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Design-driven LO: The discovery of new ultra long acting dibasic β_2-adrenoceptor agonists

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ABSTRACT

Starting with the molecular scaffold of the DA_2/β_2 dual agonist sibenadet (Viozan™), a number of molecular changes were incorporated, which were designed to increase the potency and selectivity of the target molecule, and improve its pharmacokinetics. Through this process a novel, high potency, full β_2-agonist with high selectivity and long duration capable of being dosed once daily has been discovered.

Inhaled β_2-agonists have formed the mainstay of asthma and COPD (chronic obstructive pulmonary disease) treatment for many years.[1] Treatment options were improved with the introduction of second generation long-acting β_2-agonists (LABA's). In particular, the inhaled combination of the long-acting β_2-agonist formoterol (**1**) with the steroid budesonide (Symbicort™) and the combination of the long-acting β_2-agonist salmeterol (**2**) with the steroid fluticasone (Seretide™) have provided enhanced benefit to patients in recent years.[2]

However, both aforementioned clinically used combinations contain LABA's which have insufficient duration for once-daily (uid) dosing, and need to be taken twice-daily (bid), which may mean that they deliver a sub-optimal bronchodilation effect to patients, while a bid dosing regime also introduces compliance difficulties. It has been proposed that an inhaled ultra long acting β_2-agonist (uLABA), capable of bringing optimal 24-h bronchodilation through a uid dosing regime, would be likely to improve patient outcomes.[3] Pharmaceutical companies have responded to this need by designing such uid uLABA's, and a variety of this work has recently been published.[4] Notably, the earliest of these uLABA's, indacaterol (**3**), has recently been accepted for registration in Europe.[5] and more lately two further clinical candidates vilanterol and olodaterol have also been described.[6] We wish to describe some of our own efforts in this area towards an inhaled uLABA, which has high efficacy with full agonism, with a formoterol-like fast-acting onset of action, the potential for a superior therapeutic index, and uid duration. The latter was driven by ensuring a sufficiently long terminal pharmacokinetic (PK) half-life in pre-clinical species and was achieved by a combination of reducing clearance and increasing distribution into lung tissue. Although ultimately targeted for lung delivery by inhalation, the compounds were dosed intravenously as in-house experience had shown that lung half-life correlated with plasma half-life.[7]

Our group has previously described the dual DA_2/β_2-agonist sibenadet (**4**) (Viozan™).[8] Since this compound had a safety profile commensurate with reaching phase III clinical trials, it was decided to use this scaffold as a starting point to search for a new ultra long acting β_2-agonist. To eliminate the DA_2 activity of sibenadet the ubiquitous chiral hydroxyl group, which was uniquely absent in sibenadet, was re-installed, and it was hoped that this would also ensure high agonist activity at the β_2-receptor. In practise, introduction of the hydroxyl group successfully gave compounds with

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excellent agonism, and reduced activity at the DA_2 receptor to produce high selectivity (see Supplementary data). However, this tactic also reduced β_1 selectivity such that it had to be re-optimised in this full agonist series. It is worth noting that initial β_2:β_1 selectivity was measured as β_2 functional potency versus β_1 binding potency (as shown in Tables 1–3). As binding potency is always greater than or equal to functional potency selectivity measured in this way approximates to the minimum value, and could be much higher if binding potency translates to reduced functional potency. In reality, when selectivity was later measured as a ratio of β_2:β_1 functional:functional potencies for selected compounds, the receptor selectivities were indeed similar (see Supplementary data). In addition, the chain sulphone group in sibenadet was replaced by a simple sulphide, thereby removing a major electron-withdrawing effect on the basic chain amino-group. Indeed the first molecule in this series, compound **5**, showed extremely high potency, and equivalent agonism to formoterol. However, this compound, and the analogous compounds **6** and **7** with subtle changes to the linking alkyl chain, all showed high rat hepatic turnover precluding in vivo PK testing. Compound **8** with a naphthyl group terminating the chain also had excellent potency and agonism, but, in spite of a somewhat lower rat hepatocyte turnover, when measured in vivo it had a mediocre intravenous (iv) half-life (3.6 h) as well as insufficient β_1-receptor selectivity.

To reduce the lipophilicity of compound **5**, the sulphide was replaced by an ether link to give compound **9**, and this had the desired effect of reducing both lipophilicity and hepatic turnover. Disappointingly, when this compound was measured in vivo the rat iv PK half-life was rather short (1.4 h), and in this series inclusion of naphthyl as in compound **10**, only gave increased rat hepatic turnover.

Since the hydroxyl benzothiazolone head group used as a catechol mimic in this series is more acidic than the more usual catechol mimic groups it was decided to incorporate a second basic group in the molecule with a view to increasing the volume of distribution and increasing the half-life. Replacing the distal O-atom in the chain by NH gave a dibasic β-agonist, compound **11**. Pleasingly this compound retained good potency and high agonism, and had low hepatic turnover. When dosed in vivo **11** had an encouraging rat iv PK half-life of >10 h, and also displayed excellent β_1-selectivity.

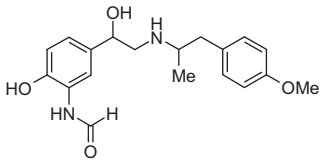
Compound **11** met all our criteria for a uid LABA at this stage. However, when tested in vivo in a guinea-pig model of duration this compound narrowly failed to show activity at 24 h. Since this guinea-pig model of duration showed excellent correlation with the duration of known β_2-agonists in man it was clear that this dibasic series could be optimised by increasing duration further.

It was rationalised that the improved duration of dibasic β_2-agonists was due to the increased volume of distribution (V_{ss}) obtained by incorporation of a second amino-group, but that this also had the effect of reducing the lipophilicity drastically (compare **5** with **11**), and so we reasoned that addition of lipophilic groups on the terminal phenyl would further increase V_{ss} and iv half-life.

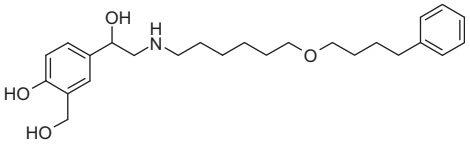
Addition of groups to the *para*-position (compounds **12** and **13**) reduced potency somewhat, and removed good β_1-selectivity. A *meta*-trifluoromethyl group (as in compound **14**) was also bad for β_1-selectivity, but a *meta*-chloro substituent (as in compound **15**) gave excellent potency and intrinsic activity, as well as increased lipophilicity, and still retained excellent rat hepatocyte stability. When tested in vivo compound **15** did indeed have an increased rat iv half-life, but at 34 h was, in fact, deemed too long. On the other hand the corresponding *ortho*-chloro analogue **16** showed equivalent potency, intrinsic activity and β_1-selectivity to **15**, but, due to a slightly higher rat hepatocyte turnover, **16** showed an intermediate rat iv half-life of almost 16 h, exactly as desired to predict excellent uid duration in man.

Addition of a second chloro-atom gave the dichloro-analogue **17**, which surprisingly retained good potency and agonism, but, presumably due to its higher lipophilicity, had increased rat hepatocyte turnover and a shorter rat iv PK half-life. Thus both unsubstituted phenyl and dichlorophenyl groups (compounds **11** and **17**)

Table 1
Known β_2-agonists



(1)



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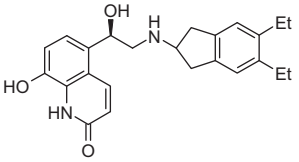

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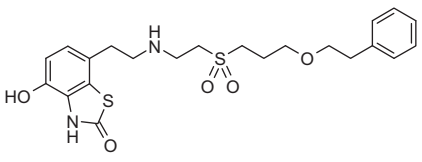
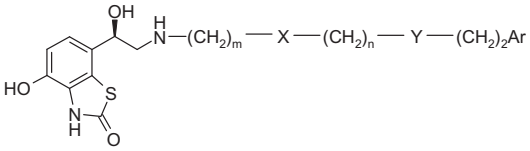


(4)

Compound	Name	β_2 potency[a] (IA[b]) pEC_{50}	log D[c]	Rat Hep[d]	Duration	β_1 binding (selectivity) pIC_{50} (ratio)
(**1**)	Formoterol	9.0 (1.0)	0.4	76	bid	<6.2 (>600)
(**2**)	Salmeterol	9.1 (0.55)	1.9	85	bid	6.3 (769)
(**3**)	Indacaterol	7.8 (0.9)	2.7	51	uid	6.5 (21)
(**4**)	Sibenadet	9.2 (0.7)	2.6	>117		<5 (>14,000)

[a] Stimulation of cAMP accumulation in H292 cells expressing human β_2, pEC_{50} is the negative logarithm of the molar drug concentration that produces a cAMP response equal to 50% of its maximum.
[b] IA is intrinsic activity measured as an agonist relative to formoterol (IA = 1).
[c,d] Log D and rat hepatic turnover measured as described in Supplementary data.

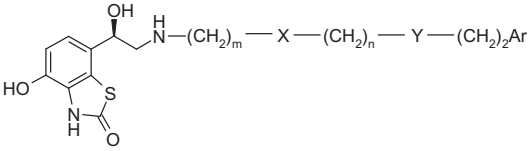
Table 2
β_2-Agonists with extended side-chains akin to sibenadet



Compound	*m*	X	*n*	Y	Ar	β_2 potency[a] (IA[b]) pEC_{50}	log *D*[c]	Rat Hep[d]	iv PK $t_{1/2}$ (h)	β_1 binding (selectivity) pIC_{50} (ratio)
(**4**) sibenadet	2	SO_2	3	O	Ph	9.2 (0.7)	2.6	>117		<5 (>14,000)
(**5**)	2	S	3	O	Ph	10.2 (1.0)	2.5	>150		8.1 (136)
(**6**)	3	S	2	O	Ph	10.1 (1.0)	2.3	>113		8.1 (108)
(**7**)	3	S	3	O	Ph	10.1 (0.9)	>2.5	96		8.4 (47)
(**8**)	3	S	2	O	1-Naphthyl	10.0 (1.0)	3.1	85	3.5	8.1 (76)
(**9**)	3	O	2	O	Ph	9.9 (0.9)	1.1	58	1.4	8.5 (27)
(**10**)	3	O	2	O	1-Naphthyl	9.9 (1.0)	2.3	118		8.5 (27)
(**11**)	2	S	3	NH	Ph	9.1 (0.9)	0.1	9	10.8	6.6 (307)

[a] Stimulation of cAMP accumulation in H292 cells expressing human β_2, pEC_{50} is the negative logarithm of the molar drug concentration that produces a cAMP response equal to 50% of its maximum.
[b] IA is intrinsic activity measured as an agonist relative to formoterol (IA = 1).
[c,d] Log *D* and rat hepatic turnover measured as described in Supplementary data.

Table 3
β_2-Agonists incorporating a second basic centre



Compound	*m*	X	*n*	Y	Ar	β_2 potency[a] (IA[b]) pEC_{50}	log *D*[c]	Rat Hep[d]	iv PK $t_{1/2}$ (h)	β_1 binding (selectivity) pIC_{50} (ratio)
(**11**)	2	S	3	NH	Ph	9.1 (0.9)	0.1	9	10.8	6.6 (307)
(**12**)	2	S	3	NH	4-Et Ph	8.4 (0.9)	0.9			7.3 (11)
(**13**)	2	S	3	NH	4-OEt Ph	7.9 (0.7)	0.4	8		6.9 (11)
(**14**)	2	S	3	NH	3-CF3 Ph	8.5 (0.8)	1.2	6		7.0 (32)
(**15**)	2	S	3	NH	3-Cl Ph	9.0 (0.8)	1.0	7	33.7	6.8 (183)
(**16**)	2	S	3	NH	2-Cl Ph	9.2 (0.8)	1.0	11	15.9	6.9 (187)
(**17**)	2	S	3	NH	2,3-diCl Ph	8.8 (0.9)	2.2	19	10.1	7.1 (62)
(**18**)	2	SO	3	NH	3-Cl Ph	8.3 (0.8)	0.2	7		6.8 (26)
(**19**)	2	SO_2	3	NH	3-Cl Ph	9.2 (1.0)				6.1 (1259)
(**20**)	2	O	3	NH	3-Cl Ph	9.3 (1.0)	0.8			7.0 (178)
(**21**)	3	S	2	NH	3-Cl Ph	8.9 (1.1)	1.1			6.9 (89)
(**22**)	3	S	2	NH	2-Cl Ph	9.4 (0.8)	1.0	12		7.4 (100)
(**23**)	3	S	2	NH	2,3-diCl Ph	8.8 (1.0)	1.7			7.1 (45)
(**24**)	3	O	2	NH	3-Cl Ph	9.7 (1.0)	0.0	<3		7.2 (45)
(**25**)	3	O	2	NH	2,3-diCl Ph	9.1 (0.9)	0.6	10		7.3 (63)
(**26**)	3	O	2	NMe	Ph	8.6 (0.9)				6.4 (150)

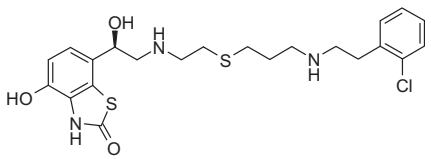
[a] Stimulation of cAMP accumulation in H292 cells expressing human β_2, pEC_{50} is the negative logarithm of the molar drug concentration that produces a cAMP response equal to 50% of its maximum.
[b] IA is intrinsic activity measured as an agonist relative to formoterol (IA = 1).
[c,d] Log *D* and rat hepatic turnover measured as described in Supplementary data.

have shorter iv PK half-lives than the intermediate monochloro compound **16**. This is likely due to opposing effects on volume of distribution and clearance.

With monochloro phenyl substitution appearing optimal we next examined other effects in the linking chain. Replacement of the S atom with SO or SO_2 reduced lipophilicity (compounds **18** and **19**). However, incorporation of a sulphoxide group reduces β_2-potency such that β_1-selectivity is eroded. In contrast sulphone **19** has excellent β_2-potency and reduced β_1-activity giving it the best selectivity in this series, however its very low lipophilicity made it unattractive, and this compound was not progressed. Replacement of the S-atom with an O-link gave compound **20**, whose profile was very similar to compound **16**.

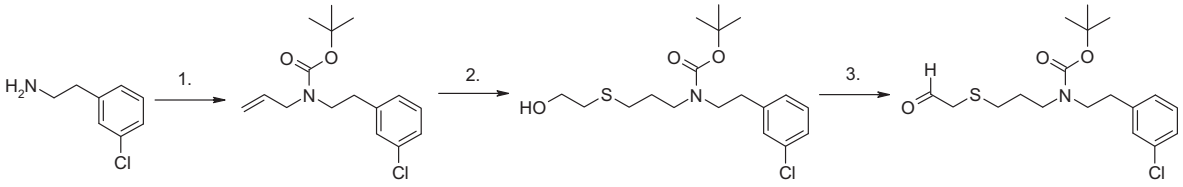
Moving the S-link along the chain by one atom to give an analogous series as in compounds **21**–**23** gave compounds with similar profile to compounds **15**–**17** but with reduced β_1-selectivity, while a similar reduction in β_1-selectivity is also observed by incorporation of an O-atom one atom further along the chain (compare **24** and **25** with **15** and **17**). Finally, methylating the linking second base N-atom, as in **26**, reduced both potency and β_1-selectivity.

From this series compound **16** appeared to have the optimal profile, and was chosen for further evaluation.

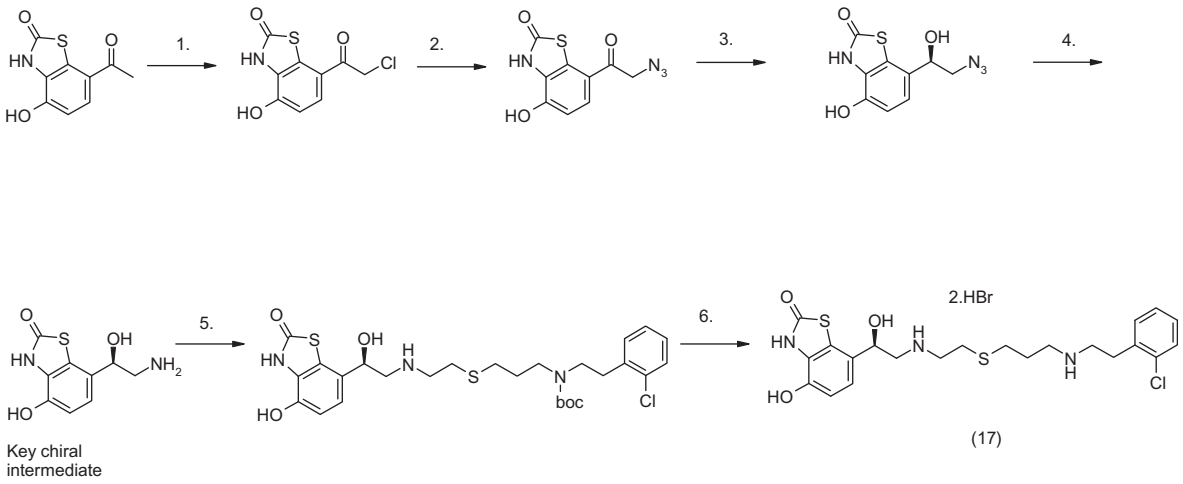


16

The synthetic sequence for compound **16** is shown below to illustrate the process for all analogues.[9]



Scheme 1. Reagents: (1) (a) Boc_2O, Et_3N, 100%; (b) NaH, allyl bromide, 64%; (2) 2-mercaptoethanol, AIBN, 81%; (3) sulphur trioxide–pyridine complex, 52%.



Scheme 2. Reagents: (1) chlorination, 95%; (2) NaN_3 88%; (3) B_2H_6, Corey's reagent, 99%, 96% enantiomeric purity; (4) H_2, Pd–C, 64%; (5) $NaCNBH_3$, AcOH 42%; (6) (a) TFA, CH_2Cl_2 (b) aqueous HBr, 58% for two steps.

The aldehydes necessary for coupling were prepared by Boc-protection of the appropriate phenethylamine and subsequent N-allylation. This was followed by radical addition of 2-mercaptoethanol, and finally oxidation by Dess–Martin reagent (see Scheme 1).

The known acetyl benzothiazolone,[10] used in the large-scale synthesis of sibenadet, was available to us in large quantities. This material was selectively chlorinated on the acetyl group, and the chloro-group replaced by azide. At this stage an enantiospecific reduction, using Corey reagent,[11] successfully installed the required chiral alcohol group, and the azide was reduced to give the key chiral amino-alcohol used to prepare all compounds in this series.

The aldehyde and chiral amino-alcohol were coupled by reductive amination. The Boc-group was removed with trifluoroacetic acid, and the free base was converted to the crystalline dihydrobromide salt with aqueous hydrobromic acid (see Scheme 2).

Compounds which demonstrated required potency and agonism, and had convincing stability against rat hepatocyte turnover were measured for plasma half-life in rat. Later measurements of lung concentration confirmed this equivalence of half-life in lung. When dosed iv in rat compounds **11** and **15**–**17** all showed long plasma half-lives, and when dosed intra-tracheally (i.t.) the lung half-life's were essentially identical. Compound **16** with a 15.9 h rat plasma half-life was selected for testing in a guinea-pig model of bronchoconstriction.

Inhaled β-agonists could have systemic side effects from the swallowed fraction. However, as expected from a phenol, when tested orally **16** had extremely low bioavailability (<1%) precluding any systemic activity via the oral route.

Histamine-induced bronchoconstriction in guinea-pig is a well characterised model of human lung disease,[12] and bronchodilators offering protection in this model have historically shown good efficacy in man. Compound **16** was first tested at various concentrations dosed by intra-tracheal instillation (i.t.) to establish a dose–response for protection against histamine-induced bronchoconstriction. In this model **16** had an ED_{80} of 7 μg/kg. To measure the duration of the bronchoprotective effect in vivo **16** was then dosed intra-tracheally at its measured ED_{80}, and the remaining level of bronchoprotection measured at various time points over the next 24 h. To compare compounds fairly all compounds were dosed at their ED_{80} value, this concentration being measured in a separate full dose–response curve for each compound. This level of inhibition was reproduced in the duration experiment as clearly shown by the inhibition measured for each compound at the initial time point. Therefore duration is measured as maintenance of inhibition from an equivalent level at the initial time point. By measuring the bronchoprotection remaining, and comparing this with standard bid compounds salmeterol and formoterol it was judged that >40% bronchodilation should remain at 24 h to predict an inhaled 24-h bronchodilator effect in man. As shown in Figure 1 compound **16** showed 49% inhibition at 24 h, very similar to indacaterol.

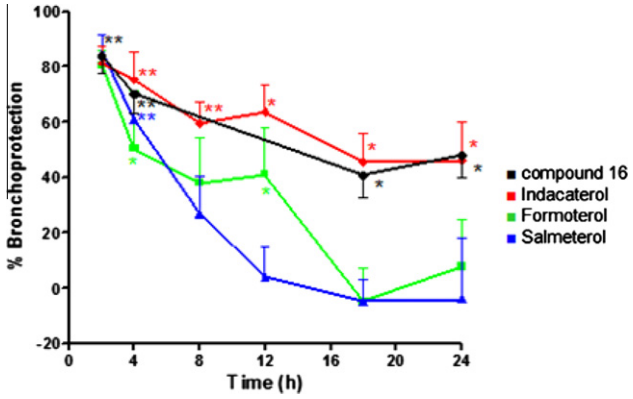


Figure 1. Duration of action of compound **16** versus standards (dosed i.t.).

A further criterion for inhaled compounds is that they must have good solid state properties to allow for micronisation. A salt screen was performed, and it was found that the di-hydrobromide salt of compound **16** showed excellent crystallinity, a high melting point and no hygroscopicity. This salt was subsequently shown to micronise to particles <5 μm without issue, and have acceptable inhaled properties.

Starting with the dual DA_2/β_2-agonist sibenadet structure we have designed new inhaled ultra long acting β_2-agonists (uLABA's). Firstly, addition of a benzylic hydroxyl group improved potency, intrinsic activity and selectivity against the dopamine receptor. Secondly, incorporation of a second base along the chain increased V_{ss} and rat plasma PK half-life. Half-life in the dibasic series was then optimised by adjusting lipophilicity to an appropriate level until the desired plasma half-life was achieved in rat. This long rat plasma half-life translated well into rat lung half-life, and also to guinea-pig duration of bronchoprotection, as well as predicting an appropriately long half-life in man. In summary, compound **16** met all our criteria, and the dihyrobromide salt of this compound was selected to progress into development.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.05.097.

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