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The Synthesis of Substituted Fluorenes as Novel Non-Imidazole Histamine H_3 Inhibitors

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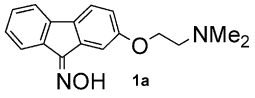
Abstract—A novel non-imidazole fluorene oxime **1a** has been identified as a histamine H_3 inhibitor, and its structure–activity relationship has been evaluated.

While the roles of H_1 receptor antagonists in the treatment of allergy and H_2 receptor antagonists in the treatment of gastric ulcers are well known, a pharmacological role for H_3 receptor antagonists has not yet been well delineated since its initial discovery in 1983.[1–3] The H_3 receptor is present in highest concentrations in the brain and may therefore be useful for central nervous system disorders such as attention-deficit disorder, Alzheimer's disease, narcolepsy, epilepsy, or schizophrenia. However, the H_3 receptor is also present in the peripheral nervous system, and recent research indicates that a combination of an H_1 antagonist with an H_3 antagonist may be useful in the treatment of nasal congestion associated with allergic rhinitis, which is not treated by an H_1 antagonist alone.[4] Allergic rhinitis affects over 20% of the US population and can result in sinusitis, otitis media, or nasal polyps. Current therapies for the treatment of congestion include oral decongestants such as pseudoephedrine, topical decongestants such as oxymetazoline, and nasal steroids all of which are known to have side effects such as hypertension, agitation, or insomnia.[4]

During a nasal allergic reaction, H_1 antihistamines minimize the plasma extravasation and mucus secretion caused by the release of histamine from mast cells. An H_3 antagonist, when used in conjunction with an H_1 antagonist, promotes decongestion by increasing vasoconstriction and blood flow by restoring the release of the neurotransmitter norepinephrine, an endogenous decongestant, which is reduced by histamine activation of the H_3 receptor. This decongestive effect is not observed for an H_3 antagonist alone. This hypothesis has been verified in a histamine-driven cat model of nasal congestion.[5] Our goal is to discover a novel, selective H_3 antagonist that can be used in combination with an H_1 antihistamine to relieve the nasal congestion associated with seasonal or perennial allergic rhinitis.

The first potent H_3 agonist and antagonist have been reported by Arrang and coworkers in 1987.[6] A qualitative model describing receptor-inhibitor binding for the H_3 receptor has been proposed by Timmerman and coworkers.[7,8] It is based on two hydrogen binding interactions between the receptor and an imidazole based inhibitor: one to the imidazole ring and one to a basic nitrogen in the side chain. The imidazole ring is considered important for biological activity, but the class of non-imidazole H_3 receptor ligands is expanding.[9–12] We have found the imidazole ring to be a liability in terms of liver enzyme inhibition and decided to focus our research efforts on a non-imidazole lead structure. Biological screening, using our in vitro H_3 receptor binding assay,[13] of our internal compound database identified compound **1a** as a novel H_3 receptor ligand.



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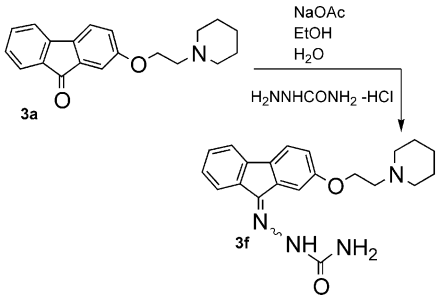
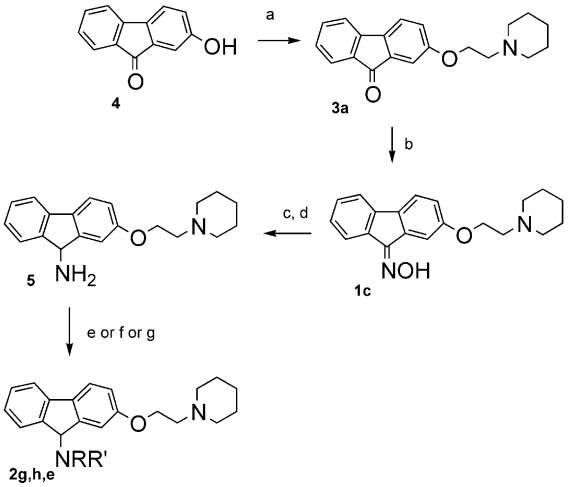
Compound **1a** has two possible hydrogen binding sites to fit the Timmerman model: the key oxime substituent and the dimethylamine side chain. Stark and coworkers have previously reported imidazole-based H_3 antagonists which contain an oxime moiety.[14] In this communication, we describe a series of analogues which study the SAR relationship of **1a**.

Analogues **1a**–**h** that have diverse substituents replacing the dimethylaminoethyl side chain were prepared by alkylation of commercially available 2-hydroxy-9-fluorenone **4** followed by oxime formation (1:1 *E*:*Z* isomer mixture) as shown for the piperidinoethyl compound **1c** in Scheme 1.[15] Further derivization of oxime **1c** with potassium bis(trimethylsilyl)amide as the base and the appropriate alkylating reagent yielded analogues **3d** and **3e**.

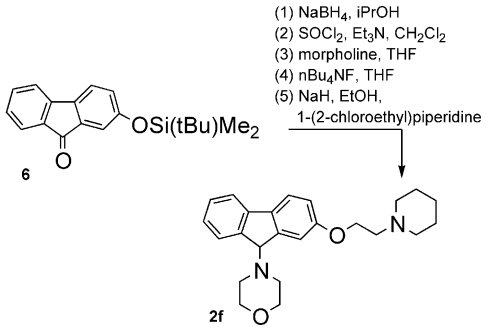
To replace the oxime moiety with a substituted nitrogen analogue, raney nickel reduction of oxime **1c** afforded amine **5** (Scheme 1). Amine **5** was not stable as the free base, and was stored and used as its hydrochloride salt. Acetylation of **5** produced amide **2g**, mesylation of **5** produced sulfonamide **2h**, and methylation of **5** produced amine **2e**.



The semicarbazone analogue **3f** was prepared by condensation of ketone **3a** with semicarbazide. Another nitrogen analogue, the morpholine compound **2f**, was prepared from ketone **6** by the following staightforward synthesis.



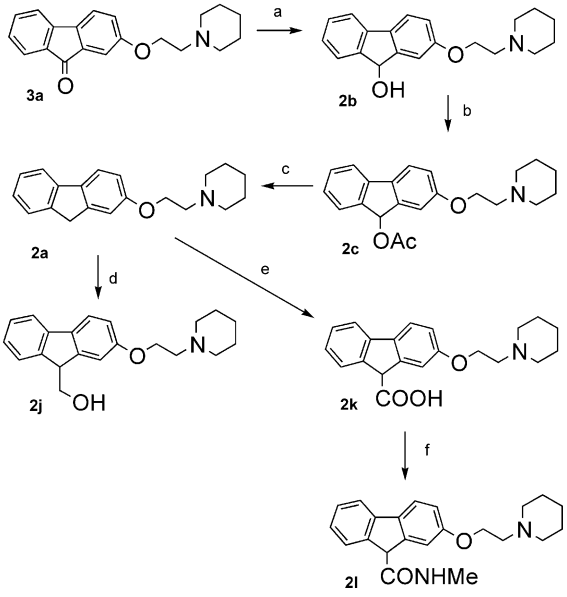
Scheme 1. (a) NaH, EtOH, 1-(2-chloroethyl)piperidine, Δ, 100%; (b) NH_2OH-HCl, pyridine, 89%; (c) H_2, RaNi, EtOH; (d) HCl/EtOH 86% for steps c and d; (e) AcCl, Et_3N, CH_2Cl_2, 50% for **2g**; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 40% for **2h**; (g) HCHO, HCOOH, Δ, 46% for **2e**.



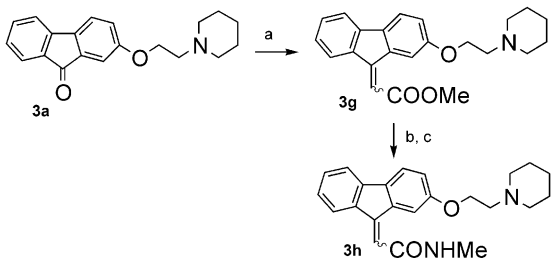
To replace the oxime moiety with a substituted oxygen analogue, ketone **3a** was reduced with sodium borohydride to give alcohol **2b** (Scheme 2). Acetylation of alcohol **2b** provided ester **2c** while addition to isopropylisocyanate provided carbamate **2d**.

To replace the oxime moiety with a substituted carbon analogue, acetate **2c** was hydrogenated to yield **2a**.[16] Formation of the anion of **2a** with *n*-butyl lithium and trapping with formaldehyde gave alcohol **2j**.[17] The anion was also trapped with carbon dioxide (solid dry ice powder) to afford acid **2k**.[18] Standard DEC coupling protocol converted acid **2k** to amide **2l**. Olefinic analogues were synthesized by a Wadsworth-Emmons reaction on ketone **3a** to provide the unsaturated ester **3g** (Scheme 3). Basic hydrolysis of **3g** and amide formation produced **3h**.

The biological activity of our side chain analogues **1a**–**h** are summarized in Table 1. Extension of the two carbon linker to a three carbon linker in **1b** retains H_3 activity. The dimethylamino group can be replaced with a cyclic piperidine **1c** or pyrrolidine **1d** and maintain H_3 potency indicating that there is some steric space available



Scheme 2. (a) $NaBH_4$, EtOH, 100%; (b) AcCl, Et_3N, DMAP, CH_2Cl_2, 100%; (c) H_2, Pd/C, EtOH, 82%; (d) *n*-BuLi, THF, 0 °C, HCHO, 51%; (e) *n*-BuLi, THF, 0 °C, CO_2, 31%; (f) DEC, HOBT, $MeNH_2$ in THF, CH_2Cl_2, 30%.

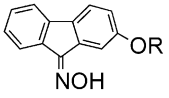


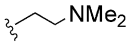
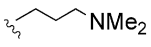
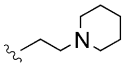
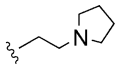
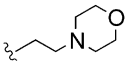
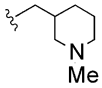
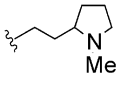
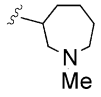
Scheme 3. (a) $(MeO)_2POCH_2COOMe$, NaH, DMF, 83%; (b) NaOH, THF, MeOH, H_2O, 90%; (c) DEC, HOBT, $MeNH_2$ in THF, CH_2Cl_2, 82%.

around the binding site of this nitrogen atom. In contrast, the morpholine analogue **1e** shows a decrease in biological activity. The spacial position of this nitrogen atom relative to the fluorene ring is important since the more constrained cyclic analogues **1f–h** are less active.

The analogues **2a–l** in Table 2 focus on the SAR of the oxime moiety with the side chain fixed as the piperidinoethyl ether. As the data indicates, the SAR of this position is very restrictive. Removal of the oxime moiety results in the inactive saturated analogue **2a**. Replacement of the oxime with a hydroxy group as in **2b** decreases H_3 activity slightly, and additional substitution as the acetate **2c** or the carbamate **2d** is even more

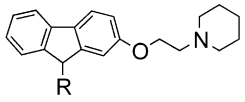
Table 1. In vitro H_3 activity of fluorene oximes **1a–h**



Example No.	R[a]	K_i (nM)[b]
1a		40
1b		48
1c		45
1d		65
1e		325
1f		920
1g		310
1h		110

[a]Compounds are a mixture of *E* and *Z* isomers.
[b]K_i values are the average of at least two independent determinations.

Table 2. In vitro H_3 activity of fluorenes **2a–l**



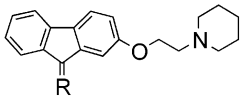
Example No.	R	K_i (nM)[a]
2a	H	20%[b]
2b	OH	190
2c	OAc	40%[b]
2d	OCONHiPr	20%[b]
2e	NMe_2	650
2f	Morpholine	15%[b]
2g	NHAc	27%[b]
2h	$NHSO_2Me$	13%[b]
2i	NHCONHiPr	17%[b]
2j	CH_2OH	570
2k	COOH	39%[b]
2l	CONHMe	19%[b]

[a]K_i values are the average of at least two independent determinations.

detrimental. Similarly, replacement of the oxime with a dimethylamino group as in **2e** reduces H_3 activity, and various nitrogen analogues **2f–i** are completely inactive. Several carbon analogues **2j–l** were synthesized, and only the hydroxymethyl compound **2j** shows some weak H_3 activity.

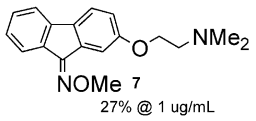
Due to the poor biological activity observed with analogues **2a–l**, we decided that the sp2 hybridization of the oxime must be important for achieving H_3 potency. The oxime isomers of **1c** were separated by preparative thin layer chromatography to give the *E* isomer **3b** and the *Z* isomer **3c**, and the biological activity resides in the *Z* isomer **3c** (Table 3). Ketone **3a** shows reduced activity as do the substituted oxime analogues **3d** and **3e** and the substituted hydrazine analogue **3f**. Even the simple methyl oxime **7** is inactive and indicates that the hydrogen bonding characteristic of the oxime is important for binding. The alkene analogues **3g** and **3h** also exhibit no H_3 activity. Therefore, the oxime substituent is unique in its small size and directionality of hydrogen binding capability to impart potent H_3 activity.

Table 3. In vitro H_3 activity of fluorenes **3a–h**



Example No.	R[a]	K_i (nM)[b]
3a	O	47%[c]
1c	NOH	45
3b	NOH (E)	690
3c	NOH (Z)	65
3d	$NOCH_2CN$	24%[c]
3e	$NOCH_2CH_2OH$	24%[c]
3f	$NNHCONH_2$	27%[c]
3g	CHCOOMe	20%[c]
3h	CHCONHMe	20%[c]

[a]Compounds are a mixture of *E* and *Z* isomers unless otherwise noted.
[b]K_i values are the average of at least two independent determinations.
[c]% Inhibition at 1 μg/mL.



In conclusion, SAR studies based on the lead structure **1a** have led to identification of other analogues in this series with equivalent binding potency, although none demonstrated an improved profile. Nevertheless, the identification of this novel non-imidazole series of H_3 inhibitors has encouraged our search for other possible non-imidazole lead structures. Additional studies will be reported in future publications.

Acknowledgements

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