N^1-Benzoyl-N^2-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexanes: Development of 4-Chlorophenylcarboxamide (Calhex 231) as a New Calcium Sensing Receptor Ligand Demonstrating Potent Calcilytic Activity

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A structure−activity relationship (SAR) study was performed principally at the N^1 position of N^1-arylsulfonyl-N^2-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexanes, a new family of calcilytics acting at the calcium sensing receptor (CaSR). The most active compound in this series was the 4-(trifluoromethoxy)-benzenesulfonyl derivative **7e**, which displayed an IC_{50} of 5.4 ± 0.5 μM with respect to the inhibition of calcium-induced tritiated inositol phosphate ([^{3}H]IP) accumulation in Chinese hamster ovarian (CHO) cells expressing the CaSR. Replacement of the sulfonamide linkage of this compound by a carboxamide led to a 6-fold increase in activity (**7m**, IC_{50} = 0.9 ± 0.2 μM). Among the carboxamides synthesized, one of the most active compounds was the 4-chlorophenylcarboxamide (1*S*,2*S*,1′*R*)-**7n** (Calhex 231, IC_{50} = 0.33 ± 0.02 μM). The absolute configuration of (1*S*,2*S*,1′*R*)-**7n** was deduced from an X-ray crystallographic study of one of the diastereomers of compound **7d**. The stereochemical preference for the (1*S*,2*S*,1′*R*)-isomers can be rationalized on the basis of a three-dimensional model of the calcilytic binding pocket of the CaSR. Removal of the C-1′ methyl group or replacement of the 1-naphthyl group by a 2-naphthyl or biphenyl moiety led to appreciable loss of calcilytic activity. Compounds **7e**, **7m**, and Calhex 231 did not stimulate [^{3}H]IP accumulation in CHO cells expressing or not expressing the CaSR.

Introduction

The development of an effective therapy for the treatment or prevention of osteoporosis remains today a major challenge. While this debilitating disease is considered a major risk factor in menopausal women, projections show that in an increasingly aging population men will also be targeted.[1] Ideally, a therapeutic approach to osteoporosis should aim at regeneration or reconstruction of lost bone tissue. One possible way of achieving this is by use of parathyroid hormone (PTH) as an anabolic agent. It has been found that, in vivo, intermittent administration of PTH[2−6] (or of certain fragments thereof)[7] stimulates bone formation in animal models of osteoporosis, increasing both bone density and strength. However, the peptide nature of these substances complicates their administration.

An indirect way of controlling PTH secretion is via up- or down-regulation of the cell surface calcium sensing receptor (CaSR) of the parathyroid.[8] The CaSR belongs to family 3 of heptahelical G-protein-coupled receptors, which also includes metabotropic glutamate receptors (mGluRs), the B-type γ-aminobutyric acid receptor ($GABA_B$-R), the GPRC6A receptor, and certain pheromone and taste receptors.[9−11] Cloning of CaSR cDNA has shown this receptor to be present in many tissues including kidney, intestine, lung, brain, bone, and the parathyroid gland.[8,12−17] At the surface of the latter, the CaSR is stimulated by extracellular calcium $[Ca^{2+}]_e$, thereby controlling PTH release.[8] While high levels of $[Ca^{2+}]_e$ inhibit PTH secretion via activation of the CaSR, low $[Ca^{2+}]_e$ levels no longer able to activate the CaSR result in increased PTH secretion. It can thus be conjectured that compounds that can block the action of the CaSR (CaSR antagonists or calcilytics) should stimulate bone formation due to the resulting increase in plasma PTH levels. These potentially anabolic effects would thus represent an innovative therapy for osteoporosis whereby new bone tissue is actually generated, in contrast to most present therapies that merely retard bone resorption.

While other divalent cations (Mg^{2+}, Sr^{2+})[12,17] activate, though nonspecifically, the CaSR, the first small molecules shown to bind specifically to the CaSR were **1a** and **1b** (Chart 1, NPS *R*-467 and NPS *R*-568, respectively), which display good affinities for the CaSR and which act as agonists (or calcimimetics).[18−20] Thus, in the presence of $[Ca^{2+}]_e$, both compounds lead to an increase in cytoplasmic calcium concentrations $[Ca^{2+}]_i$ in bovine parathyroid cells leading, as predicted, to an inhibition of PTH secretion. An analogue of **1a** and **1b**, cinacalcet (**2**) has recently been proposed for the treatment of secondary hyperparathyroidism.[21,22]

The discovery of calcilytics has proven to be more difficult and **3** (NPS 2143) was the first calcilytic, or negative allosteric modulator of the CaSR, to be described.[23,24] This compound significantly increased PTH secretion in cultured bovine parathyroid cells, while in ovariectomized rats, the classical animal model of osteoporosis, this compound produced an increase of plasma PTH. However, these increased plasma PTH levels were too sustained over time to produce a positive effect on bone density, a not unexpected result because it has been shown that chronically high PTH levels lead to bone loss.[25] The need for

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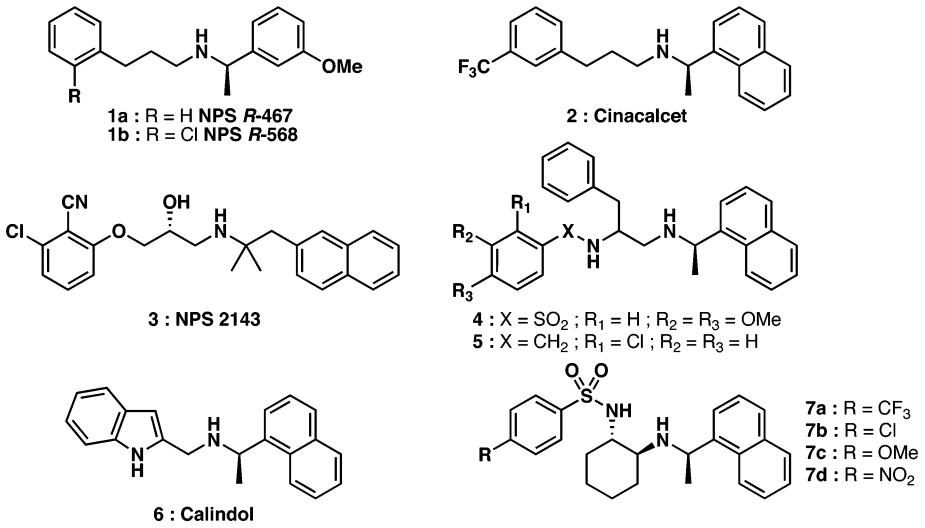
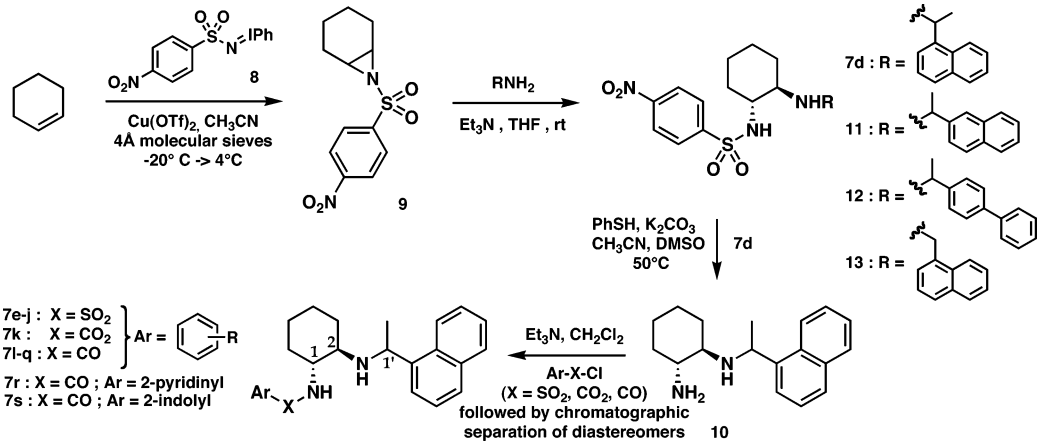
Chart 1



Scheme 1



new families of calcilytics displaying high affinities for the CaSR with a more favorable pharmacodynamic profile thus remains cogent.

In our own laboratories, we were able to use the structure of **1b** as the starting point for the development of several new families of calcimimetic compounds including the N^1-(arylsulfonyl)-1,2-diaminopropanes, represented by the 3,4-dimethoxy derivative **4**,[26] the closely related *N*-benzyl analogues (e.g., the 2-chlorobenzyl derivative **5**), and their conformationally restrained and more active 2-aminomethylindole analogues (e.g., calindol, **6**).[27]

In a recent communication, we described a second series of rigid CaSR ligands having a diaminocyclohexane backbone and that now displayed calcilytic rather than calcimimetic properties. The measured in vitro activities for the most active of these compounds synthesized, the 4-trifluoromethyl- and 4-chlorobenzenesulfonamides **7a** and **7b**, respectively, were approximately 1 order of magnitude inferior to that of **3** in blocking the action of calcium at the CaSR.[28] Nevertheless, these compounds represented the first new family of calcilytic agents after **3**. Since then, only a few reports of alternative chemical structures demonstrating calcilytic activity have appeared.[29−31] In this paper, we describe the study of the structure−activity relationships of this new family of calcilytics, which has led to significantly more active compounds. The stereochemical aspects of binding of these calcilytics is also presented with respect to a rhodopsin-based model of the calcilytic binding pocket of the CaSR.[32]

Chemistry

In our preliminary study,[28] we showed that replacement of the cyclohexane ring of the 4-methoxybenzenesulfonamide derivative **7c** by a cyclopentane or a cycloheptane ring led to a complete loss of the calcilytic activity while introduction of a double bond in the cyclohexyl ring resulted in a considerably less active compound. It thus seemed unwise at this point to modify the nature of this apparently essential six-membered scaffold. Instead, our efforts were concentrated on modifying the amine substituents. Thus, as shown previously,[28] the key intermediate N^1-(4-nitrobenzenesulfonyl)-N^2-[1-(1-naphthyl)-ethyl]-1,2-diaminocyclohexane (**7d**) was prepared as a mixture of diastereomers with (1*R**,2*R**) configuration by copper-catalyzed aziridination[33,34] of cyclohexene with [(*N*-*p*-nitrophenylsulfonyl)imino]phenyliodane (**8**)[35] followed by reaction of the resulting product **9** with (*R*,*S*)-1-(1-naphthyl)ethylamine (Scheme 1). Removal of the nosyl protecting group with thiophenolate[36] afforded the primary amine **10**, which could then be reacted with various substituted benzenesulfonyl chlorides to give the corresponding benzenesulfonamides (**7e**−**j**). Replacement of the *N*-sulfonyl linkage by an *N*-carbonyl was also investigated. These compounds (**7k**−**s**) could be obtained simply by reacting amine **10** with the appropriate acid chloride. Ring-opening of aziridine **9** with (*R*,*S*)-1-(2-naphthyl)ethylamine, (*R*,*S*)-1-(4-biphenyl)ethylamine, or 1-naphthylmethylamine provided compounds **11**, **12**, or **13**, respectively. For this study, chemical characterization and pharmacological results of only

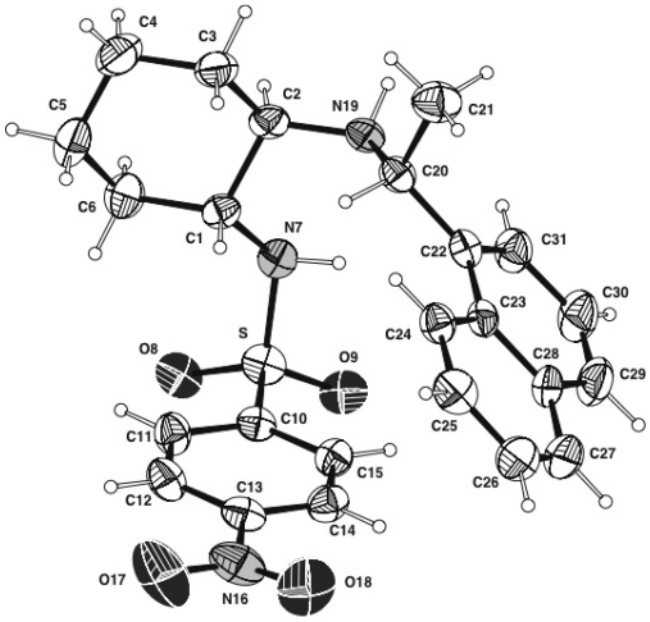


Figure 1. X-ray crystal structure of (1*R*,2*R*,1′*R*)-**7d**.

the more polar (and, as shown below, more active) of the isomeric products (except for **7e** and **7m**) are presented.[37] Diastereomeric mixtures were separated by column chromatography.

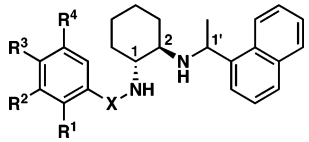
To study the relationship between stereochemistry and activity, the four trans isomers of both the 4-trifluoromethoxybenzenesulfonamide **7e** and its carboxamide counterpart **7m** were prepared by the procedure of Scheme 1 but using this time optically pure (*R*)- or (*S*)-(1-naphthyl)ethylamine in the aziridine ring opening step. Each reaction in turn gave two diastereomeric products that could be easily separated by column chromatography on silica gel.

X-ray crystallographic analysis was used to establish the absolute configuration of these compounds. Because of the well-known facility of nitrophenyl derivatives to crystallize, attempts were made to obtain crystals of compound **7d** suitable for X-ray studies. Only the less polar isomer (on silica gel) of the two (1′*R*) isomers of **7d** gave appropriate crystals, the X-ray structure of which allowed attribution of the (1*R*,2*R*,1′*R*)-configuration (Figure 1).[38] A similar trend has been observed in a recent X-ray study concerning the desymmetrization of *N*-(tosyl)cyclohexylaziridines in which (1*R*,2*R*,1′*R*)-1,2-diaminocyclohexanes were found to be less polar on silica gel than their (1*S*,2*S*,1′*R*)-counterparts.[39] Biological assays were thus conducted on the racemate formed by the (1*S**,2*S**,1′*R**)-enantiomers.

Biological Results and Discussion

The calcilytic activities of the synthesized compounds as well as of **3** were then evaluated in Chinese hamster ovarian cells expressing the CaSR [CHO(CaSR)] by measuring their ability to inhibit the stimulation of tritiated inositol phosphate ([^{3}H]-IP) production induced by 9 mM Ca^{2+}. As shown in Table 1, replacement of the electron-donating *p*-methoxy group of **7c** by an electron-withdrawing *p*-nitro group (**7d**) led to essentially no change in calcilytic activity (62 ± 9% vs 56 ± 4% inhibition of [^{3}H]IP accumulation at 10^{-5} M) while a trifluoromethoxy group at the same position (**7e**) produced a small but significant increase in activity (78 ± 5% inhibition). The 3-chloro, 3,4-dichloro, and 2,3,4-trichloro derivatives (**7f**, **7g**, and **7h**, respectively) also all inhibited Ca^{2+}-induced [^{3}H]IP production by about 60% at 10^{-5} M, which is somewhat weaker than the

Table 1. Inhibition of [^{3}H]IP Accumulation Produced by Ca^{2+} (9 mM) in CHO Cells Expressing Rat Cloned CaSR by the Test Compounds **7a**−**q**



						% inhibition of [^{3}H]IP accumulation[b]	
compd[a]	X	R^1	R^2	R^3	R^4	10^{-5} M	10^{-6} M
3						87 ± 6	77 ± 16
7a[c]	SO_2	H	H	CF_3	H	75 ± 7	ND
7b[c]	SO_2	H	H	Cl	H	73 ± 4	ND
7c[c]	SO_2	H	H	CH_3O	H	62 ± 9	12 ± 7
7d	SO_2	H	H	NO_2	H	56 ± 4	ND
7e	SO_2	H	H	CF_3O	H	78 ± 5	8 ± 5
7f	SO_2	H	Cl	H	H	60 ± 6	ND
7g	SO_2	H	Cl	Cl	H	60 ± 4	ND
7h	SO_2	Cl	Cl	Cl	H	59 ±4	ND
7i	SO_2	CH_3O	H	H	CH_3O	0 ± 6	ND
7j	SO_2	H	CF_3	H	H	44 ± 8	ND
7k	CO_2	H	H	H	H	1 ± 9	ND
7l	C=O	H	H	H	H	78 ± 5	33 ± 11
7m	C=O	H	H	CF_3O	H	95 ± 3	50 ± 1
7n	C=O	H	H	Cl	H	106 ± 3	90 ± 8
7o	C=O	H	Cl	Cl	H	103 ± 3	82 ± 12
7p	C=O	Cl	H	H	H	68 ± 6	19 ± 4
7q	C=O	CF_3	H	H	H	ND	36 ± 7

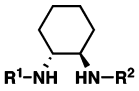
[a] As the hydrochloride salt. [b] Values are the mean ± SEM. [c] From ref 28.

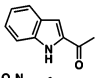
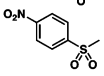
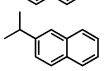
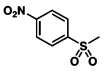
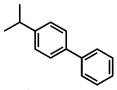
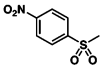
4-chloro analogue **7b**[28] (73 ± 4% inhibition). Interestingly, the 2,5-dimethoxy derivative **7i** was completely inactive at this concentration. It thus became quickly evident that while these sulfonamides all displayed distinct calcilytic activity (except **7i**), they remained significantly less active than **3**, which exhibited an equivalent effect (77 ± 16% inhibition) at a 10-fold lower concentration (10^{-6} M).

In the case of the *N*-carbonyl derivatives, however, while the phenyl carbamate derivative (**7k**) was inactive as a calcilytic, the phenylcarboxamide analogue **7l** revealed itself to be as active a calcilytic as the most active of the sulfonamide derivatives (**7e**), inhibiting [^{3}H]IP production by 78 ± 5% at 10^{-5} M. The 4-trifluoromethoxycarboxamides and 4-chlorophenylcarboxamides **7m** and **7n** (analogous to the most active sulfonamides **7e** and **7b**, respectively) exhibited high calcilytic activity, providing 95 ± 3% and 106 ± 3% inhibition at 10^{-5} M (50 ± 1% and 90 ± 8% at 10^{-6} M), respectively. Addition of another chloro atom at the C-3 position of the phenyl ring of **7n** (i.e., **7o**, 82 ± 12% inhibition at 10^{-6} M) had little significant effect on activity, while the presence of a chloro atom (**7p**) or trifluoromethyl (**7q**) group at C-2 was somewhat unfavorable to the activity (19 ± 4 and 36 ± 7% inhibition at 10^{-6} M, respectively).

Replacement of the phenyl ring of **7l** by a pyridine (**7r**) or indole (**7s**) ring provided compounds that were of comparable activity (35 ± 17% and 33 ± 22% inhibition for **7r** and **7s**, respectively, at 10^{-6} M (Table 2) compared to 33 ± 11% inhibition for **7l** (Table 1)), indicating that nitrogen-containing heterocycles are well tolerated at this position. Furthermore, attachment of the naphthyl group at the C-2 position (i.e., compound **11)** resulted in considerably reduced calcilytic activity (20 ± 3% inhibition at 10^{-5} M) compared to the C-1 regioisomer **7d (**56 ± 4% inhibition). The α-methylbiphenyl derivative **12** was also practically inactive as a calcilytic (7 ± 1% inhibition at 10^{-5} M). Moreover, the importance of the C-1′

Table 2. Inhibition of [^{3}H]IP Accumulation Produced by Ca^{2+} (9 mM) in CHO Cells Expressing Rat Cloned CaSR by the Test Compounds **7r**, **7s**, **11**−**13**



Compound[a]	R^1	R^2	% inhibition of ^{3}H-IP accumulation[b] 10^{-5}M	10^{-6}M
7r			76 ± 2	35 ± 17
7s			ND	33 ± 22
11			20 ± 3	1 ± 10
12			7 ± 1	ND
13			6 ± 8	1 ± 3

[a] As the hydrochloride salt. [b] Values are the mean ± SEM.

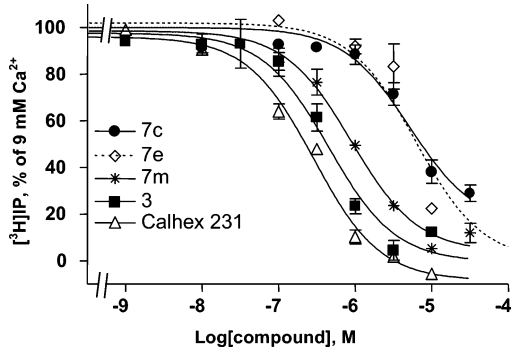


Figure 2. Calcilytic potency of selected compounds **7** compared to compound **3**: concentration response curves for inhibition of calcium induced IP accumulation in CHO (CaSR) cells. Data (mean ± SEM) are expressed as the percentage of 9 mM extracellular Ca^{2+} IP response over the basal level at 2 mM extracellular Ca^{2+}: **7c**, $IC_{50} = 8 \pm 2$ μM; **7e**, $IC_{50} = 5.4 \pm 0.5$ μM; **7m**, $IC_{50} = 0.9 \pm 0.2$ μM; **3**, $IC_{50} = 0.46 \pm 0.05$ μM; (1*S*,2*S*,1′*R*)-**7n** (Calhex 231), $IC_{50} = 0.33 \pm 0.02$ μM.

methyl group for calcilytic activity was firmly established by the complete loss of activity when this group was absent (i.e., compound **13**).

The IC_{50} values of a selection of these new calcilytics were then determined and compared to that of **3**. Thus, as shown in Figure 2, compounds **7c**, **7e**, and **7m** displayed IC_{50} values slightly higher than that of **3** (8 ± 2, 5.4 ± 0.5, and 0.9 ± 0.2 μM, respectively, compared to 0.46 ± 0.05 μM for **3**).

To address the question of stereochemistry, each of the four isomers of **7e** and **7m** was evaluated independently for calcilytic activity at 10^{-5} M (Table 3). For both **7e** and **7m**, the (*R*)-configuration of the methyl group was considerably more active than the (*S*)-isomer. Thus, the (1′*R*)-diastereomers of the 4-trifluoromethoxyphenylcarboxamide **7m** inhibited [^{3}H]IP production by 95 ± 4% and 100 ± 3% while the two (1′*S*)-isomers showed only 22 ± 3% and 0% inhibition. A similar pattern was observed for the four isomers of the sulfonamide analogues **7e**. These results were confirmed by dose response curves for each isomer (Figure 3). Interestingly, and as briefly mentioned above, in the case of the (1′*R*)-isomers of **7e** and **7m**, the faster moving component on silica gel (corresponding to the (1*R*,2*R*,1′*R*)-isomer by extrapolation of the X-ray structure of the faster moving component of **7d** shown in Figure 1) was the

Table 3. Comparison of the Calcilytic Activities of the Four Isomers of Compounds **7e** and **7m**

isomer[a]	% inhibition of [^{3}H]IP accumulation (10^{-5} M)[b]
(1*R*,2*R*,1′*R*)-**7e**	32 ± 5
(1*S*,2*S*,1′*R*)-**7e**	90 ± 1
(1*S*,2*S*,1′*S*)-**7e**	20 ± 4
(1*R*,2*R*,1′*S*)-**7e**	inactive
(1*R*,2*R*,1′*R*)-**7m**	95 ± 4
(1*S*,2*S*,1′*R*)-**7m**	100 ± 3
(1*S*,2*S*,1′*S*)-**7m**	inactive
(1*R*,2*R*,1′*S*)-**7m**	22 ± 3

[a] As the hydrochloride salt. [b] Values are the mean ± SEM.

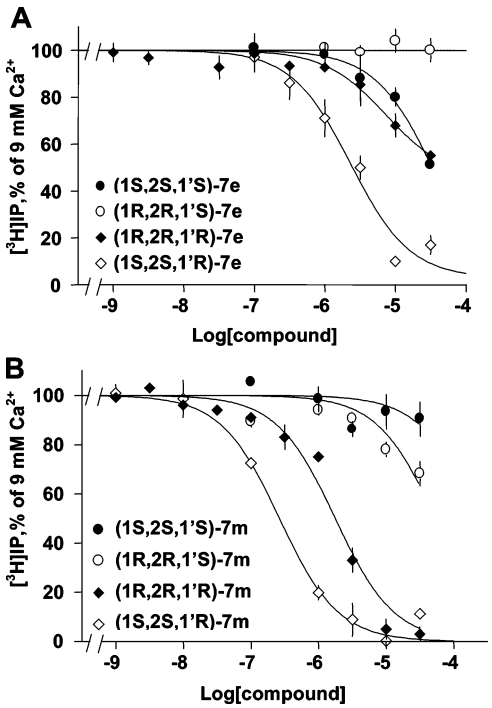


Figure 3. Calcilytic activities of compounds **7e** and **7m** as a function of stereochemistry. Each isomer was tested independently on CHO (CaSR) cells as in Figure 2: (1*S*,2*S*,1′*R*)-**7e**, $IC_{50} = 2.6 \pm 0.2$ μM; (1*S*,2*S*,1′*R*)-**7m**, $IC_{50} = 0.25 \pm 0.03$ μM; (1*R*,2*R*,1′*R*)-**7m**, $IC_{50} = 1.7 \pm 0.2$ μM.

less active. Thus, (1*R*,2*R*,1′*R*)-**7e** did not allow full inhibition of the IP response while (1*S*,2*S*,1′*R*)-**7e** displayed an IC_{50} of 2.6 ± 0.2 μM (Figure 3A). Similarly, the IC_{50} of compound (1*R*,2*R*,1′*R*)-**7m** corresponded to 1.7 ± 0.2 μM compared to 0.25 ± 0.03 μM for (1*S*,2*S*,1′*R*)-**7m** (Figure 3B**)**. In view of these results, the (1*S*,2*S*,1′*R*)-isomer of **7n**, one of the most active calcilytics in our series (Table 1),[40] was prepared in an analogous fashion. This compound, (1*S*,2*S*,1′*R*)-**7n** (Calhex 231), was found to have an IC_{50} of 0.33 ± 0.02 μM comparable to that of (1*S*,2*S*,1′*R*)-**7m**. These two compounds are thus more active than **3** (Figure 2).

Finally, we also investigated whether these compounds could stimulate IP production in CHO (WT*) cells (i.e., not expressing the CaSR receptor) in a nonspecific manner or if a particular stereoisomer having no apparent calcilytic activity could display calcimimetic activity (i.e., stimulation of IP secretion) in the presence of a low calcium concentration (2 mM). As shown in Figure 4, Calhex 231 and the four stereoisomers of compounds **7e** and **7m** have little or no effect on the basal level activity in CHO cells transfected or not with the CaSR. These results thus confirm that the compounds that were inactive as calcilytics ((1*R*,2*R*,1′*S*)-**7e**, (1*S*,2*S*,1′*S*)-**7m**), Table 3) are also inactive as calcimimetics and that furthermore the remaining compounds,

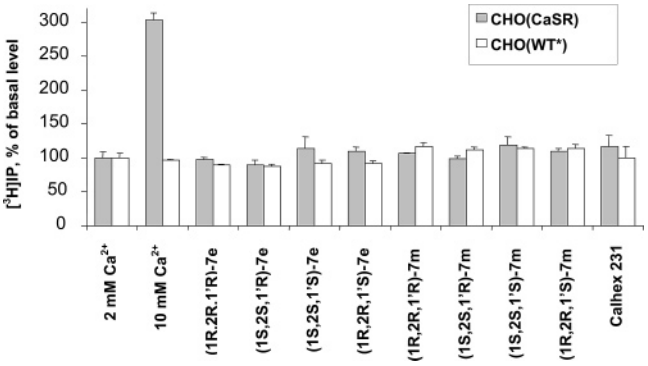


Figure 4. Basal activity of compound Calhex 231 compared to the four different isomers of **7e** and **7m**. Compounds at 10 μM were applied to CHO (CaSR) or CHO (WT*) cells in the presence of a basal level of extracellular Ca^{2+} (2 mM). In both cell types, compounds, including Calhex 231, had limited effects on IP production. Data (mean ± SEM) are expressed as the percentage of the basal response. Maximal response on IP accumulation was evaluated at 10 mM extracellular Ca^{2+}.

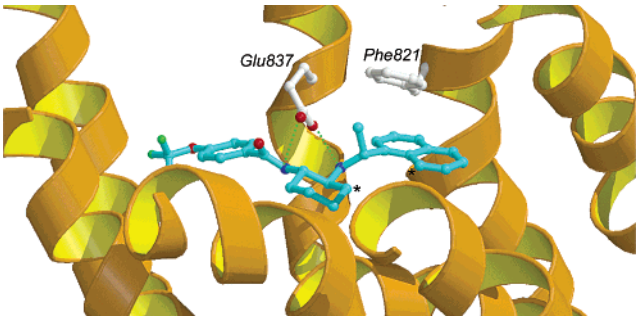


Figure 5. Model of (1*S*,2*S*,1′*R*)-**7m** binding to the CaSR showing the interaction of the Phe821 residue with the (*R*)-CH_3 group. Two carbon atoms (labeled by an asterisk) of the ligand preclude the establishment of a bioactive conformation of the stereoisomer having an (*S*)-CH_3 group.

all displaying calcilytic activities to a greater or lesser degree (Table 3), do not have any stimulatory effects in CHO cells expressing or not expressing the CaSR.

Molecular Modeling

We have recently developed a model of the human CaSR[32] based on the X-ray structure of bovine rhodopsin, used as a template to model the seven transmembrane domains of the CaSR.[41] Using the Surflex docking program,[42] automated docking of Calhex 231 revealed a preferred binding mode to the transmembrane domain in which some of the principal features are H-bonding of both nitrogen atoms to Glu-837 and interaction of the naphthalene ring with neighboring hydrophobic side chains such as Phe-821. This model was confirmed by the subsequent mutation of these and several other residues (to alanine) forming the binding cavity, which led to important effects on the affinity of Calhex 231.[43] Significantly, this calcilytic binding model helps to explain the stereochemical preference of the calcilytic compounds observed in this study. Thus, as depicted in Figure 5, in which (1*S*,2*S*,1′*R*)-**7m** (the most active of the **7m** isomers, Table 3) has been docked into the binding pocket, the C-1′ methyl group having the favored *R* configuration displays strong hydrophobic interactions with Phe-821, a residue shown by our mutagenesis studies to be important for binding. The orientation of this methyl group is strongly constrained by Glu-837, which is the main anchor of the secondary amine, and by Phe-821, which stacks with the naphthalene ring of the calcilytic. These interactions are lost (together with substantial binding affinity) when the same methyl group has the unfavored *S* configuration due to the resulting steric repulsion between the methyl group and two neighboring carbon atoms (one on the naphthalene moiety, one on the cyclohexane ring; see Figure 5)

Conclusion

A new family of calcilytic agents, N^1-benzoyl-N^2-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexanes, acting specifically at the CaSR, has been developed. These ligands were derived from a systematic study of rigid analogues of the calcimimetic **1b**. In particular, the present structure−activity relationship study has led to the generation of Calhex 231, one of the most potent calcilytics known to date. A three-dimensional model of the CaSR binding pocket, derived from the crystal structure of bovine rhodopsin, helps to explain the stereochemical preference for the 1′*R* isomers of these calcilytics and should also be highly useful for the design of more potent analogues of Calhex 231.

Experimental Section

General. Melting points were determined in capillary tubes on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as films or as KBr pellets with a Nicolet 205 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker 250 or 300 MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on AEI MS-50 and AEI MS-9 spectrometers, respectively. Electron spray ionization mass spectra were determined on a Navigator Thermo Finnigan instrument. High-resolution mass spectra were obtained using a Kratos MS-80 or an ESI-TOF LCT Micromass spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230−400 mesh) at medium pressure (200 mbar). Only data for the more polar component is reported in each case. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

(±)-7-(4-Nitrobenzenesulfonyl)-7-azabicyclo[4.1.0]heptane (9). A mixture of cyclohexene (4.87 mL, 48 mmol), copper(II) triflate (569 mg, 1.6 mmol), and 4 Å molecular sieves in acetonitrile (32 mL) was cooled to −20 °C, and solid (4-nitrobenzenesulfonyl)-iminophenyliodane (**8**, 6.49 g, 16 mmol) was added in portions with stirring. Stirring was maintained for 6 h at −20 °C after completion of the addition and then for 16 h at 4 °C. The reaction mixture was filtered through Celite, the filtrate was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (heptane−ethyl acetate, 8:2), affording aziridine **9** as a pale-yellow solid (57%): mp 134−136 °C (lit.[44] mp 142 °C); IR (film) 1172, 1347, 1540 cm^{-1}; ESMS *m*/*z* 282 $(MH)^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24−1.44 (m, 4H, H-3, H-4), 1.82 (m, 4H, H-2, H-5), 3.13 (m, 2H, H-1, H-6), 8.15 (d, 2H, $J_{2',3'}$ = 11.3 Hz, H-2′), 8.39 (d, 2H, $J_{3',2'}$ = 11.3 Hz, H-3′); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ19.2, 22.7, 41.0, 124.2, 128.8, 145.0, 151.0. Anal. ($C_{12}H_{14}N_2O_4S$) C, H, N, S.

***N*^{1}-(4-Nitrobenzenesulfonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7d).** A solution of aziridine **9** (1 equiv), (*R*,*S*)-1-(1-naphthyl)ethylamine (2 equiv), and triethylamine (0.7 equiv) in anhydrous THF (0.25 M) was stirred for 16 h at room temperature. The solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (heptane−ethyl acetate, 8:2 then 7:3) to give **7d** (50%). A sample was resubmitted to silica gel chromatography, allowing isolation of the slower running component, which was used for the biological assays: IR (KBr) 1165, 1348, 1529, 3303 cm^{-1}; ESMS *m*/*z* 454 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80−1.27 (m, 4H, H-4, H-5), 1.41 (d, 3H, J = 6.0 Hz, $CHCH_3$), 1.46−1.60 (m, 2H, H-3),

1.92−2.00 (m, 2H, H-6), 2.19−2.22 (m, 1H, H-1), 2.80 (dt, 1H, J = 6.0 and 12.0 Hz, H-2), 4.70 (q, 1H, J = 6.0 Hz, C*H*CH_3), 7.45−7.50 (m, 4H, ArH), 7.74−7.77 (m, 1H, ArH), 7.86−7.90 (m, 3H, ArH), 8.20−8.27 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 24.2, 24.6, 31.7, 32.4, 49.9, 57.7, 58.5, 122.4, 122.9, 124.2, 125.7, 126.2, 127.9, 128.3, 129.3, 131.3, 134.3, 141.4, 147.1, 149.8. Anal. ($C_{24}H_{27}N_3O_4S$) C, H, N, S.

Use of (*R*)-(1-naphthyl)ethylamine in the same reaction sequence provided, after isolation by chromatography, (1*R*,2*R*,1′*R*)-**7d** (faster moving fraction) and (1*S*,2*S*,1′*R*)-**7d** (slower moving fraction). The former isomer was crystallized for the X-ray diffraction studies: mp 159−161 °C; $[\alpha]^{25}_D$ −56 (*c* 1.0, $CHCl_3$); IR (KBr) 1165, 1348, 1529, 3303 cm^{-1}; ESMS *m*/*z* 454 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83−1.01 (m, 1H, H-4a), 1.16−1.34 (m, 3H, H-4, H-5b, H-5), 1.44 (d, 3H, J = 6.0 Hz, CHC*H*$_3$), 1.62−1.78 (m, 2H, H-3), 2.14−2.26 (m, 2H, H-6), 2.47 (dt, 1H, J = 3.0 and 9.0 Hz, H-1), 2.65 (dt, 1H, J = 3.0 and 9.0 Hz, H-2), 4.67 (q, 1H, J = 6.0 Hz, C*H*CH_3), 7.43−7.50 (m, 4H, ArH), 7.69−7.76 (m, 1H, ArH), 7.87−7.92 (m, 3H, ArH), 8.00−8.35 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 24.1, 24.7, 31.7, 32.6, 49.6, 57.8, 58.4, 122.4, 122.8, 123.9, 124.4, 125.5, 125.6, 126.0, 127.7, 128.3, 129.2, 130.5, 134.0, 140.5, 146.0, 149.8.

***N*^{1}-[1-(1-Naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (10).** A solution of compound **7d** (1 equiv of the mixture of diastereomers) in a mixture of acetonitrile−DMSO (96:4, concentration 0.165 mmol in 2 mL) was treated with solid potassium carbonate (4 equiv) and thiophenol (3 equiv). The reaction mixture was stirred for 6 h at 50 °C and cooled, and the solvents were evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (ethyl acetate−methanol, 2:1 then 1:1) afforded compound **10** (1:1 mixture of diastereomers) as a pale-yellow oil in quantitative yield: ESMS *m*/*z* 268 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84−1.03 (m, 3H, $H_{cyclohex}$), 1.05−1.26 (m, 3H, $H_{cyclohex}$), 1.47 (d, 1.5H, J = 6.0 Hz, CHC*H*$_3$ of diastereomer 1), 1.48 (d, 1.5H, J = 6.0 Hz, CHC*H*$_3$ of diastereomer 2), 1.56−1.67 (m, 1H, $H_{cyclohex}$), 1.85−1.98 (m, 1H, $H_{cyclohex}$), 2.06−2.18 (m, 1H, H-2), 2.29 (dt, 0.5H, J = 5.5 and 11.5 Hz, H-1 of diastereomer 1), 2.37 (dt, 0.5H, J = 5.5 and 11.5 Hz, H-1 of diastereomer 2), 4.77 (q, 0.5H, J = 6.0 Hz, C*H*CH_3 of diastereomer 1), 4.88 (q, 0.5H, J = 6.0 Hz, C*H*CH_3 of diastereomer 2), 7.42−7.52 (m, 3H, ArH), 7.65−7.74 (m, 2H, ArH), 7.84−7.87 (m, 1H, ArH), 8.18−8.23 (m, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.9, 24.8, 24.9, 25.0, 25.3, 31.4, 32.1, 34.5, 35.4, 50.4, 50.5, 55.6, 55.7, 60.1, 61.2, 122.7, 122.9, 123.1, 123.3, 125.2, 125.5, 125.6, 125.7, 127.0, 127.1, 128.9, 130.6, 133.8, 134.6, 141.3, 142.9.

***N*^{1}-[4-(Trifluoromethoxy)benzenesulfonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7e).** A solution of compound **10** (1 equiv) in dichloromethane (0.5 mmol in 6 mL) was treated with triethylamine (1 equiv) at room temperature and, after 10 min, with 4-(trifluoromethoxy)benzenesulfonyl chloride. The reaction mixture was stirred for 15 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (heptane−ethyl acetate, 8:2 then 7:3).The slower running component provided compound **7e** (40%): mp 139−141 °C (as the hydrochloride); EIMS *m*/*z* 492 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86−0.99 (m, 2H, H-4), 1.08−1.26 (m, 2H, H-5), 1.40 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.50−1.61 (m, 2H, H-3), 1.95−2.00 (m, 2H, H-6), 2.20−2.22 (m, 1H, H-1), 2.78 (dt, 1H, $J_{2,3}$ = 3.8 Hz, $J_{1,2}$ = 10.6 Hz, H-2), 4.73 (q, 1H, J = 6.5 Hz, C*H*CH_3), 5.35 (m, 1H, NH, exchangeable with D_2O), 7.29−7.32 (m, 2H, ArH), 7.47−7.59 (m, 4H, ArH), 7.77 (dd, 1H, ArH), 7.90 (d, 3H, ArH), 8.24 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.4, 24.6, 31.5, 32.5, 57.3, 58.2, 120.7, 122.6, 123.7, 125.5, 125.6, 126.0, 127.5, 129.2, 131.2, 134.1, 139.3, 140.4, 151.8. Anal. ($C_{25}H_{27}F_3N_2O_3S\cdot HCl\cdot H_2O$) C, H, N.

Use of (*R*)-(1-naphthyl)ethylamine in the same reaction sequence that gave **7e** from **9** provided, after isolation by chromatography, (1*R*,2*R*,1′*R*)-**7e** (faster moving fraction, $[\alpha]^{25}_D$ −40 (*c* 1.0, $CHCl_3$)) and (1*S*,2*S*,1′*R*)-**7e** (slower moving fraction, $[\alpha]^{25}_D$ −30 (*c* 1.0, $CHCl_3$)). Similarly, use of (*S*)-(1-naphthyl)ethylamine afforded (1*S*,2*S*,1′*S*)-**7e** (faster moving fraction, $[\alpha]^{25}_D$ +43 (*c* 1.0, $CHCl_3$)) and (1*R*,2*R*,1′*S*)-**7e** (slower moving fraction, $[\alpha]^{25}_D$ +27 (*c* 1.0, $CHCl_3$)).

Selected data for (1*R*,2*R*,1′*R*)-**7e**: mp 144 °C (as the hydrochloride); EIMS *m*/*z* 492 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83−0.92 (m, 2H, H-4), 1.15−1.29 (m, 2H, H-5), 1.44 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.56−1.71 (m, 2H, H-3), 2.11−2.20 (m, 2H, H-6), 2.44 (dt, 1H, $J_{1,6}$ = 4.1 Hz, $J_{1,2}$ = 10.6 Hz, H-1), 2.62 (dt, 1H, $J_{2,3}$ = 3.9 Hz, $J_{1,2}$ = 10.6 Hz, H-2), 4.69 (q, 1H, J = 6.5 Hz, C*H*CH_3), 5.55 (s, 1H, NH, exchangeable with D_2O), 7.08 (d, 2H, ArH), 7.37−7.46 (m, 4H, ArH), 7.69 (m, 1H, ArH), 7.77−7.82 (m, 3H, ArH), 7.98−8.02 (m, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.5, 24.1, 24.7, 31.9, 32.6, 49.6, 58.1, 58.3, 120.6, 122.5, 123.0, 125.5, 126.0, 127.5, 129.1, 129.3, 130.4, 133.9, 138.5, 141.7. Anal. ($C_{25}H_{27}F_3N_2O_3S\cdot HCl\cdot 2H_2O$) C, H, N.

***N*^{1}-(3-Chlorobenzenesulfonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7f).** Using the same procedure as for the preparation of **7e**, amine **10** was reacted with 3-chlorobenzenesulfonyl chloride to provide compound **7f** (45%): IR (film) 1162, 1331, 3419 cm^{-1}; ESMS *m*/*z* 443 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84−1.15 (m, 4H, H-4, H-5), 1.41 (d, 3H, J = 6.4 Hz, CHC*H*$_3$), 1.49−1.60 (m, 2H, H-3), 1.95−1.99 (m, 2H, H-6), 2.19−2.22 (m, 1H, H-1), 2.74 (m, 1H, H-2), 4.72 (q, 1H, J = 6.4 Hz, C*H*CH_3), 7.40−7.46 (m, 6H, ArH), 7.72−7.78 (m, 2H, ArH), 7.87−7.89 (m, 2H, ArH), 8.23−8.25 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.4, 24.6, 24.8, 31.7, 32.8, 57.4, 58.4, 122.8, 123.9, 125.4, 125.6, 126.1, 126.8, 127.4, 127.4, 127.7, 129.3, 130.3, 131.4, 132.6, 134.2, 135.2, 140.4, 142.7; HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{24}H_{28}N_2O_2S^{35}Cl$ 443.1560, found 443.1565.

***N*^{1}-(3,4-Dichlorobenzenesulfonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7g).** Using the same procedure as for the preparation of **7e**, amine **10** was reacted with 3,4-dichlorobenzenesulfonyl chloride to provide compound **7g** (48%): mp 132−138 °C (as the hydrochloride); IR (KBr) 1164, 1332, 3066 cm^{-1}; ESMS *m*/*z* 477 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86−1.40 (m, 4H, H-4, H-5), 1.44 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.47−1.61 (m, 2H, H-3), 1.92−2.04 (m, 2H, H-6), 2.21−2.24 (m, 1H, H-1), 2.75 (dt, 1H, $J_{2,3}$ = 4.0 Hz, $J_{1,2}$ = 10.6 Hz, H-2), 4.72 (q, 1H, J = 6.5 Hz, C*H*CH_3), 5.40 (m, 1H, NH, exchangeable with D_2O), 7.48−7.54 (m, 5H, ArH), 7.63−7.68 (m, 1H, ArH), 7.77−7.81 (m, 1H, ArH), 7.89−7.93 (m, 1H, ArH), 7.97−7.99 (m, 1H, ArH), 8.28 (d, 1H, NH, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.5, 24.6, 31.6, 32.5, 57.4, 58.3, 122.6, 125.6, 126.2, 127.6, 129.0, 129.2, 130.8, 131.2. Anal. ($C_{24}H_{26}Cl_2N_2O_2S\cdot HCl$) C, H, N.

***N*^{1}-(2,3,4-Trichlorobenzenesulfonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7h).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 2,3,4-trichlorobenzenesulfonyl chloride to provide compound **7h** (31%): EIMS *m*/*z* 511 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.81−0.95 (m, 2H, H-4 or H-5), 1.05−1.35 (m, 2H, H-5 or H-4), 1.47 (d, 3H, J = 6.0 Hz, CHC*H*$_3$), 1.51−1.62 (m, 2H, H-3), 1.88−1.99 (m, 2H, H-6), 2.15−2.25 (m, 1H, H-1), 2.77 (dt, 1H, $J_{2,3}$ = 3.7 Hz, $J_{1,2}$ = 10.1 Hz), 4,78 (q, 1H, J = 6.0 Hz, C*H*CH_3), 5.84 (m, 1H, NH, exchangeable with D_2O), 7.45−7.62 (m, 5H, ArH), 7.79 (d, 1H, ArH), 7.85−7.92 (m, 1H, ArH), 7.97 (d, 1H, ArH), 8.24−8.27 (m, 1H, ArH); HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{24}H_{26}N_2O_2S^{35}Cl_3$ 511.0781, found 511.0773; HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{24}H_{26}N_2O_2S^{35}Cl_2{}^{37}Cl$ 513.0751, found 513.0745.

***N*^{1}-(2,5-Dimethoxybenzenesulfonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7i).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 2,5-dimethoxybenzenesulfonyl chloride to provide compound **7i** (25%): IR (KBr) 1155, 1324, 3180 cm^{-1}; ESMS *m*/*z* 469 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.80−1.16 (m, 4H, H-4, H-5), 1.43 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.47−1.54 (m, 2H, H-3), 1.79−1.89 (m, 2H, H-6), 2.04−2.17 (m, 1H, H-1), 2.73−2.82 (m, 1H, H-2), 4.83 (q, 1H, J = 6.5 Hz, C*H*CH_3), 5.47 (d, 1H, J = 5.2 Hz, NH, exchangeable with D_2O), 6.96 (d, 1H, J = 8.9 Hz, ArH), 7.08 (dd, 1H, J = 8.7 and 2.9 Hz, ArH), 7.46−7.58 (m, 4H, ArH), 7.64 (d, 1H, J = 6.9 Hz, ArH), 7.77 (d, 1H, J = 7.9 Hz, ArH), 7.88−7.91

(m, 1H, ArH), 8.16−8.19 (m, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.1, 24.6, 25.1, 31.2, 32.4, 50.8, 56.2, 57.0, 57.5, 58.3, 113.8, 114.8, 120.5, 122.6, 123.2, 125.5, 125.9, 126.0, 127.3, 129.2, 131.5, 134.1, 140.6, 143.2, 150.4, 153.3; HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{26}H_{33}N_2O_4S$ 469.2161, found 469.2162.

***N*^{1}-[3-(Trifluoromethyl)benzenesulfonyl]-*N*^{2}-[1-(1-naphthyl)-ethyl]-*trans*-1,2-diaminocyclohexane (7j).** Using the same procedure as for the preparation of **7e**, amine **10** was reacted with 3-(trifluoromethyl)benzenesulfonyl chloride to provide compound **7j** (colorless oil, 50%): IR (film) 1161, 1327, 3057 cm^{-1}; ESMS *m*/*z* 477 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84−0.97 (m, 2H, H-4), 1.12−1.20 (m, 2H, H-5), 1.42 (d, 3H, J = 6.4 Hz, CHC*H*$_3$), 1.50−1.61 (m, 2H, H-3), 1.91−1.99 (m, 2H, H-6), 2.22−2.25 (m, 1H, $J_{1,6}$ = 3.4 Hz, $J_{1,2}$ = 10.1 Hz, H-1), 2.76 (dt, 1H, $J_{2,3}$ = 3.4 Hz, $J_{1,2}$ = 10.1 Hz, H-2), 4.72 (q, 1H, J = 6.4 Hz, C*H*CH$_3$), 5.40 (m, 1H, NH, exchangeable with D_2O), 7.47−7.66 (m, 5H, ArH), 7.75−7.91 (m, 3H, ArH), 8.02−8.05 (m, 1H, ArH), 8.18 (s, 1H, ArH), 8.25−8.27 (m, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.5, 31.6, 32.6, 57.3, 58.4, 122.6, 124.1, 125.5, 125.7, 126.0, 127.7, 129.0, 129.2, 129.6, 130.4, 131.2, 134.1, 142.1. Anal. ($C_{25}H_{27}F_3N_2O_2S\cdot HCl\cdot H_2O$) C, H, N.

***N*^{1}-(Phenyloxycarbonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7k).** Using the same procedure as for the preparation of **7e**, amine **10** was reacted with phenyl chloroformate to provide compound **7k** (50%): EIMS *m*/*z* 389 $[MH]^+$; IR (film) 3319, 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10−1.35 (m, 4H, H-4, H-5), 1.49 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.56−1.71 (m, 2H, H-3), 2.09−2.11 (m, 1H, H-6), 2.23−2.28 (m, 1H, H-6), 2.47 (dt, 1H, $J_{1,2}$ = $J_{1,6a}$ = 9.9 Hz, $J_{1,6b}$ = 3.7 Hz, H-1), 3.38−3.41 (m, 1H, H-2), 4.87 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 5.26 (m, 1H, NH), 7.16−7.25 (m, 2H, ArH), 7.36−7.55 (m, 5H, ArH), 7.77 (d, 2H, ArH), 7.87−7.91 (m, 2H, ArH), 8.22−8.25 (m, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.7, 24.7, 24.9, 32.6, 51.5, 59.5, 60.6, 121.7, 123.0, 123.5, 125.3, 125.4, 125.8, 125.9, 127.3, 129.1, 129.3, 131.0, 134.0, 142.3, 151.2; HRESMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{25}H_{28}N_2O_2Na$ 411.2048, found 411.2040.

***N*^{1}-Benzoyl-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7l)**. Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with benzoyl chloride to provide compound **7l** (50%): IR (film) 1636, 3307 cm^{-1}; ESMS *m*/*z* 373 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80−1.24 (m, 4H, H-4, H-5), 1.38 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.52−1.65 (m, 2H, H-3), 2.13−2.22 (m, 1H, H-6), 2.37−2.54 (m, 2H, H-1, H-6), 3.66−3.77 (m, 1H, H-2), 4.73 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 6.41 (m, 1H, NH, exchangeable with D_2O), 7.23−7.52 (m, 6H, ArH), 7.59−7.82 (m, 4H, ArH), 7.99 (d, 2H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.6, 24.8, 32.1, 32.4, 54.1, 58.3, 123.0, 123.9, 125.3, 125.4, 125.7, 126.9, 127.3, 128.3, 128.9, 131.1, 131.3, 133.9, 134.8, 143.3, 167.5; HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{25}H_{29}N_2O$ 373.2270, found 373.2280.

***N*^{1}-[4-(Trifluoromethoxy)benzoyl]-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7m).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 4-(trifluoromethoxy)benzoyl chloride to provide compound **7m** (50%): IR (film) 1542, 1636, 3291 cm^{-1}; ESMS *m*/*z* 457 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83−1.38 (m, 4H, H-4, H-5), 1.46 (d, 3H, J = 6.4 Hz, CHC*H*$_3$), 2.11 (dt, 1H, $J_{1,2}$ = 3.7 Hz, $J_{1,6}$ = 10.1 Hz, H-1), 2.25−2.30 (m, 2H, H-3), 2.40−2.44 (m, 2H, H-6), 3.63 (m, 1H, H-2), 4.74 (q, 1H, J = 6.4 Hz, C*H*CH$_3$), 6.09 (d, 1H, NH, exchangeable with D_2O), 7.23−7.46 (m, 5H, ArH), 7.55 (d, 1H, ArH), 7.63 (d, 2H, ArH), 7.76 (d, 1H, ArH), 7.88 (d, 1H, ArH), 8.37 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.5, 24.5, 24.9, 32.2, 53.3, 54.5, 58.4, 120.4, 122.7, 123.2, 125.3, 125.7, 127.5, 128.6, 128.7, 128.8, 131.2, 134.1, 166.2. Anal. ($C_{26}H_{27}F_3N_2O_2$) C, H, N.

Use of (*R*)-(1-naphthyl)ethylamine in the same reaction sequence that gave **7m** from **9** provided, after isolation by chromatography, (1*R*,2*R*,1′*R*)-**7m** (faster moving fraction, $[\alpha]^{25}_D$ −36 (*c* 1.0, $CHCl_3$)) and (1*S*,2*S*,1′*R*)-**7m** (slower moving fraction, $[\alpha]^{25}_D$ −9 (*c* 1.0, $CHCl_3$)). Similarly, use of (*S*)-(1-naphthyl)ethylamine afforded (1*S*,2*S*,1′*S*)-**7m** (faster moving fraction, $[\alpha]^{25}_D$ +40 (*c* 1.0, $CHCl_3$)) and (1*R*,2*R*,1′*S*)-**7m** (slower moving fraction, $[\alpha]^{25}_D$ +10 (*c* 1.0, $CHCl_3$)). Selected data for (1*R*,2*R*,1′*R*)-**7m**: IR (film) 1542, 1636, 3291 cm^{-1}; ESMS *m*/*z* 457 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21−1.39 (m, 4H, H-4, H-5), 1.47 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.63−1.75 (m, 2H, H-3), 2.14−2.20 (m, 1H, H-6), 2.29−2.33 (m, 1H, H-6), 2.44 (dt, 1H, $J_{1,2}$ = 3.7 Hz, $J_{1,6}$ = 10.1 Hz, H-1), 3.62 (m, 1H, H-2), 4.72 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 6.26 (d, 1H, NH, exchangeable with D_2O), 7.15−7.18 (m, 2H, ArH), 7.25−7.35 (m, 3H, ArH), 7.54−7.74 (m, 4H, ArH), 7.98 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 23.5, 24.5, 24.9, 32.2, 32.5, 51.1, 55.1, 58.9, 120.5, 122.7, 123.1, 125.2, 125.5, 125.6, 127.2, 128.6, 128.9, 130.7, 133.4, 133.8, 141.7, 166.3.

***N*^{1}-(4-Chlorobenzoyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7n) and (1*S*,2*S*,1′*R*)-7n (Calhex 231).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 4-chlorobenzoyl chloride to provide compound **7n** (50%): mp 66−68 °C (as the hydrochloride); ESMS *m*/*z* 407 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84−1.37 (m, 4H, H-4, H-5), 1.44 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.65−1.75 (m, 2H, H-3), 2.10 (dt, 1H, $J_{1,2}$ = 3.6 Hz, $J_{1,6}$ = 10.4 Hz, H-1), 2.23−2.27 (m, 1H, H-6), 2.37−2.42 (m, 1H, H-6), 3.63 (m, 1H, H-2), 4.74 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 6.10 (d, 1H, exchangeable with D_2O), 7.30−7.47 (m, 6H, ArH), 7.55 (d, 2H, ArH), 7.75 (d, 1H, ArH), 7.87 (d, 1H, ArH), 8.34 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.7, 25.0, 32.3, 32.4, 51.7, 54.5, 58.5, 123.2, 124.2, 125.5, 125.9, 127.5, 128.5, 128.6, 129.1, 133.3, 134.2, 137.4, 141.7, 154.5, 166.5. Anal. ($C_{25}H_{27}ClN_2O$) C, H, N.

Use of (*R*)-(1-naphthyl)ethylamine in the same reaction sequence that gave **7n** from **9** provided, after isolation by chromatography of the slower moving component, (1*S*,2*S*,1′*R*)-**7n** (Calhex 231): $[\alpha]^{25}_D$ −28.9 (*c* 0.28, $CHCl_3$).

***N*^{1}-(3,4-Dichlorobenzoyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7o).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 3,4-dichlorobenzoyl chloride to provide compound **7o** (50%): ESMS *m*/*z* 441 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94−1.34 (m, 4H, H-4, H-5), 1.61 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.51−1.78 (m, 2H, H-3), 2.12−2.23 (m, 2H, H-6), 2.76 (dt, 1H, $J_{1,2}$ = 3.4 Hz, $J_{1,6}$ = 10.1 Hz, H-1), 3.77−3.84 (m, 1H, H-2), 5.00 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 7.37−7.58 (m, 4H, ArH), 7.70 (d, 1H, ArH), 7.78−7.85 (m, 2H, ArH), 7.90−7.95 (m, 1H, ArH), 8.05 (s, 1H, ArH), 8.22 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.3, 24.4, 29.7, 31.0, 52.0, 58.4, 121.4, 125.7, 126.4, 127.0, 127.7, 128.9, 129.2, 129.6, 130.3, 130.5, 130.7, 131.6, 132.1, 132.9, 133.7, 134.1, 136.2, 165.8. HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{25}H_{27}N_2O^{35}Cl_2$ 441.1500, found 441.1525.

***N*^{1}-(2-Chlorobenzoyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7p).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 2-chlorobenzoyl chloride to provide compound **7p** (41%): ESMS *m*/*z* 407 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84−1.37 (m, 4H, H-4, H-5), 1.48 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.54−1.72 (m, 2H, H-3), 2.12 (dt, 1H, $J_{1,2}$ = 2.9 Hz, $J_{1,6}$ = 9.6 Hz, H-1), 2.25−2.30 (m, 2H, H-6), 2.73−2.80 (m, 1H, H-2), 4.78 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 6.01 (d, 1H, NH, exchangeable with D_2O), 7.20−7.24 (m, 2H, ArH), 7.34−7.42 (m, 4H, ArH), 7.53−7.60 (m, 2H, ArH), 7.68 (d, 1H, ArH), 7.83 (d, 1H, ArH), 8.30−8.33 (m, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.6, 24.1, 24.4, 28.5, 29.8, 32.3, 51.3, 59.6, 121.8, 125.3, 125.8, 126.4, 127.2, 127.7, 129.5, 129.6, 130.1, 130.2, 130.4, 131.0, 131.4, 133.5, 134.0, 134.9, 168.0.

***N*^{1}-[2-(Trifluoromethyl)benzoyl]-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7q).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with 2-(trifluoromethyl)benzoyl chloride to provide compound **7q** (50%): ESMS *m*/*z* 441 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78−1.33 (m, 4H, H-4, H-5), 1.42 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.53−1.62 (m, 2H, H-3), 1.98 (dt, 1H, $J_{1,2}$ = 3.8 Hz, $J_{1,6}$ = 10.1 Hz, H-1), 2.23−2.27 (m, 1H, H-6), 2.40−2.44 (m, 1H, H-6), 3.59 (m, 1H, H-2), 4.67 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 5.66 (d, 1H, NH, exchangeable with D_2O), 7.11−7.13 (m, 1H, ArH), 7.21 (t, 1H, ArH), 7.35 (t, 1H, ArH), 7.52 (d, 2H, ArH), 7.62 (m, 2H, ArH),

7.69 (d, 1H, ArH), 7.74−7.76 (m, 1H, ArH), 7.83 (d, 1H, ArH), 8.37 (d, 1H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.7, 24.8, 25.0, 32.1, 32.2, 55.0, 58.0, 123.3, 124.3, 125.4, 126.4, 127.5, 128.7, 129.1, 129.6, 131.3, 132.0, 137.5, 140.3; HRESMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{26}H_{27}N_2OF_3Na$ 463.1973, found 463.1967.

***N*^{1}-(Pyridine-2-carbonyl)-*N*^{2}-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (7r).** Using the same procedure as for the preparation of **7e**, amine **10** was reacted with pyridine-2-carbonyl chloride to provide compound **7r** (18%): ESMS *m*/*z* 374 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01−1.37 (m, 4H, H-4, H-5), 1.41 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.60−1.75 (m, 1H, H-3), 2.07−2.15 (m, 1H, H-3), 2.19−2.35 (m, 2H, H-6), 3.79−3.92 (m, 1H, H-2), 4.84 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 7.33−7.50 (m, 3H, ArH), 7.65 (d, 1H, ArH), 7.72 (m, 1H, ArH), 7.85−8.01 (m, 3H, ArH), 8.20−8.28 (m, 2H, ArH), 8.64 (d, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 25.0, 32.4, 32.8, 53.6, 58.5, 122.4, 123.0, 123.6, 124.0, 125.3, 125.8, 125.9, 126.1, 127.0, 129.0, 134.0, 137.4, 148.1; HRESMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{24}H_{27}N_3ONa$ 396.2052, found 396.2033.

***N*^{1}-(Indole-2-carbonyl)-*N*^{2}-[1-(1-naphthyl)ethyl)]-*trans*-1,2-diaminocyclohexane (7s).** Using the same procedure as for the preparation of compound **7e**, amine **10** was reacted with indole-2-carbonyl chloride to provide compound **7s** (23%): ESMS *m*/*z* 412 $[MH]^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01−1.39 (m, 4H, H-4, H-5), 1.47 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.64−1.76 (m, 2H, H-3), 2.15 (dt, 1H, $J_{1,6}$ = 3.7 Hz, $J_{1,2}$ = 10.3 Hz, H-1), 2.26−2.30 (m, 1H, H-6), 2.40 (m, 1H, H-6), 3.74 (ddt, 1H, $J_{2,3}$ = 4.2 Hz, $J_{1,2}$ = 10.3 Hz, $J_{2,NH}$ = 7.1 Hz, H-2), 4.78 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 6.16 (d, 1H, NH, exchangeable with D_2O), 6.58 (s, 1H, indole H-3), 7.17 (t, 1H, ArH), 7.29 (t, 1H, ArH), 7.39−7.50 (m, 4H, ArH), 7.64 (d, 1H, ArH), 7.70 (d, 1H, ArH), 7.79 (d, 1H, ArH), 7.91 (d, 1H, ArH), 8.34 (d, 1H, ArH), 9.61 (s, 1H, indole NH, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.8, 25.0, 32.4, 32.7, 54.2, 58.6, 102.1, 112.0, 120.7, 122.0, 123.2, 124.2, 124.4, 125.6, 125.8, 126.1, 127.6, 127.8, 129.2, 131.2, 131.5, 134.3, 136.3, 141.8, 161.8; HRESMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{27}H_{30}N_3ONa$ 434.2208, found 434.2205.

***N*^{1}-(4-Nitrobenzenesulfonyl)-*N*^{2}-[1-(2-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexane (11).** Using the same procedure as for the preparation of compound **7d**, aziridine **9** was treated with (*R*,*S*)-1-(2-naphthyl)ethylamine to afford compound **11** (43%): ESMS *m*/*z* 454 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) 0.74−1.19 (m, 4H, H-4, H-5), 1.35 (d, 3H, J = 5.0 Hz, CHC*H*$_3$), 1.49−1.54 (m, 1H, H-3), 1.63−1.66 (m, 1H, H-3), 1.86−1.95 (m, 2H, H-6), 2.22−2.25 (m, 1H, H-1), 2.76 (dt, 1H, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 2.5 Hz, H-2), 4.03 (q, 1H, J = 5.0 Hz, C*H*CH$_3$), 5.49 (m, 1H, NH), 7.44−7.55 (m, 3H, ArH), 7.65 (s, 1H, ArH), 7.81−7.93 (m, 5H, ArH), 8.21 (d, 2H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.2, 24.7, 25.1, 31.5, 32.1, 54.8, 57.3, 58.4, 124.2, 124.3, 126.0, 126.1, 126.4, 127.8, 127.9, 128.4, 129.1, 133.1, 133.5, 142.4, 145.1, 193.8; HRESMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{24}H_{27}N_3O_4SNa$ 476.1620, found 476.1613.

***N*^{1}-(4-Nitrobenzenesulfonyl)-*N*^{2}-[1-(4-biphenyl)ethyl]-*trans*-1,2-diaminocyclohexane (12).** Using the same procedure as for the preparation of **7d**, aziridine **9** was treated with (*R*,*S*)-1-(4-biphenyl)ethylamine to afford compound **12** (43%): mp 152−154 °C; ESMS *m*/*z* 480 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.83−1.17 (m, 4H, H-4, H-5), 1.30 (d, 3H, J = 6.5 Hz, CHC*H*$_3$), 1.54−1.58 (m, 1H, H-3), 1.64−1.68 (m, 1H, H-3), 1.91−2.00 (m, 2H, H-6), 2.20−2.23 (m, 1H, H-1), 2.74 (dt, 1H, $J_{1,2}$ = 10.1 Hz, $J_{2,6a}$ =10.1 Hz, $J_{2,6b}$ = 3.7 Hz, H-2), 3.91 (q, 1H, J = 6.5 Hz, C*H*CH$_3$), 5.49 (m, 1H, NH), 7.33 (d, 4H, ArH), 7.46 (t, 1H, ArH), 7.60 (d, 4H, ArH), 8.01 (d, 2H, ArH), 8.30 (d, 2H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.3, 24.7, 25.3, 31.5, 32.3, 54.3, 57.3, 58.5, 124.3, 127.1, 127.3, 127.5, 127.6, 128.5, 128.9, 140.5, 140.7, 144.1, 201.4; HRESMS (*m*/*z*) $[MH]^+$ calcd for $C_{26}H_{30}N_3O_4S$ 480.1957, found 480.1991.

***N*^{1}-(4-Nitrobenzenesulfonyl)-*N*^{2}-(1-naphthylmethyl)-*trans*-1,2-diaminocyclohexane (13).** Using the same procedure as for the preparation of compound **7d**, aziridine **9** was treated with 1-naphthylmethylamine to afford compound **13** (82%) after chromatography: mp 148−150 °C; IR (film) 3276, 2930, 1531, 1348, 1165 cm^{-1}; ESMS *m*/*z* 440 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.81−1.51 (m, 4H, H-4, H-5), 1.66−1.81 (m, 2H, H-3), 2.12−2.20 (m, 2H, H-6), 2.29 (dt, 1H, $J_{1,6a}$ = 3.9 Hz, $J_{1,2}$ = 10.5 Hz, H-1), 2.67−2.88 (m, 1H, H-2), 3.81 (d, 1H, J_{gem} = 12.4 Hz, CH_2N), 7.33−7.36 (m, 1H, ArH), 7.47−7.55 (m, 2H, ArH), 7.63 (s, 1H, ArH), 7.77−7.85 (m, 3H, ArH), 7.93 (d, 2H, ArH), 8.10 (d, 2H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 24.4, 24.6, 31.3, 33.3, 48.0, 58.1, 60.3, 123.2, 123.7, 125.3, 125.9, 126.1, 126.3, 128.1, 128.2, 129.0, 131.4, 133.8, 135.1, 145.8, 149.4. Anal. ($C_{23}H_{25}N_3O_4S$) C, H, N, S.

X-ray Crystal Structure of (1*R*,2*R*,1′*R*)-7d. Crystal data for the compound are as follows: $[C_{24}H_{27}N_3O_4S]$, M = 453.55, monoclinic, space group $P21$, a = 7.199(3) Å, b = 13.796(6) Å, c = 11.455(5) Å, β = 94.36(4)°, V = 1134.4(8) Å^3, Z = 2, λ = 0.7107 Å, d_c = 1.328 g cm^{-3}, $F(000)$ = 480, μ = 0.179 mm^{-1}.

A small crystal of 0.2 mm × 0.3 mm × 0. 35 mm was mounted on an Enraf-Nonius KappaCCD diffractometer. A full sphere of data was collected by *f* axis rotation with an increment of 2° over 360° and 50 s of exposure per degree. "Denzingering" was accomplished by measuring each frame twice. Data were analyzed using KappaCCD software (Enraf-Nonius, Delft, The Netherlands, 1997). Cell dimensions were refined with HKL-scalepack,[45] and data reduction was performed with Denzo.[45] The structure was solved by direct methods (SHELX-S86)[46] and was refined on F^2 for all reflections by least-squares methods using SHELXL-93.[47] All hydrogen atoms were located on difference Fourier syntheses. They were modeled at their theoretical positions using an isotropic thermal factor equal to 1.2 times that of the bonded atom and introduced in the refinement cycles. The final conventional R is 0.0353 for 3359F_o > 4s(F_o) and 290 parameters, 0.0387 for all data, wR(F^2) = 0.11 for all, $w = 1/[s^2(F_o)^2 + (0.1384P)^2 + 0.33P]$, where $P = (F_o^2 + 2F_c^2)/3$. The largest difference peak and hole are 0.13 and −0.16 e Å^{-3}. The ORTEP plot of the compound is shown in Figure 1.[38]

Determination of Calcilytic Activity. Chinese hamster ovary cells, transfected (CHO (CaSR)) or not ((CHO (WT*)) with rat calcium sensing receptor, were cultured in basal Ham's F-12 medium (0.3 mM Ca^{2+}, 0.6 mM Mg^{2+}) as previously described.[17] Prior to experiments, cells were cultured overnight in their growth medium containing myo-[^{3}H]inositol (0.5 μCi mL^{-1}, Amersham Biosciences) in 24-well plates. Test compounds were dissolved at 10 mM in ethanol and then diluted in basal medium. The activation of phospholipase C was estimated after quantification of [^{3}H]IP accumulation. Briefly, cells were washed twice with 1 mL of basal medium containing 10 mM LiCl, incubated for 15 min in the same medium at 37 °C. Then cells were incubated for 30 min in the same medium at 37 °C in the presence of 9 mM Ca^{2+} and the test compound at the indicated concentration. Reactions were stopped by addition of 0.5 mL of 10% $HClO_4$, and [^{3}H]inositol phosphates were isolated by ion exchange chromatography as described.[17] Results are expressed as a percentage of 9 mM extracellular Ca^{2+} IP response over basal level at 2 mM extracellular Ca^{2+} and are the mean ± SEM of two to five independent experiments performed in triplicate. Where applicable, IC_{50} values of compounds were calculated with GraphPad Prism, version 2.01. For compounds **7a**−**s**, **11**, and **12** only the slower running components on silica gel were tested unless otherwise noted.

Molecular Modeling. The three-dimensional model of the human CaSR was constructed starting from the X-ray structure of bovine rhodopsin (Protein Data Bank code 1f88) using a previously described procedure.[32] The Surflex docking program[42] was then used to automatically dock (1*S*,2*S*,1′*R*)-**7m**. An idealized active-site ligand or protomol[48] was first generated from 33 consensus positions[41] supposed to map the transmembrane cavity of most GPCRs. This protomol consists of the preferred locations of various molecular probes (CH_4, C═O, N−H) that are then used by the docking engine to search for the three-dimensional morphological similarity between the protomol and the ligand to dock. A proto_thresh value of 0.5 and a proto_bloat value of 0 were used to generate a compact protomol. A Tripos mol2file of (1*S*,2*S*,1′*R*)-**7m**, obtained from a two-dimensional sketch as previously re-

ported,[41] was docked into the transmembrane cavity using standard parameters of Surflex used in the "whole" docking approach.[42] The best 30 solutions were finally stored in mol2 format.[49]

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Supporting Information Available: Microanalytical, physical, and spectral data for the less polar diastereomers of **7f**−**h**,**j**,**l**,**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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