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Tricyclic aminopyrimidine histamine H_4 receptor antagonists

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ABSTRACT

This report discloses the development of a series of tricyclic histamine H_4 receptor antagonists. Starting with a low nanomolar benzofuranopyrimidine HTS hit devoid of pharmaceutically acceptable properties, we navigated issues with metabolism and solubility to furnish a potent, stable and water soluble tricyclic histamine H_4 receptor antagonist with desirable physiochemical parameters which demonstrated efficacy a mouse ova model.

The histamine H_4 G-protein coupled receptor is expressed on various cells of the immune system and has been demonstrated to influence chemotaxis and cytokine production.[1–6] Consequently, histamine H_4 antagonists have been shown to have a role in several animal models of human inflammatory diseases such as asthma, pruritis, and colitis as well as pain.[7,8]

Initial High Throughput Screening (HTS) identified several leads (Fig. 1), the most tractable of which were the three structurally distinct series; indole/benzimidazole carboxamides (JNJ 7777120, JNJ 10191584),[9] tricyclic aminopyrimidines (**1** and **2**), and the 2-aryl-benzimidazoles[10] (**3**). We[10] and others[11] have reported extensively on the indole carboxamides typified by JNJ 7777120, while more recently we disclosed H_4 functional attributes for a series of 2-aryl- benzimidazoles.[12] Recent reports describing aryl tricyclic aminopyrimidines[13,14] as H_4 receptor ligands have prompted us to disclose our efforts in this area.

The structural similarity between the indole carboxamides and the tricycles was readily apparent where the tricycles represent a constrained version of the carboxamides (Fig. 2). In this model, if the distal nitrogens are aligned, then the aryl nucleus in both series have reasonable overlap. Additionally, chlorine substitution (**2** vs **1**) increased activity in this series as reported with the carboxamides.[9] Although compounds **1** and **2** were unstable to human liver microsomes ($t_{1/2}$ <5 min), they nonetheless represented a potent series worthy of additional study.

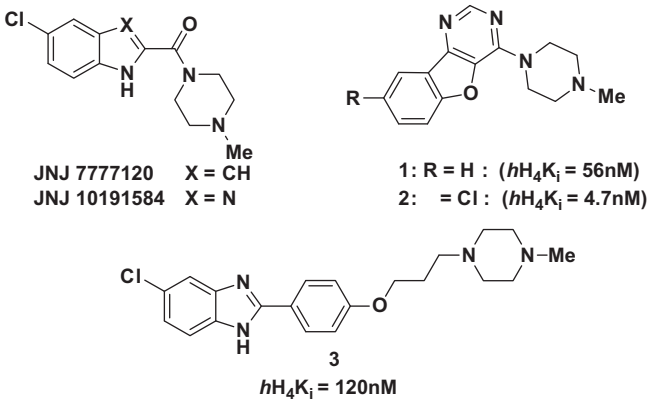

Figure 1. Select histamine H_4 ligands.

Our initial work to explore this new series was carried out on the related benzothienopyrimidines, which were obtained by diamine displacement of the corresponding chloride. Initial efforts demonstrated that piperazine (**4**) was preferred as other diamines (**5–7**) were less active (Fig. 3); similar to the trends that we

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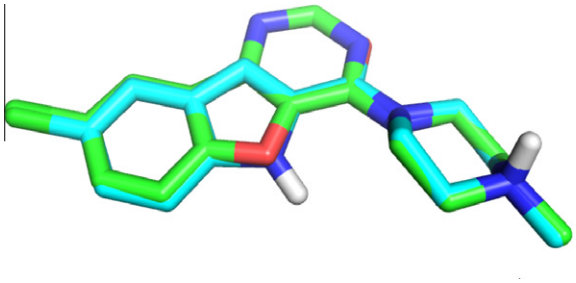


Figure 2. Overlap of JNJ 7777120 (cyan) with HTS hit **2** (green).

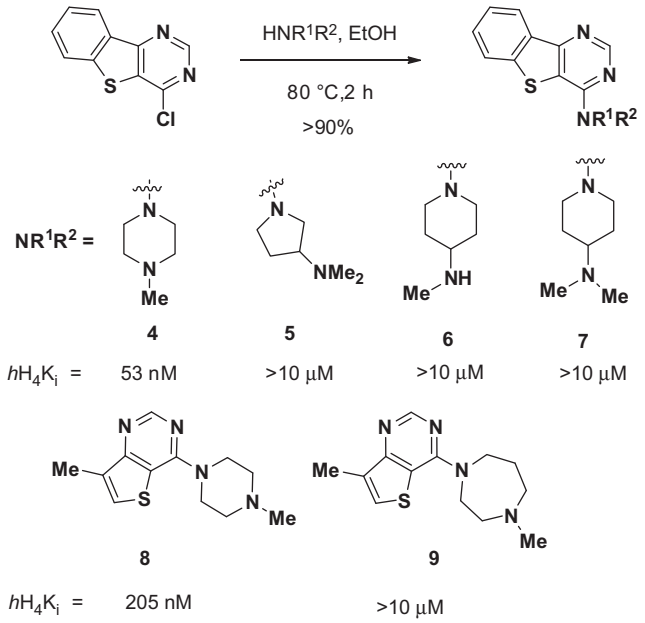


Figure 3. Initial (benzo)thienopyrimidine SAR.

observed with the indole carboxamides. Additionally, derivatives which lacked the fused phenyl ring (**8** and **9**) were also less active.

In our efforts to probe the pharmacophore, we began to introduce polar substituents onto the benzofuranopyrimidines to address the two liabilities of this series, namely the poor metabolic stability and the low aqueous solubility (vide infra, Fig. 4).

The first generation synthesis of the benzofuranopyrimidines is shown in Scheme 1. Alkylation of a corresponding cyanophenol with ethyl bromoacetate followed by base mediated ring closure afforded the bicyclic amino ester. Acylation followed by condensation with hydrazine and subsequent reduction yielded the tricyclic pyrimidine dione. Conversion to the dichloro pyrimidine was followed by displacement with diamines at the more reactive 4-chloro-position. Finally the 2-amino group was introduced via a two step process of displacement with 4-methoxybenzylamine followed by TFA mediated debenzylation.

Concurrent with the synthesis of the benzofuranopyrimidines, an alternative strategy was pursued for the assembly of the 2-amino-benzothienopyrimidines (Scheme 2). Treatment of the readily available *ortho*-fluoronitriles with methylthioglycolate and base delivered the bicyclic amino esters in one pot. Condensation of the amino ester with chloroformamidine·HCl led to the production of the tricyclic pyrimidinone with the 2-amino group installed. Conversion to the chloride[15] followed by displacement with diamines delivered the desired products. A similar sequence using ethyl glycolate (not shown) was subsequently applied to the synthesis of the benzofuranopyrimidines.

One of the earlier molecules made in this series was compound **10b** (Fig. 4), which maintained potency and also increased the stability in rat in vitro metabolism assays relative to compound **2**. Replacing the piperazine with methylamino pyrrolidine provided compound **11** which was stable in both human and rat liver microsomes.

Following these promising results, we scanned a series of diamines (Table 1) and observed that the 2-amino tricycles tolerated a wider range of diamines at the 4-position, in contrast to the carboxamides and the 2-des-amino tricycles. *N*-Methyl piperazine (**10b**) and (*R*)-*N*-methyl pyrrolidine (**10e**) are more potent than the *des*-methyl counterparts (**10b, 10f**), while the (*R*)-*N*-ethylamino pyrrolidine (**10g**) reduces affinity relative to **10d**, the addition of a hydroxyl (**10h**) regains some affinity. Though the *R*-enatiomer is preferred for the pyrrolidine derivatives (**10d, e**, **o**, and **p**), the 3-amino piperidines did not show a preference between enantiomers (**10k and l**), and the [2.2.1] bicyclic piperazine favored the *S,S* isomer (**10q and r**). The azetidine derivative (**10i**) was less potent than parent piperazine, but extension of the amine by a methylene spacer (**10j**) improved potency. However, the same modification led to decreased potency on the pyrrolidine core (**10m**).

In addition to scanning the right hand side diamines, we investigated the effect of different substituents around the aryl ring in the thieno and furano systems (Table 2). Because the thieno and

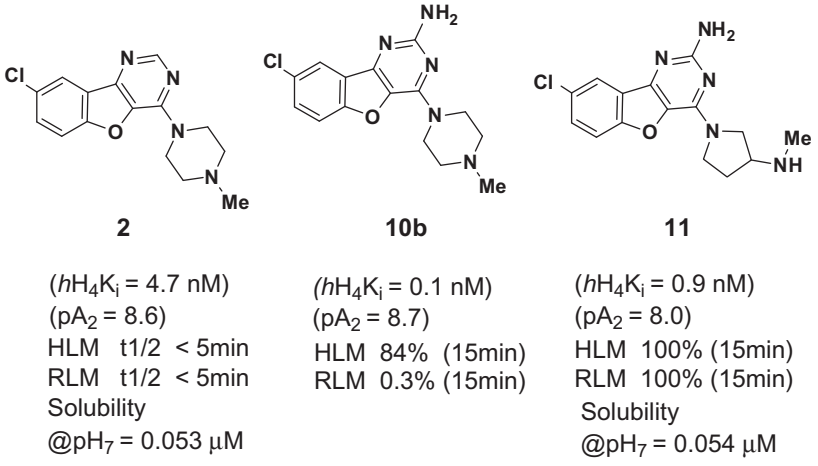
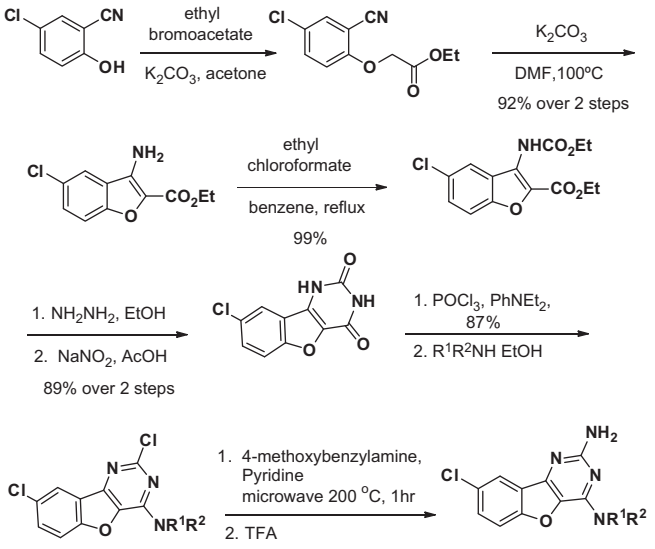
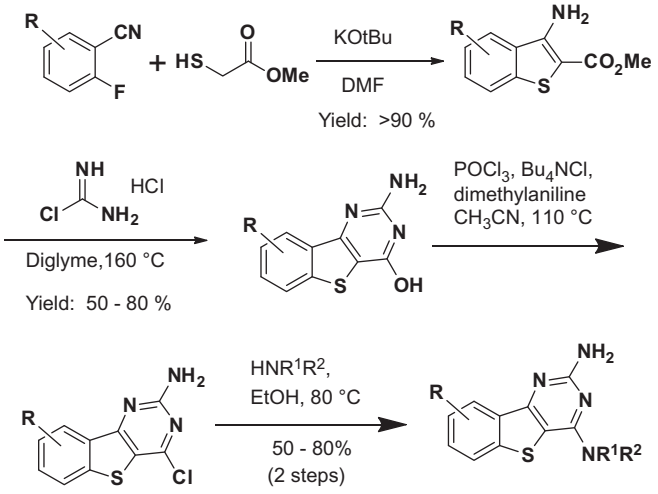


Figure 4. 2-Amino versus des-amino tricycle comparison.



Scheme 1. First generation synthesis of 2-aminopyrimidines



Scheme 2. Second generation synthesis of 2-aminopyrimidines.

furano series were screened in a complimentary fashion, there are few direct comparisons. However, a comparison of the 8-chloro derived *N*-methylpiperazines shows that the thieno derivative (**26b**) is of comparable activity to the furano counterpart (**10b**), and this holds with (*R*)-methylamino pyrrolidine (**26d, 10d**). In both the furano and thieno series, the 8 position was preferred with substitution at the 7 or 9 position usually reducing affinity. It is interesting to note that the 8-chloro furano series with certain diamines is significantly more active than with other substituents (**10b–e, k and q**). For example, the *S*-amino piperdine (**10k**) and the [2.2.1] bicyclic diamine (**10q**) have reasonable affinity with the 8-chloro substitution, while significantly reduced with other aryl substituents.

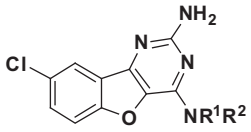
Though we had improved the potency and addressed the issues with metabolism, the tricyclic 2-aminopyridines had low aqueous solubility (Fig. 4, vide supra). Additionally many members of this series showed unacceptable signals in *h*ERG patch clamp assays not always concordant with the *h*ERG binding results (data not shown). Subsequently, we sought to simultaneously address the solubility and *h*ERG[17] issues by the incorporation of a pyridine into the left side aryl ring.

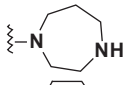
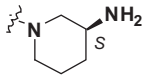
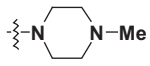
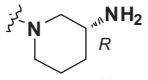
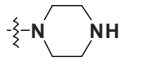
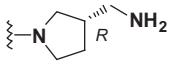
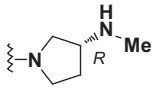
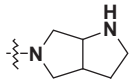
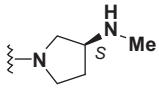
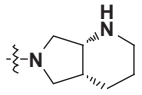
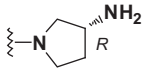
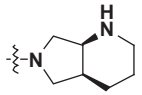
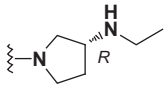
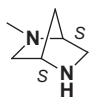
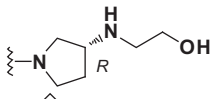
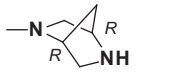
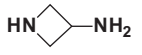
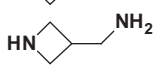
Synthetically (Scheme 3), the most readily accessible derivatives were obtained from commercially available 2-chloro-3-cyanopyridine in a similar method as previously demonstrated in Scheme 2. However, attempts to convert the pyrimidinone to the chloropyrimidine were not successful with a variety of reagents, and an alternate benzotriazole-1-yl-oxy-tris(dimethylamino) phosphonium hexafluoro phosphate (BOP) mediated method[18] of direct amine coupling to the pyrimidinone was employed.

In general, the pyridyl series was less potent relative to the carbon analogs, though several compounds still had respectable affinity (Table 3). Similar to the carbon series, a chlorine in the 8-position boosted affinity (des-chloro **37** $\underline{K}_i$ = 71 nM). The influence of a methyl group was not as pronounced in this series as *N*-methyl piperazine (**33**) and piperazine (**34**) were of equivalent potency as were the mono methyl (**37**) and desmethyl (**38**) *R*-aminopyrrolidines. The most notable compound from this series was JNJ 40279486 (**37**).

Subsequent profiling revealed that JNJ 40279486 had significantly improved solubility and no interaction with the *h*ERG channel up to 10 μM in binding assay, or 3 μM in a patch clamp assay. In addition, JNJ 40279486 showed good metabolic stability in all

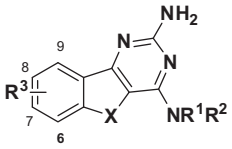
Table 1
Evaluation of diamine substitution



Compd #	NR^1R^2	hH_4 K_i[a] (nM)	Compd #	NR^1R^2	hH_4 K_i[a] (nM)
10a		1.1	**10k**		5.7
10b		0.1	**10l**		9.1
10c		1.1	**10m**		137
10d		0.4	**10n**		3.6
10e		2.1	**10o**		4.7
10f		2.4	**10p**		21
10g		75	**10q**		26
10h		46	**10r**		104
10i		19			
10j		3.4			

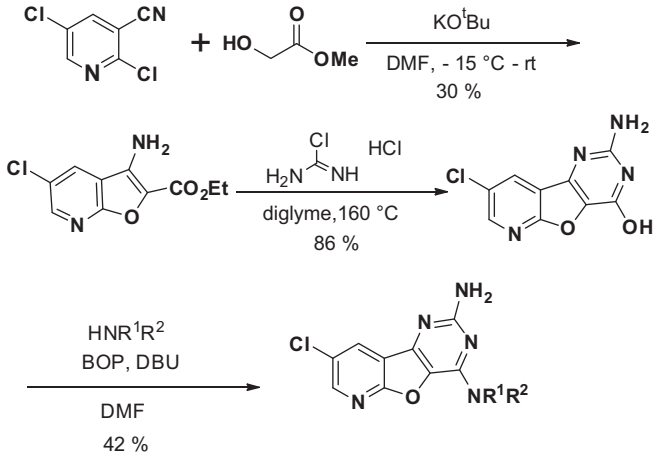
[a] Displacement of [^{3}H]histamine from the recombinant histamine H_4 receptor. K_i values are the geometric mean of three or more independent determinations.[16]

Table 2
SAR of furano and thieno pyrimidines



Compd #	X	R^3	NR^1R^2 = b	c	d	e	k	q
12	O	H		21	3.4			196
13		9-Cl	74	1049	40		>10,000	443
14		9-F	21	145	10			
15		9-CF_3	50	121	>10,000		>10,000	884
16		9-OMe	30	47	20		>10,000	>10,000
17		8-Br			0.7			
10		8-Cl	0.1	1.1	0.4	2.0	5.7	27
18		8-F			2.0			
19		8-CF_3	0.8	13	1.0		42	272
20		8-OMe	12		11		363	416
21		6,8-di-Cl		138	8.0			>10,000
22		8,9-di-Cl	7.7	7.7	10		>10,000	>10,000
23		8,9-di-F	156	156	39		>10,000	>10,000
24	S	H	29					
25		8-Br	1.0		2.1	65		346
26		8-Cl	0.3		10	76		837
27		8-F	19		31			
28		7-Br	43		25	149		3227
29		7-Cl	18		5.2	33		882
30		7-CF_3	440		125	>10,000		>10,000
31		7-OMe	180		155	250		
32	S=O	8-Cl	1280					

Displacement of [^{3}H]histamine from the recombinant histamine H_4 receptor. K_i values are the geometric mean of three or more independent determinations.[16]

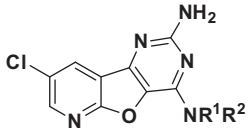


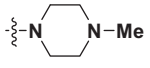
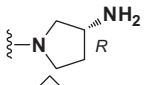
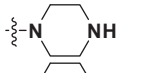
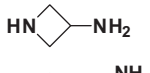
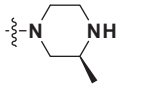
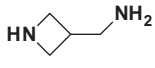
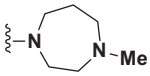
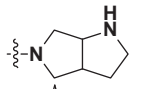
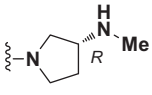
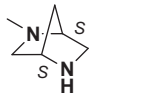
Scheme 3. Synthesis of pyridyl 2-aminopyrimidines.

species tested and was clean in the CEREP and Upstate cross reactivity and kinase panels. When dosed orally in rats, JNJ 40279486 achieved a C_{max} of 1.2 μM with a half-life 6.8 h and a bioavailability of 91%, while PK in the dog confirmed that JNJ 40279486 had desirable physiochemical properties achieving a C_{max} of 1.8 μM, with a half-life of 10.5 h and bioavailability identical to the rat (Fig. 5).

In vivo, JNJ 40279486 significantly reduced the number of inflammatory eosinophils found in lung lavage 24 h after the last of four antigen challenges when dosed orally 20 min before each antigen challenge (Fig. 6). For methods see Ref. 19.

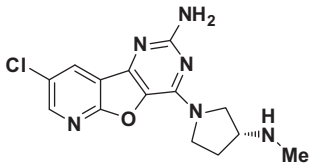
Table 3
Pyridyl series SAR



Compd #	NR^1R^2	hH_4 K_i[a] (nM)	Compd #	NR^1R^2	hH_4 K_i[a] (nM)
33		33	**38**		16
34		35	**39**		613
35		885	**40**		376
36		37	**41**		139
37		9.4	**42**		>10,000

[a] Displacement of [^{3}H]histamine from the recombinant histamine H_4 receptor. K_i values are the geometric mean of three or more independent determinations.[16]

In summary, starting with a high affinity tricyclic pyrimidine lead series devoid of physiochemical acceptable properties, the



JNJ 40279486

hH_4 Ki (nM)	9.4	Sol (pH = 7)	>0.4 μM
hH_4 pA_2	8.3	(pH = 2)	>0.4 μM
Metabolism		PPB % free	
human ($t_{1/2}$)	>180	(human)	43%
rat ($t_{1/2}$)	>61	(mouse)	18%
dog ($t_{1/2}$)	>180	Caco (cm/s*10^6)	
*h*ERG (IC_{50})	>10 μM	(A->B)	23
*h*ERG (PX)	>3 μM	(B->A)	22

PK Data	Rat	Dog
i.v. (2 mg/kg)		
$t_{1/2}$ (h)	1.2	9.7
AUC (μM*h)	1.6	5.2
Cl (L/h/kg)	4.1	1.3
Vss (L/kg)	6.9	16.5
p.o. (10 mg/kg)		
$t_{1/2}$ (h)	6.8	10.5
C_{max} (μM)	1.2	1.8
%F	91	91

Figure 5. Profile of JNJ 40279486.

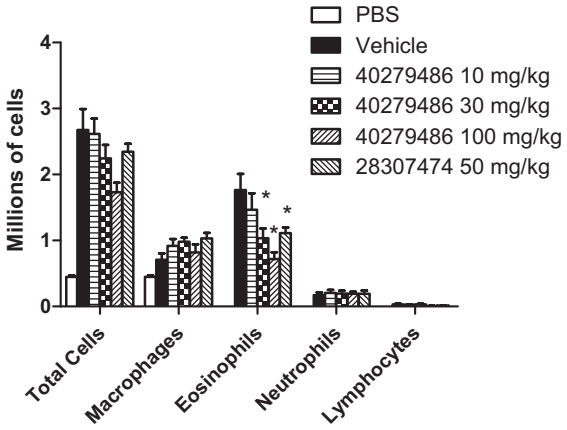


Figure 6. JNJ 40279486 inhibits eosinophils in the lung lavage in a mouse antigen asthma model. JNJ 28307474 used as a comparator.[19] Animals were dosed P.O. BID 20 min prior to each antigen challenge $^*P < 0.05$.

introduction of a 2-amino group maintained the affinity while improving human microsomal stability. Subsequently diamine tolerance was increased which delivered compounds which were stable in rat and human, but were poorly soluble and had undesirable signals in hERG assays. The substitution of an aryl ring with a pyridyl ring delivered JNJ 40279486 as a potent and selective H_4 receptor antagonist with desirable pharmaceutical properties that demonstrated acceptable pharmacokinetic profile and efficacy in a mouse model of inflammation.

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