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# Synthesis of a novel fused tricyclic heterocycle, pyrimido[5,4-*e*][1,4]thiazepine, and its derivatives

**Abstract:** Sequential treatment of 5-bromo-2,4-dichloro-6-(chloromethyl)pyrimidine with 2-aminothiophenol and secondary amines afforded a series of 2-[(5-bromo-2-chloro-6-aminopyrimidin-4-yl)methylthio]aniline derivatives. Reaction of the latter compounds with secondary amines in ethanol gave a family of new 5,7-diamino-5,11-dihydropyrimido[5,4-*e*][1,4]benzothiazepines.

**Keywords:** [5,4-*e*][1,4]benzothiazepines; nucleophilic substitution; secondary amines; 1,4-thiazepine.

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## Introduction

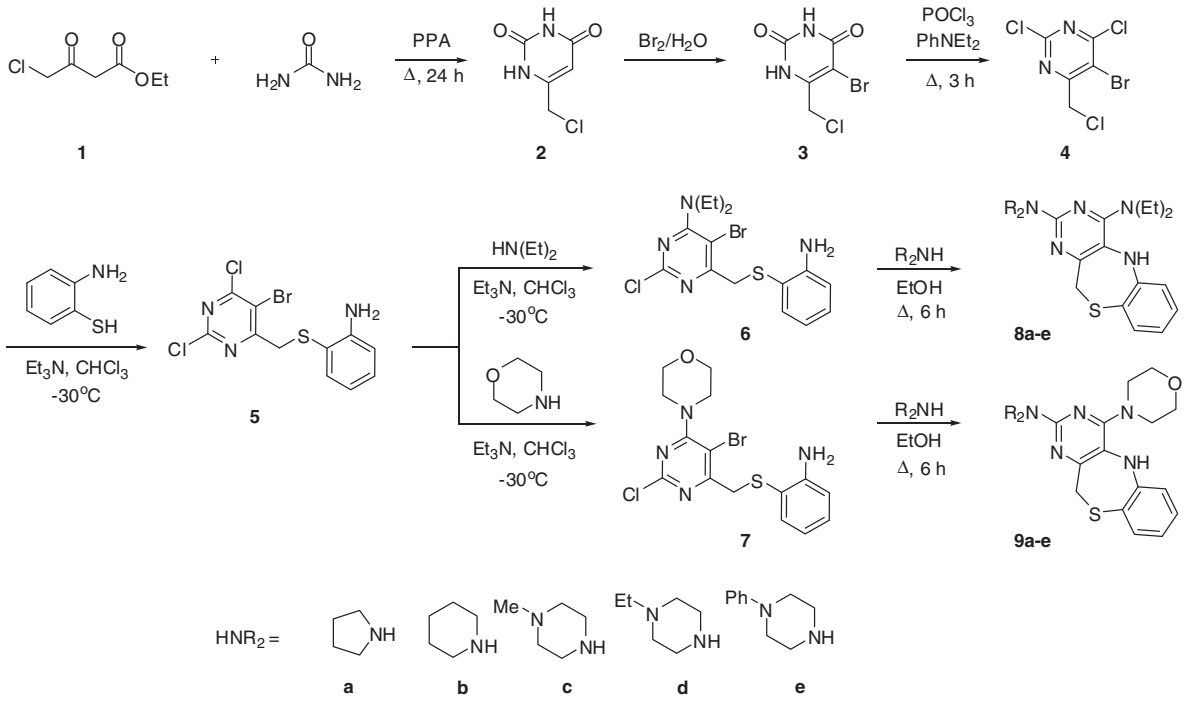
1,4-Thiazepine is a privileged structure because of its presence in a number of pharmacologically important compounds [1–2]. Derivatives of 1,4-thiazepin-5-ones [3–8] and -2,4-diones [9] are drug candidates for the treatment of cancer, heart diseases, and inflammatory diseases. Synthetic approaches to these compounds are varied and involve addition, condensation, coupling, rearrangement, and thermolysis methods in multistep synthesis [10, 11]. Fused thiazepines such as dihydrodibenzothiazepines have also been in focus because of their high potential for discovery of drug candidates. Pyrimido[5,4-*e*][1,4]thiazepines are a new class of heterocyclic compounds that are structurally related to dibenzothiazepines. Therefore, it seems likely that these compounds might exhibit some biological activities. In line with these assumptions and owing to our interest in the synthesis of bioactive heterocycles [12–15], in the present study we wish to report on the synthesis and structural elucidation of pyrimido[5,4-*e*][1,4]benzothiazepines as a new class of heterocyclic compounds.

## Results and discussion

Ethyl 4-chloro-3-oxobutanoate (**1**) was conveniently synthesized according to the literature procedure [16]. Treatment of this compound with urea in polyphosphoric acid under reflux conditions for 24 h gave 6-(chloromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**2**), the treatment of which with $Br_2$ in water gave 5-bromo-6-(chloromethyl) pyrimidine-2,4(1*H*,3*H*)-dione (**3**). Reaction of **3** with *N,N*-diethylaniline and $POCl_3$ under reflux conditions afforded 5-bromo-2,4-dichloro-6(chloromethyl)pyrimidine (**4**), which was subsequently transformed into 2-[(5-bromo-2,6-dichloropyrimidin-4-yl)methylthio] aniline (**5**) when treated with *o*-aminothiophenol and $Et_3N$ at -30°C. The structure of compound **5** was characterized by spectroscopic data and elemental analysis. The IR spectrum of **5** showed stretching vibration bands at 3340 and 3460 $cm^{-1}$ due to its $NH_2$ group. In the $^1H$ NMR spectrum, the $CH_2Cl$ group signal of **4** appeared at δ 4.7, while in compound **5** the same hydrogen signal was shifted to δ 4.1. The striking chemical shift difference of $\Delta\delta = 0.6$ between the $CH_2$ moieties of **4** and **5** together with the presence of an $NH_2$ moiety in compound **5** clearly demonstrated the replacement of the chlorine atom of compound **4** by the sulfur atom of *o*-aminothiophenol to obtain compound **5**.

2-[(5-Bromo-2-chloro-6-*N,N*-dialkylaminopyrimidin-4-yl)methylthio]anilines **6** and **7** were obtained by treatment of **5** in the presence of secondary amines and $Et_3N$ in chloroform at -30°C. Compounds **6** and **7** on treatment with secondary amines underwent simultaneous nucleophilic substitution and cyclization to give the desired products **8a–e** and **9a–e** (Scheme 1).

The structural assignments of the compounds **8a–e** and **9a–e** were based on the spectral and microanalytical data. The IR spectra did not exhibit stretching vibration bands at 3340 and 3460 $cm^{-1}$ ($NH_2$) observed for the precursors, but showed a sharp band at 3440 $cm^{-1}$ for the NH vibration. Further proof came from the $^1H$ NMR spectra, which showed a sharp NH signal. Elimination of HBr was observed in the mass spectra of compounds **8a–e** and **9a–e**.




**Scheme 1** Synthetic pathway of the title compound.

## Conclusion

The synthesis of a new family of tricyclic heterocycles, 5,7 diamino-5,11-dihydropyrimido[5,4-*e*][1,4]benzothiazepines, through simultaneous nucleophilic substitution and heterocyclization of 2-[(5-bromo-2-chloro-6-*N*,*N*-dialkylaminopyrimidin-4-yl)methylthio] anilines with secondary amines in ethanol is described.

# Experimental

Melting points were recorded on an Electro thermal type 9100 melting point apparatus (UK). The IR spectra were obtained on an AVATAR 370FT-IR Thermo Nicolet spectrometer (Germany) using KBr discs. $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer (Germany) at 400 MHz and 100 MHz, respectively. The mass spectra were scanned on a Varian Mat CH-7 instrument (Germany) at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer (Italy).

## Synthesis of 6-(chloromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (2)

A mixture of ethyl 4-chloro-3-oxobutanoate **(1)** (10 mmol, 1.64 g) and urea (10 mmol, 0.60 g) in polyphosphoric acid (5 mL) was heated under reflux for 24 h. After the reaction was completed, the mixture was cooled and poured into an ice-cold water bath (30 mL). The precipitate was filtered, washed well with cold water, and dried at 80°C. This compound was pure enough for the next reactions. It was obtained in 60% yield as a brown powder; mp 253–255°C (decomp.); $^1$H NMR: δ 4.33 (s, 2H, $CH_2$), 5.64 (s, 1H, CH), 11.11 (brs, 2H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 161.2, 151.5, 150.5, 101.8, 39.9; IR: ν 3150, 3041 cm$^{-1}$ (NH); MS: m/z 160. Anal. Calcd for $C_5H_5ClN_2O_2$: C, 37.40; H, 3.14; N, 17.45. Found: C, 37.38; H, 3.09; N, 17.42.

## Synthesis of 5-bromo-6-(chloromethyl) pyrimidine-2,4(1*H*,3*H*)-dione (3)

To a suspension of 6-(chloromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**2**, 10 mmol, 1.60 g) in water (20 mL), a mixture of molecular bromine (10 mmol, 1.80 g) and water (5 mL) was added dropwise with vigorous stirring over a period of 1 min. Stirring was continued for further 30 min. The mixture was heated under reflux and then cooled to room temperature to give a solid residue, which was collected by filtration, washed with warm water (2 × 30 mL), and dried at 80°C. This compound was pure enough for the next reactions. It was obtained in 58% yield as a brown powder; mp 273–275°C; $^1$H NMR: δ 4.75 (s, 2H, $CH_2$), 11.21 (brs, 2H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 158.6, 150.3, 148.7, 84.5, 31.8; IR: ν 3185, 3146 cm$^{-1}$ (NH); MS m/z 238. Anal. Calcd for $C_5H_4BrClN_2O_2$: C, 25.08; H, 1.68; N, 11.70. Found: C, 25.12; H, 1.63; N, 11.66.

## Synthesis of 5-bromo-2,4-dichloro-6-(chloromethyl)pyrimidine (4)

A mixture of 5-bromo-6-(chloromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**3**,10 mmol, 2.39 g) and *N*,*N*-diethylaniline (3 mmol, 0.46 g)

in phosphorus oxychloride (10 mL) was heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue was treated with ice. The precipitate was collected by filtration and crystallized from *n*-hexane. It was obtained in 66% yield as a yellow powder; mp 32–34°C; $^1$H NMR: δ 4.79 (s, 2H, $CH_2$); $^{13}$C NMR: δ 170.6, 164.7, 159.7, 115.3, 39.2; MS: m/z 274. Anal. Calcd for $C_5H_2BrCl_3N_2$: C, 21.73; H, 0.73; N, 10.14. Found: C, 21.90; H, 0.68; N, 10.61.

## Synthesis of 2-[(5-bromo-2,6-dichloropyrimidine-4-yl)methylthio]aniline (5)

To a solution of 5-bromo-2,4-dichloro-6-(chloromethyl)pyrimidine (**4**, 10 mmol, 2.76 g) and triethylamine (0.11 mmol, 1.20 g) in chloroform (30 mL), 2-aminothiophenol (10 mmol, 1.25 g) was added dropwise with vigorous stirring over a minute at -30°C. After the reaction was completed, which was monitored by TLC using chloroform/methanol (20:1) as eluent, the solvent was removed under reduced pressure and the residue was washed with warm water and crystallized from ethanol. It was obtained in 63% yield as a yellow powder; mp 121–123°C; $^1$H NMR: δ 4.15 (bs, 2H, $NH_2$, $D_2O$ exchangeable), 4.65 (s, 2H, $CH_2$), 6.53–7.55 (m, 4H, Ar); $^{13}$C NMR: δ 170.9, 165.6, 158.7, 147.9, 133.5, 128.0, 119.2, 117.6, 116.4, 114.0, 34.6. IR: ν 3452, 3431 cm$^{-1}$ ($NH_2$); MS m/z 363; Anal. Calcd for $C_{11}H_8BrCl_2N_3S$: C, 36.19; H, 2.21; N, 11.51. Found: C, 36.11; H, 2.19; N, 11.49.

## General procedure for the preparation of 6 and 7

A mixture of 2-[(5-bromo-2,6-dichloropyrimidine-4-yl)methylthio]benzenamine (**5**, 10 mmol, 3.65 g) and appropriate secondary amine (30 mmol) in ethanol (20 mL) was stirred at -30°C. After addition of water (30 mL), the precipitate was filtered off and crystallized from ethanol.

**2-[(5-Bromo-2-chloro-6-*N*,*N*-diethyl amino pyrimidin-4-yl)methylthio]aniline (6)** This compound was obtained in 65% yield as a brown powder; mp 60–62°C; $^1$H NMR: δ 1.14 (t, 6H, $CH_3$, $J$ = 7 Hz), 2.81(q, 4H, $CH_2$, $J$ = 7 Hz), 4.15 (s, 2H, $CH_2$), 5.12 (bs, 2H, $NH_2$, $D_2O$ exchangeable), 6.65–6.93 (m, 1H, $CH_{Ar}$), 6.95–7.43 (m, 3H, Ar); $^{13}$C NMR: δ 172.4, 169.1, 157.3, 146.8, 134.0, 127.2, 118.4, 117.9, 112.9, 106.7, 44.6, 35.4, 11.9. IR: 3481, 3432 cm$^{-1}$ ($NH_2$); MS m/z 400. Anal. Calcd for $C_{15}H_{18}BrClN_4S$: C, 44.84; H, 4.52; N, 13.95; S, 7.98. Found: C, 44.82; H, 4.51; N, 13.92; S, 7.96.

**2-[(5-Bromo-2-chloro-6-morpholinopyrimidin-4-yl)methylthio]aniline (7)** This compound was obtained in 60% yield as a brown powder; mp 108–110°C; $^1$H NMR: δ 3.31–3.80 (m, 8H, $CH_2$-N, $CH_2$-O), 4.05 (s, 2H, $CH_2$), 5.15 (bs, 2H, $NH_2$, $D_2O$ exchangeable), 6.45–6.85 (m, 1H, $CH_{Ar}$), 6.85–7.45 (m, 3H, Ar); $^{13}$C NMR: δ 173.6, 168.4, 157.3, 146.5, 133.6, 126.0, 117.9, 116.7, 112.5, 106.4, 63.9, 47.6, 34.8. IR: ν 3452, 3349 cm$^{-1}$ ($NH_2$); MS m/z 414. Anal. Calcd for $C_{15}H_{16}BrClN_4OS$: C, 43.34; H, 3.88; N, 13.48; S, 7.71. Found: C, 43.32; H, 3.83; N, 13.43; S, 7.68.

## General procedure for the preparation of 8a–e and 9a–e

A mixture of 2-[(5-bromo-2-chloro-6-aminopyrimidin-4-yl)methylthio]aniline (10 mmol) and secondary amine (30 mmol) in ethanol (20 mL) was heated under reflux for about 6 h. Then, the mixture was cooled and the solvent was removed under reduced pressure. The residue was washed with cooled ethanol (20 mL) and dried.

***N*,*N*-Diethyl-2-(pyrrolidino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepin-4-amine (8a)** It was obtained in 58% yield as a yellow viscous liquid; $^1$H NMR: δ 1.28 (t, 6H, $CH_3$, $J$ = 7 Hz), 1.91–2.85 (m, 12H, $CH_2$, $CH_2$-N), 3.51 (s, 2H, $CH_2$-S), 6.17–6.68 (m, 4H, Ar),7.13 (bs, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 154.6, 152.8, 149.7, 140.5, 133.9, 123.6, 117.9, 116.8, 115.3, 109.9, 52.6, 45.4, 31.6, 23.5, 12.0; IR: ν 3444 cm$^{-1}$ (NH); MS: m/z 355. Anal. Calcd for $C_{19}H_{25}N_5S$: C, 64.19; H, 7.09; N, 19.70; S, 9.02. Found: C, 64.19; H, 7.11; N, 19.65; S, 9.00.

***N*,*N*-Diethyl-2-(piperidino)-5,11-dihydrobenzo[b]pyrimido[5,4-*e*][1,4]thiazepin-4-amine (8b)** This compound was obtained in 62% yield as a yellow viscous liquid; $^1$H NMR: δ 1.31 (t, 6H, $CH_3$, $J$ = 7Hz), 1.88–2.92 (m, 14H, $CH_2$, $CH_2$-N), 3.49 (s, 2H, $CH_2$-S), 6.21–6.74 (m, 4H, Ar), 7.20 (bs, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 154.0, 153.7, 149.6, 140.5, 133.6, 123.9, 118.9, 118.7, 118.7, 115.0, 109.3, 52.8, 46.4, 31.7, 23.6, 22.5, 12.3; IR: ν 3456 cm$^{-1}$ (NH); MS: m/z 369. Anal. Calcd for $C_{20}H_{27}N_5S$: C, 65.01; H, 7.36; N, 18.95; S, 8.68. Found: C, 65.11; H, 7.34; N, 18.89; S, 8.66.

***N*,*N*-Diethyl-2-(4-methylpiperazino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepin-4-amine (8c)** This compound was obtained in 64% yield as a brown powder; mp 90–92°C; $^1$H NMR: δ 1.21–1.42 (m, 9H, $CH_3$), 1.99–3.11 (m, 12H, $CH_2$, $CH_2$-N), 3.49 (s, 2H, $CH_2$-S), 6.21–6.88 (m, 4H, Ar), 7.17 (bs, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 155.0, 152.7, 149.5, 139.6, 133.9, 123.4, 117.6, 116.7, 115.4, 110.2, 55.6, 50.3, 46.3, 45.6, 31.7, 12.3; IR: ν 3445 cm$^{-1}$ (NH); MS: m/z 384. Anal. Calcd for $C_{20}H_{28}N_6S$: C, 62.47; H, 7.34; N, 21.85; S, 8.34. Found: C, 62.44; H, 7.31; N, 21.82; S, 8.30.

***N*,*N*-Diethyl-2-(4-ethylpiperazino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepin-4-amine (8d)** This compound was obtained in 59% yield as a yellow viscous liquid; $^1$H NMR: δ 1.12–1.33 (m, 9H, $CH_3$), 1.78–2.93 (m, 14H, $CH_2$, $CH_2$-N), 3.52 (s, 2H, $CH_2$-S), 6.15–6.82 (m, 4H, Ar ), 7.22 (bs, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 154.3, 152.7, 148.6, 140.2, 133.3, 1234, 118.2, 116.9, 115.4, 110.6, 53.1, 50.5, 47.8, 46.4, 31.6, 11.9, 12.1. IR: ν 3440 cm$^{-1}$ (NH); MS: m/z 398. Anal. Calcd for $C_{21}H_{30}N_6S$: C, 63.28; H, 7.59; N, 21.09; S, 8.05. Found: C, 63.30; H, 7.53; N, 21.06; S, 8.10.

***N*,*N*-Diethyl-2-(4-phenylpiperazino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepin-4-amine (8e)** This compound was obtained in 55% yield as a yellow viscous liquid; $^1$H NMR: δ 1.35 (t, 6H, $CH_3$, $J$ = 7 Hz), 1.93–3.05 (m, 12H, $CH_2$, $CH_2$-N), 3.51 (s, 2H, $CH_2$-S), 6.73–7.51 (m, 9H, Ar), 7.63 (bs, 1H, NH, $D_2O$ exchangeable); $^{13}$C NMR: δ 155.5, 152.5, 150.0, 148.6, 140.5, 133.6, 127.5, 123.6, 120.8, 117.9, 116.9, 115.0, 112.3, 109.3, 45.3, 47.4, 45.6, 33.0, 12.4; IR: ν 3440 cm$^{-1}$ (NH). MS: (m/z) 446. Anal. Calcd for $C_{25}H_{30}N_6S$: C, 67.23; H, 6.77; N, 18.82; S, 7.18. Found: C, 67.23; H, 6.70; N, 18.79; S, 7.10.

**4-(2-(Pyrrolidino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepino)morpholine (9a)** This compound was obtained in 64% yield as a yellow powder; mp 129–131°C; $^1$H NMR: δ 1.44 (t, 4H, $CH_2$, $J$ = 7 Hz), 1.81–2.20 (m, 8H, $CH_2$, $CH_2$-N), 3.11–3.17 (m, 4H, $CH_2$-O), 4.62 (s, 2H, $CH_2$-S), 6.84–7.85 (m, 5H, NH, Ar); $^{13}$C NMR: δ 154.5, 152.4, 149.6, 128.3, 127.8, 123.3,121.2, 115.0, 64.8, 61.5, 52.7, 46.4, 45.0, 30.2, 23.5. IR: ν 3342 cm$^{-1}$ (NH); MS: (m/z) 369. Anal. Calcd for $C_{19}H_{23}N_5OS$: C, 61.76; H, 6.27; N, 18.95; S, 8.68. Found: C, 61.765; H, 6.23; N, 18.85; S, 8.60.

**4-(2-Piperidino-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepino)morpholine (9b)** This compound was obtained in 60% yield as a yellow powder; mp 91–93°C; $^1$H NMR: δ 1.02–1.51 (m, 2H, $CH_2$), 1.63–2.01 (m, 4H, $CH_2$), 2.51–3.11 (m, 4H, $CH_2$-N), 3.63–4.15 (m, 8H, $CH_2$-N, $CH_2$-O), 4.22–4.31 (m, 2H, $CH_2$-S), 6.61–7.62 (m, 5H, NH, Ar); $^{13}$C NMR: δ 155.2, 154.5, 148.6, 129.4, 127.6, 123.2, 121.4, 116.3, 66.0, 61.7, 52.8, 46.4, 45.0, 29.8, 23.2, 22.5. IR: ν 3452 cm$^{-1}$ (NH); MS: m/z 383. Anal. Calcd for $C_{20}H_{25}N_5OS$: C, 62.64; H, 6.57; N, 18.26; S, 8.36. Found: C, 62.59; H, 6.53; N, 18.25; S, 8.36.

**4-(2-(4-Methylpiperazino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepino)morpholine (9c)** This compound was obtained in 57% yield as a yellow powder; mp 187–189°C; $^1$H NMR: δ 1.80–2.65 (m, 11H, $CH_3$, $CH_2$-N), 2.95–3.42 (m, 4H, $CH_2$-N), 3.45–3.95 (m, 6H,$CH_2$-O, $CH_2$-S), 6.25–6.91 (m, 5H, NH, Ar); $^{13}$C NMR: δ 155.0, 152.5, 148.7, 148.2, 139.2, 123.8, 117.9, 116.4, 115.2, 110.3, 64.9, 55.8, 50.5, 48.2, 44.3, 31.9. IR: ν 3446 cm$^{-1}$ (NH); MS: m/z 398. Anal. Calcd for $C_{20}H_{26}N_6OS$: C, 60.28; H, 6.58; N, 21.09; S, 8.05. Found: C, 60.20; H, 6.49; N, 21.12; S, 8.00.

**4-(2-(4-Ethylpiperazino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepino)morpholine (9d)** This compound was obtained in 57% yield as a yellow powder; mp 149–151°C; $^1$H NMR: δ 1.38 (t, 3H, $CH_3$, $J$ = 7 Hz), 1.52–2.63 (m, 8H, $CH_2$-N), 2.75–3.25 (m, 6H, $CH_2$-N), 3.35–3.55 (m, 6H, $CH_2$-O, $CH_2$-S), 6.05–6.76 (m, 5H, NH, Ar); $^{13}$C NMR: δ 154.3, 152.3, 148.7, 140.2, 134.2, 123.6, 117.4, 116.3, 115.5, 110.2, 64.8, 53.2, 50.0, 48.2, 47.6, 33.0, 11.2. IR: ν 3341 cm$^{-1}$ (NH); MS: m/z 412. Anal. Calcd for $C_{21}H_{28}N_6OS$: C, 61.14; H, 6.84; N, 20.37; S, 7.77. Found: C, 61.20; H, 6.84; N, 20.30; S, 7.80.

**4-(2-(4-Phenylpiperazino)-5,11-dihydrobenzo[*b*]pyrimido[5,4-*e*][1,4]thiazepino)morpholine (9e)** This compound was obtained in 59% yield as a yellow powder; mp 86–88°C; $^1$H NMR: δ 3.00–3.41 (m, 8H, $CH_2$-N), 3.41–3.72 (m, 4H, $CH_2$-N), 3.72–4.12 (m, 6H, $CH_2$-O, $CH_2$-S), 6.64–7.45 (m, 10H, NH, Ar); $^{13}$C NMR: δ 154.7, 152.3, 148.7, 147.8, 141.0, 134.4, 128.4, 123.6, 120.4, 118.8, 117.4, 115.3, 112.8, 110.9, 65.3, 48.8, 46.3, 31.2. IR: ν 3333 cm$^{-1}$ (NH); MS: m/z 460. Anal. Calcd for $C_{25}H_{28}N_6OS$: C, 65.19; H, 6.13; N, 18.25; S, 6.96. Found: C, 65.19; H, 6.10; N, 18.15; S, 6.95.

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# References

[1] Bakavoli, M.; Rahimizadeh, M.; Raissi, H.; Beyzaei, H.; Tajabadi, J. Synthesis of a functionalized tetrahydro-1,4-thiazepine in water as the solvent and theoretical investigation of its tautomeric structures. *Monatsh Chem*. **2008**, *139*, 1211–1215.

[2] Calvo, L. A.; Gonzalez-Ortega, A.; Marcos, R.; Perez, M.; Carmen Sanudo, M. Synthesis of 2,3,4,7-tetrahydro[1,4]thiazepines from thiazolidines and *b*-enaminonitriles. *Tetrahedron* **2008**, *64*, 3691–3700.

[3] Strzelczyk, M.; Matyjewska, H.; Strozynski, H. P. Some pharmacological properties of perhydro-1,4-thiazepine and perhydro-1,2,5-dithiazepine derivatives. *J. Pharmacol. Pharm*. **1990**, *42*, 377–385.

[4] Ueyama, N.; Wakabayashi, S.; Tomiyama, T. New intracellular calcium antagonists: I. Synthesis and pharmacological evaluation of 2,3,4,5-tetrahydro-1,5-benzothiazepine analogs. *J. Pharm. Soc. Jpn* (*Yakugaku Zasshi*) **1996**, *116*, 106–124.

[5] Lee, C. L.; Lam, Y.; Lee, S. Y. Solid-phase combinatorial synthesis of benzothiazole and 2,3-dihydro-[1,5]-benzothiazepine derivatives. *Tetrahedron Lett*. **2001**, *42*, 109–111.

[6] Dandia, A.; Sehgal, V.; Upreti, M. Synthesis of dihydro-2-(2-phenyl-indole-3-yl)-4-aryl-1,5-benzothiazepines. *Phosphorus Sulfur Silicon Relat. Elem*. **1995**, *105*, 93–99.

[7] Van den Hoven, B. G.; Alper, H. Remarkable synthesis of 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones by zwitterionic rhodium-catalyzed chemo- and regioselective cyclohydrocarbonylative ring expansion of acetylenic thiazoles. *J. Am. Chem. Soc*. **2001**, *123*, 1017–1022.

[8] Hankovszky, O. H.; Hideg, K.; Lloyd, D. Reaction products from 4-phenylbut-3-yn-2-one and aliphatic diamines or 2-aminoethanethiol, and from 2-aminoethanethiol and some α,β-enones. *J. Chem. Soc. Perkin Trans*. **1974**, *1*, 1614–1619.

[9] Calvo, L.; Gonzalez-Ortega, A.; Perez, M.; Sanudo, M. C. Expansive rearrangement of *N*-vinylthiazolidines to 2,3,4,7-tetrahydro-1,4-thiazepines and their transformation in 3-thia-6-azabicyclo[3.2.1]oct-6-enes. *Synlett* **2005**, 239–242.

[10] Hackler, R. E.; Burow, K. W.; Kaster, S. V.; Wickiser, D. I. The syntheses of 5-amino-3-*t*-butylisothiazole and 3-amino-5-*t*-butylisothiazole. *J. Heterocycl. Chem*. **1989**, *26*, 1575–1578.

[11] Ridge, D. N.; Hanifin, J. W.; Harten, L. A.; Johnson, B. D.; Menschik, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. Potential antiarthritic agents 2-benzoylacetonitriles and β-aminocinnamonitriles. *J. Med. Chem*. **1979**, *22*, 1385–1389.

[12] Bakavoli, M.; Seyedi, S. M.; Shiri, A.; Saberi, S.; Gholami, M.; Sadeghian, H. Synthesis of new derivatives of pyrimido[5,4-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine and their enzyme inhibitory activity assessment on soybean 15-lipoxygenase. *J. Chem. Res*. **2013**, *36*, 48–50.

[13] Rahimizadeh, M.; Shiri, A.; Ranaei, M.; Bakavoli, M. Synthesis and antibacterial evaluation of new heterocyclic system: [1,2,4]triazolo[3′,4′:6,1]pyridazino[4,3-*e*][1,3,4]thiadiazine. *Heterocycl. Commun*. **2012**, *18,* 39–42.

[14] Bakavoli, M.; Bagherzadeh, G.; Vaseghifar, M.; Shiri, A.; Pordel, M.; Mashreghi, M. Molecular iodine promoted synthesis of new pyrazolo[3,4-*d*] pyrimidine derivatives as potential antibacterial agents. *Eur. J. Med. Chem*. **2010**, *45*, 647–650.

[15] Pooryaghoobi, M.; Bakavoli, M.; Alimardani, M.; Bazzazan, T.; Sadeghian, H. New insight into the SAR of pyrimido[4,5-*b*][1,4] benzothiazines as 15-lipoxygenase inhibitors. *Iran. J. Basic Med. Sci*. **2013**, *16*, 784–789.

[16] Lonza, L. Process for the production of 4-chloroacetyl chloride, 4-chloroacetic acid esters, amides and imides. E.P. Patent 2 518 043 A1, 2012.