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SYNTHESIS OF BICYCLIC THIAZOLIDINE PAF ANTAGONISTS

Steven K. Davidsen*, James B. Summers, Richard G. Conway, David A. Rhein and George W. Carter
Immunosciences Research Area, Department 47J, AP-10
Abbott Laboratories, Abbott Park, IL 60064

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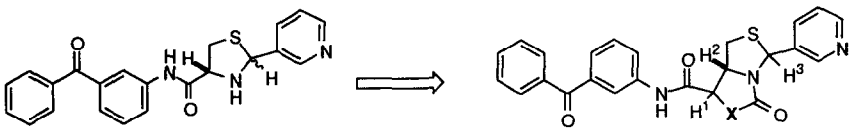
Abstract: PAF antagonist **1** is susceptible to thiazolidine ring fragmentation *in vitro* and *in vivo*. The search for a more stable compound prompted the synthesis of a series of bicyclic analogs. Three classes of bicyclic thiazolidines (**2**: X = O, CH_2, NCH_3) were prepared using a common synthetic pathway which generated all the possible diastereomers. The most potent PAF antagonists were the oxygen-substituted analogs which possessed receptor binding affinities largely dependent on stereochemistry.

Platelet activating factor (PAF) is a highly potent phospholipid mediator which induces a range of biological effects.[1] It has been implicated in a number of disorders including asthma, psoriasis and septic shock.[2] In view of the broad scope of diseases in which PAF plays a role, there appears to be significant therapeutic potential for PAF antagonists. A number of structurally diverse PAF antagonists have been identified to date, several of which are currently being evaluated in clinical trials.[3]

We have studied the structure-activity relationships of 3-pyridyl substituted thiazolidines and have demonstrated that **1** blocks the effects of PAF *in vitro* and *in vivo*.[4] One liability of unsubstituted thiazolidines such as **1** is that they exist as an equilibrating mixture of diastereomers.[5] In addition, thiazolidine ring fragmentation leads to degradation *in vitro* and contributes to rapid metabolism *in vivo*. In an effort to avoid this metabolic pathway a series of bicyclic thiazolidines of the general structure **2** were designed. This series of compounds was chosen since fusion of an additional ring onto the thiazolidine nitrogen of **1** prevents equilibration and perhaps ultimately ring fragmentation. Bicyclic thiazolidine **2**

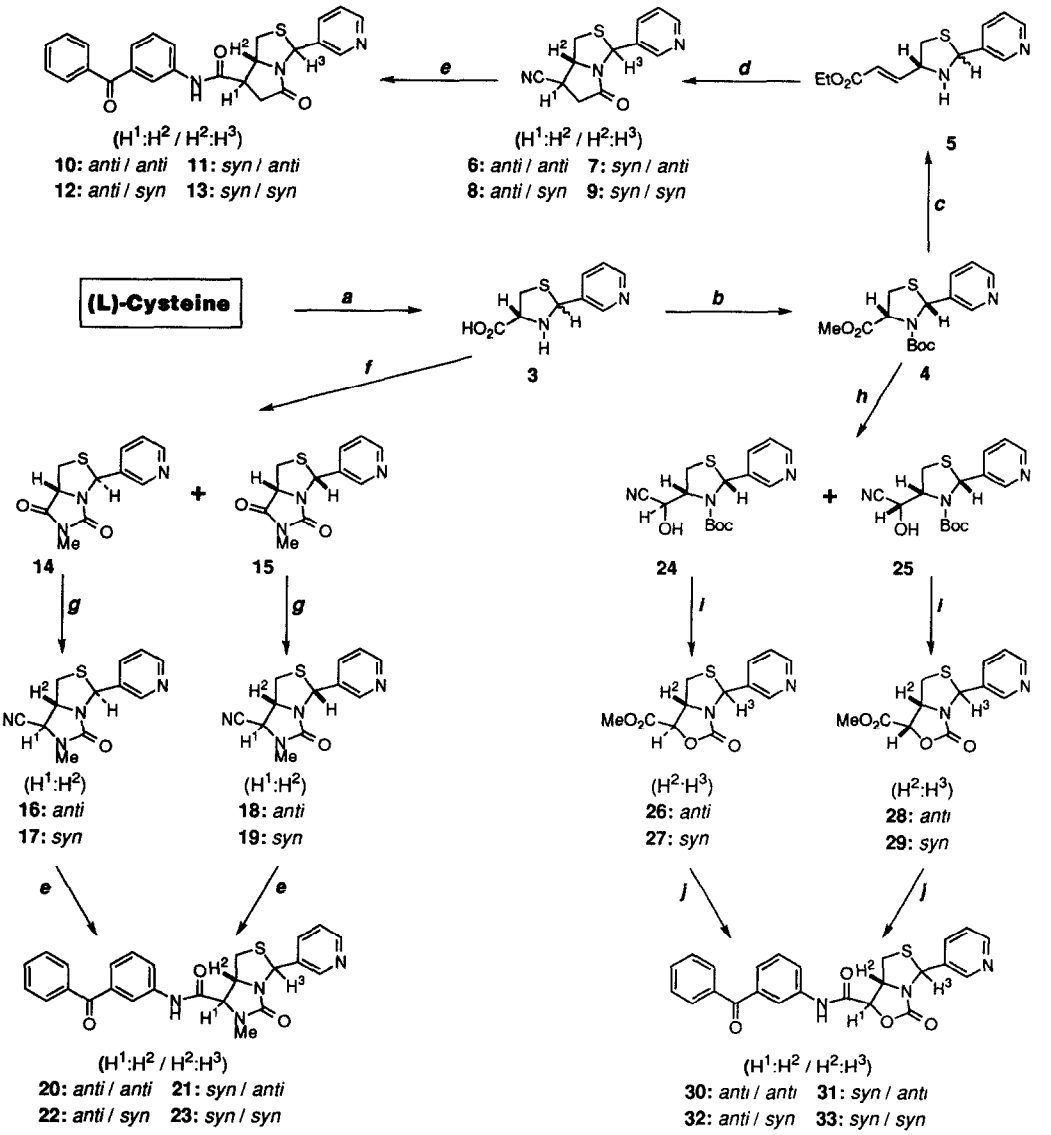


1 **2**: X = O, CH_2, NCH_3

also provides the opportunity to analyze PAF antagonism with respect to the type of heterocycle (X = O, CH_2, NCH_3) and with respect to the stereochemical relationship between H^1, H^2 and H^3. In this paper, we describe the synthesis and PAF binding potency of bicyclic thiazolidines represented by **2**.

The synthesis of amino acid-derived bicyclic thiazolidines[6] and oxazolidines[7] have been recently reported. Our synthetic route to **2** is given in Scheme 1 and illustrates how all the possible diastereomers in each of the three classes of bicyclic thiazolidines were synthesized from (L)-cysteine. Thus, synthesis of the carbon-substituted analogs **10** - **13** required intermediates **3** and **4** which were subsequently parlayed into the nitrogen- and oxygen-substituted compounds. Amino acid **3** was prepared by condensation of (L)-cysteine with nicotinaldehyde. Protection of the nitrogen atom and methyl ester formation gave **4** after chromatographic removal of the minor *trans* isomer.[5c] Reduction and chain homologation gave α,β-

Scheme 1



Key: ***a***. nicotinaldehyde, EtOH:H_2O, 25°C (87%) ***b***. 1) Boc_2O, aqu. NaOH:*p*-dioxane, 25°C (70%) 2) CH_2N_2, MeOH:Et_2O (68%) ***c***. 1) Dibal, CH_2Cl_2, -78°C (74%) 2) Ph_3PCHCO_2Et, PhH, 25°C (72%) 3) HCl:*p*-dioxane, 25°C (94%) ***d***. Et_2AlCN, PhH, Δ (42%) ***e***. 1) HCl:MeOH, 0°C 2) LiOH, THF:H_2O, 0°C 3) 3-aminobenzophenone, BOP-Cl, NEt_3, THF:DMF; 25°C (see text) ***f***. MeNCO, pyridine, Δ, (43%) ***g***. 1) Dibal, CH_2Cl_2, -78°C (46-65%) 2) Ac_2O, NEt_3, CH_2Cl_2 then Et_2AlCN, THF, 0°C (56-74%) ***h***. 1) Dibal, CH_2Cl_2, -78°C (74%) 2) Et_2AlCN, toluene, 0°C (81%) ***i***. 1) HCl:MeOH, 0°C (66-74%) 2) $(Cl_3CO)_2CO$, NEt_3, CH_2Cl_2, 25°C (58-68%) ***j***. 1) LiOH, THF:H_2O, 0°C 2) 3-aminobenzophenone, BOP-Cl, NEt_3,THF:DMF; 25°C (56-61%).

unsaturated ester **5** in 53% yield from **4**.[8] Treatment of **5** with diethylaluminum cyanide in refluxing benzene caused a conjugate addition/cyclization reaction and gave a mixture of the four diastereomers **6** - **9** in 42% yield (relative ratios: **6** = 3.5, **7** = 3.7, **8** = 1.0, **9** = 1.0). The stereochemical relationship between H^1:H^2 and between H^2:H^3 in **6** - **9** was defined by ROESY NMR studies. These nitriles were then individually converted to the corresponding methyl esters by treatment with methanolic HCl (45 - 70%).[9] Hydrolysis of each ester followed by BOP-Cl mediated coupling with 3-aminobenzophenone gave the carbon-substituted bicyclic thiazolidines **10** - **13** (47 - 64%).

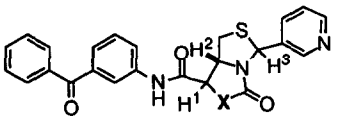
Synthesis of the *N*-methyl substituted bicyclic thiazolidines **20** - **23** parallels the synthesis of (+)-biotin described by Poetsch.[10] Thiazolidine acid **3** was heated with methyl isocyanate which gave a 1.9:1 ratio of separable diastereomers **14** and **15**. These compounds were individually converted to a separable mixture of nitriles by reduction, acetylation and cyanide addition (this gave a 1:1 mixture of nitrile isomers in both cases). Nitriles **16** - **19** were then subjected to the same acidic methanolysis, hydrolysis and coupling procedure described above which gave **20** - **23** in 43 - 67% yield.

Preparation of the oxygen-substituted bicyclic thiazolidines **30** - **33** originated from intermediate **4** which was transformed into the two separable cyanohydrins **24** and **25** (1.0 : 1.6 ratio). Acidic methanolysis converted the nitriles to methyl esters and removed the Boc-protecting group; subsequent treatment with triphosgene gave the bicyclic methyl esters **26** - **29**.[11] Once again, hydrolysis and coupling with 3-aminobenzophenone gave **30** - **33** in 56 - 61% yield.

Binding constants for these bicyclic thiazolidines were established for inhibition of [^{3}H]PAF binding to rabbit platelet membranes and are shown in Table 1.[12] *N*-Methyl substituted analogs **20** - **23** exhibited

Table 1:

PAF Receptor Binding Activity of Bicyclic Thiazolidines



Compound : K_i

Stereochemistry (H^1:H^2 / H^2:H^3)	**X** = NCH_3	**X** = CH_2	**X** = O
anti / anti	**20**: 14,000 nM	**10**: 1,000 nM	**30**: 2,500 nM
syn / anti	**21**: 2,200 nM	**11**: 600 nM	**31**: 150 nM
anti / syn	**22**: 9,500 nM	**12**: 1,800 nM	**32**: 1,200 nM
syn / syn	**23**: 1,450 nM	**13**: 540 nM	**33**: 24 nM

poor binding affinities regardless of the stereochemical relationship between H^1 and H^2 and across the thiazolidine ring (H^2 and H^3). The carbon-substituted series (**10** - **13**) exhibited better binding in all cases although stereochemistry was less of a factor within this set. In contrast, the binding constants for the oxygen-substituted bicyclic thiazolidines **30** - **33** exhibited a large dependence on stereochemisty. By far the most potent analog was the *syn, syn* stereoisomer **33** which displayed a binding constant of 24 nM. Interestingly, compounds possessing the *syn, syn* stereochemistry proved to be the most potent analogs within each of the three sets (**23** vs. **20** - **22**; **13** vs. **10** - **12**; **33** vs. **30** - **32**). Compound **33** is only slightly less potent than **1** (K_i = 5 nM) and is more potent than the well known PAF antagonist WEB 2086 (K_i = 98 nM). As mentioned, the thiazolidine ring of **1** is susceptable to fragmentation inasmuch as **1** generates nicotinaldehyde upon treatment with aqueous acid and after *iv* dosing in rats ($t_{1/2}$ = 1.0 h). While **33** is stable under acidic conditions, its half-life in rats is also short ($t_{1/2}$ = 0.7 h). Metabolic routes other than thiazolidine ring fragmentation contribute to the degradation of **33**. Regardless of its pharmacokinetic profile, **33** is a single stereoisomer which serves as an appropriate lead for future investigation.

In conclusion, we have carried out the preparation of three classes of bicyclic thiazolidines using a common synthetic route. We have demonstrated that the labile thiazolidine ring in **1** can be replaced with the *syn, syn* oxygen-substituted analog **33** without substantial loss in binding potency and that this prevents thiazolidine ring fragmentation but does not produce a longer *in vivo* half-life.

Reference and Notes:

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9. Direct hydrolysis of these nitriles to the corresponding acid could be achieved using KOH in hot butanol, however epimerization occurred at the carbon bearing H^1 giving raise to products with predominately the *anti* relationship between H^1 and H^2.
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11. An X-ray crystal structure for ester **29** was obtained which was consistent with the stereochemistry assigned by NMR experiments (**29** is the precursor of the most potent analog **33**).
12. The method used for this binding assay follows: Rabbit platelets were lysed by freeze-thaw and sonicated and membranes were prepared by centrifugation and washing. Membranes (10 μg of protein) were incubated with 0.6 nM [^{3}H] PAF, and test antagonist for 60 min. To assess non-specific binding, 1 μM PAF was added to some incubations. The membranes were filtered, washed and the filters were dried and the bound radioactivity measured.