Synthesis, antiasthmatic, and insecticidal/antifungal activities of allosamidins

Gangliang Huanga and Hualiang Huangb

aChongqing Key Laboratory of Green Synthesis and Application, Active Carbohydrate Research Institute, Chongqing Normal University, Chongqing, China; bSchool of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan, China

ABSTRACT

Allosamidins come from the secondary metabolites of Streptomyces species, and they have the pseudotrisaccharide structures. Allosamidins are chitinase inhibitors that can be used to study the physiological effects of chitinases in a variety of organisms. They have the novel antiasthmatic activity and insecticidal/antifungal activities. Herein, the synthesis and activities of allosamidins were summarized and analyzed.

Introduction

An effective chitinase inhibitor was found in screening metabolites of actinomycetes, which was isolated from the mycelium extract of Streptomyces 1713,1,2. Its new structure was elucidated, which was a pseudotrisaccharide containing two β-linked N-acetyl-2-amino-2-deoxy-D-allopyranoside building blocks. The new disaccharide is linked to allosamizoline 2 (Figure 1) through its reducing terminal. It is a new family-18 chitinase inhibitor, named allosemidin 1. The compound has a unique chemical structure and its synthetic method is very challenging3–29. The selection of glycosylation methods to assemble the structural units of allosamidin and its analogues is the essential difference between each reported total synthesis method. The main goal of these glycosylation methods is to produce β-configuration products. This article analyses the synthesis and activity of isomides. The synthesis and activities of allosamidins were reviewed herein.

Preparation of allosamizoline 2

Allosamizoline 2 is an important unit of allosamidin 1. Compound 2 and its analogues were mainly synthesized with non-sugar compounds as raw materials30–43. Sugar was also used in the synthesis of compound 244–11. Under proper protection, sugar-based receptors were prepared first, and then combined with the required oligosaccharide donors to complete the synthesis of compound 1.

The regio- and stereocontrolled total synthesis of (+)-allosamizoline 2 was studied (Scheme 1)26. Using D-glucosamine as raw material, aldehyde 3 was synthesized by five-step reaction. The Wittig olefination of aldehyde 3 was carried out by using ylide Ph3P=CHCO2Me to obtain a high yield (91%) of acrylate 4. In the ring-closed metathesis reaction, the terminal substituent of the alken e was not transferred to the cyclized product. The ring-closing metathesis also took place smoothly and cyclopentene 5 was obtained in 88% yield. The key steps of the synthesis included halogen cyclization to provide oxazoline ring, followed by stereoselective addition of alkene radical, and finally carried out alkene isomerization to form hydroxymethyl. (+)-Allosamizoline 2 was prepared by 13-step reaction with an overall yield of 22%.

Rhodium-catalyzed oxidative cyclization of glucal 3-carbamates to oxazolidinone-protected mannosamine derivatives (Scheme 2)44 could be used to synthesize various allosamidin analogues. The stereoselectivity of anomeric centers relied on the properties of protective groups and solvents. It was proved that benzylic protection mainly produced a product of α-configuration. Solvents with lower polarity, such as hexane and benzene, also increased the anomeric proportion. Its formation was with a primary amide containing carbamate as a raw material.

Synthesis of allosamidin compounds

Solid phase synthesis is a fast and effective method for the synthesis of oligosaccharides30,51. In the multi-step solid phase synthesis of oligosaccharides, excess reactants or by-products can be easily removed. Oligosaccharide synthesis is important for glycosylation, which involves sugar-based donors and receptors. For example, Huang’s group first synthesized the α-trichloroacetimidate donors 8, 9 and allosamizoline-derived acceptor 10. Moreover, the solid-state synthesis of allosamidin 1 was developed12.

To synthesize α-trichloroacetimidate donor 8 (Scheme 3), the preparation of α-D-allosamine-hydrochloride 11 was carried out23. Compound 11 was treated with benzoylcarbonyl (Cbz)-Cl and NaHCO3/H2O, N-benzoylcarbonyl protected allosamine 12 in 85% yield was obtained. Compound 12 was acetylated in pyridine to obtain the α/β isomer (4:1) mixture of tetracete 13. The anomeric acetyl group was selectively removed in N,N-Dimethylformamide (DMF) with hydrazine acetate to obtain the...
hemiacetal 14. In the compound 14, the compound 14 reacted with the 
CCl₃CN to obtain 82% yield of α-trichloroacetimidate donor 8.

The hemiacetal 14, which was directly carried out without puri-
fication, was produced in DMF with the hydrazine acetate-treated
compound 13. Compound 14 was reacted with tert-butyldimethyl-
silyl (TBDMs)-Cl in imidazole to give a β-configuration TBDMs
derivative 15. A 95% yield of TBDMS 2-deoxy-N-benzyloxycarbonyl-
limino-β-D-allopyranoside 16 was obtained by deacetylation of
compound 15 with NaOME/MeOH. Compound 16 was treated
with benzaldehyde dimethylacetal to obtain 4,6-O-benzylidene
derivative 17. The reaction of compound 17 and Ac₂O was carried
out in the presence of pyridine to give acetate 18 in a yield of
94%. 6-O-Bn acceptor 19 was obtained by regioselective reduction
of benzylidene acetate 18 with CF₃COOH/Et₃SiH at 0°C in a yield of
86%. In the presence of N,N-diisopropylpropylcarbodiimide (DIPC),
compound 19 was reacted with levulinic acid to give the orthogonally
protected alloamine 20 in 95% yield. In the presence of acetic
acid, tetrabutylammonium fluoride (TBAF) was used to remove the
anomeric TBDMS group. The crude product was then reacted with
the CCCl₃CN and DBU to give the α-trichloroacetimidate donor 9
(Scheme 4).

Dial 21 was prepared (Scheme 5)54. Compound 21 was select-
ively benzylated on C-3 hydroxyl group by the method of stanny-
lene55 to produce the dibenzylated unit 10 in a yield of 45%. The
glycosylation was carried out by using 3.0 equivalent donor and
1.2 equivalent trimethylsilyl trifluoromethanesulfonate (TMSOTf) as
promoter to activate trichloroacetimidate donor. TMSOTf pro-
moted the glycosylation of trichloroacetimidate donor 9 with 6-O-
benzylalloosaminoligosaccharin alcohol acceptor 10 at low temperature.
The corresponding β-pseudodisaccharide 22 was obtained with a yield of
68%. Wang resin was removed from building block 22 with tri-
fluoroacetic acid. The product was analyzed by high pressure
liquid chromatography (HPLC). The receptor 23 was obtained by
cleaving the levulinoyl ester with hydrazine acetate dissolved in
methanol. After the glycosylation was carried out with acceptor
23 and donor 8, the resin was washed, filtered, and dried in vac-
uum for 12 h. Sugar-based resin were catalytically hydrogenated
with benzaldehyde dimethylacetal to obtain 4,6-O-benzylidene
derivative 17. The reaction of compound 17 and Ac₂O was carried
out in the presence of pyridine to give acetate 18 in a yield of
94%. 6-O-Bn acceptor 19 was obtained by regioselective reduction
of benzylidene acetate 18 with CF₃COOH/Et₃SiH at 0°C in a yield of
86%. In the presence of N,N-diisopropylpropylcarbodiimide (DIPC),
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out in the presence of pyridine to give acetate 18 in a yield of
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of benzylidene acetate 18 with CF₃COOH/Et₃SiH at 0°C in a yield of
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the CCCl₃CN and DBU to give the α-trichloroacetimidate donor 9
(Scheme 4).

An international group has developed a new type of chiti-
nase inhibitor55. The core building block is a cyclic sugar fused
with thiazoline, a five-membered ring consisting of one N, one S
and three C atoms (Scheme 6). This arrangement simulates a
ring intermediate product formed during chitinase degradation
and interacts with the binding sites on chitinase. To enhance
the inhibition, the researchers added two or three additional
sugar building blocks, similar to chitin (chitobiose or chitotrios).

The synthesis of disaccharide and trisaccharide thiazolines 24
and 25 began with octaacetylethiose 26 and undecaacetyle-
chitositrone 27 in turn (Scheme 6)36. The α-configuration of ace-
toxy groups of compounds 26 and 27 was reversed to give the
corresponding β-anomers, the anomic chlorides were obtained
by the initial treatment with HCl and AcOH, and then treated
with AgOAc/AgOH. After treatment with Lawesson reagent, thia-
zolines 28 and 29 were obtained by affecting both the conver-
sion of amides to thioamides and the intramolecular substitu-
tion of adjacent thioamide sulfur atom to the anomeric
β-acetoxy group. The partial deacetylation of per-O-acetylated
thiazolines 28 gave two additional chitinase inhibitors,
namely the chitobiose thiazoline thioamide 30 in a yield of 89%
and chitotriose thiazoline dithioamide 31 in a yield of 80%. To
synthesize target compounds 24 and 25, thioamides 28 and 29
were converted to diacytymides 32 and 33 (81% and 60% yields in turn)
with silver acetate/dichloromethane without destroying the thiazoline part. Finally, chitobiose thiazoline 24
(69% yield) and chitotriose thiazoline 25 (78% yield) were obtained by O-deacylation and mono-N-deacylation of imides
32 and 33 with sodium methanol/methanol.

It was indicated that chitobiose and chitotriose thiazolines (24
and 25) were synthesized by traditional method. As above-men-
tioned, the of allosamidin 1 was synthesized by solid phase
method. So, compound 25 was successfully synthesized by the
similar approach (Scheme 7)57. Compounds 36 and 39 were used
as the corresponding α-trichloroacetimidate donors.

GlCN thiazoline is a poor chitinase A (ChiA) inhibitor whose
Kₐ>1 mM. However, adding one GlCN residue to compound 24
increased the binding power by at least 40 times, and the second
GlCN residue further increased the affinity by 100 times. The Kᵢ
value of pseudotrisaccharide 25 was much lower than that of

Figure 1. Structures of allosamidin 1 and allosamizoline 2.

Scheme 1. Preparation of (-)-allosamizoline 2.
allosamidin ($K_i=0.6 \mu M$) in inhibition of ChiA. This result contrasted with recent finding that the disaccharide thiazoline with sulfur linkage was not a significant ChiA inhibitor. No significant inhibition was observed in this study might be due to the different geometric structure imposed by the thioglycosidic linkage.

The main methods of synthesis of compound 25 were compared as shown in Table 1.

The activities of allosamidins

In mouse asthma model, allosamidin showed antiasthmatic activity and decreased inflammatory symptoms were observed in rabbits with endotoxin-induced uveitis. Demethylallosamidin, a derivative of allosamidin, had strong inhibitory activity on yeast chitinase and human chitosidase. The inhibitory effect of

**Scheme 3.** Synthesis of donor 8 with N-Cbz protection.

**Scheme 4.** Synthesis of donor 9 with N-Cbz protection.

**Scheme 5.** Solid phase synthesis of allosamidin 1.

**Scheme 6.** Synthesis of chitobiose and chitotriose thiazolines (24 and 25), and their thioamide analogues (30 and 31).
demethylallosamidin on acidic mammalian chitinase (AMCase) was stronger than that of allosamidin and had strong anti-asthma activity. Demethylallosamidin inhibited IL-13-induced hyperresponsiveness and had better potential as an anti-asthma drug than allosamidin. There is a need to use other target molecules in the future to investigate the difference in the anti-asthma activity of allosamidin and demethylallosamidin.

Allosamidins can inhibit chitinase activity. So, they can prevent the ecdysis of insect larvae and pupae, and isolation of fungal microspore mother cells. As a result, they play a role in insecticidal and antifungal activities. At very low concentrations, pseudo-trisaccharide allosamidin 1 has competitive inhibitory activity against chitinases. The injection of compound 1 into silkworm (Bombyx mori) larvae and armyworm (Leucania separata) strongly interfered with larval molting and increased the mortality of lepidopterous pests. The inhibitory effects of allosamidin 1 on Bombyx mori larvae and Leucania separata larvae were EI50 = 2 μg and 4 μg, respectively. EI50 is a 50% molting inhibition. Compound 1 and its derivatives could significantly increase the mortality of fly larvae (Lucilia cuprina) after exposure or feeding test. Allosamidin 1 could result in larval mortality in the webbing clothes moth Tineola bisselliella because of severe morphological alterations, namely delaying growth and interrupting molting. This occurred during larval development. Compound 1 could also induce the killing effect of aphids, increase larval mortality and decrease the reproductive ability of aphid Myzus persicae.

Allosamidin 1 has the broad-spectrum chitinase inhibitory activity. Compound 1 and its derivatives, i.e., methylallosamidin, demethylallosamidin, glucoallosamidin A, glucoallosamidin B, and methyl-N-demethylallosamidin, could also kill different human pests and pathogens, such as plasmodium and nematode. Allosamidin 1 also had antibacterial and insecticidal/antifungal activities. In Streptomyces species producing compound 1, this inhibitor was beneficial to the production of chitinase insensitive to compound 1, which was beneficial to fungal growth.

The binding mode to chitinases of allosamidins

According to the NMR spectrum information, ab initio calculations and the spatial squeezing effect between molecules, it could be proved that the binding power in the allosamizoline part of allosamidin 1 was the strongest.

The pseudotrisaccharide allosamidin is an effective family-18 chitinase inhibitor, which has obvious biological activity against insects, fungi and Plasmodium falciparum, and affects their life cycle. Similar to other chitinases, demethylallosamidin derivatives have a 10-fold inhibitory effect on human chitinase. These structures explained the effects of changing hydrogen bonds and hydrophobic interactions as well as the effect of substituted water molecules on the inhibition.

Allosamidin 1 is located in the deep active site of ChiA from S. marcescens and interacts with three important residues: Glu315 is the catalyzed proton donor. Asp313 takes two conformations in the primary structure, but faces toward Glu315 in the inhibitor complex. Tyr390 is located opposite Glu315 in the active site tunnel.

The inhibition of the family-18 chitinase is becoming a target for pest and fungal control and the treatment of asthma and inflammation. Under the condition of pH 6.0, the binding of allosamidin 1 required the deprotonation of Asp142-Glu144 catalytic diad.

The structure-activity relationships of allosamidins

The structure-activity relationship of allosamidins is as follows. Allosamidins can inhibit the enzymes of GH18 and GH20 families. NAG-thiazoline is a potential inhibitor of N-acetylhexosaminase of GH20 family. It is introduced into the structure of allosamidin analogues. The obtained compounds have been proved to have good inhibitory activity against 18 family chitinases. Substituted N-glycosyl oxazolines, N-glycosyl aminooxazolines, and N-glycosyl thiazolines also exhibit enzymatic inhibition. Allosamidins containing N-acetylgulosamine structural unit have the good inhibitory effect on chitinases. In addition, the side chain groups of allosamidin analogues structural units can be extended appropriately, but if the side chain groups are prolonged too much, the volume of side chain groups will be too large and the steric hindrance will increase, which will reduce the affinity to 20 family glycosylhydrolases.

Table 1. Comparison of the three synthetic methods of compound 25.

| Synthetic method of compound 25 | Number of synthetic steps | Number of column chromatography separation |
|--------------------------------|--------------------------|------------------------------------------|
| Solid-liquid phase              | 7                        | 3                                        |
| Total solid phase               | 8                        | 0                                        |
| Total liquid phase              | 6                        | 6                                        |

Scheme 7. Solid phase synthesis of chitotriose thiazoline 25.
Conclusion

To sum up, the synthesis efficiency of allosamidin 2 and its analogues can be greatly improved by introducing related metal catalytic reactions, which is beneficial to improve the selectivity of the reactions. At the same time, it is proved that the synthesis efficiency of allosamidin 1 and its analogues can also be improved by solution phase synthesis and solid phase synthesis. The activities of allosamidin 1 and its analogues showed that they can not only be used as lead compounds to develop the effective anti-asthma drugs and insecticidal/antifungal agents, but also as probes to investigate the physiological effects of chitin-like proteins. The development trend in this field is to develop new synthesis methods, improve synthesis efficiency, and screen out new allosamidins which can significantly inhibit chitinases and have high anti-asthma and insecticidal/antifungal activities.

Disclosure statement

No potential conflict of interest was reported by the authors.

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