PYRROLIDINE DERIVATIVES AS INHIBITORS OF PLATELET AGGREGATION INDUCED BY PLATELET ACTIVATING FACTOR

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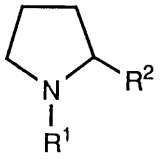
Newly synthesized pyrrolidine derivatives inhibited rabbit platelet aggregation induced by platelet activating factor.

KEYWORDS pyrrolidine derivative; sulfide; phosphate; platelet activating factor; platlet aggregation; inhibitor

After elucidation of the structure of Platelet Activating Factor (PAF),[1,2] many PAF antagonists have been proposed.[3] It is of interest that some of them do not contain any glycerol frameworks.[4] Recently, we have found that some pyrrolidine derivatives also are potent inhibitors of rabbit platelet aggregation induced by PAF.

A variety of 2-substituted-N-alkoxycarbonylpyrrolidines were synthesized from D- or L-proline in several steps[5] and subjected to screening tests for the inhibitory activity.



R^1; $COO(CH_2)_nCH_3$

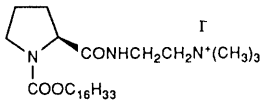
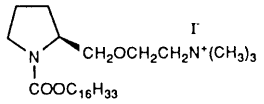
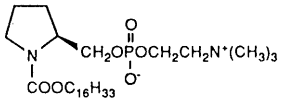
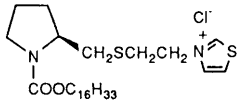
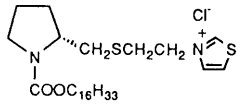
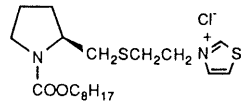
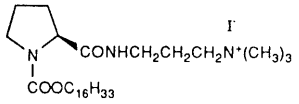
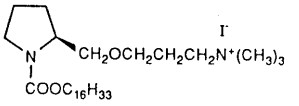
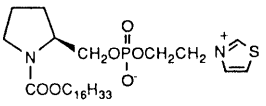
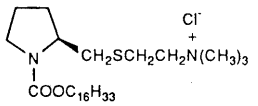
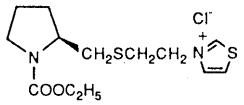
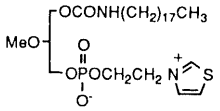
R^2; $CONH(CH_2)_nN^+R_3I^-$, $CH_2O(CH_2)_nN^+R_3I^-$, $CH_2OP(O)(O^-)OCH_2CH_2N^+R_3$, $CH_2SCH_2CH_2N^+R_3Cl^-$

Typical compounds that inhibit PAF-induced rabbit platelet aggregation are shown in Table I. The activity is expressed as the concentration which causes 50% inhibition (IC_{50}) of platelet aggregation. The phosphate-type compounds (AKS-145 and 160) showed no activity, but the amide-types (AKS-139 and 140) and the ether-types (AKS-149 and 159) were inhibitory. It is noteworthy that the activities of the sulfide-type compounds (AKS-161, 162, 164, 167, and 168) were equal to or more potent than that of CV-3988,[6] a well known PAF antagonist.

The efficacy of substituents at the 2-position on the inhibitory activity was in approximately the following order: sulfide > ether > amide >> phosphate. The N-substituents also affected the activities thus: octyloxycarbonyl > ethoxycarbonyl > hexadecyloxycarbonyl. The absolute configuration at the 2-position showed a little difference between the S-form (AKS-161) and the R-form (AKS-164).

The inhibitory activity of these pyrrolidine derivatives is reported for the first time in this paper. Various pharmacological uses as PAF-antagonists are expected for this type of pyrrolidine derivative.

Table I. Inhibitory Activity against PAF-Induced Rabbit Platelet Aggregation [a)]

Compd. No.	Compound	IC_{50} (10^{-6}M)
AKS-139		44.0
AKS-149		21.2
AKS-145		—
AKS-161		6.3
AKS-164		17.5
AKS-168		0.13
AKS-140		32.7
AKS-159		25.9
AKS-160		—
AKS-162		12.1
AKS-167		0.69
CV3988		10.4

a) The platelet rich plasma (PRP) was obtained by centrifuging citrated rabbit blood (final concentration, 0.31%) at 190 x g for 10 min, and the cell density was adjusted to 8 x 10^5 cells/μl with platelet poor plasma (PPP). Various concentrations of test compounds (20 μl) were added to PRP (210 μl) 3 min prior to the addition of PAF (3 x 10^{-8}M). Platelet aggregation was measured using a six-channel aggregometer (Niko Bioscience Inc., Tokyo, Japan).

REFERENCES AND NOTES

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5) Synthetic procedures will be reported elsewhere in near future.
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