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# Synthesis and Structure−Activity Relationships of Long-acting $\beta_2$ Adrenergic Receptor Agonists Incorporating Metabolic Inactivation: An Antedrug Approach

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A series of saligenin $\beta_2$ adrenoceptor agonist antedrugs having high clearance were prepared by reacting a protected saligenin oxazolidinone with protected hydroxyethoxyalkoxyalkyl bromides, followed by removal of the hydroxy-protecting group, alkylation, and final deprotection. The compounds were screened for $\beta_2$, $\beta_1$, and $\beta_3$ agonist activity in CHO cells. The onset and duration of action in vitro of selected compounds were assessed on isolated superfused guinea pig trachea. Compound **13f** had high potency, selectivity, fast onset, and long duration of action in vitro and was found to have long duration in vivo, low oral bioavailability in the rat, and to be rapidly metabolized. Crystalline salts of **13f** (vilanterol) were identified that had suitable properties for inhaled administration. A proposed binding mode for **13f** to the $\beta_2$-receptor is presented.

## Introduction

Asthma is a common and chronic disease characterized by an increase in inflammatory cell population in the epithelium and submucosa of the airways.[1] There are two major components of asthma pathophysiology, airway inflammation and smooth muscle dysfunction, leading to two major categories of medicines used in asthma treatment: anti-inflammatories and bronchodilators. Inhaled corticosteroids are the mainstay anti-inflammatory treatment for asthma and $\beta_2$-agonists are the most effective bronchodilators, offering proven benefits in reducing the burden of this disease.[2,3] There are two classes of $\beta_2$-agonists: the short-acting (first generation) and the long-acting (second generation) agonists. The short-acting agonists, typified by salbutamol (**1**) (Chart 1), have a rapid onset of action and relieve symptoms for 3−6 h. The two currently prescribed inhaled long-acting $\beta_2$-agonists are salmeterol (**2**) and formoterol (**3**). Salmeterol xinafoate (1-hydroxy-2-naphthoic acid) salt, a racemic mixture, marketed by GlaxoSmithKline, has lower intrinsic activity than salbutamol and a delayed onset of action, but a duration of action of 12 h, which is independent of dose.[4,5] In contrast, formoterol fumarate salt, marketed by Novartis is a single racemic diastereoisomer (*RR*,*SS*), high intrinsic efficacy agonist with onset of action similar to salbutamol, and a dose dependent duration of action.[5,6] In the last 10 years, there has been great interest within the pharmaceutical industry in the discovery of a third generation once daily $\beta_2$ adrenoceptor agonist to be used as a part of a combination therapy for the treatment of asthma and chronic obstructive pulmonary disease (COPD[a]). Novartis has recently published data on their clinical candidate, indacaterol (**4**).[7] A review by Glossop and Price summarizes the progress up to 2006 made by other pharmaceutical companies in identifying inhaled $\beta_2$-agonists with extended duration of action.[8] More recently, the Pfizer group has published three communications describing their studies in identifying long-acting $\beta_2$-adrenoceptor agonists such as **5**−**7**.[9−11] We have just published our efforts in identifying the sulfonamide **8** as our own inhaled $\beta_2$-agonist development candidate, which is suitable for once-daily dosing.[12] Finally the Boehringer-Ingelheim group has published three communications on their benzo[1,4]oxazinone alternative phenethanolamine.[13−15] In this report, we outline our studies in identifying our second development candidate.

In the search for a once-daily $\beta_2$ agonist, candidates have been sought showing reduced systemic exposure/improved therapeutic index and/or an inherently longer duration of action at the $\beta_2$ adrenoceptor. Increasing the dose of a $\beta_2$-agonist would increase its duration of action but would also increase unwanted cardiac side effects arising from excessive systemic exposure. A major fraction of the dose (80−90%) of an inhaled drug is swallowed and liable to be absorbed from the gastrointestinal tract.[16] One approach to avoiding these consequences is to investigate structural features which may have the potential to minimize absorption, and this strategy was used in identifying our first candidate.[12] An alternative method to reducing systemic exposure would be the "antedrug" approach. The terms antedrug[17] or "soft drug"[18] were introduced to describe drugs which act topically at the site of application but that are transformed into inactive metabolites upon entry into the systemic circulation. Our group has reported on glucocorticoid

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[a] Abbreviations: CHO, Chinese hamster ovary; cAMP, adenosine 3′,5′-monophosphate; COPD, chronic obstructive pulmonary disease; DMA, dimethyl acetamide; MDCK MDR1, Madin−Darby canine kidney cells (MDCK)−multidrug resistance 1 (MDR1).

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**Chart 1.** Clinically Used $\beta_2$ Agonists and Recent Development Candidates

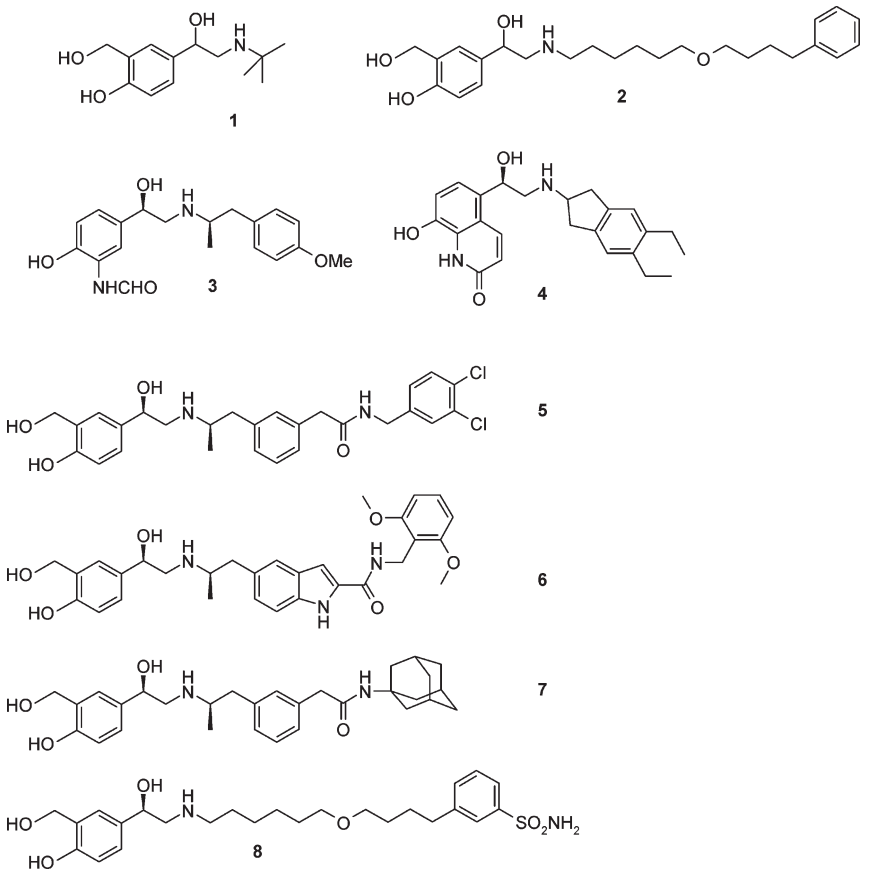
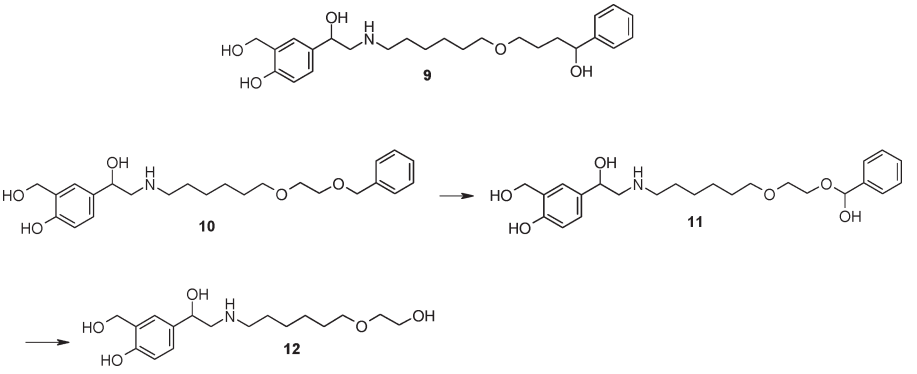


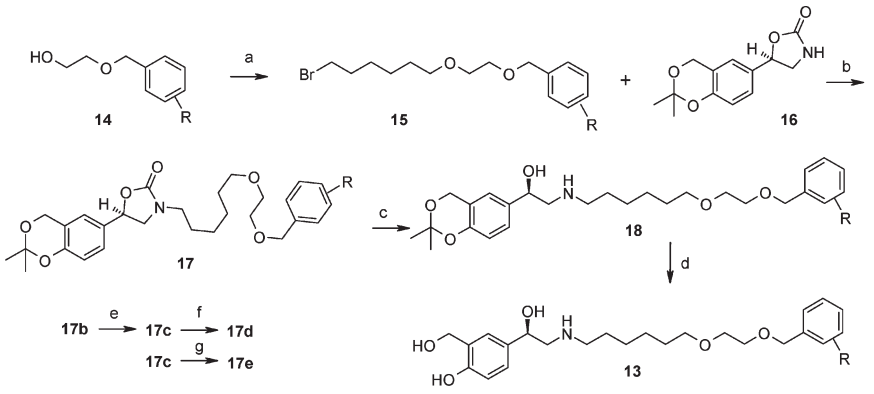

**Chart 2.** Hypothesis of Metabolic Inactivation of Salmeterol Analogues




antedrugs possessing a butyrolactone ring, which are rapidly hydrolyzed by paraoxonase on entry into the systemic circulation.[19−22] Salmeterol is metabolized in humans by benzylic hydroxylation, giving **9** (Chart 2).[23,24] We therefore decided to investigate alternative $\beta_2$ agonist structures which might produce a less active or inactive metabolite in addition to possessing the other requisite features of a long-acting $\beta_2$ agonist. The profile of the target molecule was a potent, homochiral, and selective $\beta_2$-agonist with intrinsic activity similar to that of salmeterol, long duration of action, with rapid metabolic inactivation, which might offer safe once-daily bronchodilation in the clinic. Our initial efforts involved replacement of the right-hand side phenyl ring of $\beta_2$ agonists with a $\gamma$-lactone moiety,[25] which would be expected to be rapidly hydrolyzed by paraoxonase on entry into the systemic circulation. Such analogues were found to have low efficacy. In a further approach, we investigated replacing a methylene group of the salmeterol chain with an oxygen atom, as for example in compound **10**. Assuming that benzylic hydroxylation is still the main route of metabolism, we postulated that the corresponding metabolite would be an unstable hemiacetal (**11**), which may cleave to the alcohol **12** and benzaldehyde (in the first instance). Analogues such as **12** might be less potent than **10**, whereas the smaller fragment would be expected to be either oxidized to benzoic acid, or reduced to benzyl alcohol, both of which are nontoxic and would be rapidly excreted.

The (*R*)-enantiomer of salmeterol is known to be the more potent isomer, so from the outset it was decided to prepare homochiral compounds with the (*R*)-configuration.[4] The optimal position of the ether oxygen in the chain of salmeterol for both potency and duration is six carbon atoms from the

**Scheme 1**[a]




**R =**

| | | | |
|---|---|---|---|
| **a** | -H | **h** | 3,5-dimethyl- |
| **b** | 3-$NO_2$ | **i** | 4-Me |
| **c** | 3-$NH_2$ | **j** | 4-Cl |
| **d** | 3-$NHCONH_2$ | **k** | 4-$SO_2NH_2$ |
| **e** | 3-$NHSO_2Me$ | **l** | 3-$SO_2NH_2$ |
| **f** | 2,6-dichloro- | **m** | 4-OH |
| **g** | 2,5-dichloro- | **n** | 3-OH |

[a] Reagents and conditions: (a) 1,6-dibromohexane (3 equiv), 50% aq NaOH (4.7 equiv), tetrabutylammonium bromide (0.02 equiv), 3 days, 63%; (b) NaH, DMF, 1.5 h, 73−82%; (c) $KOSiMe_3$ (4 equiv), THF, 80 °C, 3 h, 76−98%; (d) AcOH−water (2:1), 70 °C, 2 h, 36−95%; (e) $H_2$, $PtO_2$, EtOH, EtOAc, 2 h, 99%; (f) NaOCN, AcOH, water, 20 °C, 0.5 h, 38%; (g) MsCl, pyridine, 20 °C, 2 h, 77%.

basic nitrogen,[26] and confirmed by us with the related series of sulfonamide salmeterol analogues.[12] This part of the chain was therefore retained for our investigations.

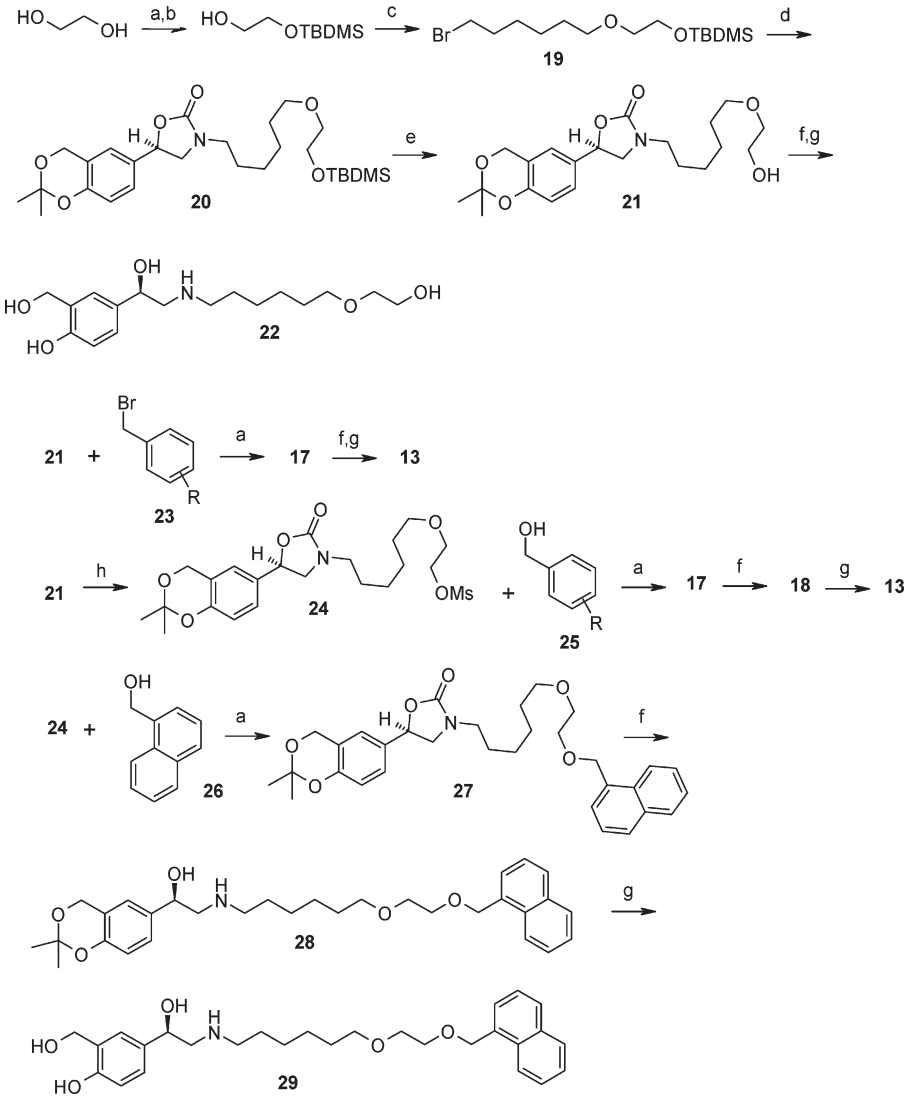
## Chemistry

The first target compound to test the metabolic inactivation hypothesis, but also for the retention of $\beta_2$ agonism, was **13a** (the *R*-enantiomer of **10**). This was prepared by first alkylating 2-benzyloxyethanol (**14a**) with excess 1,6-dibromohexane under phase transfer conditions, followed by reaction of the resulting bromide **15** with the homochiral (*R*)-oxazolidinone-protected saligenin **16**[27] in the presence of sodium hydride to give **17**. Deprotection of oxazolidinone **17** using the mild potassium trimethylsilanolate in THF conditions gave **18**,[27] which was further deprotected by aqueous acetic acid cleavage of the acetonide moiety to provide **13a** (Scheme 1).

The *meta*-nitro intermediate **17b** was also prepared by this approach. The nitro group of **17b** was reduced using hydrogen over $PtO_2$, the resulting aniline **17c** was then converted to the primary urea **17d** by treatment with acidic sodium cyanate, or to the methanesulfonamide **17e** by treatment with MsCl in pyridine. Finally **17d**,**e** were deprotected using KOTMS, followed by aqueous AcOH to give **13d**,**e**, respectively. In principle, most analogues could have been prepared by this linear approach, however, it was more efficient to use a convergent route, where a late-stage common intermediate was alkylated with a variety of substituted benzylic moieties, followed by deprotection as outlined in Scheme 2. Thus *tert*-butyl-dimethylsilyl monoprotected ethylene glycol was reacted with excess 1,6-dibromohexane under phase transfer conditions, and the resulting bromide **19** was further reacted with the anion of oxazolidinone **16** to provide **20**. The silyl protecting group was then removed using tetrabutylammonium fluoride, giving the common intermediate alcohol **21**. A sample of **21** was deprotected first with KOTMS in THF and then with aqueous AcOH to give the putative metabolite **22** [(*R*)-enantiomer of **12**]. Generally, alcohol **21** was either alkylated with benzyl bromides **23f**−**h** where available or it was converted into the mesylate **24** and then reacted with substituted benzyl alcohols **25i**−**n** (or protected derivatives thereof), giving ethers **17**. The latter were fully deprotected by the two-step procedure as before, giving the target compounds **13a**,**d**−**n**. The naphthyl derivative **29** was made in a similar way from **26** (Scheme 2).

Intermediate (aminosulfonyl)benzyl alcohols **25k**,**l** were prepared from (aminosulfonyl)benzoic acid **30k**,**l** respectively by borane−THF reduction (Scheme 3). Alcohol **25k**,**l** required further protection as the bis-SEM protected sulfonamide in order to block alkylation on the sulfonamide moiety. The target sulfonamide derivatives **13k**,**l** were obtained after alkylation with mesylate **24**, cleavage of oxazolidinone ring with

**Scheme 2**[a]




[a] Reagents and conditions: (a) NaH, DMF, 0.75 h; (b) TBDMS-Cl 0.75 h, 67%; (c) 1,6-dibromohexane (3 equiv), 50% aq NaOH (9.8 equiv), tetrabutylammonium bromide (0.02 equiv), 7 days, 90%; (d) **16**, NaH, DMF, 1.5 h, 61%; (e) TBAF-$SiO_2$, (2 equiv), THF, 2 h, 87%; (f) $KOSiMe_3$ (4 equiv), THF, 80 °C, 3 h, 80−97%; (g) AcOH−water (2:1), 70 °C, 0.5 h, 40−95%; (h) MsCl, $iPr_2NEt$, DCM, 91%.

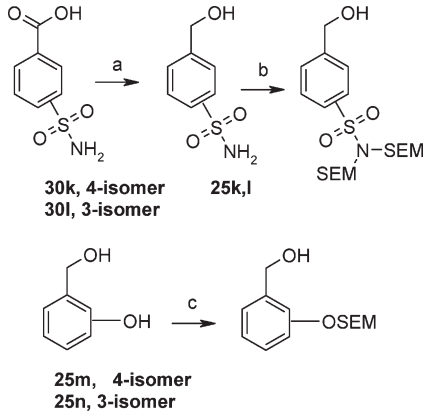
KOTMS, and final aqueous acetic acid deprotection, which removed the acetonide and SEM groups, although a longer heating time was required (Scheme 2). The commercially available hydroxybenzyl alcohols **25m**,**n** were selectively protected on the phenolic hydroxy group (Scheme 3) before they were reacted with mesylate **24** and deprotected to give **13m**,**n**.

## Results and Discussion

Compounds in Table 1 were tested for their ability to cause cyclic AMP accumulation in Chinese hamster ovary (CHO) cells transfected with human $\beta_1$, $\beta_2$, or $\beta_3$ adrenoceptors. Agonist activity was assessed by measuring changes in intracellular cyclic AMP, and the potency is reported in terms of $pEC_{50}$ (negative $\log_{10}$ molar concentration for half-maximal response) ± SEM. The efficacy of the test compounds was expressed as intrinsic activity (IA), which is defined as the maximal response of the test compound, relative to the maximum effect of the high intrinsic efficacy agonist isoprenaline. By definition, isoprenaline's intrinsic activity is 1. The IA for formoterol was 0.97, whereas that of salmeterol was 0.37. Preferred compounds had IA > 0.37. The $\beta_1$ adrenoceptors are found in heart tissue, and their activation causes tachycardia, whereas the $\beta_3$ adrenoceptors are found in adipose tissue and are thought to be involved in the regulation of lipid metabolism. Required selectivity for $\beta_2$ over $\beta_1$ and $\beta_3$ adrenoceptors was set as better than that of (*R*,*R*)-formoterol. All the compounds tested showed high affinity for the $\beta_2$ receptor (more potent than the standard, isoprenaline). It was important to find from the outset of the project whether the introduction of the second oxygen atom in the chain had a deleterious effect on the potency against the $\beta_2$ adrenoceptor. The salmeterol analogue **13a** was found to be less potent than salmeterol ($pEC_{50}$ at $\beta_2$ 8.6 vs 9.6), and this was also the case with the sulfonamide pair **13l** and **8** ($pEC_{50}$ at $\beta_2$ 8.8 vs 9.8). Despite the fact that there was a reduction by 10-fold in the potency, it was explored whether further substitution in the terminal phenyl ring might increase the potency and compensate for the loss. Indeed, compounds **29** and **13e**−**h** had the highest $\beta_2$ $pEC_{50}$ values. The most potent and selective analogues were **13f** and **29**, however, the latter was not as

selective for the $\beta_2$ receptor as **13f**. All test compounds in Table 1, except **13h**, had intrinsic activity higher than salmeterol (IA > 0.37). Microsomal instability of the compounds toward high first-pass metabolism in the liver was assessed by incubating samples with human liver microsomes ($P_{450}$ content = 125 pmol/mL) at a compound concentration of 5 $\mu$M for 30 min at 37 °C. Compound turnover was expressed as a ratio relative to the assay standard, verapamil, where verapamil has a turnover ratio of 1. Salmeterol, which had a slightly higher turnover ratio (1.2), was also included as a standard. The salmeterol analogue **13a** had a turnover ratio of 1.3, however, the analogue of **8**, **13l**, had a very low ratio and this is probably a reflection of its reduced lipophilicity. All the analogues prepared with lower clogP values showed lower turnover ratios, for example, the sulfonamide **13k**, reverse-sulfonamide **13e**, urea **13d**, and the two phenols **13m** and **13n**. Conversely, analogues with more lipophilic substituents were metabolized to a greater extent, for example, the 2,6-dichloro- (**13f**) and the naphthyl- (**29**) analogues. The putative metabolite alcohol **22** devoid of an aryl terminus was approximately 1000-fold less potent than **13a** at $\beta_2$. The human liver microsomal incubation of the dichloro-analogue **13f** was repeated on a larger scale, and the $\beta_2$ potency of the resulting mixture of metabolites was found to be very low. The main metabolite was isolated and confirmed to be the alcohol **22**. The metabolic leaving group, 2,6-dichlorobenzoic acid or 2,6-dichlorobenzyl

**Scheme 3**[a]




[a] Reagents and conditions: (a) $BH_3$-THF, 0−20 °C, 73−74%; (b) NaH (2.2 equiv), DMF, 20 °C, 0.25 h, then SEM chloride (2 equiv), 20 °C, 1 h, 38−61%; (c) NaH (1.1 equiv), DMF, 20 °C, 0.15 h, then SEM chloride (1 equiv), 20 °C, 2 h, 36−70%.

**Table 1.** Stimulation of cAMP Accumulation in CHO Cells Expressing Human $\beta_2$, $\beta_1$ and $\beta_3$ Adrenoceptors, Human Liver Microsomal Turnover Ratio against Verapamil, and clogP

| | compd | $\beta_2$[a] pEC$_{50}$ (n) | IA (L95%conf-U95% conf)[b] | $\beta_1$[a] pEC$_{50}$ (n) | $\beta_2-\beta_1$[c] | $\beta_3$[a] pEC$_{50}$ (n) | $\beta_2-\beta_3$[d] | Turnover ratio[e] | clogP |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **13a.AcOH** | 8.6 ± 0.1 (2) | 0.44 0.41−0.47 | 7.5 ± 0.1 (4) | 1.1 | 7.4 ± 0.1 (4) | 1.2 | 1.3 | 2.3 |
| 2 | **13d.AcOH** | 8.8 ± 0.1 (4) | 0.52 0.47−0.58 | 7.7 ± 0.1 (4) | 1.1 | 6.5 ± 0.1 (4) | 2.3 | 0.3 | 1.0 |
| 3 | **13e.AcOH** | 9.6 ± 0.5 (2) | 0.52 0.52−0.52 | 7.9 ± 0.1 (4) | 1.7 | 7.1 ± 0.0 (4) | 2.5 | 0.2 | 0.5 |
| 4 | **13f.AcOH** | 9.4 ± 0.0 (8) | 0.69 0.64−0.74 | 6.4 ± 0.1 (8) | 3.0 | 6.1 ± 0.2 (8) | 3.3 | 1.65 | 3.2 |
| 5 | **13g.AcOH** | 9.4 ± 0.1 (4) | 0.56 0.48−0.64 | 7.9 ± 0.1 (4) | 1.5 | 8.1 ± 0.0 (4) | 1.3 | ND | 3.5 |
| 6 | **13h.AcOH** | 9.4 ± 0.1 (4) | 0.37 0.30−0.45 | 8.1 ± 0.0 (4) | 1.3 | 8.3 ± 0.1 (4) | 1.1 | 1.1 | 3.4 |
| 7 | **13i.AcOH** | 8.6 ± 0.1 (2) | 0.42 0.38−0.46 | ND | | ND | | 1.0 | 2.8 |
| 8 | **13j.AcOH** | 8.6 ± 0.0 (2) | 0.43 0.40−0.46 | ND | | ND | | 1.0 | 2.9 |
| 9 | **13k** | 8.7 ± 0.1 (2) | 0.60 0.55−0.65 | 7.0 ± 0.1 (3) | 1.7 | 6.4 ± 0.1 (3) | 2.3 | 0.0 | 0.0 |
| 10 | **13l.AcOH** | 8.8 ± 0.0 (2) | 0.58 0.56−0.59 | 7.3 ± 0.0 (4) | 1.5 | 6.9 ± 0.0 (4) | 1.9 | 0.2 | 0.0 |
| 11 | **13m** | 8.1 ± 0.1 (4) | 0.41 0.33−0.49 | 7.1 ± 0.1 (4) | 1.0 | 7.2 ± 0.1 (4) | 0.9 | 0.4 | 1.6 |
| 12 | **13n.AcOH** | 9.1 ± 0.1 (2) | 0.66 0.61−0.71 | 7.7 ± 0.1 (4) | 1.4 | 7.5 ± 0.0 (4) | 1.6 | 0.3 | 1.8 |
| 12 | **29.AcOH** | 9.9 ± 0.0 (6) | 0.56 0.48−0.63 | 7.9 ± 0.1 (8) | 2.0 | 8.3 ± 0.1 (8) | 1.6 | 1.9 | 3.5 |
| 13 | **22.AcOH** | 5.6 ± 0.3 (7) | 0.62 0.52−0.73 | < 4.6 (10) | > 1.0 | 4.9 ± 0.3 (4) | 0.7 | | −0.5 |
| 14 | **8.cinnamate** | 9.8 ± 0.2 (4) | 0.54 0.50−0.59 | 6.5 ± 0.1 (4) | 3.3 | 5.8 ± 0.2 (4) | 4.0 | 0.9 | 1.2 |
| 15 | **2** | 9.6 ± 0.0 (929) | 0.37 0.36−0.38 | 6.1 ± 0.0 (656) | 3.5 | 5.9 ± 0.0 (849) | 3.7 | 1.2 | 3.0 |
| 16 | (*R*,*R*)-**3.fumarate** | 9.3 ± 0.0 (791) | 0.97 0.97−0.98 | 7.4 ± 0.0 (670) | 1.9 | 7.6 ± 0.0 (653) | 1.7 | ND | 1.3 |
| 17 | isoprenaline | 7.4 ± 0.0 (767) | 1.00 | 8.1 ± 0.0 (641) | −0.7 | 7.4 ± 0.0 (659) | 0.0 | | 0.15 |

[a] Human $\beta_1$, $\beta_2$, and $\beta_3$ 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. If $n < 3$, the range is quoted. [b] L95%conf = lower 95% confidence limit. U95%conf = upper 95% confidence limit. [c] Selectivity for $\beta_2$ over $\beta_1$ expressed as pEC$_{50}$ at $\beta_2$ receptor − pEC$_{50}$ at $\beta_1$. [d] Selectivity for $\beta_2$ over $\beta_3$ expressed as pEC$_{50}$ at $\beta_2$ receptor − pEC$_{50}$ at $\beta_3$. [e] Compound turnover in human liver microsomes expressed as a ratio ralative to verapamil, where verapamil has a turnover ratio of 1.

**Table 2.** Onset and Duration of Action of Selected Compounds on Electrically Stimulated Isolated Superfused Guinea Pig Trachea (Minimum $n = 2$)

| entry | compd | onset time (min) | shift (1 h) | shift (3 h) |
|---|---|---|---|---|
| 1 | **13a.AcOH** | 4.8 | 7.6 | 21 |
| 2 | **13f.AcOH** | 6.6 | 1.0 | 1.0 |
| 3 | **13 h.AcOH** | 6.9 | 2.2 | 2.4 |
| 4 | **29.AcOH** | 10.2 | 1.5 | 4.2 |
| 5 | **2** | 27.6 | 1.0 | 1.1 |
| 6 | (*R*,*R*)-**3.fumarate** | 10 | 20 | >1940 |

alcohol, are not reported to have any toxicological issues associated with them. The work describing the metabolite identification will be published elsewhere.[28]

The pharmacology of salmeterol assessed on isolated superfused guinea pig trachea strips correlates well with clinical data and gives a measurement of potency, efficacy, onset time, and duration of action.[29] Selected test compounds were therefore investigated for their ability to inhibit the contraction of electrically stimulated guinea pig trachea strips expressed as a measure of the functional response at the $\beta_2$ adrenoceptor. The onset time and duration of action in vitro of selected compounds were assessed on guinea pig isolated superfused trachea strips. Tissues were contracted electrically, different concentrations of agonist were perfused over the tissue until maximum relaxation was achieved, and onset of action was determined. Perfusion of the agonist was then ceased, tissue continued to be perfused with buffer and duration of action determined by the time taken for the contractile response to re-establish.

In Table 2, the onset time and duration after 1 and 3 h is presented. Onset of action was calculated as the time taken for an $EC_{50}$ concentration to achieve 50% maximum relaxant effect. Duration of action was determined by measuring the recovery of electrically induced contraction following washout of agonist. This was expressed as the rightward shift in the agonist concentration-effect curve following 60 and 180 min of washout ($EC_{50}$ for test compound after 60 or 180 min of washout/$EC_{50}$ at equilibrium, time 0 min). With this analysis, the greater the shift values the greater the recovery. Shift values of 1 (1 h) and 1 (3 h) indicate no washout (a salmeterol-like profile). Shift values of about 20 (1 h) and >300 (3 h) indicate slow continuous washout (formoterol-like profile). Shift values of infinity indicate rapid and complete washout (isoprenaline-like profile). All the test compounds in Table 2 exhibited onset times faster than salmeterol. Two lipophilic analogues, the 2,6-dichloro- (**13f**), and the 3,5-dimethyl-analogue (**13h**) indicated very little washout and thus would be expected to be long-acting bronchodilators.

On the basis of the data in Tables 1 and 2, the 2,6-dichloro analogue **13f**, which had high potency, fast onset, and long duration of action, and selectivity for $\beta_2$ over $\beta_1$ and $\beta_3$ receptors, was progressed to pharmacokinetic studies. The passive membrane permeability ($P_{exact}$) of **13f** across MDCKII-MDR1 cells in the presence of a potent P-glycoprotein inhibitor was measured as 34 nm $s^{-1}$, whereas salmeterol xinafoate was 119 nm $s^{-1}$. The in vitro metabolic stability of **13f** was measured as a ratio vs verapamil in human microsomes and was found to have higher turnover than salmeterol, which would suggest that any absorbed fraction of the dose would be rapidly metabolized. Pharmacokinetic studies in vivo with **13f** were initiated and compared with salmeterol xinafoate. The acetate salt of **13f** was dosed as a solution orally and intravenously to Han Wistar rats, and the data are presented in Table 3. High plasma clearance (123 mL/min/kg), a moderate volume of distribution (4.4 L/kg) and a short half-life (0.8 h) were obtained. Compound **13f** was not quantifiable in plasma at any time-point after oral dosing. A maximum oral AUC was assumed to be the lower limit of quantification (2 ng/mL), and the maximum oral bioavailability calculated was 5%, which is therefore likely to be an overestimate. This oral bioavailability was lower than that previously reported for salmeterol (10−12% in rat)[23] and strengthened the confidence that the swallowed fraction of the inhaled dose in humans would be unlikely to contribute to the systemic exposure of **13f.**

**Table 3.** Rat Pharmacokinetic Data for **13f** Acetate in the Han Wistar Rat[a]

| species | route | dose (mg/kg) | Clp (mL/min/kg) | Vdss (L/kg) | $T_{1/2}$ (h) | $C_{max}$ (ng/mL) | *F*% |
|---|---|---|---|---|---|---|---|
| rat | intravenous | 0.25 | 123 | 4.4 | 0.8 | | |
| | oral | 2 | | | | <2 | <5 |

[a] Clp = plasma clearance; Vdss = volume of distribution at steady state; *F*% = bioavailability.

A variety of salts of **13f** were prepared and examined for crystallinity, and two such salts were identified, the α-phenylcinnamate (mp 116−118 °C) and triphenylacetate (mp 132−134 °C).[30] The α-phenylcinnamic and triphenylacetic acids are not precedented in marketed inhaled products and therefore require further toxicological investigation. The α-phenylcinnamate salt (solubility 0.190 mg/mL at pH 7.4) and triphenylacetate salt (solubility 0.033 mg/mL at pH 7.4) were screened for stability in a range of humidity and thermal conditions, for lactose compatibility, for particle size after micronization, and were found to be suitable for inhaled development.

The acetate salt of **13f** was also investigated in vivo in histamine-induced bronchospasm in the guinea pig in a plethysmograph chamber (Buxco) and found to have similar potency to salmeterol ($EC_{90}$ 30 $\mu$M and 50 $\mu$M, respectively, nebulizer concentration). At an equi-effective ($EC_{90}$) dose, the duration of action of **13f** acetate (time to 50% recovery) was similar to that of salmeterol (10 h) when administered as a nebulized solution in a DMA/saline vehicle. Furthermore the duration of **13f** was extended to 17 h when the dose was increased to 10-fold the $EC_{90}$.[31] This data suggests that **13f** is a long-acting $\beta_2$ agonist in the guinea pig; prolonged bronchodilation over 24 h has now been demonstrated in asthmatic patients, suggesting the potential for once daily administration.[32]

Finally, the binding of **13f** to the receptor was examined by docking in our model and compared with **8**. This model was built several years ago, when this research work was underway, and well before the recent publication of the structure of the human $\beta_2$ receptor which was crystallized in a lipid environment when bound to the inverse agonist carazolol.[33−35] The model was superimposed and compared with the recent crystal structure for the $\beta_2$ receptor with carazolol bound (PDB ID 2rh1), and all the proposed interacting residues were similarly placed in the model and the crystal structure. The following interactions were clearly observed in the docking and were identical with those reported for **8**: Ser-207 was found to H-bond to the phenolic hydroxyl, while Ser-204 and Ser-203 were found to interact with the primary benzylic hydroxyl. A potential H-bonding interaction was identified between Asn-293 and the asymmetric benzylic hydroxyl, while Asp-113 and the amine were in proximity, allowing for a strong charge interaction. The middle ether oxygen in the chain was seen to

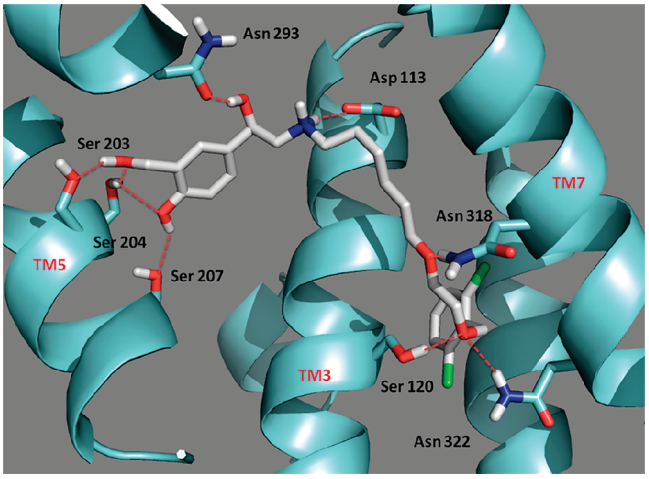



**Figure 1.** Postulated interactions of **13f** with the $\beta_2$ receptor, figure generated by PyMOL (The PyMOL Molecular Graphics System, Version 1.2b2, Schrodinger, LLC).

be positioned within H-bonding range of Asn-318 (TM7) while the benzylic ether oxygen was seen to be ideally situated to form H-bonds to both Ser-120 (TM3) and Asn-322 (TM7) (Figure 1). The latter two interactions are similar to those seen for the *meta*-sulfonamide group of **8**.

## Conclusion

A series of novel $\beta_2$ agonist antedrugs were synthesized. Incorporation of an oxygen atom at the homobenzylic position of the right-hand side phenyl ring of (*R*)-salmeterol has given a series of potent human $\beta_2$ adrenoceptor agonists that were rapidly metabolized by human liver microsomes. The 2,6-dichlorobenzyl analogue **13f** fulfilled all the criteria of potency, selectivity, rapid onset of action on guinea pig trachea, long duration of action, rapid turnover, and in vivo efficacy with a long duration that increased with increasing dose. The α-phenylcinnamate and triphenylacetate salts of **13f** were found to have suitable properties for inhaled administration and were therefore selected as candidates for further development. Further preclinical pharmacokinetic and metabolite identification[28] and additional pharmacological[31] data for **13f** will be reported elsewhere. Compound **13f.triphenylacetate** (vilanterol trifenatate) is currently undergoing clinical trials for the treatment of COPD and asthma, as a combination with fluticasone furoate, and the clinical data from these studies will be reported in due course.

## Experimental Section

Organic solutions were dried over anhydrous $Na_2SO_4$. TLC was performed on Merck 0.25 mm Kieselgel 60 $F_{254}$ plates. Products were visualized under UV light and/or by staining with aqueous $KMnO_4$ solution. LCMS analysis was conducted on a Supelcosil LCABZ+PLUS column (33 mm ×4.6 mm) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A) and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient 0−0.7 min 0% B, 0.7−4.2 min 100% B, 4.2−5.3 min 0% B, 5.3−5.5 min 0% B at a flow rate of 3 mL/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES +ve and ES −ve). Column chromatography was performed on Merck Kieselgel 60 (art. 9385), or Biotage prepacked silica gel cartridges containing KP-Sil run on a flash 12i chromatography module. $^1$H NMR spectra were recorded at 400 MHz unless otherwise stated. The chemical shifts are expressed in ppm relative to tetramethylsilane. High resolution positive ion mass spectra were acquired on a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer. The elemental composition was calculated using MassLynx v4.0 for the $[M + H]^+$. All separations for HRMS were achieved using a Phenomenex Luna C18(2) reversed phase column (150 mm × 2.1 mm, 3 $\mu$m particle size). Gradient elution was carried out with the mobile phases as (A) water containing 0.1% (v/v) formic acid and (B) MeCN containing 0.1% (v/v) formic acid. The conditions for the gradient elution were initially 0% B for 2 min, increasing linearly to 100% B over 25 min, remaining at 100% B for 2 min then decreasing linearly to 0% B over 0.5 min, followed by an equilibration period of 2.5 min prior to the next injection. The flow rate was 0.4 mL/min, temperature controlled at 25 °C with an injection volume of 5 $\mu$L. All compounds screened in the biological assays were either acetate salts or free-bases, which were gums (or glasses). Their purity was examined by LCMS analysis and was found to be ≥95%, unless otherwise specified. The purity of crystalline salts was additionally assessed by elemental microanalysis.

**General Procedure for the Preparation of 17 from 24 and Benzyl Alcohols 25.** Benzyl alcohol **25** (0.38 mmol) was stirred with sodium hydride (60% oil dispersion; 17 mg, 0.43 mmol) in DMF (1 mL) under nitrogen for 10 min at 20 °C and then **24** (120 mg, 0.25 mmol) in DMF (0.5 mL) was added. The mixture was stirred at 20 °C for 3 days and then phosphate buffer (pH 6.5, 15 mL) was added, followed by EtOAc (20 mL). The organic phase was washed with water (2 × 20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with EtOAc−cyclohexane (1:1) to give **17**:

**(5*R*)-3-{6-[(2-{[(2,6-Dichlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (17f).** MS ES +ve *m*/*z* 552/554 $(M + H)^+$. $^1$H NMR $\delta$ ($CDCl_3$) 7.31 (2H, d, *J* 8 Hz), 7.20−7.14 (1H, m), 7.12 (1H, dd, *J* 8, 2 Hz), 7.00 (1H, d, *J* 2 Hz), 6.83 (1H, d, *J* 8 Hz), 5.39 (1H, t, *J* 8 Hz), 4.84 (2H, s), 4.82 (2H, s), 3.85 (1H, t, *J* 8 Hz), 3.72−3.66 (2H, m), 3.63−3.57 (2H, m), 3.46 (2H, t, *J* 6 Hz), 3.42−3.20 (3H, m), 1.62−1.48 (10H, m), 1.43−1.27 (4H, m).

**General Two-Step Procedure for the Deprotection of 17. Step 1. Cleavage of Oxazolidinone Ring with KOTMS.** A solution of **17** (0.68 mmol) in THF (20 mL) was treated with potassium trimethylsilanolate (2.7 mmol), and the mixture was stirred at 80 °C under nitrogen for 3 h. The mixture was partitioned between EtOAc and pH 6.4 phosphate buffer, and the aqueous layer was extracted with more EtOAc. The combined organic layers were dried and evaporated under reduced pressure to give the expected product.

**(1*R*)-2-({6-[(2-{[(2,6-Dichlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}amino)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (18f).** MS ES +ve *m*/*z* 526/528 $(M + H)^+$. $^1$H NMR $\delta$ ($CDCl_3$) 7.30 (2H, d, *J* 8 Hz), 7.20−7.14 (1H, m), 7.12 (1H, dd, *J* 8, 2 Hz), 7.01 (1H, d, *J* 2 Hz), 6.78 (1H, d, *J* 8 Hz), 4.83 (2H, s), 4.82 (2H, s), 4.67−4.61 (1H, m), 3.72−3.67 (2H, m), 3.63−3.58 (2H, m), 3.46 (2H, t, *J* 6 Hz), 2.87 (1H, dd, *J* 12, 3 Hz), 2.74−2.58 (3H, m), 1.78 (2H, br), 1.60−1.46 (10H, m), 1.37−1.28 (4H, m).

**Step 2. Acidic Hydrolysis of Acetonide (and Concurrent Removal of Any Additional Acid-Labile Group).** The crude product from step 1 above (0.66 mmol) in acetic acid (12 mL) and water (6 mL) was heated at 70 °C for 2 h. The mixture was cooled to 20 °C, and the solvent was removed under reduced pressure. The residue was re-evaporated with MeOH (2 × 20 mL) to give **13.**

**2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-({2-[(phenylmethyl)-oxy]ethyl}oxy)hexyl]amino}ethyl)phenol (13a) acetate salt.** MS ES +ve *m*/*z* 418 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.44−7.28 (6H, m), 7.23 (1H, dd, *J* 8, 2 Hz), 6.85 (1H, d, *J* 8 Hz), 4.73 (2H, s), 4.61 (2H, s), 3.72−3.64 (4H, m), 3.56 (2H, t, *J* 6 Hz), 3.21−3.03 (4H, m), 1.99 (3H, s), 1.84−1.73 (2H, m), 1.72−1.63 (2H, m), 1.56−1.44 (4H, m). HRMS found: 418.2586 $C_{24}H_{36}NO_5$ requires 418.2588.

***N*-(3-{[(2-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)hexyl]oxy}ethyl)oxy]methyl}phenyl)urea (13d) Acetate salt.** MS ES +ve *m*/*z* 476 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.44 (1H, br s), 7.34 (1H, br s), 7.26−7.20 (2H, m), 7.16 (1H, dd, *J* 8, 2 Hz), 7.00 (1H, br s), 6.78 (1H, d, *J* 8 Hz), 4.65 (2H, s), 4.51 (2H, s), 3.66−3.57 (4H, m), 3.49 (2H, t, *J* 6 Hz), 3.11−3.04 (2H, m), 3.04−2.95 (2H, m), 1.93 (3H, s), 1.74−1.65 (2H, m), 1.64−1.56 (2H, m), 1.48−1.36 (4H, m).

***N*-(3-{[(2-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]-ethyl}amino)hexyl]oxy}ethyl)oxy]methyl}phenyl)methanesulfonamide Acetate Salt (13e).** MS ES +ve *m*/*z* 511 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.49−7.41 (3H, m),7.32−7.23 (3H, m), 6.92 (1H, d, *J* 8 Hz), 4.79 (2H, s), 4.67 (2H, s), 3.80−3.72 (4H, m), 3.64 (2H, t, *J* 6 Hz), 3.29−3.20 (2H, m), 3.20−3.11 (2H, m), 3.08 (3H, s), 2.08 (3H, s), 1.89−1.79 (2H, m), 1.79−1.70 (2H, m), 1.61−1.52 (4H, m). HRMS found: 511.24708 $C_{25}H_{39}N_2O_7S$ requires 511.24725.

**4-[(1*R*)-2-({6-[(2-{[(2,6-Dichlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}-amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (13f) Acetate Salt.** MS ES +ve *m*/*z* 486/488 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.42−7.25 (4H, m), 7.16 (1H, dd, *J* 8, 2 Hz), 6.78 (1H, d, *J* 8 Hz), 4.82 (2H, s) 4.65 (2H, s), 3.72−3.64 (2H, m), 3.63−3.54 (2H, m), 3.48 (2H, t, *J* 6 Hz), 3.14−2.95 (4H, m), 1.93 (3H, s), 1.77−1.64 (2H, m), 1.64−1.52 (2H, m), 1.47−1.34 (4H, m). HRMS found: 486.1806 $C_{24}H_{34}Cl_2NO_5$ requires 486.1809.

**4-[(1*R*)-2-({6-[(2-{[(2,6-Dichlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}-amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (13f) Triphenylacetate Salt.** Triphenylacetic acid (1.81 g, 6.28 mmol) was added to a solution of 4-((*R*)-2-{6-[2-(2,6-dichlorobenzyl-oxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxymethyl-phenol (95% pure; 3.28 g, 6.41 mmol) in EtOH (20 mL), and the mixture heated to 80 °C to obtain a solution. The mixture was allowed to cool to ambient temperature, and the resulting product filtered, washed with a little ethanol, then dried in vacuo at 50 °C to afford **13f**-triphenylacetate salt (4.3 g, 88%) as a white crystalline solid: mp (DSC) 131.9−134.2 °C, $[\alpha]_D^{20}$ −14.6 (*c* 1.034 in MeOH). MS ES +ve *m*/*z* 289, 486/488 $(M + H)^+$. $^1$H NMR $\delta$ (500 MHz, $CD_3OD$) 7.47 (2H, m), 7.38 (8H, m), 7.28 (6H, tt, *J* 7.1, 1.8 Hz), 7.22 (4H, m), 6.86 (1H, d, *J* 7.9 Hz), 4.94 (1H, dd, *J* 9.7, 4.6 Hz), 4.91 (2H, s), 4.74 (2H, s), 3.79 (2H, m), 3.69 (2H, m), 3.56 (2H, t, *J* 6.1 Hz), 3.10 (2H, m), 2.99 (2H, m), 1.72 (2H, m), 1.65 (2H, m), 1.45 (4H, m). $^{13}$C NMR $\delta$ (125 MHz, $CD_3OD$) 180.1, 156.2, 147.7, 140.3, 137.9, 134.5, 133.0, 131.9, 131.6, 129.6, 128.9, 128.1, 127.1, 127.0, 126.7, 116.0, 72.1, 71.4, 71.3, 71.1, 70.1, 68.4, 60.9, 55.4, 48.9, 30.5, 27.4, 27.1, 26.8. Anal. found: C, H, N, Cl.

**4-[(1*R*)-2-({6-[(2-{[(2,6-Dichlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}-amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol (13f) α-Phenylcinnamate Salt.** α-Phenylcinnamic acid (249 mg, 1.1 mmol) was added to a solution of 4-((*R*)-2-{6-[2-(2,6-dichloro-benzyloxy)-ethoxy]-hexylamino}-1-hydroxyethyl)-2-hydroxy-methyl-phenol (540 mg, 1.1 mmol) in isopropyl alcohol (5 mL). The solution was seeded with product and allowed to stir at ambient temperature for 20 h. The product was filtered, washed with a little isopropyl alcohol, then dried in vacuo at 50 °C to afford **13f**-α-phenylcinnamate salt (0.56 g, 72%) as a crystalline white solid: mp (DSC) 116.1−117.9 °C, $[\alpha]_D^{20}$ −15.8 (*c* 1.172 in MeOH). MS ES +ve *m*/*z* 225, 486/488 $(M + H)^+$. $^1$H NMR $\delta$ (300 MHz, $CD_3OD$) 7.62 (1H, s), 7.48 (2H, m), 7.40 (5H, m), 7.26 (3H, m), 7.18 (3H, m), 7.08 (2H, m), 6.87 (1H, d, *J* 8.3 Hz), 4.94 (1H, dd, *J* 8.5, 5.7 Hz), 4.91 (2H, s), 4.74 (2H, s), 3.79 (2H, m), 3.69 (2H, m), 3.57 (2H, t, *J* 6.4 Hz), 3.14 (2H, m), 3.05 (2H, m), 1.77 (2H, m), 1.67 (2H, m), 1.48 (4H, m). $^{13}$C NMR $\delta$ (125 MHz, $CD_3OD$) 176.1, 156.2, 141.4, 140.3, 137.9, 137.6, 135.8, 134.5, 133.0, 131.6, 131.0, 130.9, 129.6, 129.3, 128.9, 128.6, 127.9, 127.0, 127.0, 72.0, 71.3, 71.1, 70.2, 68.4, 60.9, 55.4, 48.9, 30.4, 27.4, 27.1, 26.8. Anal. C, H, N, Cl.

**4-[(1*R*)-2-({6-[(2-{[(2,5-Dichlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}-amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol Acetate Salt (13g).** MS ES +ve *m*/*z* 486/488 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.57 (1H, d, *J* 2 Hz), 7.38−7.32 (2H, m), 7.27 (1H, dd, *J* 8, 2 Hz), 7.15 (1H, dd, *J* 8, 2 Hz), 6.78 (1H, d, *J* 8 Hz), 4.85 (1H, dd, *J* 9, 4 Hz), 4.65 (2H, s), 4.62 (2H, s), 3.75−3.69 (2H, m), 3.68−3.63 (2H, m), 3.52 (2H, t, *J* 6 Hz), 3.13−2.96 (4H, m), 1.92 (3H, s), 1.77−1.65 (2H, m), 1.65−1.58 (2H, m), 1.51−1.37 (4H, m).

**4-[(1*R*)-2-({6-[(2-{[(3,5-Dimethylphenyl)methyl]oxy}ethyl)oxy]-hexyl}-amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol Acetate Salt (13h).** MS ES +ve *m*/*z* 446 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.34 (1H, d, *J* 2 Hz) 7.15 (1H, dd, *J* 8, 2 Hz), 6.94 (2H, s), 6.91 (1H, s), 6.79 (1H, d, *J* 8 Hz), 4.85 (1H, dd, *J* 9, 4 Hz), 4.65 (2H, s), 4.45 (2H, s), 3.59 (4H, s), 3.48 (2H, t, *J* 6 Hz), 3.12−2.94 (4H, m), 2.28 (6H, s), 1.91 (3H, s), 1.76−1.65 (2H, m), 1.65−1.56 (2H, m), 1.50−1.36 (4H, m). HRMS, found: 446.2901 $C_{26}H_{40}Cl_2NO_5$ requires 446.2901.

**2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(2-{[(4-methyl-phenyl)methyl]oxy}ethyl)oxy]hexyl}amino)ethyl]phenol Acetate Salt (13i).** MS ES +ve *m*/*z* 432 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.34 (1H, d, *J* 2 Hz), 7.22 (2H, d, *J* 8 Hz), 7.18−7.11 (3H, m), 6.78 (1H, d, *J* 8 Hz), 4.86 (1H, dd, *J* 9, 4 Hz), 4.65 (2H, s) 4.49 (2H, s), 3.59 (4H, s), 3.48 (2H, t, *J* 6 Hz), 3.13−2.96 (4H, m), 2.31 (3H, s), 1.91 (3H, s), 1.76−1.65 (2H, m), 1.65−1.55 (2H, m), 1.47−1.36 (4H, m). HRMS found: 432.2743 $C_{25}H_{38}Cl_2NO_5$ requires 432.2744.

**4-[(1*R*)-2-({6-[(2-{[(4-Chlorophenyl)methyl]oxy}ethyl)oxy]-hexyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol Acetate Salt (13j).** MS ES +ve *m*/*z* 452/454 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.36−7.28 (5H, m), 7.16 (1H, dd, *J* 8, 2 Hz), 6.78 (1H, d, *J* 8 Hz), 4.82 (obscured by $CD_3OH$), 4.65 (2H, s), 4.52 (2H, s), 3.65−3.56 (4H, m), 3.49 (2H, t, *J* 6 Hz), 3.14−2.95 (4H, m), 1.92 (3H, s), 1.76−1.65 (2H, m), 1.64−1.55 (2H, m), 1.46−1.35 (4H, m). HRMS found: 452.2198 $C_{24}H_{35}ClNO_5$ requires 452.2198.

**4-{[(2-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]-ethyl}amino)hexyl]oxy}ethyl)oxy]methyl}benzenesulfonamide (13k).** MS ES +ve *m*/*z* 497 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.90 (2H, d, *J* 8 Hz), 7.56 (2H, d, *J* 8 Hz), 7.33 (1H, d, *J* 2 Hz), 7.15 (1H, dd, *J* 8, 2 Hz), 6.79 (1H, d, *J* 8 Hz), 4.78−4.73 (2H, m), 4.68 (2H, s), 4.67 (2H, s), 3.72−3.64 (4H, m), 3.52 (2H, t, *J* 6 Hz), 2.91−2.78 (2H, m), 2.76−2.65 (2H, m), 1.67−1.53 (4H, m), 1.48−1.34 (4H, m). HRMS found: 495.2154 $C_{24}H_{35}N_2O_7S$ requires 495.2165.

**3-{[(2-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]-ethyl}amino)hexyl]oxy}ethyl)oxy]methyl}benzenesulfonamide acetate salt (13l).** MS ES +ve *m*/*z* 497 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.93 (1H, s), 7.81 (1H, br d, *J* 8 Hz), 7.58−7.48 (2H, m), 7.36 (1H, d, *J* 2 Hz), 7.16 (1H, dd, *J* 8, 2 Hz), 6.79 (1H, d, *J* 8 Hz), 4.85 (1H, dd, *J* 9, 4 Hz), 4.65 (2H, s), 4.63 (2H, s), 3.70−3.61 (4H, m), 3.51 (2H, t, *J* 6 Hz), 3.15−2.98 (4H, m), 1.94 (3H, s), 1.76−1.66 (2H, m), 1.65−1.57 (2H, m), 1.48−1.37 (4H, m).

**4-[(1*R*)-1-Hydroxy-2-({6-[(2-{[(4-hydroxyphenyl)methyl]oxy}-ethyl)oxy]hexyl}amino)ethyl]-2-(hydroxymethyl)phenol (13m).** MS ES +ve *m*/*z* 434 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.30 (1H, d, *J* 2 Hz), 7.18 (2H, d, *J* 8 Hz), 7.12 (1H, dd, *J* 8, 2 Hz), 6.79−6.73 (3H, m), 4.71 (1H, dd, *J* 9, 4 Hz), 4.66 (2H, s), 4.45 (2H, s), 3.59 (4H, s), 3.47 (2H, t, *J* 6 Hz), 2.85−2.59 (4H, m), 1.63−1.50 (4H, m), 1.43−1.32 (4H, m).

**4-[(1*R*)-1-Hydroxy-2-({6-[(2-{[(3-hydroxyphenyl)methyl]oxy}-ethyl)oxy]-hexyl}amino)ethyl]-2-(hydroxymethyl)phenol Acetate Salt (13n).** MS ES +ve *m*/*z* 434 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.34 (1H, d, *J* 2 Hz), 7.18−7.10 (2H, m), 6.81−6.76 (3H, m), 6.69 (1H, d, *J* 8 Hz), 4.85 (1H, dd, *J* 9, 4 Hz), 4.65 (2H, s), 4.47 (2H, s), 3.60 (4H, s), 3.49 (2H, t, *J* 6 Hz), 3.14−2.97 (4H, m), 1.94 (3H, s), 1.76−1.65 (2H, m), 1.64−1.56 (2H, m), 1.49−1.37 (4H, m). HRMS found: 434.2536 $C_{24}H_{36}NO_6$ requires 434.2537.

**2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-({2-[(1-naphthalenyl-methyl)oxy]ethyl}oxy)hexyl]amino}ethyl)phenol Acetate Salt (29).** MS ES +ve *m*/*z* 468 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 8.14 (1H, br d, *J* 8 Hz), 7.86 (1H, dd, *J* 8, 2 Hz), 7.81 (1H, d, J 8 Hz), 7.54−7.45 (3H, m), 7.44−7.39 (1H, m), 7.33 (1H, d, *J* 2 Hz), 7.14 (1H, dd, *J* 8, 2 Hz), 6.78 (1H, d, *J* 8 Hz), 4.99 (2H, s), 4.83 (1H, dd, *J* 8, 5 Hz), 4.65 (2H, s), 3.73−3.69 (2H, m), 3.63−3.60 (2H, m), 3.47 (2H, t, *J* 6 Hz), 3.14−2.89 (4H, m), 1.92 (3H, s), 1.69−1.62 (2H, m), 1.62−1.53 (2H, m), 1.43−1.35 (4H, m). HRMS found: 468.2744 $C_{28}H_{38}NO_5$ requires 468.2745.

**4-[(1*R*)-1-Hydroxy-2-({6-[(2-hydroxyethyl)oxy]hexyl}amino)-ethyl]-2-(hydroxymethyl)phenol (22) Acetate Salt.** MS ES +ve $m/z$ 328 $(M + H)^+$. $^1$H NMR $\delta$ ($CD_3OD$) 7.35 (1H, d, $J$ 2 Hz), 7.25−7.07 (5H, m), 6.79 (1H, d, $J$ 8 Hz), 4.65 (2H, s), 3.66 (2H, t, $J$ 5 Hz), 3.53−3.46 (4H, m), 3.15−2.98 (4H, m), 1.93 (3H, s), 1.78−1.66 (2H, m), 1.66−1.57 (2H, m), 1.49−1.36 (4H, m).

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**Supporting Information Available:** Preparative details and spectroscopic data for **14b**, **15a**, **15b**, **17a**−**e**, **19**, **17h**, **20**, **21**, **24**, **17**, **17g**, **25k**, **25l**, **25k-bisSEM**, **25l-bisSEM**, **25m-SEM**, **25n-SEM**, **17i**, **17j**, **17k-bisSEM**, **17l-bisSEM**, **17m-SEM**, **17n-SEM**, **27**, **18a**, **18d**, **18e**, **18g**, **18h**, **18i**, **18j**, **18k-bisSEM**, **18l-bisSEM**, **18m-SEM**, **18n-SEM**, **28**, biological screens, pharmacokinetic studies, cell permeability, table of LCMS purity, and retention times and microanalytical data on **13f.triphenylacetate** and **13f. α-phenylcinnamate**. This material is available free of charge via the Internet at http://pubs.acs.org.

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