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Original paper

Non-basic histamine H_1-antagonists. I. Synthesis and biological evaluation of some substituted 2-(2-pyridylaminoalkylamino) pyrimidones and related compounds

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Summary — Using the combined H_1/H_2-receptor histamine antagonist, icotidine (SK&F 93319, **5b**) as a starting point, a series of pyridylaminoalkylaminopyrimidones has been evaluated as potential selective H_1-receptor antagonists with low ability to penetrate the CNS. The most potent compound, SK&F 94070, **34**, 2-[3-(5-chloro-3-methyl-2-pyridylamino)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone is shown to be a highly selective H_1-receptor antagonist of potency comparable with classical antihistamines, both *in vitro* and *in vivo*. This compound, which has no strongly basic centre and is mainly unprotonated at physiological pH, most likely binds to the receptor as a neutral (uncharged) molecule. It exemplifies a new structural type of antagonist which represents an important departure from the conventional view of antihistamines as strongly basic amines which are predominantly protonated under physiological conditions and believed to interact with the receptor in the cationic form.

Résumé — Antagonistes non basiques des récepteurs histamine-H_1: synthèse et évaluation biologique de quelques (pyridyl-2 aminoalkylamino)-2 pyrimidones substituées et de produits apparentés. *L'antagoniste des récepteurs histaminiques H_1/H_2 combinés, l'icotidine (SK&F 93319, **5b**), a fourni le point de départ pour la conception des composés anti-histaminiques aux récepteurs H_1 qui ont une faible aptitude à la pénétration du SNC. Le composé le plus puissant, SK&F 94070, **34**, [(chloro-5-méthyl-3-pyridylamino-2)-3 propylamino]-2-(méthyl-6-pyridylméthyl-3)-2-pyrimidone-4, se montre être un antagoniste des récepteurs histaminiques H_1 extrêmement sélectif dont la puissance est comparable à celle des anti-histaminiques classiques,* in vivo *tout comme* in vitro. *Ce composé, qui n'a pas de centre fortement basique et qui est en grande partie non protoné au pH physiologique, se lie très probablement au récepteur sous forme d'une molécule neutre (non chargée). Il représente l'exemple même d'un nouveau type structurel d'antagoniste, ce qui est une déviation importante de la vue conventionnelle des anti-histaminiques comme amines fortement basiques qui sont en grande partie protonées dans des conditions physiologiques et qui, comme on le croit, réagissent avec le récepteur sous la forme de cation.*

H_1-antagonists / antihistamines / histamine / isocytosines / aminopyrimidones / halopyridines / CNS penetration

Introduction

For many years histamine H_1-receptor antagonists, "antihistamines", have been represented by the general structure **1** [1–3]. Without exception, all contain a basic centre, usually a tertiary acyclic or alicyclic amine and are predominantly protonated at physiological pH. The link, B, between the amine and the Ar groups can take many forms; a simple aliphatic chain, a double bond, or it can be part of an additional ring system. The Ar groups, one of which can be heterocyclic, may be linked directly to A (which can be carbon or a heteroatom) or separated by an additional methylene. They can be isolated or part of a tricyclic system.

Attempts have been made to establish the 3-dimensional requirements of H_1-antagonists and the critical distances between the various components of this general structure [4–7]. However, compounds of high potency which do not appear to fit in with this general structure have been reported. For example, the hypotensive agent indoramine **2** is also a highly potent antihistamine, comparable to standard H_1-antagonists, and the related compound **3** is even more potent [8]. Both compounds lack the double aromatic ring system. More recently Janssens *et al.* have describ-

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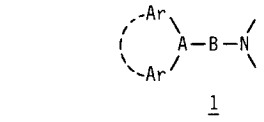

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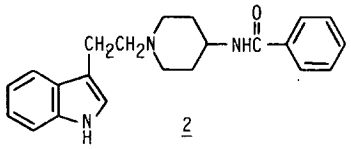

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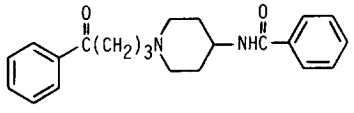

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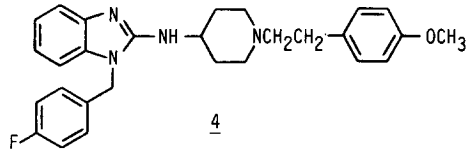


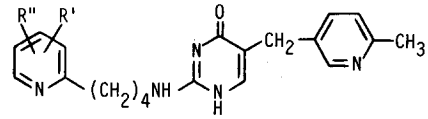
4

ed their work on 2-aminobenzimidazole derivatives which has led to the development of the highly specific H_1-antagonist, astemizole **4** [9–11]. Although novel, elements of the general structure can be discerned.

The use of classical H_1-antagonists in the treatment of, for example, allergic rhinitis is associated with a multitude of side effects, most significant among these being sedation arising from their central nervous system (CNS) depressant activity [12]. These side effects, both central and peripheral, arise partly from a lack of selectivity with respect to other receptor systems [13] and, in the case of the former, the ability of the compounds to cross the blood–brain barrier. Thus a compound with high H_1-receptor specificity combined with an inability to enter the CNS would offer a significant advantage.

During our work on the design of new H_2-antagonists, it was found that, in compounds where the cyanoguanidine group in cimetidine was replaced by a 5-substituted isocytosine group, significant H_1-antagonist activity could be detected. This led to the development of the combined H_1/H_2-antagonist, icotidine **5b** [14]. This compound bears little relationship to the general structure **1**; most importantly it does not contain a strongly basic centre and is predominantly neutral at physiological pH. It was established that, in common with other H_2-antagonists, icotidine **5b** did not penetrate significantly the blood–brain barrier [14] and subsequent work led to the development of the highly selective non-CNS penetrating H_1-antagonist, temelastine, **5c**, [15–17] which has undergone clinical trials [18].

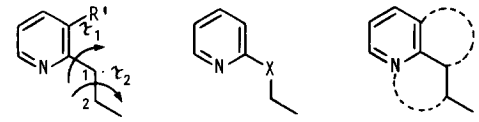
During this work, the importance of the size of the pyridine 3-substituent for determining both high H_1-antagonist activity and selectivity with respect to H_2-antagonist activity was established [14]. One possible role considered for this substituent is to restrict rotation about the C_{ring}-C_1 bond (τ_1) and thus force C_2 to lie *syn* to the pyridine nitro-



5a R'=H, R"=H

5b R'=3-OCH_3, R"=H (icotidine)

5c R'=3-CH_3, R"=5-Br (temelastine)



$\tau_1 = \tau_2 = 180°$

6a 6b 6c

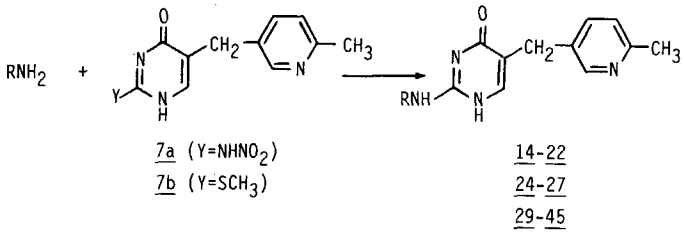
gen, in a plane extending out from the ring, **6a**. In addition, if rotation about τ_2 is also restricted, a *trans* arrangement of the first 3 bonds of the side chain is achieved. Evidence in support of this hypothesis was obtained from molecular mechanics and extended Huckel theory calculations on model compounds [19]. Thus, we speculated that for optimum binding to the H_1-receptor, a coplanar arrangement was required (τ_1 and probably τ_2 close to 180°) whereas binding to the H_2-receptor required a twisted conformation.

Based on this hypothesis, a number of alternative ways of achieving coplanarity were considered. Notably, the replacement of the first methylene group of the tetramethylene side chain by an sp^2 hybridised atom, **6b**, (X = C=O, O, and NH) has been studied and the incorporation of part of the side chain into a bicyclic system, **6c**, investigated. Most of these modifications, however, probably introduce additional conformational effects and the bicyclic structures, in particular, will be considered in the following paper. This paper is concerned with the evaluation of a small number of alternative monocyclic side chains and the subsequent investigation of 2-(2-pyridylaminoalkylamino)pyrimidones, **20–45**, as selective H_1-antagonists.

Chemistry

With the exception of the cyanopyridine analogues, **23** and **28**, all compounds were synthesized using the route indicated in Scheme 1 [20]. The appropriate amine, RNH_2, was reacted with the 5-substituted pyrimidone, **7a** or **7b**, either by fusion, method B, or preferably by refluxing in pyridine, method A or C. The preparation of intermediates, **7a** and **7b**, and their use in the synthesis of H_2-antagonists has been described elsewhere [21, 22].

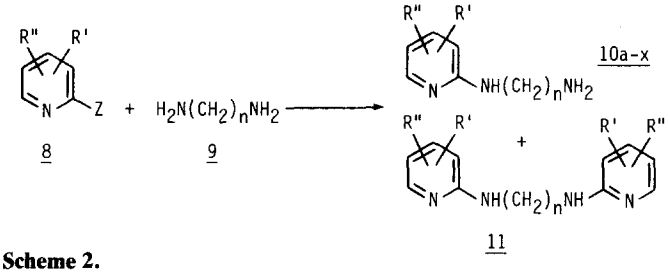
For compound **15**, the keto group was protected during this reaction as the 1,3-dioxolane derivative and subsequently removed. The amine was prepared according to literature methods [23]. The amine for compound **16** was prepared from the reaction of 1,2-diaminoethane and ethyl 2-picolinate. 3-(2-Pyridyloxy)propylamine for com-



7a (Y=NHNO$_2$)
7b (Y=SCH$_3$)

14-22
24-27
29-45

Scheme 1.



8 9 10a-x 11

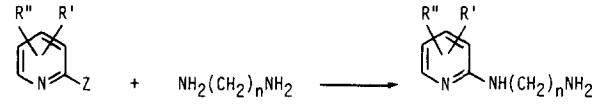
Scheme 2.

pound **17** was obtained from the reaction of 2-bromopyridine with 3-aminopropanol and sodium hydride in THF. The pyrimidine and pyrazine amines for compounds **18** and **19** were prepared by the reaction of 2-chloropyrimidine and 2-chloropyrazine respectively, with excess 1,3-diaminopropane.

All pyridylaminoalkylamines, **10a–x** (Table I), were prepared by reaction of the appropriately substituted 2-halopyridine, **8**, with excess diaminoalkane, **9**, Scheme 2. Mostly, the amines were obtained as oils; freed of the dimeric product **11** and unreacted diaminoalkane by a simple extraction procedure. This usually gave a product of sufficient purity, by NMR, for the final stage of the synthesis without the need for distillation. In the case of **8** (R′=5-F; R″=H; Z=Cl), halogen displacement did not take place selectively in the 2-position. Displacement of fluorine in the 5-position occurred preferentially and a mixture of the 2 products in the ratio 4:1 by NMR was obtained.

The 2-halopyridines, **8**, were either obtainable from outside sources or prepared by literature methods

Table I. *N*-(2-Pyridyl)diaminoalkanes: preparation.



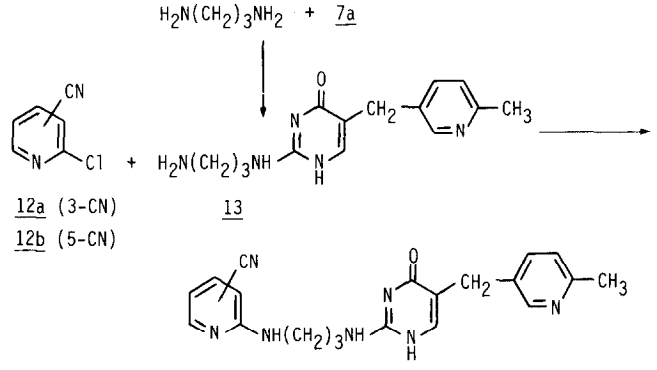
8a-o 9 10a-x

Cmpd	R′	R″	Z	n	Reaction time (hr)/ yield, %[a]	Product ^{1}H-NMR data δ ppm ($CDCl_3$, pyridine protons) Py-3H	Py-4H	Py-5H	Py-6H
10a	H	H	Br	3	3/72	6.35(br d,J=8Hz)	7.38(m)	6.57(br d,J=6Hz)	8.05(br d,J=6Hz)
10b	3-CH_3	H	Br	3	23/72	-	7.15(br d,J=8Hz)	6.45(dd,J=5,8Hz)	7.96(br d,J=5Hz)
10c	3-Cl	H	Cl	3	2.5/78	-	7.41(dd,J=2,8Hz)	6.48(dd,J=5,8Hz)	7.99(dd,J=2,5Hz)
10d	3-OCH_3	H	Cl	3	7.5/20	-	6.80(dd,J=2,9Hz)	6.48(dd,J=5,9Hz)	7.68(dd,J=2,5Hz)
10e	4-CH_3	H	Br	3	6/65	6.20(br s)	-	6.37(br d,J=5Hz)	7.92(d,J=5Hz)
10f	5-CH_3	H	Br	3	6/60	6.30(d,J=8Hz)	7.22(dd,J=3,8Hz)	-	7.87(br d)
10g	5-Cl	H	Cl	3	2.5/22	6.30(d,J=10Hz)	7.33(dd,J=3,10Hz)	-	7.98(d,J=3Hz)
10h	5-Br	H	Br	3	2.5/31	6.22(d,J=8Hz)	7.38(dd,J=2,8Hz)	-	8.02(d,J=2Hz)
10i	5-CF_3	H	Cl/F	3	24/44	6.40(d,J=9Hz)	7.55(dd,J=2,9Hz)	-	8.30(br s)
10j	6-CH_3	H	Br	3	6/58	6.16(d,J=9Hz)	7.30(dd,J=7,9Hz)	6.40(d,J=7Hz)	-
10k	3-Cl	5-Cl	Br	3	1.5/68	-	7.34(d,J=2Hz)	-	7.88(d,J=2Hz)
10l	3-Br	5-Br	Br	3	3.5/50	-	7.95(d,J=2Hz)	-	8.08(d,J=2Hz)
10m	3-CH_3	5-CH_3	Br	3	12/20	-	7.03(br s)	-	7.80(br s)
10n	3-CH_3	5-Br	Br	3	4/29	-	7.28(br d)	-	7.98(d,J=3Hz)
10o	3-CH_3	5-Cl	Br	3	3.5/76	-	7.17(br d)	-	7.93(d,J=2Hz)
10p	3-CH_3	5-NO_2	Cl	3	1.5/68	-	7.95(br d,J=3Hz)	-	8.95(d,J=3Hz)
10q	3-CH_3	5-F	Cl	3	-[b]	-	7.07(m)	-	7.82(m)
10r	3-Cl	H	Cl	2	4/69	-	7.40(dd,J=2,8Hz)	6.47(dd,J=4,8Hz)	7.97(dd,J=2,4Hz)
10s	5-Cl	H	Cl	2	4.5/62	6.36(dd,J=1,8Hz)	7.32(dd,J=2,8Hz)	-	7.99(dd,J=1,2Hz)
10t	3-CH_3	5-Cl	Br	2	6.5/73	-	7.19(d,J=2Hz)	-	7.94(d,J=2Hz)
10u	H	H	Br	4	4/67	6.35(br d,J=6Hz)	7.45(m)	6.50(br t,J=6Hz)	8.05(br d,J=6Hz)
10v	3-Cl	H	Cl	4	3/69	-	7.40(dd,J=2,7Hz)	6.43(dd,J=5,7Hz)	7.98(dd,J=2,5Hz)
10w	5-Cl	H	Cl	4	3.5/90	6.30(d,J=9Hz)	7.31(dd,J=3,9Hz)	-	7.98(d,J=3Hz)
10x	3-CH_3	5-Cl	Br	4	4/72	-	7.10(d,J=2Hz)	-	7.88(d,J=2Hz)

[a]Yields have not been optimised.
[b]Obtained as a mixture, see Experimental protocols.

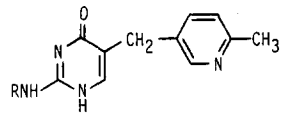
[24–33]. In particular, **8** (R′=3-CH_3; R″=5-CH_3; Z=Br) was obtained by amination of 3,5-lutidine [24] followed by diazotisation in HBr/Br_2 using the Craig procedure [25, 26]. Compounds **8** (R′=3-CH_3; R″=5-Cl; Z=Br) and **8** (R′=3-CH_3; R″=5-Br; Z=Br) were obtained by chlorination [27] and bromination [28] of 2-amino-3-picoline respectively, followed by diazotisation. Similarly **8** (R′=3-Cl; R″=5-Cl; Z=Br) and **8** (R′=3-Br; R″=5-Br; Z=Br) were obtained by diazotisation of the corresponding commercially available amine. **8** (R′=3-CH_3; R″=5-F; Z=Cl) was obtained from 5-amino-2-chloro-3-picoline [29] by diazotisation in hexafluorophosphoric acid [30]. Treatment of 2-chloro-5-trichloromethylpyridine with antimony trifluoride [31] was found to give a mixture of 2-chloro- and 2-fluoro-5-trifluoromethylpyridine in the ratio of *ca.* 3:1 (GC/MS) which was used as such.

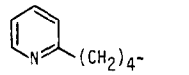
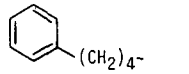
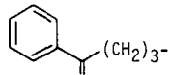
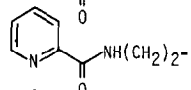
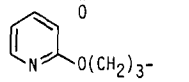
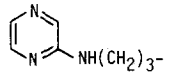
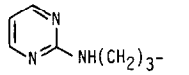
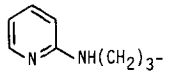
The reaction Scheme 2 fails for the cyanopyridine analogues, due to amidine formation between the diaminoalkane and the nitrile. Compounds **23** and **29** were therefore prepared using Scheme 3. The pyrimidone intermediate **7a** was first reacted with 1,3-diaminopropane to give **13** which was subsequently reacted with **12a** or **12b** [34, 35], method D.



Scheme 3.

Table II. Primary series: histamine antagonist activity.



Compound	R	H_1 in vitro[a] g.p. ileum pA_2 (slope)	H_2 in vitro[a] g.p. atrium pA_2 (slope)
5a		7.28 (0.91) [6.83–7.65]	6.48 (1.37) [6.31–6.65]
14		7.46 (1.00) [7.08–8.02]	5.93 (0.69) [5.62–6.10]
15		6.80 (1.26) [6.62–7.05]	ca. 4.0
16		5.07 (1.17) [4.25–5.66]	< 4.3
17		7.00 (0.88) [6.92–7.55]	5.72 (0.84) [5.28–6.10]
18		7.43 (0.96) [6.55–8.07]	5.87 (0.87) [5.40–6.27]
19		7.60 (0.65) [7.09–8.87]	4.48 (1.05) [4.41–4.86]
20		7.58 (0.95) [6.49–8.27]	ca. 4.5
mepyramine		8.89 (1.16) [8.77–9.0]	< 5.0
chlorpheniramine		8.41 (1.41) [8.28–8.53]	-

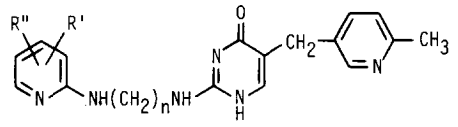
[a]95% confidence limits are indicated together with the slope of the Schild plot.

Biological results and Discussion

All compounds synthesized were initially tested *in vitro* for H_1-antagonist potency and selectivity with respect to H_2-antagonist activity. Histamine H_1-antagonist activity was assessed by measuring inhibition of the histamine induced contraction of the isolated guinea pig ileum and H_2-antagonist activity assessed by the ability of the compound to inhibit the histamine induced positive chronotropic effect on the isolated guinea-pig right atrium. Activities are expressed logarithmically as pA_2 values [36]. Some of the more interesting compounds were assessed for *in vivo* potency by their ability to inhibit histamine induced bronchoconstriction in the guinea-pig. Activities are expressed here as the intravenous dose required to give a dose ratio−1 equal to 10.

Table II summarises the results obtained on an initial series of compounds and compares them with the prototype pyridylbutyl analogue **5a**. A heterocyclic system is clearly not essential for H_1-antagonist activity as indicated by compound **14** and only a small reduction in H_2-antagonist activity is observed. Introducing the keto function, compound **15**, leads to a small loss of H_1-antagonist activity but greatly improves selectivity. Compounds **16** and **17** offer no significant advantage. The amino analogue, **20**, however, demonstrates a significant advance on **5a**. High H_1-antagonist activity is retained (pA_2=7.58) with a dramatic improvement in selectivity (H_1:H_2 ratio of *ca.* 1000 compared with 6 for **5a**). Since we were interested in keeping lipophilicity as low as possible, to reduce the probability of CNS penetration, the pyrazine and pyrimidine analogues **18** and **19** were also investigated. Both compounds retained high H_1-antagonist activity. However, compound **18** was less selective and, since we intended to evaluate the effect of substituents *ortho* to the side chain for comparison with the tetramethylene series **5**, compound **19** was also unsuitable for further study. The aminopyridine, **20**, offered 3 potential advantages over **5a**; namely improved H_1:H_2 selectivity, greater synthetic

accessibility and lower lipophilicity (log $P_{oct/water}$ estimated to be lower by *ca.* −0.6, from comparison between 2-ethylpyridine and 2-methylaminopyridine [37]). These compounds were therefore investigated in more detail. The results obtained are summarised in Table III.



20-45

Both H_1-antagonist potency and selectivity are affected by substitution in the pyridine ring. However, substitution in the 3-position alone, increases H_2-antagonist activity and actually leads, in some cases, to compounds that are less selective than **20**; for example, the 3-methoxy analogue, compound **24**. It is worth noting though, that the slope of the Schild plot is low for some of these compounds, *e.g.* compound **22**, suggesting there may be a non-competitive component to the H_2-antagonist activity. By appropriate substitution in the 3- and 5-positions, however, H_1-antagonist activity can be increased to the level of standard antihistamines, *e.g.* mepyramine and chlorpheniramine, and H_2-antagonist activity effectively abolished.

Although we have only looked at a small number of compounds, the increase in H_1-antagonist activity on introducing a substituent into the 3-position appears to be related simply to the lipophilicity of the substituent (r^2=0.988, n=5) [38]. Interestingly, this contrasts with the ring system itself which appears to be relatively insensitive to changes in lipophilicity (compare the activity of compounds **18** to **20** and compounds **5a** and **14**). Within those substituents chosen for study, lipophilicity is not correlated with other standard parameters, steric or electronic. The steric effect of the 3-substituent, therefore, appears to be no longer important in this series of compounds. This would follow from our original hypothesis, however, since the required conformation is not dependent on sterically restricting rotation, as in the pyridylbutyl series, but is achieved by the conjugated trigonal amino nitrogen.

Introducing substituents into the 5-position on the pyridine also affects activity, but a simple relationship between lipophilicity and H_1-antagonist potency for compounds **20** and **25** to **29** is not apparent. No single parameter adequately describes these compounds and, with only a limited series, a more detailed analysis is not justified. However, the introduction of a 5-halo substituent, compound **27**, as in the case of substitution in the 3-position, leads to a marked increase in H_1-antagonist activity. In contrast, a 5-methyl substituent, compound **25**, has little effect on H_1-antagonist activity. Similarly, H_1-antagonist activity is also not increased by methyl substitution in the 4- and 6-positions, compounds **37** and **38**. Most importantly, however, substitution in the 5-position results in compounds with very low H_2-antagonist activity.

Placing substituents in both the 3- and 5-positions, non-additive effects become apparent. Thus, for example, the effect of a methyl group in the 3-position depends on the nature of the substituent in the 5-position; the increase in H_1-antagonist potency ranging from 0.14 when the 5-substituent is Br (compounds **27** and **33**) to 0.92 when the 5-substituent is CH_3 (compounds **25** and **32**). This non-additivity does not appear to be due to a lipophilicity optimum and no satisfactory multiple regression equation could be obtained to describe the H_1-antagonist activity of the complete series from compound **20** through to **36**. However, the 3,5-disubstituted compounds do provide the most potent and selective derivatives.

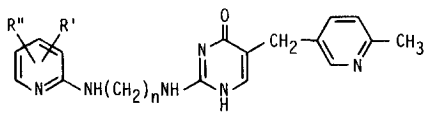
In part two of this series, evidence will be presented for 2 alternative binding sites for the pyridylaminoalkyl moiety at the H_1-receptor. In particular, it will be shown that at only one of these sites does substitution in the 5-position lead to increased activity. One possible explanation, therefore, for the apparent non-additivity observed here is that it may arise, in part, from changes in the preferred pyridine binding site with different substitution patterns.

The effect of modifying the chain length was also investigated. Here again non-additive effects are observed. Thus, with a 3- or 5-chloro substituent, the aminobutyl analogues (compounds **43** and **44**) are of comparable H_1-antagonist potency to the aminopropyl derivatives (compounds **22** and **26**) whereas the aminoethyl analogues (compounds **39** and **40**) are less potent. However, the reverse is true for the disubstituted analogues. Thus potency is essentially maintained in the aminoethyl analogue of compound **34**, compound **41**, but reduced in the aminobutyl analogue, compound **45**.

The compounds in Table III possess 4 ionisable sites and, while the basicity of the aminopyridine will vary, the 3 p*K*a's of the isocytosine moiety will remain essentially constant. These are, as previously discussed [14], *ca.* 3.2 and 5.9 for protonation of the pyrimidone and methylpyridine respectively and *ca.* 9.8 for loss of a proton from the pyrimidone. Under physiological conditions, therefore, this part of the molecule will be predominantly unionised. The p*K*a of the substituted aminopyridine varies over a wide range; one of the most basic being the dimethyl analogue, compound **32** (estimated p*K*a *ca.* 7.5 by comparison with pyridine, 2-aminopyridine and 3,5-lutidine [39]). However, very weakly basic compounds are highly potent, for example the dichloro analogue, compound **30**, (2-amino-3,5-dichloropyridine p*K*a = 2.75 [39]). Thus, while compound **32** may be much as 50% protonated under physiological conditions, it is most probable that, as with all these compounds, it is the neutral molecule that is involved in binding to the H_1-receptor.

The ability of some of these compounds to inhibit histamine induced bronchoconstriction in the guinea-pig is summarised in Table IV. Activities approaching those of the standard H_1-antagonists are observed. Compound **34**, SK&F 94070, proved to be the most interesting. Compound **34** is a potent and highly selective H_1-antagonist. Its potency as an H_1-antagonist *in vitro* (pA_2 8.80) is comparable with that observed for mepyramine under similar conditions. Its selectivity with respect to H_2-antagonist activity is high (>30,000:1). The compound also has little

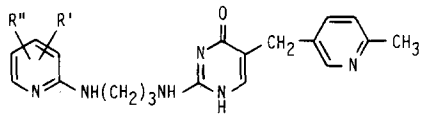
Table III. 2-(2-Pyridylaminoalkylamino)-4-pyrimidones: preparation and histamine antagonist activity.



Compound	R'	R''	n	recryst. solvent	yield,%[a]	mp,°C	formula[b]	H_1 in vitro[c] g.p. ileum pA_2 (slope)	H_2 in vitro[c] g.p. atrium pA_2 (slope)
20	H	H	3	2-PrOH	70	163-65	$C_{19}H_{22}N_6O$(1.6% 2-PrOH)	7.58 (0.95) [6.49-8.27]	ca. 4.5
21	3-CH_3	H	3	2-PrOH/water	68	119-23	$C_{20}H_{24}N_6O,1.75H_2O$	8.20 (1.07) [7.72-8.57]	5.19 (0.91) [4.90-5.43]
22	3-Cl	H	3	2-PrOH/water	86	91-94	$C_{19}H_{21}ClN_6O,1.8H_2O$	8.45 (1.04) [7.86-8.72]	6.50 (0.52) [5.72-7.77]
23	3-CN	H	3	EtOH/water	26[d]	75-80	$C_{20}H_{21}N_7O,0.8H_2O$	6.97 (1.06) [6.70-7.44]	4.95 (0.71) [4.04-5.57]
24	3-OCH_3	H	3	2-PrOH/water	68	78-81	$C_{20}H_{24}N_6O_2,0.3H_2O$	7.45 (0.60) [6.96-8.38]	6.50 (0.69) [6.23-6.95]
25	5-CH_3	H	3	2-PrOH/water	50	164-66	$C_{20}H_{24}N_6O,2.2H_2O$	7.36 (1.09) [6.89-7.76]	ca. 4.3
26	5-Cl	H	3	2-PrOH/water	58	173-75	$C_{19}H_{21}ClN_6O,1.9H_2O$	8.30 (0.99) [7.57-8.88]	ca. 4.8
27	5-Br	H	3	2-PrOH/water	28[e]	186-87	$C_{19}H_{21}BrN_6O,1.0H_2O$	8.59 (0.80) [8.38-8.77]	low solubility
28	5-CN	H	3	EtOH	25[d]	175-77	$C_{20}H_{21}N_7O,0.2H_2O$	7.40 (0.91) [7.01-8.05]	ca. 4.0
29	5-CF_3	H	3	2-PrOH/water	75	220-23	$C_{20}H_{21}F_3N_6O,2.0H_2O$	7.30 (1.31) [6.62-7.75]	< 4.3
30	3-Cl	5-Cl	3	MeOH	33[f,g]	147-48	$C_{19}H_{20}Cl_2N_6O$	8.78 (0.70) [8.32-9.16]	no dose response
31	3-Br	5-Br	3	2-PrOH/water	81	160-62	$C_{19}H_{20}Br_2N_6O,2.0H_2O$	8.67 (0.96) [8.37-8.93]	< 3.8
32	3-CH_3	5-CH_3	3	EtOH/water	49[f]	104-5	$C_{21}H_{26}N_6O,2.4H_2O$	8.28 (0.82) [7.83-8.63]	ca. 4.6
33	3-CH_3	5-Br	3	2-PrOH/water	85	48-51	$C_{20}H_{23}BrN_6O,2.1H_2O$	8.73 (1.18) [8.54-8.87]	ca. 4.0
34	3-CH_3	5-Cl	3	2-PrOH/water	83	140-43	$C_{20}H_{23}ClN_6O,2.0H_2O$	8.80 (0.99) [8.54-9.00]	ca. 4.3
35	3-CH_3	5-NO_2	3	DMF/EtOH DMF/water	74	166-68 110	$C_{20}H_{23}N_7O_3,0.5H_2O$	7.98 (0.85) [7.49-8.34]	< 4.3
36	3-CH_3	5-F	3	MeOH/water	-[h]	120-25	$C_{20}H_{23}FN_6O,1.75H_2O$	8.32 (1.33) [8.03-8.54]	ca. 4.7
37	4-CH_3	H	3	EtOH/water	77	indeterminate	$C_{20}H_{24}N_6O,0.3H_2O$	7.20 (0.64) [6.77-7.54]	ca. 4.6
38	6-CH_3	H	3	EtOH/water	65	113-20	$C_{20}H_{24}N_6O,0.5H_2O$	7.40 (1.04) [6.60-7.38]	< 4.3
39	3-Cl	H	2	2-PrOH/water	75	139-41	$C_{18}H_{19}ClN_6O,1.0H_2O$	6.64 (0.68) [5.03-7.59]	< 4.3
40	5-Cl	H	2	2-PrOH/water	75	164-66	$C_{18}H_{19}ClN_6O,0.50H_2O$	7.84 (0.94) [7.14-8.37]	ca. 4.4
41	3-CH_3	5-Cl	2	2-PrOH/water	86	112-15	$C_{19}H_{21}ClN_6O,1.45H_2O$	8.43 (0.92) [7.91-8.95]	< 4.3
42	H	H	4	EtOH	76	184	$C_{20}H_{24}N_6O$	7.30 (1.0) [6.44-7.88]	ca. 4.2
43	3-Cl	H	4	EtOH	78	180-82	$C_{20}H_{23}ClN_6O$	8.42 (0.76) [7.74-8.90]	6.74 (0.58) [6.40-8.01]
44	5-Cl	H	4	DMF/EtOH	76	214-15	$C_{20}H_{23}ClN_6O$	8.48 (1.10) [8.07-8.81]	< 4.3
45	3-CH_3	5-Cl	4	DMF/water	39[f]	202-3	$C_{21}H_{25}ClN_6O$	7.47 (1.01) [6.84-7.94]	< 4.3

[a]Yields have not been optimised. All compounds synthesised using method A unless indicated otherwise.
[b]In the case of non-stoichiometric hydrates, the molecular formula as isolated and used for the determination of biological activity is shown. ^{1}H-NMR and IR were consistent with the assigned structures. All values for C,H,N were within ±0.4% of calculated values.
[c]95% confidence limits are indicated together with the slope of the Schild plot.
[d]Method D used for synthesis.
[e]Chromatography required (silica gel CH_2Cl_2 / MeOH−NH_3, 20:1).
[f]Method B used for synthesis.
[g]Chromatography required (silica gel $CHCl_3$ / MeOH, graded 50:1 to 35:1).
[h]See Experimental protocols.

Table IV. *In vivo* histamine H_1 antagonist activity.



Compound	R'	R"	g.p. bronchoconstriction dose for DR-1=10 (μmol/Kg iv)
27	5-Br	H	1.80
30	3-Cl	5-Cl	0.23
31	3-Br	5-Br	0.60
33	3-CH_3	5-Br	0.19
34	3-CH_3	5-Cl	0.075
mepyramine			0.028
chlorpheniramine			0.063

antimuscarinic activity (pA_2 against carbachol stimulation of the guinea-pig ileum *in vitro*, *ca.* 4.3) and β-adrenergic antagonist activity (pA_2 against isoprenaline stimulation of the guinea-pig atrium *in vitro*, *ca.* 4.3). *In vivo*, in the guinea-pig bronchoconstriction assay, compound **34** was found to be of similar potency to chlorpheniramine but slightly less potent than mepyramine.

Compound **34** was also evaluated for its ability to inhibit the 2-pyridylethylamine-induced depressor response in the anaesthetised cat [17], both intravenously and after intraduodenal administration. After intravenous administration similar activity to that of mepyramine was observed (dose for DR-1=1 = 0.68 μmol/kg compared with 0.55 μmol/kg for mepyramine). Bioavailability after intraduodenal administration was calculated to be ≈ 80% but with a short half-life ($t_{1/2}$ 30 min). Compound **34** has also been found to possess, in comparison to mepyramine, negligible ability to penetrate into the CNS [17].

Thus, in this paper we have described a novel series of histamine H_1-antagonists which do not obviously fit the classical description of antihistamines. The most active compounds are of comparable potency to standard H_1-antagonists both in *in vitro* and *in vivo*. Unlike classical H_1-antagonists, however, these compounds do not possess a strongly basic centre and therefore are unlikely to bind to the H_1-receptor as a protonated cation.

Experimental protocols

Chemistry

Melting points were determined with a Buchi 510 melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin–Elmer model PE580 spectrometer. ^{1}H-NMR spectra were recorded either at 100 MHz on a JEOL PFT100P or at 60 MHz on a JEOL FX60Q spectrometer and chemical shifts are reported in parts per million (δ) downfield from the internal standard Me_4Si (or sodium trimethylsilylpentane sulphonate-d_4 in D_2O). Mass spectra were obtained on a VG Analytical VG7070/VG2050 system. Elemental analyses (C,H,N) were performed on a Perkin–Elmer PE240 instrument. Analytical figures were all within ±0.4% of theoretical values unless otherwise indicated. Preparative column chromatography was conducted using silica gel 60 (70–230 mesh ASTM) from Merck.

Preparation of 2-bromopyridines: general procedure [25, 26]

2-Bromo-5-chloro-3-methylpyridine ***8o***

Bromine (15 ml, 290 mmol) was added slowly to a stirred suspension of 2-amino-5-chloro-3-methylpyridine [27] (14.3 g, 100 mmol) in 48% hydrobromic acid (75 ml) held at −10°C. A solution of sodium nitrite (20 g, 290 mmol) in water (35 ml) was added and the mixture stirred vigorously at −10°C for 1.5 h. After a further 0.5 h at 0°C the mixture was neutralised (NaOH) maintaining the temperature below 25°C. The reaction mixture was stirred vigorously until a fine crystalline suspension was obtained. This was filtered off and dried over KOH at normal pressure to give an essentially quantitative yield of **8o**, mp 36–37°C (lit 30–31°C [40]) which was used without further purification. NMR ($CDCl_3$) δ 2.38 (3H, s, CH_3), 7.53 (1H, br d, *J*=3 Hz, *py*-4H), 8.18 (1H, br d, *J*=3 Hz, *py*-6H).

Preparation of diaminoalkanes: general procedure

N-*(5-Chloro-3-methyl-2-pyridyl)-1,3-diaminopropane* ***10o***

2-Bromo-5-chloro-3-methylpyridine (21 g, 102 mmol), 1,3-diaminopropane (50 ml, 600 mmol) and pyridine (10 ml, 124 mmol) were heated together under reflux for 3.5 h. The excess diaminopropane was removed under reduced pressure and the residue taken up in water. The pH was adjusted to 6 (HCl) and the solution extracted with chloroform to remove the bis-product **11o**. The solution was finally basified (NaOH) and extracted with ether. The ether extracts were dried (K_2CO_3) and concentrated under reduced pressure to give **10o** (15.5 g, 76%) as an oil. NMR ($CDCl_3$) δ 1.54 (2H, s, NH_2), 1.77 (2H, m, *J*=6 Hz, CH_2), 2.04 (3H, s, CH_3), 2.86 (2H, t, *J*=6 Hz, CH_2N), 3.35 (2H, br q, *J*=6 Hz, CH_2N-*py*), 5.13 (1H, br, NH), 7.17 (1H, br d, *py*-4H), 7.93 (1H, d, *J*=2 Hz, *py*-6H). MS (EI 70 eV) *m/z* 199($M^{\cdot+}$), 182, 169, 156(base), 155, 142, 128, 126, 30.

Preparation of 2-amino-4-pyrimidones: general procedure

Method A: 2-[3-(5-chloro-3-methyl-2-pyridylamino)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***34***

N-(5-Chloro-3-methyl-2-pyridyl)-1,3-diaminopropane (10 g, 50 mmol) and 2-nitroamino-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone [22] **7a** (11 g, 42.1 mmol) were heated together under reflux in pyridine (75 ml) for 22 h. The reaction mixture was evaporated under reduced pressure and the residue crystallised from isopropanol/water to give **34** as a dihydrate (15.25 g, 83%), mp 140–43°C. IR ($CHBr_3$) ν_{max} 3670, 3590 (H_2O), 3460, 3420, 3270 (NH), 1650 (C=O), 1600 (C=N) cm^{-1}. NMR (Me_2SO-d_6) δ 1.74 (2H, m, CH_2), 2.07 (3H, s, 3-CH_3), 2.40 (3H, s, 6-CH_3), 3.40 + 3.50 (6H, m, s, 2 × NCH_2, *py*-CH_2-*pyrim*), 6.22 + 6.50 (2H, t, m, 2 × NH), 7.13 (1H, d, *py*-H), 7.33 + 7.52 + 7.58 (3H, m, dd, s, 2 × *py*-H, *pyrim*-H), 7.89 (1H, m, *py*-H), 8.34 (1H, m, *py*-H). Anal. $C_{20}H_{23}ClN_6O$,2.H_2O (C,H,N).

Method B: 2-[3-(3,5-dichloro-2-pyridylamino)propylamino]5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***30***

N-[2-(3,5-Dichloropyridyl)]-1,3-diaminopropane (1.0 g, 4.6 mmol) and **7a** (1.04 g, 4.0 mmol) were fused together on an oil bath at 140°C for 5 h. On cooling water was added, the pH adjusted to 7 (HCl) and the solid filtered off. After chromatography (silica gel, chloroform/methanol, graded elution 50:1 to 35:1), crystallisation from methanol afforded **30** (0.55 g, 33%), mp 147–48°C. IR ($CHBr_3$) ν_{max} 3420, 3310, 3180–2500 (NH, CH), 1650 (C=O), 1615, 1595 (C=N) cm^{-1}. NMR ($CDCl_3$) δ 1.80 (2H, m, CH_2), 2.44 (3H, s, CH_3), 3.45 + 3.58 (6H, m, s, 2 × NCH_2, *py*-CH_2-*pyrim*), 5.85 (2H, t, 2 × NH), 7.02 (1H, d, *py*-H), 7.38 + 7.39 + 7.43 (3H, d, s, dd, *py*-H, *pyrim*-H, *py*-H), 7.94 (1H, d, *py*-H), 8.36 (1H, d, *py*-H). Anal. $C_{19}H_{20}C_{12}N_6O$ (C,H,N).

Method C: 2-(4-phenylbutylamino)-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***14***

Phenylbutylamine (2.7 g, 18 mmol) and 2-methylthio-5-(6-methyl-3-

pyridylmethyl)-4-pyrimidone [21] **7b** (3.0 g, 12 mmol) were heated together under reflux in pyridine (20 ml) for 40 h. After removing the solvent under reduced pressure, the residue was taken up in water and the pH adjusted to 7 (HCl). The solid thus formed (4.15 g) was filtered off and part recrystallised from ethanol/water to give **14**, mp shrinks *ca.* 100°C (−H_2O) melts 151−52°C. IR (nujol) ν_{max} 2500−3650 (NH, CH, H_2O), 1690 (C=O), 1620 (C=N) cm^{-1}. NMR (Me_2SO-d_6) δ 1.55 (4H, m, CH_2CH_2), 2.42 (3H, s, CH_3), 2.55 + 3.30 + 3.51 (m, m, s, $PhCH_2$, NCH_2, *py*-CH_2-*pyrim*, HOD), 6.48 (1H, br t, NH), 7.16 + 7.24 + 7.52 + 7.58 + 7.60 (9H, d, m, dd, s, br t, *py*-5H, Ph-H, *py*-4H, *pyrim*-H, NH), 8.36 (1H, d, *py*-2H). Anal. $C_{21}H_{24}N_4O$,1.5H_2O (C,H,N).

Method D: 2-[3-(5-cyano-2-pyridylamino)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***28***

7a (5.22 g, 20 mmol) and 1,3-diaminopropane (60 ml) were heated together under reflux for 2.5 h. After removing the excess amine at reduced pressure, the residue was crystallised from ethanol to give 2-(3-aminopropylamino)-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone **13** (4.3 g, 79%) mp 165−66°C. NMR (Me_2SO-d_6) δ 1.58 (2H, m, CH_2), 2.40 + 2.50 (5H, s, m, CH_3, CH_2N), 3.25 + 3.48 (4H, CH_2N-*pyrim*, *py*-CH_2-*pyrim*), 7.10 (1H, d, *J*=8 Hz, *py*-5H) 7.50 (2H, s, m, *pyrim*-H, *py*-4H), 8.33 (1H, d, *py*-2H). Anal. $C_{14}H_{19}N_5O$ (C,H,N).

The above material **13** (1.09 g, 4 mmol), 2-chloro-5-cyanopyridine [35] **12b** (0.61 g, 4.4 mmol) and potassium carbonate (0.61 g, 4.4 mmol) were heated together under reflux in pyridine (10 ml) for 2.5 h. The solution was evaporated under reduced pressure, the residue taken up in water and the pH adjusted to 6.5 (NaOH). The precipitate thus obtained was chromatographed (silica gel, chloroform/methanol, graded elution 1:0 to 20:1) and the required component crystallised twice from ethanol to give **28** (0.38 g, 25%), mp 175−77°C. IR ($CHBr_3$) ν_{max} 3650 (H_2O), 3420, 3260 (NH), 2220 (CN), 1670, 1650 (C=O), 1605 (C=N) cm^{-1}. NMR (Me_2SO-d_6) δ 1.75 (2H, m, CH_2), 2.41 (3H, s, CH_3), 3.30 + 3.49 (m + s, 2 × NCH_2, *py*-CH_2-*pyrim*, HOD), 6.50 + 6.56 (2H, br s, NH, *py*-H), 7.12 (1H, d, *py*-H), 7.60 (4H, m, 2 × *py*-H, *pyrim*-H, NH), 8.33 (1H, d, *py*-H), 8.41 (1H, d, *py*-H). Anal. $C_{20}H_{21}N_7O$,0.2H_2O (C,H,N).

2-(3-Benzoylpropylamino)-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***15***

Reacting 2-(3-aminopropyl)-2-phenyl-1,3-dioxolane [23] (1.26 g, 6.08 mmol) with **7a** (1.06 g, 4.05 mmol) using method A gave 2-(4-phenyl-4,4-ethylenedioxybutylamino)-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone (1.42 g, 68%) mp 115−17°C. NMR ($CDCl_3$) δ 1.65 + 1.90 (4H, m, m, CH_2CH_2), 2.47 (3H, s, CH_3), 3.25 (2H, m, CH_2N), 3.54 (2H, s, *py*-CH_2-*pyrim*), 3.82 (4H, m, OCH_2CH_2O), 7.01 (1H, d, *J*=8 Hz, *py*-5H), 7.30 (7H, m, Ph-H, *py*-4H, *pyrim*-H), 8.34 (1H, br s, *py*-2H).

The above material (1.25 g, 3.08 mmol) was taken up in ethanol (10 ml) and ethanol saturated with HCl (10 ml) added, together with a few drops of water to maintain solution. After standing for 30 min the mixture was evaporated under reduced pressure and the residue crystallised from methanol to give **15** dihydrochloride (0.83 g, 62%) mp 242−45°C. IR (nujol) ν_{max} 3280, 3220, 2620 (NH), 1685, 1675 (C=O, C=NH$^+$) cm^{-1}. NMR (D_2O) δ 2.08 (2H, m, CH_2), 2.82 (3H, s, CH_3), 3.29 + 3.57 (4H, t, t, $COCH_2$, NCH_2), 3.91 (2H, s, *py*-CH_2-*pyrim*), 7.70 + 7.76 + 7.80 (7H, m, s, m, Ph-H, *pyrim*-H, *py*-5H), 8.41 + 8.51 (2H, dd, d, *py*-4H, *py*-2H). Anal. $C_{21}H_{22}N_4O_2$,2HCl (C,H,Cl,N).

2-[2-(2-Picolinamido)ethylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***16***

Ethyl 2-picolinate (10 g, 66 mmol), 1,2-diaminoethane (22 ml, 330 mmol) and pyridine (6.9 ml, 86 mmol) were heated together under reflux for 3.5 h. The mixture was evaporated under reduced pressure, the residue taken up in water and the pH adjusted to 5 (HCl). After extracting with chloroform the pH was raised to 13 (NaOH) and extracted again with chloroform. After drying (K_2CO_3) the final extract was evaporated under reduced pressure to give *N*-(2-picolinoyl)-1,2-diaminoethane (8.02 g, 73%) as an oil. NMR ($CDCl_3$) δ 1.40 (2H, s, NH_2), 2.95 (2H, m, CH_2N), 3.55 (2H, m, CH_2NCO), 7.40 (1H, m, *py*-3H), 7.84 (1H, t of d, *J*=6.2 Hz, *py*-5H), 8.22 (1H, m, *py*-4H), 8.55 (1H, m, *py*-6H).

The above material (2.0 g, 12 mmol) and **7a** (2.64 g, 10 mmol) were heated together under reflux in pyridine (6 ml) for 24 h. The mixture was evaporated under reduced pressure and the residue triturated with ether. The solid thus obtained was recrystallised from isopropanol and finally from isopropanol/water to give **16** (1.97 g, 51%) as a monohydrate, mp 83−86°C. IR ($CHBr_3$) ν_{max} 3670, 3590 (H_2O), 3380, 3240 (NH), 1665 (C=O), 1610 (C=N) cm^{-1}. NMR (Me_2SO-d_6) δ 2.41 (3H, s, CH_3), 3.45 (m, CH_2CH_2, *py*-CH_2-*pyrim*, HOD), 6.60 (1H, br t, NH), 7.12 (1H, d, *py*-H), 7.51 + 7.58 + 7.62 (3H, dd, s, dd, *py*-H, *pyrim*-H, *py*-H), 8.33 (1H, d, *py*-H), 8.62 (1H, m, *py*-H), 9.08 (1H, br t, NH), 10.8 (1H, br, NH). Anal. $C_{19}H_{20}N_6O_2$,1.0 H_2O (C,H,N).

2-[3-(2-Pyridyloxy)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***17***

3-Aminopropanol (4.25 g, 57 mmol) was added to a stirred suspension of sodium hydride (2.64 g, 55 mmol) in dry THF. The mixture was slowly warmed and then heated under reflux for 1 h. On cooling 2-bromopyridine (7.9 g, 50 mmol) was added. The mixture was reheated to initiate an exotherm and finally heated under reflux for a further 2.5 h. The mixture was evaporated under reduced pressure, the residue taken up in water, the pH adjusted to 5 (HCl) and extracted with dichloromethane. The pH was raised to 13 (NaOH) and extracted again with dichloromethane. The final extracts were dried (K_2CO_3) and evaporated under reduced pressure to give 3-(2-pyridyloxy)propylamine (3.65 g, 48%) as an oil. NMR ($CDCl_3$) δ 1.59 (2H, s, NH_2), 1.92 (2H, m, CH_2), 2.88 (2H, t, *J*=7 Hz, CH_2N), 4.38 (2H, t, *J*=7 Hz, CH_2O), 6.77 (2H, m, *py*-3H and 5H), 7.55 (1H, m, *py*-4H), 8.12 (1H, m, *py*-6H).

The above material (0.84 g, 5.5 mmol) and **7a** (1.3 g, 5 mmol) were heated together under reflux in pyridine (10 ml) for 18 h. The mixture was evaporated under reduced pressure, the residue triturated with water and the solid thus obtained recrystallised from ethanol/water to give **17** (1.52 g, 84%) as a hemihydrate, mp 46−48°C. IR (nujol) ν_{max} 3410 (H_2O), 3240, 3170 (NH), 1660 (C=O), 1615 (C=N) cm^{-1}. NMR ($CDCl_3$) δ 2.00 (2H, m, CH_2), 2.46 (3H, s, CH_3), 3.45 + 3.53 (4H, m, s, CH_2N, NH, *py*-CH_2-*pyrim*), 4.34 (2H, t, CH_2O), 6.69 + 6.70 + 6.80 + 7.00 (4H, d, br, m, d, NH, *py*-H, *py*-H), 7.45 (3H, m, 2 × *py*-H, *pyrim*-H), 8.01 (1H, dd, *py*-H), 8.33 (1H, d, *py*-H). Anal. $C_{19}H_{21}N_5O_2$,0.5H_2O (C,H,N).

2-[3-(2-Pyrimidinylamino)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***19***

N-(2-Pyrimidinyl)-1,3-diaminopropane was obtained as an oil in 39% yield from 2-chloropyrimidine and 1,3-diaminopropane using the general method described above. NMR ($CDCl_3$) δ 1.55 (2H, s, NH_2), 1.76 (2H, m, CH_2), 2.84 (2H, t, *J*=7 Hz, CH_2N), 3.53 (2H, q, *J*=7 Hz, CH_2N-*pyrim*), 5.98 (1H, br, NH), 6.52 (1H, t, *J*=5 Hz, *pyrim*-5H), 8.28 (2H, d, *J*=5 Hz, *pyrim*-4H and 6H).

The above material was converted into **19** using method A. The crude product was chromatographed (silica gel dichloromethane/methanol−NH_3, 20:1) and crystallised from isopropanol/water to give **19** as a hydrate in 16% yield, mp softens *ca.* 94°C melts 152−53°C. IR ($CHBr_3$) ν_{max} 3670, 3590 (H_2O), 3430, 3270 (NH), 1650 (C=O), 1615 (C=N) cm^{-1}. NMR ($CDCl_3$) δ 1.82 (2H, m, CH_2), 2.46 (3H, s, CH_3), 3.42 + 3.60 (6H, m, s, 2 × CH_2N, *py*-CH_2-*pyrim*), 6.18 + 6.44 (2H, br t, t, NH, *pyrim*-H), 7.47 + 7.48 + 7.5 (3H, s, dd, br, *pyrim*-6H, *py*-H, NH), 8.22 + 8.42 (3H, d, m, 2 × *pyrim*-H, *py*-H). Anal. $C_{18}H_{21}N_7O$,1.29H_2O (C,H,N).

2-[3-(2-Pyrazinyl)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***18***

N-(2-Pyrazinyl)-1,3-diaminopropane was obtained from 2-chloropyrazine and 1,3-diaminopropane using the general method described above. The oil was distilled before use (bp 115−17°C, 0.06 mm Hg) giving a yield of 36%. NMR ($CDCl_3$) δ 1.39 (2H, s, NH_2), 1.75 (2H, m, CH_2), 2.84 (2H, t, *J*=7 Hz, CH_2N), 3.46 (2H, q, *J*=7 Hz, CH_2N-*pyraz*), 5.85 (1H, br, NH), 7.73 (1H, d, *J*=4 Hz, *pyraz*-3H), 7.90 (2H, m, *pyraz*-5H and 6H).

The above material was converted into **18** using method A in 75% yield, mp 175−78°C (from isopropanol/water). IR ($CHBr_3$) ν_{max} 3650 (H_2O), 3420, 3270 (NH), 1669 (C=O), 1612 (C=N) cm^{-1}. NMR ($CDCl_3$) δ 1.85 (2H, m, CH_2), 2.43 (3H, s, CH_3), 3.40 + 3.61 (6H, m, s, 2 × CH_2N, *py*-CH_2-*pyrim*), 6.15 (1H, br m, NH), 7.06 (1H, d, *py*-H), 7.41 + 7.49 + 7.67 + 7.80 + 8.10 (6H, s, dd, d, m, br, *pyrim*-H, *py*-H, *pyraz*-H, 2 × *pyraz*-H, NH). Anal. $C_{18}H_{21}N_7O$,0.35H_2O (C,H,N).

2-[3-(5-Fluoro-3-methyl-2-pyridylamino)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone ***36***

2-Chloro-5-fluoro-3-methylpyridine [29, 30] **8q** (5.4 g, 37 mmol), 1,3-diaminopropane (15 ml, 180 mmol) and pyridine (4 ml) were heated together under reflux for 12 h. The product was isolated as a waxy solid

(3.75 g) using the general procedure for amines described above. The ^{1}H NMR spectrum of this material indicated a mixture of *N*-(6-chloro-5-methyl-3-pyridyl-)-1,3-diaminopropane and the required product, *N*-(5-fluoro-3-methyl-2-pyridyl)-1,3-diaminopropane **10q** in the ratio 4:1.

The above mixture (2.6 g) and **7a** (2.9 g) were heated together under reflux in pyridine (20 ml) for 24 h. The mixture was evaporated under reduced pressure and the residue chromatographed (silica gel chloroform, chloroform/methanol, grade 50:1 to 20:1). Fractions containing the faster running component were combined and evaporated under reduced pressure to give a solid (0.5 g), which was recrystallised twice from methanol and finally from methanol/water to give **36** (0.26 g) as a hydrate mp 120–25°C (softens). IR ($CHBr_3$) ν_{max} 3670, 3580 (H_2O), 3450, 3410, 3300, 3260 (NH), 1645 (C=O), 1610 (C=N) cm^{-1}. NMR (Me_2SO-d_6) δ 1.75 (2H, m, CH_2), 2.06 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.40 + 3.47 (m, s, 2 × CH_2N, *py*-CH_2-*pyrim*, HOD), 5.90 + 6.15 + 6.40 (3H, br, 3 × NH), 7.11 + 7.23 (2H, d, m, 2 × *py*-H), 7.48 + 7.54 (2H, dd, s, *py*-H, *pyrim*-H), 7.83 (1H, m, *py*-H), 8.30 (1H, d, *py*-H). Anal. $C_{20}H_{23}FN_6O,1.75H_2O$ (C,H,N).

Fractions containing the slower running component were combined and evaporated under reduced pressure to give a brown oil. This was taken up in methanol treated with charcoal, and water added, to give a solid which on recrystallisation from ethanol/water gave 2-[3-(6-chloro-5-methyl-3-pyridylamino)propylamino]-5-(6-methyl-3-pyridylmethyl)-4-pyrimidone hemihydrate (0.47 g), mp 110–15°C (softens). IR ($CHBr_3$) ν_{max} 3670, 3590 (H_2O), 3415, 3260 (NH), 1670, 1655 (C=O), 1605 (C=N) cm^{-1}. NMR (Me_2SO-d_6) δ 1.75 (2H, m, CH_2), 2.19 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.20 + 3.45 (m, s, 2 × CH_2N, *py*-CH_2-*pyrim*, HOD), 5.95 (1H, br, NH), 6.45 (1H, br, NH), 6.92 (1H, d, *py*-H), 7.12 (1H, d, *py*-H), 7.49 + 7.52 + 7.55 (3H, dd, s, d, *py*-H, *pyrim*-H, *py*-H), 8.31 (1H, d, *py*-H). Anal. $C_{20}H_{23}ClN_6O,0.5H_2O$ (C,H,N).

Pharmacology

In vitro histamine H_1 and H_2-antagonist activities were assessed on isolated guinea-pig ileum and right atrium using methods previously described [17]. Cumulative dose–response curves for antagonists were obtained using incubation times of 8 and 60 min respectively (shown to be adequate for equilibrium in preliminary studies). From dose-ratios determined with different concentrations of test compound, pA_2 values were calculated [36].

In vivo H_1-antagonist potency was assessed in the anaesthetised guinea-pig by the ability of the compound to inhibit histamine induced bronchoconstriction [17]. Using increasing doses of antagonist, the displacement of histamine dose–response curves provided dose-ratios, which, after plotting on a Schild plot [36], allowed the activity to be expressed as the dose of antagonist required to give a dose-ratio −1 = 10.

The assessment of H_1-antagonist activity in the anaesthetised cat and the method used to study CNS penetration in the rat have previously been described [17].

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