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DUAL ANTAGONISTS OF PLATELET ACTIVATING FACTOR AND HISTAMINE 3. SYNTHESIS, BIOLOGICAL ACTIVITY AND CONFORMATIONAL IMPLICATIONS OF SUBSTITUTED *N*-ACYL-BIS-ARYLCYCLOHEPTAPIPERAZINES.[1]

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Abstract: A series of *N*-acyl-4-(5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperazines is described that are dual antagonists of PAF and histamine. The structural requirements for activity in this series parallel those of their previously reported piperidinylidene counterparts. Whereas their global minimum energy conformations are different for both series of compounds, computer assisted molecular modeling suggests that a common bioactive conformation is possible.

Although the involvement of histamine in various allergic and inflammatory diseases has been known for years,[2] the use of classical H_1-antihistamines for the treatment of many of these diseases has not been successful (e.g., asthma).[3] Subsequently, other mediators have been discovered, which due to their physiological effects may play important roles in these diseases. One such mediator, platelet activating factor (PAF),[4] causes smooth muscle contraction, chemotaxis, and edema.[5] Consequently, there has been an effort to identify agents that selectively attenuate PAF's biological activity.[5,6] A number of these compounds have been progressed into clinical trials, but overall clinical results in asthma with single mediator PAF antagonists have not been encouraging.[7]

The complexity of biological events that take place during the allergic response often involves multiple mediators suggesting that agents that inhibit the actions of more than one mediator probably will be more effective in treating allergic diseases than single mediator inhibitors. PAF and histamine complement each other, and consequently, dual antagonists of both of these mediators have been an attractive pursuit for drug therapy.[8,9]

Several years ago we reported on a series of *N*-acyl-4-(5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidines (**1**), which are antagonists of both PAF and histamine.[8] We now wish to report on a related series of compounds (i.e., **2–7**) that contain a piperazine in place of the piperidinylidene ring, and consequently, are conformationally more mobile than their earlier counterparts.

Chemistry

The majority of the substituted piperazine derivatives were synthesized from 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one[10] as illustrated in Scheme I. In general, they were prepared by

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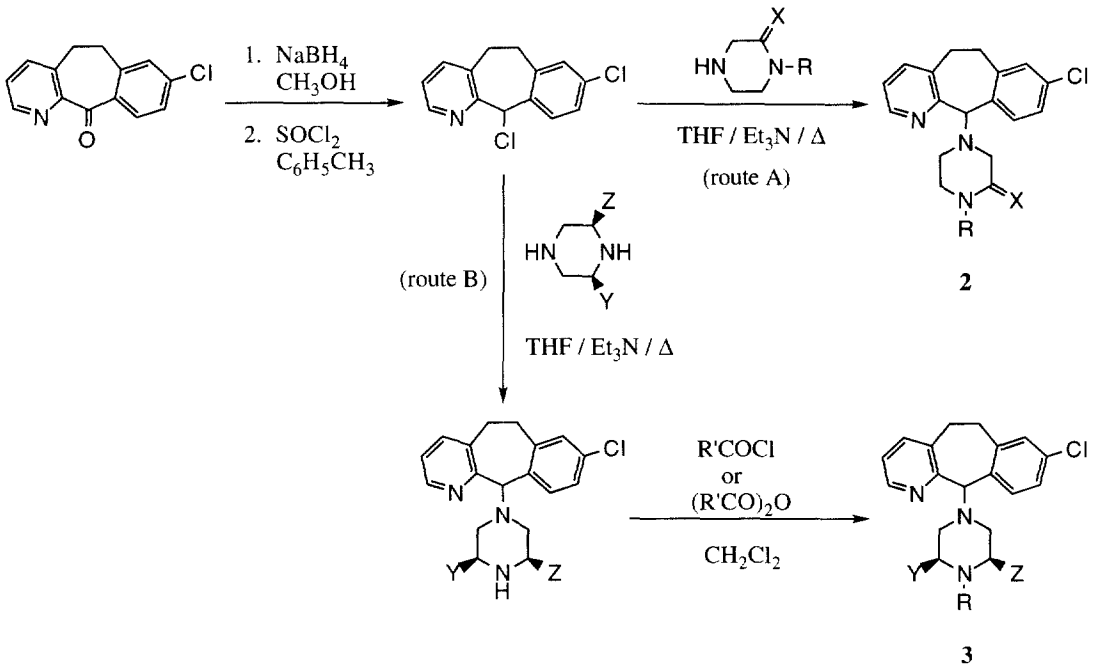
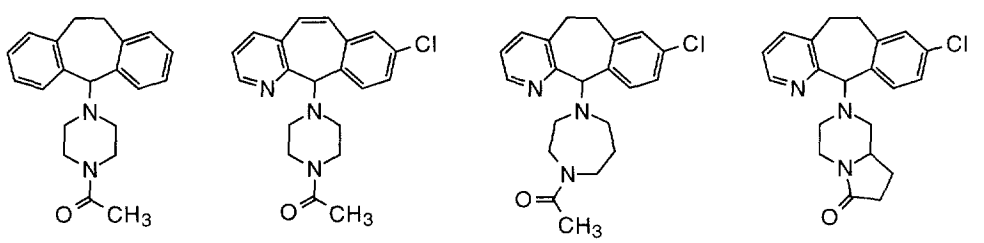
Scheme I



alkylation of the appropriately *N*-substituted piperazine with the tricyclic chloride (route A) to directly provide the targeted compounds (i.e., **2a–g**). Certain compounds (i.e., **3a–f**) were obtained by alkylation of the unsubstituted piperazine (route B) followed by subsequent *N*-substitution. Compounds **4** and **5**, which contain different substitutions in the tricyclic portion of the molecule, were prepared via route A[11] from their respective ketones.[12] Compound **6** was prepared from homopiperazine via route B and bicyclic lactam **7** was synthesized via route A from 2-methylpyrazine.[13]



4 **5** **6** **7**

Discussion

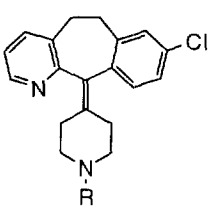
We previously reported that Sch 37370 (**1e**)[14] and a series of related piperidinylidene amides[8] are dual antagonists of PAF and histamine. The antiPAF activity was greatest with small alkyl amides and was optimal with the acetamide **1e**. The data in Table I suggests that this same trend holds true for their piperazinyl counterparts (cf: **2d**, **2e**, **3a** and **3b**). The in vitro PAF antagonist activities for both series of compounds

Table I. Comparison of In Vitro PAF Antagonist Activities of Piperazinyl and Piperidinylidenyl Derivatives[a]

Piperazinyl Derivatives			Piperidinylidenyl Derivatives	
Compound[b] (X = H_2, Y = Z = H)	PAF Antagonist[c] IC_{50} (μM)	R	Compound[b]	PAF Antagonist[c] IC_{50} (μM)
2a	≥23	H	**1a**	31 ± 6
2b	28[d]	CH_3	**1b**	≥50[e]
2c	>50	$CO_2CH_2CH_3$	**1c**	>50
2d	12 ± 7	CHO	**1d**	14 ± 4
2e	0.40 ± 0.13[f]	$COCH_3$	**1e**	0.61 ± 0.05[f]
3a	1.4 ± 0.5	$COCH_2CH_3$	**1f**	2.4 ± 1.1
3b	15 ± 3	$CO(CH_2)_2CH_3$	**1g**	33 ± 16
4	26 ± 4	---	**8**	41 ± 2[f]
5	0.66[d]	---	**9**	0.42[d]

[a]Unless otherwise noted the values represent the mean of 2 independent experiments with the associated errors representing the range from the mean. [b]All compounds gave satisfactory H^1-NMR and MS analysis. Satisfactory elemental analysis or high resolution MS was obtained on all final compounds. [c]Values are a measure of the concentration of drug required to cause a 50% inhibition of PAF-induced platelet aggregation of human platelet-rich plasma when challenged with PAF. In different experiments the aggregatory response is kept to within a set limit by varying the concentration of PAF between 10–50 nM.[14] [d]Approximate value determined from a single dose-response experiment. [e]Value determined from 3 independent experiments. [f]Value is the mean ± the standard error of the mean for 3–11 independent experiments.

containing the same nitrogen substituents are similar in value with the acetamides **1e** and **2e** being the most potent (Table I). As was true in the piperidinylidene series,[8] the pyridine nitrogen is necessary for good antiPAF activity in the piperazine series (cf: **4** with **8**, Table I) and the presence of a double bond in the bridge has little effect on the antiPAF activity in both series (cf: **5** with **9**, Table I).



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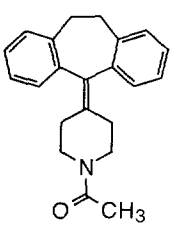

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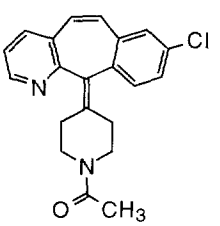

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Although replacement of the piperidinylidene ring for a piperazine has little effect on the antiPAF activity, the piperazines are somewhat weaker as antihistamines (Table II). For example, acetamide **2e** has a K_i of 5.4 μM in the H_1-binding assay, but its piperidinylidene counterpart, **1e**, is about an order of magnitude more potent (K_i = 0.32 μM). While the *N*-acylated piperazines are relatively weak in their affinity for the H_1-receptor, lactams **2f** and **2g** are good binders. Interestingly, the overall basic nature of *N*-methyl lactam **2g** and its regioisomer, formamide **2d**, is the same, but lactam **2g** is more potent in binding to the H_1-receptor, while formamide **2d** is a more potent PAF antagonist.

Table II. In Vitro PAF Antagonist and H_1-Binding Activities[a]

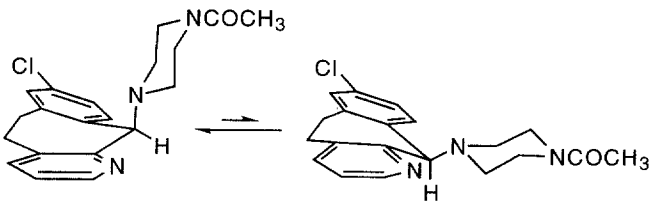
Compound[b]	R	X	Y	Z	PAF Antagonist[c] IC_{50} (μM)	H_1-Binding[d] K_i (μM)
1e	$COCH_3$	---	---	---	0.61 ± 0.05[e]	0.32 ± 0.09[e]
2a	H	H_2	---	---	≥23	0.0064 ± 0.0008
2b	CH_3	H_2	---	---	28[f]	0.0065 ± 0.0005
2c	$CO_2CH_2CH_3$	H_2	---	---	>50	≥ 3.8
2d	CHO	H_2	---	---	12 ± 7	0.29 ± 0.02
2e	$COCH_3$	H_2	---	---	0.40 ± 0.13[e]	5.4 ± 0.5[e]
2f	H	O	---	---	>50	0.14 ± 0.02[e]
2g[h]	CH_3	O	---	---	>50	0.049 ± 0.006
3a	$COCH_2CH_3$	---	H	H	1.4 ± 0.5	2.5 ± 1.3
3b	$CO(CH_2)_2CH_3$	---	H	H	15 ± 3	3.6 ± 1.8
3c	$COCH_3$	---	CH_3	H	14 ± 6	≥5.0[g]
3d	$COCH_3$	---	CH_3	CH_3	>50	≥7.1[g]
3e (*R*)	$COCH_3$	---	H	H	1.3 ± 0.3[e]	3.6 ± 1.5
3f (*S*)	$COCH_3$	---	H	H	0.21 ± 0.02[e]	>10
4	---	---	---	---	26 ± 4	3.7 ± 0.8
5	---	---	---	---	0.66[f]	---
6	---	---	---	---	13 ± 6	0.97 ± 0.26
7	---	---	---	---	1.8 ± 0.4	3.6 ± 0.7
WEB 2086	---	---	---	---	0.04 ± 0.005[e]	---
L-652,731	---	---	---	---	1.5 ± 0.5[e]	---
CTM[i]	---	---	---	---	>50	0.0055 ± 0.0011[e]

[a]See ref. *a*, Table I. [b]See ref. *b*, Table I. [c]See ref. *c*, Table I. [d]Values are determined using a receptor binding assay using rat brain membranes and the experimentally determined value of 2.7 nM for the K_D of [^{3}H]pyrilamine.[14] [e]Value is the mean ± the standard error of the mean for 3–11 independent experiments. [f]Approximate value determined from a single dose–response experiment. [g]Value determined from 3 independent experiments. [h]N-methyl lactam **2g** was obtained by treatment of **2f** with NaH/THF then CH_3I. [i]chlorpheniramine.

The nature of the piperazine ring has a significant effect on the antiPAF activity of these compounds. Increasing the size of the ring, as is the case with homopiperazine **6**, or placement of a methyl group on the carbon atom next to the acetamide of the piperazine ring (i.e., **3c**), results in a substantial loss of antiPAF activity (Table II). The addition of still another methyl group (i.e., **3d**) results in even further loss of activity. The nonbonded steric interaction between the methyl groups on the piperazine rings of **3c** and **3d** with the acetamide methyl group may inhibit the amide from adopting complete planarity with the overall plane of the piperazine ring. This may be relevant to the lower potency of these substituted derivatives relative to the sterically unencumbered derivative **2e**, since they may be unable to orient their amide carbonyls to adopt this planarity at the PAF receptor. Interestingly, the bicyclic lactam **7** is an order of magnitude more potent than **3c**, even though both compounds are mono-substituted at C-2 on the piperazine ring. Unlike **3c**, the amide of bicyclic lactam **7** is rigidly held in the same overall plane of the piperazine ring.

Except for compound **4**, all the piperazines within this series contain an asymmetric center. Since acetamide **2e** was found to be the most potent PAF antagonist within this series, it was resolved into its two

enantiomers.[15] The *S*-enantiomer **3f** is about tenfold more potent than its enantiomer **3e**. Interestingly, the *R*-isomer **3e** has a higher affinity for the H_1-receptor (Table II), indicating that the individual activities predominate in separate enantiomers.



(Axial Conformation) (Equatorial Conformation)

Figure 1. Local Energy Minima for Piperazine **2e**.

Conformational analysis of **2e** using MacroModel (MM2) suggests that the global minimum energy conformation has the piperazine ring axial relative to the central seven-membered ring (Figure 1). This observation is in agreement with experimental evidence reported for a similar system.[16] The spatial overlap of this axial conformation of **2e** with the lowest energy conformation of **1e** is poor (Figure 2). Since both compounds are approximately equipotent as PAF antagonists (Table I) this dissimilarity in conformational overlap may be puzzling. However, the spatial overlap of a slightly higher energy conformation of **2e** with piperidinylidene **1e** is very good (Figure 3). This conformation has the piperazine ring equatorial relative to the central seven-membered ring, and resides only 3.6 kcal/mol above the global minimum energy conformation. Consequently, the conformations depicted in Figure 3, or some slight variation thereof, may represent the "bioactive conformation" of these molecules at the PAF receptor.

The predominance of each activity in the separate enantiomers of **2e** is disappointing, but the conformational and enantiomeric preferences of these compounds have implications for the design of more potent antagonists of these receptors. The design and synthesis of conformationally restricted analogs will be reported elsewhere.[17]

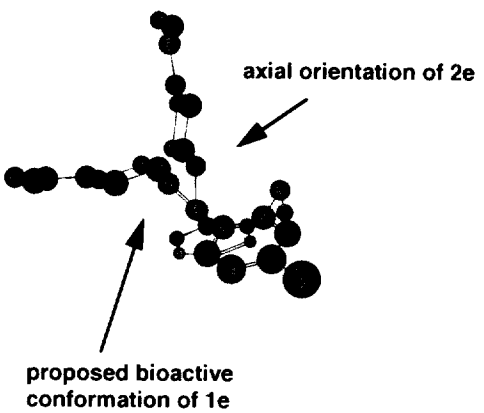


Figure 2. Global Minimum Energy Conformations of **1e** and **2e**.

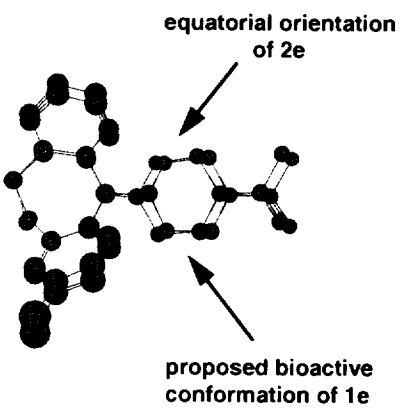


Figure 3. Higher Energy Conformation of **2e** that Mimics the Proposed Bioactive Conformation of **1e**.

Acknowledgment: We would like to thank Professor A. T. McPhail (Duke University) for determining the absolute configuration of the (-)-enantiomer of **2a** by X-ray crystallography and the staff of the Physical-Analytical Departments (Schering-Plough) for spectra and microanalyses.

References and Notes

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11. The tricyclic mesylate was prepared in place of the corresponding chloride in the preparation of compound **5**. The alkylation was conducted in situ to prevent solvolysis of the generated mesylate on workup.
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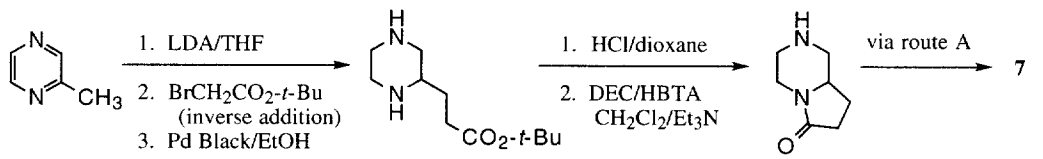
13. The preparation of bicyclic lactam **7** is shown below. We thank Dr. B. B. Bauer for his details in the conversion of 2-methylpyrazine to *t*-butyl 3-(piperazin-2-yl)propionate (unpublished results).



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15. The resolution was accomplished by repeated crystallization of **2a** as the *N*-acetyl *D*- and *L*-leucine salts from acetonitrile/water. Subsequent acylation with acetic anhydride provided **3e** and **3f** with greater than 99% ee. Their absolute configurations were infered from the resolved *S*-enantiomer of **2a** whose absolute configuration was determined by X-ray crystalligraphic analysis (McPhail, A. T., unpublished results).
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