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4 - [(1H - IMIDAZOL - 4 - YL) METHYL] BENZAMIDINES AND BENZYLAMIDINES: NOVEL ANTAGONISTS OF THE HISTAMINE H3 RECEPTOR

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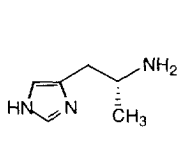
Abstract : A series of amidine substituted phenyl-, benzyl-, and phenethylimidazoles based on the known H_3 agonist SK&F 91606 (**4**) has been synthesized and tested as ligands for the histamine H_3 receptor. Insertion of a phenyl ring between the imidazole ring and the amidine moiety produces antagonists. The benzyl series was found to be the most potent and was further investigated. Compounds **9c** and **18** (entries 5 and 12, Table 1) are potent ligands for the H_3 receptor with K_i values of 16 nM and 7.2 nM respectively. In vivo, both compounds were shown to be equipotent to thioperamide (**2**), the standard H_3 antagonist.

Introduction

It is now well established that histamine exerts its biological influence via three separate receptors, namely the H_1, H_2 and H_3 receptors.[1] The existence of the H_3 receptor was originally postulated in 1983 by Arrang and coworkers who found that exogenous histamine inhibited the synthesis and release of [^{3}H]-histamine from electrically stimulated rat brain cortical slices.[2] However, it wasn't until the discovery of the potent ligands (R) - α - methylhistamine (**1**), an agonist, and thioperamide (**2**), an antagonist, that the H_3 receptor was fully characterized.[3] It is now apparent that the histamine H_3 receptor is a presynaptic receptor that controls the synthesis and release of histamine as well as other neurotransmitters such as serotonin, noradrenaline, and acetylcholine.[4] Recently this receptor has become a target for several groups interested in its pharmacology and potential therapeutic applications, especially in the CNS area. In particular, H_3 agonists and antagonists have been proposed for the treatment of, *inter alia*, sleep related disorders, cognitive disorders, and epilepsy.[5] We became interested in the potential use of H_3 agonists and antagonists for the treatment of various histamine mediated disorders and undertook a synthetic program aimed at the discovery of novel compounds based on the prototypical H_3 agonist (R)-α-methylhistamine (**1**). This work resulted in the discovery of a new class of potent H_3 agonists typified by the pyrrolidine **3**.[6] During the course of our work, a paper appeared that described the potent and selective H_3 agonist SK&F 91606 (**4**) which was reported to bind to the H_3 receptor with a K_i of 1.2 nM and to have no significant effect on H_1 or H_2 receptors at concentrations up to 10^{-5} M.[7]



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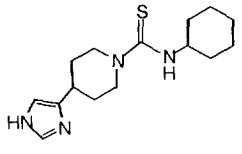

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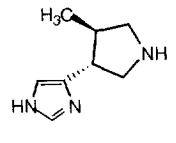

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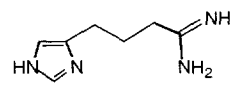

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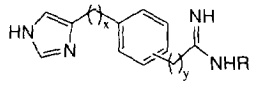
Based on its promising biological profile we choose SK&F 91606 (**4**) as a starting point in our efforts to discover novel H_3 ligands. Since the principle application of H_3 ligands appears to be in the CNS, our initial synthetic efforts were focused on increasing the lipophilicity of the parent compound **4** by synthesizing compounds of general structure **5** in which the propyl chain connecting the imidazole and amidine moieties of SK&F 91606 (**4**) was constrained in a phenyl ring. Toward this end, we have synthesized a series of amidine substituted phenyl, benzyl, and phenethyl imidazoles and assayed them for their affinity for the H_3 receptor.[8]



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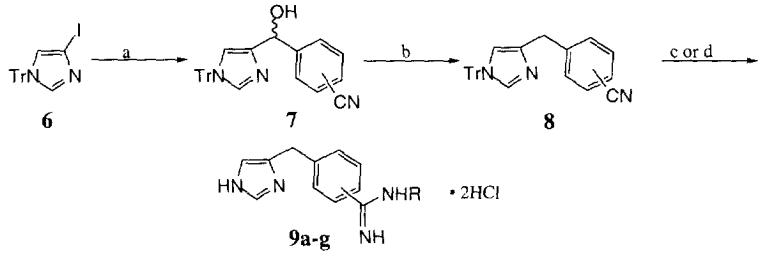
Chemistry

The syntheses of the compounds in Table 1 are given in Schemes 1- 3.[9] The compounds of entries 1 and 2 were prepared according to literature methods.[10] For those compounds in which x = 1 and y = 0, reaction of the Grignard reagent derived from 1-trityl-4-iodoimidazole (**6**) and ethyl magnesium bromide with 3- or 4-cyanobenzaldehyde gave the alcohol **7** in good yield.[11] Deoxygenation utilizing the Barton-McCombie protocol[12] gave the reduced compound **8**. Attempts to prepare **8** directly from the Grignard reagent and a substituted benzyl bromide were unsuccessful. Conversion of the nitrile in **8** into the amidine was accomplished by one of two methods. For unsubstituted amidines, treatment of the nitrile with hydroxylamine hydrochloride in ethanol/KOH gave the amidoxime.[13] Reduction of the hydroxyl group and deprotection gave the target **9** (R = H). Substituted amidines were most readily synthesized by treatment of nitrile **8** with the Weinreb reagent followed by deprotection.[14]

Scheme 1



6 **7** **8** **9a-g**

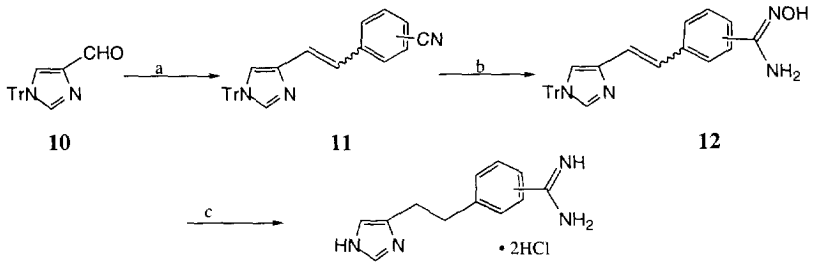
(a) i. EtMgBr, CH_2Cl_2, ii. NCC_6H_4CHO; (b) i. Thiocarbonyl diimidazole, THF, ii. n-Bu_3SnH, AIBN; (c) i. $(CH_3)_2AlNHR$ (for substituted amidines); ii. 1N HCl; (d) i. H_2NOH, KOH, EtOH (for unsubstituted amidines), ii. Ra-Ni, H_2, EtOH, iii. 1N HCl

The synthesis of those compounds in which x = 2 and y = 0 is given in Scheme 2. Wittig olefination of the protected imidazole-4-carboxaldehyde **10** gave the nitrile **11** which reacted with hydroxylamine hydrochloride to give amidoxime **12**. Reduction of the double bond and removal of the N - hydroxy group occurred concurrently to give the target compounds **13**.

Scheme 3 outlines the synthesis of those compounds in which x = 1 and y = 1 or 2. Compound **15** was obtained in the same manner as described for compound **8**. The acetal **15** was selectively hydrolyzed in the presence of the trityl group using Amberlyst 15 in aqueous acetone to give the aldehyde **16**. Aldehyde **16** was

homologated one carbon to the nitrile utilizing TosMIC® to give **17**.[15] Alternatively, **16** was homologated two carbons utilizing a Horner-Emmons reaction followed by reduction of the double bond to give the nitrile **19**. The nitriles were converted to the amidines **18** and **20** as before.

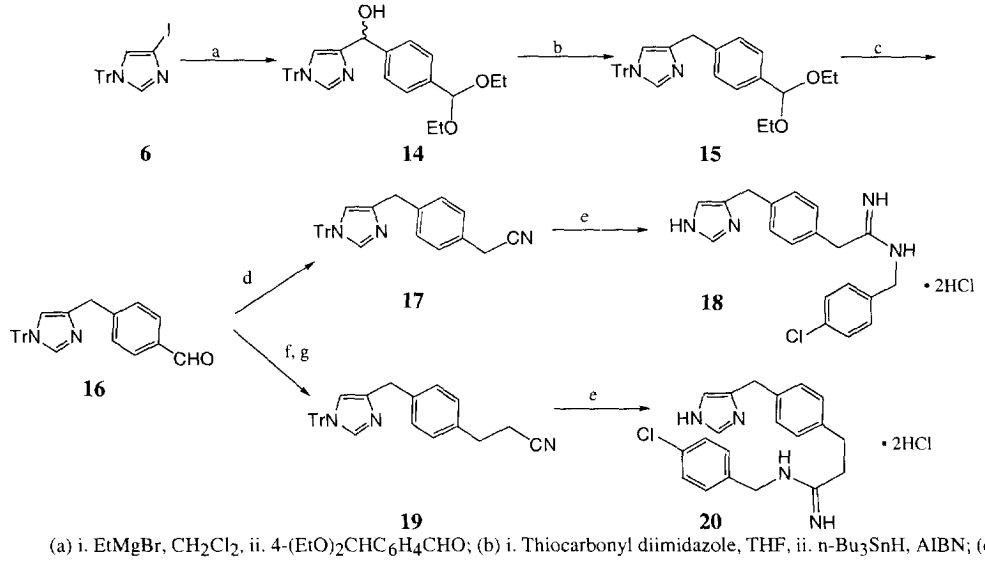
Scheme 2



13a-b

(a) t-BuOK, $Ph_3PCH_2C_6H_4CN$, THF; (b) H_2NOH, KOH, EtOH; (c)i. Ra-Ni, H_2, $MeOH/NH_3$, ii. 1N HCl

Scheme 3



(a) i. EtMgBr, CH_2Cl_2, ii. 4-$(EtO)_2CHC_6H_4CHO$; (b) i. Thiocarbonyl diimidazole, THF, ii. n-Bu_3SnH, AIBN; (c) Amberlyst-15, Acetone/Water; (d) t-BuOK, TosMIC; (e) i. $(CH_3)_2AlNHCH_2C_6H_4Cl$, ii. 1N HCl; (f) $(EtO)_2P(O)CH_2CN$, NaH, THF; (g) $NaBH_4$, MeOH, Pyridine

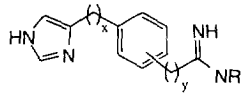
Discussion

H_3 binding activity was assayed as described by Korte et al.[16] Furthermore, all analogs were determined to be antagonists using an electrically stimulated guinea pig ileum strip as the in vitro functional assay.[17] Several notable trends are apparent from our work. First, simply bridging the three carbon side chain of SK&F 91606 (**4**) by inclusion of these carbons in a phenyl ring led to compounds with weak binding affinity for both the meta and para isomers (see Table 1; entries 1 and 2). Since biaryl systems of this type are relatively rigid, we decided to return some conformational flexibility to the molecule by the introduction of a methylene spacer

between the two aromatic rings. Although this change had no effect in the case of the meta isomer (entry 3; 310 nM), we were gratified to see that it led to a compound with significant activity for the para isomer (entry 4; 38 nM). Extending the methylene chain one additional carbon resulted in no significant change in binding for the meta isomer and a loss of activity for the para isomer (entries 10 and 11; 220 and 165 nM respectively). Based on the superior activity versus the other analogs, we decided to focus on the para substituted benzyl series for the remainder of this study.

We next turned our attention to the substituents on the amidine moiety. van der Goot et al. reported enhanced activity with the introduction of a 4-chlorobenzyl group on the terminal isothiourea moiety of a histamine analog.[18] In our series, this group also imparted enhanced activity (entry 5; 16 nM). However, other para substituted benzyl groups (entries 6 and 7), the 4-pyridylmethyl group (entry 8), or the phenethyl group (entry 9) gave analogs that were significantly less active.

Table I



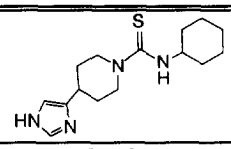
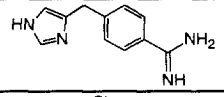
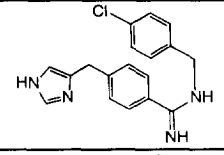
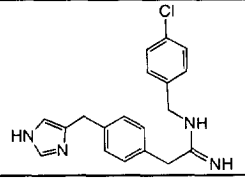
Entry	Compound Number	x	y	meta/para	R	K_i (nM) or % inhibition at 1 μM[a]
1	-	0	0	meta	H	350 ± 170
2	-	0	0	para	H	49% ± 3.5
3	9a	1	0	meta	H	310 ± 0.0
4	9b	1	0	para	H	38 ± 4
5	9c	1	0	para	4-$ClC_6H_4CH_2$	16 ± 5
6	9d	1	0	para	4-$CH_3OC_6H_4CH_2$	513 ± 74
7	9e	1	0	para	4-$CF_3C_6H_4CH_2$	140 ± 30
8	9f	1	0	para	4-PyridylCH_2	44% ± 3
9	9g	1	0	para	$C_6H_5CH_2CH_2$	445 ± 35
10	13a	2	0	meta	H	220 ± 20
11	13b	2	0	para	H	165 ± 35
12	18	1	1	para	4-$ClC_6H_4CH_2$	7.2 ± 0.4
13	20	1	2	para	4-$ClC_6H_4CH_2$	175 ± 25

[a]Determined on Guinea pig brain using N^{α}-methylhistamine as ligand. Values cited are the average of at least two independent determinations. The average K_i for thioperamide in this assay is 7.3 +/- 0.7 nM.

The importance of the relative distance between the amidine moiety and the terminal phenyl ring was investigated next by introducing one or two methylene spacers between these groups while keeping the 4-chlorobenzyl group constant. The one methylene spacer gave the most active compound in this study (entry 12; 7.2 nM). Interestingly, the two carbon homologue yielded a compound that was approximately 25 times less active (entry 13).

The most potent analogs (compounds **9b**, **9c**, and **18**, Table I) were further evaluated in an in vivo H_3 model as described by Hey et al.[19] and the results versus thioperamide, the standard H_3 antagonist, are shown in Table II. The two most potent analogs synthesized in our study were found to be slightly more potent than thioperamide (ED_{50} = 0.3 mg/kg iv for each versus 0.4 mg/kg for thioperamide) in this assay while the unsubstituted amidine was weakly active (33% inhibition at 3 mg/kg).

Table II

Structure	Compound number	Guinea Pig H_3 Binding K_i	In Vivo H_3 ED_{50} or % inhibition
	2	7.3 nM	0.4 mg/kg
	9b	38 nM	33%
	9c	16 nM	0.3 mg/kg
	18	7.2 nM	0.3 mg/kg

In conclusion, we have discovered a novel series of H_3 antagonists based on the H_3 agonist SK&F 91606 (**4**). Two of these compounds, **9c** and **18**, are equipotent, in vivo, to thioperamide (**2**), the standard H_3 antagonist.

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