Repaglinide and Related Hypoglycemic Benzoic Acid Derivatives

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The structure−activity relationships in two series of hypoglycemic benzoic acid derivatives (**5**, **6**) were investigated. Series **5** resulted from meglitinide (**3**) when the 2-methoxy was replaced by an alkyleneimino residue. Maximum activity was observed with the *cis*-3,5-dimethylpiperidino (**5h**) and the octamethyleneimino (**5l)** residues. Series **6** resulted from the meglitinide analogon **4** bearing an inversed amido function when the 2-methoxy, the 5-fluoro, and the α-methyl residue were replaced by a 2-piperidino, a 5-hydrogen, and a larger α-alkyl residue, respectively. An alkoxy residue ortho to the carboxy group further increased activity and duration of action in the rat. The most active racemic compound, **6al** (R_4 = isobutyl; R = ethoxy), turned out to be 12 times more active than the sulfonylurea (SU) glibenclamide (**1**). Activity was found to reside predominantly in the (*S*)-enantiomers. Compared with the SUs **1** and **2** (glimepiride), the most active enantiomer, **(*S*)-6al** (AG-EE 623 ZW; repaglinide; ED_{50} = 10 μg/kg po), is 25 and 18 times more active. Repaglinide turned out to be a useful therapeutic for type 2 diabetic patients; approval was granted recently by the FDA and the EMEA. From investigations on the pharmacophoric groups in compounds of type **5** and **6**, it was concluded that in addition to the two already known—the acidic group (COOH; SO_2NH) and the amidic spacer (CONH; NHCO)—the ortho residue R_1 (alkyleneimino; alkoxy; oxo) must be regarded as a third one. A general pharmacophore model suitable for hypoglycemic benzoic acid derivatives, SUs, and sulfonamides is proposed (Figure 6). Furthermore, from superpositions of low-energy conformations (LECs) of **1**, **2**, and **(*S*)-6al**, it was concluded that a common binding conformation (LEC II; Figure 10B) may exist and that differences in binding to the SU receptor and in the mechanism of insulin release between repaglinide and the two SUs may be due to specific hydrophobic differences.

Non-insulin-dependent diabetes mellitus (NIDDM) represents a common heterogeneous metabolic disorder with all its defects (e.g., impaired insulin secretion, diminished peripheral insulin action, increased hepatic glucose output) being present in variable proportions in different individuals.[1] Therapy includes diet and exercise, as well as, upon failure, drug treatment. Agents with different mechanisms of action are available: (i) stimulators/modulators of insulin secretion, (ii) enhancers of insulin action, (iii) inhibitors of hepatic glucose production, or (iv) inhibitors of glucose absorption.[2] Among the sulfonylurea (SU) compounds belonging to group i, e.g., **1** (glibenclamide) and **2** (glimepiride) (Figure 1), glibenclamide is one of the most frequently prescribed agents. One of the thiazolidine-diones of group ii, troglitazone, has recently reached the market. Contrary to the monotherapy with the biguanide metformin of group iii, acarbose of group iv is mostly used as adjunct to SU therapy. The main risks and limitations of the currently available drugs are the following: SU-induced hypoglycemia and weight gain; primary and secondary failure of SUs; metformin-associated lactic acidosis; and acarbose-associated gastrointestinal side effects as well as limited efficacy.[2]

Having in mind the limitations (above all the risk of hypoglycemia[3]) of the SU therapy, we looked for compounds being orally active but structurally different from the SUs which might avoid such risks. The substituted benzoic acids **3** (meglitinide) and **4** (Figure 1), both exhibiting tolbutamide-like hypoglycemic activity, appeared to be useful lead compounds.[4,5] The acidic (COOH in **3** or **4**, SO_2NH in the SUs) and amidic groups (CONH and NHCO, respectively) were regarded as being involved in binding to two putative binding sites of the SU receptor.[6] Meglitinide was reported to stimulate insulin secretion in vitro[7,8,9] and in vivo[4,10] by blocking the K_{ATP} channel of the pancreatic B-cell,[11,12] however less potently than glibenclamide.

Of the structural modifications investigated, replacement of the ortho methoxy group in **3** and **4** by a secondary amino (in contrast to an amino, methylamino, or ethylamino[13]) group was found to lead to an increase in hypoglycemic activity. The structure−activity relationships (SARs) observed in the resulting benzoic acid derivatives of type **5** and **6**, respectively (Figure 2), are presented in this paper.

Chemistry

The benzoic acid derivatives **5** were obtained by condensation of a substituted benzoic acid **9** with a

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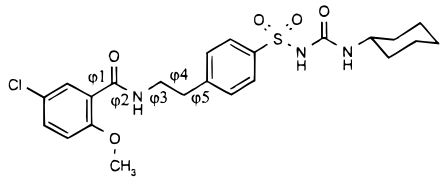
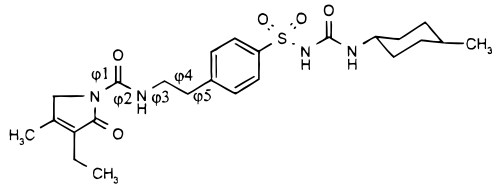
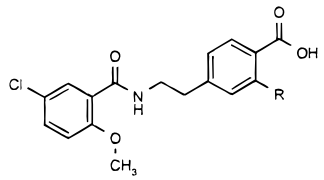


1; glibenclamide

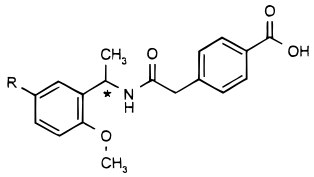


2; glimepiride



3 (R=H); meglitinide

3a (R=OEt); 2-ethoxy-meglitinide

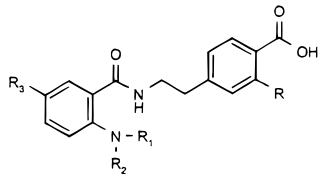


4 (R=F; C*=S)

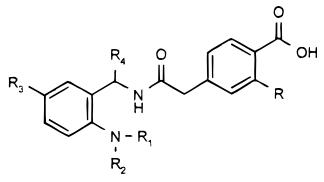
4a (R=Cl; C*=rac)

4b (R=H; C*=rac)

Figure 1. Structural formula of reference compounds **1**, **2**, **3**, **3a**, **4**, **4a**, and **4b**.



5



6

Figure 2. Structural formula of compounds of type **5** and **6**.

substituted 2-phenethylamine **10** (Scheme 1). The educts **9** were obtained mostly from 2-chloro-5-nitrobenzoic acid by reaction with a secondary amine HNR_1R_2, reduction of the nitro group, and replacement of the resulting amino group by a chlorine atom via diazotation and Sandmeyer reaction. The educts **10** were synthesized by catalytic hydrogenation from the corresponding benzylcyanides.[15,16] For the synthesis of the benzoic acid derivatives **6**, a substituted benzylamine **12** (either racemic or enantiomeric) was acylated with a substituted phenylacetic acid **13** (Scheme 2); alternatively, a ketimine **16** was acylated with a substituted phenylacetic acid **13**, and the resulting enamide **(*E*/*Z*)-17** was hydrogenated (Scheme 3). The educts **13** were obtained, analogously to literature procedures,[19] from the corresponding benzylcyanides as described in the Experimental Section. Racemic educts **12** were synthesized according to routes A−D (Scheme 4). Route A was preferred when the addition of a Grignard reagent to nitrile **15** was feasible; otherwise, route B via alkylation of the anion of aldimine **19a** was followed. To introduce R_3═Cl, routes C and D were used. For the synthesis of enantiomeric benzylamines **12**, routes E−I were applied (Scheme 5): resolution of the racemic amine **12q** by means of *N*-acetyl-glutamic acid (E); asymmetric hydrogenation of the *N*-(1-phenethyl)-ketimines **(*S*′)-31** and **(*R*′)-31**, respectively (F); asymmetric hydrogenation of the (*Z*)-*N*-acetyl-enamine **(*Z*)-33** (G); diastereoselective addition of a Grignard reagent to the *N*-(1-phenethyl)-aldimines **(*R*′)-35** and **(*S*′)-35** (H); chromatographic resolution of the diastereomeric *N*-(4-tolyl-sulfinyl)-amines **(*R*,*S*′)-37** and **(*S*,*S*′)-37** (I). The synthesis of **(*S*)-12q** was accomplished best by resolution (E); of the asymmetric routes investigated (F, G, H), route F was the most favorable one. The enantiomers of **12o** were synthesized via routes F and H, respectively.

The absolute configuration of **(+)-12q** was determined as (***S***) by X-ray structure analyses of the diastereomeric salt **(*S*,*S*′)-28** (Figure 3) and of the urea derivative **(*S*,*S*′)-38b** (Figure 4, only structural formula shown). The assignment of (***S***) to **(+)-12o** was based on the X-ray structure analysis of the urea derivative **(*S*,*S*′)-38a** (Figure 4, only structural formula shown) and on the circular dichroism (CD) spectrum[25] of **(+)-12o** being complexed with $[Rh(OAc)_2]_2$ in acetonitrile which resembled those of (***S***)-1-phenethylamine,[26] but not those of (*R*)-1-phenethylamine.[27] For **(−)-12s** and **(+)-12s**, Horeau's method[28] was used to determine the corresponding configurations (***S***) and (***R***), respectively.

Configurational stability of enantiomeric benzylamines **12** and their N-acyl-derivatives was found to be very high as exemplified for (***S***)**-12q** and **(*R*)-34** (see Experimental Section).

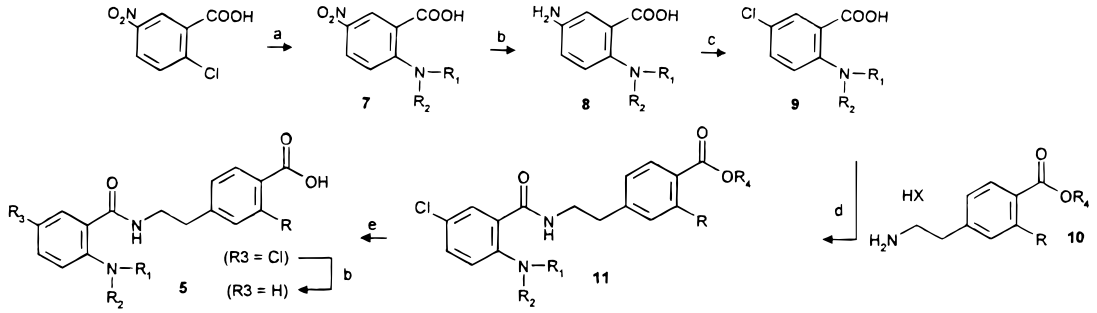
Pharmacology

The novel compounds were administered orally to adult fasted female rats. Blood glucose was monitored hourly up to 4 h after administration in comparison with a control group ($N = 7$). Statistical significance was checked with Student's t-test ($P \leq 0.05$). The maximum percentage decrease of blood sugar (ΔBG) observed within 4 h was taken as the measure for a compound's blood sugar lowering activity. For the most interesting compounds, ED_{50} values were calculated.

Structure−Activity Relationships

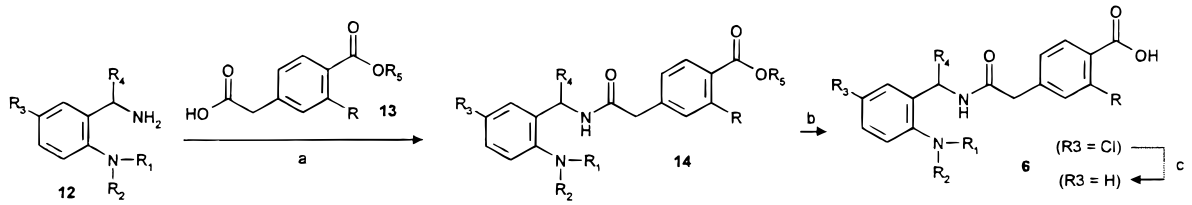
With regard to the NR_1R_2 residue in the substituted benzoic acid derivatives of type **5** (Table 1), the activity

Scheme 1.[a] Synthesis of Benzoic Acid Derivatives **5**



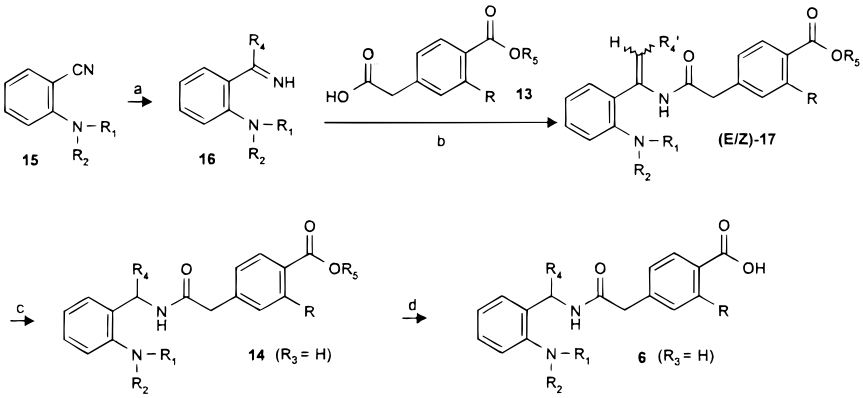
[a] (a) HNR_1R_2; (b) H_2/Pd-C; (c) (i) HCl/$NaNO_2$, (ii) copper powder; (d) $SOCl_2$ or CDI[14]; (e) KOH or NaOH.

Scheme 2.[a] Synthesis of Benzoic Acid Derivatives **6**



[a] (a) $SOCl_2$ or CDI[14] or $Ph_3P/CCl_4/NEt_3$[17] or *N,N′*-DCCD[18]; (b) NaOH; (c) H_2/Pd-C.

Scheme 3.[a] An Alternative Route to Benzoic Acid Derivatives **6**



[a] (a) (i) $R_4MgBr(Cl)$, toluene/THF, reflux; (ii) saturated aqueous NH_4Cl/concentrated ammonia; (b) CDI[14] or $Ph_3P/CCl_4/NEt_3$[15] or *N,N′*-DCCD[18]; (c) H_2/Pd-C, EtOH; (d) NaOH.

of the dimethylamino and diethylamino compounds **5a** and **5b**, respectively, is not improved with larger dialkylamino groups (not shown here) but slightly increased with $N(Me)R_2$ groups in which R_2 is changed to a cyclohexyl, phenyl, or benzyl residue (not shown here). However, activity is strongly increased with alkyleneimino groups $N(CH_2)_{5-9}$ (**5d**, **5j**, **5k**, **5l**, **5p**) culminating in the octamethyleneimino compound **5l** which was found to be almost equipotent with glibenclamide. Dechlorination (**5m**) or substituting R═H for methoxy (**5n**) or ethoxy (**5o**) results in decreased activity. Interestingly, methyl groups on the piperidino ring (**5d**) exert quite different effects: unfavorable in 2-, 4-, and *trans*-3,5- (**5e**, **5g**, **5i**), favorable in 3- (**5f**), and very favorable in *cis*-3,5-position (**5h**). The latter (**5h**) and the octamethyleneimino compound (**5l**) are almost equipotent, probably because their NR_1R_2 residues are similar with respect to conformation and space demand. What is not shown here: Replacement of R_3═Cl by other substituents (fluoro, bromo, iodo, methyl, ethyl, methoxy, cyano) also results in active but not superior compounds, and displacement of R_3═Cl to other positions on the benzene ring decreases the activity ($5 > 4 \approx 3 \gg 6$).

With regard to substituted benzoic acid derivatives of type **6.1** (Table 2) having R_4 = Me and R_{4a} = H (**6a**−**6e**, **6j**−**6t**), highest activity resides in compound **6e** (NR_1R_2 = piperidino, R_3 = H; ED_{50} = 0.3 mg/kg). Activity is strongly reduced if a (R_3) chloro (**6d**) or a (R_{4a}) methyl (**6g**) is added, if the (R_4) methyl (**6i**) is omitted, or if the piperidino residue is substituted by one or two methyl groups (**6k**, **6m**, **6n, 6o**). The following is not shown here: Compared with R_3 = H (**6e**), not only chloro but also further (R_3) substituents (bromo, methyl, hydroxy, methoxy, benzyloxy, nitro, amino, dimethylamino, acetylamino, benzoylamino) decrease or abolish activity.

Starting from compound **6e**, we examined the SARs in the benzoic acid derivatives of type **6.2** (Table 3) with respect to the substituents (R_4, R) and to chirality. The activity of the racemic compounds with R = H (**6e**, **6u**−**6ad**) depends on R_4. Activity is low for an isopropyl (**6w**), cyclohexyl (**6aa**), benzyl (**6ac**), or phenethyl (**6ad**) group, moderate for a phenyl (**6ab**), methyl (**6e**), ethyl (**6n**), or *n*-butyl (**6x**) group, and good for the *n*-propyl (**6v**) or isobutyl (**6y**) group. Activity is further increased if R = H is replaced for an ethoxy or methoxy group

(**6ae**, **6ah**−**6aj**, **6al**−**6an**, **6ap**, **6av**); interestingly, the duration of action is prolonged simultaneously as illustrated for compounds **6ah**/**6ai** versus **6v** (Table 4, Figure 5). However, as already mentioned above, the same R groups (ethoxy, methoxy) decreased activity in compounds of type **5** (**5n**/**5o** versus **5l**; Table 1). Compound **6al** (R_4 = isobutyl, R = ethoxy; AG-EE 388 ZW) turned out to exhibit maximum activity (ED_{50} = 22 μg/kg) and a long duration of action (>4 h after 30 μg/kg). The isobutyl group in **6al** can be mimicked to some extent by cycloalkylmethyl groups (**6aq**−**6au**), best with respect to potency by cyclopropylmethyl (**6aq**), and best with respect to duration of action (not shown) by cyclohexylmethyl (**6at**).

As one could already suggest from the higher activity of **6e** in comparison to **6g** (Table 2), chirality is highly important for the hypoglycemic activity of compounds of type **6.2** (Table 3). The enantioselectivity observed ($S \gg R$) is in accordance with that reported for the lead compound **4**.[5] The most potent enantiomer, (***S***)-**6al** (AG-EE 623 ZW; repaglinide, ED_{50} = 10 μg/kg), is ≥100 times more active than the antipode, (***R***)-**6al** (AG-EE 624 ZW). Compared with the SUs glibenclamide (**1**, ED_{50} = 255 μg/kg) and glimepiride (**2**, ED_{50} = 182 μg/kg), repaglinide is 25 and 18 times more active. The blood sugar lowering effects of (***S***)-**6al** in rats and dogs are described in more detail elsewhere.[33] Clinically, repaglinide turned out to be an efficious and surprisingly short acting therapeutic for type 2 diabetic patients;[34] approval was granted recently by the FDA and the EMEA. The enantiomer (***S***)-**6am** was used to synthesize **[^{3}H]-(*S*)-6al** (not described here).

Investigations on a General Pharmacophore Model for Hypoglycemic Benzoic Acid Derivatives and Sulfonylureas[35,36]

To gain information beyond that already published[5,6,9,21] about the pharmacophoric groups of hypoglycemic benzoic acid derivatives and SU compounds, we have investigated how important specific residues, positions, and spacers are. For this purpose, compounds of type **5.1** (Table 5) and of type **6.3** to **6.7** (Tables 6−10) were examined.

(a) Replacement of (R_1) alkyleneimino or (W) carboxy in **5l** (Table 5) and **6v** (Table 6) for a hydrogen atom resulted in loss or drastic decrease of activity (**39**, **40**; **42**, **43**). Replacement of R_2 = Cl in **5l** (Table 5) or **41** (Table 6) for a hydrogen atom decreased (**5m**) or increased (**6v**) activity. Replacement of R_2 = H in **5l** or **6v** for an ethoxy group decreased (**5o**) or increased (**6ai**) activity. As already mentioned (Table 3), activity of type **6.3** compounds resides in the (***S***)-enantiomers.

(b) Displacement of compound **6e**'s (Table 7) 2′-piperidino group to the 3′-position (**44**) or of its 4-carboxy group to the 3-position (**46**) led to 100-fold lower activity. For the respective 4′-piperidino (**45**) and the 2-carboxy (**47**), no activity was detected at 25 mg/kg.

(c) Replacement of the 4-carboxy group in **6e** (Table 8) by residues which might serve as (bio)isosteric substitutes resulted in a 10-fold lower activity for the substituted SU residue (**50**) or in loss of activity for the tetrazolo (**48**) and sulfonamido (**49**) residue at the doses tested.

(d) Replacement of the amido spacer −NH−CO− in **6e** (Table 9) by the inversed amido spacer −CO−NH− (**51**) led to diminished activity; for the −NH−SO_2− spacer (**52**), no activity was detected at 25 mg/kg.

(e) Modifications of the R_1 residue and of the −NH−CO− spacer in **6v** (Table 10) were also examined. For R_1 residues differing in lipophilicity and space demand, a potency ranking order was found: piperidino (**6v**) > methoxy (**56**) > cyclohexene-1-yl (**54**) ≥ cyclohexyl (**53**) > phenyl (**55**) ≈ H (**42**). For the spacers −NH−CS− (**58**), −NMe-CO− (**57**), and −CH_2−CO− (**60**), activity was ≥10-fold lower; for the spacers −NH−CH_2− (**59**) and −CH_2−CH_2− (**61**), no activity was detected at the doses tested.

We conclude the following from the above investigations: (i) In addition to the two well-known pharmacophoric groups, the acidic group W (COOH; SO_2NH) and the amidic spacer (CONH; NHCO), the residue R_1 (alkyleneimino; alkoxy; oxo) must be regarded as an important third one. (ii) Within the amidic spacer, the oxo part seems to be more important than the imino part (**60** > **59**), possibly for enabling hydrogen bonding to a distinct H-donor on the SU receptor site. (iii) The residues R, R_2, and most strongly, R_3 seem to modify activity; a distinct R or R_2 residue can exert opposite effects in type **5** and type **6** compounds. (iv) In summary, a general pharmacophore model containing three pharmacophoric groups is proposed (Figure 6).

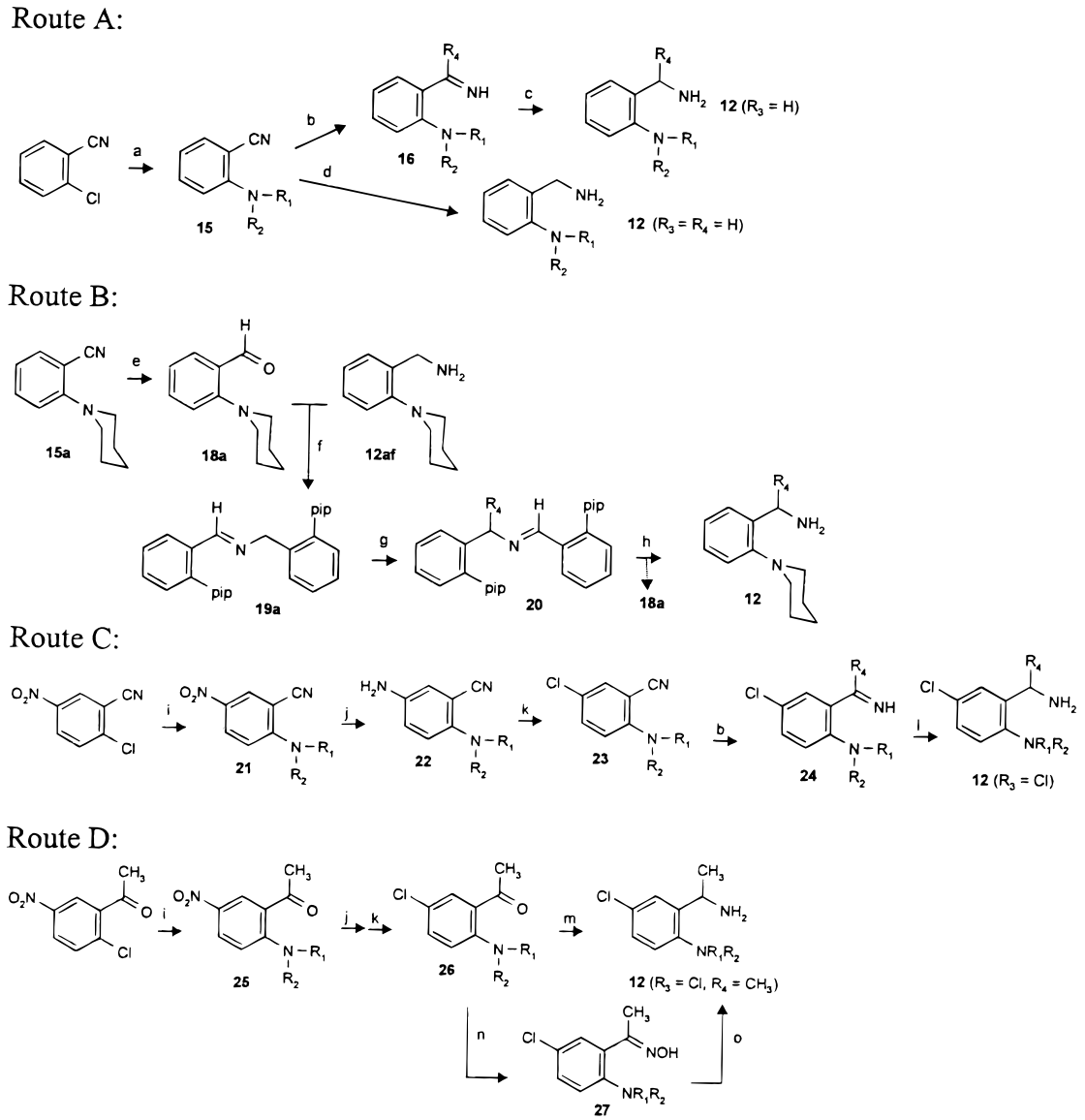
Investigations on Potential Binding Conformations of (*S*)-6al (REP), 1 (GLIB), and 2 (GLIM)[37,38]

REP and the SUs GLIB and GLIM (Figures 1 and 7) are binding to the SU receptor, yet differences in the binding modi[39] and the mechanisms of action,[40] at least between REP and GLIB, have been reported. On the basis of the pharmacophore model (Figure 6) which we suggest to be valid also as a model for receptor binding, we sought to gain insight into the structural basis for these differences. Therefore, we examined the X-ray structures of REP (Figure 8), GLIB,[41] and GLIM (Figure 9) and analyzed conformational space and hydrophobic and electrostatic potentials. Furthermore, and without considering potential binding sites, we performed calculations on conformational analysis and energy optimizations of selected conformations in vacuo.

By conformational analysis, several low-energy conformations (LECs) were determined, three for REP (I, II, III), two for GLIB (I, II), and two for GLIM (I, II). The minimum conformations I (LECs I) were found to be identical with the conformations observed in the crystalline state. The LECs II and III differ from the corresponding LECs I by less than 3 kcal/M (Table 11). All LECs have to be considered as potential binding conformations.

In contrast to prior analysis of conformational space described for hypoglycemic agents (i.a. for repaglinide),[42] we were considering the common pharmacophoric groups derived by SAR and have performed the superposition of different LECs in order to optimally fit the central phenylene rings and the highly important acidic groups of each molecule. The LECs observed in the crystalline state (REP-I, GLIB-I, GLIM-I) did not significantly overlap (Figure 10A). The torsion angles φ1 to φ5 (Figures 1 and 7) of REP-II, GLIB-II, and GLIM-II were found to be rather similar, whereas those of REP-III

Scheme 4.[a] Synthetic Routes A–D to Racemic Substituted Benzylamines **12**



[a] (a) HNR_1R_2/HC(O)NR_1R_2, 120–140 °C; (b) (i) $R_4MgBr(Cl)$, toluene/THF, reflux; (ii) saturated aqueous NH_4Cl/concentrated ammonia; (c) H_2/Raney-Ni, NH_3/MeOH, or $NaBH_4$/MeOH; (d) H_2/Raney-Ni, NH_3/MeOH; (e) Raney-Ni/HCOOH; (f) purum, Na_2SO_4; (g) (i) $LiN(i\text{-}Pr)_2$, THF, −25 °C; (ii) $R_4MgBr(Cl)$, −70 °C;[20] (h) (i) evaporation in vacuo; (ii) aqueous HCl; (iii) concentrated NH_4OH, 0 °C; (iv) rapid extraction (EtOAc) and chromatographic purification; (i) HNR_1R_2, EtOH, reflux; (j) H_2/Pd-C, EtOH or DMF; (k) (i) aqueous HCl/$NaNO_2$; (ii) $CuCl_2$; (l) $LiAlH_4$, Et_2O[21]; (m) (i) $HCONH_2$/$HCOONH_4$, 150 °C; (ii) concentrated HCl;[21] or $Na(CN)BH_3$/NH_4OAc, MeOH; (n) $H_2NOH{\cdot}HCl$, EtOH; (o) Zn, aqueous HCl; or H_2/Pd-C, NEt_3; or $LiAlH_4$, Et_2O.

differ largely from the others (Table 12). Therefore, it seems reasonable to consider the LECs II as favorable potential binding conformations. Their superposition (Figure 10B) supports this view: the pharmacophoric groups fit well; the amidic oxo groups are located to enable hydrogen bonding to the same binding site of the SU receptor; no counterpart to REP's (*S*)-isobutyl is found in GLIB and GLIM; and the ethoxy group of REP and the (methyl)cyclohexyl groups of GLIB and GLIM, respectively, marginally overlap.

To understand molecular features which are not apparent from a structural superposition, hydrophobic and electrostatic potential maps of REP-II, GLIB-II, and GLIM-II were also calculated. The hydrophobic potentials of REP-II differ from those of GLIB-II and GLIM-II (Figure 11). The ethoxy group of REP and the (methyl)cyclohexyl groups of GLIB and GLIM marginally overlap. The (*S*)-isobutyl group of REP is found to be unique; it obviously fits—like other (*S*)-groups of proper size—into an enantiospecific pocket of the SU receptor and is, in this respect, behaving like a further (enantiospecific) pharmacophoric group. A similar (*S*)-enantiospecificity was already observed in chiral SUs and sulfonamido-pyrimidines.[43] The electrostatic potentials of REP-II were found to be rather similar to those of GLIB-II and GLIM-II (not shown here).

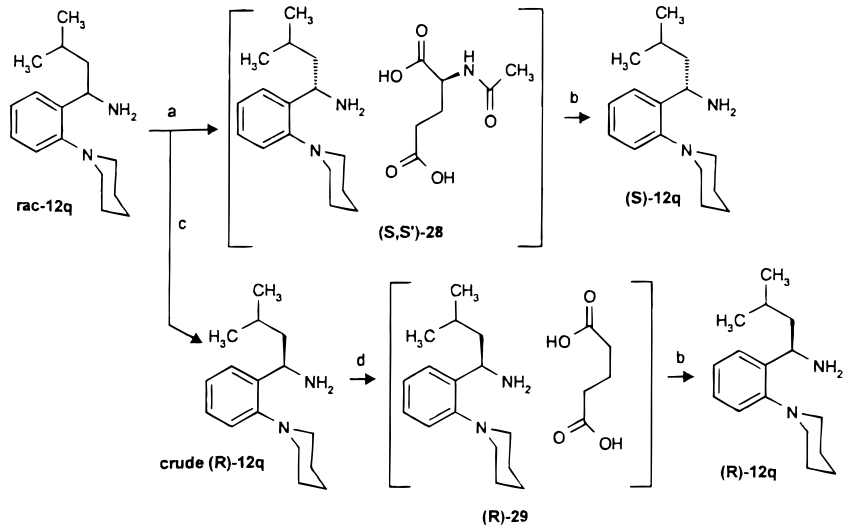
We conclude from these investigations that the LECs II of REP, GLIB, and GLIM may represent a common binding conformation and that differences in the binding to the SU receptor (involved in K_{ATP} channel closure) and also differences in the mechanism of insulin release may be due to hydrophobic differences.

Experimental Section

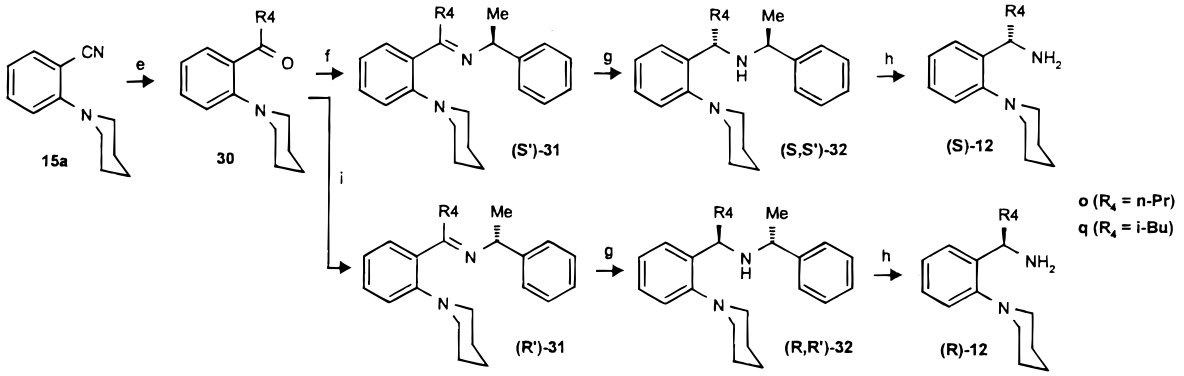
Chemistry. Melting points were determined in open glass capillaries in an electrothermal melting point apparatus and

Scheme 5.[a] Synthetic Routes E−I to Enantiomeric Substituted 2-Piperidino-benzylamines **12**

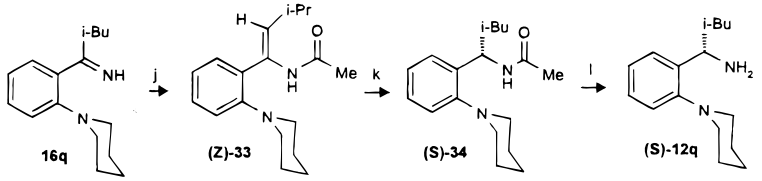
Route E:



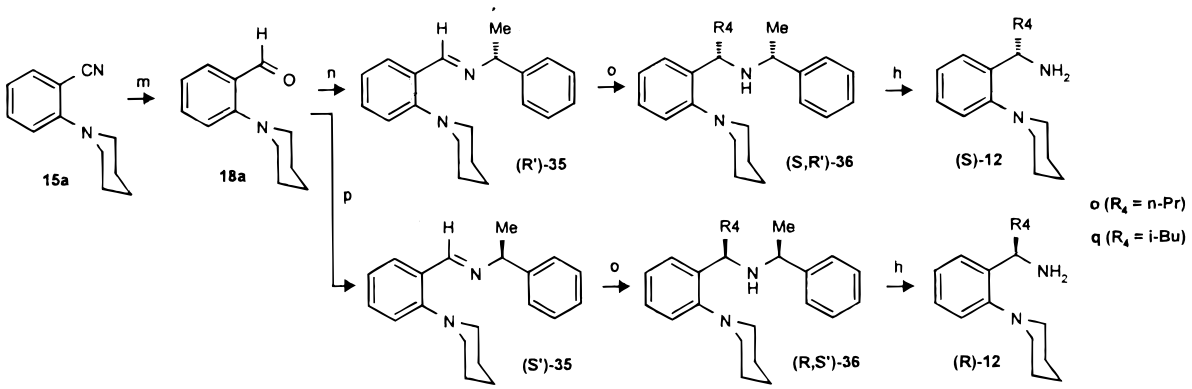
Route F:



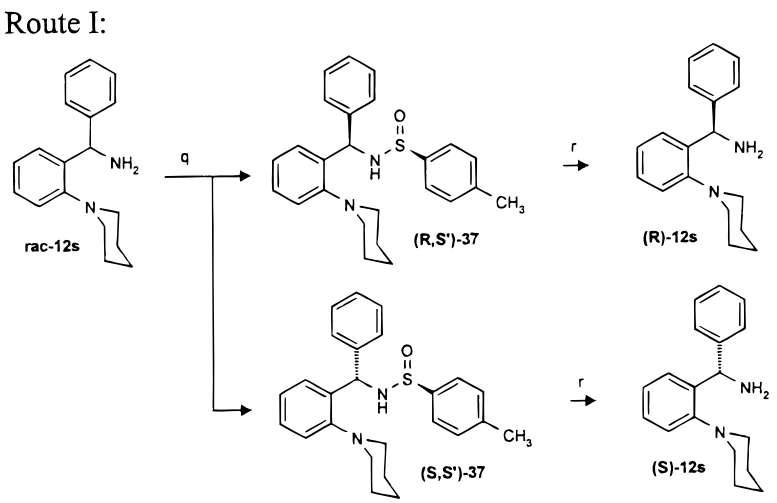
Route G:



Route H:



Scheme 5 (Continued)



[a] (a) (i) *N*-Acetyl-glutamic acid, acetone/MeOH; (ii) recrystallization; (b) aqueous ammonia or aqueous NaOH, CH_2Cl_2- or toluene-extraction; (c) (i) evaporation of the (***S,S′*)-28** filtrate to dryness; (ii) digestion with hot acetone; (iii) evaporation of the filtrate to dryness; (iv) liberation of the crude (***R*)-12q**; (d) glutaric acid, acetone; (e) (i) *i*-BuMgBr, toluene/THF, reflux; (ii) aqueous HCl, 0 °C; (f) (*S′*)-1-phenethylamine/$TiCl_4$/NEt_3, toluene, 0 °C; (g) H_2/Raney-Ni, EtOH; (h) H_2/Pd-C (10%), EtOH/1.1 equiv aqueous HCl; (i) (*R′*)-1-phenethylamine/$TiCl_4$/NEt_3, toluene, 0 °C; (j) (i) Ac_2O, toluene, 0 °C; (ii) chromatographic separation of (*E*)- and (*Z*)-isomers; (k) H_2/$Ru(OAc)_2$[(*S*)-BINAP/0.5% $Ti(O-i-Pr)_4$, MeOH/CH_2Cl_2 (5:1); (l) aqueous HCl; (m) Raney-Ni, HCOOH; (n) (*S′*)-1-phenethylamine, purum, Na_2SO_4; (o) R_4MgBr; (p) (*R′*)-1-phenethylamine, purum, Na_2SO_4; (q) (i) *n*-BuLi, THF, −15 °C; (ii) (−)(*S′*)-[(1*R*,2*S*,5*R*)-menthyl]-*p*-toluenesulfinate, THF, −10 °C, thereafter 20 °C; (iii) chromatographic separation of the diastereomers; (r) TFA, MeOH, +5 °C, thereafter 50 °C.

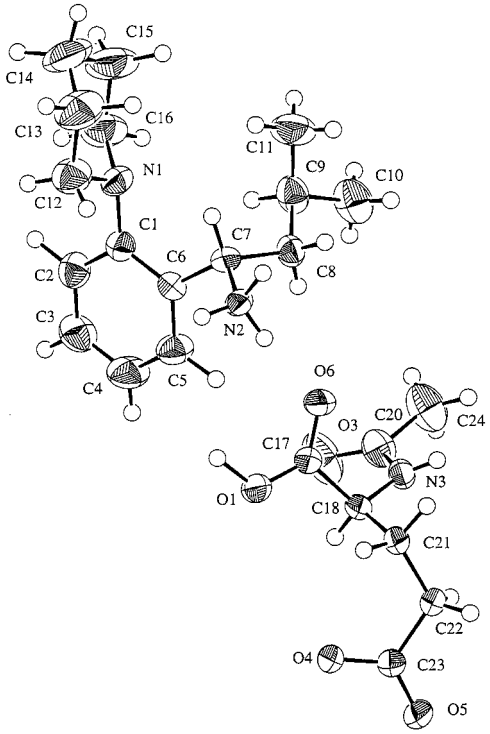
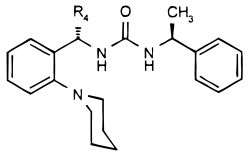


Figure 3. ORTEP plot of the X-ray structure of (***S,S′*)-28**.



(S,S')-38

a (R_4=n-Pr)

b (R_4=i-Bu)

Figure 4. Structural formula of the urea derivatives (***S,S′*)-38a** and (***S,S′*)-38b**.

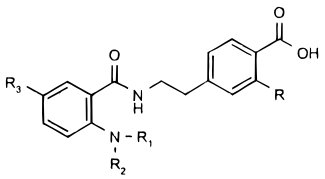
are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer model 299 spectrophotometer, KBr wafer (1 mg/300 mg KBr) or in CH_2Cl_2 (40 g/L), with a cell path length of 0.02 cm. Ultraviolet (UV) spectra were obtained on a Perkin-Elmer model 554 spectrophotometer, with a cell path length of 0.2 cm and in ethanol (0.05 g/L). Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WP80/DS, AC 200, or AMX400, respectively, with tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a Finnigan-MAT (Bremen) model 4023 or 8320, respectively. Elemental analyses were carried out on a Heraeus Merz Mikro Rapid CHN apparatus. Optical rotation was measured on a Perkin-Elmer model 241 polarimeter ($\lambda = 589$ nm, $l = 10$ cm). For TLC analysis, precoated TLC plates (Silica Gel 60 F-254, Merck, Germany) were used. For column chromatography, silica gel (Silica Woelm 32−63 μm) was used. HPLC analyses carried out mostly on a Gilson model 303 are described at the respective experiments. Organic layers obtained after extraction of aqueous solutions were dried over Na_2SO_4 and filtered before evaporation in vacuo. Petrolether (30−60 °C) was used.

Educts 9. 5-Chloro-2-dimethylamino-benzoic Acid (9a). A solution of chlorine (4.25 g, 60 mM) in glacial HOAc (35 mL) was added dropwise to a stirred cooled (0 °C) solution of *N,N*-dimethyl-anthranilic acid[44] hydrochloride (12.6 g, 60 mM) in a mixture of $CHCl_3$ (300 mL) and MeOH (40 mL). After being stirred for 0.5 h, the reaction mixture was extracted 5 times with 2 N NaOH. The combined aqueous phases were acidified to pH 3 with 2 N HCl and extracted with $CHCl_3$. The organic layer was dried and evaporated in vacuo to give the title compound (2.6 g, 22%); mp 122−125 °C (Et_2O).

5-Chloro-2-diethylamino-benzoic Acid (9b) was synthesized from 2-chloro-5-nitro-benzonitrile via 5-amino-2-diethylamino-benzonitrile analogously to **9d**; mp not determined.

5-Chloro-2-pyrrolidino-benzoic Acid (9c). (a) A mixture of 2-chloro-5-nitro-benzoic acid (Aldrich, 20.1 g, 100 mM), pyrrolidine (21.3 g, 300 mM), and EtOH (200 mL) was refluxed for 7 h and thereafter evaporated in vacuo. Water (400 mL), aqueous HCl (ad pH 3), and EtOH were added, and the mixture was stirred at room temperature for 20 min. The resulting precipitate was filtered, washed successively with 2 N HCl, EtOH, and ether, and dried at 90 °C to afford 5-nitro-2-pyrrolidino-benzoic acid (21 g, 89%); mp 226 °C. (b) The

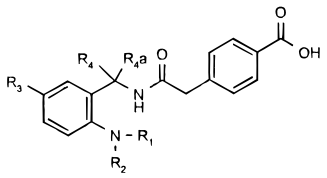
Table 1. Substituted Benzoic Acid Derivatives **5**



Compd	R_3	NR_1R_2	R	mp (°C)	solv[a]	formula[b]	Dose mg/kg (po)	ΔBG[c] (%)	ED_{50}[d] mg/kg (po)
5a	Cl		H	165	A	$C_{18}H_{19}ClN_2O_3$	25	-28	
5b	Cl		H	95	B	$C_{20}H_{23}ClN_2O_3$	25	-35	
5c	Cl		H	184	A	$C_{20}H_{21}ClN_2O_3$	25	-18	
5d	Cl		H	200	B	$C_{21}H_{23}ClN_2O_3$	5	-37	
							1	NS[e]	
5e	Cl		H	178	A	$C_{22}H_{25}ClN_2O_3$	1	-16	
5f	Cl		H	194	A	$C_{22}H_{25}ClN_2O_3$	1	-22	
5g	Cl		H	211	A	$C_{22}H_{25}ClN_2O_3$	1	NS	
5h	Cl		H	204-206	C	$C_{23}H_{27}ClN_2O_3$	1	-44	0.33 (2h)
							0.5	-29	
5i	Cl		H	164-167	C	$C_{23}H_{27}ClN_2O_3$	1	-11	
5j	Cl		H	182	B	$C_{22}H_{25}ClN_2O_3$	1	-16	
5k	Cl		H	186	A	$C_{23}H_{27}ClN_2O_3$	1	-29	
5l	Cl		H	167	D	$C_{24}H_{29}ClN_2O_3$	1	-40	0.38 (1h)
							0.5	-33	
							0.25	-13	
5l	Cl		H	205	E	$C_{24}H_{29}ClN_2O_3 \times 0.8$ HCl	1	-39	
							0.25	-18	
5m	H		H	154-156	A	$C_{24}H_{30}N_2O_3$	1	- 9	
5n	Cl		OMe	152-154	F	$C_{25}H_{31}ClN_2O_4 \times$ HCl	1	-15	
5o	Cl		OEt	128	F	$C_{26}H_{33}ClN_2O_4 \times$ HCl	1	-16	
5p	Cl		H	194-195	G	$C_{25}H_{31}ClN_2O_3$	1	-29	
5q	Cl		H	177	A	$C_{26}H_{33}ClN_2O_3$	1	NS	
3		meglitinide		170[f]	B	$C_{17}H_{16}ClNO_4$	10	-22	9.4 (1h)
							1	- 9	
3a		2-ethoxy-		116-	H	$C_{19}H_{20}ClNO_5$	10	-35	
		meglitinide		119[g]			1	- 8	
1		glibenclamide		169-	H	$C_{23}H_{28}ClN_3O_5S$	0.3	-25	0.255 (2h)
				170[h]			0.1	NS	

[a] (Re)crystallization solvents: A = water; B = diethylether; C = isopropanol; D = ethylacetate; E = acetone; F = acetone/diethylether; G = diethylether/petrolether; H = aqueous ethanol. [b] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values. [c] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [d] Minimum ED_{50} within 4 h at the time indicated. [e] NS = not significant. [f] Lit.[13] mp 170−172 °C. [g] Lit.[29] mp 115−117 °C. [h] Lit.[30] mp 172−174 °C.

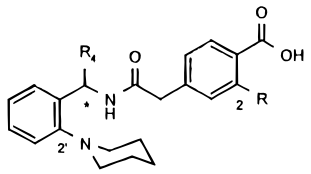
Table 2. Substituted Benzoic Acid Derivatives **6.1**



Compd	R_3	R_1, R_2	R_4	R_{4a}	mp (°C)	solv[a]	formula[b]	Dose mg/kg (po)	ΔBG[c] (%)	ED_{50}[d] mg/kg (po)
6a	Cl	NMe$_2$	Me	H	190-192	A	$C_{19}H_{21}ClN_2O_3$	10	-20	
6b	H	NMe$_2$	Me	H	165-168	B	$C_{19}H_{22}N_2O_3$	10	-20	
6c	Cl	N	Me	H	201-204	C	$C_{21}H_{23}ClN_2O_3$	10	-26	
6d	Cl	N	Me	H	212-215	A	$C_{22}H_{25}ClN_2O_3$	10	-36	
								5	-18	
6e	H	N	Me	H	170-172	A	$C_{22}H_{26}N_2O_3$	5	-49	0.3 (1h)
								1	-41	
								0.5	-31	
								0.1	-13	
6f[e]	Cl	N	Me	Me	227-229	D	$C_{23}H_{27}ClN_2O_3$	10	NS[f]	
6g[g]	H	N	Me	Me	213-215	D	$C_{23}H_{28}N_2O_3$	10	-34	
6h	Cl	N	H	H	162-166	D	$C_{21}H_{23}ClN_2O_3$	10	-37	
6i	H	N	H	H	175-177	D	$C_{21}H_{24}N_2O_3$	10	-38	
6j	Cl	N	Me	H	195-198	C	$C_{23}H_{27}ClN_2O_3 \times 0.25\ H_2O$	10	-14	
6k	H	N	Me	H	171-173	B	$C_{23}H_{28}N_2O_3$	10	-43	
								1	-13	
6l	Cl	N	Me	H	208-210	C	$C_{23}H_{27}ClN_2O_3$	10	-34	
6m	H	N	Me	H	170-173	B	$C_{23}H_{28}N_2O_3$	10	-42	
								1	-27	
6n	H	N	Me	H	172-174	E	$C_{23}H_{28}N_2O_3$	10	-46	
								1	-27	
6o	Cl	N	Me	H	210-212	A	$C_{24}H_{29}ClN_2O_3$	10	-20	
6p	Cl	N	Me	H	202-204	F	$C_{23}H_{27}ClN_2O_3$	5	NS	
6q	H	N	Me	H	174-176	C	$C_{23}H_{28}N_2O_3$	5	-29	
6r	Cl	N	Me	H	196-197	G	$C_{24}H_{29}ClN_2O_3$	25	NS	
6s	Cl	N	Me	H	204-206	H	$C_{25}H_{31}ClN_2O_3$	25	NS	
6t	H	N	Me	H	185-190	A	$C_{25}H_{32}N_2O_3$	25	NS	
4a[h]	Cl	OMe	Me	H	228-230	J	$C_{18}H_{18}ClNO_4$	10	-14	
4b[i]	H	OMe	Me	H	220-224	K	$C_{18}H_{19}NO_4$	10	-21	

[a] (Re)crystallization solvents: A = diethylether; B = petrolether/acetone; C = ethylacetate; D = acetone; E = trichloromethane; F = toluene/trichloromethane; G = petrolether/trichloromethane; H = petrolether/ethylacetate; J = ethanol; K = aqueous ethanol. [b] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values. [c] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [d] Minimum ED_{50} within 4 h at the time indicated. [e] For synthetic route see Experimental Section. [f] NS = not significant. [g] Synthesized from **6f**. [h] Synthesized analogously to **4**.[5] [i] Synthesized from **4a**.

Table 3. 2′-Piperidino-Substituted Benzoic Acid Derivatives **6.2**[a]



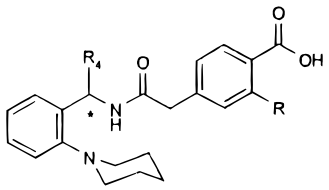
Compd	R_4	C*	R	mp (°C)	solv[b]	formula[c]	Dose mg/kg (po)	ΔBG[d] (%)	ED_{50}[e] mg/kg (po)
6e	Me	rac	H	170-172	A	$C_{22}H_{26}N_2O_3$	0.5	-31	0.3 (1h)
							0.1	-13	
6u[f]	Et	rac	H	208-210	B	$C_{23}H_{28}N_2O_3$	0.5	-28	
6v	n-Pr	rac	H	213-215	B	$C_{24}H_{30}N_2O_3$	0.1	-27	0.07 (1h)
6w	i-Pr	rac	H	215-217	C	$C_{24}H_{30}N_2O_3$	0.5	-18	
6x[f]	n-Bu	rac	H	210-215	C	$C_{25}H_{32}N_2O_3$	0.5	-32	
6y	i-Bu	rac	H	227-230	D	$C_{25}H_{32}N_2O_3$	0.1	-30	
6z[f]	n-Pent	rac	H	195-200	C	$C_{26}H_{34}N_2O_3$	1	-29	
6aa	Cyclohexyl	rac	H	198-202	E	$C_{27}H_{34}N_2O_3$	1	-27	
6ab	Phenyl	rac	H	235-236	B	$C_{27}H_{28}N_2O_3$	0.6	-36	0.38 (1h)
							0.4	-23	
6ac[f]	Benzyl	rac	H	214-215	B	$C_{28}H_{30}N_2O_3$	10	-27	
6ad[f]	2-Phenethyl	rac	H	165-170	F	$C_{29}H_{32}N_2O_3$	10	-38	
6ae	Me	rac	OEt	242-244	C	$C_{24}H_{29}N_2O_4Na \times 1.5\ H_2O$	0.1	-27	
6af	Et	rac	OEt	81-83	D	$C_{25}H_{32}N_2O_4$	0.1	-42	
							0.01	NS[g]	
6ag[h]	n-Pr	rac	OH	136-138	G	$C_{24}H_{30}N_2O_4$	10	-47	
							1	NS	
6ah	n-Pr	rac	OMe	140-143	D	$C_{25}H_{32}N_2O_4$	0.1	-43	
6ai	n-Pr	rac	OEt	85-90	H	$C_{26}H_{34}N_2O_4$[i]	0.1	-32	
6aj	n-Bu	rac	OEt	80-85	D	$C_{27}H_{36}N_2O_4$	0.5	-45	
							0.1	-24	
6ak	3-Buten-1-yl	rac	OEt	80-85	D	$C_{27}H_{34}N_2O_4$	0.1	-35	
6al		rac	OEt	140-142	D	$C_{27}H_{36}N_2O_4$	0.1	-44	0.022 (2h)
				90-92	J		0.01	-19	
6am		rac	OEt	64-66	M	$C_{27}H_{34}N_2O_4$	0.1	-31	
6an	n-Pent	rac	OEt	115-120	K	$C_{28}H_{38}N_2O_4$	0.5	-42	
							0.1	-13	
6ao	n-Hex	rac	OEt	71-73	D	$C_{29}H_{40}N_2O_4$	1	-21	
6ap	Phenyl	rac	OEt	155-156	E	$C_{29}H_{32}N_2O_4$	0.5	-40	
							0.1	-22	
6aq		rac	OEt	103-104	D	$C_{27}H_{34}N_2O_4 \times 0.5\ H_2O$	0.1	-37	
6ar		rac	OEt	140-142	L	$C_{28}H_{36}N_2O_4$[i]	0.1	-27	
6as		rac	OEt	85-88	M	$C_{29}H_{38}N_2O_4$	0.1	-17	
6at		rac	OEt	153-156	D	$C_{30}H_{40}N_2O_4$	0.1	-23	

Table 3 (Continued)

Compd	R_4	C*	R	mp (°C)	solv[b]	formula[c]	Dose mg/kg (po)	ΔBG[d] (%)	ED_{50}[e] mg/kg (po)
6au		rac	OEt	127-130	D	$C_{31}H_{42}N_2O_4$	0.5	-19	
6av	Benzyl	rac	OEt	100-105	D	$C_{30}H_{34}N_2O_4$	10	-38	
(R)-6v	n-Pr	R[k]	H	178-178.5	D	$C_{24}H_{30}N_2O_3$	1	-19	
(S)-6v	n-Pr	S[l]	H	187-188	D	$C_{24}H_{30}N_2O_3$	0.1	-29	
(R)-6ab	Phenyl	R[m]	H	180-182	A	$C_{27}H_{28}N_2O_3$	1	NS	
(S)-6ab	Phenyl	S[m]	H	181-182	A	$C_{27}H_{28}N_2O_3$	0.4	-33	
(R)-6al	i-Bu	R[n]	OEt	132-134	D	$C_{27}H_{36}N_2O_4$	1	NS	
				103-105	M				
(S)-6al	i-Bu	S[o]	OEt	131-133	D	$C_{27}H_{36}N_2O_4$	0.1	-47	0.010 (2h)
	repaglinide			102-104	M		0.01	-21	
(S)-6am[p]		S[q]	OEt	90-95	D	$C_{27}H_{34}N_2O_4$	0.1	-43	
1	glibenclamide			169-170[r]	N	$C_{23}H_{28}ClN_3O_5S$	0.3	-25	0.255 (2h)
							0.1	NS	
2	glimepiride			207-208[s]	D	$C_{24}H_{34}N_4O_5S$	0.3	-35	0.182 (2h)
							0.1	-18	

[a] The compounds were synthesized according to Scheme 2 unless otherwise indicated. [b] (Re)crystallization solvents: A = diethylether; B = ethanol; C = acetone; D = aqueous ethanol; E = acetonitrile; F = ethylacetate; G = diethylether/acetone; H = petrolether/ethanol; J = petrolether/acetone; K = petrolether/diethylether; L = petrolether/methylenechloride; M = petrolether/toluene; N = aqueous methanol. [c] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values unless otherwise indicated. [d] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [e] Minimum ED_{50} within 4 h at the time indicated. [f] Synthesized according to Scheme 3. [g] NS = not significant. [h] Synthesized from **6ai** with BBr_3 (see Experimental Section). [i] C: calcd, 71.21; found, 71.92. Molpeak M^+: calcd, 438; found, 438. [j] C: calcd, 72.39; found, 71.90. [k] ee = 99.6%. [l] ee ≥ 99.2%. [m] ee not determined. [n] ee ≥ 99.98%. [o] ee ≥ 99.8%. [p] For synthesis see Experimental Section. [q] ee = 100%. [r] Lit.[30] mp 172−174 °C. [s] Lit.[31] mp 207 °C; lit.[32] mp 168−170 °C (aqueous acetone).

Table 4. Time Course of the Hypoglycemic Activity of the Compounds **6v**, **6ah**, **6ai**, (***S***)-**6al**, **1**, and **2**



				ΔBG[a] (%) 0.5 mg/kg po					ΔBG[a] (%) 0.1 mg/kg po				
Compd	R_4	C*	R	0.5h	1h	2h	3h	4h	0.5h	1h	2h	3h	4h
6v	n-Pr	rac	H	ND[b]	-42***	-34***	-23**	-18*	ND	-27***	-17**	-16***	- 9*
6ah	n-Pr	rac	OMe	ND	-42***	-39***	-37***	-31***	-38***	-43***	-27***	NS[c]	NS
6ai	n-Pr	rac	OEt[d]	ND	-43***	-36***	-34***	-35***	ND	-32***	-30***	-25***	-18**
(S)-6al	i-Bu	S	OEt						-42***	-47***	-40***	-34***	ND
1		GLIB							NS	NS	NS	NS	ND
2		GLIM							- 8*	-17**	-18**	-14**	ND

[a] % Decrease of blood glucose (ΔBG). [b] ND = not determined. [c] NS = not significant. [d] The analogous compound with R = O-*n*-Pr was found to be less active: 0.5 mg/kg; −34% (1 h), −36% (2 h), −24% (3 h), NS (4 h). Statistical significance (vs control): *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

preceding nitro compound (21 g, 89 mM) was hydrogenatedin DMF (500 mL) over 10% Pd/C (1 g) for 1 h at 20 °C and 1 bar. After filtration and evaporation in vacuo, the residue was crystallized from hot EtOH (50 mL) to give 5-amino-2-pyrrolidino benzoic acid (14.5 g, 79%); mp not determined. (c) A solution of $NaNO_2$ (5.25 g, 75 mM) in water (21 mL) was added dropwise during 1 h to a stirred cooled (0 °C) solution of the preceding amino compouund (14 g, 68 mM) in concentrated HCl (29 mL) and water (29 mL). The resulting solution was dropped slowly at 0 °C into a vigorously stirred slurry of copper powder (6.5 g, 102 mM) and concentrated aqueous HCl (5 mL). The reaction was warmed to 20−25 °C (nitrogen escaped vigorously), kept overnight at room temperature, diluted with water to double volume, and extracted with

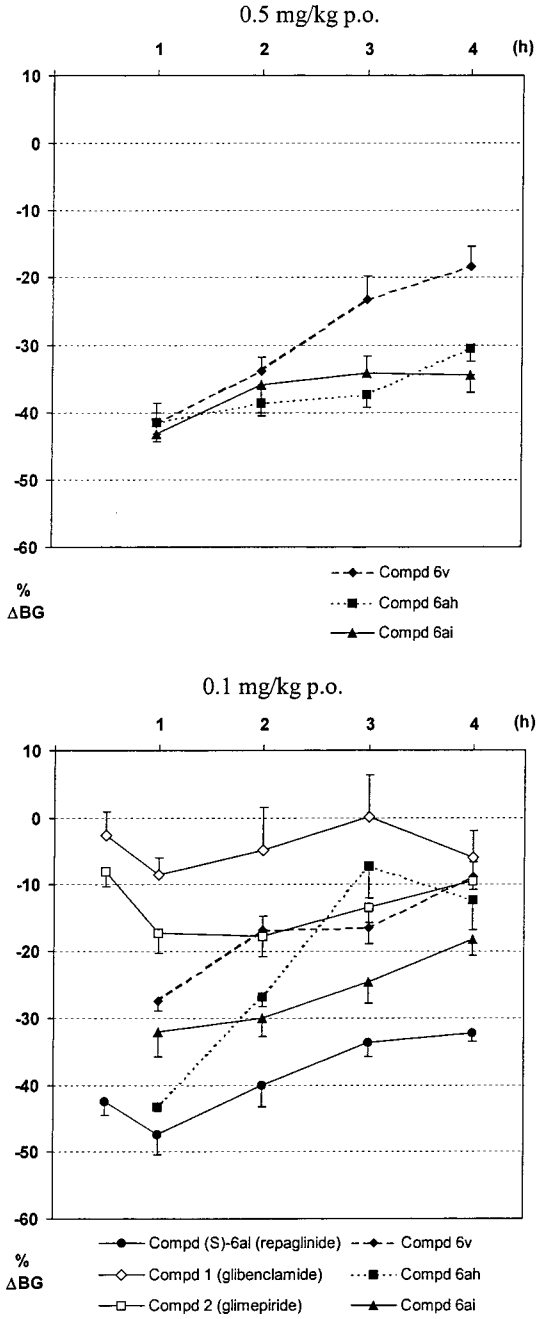


Figure 5. Time course of the hypoglycemic activity of the compounds **6v**, **6ah**, **6ai**, (***S***)**-6al** (REP), **1** (GLIB), and **2** (GLIM).

$CHCl_3$/MeOH (100:5). The organic layer was dried and evaporated in vacuo. The residue was boiled in 710 mL EtOAc/EtOH (70:1); after decanting, the solution was evaporated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH; 95:5) to give **9c** (4.6 g, 30%); mp 164 °C.

5-Chloro-2-piperidino-benzoic Acid (9d). (a) 5-Amino-2-piperidino-benzonitrile (10 g, 50 mM; mp 146 °C, obtained from 2-chloro-5-nitro-benzonitrile (Aldrich) according to literature[45]) in concentrated HCl (20 mL) and water (20 mL) was diazotized at 0−4 °C with $NaNO_2$ (3.6 g, 51 mM) in water (15 mL). This solution was slowly dropped into a stirred mixture of copper powder (4 g, 63 mM) and concentrated HCl (4 mL) at 20 °C (nitrogen escaped vigorously). After stirring at 20 °C for 2 h, the reaction was extracted with $CHCl_3$. The organic layer was dried and evaporated in vacuo. The residue was purified by column chromatography (toluene) to give 5-chloro-2-piperidino-benzonitrile (8.4 g, 76%); mp 41−43 °C. (b) A mixture of the preceding benzonitrile (4.2 g, 19 mM), powdered KOH (30 g, 535 mM), and water (12 mL) was reacted in an open flask at 160 °C for 1.5 h. After cooling and addition of concentrated HCl (ad pH 2), 1 N KOH was added (ad pH 7). The precipitate, crude 5-chloro-2-piperidino-benzamide, was filtered and refluxed for 7 h in 18% aqueous HCl. After evaporation in vacuo, addition of water, and filtration, the filtrate was adjusted to pH 6−7 with solid Na_2CO_3 and extracted with ether. The organic layer was dried and evaporated in vacuo to give **9d** (2.9 g, 65%); mp 160 °C (Et_2O).

5-Chloro-2-(2-methyl-piperidino)-benzoic Acid (9e) was obtained from 2-chloro-5-nitro-benzoic acid and 2-methyl-piperidine analogously to **9c**; mp < 20 °C.

5-Chloro-2-(3-methyl-piperidino)-benzoic Acid (9f) was obtained from 2-chloro-5-nitro-benzoic acid and 3-methyl-piperidine analogously to **9c**; mp 165 °C.

5-Chloro-2-(4-methyl-piperidino)-benzoic Acid (9g) was obtained from 2-chloro-5-nitro-benzoic acid and 4-methyl-piperidine analogously to **9c**; mp 107 °C.

5-Chloro-2-(*cis*-3,5-dimethyl-piperidino)-benzoic Acid (9h) was obtained from 2-chloro-5-nitro-benzoic acid (1 equiv) and *cis*-3,5-dimethyl-piperidine·HCl[46] (1 equiv) in the presence of dry NEt_3 (3 equiv) analogously to **9c**; mp 166−167 °C (EtOAc).

5-Chloro-2-(*trans*-3,5-dimethyl-piperidino)-benzoic Acid (9i) was obtained from 2-chloro-5-nitro-benzoic acid (1 equiv) and trans/cis (85:15) 3,5-dimethyl-piperidine·HCl[46] (1 equiv) in the presence of dry NEt_3 (3 equiv) analogously to **9c** and purified by column chromatography with $CHCl_3$/acetone (3:1). **9i** was eluted tightly after the cis isomer **9h**; mp 130−132 (EtOAc).

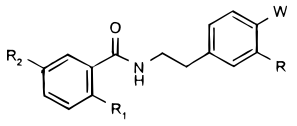
5-Chloro-2-hexamethyleneimino-benzoic Acid (9j) was synthesized from 2-chloro-5-nitro-benzonitrile via 5-amino-2-hexamethyleneimino-benzonitrile analogously to **9d**; mp 105−113 °C.

5-Chloro-2-heptamethyleneimino-benzoic Acid (9k) was obtained from 2-chloro-5-nitro-benzoic acid and 2-heptamethyleneimine analogously to **9c**; mp < 20 °C.

5-Chloro-2-octamethyleneimino-benzoic Acid (9l). (a) A mixture of 2-chloro-5-nitrobenzoic acid (36.4 g, 180 mM), octamethyleneimine[47] (23 g, 180 mM), and sodium carbonate (38.7 g, 365 mM) was refluxed in EtOH (236 mL) for 4 h. After evaporation in vacuo, the residue was dissolved in water (250 mL), acidified (pH 1), and extracted with $CHCl_3$. The organic layer was dried and evaporated in vacuo to afford 5-nitro-2-octamethyleneimino-benzoic acid (49.2 g, 93%); mp 129−131 °C. (b) The preceding nitro compound (9 g, 30.8 mM) was hydrogenated in MeOH (90 mL) over 10% Pd/C (0.5 g) at 20 °C and 5 bar for 1 h to give 5-amino-2-octamethyleneimino-benzoic acid (7.8 g, 96%); mp 191−192 °C. (c) The preceding amino compound (5.2 g, 19.8 mM) in concentrated aqueous HCl (20 mL) and water (20 mL) was diazotized with $NaNO_2$ (1.54 g, 22.3 mM) in water (6 mL) at 0 °C. After being stirred for 20 min, the suspension was added at 5−10 °C during 10 min to a stirred slurry of copper powder (2 g, 31.5 mM) in concentrated aqueous HCl (50 mL). The reaction was stirred at 5 °C for 10 min and at room temperature for 12 h, and then diluted with water (100 mL) and extracted with $CHCl_3$ (3 × 200 mL). The organic layer was dried and evaporated in vacuo. The residue was triturated with EtOAc (30 mL) to give 5-chloro-2-octamethyleneimino-benzoic acid·HCl·$2H_2O$ (4.1 g, 58%); mp 174−176 °C (Et_2O). (d) The preceding hydrochloride (4.1 g) was stirred in water (100 mL) at 35−40 °C. Solid $NaHCO_3$ (1 g, 11.9 mM) was added. After the mixture was stirred for 2 h, $CHCl_3$ (200 mL) and EtOH (20 mL) were added. After the mixture was stirred for another hour, the reaction was filtered. The aqueous layer was extracted with $CHCl_3$/EtOH (20:2) (4 × 220 mL). The combined organic layers were dried and evaporated in vacuo. The residue was triturated with diethyl ether and filtrated. The filtrate was evaporated in vacuo to afford **9l** (3.3 g, 58%); mp 80−81 °C.

5-Chloro-2-nonamethyleneimino-benzoic Acid (9m) was obtained from 2-chloro-5-nitrobenzoic acid, nonamethyleneimine,[47] and sodium carbonate analogously to **9l**; mp 87 °C.

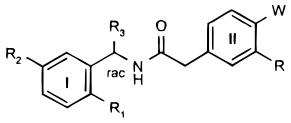
Table 5. Substituted Benzoic Acid Derivatives **5.1**



Compd	R_1	R_2	R	W	mp (°C)	solv[a]	formula[b]	Dose mg/kg (po)	ΔBG[c] (%)
5l		Cl	H	COOH	167	A	$C_{24}H_{29}ClN_2O_3$	1	-40
								0.5	-33
								0.25	-13
5o		Cl	OEt	COOH	128	B	$C_{26}H_{33}ClN_2O_4 \times HCl$	1	-16
39[d]	H	Cl	H	COOH	203[e]	C	$C_{16}H_{14}ClNO_3$	100	-23
5m		H	H	COOH	154-156	D	$C_{24}H_{30}N_2O_3$	5	-36
								1	- 9
40[f]		Cl	H	H	64-66	E	$C_{23}H_{29}ClN_2O$	100	NS[g]

[a] (Re)crystallization solvents: A = ethylacetate; B = acetone/diethylether; C = diethylether; D = water; E = toluene/ethylacetate. [b] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values. [c] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [d] Synthesized according to ref 13, example 1. [e] Lit.[13] mp 202−202 °C. [f] Synthesized according to Scheme 1 with 2-phenethylamine. [g] NS = not significant.

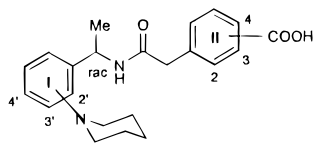
Table 6. Substituted Benzoic Acid Derivatives **6.3**[a]



Compd	R_1	R_2	R_3	R	W	mp (°C)	solv[b]	formula[c]	Dose mg/kg (po)	ΔBG[d] (%)
41		Cl	n-Pr	H	COOH	225-230	A	$C_{24}H_{29}ClN_2O_3$	1	-17
6v		H	n-Pr	H	COOH	213-215	A	$C_{24}H_{30}N_2O_3$	0.1	-27
6ai		H	n-Pr	OEt	COOH	85-90	B	$C_{26}H_{34}N_2O_4$[e]	0.1	-32
42[f]	H	H	n-Pr	H	COOH	201-203	C	$C_{19}H_{21}NO_3$	10	-18
6i		H	H	H	COOH	175-177	D	$C_{21}H_{24}N_2O_3$	10	-38
									5	-27
43g		H	n-Pr	H	H	135-137	A	$C_{23}H_{30}N_2O$	50	-10

[a] The compounds were synthesized according to Scheme 2 unless otherwise indicated. [b] (Re)crystallization solvents: A = ethanol; B = petrolether/ethanol; C = aqueous ethanol; D = acetone. [c] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values unless otherwise indicated. [d] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [e] C: calcd, 71.21; found, 71.92. Molpeak M^+: calcd, 438; found, 438. [f] Synthesized with α-propyl-benzylamine. [g] Synthesized with phenylacetic acid.

Table 7. Substituted Benzoic Acid Derivatives **6.4**[a]



Compd	 in position	COOH in position	mp (°C)	solv[b]	formula[c]	Dose mg/kg (po)	ΔBG[d] (%)
6e	2'	4	170-172	A	$C_{22}H_{26}N_2O_3$	0.5	-31
						0.1	-13
44	3'	4	206-208	B	$C_{22}H_{26}N_2O_3$	25	-15
45	4'	4	207-210	C	$C_{22}H_{26}N_2O_3$	25	NS[e]
46	2'	3	205-207	B	$C_{22}H_{26}N_2O_3$	25	-12
47	2'	2	135	A	$C_{22}H_{26}N_2O_3 \times 0.3\ H_2O$	25	NS

[a] The compounds were synthesized analogously to Scheme 2 by reaction of a corresponding α-methyl-(1-piperidinyl)-benzylamine with a corresponding [(ethoxy(or methoxy)carbonyl)phenyl]acetic acid. [b] (Re)crystallization solvents: A = diethylether; B = ethanol; C = aqueous ethanol. [c] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values. [d] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [e] NS = not significant.

5-Chloro-2-decamethyleneimino-benzoic Acid (9n) was obtained from 2-chloro-5-nitrobenzoic acid, decamethyleneimine,[47] and Na_2CO_3 analogously to **9l**; mp 70 °C.

Educts 10. Methyl 4-(2-aminoethyl)-benzoate (10a)·HCl:[15a] mp 242 °C; lit.[15a] mp 209−216 °C.

Ethyl 4-(2-aminoethyl)-benzoate (10b)·HCl: mp 255−260 °C; lit.[15b] mp 178−180 °C.

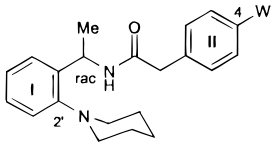
Methyl 4-(2-aminoethyl)-2-methoxy-benzoate (10c)·H_2SO_4 was prepared analogously to that in ref 16; mp 141−145 °C.

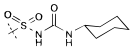
Ethyl 4-(2-aminoethyl)-2-ethoxy-benzoate (10d)·H_2SO_4: mp not determined; lit.[16] (·HCl) mp not reported.

General Procedures for Esters 11. A1. *N,N′*-Carbonyldiimidazole[14] (6.3 mM) was added at room temperature to a stirred solution of educt **9** (5.3 mM) in dry THF (5 mL). After the mixture was stirred for 2 h, a solution of **10** (6.3 mM) [freshly prepared from the corresponding salt by dissolution in iced water, alkalinization, rapid extraction with $CHCl_3$, drying, and evaporation of the organic layer in vacuo] in dry THF (5 mL) was added. After stirring overnight at room temperature, the reaction was evaporated in vacuo. The residue was purified by column chromatography with toluene/EtOAc (8.5:1.5) to give **11**.

A2. A stirred mixture of educt **9** (10 mM) and $SOCl_2$ (30 mM) in dry $CHCl_3$ (20 mL) was refluxed for 4−5 h. After evaporation in vacuo, the residue was dissolved in dry $CHCl_3$ (10 mL). This solution was added at room temperature during 15 min to the corresponding salt of **10** (10 mM) and dry NEt_3 (30 mM) in dry $CHCl_3$ (14 mL). The reaction was refluxed for 30 min, cooled to room temperature, and washed successively with water (2×), diluted aqueous HOAc, and aqueous $NaHCO_3$. The organic layer was dried and evaporated in vacuo. The

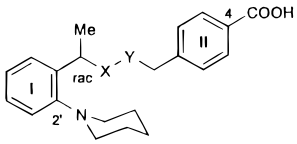
Table 8. Substituted Phenylacetamides **6.5**



Compd	W	mp (°C)	solv[a]	formula[b]	Dose mg/kg (po)	ΔBG[c] (%)
6e		170-172	A	$C_{22}H_{26}N_2O_3$	0.5	-31
					0.1	-13
48[d]		172-175	A	$C_{22}H_{26}N_6O \times 0.5\ H_2O$	50	NS[e]
49[d]		182-188	B	$C_{21}H_{27}N_3O_3S$	10	NS
50[f]		168-173	C	$C_{28}H_{38}N_4O_4S$	5	-42
					1	NS

[a] (Re)crystallization solvents: A = diethylether; B = acetone/diethylether; C = acetone. [b] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values. [c] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [d] For synthesis see Experimental Section. [e] NS = not significant. [f] Synthesized from **49**.

Table 9. Substituted Benzoic Acid Derivatives **6.6**



Compd	-X-Y-	mp (°C)	solv[a]	formula[b]	Dose mg/kg (po)	ΔBG[c] (%)
6e	-NH-CO-	170-172	A	$C_{22}H_{26}N_2O_3$	0.5	-31
					0.1	-13
51[d]	-CO-NH-	125	A	$C_{22}H_{26}N_2O_3$[e]	5	-32
52[d]	-NH-SO_2-	222-225	B	$C_{21}H_{26}N_2O_4S$	25	NS[f]

[a] (Re)crystallization solvents: A = diethylether; B = ethanol. [b] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values unless otherwise indicated. [c] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [d] For synthesis see Experimental Section. [e] C: calcd, 72.10; found, 72.59. [f] NS = not significant.

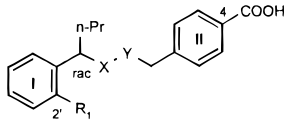
residue was purified by column chromatography with $CHCl_3$/acetone (9:1) to give **11**.

General Procedures for Substituted Benzoic Acids 5. B1. To a stirred solution of **11** (1.6 mM) in dioxane (6 mL) and MeOH (6 mL) was added at room temperature a solution of KOH (4.8 mM) in water (2 mL); thereafter, water (30 mL) was added so slowly that the solution remained clear. After the mixture was stirred at room temperature overnight, the reaction was evaporated in vacuo. The residue was dissolved in water. After extraction with $CHCl_3$ (discarded), the aqueous layer was adjusted to pH 4.5−5.5 with 2 N HCl to precipitate **5**.

B2. A mixture of ester **11** (5 mM) in EtOH (50 mL) and 1 N NaOH (10 mL) was refluxed for 30 min. After evaporation in vacuo to about one-third of the original volume, water (60 mL) and diluted aqueous HOAc (to pH 6) were added to precipitate **5**.

Compounds Synthesized According to Procedures B1/A1. *Note:* The melting points of compounds **5** are reported in Table 1. 4-(2-(5-Chloro-2-dimethylamino-benzoylamino)-ethyl)-benzoic acid (**5a**): 70%, via methyl 4-(2-(5-chloro-2-dimethylamino-benzoylamino)-ethyl)-benzoate (**11a**), 48%; mp 99 °C. 4-(2-(5-Chloro-2-diethylamino-benzoylamino)-ethyl)-benzoic acid (**5b**): 60%, via methyl 4-(2-(5-chloro-2-diethylamino-benzoyl-

Table 10. Substituted Benzoic Acid Derivatives **6.7**



Compd	R_1	-X-Y-	mp (°C)	solv[a]	formula[b]	Dose mg/kg (po)	ΔBG[c] (%)
6v		-NH-CO-	213-215	A	$C_{24}H_{30}N_2O_3$	0.5	-40
						0.1	-27
53[d]		-NH-CO-	208-211	B	$C_{25}H_{31}NO_3$	10	-31
						1	- 9
54[d]		-NH-CO-	206-210	A	$C_{25}H_{29}NO_3$	10	-48
						1	NS[e]
55[d]		-NH-CO-	217-220	A	$C_{25}H_{25}NO_3$	10	-21
56[d]	-O-CH_3	-NH-CO-	201-203	A	$C_{20}H_{23}NO_4$	10	-44
						1	-21
42[f]	-H	-NH-CO-	201-203	A	$C_{19}H_{21}NO_3$	10	-18
57[d]		-N(Me)-CO-	157-160	C	$C_{25}H_{32}N_2O_2$	10	-12
58[d]		-NH-CS-.	80-87	D	$C_{24}H_{30}N_2O_2S$	10	-35
59[d]		-NH-CH_2-	236-242	A	$C_{24}H_{32}N_2O_2$	10	NS
60[d]		-CH_2-CO-	88-92	E	$C_{25}H_{31}NO_3$	10	-11
61[d]		-CH_2-CH_2-	60-70	F	$C_{25}H_{33}NO_2$[g]	25	NS

[a] (Re)crystallization solvents: A = aqueous ethanol; B = acetonitrile; C = diethylether/petrolether; D = petrolether; E = acetone/petrolether; F = neat (on standing). [b] Analyzed for C, H, and N; results were within ±0.40% of the theoretical values unless otherwise indicated. [c] Maximum % decrease of blood glucose (ΔBG) observed within 4 h after administration to fasted female rats ($N = 7$) versus a control group ($P = 0.05$). [d] For synthesis see Experimental Section. [e] NS = not significant. [f] Synthesized according to Scheme 2 with α-propyl-benzylamine. [g] C, H, N not determined. Molpeak M^+: calcd, 379; found, 379.

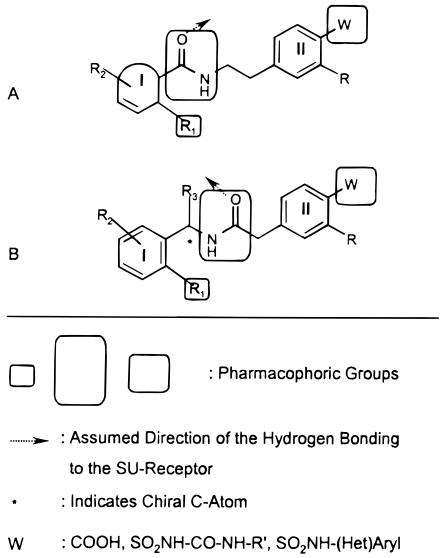
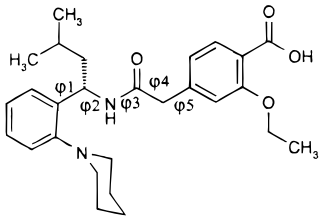


Figure 6. General pharmacophore model suitable for hypoglycemic benzoic acid derivatives, SUs, and sulfonamides of type A and B.

amino)-ethyl)-benzoate (**11b**), 51%; mp 92−93 °C. 4-(2-(5-Chloro-2-pyrrolidino-benzoylamino)-ethyl)-benzoic acid (**5c**): 68%, via methyl 4-(2-(5-chloro-2-pyrrolidino-benzoylamino)-ethyl)-benzoate (**11c**), 43%; mp 164 °C. 4-(2-(5-Chloro-2-piperidino-benzoylamino)-ethyl)-benzoic acid (**5d**): 82%, via methyl 4-(2-(5-chloro-2-piperidino-benzoylamino)-ethyl)-ben-



(S)-6al; repaglinide

Figure 7. Structural formula of (***S***)-**6al** (REP).

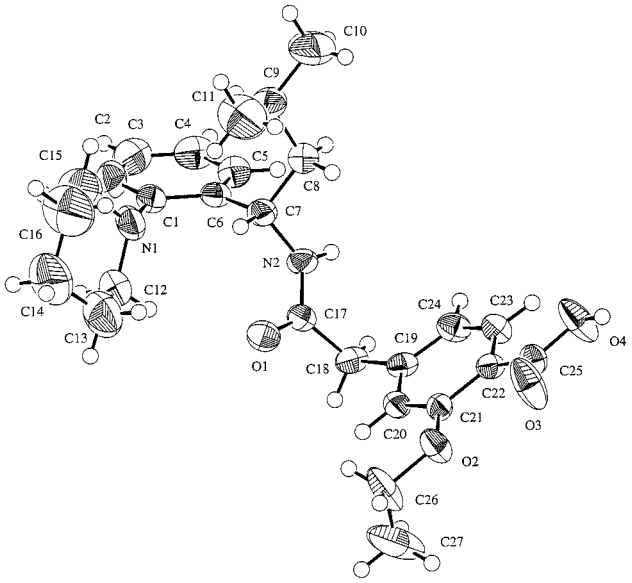


Figure 8. ORTEP plot of the X-ray structure of (***S***)-**6al** (REP).

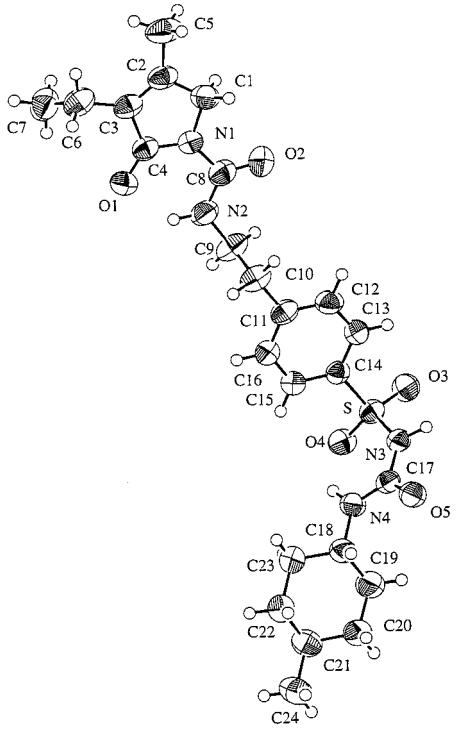


Figure 9. ORTEP plot of the X-ray structure of **2** (GLIM).

zoate (**11d**): 72%, mp 98 °C. 4-(2-(5-Chloro-2-(2-methyl-piperidino)-benzoylamino)-ethyl)-benzoic acid (**5e**): 57%, via methyl 4-(2-(5-chloro-2-(2-methyl-piperidino)-benzoylamino)-ethyl)-benzoate (**11e**), 23%; mp 82 °C. 4-(2-(5-Chloro-2-(3-methyl-piperidino)-benzoylamino)-ethyl)-benzoic acid (**5f**): 83%, via methyl 4-(2-(5-chloro-2-(3-methyl-piperidino)-benzoylamino)-ethyl)-benzoate (**11f**): 51%; mp 93 °C. 4-(2-(5-Chloro-2-(4-methyl-piperidino)-benzoylamino)-ethyl)-benzoic acid (**5g**): 83%, via methyl 4-(2-(5-chloro-2-(4-methyl-piperidino)-benzoylamino)-ethyl)-benzoate (**11g**): 45%; mp 55 °C. 4-(2-(5-Chloro-2-hexamethyleneimino-benzoylamino)-ethyl)-benzoic acid (**5j**): 89%, via methyl 4-(2-(5-chloro-2-hexamethyleneimino-benzoyl-amino)-ethyl)-benzoate (**11j**), 72%; mp 79−81 °C. 4-(2-(5-Chloro-2-heptamethyleneimino-benzoylamino)-ethyl)-benzoic acid (**5k**): 47%, via ethyl 4-(2-(5-chloro-2-heptamethyleneimino-benzoylamino)-ethyl)-benzoate (**11k**), 24%; mp < 20 °C. 4-(2-(5-Chloro-2-octamethyleneimino-benzoylamino)-ethyl)-benzoic acid (**5l**): 92%; mp 148 °C (H_2O); mp 165−167 °C (recrystallized from EtOAc); via ethyl 4-(2-(5-chloro-2-octamethyleneimino-benzoylamino)-ethyl)-benzoate (**11l**), 41%; oil. 4-(2-(5-Chloro-2-octamethyleneimino-benzoylamino)-ethyl)-benzoic acid (**5l**)·0.8HCl: 90%; mp 205 °C, obtained from **5l** in hot acetone with HCl/*i*-PrOH. 4-(2-(5-Chloro-2-octamethyleneimino-benzoylamino)-ethyl)-2-methoxy-benzoic acid (**5n**)·HCl: 96%, from **5n** in ether with HCl/*i*-PrOH, via methyl 4-(2-(5-chloro-2-octamethyleneimino-benzoylamino)-ethyl)-2-methoxy-benzoate (**11m**), 46%; oil (in dry pyridine, 48 h, 100 °C). 4-(2-(5-Chloro-2-octamethyleneimino-benzoylamino)-ethyl)-2-ethoxy-benzoic acid (**5o**)·HCl: 62%, from **5o** with HCl/*i*-PrOH, via ethyl 4-(2-(5-chloro-2-octamethyleneimino-benzoylamino)-ethyl)-2-ethoxy-benzoate (**11n**), 61%; oil (in dry pyridine, 48 h, 100 °C). 4-(2-(5-Chloro-2-nonamethyleneimino-benzoylamino)-ethyl)-benzoic acid (**5p**): 71%; via ethyl 4-(2-(5-chloro-2-nonamethyleneimino-benzoylamino)-ethyl)-benzoate (**11o**), 67%; oil (in dry pyridine, 24 h, 100 °C). 4-(2-(5-Chloro-2-decamethyleneimino-benzoylamino)-ethyl)-benzoic acid (**5q**): 58%; via ethyl 4-(2-(5-chloro-2-decamethyleneimino-benzoylamino)-ethyl)-benzoate (**11p**), 65%; oil (in dry DMF, 12 h, 90 °C).

Table 11. Calculated Energy Differences (Δ*E*, kcal/M) of the Low-Energy Conformations (LECs) of Repaglinide (REP), Glibenclamide (GLIB), and Glimepiride (GLIM) with Respect to the Corresponding Minimum Conformations I

LEC	REP ΔE	GLIB ΔE	GLIM ΔE
I (≈X-ray)	0	0	0
II (calcd.)	**2.6**	**1.3**	**2.1**
III (calcd.)	1.8	-	-

Table 12. Torsion Angles φ1 to φ5 of the Low-Energy Conformations (LECs) of Repaglinide (REP), Glibenclamide (GLIB), and Glimepiride (GLIM)

LEC	φ1	φ2	φ3	φ4	φ5
REP-I	-60°	-110°	-175°	100°	80°
REP-II	**120°**	**-163°**	**180°**	**180°**	**100°**
REP-III	-80°	70°	-177°	40°	80°
GLIB-I	175°	165°	-86°	180°	120°
GLIB-II	**180°**	**180°**	**175°**	**180°**	**90°**
GLIM-I	180°	176°	93°	-178°	88°
GLIM-II	**180°**	**180°**	**175°**	**180°**	**90°**

Compounds Synthesized According to Procedures B2/A2. 4-(2-(5-Chloro-2-(*cis*-3,5-dimethyl-piperidino)-benzoyl-amino)-ethyl)-benzoic acid (**5h**): 87%; via methyl 4-(2-(5-chloro-(2-(*cis*-3,5-dimethyl-piperidino)-benzoylamino)-ethyl)-benzoate (**11h**), 77%; mp 94−95 °C (CH_2Cl_2/petrolether); mp 122−124 °C (MeOH). 4-(2-(5-Chloro-2-(*trans*-3,5-dimethyl-piperidino)-benzoyl-amino)-ethyl)-benzoic acid (**5i**): 86%, via methyl 4-(2-(5-chloro-(2-(*trans*-3,5-dimethyl-piperidino)-benzoylamino)-ethyl)-benzoate (**11i**): 75%; mp 105−107 °C (MeOH).

Special Procedure: 4-(2-(2-Octamethyleneimino-benzoylamino)-ethyl)-benzoic Acid (5m). 5l (2.15 g; 5 mM)

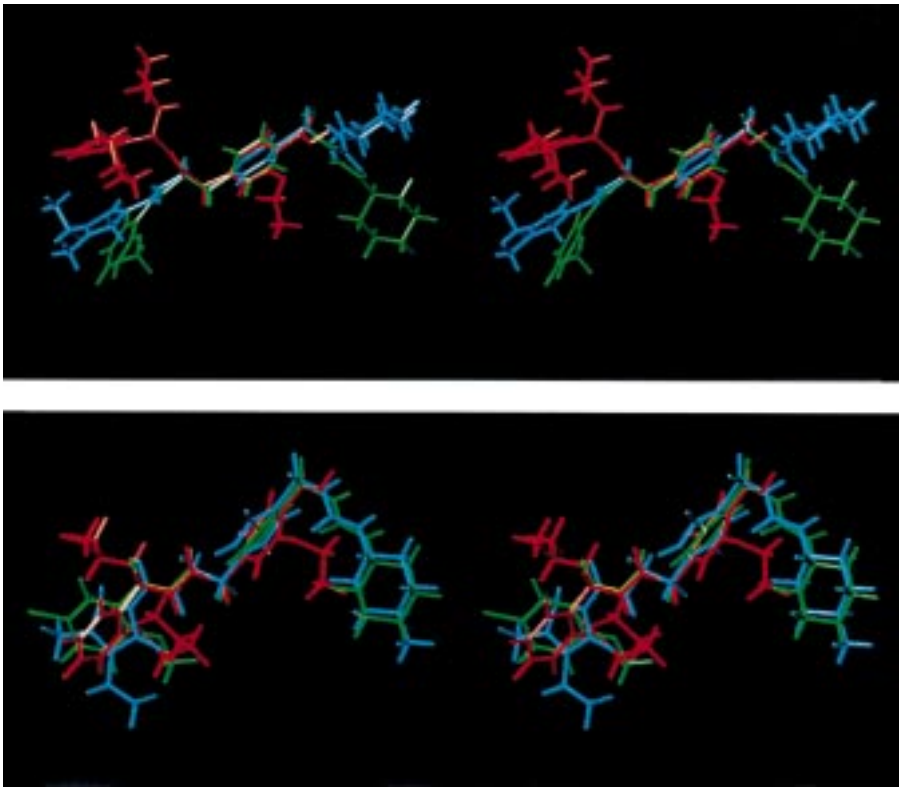


Figure 10. Stereopicture of the superposition of low-energy conformations (LECs). (A, above) LECs I (X-ray structures): REP-I (red), GLIB-I (green), and GLIM-I (blue). (B, bottom) LECs II (calculated): REP-II (red), GLIB-II (green), and GLIM-II (blue). The superpositions were performed in order to optimally fit the central phenylene ring and the acidic pharmacophoric groups of each molecule. As it turns out, the conformational differences as quantified in the list of main torsion angles (Table 12) led to drastically different positions of the two other pharmacophoric groups when comparing REP-I to GLIB-I/GLIM-I. REP-I is in a compactly folded conformation, whereas GLIB-I and GLIM-I have an extended shape. The two SU compounds differ in the configuration of their ureido moieties (cis in GLIB-I, trans in GLIM-I), resulting in distinct orientations of the cyclohexyl substituents; furthermore, a difference of 180° in the torsion angle $\varphi 3$ changes the orientation of the amide carbonyl and of its substituent.

was hydrogenated in MeOH (100 mL) for 5 h at room temperature and 5 bar over 10% Pd/C (0.5 g). After filtration and evaporation in vacuo, the residue was dissolved in aqueous NaOH. After filtration, aqueous HCl was added (ad pH 5.5) to precipitate **5m**, 71%; mp 154−156 °C.

Educts 13. (4-Methoxycarbonyl-phenyl)-acetic Acid (13a). (a) Methyl 4-methyl-benzoate was reacted with *N*-bromo-succinimide (NBS) (1 equiv) and a trace of dibenzoyl-peroxide in CCl_4 for 2.5 h under reflux to give methyl 4-bromomethyl-benzoate, 80%; $bp_{0.2}$ 90−95 °C. (b) The resulting bromo ester was dropped within 1.5 h to a warm (40 °C) solution of NaCN (1 equiv) in DMSO. After 2 h at 40 °C, workup (iced water, extraction with Et_2O) gave methyl-4-cyanomethyl-benzoate, 54%; $bp_{0.2}$ 110−112 °C. (c) The cyanomethyl compound was treated in MeOH with gaseous HCl for 8 h under reflux. After 48 h at 20 °C, the reaction was filtrated. The filtrate was evaporated in vacuo; the residue was dissolved in Et_2O and washed (H_2O, aqueous $NaHCO_3$) to yield methyl 4-methoxycarbonylmethyl-benzoate, 75%; $bp_{0.6}$ 118−122 °C. (d) The diester was stirred with NaOH (1.0 equiv) in MeOH for 4 h at 50 °C and for 24 h at 20 °C. The reaction was evaporated in vacuo; the residue was dissolved in Et_2O and extracted with water. The aqueous phase was acidified with concentrated HCl and extracted with Et_2O to yield **13a**, 74%; mp 104−106 °C (Et_2O/petrolether); mp 110−113 °C (recrystallized from Et_2O).

(4-Ethoxycarbonyl-phenyl)-acetic Acid (13b), 58%, mp 99−100 °C, was prepared from ethyl 4-ethoxycarbonylmethyl-benzoate analogously to **13a**. **13b** (63%; mp 90−95 °C) was also obtained from ethyl 4-cyanomethyl-benzoate in an one-pot reaction via intermediary ethyl 4-aminocarbonyl-methyl-benzoate, mp 135−140 °C (concentrated HCl, 1.5 h, 20−23 °C), and subsequent Bouveault reaction (aqueous $NaNO_2$, 2 h, 35 °C).

(2-Methoxy-4-methoxycarbonyl-phenyl)-acetic acid (13c), 49%, mp 50−52 °C, was prepared from methyl 4-cyanomethyl-2-methoxy-benzoate, mp 55−56 °C, via methyl 4-aminocarbonylmethyl-2-methoxy-benzoate, 79%, mp 107−109 °C, and subsequent Bouveault reaction.

(2-Ethoxy-4-ethoxycarbonyl-phenyl)-acetic Acid (13d). (a) 2-Hydroxy-4-methyl-benzoic acid (Aldrich) in acetone was stirred with K_2CO_3 (2.3 equiv) at room temperature. Ethyl-bromide (2.3 equiv) was added, and the reaction mixture was heated for 30 h at 150 °C in an autoclave under stirring to give ethyl 2-ethoxy-4-methyl-benzoate, 100% (crude). (b) The obtained compound was reacted with NBS (0.9 equiv) and 2,2′-azo-bis-(isobutyronitril) (0.082 equiv) in CCl_4 to yield ethyl 4-bromomethyl-2-ethoxy-benzoate, 57%; mp 77−80 °C (petrolether). (c) To a solution of NaCN (1.2 equiv) and *N*-benzyl-tri-*n*-butylammonium-chloride (0.046 equiv) in water (0.5 mL/mM) was dropped a solution of the 4-bromomethyl ester in CH_2Cl_2 (1 mL/mM) at 15−20 °C. After the mixture was stirred for 43 h at 20 °C, the organic phase was separated, washed with water, and evaporated in vacuo. The residue was triturated with petrolether to give ethyl 4-cyanomethyl-2-ethoxy-benzoate, 97%; mp 57−63 °C. (d) The cyanomethyl ester was treated with gaseous HCl in EtOH under reflux to yield ethyl 2-ethoxy-4-ethoxycarbonylmethyl-benzoate, 91%, crude; oil. (e) The crude diester was hydrolyzed with 2 N NaOH (0.8 equiv) in EtOH (1.5 h, 23−25 °C). EtOH was removed in vacuo at 40 °C. The aqueous phase was diluted with water and extracted several times with toluene (discarded), cooled in ice, and acidified with 2 N HCl (0.8 equiv). Further workup included extraction with toluene, washing

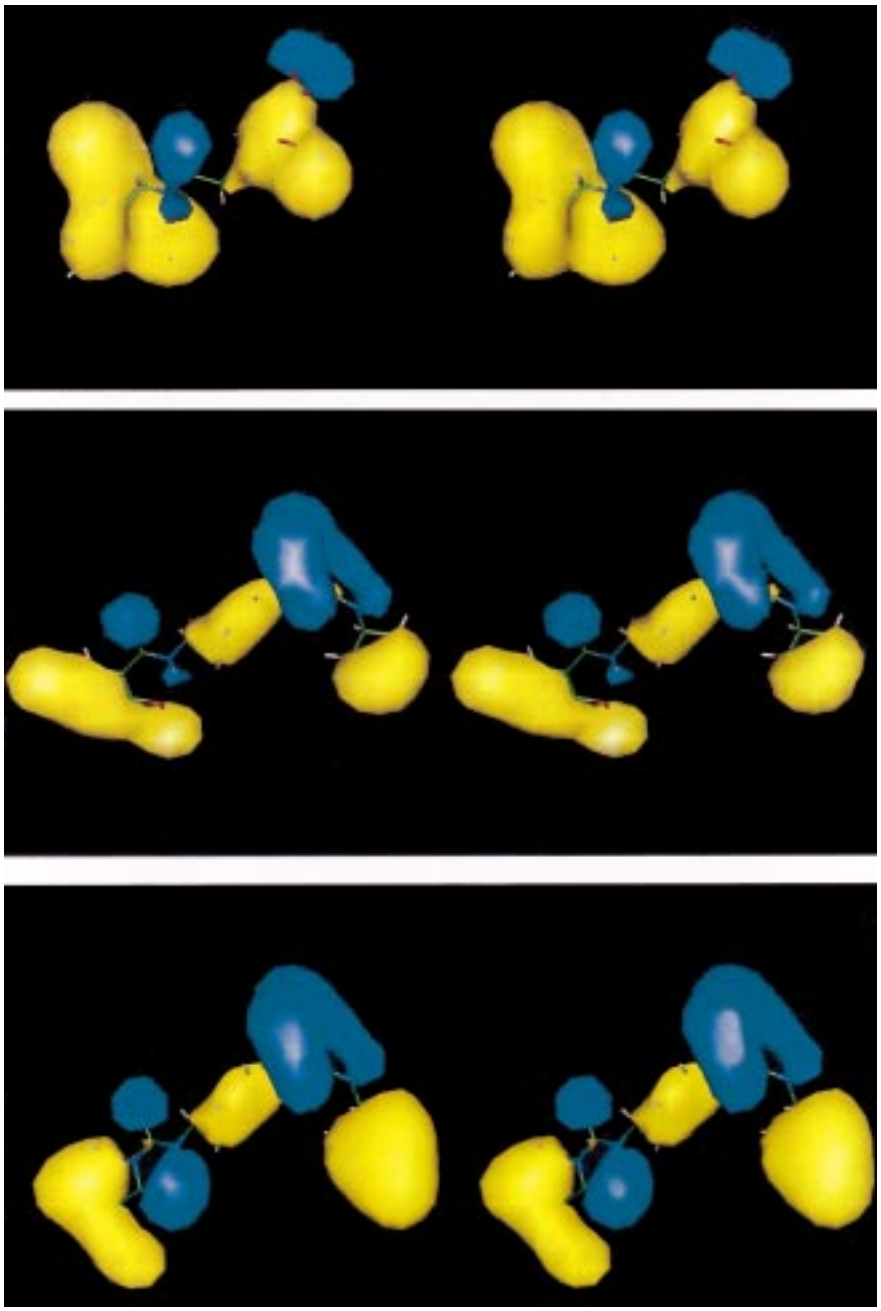


Figure 11. Stereopicture of the isocontour surfaces of the hydrophobic potential of the LECs II: REP-II (upper), GLIB-II (middle), and GLIM-II (bottom). Contour levels: blue (−6), yellow (+4 kcal/M). The yellow and the blue surfaces represent lipophilic and hydrophilic regions, respectively.

with water (to remove diacid), drying and treating of the organic phase with charcoal for 10 min at 80−90 °C, filtration, and evaporation in vacuo. The crude product (70%) was dissolved in hot toluene, and an equal volume of cyclohexane was added. On cooling, crystallization was induced to give **13d**, 59%; mp 70−75 °C. In the case of **13d**, a one-pot conversion, analogous to **13b**, starting from ethyl 4-cyanomethyl-2-ethoxy-benzoate yielded only 39% of **13d**; mainly (4-carboxy-2-ethoxy-phenyl)-acetic acid, mp 141−142 °C, was obtained.

Procedures for Racemic Amines 12. Route A. 3-Methyl-1-(2-piperidino-phenyl)-butylamine (12q). (a) 2-Piperidino-benzonitril (15a). 2-Chloro-benzonitrile (0.5 M), *N*-formyl-piperidine (1 M), and piperidine (1.5 M) were refluxed at 160−170 °C for 64 h. The reaction was dissolved in toluene (1 L), washed with water (3 × 200 mL), dried, filtrated, and evaporated in vacuo. The residue was dissolved in toluene (500 mL); the solution was stirred at room temperature with silica gel (130 g) for 1 h and with additional silica gel (130 g) for another hour. The silica gel was filtered off and washed with toluene; the filtrate was evaporated in vacuo. On distillation over a 5 cm Vigreux column, **15a** was obtained (84%; $bp_{0.6}$ 106−109 °C; mp 37−39 °C).

(b) (3-Methyl-butyl)-(2-piperidino-phenyl)-ketimine (16q). To a solution of *i*-BuMgBr (268 mM) in 135 mL of toluene/THF (4:1) was added a solution of **15a** (107 mM) in 135 mL of toluene/THF (4:1). After reflux for 3 h and standing overnight, the reaction mixture was dropped into a cold (−15 °C) mixture of concentrated ammonia (300 mL) and saturated aqueous NH_4Cl (300 mL). After the mixture was stirred for 10 min, the mixture was filtered through a layer of kieselguhr, and the organic layer was separated, dried, and evapoarted in vacuo to give **16q** as a yellow oil (crude, 100%).

(c1) 3-Methyl-1-(2-piperidino-phenyl)-butylamine (12q). Crude **16q** (45 mM) in saturated methanolic ammonia (170 mL) was hydrogenated over Raney-Ni (5.5 g) at 80 °C and 5 bar for 6 h. After filtration, the filtrate was evaporated in vacuo. The residue was dissolved in 1 N HCl and extracted

with CH_2Cl_2 (3 × 25 mL). The aqueous phase was alkalinized with concentrated NaOH and extracted with CH_2Cl_2 (2 × 25 mL); filtration through a layer of kieselguhr was needed to afford separation of the phases. The organic layer was washed with water, dried, filtrated, and evaporated in vacuo to give the title compound (59%; oil). **(c2)** Alternatively, $NaBH_4$ (161 mM) was added within 1 h to crude **16q** (80.5 mM) in MeOH (160 mL) at 0 °C; stirring was continued at 15 °C for 2 h. The reaction was evaporated in vacuo, and 10% aqueous HCl (100 mL) was added cautiously under cooling with ice. After extraction with CH_2Cl_2 (4 × 40 mL, discarded), the aqueous phase was alkalinized with 50% NaOH and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with water (40 mL), dried, and evaporated in vacuo. The residue was dissolved in EtOH (25 mL) and cooled in ice. A solid product was filtered off, and the filtrate was evaporated in vacuo to give **12q** as a yellow oil (65%) which was used for further reaction. For purification and/or storage, the salt **29** (=**12q**·glutaric acid; mp 179−180 °C) was formed.

Compounds Obtained According to Route A. (The method involved catalytic hydrogenation of the corresponding ketimine **16**.) 1-(2-Piperidino-phenyl)-ethylamine (**12d**): 69%; bp_2 110−115 °C. 1-(5-Chloro-2-(2-methyl-piperidino)-phenyl)-ethylamine (**12g**): 44%; oil, and the more polar 1-(2-(2-methyl-piperidino)-phenyl)-ethylamine, 32%; oil. 1-(2-(4-Methyl-piperidino)-phenyl)-ethylamine (**12i**): 59%; oil. 1-(2-Hexamethyl-eneimino-phenyl)-ethylamine (**12l**): 49%; $bp_{0.4}$ 103−107 °C. 1-(2-Piperidino-phenyl)-butylamine (**12o**): 68%; $bp_{1.5}$ 102−103 °C. Phenyl-(2-piperidino-phenyl)-methylamine (**12s**): 100%, crude; oil. 1-(2-Piperidino-phenyl)-pentylamine (**12u**): 100%, crude; oil. 1-(2-Piperidino-phenyl)-hexylamine (**12x**): 100%, crude; oil. 1-(2-Piperidino-phenyl)-heptylamine (**12y**): 54%; oil. 2-Cyclohexyl-1-(2-piperidino-phenyl)-ethylamine (**12ac**): 45%; oil. 2-Phenyl-1-(2-piperidino-phenyl)-ethylamine (**12ae**): 64%; oil.

Route B. 3-Methyl-1-(2-piperidino-phenyl)-3-butenyl-amine (12w) was obtained analogously to ref 20.

(a) 2-Piperidino-benzaldehyde (18a). Nitrile **15a** (536 mM) was dissolved in 98% formic acid at room temperature. The solution was stirred in a bath of 80 °C, and (wet aqueous) Raney-Ni (180 g) was added in 10−12 g portions in intervals of 15 min. After filtration over kieselguhr, the filtrate was evaporated in vacuo. The residue was dissolved in water (500 mL); solid Na_2CO_3 was added for neutralization. Extraction with CH_2Cl_2 and distillation of the extract residue over a 5 cm Vigreux column gave **18a**, 62%; $bp_{0.05}$ 97 °C.

(b) 2-Piperidino-benzylamine (12af). 15a (134 mM) in saturated methanolic ammonia (250 mL) was hydrogenated over Raney-Ni (10 g) for 4 h at 50 °C and 5 bar. Filtration and evaporation in vacuo gave **12af** as an oil (100%).

(c) *N*-(2-Piperidino-benzyl)-2-piperidino-benzaldimine (19a). To cooled (+5 °C) amine **12af** (50 mM) was dropped **18a** (50 mM). After standing for 48 h at room temperature, the reaction was dissolved in Et_2O and dried over Na_2SO_4. Evaporation in vacuo left **19a** as an honey-like product (100%, crude).

(d) 3-Methyl-1-(2-piperidino-phenyl)-3-butenylamine (12w). Under an atmosphere of dry nitrogen, a solution of *n*-BuLi (15% in hexane; 21.6 mM) was dropped at 0 to −5 °C to a solution of diisopropylamine (21.6 mM) in dry THF (10 mL). After the mixture was stirred for 15 min, the LDA solution was cooled to −20 to −25 °C, and a solution of crude **19a** (7.2 mM) was added dropwise (color changed to red-violet). After the mixture was stirred for 30 min at −20 °C, the reaction was cooled to −70 °C, and a solution of 2-methyl-allylchloride (7.2 mM) in dry THF (4 mL) was added dropwise (color changed to violet). After removal of the cooling bath, stirring was continued overnight. The reaction was evaporated in vacuo. Semiconcentrated HCl (30 mL) was added at 0 °C. After 30 min at 0 °C, the reaction was alkalinized at 0 °C with concentrated ammonia and extracted rapidly with $CHCl_3$. The organic layer was dried and evaporated in vacuo. The residue was purified immediately by column chromatography. Elution with $CHCl_3$ gave recovered **18a**, thereafter, elution with $CHCl_3$/MeOH/concentrated ammonia (10:1:0.01) resulted in **12w** as a brownish oil (46%). For storage, the salt **12w** × glutaric acid, mp 138−140 °C, was formed.

Compounds Obtained According to Route B. (The method involved reaction of the Li salt of **19a** with the corresponding halide.) 1-(2-Piperidino-phenyl)-4-pentenylamine (**12v**): 40%; oil. 2-Cyclopropyl-1-(2-piperidino-phenyl)-ethylamine (**12z**): 50%; oil. 2-Cyclobutyl-1-(2-piperidino-phenyl)-ethylamine (**12aa**): 41%; oil. 2-Cyclopentyl-1-(2-piperidino-phenyl)-ethylamine (**12ab**): 31%; oil. 2-Cycloheptyl-1-(2-piperidino-phenyl)-ethylamine (**12ad**): 46%; oil.

Route C. 1-(5-Chloro-2-pyrrolidino-phenyl)-ethylamine (12b). (a) 5-Nitro-2-pyrrolidino-benzonitrile (21a). 2-Chloro-5-nitro-benzonitrile (219 mM; Aldrich) and pyrrolidine (657 mM) in dry EtOH (400 mL) were refluxed for 2 h. The reaction was evaporated in vacuo; the residue was dissolved in water and acidified with 2 N HCl. Extraction with Et_2O and crystallization from EtOH yielded **21a**, 97%; mp 135−137 °C.

(b) 5-Amino-2-pyrrolidino-benzonitrile (22a). A mixture of **21a** (212 mM), iron powder (747 mM), water (112 mL), and NH_4Cl (125 mM) was refluxed for 2 h. After cooling to room temperature, the reaction was extracted with $CHCl_3$ to give, after crystallization from EtOH, **22a**, 86%; mp 125−127 °C.

(c) 5-Chloro-2-pyrrolidino-benzonitrile (23a). A solution of $NaNO_2$ (182 mM) in water (73 mL) was added dropwise at 0 °C to a solution of **22a** (182 mM) in semiconcentrated HCl (109 mL). The obtained cold solution was added dropwise to a mixture of Cu_2Cl_2 (238 mM) in concentrated HCl (95 mL) which was stirred in a bath of 40 °C. After 2 h at 40 °C, the reaction was cooled and extracted with $CHCl_3$. The organic phase was washed with water, dried, and evaporated in vacuo. The residue was purified by column chromatography (toluene) to yield **23a**, 57%; mp 73−75 °C.

(d) 1-(5-Chloro-2-pyrrolidino-phenyl)-ethylamine (12b). Analogous to ref 21, a solution of **23a** (68 mM) in dry Et_2O (40 mL) was added dropwise to a (freshly prepared) solution of MeMgI (270 mM) in dry Et_2O (140 mL). The reaction was refluxed for 94 h; TLC control indicated that **23a** had disappeared almost completely. $LiAlH_4$ (203 mM) was added, and reflux was continued for 4 h. After cooling to 0 °C, 2 N NaOH (135 mL) was added cautiously. The precipitate was filtered and washed with Et_2O. The organic layer was washed with water, dried, and evaporated in vacuo. The residue was purified by column chromatography with $CHCl_3$/MeOH (10:1) to give **12b**, 58%; oil (containing ∼15% of 5-chloro-2-pyrrolidino-benzylamine).

Compounds Obtained According to Route C. (The method involved reaction of **23** with R_4MgX and subsequent reduction of the intermediary MgX salt of ketimine **24** with $LiAlH_4$.) 1-(5-Chloro-2-(3-methyl-piperidino)-phenyl)-ethylamine (**12h**): 63%; oil (containing ∼5% of 5-chloro-2-(3-methyl-piperidino)-benzylamine). 1-(5-Chloro-2-(3,5-*cis*-dimethyl-piperidino)-phenyl)-ethylamine (**12j**): 67%; oil (containing ∼10% of 5-chloro-2-(3,5-*cis*-dimethyl-piperidino)-benzylamine. 1-(5-Chloro-2-piperidino-phenyl)-2-methyl-propylamine (**12p**): 56%; oil. 1-(5-Chloro-2-piperidino-phenyl)-propylamine (**12t**): 77%; oil.

Route D1. 1-(5-Chloro-2-piperidino-phenyl)-ethylamine (12c). (a) 5-Nitro-2-piperidino-acetophenon (25a). 2-Chloro-5-nitro-acetophenon (mp 62 °C; lit.[48] mp 62 °C) and piperidine (3 equiv) in dry EtOH (10 mL/g) were refluxed for 1.5 h. The reaction was evaporated in vacuo. The residue was dissolved in water and extracted with ether. The organic phase was washed with semiconcentrated HCl and H_2O, dried, and evaporated in vacuo to leave **25a** as a deep-red oil (100%, crude).

(b) 5-Chloro-2-piperidino-acetophenon (26a). Crude **25a** (62 g, 0.25 M) was hydrogenated over Pd/C (10%) (3.7 g) in DMF (620 mL) for 2 h at room temperature and 1 bar to yield 5-amino-2-piperidino-acetophenon (30 g, 55%, crude; mp 105−107 °C (EtOH)) which was dissolved in semiconcentrated HCl (82 mL). To this solution was dropped a solution of $NaNO_2$ (9.5 g, 137 mM) in water (55 mL) at 0 to 5 °C (=

solution A). Cu_2Cl_2 [freshly prepared by dropwise addition of a solution of $NaHSO_3$ (11.5 g, 91 mM) in water (36 mL) to a solution of $CuSO_4 \cdot 5H_2O$ (45.4 g, 182 mM) and NaCl (16 g, 274 mM) in water (36 mL) at $T_i = 35$ °C, filtration, and washing with water] was dissolved in concentrated HCl (72.6 mL) (=solution B). Cold (0 °C) solution A was dropped into solution B at $T_i = 0$ °C (foaming!). Thereafter, the reaction was warmed to 50 °C. After cessation of the nitrogen evolution, the reaction was cooled to 20 °C and extracted with $CHCl_3$. The organic extract was purified by column chromatography (toluene) to yield **26a** as an oil (18 g, 55%).

(c) 1-(5-Chloro-2-piperidino-phenyl)-ethylamine (12c). Analogous the literature,[21] **26a** (18 g, 75.7 mM) was added to ammonium formiate (19 g, 300 mM) heated at $T_i = 130$ °C. The temperature was kept at 150 °C for 5 h while H_2O was allowed to distill off. After cooling to room temperature, concentrated HCl (61 mL) was added, and the mixture was refluxed for 3.5 h. After standing overnight, the solution was extracted with EtOAc. The aqueous phase was acidified with concentrated NaOH and extracted with EtOAc. The organic phase was washed with water, dried, and evaporated in vacuo. The residue was purified by column chromatography ($CHCl_3$/MeOH/concentrated ammonia (10:1:0.1)) to yield **12c** (4.7 g, 26%; mp 68−70 °C); **12c·1.7HCl**, mp 258−262 °C.

Compound Obtained According to Route D1. (The method involved reaction of ketone **26** with ammoniumformiate and subsequent hydrolysis with concentrated HCl.) **1-(5-Chloro-2-dimethylamino-phenyl)-ethylamine (12a)**: 31%; oil; **12a·2HCl**, mp 216−218 °C.

Route D2. 1-(5-Chloro-2-octamethyleneimino-phenyl)-ethylamine (12n). (a) 5-Nitro-2-octamethyleneimino-acetophenon (25b). Equimolar amounts of 2-chloro-5-nitro-acetophenon, $NaHCO_3$, and octamethyleneimine[47] were refluxed in EtOH (250 mL/100 mM) for 1.5 h. The reaction was filtrated and evaporated in vacuo. The residue was triturated with H_2O and CH_2Cl_2. The organic phase was dried, filtered, and evaporated in vacuo to give **25b** (91%, crude; oil).

(b) 5-Chloro-2-octamethyleneimino-acetophenon (26b). A solution of 4 equiv of $Na_2S_2O_4$ in water (1 mL/mM) was dropped within 2 h to crude **25b** in EtOH (3 mL/mM) whereby T_i rose from 20 to 32 °C. After the mixture was stirred for further 30 min, EtOH was distilled off in vacuo. H_2O was added, and extraction was performed with CH_2Cl_2. The organic phase was dried, filtered, and evaporated in vacuo to yield 5-amino-2-octamethyleneimino-acetophenon (100%, crude; oil) which was, analogously to **26a**, diazotized, submitted to Sandmeyer reaction with Cu_2Cl_2, and purified to give to **26b** (32%, crude; oil).

(c) 5-Chloro-2-octamethyleneimino-acetophenon-oxime (27a). A mixture of crude **26b** and $NH_2OH \cdot HCl$ (1.1 equiv) was refluxed in EtOH (3.3 mL/mM) for 3.5 h. The reaction was evaporated in vacuo. H_2O was added, and extraction was performed with ether. Usual workup of the organic phase, purification by column chromatography with toluene/acetone (10:1), and crystallization from petrolether/toluene yielded **27a** (38%; mp 125−127 °C).

(d) 1-(5-Chloro-2-octamethyleneimino-phenyl)-ethylamine (12n). $LiAlH_4$ (42 mM) in dry Et_2O (50 mL) was added cautiously at room temperature to **27a** (10.5 mM) in dry Et_2O (50 mL) whereby strong hydrogen evolution occurred. Thereafter, the reaction was refluxed for 90 h. H_2O was cautiously added, and extraction was performed with ether. Usual workup of the organic phase and purification by column chromatography with $CHCl_3$/MeOH/concentrated ammonia (100:10:0.25) gave **12n** (31%; mp 68−70 °C; R_f 0.73) and, due to Neber rearrangement and subsequent reduction, 5-chloro-2-octamethyleneimino-*N*-ethyl-aniline (23%; oil; R_f 0.52).

Compounds Obtained According to Route D2. (The method involved reduction of oxime **27** with $LiAlH_4$.) 1-(5-Chloro-2-hexamethyleneimino-phenyl)-ethylamine (**12k**): 29%, oil; ·2HCl; mp 216−220 °C; containing some 5-chloro-2-hexamethyleneimino-*N*-ethyl-aniline. 1-(5-Chloro-2-heptamethyleneimino-phenyl)-ethylamine (**12m**): 36%, oil; containing ∼20% of 5-chloro-2-heptamethyleneimino-*N*-ethyl-aniline. 1-Cyclohexyl-1-(2-piperidino-phenyl)-methylamine (**12r**): In this case, the corresponding oxime (mp 173−180 °C) was reduced in glacial HOAc with Zn dust/concentrated HCl at 40 °C to yield **12r** (100%, crude; oil).

Special Procedures. 2-(5-Chloro-2-piperidino-phenyl)-2-propylamine·HCl (12e). (a) HCl was introduced for 8 h into a refluxed solution of **9d** in EtOH (2.4 mL/mM). After standing overnight at room temperature, the reaction was evaporated in vacuo. The residue was neutralized with aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with water and worked up as usual to give ethyl 5-chloro-2-piperidino-benzoate (60%; oil). (b) $LiAlH_4$ (245 mM) was stirred in dry ether (800 mL) at −60 to −70 °C, and a solution of the aforementioned ester (205 mM) in dry ether (170 mL) was added dropwise within 1.5 h at −60 to −70 °C. After the mixture was stirred at $T_i = -30$ °C for 3 h, EtOAc (8.9 mL) and, thereafter, saturated aqueous NH_4Cl (60 mL) were added at 0 °C. The resulting precipitate was filtered, and the filtrate was washed with H_2O. Workup of the etheral layer gave 5-chloro-2-piperidino-benzylalcohol (91%; oil). (c) A solution of the preceding benzylalcohol (191 mM) in $CHCl_3$ (35 mL) was added dropwise to $SOCl_2$ (423 mM) at $T_i = 10-15$ °C within 1 h. After the mixture was stirred at room temperature for 2 h, the reaction was evaporated in vacuo. Toluene was repeatedly added and distilled off in vacuo. The resulting residue was triturated with ether to yield 5-chloro-2-piperidino-benzylchloride·HCl (93%; mp 160−162 °C). (d) A solution of the preceding hydrochloride (10.7 mM) in dry DMSO (12 mL) was stirred at 45 °C in a stream of dry N_2 with a trap containing aqueous $FeSO_4$ at the outlet (for capture of HCN). NaCN (21.4 mM) dissolved in DMSO (17 mL) was added dropwise within 1 h. After the mixture was stirred for 5 h at 40−50 °C, the reaction was poured into iced water and extracted with ether. Workup of the organic layer and purification by column chromatography (toluene) gave 5-chloro-2-piperidino-benzylcyanide (64%; oil). (e) Analogous to the literature,[49] a solution of the above benzylcyanide (4.26 mM) in dry DMF (1.5 mL) was dropped slowly at room temperature to NaH (8.52 mM) in dry DMF (5 mL). After stirring for 0.5 h at $T_i = 40-50$ °C, a solution of MeI (9.37 mM) in dry DMF (1.5 mL) was added at room temperature. After the mixture was stirred for 2 h at room temperature, the reaction was poured into iced water and extracted with ether. Workup of the organic layer and purification by column chromatography with toluene/petrolether (1:1) gave 2-(5-chloro-2-piperidino-phenyl)-2-propyl-cyanide (63%; mp 82−84 °C). (f) The aforementioned cyanide (51.4 mM) was heated in 85% H_2SO_4 (135 mL) at 50 °C for 3 h. After cooling to room temperature, the reaction was dropped slowly into a mixture of excess concentrated ammonia and ice at $T_i \sim 10$ °C. The resulting precipitate was filtered and triturated with H_2O and ether. The organic layer was washed with H_2O and worked up as usual. Crystallization from EtOH gave 2-(5-chloro-2-piperidino-phenyl)-2-methyl-propanoyl-amine (68%; mp 176−178 °C). (g) Analogous to the literature,[50] the preceding amide (3.9 g, 13.9 mM) was added at 0 °C to a solution of NaOBr [freshly prepared by adding bromine (0.72 mL, 13.9 mM) at −2 to 0 °C to a solution of NaOH (3.33 g, 83.3 mM) in water (25 mL)]. After the mixture was stirred for 3 h at 0 °C, dioxane (15 mL) was added, and stirring was continued (2 h, 0 °C and 2.5 h without cooling). Some H_2O was added, and extraction was performed with toluene (4 × 500 mL). The organic layer was washed with water, and workup gave *N*,*N*′-bis-(2-(5-chloro-2-piperidino-phenyl)-2-propyl)-urea (3.6 g, 97% crude: mp 215−217 °C; recrystallized from EtOAc: mp 224−226 °C). (h) The preceding urea derivative (3.55 g, 6.68 mM) was heated with semiconcentrated HCl (70 mL) for 6 h in a glass ampule at 150 °C. The reaction was evaporated in vacuo. The residue was triturated in a mortar, suspended in water, acidified with 2 N HCl (ad pH < 3), and extracted with ether until no solid material was left. The acidic aqueous phase was extracted with $CHCl_3$. Workup of the $CHCl_3$ extract (brown solid, 2.8 g) and crystallization from *i*-PrOH gave **12e**·HCl (1.65 g, 41%; mp 229−234 °C).

(5-Chloro-2-piperidino-phenyl)-methylamine (12f)·1.5 HCl. (a) 5-Chloro-2-piperidino-benzyl chloride·HCl (89 mM) and potassium phthalimide (187 mM) were heated in dry DMF (375 mL) for 2 h at 90 °C. The reaction was evaporated in vacuo. H_2O was added to the residue. The solid material was filtered, washed with EtOH and ether, and then digested in $CHCl_3$. The remaining solid was filtered and dried to yield *N*-(5-chloro-2-piperidino-benzyl)-phthalimide (74%; mp 190−193 °C). (b) The preceding phthalimide (22 g, 62 mM) and 80% $N_2H_4 \cdot H_2O$ (4.7 g, 75 mM) in EtOH (380 mL) were refluxed for 10 h. EtOH was partially (∼50%) distilled off in vacuo; semiconcentrated HCl (ad pH < 3) and H_2O (500 mL) were added. Precipitated material was filtered off. The filtrate was evaporated in vacuo.To the residue was added concentrated ammonia, and extraction was performed with ether. The organic layer was washed with water, and usual workup gave **12f** (11.2 g, 80%; oil) which was transformed in *i*-PrOH with HCl/ether to **12f**·1.5HCl (11 g; mp 230−240 °C).

Procedures for Enantiomeric Amines 12. *Note:* Chiral stationary phase (CSP)-HPLC analysis to determine enantiomeric purity was carried out according to the following procedures.

(a) After Derivatization of the Enantiomeric Amine 12 with Acetanhydride (A) or in Situ with 1-Naphthoylchloride (N). Bakerbond DNPG (covalent) column; chiral phase: (*R*)-*N*-(3,5-dinitro-benzoyl)-2-phenyl-glycine covalently bound to aminopropyl silica gel; particle size: 5 μm; pore width: 60 Å; l = 250 mm; ∅ = 4.6 mm; flow rate: 2 mL/min; HPLC-apparatus: HP1090M with HP1040 (DAD); mobile phase: *n*-hexane/EtOH p.a.: 98.5/1.5 (A), or 99.0/1.0 (N); temperature: 20 °C (A) or 45 °C (N); UV detection: 254(10) nm, ref 550(50) nm (A), or 280(10) nm, ref 550(50) nm (N); or

(b) For the Enantiomeric Amine 12 or Salts Thereof. Chiralcel OD-R column [10 μm; l = 250 mm; ∅ = 4.6 mm; flow rate: 0.4 mL/min; mobile phase: 0.2 M aqueous $NaClO_4$ (adjusted with $HClO_4$ to pH 5.3)/ MeOH/ MeCN (32:27:41); temperature: 35 °C; UV detection: 254(10) nm, ref 450(50) nm; HPLC apparatus: HP1090 with Laserjet 4 plus printer.

Route E. (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q) and **(*R*)-3-methyl-1-(2-(1-piperidinyl)-phenyl)-butylamine (*R*)-(12q).** (a) 3-Methyl-1-(2-piperidino-phenyl)-butylamine **12q** (122 g, 495 mM; optionally purified via its glutarate of mp 179−180 °C) and (L)(−)-*N*-acetyl-glutamic acid (93.7 g, 495 mM; Fluka) were refluxed in a mixture of acetone (1000 mL) and MeOH (80 mL). After the solution had become clear, stirring was continued overnight at room temperature. By filtration and washing with cold (−15 °C) acetone, a solid (98.9 g; mp 163−166 °C) was obtained which was recrystallized from acetone (1000 mL)/MeOH (200 mL) to yield **(*S,S′*)-28** (65.1 g, 30.2%; mp 168−171 °C; $[\alpha]^{20}_D$ +35.7° (*c* 1, MeOH); ee 98.0). For X-ray structure determination, crystals (mp 173.2 °C) were grown from a solution in H_2O. (b) For synthesis, **(*S*)-12q** was liberated from an aqueous solution of **(*S,S′*)-28** with concentrated ammonia/toluene. Workup of the toluene extract gave **(*S*)-12q** ($bp_{0.6}$ 112 °C; $[\alpha]^{20}_D$ +6.9° (*c* 1, MeOH)). (c) For X-ray structure determination, **(*S*)-12q** was reacted with (*S′*)-1-phenethyl-isocyanate (ee ∼ 96%, Fluka) in ether to give N^1-[(*S*)-3-methyl-1-[2-(1-piperidinyl)phenyl] butyl-N^3-[(*S′*)-1-[phenyl]ethyl]-urea **(*S,S′*)-38b** (mp 183−184 °C; $[\alpha]^{20}_D$ −2.2° (*c* 1, MeOH)). Crystals were grown from a solution in EtOH/H_2O (5:1). (d) The filtrate of the preceding (a) 98.9 g crop of **(*S,S′*)-28** was evaporated in vacuo to dryness. The crude residue (*R*/*S* = 72:28) was digested in hot acetone (10 mL/g). After cooling to 20 °C, the solid material (*R*/*S* = 70:30) was filtered. The filtrate was evaporated in vacuo; from this residue, **(*R*)-12q** (very crude, ∼40% impurities) was liberated and purified via salt formation with glutaric acid in acetone to yield **(*R*)-29** (mp 152−155 °C; $[\alpha]^{20}_D$ −25.6° (*c* 1, MeOH); *R*/*S* = 97:3). (e) For synthesis, **(*R*)-12q** was liberated from an aqueous solution of **(*R*)-29** with concentrated ammonia/toluene.

Route F. (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q). (a) (Isobutyl)-(2-piperidino-phenyl)-ketone (30q). To a solution of *i*-BuMgBr (805 mM) in toluene/THF (4:1) (465 mL) was added a solution of nitrile **15a** (268 mM) in toluene/THF (4:1) (330 mL). After reflux for 6.5 h, the reaction was cooled to room temperature and dropped slowly into 4 N HCl (1.2 L) under stirring and adding ice (to keep T_i at 20 °C). The acidic aqueous phase was separated, alkalinized with concentrated ammonia, and extracted with EtOAc. The organic phase was washed with water; usual workup and purification by column chromatography with cyclohexane/EtOAc (10:1) gave **30q** (56%) as a yellow oil. An attempt to purify crude **30q** via distillation ($bp_{0.8}$ 125 °C) resulted mostly in decomposition.

(b) (Isobutyl)-(2-piperidino-phenyl)-*N*-[(*S′*)-1-phenethyl]-ketimine (*S′*)-(31q). To a stirred solution of **30q** (31 g, 126 mM), (*S′*)-1-phenethylamine (30.5 g, 252 mM; Fluka, ee ≥ 98%), and triethylamine (57.3 mL, 413 mM) in dry toluene (320 mL) was dropped a solution of $TiCl_4$ (11.2 mL, 100 mM) in dry toluene (38 mL) at −15 °C during 1 h. After stirring overnight at room temperature, Et_2O was added. The precipitate was filtered and washed with Et_2O. The combined filtrates were evaporated in vacuo. The tarry residue was triturated heavily with Et_2O. The filtrate was evaporated in vacuo, and the residue was triturated as before. This procedure was repeated several times until the ethereal solution remained clear. At last, the residue (red-brown oil) was distilled over a 5 cm Vigreux column to give **(*S′*)-31q** as a yellow-orange oil (27.9 g, 63%; $bp_{0.4}$ 155−165 °C). In vain was attempted to react **30q** with (*S′*)-1-phenethylamine in toluene in a Dean−Stark apparatus with *p*-TsOH or/and molecular sieves.

(c) *N*-{(*S*)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butyl}-*N*-[(*S′*)-1-phenethyl]-amine (*S,S′*)-(32q). (*S′*)-31q (17 g, 49 mM) was hydrogenated in EtOH (170 mL) in the presence of Ti(O−*i*−Pr)$_4$ (1.7 g, 6 mM) over Raney-Ni (8 g, +8 g after 20 h) for 72 h at 50 °C and 200 bar to yield **(*S,S′*)-32q** (13.2 g, 76%; $bp_{0.2}$ 152 °C; de 96.8%; $[\alpha]^{20}_D$ −55.3° (*c* 1.1, MeOH)). HPLC analysis was performed on a Lichrosorb RP18 column (Merck, Germany) [7 μm; l = 250 mm; ∅ = 4 mm; mobile phase: MeOH/dioxane/0.1% aqueous NaOAc (adjusted with HOAc to pH 4.05) (135:60); temperature: 23 °C; UV detection: 254(10) nm; peak 1 (*S,S′*)/peak 2 (*R,S′*)-ratio: 98.4:1.4]. Without Ti(O−*i*−Pr)$_4$, the hydrogenation required higher temperature and more time.

(d) (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q). (*S,S′*)-32q (12.5 g, 36 mM) was hydrogenated in water (125 mL)/concentrated aqueous HCl (3.6 mL, 44 mM) over Pd/C (10%) (1.3 g) for 10 h at 50 °C and 5 bar to give **(*S*)-12q** (6.4 g, 72%; $bp_{0.4}$ 115−117 °C; ee 93.5%).

Compounds Obtained According to Route F. (*R*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine **(*R*)-(12q)** (57%; $bp_{0.2}$ 100−105 °C; ee ≤ 95.2%) via (isobutyl)-(2-piperidino-phenyl)-N-[(*R′*)-1-phenethyl]-ketimine **(*R′*)-(31q)** (49%; $bp_{0.1}$ 142−150 °C), hydrogenation (160 h, 50 °C, 200 bar) to *N*-{(*R*)-3-methyl-1-[2-(1-piperidinyl)phenyl]butyl}-*N*-[(*R′*)-1-phenethyl]-amine **(*R,R′*)-(32q)** (66%; $bp_{0.6}$ 155−160 °C), and subsequent hydrogenolytic cleavage. (*R*)-1-(2-(1-Piperidinyl)-phenyl)-butylamine **(*R*)-(12o)** (84%; $bp_{0.2}$ 108−115 °C; ee 97.4%), via (*n*-propyl)-(2-piperidino-phenyl)-ketone (**30o**) (72%; $bp_{0.2}$ 110 °C), (*n*-propyl)-(2-piperidino-phenyl)-*N*-[(*R′*)-1-phenethyl]-ketimine **(*R′*)-(31o)** (88%, crude), hydrogenation (22 h, 50 °C, 200 bar) to *N*-{(*R*)-1-[2-(1-piperidinyl)phenyl]butyl}-*N*-[(*R′*)-1-phenethyl]-amine **(*R,R′*)-(32o)** (76%; $bp_{0.05}$ 145−153 °C; de 97.9%; $[\alpha]^{20}_D$ +55.6° (*c* 1.0, MeOH)), and subsequent hydrogenolytic cleavage. (*S*)-1-(2-(1-Piperidinyl)phenyl)-butylamine **(*S*)-(12o)** (81%; $bp_{0.6}$ 115−117 °C; ee 91.2%; $[\alpha]^{20}_D$ +18.5° (*c* 1, MeOH)), via (*n*-propyl)-(2-piperidino-phenyl)-*N*-[(*S′*)-1-phenethyl]-ketimine **(*S′*)-(31o)** (96%, crude), hydrogenation (41 h, 50 °C, 5 bar) to *N*-{(*S*)-1-[2-(1-piperidinyl)phenyl]-butyl}-*N*-[(*S′*)-1-phenethyl]-amine **(*S,S′*)-(32o)** (74%; $bp_{0.05}$ 130−140 °C; de 91.2%; $[\alpha]^{20}_D$ −52.8° (*c* 1.2, MeOH)), and subsequent hydrogenolytic cleavage. For X-ray structure determination, **(*S*)-12o** was reacted with (*S′*)-1-phenethyl-isocyanate (ee ∼ 96%) in ether to give N^1-[(*S*)-1-[2-(1-piperidinyl)phenyl]butyl-N^3-[(*S′*)-1-[phenyl]ethyl]-urea **(*S,S′*)-(38a)** (mp 183−184 °C; $[\alpha]^{20}_D$ +2.1° (*c* 1, MeOH)); crystals were grown

from a solution in EtOH/water (3:1). A CD spectrum of a complex of **(*S*)-12o** (1.24 mM/L in MeCN) with $[Rh(OAc)_2]_2$ showed a very high similarity to that of (*S*)-1-phenethylamine with $[Rh(OAc)_2]_2$.[25]

Route G. (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q). (a) *N*-Acetyl-*N*-[3-methyl-1-(2-(1-piperidinyl)phenyl)-1-(*Z*)-buten-1-yl]-amine (*Z*)-(33). To a solution of **16q** (44 g, 180 mM) in toluene (440 mL) was dropped acetanhydride (17 mL, 180 mM) at 0 °C. After the mixture was stirred (3 h at 0 °C, 15 h at room temperature), the reaction was evaporated in vacuo. The residue, dissolved in EtOAc, was washed with aqueous Na_2CO_3. Workup of the organic phase and purification by column chromatography with toluene/EtOAc (5:1) gave **(*E*)-33** (5.8%; mp 135−137 °C; R_f 0.47) and **(*Z*)-33** (31 g, 34%; mp 139−141 °C; R_f 0.40).

(b) *N*-Acetyl-*N*-[(*S*)-3-methyl-1-(2-(1-piperidinyl)phenyl)-1-butyl]-amine (*S*)-(34). (*Z*)-(33) (0.57 g, 1.99 mM) was dissolved in degassed MeOH/CH_2Cl_2 (5:1) (10 mL) under argon. The solution was added to a solution of the Noyori catalyst $Ru(OAc)_2[(S)\text{-BINAP}]$ (16.8 mg, 1 mol %) {prepared from $[Ru(COD)Cl_2]_n$ with (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP], NEt_3, and NaOAc} and $Ti(O-i-Pr)_4$ (3.4 mg, 0.5 mol %) in degassed MeOH/CH_2Cl_2 (5:1) (10 mL) under argon. The mixture was transferred to an evacuated (10^{-2} mbar) autoclave. After repeated ventilation with hydrogen (4 bar), hydrogenation took place at 30 °C and 100 bar for 170 h (end of H_2 uptake). The reaction was evaporated in vacuo. The residue was refluxed with *n*-hexane (30 mL). The hot mixture was filtered, and the filtrate was cooled to give **(*S*)-34** (0.31 g, 54%; mp 127−131 °C; ee 82%). Further extraction of the undissolved material with hot *n*-hexane gave **rac-34** (14%; mp 154−156 °C). For comparison, pure **(*S*)-34** (mp 130−132 °C; ee 99.4%; $[\alpha]^{20}_D$ +3.1° (*c* 1, MeOH)) was obtained by reaction of **(*S*)-12q** with acetanhydride). Without $Ti(O-i-Pr)_4$, no hydrogen uptake was observed over 96 h, but **(*Z*)-33** (75%) was recovered.

(c) (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q). (*S*)-34 (ee 82%) was boiled in concentrated hydrochloric acid (10 mL/g) for 5.5 h to give **(*S*)-12q** (98%; oil; ee 82%).

Route H. (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q). (a) [2-(1-Piperidinyl)phenyl]-*N*-[(*R*′)-1-phenethyl]-aldimine (*R*′)-(35). 18a was dropped at +5 °C to (*R*′)-1-phenethylamine (1 equiv, ee ≥ 98%, Fluka). After stirring overnight at room temperature, ether was added. The solution was dried over Na_2SO_4 and evaporated in vacuo to yield **(*R*′)-35** (91.8%, crude; oil).

(b) *N*-{(*S*)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butyl}-*N*-[(*R*′)-1-phenethyl]-amine (*S*,*R*′)-(36q). A solution of crude **(*R*′)-35** (2 g, 6.84 mM) in dry THF (20 mL) was added to a solution of *i*-BuMgBr (27.4 mM, 4 equiv) in dry THF (22 mL). After each stirring period (18 h at 60 °C, 12 h at 80 °C), *i*-BuMgBr/THF (2 equiv each) was added. Heating at 80 °C was continued for further 60 h. After cooling to room temperature, concentrated HCl was added and the mixture was evaporated in vacuo. To the residue was given concentrated ammonia, and extraction was performed with ether. Workup of the organic extract and purification by column chromatography with toluene/acetone (95:5) yielded **(*S*,*R*′)-36q** (0.2 g, 8.3%; oil; de 91.2%). Reaction of crude **(*R*′)-35** with *i*-BuMgBr (6 equiv) in toluene/THF (4:1) in the presence of $Ti(O-i-Pr)_4$ (0.05 equiv) for 60 h at 100 °C in a sealed glass vessel gave **(*S*,*R*′)-36q** (5%; de 97.6%).

(c) (*S*)-3-Methyl-1-(2-(1-piperidinyl)phenyl)-butylamine (*S*)-(12q). (*S*,*R*′)-36q (de 91.2%) was hydrogenated in water (+1.1 equiv HCl) over Pd/C (10%) (5 h, 50 °C, 5 bar) to yield **(*S*)-12q** (63%; oil; ee 87.6%).

Compounds Obtained According to Route H. (*R*)-1-(2-(1-Piperidinyl)phenyl)-butylamine (*R*)-(12o). (a) To a stirred and refluxed solution of aldimine **(*S*′)-35** (50%; $bp_{0.02}$ 155−157 °C; $[\alpha]^{20}_D$ −84.8° (*c* 1, MeOH)) in dry Et_2O was added *n*-PrMgBr (2 equiv, in Et_2O); further *n*-PrMgBr (2 and 4 equiv) was added after 0.5 and 4.5 h, respectively. After reflux (overall 6 h) and standing overnight at room temperature, the reaction was poured into a mixture of 2 N HCl and ice. Concentrated ammonia (+ ice) was added, and extraction was performed with Et_2O (3×). The organic extract was washed with H_2O. Workup of the organic phase gave a crude residue containing—due to HPLC-analysis—**(*S*,*S*′)-36o** (peak 1, 23.6%) and **(*R*,*S*′)-36o** (peak 2, 76.4%). Column chromatography with (i) toluene/saturated with concentrated ammonia and (ii) toluene/acetone/concentrated ammonia (10:1:0.01) gave **(*S*,*S*′)-36o** (7.2%; oil; R_f 0.60; $[\alpha]^{20}_D$ −53.5° (*c* 1, MeOH)) and **(*R*,*S*′)-36o** (33.4%; oil; R_f 0.47; de ≥ 99%; $[\alpha]^{20}_D$ −35.5° (*c* 1, MeOH)). (b) Hydrogenation of **(*R*,*S*′)-36o** (1.8 g, 5.3 mM; de ≥ 99.0%) in EtOH (20 mL) over Pd/C (10%) (0.5 g) for 5 h at 50 °C and 5 bar gave **(*R*)-(12o)** (1.1 g, 89%; oil; ee 79.8%). The surprisingly low ee value (79.8%) can be probably referred to the use of EtOH (instead of H_2O + 1.1 equiv HCl). A portion of the base in Et_2O was transformed with HCl/Et_2O to **(*R*)-(12o)**·1.4HCl (mp 90−100 °C; $[\alpha]^{20}_D$ −20.0° (*c* 1, MeOH)).

Route I. (*R*)-Phenyl-(2-(1-piperidinyl)phenyl)-methylamine (*R*)-(12s) and (*S*)-Phenyl-(2-(1-piperidinyl)phenyl)-methylamine (*S*)-(12s). (a) *N*-[(*R*)-Phenyl-(2-(1-piperidinyl)phenyl)-methyl]-*N*-[(*S*′)-*p*-toluene-sulfinyl]-amine (*R*,*S*′)-(37) and *N*-[(*S*)-Phenyl-(2-(1-piperidinyl)-phenyl)-methyl]-*N*-[(*S*′)-*p*-toluene-sulfinyl]-amine (*S*,*S*′)-(37). To a stirred solution of **12s** (44.7 g, 167.8 mM) in dry THF (400 mL) was dropped under N_2 at −15 °C a solution of *n*-BuLi (1.7 molar in *n*-hexane, 167.8 mM). After stirring for 5 min, a solution of (−)(*S*′)-[(1*R*,2*S*,5*R*)-menthyl]-*p*-toluene-sulfinate (Aldrich, 24.7 g, 83.9 mM) was added dropwise at −10 °C. The reaction mixture was stirred overnight at room temperature and then evaporated in vacuo. The residue was dissolved in water. Extraction with CH_2Cl_2, workup of the organic phase, and repeated column chromatography with cyclohexane/EtOAc (12:1) gave **(*S*,*S*′)-37** (7.85 g, 23%; mp 97−98 °C; R_f 0.39; de 99.6%; $[\alpha]^{20}_D$ +166° (*c* 1, MeOH)) and **(*R*,*S*′)-37** (6.2 g, 18.3%; oil; R_f 0.31; de ≥ 98%; $[\alpha]^{20}_D$ +52° (*c* 1, MeOH)), respectively.

(b) (*S*)-Phenyl-(2-(1-piperidinyl)phenyl)-methylamine (*S*)-(12s). To a solution of **(*S*,*S*′)-37** in dry MeOH (8 mL/mM) was added TFA (4 equiv) at +5 °C. After the mixture was stirred (1 h at 30 °C and 0.75 h at 40 °C), it was evaporated in vacuo. The residue was dissolved in aqueous HCl. After extraction with Et_2O (discarded), the aqueous phase was alkalinized with 10 N NaOH under cooling and extracted with CH_2Cl_2. The organic phase was worked up to yield **(*S*)-12s** as a yellow oil (97%; $[\alpha]^{20}_D$ −60° (*c* 1; MeOH)). To determine de, **(*S*)-12s** was reacted with (*S*)-1-phenethylisocyanate in Et_2O. The resulting urea derivative (mp 191−192 °C; $[\alpha]^{20}_D$ −8.4° (*c* 1, MeOH)) showed de = 98.6%. To determine the configuration, **(−)-12s** (1.6 mM) was reacted with 1-(rac-2-phenyl-butanoyl)-imidazol (3.29 mM) in benzene (7.8 mL) for 18 h at room temperature. After dilution with benzene (30 mL), the reaction was extracted with 2 N NaOH (2 × 20 mL). The alkaline aqueous phase was washed with benzene, acidified with 5 N HCl, and extracted with toluene. The toluene phase was worked up to give recovered 2-phenyl-butanoic acid (0.67 mM; $[\alpha]^{20}_D$ −12.3° (*c* 4, benzene). According to the literature[28] teaching that a negative sign of the optical rotation of the recovered acid correlates with (*S*), **(−)-12s** must be considered as (*S*)-configurated.

(c) (*R*)-Phenyl-(2-(1-piperidinyl)phenyl)-methylamine (*R*)-(12s). (*R*,*S*′)-37 was cleaved as described above to give **(*R*)-12s** as an oil (94%; $[\alpha]^{20}_D$ +52° (*c* 1, MeOH)). Reaction with (*S*)-1-phenethylisocyanate in Et_2O afforded the corresponding urea derivative (mp 198−200 °C; de 94.4%; $[\alpha]^{20}_D$ −11.2° (*c* 1, MeOH)). Reaction with 1-(rac-2-phenyl-butanoyl)-imidazol (2 equiv) led to recovered 2-phenyl-butanoic acid (78%; $[\alpha]^{20}_D$ +6.6° (*c* 4, benzene)). According to the literature[28] **(+)-12s** must be considered as (*R*)-configurated.

Configurational Stability of (*S*)-Amine (*S*)-12q and of *N*-Acetyl-(*R*)-amine (*R*)-34. (a) **(*S*)-12q** (10 mM; containing 0.85% **(*R*)-12q**) was heated (i) with *t*-BuOK (1.5 mM) in DMSO (4 mL) for 60 min at 90 °C or (ii) with *p*-TsOH·H_2O (30 mM) in water (12 mL) for 3 days at 100 °C in a sealed glass tube. The recovery of **(*S*)-12q** was 85% (i) and 92% (ii), and the

contents of **(*R*)-12q** were 0.88% (i) and 0.70% (ii), respectively. Under conditions comparable to (i), (*R*)-1-phenethylamine was reported to racemize completely.[51]

(b) (*R*)-34 (mp 125−130 °C; ee = 65.2%) was heated: (i) with solid NaOH (1% w/w) for 3 h at 160 °C; (ii) with solid KOH (5% w/w) for 3 h at 210 °C; (iii) with glacial HOAc (5 parts) + Ac_2O (0.2 parts) for 3 h at 160 °C; (iv) with glacial HOAc (10 parts) + NaOAc (1 equiv) for 3 h at 160 °C. **(*R*)-34** was recovered by column chromatography with 50% (i, ii, iv) and 67% (iii), respectively; ee was 59.0 ± 0.2% (each).

General Procedures A3−A7 for Esters 14. *Note:* Enantiomeric purity was determined by CSP−HPLC according to the method described for **(*S*)-14z**.

A3. *N,N′*-Carbonyl-diimidazole (10.3 mM) was added at room temperature to a stirred solution of educt **13** (10.3 mM) in dry THF (14 mL). After refluxing for 1 h, a solution of amine **12** (10.3 mM) in dry THF (7 mL) was added at room temperature. After being stirred overnight at room temperature, the reaction mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel with toluene/acetone (5:1) to afford the targeted ester **14**.

A4. A mixture of educt **13** (11.9 mM), amine **12** (11.9 mM), triphenylphosphin (14.3 mM), NEt_3 (23.8 mM), and tetrachloromethane (11.9 mM) in acetonitrile (29 mL) was stirred for 15 h at room temperature. After evaporation in vacuo, H_2O and EtOAc were added to the residue for extraction. The organic layer was dried, filtered, and evaporated in vaccuo. The residue was purified by column chromatography on silica gel with toluene/acetone (10:1) to afford ester **14**.

A5. Phosphortrichloride (1.5 mol) was added to educt **13** (0.5 mol) at room temperature. After standing overnight at room temperature, the reaction was heated for 30 min at 50 °C. The clear yellowish solution was decanted and evaporated in vacuo at 50 °C to yield the corresponding phenylacetylchloride (crude, 99%). A solution of the acid chloride (0.4 mol) in CH_2Cl_2 (490 mL) was dropped to a stirred solution of amine **12** (0.4 mol) and NEt_3 (0.44 mol) in CH_2Cl_2 (980 mL) at 20 °C within 20 min. The reaction was extracted subsequently with H_2O (3 × 500 mL), 10% aqueous HCl (2 × 500 mL), and H_2O (3 × 500 mL). The organic phase was dried, filtered, and evaporated in vacuo. The residue was crystallized from toluene/petrolether and/or acetone to afford ester **14**.

A6. To a dried and stirred solution of amine **12** (1 mM) in toluene (30 mL) was added educt **13** (1.1 mM) at room temperature. After the solution had become clear, *N,N′*-dicyclohexyl-carbodiimide (1.16 mM) was added. After stirring for 2 h at room temperature, the reaction was filtered, and the filtrate was evaporated in vacuo. The residue was crystallized from petrolether or toluene/petrolether; alternatively, it was purified by column chromatography on silica gel with petrolether/EtOAc (2:1) to afford ester **14**.

A7. Analogous to general procedure A4, educt **13**, ketimine **16**, triphenylphosphin, NEt_3, and tetrachloromethane were reacted to yield, after column chromatography, the enamidoester **(*E/Z*)-17** [(*E*) predominant and more polar]. A mixture of **(*E/Z*)-17** or **(*E*)-17** (11 mM) was hydrogenated over Pd/C (10%) (1.2 g) in EtOH (45 mL) for 5 h at 20 °C and 5 bar to yield ester **14**.

General Procedures B3−B5 for Substituted Benzoic Acids 6. *Note:* Enantiomeric purity was determined by CSP−HPLC according to the method described for **(*S*)-6am**.

B3. A solution of ester **14** (5 mM) in EtOH (23 mL) and aqueous NaOH (8 mM/7 mL H_2O) was stirred for 2 h at 50 °C. The reaction was evaporated in vacuo (not completely), poured into water, adjusted to pH 6 with 10% aqueous HCl, and extracted with EtOAc (or CH_2Cl_2). The organic phase was washed with H_2O, dried, filtered, and evaporated in vacuo. The residue was crystallized to afford the targeted acid **6** (for solvents used, see Tables 2 and 3).

B4. To a stirred warm (bath temperature 60 °C) solution of ester **14** (370 mM) in EtOH (10 mL/g) was added 1 N NaOH (480 mM; 1.3 equiv). After the mixture was stirred for 4 h at 60 °C, the heating bath was removed, and 1 N HCl (480 mM; 1.3 equiv) was added. After cooling to room temperature (or even to 0 °C), the precipitate was filtered, washed with H_2O, and dried to yield the targeted acid **6**. Mostly, enantiomeric acids **6** were recrystallized to raise enantiomeric purity.

B5. A solution of acid **6** (R_3 = Cl) [or ester **14** (R_3 = Cl)] in EtOH (4 mL/mM) was hydrogenated over Pd/C (10%) (0.2 g/mM) for 3 h at 50 °C and 1 bar. The reaction was evaporated in vacuo. H_2O and EtOAc were added; pH was adjusted to 6 with aqueous ammonia. The organic layer was separated, washed with H_2O, dried, filtered, and evaporated in vacuo. The residue was crystallized to afford the corresponding acid **6** (R_3 = H) [or ester **14** (R_3 = H)].

Compounds Obtained According to Procedure A3. Methyl 4-[2-[[1-[5-chloro-2-dimethylamino-phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14a**): 67%; mp 153−155 °C, from **12a**. Methyl 4-[2-[[1-[5-chloro-2-(1-pyrrolidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14b**): 58%; mp 132−135 °C, from **12b**. Methyl 4-[2-[[1-[5-chloro-2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14c**): 69%; mp 146−148 °C, from **12c**. Methyl 4-[2-[[2-[5-chloro-2-(1-piperidinyl)phenyl]-2-propyl]-amino]-2-oxoethyl]-benzoate (**14d**): 84%; mp 229−234 °C, from **12e**. Methyl 4-[2-[[5-chloro-2-(1-piperidinyl)phenyl]-methyl]amino]-2-oxoethyl]-benzoate (**14e**): 75%; mp 123−125 °C, from **12f**. Ethyl 4-[2-[[1-[5-chloro-2-(2-methyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14f**): 71%; viscous, from **12g**. Methyl 4-[2-[[1-[5-chloro-2-(3-methyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14g**): 54%; mp 160−162 °C, from **12h**. Methyl 4-[2-[[1-[5-chloro-2-(3,5 *cis*-dimethyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14i**): 44%; mp 190−193 °C, from **12j**. Methyl 4-[2-[[1-[5-chloro-2-hexamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14j**): 42%; mp 146−147 °C, from **12k**. Ethyl 4-[2-[[1-[2-hexamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14k**): 68%; mp 145−148 °C, from **12l**. Methyl 4-[2-[[1-[5-chloro-2-heptamethyleneimino-phenyl]-ethyl]amino]-2-oxoethyl]-benzoate (**14l**): 30%; mp 152−156 °C, from **12m**. Methyl 4-[2-[[1-[5-chloro-2-octamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14m**): 38%; mp 184−185 °C, from **12n**. Methyl 4-[2-[[1-[5-chloro-2-(1-piperidinyl)phenyl]-2-methyl-propyl]amino]-2-oxoethyl]-benzoate (**14n**): 61%; mp 155−158 °C, from **12p**.

According to procedure A4 the following compounds were obtained: Ethyl 4-[2-[[1-[2-(4-methyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14h**): 56%; mp 125−128 °C, from **12i**. Ethyl 4-[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]butyl]amino]-2-oxoethyl]-benzoate (**14o**): 73%; mp 152−155 °C, from **12q**. Ethyl 4-[2-[[cyclohexyl-[2-(1-piperidinyl)-phenyl]methyl]amino]-2-oxoethyl]-benzoate (**14p**): 54%; mp not determined, from **12r**. Ethyl 4-[2-[[phenyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoate (**14q**): 74%; mp 160−162 °C, from **12s**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14r**): 70%; mp 92−93 °C, from **12d**. Ethyl 2-ethoxy-4-[2-[[1-[5-chloro-2-(1-piperidinyl)phenyl]propyl]amino]-2-oxoethyl]-benzoate (**14s**): 51%; mp 110−112 °C, from **12t**. Methyl 2-methoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]--benzoate (**14u**): 66%; mp 128−131 °C, from **12o**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (**14v**): 81%; mp 110−115 °C, from **12o**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]pentyl]amino]-2-oxoethyl]-benzoate (**14w**): 64%; mp 113−115 °C, from **12u**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]-4-penten-1-yl]amino]-2-oxoethyl]-benzoate (**14x**): 58%; mp 117−120 °C, from **12v**. Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (**14y**): 85%; mp 143−145 °C, from **12q**. Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]-3-buten-1-yl]amino]-2-oxoethyl]-benzoate (**14z**): 34%; mp 126−128 °C, from **12w**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]hexyl]amino]-2-oxoethyl]-benzoate (**14aa**), 43%; mp 100−105 °C, from **12x**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]heptyl]amino]-2-oxoethyl]-benzoate (**14ab**): 80%; mp 100−104 °C, from **12y**. Ethyl 2-ethoxy-4-[2-[[phenyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoate (**14ac**): 77%; mp 149−151 °C, from **12s**. Ethyl 2-ethoxy-4-[2-[[2-cyclopropyl-1-[2-(1-piperidinyl)phenyl]ethyl]-

amino]-2-oxoethyl]-benzoate (**14ad**): 29%; mp 126−127 °C, from **12z**. Ethyl 2-ethoxy-4-[2-[[2-cyclobutyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14ae**): 14%; mp 116−118 °C, from **12aa**. Ethyl 2-ethoxy-4-[2-[[2-cyclopentyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14af**): 37%; mp 120−121 °C, from **12ab**. Ethyl 2-ethoxy-4-[2-[[2-cyclohexyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14ag**): 68%; mp 94−97 °C, from **12ac**. Ethyl 2-ethoxy-4-[2-[[2-cycloheptyl-1-[2-(1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoate (**14ah**): 48%; mp 96−98 °C, from **12ad**. Ethyl 2-ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14ai**): 72%; mp 102−105 °C, from **12ae**. (*R*)(+)-Ethyl 4-[2-[[phenyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzo-ate **(*R*)-(14q)**: 71%; mp 160−162 °C; ee 98.6%; $[\alpha]^{20}_D$ +2.6° (*c* 1, MeOH), from **(*R*)-12s**. (*S*)(−)-Ethyl 4-[2-[[phenyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoate **(*S*)-(14q)**: 72%; mp 164−165 °C; ee≥ 99.0%; $[\alpha]^{20}_D$ −2.9° (*c* 1, MeOH), from **(*S*)-12s**. (*R*)(−)-Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate **(*R*)-(14y)**: 19%; mp 122−123 °C; ee ≥ 99.6%; $[\alpha]^{20}_D$ −5.4° (*c* 1, MeOH), from **(*R*)-12q** (ee ≤ 95.2%). (*S*)(+)-Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate **(*S*)-(14y)**: 29%; mp 121−123 °C; ee 99.1%; $[\alpha]^{20}_D$ +7.8° (*c* 1, MeOH), from **(*S*)-12q** ($bp_{0.1}$ 96−97 °C). Ethyl 2-ethoxy-4-[2-[[1-[5-chloro-2-(1-piperidinyl)phenyl]propyl]amino]-2-oxoethyl]-benzoate (**14aq**): 80%; mp 110−112 °C, from **12e**.

Compounds Obtained According to Procedure A5. Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (**14y**): 64%; mp 140−142 °C, from **12q**. (*R*)(−) Ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]-amino]-2-oxoethyl]-benzoate **(*R*)-(14al)**: 28%; mp 122−124 °C; ee 98.7%; $[\alpha]^{20}_D$ −8.7° (*c* 1, MeOH), from **(*R*)-12o**. (*S*)(+) Ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate **(*S*)-(14al)**: 58%; mp 124−125 °C; ee 95.4%; $[\alpha]^{20}_D$ +8.6° (*c* 1, MeOH), from **(*S*)-12o**.

Compounds Obtained According to Procedure A6. Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]-3-buten-1-yl]amino]-2-oxoethyl]-benzoate (**14z**): 70%; mp 120−124 °C, from **12w·glutaric acid**. (*R*)(−)-Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate **(*R*)-(14y)**: 69%; mp 120−123 °C; ee ≥ 99.6%; $[\alpha]^{20}_D$ −9.9° (*c* 1, MeOH), from **(*R*)-29** (ee 95.1%). (*S*)(+)-Ethyl 2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate **(*S*)-(14y)**: 59%; mp 122−123 °C; ee ≥ 99.8%; $[\alpha]^{20}_D$ +9.3° (*c* 1, MeOH), from **(*S,S'*)-28** (ee 98.0%).

Compounds Obtained According to Procedure A7. Ethyl 4-[2-[[1-[2-octamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14aj**): 38%; mp 170−173 °C via ethyl 4-[2-[[1-[2-octamethyleneimino-phenyl]-1-ethenyl]amino]-2-oxoethyl]-benzoate (**17a**), 33%; mp 114−116 °C. Ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]-1-propyl]amino]-2-oxoethyl]-benzoate (**14ak**): 71%; mp 132−134 °C via ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]-1-(*E*)-propenyl]amino]-2-oxoethyl]-benzoate (**17b**), 56%; mp 82−84 °C. Ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (**14al**): 52%; mp 126−128 °C via ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]-1-(*E*)-butenyl]amino]-2-oxoethyl]-benzoate (**17c**), 35%; mp 115−117 °C. Ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]pentyl]amino]-2-oxoethyl]-benzoate (**14am**): 45%; mp 115−120 °C via ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]-1-(*E*)-pentenyl]amino]-2-oxoethyl]-benzoate (**17d**), 16%; mp 90−97 °C. Ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]hexyl]amino]-2-oxoethyl]-benzoate (**14an**): 50%; mp 105−110 °C via ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]-1-(*E*)-hexenyl]amino]-2-oxoethyl]-benzoate (**17e**), 27%; mp 80−85 °C. Ethyl 4-[2-[[2-phenyl-1-[2-(1-piperidinyl)-phenyl]ethyl]amino]-2-oxoethyl]-benzoate (**14ao**): 88%; mp 161−162 °C via ethyl 4-[2-[[2-phenyl-1-[2-(1-piperidinyl)-phenyl]-1-(*E*)-ethenyl]amino]-2-oxoethyl]-benzoate (**17f**), 47%; mp 157−159 °C. Ethyl 4-[2-[[3-phenyl-1-[2-(1-piperidinyl)-phenyl]propyl]amino]-2-oxoethyl]-benzoate (**14ap**): 57%; mp 118−119 °C via ethyl 4-[2-[[3-phenyl-1-[2-(1-piperidinyl)-phenyl]-1-(*E*)-propenyl]amino]-2-oxoethyl]-benzoate (**17g**), 62%; viscous.

Compounds Obtained According to Procedure B3. *Note*: For melting points, look at Tables 2 and 3, respectively. 4-[2-[[1-[5-Chloro-2-dimethylamino-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6a**): 88%, from **14a**. 4-[2-[[1-[5-Chloro-2-(1-pyrrolidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6c**): 81%, from **14b**. 4-[2-[[1-[5-Chloro-2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6d**): 85%, from **14c**. 4-[2-[[2-[5-Chloro-2-(1-piperidinyl)phenyl]-2-propyl]amino]-2-oxoethyl]-benzoic acid (**6f**): 83%, from **14d**. 4-[2-[[[5-Chloro-2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoic acid (**6h**): 78%, from **14e**. 4-[2-[[1-[5-Chloro-2-(2-methyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid·$0.25H_2O$ (**6j**): 64%, from **14f**. 4-[2-[[1-[5-Chloro-2-(3-methyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6l**): 69%, from **14g**. 4-[2-[[1-[2-(4-Methyl-1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoic acid (**6n**): 67%, from **14h**. 4-[2-[[1-[5-Chloro-2-(3,5-*cis*-dimethyl-1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoic acid (**6o**): 82%, **14i**. 4-[2-[[1-[5-Chloro-2-hexamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6p**): 81%, from **14j**. 4-[2-[[1-[2-Hexamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6q**): 68%, from **14k**. 4-[2-[[1-[5-Chloro-2-heptamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6r**): 44%, from **14l**. 4-[2-[[1-[5-Chloro-2-octamethyleneimino-phenyl]-ethyl]amino]-2-oxoethyl]-benzoic acid (**6s**): 75%, from **14m**. 4-[2-[[1-[2-Octamethyleneimino-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6t**): 80%, from **14aj**. 4-[2-[[1-[2-(1-Piperidinyl)phenyl]propyl]amino]-2-oxoethyl]-benzoic acid (**6u**): 71%, from **14ak**. 4-[2-[[1-[2-(1-Piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (**6v**): 45%, from **14al**. 4-[2-[[1-[2-(1-Piperidinyl)phenyl]pentyl]amino]-2-oxoethyl]-benzoic acid (**6x**): 70%, from **14am**. 4-[2-[[1-[2-(1-Piperidinyl)phenyl]hexyl]-amino]-2-oxoethyl]-benzoic acid (**6z**): 73%, from **14an**. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid sodium salt·$1.5H_2O$ (**6ae**): 76%, from **14r**. The oily acid was transformed in EtOH with 1 N NaOH (1 equiv) into the sodium salt. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (**6ai**): 69%, from **14v**. 2-Ethoxy-4-[2-[[phenyl-[2-(1-piperidinyl)phenyl]methyl]-amino]-2-oxoethyl]-benzoic acid (**6ap**): 88%, from **14ac**. (*R*)-(+)-4-[2-[[Phenyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoic acid **(*R*)-(6ab)**: 79%; $[\alpha]^{20}_D$ +5.8° (*c* 1.04, MeOH), from **(*R*)-14q** (ee 98.6%). (*S*)(−)-4-[2-[[Phenyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoic acid **(*S*)-(6ab)**: 87%; $[\alpha]^{20}_D$ −6.3° (*c* 1, MeOH), from **(*S*)-14q** (ee ≥ 99.0%). 4-[2-[[1-[5-Chloro-2-(1-piperidinyl)phenyl]-2-methyl-propyl]amino]-2-oxoethyl]-benzoic acid (**6aw**): 82%; mp 235−240 °C, from **14n**.

Compounds Obtained According to Procedure B4. *Note*: For melting points, look at Tables 2 and 3, respectively. 4-[2-[[3-Methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (**6y**): 85%, from **14y**. 4-[2-[[Cyclohexyl-[2-(1-piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoic acid (**6aa**): 58%, from **14p**. 4-[2-[[Phenyl-[2-(1-piperidinyl)phenyl]-methyl]amino]-2-oxoethyl]-benzoic acid (**6ab**): 64%, from **14q**. 4-[2-[[2-Phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6ac**): 68%, from **14ao**. 4-[2-[[3-Phenyl-1-[2-(1-piperidinyl)phenyl]propyl]amino]-2-oxoethyl]-benzoic acid (**6ad**): 68%, from **14ap**. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)-phenyl]propyl]amino]-2-oxoethyl]-benzoic acid (**6af**): 73%, from **14t**. 2-Methoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (**6ah**): 86%, from **14u**. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]pentyl]amino]-2-oxoethyl]-benzoic acid (**6aj**): 91%, from **14w**. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]-4-penten-yl]amino]-2-oxoethyl]-benzoic acid (**6ak**): 61%, from **14x**. 2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (**6al**): 88%, from **14y**. 2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]-3-buten-yl]amino]-2-oxoethyl]-benzoic acid (**6am**): 74%, from **14z**. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]hexyl]-amino]-2-oxoethyl]-benzoic acid (**6an**): 77%, from **14aa**. 2-Ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]heptyl]amino]-2-oxoethyl]-benzoic acid (**6ao**): 88%, from **14ab**. 2-Ethoxy-4-[2-[[2-cyclopropyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-

benzoic acid (**6aq**): 88%, from **14ad**. 2-Ethoxy-4-[2-[[2-cyclobutyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6ar**): 33%, from **14ae**. 2-Ethoxy-4-[2-[[2-cyclopentyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6as**): 75%, from **14af**. 2-Ethoxy-4-[2-[[2-cyclohexyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6at**): 82%, from **14ag**. 2-Ethoxy-4-[2-[[2-cycloheptyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6au**): 83%, from **14ah**. 2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6av**): 90%, from **14ai**. (*R*)(−)-4-[2-[[1-[2-(1-Piperidinyl)-phenyl]butyl]amino]-2-oxoethyl]-benzoic acid **(*R*)-(6v)**: 74%; ee 99.7%; $[\alpha]^{20}_D$ −7.1° (*c* 1, MeOH), from **(*R*)-14al**. (*S*)(+)-4-[2-[[1-[2-(1-Piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid **(*S*)-(6v)**: 46%; ee ≥ 99.2%; $[\alpha]^{20}_D$ +7.7° (*c* 1.04; MeOH), from **(*S*)-14al**. (*R*)(−)-2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid **(*R*)-(6al)**: 92%; ee ≥ 99.7%; $[\alpha]^{20}_D$ −7.9° (*c* 1.04, MeOH), from **(*R*)-14y** (ee ≥ 99.6%). (*S*)(+)-2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid **(*S*)-(6al)**: 92%; ee ≥ 99.8%; $[\alpha]^{20}_D$ +7.4° (*c* 1.07, MeOH), from **(*S*)-14y** (ee ≥ 99.8%).

Compounds Obtained According to Procedure B5. *Note*: For melting points, look at Tables 2 and 3, respectively. 4-[2-[[1-[2-Dimethylamino-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6b**): 53%, from **6a**. 4-[2-[[1-[2-(1-Piperidinyl)-phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6e**): 67%, from **6d**. 4-[2-[[2-[2-(1-Piperidinyl)phenyl]-2-propyl]amino]-2-oxoethyl]-benzoic acid (**6g**): 68%, from **6f**. 4-[2-[[[2-(1-Piperidinyl)phenyl]methyl]amino]-2-oxoethyl]-benzoic acid (**6i**): 60%, from **6h**. 4-[2-[[1-[2-(2-Methyl-1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoic acid (**6k**): 90%, from **6j**. 4-[2-[[1-[2-(3-Methyl-1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**6m**): 86%, from **6l**. 4-[2-[[2-Methyl-1-[2-(1-piperidinyl)phenyl]propyl]amino]-2-oxoethyl]-benzoic acid (**6w**): 68%, from **6aw**. Ethyl 2-ethoxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]propyl]amino]-2-oxoethyl]-benzoate (**14t**): 74%; mp 115−117 °C, from **14aq**.

Special Procedures. 2-Hydroxy-4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (6ag). BBr_3 (2.5 mM) was added slowly to a solution of 6ai (2.2 mM) in 1,2-dichloro-ethylene (20 mL) at −30 °C. The cooling bath was removed, stirring was continued for 2 h at room temperature, and EtOH/H_2O (1:1) (15 mL) was dropped in cautiously. The reaction was evaporated in vacuo. H_2O and $CHCl_3$ were added to the residue. The organic layer was washed with water, dried, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with $CHCl_3$/MeOH (10:1) to yield **6ag** (20%; mp 136−138 °C).

(*R*)(−)-Ethyl 2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (*R*)-(14y) and (*S*)(+)-Ethyl 2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoate (*S*)-(14y). **14y** (920 mg) was injected in 10 mg doses to a semipreparative CSP−HPLC Baker column; chiral phase: (*S*)-*N*-3,5-dinitrobenzoyl-leucine covalently bound to aminopropyl silica gel; particle size: 40 μm; ∅ = 20 mm; *l* = 250 mm; *n*-hexane/THF/EtOH/CH_2Cl_2 (180:20:3:2); 21.25 mL/min; temperature: 27 °C; UV detection at 285 nm. **(*R*)-14y** was eluted first, thereafter **(*S*)-14y** was eluted. The fractions containing peak 1 (crude, 423 mg) and peak 2 (crude, 325 mg) were purified by column chromatography on silica gel with toluene/acetone (10:1) to yield **(*R*)-14y** (234.5 mg, 51%; mp 122−124 °C; $[\alpha]^{20}_D$ −8.3° (*c* 1, MeOH) and **(*S*)-14y** (131.2 mg, 28.5%; mp 122−124 °C; $[\alpha]^{20}_D$ +8.3° (*c* 1, MeOH). The separation can be performed also on a Chiralcel OD column (Daicel) with EtOH/*n*-hexane + 0.2% diethylamine (5:95) at 40 °C and UV detection at 245 nm; peak 1: **(*R*)-14y**; peak 2: **(*S*)-14y**.

(*S*)(+)-2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]-4-buten-yl]amino]-2-oxoethyl]-benzoic Acid (*S*)-(6am). (a) (*S*)(+)-Ethyl 2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]-3-buten-1-yl] amino]-2-oxoethyl]-benzoate (*S*)-(14z). Semipreparative CSP−HPLC of **14z** was performed on a Chiralcel OD column (Daicel); particle size: 10 μm; ∅ = 10 mm; *l* = 250 mm; *n*-hexane/*i*-PrOH (90:10); 2.5 mL/min; 1.4 bar; 1 mL injections ($\grave{a} \sim$ 25 mg); peak 1 (4.9 min), **(*R*)-14z**; peak 2 (6.3 min), **(*S*)-14z**; ee = 100% each as proven with an analytical column. Crude **(*S*)-14z** (440 mg) was dissolved in petrolether (4.4 mL) + toluene (0.4 mL) by heating on a steam bath. After cooling to 0 °C, the precipitate was filtered and dried (45 °C/1 Torr) to yield **(*S*)-14z** (355 mg; mp 56−60 °C and 90−92 °C; ee 100%; $[\alpha]^{20}_D$ +18.5° (*c* 1.55, MeOH).

(b) (*S*)(+)-2-Ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)-phenyl]-4-buten-yl]amino]-2-oxoethyl]-benzoic Acid (*S*)-(6am). A solution of **(*S*)-14z** (320 mg, 0.6686 mM) in EtOH (3 mL) was stirred in a bath of 60 °C. 1 N NaOH (0.85 mL, 0.85 mM) was added. After 4 h at 60 °C, 1 N HCl (0.85 mL) was added, and the heating was removed. To initiate crystallization of the viscous precipitate, H_2O (7 × 0.1 mL) was added. After further addition of H_2O (0.8 mL) and standing overnight at room temperature, the precipitate was filtered, washed with H_2O, and dried (55 °C/1 Torr) to yield **(*S*)-6am** (240 mg, 79.8%; mp 90−95 °C; ee ≥ 99.9%; $[\alpha]^{20}_D$ +17.1° (*c* 1.05, MeOH). The enantiomeric purity was examined on a Chiral AGP column [5 μm; ∅ = 4 mm; *l* = 100 mm; acetonitrile/buffer of sodium phosphate pH 5.1 (30:70); 0.5 mL/min; 5.8 bar; temperature: 20 °C; UV detection at 240 nm; peak 3.2 min (*S*), peak 5.4 min (*R*)].

Compounds of Tables 5−10. For melting points, look at the respective table. 4-(2-(3-Chloro-benzoylamino)-ethyl)-benzoic acid (**39**), 61%, from methyl 4-(2-(3-chloro-benzoylamino)-ethyl)-benzoate, 43%; mp 94 °C. *N*-[5-Chloro-2-octamethyleneimino-benzoyl]-*N*-[2-phenyl-ethyl]-amine (**40**), 69%, from the imidazolide of **9l** and 2-phenethylamine. 4-[2-[[1-[5-Chloro-2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (**41**), 82%, from ethyl 4-[2-[[1-[5-chloro-2-(1-piperidinyl)phenyl]-butyl]amino]-2-oxoethyl]-benzoate, 40%; mp 135−140 °C. 4-[2-[[1-(Phenyl)butyl]amino]-2-oxoethyl]-benzoic acid (**42**), 87%, from ethyl 4-[2-[[1-(phenyl)butyl]amino]-2-oxoethyl]-benzoate, 70%; mp 105−108 °C [obtained from α-propyl-benzylamine with **13b**]. *N*-[Phenyl-acetyl]-*N*-[1-[2-(1-piperidinyl)phenyl]-butyl]-amine (**43**), 80%, from **12o** with phenylacetic acid. 4-[2-[[1-[3-(1-Piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**44**), 33%, from ethyl 4-[2-[[1-[3-(1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoate, 24%; mp 163−164 °C [obtained from crude 1-(3-piperidino-phenyl)ethylamine with **13b**]. 4-[2-[[1-[4-(1-Piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**45**), 51%, from ethyl 4-[2-[[1-[4-(1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoate, 39%; mp 118−120 °C [obtained from crude 1-(4-piperidino-phenyl)ethylamine with **13b**]. 3-[2-[[1-[2-(1-Piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**46**), 86%, from ethyl 3-[2-[[1-[2-(1-piperidinyl)phenyl]ethyl]-amino]-2-oxoethyl]-benzoate, 47%; mp 155 °C [obtained from **12d** with crude (3-ethoxycarbonyl-phenyl)-acetic acid]. 2-[2-[[1-[2-(1-Piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzoic acid (**47**)·0.3H_2O, 7%, from methyl 2-[2-[[1-[2-(1-piperidinyl)phenyl]-ethyl]amino]-2-oxoethyl]-benzoate·0.2H_2O, 82%; mp 107−108 °C [obtained from **12d** with (2-methoxycarbonyl-phenyl)-acetic acid, mp 145−147 °C].

***N*-[1-[2-(1-Piperidinyl)phenyl]ethyl]-*N*-[4-(1*H*-tetrazol-5-yl)-phenyl-acetyl]-amine (48)·0.5H_2O.** (a) The imidazolide of **6e** in dry pyridine was reacted with excessive liquid ammonia to give 4-[2-[[1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzamide, 74%; mp 197−199 °C. (b) The above benzamide (6 mM) in pyridine (13.5 mM) was reacted with *p*-toluene-sulfonylchloride (6 mM) for 0.25 h at room temperature and 1.5 h at 50 °C to give, after workup and purification by column chromatography with $CHCl_3$/MeOH (4:1), 4-[2-[[1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzonitrile, 55%; mp 155−157 °C. (c) A mixture of the above benzonitrile (0.5 g, 1.44 mM), NaN_3 (0.124 g, 1.9 mM), and glacial acetic acid (0.191 mL, 3.34 mM) in *n*-BuOH (6 mL) was refluxed for 91 h. H_2O was added, and the mixture was (not completely) evaporated in vacuo. EtOAc was added, and the organic phase was extracted several times with 10% aqueous NaOH. The aqueous phase was extracted with Et_2O (dis-

carded), acidified with semiconcentrated HCl (ad pH 5.7), and extracted with EtOAc to give, after workup of the organic phase, **48·0.5H_2O** (0.055 g, 9.8%; mp 172−175 °C).

4-[2-[[1-[2-(1-Piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]-benzene-sulfonamide (49), 15%, was obtained from **12d** with 4-(carboxy-methyl)-benzene-sulfonamide (mp 176−180 °C; lit.[52] mp 176−178 °C) and purification by column chromatography with toluene/acetone (2:1).

***N*^{1}-{Cyclohexyl}-*N*^{3}-{4-[[2-[[1-[2-(1-piperidinyl)phenyl]-ethyl]amino]-2-oxoethyl]-phenyl]-sulfonyl}-urea (50)**, 55%, was obtained from the sodium salt of **49** (3.5 mM) in dry DMF (15 mL) with cyclohexyl-isocyanate (3.7 mM) at 5 °C, stirring overnight at 5 °C, addition of H_2O (150 mL) and of 1 N HCl (3.5 mL), extraction with $CHCl_3$, washing of the organic extract with H_2O, workup of the organic phase, and crystallization from hot acteone (+ some charcoal).

4-[2-[[2-[2-(1-Piperidinyl)phenyl]propanoyl]amino]-methyl]-benzoic Acid (51). (a) 2-(2-Chloro-phenyl)-propanoic acid (mp 88 °C) in concentrated H_2SO_4 was nitrated at −25 to −15 °C with a mixture (1:2) of fuming HNO_3/concentrated H_2SO_4 to give 2-(2-chloro-5-nitro-phenyl)-propanoic acid (94%; mp 129−131 °C). (b) The aforementioned compound was refluxed with excessive piperidine for 72 h to give 2-(5-nitro-2-piperidino-phenyl)-propanoic acid (94%; mp 135−138 °C). (c) Hydrogenation of the preceding compound (b) in DMF over Pd/C (10%) for 2 h at room temperature and 5 bar gave 2-(5-amino-2-piperidino-phenyl)-propanoic acid (56%; mp 223 °C). (d) Diazotation of the preceding amino compound and subsequent Sandmeyer reaction with Cu_2Cl_2 gave 2-(5-chloro-2-piperidino-phenyl)-propanoic acid (51%; mp 130−132 °C). (e) The preceding acid (d) was reacted, according to procedure A4, with ethyl 4-(aminomethyl)-benzoate·HCl (mp 247−249 °C; lit.[53] mp 250−251 °C) to give ethyl 4-[2-[[2-[5-chloro-2-(1-piperidinyl)phenyl]propanoyl]amino]methyl]-benzoate, 70%; viscous. (f) The preceding ester was hydrolyzed with NaOH in EtOH to give 4-[2-[[2-[5-chloro-2-(1-piperidinyl)-phenyl]propanoyl]amino]methyl]benzoic acid, 74%; mp 168−170 °C. (g) The preceding chloro compound was hydrogenated over Pd/C (10%) in MeOH to give **51**, 47%; mp 125 °C.

4-{[[[1-[2-(1-Piperidinyl)phenyl]ethyl]amino]sulfonyl]-methyl}-benzoic Acid (52). (a) A hot solution of $Na_2S·5H_2O$ (26 g, 110 mM) and sulfur (3.4 g, 110 mM) in H_2O (40 mL) was added to a solution of crude (85%) ethyl 4-bromomethyl-benzoate (50 g, 175 mM) in EtOH (250 mL). The reaction was refluxed for 1 h, then evaporated in vacuo. H_2O was added to the residue, and extraction was performed with Et_2O. Workup of the organic layer gave crude bis(4-ethoxycarbonyl-benzyl)-disulfide (26 g, 76%; oil). (b) Cl_2 was introduced at 0−10 °C into a mixture of the above crude disulfide (12 g, 30.8 mM) in glacial acetic acid (150 mL) and H_2O (40 mL). After a solid began to precipitate, introduction was continued for 15 min. The reaction was added to ice−water (500 mL) while excessive Cl_2 escaped. The resulted precipitate of (4-ethoxycarbonyl-phenyl)methane-sulfonylchloride was filtered, washed with H_2O, and dissolved in CH_2Cl_2. The organic solution was dried, filtered, and adjusted to a volume of 70 mL (containing 61.5 mM of the crude sulfochloride). (c) The preceding solution of the crude sulfochloride (29 mL, 24.8 mM) was dropped to a solution of **12d** (4.5 g, 22 mM) and NEt_3 (10 mL, 71.7 mM) in CH_2Cl_2 (100 mL). After stirring for 2 h at room temperature, the reaction was evaporated in vacuo. Hydrochloric acid was added (ad pH 3−4), and extraction was performed with Et_2O. Workup of the organic extract, purification by column chromatography with toluene/EtOAc (10:1), and crystallization from cyclohexane gave ethyl 4-{[[[1-[2-(1-piperidinyl)phenyl]-ethyl]amino]sulfonyl]methyl}-benzoate (3.5 g, 37%; mp 119−120 °C). (d) The preceding ester (3 g, 7 mM) was hydrolyzed in EtOH with 1 N NaOH at 60 °C to give **52** (2.8, 100%; mp 222−225 °C).

4-[2-[[1-[2-(Cyclohexyl)-phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (53), 75%, mp 208−211 °C was synthesized from **54** by hydrogenation in EtOH over Pd/C (10%) at 50 °C and 1 bar.

4-[2-[[1-[2-(1-Cyclohexen-1-yl)phenyl]butyl]amino]-2-oxoethyl]-benzoic Acid (54). (a) 1-(2-(1-Cyclohexen-1-yl)-phenyl)-butylamine, 62%, oil was synthesized from 2-(1-cyclohexen-1-yl)-benzonitrile[54] according to route A. (b) Ethyl 4-[2-[[1-[2-(1-Cyclohexen-1-yl)phenyl]butyl]amino]-2-oxoethyl]-benzoate, 71%, mp 125−128 °C, was synthesized from the above amine with **13b** according to procedure A4. (c) Hydrolysis of the above ester according to procedure B4 gave **54**, 94%; mp 206−210 °C.

4-[2-[[1-[2-(Phenyl)-phenyl]butyl]amino]-2-oxoethyl]-benzoic acid (55), 95%, mp 217−220 °C, was synthesized, analogously to **54**, from 2-cyano-biphenyl[55] via 1-[biphenyl-2-yl)butyl-amine, 70%; oil, and ethyl 4-[2-[[1-[2-(phenyl)-phenyl]-butyl]amino]-2-oxoethyl]-benzoate, 77%; mp 137−139 °C.

4-[2-[[1-[2-Methoxy-phenyl]butyl]amino]-2-oxoethyl]-benzoic Acid (56). (a) To $AlCl_3$ (112 g, 0.84 mol) in CH_2Cl_2 (112 mL) was added dropwise at −10 °C a solution of 4-chloro-anisol (110 g, 0.70 mol) and butanoylchloride (72.7 mL, 0.70 mol). The reaction was stirred for 0.5 h at −10 °C, 2 h at 0 °C, and 2 h at room temperature. The reaction was poured into ice−water (1.5 L). Extraction was performed with Et_2O. The organic layer was washed with aqueous Na_2CO_3 to give, after workup and distillation, 1-(5-chloro-2-methoxy-phenyl)-1-oxo-butane, 43%; $bp_{0.1}$ 98−105 °C. (b) The preceding ketone (10 g, 47 mM) in EtOH (50 mL) was reacted with H_2NOH·HCl (9.8 g, 141 mM) in H_2O (25 mL) and NaOH (16.9 g, 423 mM) in H_2O for 1 h at 60 °C. The reaction was poured into ice−water and was extracted with Et_2O. Workup of the organic phase gave 1-(5-chloro-2-methoxy-phenyl)-1-oximino-butane, 9.6 g, 90%; mp 136−138 °C. (c) The preceding oxime (9.5 g, 41.7 mM) in EtOH (150 mL) and NEt_3 (12 mL, 86 mM) was hydrogenated over Pd/C (10%) (1.5 g) for 12 h at 50 °C and 3.5 bar to give, after workup and purification by column chromatography with $CHCl_3$/MeOH/concentrated ammonia (20:1:0.01), 1-(2-methoxy-phenyl)-1-butylamine, 3.1 g, 41%; oil. (d) The preceding amine was reacted with **13b** according to procedure A4 to give ethyl 4-[2-[[1-[2-methoxy-phenyl]butyl]-amino]-2-oxoethyl]-benzoate, 79%; mp 111−113 °C. (e) Hydrolysis of the above ester according to procedure B4 gave **56**, 87%; mp 201−203 °C.

4-[2-[[1-[2-(1-Piperidinyl)phenyl]butyl]-*N*-methylamino]-2-oxoethyl]-benzoic Acid (57). (a) A mixture of **12o** (55 g, 237 mM) and ethyl formiate (190 mL, 2370 mM) was refluxed for 24 h. The reaction was evaporated in vacuo. The residue was crystallized from petrolether to give *N*-formyl-1-(2-piperidino-phenyl)-butylamine, 50 g, 81%; mp 71−73 °C. (b) To $LiAlH_4$ (1.44 g, 38.4 mM) in dry THF (40 mL) was added at room temperature under N_2 a solution of the above amide (5 g, 19.2 mM) in THF (80 mL). The reaction was stirred for 2 h at 100 °C. The reaction was completed after further addition of $LiAlH_4$ (0.72 g, and 0.36 g) and heating at 100 °C for further 3 and 2 h, respectively. After standing overnight at room temperature, the reaction was stirred vigorously and, cautiously, H_2O (2.5 mL), 15% aqueous NaOH (2.5 mL), and H_2O (4.8 mL) were added. After stirring for 1 h at room temperature, the mixture was filtered through a layer of kieselguhr which was washed with THF. The filtrate was evaporated in vacuo to give, after purification by column chromatography with toluene/EtOAc/concentrated ammonia (4:2:0.01) *N*-methyl-1-(2-piperidino-phenyl)-butylamine, 4 g, 85%; oil. (c) The preceding amine was acylated with **13b** according to procedure A4 to give ethyl 4-[2-[[1-[2-(1-piperidinyl) phenyl]butyl]-*N*-methylamino]-2-oxoethyl]-benzoate, 79%; oil; ·HCl: mp 172−182 °C. (d) Hydrolysis of the above ester according to procedure B4 gave **57**, 88%; mp 157−160 °C.

4-[2-[[1-[2-(1-Piperidinyl)phenyl]butyl]amino]-2-thionoethyl]-benzoic Acid (58). (a) A mixture of **14al** (7 g, 16.5 mM) and Lawesson's reagent (2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide) (4 g, 9.9 mM) in dry toluene (42 mL) was refluxed for 4 h at 120 °C to give, after workup and purification by column chromatography ($CHCl_3$), ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-thiono-

ethyl]-benzoate, 3.2 g, 44%; mp 75−77 °C. (b) Hydrolysis of the above ester according to procedure B4 gave **58**, 76%; mp 80−87 °C.

4-[2-[[1-[2-(1-Piperidinyl)phenyl]butyl]amino]-ethyl]-benzoic Acid (59). (a) The above ethyl 4-[2-[[1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-thionoethyl]-benzoate (0.8 g, 1.82 mM) in dry dioxane (30 mL) was treated with Raney-Ni (4 g) for 0.5 h at room temperature to give, after workup and purification by column chromatography ($CHCl_3$/MeOH/concentrated ammonia (20:1:0.1) ethyl 4-[2-[[1-[2-(1-piperidinyl)-phenyl]butyl]amino]-ethyl]-benzoate, 0.7 g, 94%; oil. (b) Hydrolysis of the above ester according to procedure B4 gave **59**, 72%; mp 236−242 °C.

4-[4-[2-(1-Piperidinyl)phenyl]-2-oxo-heptyl]-benzoic Acid (60). (a) A solution of 1-(2-piperidino-phenyl)-1-oxo-butane **(30o)** (20 g, 86 mM) in dry Et_2O (50 mL) was added to a solution of the sodium salt of triethylphosphonoacetate (172 mM) in dry Et_2O (200 mL). The reaction was heated for 5 h at 40 °C and stood for 5 days at room temperature. After addition of Et_2O (250 mL), the reaction was poured into iced water. The organic phase was washed with 2 N NaOH and with H_2O, dried, filtered, and evaporated in vacuo. The residue was purified by column chromatography with toluene/cyclohexane (4:1) to give ethyl 3-[2-(1-piperidinyl)phenyl]-2-(*E*)-hexenoate (6 g, 23%; oil; R_f 0.42; ^{1}H NMR: 5.82 ppm (s, 1H, olef. H)) and ethyl 3-[2-(1-piperidinyl)phenyl]-2-(*Z*)-hexenoate (2.7 g, 10%; oil; R_f 0.24; ^{1}H NMR: 5.86 ppm (s, 1H, olef. H)). (b) The preceding (*E*) ester (4 g, 13 mM) in EtOH (40 mL) was hydrogenated over Pd/C (10%) (0.4 g) overnight at room temperature and 1 bar to give ethyl 3-[2-(1-piperidinyl)phenyl]-hexanoate (3.8 g, 96%; oil). (c) To a stirred solution of EtONa in EtOH [freshly prepared from Na (1.13 g, 49.1 mM) in EtOH (14 mL)] was added quickly at 50 °C 4-bromobenzylcyanide (7.4 g, 37.7 mM) and thereafter the above ethyl ester (18 g, 59.3 mM). The reaction was immediately heated for 2 h in a preheated bath of 90 °C. The heating was removed, and the reaction was allowed to stand overnight at room temperature. 1 N HCl (49.1 mL) was added, and extraction was performed with Et_2O. Workup of the organic phase and purification by column chromatography (toluene) gave 1-(4-bromo-phenyl)-1-cyano-4-[4-[2-(1-piperidinyl)phenyl]-2-oxo-heptane, 6.7 g, 39%; viscous oil. (d) The preceding cyano compound (19.5 g, 43 mM) in concentrated H_2SO_4 (12.5 mL) was heated in a preheated bath of 110 °C. When T_i = 80−90 °C was reached, a vigorous gas evolution occurred, and T_i rose quickly up to 140 °C. By cooling, T_i was lowered within 2 min to 80 °C. (Total time above 80 °C was ∼5 min.) The solution containing the intermediary amide was cooled to room temperature. H_2O (62.4 mL) was added, and the mixture was heated for 1 h in a bath of 110 °C. The reaction was cooled to room temperature; $CHCl_3$ and 2 N NaOH (ad alkaline pH) were added. Workup of the organic phase and purification by column chromatography (toluene) gave 1-(4-bromo-phenyl)-4-[4-[2-(1-piperidinyl)phenyl]-2-oxo-heptane, 11.6 g, 63%; viscous oil. (e) A solution of the above ketone (11.6 g, 27 mM), *p*-TsOH·H_2O (5.6 g, 29.4 mM), and ethane-1,2-diol (5 g, 80.6 mM) in dry benzene (12 mL) was refluxed in a Dean−Stark apparatus for 72 h. After cooling to room temperature, the reaction was poured into stirred semiconcentrated ammonia (100 mL). Extraction was performed with Et_2O. The organic extract was washed with 2 N NaOH and with water (ad pH 7). Workup of the organic phase and purification by column chromatography with toluene/cyclohexane (2:1) gave 1-(4-bromo-phenyl)-4-[4-[2-(1-piperidinyl)phenyl]-2,2-ethylenedioxy-heptane, 11.3 g, 88%; viscous oil. (f) To a solution of the above ketal (9.4 g, 19.9 mM) in dry Et_2O (12 mL) was added at room temperature under N_2 a solution of *n*-BuLi (25 mL, 1.6 M in hexane, 39.8 mM) in dry Et_2O (50 mL) while T_i rose to 30 °C and declined after 30 min to 25 °C. After stirring for 1 h, the reaction was poured into freshly mortared solid CO_2 and stood at room temperature overnight. Aqueous NH_4Cl was added, and extraction was performed with Et_2O. Workup of the organic phase, purification by column chromatography with $CHCl_3$/MeOH (10:0.3), and treatment with charcoal in $CHCl_3$ gave 4-[4-[2-(1-piperidinyl)phenyl]-2,2-ethylenedioy-heptyl]-benzoic acid, 2.9 g, 33%; viscous oil. (g) To a solution of the above ketal (2.3 g, 5.2 mM) in dioxane (12 mL) was added 2 N $HClO_4$ (12 mL, 240 mM). The reaction was stirred for 40 min at 80 °C; thereafter, the dioxane was evaporated in vacuo. H_2O (50 mL) was added, and the resultant viscous precipitate was extracted with $CHCl_3$. The organic phase was washed with H_2O, dried, and evaporated in vacuo to give **60·HClO$_4$** (mp 50−60 °C, dec 70−80 °C; from cyclohexane). Intensive shaking of this salt with Et_2O/saturated aqueous $NaHCO_3$/saturated aqueous NaCl, workup of the organic phase, and crystallization from acetone/petrolether (1:30) gave the betaine **60**, 0.9 g, 44%; mp 88−92 °C.

4-[4-[2-(1-Piperidinyl)phenyl]-heptyl]-benzoic Acid (61). (a) To a solution of **60** (0.23 g, 0.58 mM) in ethane-1,2-dithiol (0.26 mL, 3.1 mM) was added BF_3·Et_2O (0.5 mL). After stirring for 3 days at room temperature, MeOH (1 mL) was added, and the reaction was heated in an open flask for 0.75 h at 70 °C to evaporate the solvent. Further MeOH (1 mL) was added, and the procedure of heating and evaporating (at last in vacuo) was repeated. H_2O and $CHCl_3$ were added to the residue. The organic phase was washed with H_2O, dried, and evaporated in vacuo. The residue was purified by column chromatography (toluene/$CHCl_3$ (1:1)) to give methyl 4-[4-[2-(1-piperidinyl)phenyl]-2,2-ethylenedithio-heptyl]-benzoate, 0.18 g, 64%; oil. (b) The above dithioketal (0.15 g, 0.31 mM) in dry dioxane (5 mL) was stirred under reflux at 110 °C while Raney-Ni (∼1 g; washed previously with dioxane) was added in small portions during 2 h. The reaction was diluted with dioxane, filtered, and evaporated in vacuo to give, after purification by column chromatography with toluene/$CHCl_3$ (2:1), methyl 4-[4-[2-(1-piperidinyl)phenyl]-heptyl]-benzoate, 0.092 g, 60%; oil. (c) Hydrolysis of the above ester according to procedure B3 gave **61**, 71%; oil which crystallized on standing (mp 60−70 °C).

Single-Crystal X-ray Analysis. The crystal data for **1** (GLIB) were taken from the literature.[41]

Colorless prismatic crystals of **2** (GLIM; mp 200.4−201.3 °C) and of **(*S*)-6al** (REP; mp 134.8−135.0 °C) were grown from ethanol/water, those of **(*S*,*S*′)-28** (mp 173.2 °C) from water. A crystal of **2** (0.30 × 0.30 × 0.05 mm^3), **(*S*)-6al** (0.50 × 0.10 × 0.10 mm^3), and **(*S*,*S*′)-28** (0.50 × 0.30 × 0.30 mm^3), respectively, was measured on a Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation (λ = 1.5418 Å) and a 12 kW rotating anode generator at 20 ± 1 °C. For calculations, the teXsan crystallographic software package[56] was used. The structures were solved by direct methods[57] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included as riding atoms.

Crystal Data. 2 (GLIM): $C_{24}H_{34}N_4O_5S$, M_r = 490.62, monoclinic, space group $P2_1/n$, a = 15.283(2) Å, b = 9.804(3) Å, c = 18.149(2) Å, β = 111.916(7)°, V = 2523.0(10) Å^3, Z = 4, D_c = 1.29 g/cm^3, μ = 14.42 cm^{-1}. 3562 reflections ($\Theta \le 55°$) were observed; 3411 were unique (R_{int} = 0.026). Refinement: 2490 reflections ($I > 3.00\sigma(I)$), 307 variable parameters, R = 0.039, and R_w = 0.054.

(*S*)-6al (REP): $C_{27}H_{36}N_2O_4$, M_r = 452.59, orthorhombic, space group $P2_12_12_1$, a = 13.325(4) Å, b = 23.087(3) Å, c = 8.383(4) Å, V = 2579.0(15) Å^3, Z = 4, D_c = 1.17 g/cm^3, μ = 6.24 cm^{-1}. 1909 reflections ($\Theta \le 55°$) were unique. Refinement: 1657 reflections ($I > 3.00\sigma(I)$), 298 variable parameters, R = 0.043, and R_w = 0.055.

(*S*,*S*′)-28: $C_{23}H_{37}N_3O_5$ ($C_{16}H_{26}N_2$·$C_7H_{11}NO_5$), M_r = 435.6, orthorhombic, space group $P2_12_12_1$ (#19), a = 10.996(4) Å, b = 24.155(5) Å, c = 9.210(6) Å, V = 2422(1) Å^3, Z = 4, D_c = 1.194 g/cm^3, μ = 6.8 cm^{-1}. 1481 reflections ($\Theta \le 50°$) were unique. Refinement: 1365 reflections ($I > 3.00\sigma(I)$), 289 variable parameters, R = 0.037, and R_w = 0.045.

The X-ray crystallographic data of the three compounds are deposited at the Cambridge Structural Data (CSD) Bank.

Molecular Modeling. The conformational analysis procedure was carried out using the systematic and grid search modules of the SYBYL[58] (Tripos Inc., St. Louis, MO) program

package on Silicon Graphics Indigo2 workstations. The Tripos force field was used for all calculations without atomic charges. The superpositions were performed by using the rigid fit procedure of SYBYL in order to optimally fit the central phenylene ring and the acidic pharmacophoric group of each molecule. The identified LECs were further optimized with the ab initio program Gaussian 94[59] using Hartree−Fock calculation with the 6-31G* basis set.

For the hydrophobic potentials, the program Hint[60,61] was applied which is integrated by MSI Open Interface into InsightII.[62] For the electrostatic potentials, the point charge model implemented in SYBYL was applied. Atomic charges were determined by semiempirical quantum mechanics using the AM1 method implemented in MOPAC93.[63]

Pharmacology. Adult fasted female Wistar rats, strain Chbb THOM (SPF), with a body weight of 200−220 g were used. Animals were fed ad libitum with standard pelleted diets and were housed under a 12/12 h light/dark cycle with 7 h 00 min to 19 h 00 min being the light phase. Food was withdrawn 24 h before the start of the studies between 8 h 00 min and 10 h 00 min. The compounds were suspended in 1.5% Tylose KN 2000 (methylcellulose). The suspension containing the appropriate amount of substance was given orally via gavage. Administration volume was 10 mL/kg.

Blood was collected from the retrobulbar venous plexus under light halothane anaesthesia. Blood glucose was measured in whole blood by the hexokinase/glucose-6-phosphate dehydrogenase method (Glucoquant, Boehringer Mannheim) after the protein had been precipitated by addition of 0.5 mL of 0.33 M $HClO_4$ to 50 μL of blood; measurements were carried out with an Eppendorf 5032 automatic substrate analyzer. Blood glucose was monitored hourly up to 4 h after administration in comparison with a control group ($N = 7$). Statistical significance was checked with Student's t-test ($P \leq 0.05$). The maximum percentage decrease of blood sugar (ΔBG) observed within 4 h was taken as the measure for a compound's blood sugar lowering activity. Calculation of ED_{50} values was performed by fitting the function $y = b + [a \times k/(k + x^{nH})]$ to the data by the program Sigma Plot (Jandel Scientific) where y is the measured glucose value, x is the dose of the substance used, nH is the Hill coefficient, a is the difference between the upper and the lower asymptotes of the dose response curve, and b is the baseline level. ED_{50} values were defined as half-maximal effect doses.

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Supporting Information Available: Spectral data for **5c**, **11c**, **5d**, **11d**, **5l**, **11l**, **11j**, **11k**, **11o**, **11p**, **13d-ethylester**, **13d**, **29**, **12q**, **14y**, **6al**, **(*S*,*S*′)-28**, **(*S*)-12q**, **(*S*)-14y**, **(*S*)-6al** (25 pages). Ordering information is given on any current masthead page.

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