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Synthesis of 3,5-Disubstituted 1,2,4-Triazoles Containing an Amino Group

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Abstract—3,5-Disubstituted 1,2,4-triazoles containing linear and cyclic amine fragments have been synthesized by thermal cyclization of *N*′-(1-iminoalkyl) hydrazides prepared by condensation of imido esters with carboxylic acid hydrazides. The initial imido esters have been synthesized by the Pinner reaction, as well as by reaction of nitriles with methanol in the presence of a catalytic amount of sodium methoxide. A procedure has been developed for the synthesis of 5-substituted 3-(3-nitrophenyl)-1,2,4-triazoles which have been converted to 3-aminophenyl derivatives by reduction with hydrazine hydrate over Raney nickel.

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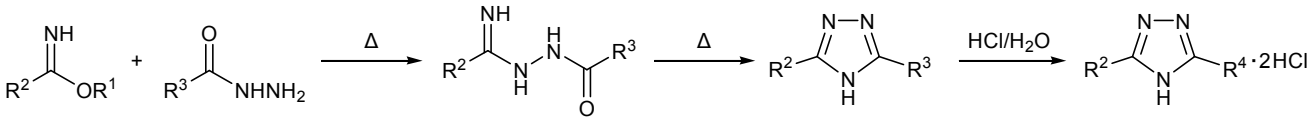
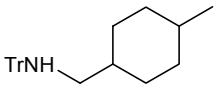
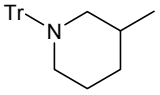
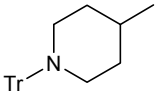
Development of methods for the synthesis of 3,5-disubstituted 1,2,4-triazoles is important from the practical viewpoint. These compounds attract interest for medicinal chemistry and are promising as new drugs due to their various biological activities, including fungicidal and antiviral [1]. Substituted 1,2,4-triazoles are widely used in medicine as some receptor agonists or antagonists with both donor and acceptor properties [2]. 1,2,4-Triazole system constitutes a structural fragment of potential therapeutic agents, such as 3-amino-1,2,4-triazole derivative ATZ and 3-sulfanyl-1,2,4-triazole derivative MTZ [3, 4]. 1,2,4-Triazole fragments were introduced into peptide molecules to surrogate *cis*-amide bonds in an attempt to increase the bioavailability of the parent bioactive molecules [5, 6].

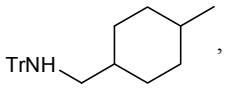
Scheme 1.

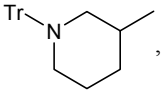
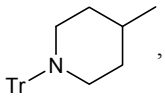


1a–1l **2a–2e** **3a–3t** **4a–4t** **5a–5t**

1, R^1 = Et, R^2 = 3,4,5-$(MeO)_3C_6H_2$ (**a**), 4-$MeOC_6H_4(CH_2)_2$ (**b**), 3,4-$Cl_2C_6H_3CH_2$ (**c**); R^1 = Me, R^2 = 3,4-$Cl_2C_6H_3$ (**d**); R^1 = Et, R^2 = Ph_2CHCH_2 (**e**), 3,4-$(MeO)_2C_6H_3CH_2$ (**f**), 3-EtO-4-$MeOC_6H_3CH_2$ (**g**); R^1 = Me, R^2 = pyridin-3-yl (**h**), pyridin-4-yl (**i**); R^1 = Et, R^2 = pyridin-3-ylmethyl (**j**), cyclopropyl (**k**), 1-(4-chlorophenyl)cyclopropyl (**l**);

2, R^3 = $TrNH(CH_2)_2$ (**a**), $TrNH(CH_2)_3$ (**b**),  (**c**),  (**d**),  (**e**);

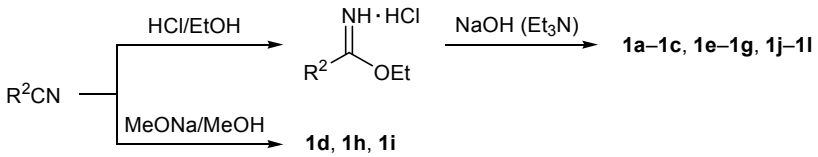
3, **4**, R^3 = $TrNH(CH_2)_2$, R^2 = 3,4,5-$(MeO)_3C_6H_2$, (**a**), 4-$MeOC_6H_4(CH_2)_2$ (**b**), 3,4-$Cl_2C_6H_3CH_2$ (**c**), 3,4-$Cl_2C_6H_3$ (**d**), Ph_2CHCH_2 (**e**), pyridin-3-yl (**f**), pyridin-3-ylmethyl (**g**), cyclopropyl (**h**), 1-(4-chlorophenyl)cyclopropyl (**i**); R^3 = $TrNH(CH_2)_3$, R^2 = 3,4-$Cl_2C_6H_3$ (**j**), 3-EtO-4-$MeOC_6H_3CH_2$ (**k**), cyclopropyl (**l**), 1-(4-chlorophenyl)cyclopropyl (**m**); R^3 =  , R^2 = cyclopropyl (**n**);

R^3 =  , R^2 = 4-$MeOC_6H_4(CH_2)_2$ (**o**), 3,4-$Cl_2C_6H_3CH_2$ (**p**), cyclopropyl (**q**); R^3 =  ,

R^2 = 4-$MeOC_6H_4(CH_2)_2$ (**r**), 3,4-$(MeO)_2C_6H_3CH_2$ (**s**), pyridin-4-yl (**t**).

Tr = Ph_3C; R^2 and R^4 in **5** are the same as R^2 and R^3 (with H instead of Tr), respectively, in **3** and **4**.

Scheme 2.



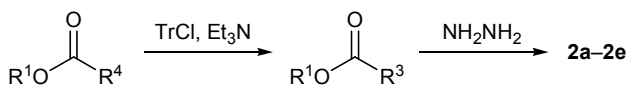
Several methods for the synthesis of 3,5-disubstituted 1,2,4-triazoles are known. The most general of these is based on the reaction of hydrazine or substituted hydrazines with appropriate electrophile [7–9]. Another approach leading to 1,2,4-triazole ring closure involves reaction of *N*-cyanoformimidates with hydrazine derivatives in triethylamine [10–12]. 4-Substituted 5-aryl-1,2,4-triazoles can be synthesized by cyclization of the corresponding thiosemicarbazides [13–15].

In this work we synthesized 3,5-disubstituted 1,2,4-triazoles **5a**–**5t** containing linear and cyclic amine fragments by cyclization of *N*′-(1-iminoalkyl)-hydrazides **3a**–**3t** which were prepared by condensation of the corresponding imidic esters **1a**–**1l** with carbohydrazides **2a**–**2e** possessing a trityl-protected amino group (modified Pellizzari reaction) (Scheme 1). The reactions were carried out by heating the reactants to the melting point under slightly reduced pressure in the absence of a solvent. After the cyclization, the trityl protection was removed by treatment with dilute (1:3) aqueous HCl.

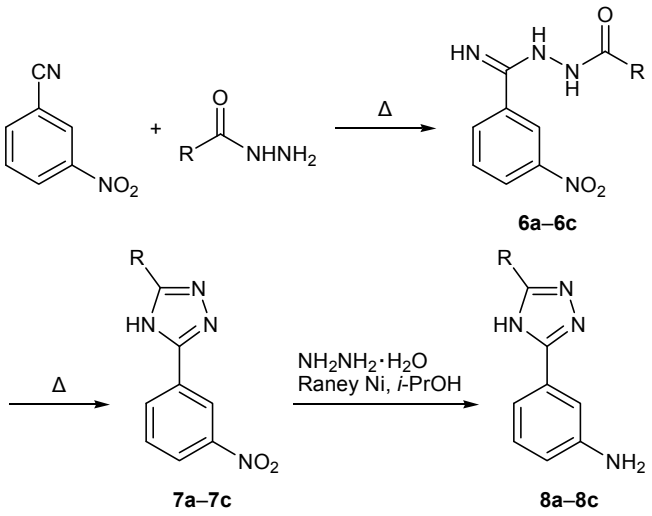
Imidic esters **1a**–**1l** were prepared from the corresponding nitriles in two ways (Scheme 2): (1) by bubbling gaseous HCl through a solution of nitrile in ethanol, followed by neutralization of the resulting hydrochloride with alkali or triethylamine (Pinner reaction; compounds **1a**–**1c**, **1e**–**1g**, **1j**–**1l**), and (2) by reaction of nitriles with methanol in the presence of a catalytic amount of metallic sodium (**1d**, **1h**, **1i)** [16]. Imidates **1a**–**1l** were brought into reaction with hydrazides **2a**–**2e** without additional purification.

3-Aminopropanoic (β-alanine), 4-aminobutyric, 4-(aminomethyl)cyclohexanecarboxylic, and piperidine-3- and piperidine-4-carboxylic acid hydrazides were prepared from the corresponding esters. The amino group therein was preliminarily protected by tritylation (Scheme 3). 3,5-Disubstituted 1,2,4-triazoles containing a 3-aminophenyl group were synthesized as shown in Scheme 4. 3-Nitrobenzonitrile was converted to imidoester by treatment with a solution of sodium methoxide in methanol. The nitro group was reduced to amino with hydrazine hydrate over Raney nickel in isopropyl alcohol.

Scheme 3.



Scheme 4.



R = Me (**a**), H (**b**), Et (**c**).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-360 spectrometer at 360.13 MHz using tetramethylsilane as internal standard. The progress of reactions was monitored by TLC on Kieselgel 60 F_{254} plates (Merck) using chloroform–methanol (9:1) as eluent; compounds containing an aromatic ring were detected under UV light; the others were detected by treatment with iodine vapor.

Ethyl 3-aminopropanoate, ethyl 4-aminobutyrate, ethyl 4-(aminomethyl)cyclohexanecarboxylate, ethyl piperidine-3-carboxylate, ethyl piperidine-4-carboxylate, and 3,4,5-trimethoxybenzonitrile were commercial products (Aldrich). The solvents used were purified according to [17].

Ethyl 3,4,5-trimethoxybenzene-1-carboximidate (1a). Gaseous hydrogen chloride was bubbled through a solution of 35.8 g (0.185 mol) of 3,4,5-trimetoxybenzonitrile and 15 mL of anhydrous ethanol in 150 mL of diethyl ether cooled to 0–5°C until a gain in

weight of 8 g. The mixture was kept for 48 h at 3–5°C, and the precipitate was filtered off and washed with diethyl ether (3×20 mL). Yield of **1a** hydrochloride 45.7 g (89%). The product was mixed with 100 mL of water and 150 mL of diethyl ether, the mixture was cooled to 4–8°C, and 15 g of sodium hydrogen carbonate was added with stirring. The mixture was stirred for 10 min, the organic phase was separated and dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield 38g (85%). Compound **1a** was then used without additional purification.

Compounds **1b** (yield 80%), **1c** (98%), **1d** (86%), **1e** (81%), **1f (**69%), **1g** (92%), **1h** (83%), **1i** (98%), and **1j** (67%) were synthesized in a similar way. Carboximidates **1k** (87%) and **1l** (85%) were used as hydrochlorides.

Ethyl 1-(triphenylmethyl)piperidine-4-carboxylate. Chloro(triphenyl)methane, 33.4 g (0.12 mol), was added in portions with stirring to a solution of 19 g (0.12 mol) of ethyl piperidine-4-carboxylate and 12.2 g (0.12 mol) of triethylamine in 150 mL of anhydrous chloroform. The mixture spontaneously warmed up to 60°C and was stirred for 12 h at 20°C. It was then washed with water (3×50 mL) and dried over magnesium sulfate, and the solvent was removed under reduced pressure. Yield 46.9 g (98%). The product was used without additional purification.

N-Trityl derivatives of 3-aminopropionic (90%), 4-aminobutyric (86%), 4-(aminomethyl)cyclohexane-1-carboxylic (96%), and piperidine-3-carboxylic acid esters (90%) were synthesized in a similar way.

3-(Triphenylmethylamino)propanehydrazide (2a). A mixture of 39.5 g (0.11 mol) of ethyl 3-(triphenylmethylamino)propanoate, 70 mL of ethanol, 50 mL of dioxane, and 30 mL of hydrazine hydrate was refluxed for 25 h until the initial ester disappeared (TLC). The mixture was poured into 300 mL of water, and the precipitate was filtered off and dried under reduced pressure. Yield 33.4 g (88%).

Carbohydrazides **2b** (91%), **2c** (84%), **2d** (90%), and **2e** (91%) were synthesized in a similar way.

2-[5-(3,4,5-Trimethoxyphenyl)-4*H*-1,2,4-triazol-3-yl]-*N*-(triphenylmethyl)ethan-1-amine (4a). Triethylamine, 22 g (0.2 mol), was added with stirring to a solution of 39.9 g (0.145 mol) of **1a** hydrochloride in 300 mL of benzene. The precipitate was filtered off, 41.5 g (0.12 mol) of hydrazide **2a** was added to the filtrate, and the mixture was refluxed for 2 h. After cooling to 20°C, the mixture crystallized. The precipitate of **3a** was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 70.2 g (93%). Compound **3a** was then heated under reduced pressure (20 mm) until a melt was obtained (180°C). Yield 67.6 g (90%).

Triazoles **4b**–**4e**, **4g**–**4i**, **4k**–**4o**, and **4q**–**4s** were synthesized in a similar way.

2-[5-(3,4-Dichlorophenyl)-4*H*-1,2,4-triazol-3-yl]-*N*-(triphenylmethyl)ethan-1-amine (4d). A solution of 0.05 g (2 mmol) of sodium in 10 mL of methanol was added to a solution of 16.2 g (0.094 mol) of 3,4-dichlorobenzonitrile in 50 ml of methanol, the mixture was stirred for 1 h at 20°C, a solution of 32.5 g (94 mmol) of carbohydrazide **2a** in 150 mL of methanol was added, and the mixture was stirred for 15 h at 40–50°C. The precipitate was filtered off and washed with methanol (2×10 ml). Yield of **3a** 41.3 g (88%), R_f 0.35. The product, 41.3 g (0.083 mol) was heated under reduced pressure (10–15 mm) to obtain a melt (210°C), and heating was continued at that temperature until water no longer evolved (10–15 min). The melt was cooled and treated with 20 mL of diethyl ether, and the precipitate was filtered off. Yield 29.8 g (72%).

Triazoles **4f** (85%), **4j** (80%), **4p** (91%), and **4t** (94%) were synthesized in a similar way.

2-[5-(3,4,5-Trimethoxyphenyl)-4*H*-1,2,4-triazol-3-yl]ethan-1-amine hydrochloride (5a). A mixture of 45.8 g (0.088 mol) of triazole **4a** and 300 mL of 10% aqueous HCl was stirred for 3 h at 50–60°C. The precipitate was filtered off and washed with water (2×40 mL), the filtrate was evaporated under reduced pressure (10–15 mm), and the residue was recrystallized from ethanol. Yield 26.4 g (90%). ^{1}H NMR spectrum (D_2O), δ, ppm: 3.02–3.16 m (2H, CH_2C), 3.11–3.24 m (2H, CH_2N), 3.70 s (3H, OCH_3), 3.83 s (6H, OCH_3), 7.32 s (2H, CH). Found, %: C 49.64; H 6.05; Cl 11.24; N 17.84. $C_{13}H_{18}N_4O_3 \cdot HCl$. Calculated, %: C 49.60; H 6.08; Cl 11.26; N 17.80.

To obtain the corresponding base, 5 g of hydrochloride **5a** was added with stirring to 20 mL of anhydrous ethanol, 5 mL of sodium methoxide solution prepared from 0.34 g of sodium was added, and the mixture was left to stand for 12 h. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure. Yield 3.9 g (88%).

Hydrochlorides **5b**–**5t** were synthesized in a similar way.

2-{5-[2-(4-Methoxyphenyl)ethyl]-4*H*-1,2,4-triazol-3-yl}ethan-1-amine hydrochloride (5b). Yield

76%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.01–3.12 m (2H, CH_2C), 3.08–3.20 m (2H, CH_2N), 3.20–3.27 m (4H, CH_2), 3.69 s (3H, OCH_3), 6.84 d and 7.16 d (2H each, H_{arom}, J = 7.4 Hz), 8.42 br.s (3H, NH, NH_2). Found, %: C 55.27; H 6.79; Cl 12.49; N 19.80. $C_{13}H_{18}N_4O \cdot HCl$. Calculated, %: C 55.22; H 6.77; Cl 12.54; N 19.81.

2-{5-[(3,4-Dichlorophenyl)methyl]-4*H*-1,2,4-triazol-3-yl}ethan-1-amine hydrochloride (5c). Yield 84%. ^{1}H NMR spectrum (D_2O), δ, ppm: 3.27 t (2H, CH_2C, J = 6.9 Hz), 3.42 t (2H, CH_2N, J = 6.9 Hz), 4.30 s (2H, CH_2), 7.20 d (1H, H_{arom}, J = 6.9 Hz), 7.47 d (1H, H_{arom}, J = 6.9 Hz), 7.49 s (1H, H_{arom}), 8.41 br.s (3H, NH, NH_2). Found, %: C 42.99; H 4.23; Cl 34.54; N 18.24. $C_{11}H_{12}Cl_2N_4 \cdot HCl$. Calculated, %: C 42.95; H 4.26; Cl 34.58; N 18.21.

2-[5-(3,4-Dichlorophenyl)-4*H*-1,2,4-triazol-3-yl]-ethan-1-amine hydrochloride (5d). Yield 72%. ^{1}H NMR spectrum (D_2O), δ, ppm: 3.13 t (2H, CH_2C, J = 6.9 Hz), 3.35 t (2H, CH_2N, J = 6.9 Hz), 7.19–7.31 m (2H, H_{arom}), 7.40 s (1H, H_{arom}), 8.39 br.s (3H, NH, NH_2). Found, %: C 40.87; H 3.81; Cl 36.20; N 19.12. $C_{10}H_{10}Cl_2N_4 \cdot HCl$. Calculated, %: C 40.91; H 3.78; Cl 36.23; N 19.08.

2-[5-(2,2-Diphenylethyl)-4*H*-1,2,4-triazol-3-yl]-ethan-1-amine hydrochloride (5e). Yield 65%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.12–3.28 m (4H, CH_2), 3.67 d (2H, CH_2, J = 6.9 Hz), 4.89 t (1H, CH, J = 6.9 Hz), 7.16 t (2H, H_{arom}, J = 7.0 Hz), 7.22–7.29 m (4H, H_{arom}), 7.32–7.37 m (4H, H_{arom}), 8.36 br.s (3H, NH, NH_2). Found, %: C 65.77; H 6.47; Cl 10.74; N 17.02. $C_{18}H_{20}N_4 \cdot HCl$. Calculated, %: C 65.74; H 6.44; Cl 10.78; N 17.04.

2-[5-(Pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl]ethan-1-amine (5f). Yield 85%. ^{1}H NMR spectrum (D_2O), δ, ppm: 3.23 t (2H, CH_2C, J = 6.9 Hz), 3.40 t (2H, CH_2N, J = 6.9 Hz), 8.05–8.11 m (1H, H_{arom}), 8.76 d (1H, H_{arom}, J = 7.3 Hz), 9.09 d (1H, H_{arom}, J = 7.3 Hz), 9.23 s (1H, H_{arom}). Found, %: C 57.17; H 5.83; N 37.00. $C_9H_{11}N_5$. Calculated, %: C 57.13; H 5.86; N 37.01.

2-{5-[(Pyridin-3-yl)methyl]-4*H*-1,2,4-triazol-3-yl}ethan-1-amine hydrochloride (5g). Yield 91%. ^{1}H NMR spectrum (D_2O), δ, ppm: 3.06 t (2H, CH_2C, J = 6.9 Hz), 3.32 t (2H, CH_2N, J = 6.9 Hz), 4.11 s (2H, CH_2), 7.31–7.41 m (1H, H_{arom}), 7.70 d (1H, H_{arom}, J = 7.3 Hz), 8.32–8.40 m (2H, H_{arom}). Found, %: C 50.08; H 5.91; Cl 14.76; N 29.25. $C_{10}H_{13}N_5 \cdot HCl$. Calculated, %: C 50.11; H 5.89; Cl 14.79; N 29.22.

2-(5-Cyclopropyl-4*H*-1,2,4-triazol-3-yl)ethan-1-amine hydrochloride (5h). Yield 17 g (79%). ^{1}H NMR spectrum (D_2O), δ, ppm: 0.96–1.05 m (2H, CH_2), 1.14–1.20 m (2H, CH_2), 2.12–2.21 m (1H, CH), 3.15 t (2H, CH_2C, J = 6.9 Hz), 3.45 m (2H, CH_2N). Found, %: C 55.29; H 7.93; N 36.78. $C_7H_{12}N_4 \cdot HCl$. Calculated, %: C 55.24; H 7.95; N 36.81.

2-{5-[1-(4-Chlorophenyl)cyclopropyl]-4*H*-1,2,4-triazol-3-yl}ethan-1-amine hydrochloride (5i). Yield 74%. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.75–1.86 m (4H, CH_2), 3.32 m (2H, CH_2C, J = 6.9 Hz), 3.52 m (2H, CH_2N, J = 6.9 Hz), 7.45–8.56 m (4H, H_{arom}). Found, %: C 52.23; H 5.41; Cl 23.66; N 18.70. $C_{13}H_{15}ClN_4 \cdot HCl$. Calculated, %: C 52.19; H 5.39; Cl 23.70; N 18.73.

3-[5-(3,4-Dichlorophenyl)-4*H*-1,2,4-triazol-3-yl]-propan-1-amine hydrochloride (5j). Yield 80%. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.13–2.17 m (2H, CH_2), 2.96 t (2H, CH_2C, J = 6.9 Hz), 3.10 t (2H, CH_2N, J = 6.9 Hz), 7.37–7.42 m (2H, H_{arom}), 7.55–7.57 m (1H, H_{arom}). Found, %: C 43.01; H 4.22; Cl 34.58; N 18.19. $C_{11}H_{12}Cl_2N_4 \cdot HCl$. Calculated, %: C 42.95; H 4.26; Cl 34.58; N 18.21.

3-{5-[(3-Ethoxy-4-methoxyphenyl)methyl]-4*H*-1,2,4-triazol-3-yl}propan-1-amine hydrochloride (5k). Yield 68%. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.27 t (3H, CH_3, J = 8.0 Hz), 2.03–2.07 m (2H, CH_2), 2.93 t (2H, CH_2C, J = 6.9 Hz), 3.01 t (2H, CH_2N, J = 6.9 Hz), 3.47 s (3H, OCH_3), 3.98–4.00 m (2H, CH_2), 4.17 s (2H, CH_2), 6.84–7.01 m (3H, H_{arom}). Found, %: C 55.16; H 7.12; Cl 10.82; N 17.13. $C_{15}H_{22}N_4O_2 \cdot HCl$. Calculated, %: C 55.13; H 7.09; Cl 10.85; N 17.14.

3-(5-Cyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-1-amine hydrochloride (5l). Yield 76%. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.34–1.42 m (2H, CH_2), 1.50–1.60 m (2H, CH_2), 2.30 m (2H, CH_2), 2.43–2.47 m (1H, CH), 3.11–3.18 m (2H, CH_2C), 3.25–3.29 m (2H, CH_2N). Found, %: C 47.37; H 7.48; Cl 17.45; N 27.70. $C_8H_{14}N_4 \cdot HCl$. Calculated, %: C 47.41; H 7.46; Cl 17.49; N 27.64.

3-{5-[1-(4-Chlorophenyl)cyclopropyl]-4*H*-1,2,4-triazol-3-yl}propan-1-amine hydrochloride (5m). Yield 94%. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.70–1.80 m (4H, CH_2), 2.19 m (2H, CH_2), 3.05 t (2H, CH_2C, J = 6.9 Hz), 3.17 t (2H, CH_2N, J = 6.9 Hz), 7.49–7.55 m (4H, H_{arom}). Found, %: C 53.71; H 5.75; Cl 22.62; N 17.92. $C_{14}H_{17}ClN_4 \cdot HCl$. Calculated, %: C 53.68; H 5.79; Cl 22.64; N 17.89.

1-[4-(5-Cyclopropyl-4*H*-1,2,4-triazol-3-yl)cyclohexyl]methanamine hydrochloride (5n). Yield 76%. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.14–1.18 m (2H, CH_2), 1.22–1.26 m (2H, CH_2), 1.32–1.36 m (2H, CH_2),

1.59–1.65 m (2H, CH_2), 1.78–1.83 m (1H, CH), 1.95–2.01 m (2H, CH_2), 2.17–2.23 m (2H, CH_2), 2.23–2.28 m (1H, CH), 2.94–2.97 m (2H, CH_2), 3.00–3.05 m (1H, CH). Found, %: C 56.16; H 8.20; Cl 13.79; N 21.85. $C_{12}H_{20}N_4 \cdot HCl$. Calculated, %: C 56.13; H 8.24; Cl 13.81; N 21.82.

3-{5-[2-(4-Methoxyphenyl)ethyl]-4*H*-1,2,4-triazol-3-yl}piperidine hydrochloride (5o). Yield 83%. ^1H NMR spectrum (D_2O), δ, ppm: 1.90–2.20 m (4H, CH_2), 3.10–3.69 m (9H, CH, CH_2), 3.79 s (3H, OCH_3), 6.90 d and 7.10 d (2H each, H_{arom}, J = 7.4 Hz). Found, %: C 59.56; H 7.20; Cl 10.94; N 17.34. $C_{16}H_{22}N_4O \cdot HCl$. Calculated, %: C 59.53; H 7.18; Cl 10.98; N 17.35.

3-[5-(3,4-Dichlorophenyl)-4*H*-1,2,4-triazol-3-yl]-piperidine hydrochloride (5p). Yield 91%. ^1H NMR spectrum (D_2O), δ, ppm: 1.84–1.88 m (2H, CH_2), 2.06–2.10 m (1H, CH_2), 2.22–2.26 m (1H, CH_2), 3.07–3.12 m (1H, CH), 3.22–3.25 m (1H, CH_2), 3.35–3.39 m (1H, CH_2), 3.48–3.53 m (1H, CH_2), 3.70–3.73 m (1H, CH_2), 7.18–7.22 m (1H, H_{arom}), 7.25–7.27 m (1H, H_{arom}), 7.35 d (1H, H_{arom}, J = 7.4 Hz). Found, %: C 46.84; H 4.55; Cl 31.85; N 16.76. $C_{13}H_{14}Cl_2N_4 \cdot HCl$. Calculated, %: C 46.80; H 4.53; Cl 31.88; N 16.79.

3-(5-Cyclopropyl-4*H*-1,2,4-triazol-3-yl)piperidine hydrochloride (5q). Yield 76%. ^1H NMR spectrum (D_2O), δ, ppm: 1.24–1.27 m (2H, CH_2), 1.46–1.49 m (2H, CH_2), 1.92–1.96 m (2H, CH_2), 2.03–2.08 m (1H, CH), 2.30–2.33 m (1H, CH_2), 2.35–2.38 m (1H, CH), 3.13–3.19 m (1H, CH_2), 3.47–3.78 m (4H, CH_2). Found, %: C 52.54; H 7.47; Cl 15.53; N 24.46. $C_{10}H_{16}N_4 \cdot HCl$. Calculated, %: C 52.51; H 7.49; Cl 15.50; N 24.50.

4-{5-[2-(4-Methoxyphenyl)ethyl]-4*H*-1,2,4-triazol-3-yl}piperidine hydrochloride (5r). Yield 90%. ^1H NMR spectrum (D_2O), δ, ppm: 2.03–2.07 m (2H, CH_2), 2.33–2.37 m (2H, CH_2), 3.13–3.15 m (2H, CH_2), 3.25–3.29 m (2H, CH_2), 3.35–3.43 m (3H, CH, CH_2), 3.56–3.63 m (2H, CH_2), 3.86 s (3H, OCH_3), 7.00 d and 7.19 d (2H each, H_{arom}, J = 7.4 Hz). Found, %: C 59.54; H 7.14; Cl 11.01; N 17.34. $C_{16}H_{22}N_4O \cdot HCl$. Calculated, %: C 59.53; H 7.18; Cl 10.98; N 17.35.

4-{5-[(3,4-Dimethoxyphenyl)methyl]-4*H*-1,2,4-triazol-3-yl}piperidine hydrochloride (5s). Yield 89%. ^1H NMR spectrum (D_2O), δ, ppm: 2.04–2.13 m (2H, CH_2), 2.38–2.43 m (2H, CH_2), 3.24–3.28 m (2H, CH_2), 3.40–3.43 m (1H, CH), 3.59–3.64 m (2H, CH_2), 3.91 s (6H, OCH_3), 4.34 s (2H, CCH_2C), 7.01–7.14 m (3H, H_{arom}). Found, %: C 56.75; H 6.82; Cl 10.45; N 16.57. $C_{16}H_{22}N_4O_2 \cdot HCl$. Calculated, %: C 56.72; H 6.84; Cl 10.46; N 16.54.

4-[5-(Piperidin-4-yl)-4*H*-1,2,4-triazol-3-yl]pyridine hydrochloride (5t). Yield 94%. ^1H NMR spectrum (D_2O), δ, ppm: 1.93–1.98 m (2H, CH_2), 2.20–2.26 m (2H, CH_2), 3.09 t (2H, CH_2, J = 7.0 Hz), 3.26–3.30 m (1H, CH), 3.43–3.50 m (2H, CH_2), 8.40 d and 8.75 d (2H each, H_{arom}, J = 7.4 Hz). Found, %: C 54.27; H 6.04; Cl 13.33; N 26.36. $C_{12}H_{15}N_5 \cdot HCl$. Calculated, %: C 54.24; H 6.07; Cl 13.34; N 26.35.

***N′*-[Imino(3-nitrophenyl)methyl]acetohydrazide (6a).** 3-Nitrobenzonitrile, 65 g (0.4 mol), was dissolved in 300 mL of methanol, 0.6 g (0.017 mol) of sodium and 74 g (0.6 mol) of acetohydrazide were added, and the mixture was stirred for 15 h at 40–50°C. The precipitate was filtered off and washed with methanol (2×40 mL). Yield 78 g (80%). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.92 s and 2.15 s (3H, CH_3), 6.65 br.s (2H, NH), 7.67–7.71 m (1H, H_{arom}), 8.20–8.25 m (2H, H_{arom}), 8.58–8.61 m (1H, H_{arom}), 9.68 s and 9.78 s (1H, NH). Found, %: C 48.68; H 4.56; N 25.18. $C_9H_{10}N_4O_3$. Calculated, %: C 48.65; H 4.54; N 25.21.

Hydrazides **6b** (86%) and **6c** (84%) were synthesized in a similar way.

3-Methyl-5-(3-nitrophenyl)-4*H*-1,2,4-triazole (7a). Hydrazide **6b**, 8 g (0.32 mol), was heated under reduced pressure (20 mm) until a melt was obtained (170–200°C). Yield 69.9 g (98%). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 s (3H, CH_3), 7.22 d (1H, H_{arom}, J = 7.5 Hz), 7.75 t (1H, H_{arom}, J = 7.5 Hz), 8.25 d (1H, H_{arom}, J = 7.5 Hz), 8.71 s (1H, CH), 13.90 br.s (1H, NH). Found, %: C 52.89; H 3.98; N 27.41. $C_9H_8N_4O_2$. Calculated, %: C 52.94; H 3.95; N 27.44.

3-(3-Nitrophenyl)-4*H*-1,2,4-triazole (7b) was synthesized in a similar way at 190–200°C. Yield 96%. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.76 t (1H, H_{arom}, J = 7.5 Hz), 8.24 d (1H, H_{arom}, J = 7.5 Hz), 8.42 d (1H, H_{arom}, J = 7.5 Hz), 8.71 s (1H, H_{arom}), 8.74 s (1H, 5-H). Found, %: C 50.57; H 3.21; N 29.42. $C_8H_6N_4O_2$. Calculated, %: C 50.53; H 3.18; N 29.46.

3-Ethyl-5-(3-nitrophenyl)-4*H*-1,2,4-triazole (7c) was synthesized in a similar way at 250–280°C. Yield 98%. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 t (3H, CH_3, J = 8.0 Hz), 2.80 q (2H, CH_2, J = 8.0 Hz), 7.73 t (1H, H_{arom}, J = 7.5 Hz), 8.20 d (1H, H_{arom}, J = 7.5 Hz), 8.36 d (1H, H_{arom}, J = 7.5 Hz), 8.69 s (1H, H_{arom}), 13.9 br.s (1H, NH). Found, %: C 55.07; H 4.65; N 25.64. $C_{10}H_{10}N_4O_2$. Calculated, %: C 55.04; H 4.62; N 25.68.

3-(5-Methyl-4*H*-1,2,4-triazol-3-yl)aniline (8a). Triazole **7a**, 69.9 g (0.34 mol), was dissolved in 500 mL of propan-2-ol heated to 60–65°C, 110 mL of hydrazine hydrate and 0.5–1.0 g of Raney nickel were added, and the mixture was heated for 1 h at 70–75°C (until it became colorless). The mixture was cooled to 20°C, the precipitate was filtered off, the filtrate was evaporated, and the residue was washed with diethyl ether and dried under reduced pressure (10–15 mm) at 20–25°C for 1 h. Yield 59 g (99%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (3H, CH_3), 5.02 br.s (2H, NH_2), 6.60 d (1H, H_{arom}, J = 7.4 Hz), 7.02–7.15 m (2H, H_{arom}), 7.25 s (1H, H_{arom}), 13.43 br.s (1H, NH). Found, %: C 62.08; H 5.80; N 32.12. $C_9H_{10}N_4$. Calculated, %: C 62.05; H 5.79; N 32.16.

Compounds **8b** and **8c** were synthesized in a similar way.

3-(4*H*-1,2,4-Triazol-3-yl)aniline (8b). Yield 90%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.21 s (2H, NH_2), 6.62 d (1H, H_{arom}, J = 7.4 Hz), 7.03–7.15 m (2H, H_{arom}), 7.27 s (1H, H_{arom}), 8.28 s (1H, 5-H). Found, %: C 60.02; H 5.05; N 34.93. $C_8H_8N_4$. Calculated, %: C 59.99; H 5.03; N 34.98.

3-(5-Ethyl-4*H*-1,2,4-triazol-3-yl)aniline (8c). Yield 86%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25 s (3H, CH_3, J = 8.0 Hz), 2.69 q (2H, CH_2), 3.38 br.s (2H, NH_2), 5.15 d (1H, NH), 6.58 d (1H, H_{arom}), 7.08 m (2H, H_{arom}), 7.24 s (1H, H_{arom}). Found, %: C 63.79; H 6.42; N 29.79. $C_{10}H_{12}N_4$. Calculated, %: C 63.81; H 6.43; N 29.77.

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