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SYNTHESIS OF 6-[4-(ALLYL/PHENYL)-5-THIOXO-1,2,4-TRIAZOL-3-YL]PYRIMIDINE-2,4-DIONES AND THEIR REACTION WITH ELECTROPHILES

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Cyclization of 1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)carbonyl-4-R-thiosemicarbazides in basic medium gave 6-(4-R-5-thioxo-1,2,4-triazol-3-yl)pyrimidine-2,4-diones (R = Allyl, Ph). Alkylation of the latter with iodomethane occurred at the sulphur atom to give the corresponding methylsulfanyl derivatives. Acetylation using acetyl chloride occurred at the $N_{(1)}$ atom of the triazole ring to the corresponding acetyl derivative when R = Ph but for R = Allyl the acetylation did not occur under the same conditions. In the presence of bromine in refluxing methanol the indicated allyl-substituted compound cyclizes to 6-bromomethyl-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)-5,6-dihydrothiazolo[2,3-c]-1,2,4-triazole. Under Mannich and bromination conditions the methylsulfanyl derivatives prepared form derivatives at the 5 position of the uracil ring: 5-methylmorpholino-(piperidino)- and 5-bromo-(4-R-5-thioxo-1,2,4-triazol-3-yl)pyrimidine-2,4-diones respectively.

Keywords: 6-[4-(allyl/phenyl)-5-thioxo-1,2,4,-triazol-3-yl]pyrimidine-2,4-diones, 6-bromomethyl-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)-5,6-dihydrothiazolo[2,3-*c*]-1,2,4-triazole, aminomethylation, acetylation, bromination, methylation, Mannich reaction products.

Noncondensed bicyclic compounds which contain uracil and 1,2,4-triazole rings are of interest not only from a chemical viewpoint for their reactions involving the heterocycles but also as potentially biologically active compounds. It has been shown that some of them increase the activity of phleomycin [1], or have tuberculostatic [2, 3], anti-inflammatory [4], anticonvulsant [5], antidepresant [6], or nematodacidal and fungicidal [7, 8] activity. We have previously synthesized 2-(3-thioxo-1,2,4-triazol-5-yl)-4,6-diphenylpyrimidines which have shown anti-inflammatory action [9, 10].

In continuing our investigation of triazolylpyrimidines we now report the synthesis of 6-(4-R-5-thioxo-1,2,4-triazol-3-yl)pyrimidine-2,4-diones **2a,b** from the 1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)carbonyl-4-R-thiosemicarbazides **1a,b** and their reaction with electrophilic reagents.

Using a known method [11] orotic acid hydrazide and allyl- or phenylisothiocyanates gave the corresponding thiosemicarbazides **1a,b** which underwent cyclization in 10% KOH to give the substituted pyrimidinediones **2a,b**.

It is known that 4-alkyl(aryl)-1,2,4-triazole-3-thiones react with different electrophiles at the S or the $N_{(2)}$ atom [12, 13]. In the case of compounds **2a,b** the formation of products at the $N_{(1)}$, $N_{(3)}$, O, or $C_{(5)}$ atoms might also be expected.

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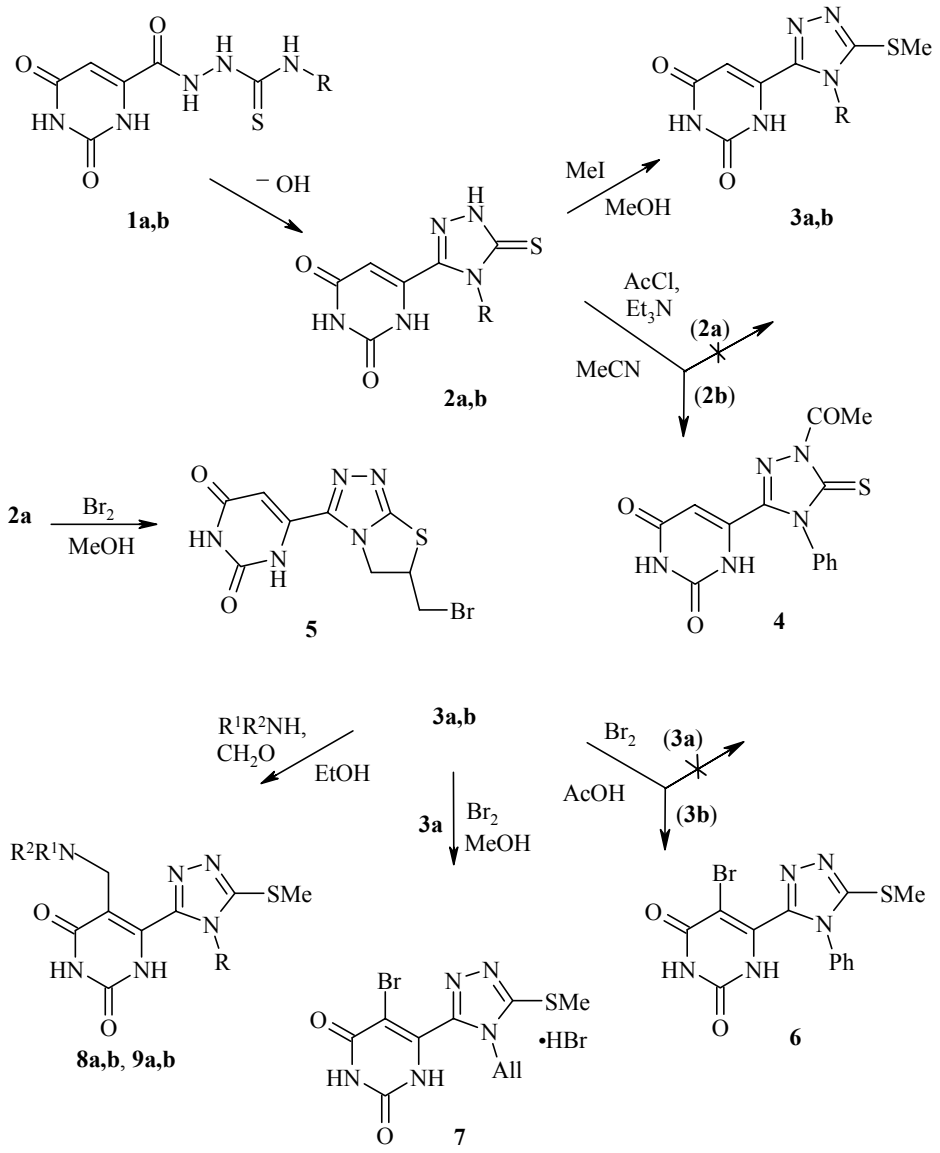


1-3, **8**, **9** **a** R = CH_2–CH=CH_2, **b** R = Ph; **8** R^1R^2N = piperidino; **9** R^1R^2N = morpholino

Treatment of compounds **2a,b** with iodomethane in refluxing methanol in the presence of MeONa gave the products of alkylation at the sulphur atom as the methylsufanyl derivatives **3a,b**. The action of acetyl chloride in refluxing acetonitrile in the presence of triethylamine occurred only in the case of the phenyl-substituted **2b** to form the product **4** (65%) which is acetylated at atom $N_{(2)}$ in the triazole ring. Under these conditions the allyl-substituted **2a** does not react in acetonitrile. Exchange of solvent and change of reaction medium temperature did not give a positive result.

Refluxing equimolar amounts of bromine and the thione **2a** in methanol gave a 44% yield of the product of intramolecular cyclization which was the substituted thiazolo[2,3-*c*]-1,2,4-triazole **5**.

Since the triazole ring in compounds **2a,b** appeared to be more reactive when reacting with C-electrophiles, for the reaction involving the pyrimidine we have used the S-methylated derivatives **3a,b**. It was found that bromination and aminomethylation (the Mannich reaction) of the latter occurred at the $C_{(5)}$ atom of the pyrimidine ring. Thus the action of bromine in glacial acetic acid on the phenyl-substituted **3b** at room temperature gave a 44% yield of the 5-bromo derivative **6**. Under the same conditions the allyl-substituted

compound **3a** did not react with bromine. The bromination product **7** was prepared in overall yield of 18% by refluxing equimolar amounts of the substituted pyrimidinedione **3a** with bromine in methanol. Treatment of equimolar amounts of the methylsulfanyl-substituted **3a,b** with formaldehyde, and piperidine or morpholine in refluxing ethanol gave the 5-aminomethyl derivatives **8a,b**, **9a,b**.

The composition and structure of the synthesized compounds were confirmed by the results of elemental analysis (Table 1) and from IR and ^{1}H NMR spectroscopic data (Table 2). The IR spectra of all of compounds **1-9** show absorption bands in the regions 3030-3381 (NH), 1702-1723 ($C_{(2)}$=O), and 1616-1691 cm^{-1} ($C_{(4)}$=O), typical of a uracil ring [14, 15]. The spectra of the thiosemicarbazides **1a,b** and compound **4** show the presence of one further absorption band for a C=O group at 1715, 1731, and 1763 cm^{-1}. The absorptions in the spectra of the thiosemicarbazides **1a,b** in the range 1319-1320 cm^{-1} and in the spectra of thiones **2a,b** and **4** at 1324-1348 and 1532-1534 cm^{-1} are typical for a C=S bond. These bands are absent in the spectra of the S-methyl-substituted **3**, **5-9**. The spectra of the bromo derivatives **6, 7** show characteristic absorption bands at 568-580 cm^{-1} which correspond to the C–Br bond.

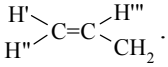
In the ^{1}H NMR spectra of all of compounds **1-5** which are not substituted at position 5 of the uracil ring there is present a signal at 5.2-6.1 ppm for the H-5 proton of this fragment and also signals for the two NH groups in the uracil at 10.9-11.8 ppm. This signal for the NH group proton of the triazole ring in compounds **2a,b** is observed at 13.9-14.5 ppm. In the spectra of compounds **6-9** substituted at uracil ring atom $C_{(5)}$ the H-5 proton signal is absent. The 5-aminomethyl derivatives **8, 9** are typified by a singlet signal for the 5-CH_2 at 4.3-5.2 ppm.

TABLE 1. Characteristics of Compounds **1-9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	Yield, %
		C	H	N		
1a	$C_{19}H_{11}N_5O_3S$	40.27 / 40.14	4.31 / 4.11	25.72 / 26.00	212-214 (DMF–EtOH)	79
2a	$C_9H_9N_5O_2S$	43.32 / 43.02	3.58 / 3.61	27.42 / 27.87	240-241 (DMF–H_2O)	87
2b	$C_{12}H_9N_5O_2S$	49.87 / 50.16	3.29 / 3.13	24.58 / 24.37	300 (DMF)	66
3a	$C_{10}H_{11}N_5O_2S$	45.03 / 45.27	4.19 / 4.18	26.47 / 26.39	162-164 (EtOH)	79
3b	$C_{13}H_{11}N_5O_2S$	51.54 / 51.77	3.47 / 3.60	23.17 / 23.33	299.5-300.5 (DMF)	60
4	$C_{14}H_{11}N_5O_3S$	51.27 / 51.06	3.42 / 3.37	21.35 / 21.26	153-154 (dioxane)	65
5	$C_9H_8BrN_5O_2S$	33.13 / 32.74	2.44 / 2.44	21.26 / 21.21	236-237 (DMF)	44
6	$C_{13}H_{10}BrN_5O_2S$	41.17 / 41.07	3.30 / 2.65	18.32 / 18.45	242.0-242.5 (EtOH–H_2O)	40
7	$C_{10}H_{10}BrN_5O_2S$·HBr	28.04 / 28.25	2.37 / 2.60	16.54 / 16.46	195-198 (DMF)	18
8a	$C_{16}H_{22}N_6O_2S$	53.36 / 53.02	6.33 / 6.12	22.95 / 23.18	167-170 (EtOH)	53
8b	$C_{19}H_{22}N_6O_2S$	57.04 / 57.27	5.80 / 5.56	20.84 / 21.08	190 (dec.) (dioxane)	54
9a	$C_{15}H_{20}N_6O_3S$	49.67 / 49.44	5.71 / 5.53	23.28 / 23.06	181-182 (MeOH)	31
9b	$C_{18}H_{20}N_6O_3S$	54.09 / 53.99	5.10 / 5.03	21.30 / 20.99	177-179 (H_2O)	30

TABLE 2. Spectroscopic Characteristics of Compounds **1-9**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz) *
1a	3289, 3170 (NH), 1715 (C=O), 1702 ($C_{(2)}$=O), 1672 ($C_{(4)}$=O), 1319 (C=S)	6.12 (1H, s, CH_{ur}); 8.39 (1H, s, $\underline{NH}CH_2$); 9.53 (1H, NHCS); 10.73 (1H, s, CONH); 10.92 (1H, s, NH_{ur}); 11.36 (1H, s, NH_{ur}). H_{all}: 5.09 (dd); 5.15 (dd); 5.83 (m); 4.13 (d); *J* = 1.7, *J* = 10.3, *J* = 17.3, *J* = 5.0
1b	3184 (NH), 1731 (C=O), 1718 ($C_{(2)}$=O), 1674 ($C_{(4)}$=O), 1320 (C=S)	6.15 (1H, s, CH_{ur}); 7.21-7.44 (5H, m, C_6H_5); 9.86 (2H, m, NHCSNH); 10.93 (1H, s, CONH); 10.98 (1H, s, NH_{ur}); 11.37 (1H, s, NH_{ur})
2a	3162, 3080 (NH), 1709 ($C_{(2)}$=O), 1679 ($C_{(4)}$=O), 1532, 1348 (C=S)	5.91 (1H, s, CH_{ur}); 11.39 (2H, s, NH_{ur}); 13.97 (1H, s, NH_{thia}). H_{all}: 5.16 (d); 4.92 (d); 5.83 (m); 4.69 (d); *J* = 0, *J* = 10.8, *J* = 17.1, *J* = 2.7
2b	3306 (NH), 1719 ($C_{(2)}$=O), 1687 ($C_{(4)}$=O), 1534, 1340 (C=S)	5.33 (1H, s, CH_{ur}); 7.42-7.51 (5H, m, C_6H_5); 11.15-11.27 (2H, m, NH_{ur}); 14.47 (1H, s, NH_{thia})
3a	3156, 3095 (NH), 1710 ($C_{(2)}$=O), 1668 ($C_{(4)}$=O), 1309 (C–S–C)	2.68 (3H, s, SCH_3); 5.88 (1H, s, CH_{ur}); 11.30-11.36 (2H, s, NH_{ur}); H_{all}: 5.26 (dd); 4.86 (dd); 5.94 (m); 4.65 (d); *J* = 0.9, *J* = 10.5, *J* = 17.3, *J* = 4.2
3b	3176, 3030 (NH), 1723 ($C_{(2)}$=O), 1670 ($C_{(4)}$=O), 1315 (C–S–C)	2.65 (3H, s, SCH_3); 5.19 (1H, s, CH_{ur}); 7.51-7.62 (5H, m, C_6H_5); 11.26 (2H, m, NH_{ur})
4	3154 (NH), 1763 (C=O), 1708 ($C_{(2)}$=O), 1667 ($C_{(4)}$=O), 1532, 1324 (C=S)	2.73 (3H, s, $COCH_3$); 5.41 (1H, s, CH_{ur}); 7.48-7.59 (5H, m, C_6H_5); 11.31-11.40 (2H, m, NH_{ur})
5	3163, 3038 (NH), 1706 ($C_{(2)}$=O), 1663 ($C_{(4)}$=O)	3.95 (2H, d, ^3J = 6.9, CH_2Br); 4.39 (1H, dd, ^2J = 11.7, ^3J = 7.5, NC$\underline{H}$H); 4.64 (1H, dd, ^2J = 11.7, ^3J = 4, NCH$\underline{H}$); 5.05 (1H, m, ^3J = 4, ^3J = 6.9, ^3J = 7.5, $CH_{тиа}$); 5.84 (1H, s, CH_{ur}); 11.26-11.34 (2H, m, NH_{ur})
6	3166 (NH), 1718 ($C_{(2)}$=O), 1691 ($C_{(4)}$=O), 1280 (C–S–C), 580 (C–Br)	2.69 (3H, s, SCH_3); 7.39-7.61 (5H, m, C_6H_5); 11.83 (2H, s, NH_{ur})
7	3381, 3165 (NH), 2726 (N^+H), 1722 ($C_{(2)}$=O), 1677 ($C_{(4)}$=O), 1284 (C–S–C), 568 (C–Br)	2.68 (3H, s, SCH_3); 11.33 (1H, s, N^+H_{thia}); 11.70 (1H, s, NH_{ur}); 11.84 (1H, s, NH_{ur}). H_{all}: 5.23 (d); 5.08 (d); 5.80 (m); 4.55 d; *J* = 0, *J* = 10.4, *J* = 17.3, *J* = 5.1
8a	3054 (NH), 1714 ($C_{(2)}$=O), 1633 ($C_{(4)}$=O), 1306 (C–S–C)	2.08–2.18 (6H, m, $(CH_2)_3$); 3.19 (3H, s, SCH_3); 3.22 (2H, m, $^2J_{ae}$ = 11.4, $^3J_{ae}$ = 9.3, N(C$\underline{H}a$He)$_2$); 3.86 (2H, d, $^2J_{ae}$ = 11.4, (NCH$a\underline{H}e$)$_2$); 4.34 (2H, s, NCH_2). H_{all}: 5.73 (d); 5.65 (d); 6.03 (m); 5.06 (d); *J* = 0, *J* = 10.6, *J* = 17.1, *J* = 6.2
8b	3249 (NH), 1721 ($C_{(2)}$=O), 1666 ($C_{(4)}$=O), 1332 (C–S–C)	1.73–2.18 (6H, m, $(CH_2)_3$); 3.06 (3H, s, SCH_3); 3.26 (2H, m, $^2J_{ae}$ = 11.69, $^3J_{aa}$ = 12.29, N(C$\underline{H}a$He)$_2$); 3.85 (2H, d, $^2J_{ae}$ = 11.69, (NCH$a\underline{H}e$)$_2$); 4.47 (2H, s, NCH_2); 7.61=7.90 (5H, m, C_6H_5)
9a	3260, 3199 (NH), 1717 ($C_{(2)}$=O), 1680 ($C_{(4)}$=O), 1306 (C–S–C)	3.67 (3H, s, SCH_3); 4.12 (2H, m, $^2J_{ae}$ = 12.5, $^3J_{aa}$ = 13.2, N(C$\underline{H}a$He)$_2$); 4.44 (2H, d, $^2J_{ae}$ = 12.5, (NCH$a\underline{H}e$)$_2$); 4.80 (2H, m, $^2J_{ae}$ = 12.7, $^3J_{aa}$ = 13.2, O(C$\underline{H}a$He)$_2$); 4.96 (2H, d, $^2J_{ae}$ = 12.7, O(CH$a\underline{H}e$)$_2$); 4.99 (2H, s, NCH_2). H_{all}: 6.24 (d); 6.16 (d); 6.55 (m); 5.57 (d); *J* = 0, *J* = 10.3, *J* = 17.1, *J* = 5.9
9b	3182, 3056 (NH), 1720 ($C_{(2)}$=O), 1682 ($C_{(4)}$=O), 1300 (C–S–C)	3.62 (3H, s, SCH_3); 4.23 (2H, m, $^2J_{ae}$ = 12.66, $^3J_{aa}$ = 11.5, N(C$\underline{H}a$He)$_2$); 4.50 (2H, d, $^2J_{ae}$ = 12.66, NCH$a\underline{H}e$)$_2$); 4.86 (2H, m, $^2J_{ae}$ = 12.5, $^3J_{aa}$ = 11.5, O(C$\underline{H}a$He)$_2$); 5.05 (2H, d, $^2J_{ae}$ = 12.5, O(CH$a\underline{H}e$)$_2$); 5.20 (2H, s, NCH_2); 8.21-8.47 (5H, m, C_6H_5)

* H_{ur} is the proton of the uracil fragment; H_{tria} the proton of the triazole ring; H_{thia} the thiazole ring proton; H_{all} the signals for the protons of the allyl substituent H', H'', H''', CH_2 and spin-spin coupling (*J*): $^2J_{H'H''}$, $^3J_{H'H'''}$, $^3J_{H''H'''}$, $^3J_{H'''CH_2}$  .

The proton signals of the allyl substituent in the spectra of compounds **1a-3a** and **6, 8a, 9a** are given in Table 2. The chemical shifts and spin-spin couplings agree well with literature data for monosubstituted alkenes [16]. The spectra of the phenyl-substituted compounds **1b-3b, 4, 6, 8b** and **9b** contain multiplet signals for the phenyl group protons at 7.2-8.5 ppm.

In the S-methyl derivatives **3, 6-9** the spectra show a typical singlet signal for the SCH_3 group at 2.6-3.7 ppm.

In the spectrum of compound **5** there is a signal for the CH_2Br substituent as a doublet at 3.9 ppm as well as signals for the thiazole ring fragments, the CH group (multiplet at 5.1 ppm) and the CH_2 group (two double doublets at 4.4 and 4.6 ppm).

A preliminary study of the anti-inflammatory activity has been made by E. Udrenaite (Vilnius Univeristy, Medical faculty) which has showed that compounds **2a,b, 3a,b** suppresses the inflammatory process to the same degree as acetylsalicyclic acid.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian Unity Inova (300 MHz) spectrometer using DMSO-d_6 (compounds **1-7**) or CF_3COOD (compounds **8a,b, 9a,b**) relative to TMS. IR spectra were obtained on a Perkin-Elmer BX FT-IR spectrometer for a suspension in vaseline oil or for KBr tablets (in the case of compounds **2b, 5, 9a,b**). Monitoring of the course of the reaction and the purity of the compounds synthesized was carried out on Silufol UV-254 plates (Kavalier) with ethyl acetate–methanol (3:1) as eluent.

4-Allyl-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)carbonylthiosemicarbazide (1a) was prepared by the method in [1] holding the mixture of orotic acid hydrazide (5.1 g, 30 mmol) and allylisothiocyanate (5.94 g, 5.84 ml, 60 mmol) for 9 h at 90°C in a mixture of absolute 2-propanol and absolute DMF (4:1) to give product **1a** (6.4 g).

4-Phenyl-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)carbonylthiosemicarbazide (1b) was synthesized similarly from orotic acid hydrazide and phenylisothiocyanate to give a yield of 82% with mp 221.5-223°C (DMF) (mp 221.5-223°C [11]).

6-(4-Allyl-5-thioxo-1,2,4-triazol-3-yl)pyrimidine-2,4-dione (2a). A mixture of the thiosemicarbazide **1a** (5.5 g, 20 mmol) and 10% KOH (40 ml) was refluxed for 4 h. After cooling, the reaction mixture was filtered and the filtrate was acidified with conc. HCl to a weakly acid reaction. The separated product **2a** was filtered, washed with water and ethanol, dried, and purified by recrystallization.

6-(4-Phenyl-5-thioxo-1,2,4-triazol-3-yl)pyrimidine-2,4-dione (2b) was synthesized similarly to compound **2a**.

6-(4-Allyl-5-methylthio-1,2,4-triazol-3-yl)pyrimidine-2,4-dione (3a) and 6-(5-Methylsulfanyl-4-phenyl-1,2,4-triazol-3-yl)pyrimidine-2,4-dione (3b) (General Method). A solution of sodium methoxide prepared from sodium (0.18 g, 8 mmol) and methanol (20 ml) was added to a solution of compound **2a,b** (8 mmol) in methanol (100 ml). Iodomethane (1.42 g, 0.62 ml, 10 mmol) was added to the solution obtained (in the case of **2b** a suspension). The mixture was refluxed for 1 h and cooled. The precipitated product **3** was filtered off, washed with water, dried, and recrystallized.

6-(1-Acetyl-4-phenyl-5-thioxo-1,2,4-triazol-3-yl)pyrimidine-2,4-dione (4). Absolute triethylamine (0.35 g, 0.48 ml, 3.5 mmol) was added to a refluxing suspension of compound **2b** (1 g, 3.5 mmol) in absolute acetonitrile (70 ml). The clear solution obtained was treated with acetyl chloride (0.273 g, 0.25 ml, 3.5 mmol) and the mixture was refluxed for 2.5 h. After cooling, the precipitated product **4** was filtered off, washed with methanol and ether, dried, and recrystallized.

6-Bromomethyl-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)-5,6-dihydrothiazolo[2,3-*c*]-1,2,4-triazole (5). A solution of bromine (0.48 g, 0.15 ml, 3 mmol) in absolute methanol (10 ml) was added dropwise with stirring to a refluxing solution of compound **2a** (0.75 g, 3 mmol) in absolute methanol (125 ml). The mixture was refluxed for 2.5 h and cooled. The precipitated product **5** was filtered off, washed with ether, dried, and recrystallized.

5-Bromo-6-(5-methylsulfanyl-4-phenyl-1,2,4-triazol-3-yl)pyrimidine-2,4-dione (6). A solution of bromine (0.29 g, 0.095 ml, 1.85 mmol) in acetic acid (2 ml) was added dropwise to a solution of compound **3b** (0.5 g,1.65 mmol) in acetic acid (3 ml). The product was stirred at room temperature for 45 min and water (5 ml) and NaOH were added to neutral reaction. The precipitated product **6** was filtered off, washed with water, dried, and recrystallized.

6-(4-Allyl-5-methylsulfanyl-1,2,4-triazol-3-yl)-5-bromopyrimidine-2,4-dione Hydrobromide (7). A solution of bromine (0.6 g, 0.19 ml, 3.76 mmol) in absolute methanol (15 ml) was added dropwise over 1 h to a refluxing solution of compound **3a** (1 g, 3.76 mmol) in absolute methanol (60 ml). The mixture obtained was refluxed with stirring for 15 h. Solvent was distilled off to dryness on a rotary evaporator and the residue was treated with acetonitrile (10 ml). The precipitated product **7**·HBr was filtered off and recrystallized.

6-(4-Allyl-5-methylsulfanyl-1,2,4-triazol-3-yl)-5-[morpholino(piperidino)methyl]pyrimidine-2,4-diones (8a, 9a) and 6-(5-Methylsulfanyl-4-phenyl-1,2,4-triazol-3-yl)-5-[morpholino(piperidino)methyl]-pyrimidine-2,4-diones (8b, 9b) (General Method). Piperidine (0.25 g, 0.29 ml, 3 mmol) or morpholine (0.26 g, 0.26 ml, 3 mmol) and a 35% solution of formaldehyde (0.24 ml, 3 mmol) were added to a solution of compound **3a** or suspension of **3b** (3 mmol) in absolute ethanol (30 ml). The mixture was refluxed for 11 h and cooled. The precipitated products **8a, 9a** were filtered off, dried, and recrystallized. For separation of the products **8b, 9b** the solvent was evaporated on a rotary evaporator and the residue was dried and recrystallized.

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