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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

efficient and environmentally benign catalyst for the various organic reactions[14-16]. Due to their unique physiochemical properties, ionic liquids have become excellent candidates for a broad range of applications. Their solvation capacity towards a variety of materials, negligible vapour pressure, high thermal stabilities and wide liquid range indicate a great potential for replacement of volatile organic solvents. There are numbers of reports in which ionic liquids act as calalysts for chemical reactions. Most of these reactions are based on their possible use as "greener" alternatives to volatile organic solvents as well as their use to improve the reaction time, selectivity and yield of the products.

Metal-mediated reactions in aqueous media have been found to be widely used in organic synthesis due to the environmentally benign conditions. Such organometallic type reactions in aqueous media have many advantages. The most general worth in changing organometallic reaction from strictly anhydrous organic solvents to aqueous media is the ease of reaction in obviating the need for inflammable anhydrous organic solvents and troublesome inert atmosphere. Furthermore, metal mediated reactions in aqueous media offer a number of advantages over conventional organometallic reaction in organic solvents: (i) there is the practical convenience, and possible environmental benefits, of not having to use inflammable and anhydrous organic solvents; (ii) the tedious task of protection deprotection chemistry for certain functional groups often encountered in organic synthesis may be obviated; (iii) water soluble 'compounds such as carbohydrates can be reacted directly without the need of derivatization; (iv) the regio- and stereochemical outcomes of the reactions may well change from organic to aqueous media and this offers new opportunities in synthesis. Thus metal-mediated reactions in aqueous media have been found to have wide applications in organic synthesis not only in economic aspects but also from the environmental consideration Various metals have been found to be effective in mediating such a reaction.

Our interest on the development of metal-proline complexes as organocatalysts for organic reactions in water medium and in continuation of our studies directed towards the synthesis of fused heterocycles[17-23], prompted us to synthesis a new series of compounds containing benzothiazolopyrimidines fused with pyrimidine ring moiety. For the first time Darbre and Machuqueiro reported the $Zn(proline)_2$ complex as highly enantioselective and competent catalyst for direct aldol reaction in aqueous media[24] and further studies of Zn-proline complex was done by many researchers in the synthesis of Pyrazole[25] and Pyrimidine derivative[26] in different solvents.

In continuation of our ongoing studies on the synthesis of new variants of metal-proline complexes and to investigate the catalytic activities in water medium, here we report the use of metal-proline complexes for one-pot three component reactions for the syntheses of 2-thio-5-arylbenzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one derivatives and the possibility of catalyst recycling. To the best of our knowledge, no reports have revealed the synthesis of these benzothiazolopyrimidines fused with pyrimidine ring moiety using metal-proline as catalyst in water.

Results and Discussion

Chemistry

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. Cd-proline complex gave the highest yield as compared to the other catalysts; the results are summarized in Table I. Complexes were characterized by NMR, IR, and ESI-MS.

X-ray patterns of the prepared metal-proline complexes were recorded at 2Θ = 0-100 range and are shown in Figure 1. The crystalline size of the proline complexes of metals like Cd, Hg, and Pb were found to be 29.19, 28.41and 30.79 nm respectively, which were calculated by using Debye-Scherrer formula. The PXRD pattern of Pb-proline complex was matched with the data card 00-048-1161PDF2, the peaks revealed that the crystal was monoclinic in shape.

The metal-proline complexes on excitation at λ 424 nm gave two excitation wavelengths at 237 and 424

Table I — Metal-proline complexes [a]

Entry	Catalyst (Metal-proline)	Yield [b] (%)	Time [c] (min)
1	Cd	96	48
2	Zn	82	48
3	Hg	73	52
4	Pb	77	56

[a] Reaction condition: metal-acetate (2.5 mmol), L-proline (5.0 mmol), triethyl amine (0.7 mL) and methanol (10.0 mL) at room temperature.
[b] Isolated yields.
[c] Reaction progress monitored by TLC.

nm. The emission spectra were taken on λ_{exc} 424, at the range of 400-750 nm, Filter 450 and Slith Width of 2.5 found emission spectra at 607nm. The emission spectrum for Cd-proline complex was found unchanged after being recovered from the reaction medium. This shows that structure of the catalyst remain unchanged after the reaction. The results of UV and Fluorescence pattern of the prepared metal-proline complexes are shown in Figure 2 and Figure 3, respectively.

For preliminary investigation, selection for catalyst and reaction condition optimization was done with thiobarbituric acid **1a** (1.0 mmol), 2-aminobenzothiazole **2** (1.0 mmol) and tolualdehyde **3a** (1.0 mmol) in presence of the catalyst. Different catalysts and their effects on the reaction are tabulated (Table II). The reaction was found to be very fast and precipitate was formed as soon as the catalyst was added. For optimization of the reaction condition, first the reaction was stirred at room temperature and in refluxing condition without any catalyst to establish the efficiency of the catalyst, it was found that no desired product was obtained (Table II, entries 1 and 2).

To optimize the reaction time and the amount of catalyst used, the reaction was carried out in the presence of different amount of catalysts (Table II). First, the effects of the concentration of catalyst for Zn-proline complex in different conditions were studied (Table II, entries 3-10). It was found that the use of zinc-proline catalyst (10 mol%) gave the product at 92% yield in 35 min at room temperature (Table II, entry 5). Similarly, the effects of the concentration of various catalysts in different conditions were also studied (Table II, entries 11-35). In all the cases, it was found that the concentration of catalysts were found to be good in 10 mol% at room temperature (Table II, entries 13, 21 and 30). Thus, from the results, 10 mol% of Zinc-proline catalyst at room temperature was used in presence of water for direct three component reactions for the ongoing research work.

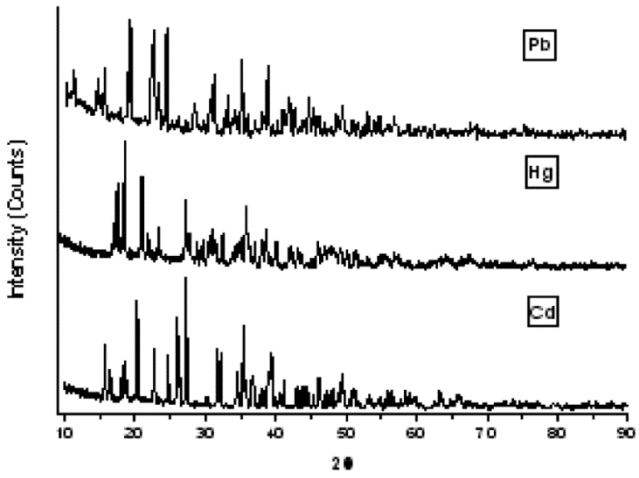


Figure 1 — PXRD pattern of metal-proline complexes

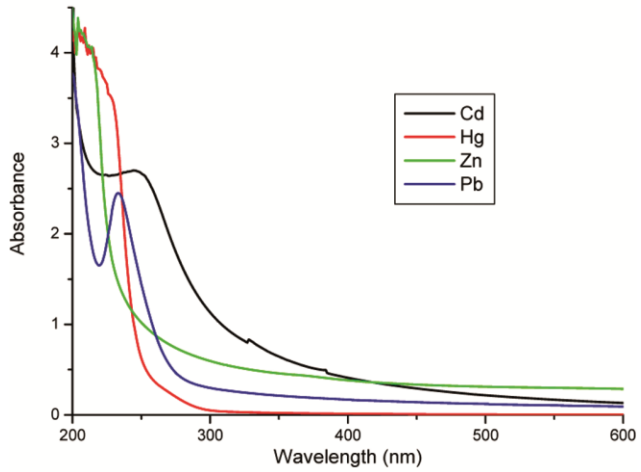


Figure 2 — UV visible spectra of metal-proline complexes

Catalytic activity and the reaction

The effect of the concentration of catalyst for metal-proline complexes in different substrates were studied; mainly the concentrations of catalysts were found to be good in 10 mol%, and the results in effect on yields were shown in Figure 4. Thus we have selected the 10 mol% of catalyst for the reaction.

Thus, encouraged by the results obtained from the optimization conditions, the reactions were further

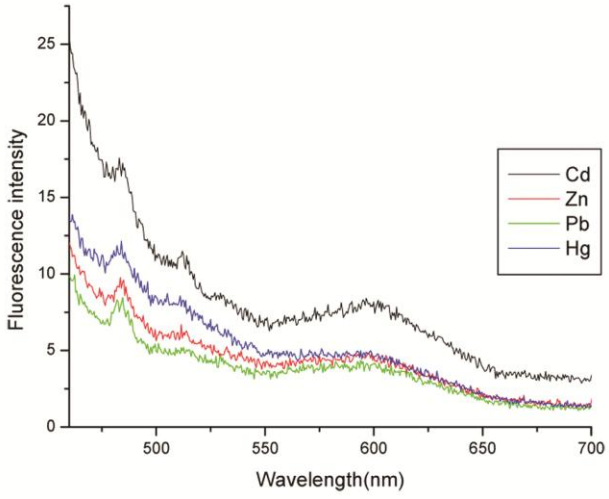
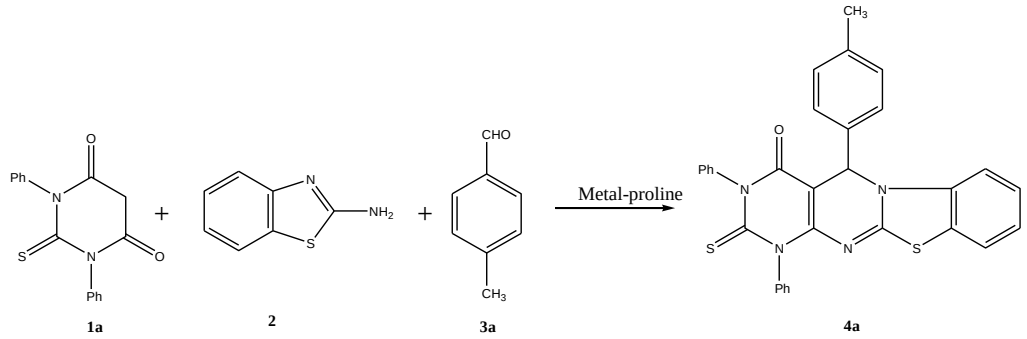


Figure 3 — Fluorescence Spectra of metal-proline complexes (λ_{exc} 247 nm)

Table II — Optimization of reaction condition using different catalysts for the synthesis of 2-thio-5-(4-methylphenyl)-benzo[4,5]thiazolopyrimido[5,4-d]pyrimidin-4-one (**4a**) in water[a]



Entry	Catalyst (mol%)	Temperature (°C)	Time (min)[b]	Yield of **4a** (%)[c]
1	No catalyst	RT[d]	180	NP[e]
2	No catalyst	100	180	NP
3	Zinc-proline (2.0)	RT	20	68
4	Zinc-proline (5.0)	RT	25	78
5	Zinc-proline (10.0)	RT	15	92
6	Zinc-proline (15.0)	RT	40	80
7	Zinc-proline (2.0)	60	22	43
8	Zinc-proline (5.0)	60	35	25
9	Zinc-proline (10.0)	60	20	62
10	Zinc-proline (15.0)	60	35	45
11	Cadmium-proline (2.0)	RT	30	45
12	Cadmium-proline (5.0)	RT	25	56
13	Cadmium-proline (10.0)	RT	20	75
14	Cadmium-proline (15.0)	RT	30	62
15	Cadmium-proline (2.0)	60	30	35
16	Cadmium-proline (5.0)	60	40	42
17	Cadmium-proline (10.0)	60	30	48
18	Cadmium-proline (15.0)	60	30	30
19	Mercury-proline (2.0)	RT	20	48
20	Mercury-proline (5.0)	RT	25	56
21	Mercury -proline (10.0)	RT	15	72
22	Mercury-proline (15.0)	RT	20	68
23	Mercury-proline (2.0)	60	25	24
24	Mercury -proline (5.0)	60	15	44
25	Mercury-proline (10.0)	60	25	55
26	Mercury -proline (15.0)	60	15	50
28	Lead-proline (2.0)	RT	20	45
29	Lead-proline (5.0)	RT	25	67
30	Lead-proline (10.0)	RT	15	82
31	Lead-proline (15.0)	RT	40	60
32	Lead-proline (2.0)	60	22	20
33	Lead-proline (5.0)	60	35	28
34	Lead-proline (10.0)	60	20	54
35	Lead-proline (15.0)	60	35	52

[a] Reaction condition: metal-proline complex (10 mol%), thiobarbituric acid (1 mmol), 2-aminobenzothiazole (1 mmol) and tolualdehyde (1.0 mmol) in 5 mL water at room temperature; [b] Monitored by TLC; [b] Isolated yields; [c] Room temperature; [d] No desired product.

conducted with different thiobarbituric acids using a wide range of aromatic aldehydes under similar conditions using 10 mol% of Zinc-proline complex as catalyst in aqueous medium as given in Table III.

Experimental Section

Melting points were determined with a Buchi Melting point M-560 apparatus and are uncorrected. IR Spectra were recorded in the solid state in the form

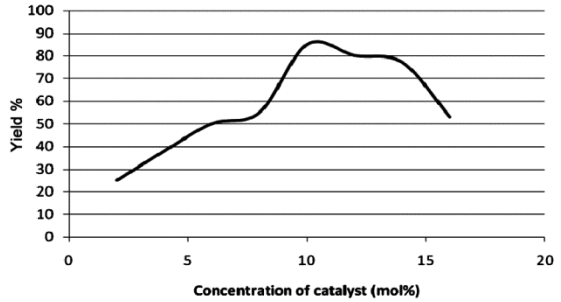
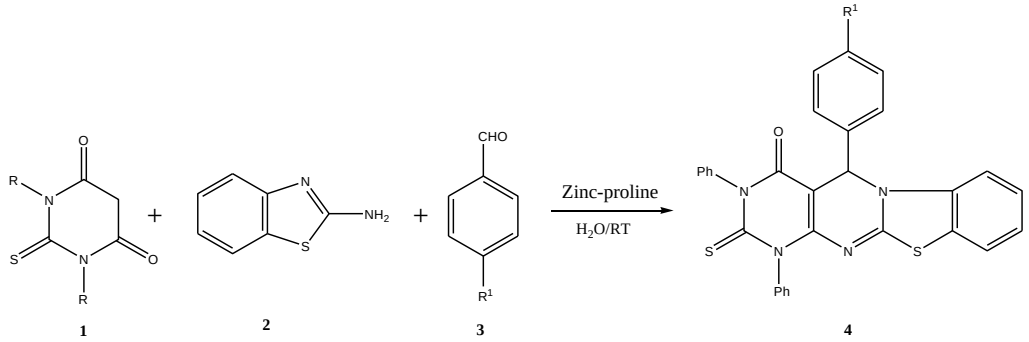


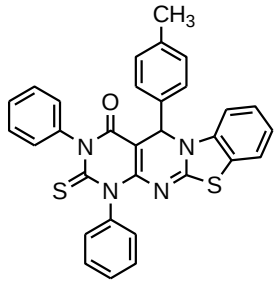
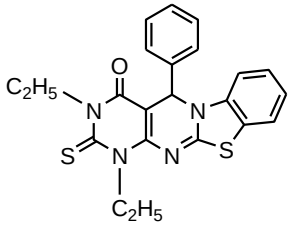
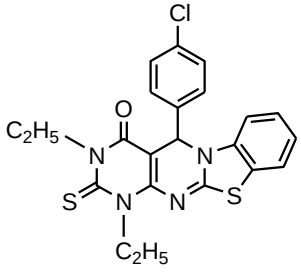
Figure 4 — Effect of concentration of catalyst on yield

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]

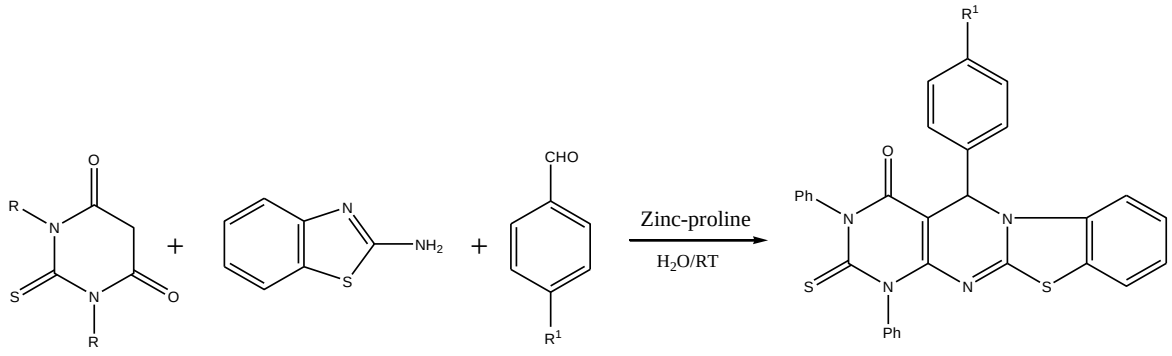


1 **2** **3** **4**

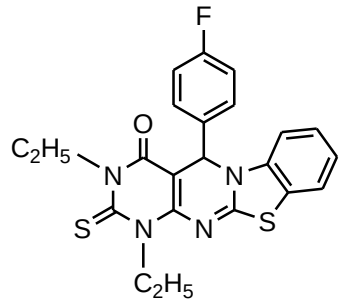
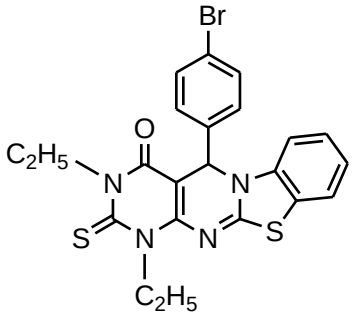
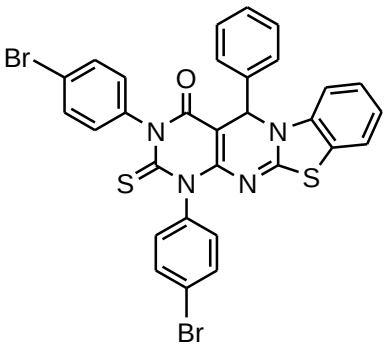
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
1	R=Ph	R^1=CH_3	 **4a**	15	92
2	R=Et	R^1=H	 **4b**	20	82
3	R=Et	R^1=4-Cl	 **4c**	30	88

(*Contd*.)

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

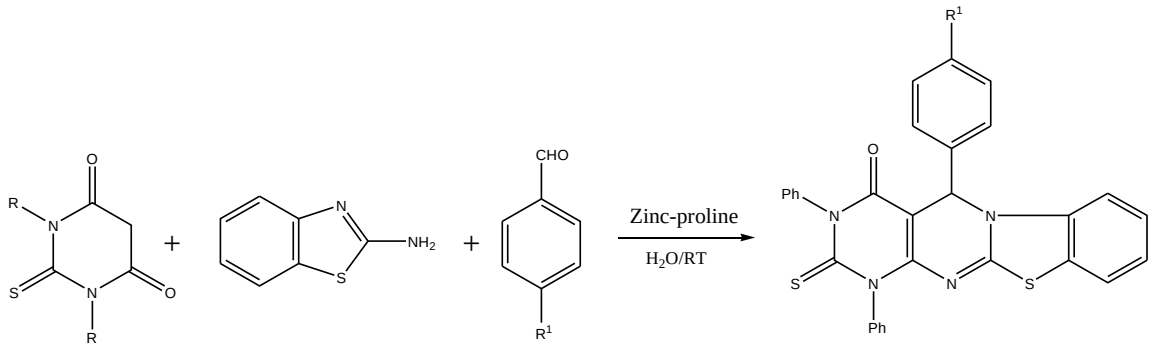


1 **2** **3** **4**

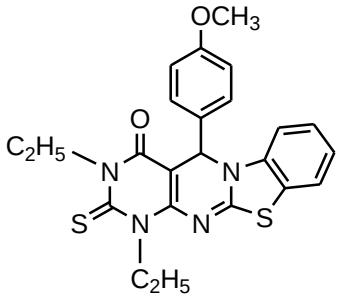
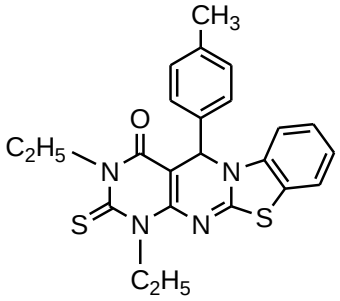
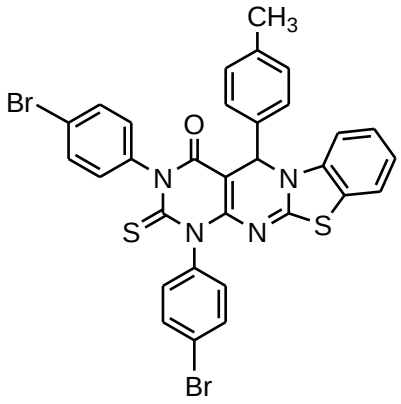
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
4	R=Et	R^1=F	 **4d**	25	78
5	R=Et	R^1=Br	 **4e**	28	88
6	R=4-BrC_6H_4	R^1=H	 **4f**	30	86

(*Contd*.)

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

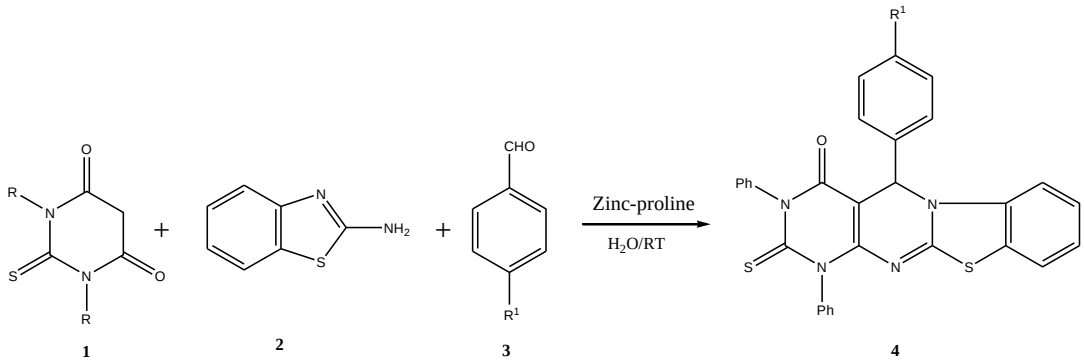


1 **2** **3** **4**

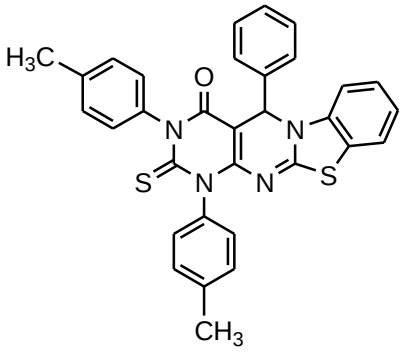
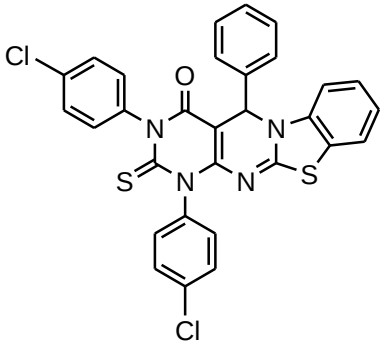
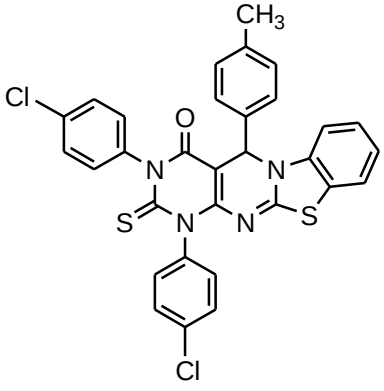
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
7	R=Et	R^1=OCH_3	 **4g**	25	83
8	R=Et	R^1=CH_3	 **4h**	20	85
9	R=4-BrC_6H_4	R^1=CH_3	 4i	55	74

(*Contd*.)

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

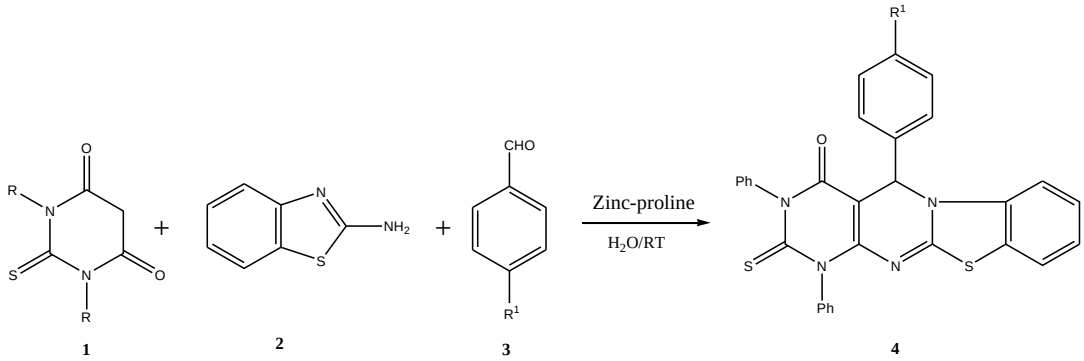


1 **2** **3** **4**

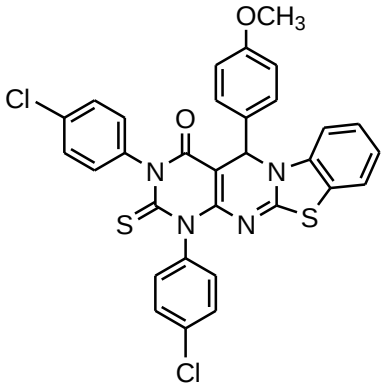
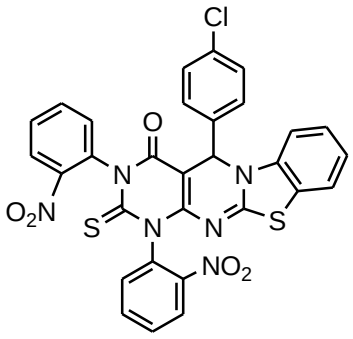
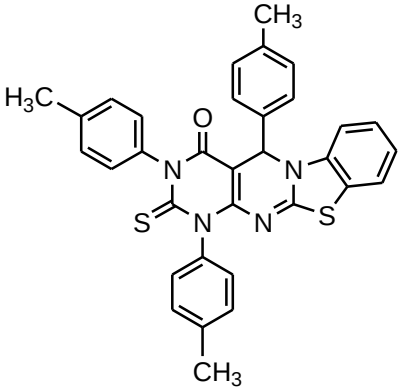
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
10	R=4-$CH_3C_6H_4$	R^1=H	 **4j**	45	78
11	R=4-ClC_6H_4	R^1=H	 **4k**	35	75
12	R=4-ClC_6H_4	R^1=CH_3	 **4l**	40	72

(*Contd*.)

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

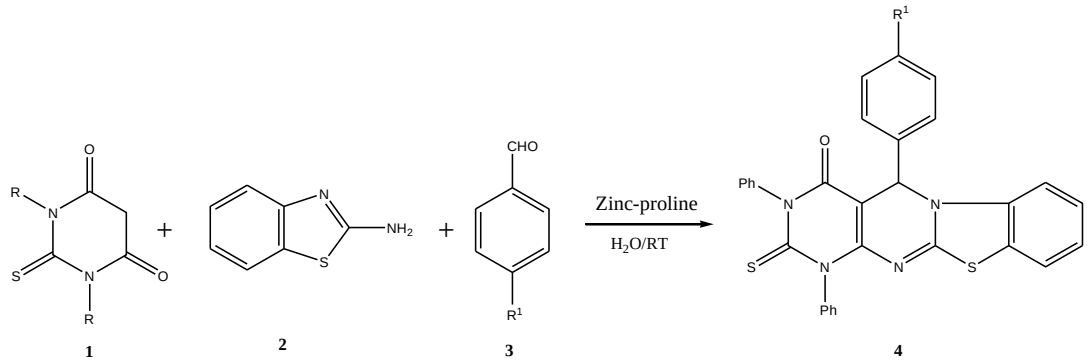


1 **2** **3** **4**

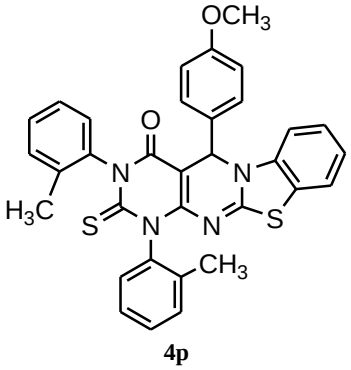
Entry	**1**	**3**	**4**	Reaction time (min)	Yield [b] (%)
13	R=4-ClC_6H_4	R^1=OCH_3	 **4m**	30	80
14	R=2-$NO_2C_6H_4$	R^1=Cl	 **4n**	20	82
15	R=4-$CH_3C_6H_4$	R^1=CH_3	 **4o**	40	74

(*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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