New Features in Synthesis of Talampanel Related 2,3-Benzodiazepines

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Abstract: Analogues of talampanel (**1**), a highly active AMPA antagonist 2,3-benzodiazepine, were synthesized, where the characteristic amino-function was either transposed or sterically shielded. For the key intermediates (hemiketals **6a**, **b**) a new synthetic method of different mechanism was developed. The inactivity of several new compounds indicates the significance of the 4-amino(phenyl) function in BDZs of type **1**.

Key Words: Oxidation, isochromane, hemiketal, 2,3-benzodiazepine, metabolism.

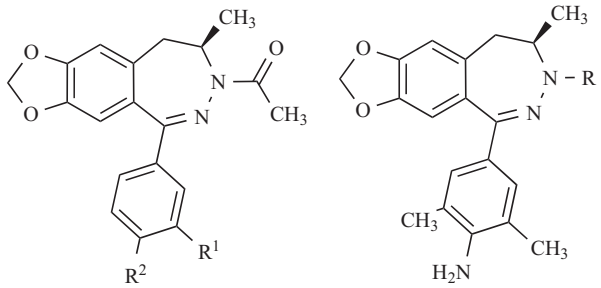
INTRODUCTION

Talampanel (**1**, (R)-7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine) is a non-competitive AMPA antagonist 2,3-benzodiazepine (BDZ) that is now under advanced Phase II clinical investigation [1-3]. Fig. (**1**). Broad structure-activity relationship studies revealed several different structural features around the BDZ ring system that beneficially influenced the AMPA antagonist activity and some successful substitutes for the functions in molecule **1** were found [4]. A characteristic substituent of the high activity BDZs is the 4-aminophenyl group. The role of the amino group was studied, thus e.g. its change in **1** for chlorine caused a heavy loss in the AMPA antagonist activity [5]. Obviously the pure H-bond acceptor character of the chlorine atom did not fulfill the requirements of the binding site. However, the amino group of active 2,3-BDZs seems not to be an indispensable prerequisite of the biological activity, because we have found some types of BDZs where a desamino compound still possessed some AMPA antagonist activity [5].

A transposition of the amino group into meta position resulted sometimes in compounds with significant *in vivo* (anticonvulsant) effect [6], however, results of *in vitro* measurements confirming the AMPA antagonist mode of action are not obvious [4,6,7].

It has been shown that the first path metabolism of **1** is the N-acetylation of the aminophenyl ring and this seems to be true for other active BDZ derivatives, bearing an aminophenyl ring, as well [8]. It was an interesting pursuit to slow down this metabolic inactivation by the introduction of a methyl substituent next to the amino function [9]. The authors of this patent application claim stronger and longer lasting effects for some analogs of **1**.

Our structure-activity relationship studies required among others to prepare the meta-amino isomer **2** and analogs **3b,c**, with completely shielded amino function, all as pure R enantiomers, of the same absolute configuration as **1.** Fig. (**1**). During the synthesis of **2** and **3b,c** an attempt was made to follow the efficient synthesis of **1** [10,11]. However, because of failures with established synthetic steps new solutions were elaborated that prompted us to publish them.



1 (R^1 = H, R^2 = NH_2)
2 (R^1 = NH_2, R^2 = H)

3a (R = H)
3b (R = $COCH_3$)
3c (R = $CONHCH_3$)

Fig. (1). Structures of talampanel (1) and addressed analogues.

RESULTS AND DISCUSSION

(S)-1-(3,4-Methylenedioxyphenyl)-2-isopropanol (**4**)[11] was converted with 3-nitrobenzaldehyde and 3,5-dimethyl-4-nitrobenzaldehyde [12] into isochromanes **5a,b** (Scheme **1**). In the synthesis of **1** the next step is a smooth conversion of the corresponding isochromane **5c** into hemiketal **6c** by using air oxidation under strongly basic conditions in a DMSO-DMF solvent mixture. However, this method was inefficient when starting with **5a** and **5b**. In the former case no reaction was observed, whereas **5b** gave an undefinable product mixture. Obviously the meta positioned nitro group in **5a** results in an electronically unfavourable transition state preventing thereby the oxidation at carbon 1, while, **5b** possesses additional exposed benzylic hydrogens, which are potentially prone to deprotonation and oxidation at the reaction conditions applied.

To circumvent these problems another oxidation method of different mechanism was looked for.

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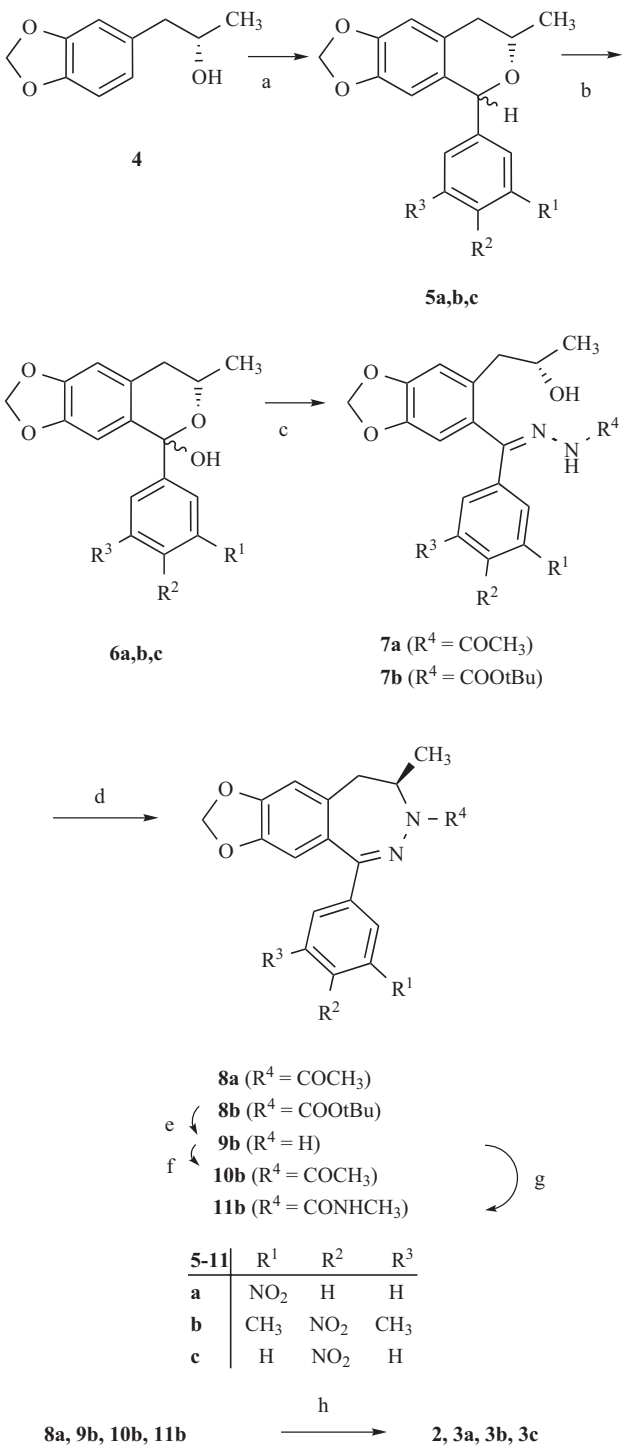

5-11	R^1	R^2	R^3
a	NO_2	H	H
b	CH_3	NO_2	CH_3
c	H	NO_2	H

Scheme (1). Synthesis and conditions: (a) benzaldehyd derivative, toluene, cat. HCl, 60°C; (b) CH_2Cl_2, 5 % H_2O, DDQ; (c) acethydrazide or *tert*-butyl carbazate, toluene, cat. HCl, reflux; (d) 1. CH_2Cl_2, Et_3N, MsCl, 0°C; 2. EtOH, NaOH; (e) HCl/ethyl acetate, rt.; (f) CH_2Cl_2, acetic anhydride, rt.; (g) CH_2Cl_2, methyl isocyanate; (h) CH_2Cl_2-MeOH (1:1), Raney Ni, $N_2H_4.H_2O$, rt.

It is known that benzylic carbon atoms can be oxidized e.g. by chromium trioxide [13,14], ceric ammonium nitrate [15] and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[16-18] providing an oxocarbenium ion, that can capture an alcohol or water molecule and depending on reaction conditions this results in acetal, hemiketal or lactone formation.

When the above methods were applied to isochromanes, however, product mixtures arose [14,18]. Nevertheless we expected that the neutral conditions of the oxidation with DDQ and the possible involvement of a cationic reactive intermediate instead of an anionic or radical intermediate could be useful in the oxidation of phenyl-substituted isochromanes **5a,b,c**. Indeed, when **5a,b,c** were treated with an excess of DDQ in dichloromethane in the presence of water, hemiketals **6a,b,c** formed in a smooth reaction with nearly quantitative yield. The further steps of the synthesis were performed in analogy of the synthesis of **1** [10]. Hemiketals **6a,b** were reacted with acetic hydrazide and *tert*-butyl carbazate, respectively, by refluxing the reactants in toluene with removal of water. The resulting hydrazones **7a,b** are mixtures of geometric isomers and were used without any purification. Mesylation of **7a,b** yielded the corresponding mesylates which after the usual workup, were treated immediately with ethanolic sodium hydroxide solution to give BDZ derivatives **8a,b**. Our strategy to synthesize **8b**, with the easily hydrolysable *tert*-butoxycarbonyl protecting group, allowed us to prepare the unsubstituted **9b** by treatment with hydrochloric acid in ethyl acetate. Simple acylations of **9b** provided nitro derivatives **10b** and **11b**. The nitro group in **8a**, **9b**, **10b**, **11b** was reduced by transfer hydrogenation using Raney Ni and hydrazine hydrate to give **2**, **3a**, **3b**, **3c**, respectively.

The latter amino compounds were subjected to in vitro screening for inhibition of AMPA (5 μM) evoked spreading depression in isolated retina prepared from young chicken [19]. Compound **2**, being the structural isomer of **1**, was also investigated for inhibition of AMPA (5 μM) induced whole-cell currents in freshly isolated cerebellar Purkinje cell [20]. The molecules were also tested for anticonvulsant activity using the maximal electroshock seizure model [21] and for muscle relaxant activity, using the inclined screen test in mice [22]. Compounds **2**, **3a**, **3b**, **3c** showed no in vitro activities up to 20 μM concentration in the retina test (IC_{50} >20 μM) and the patch clamp IC_{50} value for **2** was found >100 μM. From these compounds only **3a** revealed a weak anticonvulsant (ED_{50}: 50-100 mg/kg, po) and muscle relaxant activity (ED_{50}: 100-200 mg/kg, ip). Thereby this compound showed a quite different character than its desmethyl racemic analogue (GYKI-52895), that became known as a selective dopamine uptake inhibitor with antidepressant and antiparkinson character [23]. No appreciable anticonvulsant activity was noticed in the electroshock test with compounds **2**, **3b**, **3c** (ED_{50}: >100 mg/kg, po) and ED_{50}-s in the muscle relaxant assay were found to be ≥200 mg/kg (ip) for **3b**, **3c**. Only **2** showed a very weak muscle relaxant activity (ED_{50} between 50-200 mg/kg, ip).

CONCLUSION

The application of a neutral hemiketal-formation reaction and a *tert*-butoxycarbonyl substituted BDZ intermediate during the preparation of some talampanel analogs can enrich the scope of the 2,3-BDZ-synthesis. The findings of the biological investigations contribute to the knowledge

about the importance of the position and steric demand of the amino function of active AMPA antagonist BDZ derivatives related to **1**. They can also help refining the pharmacophore model of the AMPA antagonist BDZs [5].

EXPERIMENTAL SECTION

General Remarks

^{1}H and ^{13}C NMR spectra were measured at 500 MHz and 127 MHz, respectively on BRUKER AVENCE 500 instrument at 300K. Mass spectra were recorded on Finnigen MAT 8430 mass spectrometer, operating conditions: electron ionization, E_{el}=70 eV, I_{el}= 0.5 mA, U_{acc}= 3 kV, R=1250. Pure enantiomers **2**, **3a**,**b**,**c**, **8a**,**b**, **9b**, **10b**, **11b** were additionally characterized by optical rotation measurements.

General Procedure For Isochromanes 5a,b

Isopropanol derivative **4** (10.5 g, 50.0 mmol) and the corresponding benzaldehyde derivative (50.0 mmol) were dissolved in toluene (100 mL). Conc. HCl (4 mL) was added and the mixture was stirred at 60°C for 2h. The toluene solution was decanted from an oily residue and evaporated to dryness. The residue was suspended in ethanol, filtered and washed with ethanol.

(3S)- 3 - Methyl-6,7-methylenedioxy-1-(3-nitrophenyl)-isochromane (5a)

Yield:75% (ca. 90 % pure diastereomer): ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 6.1 Hz, 3H, CH-C<u>H</u>$_3$), 2.70 (dd, J_1 = 16.0 Hz, J_2 = 2.5 Hz, 1H) and 2.86 (dd, J_1 = 16.0 Hz, J_2 = 11.1 Hz, 1H, CH-C<u>H</u>$_2$), 4.00 (m, 1H, C<u>H</u>-CH$_3$), 5.75 (s, 1H, CH-O), 5.86 (d, J = 1.3 Hz, 1H) and 5.88 (d, J = 1.3 Hz, 1H, O-CH$_2$-O), 6.06 (s, 1H) and 6.61 (s, 1H, aryl H), 7.54 (dd, J_1 = J_2 = 8.0 Hz, 1H, 5'-CH), 7.68 (ddd, J_1 = 8.0 Hz, J_2 = 2.1 Hz, J_3 = 1.3 Hz, 1H, 6'-CH), 8.18 (ddd, J_1 = 8.0 Hz, J_2 = 2.1 Hz, J_3 = 1.3 Hz, 1H, 4'-CH), 8.21 (dd, J_1 = 2.1 Hz, J_2 = 1.3 Hz, 1H, 2'-CH); ^{13}C NMR δ 71.7 (d, C-3), 80.1 (C-1). EI-MS: m/z: 313 $[M]^{+\cdot}$ (100), 191 (80), 252 (65); CI-MS: 314 $[M+H]^+$ (100). $C_{17}H_{15}NO_5$ (313.3): calcd. C 65.17, H 4.83, N 4.47; found C 64.92, H 4.90, N 4.38.

(3S)-1-(3,5-Dimethyl-4-nitrophenyl)-3-methyl-6,7-methylenedioxy-isochromane (5b)

Yield: 63% (7:1 mixture of two stereoisomers): ^{1}H NMR (DMSO-d$_6$) major isomer: δ 1.27 (d, J = 6.1 Hz, 3H), 2.24 (s, 6H), 2.69 (d, J = 6.6 Hz, 2H), 3.89 (m, 1H), 5.63 (s, 1H), 5.88 (s, 1H), 5.92 (s, 1H), 6.13 (s, 1H), 6.71 (s, 1H), 7.21 (s, 2H). $C_{19}H_{19}NO_5$ (341.3): calcd. C 66.85, H 5.61, N 4.10; found C 66.20, H 5.75 N 3.98.

General Procedure For Preparation of Hemiketals 6a,b,c

To a stirred solution of **5a,b,c** (1.46 mmol) in dichloromethane (13 mL), containing 5 % water, DDQ (1.5 eq.) was added gradually at rt. over 15 min. After 3h TLC (eluent: hexane-ethyl acetate (3:1)) indicated full conversion, then the reaction mixture was washed several times with 1N NaOH and water. After drying evaporation gave crude **6a,b,c**, respectively.

6a

Yield: 96%; ^{1}H NMR ($CDCl_3$) (ca. 2:1 mixture of hemiketal and keto-alcohol); hemiketal: δ 1.42 (d, J = 6.2 Hz, 3H, CH-C<u>H</u>$_3$), 2.69 (dd, J_1 = 16.2 Hz, J_2 = 2.9 Hz, 1H) and 2.84 (dd, J_1 = 16.2 Hz, J_2 = 11.1 Hz, 1H, CH-C<u>H</u>$_2$), 3.54 (br s, 1H, OH), 4.41 (m, 1H, C<u>H</u>-CH3), 5.84 (d, J = 1.5 Hz, 1H) and 5.87 (d, J = 1.5 Hz, 1H, O-CH$_2$-O), 6.40 (s,1H) and 6.57 (s,1H, aryl H), 7.50 (dd, J_1 = J_2 = 8.0 Hz, 1H, 5'-CH), 7.92 (ddd, J_1 = 8.0 Hz, J_2 = 2.2 Hz, J_3 = 0.9 Hz, 1H, 6'-CH), 8.13 (dd, J_1 = 8.0 Hz, J_2 = 0.9 Hz, 1H, 4'-CH), 8.42 (dd, J_1 = 2.2 Hz, J_2 = 0.9 Hz, 1H, 2'-CH); ^{13}C NMR δ 21.4 (<u>C</u>H$_3$), 66.0 (d, <u>C</u>H-CH$_3$), 97.8 (hemiketal C), 101.3 (O-<u>C</u>H$_2$-O); keto-alcohol: ^{1}H NMR δ 1.27 (d, J = 6.1 Hz, 3H, CH-C<u>H</u>$_3$), 2.77 (dd, J_1 = 13.7 Hz, J_2 = 8.7 Hz 1H) and 2.85 (dd, J_1 = 13.7 Hz, J_2 = 4.2 Hz, 1H, CH-C<u>H</u>$_2$), 3.2 (br, 1H, OH), 3.99 (m, 1H, C<u>H</u>-CH$_3$), 6.05 (d, J = 1.3 Hz, 1H) and 6.07 (d, J = 1.3 Hz, 1H, O-CH$_2$-O), 6.75 (s, 1H) and 6.89 (s, 1H, aryl H), 7.69 (dd, J_1 = J_2 = 8.0 Hz, 1H 5'-CH), 8.14 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, 4'-CH), 8.44 (ddd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, J_3 = 1.2 Hz, 1H, 6'-CH), 8.57 (dd, J_1 = 2.5 Hz, J_2 = 1.2 Hz, 1H, 2'-CH); ^{13}C NMR δ 24.0 (<u>C</u>H$_3$), 69.5 (d, <u>C</u>H-OH), 102.2 (O-<u>C</u>H$_2$-O), 195.4 (C=O). EI-MS: m/z: 329 $[M]^{+\cdot}$ (39), 207 (100), 238 (90); CI-MS: 330 [M+H] (85), m/z 312 (100).

6b

Yield: 96%; ^{1}H NMR (DMSO-d$_6$) (ca. 2:1 mixture of hemiketal and keto-alcohol); hemiketal: δ 1.27 (d, J = 6.1 Hz, 3H, CH-C<u>H</u>$_3$), 2.24 (s, 6H, aryl CH$_3$), 2.6-2.75 (m, 2H, overlapping, CH-C<u>H</u>$_2$), 4.28 (m, 1H, C<u>H</u>-CH$_2$), 5.87 (d, J = 1.0 Hz, 1H) and 5.93 (d, J = 1.0 Hz, 1H, O-CH$_2$-O), 6.38 (s, 1H) and 6.69 (s, 1H, aryl H), 7.03 (s, 1H, OH), 7.37 (s, 2H, 2',6'-CH); ^{13}C NMR δ 64.3 (d, <u>C</u>H(O)CH$_3$), 96.5 (s, hemiketal C); keto-alcohol ^{1}H NMR δ 0.96 (d, J = 6.2 Hz, 3H, CH-C<u>H</u>$_3$), 2.29 (s, 6H, aryl CH$_3$), 2.6-2.75 (m, 2H, overlapping, CH-C<u>H</u>$_2$), 3.69 (m, 1H, C<u>H</u>-CH$_3$), 4.46 (d, J = 5.0 Hz, 1H, OH), 6.08 (d, J = 1.0 Hz, 1H) and 6.09 (d, J = 1.0 Hz, 1H, O-CH$_2$-O), 6.85 (s, 1H) and 6.98 (s, 1H, aryl H), 7.59 (s, 2H, 2',6'-CH); ^{13}C NMR δ 67.2 (d, <u>C</u>H(O)CH$_3$), 195.4 (s, C=O). EI-MS: m/z: 357 $[M]^{+\cdot}$ (18), 298 (100), 207 (52); CI-MS: 358 $[M+H]^+$ (100), m/z 340 (79).

6c

Yield: 97%; Identical (NMR) with a sample prepared according to Lit.[10].

General Procedure For Preparation of Hydrazones 7a,b

To a solution of hemiketals **6a** or **6b** (10.0 mmol) and acetic hydrazide or *tert*-butyl carbazate (1.33 eq) in toluene (60 mL) conc. HCl (0.12 mL) was added and the mixture was heated to boiling with constant removal of water. After 3-4 h the mixture was extracted with $NaHCO_3$ solution and water. After drying and evaporation the residue was either used without further characterization (as with **7a** as being an oil) or in case of **7b** it was triturated with ethanol and water to give a solid mixture of isomers (yield: 89%). A sample for structure elucidation was prepared by column chromatography using hexane-ethyl acetate (3:1) as eluent. Fractions of both isomers were collected. **7b:** (3:2 mixture of isomers): ^{1}H NMR (DMSO-d$_6$) δ 0.93 (d, J = 6.5 Hz) and 0.95 (d, J =

6.5 Hz) (3H, CH-C<u>H</u>$_3$), 1.43 (s) and 1.44 (s) (9H, tert.Bu), 2.23 (s, 6H, aryl CH_3), 2.05-2.35 (m, 2H, CH-C<u>H</u>$_2$), 3.63 (m) and 3.75 (m, 1H, C<u>H</u>-OH), 4.41 (d, J = 4.0 Hz) and 4.67 (d, J = 4.0 Hz, 1H, OH), 6.10 (br s, 2H, O-CH_2-O), 6.63 (s) and 6.66 (s, 1H, aryl H), 7.01 (s) and 7.05 (s, 1H, aryl H), 7.29 (s) and 7.30 (s, 2H, 2',6'-CH), 8.95 (br, s, 1H, NH).

General Process For Ring Closure Reaction of Hydrazones 7a,b

The hydrazone (ca. 3.17 mmol) was dissolved in CH_2Cl_2 (15 mL), triethylamine (0.67 mL, 4.75 mmol) was added and to the solution methanesulfonyl chloride (0.29 mL, 3.71 mmol) was added dropwise at 0°C over a few minutes. When TLC (eluent: benzene-ethyl acetate (4:1)) showed complete conversion, the mixture was extracted successively with ice water, 1N HCl and brine. (When the conversion was not finished another amount of triethylamine and methanesulfonyl chloride was applied.) Drying and evaporation gave a foam which was dissolved in ethanol to give a ca. 10% solution and solid NaOH (1.2 eq) was added to the stirred solution. First a darkening of the solution occurred and after half an hour generally a solid formed. After 2-3 hours the mixture was concentrated to 1/3 of its volume and water was added to bring the precipitation to completion.

(R)-7-Acetyl-8,9-dihydro-8-methyl-5-(3-nitrophenyl)-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (8a)

Yield: 52%, m. p. 157°C (EtOH), $[\alpha]_D$: +53.0° (c=0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 0.99 (d, J = 6.6 Hz, 3H, 8-CH_3), 2.16 (s, 3H, CO-CH_3), 2.78 (dd, J_1 = 14.2 Hz, J_2 = 9.0 Hz, 1H) and 2.98 (dd, J_1 = 14.2 Hz, J_2 = 2.9 Hz, 1H, 9-CH_2), 5.14 (m, 1H, C<u>H</u>-CH_3), 6.07 (br, 1H) and 6.08 (br, 1H, O-CH_2-O), 6.61 (s, 1H) and 7.04 (s, 1H, aryl H), 7.74 (dd, J_1 = J_2 = 7.8 Hz, 1H, 5'-CH), 7.99 (d, J = 7.8 Hz, 1H, 6'-CH), 8.28 (br s, 1H, 2'-CH), 8.32 (d, J = 7.8 Hz, 1H, 4'-CH). $C_{19}H_{17}N_3O_5$ (367.4): calcd. C 62.12 H 4.67, N 11.44; found C 62.06, H 4.70, N 11.29.

(R)-7-*tert*-Butoxycarbonyl-8,9-dihydro-5-(3,5-dimethyl-4-nitrophenyl)-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (8b)

Yield: 78%), m.p. 222-223°C (EtOH), $[\alpha]_D$: -443° (c=0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.16 (d, J = 6.0 Hz, 3H, 8-CH_3), 1.41 (s, 9H, *tert*.Bu), 2.28 (s, 6H, aryl CH_3), 2.45 (dd, J_1 = J_2 = 13.1 Hz, 1H) and 2.86 (dd, J_1 = 13.1 Hz, J_2 = 5.6 Hz, 1H, 9-CH_2), 4.74 (m, 1H, C<u>H</u>-CH_3), 6.06 (br s, 1H) and 6.10 (br s, 1H, O-CH_2-O), 6.62 (s, 1H) and 7.05 (s, 1H, aryl H), 7.46 (s, 2H, 2',6'-CH). EI-MS: m/z: 453 $[M]^{+\cdot}$ (13), 57 (100), 310 (40), 353 (31); CI-MS: 454 $[M+H]^+$ (100), 453 $[M]^{+\cdot}$ (36), m/z: 398 (74). $C_{24}H_{27}N_3O_6$ (453.5): calcd. C 63.56, H 6.00 N 9.27; found C 62.76, H 6.12, N 9.12.

(R)-8,9-Dihydro-5-(3,5-dimethyl-4-nitrophenyl)-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (9b)

To a stirred ethyl acetate solution (3.6 mL), containing ca. 13% HCl, **8b** (0.60 g, 1.32 mmol) was added gradually at r.t. After 20 minutes a suspension formed which was stirred for 2.5 h. The mixture was then diluted with ethyl acetate (20 mL) and extracted with water, $NaHCO_3$ solution and brine. Drying and evaporation gave the product (0.41 g, 88%), which was recrystallized from ethanol. M. p. 193°C, $[\alpha]_D$: +181° (c=0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.10 (d, J = 6.5 Hz, 3H, 8-CH_3), 2.24 (s, 6H, aryl CH_3), 2.60 (dd, J_1 = 14.0, J_2 = 6.5 Hz, 1H) and 3.82 (dd, J_1 = 14.0 Hz, J_2 = 3.0 Hz, 1H, 9-CH_2), 3.26 (m, 1H, C<u>H</u>-CH_3), 6.00 (br s, 1H) and 6.02 (br s, 1H, O-CH_2-O), 6.47 (s, 1H) and 6.86 (s, 1H, aryl H), 7.23 (d, J = 3.5 Hz, 1H, NH), 7.26 (s, 2H, 2',6'-CH). EI-MS: m/z: 353 $[M]^{+\cdot}$ (84), 310 (100), 264 (43), 338 (42); CI-MS: 354 $[M+H]^+$ (100), 353 $[M]^{+\cdot}$ (30). $C_{19}H_{19}N_3O_4$ (353.3): calcd. C 64.58, H 5.42, N 11.89; found C 64.48, H 5.48, N 11.76.

(R)-7-Acetyl-8,9-dihydro-5-(3,5-dimethyl-4-nitrophenyl)-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (10b)

9b (0.71 g, 2.0 mmol) was dissolved in dichloromethane (5 mL) and acetic anhydride (2.9 eq) was added and the solution was left at r. t. overnight. After extraction with water, $NaHCO_3$ solution and brine the solution was dried and evaporated to dryness. The product was a foam (0.79 g, 99%) that could not be crystallized. $[\alpha]_D$: -192.5° (c=0.42, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.00 (d, J = 6.7 Hz, 3H, 8-CH_3), 2.10 (s, 3H, CO-CH_3), 2.28 (s, 6H, aryl CH_3), 2.70 (dd, J_1 = 14.2, J_2 = 10.0 Hz, 1H) and 2.93 (dd, J_1 = 14.2 Hz, J_2 = 4.3 Hz, 1H, 9-CH_2), 5.12 (m, 1H, C<u>H</u>-CH_3), 6.06 (d, J = 1.1 Hz, 1H) and 6.08 (d, J = 1.1 Hz, 1H, O-CH_2-O), 6.58 (s, 1H) and 7.02 (s, 1H, aryl H), 7.45 (s, 2H, 2',6'-CH). EI-MS: m/z: 395 $[M]^{+\cdot}$ (99), 310 (100), 338 (73), 380 (48); CI-MS: 396 $[M+H]^+$ (100), 395 $[M]^{+\cdot}$ (32).

(R)-8,9-Dihydro-5-(3,5-dimethyl-4-nitrophenyl)-8-methyl-7-methylcarbamoyl-7H-1,3-dioxolo[4,5-h][2,3]-benzodiazepine (11b)

Applying methyl isocyanate as acylating agent the reaction was carried out similarly as for **10b**, however, the product solidified by trituration with ethanol. Yield: 0.71 g (86%), m. p. 232°C (EtOH), $[\alpha]_D$: +89.6° (c=1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 6.5 Hz, 3H, 8-CH_3), 2.28 (s, 6H, aryl CH_3), 2.69 (d, J = 4.8 Hz, 3H, N-CH_3), 2.73 (dd, J_1 = 14.4, J_2 = 8.7 Hz, 1H) and 2.91 (dd, J_1 = 14.4 Hz, J_2 = 3.8 Hz, 1H, 9-CH_2), 5.12 (m, 1H, C<u>H</u>-CH_3), 6.04 (d, J = 0.9 Hz, 1H) and 6.06 (d, J = 0.9 Hz, 1H, O-CH_2-O), 6.48 (s, 1H, aryl H), 6.71 (q, J = 4.8 Hz, 1H, NH), 6.97 (s, 1H, aryl H), 7.47 (s, 2H, 2',6'-CH). $C_{21}H_{22}N_4O_5$ (410.4): calcd. C 61.45, H 5.40, N 13.65; found C 61.40, H 5.38, N 13.81.

General Procedure For Reduction of Nitro Derivatives 8a, 9b, 10b, 11b

To a vigorously stirred solution of the nitro-compound (1.22 mmol) in a 1:1 mixture of dichloromethane and methanol (20 mL) an amount of Raney Ni slurry (ca.1 g) was added in one portion by a spatula. After 3-4 hours stirring the mixture was filtered and the solvent evaporated. The residue was suspended in water and the product was isolated by filtration.

(R)-7-Acetyl-5-(3-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (2)

Yield: 70%, m. p. 118-119°C (EtOH-H_2O), $[\alpha]_D$: -397° (c=0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3H,

8-CH_3), 2.10 (s, 3H, CO-CH_3), 2.66 (dd, J_1 = 14.1, J_2 = 11.4 Hz, 1H) and 2.77 (dd, J_1 = 14.1 Hz, J_2 = 4.9 Hz, 1H, 9-CH_2), 3.3-4.2 (br, 2H, NH_2), 5.27 (m, 1H, C<u>H</u>-CH_3), 5.98 (d, J = 1.1 Hz, 1H) and 6.01 (d, J = 1.1 Hz, 1H, O-CH_2-O), 6.57 (s, 1H) and 6.76 (s, 1H, aryl H), 6.81 (d, J = 7.8 Hz, 1H, 4'-CH), 6.96 (d, J = 7.8 Hz, 1H, 6'-CH), 7.00 (br s, 1H, 2'-CH), 7.20 (dd, $J_1 = J_2$ = 7.8 Hz, 1H, 5'-CH). $C_{19}H_{19}N_3O_3$ (337.4): calcd. C 67.64, H 5.68, N 12.46; found C 67.07, H 5.73, N 12.13.

(R)-8,9-Dihydro-5-(3,5-dimethyl-4-aminophenyl)-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (3a)

Yield: 51%, m. p. 108-110°C (EtOH-H_2O), $[\alpha]_D$: +265 (c=0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.2 Hz, 3H, 8-CH_3), 2.07 (s, 6H, aryl CH_3), 2.31 (dd, J_1 = 13.6, J_2 = 4.4 Hz, 1H) and 2.66 (dd, J_1 = 13.6 Hz, J_2 = 6.1 Hz, 1H, 9-CH_2), 3.88 (m, 1H, C<u>H</u>-CH_3), 4.84 (br, 2H, NH_2), 6.02 (br, 1H) and 6.03 (br, 1H, O-CH_2-O), 6.48 (s, 1H) and 6.89 (s, 1H, aryl H), 6.99 (s, 2H, 2',6'-CH). EI-MS: m/z: 323 $[M]^{+\cdot}$ (78), 280 (100), 308 (30); CI-MS: 324 $[M+H]^+$ (91), 323 $[M]^{+\cdot}$ (100). $C_{19}H_{21}N_3O_2$ (323.4): calcd. C 70.56, H 6.55, N 12.99; found C 69.58, H 6.82, N 12.50.

(R)-7-Acetyl-8,9-dihydro-5-(3,5-dimethyl-4-aminophenyl)-8-methyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (3b)

Yield: 54%, m. p. 146°C (MeOH), $[\alpha]_D$: -483° (c=0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.13 (d, J = 6.4 Hz, 3H, 8-CH_3), 1.82 (s, 3H, CO-CH_3), 2.10 (s, 6H, aryl CH_3), 2.36 (dd, $J_1 = J_2$=13.0 Hz, 1H) and 2.76 (dd, J_1 = 13.0 Hz, J_2 = 5.4 Hz, 1H, 9-CH_2), 4.93 (m, 1H, C<u>H</u>-CH_3), 5.23 (br s, 2H, NH_2), 6.03 (br s, 1H) and 6.08 (br s, 1H, O-CH_2-O), 6.58 (s, 1H) and 6.98 (s, 1H, aryl H), 7.15 (s, 2H, 2',6'-CH). $C_{21}H_{23}N_3O_3$ (365.4): calcd. C 69.02, H 6.34, N 11.50; found C 67.77, H 6.20, N 11.10.

(R)-8,9-Dihydro-5-(3,5-dimethyl-4-aminophenyl)-8-methyl-7-methylcarbamoyl-7H-1,3-dioxolo[4,5-h][2,3]benzodiazepine (3c)

Yield: 77%, m. p. 263°C (EtOH), $[\alpha]_D$: -478° (c=0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 6.4 Hz, 3H, 8-CH_3), 2.20 (s, 6H, aryl CH_3), 2.63 (dd, J_1 = 13.9, J_2 = 10.4 Hz, 1H) and 2.80 (dd, J_1 = 13.9 Hz, J_2 = 5.0 Hz, 1H, 9-CH_2), 2.85 (d, J = 4.8 Hz, 3H, N-CH_3), 3.87 (br s, 2H, NH_2), 5.16 (m, 1H, C<u>H</u>-CH_3), 5.80 (q, J = 4.8 Hz, 1H, NH), 5.96 (br s, 1H) and 6.00 (br s, 1H, O-CH_2-O), 6.58 (s, 1H) and 6.74 (s, 1H, aryl H), 7.21 (s, 2H, 2',6'-CH). EI-MS: m/z: 380 $[M]^{+\cdot}$ (43), 280 (100), 308 (31); CI-MS: 381 $[M+H]^+$ (100), 380 $[M]^{+\cdot}$ (38). $C_{21}H_{24}N_4O_3$ (380.4): calcd. C 66.30, H 6.36, N 14.73; found C 65.80, H 6.42, N 14.58.

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