

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1945-1948

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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

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> > Received 16 March 1999; accepted 25 May 1999

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 cosinophil degranulation³ and also inhibited cosinophil activation and chemotaxis.⁴ We report here the effects of *ortho*-substituent groups on inhibitory activity to cosinophil 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



(a) BnBr,K₂CO₃/CH₃CN/reflux,33%; (b) Me₂SO₄,K₂CO₃/CH₃CN/reflux,96%; (c) LiAlH₄/THF,96%; (d) NBS/CCI₄,43%; (e) BnBr,K₂CO₃/DMF/reflux,74%; (f) t-BuOK/iPr₂O/reflux,93%; (g) DEAD/PPh₃/THF,82%; (h) n-BuLi/THF,-78°C,45%; (j) PDC/DMF,54%; (j) Bu₄(NH₄)KMnO₄/Pyridine,81%; (k) Mel,K₂CO₃/DMF; (l) Pd(OH)₂-Carbon/EtOH/Cyclohexene/reflux, 81%





(m) SOCI2; (n) n-BuLi/THF, -45°C, 15%; (P) BBr3/CH2CI2, 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 μ M. These results suggest that the existence of

Scheme 1

	Compound	R ₁	IC ₅₀ (microM) 0.1			
	Sulochrin (6)	COOCH ₃				
	9	Н	>10			
	10	СООН	>10			
	11	COOCH₂CH₃	0.1			
	12	COOCH₂CH₂CH₃	0.1			
г, И Он В, О Он	13	COOCH ₂ CH ₂ CH ₂ CH ₃	0.04			
	14	COO(CH)CH ₃ CH ₂ CH ₃	0.03			
	15	COO(CH ₂) ₅ CH ₃	0.3			

Table 1a Effects of alkylester on eosinophil degranulation

Table 1b Effects of phenolic hydroxyl groups on eosinophil degranulation

	Compound	R ₂	R ₃	R4	IC ₅₀ (microM)
OR. OR.	Sulochrin (6)	Me	Н	Н	0.1
	16	н	Me	н	0.4
	17	Me	Me	Н	0.3
	18	н	Me	Ме	>10
	19	н	н	н	>10
	20	Me	(CH₂)₂OH	(CH₂)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 cosinophil degranulation.

Acknowledgements

We thank to Dr. Masakazu Sakakibara for critical reading of this manuscript.

References and Notes

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