Design and Synthesis of Bioactive Valienamine-type Chaperones

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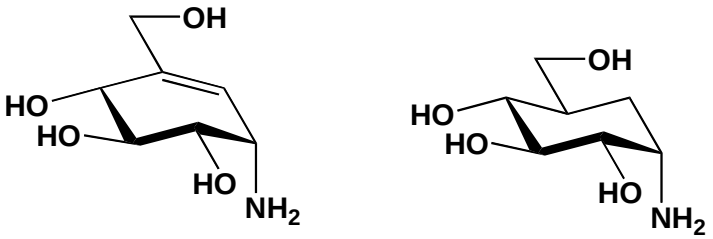
Valienamine (**1**) is the unsaturated derivative of carbocyclic analogues of glycosylamines. Its α- and β-anomeric isomers are not interconvertible each other, existing as chemically stable forms (Fig. 1). Compound **1** was first isolated from antibiotic validamycins and found to possess a strong inhibitory activity against α-glucosidase. It was also shown as one of the components of pseudo-tetrasaccharide, α-amylase inhibitor acarbose, which has been clinically important to control diabetes. Later, starting from valiolamine, the hydrated form of **1**, potent α-glucosidase inhibitor voglibose has been developed and widely used equally as acarbose.

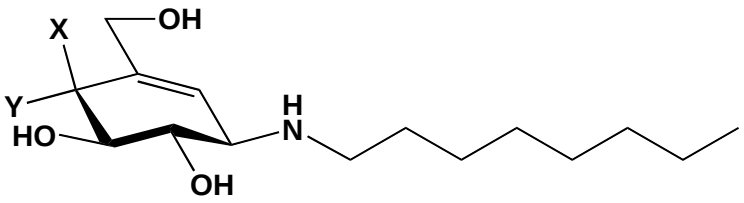


Valienamine (1) **Validamine (2)**

Fig. 1. Naturally occurring bioactive carba-glycosylamines

One of the authors has so far been engaged in a synthetic study on new glycosidase inhibitors composed of bioactive carbasugars. Inhibitory actions of valienamine (**1**) and its saturated form validamine (**2**) are likely to be understood by postulating their binding to the active site of the enzyme, adopting the activated forms mimicking a putative transition state of hydrolysis of glucopyranosides.

Concerning structural features of the carbasugar moieties of the carbaglycosylceramide analogues, designed for glycocerebrosidase inhibitors, the difference between pseudo-glucosyl and galactosyl parts have been demonstrated to be well in accord with their stereospecific inhibitory actions against two glycosylcerebrosidases, respectively. *N*-Octyl-β-valienamine (**3**, NOV) and 4-epi-β-valienamine (**4**, NOEV, Fig. 2) were first designed and synthesized during chemical modification of complex structures of carbaglycosylceramides. Both these compounds have been shown to be very strong and specific glycocerebrosidase inhibitors compatible with the lead compounds.



***N*-Octyl-β-valienemine** **NOV (3)** **X = H, Y = OH**

***N*-Octyl-4-epi-β-valienemine** **NOEV (4)** **X = OH, Y = H**

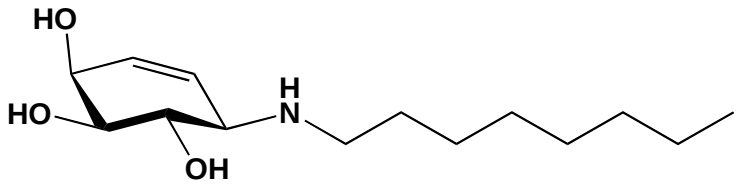
Fig. 2. Potent chaperone compounds NOV and NOEV

After a few years Prof. Yoshiyuki Suzuki had a rare opportunity to come across NOEV, finding a strong inhibitory activity toward human β-galactosidase (IC_{50} 0.13 μM), along with notable chaperone activity to increase catalytic activity of the mutant enzyme in a human genetic disease G_{M1}-gangliosidosis. Although, thanks to a lot of efforts, NOEV has been established to serve a promising candidate of therapeutic agent for the disease, further development has disappointedly been faced with a difficulty in supplying a sufficient amount of the compound needed for detailed biological assay.

Recently bioconversion of *myo*-inositol has been shown to provide synthetically useful chiral deoxyinositols (quercitols). Among three stereoisomers, obtained selectively under controlled conditions, two compounds with *vibo*- and *proto*-configurations could be easily transformed into NOV and NOEV, respectively. Actually new convenient processes would provide an effective chance for further investigation of NOEV and related analogs.

On the other hand, during elucidation of a structure-inhibitory activity of these compounds, elaboration of the second generation of NOEV has begun to attract our attention. Alternatively, in order to have an easy access to a large quantity of active compounds, an attempt has been made to improve the previous processes as well as to make NOEV simpler preserving its chaperone activity. Therefore, trimming off its C-5

hydroxymethyl of **4**, the 5-dehydroxy and 5-dehydroxymethyl derivatives could be synthesized in turn, and biological assay has been carried out.



***N*-Octyl-conduramine F-4** **5-Dehydroxymetyl NOEV (5)**

Fig. 3. *N*-Octyl-conduramine F-4, the second-generation of chaperone compound NOEV

Very recently, we have worked out a series of potent chaperone compounds, *N*-substituted conduramines, one of which the *N*-octyl derivative (**5**, Fig. 3) is demonstrated by a preliminary test to possess biochemical features, fully compatible with **4**. In this lecture we discuss the synthesis and chaperone activity of **5** and the homologous compounds, comparing with those of NOEV **4**.