.5, 176.5. Mass (m/z): 450.12 (100%), 451.15 (1.5%).

2-Thio-1,3-diethyl-5-(4-methylphenyl)-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4h: Pale

yellow solid; anal. cal. for $C_{23}H_{22}N_4OS_2$: C, 63.57; H, 5.10; N, 12.89; S, 14.75%. found C, 64.07; H, 4.98; N, 13.04%. IR (KBr, cm^{-1}): 1414, 1543, 1665, 2972, 3040, 3101. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 0.8-1.0 (6H, t, $2CH_3$), 1.5 (3H, s, CH_3), 3.9-4.2 (4H, q, $2CH_2$), 5.1 (1H, s, CH), 7.1-7.5 (8H, m, Ar-H).^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.4, 12.0, 18.7, 43.2, 45.6, 56.8, 127.2, 133.4, 136.2, 168.2, 177.8. Mass (m/z): 434.12 (100%), 435.13 (1.5%).

2-Thio-1,3-di(4-bromophenyl)-5-(4-methylphenyl)-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4i: White solid; anal. cal. for $C_{31}H_{20}N_4OS_2$: C, 54.08; H, 2.93; N, 8.14; S, 9.31%. found C, 54.19; H, 2.27; N, 8.35%. IR (KBr, cm^{-1}): 1410, 1575, 1677, 2919, 3049, 3104. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 1.2-1.5 (6H, t, $2CH_3$), 2.1 (3H, s, CH_3), 4.3-4.5 (4H, q, $2CH_2$), 4.8 (1H, s, CH), 6.3-7.8 (16H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 11.8, 12.03, 18.3, 43.7, 44.1, 57.2, 127.2, 136.6, 166.7, 178.5. Mass (m/z): 687.94 (100%), 688.94 (1.3%).

2-Thio-1,3-di(4-methylphenyl)-5-phenyl-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4j: Light Yellow solid; anal. cal. for $C_{32}H_{24}N_4OS_2$: C, 70.56; H, 4.44; N, 10.29; S, 11.77%. found C, 70.23; H, 4.42; N, 10.45%.IR (KBr, cm^{-1}): 1413, 1572, 1681, 2917, 3004, 3061.^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 1.98 (3H,s, CH_3), 2.13(3H, s, CH_3), 5.4 (1H, s, CH), 6.7-7.8 (17H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm):20.6, 21.2, 55.6, 129.4, 130.5, 131.4, 135.8, 168.8, 176.4. Mass (m/z): 544.14 (100%), 545.14 (1.5%).

2-Thio-1,3-di(4-chlorophenyl)-5-phenyl-benzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one, 4k: Yellow solid; anal. cal. for $C_{30}H_{18}Cl_2N_4OS_2$: C, 61.54; H, 3.10; N, 9.57; S, 10.95%. found C, 61.55; H, 3.48; N, 9.51%. IR (KBr, cm^{-1}): 1480, 1589, 1686, 2924, 3012. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 5.2 (1H, s, CH), 6.6-7.8 (17H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 55.4, 123.6, 129.1, 131.4, 137.2, 166.4, 178.2. Mass (m/z): 584.03 (100%), 585.03 (1.1%).

2-Thio-1,3-di(4-chlorophenyl)-5-(4-methylphenyl)-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4l: Pale yellowish solid; anal. cal. for $C_{31}H_{20}Cl_2N_4OS_2$: C, 62.10; H, 3.36; N, 9.35; S, 10.69%. Found C, 62.03; H, 3.80; N, 9.22%.IR (KBr, cm^{-1}): 1472,1599, 1720, 3309, 3113. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 2.3(3H, s, CH_3), 5.2 (1H, s, CH), 7.2-7.8 (16H, m, Ar-H).^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm: 23.2, 56.4, 128.2, 129.3, 129.6, 134.2, 166.8, 176.2. Mass (m/z): 598.05 (100%), 599.04 (1.6%).

2-Thio-1,3-di(4-chlorophenyl)-5-(4-methoxyphenyl) -benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4m: White solid; anal. cal. for $C_{31}H_{20}Cl_2N_4O_2S_2$: C, 60.49; H, 3.28; N, 9.10; S, 10.42%. found C, 60.88; H, 3.12; N, 9.27%. IR (KBr, cm^{-1}): 1485, 1681, 2976, 3045. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 3.9 (3H, s, OCH_3), 5.6 (1H, s, CH), 7.2-7.8(16H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm): 43.8, 56.2, 128.2, 129.4, 138.1, 167.8, 180.2. Mass (m/z): 614.04 (100%), 615.04 (1.0%).

2-Thio-1,3-di(2-nitrophenyl)-5-(4-chlorophenyl)-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4n: Yellowish solid; anal. cal. for $C_{30}H_{17}ClN_6O_5S_2$: C, 56.21; H, 2.67; N, 13.11; S, 10.00%. found C, 56.01; H, 2.72; N, 13.47% . IR (KBr, cm^{-1}): 1433, 1682, 2970, 3013. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 5.2 (1H, s, CH), 7.1-7.6 (16H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm: 55.2, 127.6, 128.2, 132.1, 136.1, 167.8, 177.8. Mass (m/z): 640.04 (100%), 641.04 (1.5%).

2-Thio-1,3-di(4-methylphenyl)-5-(4-methylphenyl) -benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4o: Light yellowish solid; anal. cal. for $C_{33}H_{26}N_4OS_2$: C, 70.94; H, 4.69; N, 10.03; S, 11.48% Found C, 70.81; H, 4.52; N, 10.18%. IR (KBr, cm^{-1}): 1512, 1678, 2967, 3044. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 2.32 (9H, s, $3CH_3$) 5.8 (1H, s, CH), 6.8-7.7 (16H, m, Ar-H). ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm: 23.2, 55.1, 128.3, 129.2, 132.1, 137.1, 166.8, 174.6. Mass (m/z): 558.15 (100%), 559.15 (2.7%).

2-Thio-1,3-di(2-methylphenyl)-5-(4-methoxyp henyl)-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one, 4p: Reddish yellow solid; anal. cal. for $C_{33}H_{26}N_4O_2S_2$: C, 68.97; H, 4.56; N, 9.75; S, 11.16% Found C, 68.56; H, 4.81; N, 11.23%. IR (KBr, cm^{-1}):1512, 1668, 2924, 3032, 3119. ^{1}H-NMR (500 MHz, DMSO-d_6, δ/ppm): 2.3 (6H, s, $2CH_3$), 3.8 (3H, s, OCH_3), 5.1 (1H, s, CH), 6.7-7.8 (16H, m, Ar-H),8.2 (2H, s, 2NH), ^{13}C-NMR (125 MHz, DMSO-d_6, δ/ppm: 23.1, 43.8, 55.6, 128.6, 129.4, 136.7, 167.8, 174.6. Mass (m/z): 574.15 (100%), 575.15 (1.6%).

Conclusion

The synthesis of 2-thio-5-arylbenzo[4,5] thiazolopyrimido[5,4-d]pyrimidin-4-one derivatives (**4**) under aqueous medium by condensation of thiobarbituric acids (**1**), 2-aminobenzothiazole (**2**) and aldehydes (**3**) using metal-proline as catalyst has been developed. The yields were found to be high and the reaction takes place by domino Knoevenagel, Michael

and intramolecular cyclization approach which is found to be simple and environment friendly.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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