Cyanamides in cyclization reactions with anthranilates, 2-aminophenyl ketones, and methyl 2-(3-oxopiperazin-2-yl)acetate

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Cyclization of aryl-, aroyl-, and (4,6-dimethylpyrimidin-2-yl)cyanamides with methyl anthranilates, 2-aminophenyl ketones, and methyl 2-(3-oxopiperazin-2-yl)acetate leads to 2-amino-3,4-dihydroquinazolin-4-one, 2-aminoquinazoline, and 6-amino-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione derivatives, respectively.

Key words: cyanamides, anthranilic acid, 2-aminophenyl ketones, methyl 2-(3-oxopiperazin-2-yl)acetate, 2-aminoquinazoline, 2-amino-3,4-dihydroquinazolin-4-one, 6-amino-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione, cyclization.

Achievements in preparative chemistry of cyanamides and possibility of their use in the synthesis of a number of heterocycles caused an increased attention to these compounds.[1,2] Unsaturation of the C≡N bond and its bipolar character make it possible the participation of cyanamides in cyclization reactions with various compounds, containing both electrophilic and nucleophilic reaction centers.

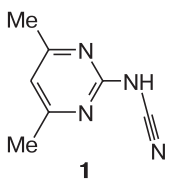
The present work is aimed at investigation of potentialities in the synthesis of compounds containing pyrimidine fragment with the use of various organic cyanamides.

Condensation of the [2+4] type, in which the two-atom fragment is represented by C(2) and N(3) atoms of the forming heterocycle, is comparatively less spread among methods for the synthesis of pyrimidine. Imino esters,[3] cyanates, isocyanates, amides, or thioamides[4] are usually used for this purpose. It turned out that they can be successfully replaced by cyanamides.

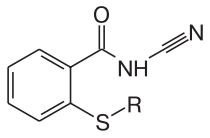
We have obtained a number of cyanamides, which were used in further work.

Cyanamide **1** was obtained by the reaction of acetylacetone with dicyanodiamide,[5] **2**, by alkaline opening of 2-imino-2,3-dihydro-4*H*-1,3-benzothiazin-4-one with subsequent alkylation,[6] **3**, by acylation of calcium cyanamide,[7] **4**, by desulfurization of the corresponding thiocarbamides.[8] Arylcyanamides **4** were used immediately after preparation because of their instability.

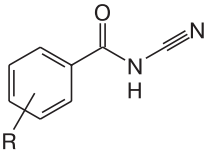
Methyl anthranilates **5a—c**, 2-aminophenyl ketones **6a—d**, 2-aminobenzonitrile (**7**), and methyl 2-(3-oxopiperazin-2-yl)acetate (**8**) were used as the reagents with



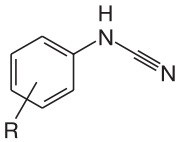
1



2a,b

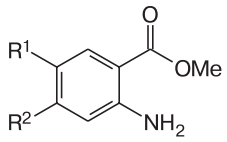


3a—d

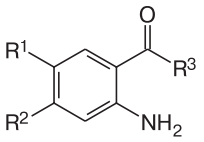


4a,b

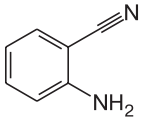
2: R = Me (**a**), Et (**b**);
3: R = H (**a**), 4-MeO (**b**), 4-Cl (**c**), 4-F (**d**);
4: R = 2-MeO (**a**), 4-MeO (**b**)



5a—c



6a—d



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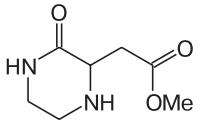

8

5	R^1	R^2
a	H	H
b	OMe	OMe
c	Br	H

6	R^1	R^2	R^3
a	H	H	Me
b	—OCH_2O—		Me
c	H	H	Ph
d	Cl	H	Ph
d	Cl	H	Ph

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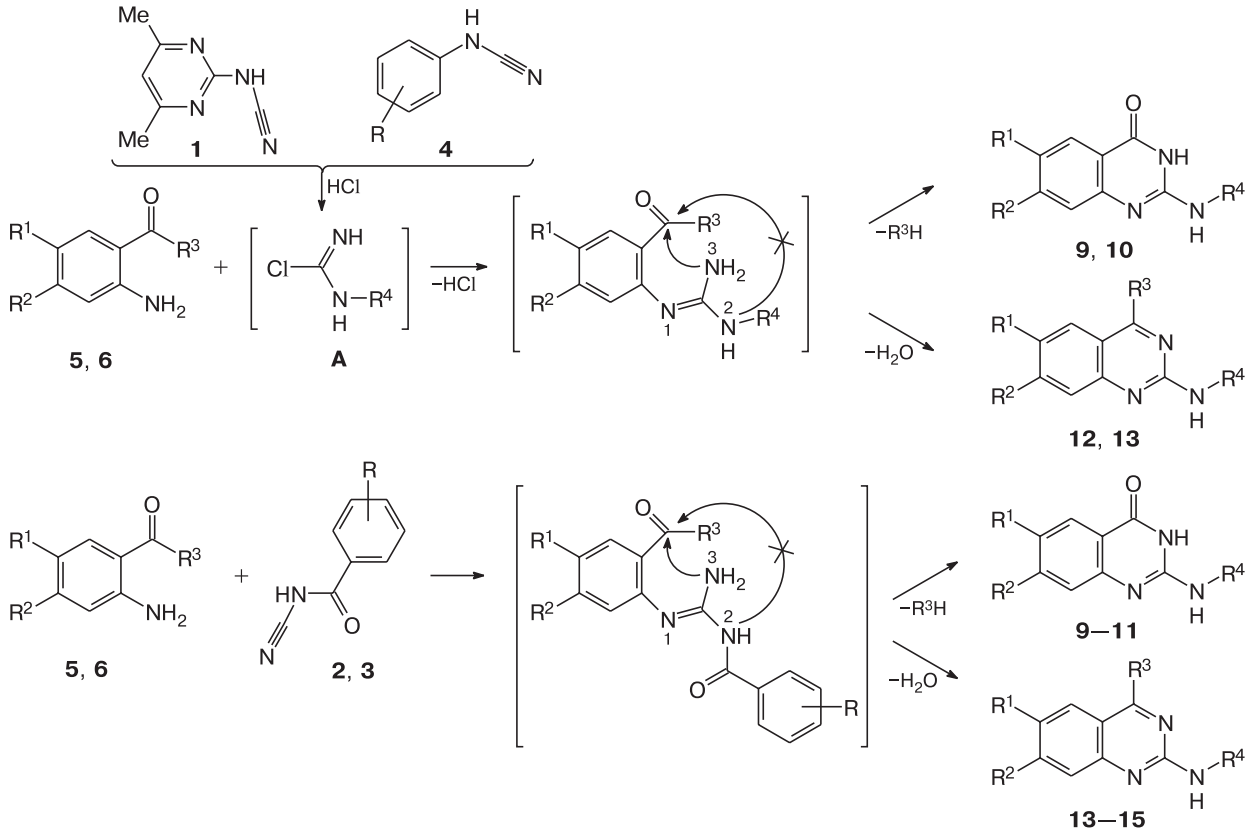
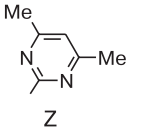
Scheme 1



9: $R^1 = R^2 = H$; R^4 = Z (**a**), 4-$MeOC_6H_4$ (**b**), 2-$MeOC_6H_4$ (**c**), 4-ClBz (**d**), 4-MeOBz (**e**), 2-MeSBz (**f**), 2-EtSBz (**g**);
10: $R^1 = R^2$ = MeO; R^4 = 4-$MeOC_6H_4$ (**a**), Bz (**b**), 4-ClBz (**c**), 4-MeOBz (**d**), 4-FBz (**e**), 2-EtSBz (**f**);
11: R^1 = Br, R^2 = H, R^4 = 4-FBz; **12:** R^1 = Cl, R^2 = H, R^3 = Ph; R^4 = 2-$MeOC_6H_4$ (**a**), Z (**b**);
13: R^1, R^2 = —OCH_2O—, R^3 = Me, R^4 = Z (**a**), Bz (**b**), 4-MeOBz (**c**), 2-MeOBz (**d**), 4-ClBz (**e**), 4-FBz (**f**), 2-EtSBz (**g**);
14: $R^1 = R^2 = H$, R^3 = Ph; R^4 = 4-MeOBz (**a**), 4-ClBz (**b**), 2-MeSBz (**c**); **15:** $R^1 = R^2 = H$, R^3 = Me, R^4 = 4-MeOBz



electrophilic and nucleophilic reaction centers. **8** was obtained by reaction of ethylenediamine with dimethyl maleate.[9]

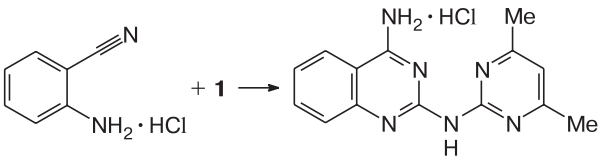
The reactions of cyanamides with anthranilates **5** and 2-aminophenyl ketones **6** are presented in Scheme 1. The cyclization, apparently, proceeds in two steps, the first of which includes formation of guanidine. The rate and direction of this process depend on the electrophilicity of the carbon atom in the nitrile group of cyanamides **1**—**4**. If it is high enough (which is characteristic of compounds **2** and **3**), the reaction proceeds in the absence of a catalyst. Thus, anthranilates **5** and aminophenyl ketones **6** react with aroylcyanamides **2** and **3** catalyst-free, whereas the presence of equimolar amount of HCl is required for their reaction with cyanamides **1** and **4**.

In the presence of HCl, formation of guanidines takes place most likely with participation of chloroformamidines (intermediate **A**, see Scheme 1) and chloroformamidinium chlorides, which are formed from cyanamides in hydrochloric acid medium.[1] The electrophilicity of the cyanamide carbon atom is significantly increased in these compounds, which allows them to enter the reaction with aromatic amines **5**—**7**.

The cyclization with aminophenyl ketones proceeds under the more drastic conditions and is slower than the one with methyl anthranilates, since H_2O is the leaving group in this case rather than methanol. The forming 2-aminoquinoline derivatives with methyl or phenyl substituent in position 4 are compounds with high melting points, which are difficult to crystallize.

Hydrochloric acid was added to the reaction mixture as the 37% aqueous solution. Attempted synthesis of 2,4-diaminoquinazoline derivative from compounds **1** and **7** by this method resulted in 2-amino-3,4-dihydroquinazolin-4-one derivative **9a**. This can be explained by the hydrolysis of the nitrile group of the benzonitrile in the presence of H_2O in acidic medium.[10] Therefore, the use of aq. HCl is inadmissible in this case. The use of 2-aminobenzonitrile hydrochloride in anhydrous dioxane allowed us to obtain hydrochloride **16** (Scheme 2).

Scheme 2



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The synthetic outcome for compounds **9—11** and their ^{1}H NMR spectral data are given in Tables 1 and 2, for compounds **12—16**, in Tables 3 and 4, respectively.

Derivatives of 2-amino-3,4-dihydroquinazolin-4-one **9—11** and of 2-aminoquinazoline **12—16**, shown in Schemes 1 and 2, are formed as a result of nucleophilic attack of N(3) atom of guanidine at the carbonyl fragment of the ester group. However, a version with participation of N(2) atom to form regioisomeric 2-aminoquinazoline derivatives with substituent in position 3 can not be excluded either. The reactions of triazolylcyanamide with

Table 1. Characteristics of synthesized quinazolinones **9—11**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula
9a	67	238	63.18 62.92	4.56 4.87	26.36 26.22	$C_{14}H_{13}N_5O$
9b*	25	283 (decomp.)	59.38 59.29	4.47 4.61	13.92 13.83	$C_{15}H_{14}ClN_3O_2$
9c*	21	275 (decomp.)	59.20 59.29	4.65 4.61	13.69 13.83	$C_{15}H_{14}ClN_3O_2$
9d	61	242	59.97 60.06	3.36 3.34	14.15 14.01	$C_{15}H_{10}ClN_3O_2$
9e	46	225	65.10 65.02	4.43 4.40	14.18 14.22	$C_{16}H_{13}N_3O_3$
9f	68	161—162	61.61 61.66	4.14 4.17	13.56 13.49	$C_{16}H_{13}N_3O_2S$
9g	52	173—174	58.94 58.89	4.29 4.33	12.13 12.12	$C_{17}H_{15}N_3O_2S$
10a*	22	292 (decomp.)	61.63 61.52	5.35 5.43	12.52 12.67	$C_{17}H_{18}ClN_3O_2$
10b	47	247	62.83 62.77	4.57 4.62	13.01 12.92	$C_{17}H_{15}N_3O_4$
10c	60	272	56.72 56.70	3.89 3.89	11.64 11.67	$C_{17}H_{14}ClN_3O_4$
10d	42	239	60.84 60.78	4.74 4.78	11.86 11.82	$C_{18}H_{17}N_3O_5$
10e	65	248	59.55 59.42	4.02 4.08	12.19 12.23	$C_{17}H_{14}FN_3O_4$
10f	67	244—245	62.63 62.58	5.47 5.48	10.92 10.95	$C_{20}H_{21}N_3O_3S$
11	55	295—299	49.63 49.70	2.41 2.48	11.48 11.60	$C_{15}H_9BrFN_3O_2$

* Hydrochlorides.

Table 2. ^{1}NMR spectra of quinazolinones **9—11**

Compound:	δ (*J*/Hz)
9a	2.39 (s, 6 H, Me); 6.96 (s, 1 H, H(5), pyrimidine); 7.35 (t, 1 H, H arom., *J* = 7.3); 7.46 (d, 1 H, H arom., *J* = 7.5); 7.73 (t, 1 H, H arom., *J* = 7.1); 8.07 (d, 1 H, H arom., *J* = 7.9); 11.03, 13.48 (both br.s, 1 H each, NH)
9b*	3.91 (s, 3 H, MeO); 7.12 (d, 2 H, H arom., *J* = 8.9); 7.46 (m, 3 H, H arom.); 7.50 (s, 1 H, NH); 7.58 (d, 1 H, H arom., *J* = 7.2); 7.66 (s, 1 H, NH); 7.81 (t, 1 H, H arom., *J* = 7.3); 8.06 (d, 1 H, H arom., *J* = 7.8); 8.32 (br.s, 1 H, HCl)
9c*	3.80 (s, 3 H, MeO); 7.19 (t, 1 H, H arom., *J* = 7.1); 7.31 (d, 1 H, H arom., *J* = 8.2); 7.40—7.68 (m, 4 H, H arom.; 1 H, NH); 7.89 (t, 1 H, H arom., *J* = 7.5); 8.04 (d, 1 H, H arom., *J* = 7.9); 8.41 (br.s, 1 H, NH; 1 H, HCl)
9d	7.31 (d, 1 H, H arom., *J* = 7.4); 7.49 (m, 3 H, H arom.); 7.72 (t, 1 H, H arom., *J* = 7.3); 8.11 (d, 1 H, H arom., *J* = 7.4); 8.16 (d, 2 H, H arom., *J* = 8.4); 12.36 (br.s, 2 H, 2 NH)
9e	3.86 (s, 3 H, Me); 7.35 (d, 1 H, H arom., *J* = 7.6); 7.51—7.83 (m, 4 H, H arom.); 8.05 (d, 1 H, H arom., *J* = 7.3); 8.13 (d, 2 H, H arom., *J* = 8.6); 12.27 (br.s, 2 H, 2 NH)
9f	2.49 (s, 3 H, MeS); 7.22 (t, 1 H, H arom., *J* = 7.6); 7.30—7.45, 7.49—7.56 (both m, 2 H each, H arom.); 7.69 (t, 1 H, H arom., *J* = 7.4); 7.78 (d, 1 H, H arom., *J* = 7.5); 8.10 (d, 1 H, H arom., *J* = 8.1); 12.02 (br.s, 2 H, 2 NH)
9g	1.32 (t, 3 H, Me, *J* = 7.7); 2.98 (q, 2 H, SH_2, *J* = 7.5); 7.21—7.57 (m, 5 H, H arom.); 7.70 (m, 2 H, H arom.); 8.11 (d, 1 H, H arom., *J* = 8.2); 11.97 (br.s, 2 H, 2 NH)
10a*	3.89, 3.95, 4.10 (all s, 3 H each, MeO); 7.02, 7.37 (both s, 1 H each, H arom.); 7.22 (d, 2 H, H arom., *J* = 7.6); 7.35 (d, 2 H, H arom., *J* = 8.5); 7.90—8.20 (br.s, 2 H, 2 NH)
10b	3.89, 3.95 (both s, 3 H each, MeO); 6.98 (s, 1 H, H arom.); 7.41—7.76 (m, 4 H, H arom.); 8.12 (d, 2 H, H arom., *J* = 7.4); 12.02 (br.s, 2 H, 2 NH)
10c	3.89, 3.95 (both s, 3 H each, MeO); 6.98 (s, 1 H, H arom.); 7.36—7.52 (m, 3 H, H arom.); 8.12 (m, 2 H, H arom.); 12.11 (br.s, 2 H, 2 NH)
10d	3.89, 3.96, 4.14 (all s, 3 H each, MeO); 7.01, 7.32 (both s, 1 H each, H arom.); 7.12 (d, 2 H, H arom., *J* = 8.6); 7.38 (d, 2 H, H arom., *J* = 8.7); 7.95—8.23 (br.s, 2 H, 2 NH)
10e	3.90, 3.97 (both s, 3 H each, MeO); 7.01 (s, 1 H, H arom.); 7.32—7.45 (m, 3 H, H arom.); 8.09 (m, 2 H, H arom.); 12.21 (br.s, 2 H, 2 NH)
10f	1.30 (t, 3 H, Me, *J* = 7.9); 3.00 (q, 2 H, SH_2, *J* = 7.7); 3.90, 3.95 (both s, 3 H each, MeO); 7.01 (s, 1 H, H arom.); 7.21—7.52 (m, 4 H, H arom.); 7.62 (s, 1 H, H arom.); 11.70—12.10 (br.s, 2 H, 2 NH)
11	6.95, 7.29 (both d, 1 H each, H arom., *J* = 8.2); 7.63 (d, 2H, H arom., *J* = 8.9); 7.81 (d, 2 H, H arom., *J* = 8.8); 8.11 (s, 1 H, H arom.); 12.17 (br.s, 2 H, 2 NH)

* Hydrochlorides.

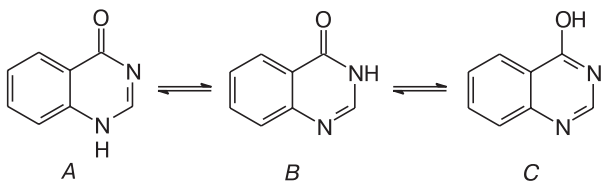
Table 3. Characteristics of synthesized quinolines **12—16**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
12a	55	152—153	69.75 69.69	4.40 4.42	11.58 11.62	$C_{21}H_{16}ClN_3O$
12b	54	140	66.42 66.37	4.51 4.42	19.39 19.36	$C_{20}H_{16}ClN_5$
13a	53	233	62.13 62.13	4.76 4.85	22.68 22.65	$C_{16}H_{15}N_5O_2$
13b	69	137	66.40 66.38	4.21 4.23	13.66 13.67	$C_{17}H_{13}N_3O_3$
13c	55	225	64.13 64.04	4.52 4.45	12.45 12.45	$C_{18}H_{15}N_3O_4$
13d	24	161	64.03 64.04	4.46 4.45	12.37 12.45	$C_{18}H_{15}N_3O_4$
13e	67	197	59.76 59.68	3.57 3.51	12.34 12.29	$C_{17}H_{12}ClN_3O_3$
13f	71	198	62.78 62.71	3.71 3.69	12.87 12.91	$C_{17}H_{12}FN_3O_3$
13g	43	135	62.01 62.06	4.71 4.63	11.43 11.43	$C_{19}H_{17}N_3O_3S$
14a	65	156—158	74.36 74.28	4.76 4.78	11.82 11.82	$C_{22}H_{17}N_3O_2$
14b	46	110—112	69.96 70.04	3.92 3.89	11.65 11.67	$C_{21}H_{14}ClN_3O$
14c	83	135—136	71.14 71.06	4.56 4.58	11.30 11.31	$C_{22}H_{17}N_3OS$
15	27	205—207	69.64 69.55	5.12 5.11	14.31 14.32	$C_{17}H_{15}N_3O_2$
16*	58	315 (deomp.)	55.44 55.52	5.06 4.96	27.74 27.76	$C_{14}H_{15}ClN_6$

* Hydrochloride.

glycine methyl ester hydrochloride[11] and of 2-amino-3-thienylcyanide with phenylcyanamides[10] are thought to follow such a pathway. Nevertheless, the results of alternative synthesis of **9a** with participation of disubstituted guanidines and isatoic anhydride[12] indicate the formation of 3,4-dihydroquinazolin-4-one with substituent in the position 2. Similar results were obtained in the synthesis of 2-phenylaminoadenosine[13] and thienopyrimidin-4(3*H*)-ones[14] with the use of phenylcyanamide.

Quinazolinones, unsubstituted at the NH group, are known to exist in various tautomeric forms: 1,4-dihydroquinazolin-4-ones (*A*), 3,4-dihydroquinazolin-4-ones (*B*), and quinazolin-4-ols (*C*).



A *B* *C*

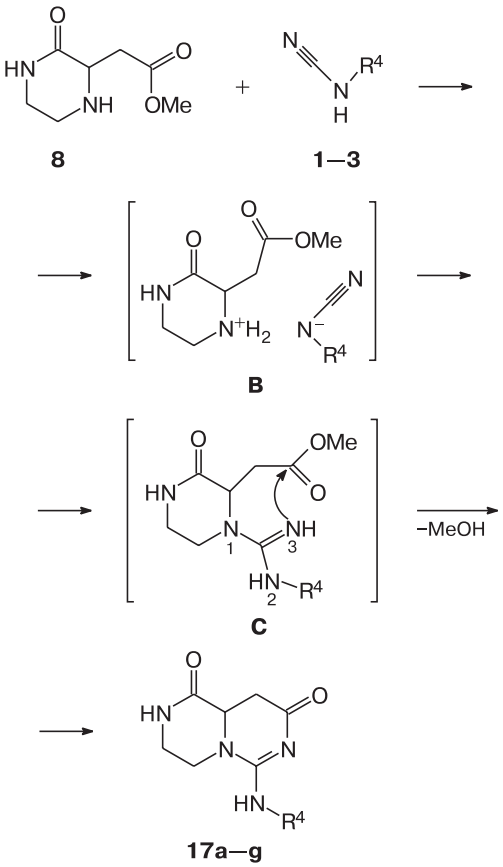
Table 4. ^{1}NMR spestra of quinolines **12—16**

Sompound:	δ (*J*/Hz)
12a	4.05 (s, 3 H, MeO); 7.01—7.12 (m, 3 H, H arom.); 7.63—7.91 (m, 8 H, H arom.); 8.13 (s, 1 H, H arom.); 8.86 (s, 1 H, NH)
12b	2.41 (s, 6 H, Me); 6.80 (s, 1 H, H(5), pyrimidine); 7.48—7.92 (m, 8 H, H arom.); 9.88 (s, 1 H, NH)
13a	2.43 (s, 6 H, Me); 2.82 (s, 3 H, Me); 6.18 (s, 2 H, SH_2); 6.80 (s, 1 H, H(5), pyrimidine); 7.09 (s, 1 H, H arom.); 7.38 (s, 1 H, H arom.); 10.35 (s, 1 H, NH)
13b	2.80 (s, 3 H, Me); 6.20 (s, 2 H, SH_2); 7.11, 7.39 (both s, 1 H each, H arom.); 7.45—7.60 (m, 3 H, H arom.); 7.98—8.08 (m, 2 H, H arom.); 10.29 (s, 1 H, NH)
13s	2.79 (s, 3 H, Me); 3.82 (s, 3 H, MeO); 6.18 (s, 2 H, SH_2); 7.10, 7.41 (both s, 1 H each, H arom.); 7.64 (d, 2 H, H arom., J = 8.3); 7.95 (d, 2 H, H arom., J = 8.5); 10.34 (s, 1 H, NH)
13d	2.80 (s, 3 H, Me); 3.85 (s, 3 H, MeO); 6.19 (s, 2 H, SH_2); 7.11, 7.40 (both s, 1 H each, H arom.); 7.45—7.76 (m, 3 H, H arom.); 8.04 (s, 1 H, H arom.); 10.38 (s, 1 H, NH)
13e	2.81 (s, 3 H, Me); 6.20 (s, 2 H, SH_2); 7.11, 7.39 (both s, 1 H each, H arom.); 7.47 (d, 2 H, H arom., J = 8.4); 8.02 (d, 2 H, H arom., J = 8.5); 10.48 (s, 1 H, NH)
13f	2.80 (s, 3 H, Me); 6.21 (s, 2 H, SH_2); 7.11, 7.40 (both s, 1 H each, H arom.); 7.19—8.10 (m, 4 H, H arom.); 10.43 (s, 1 H, NH)
13g	1.27 (t, 3 H, Me, J = 7.7); 2.71 (s, 3 H, Me); 2.93 (q, 2 H, SH_2, J = 7.5); 6.18 (s, 2 H, SH_2); 6.93 (s, 1 H, H arom.); 7.20—7.52 (m, 5 H, H arom.); 10.02 (s, 1 H, NH)
14a	3.88 (s, 3 H, MeO); 7.42—8.08 (m, 13 H, H arom.); 10.95 (s, 1 H, NH)
14b	7.45—8.12 (m, 13 H, H arom.); 11.02 (s, 1 H, NH)
14s	2.51 (s, 3 H, MeS); 7.19—8.09 (m, 13 H, H arom.); 10.90 (s, 1 H, NH)
15	2.95 (s, 3 H, Me); 3.90 (s, 3 H, MeO); 7.15—8.11 (m, 8 H, H arom.); 10.53 (s, 1 H, NH)
16*	2.47 (s, 6 H, Me); 7.14 (s, 1 H, H(5), pyrimidine); 7.59 (t, 1 H, H arom., J = 7.1); 7.88 (d, 1 H, H arom., J = 7.6); 7.96 (t, 1 H, H arom., J = 7.2); 8.46 (d, 1 H, H arom., J = 7.7); 9.22, 9.51 (both s, 1 H each, NH_2); 11.98 (s, 1 H, NH); 14.33 (s, 1 H, HSl)

* Hydroshloride.

According to modern conception, heterocycles of this type exist preferably in the oxo-form.[15] In this way, the choice should be made between forms *A* and *B*. The quantum-chemical calculations give preferences to 3,4-dihydro-4-quinazolinone tautomer *B*,[16] which is in accordance with the earlier data concerning this question.[17] Recent structural investigations of quinazolones by IR spectroscopy,[18] ^{13}C NMR (HSQC), and X-ray crystallography[19] undoubtedly confirm their existence in the form of 3,4-dihydroquinazolin-4-one (*B*).

Scheme 3



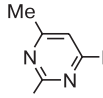
17: R^4 =  (**a**), Bz (**b**), 4-MeOBz (**c**), 2-MeOBz (**d**), 4-ClBz (**e**), 4-FBz (**f**), 2-EtSBz (**g**)

Table 5. Characteristics of synthesized 1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidines **17**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
17a	29	335—336	54.23 54.11	5.48 5.55	29.18 29.14	$C_{13}H_{16}N_6O_2$
17b	62	252	58.56 58.68	4.92 4.89	19.64 19.56	$C_{14}H_{14}N_4O_3$
17c	82	277—278	57.02 56.91	4.98 5.06	17.79 17.70	$C_{15}H_{16}N_4O_4$
17d	40	251—252	56.83 56.91	5.05 5.06	17.72 17.70	$C_{15}H_{16}N_4O_4$
17e	61	276	52.49 52.39	4.05 4.05	17.42 17.46	$C_{14}H_{13}ClN_4O_3$
17f	70	255	55.23 55.21	4.18 4.27	18.36 18.40	$C_{14}H_{13}FN_4O_3$
17g	38	230—232	55.43 55.43	5.13 5.20	16.28 16.17	$C_{16}H_{18}N_4O_3S$

2-(3-Oxopiperazin-2-yl)acetate **8** is a convenient and available b-amino ester for the construction of tetrahydropyrimidine ring. Its catalyst-free cyclization with cyanamides **1**—**3** proceeds smoothly upon heating in dioxane (Scheme 3).

Cyanamides **1**—**3** show pronounced acidic properties, while the imino group in piperazinone **8** is a strong enough organic base, therefore, in the first step they form ionic compound **B** (see Scheme 3), which upon heating undergoes the Woehler rearrangement with the formation of guanidine **C**.[20]

Table 6. ^{1}H NMR spectra of compounds **17**

Compound:	δ (*J*/Hz)
17a	2.48 (s, 6 H, Me); 2.67—2.98 (м, 2 H, COC$\underline{H}_2$CH); 3.21—3.52 (м, 3 H, NCH$_2$C$\underline{H}_2$NH, CH); 4.31 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 6.2); 4.75 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.9, *J* = 3.8); 6.73 (s, 1 H, H(5), pyrimidine); 8.19 (s, 1 H, CONH); 12.89 (s, 1 H, NH)
17b	2.81—3.01 (м, 2 H, COC$\underline{H}_2$CH); 3.33—3.61 (м, 3 H, NCH$_2$C$\underline{H}_2$NH, CH); 4.52 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.2, *J* = 6.8); 4.52 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.2, *J* = 3.6); 7.46—7.53 (м, 3 H, H arom.); 8.18 (d, 2 H, H arom., *J* = 7.4); 8.72 (s, 1 H, CONH); 12.37 (s, 1 H, NH)
17c	2.79—3.03 (м, 2 H, COC$\underline{H}_2$CH); 3.29—3.50 (м, 3 H, NCH$_2$C$\underline{H}_2$NH, CH); 3.82 (s, 3 H, MeO); 4.48 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 6.5); 4.62 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 3.6); 7.12, 7.35 (both d, 2 H each, H arom., *J* = 8.5); 8.42 (s, 1 H, CONH); 12.44 (s, 1 H, NH)
17d	2.77—3.00 (м, 2 H, COC$\underline{H}_2$CH); 3.28—3.49 (м, 3 H, NCH$_2$C$\underline{H}_2$NH, CH); 3.83 (s, 3 H, MeO); 4.47 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.2, *J* = 6.4); 4.60 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 3.5); 6.86—7.00 (м, 2 H, H arom.); 7.45 (t, 1 H, H arom., *J* = 8.4); 7.69 (d, 1 H, H arom., *J* = 8.5); 8.29 (s, 1 H, CONH); 12.24 (s, 1 H, NH)
17e	2.81—3.04 (м, 2 H, COC$\underline{H}_2$CH); 3.35—3.62 (м, 3 H, NCH$_2$C$\underline{H}_2$NH, CH); 4.50 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 6.6); 4.72 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.2, *J* = 3.7); 7.49, 8.13 (both d, 2 H each, H arom., *J* = 8.5); 8.36 (s, 1 H, CONH); 12.32 (s, 1 H, NH)
17f	2.80—3.01 (м, 2 H, COC$\underline{H}_2$CH); 3.32—3.59 (м, 3 H, NCH$_2$C$\underline{H}_2$NH, CH); 4.46 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.4, *J* = 6.5); 4.70 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 3.6); 7.22, 8.26 (both br.s, 2 H each, H arom.); 8.34 (s, 1 H, CONH); 12.16 (s, 1 H, NH)
17g	1.23 (t, 3 H, SCH$_2$C$\underline{H}_3$, *J* = 7.5); 2.74—3.01 (м, 4 H, COC$\underline{H}_2$CH, SC$\underline{H}_2$CH$_3$); 3.26—3.52 (м, 3 H, CH, NC$\underline{H}_2$CH$_2$NH); 4.58 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.4, *J* = 6.5); 4.67 (d.d, 1 H, NC$\underline{H}_2$CH$_2$NH, *J* = 14.3, *J* = 3.6); 7.14 (t, 1 H, H arom., *J* = 7.3); 7.32 (d, 1 H, H arom., *J* = 7.5); 7.41 (t, 1 H, H arom., *J* = 7.3); 8.08 (d, 1 H, H arom., *J* = 7.6); 8.39 (s, 1 H, CONH); 12.19 (s, 1 H, NH)

According to ^{1}H NMR spectroscopy data, the reaction product has the structure **17**. The downfield singlets at 8.3 and 12—13 ppm represent signals of the protons of the amide and guanidine groups. In the region 4.30—4.80 ppm, two doublets of doublets are observed, the distance between which (50—140 Hz) depends on the substituent R, which allows us to assign these signals to the protons of the —CH_2— group in position 4 of the heterocyclic system **17**. The synthetic outcome for compounds **17** and their ^{1}H NMR spectral data are given in Tables 5 and 6.

Experimental

Monitoring of the course of the reaction and purity of compounds synthesized was performed by TLC on Merck UV-254 plates (eluent: chloroform—methanol, 20 : 1). ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz) at 20 °C in DMSO-d_6, Me_4Si was used as the internal standard.

2-(4,6-Dimethylpyrimidin-2-ylamino)-3,4-dihydroquinazolin-4-one (9a) was obtained as described earlier.[20]

2-(4-Methoxyanilino)-3,4-dihydroquinazolin-4-one (9b). Concentrated HCl (1.37 mL) was added to a solution of methyl anthranilate **5a** (2.27 g, 0.015 mol) and 4-methoxyphenylcyanamide **4a** (2.22 g, 0.015 mol) in propan-2-ol (30 mL), and the mixture was refluxed for 2 h. A precipitate of hydrochloride **9b** formed was filtered off, recrystallized from propan-2-ol—DMF (1 : 2), washed with propan-2-ol, and dried at 40 °C *in vacuo* to obtain hydrochloride **9b** (1.14 g, 25%).

2-(2-Methoxyanilino)-3,4-dihydroquinazolin-4-one (9c) and **6,7-dimethoxy-2-(4-methoxyanilino)-3,4-dihydroquinazolin-4-one (10a)** were obtained similarly.

2-(4-Chlorophenylcarboxamido)-3,4-dihydroquinazolin-4-one (9d). A solution of methyl anthranilate **5a** (1.13 g, 7.5 mmol) and 4-chlorobenzoylcyanamide **3c** (1.35 g, 7.5 mmol) in dioxane (25 mL) was heated at 80 °C for 1—2 h. A precipitate was formed toward the end of heating. After cooling, the reaction mixture was poured in cold deionized water (200 mL). The precipitate was filtered off and recrystallized from propan-2-ol—dioxane (1 : 2), washed with propan-2-ol, and dried at 40 °C *in vacuo* to obtain compound **9d** (1.38 g, 61%).

2-(4-Methoxyphenylcarboxamido)-3,4-dihydroquinazolin-4-one (9e), **2-(2-methylsulfanylphenylcarboxamido)-3,4-dihydroquinazolin-4-one (9f)**, **2-(2-ethylsulfanylphenylcarboxamido)-3,4-dihydroquinazolin-4-one (9g)**, **6,7-dimethoxy-2-phenylcarboxamido-3,4-dihydroquinazolin-4-one (10b)**, **2-(4-chlorophenylcarboxamido)-6,7-dimethoxy-3,4-dihydroquinazolin-4-one (10c)**, **6,7-dimethoxy-2-(4-methoxyphenylcarboxamido)-3,4-dihydroquinazolin-4-one (10d)**, **2-(4-fluorophenylcarboxamido)-6,7-dimethoxy-3,4-dihydroquinazolin-4-one (10e)**, **2-(2-ethylsulfanylphenylcarboxamido)-6,7-dimethoxy-3,4-dihydroquinazolin-4-one (10f)**, and **6-bromo-2-(4-fluorophenylcarboxamido)-3,4-dihydroquinazolin-4-one (11)** were obtained similarly.

6-Chloro-2-(2-methoxyphenyl)amino-4-phenylquinazoline (12a). Concentrated HCl (0.91 mL) was added to a solution of 2-amino-5-chlorobenzophenone **6d** (2.32 g, 0.01 mol) and 2-methoxyphenylcyanamide **4a** (1.48 g, 0.01 mol) in propan-2-ol (30 mL), and the mixture was refluxed for 2 h. The cooled dark red reaction mixture was poured in solution of NaOH (0.5 g) in deionized water (200 mL). A tar-like precipitate formed was washed with water until neutral pH and recrystallized from propan-2-ol—dioxane (1 : 1) to obtain compound **12a** (2.0 g, 55%).

6-Chloro-2-(4,6-dimethylpyrimidin-2-yl)amino-4-phenylquinazoline (12b) was obtained similarly.

8-Methyl-6-(4,6-dimethylpyrimidin-2-yl)amino[1,3]dioxolo[4,5-*g*]quinazoline (13a). Concentrated HCl (0.92 mL) was added to a mixture of **6b** (1.79 g, 0.01 mol) and cyanamide **1** (1.48 g, 0.01 mol) in methanol (25 mL), and the reaction mixture was refluxed for 3 h. Then it was poured in cold deionized water (200 mL) and, by addition of conc. NH_4OH, pH value was raised to 9. A precipitate formed was filtered off and recrystallized from dioxane to obtain compound **13a** (1.65 g, 53%).

8-Methyl-6-phenylcarboxamido[1,3]dioxolo[4,5-*g*]quinazoline (13b). A mixture of **6b** (1.34 g, 7.5 mmol) and benzoylcyanamide **3a** (1.1 g, 7.5 mmol) was heated in dioxane (20 mL) at 80 °C for 4 h. The reaction mixture was poured in cold deionized water (200 mL), a precipitate formed was filtered off and recrystallized from dioxane to obtain compound **13b** (1.59 g, 69%).

6-(4-Methoxyphenylcarboxamido)-8-methyl[1,3]dioxolo-[4,5-*g*]quinazoline (13c), **6-(2-methoxyphenylcarboxamido)-8-methyl[1,3]dioxolo[4,5-*g*]quinazoline (13d)**, **6-(4-chlorophenylcarboxamido)-8-methyl[1,3]dioxolo[4,5-*g*]quinazoline (13e)**, **6-(4-fluorophenylcarboxamido)-8-methyl[1,3]dioxolo[4,5-*g*]quinazoline (13f)**, and **6-(2-ethylsulfanylphenylcarboxamido)-8-methyl[1,3]dioxolo[4,5-*g*]quinazoline (13g)** were obtained by similar procedure.

2-(4-Methoxyphenylcarboxamido)-4-phenylquinazoline (14a). A mixture of 2-aminobenzophenone **6c** (1.97 g, 0.01 mol) and 4-methoxybenzoylcyanamide **3b** (1.76 g, 0.01 mol) was refluxed in anhydrous dioxane (25 mL) for 10 h. The reaction mixture was poured in cold deionized water (200 mL), acidified with diluted HCl to pH 2—3. An oily precipitate formed was washed with water and dissolved in minimum propan-2-ol. A precipitate was formed after few days, which was filtered off and dried *in vacuo* at 40 °C to obtain compound **14a** (2.3 g, 65%).

2-(4-Chlorophenylcarboxamido)-4-phenylquinazoline (14b) and **2-(2-methylsulfanylphenylcarboxamido)-4-phenylquinazoline (14c)** were obtained similarly.

2-(4-Methoxyphenylcarboxamido)-4-methylquinazoline (15). A mixture of 2-aminoacetophenone **6a** (1.35 g, 10 mmol) and 4-methoxybenzoylcyanamide **4a** (1.32 g, 7.5 mmol) in anhydrous dioxane (20 mL) was kept at 80 °C for 10 h followed by pouring of the mixture in deionized water (200 mL), acidified with diluted HCl to pH 2—3. An oily precipitate formed was washed with water, recrystallized from acetonitrile, and dried *in vacuo* at 40 °C to obtain compound **15** (0.59 g, 27%).

4-Amino-2-(4,6-dimethylpyrimidin-2-yl)aminoquinazoline hydrochloride (16). A mixture of cyanamide **1** (1.48 g, 0.01 mol) and hydrochloride **7** (1.55 g, 0.01 mol) in anhydrous dioxane (30 mL) was refluxed for 4 h. A precipitate formed was filtered off, washed with hot propan-2-ol, and recrystallized from DMF to obtain hydrochloride of compound **16** (1.75 g, 58%).

6-Phenylcarboxamido-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (17b). A mixture of benzoylcyanamide **3a** (1.46 g, 0.01 mol) and **8** (1.72 g, 0.01 mol) in dioxane (20 mL) was heated at 80 °C for 3 h. A precipitate formed was filtered off and recrystallized from propan-2-ol—dimethylacetamide (2 : 1) to obtain compound **17b** (1.76 g, 62%).

6-(4,6-Dimethyl-2-pyrimidinylamino)-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (17a), **6-(4-methoxyphenylcarboxamido)-1,3,4,8,9,9a-hexahydro-2*H*-**

pyrazino[1,2-*c*]pyrimidine-1,8-dione (17c), **6-(2-methoxyphenylcarboxamido-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (17d)**, **6-(4-chlorophenylcarboxamido)-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (17e)**, **6-(4-fluorophenylcarboxamido)-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (17f)**, and **6-(2-ethylsulfanylphenylcarboxamido)-1,3,4,8,9,9a-hexahydro-2*H*-pyrazino[1,2-*c*]pyrimidine-1,8-dione (17g)** were obtained similarly.

References

1. D. D. Nekrasov, *Zh. Org. Khim.*, 2004, **40**, 1439 [*Russ. J. Org. Chem.*, 2004, **40** (Engl. Transl.)].
2. D. D. Nekrasov, *Khim. Geterotsikl. Soedin.*, 2004, 1283 [*Chem. Heterocycl. Compd.*, 2004, **40** (Engl. Transl.)].
3. V. I. Kelarev, V. N. Koshelev, *Usp. Khim.*, 1995, **64**, 339 [*Russ. Chem. Rev.*, 1995, **64** (Engl. Transl.)].
4. D. J. Brown, in *Comprehensive Heterocyclic Chem.*, Eds A. R. Katritzky, C. W. Rees, Pergamon Press, Oxford—New York, 1984, **3**, 111.
5. S. Birtwell, *J. Chem. Soc.*, 1953, 1725.
6. J. C. Howard, *J. Org. Chem.*, 1964, **29**, 761.
7. H. King, J. M. Tonkin, *J. Chem. Soc.*, 1946, 1063.
8. *Organic Syntheses*, J.Wiley, New York—London, 1951, **31**, 19.
9. M. M. Abelman, K. J. Fisher, E. M. Doerffler, P. J. Edwards, *Tetrahedron Lett.*, 2003, **44**, 1823.
10. C. J. Shishoo, K. S. Jain, *J. Heterocycl. Chem.*, 1993, **30**, 435.
11. V. V. Dovlatyan, E. N. Ambartsumyan, G. S. Amazaspyan, *Khim. Geterotsikl. Soedin.*, 1996, 84 [*Chem. Heterocycl. Compd.*, 1996, **32** (Engl. Transl.)].
12. Kh. S. Shikhaliev, D. V. Krylrskii, A. S. Shestakov, A. V. Falaleev, *Zh. Obshch. Khim.*, 2003, **73**, 1216 [*Russ. J. Gen. Chem.*, 2003, **73** (Engl. Transl.)].
13. K. Omura, R. Marumoto, Y. Furukawa, *Chem. Pharm. Bull.*, 1981, **29**, 1870.
14. K. N. Rajasekharan, L. Thomas, *Ind. J. Chem.*, 1983, **22**, 76.
15. J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Blackwell Science, Oxford, 2000.
16. M. Kh. Mamarakhmonov, L. I. Belenrkii, N. D. Chuvylkin, Kh. M. Shakhidoyatov, *Khim. Geterotsikl. Soedin.*, 2003, 1517 [*Chem. Heterocycl. Compd.*, 2003, **39** (Engl. Transl.)].
17. Y. Hagiwara, M. Kurihara, N. Yoda, *Tetrahedron*, 1969, **25**, 783.
18. V. I. Kelarev, M. A. Silin, V. N. Koshelev, O. A. Borisova, *Khim. Geterotsikl. Soedin.*, 2004, 729 [*Chem. Heterocycl. Compd.*, 2004, **40** (Engl. Transl.)].
19. O. B. Ryabova, V. A. Makarov, L. M. Alekseeva, A. S. Shashkov, V. V. Chernyshev, V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1851 [*Russ. Chem. Bull.*, 2005, **54**, 1907 (Engl. Transl.)].
20. A. S. Shestakov, N. V. Gusakova, V. N. Verezhnikov, Kh. S. Shikhaliev, *Izv. vuzov. Khimiya i khim. tekhnologiya*, 2005, **48**, 126 [*Izv. Vuz. Khim. Khim. Tekhnol.*, 2005 (Engl. Transl.)].

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