Synthesis of New Polysubstituted Pyrrolidinones with Potential Biological Activity

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The reaction of succinic anhydride and *N*-benzylidene-benzylamine gave rise to the corresponding substituted *trans*-5-oxopyrrolidine-3-carboxylic acid, which was transformed stereoselectively into two series of compounds. The first one consists of carboxamides, and the second one includes aminomethyl derivatives. The compounds prepared incorporate both a pyrrolidinone part and other nitrogen containing heterocyclic fragments of pharmacological interest.

Key words: Succinic Anhydride, Pyrrolidinones, Piperazines, Stereochemistry, Sonication

Introduction

The 2-pyrrolidinone (γ-lactam) ring is incorporated in various compounds with biological and pharmaceutical activities [1]. It is the important core structure in the molecule of Rolipram, which is a well known inhibitor of phosphodiesterase IV and thus exhibits a wide spectrum of physiological activities on the central nervous system (CNS) [2]. The synthesis of Rolipram and its analogs is an object of continuing investigations [3, 4]. Recently a novel inhibitor of 17β-hydroxysteroid dehydrogenase type II was identified for the treatment of osteoporosis [5, 6]. This disubstituted pyrrolidine is a close analog of the natural product Clausenamide, which is used to treat viral hepatitis [5]. Some 4-substituted pyrrolidinones exert significant activity as antiepileptic agents [7].

The diverse biological activities of substituted pyrrolidines have provoked numerous synthetic studies. The reaction of succinic anhydride (**1**) with *N*-arylidene-*N*-alkylamines represents a straightforward pathway to the synthesis of the pyrrolidinone ring, giving rise to *trans*- and *cis*-1-alkyl-2-aryl-5-oxopyrrolidine-3-carboxylic acids in one step [8 – 15]. Castagnoli and Cushman have shown that the reaction leads with high diastereoselectivity to the *trans*-isomers [9 – 11]. The 5-oxopyrrolidine-3-carboxylic acids thus prepared can be regarded as substituted β-aminoacids. There is a continuing interest in β-aminoacids as a tool for medicinal chemistry [16], with the purpose to increase the molecular diversity such as the number of stereoisomers and functional group variety [17]. Recently a quantum-chemical interpretation of the mechanism of the cyclocondensation between succinic anhydride and imines was published [18].

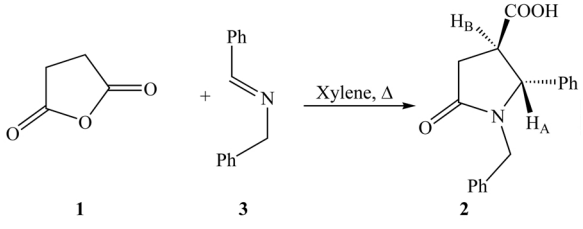
In the frames of a broader synthetic program on the preparation of polysubstituted lactams [19 – 23], we started an investigation of the carboxylic group transformations of *trans*-1-benzyl-2-phenyl-5-oxopyrrolidine-3-carboxylic acid (**2**). Such transformations have not been investigated hitherto. The starting acid **2** can be obtained by reaction of succinic anhydride (**1**) and *N*-benzylidene-benzylamine (**3**) [8]. With the present paper we report our results aiming at the preparation of two series of pyrrolidinones. The modifications of the carboxylic group were designed to incorporate an amino group in the side chain as part of another heterocycle such as 4-substituted piperazine, morpholine, piperidine, *etc*. Such heterocyclic moieties are well known pharmacophore substituents [24 – 28]. The combination of the pyrrolidinone ring with different 4-substituted piperazines in the side chain would result in a series of compounds with potential antihistaminic, antianaphilactic and anti-inflammatory activities [29].

Results and Discussion

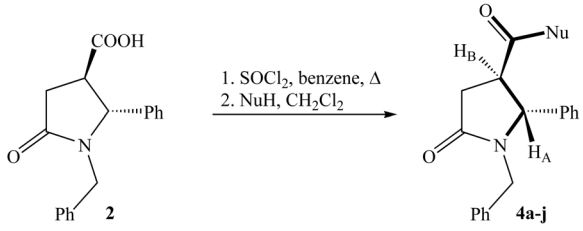
The required 1-benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (**2**) was first prepared by Shetty *et al.* [8] by refluxing of a mixture of succinic anhydride (**1**) and *N*-benzylidene-benzylamine (**3**) in *o*-xylene

NuH	Product	Yield	$J_{A,B}$	Product	Yield	$J_{A,B}$
–	**2**	53	5.5	**6**	78	4.6
–	**5**	65	5.7	**7**	94	5.4
ammonia	**4a**	66	5.6	–	–	–
pyrrolidine	**4b**	37	7.1	**8a**	69	3.6
piperidine	**4c**	40	6.7	**8b**	66	3.3
morpholine	**4d**	72	6.9	**8c**	81	3.4
1-methylpiperazine	**4e**	74	6.7	**8d**	66	3.1
1-phenylpiperazine	**4f**	55	6.9	**8e**	60	3.0
1-(4-fluorophenyl)piperazine	**4g**	58	6.9	**8f**	63	3.1
1-(3-chlorophenyl)piperazine	**4h**	40	6.9	**8g**	46	3.0
1-(3-(trifluoromethyl)phenyl)piperazine	**4i**	34	7.0	**8h**	51	3.3
tryptamine	–	–	–	**8i**	71	3.0
tert-butyl piperazine-1-carboxylate	**4j**	88	6.9	**8j**	95	3.0
–	**4k**	72	6.8	**8k**	46	5.0

Table 1. Nucleophiles NuH, yields of the prepared compounds (in %) and the corresponding $^3J_{A,B}$ values (in Hz).



Scheme 1. Synthesis of *trans*-acid **2** (for clarity only one enantiomer of **2** is shown).



Scheme 2. Synthesis of carboxamide derivatives **4a – j** (only one enantiomer is shown).

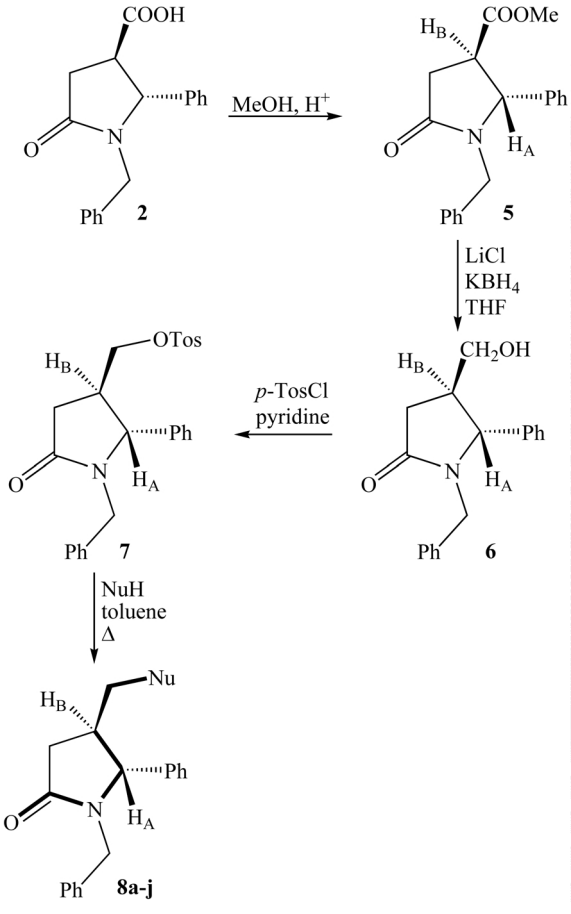
for 12 h in 34 % yield (Scheme 1). In order to raise the yield of the desired acid **2** we tried a prolonged reaction time.

After 14 h of reflux the yield of the crude product **2** was 53 %, and its purity was already comparable to that achieved by Shetty after recrystallization, as demonstrated by the m. p. of our product [8]. Recrystallization from ethyl acetate yielded an analytically pure 5-oxopyrrolidine-3-carboxylic acid **2** in 31 % yield, with m. p. 177 – 179 °C.

Shetty *et al.* did not determine the relative configuration of the acidic product **2** [8]. In our experiments the reaction of **1** with the imine **3** always gave rise to a single diastereomer. The ^{1}H NMR spectrum of **2** was measured, and it exhibited a doublet signal for the proton H_A at δ = 4.55 ppm with a coupling constant $^3J_{A,B}$ = 5.5 Hz of protons H_A and H_B. According to the literature data for similar 2,3-disubstituted pyrrolidinones, the coupling constant $^3J_{A,B}$ is in the range of 3.4 – 6.9 Hz for *trans*-compounds and in the range of 8.0 – 9.0 Hz for *cis*-pyrrolidinones [9, 11, 30 – 34]. The observed value of $^3J_{A,B}$ for the acid **2** falls in the range typical for *trans*-2,3-disubstituted pyrrolidine-5-ones. On this ground we assume a *trans* relative configuration of the substituents attached to the chiral atoms of the acid **2** prepared by us.

The preparation of carboxamides **4a – j** from *trans*-**2** *via* the corresponding acid chloride is shown in Scheme 2. The acid **2** was treated with thionyl chloride at 70 °C. It was essential not to exceed this temperature in order to avoid the formation of colored side products, which made the purification of the final carboxamides **4** very difficult. The crude acid chloride thus obtained was reacted with an excess of the corresponding amine NuH (Table 1). The compounds **4a – j** prepared were purified by recrystallization or column chromatography followed by recrystallization. Compound **4k** was synthesized by sonicated BOC cleavage of **4j** and purified by column chromatography and subsequent recrystallization. Thus, the obtained carboxamide derivatives **4a – k** contain a β-alanine subunit (the fragment given in bold in Scheme 2) [21, 35].

The preparation of the aminomethyl derivatives from the acid **2** followed a four-step reaction sequence [22, 35] (Scheme 3). Methyl ester **5** was obtained by esterification of the acid **2** with CH_3OH/H_2SO_4. The reduction of ester **5** with $LiBH_4$ proceeded selectively at the ester group to give *trans*-1-benzyl-4-(hydroxymethyl)-5-phenylpyrrolidin-2-one (**6**). The latter was converted with *p*-toluenesulfonyl chloride (*p*-TosCl) into tosylate **7**. The reaction of **7** with an excess of selected secondary heterocyclic amines NuH



Scheme 3. Synthesis of aminomethyl derivatives **8a – j** (only one enantiomer is shown).

(Table 1) was carried out in refluxing toluene. The resulting aminomethyl derivatives **8a – j** were purified by means of recrystallization or column chromatography. Compound **8k** was synthesized by sonicated BOC cleavage of **8j**. The 4-(aminomethyl)pyrrolidinone derivatives **8a – k** can be considered as inverse amide analogs of γ-aminobutyric acid (GABA) [21, 35]. This structural fragment is given in bold in Scheme 3. As it is known, the analogs of GABA exhibit biological activity on the CNS [2].

The compounds of types **4** and **8** are new. Their structure and *trans* relative configuration were established by means of ^{1}H NMR spectral data, which were compared with the data of the acid **2** as well as with the data of previously described structurally similar diastereomeric 2,3-disubstituted 5-oxopyrrolidine derivatives [9, 11, 30 – 34]. The relative *trans* configurations of methyl ester **5**, alcohol **6**, tosylate **7** as well as target amides **4** and aminomethyl derivatives **8** follow directly from the configuration of the starting acid *trans*-**2** since the subsequent transformations do not affect the stereogenic centers. Formation of the other stereoisomer was not observed. In the ^{1}H NMR spectra of the aminomethyl derivatives **8** the signal of H_A appears as a doublet with $^3J_{A,B}$ in the range of 3.0 – 5.0 Hz, which is again in agreement with the *trans* configuration of compounds **8**. In the case of the amides **4**, $^3J_{A,B}$ is in the range of 5.6 – 7.1 Hz, which is somewhat higher than the value for the pyrrolidinones **2**, **5 – 8** but still in the interval typical for the *trans*-isomers [9].

As it was already mentioned, formation of other diastereomers during the preparation of the amides **4** was not detected. On this ground a *trans* configuration of the amides **4** was also assumed. The change of the $^3J_{A,B}$ value for compounds **4a – k** and **8a – k** is probably due to a difference in the effective volume of the substituents, which influences the dihedral angle between H_A and H_B. The yields and $^3J_{A,B}$ values of the prepared compounds are summarized in Table 1. The pharmacological screening of compounds **4a – k** and **8a – k** is in course.

Experimental Section

Melting points were taken on a "Boetius" PHMK 05 micro hot-stage apparatus and are uncorrected. IR spectra were recorded on a Specord 75 instrument. ^{1}H NMR spectra (250.13 MHz) were obtained on a Bruker Avance DRX-250 spectrometer. The chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard. Electrospray ionization (ESI) mass spectra were recorded by flow injection of acetonitrile solution into an ESI source attached to a Varian Prostar 240 instrument. The microanalyses were carried out at the Faculty of Chemistry, University of Sofia. Thin layer chromatography (TLC) was performed on Merck 1.05554 silica gel 60F_{254} aluminum plates. Column chromatography purifications were performed using Acros silica gel (0.060 – 0.200 mm).

*Preparation of (±)-trans-1-benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (**2**)*

To a solution of *N*-benzylidene-benzylamine (**3**, 7.32 g, 38 mmol) in dried xylene (18 mL), succinic anhydride (**1**, 3.68 g, 37 mmol) was added. The reaction mixture was refluxed for 14 h. The separated crystals were collected by filtration (5.76 g, 53 %; m. p. 169 – 175 °C). Recrystallization from ethyl acetate afforded 3.37 g colorless needles of acid **2**. Yield 31 %. M. p. 177 – 179 °C (lit. [8]: 169 –

171 °C). – IR (nujol): ν = 2500 – 3300 (OH), 1730 (C=O), 1650 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO): δ = 2.63 (dd, ^2J = 16.9 Hz, ^3J = 6.7 Hz, 1H, CH_2CON), 2.84 (dd, ^2J = 16.9 Hz, ^3J = 9.6 Hz, 1H, CH_2CON), 3.06 (ddd, J = 5.5, 6.7, 9.6 Hz, 1H, H_B), 3.45 (d, J = 15.2 Hz, 1H, CH_2Ph), 4.55 (d, J = 5.5 Hz, 1H, H_A), 4.82 (d, J = 15.2 Hz, 1H, CH_2Ph), 6.97 – 7.45 (m, 10H, H-arom.), 12.77 (s, 1H, COOH). – $C_{18}H_{17}NO_3$ (295.34): calcd. C 73.20, H 5.80; found C 73.42, H 6.06.

*General procedure for the preparation of (±)-trans-1-benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylic acid amides (**4a – j**)*

A mixture of **2** (0.30 g, 1 mmol) and $SOCl_2$ (0.15 mL, 2 mmol) in dry benzene (4 mL) was heated at 70 °C for 1 h. The volatile products were evaporated under reduced pressure, and the slightly yellow oil was dissolved in CH_2Cl_2 (4 mL). The solution was cooled to −5 °C, and 3 mmol of the corresponding amine NuH was added dropwise. In the case of the amide **4a**, dry ammonia was bubbled through the solution at −5 °C for 30 min. The mixture was stirred at r. t. After completion of the reaction (TLC), the reaction mixture was dissolved in ethyl acetate (50 mL) and washed with water (3 × 20 mL). The organic phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The resulting oil was purified by recrystallization or by column chromatography and subsequent recrystallization from ethyl acetate-hexane if not stated otherwise. In this way the following compounds were prepared:

*(±)-trans-1-Benzyl-5-oxo-2-phenylpyrrolidine-3-carboxamide (**4a**)*

Recrystallization from water gave **4a** as colorless needle-shaped crystals. Yield 66 %. M. p. 180 – 182 °C. – IR (nujol): ν = 3190, 3360 (NH_2), 1670 (CON), 1620 ($CONH_2$) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO): δ = 2.49 (dd, ^2J = 16.5 Hz, ^3J = 6.8 Hz, 1H, CH_2CON), 2.77 (dd, ^2J = 16.5 Hz, ^3J = 9.5 Hz, 1H, CH_2CON), 2.93 (ddd, J = 5.6, 6.8, 9.5 Hz, 1H, H_B), 3.44 (d, J = 15.2 Hz, 1H, CH_2Ph), 4.50 (d, J = 5.6 Hz, 1H, H_A), 4.83 (d, J = 15.2 Hz, 1H, CH_2Ph), 6.97 – 7.51 (m, 12H, $CONH_2$, H-arom.). – $C_{18}H_{18}N_2O_2$ (294.36): calcd. C 73.45, H 6.16; found C 73.16, H 6.15.

*(±)-trans-1-Benzyl-5-phenyl-4-(pyrrolidine-1-carbonyl) pyrrolidin-2-one (**4b**)*

Column chromatography (light petroleum 37 – 50 °C/2-propanol = 8 : 1) and recrystallization gave **4b** as colorless crystals. Yield 37 %. M. p. 127 – 129 °C. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.55 – 1.85 (m, 4H, CH_2), 2.60 – 2.93 (m, 3H, H_B, CH_2N), 3.07 – 3.22 (m, 2H, CH_2CON, CH_2N), 3.29 – 3.48 (m, 2H, CH_2N), 3.53 (d, J = 14.7 Hz, 1H, CH_2Ph), 4.68 (d, J = 7.1 Hz, 1H, H_A), 5.07 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.96 – 7.43 (m, 10H, H-arom.). – MS (ESI): *m/z* (%) = 349 (100) $[M]^+$, 271 (5), 201 (9). – $C_{22}H_{24}N_2O_2$ (348.45): calcd. C 75.83, H 6.94; found C 75.44, H 7.19.

*(±)-trans-1-Benzyl-5-phenyl-4-(piperidine-1-carbonyl) pyrrolidin-2-one (**4c**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 1 : 1) and recrystallization gave **4c** as colorless crystals. Yield 40 %. M. p. 110 – 112 °C. – IR (nujol): ν = 1665, 1630 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.00 – 1.61 (m, 6H, CH_2), 2.71 – 2.95 (m, 2H, CH_2CON), 2.95 – 3.17 (m, 2H, CH_2N), 3.29 (ddd, J = 6.7, 8.5, 9.2 Hz, 1H, H_B), 3.41 – 3.58 (m, 3H, CH_2Ph, CH_2N), 4.72 (d, J = 6.7 Hz, 1H, H_A), 5.06 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.95 – 7.44 (m, 10H, H-arom.). – MS (ESI): *m/z* (%) = 363 (100) $[M]^+$, 201 (8). – $C_{23}H_{26}N_2O_2$ (362.48): calcd. C 76.21, H 7.23; found C 76.36, H 7.46.

*(±)-trans-1-Benzyl-4-(morpholine-4-carbonyl)-5-phenyl-pyrrolidin-2-one (**4d**)*

Column chromatography (light petroleum 37 – 50 °C/2-propanol = 3 : 1) gave **4d** as a colorless oil. Yield 72 %. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.76 (dd, ^2J = 16.8 Hz, ^3J = 9.3 Hz, 1H, CH_2CON), 2.86 – 3.74 (m, 11H, H_B, CH_2CON, CH_2Ph, CH_2N, CH_2O), 4.62 (d, J = 6.9 Hz, 1H, H_A), 5.07 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.94 – 7.44 (m, 10H, H-arom.). – $C_{22}H_{24}N_2O_3$ (364.45): calcd. C 72.51, H 6.64; found C 72.14, H 6.54.

*(±)-trans-1-Benzyl-4-(4-methylpiperazine-1-carbonyl)-5-phenylpyrrolidin-2-one (**4e**)*

Column chromatography (ethyl acetate/2-propanol/aqueous ammonia = 5 : 1 : 0.02) gave **4e** as a colorless oil. Yield 74 %. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.83 – 2.02 (m, 1H, CH_2N), 2.08 – 2.38 (m, 6H, CH_3, CH_2N), 2.77 (dd, ^2J = 16.7 Hz, ^3J = 9.4 Hz, 1H, CH_2CON), 2.92 (dd, ^2J = 16.7 Hz, ^3J = 8.4 Hz, 1H, CH_2CON), 3.01 (ddd, ^2J = 13.1 Hz, ^3J = 3.4, 6.7 Hz, 1H, CH_2N), 3.17 (ddd, ^2J = 13.1 Hz, ^3J = 3.2, 7.1 Hz, 1H, CH_2N), 3.28 (ddd, J = 6.7, 8.4, 9.4 Hz, 1H, H_B), 3.50 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.51 – 3.62 (m, 2H, CH_2N), 4.65 (d, J = 6.7 Hz, 1H, H_A), 5.06 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.95 – 7.43 (m, 10H, H-arom.). – MS (ESI): *m/z* (%) = 378 (98) $[M]^+$, 134 (10), 130 (72), 124 (26), 118 (42), 113 (19), 106 (12), 105 (100), 102 (16), 101 (38). – $C_{23}H_{27}N_3O_2$ (377.49): calcd. C 73.18, H 7.21; found C 73.23, H 7.49.

*(±)-trans-1-Benzyl-5-phenyl-4-(4-phenylpiperazine-1-carbonyl)pyrrolidin-2-one (**4f**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 1 : 1) and recrystallization gave **4f** as colorless crystals. Yield 55 %. M. p. 114 – 116 °C. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.53 – 2.65 (m, 1H, CH_2N), 2.80 (dd, ^2J = 16.8 Hz, ^3J = 9.4 Hz, 1H, CH_2CON), 2.86 – 3.04 (m, 3H, CH_2CON, CH_2N), 3.07 – 3.20 (m, 2H, CH_2N), 3.23 – 3.41 (m, 2H, H_B, CH_2N), 3.51 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.57 – 3.69 (m, 1H, CH_2N), 3.74 – 3.86 (m, 1H, CH_2N), 4.66 (d, J = 6.9 Hz, 1H, H_A), 5.08 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.76 – 7.44 (m, 15H, H-arom.). – MS (ESI): *m/z* (%) = 440 (100) $[M]^+$, 331 (5), 201 (7). – $C_{28}H_{29}N_3O_2$ (439.56): calcd. C 76.51, H 6.65; found C 76.68, H 6.57.

*(±)-trans-1-Benzyl-4-(4-(4-fluorophenyl)piperazine-1-carbonyl)-5-phenylpyrrolidin-2-one (**4g**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate/aqueous ammonia = 1 : 1 : 0.02) and recrystallization gave **4g** as colorless crystals. Yield 58 %. M. p. 119 – 121 °C. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.44 – 2.56 (m, 1H, CH_2N), 2.73 – 3.20 (m, 6H, CH_2CON, CH_2N), 3.23 – 3.41 (m, 2H, H_B, CH_2N), 3.51 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.57 – 3.69 (m, 1H, CH_2N), 3.73 – 3.85 (m, 1H, CH_2N), 4.66 (d, J = 6.9 Hz, 1H, H_A), 5.09 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.71 – 7.44 (m, 14H, H-arom.). – $C_{28}H_{28}FN_3O_2$ (457.55): calcd. C 73.50, H 6.17; found C 73.19, H 6.26.

*(±)-trans-1-Benzyl-4-(4-(3-chlorophenyl)piperazine-1-carbonyl)-5-phenylpyrrolidin-2-one (**4h**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 1 : 1) gave **4h** as a colorless oil. Yield 40 %. – IR ($CHCl_3$): ν = 1680, 1645 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.49 – 2.63 (m, 1H, CH_2N), 2.73 – 3.05 (m, 4H, CH_2CON, CH_2N), 3.06 – 3.19 (m, 2H, CH_2N), 3.21 – 3.41 (m, 2H, H_B, CH_2N), 3.50 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.54 – 3.66 (m, 1H, CH_2N), 3.72 – 3.86 (m, 1H, CH_2N), 4.64 (d, J = 6.9 Hz, 1H, H_A), 5.08 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.62 – 7.45 (m, 14H, H-arom.). – $C_{28}H_{28}ClN_3O_2$ (474.01): calcd. C 70.95, H 5.95; found C 70.58, H 6.26.

*(±)-trans-1-Benzyl-5-phenyl-4-(4-(3-(trifluoromethyl)phenyl)piperazine-1-carbonyl)pyrrolidin-2-one (**4i**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 1 : 1) and recrystallization gave **4i** as colorless crystals. Yield 34 %. M. p. 131 – 133 °C. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.53 – 2.66 (m, 1H, CH_2N), 2.81 (ddd, ^2J = 16.8 Hz, ^3J = 9.3 Hz, 1H, CH_2CON), 2.89 – 3.07 (m, 3H, CH_2CON, CH_2N), 3.09 – 3.24 (m, 2H, CH_2N), 3.24 – 3.42 (m, 2H, H_B, CH_2N), 3.51 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.57 – 3.69 (m, 1H, CH_2N), 3.75 – 3.88 (m, 1H, CH_2N), 4.64 (d, J = 7.0 Hz, 1H, H_A), 5.09 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.91 – 7.46 (m, 14H, H-arom.). – $C_{29}H_{28}F_3N_3O_2$ (507.56): calcd. C 68.63, H 5.56; found C 68.94, H 5.77.

*tert-Butyl 4-((±)-trans-1-benzyl-5-oxo-2-phenylpyrrolidine-3-carbonyl)piperazine-1-carboxylate (**4j**)*

Recrystallization gave **4j** as colorless crystals. Yield 88 %. M. p. 141 – 143 °C. – IR ($CHCl_3$): ν = 1695 (OCON, CON), 1630 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.42 (s, 9H, CH_3), 2.70 – 3.46 (m, 10H, CH_2CON, H_B, CH_2N), 3.49 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.54 – 3.67 (m, 1H, CH_2N), 4.62 (d, J = 6.9 Hz, 1H, H_A), 5.07 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.94 – 7.45 (m, 10H, H-arom.). – MS (ESI): *m/z* (%) = 464 (100) $[M]^+$, 412 (12), 410 (19), 408 (56), 333 (13), 218 (12), 201 (18). – $C_{27}H_{33}N_3O_4$ (463.58): calcd. C 69.96, H 7.18; found C 69.90, H 7.54.

*(±)-trans-1-Benzyl-5-phenyl-4-(piperazine-1-carbonyl)pyrrolidin-2-one (**4k**)*

A mixture of the amide **4j** (0.180 g, 0.4 mmol) and trifluoroacetic acid (0.45 mL, 6 mmol) was sonicated for 15 min. The volatile components were evaporated, and the resulting oil was dissolved in ethyl acetate (30 mL). The mixture was treated with 10 % aqueous Na_2CO_3 until pH = 10 was reached. The organic phase was washed with water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting oily product was recrystallized to give 0.105 g colorless crystals of **4k**. Yield 72 %. M. p. 159 – 162 °C. – IR ($CHCl_3$): ν = 1670, 1640 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.00 (broad s, 1H, NH), 2.28 – 2.45 (m, 1H, CH_2N), 2.58 – 3.36 (m, 8H, H_B, CH_2CON, CH_2N), 3.43 – 3.64 (m, 2H, CH_2Ph, CH_2N), 3.65 – 3.82 (m, 1H, CH_2N), 4.62 (d, J = 6.8 Hz, 1H, H_A), 5.06 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.95 – 7.46 (m, 10H, H-arom.). – $C_{22}H_{25}N_3O_2$ (363.46): calcd. C 72.70, H 6.93; found C 72.20, H 6.88.

*Preparation of the methyl ester of (±)-trans-1-benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (**5**)*

A mixture of **2** (4.43 g, 15 mmol), dry methanol (25 mL), and conc. H_2SO_4 (1.6 mL) was refluxed for 2 h. The cooled reaction mixture was poured into brine (50 mL). The suspension was neutralized with 10 % aqueous Na_2CO_3 and filtered. The resulting crystals were washed with water and dried, thus yielding 4.55 g (98 %) of the methyl ester. The crude product was recrystallized from ethyl acetate to afford 3.02 g of **5** as colorless crystals. Yield 65 %. M. p.

96 – 98 °C. – IR ($CHCl_3$): ν = 1735 ($COOCH_3$), 1680 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.80 (dd, ^2J = 17.0 Hz, ^3J = 7.8 Hz, 1H, CH_2CON), 2.91 (dd, ^2J = 17.0 Hz, ^3J = 9.0 Hz, 1H, CH_2CON), 3.08 (ddd, J = 5.7, 7.8, 9.0 Hz, 1H, H_B), 3.48 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.65 (s, 3H, CH_3), 4.61 (d, J = 5.7 Hz, 1H, H_A), 5.12 (d, J = 14.7 Hz, 1H, CH_2Ph), 6.99 – 7.45 (m, 10H, H-arom.). – $C_{19}H_{19}NO_3$ (309.37): calcd. C 73.77, H 6.19; found C 73.63, H 6.42.

*Preparation of (±)-1-benzyl-4-(hydroxymethyl)-5-phenylpyrrolidin-2-one (**6**)*

To a stirred suspension of LiCl (2.54 g, 60 mmol) and KBH_4 (3.24 g, 60 mmol) in THF (10 mL) was added dropwise a solution of **5** (6.19 g, 20 mmol) in THF (20 mL) within 15 min. The reaction mixture was stirred at r. t. for 5 h. The solvent was removed under reduced pressure, and brine (100 mL) was added. The resulting emulsion was extracted with ethyl acetate (3 × 30 mL), and the combined organic phases were dried (Na_2SO_4). After removal of the solvent, the residue was purified by recrystallization from ethyl acetate affording 4.37 g of **6** as colorless powder. Yield 78 %. M. p. 98 – 99 °C. – IR ($CHCl_3$): ν = 3370 (OH), 1675 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.83 (broad s, 1H, OH), 2.29 – 2.45 (m, 2H, H_B, CH_2CON), 2.76 (dd, ^2J = 18.5 Hz, ^3J = 10.7 Hz, 1H, CH_2CON), 3.47 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.58 (d, J = 5.7 Hz, 2H, CH_2OH), 4.24 (d, J = 4.6 Hz, 1H, H_A), 5.10 (d, J = 14.5 Hz, 1H, CH_2Ph), 7.02 – 7.43 (m, 10H, H-arom.). – $C_{18}H_{19}NO_2$ (281.36): calcd. C 76.84, H 6.81; found C 76.58, H 7.09.

*Preparation of ((±)-trans-1-benzyl-5-oxo-2-phenylpyrrolidin-3-yl)methyl 4-methylbenzenesulfonate (**7**)*

p-Toluenesulfonyl chloride (2.67 g, 14 mmol) was added in portions with stirring to a solution of **6** (1.97 g, 7 mmol) in pyridine (30 mL) maintained at −10 °C. The reaction mixture was allowed to warm to r. t., and stirring was continued for further 5 h. The mixture was poured into ice-water, and the product was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed successively with 5 % HCl, 10 % $NaHCO_3$ and water to reach a pH = 7 and dried (Na_2SO_4). Evaporation of the solvent gave 2.69 g of **7** as a non-crystallizable, slightly yellow oil. The resulting product was used in the next steps without further purification. – Yield 88 %. A sample of the latter product was purified by column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 3 : 2) for analytical purposes. – IR ($CHCl_3$): ν = 1675 (CON), 1170 (OSO_2) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.30 (dd, ^2J = 16.6 Hz, ^3J = 6.6 Hz, 1H, CH_2CON), 2.39 – 2.53 (m, 4H, H_B, CH_3), 2.73 (dd, ^2J = 16.6 Hz, ^3J = 9.0 Hz, 1H, CH_2CON), 3.43 (d, J = 14.6 Hz, 1H, CH_2Ph), 3.86 – 4.01 (m, 2H, CH_2O), 4.09 (d, J = 5.4 Hz, 1H, H_A), 5.07 (d, J = 14.6 Hz, 1H, CH_2Ph), 6.93 – 7.04 (m, 4H, H-arom.), 7.23 – 7.39 (m, 8H, H-arom.), 7.60 – 7.68 (m, 2H, H-arom.). – $C_{25}H_{25}NO_4S$ (435.55): calcd. C 68.94, H 5.79, N 3.22, S 7.36; found C 69.55, H 5.77, N 3.16, S 7.01.

*General procedure for the preparation of (±)-trans-4-((substituted amino)methyl)pyrrolidin-2-ones (**8a**–**j**)*

To a solution of the tosylate **7** in toluene (2 mL for each mmol of **7**) the threefold molar excess of the corresponding amine was added. The reaction mixture was refluxed until completion of the reaction as determined by TLC. The mixture was allowed to cool down to r. t., and ethyl acetate (50 mL) was added. The organic layer was washed with water (4 × 20 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure. The resulting oil was recrystallized or purified by column chromatography and subsequent recrystallization from ethyl acetate/hexane. In this way the following compounds were prepared:

*(±)-trans-1-Benzyl-5-phenyl-4-(pyrrolidin-1-ylmethyl) pyrrolidin-2-one (**8a**)*

Column chromatography (ethyl acetate/aqueous ammonia = 3 : 0.02) gave **8a** as a colorless oil. Yield 69 %. – IR ($CHCl_3$): ν = 1680 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.57 – 1.74 (m, 4H, CH_2), 2.22 – 2.39 (m, 7H, CH_2CON, CH_2N), 2.43 – 2.55 (m, 1H, H_B), 2.79 (dd, ^2J = 18.0 Hz, ^3J = 9.2 Hz, 1H, CH_2CON), 3.47 (d, J = 14.6 Hz, 1H, CH_2Ph), 4.23 (d, J = 3.6 Hz, 1H, H_A), 5.12 (d, J = 14.6 Hz, 1H, CH_2Ph), 7.02 – 7.41 (m, 10H, H-arom.). – $C_{22}H_{26}N_2O$ (334.47): calcd. C 79.01, H 7.84; found C 78.81, H 8.17.

*(±)-trans-1-Benzyl-5-phenyl-4-(piperidin-1-ylmethyl) pyrrolidin-2-one (**8b**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate/aqueous ammonia = 1 : 1 : 0.02) gave **8b** as a colorless oil. Yield 66 %. – IR ($CHCl_3$): ν = 1675 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.28 – 1.48 (m, 6H, CH_2), 2.02 – 2.41 (m, 8H, H_B, CH_2CON, CH_2N), 2.75 (dd, ^2J = 17.0 Hz, ^3J = 8.4 Hz, 1H, CH_2CON), 3.48 (d, J = 14.6 Hz, 1H, CH_2Ph), 4.32 (d, J = 3.3 Hz, 1H, H_A), 5.13 (d, J = 14.6 Hz, 1H, CH_2Ph), 7.05 – 7.40 (m, 10H, H-arom.). – $C_{23}H_{28}N_2O$ (348.49): calcd. C 79.27, H 8.10, N 8.04; found C 79.63, H 8.05, N 8.49.

*(±)-trans-1-Benzyl-4-(morpholinomethyl)-5-phenylpyrrolidin-2-one (**8c**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate/aqueous ammonia = 1 : 1 : 0.02) gave **8c** as a colorless oil. Yield 81 %. – IR ($CHCl_3$): ν = 1685

(CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.09 – 2.42 (m, 8H, H_B, CH_2CON, CH_2N), 2.77 (dd, ^2J = 16.9 Hz, ^3J = 8.5 Hz, 1H, CH_2CON), 3.46 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.54 (t, J = 4.8 Hz, 4H, CH_2O), 4.29 (d, J = 3.4 Hz, 1H, H_A), 5.14 (d, J = 14.5 Hz, 1H, CH_2Ph), 7.04 – 7.42 (m, 10H, H-arom.). – $C_{22}H_{26}N_2O_2$ (350.46): calcd. C 75.40, H 7.48; found C 75.60, H 7.65.

*(±)-trans-1-Benzyl-4-((4-methylpiperazin-1-yl)methyl)-5-phenylpyrrolidin-2-one (**8d**)*

Column chromatography (ethyl acetate/2-propanol/aqueous ammonia = 9 : 1 : 0.02) gave **8d** as a slightly yellow oil. Yield 71 %. – IR ($CHCl_3$): ν = 1680 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.13 – 2.44 (m, 15H, H_B, CH_2CON, CH_3, CH_2N), 2.76 (dd, ^2J = 17.1 Hz, ^3J = 7.4 Hz, 1H, CH_2CON), 3.46 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.28 (d, J = 3.0 Hz, 1H, H_A), 5.13 (d, J = 14.5 Hz, 1H, CH_2Ph), 7.03 – 7.42 (m, 10H, H-arom.). – $C_{23}H_{29}N_3O$ (363.51): calcd. C 76.00, H 8.04; found C 75.77, H 8.37.

*(±)-trans-1-Benzyl-5-phenyl-4-((4-phenylpiperazin-1-yl)methyl)pyrrolidin-2-one (**8e**)*

Recrystallization gave **8e** as colorless crystals. Yield 66 %. M. p. 147 – 149 °C. – IR ($CHCl_3$): ν = 1675 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.23 (dd, ^2J = 17.1 Hz, ^3J = 4.1 Hz, 1H, CH_2CON), 2.28 – 2.53 (m, 7H, H_B, CH_2N), 2.80 (dd, ^2J = 17.1 Hz, ^3J = 8.1 Hz, 1H, CH_2CON), 3.03 (t, J = 5.0 Hz, 4H, CH_2N), 3.47 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.34 (d, J = 3.1 Hz, 1H, H_A), 5.15 (d, J = 14.5 Hz, 1H, CH_2Ph), 6.79 – 6.93 (m, 3H, H-arom.), 7.05 – 7.42 (m, 12H, H-arom.). – $C_{28}H_{31}N_3O$ (425.58): calcd. C 79.02, H 7.34; found C 78.74, H 7.61.

*(±)-trans-1-Benzyl-4-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-5-phenylpyrrolidin-2-one (**8f**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 2 : 3) and recrystallization gave **8f** as colorless crystals. Yield 60 %. M. p. 126 – 128 °C. – IR ($CHCl_3$): ν = 1665 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.18 – 2.52 (m, 8H, H_B, CH_2CON, CH_2N), 2.80 (dd, ^2J = 16.8 Hz, ^3J = 7.7 Hz, 1H, CH_2CON), 2.95 (t, J = 4.9 Hz, 4H, CH_2N), 3.47 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.33 (d, J = 3.0 Hz, 1H, H_A), 5.15 (d, J = 14.5 Hz, 1H, CH_2Ph), 6.75 – 6.99 (m, 4H, H-arom.), 7.06 – 7.43 (m, 10H, H-arom.). – MS (ESI): *m/z* (%) = 444 (92) $[M]^+$, 130 (100), 101 (8). – $C_{28}H_{30}FN_3O$ (443.57): calcd. C 75.82, H 6.82; found C 75.45, H 7.12.

*(±)-trans-1-Benzyl-4-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-5-phenylpyrrolidin-2-one (**8g**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate/aqueous ammonia = 2 : 1 : 0.02) gave **8g** as a colorless oil. Yield 63 %. – IR ($CHCl_3$): ν = 1685 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.16 – 2.50 (m, 8H, H_B, CH_2CON, CH_2N), 2.79 (dd, ^2J = 16.8 Hz, ^3J = 8.5 Hz, 1H, CH_2CON), 3.02 (t, J = 5.1 Hz, 4H, CH_2N), 3.47 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.33 (d, J = 3.1 Hz, 1H, H_A), 5.15 (d, J = 14.5 Hz, 1H, CH_2Ph), 6.67 – 7.41 (m, 14H, H-arom.). – MS (ESI): *m/z* (%) = 460 (73) $[M]^+$, 130 (100), 127 (22), 125 (13), 115 (16), 113 (47), 101 (26). – $C_{28}H_{30}ClN_3O$ (460.02): calcd. C 73.11, H 6.57; found C 72.80, H 6.73.

*(±)-trans-1-Benzyl-5-phenyl-4-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)pyrrolidin-2-one (**8h**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 1 : 1) and recrystallization gave **8h** as colorless crystals. Yield 46 %. M. p. 100 – 102 °C. – IR ($CHCl_3$): ν = 1675 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.23 (dd, ^2J = 17.1 Hz, ^3J = 4.0 Hz, 1H, CH_2CON), 2.25 – 2.53 (m, 7H, H_B, CH_2N), 2.80 (dd, ^2J = 17.1 Hz, ^3J = 7.9 Hz, 1H, CH_2CON), 3.07 (t, J = 4.8 Hz, 4H, CH_2N), 3.47 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.33 (d, J = 3.0 Hz, 1H, H_A), 5.16 (d, J = 14.5 Hz, 1H, CH_2Ph), 6.95 – 7.45 (m, 14H, H-arom.). MS (ESI): *m/z* (%) = 494 (69) $[M]^+$, 296 (12), 131 (9), 130 (100), 113 (19), 102 (12). – $C_{29}H_{30}F_3N_3O$ (493.58): calcd. C 70.57, H 6.13; found C 70.60, H 6.23.

*(±)-trans-4-((2-(1H-Indol-3-yl)ethylamino)methyl)-1-benzyl-5-phenylpyrrolidin-2-one (**8i**)*

Column chromatography (ethyl acetate) gave **8i** as a colorless oil. Yield 46 %. – IR ($CHCl_3$): ν = 3250 (NH), 1685 (CON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 2.15 – 2.36 (m, 3H, H_B, NH, CH_2CON), 2.54 – 2.91 (m, 7H, CH_2CON, CH_2N, CH_2), 3.43 (d, J = 14.6 Hz, 1H, CH_2Ph), 4.06 (d, J = 5.0 Hz, 1H, H_A), 5.09 (d, J = 14.6 Hz, 1H, CH_2Ph), 6.90 (d, J = 2.3 Hz, 1H, CH (indole)), 6.98 – 7.56 (m, 14H, H-arom.), 8.05 (s, 1H, NH (indole)). – $C_{28}H_{29}N_3O$ (423.56): calcd. C 79.40, H 6.90; found C 79.21, H 7.09.

*tert-Butyl 4-(((±)-trans-1-benzyl-5-oxo-2-phenylpyrrolidin-3-yl)methyl)piperazine-1-carboxylate (**8j**)*

Column chromatography (light petroleum 37 – 50 °C/ethyl acetate = 1 : 1) and recrystallization gave **8j** as colorless crystals. Yield 51 %. M. p. 92 – 94 °C. – IR ($CHCl_3$): ν = 1680 (CON, OCON) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$): δ = 1.42 (s, 9H, CH_3), 2.02 – 2.42 (m, 8H, H_B, CH_2CON, CH_2N), 2.76 (dd, ^2J = 16.7 Hz, ^3J = 8.1 Hz, 1H, CH_2CON), 3.24 (t, J = 5.1 Hz, 4H, CH_2N), 3.45 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.30 (d, J = 3.3 Hz, 1H, H_A), 5.14 (d, J = 14.5 Hz, 1H, CH_2Ph), 7.04 – 7.42 (m, 10H, H-arom.). – MS (ESI): *m/z* (%) = 450 (100) $[M]^+$, 130 (28), 117 (10), 101 (13). – $C_{27}H_{35}N_3O_3$ (449.60): calcd. C 72.13, H 7.85, N 9.35; found C 72.35, H 7.62, N 9.33.

*(±)-trans-1-Benzyl-5-phenyl-4-(piperazin-1-ylmethyl) pyrrolidin-2-one (**8k**)*

A mixture of **8j** (0.45 g, 1 mmol) and trifluoroacetic acid (1.15 mL, 15 mmol) was sonicated for 15 min. The mixture was neutralized with 10 % aqueous Na_2CO_3 and extracted with ethyl acetate (3×30 mL). The organic phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Column chromatography (ethyl acetate/2-propanol/aqueous ammonia = 4 : 1 : 0.02) afforded 0.330 g of **8k** as a slightly yellow oil. Yield 95 %. – IR ($CHCl_3$): ν = 1680 (CON) cm^{-1}. – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.09 – 2.50 (m, 9H, H_B, CH_2CON, CH_2N), 2.75 (dd, ^2J = 16.8 Hz, ^3J =7.2 Hz, 1H, CH_2CON), 2.81 – 2.99 (m, 3H, CH_2N), 3.42 (d, J = 14.5 Hz, 1H, CH_2Ph), 4.20 (d, J = 3.0 Hz, 1H, H_A), 5.11 (d, J = 14.5 Hz, 1H, CH_2Ph), 7.01 – 7.41 (m, 10H, H-arom.). – $C_{22}H_{27}N_3O$ (349.48): calcd. C 75.61, H 7.79; found C 75.18, H 7.93.

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[1] F. Felluga, V. Gombac, G. Pitacco, E. Valentin, E. Zangrando, S. Morganti, E. Rizzato, D. Spinelli, G. Petrillo, *Tetrahedron* **2006**, *62*, 8787 – 8791.
[2] A. Garcia, M. Carpes, A. de Oca, M. dos Santos, C. Santana, C. Correia, *J. Org. Chem*. **2005**, *70*, 1050 – 1053.
[3] C. Yoon, A. Nagle, C. Chen, D. Gandhi, K. Jung, *Org. Lett*. **2003**, *5*, 2259 – 2262.
[4] A. Paraskar, A. Sudalai, *Tetrahedron* **2006**, *62*, 4907 – 4916.
[5] J. Cook, J. Barzya, C. Brennan, D. Lowe, Y. Wang, A. Redman, W. Scott, J. Wood, *Tetrahedron Lett*. **2005**, *46*, 1525 – 1528.
[6] D. Gunn, C. Akuche, J. Baryza, M.-L. Blue, C. Brennan, A.-M. Campbell, S. Choi, J. Cook, P. Conrad, B. Dixon, J. Dumas, P. Ehrlich, T. Gane, T. Joe, J. Johnson, J. Jordan, R. Kramss, P. Liu, J. Levy, D. Lowe, I. McAlexander, R. Natero, A. Redman, W. Scott, T. Seng, R. Sibley, M. Wang, Y. Wang, J. Wood, Z. Zhang, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 3053 – 3057.
[7] B. Kenda, A. Matagne, P. Talaga, P. Pasau, E. Differding, B. Lallemand, A. Frycia, F. Moureau, H. Klitgaard, M. Gillard, B. Fuks, P. Michel, *J. Med. Chem*. **2004**, *47*, 530 – 549.
[8] B. Shetty, A. McFadden, P. Hofer, U. S. Patent 4476311, **1984**.
[9] N. Castagnoli, *J. Org. Chem*. **1969**, *34*, 3187 – 3189.
[10] M. Cushman, N. Castagnoli, *J. Org. Chem*. **1972**, *37*, 1268 – 1271.
[11] M. Joannic, D. Humbert, M. Pesson, *C. R. Acad. Sci. Paris, Serie C* **1972**, *275*, 45 – 48.
[12] C. Masse, P. Y. Ng, Y. Fukase, M. Sanchez-Rosello, J. Shaw, *J. Comb. Chem*. **2006**, *8*, 293 – 296.
[13] P. Y. Ng, C. Masse, J. Shaw, *Org. Lett*. **2006**, *8*, 3999 – 4002.
[14] F. Dallacker, W. Jouck, *Chem.-Ztg*. **1985**, *109*, 82 – 84.
[15] J. Robert, A. Boucherle, *Ann. Pharm. Fr*. **1981**, *39*, 337 – 346.
[16] D. Cole, *Tetrahedron* **1994**, *50*, 9517 – 9582.
[17] A. Trabocchi, F. Guarna, A. Guarna, *Curr. Org. Chem*. **2005**, *9*, 1127 – 1153.
[18] J. Kaneti, S. Bakalova, I. Pojarlieff, *J. Org. Chem*. **2003**, *68*, 6824 – 6827.
[19] I. Kozekov, R. Koleva, M. Palamareva, *J. Heterocycl. Chem*. **2002**, *39*, 229 – 235.
[20] M. Kandinska, I. Kozekov, M. Palamareva, *Molecules* **2006**, *11*, 403 – 414.
[21] M. Stoyanova, I. Kozekov, M. Palamareva, *J. Heterocycl. Chem*. **2003**, *40*, 795 – 803.
[22] N. Burdzhiev, E. Stanoeva, *Tetrahedron* **2006**, *62*, 8318 – 8326.
[23] M. Kandinska, I. Todorov, B. Shivachev, M. Bogdanov, *Acta Crystallogr*. **2007**, *E63*, o2544–o2546.
[24] I. Kinoyama, N. Taniguchi, T. Yoden, H. Koutoku, T. Furutani, M. Kudoh, M. Okada, *Chem. Pharm. Bull*. **2004**, *52*, 1330 – 1333.
[25] H. Pessoa-Mahana, G. Gajardo, R. Araya-Maturana, J. Carcamo, C. Pessoa-Mahana, *Synth. Commun*. **2004**, *34*, 2513 – 2521.
[26] J. Obniska, A. Zagorska, *Il Farmaco* **2003**, *58*, 1227 – 1234.
[27] J. Obniska, M. Kolaczkowski, A. Bojarski, B. Duszynska, *Eur. J. Med. Chem*. **2006**, *41*, 874 – 881.
[28] B. Malawska, K. Kulig, A. Gippert, B. Filipek, J. Sapa, D. Maciag, *Il Farmaco* **2005**, *60*, 793 – 803.
[29] P. de Meglio, F. Corradi, F. Ravenna, P. Gentili, G. Tempra-Gabbiati, T. Cristina, M. Riva, *Il Farmaco* **1987**, *42*, 359 – 382.
[30] F. Zymalkowski, P. Pachaly, *Chem. Ber*. **1967**, *100*, 1137 – 1143.
[31] P. Pachaly, *Chem. Ber*. **1968**, *101*, 2176 – 2184.
[32] P. Pachaly, *Chem. Ber*. **1971**, *104*, 412 – 420.
[33] D. Alonso, A. Costa, B. Mancheno, C. Najera, *Tetrahedron* **1997**, *53*, 4791 – 4814.
[34] M. Novikov, A. Khlebnikov, E. Sidorina, A. Masalev, J. Kopf, R. Kostikov, *Zh. Org. Khim*. **2002**, *38*, 710 – 719.
[35] B. Bonnaud, A. Carlessi, D. Bigg, *J. Heterocycl. Chem*. **1993**, *30*, 257 – 265.