Articles

Synthesis and Evaluation of Potent and Selective β_3 Adrenergic Receptor Agonists Containing Acylsulfonamide, Sulfonylsulfonamide, and Sulfonylurea Carboxylic Acid Isosteres†

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Starting from phenethanolamine aniline leads **3a** and **3b**, we have identified a series of functionally potent and selective β_3 adrenergic receptor (AR) agonists containing acylsulfonamide, sulfonylsulfonamide, or sulfonylurea groups within the aniline phenethanolamine series. In β_3, β_2, and β_1 AR cAMP functional assays, **3a** and other right-hand side (RHS) carboxylate analogues were found to be full agonists that were modestly selective against β_1 or β_2 ARs, while analogues lacking RHS acid functionality were active at β_3 AR but not selective. Replacement of the carboxylate with acylthiazole and acylmethylsulfone gave potent, but only modestly selective, compounds. Increasing the size of the RHS sulfonamide substituent with phenyl or *p*-toluene afforded compounds with good potency and functional selectivity (β_3 AR pEC_{50} greater than 8; β_1 and β_2 AR selectivity greater than 40- and 500-fold, respectively). Our SAR studies suggest that the potency and selectivity profile of the best analogues reported here is a result of both the steric bulk and acidity of the RHS sulfonamide NH group. Although all of the analogues had a pharmacokinetic half-life of less than 2 h, acylsulfonamides **43** and **44** did show moderately low clearance in dogs. These two compounds were further evaluated by thermographic imaging in mice and were found to produce a robust thermogenic response via oral administration.

Introduction

The increasing prevalence of obesity and its associated comorbidities in industrialized nations, including type 2 diabetes mellitus and related cardiovascular disorders, has stimulated efforts to develop effective new approaches in the treatment of this condition. While most therapeutic approaches involve altering the balance of metabolic energy by reducing energy intake, an alternative approach for the management of obesity is to effect an increase in the rate of energy expenditure (thermogenesis).[1] In 1984, compounds of the phenethanolamine class having thermogenic properties in rodents were first disclosed as potential agents in the treatment of human obesity.[2] Despite their structural similarity to known β_1 and β_2 adrenoceptor (AR) ligands, pharmacological studies indicated that these compounds stimulate a third, or "atypical", β AR that is now described as "β_3" AR.[3] Although this receptor was not characterized for several years, the striking rodent pharmacology of early phenethanolamine compounds triggered considerable activity at a number of pharmaceutical companies in the search for new antidiabetic and antiobesity drugs.[4] Before the cloned human receptor became available, early efforts focused on optimization using rodent models and led to the identification of clinical candidates such as **1**[5] and **2**.[6] Unfortunately, although some indication of efficacy was seen in clinical studies with these "first generation" development candidates, these and other early β_3 AR agonists have not advanced beyond phase II clinical trials because of lack of efficacy, poor pharmacokinetics, or dose-limiting cardiovascular side effects.[7,8]

Despite the failure of early β_3 agonists as viable therapeutic agents, in the past 12 years additional evidence has accumulated to suggest that β_3 AR stimulation may have potential benefit in the treatment of diabetes and obesity. In 1989, the human,[9] rat,[10] and mouse[11] β_3 ARs were first cloned and characterized. Evaluation of the activity of numerous compounds on the cloned rodent and human receptors uncovered significant interspecies differences in their activities at the three β AR subtypes.[12] These differences may, in part, explain the poor efficacy and/or side effect profile of early clinical candidates.[7] Adding support to the validity of the β_3 AR as an important therapeutic target, rodent studies have suggested a "reawakening" of

† Dedicated to the memory of our colleague Barbara Reitter.

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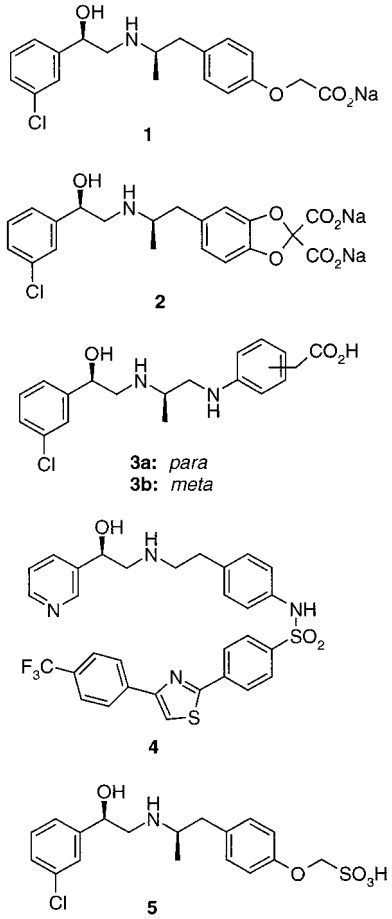
dormant β_3 AR responsive brown adipose tissue upon prolonged stimulation with **2**.[13] Recent studies in nonhuman primates treated with a selective β_3 AR agonist have demonstrated a separation in the dose response between metabolic rate and cardiovascular response, along with upregulation of uncoupling protein in axillary fat indicative of increased thermogenic potential.[14] In terms of human validation, β_3 ARs have been detected in human tissues of possible relevance to the treatment of type 2 diabetes and obesity, including fat and skeletal muscle.[15,16] In human clinical studies, significant increases in resting metabolic rate were seen using isoproterenol or **1** that were in part resistant to the β_1 AR and β_2 AR blocking effects of nadolol, implying that β_3 AR agonism plays a role in mediating human energy expenditure.[7] In other studies, compound **2**, reported to have minimal β_1 AR and β_2 AR activity,[6,12] caused increased insulin sensitivity and glucose utilization in lean, healthy volunteers.[8] Finally, it has been proposed that a Trp64Arg β_3 AR mutation in the human population plays a role in the development of diabetes and/or obesity in some individuals possessing this genetic variant.[17]

In the past decade, drug discovery efforts have shifted toward use of cell lines expressing human receptors in primary screening assays in order to identify potent β_3 AR agonists that are selective over human β_2 and β_1 ARs. Several structure−activity relationship (SAR) studies have now been published that describe compounds characterized in human β_3, β_2, and β_1 AR expressing cell lines. With the exception of two articles reporting tetrahydroisoquinoline β_3 AR agonists,[18a,b] these papers have described compounds in either the arylethanolamine or aryloxypropanolamine class. Among these analogues, a great deal of structural diversity has appeared in the right-hand side (RHS) portion of these analogues distal to the arylethanolamine or aryloxypropanolamine pharmacophore, suggesting a permissive interaction with the receptor in this portion of the molecule.[19] For example, in a series of papers by workers at Merck, phenylsulfonamides bearing a variety of RHS phenyl ring substituents have been described. A representative example of this series is the thiazole phenylsulfonamide **4** that has been described as a phase I clinical candidate.[20] In another article, a laboratory at Bristol-Myers Squibb (BMS) has reported the SAR of phenethanolamines related to **1** with modified RHS ether substituents. Consistent with earlier SAR studies in rodent systems,[3,21] the BMS work highlighted an important role of carboxylate and other negatively charged groups (such as sulfonic acid **5)** in providing β_1 and β_2 AR selectivity within certain phenethanolamine analogues[22a] (see Chart 1 for structures of some β_3 agonists). Also consistent with these results, a recent paper has described the use of thiazolidinediones as acid isostere replacements in both arylethanolamine and aryloxypropanolamine β_3 AR agonists.[22b]

In 1995, a Glaxo patent disclosed a series of phenethanolamines containing an anilinophenylacetic acid RHS subunit, as exemplified by GR9803 (**3a**).[23] Although it is a potent (<20 nM) agonist at human β_3, **3a** was found to have appreciable activity against human β_1 and β_2 ARs and was not progressed into the clinic. Nevertheless, the β_3 activity, relatively low molecular weight, and desirable physical properties of **3a** motivated us to further optimize this attractive lead. Herein, we describe SAR studies in which we have varied the size, position, and acidity of the phenyl RHS substituent of **3a.**[24] These studies have led to the discovery of a series of acyl- and sulfonylsulfonamides with very high potency and promising selectivity. In addition to in vitro SAR studies, we also describe the evaluation of certain compounds in this series in intravenous dog pharmacokinetic studies and rodent thermogenesis assays.

Chart 1. Phenethanolamine β_3 Agonists

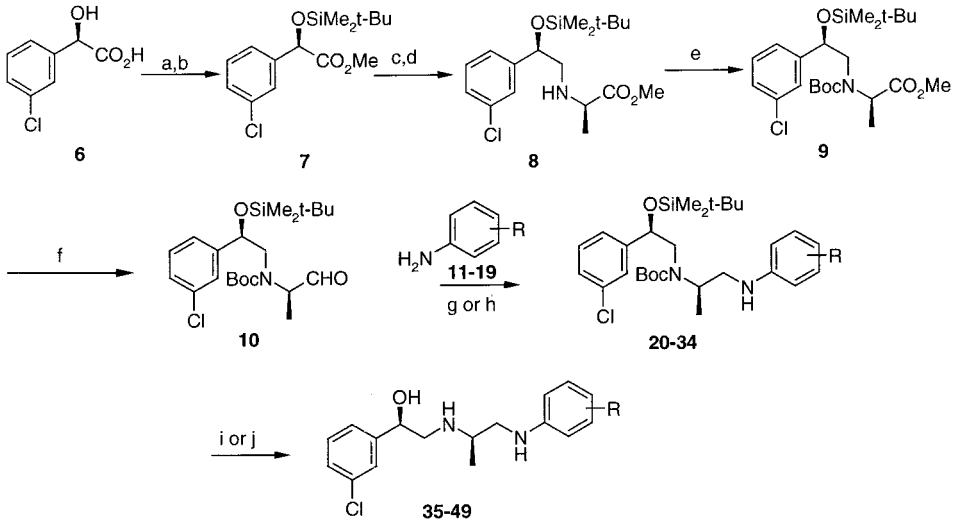


Chemistry

The general synthetic route to β_3 AR agonist targets is shown in Scheme 1. Reductive amination of aldehyde **10**[23] with either aniline itself or aniline intermediates **11**−**19** afforded the corresponding Boc amine silyl ether intermediates **20**−**34**. Removal of the Boc amine and silyl ether functionalities under acidic conditions provided the corresponding phenethanolamine hydrochlorides. In the case of amide or sulfonamide isosteric targets **35**−**49**, chromatography eluting with chloroform−methanol containing ammonium hydroxide supplied final targets **35**−**49** as the free base. For the syntheses of targets **35** and **36**, deprotection of the Boc amine silyl ether using 4 N HCl in dioxane provided the corresponding methyl ester amine hydrochloride, which was then converted into the acid target under basic saponification conditions. The syntheses of carboxylic acid targets **3a** and **3b** have been previously described.[23]

The synthesis of aldehyde **10** was carried out according to the previously disclosed route[23] starting from (*R*)-

Scheme 1. Synthetic Route to Targets **35**−**49**[a]



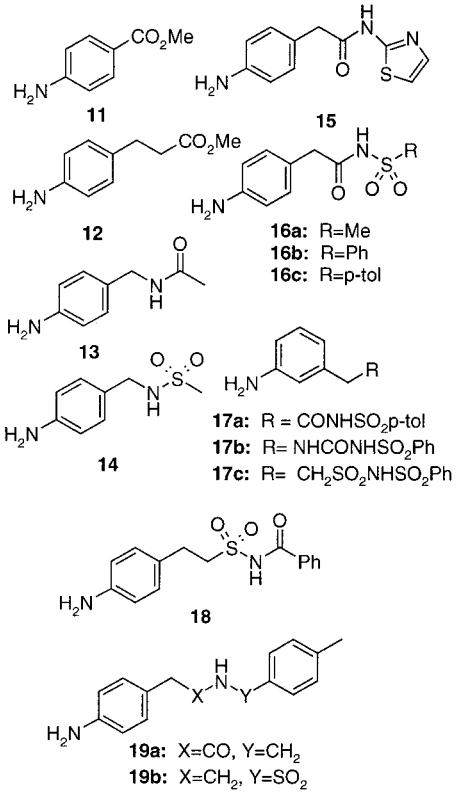
[a] (a) H_2SO_4, MeOH, reflux; (b) *tert*-butyldimethylsilyl chloride, imidazole, *N*,*N*-DMF; (c) DIBAL/toluene, Et_2O, −78 °C; (d) D-alanine methyl ester hydrochloride, $NaBH(OAc)_3$, AcOH (cat.), CH_2Cl_2; (e) di-*tert*-butyl dicarbonate, neat, 90−95 °C; (f) DIBAL, toluene; (g) $NaBH(OAc)_3$, AcOH (cat.), CH_2Cl_2; (h) $NaCNBH_3$, MeOH or *N*,*N*-DMF; (i) 6 N aqueous HCl, heat; (j) 4 N HCl/dioxane, room temp, and then LiOH, MeOH/H_2O.

mandelic acid **6**. Protection of **6** as the corresponding silyl ether methyl ester **7** and subsequent DIBAL reduction to the corresponding aldehyde followed by reductive amination with D-alanine methyl ester supplied amino methyl ester **8**, which was typically isolated in greater than 90% diastereomeric excess as the *R*,*R* diastereomer. In the key reductive amination step used to supply **8**, it was found that careful quench of the DIBAL-H reduction of methyl ester **7** with methanol at low temperature was necessary in order to minimize epimerization at the silyloxy stereocenter.

Anilines used for the synthesis of final targets via reductive amination with aldehyde **10** are shown in Chart 2. Known anilines **11**−**14** were obtained from commercial suppliers, while anilines **15**,[25] **19a**, and **19b**[26] were synthesized by standard methods. Noncommercially available anilines were prepared from the corresponding nitro intermediates by palladium-catalyzed hydrogenation or tin(II) chloride-mediated reduction. The corresponding nitro precursor to aniline **19a** was obtained through 1,1-carbonyldiimidazole-mediated coupling of 4-nitrophenyl carboxylic acid with benzylamine, while the nitro precursor to aniline **19b**[26] was obtained through reaction of *p*-toluenesulfonyl chloride with 2-(4-nitrophenyl)ethylamine.

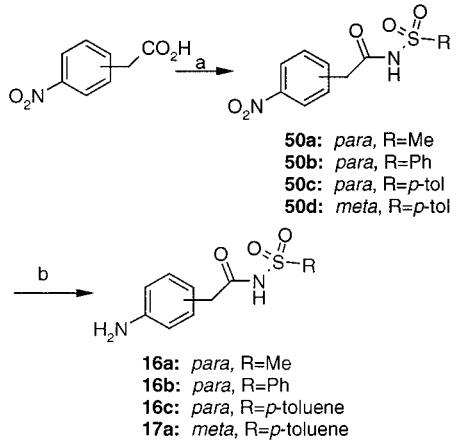
The remaining aniline intermediates and their nitro precursors were synthesized as shown in Schemes 2−4. Anilines **16a**−**c** and **17a** were synthesized employing a 1,1′-carbonyldiimidazole-promoted sulfonamide−carboxylic acid coupling procedure[27] with sulfonamides of interest and 3- or 4-nitrophenylacetic acid to give **50a**−**d**, followed by reduction of the nitro group as shown in Scheme 2. Sulfonylurea **17b** was synthesized by treating 3-nitrobenzylamine with benzenesulfonyl isocyanate followed by hydrogenation of the nitro group, as shown in Scheme 3. The ethyl-linked sulfonylsulfonamide **17c** and "reverse" acylsulfonamide **18** were made via sulfonylation or acylation of primary sulfonamides **54a** and **54b**, followed by reduction of the nitro group. Sulfonamides **54a**,**b** were obtained through nucleophilic displacement of commercially available bromide **51a** or tosylate **51b**[28] with potassium thioacetate, followed by oxidation of the alkyl thioacetate product to the corresponding sulfonic acids **53a**,**b**. The sulfonic acids were then activated by treatment with thionyl chloride and converted to the corresponding primary sulfonamide by treatment with ammonia (Scheme 4).

Chart 2. Anilines Employed in the Syntheses of Amide and Sulfonylsulfonamide Targets



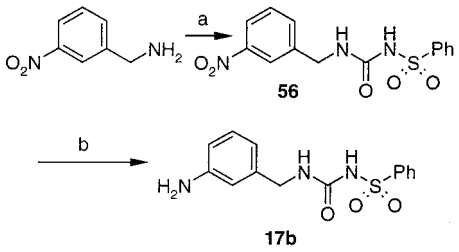
Typically, a minor degree of epimerization occurred either in the final aniline−aldehyde reductive amination step or in the final deprotection of intermediates **20**−**34**. The diastereomeric composition of purified final targets, which were observed as a single peak by

Scheme 2. Preparation of Acylsulfonamides **16**−**17a**[a]



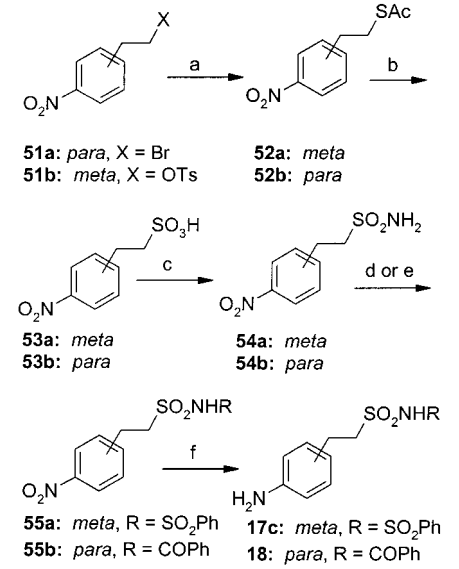
[a] (a) CDI, then methyl-, phenyl-, or *p*-toluenesulfonamide, DBU, CH_2Cl_2; (b) 10% Pd/C, MeOH or EtOAc.

Scheme 3. Preparation of Sulfonylurea Aniline Intermediate **17b**[a]



[a] (a) Benzenesulfonyl isocyanate, Et_3N, THF; (b) H_2, 10% Pd/C, MeOH/THF.

Scheme 4. Preparation of Ethyl-Linked Acyl- and Sulfonylsulfonamide Aniline Intermediates **17c** and **18**[a]



[a] (a) Potassium thioacetate, CH_3CN or *N*,*N*-DMF; (b) 30% H_2O_2, AcOH; (c) $SOCl_2$, *N*,*N*-DMF, then 0.5 M NH_3/dioxane; (d) benzenesulfonyl choride, Et_3N, CH_3CN, reflux; (e) benzoyl chloride, K_2CO_3, CH_3CN, reflux; (f) H_2, 10% Pd/C or 20% $Pd(OH)_2$/C.

reverse-phase HPLC, was determined by ^1H NMR to be at least 85% of the *R*,*R* isomer. In cases where epimerization occurred, the minor diastereomers were generally inseparable from the *R*,*R* isomer and were not characterized with regard to *R*,*S* versus *S*,*R* composition.[29]

Results and Discussion

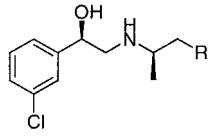
All compounds were tested for their ability to cause cAMP accumulation in cell lines that express human β_3, β_2, or β_1 ARs. The results are reported in terms of potency (pEC_{50}) and efficacy (E_{max}, the fitted maximal response to compound expressed as a percent of the maximal response) to the nonselective full β AR agonist isoprenaline (ISO). As a benchmark, lead aniline **3a** was characterized in our assays as a full and potent (pEC_{50} = 7.8, E_{max} = 100%) agonist against β_3 AR. However, this compound also generated a strong response at β_2 AR (pEC_{50} = 7.3, E_{max} = 90%), as well as significant (pEC_{50} = 7.1) albeit partial activity at the β_1 AR (24% ISO). In our cell lines, **3a** was found to have a profile at the three β AR subtypes similar to that of **2**, although it displayed slightly greater potency at both β_3 and β_1 ARs.

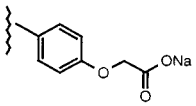
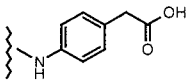
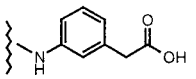
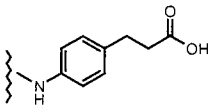
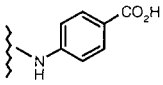
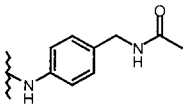
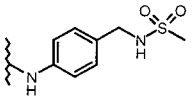
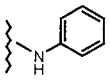
To identify compounds within our series with improved potency and selectivity, we initially compared lead compound **3a** to analogues in which the carboxylic acid was deleted, replaced with nonacidic amides, or varied in position. The role of the acetic acid substituent in the RHS phenyl ring of **3a** is revealed by comparing its β AR profile to that of analogue **39**, which lacks substitution on the RHS phenyl ring. In contrast to **3a**, which shows modest β_3 selectivity, compound **39**, which is also quite active at β_3, was even more potent at β_1 and β_2 AR subtypes (Table 1). Likewise, amide **37** and sulfonamide **38** showed a similarly poor selectivity profile as **39**. In analogy to previous SAR studies,[22a] the comparison of **3a** with **37** and **38** demonstrates that the RHS para acetic acid substitution does confer modest but appreciable β_3 selectivity compared to analogues lacking a negatively charged para substituent in our aniline series.

The effect of modifying position or tether length of the RHS carboxylate can be seen by comparing the data for compounds **3a**, **3b**, **35**, and **36**. It was found that relative to **3a**, the meta-substituted analogue **3b** has somewhat weaker β_3 AR activity at the human receptors and also somewhat poorer β_2/β_3 selectivity. However, the shift of the acetic acid substituent to the meta position significantly improves selectivity at β_1, since this compound showed negligible β_1 activity in terms of both potency and maximum response. In terms of tether length modifications, a comparison of the β_3 AR data for compounds **35** and **36** with that of **3a** indicates that both longer and shorter RHS phenyl carboxylate chains help to reduce activity at β_1 and β_2 AR subtypes. However, while increasing spacer length to ethylene (compound **35**) retained β_3 AR activity, direct attachment of the carboxylate to the RHS phenyl ring (compound **36**) led to diminished potency.

Although some of the analogues in Table 1 showed modest selectivity, we felt that the profile of these compounds was insufficiently selective to warrant further progression. Utilizing the SAR results described above, we then turned our attention to the synthesis of a series of targets containing acid isosteres with a one- or two-atom linker at the meta or para position on the RHS phenyl ring. As part of this effort,[24] we became interested in the synthesis of analogues containing acylsulfonamide, sulfonylsulfonamide, or sulfonylurea functional groups in these orientations. Because they

Table 1. RHS Carboxylic Acid Analogue Stimulation of cAMP Accumulation in CHO Cells Expressing Human β_3, β_2, and β_1 AR



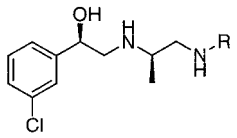
Cmpd	Structure (R)	β_3 pEC$_{50}$[a] (%Emax)[b]	β_2 pEC$_{50}$[a] (%Emax)[b]	β_2 EC$_{50}$/ β_3 EC$_{50}$	β_1 pEC$_{50}$[a] (%Emax)[b]	β_1 EC$_{50}$/ β_3 EC$_{50}$
ISO		8.5 ± 0.3 (112 ± 20)	9.8 ± 0.4 (116 ± 17)	0.1	9.0 ± 0.3 (109 ± 14)	0.3
2		7.6 ± 0.4 (91 ± 6)	7.3 ± 0.4 (80 ± 15)	2	<6.1[c] (28 ± 11)[d]	>31
3a		7.8 ± 0.5 (117 ± 7)	7.3 ± 0.3 (90 ± 1)	3.1	7.1 ± 0.4 (24 ± 3)	5.0
3b		6.5 ± 0.2 (117 ± 17)	7.3 ± 0.4 (80 ± 15)	0.2	<5[e] (6 ± 1)[d]	-
35		7.6 ± 0.2 (10 4 ± 23)	6.4 ± 0.6 (22 ± 55)	16	6.6 ± 0.1 (10 ± 1)	10
36		6.1 ± 0.2 (79 ± 11)	5.5 (70)	4	6.2 ± 0.4 (17 ± 6)	0.8
37		7.9 ± 0.1 (123±7)	8.5 ± 0.2 (75 ± 25)	0.3	8.1 ± 0.2 (15 ± 2)	0.6
38		7.7 ± 0.3 (102 ± 28)	8.3 ± 0.1 (66 ± 13)	0.4	8.3 ± 0.3 (11 ± 4)	0.4
39		7.7 ± 0.5 (105 ± 14)	8.0 ± 0.6 (100 ± 24)	0.5	8.3 ± 0.2 (27 ± 8)	0.3

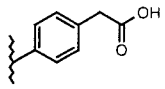
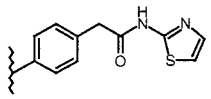
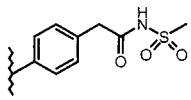
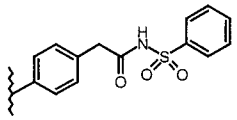
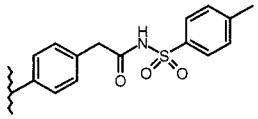
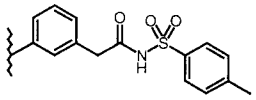
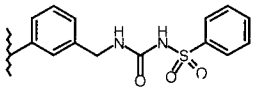
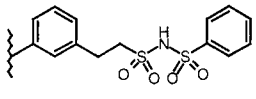
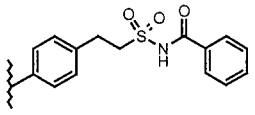
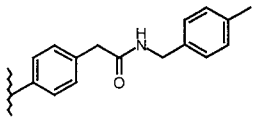
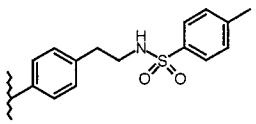
[a] Human β_1, β_2, and β_3 receptors expressed in CHO cells. pEC$_{50}$ is the negative logarithm of the molar drug concentration that produces a cAMP response equal to 50% of its maximal response. $n = 3$ for all compounds except ISO, where $n = 25$. [b] E_{max} is the fitted maximal value of the concentration−response expressed as a percent of the maximal response to *R*-(−)-isoproterenol (Iso). [c] $n = 2$ experiments. [d] Curve could not be fitted to the data, and therefore, the maximal individual response to a concentration of compound is given expressed as a percent of the maximal response to Iso. [e] The compound produced a negligible response in this experiment.

contain two electron-withdrawing groups attached to NH, the isosteres we used are comparable in acidity to that of carboxylate and therefore were seen as potentially beneficial in providing selectivity.[30,31] In addition, varying the substitution of the electron-withdrawing group on the RHS of these isosteres with large or small substituents allows for modification of steric bulk in the RHS portion of the targets relative to **3a** or **3b**, thus allowing us to explore the effect of sterics at these positions on the in vitro profile. Several of these analogues were therefore prepared and tested against β_3, β_2, and β_1 AR subtypes in functional assays. The results are shown in Table 2.

As can be seen in Table 2, analogues **40** and **41** containing either thiazole or methylsulfonyl groups respectively show good potency at β_3 AR, although their β_2 and β_1 AR selectivity is not enhanced relative to **3a**. On the other hand, increasing the steric bulk of the RHS electron-withdrawing group attached to nitrogen leads to a markedly improved profile. Phenyl and *p*-toluene-

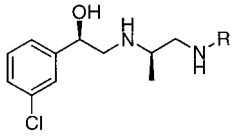
Table 2. Amide and Sulfonamide Acid Isostere Stimulation of cAMP Accumulation in CHO Cells Expressing Human β_3, β_2, and β_1 AR

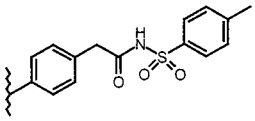
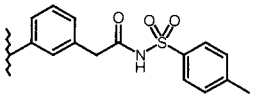
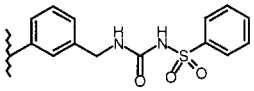
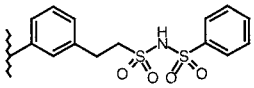
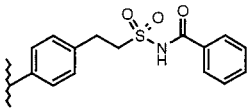


Cmpd	R	β_3 pEC_{50}[a] (%Emax)[b]	β_2 pEC_{50}[a] (%Emax)[b]	β_2 EC_{50}/ β_3 EC_{50}	β_1 pEC_{50}[a] (%Emax)[b]	β_1 EC_{50}/ β_3 EC_{50}
3a		7.8 ± 0.5 (117 ± 7)	7.3 ± 0.3 (90 ± 31)	3.1	7.1 ± 0.4 (24 ± 3)	5.0
40		8.9 ± 0.04 (101 ± 14)	8.1 ± 0.1 (31 ± 10)	6.3	8.5 ± 0.2 (14 ± 2)	2.5
41		8.3 ± 0.3 (96 ± 28)	7.7 ± 0.2 (78 ± 14)	4.0	7.0 ± 0.1 (30 ± 5)	20
42		9.1 ± 0.6 (110 ± 31)	7.5 ± 0.2 (59 ± 25)	40	6.1 ± 0.4 (22 ± 9)	1000
43		8.9 ± 0.3 (98 ± 7)	7.1 ± 0.1 (34 ± 14)	63	6.2 ± 0.2 (23 ± 8)	501
44		8.2 ± 0.1 (98 ± 20)	<6.0[c] (16 ± 5)[d]	>158	<5.3 (8 ± 13)	>794
45		7.8 ± 0.2 (105 ± 21)	6.6 ± 0.3 (23 ± 10)	16	6.4 ± 0.2 (15 ± 6)	25
46		8.8 ± 0.2 (113 ± 15)	6.0 ± 0.2 (31 ± 1)	630	<6.1[c] (21 ± 5)[d]	>500
47		8.0 ± 0.3 (100 ± 7)	6.5 ± 0.2 (52 ± 8)	32	6.1 ± 0.3 (27 ± 4)	79
48		7.2 ± 0.2 (126 ± 18)	9.0 ± 0.1 (40 ± 12)	0.02	7.6 ± 0.02[c] (12 ± 4)[d]	0.4
49		7.7 ± 0.2 (98 ± 20)	8.0 ± 0.3 (28 ± 6)	0.5	7.7 ± 0.2 (22 ± 6)	1

[a] Human β_1, β_2, and β_3 receptors expressed in CHO cells. pEC_{50} is the negative logarithm of the molar drug concentration that produces a cAMP response equal to 50% of its maximal response. $n = 3$ for all compounds except ISO, where $n = 25$. [b] E_{max} is the fitted maximal value of the concentration−response expressed as a percent of the maximal response to *R*-(−)-isoproterenol (Iso). [c] $n = 2$ experiments. [d] This number is an average of the maximal response, or point of highest activity, measuring concentration versus response for three different experiments. A curve could not be fitted to the data, and therefore, the maximal individual response to a concentration of compound is given expressed as a percent of the maximal response to Iso.

Table 3. Dog Pharmacokinetic Data for β-3 Acyl- and Sulfonylsulfonamide Acid Isosteres



Cmpd	R	Dose (mg/kg)[a]	AUC_{iv} (ng.h/mL)	Clp (mL/min/kg)	Vss (L/kg)	$t_{1/2}$ (h)	$C_{2.5\,h}$[c] (ng/mL)
43		0.2	715	4.7	200	1.0	42.1
44		0.2	279	11.9	409	1.7	10.3
45		0.2	ND[b]	ND[b]	ND[b]	<<1 h[b]	BQL[d]
46		0.2	ND[b]	ND[b]	ND[b]	<<1 h[b]	BQL[d]
47		0.2	383	8.7	478	1.2	BQL[d]

[a] Compounds were dosed intravenously to dogs (n = 1) in 0.025 M aqueous methanesulfonic acid solution with 5% mannitol at a concentration of 0.2 mg/mL. The plasma drug levels were determined by LC−MS/MS. [b] Rapid clearance resulted in an insufficient number of data points to quantitate this parameter. [c] Plasma concentration at the 2.5 h time point. [d] BQL = below quantitation limit.

containing acylsulfonamides **42** and **43** are 20 and 13 times more potent at β_3 AR than the parent carboxylic acid analogue **3a**, respectively, and in addition, are substantially less active at the β_1 AR subtype. Although of similar potency at β_2 as **3a**, both aryl acylsulfonamides **42** and **43** have a low maximum response as well as significantly higher β_2/β_3 selectivity ratios. Interestingly, shifting the acylsulfonamide substituent from the para to the meta position in analogue **44** slightly reduces β_3 potency but leads to even greater β_1 and β_2 selectivity, analogous to the change observed when shifting the acetic acid substituent (i.e., **3a** to **3b**).

Encouraged by these results, we prepared and tested additional meta- and para-substituted sulfonamide acidic isosteres with an additional electron-withdrawing group. These included the meta-substituted sulfonylurea **45** and sulfonylsulfonamide **46**, as well as the para ethylene-linked "reverse" acylsulfonamide **47**. Functional β_3 receptor data for these analogues (Table 2) showed that while sulfonylurea **45** was somewhat inferior in selectivity to the corresponding acylsulfonamide **44**, sulfonylsulfonamide **46** had an outstanding profile with respect to both potency at β_3 and selectivity against β_1 and β_2 ARs. It is unclear whether the superior profile of **46** relative to **45** is a result of increased acidity of the sulfonylsulfonamide relative to sulfonylurea functionality or a subtle conformational difference that permits a more favorable interaction with the β_3 AR (relative to β_1 and β_2) in the sulfonylsulfonamide analogue.

As mentioned previously, workers at Merck have reported extensively on a series of potent and selective benzene sulfonamide analogues such as **5**.[20,32] With only one electron-withdrawing functionality attached to nitrogen, the sulfonamide functionality of such analogues is unlikely to be as acidic as either the acylsulfonamides reported here or thiazole **40**. Given that the promising Merck analogues reported do possess a relatively bulky aromatic RHS sulfonamide group, we wondered if the profile of our best analogues described here is solely a result of steric bulk or rather a combination of both the size and acidity of the RHS phenyl substituent. In an attempt to address this question, we prepared and tested analogues **48** and **49** in which one of the NH electron-withdrawing groups of **43** was replaced with methylene. As can be seen in Table 2, these two analogues were not only less potent than **43** but were also completely nonselective, suggesting that both the size and the acidity of the RHS substituent contribute to the excellent in vitro profile of our most potent and selective acyl- and sulfonylsulfonamides.

Because of their encouraging in vitro profiles, analogues **43**−**47** were evaluated in vivo in dog pharmacokinetic (PK) assays. Each of these compounds was dosed as a solution (at 0.2 mg/kg) by intravenous administration in order to identify compounds worthy of further

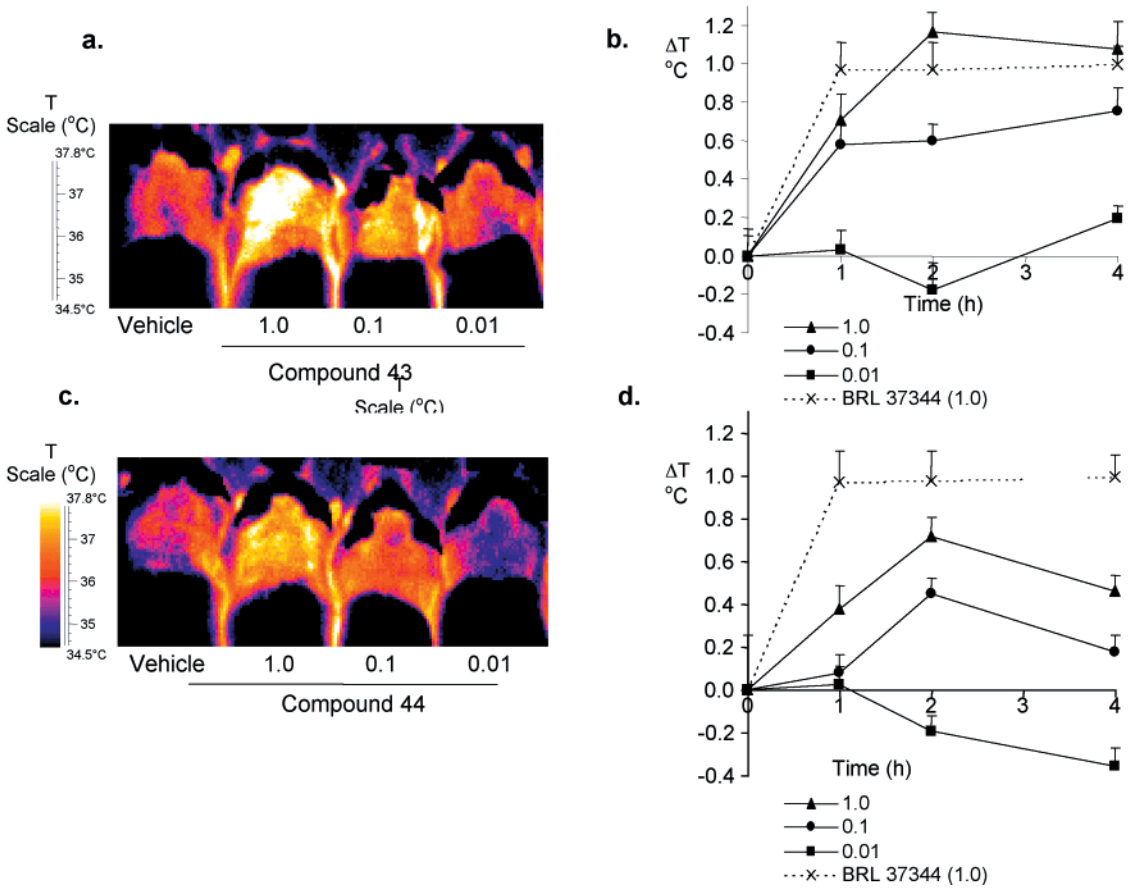


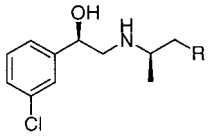
Figure 1. (a) Infrared images of the interscapular region of representative individual CD-1 mice following oral administration of **43** at 0.01, 0.1, and 1.0 mg/kg (1 h postdosing). Note: the view is from above backs of mice with heads oriented toward the top of the panel. The color scale of the image is indicated to the left of panel A and is adjusted to optimally reveal temperature changes in IBAT. (b) Graph of time versus temperature change of the interscapular region of CD-1 mice relative to that of the vehicle control group ($n = 6$ per group) following oral administration of **43**. (c) Same as (a) with compound **44**. (d) Same as (b) with compound **44**.

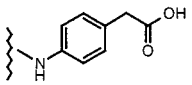
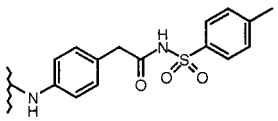
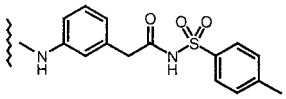
investigation, as judged by a low serum clearance and the presence of significant plasma levels of drug after 2.5 h. As can be seen in Table 3, compounds **45**−**47** had very high clearance and consequently failed to show measurable plasma concentrations after 2.5 h. On the other hand, although their half-lives were also less than 2 h, both acylsulfonamides **43** and **44** showed moderately low clearance values as well as measurable plasma levels at 2.5 h. Although follow-up studies to determine the reason for the disappointing pharmacokinetics seen with compunds **45**−**47** were not conducted, it is possible that enzymatic cleavage at one of the electrophilic atoms adjacent to nitrogen in the acid isostere may be a significant source of metabolism.[33] However, previous studies in human plasma have demonstrated relatively low cleavage rates for aliphatic acylsulfonamides and sulfonylureas,[34] suggesting that this is not likely to be an important route for elimination for analogues in our series.

Since the pharmacokinetic profiles of **43** and **44** are the best of the compounds studied, we decided to investigate their ability to elicit an in vivo β_3 AR mediated response. For this purpose, we monitored thermogenesis in the brown fat rich interscapular region of CD-1 mice by thermogenic imaging. Known β_3 AR agonists have been shown to elicit a thermogenic response in this model, causing a temperature increase in the interscapular region of the animal that is monitored using an infrared camera that generates quantifiable image-based readouts.[35] Following oral administration of the drug (0.01, 0.1, and 1.0 mg/kg), the mice were anesthetized and imaged at 1 h time points. The potent rodent β_3-selective agonist **1** was included in the experiment as a positive control.[5] The results for compounds **43**, **44**, and **1** are shown in Figure 1. We were pleased to find that, like **1**, both acylsulfonamides **43** and **44** produced significant dose-dependent increases in thermogenesis (see parts a and c of Figure 1 and legend), resulting in a maximal increase in interscapular temperature of approximately 1 °C for each compound (parts b and d of Figure 1). Although both isosteric analogues were active, we were curious to observe that the response to **43** as seen at the two lowest doses was significantly more robust than that of isomeric acylsulfonamide **44**, despite their similar structures and in vitro profiles at human receptors. Of additional note is the duration of the response seen with **43**. Like **1**, at the top dose of 1 mg/kg this compound produced a response that remained at high levels at the 4 h time point, indicating a prolonged pharmacodynamic response for both **1** and **43** in this model.

Finally, compounds **43** and **44** were evaluated along with initial lead **3a** in β_1 and β_2 binding assays in order to assess their potential liability as antagonists at β_1 and β_2 ARs. As is reported in Table 4, at least a 750-

Table 4. Comparison of β_3 AR Activation with β_2, and β_1 AR Binding for Compounds **3a**, **43**, and **44**



Cmpd	Structure (R)	β_3 Activation pEC_{50}[a] (%Emax)[b]	β_1 Binding pIC_{50}[c]	β_2 Binding pIC_{50}[c]
3a		7.8±0.5 (117 ± 7)	6.0 ± 0.0[d]	6.1 ± 0.1[d]
43		8.9 ± 0.3 (98 ± 7)	5.7 ± 0.0	5.3 ± 0.1
44		8.2 ± 0.1 (98 ± 20)	5.3 ± 0.0	4.8 ± 0.2

[a] Human β_1, β_2, and β_3 receptors expressed in CHO cells. pEC_{50} is the negative logarithm of the molar drug concentration that produces a cAMP response equal to 50% of its maximal response. $n = 3$ for all compounds except ISO, where $n = 25$. [b] E_{max} is the fitted maximal value of the concentration−response expressed as a percent of the maximal response to *R*-(−)-isoproterenol (Iso). [c] Receptor binding assays were carried out with membranes prepared from human recombinant Sf9 cells expressing the cloned human receptor in the presence of [^{125}I]iodocyanopindolol. Results are given as the mean ± SD from three experiments, unless otherwise indicated. [d] Results of two experiments ($n = 2$).

fold difference in the activation of the β_3 receptor relative to the binding affinity of either the β_1 or β_2 receptor was found for both acylsulfonamide analogues **43** and **44**. In contrast, the phenylacetic acid derivative **3a** had a difference in β_3 pEC_{50} relative to β_1 and β_2 AR IC_{50} of only ca. 60-fold.

Conclusion

We have described β_3 AR potency and selectivity data from a series of aniline phenethanolamine agonists in which the carboxylate of RHS phenyl substituents was varied in position, deleted, or replaced with amide- or sulfonamide-containing carboxylic acid isosteres. A comparison of **3a** and **3b** with other analogues reinforces earlier SAR studies that demonstrate the benefit of carboxylate on the RHS aniline ring in providing some β_1 and β_2 AR selectivity relative to compounds lacking a negatively charged group. More importantly, we were pleased to discover that substituting the carboxylate of **3a** or **3b** with acylsulfonamide and sulfonylsulfonamide isosteres augmented not only β_3 AR potency but also β_1 and β_2 AR selectivity, especially in the case of compounds bearing arylacyl- or sulfonylsulfonamides. The inclusion of amide **48** or sulfonamide **49** in these SAR investigations supports a role for both sterics and acidity of the RHS phenyl substituent in contributing to the high potency and selectivity of analogues within our series. Although some of the most potent and selective compounds we have identified showed disappointing pharmacokinetics in dogs, the potent and selective acylsulfonamides **43** and **44** had reasonably low clearance in dogs and were found to be quite orally active in rodent thermogenesis studies. The greater thermogenic efficacy of **43** compared to **44** in mice may be a result of differences in activities at the rodent receptor or differences in rodent pharmacokinetics between the two compounds, since neither rodent β_3 AR data nor rodent pharmacokinetic data were obtained. The excellent in vitro profile of several compounds we have described, combined with the potent rodent thermogenic activity of **43** and **44**, suggests that these compounds may represent a viable lead series in the discovery of new therapies for the treatment of obesity and type 2 diabetes.

Experimental Section

Chemistry. General Methods. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Unless stated otherwise, reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel (EM Science, 230−400 mesh) was used for chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from Aldrich (Sure Seal). ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer; chemical shifts are reported in parts per million (ppm) relative to TMS. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-performance liquid chromatography (HPLC) was performed on a Beckman 126 with a Beckman 166 UV detector (monitoring at 215 nm) with a Rainin Dynamax-60A column using a gradient consisting of 20/80 A/B to 10/90 A/B over 20 min, where A is 1% aqueous trifluoroacetic acid (TFA) and B is 1% TFA in CH_3CN. Results from elemental analyses, performed by Atlantic Microlab, Inc., Norcross, GA, were within 0.4% of the theoretical values calculated for C, H, and N.

Methyl (2*R*)-{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)ethanoate (7).[23] This procedure and those for the preparation of intermediates **8** and **9** follow closely the

previously disclosed method.[23] A solution of (*R*)-(−)-3-chloromandelic acid (**6**, 50 g, 0.268 mmol) in MeOH (500 mL) was treated with H_2SO_4 (2.5 mL). The mixture was heated at reflux for 4 h and allowed to cool to ambient temperature, and the solvent was removed with a rotary evaporator. The resulting oil was partitioned between EtOAc (500 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to supply 56.59 g of (*R*)-(−)-chloromandelic acid methyl ester. The ester was dissolved in anhydrous *N*,*N*-DMF (250 mL), and imidazole (38.3 g, 0.562 mmol) and *tert*-butyldimethylsilyl chloride (63.5 g, 0.422 mmol) were added. The mixture was stirred for 7 h and partitioned between water (300 mL) and 5:1 hexane/EtOAc (500 mL). The organic layer was separated, and the aqueous layer was reextracted with 5:1 hexane/EtOAc (250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to supply, after placing the residue under high vacuum for 3 days, 81.85 g (97%) of the product **7** as a colorless oil that solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 3.68 (s, 3), 5.20 (s, 1H), 7.22 (d, 2H), 7.35 (m, 1H), 7.45 (s, 1H).

Methyl (2*R*)-2-{[(2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]amino}propanoate (8).[23] A mechanically stirred mixture of methyl (2*R*)-{[*tert*-butyl(dimethyl)-silyl]oxy}(3-chlorophenyl)ethanoate (**7**, 20 g, 63.51 mmol) in anhydrous Et_2O (280 mL) under N_2 was cooled to −78 °C and treated with 1.0 M DIBAL in toluene (105 mL, 105 mmol, added dropwise over ca. 5 min). The mixture was stirred at −78 °C for 1.5 h, then quenched by slow addition of MeOH (20 mL) followed by 15% w/v aqueous potassium sodium tartrate (250 mL). The mixture was vigorously stirred for 2 h while warming to ambient temperature, was filtered through a pad of Celite, and was washed with EtOAc (200 mL). The filtrate was extracted with additional EtOAc (2 × 150 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to supply 18.19 g of a colorless liquid judged by ^{1}H NMR to be a ca. 2:1 mixture of methyl hemiacetal and aldehyde. ^{1}H NMR (400 MHZ, $CDCl_3$): δ −0.03 (0.5H, s), −0.01 (1.5H, s), 0.03 (1.5H, s), 0.05 (s, 1.5H), 0.10 (s, 1H), 0.90 (s, 6H), 0.95 (s, 3H), 3.22−3.40 (m, 3H), 4.40−4.95 (m, 1.5 H), 7.10−7.40 (m, 4H), 9.47 (s, 0.33H).

This hemiacetal/aldehyde mixture was dissolved in CH_2Cl_2 (250 mL), and D-alanine methyl ester (8.91 g, 63.81 mmol), acetic acid (1 mL), and 4 Å molecular sieves (10 g) were added. After the mixture was stirred for 1 h, $NaBH(OAc)_3$ (20.3 g, 95.7 mmol) was added. After an additional 2 h, the mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with additional saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford 22.4 g (95% overall) of the amino methyl ester **8** as a pale-green oil, which ^{1}H NMR indicated to be >95% *R*,*R* diastereomer. ^{1}H NMR (400 MHZ, $CDCl_3$): δ −0.15 (s, 3H), 0.05 (s, 3H), 0.95 (s, 9H), 1.25 (d, 3H, J = 7 Hz), 2.62−2.87 (m, 2H), 3.38 (q, 1H, J = 7 Hz), 3.67 (s, 3H), 4.65−4.75 (d, 1H), 7.18−7.23 (m, 3H), 7.25 (m, 1H).

Methyl (2*R*)-2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]amino}-propanoate (9).[23] The amine **8** (22.4 g, 60.2 mmol) and di-*tert*-butyl dicarbonate (14.3 g, 65.5 mmol) were combined and heated neat in an oil bath at 90−95 °C for 5 min. (*Caution: a blast shield should be used when heating this mixture*). After the mixture was cooled, additional di-*tert*-butyl dicarbonate (2.73 g, 12.5 mmol) was added and the mixture was heated at 95 °C for 10 min. The mixture was allowed to cool to ambient temperature and was purified by silica gel chromatography (eluting with 10:1 hexane/EtOAc followed by 5:1 hexane/EtOAc) to supply 27.1 g (96%) of Boc amine **9** as a colorless oil, which ^{1}H NMR indicated to be a 60:40 mixture of rotamers. ^{1}H NMR (400, $CDCl_3$): δ 0.06 (s, 3H), 0.89 (s, 9H), 1.09 (d, 1.25 H, J = 7.2 Hz), 1.31 (d, 1.75H, J = 6.8 Hz), 1.41 (s, 3.6 H), 1.43 (s, 5.4 H), 3.10−3.20 (m, 1H), 3.35 (d, 1H, J = 6.0 Hz), 3.40−3.50 (m, 1H), 3.69 (s, 3H), 3.82−3.93 (m, 0.5 H), 4.05−4.15 (m, 0.5H), 4.82−4.95 (m, 0.5 H), 5.00−5.05 (m, 0.5 H), 7.10−7.30 (m, 3H), 7.35 (s, 0.5 H), 7.40 (s, 0.5H).

***tert*-Butyl (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl[(1*R*)-1-methyl-2-oxoethyl]carbamate (10).**[23] To a solution of the methyl ester **9** (3.83 g, 8.15 mmol) in anhydrous toluene (40 mL) at −78 °C was added 1.5 M DIBAL in toluene (13.5 mL, 20.3 mmol) dropwise over 2 min. The mixture was stirred at −78 °C for 1 h and quenched by slow addition of MeOH (3 mL) followed by 15% w/v potassium sodium tartrate (20 mL). The resulting mixture was allowed to warm to ambient temperature, stirred vigorously for 1 h, and filtered through a pad of Celite. After the mixture was washed with additional EtOAc, the filtrate was partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was dried, filtered, and concentrated to afford the product aldehyde **10** (3.43 g, 96%) as a colorless oil judged by ^{1}H NMR integration of aldehyde peaks to be a 13:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.10 (s, 3H), 0.01 (s, 1.5 H), 0.02 (s, 1.5H), 0.85 (s, 9H), 1.20−1.25 (m, 3H), 1.38 (s, 4.5H), 1.40 (s, 4.5H), 3.0−3.15 (m, 1H), 3.25−3.40 (m, 1H), 3.3.70−3.85 (m, 1H), 4.90 (t, 0.5H), 5.02 (t, 0.5H), 7.18−7.25 (m, 3H), 7.28 (s, 0.5H), 7.35 (s, 0.5H), 9.20 (s, 0.5H), 9.38 (s, 0.5H).

***N*-[2-(4-Nitrophenyl)ethyl]-4-methylbenzenesulfonamide.**[25] An N_2-purged flask equipped with a stirring bar was charged with 2-(4-nitrophenyl)ethylamine hydrochloride (2.0 g, 9.87 mmol), *p*-toluenesulfonyl chloride (1.88 g, 9.87 mmol), and anhydrous CH_2Cl_2 (50 mL). Triethylamine (1.51 mL, 10.86 mmol) was added, and the resulting mixture was stirred at ambient temperature for 20 h, diluted with CH_2Cl_2 (25 mL), and washed with 1.0 N aqueous HCl (25 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (25 mL), dried, filtered, and concentrated to give a light-yellow solid. Trituration with MeOH afforded a solid that was washed with ether to supply 1.04 g (33% yield) of the product as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.47 (s, 3H), 2.94 (t, 2H, J = 6.9 Hz), 3.31 (q, 2H, J = 6.9 Hz), 4.51 (t, 1H, J = 6.3 Hz), 7.29−7.34 (m, 4H), 7.73 (d, 2H, J = 8.1 Hz), 8.15 (d, 2H, J = 8.4 Hz). MS (ES), *m/e* (M − H) = 320.9.

2-(4-Nitrophenyl)-*N*-4-methylbenzylacetamide. An N_2-purged flask equipped with a stirring bar was charged with 4-nitrophenylacetic acid (1.0 g, 5.52 mmol), 1,1′-carbonyldiimidazole (1.32 g, 8.1 mmol) and anhydrous CH_2Cl_2 (25 mL). The reddish-brown mixture was stirred for 45 min. 4-Methylbenzylamine (880 μL, 838 mg) was added via syringe. The cloudy yellow mixture was stirred for 1 h, then partitioned betwen CH_2Cl_2 and 1 *N* HCl. The organic layer containing a white precipitate was separated and washed with saturated aqueous $NaHCO_3$. The precipitate was collected by suction filtration, triturated with MeOH and washed with ether to provide 0.78 g (53%) of the product as a white solid. MS (electrospray), *m/e*: 283.0 (M − H). ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 3.68 (s, 2H), 4.26 (d, 2H, J = 6.0 Hz), 7.15 (s, 4H), 7.58 (d, 1H, J = 8.7 Hz), 8.22 (d, 1H, J = 8.4 Hz), 8.65 (t, 1H, J = 6.0 Hz).

***N*-[2-(4-Nitrophenyl)acetyl]methanesulfonamide (50a).** A suspension of 4-nitrophenylacetic acid (2.0 g, 11.0 mmol) in CH_2Cl_2 (30 mL) was treated with 1,1′-carbonyldiimidazole (CDI) (2.4 g, 11.0 mmol), yielding an orange solid. After the mixture was stirred for 1 h, methanesulfonamide (1.1 g, 11.0 mmol) was added and the mixture was stirred for an additional 1 h. Addition of diazobicyclo[5.4.0]undec-7-ene (1.5.5) (DBU) (1.7 mL, 11.0 mmol) yielded a purple mixture that was stirred for 16 h. The reaction mixture was then partitioned between 1 N aqueous HCl and EtOAc, during which time an orange solid fell out. The solid was partitioned between 1 N aqueous NaOH and EtOAc. The aqueous layer was acidified with 1 N aqueous HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield 1.9 g of the product (67%) as a yellow solid, mp 191−193 °C. ^{1}H NMR (DMSO): δ 3.21 (s, 3H), 3.79 (s, 2H), 7.52 (d, 2H, J = 8.6 Hz), 8.17 (d, 2H, J = 8.5 Hz).

***N*-[2-(4-Nitrophenyl)acetyl]benzenesulfonamide (50b).** The foregoing procedure was employed using benzenesulfon-

amide (945 mg, 6.0 mmol), CDI (900 mg, 5.55 mmol), 4-nitrophenylacetic acid (1.0 g, 5.52 mmol), and DBU (0.87 mL, 5.81 mmol) in CH_2Cl_2 (20 mL) to yield 1.57 g (89%) of the product as a yellow solid, mp 145−148 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (s, 2H), 7.40 (d, 2H, J = 9 Hz), 7.69−7.53 (m, 3H), 7.87 (d, 2H, J = 7 Hz), 8.11 (d, 2H, J = 9 Hz), 12.45 (s, 1H). MS (ES) *m/e*: 319 (M − H).

***N*-[2-(4-Nitrophenyl)acetyl]benzenesulfonamide (50c).** The general procedure for **50a** was employed using *p*-toluenesulfonamide (945 mg, 5.52 mmol), CDI (895 mg, 5.52 mmol), 4-nitrophenylacetic acid (1.0 g, 5.52 mmol), and DBU (0.84 g, 0.82 mL, 5.48 mmol) in CH_2Cl_2 (20 mL). The reaction yielded 1.74 g (94%) of the product as a yellow solid, mp 205−214 °C. Low-resolution ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H), 3.71 (s, 2H), 7.41−7.36 (m, 4H), 7.75 (d, 2H, J = 8 Hz), 8.11 (d, 2H, J = 8 Hz), 12.35 (s, 1H). MS (ES) *m/e*: 33.0 (M − H).

***N*-[2-(3-Nitrophenyl)acetyl]-4-methylbenzenesulfonamide (50d).** The general procedure for **50a** was employed using *p*-toluenesulfonamide (480 mg, 2.80 mmol), CDI (500 mg, 3.08 mmol), 3-nitrophenylacetic acid (450 mg, 2.48 mmol), and DBU (0.835 g, 0.82 mL, 5.48 mmol) in CH_2Cl_2 (15 mL). The product (600 mg, 65% yield) was obtained as a yellow solid, mp 175−177 °C. ^{1}H NMR (400 MHz, DMSO- d_6): δ 2.35 (s, 3H), 3.73 (s, 2H), 7.36 (d, 2H, J = 8.0 Hz), 7.59−7.52 (m, 2H), 7.74 (d, 2H, J = 8.0 Hz), 8.03 (s, 1H), 8.07 (dd, 1H, J = 2.0, 8.0 Hz), 12.35 (s, 1H). MS (ES) *m/e*: 333.1 (M − H).

1-Nitro-3-[({[(phenylsulfonyl)amino]carbonyl}amino)methyl]benzene (56). Triethylamine (1.85 mL, 13.3 mmol) was added to 3-nitrobenzylamine (1.00 g, 5.30 mmol) in THF (26.5 mL), followed by benzenesulfonyl isocyanate (709.5 μL, 5.30 mmol), and the reaction mixture was stirred for 16 h at ambient temperature. Aqueous HCl (1 N) was added, and the mixture was extracted with EtOAc. The organic extracts were combined and concentrated. The residue was purified by silica gel chromatography, eluting with EtOAc/hexanes (4:1) to give 440 mg (25%) of the product. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 4.49 (d, 2H, J = 7 Hz), 7.21 (br s, 1H), 7.53−7.68 (m, 5H), 7.99 (d, 2H, J = 7 Hz), 8.09 (d, 1H, J = 7 Hz), 8.10 (s, 1H), 9.73 (br s, 1H). MS (CI) *m/e*: 334 (M − H).

Toluene-4-sulfonic Acid 2-(3-Nitrophenyl)ethyl Ester (51b).[28] 4-(Dimethylamino)pyridine (365.4 mg, 2.99 mmol) was added to 2-(3-nitrophenyl)ethanol (5.00 g, 29.91 mmol) in $CHCl_3$ (60 mL) at ambient temperature, followed by triethylamine (5.84 mL, 38.7 mmol) and *p*-toluenesulfonyl chloride (6.84 g, 35.8 mmol). The reaction was stirred for 63 h, quenched with saturated Na_2CO_3, and extracted with $CHCl_3$. The organic layer was dried and concentrated, and the residue was purified by silica gel chromatography, eluting with EtOAc/hexanes (2:3) to give 6.14 g of the product (64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.04 (t, 2H, J = 6 Hz), 4.26 (t, 2H, J = 6 Hz), 7.24 (d, 2H, J = 8 Hz), 7.42 (t, 1H, J = 8 Hz), 7.47 (d, 1H, J = 8 Hz), 7.62 (d, 2H, J = 8 Hz), 7.87 (s, 1H), 8.05 (d, 1H, J = 8 Hz). MS (CI) *m/e*: 344 (M + Na).

Thioacetic Acid *S*-[2-(3-Nitrophenyl)ethyl] Ester (52a). Potassium thioacetate (4.36 g, 38.2 mmol) was added to tosylate **51b** (6.14 g, 19.11 mmol) in acetonitrile (64 mL) at ambient temperature, and the reaction mixture was stirred for 17 h. The mixture was quenched with water and extracted with EtOAc, and the separated organic layer was dried, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with EtOAc/hexanes (1:4) to give 4.24 g of the product (98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.96 (t, 2H, J = 7 Hz), 3.13 (t, 2H, J = 7 Hz), 7.46 (t, 1H, J = 8 Hz), 7.54 (d, 1H, J = 7 Hz), 8.07 (s, 1H), 8.08 (d, 1H, J = 7 Hz). MS (CI) *m/e*: 150 (M − AcS).

2-(3-Nitrophenyl)ethanesulfonic Acid (53a). Hydrogen peroxide (30% aqueous, 10.07 g, 5.0 equiv) was added to thioacetic acid *S*-[2-(3-nitrophenyl)ethyl]ester (**52a**, 4.24 g, 18.82 mmol) in acetic acid (38 mL) at ambient temperature, and the reaction mixture was stirred for 26 h. The mixture was concentrated, taken up in a small amount of toluene, and reconcentrated to give 4.22 g (97%) of the product. ^{1}H NMR (300 MHz, CD_3OD): δ 3.30 (dd, 2H, J = 11, 7 Hz), 3.53 (dd, 2H, J = 11, 7 Hz), 7.63 (t, 1H, J = 8 Hz), 7.82 (d, 1H, J = 8 Hz), 8.12 (d, 1H, J = 7), 8.23 (s, 1H). MS (CI) *m/e*: 230 (M − H).

4-Nitrophenethylsulfonic Acid (53b). A suspension of 4-nitrophenethyl bromide (**51a**) (12.9 g, 56.1 mmol) and potassium thioacetate (11.4 g, 99.8 mmol) was stirred in DMSO (75 mL) for 24 h, diluted with EtOAc, extracted with water, dried, and concentrated to give crude **52b** as a mobile brown oil (11.0 g). This material was dissolved in glacial acetic acid (75 mL), and 32% H_2O_2 (25 mL) was added. After 24 h, addition of water and concentration gave 10.8 g of a pale-yellow solid (84% crude yield) that was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.80 (t, 2H), 3.00 (t, 2H), 7.50 (d, 2H), 8.10 (d, 2H).

2-(3-Nitrophenyl)ethanesulfonic Acid Amide (54a). Thionyl chloride (19.7 mL, 20 equiv) was added to 2-(3-nitrophenyl)ethanesulfonic acid (**53a**, 3.13 g, 13.53 mmol), and the resulting solution was heated at reflux for 17 h. The volatiles were removed under vacuum, NH_3 in dioxane (135 mL, 0.5 M, 5.0 equiv) was added, and the reaction mixture was stirred for 5 h. Water was added followed by saturated aqueous Na_2CO_3, and the mixture was extracted with EtOAc. The extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography, eluting with EtOAc/hexanes (3:2) to give 1.83 g (59%) of the product. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 3.27−3.32 (m, 2H), 3.43−3.48 (m, 2H), 6.22 (s, 2H), 7.62 (t, 1H, J = 8 Hz), 7.79 (d, 2H, J = 8 Hz), 8.11 (d, 1H, J = 8 Hz), 8.20 (d, 1H, J = 2 Hz). MS (CI) *m/e*: 230 (M − H).

4-Nitrophenethylsulfonamide (54b). 4-Nitrophenethylsulfonic acid (**53b**, 23.1 g, 100 mmol) was heated at reflux with $SOCl_2$ (200 mL) and *N*,*N*-DMF (10 mL). After 2 h the $SOCl_2$ was removed under vacuum, and the residue was taken up in dioxane (200 mL) and added to 0.5 M NH_3/dioxane (2000 mL). The mixture was filtered through Celite and then concentrated. The residue was dissolved in EtOAc (50 mL), and after addition of hexane, the product (17.07 g, 74%) precipitated as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.12 (t, 2H), 3.30 (t, 2H), 6.90 (s, 2H), 7.58 (d, 2H), 8.18 (d, 2H). MS (ES) *m/e*: 229 (M − H).

2-(3-Nitrophenyl)ethanesulfonic Acid Benzenesulfonylamide (55a). Triethylamine (508.7 μL, 3.64 mmol) was added to 2-(3-nitrophenyl)ethanesulfonic acid amide (**54a**, 420.2 mg, 1.83 mmol) in CH_3CN (9 mL), followed by the addition of benzenesulfonyl chloride (279.4 μL, 2.19 mmol), and the reaction was heated at reflux for 4 h. Aqueous HCl (1 N) was then added, and the mixture was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with MeOH/EtOAc (1:9) to give 362.5 mg (54%) of the product. ^{1}H NMR (400 MHz, CD_3OD): δ 3.16−3.21 (m, 2H), 3.31−3.35 (m, 2H), 7.45−7.55 (m, 4H), 7.63 (d, 1H, J = 8 Hz), 7.92−7.94 (m, 2H), 8.07−8.08 (m, 2H). MS (CI) *m/e*: 369 (M − H).

4-Nitrophenethyl-*N*-benzoylsulfonamide (55b). A mixture of 4-nitrophenethylsulfonamide (2.3 g, 10.0 mmol), CH_3CN (40 mL), K_2CO_3 (2.80 g, 20.2 mmol), and benzoyl chloride (1.4 g, 10.0 mmol) was heated at reflux. After 3 h the mixture was diluted with water and EtOAc. Filtration gave the product (1.14 g) as a tan solid (34%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (t, 2H), 3.30 (m, 1H), 3.58 (t, 2H), 7.38 (t, 2H), 7.41 (m, 1H), 7.50 (d, 1H), 7.52 (d, 1H), 7.86 (d, 2H), 8.08 (d, 2H). MS *m/e*: 333 (M − H).

2-(4-Aminophenyl)-*N*-thiazol-2-ylacetamide (15). A slurry of 2-(4-nitrophenyl)-*N*-thiazol-2-ylacetamide (523 mg, 1.98 mmol) and 10% Pd/C (286 mg) in 40 mL of THF/ethanol (3:1) was stirred under 1 atm of H_2 for 8 h. The mixture was filtered through a pad of Celite, which was washed with EtOAc. The filtrate was concentrated to afford 417 mg (90%) of the product as a yellow-orange solid. ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 2H), 3.78 (bs, 2H), 6.39 (d, 1H), 6.66 (d, 1H), 6.86 (d, 1H), 7.14 (d, 1H), 11.22 (bs, 1H). MS (ES) *m/e*: 232 (M − H).

***N*-[2-(4-Aminophenyl)acetyl]methanesulfonamide (16a).** *N*-[2-(4-nitrophenyl)acetyl]methanesulfonamide (**50a**, 0.9 g, 3.5 mmol) was suspended in MeOH (25 mL) and treated with 10%

Pd/C (750 mg) under positive N_2 pressure. The reaction mixture was stirred under 1 atm of H_2 for 7 h and then was filtered through a pad of Celite that was washed with MeOH. The filtrate was concentrated to give a crude product (750 mg, 94%), which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 3.06 (s, 3H), 3.27 (s, 2H), 6.45 (d, 2H, J = 8.2 Hz), 6.85 (d, 2H, J = 8.2 Hz).

***N*-[2-(4-Aminophenyl)acetyl]benzenesulfonamide (16b).** The foregoing hydrogenation procedure was used with *N*-[2-(4-nitrophenyl)acetyl]benzenesulfonamide (**50b**, 1.0 g, 3.12 mmol) and a reaction time of 3.5 h to give 470 mg of product (52%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.25 (s, 2H), 3.28 (bs, 2H), 6.40 (d, 2H, J = 8 Hz), 6.74 (d, 2H, J = 8 Hz), 7.64−7.51 (m, 3H), 7.82 (d, 2H, J = 8 Hz). MS (ES^+) *m/e*: 313 (M + Na).

***N*-2[2-(4-Aminophenyl)acetyl]benzenesulfonamide (16c).** Tin(II) chloride hydrate (2.0 g, 8.86 mmol) was added to *N*-[2-(4-nitrophenyl)acetyl]benzenesulfonamide (**50c**, 600 mg, 1.79 mmol) in 11.5:1 EtOH/*N*,*N*-DMF (33 mL), and the resulting mixture was heated at 70 °C for 1 h. The mixture was then poured onto ice, and the pH was adjusted to 8 with saturated aqueous $NaHCO_3$. After addition of a small amount of EtOAc, the mixture was stirred at room temperature for 1 h. The layers were filtered through a pad of Celite and separated. The organic layer was dried, filtered, and concentrated to yield 140 mg of the product (26%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H), 3.14 (s, 2H), 6.75 (d, 2H, J = 8 Hz), 7.25 (d, 2H, J = 9 Hz), 7.64 (d, 2H, J = 8 Hz), 7.92 (s, 3H). MS *m/e*: 305.1 (M + H).

***N*-[2-(3-Aminophenyl)acetyl]-4-methylbenzenesulfonamide (17a).** The foregoing procedure was used with (3-nitrophenyl)acetyl]benzenesulfonamide (**50d**, 600 mg, 1.79 mmol) to give the product (230 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H), 3.24 (s, 2H), 3.30 (2H + H_2O), 5.00 (bs, 1H), 6.24 (d, 1H, J = 8 Hz), 6.32 (s, 1H), 6.35 (d, 1H, J = 8 Hz), 6.84 (t, 1H, J = 8 Hz), 7.32 (d, 2H, J = 8 Hz), 7.70 (d, 2H, J = 8 Hz). MS (ES^-) *m/e*: 303.1 (M − H).

1-Amino-3-[({[(phenylsulfonyl)amino]carbonyl}amino)methyl]benzene (17b). To 1-nitro-3-[({[(phenylsulfonyl)amino]carbonyl}amino)methyl]benzene (**56**, 431.1 mg, 1.29 mmol) was added 10% Pd/C (43.1 mg) in 3:1 MeOH/THF (12.8 mL) under an argon atmosphere. The mixture was stirred under 1 atm of H_2 for 4 h at ambient temperature, then purged with N_2, filtered through Celite, and concentrated to give 382.6 mg (98%) of the product. ^{1}H NMR (300 MHz, CD_3OD): δ 4.15 (s, 2H), 6.47 (d, 1H, J = 8 Hz), 6.54 (s, 1H), 6.58 (d, 1H, J = 8 Hz), 6.99 (t, 1H, J = 8 Hz), 7.56 (t, 2H, J = 7 Hz), 7.66 (t, 1H, J = 7 Hz), 7.94 (d, 2H, J = 7 Hz). MS (CI) *m/e*: 304 (M − H).

2-(3-Aminophenyl)ethanesulfonic Acid Benzenesulfonylamide (17c). The foregoing procedure was used with 2-(3-nitrophenyl)ethanesulfonic acid benzenesulfonylamide (**55a**, 362.5 mg, 978.7 μmol) and 10% Pd/C (36.2 mg) in MeOH (4.9 mL). Purification by silica gel chromatography, eluting with MeOH/EtOAc (1:9) gave 338.1 mg (99%) of product. ^{1}H NMR (300 MHz, CD_3OD): δ 2.90−3.01 (m, 2H), 3.22−3.26 (m, 2H), 6.50−6.57 (m, 2H), 6.67−6.81 (m, 1H), 6.97−7.12 (m, 1H), 7.43−7.51 (m, 3H), 7.92−7.94 (m, 2H). MS (CI) *m/e*: 339 (M − H).

4-Aminophenethyl-*N*-benzoylsulfonamide (18). 4-Nitrophenethyl-*N*-benzoylsulfonamide (0.60 g) in MeOH (50 mL) and acetic acid (1 mL) was shaken on a Parr apparatus with 20% $Pd(OH)_2$/C (0.2 g) under 45 psi of H_2. When no further uptake was observed, the mixture was filtered through Celite and evaporated to give a white solid (0.60 g). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.90 (t, 2H), 3.70 (m, 2H), 6.61 (d, 2H), 6.98 (d, 2H), 7.42 (m, 2H), 7.60 (m, 1H), 7.80 (m, 2H). MS (ES) *m/e*: 303 (M − H).

2-(4-Aminophenyl)-*N*-4-methylbenzylacetamide (19a). An N_2-purged flask was charged with absolute EtOH (40 mL), 2-(4-nitrophenyl)-*N*-4-methylbenzylacetamide (515 mg, 1.81 mmol), and 10% Pd/C (312 mg). The mixture was placed under 1 atm of H_2 and stirred for 16 h, then filtered through a pad of Celite, washing with additional ethanol. The filtrate was concentrated to supply the crude product as an off-white solid. Purification by silica gel chromatography (eluting with 1:1 hexane/EtOAc) afforded 303 mg (66% yield) of the product as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H), 3.48 (s, 2H), 3.62 (bs, 2H), 4.32 (d, 2H, J = 6.0 Hz), 5.60 (bs, 1H), 6.61 (d, 2H, J = 8.4 Hz), 6.99 (d, 2H, J = 8.4 Hz), 7.02 (d, 2H, J = 8.8 Hz), 7.06 (d, 2H, J = 8.0 Hz). MS (ES) *m/e*: 255.1 (M + H).

***N*-[2-(4-Aminophenyl)ethyl]-4-methylbenzenesulfonamide (19b).**[26] The foregoing procedure was employed with *N*-[2-(4-nitrophenyl)ethyl]-4-methylbenzenesulfonamide (497 mg, 1.55 mmol) and 10% Pd/C (299 mg) in absolute EtOH (35 mL). Crude product was purified by silica gel chromatography (eluting with 3:2 hexane/EtOAc) to afford 181 mg (40% yield) of the product as a pink solid. ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 2.60 (t, 2H, J = 6.8 Hz), 3.10 (q, 2H, J = 6.8 Hz), 4.21 (m, 1H), 6.55 (d, 2H, J = 8.0 Hz), 6.81 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.0 Hz).

General Procedure for Synthesis of Final Targets via Reductive Amination of Anilines with *tert*-Butyl (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl-[(1*R*)-1-methyl-2-oxoethyl]carbamate (10) and Deprotection. Procedure A. A solution of aldehyde **10** in CH_2Cl_2 (0.1−0.2 M) and aniline intermediate (0.67−1.2 equiv) was stirred for 10−30 min, and $NaBH(OAc)_3$ (2.0−2.5 equiv), followed by catalytic glacial acetic acid (1−10 drops), was added. The resulting mixture was stirred for a period of 8−48 h, then added to CH_2Cl_2 and saturated aqueous Na_2CO_3. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude aniline intermediate, which was purified by silica gel chromatography. The resulting aniline was subjected to acidic deprotection with 4 N HCl/dioxane or 6 N aqueous HCl. The crude target hydrochloride, which was obtained by concentration and/or precipitation with Et_2O, was purified by silica gel chromatography using a mixture of $CHCl_3$, MeOH, and concentrated NH_4OH to supply the target as the free base.

Procedure B. A procedure similar to procedure A was followed except that the aniline and aldehyde **10** were dissolved in MeOH and an excess of $NaCN(BH)_3$ and catalytic acetic acid were added. The mixture was stirred for 12−86 h and worked up by partitioning between water and EtOAc. The organic layer was separated and dried to give the crude intermediate that was deprotected as described in the foregoing procedure.

Methyl 4-[((2*R*)-2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]amino}-propyl)amino]benzoate (Intermediate 20). Procedure B was employed using methyl 4-aminobenzoate (430 mg, 2.84 mmol), aldehyde **10** (1.5 g, 3.41 mmol), acetic acid (650 mg, 10.8 mmol), MeOH (25 mL), and $NaCNBH_3$ (0.45 g, 7.41 mmol). The reaction mixture was stirred for 3 days, the reaction was quenched with 15% w/v solution of potassium sodium tartrate, the mixture was then stirred for 30 min, and the reaction was worked up. The crude product was purified by chromatography, eluting with 9:1 hexane/EtOAc, to afford 932 mg of intermediate **20** (59%) as a foamy oil. ^{1}H NMR ($CDCl_3$): δ −0.17 (s, 3H), −04 to 0.02 (m, 3H), 0.77−0.86 (m, 12H), 1.40 (s, 9H), 3.03−3.25 (m, 4H), 3.78 (s, 3H), 4.03−4.07 (m, 1H), 6.45 (d, 2H, J = 8.6 Hz), 7.09−7.26 (m, 4H), 7.79 (d, 2H, J = 8.6 Hz). MS (ES) *m/e*: 577 $(M + H)^+$. **4-[((2*R*)-2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)-amino]benzoic Acid (36).** Intermediate **20** (466 mg, 0.81 mmol) was treated with 4 N HCl/dioxane (10 mL) for 16 h to give, after addition of Et_2O, 323 mg (85%) of methyl 4-[((2*R*)-2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}propyl)amino]-benzoate hydrochloride as a white solid. ^{1}H NMR (CD_3OD): δ 1.37 (d, 3H, J = 6.4 Hz), 3.10−3.73 (m, 6H), 3.78 (s, 3H), 4.98 (dd, 1H, J = 2.9, 10 Hz), 6.71 (d, 2H, J = 8.8 Hz), 7.27 (m, 3H), 7.44 (s, 1H), 7.79 (d, 2H, J = 8.8 Hz). MS (ES) *m/e*: 363 (M + H).

A portion (253 mg, 0.63 mmol) of the methyl ester obtained above was dissolved in MeOH/water (12 mL) and treated with $LiOH\cdot H_2O$ (146 mg, 3.48 mmol) in water (4 mL). The mixture

was stirred for 16 h at ambient temperature, heated to 40 °C for 7 h, then heated at 60 °C for 16 h. The mixture was allowed to cool to ambient temperature, and the solvent was removed. The residue was purified by chromatography eluting with $CHCl_3$/MeOH/concentrated NH_4OH (6:1:0.1) to afford 172 mg of acid **36** (78%) as a white solid judged by ^{1}H NMR analysis to be a 5.5:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (400 MHz, CD_3OD) (*R*,*R* diastereomer): δ 1.26 (d, 3H, $J = 6.9$ Hz), 3.01−3.09 (m, 2H), 3.30−3.38 (m, 3H), 6.62 (d, 2H, $J = 8.6$ Hz), 7.24−7.39 (m, 3H), 7.41 (s, 1H), 7.76 (d, 2H, $J = 8.6$ Hz). HRMS ((M + H)$^+$ found: 349.1300. Calcd for $C_{18}H_{21}Cl_1N_2O_3$: 349.1319. Anal. ($C_{18}H_{21}Cl_1N_2O_3 \cdot 1.5H_2O$) C, H, N.

***tert*-Butyl (1*R*)-2-Anilino-1-methylethyl-[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]carbamate (Intermediate 21).** Procedure A was followed using aldehyde **10** (270.6 mg, 0.61 mmol), aniline (65 μL (0.713 mmol), $NaBH(OAc)_3$ (305 mg, 1.44 mmol), and 1 drop of AcOH in CH_2Cl_2 (4.0 mL). Workup gave the crude product, which was purified by chromatography (eluting with 10:1 followed by 5:1 hexane/ethyl acetate) to give 274.0 mg (74%) of the product as a colorless oil. ^{1}H NMR (400, $CDCl_3$): δ −0.12 (s, 3H), 0.03 (s, 3H), 0.87 (m, 12H), 1.45 (s, 9H), 3.11−3.20 (m, 4H), 6.55 (d, 2H, $J = 10.8$ Hz), 6.67 (t, 1H, $J = 10.8$), 7.13−7.26 (m, 5H), 7.32 (s, 1H).

(1*R*)-2-{[(1*R*)-2-Anilino-1-methylethyl]amino}-1-(3-chlorophenyl)ethanol Hydrochloride (39). The product of the foregoing procedure was dissolved in CH_2Cl_2 (5 mL), and TFA (1 mL) was added. The resulting mixture was stirred for 45 min and concentrated. The residue was taken up in 1:1 THF/6 N aqueous HCl (10 mL), and the mixture was stirred for 16 h. Concentration followed by chromatography (eluting with 214:15:1 $CHCl_3$/MeOH/concentrated NH_4OH) gave 119.1 mg of the free base product. This material was dissolved in 1:1 CH_3CN/H_2O (30 mL), and 2 mL of 1.0 N HCl was added. The mixture was lyophilized to afford 136.9 mg (76% yield) of the product hydrochloride judged by ^{1}H NMR analysis to be a 9.8:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (400 MHz, CD_3OD) (*R*,*R* diastereomer): δ 1.47 (d, 3H, $J = 6.4$ Hz), 3.20 (dd, 1H, $J = 13.8$, 6.0 Hz), 3.53 (dd, 1H, $J = 13.8$, 6.0 Hz), 3.70 (s, 1H), 5.04 (dd, 1H, $J = 10.0$, 2.8 Hz), 7.05 (t, 1H, $J = 7.6$ Hz), 7.34−7.38 (m, 5H), 7.50 (s, 1H, 3H), 6.62 (d, 2H, $J = 8.6$ Hz), 7.24−7.39 (m, 3H), 7.41 (s, 1H), 7.76 (d, 2H, $J = 8.6$ Hz). MS (ES) *m*/*e*: 305.3 (M + H). Anal. ($C_{17}H_{21}Cl_1N_2O \cdot 2.0HCl \cdot 0.5H_2O$) C, H, N.

***tert*-Butyl (1*R*)-2-{4-[(Acetylamino)methyl]anilino}-1-methylethyl-[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]carbamate (Intermediate 22).** General procedure A was followed using aldehyde **10** (1.68 g, 3.80 mmol), *N*-(4-aminobenzyl)acetamide (**13**, 500 mg, 3.04 mmol), 2 drops of glacial acetic acid, and $NaBH(OAc)_3$ (1.52 g, 7.17 mmol). The reaction time was 8 h. Workup and chromatography (eluting with 1:1 hexane/EtOAc) afforded 1.18 g (67%) of the intermediate **22**. ^{1}H NMR ($CDCl_3$): δ −0.16 (s, 3H), −0.03 (s, 3H), 0.82 (m, 12H), 1.41 (s, 9H), 1.95 (s, 3H), 3.03−3.19 (m, 4H), 4.05−4.11 (m, 1H), 4.25 (d, 2H, $J = 5.6$ Hz), 4.93 (bs, 0.5H), 5.20 (bs, 0.5H), 6.47 (d, 2H, $J = 8.8$ Hz), 7.03 (d, 2H, $J = 8.4$ Hz), 7.18−7.22 (m, 3H), 7.27 (s, 1H). MS (ES) *m*/*e*: 590.3, 591.6 (M + H).

***N*-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]amino}propyl)amino]benzyl}acetamide (37).** Intermediate **22** (580 mg, 0.982 mmol) was treated with 4 N aqueous HCl/dioxane (10 mL) for 3 h and worked up according to the general procedure to supply an amorphous material, which was dissolved in a small amount of 30:15:1 $CHCl_3$/MeOH/concentrated NH_4OH and purified by chromatography (eluting with 5:1 EtOAc/MeOH) to afford 256 mg of product **37** (69%) as a colorless glass judged by ^{1}H NMR analysis to be a 6:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (CD_3OD) (major diastereomer): δ 1.27 (d, 3H, $J = 6.8$ Hz), 1.91 (s, 3H), 3.02−3.08 (m, 2H), 3.22−3.33 (m, 1H), 4.17 (s, 2H), 6.62 (d, 2H, $J = 8.4$ Hz), 7.04 (d, 2H, $J = 8.4$ Hz), 7.27−7.38 (m, 3H), 7.40 (s, 1H). HRMS (M + H)$^+$ found: 376.1768. Calcd for $C_{20}H_{26}Cl_1N_3O_2$: 376.1792. Anal. ($C_{20}H_{26}Cl_1N_3O_2 \cdot 1H_2O \cdot 0.5CHCl_3$) C, H, N.

***tert*-Butyl (2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl[(1*R*)-1-methyl-2-(4-{[(methylsulfonyl)amino]methyl}anilino)ethyl]carbamate (Intermediate 23).** General procedure A was followed using aldehyde **10** (1.68 g, 3.80 mmol), *N*-(4-aminobenzyl)methanesulfonamide hydrochloride (**14**, 720 mg, 3.04 mmol), acetic acid (2 drops), and $NaBH(OAc)_3$ (1.50 g, 7.08 mmol). Workup and purification by chromatography (eluting with 2:1 hexane/EtOAc) afforded 1.32 g (69%) of intermediate **23** as a colorless glass. ^{1}H NMR ($CDCl_3$): δ −0.16 (s, 3H), −0.01 (s, 3H), 0.83 (m, 12H), 1.53 (s, 9H), 2.66 (s, 1.5H), 2.67 (s, 1.5H), 2.95−3.20 (m, 4H), 3.80−4.00 (m, 2H), 4.09 (s, 1H), 4.10 (s, 1H), 6.49 (d, 2H, $J = 8.4$ Hz), 7.11 (d, 2H, $J = 8.4$ Hz), 7.18−7.22 (m, 4H). MS (ES) *m*/*e*: 626.2, 628.4 (M + H).

***N*-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]amino}propyl)amino]benzyl}methanesulfonamide (38).** Intermediate **23** (410 mg, 0.655 mmol) was stirred in 4 N HCl/dioxane (10 mL) for 3 h and worked up according to the general procedure to supply the crude material, which was dissolved in a small amount of $CHCl_3$/MeOH/concentrated NH_4OH (30:15:1) and purified by chromatography (eluting with 5:1 EtOAc/MeOH) to supply 239 mg (89%) of target **38** as a colorless glass that was judged by ^{1}H NMR to be a 10:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (MeOD-d_4): δ 1.20 (d, 3H, $J = 7.2$ Hz), 2.57 (s, 3H), 2.95−2.97 (m, 2H), 3.18−3.20 (m, 1H) 4.13 (s, 2H), 4.78−4.83 (m, 1H), 6.62 (d, 2H, $J = 8.4$ Hz), 7.14 (d, 2H, $J = 8.4$ Hz), 7.25−7.29 (m, 3H), 7.39 (s, 1H). HRMS (M + H)$^+$ found: 412.1455. Calcd for $C_{19}H_{26}Cl_1N_3O_3S_1$: 412.1462. Anal. ($C_{19}H_{26}Cl_1N_3O_3S_1 \cdot 0.5H_2O \cdot 0.25CHCl_3$) C, H, N.

***tert*-Butyl (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl-((1*R*)-1-methyl-2-{4-[2-oxo-2-(1,3-thiazol-2-ylamino)ethyl]anilino}ethyl)carbamate (Intermediate 24)**. General procedure A was employed using aldehyde **10** (212 mg, 0.482 mmol), 2-(4-aminophenyl)-*N*-thiazol-2-ylacetamide (**15**, 215 mg, 0.922 mmol), acetic acid (2 drops), and $NaBH(OAc)_3$ (230 mg, 1.09 mmol) in 3:1 CH_2Cl_2/*N*,*N*-DMF (8 mL). The intermediate **24** (267 mg, 82%) was obtained as a pale-yellow oil following workup and chromatographic purification (eluting with 2:1 to 1:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$): δ −1.15 (s, 3H), −0.01 (s, 3H), 0.80 (m, 12H), 1.43 (s, 9H), 3.00−3.21 (m, 4H), 3.80−4.00 (m, 2H), 3.62 (s, 2H), 3.80−4.00 (m, 2H), 6.50 (d, 2H, $J = 8$ Hz), 6.95 (d, 1H, $J = 2$ Hz), 7.03 (d, 2H, $J = 8$ Hz), 7.10−7.35 (m, 4H), 7.39 (s, 1H). MS (ES) *m*/*e*: 657 (M − H).

2-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]amino}propyl)amino]phenyl}-*N*-(1,3-thiazol-2-yl)acetamide (40). To a solution of intermediate **24** (267 mg, 0.405 mmol) in THF (10 mL) was added 1.0 M tetrabutylammonium fluoride/THF (610 μL, 0.610 mmol), and the mixture was stirred for 16 h. The mixture was partitioned between EtOAc and water, and the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to provide 145 mg of a residue that was dissolved in CH_2Cl_2 (5 mL) and TFA (0.5 mL). The mixture was stirred for 16 h and concentrated. The residue was purified by chromatography (eluting with 150:30:1 $CHCl_3$/MeOH/concentrated NH_4OH) to afford 93.9 mg (52%) of the product as a bright-yellow solid judged by ^{1}H NMR analysis to be a 11:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR ($CDCl_3$) (*R*,*R* diastereomer): δ 1.12 (d, 3H, $J = 6.0$ Hz), 2.74 (dd, 1H, $J = 9.2$, 12.2 Hz), 2.89 (dd, 1H, $J = 3.6$, 12.2 Hz), 2.93−3.01 (m, 2H), 3.15 (d, 1H, $J = 8.4$ Hz), 3.70 (s, 2H), 4.11 (bs, 1H), 4.63 (dd, 1H, $J = 3.6$, 8.8 Hz), 6.59 (d, 2H, $J = 8.4$ Hz), 6.92 (d, 1H, $J = 3.6$ Hz), 7.07 (d, 2H, $J = 8.4$ Hz), 7.18−7.26 (m, 3H), 7.32 (d, 1H, $J = 3.6$ Hz), 7.35 (s, 1H). HRMS (M + H)$^+$ found: 445.1485. Calcd for $C_{22}H_{25}Cl_1N_4O_2S_1$: 445.1465. Anal. ($C_{22}H_{25}Cl_1N_4O_2S_1$) C, H, N.

***tert*-Butyl (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl[(1*R*)-1-methyl-2-(4-{2-[(methylsulfonyl)amino]-2-oxoethyl}anilino)ethyl]carbamate (Intermediate 25).** General procedure A was employed using aldehyde **10** (720 mg, 1.6 mmol), *N*-[2-(4-aminophenyl)acetyl]-methanesulfonamide (**16a**, 750 mg, 3.3 mmol), and $NaBH(OAc)_3$ (1.0 g, 4.7 mmol) in CH_2Cl_2/*N*,*N*-DMF (8:3). After the mixture was stirred for 2.5 days, 15% w/v aqueous potassium

sodium tartrate was added and standard workup gave intermediate **25** (1.0 g, 95%). ^{1}H NMR (DMSO-d_6): δ −0.16 (s, 3H), −0.19 (s, 3H), 0.70−0.89 (m, 12H), 1.28−1.32 (m, 9H), 2.04 (2, 2H), 2.46−2.47 (m, 5H), 6.39−6.45 (m, 1H), 6.91 (d, 1H, J = 8.4 Hz), 7.17−7.34 (m, 5H), 7.92 (s, 1H).

***N*-(2-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)-ethyl]amino}propyl)amino]phenyl}acetyl)methanesulfonamide (41).** Intermediate **25** (1.01 g, 1.5 mmol) was dissolved in 4 N HCl/dioxane (10 mL), and the mixture was stirred for 3 h. The solvent was removed, and the residue was purified by chromatography, eluting with $CHCl_3$/MeOH/concentrated NH_4OH (3:1:0.1 to 3:1.5:0.1), to afford target **41** as a clear oil (380 mg, 56%) judged by ^{1}H NMR to be a 12.3:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (DMSO-d_6) (*R*,*R* diastereomer): δ 1.08 (d, 3H, J = 5.9 Hz), 2.79−3.09 (m, 4 H), 3.13 (s, 3H), 3.17 (s, 2H), 4.07 (broad s, 1H), 4.71−4.77 (m, 1H), 6.48 (d, 2H, J = 8.2 Hz), 6.92 (d, 2H, J = 8.2 Hz), 7.30−7.36 (m, 3H), 7.40 (s, 1H). MS(ES) *m*/*e*: 440 (M + H)$^+$, 462 (M + Na)$^+$. HRMS (M + H)$^+$ found: 440.1407. Calcd for $C_{20}H_{26}N_3O_4S_1Cl_1$: 440.1411. Anal. ($C_{20}H_{26}N_3O_4S_1Cl_1\cdot 1.25H_2O$): C, H, N.

***N*-(2-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)-ethyl]amino}propyl)amino]phenyl}acetyl)benzenesulfonamide (42).** General procedure A was employed using aldehyde **10** (187 mg, 0.423 mmol), *N*-[2-(4-aminophenyl)-acetyl]benzenesulfonamide (**16b**, 187 mg, 0.644 mmol), $NaBH(OAc)_3$ (850 mg, 4.01 mmol), and acetic acid (3 drops) in 1:2 CH_2Cl_2/*N*,*N*-DMF (30 mL). After 16 h, the reaction was quenched with aqueous 15% w/v potassium sodium tartrate and worked up as described in the general procedure to afford, after chromatography (eluting with 7:3 hexane/EtOAc), the Boc amine silyl ether intermediate **26**. This material was dissolved in 1:1 6 N aqueous HCl/THF (6 mL), and the resulting solution was stirred for 5 h. Removal of volatiles afforded a residue that was purified by chromatography, eluting with $CHCl_3$/concentrated MeOH/NH_4OH (6:1:0.1), to supply the product (7 mg, 18%) as an off-white solid judged by ^{1}H NMR analysis to be a 26:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (400 MHz, CD_3OD) (*R*,*R* diastereomer): δ 1.33 (d, 3H, J = 6.4 Hz), 3.06−3.19 (m, 3H), 3.24−3.31 (m, 3H), 4.92 (dd, 1H, J = 9.8, 2.8 Hz), 6.57 (d, 2H, J = 8.4 Hz), 7.02 (d, 2H, J = 8.4), 7.31−7.49 (m, 7H), 7.88 (d, 2H, J = 7.2). HRMS (M + H)$^+$ found: 502.1532. Calcd for $C_{25}H_{28}N_3O_4S_1Cl_1$: 502.1567. Anal. ($C_{25}H_{28}N_3O_4S_1Cl_1\cdot 1.25H_2O$): C, H, N.

***N*-({4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]-amino}propyl)amino]phenyl}acetyl)-4-methylbenzenesulfonamide (43).** General procedure A was employed using aldehyde **10** (169 mg, 0.382 mmol), *N*-[2-(4-aminophenyl)-acetyl]-4-methylbenzenesulfonamide (**16c**, 140 mg, 0.460 mmol), $NaBH(OAc)_3$ (602 mg, 2.84 mmol), and acetic acid (3 drops) in CH_2Cl_2 (22 mL). Workup gave a residue that was purified by chromatography, eluting with hexane/EtOAc (7:3) to provide intermediate **27** as white foam (152 mg). This material was dissolved in 4 N aqueous HCl (10 mL), and the resulting solution was stirred for 6 h to give, after addition of Et_2O, an off-white solid. This material was dissolved in $CHCl_3$/MeOH/concentrated NH_4OH (6:1:0.2) and purified by chromatography (eluting with 6:1:0.1 $CHCl_3$/MeOH/concentrated NH_4OH) to yield 35 mg (33%) of product **43** as an off-white solid, mp 100−105 °C, judged by ^{1}H NMR to be >95% *R*,*R* diastereomer. ^{1}H NMR (400 MHz, CD_3OD): δ 1.36 (d, 3H, J = 6.4 Hz), 2.38 (s, 3H), 3.12−3.14 (m, 1H), 3.20 (dd, 1H, J = 12.6, 2.8 Hz), 3.30−3.40 (m, 1H), 3.49 (m, 1H), 4.94 (dd, 1H, J = 10.0, 3.2 Hz), 6.60 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.32−7.35 (m, 3H), 7.47 (s, 1H), 7.78 (d, 2H, J = 8.4 Hz). HRMS (M + H)$^+$ found: 516.1734. Calcd for $C_{26}H_{30}N_3O_4S_1Cl_1$: 516.1724. Anal. ($C_{26}H_{30}N_3O_4S_1Cl_1\cdot 0.25CHCl_3$): C, H, N.

***N*-({3-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]-amino}propyl)amino]phenyl}acetyl)-4-methylbenzenesulfonamide (44).** General procedure A was employed using aldehyde **10** (217 mg, 0.491 mmol), *N*-[2-(3-aminophenyl)-acetyl]benzenesulfonamide (**17a**, 180 mg, 0.591 mmol), $NaBH(OAc)_3$ (207 mg, 0.977 mmol), and acetic acid (3 drops) in CH_2Cl_2 (22 mL). After 16 h the reaction was worked up and the crude material was purified by chromatography, eluting with hexane/EtOAc (7:3 to 1:1) to yield intermediate **28** as a white foam (112 mg, 31%). The foam was dissolved in 4 N HCl/dioxane (10 mL), and the resulting solution was stirred for 16 h to give, after workup, a sticky solid. Purification by chromatography (eluting with 6:1:0.1 $CHCl_3$/MeOH/concentrated NH_4OH) gave 31 mg (40% from **10**) of the target **44** as an off-white solid, mp 105−110 °C, judged by ^{1}H NMR to be >95% *R*,*R* diastereomer. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (d, 3H, J = 7 Hz), 2.32 (s, 3H), 2.98−3.03 (m, 1H), 3.11−3.18 (m, 2H), 3.29 (s, 2H), 3.41−3.46 (m, 1H), 4.94 (dd, 1H, J = 10, 3 Hz), 6.48−6.52 (m, 2H), 6.59 (s, 1H), 6.96 (t, 1H, J = 8 Hz), 7.18 (d, 2H, J = 8 Hz), 7.27−7.30 (m, 3H), 7.42 (s, 1H), 7.73 (d, 2H, J = 8 Hz). HRMS (M + H)$^+$ found: 516.1728. Calcd for $C_{26}H_{30}N_3O_4S_1Cl_1$: 516.1724. Anal. ($C_{26}H_{30}N_3O_4S_1Cl_1\cdot 0.1CHCl_3\cdot 0.85CH_3OH$): C, H, N.

1-[((2*R*)-2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino}propyl)amino]-3-[({[(phenylsulfonyl)amino]-carbonyl}amino)methyl]benzene (45). General procedure B was employed using aldehyde **10** (461.6 mg, 1.04 mmol), and 1-amino-3-[({[(phenylsulfonyl)amino]carbonyl}amino)methyl]-benzene (**17b**, 382.6 mg, 1.25 mmol) in MeOH (10.4 mL). The mixture was heated to 50 °C, and $NaCNBH_3$ (44.0 mg, 0.70 mmol) and acetic acid (45.0 μL, 0.79 mmol) were added. After the mixture was stirred for 17 h, the reaction was quenched by addition of a 15% aqueous w/v solution of potassium sodium tartrate and worked up to yield the crude material. Purification by chromatography, eluting with EtOAc/hexanes (2:3), supplied intermediate **29**. This material was dissolved in 4 N HCl/dioxane (7.8 mL), and the mixture was stirred for 3 h. Workup gave a material that was purified by chromatography, eluting with $CHCl_3$/MeOH (4:1), to afford 184.2 mg (34%) of target **45** as a tan solid judged by ^{1}H NMR analysis to be a 7.7:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (300 MHz, DMSO-d_6) (*R*,*R* diastereomer): δ 1.11 (d, 3H, J = 5.6), 2.86−3.40 (m, 5H), 4.00 (bs, 2H), 4.77 (m, 1H), 5.58 (bs, 1H), 6.35 (d, 1H, J = 7.2 Hz), 6.42 (d, 2H, J = 8.0 Hz), 6.59 (bs, 1H), 6.95 (t, 1H, J = 7.6 Hz), 7.33−7.38 (m, 4H), 7.43−7.48 (m, 3H), 7.80 (d, 2H, J = 6.8 Hz). HRMS (M + H)$^+$ found: 517.1696. Calcd for $C_{25}H_{29}N_4O_4S_1Cl_1$: 517.1676. Anal. ($C_{25}H_{29}N_4O_4S_1Cl_1\cdot 0.75H_2O$): C, H, N.

3-{4-[((2*R*)-2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino}propyl)amino]phenyl}propanoic Acid (35). General procedure A was employed using aldehyde **10** (520 mg, 1.18 mmol), 3-(4-aminophenyl)propanoic acid (233 mg, 1.41 mmol), $NaBH(OAc)_3$ (394 mg, 1.76 mmol), glacial acetic acid (81.0 μL, 1.41 mmol), and 1,2-dichloroethane as solvent. The reaction mixture was stirred for 27.5 h and worked up to give intermediate **30** (332 mg). A portion of this material (321 mg) was dissolved in 4 N HCl/dioxane (4.0 mL). After 5 h, the solution was concentrated and neutralized by addition of 3 drops of concentrated NH_4OH. The residue was purified by chromatography, eluting with $CHCl_3$/MeOH/concentrated NH_4OH (80:15:2, then 60:15:2), to afford material that was dissolved in EtOH/H_2O (1:1). Lyophilization gave 137 mg (31% overall) of target **35** judged by ^{1}H NMR to be a 5.5:1 mixture of *R*,*R*/minor diasteromers. ^{1}H NMR (300 MHz, DMSO-d_6) (*R*,*R* diastereomer): δ 1.04 (d, 3H, J = 5.8 Hz), 2.40−2.46 (m, 2H), 2.64−2.69 (m, 2H), 2.72 (d, 2H, J = 6.2 Hz), 2.80−2.90 (m, 3H), 3.40 (bs, 2H), 4.64 (m, 1H), 5.30 (bs, 1H), 6.49 (d, 2H, J = 8.4 Hz), 6.92 (d, 2H, J = 8.4 Hz), 7.29−7.39 (m, 3H), 7.42 (s, 1H). Anal. ($C_{20}H_{25}N_2O_3Cl_1\cdot 0.75H_2O\cdot 0.1EtOH$): C, H, N.

2-{3-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]-amino}propyl)amino]phenyl}-*N*-(phenylsulfonyl)ethanesulfonamide (46). General procedure B was employed using aldehyde **10** (351.2 mg, 794.6 μmol), (2-(3-aminophenyl)-ethanesulfonic acid benzenesulfonylamide (**17c**, 338.1 mg, 0.993 mmol), $NaCNBH_3$ (41.8 mg, 0.67 mmol), and acetic acid (42.8 μL, 0.75 mmol). The reaction mixture was stirred for 86 h, quenched with 15% w/v solution of potassium sodium tartrate, and worked up to supply intermediate **31**, which was purified by chromatography, eluting with MeOH/EtOAc (1:4). This material was dissolved in 4 N HCl in dioxane (5.5 mL),

and the solution was stirred for 4 h. After concentration, the residue was purified by chromatography, eluting with $CHCl_3$/MeOH (3:1) containing concentrated NH_4OH, to give 142.7 mg (33%) of product **46** judged by ^{1}H NMR to be >95% *R*,*R* diastereomer. ^{1}H NMR (400 MHz, CD_3OD): δ 1.38 (d, 3H, *J* = 6.8 Hz), 2.94−3.00 (m, 2H), 3.11−3.17 (m, 1H), 3.21−3.37 (m, 3H), 3.48−3.55 (m, 3H), 4.96 (dd, 1H, *J* = 10.2, 2.8 Hz), 6.65 (d, 2H, *J* = 8.4 Hz), 7.04 (dd, 2H, *J* = 8.4 Hz), 7.30−7.46 (m, 7H), 8.00 (d, 2H, *J* = 7.2 Hz). HRMS (M + H)$^+$ found: 552.1422. Calcd for $C_{25}H_{31}Cl_1N_3O_5S_2$: 552.1394. Anal. ($C_{25}H_{31}Cl_1N_3O_5S_2 \cdot 1.0H_2O$): C, H, N.

***N*-Benzoyl-2-{4-[((2*R*)-2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}propyl)amino]phenyl}ethanesulfonamide (47).** General procedure B was employed using aldehyde **10** (1.05 g, 2.38 mmol), 4-aminophenethyl-*N*-benzoylsulfonamide (**18**, 1.2 g, 3.94 mmol), glacial acetic acid (0.3 mL), and $NaCNBH_3$ (250 mg) in MeOH (25 mL). Workup afforded crude protected intermediate **32**, which was stirred with 4 N HCl/dioxane for 4 h. The solvent was evaporated, and the residue was treated with aqueous Na_2CO_3 and EtOAc. The mixture was then filtered to give product **47** as a white solid (110 mg, 9% yield), which was judged by ^{1}H NMR to be a 22:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR (400 MHz, CD_3OD) (*R*,*R* diastereomer): δ 1.11 (d, 3H, *J* = 5.6 Hz), 2.85−3.39 (m, 5H), 4.00 (bs, 1H), 4.68−4.88 (m, 1H), 5.55 (bs, 1H), 6.35 (d, 1H, *J* = 7.2 Hz), 6.58 (bs, 1H), 6.95 (t, 1H, *J* = 7.6 Hz), 7.32−7.38 (m, 4H), 7.43−7.48 (m, 3H), 7.80 (d, 2H, *J* = 6.8 Hz). MS *m*/*e*: 515 (M − H). Anal. ($C_{26}H_{30}N_3O_4S_1Cl_1 \cdot 1.0H_2O$): C, H, N.

***tert*-Butyl (2*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl[(1*R*)-1-methyl-2-(4-{2-[(4-methylbenzyl)amino]-2-oxoethyl}anilino)ethyl]carbamate (Intermediate 33).** General procedure A was employed using aldehyde **10** (459 mg, 1.30 mmol), 2-(4-aminophenyl)-*N*-4-methylbenzylacetamide (**19a**, 264 mg, 1.04 mmol), acetic acid (3 drops), and $NaBH(OAc)_3$ (482 mg, 2.28 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 16 h and worked up. Chromatography (eluting with 5:1 hexanes/EtOAc) supplied 583 mg (82%) of intermediate **33**. ^{1}H NMR ($CDCl_3$): δ −0.09 (s, 3H), 0.06 (s, 3H), 0.90 (s, 12H), 1.48 (s, 9H), 2.35 (s, 3H), 3.10−3.30 (m, 4H), 3.55 (S, 3H), 4.1 (bs, 1H), 4.39 (d, 2H, *J* = 5.7 Hz), 6.55 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 7.10−7.40 (m, 7H). MS (ES), *m*/*e*: 679.9, 681.9 (M + H).

2-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)ethyl]amino}propyl)amino]phenyl}-*N*-(4-methylbenzyl)acetamide (48). Intermediate **33** (583 mg, 0.857 mmol) was dissolved in 4 N HCl/dioxane (10 mL), and the reaction mixture was stirred for 3 h. Approximately 50 mL of Et_2O was added, and the resulting precipitate was collected and purified by chromatography (eluting with 168:15:1 $CHCl_3$/MeOH/concentrated NH_4OH) to supply 320 mg of the target **48** (80%) as a white solid judged by ^{1}H NMR to be a 5.7:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR ($CDCl_3$) (*R*,*R* diastereomer): δ 1.11 (d, 3H, *J* = 5.6 Hz), 2.27 (s, 3H), 2.73 (dd, 1H, *J* = 8.4, 12.2 Hz), 2.84 (dd, 1H, *J* = 3.6, 12.2 Hz), 2.93−2.97 (m, 2H), 3.11 (d, 1H, *J* = 8.0 Hz), 4.31 (d, 2H, *J* = 5.6 Hz), 4.40 (dd, 1H, *J* = 3.6, 8.8 Hz), 5.68 (bs, 1H), 6.56 (d, 2H, *J* = 8.4 Hz), 7.01−7.07 (m, 6H), 7.16−6.23 (m, 3H), 7.32 (s, 1H). HRMS ((M + H)$^+$ found: 466.2250. Calcd for $C_{27}H_{32}Cl_1N_3O_2$: 466.2261. Anal. ($C_{27}H_{32}Cl_1N_3O_2$) C, H, N.

***tert*-Butyl (2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl{(1*R*)-1-methyl-2-[4-(2-{[(4-methylphenyl)sulfonyl]amino}ethyl)anilino]ethyl}carbamate (Intermediate 34).** General procedure A was employed using aldehyde **10** (309 mg, 0.7 mmol), *N*-[2-(4-aminophenyl)ethyl]-4-methylbenzenesulfonamide (**19b**, 163 mg, 0.56 mmol), $NaBH(OAc)_3$ (262 mg, 1.24 mmol), and acetic acid (3 drops) in anhydrous CH_2Cl_2 (7.0 mL). Workup afforded 359 mg (90%) of intermediate **34** as a colorless glass. ^{1}H NMR ($CDCl_3$): δ −0.08 (s, 9H), 0.07 (s, 3H), 0.91 (m, 12H), 1.49 (s, 9H), 2.46 (s, 3H), 2.66 (t, 2H, *J* = 6.9 Hz), 3.13−3.21 (m, 6H), 3.95−4.10 (m, 1H), 4.33 (m, 1H), 6.50 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.1 Hz). MS (ES) *m*/*e*: 718.9, 715.8 (M + H).

***N*-(2-{4-[((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-chlorophenyl)-ethyl]amino}propyl)amino]phenyl}ethyl)-4-methylbenzenesulfonamide (49).** Intermediate **34** (359 mg, 0.50 mmol) was dissolved in 4 N HCl/dioxane (10 mL), and the mixture was stirred for 3 h. After removal of solvent, the resulting gum was purified by chromatography (eluting with 168:15:1 $CHCl_3$/MeOH/concentrated NH_4OH) to supply 81.3 mg (32% yield) of the product **49** as a white foam judged by ^{1}H NMR analysis to be a 5.3:1 mixture of *R*,*R*/minor diastereomers. ^{1}H NMR ($CDCl_3$) (*R*,*R* diastereomer): δ 1.11 (d, 3H, *J* = 6.0 Hz), 2.38 (s, 3H), 2.59 (t, 2H, *J* = 6.8 Hz), 2.72 (dd, 1H, *J* = 8.8, 12.4 Hz), 2.84 (dd, 1H, *J* = 3.6, 12.4 Hz), 2.90−2.98 (m, 3H), 3.00−3.12 (m, 4H), 4.40 (bs, 1H), 4.61 (dd, 1H, *J* = 3.6, 8.8 Hz), 6.50 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 7.17−7.25 (m, 5H), 7.32 (s, 1H), 7.64 (d, 2H, *J* = 8.0 Hz). HRMS ((M + H)$^+$ found: 502.1949. Calcd for $C_{26}H_{32}Cl_1N_3O_3S_1$: 502.1931. Anal. ($C_{26}H_{32}Cl_1N_3O_3S_1 \cdot 0.12CHCl_3$) C, H, N.

Biological Methods. 1. In Vitro Functional Assays. In these experiments the β_3 AR clone of Granneman and coworkers was employed.[36] Chinese hampster ovary (CHO) cells expressing human β_1, β_2, or β_3 AR were grown in DMEM/F12 (with pyroxidine·HCl, 15 mM HEPES, l-glutamine), supplemented with 10% heat-inactivated FBS, 500 μg/mL G418, 2 mM L-glutamine, 100 units of penicillin G, and 100 μg of streptomycin sulfate. One confluent flask of cells was trypsinised and resuspended in the above medium at a concentration of 30−40000 cells/100 μL and plated into 96-well flat bottom plates. The cells were then used for assay within 18−24 h. The medium was aspirated from each well and replaced with 180 μL of DMEM/F12 with 500 mM IBMX. The plate was then placed back in the incubator for 30 min. Drugs were then added to the wells (20 μL, 100 × required final concentration) for 60 min. Responses were determined by measuring cAMP levels of a 20 μL sample of extracellular media using a scintillation proximity based radioimmunoassay (NEN Flashplates).

2. Binding Assays. Human recombinant Sf9 cells expressing the cloned human β_1 and β_2 receptors were obtained using the method of Smith and Teitler.[37] Receptor binding assays were carried out using the radioligand [^{125}I]cyanopindolol at a concentration of 150 pM and the compound of interest at six concentrations ranging from 0.21 to 50 μM. Binding reactions were carried out for 1 h and 30 min for β_1 and β_2 receptors, respectively, at 22 °C and terminated by filtration through glass fiber filters (GF/B, Packard). Bound radioactivity was measured with a scintillation counter (Topcount, Packard) using a liquid scintillation cocktail (Microscint 0, Packard).

3. Pharmacokinetic Studies in Dogs. Male beagle dogs (weight range: 8−12 kg) were fasted overnight. On the morning of the study, each compound was dissolved in 0.025 M methanesulfonic acid containing 5% mannitol and the dogs were each fitted with two cephalic vein cannulae. Each dog was dosed with with one compound intravenously via one cannula at a dose level of 0.2 mg/kg body weight (5 min infusion period). Blood was collected via the second cephalic vein cannula at 0, 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2.5, 4, 6, 8, and 24 h. Resulting serum samples were prepared by protein precipitation with acetonitrile and analyzed for compound content by APCI LC−MS/MS using a Hypersil BDS C18 column (30 mm × 1 mm, 3μm) at ambient temperature. A gradient mobile phase of 3−99% acetonitrile in 5 mM ammonium acetate buffer, pH 4.5, was used at a flow rate of 80 μL/min. Detection was by multiple reaction monitoring (MRM) on a Sciex API III+ with argon as the collision gas. Data reduction was performed using Sciex MacQuan software. Noncompartmental methods were used to calculate pharmacokinetic parameters from the resulting serum concentration vs time profiles.

4. Rodent Infrared Thermography Studies.[35] CD-1 mice (CD-1(ICR)BR) were anesthetized with isoflurane and shaved to expose the interscapular region before IR imaging. The animals were orally dosed, and at the appropriate times they were anesthetized and scanned. Animals were dosed by oral gavage with either vehicle (0.025 M methanesulfoxide at 10

mL/kg) or the test compound (10 mL/kg (volume), 1 mg/kg, 0.1 mg/kg, and 0.01 mg/kg (concentration)). The mice were placed in a manifold with nose ports for continual delivery of isoflurane. To maintain body core temperature during scanning, the rodents were placed on a tightly regulated heating table (37 ± 0.1 °C). The heating table was housed in an isothermal, nonreflective chamber (24 ± 0.1 °C, 50% relative humidity). Upon closure of the chamber door, heat emissions from the areas of interest were acquired using a high-resolution InSb IR scanning detector (AGEMA Thermovision 900, Thermogenic Imaging, Billerica, MA) mounted 30 cm above the area of interest. Images were recorded at 1 min intervals for 5 min. A frame-averaging rate of 16 frames per second was used for each designated time point. Acquired images were analyzed for average temperatures using a GlaxoWellcome (RTP, NC) image-processing software application (RoboImage). Data were expressed as either average temperature per area or the change in temperature per area (drug treated minus vehicle treated). The data were calculated as the mean and standard error of the mean from experiments performed on 8−10 animals per treatment group. Two tailed *t*-tests were performed to calculate *P* values. Correlation coefficients were determined by regression analysis using Sigma Plot.

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Supporting Information Available: HPLC traces of β_3 agonists **35**−**49**. This material is available free of charge via the Internet at http://pubs.acs.org.

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