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# DUAL ANTAGONISTS OF PLATELET ACTIVATING FACTOR AND HISTAMINE. 2.[1] PYRIDINE RING SUBSTITUTION OF N-ACETYL-4-(8-CHLORO-5,6-DIHYDRO-11*H*-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YLIDENE)PIPERIDINES

Jesse K. Wong,[a,*] John J. Piwinski,[a] Michael J. Green,[a] Ashit K. Ganguly,[a]
John C. Anthes[b] and M. Motasim Billah.[b]
Department of Chemical Research[a] and Allergy and Immunology[b]
Schering-Plough Research Institute
2015 Galloping Hill Road, Kenilworth, N.J. 07033-0539, U.S.A.

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**Abstract:** A series of pyridine ring substituted 1-acetyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6] cyclohepta[1,2-b]pyridin-11-ylidene)piperidines which are antagonists of both PAF and histamine were prepared by one of three different methods. Analogs with substitutents at C-3 were found to be the best dual antagonists among their corresponding regioisomers. Analogs with an electron donating substituent at the C-3 position are generally better antagonists of both PAF and histamine than analogs with electron withdrawing groups.

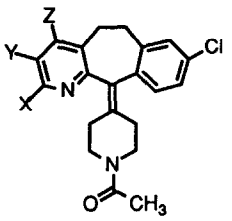
Platelet activating factor (PAF) is a bioactive ether phospholipid which is synthesized and released from a variety of cells.[2] Since its discovery,[3] PAF has received a great deal of attention due to its pathogenetic properties as a mediator in many allergic and inflammatory disorders, such as asthma[4] and endotoxin shock.[2b,e] Consequently, an intensive effort has been made in recent years on discovering PAF antagonists,[5] and currently, a number of candidates are undergoing clinical evaluation.[6]

Histamine has long been known to play a role in inflammation and the allergic response.[7] In many ways PAF and histamine are complementary to each other during an allergic or inflammatory reaction. Histamine is preformed in the cell and released when challenged with antigen, and therefore, has a rapid onset of action.[7] PAF is synthesized on demand and has a slow onset.[2] Since both mediators are released during the allergic response, we were interested in discovering agents which inhibit or antagonize the effects of both of these mediators.

Recently, 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 which are dual antagonists of PAF and histamine.[8] In these reports we discussed the effect of varying substitution in the aryl ring and its effect on the dual activity. As part of our continuing effort to discover novel compounds that are dual antagonists of PAF and histamine, we herein report on the syntheses and the biological activities of a related series of pyridine substituted analogs.

Following the discovery of the dual PAF and histamine antagonist, Sch 37370 (**1**),[8,9] we initiated an investigation of the SAR of pyridine ring substitution in order to optimize the dual activity. Since there are three substitutable positions on the pyridine ring of Sch 37370 (**Table 1**), it was essential to determine which position when substituted, would provide the best anti-PAF and antihistamine activity. Thus, we first established the position-activity-relationship (PAR) of the pyridine ring of Sch 37370 by preparing each of the regioisomers for a given substituent. Four different sets of regioisomers were prepared to investigate this positional importance. These included three electron donating groups ($CH_3$, OH and $OCH_3$) and an electron withdrawing group (Cl). From the *in vitro* data of these compounds (**2** to **13**), we found that isomers with substituents at C-2 and C-3 are usually better PAF antagonists than the

**Table 1.** *In Vitro* PAF Antagonist and $H_1$ Binding Activities[a] of Pyridinyl Substituted N-Acetyl-4-(5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidenes



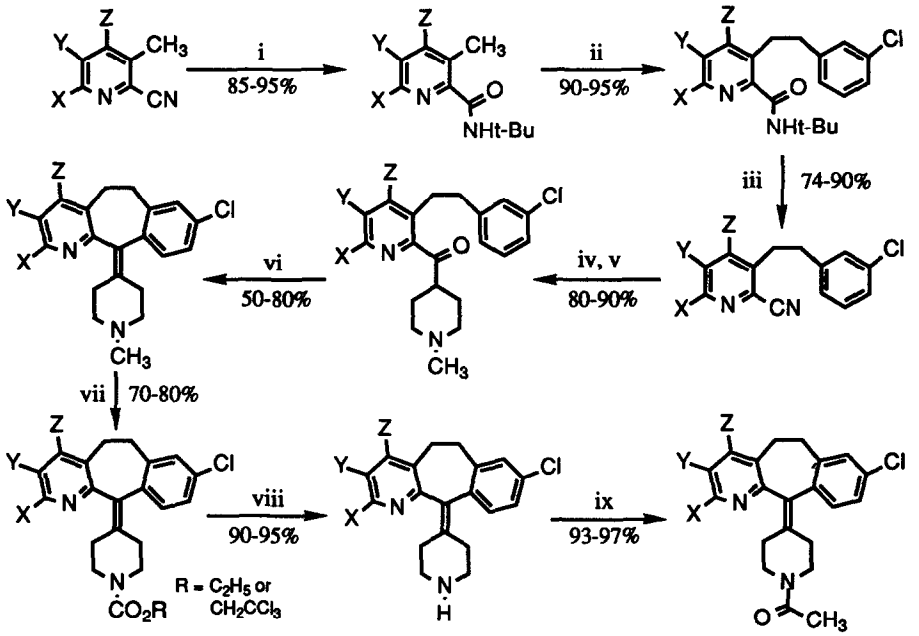

| Compound[b] | X | Y | Z | Method | PAF Antagonist[c] ($IC_{50}$, μM) | $H_1$ binding[d] ($K_i$, μM) |
|---|---|---|---|---|---|---|
| 1 (Sch 37370) | H | H | H | A | 0.61 ± 0.05[e] | 0.32 ± 0.09[f] |
| 2 | $CH_3$ | H | H | A | 0.28 ± 0.03 | 1.03 ± 0.08 |
| 3 | H | $CH_3$ | H | A | 0.34 ± 0.19 | 0.07 ± 0.03 |
| 4 | H | H | $CH_3$ | A | 6.00 ± 1.40 | 0.23 ± 0.05 |
| 5 | Cl | H | H | B | 0.61 ± 0.15 | 1.36 ± 0.50 |
| 6 | H | Cl | H | A | 0.94 ± 0.44 | 0.10 ± 0.004 |
| 7 | H | H | Cl | B | 8.00 ± 2.30 | 0.24 ± 0.003 |
| 8 | OH[g] | H | H | B | 6.75 ± 1.25 | >10.00 |
| 9[h] | H | OH | H | C | 4.13 ± 1.13 | 1.58 ± 0.33 |
| 10[i] | H | H | OH[g] | B | ≥50.00 | >10.00 |
| 11[j] | $OCH_3$ | H | H | B | 6.00 ± 2.00 | >10.00 |
| 12 | H | $OCH_3$ | H | C | 1.48 ± 0.08 | 0.43 ± 0.048 |
| 13 | H | H | $OCH_3$ | B | 3.04 ± 0.97 | >10.00 |
| 14 | H | Ph | H | A | 1.08 ± 0.02 | 0.23 ± 0.006 |
| 15 | H | $SCH_3$ | H | C | 0.60 ± 0.10 | 0.21 ± 0.03 |
| 16 | H | CHO | H | C | 2.73 ± 0.003 | 0.70 ± 0.02 |
| 17 | H | $CH_2OH$ | H | C | 0.69 ± 0.21 | 0.02 ± 0.003 |
| 18 | H | $CH(OH)CH_3$ | H | C | 1.07 ± 0.34 | 0.04 ± 0.004 |
| 19 | H | $COCH_3$ | H | C | 2.08 ± 2.61[k] | 1.16 ± 0.21 |
| 20 | H | Br | H | A | 2.29 ± 1.49 | 0.01 ± 0.002 |

[a] Unless otherwise noted the values represent the mean of two independent experiments with the associated errors representing the range from the mean. [b] All compounds have satisfactory elemental analysis, $^1H$ NMR and mass spectral data. [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 was kept to within a set limit by varying the concentration of PAF between 10-50 nM.[9a] [d] Values were determined by using a receptor binding assay using rat brain membranes and the experimentally determined value of 2.7 nM of the $K_D$ of [$^3H$]pyrilamine.[9a] [e] Value is the mean ± the standard error of the mean of eleven independent experiments. [f] Value is the mean ± the standard error of the mean of eight independent experiments. [g] As pyridone tautomer. [h] Compound 9 was obtained from the precursor 12 by cleavage of the methyl ether using $BBr_3/CH_2Cl_2$ followed by acylation. [i] Compound 10 was obtained by demethylation of the precursor 13 with EtSNa/DMF followed by acylation. [j] Compound 11 was obtained by methylation of 8 with MeI in the presence of KF-Alumina in $CH_3CN$. [k] Value is the mean ± the standard error of the mean of four independent experiments.

corresponding isomer with substitution at C-4. One exception to this was found in the methoxy series where the C-2 methoxy derivative (**11**) is slightly less potent than the C-4 methoxy analog (**13**). Among the C-2 and C-3 positions, substitution at C-3 provided the best antihistamine activity.

**Method A**

**Scheme I**[a]



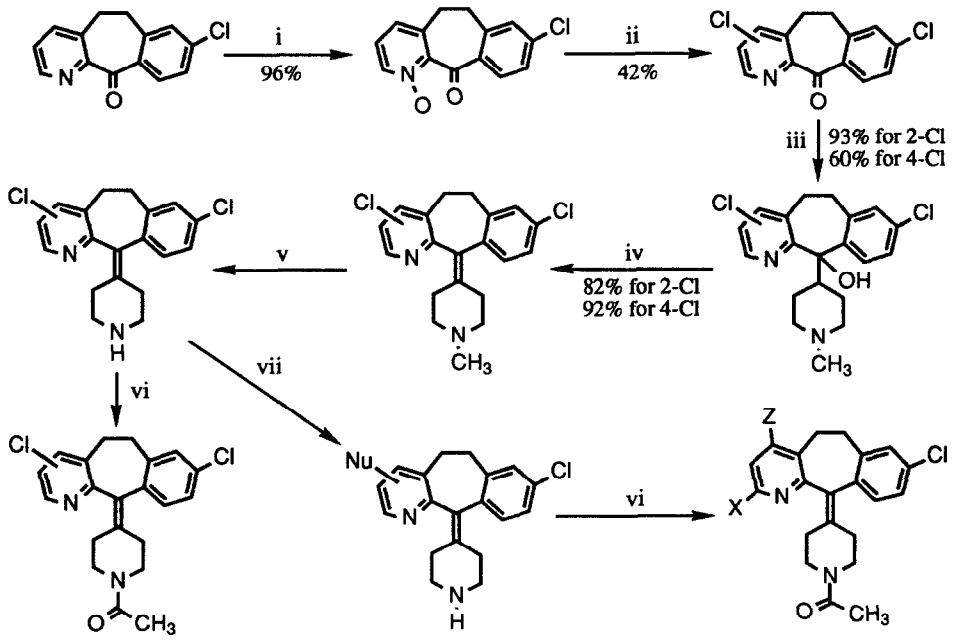

[a] (i) *t*-BuOH, $H_2SO_4$, 95°C; (ii) 2.2 eq. *n*-BuLi, THF, -50°C (2.2 eq. LDA for Y=Br), then 3-Cl-benzylbromide; (iii) $POCl_3$, tol. reflux, 6 hrs.; (iv) $ClMgC_5H_9NCH_3$, THF, 45°C; (v) HCl, $H_2O$; (vi) $CF_3SO_3H$, 65°C, 8 hrs.; (vii) $ClCO_2Et$ or $ClCO_2CH_2CCl_3$ (for Y=CHO), tol., $Et_3N$, 90°C, 2-3 hrs.; (viii) KOH & EtOH, reflux; or HCl & $H_2O$, reflux (Zn, AcOH, 60°C, 6 hrs., for 2,2,2-trichloroethylcarbamate); (ix) $(CH_3CO)_2O$, $CH_2Cl_2$, pyr., 0°C.

Consequently, the compounds with substitution at C-3 provided the best overall dual anti-PAF and antihistamine activity. Thus, a variety of compounds (**14** to **20**) with substitution at this position were prepared. These compounds included a bulky group (**14**), a bulky and electron donating group (**18**), less bulky, electron donating groups (**15** and **17**) and electron withdrawing groups (**16**, **19** and **20**). In general, those containing electron donating groups are more potent as PAF antagonist regardless of the size of the substituents. For example, the methyl and hydroxymethyl derivatives, **3** and **17**, are more potent than the formyl and bromo compounds, **16** and **20**. Virtually all the C-3 substituted derivatives are good antihistamines with the bromo analog **20** being the most potent.

The preparation of the various substituted pyridine derivatives of Sch 37370 (**1**) was accomplished in three ways. **Method A** (**Scheme I**) was developed by Schumacher and co-workers for the synthesis

**Method B**

**Scheme II**[b]

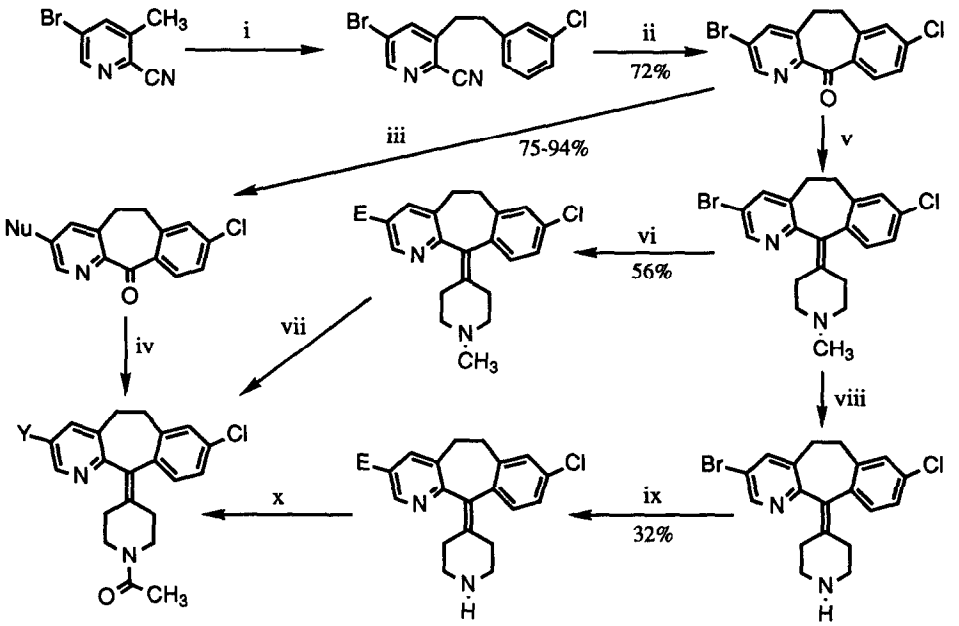



[b] (i) *m*-CPBA, $CH_2Cl_2$, r.t.; (ii) $SO_2Cl_2$, $CH_2Cl_2$, reflux, 1.5 hrs., then separated; (iii) $ClMgC_5H_9NCH_3$, THF, 0°C→r.t.; (iv) $H_2SO_4$, $H_2O$ (85:15 by volume), 65°C, 4 hrs.; (v) Method A steps vii & viii; (vi) $(CH_3CO)_2O$, $CH_2Cl_2$, pyr., 0°C; (vii) NaOH, MeOH/$H_2O$ in a sealed vessel, Δ (2-pyridone-NH was obtained in 50% yield from 2-Cl-NH after 4 days at 175°C while 4-methoxy-NH was obtained in 90% yield from 4-Cl-NH intermediate after 16 hours at 140°C).

of a related compound, loratadine,[10] which is now in clinical use as a non-sedating antihistamine.[11] This sequence focused on building the molecule with the appropriate appendages in place before cyclodehydration to provide the seven-membered ring intermediate. This intermediate was then converted to the targeted compound via demethylation (steps vii and viii) and acylation (step ix). **Method A** was preferred when the appropriately substituted starting pyridine could easily be prepared[12] and was used to synthesize several derivatives (**2**, **3**, **4**, **6**, **14** and **20**) which were substituted at any of the three possible positions of the pyridine ring. **Method B (Scheme II)** utilized the tricyclic-seven-membered ring ketone,[13] which was subsequently elaborated to introduce the acylated piperidine ring. Substitution at the C-2 or C-4 position of the pyridine ring was accomplished as illustrated in **Scheme II**. It centered on chlorination of either the C-2 or C-4 position to provide the isomeric dichloroketones which were easily

**Method C**

**Scheme III**[c]




[c] (i) Method A steps i to iii; (ii) $CF_3SO_3H$, 60°C, 2 hrs., then 5N HCl, reflux; (iii) nucleophiles, MeOH, reflux, 2-3 hrs.; (iv) Method B steps iii to vi; (v) Method B steps iii and iv; (vi) 1.1 eq. *n*-BuLi, THF, -78°C, then $HCO_2C_2H_5$; (vii) Method A steps vii to ix; (viii) Method A steps vii and viii; (ix) 2.2 equiv. *n*-BuLi, THF, -78°C, then $CH_3CHO$; (x) $(CH_3CO)_2O$, $CH_2Cl_2$, pyr., 0°C.

separated by flash chromatography (30% EtOAc in hexane). The ketones were then elaborated via addition of the piperidyl Grignard followed by dehydration, demethylation and acylation to provide the desired targeted derivatives (**5** and **7**). Displacement of the chlorine atom with the appropriate nucleophile (step vii) provided the desired intermediates which were then acylated to afford the target compounds (**8** and **13**). **Method C (Scheme III)** used the bromide at C-3 for introducing nucleophiles as well as electrophiles. The introduction of nucleophiles at the C-3 position was accomplished by displacement of the C-3 bromide of the tricyclic-seven-membered ring ketone (step iii). Subsequent elaboration of the nucleophile-substituted ketones afforded the target compounds (**12** and **15**). Electrophiles were introduced via metal-halogen exchange of the C-3 bromo piperidine intermediates (step vi or ix) followed by their treatment with the desired electrophiles, usually aldehydes. This process provided **17** and **18** which were subsequently oxidized with pyridinium dichromate to **16** and **19**, respectively.

From the data in **Table 1**, it was generally concluded that: 1) substitution at the C-3 position is more beneficial than the C-2 and C-4 position for dual activity; 2) compounds with an electron withdrawing group at the C-3 position are usually less active as PAF antagonists than those having an electron donating group; and 3) a small hydrophobic substituent ($CH_3$) is better than a hydrophilic ($CH_2OH$) substitutent for dual activity. The compound with the best overall biological profile as a dual antagonist is the C-3 methyl substituted analog (**3**) which is twice as potent as a PAF antagonist and four times as potent as an antihistamine than Sch 37370.

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## References and Notes

(1) A preliminary account of this work was presented at the 204th National Meeting of American Chemical Society, Division of Organic Chemistry, Washington, D.C., August 1992; ORG 298. For the previous paper in this series see reference 8a.

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