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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.

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]

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 conjunctivitis, 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** (Fig. 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

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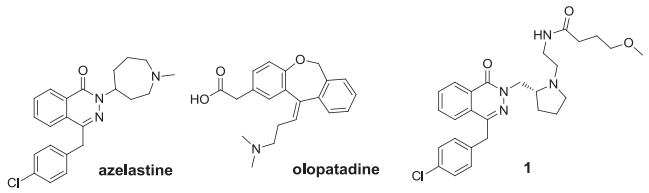


Chart 1. Representative intranasal H_1 receptor antagonists.

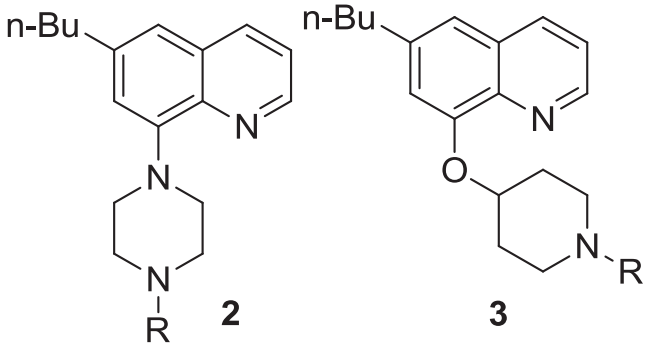
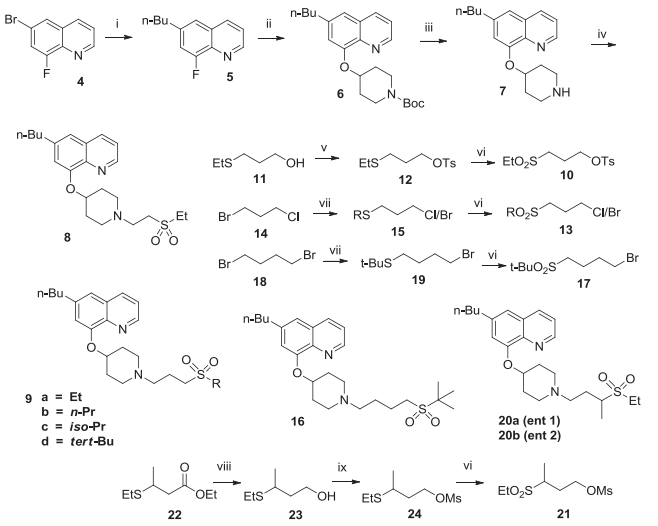


Fig. 1. Scaffolds **2** and **3**.



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%.

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.

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), conversion 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**.

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**.

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 (Scheme 3). The alkylating agents **35**, **36** and