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Short communication

Synthesis and platelet activating factor (PAF) receptor antagonist activity of 2,5-diarylcyclopentanol derivatives

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Summary — Synthesis and platelet activating factor (PAF) receptor antagonist activity of (1α, 2β, 5β)-2,5-diarylcyclopentanol derivatives is described. Compounds **2**, **4** and **9** showed significant activity.

platelet activating factor / diarylcyclopentanols / PAF antagonists

Introduction

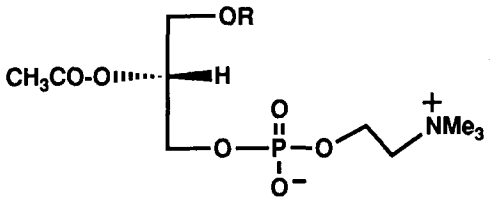
Platelet activating factor (PAF) is an endogenous, highly potent phospholipid characterized as R-1-O-hexadecyl/octadecyl-2-O-acetyl-glyceryl-3-phosphorylcholine [1]. It is produced and released by stimulated basophils, neutrophils, platelets, endothelial cells, eosinophils and macrophages [2]. In various animal models PAF induces hypotension, bronchoconstriction, neutropenia, thrombocytopenia and increased cutaneous vascular permeability [3]. PAF may also play a major role in asthma [4], gastric ulceration [5] and as a potent modulator of the immune response [6].

A wide variety of chemical structures have been reported to be potent PAF receptor antagonists [7]. 2,5-Diaryltetrahydrofurans (scheme 1) were among the first uncharged, potent PAF receptor antagonists [8]. In order to develop a more potent and orally active PAF receptor antagonist, we undertook a structure–activity relationship program to modify the 2,5-diaryltetrahydrofuran structure. Our initial goal was to replace the tetrahydrofuran ring oxygen by a methylene group and introduce this oxygen outside the ring in the form of a hydroxyl group leading to a 2,5-diarylcyclopentanol structure [9].

In this paper we describe the synthesis and PAF receptor antagonist activity of (1α, 2β, 5β)-2,5-diarylcyclopentanol (I) derivatives (scheme 1). Syntheses and PAF receptor antagonist activity of the (1α, 2α, 5β)-2,5-diarylcyclopentanols (II) and the (1α, 2α, 5α)-isomer (III) have recently been disclosed [9, 10].

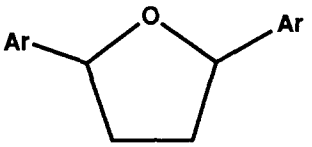
Chemistry

(1α, 2β, 5β)-2,5-Diarylcyclopentanols (**1**, **8**, **11**, **13**, **15** and **17**; scheme 2) were prepared by a stereoselective hydroboration [11] of an appropriate 1,3-diarylcyclopentene [12]. Hydroboration occurs on the face of the molecule away from the 3-aromatic group giving the desired stereoisomer as the only product. To further confirm the stereochemistry of these products, **1** was methylated by methyl iodide in the presence of sodium hydride to give 1α-methoxy-(2β, 5β)-2,5-bis(3,4,5-trimethoxyphenyl)cyclopentane (**2**). ^{1}H and ^{13}C NMR data (table I) suggest that two aromatic groups at C-2 and C-5 in **2**, are *cis* to each other. In NOE experiments of **2**, by irradiation of the aromatic protons and enhancement of the C-1 methine proton signal it was shown that the two aromatic groups at C-2 and C-5 and the C-1 methine proton are on the same face of the molecule. Conversely, irradiation of C-1 methine proton gave rise to enhancement of the aromatic protons signal. Thus, NOE experiments confirm that two benzylic protons at C-2 and C-5 were *trans* with respect to the proton at C-1 as shown in the structure **2**. Compounds **8**, **11**, **13**, **15** and **17** were also methylated to their respective methyl ethers **9**, **12**, **14**, **16** and **18** in order to test if free hydroxyl group at C-1 is necessary for biological activity. To evaluate the contribution of the hydroxyl group in binding to the receptor, des-hydroxyl compound *ie*, *cis*-1,3-bis(3,4,5-trimethoxyphenyl)-cyclopentane (**3**) was prepared by catalytic hydrogenation of 1,3-bis(3,4,5-trimethoxyphenyl)cyclo-

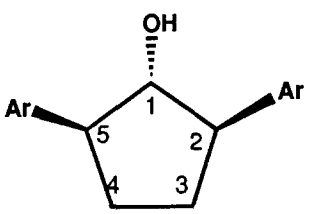


R = n-$C_{16}H_{33}$ or $C_{18}H_{37}$

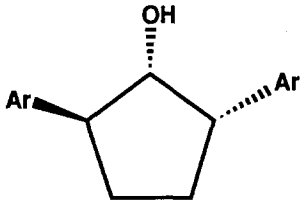
PAF



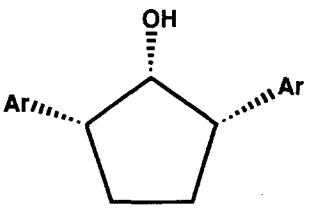
cis and trans-
2,5-Diaryltetrahydrofurans



I



II



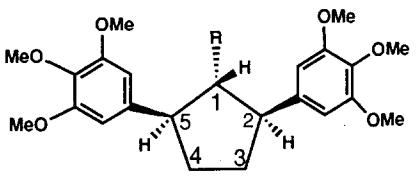
III

Scheme 1.

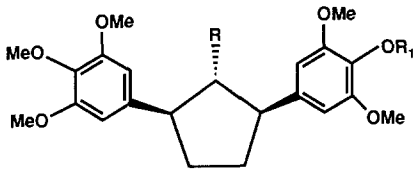
pentene [12] over 10% Pd-C. To test the effect of steric bulk at the alcoholic group on PAF receptor antagonist activity, alcohol **1** was converted to its benzyl ether (**4**), 2-methylbutyl ether (**5**), and heptyl ether (**6**) by treatment with an appropriate halide in the presence of sodium hydride. Acetate (**7**) was prepared by acetylation of **1** with acetic anhydride in pyridine–methylene chloride solution. Benzyloxy derivative **9** was hydrogenated over 10% Pd-C to the phenol **10** to test the effect of substitution at this position in one of the aromatic rings. In order to prove whether both aromatic groups are important for biological activity, compound **19**, in which one of the aromatic groups is lacking, was prepared by a stereoselective hydroboration of 1-(3,4,5-trimethoxyphenyl)cyclopentene [12]. Finally, to determine the importance of the 1,2,5 relationship of the three substituents (1α, 2β, 4β)-2,4-bis(3,4,5-trimethoxyphenyl)cyclopentanol (**20**), was prepared by a hydroboration of 1,4-bis(3,4,5-trimethoxyphenyl)cyclopentene [12]. Compound **20** was methylated with methyl iodide in the presence of sodium hydride to yield methyl ether **21**.

Biological results and discussion

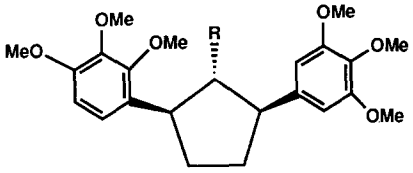
These compounds were tested in the [^{3}H]-PAF receptor binding assay on human platelets [13] and their IC_{50} values are listed in table II. Methyl ether **2** was about six times more active than the free alcohol **1**. Benzyl ether **4** has about the same activity as methyl ether **2** and compounds **5**, **6** and **7** were less active than **2** but a little more active than the parent alcohol **1**. Compound **3** was about eleven times less active than **2** suggesting that oxygen at C-1 enhances binding. A change in the substitution pattern on one of the aromatic groups (from **2** to **12**) led to a slight decrease in activity. Replacement of a 4-methoxy group in one of the aromatic rings by a 4-benzyloxy group (from **2** to **9**) resulted in almost no change in the activity, however, deprotection at this position to afford a free phenol (**10**) decreased activity. Removal of 3 and 5-methoxyl groups (**13** and **14**) or 4-methoxyl groups (**18**) in both the aromatic rings led to a complete loss of activity. Removal of the 5-methoxyl groups (**15**) retained the activity compared to that of **1**. Methyl ether **16** was about three times less active than **2**. Both the 3,4,5-trimethoxyphenyl groups are important for the biological activity, as suggested by the fact that compound **19** was inactive. Complete loss of activity in compounds **20** and **21** suggested that the 1,2,5 relationship between the hydroxyl group and the two aromatic groups is important. A comparison of the IC_{50} of cyclopentanol **1** with those of reported values [9] for its corresponding isomers **22** and **23** suggested that **1** and **22** possessed the same activity while **23** was slightly less active. These results suggested that the *trans* relationship of the two aromatic groups is not important in cyclopentanol series which is in sharp contrast to 2,5-diaryl tetrahydrofurans where the *cis* isomer was devoid of activity [8].



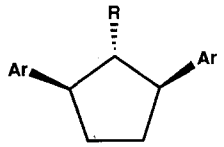
1 R = OH
2 R = OMe
3 R = H
4 R = OCH_2Ph
5 R = OCH_2CHMe_2
6 R = OC_7H_{15}
7 R = $OCOCH_3$



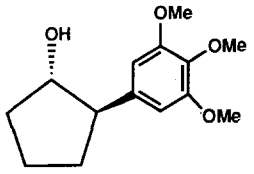
8 R = OH , R_1 = CH_2Ph
9 R = OMe , R_1 = CH_2Ph
10 R = OMe , R_1 = H



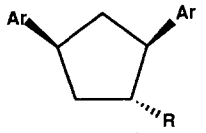
11 R = OH
12 R = OMe



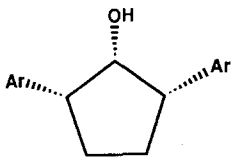
13 R = OH , Ar = 4-Methoxyphenyl
14 R = OMe , Ar = 4-Methoxyphenyl
15 R = OH , Ar = 3,4-Dimethoxyphenyl
16 R = OMe , Ar = 3,4-Dimethoxyphenyl
17 R = OH , Ar = 3,5-Dimethoxyphenyl
18 R = OMe , Ar = 3,5-Dimethoxyphenyl



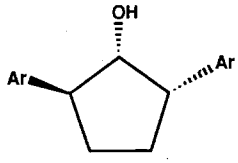
19



20 R = OH
21 R = OMe



22



23

Ar = 3,4,5-Trimethoxyphenyl

Scheme 2.

Experimental protocols

Biological methods

Inhibition of [^{3}H]PAF binding to the human platelet PAF receptor

Freshly drawn human blood was anticoagulated with 0.38% sodium citrate and 2.8 µg/ml PGI_2. PRP was prepared by centrifugation of the blood at 250 x *g* for 10 min at 24°C. The platelets were sedimented by centrifugation at 900 x *g* for 15 min at 24°C and then washed twice with a solution of Tris-Tyrode's buffer (pH 7.4) containing 0.25% bovine serum albumin (TT/BSA) and 0.3 µg/ml PGI_2. The washed platelets were resuspended to 3.5 x 10^5 per µl in TT/BSA. Aliquots of platelets (500 µl) were mixed with 1.5 nM [^{3}H]PAF (40 000 cpm; 49 Ci/mmol). Non-specific binding was estimated in duplicate tubes containing excess cold PAF (3.7 x 10^{-7} final concentration). After incubation at 24°C for 1 h, the reaction was stopped by adding 500 µl ice-cold TT/BSA. The [^{3}H]PAF bound to platelets was separated from the free radioligand by centrifugation at 900 x *g* for 10 min at 4°C. Pellets were washed with TT/BSA and centrifuged at 900 x *g* for 15 min at 4°C. The pellets were resuspended in 2.5 ml liquid scintillation fluid, and the tubes were mixed and counted for 1 min in a liquid scin-

Table I.

Comp No[a]	*Yield (%)*	*mp (°C)*	*^{1}H-NMR ($CDCl_3$, δ, ppm)*[b]
1	48	135–7	1.87 (d, 1H, OH, J = 4 Hz), 1.95 (m, 2H), 2.28 (m, 2H), 3.04 (m, 2H), 3.82–3.87 (2s, 18H, 6 x OCH_3), 4.04 (dt, 1H, CH-OH, J = 4, 10 Hz), 6.56 (s, 4H, ArH)
2	72	103–4	1.94 (m, 2H), 2.27 (m, 2H), 3.13 (m, 2H), 3.15 (s, 3H, CH-OCH_3), 3.81 (t, 1H, CH-OCH_3, J = 9 Hz), 3.86–3.88 (2s, 18H, 6 x OCH_3), 6.56 (s, 4H, ArH) ^{13}C-NMR : 30.80, 51.71, 56.26, 58.62, 60.85, 95.07, 104.65, 140.87, 153.29
3	61	oil	1.78 (q, 1H), 1.9 (m, 2H), 2.27 (m, 2H), 2.47 (m, 1H), 3.2 (m, 2H), 3.83, 3.88 (2s, 18H, 6 x OCH_3), 6.52 (s, 4H, ArH)
4	82	65–6	1.91 (m, 2H), 2.25 (m, 2H), 3.18 (bq, 2H), 3.82, 3.86 (2s, 18H, 6 x OCH_3), 3.89 (t, 1H), 4.17 (s, 2H, CH_2Ph), 6.49 (s, 4H, ArH), 6.87 (m, 2H, ArH), 7.14 (m, 3H, ArH)
5	27	oil	0.71 (d, 6H, 2 x CH_3), 1.6 (m, 1H, $CHMe_2$), 1.94 (m, 2H), 2.24 (m, 2H), 2.91 (d, 2H, OCH_2), 3.14 (bq, 2H), 3.77 (t, 1H), 3.84, 3.87 (2s, 18H, 6 x OCH_3), 6.55 (s, 4H, ArH)
6	78	oil	0.82 (t, 3H, CH_3), 1.06–1.4 (m, 10H), 1.93 (m, 2H), 2.24 (m, 2H), 3.12 (tm, 4H), 3.77 (t, 1H), 3.85–3.88 (2s, 18H, 6 x OCH_3), 6.55 (s, 4H, ArH)
7	92	oil	1.95 (m, 2H), 1.99 (s, 3H, $COCH_3$), 2.3 (m, 2H), 3.28 (bq, 2H), 3.83 (bs, 18H, 6 x OCH_3), 5.57 (t, 1H, CH-OCOMe), 6.5 (s, 4H, ArH)
8	46	oil	1.87 (d, 1H, OH, J = 4 Hz), 1.97 (m, 2H), 2.29 (m, 2H), 3.04 (bq, 2H), 3.84, 3.85, 3.89 (3s, 15H, 5 x OCH_3), 3.89 (dt, 1H, CHOH, J = 4–10 Hz), 4.98 (s, 2H, CH_2Ph), 6.56 (s, 4H, ArH), 7.28–7.56 (m, 5H, ArH)
9	86	99	1.95 (m, 2H), 2.28 (m, 2H), 3.13 (s, 3H, $CHOCH_3$), 3.14 (m, 2H), 3.80 (t, 1H), 3.85, 3.86, 3.89 (3s, 15H, 5 x OCH_3), 5.01 (s, 2H, CH_2Ph), 6.57 (s, 4H, ArH), 7.3–7.57 (m, 5H, ArH)
10	89	133–4	1.92 (m, 2H), 2.26 (m, 2H), 3.1 (m, 2H), 3.13 (s, 3H, OCH_3), 3.78 (t, 1H), 3.85, 3.9, 3.92 (3s, 15H, 5 x OCH_3), 5.42 (s, 1H, OH), 6.57 (d, 4H, ArH)
11	39	131–3	1.95 (m, 2H), 2.26 (m, 2H), 2.38 (d, 1H, OH, J = 4 Hz), 3.09 (m, 1H), 3.42 (m, 1H), 3.83, 3.88, 3.98 (3s, 18H, 6 x OCH_3), 4.1 (dt, 1H, CHOH, J = 4–9 Hz), 6.57 (s, 2H, ArH), 6.71 (d, 1H, ArH), 7.02 (d, 1H, ArH)
12	92	85–6	1.7–2.02 (m, 2H), 2.24 (m, 2H), 3.1 (s, 3H, OCH_3), 3.12 (m, 1H), 3.46 (q, 1H), 3.85, 3.88, 3.94 (3s, 18H, 6 x OCH_3), 6.58 (s, 2H, ArH), 6.68 (d, 1H, ArH), 6.98 (d, 1H, ArH)
13	39	116–7	1.73 (d, 1H, OH, J = 4 Hz), 1.92 (m, 2H), 2.25 (m, 2H), 3.04 (m, 2H), 3.8 (s, 6H, 2 x OCH_3), 4.02 (dt, 1H, CHOH, J = 4, 10 Hz), 6.9 (d, 4H, ArH), 7.28 (d, 4H, ArH)
14	98	76–8	1.9 (m, 2H), 2.24 (m, 2H), 3.05 (s, 3H, OCH_3), 3.13 (bq, 2H), 3.78 (t, 1H), 3.8 (s, 6H, 2 x OCH_3), 6.88 (d, 4H, ArH), 7.26 (d, 4H, ArH)
15	38	90–2	1.8 (d, 1H, OH, J = 4 Hz), 1.94 (m, 2H), 2.26 (m, 2H), 3.03 (m, 2H), 3.88, 3.90 (2s, 12H, 4 x OCH_3), 4.02 (dt, 1H, CHOH, J = 4, 10 Hz), 6.88 (d, 6H, ArH)
16	97	74–5	1.91 (m, 2H), 2.25 (m, 2H), 3.1 (s, 3H, OCH_3), 3.12 (m, 2H), 3.8 (t, 1H, CH-OCH_3), 3.88–3.91 (2s, 12H, 4 x OCH_3), 6.86 (d, 6H, ArH)
17	44	oil	1.83 (d, 1H, OH, J = 4 Hz), 1.95 (m, 2H), 2.28 (m, 2H), 3.05 (m, 2H), 3.81 (s, 12H, 4 x OCH_3), 4.12 (dt, 1H, CHOH, J = 4, 10 Hz), 6.35 (t, 2H, ArH), 6.5 (d, 4H, ArH)
18	90	oil	1.91 (m, 2H), 2.23 (m, 2H), 3.1 (m, 2H), 3.13 (s, 3H, OCH_3), 3.8 (s, 12H, 4 x OCH_3), 3.9 (t, 1H, CH-OCH_3), 6.35 (t, 2H, ArH), 6.51 (d, 4H, ArH)
19	62	78–9	1.68 (d, 1H, OH), 1.8 (m, 4H), 2.13 (m, 2H), 2.81 (m, 1H), 3.83, 3.87 (2s, 9H, 3 x OCH_3), 4.14 (m, 1H), 6.48 (s, 2H, ArH)
20	37	oil	1.87 (m, 2H, 1 x CH, 1 x OH), 2.25 (m, 2H), 2.51 (quintet, 1H), 3.09 (quintet, 1H), 3.48 (m, 1H), 3.85, 3.9 (2s, 18H, 6 x OCH_3), 4.4 (q, 1H), 6.52 (2s, 4H, ArH)
21	93	oil	1.79 (q, 1H), 2.04 (m, 1H), 2.3 (m, 1H), 2.5 (m, 1H), 3.16 (m, 1H), 3.32 (s, 3H, OCH_3), 3.36 (m, 1H), 3.82, 3.87 (2s, 18H, 6 x OCH_3), 3.91 (m, 1H), 6.5 (2s, 4H, ArH)

[a]Compound numbers **8–12** and **19–21** are racemic mixtures; [b]All the compounds gave satisfactory MS and/or elemental analysis.

Table II.

Comp	*PAF receptor binding inhibition, IC_{50} (μM), (human platelets)*
1	1.82
2	0.33
3	3.80
4	0.45
5	0.77
6	1.02
7	1.08
8	[b]
9	0.45[a]
10	1.47[a]
11	3.55[a]
12	0.83[a]
13	> 50.0
14	> 100.0
15	1.91
16	1.15
17	[b]
18	14.0
19	15% inhibition at 10 μM [a]
20	15% inhibition at 5 μM[a]
21	42% inhibition at 10 μM [a]
22	2.8
23	4.7

[a]Activity with racemic mixture; [b]Compound not tested.

tillation spectrometer. The amount of specific binding was calculated as the difference in cpm between the total bound [^{3}H]PAF and non specifically bound [^{3}H]PAF (bound in the presence of 3.7×10^{-7} M cold PAF). The percent inhibition of specific binding was determined by dividing the cpm specifically bound in the presence of the test compound by the cpm specifically bound in the vehicle control, multiplying by 100 and subtracting from 100. An IC_{50} (50% inhibitor concentration) value was generated by evaluating the test compound over the concentration range of 0.1–100 μM.

Chemical synthesis

All the melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Kieselgel 60 (230–400 mesh) from E Merck was used for silica gel chromatography. NMR spectra were run on a Jeol-FX200 FT NMR or Bruker-500 NMR spectrometer.

Preparation of 1,3-diarylcyclopentenes

1,3-Diarylcyclopentenes were prepared as described earlier [12].

General method for the hydroboration of 1,3-diarylcyclopentenes

To an ice-cooled solution of an appropriate 1,3-diarylcyclopentene (1 mmol) in dry THF (2ml) a solution of diborane in THF (5-9 equiv) was added. The mixture was stirred at room temperature overnight. It was cooled to 0°C and decomposed with 15% aqueous sodium hydroxide (1.25 ml) and 30% hydrogen peroxide (2.5 ml). This mixture was stirred at room temperature for 2 h and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to give a residue which was chromatographed over silica gel using a mixture of petroleum ether and ethyl acetate as the eluant to give the desired alcohols (**1**, **8**, **11**, **13**, **15** and **17**, scheme 2, table I)

Hydroboration of 1,4-bis(3,4,5-trimethoxyphenyl)cyclopentene and 1-(3,4,5-trimethoxyphenyl)cyclopentene

The procedure was essentially the same as described above for 1,3-diarylcyclopentenes to yield the desired alcohols (**19** and **20**, scheme 2, table I).

*cis-1,3-Bis(3,4,5-trimethoxyphenyl)cyclopentane (**3**)*

A solution of 1,3-bis(3,4,5-trimethoxyphenyl)cyclopentene (55 mg) was dissolved in absolute ethanol (2 ml) and to it was added 10% Pd-C (50 mg). The mixture was stirred under an atmosphere of hydrogen at room temperature for 20 h, and filtered over celite. The filtrate was concentrated and purified by silica gel chromatography using a mixture of petroleum ether and ethyl acetate (75:25) as the eluant.

General method for the preparation of ethers of cyclopentanols

To a solution of an appropriate cyclopentanol (0.4 mmol) in dry THF (3 ml) sodium hydride (10 equiv) was added followed by alkyl halide (10 equiv). The mixture was heated at 40°C for 4 h (12 h in the case of heptyl bromide and at 100°C for 16 h in the case of 2-methyl-1-iodopropane). The mixture was cooled in an ice bath, decomposed with brine, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated and chromatographed over silica gel using a mixture of petroleum ether and ethyl acetate as the eluant to yield the desired ethers (**2**, **4–6**, **9**, **12**, **14**, **16**, **18** and **21**, scheme 2, table I).

*1α-Acetoxy-2β, 5β-bis(3,4,5-trimethoxyphenyl)cyclopentane (**7**)*

To an ice cooled solution of (1α, 2β, 5β)-2,5-bis(3,4,5-trimethoxyphenyl)cyclopentanol (100 mg) in methylene chloride (1 ml) and pyridine (1 ml) acetic anhydride (4 equiv) was added. The mixture was stirred at room temperature for 3 h, evaporated *in vacuo* and the residue was chromatographed over silica gel using a mixture of petroleum ether and ethyl acetate (65:35) as the eluant.

*1α-Methoxy-2β-(3,4,5-trimethoxyphenyl)-5β-(3,5-dimethoxy-4-hydroxyphenyl)cyclopentane (**10**)*

To a solution of 1α-methoxy-2β-(3,4,5-trimethoxyphenyl)-5β-3,5-dimethoxy-4-benzyloxyphenyl)cyclopentane (150 mg) in absolute ethanol (3 ml) and ethyl acetate (1 ml) 10% Pd-C (30 mg) was added and the mixture was stirred under an atmosphere of hydrogen at room temperature for 12 h. It was filtered over celite and purified by silica gel chromatography using a mixture of petroleum ether and ethyl acetate (1:1) as the eluant.

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