LIGNANS AND SESQUITERPENOIDS AS PAF ANTAGONISTS †

Satoshi Iwakami, Yutaka Ebizuka, and Ushio Sankawa*
Faculty of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan

† Dedicated to Professor Tetsuji Kametani

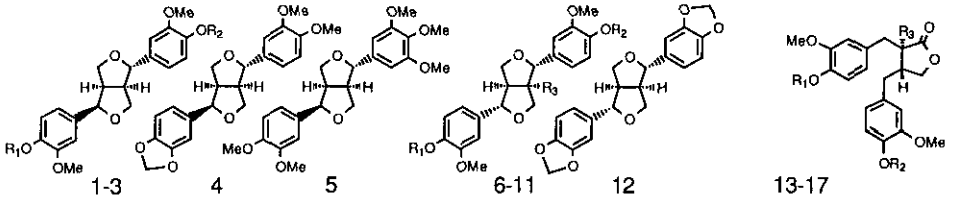
Abstract ——— Some lignans and sesquiterpenes were found to have potent PAF antagonist activities. In particular, 6-O-angeloyl- and 6-O-senecioylplenolins (18,19) are the most potent and specific PAF antagonists found in this study.

Platelet activating factor (PAF) has been known as a chemical mediator possessing etherphospholipid structure,[1] which is released from a variety of cells, such as platelets, basophiles, neutrophiles, macrophases and mast cells when they are stimulated. Since PAF causes inflammatory and allergic responses, such as bronchoconstriction and increase of vascular permeability, its receptor antagonists are expected to be useful as anti-allergic and anti-inflammatory drugs. In addition to synthetic PAF receptor antagonists having PAF analogous structures, PAF antagonists of natural origin having various structures have been isolated from oriental medicinal drugs. A neolignan kadsurenone was the first PAF antagonists of plant origin isolated from Piper futokadsura and showed anti-allergic effect in guinea pig asthma model.[2] Later two terpenoids have been reported as natural PAF antagonists, namely ginkgolide B of modified diterpene structure from Ginkgo biloba[3] and a sesquiterpene lactone (L-652,469) from a Chinese medicinal drug, Tussilago farfara.[4]

As the continuation of our studies on biologically active compounds contained in medicinal plants used in traditional oriental medicines, we introduced PAF receptor binding assay to find specific PAF antagonists from medicinal plant extracts by screening. Hot aqueous extracts of about 30 Chinese medicinal plants which have been used clinically for anti-allergic purposes were tested for PAF receptor antagonist activity by using rabbit platelets binding assay.[5] Of the

extracts tested the fruits of Forsythia suspensa (Oleaceae), the seeds of Arctium lappa (Compositae) and the herb of Centipeda minima (Compositae) showed significant anti-PAF activity. Since Forsythia and Arctium are known to contain lignans,[6,7] we first investigated PAF antagonist activity of two types of lignans, bis-tetrahydrofuran and butanolide type, which are the representative lignan groups contained in the medicinal plants under investigation. The results are summarized in Figure I. In bis-tetrahydrofuran type lignans, presence of at least one 3,4-dimethoxyphenyl or 3,4,5-trimethoxyphenyl group (2-5,7,10,11) is essential for high PAF antagonist activity. Presence of hydrophilic groups, such as glucosyl, hydroxyl and phenolic (1,6,8,9,11), lowered the activity. No significant difference was observed between trans and cis isomers of bis-tetrahydrofuran lignans. The presence of 3,4-dimethoxyphenyl group is also required for high PAF antagonist activity in butanolide type lignans. The IC_{50} values of the active lignans (3,4,5,10,15) so far found in this study fall in a range of 0.42-0.91 μM, which is comparable to that of CV-3988,[5] 0.11 μM, measured under the same assay conditions.

Figure I IC_{50} Values of Lignans on PAF Receptor Binding



1-3 4 5 6-11 12 13-17

	R_1	R_2	IC_{50} (μM)
1	H	H	---
2	Me	H	1.6
3	Me	Me	0.91
4			0.66
5			0.42

	R_1	R_2	R_3	IC_{50} (μM)
6	H	H	H	---
7	Me	Me	H	1.2
8	Glu	H	H	---
9	Glu	Glu	H	---
10	Me	Me	OAc	0.67
11	Me	Me	OH	2.8
12				---

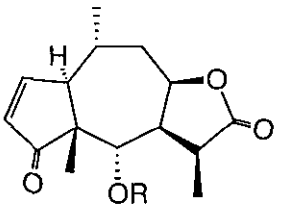
	R_1	R_2	R_3	IC_{50} (μM)
13	H	H	H	---
14	H	Me	H	2.9
15	Me	Me	H	0.56
16	H	Me	OH	57% (10μM)
17	Me	Me	OH	60% (10μM)

--- : less than 30% inhibition at 10μM

In our previous studies on anti-allergic medicinal plants, flavonoids and sesquiterpene lactones were identified as active principles contained in the herb of Centipeda minima.[8a] The herb was extracted with 70% acetone and fractionated by repeated column chromatography (silica gel and RP-18) with the aid of PAF binding bioassay to give active fraction. The fraction was found to contain sesquiterpene lactones, some of which had been isolated as anti-allergic compounds in our previous study. Four sesquiterpene lactones of plenolin esters (18-21) were isolated from this fraction and identified by comparison of their nmr and ms data

with those reported.[8] *High PAF antagonist activity was observed only in plenolin* esters having double bond in ester groups, i.e. 6-O-angeloyl- and 6-O-senecioylplenolins (18,19). Comparison of IC_{50} values of plenolin esters with saturated acyl group (20,21,22) revealed that the size of acyl group is also important for the activity, though the effects are much lower compared to those of unsaturated acyl groups. So far only one sesquiterpenoid (L-652,469) has been reported as a PAF antagonist, however its activity is one order less compared to CV-3988.[4,9] (18) and (19) are more potent receptor antagonist than L-652,469, since they have comparable activity to that of CV-3988.

Figure II IC_{50} Values of Sesquiterpenoids on PAF Binding

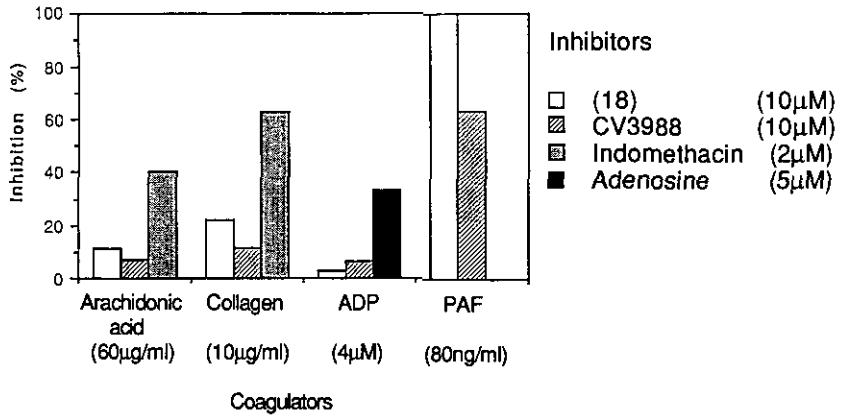


	R	IC_{50} (μM)		R	IC_{50} (μM)
18	-CO	0.30	21	-CO	2.6
19	-CO	0.25	22	-CO	48% (10μM)
20	-CO	6.7	23	H	---

--- : less than 30% inhibition at 10μM

Inhibitory effects of (18) were tested for platelet aggregation induced by several coagulators and the results are summarized in Figure III. (18) completely inhibited the platelet aggregation induced by PAF at a concentration of 10 μM, while the inhibition of aggregation induced by arachidonic acid, collagen and ADP, were less than 25% at the same concentration, demonstrating that (18) is a very specific PAF antagonist. These two plenolin esters (18,19) are very potent and

Figure III Specific Inhibition of Platelet Aggregation Induced by PAF [10]



specific PAF antagonists among sesquiterpenoids and they could have potential as the lead compounds to develop new type of anti-allergic drugs.

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