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INHIBITORY EFFECTS OF (4-ALKOXY-2, 3, 6-TRIMETHYLPHENYL) GLYCOPYRANOSIDES ON HISTAMINE RELEASE INDUCED BY ANTIGEN-ANTIBODY REACTION

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The inhibitory effects of newely synthesized 4-alkoxy-2, 3, 6-trimethylphenyl D-glycopyranosides on histamine release induced by antigen-antibody reaction were examined. Among the compounds tested, 4-hexoxy-2, 3, 6-trimethylphenyl α-D-mannopyranoside exhibited the strongest inhibitory effect. Furthermore, 4-hexoxy-2, 3, 6-trimethylphenyl α-D-glucopyranoside and α-D-galactopyranoside markedly inhibited antigen-induced histamine release, and their activities were more potent than those of the corresponding β-anomers. These results suggest that these compounds may possess excellent anti-allergic activities.

KEYWORDS histamine release; histamine release inhibition; antigen-antibody reaction; 4-alkoxy-2, 3, 6-trimethylphenyl glycopyranoside; 4-hexoxy-2, 3, 6-trimethylphenyl α-D-mannopyranoside

The cells involving immunological responses are known to be activated by a variety of stimuli via the recognition of carbohydrate chains of glycoproteins. Immunoglobulin E (IgE) contains D-mannose-containing carbohydrate chains in the crystallizable fragment (Fc) portion of its molecule. [1] Concanavalin A (Con A), a plant lectin, is specifically attached to the carbohydrate chains of IgE to induce the release of chemical mediators. [2] High concentrations of mannose and methyl α-D-mannopyranoside have been shown to inhibit histamine release from mast cells induced not only by Con A but also by antigen-antibody reaction. [3] This fact indicates the existence of the recognition of carbohydrate chains in an antigen-antibody reaction similar to the recognition of Con A of carbohydrate chains in an IgE molecule. We previously reported that alkylphenyl α-D-mannopyranosides inhibited histamine release from sensitized rat peritoneal mast cells induced by ovalbumin (antigen), and their inhibitory effects were correlated with the hydrophobic substituent constant (π) values. [4] Among the compounds tested, 2, 4, 6-trimethylphenyl α-D-mannopyranoside exhibited the strongest inhibitory effect on antigen-induced histamine release, and had inhibitory effects on Schultz-Dale reaction and 48 h homologous passive cutaneous anaphylaxis (PCA) in rats. In the present study, we newly synthesized 4-alkoxy-2, 3, 6-trimethylphenyl glycopyranosides, and investigated their inhibitory effects on histamine release induced by antigen-antibody reaction.

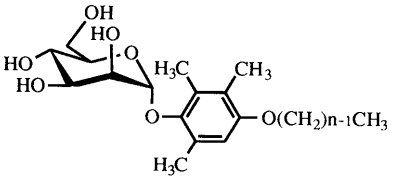
The compounds tested were synthesized according the Helferich method. [5] Namely, condensations of pentaacetyl β-D-glycopyranosides, prepared by the method of Dale, [6] with 4-alkoxy-2, 3, 6-trimethylphenols, produced from hydroquinones and alcohols by the method of Taniguchi,[7] in the presence of stannic chloride anhydrous in benzene produced 4-alkoxy-2, 3, 6-trimethylphenyl D-glycopyranoside tetraacetates, and then these compounds were deacetylated with a catalytic amount of sodium methoxide in methanol to afford the 4-alkoxy-2, 3, 6-trimethylphenyl D-glycopyranosides. The physical properties are shown in Table I. Preparation of rat peritoneal

mast cells, sensitization of the cells by rat anti-ovalbumin serum and assay of histamine release from passively sensitized rat peritoneal mast cells were carried out according to the methods described in the previous paper.[4)]

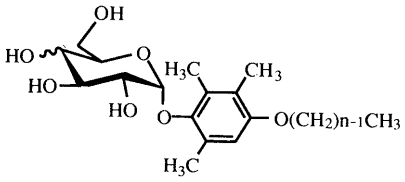
As shown in Table II, the 4-alkoxy-2, 3, 6-trimethylphenyl α-D-mannopyranosides tested inhibited histamine release induced by antigen-antibody reaction in a concentration-dependent manner, and exhibited more potent inhibitory effects than 2, 4, 6-trimethylphenyl α-D-mannopyranoside. Their inhibitory potency increased in proportion to the number of carbons in 4-alkoxy group of these compounds. These results suggest the correlation between hydrophobicities and inhibitory effects of these compounds similar to alkylphenyl α-D-mannopyranosides. Among the compounds tested, Man-α-C6 showed the strongest activity, and was approximately one thousand times more effective than 2, 4, 6-trimethylphenyl α-D-mannopyranoside. With respect to 4-alkoxy-2, 3, 6-trimethylphenyl D-glucopyranosides and D-galactopyranosides, 4-hexoxy-compounds with an α-configuration at the anomeric carbon atom exhibited good inhibitory effects, and their activities were more potent than those of the corresponding β-anomers. The inhibitory effects of Glc-α-C6 and Gal-α-C6 were almost equal, but were less potent than Man-α-C6. On the other hand, the inhibitory effects of 4-ethoxy-compounds, such as Glc-α-C2, Glc-β-C2, Gal-α-C2 and Gal-β-C2, were minor.

From the present study, it is apparent that the recognitions of not only carbohydrate chains but also hydrophobic binding portion exist in an antigen-antibody reaction. Among the componds tested in the present investigation, Man-α-C6, Glc-α-C6 and Gal-α-C6 appear to be useful lead compounds in the development of new anti-allergic drugs. The anti-allergy actions of these compounds are now in progress.

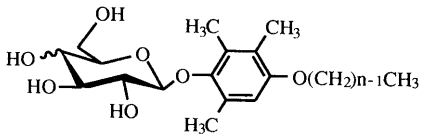
Table I. Physical Properties of 4-Alkoxy-2,3,6-trimethylphenyl D-glycopyranosides



Man-α-Cn n=2,4,6



Glc-α-Cn n=2,6
Gal-α-Cn n=2,6



Glc-β-Cn n=2,6
Gal-β-Cn n=2,6

Compound	n	mp (℃)	Yield (%)	$[\alpha]_D^{20}$ a)	NMR (ppm) b)	
					^1H	^{13}C
Man-α-C2	2	145-146	35	+ 89	5.62	105.5
Man-α-C4	4	184-183	37	+ 90	5.62	105.3
Man-α-C6	6	180-183	29	+ 87	5.61	105.5
Glc-α-C2	2	168-170	15	+ 121	5.75 (d, J=3.9Hz)	102.9
Glc-α-C6	6	143-145	19	+ 124	5.76 (d, J=3.9Hz)	103.0
Glc-β-C2	2	203-205	36	- 4.9	5.26 (d, J=7.2Hz)	106.2
Glc-β-C6	6	132-135	35	- 5.8	5.26 (d, J=7.2Hz)	106.4
Gal-α-C2	2	202-205	20	+ 121	5.83 (d, J=4.0Hz)	103.3
Gal-α-C6	6	145-148	18	+ 125	5.83 (d, J=4.0Hz)	103.4
Gal-β-C2	2	204-207	35	- 3.2	5.19 (d, J=7.8Hz)	106.1
Gal-β-C6	6	156-157	34	- 5.1	5.19 (d, J=7.8Hz)	106.1

a) Determined in methanol (c=1).

b) Chemical shifts of anomeric center measured in pyridine-d_5.

Table II. Inhibitory Effects of 4-Alkoxy-2,3,6-trimethylphenyl D-glycopyranosides on Histamine Release from Rat Peritoneal Mast Cells Induced by Antigen-Antibody Reaction

Compd.	Conc. (M)	Inhibition (%)	Compd.	Conc. (M)	Inhibition (%)
2,4,6-Trimethylphenyl α-D-mannopyranoside	$1x10^{-4}$	3.6	Glc-β-C2	$1x10^{-5}$	2.1
	$1x10^{-3}$	56.1		$1x10^{-4}$	1.8
Man-α-C2	$1x10^{-5}$	13.0	Glc-β-C6	$1x10^{-5}$	6.5
	$1x10^{-4}$	50.0		$1x10^{-4}$	28.4
Man-α-C4	$1x10^{-6}$	9.2	Gal-α-C2	$1x10^{-5}$	3.7
	$1x10^{-5}$	32.3		$1x10^{-4}$	10.3
	$1x10^{-4}$	87.1	Gal-α-C6	$1x10^{-6}$	33.7
Man-α-C6	$1x10^{-6}$	50.2		$1x10^{-5}$	69.2
	$1x10^{-5}$	91.4		$1x10^{-4}$	93.6
Glc-α-C2	$1x10^{-5}$	5.5	Gal-β-C2	$1x10^{-5}$	2.1
	$1x10^{-4}$	6.5		$1x10^{-4}$	1.8
Glc-α-C6	$1x10^{-6}$	32.3	Gal-β-C6	$1x10^{-6}$	14.3
	$1x10^{-5}$	75.4		$1x10^{-5}$	29.4
				$1x10^{-4}$	48.1

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