A convenient synthesis of novel [1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine derivatives

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Abstract
Novel tricyclic substituted 5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one derivatives were prepared by the thermal intramolecular cyclization of tetrahydro-1,5-benzodiazepin-2-one *O*-(ethoxycarbonyl)oximes. The latter were obtained from the corresponding hydroxyimino-1,5-benzodiazepines and ethyl chloroformate.

Keywords: Hydroxyimino-1,5-benzodiazepines, [1,2,4]oxadiazoles, ethyl chloroformate

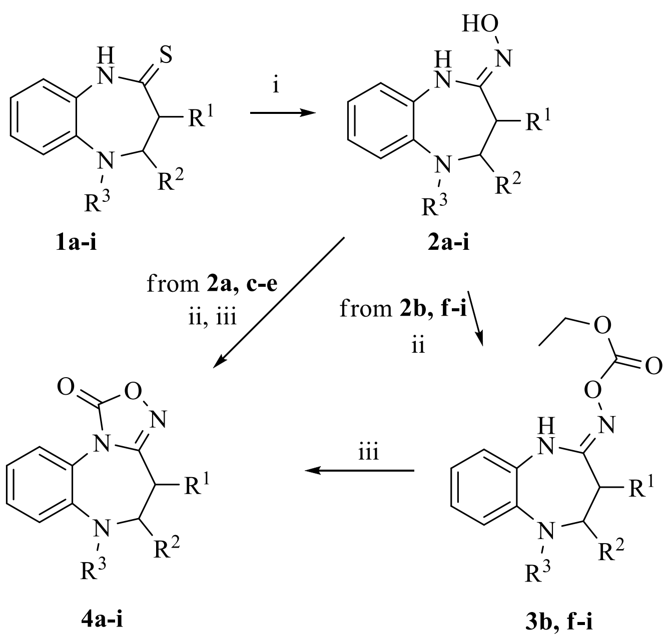
Introduction

The ability of the benzodiazepines as a chemical class to have an effect on different processes in the organism has found application as pharmaceutical.[1] It is known, in fact, that the pharmaceutical activity appears to be exchanged when different heterocyclic rings are annelated to the basic 1,4-and 1,5-benzodiazepine systems.[1,2] In previous papers we have reported the synthesis of polycyclic *peri*-annelated imidazo[1,5]benzodiazepines[3] and derivatives containing imidazo[4], triazolo[5] and thiazolo[6] nucleus fused to the "*a*" edge of the seven-membered ring of the 1,5-benzodiazepine system. In continuation of our investigation on tricyclic benzodiazepines, we have extended the cycloaddition strategy to develop a synthetic pathway towards 1,5-benzodiazepines including a 1,2,4-oxadiazole nucleus. In addition, compounds incorporating different oxadiazole rings have been attracting widespread attention due to their broad spectrum of biological activity in both agrochemical and pharmaceutical fields.[7]

A cyclofunctionalization strategy is based on exploiting the reactivity of the C=S group of the corresponding derivatives towards some nucleophiles, such as hydroxylamine. In recent years, some [1,2,4]oxadiazolo[1,5]benzodiazepine derivatives were prepared *via* the 1,3-dipolar cycloaddition to the dipolarophile C=N moiety of the diazepine skeleton.[2,8-11]

Results and Discussion

We present in this paper the preparation of the new tricyclic derivatives in 1,5-benzodiazepine series. For cyclofunctionalization of this system, we exploited the reactivity of the thiolactam function. Thiolactams **1a-i** were synthesized to supplement the lack of reactivity of the corresponding lactams[6,12] towards nucleophiles. Thiolactams **1a-i** were converted to the hydroxyimino-1,5-benzodiazepines **2a-i** in good yields by the action of hydroxylamine hydrochloride in boiling dry ethanol in the presence of sodium acetate (Scheme 1). The compounds **2a-f** were reported previously by us.[13] Thus, oximes **2a-i** were used as the starting materials for the construction of 1,2,4-oxadiazole derivatives. Furthermore, heterocyclic hydroxyimino derivatives were generally utilized as useful building blocks for the synthesis of condensed systems containing five-membered heterocyclic rings.[14-17] The structure of tetrahydro-1,5-benzodiazepinone oximes **2g-i** was supported by the following analysis of the IR and NMR spectra. The IR spectra exhibited typical NH and OH stretching bands between 3258-3131 cm^{-1} as well as stretching band for C=N at 1642-1630 cm^{-1} and C=O at 1679-1672 cm^{-1}. The ^1H NMR spectra showed sharp singlets of OH groups and broad singlets of NH groups at 9.61-9.85 and 8.33-8.38 ppm, respectively.



	R^1	R^2	R^3
1a-4a	H	H	Me
1b-4b	Me	H	Me
1c-4c	H	Me	Me
1d-4d	H	H	CONHPh
1e-4e	Me	H	CONHPh
1f-4f	H	Me	CONHPh
1g-4g	H	H	$COCH_3$
1h-4h	Me	H	$COCH_3$
1i-4i	H	Me	$COCH_3$

(i) $NH_2OH{\cdot}HCl$, CH_3COONa, C_2H_5OH, reflux, 8 h
(ii) $ClCOOC_2H_5$, $N(C_2H_5)_3$, $C_6H_5CH_3$, -3 °C, 2h
(iii) Dioxane-H_2O, reflux, 5 h

Scheme 1. The synthesis of [1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine derivatives **4a-i.**

The treatment of oximes **2a-i** with an equivalent amount of ethyl chloroformate in the presence of triethylamine led to the non cyclic corresponding products – *O*-(ethoxycarbonyl)-substituted 1,5-benzodiazepine derivatives. This reaction was accomplished during 2 hours at low temperature (-3 ºC) in toluene. The application of this pathway to the preparation of compounds **3a-i** gave intermediates suitable for the further synthesis of tricyclic oxadiazoles. The former publications reported the process of cyclization of hydroxyimino derivatives to [1,2,4]oxadiazolo derivatives where the starting compounds were allowed to react with phosgene in refluxing toluene.[14,15] An embodiment of this reaction has emphasized a preference for the presence of the base, mostly an organic base dissolved in an organic solvent inert in this reaction. An analogous synthesis of oxadiazole derivatives was described[16] but the reaction is carried out at low temperature under nitrogen. So, the treatment of **2a-i** with ethyl chloroformate enabled us to avoid phosgene for the synthesis of condensed heterocyclic compounds. The TLC monitoring showed that in these conditions only one product was obtained. Compounds **3b, f-i** were isolated as crystalline substances and identified. Decomposition or partial cyclization of oxime derivatives **3a, c-e** during the purification was observed therefore compounds **3a, c-e** were applied as crude products for further cyclization. The structure of compounds **3b, f-i** was confirmed on the basis of their spectroscopic characteristics. The long range coupling between NH proton and one proton of the methylene group of diazepine heterocycle ($^4J_{\text{H-N-C-C-H}}$ = 1.6 Hz) was observed in some spectra (**3f, i**).

Finally, the cyclocondensation of compounds **3a-i** was achieved by heating at reflux in the mixture of dioxane-water for 5 h. Oxadiazolo-benzodiazepines **4a-i** were obtained in good yields (61-91%, except **4a** which was obtained in 50% yield). The cyclization reaction was monitored by TLC analysis. The structures of novel compounds were confirmed by elemental analysis and IR, ^{1}H and ^{13}C NMR spectroscopic data. In the ^{1}H NMR spectra, the assignment of protons of benzo fragment of compounds **4a-c, g-i** was confirmed by NOE experiments. The NOEs (6-7%) were observed on aromatic proton H-7 at 7.17-7.19 ppm when methyl group (δ 2.83 ppm) was irradiated. The irradiation of acetyl group (δ 1.71-1.77 ppm) exhibited NOEs (2-3%) with H-7 at 7.38-7.39 ppm. This unequivocally proves the assignment of this proton. All other protons of this benzo fragment were assigned starting from H-7 proton signal using 2D COSY spectra. It is worth noting that essential low-field shift of H-10 proton with respect to other protons of benzene ring were observed probably due to the deshielding effect of the C=O group. After assignment of all protons of benzo fragment of compounds **4a-c, g-i**, it became possible to unambiguously identify the carbon atoms of this fragment in ^{13}C NMR spectra by means of ^{1}H-^{13}C 2D NMR (HETCOR) experiments. Moreover, in the ^{13}C NMR spectra of compounds **4a-i** the C-4, C-3a resonances are mainly influenced by the replacement of thiolactam[6,12] functionality with oxadiazole nucleus and shifted upfield (by 10-20 and 48-50 ppm, respectively) with respect to precursors **1a-i**.

Conclusions

In summary, the interaction of 4-hydroxyimino-1,5-benzodiazepines **2a-i** with ethyl chloroformate afforded the corresponding N–OH acylated compounds **3a-i**. The thermal cyclization reaction of **3a-i** provided a simple method for the preparation of novel tricyclic [1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine derivatives **4a-i**.

Experimental Section

General. Melting points were measured on a Barnstead International MEL-TEMP capillary melting point apparatus and are not corrected. Elemental analyses (C, H, N) were performed on an Elemental Analyser CE-440. IR spectra (4000-400 cm^{-1}) were recorded on a PERKIN Elmer Spectrum GX FT-IR spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Varian Unity Inova 300 spectrometer with DMSO-d_6 (compounds **2g-i**) and $CDCl_3$ (compounds **3b, f-i** and **4a-i**) as solvent. The chemical shifts are referenced to tetramethylsilane (δ ^1H = 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 groups in ^{13}C NMR were differentiated by means of the APT or DEPT method. The reactions were monitored by TLC using Silufol UV_{254} silica gel plates in the system: benzene-methanol (ν/ν, 6:1).

Thiolactams **1a-i** were synthesized according to the described procedure[6,12]. Hydroxyimino-1,5-benzodiazepines **2a-f** were synthesized from the corresponding thiolactams **1a-f** by treatment with hydroxylamine hydrochloride[13].

General procedure for the synthesis of 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one oximes (2g-i)

The mixture of thiolactam **1g-i** (10.0 mmol), hydroxylamine hydrochloride (10.4 g, 15.0 mmol) and sodium acetate (12.6 g, 15.0 mmol) in anhydrous ethanol (200 mL) was refluxed for 8 h. After cooling, the suspension obtained was filtered. The solvent was evaporated under reduced pressure. The resulted solid residue was recrystallized from an appropriate solvent to give white crystals.

5-Acetyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one oxime (2g). Yield 1.60 g, 73%, mp 187-189 ^oC (methanol). IR (ν_{max}, cm^{-1}): 3258, 3144, 1677, 1641. ^1H NMR (DMSO-d_6): δ 1.60 (3H, s, 5-CH_3), 2.22-2.38 (2H, m, 3-CH_2), 3.27 (1H, m, 4-CH_2), 4.51 (1H, m, 4-CH_2), 7.06 (1H, dt, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 8.3 Hz, Ar), 7.20-7.33 (3H, m, Ar), 8.33 (1H, br.s, NH), 9.61 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_c 22.4 (5-CH_3), 26.9 (C-3), 46.1 (C-4), 121.9, 123.2, 128.9, 129.6, 131.7, 138.3, 148.5 (C-2), 169.5 (5-CO). Anal. Calcd for $C_{11}H_{13}N_3O_2$ (219.24): C, 60.26; H, 5.98; N, 19.17. Found: C, 59.92; H, 6.04; N, 19.51.

5-Acetyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one oxime (2h). Yield 1.98g, 85%, mp 214-215 ^oC (1-propanol). IR (ν_{max}, cm^{-1}): 3235, 3135, 1679, 1642. ^1H NMR (DMSO-d_6): δ 1.04 (3H, d, $^3J_{HH}$ = 6.7 Hz, 3-CH_3), 1.62 (3H, s, 5-CH_3), 2.52 (1H, m, 3-CH), 3.32 (1H, dd, $^3J_{HH}$ = 6.0 Hz, $^2J_{HH}$ = 12.5 Hz, 4-CH_2), 4.22 (1H, dd, $^3J_{HH}$ = 12.5 Hz, $^2J_{HH}$ = 12.5 Hz, 4-CH_2), 7.07 (1H, dt, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 7.6 Hz, Ar), 7.21-7.34 (3H, m, Ar), 8.35 (1H, br.s, NH), 9.85

(1H, s, OH). ^{13}C NMR (DMSO-d$_6$): δ 13.4 (3-CH$_3$), 22.4 (5-CH$_3$), 31.7 (C-3), 53.6 (C-4), 122.0, 123.1, 128.9, 129.3, 132.7, 138.0, 150.3 (C-2), 169.3 (5-CO). Anal. Calcd for $C_{12}H_{15}N_3O_2$ (233.27): C, 61.79; H, 6.48; N, 18.01. Found: C, 61.60; H, 6.62; N, 18.45.

5-Acetyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one oxime (2i). Yield 1.89g, 81%, mp 218-220 °C (1-propanol). IR (ν_{max}, cm^{-1}): 3258, 3131, 1672, 1630. ^{1}H NMR (DMSO-d$_6$): δ 1.04 (3H, d, $^3J_{HH}$ = 6.3 Hz, 4-CH$_3$), 1.55 (3H, s, 5-CH$_3$), 1.90 (1H, dd, $^3J_{HH}$ = 12.4 Hz, $^2J_{HH}$ = 14.1 Hz, 3-CH$_2$), 2.37 (1H, dd, $^3J_{HH}$ = 5.5 Hz, $^2J_{HH}$ = 14.2 Hz, 3-CH$_2$), 4.85 (1H, m, 4-CH), 7.05 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.16 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.22 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, Ar), 7.30 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 8.38 (1H, br.s, NH), 9.63 (1H, s, OH). ^{13}C NMR (DMSO-d$_6$): δ 18.8 (4-CH$_3$), 22.6 (5-CH$_3$), 34.3 (C-3), 51.9 (C-4), 121.9, 123.0, 129.0, 129.6, 130.8, 138.6, 148.4 (C-2), 168.8 (5-CO). Anal. Calcd for $C_{12}H_{15}N_3O_2$ (233.27): C, 61.79; H, 6.48, N, 18.01. Found: C, 61.54; H, 6.66, N, 18.24.

General procedure for preparation of *O*-(ethoxycarbonyl)oximes (3b, f-i)

The solution of oxime **2b, f-i** (0.3 mmol) and triethylamine (0.42 mL, 0.3 mmol) in toluene (80 mL) was stirred and cooled to -3 °C temperature. To this mixture, ethyl chloroformate (0.29 mL, 0.3 mmol) in toluene (20 mL) was added drop wise during 2 h with stirring, maintaining temperature of the reaction mixture between -3 and 0 °C. After that the mixture was kept in a refrigerator overnight. Then triethylamine hydrochloride precipitate was filtered and the filtrate was concentrated under reduced pressure to the volume of 30 mL. After cooling, the precipitate was collected and recrystallized from an appropriate solvent to give white crystals of **3b, f-i**.

3,5-Dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one *O*-(ethoxycarbonyl)oxime (3b). Yield 0.56 g, 67%, mp 110-112 °C (diethyl ether). IR (ν_{max}, cm^{-1}): 3317, 1754, 1634. ^{1}H NMR (CDCl$_3$): δ 1.19 (3H, d, $^3J_{HH}$ = 6.8 Hz, 3-CH$_3$), 1.38 (3H, t, $^3J_{HH}$ = 7.1 Hz, 2-CH$_3$), 2.70 (1H, m, 3-CH), 2.82 (3H, s, 5-CH$_3$), 3.18-3.35 (2H, m, 4-CH$_2$), 4.33 (2H, q, $^3J_{HH}$ = 7.1 Hz, 2-CH$_2$), 6.92 (1H, dd, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 6.93-7.01 (2H, m, Ar), 7.01 (1H, br.s, NH), 7.15 (1H, dd, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 8.0 Hz, Ar). ^{13}C NMR (CDCl$_3$): δ 13.2 (3-CH$_3$), 14.4 (2-CH$_3$), 32.8 (C-3), 41.2 (5-CH$_3$), 64.4 (2-CH$_2$), 66.0 (C-4), 119.0, 121.8, 122.4, 125.8, 131.6, 142.7, 153.7, 158.2. Anal. Calcd for $C_{14}H_{19}N_3O_3$ (277.32): C, 60.63; H, 6.91; N, 15.15. Found: C, 60.97; H, 6.70; N, 15.64.

4-{[(Ethoxycarbonyl)oxy]imino}-2-methyl-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carboxamide (3f). Yield 0.95 g, 83%, mp 138-140 °C (toluene). IR (ν_{max}, cm^{-1}): 3347, 3206, 1764, 1662, 1632. ^{1}H NMR (CDCl$_3$): δ 1.27 (3H, d, $^3J_{HH}$ = 6.3 Hz, 2-CH$_3$), 1.36 (3H, t, $^3J_{HH}$ = 7.1 Hz, 4-CH$_3$), 2.13 (1H, dd, $^3J_{HH}$ = 12.4 Hz, $^2J_{HH}$ = 14.4 Hz, 3-CH$_2$), 2.72 (1H, ddd, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 5.4 Hz, $^2J_{HH}$ = 14.3 Hz, 3-CH$_2$), 4.33 (2H, q, $^3J_{HH}$ = 7.1 Hz, 4-CH$_2$), 5.13 (1H, m, 2-CH), 5.88 (1H, br.s, NHCO), 6.99 (1H, m, H-4′), 7.11 (1H, br.s, NH), 7.17 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.21-7.27 (4H, m, Ar), 7.29 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.34 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.44 (1H, m, Ar). ^{13}C NMR (CDCl$_3$): δ 14.3 (4-CH$_3$), 19.7 (2-CH$_3$), 34.3 (C-3), 54.0 (C-2), 64.8 (4-CH$_2$), 119.2 (C-2′, C-6′), 123.1 (C-4′, CH), 126.3, 128.8 (C-3′, C-5′), 129.5, 129.9, 131.4, 136.9, 138.3, 153.1, 153.2, 154.2. Anal. Calcd for $C_{20}H_{22}N_4O_4$ (382.41): C, 62.82; H, 5.80; N, 14.65. Found: C, 62.78; H, 5.96; N, 14.94.

5-Acetyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one *O*-(ethoxycarbonyl)oxime (3g). Yield 0.66 g, 76%, mp 154-156 °C (toluene). IR (ν_{max}, cm^{-1}): 3272, 1776, 1763, 1656, 1633. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, $^3J_{HH}$ = 7.1 Hz, 2-CH_3), 1.78 (3H, s, 5-CH_3), 2.48 (1H, m, 3-CH_2), 2.70 (1H, m, 3-CH_2), 3.49 (1H, m, 4-CH_2), 4.35 (2H, q, $^3J_{HH}$ = 7.1 Hz, 2-CH_2), 4.85 (1H, m, 4-CH_2), 7.06 (1H, s, NH), 7.10 (1H, dd, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 7.9 Hz, Ar), 7.19 (1H, dd, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 7.9 Hz, Ar), 7.23 (1H, dt, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.38 (1H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 14.3 (2-CH_3), 22.8 (5-CH_3), 26.7 (C-3), 47.0 (C-4), 64.8 (2-CH_2), 122.5, 126.0, 129.5, 130.0, 133.1, 135.5, 153.3 (4-CO), 154.4 (C-4), 170.6 (5-CO). Anal. Calcd for $C_{14}H_{17}N_3O_4$ (291.30): C, 57.72; H, 5.88; N, 14.42. Found: C, 57.59; H, 5.98; N, 14.80.

5-Acetyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one *O*-(ethoxycarbonyl) oxime (3h). Yield 0.74g, 81%, mp 133-135 °C (toluene). IR (ν_{max}, cm^{-1}): 3274, 1761, 1671, 1649, 1633. ^{1}H NMR ($CDCl_3$): δ 1.25 (3H, d, $^3J_{HH}$ = 6.3 Hz, 3-CH_3), 1.38 (3H, t, $^3J_{HH}$ = 7.1 Hz, 2-CH_3), 1.78 (3H, s, 5-CH_3), 2.71 (1H, m, 3-CH), 3.46 (1H, dd, $^3J_{HH}$ = 6.0 Hz, $^2J_{HH}$ = 12.9 Hz, 4-CH_2), 4.33 (2H, q, $^3J_{HH}$ = 7.1 Hz, 2-CH_2), 4.57 (1H, dd, $^3J_{HH}$ = 12.6 Hz, $^2J_{HH}$ = 12.9 Hz, 4-CH_2), 7.09 (1H, m, Ar), 7.10 (1H, s, NH), 7.18 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, Ar), 7.22 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, Ar), 7.36 (1H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 12.5 (3-CH_3), 14.3 (2-CH_3), 22.6 (5-CH_3), 32.3 (C-3), 54.4 (C-4), 64.7 (2-CH_2), 122.6, 125.8, 129.4 (2C), 133.5, 135.3, 153.3 (2-CO), 156.4 (C-2), 170.4 (5-CO). Anal. Calcd for $C_{15}H_{19}N_3O_4$ (305.33): C, 59.01; H, 6.27; N, 13.76. Found: C, 58.82; H, 6.38; N, 14.20.

5-Acetyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one *O*-(ethoxycarbonyl) oxime (3i).Yield 0.82g, 89%, mp 136-138 °C (toluene). IR (ν_{max}, cm^{-1}): 3241, 1771, 1649, 1632. ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, d, $^3J_{HH}$ = 6.3 Hz, 4-CH_3), 1.38 (3H, t, $^3J_{HH}$ = 7.2 Hz, 2-CH_3), 1.72 (3H, s, 5-CH_3), 2.12 (1H, dd, $^3J_{HH}$ = 12.4 Hz, $^2J_{HH}$ = 14.3 Hz, 3-CH_2), 2.65 (1H, ddd, $^4J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 5.4 Hz, $^2J_{HH}$ = 14.3 Hz, 3-CH_2), 4.34 (2H, q, $^3J_{HH}$ = 7.2 Hz, 2-CH_2), 5.18 (1H, m, 4-CH), 7.12 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.15 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, Ar), 7.15 (1H, s, NH), 7.24 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.7 Hz, Ar), 7.40 (1H, dt, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 7.8 Hz, Ar). ^{13}C NMR ($CDCl_3$): δ 14.3 (2-CH_3), 19.0 (4-CH_3), 22.9 (5-CH_3), 33.9 (C-3), 53.2 (C-4), 64.7 (2-CH_2), 122.4, 125.7, 129.6, 131.1, 131.2, 135.8, 153.2 (C-2), 154.2 (2-CO), 169.8 (5-CO). Anal. Calcd for $C_{15}H_{19}N_3O_4$ (305.33): C, 59.01; H, 6.27; N, 13.76. Found: C, 58.86; H, 6.47; N, 14.03.

General procedure for preparation of 5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-ones (4a, c) and 4,5-dihydro-6*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine-6-carboxamides (4d, e)

The solution of oxime **2a, c-e** (0.3 mmol) and triethylamine (0.42 mL, 0.3 mmol) in toluene (80 mL) was stirred and cooled to -3 °C temperature. To this mixture, ethyl chloroformate (0.29 mL, 0.3 mmol) in toluene (20 mL) was added drop wise during 2 h with stirring, maintaining temperature of reaction mixture between -3 and 0 °C. After that the mixture was kept in a refrigerator overnight. Then triethylamine hydrochloride precipitate was filtered. The solvent was evaporated to give a solid residue which was further dissolved in 50 mL of the mixture of dioxane-water (3:2) and heated to reflux for 4-5 h. Upon the completion of cyclization (TLC) the mixture was cooled to room temperature and was diluted with chloroform (50 mL). The organic layer was separated and aqueous phase was extracted with chloroform (2×20 mL). The combined organic solution was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The white solid was recrystallized from ethyl acetate to give **4a, c-e**.

6-Methyl-5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one (4a). Yield 0.36g, 55%, mp 155-156 °C. IR (ν_{max}, cm^{-1}): 1764. ^{1}H NMR ($CDCl_3$): δ 2.81 (2H, t, $^3J_{HH}$ = 6.7 Hz, 4-CH_2), 2.83 (3H, s, 6-CH_3), 3.41 (2H, t, $^3J_{HH}$ = 6.7 Hz, 5-CH_2), 7.20 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-7), 7.21 (1H, m, H-9), 7.40 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.56 (1H, dd, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 7.8 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 23.1 (C-4), 41.9 (6-CH_3), 55.9 (C-5), 121.0 (C-7), 123.7 (C-8), 123.8 (C-10), 126.2 (C-10a), 129.4 (C-9), 142.9 (C-6a), 156.6 (C-1), 157.6 (C-3a). Anal. Calcd for $C_{11}H_{11}N_3O_2$ (217.22): C, 60.82; H, 5.10; N, 19.34. Found: C, 60.70; H, 5.11; N, 19.65.

5,6-Dimethyl-5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one (4c). Yield 0.45 g, 65%, mp 121-123 °C. IR (ν_{max}, cm^{-1}): 1787, 1776. ^{1}H NMR ($CDCl_3$) : δ 1.19 (3H, d, $^3J_{HH}$ = 6.3 Hz, 5-CH_3), 2.29 (1H, dd, $^3J_{HH}$ = 9.7 Hz, $^2J_{HH}$ = 14.8 Hz, 4-CH_2), 2.83 (3H, s, 6-CH_3), 3.01 (1H, dd, $^3J_{HH}$ = 6.6 Hz, $^2J_{HH}$ = 14.8 Hz, 4-CH_2), 3.76 (1H, m, 5-CH), 7.20 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, H-7), 7.22 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.39 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-9), 7.57 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 15.4 (5-CH_3), 31.1 (C-4), 39.4 (6-CH_3), 60.1 (C-5), 123.6 (C-7, C-8), 124.0 (C-10), 127.2 (C-10a), 129.0 (C-9), 141.2 (C-6a), 156.6 (C-1), 157.4 (C-3a). Anal. Calcd for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.52; H, 5.57; N, 18.00.

1-Oxo-*N*-phenyl-4,5-dihydro-6*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine-6-carboxamide (4d). Yield 0.59 g, 61%, mp 214-216 °C. IR (ν_{max}, cm^{-1}): 3416, 3335, 1790, 1692, 1673. ^{1}H NMR ($CDCl_3$): δ 2.4-3.2 (2H, br.s, 4-CH_2), 3.3-4.2 (1H, br.s, 5-CH_2), 4.4-5.2 (1H, m, 5-CH_2), 6.21 (1H, s, NH), 7.02-7.29 (5H, m, Ar), 7.52-7.66 (3H, m, Ar), 7.80 (1H, m, H-10). ^{13}C NMR ($CDCl_3$): δ 22.8 (C-4), 45.7 (C-5), 119.8 (C-2′, C-6′), 123.7 (C-4′), 125.1 (C-10), 128.9 (C-3′, C-5′), 130.0 (C-10a), 130.2 (2CH), 130.3 (CH), 132.9 (C-6a), 137.7 (C-1′), 153.9 (CO), 156.1 (C-1), 156.6 (C-3a). Anal. Calcd for $C_{17}H_{14}N_4O_3$ (322.32): C, 63.35; H, 4.38; N, 17.38. Found: C, 63.56; H, 4.48; N, 17.50.

4-Methyl-1-oxo-*N*-phenyl-4,5-dihydro-6*H*-[1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepine-6-carboxamide (4e). Yield 0.65 g, 64%, mp 209-211 °C. IR (ν_{max}, cm^{-1}): 3413, 3335, 1788, 1693, 1671. ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, d, $^3J_{HH}$ = 6.7 Hz, 4-CH_3), 2.90 (1H, br.s, 4-CH), 3.77 (1H, br.s, 5-CH_2), 4.47 (1H, br.s, 5-CH_2), 6.09 (1H, s, NH), 7.04 (1H, m, H-4′), 7.20-7.29 (4H, m, Ar), 7.53-7.65 (3H, m, H-7,8,9), 7.80 (1H, m, H-10). ^{13}C NMR ($CDCl_3$): δ 11.6 (4-CH_3), 29.9 (C-4), 53.3 (C-5), 119.8 (C-2′, C-6′), 123.7 (C-4′), 125.2 (C-10), 128.9 (C-3′, C-5′), 129.9 (CH), 130.0 (C-10a), 130.1 (CH), 130.2 (CH), 133.2 (C-6a), 137.7 (C-1′), 153.8 (CO), 156.3 (C-1), 159.4 (C-

3a). Anal. Calcd for $C_{18}H_{16}N_4O_3$ (336.35): C, 64.28; H, 4.79; N, 16.66. Found: C, 64.49 H, 4.66; N, 16.72.

General procedure for preparation of 5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-ones (4b, g-i) and 4,5-dihydro-6*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine-6-carboxamides (4f)

A solution of *O*-(ethoxycarbonyl)oximes **3b, f-i** (0.3 mmol) in 50 mL of the mixture of dioxane-water (3:2) was heated to reflux for 4-5 h. Upon the completion of cyclization (TLC) the mixture was cooled to room temperature and was diluted with chloroform (50 mL). The organic layer was separated and aqueous phase was extracted with chloroform (2×20 mL). The combined organic solution was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The white solid was recrystallized from ethyl acetate to give **4b, f-i**.

4,6-Dimethyl-5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one (4b). Yield 0.59 g, 85%, mp 138-140 °C. IR (ν_{max}, cm^{-1}): 1776. ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, d, $^3J_{HH}$ = 6.8 Hz, 4-CH_3), 2.83 (3H, s, 6-CH_3), 2.85 (1H, m, 4-CH), 3.19-3.31 (2H, m, 5-CH_2), 7.17 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, H-7), 7.19 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-9), 7.39 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.54 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 11.8 (4-CH_3), 29.8 (C-4), 41.6 (6-CH_3), 64.0 (C-5), 120.6 (C-7), 123.5 (C-8), 123.9 (C-10), 126.0 (C-10a), 129.4 (C-9), 143.3 (C-6a), 156.8 (C-1), 160.4 (C-3a). Anal. Calcd for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.50; H, 5.51; N, 18.60.

5-Methyl-1-oxo-*N*-phenyl-4,5-dihydro-6*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepine-6-carboxamide (4f). Yield 0.73 g, 72%, mp 193-194 °C. IR (ν_{max}, cm^{-1}): 3369, 1789, 1775, 1669. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, d, $^3J_{HH}$ = 6.4 Hz, 5-CH_3), 2.25 (1H, dd, $^3J_{HH}$ = 11.8 Hz, $^2J_{HH}$ = 15.0 Hz, 4-CH_2), 3.15 (1H, dd, $^3J_{HH}$ = 6.5 Hz, $^2J_{HH}$ = 15.0 Hz, 4-CH_2), 5.25 (1H, m, 5-CH), 5.93 (1H, s, NH), 7.02 (1H, m, H-4′), 7.19-7.26 (4H, m, Ar), 7.49 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-7), 7.58 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.66 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-9), 7.82 (1H, dd, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 7.8 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 19.6 (5-CH_3), 30.1 (C-4), 52.4 (C-5), 119.8 (C-2′, C-6′), 123.7 (C-4′),125.2 (C-10), 128.8 (C-3′, C-5′), 130.1 (C-8), 130.6 (C-9, C-6a, C-10a), 131.8 (C-7), 137.7 (C-1′), 153.2 (CO), 156.0 (C-1), 156.5 (C-3a). Anal. Calcd for $C_{18}H_{16}N_4O_3$ (336.35): C, 64.28; H, 4.79, N, 16.66; Found: C, 64.45; H, 4.89; N, 16.39.

6-Acetyl-5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one (4g). Yield 0.60 g, 82%, mp 211-212 °C. IR (ν_{max}, cm^{-1}): 1784, 1656. ^{1}H NMR ($CDCl_3$): δ 1.77 (3H, s, 6-CH_3), 2.67 (1H, m, 4-CH_2), 3.13 (1H, m, 4-CH_2), 3.49 (1H, m, 5-CH_2), 5.05 (1H, m, 5-CH_2), 7.39 (1H, dd, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 7.8 Hz, H-7), 7.53 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.62 (1H, dt, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 7.8 Hz, H-9), 7.78 (1H, dd, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 7.8 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 22.6 (6-CH_3), 22.6 (C-4), 44.4 (C-5), 124.6 (C-10), 129.4 (C-10a), 129.8 (C-8), 130.2 (C-9), 130.4 (C-7), 134.0 (C-6a), 155.9 (C-1), 156.4 (C-3a), 170.6 (6-CO). Anal. Calcd for $C_{12}H_{11}N_3O_3$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.61; H, 4.62; N, 17.35.

6-Acetyl-4-methyl-5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one (4h). Yield 0.69 g, 89%, mp 194-196 ºC. IR (ν_{max}, cm^{-1}): 1802, 1779, 1668. ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, d, $^3J_{HH}$ = 6.7 Hz, 4-CH_3), 1.77 (3H, s, 6-CH_3), 2.88 (1H, m, 4-CH), 3.53 (1H, dd, $^3J_{HH}$ = 6.9 Hz, $^2J_{HH}$ = 12.9 Hz, 5-CH_2), 4.70 (1H, dd, $^3J_{HH}$ = 12.5 Hz, $^2J_{HH}$ = 12.9 Hz, 5-CH_2), 7.38 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-7), 7.52 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.61 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-9), 7.76 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.9 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 11.4 (4-CH_3) 22.6 (6-CH_3), 29.6 (C-4), 52.1 (C-5), 124.7 (C-10), 129.3 (C-10a), 129.8 (C-8), 130.0 (C-9), 130.3 (C-7), 134.2 (C-6a), 156.2 (C-1), 159.2 (C-3a), 170.5 (6-CO). Anal. Calcd for $C_{13}H_{13}N_3O_3$ (259.26): C, 60.22; H, 5.05; N, 16.21. Found: C, 60.02; H, 5.14; N, 16.50.

6-Acetyl-5-methyl-5,6-dihydro-4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,5]benzodiazepin-1-one (4i). Yield 0.71 g, 91%, mp 219-220 ºC. IR (ν_{max}, cm^{-1}): 1797, 1778, 1664. ^{1}H NMR ($CDCl_3$): δ 1.29 (3H, d, $^3J_{HH}$ = 6.4 Hz, 5-CH_3), 1.71 (3H, s, 6-CH_3), 2.25 (1H, dd, $^3J_{HH}$ = 11.9 Hz, $^2J_{HH}$ = 14.9 Hz, 4-CH_2), 3.10 (1H, dd, $^3J_{HH}$ = 6.3 Hz, $^2J_{HH}$ = 14.9 Hz, 4-CH_2), 5.36 (1H, m, 5-CH), 7.39 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-7), 7.53 (1H, dt, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-8), 7.64 (1H, dt, $^4J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 7.8 Hz, H-9), 7.79 (1H, dd, $^4J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 7.8 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ 19.2 (5-CH_3), 22.9 (6-CH_3), 29.8 (C-4), 51.3 (C-5), 124.6 (C-10),129.6 (C-8), 129.8 (C-10a), 130.5 (C-9), 131.7 (C-7), 132.0 (C-6a), 155.9 (C-1), 156.4 (C-3a), 170.0 (6-CO). Anal. Calcd for $C_{13}H_{13}N_3O_3$ (259.26): C, 60.22; H, 5.05; N, 16.21. Found: C, 60.46; H, 4.97; N, 16.73.

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