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Novel (4-Piperidin-1-yl)-phenyl Sulfonamides as Potent and Selective Human β_3 Agonists

Baihua Hu,[a,*] John Ellingboe,[a] Stella Han,[b] Elwood Largis,[b] Kitae Lim,[a] Michael Malamas,[a] Ruth Mulvey,[b] Chuansheng Niu,[a] Alexander Oliphant,[a] Jeffrey Pelletier,[a] Thiruvikraman Singanallore,[a] Fuk-Wah Sum,[a] Jeff Tillett[b] and Victoria Wong[a]

[a]*Chemical Sciences, Wyeth-Ayerst Research, Pearl River, NY 10965, USA*
[b]*Cardiovascular/Metabolic Diseases Research, Wyeth-Ayerst Research, Pearl River, NY 10965, USA*

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Abstract—A series of novel (4-piperidin-1-yl)-phenyl sulfonamides was prepared and evaluated for their biological activity on the human β_3-adrenergic receptor (AR). Replacement of the 3,4-dihydroxyl group of the catechol moiety with 4-hydroxyl-3-methyl sulfonamide on the left-hand side of the compounds resulted in a number of potent full agonists at the β_3 receptor. Modification of the right-hand side of the compounds by incorporation of a free carboxylic acid resulted in a few potent human β_3 agonists with low affinities for β_1- and β_2-ARs. *N*-Alkyl substitution on the 4-piperidin-1-yl-phenylamine further increased the β_3 potency while maintaining the selectivity. For example, sulfonamide **48** is a potent full β_3 agonist ($EC_{50} = 0.004$ μM, IA = 1.0) with >500-fold selectivity over β_1- and β_2-ARs.

Introduction

The subdivision of β-adrenergic receptors (β-AR) into β_1- and β_2-ARs has led to the development of β_1- and β_2-antagonists and/or agonists which have been useful for the treatment of cardiovascular disease and asthma. A third 'atypical' β-AR, now called β_3-AR, was identified in the early 80s. It was found that the β_3 receptor mediates various pharmacological and physiological effects such as lipolysis in white adipocyte tissue (WAT), thermogenesis in brown adipocyte tissue (BAT), and relaxation of urinary bladder detrusor tissue.[1] Consequently, a potent and selective β_3-AR agonist[2,3] has the potential to be a therapeutic agent in the treatment of obesity, type II diabetes, and frequent urination. Early developments in the β_3-AR agonist field, which were based on the rodent β_3-AR receptor, are represented by CL 316243 (**1**),[3c] BRL 37344 (**2**),[4] and CGP 12177A (**3**)[5] (Chart 1). These compounds produced great agonist activity for the stimulation of lipolysis and energy expenditure (β_3-AR activity), and to a small extent heart rate increase (β_1-AR activity), and muscle tremor (β_2-AR activity). In addition, these compounds have shown antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus (NIDDM).[6] However, human clinical trials with these early β3-AR agonists have been disappointing due to a lack of selectivity or potency. Subsequently, cloning and expression of the human and rat β_3-ARs indicated a significant difference between the two.[5] Thus, a cloned human receptor assay would offer major advantages over rodent models for the identification of potent and selective β_3-AR agonists.

L-770644 (**4a**),[2b] thiazole benzenesulfonamide (**4b**),[7] and SB-226552 (**5**)[8] represent the compounds of the next generation currently emerging from preclinical development. These compounds were evaluated in Chinese hamster ovary (CHO) cells expressing the cloned human β_3-AR receptor that would more accurately predict the effects that can be expected in humans. These compounds are full agonists and highly selective at the human β_3-AR. Despite all these recent developments there is still not a single therapy available for the treatment of type II diabetes (NIDDM), obesity, frequent urination and related diseases. A potent and selective

*Corresponding author. Fax: +1-845-732-5561; e-mail: hub@war.wyeth.com

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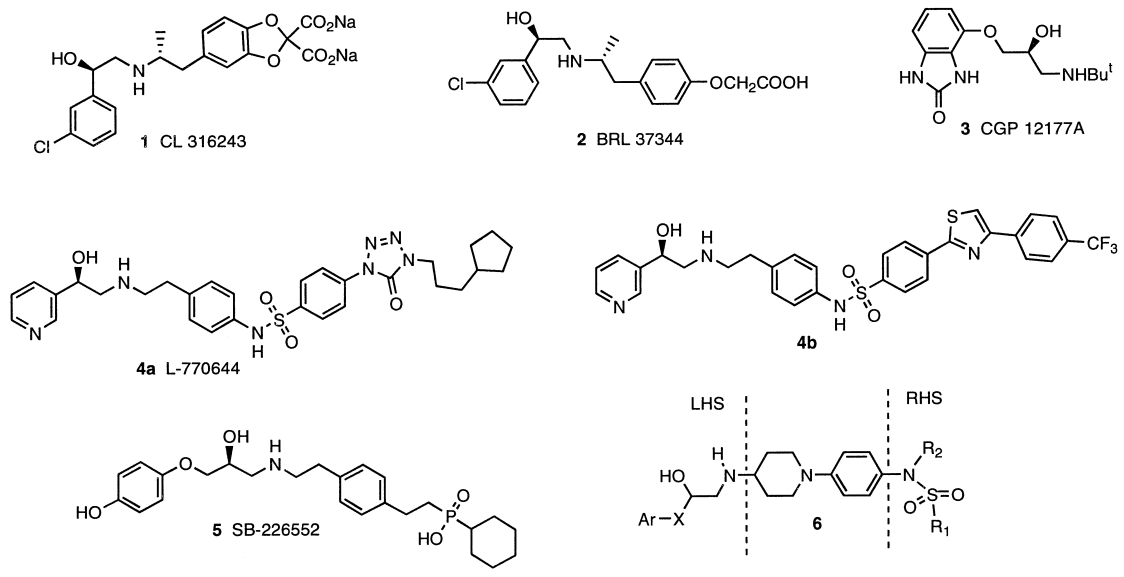


Chart 1. Compounds **1**–**6**.

β_3-AR agonist is therefore highly desirable for the potential treatment of such disease states. Herein we report the discovery of novel (4-piperidin-1-yl)-phenyl sulfonamides of general structure **6** as potent and selective agonists of the human β_3-AR receptor.

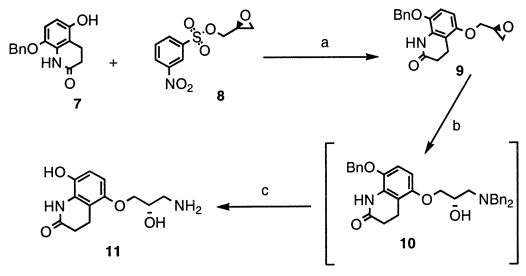
Chemistry

The (4-piperidin-1-yl)-phenyl sulfonamides of general structure **6** were readily prepared by utilizing reductive amination of right-hand side (RHS) piperidones with appropriate left-hand side (LHS) arylethanolamines or aryloxypropanolamines. Many of arylethanolamines or aryloxypropanolamines are commercially available or easily prepared by known methods.[9] A synthesis of the carbostyril LHS moiety is shown in Scheme 1. Alkylation of phenol **7**[9c] with equimolecular amounts of (2*S*)-glycidyl 3-nitrobenzene sulfonate (**8**) in DMF using potassium carbonate as a base provided enantiomerically pure oxirane **9**. Regioselective ring opening of oxirane **9** with dibenzylamine followed by debenzylation with ammonium formate/Pd on charcoal in methanol furnished the desired phenoxypropanolamine **11**.

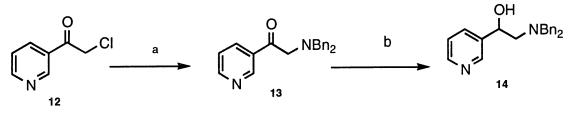
Synthesis of 3-pyridyl ethanol amine **14** was achieved as illustrated in Scheme 2. Treatment of chloracetyl pyridine **12**[10] with dibenzylamine yielded the corresponding aminoketone **13**. Reduction of **13** with $NaBH_4$ afforded the ethanolamine **14**, which was used as a LHS moiety without debenzylation.

Scheme 3 depicts the synthesis of racemic aminoalcohol **18**. The requisite dibenzylaminoalcohol **17** was obtained starting from the chloride **15**[11] by the same dibenzylamine/$NaBH_4$ sequence, which was described in Scheme 2. Compound **17** was then transformed into the desired racemic aminoalcohol **18** by catalytic hydrogenolysis with Pd on charcoal.

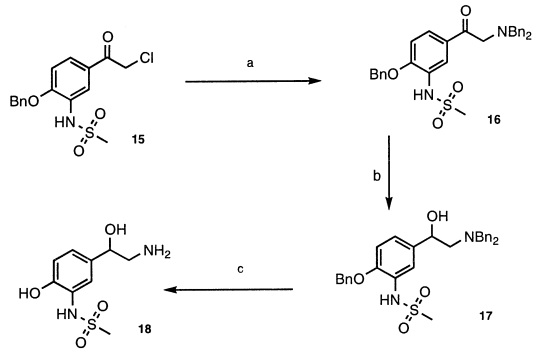
The corresponding *R*-enantiomer **21** was prepared from the enantiomerically enriched bromohydrin **19**, which was obtained according to a literature procedure.[11] Nucleophilic substitution of bromide **19** with sodium azide in DMSO at ambient temperature provided azide **20** in high yield. Debenzylation and azide reduction by



Scheme 1. Synthesis of phenoxypropanolamine **11**: (a) K_2CO_3, acetone, 75%; (b) Bn_2NH, MeOH; (c) HCO_2NH_4, Pd/C, MeOH, 78% over (b) and (c).



Scheme 2. Synthesis of pyridyl ethanol amine **14:** (a) Bn_2NH, DMF, 61%; (b) $NaBH_4$, MeOH, 73%.



Scheme 3. Synthesis of racemic **18**: (a) Bn_2NH, DMF, 61%; (b) $NaBH_4$, MeOH/THF, 90%; (c) H_2, Pd/C, MeOH, 91%.

catalytic hydrogenation with ammonium formate/Pd on charcoal furnished the desired phenethanolamine **21** (Scheme 4).

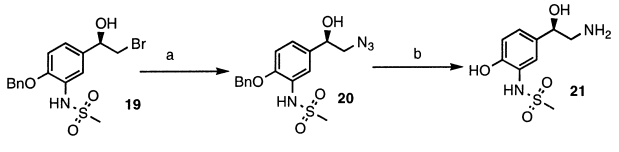
Sulfonamides of general structure **27** were conveniently prepared as outlined in Scheme 5. The nitro group in **22**[12] was reduced by catalytic hydrogenation to provide aniline **23**. Sulfonylation of the aniline **23** with sulfonyl chlorides followed by hydrolysis of the ketal with concentrated HCl gave the corresponding piperidones **27**. Alternatively, the piperidones were synthesized by the same reduction/sulfonylation sequence starting from the ketone **25**[12] instead of the ketal **22**. The desired final products (**29**–**43**) were prepared by utilizing reductive amination of piperidones **27** with the appropriate arylethanolamines or aryloxypropanolamines **28**. The reductive aminations were carried out with hydrogen and catalytic palladium in ethanol, or with sodium triacetoxyborohydride in DMF. Either hydrolysis of alkyl esters in NaOH or hydrogenation of benzyl esters with Pd on charcoal gave the desired carboxylic acids. The aniline substituents (R_1) for compounds **24**, **27, 31**, **32**, **42**, and **43** are illustrated in Figure 1.

The *N*-butyl substituted analogue **48** was prepared as outlined in Scheme 6. Reductive amination between aniline **23** and butyraldehyde furnished the desired ketal **44**, which was transformed into the corresponding ketone **45** by HCl hydrolysis. Sulfonylation followed by reductive amination, as previously described in Scheme 5, furnished the *N*-butyl analogue **47**. Carboxylic acid **48** was produced by catalytic hydrogenation of sulfonamide **46** with amine **21**.

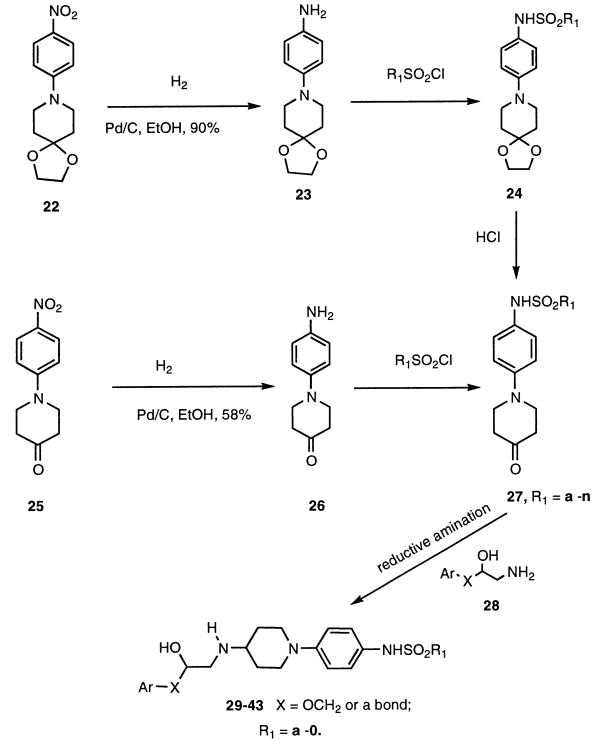
Biological Activity

In order to expedite the identification of potent β_3-AR agonists with high selectivity versus β_2- and β_1-ARs, we first optimized the LHS moiety of the agonist while holding the piperidone-aniline RHS constant. The current β_3-AR agonist LHS moieties belong to two general structural classes:[1] phenoxypropanolamines and phenethanolamines. First we examined agonists with a variety of phenoxypropanolamines for their ability to stimulate an increase in cAMP in CHO cells expressing the cloned human β_3-AR receptor. As illustrated in Table 1, unsubstituted analogue **29** is a 1.55 μM partial agonist (defined as IA = 0.2 ~ 0.90) with 57% activation relative to (−)-isoproterenol. The 4-hydroxyl analogue **30** also has low potency (EC_{50} = 0.96 μM) at the β_3-AR receptor, but it is a full agonist (defined as IA > 0.90) with IA value of 0.97. A few heterocyclic derivatives were also examined, led to the identification of three potent analogues (**31a**, **32a**, **33**). However, the carbazole[13] analogue **33** is a partial β_3-AR agonist with an IA of 0.63. Thus, only the 5-carbostyril (8-hydroxy-3,4-dihydro-*1H*-quinolin-2-one)[14] and benzimidazolone[15] LHS moieties were further explored for their β_1/β_2-AR selectivity profiles. Many sulfonamide analogues were prepared in both the benzimidazole and carbostyril series, and the results are shown in Tables 2 and 3. In both series, highly substituted benzenesulfonamides (**31a**–**31e**, **32a**, **32b**, **32e**) and simple alkyl sulfonamides (**31f**, **31g**, **32f**) (see Figure 1 for definitions of **a**–**f**) are potent (0.16 ~ 0.001 μM) at the β_3-AR receptor and selective against the β_2-AR receptor, but these derivatives showed basically no selectivity against the β_1-AR receptor. All of the tested phenoxypropanolamines showed potent activity (EC_{50} = 0.03 ~ 0.002 μM) at the β_1-AR receptor even though they are partial agonists. Hence, these phenoxypropanolamine derivatives were not pursued further due to the lack of β_3-AR selectivity.

Next, we examined various phenethanolamine LHS moieties. Since the natural agonists adrenaline and noradrenaline are catechols, many sulfonamides with different catechol bioisosteres were prepared. As anticipated, the catechol analogue **37** is a very potent (EC_{50} = 0.008 μM) full β_3-AR agonist (IA = 0.93). The orientation of the two hydroxyl groups (3,4-di-OH) is essential for maintaining β_3-AR activity as the isomeric 2,4-dihydroxyl analogue **38** and 3-methoxy-4-hydroxyl analogue **39** are both at least 100-fold less potent. Unsubstituted analogue **34**, mono hydroxyl analogues (**35** and **36**), and 7-amide indole analogue **40** all showed anticipated low potency. Surprisingly, replacement of the catechol LHS with 3-pyridine, which has been demonstrated[2] to be a potent catechol bioisostere, resulted in a low potency agonist **41** in our series (Table 4).



Scheme 4. Synthesis of *R*-enantiomer **21**. (a) NaN_3, DMSO, 94%; (b) HCO_2NH_4, Pd/C, EtOH, 76%.



Scheme 5. Synthesis of sulfonamides **29**–**43**.

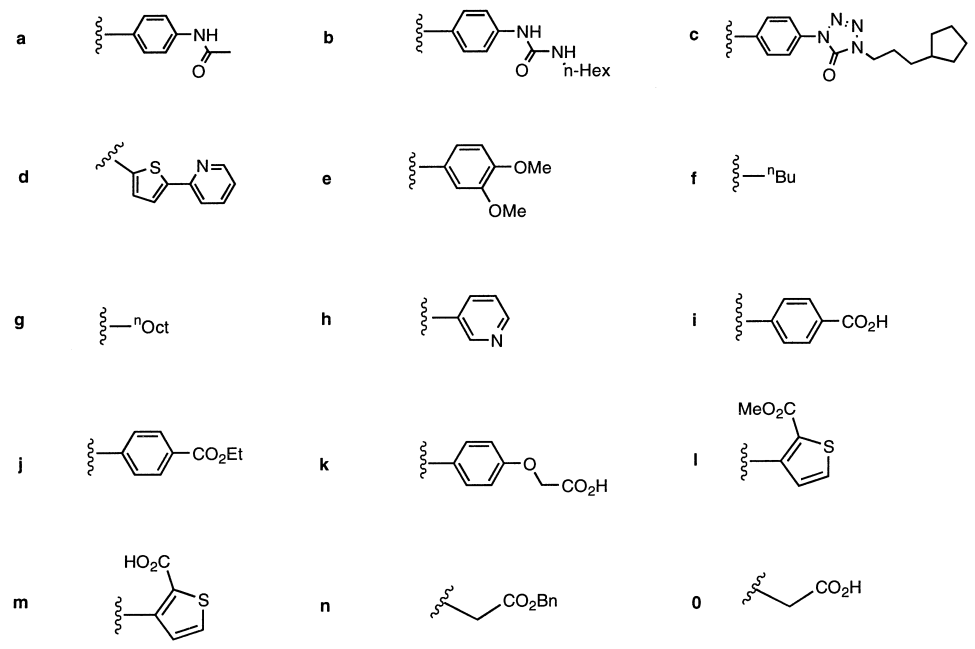
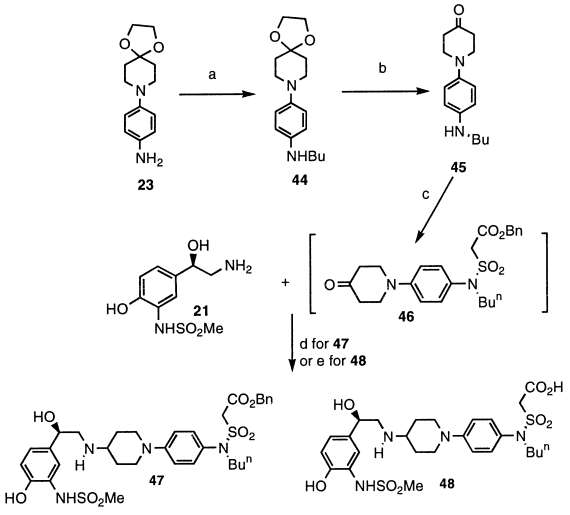


Figure 1. Anline substituents (R_1) for compounds **24**, **27**, **31**, **32**, **42** and **43**.

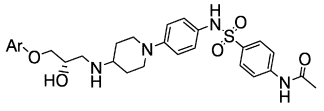


Scheme 6. Synthesis of *N*-butyl sulfonamide **48:** (a) PrCHO, $NaBH(OAc)_3$, THF, 41%; (b) HCl, 82%; (c)$BnCO_2CH_2SO_2Cl$, Et_3N, CH_2Cl_2, 19%: (d) $NaBH(OAc)_3$, DMF, 35%; (e) Pd/C, EtOH, 31%.

We speculated that the catechol portion may be chemically or enzymatically unstable. To improve the stability of the LHS moiety, a combination[2a] of 4-hydroxyl and 3-methyl sulfonamide was examined. Our results showed that **43a** is a potent (0.013 μM) β_3-AR agonist and exhibited full intrinsic activity (IA = 1.07). Presumably the bulky methyl sulfonamide improves the stability while the sulfonamide N–H is able to mimic a hydroxyl group.

Since the racemate **42b** and the *R*-isomer **43b** exhibited comparable activity/selectivity profile, the racemic mixtures **42c**–**42g** (see Figure 1 for definitions of R_1) were then screened for a structure–activity relationship study (Table 5). Although **43a** is a potent β_3-AR agonist, it showed very limited selectivity (~100-fold against β_2- and β_1-ARs). Little or no improvement in selectivity was achieved by a variety of sulfonamides, which included 3,4-dimethoxy benzenesulfonamide **42e**, heterocyclic sulfonamides (**42d** and **43h**), urea benzenesulfonamides (**42b** and **43b**, **42c**) and aliphatic sulfonamides (**42f** and **42g**). To our delight, the introduction of a free carboxylic acid group (**43i**) decreased β_1- and β_2-AR activities (for β_1-AR: IA = 0.09; for β_2-AR: EC_{50} = 7.40 μM, IA = 0.30), but retained β_3-AR activity (EC_{50} = 0.05 μM, IA = 0.97), thus providing the desired β_3-AR selectivity. The corresponding ester **43j** is much less selective. This observation seems to be consistent with an earlier discovery[16] that a free carboxylic group enhanced β_3-AR selectivity. It was subsequently found that this was a general phenomenon; the related thiophene analogue **43m**, phenoxy

Table 1. Variation of LHS of Phenoxypropanolamines

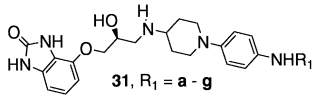


Compound	Ar	EC_{50} (μm) (β_3-AR)[a]	IA (β_3-AR)[b]
29	Phenyl	1.55	0.57
30	4-OH-Phenyl	0.96	0.97
31a	4-(2-Benzimidazolone)	0.16	1.15
32a	5-Carbostyril	0.004	1.0
33	4-(*9H*-Carbazole)	0.022	0.63

[a]β_3-AR Agonistic activity was assessed by measurement of cAMP accumulation levels in CHO cells expressing the human β_3-AR.
[b]The maximal amount of cAMP obtained by (−)-isoproterenol was defined as 100% and the relative maximal response of each compound was expressed as intrinsic activity (IA).

acetic acid **43k** and aliphatic sulfonamide **43o** were likewise found to be potent and selective at the β_3-AR receptor while the corresponding esters (such as **43l** and **43n**) were found to be much less selective (Table 6).

Table 2. Variation of RHS of Benzimidazolones

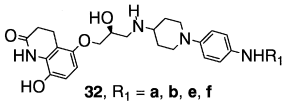


31, R_1 = **a** - **g**

Compound	β_3-AR[a] EC_{50} μm (IA)	β_2-AR EC_{50} μm (IA)[a]	β_1-AR EC_{50} μm (IA)[a]
31a	0.16 (1.15)	100 (0.4)	0.014 (0.44)
31b	0.1 (0.73)	(0)	0.023 (0.41)
31c	0.003 (0.58)	(0)	0.007 (0.33)
31d	0.01 (1.04)	(0.01)	0.01 (0.31)
31e	0.016 (0.96)	(0.03)	0.012 (0.23)
31f	0.008 (0.81)	(0)	0.002 (0.4)
31g	0.059 (0.78)	(0)	0.011 (0.34)

[a]β-ARs agonistic activities were assessed by measurement of cAMP accumulation levels in CHO cells expressing the human β-ARs; the intrinsic activities were given as a fraction of the maximal stimulation with isoproterenol.

Table 3. Variation of RHS of Carbostyrils

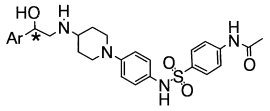


32, R_1 = **a**, **b**, **e**, **f**

Compound	β_3-AR EC_{50} μm (IA)[a]	β_2-AR EC_{50} μm (IA)[a]	β_1-AR EC_{50} μm (IA)[a]
32a	0.004 (1.1)	(0.02)	0.03 (0.63)
32b	0.001 (1.0)	(0)	0.01 (0.97)
32e	0.02 (0.96)	(0.03)	0.009 (1.04)
32f	0.005 (1.1)	(0.02)	0.03 (0.63)

[a]See footnote a in Table 2.

Table 4. Variation of LHS of Phenethanolamines



Compound	Ar	*Config.	EC_{50} (μm)[a] (β_3-AR)	IA[b] (β_3-AR)
34	Phenyl	*R*	3.16	0.7
35	3-OH-Phenyl	*R*+*S*	0.61	0.88
36	4-OH-Phenyl	*R*+*S*	0.92	0.97
37	3,4-di-OH-Phenyl	*R*	0.008	0.93
38	2,4-di-OH-Phenyl	*R*+*S*	0.80	0.64
39	3-OMe-4-OH-Phenyl	*R*+*S*	15.4	1.0
40	4-(*1H*-Indole-7-carboxylic acid amide)	*R*+*S*	3.84	1.05
41	3-Pyridyl	*R*+*S*	10.6	0.83
43a	4-OH-3-$MeSO_2NH$-Phenyl	*R*	0.013	1.07

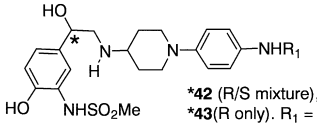
[a]See footnote a in Table 1.
[b]See footnote b in Table 1.

Both the activity and selectivity could be further modified by substitution of the sulfonamide N–H with an alkyl group. Compared to **43o**, the *N*-butyl analogue **48** has increased (9-fold) β_3-AR activity (EC_{50} = 0.004 μM, IA = 1.0) while maintaining the selectivity (1250-fold vs the β_2-AR and 500-fold vs the β_1-AR).[17]

Conclusions

In this study, we have shown that a combination of 4-hydroxyl with a 3-methyl sulfonamide substituent on the aromatic nucleus of LHS of the (4-piperidin-1-yl)-phenyl) sulfonamides is a potent bioisostere for the catechol group, resulting in the identification of many potent full agonists at the human β_3-AR. The introduction of a polar carboxylic acid functionality on the RHS of the compounds diminished both β_1- and β_2-AR activities while retaining activity at β_3-AR. *N*-Alkylation with a hydrophobic alkyl group on the (4-piperidin-1-yl)-phenyl sulfonamide (**43o**) further increased the β_3 potency. Thus, a highly potent (EC_{50} = 0.004 μM, IA = 1.0) and selective (500-fold against β_1- and 1250-fold against β_2-AR agonist activity) human β_3-AR agonist (**48**) has been identified.

Table 5. Variation of RHS of Phenethanolamines



***42** (R/S mixture), R_1 = **b**,-**g**;
***43**(R only). R_1 = **a**, **b**, **h**, **i**, **j**

Compound	β_3-AR EC_{50} μm (IA)[a]	β_2-AR EC_{50} μm (IA)[a]	β_1-AR EC_{50} μm (IA)[a]
43a	0.013 (1.07)	1.35 (0.35)	1.62 (0.99)
43b	0.001 (1.1)	1.00 (1.0)	0.09 (0.9)
42b	0.003 (1.2)	1.16 (0.94)	0.07 (1.0)
42c	0.066 (1.24)	4.47 (1.05)	0.12 (0.56)
42d	0.033 (1.07)	0.87 (0.57)	0.25 (0.65)
42e	0.02 (1.16)	0.083 (0.45)	1.33 (0.65)
42f	0.006 (0.87)	0.17 (0.5)	0.32 (0.96)
42g	0.016 (1.0)	4.55 (1.02)	0.37 (0.71)
43h	0.079 (1.3)	6.49 (1.08)	0.25 (0.99)
43i	0.05 (0.97)	7.40 (0.3)	(0.09)
43j	0.013 (1.0)	0.073 (0.46)	0.03 (0.42)

[a]See footnote a in Table 2.

Table 6. Carboxyl-promoted enhancement of β_3-AR selectivity

Compound	β_3-AR EC_{50} μm (IA)[a]	β_2-AR EC_{50} μm (IA)[a]	β_1-AR EC_{50}μm (IA)[a]
43k	0.013 (1.0)	1.87 (0.55)	4.92 (0.67)
43l	0.011 (0.87)	0.26 (0.77)	0.097 (0.61)
43m	0.013 (1.05)	1.95 (0.57)	2.40 (0.65)
43n	0.002 (0.89)	0.082 (0.46)	0.33 (0.24)
43o	0.035 (0.92)	(0.12)	(0.12)
47	0.002 (0.89)	0.082 (0.46)	0.33 (0.24)
48	0.004 (1.0)	5.0 (0.45)	2.0 (0.51)
4a	0.015 (0.9)	2.42 (0.59)	2.17 (0.86)

[a]See footnote a in Table 2.

Experimental

General

^{1}H NMR spectra were determined with a Bruker DPX-300 spectrometer at 300 MHz. Chemical shifts δ are expressed in parts per million relative to the internal standard tetramethylsilane and *J* (coupling constant) in Hz. Electrospray (ES) mass spectra were recorded in positive or negative mode on a Micromass Platform spectrometer. Electron impact and high-resolution mass spectra were obtained on a Finnigan MAT-90 spectrometer. Combustion analyses were obtained using a Perkin-Elmer Series II 2400 CHNS/O analyzer. Chromatographic purifications were performed by flash chromatography using Baker 40 μm silica gel. Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 250 M prescored plates.

8-Benzyloxy-(5*S*)-5-oxiranylmethoxy-3,4-dihydro-1H-quinolin-2-one (9). A solution of 8-benzyloxy-5-hydroxy-3,4-dihydro-1H-quinolin-2-one (**7**)[9c] (3.0 g, 11.1 mmol) and (2*S*)-(+)glycidyl 3-nitrobenzenesulfonate (2.87 g, 11.1 mmol) in 150 mL of acetone was treated with K_2CO_3 (1.84 g, 13.3 mmol) and stirred at reflux for 1 day. The suspension was cooled to rt; the solid was filtered; and the filtrate was concentrated to dryness. The residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography using 10–50% EtOAc/hexanes as eluent to give the title compound as an off-white solid (2.7 g, 75%): ^{1}H NMR (DMSO-d_6) δ 2.41 (t, *J* = 7.1 Hz, 2H), 2.69 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.75–2.86 (m, 4H), 3.78 (dd, *J* = 11.4, 6.3 Hz, 1H), 4.23 (dd, *J* = 11.4, 2.6 Hz, 1H), 5.09 (s, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.25–7.45 (m, 3H), 7.51 (d, *J* = 8.2 Hz, 2H), 9.08 (s, 1H); MS (ES) *m*/*z* 326.0 (MH^+); HRMS calcd for $C_{19}H_{20}NO_4$ (MH^+): 326.1392; found: 326.1343. Anal. calcd for $C_{19}H_{19}NO_4$: C, 70.14, H, 5.89; N, 4.30; found: C, 70.14; H, 5.69; N, 4.20.

5-(3-Amino-(2*S*)-2-hydroxy-propoxy)-8-hydroxy-3,4-dihydro-1H-quinolin-2-one (11). Dibenzylamine (1.46 g, 7.4 mmol) was added to a stirred solution of **9** (2.0 g, 6.2 mmol) in 100 mL of MeOH. After refluxing overnight the mixture was cooled down to rt and 10% Pd/C (0.5 g) and HCO_2NH_4 (3.15 g, 50 mmol) were added. The suspension was refluxed for another 2 h. After cooling the suspension the reaction mixture was filtered through Celite. The filtrate was concentrated to give the title compound as a pale grey solid (1.20 g, 78%): ^{1}H NMR (DMSO-d_6) δ 2.42 (t, *J* = 7.1 Hz, 2H), 2.74 (dd, *J* = 12.8, 8.2 Hz, 1H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.95 (dd, *J* = 12.8, 3.4 Hz, 1H), 3.65–3.95 (m, 3H), 6.45 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 8.38 (s, 1H), 8.77 (brs, 1H); MS (ES) *m*/*z* 252.9 (MH^+); HRMS calcd for $C_{12}H_{16}N_2O_4$ (M^+): 252.1188; found: 252.1199.

2-Dibenzylamino-1-pyridin-3-yl-ethanone (13). Dibenzylamine (29.6 g, 150 mmol) was added to a stirred solution of 2-chloro-1-pyridin-3-yl-ethanone (**12**)[10] (9.65 g, 50 mmol) in 100 mL of DMF. The mixture was stirred at 60 °C for 2 h. The solvent was removed and residue was purified by column chromatography on silica gel using EtOAc/hexanes (1: 4) as the eluent to give the title compound (9.6 g, 61%) as a white solid: ^{1}H NMR ($CDCl_3$) 3.72 (s, 4H), 3.78 (s, 2H), 7.20–7.50 (m, 11H), 8.02–8.07 (m, 1H), 8.73 (dd, *J* = 4.8, 1.8 Hz, 1H), 9.03 (brs, 1H); MS (ES) *m*/*z* : 317.0 (MH^+); HRMS calcd for $C_{21}H_{20}N_2O$ (M^+): 316.1576; found: 316.1547. Anal. calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85; found: C, 79.52; H, 6.41; N, 8.68.

2-Dibenzylamino-1-pyridin-3-yl-ethanol (14). To a stirred solution of **13** (0.95 g, 3 mmol) in 100 mL of MeOH at rt was added $NaBH_4$ (0.56 g, 15 mmol). After 2 h, the solution was poured into water, extracted with Et_2O, dried with $MgSO_4$, and concentrated. Recrystallization from Et_2O/hexanes gave the title compound (0.7 g, 73%) as a crystalline solid: ^{1}H NMR ($CDCl_3$) 2.55–2.70 (m, 2H), 3.53 (d, *J* = 13.3 Hz, 2H), 3.82 (s, 1H), 3.91 (d, *J* = 13.3 Hz, 2H), 4.69 (dd, *J* = 8.9, 5.9 Hz, 1H), 7.21 (dd, *J* = 7.4, 4.4 Hz, 1H), 7.20–7.50 (m, 12H), 7.50–7.60 (m, 1H), 8.47 (dd, *J* = 4.8, 1.7 Hz, 1H); MS (ES) *m*/*z*: 319.2 (MH^+); HRMS calcd for $C_{21}H_{23}N_2O$ (MH^+): 319.1810; found: 319.1809. Anal. calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80; found: C, 79.26; H, 6.92; N, 8.94.

***N*-[2-Benzyloxy-5-(2-dibenzylamino-1-oxo-ethyl)-phenyl]-methanesulfonamide (16).** Prepared from *N*-[2-benzyloxy-5-(2-chloro-1-oxo-ethyl)-phenyl]-methanesulfonamide (**15**)[11] as described for **13** to give the title compound as a white solid in 61% yield: ^{1}H NMR ($CDCl_3$) δ 2.94 (s, 3H), 3.77 (s, 2H), 3.82 (s, 2H), 5.16 (s, 2H), 6.75 (brs, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.20–7.50 (m, 15H), 7.67 (dd, *J* = 8.7, 2.1 Hz, 1H), 8.10 (d, *J* = 2.1 Hz, 1H); MS (ES) *m*/*z*: 515.2 (MH^+); HRMS calcd for $C_{30}H_{30}N_2O_4S$ (M^+): 514.1926; found: 514.1927. Anal. calcd for $C_{30}H_{30}N_2O_4S{\cdot}0.25H_2O$: C, 69.45; H, 5.92; N, 5.40; found: C, 69.15; H, 5.61; N, 5.16.

***N*-[2-Benzyloxy-5-(2-dibenzylamino-1-hydroxy-ethyl)-phenyl]-methanesulfonamide (17).** Prepared from **16** as described for **14** to give the title compound as a crystalline solid in 90% yield: ^{1}H NMR ($CDCl_3$) δ 2.58 (d, *J* = 6.7 Hz, 2H), 2.86 (s, 2H), 2.92 (s, 2H), 3.55 (d, *J* = 13.5 Hz, 2H), 3.70 (d, *J* = 13.5 Hz, 2H), 4.11 (s, 1H), 4.64 (t, *J* = 6.7 Hz, 1H), 5.10 (s, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.20–7.50 (m, 16H), 7.89 (brs, 1H); MS (ES) *m*/*z* 517.1 (MH^+); HRMS calcd for $C_{30}H_{32}N_2O_4S$ (M^+): 516.2083; found: 516.2074. Anal. calcd for $C_{30}H_{32}N_2O_4S{\cdot}0.37H_2O$: C, 68.88; H, 6.31; N, 5.36; found: C, 68.52; H, 6.13; N, 5.12.

***N*-[5-(2-Amino-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide (18).** To a stirred suspension of **17** (1.03 g, 2 mmol) and 10% Pd/C (0.4 g) in MeOH (100 mL) at rt was added anhydrous HCO_2NH_4 (1.26 g, 20 mmol) under a N_2 atmosphere. The resulting mixture was refluxed for 2 h. After cooling to rt the catalyst was removed by filtration through a Celite pad and washed with MeOH. The filtrate was evaporated under reduced

pressure to give the title compound[9b] as a pale yellowish solid (0.45 g, 91%): ^{1}H NMR (DMSO-d_6) δ 2.62 (dd, J = 12.6, 8.7 Hz, 1H), 2.75 (dd, J = 12.6, 3.7 Hz, 1H), 2.90 (s, 3H), 4.47 (dd, J = 8.7, 3.7 Hz, 1H), 6.84 (d, J = 9.1 Hz, 1H), 6.96 (dd, J = 9.1, 2.0 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 8.44 (s, 1H); MS (ES) m/z 246.7 (MH^+); HRMS calcd for $C_9H_{14}N_2O_4S$ (M^+): 246.0674; found: 246.0672. Anal. calcd for $C_9H_{14}N_2O_4S \cdot 0.7H_2O \cdot 0.4MeOH$: C, 41.58; H, 6.31; N, 10.30; found: C, 41.37; H, 5.98; N, 9.90.

***N*-[5-((1R)-2-Azido-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide (20).** To a stirred solution of *N*-[2-benzyloxy-5-(2-bromo-(1*R*)-1-hydroxy-ethyl)-phenyl]-methanesulfonamide (**19**)[11] (15.05 g, 0.038 mol) in DMSO (150 mL) was added NaI (3.76 g, 0.038 mol) and NaN_3 (9.48 g, 0.15 mol). The mixture was stirred for 5 days under a N_2 atmosphere. The reaction mixture was poured onto water and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was triturated with water and hexanes to give the title compound as a yellow solid (12.85 g, 94%): ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3H), 3.45 (d, J = 9.0 Hz, 2H), 3.46 (m, 1H), 5.11 (s, 2H), 6.80 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 6 Hz, 2.1Hz, 1H), 7.26 (s, 1H), 7.39 (s, 5H), 7.53 (d, J = 2.1 Hz, 1H); MS (ES) m/z 361.4 $(M\text{-}H)^-$. Anal. calcd for $C_{16}H_{18}N_4O_4S \cdot 0.75H_2O \cdot 0.1$ hexanes: C, 51.69; H, 5.46; N, 14.53; found: C, 51.45; H, 5.29; N, 14.52.

***N*-[5-(2-Amino-(1R)-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide (21).** Prepared from **20** as described for **18** to give the title compound as a tan solid in 76% yield: ^{1}H NMR (MeOH-d_4) δ 2.95 (s, 3H), 2.99 (dd, J = 9.7, 9.2 Hz, 1H), 3.07 (dd, J = 9.7, 3.6 Hz, 1H), 4.75 (dd, J = 9.2, 3.6 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 7.12 (dd, J = 8.3, 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 8.44 (s, 1H); MS (ES) m/z 246.7 (MH^+); HRMS calcd for $C_9H_{14}N_2O_4S$ (M^+): 246.0674; found: 246.0672. Anal. calcd for $C_9H_{14}N_2O_4S \cdot 1.6MeOH$: C, 42.78; H, 6.85; N, 9.42; found: C, 42.57; H, 6.45; N, 9.06.

4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-phenylamine (23). A mixture of 8-(4-nitro-phenyl)-1,4-dioxa-8-aza-spiro[4.5]decane (**22**)[12] (3.5 g, 13.3 mmol) and 10% Pd/C (0.5 g) in 100 mL of EtOH/CH_2Cl_2 (2:1) was pressurized with 30 psi H_2 and shaken over 1 h. The catalyst was then removed by filtering through a short pad of silica gel to give the title compound (2.8 g, 90%) as a grey solid. The compound was characterized as a di-HCl salt: ^{1}H NMR (DMSO-d_6) δ 1.85–2.00 (m, 4H), 3.00–3.10 (m, 4H), 3.93 (s, 4H), 6.60 (d, J = 6.0 Hz, 2H), 6.80 (d, J = 6.0 Hz, 2H); MS (ES) m/z 235.2 (MH^+); HRMS calcd for $C_{13}H_{18}N_2O_2$ (M^+): 234.1380; found: 234.1371. Anal. calcd for $C_{13}H_{18}N_2O_2 \cdot 0.25H_2O \cdot 2$ HCl: C, 50.01; H, 6.63; N, 8.99; found: C, 49.89; H, 6.50; N, 8.90.

***N*-{4-[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-phenylsulfamoyl]-phenyl}-acetamide (24).** To a stirred solution of **23** (2.8 g, 11.9 mol) in 1.4-dioxane (150 mL) and Et_3N (7 mL) was added a solution of N-acetylsulfanilyl chloride (3.5 g, 15 mmol) in 75 mL of 1,4-dioxane at rt. The reaction was stirred for 18 h. The reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 and washed with diluted HCl. The white solid in water layer was collected and dried to give the title compound as a white solid (2.5 g, 43%): ^{1}H NMR (DMSO-d_6) δ 1.92 (brs, 4H), 2.06 (s, 3H), 3.68 (brs, 4H), 3.93 (s, 4H), 7.06 (d, J = 8.4 Hz, 2H), 7.33 (brs, 2H), 7.68 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 9.0 Hz, 2H), 10.24 (brs, 1H), 10.38 (s, 1H); MS (ES) m/z 432.3 (MH^+); HRMS calcd for $C_{21}H_{25}N_3O_5S$ (M^+): 431.1515; found: 431.1530.

1-(4-Amino-phenyl)-piperidin-4-one hydrochloride (26). A mixture of 1-(4-nitro-phenyl)-piperidin-4-one (**25**)[12] (4.0 g, 18 mmol) and 500 mg of 10% Pd/C in 75 mL of CH_2Cl_2 was hydrogenated under H_2 (5∼10 psi) for 1 h. The catalyst was then removed by filtering through a short pad of silica gel. The filtrate was treated with HCl gas and the precipitate was collected to give 2.0 g (58%) of the title compound as a tan solid: ^{1}H NMR (DMSO-d_6) δ 2.44 (t, J = 6.0 Hz, 4H), 3.65 (t, J = 6.0 Hz, 4H), 7.14 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H); MS (ES) m/z 190.9 (MH^+); HRMS calcd for $C_{11}H_{15}N_2O$ (MH^+): 190.1106; found: 190.1096. Anal. calcd for $C_{11}H_{14}N_2O \cdot 1.8H_2O \cdot 2HCl$: C, 44.69; H, 6.68; N, 9.48; found: C, 44.57; H, 6.76; N, 9.18.

***N*-{4-[4-(4-Oxo-piperidin-1-yl)-phenylsulfamoyl]-phenyl}-acetamide (27a).** Compound **24** (2.2 g, 5.1 mmol) was treated with concentrated HCl (50 mL) at 0 °C and then allowed to warm to rt. After 30 min, ∼20 mL of 5 N NaOH was added dropwise and the precipitate was collected by filtration, and dried over P_2O_5 to give the title compound as a white solid (1.2 g, 61%): ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H), 2.43 (t, J = 5.8 Hz, 4H), 3.53 (t, J = 5.8 Hz, 4H), 6.85–7.05 (m, 4H), 7.62 (d, J = 9.0 Hz, 2H), 7.71 (d, J = 9.0 Hz, 2H), 9.81 (s, 1H), 10.35 (s, 1H); MS (ES) m/z 388.3 (MH^+); HRMS calcd for $C_{19}H_{21}N_3O_4S$ (M^+): 387.1253; found: 387.1272.

General procedure for the preparation of benzene sulfonamides 27b–h, k, l, n

To a stirred solution of **26** (1 equiv) in dioxane (0.05–0.5 M) was added Et_3N (5–10 equiv) followed by the benzenesulfonyl chloride (as specified) (1–1.5 equiv). After being stirred over 1 day, the mixture was concentrated and the residue was purified by silica gel chromatography using 0–10% MeOH/CH_2Cl_2 as eluant.

4-(3-Hexyl-ureido)-*N*-[4-(4-oxo-piperidin-1-yl)-phenyl]-benzenesulfonamide (27b). 4-(3-Hexylureido)benzenesulfonyl chloride,[2c] grey solid, 42% yield: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.60 (m, 8H), 2.45–2.60 (m, 4H), 3.20–3.75 (m, 2H), 3.50–3.60 (m, 4H), 4.90 (brs, 1H), 6.50 (brs, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H); MS (ES) m/z 473.5 (MH^+); HRMS calcd for $C_{24}H_{25}N_4O_4S$ (MH^+): 473.2233; found: 473.2220.

4-[4-(3-Cyclopentyl-propyl)-5-oxo-4,5-dihydro-tetrazol-1-yl])-*N*-[4-(4-oxo-piperidin-1-yl)-phenyl]benzenesulfona-

mide (27c). 4-[(3-Cyclopentyl-propyl)-5-oxo-4,5-dihydro-tetrazol-1-yl]-phenylsulfonyl chloride,[2b] yellowish solid, 22% yield: ^{1}H NMR (DMSO-d_6) δ 0.90–1.80 (m, 17H), 2.36 (t, J = 6.0 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 3.96 (t, J = 7.0 Hz, 2H), 6.86 (d, J = 6.7 Hz, 2H), 6.94 (d, J = 6.7 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 9.92 (s, 1H); MS (ES) m/z 525.1 (MH^+); HRMS calcd for $C_{26}H_{32}N_6O_4S$ (M^+): 524.2205; found: 524.2193. Anal. calcd for $C_{26}H_{32}N_6O_4S$: C, 59.52; H, 6.15; N, 16.02; found: C, 59.50; H, 6.28; N, 15.81.

5-Pyridin-2-yl-thiophene-2-sulfonic acid [4-(4-oxo-piperidin-1-yl)-phenyl]-amide (27d). 5-Pyridin-2-yl-thiophene-2-sulfonyl chloride, white solid, 41% yield: ^{1}H NMR (DMSO-d_6) δ 2.37 (t, J = 6.0 Hz, 4H), 3.52 (t, J = 6.0 Hz, 4H), 6.89 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 7.39 (dd, J = 4.2, 1.5 Hz, 1), 7.42 (d, J = 2.1 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 7.8, 1.5 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.53 (d, J = 4.2 Hz, 1H), 10.05 (s, 1H); MS (ES) m/z 413.9 (MH^+); HRMS calcd for $C_{20}H_{19}N_3O_3S_2$ (M^+): 413.0867; found: 413.0877. Anal. calcd for $C_{20}H_{19}N_3O_3S_2 \cdot 0.44H_2O$: C, 57.00; H, 4.74; N, 9.97; found: C, 57.01; H, 4.71; N, 9.81.

3,4-Dimethoxy-*N*-[4-(4-oxo-piperidin-1-yl)-phenyl]-benzenesulfonamide (27e). 3,4-Dimethoxybenzenesulfonyl chloride, dull yellow solid, 26%: ^{1}H NMR ($CDCl_3$) δ 2.54 (t, J = 4.5 Hz, 4H), 3.55 (t, J = 4.5 Hz, 4H), 3.83 (s, 3H), 3.91 (s, 3H), 6.21 (brs, 1H), 6.83–6.87 (m, 3H), 6.94–7.03 (m, 2H), 7.12 (d, J = 1.5 Hz, 2H); MS (ES) m/z 391.0 (MH^+); HRMS calcd for $C_{19}H_{23}N_2O_5S$ (MH^+): 391.1328; found: 391.1333.

Butane-1-sulfonic acid [4-(4-oxo-piperidin-1-yl)-phenyl]-amide (27f). 1-Butanesulfonyl chloride, crystalline solid, 55% yield: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 7.3 Hz, 3H), 1.25–1.40 (m, 2H), 1.55–1.70 (m, 2H), 2.40 (t, J = 5.9 Hz, 4H), 2.94 (t, J = 7.6 Hz, 2H), 3.54 (t, J = 5.9 Hz, 4H), 7.00 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 9.34 (s, 1H); MS (ES) m/z 311.0 (MH^+); HRMS calcd for $C_{15}H_{22}N_2O_2S$ (M^+): 310.1351; found: 310.1375. Anal. calcd for $C_{15}H_{22}N_2O_2S$: C, 58.04; H, 7.14; N, 9.02; found: C, 57.78; H, 6.95; N, 8.83.

Octane-1-sulfonic acid [4-(4-oxo-1-piperidinyl)-phenyl]-amide (27g). 1-Octanesulfonyl chloride, white solid, 60% yield: ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 5.4 Hz, 3H), 1.15–1.40 (m, 10H), 1.60–1.75 (m, 2H), 2.40 (t, J = 4.5 Hz, 4H), 2.94 (t, J = 5.7 Hz, 2H), 3.54 (t, J = 4.5 Hz, 4H), 6.99 (d, J = 6.9 Hz, 2H), 7.09 (d, J = 6.9 Hz, 2H), 9.31 (s, 1H); MS (ES) m/z 367.0 (MH^+); HRMS calcd for $C_{19}H_{30}N_2O_2S$ (M^+): 366.1977; found: 366.1969. Anal. calcd for $C_{19}H_{30}N_2O_2S$: C, 62.26; H, 8.25; N, 7.64; found: C, 62.40; H, 7.98; N, 7.59.

Pyridine-3-sulfonic acid[4-(4-oxo piperidin-1-yl)-phenyl] amide (27h). 3-Pyridinesulfonyl chloride, yellow solid, 13% yield: ^{1}H NMR ($CDCl_3$) δ 2.54 (t, J = 6 Hz, 4H), 3.56 (t, J = 6 Hz, 4H), 6.79 (s, 1H), 6.85 (d, J = 12 Hz, 2H), 6.98 (d, J = 12 Hz, 2H), 7.40 (m, 1H), 7.97 (dd, J = 3 Hz, 1H), 8.75 (dd, J = 6 Hz, 1H), 8.90 (d, J = 3 Hz, 1H); MS (ES) m/z 331.9 (MH^+); HRMS calcd for $C_{16}H_{17}N_3O_3S$ (MH^+): 332.1063; found: 332.1063. Anal. calcd for $C_{16}H_{16}N_3O_3S \cdot 0.3H_2O$: C, 57.05; H, 5.27; N, 12.48; found: C, 56.91; H, 5.31; N, 12.19.

4-[4-(4-Oxo-piperidin-1-yl)-phenylsulfamoyl]-benzoic acid (27i). To a stirred solution of **26** (free base) (2.85 g, 15 mmol) in acetone (150 mL) was added 4-(chlorosulfonyl)benzoic acid (1.10 g, 5 mmol) in three portions. After 2 h, the acetone was removed and the residue was treated with diluted aqueous $NaHCO_3$. The solid was filtered off and the filtrate was acidified with diluted HCl. The precipitate was collected and dried to give the title compound as a pale grey solid (0.9 g, 48%): ^{1}H NMR (DMSO-d_6) δ 2.36 (t, J = 6.0 Hz, 4H), 3.49 (t, J = 6.0 Hz, 4H), 6.87 (d, J = 9.3 Hz, 2H), 6.91 (d, J = 9.3 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.1 Hz, 2H), 9.97 (s, 1H), 13.10 (brs, 1H); MS (ES) m/z 374.9 (MH^+); HRMS calcd for $C_{18}H_{19}N_2O_5S$ (MH^+): 375.1009; found: 375.1009. Anal. calcd for $C_{18}H_{18}N_2O_5S \cdot 0.16H_2O$: C, 57.30; H, 4.89; N, 7.43; found: C, 57.03; H, 5.18; N, 7.35.

4-[4-(4-Oxo-piperidin-1-yl)-phenylsulfamoyl]-benzoic acid ethyl ester (27j). A stirred solution of **27i** (1.4 g, 3.74 mmol) in 50 mL of EtOH was treated with HCl gas at rt. After 4 h the solution was concentrated and the residue was dissolved in concentrated HCl (200 mL) at rt. After another 3 h the pH was adjusted to ~ 5 and the precipitate was collected by filtration, and dried over P_2O_5 to give the title compound as a yellowish solid (1.1 g, 70%): ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.1 Hz, 3H), 2.36 (t, J = 6.0 Hz, 4), 3.56 (t, J = 6.0 Hz, 4H), 4.41 (q, J = 7.1 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H); MS (ES) m/z 403.2 (MH^+); HRMS calcd for $C_{20}H_{23}N_2O_5S$ (MH^+): 403.1328; found: 403.1330. Anal. calcd for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96; found: C, 59.71; H, 5.79; N, 6.74.

{4-[4-(4-Oxo-piperidin-1-yl)-phenylsulfamoyl]-phenoxy}-acetic acid methyl ester (methyl ester of 27k). (4-Chlorosulfonyl-phenoxy)-acetic acid methyl ester,[18] grey solid, 28% yield: ^{1}H NMR ($CDCl_3$) δ 2.54 (t, J = 6.0 Hz, 4H), 3.55 (t, J = 6.0 Hz, 4H), 3.82 (s, 3H), 4.67 (s, 2H), 6.80–7.20 (m, 6H), 7.64 (d, J = 68.7 Hz, 2H); MS (ES) m/z 418.9 (MH^+); HRMS calcd for $C_{20}H_{23}N_2O_6S$ (MH^+): 419.1271; found: 419.1271.

3-[4-(4-Oxo-piperidin-1-yl)-phenylsulfamoyl]-thiophene-2-carboxylic acid methyl ester (27l)

2-(Methoxycarbonyl)thiophene-3-sulfonyl chloride, white solid, 29% yield: ^{1}H NMR (DMSO-d_6) δ 2.37 (t, J = 6.0 Hz, 4H), 3.50 (t, J = 6.0 Hz, 4H), 3.89 (s, 3H), 6.90 (d, J = 9.1 Hz, 2H), 6.96 (d, J = 9.1 Hz, 2H), 7.33 (d, J = 6.9 Hz, 1H), 7.90 (d, J = 6.9 Hz, 1H), 9.50 (s, 1H); MS (ES) m/z: 395.0 (MH^+); HRMS calcd for $C_{17}H_{19}N_2O_5S_2$ (MH^+): 395.0736; found: 395.0721. Anal. calcd for $C_{17}H_{18}N_2O_5S_2$: C, 51.76; H, 4.60; N, 7.10; found: C, 51.87; H, 4.49; N, 7.05.

[4-(4-Oxo-piperidin-1-yl)-phenylsulfamoyl]-acetic acid benzyl ester (27n)

Benzyloxycarbonylmethylsulfonylchloride,[19] white solid, 50% yield: ^{1}H NMR (DMSO-d_6) δ 2.42 (t, J = 6.0 Hz, 4H), 3.55 (t, J = 6.0 Hz, 4 H), 4.16 (s, 2H), 5.16 (s, 2H), 6.99 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 9.73 (s, 1H); MS (ES) m/z: 403.2 (MH^+); HRMS calcd for $C_{20}H_{22}N_2O_5S$ (M^+): 402.1250; found: 402.1237. Anal. calcd for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96; found: C, 59.69; H, 5.82; N, 6.90.

General procedures for the preparation of compounds 29–43, 47, 48

Method A

A mixture of the piperidone (as specified, 1 equiv) and the arylethanolamine or aryloxypropanolamine (as specified, 1 equiv) in EtOH (0.01–0.5 M) was hydrogenated in the presence of 10% Pd/C (5–15 weight%) under H_2 (5∼20 psi) for overnight. The catalyst was then removed by filtering through a short pad of silica gel. The filtrate was concentrated and purified by preparative TLC or silica gel chromatography using 0–10% MeOH/CH_2Cl_2 as eluent.

Method B

The piperidone (as specified, 1 equiv) and the arylethanolamine or aryloxypropanolamine (as specified, 1 equiv) were mixed in DMF (0.05–0.3 M) and then treated with $NaBH(OAc)_3$ (1.5–5 equiv) and acetic acid (1.5–5 equiv). After stirring at rt under a N_2 atmosphere for 1–24 h the mixture was quenched with 1 N NaOH and then poured into a saturated aqueous $NaHCO_3$. The precipitate which formed was collected and purified by preparative TLC or silica gel chromatography using 0–10% MeOH/CH_2Cl_2 as eluent.

Method C

To a stirred solution of the alkyl ester (as specified, 1 equiv) in distilled water (0.01–0.5 M) was added 1 N NaOH (1–10 equiv). The reaction was stirred at rt for 2–24 h. The reaction mixture was made acidic (pH 6) with glacial acetic acid, and the solid was collected and dried over P_2O_5.

HPLC analysis

Samples were dissolved in DMSO or ACN/water and analyzed with a Prodigy ODS3, C-18, 4.6×150 mm column. The mobile phase was a gradient of A: 10 mM phosphate buffer pH 3.0 or 0.02%TFA/water and B: acetonitrile (0 min 10%, 10∼30 min 90%). Flow rate was 1 mL/min, detection was at 215 nm, temperature was 40 °C, and injection volume was 8 μL. The retention time and HPLC purity of selected compounds were listed.

***N*-(4-{[4-(4-{[(2*S*)-2-Hydroxy-3-phenoxypropyl]amino}-1-piperidinyl) anilino] sulfonyl}phenyl)acetamide (29).** Method A, **27a** and (2*S*)-1-amino-3-phenoxy-propan-2-ol,[20] white solid, 33% yield: ^{1}H NMR (DMSO-d_6) δ 1.40–1.65 (m, 2H), 1.95–2.10 (m, 2H), 2.06 (s, 3H), 2.50–3.20 (m, 5H), 3.55–3.75 (m, 2H), 3.96 (d, J = 5.2 Hz, 2H), 4.15–4.25 (m, 1H), 5.70 (brs, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.90–7.00 (m, 3H), 7.25–7.35 (m, 2H), 7.59 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 9.70 (s, 1H), 10.37 (s, 1H); MS (ES) m/z 539.1 (MH^+); HRMS calcd for $C_{28}H_{35}N_4O_5S$ (MH^+): 539.2328; found: 539.2357.

***N*-(4-{[4-(4-{[(2*S*)-2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}-1-piperidinyl) anilino]sulfonyl}phenyl)acetamide (30).** Method A: **27a** and (2*S*)-1-amino-3-(4-benzyloxy-phenoxy)-propan-2-ol,[21] grey solid, 58% yield: ^{1}H NMR (DMSO-d_6) δ 1.40–1.65 (m, 2H), 1.95–2.15 (m, 2H), 2.06 (s, 3H), 2.50–3.20 (m, 5H), 3.55–3.70 (m, 2H), 3.80–3.90 (m, 1H), 4.05–4.20 (m, 1H), 5.70 (brs, 1H), 6.67 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6. 88 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 8.97 (s, 1H), 10.37 (s, 1H); MS (ES) m/z 555.1 (MH^+); HRMS calcd for $C_{28}H_{35}N_4O_6S$ (MH^+): 555.2277; found: 555.2267.

***N*-[4-({4-[4-({(2*S*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy] propyl}amino)-1-piperidinyl]anilino}sulfonyl)phenyl]acetamide (31a).** Method A: **27a** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one,[15] white solid, 52% yield: ^{1}H NMR (DMSO-d_6) δ 1.60–1.80 (m, 2H), 2.00–2.15 (m, 2H), 2.06 (s, 3H), 2.50–2.70 (m, 2H), 2.90–3.20 (m, 3H), 3.60–3.75 (m, 2H), 4.15–4.25 (m, 1H), 5.70 (brs, 1H), 6.61 (t, J = 8.7 Hz, 1H), 6.80–6.92 (m, 5H), 7.60 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 9.72 (brs, 1H), 10.42 (s, 1H), 10.65 (s, 1H), 10.80 (s, 1); MS (ES) m/z 595.2 (MH^+); HRMS calcd for $C_{29}H_{35}N_6O_6S$ (MH^+): 595.2339; found: 595.2332.

4-{[(Hexylamino)carbonyl]amino}-*N*-{4-[4-({(2*S*)-2-hydroxy-3-[(2-oxo-2,3-dihydro-1H-benzimidazol-4-yl)oxy]propyl}amino)-1-piperidinyl]phenyl}benzenesulfonamide (31b). Method A: **27b** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one,[15] white solid, 57% yield: ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 6.8 Hz, 3H), 1.20–1.60 (m, 10H), 1.90–2.05 (m, 2H), 2.50–3.50 (m, 9H), 3.50–3.65 (m, 1H), 3.95–4.05 (m, 2H), 6.43 (t, J = 5.6 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.70–6.89 (m, 5H), 7.46 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H), 9.06 (s, 1H), 9.60 (brs, 1H), 10.60 (s, 1H), 10.75 (s, 1H); MS (ES) m/z 680.3 (MH^+); HRMS calcd for $C_{34}H_{46}N_7O_6S$ (MH^+): 680.3230; found: 680.3221.

4-[4-(3-Cyclopentylpropyl)-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl]-*N*-{4-[4-({(2*S*)-2-hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl}amino)-1-piperidinyl]-phenyl}benzenesulfonamide (31c). Method A: **27c** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one,[15] pale green solid, 12% yield: ^{1}H NMR (DMSO-d_6) δ 0.90–4.00 (m, 29H), 5.10–5.30 (m, 1H), 6.58 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 6.81 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.90 (dd, J = 7.9, 7.9 Hz, 1H), 7.86 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H), 10.70 (s, 1H), 10.80 (s, 1H); MS (ES)

m/*z* 732.3 (MH^+); HRMS calcd for $C_{36}H_{46}N_9O_6S$ (MH^+): 732.3292; found: 732.3294.

***N*-{4-[4-({(2S)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl} amino)-1-piperidinyl]phenyl}-5-(2-pyridinyl)-2-thiophenesulfonamide (31d).** Method B: **27d** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one,[15] pale yellowish solid, 26% yield: ^{1}H NMR (DMSO-d_6) δ 1.25–1.40 (m, 2H), 1.80–1.90 (m, 2H), 2.50–2.90 (m, 5H), 3.53 (brd, J = 9.0 Hz, 2H), 3.85–4.00 (m, 2H), 4.00–4.10 (m, 1H), 4.91 (brs, 1H), 6.56 (d, J = 5.7 Hz, 1H), 6.61 (d, J = 5.7 Hz, 1H), 6.80–6.90 (m, 3H), 6.96 (d, J = 6.6 Hz, 2H), 7.36 (dd, J = 3.3, 1.2 Hz, 1H), 7.41 (d, J = 3.0 Hz, 1H), 7.75 (d, J = 3.0 Hz, 1H), 7.88 (dd, J = 6.0, 1.2 Hz, 1H), 7.98 (d, J = 6.0 Hz, 1H), 8.54 (d, J = 3.3 Hz, 1H), 10.60 (s, 1H), 10.70 (s, 1H); MS (ES) *m*/*z* 621.0 (MH^+); HRMS calcd for $C_{30}H_{33}N_6O_5S_2$ (MH^+): 621.1954; found: 621.1952.

***N*-{4-[4-({(2S)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy propyl}amino)-1-piperidinyl]phenyl}-3,4-dimethoxybenzenesulfonamide (31e).** Method B: **27e** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one,[15] gray solid, 5% yield: ^{1}H NMR (DMSO-d_6) δ 1.49–1.55 (m, 2H), 1.99–2.17 (m, 2H), 2.58–2.65 (m, 2H), 2.85–2.98 (m, 2H), 3.07–3.09 (m, 2H), 3.59–3.63 (m, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 4.01 (s, 3H), 5.35 (brs, 1H), 6.57–6.64 (m, 2H), 6.79–6.92 (m, 5H), 7.01–7.04 (d, J = 8.4 Hz, 1H), 7.18–7.25 (m, 2H), 8.18 (s, 1H), 9.62 (brs, 1H), 10.61 (s, 1H), 10.72 (s, 1H); MS (ES) *m*/*z* 598.1 (MH^+); HRMS calcd for $C_{29}H_{36}N_5O_7S$: 598.2335; found: 598.2348. HPLC purity 98% at 15.4 min.

***N*-{4-[4-({(2*S*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl} amino)-1-piperidinyl]phenyl}-1-butanesulfonamide (31f).** Method A: **27f** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2H-benzimidazol-2-one,[15] off-white solid, 12% yield: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 7.2 Hz, 3H), 1.20–1.70 (m, 6H), 1.95–2.10 (m, 2H), 2.67 (brt, J = 11.7 Hz, 2H), 2.70–3.20 (m, 7H), 3.62–3.75 (m, 2H), 3.95–4.10 (m, 3H), 6.59 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.80–7.00 (m, 3H), 7.06 (d, J = 9.0 Hz, 2H), 9.32 (brs, 1H), 10.61 (brs, 1H), 10.73 (brs, 1H); MS (ES) *m*/*z* 518.1 (MH^+); HRMS calcd for $C_{25}H_{36}N_5O_5S$ (MH^+): 518.2437; found: 518.2452. HPLC purity 99% at 2.3 min.

***N*-{4-[4-({(2*S*)-2-Hydroxy-3-[(2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)oxy]propyl} amino)-1-piperidinyl]phenyl}-1-octanesulfonamide (31g).** Method A: **27g** and (*S*)-4-[2-hydroxy-3-aminopropoxy]-1,3-dihydro-2H-benzimidazol-2-one,[15] off-white solid, 59% yield: ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7.0 Hz, 3H), 1.10–1.40 (m, 10H), 1.50–1.70 (m, 4H), 1.95–2.16 (m, 2H), 2.67 (brt, J = 11.1 Hz, 2H), 2.93 (brt, J = 7.9 Hz, 2H), 2.95–3.20 (m, 3H), 3.62–3.75 (m, 2H), 4.00–4.12 (m, 2H), 4.12–4.30 (m, 1H), 6.59 (d, J = 7.8 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.80–7.00 (m, 3H), 7.07 (d, J = 9.0 Hz, 2H), 9.33 (brs, 1H), 10.60 (brs, 1H), 10.75 (brs, 1H); MS (ES) *m*/*z* 574.1 (MH^+); HRMS calcd for $C_{29}H_{44}N_5O_5S$ (MH^+): 574.3063; found: 574.3084. HPLC purity 99% at 22.3 min.

***N*-[4-({4-[4-({(2*S*)-2-Hydroxy-3-[(8-hydroxy-2-oxo-1,2,3,4-tetrahydro-5-quinolinyl) oxy]propyl}amino)-1-piperidinyl]-anilino}sulfonyl)phenyl]acetamide (32a).** Method A: **27a** and **11**, white solid, 40% yield: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.75–1.90 (m, 2H), 2.05 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 2.50–2.80 (m, 5H), 2.83 (t, J = 7.5 Hz, 2H), 3.40–3.55 (m, 2H), 3.70–3.85 (m, 3H), 6.44 (d, J = 8.7 Hz, 1H), 6.60 (d, J = 8.7 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 8.72 (s, 1H), 10.27 (s, 1H); MS (ES) *m*/*z* 623.9 (MH^+); HRMS calcd for $C_{31}H_{38}N_5O_7S$ (MH^+): 624.2492; found: 624.2469. HPLC purity 96% at 6.0 min.

4-{[(Hexylamino)carbonyl]amino}-*N*-{4-[4-({(2S)-2-hydroxy-3-[(8-hydroxy-2-oxo-1,2,3,4-tetrahydro-5-quinolinyl)oxy]propyl}amino)-1-piperidinyl]phenyl} benzenesulfonamide (32b). Method A: **27b** and **11**, white solid, 63% yield: ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 5.1 Hz, 3H), 1.20–1.35 (m, 8H), 1.35–1.50 (m, 2H), 1.75–1.90 (m, 2H), 2.39 (t, J = 5.1 Hz, 2H), 2.50–2.75 (m, 5H), 2.82 (t, J = 5.1 Hz, 2H), 3.05 (q, J = 5.1 Hz, 2H), 3.40–3.55 (m, 2H), 3.75–3.85 (m, 3H), 4.90 (brs, 1H), 6.30 (t, J = 5.1 Hz, 1H), 6.44 (d, J = 6.6 Hz, 1H), 6.59 (d, J = 6.6 Hz, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.85 (d, J = 6.9 Hz, 1H), 7.46 (d, J = 6.9 Hz, 2H), 7.50 (d, J = 6.9 Hz, 2H), 8.67 (s, 1H), 8.84 (s, 1H), 9.10 (brs, 1H), 9.50 (brs, 1H); MS (ES) *m*/*z* 709.2 (MH^+); HRMS calcd for $C_{36}H_{49}N_6O_7S$ (MH^+): 709.3383; found: 709.3391. HPLC purity 95% at 10.9 min.

***N*-{4-[4-({(2*S*)-2-Hydroxy-3-[(8-hydroxy-2-oxo-1,2,3,4-tetrahydro-5-quinolinyl) oxy]propyl}amino)-1-piperidinyl]phenyl}-3,4-dimethoxybenzenesulfonamide (32e).** Method A: **27e** and **11**, white solid, 46% yield: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.80–1.95 (m, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.50–2.75 (m, 5H), 2.82 (t, J = 7.2 Hz, 2H), 3.45–3.55 (m, 2H), 3.63 (s, 3H), 3.72 (s, 3H), 3.70–3.85 (m, 3H), 4.91 (brs, 1H), 6.44 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 9.1 Hz, 1H), 6.88 (d, J = 9.1 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.18 (dd, J = 8.5, 2.1 Hz, 1H), 7.36 (d, J = 2.1 Hz, 1H), 8.72 (s, 1H), 9.17 (brs, 1H); MS (ES) *m*/*z*: 627.1 (MH^+); HRMS calcd for $C_{31}H_{39}N_4O_8S$ (MH^+): 627.2489; found: 627.2458.

***N*-{4-[4-({(2*S*)-2-Hydroxy-3-[(8-hydroxy-2-oxo-1,2,3,4-tetrahydro-5-quinolinyl) oxy]propyl}amino)-1-piperidinyl]phenyl}-1-butanesulfonamide (32f).** Method A: **27f** and **11**, white solid, 31% yield: ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.3 Hz, 3H), 1.20–1.40 (m, 4H), 1.50–1.70 (m, 2H), 1.80–1.95 (m, 2H), 2.39 (t, J = 7.3 Hz, 2H), 2.50–2.80 (m, 5H), 2.85 (t, J = 7.3 Hz, 2H), 2.85–3.00 (m, 2H), 3.45–3.60 (m, 2H), 3.75–3.85 (m, 3H), 6.44 (d, J = 8.7 Hz, 1H), 6.60 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 8.74 (s, 1H); MS (ES) *m*/*z* 546.9 (MH^+); HRMS calcd for $C_{27}H_{39}N_4O_6S$ (MH^+): 547.2590; found: 547.2583.

***N*-(4-{[4-(4-{[(2*S*)-3-(9*H*-Carbazol-4-yloxy)-2-hydroxypropyl]amino}-1-piperidinyl) anilino]sulfonyl}phenyl)acetamide (33).** Method A: **27a** and (2*S*)-3-(9*H*-carbazol-4-yloxy)-2-hydroxy-propylamine,[13] yellowish solid, 5%

yield: ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 2H), 2.00–2.15 (m, 2H), 2.06 (s, 3H), 2.50–2.70 (m, 2H), 3.00–3.50 (m, 3H), 3.60–3.70 (m, 2H), 4.10–4.25 (m, 2H), 4.35–4.50 (m, 1H), 5.97 (brs, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 7.10–7.50 (m, 5H), 7.59 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 7.8 Hz, 1H), 9.71 (s, 1H), 10.40 (s, 1H), 11.32 (s, 1H); MS (ES) m/z 627.9 (MH^+); HRMS calcd for $C_{34}H_{38}N_5O_5S$ (MH^+): 628.2594; found: 628.2593.

***N*-(4-{4-[4-((2*R*)-2-Hydroxy-2-phenyl-ethylamino)-piperidin-1-yl]-phenylsulfamoyl}-phenyl)-acetamide (34).** Method A: **27a** and (1*R*)-2-amino-1-(3-chloro-phenyl)-ethanol, white solid, 59% yield: ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 2H), 2.06 (s, 3H), 2.00–2.15 (m, 2H), 2.50–3.20 (m, 5H), 3.55–3.70 (m, 2H), 4.90–5.00 (m, 1H), 6.00–6.20 (brs, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 7.25–7.52 (m, 5H), 7.59 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 10.41 (s, 1H); MS (ES) m/z 509.2 (MH^+); HRMS calcd for $C_{27}H_{33}N_4O_4S$ (MH^+): 509.2223; found: 509.2194.

***N*-[4-(4-{4-[2-Hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-piperidin-1-yl}-phenylsulfamoyl)-phenyl]-acetamide (35).** Method A: **27a** and DL-norphenylephrine, white solid, 36% yield: ^{1}H NMR (DMSO-d_6) δ 1.35–1.50 (m, 2H), 1.80–2.00 (m, 2H), 2.06 (s, 3H), 2.50–2.90 (m, 5H), 3.45–3.60 (m, 2H), 4.55–4.65 (m, 1H), 5.55 (brs, 1H), 6.60–6.70 (m, 1H), 6.70–6.85 (m, 4H), 6.86 (d, J = 9.3 Hz, 2H), 7.11 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 9.35 (s, 1H), 10.33 (s, 1H); MS (ES) m/z 525.4 (MH^+); HRMS calcd for $C_{27}H_{33}N_4O_5S$ (MH^+): 525.2172; found: 525.2177.

***N*-(4-{[4-(4-{[2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino}-1-piperidinyl)anilino] sulfonyl}phenyl)acetamide (36).** Method A: **27a** and DL-octopamine, white solid, 19% yield: ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 2H), 2.00–2.15 (m, 2H), 2.06 (s, 3H), 2.50–3.20 (m, 5H), 3.60–3.70 (m, 2H), 4.80–4.90 (m, 1H), 6.00 (brs, 1H), 6.76 (d, J = 9.7 Hz, 2H), 6.80 (d, J = 9.7 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 9.47 (s, 1H), 10.43 (s, 1H); MS (ES) m/z 525.3 (MH^+); HRMS calcd for $C_{27}H_{33}N_4O_5S$ (MH^+): 525.2172; found: 525.2178.

***N*-(4-{[4-(4-{[(2*R*)-2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl]amino}-1-piperidinyl) anilino]sulfonyl}phenyl)acetamide (37).** Method A: **27a** and L-norepinephrine, grey solid, 15% yield: ^{1}H NMR (DMSO-d_6) δ 1.50–1.72 (m, 2H), 1.95–2.10 (m, 2H), 2.06 (s, 3H), 2.50–3.20 (m, 5H), 3.55–3.70 (m, 2H), 4.05–4.20 (brs, 1H), 4.60–4.75 (m, 1H), 5.75–5.90 (brs, 1H), 6.60–6.90 (m, 7H), 7.59 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 8.93 (brs, 1H), 10.42 (s, 1H); MS (ES) m/z 541.6 (MH^+); HRMS calcd for $C_{27}H_{33}N_4O_6S$ (MH^+): 541.2121; found: 541.2133.

***N*-(4-{[4-(4-{[2-(2,4-Dihydroxyphenyl)-2-hydroxyethyl]-amino}-1-piperidinyl) anilino]sulfonyl}phenyl)acetamide (38).** Method A: **27a** and 2-amino-1-(2,4-dihydroxy-phenyl)-ethanol, pale yellowish solid, 45% yield: ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 2H), 1.95–2.15 (m, 2H), 2.08 (s, 3H), 2.50–3.20 (m, 5H), 3.60–3.70 (m, 2H), 5.04–5.10 (m, 1H), 6.65–6.75 (m, 1H), 6.24 (dd, J = 8.1, 2.1 Hz, 1H), 6.32 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 9.26 (s, 1H), 9.71 (brs, 1H), 10.44 (s, 1H); MS (ES) m/z 541.4 (MH^+); HRMS calcd for $C_{27}H_{33}N_4O_6S$ (MH^+): 541.2121; found: 541.2084.

***N*-(4-{[4-(4-{[2-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-ethyl]amino} - 1 - piperidinyl)anilino]sulfonyl}phenyl)acetamide (39).** Method A: **27a** and DL-normetanephrine, white solid, 87% yield: ^{1}H NMR (DMSO-d_6) δ 1.40–1.60 (m, 2H), 1.90–2.06 (m, 2H), 2.06 (s, 3H), 2.50–3.50 (m, 5H), 3.55–3.65 (m, 2H), 3.77 (s, 3H), 4.70–4.80 (m, 1H), 5.70–5.85 (brs, 1H), 6.70–6.90 (m, 7H), 7.59 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 8.95 (brs, 1H), 10.37 (s, 1H); MS (ES) m/z 555.2 (MH^+); HRMS calcd for $C_{28}H_{35}N_4O_6S$ (MH^+): 555.2277; found: 555.2265.

5-[2-({1-[4-({[4-(Acetylamino)phenyl]sulfonyl}amino)phenyl]-4-piperidinyl}amino)-1-hydroxyethyl]-1*H*-indole-7-carboxamide (40). Method A: **27a** and 5-(2-amino-1-hydroxy-ethyl)-1H-indole-7-carboxamide,[22] pale grey solid, 36% yield: ^{1}H NMR (DMSO-d_6) δ 1.60–1.80 (m, 2H), 2.00–2.15 (m, 2H), 2.06 (s, 3H), 2.50–2.70 (m, 2H), 3.10–3.20 (m, 3H), 3.60–3.75 (m, 2H), 4.95–5.05 (m, 1H), 6.13 (brs, 1H), 6.49 (t, J = 2.7 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.35 (t, J = 2.7 Hz, 1H), 7.42 (brs, 1 H), 7.59 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.77 (s, 1 H), 8.11 (s, 1H), 9.72 (s, 1H), 10.40 (s, 1H); MS (ES) m/z 591.1 (MH^+); HRMS calcd for $C_{30}H_{35}N_6O_5S$ (MH^+): 591.2390; found: 591.2392.

***N*-(4-{4-[4-(2-Hydroxy-2-pyridin-3-yl-ethylamino)-piperidin-1-yl]-phenylsulfamoyl}-phenyl)-acetamide (41).** Method A: **27a** and **14**, pale grey solid, 30% yield: ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (m, 2H), 2.07 (s, 3H), 2.00–2.20 (m, 2H), 2.50–3.20 (m, 5H), 3.55–3.70 (m, 2H), 5.10–5.21 (m, 1H), 6.30–6.40 (brs, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 7.45–7.50 (m, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 7.8 Hz, 1H), 8.45–8.65 (m, 2H), 10.47 (s, 1H); MS (ES) m/z 510.2 (MH^+); HRMS calcd for $C_{26}H_{32}N_5O_4S$ (MH^+): 510.2175; found: 510.2201. HPLC purity 94% at 9.2 min.

4-{[(Hexylamino)carbonyl]amino}-*N*-(4-{4-[(2-hydroxy-2 - {4 - hydroxy - 3 - [(methylsulfonyl)amino]phenyl}ethyl)-amino]-1-piperidinyl}phenyl) benzenesulfonamide (42b). Method A: **27b** and **17**, grey solid, 80% yield: ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 6.9 Hz, 3H), 1.20–1.80 (m, 10H), 1.95–2.15 (m, 2H), 2.50–2.70 (m, 3H), 2.95 (s, 3H), 3.00–3.20 (m, 4H), 3.65 (brd, J = 12.3 Hz, 2H), 4.80 (brd, J = 7.9 Hz, 1H), 5.90–6.10 (m, 1H), 6.48 (t, J = 5.6 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 6.91(d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 2.0 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 9.2 Hz, 2H), 7.51 (d, J = 9.2 Hz, 1H), 8.50–8.90 (brs, 1H), 9.39 (s, 1H), 9.61 (s, 1H); MS (ES) m/z 703.4

(MH^+); HRMS calcd for $C_{33}H_{47}N_6O_7S_2$ (MH^+): 703.2948; found: 703.2968.

4-[4-(3-Cyclopentyl-propyl)-5-oxo-4,5-dihydro-tetrazol-1-yl]-*N*-(4-{4-[2-hydroxy-2-(4-hydroxy-3-methanesulfonyl-amino-phenyl)-ethaylamino]-piperidin-1-yl}-phenyl)-benzenesulfonamide (42c). Method A: **27c** and **18**, grey solid, 46% yield: ^{1}H NMR (DMSO-d_6) δ 0.95–2.80 (m, 24H), 2.95 (s, 3H), 3.55–3.70 (m, 2H), 4.70–4.85 (m, 1H), 5.50–5.80 (m, 1H), 6.80–7.60 (m, 7H), 7.86 (d, J = 8.7 Hz, 2H), 8.07(d, J = 8.7 Hz, 2H); MS (ES) m/z 754.9 (MH^+); HRMS calcd for $C_{35}H_{47}N_8O_7S_2$ (MH^+): 755.3009; found: 755.2997.

***N*-(4-{4-[(2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)-amino]phenyl}ethyl)amino]-1-piperidinyl}phenyl)-5-(2-pyridinyl)-2-thiophenesulfonamide (42d).** Method B: **27d** and **18**, off-white solid, 47% yield: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.80–1.90 (m, 2H), 2.45–2.75 (m, 5H), 2.91 (s, 3H), 3.40–3.60 (m, 2H), 4.47 (dd, J = 8.0, 4.1 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 7.00 (dd, J = 8.3, 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 4.8, 1.7 Hz, 1H), 7.40 (d, J = 3.9 Hz, 1H), 7.75 (d, J = 3.9 Hz, 1H), 7.88 (dd, J = 8.0, 1.7 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.54 (brd, J = 4.8 Hz, 1H); MS (ES) m/z 644.1 (MH^+); HRMS calcd for $C_{29}H_{34}N_5O_6S_3$ (MH^+): 644.1671; found: 644.1663. HPLC purity 98% at 15.1 min.

***N*-(4-{4-[(2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)-amino]phenyl}ethyl)amino]-1-piperidinyl}phenyl)-3,4-dimethoxybenzenesulfonamide (42e).** Method B: **27e** and **18**, brown solid, 45%: ^{1}H NMR (DMSO-d_6) δ 1.50–1.59 (m, 2H), 1.95–2.05 (m, 2H), 2.54–2.62 (m, 2H), 2.72 (brs, 2H), 2.94 (s, 3H), 3.00–3.04 (m, 2H), 3.56 (brd, J = 12.0 Hz, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 4.10 (brs, 1H), 4.70 (brd, J = 7.8 Hz, 1H), 5.95 (brs, 1H), 6.81 (d, J = 9.09 Hz, 1H), 6.86–6.92 (m, 2H), 7.01–7.04 (m, 2H), 7.17–7.24 (m, 5H), 8.45 (brs, 1H), 9.16 (s, 1H); MS (ES) m/z 621.0 (MH^+); HRMS calcd for $C_{28}H_{37}N_4O_8S_2$ (MH^+): 621.2052; found: 621.2079. HPLC purity 99% at 2.1 min.

***N*-(4-{4-[(2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)-amino]phenyl}ethyl)amino]-1-piperidinyl}phenyl)-1-butanesulfonamide (42f).** Method A: **27f** and **17**, off-white solid, 71% yield: ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 7.2 Hz, 3H), 1.20–1.40 (m, 2H), 1.50–1.70 (m, 4H), 1.95–2.10 (m, 2H), 2.40–2.60 (m, 2H), 2.94 (s, 3H), 2.90–3.20 (m, 5H), 3.62–3.75 (m, 2H), 4.70–4.80 (m, 1H), 5.95 (brs, 1H), 6.85–6.95 (m, 3H), 7.00–7.10 (m, 3H), 7.24 (d, J = 2.0 Hz, 1H), 8.70 (brs, 1H), 9.33 (brs, 1H); MS (ES) m/z 541.0 (MH^+); HRMS calcd for $C_{24}H_{37}N_4O_6S_2$ (MH^+): 541.2155; found: 541.2161. HPLC purity 97% at 22.7 min.

***N*-(4-{4-[(2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)-amino]phenyl}ethyl)amino]-1-piperidinyl}phenyl)-1-octanesulfonamide (42g).** Method A: **27g** and **17**, off-white solid, 64% yield: ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.0 Hz, 3H), 1.15–1.40 (m, 12H), 1.50–1.70 (m, 2H), 1.80–1.95 (m, 2H), 2.50–2.92 (m, 7H), 3.50–3.65 (m, 2H), 4.49 (dd, J = 8.0, 4.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 7.00 (dd, J = 8.3, 2.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 2.0 Hz, 1H); MS (ES) m/z 597.1 (MH^+); HRMS calcd for $C_{28}H_{45}N_4O_6S_2$ (MH^+): 597.2781; found: 597.2776.

***N*-{4-[(4-{4-[((2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl) amino]-1-piperidinyl}anilino)sulfonyl]phenyl}acetamide (43a).** Method A: **27a** and **21**, off-white solid, 57% yield: ^{1}H NMR (DMSO-d_6) δ 1.40–1.70 (m, 2H), 1.90–2.10 (m, 2H), 2.06 (s, 3H), 2.50–2.65 (m, 2H), 2.90–3.15 (m, 3H), 2.94 (s, 3H), 3.55–3.70 (m, 2H), 4.65–4.80 (m, 1H), 6.79 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 1H), 7.06 (dd, J = 8.0, 1.2 Hz, 1H), 7.22 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 10.42 (s, 1H), 10.44 (s, 1H); MS (ES) m/z 618.0 (MH^+); HRMS calcd for $C_{28}H_{36}N_5O_7S_2$ (MH^+): 618.2056; found: 618.2056.

4-{[(Hexylamino)carbonyl]amino}-*N*-(4-{4-[((2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}-ethyl)amino]-1-piperidinyl}phenyl) benzenesulfonamide (43b). Method A: **27b** and **21**, grey solid, 27% yield: ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 6.9 Hz, 3H), 1.20–1.80 (m, 10H), 1.95–2.15 (m, 2H), 2.50–3.30 (m, 7H), 2.95 (s, 3H), 3.63 (brd, J = 12.0 Hz, 2H), 4.76 (brd, J = 7.8 Hz, 1H), 5.90–6.10 (m, 1H), 6.44 (t, J = 5.6 Hz, 1H), 6.83 (d, J = 9.1 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 6.91(d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 1.9 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 7.46(d, J = 9.2 Hz, 2H), 7.51 (d, J = 9.2 Hz, 1H), 9.10 (brs, 1H), 9.60 (s, 1H); MS (ES) m/z 703.4 (MH^+); HRMS calcd for $C_{33}H_{47}N_6O_7S_2$ (MH^+): 703.2948; found: 703.2946.

***N*-(4-{4-[((2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}phenyl)-3-pyridinesulfonamide (43h).** Method B: **27h** and **21**, yellow solid, 15% yield: ^{1}H NMR (DMSO-d_6) δ 1.25–1.45 (m, 2H), 1.80–1.95 (m, 2H), 2.50–2.80 (m, 5H), 2.92 (s, 3H), 3.40–3.55 (m, 2H), 4.45–4.60 (m, 1H), 6.85–6.90 (m, 5H), 7.02 (dd, J = 8.3, 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 7.4, 4.4 Hz, 1H), 7.95–8.05 (m, 2H), 8.70–8.80 (m, 2H); MS (ES) m/z: 561.95 (MH^+); HRMS calcd for $C_{25}H_{32}N_5O_6S_2$ (MH^+): 562.1788; found: 562.1774. HPLC purity 95% at 6.3 min.

4-[(4-{4-[((2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}anilino)sulfonyl]benzoic acid (43i). Method B: **27i** and **21**, white solid, 31% yield: ^{1}H NMR (DMSO-d_6) δ 1.35–1.50 (m, 2H), 1.75–2.00 (m, 2H), 2.50–2.95 (m, 5H), 2.92 (s, 3H), 3.45–3.60 (m, 2H), 4.60–4.70 (m, 1H), 6.77 (d, J = 9.3 Hz, 2H), 6.80–6.90 (m, 3H), 7.02 (dd, J = 8.4, 1.8 Hz, 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H); MS (ES) m/z 603.2 $(M-H)^-$; HRMS calcd for $C_{27}H_{31}N_4O_8S_2$ $(M-H)^-$: 603.1588; found: 603.1572. HPLC purity 97% at 9.4 min.

Ethyl 4-[(4-{4-[((2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}anilino)-

sulfonyl]benzoate (43j). Method B: **27j** and **21**, pale yellowish solid, 37% yield: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.75–1.90 (m, 2H), 2.50–2.70 (m, 5H), 2.91 (s, 3H), 3.40–3.55 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.47 (dd, J = 8.1, 4.2 Hz, 1H), 6.70–6.90 (m, 5H), 6.99 (dd, J = 8.3, 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2 H), 8.07 (d, J = 8.5 Hz, 2H); MS (ES) m/z 633.3 (MH^+); HRMS calcd for $C_{29}H_{37}N_4O_8S_2$ (MH^+): 633.2047; found: 633.2013. HPLC purity 98% at 9.0 min.

4-(4-{4-[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-methanesulfonylamino-phenyl)-ethylamino]-piperidin-1-yl}-phenylsulfamoyl)-phenoxy]-acetic acid (43k). The methyl ester of **43k** was prepared from the methyl ester of **27k** and **21** as described in Method B in 7% yield as an off-white solid: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.75–1.90 (m, 2H), 2.50–2.80 (m, 5H), 2.92 (s, 3H), 3.65–3.75 (m, 2H), 3.67 (s, 3H), 4.47 (dd, J = 8.0, 4.1 Hz, 1H), 4.87 (s, 2H), 6.50–6.90 (m, 8H), 7.17 (d, J = 1.8 Hz, 1H), 7.59 (d, J = 8.9 Hz, 2H); MS (ES) m/z 649.0 (MH^+); HRMS calcd for $C_{29}H_{37}N_4O_9S_2$ (MH^+): 649.2004; found: 649.2014.

The title acid was made from the above methyl ester according to Method C in 71% yield as a pale yellowish solid: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.75–1.90 (m, 2H), 2.50–2.85 (m, 5H), 3.30–3.50 (m, 2H), 3.69 (s, 3H), 3.80–4.05 (m, 3H), 4.87 (s, 2H), 6.56 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.65–6.90 (m, 5H), 7.02 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 10.60 (s, 1H), 10.75 (br s, 1H); MS (ES) m/z 626.1 (MH^+); HRMS calcd for $C_{30}H_{36}N_5O_8S$ (MH^+): 626.2285; found: 626.2298.

Methyl 3-[(4-{4-[((2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}-anilino)sulfonyl]-2-thiophenecarboxylate (43l). Method B: **27l** and **21**, pale yellowish solid, 50% yield: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.70–1.90 (m, 2H), 2.50–2.75 (m, 5H), 3.40–3.55 (m, 2H), 3.89 (s, 2H), 4.46 (dd, J = 8.0, 4.2 Hz, 1H), 6.75–6.85 (m, 3H), 6.90 (d, J = 9.0 Hz, 2H), 7.00 (dd, J = 8.3, 2.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H); MS (ES) m/z 624.9 (MH^+); HRMS calcd for $C_{26}H_{34}N_4O_8S_3$ (MH^+): 625.1455; found: 625.1441. HPLC purity 98% at 13.2 min.

3-[(4-{4-[((2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}anilino)sulfonyl]-2-thiophenecarboxylic acid (43m). Method C: from **43l**, pale grey solid, 54% yield: ^{1}H NMR (DMSO-d_6) δ 1.50–1.70 (m, 2H), 1.95–2.10 (m, 2H), 2.50–2.70 (m, 2H), 2.95 (s, 3H), 3.00–3.30 (m, 3H), 3.60–3.70 (m, 2H), 4.75–4.85 (m, 1H), 6.10 (brs, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.85–6.95 (m, 3H), 7.04 (d, J = 5.4 Hz, 1H), 7.08 (dd, J = 8.4, 1.8 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 5.4 Hz, 1H), 8.73 (brs, 1H), 9.96 (brs, 1H); MS (ES) m/z 610.7 (MH^+); HRMS calcd for $C_{25}H_{31}N_4O_8S_3$ (MH^+): 611.1299; found: 611.1284. HPLC purity 99% at 8.0 min.

Benzyl [(4-{4-[((2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}anilino)-sulfonyl]acetate (43n). Method B: **27n** and **21**, white solid, 47% yield: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 2H), 1.70–1.95 (m, 2H), 2.50–2.75 (m, 2H), 2.92 (s, 3H), 3.50–3.60 (m, 3H), 4.13 (s, 2H), 4.48 (dd, J = 8.0, 4.3 Hz, 1H), 5.15 (s, 2H), 6.82 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.00 (dd, J = 8.3, 2.0 Hz, 1H), 7.06 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 2.0 Hz, 1H), 7.30–7.40 (m, 5H); MS (ES) m/z 633.3 (MH^+); HRMS calcd for $C_{29}H_{37}N_4O_8S_2$ (MH^+): 633.2047; found: 633.2031.

[(4-{4-[((2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl) amino]-1-piperidinyl}anilino)sulfonyl]acetic acid (43o). Method A: **27n** and **21**, off-white solid, 6% yield: ^{1}H NMR (DMSO-d_6) δ 1.40–1.60 (m, 2H), 1.90–2.05 (m, 2H), 2.50–2.90 (m, 5H), 2.94 (s, 3H), 3.50–3.65 (m, 2H), 4.65–4.75 (m, 1H), 6.80–6.90 (m, 3H), 7.00–7.10 (m, 3H), 7.23 (d, J = 2.0Hz, 1H); MS (ES) m/z 543.3 (MH^+); HRMS calcd for $C_{29}H_{37}N_4O_8S_2$ (MH^+): 543.1578; found: 543.1572.

Butyl-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-phenyl]-amine (44). To a stirred mixture, under N_2 atmosphere, of the aniline **26** (free base) (11.46 g, 49 mmol), butyaldehyde (4.43 mL, 49 mmol) in THF (250 mL) was added $NaBH(OAc)_3$ (14.62 g, 68.6 mmol), and glacial acetic acid (2.82 mL, 49 mmol). The reaction was stirred for 2 h. The reaction was quenched with 1 N NaOH (50 mL), diluted with water, extracted with Et_2O three times and dried over Na_2SO_4. The product was purified by flash silica gel chromatography eluting with 1:1 EtOAc/hexanes to give the title compound as an oil (5.80 g, 41%). The compound was characterized as a diHCl salt: ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7.0 Hz, 3H), 1.25–1.45 (m, 2H), 1.50–1.75 (m, 2H), 1.90–2.10 (m, 4H), 3.11 (t, J = 8.0 Hz, 2H), 3.35–3.50 (m, 4H), 3.95 (s, 4H), 6.90–7.20 (m, 2H), 7.20–7.60 (m, 3H); MS (ES) m/z 291.1 (MH^+); HRMS calcd for $C_{17}H_{27}N_2O_2$ (MH^+): 291.2067; found: 291.2065. Anal. calcd for $C_{17}H_{26}N_2O_2 \cdot 2HCl$: C, 56.20; H, 7.77; N, 7.71; found: C, 56.05; H, 7.52; N, 7.53.

1-[4-(Butylamino)phenyl]-4-piperidinone (45). A solution of **44** (5.80 g, 19.9) in a 1:1 mixture of perchloric acid/HCl (100 mL) was stirred at rt for three days. The reaction mixture was poured onto ice and made basic with concentrated NH_4OH, extracted with Et_2O four times, dried over Na_2SO_4 and concentrated to give a yellow oil. The yellowish oil was purified by flash silica gel chromatography eluting with 1:1 EtOAc/hexanes to give the title compound as oil (3.84 g, 82%). The compound was characterized as a diHCl salt: ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 7.0 Hz, 3H), 1.25–1.40 (m, 2H), 1.55–1.70 (m, 2H), 2.50 (t, J = 4.4 Hz, 4H), 3.16 (t, J = 5.8 Hz, 2H), 3.67 (t, J = 4.4 Hz, 4H), 7.17 (d, J = 6.3 Hz, 2H), 7.37 (d, J = 6.3 Hz, 2H), MS (ES) m/z 247.1 (MH^+); HRMS calcd for $C_{15}H_{23}N_2O_2$ (MH^+): 247.1805; found: 247.1800. Anal. calcd for $C_{15}H_{22}N_2O_2 \cdot 2HCl \cdot 0.45H_2O$: C, 55.04; H, 7.67; N, 8.56; found: C, 55.10; H, 7.45; N, 8.38.

Benzyl [(butyl-4-{4-[((2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino] phenyl}ethyl)amino]-1-piperidinyl}anilino)sulfonyl]acetate (47). To a stirred mixture of **45** (1.39 g, 5.6 mmol) in 100 mL of CH_2Cl_2, and benzyloxycarbonylmethylsulfonyl-chloride (1.39 g, 5.6 mmol)[19] was added Et_3N (2.18 g, 22 mmol) dropwise. After being stirred for 18 h the reaction mixture was washed with diluted HCl and dried over Na_2SO_4. The product was purified by flash silica gel chromatography eluting with 2–10% MeOH/CH_2Cl_2 to give {butyl-[4-(4-oxo-piperidin-1-yl)-phenyl]-sulfamoyl}-acetic acid benzyl ester (**46**) as a yellow oil (0.5 g, 19%). The title benzyl ester was prepared from **21** and **46** as described in Method B in 35% yield as an off-white solid: ^{1}H NMR (DMSO-d_6) δ 0.79 (t, J = 7.2 Hz, 3H), 1.10–1.40 (m, 6H), 1.80–1.95 (m, 2H), 2.55–2.80 (m, 5H), 2.92 (s, 3H), 3.45 (t, J = 7.1 Hz, 2H), 4.24 (s, 2H), 4.49 (dd, J = 7.9, 4.2 Hz, 1H), 5.20 (s, 2H), 6.82 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 7.00 (dd, J = 8.2, 2.0 Hz, 1H), 7.10–7.20 (m, 3H), 7.30–7.45 (m, 5H); MS (ES) m/z 689.1 (MH^+); HRMS calcd for $C_{33}H_{45}N_4O_8S_2$ (MH^+): 689.2673; found: 689.2679.

[(Butyl-4-{4-[((2*R*)-2-hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl} ethyl)amino]-1-piperidinyl}anilino)sulfonyl]acetic acid (48). Method A: **21** and **46**, pale grey solid; 31% yield: ^{1}H NMR (DMSO-d_6) δ 0.79 (t, J = 7.1 Hz, 3H), 1.10–1.35 (m, 4H), 1.50–1.70 (m, 2H), 2.00–2.10 (m, 2H), 2.55–3.10 (m, 5H), 2.92 (s, 3H), 3.55–3.70 (m, 2H), 3.70–3.85 (m, 2H), 4.75–4.85 (m, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 7.08 (dd, J = 8.3, 2.0 Hz, 1H), 7.20–7.35 (m, 3H); MS (ES) m/z 597.1 $(M-H)^-$; HRMS calcd for $C_{26}H_{39}N_4O_8S_2$ (MH^+): 599.2204; found: 599.2218.

In vitro functional assays

CHO cells expressing either human β_1-, β_2-, or β_3-AR subtypes were used as previously described.[23] Clones expressing receptor levels of 70 to 110 fmols/mg protein were used in the assays. CHO cells were grown in 24-well tissue culture plates in Dulbecco's Modified Eagle Media (DMEM) with 10% Fetal bovine serum, MEM non-essential amino acids, Penicillin-Streptomycin and Geneticin. On the day of assay, growth medium was replaced with preincubation media (Dulbecco's Modified Eagle Media (Gibco, #1199-065) and incubated for 30 min at 37 °C. Preincubation medium was replaced with 0.2 mL treatment medium containing DMEM media containing 250 uM IBMX (isobutyl-1-methylxantine) plus 1 mM ascorbic acid with test compound dissolved in DMSO. Test compounds were tested over a concentration range of 10^{-9} M to 10^{-5} M for β_3-AR cells and 10^{-8} to 10^{-4} M for β_1 and β_2 -AR transfected cells. Isoproterenol (10^{-5} M) was used as an internal standard for comparison of activity. Cells were incubated at 37 °C on a rocker for 30 min with the β_3-AR cells and 15 min for β_1- and β_2-AR cells. Incubation was stopped with the addition of 0.2 N HCl and neutralized with 2.5 N NaOH. The plates, containing the cells and neutralized media, were stored at −20 °C until ready to assay for cAMP using the SPA assay kit (Amersham). Data collected from the SPA assay was analyzed as per cent of the maximal isoproterenol response at 10^{-5} M. Activity curves were plotted using the SAS statistical and graphics software. EC_{50} values were generated for each compound and the maximal response developed for each compound was compared to the maximal response of isoproternol at 10^{-5} M from the following formula:

intrinsic activity (IA) = % activity of compound divide by% activity of isoproterenol.

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References and Notes

1. (a) For recent reviews on β3-agonists see: Katsilambros, N. *Eur. J. Intern. Med.* **2000**, *11*, 65. (b) Weyer, C.; Gautier, J. F.; Danforth, E., Jr. *Diabetes Metab.* **1999**, *25*, 11. (c) Kordik, C. P.; Reitz, A. B. *J. Med. Chem.* **1999**, *42*, 181. (d) Weber, A. E. *Ann. Rep. Med. Chem.* **1998**, *33*, 193. (e) Dow, R. L. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1811. (f) Strosberg, A. D. *Annu. Rev. Pharmacol. Toxic.* **1997**, *37*, 421. (g) Arch, J. R. S.; Wilson, S. *Int. J. of Obesity* **1996**, *20*, 191. (h) Manara, L.; Croci, T.; Landi, M. *Fundam. Clin. Pharmacol.* **1995**, *9*, 332. (i) Arch, J. R. S.; Kaumann, A. J. *Med. Res. Rev.* **1993**, *6*, 663.
2. (a) Beeley, L. J.; Berge, J. M.; Chapman, H.; Dean, D. K.; Kelly, J.; Lowden, K.; Kotecha, N. R.; Morgan, H. K. A.; Rami, H. K.; Thompson, M.; Vong, A. K. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 219. (b) Shih, T. L.; Candelore, M. R.; Cascieri, M. A.; Chiu, S.-H. L.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Strader, C. D.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1251. (c) Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Tota, L.; Deng, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1107.
3. (a) Hu, B.; Ellingboe, J.; Han, S.; Largis, E.; Mulvey, R.; Oliphant, A.; Sum, F. W.; Tillett, J. *J. Med. Chem.* **2001**, *44*, 1456. (b) Sum, F. W.; Gilbert, A.; Venkatesan, A. M.; Lim, K.; Wong, V.; O'Dell, M.; Francisco, G.; Chen, Z.; Grosu, G.; Baker, J.; Ellingboe, J.; Malamas, M.; Gunawan, I.; Primeau, J.; Largis, E.; Steiner, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1921. (c) Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081.
4. (a) Fraeyman, N.; Van Ermen, A.; Van de Velde, E.; Vanscheeuwijck, P. *Biochem. Pharm.* **1992**, *44*, 2333. (b) Cantello, B. C. C.; Smith, S. A. *Drugs of the Future* **1991**, *16*, 797.
5. Liggett, S. *Mol. Pharmacol.* **1992**, *42*, 634.
6. (a) Walston, J.; Silver, K.; Bogadus, C.; Knowler, W. C.; Celi, F. S.; Austin, S.; Manning, B.; Strosberg, A. D.; Stern, M. P.; Raben, N.; Sorkin, J. D.; Roth, J.; Shuldiner, A. R. *N. Engl. J. Med.* **1995**, *333*, 343. (b) Yoshida, T.; Sakane, N. *Diabetes Front.* **1996**, *7*, 619.
7. (a) Mathvink, R. J.; Barritta, A. M.; Candelore, M. R.; Cascieri; M. A.; Deng, L.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *19*, 1869. (b) Mathvink, R. J.; Tolman, J. S.; Chitty, D.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; Deng,

L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *J. Med. Chem.* **2000**, *43*, 3882.

8. (a) Sennitt, M. V.; Kaumann, A. J.; Molenaar, P.; Beeley, L. J.; Young, P. W.; Kelly, J.; Chapman, H.; Henson, S. M.; Berge, J. M.; Dean, D. K.; Kotecha, N. R.; Morgan, H. K. A.; Rami, H. K.; Ward, R. W.; Thompson, M.; Wilson, S.; Smith, S. A.; Cawthorne, M. A.; Stock, M. J.; Arch, J. R. S. *J. Pharmacol. Exp. Ther.* **1998**, *285*, 1084. (b) Hoffstedt, J.; Loennqvist, F.; Shimizu, M.; Blaak, E.; Arner, P. *Int. J. Obes.* **1996**, *20*, 428.

9. (a) Guy, A.; Ferroud, D. C.; Garreay, R.; Godefroy-Falguieres A. *Synthesis*, 1992, 821 (b) Leclerc, G.; Bizec, J. C. *J. Med. Chem.* **1980**, *23*, 738. (c) Tominaga, M.; Ogawa, H.; Yo, E.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1987**, *35*, 3699. (d) For a preliminary account of synthesis of **11** and **21**, see: Hu, B.; Ellingboe, J.; Gunawan, I.; Han, S.; Largis, L.; Li, Z.; Malamas, M.; Mulvey, R.; Oliphant, A.; Sum, F.-W.; Tillett, J.; Wong, V. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 757.

10. Ribereau, P.; Queguiner, G. *Can. J. Chem.* **1983**, *61*, 334.

11. Washburn, W. N.; Girotra, R. N.; Sher, P. M.; Mikkilineni, A. B.; Poss, K. M.; Mathur, A.; Gavai, A.; Bisacchi, G. S. *European Patent 659737, 1995; Chem. Abstr.* **1995**, *124*, 8408.

12. Taylor, E. C.; Skotnicki, J. S. *Synthesis* 1981, 606.

13. Zheng, L.; Berridge, M. S.; Ernsberger, P. *J. Med. Chem.* **1994**, *37*, 3219.

14. Pascal, J. C.; Patmore, L.; Pfister, J.; Blondet, D.; Armstrong, J. M. *CEP 467325, 1992; Chem. Abstr.* **1992**, *116*, 255502.

15. Bell, M. G.; Crowell, T. A.; Matthews, D. P.; McDonald, J. H., III; Neel, D. A.; Shuker, A. J.; Winter, M. A. *U.S. Patent 708, 621, 1998;* Chem. Abstr. **1998**, *129*, 148910.

16. Sher, P. M.; Fisher, L. G.; Skwish, S.; Michel, I. M.; Seiler, S. M.; Washburn, W. N.; Dickinson, K. E. J. *Med. Chem. Res.* **1997**, *7*, 109.

17. To compare the β_3 activity and selectivity of **48** with similar compounds already reported for the sulfonamide-based agonsits, the activity of the literature lead compound, **4a** (L-770644), under our assay conditions, is incorporated into the data set (Table 6, Reported data[2b] for **4a**: β_3 $EC_{50} = 0.013\,\mu M$, IA = 0.75; β_2 $EC_{50} = 1.8\,\mu M$, IA = 0.26; β_1 $EC_{50} = 1.9\,\mu M$, IA = 0.33).

18. Kawashima, Y.; Sato, M.; Yamamoto, S.; Shimazaki, Y.; Chiba, Y.; Satake, M.; Iwata, C.; Hatayama, K. *Chem. Pharm. Bull.* **1995**, *43*, 1132.

19. Vanwetswinkel, S.; Fastrez, J.; Marchand-Brynaert, J. *J. Antibiot.* **1994**, *47*, 1041.

20. Ader, U.; Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 205.

21. (a) Carlsson, E. I.; Gustafsson, B. B. R.; Kallsson, B. I. M.; Mattsson, A. H. *EP 64487, 1982; Chem. Abstr.* **1982**, *98*, 160400. (b) Siegel, M. G.; Shuker, A. J.; Droste, C. A.; Hahn, P. J.; Jesudason, C. D.; Mcdonald, J. H., III; Matthews, D. P.; Rito, C. J.; Thorpe, A. J. *Mol. Diversity* **1998**, *3*, 113.

22. Asselin, A. A.; Humber, L. G.; Crosilla, D.; Oshiro, G.; Wojdan, A.; Grimes, D.; Heaslip, R. J.; Rimele, T. J.; Shaw, C. C. *J. Med. Chem.* **1986**, *296*, 1009.

23. (a) Frielle, T.; Collins, S.; Daniel, K. W.; Caron, M. G.; Lefkowitz, R. J.; Kobilka, B. K. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7920. (b) Kobilka, B. K.; Dixon, R. A.; Frielle, T.; Dohlman, H. G.; Bolanoski, M. A.; Sigal, I. S.; Yan-Feng, T. L.; Francke, U.; Caron, M. G.; Lefkowitz, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 46.