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Short Communication

H_3 receptor ligands: new imidazole H_3-antagonists endowed with NO-donor properties

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Abstract

Synthesis and pharmacological properties of a group of compounds obtained by coupling the H_3-antagonist SKF 91486 with the NO-donor 3-phenylfuroxan-4-yloxy and 3-benzenesulfonylfuroxan-4-yloxy moieties, as well as with the corresponding furazan analogues, devoid of NO-donating properties, are reported. All the products were tested for their H_3-antagonistic and H_2-agonistic properties on electrically-simulated guinea-pig ileum segments and guinea-pig papillary muscle, respectively. All the synthesised compounds displayed good H_3-antagonistic properties (pA_2 range 7.02–8.49) while behaving only as weak partial H_2-agonists. Derivative **28**, the best NO-donor of the series, was able to trigger a dual NO-dependent muscle relaxation and H_3-antagonistic effect on guinea-pig ileum.

Keywords: H_3-antagonist; NO-donors; Furoxan derivatives

1. Introduction

Histamine triggers its pharmacological actions by three subtypes of receptors: the postsynaptic H_1 and H_2 receptors and the presynaptic H_3 receptor [1]. The H_3 receptor was first identified in 1983 [2], since then much has been written about the physiological role of this receptor. The H_3 receptor is principally located in the central nervous system (CNS), where it acts as an inhibitory autoreceptor in the central histaminergic neuronal pathways [1]. In the brain, functional studies have also provided evidence for inhibitory H_3 receptors on nerve terminals of noradrenergic, [3] serotoninergic, [4] dopaminergic, [5] and peptidergic [6] neurons. The H_3 receptor has also been found to negatively modulate transmitter release from peripheral cholinergic, adrenergic, and non adrenergic-non cholinergic (NANC) nerve endings [7].

A number of therapeutic applications have been proposed for selective H_3 receptor antagonists, including several CNS disorders (e.g. Alzheimer's disease, Attention Deficit Hyperactivity Disorder (ADHD), Schizophrenia), memory enhancing and obesity control [8]. Therapeutic uses of such antagonists in the periphery have still to be established.

Nitric oxide (NO), a recently discovered endogenous messenger displays in our body a variety of actions [9]. In the CNS it is released from neurons following stimulation of excitatory *N*-methyl-D-aspartate (NMDA) receptors, it diffuses in the adjacent presynaptic nerve terminal and astrocytes where it activates the soluble guanylate cyclase (sGC). This implies a number of physiological roles including formation of memory and control of food intake. Peripherically nitric oxide is a key messenger in cardiovascular, nervous and immune systems, where it elicits a wide range of physiological and pathophysiological effects.

There is strong evidence that furoxan system (1,2,5-oxadiazole, 2-oxide) is able to release nitric oxide (NO, family name) under the action of thiol cofactors [10]. By introducing appropriate substituents at the ring it is possible to modulate rate and amount of NO-production [11].

Today there is a great interest in 'hybrid' drugs in which NO-donor moieties are joined to appropriate pharmacophoric groups. As a further development of

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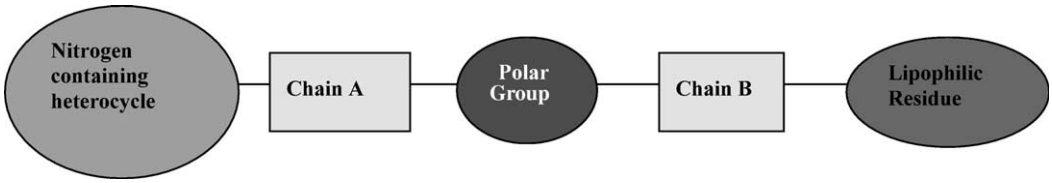
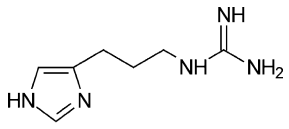


Fig. 1. General structure of H_3-antagonists.



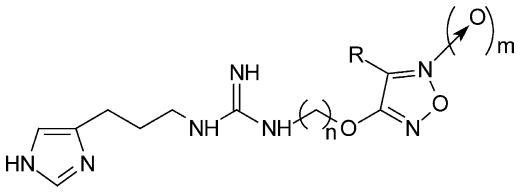
SKF91486

Fig. 2. Lead structure.

our work in this direction we designed some H_3-antagonist-NO-donor hybrid molecules.

The general structure of an H_3-antagonist is reported in Fig. 1. Current H_3-antagonists can be broadly categorised as imidazole and non-imidazole compounds depending on the employed heterocycle. The former predominates, although progress with the latter has recently been made [12].

Chain A is generally a short methylene chain with a variable length from three to five carbon atoms. Optimum antagonist activity is reached when $n = 3$. The polar group can be different in its nature: guanidine, amidine, amine, ether, urea, thiourea, oxadiazole and many other functionalities have been employed in designing selective H_3-antagonists. This part of the molecule is thought to be responsible for the affinity to H_3 receptor, thus constituting the pharmacophoric pattern. The lipophilic moiety connected to the pharmacophore through chain B usually modulates the potency of the antagonist.



Compound	n	m	R
23	2	0	Ph
24	2	1	Ph
25	3	0	Ph
26	3	1	Ph
27	3	0	SO_2Ph
28	3	1	SO_2Ph

Fig. 3. Designed molecules.

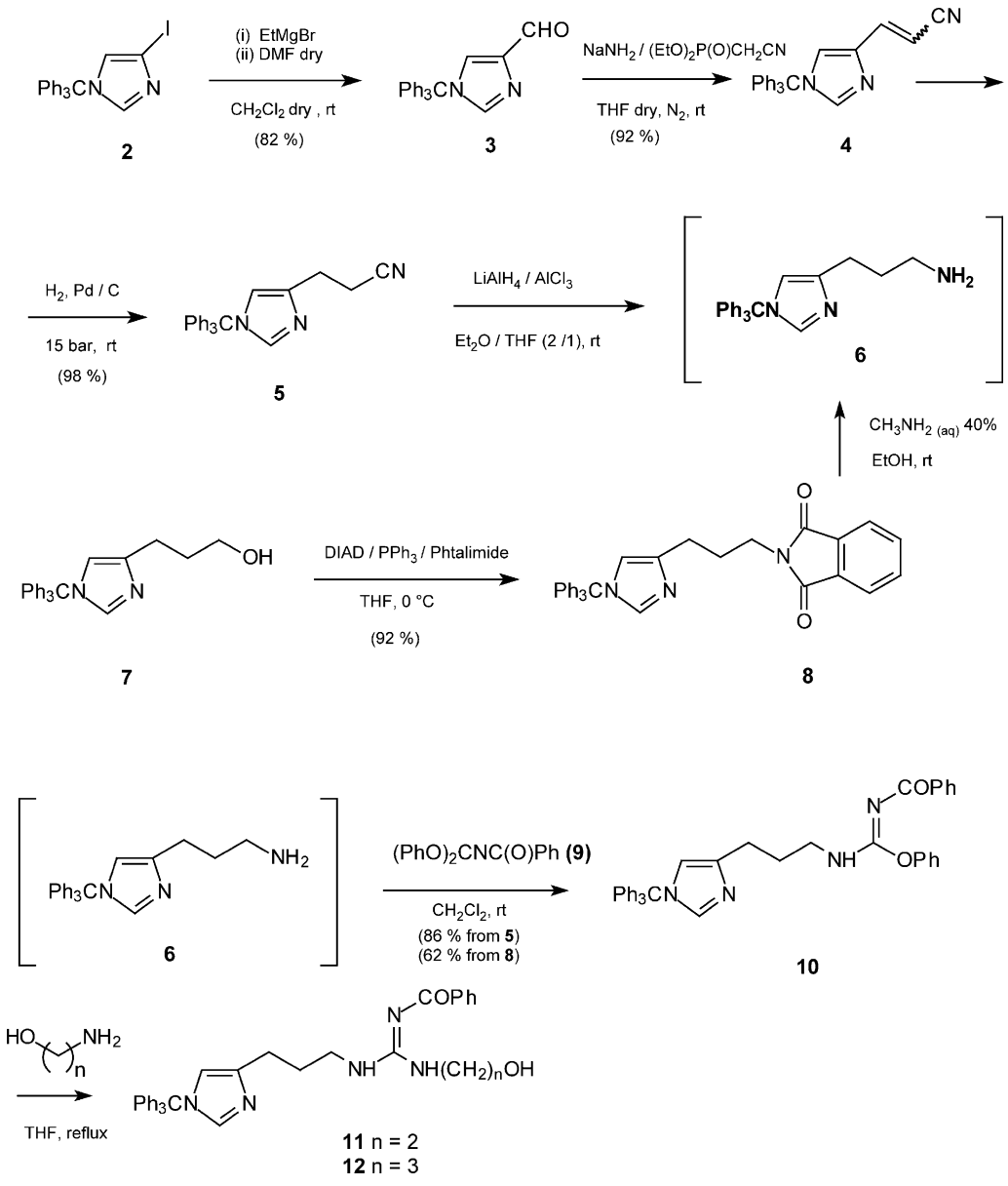
In order to obtain H_3-antagonist-NO-donors we chose SKF 91486 (Fig. 2) as the lead structure. The choice of this pharmacophore should guarantee good possibility of modulation without the loss of H_3-antagonistic properties [13].

SKF 91486 has been coupled, through appropriate spacers, with 3-phenylfuroxan-4-yloxy and 3-benzensulfonylfuroxan-4-yloxy moieties. The structure of the synthesised hybrids (**24**, **26**, **28**) is reported in Fig. 3. As reference compounds we studied the corresponding furazan models **23**, **25**, **27**, since they are unable to release NO.

2. Chemistry

According to our strategy, the synthesis of the final products **23**–**28**, requires the preparation of intermediate *N*-benzoyl-*O*-phenylisourea (**10**) (Scheme 1). This compound can be easily obtained by nucleophilic displacement of the first phenoxy group present in *N*-benzoyl-diphenylcarbonimidate (**9**), under the action of 3-(1-tritylimidazol-4-yl)propylamine (**6**). Preparation of the amine **6** was achieved by two different approaches. The first route implied the conversion of the alcohol **7** [14] into the phtalimido derivative **8**, through a modified Mitsunobu reaction and subsequent hydrolysis of this intermediate in basic medium to afford **6** in good yield. The second route started from trityl-protected iodoimidazole **2** [15], which was successfully converted into the corresponding aldehyde **3** by action of ethylmagnesium bromide and DMF in CH_2Cl_2. The carbaldehyde **3** was then converted to the α,β-unsaturated nitrile **4** by means of a modified Wittig reaction; successive catalytic hydrogenation (Pd/C) and mixed hydride reduction with $LiAlH_4$–$AlCl_3$ in ether–THF (2/1) afforded the expected aminoderivative **6**. Owing to its instability, the protected derivative **6** was reacted further with **9** to give the above-mentioned *O*-phenylisourea (**10**).

Nucleophilic substitution of the phenoxy group in **10**, by the appropriate aminoalcohol provided the intermediate **11** and **12**. Under action of alcohols **11**–**12** in basic medium selective displacement of the 4-benzenesulfonyl group present on furoxan and furazan rings was achieved to give the protected final products **17**–**22** (Scheme 2). Deprotection was performed by refluxing with 5 N HCl to obtain **23**–**26**. Surprisingly, in the same

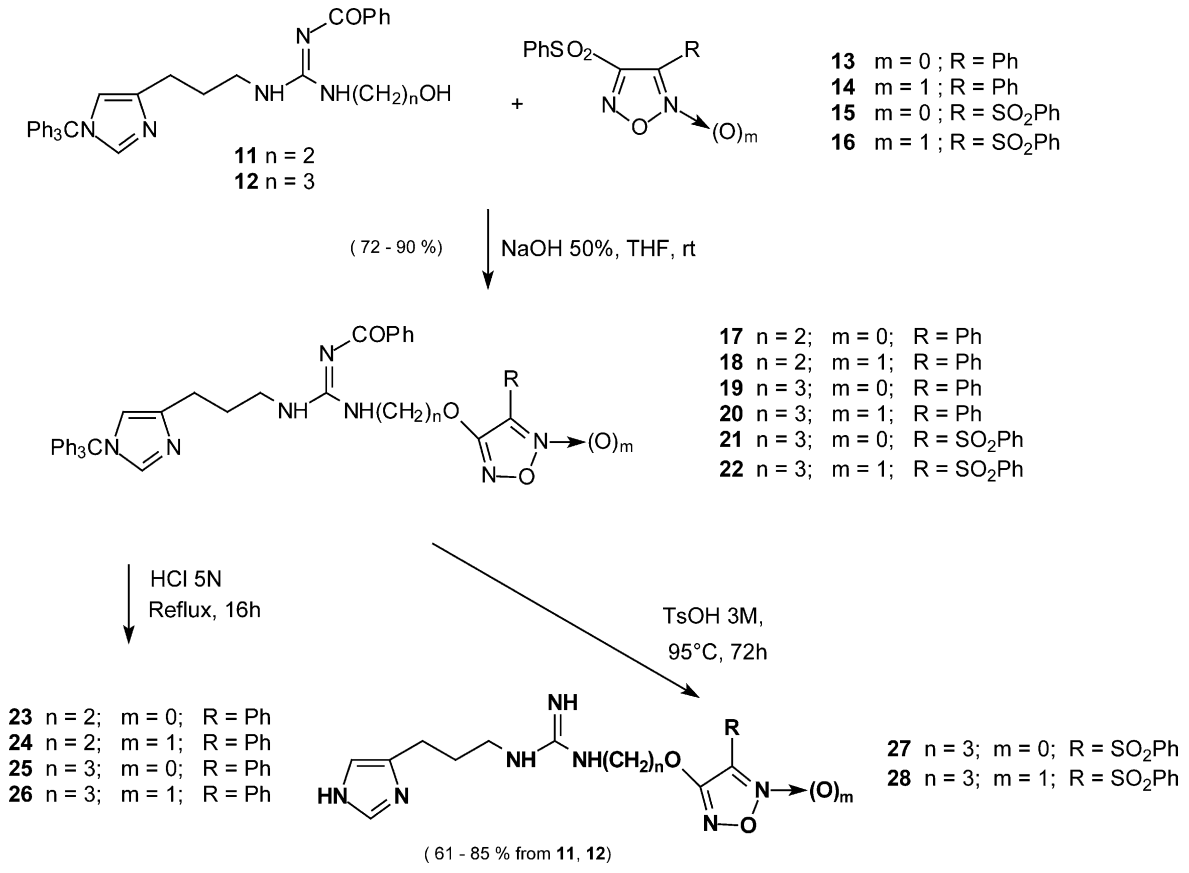


Scheme 1.

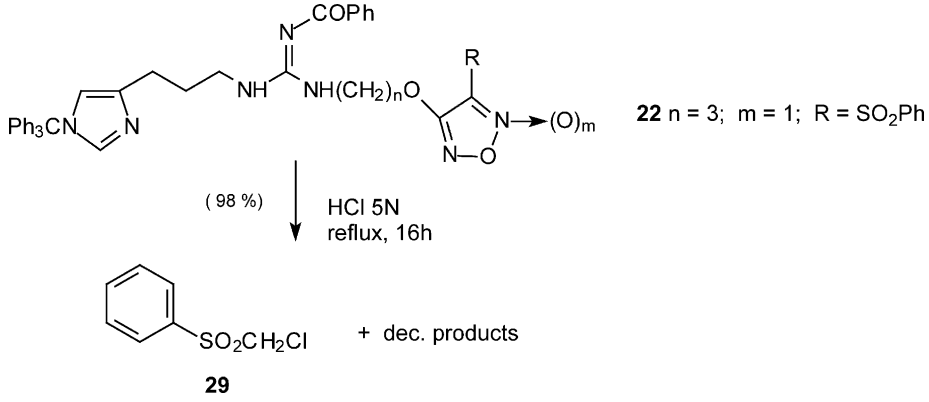
Table 1
Nitrite determination and pharmacological characterisation of derivatives **23**–**28** and reference compound SKF 91486 and impromidine

Comp.	*n*	*m*	R	NO_2^- % [a]	H_2-receptor activity $pD_2 \pm SEM$ [b]	H_3-receptor antagonism $pA_2 \pm SEM$ [c]
23	2	0	Ph		4.34±0.04	8.19±0.07
24	2	1	Ph	3.8±0.1	4.54±0.07	7.82±0.09
25	3	0	Ph		5.70±0.04	8.49±0.03
26	3	1	Ph	4.0±0.06	5.90±0.06	8.25±0.07
27	3	0	SO_2Ph		5.88±0.07	7.42±0.03
28	3	1	SO_2Ph	26.7±3.4	5.28±0.12	7.02±0.03 7.05±0.05 (+ODQ)
SKF 91486					4.49±0.07	7.24±0.07
Histamine					6.15±0.02	
Impromidine					7.49±0.04	7.59 [18]

[a] Compound 100 μM; L-Cys 5 mM.
[b] Electrically stimulated guinea-pig papillary muscle. $pD_2 = -\log EC_{50}$. Data are the mean of four to six experiments.
[c] Electrically stimulated guinea-pig ileum. pA_2 values calculated according to Gaddum's equation: $pA_2 = -\log[B] + \log[CR-1]$. Data are the mean of five to 11 experiments.



Scheme 2.



Scheme 3.

acidic conditions, derivative **21**–**22** decomposed quantitatively with formation of benzenesulfonylmethyl chloride (**29**) as the main product (Scheme 3). Derivatives **27**–**28** were finally obtained with the use of 3 M *p*-toluensulfonic acid at 95 °C (Scheme 2).

The thiol-induced NO generation from synthesised hybrids was evaluated by spectrophotometric nitrite detection according to a previously reported procedure [11]. The results expressed as NO_2^- % (mol/mol) are reported in Table 1. It is noteworthy how this kind of measure does not give information about the single NO-redox form released but nitrite production represents an approximate index of total NO generation.

3. Pharmacology

The H_3 receptor antagonism was evaluated by measuring the ability of each compound (1 μM) to inhibit the concentration dependent inhibitory effect of (*R*)-α-methylhistamine on electrically evoked contractile response of guinea-pig ileum preparation [16].

All the synthesised compounds were tested in a stimulated guinea-pig papillary muscle model [17] to determine their ability to activate H_2 receptors.

Results expressed respectively as pA_2 and pD_2 values are reported in Table 1.

All the synthesised compounds proved to be selective H_3-antagonists, with similar or greater potency than the lead compound SKF 91486.

Derivative **28**, when tested on guinea-pig ileum, showed, together with the H_3-antagonist properties, an NO-dependent effect. This effect was observed as a transient inhibition of the stimulated-tissue contraction and was prevented by prior administration of ODQ (1 μM). This observation can prove the effective 'hybrid behaviour' of this class of compounds, which represents the first example of H_3-antagonist-NO-donor molecules.

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