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β-Analogs of PLG (L-Prolyl-L-Leucyl-Glycinamide): Ex-Chiral Pool Syntheses and Dopamine D_2 Receptor Modulating Effects

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Abstract: Starting from *(S)*- and *(R)*-aspartic acid enantiomerically pure β-proline derivatives were synthesized. These chiral building blocks were transformed into β-analogs of the dopamine receptor modulating peptide PLG. According to dopamine receptor binding studies, significant enhancement of [^{3}H]pramipexole binding was observed for the isomeres **1a,b** and **2a-c**. The derivative **1b** revealed an activity comparable to PLG. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

The endogenous brain peptide L-prolyl-L-leucyl-glycinamide (PLG) has been demonstrated to exhibit a variety of biological activities including the potentiation of behavioral dopaminergic effects as well as the reversal of neuroleptic induced supersensitivity of dopamine receptors and oxotremorine induced tremors.[1, 2] PLG is proposed to exert these effects through the modulation of dopaminergic receptors in the central nervous system [3]. Thus, PLG induces an increase in the affinity of dopamine receptor agonists and enhances the number of high-affinity dopamine D_2 binding sites.[4] PLG might be also involved in the stabilization of presynaptically localized D_2 autoreceptors which are known to exist in a supersensitive state.[5, 6] Since PLG exerts an enhanced resistance to inhibition of agonist binding by GTP or Gpp(NH)p, PLG is suggested to influence the interaction between dopamine D_2 receptors and G-proteins.[4] Recent structure activity relationship studies on conformationally restricted PLG mimetics lead to the assumption that the bioactive conformation of PLG is a type-II β-turn (*Scheme 1*).[7, 8] This is also supported by an X-ray analysis of PLG which gave a type-II β-bend conformation stabilized by an intramolecular hydrogen bond connecting the Gly carboxamide and the Pro carbonyl.[9] Furthermore, an intramolecular hydrogen bond between the carboxamide NH and the amino function of the prolinamide moiety is suggested to play a role in determining the bioactive conformation indicating a ψ_1 torsional angle of approximately 0°.[10] Structural modifications on the position of the prolyl nitrogen might give interesting insights into the bioactive conformation of PLG and result in more highly active and metabolically more stable drug candidates for the treatment of parkinsonism or schizophrenia. As an extension of our previously described EPC syntheses of β-amino acids we herein report on the *(R)*- and *(S)*-configured β-prolyl analogs **1** and **2** including γ-benzyl

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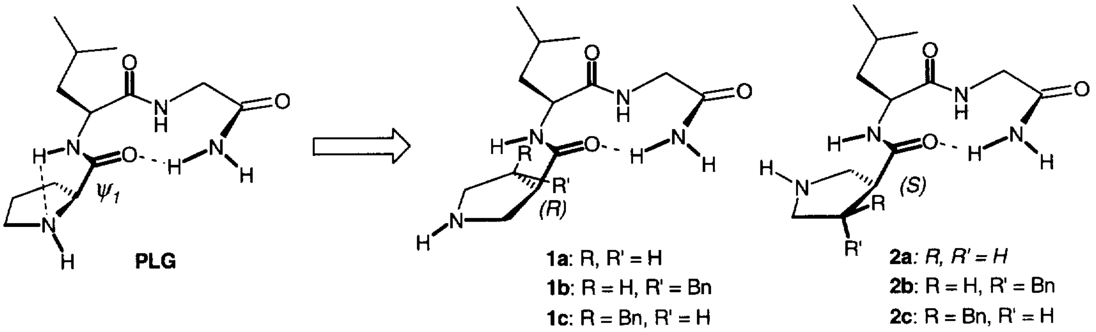
substitituted derivatives. Depending on the relative configuration, the steric demand of the benzyl group was anticipated to cause conformational restrictions on ψ_1. Furthermore the aromatic moiety might induce π-interactions with the binding site and thus enhance the biological activity.

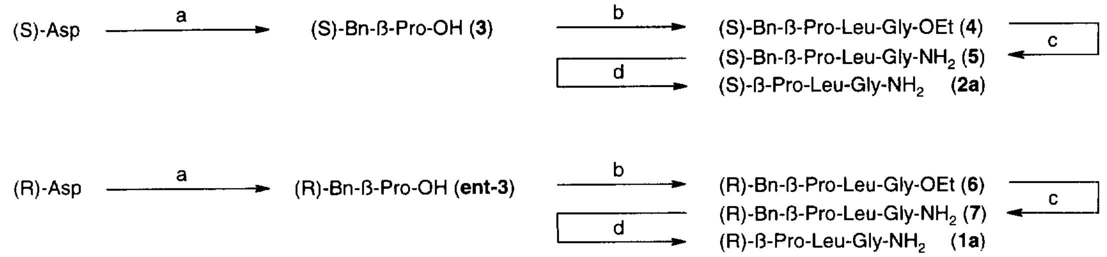
Scheme 1



Synthesis

The preparation of the β-PLG **1a** and its diastereomer **2a** was based on our previously described EPC synthesis of β-proline.[11,12] Thus, the *N*-benzyl protected *(S)*-β-proline **3** as well as the optical antipode **ent-3** were derived from *(S)*-Asp and *(R)*-Asp, respectively, when a 6-step reaction sequence afforded the final products in 67 % overall yield (*Scheme 2*).

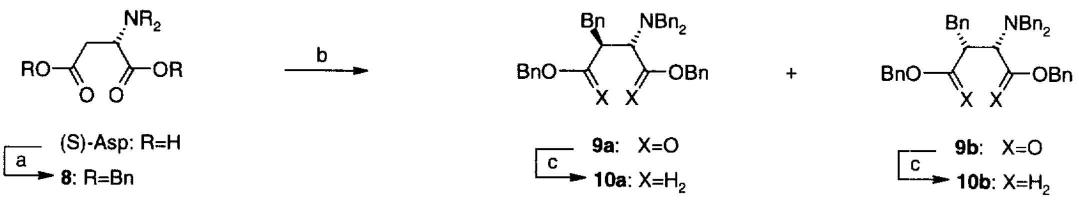
Scheme 2



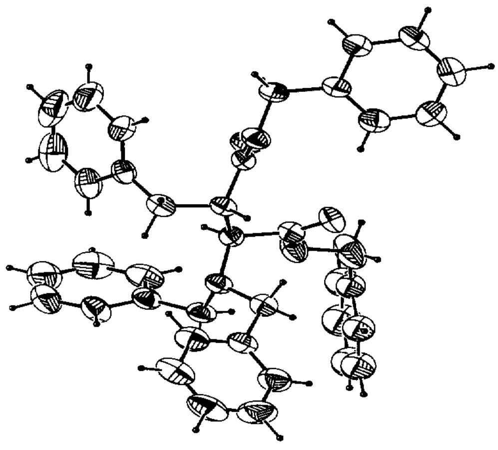
a: see: refs.[11,12] (67 %). b: NMM, isobutyl chloroformate, Leu-Gly-OEt, THF, -15°C - RT, 14h (**4**: 94 %, **6**: 51 %). c: NH_3, MeOH, -20°C - RT, 72h (98 %). d: H_2, $Pd(OH)_2/C$, MeOH, RT, 20h (91 %).

Peptide bond formation was best performed by activation of **3** with isobutyl chloroformate in presence of N-methylmorpholine and subsequent coupling of the thus formed mixed anhydride with Leu-Gly-OEt. When employing THF as a solvent the process was superior to DCC/HOBt coupling affording **4** and **6** in 94 and 51 % yield, respectively. Upon treatment of the esters **4** and **6** with NH_3 / MeOH aminolysis could be accomplished resulting in formation of the glycinamide derivatives **5** and **7**. Hydrogenolytic *N*-deprotection was achieved with *Pearlman's* catalyst to give the target compounds **1a** [13] and **2a** [14].

Scheme 3



a: see: refs.[11,13] (86 %). b: $LiN(SiMe_3)_2$, BnBr, THF, -50°C - -20°C, 2.5h. c: $LiAlH_4$, THF, 0°C, 20h (53 % **10a** + 33 % **10b** for both steps).

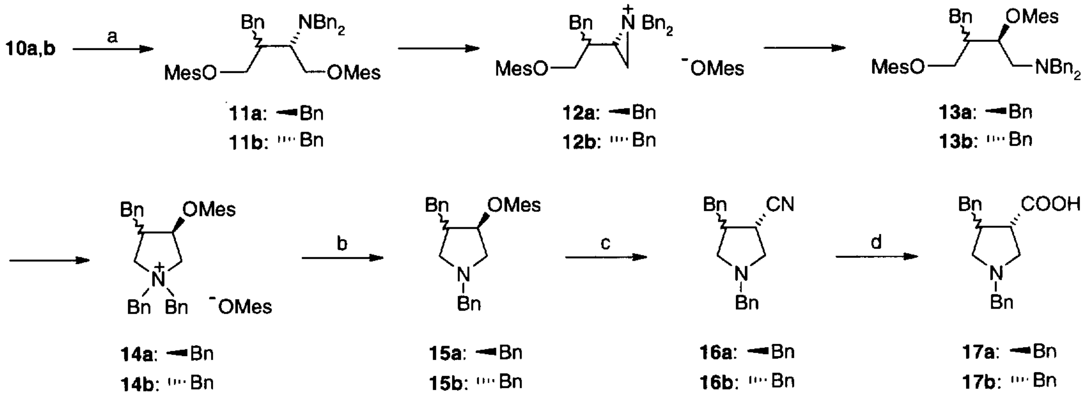


ORTEP Plot of **9a** at a probability rate of 50 %

The preparation of the benzyl substituted PLG mimetics **1b,c** and **2b,c** was started from *(R)*- and *(S)*-Asp, respectively, involving the isomerically pure β-proline derivatives **17a,b** and **ent-17a,b** as the key intermediates. In particular, the introduction of the benzyl group was accomplished by deprotonation and regiospecific β-alkylation of the dibenzyl protected aspartic acid dibenzylester **8**, which can be readily derived from *(S)*-Asp *(Scheme 3)*.[15, 16] The benzylation resulted in formation of the *threo* configured product **9a** and its *erythro* diastereomer **9b** in an 8:5 ratio. Separation of the isomers was possible whith RP column chromatography. Structural assignment was done by X-ray analysis of the homochiral isomer **9a**.

Employment of $LiN(SiMe_3)_2$ as a base and careful control of the reaction temperature was crucial in preventing the epimerization at the α-position and loss of the optical integrity of the alkylation. Reduction of **9a,b** (as a mixture of diastereomers) with $LiAlH_4$ in THF gave **10a** and **10b**, which could be easily separated by flash chromatography. The transformation of the diols **10a** and **10b** to the β-proline derivatives **17a** and **17b** involving stereospecific migration of the dibenzylamino group is outlined in *Scheme 4*. Activation of the diol **10a** (**10b**) with MesCl in the presence of Et_3N formed the dimesylate **11a** (**11b**) which was purified by low temperature flash chromatography. Subsequent rearrangement afforded the pyrrolidinium salt **14a** (**14b**) which is obviously produced via the aziridinium salt **12a** (**12b**) and the intermediate **13a** (**13b**). Monodebenzylation of **14a** (**14b**) was accomplished by catalytic hydrogenation ($Pd(OH)_2$). When using 1eq of H_2 **15a** (**15b**) could be isolated in 76 % (92 %) yield. While substitution of the *trans*-mesylate **15b** with NaCN in the presence of 18-crown-6 gave **16b** in 82 % yield, reaction of **15a** afforded only 27 % of **16a** together with 25 % of 1,3-dibenzyl-2,5-dihydropyrrole. Hydrolysis of **16a** in conc. HCl gave **17a** in 92 % yield. On the other hand, treatment of the *cis*-configured isomer **16b** showed partial epimerization resulting in formation of a 10:3 mixture of the diastereomers **17b** and **ent-17a**. Purification of **17b** was performed by esterification of the crude product ($SOCl_2$, MeOH), flash chromatography of the resulting methyl esters and subsequent hydrolysis affording **17b** in 70 % yield. Employing the same reaction sequence **ent-17a** and **ent-17b** were synthesized from *(R)*-Asp.

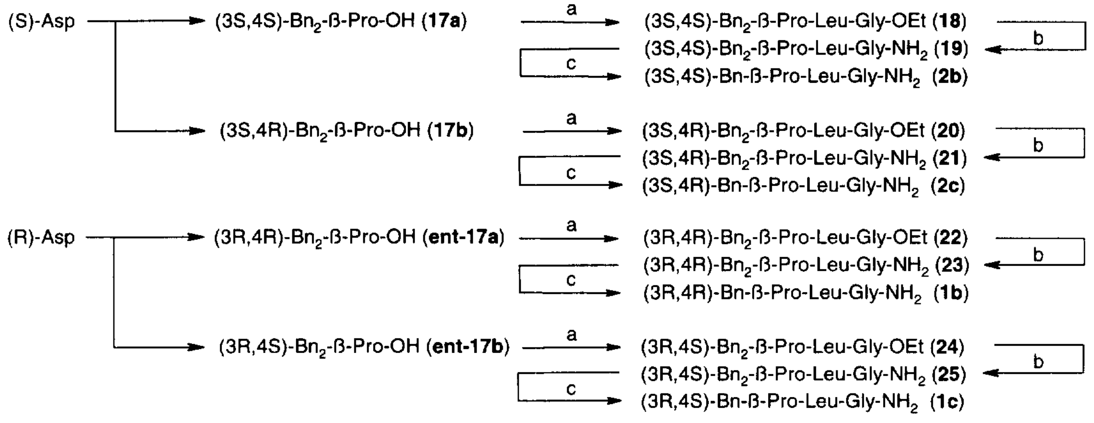
Scheme 4



a: Et_3N, MesCl, THF, -30 - -4°C, 1h, low temperature flash chromatography. b: H_2, $Pd(OH)_2/C$, MeOH, RT (**15a**: 76 %; **15b**: 92 % for both steps). c: NaCN, 18-crown-6, DMSO, 50°C, 168h (**16a**: 27 %; **16b**: 82 %). d: $HCl_{conc.}$, reflux (**17a**: 1h, 92 %; hydrolysis of **16b** (20h) gave partial epimerization, separation was performed via esterification, flash chromatography and mild hydrolysis (5 % HCl, 80°C, 3h) **17b**: 70 % for all steps).

Conversion of the β-proline derivatives **17a,b** and **ent-17a,b** into the β-PLG analogs **2b,c** and **1b,c**, respectively is outlined in *Scheme 5*. In practice, activation of **17a,b** and **ent-17a,b** by isobutyl chloroformate and N-methylmorpholine in THF, followed by addition of Leu-Gly-OEt afforded the tripeptides **18**, **20**, **22** and **24** in 87, 82, 92 and 77 % yield, respectively. Subsequent aminolysis gave the glycinamides **19**, **21**, **23** and **25**, which could be *N*-deprotected by hydrogenolysis in the presence of *Pearlman's* catalyst to leave the target compounds **1b** [17], **1c**[18], **2b** [19] and **2c** [20].

Scheme 5

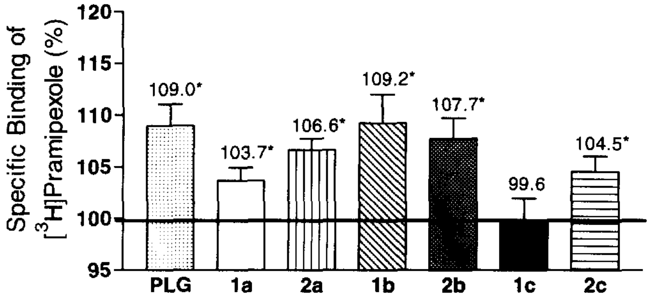


a: NMM, isobutyl chloroformate, Leu-Gly-OEt, THF, -15°C - RT, 1h, (**18**: 87 %; **20**: 82 %; **22**: 92 %; **24**: 77 %). b: NH_3, MeOH, -20°C - RT, 72h, (all: 99 %);. c: H_2, $Pd(OH)_2/C$, MeOH, RT, 20h.

Receptor Binding Studies

The PLG analogs produced in this study were tested for their ability to enhance the binding of the dopamine receptor agonist [^{3}H]pramipexole to dopamine D_2 receptors prepared from bovine striatal membranes.[21] In this assay, membranes were incubated with [^{3}H]pramipexole (0.5 nM) and the respective test compound for 2 h at 23°C. The results were expressed as percentages of specific binding compared to control membranes incubated without a modulator. Specific binding was determined as the difference between total binding and nonspecific binding measured in the presence of 1μM (+)-butaclamol. Except for **1c**, statistically significant modulatory effects were observed ($p < 0.05$).

Figure 1



Stimulation of [^{3}H]pramipexole binding to striatal membranes by **1a**, **2a**, **1b**, **2b**, **1c** and **2c** in a concentration of 10^{-9} M. Results are means ±SEM of 3 to 5 experiments each carried out in triplicate; * indicates that the data are significantly different from the control value ($p<0.05$).

Figure 1 shows the effects of PLG and the ß-prolyl analogs **1a**, **2a**, **1b**, **2b**, **1c** and **2c** at a concentration of 10^{-9}M. Compared to PLG, which enhanced the binding of [^{3}H]pramipexole to 109.0 %, the *(R)*-configured ß-prolyl-analog **1a** was less active (103.7 %). On the other hand, the *(S)*-proline derived isomer **2a** showed moderate activity (106.6 %). The effects of the benzyl substituted tripeptides are also illustrated, demonstrating that the *trans*-substituted derivatives **1b** and **2b** displayed modulating activity (109.2 %, 107.7 %) similar to PLG. The loss of activity for the *cis*-substituted compound **1c** (99.6 %) and the moderate effect of **2c** (104.5 %) might be due to conformational restrictions on ψ_1 caused by the steric demand of the *cis*-disposed benzyl substituent. Further SAR studies in this field are in progress and will be reported in due course.

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13. **1a**: ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 0.82 (d, J=6.5 Hz, 3H, $CH(\underline{CH}_3)_2$), 0.87 (d, J=6.6 Hz, 3H, $CH(\underline{CH}_3)_2$), 1.45 (dd, J=7.6/7.0 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 1.57 (tqq, J=7.0/6.6/6.5 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 1.74 (dddd, ^{2}J=0 Hz ^{3}J=7.6/7.0/7.0 Hz, 1H, $NCH_2\underline{CH}_2$), 1.74 (dddd, J=0 Hz ^{3}J=7.6/7.0/7.0 Hz, 1H, $NCH_2\underline{CH}_2$), 2.67-2.78 (m, 3H, $N\underline{CH}_2CH_2\underline{CH}$), 2.64 (dd, ^{2}J=10.6 Hz ^{3}J=6.3 Hz, 1H, $N\underline{CH}_2CH$), 2.90 (dd, ^{2}J=10.6 Hz ^{3}J=7.8 Hz, 1H, $N\underline{CH}_2CH$), 3.53 (dd, ^{2}J=16.8 Hz ^{3}J=5.6 Hz, 1H, $NH\underline{CH}_2$), 3.64 (dd, ^{2}J=16.8 Hz ^{3}J=6.0 Hz, 1H, $NH\underline{CH}_2$), 4.19 (dt, J=7.6/7.4 Hz, 1H, $NH\underline{CH}$), 7.06 (s, 1H, $\underline{NH}_2$), 7.17 (s, 1H, $\underline{NH}_2$), 8.05 (d, J=7.4 Hz, 1H, $\underline{NH}CH$), 8.11 (dd, J=6.0/5.6 Hz, 1H, $\underline{NH}CH_2$). HRMS (EI): calc.: 284.1848; found: 284.1845.α_D^{24}=-4.8° (1.0, EtOH).
14. **2a**: ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 0.82 (d, J=6.5 Hz, 3H, $CH(\underline{CH}_3)_2$), 0.87 (d, J=6.4 Hz, 3H, $CH(\underline{CH}_3)_2$), 1.44 (dd, J=7.7/7.0 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 1.57 (tqq, J=7.0/6.5/6.4 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 1.66 (dddd, ^{2}J=12.3 Hz ^{3}J=8.0/6.4/6.3 Hz, 1H, $NCH_2\underline{CH}_2$), 1.79 (dddd, ^{2}J=12.3 Hz ^{3}J=8.0/ 7.8/5.6 Hz, 1H, $NCH_2\underline{CH}_2$), 2.68 (ddd, ^{2}J=10.8 Hz ^{3}J=7.8/6.4 Hz, 1H, $N\underline{CH}_2CH_2$), 2.68-2.76 (m, 1H, $NCH_2\underline{CH}$), 2.72-2.79 (m, 1H, $N\underline{CH}_2CH_2$), 2.75 (dd, ^{2}J=13.0 Hz ^{3}J=7.9^a Hz, 1H, $N\underline{CH}_2CH$), 2.86 (dd, ^{2}J= 13.0 Hz ^{3}J=10.2 Hz, 1H, $N\underline{CH}_2CH$), 3.53 (dd, ^{2}J=16.7 Hz ^{3}J=5.5 Hz, 1H, $NH\underline{CH}_2$), 3.63 (dd, ^{2}J=16.7 Hz ^{3}J=5.9 Hz, 1H, $NH\underline{CH}_2$), 4.19 (dt, J=7.4/7.4 Hz, 1H, $NH\underline{CH}$), 7.06 (s, 1H, $\underline{NH}_2$), 7.16 (s, 1H, $\underline{NH}_2$), 8.07 (d, J=7.4 Hz, 1H, $\underline{NH}CH$), 8.10 (dd, J=5.9/5.5 Hz, 1H, $\underline{NH}CH_2$). CHN: $C_{13}H_{24}N_4O_3 \cdot ¾\ H_2O$: calc.: C 52.42 H 8.63 N 18.81; found: C 52.39 H 8.32 N 18.24. α_D^{24}=-0.7° (5.0, EtOH).
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17. **1b**: ^{1}H-NMR (DMSO-d_6, 360 MHz): δ = 0.85 (d, J=6.3 Hz, 3H, $CH(\underline{CH}_3)_2$), 0.90 (d, J=6.5 Hz, 3H, $CH(\underline{CH}_3)_2$), 1.48 (dd, J=7.4/7.0 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 1.58 (tqq, J=7.0/6.5/6.3 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 2.41-2.51 (m, 1H, $NCH_2\underline{CH}CH_2$), 2.48-2.54 (m, 1H, $N\underline{CH}_2CHCH_2$), 2.58 (dd, ^{2}J=10.9 Hz ^{3}J=7.1 Hz, 1H, $CH\underline{CH}_2Ph$), 2.67 (ddd, J=8.1/7.2/7.2 Hz, 1H, $NCH_2\underline{CH}CO$), 2.86 (dd, ^{2}J=10.9 Hz ^{3}J=6.3 Hz, 1H, $CH\underline{CH}_2Ph$), 2.90 (dd, ^{2}J=9.2 Hz ^{3}J=2.8 Hz, 1H, $N\underline{CH}_2CHCH_2$), 2.93 (dd, ^{2}J=11.1 Hz ^{3}J=7.2 Hz, 1H, $N\underline{CH}_2CHCO$), 3.18 (dd, ^{2}J=11.1 Hz ^{3}J=8.1 Hz, 1H, $N\underline{CH}_2CHCO$), 3.58 (dd, ^{2}J=16.8 Hz ^{3}J=5.6 Hz, 1H, $NH\underline{CH}_2$), 3.68 (dd, ^{2}J=16.8 Hz ^{3}J=5.9 Hz, 1H, $NH\underline{CH}_2$), 4.26 (dt, J=7.4/7.4 Hz, 1H, $NH\underline{CH}$), 7.09 (s, 1H, $\underline{NH}_2$), 7.16-7.30 (m, 5H, arom.-H), 7.21 (s, 1H, $\underline{NH}$), 8.09 (dd, J=5.9/5.6 Hz, 1H, $\underline{NH}CH$). 8.22 (d, J=7.4 Hz, 1H, $\underline{NH}CH$). HRMS: (EI) calc.: 374.2318; found: 374.2322. α_D^{24}=+10.4° (2.0, MeOH).
18. **1c**: ^{1}H-NMR (DMSO-d_6, 360 MHz): δ = 0.87 (d, J=6.6 Hz, 3H, $CH(\underline{CH}_3)_2$), 0.91 (d, J=6.4 Hz, 3H, $CH(\underline{CH}_3)_2$), 1.49 (dd, J=7.6/6.3 Hz, 2H, $\underline{CH}_2CH(CH_3)_2$), 1.60 (tqq, J=6.3/6.6/6.4 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 2.29 (dd, ^{2}J=13.2 Hz ^{3}J=10.8 Hz, 1H, $CH\underline{CH}_2Ph$), 2.39 (ddddd, J=10.8/7.1/6.4/3.5/3.5 Hz, 1H, $\underline{CH}CH_2Ph$), 2.47 (dd, ^{2}J=10.2 Hz ^{3}J=7.1 Hz, 1H, $N\underline{CH}_2CHCH_2$), 2.63 (dd, ^{2}J=10.2 Hz ^{3}J=6.4 Hz, 1H, $N\underline{CH}_2CHCH_2$), 2.76 (dd, ^{2}J=13.2 Hz ^{3}J=3.5 Hz, 1H, $CH\underline{CH}_2Ph$), 2.85-2.95 (m, 2H, $N\underline{CH}_2\underline{CH}CO$), 2.98 (dd, J=8.9/4.6 Hz, 1H, $N\underline{CH}_2CHCO$), 3.52 (dd, ^{2}J=16.9^a Hz ^{3}J=5.3^a Hz, 1H, $\underline{CH}_2CO$), 3.68a (dd, ^{2}J=16.9 Hz ^{3}J=6.2 Hz, 1H, $\underline{CH}_2CO$), 4.26 (td, J=7.6/7.2 Hz, 1H, $NH\underline{CH}$), 7.10 (s, 1H, $\underline{NH}_2$), 7.12-7.28 (m, 5H, arom.-H), 7.25 (s, 1H, $\underline{NH}_2$), 8.24 (dd, J=6.2/5.3.Hz, 1H, $\underline{NH}CH_2$), 8.24 (d, J=7.2 Hz, 1H, $\underline{NH}CH$). HRMS: (EI) calc.: 374.2318; found: 374.2317. α_D^{23}=-3.0° (2.0, MeOH).
19. **2b**: ^{1}H-NMR (DMSO-d_6, 360 MHz): δ = 0.84 (d, J=6.5 Hz, 3H, $CH(\underline{CH}_3)_2$), 0.89 (d, J=6.5 Hz, 3H, $CH(\underline{CH}_3)_2$), 1.39-1.51 (m, 2H, $\underline{CH}_2CH(CH_3)_2$), 1.59 (qqdd, J=6.5/6.5/6.8/6.8 Hz, 1H, $CH_2\underline{CH}(CH_3)_2$), 2.46-2.59 (m, 1H + DMSO, $\underline{CH}CH_2Ph$), 2.63 (dd, ^{2}J=13.3 Hz ^{3}J=9.5 Hz, $CH\underline{CH}_2Ph$), 2.77 (dd ^{2}J=11.0 Hz ^{3}J=8.0 Hz, 1H, $N\underline{CH}_2CH$), 2.80-2.89 (m, 1H, $NCH_2\underline{CH}CO$), 2.82 (dd, ^{2}J=13.3 Hz ^{3}J=5.1 Hz $CH\underline{CH}_2Ph$), 3.04 (dd ^{2}J=11.0 Hz ^{3}J=7.2 Hz, 1H, $N\underline{CH}_2CH$), 3.13 (dd ^{2}J=11.5 Hz ^{3}J=7.6 Hz, 1H, $N\underline{CH}_2CH$), 3.34 (dd ^{2}J=11.5 Hz ^{3}J=8.5 Hz, 1H, $N\underline{CH}_2CH$), 3.57 (dd, ^{2}J=16.6 Hz ^{3}J=5.8 Hz, 1H, $NH\underline{CH}_2$), 3.65 (dd, ^{2}J=16.6 Hz ^{3}J=5.8 Hz, 1H, $NH\underline{CH}_2$), 4.24 (ddd, J=7.7/7.5/7.5 Hz, 1H, $NH\underline{CH}$), 7.05 (s, 1H, $\underline{NH}_2$), 7.11-7.33 (m, 5H, H-arom.) 7.18 (s, 1H, $\underline{NH}_2$), 8.15 (dd, J=5.8/5.8 Hz, 1H, $\underline{NH}CH_2$), 8.39 (d, J=7.7 Hz, 1H, $\underline{NH}CH$). HRMS (EI): calc.: 374.2318; found: 374.2317. α_D^{20}=-27.3 (1.35, MeOH).
20. **2c**: ^{1}H-NMR (DMSO-d_6, 360 MHz): δ =0.84 (d, J=6.4 Hz, 3H, $CH(\underline{CH}_3)_2$), 0.89 (d, J=6.8 Hz, 3H, $CH(\underline{CH}_3)_2$), 1.44 (ddd, ^{2}J=13.6 Hz ^{3}J=8.8/5.6 Hz, 1H, $\underline{CH}_2CH(CH_3)_2$), 1.51 (ddd, ^{2}J=13.6 Hz ^{3}J=9.5/4.9 Hz, 1H, $\underline{CH}_2CH(CH_3)_2$), 1.60-1.75 (m, 1H, $CH_2\underline{CH}(CH_3)_2$), 2.35-2.41 (m, 1H, $CH\underline{CH_2Ph}$), 2.33-2.44 (m, 1H, $NCH_2\underline{CH}CH_2$), 2.50 (dd, ^{2}J=10.0 Hz ^{3}J=6.7 Hz, 1H, $N\underline{CH}_2CHCH_2$), 2.64 (dd, ^{2}J=10.0 Hz ^{3}J=5.7 Hz, 1H, $N\underline{CH}_2CHCH_2$), 2.69-2.74 (m, 1H, $CH\underline{CH}_2Ph$), 2.88-2.93 (m, 1H, $N\underline{CH}_2CHCO$), 2.90-2.95 (m, 1H, $NCH_2\underline{CH}CO$), 2.99-3.08 (m, 1H, $N\underline{CH}_2CHCO$), 3.57 (dd, ^{2}J=16.8 Hz ^{3}J=5.7 Hz, 1H, $NH\underline{CH}_2$), 3.65 (dd, ^{2}J=16.8 Hz ^{3}J=5.7 Hz, 1H, $NH\underline{CH}_2$), 4.24 (ddd, J=9.5/6.9/5.6 Hz, 1H, $NH\underline{CH}$), 7.07 (s, 1H, $\underline{NH}_2$), 7.13-7.19 (m, 3H, arom.-H), 7.24-7.29 (m, 3H, arom.-H, $\underline{NH}_2$), 8.36 (d, J=6.9 Hz, 1H, $\underline{NH}CH$), 8.37 (dd, J=5.8/5.7 Hz, 1H, $\underline{NH}CH_2$). HRMS: (EI) calc.: 374.2318; found: 374.2309. α_D^{20}=-8.9° (2.0, $CHCl_3$).
21. Ohnmacht, U.; Tränkle, C.; Mohr, K.; Gmeiner, P. *Pharmazie* **1998**, in press.