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Reaction between glutaric anhydride and *N*-benzylidenebenzylamine, and further transformations to new substituted piperidin-2-ones

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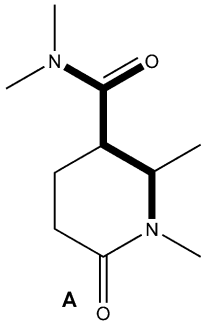
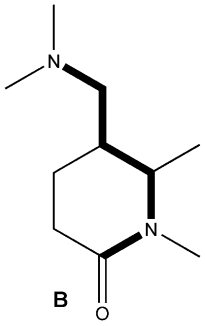
Abstract—The reaction between glutaric anhydride (**1**) and *N*-benzylidenebenzylamine (**3**) was studied in detail by ^{1}H NMR spectroscopy under different reaction conditions. The major product was (±)-*trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylic acid (**2**), which was converted into new substituted piperidin-2-ones via transformations of the carboxylic group. The final products are expected to possess pharmaceutical activities, and the relevant screenings are in course.

1. Introduction

The piperidine ring is an important core structure in organic chemistry because of its presence in many natural products.[1–4] Substituted piperidines display a wide spectrum of physiological activities such as analgesic and anti-inflammatory,[5] anticonvulsant,[6] aromatase inhibiting,[7] etc. Piperidines possessing an amino substituent show cytotoxicity,[8] and are selective human neurokinin-1 antagonists.[9] Piperidinones are often useful advanced intermediates in the preparation of piperidines[4] and scaffolds in the synthesis of β-turn peptide mimetics.[10] Piperidinones possessing piperazino substituents exhibit antihistaminic and antianaphylactic activities.[11] The diverse biological activities of substituted piperidines have provoked numerous synthetic studies. Several reviews dealing with the recent progress in the synthesis of substituted piperidines and piperidinones have been published.[4,12–14] The reaction of glutaric anhydride (**1**) with *N*-arylidene-*N*-alkylamines provides a straightforward path to the synthesis of the piperidinone ring. It affords many *trans*-1-alkyl-2-aryl-6-oxopiperidine-3-carboxylic acids in one step.[5,7,15,16] However, less attention has been paid to the functional group transformations in the piperidinones obtained. For instance, *trans*-1-methyl-2-(2-methoxyphenyl)-6-oxopiperidine-3-carboxylic acid obtained by cyclocondensation of glutaric anhydride and the appropriate Schiff base was converted to an aza analog of tetrahydrocannabinol by Grignard addition to the carboxylic group in the key step.[16] The aim of the present paper is to investigate other possible transformations of the carboxylic group in order to achieve its replacement by carboxamido or by aminomethyl groups. In this way two types of target structures, **A** and **B**, can be obtained. The carboxamides, represented by structure **A**, contain a β-alanine subunit (the fragment given in bold). The (aminomethyl)piperidinone derivatives are related to structure **B**, which can be considered as inverse amide analogs of γ-aminobutyric acid (GABA).[17–19] The two sets of piperidinone derivatives may be designed to incorporate an amino group in the side chain as a part of another heterocycle such as 4-substituted piperazine, morpholine, piperidine, etc. Such heterocyclic moieties are well known pharmacophore substituents.[20–22] The combination of the piperidinone ring with different heterocyclic moieties in the side chain would result in a series of compounds with potential biological activities. For the purposes of this



A



B

Keywords: Piperidin-2-ones; Glutaric anhydride; Piperazine; Stereochemistry.
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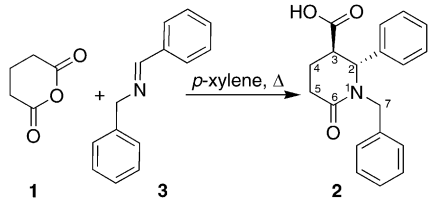
investigation we needed a great amount of *trans*-1-benzyl-2-phenyl-6-oxopiperidine-3-carboxylic acid (**2**). That made us study the reaction of **1** and *N*-benzylidenebenzylamine (**3**) in order to determine the optimal conditions for a fast and easy approach to acid **2**.

2. Results and discussion

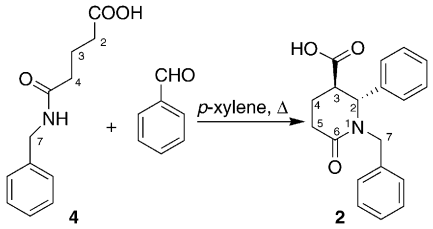
The required starting *trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylic acid (**2**) was first prepared by Shetty et al. by refluxing a mixture of glutaric anhydride (**1**) and *N*-benzylidenebenzylamine (**3**) in xylene for 10 h in 80% yield[5] (Scheme 1). Chan et al. prepared *trans*-**2** by refluxing **1** and **3** in toluene for 50 h.[15] It was shown that *trans*-**2** formed a non-stoichiometric channel inclusion complex with acetonitrile as evidenced by X-ray analysis.[15] The significant difference in the reaction times[5,15] prompted us to investigate the relationship between the temperature and the time needed for the completion of the reaction. To achieve this we chose to fix the reaction time, in order to estimate the difference in the yields. Mixtures of **1** and **3** were refluxed in aprotic solvents with different boiling points. The solvents used and the yields of *trans*-**2** after 6 h are shown in Table 1.



Scheme 1. Synthesis of compound **2**.

The results indicate that the yield of *trans*-**2** increases with the rise of the temperature. Thus *p*-xylene appears to be the most suitable solvent for this reaction. That was the reason for using *p*-xylene as the solvent in our further research. A detailed investigation of the reaction mixture by TLC showed that glutaric anhydride (**1**) disappeared after 1 h at reflux and the reaction mixture contained along with the acid *trans*-**2**, also glutaric acid mono-*N*-benzylamide **4**. Up to now, there are no literature data about the concomitant formation of acyclic monoamides of glutaric acid during the reaction of the glutaric anhydride (**1**) with imines.[5,15,16] This made us follow the course of the reaction in *p*-xylene by ^{1}H NMR spectroscopy. We prepared four reaction mixtures each containing the same equimolar amounts of the reagents **1** and **3** in *p*-xylene and heated them at different times—0.5, 1, 3 and 6 h. Aliquots were taken and investigated by ^{1}H NMR spectroscopy. The corresponding spectra are presented in Figure 1. The integral intensities are shown below every signal. They are measured relatively to the doublet signal for H-2 (δ 4.81 ppm) in the molecule of the acid **2**. The determination of the relative quantity of the monoamide **4** was done using the doublet signal at 4.25 ppm for the two benzylic CH_2 protons, arbitrarily marked as H-7. Thus, the ^{1}H NMR spectrum after 0.5 h showed the presence of the acid *trans*-**2** and the monoamide **4** in ca. 1:4 ratio. The reaction mixtures also contained benzaldehyde from hydrolysis of the corresponding Schiff base **3** as evidenced by the singlet for C*H*O at 10.0 ppm. A certain amount of benzaldehyde is lost probably during the evaporation of *p*-xylene under reduced pressure. Signals of glutaric anhydride (**1**) could not be detected due to overlap with other signals. After the longest reaction time the ratio of **2** to **4** reached 5:1 and the quantity of the aldehyde was significantly reduced. Formation of other compounds besides **2** and **4** was not detected, which gave rise to the conclusion that compound **4** was converted into **2**. Recently, a similar reactivity of the monoamide of homophthalic acid toward aldehydes to furnish *cis*-2,3-disubstituted 1-oxotetrahydroisoquinoline-4-carboxylic acids has been observed.[23] However, in the latter case the reaction took place in the presence of Al salts and yielded the cis-product.[23] In order to shed more light whether the amide **4** is an intermediate in the reaction, an equimolar mixture of the amide **4** and benzaldehyde was refluxed in *p*-xylene (Scheme 2).

^{1}H NMR analysis of the reaction mixture after 6 h at reflux showed a complex mixture and the presence of the acid *trans*-**2** in very low quantity. In order to increase the yield of *trans*-**2**, we prolonged the reflux to 40 h and isolated **2** in 11% yield. This experiment shows that the acid **2** can be formed by reaction of **4** and benzaldehyde in boiling *p*-xylene. The catalytic effect of other reaction components present in the reaction mixture of **1** and **3** is probably essential and it could explain the low yield of **2** from the reaction of **4** and benzaldehyde. Thus, the acyclic monoamide **4** seems to be an intermediate in the formation of *trans*-**2** in the reaction of **1** and **3**. The question whether the reaction pathway via **4** is the only one or more reaction pathways are possible, remains open and requires further investigations.



Scheme 2. Reaction between **4** and benzaldehyde.

The preparation of carboxamides **5** from *trans*-**2** is shown in Scheme 3. The acid **2** was refluxed with thionyl chloride and the corresponding acid chloride without further purification was treated with an excess of the corresponding amine. The compounds **5a**–**n** thus obtained were purified by recrystallization or column chromatography. Compound **5o** was synthesized by BOC cleavage of **5n** and purified by column chromatography and subsequent recrystallization. The methyl ester **6** was obtained by esterification of the acid **2** with CH_3OH–H_2SO_4. The reduction of the ester **6** with

Table 1. The yield of *trans*-**2** in the cases of different solvents, after 6 h at reflux

Solvent	bp, °C	Yield, %
THF	65	4.4
Benzene	80	9.2
Toluene	110	53.2
p-xylene	138	78.0

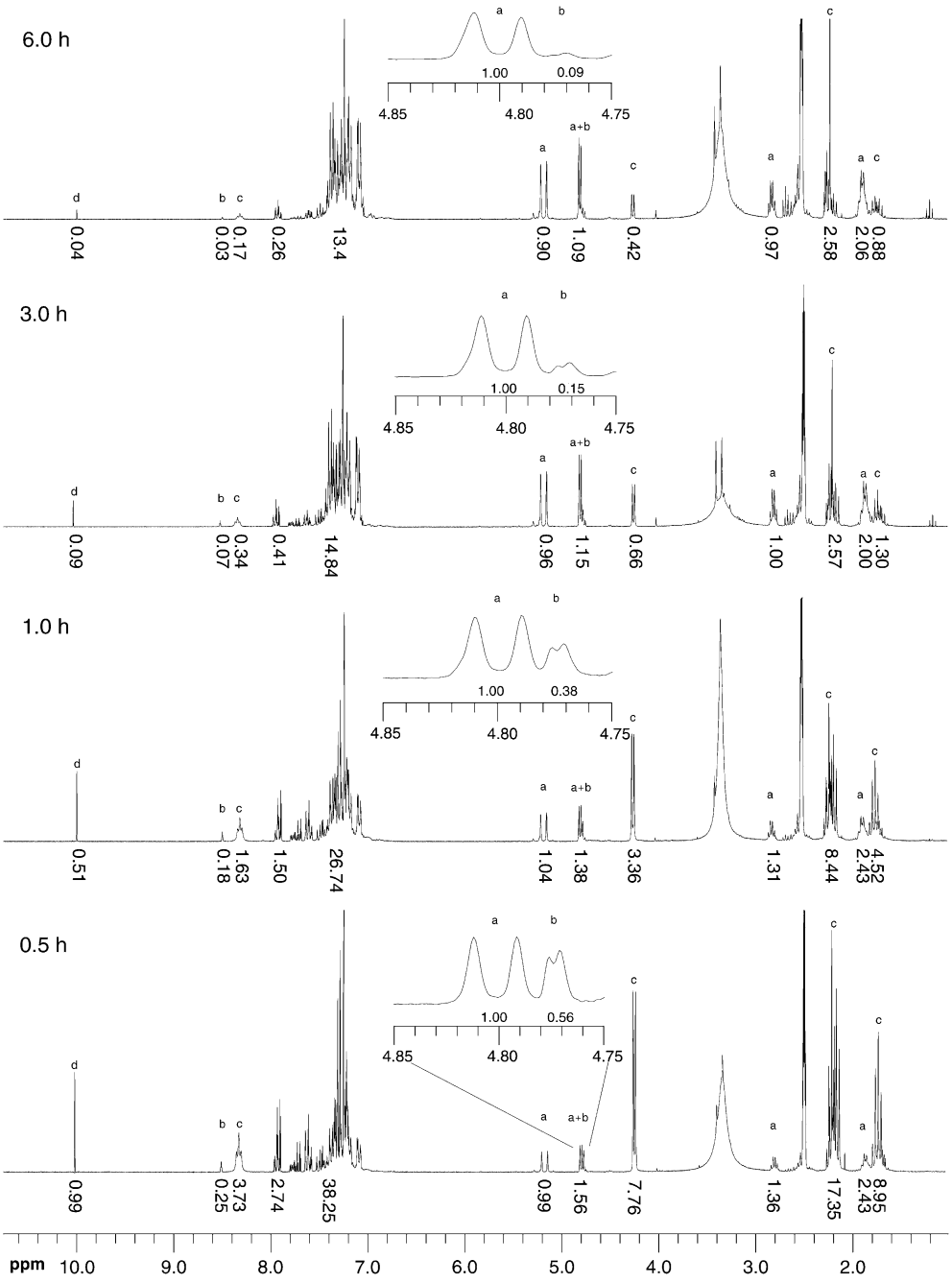
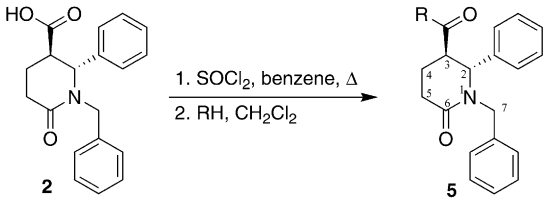


Figure 1. ^{1}H NMR spectra of the reaction mixture, where a—*trans*-**2**, b—imine **3**, c—monoamide **4**, d—benzaldehyde.

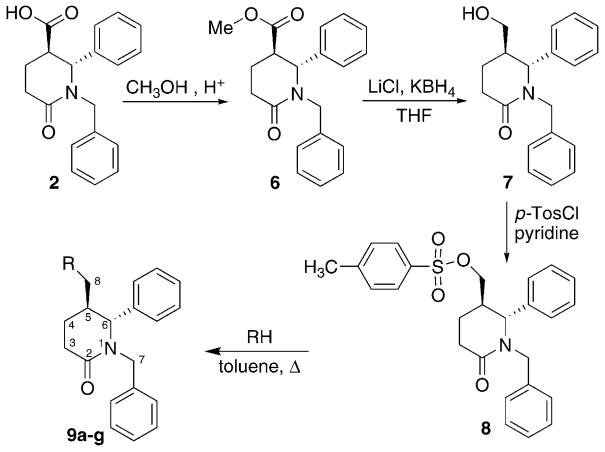
$LiBH_4$ proceeded selectively at the ester group to give *trans*-5-(hydroxymethyl)-6-phenylpiperidin-2-one (**7**). The latter was converted with *p*-toluenesulfonyl chloride (*p*-TosCl) into the tosylate **8**. The reaction of **8** with an excess of the selected secondary heterocyclic amines was carried out in refluxing toluene. The resulting aminomethyl derivatives **9a–g** were purified by means of recrystallization or column chromatography (Scheme 4). The compounds **5** and **9** 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 previously described structurally similar diastereomeric 1,2-disubstituted 6-oxopiperidine-3-carboxylic acids and their methyl esters[16,24] as well as with the spectral data of the acid **2**.

It is known that the reaction of the anhydride **1** with different *N*-arylidenealkylamines in refluxing xylene affords a mixture of *trans*- and *cis*-1,2-disubstituted 6-oxopiperidine-3-carboxylic acids, with the strong predominance for the *trans*-isomers.[16,24] It has been shown that the *trans*-isomers are thermodynamically more stable and their predominant formation is evidently favored by the reaction conditions (long reflux at ca. 140 °C).[24] The previously reported X-ray analysis of the inclusion complex of the acid *trans*-**2** with acetonitrile, shows that the piperidinone ring is in a highly distorted chair conformation due to the presence of the planar amide fragment and protons H_A and H_B occupy an axial–pseudoaxial position.[15] However, on the basis of ^{1}H NMR spectroscopy it is accepted that the conformation in



Compound	R	Yield, %	Compound	R	Yield, %
5a	H_2N	78	5h	H_3C-N-N	52
5b	N	64	5i	HO-N-N	75
5c	N	58	5j	N-N	84
5d	O-N	73	5k	F-N-N	55
5e	N	44	5l	Cl-N-N	41
5f	N	44	5m	F_3C-N-N	40
5g	HN	61	5n	$(H_3C)_3CO$-N-N	58

Scheme 3. Synthesis of compounds **5a–n**.



Compound	R	Yield, %	Compound	R	Yield, %
9a	N	57	9e	F-N-N	69
9b	O-N	92	9f	Cl-N-N	66
9c	$(H_3C)_3CO$-N-N	90	9g	F_3C-N-N	79
9d	N-N	35			

Scheme 4. Synthesis of compounds **9a–g**.

solution with a pseudoaxial phenyl, respective pseudoequatorial H_A is more favorable because of the smaller $A^{1,2}$ strain between the phenyl group and the *N*-substituent[16] (Fig. 2). In our experiments the acid **2** was isolated always as a single diastereomer. The formation of the *cis*-isomer was not detected, even when the reaction of **1** and **3** was followed by means of ^{1}H NMR spectroscopy. The signal of H_A in the ^{1}H NMR spectrum of **2** appears as a doublet with vicinal

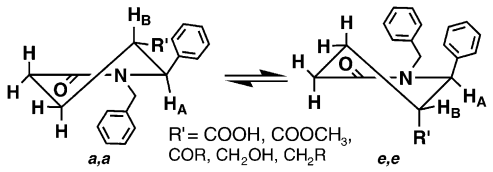


Figure 2.

coupling constant ^3J 5.0 Hz. It is known that six-membered rings in chair conformation are characterized with ^3J of the vicinal axial protons in 8–13 Hz range and ^3J of the vicinal equatorial protons in 1–4 Hz range in their ^{1}H NMR spectra.[25] In analogy to the literature data, we assume that in solution *trans*-**2** spends more time in a conformation with pseudoequatorial H_A and equatorial H_B[16,25] (Fig. 2). In the ^{1}H NMR spectrum of the methyl ester **6**, H_A exhibits a doublet with $^3J_{A,B}$ 3.9 Hz. This value of $^3J_{A,B}$ is in agreement with trans configuration and preferred pseudoequatorial–equatorial solution conformation of H_A and H_B of the ester **6**. Such conformation of the ester **6** is also preferred in solid state, which is evidenced by X-ray analysis.[15] The subsequent reactions of **2** and the intermediate ester **6** do not affect the two stereogenic centers. The trans relative configurations of the alcohol **7**, the tosylate **8** as well as the target amides **5**, and aminomethyl derivatives **9** follow directly from the configuration of the starting compounds, *trans*-**2** and the ester **6**. In the case of the amides **5**, ^3J is in the range of 6.8–9.3 Hz, which can be explained by the conformational equilibrium shifted to a greater extent to the conformer with diaxial protons. This can be due to the planarity of the carboxamido group, which leads to a smaller steric hindrance with the neighboring phenyl moiety. In the ^{1}H NMR spectra of the aminomethyl derivatives **9** the signal of H_A appears as a singlet, which is again in agreement with the trans configuration of compounds **9** and equatorial–pseudoequatorial orientation of H_A and H_B, influenced by the bigger effective volume of the aminomethyl substituent (Fig. 2). It should be noted that the ring numbering of compounds **7–9** is different from that of compounds **2**, **5**, **6** and the H_A and H_B protons have a different number, which is reflected in Section 3.

The pharmacological screening of compounds **5** and **9** is in course.

3. Experimental

3.1. General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Specord 75 instrument. ^{1}H NMR spectra (250.13 MHz) and ^{13}C NMR spectra (62.90 MHz) were obtained on a Bruker Avance DRX-250 spectrometer. The chemical shifts are given in parts per million (δ) relative to tetramethylsilane as internal standard. Assignments were made using a combination of 1D and 2D spectra (DEPT, COSY). The microanalyses were done at the Faculty of Chemistry, University of Sofia. Thin layer chromatography (TLC) was performed on Merck 1.05554 silica gel 60F254 aluminum plates. Chromatographic filtration and column chromatography were carried out using Acros silica gel (0.060–0.200 mm).

Electrospray ionization (ESI) mass spectra were recorded by flow injection of acetonitrile solution into an ESI source attached to Varian Prostar 240 instrument.

3.2. Preparation of (±)-*trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylic acid (2)

To a solution of *N*-benzylidenebenzylamine (**3**, 1.71 g, 8.8 mmol) in dried *p*-xylene (18 mL), glutaric anhydride (**1**, 1.0 g, 8.8 mmol) was added. The reaction mixture was refluxed for 6 h. The crystals separated were filtered and recrystallized from ethyl acetate–methanol to yield the acid **2** as white needles (2.12 g, 78%). Mp 168–171 °C. According to lit.,[5] mp of **2** is 171–174 °C. IR (Nujol): 3200–2500 (OH), 1705 (COOH), 1590 (CON) cm^{-1}. ^1H NMR δ (DMSO-d_6): 1.78–1.96 (2H, m, H-4), 2.42–2.65 (2H, m, H-5), 2.76–2.88 (1H, m, H-3), 3.38 (1H, d, H-7, J=15.2 Hz), 4.81 (1H, d, H-2, J=5.0 Hz), 5.19 (1H, d, H-7, J=15.2 Hz), 7.06–7.43 (10H, m, arom. H), 12.40 (1H, br s, COOH). ^{13}C NMR δ (DMSO): 20.2 (1C, C-4), 29.8 (1C, C-5), 46.5 (1C, C-3), 47.5 (1C, C-7), 61.7 (1C, C-2), 127.0 (2C, Ph), 127.7 (2C, Ph), 127.9 (2C, Ph), 128.4 (2C, Ph), 128.9 (2C, Ph), 137.2 (1C, Ph), 140.5 (1C, Ph), 169.2 (1C, C-6), 173.5 (1C, COOH). Anal. Calcd for $C_{19}H_{19}NO_3$: C 73.77%, H 6.19%; found: C 73.79%, H 6.33%.

3.3. Preparation of 5-(benzylamino)-5-oxopentanoic acid (4)

To a solution of **1** (0.228 g, 2 mmol) in CH_2Cl_2 (4 mL), benzylamine (0.22 mL, 2 mmol) was added. The mixture was stirred at room temperature for 15 min and then the solvent was evaporated. The resulting oil was triturated with ethyl acetate, the crystals were collected and recrystallized from water, to give monoamide **4** as colorless platelets (0.333 g, 75%). Mp 105–106 °C. IR (Nujol): 3300 (NH), 3200–2500 (OH), 1690 (COOH), 1635 (CON), 1540 (CONH) cm^{-1}. ^1H NMR δ (DMSO): 1.64–1.81 (2H, m, H-3), 2.12–2.26 (4H, m, H-2, H-4), 4.25 (2H, d, H-7, J=5.8 Hz), 7.17–7.43 (5H, m, arom. H), 8.34 (1H, t, NH, J=5.8 Hz). ^{13}C NMR δ ($CDCl_3$+DMSO): 20.8 (1C, CH_2), 33.2 (1C, CH_2COOH), 34.8 (1C, CH_2CON), 42.6 (1C, CH_2N), 126.8 (1C, Ph), 127.3 (2C, Ph), 128.2 (2C, Ph), 139.0 (1C, Ph), 172.4 (1C, CON), 174.7 (1C, COOH). Anal. Calcd for $C_{12}H_{15}NO_3$: C 65.14%, H 6.83%; found: C 64.86%, H 7.11%.

3.4. Reaction of 4 and benzaldehyde in boiling *p*-xylene

To a solution of **4** (0.222 g, 1 mmol) in *p*-xylene (2 mL), benzaldehyde (0.1 mL, 1 mmol) was added. After 40 h of reflux, the reaction mixture was cooled and diluted with ethyl acetate (20 mL). It was extracted with 5% aq $NaHCO_3$ (3×15 mL) and the combined water layers were acidified with 15% HCl to pH=2. The precipitated solid was filtered and dried, yielding 0.034 g (11%) of colorless crystalline *trans*-**2**, identical in all respects with *trans*-**2**, prepared as above.

3.5. Preparation of amides 5a–o

3.5.1. Preparation of (±)-*trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylic acid amides 5a–n. A mixture of **2** (0.309 g, 1 mmol) and $SOCl_2$ (0.15 mL, 2 mmol) in 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 at −5 °C and 3 mmol of the corresponding amine was added dropwise. In the case of the amide **5a**, dry ammonia was bubbled through the solution at −5 °C. The mixture was stirred at room temperature. After the 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 column chromatography and subsequent recrystallization from ethyl acetate–hexane. In this way the following compounds were prepared:

3.5.1.1. (±)-*trans*-1-Benzyl-6-oxo-2-phenylpiperidine-3-carboxamide (5a). White solid; yield: 78%, mp 101–103 °C. IR (Nujol): 3400 (NH), 1680, 1665 (CON) cm^{-1}. ^1H NMR δ (DMSO): 1.73–1.92 (2H, m, H-4), 2.41–2.58 (2H, m, H-5), 2.60–2.73 (1H, m, H-3), 3.33 (1H, d, H-7, J=15.3 Hz), 4.68 (1H, d, H-2, J=6.9 Hz), 5.18 (1H, d, H-7, J=15.3 Hz), 6.87 (1H, s, NH), 7.04–7.41 (11H, m, NH, arom. H). ^{13}C NMR δ (DMSO): 22.5 (1C, C-4), 30.8 (1C, C-5), 46.8 (1C, C-7), 47.8 (1C, C-3), 62.0 (1C, C-2), 126.9 (1C, Ph), 127.2 (2C, Ph), 127.5 (2C, Ph), 127.7 (1C, Ph), 128.4 (2C, Ph), 128.8 (2C, Ph), 137.3 (1C, Ph), 141.0 (1C, Ph), 169.5 (1C, C-6), 173.5 (1C, $CONH_2$). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C 74.00%, H 6.54%; found: C 73.65%, H 6.60%.

3.5.1.2. (±)-*trans*-1-Benzyl-2-phenyl-3-(pyrrolidine-1-carbonyl)-piperidin-6-one (5b). White needles; yield: 64%, mp 137–139 °C. IR ($CHCl_3$): 1620 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.43–1.96 (5H, m, H-4, $4CH_2$), 2.00–2.20 (1H, m, H-4), 2.39–2.69 (2H, m, 2H-5), 2.74–2.93 (2H, m, H-3, CH_2N), 3.07–3.39 (3H, m, CH_2N), 3.44 (1H, d, H-7, J=14.8 Hz), 4.67 (1H, d, H-2, J=8.6 Hz), 5.49 (1H, d, H-7, J=14.8 Hz), 7.02–7.38 (10H, m, arom. H). MS *m/z*: 363 (M^+, 100), 338 (8), 256 (20), 201 (10), 196 (95), 168 (24), 130 (45). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C 76.21%, H 7.23%; found: C 76.05%, H 7.12%.

3.5.1.3. (±)-*trans*-1-Benzyl-2-phenyl-3-(piperidine-1-carbonyl)-piperidin-6-one (5c). Colorless crystals; yield: 58%, mp 129–131 °C. IR ($CHCl_3$): 1625 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 0.61–0.79 (1H, m, CH_2), 1.11–1.33 (2H, m, CH_2), 1.34–1.49 (3H, m, CH_2), 1.81–1.93 (1H, m, H-4), 1.97–2.17 (1H, m, H-4), 2.51–2.68 (1H, m, H-5), 2.73–2.86 (1H, ddd, H-5, J=4.7, 4.7, 17.6 Hz), 2.93–3.12 (3H, m, H-3, $2CH_2N$), 3.13–3.27 (1H, m, CH_2N), 3.42 (1H, d, H-7, J=14.8 Hz), 3.48–3.63 (1H, m, CH_2N), 4.72 (1H, d, H-2, J=8.3 Hz), 5.45 (1H, d, H-7, J=14.8 Hz), 7.02–7.38 (10H, m, arom. H). Anal. Calcd for $C_{24}H_{28}N_2O_2$: C 76.56%, H 7.50%; found: C 76.80%, H 7.69%.

3.5.1.4. (±)-*trans*-1-Benzyl-3-(morpholine-4-carbonyl)-2-phenylpiperidin-6-one (5d). White powder; yield: 73%, mp 143–145 °C. IR ($CHCl_3$): 1630 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.83–1.96 (1H, m, H-4), 2.02–2.22 (1H, m, H-4), 2.53–2.95 (4H, m, 2H-5, $2CH_2N$), 2.94–3.21 (2H, m, H-3, CH_2N), 3.22–3.46 (4H, m, H-7, CH_2N, $2CH_2O$), 3.47–3.73 (2H, m, CH_2O), 4.65 (1H, d, H-2, J=8.5 Hz),

5.48 (1H, d, H-7, J=14.8 Hz), 6.96–7.41 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.2 (1C, C-4), 31.5 (1C, C-5), 42.1 (1C, CH_2N), 44.9 (1C, C-7), 45.9 (1C, CH_2N), 46.7 (1C, C-3), 63.2 (1C, C-2), 66.0 (1C, CH_2O), 66.5 (1C, CH_2O), 127.2 (3C, Ph), 128.2 (2C, Ph), 128.4 (3C, Ph), 129.0 (2C, Ph), 136.5 (1C, Ph), 139.6 (1C, Ph), 170.0 (1C, C-6), 170.3 (1C, CON). Anal. Calcd for $C_{23}H_{26}N_2O_3$: C 72.99%, H 6.92%; found: C 72.73%, H 6.92%.

3.5.1.5. (±)-*trans*-1-Benzyl-*N*,*N*-diisopropyl-6-oxo-2-phenylpiperidine-3-carboxamide (5e). Chromatographic purification (hexane–ethyl acetate=1:1) and recrystallization yielded **5e** as white powder (44%). Mp 75–77 °C. IR ($CHCl_3$): 1620 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 0.54 (3H, d, CH_3, J=6.5 Hz), 1.01 (3H, d, CH_3, J=6.6 Hz), 1.11 (3H, d, CH_3, J=6.8 Hz), 1.27 (3H, d, CH_3, J=6.8 Hz), 1.72–1.89 (1H, m, H-4), 1.99–2.19 (1H, m, H-4), 2.50–2.68 (1H, m, H-5), 2.72–2.84 (1H, m, H-5), 2.90–3.03 (1H, m, H-3), 3.14–3.37 (1H, br s, CHN), 3.45 (1H, d, H-7, J=14.8 Hz), 3.53–3.71 (1H, m, CHN), 4.81 (1H, d, H-2, J=9.3 Hz), 5.43 (1H, d, H-7, J=14.8 Hz), 7.00–7.37 (10H, m, arom. H). Anal. Calcd for $C_{25}H_{32}N_2O_2$: C 76.50%, H 8.22%; found: C 76.45%, H 8.41%.

3.5.1.6. (±)-*trans*-1-Benzyl-*N*,*N*-dicyclohexyl-6-oxo-2-phenylpiperidine-3-carboxamide (5f). Chromatographic purification (hexane–ethyl acetate=3:2) and recrystallization yielded **5f** as white powder (44%). Mp 161–163 °C. IR ($CHCl_3$): 1625 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 0.83–1.88 (20H, m, $10CH_2$), 2.00–2.21 (1H, m, H-4), 2.21–2.48 (1H, br s, CHN), 2.49–2.80 (2H, m, H-4, H-5), 2.71–2.85 (1H, m, H-5), 2.91–3.15 (2H, m, H-3, CHN), 3.44 (1H, d, H-7, J=14.8 Hz), 4.74 (1H, d, H-2, J=8.9 Hz), 5.43 (1H, d, H-7, J=14.8 Hz), 6.97–7.37 (10H, m, arom. H). MS m/z: 472 (M^+, 100), 281 (8). Anal. Calcd for $C_{31}H_{40}N_2O_2$: C 78.77%, H 8.53%; found: C 78.85%, H 8.68%.

3.5.1.7. (±)-*trans*-*N*-(2-(1*H*-indol-3-yl)ethyl)-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxamide (5g). White powder; yield: 61%, mp 178–180 °C. IR (Nujol): 3240 (NH), 1630, 1615 (CON) cm^{-1}. ^{1}H NMR δ (DMSO): 1.69–1.92 (2H, m, H-4), 2.38–2.72 (5H, m, H-3, 2H-5, $2CH_2$), 3.12–3.27 (2H, dt, CH_2N, J=7.1, 13.2 Hz), 3.33 (1H, d, H-7, J=15.3 Hz), 4.70 (1H, d, H-2, J=6.8 Hz), 5.22 (1H, d, H-7, J=15.3 Hz), 6.91–7.47 (15H, m, 1CH, 14 arom. H), 7.94 (1H, t, NHCO, J=5.6 Hz), 10.75 (1H, d, NH, J=1.0 Hz). ^{13}C NMR δ (DMSO): 22.3 (1C, C-4), 25.0 (1C, CH_2), 30.7 (1C, C-5), 39.4 (1C, CH_2N), 46.7 (1C, C-7), 48.0 (1C, C-3), 62.2 (1C, C-2), 111.4 (1C, indole), 111.6 (1C, indole), 118.2 (2C, indole), 120.9 (1C, indole), 122.6 (1C, indole), 126.9 (1C, Ph), 127.0 (2C, Ph), 127.1 (1C, indole), 127.5 (2C, Ph), 127.7 (1C, Ph), 128.3 (2C, Ph), 128.7 (2C, Ph), 136.2 (1C, indole), 137.2 (1C, Ph), 140.7 (1C, Ph), 169.5 (1C, C-6), 171.3 (1C, CON). Anal. Calcd for $C_{29}H_{29}N_3O_2$: C 77.14%, H 6.47%; found: C 77.49%, H 6.81%.

3.5.1.8. (±)-*trans*-1-Benzyl-3-(4-methylpiperazine-1-carbonyl)-2-phenylpiperidin-6-one (5h). Chromatographic purification (ethyl acetate–methanol=4:1 containing 1% aq ammonia) and recrystallization yielded **5h** as white solid (52%). Mp 100–103 °C. IR ($CHCl_3$): 1630 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.81–1.95 (1H, m, H-4), 2.00–2.19 (2H, m, H-4, CH_2N), 2.27 (3H, s, CH_3), 2.33–2.46 (1H, m, CH_2N), 2.51–2.68 (2H, m, H-5, CH_2N), 2.73–2.87 (1H, m, H-5), 2.95–3.22 (3H, m, H-3, CH_2N), 3.30–3.48 (3H, m, H-7, CH_2N), 3.71–3.92 (1H, m, CH_2N), 4.64 (1H, d, H-2, J=8.6 Hz), 5.45 (1H, d, H-7, J=14.8 Hz), 6.99–7.42 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.1 (1C, C-4), 31.5 (1C, C-5), 41.6 (1C, CH_2N), 45.0 (1C, C-7), 45.3 (1C, CH_2N), 45.6 (1C, CH_3), 46.8 (1C, C-3), 54.2 (1C, CH_2N), 54.4 (1C, CH_2N), 63.1 (1C, C-2), 127.2 (3C, Ph), 128.2 (3C, Ph), 128.3 (2C, Ph), 128.9 (2C, Ph), 136.6 (1C, Ph), 139.8 (1C, Ph), 170.1 (2C, C-6, CON). Anal. Calcd for $C_{24}H_{29}N_3O_2$: C 73.63%, H 7.47%; found: C 73.82%, H 7.32%.

3.5.1.9. (±)-*trans*-1-Benzyl-3-(4-(2-hydroxyethyl)piperazine-1-carbonyl)-2-phenylpiperidin-6-one (5i). White needles; yield: 75%, mp 136–138 °C. IR (Nujol): 3355 (OH), 1620 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.80–1.94 (1H, m, H-4), 1.99–2.29 (4H, m, H-4, $3CH_2N$), 2.31–2.45 (3H, m, CH_2N), 2.51–2.69 (1H, m, H-5), 2.73–2.87 (1H, m, H-5), 2.88–3.22 (3H, m, H-3, $2CH_2N$), 3.27–3.37 (1H, m, CH_2N), 3.41 (1H, d, H-7, J=14.8 Hz), 3.55 (2H, t, CH_2O, J=5.3 Hz), 3.58–3.64 (1H, m, CH_2N), 4.67 (1H, d, H-2, J=8.5 Hz), 5.47 (1H, d, H-7, J=14.8 Hz), 7.01–7.40 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.0 (1C, C-4), 31.4 (1C, C-5), 41.7 (1C, CH_2N), 44.9 (1C, C-7), 45.4 (1C, CH_2N), 46.8 (1C, C-3), 52.2 (1C, CH_2N), 52.5 (1C, CH_2N), 57.6 (1C, CH_2N), 59.0 (1C, CH_2O), 63.1 (1C, C-2), 127.2 (3C, Ph), 128.2 (3C, Ph), 128.4 (2C, Ph), 129.0 (2C, Ph), 136.5 (1C, Ph), 139.7 (1C, Ph), 170.1 (2C, C-6, CON). Anal. Calcd for $C_{25}H_{31}N_3O_3$: C 71.23%, H 7.41%; found: C 69.88%, H 7.77%.

3.5.1.10. (±)-*trans*-1-Benzyl-2-phenyl-3-(4-phenylpiperazine-1-carbonyl)piperidin-6-one (5j). White needles; yield: 84%, mp 181–183 °C. IR ($CHCl_3$): 1645 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.85–1.96 (1H, m, H-4), 2.04–2.26 (2H, m, H-4, CH_2N), 2.54–2.82 (3H, m, 2H-5, CH_2N), 2.82–2.94 (1H, m, CH_2N), 3.02–3.15 (3H, m, H-3, $2CH_2N$), 3.23–3.45 (1H, m, CH_2N), 3.38–3.52 (2H, m, H-7, CH_2N), 3.69–3.81 (1H, m, CH_2N), 4.68 (1H, d, H-2, J=8.6 Hz), 5.49 (1H, d, C-7, J=14.8 Hz), 6.74–6.81 (2H, m, arom. H), 6.85–6.92 (1H, m, arom. H), 7.03–7.08 (2H, m, arom. H), 7.13–7.39 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.3 (1C, C-4), 31.6 (1C, C-5), 41.7 (1C, CH_2N), 45.2 (1C, C-7), 45.4 (1C, CH_2N), 46.8 (1C, C-3), 49.0 (1C, CH_2N), 49.2 (1C, CH_2N), 63.2 (1C, C-2), 116.5 (2C, Ph), 120.5 (1C, Ph), 127.2 (3C, Ph), 128.2 (2C, Ph), 128.3 (1C, Ph), 128.4 (2C, Ph), 129.0 (1C, Ph), 129.1 (1C, Ph), 136.6 (1C, Ph), 139.8 (1C, Ph), 150.5 (1C, Ph), 170.0 (1C, C-6), 170.2 (1C, CON). MS m/z: 454 (M^+, 100), 347 (12), 294 (7), 292 (39), 251 (20), 197 (18), 196 (90), 189 (67), 163 (8), 130 (54). Anal. Calcd for $C_{29}H_{31}N_3O_2$: C 76.79%, H 6.89%; found: C 76.74%, H 7.16%.

3.5.1.11. (±)-*trans*-1-Benzyl-3-(4-(4-fluorophenyl)-piperazine-1-carbonyl)-2-phenylpiperidin-6-one (5k). White needles; yield: 55%, mp 153–155 °C. IR ($CHCl_3$): 1635 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.84–1.98 (1H, m, H-4), 2.02–2.22 (2H, m, H-4, CH_2N), 2.53–2.71 (2H, m, H-5, CH_2N), 2.73–2.89 (2H, m, H-5, CH_2N), 2.91–3.03 (1H, m, CH_2N), 3.03–3.17 (2H, m, H-3, CH_2N) 3.23–3.36 (1H, m, CH_2N) 3.37–3.51 (2H, m, H-7, CH_2N), 3.69–3.83

(1H, m, CH_2N), 4.68 (1H, d, H-2, J=8.5 Hz), 5.49 (1H, d, H-7, J=14.8 Hz), 6.67–6.80 (2H, m, arom. H), 6.88–7.00 (2H, m, arom. H), 7.01–7.11 (2H, m, arom. H), 7.13–7.40 (8H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.3 (1C, C-4), 31.5 (1C, C-5), 41.8 (1C, CH_2N), 45.1 (1C, C-7), 45.4 (1C, CH_2N), 46.8 (1C, C-3), 50.0 (1C, CH_2N), 50.3 (1C, CH_2N), 63.2 (1C, C-2), 115.6 (2C, d, Ph, J=22.2 Hz), 118.4 (2C, d, Ph, J=7.8 Hz), 127.3 (3C, Ph), 128.3 (3C, Ph), 128.4 (2C, Ph), 129.0 (2C, Ph), 136.6 (1C, Ph), 139.8 (1C, Ph), 147.2 (1C, d, Ph, J=2.3 Hz), 157.5 (1C, d, CF, J=240.2 Hz), 170.0 (1C, C-6), 170.2 (1C, CON). MS *m/z*: 472 (M^+, 100), 342 (1.75), 279 (3.75), 261 (3.50), 217 (4.25). Anal. Calcd for $C_{29}H_{30}FN_3O_2$: C 73.86%, H 6.41%; found: C 74.18%, H 6.56%.

3.5.1.12. (±)-*trans*-1-Benzyl-3-(4-(3-chlorophenyl)-piperazine-1-carbonyl)-2-phenylpiperidin-6-one (5l). Chromatographic purification (hexane–ethyl acetate=1:1) and recrystallization yielded **5l** as pale pink spheres (41%). Mp 152–154 °C. IR ($CHCl_3$): 1630 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.83–1.97 (1H, m, H-4), 2.03–2.23 (2H, m, H-4, CH_2N), 2.53–2.82 (3H, m, 2H-5, CH_2N), 2.83–2.95 (1H, m, CH_2N), 3.00–3.16 (3H, m, H-3, $2CH_2N$), 3.20–3.34 (1H, m, CH_2N), 3.35–3.48 (2H, m, H-7, CH_2N), 4.67 (1H, d, H-2, J=8.6 Hz), 5.49 (1H, d, H-7, J=14.8 Hz), 6.64 (1H, dd, arom. H, J=2.1, 8.3 Hz), 6.72 (1H, t, arom. H, J=2.1 Hz), 6.83 (1H, dd, arom. H, J=1.7, 7.8 Hz), 7.01–7.40 (11H, m, arom. H). Anal. Calcd for $C_{29}H_{30}ClN_3O_2$: C 71.37%, H 6.20%; found: C 71.71%, H 6.36%.

3.5.1.13. (±)-*trans*-1-Benzyl-2-phenyl-3-(4-(3-(trifluoromethyl)phenyl)piperazine-1-carbonyl)piperidin-6-one (5m). Chromatographic purification (hexane–ethyl acetate=2:3) and recrystallization yielded **5m** as colorless needles (40%). Mp 136–138 °C. IR ($CHCl_3$): 1645 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.85–1.97 (1H, m, H-4), 2.04–2.22 (2H, m, H-4, CH_2N), 2.54–2.83 (3H, m, 2H-5, CH_2N), 2.84–2.98 (1H, m, CH_2N), 3.04–3.18 (3H, m, H-3, $2CH_2N$), 3.24–3.35 (1H, m, CH_2N), 3.36–3.49 (2H, m, H-7, CH_2N), 3.73–3.85 (1H, m, CH_2N), 4.67 (1H, d, H-2, J=8.6 Hz), 5.50 (1H, d, H-7, J=14.8 Hz), 6.89–6.97 (2H, m, arom. H), 7.02–7.09 (2H, m, arom. H), 7.09–7.40 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.3 (1C, C-4), 31.6 (1C, C-5), 41.6 (1C, CH_2N), 45.2 (2C, C-7, CH_2N), 46.8 (1C, C-3), 48.5 (1C, CH_2N), 48.8 (1C, CH_2N), 63.2 (1C, C-2), 112.6 (1C, q, Ph, J=3.8 Hz), 116.7 (1C, q, Ph, J=3.8 Hz), 119.3 (1C, Ph), 124.1 (1C, q, CF_3, J=272.6 Hz), 127.3 (3C, Ph), 128.3 (2C, Ph), 128.4 (1C, Ph), 128.5 (2C, Ph), 129.1 (2C, Ph), 129.6 (1C, Ph), 131.4 (1C, q, CCF_3, J=31.8 Hz), 136.6 (1C, Ph), 139.8 (1C, Ph), 150.7 (1C, Ph), 170.0 (1C, C-6), 170.3 (1C, CON). MS *m/z*: 522 (M^+, 100), 292 (12), 202 (9), 196 (47), 130 (39), 120 (7). Anal. Calcd for $C_{30}H_{30}F_3N_3O_2$: C 69.08%, H 5.80%; found: C 68.79%, H 5.67%.

3.5.1.14. *tert*-Butyl-4-((±)-*trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carbonyl)piperazine-1-carboxylate (5n). White crystals; yield: 58%, mp 134–136 °C. IR ($CHCl_3$): 1680 ($COOC(CH_3)_3$), 1635 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.42 (9H, s, $3CH_3$), 1.81–2.20 (3H, m, 2H-4, CH_2N), 2.27–2.45 (1H, m, CH_2N), 2.53–2.71 (1H, m, H-5), 2.74–2.98 (2H, m, H-5, CH_2N), 2.98–3.13 (2H, m, H-3, CH_2N), 3.14–3.30 (2H, m, CH_2N), 3.31–3.45 (2H, m, H-7, CH_2N), 3.53–3.66 (1H, m, CH_2N), 4.66 (1H, d, H-2, J=8.5 Hz), 5.47 (1H, d, H-7, J=14.8 Hz), 7.01–7.40 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 23.3 (1C, C-4), 28.3 (3C, $3CH_3$), 31.6 (1C, C-5), 41.7 (2C, CH_2N), 45.3 (3C, C-7, $2CH_2N$), 46.8 (1C, C-3), 63.2 (1C, C-2), 80.3 (1C, $OC(CH_3)_3$), 127.2 (2C, Ph), 127.3 (1C, Ph), 128.3 (2C, Ph), 128.4 (3C, Ph), 129.0 (2C, Ph), 136.6 (1C, Ph), 139.7 (1C, Ph), 154.2 (1C, NCOO), 170.0 (1C, C-6), 170.4 (1C, CON). Anal. Calcd for $C_{28}H_{35}N_3O_4$: C 70.42%, H 7.39%; found: C 70.45%, H 7.32%.

3.5.2. (±)-*trans*-1-Benzyl-2-phenyl-3-(piperazine-1-carbonyl)piperidin-6-one (5o). A mixture of **5n** (0.220 g, 0.5 mmol) and F_3CCOOH (0.53 mL, 7 mmol) was sonicated for 15 min. The mixture was neutralized with 10% aq Na_2CO_3 and extracted with ethyl acetate (30 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The resulting oil was recrystallized from ethyl acetate to yield **5o** as white crystals (0.118 g, 68%). Mp 144–146 °C. IR ($CHCl_3$): 1635 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.58 (1H, s, NH), 1.80–2.19 (3H, m, 2H-4, CH_2N), 2.42–2.81 (5H, m, 2H-5, $3CH_2N$), 2.81–2.98 (1H, m, CH_2N), 2.99–3.17 (2H, m, H-3, CH_2N), 3.21–3.35 (1H, m, CH_2N), 3.41 (1H, d, H-7, J=14.8 Hz), 3.48–3.61 (1H, m, CH_2N), 4.68 (1H, d, H-2, J=8.5 Hz), 5.47 (1H, d, H-7, J=14.8 Hz), 7.01–7.41 (10H, m, arom. H). Anal. Calcd for $C_{23}H_{27}N_3O_2$: C 73.18%, H 7.21%; found: C 73.07%, H 6.83%.

3.6. Preparation of methyl (±)-*trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylate (6)

A mixture of **2** (5.89 g, 19 mmol), methanol (30 mL), and concd H_2SO_4 (2 mL) was refluxed for 2 h. The cooled reaction mixture was poured into water (100 mL). The suspension was neutralized with 10% aq 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. The crude product was recrystallized from ethyl acetate to give **6** as colorless platelets (4.53 g, 77%). Mp 125–127 °C. IR (Nujol): 1730 ($COOCH_3$), 1630 (CON) cm^{-1}. ^{1}H NMR δ ($CDCl_3$): 1.83–2.10 (2H, m, H-4), 2.52–2.66 (1H, m, H-5), 2.69–2.84 (2H, m, H-3, H-5), 3.34 (1H, d, H-7, J=14.7 Hz), 3.48 (3H, s, CH_3), 4.89 (1H, d, H-2, J=3.9 Hz), 5.60 (1H, d, H-7, J=14.7 Hz), 7.10–7.43 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 19.0 (1C, C-4), 29.3 (1C, C-5), 46.2 (1C, C-7), 47.7 (1C, C-3), 51.8 (1C, OCH_3), 60.6 (1C, C-2), 126.5 (2C, Ph), 127.2 (1C, Ph), 127.9 (1C, Ph), 128.2 (2C, Ph), 128.4 (2C, Ph), 128.9 (2C, Ph), 136.6 (1C, Ph), 139.6 (1C, Ph), 169.7 (1C, C-6), 171.9 (1C, COO). Anal. Calcd for $C_{20}H_{21}NO_3$: C 74.28%, H 6.55%; found: C 74.04%, H 6.82%.

3.7. Preparation of (±)-*trans*-1-benzyl-5-(hydroxymethyl)-6-phenylpiperidin-2-one (7)

To a stirred suspension of LiCl (1.78 g, 42 mmol) and KBH_4 (2.27 g, 42 mmol) in THF (10 mL) was added dropwise a solution of **6** (4.53 g, 14 mmol) in THF (20 mL) for 20 min. The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was poured in water (100 mL). The suspension

was extracted with ethyl acetate (3×30 mL) and the organic phase was dried (Na_2SO_4). After removal of the solvent, the residue was purified by recrystallization from ethyl acetate, to give **7** as white powder (3.71 g, 90%). Mp 134–136 °C. IR (Nujol): 3300 (OH), 1600 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.52–1.70 (1H, m, H-4), 1.82–2.08 (2H, m, H-4, H-5), 2.58 (2H, t, 2H-3, J=6.9 Hz), 3.31 (1H, d, H-7, J=14.6 Hz), 3.41–3.55 (2H, m, CH_2OH), 4.37 (1H, d, H-6, J=4.9 Hz), 5.59 (1H, d, H-7, J=14.6 Hz), 7.09–7.45 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 19.7 (1C, C-4), 29.7 (1C, C-3), 43.3 (1C, C-5), 47.5 (1C, C-7), 61.0 (1C, C-6), 62.6 (1C, CH_2O), 126.9 (2C, Ph), 127.3 (1C, Ph), 127.7 (1C, Ph), 128.2 (2C, Ph), 128.5 (2C, Ph), 128.7 (2C, Ph), 137.1 (1C, Ph), 140.6 (1C, Ph), 170.7 (1C, C-2). Anal. Calcd for $C_{19}H_{21}NO_2$: C 77.26%, H 7.17%; found: C 77.59%, H 7.00%.

3.8. Preparation of ((±)-*trans*-1-benzyl-2-oxo-6-phenylpiperidin-5-yl)methyl 4-methylbenzenesulfonate (8)

p-Toluenesulfonyl chloride (4.41 g, 23.1 mmol) was added in portions, with stirring, to a solution of **7** (3.41 g, 11.6 mmol) in pyridine (30 mL) maintained at −5 °C. The reaction mixture was allowed to warm to room temperature and the stirring continued for further 4 h. The mixture was poured into ice-water and the product was extracted with ethyl acetate (3×30 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting oil was recrystallized from ethyl acetate to yield **8** as colorless needles (4.1 g, 79%). Mp 98–100 °C. IR (Nujol): 1630 (CON), 1180 (OSO_2) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.58–1.74 (1H, m, H-4), 1.79–1.95 (1H, m, H-4), 2.08–2.22 (1H, m, H-5), 2.46 (3H, s, CH_3), 2.54 (2H, t, H-3, J=6.8 Hz), 3.28 (1H, d, H-7, J=14.7 Hz), 3.76–3.90 (2H, m, CH_2O), 4.18 (1H, d, H-6, J=6.1 Hz), 5.49 (1H, d, H-7, J=14.7 Hz), 6.93–7.08 (4H, m, arom. H), 7.22–7.35 (8H, m, arom. H), 7.59–7.65 (2H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 20.1 (1C, C-4), 21.6 (1C, CH_3), 29.8 (1C, C-3), 41.0 (1C, C-5), 47.3 (1C, C-7), 60.8 (1C, C-6), 69.5 (1C, CH_2O), 126.9 (2C, Ph), 127.4 (1C, Ph), 127.8 (2C, Ph), 128.1 (1C, Ph), 128.2 (2C, Ph), 128.5 (2C, Ph), 128.9 (2C, Ph), 129.8 (2C, Ph), 132.4 (1C, CS), 136.6 (1C, Ph), 139.4 (1C, Ph), 145.0 (1C, CCH_3), 169.8 (1C, C-2). Anal. Calcd for $C_{26}H_{27}NO_4S$: C 69.44%, H 6.05%; found: C 69.74%, H 6.22%.

3.9. Preparation of (±)-*trans*-5-aminomethylpiperidin-2-ones 9a–g

To a solution of **8** (0.90 g, 2 mmol) in toluene (5 mL) was added the corresponding amine (6 mmol). The reaction mixture was refluxed until the completion of the reaction determined by TLC. The mixture was allowed to cool down to room temperature 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, if not stated otherwise. In this way the following compounds were prepared:

3.9.1. (±)-*trans*-1-Benzyl-6-phenyl-5-((piperidin-1-yl)methyl)piperidin-2-one (9a). White powder; yield: 57%, mp 95–97 °C. IR ($CHCl_3$): 1635 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.24–1.55 (7H, m, H-4, $6CH_2$), 1.81–2.37 (8H, m, 2H-3, H-4, H-5, 2H-8, $2CH_2N$), 2.41–2.63 (2H, m, CH_2N), 3.28 (1H, d, H-7, J=14.4 Hz), 4.64 (1H, s, H-6), 5.61 (1H, d, H-7, J=14.4 Hz), 7.10–7.43 (10H, m, arom. H). Anal. Calcd for $C_{24}H_{30}N_2O$: C 79.52%, H 8.34%; found: C 79.18%, H 8.20%.

3.9.2. (±)-*trans*-1-Benzyl-5-(morpholinomethyl)-6-phenylpiperidin-2-one (9b). White powder; yield: 92%, mp 115–117 °C. IR (Nujol): 1640 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.39–1.54 (1H, m, H-4), 1.86–2.03 (4H, m, H-4, H-5, $2CH_2N$), 2.08–2.26 (2H, m, H-8, CH_2N), 2.26–2.41 (2H, m, H-8, CH_2N), 2.41–2.65 (2H, m, 2H-3), 3.24 (1H, d, H-7, J=14.3 Hz), 3.43–3.60 (4H, m, CH_2O), 4.66 (1H, s, H-6), 5.67 (1H, d, H-7, J=14.3 Hz), 7.10–7.44 (10H, m, arom. H). Anal. Calcd for $C_{23}H_{28}N_2O_2$: C 75.79%, H 7.74%; found: 75.69%, H 7.59%.

3.9.3. *tert*-Butyl-4-(((±)-*trans*-1-benzyl-2-oxo-6-phenylpiperidin-5-yl)methyl)piperazine-1-carboxylate (9c). White powder; yield: 90%, mp 162–163 °C. IR (Nujol): 1680 ($COOC(CH_3)_3$), 1625 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.45 (10H, s, H-4, $9CH_3$), 1.83–2.02 (4H, m, H-4, H-5, $2CH_2N$), 2.05–2.15 (1H, m, H-8), 2.18–2.33 (3H, m, H-8, $2CH_2N$), 2.38–2.63 (2H, m, 2H-3), 3.13–3.31 (5H, m, H-7, $4CH_2N$), 4.65 (1H, s, H-6), 5.67 (1H, d, H-7, J=14.3 Hz), 7.11–7.45 (10H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 19.4 (1C, C-4), 28.3 (4C, C-3, $3CH_3$), 37.6 (1C, C-5), 47.8 (1C, C-7), 52.9 (3C, CH_2N), 58.8 (2C, CH_2N), 61.0 (1C, C-6), 79.4 (1C, $OC(CH_3)_3$), 126.5 (2C, Ph), 127.3 (1C, Ph), 127.4 (1C, Ph), 128.3 (2C, Ph), 128.7 (2C, Ph) 128.8 (2C, Ph), 137.5 (1C, Ph), 141.5 (1C, Ph), 154.6 (1C, NCOO), 170.0 (1C, C-2). Anal. Calcd for $C_{28}H_{37}N_3O_3$: C 72.54%, H 8.04%; found: C 72.32%, H 7.95%.

3.9.4. (±)-*trans*-1-Benzyl-6-phenyl-5-((4-phenylpiperazin-1-yl)methyl)piperidin-2-one (9d). Chromatographic purification (hexane–ethyl acetate=3:2) and recrystallization yielded **9d** as white powder (35%). Mp 117–119 °C. IR (Nujol): 1635 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.40–1.55 (1H, m, H-4), 1.86–2.06 (2H, m, H-4, H-5), 2.08–2.22 (3H, m, H-8, $2CH_2N$), 2.30 (1H, dd, H-8, J=9.8, 12.4 Hz), 2.40–2.65 (4H, m, 2H-3, $2CH_2N$), 2.93–3.09 (4H, m, CH_2N), 3.25 (1H, d, H-7, J=14.3 Hz), 4.68 (1H, s, H-6), 5.66 (1H, d, H-7, J=14.3 Hz), 6.80–6.93 (3H, m, arom. H), 7.12–7.44 (12H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 19.5 (1C, C-4), 28.4 (1C, C-3), 37.7 (1C, C-5), 48.0 (1C, C-7), 49.1 (2C, CH_2N), 53.2 (2C, CH_2N), 58.8 (1C, CH_2N), 61.2 (1C, C-6), 115.9 (2C, Ph), 119.6 (1C, Ph), 126.6 (2C, Ph), 127.3 (1C, Ph), 127.4 (1C, Ph), 128.4 (2C, Ph), 128.7 (2C, Ph) 128.9 (2C, Ph), 129.0 (2C, Ph), 137.6 (1C, Ph), 141.7 (1C, Ph), 151.2 (1C, Ph), 170.1 (1C, C-2). Anal. Calcd for $C_{29}H_{33}N_3O$: C 79.23%, H 7.57%; found: C 79.49%, H 7.83%.

3.9.5. (±)-*trans*-1-Benzyl-5-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-6-phenylpiperidin-2-one (9e). Colorless crystals; yield: 69%, mp 149–151 °C. IR ($CHCl_3$): 1615 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.40–1.55 (1H, m, H-4), 1.86–2.06 (2H, m, H-4, H-5), 2.08–2.23 (3H, m, H-8, $2CH_2N$), 2.31 (1H, dd, H-8, J=9.8, 12.4 Hz), 2.39–2.65 (4H, m, 2H-3, $2CH_2N$), 2.85–3.01 (4H, m, CH_2N), 3.25 (1H, d, H-7, J=14.3 Hz), 4.68 (1H, s, H-6), 5.66 (1H, d,

H-7, J=14.3 Hz), 6.78–7.01 (4H, m, arom. H), 7.12–7.44 (10H, m, arom. H). Anal. Calcd for $C_{29}H_{32}FN_3O$: C 76.12%, H 7.05%; found: C 76.44%, H 7.14%.

3.9.6. (±)-*trans*-1-Benzyl-5-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-6-phenylpiperidin-2-one (9f). Chromatographic purification (hexane–ethyl acetate=3:2) and recrystallization yielded **9f** as white crystals (66%). Mp 155–157 °C. IR ($CHCl_3$): 1615 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.39–1.54 (1H, m, H-4), 1.86–2.05 (2H, m, H-4, H-5), 2.06–2.21 (3H, m, H-8, $2CH_2N$), 2.30 (1H, dd, H-8, J=9.8, 12.4 Hz), 2.39–2.66 (4H, m, 2H-3, $2CH_2N$), 2.91–3.09 (4H, m, CH_2N), 3.25 (1H, d, H-7, J=14.3 Hz), 4.67 (1H, s, H-6), 5.67 (1H, d, H-7, J=14.3 Hz), 6.70–6.84 (3H, m, arom. H), 7.11–7.44 (11H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 19.5 (1C, C-4), 28.4 (1C, C-3), 37.6 (1C, C-5), 47.9 (1C, C-7), 48.6 (2C, CH_2N), 52.9 (2C, CH_2N), 58.7 (1C, CH_2N), 61.2 (1C, C-6), 113.7 (1C, Ph), 115.5 (1C, Ph), 119.1 (1C, Ph), 126.6 (2C, Ph), 127.3 (1C, Ph), 127.4 (1C, Ph), 128.4 (2C, Ph) 128.8 (2C, Ph), 128.9 (2C, Ph), 129.9 (1C, Ph), 134.8 (1C, CCl), 137.6 (1C, Ph), 141.6 (1C, Ph), 152.2 (1C, Ph), 170.1 (1C, C-2). Anal. Calcd for $C_{29}H_{32}ClN_3O$: C 73.48%, H 6.80%; found: C 73.21%, H 6.71%.

3.9.7. (±)-*trans*-1-Benzyl-6-phenyl-5-((4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)piperidin-2-one (9g). White powder; yield: 79%, mp 151–153 °C (methanol). IR ($CHCl_3$): 1615 (CON) cm^{-1}. ^1H NMR δ ($CDCl_3$): 1.40–1.55 (1H, m, H-4), 1.87–2.06 (2H, m, H-4, H-5), 2.07–2.23 (3H, m, H-8, $2CH_2N$), 2.32 (1H, dd, H-8, J=9.9, 12.3 Hz), 2.40–2.66 (4H, m, 2H-3, $2CH_2N$), 2.96–3.14 (4H, m, CH_2N), 3.25 (1H, d, H-7, J=14.3 Hz), 4.68 (1H, s, H-6), 5.67 (1H, d, H-7, J=14.3 Hz), 6.98–7.44 (14H, m, arom. H). ^{13}C NMR δ ($CDCl_3$): 19.5 (1C, C-4), 28.4 (1C, C-3), 37.7 (1C, C-5), 48.0 (1C, C-7), 48.7 (2C, CH_2N), 53.0 (2C, CH_2N), 58.7 (1C, CH_2N), 61.2 (1C, C-6), 112.0 (1C, q, Ph, J=3.8 Hz), 115.7 (1C, q, Ph, J=3.8 Hz), 118.6 (1C, Ph), 124.3 (1C, q, CF_3, J=272.3 Hz), 126.6 (2C, Ph), 127.4 (1C, Ph), 127.5 (1C, Ph), 128.4 (2C, Ph) 128.8 (2C, Ph), 128.9 (2C, Ph), 129.5 (1C, Ph), 131.3 (1C, q, CCF_3, J=31.7 Hz), 137.6 (1C, Ph), 141.6 (1C, Ph), 151.3 (1C, Ph), 170.1 (1C, C-2). Anal. Calcd for $C_{30}H_{32}F_3N_3O$: C 70.99%, H 6.35%; found: C 71.21%, H 6.63%.

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