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DUAL HISTAMINE H_3 AND SIGMA-1 RECEPTOR LIGANDS AS NOVEL PHARMACOLOGICAL TOOLS IN THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS WITH THE FOCUS ON NEUROPATHIC PAIN

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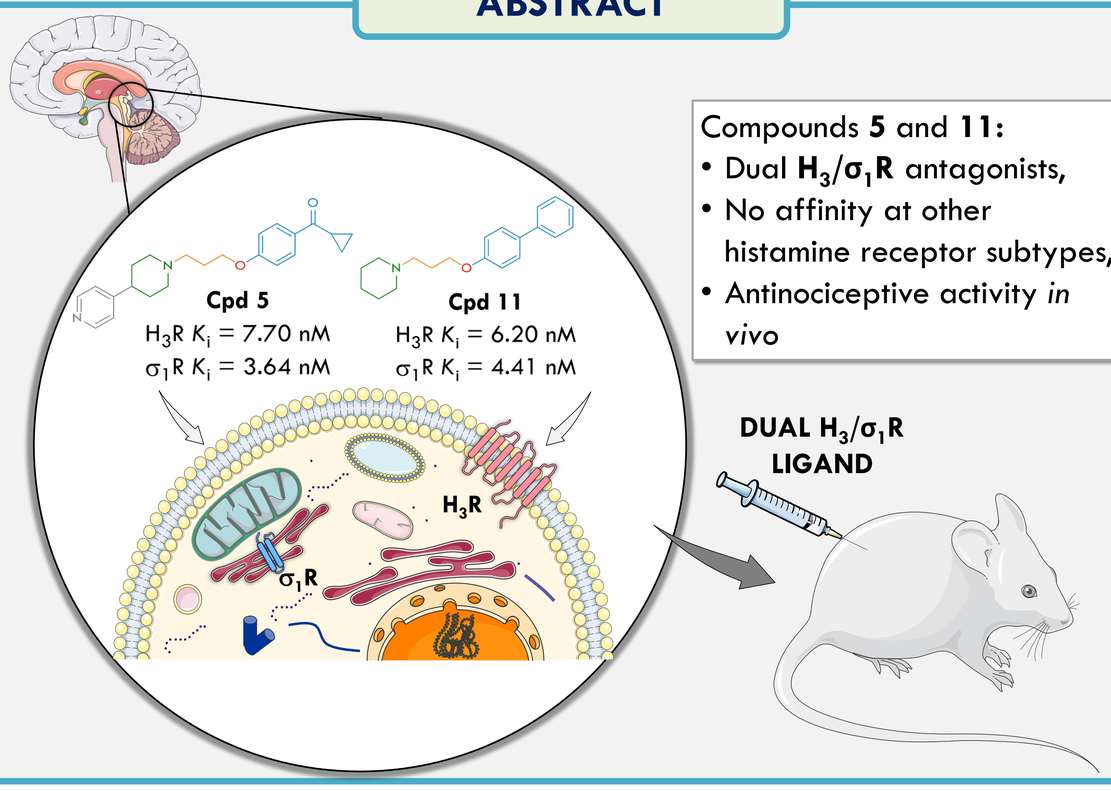
ABSTRACT

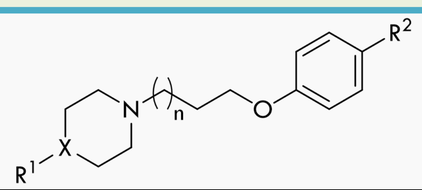


Compounds **5** and **11**:
- Dual **H_3/σ_1R** antagonists,
- No affinity at other histamine receptor subtypes,
- Antinociceptive activity *in vivo*

INTRODUCTION

Since central nervous system disorders are characterized by diverse physiological dysfunctions and deregulations of a complex network of signaling pathways, optimal multipotent drugs should simultaneously and peculiarly modulate selected groups of biological targets. Interestingly, very recent studies have shown that some clinically evaluated histamine H_3 receptor (H_3R) antagonists possess nanomolar affinities at sigma-1 receptor (σ_1R) binding sites, suggesting that this property might play a role in their overall efficacy [1]. This discovery may be a breakthrough in the therapeutic use of these compounds and opens a brand-new research area in the search for novel drugs [2].

EVALUATED COMPOUNDS



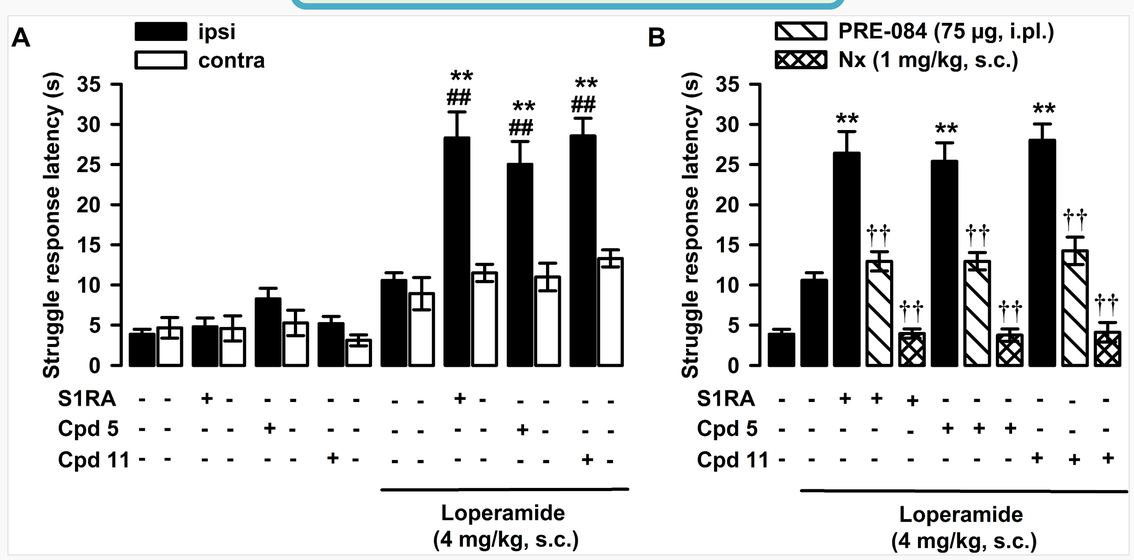
Cpd	n	X	R^1	R^2	H_3R	σ_1R	σ_2R	σ_2/σ_1 ratio
					K_i [nM]			
1	1	N	pyridin-4-yl	ethyl	40.4	592	64.3	0.1
2				*tert*-butyl	16.0	112	408	1.2
3				acetyl	10.2	1409	247	0.2
4				cyclopropyl-methanone	3.2	1531	101	0.1
5		CH			7.70	3.6	22.4	6.2
6		N		phenyl	21.1	638	108	0.2
7				4-cyanophenyl	7.9	2958	75.2	< 0.1
8				benzoyl	3.1	726	29.2	< 0.1
9				4-chlorobenzoyl	23.0	641	32.4	0.1
10				4-fluorobenzoyl	5.8	1309	164	0.1
11		CH	H	phenyl	6.2	4.4	67.9	15.4
12				benzoyl	22.0	14.8	96.2	6.5
13	2	N	pyridin-4-yl	*tert*-butyl	37.8	51.8	175	3.4
14				*tert*-pentyl	120	285	101	0.4
15	4			acetyl	115	> 10 000	1795	< 0.2
16					12.7	37.8	151	4.0
17				propionyl	16.9	248	110	0.4
18				*tert*-butyl	397	255	179	0.7
19	6			acetyl	40.5	408	59.7	0.1
20				propionyl	38.9	274	65.9	0.2

SELECTIVITY/INTRINSIC ACTIVITY

To check the selectivity of our lead structures, radioligand binding studies at other histamine receptor subtypes were carried out. Compounds **5** and **11** in their oxalate forms were tested at human recombinant histamine H_1, H_2, and H_4 receptor subtypes stably expressed in HEK293T cells. Obtained results clearly indicate high selectivity of the tested derivatives towards human H_3R. To identify the lead compounds' functional efficacy, their intrinsic activity was tested in the mini-G protein recruitment assay in response to H_3R stimulation [3]. Compounds **5** and **11** proved to be potent H_3R antagonists.

Cpd	H_1R	H_2R	H_4R	K_b [nM]
	K_i [nM]			
5	> 10 000	> 10 000	> 100 000	18.8
11	> 10 000	> 100 000	> 10 000	11.4

ANTINOCICEPTIVE ACTIVITY



Effects of S1RA and compounds **5** and **11** on loperamide-induced antinociception. The results represent the struggle response latency during stimulation with 450 g pressure in mice intraplantarly (i.pl.) administered with S1RA (σ_1R antagonist, 100 µg), **5** (100 µg), **11** (50 µg) or saline, and treated subcutaneously (s.c.) with loperamide (4 mg/kg) or its solvent (1% DMSO in ultrapure water). (A) Effect of treatments on the response latency to mechanical stimulation in the paw i.pl. injected with the σ_1R ligands (ipsi) and in the contralateral paw (contra). (B) Effect of the i.pl. administration of PRE-084 (σ_1R agonist, 75 µg), and the s.c. of Naloxone (opioid receptor antagonist, Nx, 1 mg/kg) on the potentiation of loperamide-induced antinociception by S1RA, **5** and **11**. Each bar and vertical line represents the mean ± SEM of values obtained in 6 to 8 animals. Two-way analysis of variance followed by the Bonferroni test was used to determine statistically significant differences between (A and B) the values obtained in the group treated with the solution of the drugs and the rest of the groups (*P < 0.05,**P < 0.01), (A) between the ipsi and the contra paws (##P < 0.01) and (B) between the values of the ipsi paw from loperamide-treated mice injected with S1RA, **5** or **11**, alone or co-administered with PRE-084 or with the association with Nx (†† P < 0.01). These results show that both σ_1R antagonism and opioid agonism are acting in conjunction for the effect induced by the association of S1RA and loperamide and strongly support that compounds **5** and **11** are σ_1R antagonists.

CONCLUSIONS

1. **The piperidine moiety: most likely a critical structural element for dual H_3/σ_1 receptor activity.**
2. **Compounds 5 and 11:**
   - **high affinity at H_3R and σ_1R,**
   - **no affinity at other histamine receptor subtypes, moderate selectivity towards σ_2R,**
   - **antagonistic properties towards H_3R (*in vitro*) and σ_1R (*in vivo*).**
3. **Dual H_3/σ_1 receptor modulation: an innovative therapeutic approach in the treatment of pain.**

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