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Aplysamine-1 and related analogs as histamine H_3 receptor antagonists

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Abstract—Aplysamine-1 (**1**), a marine natural product, was synthesized and screened for in vitro activity at the human and rat histamine H_3 receptors. Aplysamine-1 (**1**) was found to possess a high binding affinity for the human H_3 receptor ($K_i = 30 \pm 4$ nM). Synthetic analogs of **1**, including *des*-bromoaplysamine-1 (**10**) and dimethyl-{2-[4-(3-piperidin-1-yl-propoxy)-phenyl]-ethyl}-amine (**13**), were potent H_3 antagonists.

The histamine H_3 receptor is a G-protein-coupled receptor belonging to the family of histamine receptor subtypes (H_1, H_2, H_3, and H_4). The H_3 receptor is located presynaptically in the peripheral and central nervous systems, on both histaminergic neurons, as an autoreceptor, and other neuronal systems, as a heteroreceptor.[1] In this capacity, it functions as a negative modulator, inhibiting the release of histamine and other neurotransmitters such as acetylcholine, GABA, norepinephrine, and serotonin.[2,3] Histamine H_3 antagonists enhance levels of cerebral histamine and, therefore, may be useful for the treatment of neurological disorders affecting memory, appetite, and sleep.[4]

The histamine H_3 receptor was first characterized in 1983[1] and subsequently cloned and expressed some 15 years later.[5] Early ligand design centered around the well-known affinity of 4(5)-substituted imidazoles for the H_3 receptor.[6] Representative examples of this class of ligands include the first potent and selective agonist, (*R*)-α-methylhistamine (**2**), and the antagonist, thioperamide (**3**) (Fig. 1).[7] Historically, imidazole-based H_3 compounds have suffered from poor drug-like properties, including metabolic degradation by histamine N-methyltransferase (HMT), cytochrome P_{450} inhibition, and inability to penetrate the blood–brain barrier in high concentration.[8] Few imidazole-based H_3 ligands have advanced into human clinical development and to date, no selective H_3 receptor ligand has been approved for therapeutic use.[8,9]

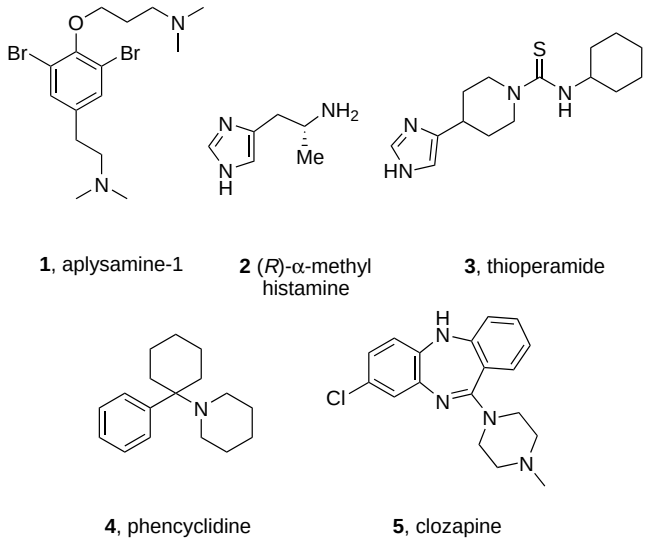

Figure 1. Early imidazole and non-imidazole-based H_3 ligands.

Isolated examples of weakly binding non-imidazole H_3 ligands were also reported prior to the cloning of the H_3 receptor. These include the stimulant phencyclidine

Keywords: Histamine; Histamine H3 receptor; Aplysamine-1; Histamine H3 receptor antagonists; Neurotransmitter; H3 ligand; Marine natural product.
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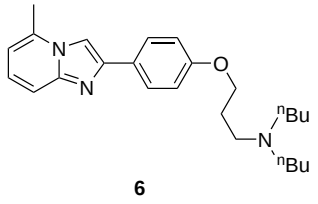

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Figure 2. HTS hit.

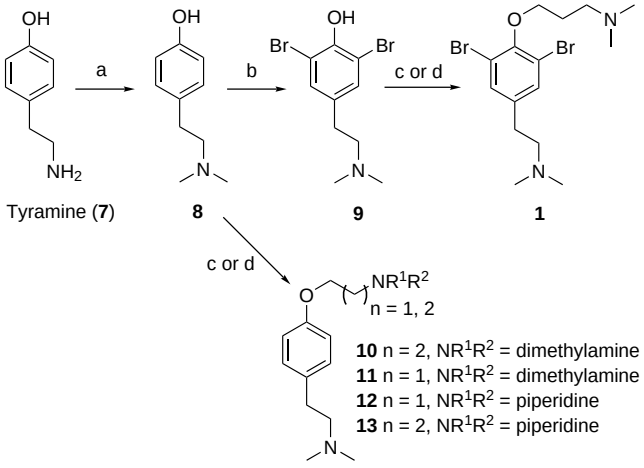
(**4**)[10], the antipsychotic clozapine (**5**)[11], and the marine natural product aplysamine-1 (**1**) (Fig. 1).[12]

Aplysamine-1 (**1**) was isolated in 1989 from an Australian sponge of the Verongidae family, *Aplysina* sp.[13] The natural product is a bromotyrosine derived metabolite consisting of two tertiary alkyl amines connected by a dibromo-phenol and has been previously synthesized.[14] Structural relatives of **1** include the marine natural products moloka'iamine,[15] ceratinamine,[16] and turbotoxins A and B.[14] These compounds possess a wide range of biological activities including acetylcholinesterase inhibition,[14] anti-HIV activity,[17] and use as antifouling agents.[16] In 1994, aplysamine-1 (**1**) was reported to have weak H_3 binding affinity in guinea pig brain and to behave as an H_3 functional antagonist in a guinea pig tissue strip assay.[12]

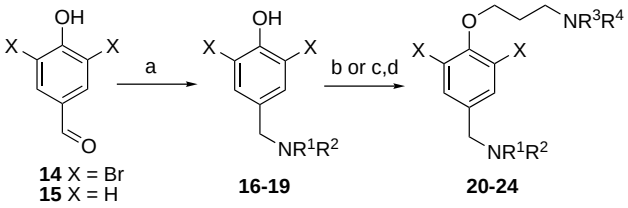
Aplysamine-1 (**1**) contains a structural motif similar to that of a series of 2-phenyl-imidazo[1,2-*a*]pyridines that were identified via high-throughput screening (HTS) efforts using the cloned human H_3 receptor. The 2-phenyl-imidazo[1,2-*a*]pyridines were first prepared as calcium channel blockers and subsequently found to be weak ligands for the H_3 receptor (e.g., RWJ-22085, **6**, H_3 $K_i = 4$ μM) (Fig. 2).[18–20] Recognizing the similarities between the natural product and the HTS hit, we chose to explore the structure–activity relationship (SAR) of aplysamine-1-based H_3 ligands. Herein the synthesis and biological activities of aplysamine-1 (**1**) and related analogs are reported.

Aplysamine-1 (**1**) was prepared in three steps from tyramine (**7**) in an approach similar to the literature precedent (Scheme 1).[14] Treatment of tyramine (**7**) with excess aqueous formaldehyde in the presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$) gave dimethyltyramine (**8**). Bromination of **8** with bromine in acetic acid afforded the dibromo-phenol, **9**. Subsequent alkylation using 3-(dimethylamino) propylchloride hydrochloride and sodium hydride gave the marine natural product, aplysamine-1 (**1**).

In order to investigate the SAR of the natural product, a series of analogs, including two compounds that were previously prepared in our laboratories (**23**, **24**),[21] were synthesized (Schemes 1 and 2). Mitsunobu etherification of dimethyltyramine (**8**) using dimethylpropanolamine or 1-piperidinepropanol, di-*tert*-butyl diazodicarboxylate (DBAD), and polymer supported triphenylphosphine gave *des*-bromoaplysamine-1 (**10**) and dimethyl-{2-[4-(3-piperidin-1-yl-propoxy)-phenyl]-



Scheme 1. Synthesis of aplysamine-1 and analogs. Reagents and conditions: (a) formaldehyde, $NaBH(OAc)_3$, MeOH, rt, 18 h, 70% (b) bromine, AcOH, rt, 3 h, 84% (c) 3-(dimethylamino)propyl chloride HCl or 2-(dimethylamino)ethyl chloride HCl, NaH, DMF, 50 °C, 30–40% (d) *N*,*N*-dimethylethanolamine, or 3-dimethylamino-1-propanol, or 1-piperidinepropanol, polymer supported PPh_3, DBAD, DCM, rt, 18 h, 30–40%.



16 X = Br, NR^1R^2 = dimethylamine. **17** X = Br, NR^1R^2 = piperidine
18 X = H, NR^1R^2 = dimethylamine. **19** X = H, NR^1R^2 = piperidine
20 X = Br, NR^1R^2 = dimethylamine, NR^3R^4 = dimethylamine
21 X = H, NR^1R^2 = dimethylamine, NR^3R^4 = dimethylamine
22 X = Br, NR^1R^2 = piperidine, NR^3R^4 = piperidine
23 X = H, NR^1R^2 = piperidine, NR^3R^4 = piperidine
24 X = H, NR^1R^2 = piperidine, NR^3R^4 = dimethylamine

Scheme 2. Synthesis of aplysamine-1 analogs. Reagents and conditions: (a) HNR^1R^2, $NaBH(OAc)_3$, DCE, rt, 18 h, 50–70% (b) 3-(dimethylamino) propyl chloride HCl, NaH, DMF, 50 °C, 30% (c) 1-bromo-3-chloropropane, K_2CO_3, acetone, reflux, 18 h (d) piperidine, KI, Na_2CO_3, 1-butanol, 95 °C, 18 h, 50% over steps c and d.

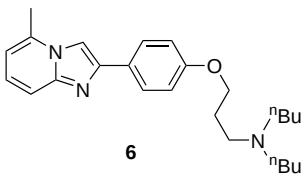
ethyl}-amine (**13**), respectively.[22] O-alkylation of **8** using sodium hydride and 2-(dimethylamino)ethyl chloride hydrochloride in dimethylformamide at 50 °C gave compound **11**.

Benzylic amines were prepared starting with several 4-hydroxybenzaldehydes (Scheme 2). Reductive amination of 3,5-dibromo-4-hydroxybenzaldehyde (**14**) using piperidine and $NaBH(OAc)_3$ in 1,2-dichloroethane provided 2,6-dibromo-4-piperidin-1-ylmethyl-phenol (**17**).[23] O-alkylation of **17** with 1-bromo-3-chloropropane in refluxing acetone followed by installation of the secondary amine using potassium iodide, Na_2CO_3, and piperidine gave **22**.

The human and rat binding affinities were determined for aplysamine-1 (**1**) and a series of analogs (**10**–**13**,

20–**24**) (Table 1). To explore the SAR of **1**, three regions were examined: (1) the bromo-substituent effect; (2) the alkoxy and alkyl amine chain lengths; and (3) size of the two amine groups. Thus, removal of the aryl bromines afforded a 5-fold increase in H_3 affinity (**10**). The presence of the *ortho*-substituents presumably induced an unfavorable conformational or steric interaction. Reduction of the alkoxy amine chain length reduced H_3 affinity (**11**, **12**), while shortening the alkyl amine portion of the molecule had little impact (**20**, **21**). Replacement of the dimethylamine on the alkoxy chain with a piperidine resulted in a 5- to 10-fold increase in H_3 affinity (**12**, **13**), while replacement of the dimethyl benzylamine with piperidine had little effect (**22**–**24**). Previously, it was established that both basic nitrogens are required to retain high affinity for the H_3 receptor in this class of phenyl diamines.[21] Hence, a summary of the SAR to date is depicted in Figure 3.

Table 1. In vitro H_3 receptor data[a]



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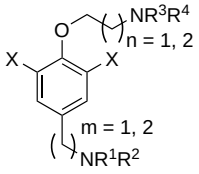

1, **10-13**, **20-24**

Compound	*n*	*m*	NR^1R^2	X	NR^3R^4	H_3 K_i(nM)[b]		Functional[c] pA_2
						Human	rat	
6						4000 ± 1000		
1	2	2		Br		30 ± 4	249 ± 54	—
10	2	2		H		6 ± 1	89 ± 14	7.77
11	1	2		H		40 ± 5	345 ± 48	—
12	1	2		H		14 ± 4	50 ± 10	—
13	2	2		H		0.5 ± 0.2	5 ± 1	9.30
20	2	1		Br		36 ± 4	319 ± 61	—
21	2	1		H		18 ± 3	255 ± 22	—
22	2	1		Br		8 ± 1	57 ± 12	8.14
23	2	1		H		0.4 ± 0.1	1 ± 0.6	9.08
24	2	1		H		3 ± 1	45 ± 3	8.03

[a] Displacement of *N*-[^{3}H]methylhistamine from human H_3 receptors expressed in SK-N-MC cells. For determination of binding to the rat receptor, the same procedure was employed, except frozen rat cortical hemispheres were used instead of cell pellets.

[b] Value reported as means of three determinations.

[c] Human pA_2 values are derived from Schlid regression analysis of the compound-induced rightward shifts in dose–response curves of histamine-induced inhibition of forskolin-stimulated cAMP accumulation in SK-N-MC cells overexpressing the histamine H_3 receptor.

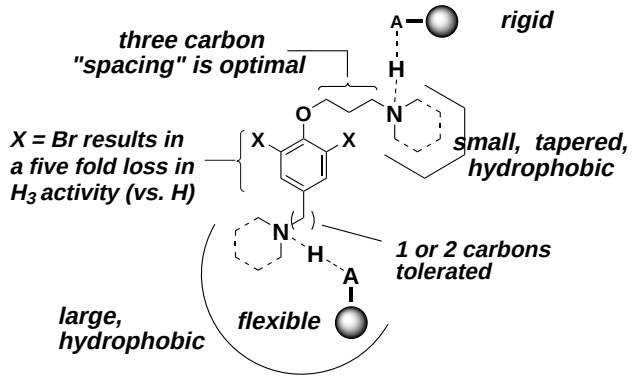

Figure 3. SAR summary.

To explore the selectivity of **1**, it was screened against a panel of 50 monoamine and hormone receptors, ion channels, and neurotransmitter uptake sites (CEREP, ExpresProfile, data not shown). Aplysamine-1 (**1**) was shown to be selective for the H_3 receptor, possessing low affinity (>1 μM) for the other histamine receptor types (H_1, H_2, and H_4). A 10-fold reduction in the binding affinities of aplysamine-1 (**1**) and analogs is consistently observed across species (human to rat). This speciation effect can be attributed to crucial structural differences between the rat and human H_3 receptors.[24]

Compounds with a high H_3 binding affinity ($K_i < 25$ nM) were further evaluated in a cell-based model of human H_3 receptor activation (Table 1, pA_2). All were found to function as competitive antagonists in good agreement with the observed H_3 binding affinities.

In conclusion, the marine natural product, aplysamine-1 (**1**), is a non-imidazole, high affinity, and selective human H_3 receptor ligand synthesized in three steps from tyramine (**7**). Modifications of **1** provide potent H_3 receptor antagonists at the human and rat H_3 receptors (**10**, **13**).

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