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Brain-penetrating 2-aminobenzimidazole H_1-antihistamines for the treatment of insomnia

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ABSTRACT

The benzimidazole core of the selective non-brain-penetrating H_1-antihistamine mizolastine was used to identify a series of brain-penetrating H_1-antihistamines for the potential treatment of insomnia. Using cassette PK studies, brain-penetrating H_1-antihistamines were identified and in vivo efficacy was demonstrated in a rat EEG/EMG model. Further optimization focused on strategies to attenuate an identified hERG liability, leading to the discovery of **4i** with a promising in vitro profile.

H_1 receptors mediate allergic responses to histamine in the periphery, while centrally they mediate the effects of histamine on arousal.[1] First generation antihistamines including diphenhydramine (**1**) cross the blood–brain barrier (BBB) and cause sedation in humans.[2] Although first generation over-the-counter (OTC) antihistamines are used extensively for the treatment of insomnia, they exhibit several undesirable side effects such as drying of mucosal membranes attributed to muscarinic receptor blockade and next day impairment as a result of protracted CNS exposure.[3] Second and third generation antihistamines have been developed with diminished side effects due to improved selectivity profile although BBB penetration is limited. Despite improved receptor selectivity, some second generation antihistamines (i.e., terfenadine and astemizole) are potent inhibitors of the human ether-a-go-go (hERG) channel[4] implicated in prolongation of cardiac QTc and leading to serious and sometimes fatal cardiac arrhythmias.[5]

We have been interested in the discovery of selective H_1-antihistamines for development of an effective insomnia therapeutic free of the issues exhibited by OTC antihistamines. The benzimidazole core of mizolastine[6] (**2**), a highly selective second generation antihistamine with no detectable brain levels (at 10 mg dose po in humans), was used as a starting point and optimized for BBB penetration. Many factors have been described to contribute to the BBB penetration of antihistamines including lipophilicity, pK_a, hydrogen bonding capacity, mw, protein binding and affinity for Pgp.[7] The pyrimidinone side chain was thought to be a key contributor to limited BBB penetration at physiological pH, due to its relatively acidic nature (pK_a 4.7) and the fact that it can form 2 hydrogen bonds resulting in a relatively high polar surface area.[8] The benzimidazole core does not appear to be a contributing factor since this motif occurs in other related compounds with CNS effects.[9] We planned to generate novel and brain-penetrating H_1-antihistamines (**4**) from modification of the *N*-methyl pyrimidinone side chain with several *N*-alkyl, aryl, alkoxy and (hetero)aryl side chains (NR^1R^2), while simultaneously exploring substitution (R^3) on the benzyl moiety (Fig. 1).

The synthesis is outlined in Schemes 1 and 2. Benzimidazole chloride (**5**) was *N*-alkylated with a variety of alkylating agents in the presence of NaOH and subsequently coupled to *N*-Boc aminopiperidine in the presence of DIPEA to yield **7**. Sodium hydride-mediated alkylation installed the methyl group and removal of the Boc group afforded **8**. Amine functionalized analogs (**9**) were obtained by reductive amination with aldehydes, alkylation with alkyl halides or acylation with acylchlorides.

Alternatively, *N*-alkylated benzimidazole chloride (**6**) was coupled to 4-hydroxypiperidine in the presence of DIPEA to yield **10**, which was converted to the mesylate (**11**). Displacement of the mesyl group with a variety of amines or heterocycles afforded ana-

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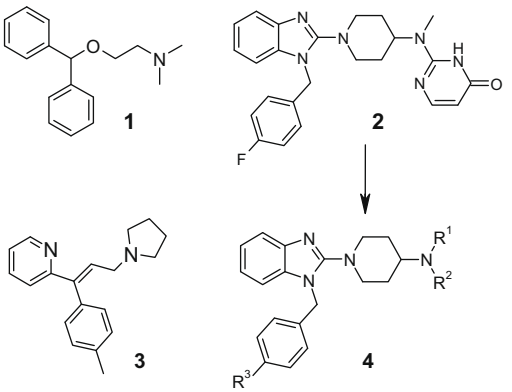
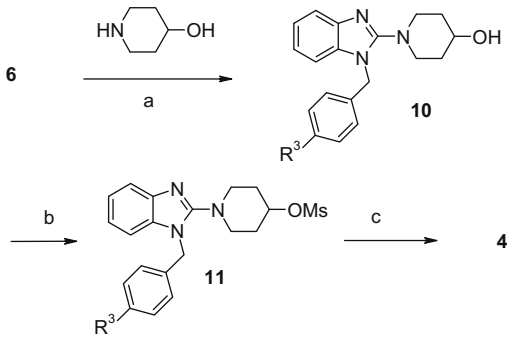


Figure 1. Diphenhydramine (**1**), mizolastine (**2**), triprolidine (**3**) and SAR explorations (**4**).

logs (**4**). All final compounds were purified by mass-triggered preparative HPLC.

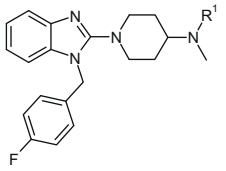
Compounds were tested in a histamine H_1 receptor binding assay (Supplementary data). To confirm initial selectivity, compounds were subsequently tested for muscarinic M_1 receptor binding affinity (Supplementary data) and inhibition of cytochrome P450 enzymes CYP2D6 and CYP3A4.[10] Data are shown in Tables 1, 4 and 5. No significant CYP3A4 inhibition (IC_{50} > 10 μM) was observed unless specifically indicated.

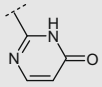
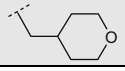
The pyrimidinone moiety was modified, while the *p*-F substituent (R^3) on the benzyl and the Me substituent (R^2) in **4** were kept constant. Removal of the keto group (**9a**) or substitution by phenyl (**9b**) significantly abolished activity. Extension to benzyl (**9c**) and phenethyl (**9d**) greatly improved H_1 binding affinity but decreased selectivity for M_1 and CYP2D6, presumably due to the additional hydrophobicity. Incorporation of heteroatoms (**9h**, **9i**) to reduce hydrophobicity (*c* Log *P* ~ 2 log units less compared to **9f** and **9e**, respectively**)** and increase polar surface area (34 vs 24 for **9e** and **9f**) improved the selectivity profile. The smaller aliphatic substituent (**9g**) resulted in a potent H_1 inhibitor with acceptable selectivity over M_1 and CYP2D6. With several selective compounds identified we then examined whether increased brain levels over mizolastine could be achieved. Compounds were assessed for their ability to penetrate the BBB in rodents using cassette PK studies (Supplementary data). Groups of 5 compounds including the short acting brain-penetrating antihistamine triprolidine[11] (**3**) were administered (iv) to rats and brain levels and B/P ratios were determined. Results for **9g**, **9h** and **9i** are shown in Table 2 and compared to **2** and **3**. All compounds had B/P ratios and brain levels that were significantly improved over **2** and comparable to or



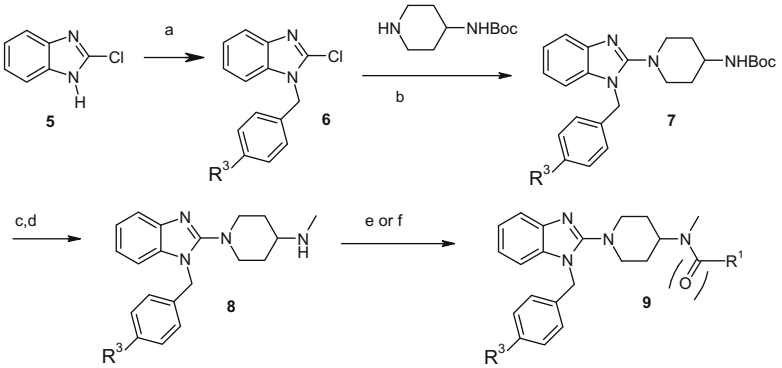
Scheme 2. Reagents and conditions: (a) DIPEA, neat, 139 °C; (b) MsCl, DIPEA, 0 °C to rt; (c) HNR^1R^2, DIPEA, 80 °C or NaH/HNR^1R^2, rt.

Table 1
Exploration of the R^1 substituent



Compound	R^1	H_1 K_i[a] (nM)	M_1 K_i[b] (nM)	CYP2D6 IC_{50} (nM)
2		2.7 ± 0.7	>10,000	>20,000
9a		75.2 ± 11.9	>10,000	1036
9b	–Ph	80.5 ± 10.2	>10,000	>20,000
9c	–Bn	3.6 ± 0.3	3581	805
9d	$-(CH_2)_2$ Ph	2.4 ± 0.4	89	502
9e	$-CH_2$–cHex	4.4 ± 0.2	3860	360
9f	–cHex	2.8 ± 0.5	2745	2053
9g	–Me	1.8 ± 0.1	1486	12,798
8a	H	2.4 ± 0.6	988	6664
9h		3.3 ± 0.2	14,747	6360
9i		3.9 ± 0.8	6486	11,017

[a] SEM for K_i values derived from dose response curves generated from triplicate or more data points.
[b] K_i values average of 2 data points.



Scheme 1. Reagents and conditions: (a) R^3BnX, NaOH; (b) DIPEA neat, 120 °C; (c) NaH, MeI; (d) TFA; (e) $R^1(=O)H$, $NaBH(OEt)_3$, HOAc; (f) R^1X, DIPEA, 95 °C or R^1COCl, DIPEA.

Table 2
Cassette PK studies (dose 1 mg/kg for each compound, iv, 2 h post dose)

Compound	[B] (ng/g)	[P] (ng/g)	B/P	[B] triprolidine (ng/g)	Pred. hCLint[a] (ml/min/kg)	Pred. rCLint[b] (ml/min/kg)
2	0	6.3	0	55.6	92	NT[c]
3	55.6	7.1	4.5	55.6	9.4	4993
9g	50	10.9	4.6	55.3	34.8	716
9h	55	18.1	3.5	39.4	126	436
9i	104	19.2	6.3	39.4	106	312

[a] Predicted based on HLM stability studies.
[b] Predicted based on RLM stability studies.
[c] NT = not tested.

better than **3**. Predicted clearance for **9h–i** was similar to **2** in human liver microsome studies.[12] Notably, the predicted intrinsic clearance in rats of all compounds was significantly higher than for human implying that brain exposure upon oral dosing might be an issue for these compounds.

As expected, at an oral dose of 10 mg/kg in Sprague Dawley rats, **9i** exhibited high clearance (134 ml/min-kg) and poor bioavailability (2% measured against an iv dose of 5 mg/kg) with measured plasma exposure of 9 ng/ml (4 h). Nevertheless, brain levels (94 ng/g at 4 h) were sufficient to assess its hypnotic potential in rats using EEG/EMG recordings. Rats, equipped with EEG and EMG biopotential leads,[13] were orally dosed with either vehicle, zolpidem[14] (GABA-A modulator) as positive control or test compound 6 h into the dark phase. EEG and EMG signals were collected 24 h prior to, and 18 h after, compound administration. As shown in Table 3, **9i** significantly increased time spent in NREM and the duration of NREM sleep bouts as compared to vehicle. Results were similar to that for the positive control zolpidem. NREM sleep latency was decreased and REM sleep latency was increased by **9i**, but these did not reach statistical significance. Analysis of effects on REM sleep indicated that **9i** did not significantly affect time in REM sleep or the length of REM sleep bouts in contrast to zolpidem at doses used. Overall, these studies were consistent with reported effects of antihistamines on sleep/wake parameters in rats.[15]

Compound **9i** was further profiled against other GPCRs and the hERG channel to examine any possible off-target liabilities. **9i** did not show appreciable binding to either H_3 or $5HT_{2a}$ (Supplementary data) excluding off-target effects on the EEG results,[16] but was a very potent hERG inhibitor (patch clamp IC_{50} of 29 nM).[12] A ^{3}H-dofetolide binding assay (Supplementary data) was used as a high-throughput screening alternative to whole cell patch clamp electrophysiology to evaluate all compounds for hERG. In this assay **9i** had a K_i of 18 nM (Table 4).

A number of strategies were explored to improve hERG selectivity (Table 4).[17] Changes in electron density in the benzyl substituent only had a modest effect on hERG based on comparison of **9g** (*p*-F) to **9j** (*p*-Me) and **9k** (*p*-OMe) or **9i** (*p*-F) to **9l** (*p*-OMe). Given our requirement for CNS activity, zwitterionic moieties were not explored to attenuate hERG function as previously described for antihistamines.[18] Reduction of pK_a[19] and/or log *P* had modest impact on hERG selectivity as exemplified by comparison of **9i** to compounds **9g**, **9m** and **9n**.[20] The more significant improvement in hERG selectivity (~20-fold increase) was noted through replacement of the tertiary amine for the secondary amine in **4c**. Once combined with the *p*-OMe benzyl substituent, (**4d**) hERG binding was decreased to 1461 nM, although H_1 binding also decreased slightly. Addition of a second positive charge in diamine **9o** offered an approximate 50-fold improvement in selectivity over hERG while maintaining H_1 potency. Removal of the basic center in some compound classes[21] including antihistamines[22] has been used to modulate hERG activity although with concomitant loss of H_1 potency.[22] In this series, removal of the basic center by incorporation of a lactam (**4e**) resulted in a potent H_1 binder with no detectable hERG inhibition. Additional heterocycles were explored at this position. Comparison of the pyrrole (**4f**), to the imidazole (**4g**) and pyrazoles (**4h–j**) indicated improved H_1 affinity for analogs **4g–j**. The pyrazoles exhibited a more promising selectivity profile. Methyl substitution in **4i** and **4j** improved both H_1 binding and selectivity over **4h**. With **4i** and **4j**, hERG selectivity was improved ~100-fold over the original lead **9i**. Patch clamp analysis showed that **4i** (IC_{50} = 809 nM) and **4j** (IC_{50} = 580 nM) had significant, yet comparable hERG inhibition to mizolastine (IC_{50} = 441 nM at 37 °C).[4b]

Both lactam **4e** and pyrazole **4i** were considered for further profiling. From in vitro studies,[12] **4e** had acceptable stability (Pred. hClint 45 ml/min/kg) and good permeability (Caco-2[12]: Papp 12.4×10^{-6} cm/s; A > B/B > A = 0.6) with no evidence for Pgp substrate. However, from cassette PK studies, no detectable brain levels and very low plasma concentrations (estimated 2 ng/ml) were observed implying a plasma stability issue, making this compound unsuitable for further evaluation. In contrast **4i** had a promising profile in comparison to **9i** (Table 5). Compound **4i** was selective for M_3, $5HT_{2a}$ and H_3 with significantly less hERG inhibition than **9i**. While intrinsic clearance was higher and brain penetrability lower than observed for **9i**, discrete rat PK studies revealed sufficient brain exposure to anticipate a hypnotic effect in EEG studies.

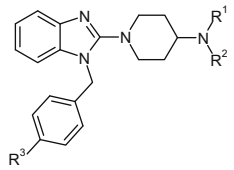
In conclusion, we were able to use the benzimidazole core of a highly selective yet non-sedating antihistamine to identify a series of brain-penetrating H_1-antihistamines. With the use of cassette PK studies, compounds suitable for in vivo efficacy studies were rapidly identified and efficacy in a rat EEG/EMG model was demonstrated with compound **9i**. Unfortunately, the series showed poor selectivity for the hERG channel. Exchange of the amine NR^1R^2 for certain heterocycles proved most beneficial in attenuation of this liability and resulted in compound **4i**, which exhibited brain exposure in rat models and had a similar hERG selectivity as

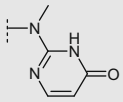
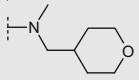
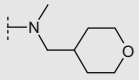
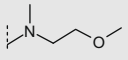
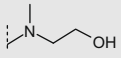
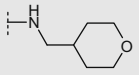
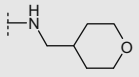
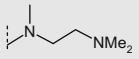
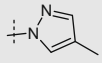
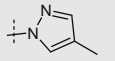
Table 3
EEG profile of **9i**

Compound	NREM in 4 h (%)	NREM latency (min)	Longest 3 NREM bouts in 6 h (min)	REM in 4 h (%)	Longest 3 REM bouts in 6 h (min)	REM Latency (min)
Vehicle	24.7 ± 2.8	47 ± 6	4.7 ± 0.9	2.9 ± 0.7	1.4 ± 0.2	94 ± 14
9i[a]	47.2 ± 3.2*	21 ± 2	11.0 ± 1.6*	2.6 ± 0.8	0.5 ± 0.2	110 ± 18
Zolpidem[b]	48.3 ± 2.1*	7 ± 1*	10.9 ± 1.6*	0.4 ± 0.1*	1.4 ± 0.3	186 ± 32*

[a,b]Dose 30 mg/kg, po.
* $P < 0.05$ versus vehicle (10% cremophor EL/H_2O).

Table 4
Exploration of R^1–R^3 substituents for H_1 affinity and attenuation of hERG



Compound	NR^1R^2	R^3	H_1[a,b] K_i (nM)	CYP2D6[c] IC_{50} (nM)	hERG[d] K_i (nM)
2		F	2.7 ± 0.7	>20,000	7258
9g		F	1.8 ± 0.1	12,798	57
9j		Me	1.5 ± 0.1	7210	73
9k		OMe	2.4 ± 0.1	6072	158
9i		F	3.9 ± 0.3	11,017	18
9l		OMe	14.1 ± 1.6	8185	102
9m		F	2.2 ± 0.3	4444	40
9n		F	3.2 ± 0.5	35,150	116
4c		F	4.5 ± 0.3	12,134	426
4d		OMe	14.1 ± 1.6	16,309	1461
9o		F	2.9 ± 0.3	6134	776
4e		F	6.6 ± 0.7	4353	>7500
4f		F	59.3 ± 10.6	1534	157
4g		F	1.30 ± 0.1	1117[e]	137
4h		F	18.3 ± 1.9	1480	3536
4i		F	6.9 ± 0.9	5219	3849
4j		OMe	7.1 ± 0.8	7319	>5000

[a] SEM for K_i values derived from dose response curves generated from triplicate or more data points.
[b] all compounds >1000× selective for M_1 (data not shown).
[c] CYP3A4 IC_{50} > 5 μM (data not shown).
[d] K_i values were derived from single or duplicate data points.
[e] CYP3A4 IC_{50} 72 nM.

mizolastine. Further evaluation of these compounds is required to determine whether the obtained profile is sufficient to support their utility as sleep aids.

Table 5
Profile of **4i** compared to **9i**

Compounds	Selectivity over M_1, M_3, $5HT_{2a}$, H_3	hERG IC_{50} (nM)	Predicted hCLint (ml/min/kg)	B/P ratio 4 h	[B] 4 h (ng/g)
9i[a]	>1000	29	106	10	94
4i[b]	>1000	809	242	2.3	262

[a] Dose 10 mg/kg, po.
[b] Dose 30 mg/kg, po.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.05.086.

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