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Microwave assisted synthesis of 3-benzazepin-2-ones as building blocks for 2,3-disubstituted tetrahydro-3-benzazepines

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ABSTRACT

Microwave assisted condensation of primary amines with keto acids **1a**–**c** provided directly 3,4-disubstituted 1,3-dihydro-3-benzazepin-2-ones **2**. Whereas small amine size, such as NH_3 afforded high yields of secondary lactams **2a**, **2d**, and **2g**, primary amines with larger substituents in α-position led to lower yields of **2** or even to regioisomeric indanone derivatives **4**. However, subsequent alkylation of **2a**, **2d**, and **2g** with various alkyl halides provided the corresponding *N*-substituted 3-benzazepin-2-ones **2** in good yields. Hydrogenation of **2** followed by BH_3 reduction led to 3-benzazepines **9**. 3-Benzyl-2-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**9c**) reveals high σ_1 affinity and selectivity over σ_2 and NMDA receptors.

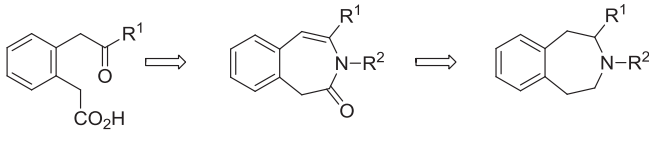
1. Introduction

Seven-membered *N*-heterocycles, in particular tetrahydro-3-benzazepines, have been extensively studied as dopamine receptor agonists and antagonists.[1–3] Furthermore, several 3-benzazepines have also been examined for pharmacological effects, which are not mediated by dopamine receptors.[4–7] Some 3-benzazepines have been shown to be active in animal models of various neurological disorders including Parkinson's disease[8] and Alzheimer's disease.[9]

Recently, it was reported that differently substituted tetrahydro-3-benzazepines interact with high affinity and selectivity with σ_1 receptors.[10–14] The σ_1 receptor represents the best characterized subtype of the σ receptor family. It is well established as non-opioid, non-phencyclidine but haloperidol sensitive receptor with a characteristic ligand binding profile and a characteristic distribution in the central nervous system (CNS) as well as in some peripheral tissues like kidney, liver, lung, and heart.[15,16] Ligands for σ_1 receptors have a potential for the treatment of epileptic disorders,[17] depression,[18] and drug abuse.[19] They also show neuroprotective,[20] antiamnesic,[21] and analgesic activity[21] and may also be used for tumor imaging purposes.[22]

The seven-membered lactam **2** represents a versatile building block for the synthesis of various 3-benzazepines **9**, since it allows the introduction of various substituents in almost all positions of the *N*-containing heterocyclic part (position 1–5) of the ring system (Fig. 1). Modifications of positions 2–4 are described in this manuscript, position 1 can be substituted by enolate chemistry as shown for similar systems[11–14] and position 5 can be modified by enamide chemistry.

In the literature only few methods for the synthesis of 3-benzazepin-2-ones of type **2** with an aldehydic/ketonic carbon at position 4 (*N*/*O*-acetal, enamine) are described. Intra- or intermolecular condensation of various 2-(2-oxoalkyl)phenylacetic acid derivatives with phenylglycinol led to 3-benzazepin-2-ones



1 2 9

Fig. 1. 3-Benzazepin-2-ones **2** as key building blocks for the synthesis of diversely substituted tetrahydro-3-benzazepines.

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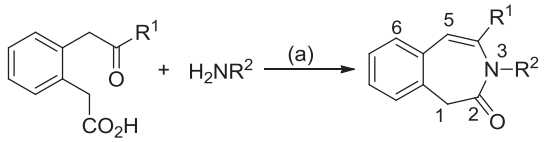
with an *N*/*O*-acetalic group in position 4.[11–14] 3-Benzazepinones of type **2** were regioselectively synthesized by intramolecular hydroamidation of *ortho*-alkynylphenylacetamides.[23] The synthesis of *N*-unsubstituted 3-benzazepinones of type **2** was reported by condensation of ε-oxo acids with ammonium acetate in glacial acetic acid.[24] Furthermore, a 3-benzazepinone of type **2** was formed as side product during the synthesis of fully conjugated seven and eight membered heterocyclic systems.[25]

Herein we wish to report the synthesis of both *N*-unsubstituted and *N*-substituted 3-benzazepin-2-ones **2** under microwave irradiation by direct combination of keto acids **1** and primary amines. According to our strategy keto acids **1** provide all carbon atoms of the final heterocyclic system and the remaining *N*-atom is coming from ammonia or a primary amine (Fig. 1). The resulting 3-benzazepin-2-ones **2** are further developed into potent σ_1 ligands **9**.

2. Synthesis

The synthesis of the 3-benzazepinones **2** started with keto acids **1**, which are available by reaction of *o*-phenylenediacetic acid with an excess of organolithium reagents[26] Reaction of methyl keto acid **1a** with benzylamine in refluxing toluene for 1 day led to the 3-benzazepinone **2c** in 20% yield together with some non-identified products (Scheme 1). Increasing the amount of benzylamine up to 10 equiv and the reaction time up to 3 days did not improve the yield of **2c**.



1a-c **2a-g**

1	R^1
a	Me
b	Bu
c	Ph

2	R^1	R^2	yield (%)
a	Me	H	50
b	Me	Me	30
c	Me	Bn	34
d	Bu	H	56
e	Bu	Me	32
f	Bu	Bn	26
g	Ph	H	60

Scheme 1. Reagents and reaction conditions: (a) microwave irradiation, toluene, 120 °C, 2–3 h, 150 W, 5 bar.

It has been shown that microwave irradiation often leads to reduced reaction times (increased reaction rate) and improved yields.[27] Thus, the mixture of keto acid **1a** and benzylamine in toluene was irradiated by microwaves, which increased the yield of the 3-benzazepinone **2c** to 34%. Replacement of the solvent toluene with DMF, THF or methanol did not lead to a further improvement of the yield. Therefore, the optimized reaction conditions (microwave irradiation, toluene) were applied on the transformation of the three keto acids **1a**–**c** with NH_4OAc, methylamine, and benzylamine, respectively, which led to the expected 3-benzazepinones **2a**–**g** in yields of 26–60 %.

The NMR data of **2a** (singlet at 6.15 ppm for 5-H; signals at 113.9 and 134.7 ppm for C-5 and C-4) show the presence of the C4–C5 double bond, which is further confirmed by recording an X-ray crystal structure. Recrystallization of **2a** with CH_2Cl_2/*n*-hexane mixture led to crystals suitable for X-ray crystal structure analysis. Moreover, the three-dimensional structure of the 3-benzazepinone system is shown by the crystal structure (Fig. 2). With exception of the sp^3-hybridized carbon atom in 1-position, all atoms of the ring

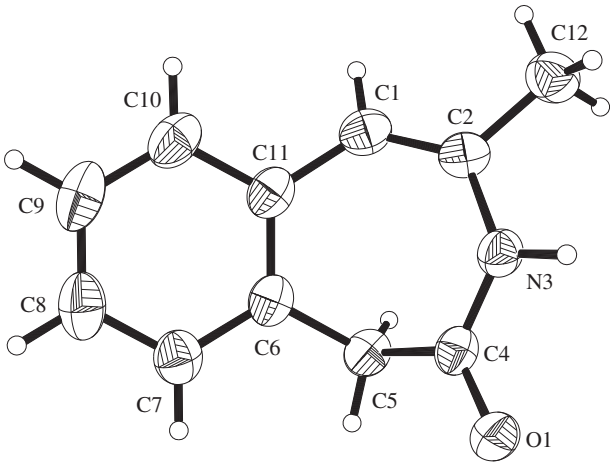


Fig. 2. X-ray crystal structure analysis of **2a**.

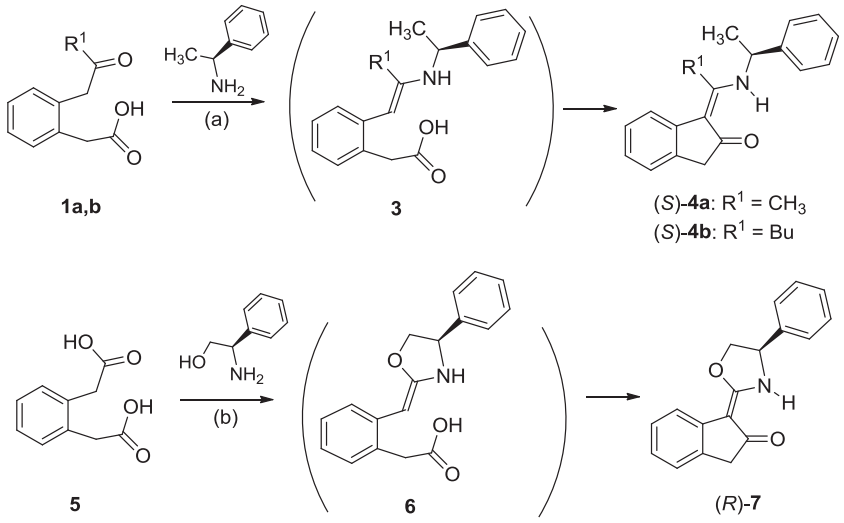
system are sp^2-hybridized indicating a rather planar system. Due to the tetrahedral structure of C-1, a deviation from coplanarity is only observed around this carbon atom. The carbonyl moiety and the adjacent *N*-atom are lying above the ring plane. This structure is very similar to the structure of a comparable 3-benzazepine reported recently by Liu and co-workers.[23b]

The table in Scheme 1 clearly indicates that the yields of the 3-benzazepinones **2** decreased with increasing size of the amine residue. The best yields (50–60 %) were obtained by reaction of keto acids **1** with the very small amine NH_3 (from NH_4OAc), the analogous condensations of **1** with methylamine and benzylamine afforded considerably lower yields of the corresponding *N*-methyl and *N*-benzyl derivatives. We assume that shielding of the *N*-atom in the intermediates analogously to **3** inhibits the formation of seven-membered lactams.

When using (*S*)-1-phenylethylamine bearing two substituents in α-position of the amino moiety for the condensation with keto acids **1a** and **1b**, the indanones (*S*)-**4a** and (*S*)-**4b** were isolated instead of the expected 3-benzazepin-2-ones **2** (Scheme 2). Careful analysis of the reaction mixtures did not provide any hints for the presence of 3-benzazepinones. We assume that the electron rich double bond of the enamine intermediate **3** reacted faster with the carboxy group than the shielded amino moiety. An analogous indanone derivative was also formed as side product during the reaction of the sterically most demanding phenyl derivative **1c** with phenylglycinol.[13]

A similar observation was made during the reaction of *o*-phenylenediacetic acid (**5**) with (*R*)-phenylglycinol, which provided exclusively the 1-substituted indanone derivative (*R*)-**7**. Again a fast reaction of the electron rich double bond of the intermediate ketene-*N*/*O*-acetal **6** with the carboxy group is the reason for the formation of the indanone (*R*)-**7**. Recrystallization of (*R*)-**7** from CH_2Cl_2/*n*-hexane led to crystals, which were suitable for an X-ray crystal structure analysis (Fig. 3). This X-ray crystal structure analysis proves the indanone structure of the product (*R*)-**7** and, moreover, the (*E*)-configuration of the exocyclic double bond leading to an *H*-bond between the carbonyl moiety and the NH-group. Due to similar chemical shifts in the ^1H and ^{13}C NMR spectra of (*S*)-**4a**,**b** and (*R*)-**7**, we assume similar structures for (*S*)-**4a** and (*S*)-**4b**, i.e. (*Z*)-configuration of the exocyclic double bond. The enantiomers (*R*)-**4a**,**b** and (*S*)-**7** were synthesized in the same way using (*R*)-1-phenylethylamine and (*S*)-phenylglycinol, respectively.

In order to improve the yields of *N*-substituted lactams, the secondary lactams **2a**, **2d**, and **2g** were alkylated with methyl iodide or benzyl bromide in the presence of concd KOH and tetrabutylammonium iodide (Bu_4NI) (Scheme 3).[28] The differently substituted dihydro-3-benzazepinones **2** were hydrogenated with



Scheme 2. Reagents and conditions: (a) microwave irradiation, toluene, 120 °C, 2–3 h, 150 W, 5 bar, (*S*)-**4a**: 36%, (*S*)-**4b**: 25%. (b) toluene, 110 °C, 3 days, 31%. The enantiomers (R)-**4a**, (R)-**4b** and (S)-7 were prepared in the same manner.

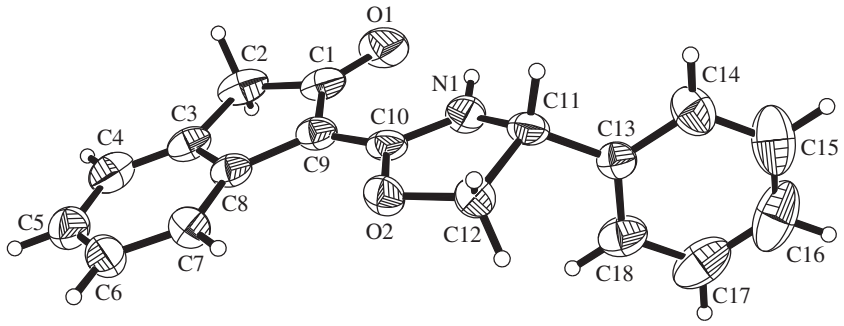
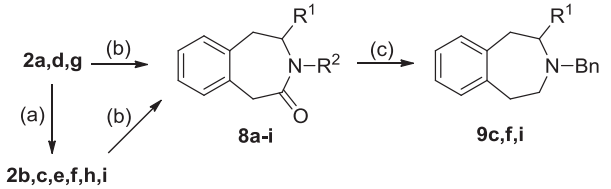


Fig. 3. X-ray crystal structure analysis of (*R*)-**7** showing (*E*)-configuration of the exocyclic double bond.

H_2 in the presence of Pd/C[29] to afford the racemic tetrahydro-3-benzazepinoes **8** in 58–97 % yield. For the synthesis of potent σ_1 receptor ligands, which require a basic amino moiety and two hydrophobic regions,[35,36] the lactam moiety of the *N*-benzyl substituted 3-benzazepinones **8c**, **8f**, and **8i** was reduced with BH_3·THF complex[30] to produce racemic 2,3-disubstituted tetrahydro-3-benzazepines **9c**, **9f**, and **9i**.



	R^1	R^2	**2** yield (%)	**8** yield (%)	**9** yield (%)
a	Me	H	-	70	-
b	Me	Me	46	70	-
c	Me	Bn	67	67	40
d	Bu	H	-	97	-
e	Bu	Me	75	69	-
f	Bu	Bn	73	83	63
g	Ph	H	-	58	-
h	Ph	Me	79	76	-
i	Ph	Bn	83	75	52

Scheme 3. Reagents and conditions:(a) R^2-X, KOH, Bu_4NI, THF, 2 h (b) H_2, 1 atm, Pd/C, THF, 24–48 h (c) BH_3·THF, THF, rt, 18 h.

3. Receptor binding studies

The affinities of the 2,3-disubstituted tetrahydro-3-benzazepines **9c**, **9f**, and **9i** toward σ_1 and σ_2 receptors were investigated in competitive receptor binding studies. In the σ_1 assay the radioligand [^{3}H]-(+)-pentazocine was used together with membrane preparations from guinea pig brains as receptor material. In the σ_2 assay rat liver preparations served as receptor material. The non-selective radioligand [^{3}H]-ditolylguanidine was combined with (+)-pentazocine to mask σ_1 receptors.[31–34]

The σ_1 receptor affinity of the racemic tetrahydro-3-benzazepines **9c**, **9f**, and **9i** decreases with increasing size of the C-2 residue R^1 (Table 1). Whereas the 3-benzazepine **9c** containing

Table 1
Affinity of 2,3-disubtituted tetrahydro-3-benzazepines **9c**, **9f**, and **9i** toward σ receptors

Compd	R^1	K_i±SEM (nM)	
		σ_1	σ_2
9c	Me	12±5.6	257
9f	Bu	437	0%[a]
9i	Ph	1940	41%[a]
(+)-Pentazocine		5.6±2.2	n.d.
Haloperidol		6.3±1.6	78±2.3
Ditolylguanidine		89±29	57±18

n.d.=not determined.
[a] Inhibition (%) of the radioligand binding at a concentration of 1 μM.

a small methyl substituent at position 2 shows high σ_1 affinity with a K_i value of 12 nM, the 3-benzazepines **9f** and **9i** with larger substituents at position 2 display moderate (K_i=437 nM) and low σ_1 affinity (K_i=1.9 μM), respectively.

According to the pharmacophore model of Glennon[35,36] a σ_1 ligand should consist of a basic amino moiety flanked by two hydrophobic regions. The amino moiety can be either a secondary or a tertiary amine. However, in case of a tertiary amine only small residues are allowed as third substituent. The substituent at position 2 of the 3-benzazepines **9** can be considered as the third substituent defined in the Glennon model. In **9c** this substituent is rather small (CH_3) and therefore the σ_1 affinity is high. As postulated in the Glennon model larger substituents (butyl (**9f**), phenyl (**9i**)) decrease or eliminate the interaction with σ_1 receptors.

A similar trend was observed for the σ_2 affinity of the 3-benzazepines. Whereas 3-benzazepine **9c** with the small 2-methyl substituent displays moderate σ_2 affinity (K_i=257 nM), the benzazepines **9f** and **9i** did not compete remarkably with the radioligand up to a concentration of 1 μM. Nevertheless 3-benzazepine **9c** can be considered as σ_1 selective ligand with a σ_1:σ_2 selectivity of 21.

Since some potent σ ligands also interact with the phencyclidine binding site of the NMDA receptor and vice versa[37,38] the affinities of the 3-benzazepines **9c**, **9f**, and **9i** toward the NMDA receptor were also determined.[11] In competition experiments with the radioligand (+)-MK-801 the investigated 3-benzazepines did not show any affinity to this receptor system.

4. Conclusion

The described microwave assisted reaction of keto acids **1** with various primary amines allows the direct synthesis of diversely substituted 3-benzazepin-2-ones **2**. Transformations of keto acids **1** with primary amines bearing larger α-substituents gave lower yields or even led to indanone derivatives **4**. Therefore, the subsequent alkylation of secondary lactams **2a**, **2d**, and **2g** with different alkyl halides represents an attractive alternative to obtain the corresponding *N*-substituted 3-benzazepinones **2**. The secondary lactams **2a**, **2d**, and **2g** were available in 50–60 % yields upon reaction of keto acids **1a**–**c** with NH_4OAc. Catalytic hydrogenation of **2** followed by BH_3 reduction produced pharmacologically attractive tetrahydro-3-benzazepines **9**. Preliminary receptor binding studies revealed promising σ_1 receptor affinity of **9c** (K_i=12 nM) stimulating the further exploitation of the 3-benzazepine compound class as CNS receptor ligands.

5. Experimental section

5.1. Chemistry, general

Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, length of column, fraction size, eluent, R_f value. Melting point: melting point apparatus SMP 3 (Stuart Scientific), uncorrected. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); δ in parts per million related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. Optical rotation: Polarimeter 341 (Perkin–Elmer); 1.0 dm tube; concentration *c* in g/100 mL; *T*=20 °C; wavelength 589 nm (D-line of Na light); the unit of the specific rotation ($[\alpha]_D^T$ grad mL dm^{-1} g^{-1}) is omitted for clarity. MS: EI=electron impact, ESI=electro spray ionization: MicroTof (Bruker Daltronics, Bremen), calibration with sodium formate clusters before measurement. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method A: column: LiChrospher® 60 RP-select B (5 μm), 250–4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ=210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A %): 0–4 min: 90%, 4–29 min: gradient from 90% to 0%, 29–31 min: 0%, 31–31.5 min: gradient from 0% to 90%, 31.5–40 min: 90%. Microwave apparatus: CEM Discover LabMate Synthesiser, single mode cavity; Discover-PC-software (CEM Corporation, NC); reactions were performed in glass vessels (capacity 10 mL) sealed with corresponding pressure adapter; pressure was controlled using a piezo-electric pressure sensor; temperature of the vessel contents was monitored by using an external infrared temperature control.

5.2. General procedures

*5.2.1. General procedure A for the synthesis of N-unsubstituted 3-benzazepin-2-ones **2**.* A mixture of keto acid **1** (1 equiv), NH_4OAc (2 equiv), and toluene was stirred under microwave irradiation (150 W, 120 °C, 5 bar pressure) for 2–3 h. The reaction mixture was concentrated in vacuum and the residue was purified by fc.

*5.2.2. General procedure B for the synthesis of N-substituted 3-benzazepin-2-ones **2**.* A mixture of keto acid **1** (1 equiv), methylamine or benzylamine (2 equiv), and toluene was stirred under microwave irradiation (150 W, 120 °C, 5 bar pressure) for 2–3 h. The reaction mixture was concentrated in vacuum and the residue was purified by fc.

*5.2.3. General procedure C for N-alkylation of **2a**, **2d**, and **2g**.* Tetrabutylammonium iodide (0.5 equiv), concd KOH in H_2O (1.2 equiv), and alkyl halide (1.5 equiv) were added to benzazepinone **2** dissolved in THF (6 mL) and the mixture was stirred at rt for 2 h. Completion of the conversion was controlled by TLC. The reaction mixture was washed with NaCl solution (10 mL) and water (10 mL), the aqueous layer was extracted with EtOAc (3×10 mL), the combined organic layers were dried (Na_2SO_4), filtered, the solvent was evaporated in vacuum, and the residue was purified by fc.

*5.2.4. General procedure D for the hydrogenation of **2**.* A mixture of **2** and Pd/C (100% by wt) in THF (5 mL) was stirred at rt under H_2 atmosphere (balloon) for 24–48 h. The reaction mixture was filtered through Celite® bed and the solvent was removed under reduced pressure to obtain a residue, which was purified by fc.

*5.2.5. General procedure E for reduction of lactams **8c**, **8f**, and **8i**.* Under N_2 BH_3·THF complex (2 equiv, 1 M in THF) was added to lactam **8** (1 equiv) dissolved in THF (5 mL) and the mixture was stirred at rt for 18 h. The reaction mixture was quenched with 1 M NaOH (5 mL). The aqueous layer was extracted with EtOAc (3×10 mL), the collected organic layers were dried (Na_2SO_4), concentrated under vacuum, and the residue was purified by fc.

5.3. Synthetic procedures

*5.3.1. 4-Methyl-1,3-dihydro-3-benzoazepin-2-one (**2a**).*[24b] Following the general procedure A, methyl keto acid **1a** (500 mg, 2.6 mmol) and NH_4OAc (401 mg, 5.2 mmol) were stirred in toluene (15 mL) under microwave irradiation for 2 h. The crude product was purified by fc (*d*=3 cm, *l*=20 cm, *V*=20 mL, cyclohexane/EtOAc 80:20, R_f=0.22 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 173 °C, yield 225 mg (50%). $C_{11}H_{11}NO$ (173.2 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2970 (aliphatic *C*–*H*), 1672 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=2.03 (d, *J*=0.9 Hz, 3H, CH_3), 3.42 (s, 2H, 1-CH_2), 6.15 (s, 1H, 5-H), 7.01–7.25 (m, 4H, arom), 7.70 (s, 1H, N–H). ^{13}C NMR ($CDCl_3$): δ (ppm)=22.9 (1C, CH_3), 43.1 (1C, C-1), 113.9 (1C, C-5), 127.0, 127.1, 127.9, 128.7 (4C, Ph–*C*H), 130.4, 133.4, 134.7 (3C, C-4/Ph–*C*),

170.0 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{11}H_{11}NONa$ 196.0733, found 196.0739. Purity (HPLC): 99.9% (t_R=15.80 min).

For X-ray crystal structure analysis **2a** was recrystallized from CH_2Cl_2/*n*-hexane mixture. Formula $C_{11}H_{11}NO$, *M*=173.21, colorless crystal 0.35×0.17×0.07 mm, *a*=4.2358(1), *b*=12.8115(3), *c*=16.5005(5) Å, *β*=91.699(1)°, *V*=895.04(4) Å^3, ρ_{calcd}=1.285 g cm^{-3}, *μ*=0.083 mm^{-1}, empirical absorption correction (0.960 T 0.994), *Z*=4, monoclinic, space group $P2_1/c$ (No. 14), *λ*=0.71073 Å, *T*=223 K, *ω* and *φ* scans, refined parameters, *R*=0.065, wR^2=0.199, GOF 1.051, max. residual electron density 0.37 (−0.25) e Å^{-3}. CCDC 832130.

*5.3.2. 3,4-Dimethyl-1,3-dihydro-3-benzoazepin-2-one (**2b**).*

(a) Following the general procedure B, methyl keto acid **1a** (100 mg, 0.52 mmol) was reacted with methylamine (2 M in THF, 0.52 mL, 1.04 mmol) in toluene (6 mL) under microwave irradiation for 2 h. Work-up and fc purification provided colorless oil, yield 29 mg (30%).

(b) Following the general procedure C, secondary lactam **2a** (50 mg, 0.29 mmol) was *N*-methylated with methyl iodide (27 μL, 0.44 mmol), concd KOH (20 mg, 0.35 mmol), and Bu_4NI (55 mg, 0.15 mmol). The crude product was purified by fc (*d*=2 cm, *l*=15 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.25 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 25 mg (46%). $C_{12}H_{13}NO$ (187.2 g/mol). FT-IR (ATR, film): *ν* (cm^{-1})=2962 (aliphatic *C*—*H*), 1655 (*C*=*O*). ^{1}H NMR ($CDCl_3$): *δ* (ppm)=2.14 (d, *J*=1.1 Hz, 3H, *CH*$_3$), 3.01 (s, 3H, *CH*$_3$), 3.45 (s, 2H, 1-CH$_2$), 6.35 (s, 1H, 5-H), 7.10—7.24 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): *δ* (ppm)=22.0 (1C, *C*H$_3$), 31.9 (1C, *C*H$_3$), 43.1 (1C, C-1), 118.1 (1C, C-5), 126.7, 126.8, 128.1, 128.2 (4C, Ph—*C*H), 132.9, 133.9, 137.9 (3C, Ph—*C*/C-4) 169.3 (1C, *C*=*O*). Exact mass (ESI): *m*/*z*=calcd for $C_{12}H_{13}NOH$ 188.1075, found 188.1118. Purity (HPLC): 95.6% (t_R=16.91 min).

*5.3.3. 3-Benzyl-4-methyl-1,3-dihydro-3-benzoazepin-2-one (**2c**).*

(a) Following the general procedure B, methyl keto acid **1a** (52 mg, 0.27 mmol) was reacted with benzylamine (59 μL, 0.54 mmol) in toluene (6 mL) under microwave irradiation for 3 h. Work-up and fc purification provided a colorless solid, yield 24 mg (34%).

(b) Following the general procedure C, secondary lactam **2a** (61 mg, 0.35 mmol) was *N*-benzylated with benzyl bromide (63 μL, 0.53 mmol), concd KOH (24 mg, 0.42 mmol), and Bu_4NI (65 mg, 0.18 mmol). The crude product was purified by fc (*d*=2 cm, *l*=15 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.42 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 119 °C, yield 62 mg (67%). $C_{18}H_{17}NO$ (263.3 g/mol). FT-IR (ATR, film): *ν* (cm^{-1})=3029 (aromatic *C*—*H*), 1656 (*C*=*O*). ^{1}H NMR ($CDCl_3$): *δ* (ppm)=2.01 (d, *J*=1.0 Hz, 3H, *CH*$_3$), 3.55 (br s, 2H, 1-CH$_2$), 4.63 (br s, 2H, NC*H*$_2$Ph), 6.34 (s, 1H, 5-H), 6.76—6.81 (m, 2H, arom), 7.05—7.30 (m, 7H, arom). ^{13}C NMR ($CDCl_3$): *δ* (ppm)=22.2 (1C, *C*H$_3$), 43.1 (1C, C-1), 46.9 (1C, NCH$_2$Ph), 120.0 (1C, C-5), 126.8, 126.9, 127.1, 127.2, 128.3, 128.6 (9C, Ph—*C*H), 132.9, 134.0, 137.0, 137.3 (4C, Ph—*C*/C-4), 169.1 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{18}H_{17}NONa$ 286.1202, found 286.1209. Purity (HPLC): 90.0% (t_R=20.25 min).

*5.3.4. 4-Butyl-1,3-dihydro-3-benzoazepin-2-one (**2d**).*[23a] Following the general procedure A, a mixture of butyl keto acid **1b** (113 mg, 0.48 mmol), NH_4OAc (74 mg, 0.96 mmol), and toluene (10 mL) was stirred under microwave irradiation for 2 h. The crude product was purified by fc (*d*=3 cm, *l*=15 cm, *V*=20 mL, cyclohexane/EtOAc 80:20, R_f=0.39 (cyclohexane/EtOAc 60:40)). Colorless solid, yield 58 mg (56%). $C_{14}H_{17}NO$ (215.3 g/mol). FT-IR (ATR, film): *ν* (cm^{-1})=2975 (aliphatic *C*—*H*), 1665 (*C*=*O*). ^{1}H NMR ($CDCl_3$): *δ* (ppm)=0.94 (t, *J*=7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.33—1.44 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.52—1.61 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.33 (t, *J*=7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 3.48 (s, 2H, 1-CH$_2$), 6.24 (s, 1H, 5-H), 7.13—7.34 (m, 4H, arom), 7.68 (s, 1H, N—*H*). ^{13}C NMR ($CDCl_3$): *δ* (ppm)=14.1 (1C, $CH_2CH_2CH_2CH_3$), 22.3 (1C, $CH_2CH_2CH_2CH_3$), 30.5 (1C, $CH_2CH_2CH_2CH_3$), 36.8 (1C, $CH_2CH_2CH_2CH_3$), 43.3 (1C, C-1), 113.9 (1C, C-5), 127.2, 127.4, 128.2, 128.9 (4C, Ph—CH), 130.8, 134.9, 137.7 (3C, C-4/Ph—*C*), 170.5 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{14}H_{17}NOH$ 216.1383, found 216.1392. Purity (HPLC): 90.9% (t_R=19.57 min).

*5.3.5. 4-Butyl-3-methyl-1,3-dihydro-3-benzazepin-2-one (**2e**).*[23a]

(a) Following the general procedure B, butyl keto acid **1b** (62 mg, 0.26 mmol) was reacted with methylamine (2 M in THF, 0.26 mL, 0.52 mmol) in toluene (6 mL) under microwave irradiation for 2 h. Work-up and fc purification provided colorless solid, yield 20 mg (32%).

(b) Following the general procedure C, **2d** (54 mg, 0.25 mmol) was methylated with methyl iodide (23 μL, 0.38 mmol), concd KOH (17 mg, 0.30 mmol), and Bu_4NI (46 mg, 0.13 mmol). The crude product was purified by fc (*d*=2 cm, *l*=15 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.48 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 58—59 °C (mp 57—58 °C[23a]), yield 40 mg (75%). $C_{15}H_{19}NO$ (229.3 g/mol). FT-IR (ATR, film): *ν* (cm^{-1})=2955 (aliphatic *C*—*H*), 1655 (*C*=*O*). ^{1}H NMR ($CDCl_3$): *δ* (ppm)=0.95 (t, *J*=7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.35—1.55 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.23—2.73 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.04 (s, 3H, C*H*$_3$), 3.44—3—65 (br s, 2H, 1-H), 6.46 (s, 1H, 5-H), 7.20—7.31 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): *δ* (ppm)=13.9 (1C, $CH_2CH_2CH_2CH_3$), 22.2 (1C, $CH_2CH_2CH_2CH_3$), 30.5 (1C, $CH_2CH_2CH_2CH_3$), 31.8 (1C, *C*H$_3$), 35.1 (1C, $CH_2CH_2CH_2CH_3$), 43.0 (1C, C-1), 118.1 (1C, C-5), 126.9, 127.0, 128.1, 128.3 (4C, Ph—CH), 133.2, 133.8, 142.5 (3C, C-4/Ph—*C*), 169.7 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{15}H_{19}NOH$ 230.1539, found 230.1562. Purity (HPLC): 93.2% (t_R=20.65 min).

*5.3.6. 3-Benzyl-4-butyl-1,3-dihydro-3-benzazepin-2-one (**2f**).*

(a) Following the general procedure B, butyl keto acid **1b** (50 mg, 0.21 mmol) was reacted with benzylamine (46 μL, 0.42 mmol) in toluene (6 mL) under microwave irradiation for 3 h. Work-up and fc purification provided colorless oil, yield 17 mg (26%).

(b) Following the general procedure C, **2d** (38 mg, 0.18 mmol) was reacted with benzyl bromide (32 μL, 0.27 mmol), concd KOH (12 mg, 0.22 mmol), and Bu_4NI (33 mg, 0.09 mmol). The crude product was purified by fc (*d*=2 cm, *l*=15 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.52 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 39 mg (73%). $C_{21}H_{23}NO$ (305.4 g/mol). FT-IR (ATR, film): *ν* (cm^{-1})=2956 (aliphatic *C*—*H*), 1659 (*C*=*O*). ^{1}H NMR ($CDCl_3$): *δ* (ppm)=0.91 (t, *J*=7.2 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.21—1.51 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.10—2.57 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.36—3.83 (m, br, 2H. 1-CH$_2$), 4.16—4.38 (m, br, 1H, NC*H*$_2$Ph), 5.30—5.52 (m, br, 1H, NC*H*$_2$Ph), 6.45 (s, 1H, 5-H), 6.79—6.85 (m, 2H, arom), 7.10—7.40 (m, 7H, arom). ^{13}C NMR ($CDCl_3$): *δ* (ppm)=13.8 (1C, $CH_2CH_2CH_2CH_3$), 22.3 (1C, $CH_2CH_2CH_2CH_3$), 30.5 (1C, $CH_2CH_2CH_2CH_3$), 34.8 (1C, $CH_2CH_2CH_2CH_3$), 43.0 (1C, C-1), 46.6 (1C, NCH$_2$Ph), 120.3 (1C, C-5), 126.8, 126.9, 127.0, 128.1, 128.2, 128.4, 128.9 (9C, Ph—CH), 133.2, 133.8, 137.3, 141.4 (4C, C-4/Ph—*C*), 169.8 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{21}H_{23}NONa$ 328.1672, found 328.1675. Purity (HPLC): 90.1% (t_R=22.71 min).

*5.3.7. 4-Phenyl-1,3-dihydro-3-benzazepin-2-one (**2g**).* Following the general procedure A, mixture of phenyl keto acid **1c** (270 mg,

1.06 mmol), NH_4OAc (164 mg, 2.12 mmol), and toluene (10 mL) was stirred under microwave irradiation for 3 h. The crude product was purified by fc (d=3 cm, l=20 cm, V=20 mL, cyclohexane/EtOAc 80:20, R_f=0.33 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 159 °C, yield 150 mg (60%). $C_{16}H_{13}NO$ (235.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2934 (aliphatic *C*–*H*), 1652 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=3.63 (s, 2H, 1-CH_2), 6.83 (s, 1H, 5-H), 7.28–7.49 (m, 7H, arom), 7.59–7.69 (m, 3H, arom/N–*H*). ^{13}C NMR ($CDCl_3$): δ (ppm)= 43.0 (1C, C-1), 115.2 (1C, C-5), 126.5, 127.2, 127.7, 128.7, 128.9, 129.0, 129.3 (9C, Ph–*C*H), 131.6, 134.5, 136.7, 137.5 (4C, C-4/Ph–*C*), 170.3 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{16}H_3NOH$ 236.1075, found 236.1111. Purity (HPLC): 92.8% (t_R=19.09 min).

*5.3.8. 3-Methyl-4-phenyl-1,3-dihydro-3-benzazepin-2-one (**2h**).* Following the general procedure C, **2g** (32 mg, 0.14 mmol) was methylated with methyl iodide (13 μL, 0.21 mmol), concd KOH (10 mg, 0.18 mmol), and Bu_4NI (26 mg, 0.07 mmol). The crude product was purified by fc (d=2 cm, l=10 cm, V=10 mL, cyclohexane/EtOAc 80:20, R_f=0.39 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 138 °C (mp 138–139 °C[23]), yield 27 mg (79%). $C_{17}H_{15}NO$ (249.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2968 (aliphatic *C*–*H*), 1654 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=2.80 (s, 3H, C*H*$_3$), 3.37–3.75 (m, 2H, 1-CH_2), 6.74 (s, 1H, 5-H), 7.16–7.45 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=35.1 (1C, *C*H$_3$), 43.0 (1C, C-1), 120.2 (1C, C-5), 127.0, 127.4, 127.5, 128.4, 128.7, 128.9 (9C, Ph–*C*H), 133.6, 133.7, 137.8, 143.3 (4C, C-4/Ph–*C*), 169.8 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{17}H_{15}NOH$ 250.1226 found 250.1296. Purity (HPLC): 96.6% (t_R=20.41 min).

*5.3.9. 3-Benzyl-4-phenyl-1,3-dihydro-3-benzoazepin-2-one (**2i**).* Following the general procedure C, **2g** (35 mg, 0.15 mmol) was reacted with benzyl bromide (27 μL 0.23 mmol), concd KOH (10 mg, 0.18 mmol), and Bu_4NI (29 mg, 0.08 mmol). The crude product was purified by fc (d=2 cm, l=10 cm, V=10 mL, cyclohexane/EtOAc 80:20, R_f=0.44 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 98 °C, yield 40 mg (83%). $C_{23}H_{19}NO$ (325.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=3026 (aliphatic *C*–*H*), 1659 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=3.45–3.94 (m, 3H, 1-CH_2/NC*H*$_2$Ph), 5.28–5.42 (m, 1H, NC*H*$_2$Ph), 6.44–6.49 (m, 2H, arom), 6.70 (s, 1H, 5-H), 6.86–7.00 (m, 3H, arom), 7.12–7.38 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=43.0 (1C, C-1), 48.6 (1C, NCH_2Ph), 122.7 (1C, C-5), 126.8, 127.1, 127.2, 127.3, 127.6, 127.9, 128.3, 128.6, 128.7, 128.9 (14C, Ph–*C*H), 133.5, 133.8, 136.9, 137.6, 142.2 (5C, C-4/Ph–*C*), 169.8 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{23}H_{19}NOH$ 326.1545 found 326.1575. Purity (HPLC): 90.8% (t_R=22.33 min).

*5.3.10. (Z)-1-{1-[(S)-(1-Phenylethyl)amino]ethylidene}indan-2-one [(S)-**4a**].* Following the general procedure B, methyl keto acid **1a** (39 mg, 0.20 mmol) was reacted with (*S*)-1-phenylethylamine (52 μL, 0.40 mmol) in toluene (6 mL) under microwave irradiation for 2 h. The crude product was purified by fc (d=3 cm, l=20 cm, V=20 mL, cyclohexane/EtOAc 85:15, R_f=0.47 (cyclohexane/EtOAc 60:40)). Pale yellow solid, mp 156–168 °C, yield 20 mg (36%). $C_{19}H_{19}NO$ (277.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2970 (aliphatic *C*–*H*), 1627 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=1.64 (d, J=6.8 Hz, 3H, C*H*$_3$), 2.23 (s, 3H, C*H*$_3$), 3.48 (s, 2H, 3-C*H*$_2$), 4.86 ('quint', J=6.8 Hz, 1H, NC*H*CH$_3$Ph), 6.94–7.40 (m, 9H, arom), 11.70 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm)=16.7 (1C, *C*H$_3$), 24.9 (1C, *C*H$_3$), 42.8 (1C, C-3), 53.4 (1C, NCHCH$_3$Ph), 107.5 (1C, C-1), 118.9, 122.9, 124.6, 125.7, 126.9, 127.6, 129.2 (9C, Ph–*C*H), 134.1, 142.9, 144.3 (3C, Ph–*C*), 160.1 (1C, C=*C*CH$_3$), 202.1 (1C, *C*=O). $[\alpha]_{589}^{23}$ +150.0 (*c* 0.13, CH_2Cl_2). Exact mass (ESI): *m*/*z*=calcd for $C_{19}H_{19}NONa$ 300.1359, found 300.1354. Purity (HPLC): 84.6% (t_R=21.81 min).

*5.3.11. (Z)-1-{1-[(R)-(1-Phenylethyl)amino]ethylidene}indan-2-one [(R)-**4a**].* Following the general procedure B, methyl keto acid **1a** (33 mg, 0.17 mmol) was reacted with (*R*)-1-phenylethylamine (43 μL, 0.34 mmol) in toluene (6 mL) under microwave irradiation for 2 h. Pale yellow solid, mp 156–158 °C, yield 20 mg (41%). $[\alpha]_{589}^{23}$ −153.0 (*c* 0.12, CH_2Cl_2). Exact mass (ESI): *m*/*z*=calcd for $C_{19}H_{19}NONa$ 300.1359, found 300.1355. Purity (HPLC): 96.5% (t_R=21.49 min).

*5.3.12. (Z)-1-{1-[(S)-(1-Phenylethyl)amino]pentylidene}indan-2-one [(S)-**4b**].* Following the general procedure A, butyl keto acid **1b** (49 mg, 0.21 mmol), (*S*)-1-phenylethylamine (52 μL, 0.42 mmol), and toluene (6 mL) was stirred under microwave irradiation (150 MW, 120 °C) for 2 h. The crude product was purified by flash chromatography (d=3 cm, l=20 cm, V=20 mL, cyclohexane/EtOAc 85:15, R_f=0.57 (cyclohexane/EtOAc 60:40)). Pale yellow solid, mp 76–78 °C, yield 16 mg (25%). $C_{22}H_{25}NO$ (319.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2960 (aliphatic *C*–*H*), 1624 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=0.84 (t, J=7.1 Hz, 3H, C*H*$_3$), 1.22–1.50 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.56 (d, J=6.8 Hz, 3H, C*H*$_3$), 2.35–2.58 (m, 2H, *CH*$_2$$CH_2CH_2CH_3$), 3.39 (s, 2H, 1-$CH_2$), 4.77 ('quint', J=7.1 Hz, NC*H*CH$_3$Ph), 6.87–7.30 (m, 9H, arom), 11.77 (br s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm)=13.7 (1C, *C*H$_3$), 22.9 (1C, *C*H$_3$), 24.9 (1C, $CH_2CH_2CH_2CH_3$), 28.5 (1C, $CH_2CH_2CH_2CH_3$), 28.7 (1C, *C*H$_2$$CH_2CH_2CH_3$), 42.6 (1C, C-3), 52.8 (1C, NCHCH$_3$Ph), 106.4 (1C, C-1), 118.2, 122.6, 124.3, 125.6, 126.9, 127.4, 128.9 (9C, Ph–*C*H), 133.9, 142.2, 144.5 (3C, Ph–*C*), 164.0 (1C, C=*C*$CH_2CH_2CH_2CH_3$), 202.6 (1C, *C*=O). $[\alpha]_{589}^{23}$ +154.6 (*c* 0.15, CH_2Cl_2). Exact mass (ESI): *m*/*z*=calculated for $C_{19}H_{19}NONa$ 342.1828, found 342.1834. Purity (HPLC): 75.9% (t_R=24.12 min).

*5.3.13. (Z)-1-{1-[(R)-(1-Phenylethyl)amino]pentylidene}indan-2-one [(R)-**4b**].* Following the general procedure B, butyl keto acid **1b** (46 mg, 0.20 mmol), (*R*)-1-phenylethylamine (52 μL, 0.40 mmol), and toluene (6 mL) were stirred under microwave irradiation for 2 h. The crude product was purified by fc (d=3 cm, l=20 cm, V=20 mL, cyclohexane/EtOAc 85:15, R_f=0.57 (cyclohexane/EtOAc 60:40)). Pale yellow solid, mp 76–78 °C, yield 17 mg (27%). $[\alpha]_{589}^{23}$ −151.5 (*c* 0.17, CH_2Cl_2). Exact mass (ESI): *m*/*z*=calcd for $C_{19}H_{19}NONa$ 342.1828, found 342.1842. Purity (HPLC): 80.0% (t_R=24.08 min).

*5.3.14. (R,E)-1-(4-Phenyloxazolidin-2-ylidene)indan-2-one [(R)-**7**].* A solution of *o*-phenylenediacetic acid (**5**, 300 mg, 1.54 mmol) and (*R*)-phenylglycinol (211 mg, 1.54 mmol) in toluene (40 mL) was heated to reflux for 3 days. Then the mixture was cooled, concentrated in vacuum, and the residue was dissolved in EtOAc (50 mL). The solution was washed with 1 M NaOH (3×15 mL), the aqueous layer was extracted thrice with EtOAc and the combined EtOAc layers were washed with 1 M HCl (3×15 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by fc (d=2 cm, l=25 cm, V=25 mL, cyclohexane/EtOAc 80:20, R_f=0.33 (petroleum ether/EtOAc 1:1). The product was further purified by recrystallization (CH_2Cl_2/*n*-hexane). Colorless solid, mp 173–175 °C, yield 133 mg (31%). $C_{18}H_{15}NO_2$ (277.3 g/mol)). FT-IR (ATR, film): ν (cm^{-1})=3211 (w, N–H), 3065, 3033 (w, arom C–H), 1658 (s, C=O). ^1H NMR ($CDCl_3$): δ (ppm)=3.46 (s, 2H, 3-H), 4.45 (dd, J=8.7/6.7 Hz, 1H, 5-H oxaz.), 4.96 (t, J=8.7 Hz, 1H, 5-H oxaz.), 5.16 (dd, J=8.6/6.8 Hz, 1H, 4-H oxaz.), 7.02 (m, 1H, arom), 7.21 (t, J=7.6 Hz, 2H, arom), 7.31–7.44 (m, 6H, arom), 9.50 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ (ppm)=42.8 (1C, C-3), 58.3 (1C, C-5 oxaz.), 76.2 (1C, C-4 oxaz), 91.0 (1C, C-1), 118.6, 122.5, 124.5, 126.9, 127.3, 128.8, 129.5 (9C, Ph–*C*H), 133.2, 141.1, 141.9 (3C, Ph–*C*), 163.6 (1C, C-2 oxaz), 199.8 (1C, C=O). $[\alpha]_{589}^{20}$ −87.8 (*c* 1.84, CH_2Cl_2). MS (EI): *m*/*z* (%)=277 [M, 100], 157 [M–PhCHCH$_2$O, 68]. Purity (HPLC): 99.2%, t_R=21.74 min.

For X-ray crystal structure analysis (*R*)-**7** was recrystallized from CH_2Cl_2/*n*-hexane mixture. Formula $C_{18}H_{15}NO_2$, M=277.31, colorless crystal 0.18×0.15×0.06 mm, a=22.845(1), b=5.296(1), c=15.997(1) Å, β=133.63(1)°, V=1400.9(3) Å^3, ρ_{calcd}=1.315 g cm^{-3}, μ=0.086 mm^{-1}, empirical absorption correction (0.985 *T* 0.995),

Z=4, monoclinic, space group $C2$ (No. 5), λ=0.71073 Å, T=223 K, ω and φ scans, refined parameters, R=0.050, wR^2=0.110, GOF 1.054, Flack parameter 0.8(18), max. residual electron density 0.22 (−0.18) e Å^{-3}. CCDC 857523.

*5.3.15. (S,E)-1-(4-Phenyloxazolidin-2-ylidene)indan-2-one (S-**7**).* As described for the synthesis of (*R*)-**7**, *o*-phenylenediacetic acid (**5**, 300 mg, 1.54 mmol) and (*S*)-phenylglycinol (211 mg, 1.54 mmol) were heated to reflux. Colorless solid, yield 149 mg (35%). $[\alpha]_{589}^{20}$ +93.3 (*c* 0.86, CH_2Cl_2). Purity (HPLC): 98.5%, t_R=21.74 min.

*5.3.16. 4-Methyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8a**).* Following the general procedure D, **2a** (30 mg, 0.17 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.10 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 21 mg (70%). $C_{11}H_{13}NO$ (175.2 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2950 (aliphatic *C*–*H*), 1670 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.20 (d, *J*=6.3 Hz, 3H, C*H*$_3$), 2.90 (dd, *J*=15.8/10.3 Hz, 1H, 5-H), 3.03 (dd, *J*=15.8/3.3 Hz, 1H, 5-H), 3.58 (d, *J*=15.2 Hz, 1H, 1-H), 3.78–3.89 (m, 1H, 4-H), 3.93 (d, *J*=15.2 Hz, 1H, 1-H), 5.57 (br s, 1H, N-*H*), 7.02–7.20 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=21.9 (1C, *C*H$_3$), 39.3 (1C, C-5), 41.5 (1C, C-1), 47.7 (1C, C-4), 126.0, 126.3, 128.6, 128.9 (4C, Ph–*C*H), 131.5, 135.3 (2C, Ph–*C*), 170.7 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{11}H_{13}NOH$ 176.1070, found 176.1083. Purity (HPLC): 99.5% (t_R=14.60 min).

*5.3.17. 3,4-Dimethyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8b**).* Following the general procedure D, **2b** (40 mg, 0.21 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.12 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 28 mg (70%). $C_{12}H_{15}NO$ (189.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2960 (aliphatic *C*–*H*), 1654 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.18 (d, *J*=6.5 Hz, 3H, C*H*$_3$), 2.81 (s, 3H, C*H*$_3$), 2.90 (dd, *J*=15.5/9.7 Hz, 1H, 5-H), 3.11 (dd, *J*=15.5/3.9 Hz, 1H, 5-H), 3.65 (d, *J*=15.4 Hz, 1H, 1-H), 3.78–3.88 (m, 1H, 4-H), 3.94 (d, *J*=15.4 Hz, 1H, 1-H), 6.98–7.26 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=20.2 (1C, *C*H$_3$), 33.3 (1C, *C*H$_3$), 39.3 (1C, C-5), 43.3 (1C, C-1), 55.1 (1C, C-4), 126.9, 127.1, 129.2, (4C, Ph–*C*H), 134.3, 136.0 (2C, Ph–*C*), 170.2 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{12}H_{15}NOH$ 190.1226, found 190.1239. Purity (HPLC): 94.1% (t_R=16.06 min).

*5.3.18. 3-Benzyl-4-methyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8c**).* Following to the general procedure D, **2c** (36 mg, 0.14 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.34 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 90 °C, yield 24 mg (67%). $C_{18}H_{19}NO$ (265.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2928 (aliphatic *C*–*H*), 1635 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=1.23 (d, *J*=6.6 Hz, 3H, C*H*$_3$), 2.88 (dd, *J*=15.6/9.4 Hz, 1H, 5-H), 3.13 (dd, *J*=15.6/4.4 Hz, 1H, 5-H), 3.83 (d, *J*=15.2 Hz, 1H, 1-H), 3.88–3.96 (m, 1H, 4-H), 4.09 (d, *J*=15.2 Hz, 1H, 1-H), 4.20 (d, *J*=15.6 Hz, 1H, NC*H*$_2$Ph), 5.07 (d, *J*=15.5 Hz, 1H, NC*H*$_2$Ph), 6.97–7.28 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=20.4 (1C, *C*H$_3$), 39.9 (1C, C-5), 43.5 (1C, C-1), 48.1 (1C, C-4), 52.9 (1C, N*C*H$_2$Ph), 126.9, 127.0, 127.1, 127.2, 128.4, 129.2, 129.3 (9C, Ph–*C*H), 134.1, 136.0, 138.2 (3C, Ph–*C*), 170.8 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{18}H_{19}NONa$ 288.1359, found 288.1347. Purity (HPLC): 98.4% (t_R=19.27 min).

*5.3.19. 4-Butyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8d**).* Following to the general procedure D, **2d** (34 mg, 0.16 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.17 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 110 °C, yield 33 mg (97%). $C_{14}H_{19}NO$ (217.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2975 (aliphatic *C*–*H*), 1665 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=0.86 (t, *J*=7.0 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.22–1.52 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.90 (dd, *J*=15.8/10.5 Hz, 1H, 5-H), 3.02 (dd, *J*=15.8/3.3 Hz, 1H, 5-H), 3.56 (d, *J*=15.2 Hz, 1H, 1-H), 3.59–3.68 (m, 1H, 4-H), 3.92 (d, *J*=15.2 Hz, 1H, 1-H), 5.59 (br s, 1H, N*H*), 6.92–7.23 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=14.2 (1C, $CH_2CH_2CH_2CH_3$), 22.7 (1C, $CH_2CH_2CH_2CH_3$), 28.1 (1C, $CH_2CH_2CH_2CH_3$), 36.6 (1C, $CH_2CH_2CH_2CH_3$), 38.8 (1C, C-5), 42.8 (1C, C-1), 53.2 (1C, C-4), 127.2, 127.5, 129.9, 130.1 (4C, Ph–*C*H), 132.7, 136.7 (2C, Ph–*C*), 172.3 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{14}H_{19}NOH$ 218.1539, found 218.1570. Purity (HPLC): 90.3% (t_R=19.17 min).

*5.3.20. 4-Butyl-3-methyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8e**).* Following to the general procedure D, **2e** (40 mg, 0.17 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.21 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 28 mg (69%). $C_{15}H_{21}NO$ (231.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2960 (aliphatic *C*–*H*), 1648 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=0.86 (t, *J*=6.9 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.21–1.35 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.38–1.70 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.81 (s, 3H, C*H*$_3$), 2.96–3.02 (m, 2H, 5-H), 3.62–3.76 (m, 2H, 1-H/4-H), 3.94 (d, *J*=15.3 Hz, 1H, 1-H), 7.03–7.16 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=14.0 (1C, $CH_2CH_2CH_2CH_3$), 22.6 (1C, $CH_2CH_2CH_2CH_3$), 27.9 (1C, $CH_2CH_2CH_2CH_3$), 32.9 (1C, *C*H$_3$), 33.2 (1C, $CH_2CH_2CH_2CH_3$), 36.6 (1C, C-5), 43.2 (1C, C-1), 59.2 (1C, C-4), 126.9, 127.1, 129.3, 129.4 (4C, Ph–*C*H), 134.1, 136.0 (2C, Ph–*C*), 171.1 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{15}H_{21}NOH$ 232.1701, found 232.1710 Purity (HPLC): 94.8% (t_R=20.19 min).

*5.3.21. 3-Benzyl-4-butyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8f**).* Following to the general procedure D, **2f** (46 mg, 0.15 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.40 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 38 mg (83%). $C_{21}H_{25}NO$ (307.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2960 (aliphatic *C*–*H*), 1655 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=0.80 (t, *J*=6.9 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.10–1.31 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.41–1.71 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.84 (dd, *J*=15.6/9.3 Hz, 1H, 5-H), 2.97 (dd, *J*=15.6/5.1 Hz, 1H, 5-H), 3.52–3.62 (m, 1H, 4-H), 3.81 (d, *J*=15.1 Hz, 1H, 1-H), 3.89 (d, *J*=15.1 Hz, 1-H), 4.05 (d, *J*=15.4 Hz, 1H, NC*H*$_2$Ph), 5.02 (d, *J*=15.4 Hz, 1H, NC*H*$_2$Ph), 6.81–6.87 (m, 2H, arom), 6.95–7.19 (m, 7H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=14.0 (1C, $CH_2CH_2CH_2CH_3$), 22.6 (1C, $CH_2CH_2CH_2CH_3$), 28.2 (1C, $CH_2CH_2CH_2CH_3$), 33.7 (1C, $CH_2CH_2CH_2CH_3$), 37.3 (1C, C-5), 43.6 (1C, C-1), 48. 9 (1C, N*C*H$_2$Ph), 57.3 (1C, C-4), 126.9, 127.0, 127.2, 127.3, 128.4, 129.0, 129.3 (9C, Ph–*C*H), 134.3, 136.1, 138.0 (3C, Ph–*C*), 171.3 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{21}H_{25}NOH$ 308.2009, found 308.2012. Purity (HPLC): 98.3% (t_R=22.44 min).

*5.3.22. 4-Phenyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8g**).* Following the general procedure D, **2g** (26 mg, 0.11 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.12 (cyclohexane/EtOAc 60:40)). Colorless solid, mp 137 °C, yield 15 mg (58%). $C_{16}H_{15}NO$ (237.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2922 (aliphatic *C*–*H*), 1653 (*C*=*O*). ^{1}H NMR ($CDCl_3$): δ (ppm)=3.18 (dd, *J*=15.0/4.2 Hz, 1H, 5-H), 3.26 (dd, *J*=15.0/9.7 Hz, 1H, 5-H), 3.85 (d, *J*=15.6 Hz, 1H, 1-H), 3.92 (d, *J*=15.5 Hz, 1H, 1-H), 4.69 (dd, *J*=9.7/4.2 Hz, 1H, 4-H), 5.70 (br s, 1H, N*H*), 6.91–7.35 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=40.6 (1C, C-5), 42.5 (1C, C-1), 59.3 (1C, C-4), 126.1, 127.5, 127.6, 128.2, 128.9, 129.1, 129.2 (9C, Ph–*C*H), 133.4, 136.2, 142.2 (3C, Ph–*C*), 171.0 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{16}H_{15}NOH$ 238.1226, found 238.1238. Purity (HPLC): 98.6% (t_R=18.07 min).

*5.3.23. 3-Methyl-4-phenyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8h**).* Following the general procedure D, **2h** (25 mg, 0.10 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.23 (cyclohexane/

EtOAc 60:40)). Colorless oil, yield 19 mg (76%). $C_{17}H_{17}NO$ (251.3 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2953 (aliphatic *C*–*H*), 1648 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=2.62 (s, 3H, CH_3), 3.16 (dd, *J*=14.8/9.6 Hz, 1H, 5-H), 3.30 (dd, *J*=14.8/4.8 Hz, 1H, 5-H), 3.85 (d, *J*=15.4 Hz, 1H, 1-H), 4.02 (d, *J*=15.4 Hz, 1H, 1-H), 4.54 (dd, *J*=9.6/4.8 Hz, 1H, 4-H), 6.83–7.28 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=36.5 (1C, CH_3), 40.9 (1C, C-5), 43.3 (1C, C-1), 66.8 (1C, C-4), 126.1, 127.4, 127.5, 127.7, 128.3, 128.5, 128.8 (9C, Ph–*C*H), 135.4, 135.8, 141.5 (3C, Ph–*C*), 169.8 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{17}H_{17}NOH$ 252.1383, found 252.1390. Purity (HPLC): 98.4% (t_R=19.35 min).

*5.3.24. 3-Benzyl-4-phenyl-1,3,4,5-tetrahydro-3-benzazepin-2-one (**8i**).* Following the general procedure D, **2i** (40 mg, 0.12 mmol) was hydrogenated and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 80:20, R_f=0.42 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 30 mg (75%). $C_{23}H_{21}NO$ (327.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2930 (aliphatic *C*–*H*), 1654 (*C*=*O*). ^1H NMR ($CDCl_3$): δ (ppm)=3.10 (dd, *J*=14.8/8.9 Hz, 1H, 5-H), 3.23–3.37 (m, 2H, 5-H/NCH_2Ph), 3.93 (d, *J*=15.3 Hz, 1H, 1-H), 4.06 (d, *J*=15.3 Hz, 1H, 1-H), 4.52 (dd, *J*=8.9/5.0 Hz, 1H, 4-H) 5.36 (d, *J*=15.3 Hz, 1H, NCH_2Ph), 6.72–6.85 (m, 3H, arom), 6.92–7.25 (m, 11H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=40.4 (1C, C-5), 43.5 (1C, C-1), 49.6 (1C, NCH_2Ph), 62.9 (1C, C-4), 126.3, 127.0, 127.3, 127.4, 127.5, 127.7, 128.2, 128.5, 128.7, 128.8 (14C, Ph–*C*H), 135.1, 135.6, 137.3, 141.3 (4C, Ph–*C*), 170.1 (1C, *C*=O). Exact mass (ESI): *m*/*z*=calcd for $C_{23}H_{21}NOH$ 328.1696, found 328.1701. Purity (HPLC): 94.6% (t_R=21.67 min).

*5.3.25. 3-Benzyl-2-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**9c**).* Following the general procedure E, **8c** (35 mg, 0.13 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.26 mL, 0.26 mmol) and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 90:10, R_f=0.56 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 13 mg (40%). $C_{18}H_{21}N$ (251.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2975 (aliphatic *C*–*H*). ^1H NMR ($CDCl_3$): δ (ppm)=0.76 (d, *J*=6.7 Hz, 3H, CH_3), 2.50–2.62 (m, 2H, 1-H/5-H), 2.66–2.76 (m, 2H, 4-H/5-H), 3.10–3.17 (m, 2H, 2-H/4-H), 3.30 (d, *J*=14.2 Hz, 1H, 1-H), 3.73 (d, *J*=13.8 Hz, 1H, NCH_2Ph), 3.79 (d, *J*=13.8 Hz, 1H, NCH_2Ph), 6.89–7.37 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=12.7 (1C, CH_3), 35.8 (1C, C-5), 41.9 (1C, C-1), 47.5 (1C, C-4), 54.2 (1C, C-2), 59.1 (1C, NCH_2Ph), 126.1, 126.3, 127.0, 128.5, 128.8, 130.3 (9C, Ph–*C*H), 139.6, 140.3, 142.3 (3C, Ph–*C*). Exact mass (ESI): *m*/*z*=calcd for $C_{18}H_{21}NH$ 252.1747, found 252.1783. Purity (HPLC): 96.6% (t_R=15.41 min).

*5.3.26. 3-Benzyl-2-butyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**9f**).* Following the general procedure E, **8f** (40 mg, 0.13 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.26 mL, 0.26 mmol) and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 90:10, R_f=0.64 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 24 mg (63%). $C_{21}H_{27}N$ (293.5 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2960 (aliphatic *C*–*H*). ^1H NMR ($CDCl_3$): δ (ppm)=0.75 (t, *J*=7.1 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.02–1.38 (m, 6H, $CH_2CH_2CH_2CH_3$), 2.46 (dd, *J*=14.7/6.4 Hz, 1H, 1-H), 2.58 (dd, *J*=14.6/5.9 Hz, 1H, 1-H), 2.71 (dd, *J*=13.5/6.0 Hz, 1H, 5-H), 2.79–2.83 (m, 2H, 4-H/5-H), 3.08–3.19 (m, 1H, 2-H), 3.32 (d, *J*=15.0 Hz, 1H, 4-H), 3.81 (d, *J*=13.9 Hz, 1H, NCH_2Ph), 3.87 (d, *J*=13.8 Hz, 1H, NCH_2Ph), 6.91–7.37 (m, 9H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=14.4 (1C, $CH_2CH_2CH_2CH_3$), 22.9 (1C, $CH_2CH_2CH_2CH_3$), 28.9 (1C, $CH_2CH_2CH_2CH_3$), 29.8 (1C, $CH_2CH_2CH_2CH_3$), 34.0 (1C, C-5), 38.1 (1C, C-1), 47.3 (1C, C-4), 57.6 (1C, C-2), 59.0 (1C, NCH_2Ph), 126.1, 126.7, 127.1, 128.0, 128.4, 128.9, 129.0, 129.2, 130.3 (9C, Ph–*C*H), 132.9, 133.4, 142.4 (3C, Ph–*C*). Exact mass (ESI): *m*/*z*=calcd for $C_{21}H_{27}NH$ 294.2216, found 294.2209. Purity (HPLC): 96.4% (t_R=19.60 min).

*5.3.27. 3-Benzyl-2-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (**9i**).* Following the general procedure E, **8i** (30 mg, 0.09 mmol) was reduced with BH_3·THF complex (1 M in THF, 0.18 mL, 0.18 mmol) and the crude product was purified by fc (*d*=2 cm, *l*=10 cm, *V*=10 mL, cyclohexane/EtOAc 90:10, R_f=0.69 (cyclohexane/EtOAc 60:40)). Colorless oil, yield 15 mg (52%). $C_{23}H_{23}N$ (313.4 g/mol). FT-IR (ATR, film): ν (cm^{-1})=2968 (aliphatic *C*–*H*). ^1H NMR ($CDCl_3$): δ (ppm)=2.21–2.30 (m, 1H, 4-H), 2.74 (dd, *J*=15.0/7.3 Hz, 1H, 5-H), 2.84 (d, *J*=14.6 Hz, 1H, 1-H), 2.96 (d, *J*=13.8 Hz, 1H, NCH_2Ph), 3.04 (dd, *J*=15.0/10.2 Hz, 1H, 5-H), 3.15 (dd, *J*=12.8/7.5 Hz, 1H, 4-H), 3.32 (dd, *J*=14.6/9.6 Hz, 1H, 1-H), 3.46 (d, *J*=9.3 Hz, 1H, 2-H), 3.66 (d, *J*=13.8 Hz, 1H, NCH_2Ph), 6.92–7.45 (m, 14H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm)=35.2 (1C, C-5), 45.0 (1C, C-1), 52.7 (1C, C-4), 59.8 (1C, NCH_2Ph), 69.1 (1C, C-2), 126.3, 126.7, 126.9, 127.2, 127.5, 128.4, 128.5, 128.7, 128.9, 129.8 (14C, Ph–*C*H), 140.1, 140.3, 142.7, 146.4 (4C, Ph–*C*). Exact mass (ESI): *m*/*z*=calcd for $C_{23}H_{23}NH$ 314.1903, found 314.1919. Purity (HPLC): 95.3% (t_R=19.24 min).

5.4. Receptor binding studies

5.4.1. Determination of σ_1 receptor affinity. Guinea pig brains were used as receptor material. The radioligand was [^3H]-(+)-pentazocine. The assay was performed as described in Refs. 11,31.

5.4.2. Determination of σ_2 receptor affinity. Membrane preparations of rat liver served as receptor material in the σ_2 assay. The radioligand [^3H]-di-*o*-tolylguanidine was employed in the presence of a large excess of (+)pentazocine to occupy σ_1 receptors.[11,31]

5.4.3. Determination of the affinity to the phencyclidine binding site of the NMDA receptor. The preparation of the membranes from pig brain cortex and the performance of the assay with [^3H]-MK-801 were done according to the literature.[11]

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Supplementary data

In the Supplementary data ^1H and ^{13}C NMR spectra of described compounds, details of the X-ray crystal structure analyses and discussion of the (*Z*)-configuration of (*S*)-**4a** are given. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.052.

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