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2-Amino-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidines: Synthesis and Reactions with Electrophilic Reagents

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Abstract—The hydrogenation of 2-amino-5-R-7-R'-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines with $NaBH_4$ led to the formation of 2-amino-5-*R*-7-*R*'-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidines. Acylation, sulfonylation, and alkylation of these compounds depending on conditions and the reagent character occur at the amino group, atoms N^3 or N^4. The treatment with alkali of 2-amino-3-benzyl-5-*R*-7-*R*'-4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidinium bromide resulted in 2-amino-3-benzyl-5-*R*-7-*R*'-3,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidine, similar reaction of 2-acetamido-3-benzyl-5-*R*-7-*R*'-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidinium bromide gave a mesoionic product of a hydrogen elimination from the amide nitrogen atom.

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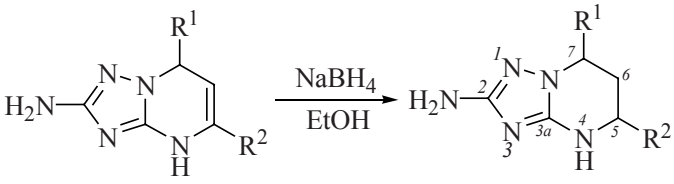
A considerable interest was recently turned to triazolopyrimidines with partially hydrogenated pyrimidine fragment [1–3]. These compounds exhibit versatile biological activity [4, 5] and are used in the studies of structure and reactivity of partially hydrogenated heterocycles [2, 3]. Certain opportunities for modification of physiological properties of triazolopyrimidines provide the functional groups in the position *2* of the bicycle [2, 5, 6]. For instance, 2-amino-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidines **I** are easily acylated at the amino group forming amides possessing a pronounced analgesic and hypoglycemic action [5, 6]. More hydrogenated analogs of these compounds, 2-amino-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidines **II**, and their derivatives were not documented up till now.

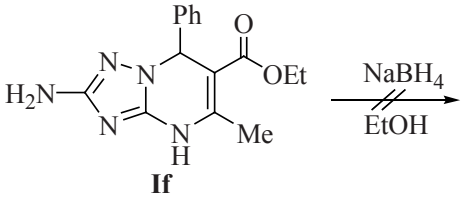
The target of the present study was the synthesis of amines **II** and investigation of their acylation, sulfonylation, and alkylation.

2-Amino-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidines **IIa**–**IIe** we obtained in 71–91% yield by hydrogenation of compounds **Ia**–**Ie** with sodium borohydride in ethanol (Scheme 1). Compound **If** turned out to be stable against hydrogenation even at the use of a large excess of $NaBH_4$, prolonging the reaction to 4 h and performing it in boiling 2-propanol or 1-butanol. Dihydrotriazolopyrimidines with a 6-arylcarboxamide group according to [2] were hydrogenated with $NaBH_4$ in 2-propanol yielding the corresponding tetrahydro derivatives. The reason of the different effect of ethoxycarbonyl and arylcarboxamide groups on the stability of the dihydropyrimidine ring against hydrogenation is unclear.

The composition and structure of compounds **IIa**–**IIe** were confirmed by elemental analysis and spectral data. ^1H NMR spectra indicate the formation of a single diastereomer (also for crude substances) and are unlike the spectra of other 4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidines [7, 8] because of the presence of a two-proton singlet of the amino group in the region

Scheme 1.





I, II: R^1 = Ph (**a**–**d**), 4-$MeOC_6H_4$ (**e**); R^2 = Me (**a**), Ph (**b, e**), 4-MeC_6H_4 (**c**), 4-ClC_6H_4 (**d**).

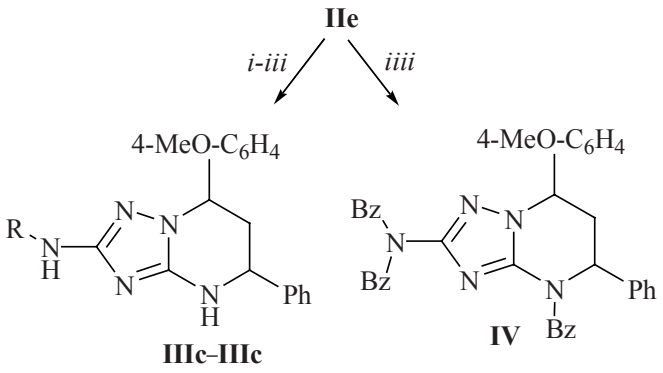
4.8 ppm. Inasmuch as the coupling of protons H^5 and H^7 with one of the methylene group protons is characterized by the coupling constant 10.6–11.4 Hz typical for J_{aa} [9], to compounds **II** should be assigned a *cis*-structure with the equatorial orientation of substituents in the positions *5* and *7* of the bicycle [8].

Compounds **IIa**–**IIe** contain in their molecules several nucleophilic centers (NH_2, N^1, N^3, and N^4H) prone to the probable attack of electrophilic reagents. The reactivity of compounds **II** was studied by an example of amine **IIe**.

The reaction of compound **IIe** with a small excess of acetic anhydride or *p*-toluenesulfonyl chloride in pyridine at boiling led to the formation of acetyl derivative **IIIa** and tosyl derivative **IIIb** (Scheme 2). We succeeded to synthesize benzoyl derivative **IIIc** by acylating amine **IIe** with an equimolar amount of benzoyl chloride in pyridine at 0–5°C for at higher themperature an intractable mixture of compounds was obtained. The reaction of amine **IIe** with excess benzoyl chloride in boiling pyridine gave tribenzoyl derivative **IV** in 71% yield (Scheme 2).

In the ^{1}H NMR spectra of compounds **IIIa–IIIc** the amino group signal is lacking, and appears a broadened singlet of amide proton in the region 10.0–10.6 ppm, and the singlet of N^4H remains. Also in the ^{13}C NMR spectra of compounds **IIIb** and **IIIc** an upfield shift was observed of C^2 atom by nearly 8 ppm as compared with the spectrum of initial amine **IIe** apparently due to the magnetic anisotropy of sulfonyl and carbonyl groups, whereas the position of the peak of C^{3a} atom virtually remained unchanged. In the ^{1}H NMR spectrum of compound **IV** the NH signals are absent, the multiplet of H^5 is shifted downfield by ~1 ppm compared with the spectrum of initial amine **IIe** and those of acyl derivatives **IIa** and **IIc**; besides, in the ^{13}C NMR spectrum of compound **IV** signals of both carbons of the triazole ring are shifted upfield due to the effect of the magnetic anisotropy of the carbonyl groups. The complete equivalence of two C=O groups in the ^{13}C NMR spectrum unambiguously confirms the structure of compound **IV** and excludes the possible isomers with a benzoyl group at N^1 or N^3.

Scheme 2.



Reagents and conditions: *i*, Ac_2O/Py, boiling (**IIIa**); *ii*, TsCl/Py, boiling (**IIIb**); *iii*, BzCl/MeCN-Py, 0–5°C (**IIIc**); *iiii*, BzCl/Py, boiling (**IV**); R = Ac (**a**), Ts (**b**), Bz (**c**).

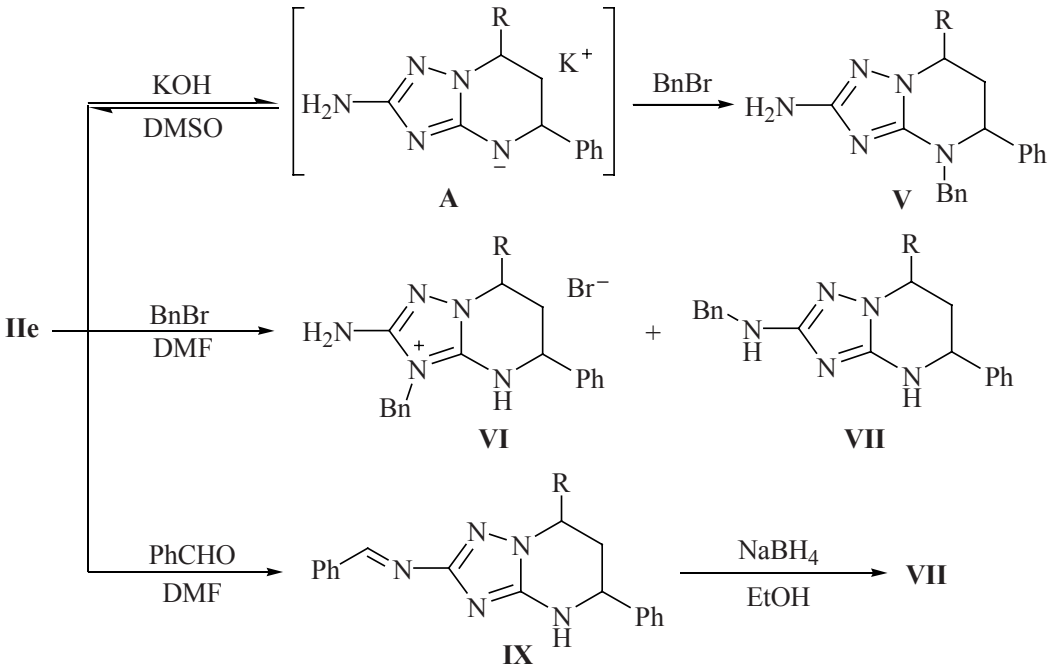
The results obtained in acylation and sulfonylation of compound **IIe** show that 2-amino-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidine **II** behaves in these reactions analogously to 1-substituted 3,5-diamino-1,2,4-triazoles [10].

This originates from the fact that the pyrimidine ring in compounds **II** is unsaturated and does not sifnificanly affect the distribution of the electron density in the diaminotriazole fragment.

The alkylation of compound **IIe** with benzyl bromide in DMSO in the presence of powdered KOH led to the formation of 4-benzyl derivative **V** in 81% yield (Scheme 3). The reaction is likely to proceed through the intermediate formation of salt **A**, as by alkylation of 5,7-diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine [8] or 1-phenyl-3,5-diamino-1,2,4-triazole [11] in the presence of strong bases. The alkylation in a neutral medium resulted in a mixture of quaternary salt **VI** (70%) with alkylamino derivative **VII** (12%) that were successfully separated by column chromatography.

The position of the benzyl group in compounds **V–VII** was established with the use of heteronuclear correlation NMR spectra HMBC and HSQC. In the HMBC spectrum of compound **V** appeared a correlation peak of vicinal spin-spin coupling of the methylene protons of the benzyl group (3.86 and 4.82 ppm) with the nuclei C^{3a} (155.4 ppm) and C^5 (48 ppm), and the analogous peak of carbon atom in the position *2* (160.5 ppm) was absent. In the HMBC spectrum of compound **VI** the benzyl protons (5.18 ppm) correlate with atoms C^2 (149.8 ppm) and C^{3a} (146.7 ppm), but have no correlation with atom C^5 (54.1 ppm). In the HMBC spectrum of compound **VII** in its turn appears a correlation peak of benzyl protons (4.2 ppm) only with atom C^2 (160.8 ppm). Besides the structure of the alkyl derivative **VII** was unambiguously proved by an independent synthesis: by hydrogenation of azomethine **IX** obtained by condensation of amine **IIe** with benzaldehyde (Scheme 3).

Scheme 3.



R = 4-MeOC$_6$H$_4$.

The formation of compound **VII** in the alkylation of amine **IIe** is somewhat unexpected for according to published data [12] the alkylation of aminotriazoles in neutral media occurrs at the nitrogen atoms of the heterocycle and does not involve the exocyclic amino group. In similar way behaves the majority of amino derivatives of azoles and azines where the amino group is conjugated with the "pyridine" nitrogen atom of the heterocycle [13]. It is presumable that compound **VII** forms from salt **VI** by a rearrangement proceeding by the type of Dimroth rearrangement. However the heating of solutions of pure salt **VI** in ethanol or DMF in the presence of acids or bases did not yield even traces of compound **VII**. Consequently, the alkyl derivative **VII** results from a direct attack of the alkylation agent on the amino group of compound **IIe**.

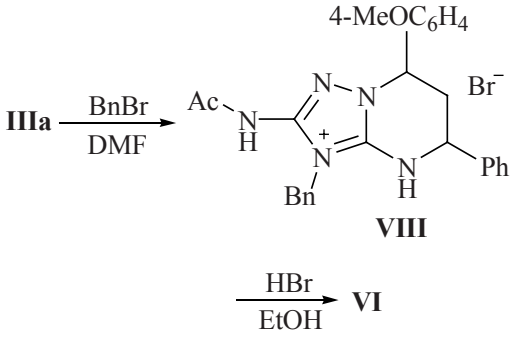
The more convenient preparative synthesis of compound **VI** consists in benzylation of acetyl derivative **IIIa** followed by hydrolysis of compound **VIII** with an aqueous-alcoholic solution of hydrobromic acid (Scheme 4).

The treatment of salt **VI** with an alcoholic solution of KOH yields 3-benzyl-3,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (**X**) that can also be obtained by alkaline hydrolysis of acetyl **VIII** (Scheme 5). The ^{1}H NMR spectrum of compound **X** contains a two-proton singlet of the amino group at 5.8 ppm, but the signal of the group N^{4}H is absent. Thus in the basic medium the deprotonation of salt **VI**, same as that of triazolopyrimidines **II**, occurs with the elimination of proton N^{4}H.

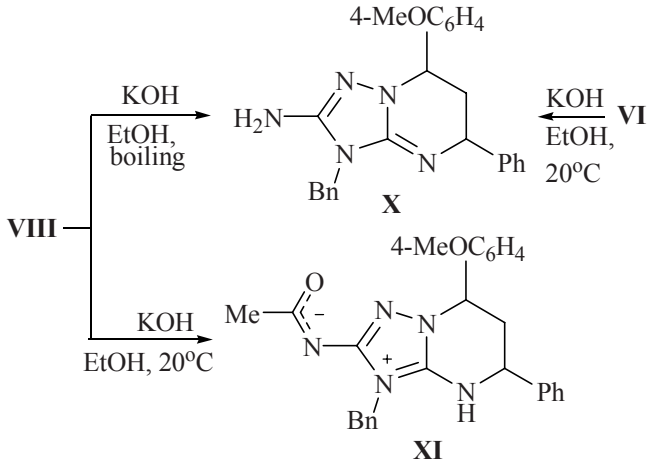
The treatment of compound **VIII** with alcoholic solution of KOH at cooling results in the formation of mesoionic compound **XI** (Scheme 5). The proton elimination in initial bromide **VIII** may occur both from the amide group and N^{4}H. Since the ^{1}H NMR spectrum did not unambiguously prove the structure of compound **XI**, we compared its acid-base characteristics with those of compound **X**. The basicity of compound **XI** (pK_a 7.90 ± 0.02) proved to be significantly lower than that of amine **X** (pK_a 9.79±0.05). We believe that if the dehydrobromination product obtained from compound **VIII** possesses the structure similar to compound **X**, the acetyl group should not so strongly affect the basicity. The structure **XI** is also consistent with the high solubility of this substance in polar and nonpolar solvents and with its yellow color, whereas compound **X** is colorless. For instance, it is known that the mesoionic compounds obtained by treating with bases 2-amino-3-alkyl-1,2,4-triazolo-[1,5-*a*]pyrimidinium salts also are colored substances [14].

The experimental findings obtained in this study suggest a conclusion on a high reactivity of 2-amino-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidines

Scheme 4.



Scheme 5.



toward electrophilic reagents and on the opportunity of purposeful modification of their structure by acylation, sulfonylation, and alkylation.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on spectrometers Varian Unity-300 (300 and 75 MHz respectively) and Bruker DRX-500 (500 and 125 MHz respectively), solvent DMSO-d_6, internal reference TMS. The assignment of ^{13}C NMR signals was performed based on heteronuclear correlation spectra HSQC and HMBC. Mass spectra were measured on an instrument Finnigan MAT INCOS-50 with a direct admission of the sample into the ion source, ionizing ions energy 70eV. The elemental analysis was carried out on an analyzer Perkin-Elmer 2400. Ionization constants of compounds **X** and **XI** were estimated by potentiometric titration of 0.01 M solutions in 80% ethanol at 23°C along procedure [15] applying a pH-meter pH-150M, glass electrode ESL-63-07, and reference electrode EVL-1M3. The melting points were measured on PTP device by the capillary method.

Initial compounds **Ia–Ie** were obtained by procedures [8, 16], **If**, by procedure [17].

2-Amino-4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidines IIa–IIe. To a dispersion of 1.5 mmol of an appropriate dihydrotriazolopyrimidine **Ia–Ie** in 5 ml of ethanol was added by portions within 30 min 0.11 g (3 mmol) of $NaBH_4$ powder at 50–60°C. After the end of gas evolution the reaction mixture was cooled and diluted with 20 ml of water, the separated precipitate was filtered off and crystallized from a mixture DMF–ethanol, 1:5.

2-Amino-5-methyl-7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIa). Yield 0.31 g (91%), mp >320°C. ^{1}H NMR spectrum, δ, ppm: 1.11 d (3H, CH_3, J 6.2 Hz), 1.65 m (1H, C^6H_2), 2.20 m (1H, C^6H_2), 3.49 m (1H, H^5), 4.77 s (2H, NH_2), 4.96 d.d (1H, H^7, $J_{6A,7}$ 4.8, $J_{6B,7}$ 11.0 Hz), 6.63 C (1H, NH), 7.12–7.34 m (5H, C_6H_5). ^{13}C, δ, ppm: 20.90 (CH_3), 41.43 (C^6), 45.64 (C^5), 57.95 (C^7), 127.02, 127.30, 128.21, 141.36, 154.55 (C^{3a}), 160.72 (C^2). Mass spectrum, *m/z* (I_{rel}, %): 229 (85.1) $[M]^+$, 131 (77.6), 125 (100), 115 (12.1), 99 (11.5), 91 (16.9), 43 (22.3). Found, %: C 62.73; H 6.69; N 30.58. $C_{12}H_{15}N_5$. Calculated, %: C 62.86; H 6.59; N 30.54. M 229.28.

2-Amino-5,7-diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIb). Yield 0.36 g (82%), mp 279–280°C. ^{1}H NMR spectrum, δ, ppm: 1.99 m (1H, C^6H_2), 2.33 m (1H, C^6H_2), 4.60 d.d (1H, H^5, $J_{5,6A}$ 1.9, $J_{5,6B}$ 11.4 Hz), 4.85 s (2H, NH_2), 5.12 d.d (1H, H^7, $J_{6A,7}$ 4.8, $J_{6B,7}$ 10.8 Hz), 7.03 s (1H, NH), 7.18–7.37 m ($8H_{arom}$), 7.42 m ($2H_{arom}$). Mass spectrum, *m/z* (I_{rel}, %): 291 (50.0) $[M]^+$, 193 (16.9), 186 (100), 115 (50.1), 104 (10.4), 90 (27.1), 43 (29.9). Found, %: C 70.13; H 5.92; N 23.95. $C_{17}H_{17}N_5$. Calculated, %: C 70.08; H 5.88; N 24.04. M 291.36.

2-Amino-5-(4-methylphenyl)-7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIc). Yield 0.35 g (77%), mp 223–224°C. ^{1}H NMR spectrum, δ, ppm: 1.97 m (1H, C^6H_2), 2.26 s (3H, CH_3), 2.30 m (1H, C^6H_2), 4.55 d (1H, H^5, J 11.1 Hz), 4.83 s (2H, NH_2), 5.11 d.d (1H, H^7, $J_{6A,7}$ 4.8, $J_{6B,7}$ 10.9 Hz), 6.97 s (1H, NH), 7.13 d (2H, C_6H_4, J 7.8 Hz), 7.08–7.34 m ($7H_{arom}$). Mass spectrum, *m/z* (I_{rel}, %): 305 (98.2) $[M]^+$, 207 (66.1), 200 (47.9), 192 (19.1), 186 (100), 129 (31.0), 115 (44.7), 91 (42.8), 43 (27.3). Found, %: C 71.00; H 6.33; N 22.66. $C_{18}H_{19}N_5$. Calculated, %: C 70.80; H 6.27; N 22.93. M 305.38.

2-Amino-7-phenyl-5-(4-chlorophenyl)-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IId).

Yield 0.35 g (71%), mp 239–240°C. ^{1}H NMR spectrum, δ, ppm: 1.99 m (1H, C^{6}H$_2$), 2.33 m (1H, C^{6}H$_2$), 4.61 d.d (1H, H^5, $J_{5,6A}$ 1.9, $J_{5,6B}$ 11.4 Hz), 4.86 s (2H, NH$_2$), 5.11 d.d (1H, H^7, $J_{6A,7}$ 4.3, $J_{6B,7}$ 10.6 Hz), 7.06 s (1H, NH), 7.19–7.31 m (5H, C$_6$H$_5$), 7.37 d (2H, C$_6$H$_4$, *J* 8.5 Hz), 7.44 d (2H, C$_6$H$_4$, *J* 8.5 Hz). Mass spectrum, *m/z* (I_{rel}, %): 325 (44.7) [*M*]$^+$, 220 (17.7), 192 (12.9), 186 (100), 115 (20.5), 101 (16.7), 59 (73.2), 43 (33.2). Found, %: C 62.74; H 4.99; N 21.78. $C_{17}H_{16}ClN_5$. Calculated, %: C 62.67; H 4.95; N 21.50. *M* 325.80.

2-Amino-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIe). Yield 0.36 g (74%), mp 282–283°C. ^{1}H NMR spectrum, δ, ppm: 1.99 m (1H, C^{6}H$_2$), 2.27 m (1H, C^{6}H$_2$), 3.70 s (3H, CH$_3$O), 4.58 d.d (1H NMR spectrum, H^5, $J_{5,6A}$ 1.8, $J_{5,6B}$ 11.4 Hz), 4.84 s (2H, NH$_2$), 5.06 d.d (1H, H^7, $J_{6A,7}$ 5.0, $J_{6B,7}$ 10.8 Hz), 6.84 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 6.99 s (1H, NH), 7.14 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.23–7.43 m (5H, C$_6$H$_5$). ^{13}C NMR spectrum, δ, ppm: 42.52 (C^6), 54.00 (C^5), 55.02 (CH$_3$O), 57.56 (C^7), 113.51, 126.47, 127.39, 128.20, 128.29, 132.56, 142.07, 154.57 (C^{3a}), 158.50, 160.61 (C^2). Mass spectrum, *m/z* (I_{rel}, %): 321 (39.8) [*M*]$^+$, 223 (15.3), 186 (100), 117 (22.1), 115 (12.6), 43 (26.1). Found, %: C 67.44; H 5.97; N 21.93. $C_{18}H_{19}N_5O$. Calculated, %: C 67.27; H 5.96; N 21.79. *M* 321.38.

2-Acetamido-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIIa). A mixture of 0.5 g (1.6 mmol) of amine **IIe**, 0.21 g (2.1 mmol) of acetic anhydride, and 3 ml of pyridine was boiled for 5 min, then it was diluted with 10 ml of water. The precipitate formed on cooling was filtered off and recrystallized from a mixture DMF–ethanol, 1:5. Yield 0.48 g (83%), mp 233–235°C. ^{1}H NMR spectrum, δ, ppm: 1.89 br.s (3H, CH$_3$), 2.07 m (1H, C^{6}H$_2$), 2.33 m (1H, C^{6}H$_2$), 3.71 s (3H, CH$_3$O), 4.66 d.d (1H, H^5, $J_{5,6A}$ 1.8, $J_{5,6B}$ 11.4 Hz), 5.25 d.d (1H, H^7, $J_{6A,7}$ 4.6, $J_{6B,7}$ 10.9 Hz), 6.87 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.16 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.23–7.46 m (5H, C$_6$H$_5$, 1H, NH), 9.96 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 363 (38.2) [*M*]$^+$, 321 (25.2), 229 (22.1), 223 (90.7), 186 (100), 115 (40.5), 43 (36.7). Found, %: C 66.29; H 5.91; N 19.02. $C_{20}H_{21}N_5O_2$. Calculated, %: C 66.10; H 5.82; N 19.27. *M* 363.42.

7-(4-Methoxyphenyl)-2-(*p*-toluenesulfonylamino)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidine (IIIb). A mixture of 0.5 g (1.6 mmol) of amine **IIe**, 0.36 g (1.9 mmol) of *p*-toluenesulfonyl chloride, and 3 ml of pyridine was boiled for 5 min, then it was diluted with 10 ml of water. The precipitate formed on cooling was filtered off and recrystallized from a mixture DMF–ethanol, 1:5. Yield 0.69 g (91%), mp 286–287°C. ^{1}H NMR spectrum, δ, ppm: 1.99 m (1H, C^{6}H$_2$), 2.29 m (1H, C^{6}H$_2$), 2.36 s (3H, CH$_3$), 3.74 s (3H, CH$_3$O), 4.61 d.d (1H, H^5, $J_{5,6A}$ 1.7, $J_{5,6B}$ 11.6 Hz), 5.19 d.d (1H, H^7, $J_{6A,7}$ 4.7, $J_{6B,7}$ 10.9 Hz), 6.85 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.06 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.22–7.45 m (7H$_{arom}$; 1H, NH), 7.66 d (2H, C$_6$H$_4$, *J* 8.3 Hz), 10.59 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.06 (CH$_3$), 41.98 (C^6), 53.75 (C^5), 55.17 (CH$_3$O), 57.95 (C^7), 113.67, 126.58, 127.18, 127.62, 128.44, 129.18, 131.65, 137.83, 141.65, 142.82, 152.62 (C^2), 154.69 (C^{3a}), 158.80. Mass spectrum, *m/z* (I_{rel}, %): 475 (48.6) [*M*]$^+$, 321 (20.9), 277 (78.8), 223 (100), 200 (80.1), 187 (66.2), 134 (57.0), 131 (62.5), 117 (57.4), 115 (30.7), 91 (65.6), 43 (13.2). Found, %: C 63.37; H 5.21; N 14.81. $C_{25}H_{25}N_5O_3S$. Calculated, %: C 63.14; H 5.30; N 14.73. *M* 475.57.

2-Benzamido-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIIc). To a dispersion of 0.5 g (1.6 mmol) of amine **IIe** in 2 ml of acetonitrile and 0.5 ml of pyridine was added while stirring at cooling to 0–5°C a solution of 0.25 g (1.8 mmol) of benzoyl chloride in 1 ml of acetonitrile. The reaction mixture was stirred for 30 min and then diluted with 10 ml of water, the separated precipitate was filtered off and recrystallized from ethanol. Yield 0.52 g (77%), mp 210–212°C. ^{1}H NMR spectrum δ, ppm: 2.14 m (1H, C^{6}H$_2$), 2.37 m (1H, C^{6}H$_2$), 3.71 s (3H, CH$_3$O), 4.71 d.d (1H, H^5, $J_{5,6A}$ 1.9, $J_{5,6B}$ 11.4 Hz), 5.31 d.d (1H, H^7, $J_{6A,7}$ 4.6, $J_{6B,7}$ 10.9 Hz), 6.88 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.20 d (2H, C$_6$H$_4$, *J* 8.6 Hz), 7.26–7.55 m (8H$_{arom}$; 1H, NH), 7.87 m (2H, C$_6$H$_5$), 10.37 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 42.03 (C^6), 53.86 (C^5), 55.05 (CH$_3$O), 58.12 (C^7), 113.72, 126.49, 127.50, 127.63, 128.16, 128.33, 128.45, 131.48, 131.69, 133.98, 141.69, 153.03 (C^2), 154.88 (C^{3a}), 158.80, 165.10 (CO). Mass spectrum, *m/z* (I_{rel}, %): 425 (22.3) [*M*]$^+$, 397 (24.2), 290 (16.8), 263 (25.4), 223 (45.8), 186 (26.4), 134 (21.0), 115 (15.1), 105 (94.3), 91 (25.6), 77 (100), 43 (33.4). Found, %: C 70.87; H 5.39; N 16.28. $C_{25}H_{23}N_5O_2$. Calculated, %: C 70.57; H 5.45; N 16.46. *M* 425.49.

4-Benzoyl-2-dibenzoylamino-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidine (IV). A mixture of 0.5 g (1.6 mmol) of amine **IIe**, 0.9 g (6.4 mmol) of benzoyl chloride, and 3 ml of pyridine was boiled for 30 min, then it was diluted with 10 ml of water. The precipitate formed on cooling was filtered off and recrystallized from a mixture DMF–

ethanol, 1:5. Yield 0.72 g (71%), mp 210–211°C. ^{1}H NMR spectrum, δ, ppm: 2.76 m (1H, C^{6}H$_2$), 3.10 m (1H, C^{6}H$_2$), 3.58 s (3H, CH$_3$O), 5.53 d.d (1H, H^5, $J_{5,6A}$ 3.1, $J_{5,6B}$ 6.7 Hz), 5.66 t (1H, H^7, J 4.2 Hz), 6.00 d (2H, C$_6$H$_4$, J 8.5 Hz), 6.25 d.d (2H, C$_6$H$_4$, J 8.5 Hz), 6.88–7.11 m (5H, C$_6$H$_5$), 7.31–7.69 m (15H, 3C$_6$H$_5$). ^{13}C NMR spectrum, δ, ppm: 36.51 (C^6), 54.65 (C^5), 54.86 (CH$_3$O), 56.63 (C^7), 112.83, 125.26, 126.57, 126.63, 127.77, 127.97, 128.59, 128.65, 128.73, 130.68, 131.51, 132.82, 133.04, 134.30, 138.13, 150.41 (C^{3a}), 153.73 (C^2), 157.47, 168.51 (CO), 170.81 (2CO). Found, %: C 73.67; H 5.05; N 11.19. $C_{39}H_{31}N_5O_4$. Calculated, %: C 73.92; H 4.93; N 11.05.

2-Amino-4-benzyl-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidine (V). A mixture of 0.5 g (1.6 mmol) of amine **IIe**, 0.1 g (1.8 mmol) of KOH powder, and 2 ml of DMSO was stirred for 15 min and then 0.3 g (1.7 mmol) of benzyl bromide was added. The reaction mixture was stirred for 30 min at room temperature, then 6 ml of water was added, the precipitated substance was filtered off, washed on the filter with 5 ml of water, and recrystallized from a mixture DMF–ethanol, 1:5. Yield 0.52 g (81%), mp 224–225°C. ^{1}H NMR spectrum, δ, ppm: 2.32 m (2H, C^{6}H$_2$), 3.71 s (3H, CH$_3$O), 3.86 d (1H, CH$_2$C$_6$H$_5$, J 15.5 Hz), 4.42 d.d (1H, C^{5}H, $J_{5,6A}$ 3.6, $J_{5,6B}$ 10.1 Hz), 4.82 d (1H, CH$_2$C$_6$H$_5$, J 15.5 Hz), 5.03 s (2H, NH$_2$), 5.11 m (1H, H^7), 6.83 d (2H, C$_6$H$_4$, J 8.7 Hz), 7.03 m (2H, C$_6$H$_5$), 7.17 d (2H, C$_6$H$_4$, J 8.7 Hz), 7.29–7.35 m (8H$_{arom}$). ^{13}C NMR spectrum, δ, ppm: 41.79 (C^6), 49.98 (CH$_2$C$_6$H$_5$), 55.01 (CH$_3$O), 56.82 (C^5), 57.97 (C^7), 113.42, 126.86, 127.39, 127.69, 128.04, 128.30, 128.34, 128.47, 132.08, 137.29, 139.62, 155.41 (C^{3a}), 158.53, 160.53 (C^2). Mass spectrum, *m/z* (I_{rel}, %): 411 (78.3) [M]$^+$, 276 (38.0), 223 (100), 186 (19.8), 115 (93.7), 91 (74.5), 43 (24.3). Found, %: C 73.11; H 6.18; N 17.23. $C_{25}H_{25}N_5O$. Calculated, %: C 72.97; H 6.12; N 17.02. M 411.51.

2-Amino-3-benzyl-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidinium bromide (VI). A mixture of 0.5 g (1.0 mmol) of acetyl derivative **VIII**, 2 ml of ethanol, and 0.5 ml of 40% hydrobromic acid was boiled for 2 h and then cooled. The settled precipitate was recrystallized from acetonitrile. Yield 0.45 g (85%), mp 209–210°C. ^{1}H NMR spectrum, δ, ppm: 2.35 m (1H, C^{6}H$_2$), 2.46 m (1H, C^{6}H$_2$), 3.74 s (3H, CH$_3$O), 4.91 d.d (1H, H^5, $J_{5,6A}$ 3.1, $J_{5,6B}$ 10.9 Hz), 5.18 s (2H, CH$_2$C$_6$H$_5$), 5.28 d.d (1H, H^7, $J_{6A,7}$ 4.2, $J_{6B,7}$ 10.5 Hz), 6.72 s (2H, NH$_2$), 6.90 d (2H, C$_6$H$_4$, J 8.6 Hz), 7.31–7.47 m (12H$_{arom}$), 9.24 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 39.8 (C^6), 44.31 (CH$_2$C$_6$H$_5$), 54.14 (C^5), 55.26 (CH$_3$O), 58.49 (C^7), 113.89, 126.99, 127.10, 128.02, 128.41, 128.72, 128.80, 128.99, 129.32, 134.26, 139.54, 146.73 (C^{3a}), 149.81 (C^2), 159.37. Found, %: C 70.17; H 5.20; N 14.27. $C_{25}H_{26}BrN_5O$. Calculated, %: C 60.98; H 5.32; N 14.22.

2-Benzylamino-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (VII). To a dispersion of 0.5 g (1.2 mmol) of azomethine **IX** in 5 ml of boiling ethanol was added by portions within 30 min 0.11 g (3 mmol) of NaBH$_4$ powder. After the end of hydrogen evolution 15 ml of water was poured into the reaction mixture, the separated precipitate was filtered off and recrystallized from ethanol. Yield 0.37 g (74%), mp 184–186°C. ^{1}H NMR spectrum, δ, ppm: 1.96 m (1H, C^{6}H$_2$), 2.30 m (1H, C^{6}H$_2$), 3.72 s (3H, CH$_3$O), 4.15 m (2H, CH$_2$C$_6$H$_5$), 4.60 d.d (1H, H^5, $J_{5,6A}$ 2.1, $J_{5,6B}$ 11.2 Hz), 5.12 d.d (1H, H^7, $J_{6A,7}$ 4.7, $J_{6B,7}$ 10.7 Hz), 6.04 t (1H, NH, J 5.9 Hz), 6.85 d (2H, C$_6$H$_4$, J 8.8 Hz), 7.13 d (2H, C$_6$H$_4$, J 8.8 Hz), 7.16–7.43 m (10H, 2C$_6$H$_5$; 1H, NH). ^{13}C NMR spectrum, δ, ppm: 42.66 (C^6), 46.06 (CH$_2$C$_6$H$_4$), 53.78 (C^5), 54.98 (CH$_3$O), 57.57 (C^7), 113.48, 126.19, 126.38, 127.09, 127.35, 127.82, 128.05, 128.24, 132.46, 141.01, 141.81, 154.37 (C^{3a}), 158.47, 160.79 (C^2). Mass spectrum, *m/z* (I_{rel}, %): 411 (100) [M]$^+$, 277 (91.2), 223 (78.7), 115 (35.0), 91 (35.5), 43 (40.1). Found, %: C 73.16; H 6.24; N 17.07. $C_{25}H_{25}N_5O$. Calculated, %: C 72.97; H 6.12; N 17.02. M 411.51.

2-Acetamido-3-benzyl-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidinium bromide (VIII). A mixture of 1.0 g (2.8 mmol) of finely dispersed acetyl derivative **IIIa**, 2 ml of DMF, and 0.52 g (3.0 mmol) of benzyl bromide was stirred for 3 h at 80°C, then it was diluted with 50 ml of water and cooled. After 3 days the settled precipitate was filtered off and recrystallized from acetonitrile. Yield 1.3 g (89%), mp 233–235°C. ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, CH$_3$), 2.45 m (2H, C^{6}H$_2$), 3.75 s (3H, CH$_3$O), 5.01 t (1H, H^5, J 6.8 Hz), 5.16 s (2H, CH$_2$C$_6$H$_5$), 5.45 t (1H, H^7, J 7.7 Hz), 6.93 d (2H, C$_6$H$_4$, J 8.6 Hz), 7.30–7.53 m (12H$_{arom}$), 9.69 s (1H, NH), 10.73 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 22.45 (CH$_3$), 38.67 (C^6), 46.22 (CH$_2$C$_6$H$_5$), 54.39 (C^5), 55.27 (CH$_3$O), 59.45 (C^7), 114.03, 127.25, 127.34, 128.12, 128.27, 128.56, 128.77, 128.82, 129.63, 133.61, 139.28, 141.87 (C^2), 148.43 (C^{3a}), 159.60, 170.50 (CO). Found, %: C 60.51; H 5.41; N 13.29. $C_{27}H_{28}BrN_5O_2$. Calculated, %: C 60.68; H 5.28; N 13.10.

Alkylation of compound (IIe). A mixture of 1.5 g (4.7 mmol) of amine **IIe**, 4 ml of DMF, and 0.86 g (5.0 mmol) of benzyl bromide was stirred for 3 h at 80°C. Then the solvent was distilled off in a vacuum, the residue was dissolved in 10 ml of chloroform and subjected to column chromatography on aluminum oxide (column 2.5×15 cm, eluent chloroform). We isolated 0.12 g (8%) of initial amine **IIe**, R_f 0.3, and 0.23 g (12%) of compound **VII**, R_f 0.5.

The sorbent after isolation of compounds **VII** and **IIe** was boiled in 200 ml of ethanol, filtered off, the filtrate was evaporated to a volume of 2–3 ml and diluted with 5 ml of water. The separated precipitate was filtered off and dried. We obtained 1.67 g (70%) of compound **VI**.

The properties of compounds obtained were identical to those synthesized by the above procedures.

2-Benzylydeneamino-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IX). A mixture of 1 g (3.2 mmol) of amine **IIe**, 0.36 g (3.4 mmol) of benzaldehyde, and 2 ml of DMF was boiled for 15 min. Then 5 ml of ethanol was added to the reaction mixture, and it was cooled. The settled precipitate was filtered off and washed on the filter with 5 ml of ethanol. Yield 1.1 g (82%), mp 198–199°C. ^{1}H NMR spectrum, δ, ppm: 2.16 m (1H, C^{6}H$_2$), 2.38 m (1H, C^{6}H$_2$), 3.74 s (3H, CH$_3$O), 4.74 d.d (1H, H^5, $J_{5,6A}$ 2.2, $J_{5,6B}$ 11.4 Hz), 5.06 d.d (1H, H^7, $J_{6A,7}$ 4.6, $J_{6B,7}$ 11.1 Hz), 6.91 d (2H, C$_6$H$_4$, J 8.5 Hz), 7.23 d (2H, C$_6$H$_4$, J 8.5 Hz), 7.26–7.60 m (8H$_{arom}$; 1H, NH), 7.89 m (2H$_{arom}$), 9.01 s (1H, CH=N). Mass spectrum, *m/z* (I_{rel}, %): 409 (76.6) $[M]^+$, 274 (92.8), 223 (100), 186 (28.9), 131 (34.7), 115 (44.1), 91 (25.1), 43 (11.4). Found, %: C 73.61; H 5.29; N 17.17. $C_{25}H_{23}N_5O$. Calculated, %: C 73.33; H 5.66; N 17.10. *M* 409.49.

2-Amino-3-benzyl-7-(4-methoxyphenyl)-5-phenyl-3,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidine (X). *a*. To a solution of 0.5 g (1.0 mmol) of compound **VI** in 1 ml of ethanol was added at stirring a solution of 0.06 g (1.1 mmol) of KOH in 1 ml of ethanol and then 5 ml of water. The separated precipitate was filtered off, washed on the filter with 5 ml of water, and recrystallized from ethanol. Yield 0.33 g (83%), mp 202–203°C. ^{1}H NMR spectrum, δ, ppm: 1.61 m (1H, C^{6}H$_2$), 2.32 m (1H, C^{6}H$_2$), 3.70 s (3H, CH$_3$O), 4.56 d.d (1H, H^5, $J_{5,6A}$ 2.5, $J_{5,6B}$ 11.4 Hz), 4.78 s (2H, CH$_2$C$_6$H$_4$), 4.90 d.d (1H, H^7, $J_{6A,7}$ 4.1, $J_{6B,7}$ 10.5 Hz), 5.79 s (2H, NH$_2$), 6.81 d (2H, C$_6$H$_4$, J 8.3 Hz), 7.10 d (2H, C$_6$H$_4$, J 8.3 Hz), 7.15 m (1H$_{arom}$), 7.22–7.43 m (9H$_{arom}$). ^{13}C NMR spectrum, δ, ppm: 42.55, 43.49, 55.10, 56.63, 57.85, 113.54, 125.96, 126.56, 127.20, 127.46, 127.83, 128.35, 128.41, 133.14, 137.53, 146.80, 148.15, 150.40, 158.50. Mass spectrum, *m/z* (I_{rel}, %): 411 (1.8) $[M]^+$, 276 (55.9), 119 (10.9), 116 (56.5), 91 (100), 65 (32.0), 39 (13.0). Found, %: C 73.19; H 5.96; N 17.20. $C_{25}H_{25}N_5O$. Calculated, %: C 72.97; H 6.12; N 17.02. *M* 411.51.

b. A mixture of 0.5 g (0.9 mmol) of acetyl derivative **VIII**, 0.16 g (2.7 mmol) of KOH, and 3 ml of ethanol was boiled for 2 h and then cooled. The reaction product was isolated as described above. Yield 0.29 g (75%).

***N*-{3-Benzyl-7-(4-methoxyphenyl)-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]-pyrimidin-2-yl}acetamidate (XI)**. To a solution of 0.5 g (0.9 mmol) of compound **VIII** in 2 ml of ethanol was added a solution of 0.05 g (0.95 mmol) of KOH in 1 ml of ethanol, then 10 ml of water. The reaction product was extracted into chloroform (10 ml), the extract was washed with water, dried over sodium sulfate, and chloroform was distilled off. To the residue 3 ml of hexane was poured, the formed crystalline precipitate was filtered off. Yield 0.13 g (31%), mp 146–148°C. ^{1}H NMR spectrum, δ, ppm: 1.90 s (1H, CH$_3$), 2.41 m (2H, C^{6}H$_2$), 3.72 s (3H, CH$_3$O), 4.73 m (1H, H^5), 4.85 s (2H, CH$_2$C$_6$H$_5$), 5.22 m (1H, H^7), 6.87 d (2H, C$_6$H$_4$, J 8.5 Hz), 7.20 d (2H, C$_6$H$_4$, J 8.5 Hz), 7.28–7.44 m (10H$_{arom}$), 10.22 br.s (1H, NH). Found, %: C 71.19; H 5.94; N 15.62. $C_{27}H_{27}N_5O_2$. Calculated, %: C 71.50; H 6.00; N 15.44.

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