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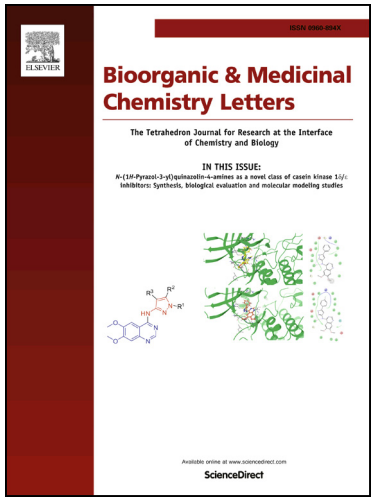

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Identification of selective 8-(piperidin-4-yloxy)quinoline sulfone and sulfonamide histamine H_1 receptor antagonists for use in allergic rhinitis.

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Abstract

A series of potent, selective and long-acting quinoline-based sulfonamide human H_1 histamine receptor antagonists, designed for once-daily intranasal administration for the treatment of rhinitis were developed. Sulfonamide **33b** had a slightly lower affinity for the H_1 receptor than azelastine, had low oral bioavailability in the rat and dog, and was turned over to five major metabolites. Furthermore, **33b** had longer duration of action than azelastine in guinea pigs, lower rat brain-penetration, and did not cause time dependent inhibition of CYP2D6 or CYP3A4. The clinical dose in humans is expected to be low (approximately 0.5 mg per day) based on the clinical dose used for azelastine and a comparison of efficacy data from animal models for **33b** and azelastine

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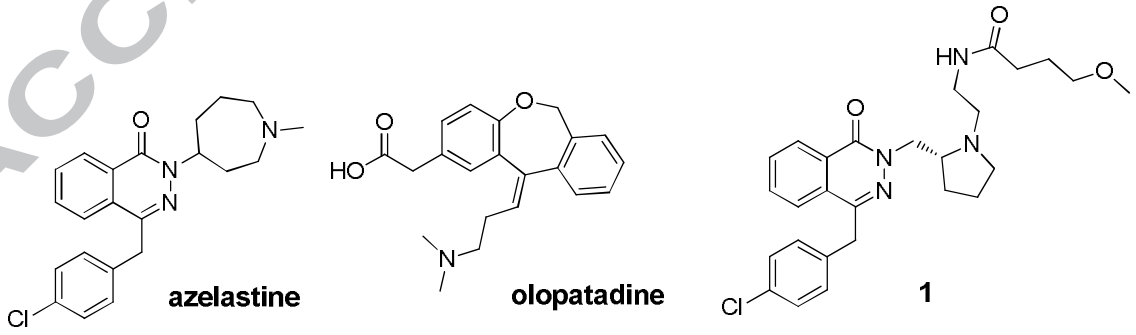
Introduction

Allergic rhinitis is a condition that affects a large number of people, approximately 25% of the global population, with high prevalence in the industrialised world, and a near quadrupling of medical care consultations over the last 50 years.[1,2] Symptoms include irritation and repetitive sneezing, rhinorrhoea, pruritus, headache, epiphora, nasal congestion, irritation of the throat, and oedema. Nasal congestion may lead to breathing through the mouth, snoring,[3] and hyposmia.[4] Allergic rhinitis is mainly treated with antihistamines and corticosteroids,[5] with H_1 receptor antagonists (antihistamines) being the most frequently used medication.[6] In addition to oral antihistamines intranasal treatments, such as azelastine[7] and olopatadine (Chart 1) have gained popularity because the dose for topical treatments is generally lower, and hence their side-effects are fewer. Treatments destined for intranasal dosing must be delivered in a small volume, have high potency, and also have low oral absorption because a significant portion of the dose is swallowed and becomes available for absorption through the gastrointestinal track. Azelastine and olopatadine have comparable efficacy and duration of action (12 h), however, both suffer from dysgeusia, headache and epistaxis.[8]

Chart 1 Representative intranasal H_1 receptor antagonists

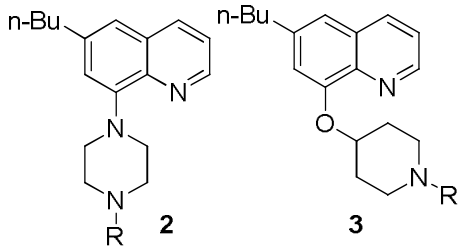


Our group has published on selective histamine H_3 receptor antagonists,[9] on dual H_1H_3 antagonists,[10,11] and on selective H_1 antagonists.[12,13] More recently we have focussed our

efforts in identifying potent and selective human H_1 receptor antagonists with low oral absorption and long duration of action, suitable for once-daily intranasal administration. Due to allergic rhinitis' close links to other inflammatory diseases such as allergic conjuctivitis, rhinosinusitis and asthma, we envisaged using a novel H_1 receptor antagonist in combination with the long-acting glucocorticoid fluticasone furoate. We have very recently reported our efforts in identifying phthalazinone **1** as a preclinical candidate for rhinitis, which fulfils all of the above requirements.[13] In this publication we describe our efforts in identifying another candidate as a back-up to **1**, which is derived from a non-phthalazinone scaffold.

Azelastine which has a phthalazinone core has a bitter taste and we wished to avoid this problem, if possible. We considered starting our investigations from the 8-(piperazin-1-yl)quinoline scaffold **2** (Figure 1),[11] however, we opted for the 8-(piperidin-4-yloxy)quinoline scaffold **3** that we briefly examined previously as part of our dual H_1H_3 antagonist project. Scaffold **3** was slightly less potent at the histamine H_1 receptor, however, it was significantly more selective than equivalent piperazines across a range of aminergic GPCRs, particularly α_{1A}. We were also interested in the introduction of the strongly electron-withdrawing sulfone or sulfonamide groups in substituent R in order to reduce the basicity of the piperidine amino group of **3**, and concurrently reduce any hERG channel liability associated with strongly basic and lipophilic compounds. Our strategy was to optimise potency by investigating the chain-length between the piperidine nitrogen and the sulfone/sulfonamide groups and also the substituent on these groups. We considered that a compound with H_1 receptor affinity close to that of azelastine was a good target to aim for in order to achieve the small volume – low dose requirement for topical administration. Increasing the duration of action to twenty-four hours was hoped to be achievable from SAR optimisation of analogues with duration in vitro of at least as long as azelastine.

Figure 1 Scaffolds **2** and **3**

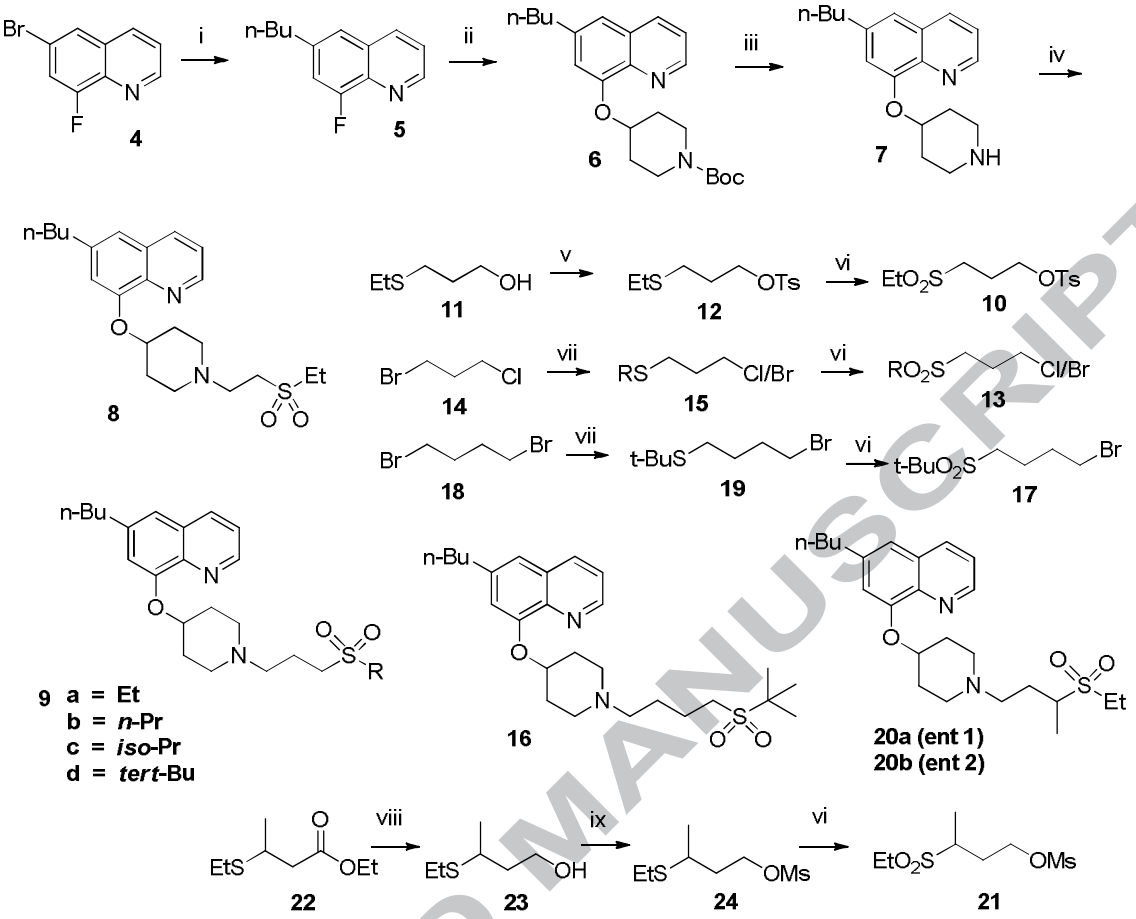


Chemistry

The synthesis of target sulfones commenced from 6-bromo-8-fluoroquinoline **4** with the introduction of the C6 substituent using a selective Suzuki reaction to provide the cross-coupled product **5** as outlined in Scheme 1. The Suzuki reaction utilised tributylborane and was catalysed by [1,1'-bis(diphenylphosphino)ferrocene palladium (II)] chloride [$Pd(dppf)Cl_2$] to give **5** in 67% yield. Fluoride displacement with the alkoxide of *N*-Boc-4-hydroxypiperidine in *N*-methylpyrrolidone (NMP) provided ether **6** in 81% yield, which was then deprotected with TFA to give the piperidine **7** in quantitative yield. This compound was a common intermediate for the preparation of all target sulfones and sulfonamides. The ethyl sulfone with the two-carbon chain **8** was obtained in 70% yield by heating **7** with ethyl vinyl sulfone in DMF at 100°C under microwave irradiation. The analogous ethyl sulfone with the three-carbon chain **9a** was prepared in 61% yield from **7** and the tosylate **10** in the presence of NaI, $NaHCO_3$ in DMF at 100°C. The tosylate **10** was prepared from commercially available 3-(ethylthio)propanol **11** which was converted to the tosylate **12** (24% yield) and then oxidised with mCPBA to provide **10** in 99% yield. Alternatively, compound **9a** and the homologues *n*-Pr, *iso*-Pr and *tert*-Bu sulfones **9b-d** were prepared by alkylating **7** in a similar way (NaI, $NaHCO_3$ in DMF at elevated temperature) using the halides **13**, which in turn were made from 1-bromo-3-chloropropane **14** by reaction with the appropriate sodium thiolate in DMF, followed by mCPBA oxidation of the resulting sulfide **15** to the corresponding sulfone. The halides **13** and **15** were obtained as mixtures of chlorides and bromides (variable ratios

from 2:1 to 2:3), and were used without any further purification. The four-carbon *tert*-butyl sulfone **16** was made from **7** and the bromide **17** using the same alkylation conditions (NaI, $NaHCO_3$, DMF, 150°C, microwave irradiation) in 46% yield. The bromide **17** was prepared from 1,4-dibromobutane **18** and *tert*-butyl thiolate to give sulfide **19** (21% yield), which was then oxidised to the sulfone (71% yield). Finally, the branched four-carbon chain ethyl sulfone **20** was prepared from **7** and the mesylate **21**. The mesylate **21** synthesis commenced with $LiAlH_4$ reduction of commercially available ethyl ester **22** to give the alcohol **23** (quantitative yield), convertion to mesylate **24** (92% yield), and finally oxidation to sulfone (95% yield). The racemic sulfone **20** was resolved using preparative HPLC on a Chiralpak AD column eluting with 15% ethanol-heptane containing 0.1% trifluoroacetic acid. The enantiomer eluting first off the column was labelled **20a**, and the enantiomer eluting last was labelled **20b**.

Scheme 1 Synthesis of sulfones **8**, **9a-d**, **16**, **20a** and **20b**

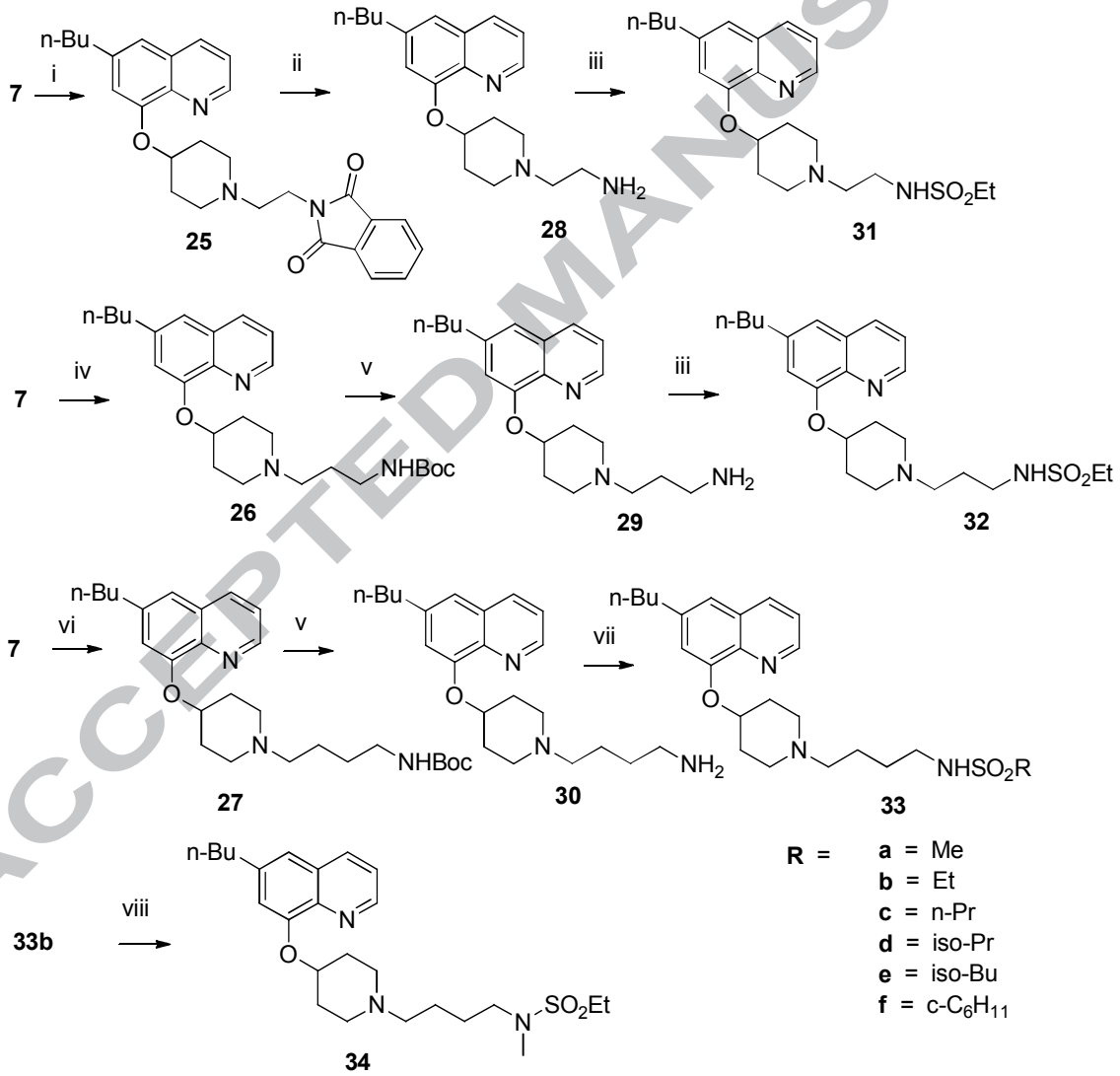


Reagents and Conditions: i) *n*-Bu_3B solution in THF, $Pd(dppf)Cl_2$, DMF, 75°C, 67%; ii) *N*-Boc-4-hydroxypiperidine, *tert*-BuONa, NMP, 140°C, 81%; iii) TFA, DCM, 100%; iv) ethyl vinyl sulfone, $NaHCO_3$, DMF, microwave, 100°C, 15 min, 70%; v) TsCl, pyridine, 24%; vi) m-CPBA, DCM; vii) RSNa, (R=Et-, *n*-Pr-, *iso*-Pr-, *tert*-Bu-), DMF; viii) $LiAlH_4$, THF, 100%; ix) MsCl, DCM, 0°C, 92%.

The sulfonamide series were prepared from intermediate **7** which was alkylated with 2-phthalimidoethyl bromide, 3-(Boc-amino)propyl bromide and 4-(Boc-amino)butyl bromide to give the protected amines **25**, **26** and **27** in 70, 78 and 94% yield respectively (Scheme 2). Amine **25** was deprotected with hydrazine monohydrate to give the amine **28** (100%),

whereas **26** and **27** were deprotected by treatment with HCl to give **29** and **30** in 76 and 88% yield respectively. The amines **28** and **29** were sulfonylated with ethanesulfonyl chloride to give **31** and **32** (38 and 67% yield respectively). The butylamine **30** was similarly treated with a number of sulfonyl chlorides to give sulfonamides **33a-f**. The sulfonamide **33b** was alkylated with methyl iodide in the presence of sodium hydride to give the *N*-methylsulfonamide **34**.

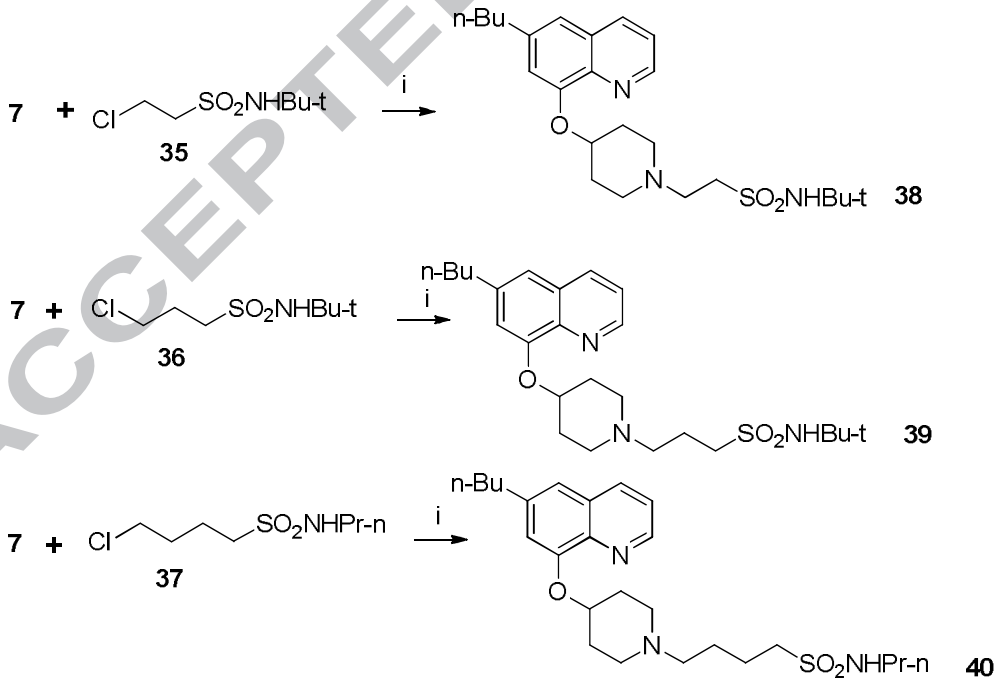
Scheme 2. Synthesis of sulfonamides **31**, **32**, **33a-f** and **34**.



Reagents and Conditions: i) 2-phthalimidoethyl bromide, K_2CO_3, 2-butanone, 80°C, 70%; ii) $NH_2NH_2.H_2O$, EtOH, 80°C, 100%; iii) $EtSO_2Cl$, Et_3N, DCM, 38% for **31** and 67% for **32**; iv) 3-(Boc-amino)propyl bromide, K_2CO_3, 2-butanone, 80°C, 78%; v) 4M HCl, dioxane, 76% for **29** and 88% for **30**; vi) 4-(Boc-amino)butyl bromide, K_2CO_3, 2-butanone, 80°C, 94%; vii) RSO_2Cl, Et_3N, DCM, 36% for **33a**, 53% for **33b**, 32% for **33c**, 39% for **33d**, 18% for **33e**, 23% for **33f**; viii) NaH, MeI, DMF, 52%.

The reverse sulfonamide analogues were prepared by alkylation of piperidine **7** with 2-chloro-*N*-(1,1-dimethylethyl)ethanesulfonamide **35**, 3-chloro-*N*-(1,1-dimethylethyl)-1-propanesulfonamide **36** and 4-chloro-*N*-propyl-1-butanesulfonamide **37** to give **38**, **39** and **40** respectively. The alkylating agents **35**, **36** and **37** were prepared by treatment of the commercially available chloroalkylsulfonyl chlorides with one equivalant of *tert*-butylamine or *n*-propylamine.

Scheme 3 Synthesis of reverse sulfonamides **38**, **39** and **40**



Reagents and Conditions: i) NaI, K_2CO_3, DMF, 4-33%

Results and discussion

The H_1 receptor affinity of compounds was evaluated in vitro using recombinant human histamine H_1 receptor in intact CHO cells which provided apparent pA_2 values. The hERG activity was measured in [^{3}H]-dofetilide radioligand binding assay, and the data from all the above screens are summarised in Table 1. Azelastine was used as a reference compound and exhibited high affinity for both the H_1 receptor (pA_2 = 9.7) and the hERG channel (pIC_{50} = 7.0). Similarly, the data for our phthalazinone candidate **1** is also included in Table 1 for comparison (pA_2 = 9.7 and hERG pIC_{50} = 6.4). The experimental details on the assays were reported in our earlier publications.[9,10] Duration of action in vitro was determined in the CHO cell assay by incubation with antagonist for 30 min, followed by washing, and then by repeat histamine challenges at intervals of 90 and 270 min at 37°C. The duration of action in vitro for these analogues is expressed as faster, slower or no-difference wash-out time relative to azelastine. Slower wash-out equated to longer duration of action than azelastine, whereas faster wash-out to shorter duration.

The ethyl sulfones with the two-carbon (**8**) and branched four-carbon (**20**) chains had lower affinity for the H_1 receptor (Table 1), however, sulfone **8** which was the least basic compound tested (measured pK_a 6.5) had also the lowest hERG affinity (pIC_{50} 5.8). The three-carbon linked sulfones were more potent than the other chains tested. The terminal alkyl group of these sulfones did not influence the H_1 activity with the ethyl (**9a**), *iso*-propyl (**9c**) and *tert*-butyl (**9d**) sulfones being equipotent (pA_2 9.5, 9.4 and 9.6 respectively), and also maintaining lower affinity for the hERG channel (pIC_{50} 7.1, 7.0 and 6.3 respectively). The duration of action in vitro for **9a** was longer than azelastine, whereas for **9c** and **9d** was the same, making all three compounds worthy of further investigation in pharmacokinetic studies. The

lipophilic (clogP = 4.4) four-carbon chain *tert*-butyl sulfone **16** was less potent than the analogous three-carbon chain sulfone **9d** (pA_2 8.85) and was rejected, although its hERG affinity was low (pIC_{50} 6.5) and its duration of action not different from azelastine.

For the sulfonamide series the optimal linker was the four-carbon chain when comparing the ethylsulfonamides **31**, **32** and **33b** (pA_2 8.7, 8.9 and 9.3 respectively). Investigation of the sulfonamide nitrogen substituent in the four-carbon chain series (**33a-f**) identified three potent analogues **33a-c**. Compound **33a** was however rejected due to its higher hERG activity. The calculated pK_a for analogues **33a-f** was 8.42, however a drop in the hERG activity was observed with increasing substitution from the methyl **33a** to isopropyl analogues **33d** and then an increase with increasing lipophilicity for the isobutyl **33e** and cyclohexyl **33f** analogues. The duration of action in vitro of sulfonamide **33c** was longer than azelastine's, whereas for **33b** was similar. Both **33b** and **33c** were progressed for further investigation. The H_1 affinity of the *N*-methyl sulfonamide **34** was reduced slightly by comparison to **33b** and was rejected.

The reverse sulfonamides **38**-**40** with the two-, three- and four-carbon linker chains had lower H_1 receptor affinity and were also rejected. The hERG activity of **38**, which was less basic than both **39** and **40**, was lower. The more branched *tert*-butyl **39** had lower hERG activity than the *n*-propyl analogue **40**, despite the fact that both **39** and **40** had the same basicity (calc. pK_a 8.1).

Pharmacokinetic studies

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals. Experimental procedures for the PK studies in vivo and rat CNS penetration were reported in our earlier publications and outlined in the suplementary information section.[9,10]

From the three sulfones and two sulfonamides selected for further investigation **9a**, **33b** and **33c** had low CNS penetration in the rat, assessed in samples taken 5 min after an intravenous bolus dose of 1 mg/kg (mean brain concentration of 62, 26 and 41 ng/g of tissue respectively), and low brain-blood ratios (0.09, 0.10 and 0.16 respectively). Sulfone **9d** had higher levels of concentration in the brain 133 ng/g (presumably due to its higher lipophilicity, clogP 4.7), and a higher brain-blood ratio of 0.77 and was therefore rejected. The sulfones (**9a** and **9c**) had higher systemic exposure in the rat after oral administration at 3 mg/kg (mean $AUC_{0\text{-last}}$ 568 and >361 h.ng/mL respectively) than the sulfonamides (**33b** and **33c**, mean $AUC_{0\text{-last}}$ 62 and 63 h.ng/mL respectively). The sulfones **9a** and **9c** were therefore rejected as the aim of this project was to identify compounds with low systemic exposure, suitable for intranasal dosing. Sulfonamide **33b** having the lower AUC was progressed to pharmacokinetic studies in vivo in both the male CD Sprague Dawley rat and Beagle dog and the data are shown in Table 2. The compound was dosed as a solution in H_2O−PEG200−DMSO (50:45:5) at 1 mg/kg (both species) iv, at 3 mg/kg for the rat po, and 1 and 2 mg/kg for the dog po studies. In addition one dog was also dosed subcutaneously. The blood clearance was moderate compared to liver blood flow (means of 38 and 20 mL/min/kg in rat and dog respectively) and the volume of distribution was also moderate (means of 4.2 and 4.5 L/kg in rat and dog respectively). The resultant elimination half-life was moderate (means of 1.8 and 3.8 h in rat and dog respectively). Elimination of parent compound via urine was low following oral and intravenous administration of **33b** to the dog (<0.1% following oral administration and <1% following intravenous administration). Following oral administration of **33b** bioavailability was low using low doses (9 and 5% for rat and dog respectively). Rat absorption of **33b** into the hepatic portal vein following oral administration was low (13 to 16% using a 3 mg/kg dose). Sulfonamide **33b** was also dosed orally to rats at 10 mg/kg using a hydroxypropylmethyl cellulose formulation. The animals dosed at 10

mg/kg showed a proportional increase in C_{max} compared to the 3 mg/kg data and bioavailability was estimated to be 4%. Following subcutaneous administration to the rat bioavailability was estimated to be 45%. The *in vitro* plasma protein binding for **33b** was determined using an ultrafiltration technique and was found to be high across all species tested (means of 97.9, 91.1, 97.7 and 98.2% for rat, guinea pig, dog and human respectively at 10 µg/mL). Plasma protein binding did not appear to be concentration dependent across the three concentrations tested, 0.5 or 1 µg/mL and 10 µg/mL. The *in vitro* blood cell binding was low to moderate at nominal concentrations of 1 and 10 µg/mL in all species tested (means of 27, 42, 49 and 23% for rat, guinea pig, dog and human respectively at 1 µg/mL). The *in vitro* rate of metabolism for **33b** was moderate using rat and human liver microsomes (2.9 and 1.4 mL/min/g tissue respectively); moderate to high using dog liver microsomes (3.6 mL/min/g) and high using mouse liver microsomes (3.7 mL/min/g). The rat and dog *in vitro* microsomal clearance data is in keeping with the *in vivo* clearance data for rat and dog. Incubation of **33b** with cryopreserved human hepatocytes resulted in extensive metabolism of the compound with at least 35 metabolites being formed. Five major metabolites, labelled M11, M15, M19, M24 and M26 were observed, which were identified by mass spectrometry as M11 and M15 hydroxylation products on the C6-butyl group (M+16), M19 oxidation product of either M11 or M15 (M+14), M24 *N*-dealkylation of the piperidine nitrogen (M-163) and M26 oxidative *N*-dealkylation of the sulfonamide nitrogen (M-77). Sulfonamide **33b** had an acceptable profile (IC_{50} >4 µM) against human CYP450 enzymes (CYP1A2, >100 µM; CYP2C9, 31 µM; CYP2C19, >40 µM; CYP2D6, 15 µM and CYP3A4, 4 µM). Furthermore, **33b** did not cause time-dependent inhibition with CYP2D6 or CYP3A4 (less than two-fold change in IC_{50} values over a 30 min incubation).

The MDCK permeability of **33b** was low (52 nm/s; n=3), however, the compound was found to be a P-glycoprotein (PgP) substrate. The brain levels of **33b** determined 30 min post a 300

mg/kg oral dose in rat were found to be very high (14,480 ng/g) with high brain-blood ratio of 11.0. This increase in brain penetration observed at higher doses is thought to be a consequence of **33b** being a PgP substrate.

Effect of 33b on histamine-induced nasal congestion in guinea pigs.

We have used the previously reported Buxco whole body plethysmography technique to investigate the effect of intranasally dosed **33b** on histamine-induced nasal congestion in conscious, unrestrained guinea pigs, which were previously sensitised with ovalbumin and aluminum hydroxide intranasally over a 3 week period prior to the study (further information in SI section). Recording PenH (enhanced pause) AUC over 40 min following bilateral histamine challenge (10 mM, 25 µL/nostril, under light isoflurane anaesthesia) allows for the assessment of efficacy and duration of action of intranasally dosed antihistamines.[13,14] Significant inhibition of histamine-induced congestion, compared to a vehicle-pretreated/histamine challenged control group, at both 3 and 24 h after intranasal administration of a 1 mg/mL solution of **33b** (25 µL/nostril). In contrast, azelastine failed to show a similar duration of action when administered at the same concentration (Figure 2). Arterial blood samples taken immediately following evaluation of nasal congestion (4 or 25 h after intranasal dosing) show negligible systemic exposure following 1 mg/mL **33b**, suggesting a low bioavailability by this route and a local mechanism of action. A separate study was performed in order to investigate the onset of action *in vivo*. Significant inhibition of histamine-induced congestion 1 h after intranasal administration of a 1 mg/mL solution (25 µL/nostril, data not shown) which suggests that an early onset time could be clinically achievable. Neither **33b** nor azelastine produced a pro-congestant response at any time-point studied (effect on baseline PenH – data not shown).

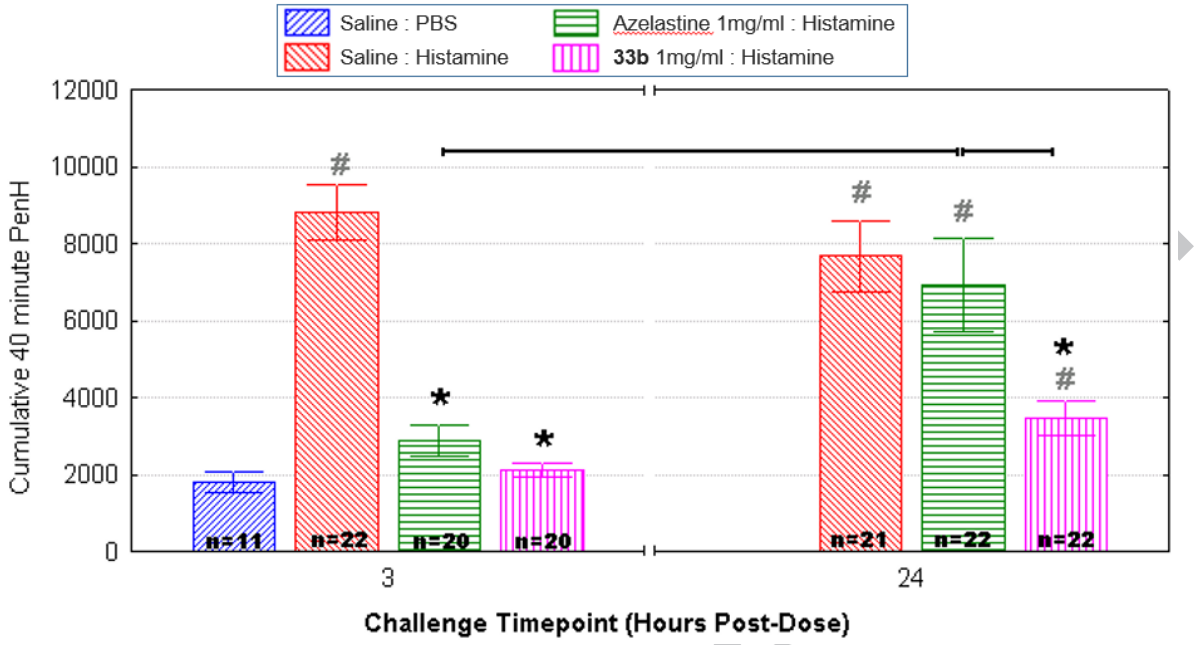


Figure 2. Duration of action of **33b** and azelastine in a conscious guinea pig model of histamine-induced nasal congestion. Animals were exposed to histamine at the time indicated after an intranasal dose of 1 mg/mL **33b** or azelastine. Mean ± SEM (n = 11-22 per group as indicated). (*p<0.05 compared to time-matched histamine control group; # p<0.05 compared to vehicle/PBS control group. Bar indicates p<0.05 individual comparison as indicated. ANOVA with post-hoc Hochberg analysis)

Predicted human dose

The clinical dose of **33b** is expected to be appoximately 0.5 mg per day, based on the clinical dose used for azelastine and a comparison of efficacy data from animal models for **33b** and azelastine. Using the low oral bioavailability in rat and dog, moderate blood clearance and a low clinical dose the systemic exposure in humans is expected to be very low. The concentration of **33b** was less than 7 nM (3 ng/mL) in all assayed blood samples taken from guinea pigs showing a pharmacological response in the histamine induced nasal congestion model. The pharmacokinetic profiles in preclinical species following intravenous administration were used to give estimates of the maximum systemic exposure in humans if

most of the intranasal dose was swallowed and bioavailability was complete. A standard absorption rate was assumed, the volume of distribution was kept constant and the elimination rate was scaled based on liver blood flow. Using these simulations the maximum estimates for exposure in humans following a 0.5 mg dose are a total drug C_{max} of 0.89 ng/mL and 0.99 ng/mL (based on rat and dog data respectively) and an AUC_{0-24} of 10.5 h.ng/mL and 7.4 h.ng/mL (based on rat and dog data respectively).

Specificity profiling of 33b

The specificity profiles for both **33b** and azelastine were evaluated in the CEREP Specificity Screen at 50 different receptors, ion channels and transporters). Off-target activity was observed with 5-HT_{2B} (antagonist, pK_i 6.1), 5-HT_{2C} (antagonist, pK_i 5.7), α_{1A} (antagonist, pK_i 5.7) and M_2 (antagonist, pIC_{50} 6.2). The data for azelastine against these targets were 5-HT_{2B} (antagonist, pK_i 7.7), 5-HT_{2C} (antagonist, pK_i 6.3), α_{1A} (antagonist, pK_i 7.3) and M_2 (antagonist, pIC_{50} 5.2). For all of these targets relative to histamine H_1 receptor (pA_2=9.3) **33b** shows >1000-fold specificity. As mentioned earlier **33b** also showed significant affinity (pIC_{50} 7.1) for the hERG channel, having a similar potency to azelastine (pIC_{50} = 7.0) in the hERG dofetilide binding assay. Evaluation in rabbit hearts in vitro (SCREENIT model) suggests that the risk of **33b**-induced QT prolongation is low at therapeutically relevant predicted exposure levels.

The mutagenic and clastogenic potential of **33b** was assessed in the AMES test, Mouse Lymphoma screen and DEREK-structure activity relationship in silico analysis). No evidence of mutagenic, clastogenic or toxic potential was detected in these assays up to the maximum concentrations tested.

Conclusion

A series of quinoline sulfone and sulfonamide human H_1 histamine receptor antagonists were prepared using a four- and six-step linear synthesis respectively. The sulfone series although highly potent were orally absorbed and were not progressed any further. In contrast the sulfonamides were not orally absorbed, and had low brain penetration. The optimal chain-length between the piperidine nitrogen and the sulfonamide group was the four-carbon chain, and the optimal sulfonamide nitrogen substituents were methyl, ethyl or n-propyl group. The ethyl analogue **33b** had slightly lower potency than azelastine, however, it had longer duration of action in a nasal congestion model in vivo. The compound was metabolised in human hepatocytes to 5 major metabolites, and at least another 30 minor ones. The main routes of metabolism were oxidation in the butyl substituent (hydroxylation and oxidation to ketone), and *N*-dealkylation of the piperidine or sulfonamide nitrogens. Sulfonamide **33b** was selective for the H_1 receptor over 50 other different receptors, ion channels and transporters with >1000-fold selectivity, and did not have any issues with P450 inhibition. It showed similar affinity to azelastine for the hERG channel and evaluation in rabbit hearts in vitro suggested that the risk of **33b**-induced QT prolongation is low at therapeutically relevant predicted exposure levels. The predicted dose for humans is 0.5 mg per day. **33b** may have increased brain penetration in human if administered with a PgP inhibitor. The low clinical dose and low bioavailability reduces the potential for significant clinical effects. In summary, **33b** is suitable for progression as a back-up to our phthalazinone intra-nasal candidate for the treatment for allergic rhinitis.

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Conflicts of Interest: none

Supplementary Information

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017. These include experimental details for the synthesis of compounds **5**, **6**, **7**, **27**, **30**, **33b** and **33b.2HCl**, and for the pharmacokinetic and pharmacodynamic studies.

Table 1. Antagonist pA_2 Affinity at the Human H_1 Receptor, in vitro Duration, dofetilide hERG binding affinity, calculated logP and pK_a, and measured pK_a for the piperidine nitrogen

Compound[a]	pA_2±SEM[b] (n)	Wash-out[c]	hERG pIC_{50} (n)	clogP[d]	cpK_a[e]	pK_a
Azelastine	9.7±0.1 (19)	Ref.	7.0±0.0 (114)	4.0	8.9	
1	9.7±0.1 (20)	S	6.4±0.0 (16)	3.7	7.3	
8	8.43±0.01 (2)	-	5.78±0.01 (2)	3.9	6.7	6.5
9a	9.46±0.04 (13)	S	7.12±0.04 (5)	4.0	6.9	7.9
9b	9.13±0.06 (3)	-	7.54±0.04 (4)	4.5	6.9	-
9c	9.4±0.1 (16)	ND	7.04±0.02 (4)	4.3	6.9	-
9d	9.58±0.09 (6)	ND	6.33±0.03 (5)	4.7	6.9	8.0
16	8.85±0.08 (12)	ND	6.52±0.01 (4)	4.4	7.0	-
20a	8.7±0.2 (4)	-	6.7±0.0 (2)	4.3	7.2	-
20b	8.6±0.2 (4)	-	6.88±0.02 (2)	4.3	7.2	-
31	8.68±0.08 (13)	ND	7.12±0.03 (4)	4.4	7.2	-
32	8.9±0.4 (2)	-	7.2±0.1 (2)	4.5	8.0	8.5
33a	9.4±0.1 (10)	ND	7.7±0.2 (6)	3.8	8.4	-
33b	9.27±0.08 (18)	ND	7.11±0.02 (9)	4.3	8.4	-
33c	9.7±0.2 (16)	S	7.06±0.02 (6)	4.8	8.4	-
33d	8.7±0.2 (3)	-	6.89±0.05 (4)	4.6	8.4	-

33e	9.08±0.08 (13)	S	7.36±0.00 (2)	5.3	8.4	-
33f	9.0±0.2 (3)	-	7.74±0.06 (4)	5.8	8.4	-
34	9.0±0.2 (3)	-	6.6±0.1 (4)	4.6	8.4	-
38	8.7±0.1 (8)	F	6.20±0.04 (4)	5.1	7.2	-
39	9.2±0.1 (14)	ND	6.55±0.03 (4)	5.2	8.1	-
40	9.0±0.1 (3)	-	7.02±0.07 (4)	4.9	8.1	-

[a] All compounds were tested as dihydrochloride salts except for **9d**, **38** and **40** which were mono formate salts, **16** which was a diformate salt, azelastine was the hydrochloride salt, and **1** was the free base, [b] All pA_2 values calculated from curve shifts generated at 30 min incubation time and at 100 nM antagonist concentration. Table 1 shows mean $pA_2 \pm$ SEM for n<3 the SEM is the SD. n = number of experiments, [c] the duration of action in vitro for these analogues is expressed as faster (F), slower (S) or no-difference (ND) wash-out time relative to azelastine, [d] calculated logP value from Biobyte v4.3, [e] calculated pK_a from Chemaxon v5.4.1.1

Table 2. Pharmacokinetic parameters for **33b.2HCl** in the rat and dog.

Species	**CD Rat (n=4 iv, n=3 po)**	**Beagle Dog (n=4 iv, n=4 po)**
Clb (mL/min/kg) (% LBF)	38 (45)	20 (65)
V_{ss} (L/kg)	4.2	4.5
$T_{1/2}$ (h) (IV)	1.8	3.8
Oral bioavailability (%)	9[a,b]	5[c]
Calculated fraction of oral dose absorbed.	13 to 16%	

[a] **33b** was also dosed sub-cutaneously to one rat at 2 mg/kg formulated in DMSO-PEG 200-Water (5:45:50). Bioavailability was determined to be at least 45% and the C_{max} was approximately six-fold higher than achieved following oral administration at 3 mg/kg in the same study.
[b] **33b** was also dosed orally to 3 rats at 10 mg/kg formulated in 0.5% (hydroxylpropylmethyl cellulose). Bioavailability was determined to be at least 4%, the terminal phase was not sufficiently well defined to give a more accurate value.
[c] Mean of data from n=2 dosed at 1 mg/kg and n=2 dosed at 2 mg/kg.

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Graphical Abstract

Identification of selective 8-(piperidin-4-yloxy)quinoline sulfone and sulfonamide histamine H_1 receptor antagonists for use in allergic rhinitis.

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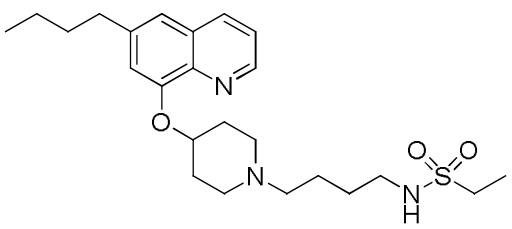

Selective human H_1 histamine receptor antagonist $pA_2 = 9.3$ with 24 h duration of action