Synthesis of tetrazolodiazepines by a five-centered four-component azide Ugi reaction. Scope and limitations

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Tetrazolo[1,5-*a*][1,4]benzodiazepines were obtained by an efficient azide five-centered four-component Ugi reaction, which used ketones, sodium azide, ammonium chloride, and the corresponding isonitrile. Scope and limitations of this multi-component reaction were considered.

Key words: azide, 1,4-benzodiazepines, Ugi reaction, tetrazolodiazepines, isonitriles.

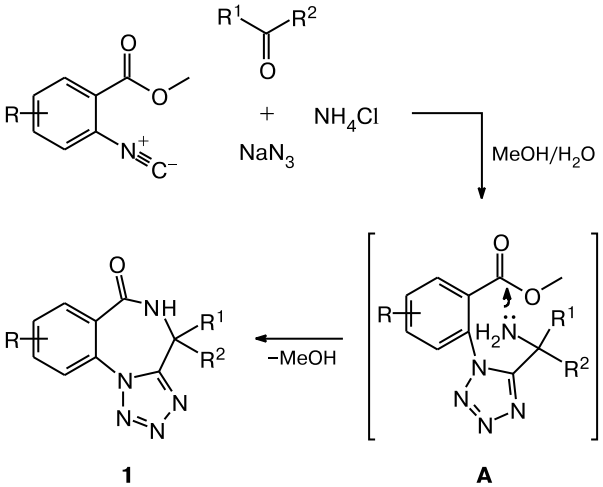
1,4-Benzodiazepines are a unique class of compounds possessing significant tranquilizing,[1] antitumor,[2] muscle relaxant,[3] anticonvulsive,[4] antiepileptic,[5] and antitripanosomic[6] activity. Due to the high therapeutic index and low toxicity, benzodiazepines have been widely used in medicine for more than 45 years. Many derivatives of this compounds are used either exclusively as sleeping drugs, or as sleep inducers in addition to their sedative function.[7] Exceptional pharmacological and clinical usefulness of these compounds is pointed out in numerous reviews and monographs devoted to the description of their properties.[8] Tetrazolobenzodiazepines were confirmed to possess significant antiaggregation[9] activity and to be cholecystokinin antagonists.[10] Among various approaches to the synthesis of 1,4-benzodiazepine derivatives, a special attention is deserved by the methods based on multi-component reactions (MCR) with participation of isonitriles due to the distinct advantage of the cost and efficiency of these methods.

In the present work, we represented a multi-component synthesis of tetrazolobenzodiazepine derivatives using a five-centered four-component Ugi reaction involving sodium azide and studied the scope and limitations of this method.

The Ugi reaction with participation of azides was described for the first time back in 1961 and was found to include the step of the formation of a Schiff base from the corresponding aldehyde or ketone and primary amine with subsequent reaction of the imine obtained with isonitrile. The intermediately formed nitrilium ion reacted with azide, giving substituted tetrazoles in good yields.[11]

Recently, we have described a new Ugi reaction with participation of sodium azide for the synthesis of tetrazolo[1,5-*a*][1,4]benzodiazepines **1** resulting from a multi-component reaction of methylisocyanobenzoate, sodium azide, ammonium chloride, and various aliphatic ketones[12] (Scheme 1).

Scheme 1



1 **A**

The starting isonitriles were obtained from commercially available methyl 2-aminobenzoate, methyl 2-ami-

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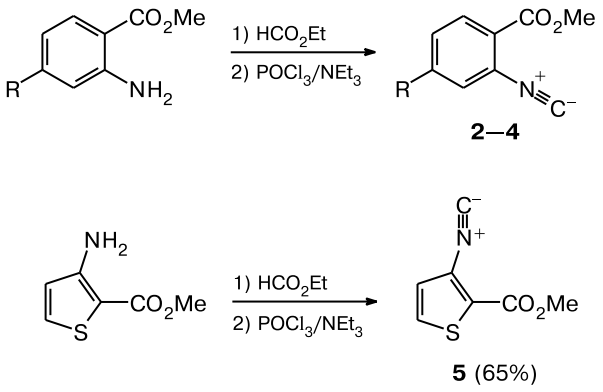
no-4-bromobenzoate (**2**), dimethyl 2-aminoterephthalate (**3**), and methyl 3-aminothiophene-2-carboxylate (**4**) according to the standard procedure, including formylation with subsequent dehydration (Scheme 2). Attempted synthesis of isonitrile from methyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate failed. According to the LCMS and NMR data, a complicated mixture of products was formed, probably, because of extremely low stability of the target isonitrile.

Scheme 2



R = H (**2**, 68%), Br (**3**, 56%), CO_2Me (**4**, 61%)

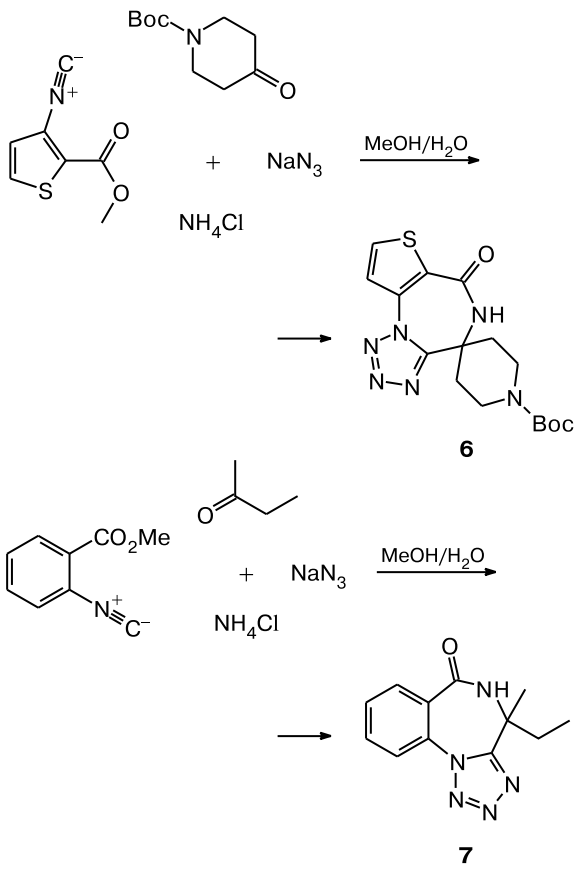
Because of instability of isonitriles **2—5** obtained (dark oils with pungent odor) were used without additional purification.

The model experiments showed that the use of crude isonitriles had no significant effect on the yields of the target products as compared to the use of commercially available isonitriles[12] (Scheme 3).

Later, we studied activities of various carbonyl compounds in this reaction. It was shown that this multicomponent reaction was efficient in the case of aliphatic ketones (below are given tetrazolobenzodiazepines **8—25** obtained by the MCR with participation of various aliphatic ketones), whereas the use of 2-acetylthiophene, acetophenone and benzophenone did not lead to the formation of the target products. The latter only gave a hydrolysis product of isonitrile, the corresponding *N*-formylmethylanthranylate. We suppose that this fact can be explained by the low activity of the carbonyl carbon atom of the aromatic ketones as compared to the aliphatic carbonyl components, which facilitates hydrolysis. No formation of the target products was observed either when acetaldehyde, 2-methylpropanal, and 2,4-dichlorobenzaldehyde were used instead of ketones.

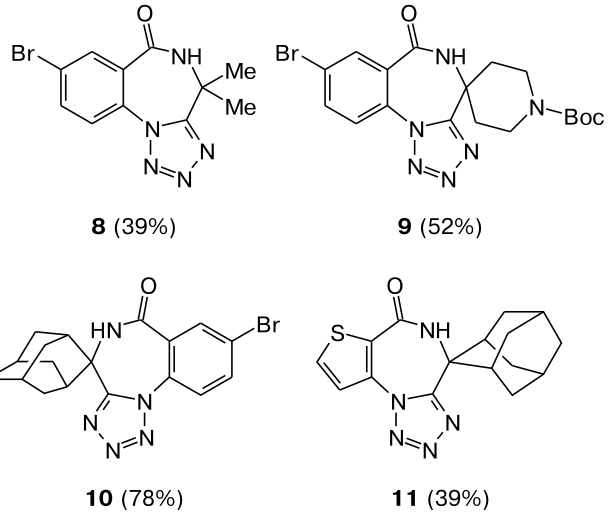
The reaction of aliphatic aldehydes after 72 h of stirring leads to hydration of the isonitrile and is accompanied by significant resinification, probably, resulted from the self-condensation of the aldehyde molecules. The use of aromatic aldehyde allowed us to isolated an acyclic

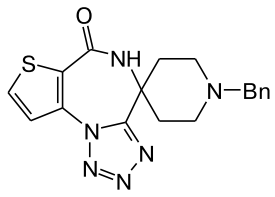
Scheme 3



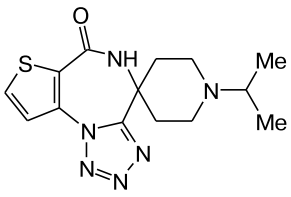
Product	Yield (%)	
	Present work	Literature data[12]
6	40	46
7	53	55

Schiff base **26** in 46% yield. The latter reaction is an alternative intermolecular reaction, in which the initially formed aminotetrazole **A** reacts with the second molecule

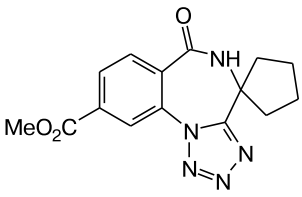




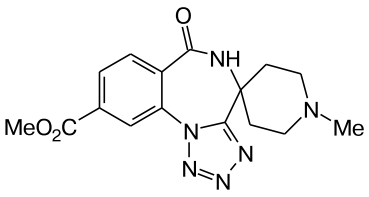
12 (50%)



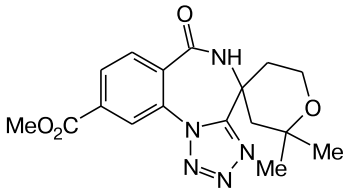
13 (43%)



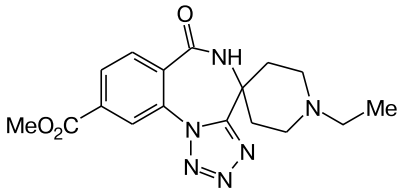
14 (42%)



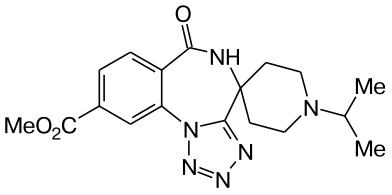
15 (63%)



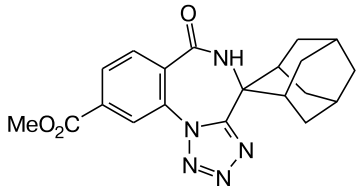
16 (38%)



17 (54%)



18 (53%)



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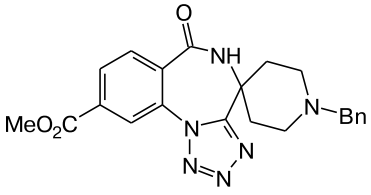
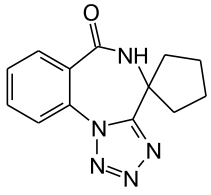
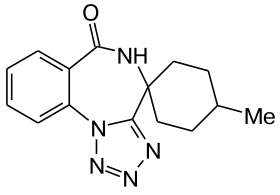


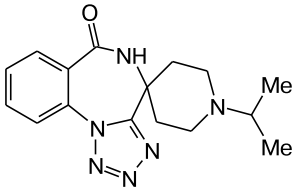
20 (57%)



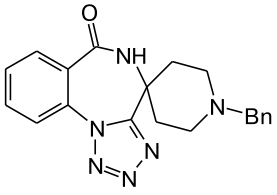
21 (40%)



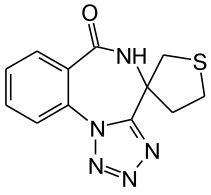
22 (40%)



23 (53%)



24 (72%)

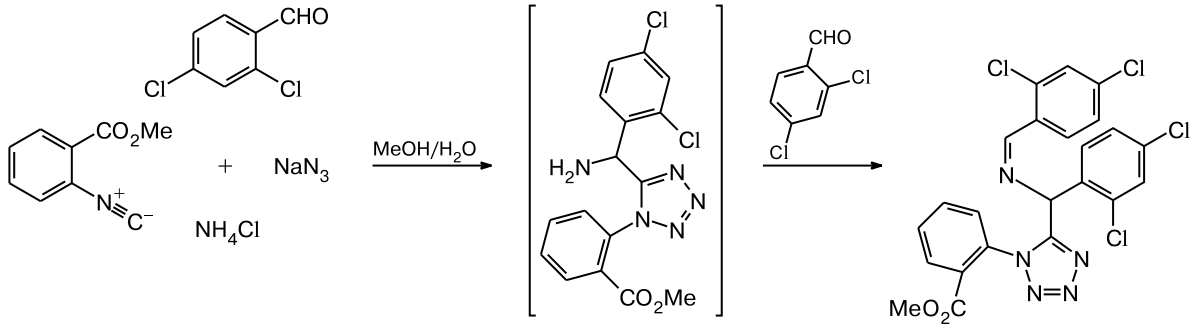


25 (50%)

of 2,4-dichlorobenzaldehyde, giving rise to the Schiff base **26** (Scheme 4).

Our studies also included the use of primary amines instead of ammonium chloride. Both methylamine and benzylamine hydrochlorides were easily involved in the reaction, however, no formation of the expected tetrazolo[1,5-*a*]benzodiazepines was observed: the only reaction products were the corresponding aminotetrazoles **27** and

Scheme 4

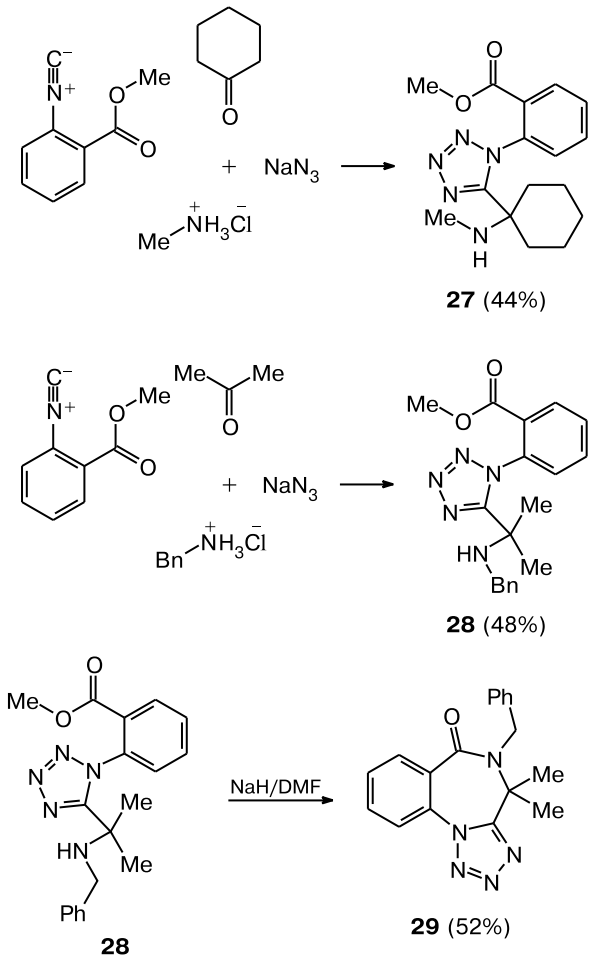


A

26 (46%)

28. The target derivatives of benzodiazepine **29** was obtained from compound **28** through the Ugi post-condensation upon the action of NaH in DMF (Scheme 5).

Scheme 5



In conclusion, using a new multi-component reaction we studied an approach to the synthesis of tetrazolo[1,5-*a*]-[1,4]benzodiazepines. This reaction was shown to be efficient in the case when aliphatic ketones and ammonia were used. The mild reaction conditions and easy isolation of the products make this MCR very attractive. Aliphatic aldehydes and aromatic ketones give no desired products, whereas aromatic aldehydes and primary amines can be used for the synthesis of acyclic compounds, which can further be transformed to the benzodiazepine derivatives by the Ugi post-condensation.

Experimental

Elemental analysis was performed on a Carlo Erba 1106 instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker-400 and JEOL JNM-ECA600 spectrometers (^{1}H, 400 and 600 MHz) in $CDCl_3$ and DMSO-d_6, using residual signals of the solvents as the reference. Mass spectra were recorded on Finnigan MAT 95 XL GLC-MS spectrometer (EI, 70 eV). LCMS spectra were obtained using a system including an Agilent 1100 Series liquid chromatograph, an Agilent Technologies LC/MSD VL mass spectrometer (electro spray ionization, APCI), ELSD Sedex 75.

The following reagents were purchased from commercial companies and were used without additional purification: acetone, adamantanone, tetrahydro-2,2-dimethylpyran-4-one, cyclohexanone, 4-methylcyclohexanone, cyclopentanone, dihydrothiophene-3(2*H*)-one, *N*-Boc-, *N*-methyl-, *N*-ethyl-, *N*-isopropyl-, *N*-benzylpiperidin-4-one, ammonium chloride, methylamine and benzylamine hydrochlorides, sodium azide.

Silufol-254 plates were used for TLC, Fluka neutral alumina of II degree of activity, 60 mesh was used for column chromatography.

Synthesis of isonitriles 2—5 (general procedure). A solution of the corresponding amine (0.1 mmol) in ethyl formate (85 mL) was refluxed for 7 h (TLC monitoring). The reaction mixture was concentrated at reduced pressure and suspended in anhydrous dichloromethane (250 mL). Freshly distilled triethylamine (51 g, 0.5 mmol) was added and the mixture was cooled to –5 °C, followed by a dropwise addition of freshly distilled $POCl_3$ (32 g, 0.21 mmol) so that to keep the temperature of the reaction mixture below 5 °C. The mixture was vigorously stirred for 3 h (LCMS monitoring) and poured on a finely crushed ice (300 g), containing sodium carbonate (85 g). The emulsion obtained was stirred for 1 h at 20 °C, extracted with dichloromethane (3×75 mL). The organic layer was concentrated *in vacuo* at 20 °C (*Attention! No heating!*). The isonitriles obtained were dark brown oils, which were used in subsequent reactions without additional purification. (*Caution! Good exhaust hood is required!*).

Synthesis of tetrazolobenzodiazepines 6—25 (general procedure). A solution of ketone (1 mmol), sodium azide (78 mg, 1.2 mmol), ammonium chloride (64 mg, 1.2 mmol), and the corresponding freshly prepared isonitrile (1 mmol) in a mixture of water—methanol (1 : 3) (15 mL) was vigorously stirred for 24—45 h at room temperature. The reaction progress was monitored by TLC (Silufol-UV-254, ethyl acetate—hexane, 1 : 3). The indicated time corresponded to the time when the spot of the isonitrile disappeared. The target product precipitated from the reaction mixture, it was filtered off and dried in air (compounds **8**, **11**, **13**, and **16** were additionally purified by recrystallization from ethyl acetate). The procedure was used for the preparation of tetrazolobenzodiazepines **6**—**25**.

***tert*-Butyl 6-oxo-4,5-dihydrotetrazolo[1,5-*a*]thieno[2,3-*f*]-[1,4]diazepine-4-spiro-4′-(piperidin-1′-carboxylate) (6).** The yield was 160 mg (40%), m.p. 241—242 °C. The compound was obtained from *N*-Boc-piperidin-4-one (200 mg) and methyl 3-isocyanothiophene-2-carboxylate **5** (170 mg), NaN_3, and NH_4Cl. The reaction required 30 h to reach completion. Spectral characteristics correspond to the literature data.[12]

4-Ethyl 4-methyl-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepin-6-one (7). The yield was 128 mg (53%), m.p. 135 °C. The compound was obtained from methyl ethyl ketone (72 mg, 0.1 mL), methyl 2-isocyanobenzoate (160 mg), NaN_3, and NH_4Cl. The reaction required 25 h to reach completion. Spectral characteristics correspond to the literature data.[12]

8-Bromo-4,4-dimethyl-4,5-dihydrotetrazolo[1,5-*a*][1,4]-benzodiazepin-6-one (8). The yield was 120 mg (39%), m.p.

210 °C. The compound was obtained from acetone (60 mg, 0.08 mL), methyl 5-bromo-2-isocyanobenzoate (240 mg), NaN_3, and NH_4Cl. The reaction required 24 h to reach completion. Found (%): C, 42.81; H, 3.25; N, 22.65. $C_{11}H_{10}BrN_5O$. Calculated (%): C, 42.88; H, 3.27; N, 22.73. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.62 (s, 6 H, 2 Me); 7.92, 8.06 (both d, 1 H each, C(9)H, C(10)H, J = 8.2 Hz); 8.16 (s, 1 H, C(7)H); 9.12 (br.s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 25.8 (2 C), 49.7, 122.1, 126.5, 129.8, 134.6, 136.5, 150.3, 156.8, 165.1. MS, EI MS: $M^+ = [M - N_2] = 280$.

***tert*-Butyl 8-bromo-6-oxo-4,5-dihydrotetrazolo[1,5-*a*][1,4]-benzodiazepine-4-spiro-4′-(piperidin-1′-carboxylate) (9).** The yield was 233 mg (52%), m.p. 255 °C. The compound was obtained from *N*-Boc-piperidin-4-one (200 mg), methyl 5-bromo-2-isocyanobenzoate (240 mg), NaN_3, and NH_4Cl. The reaction required 45 h to reach completion. Found (%): C, 48.08; H, 4.62; N, 18.67. $C_{18}H_{21}BrN_6O_3$. Calculated (%): C, 48.12; H, 4.71; N, 18.70. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.37 (s, 9 H, $(CH_3)_3$); 1.91—2.10 (m, 4 H, $(CH_2)_2$); 3.30—3.52 (m, 4 H, $(CH_2)_2$); 7.90, 8.08 (both d, 1 H each, C(9)H, C(10)H, J = 8.2 Hz); 8.12 (s, 1 H, C(7)H); 9.15 (br.s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 27.6 (3 C), 34.2 (2 C), 45.9 (2 C), 50.1, 79.0, 121.7, 126.8, 128.3, 139.3 (2 C), 153.7, 156.7, 160.0, 166.3. MS, EI MS: $M^+ = [M - N_2] = 421$.

8-Bromo-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-2′-tricyclo[3.3.1.1^{3,7}]decan-6-one (10). The yield was 312 mg (78%), m.p. 270 °C. The compound was obtained from adamantan-2-one (150 mg), methyl 5-bromo-2-isocyanobenzoate (240 mg), NaN_3, and NH_4Cl. The reaction required 45 h to reach completion. Found (%): C, 53.92; H, 4.51; N, 17.43. $C_{18}H_{18}BrN_5O$. Calculated (%): C, 54.01; H, 4.53; N, 17.50. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.01 (m, 1 H, Ad); 1.40—2.20 (m, 10 H, Ad); 2.31—2.42 (m, 1 H, Ad); 2.61 (s, 1 H, Ad); 2.88 (m, 1 H, Ad); 7.92, 8.08 (both d, 1 H each, C(9)H, C(10)H, J = 7.9 Hz); 8.13 (s, 1 H, C(7)H); 9.02 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 25.6 (2 C), 30.7, 31.0, 32.1 (2 C), 32.6, 33.4, 38.2, 57.5, 123.2, 127.5, 131.2, 133.7, 134.1, 152.4, 157.5, 164.8. MS, EI MS: $M^+ = [M - N_2] = 372$.

4,5-Dihydrotetrazolo[1,5-*a*]thieno[2,3-*f*][1,4]diazepine-4-spiro-2′-tricyclo[3.3.1.1^{3,7}]decan-6-one (11). The yield was 65 mg (39%), m.p. 275 °C. The compound was obtained from adamantan-2-one (150 mg), methyl 3-isocyanothiophene-2-carboxylate (167 mg), NaN_3, and NH_4Cl. The reaction required 24 h to reach completion. Found (%): C, 58.68; H, 5.20; N, 21.37. $C_{16}H_{17}N_5OS$. Calculated (%): C, 58.70; H, 5.23; N, 21.39. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.97 (m, 1 H, Ad); 1.55—1.94 (m, 10 H, Ad); 2.32 (m, 1 H, Ad); 2.68 (m, 1 H, Ad); 3.02 (m, 1 H, Ad); 7.72, 8.18 (both d, 1 H each, thienyl, J = 4.9 Hz); 8.52 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 24.8 (2 C), 26.5, 29.8, 34.7 (2 C), 35.4 (2 C), 39.1 (overlaps with the signal for DMSO-d_6), 56.7, 117.3, 123.2, 126.1, 142.3, 157.4, 159.7. MS, ESI MS: 328 $[M + 1]^+$.

1′-Benzyl-4,5-dihydrotetrazolo[1,5-*a*]thieno[2,3-*f*][1,4]-diazepine-4-spiro-4′-piperidin-6-one (12). The yield was 183 mg (50%), m.p. 189—190 °C. The compound was obtained from methyl 3-isocyanothiophene-2-carboxylate (167 mg), *N*-benzylpiperidin-4-one (190 mg, 0.18 mL), NaN_3, and NH_4Cl. The reaction required 40 h to reach completion. Found (%): C, 58.91; H, 4.84; N, 22.87. $C_{18}H_{18}N_6OS$. Calculated (%): C, 59.00; H, 4.95; N, 22.93. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.03—2.25 (m, 4 H, $(CH_2)_2$); 3.30—3.48 (m, 4 H, $(CH_2)_2$); 3.51 (s, 2 H, $\underline{CH_2}$-Ph); 7.25—7.32 (m, 5 H, C_6H_5); 7.72, 8.19 (both d, 1 H each, thienyl, J = 5.3 Hz); 8.70 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 29.4, 32.1, 46.4, 57.6 (2 C), 61.5, 112.7, 123.4, 125.8, 127.8, 133.1 (2 C), 134.5 (2 C), 136.4, 141.5, 158.4, 160.1. MS, ESI MS: 367 $[M + 1]^+$.

1′-Isopropyl-4,5-dihydrotetrazolo[1,5-*a*]thieno[2,3-*f*][1,4]-diazepine-4-spiro-4′-piperidin-6-one (13). The yield was 137 mg (43%), m.p. 210—213 °C. The compound was obtained from methyl 3-isocyanothiophene-2-carboxylate (167 mg), *N*-isopropylpiperidin-4-one (140 mg, 0.15 mL), NaN_3 and NH_4Cl. The reaction required 38 h to reach completion. Found (%): C, 52.76; H, 5.64; N, 26.40. $C_{14}H_{18}N_6OS$. Calculated (%): C, 52.81; H, 5.70; N, 26.39. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.94 (d, 6 H, $(CH_3)_2$, J = 6.2 Hz); 2.02—2.20 (m, 4 H, $(CH_2)_2$); 2.52—2.55 (m, 4 H, $(CH_2)_2$); 2.68 (m, 1 H, $CH(CH_3)_2$); 7.71, 8.18 (both d, 1 H each, H (thienyl), J = 5.3 Hz); 8.67 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 17.2 (2 C), 28.4, 31.2, 47.5 (2 C), 53.8, 54.8, 98.7, 117.3, 125.6, 136.5, 148.3, 154.6. MS, EI MS: $M^+ = [M - N_2] = 290$.

Methyl 6-oxo-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-1′-(cyclopentane)-9-carboxylate (14). The yield was 132 mg (42%), m.p. 230 °C (decomp.). The compound was obtained from dimethyl 2-isocyanoterephthalate (220 mg), cyclopentanone (84 mg, 0.09 mL), NaN_3, and NH_4Cl. The reaction required 25 h to reach completion. Found (%): C, 57.42; H, 4.81; N, 22.37. $C_{15}H_{15}N_5O_3$. Calculated (%): C, 57.50; H, 4.83; N, 22.35. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.61—2.31 (m, 8 H, $(CH_2)_4$); 3.93 (s, 3 H, CO_2Me); 8.18 (s, 2 H, H_{arom}); 8.39 (s, 1 H, H_{arom}); 9.26 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 21.7 (2 C), 38.4, 40.1 (overlaps with the signals for DMSO-d_6), 49.7, 51.6, 124.1, 125.4, 126.2, 131.8, 137.2, 144.5, 146.5, 167.9, 168.2. MS, EI MS: $M^+ = [M - N_2] = 285$.

Methyl 1′-methyl-6-oxo-4,5-dihydrotetrazolo[1,5-*a*][1,4]-benzodiazepine-4-spiro-4′-(piperidine)-9-carboxylate (15). The yield was 215 mg (63%), m.p. 240—242 °C. The compound was obtained from dimethyl 2-isocyanoterephthalate (220 mg), *N*-methylpiperidin-4-one (113 mg, 0.12 mL), NaN_3, and NH_4Cl. The reaction required 27 h to reach completion. Found (%): C, 56.06; H, 5.26; N, 24.52. $C_{16}H_{18}N_6O_3$. Calculated (%): C, 56.13; H, 5.30; N, 24.55. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.92—2.13 (m, 4 H, $(CH_2)_2$); 2.19 (s, 3 H, CH_3—N); 3.23—3.55 (m, 4 H, $(CH_2)_2$); 3.94 (s, 3 H, CO_2Me); 8.18 (s, 2 H, H_{arom}); 8.41 (s, 1 H, H_{arom}); 9.04 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 31.4, 32.6, 45.8, 47.3, 51.6 (2 C), 53.1, 122.6, 124.2, 126.9, 128.7, 136.5, 145.4, 148.1, 166.9, 170.1. MS, ESI MS: 343 $[M + 1]^+$.

Methyl 2′,2′-dimethyl-6-oxo-4,5,3′,4′,5′,6′-hexahydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-4′-(2*H*-pyran)-9-carboxylate (16). The yield was 136 mg (38%), m.p. 265 °C. The compound was obtained from dimethyl 2-isocyanoterephthalate (220 mg), 2,2-dimethyltetrahydropyran-4-one (128 mg, 0.13 mL), NaN_3, and NH_4Cl. The reaction required 28 h to reach completion. Found (%): C, 57.08; H, 5.34; N, 19.58. $C_{17}H_{19}N_5O_4$. Calculated (%): C, 57.14; H, 5.36; N, 19.60. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.87, 1.13 (both s, 3 H each, 2 CH_3); 1.52—1.77 (m, 2 H, CH_2); 2.05—2.18 (m, 1 H, CH_2); 2.42—2.53 (m, 1 H, CH_2); 3.93 (s, 3 H, CO_2Me); 3.95—4.08 (m, 2 H, CH_2—O); 8.18 (m, 2 H, H_{arom}); 8.42 (s, 1 H, H_{arom}); 9.31 (s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 27.1, 29.8, 33.4, 42.1, 48.6, 53.9, 60.2, 77.5, 124.8, 126.2, 128.3, 131.4, 137.2, 150.4, 152.6, 166.1, 169.7. MS, ESI MS: 358 $[M + 1]^+$.

Methyl 1´-ethyl-6-oxo-4,5-dihydrotetrazolo[1,5-*a*][1,4]-benzodiazepine-4-spiro-4´-piperidin-9-carboxylate (17). The yield was 192 mg (54%), m.p. 210 °C. The compound was obtained from dimethyl 2-isocyanoterephthalate (220 mg), *N*-ethylpiperidin-4-one (127 mg, 0.130 mL), NaN_3, and NH_4Cl. The reaction required 24 h to reach completion. Found (%): C, 57.22; H, 5.65; N, 23.60. $C_{17}H_{20}N_6O_3$. Calculated (%): C, 57.29; H, 5.66; N, 23.58. ^{1}H NMR (600 MHz, DMSO-d_6),, δ: 0.98 (t, 3 H, $\underline{CH_3}$—CH_2, J = 7.2 Hz); 1.91—2.18 (m, 4 H, $(CH_2)_2$); 2.31 (q, 2 H, CH_3—$\underline{CH_2}$); 2.39—2.53 (m, 4 H, $(CH_2)_2$); 3.94 (s, 3 H, CO_2Me); 8.18 (s, 2 H, H_{arom}); 8.41 (s, 1 H, H_{arom}); 9.09 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 14.8, 28.7, 31.4, 45.2, 49.7 (2 C), 50.4, 52.8, 123.6, 125.4, 126.9, 130.5, 134.9, 147.2, 149.7, 166.3, 169.8. MS, ESI MS: 357 $[M + 1]^+$.

Methyl 1´-isopropyl-6-oxo-4,5-dihydrotetrazolo[1,5-*a*]-[1,4]benzodiazepine-4-spiro-4´-piperidine-9-carboxylate (18). The yield was 196 mg (53%), m.p. 265 °C. The compound was obtained from dimethyl 2-isocyanoterephthalate (220 mg), *N*-isopropylpiperidin-4-one (140 mg, 0.15 mL), NaN_3, and NH_4Cl. The reaction required 30 h to reach completion. Found (%): C, 58.25; H, 5.93; N, 22.66. $C_{18}H_{22}N_6O_3$. Calculated (%): C, 58.37; H, 5.99; N, 22.69. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.24 (d, 6 H, $(CH_3)_2$, J = 6.2 Hz); 2.32—2.61 (m, 5 H, $(CH_2)_2$ + + $\underline{CH}(CH_3)_2$); 3.27—3.38 (m, 4 H, $(CH_2)_2$); 3.98 (s, 3 H, CO_2Me); 8.21 (s, 2 H, H_{arom}); 8.42 (s, 1 H, H_{arom}); 9.33 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 20.1 (2 C), 33.4, 34.9, 48.5 (2 C), 49.2, 52.1, 54.6, 122.1, 124.8, 127.3, 131.6, 138.2, 151.7, 154.8, 166.4, 169.2. MS, ESI MS: 371 $[M + 1]^+$.

Methyl 6-oxo-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-2´-(tricyclo[3.3.1.1^{3,7}]decane)-9-carboxylate (19). The yield was 280 mg (74%), m.p. 165 °C. The compound was obtained from dimethyl-2-isocyanoterephthalate (220 mg), adamantan-2-one (150 mg), NaN_3, and NH_4Cl. The reaction required 31 h to reach completion. Found (%): C, 63.27; H, 5.54; N, 18.43. $C_{20}H_{21}N_5O_3$. Calculated (%): C, 63.31; H, 5.58; N, 18.46. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.40—2.20 (m, 14 H, Ad); 3.90 (s, 3 H, CO_2Me); 8.15, 8.25 (both d, 1 H each, H_{arom}, J = 8.3 Hz); 8.38 (s, 1 H, H_{arom}); 9.03 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 26.8 (2 C), 28.4, 31.2, 32.8 (2 C), 34.6 (2 C), 39.9 (overlaps with the signals for DMSO-d_6), 50.7, 58.1, 123.5, 126.1, 128.5, 133.4, 139.7, 152.1, 155.7, 167.1, 168.9. MS, ESI MS: 380 $[M + 1]^+$.

Methyl 1´-benzyl-6-oxo-4,5-dihydrotetrazolo[1,5-*a*][1,4]-benzodiazepine-4-spiro-4´-(piperidine)-9-carboxylate (20). The yield was 238 mg (57%), m.p. 154 °C. The compound was obtained from dimethyl 2-isocyanoterephthalate (220 mg), *N*-benzylpiperidin-4-one (190 mg, 0.18 mL), NaN_3, and NH_4Cl. The reaction required 37 h to reach completion. Found (%): C, 63.10; H, 5.28; N, 20.07. $C_{22}H_{22}N_6O_3$. Calculated (%): C, 63.15; H, 5.30; N, 20.08. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.91—2.46 (m, 8 H, $(CH_2)_4$); 3.48 (s, 2 H, $\underline{CH_2}$—Ph); 3.96 (s, 3 H, CO_2Me); 7.27 (m, 5 H, C_6H_5); 8.18 (m, 2 H, H_{arom}); 8.40 (s, 1 H, H_{arom}); 9.10 (s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 28.6, 31.1, 47.5, 50.6, 55.9 (2 C), 61.4, 123.6, 124.8, 127.3, 128.5, 129.8 (2 C), 131.2 (2 C), 132.4, 135.8, 137.4, 148.2, 150.5, 164.6, 166.7. MS, ESI MS: 419 $[M + 1]^+$.

4,5-Dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-1´-cyclopentan-6-one (21). The yield was 102 mg (40%), m.p. 250 °C. The compound was obtained from methyl 2-isocyanobenzoate (160 mg), cyclopentanone (84 mg, 0.09 mL), NaN_3, and NH_4Cl. The reaction required 26 h to reach completion. Found (%): C, 61.15; H, 5.11; N, 27.41. $C_{13}H_{13}N_5O$. Calculated (%): C, 61.17; H, 5.13; N, 27.43. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.65—2.23 (m, 8 H, $(CH_2)_4$); 7.75, 7.89 (both t, 1 H each, H_{arom}, J = 7.2 Hz); 8.05, 8.10 (both d, 1 H each, H_{arom}, J = 7.9 Hz); 9.08 (s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 21.7 (2 C), 36.5, 37.3, 51.4, 117.8, 122.6, 125.4, 132.7, 137.9, 143.8, 145.6, 164.5. MS, EI MS: $M^+ = [M - N_2] = 227$.

4´-Methyl-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-1´-cyclohexan-6-one (22). The yield was 113 mg (40%), m.p. 210—213 °C. The compound was obtained from methyl 2-isocyanobenzoate (160 mg), 4-methylcyclohexanone (112 mg, 0.12 mL), NaN_3, and NH_4Cl. The reaction required 36 h to reach completion. Found (%): C, 63.55; H, 6.02; N, 24.67. $C_{15}H_{17}N_5O$. Calculated (%): C, 63.59; H, 6.05; N, 24.72. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.79 (d, 3 H, CH_3, J = 6.2 Hz); 1.02—1.78 (m, 7 H, H_{Alk}); 2.15—2.28 (m, 2 H, H_{Alk}); 7.71 (m, 1 H, H_{arom}); 7.86 (m, 1 H, H_{arom}); 7.95—8.09 (m, 2 H, H_{arom}); 8.93 (s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 19.7, 23.4, 29.5 (2 C), 31.4, 33.7, 45.8, 122.6, 124.5, 126.3, 133.8, 136.7, 144.3, 148.6, 164.5. MS, EI MS: $M^+ = [M - N_2] = 255$.

1´-Isopropyl-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-4´-piperidin-6-one (23). The yield was 165 mg (53%), m.p. 238 °C. The compound was obtained from methyl 2-isocyanobenzoate (160 mg), *N*-isopropylpiperidin-4-one (140 mg, 0.15 mL), NaN_3, and NH_4Cl. The reaction required 26 h to reach completion. Found (%): C, 61.46; H, 6.43; N, 26.87. $C_{16}H_{20}N_6O$. Calculated (%): C, 61.52; H, 6.45; N, 26.90. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.97 (d, 6 H, $(CH_3)_2$, J = 6.2 Hz); 1.92—2.18 (m, 4 H, $(CH_2)_2$); 2.66 (m, 1 H, $\underline{CH}(CH_3)_2$); 3.29—3.32 (m, 4 H, $(CH_2)_2$); 7.72 (m, 1 H, H_{arom}); 7.86 (m, 1 H, H_{arom}); 7.95—8.07 (m, 2 H, H_{arom}); 8.84 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 19.7 (2 C), 29.8, 31.4, 42.8 (2 C), 48.5, 49.4, 118.6, 121.7, 124.6, 129.8, 132.5, 146.8, 147.3, 164.1. MS, EI MS: $M^+ = [M - N_2] = 284$.

1´-Benzyl-4,5-dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-4´-piperidin-6-one (24). The yield was 260 mg (72%), m.p. 213—214 °C. The compound was obtained from methyl 2-isocyanobenzoate (160 mg), *N*-benzylpiperidin-4-one (190 mg, 0.18 mL), NaN_3, and NH_4Cl. The reaction required 37 h to reach completion. Found (%): C, 66.59; H, 5.55; N, 23.37. $C_{20}H_{20}N_6O$. Calculated (%): C, 66.65; H, 5.59; N, 23.32. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.95—2.18 (m, 4 H, $(CH_2)_2$); 2.41—2.49 (m, 4 H, $(CH_2)_2$); 3.44 (s, 2 H, $\underline{CH_2}$—Ph); 7.25 (m, 5 H, C_6H_5); 7.70 (m, 1 H, H_{arom}); 7.84 (m, 1 H, H_{arom}); 7.95—8.05 (m, 2 H, H_{arom}); 8.92 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 28.7, 29.8, 48.1, 56.9 (2 C), 65.7, 117.3, 122.8, 124.6, 126.5, 130.7 (2 C), 132.5 (2 C), 135.4, 139.7, 141.9, 150.3, 151.6, 167.7. MS, EI MS: $M^+ = [M - N_2] = 332$.

4,5-Dihydrotetrazolo[1,5-*a*][1,4]benzodiazepine-4-spiro-3´-thiophen-6-one (25). The yield was 137 mg (50%), m.p. 240 °C (decomp.). The compound was obtained from methyl 2-isocyanobenzoate (160 mg), dihydrothiophen-3(2*H*)-one (100 mg, 0.085 mL), NaN_3, and NH_4Cl. The reaction required 24 h to reach completion. Found (%): C, 52.71; H, 3.98; N, 25.57. $C_{12}H_{11}N_5OS$. Calculated (%): C, 52.73; H, 4.06; N, 25.62. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.52—2.75 (m, 2 H, CH_2); 2.98—3.19 (m, 4 H, $(CH_2)_2$); 7.68 (m, 1 H, H_{arom}); 7.83 (m, 1 H, H_{arom}); 7.93—8.08 (m, 2 H, H_{arom}); 8.86 (br.s, 1 H, CONH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 28.7, 36.1, 47.8, 50.2, 119.3, 125.6, 127.8, 133.4, 136.8, 146.9, 153.4, 167.8. MS, EI MS: $M^+ = [M - N_2] = 245$.

Methyl 2-{5-[(2,4-dichlorophenyl)[(2,4-dichlorophenyl)-methylidene]amino}methyl]-1*H*-tetrazole-1-yl}benzoate (26). A solution of 2,4-dichlorobenzaldehyde (250 mg, 1.4 mmol), freshly prepared isonitrile **2** (160 mg, 1 mmol), NaN_3 (78 mg, 1.2 mmol), and NH_4Cl (64 mg, 1.2 mmol) in a mixture of water—methanol (1 : 3) (10 mL) was vigorously stirred for 10 h at room temperature. A precipitate formed was filtered off and purified by column chromatography (a 1.5×25-cm column, eluent ethyl acetate—hexane, 1 : 3) to obtain compound **26** (0.25 g, 46%) as a gray powder, m.p. 149—151 °C. Found (%): C, 51.57; H, 2.72; N, 13.12. $C_{23}H_{15}Cl_4N_5O_2$. Calculated (%): C, 51.61; H, 2.82; N, 13.09. ^{1}H NMR (600 MHz, $CDCl_3$), δ: 3.49 (s, 3 H, CO_2Me); 6.32 (s, 1 H, CH_{aliph}); 7.12, 7.28 (both dd, 1 H each, H_{arom}, J = 8.2 Hz, J = 2.0 Hz); 7.21 (d, 1 H, H_{arom}, J = 7.2 Hz); 7.33 (d, 1 H, H_{arom} J = 2.0 Hz); 7.38—7.41 (m, 2 H, 2 CH_{arom}); 7.57—7.65 (m, 2 H, 2 CH_{arom}); 7.91 (d, 1 H, CH_{arom}, J = 8.2 Hz); 8.12 (d, 1 H, H_{arom}, J = 7.2 Hz); 8.61 (s, 1 H, N=CH). ^{13}C NMR (150.9 MHz, $CDCl_3$), δ: 52.0, 54.8, 122.7 (2 C), 123.0, 126.7, 128.1, 129.6, 130.1, 130.2, 130.0, 130.8, 131.9, 132.4, 133.4, 134.6 (2 C), 136.5, 141.0, 155.3, 162.2, 164.6, 165.5. MS, EI MS: $M^+ = [M - N_2] = 507$.

Methyl 2-{5-[1-(methylamino)cyclohexyl]-1*H*-tetrazole-1-yl}benzoate (27). A solution of cyclohexanone (98 mg, 0.11 mL, 1 mmol), freshly prepared isonitrile **2** (160 mg, 1 mmol), NaN_3 (78 mg, 1.2 mmol), and methylamine hydrochloride (82 mg, 1.2 mmol) in a mixture of water—methanol (1 : 3) (10 mL) was vigorously stirred for 32 h at room temperature. A precipitate formed was filtered off and purified by column chromatography (a 1.5×25-cm column, eluent ethyl acetate—hexane, 1 : 5) to obtain compound **27** (0.14 g, 44%), colorless needles, m.p. 137—138 °C. Spectral data are identical to those described earlier.[12]

Methyl 2-{5-[2-(benzylamino)propan-2-yl]-1*H*-tetrazol-1-yl}benzoate (28). Colorless prisms, m.p. 151—152 °C. The yield was 0.16 g (48%). The compound was obtained according to the procedure described for compound **7** from freshly prepared isonitrile **2** (160 mg, 1 mmol), acetone (60 mg, 0.08 mL, 1 mmol), $BnNH_2 \cdot HCl$ (0.17 g, 1.18 mmol), and NaN_3 (78 mg, 1.2 mmol). The reaction required 48 h to reach completion. Found (%): C, 65.15; H, 6.00; N, 19.87. $C_{19}H_{21}N_5O_2$. Calculated (%): C, 64.94; H, 6.02; N, 19.93. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 1.43 (s, 6 H, 2 CH_3); 2.33 (br.s, 1 H, NH); 3.55 (s, 2 H, $\underline{CH_2}$—Ph); 3.95 (s, 3 H, CO_2Me); 7.05—7.07 (m, 2 H, 2 H_{arom}); 7.15—7.25 (m, 3 H, 3 H_{arom}); 7.71—7.73 (m, 1 H, H_{arom}); 7.78—7.81 (m, 2 H, 2 H_{arom}); 8.08—8.10 (m, 1 H, H_{arom}). ^{13}C NMR (150 MHz, DMSO-d_6), δ: 27.1 (2 C), 48.7, 52.7, 57.3, 121.3, 123.6, 127.4, 127.9, 129.5 (2 C), 130.7 (2 C), 132.6, 140.2, 141.7, 147.4, 153.1, 164.7. MS, ESI MS: 352 $[M + 1]^+$.

5-Benzyl-4,4-dimethyl-4,5-dihydrotetrazolo[1,5-*a*][1,4]-benzodiazepin-6-one (29). Sodium hydride (12 mg, 0.5 mmol) was added in one portion to a solution of aminotetrazole **28** (100 mg, 0.3 mmol) in anhydrous DMF (5 mL). The reaction mixture was stirred for 5 h at room temperature under argon, the reaction progress was monitored by TLC (ethyl acetate—hexane, 1 : 3). Dimethylformamide was evaporated at reduced pressure, the oily residue obtained was purified by column chromatography (a 1.5×25-cm column, eluent ethyl acetate—hexane, 1 : 10). The yield was 50 mg (52%), yellowish powder, m.p. 190 °C (decomp.). Found (%): C, 67.67; H, 5.32; N, 21.81. $C_{18}H_{17}N_5O$. Calculated (%): C, 67.70; H, 5.37; N, 21.93. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.73 (br.s, 6 H, 2 CH_3); 5.00 (br.s, 2 H, $\underline{CH_2}$—Ph); 7.05 (d, 1 H, H_{arom}, J = 7.7 Hz); 7.10—7.23 (m, 4 H, H_{arom}); 7.56 (m, 1 H, H_{arom}); 7.68 (m, 1 H, H_{arom}); 7.93 (d, 1 H, H_{arom}, J = 8.7 Hz); 8.19 (dd, 1 H, H_{arom}, J = 8.7 Hz, J = 1.3 Hz). ^{13}C NMR (150.9 MHz, $CDCl_3$), δ: 23.4, 24.3, 43.5, 58.3, 124.3, 124.6, 125.3, 128.7, 129.1 (2 C), 129.3 (2 C), 132.5, 135.7, 136.9, 137.6, 151.5, 166.2. MS, ESI MS: 320 $[M + 1]^+$.

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