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Conformationally-restricted Ligands for the Histamine H_1 Receptor

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Abstract—Potent H_1-antagonistic activity in a series of novel indeno[2,1-*c*]pyridines and their 4-arylpiperidinol precursors is reported; one compound shows an in vitro activity four times that of the standard mepyramine that it was screened against. Their failure to translate this protection to in vivo tests is discussed.

As part of a continuing project concerned with probing the H_1-histamine receptor,[1–8] we report the novel biological activity of a series of ligands at this site. Relatively little biological work has been reported for these synthetically-accessible piperidines and tricyclic derivatives.[9–11] Earlier work describing the preparation and biology of analogous compounds[12,13] suggested that the antihistaminic activity in such tricyclic compounds resided in the 2,3,4,9-tetrahydro derivatives (**19**–**22**) and no data were reported for their precursor piperidines and 2,3-dihydroindenopyridines (**1**–**14**) respectively. We describe our biological results for these compounds below.

For in vitro activity, dose–response curves were constructed for histamine in the absence and presence of mepyramine, phenindamine and test substances. The tissue was allowed to equilibrate with each concentration of antagonist for 30 min prior to retesting the agonist action of histamine.[14]

Dose–response curves were plotted as a percentage of the histamine maximum response in the absence of antagonists against $\log_{10}$ of the molar concentration of histamine; selected IC_{50} values calculated from these data are recorded in Table 1. For in vivo activity compounds tested were administered at doses of 40 or 10 mg/kg, s.c. before challenging the animal with the potent, histamine-releasing oligomer 48/80 (0.5 mg/kg, iv).[15] A successful outcome in these tests is protection against lethal, histamine-induced anaphylaxis. Two mice were assigned to each dose group and the number of mice to survive more than 240 min was recorded. Results are displayed in Table 1.

Preliminary results from experiments designed to examine antagonistic activity at the H_1-histamine receptor in guinea pig ileum showed that piperidines **1** and **2** were effective in this screen with IC_{50} values of 26 and 23 nM, respectively. These figures were comparable with those for the clinically-established phenindamine (36 nM, determined at the same time) and led us to screen a range of piperidines (**1**–**11**) in vivo, using the 48/80 challenge test. All 11 compounds, including **1** and **2** which had showed in vitro activity, were not capable of protecting mice against a lethal dose of 48/80 in this screen. The calculated lipophilicity[16] for piperidines **3**–**11**, were between 10 and 100 times that of **1** (log P 2.6) and may have affected the pharmacokinetics of distribution of the drug with respect to its site of action. Alternatively, these 4-aryl-4-hydroxypiperidines have been shown to be metabolically labile[19,20] and this susceptibility may have a role in the failure to transfer this in vitro activity to the whole animal.

Cyclisation of the appropriate piperidines in the presence of 48% w/v HBr produces the tricyclic nucleus of the dienes[5] of which 3 were screened, **12**–**14**, (Scheme 1 and Table 1) as they have not been scrutinised for antihistaminic activity. The diene **13** has about one tenth of the activity of the clinical-used drug mepyramine but the *N*-ethyl analogue **14** appeared not to act in a similar manner as it would not produce an inhibition of 50% and the shape of the dose–response curve suggested that a non-competitive mode of action may be in evidence.

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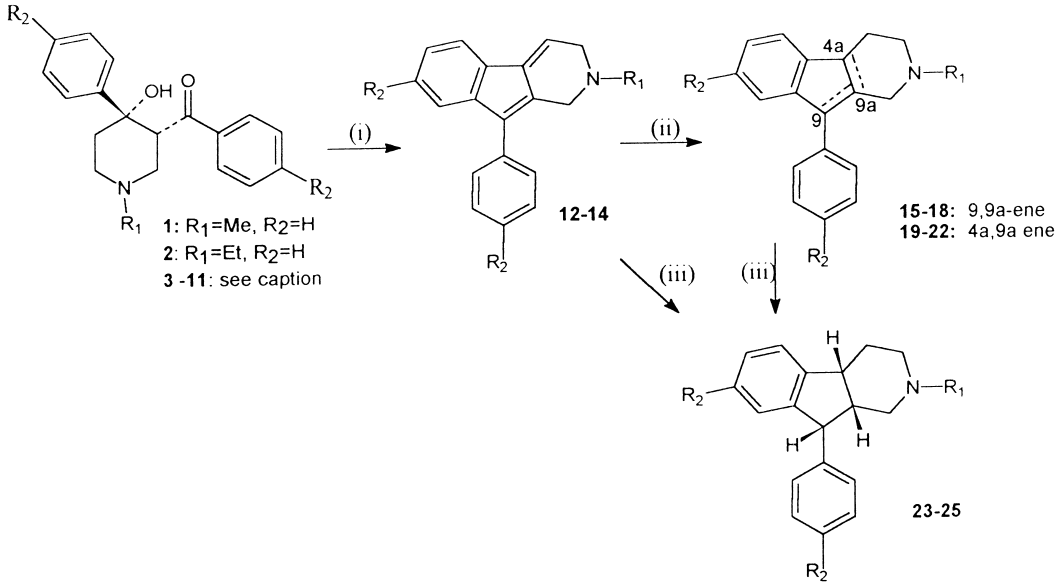
Table 1. In vitro and in vivo antihistaminic activity of the tricyclic nuclei **12**–**22**

Compound[a]	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
R_1	H	Me	Et	Me	Et	$PhCH_2$	PhEt	Me	Et	$PhCH_2$	PhEt
R_2	H	H	H	H	H	H	H	7,4′-Et	H	H	H
IC_{50}[b]	53	220	NI[c]	28	—	10.8	—	—	17	470	—
48/80[d]	1/2, 0/2	0/2, 0/2	—	2/2, 1/2	2/2, 1/2	0/2, 0/2	1/2, 0/2	0/2, 0/2	1/2, 0/2	0/2, 0/2	0/2, 0/2
Log P[e]	4.41	4.94	—	5.23	5.76	7.03	7.43	—	4.92	6.02	6.59

[a]See Scheme 1 for structures.
[b]The number of determinations made for each compound was 5 or 6, the clinically-established mepyramine and phenindamine were also included in these determinations and had IC_{50} of 34 and 36 nM resp., concentrations of test substances are cited similarly.
[c]NI: did not cause 50% inhibition.
[d]Determined at doses of 40 and 10 mg/kg, resp. in the 48/80 challenge, numbers given are mice surviving for more that 240 min; under these conditions the ED_{50} for mepyramine was < 2.5 mg/kg.
[e]Derived as described in ref 16, errors were between ± 0.37 and ± 0.39.



Scheme 1. Reagents: (i) 48% w/v HBr; (ii) H_2, 10% Pd on C, RT; (iii) H_2, 5% Pt on C, 80 psi, 75 °C, 20 h. **3**–**8**: R_1 = benzyl, phenethyl, cyclopropyl, butyl, hexyl and cyclohexylmethyl, resp.: R_2 = H. **9**–**11**: R_1 = Me, R_2 = 4-Cl, 4-Me and 3-Br resp.

Some H_1-antagonism was endowed by the *N*-dealkylated diene **12** in the in vivo tests, ED_{50} 40 mg/kg.

The next group of compounds described, **15**–**22**, differ in the position of the double bond which remains following the partial reduction of the precursor dienes (e.g., **12**–**14**). In previous work, the outcome of this reduction to either a 9,9a-ene (**15**–**18**) or a 4a,9a-ene (**19**–**22**) was dependent upon which proton salt was used to isolate the reduced product, though not in a consistent way.[2,12,13] We have recently established predictable methods for the selection of one or other of the reduction products.[8] The IC_{50} values of the *N*-methyl 9,9a-ene, **15** (28 nM) is close to that of the 4a,9a-ene (and mepyramine, the test substance), showing that the two compounds are of similar affinity at this receptor. Previous reports suggested that the majority of biological activity resides in the latter, geometric isomer. This discrepancy is even more pronounced in the case of the *N*-benzyl analogues (**17** and **21**) where the former 9,9a-isomer is over 40 times as active as its 4a,9a-isomer and has an activity 3–4 times that of both standard test substances. However, as with results for piperidines **1** and **2** these antagonistic properties did not manifest themselves in the in vivo 48/80 challenge: the only successful activities from this screen of tricyclic molecules were for **15** and **16**, at the higher dose level screened (phenindamine confers the same protection at 10 mg/kg). The log P values (Table 1) for pairs of isomers are consistently higher for the 9,9a-ene compared with the 4a,9a-ene as induced co-planarity, through the conjugated system, between the ene and the 9-aryl substituent, enhances lipophilicity, which can affect drug distribution.

Differing conformations in the two enes may also contribute to these differences allowing one to comply more closely with the 3-dimensional criteria previously identified[21] for activity at this receptor, and offering a more suitably-disposed 9-aryl substituent to the receptor.

Within the fully reduced series, **23**–**25**, derived from either of the corresponding dienes or monoenes by a more vigorous reduction with platinum, little or no in vivo activity was seen. The all-*cis* compound **23** (R_1 = Me, R_2 = H, conventionally so described; H-4a, 9- and 9a- all on same face of tricyclic nucleus) was inactive providing no protection against 48/80 with both mice dying at 36 min.

The H-9 epimer **24** of compound **23** had an ED_{50} of 40 mg/kg and **25** (all *cis*, $R_1 = Me$, $R_2 = Et$) was ineffective at these doses.

In conclusion, it is clear from the IC_{50} results that H_1-antagonist activity is not restricted solely to the 2,3,4,9-tetrahydroindeno[2,1-*c*]pyridine nucleus, (the 4a,9a-enes), as previously thought. In the case of **15**, the 9,9a-ene, it exhibits activity comparable to the two test substances, phenindamine and mepyramine, and the *N*-benzyl 9,9a-ene, **17**, is 3–4 times as active as these standards. Notably its 4a,9a-isomer **21** has less than one fortieth of the activity of the 9,9a-ene. Furthermore, H_1 antagonism seems apparent in the even more conformationally-restricted dienes such as **12**. Similarly, this previously unreported activity in the precursor piperidines such as **1** and **2** also offers new potential avenues for investigation.

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References and Notes

1. Branch, S. K.; Casy, A. F.; Hussain, R. B.; Upton, C. *J. Pharm. Pharmacol.* **1988**, *40*, 83.
2. Casy, A. F.; Hussain, R. B.; Upton, C. *Mag. Reson. Chem.* **1992**, *30*, 621.
3. Casy, A. F.; Drake, A. F.; Ganellin, C. R.; Mercer, A. D.; Upton, C. *Chirality* **1992**, *4*, 356.
4. Casy, A. F.; Ganellin, C. R.; Mercer, A. D.; Upton, C. *J. Pharm. Pharmacol.* **1992**, *44*, 791.
5. Jaffar, M.; Upton, C. *J. Pharm. Pharmacol.* **1996**, *48*, 444.
6. Salunga, T. L.; Han, X. Y.; Wong, S. M.; Takeuchi, H.; Matsunami, K.; Upton, C.; Mercer, A. D. *Eur. J. Pharmacol.* **1996**, *304*, 163.
7. Upton, C.; Jaffar, M. *Pharm. Sci.* **1996**, *2*, 411.
8. Upton, C.; Jaffar, M. *J. Pharm. Pharmacol.* **1998**, *50*, 829.
9. Kubela, R.; DoNascimento, J. M. **1977** for Delmer Chemicals Ltd., German Patent: Ger. Offen. 2,600,557, July 1977; *Chem. Abs.* **1978**, *88*P, 6727f.
10. Stenlake, J. B.; Patrick, G. L.; Sneader, W. E. *Eur. J. Med. Chem.* **1989**, *24*, 591.
11. Cook, C. E.; Wani, M. C.; Jump, J. M.; Lee, Y. W.; Fail, P. A.; Anderson, S. A.; Gu, Y. Q.; Petrow, V. *J. Med. Chem.* **1995**, *38*, 753.
12. Plati, J. T.; Wenner, W. *J. Org. Chem.* **1949**, *14*, 543.
13. Plati, J. T.; Wenner, W. *J. Org. Chem.* **1955**, *20*, 1412.
14. Brimblecombe, R. W.; Green, D. M.; Inch, T. D.; Thompson, B. J. *J. Pharm. Pharmacol.* **1971**, 745
15. Niemegeers, C. J. E.; Awouters, F.; Van Neuten, J. M.; De Nollin, S.; Janssen, P. J. A. *Arch. Int. Pharmacodyn. Ther.* **1978**, *234*, 164.
16. Determined using software from Advanced Chemical Co., San Francisco; we have recently shown[17] that results obtained from this package compare favourably with those derived using Clog P and KOWWIN software, the most highly rated for this purpose.[18]
17. Upton, M.; Upton, C. *Mutagenesis* **1999**, *14*, 101.
18. Mannhold, R.; Dross, K. *Quant. Struct.-Act. Relat.* **1996**, *15*, 403.
19. Casy, A. F.; Beckett, A. H.; Iorio, M. A. *Tetrahedron* **1967**, *23*, 1405.
20. Hardy, R.A.; Howell, M.G. In *Medicinal Chemistry*; de Stevens, G., Ed.; Academic: New York, 1965; Vol. 5, pp 196–206.
21. Borea, P. A.; Bertolasi, V.; Gilli, G. *Arzneim.-Forsch.* **1986**, *36*, 895.