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Synthesis and structure–activity relationships of piperidinylpyrrolopyridine derivatives as potent and selective H_1 antagonists

Silvia Fonquerna,* Montse Miralpeix,* Lluís Pagès, Carles Puig, Arantxa Cardús, Francisca Antón, Dolors Vilella, Mónica Aparici, José Prieto, Graham Warrellow, Jorge Beleta and Hamish Ryder

Almirall Prodesfarma, Research Center, Cardener 68-74, 08024 Barcelona, Spain

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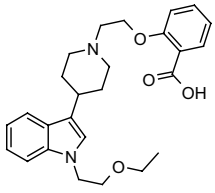
Abstract—The synthesis and structure–activity relationships of piperidinylpyrrolopyridines as potent and selective H_1 antagonists are discussed. It was found that the nature of the acid chain bonded to piperidine was a key feature for maintaining both the duration of action in vivo and lack of sedative properties.

H_1 antagonists are used as the first-line treatment of allergic rhinitis.[1] First-generation antihistamines are effective but they cause sedation and dry mouth due to blood–brain barrier and lack of specificity,[2] respectively. Second-generation H_1 antagonists have low sedative potential although most of them present cardiotoxic side effects.[3] New compounds being characterised and recently launched to market have much reduced risk of causing cardiac adverse effects and should also have no sedative effects.

We have recently reported[4] the identification of a new series of indolylpiperidine derivatives as potent, selective and nonsedative H_1 antagonists. SAR studies on this series showed the relevance of the nature of the acidic chain on the in vivo duration of action. In this paper we describe our efforts in developing a new series of H_1 antagonists in which the indole ring has been replaced by a pyrrolopyridine group. We wished to investigate the effect of this substitution on the in vivo H_1 activity and on sedative potential.



Compound **1**

The piperidinylpyrrolopyridinyl derivatives were typically synthesised according to a procedure described in Scheme 1. Pyrrolopyridine was condensed with 4-oxo-piperidine-1-carboxylic acid ethyl ester and further hydrogenation led to the core intermediate **22**. Alkylation of azaindolylpiperidine derivative **22** with appropriate alkyl and arylalkyl halides provided intermediates **23**. Deprotection of the ethyl carbamate moiety was achieved by heating in the presence of potassium hydroxide leading to derivatives **24**. Alkylation of piperidinylpyrrolopyridinyl derivatives **24** with appropriately substituted halides and further saponification afforded azaindolylpipepiridinyl derivatives **2**–**21**.

In order to determine structure–activity relationships, all compounds described herein were evaluated for their affinity for the guinea-pig cerebellum H_1 receptor in a radioligand binding assay.[5] Selectivity was assessed by testing their binding affinity against the human 5-HT_2 and the rat α_1 receptors.[6,7] High affinity compounds

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* Corresponding authors. Tel.: +34 932913999; fax: +34 3128635 (S.F.); tel.: +34 291 3468; fax: +34 93 2912827 (M.M.); e-mail addresses: sfonquerna@almirall.es; mmiralpe@almirall.es

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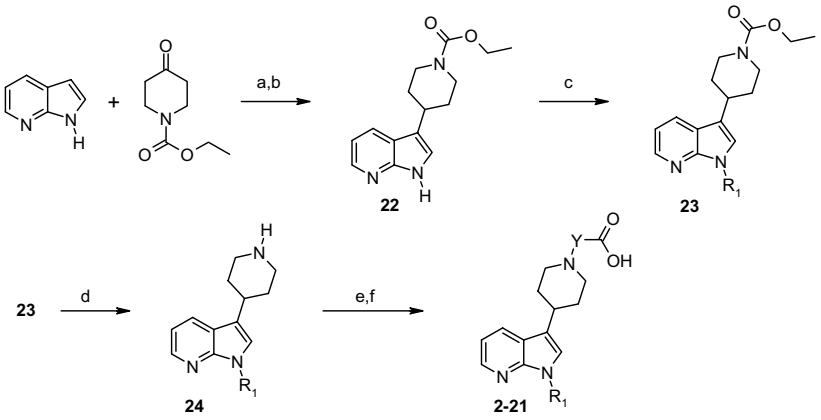
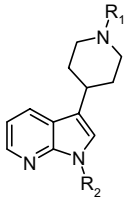


Scheme 1. Reagents and conditions: (a) KOH, MeOH, 60 °C, 15 h; (b) H_2, PtO_2, MeOH, 1 h, 30 psi; (c) R_1–X, NaH, DMF, 25 °C; (d) KOH, *i*-PrOH, 60 °C, 15h; (e) X–Y–CO_2 R_2, MEK, 90 °C, 15 h; (f) NaOH, THF–MeOH, 60 °C, 1 h.

for the H_1 receptor, with at least 10 times selectivity versus the other two receptors, were evaluated for their antihistamine activity in the rat histamine-induced skin vascular permeability model. Compounds showing potent and stable oral antihistamine activity after 8 h post-administration in this model, were then tested for their capacity to cross the blood–brain barrier in the H_1 ex vivo binding assay in mice.[8] For the most promising compounds, the effect on QT prolongation interval[9] was measured.

Compound **1** was the lead structure in the previous reported series, the indolylpiperidines. It was a potent and selective H_1 antagonist in vitro and in vivo with

Table 1. Pharmacological profile of piperidinepyrrolopyridinyl derivatives **2**–**21**



Compd	R_1	R_2	H_1[a]	$5HT_2$[a]	α_1[c]	HISVP[e] (4 h)[f]	HISVP[e] (8 h)[f]	H_1 ex vivo[h]
1	—	—	86	3272	10	0.1	0.22	8
2	A	2-Ethoxyethyl	190	>10,000	>10	0.08	0.20	34
3	A	Butyl	235	>10,000	4.9	1	—	—
4	A	3-Furanylmethyl	225	10,000	10	35 (1)[g]	—	—
5	A	5-Chloro-2-thiophenylmethyl	295	>10,000	>10	1	—	—
6	B	2-Ethoxyethyl	185	3900	>10	0.21	0.20	18
7	B	Butyl	215	10,000	>10	11 (1)[g]	—	—
8	B	3-Furanylmethyl	170	7600	>10	24 (1)[g]	—	—
9	B	5-Chloro-2-thiophenylmethyl	240	>10,000	>10	24 (1)[g]	—	—
10	C	2-Ethoxyethyl	90 (500)[b]	13 (500)[b]	83 (10)[d]	—	—	—
11	C	Butyl	120	>10,000	>10	5 (1)[g]	—	—
12	C	3-Furanylmethyl	70	>10,000	2.6	3 (1)[g]	—	—
13	C	5-Chloro-2-thiophenylmethyl	135	>10,000	>10	20 (1)[g]	—	—
14	D	2-Ethoxyethyl	403	4950	>10	0.07	0.45	16
15	D	Butyl	275	>10,000	>10	1	—	—
16	D	3-Furanylmethyl	560	10,000	>10	1	—	—
17	D	5-Chloro-2-thiophenylmethyl	330	>10,000	>10	7 (1)[g]	—	—
18	E	2-Ethoxyethyl	690	10,000	>10	0.05	—	5.4
19	E	Butyl	475	>10,000	>10	0.08	0.13	69
20	E	3-Furanylmethyl	205	10,000	>10	0.20	0.20	15
21	E	5-Chloro-2-thiophenylmethyl	365	10,000	>10	0.5	0.7	57

[a] Data correspond to the average of IC_{50} (nM) obtained from at least two independent experiments.
[b] Data correspond to the average of % of inhibition (nM dose) obtained from at least two independent experiments.
[c] Data correspond to the average of IC_{50} (μM dose) obtained from at least two independent experiments.
[d] Data correspond to the average of % of inhibition (μM dose) obtained from at least two independent experiments.
[e] Histamine-induced skin vascular permeability model.
[f] Data are indicated as ED_{50} (mg/kg); five animals were used for each tested dose.
[g] Data correspond to the average of % of inhibition (mg/kg) obtained from five animals.
[h] Data are indicated as ED_{50} (mg/kg); three animals were used for each tested dose.

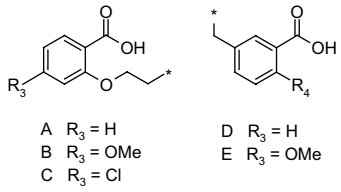


Figure 1. Substituents for R_1 in Table 1.

low sedative potential. From the extensive optimisation work carried out within this series, other promising candidates with long duration of action in vivo and better pharmacokinetic profile were identified.[4]

In order to evaluate the impact of the substitution of the indole group by a pyrrolopyridine moiety a selected set of compounds were synthesised and their pharmacological profiles are reported in Table 1.

Compound **2**, with identical pattern of substitution as compound **1**, showed similar in vitro and in vivo H_1 activities with enhanced selectivity versus $5HT_2$. Encouragingly, compound **2** had a 4-fold reduced sedative potential measured in the H_1 ex vivo assay. This interesting result prompted us to synthesise other derivatives with selected substitution in R_2 previously known to provide long duration of action in the indolylpiperidine series. Maintaining the ethoxyethyl chain in R_2, we then proceeded to explore several substituents on the piperidine. As a general trend, we obtained compounds (**6**, **14** and **18**) with high in vivo potencies similar to compound **1** in spite of the fact that **14** and **18** showed lower in vitro H_1 activity. Moreover, compounds **6** and **14** showed an interesting 2-fold reduction of sedative potential compared to **1**.

The most promising benzoic acid chain was **E** (Fig. 1) as all the compounds containing this group showed high in vivo potencies after 4 h and in particular compounds **19**, **20** and **21** showed long duration of action keeping activity after 8 h. Furthermore, compound **20** and particularly **19** and **21** proved to have a reduced capacity to cross blood–brain barrier compared to compound **1** and therefore less sedative properties should be expected. Finally, the potential to cause adverse cardiac adverse effects was also assessed for compounds **19**, **20** and **21**. The effect in the QT prolongation interval was measured in anesthetised guinea-pigs at a prefixed dose of 10 mg/kg and compounds **19**, **20** and **21** did not produce any significant increase.

Regarding solubility in water, compounds from the pyrrolopyridinepiperidine series showed typically at least a 2-fold increase when comparing to structural equivalent ones from the previous series. The range of solubility moved from 1224 μg/mL (compound **2**) to 115 μg/mL (compound **20**) whereas in the previous series the values of solubility obtained ranged between 100 μg/mL (compound **1**) and 22 μg/mL.

In conclusion, we have identified a new series of potent and selective H_1 antagonists. We also have discovered that the nature of the acid chain bond to piperidine is a key feature for maintaining both the duration of action in vivo and lack of sedative properties. Further work is underway and will be reported in due course.

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