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Bioisosteric Design of Conformationally Restricted Pyridyltriazole Histamine H_2-Receptor Antagonists

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A process of bioisosteric drug design is described whereby, in a manner analogous to synthesis, key portions of an effector molecule are successively replaced by pharmacophores or bioisosteres. This process, when applied to histamine, leads to the competitive histamine H_2-receptor antagonist prototype 3-amino-5-(2-amino-4-pyridyl)-1,2,4-triazole (7). The biaryl nature of 7 fixes internitrogen distances, and comparison of these with histamine suggests that 7 shares structural features more in common with histamine trans rather than histamine gauche conformations. Alkylation of the prototype pyridylamino group in 7 markedly improves both histamine H_2-receptor antagonist and gastric acid antisecretory activity so that the resulting agent, 3-amino-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole (8), is more active than cimetidine.

Bioisosteres have been defined as groups or molecules that have chemical and physical similarities producing broadly similar biological properties, and the suggestion has been made that "molecular modifications based on bioisosterism principles can generate new series or even develop new leads if an agonist is used as the starting point for the design of an antagonist".[1] In the synthetic process, a target molecule can be considered to arise from a search tree of precursor molecules. Combination of the principles of synthesis and bioisosterism suggests that successive bioisosteric replacement of key portions of a biologically important molecule to generate a bioisosteric search tree might be an approach to developing a new lead. The successful use of this process is exemplified by the design of a novel series of competitive histamine H_2-receptor antagonists using the agonist molecule histamine as a starting point.

Chemistry. Compounds were prepared from pyridinecarboxylic acid hydrazides by literature procedures (**1–3**, Table II) or from pyridineacetic acid hydrazides by closely analogous procedures (**4–6**, Table II). Compounds **7** and **8** were most conveniently prepared by an analogous route starting with 2-chloroisonicotinic acid hydrazide. Conversion of the acid hydrazide to the amidino hydrazide and reaction with the appropriate amine at elevated temperature resulted in both halogen displacement and cyclization to the final triazole product (Scheme I).

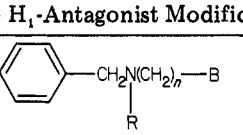
Results and Discussion

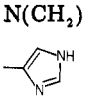
Target Design. The agonist effector molecule histamine is a particularly likely target for bioisosteric analysis, since it can be divided into just two components, an aminoethyl side chain and an imidazole ring. Focusing first on the aminoethyl side chain, one can search for bioisosteres of this group. A reasonable approach toward development of a histamine antagonist might be a search for aminoethyl bioisosteres in the histamine H_1-receptor antagonist literature.

The early ethylenediamine histamine H_1-receptor antagonist antergan (Table I) provides a starting point. In this molecule, replacement of the dimethylaminoethyl moiety by a 2-imidazolinomethyl group enhances antihistamine activity and leads to the histamine H_1-receptor antagonist antistine.[2] Further replacement of the 2-imidazoline moiety by a 4(5)-imidazole group results in retention of one-half of the H_1-receptor antagonist activity.[3] These two literature references taken together suggest that replacement of an aminoalkyl side chain by a side chain containing a 4-substituted imidazole may be compatible with retention of biological effects at the histamine receptor.

Further support for this type of replacement is found in literature related to the H_1-receptor antagonist pyribenzamine. A compound containing a 4-imidazolyl sidechain moiety and identified as compound IIm was reported to have 0.5% of the antihistamine activity of pyribenzamine.[4] That any activity was observed with IIm is re-

Table I. Histamine H_1-Antagonist Modifications



	R	*n*	B	rel histamine H_1 antagonist act.
antergan	C_6H_5	2	$N(CH_3)_2$	1[b]
antistine	C_6H_5	1		>1
ref 3	C_6H_5	1		>0.5
pyribenzamine	2-C_6H_4N	2	$N(CH_2)_2$	2[b]
Compd IIm	$CH_2C_6H_5$	2		0.01[c]
RP 2503	$CH_2C_6H_5$	2	$N(CH_3)_2$	inactive[d]

[a] Approximate histamine-H_1 antagonist activity based on literature. See text. [b] Idson, H. *Chem. Rev.* **1950**, *47*, 307–527. [c] Reference 4. [d] Reference 5.

(1) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563–80.

(2) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1947**, *69*, 1688–92.

(3) Turner, R. A.; Huebner, C. F.; Scholz, C. R. *J. Am. Chem. Soc.* **1947**, *71*, 2801–3.

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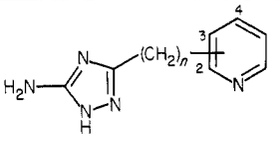
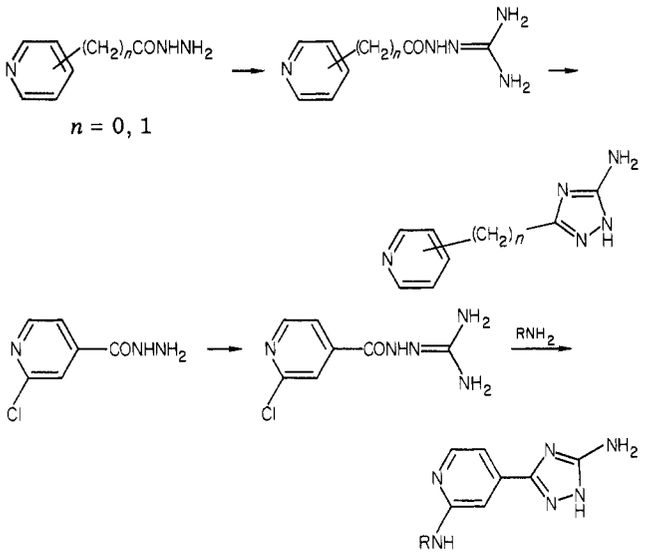
Table II. Pyridyltriazole Probes for Histamine H_2-Antagonist Activity



no.	*n*	pyridine isomer	mp, °C	crystn solvent	mol formula[a]	H_2-receptor antagonist act. (guinea pig atrium): K_B, 10^{-5} M (±SD)	acid antisecretory act.: max % inhibn in dogs (at dose)[c]
1	0	2	213–217	H_2O	$C_7H_7N_5$	–ve	0 (5), 0 (10)
2	0	3	230–231	H_2O	$C_7H_7N_5 \cdot {}^2/_3H_2O$	–ve	22 (10), 11 (25)
3	0	4	279–281	H_2O	$C_7H_7N_5$	4.19 (±2.88)[d]	43 (10), 73 (23)
4	1	2	160–163	H_2O	$C_8H_9N_5 \cdot H_2O$	–ve	18 (5), 0 (10)
5	1	3	194–197	H_2O	$C_8H_9N_5$	–ve	0 (10)
6	1	4	220–223	H_2O	$C_8H_9N_5$	–ve	26 (10), 30 (25)

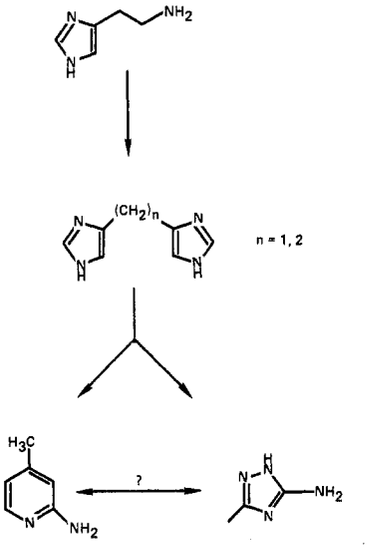
[a] All compounds were analyzed for C, H, and N. [b] The dissociation constant (K_B) was calculated from the equation $K_B = B/(DR - 1)$, where DR is the respective ratio of concentrations of histamine needed to produce half-maximal responses in the presence and absence of different concentrations (B) of antagonists. [c] Maximum percent inhibition of acid output in single experiments in pentagastrin-stimulated Heidenhain pouch dogs at a dose in milligrams per kilogram, given intravenously. [d] Slope of the plot of log (DR – 1) on log B = 1.22 (n = 2 atria).

Scheme I



7, R = H
8, R = C_2H_5

Scheme II. Histamine Bioisosteric Search Tree



markable, since the dibenzylamino substitution pattern in IIm is not optimal for H_1-receptor antagonist activity. This can be seen from the inactivity reported for RP 2503, an early H_1-receptor antagonist probe that contains an acceptable side chain but the suboptimal dibenzylamino moiety.[5] The weak activity reported for IIm is therefore also consistent with the hypothesis that an aminoalkyl side chain may be replaced by a 4-substituted imidazole side chain.

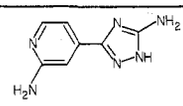
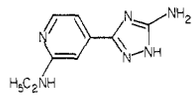
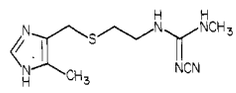
A good bioisosteric replacement in one series of compounds will not necessarily be useful in another.[1] However, it is not necessary to have experimental proof for a bioisosteric replacement, since the idea is to generate one or more theoretical intermediates in a bioisosteric search tree as a method of generating biological probes. Using the 4-substituted imidazole as an aminoalkyl replacement in the case of histamine leads to a bis(4-substituted imidazolyl)methane or -ethane (Scheme I). The compounds in this step in the bioisosteric search tree are symmetrical structures, with the result that in subsequent steps the asymmetry in histamine is lost and bioisosteric groups cannot be unambiguously considered either as imidazole or aminoethyl replacements.

The next step in the search tree follows from a consideration of how one can reintroduce an element of pseudosymmetry into the bisimidazole structures, since histamine itself is asymmetric. Preferably this transformation would be done in such a manner as to eliminate some of the rotational ambiguity in bis(imidazolyl)methane or -ethane. The key to this step lies in focusing on the sequence of histamine H_1-receptor antagonist modifications shown in Table I. The sequence of changes, aminoethyl to cyclized amidine to imidazole, leads to a search for amidine and imidazole surrogates.

Fastier, in a review on structure–activity relationships of amidine derivatives, has suggested that 4-methyl-2-aminopyridine can be viewed as an amidine derivative.[6] 3-Amino-1,2,4-triazole can be viewed as an imidazole surrogate, since workers have reported that 5-(aminoethyl)-3-amino-1,2,4-triazole is a selective histamine H_2-receptor agonist.[7] Incorporation of these two replacement

(4) Huebner, C. F.; Turner, R. A.; Scholz, C. R. *J. Am. Chem. Soc.* **1949**, *71*, 3942–4.
(5) Viand, P. *Prod. Pharm.* **1947**, *2*, 53–64.
(6) Fastier, F. N. *Pharmacol. Rev.* **1962**, *14*, 37–90.
(7) Grechishkin, L. L.; Goldfarb, V. L.; Gavrovskaya, L. K.; Brovtsyna, N. B. *Gen. Pharmacol.* **1980**, *11*, 33–6.

Table III. Aminopyridylaminotriazole Histamine H_2-Antagonists

compd	structure	$pH_{1/2}$[a]	log D[b] pH 7.4	log D[b] pH 9.2	H_2-receptor antagonist act. (guinea pig atrium): K_B, 10^{-9} M (±SD)[c]	Schild plot,[d] slope (±SD)	ID_{50}, mg/kg iv, (pentagastrin-stimulated Heidenhain dogs)[e]
7		9.56 6.13 2.36	0.11	−0.06	2221 (±180)	0.91 (±0.11), $n = 4$	2.35 ($r = 0.95$, $n = 7$)
8		9.70 6.48 2.49	1.13	0.97	235 (±56)	1.00 (±0.10), $n = 7$	0.87 ($r = 0.98$, $n = 3$)
cimetidine		7.02 6.80[f]		0.54 0.40[f]	630 (±360) 790[f]	0.87 (±0.31), $n = 11$	1.02 ($r = 0.97$, $n = 22$)

[a] Observed $pH_{1/2}$, titration at 23 °C. 7·2HCl, H_2O solvent. 7 free base, 1:1 CH_3OH-H_2O, 5.91. 8·2HCl·H_2O, H_2O solvent. 8 free base, 1:1 CH_3OH, H_2O, 6.0. [b] Log distribution coefficient 1-octanol, aqueous buffer at specified pH, 23 °C, shaker flask method. [c] Footnote *b*, Table II. [d] Arithmetic mean of slope of plot of log (DR − 1) on log B ± standard deviation in n atria. [e] Intravenous dose required for 50% inhibition (ID_{50}), calculated from linear regression of log dose on percent inhibition in n dogs. Correlation coefficient = r. [f] Literature values ref 8.

groups while keeping internitrogen distances similar to those in histamine leads to step 2 in the bioisosteric search tree (Scheme II). The choice of the aminotriazole moiety as an imidazole replacement leads to considerable simplification in the chemistry of possible synthetic target compounds, since, in general, triazoles are more readily prepared than are imidazoles. Further simplification in probe compounds is possible by preparation of monosubstituted pyridines with follow-up by 2-aminopyridines once the optimum pyridine substitution pattern is known.

Biological Results

Based on this analysis, the relatively simple probe compounds chosen for preparation were the six possible combinations of a 3-amino-1,2,4-triazole linked at the 5-position either directly or via a methylene spacer to the three possible positions on a pyridine ring. These compounds were tested in the histamine-stimulated isolated guinea pig right atrium, a test for in vitro histamine H_2-receptor antagonist activity. Only one of these compounds, 3-amino-5-(4-pyridyl)-1,2,4-triazole (**3**), exhibited very weak competitive histamine H_2-antagonist activity (Table II), as well as weak gastric acid antisecretory activity, in pentagastrin-stimulated Heidenhain pouch dogs.

The weak activity of **3** suggested that a 2-aminopyridine should be linked to an aminotriazole at the 4-position of the pyridine ring. This compound (**7**, Table III) when tested showed a marked improvement in both histamine H_2-receptor antagonist and gastric acid antisecretory activity over **3**. Elaboration of the pyridylamino group to an ethylamino moiety further increased activity such that the resulting compound, **8**, was over 100 times as active in vitro as the original lead compound, **3**, and, when compared to cimetidine, was more active both as a histamine H_2-receptor antagonist and as an acid antisecretory agent.

Discussion

Compounds **7** and **8** do not exhibit physical properties greatly different from cimetidine. Table IV shows that **3**, **7**, and **8** exhibit three pK_a values. The pK_a of about 9.5 is due to the loss of the acidic triazole hydrogen. That at about pK_a 6 in **7** and **8** is due to loss of a proton from the protonated pyridine ring, and that at about pK_a 2.4 is due to loss of a proton from protonated aminotriazole. The

Table IV. Mole Percent of Species at Physiological pH (7.4)

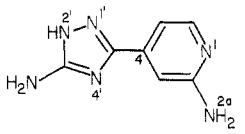
compd	pK_a[a]	anion	neutral	cation
3	9.50[b] 4.74 2.38[b]	0.8	99.0	0.2
7	9.56 6.13 2.36	0.7	94.2	5.1
8	9.70 6.48 2.49	0.5	88.8	10.7
cimetidine	7.02 6.8[c]	0	70.6	29.4

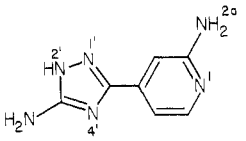
[a] Footnote *a*, Table III. [b] Literature pK_a (H_2O) of aminotriazole: proton lost, 11.1; proton gained, 4.0 (Kroeger, C. F.; Freiberg, W. *Z. Chem.* **1965**, *5*, 381-2). [c] Reference 8.

pK_a's for proton loss from protonated aminotriazole (2.4) and neutral aminotriazole (9.5) are about 1.6 pK_a units lower than literature values for unsubstituted aminotriazole and reflect the large electron-withdrawing effect of the pyridine ring. The pK_a 9.5 value for neutral aminotriazole hydrogen loss is in agreement with the smaller measured value of log D at pH 9.2 over that at 7.4, since the smaller log D value at pH 9.2 reflects the greater aqueous solubility of the 30 mol % of triazole anion present at this pH. The pK_a value of 4.74 in **3** is assigned to loss of a proton from the protonated pyridine ring. Unambiguous assignment of pK_a values allows calculation of the mol % of anionic, neutral, and pyridine monocation species at physiological pH (7.4). For all four compounds in Table IV, the neutral molecule is the predominant species, and it is likely that **7** and **8** interact at the histamine H_2-receptor as the neutral species.

Table III shows the values for the log of the distribution coefficient for **7**, **8**, and cimetidine at pH 7.4 and 9.2. Compound **7** is only slightly more and **8** slightly less hydrophilic than cimetidine, irrespective of whether experimental log D or calculated log P values are used. In summary, although differing in details, both **7** and **8** are similar to cimetidine with regard to the major species present at physiological pH and are similar in octanol–

Table V. Compound 7 Pairs of Internitrogen Distances[a,b]





pair	atoms	distance, Å	pair	atoms	distance, Å
A	1-4′	5.17	C	1′-1	5.17
	1-2′	6.36		1′-2a	5.18
B	2a-4′	5.16	D	4′-1	5.17
	2a-1′	6.02		4′-2a	6.04

[a] Calculated from minimum-energy geometry: Wertz, D. H.; Allinger, N. L. *Tetrahedron* **1974**, *30*, 1579-86. Program source is Allinger, N. L; *QCPE* **1976**, catalog 11, program 318. [b] Triazole tautomer drawn as 2′ N-H by analogy with X-ray on 3-amino-1,2,4-triazole: Starova, G. L.; Frank-Kamensetskaya, O. V.; Makarskii, V. V.; Lopyrev, V. A. *Kristallografiya* **1978**, *23*(4), 849-51.

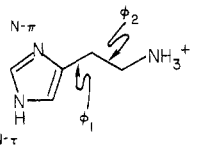
water partitioning behavior.

In contrast to the comparison of physical properties, **7** and **8** differ markedly from the now "classical" histamine H_2-receptor antagonist cimetidine in chemical structure (Table III). In particular, the 4-atom conformationally flexible side chain terminating in a polar moiety found in histamine H_2-receptor antagonists, such as cimetidine,[8] ranitidine,[9] and tiotidine (ICI 125,211),[10] is not present. The axis in **7** passing through the pyridine *N-1–C-4* atoms fixes the pyridine *N-1* and triazole *N-1′* and *N-4′* distances at 5.17 Å, regardless of the torsion angle between the pyridine and triazole rings and also places limits on the distances between the *C-2a* pyridine amino nitrogen and the triazole nitrogens (Table V).

Structural features and modes of receptor binding found in an agonist molecule are not necessarily found in a competitive antagonistic molecule. Moieties found in the agonist may be lacking in the antagonist. Alternatively, moieties found in the antagonist but not the agonist may be important for receptor binding. Keeping this caveat in mind, it is instructive to compare structural features of antagonist **7** with those of histamine and of cimetidine.

The nitrogen atoms of **7** are likely involved in receptor binding. In trying to compare **7** with histamine, similar effects of functional groups need not imply atom upon atom overlap;[1] however, a comparison of the nitrogen arrays in **7** with those in histamine might suggest common hydrogen bonding receptor interactions. The three nitrogens of the agonist histamine are arranged as a single side-chain nitrogen to imidazole ring amidine-like pair. Inspection of **7** in the two ring-coplanar forms indicates that there are no arrays of single nitrogen to amidine-like pairs between the two rings with distances of less than 5.0 Å. There are three arrays of single nitrogens to amidine-pairs with similar distances of 5.2 and 6.2 ± 0.2 Å and one pair (C) with distances of 5.2 Å (Table V). In two of these pairs (A, B) the single nitrogen is located on the pyridine ring, while in pairs C and D the single nitrogen is on the triazole ring. The types of single nitrogen (imine in A, C, and D) and NH_2 in B being compared with NH_3^+ in histamine differ, but a priori this does not exclude similar hydrogen-bonding possibilities, since no single relationship exists to correlate basicity and hydrogen bonding.[11]

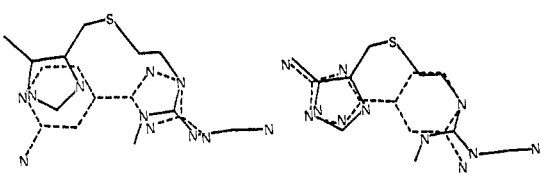
Table VI. Histamine Internitrogen Distances[a]



ϕ_1,[b] deg	ϕ_2,[c] deg	N_π-N^+, Å	N_τ-N^+, Å
0	60/300	4.23	4.17
60	60/300	4.22	4.17
120	60/300	3.60	4.52
180	60/300	2.86	4.83
240	60/300	2.87	4.83
300	60/300	3.62	4.51
0	180	5.07	5.74
60	180	4.90	5.83
120	180	4.55	6.00
180	180	4.37	6.08

[a] Adapted from Kier, L. B. *J. Med. Chem.* **1968**, *11*, 441-5. [b] Rotational angle between imidazole ring plane and side chain plane. [c] Side-chain rotational angle: 60°/300° = gauche conformation; 180° = trans conformation.

Chart I. Compound 7[a] and Cimetidine X-ray[b,c]



[a] At left, rotamer A, B (Table V) (dashed lines) compared to cimetidine (solid lines). At right, rotamer C, D (Table V) compared to cimetidine. [b] Reference 12. [c] Atomic coordinate numbering of **7** and cimetidine shown in Tables VII and VIII.

Table VI presents internitrogen distances in histamine as a function of ring to side chain angle (ϕ_1) and side-chain conformation angle (ϕ_2). For all histamine gauche conformations (ϕ_2 = 60/300°), the distances of single nitrogen to amidine pairs are less than 5 Å. This suggests that **7** does not interact with moieties at the histamine H_2-receptor that might recognize a histamine gauche conformation. The weak activity observed in **3**, which lacks the pyridylamino group as well as the invariant distance of 5.17 Å between the pyridine N-1 and the triazole nitrogens N-1′ and N-4′, suggests that the shorter distance of about 5.2 Å may be the more critical parameter for binding to the histamine H_2 receptor. It is intriguing that this shorter 5.2 Å value is relatively close to the N-π side chain nitrogen distance of 5.1 Å in histamine trans (ϕ_2 = 180°) side-chain conformations (Table VI), and this observation suggests that **7** could share common binding features with moieties at the histamine H_2 receptor recognizing one of the possible trans rather than gauche conformations of histamine.

Comparison of **7** with cimetidine is speculative, since **7** exhibits only a single major torsional degree of freedom about the bond joining the pyridine and triazole rings, while cimetidine may exhibit considerable flexibility about the 4-atom side chain. In Chart I, compound **7** is compared with the X-ray[12] structure of cimetidine, while in Chart

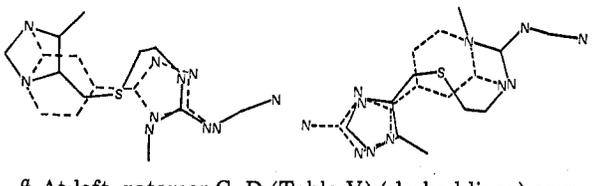
(8) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901-6.
(9) Daly, M. J.; Humphray, J. M.; Stables, R. *Br. J. Pharmacol.* **1981**, *72*, 49-54.
(10) Yellin, T. O.; Buck, S. H.; Gilman, D. J.; Jones, D. F.; Wardleworth, J. M. *Life Sci.* **1979**, *25*, 2001-9.
(11) Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875-91.

Table VII. Final Atomic Coordinates for Compound 7[a]

atom	X	Y	Z
	Rotamer C, D		
N(1)	10.06535	11.18179	1.00523
C(2)	8.98214	10.40653	1.00785
C(3)	9.04069	9.00506	1.02769
C(4)	10.29341	8.37732	1.04571
C(5)	11.42970	9.20810	1.04261
C(6)	11.26776	10.59773	1.02223
C(7)	10.40882	6.90956	1.06734
N(8)	11.54509	6.23134	1.08479
N(9)	11.21373	4.92726	1.10149
C(10)	9.87713	4.82619	1.09413
N(11)	9.36965	6.05527	1.07284
N(12)	12.27187	11.35524	1.01927
N(13)	9.19261	3.77927	1.10486
H(14)	7.99818	10.90289	0.99368
H(15)	8.10746	8.41766	1.02896
H(16)	12.44034	8.76636	1.05631
H(17)	11.82897	4.16379	1.11672
H(18)	13.18779	10.99416	1.03110
H(19)	12.16138	12.33375	1.00496
H(20)	9.61792	2.89217	1.12064
H(21)	8.20967	3.82471	1.09771
	Rotamer A, B		
N(1)	10.04003	11.18047	1.02380
C(2)	8.96743	10.39043	1.02583
C(3)	9.04451	8.98893	1.03390
C(4)	10.30571	8.37905	1.04018
C(5)	11.43069	9.22605	1.03795
C(6)	11.25038	10.61290	1.02973
C(7)	10.45326	6.91408	1.04874
N(8)	9.45513	6.04500	1.05133
N(9)	10.01234	4.82022	1.05947
C(10)	11.34572	4.95789	1.06176
N(11)	11.62736	6.25760	1.05511
N(12)	12.24437	11.38364	1.02763
N(13)	12.20497	4.04885	1.06882
H(14)	7.97681	10.87353	1.02087
H(15)	8.12006	8.38782	1.03520
H(16)	12.44776	8.79911	1.04265
H(17)	9.54214	3.95967	1.06322
H(18)	13.16520	11.03510	1.03167
H(19)	12.12054	12.36065	1.02184
H(20)	11.94357	3.10030	1.07354
H(21)	13.16430	4.26784	1.06979

[a] Atom number, Table V numbering: N-1′, N(8); N-2′, N(9); N-4′, N(11); C-4, C(4); N-1, N(1); N-1a, N(12).

Chart II. Compound 7[a] and Cimetidine[b,c]



[a] At left, rotamer C, D (Table V) (dashed lines) compared to cimetidine non-X-ray conformation (solid lines). Pyridine related to cimetidine imidazole. At right, rotamer C, D (Table V). Triazole related to cimetidine imidazole. [b] Non-X-ray conformation (see Table VIII). [c] See footnote *c*, Chart I.

II, two possible modes of comparison with a non-X-ray conformation of cimetidine are shown. The data presented do not permit definitive conclusions, and the possibility remains open as to whether 7 and cimetidine share common receptor binding sites.

In the design of 7 and 8, a symmetrical intermediate was proposed as the middle step in the bioisosteric search tree

(12) Haedicke, E.; Frickel, F.; Franke, A. *Chem. Ber.* **1978**, *111*, 3222–32.

Table VIII. Final Atomic Coordinates of Cimetidine[a]

atom	Non-X-ray Conformation X	Y	Z
S(1)	−1.46743	2.48727	0.21777
N(2)	−3.24486	−1.93372	0.54866
N(3)	−1.35005	−0.92376	0.12262
N(4)	2.29944	0.91607	−0.05522
N(5)	1.48788	−1.22427	−0.27635
N(6)	3.71105	−0.95530	0.14301
N(7)	5.77941	0.38793	0.11411
C(8)	−1.91821	−1.99350	0.61310
C(9)	−2.40298	−0.11654	−0.26947
C(10)	−3.58864	−0.73451	−0.01836
C(11)	−4.99759	−0.36301	−0.29039
C(12)	−2.14712	1.21185	−0.89226
C(13)	0.11919	1.77689	0.72926
C(14)	1.05574	1.57924	−0.43091
C(15)	2.50551	−0.39797	−0.07063
C(16)	1.63627	−2.64495	−0.49488
C(17)	4.77602	−0.17983	0.12864
H(18)	−3.72680	−2.51778	0.80386
H(19)	−1.46054	−2.73987	0.95055
H(20)	2.91360	1.39566	0.14093
H(21)	0.67777	−0.91723	−0.21865
H(22)	−5.04805	0.47024	−0.59655
H(23)	−5.49417	−0.37339	0.56716
H(24)	−5.47413	−0.99405	−0.85034
H(25)	−1.55136	1.10721	−1.66210
H(26)	−2.94785	1.58602	−1.18882
H(27)	−0.04781	0.86290	1.21962
H(28)	0.50833	2.42800	1.35931
H(29)	1.25984	2.44201	−0.81201
H(30)	0.60510	1.03617	−1.15720
H(31)	0.77450	−2.94276	−0.94486
H(32)	1.80921	−3.06148	0.16440

[a] Atom (N), ref 12 numbering: S(1), S(1); N(2), N(1); N(3), N(2); N(4), N(3); N(5), N(4); N(6), N(5); N(7), N(6).

leading from histamine to the final target compounds. Using this approach, the asymmetry of histamine is lost, and it is not possible to relate either the aminopyridine or the aminotriazole rings to the imidazole ring of histamine. In Table V, as a first approximation to hydrogen-bonding possibilities, pairs of internitrogen distances are shown in which the histamine imidazole surrogate is either the aminopyridine ring (pairs A, B) or the aminotriazole ring (pairs C, D). Therefore, using the data presented here, one cannot unambiguously assign the aminopyridine or the aminotriazole ring as a histamine imidazole surrogate. Compounds 7 and 8 are pseudosymmetric molecules,[13] and this, coupled with the parallelism between pseudosymmetry in small effector molecules and pseudosymmetry in receptors,[13] suggests the speculation that there may be an element of symmetry in the histamine H_2 receptor.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Analytical Department of Pfizer Inc. Where analyses are indicated only by symbols of the elements, analytical values were within ±0.4% of theoretical values. NMR and/or mass spectra were obtained on all compounds and were consistent with structures and assignments. NMR spectra were recorded on a Varian T-60 spectrometer, and the mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer.

3-Amino-5-(2-pyridyl)-1,2,4-triazole (1). To a solution of 1.489 g (37.2 mmol) of NaOH in 50 mL of H_2O were added 4.94

(13) Goodford, P. "Medicinal Chemistry", Proceed of the International Symposium on Medicinal Chemistry, 6th, Brighton, England, Sept. 4–7, 1978; Simkins, M. A., Ed.; Cotswold Press: Oxford, 1979; pp 255–63.

g (36.0 mmol) of picolinic acid hydrazide and 10.13 g (36.4 mmol) of *S*-methylthiopseudourea sulfate. The clear solution was stirred at 23 °C for 20 h, and the resultant precipitate was collected by filtration, washed with H_2O and ether, and dried in vacuo at 23 °C to give 4.09 g (52.8%) of picolinoylaminoguanidine. In a preheated oil bath at 250 °C, 3.84 g (17.82 mmol) of picolinoylaminoguanidine was heated for 0.5 h. Initially, a melt formed, evolution of H_2O occurred followed by resolidification of the melt. The resultant tan solid was recrystallized from H_2O to give 2.73 g (95%) of 3-amino-5-(2-pyridyl)-1,2,4-triazole, mp 213–217 °C (lit.[14] mp 217 °C). Anal. ($C_7H_7N_5$) C, H, N.

3-Amino-5-(3-pyridyl)-1,2,4-triazole (2). This material was prepared in 78% overall yield by the procedure described for 1, mp 230–231 °C (lit.[15] mp 233 °C). Anal. ($C_7H_7N_5 \cdot {}^2/_3H_2O$) C, H, N.

3-Amino-5-(4-pyridyl)-1,2,4-triazole (3). A simplified one-step procedure over that described for 1 is as follows. Into a 2-L flask equipped with an overhead stirrer and gas outlet tube were added 61.5 g (0.5 mol) of isonicotinic acid and 148.0 g (1.2 mol) of aminoguanidine sulfate. The well-stirred mixture was heated neat in an oil bath at 210 °C for 2 h. Upon reaching 210 °C, melt occurred, followed by bubbling and H_2O evolution, which stopped after 2 h. The reaction was cooled slightly; before the melt solifified, 250 mL of H_2O was cautiously added, and heating was resumed to obtain solution of the initially formed slurry. The pH was brought to 9.5 with 20% NaOH. The mixture was cooled to 0 °C, and the resultant precipitate was collected by filtration. An adherent oily orange impurity was removed by repeated washing with ice–water. After washing with isopropyl alcohol, followed by ether, the material was dried in vacuo for 24 h to give 72.3 g (90%) of 3-amino-5-(4-pyridyl)-1,2,4-triazole, mp 277–279 °C. Recrystallization from H_2O gave an analytical sample: mp 279–281 °C (lit.[16] mp 276–278 °C); NMR (Me_2SO) δ 12.4 (very br s, 1, N-H), 8.67 (m, 2), 7.83 (m, 2), 6.25 (br s, 2, NH_2). Anal. ($C_7H_7N_5$) C, H, N.

3-Amino-5-(2-pyridylmethyl)-1,2,4-triazole Hydrate (4). To a solution of 6.6 g (0.165 mol) of NaOH in 24 mL of H_2O were added 25.0 g (0.165 mol) of 2-pyridylacetic acid hydrazide and 23.0 g (0.083 mol) of *S*-methylthiopseudourea sulfate. The slurry was stirred for 24 h, during which time a new solid formed. This material was collected by filtration, washed with H_2O and then ether, and dried. The solid was fused for 0.25 h in a flask preheated to 230 °C in an oil bath. During the heating period, the solid was periodically crushed with a spatula. After cooling, the solid was triturated with ether and collected by filtration. Recrystallization from H_2O gave 4.0 g (13%) of 3-amino-5-(2-pyridylmethyl)-1,2,4-triazole: mp 160–163 °C; NMR (Me_2SO) δ 11.8 (very br s, 1, N-H), 8.42 (m, 1, Pyr α-H), 7.67 (m, 1), 7.2 (m, 2 H), 5.63 (br s, 2, NH_2), 3.93 (s, 2, CH_2), 3.4 (br s, 2, H_2O). Anal. ($C_8H_9N_5 \cdot H_2O$) C, H, N.

3-Amino-5-(3-pyridylmethyl)-1,2,4-triazole (5). This material was prepared in 26% overall yield from 3-pyridylacetic acid hydrazide by the procedure described for 4, except that a fusion temperature of 270 °C was used: mp 194–197 °C; NMR (Me_2SO) δ 11.73 (very broad s, 1, NH), 8.4 (m, 2, Pyr α-H), 7.63 (m, 1), 7.23 (m, 1), 5.73 (br s, 2, NH_2), 3.8 (s, 2, CH_2). Anal. ($C_8H_9N_5$) C, H, N.

3-Amino-5-(4-pyridylmethyl)-1,2,4-triazole (6). This material was prepared in 34% overall yield from 4-pyridylacetic acid hydrazide by the procedure described for 4, except that a fusion temperature of 260 °C was used: mp 220–223 °C; NMR (Me_2SO) δ 11.65 (very broad s, 1, NH), 8.38 (m, 2, Pyr α-H), 7.2 (m, 2, Pyr β-H), 5.75 (br s, 2, NH_2), 3.8 (s, 2, CH_2). Anal. ($C_8H_9N_5$) C, H, N.

3-Amino-5-(2-amino-4-pyridyl)-1,2,4-triazole (7). The monohydrate was prepared according to the published procedure: mp 246–247 °C;[17] NMR (Me_2SO) δ 12.23 (very br s, 1, NH), 7.92 (m, 1, Pyr α-H), 7.03 (m, 2, Pyr β-H), 6.08 (br s, 2, NH_2), 5.95 (br s, 2, NH_2), 3.5 (br s, 2, H_2O). Anal. ($C_7H_8N_6 \cdot H_2O$) C, H, N. The dihydrochloride salt, mp 280–282 °C, was prepared by slow diffusion of ethanol into a solution of the monohydrate in concentrated hydrochloric acid. Anal. ($C_7H_8N_6 \cdot 2HCl$) C, H, N, Cl.

3-Amino-5-[2-(ethylamino)-4-pyridyl]-1,2,4-triazole (8). The free base was prepared by the published procedure.[17] Differential thermal analysis showed equally sharp endothermic transitions at 255 and 260 °C; NMR (Me_2SO) δ 12.23 (very br s, 1, N-H), 8.05 (d, 1, Pyr α-H), 6.93 (m, 2, Pyr β-H), 6.45 (t, 1, NH), 6.07 (br s, 2, NH_2), 3.3 (m, 2, CH_2), 1.17 (t, 3, CH_3). Anal. ($C_9H_{12}N_6$) C, H, N. The dihydrochloride monohydrate, mp 275–278 °C, was prepared by slow cooling of a solution of the free base in concentrated hydrochloric acid. The resultant solid was collected by filtration, washed well with ethanol, and dried in vacuo for 20 h at 110 °C. Anal. ($C_9H_{12}N_6 \cdot 2HCl \cdot H_2O$) C, H, N, Cl.

Histamine H_2-Antagonist Activity. The procedure is a modification of that described by Black.[18] Guinea pigs were killed rapidly with a blow to the head, the heart was removed, and the right atria were dissected free. Atria were suspended, isometrically, in a temperature-controlled (32 ± 2 °C) tissue bath (10 mL) containing oxygenated (95% O_2/5% CO_2) Krebs–Henseleit buffer (pH 7.4) and allowed to stabilize approximately 1 h, during which time the tissue bath was flushed several times. Individual atrial contractions were followed with a force-displacement transducer connected to a cardiotachometer and Grass polygraph recorder. After obtaining a dose–response curve to histamine, the bath containing each atrium was flushed several times with fresh buffer, and the atria were reequilibrated to basal rates. Following the return to basal rate, test compounds were added at selected final concentrations, and the histamine dose–response curve was again determined in the presence of antagonist. Dose ratios (DR) were calculated as the ratio of histamine concentrations required to produce one-half of maximal stimulation in the presence and absence of antagonist concentration, *B*. The arithmetic means plus or minus standard deviation of the Schild plots in *n* atria of log (DR – 1) vs. log *B* were not significantly different from unity. Dissociation constants ($K_{B\,app}$) were calculated using the theoretical value of 1.00 required for competitive antagonism.

Gastric Acid Antisecretory Activity. Compounds were tested for their ability to inhibit gastric acid secretion in fasted unanesthetized Heidenhain pouch dogs. Animals were first administered pentagastrin in order to stimulate acid output by continuous infusion of drug into a superficial leg vein at doses earlier determined to stimulate near maximal acid output from the gastric pouch. Gastric juice was then collected at 30-min intervals following the start of a pentagastrin infusion, and volume was measured to the nearest one-tenth of a millimeter (0.1 mL). Ten collections were taken for each dog during an experiment. Acid concentration was determined by titrating 1.0 mL of gastric juice to a pH value of 7.4 with 0.1 N aqueous sodium hydroxide, using an Autoburette and a glass electrode pH meter (Radiometer). Animals were administered the test compounds at a specified dose in milligrams per kilogram, respectively, or the control vehicle alone, via the intravenous route of administration, at 90 min following the start of the pentagastrin infusion. Gastric antisecretory effects were calculated by comparing the lowest acid output after drug administratin with the mean acid output immediately prior to drug administration. The results obtained in this manner were expressed in terms of percent inhibition. The dose required for 50% inhibition (ID_{50}) was calculated from the linear regression of log dose on percent inhibition in *n* dogs.

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Registry No. 1, 83417-23-6; 2, 35607-27-3; 3, 3652-17-3; 4, 83417-24-7; 5, 83417-25-8; 6, 83417-26-9; 7, 77314-75-1; 7·2HCl, 83417-27-0; 8, 77314-77-3; 8·2HCl, 83417-28-1; picolinic acid hydrazide, 1452-63-7; *S*-methylthiopseudourea sulfate, 2260-00-6; picolinoylaminoguanidine, 83417-22-5; isonicotinic acid, 55-22-1; aminoguanidine sulfate, 1068-42-4; 2-pyridylacetic acid hydrazide, 673-05-2; 3-pyridylacetic acid hydrazide, 19730-99-5; 4-pyridylacetic acid hydrazide, 69583-00-2.

(14) Komzak, A. A.; Parkes, E. A.; Polya, J. B. *J. Chem. Soc.* **1954**, 4256–62.
(15) Giuliano, R.; Leonardi, G. *Farmaco, Ed. Sci.* **1954**, *9*, 529–34.
(16) Biemann, K.; Bretschneider, H. *Monatsh. Chem.* **1958**, *89*, 1958.
(17) Lipinski, C. A. U.S. Patent 4 276 297, 1981.
(18) Black, J. W.; Duncan, W. A. M.; Durant, G. J.; Ganellin, C. R.; Parsons, M. E. *Nature (London)* **1972**, *236*, 385–90.