Synthesis of (S)-3,4-Diaminobutanenitriles as Precursors for 3-Amino-GABA Derivatives

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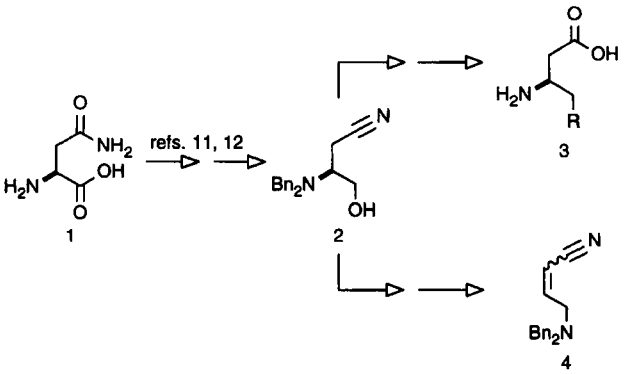
Starting from natural asparagine (**1**) a synthesis of the protected (S)-3,4-diaminobutanenitriles **5** and **8a-c** *via* the β-homoserine derivative **2** is described. The amino function in position 4 was introduced by *Mitsunobu*-coupling or by reductive amination when a strange deformylation of the amino aldehyde **7** was observed as a side reaction. The *Mitsunobu*-product **5** was converted into the dibenzylamine substituted GABA **6b** which was investigated for its affinity at the GABA-A receptor.

Synthese von (S)-3,4-Diaminobutyronitrilen als Vorstufen für 3-Amino-GABA - Derivate

Ausgehend von natürlichem Asparagin (**1**) wird über die Synthese geschützter (S)-3,4-Diaminobutannitrile berichtet. Die Aminofunktion in Position 4 wurde mit Hilfe der *Mitsunobu*-Reaktion oder durch reduktive Aminierung eingeführt, wobei eine ungewöhnliche Deformylierung des Aminoaldehyds **7** als Nebenreaktion zu beobachten war. Das *Mitsunobu*-Produkt **5** konnte in die dibenzylaminsubstituierte γ-Aminobuttersäure **6b** übergeführt werden. die Affinität von **6b** zum GABA-A Rezeptor wurde untersucht.

4-Aminobutyric acid (GABA) derivatives with substituents in position 3 have attracted major interest in recent years. Thus, 3-alkyl-4-aminobutyric acids have been described as the first anticonvulsants that activate L-glutamic acid decarboxylase[1]. Furthermore, the 3-hydroxyl derivatives GABOB[2] and carnitine[3] are of considerable pharmacological and physiological relevance. The emericidines A, B, C which show inhibitory activity on the long chain fatty acid oxidation, were identified as the acyl derivatives of (R)-3-amino-4-trimethylammonium butyric acid[4]. 3,4-Diaminobutyric acids[5] are also of great importance as aspartic acid analogs in reduced peptide bond isosters and have been successfully employed in peptidomimetics of growth releasing-factor[6], secretin[7], cholecystokinin[8], and tetragastrin[9]. On the other hand, 3,4-diaminobutanenitriles have been reported rarely[10]. To the best of our knowledge, syntheses of nonracemic members of this family of compounds have not yet been published.

We have recently shown that the β-homoserine derivative **2** which can be prepared from L-asparagine (**1**) in 61% overall yield, can serve as a valuable intermediate in the synthesis of enantiomerically pure β-amino acids (**3**) (Scheme 1)[11]. For the construction of the respective side chains the hydroxyl function of **2** was activated by conversion into a methansulfonate and subsequently reacted with lower order organo cuprates or $LiBH_4$. This strategy was also expected to provide a straightforward access to 3,4-diaminobutanenitriles and the respective amino acids. Employing amines as nucleophiles, however, did not give the projected displacement reaction. Instead, the aminobutenenitrile **4** was formed. We assume, that this is due to intramolecular attack of the sulfonate to give aziridinium intermediate followed by ring opening and deprotonation[12].



Scheme 1

To circumvent this side reaction we envisioned to introduce a phthalimido group as a precursor for a primary amine by *Mitsunobu*-coupling[13] which usually works under very mild conditions. Thus, treatment of the β-homoserine derivative **2**, prepared from L-asparagine (**1**)[11,12], with phthalimide and PPh_3/DEAD*) at room temp. afforded the substitution product **5** in 67% yield after flash chromatography (Scheme 2).

As an alternative for the synthesis of 3,4-diaminobutanenitrile derivatives, *Swern* oxidation of **2** followed by reductive amination was investigated. The projected *N,N*-dibenzylamino aldehyde **7**[14] could be prepared from **2** in 82% yield employing oxalyl chloride, DMSO, and Et_3N. Simple extraction of the reaction mixture afforded the analytically pure product. However, when **7** was stored at room temp. (or during our attempts to crystallize it) the elimination product **9** was isolated in almost quantitative yield. The

*) DEAD: Diethyl azodicarboxylate

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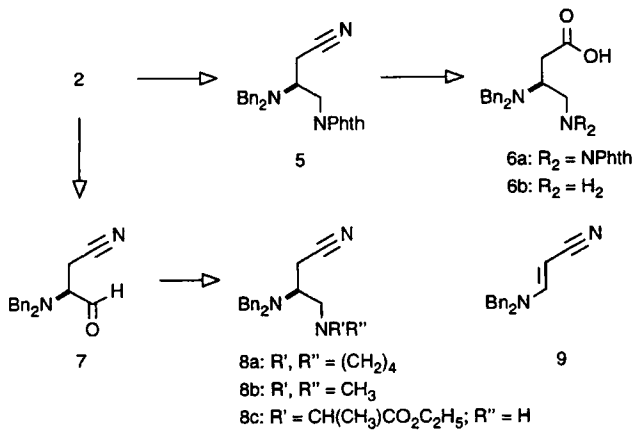

Scheme 2

structure of **9** was determined unambiguously by MS, IR-spectroscopy, and micro analysis as well as by comparison of the ^{1}H and ^{13}C-NMR spectra with those of commercially available 3-dimethylaminopropenenitrile. Formally, this deformylation reaction includes the removal of a formyl anion which is extremely uncommon. An important factor facilitating the elimination seems to be the CH-acidity in the nitrile α-position of **7**. This reaction has not yet been observed with common *N,N*-dibenzylamino aldehydes[15].

Freshly prepared amino aldehyde **7** could be reacted with pyrrolidine or dimethylamine in the presence of $NaCNBH_3$ to give the diamino nitriles **8a** and **8b**, respectively. The moderate yields (20 and 42%) are due to the formation of **9**, which was detected again as a side reaction. Using the same reaction conditions, reductive coupling of **7** with alanine ethyl ester was performed to give the reduced peptide bond analogue (**8c**) of the β-cyanoala-ala dipeptide. Examination of the ^{1}H-NMR spectrum of **8c** compared to the 1:1 mixture of diastereomers obtained by the reaction of **7** with rac. alanine ethyl ester revealed the synthetic material to be diastereomerically pure. This proves the optical integrity of the synthesis. Using **5** as an example, the cyano function was hydrolized to give the protected amino acid **6a**. Surprisingly, the imido group remained untouched under the fairly drastic reaction conditions (conc. HCl, 80°C). Liberation of the prim. amine in position 4 was accomplished by hydrazinolysis to give the dibenzylamine substituted GABA derivative **6b**.

Using bovine cortical membranes the GABA analogue **6b** was investigated for its affinity to the GABA-A receptor, labelled with [^{3}H]-GABA.

Evaluation of the data did not show significant binding properties (IC_{50} > 100 μM). However, further efforts are necessary to estimate the capability of **6b** to interact with the GABA ergic system including the investigation of the GABA-B receptor[16], modulatory sites, the regulatory enzymes GABA aminotransferase, and glutamic acid decarboxylase[1] or transport proteins[17].

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Experimental Part

General Remarks

THF was distilled from Na/benzophenone, and CH_2Cl_2 from CaH_2, immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted, reactions were conducted under dry N_2.- Evaporations of product solutions were done *in vacuo* with a rotatory evaporator.- Flash chromatography: 230-400 mesh silica gel.- Melting points: Büchi melting point apparatus, uncorrected.- IR spectra: Perkin Elmer 881 spectrometer.- Mass spectra: Varian CH7 instrument, methane was employed for CI-MS.- NMR spectra: Jeol JNM-GX 400 spectrometer at 400 MHz, $CDCl_3$, tetramethylsilane as internal standard.- Elemental analyses: Heraeus CHN Rapid instrument. *trans*-3-*N,N*-Dimethylamino-2-propenenitrile was purchased from Aldrich Inc.

(S)-1-(2-N,N-Dibenzylamino-3-cyano)-propyl-N-phthalimide (**5**)

To a solution of **2**[12] (1.02 g, 3.65 mmol), phthalimide (590 mg, 4.02 mmol), and PPh_3 (1.07 g, 4.02 mmol) in THF (70 ml) was added DEAD (1.82 ml, 4.02 mmol, 39 proz. solution in toluene). After being stirred for 3 d at room temp. the solvent was evaporated and the residue was purified by flash chromatography (petrol ether - EtOAc 9:1) to give **5** (1.00 g, 67%) as a colorless solid; mp. 136°C; $[\alpha]^{20}_D$ +33 (c = 1.54, $CHCl_3$).- $C_{26}H_{23}N_3O_2$ (409.5) Calcd C 76.26 H 5.66 N 10.26 Found C 76.16 H 5.71 N 10.42; mol.-mass 410 (CI-MS).- IR (KBr): 3020; 2930; 2240; 1760; 1710 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.51 (dd, J = 16.9, 5.9 Hz, 1H, 3-H), 2.68 (dd, J = 16.9, 8.4 Hz, 1H, 3-H), 3.45-3.52 (m, 1H, 2-H), 3.57 (dd, J = 13.6, 7.0 Hz, 1H, 1-H), 3.68 (d, J = 13.5 Hz, 2H, CH_2N), 3.82 (d, J = 13.5 Hz, 2H, CH_2N), 4.12 (dd, J = 13.6, 6.6 Hz, 1H, 1-H), 7.14-7.26 (m, 6H arom.), 7.33 (d, J = 7.3 Hz, 4H arom.), 7.74 (dd, J = 5.1, 2.9 Hz, 2H arom.), 7.82 (dd, J = 5.1, 2.9 Hz, 2H arom.).

(S)-3-N,N-Dibenzylamino-4-(N-phthalimido)-butyric acid (**6a**)

A mixture of **5** (440 mg, 1.07 mmol) in conc. aqueous HCl (40 ml) was stirred for 4 h at 80°C. After being cooled to room temp. the mixture was neutralized by $NaHCO_3$. After extraction with Et_2O the org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (CH_2Cl_2 - MeOH 95:5) to give **6a** (276 mg, 60%) as a colorless solid; mp. 161°C; $[\alpha]^{20}_D$ -16 (c = 0.9, $CHCl_3$).- $C_{26}H_{24}N_2O_4$ (428.5) Calcd. C 72.88 H 5.65 N 6.54 Found C 72.73 H 5.86 N 6.47; mol.-mass 429 (CI-MS).- IR (NaCl): 3470; 3020; 2940; 1770; 1720 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.37 (dd, J = 16.1, 5.1 Hz, 1H, 2-H), 2.74 (dd, J = 16.1, 9.5 Hz, 1H, 2-H), 3.51-3.58 (m, 1H, 3-H), 3.63-3.70 (m, 1H, 4-H), 3.73 (d, J = 13.2 Hz, 2H, CH_2N), 3.84 (d, J = 13.2 Hz, 2H, CH_2N), 4.11 (dd, J = 13.5, 5.4 Hz, 1H, 4-H), 7.23-7.38 (m, 10 H arom.), 7.72 (dd, J = 5.5, 3.2 Hz, 2H arom.), 7.83 (dd, J = 5.5, 3.2 Hz, 2H arom.).

(S)-4-Amino-3-N,N-dibenzylaminobutyric acid (**6b**)

To a solution of **6a** (110 mg, 0.26 mmol) in EtOH (16 ml) was added hydrazine · H_2O (0.127 ml, 2.57 mmol). After being stirred for 4 h at 80°C the solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2 - MeOH 4:1) to give **6b** (73 mg, 95%) as colorless crystals; mp. 160°C; $[\alpha]^{20}_D$ +16 (c = 1.03, CH_3OH).- $C_{18}H_{22}N_2O_2$ (298.4) Calcd. C 72.46 H 7.43 N 9.39 Found C 72.74 H 7.61 N 9.31; mol.-mass 299 (CI-MS).- IR (NaCl): 3390; 3280; 2930; 2640; 1710 cm^{-1}.- ^{1}H-NMR ([D_4]MeOH): δ (ppm) = 2.30 (dd, J = 15.1, 9.8 Hz, 1H, 2-H), 2.77 (dd, J = 15.1, 3.2 Hz, 1H, 2-H), 2.96-3.03 (m, 2H, 4-H), 3.23-3.31 (m, 1H, 3-H), 3.48 (d, J = 13.5 Hz, 2H, CH_2N), 3.73 (d, J = 13.5 Hz, 2H, CH_2N), 7.20-7.23 (m, 2H arom.), 7.28-7.37 (m, 8H arom.).

(S)-3-N,N-Dibenzylamino-3-formylpropane-1-nitrile (**7**)

To a solution of oxalyl chloride (0.20 ml, 2.36 mmol) in CH_2Cl_2 (2 ml) at -60°C was slowly added a solution of DMSO (0.34 ml, 4.74 mmol) in CH_2Cl_2 (2 ml). After being stirred for 15 min, a solution of **2** (600 mg, 2.15 mmol) in CH_2Cl_2 (4 ml) and, subsequently, Et_3N (1.49 ml, 5.37 mmol) was added at -60°C. 10 min later, H_2O (10 ml) was added and the pH was adjusted to 5 by aqueous citric acid (10%). Then, the mixture was extracted with CH_2Cl_2 and the org. layer was dried ($MgSO_4$) and evaporated at room temp. to leave pure **7** (490 mg, 82%) as a light yellowish oil; $[\alpha]^{20}_D$ -31 (c = 1.21, $CHCl_3$).- $C_{18}H_{18}N_2O$ (278.4) Calcd. C 77.67 H 6.52 N 10.06 Found C 77.52 H 6.69 N 10.28; mol.-mass 279 (CI-MS).- IR (NaCl): 3030; 2920; 2250; 1730 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.61 (dd, J = 16.9, 7.7 Hz, 1H, 2-H), 2.75 (dd, J = 16.9, 5.7 Hz, 1H, 2-H), 3.76 (dd, J = 7.7, 5.7 Hz, 1H, 3-H), 3.81 (d, J = 13.5 Hz, 2H, CH_2N), 3.85 (d, J = 13.5 Hz, 2H, CH_2N), 7.30-7.43 (m, 10 H arom.), 9.61 (s, 1H, CHO).

(S)-3-N,N-Dibenzylamino-4-(1-pyrrolidinyl)butane-1-nitrile (**8a**)

To a solution of **7** (80 mg, 0.29 mmol) in MeOH (10 ml) was added pyrrolidine · HCl. After being cooled to 0°C, $NaCNBH_3$ (32 mg, 0.46 mmol) was added. Then the mixture was brought to room temp. and stirring was continued for 20 h. The solvent was evaporated and Et_2O and satd. aqueous $NaHCO_3$ were added to the residue. The org. layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (n-hexane - acetone 85:15) to give **8a** (19 mg, 20%) as a colorless oil; $[\alpha]^{20}_D$ +8 (c = 0.18, $CHCl_3$).- $C_{22}H_{27}N_3$ (333.5) Calcd. C 79.24 H 8.16 N 12.60 Found C 79.34 H 8.00 N 12.68; mol.-mass 334 (M + H)$^+$ (EI-MS).- IR (NaCl): 3030; 2930; 2250 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.70-1.73 (m, 4H, CH_2-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-N), 2.31-2.36 (m, 4H, C$\underline{H}_2$-CH_2-CH_2-C$\underline{H}_2$-N), 2.57 (dd, J = 16.9, 9.5 Hz, 1H, 2-H), 2.72 (dd, J = 16.9, 4.4 Hz, 1H, 2-H), 3.16-3.23 (m, 1H, 3-H), 3.62-3.67 (m, 2H, 4-H), 3.66 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 3.79 (d, J = 13.5 Hz, 2H, $PhCH_2N$), 7.22-7.44 (m, 10 H arom.).

(S)-3-N,N-Dibenzylamino-4-dimethylaminobutane-1-nitrile (**8b**)

A mixture of **7** (509 mg, 1.83 mmol) and dimethylammonium · HCl (752 mg, 9.15 mmol) in MeOH (20 ml) and $NaCNBH_3$ (108 mg, 1.46 mmol) was reacted and worked up as described for **8a** to give **8b** (236 mg, 42%) as a colorless oil; $[\alpha]^{20}_D$ -29 (c = 1.94, $CHCl_3$).- $C_{20}H_{25}N_3$ (307.4) Calcd. C 78.14 H 8.20 N 13.67 Found C 78.32 H 8.40 N 13.28; mol.-mass 308 (M + H)$^+$ (EI-MS).- IR (NaCl): 3030; 2930; 2250 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.12 (s, 6H, CH_3), 2.36 (dd, J = 12.0, 9.8 Hz, 1H, 4-H), 2.42-2.50 (m, 2H, 2-H, 4-H), 2.66 (dd, J = 17.0, 5.2 Hz, 1H, 2-H), 3.12-3.19 (m, 1H, 3-H), 3.64 (d, J = 13.5 Hz, 2H, CH_2N), 3.78 (d, J = 13.5 Hz, 2H, CH_2N), 7.23 (m, 2H arom.), 7.26-7.34 (m, 4H arom.), 7.43 (d, J = 7.3 Hz, 4H arom.).

(S)-Ethyl 2-[(S)-(2-N,N-dibenzylamino-3-cyano)-propylamino]-propionate (**8c**)

A mixture of **7** (80 mg, 0.29 mmol) and (S)-alanine ethyl ester · HCl (219 mg, 1.43 mmol) in MeOH (8 ml) and $NaCNBH_3$ (16 mg, 0.23 mmol) were reacted and worked up as described for **8a** to give **8c** (236 mg, 42%) as a colorless oil; $[\alpha]^{20}_D$ -22.3 (c = 0.48, $CHCl_3$).- $C_{23}H_{29}N_3O_2$ (379.4) Calcd. C 72.79 H 7.70 N 11.07 Found C 72.45 H 7.42 N 10.81; mol.-mass 380 (M + H)$^+$ (EI-MS).- IR (NaCl): 3340; 3030; 2930; 2240; 1730 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.24 (d, J = 7.3 Hz, 3H, CH-C$\underline{H}_3$), 1.28 (t, J = 7.0 Hz, 3H, $CH_2C\underline{H}_3$), 2.52 (dd, J = 16.9, 7.4 Hz, 1H, 3'-H), 2.60 (dd, J = 16.9, 5.9 Hz, 1H, 3'-H), 2.71 (dd, J = 12.5, 7.3 Hz, 1H, 1'-H), 2.82 (dd, J = 12.5, 6.6 Hz, 1H, 1'-H), 3.13-3.22 (m, J = 7.3, 6.6 Hz, 2H, 2-H, 2'-H), 3.68 (d, J = 14.7 Hz, 2H, $PhCH_2N$), 3.71 (d, J = 14.7 Hz, 2H, $PhCH_2N$), 4.15-4.23 (m, 2H, OCH_2), 7.23-7.40 (m, 10 H arom.).

For optical purity studies, the crude product (before flash chromatography) was investigated, compared to the 1:1 mixture of diastereomers obtained from **7** and *rac.* alanine ethyl ester · HCl [^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.23-1.30 (m, 12H, 3-H, $CH_2C\underline{H}_3$), 2.48-2.55 (m, J = 11.7, 8.8, 6.6 Hz, 4H, 3'-H, 1'-H), 2.60 (dd, J = 16.9, 5.9 Hz, 1H, 3'-H), 2.71 (dd, J = 12.5, 7.3 Hz, 1H, 1'-H), 2.82 (dd, J = 12.5, 6.6 Hz, 1H, 1'-H), 2.97 (dd, J = 11.0, 7.3 Hz, 1H, 1'-H), 3.13-3.25 (m, J = 7.3, 6.6 Hz, 4H, 2-H, 2'-H), 3.59 (d, J = 13.9 Hz, 2H, $PhCH_2N$), 3.68 (d, J = 14.7 Hz, 2H, $PhCH_2N$), 3.71 (d, J = 14.7 Hz, 2H, $PhCH_2N$), 3.78 (d, J = 13.9 Hz, 2H, $PhCH_2N$), 4.14-4.22 (m, 4H, CH_2O), 7.20-7.44 (m, 20 H arom.)].

trans-3-N,N-Dibenzylamino-2-propenenitrile (**9**)

Compound **7** (509 mg, 1.83 mmol) was stored for 2-5 d at room temp. Then, it was treated with CH_2Cl_2 and diisopropyl ether. When the crystallization was complete the mixture was filtered to give **9** (386 mg, 85%) as colorless crystals; mp. 82°C.- $C_{17}H_{16}N_2$ (248.3) Calcd. C 82.22 H 6.49 N 11.28 Found C 82.18 H 6.72 N 11.08; mol.-mass 249 (CI-MS).- IR (KBr): 3060; 3030; 2920; 2850; 2190 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.94 (d, J = 13.9 Hz, 1H, 2-H), 4.26 (s, 4H, CH_2N), 7.15 (d, J = 6.6 Hz, 4H arom.), 7.21 (d, J = 13.9 Hz, 1H, 3-H), 7.26-7.38 (m, 6H arom.).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 44.6 ($PhCH_2$), 50.2 ($PhCH_2$), 62.4 (2-CH), 121.9 (CN), 127.4 (ar-CH), 128.1 (ar-CH), 129.0 (ar-CH), 135.2 (ar-C), 153.9 (3-CH). For comparison, diagnostic signals of *trans*-3-*N*,*N*-dimethylamino-2-propenenitrile: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.67 (d, J = 13.5 Hz, 1H, 2-H), 6.91 (d, J = 13.5 Hz, 1H, 3-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 59.5 (2-CH), 154.3 (3-CH).

Binding Experiments

The affinity of our compound for GABA-A receptors was determined according to standard radioligand binding assays[18,19] which were slightly modified as described below:

Membrane preparation: Bovine brains were obtained from a local slaughter house. Cortices were dissected and homogenized with a Potter (PotterS Braun, 800 rpm, 8 up-and-down strokes) in 10 vol. of ice-cold 0.32 M sucrose and centrifuged at 1000xg for 10 min at 4°C. The supernatant was centrifuged at 48000xg for 60 min at 4°C. The resulting pellet was homogenized in 20 vol. aqua bidest with a Polytron (Kinematica) and centrifuged at 48000xg for 30 min at 4°C. Osmotic shock and following centrifugation were repeated, the resulting pellet was homogenized in 50 mM Tris-citrate pH 7.1 and frozen at -20°C. After thawing and homogenizing the cortical membranes were centrifuged at 48000xg for 30 min at 4°C and homogenized again in 50 mM Tris-citrate pH 7.1. The last centrifugation was repeated. Protein was determined according to *Bradford*[20] using BSA as a standard. Samples of tissue homogenate were frozen in plastic tubes (liquid N_2) and stored at -80°C. On the day of the assay the samples were thawed and centrifuged at 48000xg for 30 min at 4°C and the pellets were homogenized in 50 mM Tris-citrate pH 7.1.

[^{3}H]-GABA binding: Homogenate (about 250 µg protein) was incubated in 500 µl of medium containing 50 mM Tris-citrate pH 7.1, about 3 nM [^{3}H]-GABA (DuPont NEN), and various concentrations of competing drugs for 15 min at 4°C in 1.5 ml Eppendorf caps. The samples were centrifuged at 20000 rpm (Sorvall RC 5C, SS34 rotor, adapter for Eppendorf caps) for 10 min at 4°C. The supernatants were discarded and the pellets were twice rinsed superficially with 1 ml cold buffer. The tips of the Eppendorf caps containing the rinsed pellets were cut off and put into scintillation vials which were filled with scintillation cocktail (rotiszint eco plus). Bound radioactivity was determined by liquid scintillation spectrometry (Canberra Packard TriCarb 1600) after 18 h. Non specific binding was defined using 100 µM GABA.

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[Ph285]