

# Glucosamine Derivatives Sulfo Disaccharides Co-Working with Klotho

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## Abstract

I found sulfo disaccharides which co-working with Klotho. The disaccharides have glucosamine structure and similar structure with hyaluronic acid and chondroitin. Relations of the disaccharide, Klotho, hyaluronic acid, chondroitin, glucosamine with health and anti-ageing were discussed. Klotho makes disaccharide from glucosamin and glucuronic acid and co-works on site with produced disaccharide and gives stable Ca homeostasis and consequent health, anti-ageing and long life.

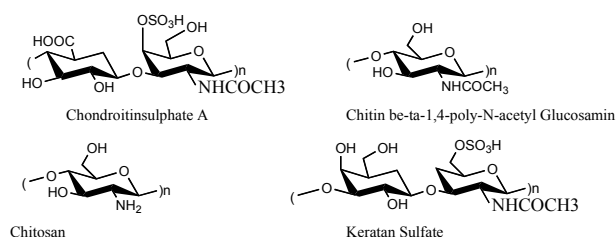
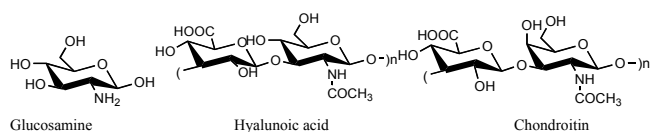
**Keywords:** Sulfo disaccharide; Klotho; Glucosamine; Hyaluronic acid; Chondroitin; Anti-ageing; Health food; Long life.

## Introduction

Glucosamine, hyaluronic acid, chondroitin are now used as health food by many persons in Japan. Suntory sold 19 million bottles of glucosamine and chondroitin as nutrition supporting food. Setagaya shizenshokuhin sold 200 million bags of glucosamin, hyaluronic acid and chondroitin as health food for 11 years. Taishoseiyaku are selling glucosamine and chondroitin. Zeria Shinyaku is selling chondroitin as medicine for 60 years. Wada calcium pharmaceutical sold 10 million bags containing glucosamin, chondroitin sulfate and collagen as nutrition supporting food. About 5 million persons are drinking and eating these materials and enjoying health and long life. Average life in Japan: male is 80.50 (third) female is 86.83 (top in the world). Food will be concerned with long life. I am trying to find the reason why glucosamine; hyaluronic acid and chondroitin are so much used. By the studies of glucosamine derivatives. I found one reason why these compounds are consumed as health food.

## Glucosamine derivatives

When we look at glucosamine derivative from natural products, we can find many compounds like hyaluronic acid, chondroitin, chondroitin sulfate, chitin, chitosan, keratan sulfate, proteoglycan sulfate (chondromucoprotein). Hyaluronic acid is poly (glucuronosyl (1-3) glucoside) and chondroitin is poly (glucuronosyl (1-3) galactoside).



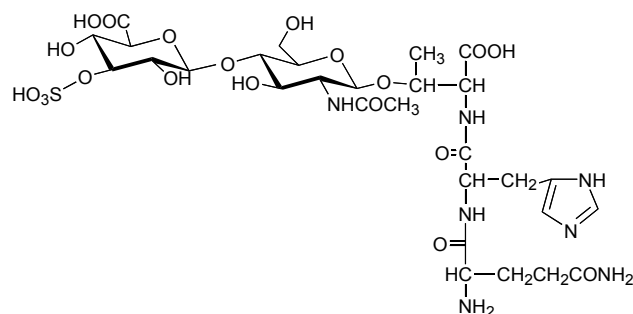
Soft bone, cartilage: Proteoglycan sulfate is proteoglycan aggregate composed of Hyaluronic acid and core-protein.

## Klotho and sulfo disaccharide

Nabeshima found that mutation of mouth Klotho gene leads to

a syndrome resembling ageing [1]. Since then many reports [2-29] are published. Petouou et al. reported that saccharides are involved in the binding of Klotho and FGF. Martin-Lumas report the activation of fibroblast growth factors by heparin Klotho is a novel  $\beta$ -glucuronidase capable of hydrolyzing steroid  $\beta$ -glucuronides.

Nabeshima found a sulfo disaccharide from mouse liver cell. This saccharide binds with  $\alpha$ Klotho and regulates the binding of  $\alpha$ Klotho and FGF23. Mass analysis of this compound showed Mass number 843.28.  $C_{30}H_{49}N_7O_{19}S$  corresponding Thr-His-Gln-O-( $\beta$ -D-3-sulfo-glucuronosyl) (1-4)-2-acetoamid-2-deoxy-D-glucopyranoside 9205



Gln-His-Thr-( $\beta$ -D-3-sulfo-glucuronosyl) (1-3)-2-acetamido-2-deoxy-glucopyranoside 9205

I planned to identify the real structure of this natural disaccharide by organic synthesis starting from known starting materials. Several disaccharides having similar structures were synthesized and relation of chemical structure and binding activity with Klotho and FGF 23 were studied

## Synthesis of sulfo disaccharide and measurements of binding activity

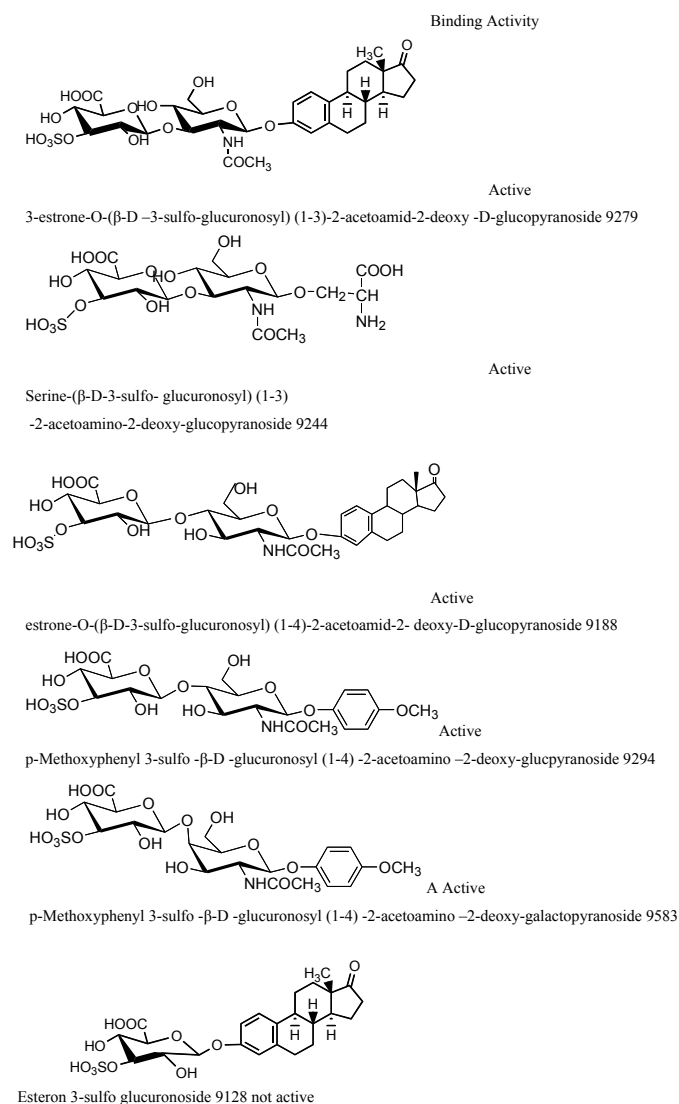
I have synthesized following compounds and measured their binding activity with Klotho and FGF23

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Received August 28, 2015; Accepted September 07, 2015; Published September 14, 2015

**Citation:** Ozaki O (2015) Glucosamine Derivatives Sulfo Disaccharides Co-Working with Klotho. J Nutr Food Sci 5: 416. doi:10.4172/2155-9600.1000416

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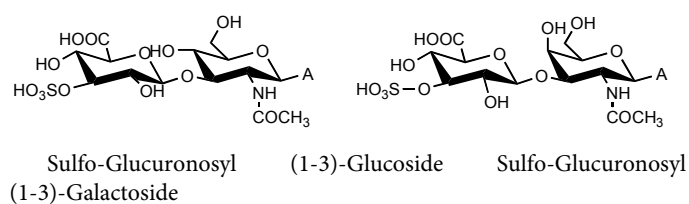


### Structure activity relationship

The binding activities of synthesized compounds, 9214, 9188, 9583, 9279, 9244 were measured. The activities of these 5 compounds were almost same irrespective of (1-4) or (1-3) bond, glucopyranoside or galactopyranoside, p-methoxyphenyl, or esterone, or serine.

### Structure of sulfo disaccharides

I planned to determine chemical structure of natural disaccharide by synthesis. But I cannot determine (1-3) bond or (1-4) bond. Because both bond compounds showed activity. Disaccharides have close relation with hyaruronic acid and chabdroitin. Hyaruronic acid and chodroitin have (1-3) bond. Therefore I wish to propose (1-3) bonded two structures: Sulfo-Glucuronosyl (1-3)-Glucoside, Sulfo-Glucuronosyl (1-3)-Galactoside as natural disaccharide

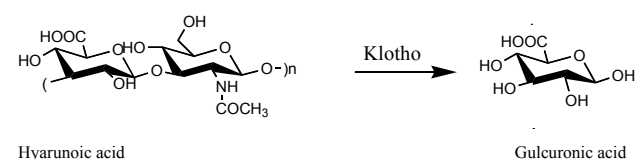


(A: attached molecule like estrone, vitamine D, amino acid, oligo peptide)

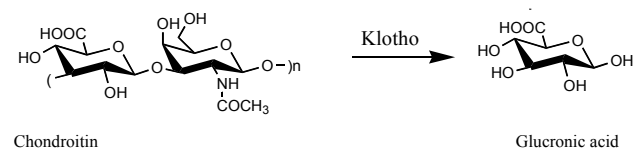
### Relation of Klotho, sulfo-disaccharide, glucosamin, hyaruronic acid and chondroitin

Klotho is an enzyme that in humans is encoded by the KL gene [2]. This gene encodes protein that is related to β-glucuronidases. Klotho is a novel β-glucuronidases. β-Glucuronidase is an enzyme that can cleave glucuronosyl bond and this enzyme must do reverse reaction that is this enzyme can bind glucuronosyl group. Therefore Klotho can make disaccharide from glucuronic acid and glucosamine. Hyaluronic acid is poly (glucuronosyl(1-3)glucoside) and chondroitin is poly(glucuronosyl(1-3)galactoside).

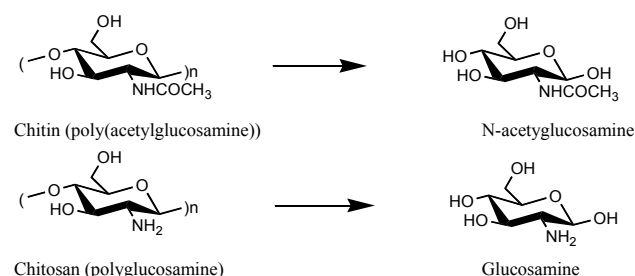
#### Hyaluronic acid gives gulcuronic acid by Klotho



#### Chondroitin gives glucronic acid by Klotho

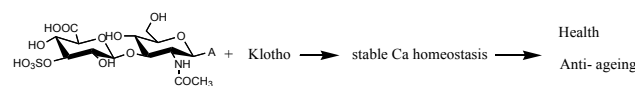


#### Depolymerization of chitin gives N-acetylglucosamine. Depolymerization of chitosan gives glucosamine



#### Klotho combine glucuronic acid and glucosamine to afford disaccharide

Klotho co-work with produced disaccharide on site to afford stable Ca homeostasis and subsequent Health and Anti-aging.



#### These schemes indicate that Klotho is playing multiple roles

- Production of glucuronic acid
- Production of disaccharide
- Production of stable Ca homeostasis co-working with disaccharide

These schemes show that disaccharides, Klotho, Hyaluronic acid, Chondroitin, glucosamine are working closely related all together and giving us heath and anti-aging.

## Function of Klotho and sulfo disaccharide

To show the function of Klotho and disaccharide, I picked up typical papers about anti-aging, Ca homeostasis, phosphate balance, and control of other compounds

### Anti-aging

- Mutation of the mouse klotho gene leads to a syndrome resembling ageing» [1]

«Suppression of Aging in Mice by the Hormone Klotho» [3]

«Association of human aging with a functional variant of klotho» [4]

Life Extension Factor Klotho Enhances Cognition, [5,6]

Challenge of overcoming aging-related disorders [7]

«Klotho and aging» [8]

«Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system». [9]

«Klotho is a serum factor related to human aging» [10]

«PPAR-gamma and aging: one link through klotho?» [11]

### Ca homeostasis

- Alpha-Klotho as a regulator of calcium homeostasis [12]
- Chronic kidney disease (CKD) and bone. Regulation of calcium and phosphate metabolism by FGF23/Klotho» [13]
- Discovery of alpha-Klotho and FGF23 unveiled new insight into calcium and phosphate homeostasis» [14]
- Molecular function of  $\alpha$ -Klotho in calcium homeostasis [15]

### Phosphate balance

- «Fibroblast Growth Factor 23-Klotho: a new axis of phosphate balance control» [16]
- «FGF23-mediated regulation of systemic phosphate homeostasis: is Klotho an essential player?» [17].
- «Fibroblast Growth Factor 23-Klotho: a new axis of phosphate balance control» [18].
- «Klotho gene, phosphocalcic metabolism, and survival in dialysis» [19].
- «Discovery of alpha-Klotho and FGF23 unveiled new insight into calcium and phosphate homeostasis» [20].
- Control of other compounds
- «Functional variant of KLOTHO: a breast cancer risk modifier among BRCA1 mutation carriers of Ashkenazi origin» [21].
- «Klotho: an anti-aging protein involved in mineral and vitamin D metabolism [22].
- «Genetic variation in healthy oldest-old» [23].
- «KLOTHO gene polymorphisms G-395A and C1818T are associated with lipid and glucose metabolism, bone mineral density and systolic blood pressure in Japanese healthy subjects» [24].

- «The Klotho gene family and the endocrine fibroblast growth factors» [25].

Klotho is a regulator of Calcium homeostasis [12,15] working with produced disaccharide Klotho makes disaccharide from glucosamine and glucuronic acid and co-works with produced disaccharide on site and gives stable Ca homeostasis and consequent health and anti-ageing.

### Summary

Klotho makes disaccharide from glucosamin and glucuronic acid and co-working with produced disaccharide and contribute to Ca homeostasis and subsequent health and anti-ageing Glucosamine, chondroitin and hyarunoic acid are starting material to make sulfo disaccharide.

### Acknowledgements

The author wish to express gratitude to Dr Yoichi Nabeshima and Dr.Katsuhiko Mikoshiba for their advice and suggestion and Dr. Ryota Maeda for activity measurement and Dr Yukito Ito, Dr Yuji Matsuzaki and Dr.Hideeki Ishida for helpful advices for the synthesis of compounds.

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