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Original article

EPC syntheses and structure–activity relationships of hypoglycaemic semicyclic amidines

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Abstract – A series of homochiral sterically hindered mono- and bicyclic amidines was prepared as hypoglycaemic agents by lethargic reaction of O-methylcaprolactim and 3-ethoxy-2-azabicyclo[2.2.2]oct-2-ene, respectively, with homochiral *cis*-2-substituted cyclopentane amines provided by asymmetrical reductive amination of racemic 2-substituted cyclopentanones. All compounds, except the cyclohexylmethyl-isoquinuclidone derivative which inhibited secretion at 100 μM, significantly stimulated insulin secretion 2–8-fold at 10 μM and 100 μM in INS-1 cells. The most potent activator was the 2-cyclopentyl-substituted caprolactam derivative **5e**. The stimulatory effects on secretion increased with rising steric hindrance of both the amidine α-carbon and the bicyclic amidine moiety itself. Enantiomeric discrimination was observed for the 2-[(*cis*-2-bulkysubstituted cyclopentyl)imino]hexahydroazepine halides **5e** and **5f** and for the 3-[(*cis*-2-substituted cyclopentyl)imino]-2-azabicyclo[2.2.2]octane halides **6a** and **6c**. The amidines depolarized INS-1 cells and generated action potentials, accompanied by a decrease of membrane conductance. Simultaneously $[Ca^{2+}]_i$ increased, probably due to Ca^{2+}-entry through voltage-dependent Ca^{2+}-channels. At high concentrations, where inhibition of secretion was observed, $[Ca^{2+}]_i$ still rose upon application of the amidines, indicating an additional inhibitory pathway downstream to the elevation of $[Ca^{2+}]_i$. Even at high concentrations (100 μM), the amidines had no toxic effects on insulin secreting INS-1 cells. © 2000 Éditions scientifiques et médicales Elsevier SAS

asymmetric reductive amination / mono- and bicyclic amidines / insulin secretion / INS-1 cells / structure–activity relationship

1. Introduction

Although achiral sulfonylureas, which improve insulin secretion from pancreatic β-cells, are widely used for the treatment of type 2 diabetes (NIDDM or non-insulin-dependent diabetes mellitus), enantiomerically pure oral antidiabetics of different mechanisms of action are gaining growing interest in the treatment of type II-hyperglycaemia. The sulfonylamidopyrimidine gliflumide [1, 2] was one of the first homochiral compounds interacting with the sulfonylurea receptor [3], the (S)-enantiomer being 20-fold more efficacious than the (R)-enantiomer [4]. The insulinotropic non-sulfonylurea (+)-repaglinide was recently launched and is twice as active as its (–)-enantiomer [5, 6].

The phenolethanolamine derivative (R, R)-CL 316,243 [7, 8], a highly selective β_3-receptor agonist, is a promising phase II candidate for the new target β_3-receptors [9] in treatment of diabetes mellitus type IIb. (R)-(+)-Etomoxir, withdrawn from development due to myocardial hypertrophy, lowers blood glucose via irreversible inhibition of carnitin-palmitoyl-transferase I (CPT I), while the (S)-(–)-enantiomer does not show any activity [10, 11]. N-Palmitoylcarnitine and its phosphate analogues are reversible inhibitors of CPT I [12]. The naturally occurring, highly potent (R)-enantiomers are by far superior to the corresponding (S)-enantiomers.

Semicyclic amidines are also known for their hypoglycaemic effects, with racemic 2-[(*cis*-2-cyclohexyl-cyclopentyl)imino]-hexahydroazepine hydrochloride as the most efficacious representative developed as a result of extensive structure–activity relationship studies [13]. Dose-dependent blood glucose lowering effects could be observed in rats after oral application according to a

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Dedicated to Prof. Dr. Woldemar Schneider on the occasion of his 80th birthday.

generally accepted method [14]. Increasing steric hindrance of the C-1 atom neighbouring the amidino function by spatially demanding 2-substituents correlated with an increasing hypoglycaemic effect. However, chiral differentiating efficacy of the enantiomerically pure compounds of this new class of hypoglycaemic agents has yet to be elucidated.

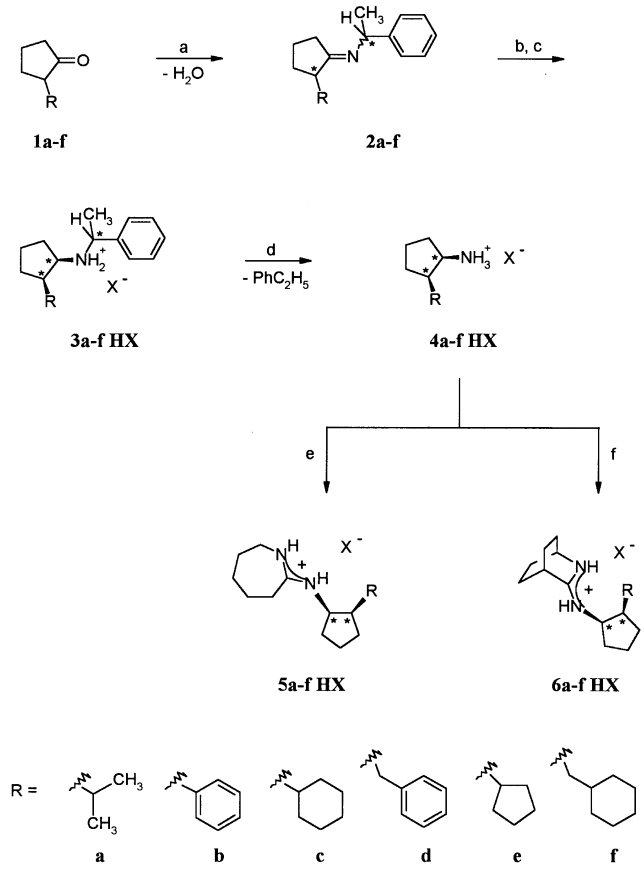
Therefore, we have developed the EPC (enantiomerically pure compounds) synthesis of homochiral semicyclic amidines derived from ε-caprolactam and have tested their chiral differentiating insulinotropic activity in vitro in INS-1 cells and by means of electrophysiological methods. Besides introduction of various spatially demanding substituents in position 2 of the aminocyclopentane moiety (isopropyl, phenyl, cyclohexyl, benzyl, cyclopentyl and cyclohexylmethyl) we were especially interested in the influence of increasing steric hindrance of the semicyclic amidine moiety. Thus, the hexahydroazepine system was also replaced by the bicyclic isoquinuclidine in a second series of semicyclic amidines.

In 1989 Palfreyman et al. [15] reported lactamimide analogues representing a new chemical class of calcium antagonists with diltiazem-like properties in in vitro test systems. However, the most potent member N-(2,2-diphenylpentyl)azacyclotridecan-2-imine hydrochloride contains a large 13-membered ring, whereas the racemic forms of the 7-membered hexahydroazepines **5b** and **5c** are only weak competitive antagonists of the calcium-induced contractions.

2. Chemistry

The homochiral semicyclic amidines **5a–f** HX and **6a–f** HX were prepared from the racemic 2-substituted cyclopentanones **1a–f** by means of asymmetric reductive amination [16] and subsequent lethargic reaction of the homochiral 2-substituted cyclopentaneamine halides **4a–f** HX with O-methylcaprolactim and 3-ethoxy-2-azabicyclo[2.2.2]oct-2-ene, respectively, in a four-step procedure (*figure 1*).

2-Isopropylcyclopentanone (**1a**) [17, 18], 2-phenylcyclopentanone (**1b**) [19–21], 2-benzylcyclopentanone (**1d**) [22, 23], and 2-cyclopentylcyclopentanone (**1e**) [24, 25] were synthesized according to common literature. 2-Cyclohexylcyclopentanone (**1c**) and 2-cyclohexylmethylcyclopentanone (**1f**) were accessible from **1b** and **1d**, respectively, by hydrogenation of the aromatic ring. Hydrogenation of unprotected **1b** with Rh/γ-Al_2O_3 in methanol/acetic acid [26] furnished a diastereomeric mixture of 2-cyclohexylcyclopentanols and **1c** in a 5:4 ratio, which was oxidized in situ to pure **1c** with pyridiniumchlorochromate on Al_2O_3 [27]. However, hydrogenation of **1d** yielded 97% **1f** with only negligible amounts of the respective cyclopentanols.



[a](a) (R)-(+)-PEA or (S)-(-)-PEA, p-toluenesulfonic acid, toluene; (b) H_2/RaneyNi; (c) HCl, HBr or TFA; (d) H_2/PdC 10 %; (e) O-methylcaprolactim; (f) 3-ethoxy-2-azabicyclo[2.2.2]oct-2-ene

Figure 1. Four-step procedure for the preparation of amidines **5a–f** HX and **6a–f** HX.

Condensation of the racemic 2-substituted cyclopentanones **1a–f** with optically active (R)-(+)- and (S)-(–)-1-phenylethylamine (PEA), respectively, led to the imines **2a–f**. The latter were hydrogenated in situ with Raney nickel at room temperature in a Parr shaker for a period of 5–11 days to give the optically active, diastereomerically pure secondary *cis*-2-substituted N-(1-phenylethyl)-cyclopentaneamines **3a–f** in yields up to 73%. Their halides **3a–f** HX were hydrogenolysed with palladium-on-charcoal (10%) at 50 °C in a Parr shaker within 24 h to give the enantiomerically high grade pure primary

Table I. Reaction times and yields of the lethargic reaction to the semicyclic amidines **5a–f** HX and **6a–f** HX.

Compound	Reaction time (days)	Yield (%)
5a HCl	30	90
5b HCl	16	86
5c HBr	42	79
5d HCl	17	79
5e HBr	35	85
5f HBr	21	92
6a HCl	84	56
6b HCl	63	91
6c HBr	105	73
6d HCl	63	86
6e HBr	154	76
6f HBr	42	90

cis-2-substituted cyclopentaneamine halides **4a–f** HX in yields of about 90%.

Lethargic reaction [13, 28] of **4a–f** HX with O-methylcaprolactim and 3-ethoxy-2-azabicyclo-[2.2.2]oct-2-ene, respectively, led to **5a–f** HX in yields of about 85% in a period of 17–42 days, and to **6a–f** HX in yields of about 85% (with one exception) within 6–15 weeks (*table I*). The extremely long reaction times for the lethargic reactions could not be overcome by well-known accelerating methods of organic synthesis, such as acid catalysis, pressure, sonication or microwave, partly because of the instability of the lactimethers used [13]. **5a–f** HX and **6a–f** HX show E/Z-equilibria in solution. Their composition has been reported elsewhere [29]. In solid state Z-configuration is observed [30]. The Z-configured species is supposed to produce the biological effect, since a complete shift of the equilibria towards Z-**5a–f** HX and Z-**6a–f** HX was observed in polar solvents such as methanol and dimethylsulfoxide.

Various 1-D and 2-D ^{1}H- and ^{13}C-NMR techniques, including lr (longrange)-INEPT, COSY, HETCOR, GH-SQCR and INADEQUATE, were used to elucidate the structure and relative configuration of all compounds and to analyse the E/Z-equilibria of the semicyclic amidines in solution.

The absolute configuration of **4a–f** was determined indirectly by CD correlation spectroscopy of the corresponding *cis*-2-substituted (1S, 2S)-cyclopentaneaminesalicylidenes (1S, 2S)-**7a–f** (*figure 2*) with reference to *cis*-(1S, 2S)-2-phenylcyclopentaneamine-N-salicylidene ((1S, 2S)-**7b**) [16] of known absolute configuration. The results relate well to findings in literature [16], where like-induction [31] was reported for the reductive amination step, thus (R)-(+)-PEA leading to secondary *cis*-(1R, 1'R)-2-substituted cyclopentaneamines and (S)-(–)PEA to corresponding *cis*-(1S, 1'S)-2-substituted cyclopentaneamines. The CD spectra are congruent in their positive Cotton effects at 315 and 255 nm and their negative Cotton effect at 225 nm. Divergence in intensity is caused by differing conformative arrangements of the 2-substituents. The CD curves with extrema at comparable wavelength ranges, but with actually slightly deviating τ-values are strongly indicative of the identical absolute configuration of (1S, 2S)-**7b** and (1S, 2S)-**7a**, **-7c–f**.

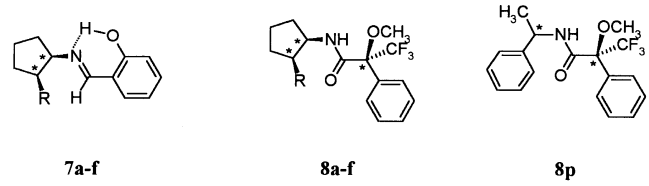


Figure 2. Configurations of **7a–f**, **8a–f** and **8p**.

The enantiomeric excesses (*ee*%) of **4a–f** and of the auxiliary amines were determined by ^{19}F-NMR spectroscopy and HPLC via derivatization with (S)-(+)-α-methoxy-α-trifluoro-methylphenylacetylchloride (Mosher's reagent) [32, 33] to the diastereomeric Mosher's amides **8a–f** and **8p** (*figure 2*). With more than 99.0% the *ee* values of **8a–f** exceeded those of the auxiliary amines, 97.9% for (R)-(+)-PEA and 97.0% for (S)-(–)-PEA, which provides evidence for a recrystallization effect of the secondary and primary amines **3a–f** HX and **4a–f** HX. The ^{19}F-NMR spectra of **8a–f** and **8p** show two singlets for a couple of diastereomeric Mosher's amides each, which are slightly widened by lr-coupling to the methoxy protons. The diastereotopic CF_3 signals of **8a**, **8b**, **8d**, **8f** and **8p** range between 50 and 230 Hz, sufficient for precise quantification. However, the corresponding signals of **8c** and **8e** diverge by only 14 and 17 Hz, respectively. Reliable spectroscopic determination of *ee* values was impossible in these two cases, even though the signals of the major diastereomer did not reveal any shoulder in the expanded spectra. The HPLC separation of the Mosher's amides **8a–f** and **8p** were in accordance with results derived from ^{19}F-NMR spectroscopy. The subsidiary diastereomer of **8c** and **8e**, respectively, was below the detection limit (< 0.5%) each time.

3. Physiology

3.1. Effects of semicyclic amidines on insulin secretion in INS-1 cells

The insulin secreting cell line INS-1 was used to test the insulinotropic effect of the semicyclic amidines **5a–f**

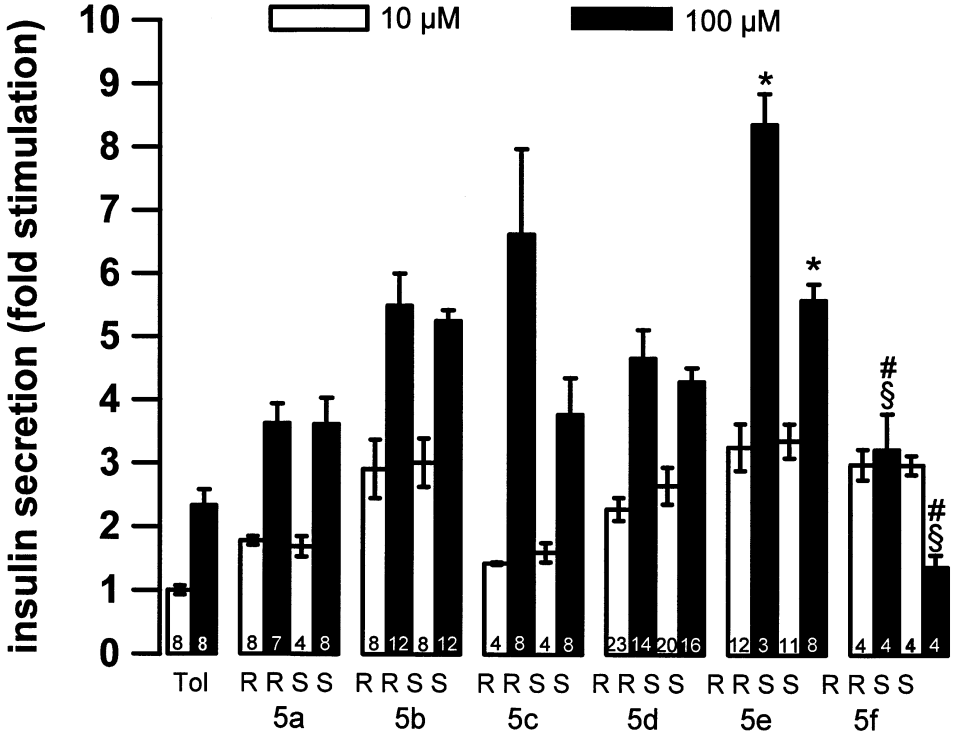


Figure 3. Effects of caprolactame derivatives **5a–f** HX on insulin secretion of INS-1 cells. INS-1 cells were incubated and insulin secretion measured as described in Experimental protocols. The compounds were tested at 10 and 100 µM in the presence of 0.5 mM glucose and 5 µM forskolin. Results are expressed as fold-stimulation over forskolin alone and are means ± SEM for the indicated number of observations (resulting from up to five independent experiments). #50 µM. * and §; significant differences between the enantiomers.

HX and **6a–f** HX. Forskolin was present throughout incubations since it potentiated the stimulatory effect of amidines on secretion (data not shown). All compounds increased insulin release at 10 µM (*figures 3* and *4*). The effect varied between 43% and 369%. The most potent activators of secretion were cyclohexyl-, benzyl-, and cyclohexylmethyl substituted isoquinuclidone derivatives **6c** HBr, **6d** HCl and **6f** HBr, respectively, and the cyclopentyl substituted caprolactam derivate **5e** HBr. However, the caprolactam-derived cyclohexyl substituted compound **5c** HBr in contrast to in vivo data [13], together with the isopropyl-derivates **5a** HCl and **6a** HCl were the weakest stimulators of insulin secretion. Comparing the respective enantiomers, only (1'R, 2'R)-**6c** HBr increased secretion more effectively than the (1'S, 2'S)-**6c** HBr distomer. All other enantiomers showed no chiral differentiation at this concentration.

The substances were also tested at 100 µM. Isopropyl, phenyl and benzyl derivates of both series of amidines, **5a** HCl, **5b** HCl, **5d** HCl, **6a** HCl, **6b** HCl and **6d** HCl, respectively, as well as cyclohexyl and cyclopentyl derivates **5c** HBr and **5e** HBr further augmented insulin release at the higher concentration. In contrast, cyclohexyl and cyclopentyl derivates (1'R, 2'R)-**6c** HBr and (1'R, 2'R)-**6e** HBr showed similar effects at 100 and 10 µM. Surprisingly, the cyclohexylmethyl derivate **6f** HBr inhibited secretion at 100 µM but had a stimulatory effect at 10 µM. However, the cyclohexylmethyl derivate **5f** HBr had a smaller activating effect at 100 µM than at 10 µM. The sulfonylurea tolbutamide was tested simultaneously and did not affect secretion at 10 µM but increased insulin release 2.46 ± 0.13-fold (n = 20) at 50 µM and 2.33 ± 0.25-fold (n = 8) at 100 µM (cf. also reference [34]). Thus, semicyclic amidines stimulate insulin secretion in a similar concentration range to tolbutamide. The semicyclic amidines **6c** HBr, **6d** HCl and **6f** HBr with the bicyclic lactam moiety were more potent at 10 µM than the respective sterically less hindered caprolactam compounds **5c** HBr, **5d** HCl and **5f** HBr.

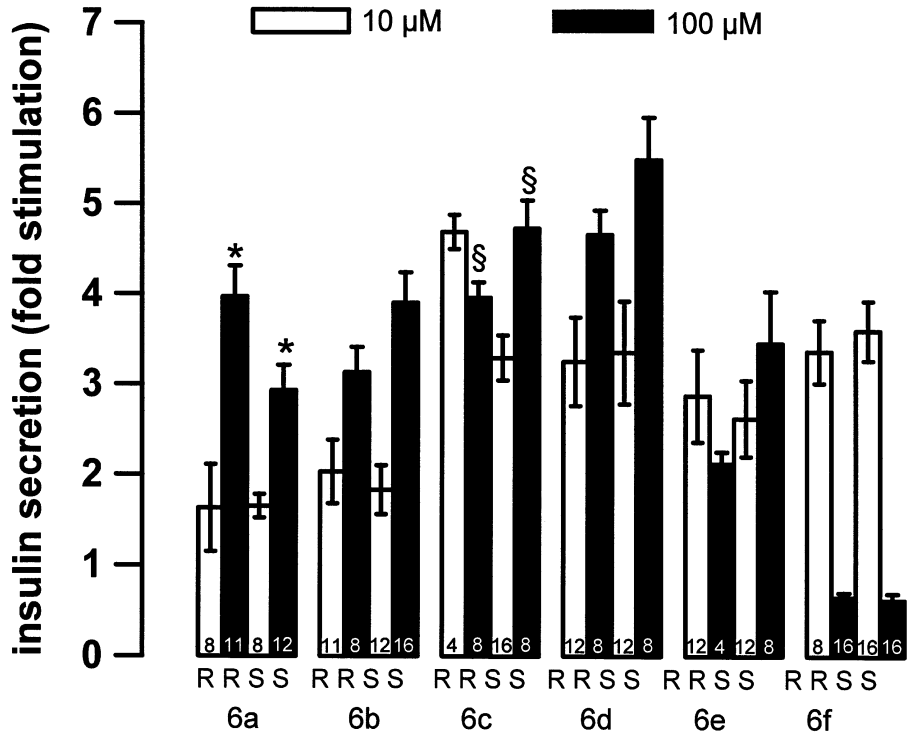


Figure 4. Effects of isoquinuclidone derivatives **6a–f** HX on insulin secretion of INS-1 cells. INS-1 cells were incubated and insulin secretion measured as described in Experimental protocols. The compounds were tested at 10 and 100 µM in the presence of 0.5 mM glucose and 5 µM forskolin. Results are expressed as fold-stimulation over forskolin alone and are means ± SEM for the indicated number of observations (resulting from up to five independent experiments). * and §; significant differences between the enantiomers.

3.2. Effects of semicyclic amidines on $[Ca^{2+}]_i$ in INS-1 cells

The observation that forskolin potentiated amidine-induced secretion suggests that the amidines mainly act by increasing $[Ca^{2+}]_i$. They might activate the cells at least in part by inducing depolarization due to closure of K^+_{ATP}-channels and by subsequent activation of voltage-dependent Ca^{2+}-channels.

Indeed, when measuring $[Ca^{2+}]_i$ in fura-2 loaded INS-1 cells, $[Ca^{2+}]_i$ increased upon amidine addition (*figures 5* and *6*). The effect was comparable to tolbutamide-induced $[Ca^{2+}]_i$-increase (100 µM). $[Ca^{2+}]_i$ returned to basal levels after removal of (1'R, 2'R)-**6a** HCl with a delay indicating that the wash-out of the compound was slow. Since $[Ca^{2+}]_i$ oscillated in 68% of INS-1 cells, which probably followed membrane voltage oscillations observed previously [35], the effects on $[Ca^{2+}]_i$ were not quantified.

In another series of experiments the effects on $[Ca^{2+}]_i$ of 10 µM and 100 µM (1'R, 2'R)-**6f** HBr were compared. At 10 µM, (1'R, 2'R)-**6f** HBr increased the fura-2 fluorescence ratio 340/380 nm from 1.32 ± 0.08 (n = 12) to 1.57 ± 0.15 (n = 5), at 100 µM to 1.84 ± 0.09 (n = 7). Thus, although (1'R, 2'R)-**6f** HBr stimulated secretion only at the lower concentration (*figure 4*), it further increased $[Ca^{2+}]_i$ more consistently at the higher concentration. In the case of 100 µM (1'R, 2'R)-**6f** HBr the increase in $[Ca^{2+}]_i$ was transient and returned to basal level before the removal of the drug.

3.3. Effects of semicyclic amidines on membrane voltage and membrane conductance in INS-1 cells

As the increase of $[Ca^{2+}]_i$ may be due to depolarization of the plasma membrane, membrane voltage and conductance were measured using the standard whole cell mode of the patch clamp method. *Figure 7*A shows a representative registration of membrane voltage $[V_m]$ in INS-1 cells, depolarized with 100 µM (1'R, 2'R)-**5a** HCl. The effects of (1'R, 2'R)-**5a** HCl on membrane voltage and membrane conductance are summarized in *figure 7B.*

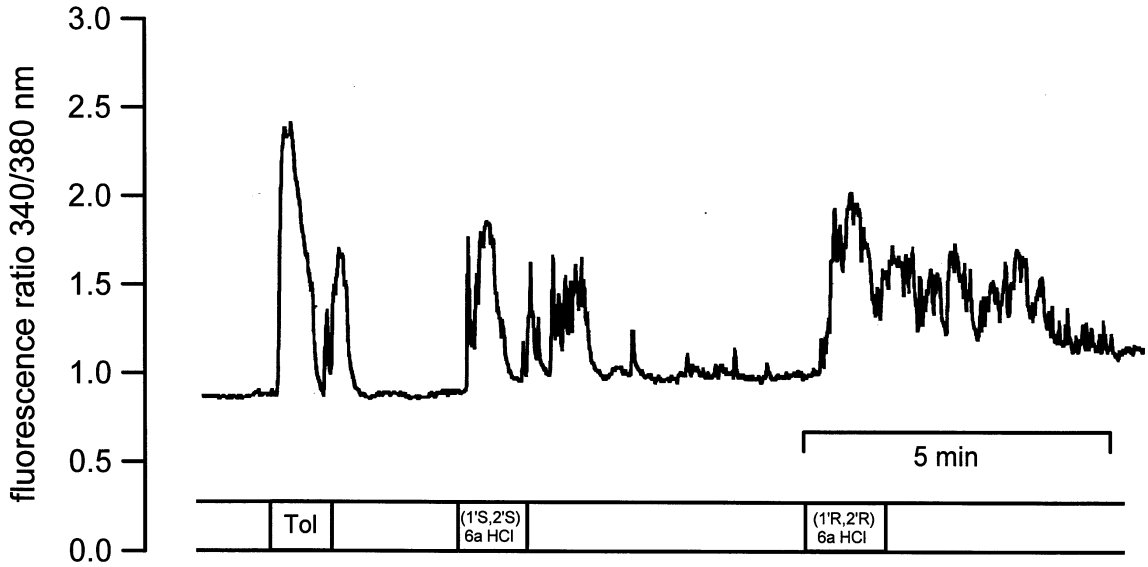


Figure 5. Effects of tolbutamide (Tol), (1'S, 2'S)-**6a** HCl (S6a) and (1'R, 2'R)-**6a** HCl (R6a) on $[Ca^{2+}]_i$ in INS-1 cells. Shown is a representative trace of continuous $[Ca^{2+}]_i$ recording. The compounds were added as indicated, each at a concentration of 100 µM.

Membrane conductance was decreased 80% by 100 µM (1'R, 2'R)-**5a** HCl, whereas the sulfonylurea tolbutamide reduced membrane conductance by 95% at the same concentration. The depolarizing effect of (1'R, 2'R)-**5a** HCl was also smaller than that of tolbutamide, 15 mV and 45 mV, respectively. These observations indicate that

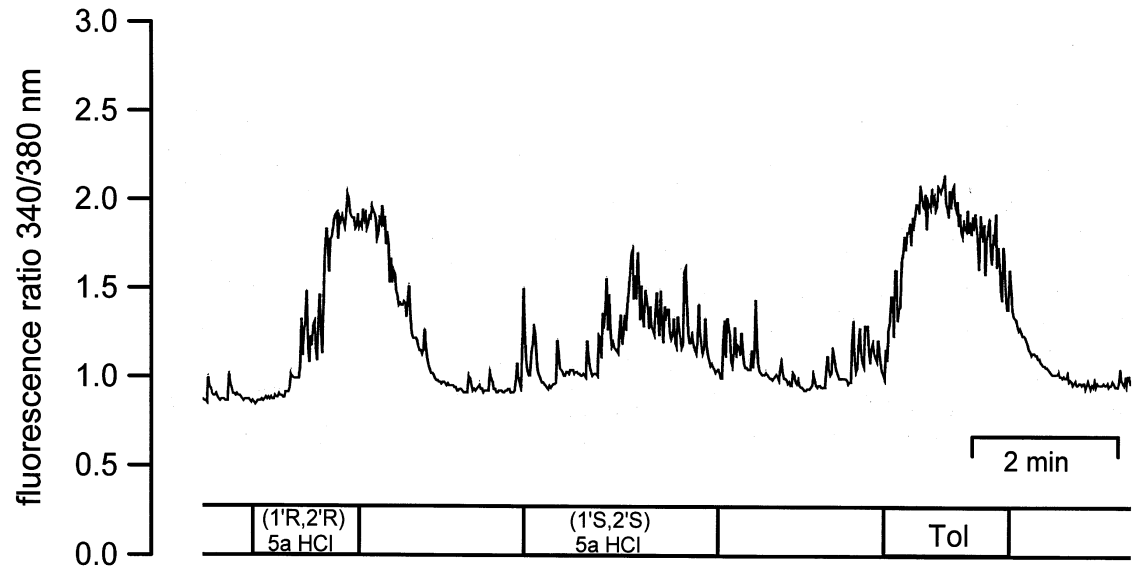


Figure 6. Effects of tolbutamide (Tol), (1'R, 2'R)-**5a** HCl (R5a) and (1'S, 2'S)-**5a** HCl (S5a) on $[Ca^{2+}]_i$ in INS-1 cells. Shown is a representative trace of continuous $[Ca^{2+}]_i$ recording. The compounds were added as indicated, each at a concentration of 100 µM.

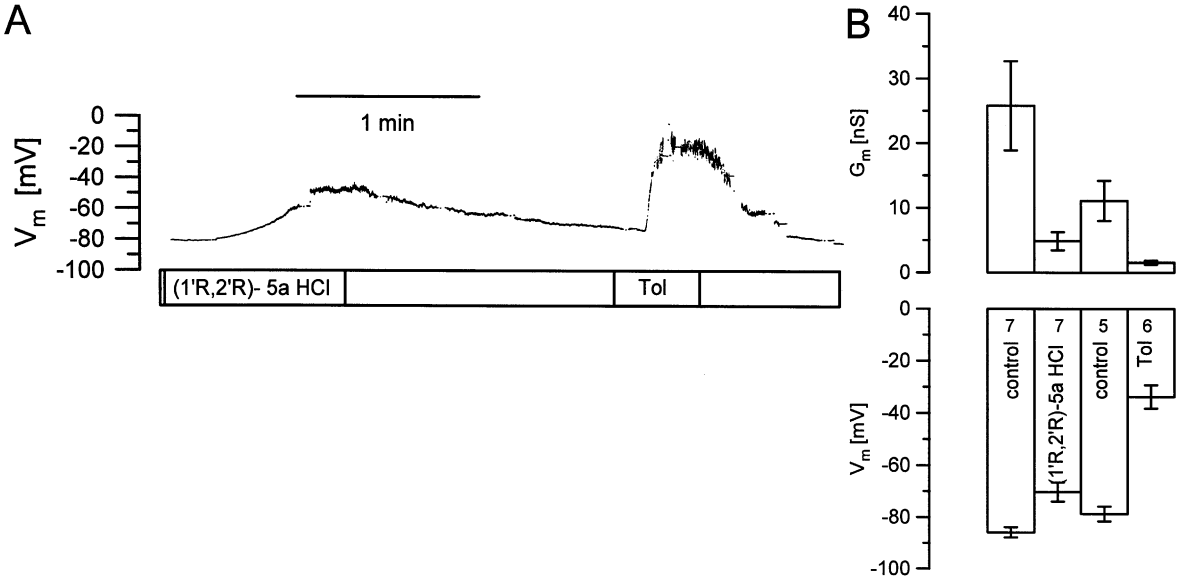


Figure 7. Effect of (1'R, 2'R)-**5a** HCl on membrane voltage in INS-1 cells. **A**: Shown is a representative trace of continuous membrane voltage recording. 100 µM (1'R, 2'R)-**5a** HCl and 100 µM tolbutamide (Tol) were added as indicated. **B**. Mean ± SEM of seven experiments.

semicyclic amidines at least partially stimulate insulin release by depolarizing the INS-1 cells, which in succession leads to the opening of voltage-sensitive Ca^{2+} channels and to an increase of $[Ca^{2+}]_i$.

4. Results and discussion

Sulfonylureas improve insulin secretion by a receptor mediated mechanism. Structurally unrelated racemic amidines have been described as hypoglycaemic agents with an unelucidated mode of action [13]. In this study we have prepared enantiomerically pure semicyclic amidines in order to test their ability to stimulate insulin secretion and to examine their mode of action.

The compounds had no toxic effects in INS-1 cells at the highest concentration tested (100 µM), since i) depolarization and increase of $[Ca^{2+}]_i$ were reversible (*figures 5–7*), ii) insulin content and the secretory behaviour of the cells were unchanged under conditions of cell culturing for 24 h in the presence of amidines (not shown), iii) the stimulatory effect of amidines was inhibited by adrenaline, which is a physiological inhibitor of insulin secretion (not shown). Thus, these substances stimulate β-cell secretion via a controllable mechanism.

All semicyclic amidines increased insulin secretion of INS-1 cells at 10 µM (*figures 3* and *4*). The flexible, spatially demanding cyclohexylmethyl substituted amidines **5f** HBr and **6f** HBr stimulated insulin release 3–4-fold at 10 µM. At this concentration the sulfonylurea tolbutamide had no significant effect on insulin release (*figure 3*). At 100 µM, the most potent secretagogue was the compound (1'R, 2'R)-**5e** HBr, increasing insulin release 8-fold. In comparison, 100 µM tolbutamide increased secretion 2–3-fold.

Significant differences between the potency of enantiomers to stimulate insulin release was observed for **5e** HBr, **5f** HBr, **6a** HCl and **6c** HBr. Thus, the (1'R, 2'R)-eutomers of **5e** HBr, **5f** HBr, **6a** HCl induced a 37%, 95% and 33% higher secretion than the respective (1'S, 2'S)-enantiomers. In contrast, the (1'R, 2'R)-enantiomer of **6c** HBr was 22% less potent than its (1'S, 2'S)-enantiomer. These observations show the site of action to possess only a weak stereoselectivity for these amidines.

In contrast to findings with other insulin secreting cells, tolbutamide induced secretion in INS-1 cells only in the presence of increased adenylyl cyclase activity [34]. Synergistic effects of cAMP and $[Ca^{2+}]_i$ on insulin secretion are also well described for native β-cells [36]. Thus, the potentiation of amidine induced secretion by cAMP suggests a site of action involving increases in $[Ca^{2+}]_i$. Indeed, pronounced elevation of $[Ca^{2+}]_i$ is observed upon amidine addition (*figures 5* and *6*). This

effect is reversible, but after removal of the drug, $[Ca^{2+}]_i$ returns only slowly to basal levels indicating a reduced wash-out of the substance. The measurements of membrane voltage and membrane conductance revealed that amidines depolarized the cells and reduced the membrane conductance by 80% under control conditions (*figure 7*). Since the whole cell conductance under control conditions has been shown to result mainly from K^+_{ATP}-channel activity, the observed effects of amidines are due to inhibition of these channels [34].

Thus, the proposed mechanism of action involves the closure of K^+_{ATP}-channels which leads to a decrease of membrane conductance, depolarization and subsequent opening of voltage-activated Ca^{2+}-channels. Whether the site of action is also the SUR-molecule [35] as for sulfonylureas, remains obscure and further studies are needed for clarification.

Since the flexible, spatially demanding cyclohexylmethyl-substituted amidine **6f** HBr inhibited secretion at the highest concentration tested (100 µM) while increasing $[Ca^{2+}]_i$, it is suggested that accumulation of this compound leads to the interference with further membrane proteins resulting in an inhibition of secretion.

In conclusion, this study shows that enantiomerically pure semicyclic amidines induce insulin secretion with only weak stereoselectivity, at least in part through inhibition of K^+_{ATP}-channels and a subsequent rise in $[Ca^{2+}]_i$.

5. Experimental protocols

5.1. Chemistry

Hydrogenation reactions were carried out in a Parr shaker, constructed by the Pharmaceutical Institute of the University of Freiburg using Rh/γ-Al_2O_3 (5%) type G 207 R, Raney-nickel suspended under water type B 113 W and Pd/C (10%) type E 10 N/D (all Degussa, Frankfurt a. M., D). Melting points (m.p.) were determined on a Mel Temp II capillary melting point apparatus (Laboratory Devices, USA) and are uncorrected. IR spectra were recorded on a Perkin Elmer 841 infrared spectrometer. Optical rotation was determined on a Perkin Elmer 241 polarimeter with c = 1.0, ethanol. CD spectra were recorded on a CD 6 Dichrograph System, ISA Instruments Jobin Yvon, Longjumeau, F. ^{1}H-, ^{13}C-, ^{19}F- 1-D and 2-D-NMR spectra were recorded on a Varian Unity 300 spectrometer operating at 300, 75 and 282 MHz, respectively. Chemical shift values are referenced to $CHCl_3$, δ 7.24 in $CDCl_3$ for ^{1}H-NMR, to $CDCl_3$, δ 77.00 for ^{13}C-NMR and to 1,1,2-trichlorotrifluoroethane, δ –68.03 for ^{19}F-NMR. The chemical shifts of proton multiplets were determined by the corresponding ^{1}H-^{13}C-Hetcor spectra. ^{1}H-NMR data are always listed in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; mc, centric multiplet), number of nuclei, coupling constant(s) in Hz, assignment. *, #, §, ◆ indicate protons/carbon atoms that can be exchanged. GC MS spectra were recorded on a Perkin Elmer QMASS 910 spectrometer on an Rtx®-35 column (Restek, Bellefonte, USA), crossbond® (35% diphenyl-, 65% dimethylpolysiloxane) 0.25 µm, 35 m. HPLC separation of the Mosher amides (enantiomeric excesses (*ee*%)) was performed on a Lichrosorb® Si-60 column (5 µm, 250 × 4 mm, Bischoff, Leonberg, D) with a Waters 600 multisolvent delivery system with a diode-array detector Waters 990 or a Waters 486 Tunable Absorbance Detector. Flash chromatography was carried out on E. Merck silica gel 60 (0.040–0.068 mm). Thin layer chromatography (TLC) was performed on silica gel F_{254} plates from E. Merck, Darmstadt, D. Visualization was done using ninhydrin reagent (Stahl) and heating. Analyses (Analytical Laboratories, Chemical Institutes, University of Freiburg, D) indicated by the symbols of the elements or functions were within ± 0.4% of theoretical values.

*5.1.1. 2-Cyclohexylcyclopentanone (***1c***)*

To a solution of 3.2 g (20 mmol) 2-phenylcyclopentanone (**1b**) in 40 mL methanol abs were added 0.6 g of Rh/γ-Al_2O_3 (5%) and 0.5 mL acetic acid [26]. The mixture was hydrogenated at an initial pressure of 5 bar and at room temperature in a Parr shaker. The progress of the reaction was observed by GC/MS. After 10.5 h the reaction mixture was filtered (Celite 535), the catalyst was washed with five portions of 20 mL methanol each and the filtrate was evaporated after addition of 5 mL toluene for complete removal of the acetic acid. The residue was oxidized in situ.

Hydrogenation mixture (3.2 g) was added dropwise to 22.6 g (17.6 mmol) pyridiniumchlorochromate-Al_2O_3 [27] suspended in 50 mL toluene, and stirred at room temperature over night. The oxidant was filtered off and washed with five portions of 30 mL diethylether each. The organic phase was dried with sodium sulfate, filtered and evaporated in vacuo. A 2.9 g (88%) yield of a colourless oil, containing 96.5% **1c** (GC-MS) was condensed in situ with (R)-(+)- and (S)-(–)-phenylethylamine, respectively. MS (EI) m/e 166 ($[M]^+$); ^{1}H-NMR ($CDCl_3$) δ 0.97–1.32 (m, 5H, H-2'b, H-6'b, H-3'b, H-4'b, H-5'b), 1.42 (mc, 1H, H-6'a*), 1.58–1.82 (m, 7H, H-3'a, H-4'a, H-5'a, H-3b, H-4b, H-2'a*, H-1'), 1.89–2.06 (m, 4H, H-4a, H-2, H-3a, H-5b), 2.19–2.31 (m, 1H, H-5a); ^{13}C-NMR ($CDCl_3$) δ 20.68 (C-4), 25.33 (C-3), 26.22 (C-3'*), 26.24 (C-4'),

26.44 (C-5'*), 28.74 (C-2'$^{\#}$), 31.56 (C-6'$^{\#}$), 37.49 (C-1'), 39.11 (C-5), 54.46 (C-2), 221.16 (C-1); IR (NaCl, cm^{-1}) 1 737 (C=O).

5.1.2. 2-Cyclohexylmethylcyclopentanone **1f**

To a solution of 8.7 g (50 mmol) 2-benzylcyclopentanone (**1d**) in 100 mL methanol abs were added 2.4 g of Rh/γ-Al_2O_3 (5%) and 1.6 mL acetic acid. The mixture was hydrogenated at an initial pressure of 5 bar and at room temperature in a Parr shaker. The progress of the reaction was observed by GC/MS. After 20.5 h the reaction mixture was filtered (Celite 535), the catalyst was washed with five portions of 20 mL methanol each and the filtrate was evaporated after addition of 5 mL toluene for complete removal of the acetic acid. An 8.8 g (98%) yield of a colourless oil, containing 98.5% **1f** (GC-MS) was condensed in situ with (R)-(+)- and (S)-(–)-phenylethylamine, respectively. MS (EI) m/e (M), 84 (100); ^{1}H-NMR ($CDCl_3$) δ 0.70–0.92 (m, 2H, H-2'b, H-6'b), 0.97–1.29 (m, 5H, H-7'b, H-3'b, H-4'b, H-5'b, H-1'), 1.33–1.46 (m, 1H, H-3b), 1.51–1.75 (m, 7H, H-2'a*, H-7'a, H-6'a*, H-3'a, H-4'a, H-5'a, H-4b), 1.86–2.25 (m, 5H, H-4a, H-5b, H-2, H-3a, H-5a); ^{13}C-NMR ($CDCl_3$) δ 20.54 (C-4), 25.99 (C-3'$^{\#}$), 26.11 (C-5'$^{\#}$), 26.35 (C-4'), 30.00 (C-3), 32.12 (C-2'*), 33.98 (C-6'*), 35.48 (C-1'), 37.27 (C-7'), 37.74 (C-5), 46.60 (C-2), 221.61 (C-1); IR (NaCl, cm^{-1}) 1 739 (C=O).

5.1.3. Preparation of 2-substituted cyclopentaneimines **2a–f**

The 2-substituted cyclopentaneimines **2a–f** were prepared according to a common procedure [16]. Toluene was used as solvent. The optimized reaction times and yields of imine condensation are: 25 h, 88% for **1c**, 22 h, 80% for **1e** and 14 h, 90% for **1f**. The yields were determined by ^{1}H-NMR (α-H-signal imine 4.48 and 4.43 ppm/PEA 4.1 ppm). For the complete NMR data see the supporting information.

5.1.4. Preparation of cis-2-substituted N-(1-phenylethyl)-cyclopentaneamine halides **3a–f** *HX*

The *cis*-2-substituted N-(1-phenylethyl)-cyclopentaneamine halides **3a–f** HX were prepared according to a common procedure [16]. The optimized hydrogenation conditions and yields (calculated from ketones over both steps) are 11 days hydrogenation time, 73% (oil) for **2c**, 11 days hydrogenation time, 54% for **2e** and 5 days hydrogenation time, 60% for **2f** with 1.9 g Raney-nickel/10 mmol 2-substituted cyclopentaneimines **2c**, **2e** and **2f**, respectively.

The ice-cooled solution of the hydrogenation product of **2c**, **2e** and **2f** in ethanol was acidified with hydrobromic acid 48%. The volume of the solution was reduced to one third and the *sec* amine hydrobromide was precipitated by adding diethylether and recrystallized from ethanol/ether to give **3e** HBr and **3f** HBr, respectively. The ice-cooled solution of an aliquot amount of *sec cis*-2-cyclohexylcyclopentaneamine **3c**, rectified by column chromatography, was acidified with trifluoroacetic acid. **3c** TFA was recrystallized from *n*-hexane/diethylether (2:1). **3c** HBr (73%) was hydrogenated in situ.

5.1.4.1. cis-*2-Cyclohexyl-N-(1-phenylethyl)-cyclopentaneamine trifluoroacetate* **3c** *TFA*

(1R, 2R)-**3c** TFA: m.p. 117–119 °C, $[\alpha]_D^{25}$ –7.9°; (1S, 2S)-**3c** TFA: m.p. 119–121 °C, $[\alpha]_D^{25}$ +8.2°; ^{1}H-NMR ($CDCl_3$) δ 0.86 (mc, 2H, H-2'b, H-6'b), 1.05–1.21 (m, 1H, H-3b), 1.21–1.39 (m, 2H, H-3'b, H-5'b), 1.42–1.71 (m, 9H, H-2'a*, H-4b, H-1', H-2, H-3'a, H-5'a, H-5b, H-3a, H-4'b), 1.75 (d, 3H, 6.8, β-CH_3), 1.71–1.92 (m, 4H, H-4'a, H-6'a*, H-5a, H-4a), 3.35 (s (broad (br)), 1H, H-1), 4.35 (q, 1H, 6.8, α-CH), 7.37–7.47, (m, 3H, H-3″, H-4″, H-5″), 7.50–7.55 (m, 2H, H-2″, H-6″), 7.71 (s (br), 1H, $^+$NH-b), 10.02 (s (br), 1H, $^+$NH-a); ^{13}C-NMR ($CDCl_3$) δ 18.96 (β-CH_3), 20.12 (C-4), 24.97 (C-3', C-5'), 25.16 (C-4'), 25.55 (C-3), 29.95 (C-5), 31.24 (C-2'*), 32.50 (C-6'*), 34.91 (C-1'), 50.65 (C-2), 58.68 (C-1), 59.06 (α-CH), 116.17 (q, $^1J_{C,F}$ = 294 Hz, CF_3), 127.34 (C-2″, C-6″), 128.63 (C-3″, C-5″), 128.67 (C-4″), 135.89 (C-1″), 161.35 (q, $^2J_{C,F}$ = 35 Hz, F_3C–COO^-). (1R, 2R)-**3c** TFA anal. $C_{21}H_{30}F_3NO_2$ (H, N); C: calcd., 65.43; found 64.80; (1S, 2S)-**3c** TFA anal. $C_{21}H_{30}F_3NO_2$ (C, H, N).

5.1.4.2. cis-*2-Cyclopentyl-N-(1-phenylethyl)-cyclopentaneamine hydrobromide* **3e** *HBr*

(1R, 2R)-**3e** HBr: m.p. 165–167 °C, $[\alpha]_D^{25}$ +1.4°; (1S, 2S)-**3e** HBr: m.p. 164–165 °C, $[\alpha]_D^{25}$ –1.7°; ^{1}H-NMR ($CDCl_3$) δ 0.96–1.18 (m, 2H, H-2'b, H-5'b), 1.48–1.75 (m, 8H, H-4b, 3'-CH_2, 4'-CH_2, H-3b, H-2'a*, H-2), 1.80 (mc, 1H, H-5b), 1.92–2.13 (m, 3H, H-5'a*, H-4a, H-3a), 2.09 (d, 3H, 6.9, β-CH_3), 2.26–2.46 (m, 2H, H-5a, H-1'), 3.17 (s (br), 1H, H-1), 4.55 (s (br), 1H, α-CH), 7.36 (tt, 1H, 7.2, 1.3, H-4″), 7.43 (dt, 2H, 7.0, 1.8, H-3″, H-5″), 7.81 (td, 2H, 6.9, 1.5, H-2″, H-6″), 8.49 (s (br), 1H, $^+$NH-b), 9.27 (s (br), 1H, $^+$NH-a); ^{13}C-NMR ($CDCl_3$) δ 20.41 (β-CH_3), 21.08 (C-4), 25.08 (C-4'$^{\#}$), 25.10 (C-3'$^{\#}$), 27.22 (C-3), 30.39 (C-5), 31.89 (C-5'*), 32.77 (C-3'*), 38.00 (C-1'), 49.38 (C-2), 59.98 (α-CH), 60.91 (C-1), 128.48 (C-2″, C-6″), 129.18 (C-4″), 129.25 (C-3″, C-5″), 136.34 (C-1″). Anal. $C_{18}H_{28}NBr$ (C, H, N).

5.1.4.3. cis-*2-Cyclohexylmethyl-N-(1-phenylethyl)-cyclopentaneamine hydrobromide* **3f** *HBr*

(1R, 2R)-**3f** HBr: m.p. 240–241 °C decomposition, $[\alpha]_D^{25}$ +54.9°; (1S, 2S)-**3f** HBr: m.p. 241–242 °C decom-

position, $[\alpha]_D^{25}$ –55.0°; ^{1}H-NMR ($CDCl_3$) δ 0.86–1.00 (m, 1H, H-6'b*), 1.06–1.32 (m, 5H, H-2'b*, H-1', H-3'b, H-4'b, H-5'b), 1.36–1.53 (m, 4H, H-4b, 7'-CH_2, H-3b), 1.58–1.80 (m, 6H, H-3a, H-3'a, H-4'a, H-5'a, H-2'a$^{\#}$, H-4a), 1.80–1.92 (m, 1H, H-6'a$^{\#}$), 1.99–2.30 (m, 3H, H-2, 5-CH_2), 2.03 (d, 3H, 6.9, β-CH_3), 2.99 (quint, 1H, 7.0, H-1), 4.30 (quint, 1H, 6.5, α-CH), 7.31–7.46 (m, 3H, H-3″, H-4″, H-5″), 7.75 (dt, 2H, 7.4, 1.4, H-2″, H-6″), 9.11 (s (br), 1H, $^+$NH-b), 9.66 (s (br), 1H, $^+$NH-a); ^{13}C-NMR ($CDCl_3$) δ 19.80 (C-4), 21.32 (β-CH_3), 26.15 (C-3'$^{\#}$), 26.29 (C-5'$^{\#}$), 26.50 (C-4'), 27.12 (C-5), 27.64 (C-3), 32.23 (C-6'*), 34.54 (C-2'*), 35.21 (C-7'), 35.37 (C-1'), 35.97 (C-2), 58.88 (α-C), 59.80 (C-1), 128.19 (C-2″, C-6″), 129.10 (C-4″), 129.25 (C-3″, C-5″), 136.25 (C-1″). Anal. $C_{20}H_{32}NBr$ (C, H, N).

5.1.5. Preparation of cis*-2-substituted cyclopentaneamine halides* **4a–f** *HX*

The *cis*-2-substituted cyclopentaneamine halides **4a–f** were prepared according to a common procedure [16]. The optimized hydrogenolysis conditions and yields are: 0.8 g Pd/C / 10 mmol **3c** HBr, 24 h, 61% **4c** HBr, 1.0 g Pd/C / 10 mmol **3e** HBr, 24 h, 93% **4e** HBr and 0.9 g Pd/C / 10 mmol **3f** HBr, 24 h, 81% **4f** HBr.

5.1.5.1. cis*-2-Cyclohexylcyclopentaneamine hydrobromide* **4c** *HBr*

(1R, 2R)-**4c** HBr: m.p. 275–278 °C decomposition, $[\alpha]_D^{25}$ –16.5°; (1S, 2S)-**4c** HBr: m.p. 277–280 °C decomposition, $[\alpha]_D^{25}$ +16.1°; ^{1}H-NMR ($CDCl_3$) δ 0.88 (mc, 2H, H-2'b, H-6'b), 1.02–1.30 (m, 2H, H-3'b, H-5'b), 1.35 (mc, 1H, H-1'), 1.43–1.71 (m, 6H, H-2, H-3'a, H-5'a, H-4'b, H-4b, H-3b), 1.71–1.83 (m, 2H, H-3b, H-6'a*), 1.83–2.05 (m, 4H, H-5b, H-3a, H-2'a*, H-4a), 2.11–2.23 (m, 1H, H-5a), 3.71 (s (br), 1H, H-1), 7.86 (s (br), 3H, $^+$$NH_3$); ^{13}C-NMR ($CDCl_3$) δ 20.70 (C-4), 25.45 (C-4'), 26.04 (C-3'$^{\#}$), 26.07 (C-3), 26.14 (C-5'$^{\#}$), 30.67 (C-5), 32.25 (C-2'*), 32.65 (C-6'*), 36.88 (C-1'), 50.44 (C-2), 54.53 (C-1); C-3, C-3', C-4', C-5' were assigned using lr INEPT spectroscopy. Anal. $C_{11}H_{22}NBr$ (C, H, N).

5.1.5.2. cis*-2-Cyclopentylcyclopentaneamine hydrobromide* **4e** *HBr*

(1R, 2R)-**4e** HBr: m.p. 266–267 °C decomposition, $[\alpha]_D^{25}$ –21.9°; (1S, 2S)-**4e** HBr: m.p. 270–271 °C decomposition, $[\alpha]_D^{25}$ +21.6°; ^{1}H-NMR ($CDCl_3$) δ 0.95–1.23 (m, 2H, H-5'b, H-2'b), 1.42–2.04 (m, 12H, 3'-CH_2, 4'-CH_2, H-2, H-4b, H-1', 3-CH_2, H-2'b*, H-5b, H-4a), 2.07–2.26 (m, 2H, H-5a, H-5'b*), 3.65 (mc, 1H, H-1), 7.95 (s (br), 3H, $^+$$NH_3$); ^{13}C-NMR ($CDCl_3$) δ 21.24 (C-4), 24.81 (C-4'$^{\#}$), 25.13 (C-3'$^{\#}$), 27.65 (C-3), 30.85 (C-5), 32.26 (C-5'*), 32.32 (C-2'*), 39.99 (C-1'), 50.14 (C-2), 56.06 (C-1). Anal. $C_{10}H_{20}NBr$ (C, H, N).

5.1.5.3. cis*-2-Cyclohexylmethylcyclopentaneamine hydrobromide* **4f** *HBr*

(1R, 2R)-**4f** HBr: m.p. 212–213 °C decomposition, $[\alpha]_D^{25}$ +6.5°; (1S, 2S)-**4f** HBr: m.p. 213–214 °C decomposition, $[\alpha]_D^{25}$ –7.3°; ^{1}H-NMR ($CDCl_3$) δ 0.77–1.01 (m, 2H, H-6'b, H-2'b), 1.03–1.40 (m, 5H, H-3'b, H-4'b, H-5'b, H-1', H-7'b), 1.51 (mc, 1H, H-7'a), 1.55–1.73 (m, 6H, H-3'a, H-4'a, H-5'a, H-3b, H-4b, H-2'a*), 1.73–1.90 (m, 2H, H-6'a*, H-3a), 1.90–2.14 (m, 4H, H-4a, 5-CH_2, H-2), 3.60 (mc, 1H, H-1), 7.92 (s (br), 3H, $^+$$NH_3$); ^{13}C-NMR ($CDCl_3$) δ 21.60 (C-4), 26.09 (C-3'*), 26.19 (C-5'*), 26.54 (C-4'), 28.72 (C-3), 30.80 (C-5), 32.79 (C-2'$^{\#}$), 33.74 (C-6'$^{\#}$), 35.92 (C-1'), 37.04 (C-7'), 40.02 (C-2), 56.22 (C-1). Anal. $C_{12}H_{24}NBr$ (C, H, N).

*5.1.6. Preparation of 2-[(*cis*-2-substituted cyclopentyl)imino]hexahydroazepine halides* **5a–f** *HX and 3-[(*cis*-2-substituted cyclopentyl)imino]-2-azabicyclo[2.2.2]octane halides* **6a–f** *HX*

Five mmol of the primary *cis*-2-substituted cyclopentaneamine halide **4a–f** HX in 1 mL ethanol abs and 5.5 mmol of O-methylcaprolactim (0.7 g) and 3-ethoxy-2-azabicyclo[2.2.2]oct-2-ene (0.84 g), respectively, were carefully dispersed in an ultrasonic device. The reaction mixture was stirred at room temperature. The progress of the lethargic reaction [13] was observed by TLC (ethyl acetate/ethanol/ammonia conc.: 90/10/1, ninhydrin reagent). When necessary, further ethanol abs was added to keep the suspension liquid and further lactimether was added to achieve complete turnover. Reaction times and yields are listed in *table I*. The reaction mixture was then resolved in methanol, filtered and the filtrate was evaporated. The white residues were recrystallized from methanol/acetone to give the semicyclic amidines **5a–e** HX and **6a–f** HX. Analytically pure **5f** HBr was collected as residue after extraction of the raw **5f** HBr with ethyl acetate.

*5.1.6.1. 2-[(*cis*-2-Isopropylcyclopentyl)-imino]hexahydroazepine hydrochloride* **5a** *HCl*

(1'R, 2'R)-**5a** HCl: m.p. 256–258 °C decomposition, $[\alpha]_D^{25}$ –122.8°; (1'S, 2'S)-**5a** HCl: m.p. 259–263 °C decomposition, $[\alpha]_D^{25}$ +115.9°; ^{1}H-NMR ($CDCl_3$) δ 0.81 (d, 3H (Z), 6.4, 3″-CH_3*), 0.85 (d, 3H (E), 6.4, 3″-CH_3*), 0.87 (d, 3H (Z), 6.4, 2″-CH_3*), 0.90 (d, 3H (E), 6.4, 2″-CH_3*), 1.40–2.05 (m, 14H, H-4'b, H-2', 6-CH_2, H-3'b, H-5'b, 4-CH_2, 5-CH_2, H-4'a, H-1″, H-3'a, H-5'a),

2.66 (mc, 2H (E), 3-CH_2), 2.91 (dd, 1H (Z), 14.0, 7.7, H-3b), 3.19 (dd, 1H (Z), 14.0, 9.6, H-3a), 3.32–3.39 (m, 2H (E), 7-CH_2), 3.39–3.51 (m, 1H (Z), H-7b), 3.51–3.64 (m, 1H (Z), H-7a), 3.94 (mc, 1H (E), H-1'), 4.40 (mc, 1H (Z), H-1'), 9.30 (d, 1H (Z), 9.3, NH_{exo}), 9.68 (d, 1H (E), 9.3, NH_{exo}), 9.72 (t, 1H (Z), 5.6, NH_{endo}), 10.43 (t, 1H (E), 5.6, NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**5a** HCl: 22.03 (C-2″, C-3″), 22.10 (C-4'), 23.97 (C-4), 27.68 (C-3'), 27.76 (C-1″), 28.29 (C-6), 29.70 (C-5), 31.16 (C-3), 33.15 (C-5'), 43.59 (C-7), 51.61 (C-2'), 55.80 (C-1'), 168.02 (C-2); E-**5a** HCl: 21.03 (C-4'), 21.75 (C-3″*), 21.83 (C-2″*), 22.95 (C-4), 26.37 (C-3), 27.58 (C-3'), 27.89 (C-1″), 28.29 (C-6), 29.70 (C-5), 34.74 (C-5'), 43.74 (C-7), 52.16 (C-2'), 57.37 (C-1'), 171.46 (C-2); IR (KBr, cm^{-1}) 3 434 (ν (NH)), 1 641 (ν (C=N)). Anal. $C_{14}H_{27}N_2Cl$ (C, H, N).

*5.1.6.2. 2-[(*cis*-2-Phenylcyclopentyl)-imino]hexahydroazepine hydrochloride* **5b** *HCl*

(1'R, 2'R)-**5b** HCl: m.p. 184–185 °C, $[\alpha]_D^{25}$ +113.4°; (1'S, 2'S)-**5b** HCl: m.p. 182–184 °C, $[\alpha]_D^{25}$ –114.1°; ^{1}H-NMR ($CDCl_3$) δ 0.82 (mc, 1H, H-4b), 0.99 (mc, 1H, H-6b), 1.11–1.67 (m, 5H, H-5b, H-6a, H-4a, H-5a, H-4'b), 1.98–2.12 (m, 2H, H-4'a, H-3'b), 2.13–2.23 (m, 1H, H-3'a), 2.28 (mc, 2H (Z) + 1H (E), 5'-CH_2 (Z), H-3b (E)), 2.43 (dd, 1H (Z), 14.2, 11.2, H-3b), 2.82 (dd, 1H (Z), 14.2, 7.8, H-3a), 3.05–3.18 (m, 1H (Z) + 2H (E), H-7b (Z + E), H-2' (E)), 3.18–3.25 (m, 2H (E), H-3a, H-7a), 3.25–3.37 (m, 1H (Z), H-7a), 3.69 (ddd, 1H (Z), $J_{2'\text{-H}/3'\text{a-H}}$ = 11.5, $J_{2'\text{-H}/3'\text{-b}}$ = $J_{2'\text{-H}/1'\text{-H}}$ = 7.5, H-2'), 4.04 (mc, 1H (E), H-1'), 4.85 (mc, 1H (Z), H-1'), 7.18 (tt, 1H (Z), 7.1, 1.2, H-4″), 7.24–7.34 (m, 2H (Z) + 5H (E), H-3″, H-5″ (Z), H-2″, H-3″, H-4″, H-5″, H-6″ (E)), 7.59 (td, 2H (Z), 7.1, 1.2, H-2″, H-6″), 9.29 (t, 1H (Z), 5.0, NH_{endo}), 9.59 (d, 1H (Z), 8.8, NH_{exo}), 10.06 (s (br), 1H (E), NH_{exo}), 10.09 (s (br), 1H (E), NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**5b** HCl: 22.83 (C-4), 24.33 (C-4'), 27.08 (C-6), 29.37 (C-5), 31.10 (C-3), 31.91 (C-5'), 32.29 (C-3'), 43.26 (C-7), 49.58 (C-2'), 56.07 (C-1'), 126.19 (C-4″), 127.54 (C-3″, C-5″), 129.92 (C-2″, C-6″), 139.81 (C-1″), 167.08 (C-2); E-**5b** HCl: 21.94 (C-4), 24.33 (C-4'), 25.83 (C-3), 27.34 (C-6), 28.62 (C-5), 31.63 (C-3'), 31.91 (C-5'), 43.66 (C-7), 51.88 (C-2'), 59.65 (C-1'), 127.10 (C-4″), 128.38 (C-3″, C-5″), 129.16 (C-2″, C-6″), 138.58 (C-1″), 171.77 (C-2); IR (KBr, cm^{-1}) 3 430 (ν (NH)), 1 650 (ν (C=N)). Anal. $C_{17}H_{25}N_2Cl$ (C, H, N).

*5.1.6.3. 2-[(*cis*-2-Cyclohexylcyclopentyl)-imino]hexahydroazepine hydrobromide* **5c** *HBr*

(1'R, 2'R)-**5c** HBr: m.p. 218–220 °C, $[\alpha]_D^{25}$ –75.0°; (1'S, 2'S)-**5c** HBr: m.p. 217–218 °C, $[\alpha]_D^{25}$ +71.8°; ^{1}H-NMR ($CDCl_3$) δ 0.88 (mc, 2H, H-2″b, H-6″b), 1.03–1.31 (m, 3H, H-3″b, H-4″b, H-5″b), 1.42–2.07 (m, 19H, H-6b, H-4'b, H-2″a, H-1″, H-4b, H-4″a, H-5b, H-3″a, H-5″a, H-2', H-5'b, H-6a, H-4a, H-6″a, H-3'b, H-4'a, H-5a, H-3'a, H-5'a), 2.66 (mc, 2H (E), 3-CH_2), 2.90 (dd, 1H (Z), 13.8, 10.1, H-3b), 3.24 (dd, 1H (Z), 13.8, 7.9, H-3a), 3.38 (mc, 2H (E), 7-CH_2), 3.46 (mc, 1H (Z), H-7b), 3.61 (mc, 1H (Z), H-7a), 3.99 (s (br), 1H (E), H-1'), 4.47 (s (br), 1H (Z), H-1'), 8.64 (d, 1H (Z), 7.3, $^+NH_{exo}$), 9.09 (d, 1H (E), 7.3, $^+NH_{exo}$), 9.20 (s (br), 1H (Z), NH_{endo}), 10.06 (s (br), 1H (E), NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**5c** HBr: 21.89 (C-4'), 23.99 (C-4), 25.91 (C-3″*), 26.00 (C-5″*), 26.36 (C-4″), 27.25 (C-3'), 28.23 (C-6), 29.66 (C-5), 31.71 (C-3), 32.26 (C-2″$^{\#}$), 32.56 (C-6″$^{\#}$), 32.89 (C-5'), 37.20 (C-1″), 43.61 (C-7), 50.25 (C-2'), 55.63 (C-1'), 168.10 (C-2); **E-5c** HBr: 20.80 (C-4'), 23.03 (C-4), 25.69 (C-3″*), 25.73 (C-5″*), 26.23 (C-4″), 26.66 (C-3), 27.61 (C-3'), 28.23 (C-6), 29.66 (C-5), 32.13 (C-2″$^{\#}$), 32.34 (C-6″$^{\#}$), 34.58 (C-5'), 36.90 (C-1″), 43.83 (C-7), 50.74 (C-2'), 57.06 (C-1'), 171.44 (C-2); IR (KBr, cm^{-1}) 3 432 (ν (NH)), 1 643 (ν (C=N)). Anal. $C_{17}H_{31}N_2Br$ (C, H, N).

*5.1.6.4. 2-[(*cis*-2-Benzylcyclopentyl)-imino]hexahydroazepine hydrochloride* **5d** *HCl*

(1'R, 2'R)-**5d** HCl: m.p. 164–166 °C, $[\alpha]_D^{25}$ +30.4°; (1'S, 2'S)-**5d** HCl: m.p. 164–166 °C, $[\alpha]_D^{25}$ –30.3°; ^{1}H-NMR ($CDCl_3$) δ 1.33–1.69 (m, 9H, H-4'b, 6-CH_2, 4-CH_2, 5-CH_2, 3'-CH_2), 1.77 (mc, 1H, H-4'a), 2.02 (mc, 2H, 5'-CH_2), 2.35 (m, 1H (E), H-2'), 2.51 (part B, 1H, J_{BA} = 13.0, J_{BX} = 9.6, H-7″b), 2.63 (mc, part X, 1H (Z), H-2'), 2.72 (mc, 2H, 3-CH_2), 2.87 (part A, 1H, J_{AB} = 13.0, J_{AX} = 5.4, H-7″a), 3.27 (mc, 2H (E), 7-CH_2), 3.36 (s (br), 2H (Z), 7-CH_2), 3.55 (s (br), 1H (E), H-1'), 4.39 (mc, 1H (Z), H-1'), 7.02–7.09 (m, 1H, H-4″), 7.10–7.19 (m, 4H, H-2″, H-3″, H-5″, H-6″), 9.60 (s (br), 1H (Z), NH_{endo}), 9.75 (d, 1H (Z + E), 6.4, NH_{exo}), 10.08 (s (br), 1H (E), NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**5d** HCl: 21.92 (C-4'), 23.93 (C-4), 28.16 (C-6), 29.75 (C-5), 29.85 (C-3'), 30.93 (C-5'), 31.41 (C-3), 35.45 (C-7″), 43.16 (C-2'), 43.71 (C-7), 56.44 (C-1'), 125.55 (C-4″), 128.04 (C-2″, C-6″), 128.83 (C-3″, C-5″), 141.10 (C-1″), 168.18 (C-2); E-**5d** HCl: 21.65 (C-4'), 22.19 (C-4), 26.15 (C-3), 27.67 (C-6), 29.42 (C-5), 29.59 (C-3'), 33.56 (C-5'), 35.45 (C-7″), 43.71 (C-7), 45.19 (C-2'), 57.36 (C-1'), 126.03 (C-4″), 128.35 (C-2″, C-6″), 128.60 (C-3″, C-5″), 140.33 (C-1″), 171.49 (C-2); IR (KBr, cm^{-1}) 3 436 (ν (NH)), 1 644 (ν (C=N)). Anal. $C_{18}H_{27}N_2Cl$ (C, H, N).

*5.1.6.5. 2-[(*cis*-2-Cyclopentylcyclopentyl)-imino]hexahydroazepine hydrobromide* **5e** *HBr*

(1'R, 2'R)-**5e** HBr: m.p. 227–229 °C decomposition, $[\alpha]_D^{25}$ –55.4°; (1'S, 2'S)-**5e** HBr: m.p. 227–229 °C de-

composition, $[\alpha]_D^{25}$ +55.4°; ^{1}H-NMR ($CDCl_3$) δ 1.00–1.22 (m, 2H, H-2″b, H-5″b), 1.37–2.12 (m, 20H, 3″-CH_2, 4″-CH_2, H-4'b, H-4b, H-5″a, 6-CH_2, H-5b, H-2″a, H-3'b, H-4a, H-2', H-4'a, H-5'b, H-5a, H-3'a, H-1″, H-5'a), 2.64 (mc, 2H (E), 3-CH_2), 2.92 (dd, 1H (Z), 14.2, 9.3, H-3b), 3.15 (dd, 1H (Z), 14.3, 7.9, H-3a), 3.37 (dd, 2H (E), 10.0, 5.4, 7-CH_2), 3.42–3.65 (m, 2H (Z), 7-CH_2), 3.92 (mc, 1H (E), H-1'), 4.44 (mc, 1H (Z), H-1'), 8.76 (d, 1H (Z), 9.3, $^+NH_{exo}$), 9.16 (t, 1H (Z), 5.0, NH_{endo}), 9.23 (d, 1H (E), 8.3, $^+NH_{exo}$), 10.03 (s (br), 1H (E), NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**5e** HBr: 22.38 (C-4'), 23.92 (C-4), 25.27 (C-4″$^{\#}$), 25.40 (C-3″$^{\#}$), 28.28 (C-6), 29.13 (C-3'), 29.74 (C-5), 31.85 (C-5″*), 31.83 (C-3), 32.40 (C-2″*), 32.66 (C-5'), 39.79 (C-1″), 43.72 (C-7), 49.88 (C-2'), 56.85 (C-1'), 168.01 (C-2); **E-5e** HBr: 21.45 (C-4'), 23.04 (C-4), 25.11 (C-4″$^{\#}$), 25.14 (C-3″$^{\#}$), 26.69 (C-3), 27.71 (C-6), 28.12 (C-3'), 29.74 (C-5), 31.74 (C-5″*), 32.26 (C-2″*), 34.46 (C-5'), 39.94 (C-1″), 43.87 (C-7), 50.90 (C-2'), 58.60 (C-1'), 171.37 (C-2); IR (KBr, cm^{-1}) 3 433 (ν (NH)), 1 644 (ν (C=N)). Anal. $C_{16}H_{29}N_2Br$ (C, H, N).

*5.1.6.6. 2-[(*cis*-2-Cyclohexylmethylcyclopentyl)-imino]hexahydroazepine hydrobromide* **5f** *HBr*

(1'R, 2'R)-**5f** HBr: m.p. 217–218 °C, (1'R, 2'R)-**5f**: $[\alpha]_D^{25}$ +27.3° (free base); (1'S, 2'S)-**5f** HBr: m.p. 216–217 °C, $[\alpha]_D^{25}$ –41.0°; **5f** HCl: ^{1}H-NMR ($CDCl_3$) δ 0.66–0.90 (m, 2H, H-2″b, H-6″b), 0.98–1.28 (m, 6H, H-3″b, H-4″b, H-5″b, H-1″, 7″-CH_2), 1.36–1.89 (m, 16H, H-4'b, H-5b, H-3″a, H-4″a, H-5″a, H-3'b, 4-CH_2, 6-CH_2, H-2″a, H-6″a, H-5a, H-3'a, H-4'a, H-5'b), 1.96 (mc, 1H, H-5'a), 2.19–2.32 (m, 1H, H-2'), 2.58–2.65 (m, 2H (E), 3-CH_2), 2.73–2.86 (m, 1H (Z), H-3b), 3.04–3.17 (m, 1H (Z), H-3a), 3.32–3.47 (m, 1H (Z) + 2H (E), H-7b (Z), 7-CH_2 (E)), 3.49–3.61 (m, 1H (Z), H-7a), 3.86 (mc, 1H (E), H-1'), 4.31 (mc, 1H (Z), H-1'), 9.44 (d, 1H (Z), 8.6, $^+NH_{exo}$), 9.53 (d, 1H (E), 8.6, $^+NH_{exo}$), 9.59, (t, 1H (Z), 5.0, NH_{endo}), 10.15 (t, 1H (E), 5.0, NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**5f** HBr: 22.00 (C-4'), 24.11 (C-4), 26.22 (C-3″*), 26.31 (C-5″*), 26.52 (C-4″), 28.32 (C-6), 29.69 (C-3'), 29.83 (C-5), 31.14 (C-5'), 31.41 (C-3), 32.69 (C-2″$^{\#}$), 34.39 (C-6″$^{\#}$), 35.97 (C-1″), 36.45 (C-7″), 39.44 (C-2'), 43.66 (C-7), 56.72 (C-1'), 167.93 (C-2); **E-5f** HBr: 21.23 (C-4'), 22.93 (C-4), 26.22 (C-3″*), 26.31 (C-5″*), 26.39 (C-4″, C-3), 27.69 (C-6), 28.66 (C-3'), 30.07 (C-5), 32.85 (C-2″$^{\#}$), 33.31 (C-5'), 34.03 (C-6″$^{\#}$), 36.06 (C-1″), 37.01 (C-7″), 41.16 (C-2'), 43.81 (C-7), 58.81 (C-1'), 171.39 (C-2); **5f** HBr: IR (KBr, cm^{-1}) 3 440 (ν (NH)), 1 650 (ν (C=N)); (1'R, 2'R)-**5f** HBr Anal. $C_{18}H_{33}N_2Br$ (H, N); C: calcd, 60.50; found, 59.67; (1'S, 2'S)-**5f** HBr Anal. $C_{18}H_{33}N_2Br$ (H, N); C: calcd, 60.50; found, 59.77.

*5.1.6.7. 3-[(*cis*-2-Isopropylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrochloride* **6a** *HCl*

(1'R, 2'R)-**6a** HCl: m.p. 229–231 °C decomposition, $[\alpha]_D^{25}$ –103.3°; (1'S, 2'S)-**6a** HCl: m.p. 226–228 °C decomposition, $[\alpha]_D^{25}$ +107.5°; ^{1}H-NMR ($CDCl_3$) δ 0.84 (d, 3H (Z), 6.6, 3″-CH_3*), 0.86 (d, 3H (E), 6.8, 3″-CH_3*), 0.90 (d, 3H (Z), 6.4, 2″-CH_3*), 0.93 (d, 3H (E), 6.4, 2″-CH_3*), 1.48–2.10 (m, 16H, H-4'b, H-2', H-8a$^{\#}$, H-5'b, 5-$CH_2^{\#}$, 6-CH_2, 7-CH_2, H-8b$^{\#}$, 3'-CH_2, H-4'a, H-1″, H-5'a), 3.14 (mc, 1H (E), H-4), 3.80 (s (br), 1H (Z) + 1H (E), H-4 (Z), H-1 (E)), 3.99 (mc, 1H (E), H-1'), 4.00 (s (br), 1H (Z), H-1), 4.37 (mc, 1H (Z), H-1'), 9.50 (d, 1H (Z), 9.3, NH_{exo}), 9.77 (d, 1H (E), 9.0, NH_{exo}), 10.35 (s (br), 1H (E), NH_{endo}), 10.52 (d, 1H (Z), 6.0, NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**6a** HCl: 22.01 (3″-CH_3*), 22.06 (C-4'), 22.09 (2″-CH_3*), 22.87 (C-5$^{\#}$), 23.54 (C-8$^{\#}$), 26.78 (C-6, C-7), 27.77 (C-3'), 28.06 (C-1″), 31.33 (C-4), 33.19 (C-5'), 45.97 (C-1), 51.78 (C-2'), 55.42 (C-1'), 167.66 (C-3), **E-6a** HCl: 21.02 (C-4'), 21.74 (3″-CH_3*), 21.83 (2″-CH_3*), 23.02 (C-5$^{\#}$), 23.07 (C-8$^{\#}$), 25.91 (C-7§), 26.35 (C-6§), 26.99 (C-3'), 28.06 (C-1″), 28.36 (C-4), 34.81 (C-5'), 46.32 (C-1), 52.08 (C-2'), 56.54 (C-1'), 170.52 (C-3); IR (KBr, cm^{-1}) 3 435 (ν (NH)), 1 665 (ν (C=N)). Anal. $C_{15}H_{27}N_2Cl$ (C, H, N).

*5.1.6.8. 3-[(*cis*-2-Phenylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrochloride* **6b** *HCl*

(1'R, 2'R)-**6b** HCl: m.p. 255–257 °C decomposition, $[\alpha]_D^{25}$ +96.3°; (1'S, 2'S)-**6b** HCl: m.p. 256–258 °C decomposition, $[\alpha]_D^{25}$ –94.2°; ^{1}H-NMR ($CDCl_3$) δ 0.72 (mc, 1H, H-8b$^{\#}$), 0.92 (mc, 1H, H-7b*), 1.34 (mc, 2H, H-8a$^{\#}$, H-7a*), 1.46–1.72 (m, 5H, 5-CH_2, 6-CH_2, H-4'b), 1.98–2.16 (m, 2H, H-3'b, H-4'a), 2.16–2.41 (m, 3H, H-3'a, 5'-CH_2), 2.55 (s (br), 1H (E), H-4), 3.16 (mc, 1H (E), H-2'), 3.26 (s (br), 1H (Z), H-4), 3.65 (ddd, 1H (Z), 11.7, 7.5, 7.5, H-2'), 3.72 (s (br), 1H (Z + E), H-1), 4.04 (mc, 1H (E), H-1'), 4.78 (mc, 1H (Z), H-1'), 7.12–7.37 (m, 3H (Z) + 5H (E), H-3″, H-4″, H-5″ (Z), H -2″, H-3″, H-4″, H-5″, H-6″ (E)), 7.62 (d, 2H (Z), 7.1, H-2″, H-6″), 9.84 (d, 1H (Z), 9.3, NH_{exo}), 9.92 (d, 1H (E), 3.8, NH_{endo}), 10.05 (d, 1H (E), 10.6, NH_{exo}), 10.16 (d, 1H (Z), 3.8, NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**6b** HCl: 22.52 (C-8$^{\#}$), 23.07 (C-5$^{\#}$), 24.25 (C-4'), 26.28 (C-7*), 26.37 (C-6*), 31.19 (C-4), 32.00 (C-3'), 32.08 (C-5'), 45.51 (C-1), 49.86 (C-2'), 55.73 (C-1'), 126.24 (C-4″), 127.54 (C-3″, C-5″), 129.93 (C-2″, C-6″), 139.84 (C-1″), 166.74 (C-3), E-**6b** HCl: 21.91 (C-8$^{\#}$), 24.25 (C-4'), 26.05 (C-7*), 26.20 (C-6*), 28.62 (C-4), 30.95 (C-3'), 32.64 (C-5'), 46.32 (C-1), 51.83 (C-2'), 59.02 (C-1'), 127.10 (C-4″), 128.44 (C-3″, C-5″), 129.14 (C-2″, C-6″), 138.74

(C-1″), 170.54 (C-3); C-5[#] (E) hidden; IR (KBr, cm^{-1}) 3 435 (ν (NH)), 1 656 (ν (C=N)). Anal. $C_{18}H_{25}N_2Cl$ (C, H, N).

*5.1.6.9. 3-[(*cis*-2-Cyclohexylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrobromide* **6c** *HBr*

(1'R, 2'R)-**6c** HBr: m.p. 227–228 °C decomposition, $[\alpha]_D^{25}$ –59.6°; (1'S, 2'S)-**6c** HBr: m.p. 225–227 °C decomposition, $[\alpha]_D^{25}$ +61.1°; ^{1}H-NMR ($CDCl_3$) δ 0.87 (mc, 2H, H-2″b, H-6″b), 1.01–1.28 (m, 3H, H-3″b, H-4″b, H-5″b), 1.38–2.05 (m, 21H, H-1″, H-4'b, H-2″a, H-8b, H-2', H-3″a, H-4″a, H-5″a, 5-CH_2, 6-CH_2, 7-CH_2, H-5'b, H-6″a, H-8a, H-3'b, H-4'a, H-3'a, H-5'a), 3.12 (s (br), 1H (E), H-4), 3.83 (s (br), 1H (Z) + 1H (E), H-4 (Z), H-1 (E)), 3.92 (s (br), 1H (E), H-1'), 4.00 (s (br), 1H (Z), H-1), 4.40 (mc, 1H (Z), H-1'), 8.86 (d, 1H (Z), 9.8, $^+NH_{exo}$), 9.20 (d, 1H (E), 8.8, $^+NH_{exo}$), 9.94 (s (br), 1H (Z), NH_{endo}), 10.02 (s (br), 1H (E), NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**6c** HBr: 21.89 (C-4'), 22.76 (C-5[◊]), 23.71 (C-8[◆]), 25.86 (C-3″[§]), 26.05 (C-5″[§]), 26.33 (C-4″), 26.68 (C-6[#]), 26.78 (C-7[#]), 27.30 (C-3'), 31.83 (C-4), 32.24 (C-2″*), 32.61 (C-6″*), 32.79 (C-5'), 37.57 (C-1″), 46.00 (C-1), 50.40 (C-2'), 55.24 (C-1'), 167.69 (C-3); E-**6c** HBr: 20.73 (C-4'), 23.04 (C-5[◆]), 23.12 (C-8[◆]), 25.67 (C-3″[#]), 25.71 (C-5″ [#]), 26.19 (C-4″), 28.65 (C-4), 32.07 (C-2″*), 32.37 (C-6″*), 34.39 (C-5'), 37.03 (C-1″), 46.46 (C-1), 50.62 (C-2'), 56.19 (C-1'), 170.46 (C-3); C-6 (E), C-7 (E), C-3' (E) hidden; IR (KBr, cm^{-1}) 3 429 (ν (NH)), 1 657 (ν (C=N)). Anal. $C_{18}H_{31}N_2Br$ (C, H, N).

*5.1.6.10. 3-[(*cis*-2-Benzylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrochloride* **6d** *HCl*

(1'R, 2'R)-**6d** HCl: m.p. 244–246 °C decomposition, $[\alpha]_D^{25}$ +5.5°; (1'S, 2'S)-**6d** HCl: m.p. 243–245 °C decomposition, $[\alpha]_D^{25}$ –5.5°; ^{1}H-NMR ($CDCl_3$) δ 1.32–1.72 (m, 11H, H-4'b, H-7b*, 6-CH_2*, H-7a*, 3'-CH_2, 5-CH_2, 8-CH_2), 1.72–1.86 (m, 1H, H-4'a), 1.92 (mc, 1H, H-5'a), 2.03 (mc, 1H, H-5'b), 2.34 (m, 1H (E), H-2'), 2.49 (mc, part B, 1H (Z + E) + 1H (Z), J_{AB} = 17.7, H-7″b (Z + E), H-2' (Z)), 2.80 (m, 1H (E), H-4), 2.92 (part A, 1H (Z + E), J_{AB} = 17.7, H-7″a), 3.63 (s (br), 1H (Z), H-4), 3.74 (s (br), 2H (E), H-1, H-1'), 3.90 (s (br), 1H (Z), H-1), 4.35 (mc, 1H, H-1'), 7.02–7.09 (m, 1H, H-4″), 7.09–7.21 (m, 4H, H-2″, H-3″, H-5″, H-6″), 9.86 (d, 1H (Z + E), 8.8, NH_{exo}), 10.13 (s (br), 1H (E), NH_{endo}), 10.48 (d, 1H (Z), 4.0, NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**6d** HCl: 22.49 (C-4'), 23.12 (C-8[#]), 23.42 (C-5[#]), 26.66 (C-7*), 26.75 (C-6*), 29.56 (C-3'), 31.87 (C-5'), 31.49 (C-4), 35.21 (C-7″), 44.10 (C-2'), 46.02 (C-1), 56.05 (C-1'), 125.56 (C-4″), 128.04 (C-2″, C-6″), 128.71 (C-3″, C-5″), 141.08 (C-1″), 167.79 (C-3); E-**6d** HCl: 21.49 (C-4'), 22.20 (C-8[#]), 23.12 (C-5[#]), 25.80 (C-7*), 26.47 (C-6*), 28.32 (C-4), 29.08 (C-3'), 33.87 (C-5'), 35.33 (C-7″), 45.17 (C-2'), 46.39 (C-1), 56.58 (C-1'), 126.06 (C-4″), 128.23 (C-2″, C-6″), 128.42 (C-3″, C-5″), 140.32 (C-1″), 170.61 (C-3); IR (KBr, cm^{-1}) 3 440 (ν (NH)), 1 642 (ν (C=N)). Anal. $C_{19}H_{27}N_2Cl$ (C, H, N).

*5.1.6.11. 3-[(*cis*-2-Cyclopentylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrobromide* **6e** *HBr*

(1'R, 2'R)-**6e** HBr: m.p. 211–212 °C, $[\alpha]_D^{25}$ –47.6°; (1'S, 2'S)-**6e** HBr: m.p. 209–211 °C, $[\alpha]_D^{25}$ +49.2°; ^{1}H-NMR ($CDCl_3$) δ 1.02–1.23 (m, 2H, H-2″b, H-5″b), 1.36–2.10 (m, 22H, 3″-CH_2, 4″-CH_2, H-4'b, H-5″a*, H-8b[#], 5-CH_2[#], 6-CH_2, 7-CH_2, H-2″a*, H-5b, H-8a[#], 3'-CH_2, H-2', H-4'a, H-1″, H-5'a), 3.13 (s (br), 1H (E), H-4), 3.79 (s (br), 1H (Z) + 1H (E), H-4 (Z), H-1 (E)), 3.94 (mc, 1H (E), H-1'), 4.01 (s (br), 1H (Z), H-1), 4.36 (mc, 1H (Z), H-1'), 8.97 (d, 1H (Z), 9.6, $^+NH_{exo}$), 9.34 (d, 1H (E), 7.9, $^+NH_{exo}$), 9.92 (s (br), 1H (Z), NH_{endo}), 9.97 (s (br), 1H (E), NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**6e** HBr: 22.34 (C-4'), 22.99 (C-5[§]), 23.47 (C-8[§]), 25.20 (C-4″[#]), 25.34 (C-3″[#]), 26.76 (C-6, C-7), 29.10 (C-3'), 31.82 (C-4, C-5″*), 32.36 (C-2″*), 32.67 (C-5'), 40.03 (C-1″), 46.01 (C-1), 50.05 (C-2'), 56.39 (C-1'), 167.56 (C-3); E-**6e** HBr: 21.31 (C-4'), 23.08 (C-5, C-8), 25.02 (C-3″, C-4″), 26.06 (C-7[#]), 26.37 (C-6[#]), 27.90 (C-3'), 28.57 (C-4), 31.67 (C-5″*), 32.12 (C-2″*), 34.55 (C-5'), 40.03 (C-1″), 46.49 (C-1), 50.73 (C-2'), 57.73 (C-1'), 170.43 (C-3); IR (KBr, cm^{-1}) 3 444 (ν (NH)), 1 663 (ν (C=N)). Anal. $C_{17}H_{29}N_2Br$ (C, H, N).

*5.1.6.12. 3-[(*cis*-2-Cyclohexylmethylcyclopentyl)imino]-2-azabicyclo[2.2.2]octane hydrobromide* **6f** *HBr*

(1'R, 2'R)-**6f** HBr: m.p. 233–234 °C, $[\alpha]_D^{25}$ +37.9°; (1'S, 2'S)-**6f** HBr: m.p. 233–234 °C, $[\alpha]_D^{25}$ –37.8°; ^{1}H-NMR ($CDCl_3$) δ 0.78–0.89 (m, 2H, H-2″b, H-6″b), 1.00–1.32 (m, 6H, H-3″b, H-4″b, H-5″b, H-1″, H-7″b, H-7″a), 1.49 (mc, 1H, H-4'b), 1.49–1.89 (m, 17H, H-3'b, H-3″a, H-4″a, H-5″a, H-8b*, H-2″a, H-6″a, 5-CH_2*, 6-CH_2, 7-CH_2, H-8a*, H-3'a, H-4'a, H-5'b), 1.99 (mc, 1H, H-5'a), 2.22 (mc, 1H, H-2'), 3.08 (s (br), 1H (E), H-4), 3.71 (s(br), 1H (Z), H-4), 3.80 (s (br), 1H (E), H-1), 3.87 (mc, 1H (E), H-1'), 3.99 (s (br), 1H (Z), H-1), 4.27 (mc, 1H (Z), H-1'), 9.03 (d, 1H (Z), 9.3, $^+NH_{exo}$), 9.26 (d, 1H (E), 9.0, $^+NH_{exo}$), 9.92 (d, 1H (Z + E), 3.7, NH_{endo}); ^{13}C-NMR ($CDCl_3$) δ Z-**6f** HBr: 22.09 (C-4'), 23.04 (C-5*), 23.66 (C-8*), 26.28 (C-3″, C-5″), 26.53 (C-4″), 26.69 (C-7[#]), 26.84 (C-6[#]), 29.79 (C-3'), 31.27 (C-5'), 31.78 (C-4), 32.82 (C-6″ [§]), 34.28 (C-2″ [§]), 35.98 (C-1″), 36.63 (C-7″), 39.88 (C-2'), 45.98 (C-1), 56.62 (C-1'), 167.72 (C-3); E-**6f** HBr: 21.28 (C-4'), 23.04 (C-5*), 23.66 (C-8*), 26.28 (C-3″, C-5″), 26.40 (C-4″), 26.69 (C-7[#]), 26.84 (C-6[#]), 28.57 (C-4), 28.72 (C-3'), 32.94

(C-6″ §), 33.36 (C-5'), 34.02 (C-2″ §), 36.11 (C-1″), 37.22 (C-7″), 41.15 (C-2'), 46.52 (C-1), 58.28 (C-1'), 170.53 (C-3); IR (KBr, cm^{-1}) 3 440 (ν (NH)), 1 657 (ν (C=N)). Anal. $C_{19}H_{33}N_2Br$ (C, H, N).

5.1.7. Preparation of cis*-2-substituted cyclopentaneaminesalicylidenes* **7a–f**

The *cis*-2-substituted cyclopentaneaminesalicylidenes **7a–f** were prepared according to a common procedure [16].

5.1.7.1. (1S, 2S)-cis-*Cyclohexylcylopentaneaminesalicylidene (1S, 2S)*-**7c**

88%; m.p. 105–106°; $[\alpha]_D^{25}$ +215°; ^{1}H-NMR ($CDCl_3$) δ 0.81–0.99 (m, 2H, H-6'b, H-2'b), 0.99–1.26 (m, 4H, H-3'b, H-4'b, H-5'b, H-1'), 1.48–1.79 (m, 9H, H-3b, H-3'a, H-4'a, H-5'a, H-2, H-5b, H-6'a*, H-4b, H-2'a*), 1.82–2.01 (m, 3H, H-4a, H-3a, H-5a), 3.79 (t, 1H, 3.8, H-1), 6.85 (dt, 1H, 7.5, 1.1, H-5″), 6.94 (d, 1H, 8.2, H-3″), 7.25 (dt, 1H, 8.3, 1.6, H-4″), 7.29 (dd, 1H, 8.6, 1.8, H-6″), 8.30 (s, 1H, H-α), 13.87 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ 21.82 (C-4), 25.89 (C-5'$^{\#}$), 26.03 (C-3'$^{\#}$), 26.54 (C-4'), 27.55 (C-3), 31.71 (C-6'*), 32.38 (C-2'*), 34.73 (C-5), 37.89 (C-1'), 52.29 (C-2), 70.71 (C-1), 116.94 (C-3″), 118.31 (C-5″), 118.90 (C-1″), 130.99 (C-4″), 131.85 (C-6″), 161.36 (C-2″), 162.20 (C-α); IR (KBr, cm^{-1}) 3 431 (ν (OH)), 1 630 (ν (C=N)). Anal. $C_{18}H_{25}NO$ (C, H, N).

5.1.7.2. (1S, 2S)-cis-*Cyclopentylcylopentaneaminesalicylidene (1S, 2S)*-**7e**

87%; m.p. 84–85°; $[\alpha]_D^{25}$ +242°; ^{1}H-NMR ($CDCl_3$) δ 1.01–1.19 (m, 2H, H-5'b*, H-2'b*), 1.33–1.48 (m, 2H, H-3'b, H-4'b), 1.48–1.80 (m, 9H, H-3'a, H-4'a, H-1', H-5'a*, H-3b, H-5b, H-2, H-4b, H-2'a*), 1.83–2.00 (m, 3H, H-3a, H-4a, H-5a), 3.69 (t, 1H, 4.1, H-1), 6.85 (dt, 1H, 7.6, 1.1, H-5″), 6.93 (d, 1H, 8.2, H-3″), 7.25 (dt, 1H, 7.9, 1.6, H-4″), 7.29 (dd, 1H, 8.2, 1.6, H-6″), 8.30 (s, 1H, H-α), 13.77 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ 22.45 (C-4), 25.09 (C-4'$^{\#}$), 25.21 (C-3'$^{\#}$), 29.10 (C-3), 30.90 (C-5'*), 32.46 (C-2'*), 34.61 (C-5), 41.03 (C-1'), 53.01 (C-2), 72.58 (C-1), 116.95 (C-3″), 118.34 (C-5C″), 118.87 (C-1″), 130.99 (C-4″), 131.86 (C-6″), 161.38 (C-2″), 162.06 (C-α); IR (KBr, cm^{-1}) 3 452 (ν (OH)), 1 631 (ν (C=N)). Anal. $C_{17}H_{23}NO$ (C, H, N).

5.1.7.3. (1S, 2S)-cis-*Cyclohexylmethylcylopentaneaminesalicylidene (1S, 2S)*-**7f**

87%; m.p. 66–67°; $[\alpha]_D^{25}$ +216°; ^{1}H-NMR ($CDCl_3$) δ 0.79–0.92 (m, 2H, H-6'b*, H-2'b*), 1.02–1.29 (m, 6H, H-7'b, H-7'a, H-3'b, H-4'b, H-5'b, H-1'), 1.43–1.79 (m, 8H, H-3b, H-3'a, H-4'a, H-5'a, H-6'a*, H-2'a*, H-4b, H-5b), 1.81–2.00 (m, 3H, H-3a, H-4a, H-5a), 2.00–2.14 (m, 1H, H-2), 3.63 (dt, 1H, 4.9, 1.6, 1-H), 6.85 (dt, 1H, 7.4, 1.1, H-5″), 6.93 (dd, 1H, 8.2, 0.55, H-3″), 7.25 (dt, 1H, 8.2, 1.6, H-4″), 7.29 (dd, 1H, 8.6, 1.6, H-6″), 8.27 (s, 1H, H-α), 13.71 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ 22.39 (C-4), 26.37 (C-3'$^{\#}$), 26.39 (C-5'$^{\#}$), 26.65 (C-4'), 29.86 (C-3), 33.23 (C-2'*), 34.06 (C-6'*), 34.36 (C-5), 36.17 (C-1'), 38.09 (C-7'), 42.78 (C-2), 73.04 (C-1), 116.93 (C-3″), 118.31 (C-5″), 118.86 (C-1″), 130.98 (C-4″), 131.82 (C-6″), 161.36 (C-2″), 162.23 (C-α); IR (KBr, cm^{-1}) 3 447 (ν (OH)), 1 629 (ν (C=N)). Anal. $C_{19}H_{27}NO$ (C, H, N).

5.1.8. Correlation of absolute configuration

A solution of the *cis*-2-substituted cyclopentaneaminesalicylidenes **7a–f** in acetonitrile (c = 10^{-3} M) was measured CD-spectroscopically. λ (nm) (θ). (1S, 2S)-**7a**: 313 (+1 725), 260 (+3 113), 228 (–2 381) [16]; (1S, 2S)-**7b**: 314 (+6 981), 252 (+12 929), 228 (+7 657) [16]; (1S, 2S)-**7c**: 312 (+7 276), 259 (+11 415), 225 (–3 763); (1S, 2S)-**7d**: 311 (+3 469), 252 (+7 811), 220 (–1 649) [16]; (1S, 2S)-**7e**: 311 (+2 864), 255 (+4 077), 225 (–3 664); (1S, 2S)-**7f**: 312 (+2 878), 256 (+3 747), 226 (–2 235).

5.1.9. Determination of enantiomeric excess

The diastereomeric Mosher amides: *cis*-2-substituted cyclopentaneamine-α-methoxy-α-trifluoro-methylphenylacetic acid amides (**8a–f**) and 1-phenylethyl-amine-α-methoxy-α-trifluoromethyl-phenylacetic acid amides (**8p**) were prepared according to a common procedure [16]. The residue was directly used for HPLC and ^{19}F-NMR spectroscopy.

5.1.9.1. HPLC

Twenty microlitres of a 10–20 mg/mL solution of the Mosher amides in ethyl acetate were injected on a Lichrosorb® Si-60 column (5 µm). The flow rate was 2 and 3 mL/min, respectively. The Mosher amides were detected at 260 nm (λ_{max}): retention time (min) major diastereomer/subsidiary diastereomer, α (*ee%*). (R)-**8p** 17.06/22.52, α = 1.32 (98.3%); (S)-**8p**: 21.49/18.76, α = 1.15 (95.8%); (1R, 2R)-**8a**: 9.73–10.26/–* (> 99.0%); (1S, 2S)-**8a**: 12.87–13.40/–* (> 99.0%); (1R, 2R)-**8a** + (1S, 2S)-**8a**$^{\#}$: 9.87–10.40/13.07, α = 1.26; (1R, 2R)-**8b**$^{\blacklozenge}$: 23.11/17.68, α = 1.31 (99.9%); (1S, 2S)-**8b**$^{\blacklozenge}$: 16.80/–* (> 99.0%); (1R, 2R)-**8c**: 2.77–3.54/–* (> 99.0%); (1S, 2S)-**8c**: 4.90/–* (> 99.0%); (1R, 2R)-**8c** + (1S, 2S)-**8c**$^{\#}$: 3.40/4.70, α = 1.38; (1R, 2R)-**8d**$^{\blacklozenge}$: 12.54/–* (> 99.0%); (1S, 2S)-**8d**$^{\blacklozenge}$: 18.19/14.59, α = 1.25 (98.8%); (1R, 2R)-**8e**: 4.90–6.61/–* (> 99.0%); (1S, 2S)-**8e**: 7.64–9.53/–* (> 99.0%); (1R, 2R)-**8e** + (1S, 2S)-**8e**$^{\#}$: 5.40–6.50/8.07–8.30, α = 1.24; (1R, 2R)-**8f**: 5.04–7.14/–*

(> 99.0%); (1S, 2S)-**8f**: 10.00–10.50/–* (> 99.0%); (1R, 2R)-**8f** + (1S, 2S)-**8f**$^{\#}$: 5.91–7.17/9.51–10.90, α = 1.33; *below detection limit (< 0.5%), $^{\#}$artificial mixture; $^{\blacklozenge}$3 mL/min.

5.1.9.2. ^{19}F-NMR

$CDCl_3$, standard: 1,1,2-trichlorotrifluoroethane, δ major diastereomer/subsidiary diastereomer (*ee%*). **8**-(R)-PEA: –64.60/–64.42 (97.9%); **8**-(S)-PEA: –64.42/–64.60 (97.0%); (1R, 2R)-**8a**: –64.72/–* (> 99.0%); (1S, 2S)-**8a**: –64.55/–64.71 (97.4%); (1R, 2R)-**8b**: –65.21/–64.38 (99.0%); (1S, 2S)-**8b**: –64.38/–* (> 99.0%); (1R, 2R)-**8c**: –64.63/–* (> 99.0%); (1S, 2S)-**8c**: –64.58/–* (> 99.0%); (1R, 2R)-**8d**: –64.49/–* (> 99.0%); (1S, 2S)-**8d**: –64.26/–64.49 (98.8%); (1R, 2R)-**8e**: –64.59/–* (> 99.0%); (1S, 2S)-**8e**: –64.53/–* (> 99.0%); (1R, 2R)-**8f**: –64.60/–64.40 (99.6%); (1S, 2S)-**8f**: –64.40/–* (> 99.5%); *below detection limit (< 0.5%).

5.2. Physiology

5.2.1. Cell culture

The effects of semicyclic amidines on insulin secretion, $[Ca^{2+}]_i$ and membrane voltage were tested in the insulin secreting cell line INS-1 [37]. Cells were cultured at a cell density of 250×10^6 cells/L in RPMI 1640 culture medium (GIBCO BRL, Eggenstein, Germany) containing 11 mM glucose and supplemented with 50 µM 2-mercaptoethanol, 1 mM sodiumpyruvate, 10 mM Hepes, 10 0000 IU/L penicillin, 100 mg/L streptomycin and 100 g/L decomplemented foetal calf serum (Seromed, Berlin, Germany). The medium was changed twice a week. Every week cells were trypsinized and re-seeded at the same cell density.

5.2.2. Insulin secretion

For measurements of insulin secretion cells (0.25×10^6 cells per well) were cultured for 2 days in 24-well dishes. After washing the cells with a modified Krebs-Ringer-hydrogen carbonate (KRB) buffer containing (in mM): 136 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 1.0 $CaCl_2$, 1.2 KH_2PO_4, 5.0 $NaHCO_3$, 0.5 glucose, 10.0 Hepes, pH 7.4 and 5 g/L BSA (fraction V, Sigma, Munich, Germany), they were pre-incubated at 37 °C for 30 min in the same buffer and incubated for another 30 min in buffer containing the tested compounds as indicated in each experiment. Insulin released into the supernatant and insulin content of the cells after acidic ethanol (1.5% (v/v) HCl in 75% (v/v) ethanol) extraction was measured by a radio-immunoassay as described previously [38] using rat insulin (Novo Nordisk, Bagsvaerd, Denmark) as standard, rabbit anti-insulin porcine antiserum (Linco, Biotrend, Germany) and ^{125}I-labelled insulin (CIS Diagnostik GmbH, Dreieich, Germany).

5.2.3. Patch clamp measurements

For patch clamp measurements, cells (0.2×10^6 cells) were seeded onto glass coverslips coated with poly-L-Orn (10 mg/L, Sigma, Munich, Germany) and used after 2–5 days of culture in standard culture medium. The coverslip was mounted on the stage of an inverted microscope (Axiovert 10, Zeiss, Germany) and perifused continuously at 37 °C with a solution containing (in mM): 140 NaCl, 5.6 KCl, 1.2 $MgCl_2$, 2.6 $CaCl_2$, 0.5 Glucose and 10.0 Hepes, pH 7.4. A flowing KCl-electrode served as a reference and appropriate corrections for liquid junction voltages were made. The patch clamp pipettes (Clark-Medical, Reading, GB) were pulled automatically (DMZ Universal Puller, Zeitz, Augsburg, Germany) and had an input *R* of 6–8 MΩ. They were filled with a solution containing in (mM): 30 KCl, 95 potassium gluconate, 1.0 $MgCl_2$, 1.2 NaH_2PO_4, 4.8 Na_2HPO_4, 5.0 Na_2ATP, 0.5 Na_2GTP, pH 7.15. After a GΩ seal was achieved, the standard whole cell configuration was obtained by sucking of the membrane underneath the pipette. Membrane voltage (V_m) was measured continuously using the current-clamp-mode of the patch-clamp amplifier (Fröbe, U. and Busche, R., Institute of Physiology of the University of Freiburg, Germany) and was displayed by a pen recorder. After pipette capacitance was compensated, the access conductance (G_a) was measured as previously described [39]. Whole cell conductance (G_m) was calculated from the total conductance (G_t) measured in the voltage clamp mode using the equation $G_m = G_a\ (G_t\ /(G_a - G_t)$.

5.2.4. $[Ca^{2+}]_i$-Measurements

For $[Ca^{2+}]_i$ measurements cells were incubated at room temperature with 2 µmol/L fura-2 AM for 30 min. The fluorescence was monitored with a photomultiplier system at excitation wavelengths of 340, 360 and 380 nm, with a filter rotation rate of 10 per second. As a measure of $[Ca^{2+}]_i$ the fluorescence emission ratio at 340/380 nm excitation was calculated after subtraction of the autofluorescence as described previously [40].

5.2.5. Statistical analysis

Data are presented as mean ± SEM. Student's paired *t*-test (for patch clamp data) or Mann-Whitney U- Wilcoxon Rank Sum W Test (for insulin secretion) ($P < 0.05$) was used for statistical analyses.

Supporting information is available (4 pages).

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