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An Efficient Synthesis of Novel 4-Aryl-2-thioxo-3,4-dihydro-1*H*-pyrimido[1,2-a][1,3,5]triazin-6(2*H*)-ones and Their Antibacterial Activity

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Abstract: New substituted 4-aryl-8-methyl-2-thioxo-1,2,3,4-tetrahydro-6*H*-pyrimido[1,2-a][1,3,5]triazin-6-one **8a–b** and ethyl 4-aryl-6-oxo-2-thioxo-1,3,4,6-tetrahydro-2*H*-pyrimido[1,2-a][1,3,5]triazine-7-carboxylate **8c–e** were synthesized by the reaction of the corresponding 4-oxopyrimidin-2-ylthioureas with arylaldehydes. The formation of only one regioisomer was proven using complex spectral data and its structure was characterized. It was found that the interaction of 6-amino-4-phenyl-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione with ethyl acetoacetate and diethyl ethoxymethylenemalonate leads to the formation of the same regioisomer. That is, changing the sequence of stages in this cascade process does not affect the structure of the final reaction product. All synthesized compounds exhibit antibacterial activity against *E. coli* and *S. aureus* cultures at a concentration (MIC) of 256 μg/mL.

Keywords: pyrimido[1,2-a][1,3,5]triazine; cyclization; antibacterial; pyrimidin-2-ylthiourea

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1. Introduction

Pyrimidine and 1,3,5-triazine cycles are preferred scaffolds for obtaining substances with a wide spectrum of biological activity [1–4]. Various drugs based on these cycles are used in practice. Among these, for example, the respiratory stimulant Almitrin, the phos-phodiesterase inhibitor Irsogladin, the antitumor agent Altretamine, and the EGFR tyrosine kinase inhibitors Erlotinib and Gefitinib (Figure 1), etc.

The combination of two pharmacophore fragments in one molecule can lead to an increase in biological effects [5,6]. Fused pyrimido[1,2-a][1,3,5]triazines 1 (Figure 2) are known to have anticarcinogenic [7], antibacterial [8,9], and antiviral [10] effects.

Only a small number of methods for the synthesis of pyrimido[1,2-a][1,3,5]triazines is known [11]. There are two main strategies to obtain the pyrimido[1,2-a][1,3,5]triazine matrix. The first one is the formation of a triazine cycle based on 2-aminopyrimidines (path A). The second one is the formation of a pyrimidine ring based on 2-amino-1,3,5-triazines (path B) [11].

The Mannich reaction is widely used to obtain pyrimido[1,2-a][1,3,5]triazines from 2-aminopyrimidines (path A) and consists in a reaction with a substituted amine and formaldehyde [12,13]. Such cycles can also be obtained in the reactions of 2-aminopyrimidines with N-cyanoformimidate [11,14], chlorocarbonyl isocyanate [15], and aroylisothiocyanates [16].

Pyrimidines containing a substituted amino group in position 2, which is included in the structural fragment of amidines, guanidines, ureas, or thioureas, can be used to form a triazine ring as a result of their reaction with monoelectrophilic reagents. This reaction leads to the introduction of various substituents into the fourth position of the triazine ring. Phosgene [17], ethyl chloroformate [9], carbon disulfide [18], orthoesters [18–20], and

carbonyl compounds [21,22] can be used as monoelectrophiles. The regioselectivity of ring closure in such reactions is currently an important problem [11].

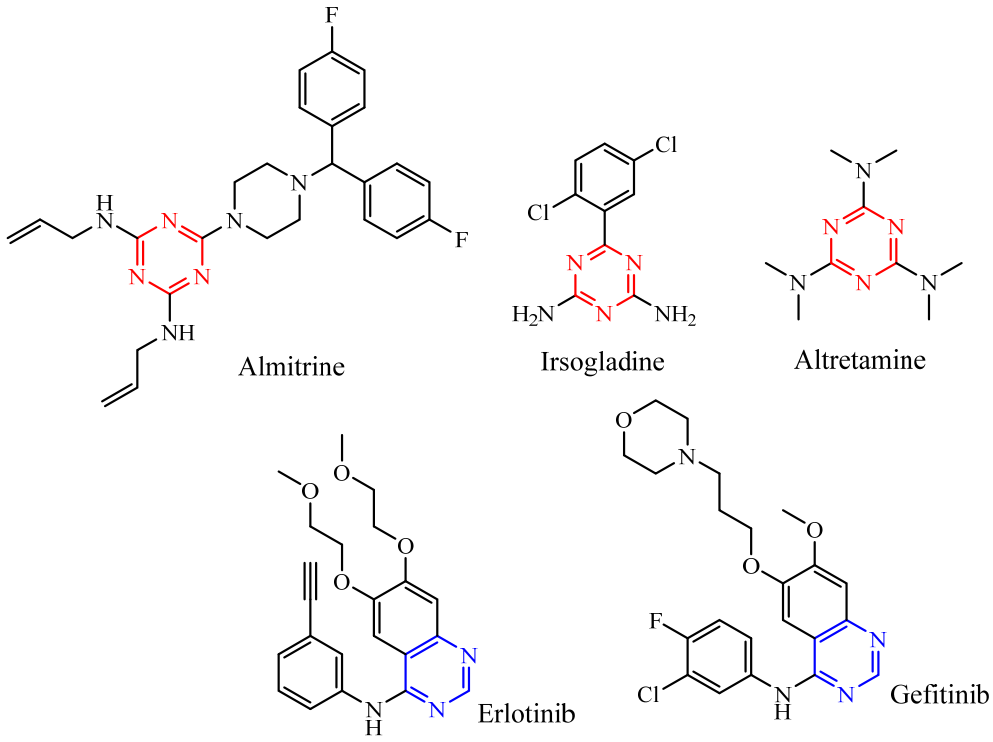

Figure 1. Examples of drugs in the 1,3,5-triazines and pyrimidines series.

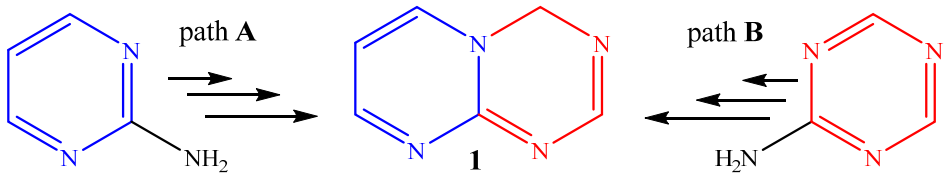

Figure 2. The structure of pyrimido[1,2-a][1,3,5]triazines and the main routes of their synthesis.

The number of reactions of 2-aminotriazines leading to the formation of pyrimido[1,2-a][1,3,5]triazines is extremely limited (path B). In most cases, malonic acid derivatives are used to annulate the pyrimidine ring [11,23–25].

Thus, at the moment, research on methods for the synthesis of pyrimido[1,2-a][1,3,5] triazines is relevant. The aim of this work was to study the chemo- and regioselectivity of reactions of substituted N-4-oxopyrimidin-2-ylthioureas and arylaldehydes to obtain new 4-aryl-2-thioxo-3,4-dihydropyrimido[1,2-a][1,3,5]triazine-6-ones. We also carried out preliminary tests of the antibacterial activity of the synthesized compounds against *S. aureus* and *E. coli*.

2. Results and Discussion

2.1. Chemistry

It has already been noted that the reaction of pyrimidin-2-ylguanidines or pyrimidin-2-ylthioureas with monoelectrophiles leads to the formation of a pyrimido[1,2-a][1,3,5]triazine heterocyclic system [9,17–22]. However, the reactions of substituted 4-oxopyrimidin-2-ylthioureas with arylaldehydes have not been studied.

We used 4-oxopyrimidin-2-ylthiourea **7a–b** as starting compounds, which were obtained according to the known method [4], through the interaction of amidinothiourea with ethyl acetoacetate or diethyl ethoxymethylenemalonate (Figure 3).

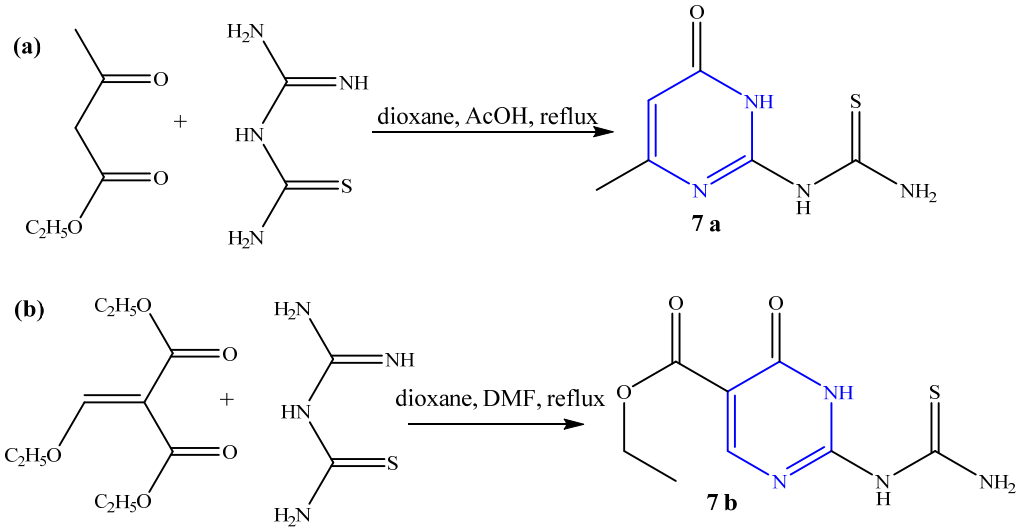

Figure 3. Synthesis of 4-oxopyrimidin-2-ylthioureas from amidinothiourea and ethyl acetoacetate (**a**) or diethyl ethoxymethylenemalonate (**b**).

The formation of two regioisomers **8** or **9** is possible, depending on which of the tautomeric forms (**7**, **7′** or **7″**) will take part in the reaction with arylaldehyde (Figure 4). It is known that the amide form is a more typical tautomeric form for pyrimidin-4-ones [26]. Probably, tautomeric form **7** will also be preferred for 4-oxopyrimidin-2-ylthioureas.

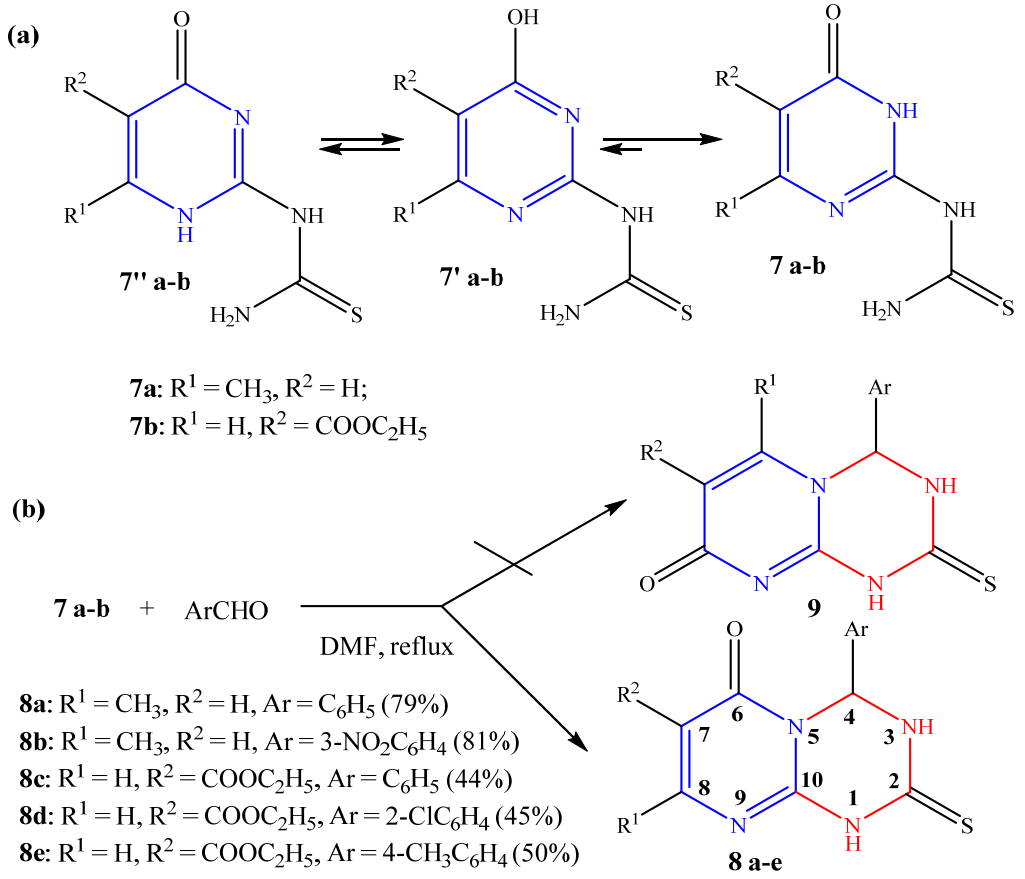

Figure 4. Tautomeric forms of 4-oxopyrimidin-2-ylthioureas **7a–b** (**a**). Reaction of 4-oxopyrimidin-2-ylthioureas **7a–b** with arylaldehydes (**b**).

In addition, reactions of thiols with arylaldehydes leading to the formation of sulfur-containing heterocycles of thiazines [27] or thiazoles [28] are known. Thione–thiol tautomerism is possible for compounds having a thioamide fragment in their structure. Thus, we can assume the formation of two more regioisomeric thiazine products in the reactions of 4-oxopyrimidin-2-ylthioureas **7a**–**b** with arylaldehydes.

However, based on the complex spectral data for the products of the interaction of substituted 4-oxopyrimidin-2-ylthioureas with arylaldehydes, we can conclude that 4-aryl-6-oxo-2-thioxo-1,3,4,6-tetrahydro-2*H*-pyrimido[1,2-a][1,3,5]triazines **8a**–**e** were formed. Competing formation of chemo- and regioisomers was not observed. The ethoxycarbonyl group at position 5 of the pyrimidine ring of thiourea **7b** had no effect on the direction of the reaction. Thus, the unsubstituted amino group of thiourea and the NH group of the dihydropyrimidine ring adjacent to the carbonyl group participated in the reaction.

The structure of the synthesized compounds **8a**–**e** was proved by a complex of spectral methods: ^{1}H-NMR, ^{13}C-NMR, as well as two-dimensional experiments COZY, HSQC, HMBC, and NOESY. All spectra are presented in the Supplementary Materials.

Aromatic proton signals in the region of 7.15–8.28 ppm, singlet of CH-proton (4) of the triazine ring in the region of 6.70–6.88 ppm, and two broadened singlets of the NH groups of the triazine ring (1,3) at 10.59–10.80 and 12.00–12.52 ppm, respectively, were found in the ^{1}H-NMR spectra of compounds **8a**–**e**. The peak of the CH-proton in the pyrimidine ring (7) for compounds **8a**–**b** was observed at 6.06–6.09 ppm, while for compounds **8c**–**e** the CH-proton singlet (8) was located at 8.51 ppm. Such a shift in the CH-proton signal in the spectra of compounds **8c**–**e** was due to the acceptor effect of the neighboring ethoxycarbonyl group.

The COZY spectrum of compound **8a** (provided in Supplementary Materials) makes it possible to make a correlation between CH protons and NH protons. It shows the interactions of NH– (3) and CH– (4) protons from the triazine cycle. We can conclude that the broadened upfield singlet (at 10.59 ppm) corresponds to the NH group (3), associated with CH (4), and the broadened singlet at 12.00 ppm corresponds to an NH group (1), linked to a thiocarbonyl group (2). The presence of such an interaction makes it possible to exclude the formation of pyrimidothiadiazines in this reaction.

^{13}C-NMR signals were interpreted based on the HSQC and HMBC spectra of compound **8a** (provided in Supplementary Materials). The positions of the carbon signals for compounds **8a**–**b** and **8c**–**e** are almost similar. The following signals of carbon atoms were found on the spectra: C (2) of the thione group at 174.0–176.4 ppm, C (4) of the triazine ring at 61.4–62.9 ppm, C (6) of the carbonyl group at 163.0–165.2 ppm, C (7) of the pyrimidine ring at 106.0–110.0 ppm, C (8) of the pyrimidine ring at 144.8–148.9 ppm, and C (10) at 155.1–158.6 ppm.

We can make an unambiguous choice in favor of the formation of regioisomer **8** over **9** based on the analysis of the NOESY spectrum of compound **8a** (presented in Supplementary Materials). There are no interactions of aromatic ring protons with other protons in the spectrum. However, for the regioisomer **9a**, the protons in the methyl group and the protons of the benzene ring would have to interact with each other. The formation of regioisomers **8a**–**e** is also indirectly confirmed by the literature data, which present a similar reaction for 6-alkyl-4-oxopyrimidin-2-ylguanidines [21,22].

The structures of compounds **8a**–**e** were also confirmed by HPLC analysis. Chromatograms and mass spectra are available in the Supplementary Materials.

To study the possibility of obtaining regioisomer **9**, we carried out a counter synthesis. It consisted of an interaction of 6-amino-4-phenyl-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione **10** (Figure 5) with ethyl acetoacetate and diethyl ethoxymethylenemalonate by mixing their hot solutions in dioxane followed by reflux for 4–6 h. This reaction is an alternative approach to the formation of pyrimido[1,2-a][1,3,5]triazines based on pyrimidine ring closure. Compound **10** was obtained according to known methods [29,30] by the reaction of amidinothiourea with benzaldehyde.

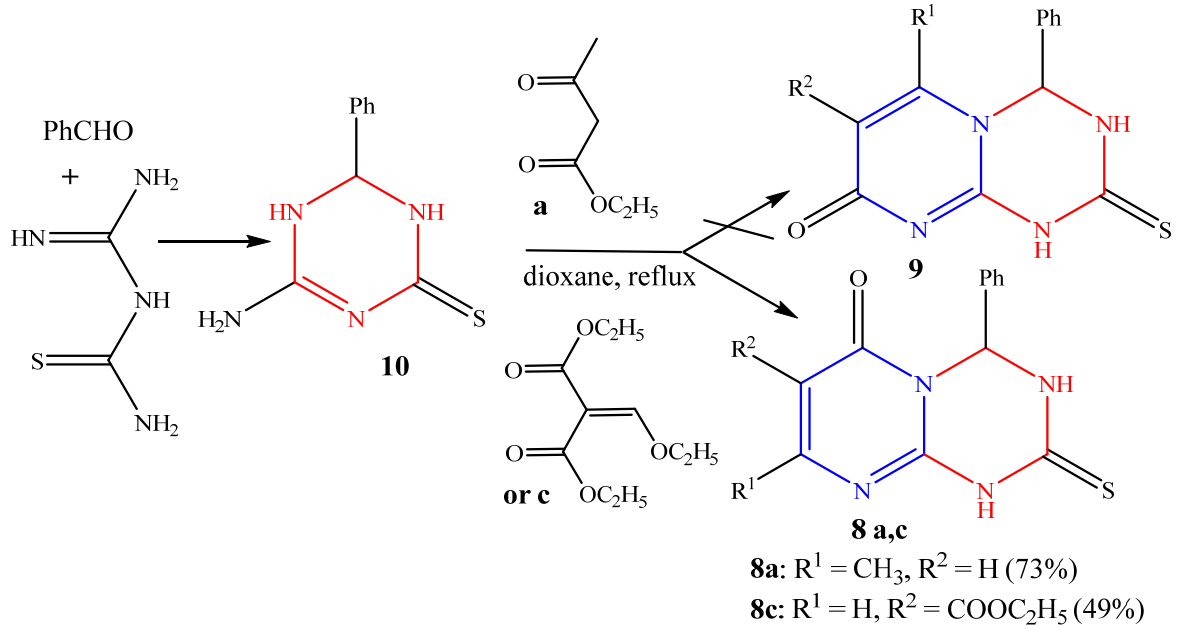

Figure 5. Reaction of 6-amino-4-phenyl-3,4-dihydro-1,3,5-triazine-2(1*H*)-thione **10** with ethyl acetoacetate (**a**) and diethyl ethoxymethylenemalonate (**c**).

Based on the data of HPLC analysis, ^{1}H-NMR, and ^{13}C-NMR spectroscopy, we proved that these reactions produce compounds identical to those obtained, according to the scheme in Figure 4, through by the reaction of 4-oxopyrimidin-2-ylthioureas **7a–b** with arylaldehydes.

The yields of products (Figures 4 and 5) in both processes were close, so compounds **8** can be obtained by any of the presented methods. That is, a change in the sequence of stages does not affect the structure and total yields of the obtained products.

2.2. Antibacterial Activity of the 2-Thioxo-1,2,3,4-tetrahydro-6H-pyrimido[1,2-a][1,3,5] triazin-6-one **8a–e**

Pyrimido[1,2-a][1,3,5]triazine derivatives expressed significant antibacterial activity [8,9]. In this regard, the antibacterial action of the synthesized compounds was investigated. An in vitro micromethod for two-fold serial dilutions in a liquid medium was used to study the antimicrobial activity of various compounds against cultures of *E. coli* and *S. aureus*. Cell viability was assessed using a resazurin test [31]. The test results are shown in Table 1.

Table 1. Results of studying the antibacterial activity of 2-thioxo-1,2,3,4-tetrahydro-6H-pyrimido[1,2-a][1,3,5]triazin-6-one **8a–e**.

Compound	Minimum Inhibitory Concentration (MIC), μg/mL	
	E. coli	*S. aureus*
8a	256	256
8b	256	256
8c	256	256
8d	256	256
8e	256	256
Chloramphenicol	128	256
Sulfathiazole	128	256
Metronidazole	128	256

All synthesized compounds showed antibacterial activity against *E. coli* and *S. aureus* cultures at an MIC of 256 μg/mL. The drugs Chloramphenicol, Sulfathiazole, and Metronidazole show the same activity in relation to the culture of *S. aureus*. These drugs are active against the *E. coli* culture at a lower MIC than the compounds synthesized by us.

3. Materials and Methods

^{1}H- and ^{13}C-NMR spectra were acquired on a Bruker DRX-500 spectrometer (500 and 125 MHz, respectively) in DMSO-d6 at 30 °C with TMS as internal standard. High-resolution mass spectra were recorded on an Agilent Technologies LCMS 6230B spectrometer (electrospray ionization). Melting points were determined on a Stuart SMP30 apparatus.

Assaying of the purity of the starting materials and the synthesized compounds, as well as the analysis of reaction mixtures, was conducted by TLC on Merck TLC Silica gel 60 F254 plates; eluents: MeOH, $CHCl_3$, and their mixtures in different ratios. Visualization of TLC plates was prepared under UV light or in iodine vapor. N-amidinothiourea, arylaldehydes, ethyl acetoacetate, and diethyl ethoxymethylenemalonate were supplied by Acros.

Staphylococcus aureus subsp. aureus (ATCC®29213™) and *Escherichia coli* (ATCC®25922™), obtained from the Kazan Federal University, Kazan, Russia, were the used strains, cultivated using LB medium. To study the antimicrobial activity of various compounds against cultures of *E. coli* and *S. aureus*, an in vitro micromethod for 2-fold serial dilutions in a liquid medium was used. Cell viability was assessed using a resazurin test [31].

8-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro-6H-pyrimido[1,2-a][1,3,5]triazin-6-one **8a**

Method 1*:* A mixture of 1-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thiourea **7a** (184 mg, 1.00 mmol) and benzaldehyde (127 mg, 1.20mmol) was refluxed in ethanol (10 mL) and DMF (5 mL) for 10 h. The reaction mixture was poured into 100 ml of cold distilled water. The resulting precipitate obtained was filtered off, dried, and recrystallized from dioxane and DMF to give **8a** as a white powder (215 mg, 0.79 mmol, 79%).

Method 2*:* To a hot solution of 6-amino-4-phenyl-3,4-dihydro-1,3,5-triazine-2(1H)-thione **10** (206 mg, 1.00 mmol) in dioxane (10 mL), ethyl acetoacetate (143 mg, 1.10 mmol) was added to a hot solution in dioxane. The mixture was refluxed for 6 h. The resulting precipitate obtained after cooling was filtered off, dried, and recrystallized from dioxane and DMF to give **8 a** as a white powder (199 mg, 0.73 mmol, 73%); mp 240–242 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.15 (3H, s, CH_3), 6.06 (1H, s, $CH_{pyrimidine}$), 6.70 (1H, s, $CH_{triazine}$), 7.25 (2H, d, *J* = 7.4 Hz $2CH_{aryl}$), 7.35–7.45 (3H, m, $3CH_{aryl}$), 10.59 (1H, br s, NH), 12.00 (1H, br s, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 23.4 (CH_3), 61.9 (C (4)), 106.0 (C (7)), 125.3 (C_{aryl}), 129.1 (C_{aryl}), 129.2 (C_{aryl}), 137.7 (C_{aryl}), 145.2 (C (8)), 158.6 (C (10), 165.1 (C (6)), 176.4 (C (2)). Found, *m*/*z*: 273.0808 $[M + H]^+$. $C_{13}H_{12}N_4OS$. Calculated, *m*/*z*: 273.0805.

8-Methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydro-6H-pyrimido[1,2-a][1,3,5]triazin-6-one **8b**

A mixture of 1-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thiourea **7a** (184 mg, 1.00 mmol) and 3-nitrobenzaldehyde (181 mg, 1.20mmol) was refluxed in ethanol (10 mL) and DMF (5 mL) for 10 h. The reaction mixture was poured into 100 ml of cold distilled water. The resulting precipitate obtained was filtered off, dried, and recrystallized from dioxane and DMF to give **8b** as a white powder (257 mg, 0.81 mmol, 81%); mp 231–233 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.18 (3H, s, CH_3), 6.09 (1H, s, $CH_{pyrimidine}$), 6.82 (1H, s, $CH_{triazine}$), 7.65–7.67 (1H, m, CH_{aryl}), 7.77 (1H, t, *J* = 8.0 Hz, $1CH_{aryl}$), 8.18 (1H, t, *J* = 2.0 Hz, $1CH_{aryl}$), 8.26–8.28 (1H, m, CH_{aryl}), 10.69 (1H, br s, NH), 12.13 (1H, br s, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 23.3 (CH_3), 61.4 (C (4)), 106.0 (C (7)), 120.5 (C_{aryl}), 124.2 (C_{aryl}), 130.8 (C_{aryl}), 130.9 (C_{aryl}), 131.6 (C_{aryl}), 139.6 (C_{aryl}), 144.8 (C (8)), 158.6 (C (10), 165.2 (C (6)), 176.4 (C (2)). Found, *m*/*z*: 318.0657 $[M + H]^+$. $C_{13}H_{11}N_5O_3S$. Calculated, *m*/*z*: 318.0656.

*Ethyl 6-oxo-4-Phenyl-2-thioxo-1,3,4,6-tetrahydro-2H-pyrimido[1,2-a][1,3,5]*triazine-7-*carboxylate* **8c**

Method 1*:* A mixture of ethyl 6-oxo-2-thioureido-1,6-dihydropyrimidine-5-carboxylate **7b** (242 mg, 1.00 mmol) and benzaldehyde (127 mg, 1.20 mmol) was refluxed in ethanol (10 mL) and DMF (5 mL) for 10 h. The reaction mixture was poured into 100 ml of cold distilled water. The resulting precipitate obtained was filtered off, dried, and recrystallized from dioxane and DMF to give **8c** as a white powder (146 mg, 0.44 mmol, 44%).

Method 2: To a hot solution of 6-amino-4-phenyl-3,4-dihydro-1,3,5-triazine-2(1H)-thione **10** (206 mg, 1.00 mmol) in dioxane (10 mL) was added diethyl ethoxymethylenemalonate (237 mg, 1.10 mmol). The mixture was refluxed for 6 h. The resulting precipitate obtained after cooling was filtered off, dried, and recrystallized from dioxane and DMF to give **8c** as a white powder (162 mg, 0.49 mmol, 49%); mp 235–237 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 1.24 (3H, t, *J* = 7.1 Hz, CH_3), 4.16–4.23 (2H, m, CH_2), 6.73 (1H, s, $CH_{triazine}$), 7.26–7.29 (2H, m, $2CH_{aryl}$), 7.41–7.46 (3H, m, $3CH_{aryl}$), 8.51 (1H, s, $CH_{pyrimidine}$), 10.80 (1H, br s, NH), 12.52 (1H, br s, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 14.2 (CH_3), 60.3 (CH_2), 62.6 (C (4)), 110.0 (C (7)), 125.6 (C_{aryl}), 129.3 (C_{aryl}), 129.5 (C_{aryl}), 137.5 (C_{aryl}), 148.7 (C (8)), 155.3 (C (10), 160.8 (C (6)), 163.1 (C=O), 175.5 (C (2)). Found, *m*/*z*: 331.0860 $[M + H]^+$. $C_{15}H_{14}N_4O_3S$. Calculated, *m*/*z*: 331.0860.

Ethyl 4-(2-Chlorophenyl)-6-oxo-2-thioxo-1,3,4,6-tetrahydro-2H-pyrimido[1,2-a][1,3,5]triazine-7-carboxylate **8d**

A mixture of ethyl 6-oxo-2-thioureido-1,6-dihydropyrimidine-5-carboxylate **7b** (242 mg, 1.00 mmol) and 2-chlorobenzaldehyde (169 mg, 1.20mmol) was refluxed in ethanol (10 mL) and DMF (5 mL) for 10 h. The reaction mixture was poured into 100 ml of cold distilled water. The resulting precipitate obtained was filtered off, dried, and recrystallized from dioxane and DMF to give **8d** as a white powder (164 mg, 0.45 mmol, 45%); mp 228–230 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 1.21 (3H, t, *J* = 6.9 Hz, CH_3), 4.13–4.17 (2H, m, CH_2), 6.88 (1H, s, $CH_{triazine}$), 7.22 (1H, d, *J* = 7.5 Hz, $1CH_{aryl}$), 7.37–7.45 (2H, m, $2CH_{aryl}$), 7.53 (1H, d, *J* = 7.8 Hz, $1CH_{aryl}$), 8.51 (1H, s, $CH_{pyrimidine}$), 10.71 (1H, br s, NH), 12.50 (1H, br s, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 14.2 (CH_3), 60.2 (CH_2), 62.7 (C (4)), 109.7 (C (7)), 128.1 (C_{aryl}), 128.2 (C_{aryl}), 130.4 (C_{aryl}), 131.1 (C_{aryl}), 131.7 (C_{aryl}), 135.3 (C_{aryl}), 148.9 (C (8)), 155.0 (C (10), 160.8 (C (6)), 163.0 (C=O), 174.0 (C (2)). Found, *m*/*z*: 365.0469 $[M + H]^+$. $C_{15}H_{13}ClN_4O_3S$. Calculated, *m*/*z*: 365.0470.

Ethyl 6-oxo-2-Thioxo-4-(p-tolyl)-1,3,4,6-tetrahydro-2H-pyrimido[1,2-a][1,3,5]triazine-7-carboxylate **8e**

A mixture of ethyl 6-oxo-2-thioureido-1,6-dihydropyrimidine-5-carboxylate **7b** (242 mg, 1.00 mmol) and 4-methylbenzaldehyde (144 mg, 1.20mmol) was refluxed in ethanol (10 mL) and DMF (5 mL) for 10 h. The reaction mixture was poured into 100 mL of cold distilled water. The resulting precipitate obtained was filtered off, dried, and recrystallized from dioxane and DMF to give **8e** as a white powder (172 mg, 0.50 mmol, 50%); mp 228–230 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 1.24 (3H, t, *J* = 7.1 Hz, CH_3), 2.29 (3H, s, CH_3), 4.16–4.23 (2H, m, CH_2), 6.72 (1H, s, $CH_{triazine}$), 7.15 (2H, d, *J* = 8.2 Hz, $2CH_{aryl}$), 7.24 (2H, d, *J* = 8.2 Hz, $2CH_{aryl}$), 8.51 (1H, s, $CH_{pyrimidine}$), 10.77 (1H, br s, NH), 12.51 (1H, br s, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (ppm): 14.2 (CH_3), 20.7 (CH_3), 60.2 (CH_2), 62.5 (C (4)), 110.0 (C (7)), 125.4 (C_{aryl}), 129.7 (C_{aryl}), 134.6 (C_{aryl}), 139.1 (C_{aryl}), 148.7 (C (8)), 155.2 (C (10), 160.7 (C (6)), 163.0 (C=O), 175.4 (C (2)). Found, *m*/*z*: 345.1019 $[M + H]^+$. $C_{16}H_{16}N_4O_3S$. Calculated, *m*/*z*: 345.1017.

4. Conclusions

Novel substituted 4-aryl-8-methyl-2-thioxo-1,2,3,4-tetrahydro-6H-pyrimido[1,2-a][1,3,5] triazin-6-one **8a**–**b** and ethyl 4-aryl-6-oxo-2-thioxo-1,3,4,6-tetrahydro-2H-pyrimido[1,2-a][1,3,5]triazine-7-carboxylate **8c**–**e** were synthesized in a moderate and high yield.

We established that the interaction of both 4-oxopyrimidin-2-ylthioureas with arylaldehydes as well as 6-amino-4-phenyl-3,4-dihydro-1,3,5-triazine-2(1H)-thione with ethyl acetoacetate and diethyl ethoxymethylenemalonate leads to the formation of the same pyrimido[1,2-a][1,3,5]triazine regioisomer. Structures of the targeted compounds were determined using ^{1}H-NMR, ^{13}C-NMR, HSQC, HMBC, COSY, NOESY, and HPLC.

All synthesized compounds exhibit antibacterial activity against *E. coli* and *S. aureus* cultures at a concentration of 256 μg/mL.

Supplementary Materials: The following data are available online: ^{1}H-NMR spectra (Figures S1–S5), ^{13}C-NMR spectra (Figures S6–S10), and data HPLC (Figures S11–S15) of compounds **8a**–**e**. And for compound **8a** spectrum COSY (Figure S16), spectrum HSQC (Figure S17), spectrum HMBC (Figure S18), spectrum NOESY (Figure S19).

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