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Synthesis of Novel 5,6-dihydro-4H-[1,2,4]triazolo[4,3-a][*1*,*5*]benzodiazepines

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Abstract: **The series new fused tricyclic [1,2,4]triazolo[4,3-a][1,5]benzodiazepines have been synthesized by condensation-cyclization reaction of 1,5-benzodiazepine hydrazine derivatives as starting materials and triethyl orthoformate or triethyl orthoacetate. After screening various solvents like ethanol, isopropanol, xylene, we have found that xylene was the best choice for this reaction, because the reaction proceeds well in high boiling solvent. The 1,5-benzodiazepine hydrazines with electron-releasing methyl group gave a products in a poorer yield after a longer period of time, whereas compounds with electron-withdrawing group afforded a better yield of corresponding triazoles. The structure of the cycloadducts has been assigned by means of IR, ^{1}H and ^{13}C NMR spectroscopic measurements.**

Keywords: **[1,2,4]triazolo[4,3-a][1,5]benzodiazepine, 4-hydrazino-2,3-dihydro-1H-1,5-benzodiazepine, condensation-cyclization, synthesis, five-membered fused heterocycles.**

I. INTRODUCTION

The synthesis of fused heterocycles containing the triazole moiety is very attracting and has generated an intense of the chemical and pharmacological properties of this system. Some derivatives are known as analgesics, anticonvulsant, central nervous system (CNS) agents, some show anti-inflammatory activity or moderate affinity for the benzodiazepine receptor. As a result of the broad screening of a wide variety of these compounds in test systems designed to evaluate CNS activity other than that generally associated with the benzodiazepines [1-6].

The l-methyl-6-phenyl-4*H*-triazolo [4,3-a][1,4]benzodiaze-pines (triazolam) and (alprazolam), respectively had interesting hypnotic or anxiolytic activity and the finding that the pharmacological activity of this system could be qualitatively modified by substitution at C-l atom [7]. Such a broad spectrum of activities prompted us to initiate a synthesis of some new members of these compounds. We recently described the preparation of hydrazidines by treatment of thiolactams with an excess of hydrazine hydrate [8]. The synthesis of 4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines by thermal cyclization of 4-acylhydrazino-2,3-dihydro-1*H*-1,5-benzodiazepines was described by us too [9].

As a continuation of our investigation on tricyclic fused benzodiazepines we have extended synthetic pathway by condensation-cyclization reaction of novel 4-hydrazino-2,3-dihydro-1*H*-1,5-benzodiazepine and the physical-chemical properties of new tricyclic substituted triazolo 1,5-benzodiazepines were investigated by treatment of corresponding hydrazidines with triethyl orthoformate or triethyl orthoacetate.

II. RESULTS AND DISCUSSION

Herein we report the preparation of novel [1,2,4]triazolo[4,3a][1,5] benzodiazepines (Scheme 1), that were synthesized by the condensation of 4-hydrazino-2,3-dihydro-1*H*-1,5-bezodiazepines **2a-g** and triethyl orthoformate **3b-g** or triethyl orthoacetate **4a,b,d,e,g** in refluxing xylene (Table 1). The new 4-hydrazino-2,3-dihydro-1H-1,5-bezodiazepines **2a-g** were synthesized by the reaction of corresponding thiolactams **1a-g** with 4 equivalents of a hydrazine hydrate. The reaction was conducted by stirring at room temperature in methanol. Thiolactams **1a-g** were previously described by us [8,10,11]. The synthesis, physical and analytical data and ^{1}H NMR spectrum of 4-hydrazino-2,3-dihydro-1,3-dimethyl-1*H*-1,5-bezodiazepine (**2b**) were previously described by us [8].

Under the optimized reaction conditions triethyl orthoformate or triethyl orthoacete with 4-hydrazino-2,3-dihydro-1*H*-1,5-bezodiazepines in xylene form the corresponding 4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines in good yield. The 1,5-benzodiazepine hydrazines with electron-releasing methyl group (**2a,2b**) gave products (**3b, 4a, 4b**) in a poorer yield after a longer period of time, whereas compounds with carbomoyl (**2c-2e**) or acetyl (**2f, 2g**) electron-withdrawing group afforded a better yield of corresponding triazoles (**3c-3g, 4d, 4e, 4g**).

The structures of the newly synthesized compounds were confirmed by elemental analysis and IR, ^{1}H and ^{13}C NMR spectroscopic data (experimental). The ^{1}H NMR spectra of compounds **3b-g** and **4a,b,** d, e, g showed characteristics signals for triazolo ring system–the singlet at 8.32–8.46 or the singlet at 2.47–2.56 ppm, respectively. Moreover, in the ^{13}C NMR spectra the C–4, C-3a resonances are mainly influenced by replacement of thiolactam functionality with triazole nucleus and shifted upfield (about 10–12 and 53–55 ppm, respectively) with respect to precursors **1a-g**. In addition, in triazole ring the C-1 resonances were observed at 140.9–141.8 (for compound **3f** $^{1}J_{C\text{-}H}$=212 Hz) and 149.5-150.0 ppm for **3b–g** and **4a**, **b**, **d**, **e**, **g**, respectively and 1-CH_3 resonances were recognized at 11.3-11.6 ppm.

After screening various solvents like ethanol, isopropanol, xylene, we found that xylene was the best choice for this reaction, because the reaction proceeds well in high boiling solvent (Table 2).

Scheme 1.

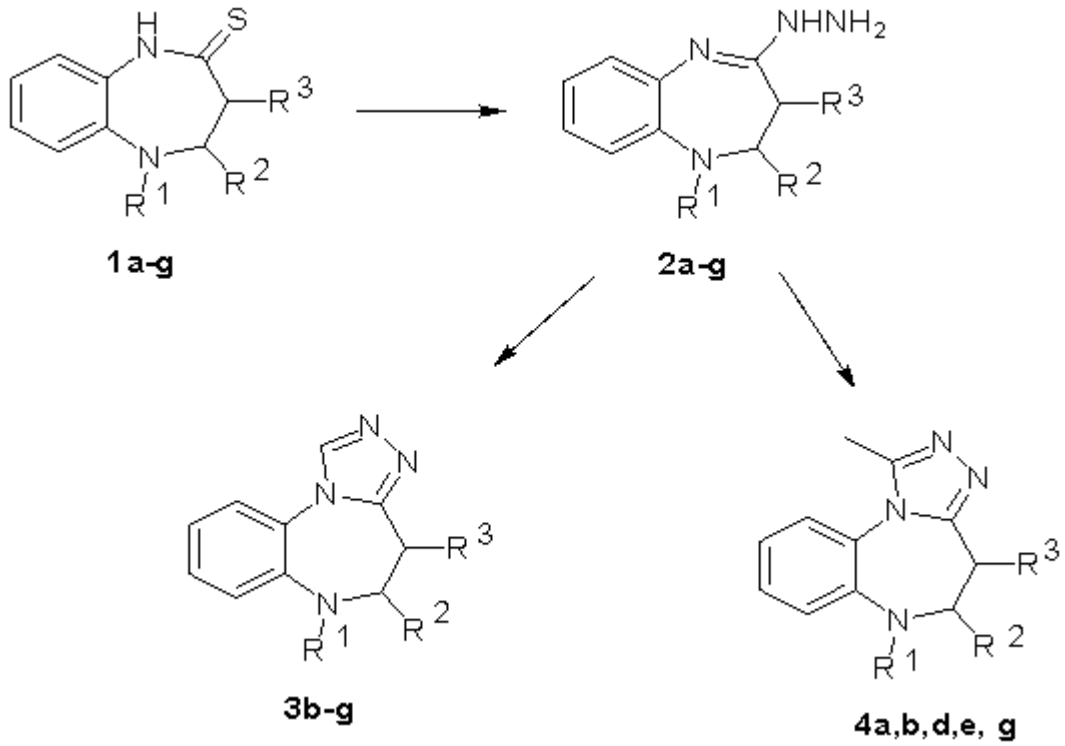

TABLE 1.

STARTING MATERIALS AND PRODUCTS WITH YIELDS

Entry	Starting material				Products		
	Compound 1	R^1	R^2	R^3	Product 2	Product 3	Product 4
1.	**1a**	Me	H	H	**2a**, 55%	-	**4a**, 32%
2.	**1b**	Me	H	Me	**2b**, 60%	**3b**, 41%	**4b**, 46%
3.	**1c**	CONHPh	H	H	**2c**, 56%	**3c**, 32%	-
4.	**1d**	CONHPh	H	Me	**2d**, 68%	**3d**, 65%	**4d**, 67%
5.	**1e**	CONHPh	Me	H	**2e**, 82%	**3e**, 56%	**4e**, 55%
6.	**1f**	COMe	H	H	**2f**, 48%	**3f**, 47%	-
7.	**1g**	COMe	H	Me	**2g**, 83%	**3g**, 58%	**4g**, 70%

TABLE 2.

SOLVENT EFFECTS IN THE REACTION

Compound	Solvent	Time (h)	Yield (%)
3b	EtOH	10,5	36
3b	IPA	10	38
3b	xylene	5	41
3d	EtOH	6	59
3d	xylene	2,5	65
3g	EtOH	8	49
3g	xylene	3	58
4b	EtOH	16	45
4b	xylene	7	46
4d	EtOH	9	63
4d	xylene	3	67

III. EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were taken on a PERKIN Elmer Spectrum GX FT-IR spectrometer in KBr tablets. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Unity Inova 300 spectrometer in $CDCl_3$ (compounds **2a-c**, **2f, g**, **3b-g**, **4a**, **b**, **d**, **e**, **g**) and DMSO-d_6 (compounds **2d**, **e**). The chemical shifts are referenced to tetramethylsilane (δ ^{1}H=0 ppm) and the solvent signal $CDCl_3$ (δ ^{13}C=77.0 ppm) and DMSO-d_6 (δ ^{13}C=39.5 ppm). The CH_3, CH_2, CH and C_{quart} groups in ^{13}C NMR were differentiated by means of the APT or DEPT methods. The reactions were controlled by TLC method and performed on Silufol UV_{254} silica gel plates in the system: n-butanol–acetic acid–water (v/v, 4:2:1).

4-Hydrazino-2,3-dihydro-1*H*-1,5-bezodiazepines (2a-g). General procedure. A mixture of 10 mmol 1,3,4,5-tetrahydro-1,5-benzodiazepin-2-thione **1a-g**, 2 mL (40 mmol) 98% hydrazine hydrate and 60 mL of methanol was stirred at room temperature for 4-8 h until TLC analysis indicated the completion of the reaction. Then the reaction mixture was concentrated to 1/3 of volume and cooled. The precipitated crystals were filtered. The solid residue was recrystallized from appropriate solvents to give **2a-g.**

4-Hydrazino-2,3-dihydro-1-methyl-1*H*-1,5-bezodiazepine (2a).

The solid residue was crystallized from ether to yield **1.05** g (55%) of compound **2a**. M.p. 127 ^{o}C (dec.). IR, ν, cm^{-1}: 3421, 3318, 3188, 1617, 1547, 1504. ^{1}H NMR ($CDCl_3$), δ, ppm, (J, Hz): 2.44 (2H, t, J=6.6, CH_2), 2.82 (3H, s, CH_3), 3.33 (2H, t, J=6.6, CH_2), 3.6-5.6 (3H, brs, $NHNH_2$), 6.85 (1H, dd, J=1.5, 7.7, Ar), 6.92-7.00 (2H, m, Ar), 7.06 (1H, m, Ar). ^{13}C NMR ($CDCl_3$), δ, ppm: 30.3 (C-3), 41.4 (1-CH_3), 58.3 (C-2), 119.3, 120.0, 122.6, 124.1, 134.4, 141.1, 153.4. Anal. Calc. for $C_{10}H_{14}N_4$ (190.245): C, 63.13; H, 7.42; N, 29.45. Found: C, 62.90; H, 7.60; N, 29.50.

4-Hydrazino-2,3-dihydro-1,3-dimethyl-1*H*-1,5-bezodiazepine (2b).

The solid residue was crystallized from ether to yield 1.23 g (60%) of compound **2b**. M.p.: 106 ^{o}C (dec.). ^{13}C NMR ($CDCl_3$), δ, ppm: 13.5 (3-CH_3), 33.4 (C-3), 41.3 (1-CH_3), 66.4 (C-2), 118.8, 119.7, 122.6, 124.0, 134.2, 141.5, 154.9.

4-Hydrazino-2,3-dihydro-N-phenyl-1*H*-1,5-bezodiazepine-1-carboxamide (2c).

The solid residue was crystallized from ethanol to yield 1.66 g (56%) of compound **2c**. M.p. 211 ^{o}C (dec.). IR, ν, cm^{-1}: 3346, 3300, 1661. ^{1}H NMR ($CDCl_3$), δ, ppm: (J, Hz): 2.54 (2H, br m, 3-CH_2), 3.2-4.8 (5H, br m, 4-CH_2, $NHNH_2$), 6.12 (1H, br s, NH), 6.99 (1H, m, H-4′), 7.08 (1H, dd, J=1.3, 7.9, Ar), 7.15 (1H, dt, J=1.4, 7.8, Ar), 7.18-7.27 (4H, m, H-2′,3′,5′,6′), 7.33 (1H, dd, J=1.5, 7.9, Ar), 7.36 (1H, dt, J=1.5, 7.8, Ar). ^{13}C NMR ($CDCl_3$), δ, ppm: 29.9 (C-3), 47.8 (br s, C-2), 119.1 (C-2′,6′), 121.7 (br s), 123.0, 124.5, 128.8 (C-3′,5′), 129.6, 129.9, 130.0, 138.5, 154.1, 154.2 (br s). Anal. Calc. for $C_{16}H_{17}N_5O$ (295.339): C, 65.07; H, 5.80; N, 23.71. Found: C, 64.78; H, 6.02; N, 23.82

4-Hydrazino-2,3-dihydro-3-methyl-N-phenyl-1*H*-1,5-bezodiazepine-1-carboxamide (2d).

The solid residue was crystallized from ethanol to yield 2.10 g (68%) of compound **2d**. M.p. 184 ^{o}C (dec.). IR, ν, cm^{-1}: 3419, 3358, 3283, 1646. ^{1}H NMR (DMSO-d_6), δ, ppm: 1.03 (3H, d, J=6.9, 4-CH_3), 2.53 (1H, m, CH), 3.57 (1H, dd, J=5.3, 11.9, CH_2), 3.84 (1H, t, J=11.9, CH_2), 4.6-5.8 (3H, br s, $NHNH_2$), 6.93 (1H, m, H-4′), 6.99-7.39 (8H, m Ar), 7.69 (1H, br s, NHCO). ^{13}C NMR (DMSO-d_6), δ, ppm: 14.2 (3-CH_3), 33.3 (C-3), 55.9 (br s, C-2), 119.7 (C-2′,6′), 121.0 (br s), 121.9, 122.6, 128.1, 128.2 (C- 3′,5′), 129.0, 130.6, 139.4 (br s), 139.8, 145.7 (br s), 154.4. Anal. Calc. for $C_{17}H_{19}N_5O$ (309.366): C, 66.00; H, 6.19; N, 22.64. Found: C, 66.25; H, 6.40; N, 22.42.

4-Hydrazino-2,3-dihydro-2-methyl-N-phenyl-1*H*-1,5-bezodiazepine-1-carboxamide (2e).

The solid residue was crystallized from ethanol to yield 2.53 g (82%) of compound **2e** M.p. 201 ^{o}C (dec.). IR, ν, cm^{-1}: 3420, 3303, 1660. ^{1}H NMR (DMSO-d_6), δ, ppm: 1.08 (3H, d, J=6.1, 4-CH_3), 1.96 (1H, dd, J=12.6, 13.2, CH_2), 2.36 (1H, dd, J=5.6, 13.8, CH_2), 4.3-5.4 (3H, br s, $NHNH_2$), 4.70 (1H, m, CH), 5.97 (1H, br s, NH), 6.88-7.35 (9H, m, Ar, NHCO). ^{13}C NMR (DMSO-d_6), δ, ppm: 19.0 (2-CH_3), 37.3 (br s, C-3), 54.0 (C-2), 119.6 (C-2′,6′), 122.0, 122.6, 127.7 (br s), 128.2 (C-3′,5′), 128.6, 130.7, 139.7, 153.6. Anal. Calc. for $C_{17}H_{19}N_5O$ (309.366): C, 66.00; H, 6.19; N, 22.64. Found: C, 65.76; H, 6.36; N, 22.70.

1-Acetyl- 4-hydrazino-2,3-dihydro-1*H*-1,5-bezodiazepine (2f).

The solid residue was crystallized from ether to yield 1.05 g (48%) of compound **2f**. M.p. 129 ^{o}C (dec.). IR, ν, cm^{-1}: 3370, 3249, 3192, 1646. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.79 (3H, s, CH_3), 2.44 (1H, br m, 3-CH_2), 2.57 (1H, m, 3-CH_2), 3.43 (1H, m, 2-CH_2), 3.5-5.0 (3H, br s, $NHNH_2$), 4.79 (1H, m, 2-CH_2), 7.03 (1H, dd, Ar), 7.07-7.16 (2H, m, Ar), 7.32 (1H, m, Ar). ^{13}C NMR ($CDCl_3$), δ, ppm: 22.8 (1-CH_3), 29.6 (C-3), 47.1 (C-2), 121.0, 123.9, 129.3, 129.6, 131.9, 138.3, 151.5 (C-4), 170.9 (CO). Anal. Calc. for $C_{11}H_{14}N_4O$ (218.255): C, 60.53; H, 6.47; N, 25.67. Found: C, 60.28; H, 6.65; N, 25.59.

1-Acetyl-4-hydrazino-2,3-dihydro-3-methyl-1*H*-1,5-bezodiazepine (2g).

The solid residue was crystallized from ether to yield 1.93 g (83%) of compound **2g**. M.p. 169 ^{o}C (dec.). IR, ν, cm^{-1}: 3320, 1661.^{1}H NMR ($CDCl_3$), δ, ppm: 1.14 (3H, d, J=6.7, 3-CH_3), 1.73 (3H, s, 1-CH_3), 2.70 (1H, m, CH), 3.39 (1H, dd, J=5.8, 12.5, CH_2), 4.0-6.8 (3H, br s, $NHNH_2$), 4.44 (1H, dd, J=12.6, 12.6, CH_2), 7.00 (1H, br dd, Ar), 7.06-7.16 (2H, m, Ar), 7.28–7.34 (1H, m, Ar). ^{13}C NMR ($CDCl_3$), δ, ppm: 13.2 (3-CH_3), 22.7 (1-CH_3), 32.9 (C-3), 54.2 (C-2), 120.6, 123.8, 129.3 (2CH), 132.1, 137.9, 152.4 (C-4), 170.7 (CO). Anal. Calc. for $C_{12}H_{16}N_4O$ (232.282): C, 62.05; H, 6.94; N, 24.12. Found: C, 61.81; H, 7.10; N, 24.25.

5,6-Dihydro-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines (3b-g). General procedure. A mixture of 2 mmol of hydrazine **2b-g** and 1.68 mL (10 mmol) of triethyl orthoformate and 10 mL of xylene was boiled with reflux for 2-5 h. Upon cooling, 20 mL of diethyl ether was added and precipitated crystals were filtered, recrystallized from corresponding solvents to give **3b-g.**

5,6-Dihydro-4,6-dimethyl-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine (3b).

The solid residue was crystallized from ethanol to yield 0.18 g (41%) of compound **3b**. M.p. 119-122 °C. IR, ν, cm^{-1}: 1602, 1524, 1505. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.54 (3H, d, J=6.8, CH_3), 2.82 (3H, s, NCH_3), 3.07 (1H, m, CH), 3.37 (2H, m, CH_2), 7.13 (1H, dt, J=1.5, 7.7, H-9), 7.19 (1H, dd, J=1.5, 7.9, H-7), 7.27 (1H, dd, J=1.5, 7.8, H-10), 7.41 (1H, dt, J=1.5, 7.9, H-8), 8.32 (1H, s, H-1). ^{13}C NMR ($CDCl_3$), δ, ppm: 13.9 (4-CH_3), 29.0 (C-4), 41.5 (6-CH_3), 66.7 (C-5), 120.7, 122.6, 122.7, 128.0 (C-10a), 129.4, 141.8 (C-1), 143.3 (C-6a), 155.7 (C-3a). Anal. Calc. for $C_{12}H_{14}N_4$ (214.269): C, 67.27; H, 6.59; N, 26.15. Found: C, 67.08; H, 6.88; N, 26.04.

4,5-Dihydro-N-phenyl-6*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-6-carboxamide (3c).

The solid residue was crystallized from ethanol to yield 0.20 g (32%) of compound **3c**. M.p. 169-171 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 2.6-4.8 (4H, br s, CH_2CH_2), 6.07 (1H, s, NH), 7.04 (1H, m, H-4′), 7.17-7.26 (4H, m, Ar), 7.52-7.66 (4H, m, H-7,8,9,10), 8.46 (1H, s, H-1). ^{13}C NMR ($CDCl_3$), δ, ppm: 23.0 (C-4), 48.5 (C-5), 119.7 (C-2′,6′), 123.7 (C-4′), 124.1, 128.3, 128.9 (C-3′,5′), 130.1, 130.9, 132.5, 133.3, 137.8 (C-1′), 141.2 (C-1), 151.7 (C-3a), 153.6 (CO). Anal. Calc. for $C_{17}H_{15}N_5O$ (305.334): C, 66.87; H, 4.95; N, 22.94. Found: C, 66.65; H, 5.11; N, 23.02.

4,5-Dihydro-4-methyl-N-phenyl-6*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-6-carboxamide (3d).

The solid residue was crystallized from benzene to yield 0.42 g (65%) of compound **3d.** M.p. 144-146 °C. IR, ν, cm^{-1}: 3288, 3122, 1665. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.57 (3H, d, J=6.8, 5-CH_3), 3.16 (1H, br s, CH), 4.00 (1H, br s, CH_2), 4.27 (1H, br s, CH_2), 6.28 (1H, s, NH), 7.00 (1H, m, H-4′), 7.17-7.27 (4H, m, Ar), 7.48-7.62 (4H, m, H-7,8,9,10), 8.39 (1H, s, H-1). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.1 (4-CH_3), 29.4 (C-4), 55.7 (C-5), 119.7 (C-2′,6′), 123.6 (C-4′), 124.0, 128.8 (C-3′,5′), 129.8, 130.0, 130.4, 132.3 (C-7), 133.7, 137.9 (C-1′), 141.3 (C-1), 153.6 (CO), 154.9 (C-3a).

Anal. Calc. for $C_{18}H_{17}N_5O$ (319.365): C, 67.70; H, 5.37; N, 21.93. Found: C, 67.90; H, 5.20; N, 21.79.

4,5-Dihydro-5-methyl-N-phenyl-6*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-6-carboxamide (3e).

The solid residue was crystallized from benzene to yield 0.36 g (56%) of compound **3e**. M.p. 140-142 °C. IR, ν, cm^{-1}: 3256, 3155, 1681. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.39 (3H, d, J=6.3, 5-CH_3), 2.38 (1H, dd, J=12.1, 15.0, CH_2), 3.48 (1H,dd, J= 6.2, 15.0, CH_2), 5.27 (1H, m, CH), 5.95 (1H, s, NH), 7.00 (1H, m, H-4′), 7.14-7.24 (4H, m, Ar), 7.52-7.67 (4H, m, H-7,8,9,10), 8.41 (1H, s, H-1). ^{13}C NMR ($CDCl_3$), δ, ppm: 19.8 (5- CH_3), 30.0 (C-4), 55.7 (C-5), 119.7 (C-2′,6′), 123.6 (C-4′), 124.2, 128.8 (C-3′,5′), 130.1, 130.4, 131.0, 132.5, 133.2, 137.9 (C-1′), 140.9 (C-1), 151.9 (C-3a), 153.1 (CO). Anal. Calc. for $C_{18}H_{17}N_5O$ (319.365): C, 67.70; H, 5.37; N, 21.93. Found: C, 67.85; H, 5.31; N, 21.81.

6-Acetyl-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine (3f).

The solid residue was crystallized from ethanol to yield 0.22 g (47%) of compound **3f**. M.p. 224-226 °C. IR, ν, cm^{-1}: 1655. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.74 (3H, s, CH_3), 2.84 (1H, m, 4-CH_2), 3.48 (2H, m, 4-CH_2, 5-CH_2), 5.01 (1H, m 5-CH_2), 7.43-7.63 (4H, m, Ar), 8.45 (1H, s, H-1). ^{13}C NMR ($CDCl_3$), δ, ppm: 22.5 (C-4), 22.7 (6-CH_3), 47.5 (C-5), 123.4, 129.7, 130.1, 130.9, 131.7, 134.4, 141.0 (C-1), 151.5 (C-3a), 170.1 (CO). Anal. Calc. for $C_{12}H_{12}N_4O$ (228.550): C, 63.15; H, 5.30; N, 24.55. Found: C, 62.91; H, 5.45; N, 24.65.

6-Acetyl-5,6-dihydro-4-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine (3g).

The solid residue was crystallized from ethanol to yield 0.28 g (58%) of compound **3g**. M.p. 239-241 °C. IR, ν, cm^{-1}: 1662, ^{1}H NMR ($CDCl_3$), δ, ppm: 1.60 (3H, d, J=6.8, CH_3), 1.71 (3H, s, 6-CH_3), 3.02 (1H, m, CH), 3.64 (1H, dd, J=6.5, 12.8, CH_2), 4.66 (1H, t, J=12.7, CH_2), 7.41-7.63 (4H, m, Ar), 8.45 (1H, s, H-1). ^{13}C NMR ($CDCl_3$), δ, ppm: 13.4 (4-CH_3), 22.7 (6-CH_3), 28.5 (C-4), 55.4 (C-5), 123.6, 129.7, 130.1, 130.8, 131.7, 134.6, 141.1 (C-1), 154.6 (C-3a), 170.2 (CO). Anal. Calc. for $C_{13}H_{14}N_4O$ (242.277): C, 64.45; H, 5.82; N, 23.13. Found: C, 64.57; H, 5.97; N, 22.86.

1-Methyl-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines (4a, b, d, e, g). General procedure. A mixture of 2 mmol of hydrazine **2a, b, d, e, g** and 1.46 mL (8 mmol) of triethyl orthoacete and 15 mL of xylene was boiled with reflux for 3-8 h. and solvent was removed under reduced pressure. The white solid was recrystallized from ethanol to give **4a, b, d, e, g.**

5,6-Dihydro-1,6-dimethyl-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine (4a).

The solid residue was crystallized from ethanol to yield 0.14 g (32%) of compound **4a**. M.p. 151-153 °C. IR, ν, cm^{-1}: 1599, 1536, 1501. ^{1}H NMR ($CDCl_3$), δ, ppm: 2.47 (3H, s, 1-CH_3), 2.77 (3H, s, NCH_3), 2.92 (2H, br s, CH_2), 3.39 (2H, br m, CH_2), 7.14 (1H, m, H-9), 7.17 (1H, m, H-7), 7.20 (1H, br dd, H-10), 7.39 (1H, m, H-8). ^{13}C NMR ($CDCl_3$), δ, ppm: 11.5 (1-CH_3), 23.2 (C-4), 41.4 (6-CH_3), 59.1 (C-5), 121.2, 122.7, 123.9, 128.2 (C-10a), 129.2, 143.7 (C-6a), 150.0 (C-1), 153.2 (C-3a). Anal. Calc. for $C_{12}H_{14}N_4$ (214.267): C, 67.27; H, 6.59; N, 26.15. Found: C, 67.03; H, 6.73; N, 26.24.

5,6-Dihydro-1,4,6-trimethyl-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine (4b).

The solid residue was crystallized from ethanol to yield 0.21 g (46%) of compound **4b**. M.p. 195-197 °C. IR, ν, cm^{-1}: 1600, 1538, 1500. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.47 (3H, d, J=6.8, CH_3), 2.47 (3H, s, 1-CH_3), 2.75 (3H, s, 6-CH_3), 2.89 (1H, m, CH), 3.18-3.28 (1H, m, CH_2), 7.10-7.20 (3H, m, Ar) 7.34-7.42 (1H, m, H-8). ^{13}C NMR ($CDCl_3$), δ, ppm: 11.4 (1-CH_3), 13.5 (4-CH_3), 29.1 (C-4), 41.3 (6-CH_3), 67.0 (C-5), 120.7, 122.5, 124.0, 128.1 (C-10a), 129.2, 144.2 (C-6a), 150.1 (C-1), 155.3 (C-3a). Anal. Calc. for $C_{13}H_{16}N_4$ (228.294): C, 68.39; H, 7.06; N, 24.54. Found: C, 68.56; H, 6.90; N, 24.65.

4,5-Dihydro-1,4-dimethyl-N-phenyl-6*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-6-carboxamide (4d).

The solid residue was crystallized from ethanol to yield 0.45 g (67%) of compound **4d**. M.p. 175-177 °C. IR, ν, cm^{-1}: 3395, 3266, 1656, 1658. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.56 (3H, br d, 4-CH_3), 2.53 (3H, s, 1-CH_3), 2.88 (1H, br m, CH), 3.72 (1H, br m, CH_2), 4.41 (1H, br m, CH_2), 6.06 (1H, br s, NH), 7.01 (1H, m, H-4′), 7.17-7.25 (4H, m, Ar), 7.41-7.45 (1H, m, Ar), 7.58-7.65 (3H, m, Ar). ^{13}C NMR ($CDCl_3$), δ, ppm: 11.4 (1-CH_3), 13.2 (br s, 5-CH_3), 29.2 (C-4), 56.5 (C-5), 119.9 (C-2′,6′), 123.7 (C-4′), 125.4, 128.9 (C-3′,5′), 129.8, 130.1, 130.8, 132.7, 134.4, 137.8 (C-1′), 149.8 (C-1), 153.7(CO) 155.4 (C-3a). 123.5 (C-10), 129.7, 130.3, 132.2, 132.4, 132.5, 140.7 (C-1), 151.8 (C-3a), 169.5 (CO). Anal. Calc. for $C_{19}H_{19}N_5O$

(333.387): C, 68.45; H, 5.74; N, 21.01. Found: C, 68.63; H, 5.58; N, 21.12.

4,5-Dihydro-1,5-dimethyl-N-phenyl-6*H*--[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-6-carboxamide (4e).

The solid residue was crystallized from ethanol to yield 0.37 g (55%) of compound **4e**. M.p. 114-116 °C. IR, ν, cm^{-1}: 3390, 3333, 1658. ^{1}H NMR ($CDCl_3$), δ, ppm: 1.35 (3H, d, J=6.3, 5-CH_3), 2.27 (1H, dd, J=12.2, 14.9, CH_2), 2.56 (3H, s, 1-CH_3), 3.43 (1H, dd, J=6.1, 14.9, CH_2), 5.21 (1H, m, CH), 7.01 (1H, m, H-4′), 7.13-7.25 (4H, m, Ar), 7.49 (1H, dd, J=2.0, 8.0, H-10), 7.57 (1H, dd, J=1.8, 7.7, H-7), 7.63 (1H, dt, J=2.0, 7.6, H-8), 7.68 (1H, dt, J=1.9, 7.4, H-9). ^{13}C NMR ($CDCl_3$), δ, ppm: 11.6 (1-CH_3), 19.7 (5-CH_3), 30.5 (C-4), 55.8 (C-5), 119.9 (C-2′,6′), 123.7 (C-4′), 125.3 (C-10), 128.9 85 (C-3′,5′), 130.0, 130.3, 131.9, 132.6 (C-7), 133.5, 137.8 (C-1′), 149.6 (C-1), 152.5 (C-3a), 152.9 (CO). Anal. Calc. for $C_{19}H_{19}N_5O$ (333.387): C, 68.45; H, 5.74; N, 21.01. Found: C, 68.20; H, 5.90; N, 21.14.

6-Acetyl-5,6-dihydro-1,4-dimethyl-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine (4g).

The solid residue was crystallized from ethanol to yield 0.36 g (70%) of compound **4g**. M.p. 253-254 °C. IR, ν, cm^{-1}: 1656, ^{1}H NMR ($CDCl_3$), δ, ppm: 1.56 (3H, d, J=6.7, CH_3), 1.71 (3H, s, 6-CH_3), 2.56 (3H, s, 1-CH_3), 2.89 (1H, m, CH), 3.55 (1H, dd, J=6.5, 12.8, CH_2), 4.57 (1H, t, J=12.7, CH_2), 7.40 (1H, dd, J=1.8,7.9, Ar), 7.43 (1H, dd, J=1.9, 7.8, Ar), 7.56 (1H, dt, J=1.9, 7.9, Ar), 7.62 (1H, dt, J=1.8, 7.8, Ar). ^{13}C NMR ($CDCl_3$), δ, ppm: 11.3 (1-CH_3), 13.1 (br, 4-CH_3), 22.6 (6-CH_3) 28.9 (C-4), 55.4 (C-5), 124.7, 129.7, 129.9, 130.7, 131.8, 135.5, 149.6 (C-1), 155.2 (C-3a), 170.2 (CO) Anal. Calc. for $C_{14}H_{16}N_4O$ (256.303): C, 65.61; H, 6.29; N, 21.86. Found: C, 65.94; H, 6.10; N, 21.72.

IV. Conclusions

1. New 4-hydrazino-2,3-dihydro-1*H*-1,5-bezodiazepines were synthesized by the reaction of corresponding thiolactams with hydrazine hydrate.
2. New 5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines and 1-methyl-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines were synthesized by condensation of corresponding novel hydrazidines with triethyl orthoformate or triethyl orthoacetate.

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Lidija Kosihova, Zita Stumbrevičute, Regina Janciene, Vida Ragalevičiene, Lina Pleckaitiene, Zita Staniulite, Dalia Puodžiunaite, Algirdas Palaima. Jaunu 5,6-dihidro-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepīnu sintēze.

Sintezēta virkne jaunu 5,6-dihidro-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepīnu. Sintēzei nepieciešamās izejvielas 2,3-dihidro-1H-1,5-benzodiazepīnhidrazīni iegūti attiecīgo 2,3-dihidro-1H-1,5-benzodiazepīn-2-tionu reakcijā ar hidrazīnhidrāta pārākumu metanola šķīdumā un istabas temperatūrā. Visi 2,3-dihidro-1H-1,5-benzodiazepīnhidrazīni ir kristāliskas vielas. Heterocikliskie 4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepīni iegūti kondensējot [1,5]benzodiazepīna hidrazīnus ar trietilortoformiātu vai trietilortoacetātu ksilolā. Ksilola izvēli ciklizācijas reakcijai noteica eksperimenta rezultāti. Izmantojot šai reakcijai šķīdinātājus ar dažādu polaritāti un viršanas temperatūru – metanolu, izopropanolu, ksilolu, konstatēts, ka reakcijas norises laiks ir atkarīgs no šķīdinātāja viršanas temperatūras. Jāpiezīmē, ka augsti virstoša šķīdinātāja izmantošana palielina arī reakcijas produktu iznākumu. Novērots, ka elektrondonoro 5N-metilgrupu saturošā [1,5]benzodiazepīna hidrazīnu gadījumā ciklizācija notiek ilgāk un ar mazāku reakcijas iznākumu, nekā elektronakceptorās karbomoil- vai acetilgrupas saturošo [1,5]benzodiazepīna hidrazīnu gadījumā. ^{1}HKMRspektros cikliskiem triazoliem raksturīgo singletu ar ķīmiskām nobīdēm 8,32 – 8,46 ppm vai 2,47-2,56 ppm esamība norāda uz heterociklisko 5,6-dihidro-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepīnu vai 5,6-dihidro-1-metil-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepīnu veidošanos. Jauno 2,3-dihidro-1H-1,5-benzodiazepīnhdrazīnu un triciklisko 4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepīnu struktūras pētītas ar IS, ^{1}H un ^{13}C kodolmagnētiskās rezonanses spektroskopijas metodēm un apstiprinātas ar elementanalīžu rezultātiem

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Синтезирован ряд новых 5,6-дигидро-4H-[1,2,4]триазоло[4,3a][*1,5*]бензодиазепинов. Необходимые для синтеза исходные 2,3-дигидро-1H-1,5-бензодиазепингидразины получены в результате реакции соответствующих 2,3-дигидро-1H-1,5-бензодиазепин-2-тионов с избытком гидгазин гидрата в метаноле при комнатной температуре. Все 2,3-дигидро-1H-1,5-бензодиазепингидразины кристаллические вещества. Гетероциклические 4H-[1,2,4]триазоло[4,3a][*1,5*]бензодиазепины получены путем конденсации [*1,5*]бензодиазепингидразинов с триэтил ортоформиатом или триэтил ортоацетатом в ксилоле. Проведение циклизации в ксилоле обосновано результатами эксперимента. Используя для этой реакции различные по полярности и температуре кипения растворители - этанол, изопропанол, ксилол установлено,что время реакции зависит от температуры кипения растворителя. Отмечается, что используя высоко кипящие растворители наблюдается увеличение выхода целевого продукта. Замечено, что для *1,5*-бензодиазепингидразинов, имеющих электрон-донорную 5N-метильную группу, время образования цикла дольше, а выход продукта меньше, чем для *1,5*-бензодиазепингидразинов, имеющих электрон-акцепторную 5N-карбомоильную или ацетильную группу. Появление в ^{1}H ЯМРспектрах характерных циклическим триазолам синглетов, с химическим сдвигом 8.32–8.46 или 2.47–2.56 м.д., свидетельствует об образовании гетероциклических 5,6-дигидро-4H-[1,2,4]триазоло[4,3-a][1,5]бензодиазепинов или 5,6-дигидро-1-метил-4H-[1,2,4]триазоло[4,3-a][1,5] бензодиазепинов. Структура новых 2,3-дигидро-1H-1,5-бензодиазепингидразинов и трициклических 4H-[1,2,4]триазоло[4,3a][*1,5*]бензодиазепинов изучена методами ИК, ^{1}H и ^{13}C ЯМР спектроскопии и подтверждена данными элементного анализа.