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SYNTHESIS AND REACTIONS OF THIOAMIDES OF 5-AMINO-2-ARYL-2H-1,2,3-TRIAZOLE-4-CARBOXYLIC ACID

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A method has been developed for obtaining thioamides of 5-amino-2-aryl-2H-1,2,3-triazole-4-carboxylic acid. Their heterocyclization reactions with bifunctional reagents has been studied. New heterocyclic polycyclic ensembles have been synthesized containing a 1,2,3-triazole fragment, a thiazole, and a residue of the natural alkaloid cytisine.

Keywords: aminoimidazoles, α-halo ketones, thiazoles, thioamides, thioimidinium salts, 1,2,3-triazoles, 1,2,4-triazoles.

We previously developed a procedure for the synthesis of arylhydrazonoacetamidines containing fragments of natural compounds and pharmacophoric groups, and also substituents differing in spatial and electronic effects at the nitrogen atom of the amidine group [1]. A broad series of 5-amino-2-aryl-2H-1,2,3-triazole-4-carbonitriles was obtained by the oxidative cyclization reaction of the synthesized arylhydrazonoacetamidines. The new compounds showed good fungicidal activity at concn. = 50 μg/ml in experiments *in vitro* [1]. It should be noted that the synthesized 2H-1,2,3-triazoles contain a cyano group at the C-5 atom of the heterocycle and are of interest as building blocks for obtaining new heterocyclic compounds and for studying their biological activity. Its transformation into a thioamide function is the most widespread direction of modification of the cyano group. Such a transformation is of undoubted interest, since thioamides, although being a long established and widely known class of compounds, and up to the present time continue to be the focus of intensive investigations in organic, and especially heterocyclic chemistry. The main reason for such steady attention is the large variety of chemical reactions of thioamides [2-4].

* Dedicated to Academician of the Russian Academy of Sciences O. N. Chupakhin on his 75th jubilee.

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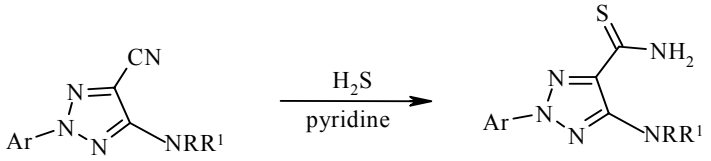
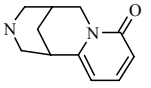
The present work is devoted to the synthesis and investigation of the reactions of thioamides of 5-amino-2-aryl-2H-1,2,3-triazole-4-carboxylic acid for constructing new polyheterocycles and the study of their biological action.

Various methods are proposed in the literature for obtaining thioamides [5, 6]. Of them the most convenient methods are based on the reaction of nitriles with hydrogen sulfide, the important special feature of which is the possibility of carrying it out without the formation of side products. Thioamides **2** were obtained in good yield on passing hydrogen sulfide through a cooled solution of 2H-1,2,3-triazole-4-carbonitriles **1a-f** in pyridine in the presence of triethylamine. The structure of compounds **2a-f** was confirmed by spectral data and by data of elemental analysis.

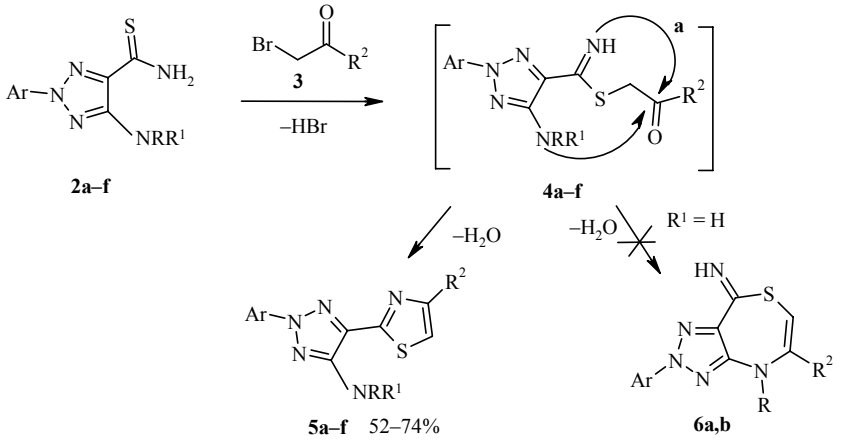


1a–f **2a–f** 55–95%

1, 2 a–e Ar = 4-$MeOC_6H_4$, **a** NRR^1 = NHMe, **b** NRR^1 = NHC_6H_{11}-*cyclo*,
c NRR^1 = piperidino,, **d** NRR^1 = morpholino, **e** NRR^1 = 4-(pyrimidin-2-yl)piperazin-1-yl;

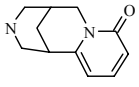
f Ar = 4-FC_6H_4, NRR^1 = 

Transformation of the nitrile group of triazoles **1** into a thioamide allows the introduction of two additional nucleophilic centers into position 4 of the triazole ring and an electrophilic center associated with the thiocarbonyl carbon atom. Thanks to the presence of these reactive centers, and also the amino group in the *ortho* position in compounds **2a,b** the reaction of triazoles **2** with various bifunctional reagents becomes practicable.



2a–f **4a–f** **5a–f** 52–74% **6a,b**

3 a R^2 = 4-ClC_6H_4, **b** R^2 = 4-$MeOC_6H_4$, **c** R^2 = pyridin-3-yl; **4, 5 a–e** Ar = 4-$MeOC_6H_4$,
a NRR^1 = HNMe, R^2 = 4-ClC_6H_4; **b** NRR^1 = HNC_6H_{11}-*cyclo*, R^2 = 4-ClC_6H_4;
c NRR^1 = piperidino, R^2 = pyridin-3-yl; **d** NRR^1 = morpholino, R^2 = 4-ClC_6H_4;
e NRR^1 = 4-(pyrimidin-2-yl)piperazin-1-yl, R^2 = pyridin-3-yl; **f** Ar = 4-FC_6H_4,

NRR^1 =  , R^2 = 4-ClC_6H_4; **6 a, b** Ar = 4-$MeOC_6H_4$, R^2 = 4-ClC_6H_4,

a R = Me, **b** R = C_6H_{11}-*cyclo*

One of the most convenient and widespread methods of heterocyclization of thioamides is their interaction with α-halo ketones (Hantzsch reaction) [7, 8]. The interaction usually occurs on boiling the initial reactants in an organic solvent.

Reaction of thioamides **2** with α-halo ketones was carried out on heating in ethyl alcohol for 5-6 h. The crystalline product was separated by filtration. Signals appeared in the ^{1}H NMR spectra of 5-amino-2-aryl-4-(thiazol-2-yl)-2H-1,2,3-triazoles **5a-f** corresponding to the proton-containing group in position 4 of the thiazole ring and a singlet for the proton in position 5 of the thiazole ring at 7.14-8.64 ppm.

The structure of compound **5d** was investigated by X-ray crystallography (Fig. 1). The overall organization of the molecule, bond lengths, and valence angles were close to usual for such a system. The heterocycles form a planar conjugated system, with deviation of atoms from the mean square plane no more than 0.04 Å. The plane of the 4-methoxyphenyl substituent is twisted relative to the conjugation plane of the heterocycles by 14.0°, the 4-chlorophenyl substituent forms an angle of 3.8° with the conjugation plane of the heterocycles, which shows its participation in the conjugation system of the heterocyclic system.

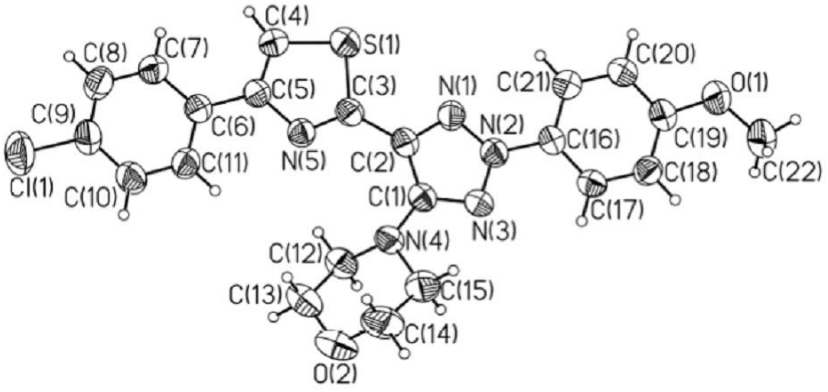


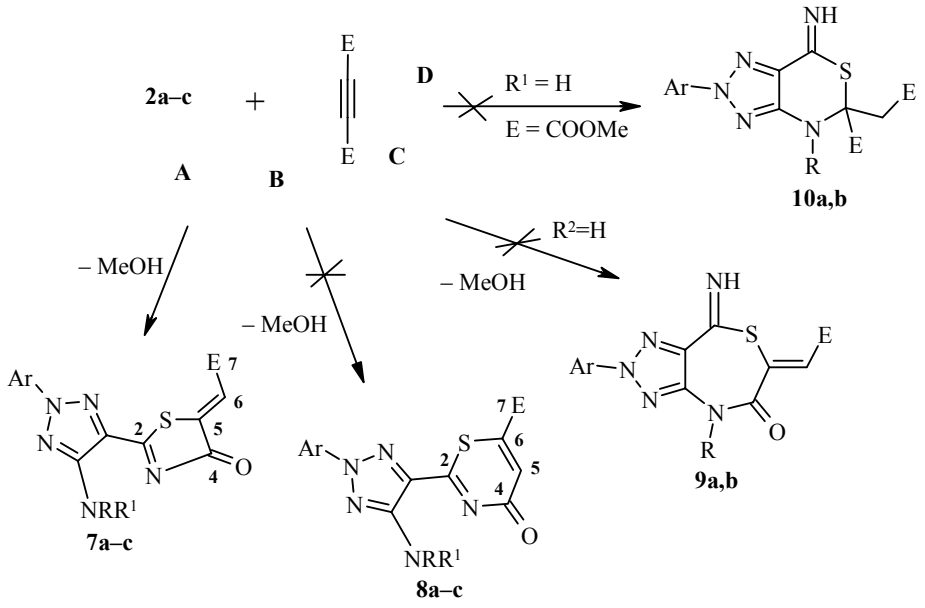
Fig. 1. Overall shape of the **5d** molecule according to data of X-ray structural analysis.

It must be noted that in this reaction for thioamides **2a,b** containing a secondary amino group in position 5 of the heterocycle, an alternative direction is possible for cyclization to 2,4-dihydro-1,2,3-triazolo[4,5-*e*]-1,4-thiazepines **6a,b**. However on measuring the ^{1}H NMR spectrum of product **6a** in $CDCl_3$ the signal of the protons of the methyl group of the methylamino fragment was fixed as a doublet at 3.14 ppm (J = 4.8 Hz), which confirms the formation of a thiazole and not a thiazepine ring.

Esters of acetylenedicarboxylic acid are convenient biselectrophilic reagents, the reaction of which with thioamides is used for the synthesis of various heterocyclic systems due to their high reactivity and the possibility of obtaining new compounds with various sizes of heterocyclic fragment depending on the structure of the reacting substances [9, 10].

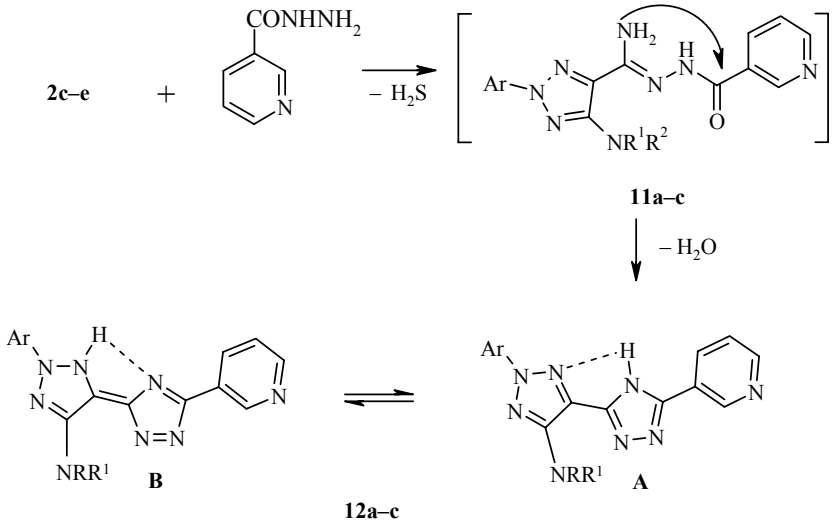
Interaction of 1,2,3-triazole-4-thioamides **2** with the dimethyl ester of acetylenedicarboxylic acid (DMAD) was carried out in methanol at room temperature. The reaction was completed 5-10 min after mixing the reactants. It should be noted that on interacting thioamides with DMAD the formation is possible of several heterocyclic products by an addition–elimination mechanism (routes **A, B, C**) and also by addition and cyclization (**D**).

The reaction products were isolated in 63-70% yield. Their structure was identified with the aid of ^{1}H, ^{13}C NMR, mass spectra and data of elemental analysis. Mass spectral data enabled exclusion of the formation of 2,4,5,7-tetrahydro-1,2,3-triazolo[4,5-*d*]-1,3-thiazines **10**, since the molecular ion peak in the mass spectrum of the obtained products corresponded to the mass of cyclization products with elimination of a molecule of



7, **8 a–c**, **9**, **10 a,b** Ar = 4-MeOC$_6$H$_4$, **7**, **8 a** NRR^1 = NHMe, **b** NRR^1 = NHC$_6$H$_{11}$-*cyclo*, **c** NRR^1 = piperidino; **9**, **10 a** R = Me, **b** R = C$_6$H$_{11}$-*cyclo*

methanol. In addition signals were absent from the ^{1}H NMR spectra for CH_2 group protons. The multiplicity of the NHR group signals (quartet for compound **7a** with J = 4.8 and a doublet for compound **7b** with J = 7.6 Hz) indicates that this nucleophilic center does not participate in the heterocyclization and excludes the formation of 2,4,5,8-tetrahydro-1,2,3-triazolo[4,5-*e*][1,4]thiazepinones **9a,b**. The position of the vinylic proton H-6 in the 6.87-6.97 ppm region and the absence of an interaction of this atom with the C-4 carbonyl atom in the ^{13}C NMR spectrum are characteristic differences of thiazoles with an exocyclic double bond. The interaction with DMAD therefore occurs exclusively with the participation of the thioamide fragment and leads to the formation of the methyl esters of [2-(5-amino-2-aryl-2H-1,2,3-triazol-4-yl-4-oxo-4H-thiazol-5-ylidene]acetic acids **7a-c**, and not 2H-(1,2,3-triazol-4-yl)-4H-1,3-thiazines **8a-c**.

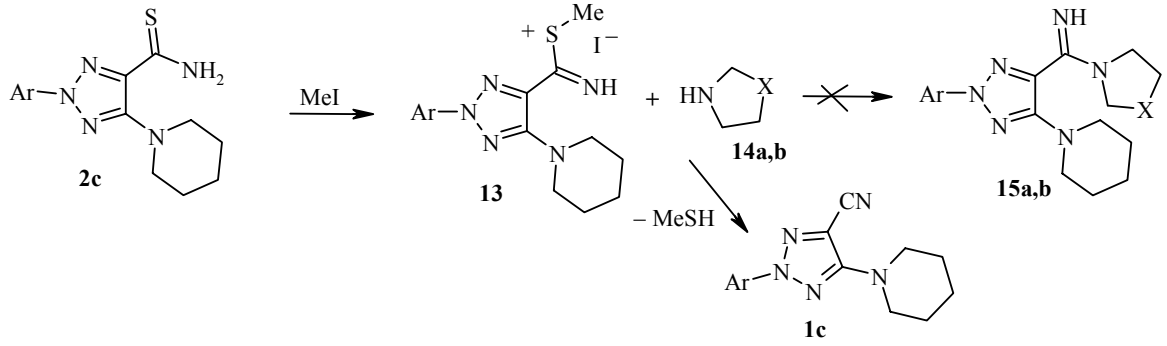


11, 12a–c Ar = 4-MeOC$_6$H$_4$, **a** NRR^1 = piperidino, **b** NRR^1 = morpholino, **c** NRR^1 = 4-(pyrimidin-2-yl)piperazin-1-yl

Of interest in the special features of the structure of the thioamide group is the presence not only of nucleophilic centers (nitrogen and sulfur atoms) but also of an electrophilic carbon atom, which permits these compounds to react with nucleophilic reagents [2, 3]. Heating thioamides **2** with nicotinic acid hydrazide leads to the formation of new 1,2,3-triazoles **12a-c** with a 1,2,4-triazole ring in position 4, probably through the intermediate amidrazones **11a-c**. Triazoles **12** were obtained in 55-94% yield.

Signals were present in the ^{1}H NMR spectra of compounds **12** for the proton-containing groups of the pyridine ring at the C-3 atom of the 1,2,4-triazole ring. The signal of the NH proton of the heterocycle is displaced to a significant extent towards low field (up to 14.5 ppm) and is displayed as two broad singlets. This may be the result of the existence of an equilibrium between forms **A** and **B** of compounds **12**.

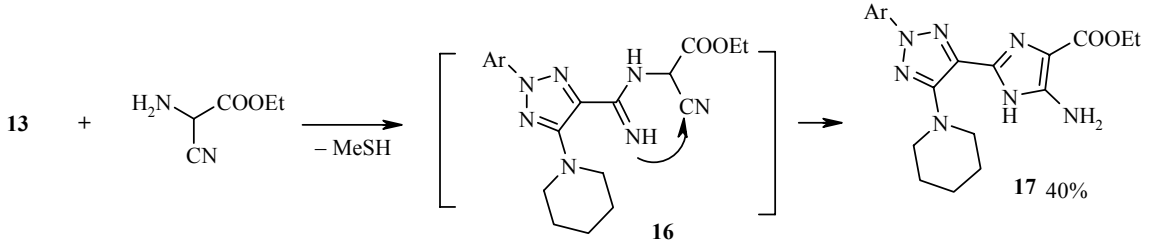
It is known that alkylation of the sulfur atom in the thiocarbamoyl fragment leads to an increase in the reactivity of thioamides in relation to nucleophilic reagents, and also blocks the sulfur atom in heterocyclization reactions [12]. Alkylation of thioamides was carried out in acetone using an excess of alkylating agent. The thioimidium salt **13** was isolated in good yield. However the interaction of the obtained salt **13** with primary and secondary amines did not lead to the preparation of amidino derivatives **15**. The sole product of this reaction was in all cases the cyanotriazole **1c.**



2c **13** **14a,b** **15a,b** **1c**

13, 15a,b Ar = 4-MeOC$_6$H$_4$; **14, 15 a** X = CH$_2$, **b** X = (CH$_2$)$_2$; Ar = 4-MeOC$_6$H$_4$

The use in the reaction of the ethyl ester of aminocyanoacetic acid lead to the preparation of aminoimidazole **17**, probably as a result of cyclization of amidine **16** formed in the first stage.



16 **17** 40%

13, 16, 17 Ar = 4-MeOC$_6$H$_4$

As a result of the investigations carried out we have shown that 5-amino-2H-1,2,3-triazole-4-carbonitriles **1** are convenient starting materials for the synthesis of the corresponding thioamides. The latter interact with a wide circle of cyclizing agents differing in nature and reactivity, leading to the formation of polyheterocyclic ensembles containing not only new, but also in certain cases a unique combination of heterocycles. These include the 1,2,3-triazole fragment, thiazole, imidazole, 1,2,4-triazole, and various tertiary cycloalkylamines, including substituted piperazines or a residue of the natural alkaloid cytisine.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 instrument (400 and 100 MHz respectively) in DMSO-d_6, internal standard was TMS. A check on the progress of reactions and the homogeneity of the obtained substances was effected by TLC on Sorbfil UV-254 plates in the system ethyl acetate–hexane, 1:1. The mass spectra were recorded on a Varian MAT 311A instrument, accelerating voltage was 3 kV, ionization energy 70eV.

The X-ray structural investigations of a crystal of compound **5d** (from acetone) were carried out by the standard procedure on an automatic four-circle X-ray Xcalibur 3 diffractometer with a CCD detector (λMoK, graphite monochromator, ω-scanning). The analysis used a fragment of a colorless laminar crystal of size 0.47×0.36×0.09 mm. The structure was solved by the direct method with the SHELXS97 program [13] and was refined with the SHELXL97 program [14] by the least squares method in an anisotropic approximation for the non-hydrogen atoms. The hydrogen atoms were located by the peaks of electron density distribution and were included in the refinement in the isotropic approximation in the "rider" model. No corrections for absorption were introduced.

5-Amino-2H-1,2,3-triazole-4-carbonitriles **1** were obtained by the method of [1] developed previously.

Preparation of Thioamides 2a-f (General Method). A solution of 5-amino-2H-1,2,3-triazole-4-carbonitrile **1** and triethylamine (0.3 ml, 0.002 mmol) in dry pyridine (50 ml) was saturated with hydrogen sulfide for 2 h. After leaving for 8-10 h the reaction mixture was poured onto ice. The solid was filtered off and thoroughly washed with water.

2-(4-Methoxyphenyl)-5-methylamino-2H-1,2,3-triazole-4-thiocarboxamide (2a). Yield was 96%; mp 149-150 °C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.97 (3H, br. s, CH_3); 3.84 (3H, s, OCH_3); 7.05 (1H, br. s, NH); 7.00 and 7.94 (4H, *J* = 9.5, AA'XX', H Ar); 8.92 (H, s, CSNH); 9.23 (H, s, CSNH). ^{13}C NMR spectrum, δ, ppm: 30.3; 56.0; 115.1; 120.1; 128.6; 132.9; 156.7; 159.1; 187.0. Mass spectrum, *m/z* (I_{rel}, %): 263 $[M]^+$ (56). Found, %: C 50.35; H 5.18; N 26.83; S 12.31. $C_{11}H_{13}N_5OS$. Calculated, %: C 50.18; H 4.98; N 26.60; S 12.18.

5-Cyclohexylamino-2-(4-methoxyphenyl-2H-1,2,3-triazole-4-thiocarboxamide (2b). Yield was 94%; mp 129-130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32-1.42 (5H, m, $2CH_2$ + CH); 1.43-1.45 (1H, m, CH); 1.59-1.62 (2H, m, CH_2); 2.03-2.04 (2H, m, CH_2); 3.59-3.61 (1H, m, CH); 3.83 (3H, s, OCH_3); 6.91 (1H, br. s, CSNH); 6.99 and 7.91 (4H, *J* = 9.0, AA'XX', H Ar); 7.3 (1H, d, *J* = 7.5, NH); 9.0 (2H, br. s, CSNH). ^{13}C NMR spectrum, δ, ppm: 23.8; 25.2; 32.1; 51.4; 55.4; 114.5; 119.6; 127.9; 132.3; 154.5; 158.6; 186.5. Mass spectrum, *m/z* (I_{rel}, %): 331 $[M]^+$ (73). Found, %: C 58.16; H 6.55; N 21.35; S 9.78. $C_{16}H_{21}N_5OS$. Calculated, %: C 57.98; H 6.39; N 21.13; S 9.67.

2-(4-Methoxyphenyl)-5-piperidino-2H-1,2,3-triazole-4-thiocarboxamide (2c). Yield was 94%; mp 145-146°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60-1.70 (6H, m, $3CH_2$); 3.25-3.29 (4H, m, $2CH_2$); 3.83 (3H, s, OCH_3); 6.98 and 7.88 (4H, *J* = 7.1, AA'XX', H Ar); 9.15 (1H, br. s, CSNH); 9.48 (1H, br. s, CSNH). ^{13}C NMR spectrum, δ, ppm: 23.6; 24.8; 50.6; 55.5; 114.8; 120.2; 132.5; 135.2; 155.1; 158.4; 190.0. Mass spectrum, *m/z* (I_{rel}, %): 317 $[M]^+$ (65). Found, %: C 56.81; H 6.15; N 22.31; S 10.25. $C_{15}H_{19}N_5OS$. Calculated, %: C 56.76; H 6.03; N 22.06; S 10.10.

2-(4-Methoxyphenyl)-5-morpholino-2H-1,2,3-triazole-4-thiocarboxamide (2d). Yield was 66%; mp 153-154°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.33-3.36 (4H, m, $2CH_2$); 3.75-3.77 (4H, m, $2CH_2$); 3.81 (3H, s, OCH_3); 7.0 and 7.89 (4H, *J* = 9.0, AA'XX', H Ar); 9.3 (2H, br. s, CSNH); 9.7 (2H, br. s, CSNH). ^{13}C NMR spectrum, δ, ppm: 114.7; 119.53; 132.4; 135.1; 154.6; 158.6; 189.5. Mass spectrum, *m/z* (I_{rel}, %): 319 $[M]^+$ (70.4). Found. %: C 52.76; H 5.45; N 21.7; S 10.34. $C_{14}H_{17}N_5O_2S$. Calculated, %: C 52.65; H 5.37; N 21.93; S 10.04.

2-(4-Methoxyphenyl)-5-[4-(pyrimidin-2-yl)piperazin-1-yl]-2H-1,2,3-triazole-4-thiocarboxamide (2e). Yield was 94%; mp 190-191°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.40-3.50 (4H, m, CH_2); 3.55-3.60 (2H, m, CH_2); 3.83 (3H, s, OCH_3); 3.90-4.00 (4H, m, $2CH_2$); 6.55 (1H, t, *J* = 4.8, H Pyr); 7.0 and 7.9 (4H, *J* = 9.0,

AA'XX', H Ar); 8.30 (2H, d, J = 4.8, H Pyr); 9.2 (2H, br. s, CSNH); 9.6 (2H, br. s, CSNH). Mass spectrum, *m/z* (I_{rel}, %): 396 $[M]^+$ (65.4). Found, %: C 54.18, H 5.00; N 28.48; S 8.25. $C_{18}H_{20}N_8OS$. Calculated, %: C 54.53; H 5.08; N 28.26; S 8.09.

2-(4-Fluorophenyl)-5-(8-oxo-1,5,6,8-tetrahydro-2H,4H-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3-yl)-2H-1,2,3-triazole-4-thiocarboxamide (2f). Yield was 95%; mp 159-160°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.91 (2H, br. s, CH_2); 2.55 (1H, br. s, CH); 3.00 (1H, d, J = 10.8, CH); 3.14 (1H, dd, J = 11.6, J = 2.0, CH); 3.21 (1H, s, CH); 3.73 (1H, dd, J = 15.6, J = 6.3, CH); 3.79 (1H, d, J = 11.6, CH); 4.10 (1H, d, J = 11.2, CH); 4.23 (1H, d, J = 15.6, CH); 6.16 (1H, d, J = 7.0, H Ar); 6.18 (1H, d, J = 8.8, H Ar); 7.29 (1H, dd, J = 7.8, J = 8.8, H Ar); 7.40 (1H, t, J = 8.80, H Ar); 7.90 (2H, dd, J = 8.30, J = 4.8, H Ar); 9.57 (1H, br. s, NH); 9.94 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 410 $[M]^+$ (52.2). Found, %: C 58.15; H 4.37; N 20.72; S 7.93. $C_{20}H_{19}FN_6OS$. Calculated, %: C 58.52; H 4.67; N 20.47; S 7.81.

Synthesis of Compounds 5a-f (General Method). A solution of thiocarboxamide **2** (0.5 mmol) and bromoacetophenone (0.5 mmol) in ethyl alcohol (50 ml) was boiled for 3-6 h. The solvent was evaporated under vacuum, and the residue recrystallized from ethyl alcohol.

{5-[4-(4-Chlorophenyl)thiazol-2-yl]-2-(4-methoxyphenyl)-2H-1,2,3-triazol-4-yl}methylamine (5a). Yield was 77%; mp 179-181°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.18 (3H, d, J = 4.0, $NHCH_3$); 3.86 (3H, s, OCH_3); 5.89 (1H, br. s, NH); 6.93 and 7.83 (4H, J = 8.9, AA'XX', H Ar); 7.40 (1H, s, CH); 7.43 and 7.97 (4H, J = 8.0, AA'XX', H Ar). ^{13}C NMR spectrum, δ, ppm: 30.5; 55.5; 113.8; 114.6 (2C); 119.0 (2C); 127.3; 128.2 (2C); 128.8 (2C); 132.4; 132.7; 132.8; 152.6; 153.5; 158.1; 158.7. Mass spectrum, *m/z* (I_{rel}, %): 397 $[M]^+$ (73). Found, %: C 57.54; H 4.17; Cl 9.01; N 17.83; S 8.15. $C_{19}H_{16}ClN_5OS$. Calculated, %: C 57.36; H 4.05; Cl 8.91; N 17.60; S 8.06.

{5-[4-(4-Chlorophenyl)thiazol-2-yl]-2-(4-methoxyphenyl)-2H-1,2,3-triazol-4-yl}cyclohexylamine (5b). Yield was 83%; mp 149-151°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.29-1.55 (5H, m, $2CH_2$ + CH); 1.60-1.70 (1H, m, CH); 1.74-1.85 (2H, m, CH_2); 2.10-2.18 (2H, m, CH_2); 3.62-3.72 (1H, m, CH); 3.84 (3H, s, OCH_3); 6.14 (1H, br. s, NH); 6.99 and 7.88 (4H, J = 9.0, AA'XX', H Ar); 7.45 and 7.96 (4H, J = 8.8, AA'XX', H Ar); 7.98 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 23.9 (2C); 25.3; 32.2 (2C); 51.6; 55.4; 114.0; 114.7 (2C); 119.1 (2C); 127.4; 127.6; 128.9 (2C); 132.3; 132.6; 132.8; 150.9; 153.1; 158.1; 158.8. Mass spectrum, *m/z* (I_{rel}, %): 465 $[M]^+$ (77). Found, %: C 61.98; H 5.25; Cl 7.43; N 15.36; S 6.95. $C_{24}H_{24}ClN_5OS$. Calculated, %: C 61.86; H 5.19; Cl 7.61; N 15.03; S 6.88.

3-{2-[2-(4-Methoxyphenyl)-5-piperidino-2H-1,2,3-triazol-4-yl]thiazol-4-yl}pyridine (5c). Yield was 78%; mp 250-251°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.63-1.69 (2H, m, CH_2); 3.45-3.65 (4H, m, $2CH_2$); 3.83 (3H, s, OCH_3); 7.12 and 7.88 (4H, J = 9.2, AA'XX', H Ar); 8.05 (1H, t, J = 7.6, H Py); 8.64 (1H, s, CH); 8.85 (1H, br. s, H Py); 8.90 (1H, d, J = 8.0, H Py); 9.40 (1H, br. s, H Py). Mass spectrum, *m/z* (I_{rel}, %): 418 $[M]^+$ (60.1). Found, %: C 63.35; H 5.46; N 20.51; S 7.47. $C_{22}H_{22}N_6OS$. Calculated, %: C 63.14; H 5.30; N 20.08; S 7.66.

1-{5-[4-(4-Chlorophenyl)thiazol-2-yl]-2-(4-methoxyphenyl)-2H-1,2,3-triazol-4-yl}morpholine (5d). Yield was 66%; mp 189-190°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.49-3.54 (4H, m, $2CH_2$); 3.83 (3H, s, OCH_3); 3.84-3.89 (4H, m, $2CH_2$); 7.12 and 7.89 (4H, J = 9.1, AA'XX', H Ar); 7.57 and 8.05 (4H, J = 8.6, AA'XX', H Ar); 8.29 (1H, s, CH). Mass spectrum, *m/z* (I_{rel}, %): 453 $[M]^+$ (43.1). Found, %: C 58.21; H 4.44; Cl 7.81; N 15.43; S 7.06. $C_{22}H_{20}ClN_5O_2S$. Calculated, %: C 58.20; H 4.40; Cl 7.80; N 15.40; S 7.00.

2-{4-[2-(4-Methoxyphenyl)-5-(4-pyridin-3-yl)thiazol-2-yl]-2H-1,2,3-triazol-4-yl}piperazin-1-ylpyrimidine (5e). Yield was 94%; mp 210-211°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 3.50-3.65 (4H, m, $2CH_2$); 3.84 (3H, s, OCH_3); 3.85-4.50 (4H, m, $2CH_2$); 6.55-6.65 (1H, m, H Pyr); 7.05 and 7.91 (4H, J = 8.8, AA'XX', H Ar); 7.43 (1H, dd, J = 4.3, J = 5.0, H Py); 8.19 (1H, s, CH); 8.25-8.30 (1H, m, H Py); 8.33 (2H, d, J = 4.3, H Py); 8.53 (1H, d, J = 5.0, H Py); 9.2 (1H, br. s, Py). Mass spectrum, *m/z* (I_{rel}, %): 497 $[M]^+$ (43.6). Found, %: C 60.31; H 5.00; N 25.42; S 6.24. $C_{25}H_{25}N_9OS$. Calculated, %: C 60.35; H 4.66; N 25.33; S 6.44.

3-{5-[4-(4-Chlorophenyl)thiazol-2-yl]-2-(4-fluorophenyl)--2H-1,2,3-triazol-4-yl}-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (5f). Yield was 41%, mp 219-221°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.0 (2H, br. s, CH_2); 2.57 (1H, br. s, CH); 2.93 (1H, d, *J* = 11.0, CH); 3.22 (1H, br. s, CH); 3.32 (1H, d, *J* = 12.10, CH); 3.82-3.94 (2H, m, CH_2); 4.45 (2H, d, *J* = 14.9, CH_2); 6.08 (1H, d, *J* = 6.8, H Ar); 6.21 (1H, d, *J* = 9.2, H Ar); 7.22 (1H, dd, *J* = 6.8, *J* = 9.2, H Ar); 7.23 (2H, dd, *J* = 8.8, *J* = 8.4, H Ar); 7.53 and 8.04 (4H, *J* = 8.8, AA'XX',H Ar); 7.96 (2H, dd, *J* = 4.4, *J* = 8.8, H Ar); 8.03 (1H, s, CH). Mass spectrum, *m/z* (I_{rel}, %): 544 $[M]^+$ (43.6). Found, %: C 61.50; H 4.00; Cl 6.00; N 15.00; S 5.50. $C_{28}H_{22}ClFN_6OS$. Calculated, %: C 61.70; H 4.07; Cl 6.50; N 15.42; S 5.88.

Synthesis of Methyl Esters of [2-(5-Amino-2-aryl-2H-1,2,3-triazol-4-yl)-4-oxo-4H-thiazol-5-ylidene]acetic Acid 7a-c (General Method). The dimethyl ester of acetylenedicarboxylic acid (DMAD) (0.061 ml, 0.5 mmol) was added to a solution of thioamide **2** (0.5 mmol) in methanol at room temperature. After the reaction was complete (TLC) the solid was filtered off.

Methyl Ester of {2-[2-(4-Methoxyphenyl)-5-methylamino-2H-1,2,3-triazol-4-yl]-4-oxo-4H-thiazol-5-ylidene}acetic Acid (7a). Yield was 71%; mp 229-230°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.08 (3H, d, *J* = 5.2, CH_3); 3.86 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 6.68 (1H, q, *J* = 5.2, NH); 7.06 and 8.02 (4H, *J* = 9.3, AA'XX', H Ar); 6.92 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 30.1; 52.8; 55.7; 100.0; 114.5 (2C); 120.9 (2C); 126.6; 132.7; 143.6; 156.8; 160.2; 166.3; 179.8; 181.4. Mass spectrum, *m/z* (I_{rel}, %): 373 $[M]^+$ (43.5). Found, %: C 51.22; H 4.31; N 18.41; S 8.36. $C_{16}H_{15}N_5O_4S$. Calculated, %: C 51.47; H 4.05; N 18.76; S 8.59.

{2-[5-Cyclohexylamino-2-(4-methoxyphenyl)-2H-1,2,3-triazol-4-yl]-4-oxo-4H-thiazol-5-ylidene}-acetic Acid Methyl Ester (7b). Yield was 64%; mp 189-190°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23-1.36 (1H, m, CH); 1.38-1.51 (4H, m, $2CH_2$); 1.61-1.70 (1H, m, CH); 1.74-1.83 (2H, m, CH_2); 2.05-2.14 (2H, m, CH_2); 3.63-3.74 (1H, m, CH); 3.86 (3H, s, CH_3); 3.87 (3H, s, OCH_3); 6.36 (1H, d, *J* = 7.6, NH); 6.94 (1H, s, CH); 7.06 and 8.00 (4H, *J* = 9.2, AA'XX', H Ar). ^{13}C NMR spectrum, δ, ppm: 24.9 (2C); 25.6; 33.0 (2C); 52.7; 55.6; 100.0; 114.5 (2C); 120.8; 120.9 (2C); 126.6; 132.7; 143.8; 155.1; 160.1; 166.4; 179.6; 181.4. Mass spectrum, *m/z* (I_{rel}, %): 441 $[M]^+$ (74.5). Found, %: C 57.22; H 5.31; N 15.41; S 7.36. $C_{21}H_{23}N_5O_4S$. Calculated, %: C 57.13; H 5.25; N 15.86; S 7.26.

Methyl Ester of {2-[2-(4-Methoxyphenyl)-5-piperidino-2H-1,2,3-triazol-4-yl]-4-oxo-4H-thiazol-5-ylidene}acetic Acid (7c). Yield was 65%; mp 147-149°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.6-1.8 (6H, m, $3CH_2$); 3.5-3.67 (4H, m, $2CH_2$); 3.86 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 6.90 (1H, s, CH); 7.05 and 7.98 (4H, *J* = 9.1, AA'XX', H Ar). Mass spectrum, *m/z* (I_{rel}, %): 427 $[M]^+$ (65.1). Found, %: C 55.85; H 4.65; N 16.21; S 7.63. $C_{20}H_{21}N_5O_4S$. Calculated, %: C 56.19; H 4.90; N 16.38; S 7.50.

Synthesis of 5-(2H-1,2,3-Triazol-4-yl)-4H-1,2,4-triazoles 12a-c (General Method). A mixture of thioamide **2** (0.5 mmol) and nicotinic acid hydrazide (0.123 g, 1.0 mmol) was heated at 200°C for 3 h. Separation and purification of the obtained product was carried out with the aid of column chromatography (chloroform–ethanol, 30:1). Yields were 55-94%.

3-{5-[2-(4-Methoxyphenyl)-(5-piperidin-1-yl)-2H-1,2,3-triazol-4-yl]-4H-1,2,4-triazol-3-yl}pyridine (12a). Yield was 64%; mp 153-155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.62 (2H, br. s, CH_2); 1.67 (4H, br. s, $2CH_2$); 3.45 (4H, br. s, $2CH_2$); 3.84 (3H, s, OCH_3); 7.00 and 7.90 (4H, *J* = 9.0, AA'XX', H Ar); 7.47 (1H, br. s, H Py); 8.58 (1H, d, *J* = 7.0, H Py); 8.60 (1H, br. s, H Py); 9.26 (1H, s, H Py); 14.20 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 402 $[M]^+$ (56.1). Found, %: C 62.59; H 5.83; N 27.69. $C_{21}H_{22}N_8O$. Calculated, %: C 62.67; H 5.51; N 27.84.

3-{5-[2-(4-Methoxyphenyl)-(5-morpholin-1-yl)-2H-1,2,3-triazol-4-yl]-4H-1,2,4-triazol-3-yl}pyridine (12b). Yield was 94%, mp 169-170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.35-3.60 (4H, m, $2CH_2$); 3.65-3.95 (4H, br. s, $2CH_2$); 3.85 (3H, s, OCH_3); 7.00 and 7.93 (4H, *J* = 8.8, AA'XX', H Ar); 7.46 (1H, br. s, H Py); 7.45 (1H, d, *J* = 7.0, H Py); 8.58 (1H, br. s, H Py); 8.57 (1H, br. s, H Py); 9.24 (1H, s, H Py); 14.57 and 14.65 (1H, br. s + br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 404 $[M]^+$ (65.1). Found, %: C 59.21; H 4.71; N 27.95. $C_{20}H_{20}N_8O_2$. Calculated, %: C 59.40; H 4.98; N 27.71.

2-{4-[2-(4-Methoxyphenyl)-5-(5-pyridin-3-yl-1H-1,2,4-triazol-3-yl)-2H-1,2,3-triazol-4-yl]piperazin-1-yl}pyrimidine (12c). Yield was 55%; mp 229-230°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.40-3.65 (4H, m, $2CH_2$); 3.84 (3H, s, OCH_3); 3.90-4.11 (4H, m, $2CH_2$); 6.55-6.60 (1H, m, H Py); 6.80-7.05 (3H, m, H Ar + H Pyr); 7.85 (2H, d, *J* = 8.8, H Ar); 7.94 (1H, d, *J* = 5.4, H Py); 8.30-8.34 (3H, m, H Pyr and H Py); 8.8 (1H, br. s, Py); 14.55 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 481 $[M]^+$ (51.6). Found, %: C 60.01; H 4.95; N 31.76. $C_{24}H_{23}N_{11}O$. Calculated, %: C 59.87; H 4.81; N 32.00.

{[2-(4-Methoxyphenyl)-5-piperidino-2H-1,2,3-triazol-4-yl]iminomethyl}methylsulfonium Iodide (13). A solution of thioamide **2c** (0.160 g, 0.5 mmol) and methyl iodide (0.3 ml, 5 mmol) in acetone (30 ml) was boiled for 5 h. The reaction mixture was cooled, and the solid filtered off. Yield 75%, mp 105-106°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.71 (2H, br. s, CH_2); 1.73 (4H, br. s, $2CH_2$); 2.77 (3H, s, SCH_3); 3.60 (4H, m, $2CH_2$); 3.86 (3H, s, OCH_3); 7.05 and 7.92 (4H, *J* = 8.8, AA'XX', H Ar). Mass spectrum, *m/z* (I_{rel}, %): 316 $[M-142]^+$ (55.4). Found, %: C 41.61; H 4.74; N 15.53. $C_{16}H_{21}IN_5OS$. Calculated, %: C 41.92; H 4.59; N 15.28.

Ethyl Ester of 5-Amino-2-[2-(4-methoxyphenyl)-5-piperidino-2H-(1,2,3-triazol-4-yl)-1H-imidazole-4-carboxylic Acid (17). A solution of compound **13** (0.215 g, 0.5 mmol) and aminocyanoacetic acid ethyl ester (0.46 g, 3.6 mmol) in chloroform was boiled. The reaction mixture was cooled, and the solid filtered off. Yield 40%; mp 83-85°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.0, CH_3); 1.60-1.73 (6H, m, $3CH_2$); 3.35 (4H, br. s, $2CH_2$); 3.82 (3H, s, OCH_3); 4.23 (2H, q, *J* = 7.1, CH_2); 5.51 (2H, s, NH_2); 7.00 and 7.87 (4H, *J* = 8.8, AA'XX', H Ar). Mass spectrum, *m/z* (I_{rel}, %): 411 $[M]^+$ (45.1). Found, %: C 58.44; H 5.95; N 24.03. $C_{20}H_{25}N_7O_3$. Calculated, %: C 58.38; H 6.12; N 23.83.

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