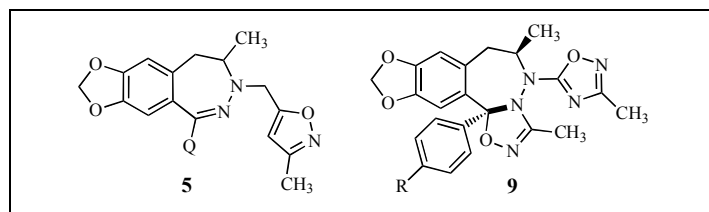


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We report here on some 3+2 dipolar cycloaddition reactions of propargyl, allyl and cyano substituted 2,3-benzodiazepines with *in situ* generated nitrile oxides and diazomethane. The reactivity of carbon-nitrogen double bonds of the 5*H*-[2,3]benzodiazepine ring system was also noticed.

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INTRODUCTION

AMPA (2-amino-3-(3-hydroxy-5-methyl-4-isoxazol-yl)propionic acid) antagonists play a significant role among the ionotropic glutamate receptor ligands and possess the capacity among others to serve as anticonvulsant and neuroprotective drugs [1,2]. Some 2,3-benzodiazepine (BDZ) derivatives have been recognized as highly active non-competitive AMPA antagonists and talampanel **1** is now under advanced Phase II clinical investigation [3]. Recently BDZ-s with heterocyclic substituents on the 7-membered ring nitrogen of general structure **2**, were discovered as very promising AMPA antagonists [4] (Figure 1). For further structure-activity relationship studies we intended to synthesize some cycloadducts from propargyl, allyl and cyano substituted BDZ-s **3a,b,c**.

RESULTS AND DISCUSSION

The starting compounds **3a,b,c** were prepared from 8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7*H*-(1,3)-dioxolo-[4,5-*h*][2,3]benzodiazepine (**4**) [4] by general alkylation procedures using propargyl, allyl bromide and cyanogen bromide, respectively. Cyclocondensations of **3a,b** with methyl nitrile

Scheme 1

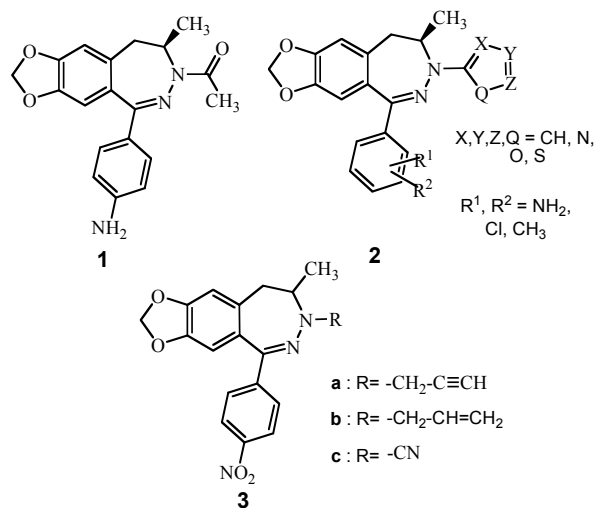
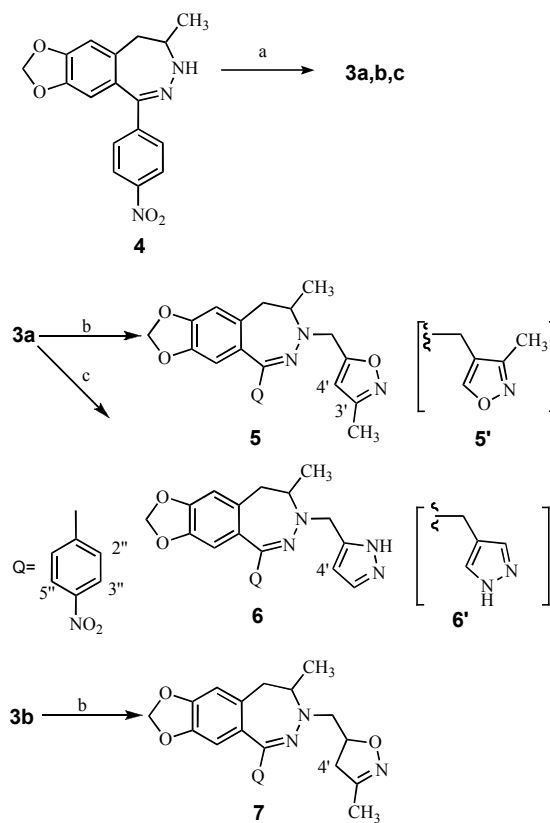


Figure 1. Precedents and starting materials.

a) propargyl or allylbromide or BrCN, DMF, K₂CO₃, 80°C; b) nitroethane, Et₃N, PhNCO, benzene, reflux; c) CH₂N₂, ether, rt.

oxide were carried out by a procedure according to ref. [5], where the nitrile oxide was prepared *in situ* from the thermal decomposition of an adduct from nitroethane and phenyl isocyanate. Thus isoxazole **5** and dihydro isoxazole **7** derivatives were prepared with acceptable yield (Scheme 1). The regioselectivity of the cycloaddition was proven by ^1H NMR NOESY experiments. Thus irradiation of isoxazole 4'-H gave intensity enhancements of the N-methylene and 3'-CH₃ signals, excluding by this the formation of the isomeric structure **5'** (partial structure in brackets). Similarly the irradiation of one of 4'-methylene protons in **7** gave intensity enhancements of the N-methylene and 3'-CH₃ signals.

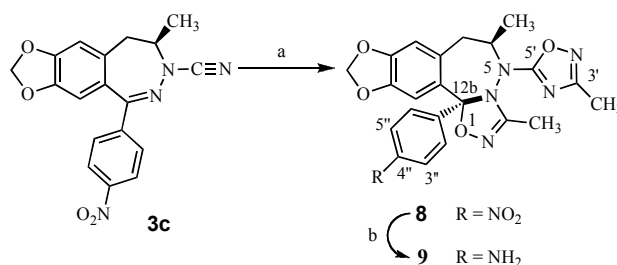
A cycloaddition reaction of **3a** with diazomethane resulted, on the other hand, in the formation of **6**. ^1H NMR investigations of **6** have shown two adjacent pyrrole ring protons and NOE effects were observed on N-methylene as well as the *ortho* proton signals of the nitrophenyl ring, when 4'-H was irradiated. These observations speak rather for pyrrole ring arrangement of **6** than **6'**.

When carbonitrile **3c** [4] was reacted with *in situ* generated methyl nitrile oxide a mixture formed, from which the main product was isolated by chromatography with modest yield. However, characterization of this nitro-compound was still not completely unambiguous, therefore a reduction to the corresponding amino compound **9** was performed in nearly quantitative yield (Scheme 2). Structure elucidation showed that two methyl nitrile oxide molecules have added and beside the nitrile group the carbon-nitrogen double bond of the seven membered ring has reacted as a dipolarophile as well. The *trans* position of the methyl and nitrophenyl groups was verified by NOESY spectra.

A similar reactivity of the carbon-nitrogen double bond of a 3,5-dihydro-4-oxo-4H-2,3-benzodiazepine with phenyl nitrile oxide was found by an Italian group as well [7].

The observed cycloaddition reaction of the ring carbon-nitrogen double bond prompted us to investigate the

Scheme 2

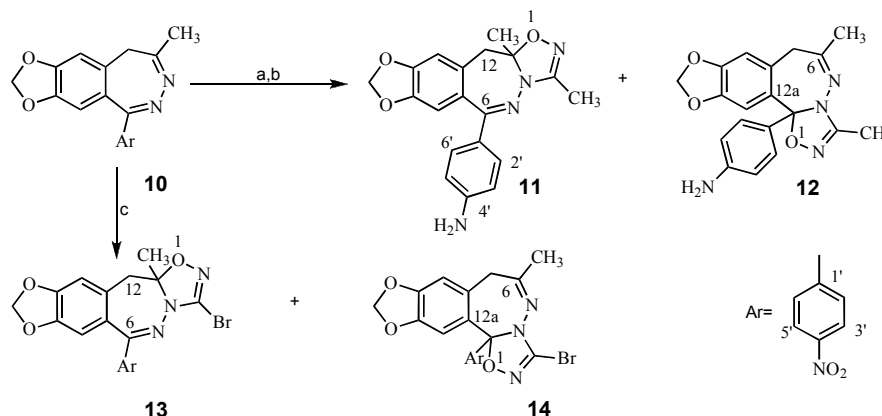


a) nitroethane, Et₃N, PhNCO, benzene, reflux; b) SnCl₂, MeOH, reflux.

reactivity of both possible C=N bonds of the 5H-2,3-benzodiazepine ring system with nitrile oxides, as well. Therefore **10** [6] was reacted with methyl and bromo nitrile oxide [8] (Scheme 3). In the first case with methyl nitrile oxide a chromatographically uniform mixture of compounds formed with acceptable yield that could not be separated. Therefore the mixture was reduced to give the corresponding amino compounds, which were easily separable. In the reaction of **10** with bromo nitrile oxide a well separable mixture of nitro adducts **13**, **14** formed. In both cycloaddition reactions the predominant formation of cycloadduct **11**, **13** was noticed, where addition took place next to the methyl substituent. As a reason for this we guess steric motives. The structure of the synthesized compounds was assessed by one-dimensional NOESY and two dimensional ^1H , ^1H -COSY measurements.

As the expected biological activity of BDZ derivatives resides generally in the amino compounds[3], the nitrophenyl derivatives **5**, **6**, **7**, **13**, prepared by above methods, were reduced to the corresponding amino compounds by known methods (see Experimental) providing amino compounds **15**, **16**, **17**, **18**, respectively

Scheme 3



a) nitroethane, Et₃N, PhNCO, benzene, reflux; b) SnCl₂, MeOH, reflux; c) formaldoxim dibromide, KHCO₃, toluene, rt.

(for formulae see **5**, **6**, **7**, **13** with Q = 4-aminophenyl). Compounds **9**, **11**, **12**, **15-18** were investigated for AMPA antagonist activity by using an established screening system [9]. They were subjected to *in vitro* screening for inhibition of AMPA (5 μ M) evoked spreading depression in isolated retina prepared from young chicken [10]. In addition, the molecules were also tested for anticonvulsant activity using the maximal electroshock seizure model [11], as well as for muscle relaxant activity, using the inclined screen test in mice [12]. With the new compounds no appreciable biological activity was noticed (IC_{50} s: >20 μ M, ED_{50} s: >100 mg/kg). This means that a tethered heterocyclic substituent at nitrogen atom 3 and condensed heterocycles on atoms 1-2 as well as next to the 4-methyl group of the BDZ ring system (BDZ numbering) seem unfavourable concerning the fitting ability of these BDZs to the active site.

EXPERIMENTAL

All melting points are uncorrected. 1H and ^{13}C nmr spectra were recorded on a Bruker Avance 500 MHz spectrometer with dimethyl- d_6 -sulfoxide as solvent and tetramethylsilane (TMS) as an internal standard. All reagents were obtained from commercial sources and used without further purification. Formaldoxime dibromide was prepared in practically quantitative yield according to ref. [8].

(\pm)-8-Methyl-5-(4-nitrophenyl)-7-propargyl-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (3a). A mixture of **4** (1.50 g, 4.6 mmol), potassium carbonate (0.91 g, 6.0 mmol) and propargyl bromide (0.52 mL, 6.9 mmol) in DMF (20 mL) was stirred at 80°C for 3 h. The reaction mixture was cooled to room temperature then poured into ice water. The precipitate was collected by filtration and recrystallized from ethanol to give yellow crystals, 1.21 g, 90 %, mp 132 °C; 1H nmr ($CDCl_3$): δ 8.19 (d, 2H, 3'-H, 5'-H, J = 8.8 Hz), 7.77 (d, 2H, 2'-H, 6'-H, J = 8.8 Hz), 6.79 (s, 1H, 10-H), 6.53 (s, 1H, 4-H), 6.02 (d, 1H, 2-H, J = 1.2 Hz), 5.98 (d, 1H, 2-H, J = 1.2 Hz), 4.17 (m, 1H, H-8), 3.94 (d, 1H, NCH_2 , J = 2.4 Hz), 2.98 (dd, 1H, 9-H, J_1 = 14.0 Hz, J_2 = 5.0 Hz), 2.46 (dd, 1H, 9-H, J_1 = 14.0 Hz, J_2 = 3.3 Hz), 2.30 (t, 1H, propargyl-CH, J = 2.4 Hz), 1.17 (d, 3H, CH_3 , J = 6.2 Hz). *Anal.* Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 65.16; H, 4.51; N, 11.27.

(\pm)-7-Allyl-8-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-[1,3]-dioxolo[4,5-*h*][2,3]benzodiazepine (3b). Prepared similarly to **3a**. The solid crude product was recrystallized from ethanol to give brown crystals, 1.89 g, 85 %, mp 127-128 °C; 1H nmr ($CDCl_3$): δ 8.17 (d, 2H, 3'-H, 5'-H, J = 8.5 Hz), 7.71 (d, 2H, 2'-H, 6'-H, J = 8.5 Hz), 6.75 (s, 1H, 10-H), 6.53 (s, 1H, 4-H), 6.01 (s, br, 1H, 2-H), 5.98 (s, br, 1H, 2-H), 5.98 (m, 1H, $-CH_2-CH=CH_2$), 5.23 (d, 1H, $CH_2-CH=CH_2$, J = 17.0 Hz), 5.19 (d, 1H, $CH_2-CH=CH_2$, J = 10.6 Hz), 4.02 (m, 1H, 8-H), 3.88 (d, 2H, $CH_2-CH=CH_2$, J = 6.2 Hz), 2.98 (dd, 1H, 9-H, J_1 = 14.0 Hz, J_2 = 4.0 Hz), 2.52 (dd, 1H, 9-H, J_1 = 14.0 Hz, J_2 = 4.5 Hz), 1.10 (d, 3H, CH_3 , J = 6.5 Hz). *Anal.* Calcd. for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.06; H, 5.08; N, 11.32.

General Procedure for Preparation of 5 and 7. A mixture of **3a** (1.0 g, 2.9 mmol) or **3b** (1.1 g, 2.9 mmol) and phenyl isocyanate (0.9 mL, 8.1 mmol) in benzene (15 mL) was added

dropwise to the solution of nitroethane (0.62 mL, 8.1 mmol) in benzene (15 mL) containing a few drops of triethylamine. After the addition was complete the solution was refluxed for 3 h. The reaction mixture was cooled to room temperature and the separated diphenylurea was filtered and the filtrate was evaporated in vacuo to give the solid product, which was recrystallized from ethanol.

(\pm)-8-Methyl-7-(3-methyl-isoxazol-5-yl)-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (5). Red crystals, 0.94g, 78 %, mp 179-180 °C; 1H nmr ($CDCl_3$): δ 8.17 (d, 2H, 3'-H, 5'-H, J = 8.9 Hz), 7.67 (d, 2H, 2'-H, 6'-H, J = 8.9 Hz), 6.78 (s, 1H, 10-H), 6.51 (s, 1H, 4-H), 6.01 (s, br, 1H, 2-H), 6.00 (s, br, 1H, 2-H), 5.94 (s, 1H, 4'-H), 4.42 (d, 1H, NCH_2 , J = 15.4 Hz), 4.37 (d, 1H, NCH_2 , J = 15.4 Hz), 4.01 (m, 1H, 8-H), 2.94 (dd, 1H, 9-H, J_1 = 13.8 Hz, J_2 = 4.8 Hz), 2.47 (dd, 1H, 9-H, J_1 = 13.8 Hz, J_2 = 4.0 Hz), 2.27 (s, 3H, CH_3), 1.19 (d, 3H, CH_3 , J = 6.1 Hz). *Anal.* Calcd. for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.52; H, 4.85; N, 13.14.

(\pm)-8-Methyl-7-(3-methyl-4,5-dihydro-isoxazol-5-yl)-methyl-5-(4-nitrophenyl)-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (7). Red crystals, 0.86g, 70 %, mp 123 °C; 1H nmr ($CDCl_3$, the ratio of two diastereomeric isomers was 1:1): δ 8.18 (d, 2H, 3'-H, 5'-H, J = 8.1 Hz), 7.67 (d, 2H, 2'-H, 6'-H, J = 8.1 Hz), 6.95 (s, 1H, 10-H), 6.51 (s, 1H, 4-H), 6.03 (s, br, 2H, 2-H), 4.8 - 4.6 (m, 1H, 5'-H), 4.08 - 4.03/4.03 - 3.95 (m, 1H, 8-H), 3.44/3.41 (dd, 1H, J_1 = 13.5 Hz, NCH_2 , J_2 = 6.4 Hz and dd, 1H, NCH_2 , J_1 = 13.6 Hz, J_2 = 4.8 Hz), 3.28/3.19 (dd, 1H, NCH_2 , J_1 = 13.6 Hz, J_2 = 6.7 Hz and dd, 1H, NCH_2 , J_1 = 13.5 Hz, J_2 = 5.9 Hz), 3.05 - 2.95 (m, 1H, 4'-H), 2.92 - 2.83 (m, 1H, 9-H), 2.75 - 2.65 (m, 1H, 4'-H), 2.65-2.58 (m, 1H, 9-H), 1.85/1.84 (s, 3H, CH_3), 0.96/0.95 (d, 3H, CH_3 , J = 6.7 Hz). *Anal.* Calcd. for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.16; H, 5.16; N, 12.93.

(\pm)-8-Methyl-5-(4-nitrophenyl)-7-(1H-pyrazol-3-yl)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (6). To a stirred and cooled (0 °C) solution of **3a** (0.70 g, 2.0 mmol) in dry dichloromethane (14 mL) a solution of diazomethane (0.14 g, 4.0 mmol) in dry ether (17 mL) was added dropwise for 20 minutes. After the addition was complete the reaction mixture was stirred overnight at room temperature. The ether was evaporated to give an oily residue, which was chromatographed on a silica gel column. Elution was made with chloroform-methanol (98:2) and the main fraction gave after evaporation a solid residue, 0.45 g, 55 %. mp. 186 °C; 1H nmr ($DMSO-d_6$ T = 348K): δ 8.14 (d, 2H, 3'-H, 5'-H, J = 8.9 Hz), 7.66 (d, 2H, 2'-H, 6'-H, J = 8.9 Hz), 7.50 (s, br, 1H, 3'-H), 6.88 (s, 1H, 10-H), 6.50 (s, 1H, 4-H), 6.13 (d, 1H, 4'-H, J = 2.0 Hz), 6.01 (d, 1H, 2-H, J = 1.0 Hz), 6.00 (d, 1H, 2-H, J = 1.0 Hz), 4.46 (d, 1H, NCH_2 , J = 14.3 Hz), 4.19 (d, 1H, NCH_2 , J = 14.3 Hz), 4.10 (m, 1H, 8-H), 2.84 (dd, 1H, 9-H, J_1 = 14.3 Hz, J_2 = 3.6 Hz), 2.61 (dd, 1H, 9-H, J_1 = 14.3 Hz, J_2 = 4.8 Hz), 0.98 (d, 3H, CH_3 , J = 5.5 Hz). *Anal.* Calcd. for $C_{21}H_{19}N_5O_4$: C, 62.22; H, 4.72; N, 17.27. Found: C, 61.92; H, 4.78; N, 16.98.

(6R,12bS)-12b-(4-Aminophenyl)-3,6-dimethyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-7,12b-dihydro-(1,2,4)-oxadiazolo[5,4-*a*]-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine (9). **3c** [4] (1.00 g, 2.86 mmol) was reacted with methyl nitrile oxide similarly as described for **5**. The crude product was chromatographed (silica gel, hexane-ethylacetate 3:1) and 0.35 g of a hogenous substance with R_f : 0.45 was isolated that was subjected to a nitro group reduction process, similarly to a General procedure (described later). The solid product was recrystallized from

dichloromethane to give **9**, 0.29 g, 24 %, mp 196 °C; ^1H nmr (DMSO- d_6): δ 7.13 (d, 2H, 2''-H, 6''-H, $J = 8.6$ Hz), 6.92 (s, 1H, 8-H), 6.50 (d, 2H, 3''-H, 5''-H, $J = 8.6$ Hz), 6.47 (s, br, 1H, 12-H), 6.01 (s, br, 1H, 10-H), 6.00 (s, br 1H, 10-H), 5.42 (s, br, 2H, NH_2), 4.42 (m, 1H, 6-H), 3.00 (dd, 1H, 7-H, $J_1 = 14.8$ Hz, $J_2 = 9.2$ Hz), 2.92 (dd, 1H, 7-H, $J_1 = 14.8$ Hz, $J_2 = 3.6$ Hz), 2.12 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.20 (d, 3H, CH_3 , $J = 6.6$ Hz). ^{13}C nmr: δ 170.7 (s, C-5'), 167.4 (s, C-3'), 152.7 (s, C-3), 149.3 (s, C-4''), 129.0 (d, C-2'', C-6''), 124.5 (s, C-1''), 112.9 (d, C-3'', C-5''), 111.0 (d, C-8), 109.1 (d, br, C-12), 101.5 (t, C-10), 100.9 (s, C-4a), 57.4 (d, br, C-6), 37.7 (t, br, C-7), 11.4 (q, CH_3), 9.0 (q, CH_3). *Anal.* Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_4$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.43; H, 4.97; N, 19.02.

(\pm)-6-(4-Aminophenyl)-3,12a-dimethyl-12,12a-dihydro-(1,2,4)-oxadiazolo[4,5-*c*][1,3]dioxolo[4,5-*h*][2,3]benzodiazepine (11) and (\pm)-12b-(4-Aminophenyl)-3,6-dimethyl-7,12b-dihydro-(1,2,4)-oxadiazolo[5,4-*a*][1,3]dioxolo[4,5-*h*][2,3]benzodiazepine (12). A mixture of 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (**10**) (1.00 g, 3.1 mmol) and phenyl isocyanate (1.71 mL, 15.5 mmol) in benzene (15 mL) was added dropwise to the solution of nitroethane (1.10 mL, 15.5 mmol) and a few drops of triethylamine in benzene (15 mL). After the addition was complete, the solution was refluxed for 3 h. The reaction mixture was cooled to room temperature and the diphenylurea formed was separated by filtration. The filtrate was evaporated *in vacuo* to give an oily residue (0.9 g).

This residue was dissolved in methanol (40 mL) and tin(II) chloride-2-hydrate (3.23 g, 14.4 mmol) was added and the solution was refluxed for 4 hours. Evaporation gave an oily residue, which was taken up in ethyl acetate (60 mL) and washed with 1 N sodium hydroxide (20 mL) and water (20 mL). The organic layer was dried and evaporated to yield an oil which was chromatographed (silica gel, chloroform-methanol 98:2) to give **11** and **12**.

11, Yellow crystals, R_F : 0.6, 0.65 g, 60 % yield, mp 189-191 °C; ^1H nmr (CDCl_3): δ 7.31 (d, 2H, 2'-H, 6'-H, $J = 8.6$ Hz), 6.78 (s, 1H, 11-H), 6.74 (s, 1H, 7-H), 6.68 (d, 2H, 3'-H, 5'-H, $J = 8.6$ Hz), 6.02 (d, $J_2 = 1.3$ Hz, 1H, 9-H), 6.00 (d, $J_2 = 1.3$ Hz, 1H, 9-H), 4.5 - 3.3 (br, 2H, NH_2), 3.13 (d, 1H, 12-H, $J = 13.5$ Hz), 3.03 (d, 1H, 12-H, $J = 13.5$ Hz), 2.26 (s, 3H, CH_3), 1.12 (s, 3H, CH_3). ^{13}C NMR δ 155.2 (s, C-3), 149.0 (s, C-10a), 146.6 (s, C-4'), 146.2 (s, C-7a), 145.9 (s, C-6), 132.9 (s, C-11a), 131.0 (s, C-1'), 130.3 (d, C-2', C-6'), 126.1 (s, C-6a), 114.6 (d, C-3', C-5'), 110.7 (d, C-7), 109.4 (d, C-11), 101.6 (t, C-9), 100.9 (s, C-12a), 42.2 (t, C-12), 25.9 (q), 10.3 (q). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_3$: C, 65.15; H, 5.18; N, 15.99. Found: C, 64.91; H, 5.43; N, 15.44.

12, Yellow crystals, R_F : 0.5, 0.18g, 15 % yield, mp 211-213 °C; ^1H nmr (DMSO- d_6): δ 7.10 (s, H-8), 6.78 (s, 1H, H-12), 6.76 (d, 2H, 2'-H, 6'-H, $J = 8.7$ Hz), 6.52 (d, 2H, 3'-H, 5'-H, $J = 8.7$ Hz), 6.03 (s, br, 1H, H-10), 6.02 (s, br, 1H, H-10), 5.30 (s, br, 2H, NH_2), 3.35 (d, 1H, H-7, $J = 16.7$ Hz), 3.00 (d, 1H, H-7, $J = 16.7$ Hz), 1.98 (s, 3H, CH_3), 1.87 (s, 3H, CH_3). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_3$: C, 65.15; H, 5.18; N, 15.99. Found: C, 64.83; H, 5.01; N, 15.44.

(\pm)-6-(4-Nitrophenyl)-3-bromo-12a-methyl-12,12a-dihydro-(1,2,4)-oxadiazolo[4,5-*c*]-[1,3]dioxolo[4,5-*h*][2,3]benzodiazepine (13) and (\pm)-12b-(4-Nitrophenyl)-3-bromo-6-methyl-7,12b-dihydro-(1,2,4)-oxadiazolo[5,4-*a*][1,3]dioxolo[4,5-*h*][2,3]benzodiazepine (14). A mixture of 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (**10**) (0.70 g, 2.1 mmol) formaldoxime dibromide (0.24 g, 1.1 mmol) and potassium hydrogencarbonate (0.21 g, 2.1 mmol) in toluene

(15 mL) was stirred at room temperature for 24 hours. The reaction mixture was washed with water and after drying the solvent was evaporated to give a mixture of two compounds. Separation was performed by column chromatography (silica gel, ethylacetate-hexane 1:4) to give **13** and **14**.

13, Yellow crystals, R_F : 0.5, 0.46 g, 50 %, mp 215 °C; ^1H nmr (CDCl_3): δ 8.24 (d, 2H, 3'-H, 5'-H, $J = 8.9$ Hz), 7.73 (d, 2H, 2'-H, 6'-H, $J = 8.9$ Hz), 6.85 (s, 1H, H-11), 6.59 (s, 1H, H-7), 6.08 (d, $J_2 = 1.2$ Hz, 1H, H-9), 6.05 (d, $J_2 = 1.2$ Hz, 1H, H-9), 3.24 (d, 1H, H-12, $J = 13.9$ Hz), 3.13 (d, 1H, H-12, $J = 13.9$ Hz), 1.28 (s, 3H, CH_3). ^{13}C NMR δ 150.1 (s, C-10a), 148.0 (s, C-4'), 147.0 (s, C-7a), 145.7 (s, C-6), 145.6 (s, C-1'), 139.2 (s, C-3), 132.6 (s, C-11a), 130.0 (d, C-2', C-6'), 125.5 (d, C-3', C-5'), 109.9 (d, C-11), 109.8 (d, C-7), 103.6 (s, C-12a), 102.1 (t, C-9), 41.5 (t, C-12), 25.7 (q, CH_3). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_5\text{Br}$: C, 48.56; H, 2.94; N, 12.58. Found: C, 48.80; H, 2.96; N, 12.65.

14, Yellow crystals, R_F : 0.35, 0.07 g, 10 %, mp 237 °C; ^1H nmr (DMSO- d_6): δ 8.28 (d, 2H, 3'-H, 5'-H, $J = 8.9$ Hz), 7.46 (d, 2H, 2'-H, 6'-H, $J = 8.9$ Hz), 7.09 (s, 1H, H-8), 6.93 (s, 1H, H-12), 6.08 (s, br, 2H, H-10), 3.37 (d, 1H, H-7, $J = 16.1$ Hz), 3.25 (d, 1H, H-7, $J = 16.1$ Hz), 2.01 (s, 3H, CH_3). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_5\text{Br}$: C, 48.56; H, 2.94; N, 12.58. Found: C, 48.70; H, 2.90; N, 12.08.

General Procedure for Reduction of Nitro Compounds 5, 6, 7, 13. A mixture of the nitro compound (1.0 mmol) and tin(II) chloride-2-hydrate (6.0 mmol) in methanol (30 mL) was refluxed for 4 h, then the solution was evaporated *in vacuo* to give an oily residue. The residue was taken up in ethyl acetate (60 mL) and washed with 1 N sodium hydroxide (20 mL) and water (20 mL). The organic layer was dried (magnesium sulfate) and evaporated to yield an oil which was crystallized from ethanol. The yields vary between 89 and 96%.

(\pm)-5-(4-Aminophenyl)-8-methyl-7-(3-methylisoxazol-5-yl)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (15). Yellow crystals, 96 %, mp 180-182 °C; ^1H nmr (CDCl_3): δ 7.35 (d, 2H, 2''-H, 6''-H, $J = 8.3$ Hz), 6.79 (s, 1H, 10-H), 6.63 (s, 1H, 4-H), 6.62 (d, 2H, 3''-H, 5''-H, $J = 8.3$ Hz), 6.00 (s, br, 1H, 2-H), 5.99 (s, br, 1H, 2-H), 5.83 (s, 1H, 4'-H), 4.26 (d, 1H, NCH_2 , $J = 15.4$ Hz), 4.20 (d, 1H, NCH_2 , $J = 15.4$ Hz), 3.85 (s, br, 2H, NH_2), 3.77 (m, 1H, 8-H), 2.83 (dd, 1H, 9-H, $J_1 = 13.8$ Hz, $J_2 = 6.4$ Hz), 2.34 (dd, 1H, 9-H, $J_1 = 13.8$ Hz, $J_2 = 4.2$ Hz), 2.24 (s, 3H, CH_3), 1.25 (d, 3H, CH_3 , $J = 6.0$ Hz). *Anal.* Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.06; H, 5.75; N, 13.94.

(\pm)-8-Methyl-5-(4-aminophenyl)-7-(1H-pyrazol-3-yl)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (16). Yellow crystals, 86 %, mp 96-98 °C; ^1H nmr (DMSO- d_6 T = 348K): δ 7.42 (s, br, 1H, 3'-H), 7.18 (d, 2H, 2''-H, 6''-H, $J = 8.3$ Hz), 6.93 (s, 1H, 10-H), 6.51 (d, 2H, 3''-H, 5''-H, $J = 8.3$ Hz), 6.47 (s, 1H, 4-H), 6.02 or 5.97 (s, 1H, 4'-H), 6.02 (s, 2H, 2-H) or 6.02 (s, 1H, 2-H) and 5.97 (s, 1H, 2-H), 4.09 (d, 1H, NCH_2 , $J = 14.4$ Hz), 4.00 (d, 1H, NCH_2 , $J = 14.4$ Hz), 3.63 (m, 1H, 8-H), 2.64 (dd, 1H, 9-H, $J_1 = 13.7$ Hz, $J_2 = 6.1$ Hz), 2.28 (dd, 1H, 9-H, $J_1 = 13.7$ Hz, $J_2 = 4.9$ Hz), 1.12 (d, 3H, CH_3 , $J = 5.8$ Hz). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 66.86; H, 5.41; N, 18.44.

(\pm)-5-(4-Aminophenyl)-8-methyl-7-(3-methyl-4,5-dihydroisoxazol-5-yl)-methyl-8,9-dihydro-7H-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine (17). Yellow crystals, 92 %, mp 103-104 °C; ^1H nmr (CDCl_3): δ 7.40/7.39 (d, 2H, 2''-H, 6''-H, $J = 8.9$ Hz), 6.76/6.75 (s, 1H, 10-H), 6.65 (d, 2H, 3''-H, 5''-H, $J = 8.9$ Hz), 6.58/6.57 (s, 1H, 4-H), 5.99 (s, br, 2H, 2-H)/ 5.99 (d, 1H, 2-H, $J = 1.0$ Hz) and 5.98 (d, 1H, 2-H, $J = 1.0$ Hz), 4.78/4.63 (m, 1H,

8-H), 3.83 (s, br, 2H, NH₂), 3.70 (m, 1H, 8-H), 3.38/3.35 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 5.1$ Hz and dd, 1H, $J_1 = 12.5$ Hz, $J_2 = 4.9$ Hz), 3.03/3.00 (dd, 1H, $J_1 = 12.8$ Hz, $J_2 = 5.9$ Hz and dd, 1H, $J_1 = 12.5$ Hz, $J_2 = 6.0$ Hz), 2.86 - 2.66 (m, 3H), 2.34/2.30 (dd, 1H, $J_1 = 13.8$ Hz, $J_2 = 6.1$ Hz and dd, 1H, $J_1 = 13.7$ Hz, $J_2 = 3.8$ Hz), 1.90 (s, 3H, CH₃), 1.17/1.15 (d, 3H, CH₃, $J = 6.2$ Hz). *Anal.* Calcd. for C₂₂H₂₄N₄O₃: C, 67.33; H, 6.16; N, 14.28. Found: C, 66.86; H, 6.32; N, 14.08.

(±)-6-(4-Aminophenyl)-3-bromo-12a-methyl-12,12a-dihydro-(1,2,4)-oxadiazolo[4,5-c]-[1,3]dioxolo[4,5-h][2,3]benzodiazepine (18). Yellow crystals, 68 %, mp 165-167 °C; ¹H nmr (DMSO-*d*₆): δ 7.15 (s, 1H, H-11), 7.14 (d, 2H, 2'-H, 6'-H $J = 8.6$ Hz), 6.63 (s, 1H, H-7), 6.55 (d, 2H, 3'-H, 5'-H, $J = 8.6$ Hz), 6.11 (s, br, 1H, H-9), 6.10 (s, br, 1H, H-9), 5.50 (s, br, 2H, NH₂), 3.32 (d, 1H, H-12, $J = 13.3$ Hz), 2.88 (d, 1H, H-12, $J = 13.3$ Hz), 1.14 (s, 3H, CH₃). *Anal.* Calcd. For C₁₈H₁₅N₄O₃Br: C, 52.06; H, 3.64; N, 13.49. Found: C, 51.76; H, 3.42; N, 13.39.

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