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EFFECTS OF *ORTHO*-SUBSTITUENT GROUPS OF SULOCHRIN ON INHIBITORY ACTIVITY TO EOSINOPHIL DEGRANULATION

Hiroshi Ohashi*, Akihiro Ueno, Toyoo Nakao, Junko Ito, Kaname Kimura, Masaharu Ishikawa, Hiroyuki Kawai, Hiroshi Iijima and Tatsushi Osawa

Pharmaceutical Research Laboratory, Kirin Brewery Co., Ltd.,
3 Miyahara-cho, Takasaki, Gunma 370-1295, Japan

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Abstract: Sulochrin, a metabolite of fungi, has been shown to have an inhibitory activity to eosinophil degranulation. A series of sulochrin derivatives substituted at *ortho*-positions to the 10-carbonyl group was examined the activity. The importance of alkylester at C-6 position and several chemical properties of substituted groups at *ortho*-positions to exhibit activity are described. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

Eosinophils may play important roles in allergic diseases such as asthma and atopic dermatitis.[1, 2] In such diseases, eosinophils migrate to inflammatory sites and degranulate cytotoxic proteins such as major basic protein and eosinophil-derived neurotoxin (EDN). The cytotoxic proteins damage tissues and cause physiologic abnormalities in patients with allergic diseases. Therefore, eosinophil degranulation inhibitors may be anti-allergic drugs.

Recently, we found that sulochrin (**6**), a metabolite of fungi, was a specific inhibitor of eosinophil degranulation[3] and also inhibited eosinophil activation and chemotaxis.[4] We report here the effects of *ortho*-substituent groups on inhibitory activity to eosinophil degranulation.

Chemistry

Sulochrin (**6**) was synthesized as shown in scheme 1. Benzoic acid benzyl ester (**5**) was obtained by the condensation of 2-bromo benzyl alcohol (**2**) and benzoic acid (**4**). Anion induced rearrangement of (**5**) gave 1-benzoyl benzyl alcohol, which was oxidized to benzoyl benzoic acid without isolation.[5, 6] Esterification of the benzoyl benzoic acid followed by debenzylation afforded sulochrin (**6**).[7] All other sulochrin derivatives except for (**9**) were obtained through a modified methodology. Compound **9** was prepared as shown in scheme 2.

Results and Discussion

The derivatives of sulochrin (**6**) were examined for their inhibitory activity against eosinophil degranulation as described previously.[3] At first, ester derivatives were synthesized to examine the structure-activity relationship. As shown in Table 1a, alkyl esters (**11-15**) retained activity, and in particular, n-butyl and sec-butyl esters

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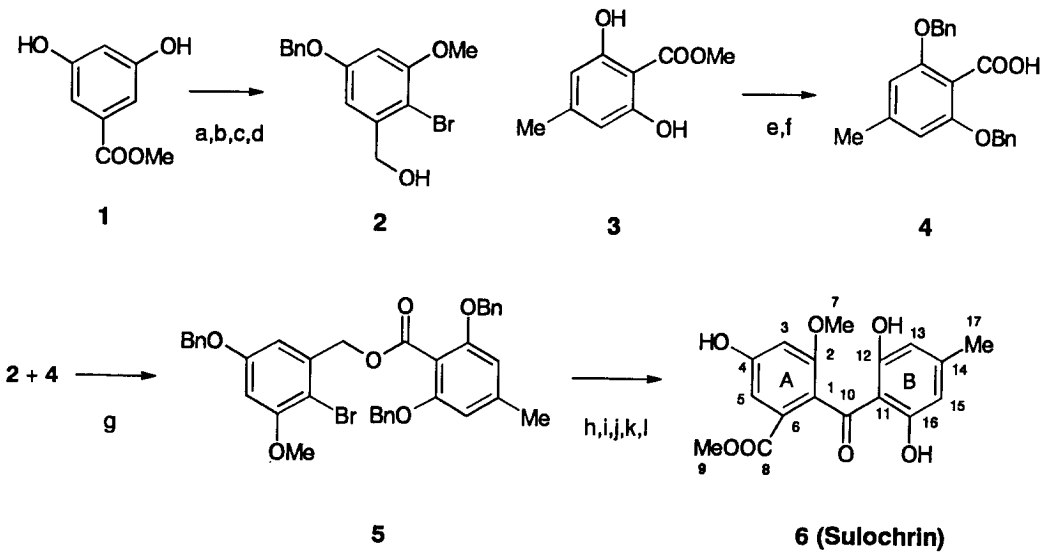
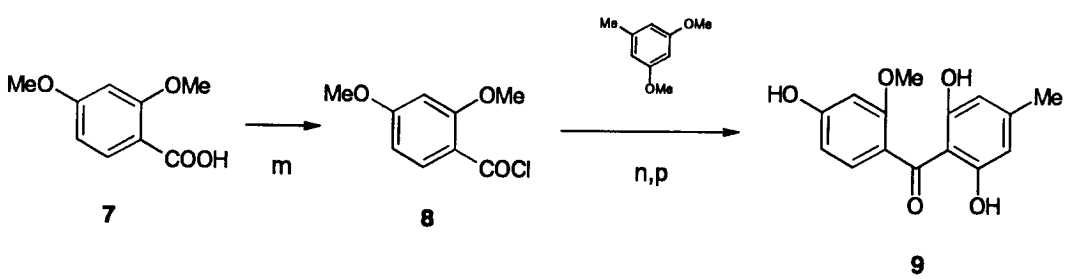
Scheme 1



(a) $BnBr,K_2CO_3/CH_3CN$/reflux,33%; (b) $Me_2SO_4,K_2CO_3/CH_3CN$/reflux,96%; (c) $LiAlH_4$/THF,96%; (d) NBS/CCl_4,43%; (e) $BnBr,K_2CO_3$/DMF/reflux,74%; (f) t-BuOK/iPr_2O/reflux,93%; (g) DEAD/PPh_3/THF,82%; (h) n-BuLi/THF,-78°C,45%; (i) PDC/DMF,54%; (j) $Bu_4(NH_4)KMnO_4$/Pyridine,81%; (k) MeI,K_2CO_3/DMF; (l) $Pd(OH)_2$-Carbon/EtOH/Cyclohexene/reflux, 81%

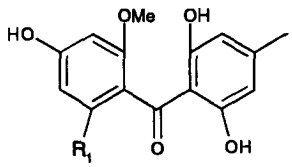
Scheme 2



(m) $SOCl_2$; (n) n-BuLi/THF, -45°C,15%; (P) BBr_3/CH_2Cl_2,64%

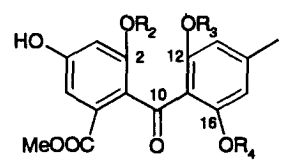
(**13** and **14**) showed more potent activity than sulochrin (**6**). On the other hand, decarboxyl and free carboxylic acid derivatives (**9** and **10**) did not show any activity even at 10 μM. These results suggest that the existence of

Table 1a Effects of alkylester on eosinophil degranulation



Compound	R_1	IC_{50} (microM)
Sulochrin (**6**)	$COOCH_3$	0.1
9	H	>10
10	COOH	>10
11	$COOCH_2CH_3$	0.1
12	$COOCH_2CH_2CH_3$	0.1
13	$COOCH_2CH_2CH_2CH_3$	0.04
14	$COO(CH)CH_3CH_2CH_3$	0.03
15	$COO(CH_2)_5CH_3$	0.3

Table 1b Effects of phenolic hydroxyl groups on eosinophil degranulation



Compound	R_2	R_3	R_4	IC_{50} (microM)
Sulochrin (**6**)	Me	H	H	0.1
16	H	Me	H	0.4
17	Me	Me	H	0.3
18	H	Me	Me	>10
19	H	H	H	>10
20	Me	$(CH_2)_2OH$	$(CH_2)_2OH$	>10

alkyl ester at C-6 position is essential and sec-butyl ester is most suitable for activity.

Next, we examined the importance of methoxy and hydroxyl groups at C-2, C-12 and C-16 positions (Table 1b). Compared to sulochrin (**6**), **19** showed much less activity. Activity of **16** approached that of sulochrin (**6**) after methylation of hydroxyl group at C-12 position in **19**. Furthermore, compound **17** also showed activity. These results indicate that at least one methoxy group at C-2 or C-12 position is required for activity.

Compound **18**, in which two methoxy groups at C-12 and C-16 positions on the ring B were introduced, showed much less activity than **16** or **17**. Furthermore, compound **20** also lost activity. These results indicate that at least one free hydroxyl group at *ortho*-position on the ring B is required for activity, suggesting that hydrogen bond between 16-OH and carbonyl at C-10 might contribute to activity. We have recently shown that substituents at *ortho*-positions showed effect on the conformation from the analysis of crystal structures of sulochrin derivatives.[8] The hydrogen bond between 16-OH and carbonyl at C-10 may contribute to the conformation where the ring B and the central carbonyl planes are co-planner and cross at a right angle to the

ring A. This conformation would be inaccessible to the less active compounds that lack the hydrogen bond, supporting the speculation. Compounds **10** and **19**, which have more hydrophilic substitution at *ortho*-positions, lost activity. Therefore, hydrophobicity is also important for activity.

In conclusion, we found that i) alkylester at C-6 position is required; ii) sec-butyl ester at C-6 position is optimal for activity; iii) optimal hydrophobicity of the *ortho*-substituents may exist; and iv) the conformation of sulochrin may influence to the inhibitory activity against eosinophil degranulation.

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