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Synthesis of Partially Hydrogenated 1,2,4-Triazoloquinazolines by Condensation of 3,5-Diamino-1,2,4-triazole with Aromatic Aldehydes and Dimedone

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Abstract—Three-component condensation of 3,5-diamino-1,2,4-triazole with aromatic aldehydes and dimedone in dimethylformamide gives 2-amino-5-aryl-8,8-dimethyl-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[3,2-*b*]quinazolin-6-ones. The reaction of 3,5-diamino-1,2,4-triazole with dimedone in the absence of aldehyde involves dimethylformamide as one of the carbonyl components to afford 2-amino-8,8-dimethyl-6,7,8,9-tetrahydro[1,2,4]triazolo-[2,3-*a*]quinazolin-6-one.

Interest in multicomponent condensations and cascade reactions of aryl(heteryl)amines with carbonyl compounds or their synthetic equivalents, which ensure one-pot assembly of various heterocyclic systems, originates mainly from needs of combinatorial synthesis. The set of appropriate transformations is now fairly broad [1, 2]; nevertheless, search for both new reactions and new building blocks for creation of fused nitrogen-containing heterocyclic systems is in progress. Fused systems incorporating a partially hydrogenated pyrimidine ring attract increased attention [3, 4]. We previously showed that three-component condensation of 3-amino- and 3,5-diamino-1,2,4-triazoles with substituted benzaldehydes and acetophenones or cycloalkanones in dimethylformamide (DMF) leads to formation of 4,7-dihydro[1,2,4]triazolo[2,3-*a*]pyrimidines or 5,6,7,9-tetrahydro-4*H*-[1,2,4]triazolo[3,2-*b*]quinazolines, respectively [5–8]. These compounds are dihydro hetero analogs of both natural biologically important compounds (such as adenine and guanine) and synthetic pharmaceutical agents, specifically Bumepidil and Trapidil which are broncho- and vasodilators [9].

With the goal of extending the set of reagents for the synthesis of partially hydrogenated azolopyrimidine systems, in the present work we examined three-component condensation of 3,5-diamino-1,2,4-triazole (**I**) with *para*-substituted benzaldehydes **II**–**VI** and 5,5-dimethylcyclohexane-1,3-dione (**VII**, dimedone) in DMF. Depending on the nature of the carbonyl components, the condensation takes one of the two alternative pathways leading to pyrimidine ring closure (*a* or *b*). Heating of equimolar amounts of amine **I**, aldehyde **II**–**VI**, and dimedone (**VII**) in boiling DMF for a short time (10–15 min) resulted in formation of 2-amino-5-aryl-8,8-dimethyl-5,6,7,8,9,10-hexahydro[1,2,4]triazol[3,2-*b*]-quinazolin-6-ones **VIII**–**XII** (Scheme 1). Analogous results were obtained in reactions of compound **I** with 2-arylmethylene-5,5-dimethylcyclohexane-1,3-diones **XIV** and **XV** or xanthenediones **XVI** and **XVII**, as well as in reactions of Schiff bases **XVIII**–**XX** with dimedone (**VII**) in the absence of a catalyst and of enaminoketone **XXI** with aldehydes **II** and **III** in the presence of a catalytic amount of an acid. In all cases, the yields of the final products, triazoloquinazolinones **VIII**–**XII** were approximately similar. However, the reaction between equimolar amounts of diaminotriazole **I** and dimedone (**VII**) in DMF follows pathway *b* which leads to compound **XXIII** with a different mode of fusion of the triazole and quinazoline fragments.

The structure of the newly synthesized compounds **VIII**–**XII**, **XVIII**–**XX**, **XXI**, and **XXIII** was confirmed by spectral methods (Tables 1, 2) and analytical data (Table 1).

Compounds **VIII**, **XXI**, and **XXIII** showed in the mass spectra the molecular ion peaks with *m*/*z* values of 309,

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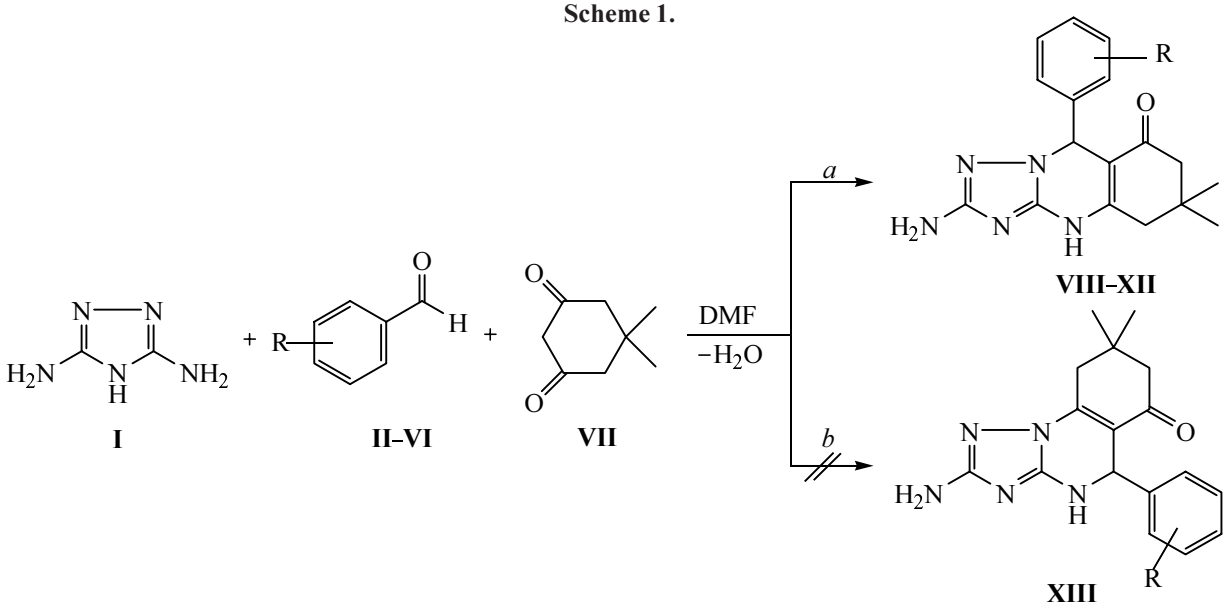
Scheme 1.



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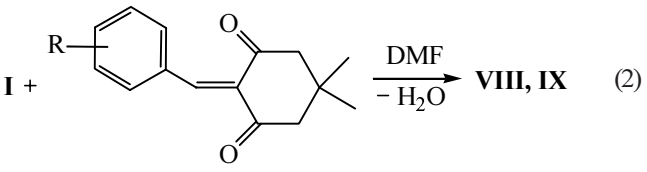

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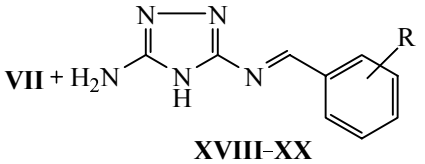

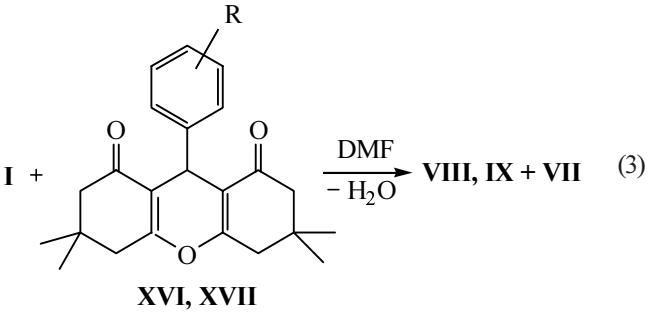

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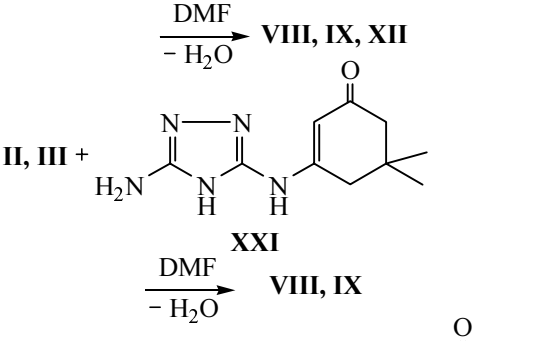

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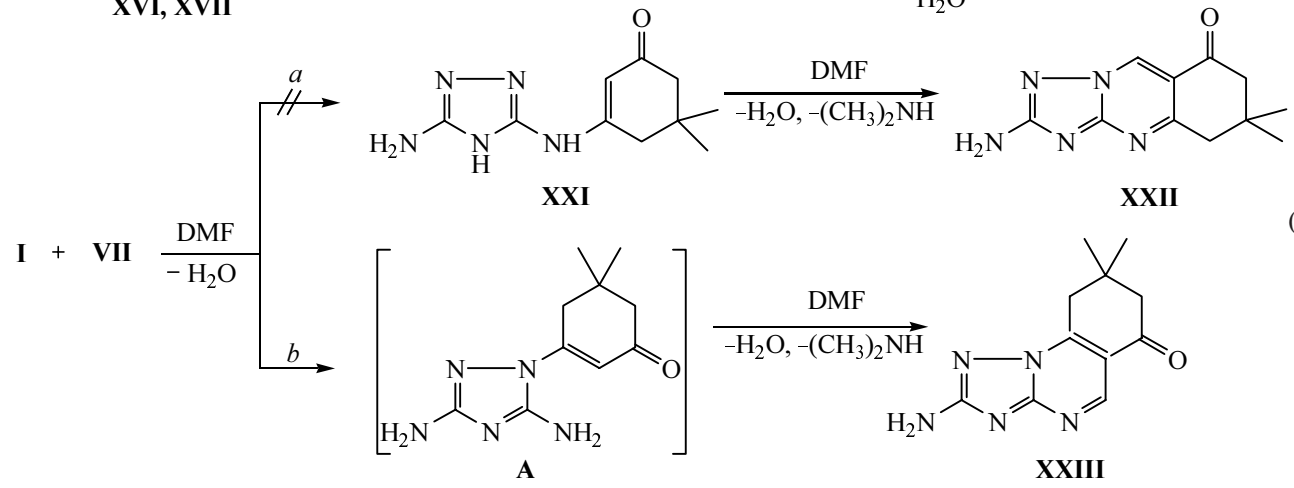
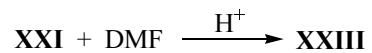


(6)



(7)

II, **VIII**, **XIV**, **XVI**, **XVIII**, R = H; **III**, **IX**, **XV**, **XVII**, **XIX**, R = 4-Cl; **IV**, **X**, R = 4-MeO; **V**, **XI**, R = Me_2N; **VI**, **XII**, **XX**, R = 2,4-Cl_2.

Table 1. Yields, melting points, IR spectra, and elemental analyses of compounds **VIII**–**XII**, **XVIII**–**XXI**, and **XXIII**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}	Found,[a] %			Formula	Calculated,[b] %		
				C	H	N		C	H	N
VIII	57	254–256	3460, 3308 (NH_2), 3188–2780 (NH, CH_2, CH_3), 1648 (C=O)	65.98	6.09	22.57	$C_{17}H_{19}N_5O$	66.02	6.15	22.65
IX	61	335–337	3468, 3304 (NH_2), 3184–2760 (NH, CH_2, CH_3), 1652 (C=O)	59.29	5.18	20.31	$C_{17}H_{18}N_5ClO$	59.39	5.24	20.38
X	65	289–291	3468, 3304 (NH_2), 3184–2800 (NH, CH_2, CH_3), 1648 (C=O)	63.76	6.08	20.61	$C_{18}H_{21}N_5O_2$	63.72	6.19	20.65
XI	54	290–293	3472, 3384 (NH_2), 3180–2800 (NH, CH_2, CH_3), 1652 (C=O)	64.62	6.79	23.81	$C_{19}H_{24}N_6O$	64.77	6.82	23.86
XII	66	>350	3460, 3324 (NH_2), 3240–2800 (NH, CH_2, CH_3), 1648 (C=O)	54.03	4.54	18.49	$C_{17}H_{17}N_5Cl_2O$	53.97	4.50	18.52
XVIII	80	149–152	3272–2800 br (NH_2, NH), 1664 (C=N)	57.70	4.75	37.48	$C_9H_9N_5O$	57.75	4.81	37.43
XIX	68	262–264	3316–2800 br (NH_2, NH), 1664 (C=N)	48.82	3.64	31.57	$C_9H_8N_5Cl$	48.76	3.61	31.60
XX	82	156–158	3368–2880 br (NH_2, NH), 1656 (C=N)	28.20	2.90	27.30	$C_6H_7N_5Cl_2$	28.13	2.73	27.34
XXI	45	293–295	3396–2650 br (NH_2, NH), 1628 (C=O)	54.31	6.83	37.69	$C_{10}H_{15}N_5O$	54.30	6.79	31.67
XXIII	32	305–307	3388, 3308 (NH_2), 1684 (C=O)	57.17	5.58	30.32	$C_{11}H_{13}N_5O$	57.14	5.63	30.30

[a] Found, %: Cl 10.29 (**IX**), 18.75 (**XII**), 16.03 (**XIX**), 27.75 (**XX**).
[b] Calculated, %: Cl 10.33 (**IX**), 18.78 (**XII**), 16.03 (**XIX**), 27.73 (**XX**).

221, and 231, respectively. The molecular weight of **XXIII** suggests that a DMF molecule was involved as one carbonyl component in the formation of this compound.

The IR spectra of compounds **VIII**–**XII** are alike; they contain absorption bands at 3460–3468 and 3324–3304 cm^{-1}, belonging to stretching vibrations of the amino group, a broad band in the region 3184–2800 cm^{-1}, which is a superposition of bands due to vibrations of the associated NH group and methyl and methylene C–H bonds, and carbonyl absorption band at 1652–1648 cm^{-1}. In the IR spectrum of **XXIII**, the most characteristic are stretching vibration bands of the NH_2 (3388 and 3308 cm^{-1}) and CO groups (1684 cm^{-1}).

Reactions of amine **I** with benzaldehydes **II**–**VI** and dimedone (**VII**) could give rise to fused systems of two kinds, compounds **VIII**–**XII** and **XIII**. The choice between the isomeric structures was made on the basis of the ^1H NMR data (Table 2). The ^1H NMR spectra contain multiplet signals from the aromatic protons, singlets from the NH, NH_2, and 5-H protons, signals from two methylene groups (*AB* spin system), and singlets from the two methyl groups. In the spectra of structurally related systems (dihydroazolopyrimidines with a fused carbocycle) [5, 8] we previously revealed a strong relation between the position of the NH signal and the type of the dihydropyrimidine fragment. The NH signal in the ^1H NMR spectra of 5,6,7,9-tetrahydro-4*H*-[1,2,4]triazolo-[3,2-*b*]-quinazolines (which are analogs of compounds **VIII**–**XII**) appeared at δ 9.5–10.5 ppm (in DMSO-d_6), while the corresponding signal from isomeric structures **XIII** was located considerably more upfield (by 2–3 ppm) [5, 8]. Taking these data into account, the observed position of the NH signal (δ 10.6–11.0 ppm) is typical of dihydroazolopyrimidine systems containing a C=C–NH fragment; an additional downfield shift of that signal should be attributed to electron-acceptor effect of the conjugated carbonyl group. Thus the isolated compounds have the structure of 2-amino-5-aryl-8,8-dimethyl-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[3,2-*b*]quinazolin-6-ones **VIII**–**XII**.

The reaction of amine **I** with dimedone (**VII**) and DMF can also take two pathways, *a* and *b*, leading to structures

Table 2. ^{1}H NMR spectra of compounds **VIII**–**XII**, **XVIII**–**XXI**, and **XXIII**, δ, ppm

Comp. no.	5-H (1H, s)	9-H_A and 7-H_A (1H, d, and 1H, d)[a]	9-H_B and 7-H_B (1H, d, and 1H, d)[b]	Aromatic protons (*J*, Hz)	CH_3 (3H, s, and 3H, s)	NH (1H, s)	NH_2 (2H, s)
VIII	5.94	2.05	2.56, 2.25	7.48–7.93 m	0.96, 1.04	11.04	5.07
IX	5.92	2.06	2.54, 2.20	7.17 d, 7.31 d (*J* = 8.0)	0.96, 1.04	10.72	5.13
X	5.85	2.10	2.58, 2.24	7.04 d, 7.15 d (*J* = 8.2)	0.98, 1.05	10.96	5.06
XI	5.79	2.46, 2.04	2.54, 2.20	6.58 d, 6.94 d (*J* = 8.2)	0.97, 1.04	10.52	5.03
XII	6.24	2.01	2.54, 2.20	7.26–7.43 m	0.99,1.04	10.80	5.14
XVIII	(CH, s) 9.00	–	–	7.48–8.04 m	–	11.88	5.90
XIX	(CH, s) 8.99	–	–	7.54 d, 7.92 d (*J* = 8.2)	–	11.98	5.96
XX	(CH, s) 9.32	–	–	7.49–8.22 m	–	12.06	6.07
XXI	(CH, s) 6.73	(CH_2, 2H, s) 2.12, 2.51		–	(CH_3, 6H, s) 1.01	13.67 9.62	5.43
XXIII	(CH, s) 8.80	(CH_2, 2H, s) 2.54, 3.17			(CH_3, 6H, s) 1.01		6.71

[a] Partially overlapped by the solvent signal.
[b] J_{AB} = –15 to –15.2 Hz (**VIII**–**XII**).

XXII and **XXIII**, respectively. The ^{1}H NMR spectrum of the isolated product contained signals from all groups and fragments present in possible structures (Table 2). An appreciable downfield shift of the signal from one of the methylene groups, as compared to **VIII**–**XII**, should be noted. The observed shift may be caused by electron-acceptor effect of the triazolopyrimidine fragment, as well as by strong deshielding effect of the triazole ring (through space). An analogous shift was observed in the spectrum of a structurally related compound, 2,2-dimethyl-2,4-dihydrobenzimidazo[1,2-*a*]quinazolin-4(1*H*)-one, which was obtained under similar conditions by condensation of 2-aminobenzimidazole with dimedone in DMF; its structure was proved by the X-ray diffraction data [10]. Therefore, the condensation product was assigned structure **XXIII**.

The assumed structure of compounds **VIII**–**XII** corresponds to the reaction direction found for the condensation of diamine **I** with arylmethylenecycloalkanones [5, 6]. The formation of pyrimidine ring from arylmethylene derivatives **XIV** and **XV** involves interactions between the β-carbon atom in the enone and the imino group in the aminoazole and between the carbonyl group of the former and the amino group of the latter.

It is known that, apart from the corresponding arylmethylene derivatives, xanthenediones **XVI** and **XVII** are formed in reactions of dimedone (**VII**) with benzaldehydes **II** and **III** [11, 12]. Compounds **XVI** and **XVII** in turn may undergo retro-condensation. Therefore, taking into account that reactions (1)–(3) (Scheme 1) give the same products, the above processes may be presumed to involve intermediate formation of α,β-unsaturated diketones **XIV** and **XV** rather than to occur independently. In fact, TLC analysis of the reaction mixture obtained from benzaldehyde (**II**) and dimedone (**VII**) in DMF showed the presence of both arylmethylene derivative **XIV** and xanthenedione **XVI**. On the other hand, no new substances were detected when compound **XVI** was heated in boiling DMF for a long time. These results indicate that amine **I** directly reacts with xanthenediones **XVI** and **XVII** without preliminary decomposition of the latter into arylmethylene derivatives **XIV** and **XV** and dimedone (**VII**). Presumably, the first stage in reaction (3) is attack by the amino group of azole **I** on electrophilic center in the α-position with respect to the bridging oxygen atom in **XVI** or **XVII**. This attack leads to opening of the pyran ring and elimination of dimedone molecule. Closure of the pyrimidine ring occurs via interaction between the endocyclic imino group in **I** and electrophilic β-carbon atom, which also results in formation of structure **VIII** or **IX**.

The three-component condensation [reaction (1)] is likely to follow both the above mechanisms, for the reaction mixture contains arylmethylene derivative and xanthenedione simultaneously. However, other reaction pathways cannot be ruled out. One of these includes initial formation of Schiff base via reaction of aminoazole **I**

with benzaldehyde, and the other involves possible formation of enaminoketone by condensation of amine **I** with diketone **VII**. Analogous processes were postulated in reactions of dimedone with aromatic amines [13].

In order to verify the possibility for the three-component condensation to occur via successive reactions of diaminotriazole **I** with benzaldehyde **II**, **III**, or **VI** and dimedone, we examined the reaction of the latter with Schiff bases **XVIII**–**XX**. Compounds **XVIII**–**XX** (Tables 1, 2) were synthesized by heating equimolar amounts of the corresponding aldehyde with aminoazole **I** in boiling alcohol and were brought into reaction with dimedone in DMF. As a result, we isolated only triazoloquinazolinones **VIII**, **IX**, **XII**. No alternative products like **XIII** were detected. Therefore, Schiff bases **XVIII**–**XX** act in this reaction as synthetic equivalents of aldehydes.

Enaminoketone **XXI** was obtained by heating a mixture of dimedone and amine **I** in DMSO. Its structure was determined on the basis of the spectral data (Tables 1, 2). According to the mass spectrum, the molecular weight of **XXI** is 221, i.e., the reaction of **I** with dimedone is accompanied by liberation of water molecule. The ^{1}H NMR spectrum of compound **XXI** (Table 2) contains signals from amino, methyl, and methylene groups and singlets due to two NH protons and CH proton in the enone fragment. These data support structure **XXI**. Enaminoketone **XXI** was heated with benzaldehyde **II** in DMF in the absence of a catalyst and in the presence of a catalytic amount of hydrochloric acid. Triazoloquinazolinone **VIII** was obtained only in the presence of hydrochloric acid. According to the TLC data ($CHCl_3$–MeOH, 9 : 1), under these conditions compound **XXI** decomposes to initial amine **I** and dimedone (**VII**). On prolonged heating in the absence of an aromatic aldehyde, reaction (7) involves DMF as carbonyl component, and quinazolinone **XXIII** is formed. If benzaldehyde (**II**) is present in the reaction mixture, it reacts with dimedone to form arylmethylene derivative **XIV** or xanthenedione **XVI**. In the next stage, the latter reacts with diaminotriazole **I**, following one of the above mechanisms. Thus the formation of compounds **VIII**–**XII** through intermediate enaminoketone **XXI** [reaction (1)] seems to be improbable.

Our experimental data give us grounds to believe that arylmethylene derivatives of dimedone and xanthen diones are the key intermediates in the three-component condensation leading to the triazolo[3,2-*b*]quinazolin-6-one system. In the absence of an aromatic aldehyde, dimethylformamide is involved in the process, and the mode of pyrimidine ring closure changes. Probably, the mechanism of these reaction includes formation of intermediate **A** which undergoes cyclization to triazolo-[2,3-*a*]quinazolin-6-one with participation of DMF molecule.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-82 spectrometer from samples prepared as KBr pellets. The ^{1}H NMR spectra were obtained on a Varian 200 instrument from solutions in DMSO-d_6 using TMS as internal reference. The mass spectra were recorded on an MSBC SELMI spectrometer with a 10 μCi ^{252}Cf source for positive and negative ions (accelerating voltage ±20 kV). The reaction mixtures and products were analyzed by TLC on Silufol UV-254 plates using $CHCl_3$–MeOH (9 : 1) as eluent. The melting points were determined on a Kofler device.

2-Arylmethylene-5,5-dimethylcyclohexane-1,3-diones **XIV** and **XV** were synthesized by the procedure reported in [11]. The procedure for preparation of xanthenediones **XVI** and **XVII** and their properties were described in [12].

2-Amino-5-aryl-8,8-dimethyl-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[3,2-*b*]quinazolin-6-ones VIII–XII (*general procedure*). *a.* A mixture of 1 mmol of 3,5-diamino-1,2,4-triazole (**I**), 1 mmol of dimedone (**VII**), and 1 mmol of aldehyde **II–VI** in 1 ml of DMF was heated for 10 min under reflux until a solid material began to separate from the mixture. The mixture was cooled, 5 ml of 2-propanol was added, and the precipitate was filtered off and recrystallized from DMF–2-propanol (1 : 2). Mass spectrum of **VIII**: *m*/*z* 310/308 [*M* + H]/ [*M* – H].

b. A mixture of 1 mmol of amine **I** and 1 mmol of 2-arylmethylene-5,5-dimethylcyclohexane-1,3-dione **XIV** or **XV** in 1 ml of DMF was heated for 10 min until a solid material began to separate from the mixture. Products **VIII** and **IX** were isolated as described above. Yield of quinazolines **VIII** and **IX** 55 and 63%, respectively.

c. A mixture of 1 mmol of amine **I** and 1 mmol of 9-aryl-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydroxanthene-1,8(2*H*)-dione **XVI** and **XVII** in 1 ml of DMF was heated for 10 min under reflux. Products **VIII** and **IX** were isolated as described above. Yield of quinazolines **VIII** and **IX** 51 and 56%, respectively. Dimedone (**VII**) was extracted from the filtrate with chloroform. The solvent was removed, and the oily residue was crystallized from methanol to isolate diketone **VII** with mp 150–151°C; published data [14]: mp 148–150°C.

d. A mixture of 1 mmol of dimedone (**VII**) and 1 mmol of Schiff base **VIII–XX** in 1 ml of DMF was heated for 30 min under reflux. Products **VIII**, **IX**, **XII** were isolated as described above; yield 49, 54, and 63%, respectively.

e. A mixture of 1 mmol of enaminoketone **XXI** and 1 mmol of aldehyde **II** or **III** in 1 ml of DMF containing a catalytic amount of hydrochloric acid was heated for 30 min under reflux. The products were isolated as described above. Yield of quinazolines **VIII** and **IX** 56 and 58%, respectively.

3-Benzylidene-4*H*-1,2,4-triazole-3,5-diamine (XVIII). A solution of 2 mmol of amine **I** and 2 mmol of benzaldehyde (**II**) in 10 ml of 2-propanol was heated for 1 h under reflux. The mixture was cooled, and the precipitate was filtered off. Compounds **XIX** and **XX** were synthesized in a similar way.

3-(5-Amino-4*H*-1,2,4-triazol-3-ylamino)-5,5-dimethyl-2-cyclohexen-1-one (**XXI**). A solution of 2 mmol of amine **I** and 2 mmol of dimedone (**VII**) in 1 ml of DMSO was heated for 1 h under reflux. The mixture was cooled and diluted with 5 ml of 2-propanol, and the precipitate was filtered off. Mass spectrum: *m*/*z* 222/220 [*M* + H]/[*M* – H].

2-Amino-8,8-dimethyl-6,7,8,9-tetrahydro[1,2,4]-triazolo[2,3-*a*]quinazolin-6-one (XXIII). *a*. A solution of 1 mmol of amine **I** and 1 mmol of dimedone (**VII**) in 2 ml of DMF was heated for 45 min under reflux. The mixture was cooled and diluted with 5 ml of 2-propanol, and the precipitate was filtered off. Mass spectrum: *m*/*z* 232/230 [*M* + H]/[*M* – H].

b. A solution of 2 mmol of enaminoketone **XXI** in 2 ml of DMF containing a catalytic amount of hydrochloric acid was heated for 1 h under reflux. Compound **XXIII** was isolated as described above; yield 27%.

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