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Synthesis of Substituted Aminopyrimidines as Novel Promising Tyrosine Kinase Inhibitors

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Abstract—A procedure has been proposed for the synthesis of a series of substituted *N*-(1,3-thiazol-2-yl)-pyrimidin-2-amines and *N*-(pyrimidin-2-yl)thioureas by reactions of diethyl 2-(ethoxymethylidene)malonate and ethyl 2-(ethyoxymethylidene)-3-oxobutanoate with 1,3-thiazol-2-ylguanidines and amidinothiourea, respectively. Preliminary screening has revealed high inhibitory activity of ethyl 2-(carbamothioylamino)-4-methylpyrimidine-5-carboxylate and ethyl 2-(carbamothioylamino)-6-oxo-1,6-dihydropyrimidine-5-carboxylate toward several protein kinases.

Keywords: pyrimidines, thiazoles, protein kinase inhibitors, EGFR tyrosine kinase, amidinothiourea.

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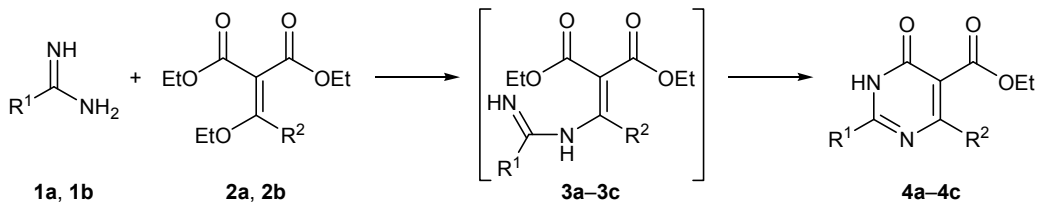
Nowadays, design of drugs for the treatment of oncological diseases is one of the most important directions of the synthesis of new organic compounds. In recent years, main advances in this field have been related to targeted kinase inhibitors that exert a selective pathogenetic effect. There is a trend of using low-molecular-weight organic compounds as kinase inhibitors.

Aminopyrimidine fragment is a structural unit of the currently used EGFR tyrosine kinase inhibitors erlotinib and gefitinib [1, 2]; therefore, it seemed reasonable to search for new EGFR tyrosine kinase inhibitors among 2-aminopyrimidine derivatives. Herein, we report the synthesis of some pyrimidin-2-ylthioureas and the results of their preliminary screening for inhibitory activity against several tyrosine kinases.

Among numerous methods of cyclization of guanidine derivatives to pyrimidines, reactions of guanidines with ethoxymethylidene derivarives of dicarbonyl compounds occupy an important place. In most cases, these reactions follow a general scheme according to which in the first stage the ethoxy group is replaced by amino group of guanidine. The second stage is cyclization involving one carbonyl group and imino group of intermediate imino enamine (Scheme 1). As a result, pyrimidines with various substituents in positions *4*, *5*, and *6* are formed [3–6]. Apart from 2-(alkoxymethylidene)-1,3-dicarbonyl compounds, their 2-(arylmethylidene) analogs possess a high synthetic potential. Their reactions with acetamidine, benzamidine, guanidine, and *N*,*N*-dimethylguanidine with the formation of 4,5,6-trisubstituted pyrimidines were studied. Different conditions of these reactions, includ-

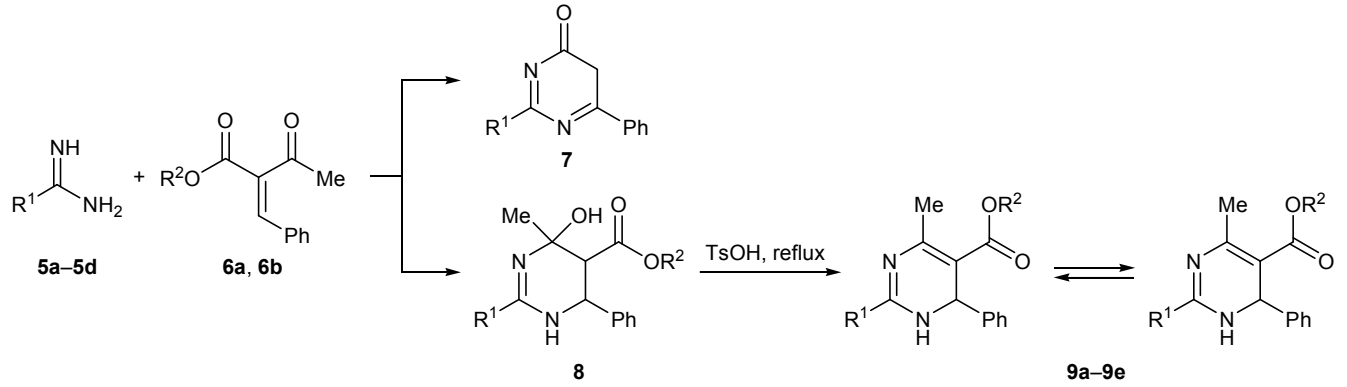
Scheme 1.



1a, **1b** **2a**, **2b** **3a–3c** **4a–4c**

1, R^1 = Me (**a**), Et (**b**); **2**, R^2 = Me (**a**), H (**b**); **4**, R^1 = Me, R^2 = H (**a**), $R^1 = R^2$ = Me (**b**), R^1 = Et, R^2 = H (**c**).

Scheme 2.



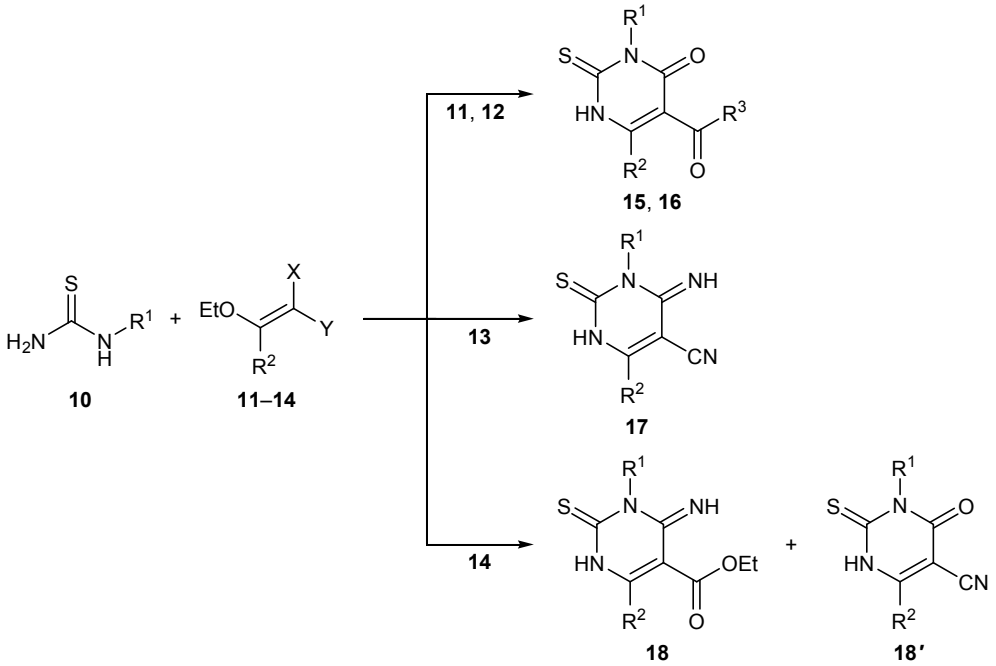
5, R^1 = Me (**a**), Ph (**b**), NH_2 (**c**), NMe_2 (**d**); **6**, R^2 = Et (**a**), *t*-Bu (**b**); **9**, R^1 = Me, R^2 = Et (**a**), R^1 = Me, R^2 = *t*-Bu (**b**), R^1 = Ph, R^2 = Et (**c**), R^1 = NH_2, R^2 = Et (**d**), R^1 = NMe_2, R^2 = Et (**e**).

ing fairly mild (stirring at room temperature), were given in different publications (Scheme 2). Similar reactions were reported for derivatives of thiourea and 2-(ethoxymethylidene)malonic acid [10]. These reactions afforded pyrimidine-2-thiones with various substituents in positions *4*, *5*, and *6*. Here, the sulfur atom is not involved, and the reaction occurs at the amidine fragment (Scheme 3).

The goal of the present work was to study reactions of amidinothiourea **19** with ethoxymethylidene derivatives of diethyl malonate, ethyl acetoacetate, and malononitrile (compounds **11**, **13**, and **20**, respectively) with a view to obtaining pyrimidine-containing thioureas and evaluating their inhibitory activity against some tyrosine kinases.

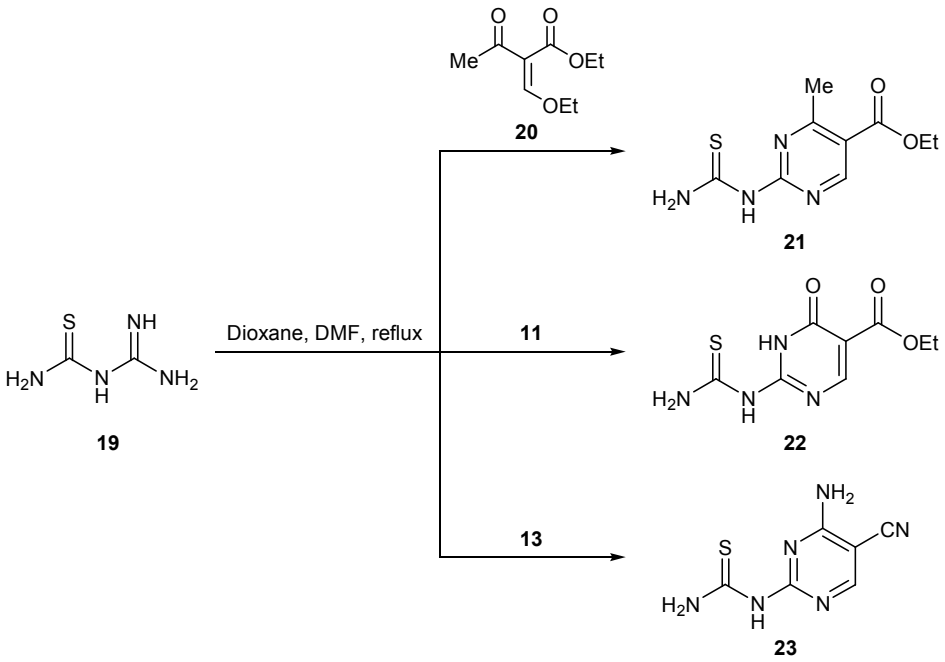
As expected, the reactions involved the amidine fragment of **19**. Presumably, as in reactions with some guanidines [11], the first stage is substitution of the ethoxy group in the 1,3-dicarbonyl component by nucleophilic amino group of the guanidine fragment of **19**, and next follows intramolecular nucleophilic addition of the imino nitrogen atom to the electrophilic

Scheme 3.

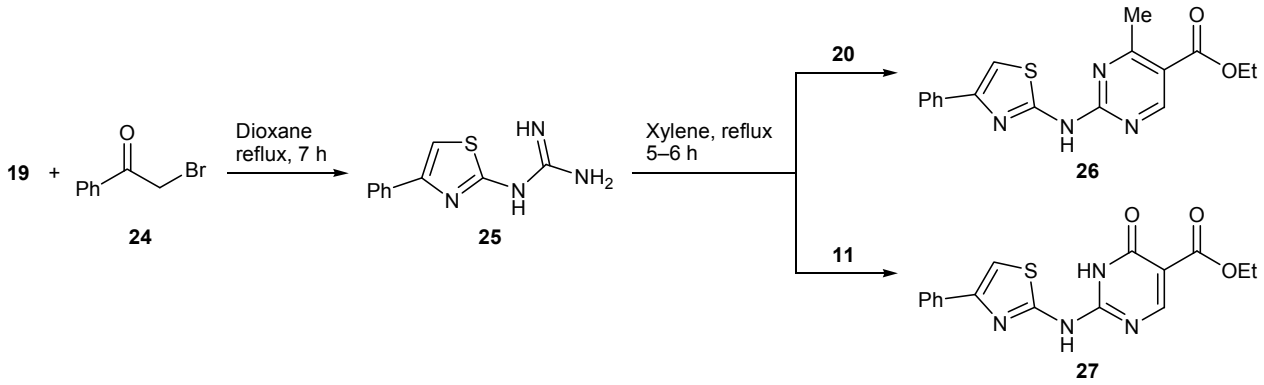


10, R^1 = H, Alk, cycloalkyl, Ar; **11**, X = Y = COOEt; **12**, X = COOEt, Y = COR^3; **13**, X = Y = CN; **14**, X = CN, Y = COOEt; **11**, **15**, R^2 = H, Me, Et, R^3 = OEt; **12**, **16**, R^2 = H, R^3 = Me, Ph; **17**, **18**, R^2 = H, Me, Et.

Scheme 4.



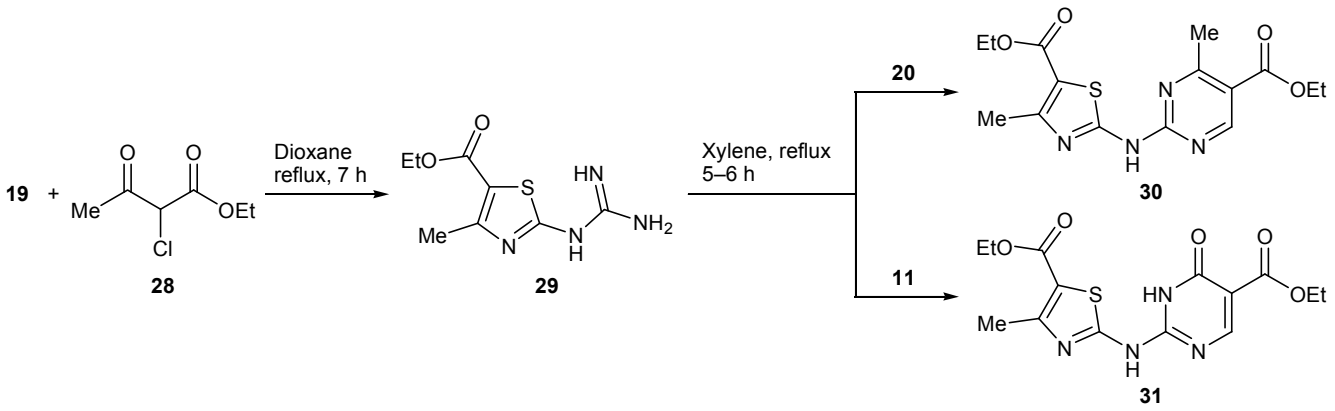
Scheme 5.



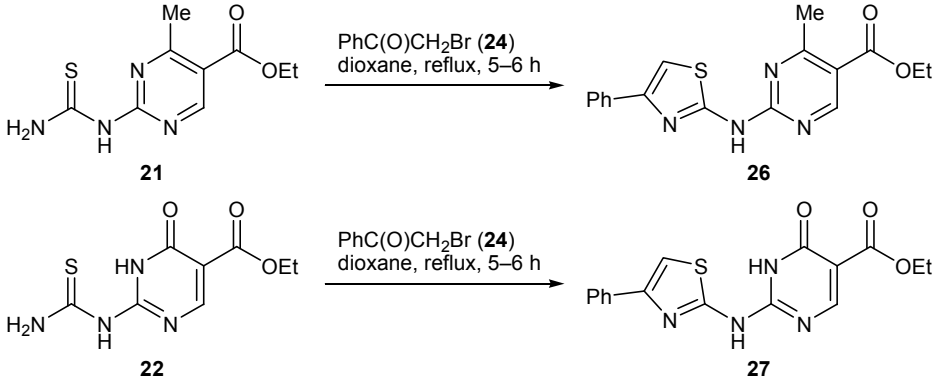
carbon atom of the intermediate (Scheme 4). Similar reactions were studied for thiazolylguanidines **25** and **29** which were prepared according to known procedures [12]. When the reactants were heated in *o*-xylene for 5–6 h, cyclization involving the amidine fragment of **25** and **29** afforded 2-(1,3-thiazol-2-ylamino)-pyrimidine-5-carboxylates **26**, **27**, **30**, and **31** (Schemes 5, 6). It should be noted that the cyclization in the second stage of the reactions of **25** and **29** with ethyl 2-(ethoxymethylidene)-3-oxobutanoate (**20**) is possible with participation of both ketone and ester carbonyl groups. According to [10], substituted thioureas **10** reacted with 2-(ethoxymethylidene)-3-oxo esters **12** in ethanol in the presence of sodium ethoxide to give pyrimidinones **16** as a result of cyclization at the ester fragment. We found that the reaction of thiourea **19** with keto ester **20** in a dioxane–DMF mixture involved the ketone carbonyl group, as followed from the ^{1}H NMR spectra of compounds **21**, **26**, and **31**, which contained signals typical of ethoxy group. This result was consistent with the data of [11].

Ethyl 4-methyl-2-(4-phenyl-1,3-thiazol-2-ylamino)-pyrimidine-5-carboxylate (**26**) and ethyl 6-oxo-2-(4-phenyl-1,3-thiazol-2-ylamino)-1,6-dihydropyrimidine-5-carboxylate (**27**) were also synthesized independently, by reaction of thioureas **21** and **22** with phenacyl bromide (**24**). The reactions were carried out by heating the initial compounds in boiling dioxane for 5–6 h (Scheme 7). The ^{1}H NMR spectra of **26** and **27** obtained by the two methods were identical. These findings provide an additional support to the participation of the amidine fragment of **19** in the reactions with ethoxymethylidene derivatives **11**, **13**, and **20**.

Scheme 6.



Scheme 7.



Thioureas **21**–**22** and thiazolylamino derivatives **30** and **31** obtained therefrom were tested for inhibitory activity against NPM1-ALK (anaplastic lymphoma kinase), mutated forms of EGFR (epidermal growth factor receptor) tyrosine kinase (EGFR[L858R], EGFR T790M/L858R), and signal transducer and activator of transcription kinases (Janus kinases JAK2, JAK3). This panel of tyrosine protein kinases was selected taking into account that many inhibitors of these kinases contain an aminopyrimidine fragment [15–17]. Enzyme-linked immunosorbent assay (ELISA) was performed in two steps: preliminary screening in a single experiment, and validation of the results in duplicate provided that the inhibition percentage in the preliminary experiment was higher than 50%; the half maximal inhibitory concentrations IC_{50} were determined in duplicate (Table 1). Compound **31** showed no inhibitory activity against the above listed tyrosine kinases or its activity was insignificant. The highest inhibitory effect was observed for thiourea **21** with respect to EGFR [L858R] (IC_{50} = 1.52 μM).

Thus, we were the first to reveal inhibitory activity of some substituted pyrimidin-2-ylthioureas against several tyrosine kinases. In the future, we plan to optimize the structure of the synthesized pyrimidine derivatives in order to extend the series of compounds promising for use as protein kinase inhibitors, as well as to obtain hybrid molecules exhibiting various physiological activities, including anticoagulant activity.

Table 1. Tyrosine kinase inhibitory activity of compounds **21**, **22**, and **31**

Compound no.	Inhibition, %			
	NPM1-ALK	ALK	EGFR [L858R] [T790]	EGFR [L858R]
21	35	70	62	89
22	36	70	76	86
31	–	–	11	10

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 30°C on a Bruker DRX 500 spectrometer (500 and 125 MHz, respectively) using DMSO-d_6 as solvent and tetramethylsilane as internal standard. HPLC/MS analyses were performed with an Agilent Infinity 1260 liquid chromatograph coupled with an Agilent 6230 TOF mass-selective detector; Poroshell 120 EC-C18 column, 4.6 × 50 mm, grain size 2.7 μm; eluent 0.1% formic acid in acetonitrile (A)/0.1% formic acid in water (B), gradient 0–100%: A, 3.5 min, 50%; A, 1.5 min, 50–100%; B, 3.5 min, 50%; B, 1.5 min, 50–0%; flow rate 0.4 mL/min; column temperature 28°C; electrospray ionization, positive ion detection, capillary voltage –3.5 kV; fragmentor voltage +191 V; OctRF voltage +66 V. The IR spectra were recorded on a Bruker Vertex-70 spectrometer with Fourier transform. The melting points were measured with a Stuart SMP30 melting point apparatus. The progress of reactions and the purity of the initial reactants and reaction products were monitored by TLC on Silufol UV-254 plates using chloroform, methanol, or their mixtures at different ratios as eluents; spots were visualized under UV light and by treatment with iodine vapor.

Amidinothiourea **19** (Alinda Chemical) and ethyl 2-chloro-3-oxobutanoate (**28**) (Sigma–Aldrich) were commercial products. Ethoxymethylidene derivatives **11**, **13**, **20**, and **30** were synthesized according to the procedure described in [14].

The kinase inhibitory activity was evaluated using polypropylene microplates (Costar, 3363) in a reaction buffer consisting of 20 mM HEPES, pH 7.5, 15 mM $MgCl_2$, 2 mM DTT, 0.2 mM Na_3VO_4, and 0.005% Triton X-100 for 60 min at 30°C under vigorous stirring. The final concentrations were 0.05 μg/mL kinase, 5 nM substrat Histone H3 (1–21) biotinylated substrate (Anaspec, 61702), 150 μM ATP (Sigma, A6419), 10 μM compound to be tested, 5% DMSO. The enzymatic reaction was terminated with a buffer containing 20 mM HEPES (Sigma, H4034), pH 7.5, and 150 mM EDTA (Sigma, E5513). To detect the phosphorylated substrate, the reaction mixtures were transferred to preliminarily prepared microplates (Nunc, 468667) covered with NeutrAvidin (1 ng per well; Pierce, 31000) and treated with bovine serum albumin (BSA) to block nonspecific binding sites. The microplates were incubated for 1 h at room temperature, washed three times with phosphate-buffered saline (PBS) containing Tween-20, and incubated in succession with anti-phospho-Histone H3 antibodies (0.3 ng/μL; Millipore, 04-746) and with specific antibodies conjugated to enzyme label (peroxidase) (Anti-rabbit IgG, HRP-linked Antibody, 1/5000; Cell Signaling, 7074). After each incubation stage (60 min at room temperature with continuous stirring), the plates were washed thrice with PBS/Tween-20 to remove unbound antibodies, and 100 μL of TMB substrate (Sigma, T8768) was added, which was prepared according to manufacturer's manual.

Before measuring the optical density, the reaction was terminated with 0.5 M H_2SO_4. The optical density was measured at λ 450 nm with a Tecan Safire microplate reader. The data were processed and imported into HTSCalc.

Ethyl 2-(carbamothioylamino)-4-methylpyrimidine-5-carboxylate (21). A mixture of 0.35 g (3 mmol) of thiourea **19**, 0.59 g (3 mmol) of ester **20**, 10 mL of dioxane, and 2 mL of DMF was refluxed for 5–6 h. The mixture was poured into 100 mL of water, and the precipitate was filtered off. Acetone was added to the product, and the mixture was heated to the boiling point and filtered while hot. After cooling, the precipitate was filtered off and dried. Yield 0.53 g (74%), white crystals, mp 232–234°C. IR spectrum, ν, cm^{-1}: 1716 (C=O), 1568 (pyrim.), 1519 (δNH$_2$), 1280 (NCSN), 1228 (C–O), 1012 (pyrim.), 798 (pyrim.), 576 (NCSN). ^{1}H NMR spectrum, δ, ppm: 1.33 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.69 s (3H, 4-CH_3), 4.30 q (2H, OCH_2, J = 7.1 Hz), 8.95 s (1H, 6-H), 9.32 br.s (1H, NH), 10.23 br.s (1H, NH), 10.88 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.93 ($CH_2\mathbf{C}H_3$), 24.02 (4-CH_3), 60.95 (OCH_2), 116.99 (C^5), 157.66 (C^6), 159.97 (C^2), 163.82 (C^4), 169.79 (C=O), 180.82 (C=S). Found: m/z 241.0759 $[M + H]^+$. $C_9H_{12}N_4O_2S$. Calculated: $[M + H]$ 241.0754.

Ethyl 2-(carbamothioylamino)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (22). A mixture of 0.35 g (3 mmol) of thiourea **19**, 0.65 g (3 mmol) of diester **11**, 10 mL of dioxane, and 2 mL of DMF was refluxed for 5–6 h. The mixture was poured into 100 mL of water, and the precipitate was filtered off. Acetone was added to the product, and the mixture was heated to the boiling point and filtered while hot. After cooling, the precipitate was filtered off and dried. Yield 0.46 g (64%), white crystals, mp 254–256°C. IR spectrum, ν, cm^{-1}: 1699 (C=O), 1633 (pyrim.), 1498 (pyrim.), 1244 (COEt), 1186 (NHCSNH), 1037 (pyrim.), 808 (pyrim.). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 4.20 q (2H, OCH_2,

J = 7.1 Hz), 8.45 s (1H, 4-H), 9.55 br.s (1H, NH), 9.90 br.s (1H, NH), 11.80 br.s (1H, NH), 12.80 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.05 ($CH_2\mathbf{C}H_3$), 60.07 (OCH_2), 109.54 (C^5), 152.93 (C^4), 155.36 (C^6), 158.77 (C^2), 162.94 (5-C=O), 180.09 (C=S). Found: m/z 243.0552 $[M + H]^+$. $C_8H_{10}N_4O_3S$. Calculated: M + H 243.0547.

***N*-(4-Amino-5-cyanopyrimidin-2-yl)thiourea (23).** A mixture of 0.35 g (3 mmol) of thiourea **19**, 0.37 g (3 mmol) of dinitrile **13**, 10 mL of dioxane, and 2 mL of DMF was refluxed for 5–6 h. The mixture was poured into 100 mL of water, and the precipitate was filtered off. Acetone was added to the product, and the mixture was heated to the boiling point and filtered while hot. After cooling, the precipitate was filtered off and dried. Yield 0.34 g (58%), yellow crystals, mp 290–292°C. IR spectrum, ν, cm^{-1}: 2229 (CN), 1573 (pyrim.), 1521 (δNH$_2$), 1280 (NHCSN), 1014 (pyrim.), 792 (pyrim.), 605 (NHCSNH). ^{1}H NMR spectrum, δ, ppm: 7.95 br.s (2H, NH$_2$), 8.49 s (1H, 6-H), 9.25 br.s (1H, NH), 10.20 br.s (1H, NH), 12.85 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 115.50 (CN), 155.40 (C^5), 157.74 (C^6), 161.98 (C^4), 162.50 (C^2), 180.70 (C=S). Found: m/z 195.0451 $[M + H]^+$. $C_6H_6N_6S$. Calculated: M + H 195.0448.

***N*-(4-Phenyl-1,3-thiazol-2-yl)guanidine (25)** was synthesized according to known procedure [12]. Yield 88%, mp 225–227°C. ^{1}H NMR spectrum, δ, ppm: 6.90 br.s (4H, NH), 7.15 s (1H, 5-H), 7.27 t (1H, H$_{arom}$, J = 7.3 Hz), 7.38 t (2H, H$_{arom}$, J = 7.7 Hz), 7.83 d (2H, H$_{arom}$, J = 7.2 Hz). Found: m/z 219.0703 $[M + H]^+$. $C_{10}H_{10}N_4S$. Calculated: M + H 219.0699.

Ethyl 4-methyl-2-(4-phenyl-1,3-thiazol-2-ylamino)pyrimidine-5-carboxylate (26). A mixture of 0.65 g (3 mmol) of **25** and 0.56 g (3 mmol) of **20** in 15 mL of xylene was refluxed for 5–6 h. The precipitate was filtered off and recrystallized from toluene. Yield 0.76 g (75%), white crystals, mp 266–267°C. IR spectrum, ν, cm^{-1}: 1716 (C=O), 1591 (C=C$_{arom}$), 1568 (pyrim.), 1519 (δNH$_2$), 1440 (arom.), 1280 (NCSN), 1228 (COEt), 1012 (pyrim.), 798 (pyrim.), 576 (NCSN). ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, CH$_2$C**H**$_3$, J = 6.9 Hz), 2.75 s (3H, 4-CH$_3$), 4.32 m (2H, OCH$_2$), 7.32 t (1H, H$_{arom}$, J = 7.1 Hz), 7.43 t (2H, H$_{arom}$, J = 7.5 Hz), 7.60 s (1H, 5′-H), 7.93 d (2H, H$_{arom}$, J = 7.6 Hz), 8.97 s (1H, 6-H), 12.20 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.55 ($CH_2\mathbf{C}H_3$), 24.21 (4-CH_3), 61.18 (OCH_2), 108.61 (C^5), 116.23 ($C^{5'}$), 126.36 (C^o), 128.10 (C^p), 129.05 (C^m), 135.26 (C^i), 150.07 ($C^{4'}$), 158.17 (C^4), 159.53 (C^6), 160.65 (C^2), 164.91 ($C^{2'}$), 170.05 (C=O). Found: m/z 341.1071 $[M + H]^+$. $C_{17}H_{16}N_4O_2S$. Calculated: M + H 341.1067.

Ethyl 6-oxo-2-(4-phenyl-1,3-thiazol-2-ylamino)-1,6-dihydropyrimidine-5-carboxylate (27). A mixture of 0.65 g (3 mmol) of guanidine **25** and 0.65 g (3 mmol) of diester **11** in 15 mL of xylene was refluxed for 5–6 h. The precipitate was filtered off and recrystallized from toluene. Yield 0.72 g (70%), white crystals, mp > 300°C. IR spectrum, ν, cm^{-1}: 1689 (C^6=O), 1654 (C=O, ester), 1633 (pyrim.), 1566 (C=C$_{arom}$), 1517 (pyrim.), 1423 (arom.), 1280 (COOEt), 1186 (NHCSNH), 1012 (pyrim.), 719 (pyrim.). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, CH$_2$C**H**$_3$, J = 7.1 Hz), 4.22 m (2H, OCH$_2$), 7.36 t (1H, H$_{arom}$, J = 7.4 Hz), 7.45 t (2H, H$_{arom}$, J = 7.7 Hz), 7.61 s (1H, 5′-H), 7.89 d (2H, H$_{arom}$, J = 7.7 Hz), 8.50 s (1H, 4-H), 12.00 br.s (2H, NH). Found: m/z 343.0854 $[M + H]^+$. $C_{16}H_{14}N_4O_3S$. Calculated: M + H 343.0860.

Ethyl 2-(carbamimidoylamino)-4-methyl-1,3-thiazole-5-carboxylate (29) was synthesized according to the procedure described in [12]. Yield 60%, mp 271–273°C. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH$_2$C**H**$_3$, J = 7.1 Hz), 2.46 s (3H, 4-CH$_3$), 4.17 m (2H, OCH$_2$), 7.20 br.s (4H, NH, NH$_2$). Found: m/z 229.0758 $[M + H]^+$. $C_8H_{12}N_4O_2S$. Calculated: M + H 229.0754.

Ethyl 2-[(5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-yl)amino]-4-methylpyrimidine-5-carboxylate (30). A mixture of 0.68 g (3 mmol) of guanidine **29** and 0.56 g (3 mmol) of ester **20** in 15 mL of xylene was refluxed for 5–6 h. The precipitate was filtered off and recrystallized from toluene. Yield 0.68 g. (65%), white crystals, mp 233–235°C. IR spectrum, ν, cm^{-1}: 1704 (C=O), 1568 (pyrim.), 1519 (δNH$_2$), 1440 (arom.), 1280 (NCSN), 1228 (COEt), 1012 (pyrim.), 798 (pyrim.), 576 (NCSN). ^{1}H NMR spectrum, δ, ppm: 1.27–1.36 m (6H, CH$_2$C**H**$_3$), 2.52 s (3H, 4′-CH$_3$), 2.73 s (3H, 4-CH$_3$), 4.23–4.35 m (4H, OCH$_2$), 9.00 s (1H, 6-H), 12.40 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.50 and 14.73 ($CH_2\mathbf{C}H_3$), 17.48 (CH_3), 60.73 and 61.33 (OCH_2), 115.12 ($C^{5'}$), 116.94 (C^5), 156.88 ($C^{2'}$), 157.73 (C^4), 160.55 ($C^{4'}$), 161.39 (C^6), 162.80 (C^2), 164.74 and 170.18 (C=O). Found: m/z 351.1117 $[M + H]^+$. $C_{15}H_{18}N_4O_4S$. Calculated: M + H 351.1122.

Ethyl 2-[(5-ethoxycarbonyl-4-methyl-1,3-thiazol-2-yl)amino]-6-oxo-1,6-dihydropyrimidine-5-carboxylate (31). A mixture of 0.68 g (3 mmol) of guanidine **29** and 0.65 g (3 mmol) of diester **11** in 15 mL of xylene was refluxed for 5–6 h. The precipitate was

filtered off and recrystallized from toluene. Yield 0.63 g (60%), white crystals, mp 292–294°C. IR spectrum, ν, cm^{-1}: 1703 (C^6=O), 1666 (C=O, ester), 1523 (pyrim.), 1365, 1263 (COOEt), 1095 (pyrim.), 605 (pyrim.). ^{1}H NMR spectrum, δ, ppm: 1.20–1.30 m (6H, $CH_2C\mathbf{H}_3$), 2.51 s (3H, 4′-CH_3), 4.16–4.29 m (4H, OCH_2), 8.52 s (1H, 4-H), 12.20 br.s (2H, NH). Found: *m*/*z* 353.0918 $[M + H]^+$. $C_{14}H_{16}N_4O_5S$. Calculated: *M* + H 353.0915.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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