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SYNTHESIS AND SAR OF 4-(1*H*-BENZIMIDAZOLE-2-CARBONYL)PIPERIDINES WITH DUAL HISTAMINE H_1/TACHYKININ NK_1 RECEPTOR ANTAGONIST ACTIVITY

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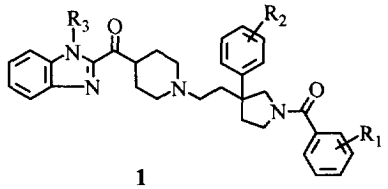
Abstract: A series of 4-(1*H*-benzimidazole-2-carbonyl)piperidines with dual histamine H_1/tachykinin NK_1 receptor antagonist activity has been prepared. Factors affecting receptor binding affinities and oral activity in this series are described. © 1997 Elsevier Science Ltd.

Due probably to the involvement of other mediators such as Substance P (SP), histamine H_1 receptor antagonists provide incomplete symptomatic relief in allergic rhinitis and related allergic inflammatory conditions.[1] The possibility that combined blockade of both histamine and substance P receptors might produce a significantly improved reduction of allergic symptoms has prompted us to explore the therapeutic potential of dual H_1/NK_1 receptor antagonism.[2] To this end, we have utilized molecular modeling as described in the accompanying paper[3] to design 4-(1*H*-benzimidazole-2-carbonyl)piperidines **1** with dual H_1/NK_1 receptor antagonist activity (Figure 1). The chemical synthesis and structure–activity relationships (SAR) of this series are described.

Figure 1

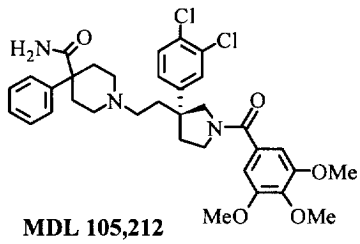


1

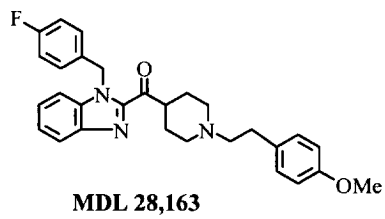
The design and synthesis of potent dual NK_1/NK_2 receptor antagonists, including MDL 105,212,[4] and selective H_1 receptor antagonists, including MDL 28,163,[5] has previously been reported from our laboratories (Figure 2). Based on SAR observed with the NK_1/NK_2 dual antagonists, we anticipated that NK_1 receptor affinity could be retained in hybrid structures **1** incorporating features from antihistamines such as MDL 28,163 in combination with the N-(3,4,5-trimethoxybenzamido)-3-arylpyrrolidine substructure. Since methoxylation of the phenethyl group of MDL 28,163 analogs significantly improves antihistaminic activity, we hoped that antihistaminic activity might likewise be enhanced by appropriately positioned methoxy groups in the dual H_1/NK_1 receptor antagonists. Hence, molecular modeling overlaps[3] between the histamine H_1 receptor

antagonist MDL 28,163 and the proposed 3-arylpyrrolidines led us to select the 3-(3,4-dimethoxyphenyl)-pyrrolidines **1a** and **1b** as initial targets (see Table 1). Our SAR exploration then focused on varying R_1, R_2, and R_3 on structure **1**.

Figure 2



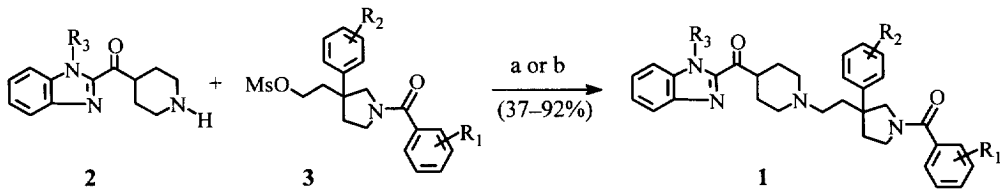
MDL 105,212
NK_1 IC_{50} = 3 nM
NK_2 IC_{50} = 8 nM
H_1 IC_{50} >10,000 nM



MDL 28,163
H_1 IC_{50} = 59 nM
NK_1 IC_{50} = 5200 nM
NK_2 IC_{50} = 3388 nM

Target compounds **1** were obtained either by reaction of benzimidazoylpiperidines **2** with mesylates **3** as shown in Scheme 1 or by alkylation of the benzimidazole 1-position as illustrated in Scheme 4. The various 4-(1*H*-benzimidazole-2-carbonyl)piperidines **2** were prepared via the methods outlined in Schemes 2 and 3 and applied to the preparation of specific examples as listed in Table 1. Racemic 3-arylpyrrolidines **3** were prepared from the corresponding phenylacetonitriles in five steps with minor variations from the published route.[4,6]

Scheme 1



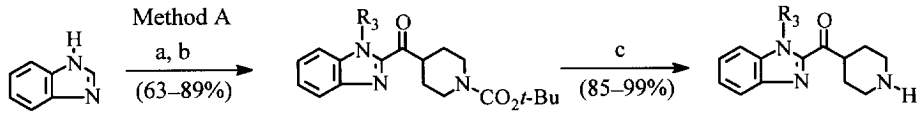
2 **3** **1**

Reaction conditions: (a) aq $NaHCO_3$/THF or aq Na_2CO_3/THF, (b) DIEA/CH_3CN.

In Scheme 1, nucleophilic displacement of the mesylate function, which is at a sterically hindered center, with the relatively bulky benzimidazoylpiperidines was often a slow reaction. Reactions between amines and mesylates in THF/water in the presence of sodium bicarbonate or sodium carbonate often required heating at reflux for 2–3 days for complete consumption of mesylate. Yields obtained by this method varied considerably and were often less than 50% of theory. Improvements in the rates of reactions and yields were effected by conducting the displacement reactions in refluxing anhydrous acetonitrile in the presence of diisopropylethylamine. Displacement reactions conducted in acetonitrile/DIEA were sometimes accelerated by using the benzimidazoylpiperidine hydriodic acid salts. To improve solubility for oral administration and handling characteristics, the product benzimidazoylpiperidines **1** were often converted to acid salts.

The preparation of **2** (R_3 = 4-F-PhCH$_2$) was accomplished using an adaptation of previously published chemistry from our laboratories (Scheme 2).[5,7] By this route, R_3 is incorporated in the first step of the synthesis (Method A) and must be stable to metallation at the benzimidazole 2-position. The desire for a more versatile and convenient means of varying R_3 prompted us to devise the new route shown in Scheme 3.

Scheme 2

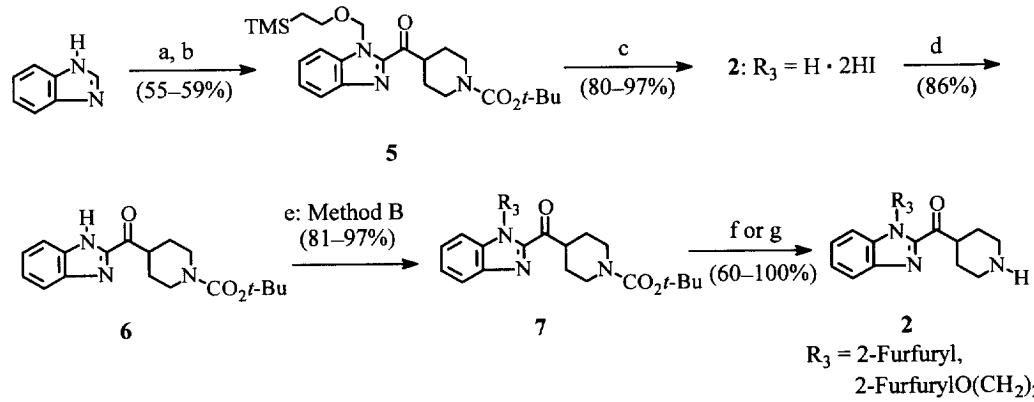


4 **2**: R_3 = 4-F-PhCH$_2$

Reaction conditions: (a) *i:* NaH, DMF; *ii:* 4-F-PhCH$_2$Cl; (b) *i:* *n*-BuLi, THF; *ii:* *N*-*tert*-butylcarbonate-protected 4-(*N*-methoxy-*N*-methyl-carboxamido)-1-piperidine, (c) *i:* trifluoroacetic acid; *ii:* aq NaHCO$_3$.

As shown in Scheme 3, protection of benzimidazole with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) followed by metallation and reaction with *N*-*tert*-butylcarbonate-protected 4-(*N*-methoxy-*N*-methyl-carboxamido)-1-piperidine provided benzimidazoylpiperidine **5** in good yield. Although selective removal of the SEM group proved difficult, simultaneous removal of both protecting groups from **5** with hydriodic acid efficiently gave the bis-hydriodic acid salt **2** (R_3 = H). Treatment of this material with di-*tert*-butyldicarbonate in

Scheme 3



5

6 **7** **2**
R_3 = 2-Furfuryl,
2-FurfurylO(CH$_2$)$_2$

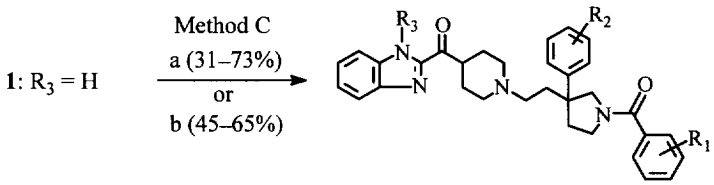
Reaction conditions: (a) *i:* NaH, DMF; *ii:* SEMCl; (b) *i:* *n*-BuLi, THF; *ii:* *N*-*tert*-butylcarbonate-protected 4-(*N*-methoxy-*N*-methyl-carboxamido)-1-piperidine, (c) 48% HI, 50 °C; (d) (BOC)$_2$O, 1 M NaHCO$_3$, *t*-BuOH; (e) R_3OH, DEAD, Ph$_3$P, THF; (f) *i:* trifluoroacetic acid, *ii:* aq NaHCO$_3$, CH$_2$Cl$_2$. (g) *i:* 4 N HCl dioxane, *ii:* aq NaHCO$_3$, CH$_2$Cl$_2$.

the presence of sodium bicarbonate selectively protected the piperidine nitrogen to give **6**. As exemplified, **6** efficiently participates in the Mitsunobu reaction[8] to give alkylation at the benzimidazole 1-position (Method B). Removal of the *tert*-butylcarbonate protecting group in **7** was accomplished under acidic conditions with 4

N HCl in dioxane, conditions which provided the best results with analogs bearing acid-sensitive functionality at R_3. The resulting acid salts were neutralized prior to their use in Scheme 1.

Alternatively, variation of the benzimidazole 1-substituent was accomplished as exemplified in Scheme 4. Unsubstituted benzimidazoylpiperidines **1** (R_3 = H) were readily prepared from the bis-hydriodic acid salt of **2** (R_3 = H) as described in Scheme 1. These compounds were then alkylated at the benzimidazole 1-position with various electrophiles to obtain the desired final products.

Scheme 4



1e, j–m, o–s

Reaction conditions: (a) R_3X (X = halogen), K_2CO_3, acetone/water, reflux., (b) R_3X (X = halogen), DBU, CH_3CN, reflux.

The human histamine H_1 and guinea pig lung tachykinin NK_1 receptor IC_{50} values of key compounds from this effort are summarized in Table 1.[9,10] Entries **1a–c** of Table 1 illustrate that, consistent with the SAR that we have observed with other substituted pyrrolidine derivatives (e.g., MDL 105,212), the 3,4,5-trimethoxybenzamide substituent is important for maintaining adequate NK_1 receptor binding affinity. Modifications in this region of the molecule did not produce large effects on H_1 receptor binding. In contrast to our expectations based on the SAR of MDL 28,163 and analogs, it was found that methoxylation of the phenyl ring at the pyrrolidine 3-position did not enhance H_1 receptor binding affinity (e.g., **1b** vs. **1i**). As illustrated by entry **1g**, ortho substitution on the 3-phenyl ring decreased binding affinity at both receptors of interest. Derivatives with R_2 = H such as **1i** and **1k**, displayed equivalent or improved dual receptor binding relative to the corresponding substituted analogs.

H_1 receptor binding affinities were profoundly affected by modifications at the benzimidazole 1-position. Lipophilic benzimidazole 1-substituents are required for good H_1 receptor binding. Hence, carboxylic acid-containing benzimidazole 1-substituents gave very poor binding affinity at the H_1 receptor whereas less polar heteroatom–containing substituents such as 2-ethoxyethyl or picolyl were compatible with adequate H_1 receptor binding affinity. Benzimidazole 1-substituents with suitably positioned heteroatoms slightly enhanced NK_1 receptor binding (e.g., **1h** vs. **1j**). A more quantitative accounting of substituent effects in this series of compounds was obtained using comparative molecular field analysis (CoMFA).[3]

In vitro, compound **1b** acted as a pure antagonist at both receptors of interest. Thus, compound **1b** inhibited histamine-induced contraction of guinea pig ileum in a concentration-dependent fashion with a

calculated pA_2 value of 7.52 and produced a dose-dependent inhibition of SP-induced increases in phosphatidylinositol turnover in UC11 cells with a computed pA_2 value of 7.18.[9] Based on this data, it was anticipated that **1b** and analogs possessing a similar balance of receptor binding affinities would act as dual antagonists in vivo.

Table 1

Compd	R_3 Attachment Method	R_1	R_2	R_3	H_1 IC_{50} (nM)[9]	NK_1 IC_{50} (nM)[9]
1a	A	H	3,4-$(MeO)_2$	4-F-$PhCH_2$	240	611
1b	A	3,4,5-$(MeO)_3$	3,4-$(MeO)_2$	4-F-$PhCH_2$	309	31
1c[a]	A	3,4,5-$(EtO)_3$	3,4-$(MeO)_2$	4-F-$PhCH_2$	158	1239
1d[b]	A	3,4,5-$(MeO)_3$	3,4-OCH_2O	4-F-$PhCH_2$	204	146
1e[a]	C	3,4,5-$(MeO)_3$	4-MeO	2-Picolyl	500	42
1f	A	3,4,5-$(MeO)_3$	4-CF_3	4-F-$PhCH_2$	473	117
1g	A	3,4,5-$(MeO)_3$	2,4-F_2	4-F-$PhCH_2$	436	296
1h[a]	A	3,4,5-$(MeO)_3$	3,4-Cl_2	4-F-$PhCH_2$	124	92
1i[a]	A	3,4,5-$(MeO)_3$	H	4-F-$PhCH_2$	233	34
1j[b]	C	3,4,5-$(MeO)_3$	3,4-Cl_2	2-Picolyl	437	32
1k	C	3,4,5-$(MeO)_3$	H	2-Picolyl	366	27
1l	C	3,4,5-$(MeO)_3$	H	3-Picolyl	416	27
1m	C	3,4,5-$(MeO)_3$	H	4-Picolyl	285	37
1n	-	3,4,5-$(MeO)_3$	H	H	500	36
1o	C	3,4,5-$(MeO)_3$	H	4-MeO_2C-$PhCH_2$	1210	23
1p[c]	C[d]	3,4,5-$(MeO)_3$	H	4-HO_2C-$PhCH_2$	3420	36
1q	C	3,4,5-$(MeO)_3$	H	2-MeO_2C-$PhO(CH_2)_3$	994	16
1r[c]	C[d]	3,4,5-$(MeO)_3$	H	2-HO_2C-$PhO(CH_2)_3$	9447	27
1s[b]	C	3,4,5-$(MeO)_3$	H	$EtO(CH_2)_2$	381	26
1t	B	3,4,5-$(MeO)_3$	H	2-Furfuryl	293	21
1u	B	3,4,5-$(MeO)_3$	H	2-Furfuryl$O(CH_2)_2$	446	12

[a]Maleate salt, [b]Methane sulfonate salt, [c]Hydrochloride salt, [d]Prepared by hydrolysis of the corresponding ester derivative, [e]Data for selective receptor ligands: Histamine, H_1 $IC_{50} \approx 1$ μM; Terfenadine, H_1 IC_{50} = 563 nM, NK_1 IC_{50} >10,000 nM; Substance P, NK_1 IC_{50} = 0.24 nM; CP 96,345, H_1 $IC_{50} \approx$ 10,000 nM, NK_1 IC_{50} = 0.56 nM.

Unfortunately, oral administration of **1b** as a solution was precluded by poor solubility in a variety of vehicles. Subsequently, it was found that the maleate salt of **1b** could be administered orally as a solution in 40% hydroxypropyl-β-cyclodextrin and that it inhibited the histamine-induced skin wheal response in guinea

pigs with an ED_{50} of 18.9 mg/kg.[9] The relatively poor oral potency was hypothesized to arise primarily from a combination of low aqueous solubility (< 0.1 μg/mL in 50 mM pH 7.4 phosphate buffer) and high lipophilicity (calculated log P = 4.72).[11] In support of this idea, the more soluble and less lipophilic picolyl derivative **1k** (solubility at pH 7.4 = 38 μg/mL, calculated log P = 3.22) was found to inhibit the histamine-induced skin wheal response with an oral ED_{50} = 10.3 mg/kg. Further studies to demonstrate similar oral activity at histamine H_1 and tachykinin NK_1 receptors and to explore the effect of dual receptor antagonism on allergen–induced responses were reserved for improved compounds and the results of these studies are in press.[2]

In summary, we have designed a series of benzimidazoylpiperidines with dual histamine H_1/tachykinin NK_1 receptor affinity. The lead compound from this series, **1b**, was shown to act as an antagonist with similar potency at both receptors in vitro. Compound **1b** is lipophilic, has poor solubility in pH 7.4 buffer, and shows relatively weak activity against histamine-induced skin wheal formation following oral administration. Future reports from our laboratories will describe the design of dual histamine H_1/tachykinin NK_1 receptor antagonists with significantly improved physiochemical properties and oral efficacy.

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References and Notes

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6. As with compounds in reference 3, most of the NK_1 receptor affinity is expected to reside in the (*R*) enantiomers of **1**. Preparation of optically pure pyrrolidinyl dual H_1/NK_1 receptor antagonists and the dependence of each of these activities on the absolute configuration at the pyrrolidine 3-position will be presented in future publications covering structurally related series of compounds.
7. Maynard, G. D.; Cheng, H. C.; Kane, J. M.; Staeger, M. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 753.
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9. For a detailed description of the biological assays used see ref 2.
10. All new compounds displayed spectra consistent with assigned structure and analytical data and are ≥95% pure by reverse-phase HPLC analysis.
11. Log P values were calculated using PCMODELS 4.41.

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