New Antihistamines: Substituted Piperazine and Piperidine Derivatives as Novel H_1-Antagonists

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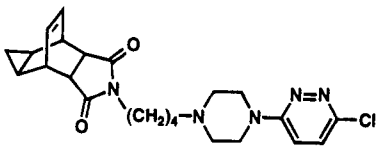
Structural manipulation of polycyclic piperazinyl imide serotonergic agents led to the synthesis of compound **8**, 2-[4-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]butyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethenocycloprop[*f*]isoindole-1,3(2*H*,3a*H*)-dione, which demonstrated good H_1-antagonist activity. Substitution of a xanthinyl moiety for the polycyclic imide group led to the identification of novel xanthinyl-substituted piperazinyl and piperidinyl derivatives with potent antihistamine H_1-activity without the undesirable antidopaminergic activity of **8**. One compound, **24**, 7-[3-[4-(diphenylmethoxy)-1-piperidinyl]propyl]-3,7-dihydro-1,3-dimethyl-1*H*-pyrine-2,6-dione (WY-49051), is a potent, orally active H_1-antagonist with a long duration of action and a favorable central nervous system profile.

Introduction

It has been widely recognized that histamine is an important intercellular chemical messenger, and its role as a mediator of inflammation and allergy is well-established.[1,2] Three histamine receptor subtypes (H_1, H_2, H_3) have been identified and characterized in vertebrates,[1,2] and the molecular properties of these receptors have recently been reviewed.[3] The H_1 receptor has been a target for drug discovery for many years, and H_1 receptor antagonists have proved to be effective therapeutic agents for the treatment of allergic rhinitis. However, classical antihistaminic agents have several limitations which complicate their clinical use including nonselective pharmacological activity and central nervous system (CNS) activity. H_1-Antagonists (promethazine, diphenhydramine, cyclazine) demonstrate muscarinic receptor antagonist activity, and this may produce cholinergic side effects; cyproheptadine has shown potent serotonin receptor antagonist activity.[4] In addition, high doses of many H_1-antagonists are often required to effectively block histamine-induced reactions, and these high doses produce limiting CNS sedative or stimulant activity.[5] The sedative activity of H_1-antagonists is associated with binding to cerebral H_1 receptors.[6,7] The focus of newer H_1-antagonists has been efficacy in allergic rhinitis with diminished sedative liability. These agents may have utility in asthma and obstructive airway diseases as well.[4,8,9] As opposed to classical antihistamines, the more recent H_1-antagonists terfenadine,[10] astemazole,[11] and temelastine[12] have poor access to the CNS which produces nonsedating antihistaminic activity in the clinic. Additional H_1-antagonists are undergoing clinical evaluation and development.[13–15]

Our interest in this area led us to screen several structurally divergent classes of compounds for their potential H_1-antagonist activity. Compound **1**, a polycyclic imide synthesized earlier as a 5-HT_{1A} ligand,[16] was identified as an early lead. *In vitro*, **1** antagonized the histamine-induced contractile response in isolated guinea pig ileum, producing 76% inhibition at a concentration of 1×10^{-7} M. Our efforts to optimize this antihistaminic activity led to the synthesis of a number of polycyclic imides, **2**–**8** (Table 1). Compound **8**, in which the chloropyridazinyl moiety was replaced by a bis(4-fluorophenyl)methyl group, a known pharmacophore in many antihistamines, emerged as the most potent azabicyclic imide with H_1-antagonist activity.



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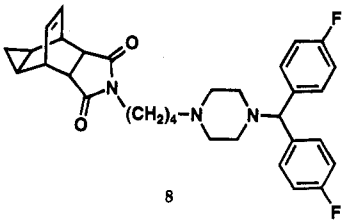

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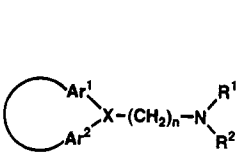

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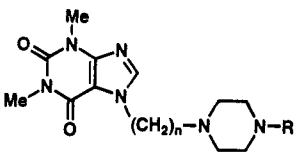

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In vitro, **8** competitively antagonized the histamine-induced contractile response of the isolated guinea pig ileum with 92% inhibition at a concentration of 1×10^{-7} M. Compound **8** was of interest because, to the best of our knowledge, it is the first reported class of H_1-antagonists in which a polycyclic imide moiety is being incorporated into the general structural feature common to other antihistamine compounds,[17–19] wherein an aromatic functionality is linked through a spacer to a basic moiety as in **9**.

Compound **8** was assessed in various receptor binding assays to determine its selectivity. As expected, **8** demonstrated high affinity for the dopamine receptor (K_i = 5 nM) similar to that shown by several anti-

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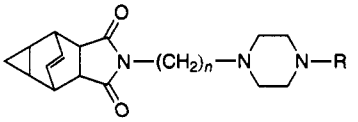
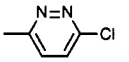
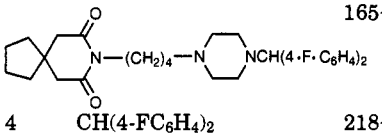
Table 1. Polycyclic Imides



compd	*n*	R	mp (°C)	yield (%)	formula[a]	inhibition[e] at 1×10^{-7} M (%)
1	4		271–272	48	$C_{23}H_{28}ClNO_2 \cdot HCl$	76
2	2	$CH(C_6H_5)_2$	220–222	41	$C_{30}H_{33}N_3O_2 \cdot 2HCl$[b]	<10
3	4	$CH(C_6H_5)_2$	250–253	37	$C_{32}H_{37}N_3O_2 \cdot 2HCl$[c]	50
4	3	$CH(C_6H_5)(4\text{-}Cl\text{-}C_6H_4)$	150–153	31	$C_{31}H_{34}ClN_3O_2 \cdot 2HCl$[d]	<10
5	2	$CH(4\text{-}F\text{-}C_6H_4)_2$	266–268	40	$C_{30}H_{31}F_2N_3O_2 \cdot 2HCl$[c]	<10
6	3	$CH(4\text{-}F\text{-}C_6H_4)_2$	239–240	35	$C_{31}H_{33}F_2N_2O_2 \cdot 2HCl$[b]	29
7			165–169	30	$C_{30}H_{37}F_2N_3O_2 \cdot 2HCl$[d]	77
8	4	$CH(4\text{-}FC_6H_4)_2$	218–220	46	$C_{32}H_{35}N_3F_2O_2 \cdot 2HCl$[c]	98

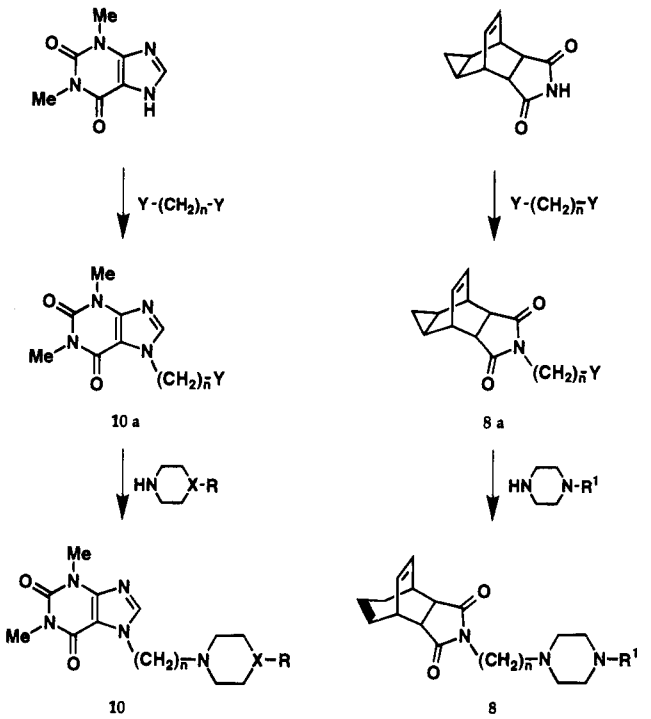
[a] All compounds exhibited IR and ^1H NMR spectra consistent with their structures. All compounds were analyzed for C, H, and N to within ±0.4% of the theoretical value. [b] Hemihydrate. [c] Hydrate. [d] Dihydrate. [e] Histamine-induced contraction of guinea pig ileum.

dopaminergic agents which contain polycyclic imide pharmacophores,[20–22] and this feature suggests that **8** may possess sedative and other undesirable CNS effects. This finding prompted further synthetic efforts to find a replacement for the polycyclic imide moiety in **8** which would eliminate the dopaminergic activity and maintain antihistaminic properties. Among several antihistaminic pharmacophores[23,24] considered as substitutes for the polycyclic imide moiety, the dimethylxanthine system (theophylline) was particularly attractive. Theophylline offered elements of both imide **8** and general structure **9**, while the weakly acidic N-7 hydrogen of the xanthine ring system provided convenient synthetic access to a variety of analogs. Theophylline, a potent bronchodilator in its own right, has been used clinically for many years for the relief of acute asthma.[23–25] Combining structural features of **1** and **8** with theophylline generated hybrid **10**, which was anticipated to possess favorable antihistaminic and bronchodilatory properties. Accordingly, compounds **11–24** (Table 2) were prepared and subjected to a battery of *in vitro* and *in vivo* screens.

Chemistry

Compounds **8** and **10** were prepared following the general procedure of Scheme 1. Alkylation of polycyclic imide or theophylline with the appropriate dihaloalkane in DMF in the presence of triethylamine afforded haloalkanes **8a** and **10a**, respectively, in 60–75% yields which were further alkylated with the appropriately substituted piperazine or piperidine derivatives.[26,27]

Scheme 1[a]



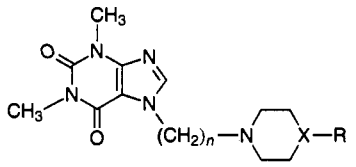
[a] **8**: Y = Br, n = 4, $R^1 = CH(4\text{-}F\text{-}C_6H_4)_2$. **10**: Y = Br, n = 2–4, X = CH or N, R = substituted pyridazinyl or diphenylmethyl.

Results and Discussion

As an initial screening test, all synthesized compounds were assessed *in vitro* for their ability to antagonize histamine-induced contraction of the guinea pig ileum at a concentration of 1×10^{-7} M (Tables 1 and 2). This test is a reliable *in vitro* measure of H_1-antagonist activity. Compounds with significant *in vitro* H_1-antagonist activity were examined, in comparison to standard H_1-antagonists with respect to relative H_1-receptor binding affinities, to assess competitive or noncompetitive antagonism (Table 3). Selected compounds which demonstrated significant *in vitro* inhibition in the guinea pig ileum assay were then tested *in vivo* for their ability to antagonize histamine-induced lethality (Table 4) and histamine-induced cutaneous vascular permeability (wheal formation) (Table 5) in guinea pigs. These functional *in vivo* models are indicative of antihistaminic activity in man.[24] Compounds of major interest were then compared to standard H_1-antagonists in duration of action studies (Figure 1). Compounds with a favorable profile also were examined for neuroreceptor site selectivity (H_1, α_1, M_1, M_2, 5-HT_{1A}, D_2), and log P values were determined (Table 6). Spontaneous motor activity tests were also conducted on selected compounds to assess the potential for CNS side effects.

Most polycyclic imide compounds (Table 1) produced only weak to moderate H_1-antagonist activity (10–77%

Table 2. Xanthinyl-Substituted Piperazinyl and Piperidinyl Derivatives



compd[a]	n	X	R	mp (°C)	yield (%)	formula[a]	inhibition[j] at 1×10^{-7} M (%)
11	3	N	5-chloro-3-pyrazinyl	254–256	35	$C_{18}H_{23}N_8ClO_2 \cdot HCl$[b,f]	29
12	3	N	3-chloro-2-pyrazinyl	205–207	42	$C_{18}H_{23}N_5O_2Cl \cdot HCl$[c]	<10
13	2	N	$CH(C_6H_4F)_2$	253–255	46	$C_{26}H_{28}N_6F_2O_2 \cdot 2\ HCl$[d]	34
14	3	N	$CH(C_6H_5)(C_6H_4Cl)$	244–245	40	$C_{27}H_{31}N_6ClO_2 \cdot 2HCl$[d]	29
15	3	N	6-chloro-6-pyridazinyl	285–287	61	$C_{18}H_{23}N_8ClO_2 \cdot 3HCl$[b]	17
16	3	N	3-chloro-6-pyrizidinyl	297–300	42	$C_{18}H_{23}N_8ClO_2 \cdot 2HCl$[e]	50
17	3	N	$CH(4\text{-}F\text{-}C_6H_4)_2$	240–242	38	$C_{27}H_{30}N_2F_2O_2 \cdot 2HCl$[e]	92
18	4	N	$CH(4\text{-}Cl\text{-}C_6H_4)_2$	226–227	46	$C_{28}H_{32}N_6Cl_2O_2 \cdot 2HCl$[c]	14
19	3	CH	$CH(4\text{-}F\text{-}C_4H_6)_2$	195–196	28	$C_{28}H_{31}F_2N_5O_3 \cdot C_4H_4O_4$	70
20	2	CH	$CH(C_6H_5)_2$	176–181	25	$C_{27}H_{31}N_5O_3 \cdot C_4H_4O_4$	86
21	2	CH	$CH(4\text{-}F\text{-}C_6H_4)_2$	191–193	30	$C_{27}H_{29}F_2N_5O_3 \cdot C_4H_4O_4$	62
22	3	CH	$CH(C_6H_5)(C_6H_4OMe)$	187–190	18	$C_{29}H_{35}N_5O_4 \cdot C_4H_4O_4$[b,g]	85
23	3	CH	$CH(C_6H_5)(C_6H_4OMe)$	172–173	15	$C_{29}H_{35}N_5O_4 \cdot C_4H_4O_4$[b,h,i]	78
24	3	CH	$CH(C_6H_5)_2$	183–185	20	$C_{28}H_{33}N_5O_3 \cdot C_4H_4O_4$[b]	92

[a] All compounds exhibited IR and ^1H NMR spectra consistent with their structures. All compounds were analyzed for C, H, and N to within ±0.4% of the theoretical value. [b] Monohydrate. [c] Dihydrate. [d] Hemihydrate. [e] Sesquihydrate. [f] C: calcd, 61.73; found, 62.14. [g] C: calcd, 60.81; found, 60.34. [h] C: calcd, 60.81; found, 60.34. [i] N: calcd, 10.75; found, 10.16. [j] Histamine-induced contraction of guinea pig ileum.

Table 3. Relative H_1 Receptor Binding Affinities of Various Antihistamines in the Guinea Pig Ileum

antihistamine	pA_2	K_D (M)	potency relative to **24**
ebastine	7.4	4.0×10^{-8}	1/5000
terfenadine	7.5	3.3×10^{-8}	1/4200
17	8.2	6.6×10^{-9}	1/840
astemizole	8.3	5.5×10^{-9}	1/700
chlorpheniramine	8.4	3.7×10^{-9}	1/470

inhibition of the guinea pig ileum histamine-induced contraction) with the exception of compound **8** which produced 98% inhibition. This compound was not studied further because of structural liabilities associated with polycyclic imide compounds which include dopaminergic activity and potential CNS effects such as sedation and movement disorders.[20–22]

In general, compounds containing heteroarylpiperazines (compounds **11–24**) also demonstrated only weak to moderate H_1-antagonist activity (10–86% inhibition of the guinea pig ileum contraction). In contrast, bis(arylmethyl)piperazinyl or bis(arylmethoxy)piperidinyl substituents greatly enhanced H_1-antagonist activity. Compounds **17** and **24** were the most active, each producing 92% inhibition of the histamine-induced contraction of the guinea pig ileum at a concentration of 1×10^{-7} M (Table 2).

On the basis of the considerable H_1-antagonist activity of compounds **17** and **24**, relative binding affinities and pA_2 values were determined for these compounds compared to standard H_1-antagonists (Table 3). Compounds **17** and **24** demonstrated competitive antagonism at the H_1-receptor. These compounds shifted the histamine dose–response curve to the right in a parallel fashion with pA_2 values of 8.2 and 11, respectively, which indicates they are competitive antagonists. Both compounds are more potent than ebastine ($pA_2 = 7.4$) and terfenadine ($pA_2 = 7.5$). *In vitro*, compound **24** is the most potent compound with 700 times the potency of astemazole, 470 times the potency of chlorpheniramine, and 840 times the potency of **17**.

Table 4. Protection by Antihistamines against Histamine-Induced Lethality in the Guinea Pig

H_1-antagonist	pretreatment period (h)	administration route	ED_{50} (95% conf limits) (mg/kg)
17	1	po	1.96 (no CI)
24	1	po	1.91 (1.20–3.02)
	1	ip	0.70 (0.22–2.23)
	1	iv	0.01 (0.00–0.10)
	2	po	1.11 (0.64–1.95)
	18	po	0.92 (0.47–1.80)
ebastine	1	po	0.45 (0.36–0.57)
	18	po	1.71 (1.06–2.75)

The two lead compounds, **17** and **24**, also demonstrated activity in a series of *in vivo* tests predictive of antihistaminic activity. Both compounds antagonized histamine-induced death in guinea pigs in a dose-dependent manner (Table 4). Compound **24** showed comparable H_1-antagonist activity following ip, iv, and po administration. The duration of action of **24** was also favorable since there was no decrease in oral efficacy up to 18 h posttreatment. The potent activity of compound **24** after iv administration also suggests that, unlike ebastine, its H_1-antagonist activity is not dependent on the formation of an active metabolite.

On the basis of the duration of H_1-antagonist activity observed for **24**, more detailed duration of action studies were conducted on **17** and **24** using survival of histamine-induced lethality as the measurable end point. The results of these studies (Figure 1) showed that the onset of action of **24** and **17** was more rapid than that of astemizole and terfenadine but less rapid than that of ebastine. The duration of action of **17**, **24**, astemizole, and ebastine was greater than 18 h. While efficacies of **17**, **24**, astemizole, and ebastine were comparable at 8 h, **24** was slightly more efficacious at 18 h than **17** and ebastine but not as efficacious as astemizole.

Functional H_1-antagonism for **17** and **24** compared to standard H_1-antagonists was also assessed in the guinea pig histamine-induced wheal formation test (Table 5). In this test, both **17** and **24** antagonized

Table 5. Inhibition by H_1-Receptor Antagonists of Histamine-Induced Skin Wheal Formation in the Guinea Pig[a]

compd	ED_{50} value (95% confidence limits) pretreatment interval prior to histamine challenge (h)		
	1	2	18
astemizole	0.53 (0.37−0.92)	NT	NT
chlorpheniramine	0.79 (0.70−0.95)	NT	1.07 (0.69−1.45)
17	0.45 (no CI)	NT	NT
24	0.42 (no CI)	1.14 (1.03−1.37)	1.14 (1.02−1.40)

[a] Values are expressed in mg/kg, po. NT = not tested.

Table 6. *In Vitro* Receptor Binding Profile and log *P* Values of Selected Antihistamines[a]

compd	receptor						log *P*
	H_1	α_1	M_1	M_2	5-HT_{1A}	D_2	
terfenadine	94 (63−142)	2340 (2013−2725)	2900 ± 960	>10 000	38%	26%	2.35
ebastine	45 (28−72)	183 (150−223)	1100 ± 330	>10 000	47%[b]	61%	2.74
17	220 (180−270)	59 (47−74)	670 ± 147	>10 000	38%	43%	1.81
24	44 (26−68)	8 (6−10)	46 ± 12	7300 ± 2900	40%	41%	1.77

[a] Receptor binding data shown are IC_{50} values (nM, 95% CI for single determination or ±SEM for multiple determination, $N = 3-4$). When full inhibition curves were not performed, values indicate percent inhibition seen at 1 μM. [b] At 10 μM.

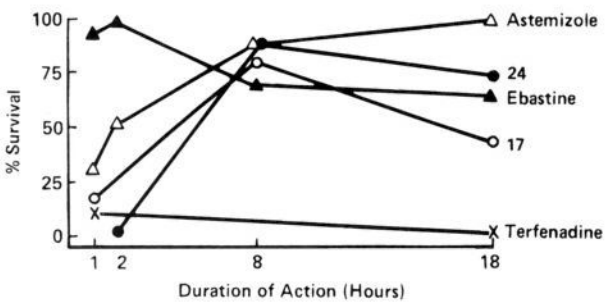


Figure 1. Protection from histamine-induced lethality as a function of time. All standard and experimental antihistamines were administered at a dose of 1 mg/kg po and challenged at varying time intervals with histamine (1.25 mg/kg iv).

histamine-induced cutaneous vascular permeability (wheal formation response). **24** also demonstrated an extended duration of action up to 18 h prior to histamine challenge with potency similar to chlorpheniramine.

A CNS profile of the lead compounds, **17** and **24**, was assessed by measuring their ability to displace various receptor radioligands from respective binding sites and by examining their effects in spontaneous motor activity models. Receptor binding results (Table 6) show that **17** and **24** both possess potent affinity for H_1-receptors and that **24** and ebastine are more potent than compound **17** and terfenadine. Interestingly, these compounds also showed weak affinity for dopamine and 5-HT_{1A} receptors. Although **24** demonstrated high affinity for the α_1-receptor, it did not produce adverse cardiovascular effects in the spontaneously hypertensive rat (SHR) at doses higher that its H_1-antagonist activity (unpublished data).

Lipophilicity of the lead compounds, **17** and **24**, was experimentally determined as octanol−water partition coefficients (log *P*, Table 6) using an adaptation of McCall.[27] The results of these tests showed that **17** and **24** are considerably less lipophilic than terfenadine and ebastine with log $P < 2$. These results indicate that the CNS activity of antihistamines observed in the clinic, such as sedation, might be attributed to the lipophilic properties of these molecules and their ability to cross the blood−brain barrier.[1,4]

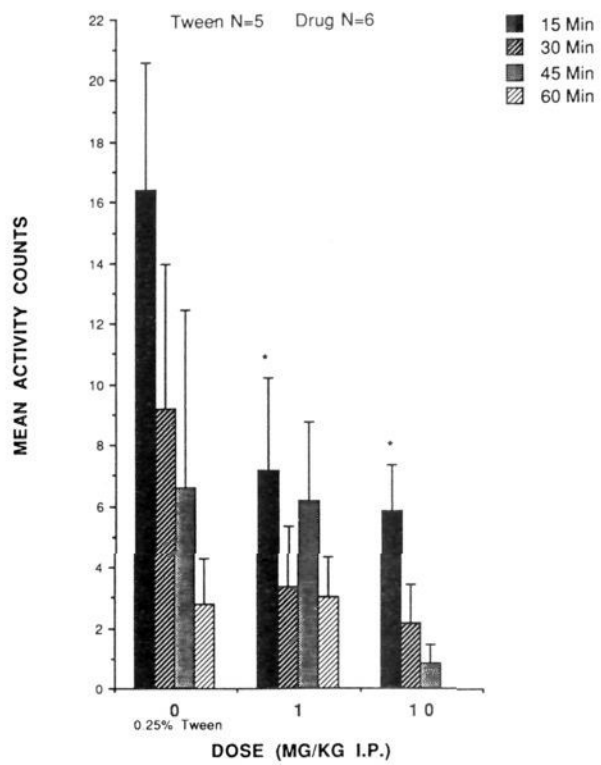


Figure 2. Effects of terfenadine in the confinement motor activity test. Male rats were tested with vehicle (0.25% Tween 80) or terfenadine (1 and 10 mg/kg ip) and placed into a motor activity chamber. Following a 15 min acclimation period, rearing activity was assessed for 15 min periods for 1 h; $^*p < 0.05$.

Compound **17**, terfenadine, and chlorpheniramine were also examined in preclinical behavioral tests to determine potential sedative effects. In confinement motor activity tests, compound **17** produced significant sedative activity only at relatively high doses (20 and 40 mg/kg ip). In contrast, terfenadine produced sedation at much lower doses (1 and 10 mg/kg ip; Figures 2 and 3). In these tests, chlorpheniramine produced significant stimulant activity at 10 mg/kg ip (Figure 4). The sedative effects of **17** and terfenadine were primarily observed 30 min after drug treatment. These

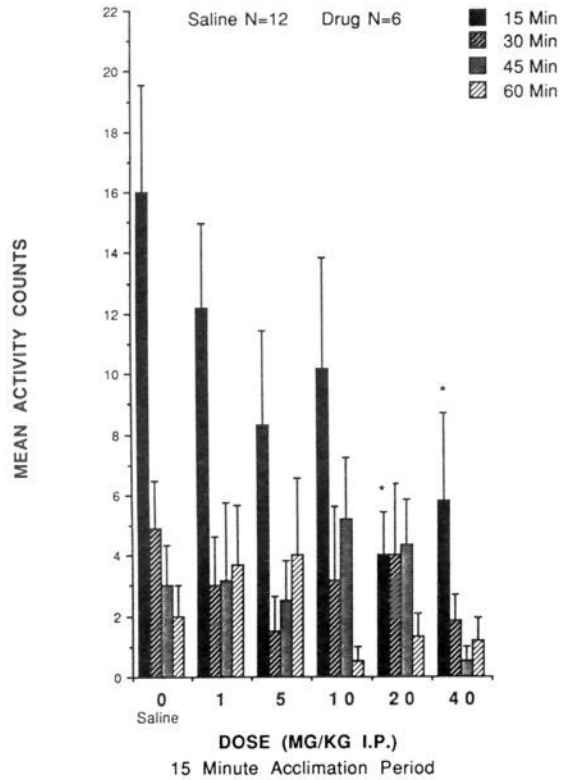


Figure 3. Effects of compound **17** in the confinement motor activity test. Male rats were treated with vehicle (0.25% Tween 80) or compound **17** (1, 5, 10, 20, and 40 mg/kg ip) and placed into a motor activity chamber. Following a 15 min acclimation period, rearing activity was assessed for 15 min periods for 1 h; $^*p < 0.05$

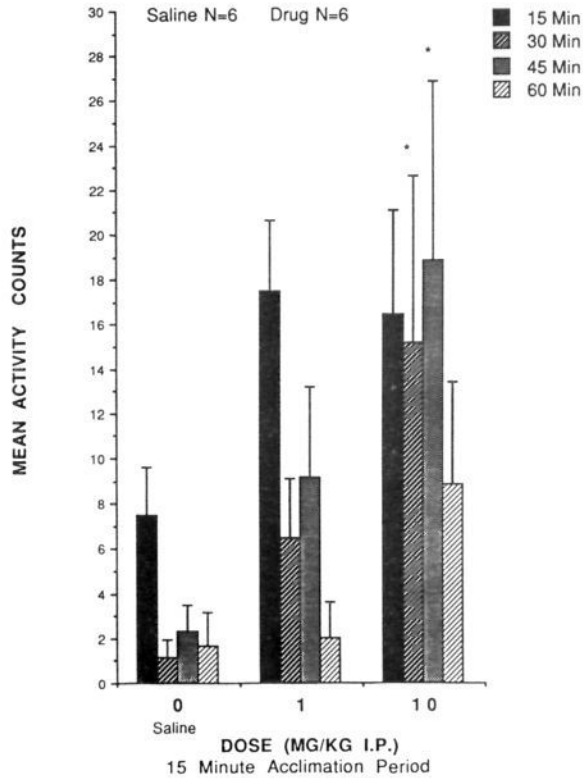


Figure 4. Effects of chlorpheniramine in the confinement motor activity test. Male rats were treated with vehicle (0.25% Tween 80) or chlorpheniramine (1 and 10 mg/kg ip) and placed into a motor activity chamber. Following a 15 min acclimation period, rearing activity was assessed for 15 min periods for 1 h; $^*p < 0.05$

results indicate that **17** has less sedative activity than terfenadine. Furthermore, in rotorod tests, sedative/ataxic effects were not observed for compounds **17** and **24**, terfenadine, or chlorpheniramine when tested at 20 mg/kg ip (unpublished data). Previous reports[28,29] have indicated that terfenadine lacks effects on locomotor activity below 250 mg/kg ip. It should be noted that different locomotor activity tests were used in these experiments. Taken together, these results may seem contradictory. However, preclinical tests of antihistamines do not always reliably predict sedation or CNS-depressant effects in man.[30]

In summary, structure−activity relationship studies in a series of polycyclic imides led to the identification of two novel and potent, orally active H_1-antagonists, **17** and **24**. While both of these compounds demonstrated potent H_1-antagonist activity in *in vitro* and *in vivo* functional tests, compound **24** (WY-49,051) was the more potent compound with a longer duration of action. This compound is currently available for worldwide outlicensing. In CNS tests, both **17** and **24** demonstrated a motor activity profile with limited sedative/stimulant activity compared to terfenadine and chlorpheniramine. However, additional CNS testing would be required to more clearly define the possible CNS effects of these compounds. While the H_1-neuroreceptor selectivity of **17** and **24** is encouraging, a broad receptor screen of these compounds is required and additional examination of the possible α_1-effects of **24** is needed.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and are consistent with assigned structures. NMR spectra were recorded on Varian XL-300 and XL-100 instruments. Mass spectra were recorded with a Kratos MS-25 mass spectrometer. IR spectra were recorded with a Perkin-Elmer 299 infrared spectrophotometer. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the analytical section of our laboratories, and analyses are within 0.4% of the theoretical values.

General Procedure for Preparation of Compounds in Table 1: 2-[4-[4-[Bis(4-fluorophenyl)methyl]-1-piperazinyl]butyl]-4,4a,5,5a,6,6a-hexahydro-4,6-ethenocycloprop[*f*]isoindole-1,3(2*H*,3a*H*)-dione, 8. To a stirred solution of 1,3-dioxo-2*H*-4,6-etheno-1,3,3a,6a-tetrahydrocycloprop[*f*]isoindole[11] (3.4 g, 1.7 mmol) in 50 mL of DMF was added sodium hydride (0.9 g, 3.7 mmol). The suspension was stirred at 60 °C for 3 h and poured into a stirred solution of 1,4-dibromobutane (4 g, 20 mmol) in 25 mL of DMF. The reaction mixture was stirred at room temperature for 25 h, DMF was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2 (3 × 200 mL). The CH_2Cl_2 extracts were collected, washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue solidified to a waxy material affording 3.6 g (67% yield) of the corresponding 2-(4-bromobutyl)hexahydro-4,6-ethenocycloprop[*f*]isoindole-1,3(2*H*,3*H*)-dione, **8a**.

The title compound was prepared by dissolving **8b** (2.5 g, 7 mmol) in 50 mL of DMF and adding to this solution 6 mL of triethylamine and 2 g (7 mmol) of 1-[bis(4-fluorophenyl)methyl]-piperazine. The reaction mixture was stirred at room temperature for 48 h. The DMF was removed under reduced pressure, and the remaining solid was extracted with 2 × 100 mL of CH_2Cl_2. The CH_2Cl_2 extracts were collected, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The remaining oil was triturated with ethyl acetate:diethyl ether (1:1 mixture), and the title compound was separated by filtration and converted to the dihydrochloride salt by dissolving in ethanol and adding to that solution 2 mL of ethanol saturated with

hydrogen chloride, mp 218–220 °C. Anal. ($C_{32}H_{35}N_3F_2O_2$·2HCl), C,H,N.

General Procedure for Preparation of Compounds in Table 2: 7-[3-[4-(Diphenylmethoxy)-1-piperidinyl]-propyl]-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione, 24. A solution of theophylline (10.0 g, 55.5 mmol), 1,3-dibromopropane (11.6 mL, 23.1 g, 0.114 mol), and triethylamine (10.5 mL, 7.62 g, 75.3 mmol) in DMF (250 mL) was stirred at 60 °C overnight. The stirring was continued for 1 day at room temperature. The solvent was evaporated under reduced pressure, and the residue was suspended in CH_2Cl_2 and water. An emulsion was caused by a fine solid suspended in the mixture which was filtered out and discarded. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic layers were dried with anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave 7-(3-bromopropyl)-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione, **10a** (12.8 g, 77% yield).

7-(3-Bromopropyl)-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione (4.0 g, 0.013 mol), 4-hydroxypiperidine (1.3 g, 13 mmol), and $NaHCO_3$ (2.0 g, 24 mmol) were stirred in DMF (50 mL) at 140 °C overnight. The mixture was then refluxed for 24 h. The DMF was evaporated under reduced pressure. The resulting residue was insoluble in water or CH_2Cl_2 and was dissolved in aqueous HCl. The solution was filtered, and the separated solid was discarded. The filtrate was treated with aqueous NaOH, and the solution (pH 10) was extracted with CH_2Cl_2. The extracts were combined and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by HPLC to give 7-[3-(4-hydroxy-1-piperidinyl)-propyl]-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione (1 g, 31% yield).

The title compound was prepared by adding 7-[3-(4-hydroxy-1-piperidinyl)]propyl-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione (1.15 g, 3.58 mmol) and diphenylmethyl bromide (1.80 g, 7.28 mmol) to a suspension of $NaHCO_3$ (0.80 g, 9.5 mmol) in DMF (60 mL), and the reaction mixture was refluxed overnight. The DMF was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined CH_2Cl_2 extracts were dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by HPLC to give the desired product, 7-[3-[4-(diphenylmethoxy)-1-piperidinyl]propyl]-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione (0.50 g, 29% yield). The fumarate salt was prepared by dissolving the free base in EtOH and adding a solution of fumaric acid in EtOH. The crystalline product was filtered after standing at room temperature for 2 h to afford the fumarate salt: mp 183–185 °C; ^{1}H NMR (DMSO-d_6) δ 1.49–1.60 (2H, m), 1.78–1.87 (2H, m), 1.89–1.98 (2H, m), 2.05–2.15 (2H, m), 2.29 (2H, t, J = 7.0 Hz), 2.65–2.73 (2H, m), 3.22 (3H, s), 3.31–3.39 (1H, m), 3.41 (3H, s), 4.24 (2H, t, J = 7.0 Hz), 5.62 (1H, s), 6.59 (2H, s), 7.19–7.25 (2H, m), 7.28–7.37 (8H, m), 8.02 (1H, s). Anal. ($C_{28}H_{33}N_5O_3$·$C_4H_4O_4$) C,H,N.

Biological Tests. Agonist-induced contraction of the guinea pig ileum was conducted using the modified procedures of Van Neuten and Janssen[30] and which was reported by Abou-Gharbia et al.[31] in 1990. Histamine-induced lethality in guinea pigs was conducted following the reported procedure of Van Waume.[32] Histamine-induced cutaneous vascular permeability tests were conducted according to a modified procedure of Chen and Woodward and which was described previously by Abou-Gharbia et al.[31] *In vitro* neuroreceptor binding assays were conducted according to methods we reported earlier.[31] Confinement motor activity tests were conducted according to the methods previously described by Moyer et al.[33]

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