inhibition was calculated in percent of the active uptake. The IC_{50} values were obtained from log concentration–response curves.

Behavioral Studies in Reserpinized Rats. Reserpine, 5 mg/kg sc, was injected 18 h before the oral administration of the test compound. Behavioral changes (abduction of hind legs, wet dog shake, forepaw treading, Straub tail, and ptosis) were observed for 1 h after the administration of the test compound.[22] The lowest doses causing these changes were noted.

Registry No. (±)-1, 103882-44-6; (±)-2, 103818-17-3; (±)-3, 103818-19-5; (±)-4, 103818-21-9; (±)-5, 103834-90-8; (±)-6, 103818-23-1; (±)-7, 103882-46-8; (±)-7 (*N,N'*-diacetate), 103818-35-5; 8, 103818-25-3; 9, 103834-92-0; 10, 103818-27-5; 11, 55197-79-0; 12, 89170-76-3; 13, 103818-28-6; 14, 103818-29-7; 15, 1424-65-3; 16, 89115-16-2; 17, 103818-30-0; 18, 103818-31-1; 19, 103818-32-2; 20, 103818-33-3; (±)-21, 103818-34-4; MAO, 9001-66-5; F-*m*-$C_6H_4NH_2$, 372-19-0; $EtNO_2$, 79-24-3; *i*-PrBr, 75-26-3.

Syntheses of 5,6,7- and 5,7,8-Trioxygenated 3',4'-Dihydroxyflavones Having Alkoxy Groups and Their Inhibitory Activities against Arachidonate 5-Lipoxygenase

Tokunaru Horie,* Masao Tsukayama, Hiroki Kourai, Chieko Yokoyama,† Masayuki Furukawa,† Tanihiro Yoshimoto,† Shozo Yamamoto,† Shigekatsu Watanabe-Kohno,‡ and Katsuya Ohata‡

Department of Applied Chemistry, Faculty of Engineering, Tokushima University, Minamijosanjima-cho, Tokushima 770, Japan, Department of Biochemistry, School of Medicine, Tokushima University, Kuramoto-cho, Tokushima 770, Japan, and Department of Pharmacology, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan. *Received March 5, 1986*

Arachidonate 5-lipoxygenase plays a pivotal role in the biosynthesis of leukotrienes. Cirsiliol (3',4',5-trihydroxy-6,7-dimethoxyflavone), a selective inhibitor of the enzyme, was derivatized by introducing alkyl groups of various chain lengths at positions 5, 6, 7, and 8 of the A ring of the flavone skeleton. Modification of the positions 5 and 6 with an alkyl group of 5–10 carbons markedly decreased the IC_{50} values for 5-lipoxygenase inhibition to the order of 10 nM. As tested with 5- or 6-hexyloxy derivatives, a relatively selective inhibition of 5-lipoxygenase was shown. Inhibition of 12-lipoxygenase required much higher concentrations of these compounds, and cyclooxygenase was not inhibited. Modification of positions 7 and 8 did not increase the inhibitory effect of most flavone compounds.

Arachidonate 5-lipoxygenase catalyzes the oxygenation of arachidonic acid at the 5-position to produce 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid, which is further transformed to various leukotrienes.[1] In view of the important role of leukotrienes as mediators of anaphylactic reactions,[1] various synthetic compounds have been reported as specific inhibitors of the 5-lipoxygenase.[2-10] Previously we reported that cirsiliol (3',4',5-trihydroxy-6,7-dimethoxyflavone)[11] (**1a**) and pedalitin (3',4',5,6-tetrahydroxy-7-methoxyflavone)[12] were the most potent 5-lipoxygenase inhibitors (IC_{50} 0.1 μM) among about 80 flavones tested.[13,14] The vicinal diol on the 2-phenyl substituent (the B ring) was necessary for the inhibition of 5-lipoxygenase. On the basis of this finding we derivatized cirsiliol in a variety of ways to find out the structure–activity relationship and to develop a more potent and selective inhibitor. The results suggest that the activity of the 3',4'-dihydroxyflavones such as cirsiliol was enhanced by modifying the oxygenated functions in the A ring with lipophilic alkyl groups. In this paper we report the synthesis of these flavones with alkoxy groups and their structure–activity relationship as inhibitors of 5-lipoxygenase.

Chemistry. The synthetic routes employed for the preparation of the 5,6,7- and 5,7,8-trioxygenated 3',4'-dihydroxyflavones are illustrated in Schemes I and II. As shown in Scheme I, the crude 3-alkyl ethers **13a–k** derived from 3,6-dihydroxy-2,4-dimethoxyacetophenone (**12**)[15] by the partial alkylation were condensed with 3,4-bis(benzyloxy)benzoyl chloride in pyridine, and the resultant benzoates were converted into the diketone derivatives **14a–k** by the Baker–Venkataraman transformation. Cyclization of **14** with anhydrous sodium acetate afforded 6-alkoxy-3',4'-bis(benzyloxy)-5,7-dimethoxyflavones **15a–k**. The flavones **15** were also synthesized from 3',4'-bis(benzyloxy)-6-hydroxy-5,7-dimethoxyflavone (**16**)[16,17] by the alkylation with alkyl iodides. The hydrogenolysis of compounds **15** with palladium on charcoal afforded 6-alkoxy-3',4'-dihydroxy-5,7-dimethoxyflavones (**6a–k**), which were

† Department of Biochemistry, Tokushima University.
‡ Department of Pharmacology, Kyoto Pharmaceutical University.

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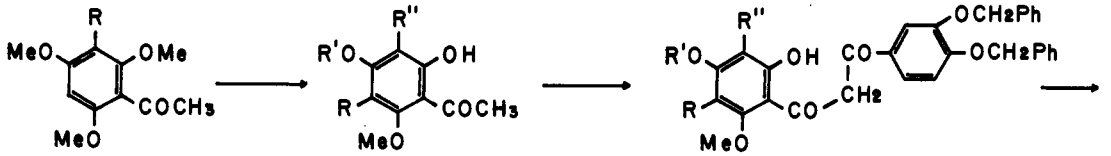
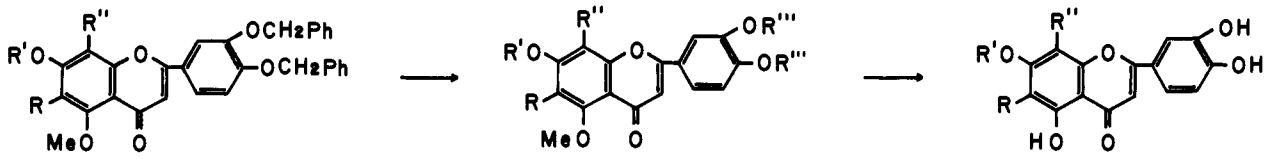
Scheme I[a]



30: R = OH
31h: R = $OC_{12}H_{25}$

12: R = OH, R′ = Me, R″ = H
13a–k: R = O-alkyl, R′ = Me, R″ = H
17: R = OMe, R′ = R = H
18h: R = OMe, R′ = $C_{12}H_{25}$, R″ = H
26: R = R′ = H, R″ = OMe
27a,h: R = H, R′ = alkyl, R″ = OMe
32h: R = H, R′ = Me, R″ = $OC_{12}H_{25}$

14a–k: R = O-alkyl, R′ = Me, R″ = H
19h: R = OMe, R′ = $C_{12}H_{25}$, R″ = H
28a,h: R = H, R′ = alkyl, R″ = OMe
33h: R = H, R′ = Me, R″ = $OC_{12}H_{25}$



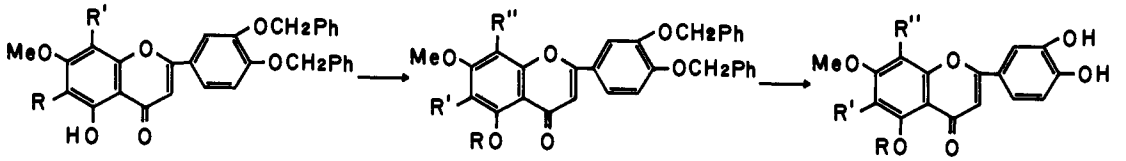
15a–k: R = O-alkyl, R′ = Me, R″ = H
16: R = OH, R′ = Me, R″ = H
20h: R = OMe, R′ = $C_{12}H_{25}$, R″ = H
24a: R = H, R′ = Me, R″ = OMe
29h: R = H, R′ = $C_{12}H_{25}$, R″ = OMe
34h: R = H, R′ = Me, R″ = $OC_{12}H_{25}$

6a–k: R = O-alkyl, R′ = Me, R″ = R‴ = H
7a–k: R = O-alkyl, R′ = Me, R″ = H, R‴ = Ac
8h: R = OMe, R′ = $C_{12}H_{25}$, R″ = R‴ = H
21h: R = OMe, R′ = $C_{12}H_{25}$, R″ = H, R‴ = Ac
9a: R = R‴ = H, R′ = Me, R″ = OMe
10h: R = R‴ = H, R′ = $C_{12}H_{25}$, R″ = OMe
11h: R = R‴ = H, R′ = Me, R″ = $OC_{12}H_{25}$

1a–k: R = O-alkyl, R′ = Me, R″ = H
2h: R = OMe, R′ = $C_{12}H_{25}$, R″ = H
3a,h: R = H, R′ = alkyl, R″ = OMe
4h: R = H, R′ = Me, R″ = $OC_{12}H_{25}$

[a] **a**, CH_3; **b**, C_4H_9; **c**, C_5H_{11}; **d**, *i*-C_5H_{11}; **e**, C_6H_{13}; **f**, C_8H_{17}; **g**, $C_{10}H_{21}$; **h**, $C_{12}H_{25}$; i, $C_{14}H_{29}$; **j**, $C_{16}H_{33}$; **k**, $C_{18}H_{37}$.

Scheme II[a]



22: R = OMe, R′ = H
25: R = H, R′ = OMe

23a–k: R = alkyl, R′ = OMe, R″ = H
24h: R = $C_{12}H_{25}$, R′ = H, R″ = OMe

5b–k: R = alkyl, R′ = OMe, R″ = H
9h: R = $C_{12}H_{25}$, R′ = H, R″ = OMe

[a] **a**, CH_3; **b**, C_4H_9; **c**, C_5H_{11}; **d**, *i*-C_5H_{11}; **e**, C_6H_{13}; **f**, C_8H_{17}; **g**, $C_{10}H_{21}$; h, $C_{12}H_{25}$; i, $C_{14}H_{29}$; **j**, $C_{16}H_{33}$; **k**, $C_{18}H_{37}$.

easily converted into the diacetates **7a–k**. The diacetates **7** were demethylated with anhydrous aluminum chloride in acetonitrile and subsequently hydrolyzed with hydrochloric acid in methanol[18] to give quantitatively 6-alkoxy-3′,4′,5-trihydroxy-7-methoxyflavones **1a–k**. By a similar method, 7-(dodecyloxy)-3′,4′-dihydroxy-5,6-dimethoxyflavone (**8h**) and 7-(dodecyloxy)-3′,4′,5-trihydroxy-6-methoxyflavone (**2h**) were also synthesized from 4,6-dihydroxy-2,3-dimethoxyacetophenone (**17**), which was easily obtained from 4-(benzyloxy)-6-hydroxy-2,3-dimethoxyacetophenone.[19]

5-Alkoxy-3′,4′-dihydroxy-6,7-dimethoxyflavones **5b–k** were synthesized as shown in Scheme II. The 5-methoxy group in 3′,4′-bis(benzyloxy)-5,6,7-trimethoxyflavone (**15a**)[20] was selectively split with anhydrous aluminum chloride in acetonitrile to give the 5-hydroxyflavone **22** in a good yield. The alkylation of **22** with alkyl iodides in acetone–*N*,*N*-dimethylformamide afforded 5-alkoxy-3′,4′-bis(benzyloxy)-6,7-dimethoxyflavones **23a–k**, which were converted into the desired flavones **5b–k** by the hydrogenolysis with palladium on charcoal. 5-(Dodecyloxy)-3′,4′-dihydroxy-7,8-dimethoxyflavone (**9h**) was also synthesized from 3′,4′-bis(benzyloxy)-5-hydroxy-7,8-dimethoxyflavone (**25**). However, the selective cleavage of the 5-methoxy group in 3′,4′-bis(benzyloxy)-5,7,8-trimethoxyflavone (**24a**) could not be achieved with anhydrous aluminum chloride in acetonitrile since the cleavage of the 5-methoxy group in 5,7,8-trioxygenated flavones was more difficult than that of the 5-methoxy group in 5,6,7-trioxygenated flavones.[21] Therefore, the selective demethylation of **24a** was carried out with anhydrous aluminum bromide in acetonitrile to give the 5-hydroxyflavone **25** in 30–35% yield.

7-Alkoxy-3′,4′,5-trihydroxy-8-methoxyflavones **3a** and **3h** and 8-(dodecyloxy)-3′,4′,5-trihydroxy-7-methoxyflavone (**4h**) were also synthesized as shown in Scheme I. 4-Alkoxy-6-hydroxy-2,5-dimethoxyacetophenones **27a**[22] and **27h**, derived from 4,6-dihydroxy-2,5-dimethoxyacetophenone (**26**),[23] were converted into 7-alkoxy-3′,4′-bis(benzyloxy)-5,8-dimethoxyflavones **24a** and **29h** via the corresponding diketone derivatives **28a** and **28h**. Hydrogenolysis of the flavones **24a** and **29h** afforded 7-alkoxy-3′,4′-dihydroxy-5,8-dimethoxyflavones **9a** and **10h**, which were demethylated with anhydrous aluminum bromide in acetonitrile to give the desired flavones **3a** and **3h**.

The 6-methoxy group of 5-(dodecyloxy)-2,4,6-trimethoxyacetophenone (**31h**), derived from 5-hydroxy-2,4,6-

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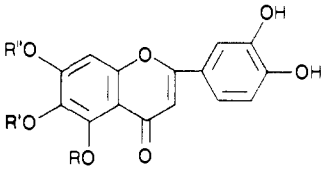
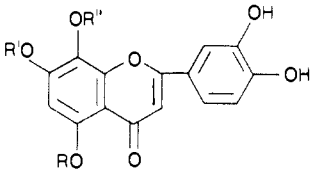
Table I. 6-Alkoxy-3′,4′-dihydroxy-5,7-dimethoxyflavones **6**, 5-Alkoxy-3′,4′-dihydroxy-6,7-dimethoxyflavones **5**, 7-(Dodecyloxy)-3′,4′-dihydroxy-5,6-dimethoxyflavone (**8h**), and Their Isomers **9**, **10h**, and **11h**



5, 6, and 8



9, 10, and 11

compd	R	R′	R″	mp, °C	recrystn solvent	yield, %	^{1}H NMR (Me_2SO) C_3-H	^{1}H NMR (Me_2SO) C_8- or C_6-H	formula	anal.	IC_{50}, nM
6a[20]	Me	Me	Me	246–247	MeOH	97	6.50	7.11	$C_{18}H_{16}O_7$	C, H	240
6b	Me	C_4H_9	Me	232–233	MeOH	91	6.51	7.12	$C_{21}H_{22}O_7$	C, H	52
6c	Me	C_5H_{11}	Me	181–183	MeOH	88	6.50	7.12	$C_{22}H_{24}O_7$	C, H	35
6d	Me	i-C_5H_{11}	Me	228–229	MeOH	90	6.50	7.09	$C_{22}H_{24}O_7$	C, H	26
6e	Me	C_6H_{13}	Me	178–180	MeOH	95	6.51	7.12	$C_{23}H_{26}O_7$	C, H	14
6f	Me	C_8H_{17}	Me	183–184	MeOH	88	6.51	7.13	$C_{25}H_{30}O_7$	C, H	22
6g	Me	$C_{10}H_{21}$	Me	177–178	MeOH	90	6.51	7.12	$C_{27}H_{34}O_7$	C, H	17
6h	Me	$C_{12}H_{25}$	Me	176–178	EtOAc–MeOH	86	6.50	7.12	$C_{29}H_{38}O_7$	C, H	30
6i	Me	$C_{14}H_{29}$	Me	177–178	EtOAc–MeOH	82	6.49	7.11	$C_{31}H_{42}O_7$	C, H	70
6j	Me	$C_{16}H_{33}$	Me	176–177	EtOAc–MeOH	91	6.49	7.10	$C_{33}H_{46}O_7$	C, H	1500
6k	Me	$C_{18}H_{37}$	Me	174–175	EtOAc–MeOH	80	6.49	7.10	$C_{35}H_{50}O_7$	C, H	10000
5b	C_4H_9	Me	Me	182–183	MeOH	90	6.47	7.10	$C_{21}H_{22}O_7$	C, H	45
5c	C_5H_{11}	Me	Me	154–156	MeOH	92	6.46	7.08	$C_{22}H_{24}O_7$	C, H	32
5d	i-C_5H_{11}	Me	Me	189–190	MeOH	97	6.46	7.08	$C_{22}H_{24}O_7$	C, H	16
5e	C_6H_{13}	Me	Me	192–193	EtOAc–MeOH	81	6.50	7.12	$C_{23}H_{26}O_7$	C, H	15
5f	C_8H_{17}	Me	Me	163–165	EtOAc	80	6.43	7.05	$C_{25}H_{30}O_7$	C, H	19
5g	$C_{10}H_{21}$	Me	Me	153–154	MeOH–hexane	78	6.46	7.09	$C_{27}H_{34}O_7$	C, H	18
5h	$C_{12}H_{25}$	Me	Me	150–151	MeOH	86	6.48	7.11	$C_{29}H_{38}O_7$	C, H	18
5i	$C_{14}H_{29}$	Me	Me	146–147	MeOH	89	6.46	7.08	$C_{31}H_{42}O_7$	C, H	28
5j	$C_{16}H_{33}$	Me	Me	140–141	MeOH	93	6.46	7.10	$C_{33}H_{46}O_7$	C, H	140
5k	$C_{18}H_{37}$	Me	Me	141–142	MeOH	80	6.47	7.10	$C_{35}H_{50}O_7$	C, H	9000
8h	Me	Me	$C_{12}H_{25}$	180–181	EtOAc–MeOH	85	6.45	7.07	$C_{29}H_{38}O_7$	C, H	100
9a	Me	Me	Me	294–297	methyl Cellosolve	91	6.44	6.62	$C_{18}H_{16}O_7$	C, H	430
9h	$C_{12}H_{25}$	Me	Me	143–144	MeOH	87	6.41	6.62	$C_{29}H_{38}O_7$	C, H	22
10h	Me	$C_{12}H_{25}$	Me	180–181	EtOAc–MeOH	96	6.43	6.60	$C_{29}H_{38}O_7$	C, H	33
11h	Me	Me	$C_{12}H_{25}$	170–172	EtOAc–MeOH	95	6.41	6.63	$C_{29}H_{38}O_7$	C, H	110

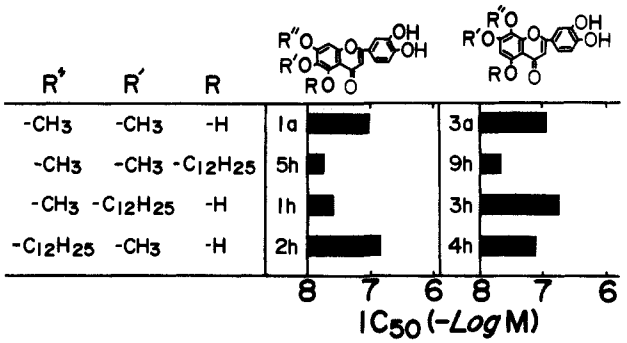


Figure 1. Inhibition of 5-lipoxygenase by 5,6,7- and 5,7,8-trioxygenated 3′,4′-dihydroxyflavones with a dodecyl group in the A ring. 5-Lipoxygenase (68 μg of protein) was assayed under the standard conditions described in the Experimental Section with each compound at various concentrations, and IC_{50} values were calculated.

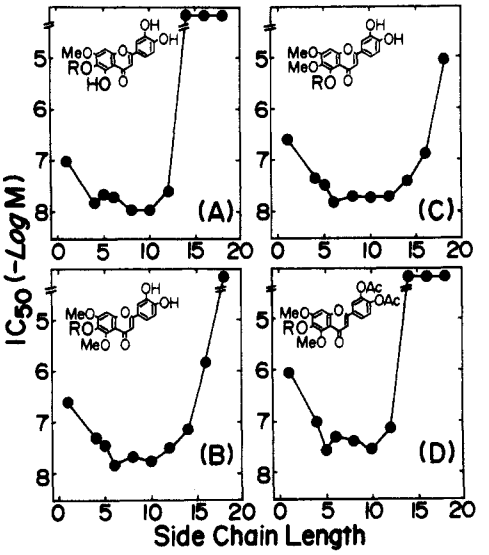


Figure 2. Optimal chain length of alkoxyflavones for 5-lipoxygenase inhibition. (A) 6-Alkoxy-3′,4′,5-trihydroxy-7-methoxyflavones (**1**), (B) 6-alkoxy-3′,4′-dihydroxy-5,7-dimethoxyflavones (**6**), (C) 5-alkoxy-3′,4′-dihydroxy-6,7-dimethoxyflavones (**5**), (D) 3′,4′-diacetoxy-6-alkoxy-5,7-dimethoxyflavones (**7**). 5-Lipoxygenase (68 μg of protein) was assayed under the standard conditions described in the Experimental Section with each compound at various concentrations, and IC_{50} values were calculated.

trimethoxyacetophenone (**30**),[24] was selectively split to give 5-(dodecyloxy)-6-hydroxy-2,4-dimethoxyacetophenone (**32h**) in a good yield. The 8-(dodecyloxy)-3′,4′-dihydroxyflavones **11h** and **4h** were synthesized from the acetophenone **32h** via the diketone derivative **33h**.

Results and Discussion

With use of two 3′,4′,5-trihydroxyflavones [3′,4′,5-trihydroxy-6,7-dimethoxyflavone (**1a**, cirsiliol) and 3′,4′,5-trihydroxy-7,8-dimethoxyflavone (**3a**)] as mother compounds, a dodecyl group was introduced at various positions of the A ring of the flavone skeleton. The 5-lipoxygenase of rat basophilic leukemia cells was assayed in the presence of these derivatives. Their IC_{50} values were

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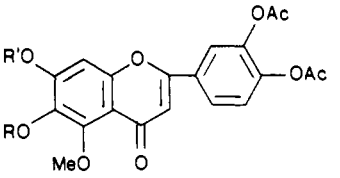
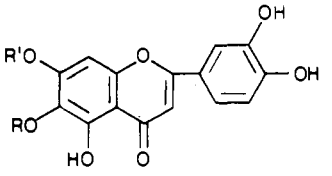
Table II. 3′,4′-Diacetoxy-6-alkoxy-5,7-dimethoxyflavones **7** and 3′,4′-Diacetoxy-7-(dodecyloxy)-5,6-dimethoxyflavone (**21h**)

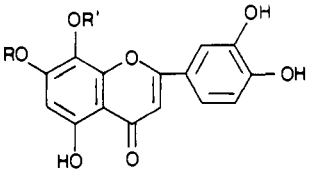


compd	R	R′	mp, °C	recrystn solvent	^{1}H NMR ($CDCl_3$) C_3-H	^{1}H NMR ($CDCl_3$) C_8-H	formula	anal.	IC_{50}, nM
7a	Me	Me	159–160	MeOH	6.58	6.77	$C_{22}H_{20}O_9$	C, H	1000
7b	C_4H_9	Me	147–148	MeOH	6.60	6.78	$C_{25}H_{26}O_9$	C, H	100
7c	C_5H_{11}	Me	139–140	MeOH	6.60	6.76	$C_{26}H_{28}O_9$	C, H	28
7d	*i*-C_5H_{11}	Me	163–164	MeOH	6.61	6.78	$C_{26}H_{28}O_9$	C, H	
7e	C_6H_{13}	Me	123–124	MeOH	6.60	6.76	$C_{27}H_{30}O_9$	C, H	50
7f	C_8H_{17}	Me	113–114	MeOH	6.61	6.78	$C_{29}H_{34}O_9$	C, H	42
7g	$C_{10}H_{21}$	Me	114–115	MeOH	6.60	6.76	$C_{31}H_{38}O_9$	C, H	30
7h	$C_{12}H_{25}$	Me	115–116	MeOH	6.61	6.77	$C_{33}H_{42}O_9$	C, H	75
7i	$C_{14}H_{29}$	Me	116–117	MeOH	6.62	6.79	$C_{35}H_{46}O_9$	C, H	10000
7j	$C_{16}H_{33}$	Me	116–117	MeOH	6.62	6.79	$C_{37}H_{50}O_9$	C, H	10000
7k	$C_{18}H_{37}$	Me	115–116	MeOH	6.63	6.80	$C_{39}H_{54}O_9$	C, H	10000
21h	Me	$C_{12}H_{25}$	102–103	MeOH	6.59	6.76	$C_{33}H_{42}O_9$	C, H	

Table III. 6-Alkoxy-3′,4′,5-trihydroxy-7-methoxyflavones **1**, 7-(Dodecyloxy)-3′,4′,5-trihydroxy-6-methoxyflavone (**2h**), and Their Isomers **3** and **4h**



1 and 2



3 and 4

compd	R	R′	mp, °C	recrystn solvent	yield, %	^{1}H NMR (Me_2SO) C_3-H	^{1}H NMR (Me_2SO) C_8- or C_6-H	formula	anal.	IC_{50}, nM
1a[20]	Me	Me	286–288	methyl Cellosolve	85	6.69	6.82	$C_{17}H_{14}O_7$	C, H	95
1b	C_4H_9	Me	257–258	EtOH	90	6.68	6.81	$C_{20}H_{20}O_7$	C, H	15
1c	C_5H_{11}	Me	253–254	MeOH	98	6.68	6.81	$C_{21}H_{22}O_7$	C, H	22
1d	*i*-C_5H_{11}	Me	228–229	MeOH	95	6.67	6.80	$C_{21}H_{22}O_7$	C, H	9
1e	C_6H_{13}	Me	252–253	MeOH	95	6.69	6.82	$C_{22}H_{24}O_7$	C, H	20
1f	C_8H_{17}	Me	250–252	EtOH	88	6.69	6.82	$C_{24}H_{28}O_7$	C, H	11
1g	$C_{10}H_{21}$	Me	249–250	EtOH	92	6.70	6.83	$C_{26}H_{32}O_7$	C, H	11
1h	$C_{12}H_{25}$	Me	248–249	methyl Cellosolve	85	6.69	6.83	$C_{28}H_{36}O_7$	C, H	26
1i	$C_{14}H_{29}$	Me	246–247	EtOH	84	6.70	6.83	$C_{30}H_{40}O_7$	C, H	10000
1j	$C_{16}H_{33}$	Me	245–246	EtOH	97	6.69	6.83	$C_{32}H_{44}O_7$	C, H	10000
1k	$C_{18}H_{37}$	Me	243–244	EtOAc–MeOH	97	6.69	6.83	$C_{34}H_{48}O_7$	C, H	10000
2h	Me	$C_{12}H_{25}$	240–242	EtOAc–MeOH	92	6.72	6.87	$C_{28}H_{36}O_7$	C, H	140
3a	Me	Me	268–270	aq MeOH	80	6.68	6.52	$C_{17}H_{14}O_7$	C, H	110
3h	$C_{12}H_{25}$	Me	202–203	MeOH	95	6.66	6.48	$C_{28}H_{36}O_7$	C, H	180
4h	Me	$C_{12}H_{25}$	223–224	EtOAc–MeOH	90	6.65	6.51	$C_{28}H_{36}O_7$	C, H	110

compared in Figure 1. It was noted that IC_{50} values (see Tables I and III) were lowered by about 5-fold by introducing a dodecyl group at position 5 or 6.

Considering that the lipophilic nature of the dodecyl group may contribute to the inhibitory activity, the chain length of the alkyl groups to be introduced was varied. Figure 2 and Tables I-III show four types of compounds derivatized in this way. In both 5- and 6-alkoxy compounds the inhibition of 5-lipoxygenase was prominent when an alkyl group of 5–10 carbons was introduced. Compounds with shorter or longer alkyl groups were less active. Modification at positions 7 and 8 were not so critical as examined by introduction of a dodecyl group (**6a** vs. **8h** in Table I; **9a** vs. **11h** in Table I; **3a** vs. **3h** and **4h** in Table III).

In addition to 5-lipoxygenase, representative compounds out of the above-mentioned alkoxyflavones were tested with 12-lipoxygenase (porcine leukocytes) and cyclooxygenase (bovine vesicular gland). Both 6- and 5-hexyloxy derivatives (**1e** and **5e**) of cirsiliol (**1a**) inhibited 12-lipoxygenase, but their IC_{50} values were higher by more than 2 orders of magnitude than those for 5-lipoxygenase inhibition (Figure 3A,C). This was also the case of 5-methoxy-6-hexyloxy derivative (**6e**) of cirsiliol (**1a**) (Figure 3B). When parts B and D of Figure 3 are compared, it can be noted that the compound with a 3′,4′-diacetoxy group (**7e**) did not inhibit 12-lipoxygenase. According to our earlier finding,[13,14] the 3′,4′-diol in a free form was required for a potent inhibition of 5-lipoxygenase. When one or both of the two hydroxy groups of cirsiliol were methylated, the methoxy derivatives were much less active than cirsiliol.[13,14] As can be seen from comparison of **7a** (Table II) with **6a** (Table I), less potent inhibition was observed by acetylation of the 3′,4′-diol. However, the IC_{50} value was lowered by modification of the position 6 with an alkyl group of 5–10 carbons (Table II). Cyclooxygenase was not inhibited by any of these compounds (Figure 3A–D).

Thus, modification of cirsiliol (**1a**) by replacing the 5- or 6-oxygenated group of the A ring with an alkoxy group of 5–10 carbons brought about more potent inhibitors of 5-lipoxygenase with IC_{50} values as low as 10 nM. A relatively selective inhibition of 5-lipoxygenase was shown with

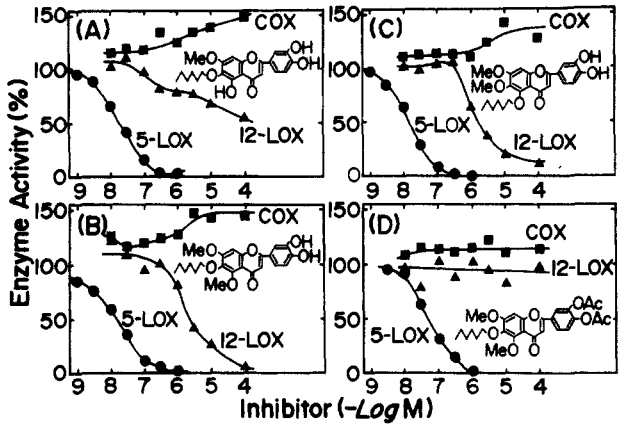


Figure 3. Selective inhibition of 5-lipoxygenase by flavones with a hexyloxy group. (A) 6-(Hexyloxy)-3′,4′,5-trihydroxy-7-methoxyflavone (**1e**), (B) 6-(hexyloxy)-3′,4′-dihydroxy-5,7-dimethoxyflavone (**6e**), (C) 5-(hexyloxy)-3′,4′-dihydroxy-6,7-dimethoxyflavone (**5e**), (D) 3′,4′-diacetoxy-6-(hexyloxy)-5,7-dimethoxyflavone (**7e**). 5-Lipoxygenase (68 μg of protein) (5-LOX, closed circles), 12-lipoxygenase (3.3 μg of protein) (12-LOX, closed triangles), and cyclooxygenase (4 μg of protein) (COX, closed squares) were assayed under the standard conditions described in the Experimental Section with each compound at various concentrations.

the 5- or 6-hexyloxy derivatives of cirsiliol, which inhibited 12-lipoxygenase at much higher concentrations and did not inhibit cyclooxygenase. Their in vivo effect is now under investigations with a disease model of bronchial asthma. An important aspect in the development of a 5-lipoxygenase inhibitor as a useful pharmacological agent or clinically applicable drug is the water solubility of the compound. Chemical modifications to improve water solubility of the 5-lipoxygenase inhibitors are under investigation.

Experimental Section

Chemistry. All melting points were determined in glass capillaries and were uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-24 spectrometer (60 MHz), using tetramethylsilane as an internal standard, and chemical shifts were given in δ values. UV spectra were recorded on a Hitachi 124 spectrophotometer. Elemental analyses were performed with a Yanaco CHN corder Model MT-2.

3-Alkoxy-6-hydroxy-2,4-dimethoxyacetophenones 13a–k. A mixture of 3,6-dihydroxy-2,4-dimethoxyacetophenone (**12**) (3 g, 14.2 mmol), alkyl iodide (17 mmol), and anhydrous potassium carbonate (7 g, 50 mmol) in acetone (25–30 mL) was refluxed with stirring for 10–20 h. The mixture was diluted with water (150–200 mL), concentrated under reduced pressure, and extracted with ether. The extract was washed with water and dried over sodium sulfate, and the solvent was evaporated to give crude oily monoalkyl ether **13a–k**.

4-(Dodecyloxy)-6-hydroxy-2,3-dimethoxyacetophenone (18h). 4,6-Dihydroxy-2,3-dimethoxyacetophenone (**17**), which was synthesized from 4-(benzyloxy)-6-hydroxy-2,3-dimethoxyacetophenone[19] by the hydrogenolysis with palladium on charcoal, was alkylated with dodecyl iodide to give crude oily dodecyl ether **18h**.

4-(Dodecyloxy)-6-hydroxy-2,5-dimethoxyacetophenone (27h). 4,6-Dihydroxy-2,5-dimethoxyacetophenone (**26**)[23] (3.5 g) was alkylated with dodecyl iodide (5.4 g), and the resultant dodecyl ether was recrystallized from ethyl acetate–methanol to give pale yellow prisms (5.76 g, 92%); mp 55–56 °C. Anal. ($C_{22}H_{36}O_5$) C, H.

5-(Dodecyloxy)-6-hydroxy-2,4-dimethoxyacetophenone (32h). A mixture of 5-hydroxy-2,4,6-trimethoxyacetophenone (**30**) (3.5 g), dodecyl iodide (5.5 g), and anhydrous potassium carbonate (10 g) in acetone (40 mL) was refluxed with stirring for 12 h and then treated by the usual way to give crude oily dodecyl ether **31h**. The ether **31h** was dissolved in a solution of anhydrous aluminum chloride (4 g) in acetonitrile (40 mL), and the solution was heated at 60 °C for 1.5 h and poured into a mixture of ice and hydrochloric acid. The mixture was extracted with ether, and the extract was washed with water and then the solvent was evaporated. The residue was recrystallized from methanol to give pale yellow plates (5.2 g, 83%); mp 53–54 °C. Anal. ($C_{22}H_{36}O_5$) C, H.

Table IV. 3-Alkoxy-6-hydroxy-2,4-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]acetophenones **14**, 4-(Dodecyloxy)-6-hydroxy-2,3-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]acetophenone (**19h**), 4-Alkoxy-6-hydroxy-2,5-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]-acetophenones **28**, and 5-(Dodecyloxy)-6-hydroxy-2,4-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]acetophenone (**33h**)

compd	mp, °C	recrystn solvent	yield, %	formula	anal.
14a	145–147	EtOAc–MeOH	54[a]	$C_{32}H_{30}O_8$	C, H
14b	102–103	EtOAc–MeOH	51[a]	$C_{35}H_{36}O_8$	C, H
14c	99–100	EtOAc–MeOH	41[a]	$C_{36}H_{38}O_8$	C, H
14e	96–97	EtOAc–MeOH	43[a]	$C_{37}H_{40}O_8$	C, H
14f	87–88	EtOAc–MeOH	47[a]	$C_{39}H_{44}O_8$	C, H
14g	79–80	EtOAc–MeOH	49[a]	$C_{41}H_{48}O_8$	C, H
14h	76–77	EtOAc–MeOH	43[a]	$C_{43}H_{52}O_8$	C, H
14i	73–74	EtOAc–MeOH	38[a]	$C_{45}H_{56}O_8$	C, H
14j	60–61	EtOAc–MeOH	47[a]	$C_{47}H_{60}O_8$	C, H
14k	64–65	EtOAc–MeOH	36[a]	$C_{49}H_{64}O_8$	C, H
19h	83–84.5	EtOAc–MeOH	69[b]	$C_{43}H_{52}O_8$	C, H
28a	119–121	EtOAc–MeOH	70	$C_{32}H_{30}O_8$	C, H
28h	88–89	EtOAc–MeOH	73	$C_{43}H_{52}O_8$	C, H
33h	95–96	EtOAc–MeOH	75	$C_{43}H_{52}O_8$	C, H

[a] Overall yield from **12**. [b] Overall yield from **17**.

3-Alkoxy-6-hydroxy-2,4-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]acetophenones 14a–k, 4-(Dodecyloxy)-6-hydroxy-2,3-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]-acetophenone (19h), 4-Alkoxy-6-hydroxy-2,5-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]acetophenones 28a and 28h, and 5-(Dodecyloxy)-6-hydroxy-2,4-dimethoxy-ω-[3,4-bis(benzyloxy)benzoyl]acetophenone (33h). A mixture of the 6-hydroxyacetophenone **13**, **18**, **27**, or **32** (14 mmol), 3,4-bis(benzyloxy)benzoyl chloride (6.5 g, 18.5 mmol), and pyridine (10 mL) was heated at 120 °C for 2–3 h. The mixture was poured into a mixture of ice and hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and aqueous sodium carbonate and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the crude benzoate. To a solution of the benzoate in pyridine (10–15 mL) was added freshly powdered potassium hydroxide (4–5 g), and the mixture was vigorously stirred at 60 °C for 4 h. The mixture was poured into a mixture of ice and hydrochloric acid and extracted with ethyl acetate. The extract was washed with diluted hydrochloric acid and aqueous sodium carbonate, and the solvent was evaporated. The residue was recrystallized to give the corresponding ω-[3,4-bis(benzyloxy)benzoyl]acetophenone as yellow needles (Table IV).

3′,4′-Bis(benzyloxy)-5-hydroxy-6,7-dimethoxyflavone (22). Compound **15a** (15 g) was dissolved in a solution of anhydrous aluminum chloride (10 g) in acetonitrile (200 mL) and heated at 50 °C for 1.5 h. The solution was poured into 0.1 M hydrochloric acid and warmed at 60–70 °C for 1 h. The separated yellow precipitate was recrystallized from chloroform–methanol to give pale yellow needles (12.7 g, 87%); mp 166–167 °C; UV λ_{max} nm (log ε) (EtOH) 277 (4.25), 340 (4.43), (EtOH–$AlCl_3$) 258 (4.17), 292 (4.29), 358 (4.41); ^{1}H NMR ($CDCl_3$) δ 3.86, 3.88 (each 3 H, s, OMe), 5.15 (4 H, s, 2 OCH_2Ph), 6.38 (2 H, s, C_3- and C_8-H), 6.89 (1 H, d, J = 8.5 Hz, C_5-H), 12.60 (1 H, s, C_5-OH). Anal. ($C_{31}H_{26}O_7$) C, H.

3′,4′-Bis(benzyloxy)-5-hydroxy-7,8-dimethoxyflavone (25). Compound **24a** (500 mg) was dissolved in a solution of anhydrous aluminum bromide (3 g) in acetonitrile (30 mL), and the solution was heated at 40 °C for 30 min. The solution was poured into a mixture of ice and hydrochloric acid, and the separated precipitate was chromatographed on a silica gel column with chloroform. The first eluate was evaporated and recrystallized from ethyl acetate–methanol to give yellow needles (165 mg, 34%); mp

Table V. 6-Alkoxy-3′,4′-bis(benzyloxy)-5,7-dimethoxyflavones **15**, 5-Alkoxy-3′,4′-bis(benzyloxy)-6,7-dimethoxyflavones **23**, 3′,4′-Bis(benzyloxy)-7-(dodecyloxy)-5,6-dimethoxyflavone (**20h**), 5-Alkoxy-3′,4′-bis(benzyloxy)-7,8-dimethoxyflavones **24**, 3′,4′-Bis(benzyloxy)-7-(dodecyloxy)-5,8-dimethoxyflavone (**29h**), and 3′,4′-Bis(benzyloxy)-8-(dodecyloxy)-5,7-dimethoxyflavone (**34h**)

compd	synth method	mp, °C	recrystn solvent	yield, %	formula	anal.
15a[20]	A	123–125	MeOH	88	$C_{32}H_{28}O_7$	C, H
15b	A	109–111	EtOAc	73	$C_{35}H_{34}O_7$	C, H
15c	A	128–129	EtOAc	83	$C_{36}H_{36}O_7$	C, H
15d	B	89–90	MeOH	88	$C_{36}H_{36}O_7$	C, H
15e	A	135–137	EtOAc	90	$C_{37}H_{38}O_7$	C, H
15f	A	97–99	EtOAc	89	$C_{39}H_{42}O_7$	C, H
15g	A	97–98	EtOAc	86	$C_{41}H_{46}O_7$	C, H
15h	A	108–109	EtOAc	83	$C_{43}H_{50}O_7$	C, H
15i	A	98–100	EtOAc	68	$C_{45}H_{54}O_7$	C, H
15j	A	100–101	EtOAc	75	$C_{47}H_{58}O_7$	C, H
15k	A	101–102	EtOAc	80	$C_{49}H_{62}O_7$	C, H
23b	B	92–93	$CHCl_3$–hexane	78	$C_{35}H_{34}O_7$	C, H
23c	B	73.5–74.5	Et_2O–hexane	70	$C_{36}H_{36}O_7$	C, H
23d	B	92–93	$CHCl_3$–hexane	71	$C_{36}H_{36}O_7$	C, H
23e	B	89–90	EtOAc–hexane	90	$C_{37}H_{38}O_7$	C, H
23f	B	70–71	Et_2O–hexane	65	$C_{39}H_{42}O_7$	C, H
23g	B	90–91	Et_2O–hexane	67	$C_{41}H_{46}O_7$	C, H
23h	B	78–79	EtOAc–hexane	89	$C_{43}H_{50}O_7$	C, H
23i	B	81–82	hexane	80	$C_{45}H_{54}O_7$	C, H
23j	B	63–64	hexane	77	$C_{47}H_{58}O_7$	C, H
23k	B	45–46	hexane	60	$C_{49}H_{62}O_7$	C, H
20h	A	90–91	EtOAc–MeOH	78	$C_{43}H_{50}O_7$	C, H
24a	A	164–165	EtOAc	90	$C_{32}H_{28}O_7$	C, H
24h	B	114–115	MeOH	85	$C_{43}H_{50}O_7$	C, H
29h	A	105–107	EtOAc–Et_2O	94	$C_{43}H_{50}O_7$	C, H
34h	A	124–125	EtOAc	91	$C_{43}H_{50}O_7$	C, H

177–178 °C; UV λ_{max} nm (log ϵ) (EtOH) 254 (4.27), 276 (4.31), 337 (4.30), (EtOH–$AlCl_3$) 261 (4.23), 285 (4.29), 302 (4.22), 348 (4.33), 404 (4.05); ^1H NMR ($CDCl_3$) δ 3.85, 3.90 (each 3 H, s, OMe), 5.21 (4 H, s, 2 OCH_2Ph), 6.35 (1 H, s, C_6-H), 6.44 (1 H, s, C_3-H), 6.97 (1 H, d, J = 8.5 Hz, $C_{5'}$-H), 12.48 (1 H, s, C_5-OH). Anal. ($C_{31}H_{26}O_7$) C, H.

6-Alkoxy-3′,4′-bis(benzyloxy)-5,7-dimethoxyflavones 15a–k, 5-Alkoxy-3′,4′-bis(benzyloxy)-6,7-dimethoxyflavones 23b–k, 3′,4′-Bis(benzyloxy)-7-(dodecyloxy)-5,6-dimethoxyflavone (20h), 5-Alkoxy-3′,4′-bis(benzyloxy)-7,8-dimethoxyflavones 24a and 24h, 3′,4′-Bis(benzyloxy)-7-(dodecyloxy)-5,8-dimethoxyflavone (29h), and 3′,4′-Bis(benzyloxy)-8-(dodecyloxy)-5,7-dimethoxyflavone (34h). Synthetic Method A. A mixture of the ω-[3,4-bis(benzyloxy)benzoyl]acetophenone **14**, **19**, **28**, or **33** (6–7 mmol) and anhydrous sodium acetate (2 g) in acetic acid (15 mL) was heated at 140–145 °C for 2–3 h, diluted with water, and then extracted with ethyl acetate. The extract was washed with aqueous sodium carbonate, and the solvent was evaporated. The residue was recrystallized to give the corresponding alkoxyflavone as colorless needles (Table V).

Synthetic Method B. A mixture of the monohydroxyflavone **16**, **22**, or **25** (1 g, 2 mmol), the corresponding alkyl iodide (3–4 mmol), and anhydrous potassium carbonate (5 g) in acetone–*N*,*N*-dimethylformamide (1:1, 30 mL) was refluxed with stirring for 5–8 h. The mixture was diluted with water (50–60 mL) and concentrated to 20–30 mL under reduced pressure. The separated oily materials were extracted with ethyl acetate. The extract was washed with diluted hydrochloric acid and water, and then the solvent was evaporated. The residue was purified by recrystallization or by silica gel column chromatography using chloroform to give the corresponding alkoxyflavone as colorless needles or prisms (Table V).

5-Alkoxy-3′,4′-dihydroxy-6,7-dimethoxyflavones 5b–k, 6-Alkoxy-3′,4′-dihydroxy-5,7-dimethoxyflavones 6a–k, 7-(Dodecyloxy)-3′,4′-dihydroxy-5,6-dimethoxyflavone (8h), 5-Alkoxy-3′,4′-dihydroxy-7,8-dimethoxyflavones 9a and 9h, 7-(Dodecyloxy)-3′,4′-dihydroxy-5,8-dimethoxyflavone (10h), and 8-(Dodecyloxy)-3′,4′-dihydroxy-5,7-dimethoxyflavone (11h). The 3′,4′-bis(benzyloxy)flavone **15**, **20**, **23**, **24**, **29**, or **34** (600–900 mg) was hydrogenated over palladium on charcoal (10%, 100–150 mg) in methanol (60 mL)–ethyl acetate (20–30 mL) until the uptake of hydrogen ceased. After the catalyst was filtered off, the filtrate was evaporated. The residue was recrystallized to give the corresponding 3′,4′-dihydroxyflavone as colorless (or pale yellow) prisms or needles (Table I).

3′,4′-Diacetoxy-6-alkoxy-5,7-dimethoxyflavones 7a–k and 3′,4′-Diacetoxy-7-(dodecyloxy)-5,6-dimethoxyflavone (21h). The 3′,4′-dihydroxyflavone **6** or **8** was treated with hot acetic anhydride–pyridine to give quantitatively the diacetate as colorless needles (Table II).

6-Alkoxy-3′,4′,5-trihydroxy-7-methoxyflavones 1a–k and 7-(Dodecyloxy)-3′,4′,5-trihydroxy-6-methoxyflavone (2h). The diacetoxyflavone **7** or **21** (1.2 mmol) was dissolved in a solution of anhydrous aluminum chloride (1 g) in acetonitrile (20 mL) and heated at 60 °C for 1.5 h. The solution was poured into 0.1 M hydrochloric acid and warmed at 60–70 °C for 30 min, and then the separated precipitate was collected. A mixture of the precipitate and 6 M hydrochloric acid (30 mL) in methanol (200 mL) was refluxed for 3–4 h, diluted with water, and concentrated to 50–60 mL under reduced pressure. The separated crystals were recrystallized to give the corresponding 3′,4′,5-trihydroxyflavone as pale yellow prisms or needles (Table III).

7-Alkoxy-3′,4′,5-trihydroxy-8-methoxyflavones 3a and 3h and 8-(Dodecyloxy)-3′,4′,5-trihydroxy-7-methoxyflavone (4h). Compound **9a**, **10h**, or **11h** (0.5 mmol) was dissolved in a solution of anhydrous aluminum bromide (1.2 g) in acetonitrile (6 mL) and heated at 50 °C for 1 h. The solution was poured into 0.2 M hydrochloric acid and warmed at 50–60 °C for 1 h. The separated precipitate was recrystallized to give the corresponding 3′,4′,5-trihydroxyflavone as yellow needles (Table III).

Preparation and Assay of Enzymes. As the source of 5-lipoxygenase, rat basophilic leukemia cells were cultured, and the cells were disrupted by sonication followed by centrifugations as described previously.[25] The high-speed supernatant was fractionated by ammonium sulfate at 25–50% saturation. The precipitated enzyme was dissolved in 50 mM potassium phosphate buffer at pH 7.4 containing 10% ethylene glycol and 1 mM EDTA. The enzyme solution was applied to Sephadex G-25 gel filtration to remove ammonium sulfate. 12-Lipoxygenase was partially purified from procine leukocytes by ammonium sulfate fractionation and DEAE-cellulose chromatography as described earlier.[26] Prostaglandin endoperoxide synthase (cyclooxygenase) was purified from bovine vesicular gland by the method previously reported.[27]

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The 5-lipoxygenase reaction (arachidonic acid → 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid) was performed at 30 °C for 5 min in a 200-μL mixture containing 50 mM potassium phosphate buffer at pH 7.4, 2 mM ATP, 2 mM $CaCl_2$, 25 μM [1-^{14}C]arachidonic acid (50 000 cpm), and enzyme. The 12-lipoxygenase reaction (arachidonic acid → 12-hydroperoxy-5,8,10,14-eicosatetraenoic acid) was performed at 30 °C for 5 min in a 200-μL mixture containing 50 mM Tris·HCl buffer at pH 7.4, 25 μM [1-^{14}C]arachidonic acid (50 000 cpm), and enzyme. The prostaglandin endoperoxide synthase reaction (arachidonic acid → prostaglandin H_2) was performed at 24 °C for 2 min in a 200-μL mixture containing 0.1 M Tris·HCl buffer at pH 8.0, 2 μM hematin, 5 mM L-tryptophan, 25 μM [1-^{14}C]arachidonic acid (50 000 cpm), and enzyme. Termination of these enzyme reactions, extraction from the reaction mixtures, separation of substrates and products by thin-layer chromatography, and determination of radioactivity were described in individual papers.[25-27] The enzyme reaction was started by the addition of [1-^{14}C]arachidonic acid dissolved in 5 μL of ethanol. Each flavone compound at varying concentrations was dissolved in 4 μL of ethanol and added to the reaction mixture for 5-min preincubation with enzyme. Under the standard conditions the coefficient of intraassay variation was about 5.2% (n = 10). The intraassay variation of inhibitory effect of flavone compounds was determined with cirsiliol (**1a**) as a representative inhibitor. The coefficient of intraassay variation was 4.2% (n = 7) with 30 nM cirsiliol and 8.0% (n = 8) at 100 nM.

Registry No. **1a**, 34334-69-5; **1b**, 103776-90-5; **1c**, 102508-37-2; **1d**, 103776-91-6; **1e**, 103776-92-7; **1f**, 103776-93-8; **1g**, 103776-94-9; **1h**, 98892-90-1; **1i**, 103776-95-0; **1j**, 103776-96-1; **1k**, 102508-39-4; **2h**, 102508-35-0; **3a**, 10568-41-9; **3h**, 102508-36-1; **4h**, 102508-38-3; **5b**, 103776-66-5; **5c**, 103776-67-6; **5d**, 103776-68-7; **5e**, 103776-69-8; **5f**, 103776-70-1; **5g**, 103776-71-2; **5h**, 103776-72-3; **5i**, 103776-73-4; **5j**, 103776-74-5; **5k**, 103776-75-6; **6a**, 51145-79-0; **6b**, 103776-58-5; **6c**, 103776-59-6; **6d**, 103776-60-9; **6e**, 98892-88-7; **6f**, 103776-61-0; **6g**, 103776-62-1; **6h**, 98892-89-8; **6i**, 103776-63-2; **6j**, 103776-64-3; **6k**, 103776-65-4; **7a**, 97389-88-3; **7b**, 103776-80-3; **7c**, 103776-81-4; **7d**, 103776-82-5; **7e**, 98892-91-2; **7f**, 103776-83-6; **7g**, 103776-84-7; **7h**, 103776-85-8; **7i**, 103776-86-9; **7j**, 103776-87-0; **7k**, 103776-88-1; **8h**, 103776-76-7; **9a**, 90126-12-8; **9h**, 103776-77-8; **10h**, 103776-78-9; **11h**, 103776-79-0; **12**, 6962-57-8; **13a**, 22248-14-2; **13b**, 103777-33-9; **13c**, 103777-34-0; **13d**, 103777-35-1; **13e**, 98892-84-3; **13f**, 103777-36-2; **13g**, 103777-37-3; **13h**, 103777-38-4; **13i**, 103777-39-5; **13j**, 103777-40-8; **13k**, 103777-41-9; **14a**, 55274-37-8; **14a** (benzoate), 103777-48-6; **14b**, 103776-97-2; **14b** (benzoate), 103777-49-7; **14c**, 103776-98-3; **14c** (benzoate), 103777-50-0; **14e**, 98892-86-5; **14e** (benzoate), 103793-61-9; **14f**, 103776-99-4; **14f** (benzoate), 103777-51-1; **14g**, 103777-00-0; **14g** (benzoate), 103777-52-2; **14h**, 103777-01-1; **14h** (benzoate), 103777-53-3; **14i**, 103777-02-2; **14i** (benzoate), 103793-62-0; **14j**, 103777-03-3; **14j** (benzoate), 103777-54-4; **14k**, 103777-04-4; **14k** (benzoate), 103777-55-5; **15a**, 51145-78-9; **15b**, 103777-09-9; **15c**, 103777-10-2; **15d**, 103777-11-3; **15e**, 98892-87-6; **15f**, 103777-12-4; **15g**, 103777-13-5; **15h**, 103777-14-6; **15i**, 103777-15-7; **15j**, 103777-16-8; **15k**, 103777-17-9; **16**, 27181-96-0; **17**, 103777-42-0; **18h**, 103777-43-1; **19h**, 103777-05-5; **19h** (benzoate), 103777-56-6; **20h**, 103777-28-2; **21h**, 103776-89-2; **22**, 103777-60-2; **23b**, 103777-18-0; **23c**, 103777-19-1; **23d**, 103777-20-4; **23e**, 103777-21-5; **23f**, 103777-22-6; **23g**, 103777-23-7; **23h**, 103777-24-8; **23i**, 103777-25-9; **23j**, 103777-26-0; **23k**, 103777-27-1; **24a**, 103777-29-3; **24h**, 103777-30-6; **25**, 103777-61-3; **26**, 7499-99-2; **27a**, 7507-98-4; **27h**, 103777-44-2; **28a**, 103777-06-6; **28a** (benzoate), 103777-57-7; **28h**, 103777-07-7; **28h** (benzoate), 103777-58-8; **29h**, 103777-31-7; **30**, 103777-45-3; **31h**, 103777-46-4; **32h**, 103777-47-5; **33h**, 103777-08-8; **33h** (benzoate), 103777-59-9; **34h**, 103777-32-8; $H_3C(CH_2)_4I$, 628-17-1; $ICH_2CH_2CH(CH_3)_2$, 541-28-6; $H_3C(CH_2)_5I$, 638-45-9; $H_3C(CH_2)_7I$, 629-27-6; $H_3C(CH_2)_9I$, 2050-77-3; $H_3C(CH_2)_{11}I$, 4292-19-7; $H_3C(CH_2)_{13}I$, 19218-94-1; $H_3C(CH_2)_{15}I$, 544-77-4; $H_3C(CH_2)_{17}I$, 629-93-6; 4-(benzyloxy)-6-hydroxy-2,3-dimethoxyacetophenone, 25892-95-9; 3,4-bis(benzyloxy)benzoyl chloride, 1486-54-0; arachidonate 5-lipoxygenase, 80619-02-9.

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Studies on 1,2,3-Triazoles.[1] 13. (Piperazinylalkoxy)[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-ones with Combined H_1-Antihistamine and Mast Cell Stabilizing Properties

Derek R. Buckle,* Caroline J. M. Rockell, Harry Smith, and Barbara A. Spicer

Beecham Pharmaceuticals Research Division, Biosciences Research Centre, Great Burgh, Epsom, Surrey, KT18 5XQ England.
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Several *N*-benzylpiperazino derivatives of [1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one and its 5-methyl homologue have been prepared and evaluated for H_1-antihistamine activity on guinea pig ileum. The most potent compounds were also evaluated for their ability to stabilize mast cells in the rat passive peritoneal anaphylaxis (PPA) system and were shown to inhibit histamine release at concentrations below those required to inhibit extravasation, suggesting that this might be relevant to their antianaphylactic activity in this system. The compound tested with the most potent H_1-antihistamine activity was 6-[3-[4-(4-chlorobenzyl)-1-piperazinyl]propoxy][1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one, **28**, which had a pA_2 of 9.1 against histamine on guinea pig ileum, comparable to that of mepyramine, and inhibited histamine release in the rat PPA system with an IC_{50} value of 5.4×10^{-6} M.

In an earlier publication,[2] we reported the synthesis and biological evaluation of a small range-finding series of nitrocoumarin derivatives that combined potent H_1-antihistamine activity with mast cell stabilization. From this series, compound **1** was the most potent of the compounds studied. Subsequently, we have identified other potent mast cell stabilizing compounds based on [1]-benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (**2**)[3,4] and the related naphtho[2,3-*d*]-1,2,3-triazole **3**,[5] and we have now

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