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PII: S0960-894X(16)31162-3
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.11.022
Reference: BMCL 24417

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 6 October 2016
Revised Date: 8 November 2016
Accepted Date: 9 November 2016

Please cite this article as: Procopiou, P.A., Ancliff, R.A., Gore, P.M., Hancock, A.P., Hodgson, S.T., Holmes, D.S., Keeling, S.P., Looker, B.E., Parr, N.A., Rowedder, J.E., Slack, R.J., The Discovery of Quinoline Based Single-ligand Human H_1 and H_3 Receptor Antagonists, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.11.022

The Discovery of Quinoline Based Single-ligand Human H_1 and H_3 Receptor Antagonists

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Abstract

A novel series of potent quinoline-based human H_1 and H_3 bivalant histamine receptor antagonists, suitable for intranasal administration for the potential treatment of allergic rhinitis associated nasal congestion, were identified. Compound **18b** had slightly lower H_1 potency (pA_2 8.8 vs 9.7 for the clinical goldstandard azelastine), and H_3 potency (pK_i 9.1 vs 6.8 for azelastine), better selectivity over α_A, α_B and hERG, similar duration of action, making **18b** a good back-up compound to our previous candidate, but with a more desirable profile.

Key words:

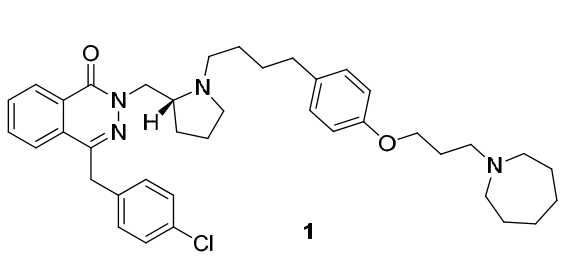
H_1H_3 Histamine receptor antagonist, single ligand, quinoline, allergic rhinitis, nasal congestion.

Allergic rhinitis, also known as "hay fever" is a condition affecting at least 10 – 25% of the world's population and has shown a steady increase in prevalence during the last 50 years.[1] Rhinitis and other allergic conditions are associated with the release of histamine from various cell types, but particularly mast cells. The physiological effects of histamine are mediated by four major G-protein-coupled receptors, termed H_1, H_2, H_3, and H_4, which differ in their expression, signal transduction and histamine-binding characteristics.[2] H_1 receptor antagonists, are the most commonly used first-line medication for allergic rhinitis.[2,3] H_1 receptor antagonists are effective in treating all the symptoms of allergic rhinitis (nasal itching, sneezing and rhinorrhea), apart from nasal congestion. Hence they are often used in combination with short-acting αadrenergic agonist decongestants, such as ephedrine and pseudoephedrine. These are potent vasoconstrictors with fast onset-time, available as over-the counter oral preparations. However, the use of such agents is limited due to their potential to produce hypertension, agitation, headache, tachycardia and insomnia.[4] Novel decongestant agents with a superior side effect profile and efficacy profile would be advantageous in the treatment of allergic rhinitis.

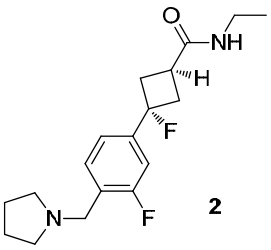
The H_3 receptor subtype is a presynaptic autoreceptor that controls the synthesis and release of histamine as well as other neurotransmitters, such as acetylcholine, dopamine, GABA, glutamate, 5-HT, substance P and noradrenaline.[3] H_3 receptors are expressed widely on both CNS and peripheral tissues and are localised on the epithelium and nerves in human nasal mucosa.[5] *In vitro* experiments with isolated human turbinate mucosa have shown that (*R*)-α-methylhistamine, an H_3 receptor agonist, inhibited sympathetic vasoconstriction, whereas clopenpropit, a selective H_3 receptor antagonist, blocked this effect by reducing noradrenaline release from sympathetic nerve endings in the nasal mucosa.[6] It is thought that activation of the H_3 receptor on the presynaptic terminals of sympathetic neurones reduces noradrenaline release and this may contribute, together with the activation of the postsynaptic H_1 receptors,

to the nasal blockage caused by histamine release. Consistent with this hypothesis, combination treatment of H_1 and H_3 antagonists have been shown to inhibit nasal congestion in animal models.[7] Further evidence for the contribution of H_3 receptors to histamine-induced blockage of the nasal airway in normal healthy human volunteers was provided by acoustic rhinometry.[8] In principle there are two ways of targeting dual H_1H_3 pharmacology, either by using a combination of two individual selective antagonists or identifying a molecule that exhibits antagonism at both receptors. Our group reported on a dual H_1H_3 receptor antagonist suitable for topical administration.[9] A review of the patent literature on H_3 receptor antagonists covering the four-year period from 2010 was published recently.[10] In addition three compounds, our dual H_1H_3 receptor antagonist **1**,[9] Pfizer's PF-03654746 (**2**),[11] and J&J's JNJ-39220675 (**3**)[12] progressed to the clinic. Data from clinical trials investigating the effects of **1**,[13] the H_3 receptor antagonist **2** in the presence of the H_1 receptor antagonist fexofenadine (**4**),[14] and the H_3 receptor antagonist **3**[15] in allergen-induced nasal congestion were published recently. Nasal discomfort, such as burning sensation, irritation or itching were reported by subjects dosed with **1** (1 mg *i.n.*)[13] and development of this compound was discontinued. In humans a combination of fexofenadine and **2** (1 or 10 mg *p.o.*) induced a reduction in allergen-induced nasal congestion, however, moderate adverse effects, such as insomnia, disorientation and anorexia were reported.[14] The data from trials with **3** (10 mg, single-dose, in the absence of any H_1 receptor activity), showed a reduction of nasal congestion by the equivalent of at least a 60 mg dose of pseudoephedrine as assessed by acoustic rhinometry.[15] In this paper we report our efforts in identifying an alternative series of H_1H_3 dual receptor antagonists as back-up to **1**.

Chart 1 Structures of H_3 receptor antagonists recently investigated in the clinic for allergic rhinitis (**1**-**3**) together with the structures of H_1 receptor antagonists fexofenadine (**4**) and azelastine (**5**)



1



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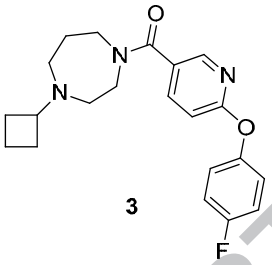

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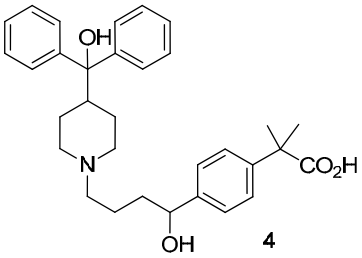

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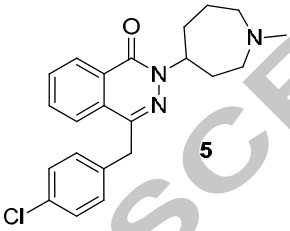

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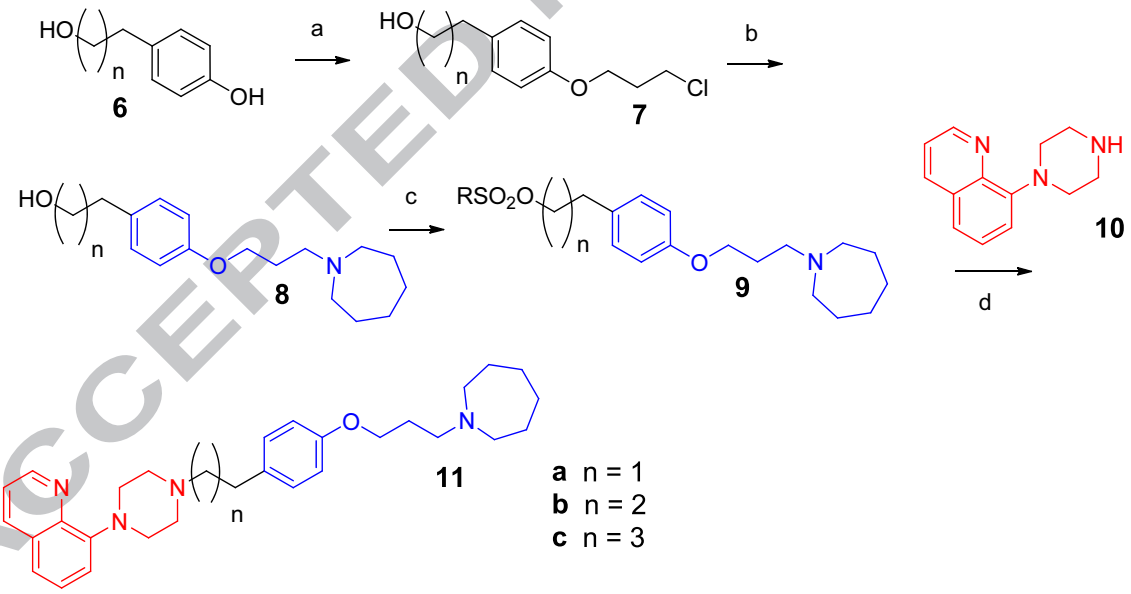
The target profile for this work was a high affinity non-phthalazinone, human H_1 and H_3 antagonist, with selectivity over α_{1A} and α_{1B} receptors, low brain penetration to avoid CNS H_3 effects, low oral bioavailability and no hERG liability. For this work we focused on replacing the phthalazinone group present in our clinical candidate **1** with another template in order to eliminate the possibility of the nasal irritancy observed with **1** being due the specific chemotype used. Identification of novel H_1 fragments was undertaken from compound collection data mining and found 8-piperazine substituted quinolines to be potent H_1 fragments (in red, scheme 1). A basic amine connected through an alkoxy chain to a lipophilic group (in blue, scheme 1) is a common structural feature shared by several classes of H_3 antagonists, including our own dual antagonist **1**.[9] Initially, the chain-length (in black) connecting the H_1 and H_3 fragments was investigated, starting with the two-carbon chain and going up to four-carbons as in the case of **1**. The compounds were synthesised by the route outlined in scheme 1 starting with the appropriate hydroxyalkylphenol **6**, alkylating the phenolic hydroxyl with 1-bromo-3-chloropropane, followed by reaction with homopiperidine, mesylation of the hydroxy group and finally reaction with 8-(piperazin-1-yl)quinoline **10** to provide **11a-c**. The compounds were screened for antagonist affinity at the human H_1

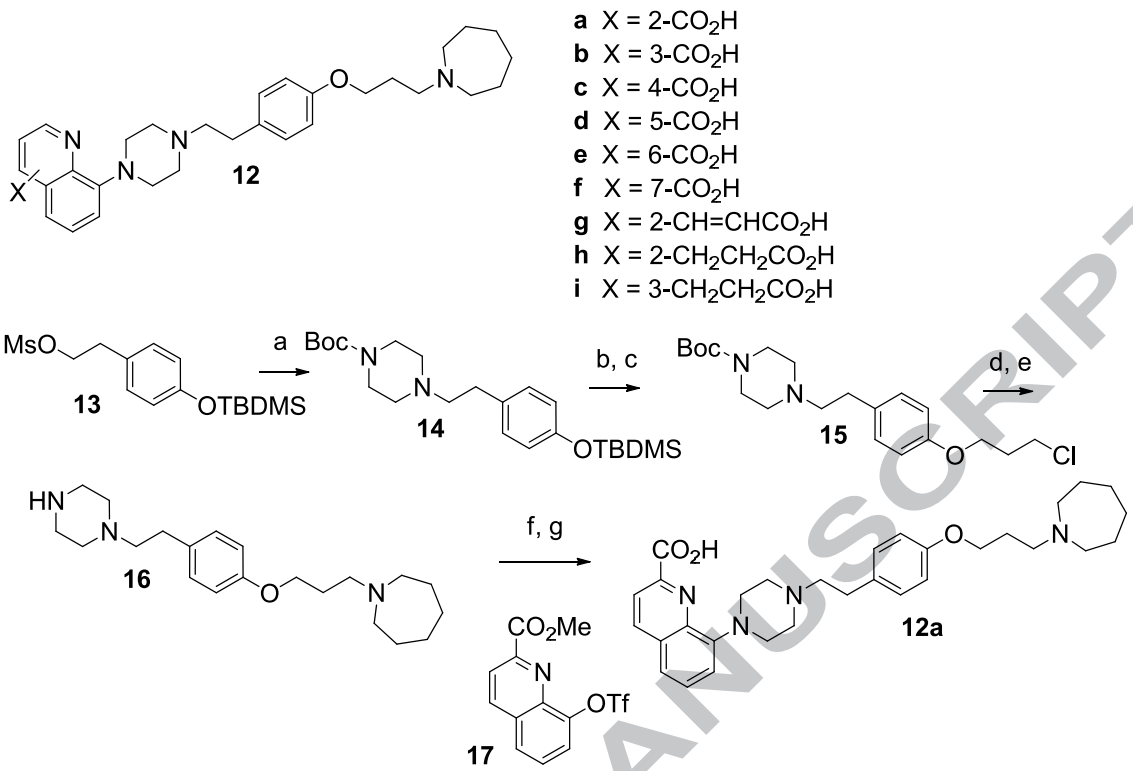
receptor (determined by fluorescence imaging plate reader), human H_3 receptor (determined by a functional GTPγ[S]-assay), human α_{1A} and α_{1B} receptors (determined in intact fibroblast cells by means of plate-based calcium imaging) and ^{3}H-dofetilide hERG radioligand binding affinity as described in our previous publications.[9,16] Phthalazinone **1** and azelastine (**5**) were used as reference compounds and the data from all the above screens together with the clogP and measured logD at pH 7.4 are summarised in Table 1. Despite the impressive H_1 and H_3 affinities of these compounds, they lacked selectivity against α_{1A} and α_{1B} adrenoceptors. The effects of antagonising α_1-adrenergic activity are hypotension, dizziness, lightheadedness, or orthostatic hypotension (fainting when rising from a lying or sitting posture). Furthermore, the more lipophilic compounds **11b** and **11c** (clogP 6.9 and 7.4 respectively) had increased levels of hERG affinity, so further work focused on analogues having the two-carbon chain linker.



Scheme 1. *Reagents and conditions*: a) 1-bromo-3-chloropropane, K_2CO_3, 2-butanone, reflux, 18 h, 90-91%; b) homopiperidine, KI, K_2CO_3, 2-butanone, 78-81%; c) for **9a** and **9c** MsCl, DIPEA, DCM, 94-100%, for **9b** TsCl, pyridine, DCM, 60%; d) 8-(piperazin-1-

yl)quinoline, Et_3N, NMP, microwave, 160°C, 15 min, for **11a** 47%, for **11b** 34%, for **11c** 27%.

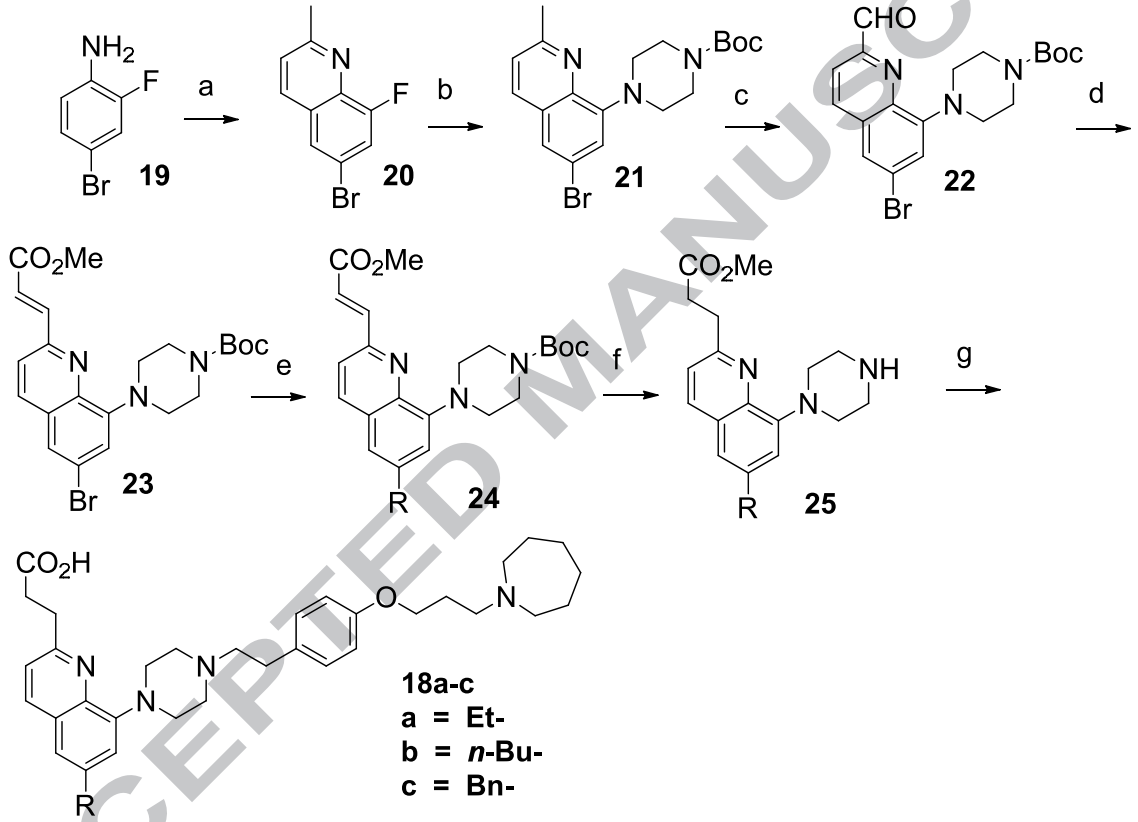
It is necessary to have a low brain concentration of H_1 receptor antagonist in order to avoid sedation. Azelastine, which is dosed intranasally, gave a brain-blood ratio of 7.5 following intravenous infusion to the male CD rat.[9] Studies with **11a** have demonstrated even higher brain-penetration (ratio of >13), so the addition of polar groups on the quinoline moiety to reduce CNS penetration was investigated. Carboxylic acids **12a-f** were synthesised using the route outlined in scheme 2, starting from mesylate **13**, reacting with *N*-Boc-piperazine to give **14**, deprotecting the silyl ether with fluoride and converting the resulting phenol to the chloride **15** using 1-bromo-3-chloropropane, followed by cleavage of the Boc protecting group to give key intermediate **16**. Aromatic nucleophilic substitution of triflate **17** with piperazine **16**, followed by ester hydrolysis provided analogue **12a**. The remaining analogues were prepared in a similar way using intermediate **16** and the appropriately substituted quinoline ester possessing a triflate or halide leaving group, followed by ester hydrolysis. The binding affinities of these analogues are presented in Table 1. The general consequence of introducing a carboxylic acid group into the quinoline ring (**12a-f**) was the reduction of lipophilicity ($logD_{7.4}$ between – 1 and – 0.12) and a corresponding reduction of hERG and H_1 affinity, but with little effect on H_3 activity. The reduction of the H_1 affinity for the C2 and C3 substituted quinolines **12a** and **12b** was less severe than the remaining C4-C8 positions, so additional compounds with substituents containing a carboxylic acid at these two positions (**12g-i**) were synthesised.[17] These analogues retained high affinity for both H_1 and H_3 and selectivity against hERG, α_{1A} and α_{1B} receptors with **12h** showing higher H_1 affinity than the C3 substituted analogue **12i**.



Scheme 2. *Reagents and conditions*: a) *N*-Boc-piperazine, $NaHCO_3$, MeCN, reflux, 2 d, 77%; b) TBAF, THF, 20°C, 3 h, 95%; c) 1-bromo-3-chloropropane, K_2CO_3, 2-butanone, reflux, 24 h, 76%; d) homopiperidine, KI, K_2CO_3, 2-butanone, 57%; e) TFA, DCM, 100%; f) $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, Cs_2CO_3, THF, reflux, 15%; g) NaOH, H_2O, MeOH, 43%.

Additional targets (**18a-c**) combining this promising quinoline C2 position with a second hydrophobic substituent at C6 aiming to slightly increase lipophilicity of **12h** ($logD_{7.4}$ = 0.18) to the $logD_{7.4}$ of azelastine i.e. between 1 and 2) in order to maintain or increase duration of action. Substituents at positions other than the quinoline C6 were investigated, but had reduced affinity. Analogues **18a-c** were prepared from 4-bromo-2-fluoroaniline (**19**), which was converted to quinoline **20** using the Skraup synthesis, followed by aromatic nucleophilic substitution of fluoride with piperazine and protection with Boc_2O to provide **21** (scheme 3).[17] The latter was oxidised with SeO_2 to aldehyde **22** and converted to **23**, which was a

common intermediate for the synthesis of all three analogues **18a-c** by reacting with the appropriate *B*-alkyl-9-BBN derivative in the presence of 1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) to provide **24**. Deprotection with TFA, followed by hydrogenation gave **25**, which was then alkylated with mesylate **9a**, and finally the ester group was hydrolysed to give **18**. These analogues retained H_1 and H_3 affinity, however, for **18c** the selectivity against the human α_{1A} receptor almost disappeared.



Scheme 3. *Reagent and conditions*: a) crotonaldehyde, 5M HCl, PhMe, 100°C, 3 h, 57%; b) (i) piperazine, 150°C, microwave, 30 min, (ii) Boc_2O, Et_3N, DMAP, MeCN, 16 h, 90%; c) SeO_2, 1,4-dioxane, 55-80°C, 16 h, 97%; d) $Ph_3P{=}CHCO_2Me$, THF, 65°C, 40 h, 70%; e) *B*-Bn-9-BBN, K_2CO_3, 1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), THF, DMF, 65°C, 95 h; f) (i) TFA, DCM (ii) H_2, 10% Pd/C, AcOH, EtOAc, 2 h, 33% (for three steps); g) (i) **9a**, $NaHCO_3$, MeCN, 80°C, 65 h, 36%, (ii) NaOH, H_2O, MeOH, 35%.

In addition to the assays reported above, a more precise, lower throughput, modified version of the human H_1 FLIPR assay was run, which provided apparent pA_2 values. Antagonist pA_2 values were determined by generating histamine concentration – response curves either in the absence or presence of a single concentration of antagonist (100 nM) at 30 min incubation.[9] The data for **11a**, **11c**, and **18a-c** are summarised in Table 2 and the compounds are compared to **1** and **5**. Duration of action *in vitro* was determined in the FLIPR assay by incubation of adherent CHO cells with antagonist for 30 min, followed by washing, and then by repeat histamine challenges at intervals of 90 and 270 min at 37 ℃. Agonist dose ratios were converted to receptor occupancies, which were plotted against time. A measure of duration was obtained from the gradient of the percent receptor occupancy versus time plot. Results were statistically analysed and related to azelastine in the same assay, and expressed as slower, no-difference or faster wash-out than azelastine, with slower wash-out equating to longer duration of action. The C3 propanoic acid derivative **12i** was confirmed as low potency and was rejected. The quinolines **11a** and **11c** possessing no carboxylic acid substituents were equipotent, confirming the data from the first assay, and showing duration of action longer than azelastine at both time points. The C6 ethyl substituted analogue **18a** had high affinity for H_1 receptor (pA_2 = 8.6), however, it had a shorter duration of action than azelastine and was rejected. The remaining two analogues, **18b** and **18c** had high affinity for the H_1 receptor with the C6 butyl analogue **18b** being more potent (pA_2 = 8.8). The C6 benzyl analogue **18c** was longer acting than azelastine at 90 min and had the same duration at 270 min, however, this compound was not selective against the human α_{1A} receptor and was therefore rejected. The C6 butyl analogue **18b** had the same duration of action as azelastine at 270 min. Selected compounds possessing a carboxylic acid substituent were screened for brain penetration in the rat and shown to have a low brain concentration (for example brain to

plasma ratio for **18c** was 0.15), a vast improvement over **11a** (ratio >13) and significantly lower than azelastine (ratio 7.5) and **1** (0.6).[18]

In summary **18b** compared to phthalazinone **1** had similar affinity for the human H_1 and H_3 receptors, better selectivity over α_A, α_B and hERG, lower $logD_{7.4}$, higher PSA (69 vs 50), and similar duration of action making **18b** an alternative to **1** with a more desirable profile. In the meantime the Pfizer group published a second paper with clinical data on a second H_3 antagonist, PF-03654764, which is the *iso*-butyl amide analogue of **2.**[19] In this study the H_3 antagonist plus fexofenadine was compared to pseudoephedrine plus fexofenadine. Although the former group provided relief to allergic rhinitis nasal congestion compared to placebo, it was not superior to the pseudoephedrine plus fexofenadine group.[19] Furthermore side effects, such as insomnia, headache and nausea were observed, which were clinically significant compared to controls. Based on the data from the four clinical trials mentioned above it seems that the combination of H_3 with H_1 antagonists cause significant relief of nasal congestion, which is not as high as that obtained by the use of antihistamines in combination with short-acting αadrenergic agonist decongestants. This coupled with the reported observation of side-effects associated with the use of oral H_3 receptor antagonists, it was decided not to progress **18b**.[20]

Acknowledgements: We thank Yvonne. C. Fogden, Caroline Cook, Carla Daniel, Lisette Magnee and Jonathan Raynor for technical assistance, Christopher Browning and Ms Linda J. Russell for the duration studies, Yogini Patel, Clarissa Watts and Liz Pickup for the rat brain penetration studies, and the late Michael Kranz for the modelling work. The authors were all GSK employees and did not receive any financial support from any other funding authority.

Table 1. Antagonist affinity[a] of target compounds at the human H_1 receptor (determined by fluorescence imaging plate reader), human H_3 receptor (determined by a functional GTP[γS]-assay), affinity at the human α_{1A} and α_{1B} receptors (determined in intact fibroblast cells by means of plate-based calcium imaging), measured logD at pH 7.4, clogP (daylight) and dofetilide hERG binding affinity.

cmpd	H_1 pK_i (n)	H_3 pK_i (n)	α_{1A} pK_i (n)	α_{1B} pK_i (n)	$logD_{7.4}$	clogP	hERG pIC_{50}
1	8.0±0.1 (36)	9.6±0.0 (33)	7.4±0.0 (17)	7.5±0.1 (14)	3.2 (8)	8.6	7.3 (7)
5	8.92±0.02 (364)	6.83±0.05 (56)	7.3±0.0 (145)	7.3±0.0 (97)	2.3 (13)	4.0	7.0 (116)
11a	7.7±0.1 (17)	9.3±0.1 (14)	8.1± 0.1 (12)	7.8± 0.1 (10)	1.9 (1)	6.5	5.1±0.1 (6)
11b	7.1±0.1 (10)	9.4± 0.0 (2)	7.5±0.1 (4)	7.0±0.1 (4)	1.8 (1)	6.9	6.0±0.2 (2)
11c	7.8±0.1 (6)	9.2±0.0 (4)	7.1±0.2 (4)	7.3±0.1 (4)	2.2 (1)	7.4	5.8 (1)
12a	6.6±0.1 (11)	9.3±0.1 (10)	<5.7 (7)	<5.7 (14)	-0.37 (1)	4.6	-

12b	6.4±0.1	8.8±0.1	<5.7	<5.7	-0.78	4.4	4.7±0.1
	(11)	(14)	(3)	(6)	(2)		(5)
12c	<5.6	8.8±0.2	<5.7	<5.7	-0.24	4.4	<4.2
	(7)	(10)	(6)	(8)	(2)		(5)
12d	6.0±0.2	8.5±0.2	<5.7	<5.7	-	4.3	<4.2
	(3)	(6)	(2)	(6)			(2)
12e	<5.6	8.7±0.1	<5.7	<5.7	-1.0	4.3	4.4
	(4)	(6)	(2)	(6)	(1)		(1)
12f	<5.6	8.9±0.1	<5.7	<5.7	-0.12	4.3	4.5±0.0
	(6)	(10)	(5)	(8)	(3)		(2)
12g	6.7±0.3	8.8± 0.1	7.2±0.1	7.1±0.0	0.34	4.4	<4.2
	(2)	(4)	(2)	(2)	(1)		(2)
12h	7.9±0.1	8.8±0.1	<5.7	6.7±0.4	0.18	4.0	4.8±0.1
	(10)	(10)	(3)	(2)	(4)		(7)
12i	7.4±0.1	8.9±0.1	<5.7	<5.7	-0.63	4.0	4.5±0.1
	(10)	(10)	(4)	(3)	(2)		(3)
18a	7.8±0.1	8.7±0.1	6.6±0.1	<5.7	1.0	5.1	4.3

	(8)	(7)	(5)	(3)	(1)		(1)
18b	7.9±0.1	9.1±0.2	6.5±0.2	6.4±0.2	2.3	6.1	5.6±0.1
	(8)	(8)	(6)	(4)	(1)		(5)
18c	7.6±0.1	9.5±0.0	7.3±0.1	6.6±0.1	1.9	6.1	5.2±0.0
	(22)	(22)	(9)	(6)	(2)		(2)

[a] Table 1 shows mean ± SEM (where applicable) of estimated functional pK_i for n<3 the SEM is the SD. n = number of experiments

Table 2. Antagonist pA_2 Affinity at the Human H_1 Receptor, determined by Fluorescence Imaging Plate Reader, and in vitro Duration

Compound	pA_2 ±SEM[a]	n	Wash out at	
			90 min	270 min
5	9.7 ±0.1	19	Reference	Reference
1	9.1 ±0.1	11	S	S
11a	8.0 ±0.2	6	S	S
11c	8.3 ±0.1	5	S	S
18a	8.6 ±0.1	6	F	--
18b	8.8 ±0.1	9	--	ND
18c	8.2 ±0.1	19	S	ND

[a] All pA_2 values taken from curve shifts generated at 30 min incubation time and with 100 nM antagonist. Table 2 shows mean pA_2 ± SEM for n<3 the SEM is the SD. n = number of experiments.

References and notes

1. Bousquet, J.; Van Cauwnberge, P.; Khaltaev, N. *J. Allergy Clin. Immunol.* **2001**, 108(5 Suppl):S147.

2. Simons, F. E. R.; Simons, K. J. *J. Allergy Clin. Immunol*. **2011**, *128*, 1139.

3. Gushchin, I. S. *Pharm. Chem. J*. **2010**, *44*, 1-6.

4. Laccourreye, O.; Werner, A.; Giroud, J.-P.; Couloigner, V.; Bonfils, P.; Bondon-Guitton, E. *Eur. Ann. Otol. Rhinol. Laryngol. Head & Neck Diseases* **2015**, *132*, 31-34.

5. Nakaya, M.; Takeuchi, N.; Kondo, K. *Ann. Otol. Rhinol. Laryngol*. **2004**, *113*, 552-557.

6. Varty, L. M.; Gustafson, E.; Laverty, M.; Hey, J. A. *Eur. J. Pharmacol.* **2004**, *484*, 83-89.

7. McLeod, R. L.; Mingo, G. G.; Herczku, C.; DeGennaro-Culver, F.; Kreutner, W.; Egan, R. W.; Hey, J. A. *Am. J. Rhinol*. **1999**, *13*, 391-399.

8. Taylor-Clark, T.; Sodha, R.; Warner, B.; Foreman, J. *Br. J. Pharmacol*. **2005**, *144*, 867-874.

9. Procopiou, P. A.; Browning, C.; Buckley, J. M.; Clark, K. L.; Fechner, L.; Gore, P. M.; Hancock, A. P.; Hodgson, S. T.; Holmes, D. S.; Kranz, M.; Looker, B. E.; Morriss, K. M. L.; Parton, D. L.; Russell, L. J.; Slack, R. J.; Sollis, S. L.; Vile, S.; Watts, C. J. *J. Med. Chem.*, **2011**, *54*, 2183-2195.

10. Łazewska, D.; Kieć-Kononowicz, K. *Expert Opin. Ther. Patents*, **2014**, *24*, 89-111.

11. Wager, T. T.; Pattersen, B. A.; Schmidt, A. W.; Spracklin, D. K.; Mente, S.; Butler, T. W.; Howard, H. Jr; Lettiere, D. J.; Rubitski, D. M.; Wong, D. F.; Nedza, F. M.; Nelson, F. R.; Rollema, H.; Raggon, J. W.; Aubrecht, J.; Freeman, J. K.; Marcek, J. M.; Cianfrogna, J.; Cook, K. W.; James, L. C.; Chatman, L. A.; Iredale, P. A.; Banker, M. J.; Homiski, M. L.; Munzner, J. B.; Chandrasekaran, R. Y. *J. Med. Chem.*, **2011**, *54*, 7602-7620.

12. Letavic, M. A.; Aluisio, L.; Atack, J. R.; Bonaventure, P.; Carruthers, N. I.; Dugovic, C.; Everson, A.; Feinstein, M. A.; Fraser, I. C.; Hoey, K.; Jiang, X.; Keith, J. M.; Koudriaova, T.; Leung, P.; Lord, B.; Lovenberg, T. W.; Ly, K. S.; Morton, K. L.; Motley, S. T.; Nepomuceno, D.; Rizzolio, M.; Rynberg, R.; Sepassi, K.; Shelton, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4210-4214.

13. Daley-Yates, P.; Ambery, C.; Watson, J.; Oliver, A.; McQuade, B. *Int. Arch. Allergy Immunol*. **2012**, *158*, 84-98.

14. Stokes, J. R.; Romero, F. A.; Allan, R. J.; Phillips, P. G.; Hackman, F.; Misfeldt, J.; Casale, T. B. *J. Allergy Clin. Immunol*. **2012**, *129*, 409-412.

15. Barchuk, W. T.; Salapatek, A. M.; Tingting, G.; D'Angelo, P.; Liu, X. *J. Allergy Clin. Immunol*. **2013**, *132*, 838-846.

16. Procopiou, P. A.; Ancliff, R. A.; Bamford, M. J.; Browning, C.; Connor, H.; Davies, S.; Fogden, Y. C.; Hodgson, S. T.; Holmes, D. S.; Looker, B. E.; Morriss, K. M. L.; Parr, C. A.; Pickup, E. A.; Sehmi, S. S.; White, G. V.; Watts, C. J.; Wilson, D. M.; Woodrow, M. D. *J. Med. Chem*. **2007**, *50*, 6706–6717.

17. Ancliff, R. A.; Hancock, A. P.; Kranz, M. J.; Parr, N. J. WO2007135081

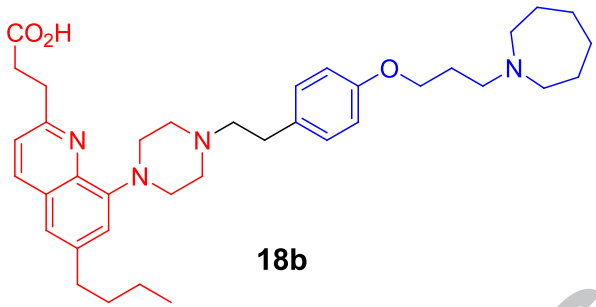
18. All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.

19. North, M. L.; Walker, T. J.; Steacy, L. M.; Hobsbawn, B. G.; Allan, R. J.; Hackman, F.; Sun, X.; Day, A. G.; Ellis, A. K. *Allergy, Asthma & Clinical Immunology*, **2014**, *10*, 33.

20. Spectroscopic data for **18b**: LCMS RT=2.38 min, 100%, ES+ve *m/z* 601 $(M+H)^+$ and ES-ve *m/z* 599 $(M-H)^-$; ^1H NMR (CD_3OD, 400 MHz) 8.50 (1H, s), 8.07 (1H, d, J 8.5 Hz), 7.37 (1H, d, J 8.5 Hz), 7.32 (1H, br s), 7.24 (2H, d, J 8.5 Hz), 7.10 (1H, br s), 6.92 (2H, d, J 8.5 Hz), 4.08 (2H, t, J 6 Hz), 3.63-3.52 (4H, m), 3.40-3.26 (11H, m, obscured by solvent),

3.20-3.14 (2H, m), 3.03-2.97 (2H, m), 2.83 (2H, t, J 7 Hz), 2.75 (2H, t, J 7.5 Hz), 2.26-2.18 (2H, m), 1.95-1.88 (4H, m), 1.77-1.64 (6H, m), 1.45-1.35 (2H, m), 0.96 (3H, t, J 7.5 Hz).

Graphical abstract



18b

3-(8-(4-(4-(3-(azepan-1-yl)propoxy)phenethyl)piperazin-1-yl)-6-butylquinolin-2-yl)propanoic acid
pA_2 = 8.8 for H_1 receptor
pKi = 9.1 for H_3 receptor