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

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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. © 2004 Elsevier Ltd. All rights reserved.

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 $H_1$  antagonists are used as the first-line treatment of allergic rhinitis.<sup>1</sup> First-generation antihistamines are effective but they cause sedation and dry mouth due to blood-brain barrier and lack of specificity,<sup>2</sup> respectively. Second-generation  $H_1$  antagonists have low sedative potential although most of them present cardiotoxic side effects.<sup>3</sup> 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<sup>4</sup> 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 In this paper we describe our efforts in developing a new series of  $H_1$  antagonists in which the indole ring has been replaced by a pyrrolopyridine group.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.



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.<sup>5</sup> Selectivity was assessed by testing their binding affinity against the human 5-HT<sub>2</sub> and the rat  $\alpha_1$  receptors.<sup>6,7</sup> High affinity compounds

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Scheme 1. Reagents and conditions: (a) KOH, MeOH, 60 °C, 15 h; (b) H<sub>2</sub>, PtO<sub>2</sub>, MeOH, 1 h, 30 psi; (c) R<sub>1</sub>–X, NaH, DMF, 25 °C; (d) KOH, *i*-PrOH, 60 °C, 15h; (e) X–Y–CO<sub>2</sub> R<sub>2</sub>, 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 8h 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.<sup>8</sup> For the most promising compounds, the effect on QT prolongation interval<sup>9</sup> 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

## $\mathbb{R}$

				2				
Compd	$R_1$	R <sub>2</sub>	$H_1^a$	$5HT_2^a$	$\alpha_1^{c}$	$HISVP^{e} (4 h)^{f}$	HISVP <sup>e</sup> (8 h) <sup>f</sup>	H <sub>1</sub> ex vivo <sup>h</sup>
1	_	_	86	3272	10	0.1	0.22	8
2	Α	2-Ethoxyethyl	190	>10,000	>10	0.08	0.20	34
3	Α	Butyl	235	>10,000	4.9	1	_	_
4	Α	3-Furanylmethyl	225	10,000	10	35 (1) <sup>g</sup>	_	_
5	Α	5-Chloro-2-thiophenylmethyl	295	>10,000	>10	1	_	
6	В	2-Ethoxyethyl	185	3900	>10	0.21	0.20	18
7	В	Butyl	215	10,000	>10	11 (1) <sup>g</sup>	_	
8	В	3-Furanylmethyl	170	7600	>10	24 (1) <sup>g</sup>	_	
9	В	5-Chloro-2-thiophenylmethyl	240	>10,000	>10	24 (1) <sup>g</sup>	_	
10	С	2-Ethoxyethyl	90 (500) <sup>b</sup>	13 (500) <sup>b</sup>	83 (10) <sup>d</sup>	_	_	_
11	С	Butyl	120	>10,000	>10	5 (1) <sup>g</sup>	_	
12	С	3-Furanylmethyl	70	>10,000	2.6	3 (1) <sup>g</sup>	_	_
13	С	5-Chloro-2-thiophenylmethyl	135	>10,000	>10	20 (1) <sup>g</sup>	_	_
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) <sup>g</sup>	_	_
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	Е	5-Chloro-2-thiophenylmethyl	365	10,000	>10	0.5	0.7	57

<sup>a</sup> Data correspond to the average of IC<sub>50</sub> (nM) obtained from at least two independent experiments.

<sup>b</sup> Data correspond to the average of % of inhibition (nM dose) obtained from at least two independent experiments.

<sup>c</sup> Data correspond to the average of IC<sub>50</sub> (µM dose) obtained from at least two independent experiments.

<sup>d</sup> Data correspond to the average of % of inhibition ( $\mu$ M dose) obtained from at least two independent experiments.

<sup>e</sup> Histamine-induced skin vascular permeability model.

<sup>f</sup> Data are indicated as ED<sub>50</sub> (mg/kg); five animals were used for each tested dose.

 $^{\rm g}\, Data$  correspond to the average of % of inhibition (mg/kg) obtained from five animals.

<sup>h</sup> Data are indicated as ED<sub>50</sub> (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.<sup>4</sup>

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<sub>2</sub>. 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<sub>2</sub> 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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