

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

Tzer Chuan WANG, Hisao KAKEGAWA, Shigeru NAKAISHI, Hitoshi MATSUMOTO, and Toshio SATOH*
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

The inhibitory effects of newly 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.

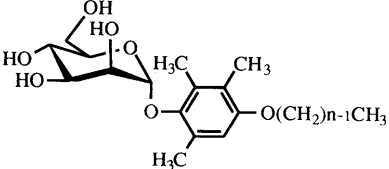
The compounds tested were synthesized according the Helferich method. ⁵⁾ Namely, condensations of pentaacetyl β -D-glycopyranosides, prepared by the method of Dale, ⁶⁾ with 4-alkoxy-2, 3, 6-trimethylphenols, produced from hydroquinones and alcohols by the method of Taniguchi,⁷⁾ in the presence of stannic 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⁾

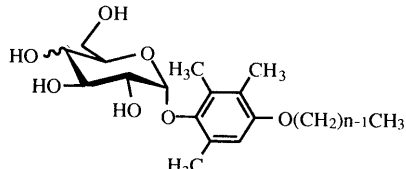
As shown in Table II, the 4-alkoxy-2, 3, 6-trimethylphenyl α -D-mannopyranosides tested inhibited histamine release induced by antigen-antibody reaction in a concentration-dependent manner, and exhibited more potent inhibitory effects than 2, 4, 6-trimethylphenyl α -D-mannopyranoside. Their inhibitory 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 compounds 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.

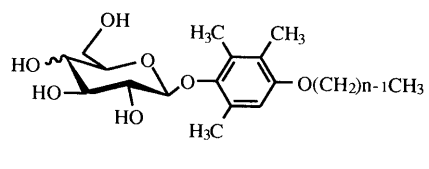
Table I. Physical Properties of 4-Alkoxy-2,3,6-trimethylphenyl D-glycopyranosides



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 (°C)	Yield (%)	[α] _D ^{20 a)}	NMR (ppm) ^{b)}	
					¹ H	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, <i>J</i> =3.9Hz)	102.9
Glc- α -C6	6	143-145	19	+ 124	5.76 (d, <i>J</i> =3.9Hz)	103.0
Glc- β -C2	2	203-205	36	- 4.9	5.26 (d, <i>J</i> =7.2Hz)	106.2
Glc- β -C6	6	132-135	35	- 5.8	5.26 (d, <i>J</i> =7.2Hz)	106.4
Gal- α -C2	2	202-205	20	+ 121	5.83 (d, <i>J</i> =4.0Hz)	103.3
Gal- α -C6	6	145-148	18	+ 125	5.83 (d, <i>J</i> =4.0Hz)	103.4
Gal- β -C2	2	204-207	35	- 3.2	5.19 (d, <i>J</i> =7.8Hz)	106.1
Gal- β -C6	6	156-157	34	- 5.1	5.19 (d, <i>J</i> =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	1×10^{-4}	3.6	Glc- β -C ₂	1×10^{-5}	2.1
α -D-mannopyranoside	1×10^{-3}	56.1		1×10^{-4}	1.8
Man- α -C ₂	1×10^{-5}	13.0	Glc- β -C ₆	1×10^{-5}	6.5
	1×10^{-4}	50.0		1×10^{-4}	28.4
Man- α -C ₄	1×10^{-6}	9.2	Gal- α -C ₂	1×10^{-5}	3.7
	1×10^{-5}	32.3		1×10^{-4}	10.3
	1×10^{-4}	87.1	Gal- α -C ₆	1×10^{-6}	33.7
Man- α -C ₆	1×10^{-6}	50.2		1×10^{-5}	69.2
	1×10^{-5}	91.4		1×10^{-4}	93.6
Glc- α -C ₂	1×10^{-5}	5.5	Gal- β -C ₂	1×10^{-5}	2.1
	1×10^{-4}	6.5		1×10^{-4}	1.8
Glc- α -C ₆	1×10^{-6}	32.3	Gal- β -C ₆	1×10^{-6}	14.3
	1×10^{-5}	75.4		1×10^{-5}	29.4
				1×10^{-4}	48.1

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