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1,6-Diamino-2-oxopyridine-3,5-dicarbonitrile Derivatives in the Mannich Reaction

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Abstract—1,6-Diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitriles under the action of primary aliphatic amines and an excess of 37% formalin in ethanol were converted into 2,3,8,9-tetrahydro-6,10-methano[1,2,4]-triazolo[1,5-*a*][1,5]diazocine-6,10(7*H*)-dicarbonitrile derivatives. At the same time, the Mannich reaction in the case of 1,6-diamino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles proceeds ambiguously, and, depending on the conditions, gives either N-ethoxymethylation products or 1,2,4-triazolo[1,5-*a*]pyridine derivatives. *In silico* predictive analysis of the biological activity of new compounds was carried out.

Keywords: 2-cyanoacethydrazide, aminomethylation, Mannich reaction, 1,2,4-triazolo[1,5-*a*]pyridines, 3,7-diazabicyclo[3.3.1]nonanes

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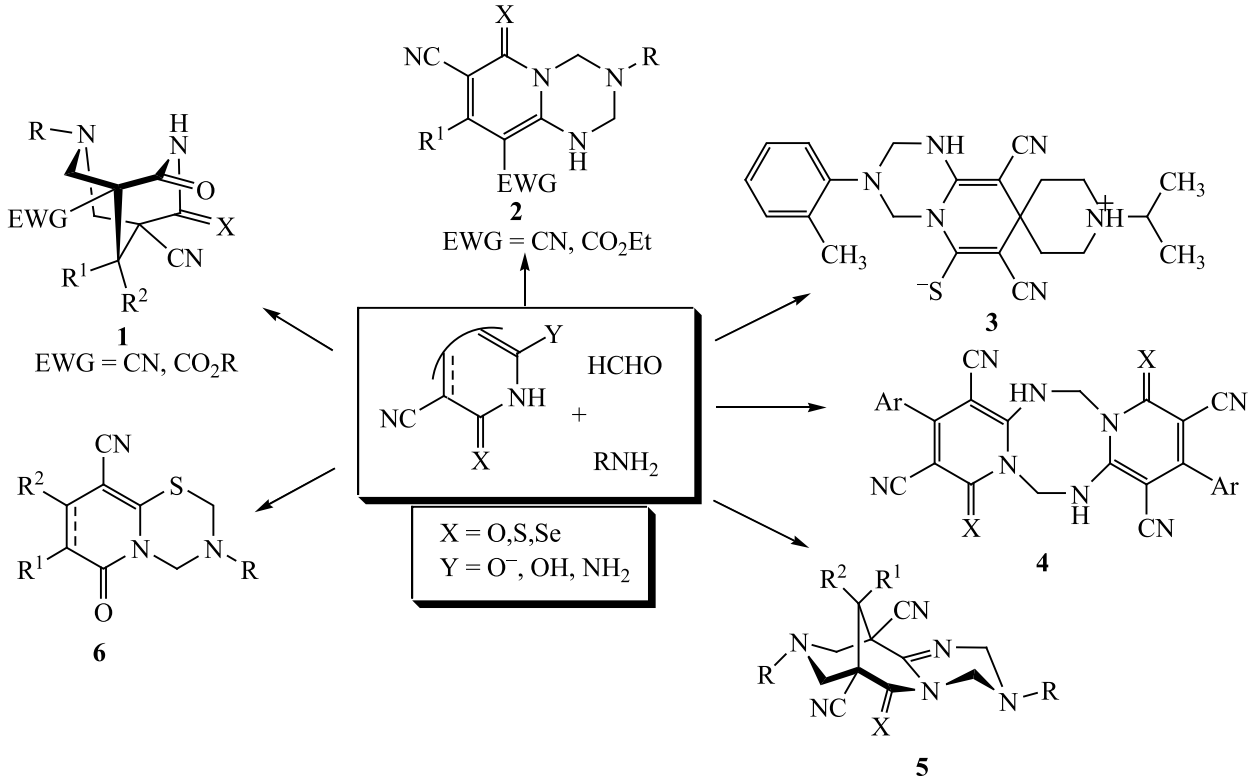
3-Cyanopyridine-2(1*H*)-chalcogenones are of interest due to the high synthetic potential, as well as due to the diverse biological activity (for reviews see [1–9]). It is known [10, 11] that the Mannich reaction with the participation of 3-cyanopyridine-2(1*H*)-chalcogenones is very sensitive to the substrate structure, the amine component, and the ratio of the starting reactants. The degree of saturation of the pyridine ring, the presence and position of electron-donor (NH_2, OH) or -acceptor (CN, COOEt, CONHR) groups in the ring are very important factors that affect aminomethylation regioselectivity. Thus, starting from substituted 3-cyanopyridine-2(1*H*)-chalcogenones, we have previously managed to synthesize 3,7-diazabicyclo[3.3.1]nonane **1** [12–15], pyrido[1,2-*a*]-[1,3,5]triazine **2**, **3** [16–18], dipyrido[1,2-*a*:1′2′-*e*][1,3,5,7]-tetrazocine **4** [19], 3,5,7, 11-tetraazatricyclo[7.3.1.$0^{2,7}$]-tridec-2-ene **5** [20–24], pyrido[2,1-*b*][1,3,5]thiadiazine **6** derivatives [25, 26] (Scheme 1), and more complex polycyclic structures.

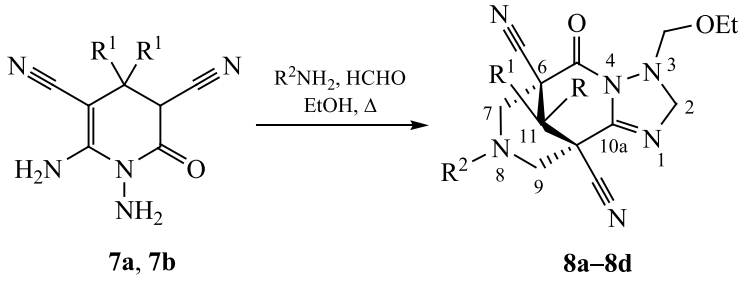
Continuing the study of the Mannich reaction in a series of heterocyclic substrates [27, 28], herein we reported the aminomethylation of available 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile derivatives [29, 30]. The starting compounds **7a**, **7b** were obtained by a one-pot method [31] based on the condensation of the corresponding ketone with malononitrile, ethyl cyanoacetate, and hydrazine hydrate under ultrasonic irradiation. It was found that refluxing compounds **7** with primary aliphatic amines and an excess of formalin leads to aminomethylation at the C^3 and C^5 positions of the pyridine ring. In addition, aminomethylation and ethoxymethylation involving both amino groups took place to form a substituted 1,2,4-triazoline ring. As a result, 3-ethoxymethyl-2,3,8,9-tetrahydro-6,10-methano[1,2,4]triazolo[1,5-*a*][1,5]diazocine-6,10(7*H*)-dicarbonitriles **8a–8d** were obtained in 29–61% yields (Scheme 2). It should be noted that the primary amine reacts in equimolar amount (1 equiv.) even if the amine was taken in an excess.

Compounds **8a–8d** are white crystalline substances, poorly soluble in ethanol and diethyl ether, moderately soluble in acetone and DMSO. Their structure was proved by ^1H, ^{13}C NMR, IR spectroscopy methods, as well as elemental analysis data. The IR spectra of compounds **8a–8d** show no absorption bands of N–H bonds, but there are strong absorption bands in the range of 1695–

Scheme 1.



Scheme 2.



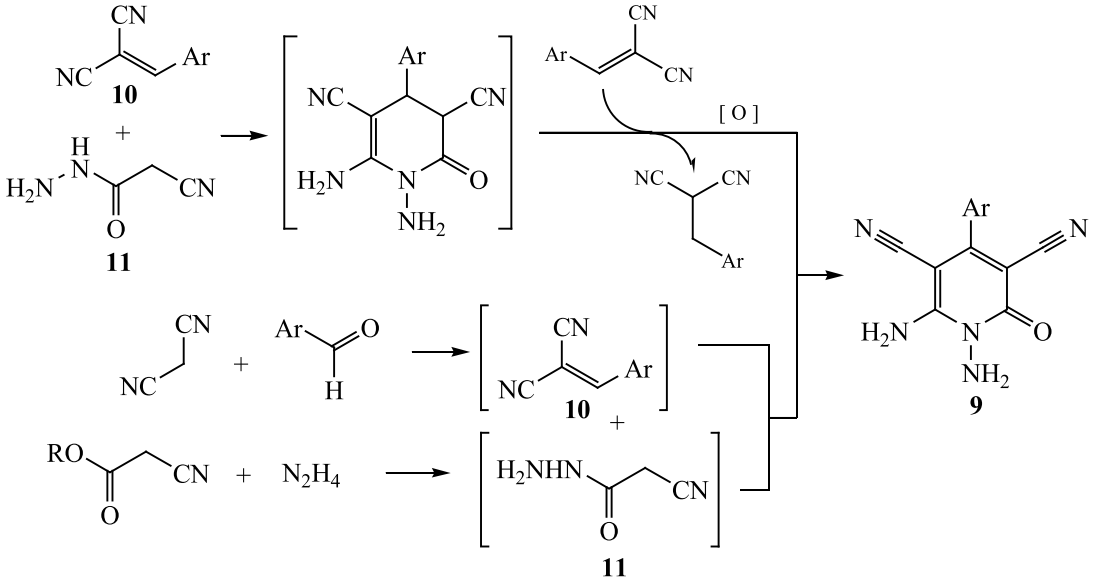
$R^1 = CH_3$ (**7a**); $R^1+R^1 = (CH_2)_5$ (**7b**); $R^1 = CH_3$, R^2 = *i*-Pr (**8a**); $R^1+R^1 = (CH_2)_5$, $R^2 = CH_3$ (**8b**), CH_2Ph (**8c**), *i*-Bu (**8d**).

1709 cm^{-1} (C=O), as well as low-intensity bands corresponding to stretching vibrations of non-conjugated nitrile groups at 2247–2257 cm^{-1}.

In the ^1H NMR spectra of compounds **8**, the signals of the protons of two methylene groups C^7H_2 and C^9H_2 are found in the form of two pairs of doublets in the 2.88–3.30 ppm range (^2J = 11.5–12.2 Hz). Among other characteristic signals, the AB system of protons of the endocyclic methylene group C^2H_2 (in the form of two doublets at 4.88–4.97 and 5.06–5.15 ppm, ^2J = 12.4–13.0 Hz) and the $NCH_2OCH_2CH_3$ fragment should also be noted.

In order to identify the possibility of using this method for the preparation of other compounds with the [1,2,4]triazolo[1,5-*a*]pyridine fragment, we studied the Mannich reaction of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **9**, which are the dehydrogenated analogs of compounds **7**. Compounds **9** have been first obtained by Soto et al. [32] in 1981 through the piperidine-catalyzed condensation of 2 equiv. of arylmethylenemalononitrile **10** with cyanoacetohydrazide **11** (Scheme 3). The availability of the starting reagents and the ease of practical implementation of this method for the preparation of *N*-aminopyridones **9** have led to the

Scheme 3.



fact that a large variety of synthetic procedures has been accumulated to date, leading to compounds **9** with yields close to quantitative. The general trend in this area is the use of multicomponent one-pot approaches (Scheme 3) and new catalytic systems. A number of approaches have been described in [33–53] and are summarized in Table 1.

We have tested some of the described approaches. It was found that the high (>70%) yields of compounds **9** described (for example, in [33, 40–44, 46, 48, 50–53]) are unreachable when using <2 equiv. of dinitrile **10** (or 2 equiv. of aldehyde and malononitrile) relative to hydrazide **11**, which confirms the data reported in [32].

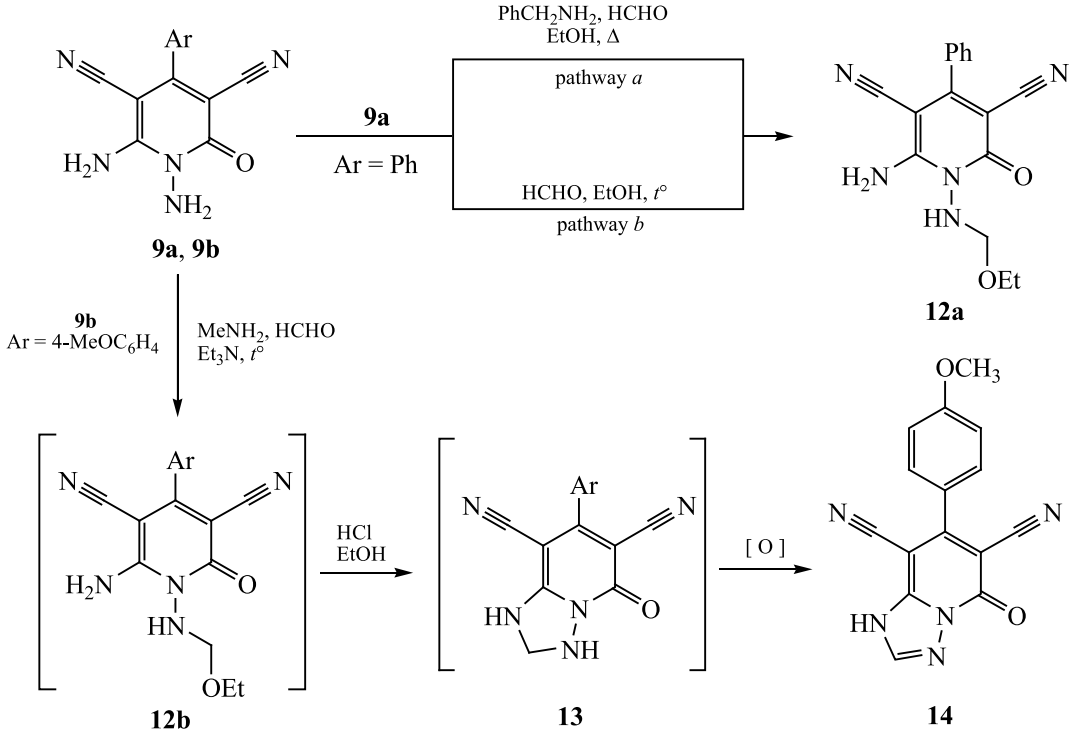
Table 1. Methods for the preparation of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **9**

Catalyst	Reaction conditions	Yield %	Reference
Piperidine	H_2O, 20°C, 11–17 h[a]	75–93	[33]
MOF MIL-101(Cr)-N($CH_2PO_3H_2$)$_2$	H_2O, reflux, 20–40 min[b]	74–92	[34]
KF-Al_2O_3	EtOH–H_2O, 20°C, 30–40 min[a]	84–96	[35]
Piperidine	EtOH, 20°C, 3 h[a]	65–80	[36]
0.4 mol% nano-Co_3S_4	EtOH, reflux, 30–55 min[b]	75–94	[37]
0.06 mol % nano-$CdZr_4(PO_4)_6$	EtOH, reflux, 30–45 min[b]	82–93	[38]
8 mol % nano-ZnO	EtOH, reflux, 40 min[b]	82–92	[39]
Et_3N	abs. EtOH, 20°C, 12 h	71	[40]
Piperidine	abs. EtOH, reflux, 5 h	85	[41]
Piperidine	EtOH, 40°C → 20°C	80	[42]
Piperidine	EtOH, 80–85°C	30-50	[43]
Piperidine	abs. EtOH, reflux, 4 h	–	[44]
No catalyst	abs. EtOH, reflux, 3 h	60	[45]
Piperidine	abs. EtOH, reflux, 6–8 h	71	[46]
Bu_4NBr	H_2O, 70°C, 10–20 min[a]	93–9	[47]
Piperidine	abs. EtOH, 20°C, 5 h	80–95	[48]
nano-ZrP_2O_7	EtOH, reflux, 20–35 min[b]	83–92	[49]
Piperidine	abs. EtOH, 20°C, night	71	[50]
Et_3N	EtOH, 20°C, 1 h	85	[51]
Piperidine	abs. EtOH, reflux, 3 h	74–75	[52, 53]

[a] Multicomponent reaction of malononitrile, aldehyde and cyanoacetohydrazide **11**.

[b] Multicomponent reaction of malononitrile, aldehyde, cyanoacetic ester and hydrazine hydrate.

Scheme 4.



It was found that the nature of the base (Et_3N, piperidine, morpholine, EtONa) does not significantly affect the product yields. Thus, the reaction of malononitrile with benzaldehyde and cyanoacethydrazide **11** (1 : 1 : 1 molar ratio) in the presence of catalytic amounts of piperidine in EtOH at 25°C gave rise to the target product **9a** (Ar = Ph) with yield of 32%, and 34% upon refluxing for 2 h.

A similar three-component reaction using anisaldehyde at 25°C afforded compound **9b** (Ar = 4-$CH_3OC_6H_4$) with yield of 36%, and 46% when boiling for 2 h. The reaction of (4-methoxybenzylidene)malononitrile **10b** with hydrazide **11** (1:1) in the presence of an excess of EtONa (1.5 equiv.) under reflux in anhydrous ethanol (3 h) furnished compound **9b** in 41% yield. At the same time, the use of 2 equiv. of nitrile **10b** relative to hydrazide **11** made it possible to complete the reaction in 30 min with a yield of 83–86% when catalyzed by morpholine or Et_3N.

In our opinion, the use of peculiar catalysts (for example, those described in [34, 35, 37, 38, 49]) does not provide significant advantages from the point of view of efficiency or cheapening of the process.

Surprisingly, the reaction of compounds **9a**, **9b** with formaldehyde and primary amines under conditions similar to those in the synthesis using tetrahydropyridines **7**, did not lead to the formation of [1,2,4]triazolo[1,5-*a*]-pyridine derivatives analogous to compounds **8**. Thus, in the reaction of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **9a** (Ar = Ph) with benzylamine and formalin in boiling alcohol (pathway *a*, Scheme 4), only the *N*-ethoxymethylation product **12a** was isolated. The same compound was obtained in comparable yield by refluxing 1-aminopyridine **9a** in ethanol with formalin and in the absence of an amine (pathway *b*, Scheme 4). At the same time, compound **9b** (Ar = 4-$MeOC_6H_4$) reacted with $MeNH_2$ and HCHO followed by acidification to give [1,2,4]triazolo[1,5-*a*]-pyridine **14**. Presumably, the ethoxymethylation product **12b** (not isolated) undergoes cyclization to a fused derivative of 1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-*a*]-pyridine **13** when treated with an acid. Further oxidation of **13** with atmospheric oxygen leads to the formation of compound **14**.

It should be noted that the reactions of 1,6-diamino-pyridin-2-ones **9** with carbonyl compounds leading to the formation of tetrahydro[1,2,4]triazolo[1,5-*a*]pyridines [30, 46–48, 53] and their oxidation reactions leading to triazolopyridines similar to compound **14** [45, 53, 54] have been known. However, to our knowledge, the

Table 2. Toxicity risks and physicochemical parameters of compounds **8a**–**8d**, **12a**, **14**, predicted using OSIRIS Property Explorer service

Compound	Toxicity risks[a]				Physicochemical parameters					
	A	B	C	D	c*Log*P	log*S*	MW	TPSA	drug likeness	drug Score
8a	–	–	–	+	–1.15	–2.75	358	96.0	–0.81	0.34
8b	–	–	–	+	–1.19	–2.97	370	96.0	–3.95	0.26
8c	–	–	–	+	0.23	–4.29	446	96.0	–4.62	0.21
8d	–	–	–	+	–0.11	–3.70	412	96.0	–10.54	0.23
12a	–	–	–	–	–0.79	–4.15	309	115.1	–1.19	0.50
14	–	–	–	+	0.40	–4.24	291	101.5	0.80	0.41

[a] Sign "+" indicates high risk of toxicity, "±"—moderate risk, "-"—no toxicity; A—mutagenicity, B—carcinogenicity, C—irritant effect, D—reproductive effects.

formation of structures like compound **14** in the Mannich reaction has not been previously observed.

Structure of compounds **12a** and **14** was confirmed by IR, NMR spectroscopy and HPLC-MS methods. The ^{1}H NMR spectrum of compound **12a** shows signals of the acyclic –NHCH$_2$O– fragment as a doublet of the methylene group (4.34 ppm) and a triplet of the NH proton (7.32 ppm) with a spin-spin coupling constant of $^3J_{NH–CH}$ 3.5 Hz. The protons of the amino group resonate as two broadened signals in the range of 8.22–8.68 ppm corresponding to the C^{6}NH$_2$ group. According to [32, 33, 38], the protons of the N–NH$_2$ group resonate in a stronger field (5.50–6.00 ppm). HPLC-MS data are consistent with the structures shown.

It should be noted that [1,2,4]triazolo[1,5-*a*]pyridines are of interest due to the broad spectrum of biological activity [30, 46, 47, 55–60]. On the other hand, due to the presence of a privileged 3,7-diazabicyclo[3.3.1]nonane (bispidine) fragment in the molecule of tricyclic structures **8a**–**8d** (see [61–65] for recent reviews on bispidine chemistry), these compounds are promising objects for biological screening.

In this regard, we carried out predictive analysis and *in silico* calculation of possible targets, ADMET parameters and compliance with the bioavailability criteria for new compounds **8a**–**8d**, **12a**, **14**. Analysis of the structures for compliance with the Lipinski Rule of Five [molecular weight (MW) ≤ 500, *c*Log*P* ≤ 5.0, TPSA ≤ 140 Å^2, number of hydrogen bond acceptors ≤ 10, donors ≤ 5] [66–68] was carried out using the OSIRIS Property Explorer software service [69]. The following parameters were calculated: *c*Log*P* [logarithm of the partition coefficient between *n*-octanol and water, log($c_{octanol}$/*cwater*], solubility (log*S*), Topological Polar Surface Area (TPSA), a number of toxicological characteristics such as risks of side effects (mutagenic, oncogenic, reproductive effects), similarity with known drugs (drug-likeness), as well as the overall assessment of the pharmacological potential of the compound (drug score). The calculated data are presented in Table 2.

As can be seen from Table 2, the *c*Log*P* value for all tested compounds is in the range –1.19…0.40, which indicates the probable good absorption and permeability [66–68]. At the same time, $S < –4.0$ for compounds **8c**, **12a**, and **14** indicates low solubility ($<1\times10^{-4}$ mol/L). The molecular weights of all the compounds and the TPSA parameter met the criteria for oral bioavailability. Almost all the tested compounds demonstrate the risk of possible effects on the reproductive system. For compounds **8a**, **12a** and **14**, the highest values of the drug-likeness parameter and the drug score of the compound were noted. It can also be noted that for compounds **8**, the replacement of two methyl groups in the position 11 of tricyclic system with the spiro-fused cyclohexane moiety generally adversely affected the pharmacological potential.

To predict biological activity, PASS Online [70, 71] and AntiBac-Pred software packages [72] were also used. According to the data obtained, an anticonvulsant effect is predicted for compound **12a** (*p* 0.57), and compound **14** (*p* 0.743) enhances expression of the HMGCS2 protein (3-hydroxy-3-methylglutaryl-CoA synthase 2). The best antibacterial action is predicted for compound **8b** against the pathogenic bacteria *Dialister pneumosintes* and *Dialister micraerophilus* (*p* 0.2122; $p > 0$ if the probability of activity is greater than the probability of inactivity $P_a > P_i$).

To predict the ADMET parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) and probable targets, the SwissADME [73] and admetSAR

Table 3. Calculated ADMET parameters for compounds **8a**–**8d**, **12a**, **14**

Comp. no.	BBB penetration[a]	Gastro-intestinal absorption[a]	Inhibition of cytochromes P450[a]					Ames test[a]	Acute toxicity (rats) pLD_{50}, log [1/(mol/kg)]
			CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4		
8a	+	+	–	–	–	–	–	–	2.7881
	0.8820	1.0000						0.5219	
8b	+	+	–	–	–	–	–	–	2.7965
	0.9476	1.0000						0.5000	
8c	+	+	–	+	+	+	+	–	2.8112
	0.9577	1.0000						0.5000	
8d	+	+	–	+	–	–	+	–	2.7919
	0.8961	1.0000						0.5273	
12a	+	+	–	–	–	–	–	–	2.5407
	0.9193	1.0000						0.5663	
14	+	+	+	–	–	–	–	+	2.6917
	0.9590	1.0000						0.5435	

[a] Sign "+" indicates high risk of toxicity, "±"—moderate risk, "–"—no toxicity; A—mutagenicity, B—carcinogenicity, C—irritant effect, D—reproductive effects.

[74] software packages were used. According to the US EPA criteria, in terms of acute oral toxicity, the tested compounds can be classified into II (compound **14**, 50 mg/kg < LD50 < 500 mg/kg) and III (other compounds, 500 mg/kg < LD50 < 5000 mg/kg) categories. For all the tested compounds, high gastroenteric absorption and the ability to penetrate the blood-brain barrier (BBB) are predicted, as well as the predominant absence of inhibitory action against cytochromes P450 (Table 3). Evaluation of the possible mutagenic/carcinogenic effect in the Ames test does not give unambiguous results.

Possible protein targets for the obtained compounds were predicted using the new Galaxy Sagittarius protein ligand docking protocol [75] based on the GalaxyWeb web service [76, 77]. The 3D structures of the compounds were preliminarily optimized by means of molecular mechanics in the MM2 force field to optimize the geometry and minimize energy. Docking using the Galaxy Sagittarius protocol was carried out in the Binding compatibility prediction and Re-ranking using docking modes. Table 4 shows the results of docking for each of 10 target–ligand complexes with the minimum free binding energy ΔG_{bind} and the best value of the protein–ligand interaction. Predicted protein targets are specified using ID-identifiers in the Protein Data Bank (PDB) and in the UniProt database. As you can see from Table 4, the obtained compounds show affinity for a wide group of proteins – transferases and hydrolases. In particular, compounds **8a**, **8b**, **8d** are predicted to have affinity for the protooncogene Ser/Thr-protein kinase Pim-1 [78] (PDB ID 4rc3) (Fig. 1), which makes this group of compounds promising for studying antitumor activity.

In conclusion, a method was proposed for the preparation of 3-ethoxymethyl-2,3,8,9-tetrahydro-6,10-metano[1,2,4]triazolo[1,5-*a*][1,5]diazocine-6,10(7*H*)-dicarbonitriles through the aminomethylation of 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitriles by primary amines and formalin in boiling ethanol. Dehydrated analogs of the above pyridine

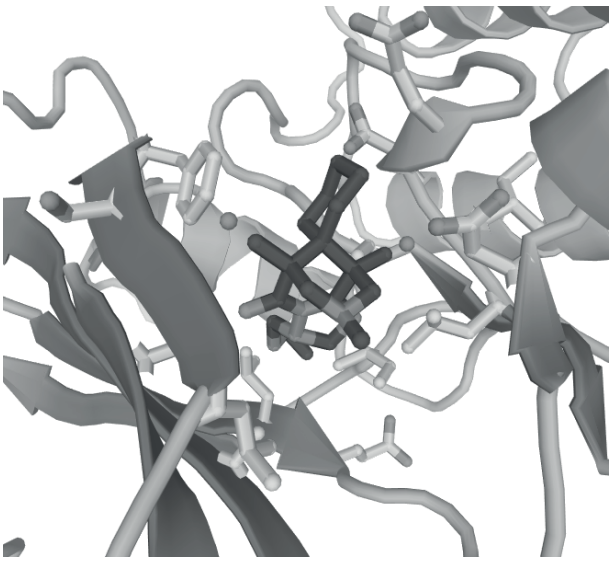


Fig. 1. Predicted structure of the protein-ligand complex of compound **8b** and serine/threonine-protein kinase pim-1 (PDB ID 4rc3) (obtained with the GalaxySagittarius protocol).

Table 4. Results of predicting protein–ligand interaction for compounds **8a**–**8d**, **12a**, **14**

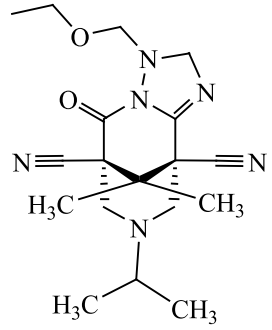
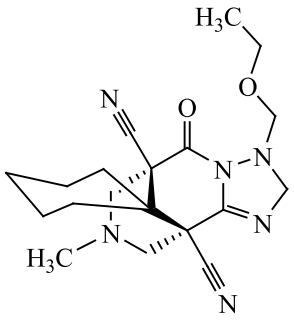
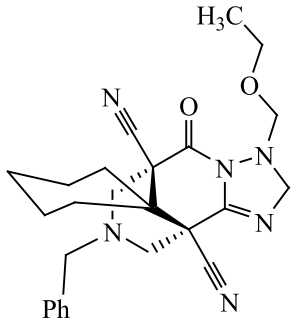
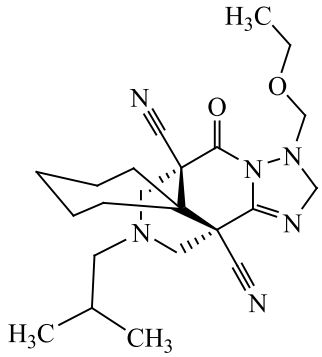
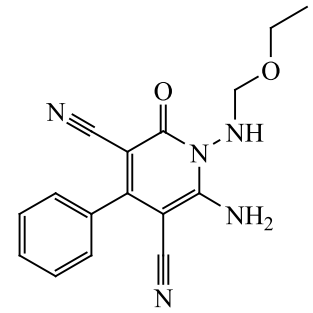
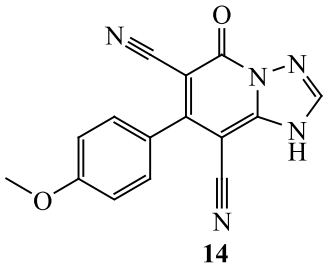
Compound	Protein identifier PDB ID	Protein identifier UniProt ID	Pre-docking assessment of protein-ligand interaction (predock score)	Free binding energy, kcal/mol (docking score)	Overall assessment of protein–ligand interaction
 **8a**	4rc3	P11309	0.226	–13.984	0.331
	5hic	P00533	0.192	–16.361	0.315
	2xe6	P00558	0.189	–15.353	0.305
	4fki	P24941	0.175	–15.503	0.291
	3o9v	P27487	0.182	–13.358	0.282
	4k77	P23458	0.164	–15.193	0.278
	5ekn	O15264	0.144	–16.734	0.270
	3uuo	Q9Y233	0.167	–13.374	0.267
	3zep	P52333, P52333	0.146	–16.026	0.267
	2i6b	P55263	0.147	–15.628	0.264
 **8b**	4rc3	P11309	0.244	–16.144	0.366
	5hcx	P00533	0.199	–15.632	0.316
	2xe6	P00558	0.195	–15.951	0.315
	6n7a	P23458	0.185	–16.849	0.312
	5kby	P27487	0.190	–15.513	0.306
	4z16	P52333, P52333	0.173	–17.451	0.304
	4fki	P24941	0.185	–15.148	0.299
	3uuo	Q9Y233	0.184	–14.592	0.294
	2i6b	P55263	0.160	–16.169	0.281
	5ekn	O15264	0.146	–17.854	0.280
 **8c**	6aak	P52333	0.244	–21.954	0.409
	5tel	P11309	0.252	–20.343	0.404
	5tq4	O60674	0.221	–24.157	0.402
	6n7a	P23458	0.231	–21.311	0.391
	5c8k	P00533	0.230	–21.071	0.388
	4wnp	O75385	0.230	–19.987	0.380
	2vd5	Q09013	0.214	–22.082	0.380
	3fxz	Q13153	0.234	–19.175	0.378
	2bro	O14757	0.215	–21.622	0.377
	3v8w	Q08881, Q08881	0.209	–21.650	0.371
 **8d**	5c8k	P00533	0.228	–19.748	0.376
	5ane	P24941	0.239	–17.498	0.370
	6eo9	P00734	0.198	–21.539	0.359
	4rc3	P11309	0.213	–18.430	0.352
	4ivd	P23458	0.192	–20.878	0.348
	5tq4	O60674	0.178	–21.444	0.339
	4fyo	P43405	0.200	–16.634	0.325
	5jzn	O15075, O15075	0.173	–19.799	0.321
	5ih9	Q14680	0.187	–17.882	0.321
	6dud	P52333	0.181	–18.561	0.320

Table 4. *(*Contd.*)*

Compound	Protein identifier PDB ID	Protein identifier UniProt ID	Pre-docking assessment of protein-ligand interaction (predock score)	Free binding energy, kcal/mol (docking score)	Overall assessment of protein–ligand interaction
 **12a**	6aaj	O60674	0.215	–19.233	0.359
	1uwj	P15056, P15056	0.202	–20.223	0.354
	5hsu	P00374	0.200	–19.366	0.345
	6da4	P52333	0.200	–18.241	0.337
	3mpm	P06239	0.198	–18.207	0.334
	5kx8	Q9NWZ3	0.182	–20.178	0.333
	5kwh	P68400	0.189	–18.857	0.330
	2xir	P35968	0.193	–17.970	0.327
	2jbp	P49137	0.194	–17.716	0.327
	4mha	Q12866, Q12866	0.192	–18.038	0.327
	6hmb	P19784	0.193	–17.379	0.323
 **14**	3vhe	P35968	0.160	–19.863	0.309
	1jwh	P67870, P68400	0.162	–18.322	0.299
	5cqw	P68400	0.170	–17.195	0.299
	4xmo	P08581	0.162	–17.116	0.290
	4q4d	O43314	0.154	–16.934	0.281
	5ji8	Q9H8M2	0.155	–15.999	0.274
	3cnk	P21333, P21333	0.122	–20.190	0.273
	5up3	Q99683	0.143	–17.356	0.273
	5lqf	P06493, P14635	0.129	–18.688	0.269

substrates, 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles, react ambiguously under the Mannich reaction conditions. The reactions of alkoxy- and aminomethylation of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles requires a more detailed study and will be the subject of our further research. In addition, analysis of the literature data on the methods of obtaining 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles was carried out, the optimal synthesis conditions were found. The results of *in silico* calculations of the biological activity and bioavailability parameters make it possible to consider the obtained compounds as promising objects for further biological screening.

EXPERIMENTAL

IR spectra were recorded on an IKS-29 (LOMO) spectrometer in mineral oil. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer (400.17 and 100.63, MHz respectively) from a solution in DMSO-d_6 (compounds **8a**–**8c**) or $CDCl_3$ (**8d**); TMS and residual solvent signals were used as a standard. Elemental analysis was performed on a Carlo Erba 1106 Elemental Analyzer. HPLC-MS analysis was carried out on an Agilent 1100 liquid chromatograph equipped with DAD detectors, ELSD Sedex 75, combined with an Agilent LC/MSD VL mass spectrometer, (ESI-API, positive and negative modes). Individuality of obtained compounds was monitored by TLC on Silufol UV-254 plates, eluting with an acetone–hexane mixture (1:1) and detecting with iodine vapors or UV light. Melting points were determined on a Kofler table and were not corrected.

Malononitrile is a commercially available reagent (Acros). Cyanoacethydrazide was prepared by the reaction of cyanoacetic ester with hydrazine hydrate according to the known procedure [79].

General procedure for the synthesis of 5-oxo-3-ethoxymethyl-2,3,8,9-tetrahydro-6,10-methano[1,2,4]-triazolo[1,5-*a*][1,5]diazocin-6,10(7*H*)-dicarbonitriles 8a–8d. To a mixture of 2.0 mmol of tetrahydropyridine

7a, **7b** and an aliphatic amine (4.0 mmol) in 10–12 mL of 96% EtOH was added an excess (2.0 mL, 26.6 mmol) of 37% formalin free from paraform impurities. The reaction mixture was refluxed for 2 h, then filtered through a folded filter paper and kept at room temperature. After 72 h the crystals of the product **8c**–**8d** were filtered off (in the case of compound **8a** preliminary acidification of the reaction mixture with aqueous HCl to pH 4 was required), washed with EtOH and dried. Compounds **8a**–**8d** were obtained in analytically pure form.

11,11-Dimethyl-8-isopropyl-3-(ethoxymethyl)-5-oxo-2,3,8,9-tetrahydro-6,10-methano[1,2,4]triazolo[1,5-*a*][1,5]diazocine-6,10(7*H*)-dicarbonitrile (8a). Yield 300 mg (42%), white fine-crystalline powder, mp 166–168°C. IR spectrum, ν, cm^{-1}: 2257 w (C≡N), 1709 br. s (C=O). ^{1}H NMR spectrum, δ, ppm: 0.90 d [6H, CH(CH$_3$)$_2$, ^3J = 6.6 Hz], 1.06 t (3H, OCH$_2$CH$_3$, ^3J = 7.1 Hz), 1.34 s (3H, CH$_3$), 1.43 s (3H, CH$_3$), 2.80–2.88 m [1H, CH(CH$_3$)$_2$], 3.04 d (1H, C^{7}H$_2$ or C^{9}H$_2$, ^2J = 12.2 Hz), 3.06 d (1H, C^{9}H$_2$ or C^{7}H$_2$, ^2J = 11.7 Hz), 3.21 d (1H, C^{7}H$_2$ or C^{9}H$_2$, ^2J = 12.2 Hz), 3.22 d (1H, C^{9}H$_2$ or C^{7}H$_2$, ^2J = 11.7 Hz), 3.50 q (2H, OCH$_2$CH$_3$, ^3J = 7.1 Hz), 4.18 d (1H, CH$_2$OEt, ^2J = 9.4 Hz), 4.45 d (1H, CH$_2$OEt, ^2J = 9.4 Hz), 4.88 d (1H, NCH$_2$N, ^2J = 13.0 Hz), 5.06 d (1H, NCH$_2$N, ^2J = 13.0 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 14.9 (CH$_3$CH$_2$O), 17.3 [CH(CH$_3$)$_2$], 18.2 [CH(CH$_3$)$_2$], 19.3 (CH$_3$), 23.3 (CH$_3$), 38.9 (C^{11}), 45.1 [CH(CH$_3$)$_2$], 49.3 (C^{10}), 50.7 (C^6), 53.2 (C^7 or C^9), 53.3 (C^9 or C^7), 63.8 (CH$_3$CH$_2$O), 77.2 (NCH$_2$O), 82.8 (C^2), 115.2 (C≡N), 115.4 (C≡N), 151.9 (C^{10a}), 157.1 (C^5). Found, %: C 60.25; H 7.35; N 23.41. $C_{18}H_{26}N_6O_2$. Calculated, %: C 60.32; H 7.31; N 23.45. *M* 358.44

3-(Ethoxymethyl)-8-methyl-5-oxo-2,3,8,9-tetrahydrospiro[6,10-methano[1,2,4]triazolo[1,5-*a*][1,5]diazocine-11,1′-cyclohexane]-6,10(5*H*,7*H*)-dicarbonitrile (8b). Yield 415 mg (56%), white fine-crystalline powder, mp 142–144°C. IR spectrum, ν, cm^{-1}: 2247 w (C≡N), 1695 br. s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.06 t (3H, OCH$_2$CH$_3$, ^3J = 7.1 Hz), 1.41–1.57 m [2H, (CH$_2$)$_5$], 1.73–2.00 m [7H, (CH$_2$)$_5$], 2.18–2.23 m [1H, (CH$_2$)$_5$], 2.27 s (3H, NCH$_3$), 2.97–3.09 m (3H, overlapping of C$_7$H$_2$ and C$_9$H$_2$ signals), 3.21 d (1H, C^{9}H$_2$ or C^{7}H$_2$, ^2J = 11.5 Hz), 3.40–3.55 m (2H, OCH$_2$CH$_3$), 4.19 d (1H, CH$_2$OEt, ^2J = 9.5 Hz), 4.51 d (1H, CH$_2$OEt, ^2J = 9.5 Hz), 4.93 d (1H, NCH$_2$N, ^2J = 12.7 Hz), 5.08 d (1H, NCH$_2$N, ^2J = 12.7 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 15.1 (CH$_3$CH$_2$O), 20.0 [(CH$_2$)$_5$], 20.6 [(CH$_2$)$_5$], 24.0 [(CH$_2$)$_5$], 27.2 [(CH$_2$)$_5$], 31.7 [(CH$_2$)$_5$], 39.6 (C^{11}), 42.9 (NCH$_3$), 44.5 (C^{10}), 53.7 (C^7 or C^9), 54.2 (C^9 or C^7), 56.4 (C^6), 63.9 (CH$_3$CH$_2$O), 77.1 (NCH$_2$O), 82.6 (C^2), 116.5 (C≡N), 116.8 (C≡N), 151.7 (C^{10a}), 156.7 (C^5). Found, %: C 61.53; H 7.14; N 22.65. $C_{19}H_{26}N_6O_2$. Calculated, %: C 61.60; H 7.07; N 22.69. *M* 370.45

8-Benzyl-3-(ethoxymethyl)-5-oxo-2,3,8,9-tetrahydrospiro[6,10-methano[1,2,4]triazolo[1,5-*a*][1,5]diazocine-11,1′-cyclohexane]-6,10(5*H*,7*H*)-dicarbonitrile (8c). Yield 545 mg (61%), white fine-crystalline powder, mp 175–177°C. IR spectrum, ν, cm^{-1}: 2250 w (C≡N), 1695 br. s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.07 t (3H, OCH$_2$CH$_3$, ^3J = 7.1 Hz), 1.44–1.53 m [2H, (CH$_2$)$_5$], 1.73–1.83 m [5H, (CH$_2$)$_5$], 1.92–1.97 m [2H, (CH$_2$)$_5$], 2.18–2.23 m [1H, (CH$_2$)$_5$], 2.88 d (1H, C^{7}H$_2$ or C^{9}H$_2$, ^2J = 11.5 Hz), 3.07 d (1H, C^{9}H$_2$ or C^{7}H$_2$, ^2J = 12.0 Hz), 3.24 d (1H, C^{9}H$_2$ or C^{7}H$_2$, ^2J = 12.0 Hz), 3.30 d (1H, C^{7}H$_2$ or C^{9}H$_2$, ^2J = 11.5 Hz), 3.46–3.55 m (2H, OCH$_2$CH$_3$), 3.68 q (2H, PhCH$_2$, ^2J = 13.6 Hz, AB-system), 4.23 d (1H, CH$_2$OEt, ^2J = 9.5 Hz), 4.55 d (1H, CH$_2$OEt, ^2J = 9.5 Hz), 4.91 d (1H, NCH$_2$N, ^2J = 12.8 Hz), 5.12 d (1H, NCH$_2$N, ^2J = 12.8 Hz), 7.13 d (2H, H^2 and H^6 Ph, ^3J = 7.0 Hz), 7.24–7.34 m (3H, H^3–H^5 Ph). ^{13}C NMR spectrum, δ$_C$, ppm: 15.0 (CH$_3$CH$_2$O), 20.0 [(CH$_2$)$_5$], 20.6 [(CH$_2$)$_5$], 23.9 [(CH$_2$)$_5$], 27.3 [(CH$_2$)$_5$], 31.7 [(CH$_2$)$_5$], 40.1 (C^{11}), 44.4 (C^{10}), 52.0 (C^7 or C^9), 54.31 (C^9 or C^7), 54.34 (CH$_2$Ph), 58.3 (C^6), 63.7 (CH$_3$CH$_2$O), 77.4 (NCH$_2$O), 82.8 (C^2), 116.5 (C≡N), 116.7 (C≡N), 127.5 (C^4 Ph), 128.3 (2C, Ph), 128.4 (2C, Ph), 136.4 (C^1-Ph), 151.9 (C^{10a}), 156.7 (C^5). Found, %: C 67.19; H 6.88; N 18.77. $C_{25}H_{30}N_6O_2$. Calculated, %: C 67.24; H 6.77; N 18.82. *M* 446.55

3-(Ethoxymethyl)-8-isobutyl-5-oxo-2,3,8,9-tetrahydrospiro[6,10-methano[1,2,4]triazolo[1,5-*a*][1,5]diazocine-11,1′-cyclohexane]-6,10(5*H*,7*H*)-dicarbonitrile (8d). Yield 240 mg (29%), white fine-crystalline powder, mp 101–103°C. IR spectrum, ν, cm^{-1}: 2250 w (C≡N), 1695 br. s (C=O). ^{1}H NMR spectrum, δ, ppm: 0.75–0.78 m [6H, CH(CH$_3$)$_2$], 1.02–1.07 m [1H, CH(CH$_3$)$_2$], 1.14 t (3H, OCH$_2$CH$_3$, ^3J = 7.1 Hz), 1.50–1.57 m [2H, (CH$_2$)$_5$], 1.61–1.71 m [2H, (CH$_2$)$_5$], 1.83–2.00 m [5H, (CH$_2$)$_5$], 2.15–2.19 m [3H, overlapping CH$_2$CH(CH$_3$)$_2$, (CH$_2$)$_5$], 3.02 d (1H, C^{7}H$_2$ or C^{9}H$_2$, ^2J = 12.0 Hz), 3.07–3.16 m (3H, overlapping of C^{7}H$_2$ and C^{9}H$_2$ signals), 3.48–3.54 m (2H, OCH$_2$CH$_3$), 4.09 d (1H, CH$_2$OEt, ^2J = 9.4 Hz), 4.71 d (1H, CH$_2$OEt, ^2J = 9.4 Hz), 4.97 d (1H, NCH$_2$N, ^2J = 12.4 Hz), 5.15 d (1H, NCH$_2$N, ^2J = 12.4 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 15.1 (CH$_3$CH$_2$O), 20.0 [(CH$_2$)$_5$], 20.1 [(CH$_3$)$_2$CH], 20.5

[$(CH_2)_5$], 21.0 [$(CH_3)_2\underline{C}H$], 24.2 [$(CH_2)_5$], 27.9 [$(CH_2)_5$], 29.7 [$(CH_2)_5$], 32.2 [$\underline{C}H_2CH(CH_3)_2$], 40.6 ($C^{11}$), 44.9 ($C^{10}$), 53.8 ($C^7$ or C^9), 54.6 (C^9 or C^7), 56.5 (C^6), 63.7 ($CH_3\underline{C}H_2O$), 78.1 ($N\underline{C}H_2O$), 83.3 (C^2), 116.1 (C≡N), 116.5 (C≡N), 152.9 (C^{10a}), 157.3 (C^5). Found, %: C 64.21; H 8.00; N 20.23. $C_{22}H_{32}N_6O_2$. Calculated, %: C 64.05; H 7.82; N 20.37. *M* 412.53

1,6-Diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (9a) was obtained by refluxing a mixture of cyanoacethydrazide **11** (0.99 g, 1 mmol), benzaldehyde (1.0 mL, 1 mmol) and malononitrile (0.66 g, 1 mmol) in EtOH (15 mL) in the presence of 3 drops of piperidine for 2 h. The precipitate formed was filtered off, washed with ethanol and dried. Yield 850 mg (34%), pale yellow powder, mp 240°C (mp 240°C [32], 332–334°C [33], 237–239°C [39], 238–240°C [47]). The spectral characteristics correspond to those described earlier.

1,6-Diamino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (9b) was obtained by refluxing a mixture of cyanoacethydrazide **11** (0.99 g, 1 mmol) and 2-(4-methoxybenzylidene)-malononitrile **10b** (1.84 g, 1 mmol) in a solution of sodium ethylate (1.5 mmol) in EtOH (15 mL) for 3 h (41% yield), as well as by the reaction of **11** (1 mmol) with **10b** (2 mmol) in 20 mL of EtOH in the presence of 3 drops of morpholine with stirring for 30 min with moderate heating (50°C). Yield 86% based on cyanoacethydrazide, pale yellow powder, mp 223–224°C (mp 225°C [32], 321–323°C [33], 221–224°C [35]). Spectral characteristics correspond to those described in the literature.

6-Amino-2-oxo-4-phenyl-1-[(ethoxymethyl)-amino]-1,2-dihydropyridine-3,5-dicarbonitrile (12a). *a*. To a mixture of 500 mg (1.99 mmol) of 1,6-diaminopyridone **9a** and 430 mg (4.0 mmol) of benzylamine in 10 mL of 96% EtOH was added an excess (2.0 mL, 26.6 mmol) of 37% formalin free from paraform impurities. The reaction mixture was refluxed for 5 min, then filtered through a pleated paper filter. After 72 h product **12a** was isolated, washed with ethanol and dried. Yield 190 mg (31%), white fine-crystalline powder. IR spectrum, ν, cm^{-1}: 3380 w, 3220 br. s (N–H), 2217 s (2 C≡N), 1670 s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.06 t (3H, $OCH_2C\underline{H}_3$, ^3J = 7.0 Hz), 3.62 q (2H, $OC\underline{H}_2CH_3$, ^3J = 7.0 Hz), 4.34 d (1H, $NHC\underline{H}_2OEt$, $^3J_{NH–CH}$ 3.5 Hz), 7.32 t (1H, $N\underline{H}CH_2OEt$, $^3J_{NH–CH}$ 3.5 Hz), 7.48–7.54 m (5H, Ph), 8.22 br. s (1H, $N\underline{H}_2$), 8.68 br. s (1H, $N\underline{H}_2$). Mass spectrum, *m/z*: 310.0 $[M+H]^+$, 264.0 $[M-EtOH]^+$, 320.2 $[M+H_2O-H]^-$, 308.2 $[M-H]^-$, 262.0 $[M-EtOH-H]^-$. Found, %: C 62.17; H 4.94; N 22.60. $C_{16}H_{15}N_5O_2$. Calculated, %: C 62.13; H 4.89; N 22.64. *M* 309.32

b. To a mixture of 500 mg (1.99 mmol) of 1,6-diaminopyridone **9a** in 10 mL of 96% EtOH was added an excess (2.0 mL, 26.6 mmol) of 37% formalin free from paraform impurities. The reaction mixture was refluxed for 2 h, then filtered through a folded paper filter and left at room temperature. Crystallization of product **12a** was observed after 24 h, after 72 h the crystals were filtered off, washed with cold ethanol and dried. Yield 150 mg (25%). Analytical data correspond to those for the sample obtained by method *a*.

7-(4-Methoxyphenyl)-5-oxo-1,5-dihydro[1,2,4]-triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (14). To a mixture of 560 mg (1.99 mmol) of 1,6-diaminopyridone **9b**, 340 mg (4.0 mmol) of a 40% aqueous solution of methylamine (*d* 0.9 g/mL) and 200 mg (1.98 mmol) Et_3N in 12 mL of 96% EtOH was added an excess (2.0 mL, 26.6 mmol) of 37% formalin free from paraform impurities. The reaction mixture was refluxed for 2 h, then filtered through a folded paper filter and left at room temperature. After 24 h the solution was acidified with HCl to pH 5 (due to the pronounced peculiarity of 1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile derivatives to the formation of salts with bases [80, 81]) and after 48 h the crystals were filtered off, washed with ethanol, and dried. Yield 151 mg (26%), pale yellow crystals, mp > 300°C. IR spectrum, ν, cm^{-1}: 3146 br. w (N–H), 2218 s (2 C≡N), 1664 s (C=O). ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, OCH_3), 7.09 d (2H, H^3, H^5 Ar, ^3J = 8.8 Hz), 7.47 d (2H, H^2, H^6 Ar, ^3J = 8.8 Hz), 7.68 br. s (1H, NH), 8.51 s (1H, H^2). ^{13}C NMR spectrum, δ_C, ppm: 55.4 (OCH_3), 76.2 (C^8), 85.0 (C^6), 113.9 (C^3, C^5 Ar), 116.3 (C≡N), 117.9 (C≡N), 127.4 (C^2, C^6 Ar), 130.2 (C^1 Ar), 149.9 (C^2), 150.8 (C^7), 155.7 (C^{8a}), 155.9 (C–OMe), 160.3 (C=O). Mass spectrum, *m/z*: 292.0 $[M+H]^+$, 371.0 $[M+DMSO+H]^+$, 290.0 $[M-H]^-$. Found, %: C 61.80; H 3.24; N 24.00. $C_{15}H_9N_5O_2$. Calculated, %: C 61.85; H 3.11; N 24.04. *M* 291.26

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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