Synthesis and Functionalization of 8-Methyl-2*h*-pyrimido [2,1-*c*][1,2,4]triazine-3,6(1*h*,4*h*)-dione

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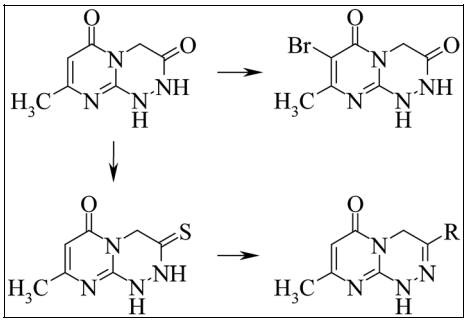

6-Methyl-2-methylthio-4-oxopyrimidin-3(4*H*)-yl)acetohydrazide on heating in benzylamine undergo cyclization to 8-methyl-2*H*-pyrimido[2,1-*c*][1,2,4]triazine-3,6(1*H*, 4*H*)-dione, which under treatment with bromine in glacial acetic acid was converted to 7-bromo substituted derivative and at reflux with Lawesson's reagent yielded 3-thioxo compound. The latter reacted with primary and secondary amines to give 3-amino substituted pyrimidotriazines and on alkylation—the corresponding S-alkyl derivatives.

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INTRODUCTION

Pyrimidines and condensed pyrimidines represent an important group of heterocyclic compounds exhibiting broad spectrum of biological activity. Some of them show anti-inflammatory [1–4], analgetic [4,5], others—antimicrobial [6], antiviral [7], or anticancer activity [8–13]. Pyrimidotriazines possess diverse valuable biological properties too. They exhibit various types of pharmacological properties, such as antibacterial, antiviral, and anticancer activities [14], they are referred as hypoglycemic agents [15] or small molecule chaperone amplifiers [16]. Pyrimidotriazine is the core structure of natural antibiotics as fervenuline, 2-methylfervenuline, xantotricine, and reumicine, and this gives more attractivity to the said heterocyclic system [17].

Earlier, we reported the intramolecular cyclization of (2-methylthio-3-pyrimidinyl)acetohydrazides to the corresponding pyrimido[2,1-*c*][1,2,4]triazinediones [18] (Scheme 1).

In this connection and in continuation of our ongoing program on the synthesis of heterocyclic compounds, herein we report new derivatives of the above mentioned pyrimidotriazine system with substituents both in pyrimidine and triazine ring.

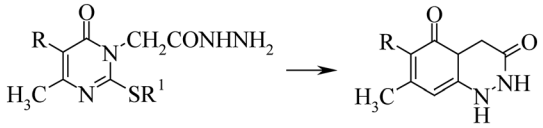
RESULTS AND DISCUSSION

Pyrimidotriazinedione **3** was synthesized from ester **1** as previously described [18] (Scheme 2).

There are two possible pathways for 7-bromo substituted pyrimidotriazinedione **6** formation, i.e., either by introduction of bromine into *a priori* synthesized pyrimidotriazine ring or by cyclization of 5-bromo substituted pyrimidinone. Thus, ester **1** was treated with bromine in glacial acetic acid to produce 5-bromo derivative **4**, which in reaction with hydrazine hydrate gave hydrazide **5**. Attempts to synthesize pyrimidotriazine **6** *via* intramolecular cyclization of hydrazide **5** by heating for 10 min in an excess of benzylamine at 160°C failed. It will be observed that under the same conditions formation of triazine **3** from hydrazide **2** was achieved in 82% yield. Instead of expected cyclization product **6**, the complex mixture of compounds was obtained, from which amide **7** was isolated in a low yield. The structure of this unexpected compound was confirmed by the data of ^{1}H, ^{13}C, IR, and additionally by the mass-spectra. In the ^{1}H-NMR spectrum of compound **7**, characteristic for benzylamine fragment shifts was observed along with the two singlets at 6.28 and 8.32 ppm, which were assigned to the protons of positions 5 and 2 of the pyrimidine ring. Prolonged heating (7 h) of hydrazide **5** with benzylamine at lower temperature (80°C) yielded amide **8**. The analogous structure amide **9** was obtained on reflux of hydrazide **5** with butylamine.

Bromination of compound **3** yielded **7**-bromo substituted pyrimidotriazinedione **6** (87%). The latter on heating at reflux with benzylamine in ethanol resulted in amide **7** formation.

Scheme 1



R = H, C_2H_5, $CH(CH_3)_2$; R^1 = CH_3, C_2H_5.

Pyrimidotriazinedione **3** under treatment with Lawesson's reagent yielded thioxo derivative **10** (Scheme 3).

The argument for replacement of oxygen by sulfur in triazine ring as opposed to pyrimidine was made by comparison of ^{1}H-, ^{13}C-NMR, and IR data of starting pyrimidotriazinedione **3** with that of the thioxo compound **10**. In ^{1}H-NMR signals of protons of compound **10** are downfield shifted and the NH group protons are much more of influence. Additionally, the signal of CH_2 group protons of triazine ring is shifted downfield by 0.36 ppm, whereas CH proton of pyrimidine is shifted downfield only by 0.18 ppm. Analogously, in ^{13}C-NMR spectra of compound **10**, the CH_2 group adjacent to triazine $C_{(3)}$=S is observed downfield by 5.4 ppm in comparison with that $C_{(3)}$=O of pyrimidotriazinedione **3**. The IR spectra of thioxo derivative **10** display absorption band of C=O group at 1686 cm^{-1} characteristic for pyrimidin-4-one, whereas in starting **3** intense absorptions due to two C=O groups were observed at 1664 and 1709 cm^{-1}.

Unfortunately, reaction of pyrimidotriazinedione **6** with Lawesson's reagent gave unidentified dark resinous mixture.

Compound **10** on heating at reflux (in the case of **11**—at 130 to 140°C) with an excess of amines afforded high yields of 3-amino substituted derivatives **11**–**14**. The thioxoderivative **10** easily reacted with alkylating agents in methanol in the presence of triethylamine at room temperature to yield 82–95% of S-alkyl derivatives **15**–**19**. Alkylation with epichlorohydrin undergo epoxide ring opening to give compound **18**. Interestingly, the end of these alkylation reactions could be observed visually by turn yellow starting thioxo derivative **10** into white precipitate of reaction products **15**–**19**.

The data of preliminary biological activity tests of some synthesized compounds showed weak antiproliferative activity of pyrimidotriazine **3**.

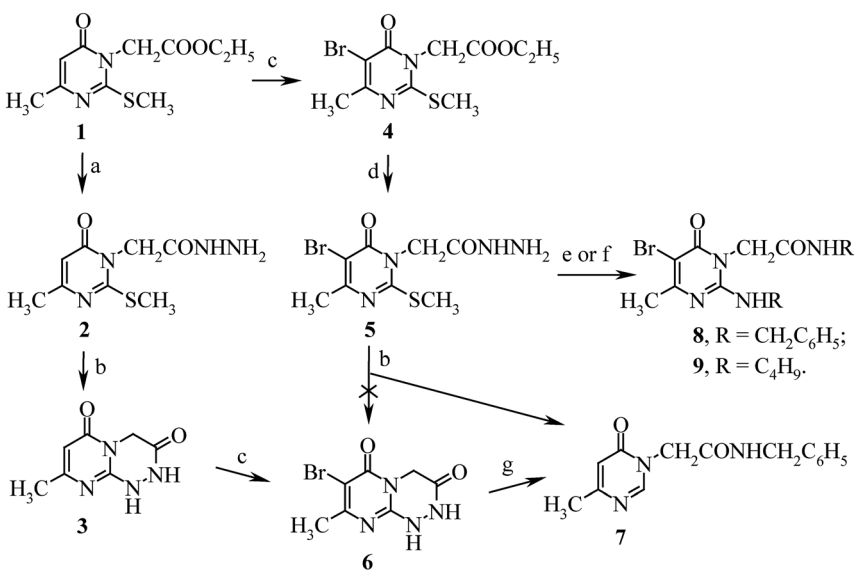
CONCLUSIONS

Thus, pyrimidotriazinedione **3** easily obtainable by the intramolecular cyclization reaction of hydrazide **2** is a convenient synthon for the synthesis of new pyrimido[2,1-*c*][1,2,4]triazine derivatives. Pyrimidotriazinedione **3** takes place in an electrophilic substitution reaction with bromine at the fifth position of pyrimidine ring, whereas amino and alkylthio substituents could be introduced into triazine ring of this heterosystem.

EXPERIMENTAL

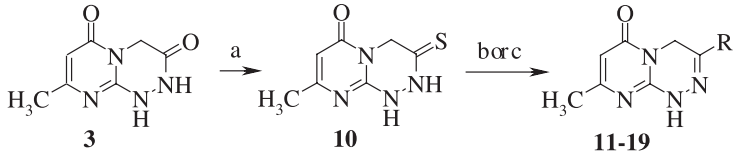
Melting points were determined on a ThermoFisher SCIENTIFIC IA9000 apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Unity Varian INOVA spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are

Scheme 2



Reagents and conditions: (a) $N_2H_4 \cdot H_2O$, CH_3OH, 5-10 °C, 4 h; (b) $C_6H_5CH_2NH_2$, 160 °C, 10 min; (c) Br_2, CH_3COOH, rt, 1 h; (d) $N_2H_4 \cdot H_2O$, CH_3OH, rt, 4 h; (e) $C_6H_5CH_2NH_2$, 80 °C, 7 h; (f) $C_4H_9NH_2$, reflux, 8 h; (g) $C_6H_5CH_2NH_2$, abs. C_2H_5OH, reflux, 10 min.

Scheme 3



R = $NHCH_2C_6H_5$ (**11**), NHC_4H_9 (**12**), N⟨⟩O (**13**), N⟨⟩ (**14**), $SCH_2COOC_2H_5$ (**15**), SCH_2CN (**16**), SCH_2CONH_2 (**17**), $SCH_2CH(OH)CH_2Cl$ (**18**), $SCH_2COC_6H_5$ (**19**).

Reagents and conditions: (a) L.R., toluene-HMPA, reflux, 2 h; (b) amine, reflux (130-140 °C for **11**), 10 min; (c) alkylating agent, $(C_2H_5)_3N$, CH_3OH, rt, 10 min (3 h for **16**, 1 h for **18**).

reported in ppm relative to TMS. The IR spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) as potassium bromide pellets. High-resolution mass spectra (HRMS) were recorded on a Dual-ESI Q-TOF 6520 mass spectrometer (Agilent Technologies). The reactions and purity of compounds was controlled by TLC on Silica gel 60 F_{254} plates (MERCK, Germany). Elemental analyses were performed at the Microanalytical Laboratory of the Department of Organic Chemistry of Vilnius University. All solvents were dried and distilled before use.

Ethyl(6-methyl-2-methylthio-4-oxopyrimidin-3(4*H*)-yl)acetate (**1**), (6-methyl-2-methylthio-4-oxopyrimidin-3(4*H*)-yl)acetohydrazide (**2**), and ethyl (5-bromo-6-methyl-2-methylthio-4-oxopyrimidin-3(4*H*)-yl) acetate (**4**) were synthesized as reported in refs. [19–21].

8-Methyl-2*H*-pyrimido[2,1-*c*][1,2,4]triazine-3,6(1*H*,4*H*)-dione (3). A mixture of 2.28 g (10 mmol) of hydrazide **2** and 2 mL (1.96 g, 18 mmol) of benzylamine was heated in an oil bath at 160°C temperature for 10 min. The reaction mixture was cooled to 80°C, then 5 mL of abs. ethanol was added and heated at reflux for 10 min. The reaction mixture was allowed to cool to room temperature, the solid was collected by filtration, washed with abs. ethanol, and dried to yield **3**, 1.48 g (82%) as a white solid, mp > 300°C (mp 334–336°C, ref. 18); IR: 1664, 1709 (C═O), 3312 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.98 (s, 3H, CH_3), 4.12 (s, 2H, NCH_2), 5.04 (s, 1H, CH); 10.20, 10.61 (2 s, 2H, 2NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 18.9, 43.0, 93.8, 139.6, 153.5, 159.8, 161.7 ppm.

(5-Bromo-6-methyl-2-methylthio-4-oxopyrimidin-3(4*H*)-yl) acetohydrazide (5). To a suspension of 3.21 g (10 mmol) of ester **4** in 20 mL of methanol, 1.5 mL (1.5 g, 30 mmol) of 100% hydrazine hydrate was added and the mixture was stirred at room temperature for 4 h. The solid formed was collected by filtration, washed with methanol-ether (1:1), and crystallized from methanol to yield **5**, 1.64 g (53%) as a white precipitate, mp 193–194°C; IR: 1661, 1676 (C═O), 3294, 3329, 3430 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 4.32, 4.98 (2s, 2H, NH_2), 4.62 (s, 2H, NCH_2), 8.86, 9.40 (2s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 15.5, 25.3, 46.5, 107.0, 158.2, 160.9, 161.5, 165.1 ppm. Anal. calcd. for $C_8H_{11}BrN_4O_2S$ (307.17): C 31.28; H 3.61. Found: C 31.59; H 3.48.

7-Bromo-8-methyl-2*H*-pyrimido[2,1-*c*][1,2,4]triazine-3,6(1*H*,4*H*)-dione (6). To a stirred solution of 1.8 g (10 mmol) of compound **3** in 10 mL of glacial acetic acid, 0.62 mL (2 g, 12 mmol) of bromine was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1 h and 6 mL of methanol-ether (1:1) was added. The precipitate formed was collected by filtration, washed with methanol-ether (1:1), and dried to yield **6**, 2.25 g (87%) as a yellowish solid, mp > 290°C (decomp.); IR: 1665, 1702 (C═O), 3071, 3174 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 4.19 (s, 2H, NCH_2), 10.33, 11.16 (2s, 2H, 2NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 20.4, 44.0, 88.6, 138.4, 152.2, 157.9, 159.6 ppm. Anal. calcd. for $C_7H_7BrN_4O_2$ (259.06): C 32.45; H 2.72. Found: C 32.69; H 3.04.

N*-Benzyl-(6-methyl-4-oxopyrimidin-3(4*H*)-yl)acetamide (7)*Method A (from hydrazide 5). A mixture of 0.31 g (1mmol) of hydrazide **5** and 0.4 mL (0.39 g, 3.6 mmol) of benzylamine was heated in an oil bath at 160°C temperature for 10 min. The reaction mixture was cooled to 80°C, and then 2 mL of abs. ethanol was added and heated at reflux for 10 min. The reaction mixture was allowed to cool to room temperature. The solid was collected by filtration and crystallized from water to yield **7**, 0.08 g (31%) as a white precipitate, mp 218–220°C; IR: 1658, 1668 (C═O), 3281 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.22 (s, 3H, CH_3), 4.33 (d, *J* = 5.7 Hz, 2H, NH*CH*$_2$), 4.60 (s, 2H, NCH_2), 6.28 (s, 1H, 5-CH), 7.2–7.4 (m, 5H, Ar-H) 8.32 (s, 1H, 2-CH), 8.79 (t, *J* = 5.7 Hz, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 23.8, 42.9, 48.4, 112.3, 127.6, 128.0, 129.0, 139.6, 152.9, 161.0, 164.6, 167.1. ppm; HRMS (*m/z*) calcd. for $C_{14}H_{15}N_3O_2$ ($[M + H]^+$): 258.1237. Found: 258.1244.

Method B (from pyrimidotriazinedione 6). A mixture of 0.26 g (1 mmol) of pyrimidotriazinedione **6**, 0.22 mL (0.21 g, 2 mmol) of benzylamine, and 8 mL of abs. ethanol was heated at reflux for 10 h. The reaction mixture was allowed to cool to room temperature. The resultant violet solid was filtered, and the filtrate was acidified to pH 6 by dropwise addition of conc. HCl. The white precipitate formed was collected by filtration and crystallized from water to yield 0.13 g (51%) of compound **7**.

***N*-Benzyl-(2-benzylamino-5-bromo-6-methyl-4-oxopyrimidin-3(4*H*)-yl)acetamide (8).** A mixture of 0.31 g (1 mmol) of hydrazide **5** and 0.4 mL (0.39 g, 3.6 mmol) of benzylamine was heated in an oil bath at 80°C for 7 h. To a reaction mixture, 5 mL of methanol was added, then heated at reflux for 10 min, and cooled to room temperature. The solid formed was collected by filtration, washed with methanol-ether (1:1), and crystallized from ethanol to yield **8**, 0.14 g (32%) as a white solid, mp 234–235°C; IR: 1651 (C═O), 3263, 3322 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 4.34 (d, *J* = 5.4 Hz, 2H, NH*CH*$_2$), 4.57 (d, *J* = 5.4 Hz, 2H, NH*CH*$_2$), 4.71 (s, 2H, NCH_2), 7.2–7.36 (m, 5H, Ar-H), 7.93 (t, *J* = 5.4 Hz, 1H, NH), 8.69 (t, *J* = 5.4 Hz, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 25.6, 43.0, 45.1, 45.3, 97.1, 127.4, 127.6, 127.8, 128.0, 128.9, 129.0, 139.7, 139.9, 153.1, 158.8, 162.4, 166.6 ppm.

Anal. calcd. for $C_{21}H_{21}BrN_4O_2$ (441.32): C 57.15; H 4.80. Found: C 57.43; H 5.02.

(5-Bromo-2-butylamino-6-methyl-4-oxopyrimidin-3(4*H*)-yl)-*N*-butylacetamide (9). A mixture of 0.31 g (1 mmol) of hydrazide **5** and 1.2 mL (0.89 g, 12 mmol) of butylamine was heated at reflux for 8 h. The cold reaction mixture was worked up with 4 mL of methanol to give a solid, which was filtered, washed with methanol-ether (1:1), and crystallized from methanol to yield **9**, 0.17 g (46%) as a white precipitate, mp 197–199°C; IR: 1648, 1668 (C═O), 3091, 3267, 3328 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 0.84–0.95 (m, 6H, $2CH_3$), 1.22–1.56 (m, 8H, $2CH_2CH_2$), 2.26 (s, 3H, CH_3), 3.02–3.12 (m, 2H, NHCH_2), 3.24–3.35 (m, 2H, NHCH_2), 4.55 (s, 2H, NCH_2), 7.17 (t, J = 5.4 Hz, 1H, NH), 8.08 (t, J = 5.4 Hz, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 14.3, 14.4, 20.1, 20.2, 25.6, 31.3, 31.9, 39.2, 41.7, 45.0, 96.6, 153.1, 158.8, 162.3, 166.3 ppm. Anal. calcd. for $C_{15}H_{25}BrN_4O_2$ (373.29): C 48.26; H 6.75. Found: C 48.08; H 6.76.

8-Methyl-3-thioxo-1,2,3,4-tetrahydro-6*H*-pyrimido[2,1-*c*][1,2,4]triazin-6-one (10). To a hot solution of 1.8 g (10 mmol) of compound **3** in 30 mL of dry toluene and 20 mL abs. hexamethylphosphoramide, 2.84 g (7 mmol) of Lawesson's reagent was added. The reaction mixture was stirred and heated at reflux for 2 h, and the toluene was evaporated in vacuum. The hot residual solution was diluted with water till precipitates appear and then left at room temperature for 2 h. The precipitate formed was collected by filtration, washed with water, and dried to yield **10**, 1.58 g (81%) as a yellow solid, mp 280–282°C (dimethylformamide-water); IR: 1472 (C═S), 1687 (C═O), 3242 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.01 (s, 3H, CH_3), 4.48 (s, 2H, NCH_2), 5.23 (s, 1H, CH), 11.04, 12.22 (2s, 2H, 2NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 19.0, 48.1, 96.5, 114.5, 153.2, 160.6, 177.4 ppm. Anal. calcd. for $C_7H_8BrN_4OS$ (196.23): C 42.84; H 4.11. Found: C 43.02; H 4.15.

General procedure for the synthesis of compounds 11–14. A mixture of 0.098 g (0.5 mmol) of compound **10** and 0.5 mol of the corresponding amine was heated at reflux (in the case of compound **11** at 130–140°C) for 10 min. To a reaction mixture, 5 mL of 2-propanol was added and heating at reflux was continued for 5 min. After cooling to room temperature, the precipitate formed was filtered off, washed with ethanol, and dried.

3-Benzylamino-8-methyl-1,4-dihydro-6H-pyrimido[2,1-c] [1,2,4] triazin-6-one (11). Yield 0.11 g (82%), white solid, mp > 290°C (dimethylformamide); IR: 1654 (C═O), 3307 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.03 (s, 3H, CH_3), 4.29 (d, J = 5.4 Hz, 2H, NHCH_2), 4.41 (s, 2H, NCH_2), 5.55 (s, 1H, CH), 7.06 (t, J = 5.4 Hz, 1H, NH), 7.22–7.4 (m, 5H, Ar-H), 10.18 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 24.2, 37.6, 45.0, 100.3, 127.5, 128.0, 129.0, 140.0, 146.4, 150.8, 161.1, 165.0 ppm. Anal. calcd. for $C_{14}H_{15}N_5O$ (269.30): C 62.44; H 5.61. Found: C 62.58; H 5.66.

3-Butylamino-8-methyl-1,4-dihydro-6H-pyrimido[2,1-c][1,2,4] triazin-6-one (12). Yield 0.105 g (89%), white solid, mp 297–298°C (dimethylformamide); IR: 1654 (C═O), 3326 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 0.89 (t, J = 7.2 Hz, 3H, CH_3), 1.24–1.4 (m, 2H, CH_2), 1.4–1.54 (m, 2H, CH_2), 2.03 (s, 3H, CH_3), 3.0–3.12 (m, 2H, NHCH_2), 4.32 (s, 2H, NCH_2), 5.53 (s,1H, CH), 6.52 (t, J = 4.8 Hz, 1H, NH), 10.15 (br s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 14.4, 20.5, 24.2, 31.1, 37.6, 41.1, 100.1, 146.7, 150.9, 161.1, 165.0 ppm. Anal. calcd.for $C_{11}H_{17}N_5O$ (235.29): C 56.15; H 7.28. Found: C 56.31; H 7.18.

8-Methyl-3-morpholin-4-yl-1,4-dihydro-6H-pyrimido[2,1-c] [1,2,4] triazin-6-one (13). Yield 0.1 g (80%), white solid, mp 287–288°C (dimethylformamide); IR: 1679 (C═O), 3078, 3440 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.05 (s, 3H, CH_3), 3.20 (t, J = 4.8 Hz, 4H, $2CH_2$), 3.65 (t, J = 4.8 Hz, 4H, $2CH_2$), 4.51 (s, 2H, NCH_2), 5.60 (s, 1H, CH), 10.43 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 24.1, 36.9, 46.1, 66.2, 100.8, 147.2, 149.6, 161.0, 165.1 ppm. Anal. calcd. for $C_{11}H_{15}N_5O_2$ (249.27): C 53.00; H 6.07. Found: C 53.35; H 6.34.

8-Methyl-3-piperidin-1-yl-1,4-dihydro-6H-pyrimido[2,1-c] [1,2,4] triazin-6-one (14). Yield 0.086 g (70%), white solid, mp 244–245°C (dimethylformamide-water); IR: 1687 (C═O), 3242 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.55 (s, 6H, $3CH_2$), 2.04 (s, 3H, CH_3), 3.22 (s, 4H, $2CH_2$), 4.49 (s, 2H, NCH_2), 5.58 (s, 1H, CH), 10.39 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 24.2, 24.6, 25.5, 36.9, 46.6, 100.5, 147.0, 150.0, 161.1, 165.1 ppm. Anal. calcd. for $C_{12}H_{17}N_5O$ (247.30): C 58.28; H 6.93. Found: C 58.41; H 6.98.

General procedure for the synthesis of compounds 15–19. To a suspension of 0.147 g (0.75 mmol) of compound **10** in 5 mL of methanol, 0.115 mL (0.076 g, 0.75 mmol) of triethylamine was added and the mixture was stirred at room temperature for 3 min. To a reaction mixture, 0.75 mol of corresponding alkylation agent (in the case of compound **15**—0.083 mL of ethyl bromoacetate, **16**—0.047 mL of chloroacetonitrile, **17**—a solution of 0.139 g of iodoacetamide in 1 mL of methanol, **18** – 0.048 mL of epichlorohydrin, **19**—a solution of 0.15 g of 2-bromoacetophenone in 1 mL of methanol) was added, and stirring was continued at room temperature for 10min (in the case of compound **16**—3 h, **19**—1 h). The precipitate was filtered off, washed with ether, and crystallized.

Ethyl[(8-methyl-6-oxo-1,6-dihydro-4H-pyrimido[2,1-c][1,2,4] triazin-3-yl)thio]acetate (15). Yield 0.18 g (86%), white solid, mp 214–215°C (methanol); IR: 1687, 1743 (C═O), 3144, 3210 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.21 (t, J = 7.2 Hz, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.92 (s, 2H, SCH_2), 4.14 (q, J = 7.2 Hz, 2H, CH_2), 4.47 (s, 2H, NCH_2), 5.76 (s, 1H, CH), 11.26 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 14.7, 24.1, 32.4, 40.0, 61.9, 103.4, 144.1, 149.0, 160.3, 165.2, 168.8 ppm. Anal. calcd. for $C_{11}H_{14}N_4O_3S$ (282.32): C 46.80; H 5.00. Found: C 46.96; H 5.09.

[(8-Methyl-6-oxo-1,6-dihydro-4H-pyrimido[2,1-c][1,2,4]triazin-3-yl)thio]acetonitrile (16). Yield 0.145 g (82%), white solid, mp 234–236°C (methanol); IR: 1703 (C═O), 2250 (C≡N), 3141, 3211 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.08 (s, 3H, CH_3), 4.14 (s, 2H, SCH_2), 4.52 (s, 2H, NCH_2), 5.78 (s, 1H, CH), 11.45 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 15.7, 24.1, 40.2, 103.7, 118.0, 142.5, 148.8, 160.3, 165.2, 168.8 ppm. Anal. calcd. for $C_9H_9N_5OS$ (235.27): C 45.95; H 3.86. Found: C 46.16; H 4.01.

[(8-Methyl-6-oxo-1,6-dihydro-4H-pyrimido[2,1-c][1,2,4] triazin-3-yl)thio]acetamide (17). Yield 0.24 g (95%), white solid, mp 286–287°C (dimethylformamide-water); IR: 1684 (C═O), 3196, 3363 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.08 (s, 3H, CH_3), 3.71 (s, 2H, SCH_2), 4.45 (s, 2H, NCH_2), 5.76 (s, 1H, CH), 7.24, 7.61 (2s, 2H, NH_2), 11.22 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 24.1, 34.0, 40.3, 103.3, 144.9, 149.1, 160.4, 165.2, 169.2 ppm. Anal. calcd. for $C_9H_{11}N_5O_2S$ (253.28): C 42.68; H 4.38. Found: C 42.75; H 4.36.

3-[(3-Chloro-2-hydroxypropyl)thio]-8-methyl-1,4-dihydro-6H-pyrimido[2,1-c][1,2,4]triazin-6-one (18). Yield 0.18 g (83%), white solid, mp 196–197°C (acetonitrile); IR: 1680 (C═O), 3131 (NH), 3407 (OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.07 (s, 3H, CH_3), 3.02–3.28 (m, 2H, SCH_2), 3.57–3.72 (m, 2H, CH_2Cl), 3.88–4.0 (m, 1H, CH), 4.43 (s, 2H, NCH_2), 5.69 (d, J = 5.1 Hz, 1H, OH), 5.75 (s, 1H, CH), 11.21 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 24.1, 34.1, 40.5, 49.2, 69.2, 103.3, 145.1, 149.1, 160.4, 165.2 ppm. Anal. calcd. for $C_{10}H_{13}ClN_4O_2S$ (288.76): C 41.59; H 4.54. Found: C 41.60; H 4.38.

8-Methyl-3-[(2-oxo-2-phenylethyl)thio]-1,4-dihydro-6H-pyrimido [2,1-c][1,2,4]triazin-6-one (19). Yield 0.28 g (89%), white solid,

mp 240–242°C (dioxane); IR: 1686 (C═O), 3137 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.06 (s, 3H, CH_3), 4.49(s, 2H, NCH_2), 4.76 (s, 2H, SCH_2), 5.76 (s, 1H, CH), 7.53–7.6 (m, 2H, 3,5-CH), 7.66–7.72 (m, 1H, 4-CH), 7.99–8.05 (m, 2H, 2,6-CH), 11.15 (s, 1H, NH) ppm; ^{13}C-NMR (DMSO-d_6): δ 24.1, 38.4, 103.4, 129.1, 129.6, 134.4, 136.1, 144.4, 149.1, 160.3, 165.2, 193.4 ppm. Anal. calcd. for $C_{15}H_{14}N_4O_2S$ (314.3 6): C 57.31; H 4.49. Found: C 57.35; H 4.57.

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