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CONVENIENT AND EFFICIENT SYNTHESIS OF SOME NOVEL FUSED THIENO PYRIMIDINES USING GEWALD'S REACTION

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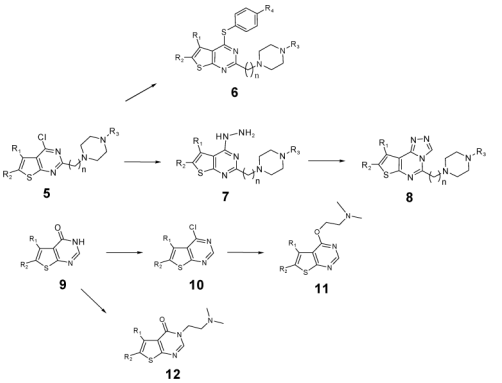
GRAPHICAL ABSTRACT



Abstract *Several functionalized thienopyrimidines were synthesized by a facile synthetic method, which includes Gewald's reaction, and were characterized by spectral and analytical data. These functionalized thienopyrimidines were converted to various new chemical entities of biological importance, such as 2-piperazinymethyl thienopyrimidines (**6, 8**), 4-dimethylaminoethoxy thienopyrimidines (**11**), and 3-dimethylaminoethyl thienopyrimidines (**12**). All the compounds thus synthesized were screened for their invitro biological activities. Some of the compounds displayed promising serotonin 5-HT$_6$ receptor antagonist activities.*

Keywords Cyclizations; fused thiophenes; Gewald reaction; thieno pyrimidines

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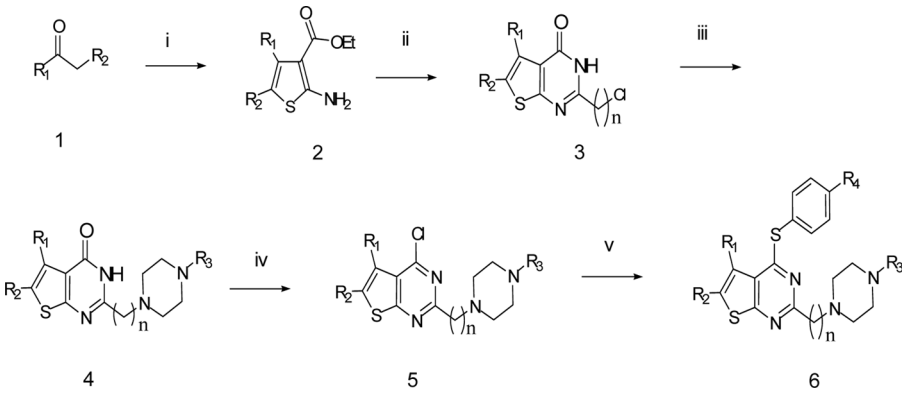
INTRODUCTION

The chemistry of pyrimidine and its derivatives has been studied for more than a century because of their diverse biological activities.[1–4] They possess antitumor,[5,6] antihypertensive,[7] and anti-inflammatory[8] activities. Thieno pyrimidines, formed by the fusion of thiophene moiety with pyrimidine ring have been reported to be chemotherapeutically more active.[9] The derivatives of the thienopyrimidine system, which are well-known bioisosteres of quinazolines, are of great importance because of their remarkable biological properties. For example, some 2-alkyl substituted thienopyrimidinones show significant antifungal and antibacterial activities,[10–13] whereas others exhibited good anticonvulsant and angiotensin or H1 receptor antagonistic activities.[14–16] The chemistry of thienopyrimidinones has also received great attention because their starting materials, 2-amino-3-carboxythiophenes, can be conveniently synthesized. Though there are many literature methods for the synthesis of thienopyrimidinones,[17–19] synthesis of various thiophenes and fused thiophenes by the Gewald method[20–23] followed by their reaction with nitriles to yield thienopyrimidinones was found to be very attractive. Recently, we reported substituted 3-piperazinylmethylindole derivatives as highly potent, safe, and orally bioavailable serotonin 5-HT_6 receptor ligands. To explore the structure–activity relationship (SAR) scope and to see the effect of scaffold hopping on the binding affinities, a series of thienopyrimidine derivatives were designed, synthesized, and evaluated. The preliminary molecular modeling studies were carried out using CS ChemOffice software, which showed that the desired pharmacophoric arrangement required for serotonin 5-HT_6 receptor ligands was maintained in the proposed compounds. In vitro studies were carried out by radio-ligand binding assay.

RESULTS AND CONCLUSIONS

Gewald's reaction of substituted ketones with ethyl cyanoacetate and sulfur in morpholine and ethanol gave the intermediates **2,** which were confirmed by mass and ^{1}H NMR. The reaction of intermediates **2** with chloro acetonitrile or acrylonitrile and dry hydrogen chloride gas in 1,4-dioxane solvent at 50 °C gave the cyclized chloroalkyl derivative **3,** which was confirmed by the presence of pyrimidine NH proton at 10 to 12.5 ppm apart from mass. The product, thus obtained, was reacted with N-alkyl piperazines in the presence of triethylamine in dimethylformamide solvent at 5–10 °C to obtain the intermediate **4**. The latter compounds were converted to the corresponding 4-chloro derivatives **5** by the reaction of intermediates **4** with phosphorus oxychloride in the presence of triethylamine at reflux temperature. The formation of intermediate **5** was confirmed by mass and the absence of pyrimidine NH proton in ^{1}H NMR. The 4-chloropyrimidine derivatives **5**, thus obtained, were further reacted with various substituted/unsubstituted thiophenols in acetone in the presence of potassium carbonate to obtain series 1, compounds **6** (Scheme 1), which were confirmed by mass and the presence of aromatic protons due to the presence of substituted phenyl mercapto group in proton NMR.

Chloro compound **5** was reacted with hydrazine hydrate to give the compound **7**. The compound **7** was cyclized with formamide to obtain series 2 compounds **8** (Scheme 2), which were confirmed by mass and ^{1}H NMR. Especially the formation

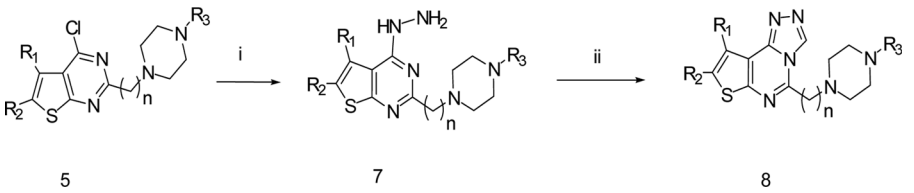


Scheme 1. Reagents and conditions: (i) morpholine, sulfur, absolute ethanol, ethyl cyanoacetate, 60 °C; (ii) chloroacetonitrile/acrylonitrile, HCl gas passing, 1,4-dioxane, 50 °C; (iii) DMF, substituted piperazines, TEA, 10 °C to rt; (iv) $POCl_3$, TEA, reflux; (v) K_2CO_3, substituted thiophenols, acetone, reflux. R_1, R_2: ethyl, methyl, or together form a five- or six-membered carbocyclic ring; R_3: methyl, ethyl; R_4: hydrogen, methyl, methoxy, chloro, and fluoro; n: 1, 2.

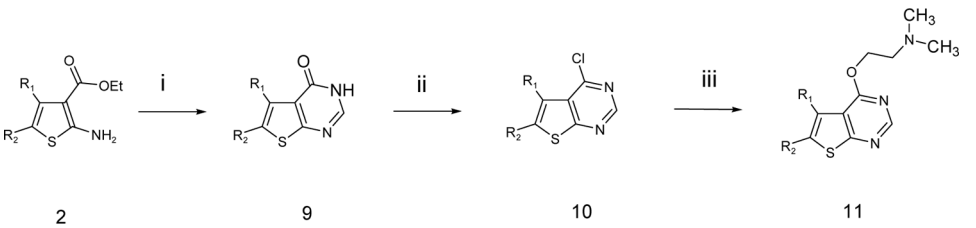
of 8 was confirmed by the appearance of an aromatic proton at a chemical shift value of 9.38 ppm due to the aromatic CH proton at position 3 on the triazole ring.

The compound **2** was treated with formamide to give the compound **9**. The formation of the product was confirmed by mass and ^{1}H NMR. The appearance of a peak at the chemical shift value of 8.75 ppm due to aromatic CH proton at position 2 of the pyrimidine ring confirmed the formation of the product. The compound **9** was further treated with phosphorous oxychloride to obtain compound **10**. The compound **10** was treated with dimethylamino ethanol in the presence of a base to obtain series 3 compounds **11** (Scheme 3). The formation of the product was once again confirmed by the mass and proton NMR. The appearance of an additional 10 protons in the upfield due to the introduction of the dimethylaminoethyl grouping confirms the formation of the product **11**.

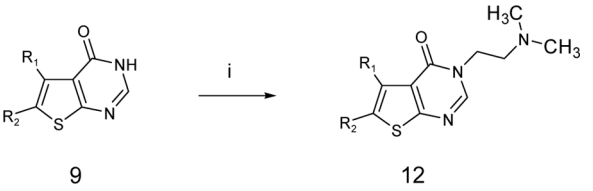
The compound **9** was treated with N,N-dimethylaminoethylchloride to obtain series 4 compounds **12** (Scheme 4). The formation of the product was confirmed by infrared (IR), ^{1}H NMR, and mass spectral data. The presence of an absorption peak at 1672 cm^{-1} in IR confirms the pyrimidin-4-one grouping. The appearance of an additional 10 protons in the upfield in ^{1}H NMR due to dimethylaminoethyl group



Scheme 2. Reagents and conditions: (i) hydrazine hydrate, ethanol, 100 °C; (ii) trimethylorthformate, reflux. R_1, R_2: ethyl, methyl, together form a five- or six-membered carbocyclic ring, R_3: methyl, ethyl; n: 1, 2.



Scheme 3. Reagents and conditions: (i) formamide, 170 °C; (ii) $POCl_3$, TEA, 100 °C; (iii) N,N-dimethylaminoethanol, Na, toluene, 110 °C. R_1, R_2: ethyl, methyl, or together form a five- or six-membered carbocyclic ring; R_3: methyl, ethyl; n: 1, 2.



Scheme 4. Reagents and conditions: (i) N,N-dimethylamino ethylchloride hydrochloride, K_2CO_3, acetone, 60 °C. R_1, R_2: ethyl, methyl, or together form a five- or six-membered carbocyclic ring.

confirms the introduction of the group at position 3 of the pyrimidine ring. The binding affinities of thienopyrimidine derivatives were found to be moderate in the micromolar range. Further structural modifications are under way to achieve the binding affinity at the desired levels in the nanomolar range. The major aim of this article was to report the facile methods leading to the synthesis of novel heterocycles in good to excellent yields.

EXPERIMENTAL

Melting points were obtained on a B-540 Buchi melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 400-MHz spectrometer with tetramethylsilane (TMS) as the internal standard in deutirated chlorofom or dimethylsulfoxide (DMSO-d_6). Element analysis was performed on a Vario EL (Elementar, Germany) instrument. IR spectra were recorded on a Fourier transform (FT–IR)—(Shimadzu, model IR Prestige-21) spectrophotometer. Chromatography refers to column chromatography performed using 100- to 200-mesh silica gel executed under nitrogen pressure (flash chromatography) conditions.

Ethyl 2-Amino-4,5,6,7-tetrahydro Benzothiophene-3-carboxylate (2)

Morpholine (20.4 g, 0.234 mol) was added dropwise to a mixture of cyclohexanone (10.0 g, 0.102 mol), ethyl cyanoacetate (11.53 g, 0.102 mol), and sulfur (2.9 g, 0.094 mol) in 30 mL of rectified spirit at ambient temperature in 10 min. The reaction was exothermic, the mass temperature shot up to 60 °C, and a clear solution was

obtained. It was filtered from suspended solids, and the clear solution was cooled to 0–5 °C, 30 min, and the solids separated. The product was filtered, washed well with chilled rectified spirit (20 mL), and sucked dry, and finally the cake was dried in an oven at 50 °C for 2 h to obtain 15.1 g of the title product. Melting point: 110–112 °C, purity (HPLC) = 99%. Mother liquors were diluted with ice water, and the isolated second crop was washed with chilled rectified spirit and dried to obtain the product in an overall yield of 85.0% on sulfur. IR (cm^{-1}): 3414, 3294, 1643, 1601, 1493, 1369, 1264, 1163, 1034, 781; mass (m/z): 226.30 $(M + H)^+$; % purity (HPLC) = 99.0; ^1H NMR (ppm): 1.34 (3H, t), 2.30–2.69 (4H, m), 2.70–2.73 (2H, m), 2.79–2.83 (2H, m), 4.21–4.26 (2H, m), 5.84 (2H, bs).

2-Chloromethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (3, n = 1)

Ethyl-2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate (2.25 g, 0.01 mol) and chloroacetonitrile (1.0 g, 0.012 mol) were taken in 1,4-dioxane solvent, heated to 50 °C, and passed with dry hydrogen chloride gas until the starting material was absent in 3 h. Then the solvent was removed under vacuum. The residual mass was triturated with hexane, and solids separated as fine powder. The product was filtered, washed with hexane, and air dried to obtain 1.72 g of the compound, the yield being 67.6%. mass (m/z): 255.73 $(M + H)^+$; ^1H NMR (ppm): 1.80–1.83 (4H, m), 2.89 (2H, m), 2.92–2.99 (2H, m), 3.89–3.93 (2H, t), 12.12 (1H, bs).

2-[(4-Methylpiperazin-1-yl) methyl]-5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3-d]pyrimidin-4-one (4, n = 1)

N-Methylpiperazine (120 mg, 1.21 mmol) was added to a mixture of 2-chloromethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (0.248 g, 0.97 mmol), dimethyl formamide (5 mL), and triethylamine (0.5 mL) at 5–10 °C, and the reaction mass reached ambient temperature under stirring. The reaction mass was further stirred at room temperature until the reaction was complete in 2 h. Then the mass was quenched in ice water and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine solution (2 × 20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residual mass was purified by column chromatography, eluent system being 1% triethylamine in ethylacetate, to obtain 0.21 g of the title product. The yield was 71.3%.

Melting range (°C): 218.5–223.1, IR spectra (cm^{-1}): 2938, 2792, 1655, 1588, 1445, 1288, 1198, 1138, 1010, 826; mass (m/z): 319.3 $(M + H)^+$; % purity (HPLC) = 98.36, ^1H NMR (ppm): 1.83–1.89 (4H, m), 2.31 (3H, s), 2.4–2.7 (8H, m), 2.75–2.78 (2H, m), 2.99–3.02 (2H, m), 3.53 (2H, s), 9.82 (1H, s).

2-Chloroethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (3, n = 2)

Ethyl-2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate (18.6 g, 0.083 mol) and acrylonitrile (7.7 g, 0.145 mol) were dissolved in 1,4-dioxane (100 mL),

and dry hydrogen chloride gas was passed at 50 °C slowly until the reaction was complete in 3 h, the progress of the reaction being monitored by thin-layer chromatography (TLC). After completion of the reaction, nitrogen gas was flushed through the mass to remove the excess hydrogen chloride gas, and then solvent was removed under reduced pressure. The solids that separated were triturated with hexane and filtered, and the product was washed with fresh hexane to obtain 19.2 g product. The yield was 86.5%. % Purity (HPLC) = 95.48; mass (m/z): 269.1 $(M+H)^+$; ^{1}H NMR (ppm): 1.83–1.86 (4H, m), 2.87 (2H, m), 2.96–2.98 (2H, m), 3.11–3.15 (2H, m) 3.91–3.97 (2H, t), 12.05 (1H, bs).

2-[(4-Methylpiperazin-1-yl)ethyl]-5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3-d]pyrimidin-4-one (4, n = 2)

N-Methylpiperazine (120 mg, 1.21 mmol) was added to a mixture of 2-chloroethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (0.248 g, 0.92 mmol), dimethyl formamide (5 mL), and triethylamine (0.5 mL) at 5–10 °C, and the reaction mass reached ambient temperature under stirring. The reaction mass was further stirred at room temperature until the reaction was complete in 2 h. The progress of the reaction was followed by TLC. Then the mass was quenched in ice water and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine solution (2 × 20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum, and the residual mass was purified by column chromatography. IR (cm^{-1}): 2938, 2792, 1665, 1594, 1449, 1291, 1166, 1012, 921, 626; mass (m/z): 333.4 $(M+H)^+$; % purity (HPLC) = 97.03; ^{1}H NMR (ppm): 1.82–1.88 (4H, m), 2.34 (3H, s), 2.5–2.85 (14H, m), 2.98–2.99 (2H, m), 12.5 (1H, bs).

4-Chloro-2-[(4-methylpiperazin-1-yl)methyl]-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3-d]pyrimidine (5)

Triethylamine (3.16 g, 31.28 mmol) was slowly added to a mixture of 2-[(4-methylpiperazin-1-yl)methyl]-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (1.9 g, 5.97 mmol) and phosphorous oxychloride (10 g, 65.1 mmol), and the mass was heated at reflux temperature until the reaction was complete in 2 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mass was quenched in ice water. The pH of the solution was adjusted to 12.0 with aqueous sodium carbonate solution, and the product was extracted with 3 × 30 mL of ethyl acetate. The combined organic layer was washed with brine solution (2 × 20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residual mass was purified by column chromatography, the eluent system being 1% triethylamine in ethylacetate. Weight of the product is 1.08 g, purity (HPLC) = 94.0% yield = 53.7%. IR (cm^{-1}): 3401, 2939, 1673, 1564, 1484, 1129, 1013, 843, 753, 662; mass (m/z): 337.88 $(M+H)^+$; ^{1}H NMR (ppm): 1.83–1.94 (4H, m), 2.22 (3H, s), 2.25–2.39 (8H, m), 2.81–2.84 (2H, m), 3.16–3.19 (2H, m), 3.55 (2H, s).

2-[(4-Methylpiperazin-1-yl)methyl]-4-(phenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6a)

4-Chloro-2-[(4-methylpiperazin-1-yl)methyl]-5,6,7,8-tetrahydrobenzo[4,5]thieno-[2,3-d]pyrimidine (1.0 g, 2.97 mmol), thiophenol (0.393 g, 3.57 mmol), and anhydrous potassium carbonate (0.616 g, 4.46 mmol) were taken in acetone (10 mL) and refluxed under a nitrogen blanket until completion of the reaction. The progress of the reaction was monitored by TLC. After refluxing for a period of 6 h, the solvent was removed under reduced pressure. The residual mass was suspended in 10 mL water, and the product was extracted with 3×30 mL of ethyl acetate. The combined organic layer was washed with brine solution (2×10 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residual mass was purified by column chromatography to obtain 0.77 g of the title product, the yield being 63.2%.

Melting range (°C) 100.6–107.5; IR spectra (cm^{-1}): 2932, 2783, 1559, 1492, 1294, 1124, 1017, 743; mass (m/z): 411.3 $(M+H)^+$; ^1H NMR (ppm): 1.85–1.96 (4H, m), 2.26 (3H, s), 2.28–2.42 (8H, m), 2.84–2.86 (2H, m), 3.14–3.17 (2H, m), 3.6 (2H, s), 7.4–7.44 (3H, m), 7.55–7.58 (2H, m). Anal. calcd. for $C_{22}H_{26}N_4S_2$: C, 64.35; H, 6.38; N, 13.64; S, 15.62. Found: C, 64.29; H, 6.34; N, 13.53; S, 15.61%.

5-Ethyl-6-methyl-2-[2-(4-ethylpiperazin-1-yl)methyl]-4-phenylthio-thieno[2,3-d]pyrimidine (6b)

IR spectra (cm^{-1}): 2968, 2932, 2812, 1644, 1487, 1303, 1143, 835, 748; mass (m/z): 413.3 $(M+H)^+$; ^1H NMR (ppm): 1.06–1.09 (3H, t, $J = 7.2$ Hz), 1.29 – 1.33 (3H, t, $J = 7.48$ Hz), 2.35–2.45 (10H, m), 2.5 (3H, s), 3.06–3.12 (2H, q, $J = 7.48$ Hz), 3.61 (2H, s), 7.41–7.44 (3H, m), 7.58–7.60 (2H, m). Anal. calcd. for $C_{22}H_{28}N_4S_2$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 64.12; H, 6.83; N, 13.64; S, 15.58%.

5-Ethyl-6-methyl-2-[2-(4-ethylpiperazin-1-yl)methyl]-4-(4-methoxy Phenyl Thio)thieno[2,3-d]pyrimidine (6c)

IR spectra (cm^{-1}): 2966, 2933, 2807, 1591, 1486, 1299, 1249, 1143, 826; mass (m/z): 443.5$(M+H)^+$; ^1H NMR (ppm): 1.06–1.1 (3H, t, $J = 7.28$ Hz), 1.28–1.32 (3H, t, $J = 7.44$ Hz), 2.4–2.49 (8H, m), 2.5 (3H, s), 2.85–2.95 (2H, m), 3.05–3.11 (2H, q), 3.62 (2H, s), 3.86 (3H, s), 6.94–6.97 (2H, m), 7.47–7.51 (2H, m). Anal. calcd. for $C_{23}H_{30}N_4OS_2$: C, 62.41; H, 6.83; N, 12.66; O, 3.61; S, 14.49. Found: C, 62.31; H, 6.85; N, 12.75; O, 3.58; S, 14.45%.

2-[2-(4-Methylpiperazin-1-yl)-ethyl]-4-(4-methoxyphenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6d)

IR spectra (cm^{-1}): 2935, 2837, 1591, 1488, 1416, 1291, 1249, 1130, 834; mass (m/z): 455.2 $(M+H)^+$; ^1H NMR (ppm): 1.92–1.93 (2H, b), 2.0 (2H, s), 2.3 (3H, s), 2.4–2.62 (8H, m), 2.64–2.68 (2H, t, $J = 7.36$ Hz), 2.84–2.85 (2H, m), 2.9–2.93 (2H, t, $J = 7.64$ Hz), 3.13–3.15 (2H, m), 3.86 (3H, s), 6.94–6.98 (2H, m), 7.43–7.46

(2H, m). Anal. calcd. for $C_{24}H_{30}N_4OS_2$: C, 63.40; H, 6.65; N, 12.32; O, 3.52; S, 14.10. Found: C, 62.99; H, 6.62; N, 11.99; O, 3.50; S, 13.99%.

5-Ethyl-6-methyl-2-[2-(4-methylpiperazin-1-yl)methyl]-4-(4-methoxy phenyl thio)thieno[2,3-d]pyrimidine (6e)

IR spectra (cm^{-1}): 2964, 2933, 2794, 1591, 1485, 1290, 1248, 1143, 1031, 825; mass (m/z): 429.1 $(M+H)^+$; ^1H NMR (ppm): 1.28–1.32 (3H, t, $J=7.48$), 2.2 (3H, s), 2.21–2.49 (6H, m), 2.5 (3H, s), 2.91–2.96 (2H, m), 3.05 (2H, q), 3.62 (2H, s), 3.88 (3H, s), 6.94–6.97 (2H, m), 7.47–7.51 (2H m). Anal. calcd. for $C_{22}H_{28}N_4OS_2$: C, 61.65; H, 6.58; N, 13.07; O, 3.73; S, 14.96. Found: C, 61.98; H, 6.53; N, 12.99; O, 3.02; S, 14.86%.

2-[2-(4-Ethylpiperazin-1-yl)-ethyl]-4-(4-methoxyphenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6f)

IR spectra (cm^{-1}): 2935, 2808, 1591, 1488, 1416, 1310, 1248, 1129, 834; mass (m/z): 469.4 $(M+H)^+$; ^1H NMR (ppm): 1.06–1.1 (3H, t), 1.83–1.95 (4H, m), 2.38–2.44 (10H, m), 2.61–2.65 (2H, m), 2.84–2.85 (2H, m), 2.9–2.94 (2H, m), 3.13–3.15 (2H, m), 3.85 (3H, s), 6.93–6.99 (2H, m), 7.43–7.52 (2H, m). Anal. calcd. for $C_{25}H_{32}N_4OS_2$: C, 64.07; H, 6.88; N, 11.95; O, 3.41; S, 13.68. Found: C, 63.95; H, 6.91; N, 11.55; O, 3.52; S, 13.64%.

2-[2-(4-Methylpiperazin-1-yl)-ethyl]-4-phenylthio-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6g)

IR spectra (cm^{-1}): 2937, 2847, 1647, 1489, 1417, 1312, 1130, 835, 753; mass (m/z): 425.1 $(M+H)^+$; ^1H NMR (ppm): 1.92–1.93 (4H, m), 2.31 (3H, s), 2.46–2.48 (6H, m), 2.6–2.63 (2H, m), 2.83–2.86 (2H, m), 2.89–2.93 (2H, m), 3.14–3.16 (4H, m), 7.42–7.44 (3H, m), 7.54–7.56 (2H, m). Anal. calcd. for $C_{23}H_{28}N_4S_2$: C, 65.06; H, 6.65; N, 13.19; S, 15.10. Found: C, 64.92; H, 6.71; N, 12.98; S, 14.98%.

5-Ethyl-6-methyl-2-[2-(4-methylpiperazin-1-yl)methyl]-4-phenylthio-thieno[2,3-d]pyrimidine (6 h)

IR spectra (cm^{-1}): 2965, 2932, 2798, 1648, 1486, 1143, 1012, 835, 748; mass (m/z): 399.2 $(M+H)^+$; ^1H NMR (ppm): 1.29–1.33 (3H, t, $J=7.52$ Hz), 2.26 (3H, s), 2.3–2.5 (8H, b), 2.5 (3H, s), 3.06–3.11 (2H, q, $J=7.48$ Hz), 3.6 (2H, s), 7.42–7.44 (3H, m), 7.57–7.6 (2H, m). Anal. calcd. for $C_{21}H_{26}N_4S_2$: C, 63.28; H, 6.57; N, 14.06; S, 16.09. Found: C, 62.98; H, 6.52; N, 13.94; S, 15.96%.

2-[2-(4-Ethylpiperazin-1-yl)-ethyl]-4-phenylthio-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6i)

IR spectra (cm^{-1}): 2936, 2813, 1488, 1311, 1130, 835, 750; mass (m/z): 439.3 $(M+H)^+$; ^1H NMR (ppm): 1.07–1.11 (3H, t, $J=7.64$ Hz), 1.92–1.98 (4H, m), 2.43–2.48 (8H, m), 2.59–2.63 (2H, m), 2.83–2.85 (2H, m), 2.90–2.94 (2H, m),

3.0–3.1 (2H, m), 3.14–3.16 (2H, m), 7.40–7.44 (3H, m), 7.54–7.56 (2H, m). Anal. calcd. for $C_{24}H_{30}N_4S_2$: C, 65.72; H, 6.89; N, 12.77 S, 14.62. Found: C, 65.01; H, 6.91; N, 12.61; S, 14.54%.

4-(4-Chlorophenylthio)-6-(4-ethylpiperazin-1-ylmethyl)-2,3-dihydro-1H-8-thia-5,7-diazacyclopenta[a]indene (6j)

IR spectra (cm^{-1}): 2942, 2809, 1489, 1477, 1443, 1300, 1092, 821; mass (m/z): 445.4 $(M+H)^+$; ^1H NMR (ppm): 1.09–1.13 (3H, t, $J = 7.52$ Hz), 2.46–2.58 (12H, m), 3.02–3.06 (2H, m), 3.18–3.21 (2H, m), 3.69 (2H, s), 7.39–7.42 (2H, m), 7.51–7.54 (2H, m). Anal. calcd. for $C_{22}H_{25}ClN_4S_2$: C, 59.37; H, 5.66; Cl, 7.97; N, 12.59; S, 14.41. Found: C, 58.96; H, 5.62; Cl, 7.91; N, 12.63; S, 14.42%.

4-(4-Chlorophenylthio)-6-(4-methylpiperazin-1-ylmethyl)-2,3-dihydro-1H-8-thia-5,7-diazacyclopenta[a]indene (6k)

Melting range (°C) 126.9–129.4; IR spectra (cm^{-1}): 2950, 2808, 1484, 1296, 1148, 1011, 818; mass (m/z): 431.4 $(M+H)^+$; ^1H NMR (ppm): 2.41 (3H, s), 2.5–2.7 (10H, m), 3.03–3.06 (2H, m), 3.18–3.22 (2H, m), 3.7 (2H, s), 7.4–7.43 (2H, m), 7.5–7.53 (2H, m). Anal. calcd. for $C_{21}H_{23}ClN_4S_2$: C, 58.52; H, 5.38; Cl, 8.23; N, 13.00; S, 14.88. Found: C, 57.96; H, 5.41; N, 12.99; S, 14.83%.

4-(Phenylthio)-6-(4-methylpiperazin-1-ylmethyl)-2,3-dihydro-1H-8-thia-5,7-diazacyclopenta[a]indene (6l)

Melting range (°C) 105.4–118.1; IR spectra (cm^{-1}): 2950, 2808, 1484, 1296, 1148, 1011, 818; mass (m/z): 397.2 $(M+H)^+$; ^1H NMR (ppm): 2.31 (3H, s), 2.48–2.57 (10H, m), 3.02–3.06 (2H, m), 3.2–3.23 (2H, m), 3.66 (2H, s), 7.39–7.45 (3H, m), 7.56–7.61 (2H, m). Anal. calcd. for $C_{21}H_{24}N_4S_2$: C, 63.60; H, 6.10; N, 14.13; S, 16.17. Found: C, 63.96; H, 5.99; N, 13.86; S, 15.98%.

2-[(4-Ethylpiperazin-1-yl) Methyl]-4-(4-methoxyphenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6m)

IR spectra (cm^{-1}): 2935, 2800, 1590, 1490, 1289, 1245, 1179, 822; mass (m/z): 455.2 $(M+H)^+$; ^1H NMR (ppm): 1.1–1.14 (3H, t, $j = 7.64$ Hz), 1.92–1.93 (4H, m), 2.5–2.62 (10H, m), 2.84–2.86 (2H, m), 3.14–3.16 (2H, m), 3.63 (2H, s), 3.86 (3H, s), 6.94–6.97 (2H, m), 7.46–7.48 (2H, m). Anal. calcd. for $C_{24}H_{30}N_4OS_2$: C, 63.40; H, 6.65; N, 12.32; O, 3.52; S, 14.10. Found: C, 62.98; H, 6.68; N, 12.66; O, 3.48; S, 13.96%.

4-(4-Methoxyphenylthio)-6-(4-methylpiperazin-1-ylmethyl)-2,3-dihydro-1H-8-thia-5,7-diazacyclopenta[a]indene (6n)

Melting range (°C) 117.5–128.8; IR spectra (cm^{-1}): 2932, 2785, 1589, 1489, 1246, 1179, 1019, 822; mass (m/z): 427.2 $(M+H)^+$; ^1H NMR (ppm): 2.37 (3H, s), 2.5–2.58 (10H, m), 3.02–3.06 (2H, m), 3.19–3.23 (2H, m), 3.67 (2H, s), 3.87 (3H,

s), 6.94–6.97 (2H, m), 7.47–7.5 (2H, m). Anal. calcd. for $C_{22}H_{26}N_4OS_2$: C, 61.94; H, 6.14; N, 13.13; O, 3.75; S, 15.03. Found: C, 62.01; H, 6.09; N, 12.99; O, 3.72; S, 15.08%.

2-[(4-Methylpiperazin-1-yl)methyl]-4-(4-methoxyphenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6o)

Melting range (°C) 85.4–92.1, IR spectra (cm^{-1}): 2931, 2783, 1591, 1488, 1294, 1252, 1128, 1016, 828; mass (m/z): 441.3 $(M+H)^+$; ^1H NMR (ppm): 1.21–1.25 (4H, m), 2.4 (3H, s), 2.53 (8H, m), 2.84–2.86 (2H, m), 3.14–3.16 (2H, m), 3.63 (2H, s), 3.86 (3H, s), 6.94–6.98 (2H, m), 7.45–7.48 (2H, m). Anal. calcd. for $C_{23}H_{28}N_4OS_2$: C, 62.70; H, 6.41; N, 12.72; O, 3.63; S, 14.55. Found: C, 62.11; H, 6.44; N, 12.74; O, 3.52; S, 14.51%.

2-[(4-Ethylpiperazin-1-yl)methyl]-4-phenylthio-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6p)

IR spectra (cm^{-1}): 2934, 2808, 1488, 1300, 1162, 1130, 1023, 834, 748; mass (m/z): 424.63 $(M+H)^+$; ^1H NMR (ppm): 1.05–1.09 (3H, t, $J=7.6$ Hz), 1.92–1.96 (4H, m), 2.38–2.44 (10H, m), 2.85–2.86 (2H, m), 3.15–3.17 (2H, m), 3.61 (2H, s), 7.4–7.44 (3H, m), 7.56–7.58 (2H, m). Anal. calcd. for $C_{23}H_{28}N_4S_2$: C, 65.06; H, 6.65; N, 13.19; S, 15.10. Found: C, 64.95; H, 6.66; N, 12.99; S, 14.98%.

4-(4-Phenylthio)-6-(4-ethylpiperazin-1-ylmethyl)-2,3-dihydro-1H-8-thia-5,7-diazacyclopenta[a]indene (6q)

IR spectra (cm^{-1}): 2931, 2808, 1529, 1483, 1300, 1148, 1023, 784; mass (m/z): 411.2 $(M+H)^+$; ^1H NMR (ppm): 1.07–1.11 (3H, t, $J=7.6$ Hz), 2.44–2.57 (12H, m), 3.02–3.06 (2H, m), 3.2–3.23 (2H, m), 3.67 (2H, s), 7.42–7.44 (3H, m), 7.58–7.6 (2H, m). Anal. calcd. for $C_{22}H_{26}N_4S_2$: C, 64.35; H, 6.38; N, 13.64; S, 15.62. Found: C, 63.98; H, 6.42; N, 13.61; S, 15.51%.

4-(4-Methoxyphenylthio)-6-(4-ethylpiperazin-1-ylmethyl)-2,3-dihydro-1H-8-thia-5,7-diazacyclopenta[a]indene (6r)

Melting range (°C) 93.3–105.3, IR spectra (cm^{-1}): 2930, 2808, 1589, 1490, 1298, 1248, 1019, 830; mass (m/z): 441.3 $(M+H)^+$; ^1H NMR (ppm): 1.12–1.16 (3H, t, $J=7.6$ Hz), 2.44–2.56 (12H, m), 3.02–3.05 (2H, t, $J=7.6$ Hz), 3.19–3.23 (2H, t, $J=7.52$ Hz), 3.67 (2H, s), 3.87 (3H, s), 6.94–6.98 (2H, m), 7.48–7.51 (2H, m). Anal. calcd. for $C_{23}H_{28}N_4OS_2$: C, 62.70; H, 6.41; N, 12.72; O, 3.63; S, 14.55. Found: C, 62.81; H, 6.43; N, 12.82; O, 3.51; S, 14.62%.

5,6-Dimethyl-2-[(4-methylpiperazin-1-yl)methyl]-4-phenylthio Thieno[2,3-d]pyrimidine (6s)

IR spectra (cm^{-1}): 2932, 2793, 1560, 1488, 1289, 1145, 1013, 835, 746, 688; mass (m/z): 384.57 $(M+H)^+$; ^1H NMR (ppm): 2.25 (3H, s), 2.3–2.43 (8H, m), 2.47 (3H, s), 2.62 (3H, s), 3.59 (2H, s), 7.41–7.44 (3H, m), 7.56–7.58 (2H, m). Anal.

calcd. for $C_{20}H_{24}N_4S_2$: C, 62.47; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.31; H, 6.28; N, 13.99; S, 16.72%.

4-(4-Fluorophenylthio)-6-(4-ethylpiperazin-1-ylmethyl)-2,3-dihydro-1h-8-thia-5,7-diazacyclopenta[a]indene (6t)

Melting range (°C) 99.3–102.4, IR spectra (cm^{-1}): 2937, 2810, 1587, 1483, 1300, 1148, 837; mass (m/z): 429.3 $(M+H)^+$; ^1H NMR (ppm): 1.14–1.17 (3H, t, $j=7.64$ Hz), 2.51–2.68 (12H, m), 3.03–3.06 (2H, t, $j=7.6$ Hz), 3.19–3.23 (2H, t, $j=7.6$ Hz), 3.68 (2H, s), 7.11–7.17 (2H, m), 7.54–7.59 (2H, m). Anal. calcd. for $C_{22}H_{25}FN_4S_2$: C, 61.65; H, 5.88; F, 4.43; N, 13.07; S, 14.96. Found: C, 60.95; H, 5.91; F, 4.38; N, 12.98; S, 14.84%.

4-(4-Fluorophenylthio)-6-(4-methylpiperazin-1-ylmethyl)-2,3-dihydro-1h-8-thia-5,7-diazacyclopenta[a]indene (6u)

Melting range (°C) 126.2–127.2, IR spectra (cm^{-1}): 3048, 2924, 1609, 1486, 1302, 1148, 838;,mass (m/z): 415.2 $(M+H)^+$; ^1H NMR (ppm): 2.51–2.57 (2H, m), 2.58 (3H, s), 2.66–3.0 (8H, m), 3.02–3.08 (2H, m), 3.18–3.24 (2H, m), 3.71 (2H, s), 7.13–7.19 (2H, m), 7.53–7.58 (2H, m). Anal. calcd. for $C_{21}H_{23}FN_4S_2$: C, 60.84; H, 5.59; F, 4.58; N, 13.51; S, 15.47. Found: C, 60.73; H, 5.61; F, 4.56; N, 13.61; S, 15.50%.

2-[(4-Methylpiperazin-1-yl)methyl]-4-(4-fluorophenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6v)

Melting range (°C) 98.2–110.2, IR spectra (cm^{-1}): 2927, 2789, 1588, 1488, 1221, 1016, 817; mass (m/z): 429.3 $(M+H)^+$; ^1H NMR (ppm): 1.88–1.98 (4H, m), 2.27 (3H, s), 2.3–2.5 (8H, m), 2.84–2.86 (2H, m), 3.13–3.15 (2H, m), 3.61 (2H, s), 7.1–7.14 (2H, m), 7.52–7.56 (2H, m). Anal. calcd. for $C_{22}H_{25}FN_4S_2$: C, 61.65; H, 5.88; F, 4.43: N, 13.07; S, 14.96. Found: C, 61.13; H, 5.86; F, 4.47; N, 13.68; S, 14.90%.

2-[(4-Methylpiperazin-1-yl)methyl]-4-(4-chlorophenylthio)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (6w)

Melting range (°C) 106.5–110.7, IR spectra (cm^{-1}): 2931, 2792, 1489, 1475, 1293, 1164, 1012, 844; mass (m/z): 445.4 $(M+H)^+$; ^1H NMR (ppm): 1.88–1.96 (4H, m), 2.28 (3H, s), 2.3–2.55 (8H, m), 2.84–2.86 (2H, m), 3.12–3.14 (2H, m), 3.63 (2H, s), 7.39–7.41 (2H, m), 7.48–7.51 (2H, m). Anal. calcd. for $C_{22}H_{25}ClN_4S_2$: C, 59.37; H, 5.66; Cl, 7.97; N, 12.59; S, 14.41. Found: C, 59.13; H, 5.68; Cl, 7.17; N, 12.68; S, 14.14%.

4-Hydrazino-2-[(4-methylpiperazin-1-yl)methyl]-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (7)

4-Chloro-2-[(4-methylpiperazin-1-yl)methyl]-5,6,7,8-tetrahydrobenzo[4,5]thieno-[2,3-d]pyrimidine (600 mg, 1.78 mmol) and hydrazine hydrate (107.2 mg, 2.14 mmol)

were taken in absolute ethanol (30 mL) and heated at 100 °C for 3 h under a nitrogen blanket. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent ethanol was removed under reduced pressure. The residual Mass was diluted with water, and the pH of the resulting solution was adjusted to 10.0 using aqueous ammonia solution. The product was extracted with 3×50 mL of chloroform. The combined organic layer was washed with brine solution (2×30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to obtain 320 mg of the product. It was used as such without further purification in the next step for the preparation of triazole derivative. IR (cm^{-1}): 3273, 2918, 1625, 1550, 1449, 1182, 1161, 942, 882, 756; mass (m/z): 333.1 $(M + H)^+$; ; ^1H NMR (ppm): 1.94–1.97 (4H, m), 2.34 (3H, s), 2.44–2.59 (8H, m), 2.9 (2H, m), 3.26–3.27 (2H, m), 4.04 (2H, s), 4.54 (3H, bs).

2-[(4-Methylpiperazin-1-yl)methyl]-6,7,8,9-tetrahydrobenzo[4,5]-thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (8a)

4-Hydrazino-2-[(4-methylpiperazin-1-yl)methyl]-5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3-d]pyrimidine (0.32 g, 0.96 mmol) and trimethyl orthoformate (3.0 mL) were refluxed under a nitrogen atmosphere. The reaction was complete in 5 h, and the progress of the reaction was monitored by TLC. The excess trimethyl orthoformate was disuntiled off under reduced pressure, and the residual Mass was purified by column chromatography to obtain 60 mg of the title product.

IR spectra (cm^{-1}): 2938, 2791, 1613, 1456, 1291, 1165, 1012, 821; mass (m/z): 343.1 $(M + H)^+$; ^1H NMR (ppm): 1.96–1.99 (4H, m), 2.32 (3H, s), 2.48–2.63 (8H, m), 2.9 (2H, m), 3.25–3.26 (2H, m), 4.01 (2H, s), 9.38 (1H, s). Anal. calcd. for $C_{17}H_{22}N_6S$: C, 59.62; H, 6.48; N, 24.54; S, 9.36. Found: C, 59.02; H, 6.49; N, 24.24; S, 9.41%.

6,7-Dimethyl-2-[(4-methylpiperazin-1-yl)methyl]thieno[3,2-e]-[1,2,4]triazolo [4,3-c]pyrimidine (8b)

IR spectra (cm^{-1}): 2925, 1610, 1457, 1290, 1162, 1010, 821; mass (m/z): 317.2 $(M + H)^+$; ^1H NMR (ppm): 2.3 (3H, s), 2.55 (3H, s), 2.62 (8H, m), 2.75 (3H, s), 4.0 (2H, s), 9.4 (1H, s). Anal. calcd. for $C_{15}H_{20}N_6S$: C, 56.94; H, 6.37; N, 26.56; S, 10.13. Found: C, 56.74; H, 6.39; N, 26.66; S, 10.01%.

2-[(4-Methylpiperazin-1-yl)methyl]cyclopentathieno[3,2-e]-[1,2,4]triazolo[4,3-c]pyrimidine (8c)

Melting range (°C) 178.5–183.4; IR spectra (cm^{-1}): 2938, 2792, 1616, 1456, 1287, 1166, 1016, 987, 819, 641; Mass (m/z): 329.3 $(M + H)^+$; ^1H NMR (ppm): 2.3 (3H, s), 2.47–2.63 (10H, m), 3.1–3.14 (2H, m), 3.28–3.32 (2H, m), 4.01 (2H, s), 9.39 (1H, s). Anal. calcd. for $C_{16}H_{20}N_6S$: C, 58.51; H, 6.14; N, 25.59; S, 9.76. Found: C, 58.01; H, 6.09; N, 25.49; S, 9.82%.

6,7-Dimethyl-2-[(4-ethylpiperazin-1-yl)methyl]thieno[3,2-e]-[1,2,4]triazolo[4,3-c]pyrimidine (8d)

IR spectra (cm^{-1}): 2924, 2808, 1611, 1452, 1303, 1161, 1015, 806; mass (m/z): 331.3 $(M+H)^+$; ^1H NMR (ppm): 1.07–1.11 (3H, t, $J=7.6$ Hz), 2.43–2.49 (2H, q, $J=7.6$ Hz), 2.52 (3H, s), 2.6–2.7 (8H, m), 2.75 (3H, s), 4.0 (2H, s), 9.4 (1H, s). Anal. calcd. for $C_{16}H_{22}N_6S$: C, 58.15; H, 6.71; N, 25.43; S, 9.70. Found: C, 57.85; H, 6.76; N, 25.33; S, 9.72%.

2-[(4-Ethylpiperazin-1-yl)methyl]-6,7,8,9-tetrahydrobenzo[4,5]thieno [3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (8e)

IR spectra (cm^{-1}): 2938, 2809, 1612, 1470, 1303, 1168, 1083; mass (m/z): 357.1 $(M+H)^+$; ^1H NMR (ppm): 1.07–1.11 (3H, t, $J=7.68$ Hz), 1.96–1.99 (2H, m), 2.03 (2H, m), 2.4–2.47 (2H, q, $J=7.64$ Hz), 2.49–2.63 (8H, m), 2.9–2.95 (2H, m), 3.25–3.3 (2H, m), 4.01 (2H, s), 9.4 (1H, s). Anal. calcd. for $C_{18}H_{24}N_6S$: C, 60.65; H, 6.79; N, 23.57; S, 8.99. Found: C, 60.05; H, 6.82; N, 23.59; S, 8.89%.

2-[(4-Ethylpiperazin-1-yl)methyl]cyclopentathieno[3,2-e][1,2,4]-triazolo[4,3-c]pyrimidine (8f)

Melting range (°C) 124.6–127.8; IR spectra (cm^{-1}): 2946, 2813, 1617, 1566, 1475, 1452, 1304, 1165, 1016, 641; mass (m/z): 343.2 $(M+H)^+$; ^1H NMR (ppm): 1.11–1.13 (3H, t, $J=7.68$ Hz), 2.48–2.53 (2H, q, $J=7.64$ Hz), 2.58–2.63 (2H, quin, $J=7.6$ Hz), 2.67 (6H, s), 3.1–3.14 (4H, m), 3.27–3.31 (2H, m), 4.02 (2H, s), 9.38 (1H, s). Anal. calcd. for $C_{17}H_{22}N_6S$: C, 59.62; H, 6.48; N, 24.54; S, 9.36. Found: C, 59.39; H, 6.51; N, 24.61; S, 9.29%.

2-[(4-Ethylpiperazin-1-yl)ethyl]-6,7,8,9-tetrahydrobenzo[4,5]thieno-[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (8g)

IR spectra (cm^{-1}): 2920, 284909, 1616, 1453, 1274, 1163, 1006; mass (m/z): 371.3 $(M+H)^+$; ^1H NMR (ppm): 1.08–1.12 (3H, t, $J=7.2$ Hz), 1.96–1.99 (4H, m), 2.42–2.48 (2H, q, $J=7.2$ Hz), 2.2–2.7 (8H, m), 2.9–2.94 (2H, m), 3.01–3.05 (2H, t, $J=7.12$ Hz), 3.2–3.25 (2H, m), 3.32–3.35 (2H, t, $J=7.12$ Hz), 8.93 (1H, s). Anal. calcd. for $C_{19}H_{26}N_6S$: C, 61.59; H, 7.07; N, 22.68; S, 8.65. Found: C, 61.62; H, 7.11; N, 22.53; S, 8.58%.

5,6,7,8-Tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (9)

Ethyl-2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate (10.32 g, 45.86 mmol) was taken in formamide (44 mL) and heated to 170 °C Mass temperature under a nitrogen atmosphere. The heating was continued until the reaction was complete, and the progress of the reaction was monitored by TLC. After 8 h, the reaction Mass was cooled to 10 °C, and solids were thrown out. The solids were filtered, and the cake was washed with 50 mL of hexane. The product was sucked dry and finally dried in an oven at 50 °C, the yield being quantitative. IR spectra (cm^{-1}): 3156, 3007, 2939, 2923,

1659, 1590, 1372, 990, 913, 580; mass (m/z): 207.1 $(M+H)^+$; % purity (HPLC) = 98.85. The material was utilized in the next step without any further purification. IR (cm^{-1}): 2939, 2857, 1659, 1590, 1372, 1170, 990, 913, 580; mass (m/z): 207.0 $(M+H)^+$; ^1H NMR (ppm): 1.86–1.88 (4H, m), 2.91–2.93 (4H, m), 8.75 (1H, s).

4-Chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (10)

5,6,7,8-Tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-one (10 g, 48.54 mmol) was taken in 40 mL of phosphorousoxychloride, the mass was cooled to 15–20 °C, and triethyl amine (32 mL) was added dropwise, maintaining the temperature below 20 °C, for 15 min. Then, the reaction Mass was slowly heated to 100 °C and maintained there for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was quenched in 250 mL of ice water, and the product was extracted with 3×50 mL of ethyl acetate. The combined organic layer was washed with brine solution (2×30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residual mass (10.5 g, yield = 96.3%) was used for the next step without further purification. IR (cm^{-1}): 2938, 1647, 1596, 1491, 1295, 1153, 1027, 781, 640; mass (m/z): 224.9 $(M+H)^+$; ^1H NMR (ppm): 1.84–1.89 (4H, m), 2.93–2.98 (4H, m), 8.72 (1H, s).

4-Dimethylaminoethoxy-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (11a)

Sodium (94.6 mg, 4.11 mmol) was taken in 50 mL of toluene, and 2-dimethylaminoethanol (284 mg, 4.11 mmol) was added dropwise at ambient temperature. Then, the mass was heated to reflux and maintained under reflux for 1 h. To this mass was added the prepared 4-chloro derivative **10** (0.6 g dissolved in 5 mL toluene) at 90 °C. The mass was once again heated to 110 °C and maintained at reflux until the completion of the reaction. The progress of the reaction was monitored by TLC. Then the reaction mass was cooled to 25 °C, and toluene was removed under reduced pressure. The residual mass was dissolved in chloroform and filtered from inorganic matter. The filtrate was concentrated under reduced pressure, and the technical product, thus obtained, was purified by column chromatography to get 300 mg of the pure product, the yield being 40%.

IR spectra (cm^{-1}): 2937, 2858, 1562, 1508, 1448, 1316, 1035; mass (m/z): 278.2 $(M+H)^+$; ^1H NMR (ppm): 1.85–1.91 (4H, m), 2.42 (6H, s), 2.81–2.84 (2H, m), 2.9–2.96 (4H, m), 4.65–4.68 (2H, m), 8.76 (1H, s). Anal. calcd. for $C_{14}H_{19}N_3OS$: C, 60.62; H, 6.90; N, 15.15; O, 5.77; S, 11.56. Found: C, 60.92; H, 6.89; N, 15.20; O, 5.69; S, 11.62%.

[2-(2,3-Dihydro-1H-8-thiA-5,7-diazacyclopenta[a]inden-4-yloxy)-ethyl]dimethylamine(11b)

Melting range: 170–180 °C, IR spectra (cm^{-1}): 2958, 2680, 1562, 1578, 1452, 1335, 1049, 1001; mass (m/z): 264.3 $(M+H)^+$; ^1H NMR (ppm): 2.52–2.58 (2H, m), 3.03–3.11 (10H, m), 3.7–3.73 (2H, s), 4.93–4.95 (2H, m), 8.54 (1H, s). Anal.

calcd. for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96; O, 6.08; S, 12.18. Found: C, 58.99; H, 6.53; N, 15.89; O, 6.12; S, 12.22%.

5,6-Dimethyl-4-dimethylaminoethoxythieno[2,3-d]pyrimidine (11c)

IR spectra (cm^{-1}): 2924, 1561, 1509, 1449, 1327, 1159, 1035, 788; mass (m/z): 252.3 $(M+H)^+$; ^1H NMR (ppm): 2.43 (3H, s), 2.44 (9H, s), 2.95–2.98 (2H, m), 4.68–4.72 (2H, m), 8.51 (1H, s). Anal. calcd. for $C_{12}H_{17}N_3OS$: C, 57.34; H, 6.82; N, 16.72; O, 6.37; S, 12.76. Found: C, 57.44; H, 6.85; N, 16.81; O, 6.41; S, 12.81%.

5-Ethyl-6-methyl-4-dimethylaminoethoxythieno[2,3-d]pyrimidine (11d)

IR spectra (cm^{-1}): 2925, 1557, 1508, 1441, 1326, 1158, 1034, 756; mass (m/z): 266.0 $(M+H)^+$; ^1H NMR (ppm): 1.03–1.07 (3H, t, $J=7.0$ Hz), 2.51 (2H, t), 2.86–2.92 (8H, m), 3.36 (3H, bs), 4.87–4.9 (2H, t, $J=5.04$ Hz), 8.6 (1H, s). Anal. calcd. for $C_{13}H_{19}N_3OS$: C, 58.84; H, 7.22; N, 15.83; O, 6.03; S, 12.08. Found: C, 58.64; H, 7.24; N, 15.91; O, 6.06; S, 12.12%.

5-(2-Dimethylaminoethyl)-1,2,3,5-tetrahydro-8-thia-5,7-diazacyclopenta[a]inden-4-one (12a)

The raw material, 1,2,3,5-tetrahydro-8-thia-5,7-diazacyclopenta[a]inden-4-one (392 mg, 2.02 mmol), was taken in acetone (10 mL). To this reaction Mass, 2-dimethylaminoethylchloride hydrochloride, (319.1 mg, 2.215 mmol) and potassium carbonate (562.6 mg, 4.07 mmol) were added, and the resulting mass was heated to reflux. It was maintained under reflux (55 °C to 60 °C) until completion of the reaction. The progress of the reaction was monitored by TLC. The mass was cooled to 25 °C, the solids were filtered and washed with acetone (10 mL), and the filtrate was concentrated under reduced pressure. The residual Mass was purified by column chromatography to obtain 288 mg of the title product, the yield being 53.68%. Melting range of the hydrochloride salt was 210–217 °C.

IR spectra (cm^{-1}): 2951, 2855, 1672, 1570, 1443, 1391, 1141, 974; mass (m/z): 264.0 $(M+H)^+$; ^1H NMR (ppm): 2.3 (6H, s), 2.44–2.48 (2H, m, $J=7.28$ Hz), 2.65–2.68 (2H, t, $J=6.32$ Hz), 2.94–2.97 (2H, t, $J=7.24$ Hz), 3.07–3.09 (2H, t, $J=7.2$ Hz), 4.07–4.1 (2H, t, $J=6.28$ Hz), 7.93 (1H, s). Anal. calcd. for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96; O, 6.08; S, 12.18. Found: C, 59.36; H, 6.55; N, 15.95; O, 6.04; S, 12.15%.

5-Ethyl-6-methyl-3-dimethylaminoethyl-4-thieno[2,3-d]pyrimidin-4-one (12b)

IR spectra (cm^{-1}): 2968, 2768, 1658, 1571, 1458, 1285, 1141, 1037, 790; mass (m/z): 266.0 $(M+H)^+$; ^1H NMR (ppm): 1.15–1.19 (3H, t, $J=7.44$ Hz), 2.28 (6H, s), 2.41 (3H, s), 2.61–2.64 (2H, t, $J=6.24$ Hz), 2.91–2.96 (2H, q, $J=7.44$ Hz), 4.04–4.07 (2H, t, $J=6.2$ Hz), 7.94 (1H, s). Anal. calcd. for $C_{13}H_{19}N_3OS$: C,

58.84; H, 7.22; N, 15.83; O, 6.03; S, 12.08. Found: C, 58.44; H, 7.18; N, 15.75; O, 6.05; S, 12.02%.

3-Dimethylaminoethyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]-pyrimidin-4-one (12c)

IR spectra (cm^{-1}): 2936, 1670, 1571, 1385, 1137, 775; mass (m/z): 278.2 $(M+H)^+$; ^1H NMR (ppm): 1.83–1.88 (4H, m), 2.28 (6H, s), 2.6–2.63 (2H, t, $J = 6.2$ Hz), 2.76–2.79 (2H, m), 3.01–3.04 (2H, m), 4.02–4.05 (2H, t, $J = 6.2$ Hz), 7.91 (1H, s). Anal. calcd. for $C_{14}H_{19}N_3OS$: C, 60.62; H, 6.90; N, 15.15; O, 5.77; S, 11.56. Found: C, 60.42; H, 6.94; N, 15.22; O, 5.79; S, 11.53%.

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