Synthesis and Platelet-Activating Factor (PAF)-Antagonistic Activities of 1,4-Disubstituted Piperazine Derivatives

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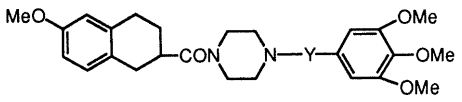
During the screening of novel platelet-activating factor (PAF) antagonists, we found that 1-(6-methoxy-3,4-dihydro-2-naphthoyl)-4-(3,4,5-trimethoxybenzyl)piperazine and its 4-(3,4,5-trimethoxybenzoyl)piperazine derivatives (1b, 2b) exerted *in vitro* and *in vivo* PAF-antagonistic activities. Modifications of the 1-acyl group, the substituent at the 4-position and the piperazine ring of 1a and 2b were examined and from this series 1-(2,3-dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)-4-(3,4,5-trimethoxybenzoyl)piperazine (2g) was found to be one of the most potent PAF antagonists.

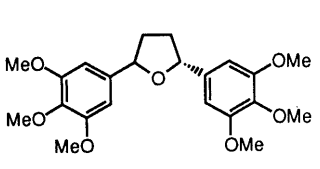
Keywords PAF antagonist; structure–activity relationship; 1,4-disubstituted piperazine; 1-(6-methoxy-3,4-dihydro-2-naphthoyl)-4-(3,4,5-trimethoxybenzyl)piperazine; 1-(2,3-dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)-4-(3,4,5-trimethoxybenzoyl)piperazine

Platelet-activating factor (PAF) is an ether phospholipid which possesses potent platelet-aggregating, proinflammatory, smooth-muscle-contractile and hypotensive activities, and appears to be crucial in the pathogenesis of bronchial asthma and in the lethality of endotoxin shock and anaphylactic shock.[1,2] Intensive efforts to find drugs which attenuate the effects of PAF using a variety of *in vitro* screening techniques have resulted in the discovery of a number of specific PAF antagonists, some of which are being tested for their clinical effectiveness.[3–6] During the screening of novel PAF antagonists using the assays for the inhibitory activities against PAF-induced platelet aggregation of rabbit plasma (*in vitro*) and PAF-induced hypotension in conscious rats (*in vivo*, *p.o.*), we found that 1-(6-methoxy-3,4-dihydro-2-naphthoyl)-4-(3,4,5-trimethoxybenzyl)piperazine and its 4-(3,4,5-trimethoxybenzoyl)piperazine derivatives (**1b**, **2b**) exerted *in vitro* and *in vivo* PAF-antagonistic activities, and we have conducted modification studies aiming the improvement of these activities. Initial modifications of **1b** by aromatization to **3** and saturation to **4**, resulted in the reduction of *in vitro* and/or *in vivo* activities. Therefore, we successively examined modifications of the ethylene moiety ($-CH_2CH_2-$) in the dihydronaphthalene ring at the 1 position of the piperazine ring, trimethoxybenzyl or trimethoxybenzoyl moiety at the 4-position of the piperazine ring, and the piperazine ring, and evaluated the activities of the resulting compounds in comparison with those of L-652731[7] and WEB-2086.[6] In this paper, we describe the structure–activity relationships (SARs) in PAF-antagonistic activities of 1,4-disubstituted piperazine derivatives and related compounds.

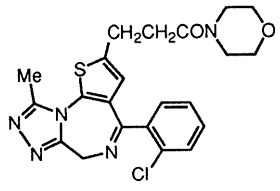


1b : Y = CH_2

2b : Y = CO



L-652731

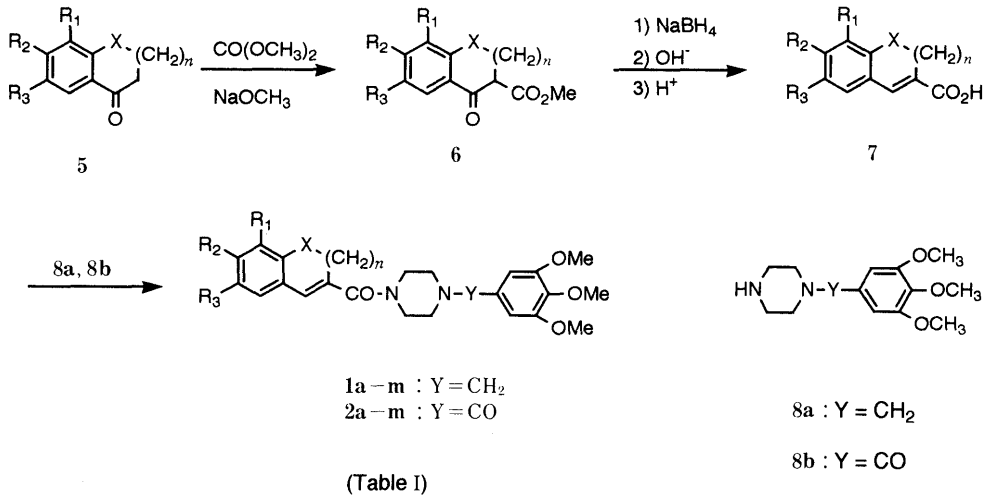


WEB-2086

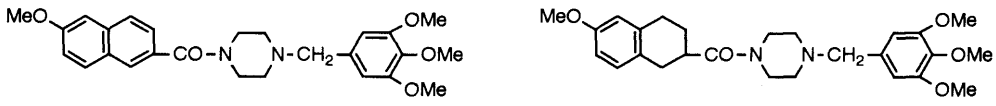
Chart 1

Synthesis

1-Acyl-4-(3,4,5-trimethoxybenzyl)- and 1-acyl-(3,4,5-trimethoxybenzoyl)piperazine derivatives (**1a—k**, **2a—k**) were synthesized by coupling benzocycloalkenoic acids (**7a—k**) with 1-(3,4,5-trimethoxybenzyl)piperazine (**8a**)[8] or 1-(3,4,5-trimethoxybenzoyl)piperazine (**8b**)[9] as shown in Chart 2. Benzocycloalkenoic acids were prepared from benzocycloalkanones by the following four-step procedure, which is similar to that described by Jacques and Horeau.[10] Methoxycarbonylation of benzocycloalkanones (**5a—k**) using dimethyl carbonate and sodium methoxide in methanol provided the α-methoxycarbonyl derivatives (**6a—k**, Table V). Sodium borohydride ($NaBH_4$) reduction of these β-oxo-esters (**6a—k**), subsequent alkaline hydrolysis and finally dehydration in a solution of dioxane containing concentrated hydrochloric acid afforded the desired bezocycloalkenoic acids (**7a—k**, Table VI). Conversion of **7a—k** into the corresponding acid chlorides with thionyl chloride and subsequent condensation with **8a, b** (method A) or treatment of **7a—k** and **8a, b** with diethyl phosphorocyanidate (DEPC) in *N*,*N*-dimethylformamide (DMF) (method B) gave 1-acyl-4-(3,4,5-trimethoxybenzyl)- and 1-acyl-4-(3,4,5-trimethoxybenzoyl)piperazines (**1a—k**, **2a—k**). Similarly, **3** and **4** were prepared by acylation of **8b** with 6-methoxynaphthoic acid and 6-methoxy-1,2,3,4-



5 6 7



3 4

Chart 2

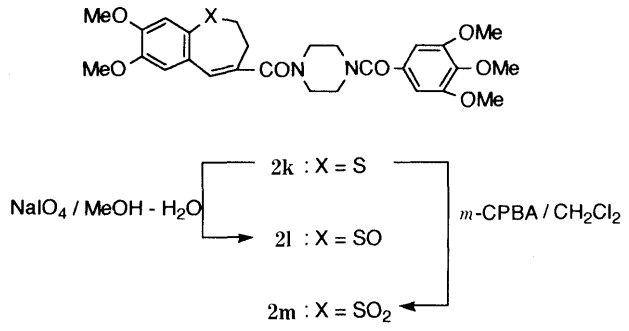


Chart 3

tetrahydro-2-naphthoic acid.

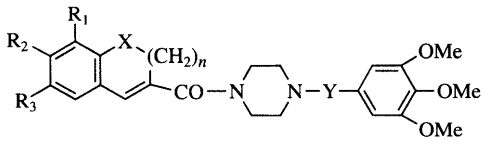
Oxidation of **2k** with sodium periodate in aqueous methanol or with two equivalents of *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride gave its sulfoxide (**21**) and sulfone (**2m**) derivatives, respectively (Chart 3). The physicochemical properties of the compounds thus obtained (**1a—m**, **2a—m**, **3**, **4**) are summarized in Table I.

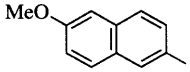
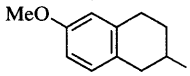
Modification of the spacer between the piperazine ring and the aromatic substituents at the 1- and 4-positions of **1** and **2** was carried out in the **g** series fixing the 2,3-dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-2-yl moiety and the 3,4,5-trimethoxyphenyl ring (Chart 4, Table II). Amidation of 2,3-dimethoxy-6,7-dihydro-5*H*-benzocyclophepten-8-carboxylic acid (**7g**) with *N*-(3,4,5-trimethoxythiobenzoyl) (**8c**),[11] *N*-(3,4,5-trimethoxybenzenesulfonyl) (**8d**), *N*-(3,4,5-trimethoxyphenyl) (**8e**),[12] *N*-(3,4,5-trimethoxyphenethyl) (**8f**) and *N*-(3,4,5-trimethoxyphenylacetyl)piperazine (**8g**) afforded compounds with a variety of spacers between the piperazine and 3,4,5-trimethoxyphenyl rings (**11—15**). 1-(2,3-Dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)piperazine (**9a**) obtained by coupling **7g** with 1-formylpiperazine, followed by selective deformylation in dilute hydrochloric acid was converted into its thiocarbonyl derivative (**9b**) using Lawesson's reagent.[13] Acylation of **9b** with 3,4,5-trimethoxybenzoyl chloride gave the 1-benzocycloheptenethiocarbonyl derivative (**16**). Mannich reaction of 2,3-dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-5-one (**5g**) with paraformaldehyde and **8a,b** gave Mannich bases (**10a,b**), which were led to 1-benzocycloheptenylmethylpiperazine derivatives (**17**, **18**) by $NaBH_4$ reduction and subsequent dehydration.

The 4-(2,3,4-trimethoxybenzoyl) derivative (**19**) was prepared by condensation of **9g** with 2,3,4-trimethoxybenzoyl chloride. The compounds thus prepared (**11—19**) are listed in Table II.

Replacement of the piperazine ring including the spacer between the *N*-heterocyclic ring and the 3,4,5-trimethoxyphenyl group was the final structural feature examined. The required amines, *i.e.*, 4-(3,4,5-trimethoxybenzoyl)-aminopiperidine **20b**, 4-(3,4,5-trimethoxybenzoyl)oxypiperidine (**20d**), 4-(3,4,5-trimethoxyanilino)piperidine (**20e**), and 4-(3,4,5-trimethoxyphenoxyl)piperidine (**20f**), were synthesized as follows. Acylation of 4-amino-1-benzylpiperidine or 1-benzyl-4-hydroxypiperidine with 3,4,5-trimethoxybenzoyl chloride and subsequent catalytic reduction using 5% palladium charcoal afforded **20b** and **20d**, respectively. Reductive amination of 1-benzyl-4-piperidone with 3,4,5-trimethoxyaniline and subsequent debenzylation by catalytic reduction gave **20e**. Mitsunobu reaction of 1-benzyl-4-hydroxypiperidine with 3,4,5-trimethoxyphenol and subsequent debenzylation gave **20f**. Know amines, 1-(3,4,5-trimethoxybenzoyl)-1,2,3,4,5,6-hexahydro-1,4-diazepine (**20a**),[14] 3-(3,4,5-tri-

TABLE I. Physicochemical Data for 1-Acyl-4-(3,4,5-trimethoxybenzoyl)piperazines and 1-Acyl-4-(3,4,5-trimethoxybenzyl)piperazines (**1a—m**, **2a—m**, **3**, **4**)

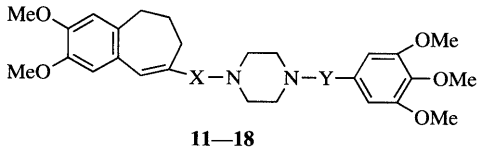


Compd. No.	R_1	R_2	R_3	X	*n*	Y	Method[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
											C	H	N
1a	H	MeO	MeO	CH_2	0	CH_2	B	88	240—250	$C_{26}H_{32}N_2O_6 \cdot HCl \cdot 1/2H_2O$	60.75 (60.85)	6.67 6.66	5.45 5.44)
2a	H	MeO	MeO	CH_2	0	CO	A	94	183—185	$C_{26}H_{30}N_2O_7$	64.71 (64.77)	6.26 6.31	5.81 5.76)
1b	H	MeO	H	CH_2	1	CH_2	A	60	210—215	$C_{26}H_{32}N_2O_5 \cdot HCl$	63.86 (63.66)	6.80 6.88	5.73 5.62)
2b	H	MeO	H	CH_2	1	CO	A	83	128—130	$C_{26}H_{30}N_2O_6$	66.94 (67.04)	6.48 6.51	6.00 6.04)
1c	H	MeO	MeO	CH_2	1	CH_2	A	66	215—220	$C_{27}H_{34}N_2O_6 \cdot HCl$	62.48 (62.40)	6.80 6.85	5.40 5.31)
2c	H	MeO	MeO	CH_2	1	CO	A	94	183—185	$C_{27}H_{32}N_2O_7$	65.31 (65.50)	6.50 6.53	5.64 5.64)
1d	H	EtO	EtO	CH_2	1	CH_2	A	87	204—208	$C_{29}H_{38}N_2O_6 \cdot HCl$	63.67 (63.54)	7.19 7.13	5.12 5.11)
2d	H	EtO	EtO	CH_2	1	CO	A	90	127—129	$C_{29}H_{36}N_2O_7$	66.40 (66.42)	6.92 6.88	5.34 5.32)
1e	H	*n*-PrO	*n*-PrO	CH_2	1	CH_2	A	80	203—207	$C_{31}H_{42}N_2O_6 \cdot HCl$	64.74 (64.73)	7.54 7.61	4.83 4.87)
2e	H	*n*-PrO	*n*-PrO	CH_2	1	CO	A	92	124—126	$C_{31}H_{40}N_2O_7$	67.37 (67.49)	7.30 7.33	5.07 5.05)
1f	MeO	MeO	MeO	CH_2	1	CH_2	B	72	203—206	$C_{28}H_{36}N_2O_7 \cdot HCl \cdot 1/2H_2O$	60.26 (60.27)	6.86 6.81	5.02 4.90)
2f	MeO	MeO	MeO	CH_2	1	CO	A	97	172—173	$C_{28}H_{36}N_2O_8$	63.87 (63.83)	6.51 6.55	5.32 5.27)
1g	H	MeO	MeO	CH_2	2	CH_2	A	74	195—203	$C_{28}H_{36}N_2O_6 \cdot HCl \cdot 1/2H_2O$	62.04 (61.78)	7.07 7.24	5.17 5.10)
2g	H	MeO	MeO	CH_2	2	CO	A	97	164—165	$C_{28}H_{34}N_2O_7$	65.87 (65.87)	6.71 6.75	5.49 5.44)
1h	MeO	MeO	H	CH_2	2	CH_2	B	43	225—229	$C_{28}H_{36}N_2O_6 \cdot HCl$	63.09 (62.71)	7.00 7.07	5.26 5.15)
2h	MeO	MeO	H	CH_2	2	CO	A	92	133—134	$C_{28}H_{34}N_2O_7$	65.87 (65.84)	6.71 6.79	5.49 5.52)
1i	H	MeO	MeO	CH_2	3	CH_2	A	93	200—203	$C_{29}H_{38}N_2O_6 \cdot HCl$	63.67 (63.67)	7.19 7.20	5.12 5.03)
2i	H	MeO	MeO	CH_2	3	CO	A	78	170—171	$C_{29}H_{36}N_2O_7$	66.40 (66.50)	6.92 7.00	5.34 5.28)
1j	H	MeO	MeO	O	2	CH_2	A	61	208—210	$C_{27}H_{34}N_2O_7 \cdot HCl \cdot 1/2H_2O$	59.61 (60.00)	6.67 6.57	5.17 5.20)
2j	H	MeO	MeO	O	2	CO	A	98	132—134	$C_{27}H_{32}N_2O_8$	63.27 (63.23)	6.29 6.39	5.47 5.34)
1k	H	MeO	MeO	S	2	CH_2	A	83	187—189	$C_{27}H_{34}N_2O_6S \cdot HCl \cdot 1/2H_2O$	57.90 (58.33)	6.48 6.44	5.00 4.97)
2k	H	MeO	MeO	S	2	CO	A	85	113	$C_{27}H_{32}N_2O_7S$	61.35 (61.48)	6.10 6.20	5.30 5.24)
2l	H	MeO	MeO	SO	2	CO	C	83	138	$C_{27}H_{32}N_2O_8S \cdot 1/2H_2O$	58.57 (58.35)	6.01 5.87	5.06 4.90)
2m	H	MeO	MeO	SO_2	2	CO	C	83	226—229	$C_{27}H_{32}N_2O_9S \cdot H_2O$	56.04 (56.34)	5.92 5.67	4.84 4.78)
3						CH_2	B	48	169—173	$C_{26}H_{30}N_2O_5 \cdot HCl$	61.83 (62.10)	6.59 6.52	5.55 5.49)
4						CH_2	B	67	220—225	$C_{26}H_{34}N_2O_5 \cdot HCl$	63.60 (63.56)	7.18 7.20	5.71 5.72)

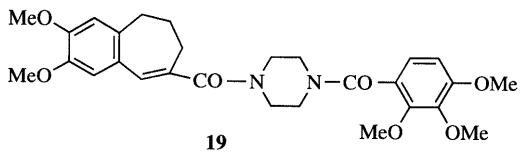
a) Method A: acylation of **8a**, **8b** with acid chloride. Method B: condensation of acids with **8a**, **8b** using DEPC. Method C: see experimental section.

methoxybenzoyl)aminopiperidine (**20c**),[15] and 2-(3,4,5-trimethoxybenzoyl)aminoethylamine (**20g**),[16] were prepared according to the cited methods. Condensation of **7g** with various amines (**20a—g**) gave compounds **21—26** (Chart 5, Table III).

TABLE II. Physicochemical Data for 1,4-Disubstituted Piperazines (**11**—**19**)



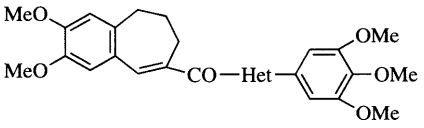
11—**18**

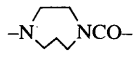
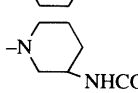
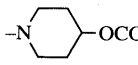
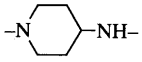
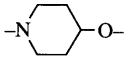
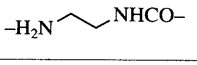


19

Compound No.	X	Y	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
						C	H	N	C	H	N
11	CO	CS	94	172—173	$C_{28}H_{34}N_2O_6S$	63.86	6.51	5.32	63.59	6.54	5.31
12	CO	SO_2	79	180—181	$C_{27}H_{34}N_2O_8S$	59.33	6.27	5.12	59.17	6.14	5.17
13	CO	—	88	161—162	$C_{27}H_{34}N_2O_6$	67.20	7.10	5.80	66.96	7.20	5.59
14	CO	$(CH_2)_2$	96	245—250	$C_{29}H_{38}N_2O_6 \cdot HCl$	63.67	7.19	5.12	63.42	7.24	5.01
15	CO	$COCH_2$	87	114—115	$C_{29}H_{36}N_2O_7$	66.40	6.92	5.34	66.25	7.04	5.52
16	CS	CO	90	204—206	$C_{28}H_{34}N_2O_6S$	63.86	6.51	5.32	63.68	6.52	5.19
17	CH_2	CH_2	83	155—156	$C_{28}H_{38}N_2O_5$	69.68	7.94	5.80	69.78	8.03	5.70
18	CH_2	CO	70	235—240	$C_{28}H_{36}N_2O_6 \cdot HCl$	63.09	7.00	5.26	62.93	7.01	5.24
19	—	—	87	125—126	$C_{28}H_{34}N_2O_7$	65.87	6.71	5.49	65.99	6.75	5.40

TABLE III. Physicochemical Data for *N*-Heterocyclic Ring Derivatives (**21**—**27**)



Compound No.	Het	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
					C	H	N	C	H	N
21		71	a)	$C_{29}H_{36}N_2O_7$	64.19	7.06	5.16	64.29	7.05	4.89
22		85	198—200	$C_{29}H_{36}N_2O_7$	66.40	6.92	5.34	66.54	6.95	5.29
23		83	164—166	$C_{29}H_{36}N_2O_7$	66.40	6.92	5.34	66.20	6.95	5.29
24		87	126—128	$C_{29}H_{35}NO_8$	66.27	6.71	2.66	66.08	6.60	2.55
25		68	118—120	$C_{28}H_{36}N_2O_6$	67.72	7.31	5.64	67.53	7.16	5.42
26		87	128—129	$C_{28}H_{35}NO_7$	67.59	7.09	2.81	67.48	7.21	2.86
27		64	169—173	$C_{26}H_{32}N_2O_7$	64.44	6.66	5.78	64.61	6.68	5.56

a) Amorphous powder.

Biological Results and Discussion

PAF-antagonistic activities of 1,4-disubstituted piperazines and related compounds synthesized in the present study were evaluated in terms of inhibitory activities on PAF-induced rabbit platelet aggregation (*in vitro*) and PAF-induced hypotension in rats (*in vivo*).[17] The results are shown in Table IV.

1-Acyl-4-(3,4,5-trimethoxybenzyl)- and 1-acyl-4-(3,4,5-trimethoxybenzoyl)piperazine derivatives (**1a**—**k**, **2a**—**k**) showed potent PAF-antagonistic activities. Among modifications of the methylene moiety in the dihydronaphthalene ring at the 1-position, the inhibitory potency increased in the order of **1g**, **2g** > **1c**, **2c**, **1i**, **2i** > **1a**, **2a**. Transformation of the benzocycloheptene ring (**1g**, **2g**) into the benzoxepine ring (**1j**, **2j**) and the benzothiepine ring (**1k**, **2k**) analogues resulted in no significant reduction in activities. Oxidation of the sulfide group (**21**, **2m**) reduced both *in vitro* and *in vivo* activities. Alkoxy substituents on the phenyl ring of the 1-acyl groups influenced the biological activities; 6,7-dimethoxy substituents (**1c**, **2c**) in the dihydronaphthalene series and a 2,3-dimethoxy arrangement (**1g**, **2g**) in the 5,6-dihydro-5*H*-benzocycloheptene ring gave optimum activity (Table IV). Increasing hydrophobicity of the alkoxy group

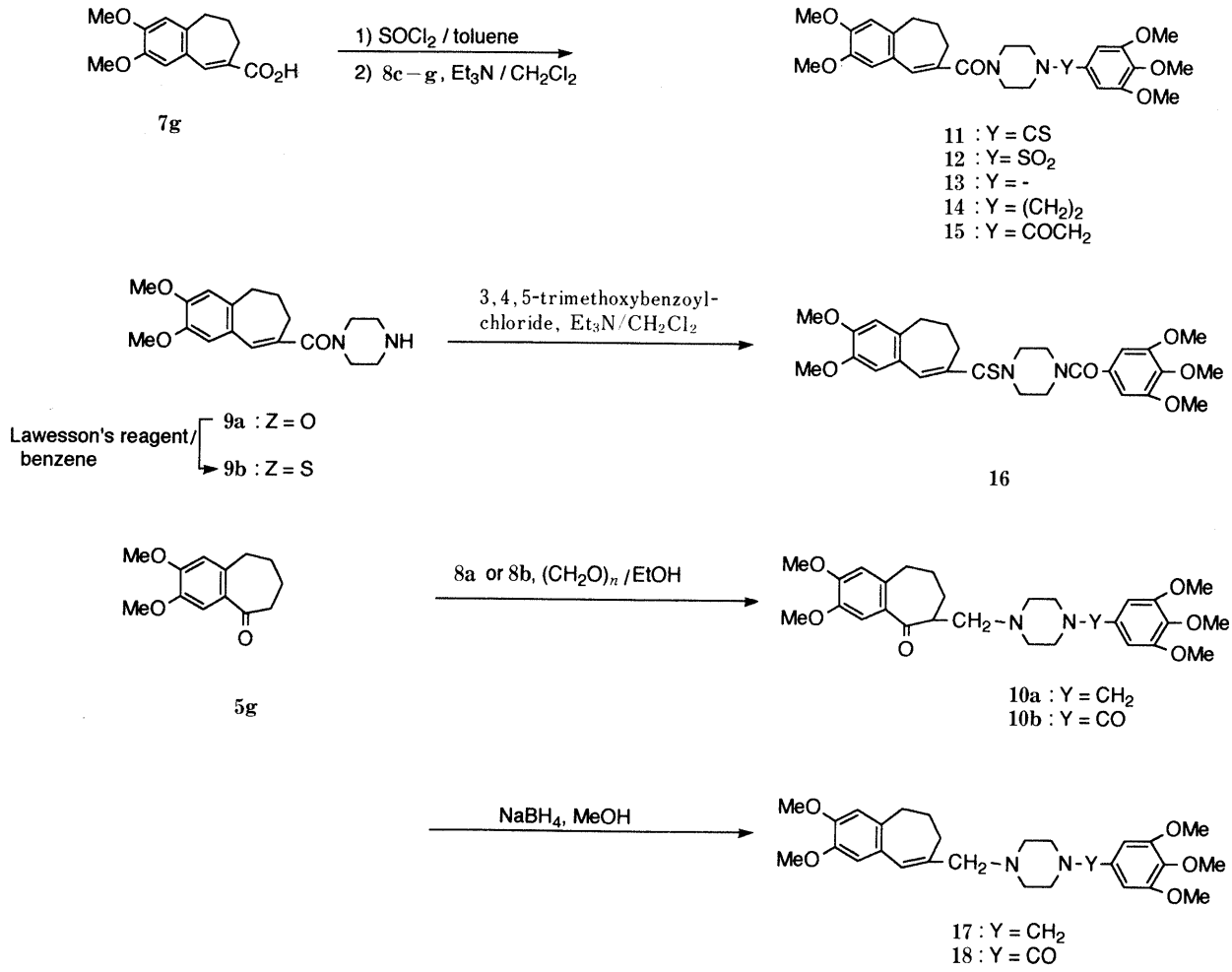


Chart 4

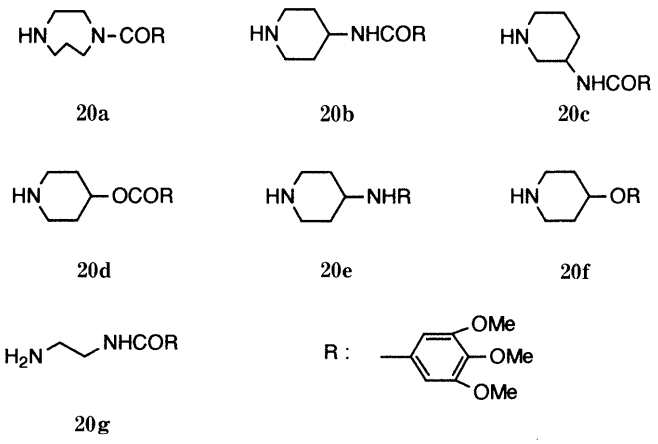


Chart 5

(**1c**→**1d**, **1e**) enhanced *in vitro* affinity toward the PAF receptor, but decreased the inhibitory potency against PAF-induced hypotension in rats (*in vivo*). Modifications of the spacers between the piperazine ring and the aromatic moieties at the 1- and 4-positions gave compounds **11**—**18**. The 4-(3,4,5-trimethoxythiobenzoyl) derivatives (**11**) showed enhanced activities, and the 1-thiocarbonyl derivative (**16**) showed comparable activity to **11** *in vitro*. PAF-antagonistic activities *in vitro*, however, were reduced by other transformations of the carbonyl group or the methylene moiety at the 4-position to give the sulfonyl (**12**), ethylene (**14**) and acetyl (**15**) compounds, or by deletion of the spacer (**13**). The 1-(2,3-dimethoxy-5,6-dihydro-5*H*-benzocyclohepten-8-yl)methyl derivatives (**17**, **18**) diminished the activities. The presence of the 3,4,5-trimethoxybenzoyl moiety at the 4 position was thought to be critical for biological activity because its replacement by a 2,3,4-trimethoxybenzoyl group (**19**) markedly reduced both *in vitro* and *in vivo* activities. In this series of 1,4-disubstituted piperazine derivatives, compounds **2g** and **2j** showed the most potent inhibition of PAF-induced platelet aggregation and of PAF-induced hypotension in rat (*p.o.*). Compared with L-652731 and WEB-2086, 1,4-disubstituted piperazine derivatives showed lower affinities for PAF-receptors, but more potent activities against PAF-induced hypotension *in vivo*. Modification of the piperazine ring (**21**—**27**) gave the following results; the 4-(3,4,5-trimethoxybenzoyl)-1,2,3,4,5,6-hexahydro-1,4-diazepine (**21**), as well as the 3-(3,4,5-trimethoxybenzoyl)amino- (**23**), 4-(3,4,5-trimethoxyanilino)- (**25**) and 4-(3,4,5-trimethoxyphenoxyl)-piperidine (**26**) compounds, retained PAF-antagonistic activities, but, the 4-(3,4,5-trimethoxybenzoyl)amino (**22**) and 4-(3,4,5-trimethoxybenzoyl)-oxypiperidine (**24**), and the ring-opened compound (**27**) did not inhibit PAF-

TABLE IV. PAF-Antagonistic Activities of 1,4-Disubstituted Piperazine Derivatives and Related Compounds

Compound No.	Inhibitory activities against PAF-induced platelet aggregation[a] (% inhibition)			Inhibitory activities against PAF-induced hypotension in rats[b] (% inhibition)					
	3×10^{-7}	3×10^{-6}	3×10^{-5} M	Dose (*p.o.*) (mg/kg)	1 h	2 h	4 h	6 h	8 h
1a	—	0	34	30	77	58	23	3	—
2a	—	—	26	30	86	82	74	40	20
1b	—	16	100	30	74	56	40	12	5
2b		—	80	30	100	100	97	60	—
1c		32	100	30	77	75	49	30	—
				10	49	53	25	10	—
2c	—	30	100	30	100	97	88	79	61
				10	99	91	70	41	22
1d	—	34	100	30	88	95	65	52	26
2d	—	64	100	30	100	100	77	58	55
				3	59	30	15	5	3
1e	—	43	100	30	79	69	60	33	2
2e	—	85	100	30	82	81	59	48	34
1f	—	10	87	30	75	60	4	—	—
2f	—	9	100	30	89	84	61	—	—
1g	—	28	100	30	94	97	88	72	41
				10	95	83	41	26	13
				3	79	66	33	17	3
2g	—	64	99	30	100	100	100	100	87
				10	100	100	93	89	74
				3	78	72	53	24	18
1h	—	20	88	30	65	52	21	0	—
2h	—	—	77	30	73	57	26	—	—
1i	—	20	100	30	100	100	73	44	31
2i	—	23	100	30	100	100	100	91	75
1j	—	12	100	30	100	97	70	75	52
2j	—	45	100	30	97	100	100	95	99
				10	100	100	87	82	61
				3	74	70	44	33	28
1k	—	8	78	30	94	94	67	49	45
2k	—	20	100	30	94	91	78	64	54
2l	—	—	50	30	7	0	8	—	—
2m	—	—	73	30	7	12	12	—	—
3	—	—	87	30	81	81	64	48	—
4	—	—	28	30	47	34	14	—	—
11	—	100	100	30	96	100	100	100	96
				10	93	99	99	96	85
				3	72	69	60	38	27
12	—	—	21	30	7	5	—	—	—
13	—	—	13	30	0	10	—	—	—
14	—	—	3	30	22	20	—	—	—
15	—	—	0	30	0	20	—	—	—
16	3	56	100	30	2	14	39	22	—
17	—	—	18	30	5	7	7	7	—
18	—	—	37	30	64	79	71	60	30
19	—	—	0	30	9	12	—	—	—
21	—	0	100	30	86	86	72	64	—
22	—	—	2	30	6	6	2	—	—
23	—	8	97	30	26	42	57	60	54
24	—	—	0	30	5	3	3	—	—
25	—	16	100	30	61	79	79	73	56
26	—	2	100	30	61	75	88	91	90
				10	30	48	51	50	39
27	—	—	6	30	10	10	3	—	—
L-652731	12	88	99	30	34	63	49	31	—
				10	19	23	15	12	—
WEB-2086	81	100	—	30	85	81	59	45	17
				10	55	61	33	20	6
				3	20	19	16	13	6

a) Percent inhibition of platelet aggregation induced by PAF (3.0—10 nM). *b*) Percent inhibition of hypotension induced by PAF (0.5 μg/kg) in rats.

induced platelet aggregation. These results indicate that the manifestation of biological activities requires a particular spatial arrangement between the two aromatic moieties as well as polyalkoxy substituents and a carbonyl oxygen at the 1-position of the piperazine ring and that the piperazine or piperidine ring should provide a dom-

inant framework, in conformationally restricting the two aromatic rings. Further modification of the piperazine ring of **2g** will be dealt with in a subsequent paper.[18]

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus (hot stage type) and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi 260-01 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in the indicated solvents on a Varian EM-390 instrument. Chemical shifts are reported as δ-values relative to tetramethylsilane (TMS) as internal standard.

Starting Benzocycloalkanones and Related Compounds 5,6-Dimethoxy-1-indanone (**5a**) and 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**5b**) are commercially available (Aldrich Chemical Company, Inc.). 6,7-Dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone (**5c**),[19] 2,3-dimethoxy- (**5g**),[20] 3,4-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**5h**),[21] and 2,3-dimethoxy-5,6,7,8,9,10-hexahydrobenzocycloocten-5-one (**5i**)[22] were prepared according to the cited methods. Other materials were synthesized as described below.

6,7-Diethoxy-3,4-dihydro-1(2*H*)-naphthalenone (5d) A mixture of 6,7-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**5g**),[23] diethyl sulfate (13 g), anhydrous K_2CO_3 (13.6 g) and acetone (150 ml) was refluxed with stirring for 6 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in H_2O and AcOEt, and the organic layer was separated, washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was recrystallized from AcOEt–hexane to give **5d** (5.9 g, 90% yield) as colorless needles, mp 77—78 °C. IR ν_{max}^{KBr} cm^{-1}: 2930, 1660, 1590, 1500, 1360. ^{1}H-NMR ($CDCl_3$) δ: 1.41, 1.45 (6H, t, J=7.5 Hz, $OCH_2\underline{CH}_3$), 2.13 (2H, m, C_3-H), 2.60 (2H, t, J=6 Hz, C_4-H), 2.87 (2H, t, J=6 Hz, C_2-H), 4.12, 4.14 (4H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.65 (1H, s, C_8-H), 7.50 (1H, s, C_5-H). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.91; H, 7.86.

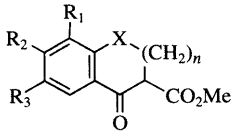
6,7-Dipropoxy-3,4-dihydro-1(2*H*)-naphthalenone (5e) Similarly, **5e** was prepared by alkylation of 6,7-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone with 1-iodopropane and anhydrous K_2CO_3 in DMF in 77% yield. Recrystallization from Et_2O–hexane gave colorless needles, mp 63—64 °C. *Anal.* Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.32; H, 8.46.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1-benzoxepin-5-one (5j) A mixture of 3,4-dimethoxyphenol (10 g), ethyl 4-bromobutyrate (15.2 g), anhydrous K_2CO_3 (11.7 g) and DMF (40 ml) was stirred at 70 °C for 15 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A solution of NaOH (6.8 g) in MeOH (30 ml) and H_2O (60 ml) was added to the residue, and the mixture was stirred at 60 °C for 40 min, then concentrated to *ca.* 60 ml *in vacuo*. The residual mixture was acidified with 10% HCl (pH 3) and extracted with AcOEt. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from AcOEt–hexane to yield 4-(3,4-dimethoxyphenoxy)butyric acid (12.5 g; 81% yield) as colorless prisms, mp 90—91 °C. A mixture of this acid (6 g) and polyphosphoric acid (50 g) was agitated at 100 °C for 30 min. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was crystallized from AcOEt–hexane to yield **5j** (4.55 g; 82% yield) as colorless prisms, mp 87—88 °C. IR ν_{max}^{KBr} cm^{-1}: 1660, 1600, 1500, 1440, 1370, 1260, 1140, 1060, 1010. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (2H, m, C_3-H), 2.87 (2H, t, J=7.5 Hz, C_4-H), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.22 (2H, t, J=7.0 Hz, C_2-H), 6.58 (1H, s, C_6-H), 7.30 (1H, s, C_9-H). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.85; H, 6.38.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1-benzothiepin-5-one (5k) A 2.5 M solution of ethanolic sodium ethoxide (77 ml) was added to a solution of 3,4-dimethoxythiophenol (28 g) in EtOH (50 ml) and the whole was refluxed for 10 min. Then γ-butyrolactone (18.5 g) was added, and the mixture was refluxed for 3 h. The reaction mixture was poured into ice-water and the mixture was concentrated to *ca.* 100 ml *in vacuo*. The resultant mixture was acidified with 1 N HCl and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from AcOEt to give 4-(3,4-dimethoxythiophenoxy)butyric acid (20.8 g) as colorless prisms, mp 78 °C. The acid was mixed with polyphosphoric acid (183 g) and the mixture was stirred at 100 °C for 2 h. The reaction mixture was poured into ice-water (500 ml) and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane : AcOEt = 5 : 1) to give **5k** (12.0 g; 92% yield) as colorless prisms (from hexane–CH_2Cl_2), mp 128—129 °C. IR ν_{max}^{KBr} cm^{-1}: 2930, 1660, 1590, 1250. ^{1}H-NMR ($CDCl_3$) δ: 2.00—3.16 (6H, m, $C_{2,3,4}$-H), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.87 (1H, s, C_9-H), 7.37 (1H, s, C_6-H), *Anal.* Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.62; H, 6.00.

Methyl 2,3-Dimethoxy-5-oxo-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-carboxylate (6g) A mixture of **5g** (10 g), $NaOCH_3$ (11.2 g) and dimethylcarbonate (150 ml) was heated under reflux in a stream of N_2 for 8 h. After cooling, the reaction mixture was treated with 1 N HCl (210 ml) and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crystalline solid obtained was recrystallized from EtOH to give **6g** (11.1 g;

TABLE V. Physicochemical Data for Methoxycarbonyl-Substituted Benzocycloalkenones (**6a—k**)



Compound No.	R_1	R_2	R_3	X	n	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Found C	Found H
6a	H	MeO	MeO	CH_2	0	86	162—163	$C_{13}H_{14}O_5$	62.39	5.64	62.32	5.63
6b	H	MeO	H	CH_2	1		[a]					
6c	H	MeO	MeO	CH_2	1		[b]					
6d	H	EtO	EtO	CH_2	1	88	115—116	$C_{16}H_{20}O_5$	65.74	6.90	65.74	6.93
6e	H	*n*-PrO	*n*-PrO	CH_2	1	96	116—117	$C_{18}H_{24}O_5$	73.25	8.45	73.32	8.56
6f	MeO	MeO	MeO	CH_2	1		[c]					
6g	H	MeO	MeO	CH_2	2	88	91—92	$C_{15}H_{18}O_5$	64.74	6.52	64.65	6.58
6h	MeO	MeO	H	CH_2	2	82	Oil	$C_{15}H_{18}O_5$	64.74	6.52	64.38	6.63
6i	H	MeO	MeO	CH_2	3	85	Oil	$C_{16}H_{20}O_5$	65.74	6.90	65.51	7.20
6j	H	MeO	MeO	O	2	78	120—121	$C_{14}H_{16}O_6$	60.00	5.75	59.91	5.71
6k	H	MeO	MeO	S	2	80	132—133	$C_{14}H_{16}O_5S$	56.74	5.44	56.51	5.46

a) MM. J. Jacques, A. Horeau, *Bull. Soc. Chim. Fr.*, **1950**, 512. *b*) M. M. Hashem, K. D. Berlin, R. W. Chenut, N. N. Durhan, *J. Med. Chem.*, **19**, 229 (1976). *c*) E. A. Mawdsley, K. D. Berlin, R. W. Chenut, N. N. Durhan, *J. Med. Chem.*, **19**, 239 (1976).

88% yield) as colorless needles, mp 91—92 °C. IR ν_{max}^{KBr} cm^{-1}: 2950, 1740, 1630, 1600, 1570, 1510, 1440, 1360, 1240, 1200, 1130, 1090. ^{1}H-NMR ($CDCl_3$) δ: 1.8—3.15 (7H, m), 3.81 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.65—7.5 (2H, m). *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.65; H, 6.58.

Compounds **6a—k** were similarly prepared, and their physicochemical properties are summarized in Table V.

2,3-Dimethoxy-6,7-dihydro-5*H*-benzocycloheptene-8-carboxylic Acid (7g) A solution of **6g** (82 g) in MeOH (500 ml) and CH_2Cl_2 (500 ml) was treated with $NaBH_4$ (10 g) in small portions at room temperature with stirring over a period of 2 h. The reaction mixture was then stirred for a further 30 min, poured into ice-water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A 10% NaOH solution (350 ml) was added dropwise to a solution of the above residue in MeOH (50 ml) and the mixture was stirred at room temperature for 1 h. After acidification with concentrated HCl (100 ml), the reaction mixture was extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Concentrated HCl (40 ml) was added to a solution of this residue in dioxane (200 ml) and the mixture was stirred at 90 °C for 40 min. The reaction mixture was concentrated to *ca.* 40 ml, then poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from AcOEt to yield **7g** (54 g; 74% yield) as colorless prisms, mp 158—159 °C. IR ν_{max}^{KBr} cm^{-1}: 3600—2000, 1670, 1600, 1570, 1520, 1450, 1360, 1240, 1120, 1030, 850. ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.95 (6H, m), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.68 (1H, s, C_9-H), 6.86 (1H, s), 7.80 (1H, s). *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.63; H, 6.50. Found: C, 67.97; H, 6.55.

Compounds **7a—k** were similarly prepared, and their physicochemical properties are listed in Table VI.

1-(2,3-Dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)-4-(3,4,5-trimethoxybenzoyl)piperazine (2g) Method A: A mixture of **7g** (0.5 g), $SOCl_2$ (1 ml) and toluene (10 ml) was stirred at 100 °C for 30 min and then concentrated *in vacuo*. A solution of the above-obtained acid chloride in CH_2Cl_2 (8 ml) was added dropwise to a solution of 1-(3,4,5-trimethoxybenzoyl)piperazine **8b** (0.62 g), Et_3N (1.2 ml) and CH_2Cl_2 (10 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h, washed with 1 N HCl and subsequently with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (AcOEt : acetone : hexane = 10 : 8 : 5) to yield crude **2g**. Recrystallization from AcOEt gave **2g** (0.9 g, 87%) as colorless prisms, mp 164—165 °C. IR ν_{max}^{KBr} cm^{-1}: 2930, 1630, 1580, 1510, 1460, 1420, 1320, 1230, 1120. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.9 (6H, m), 3.66 (8H, br s, $-CH_2-$), 3.78 (3H, s, OCH_3), 3.83 (12H, s, OCH_3), 6.45 (1H, br s), 6.68 (4H, s). *Anal.* Calcd for $C_{28}H_{34}N_2O_7$: C, 65.87; H, 6.71; N, 5.49. Found: C, 65.87; H, 6.75; N, 5.44. Method B: Diethyl phosphorocyanidate (1.0 g) was added to a mixture of **7g** (1.0 g), **8b** (1.25 g) and DMF (12 ml) with stirring under ice-cooling. Stirring was continued for 30 min, then Et_3N (1.1 g) was added to the mixture. The reaction mixture was stirred at room temperature for 1 h, poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel to yield **2g** (1.54 g, 75% yield).

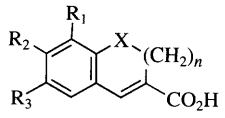
Compounds **1a—k**, **2a—k**, **3** and **4** were synthesized by a similar condensation of **8a, b** with corresponding carboxylic acids, and their physicochemical properties are summarized in Table I.

1-(7,8-Dimethoxy-2,3-dihydro-1-benzothiepin-4-ylcarbonyl)-4-(3,4,5-trimethoxybenzoyl)piperazine *S*-Oxide (2l) A solution of $NaIO_4$ (0.96 g) in H_2O (1 ml) was added to a solution of **2k** (1.6 g) in MeOH (10 ml) with stirring under ice-cooling. Stirring was continued for 1 h, then the reaction mixture was allowed to stand in a refrigerator for 48 h, poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual solid was recrystallized from EtOH–Et_2O to afford **2l** (1.3 g, 83% yield) as colorless prisms, mp 138 °C. IR ν_{max}^{KBr} cm^{-1}: 1630, 1590, 1410, 1110, 1050. ^{1}H-NMR ($CDCl_3$) δ: 2.73 3.00 (2H, m, SO–CH_2-), 3.50—3.96 (8H, m, $-CH_2-$), 3.87 (12H, br s, OCH_3), 3.96 (3H, s, OCH_3), 6.63 (2H, s), 6.53 (1H, s), 6.80 (1H, s), 7.37 (1H, s). *Anal.* Calcd for $C_{27}H_{32}N_2O_8S \cdot 1/2H_2O$: C, 58.57; H, 6.01; N, 5.06. Found: C, 58.35; H, 5.87; N, 4.90.

1-(7,8-Dimethoxy-2,3-dihydro-1-benzothiepin-4-ylcarbonyl)-4-(3,4,5-trimethoxybenzoyl)piperazine *S*-Dioxide (2m) *m*-CPBA (1.71 g) was added in small portions to a solution of **2k** (1.6 g) in CH_2Cl_2 (10 ml) with stirring under ice-cooling. Stirring was continued for 1 h, then the reaction mixture was allowed to stand at −5 °C for 15 h. After decomposition of excess peracid with Na_2SO_3, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual crystals were recrystallized from EtOH to give **2m** (1.4 g, 83%) as colorless prisms, mp 226—229 °C. IR ν_{max}^{KBr} cm^{-1}: 2950, 1630, 1410, 1230, 1125. ^{1}H-NMR ($CDCl_3$) δ: 2.90—3.13 (2H, m, $SO_2CH_2CH_2-$), 3.46—3.86 (10H, m, $-CH_2-$), 3.87 (9H, br s, OCH_3), 3.90 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.60 (2H, s), 6.53 (1H, s), 6.80 (1H, s), 7.57 (1H, s). *Anal.* Calcd for $C_{27}H_{32}N_2O_9S \cdot H_2O$: C, 56.04; H, 5.92; N, 4.84. Found: C, 56.34; H, 5.67; N, 4.78.

1-(3,4,5-Trimethoxybenzenesulfonyl)piperazine (8d) A solution of 3,4,5-trimethoxybenzenesulfonyl chloride[24] (4.1 g) in CH_2Cl_2 (5 ml) was added dropwise to a mixture of 1-formylpiperazine (1.5 g), Et_3N (1.5 g) and CH_2Cl_2 (10 ml) with stirring under ice-cooling. Stirring was continued for 1 h, then the reaction mixture was poured into ice-water and the whole was extracted with CH_2Cl_2. The organic layer was washed with 5% citric acid and then with aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. A mixture of the above obtained residue, conc. HCl (2 ml) and dioxane (20 ml) was stirred at 70 °C for 3 h. After

TABLE VI. Physicochemical Data for Benzocycloalkenoic Acids (**7a—k**)



Compound No.	R_1	R_2	R_3	X	*n*	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Found C	Found H
7a	H	MeO	MeO	CH_2	0	34	251—252 *a)*	$C_{12}H_{12}O_4$	65.45	5.49	65.19	5.52
7b	H	MeO	H	CH_2	1							
7c	H	MeO	MeO	CH_2	1		*b)*					
7d	H	EtO	EtO	CH_2	1	86	182—184	$C_{15}H_{18}O_4$	68.69	6.92	68.81	6.99
7e	H	*n*-PrO	*n*-PrO	CH_2	1	67	140—141	$C_{17}H_{22}O_4$	70.32	7.64	70.50	7.67
7f	MeO	MeO	MeO	CH_2	1		*c)*					
7g	H	MeO	MeO	CH_2	2	74	158—159	$C_{14}H_{16}O_4$	67.73	6.50	67.97	6.55
7h	MeO	MeO	H	CH_2	2	44	208—209	$C_{14}H_{16}O_4$	67.73	6.50	67.97	6.49
7i	H	MeO	MeO	CH_2	3	79	200—201	$C_{15}H_{18}O_4$	68.69	6.92	68.56	6.99
7j	H	MeO	MeO	O	2	70	209—210	$C_{13}H_{14}O_5$	62.39	5.64	62.15	5.48
7k	H	MeO	MeO	S	2	64	192—193	$C_{13}H_{14}O_4S$	58.63	5.30	58.55	5.37

a) MM. J. Jacques, A. Horeau, *Bull. Soc. Chim. Fr.*, **1950**, 512. *b)* H. L. Holmes, L. W. Trevoy, *Org. Syn.*, **26**, 28 (1946). *c)* Commercially available.

condensation and subsequent addition of H_2O, the mixture was made alkaline with 2 N NaOH and extracted with CH_2Cl_2. The organic layer was worked up.

The residue was crystallized from AcOEt–Et_2O to give **8d** (0.93 g, 20% yield) as colorless prisms, mp 143 °C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1590, 1320, 1160, 1130. ^{1}H-NMR ($CDCl_3$) δ: 2.83—3.17 (8H, m, $-CH_2-$), 3.89 (9H, s, OCH_3), 6.93 (2H, s). *Anal.* Calcd for $C_{13}H_{20}N_2O_5S$: C, 49.35; H, 6.37, N, 8.85. Found: C, 49.34; H, 6.44; N, 8.93.

1-(3,4,5-Trimethoxyphenethyl)piperazine Dihydrochloride (8f)[25] **8f** was prepared by $LiAlH_4$ reduction of **8g** and isolated as the dihydrochloride. Colorless needles, mp 210—220 °C (from aqueous EtOH). *Anal.* Calcd for $C_{15}H_{24}N_2O_3 \cdot 2HCl$: C, 50.99; H, 7.42; N, 7.93. Found: C, 50.73; H, 7.58; N, 7.78.

1-(3,4,5-Trimethoxyphenylacetyl)piperazine Hydrochloride (8g) A mixture of 3,4,5-trimethoxyphenylacetyl chloride (3 g) in CH_2Cl_2 (10 ml) was added dropwise to a solution of *N*-formylpiperazine (1.7 g), Et_3N (2.5 ml) and CH_2Cl_2 (30 ml) with stirring under ice-cooling. Stirring was continued for 2 h, then the reaction mixture was poured into ice-water and extracted withCH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A mixture of the above-obtained residue, 10% HCl (15 ml) and MeOH (5 ml) was stirred at 80 °C for 1 h. The reaction mixture was poured into a mixture of ice-water and AcOEt, mixed and separated. The aqueous layer was made alkaline with 2 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in MeOH (5 ml) and treated with 5 N methanolic HCl to afford a crystalline hydrochloride. Recrystallization from EtOH–Et_2O gave **8g** (2.1 g, 48% yield) as colorless prisms, mp 153—154 °C. *Anal.* Calcd for $C_{15}H_{22}N_2O_4 \cdot HCl \cdot 1/2H_2O$: C, 53.01; H, 7.12; N, 8.26. Found: C, 52.75; H, 7.10; N, 8.11.

1-(2,3-Dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)-piperazine (9a) Compound **9a** was synthesized in 76% yield according to a method similar to that described for **8g** using the acid chloride of **7g**, instead of 3,4,5-trimethoxyphenylacetyl chloride. Recrystallization from AcOEt afforded colorless needles, mp 137—138 °C. IR ν_{max}^{KBr} cm^{-1}: 3300, 2950, 1620, 1520,1450,1340, 1240, 1130, 1005. ^{1}H-NMR ($CDCl_3$) δ: 1.8 (1H, s, NH), 1.9—3.7 (14H, m), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.3—6.7 (3H, m). *Anal.* Calcd for $C_{18}H_{24}N_2O_3 \cdot 1/2H_2O$: C, 66.44; H, 7.74; N, 8.61. Found: C, 66.49; H, 7.73; N, 8.55.

1-(2,3-Dimethoxy-6,7-dihydro-5*H*-benzocycloheptene-8-thiocarbonyl)-piperazine Hydrochloride (9b) A mixture of **9a** (0.8 g), Lawesson's reagent (0.61 g) and benzene (15 ml) was stirred under reflux for 2 h. After cooling, the reaction mixture was filtered. To the filtrate, 10% HCl and AcOEt were added, vigorously mixed and separated. The aqueous layer was made alkaline with 10% NaOH and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in EtOH and treated with ethanolic HCl. The mixture was allowed to stand in a refrigerator for 2 d. The resulting precipitates were collected by filtration and recrystallized from EtOH to give **9b** (0.38 g, 41% yield) as pale yellow prisms, mp 252—256 °C. IR ν_{max}^{KBr} cm^{-1}: 3320, 2950, 1610, 1520, 1480, 1440, 1320, 1240, 1120, 1000. ^{1}H-NMR ($CDCl_3$) δ: 1.9—4.5 (15H, m), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.15—6.72 (3H, m). *Anal.* Calcd for $C_{18}H_{24}N_2O_5S \cdot HCl \cdot 1/2H_2O$: C, 57.21; H, 6.93; N, 7.41. Found: C, 57.34; H, 7.04; N, 7.28.

1-(2,3-Dimethoxy-5-oxo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ylmethyl)-4-(3,4,5-trimethoxybenzyl)piperazine Dihydrochloride (10a) A mixture of **5g** (2.0 g), **8a**·2HCl (3.25 g), paraformaldehyde (2.0 g) and EtOH (100 ml) was refluxed for 12 h. After cooling, the resulting precipitates were collected, washed with EtOH and recrystallized from MeOH to give **10a** (2.5 g, 46% yield) as colorless needles, mp 185—186 °C. IR ν_{max}^{KBr} cm^{-1}: 2930, 1660, 1590, 1500, 1450, 1350, 1330, 1260, 1230, 1200, 1120, 1010. ^{1}H-NMR ($CDCl_3$) δ: 1.30—3.48 (19H, m), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.88 (6H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.55 (2H, s), 6.70 (1H, s), 7.28 (1H, s). *Anal.* Calcd for $C_{28}H_{38}N_2O_6 \cdot 2HCl \cdot 3/2H_2O$: C, 56.19; H, 7.24; N, 4.68. Found: C, 56.33; H, 6.92; N, 4.59.

1-(2,3-Dimethoxy-5-oxo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ylmethyl)-4-(3,4,5-trimethoxybenzoyl)piperazine Hydrochloride (10b) **10b** was similarly synthesized in 38% yield by a Mannich reaction of **5g**, **8b**·HCl and paraformaldehyde as colorless needles from EtOH–AcOEt, mp 187—189 °C. *Anal.* Calcd for $C_{28}H_{36}N_2O_7 \cdot HCl$: C, 61.25; H, 6.79; N, 5.10. Found: C, 61.02; H, 6.87; N, 5.08.

1-(2,3-Dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylmethyl)-4-(3,4,5-trimethoxybenzyl)piperazine (17) A solution of **10a** (1.8 g) in MeOH (50 ml) was treated with $NaBH_4$ (0.8 g) in small portions at room temperature with stirring. Stirring was continued for a further 20 min, then the reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A mixture of the residue obtained by the above procedure and 2 N ethanolic HCl (30 ml) was stirred at 90 °C for 30 min. The mixture was concentrated *in vacuo*. The residue was poured into ice-water containing Na_2CO_3 (8 g) and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give **17** (1.47 g, 83% yield) as colorless prisms, mp 155—156 °C. IR ν_{max}^{KBr} cm^{-1}: 2940, 2800, 1590, 1450, 1420, 1350, 1240, 1120, 1020. ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.8 (6H, m), 2.46 (8H, br s), 2.97 (2H, s, CH_2N), 3.40 (2H, s, NCH_2-), 3.80 (3H, s, OCH_3), 3.84 (12H, s, OCH_3), 6.22—7.69 (5H, m). *Anal.* Calcd for $C_{28}H_{38}N_2O_5$: C, 69.68; H, 7.94; N, 5.80. Found: C, 69.78; H, 8.03; N, 5.70.

Compound **18** was similarly prepared by reduction of **10b** and subsequent dehydration. Condensation of **7g** with **8c—g** (method A) gave compounds **11—15**. Acylations of **9b** and **9a** with the corresponding benzoyl chlorides (method A) gave **16** and **19**, respectively. The physicochemical properties of **11—19** are shown in Table II.

4-(3,4,5-Trimethoxybenzoyl)aminopiperidine Hydrochloride (20b) A solution of 3,4,5-trimethoxybenzoyl chloride (1.5 g) in CH_2Cl_2 (10 ml) was added dropwise to a mixture of 4-amino-1-benzylpiperidine (1.35 g), Et_3N (1.8 g) and CH_2Cl_2 (10 ml) with stirring under ice-cooling. Stirring was continued for 1 h, then the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A mixture of the residual crystals (0.7 g), 10% Pd–C (0.3 g) and MeOH (20 ml) was hydrogenated in a stream of H_2 under atmospheric pressure for 4 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in EtOH and treated with ethanolic HCl to give a crystalline hydrochloride, which was recrystallized from EtOH–Et_2O to yield **20b** (0.44 g, 22% yield) as colorless needles, mp 135—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.20—3.30 (10H, m), 3.84 (3H, s, OCH_3), 3.87 (6H, s, OCH_3), 6.12 (1H, m, NHCO), 6.98 (2H, s). *Anal.* Calcd for $C_{15}H_{22}N_2O_4 \cdot HCl \cdot H_2O$: C, 51.64; H, 7.22; N, 8.03. Found: C, 51.42; H, 7.36; N, 7.92.

4-(3,4,5-Trimethoxybenzoyl)oxypiperidine Hydrochloride (20d) **20d** was prepared by benzoylation of 1-benzyl-4-hydroxypiperidine with 3,4,5-trimethoxybenzoyl chloride and subsequent catalytic hydrogenation. Colorless needles, mp 162—164 °C (from EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3520, 3350, 1685, 1600, 1510. ^{1}H-NMR ($CDCl_3$) δ: 2.10—3.70 (9H, m), 3.90 (9H, s, OCH_3),5.25 (1H, m), 7.28 (2H, s), 9.60 (1H, br s). *Anal.* Calcd for $C_{15}H_{21}NO_5 \cdot HCl$: C, 54.30; H, 6.68; N, 4.22. Found: C, 54.06; H, 6.65; N, 4.07.

4-(3,4,5-Trimethoxyanilino)piperidine Hydrochloride (20e) A mixture of $NaBH_3CN$ (0.48 g) in EtOH (10 ml) was added dropwise to a solution of 1-benzyl-4-piperidone (1.0 g), 3,4,5-trimethoxyaniline (0.97 g), AcOH (0.6 g) and EtOH (15 ml) at room temperature with stirring. The mixture was stirred for 3 h and then poured into ice-water, made alkaline with 1 N NaOH (5 ml) and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane : AcOEt : EtOH = 10 : 10 : 1). The oily 1-benzyl-4-(3,4,5-trimethoxyanilino)piperidine thus obtained was dissolved in MeOH (40 ml). The mixture was hydrogenated in the presence of 10% Pd–C (0.5 g) at room temperature under atmospheric pressure for 4 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOH and treated with ethanolic HCl. The resulting precipitates were collected and recrystallized from EtOH to give **20e** (0.8 g, 56% yield) as colorless plates, mp 288—290 °C. *Anal.* Calcd for $C_{14}H_{22}N_2O_3 \cdot HCl$: C, 55.52; H, 7.66; N, 9.25. Found: C, 55.42; H, 7.79; 9.15.

4-(3,4,5-Trimethoxyphenoxy)piperidine Hydrochloride (20f) A solution of diethyl azodicarboxylate (0.91 g) in tetrahydrofuran (THF) (5 ml) was added dropwise to a mixture of 1-benzyl-4-hydroxypiperidine (1.0 g), 3,4,5-trimethoxyphenol (0.96 g), PPh_3 (1.37 g) and THF (15 ml) at room temperature with stirring. The mixure was stirred for 24 h, then poured into ice-water and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane : AcOEt : EtOH = 10 : 10 : 1) to give 1-benzyl-4-(3,4,5-trimethoxy-

phenoxy)piperidine as an oil, which was converted into the hydrochloride by treatment with ethanolic HCl. A mixture of the hydrochloride (0.8 g), 10% Pd–C (0.4 g) and MeOH (30 ml) was hydrogenated at room temperature under atmospheric pressure for 4 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized from EtOH–Et_2O to give **20f** (0.5 g, 31% yield) as colorless needles, mp 226—228 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40—3.50 (8H, m), 3.75 (3H, s, OCH_3), 3.80 (6H, s, OCH_3), 4.2 (1H, m), 6.15 (2H, s). *Anal.* Calcd for $C_{14}H_{21}NO_4 \cdot HCl$: C, 55.35; H, 7.30; N, 4.61. Found: C, 55.16; H, 7.43; N, 4.58.

1-(2,3-Dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-ylcarbonyl)-4-(3,4,5-trimethoxybenzoyl)perhydro-1,4-diazepine (21) Condensation of **7g** with **20a** by a method similar to that described for **2g** (method A) gave **21** in 71% yield as a colorless powder. IR ν_{max}^{KBr} cm^{-1}: 2940, 1630, 1590, 1520, 1470, 1420, 1330, 1240, 1130, 1010. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.95 (8H, m), 3.30—4.05 (8H, m), 3.81 (3H, s, OCH_3), 3.85 (12H, s, OCH_3), 6.42 (1H, br s), 6.63 (2H, s), 6.68 (1H, s), 6.70 (1H, s). *Anal.* Calcd for $C_{29}H_{36}N_2O_7 \cdot H_2O$: C, 64.19; H, 7.06; N, 5.16. Found: C, 64.29; H, 7.05; N, 4.89.

Compounds **21**—**27** were similarly prepared by condensation of **7g** with **20a**—**g**, and their physicochemical properties are listed in Table III.

Evaluation of Inhibitory Activity against PAF-Induced Platelet Aggregation in Rabbit Platelet-Rich Plasma Experiments were done according to the method reported in the literature.[17] In brief, citrated (final concentration, 0.315%) blood of male New Zealand White rabbits (3—4 kg) was used. The blood was centrifuged at 3000 × *g* for 3 s and 3000 × *g* for 10 min to obtain platelet-rich plasma (PRP) and platelet-poor plasma (PPP), respectively. The platelet density of PRP was adjusted to 400000 cell/μl with PPP. The volume of PRP, PAF antagonists and aggregation inducers was 250, 25, and 25 μl, respectively. Platelet aggregation was measured using an 8 channel aggregometer (Hematracer VI, Niko Bioscience, Japan). PAF was dissolved in 0.9% saline containing 0.25% bovine serum albumin (BSA) and PAF antagonists were dissolved in 0.9% saline. The concentration of PAF was chosen to provide submaximal aggregation (3.0 to 10 nM).

Effect on PAF-Induced Hypotension in Conscious Rats[17] Male Sprague-Dawley (S-D) (Japan Clea Laboratories, Tokyo; Jcl) rats, 6—10 weeks old, were used. The rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and the right femoral artery and left femoral vein were cannulated for measurement of mean arterial blood pressure and for injection of PAF, respectively. Experiments were carried out 20 h after surgery. PAF (0.5 μg/kg, i.v.) was injected 20 min before and 1 to 8 h after administration of PAF antagonists (one *p.o.* dose per rat). PAF antagonists were given orally in a volume of 10 ml/kg. PAF was injected in a volume of 0.25 ml/kg, and was flushed with 0.25 ml of saline for 25 s. During these experiments, rats had free access to food and tap water.

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