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Enzymatic synthesis of a series of thioglycosides, analogs of arbutin, owing efficient antipigmentation properties

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Supporting information for this article is given via a link at the end of the document

Abstract: Arbutin, a natural glycoside, is well known as a commercial tyrosinase inhibitor and thus to prevent pigmented disorders of skin. Indeed, tyrosinase is involved in the biosynthesis of melanin, the skin main pigment. However, arbutin is subject to hydrolysis, which limits its bioactivity. In general, thioglycosides are known to be very resistant to both chemical and enzymatic hydrolysis, which increases the interaction time with their biological targets. A biocatalytic approach allowed us to access to thioglycosidic analogs of arbutin in a green approach with good to excellent yields. Such compounds have then been tested as tyrosinase inhibitors and also as inhibitors of melanin transfer from melanocytes to keratinocytes. This latter mechanism takes place via lectin (or lectin-like) receptors present on the cells surface. p-Aminophenyl ß-D-thiogalactopyranoside appears to be an excellent candidate thanks to its tyrosinase inhibitory activity comparable to arbutin, while having the ability to interact with glycan receptors allowing to reduce melanin transfer.

Introduction

Due to the global warming, the world population is more and more exposed to the sun, thus leading to a continuous rise in the appearance of skin pigmentation disorders. One of them, namely hyperpigmentation, is generally due to a local overproduction of melanin correlated to a significant increase of melanosome number in the epidermis. However, sun exposure is not the only external parameter, and hormonal or contraceptive treatments can also trigger this kind of disorders. To limit these unsightly aspects, there are common physical or chemical skin treatments [1], but other approaches have been also developed, including melanin transfer inhibition from melanosomes to keratinocytes, melanosomes alteration or inhibition of the DNA transcription coding for tyrosinase [2]. Some chemical treatments, notably hydroquinone [3], have effects on these targets (Figure 1). It has been part of the reference molecules as whitening agent for more than 50 years. However, its significant side effects like irritation or itch phenomena, have led to its disappearance in cosmetic products [4]. Indeed, its oxidation leads to quinones formation and generation of free radicals which can cause cell membrane alterations and induce the effects mentioned above [5]. To restrict these side-effects, manufacturers have turned their attention to hydroquinone analogs, with one protected phenolic moiety, such as mequinol or monomethyl ether of hydroquinone (MMEH) [4a]. Nevertheless, the current best alternative is the use of its ß-glucosylated substituent, namely arbutin (Figure 1). This natural compound is extracted from the leaves and barks of many plants such as bearberry [6]. The presence of the glucosyl moiety increases its water solubility while retaining a good anti-pigmentation activity [7]. In addition, this molecule has the advantage of being less toxic to cells. Moreover, glycoconjugates are described as being capable to interact with the membrane receptors present on the cell surfaces (lectins) thanks to their sugar moiety so as to inhibit the melanin transfer from melanocytes to keratinocytes [8] (Figure 2).

Figure 1: Hydroquinone and Arbutin analogues
In an attempt to obtain improved tyrosinase inhibitors, various arbutin analogs have been proposed, i.e. α-arbutin, deoxy-arbutin or analogs in the form of disaccharides[10]. All these glycosides present interesting properties but, in all the cases mentioned above, their chemical and/or enzymatic hydrolysis leads to hydroquinone release, which might cause serious skin disorders. The use of a thioglycoside, more resistant against chemical or enzymatic hydrolysis, would limit the hydroquinone release while retaining biological activities[10]. Thioglycoconjugates are already commonly used as stable ligands for the crystallographic analysis of protein structures or as glycosidase inhibitors[11]. They can even serve for the development of carbohydrate-based vaccine antigens[12]. Until recently, their only access was through very tedious chemical synthesis steps[13], or through metallic catalysis reactions[14], in particular because of numerous protection and deprotection steps[15], thus limiting drastically the commercial applications. One solution to overcome this limitation relies in the use of enzymatic synthesis, which in addition will owe the advantage of decreasing environmental impact[16]. In 2003, Withers et al described a major advance in terms of thioglycoconjugates synthesis by proposing the first enzymes capable to promote the formation of this type of linkage[17], a biocatalyst obtained thanks to judicious mutations on the acid/base residue of the catalytic site starting from a native glucosidase[18]. With a similar approach based on site-directed mutagenesis, our group has been able to access to a novel thioglycoligase (DIGlyE159Q) from Dictyoglomus thermophilum[19]. In particular, this mutant, whose hydrolytic activity has been greatly reduced by the replacement of the catalytic E159 by a glutamine, has the capacity to efficiently catalyze the binding of a saccharidic unit on thiophenolic derivatives, which pKa (around 7) is of high importance to lead to very good reaction yields.

Herein, we thus wish to report the efficient biocatalyzed synthesis of numerous S-arbutin analogs and their biological properties as promising whitening agents. We therefore focused on cosmetic alternatives that rely on tyrosinase inhibition at the melanosome level and therefore prevent the synthesis of melanin[20].

Results and discussion

1) Biocatalyzed synthesis

In order to obtain arbutin analogs, we particularly focused on thiophenolic compounds, which could mimic hydroquinone. First, to keep a good analogy, our choice fell on p-hydroxythiophenol, as well as p-aminophenol to rule on the phenolic moiety influence on the biological activities (Scheme 1). Second, the acid/base catalytic residue being mutated, it was essential to use activated sugars to carry out the enzymatic glycosylation step. For this, we chose p-nitrophenyl-β-D-glucopyranoside (pNPGLc) as sugar donor. In order to favor the nucleophilic attack of sulfur moiety on the glycosyl-enzyme complex, we kept the pH of the reaction buffer fixed at 9 (Tris-HCl, 20mM), so that thiophenol acceptors were mostly present in their thiophenolate forms. The reactions were thus carried out and followed by TLC. p-Hydroxythiophenol did not react, as only starting material could be detected after enzymatic incubation. This absence of reactivity was thought to be related to the formation of unreactive quinone. Regarding p-aminophenol acceptor, a new glucosylated compound S-1 was detected and, after purification, characterized by NMR. We therefore sought to optimize the enzymatic thioglycosylation reaction based on the same conditions as those used previously. The examples present in the literature highlight the necessity to use a large excess of acceptor equivalents[21]. Thus, we initially decided to carry out the reaction in the presence of 40, 30 and 20 eq of acceptors (Table 1 entries 1-3) and we did not observe any degradation of the enzyme due to the acceptor under the thiol or disulfide forms.

![Scheme 1: Enzymatic thioglycosylation scheme](image)

**Table 1. Optimization of enzymatic thioglycosylation conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>pNPGLc</th>
<th>Acceptor</th>
<th>DIGlyE159Q</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>1.3 10⁻¹</td>
<td>40</td>
<td>2.9 10⁻⁵</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>1.3 10⁻¹</td>
<td>30</td>
<td>2.9 10⁻⁵</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>1.3 10⁻¹</td>
<td>20</td>
<td>2.9 10⁻⁵</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>1.3 10⁻¹</td>
<td>20</td>
<td>1.4 10⁻⁴</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>1.3 10⁻¹</td>
<td>10</td>
<td>1.4 10⁻⁴</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>1.3 10⁻¹</td>
<td>5</td>
<td>1.4 10⁻⁴</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>3.3 10⁻¹</td>
<td>5</td>
<td>8.4 10⁻³</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>600</td>
<td>2.0</td>
<td>5</td>
<td>8.4 10⁻³</td>
<td>24</td>
</tr>
</tbody>
</table>

[a] Isolated yields after column purification step

The yields obtained after purification demonstrated that an excess of acceptor caused a negative effect, with 20 eq. leading to the best yield (Table 1, entries 1-3). In parallel, the reaction time, initially set at 48 hours, was reduced to 24 hours. In addition, to limit the potential negative impact of this reduction time, the

![Figure 2: Tyrosinase and melanin transfer inhibitions.](image)
quantity of enzyme was multiplied by 5. The reactions were carried out under these conditions in the presence of 20, 10 and 5 equivalents of acceptor (Table 1, Entries 4-6). Indeed, when the number of acceptor equivalents decreased, so did the yield. However, the conditions of entry 4 allowed an optimized yield of 99% in just 24 hours. The increase of the quantity of enzyme had a very positive effect on the reaction, while remaining in catalytic quantity. In addition, when the acceptor equivalents decreased, we still kept excellent yields (Table 1, Entries 5-6: 92% and 82%, respectively). Two stages of gradual scale up were carried out, starting from 100 mg and then 600 mg of sugar donor (Table 1, Entries 7-8). The yields being good in 24 hours on small quantities, we tried to reduce by 1.7 the enzyme equivalents for the scaling up reaction. The yields obtained for both conditions were very good with respective values of 91% and 96%. Under these conditions, they were even quite higher than those obtained previously while the amount of enzyme has been reduced. At this stage, we were therefore able to significantly optimize the reaction by reducing the number of acceptor equivalents required while retaining excellent yields. The reaction time has also been reduced and the enzyme quantity fine-tuned.

We then sought to obtain analogues of molecule S-1 carrying different saccharidic moieties. In the literature, numerous glycosidases are described as being different saccharidases. Using a simple and rapid methodology, already published by Peyrot et al, we were able to quickly access the p-galactosidase activity by reducing and the enzyme quantity fine-tuned. We therefore carried out the same reaction with arbutin, S-arbutin was synthesised using the methodology developed by Brachet et al through nickel catalysis allowing to access to the perfect analog with a thioglycosides linkage[14].

This allowed us to obtain a library of 8 arbutin analogs in S- or O-glycosidic series carrying different substituents on the aromatic ring (Figure 3). We were then able to assess the anti-pigmentation activity of these 7 compounds on different targets. To compare with arbutin, S-arbutin was synthesized using the methodology developed by Brachet et al through nickel catalysis allowing to access to the perfect analog with a thioglycosides linkage[14].

![Figure 3](image_url)

**Figure 3. Target molecules for biological evaluations. A) this study. B) Peyrot et al.**

2) Tyrosinase inhibition.

According to the targeted mechanism intended to decrease pigmentation, various types of approaches exist to evaluate the anti-pigmentation activity. The simplest and most common is to assess tyrosinase inhibition, the enzyme producing melanin in melanosomes. Based on a protocol described by Masamoto et al., we were able to perform in-vitro inhibition studies for each molecule[24]. The enzymatic activity was monitored by spectrophotometry and the IC50 values were recovered with GraphPad. The IC50 correspond to the concentrations needed to observe 50% of activity loss. All the data have been grouped in Table 3, and arbutin was used as the positive control.

![Table 3](image_url)

**Table 3. Tyrosinase inhibition IC50 for each arbutin analog according to the Masamoto protocol[24].**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC50 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbutin</td>
<td>0.5 ± 0.8</td>
</tr>
<tr>
<td>S-Arbutin</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>S-1</td>
<td>2.0 ± 0.7</td>
</tr>
<tr>
<td>S-2</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>S-3</td>
<td>4.1 ± 0.5</td>
</tr>
<tr>
<td>O-1</td>
<td>2.4 ± 0.8</td>
</tr>
</tbody>
</table>

Finally, we were also wondering whether the nature of the glycosidic linkage could also have an effect on anti-pigmentation activity. Using a simple and rapid methodology, already published by Peyrot et al, we were able to quickly access the p-amino-phenyl β-D-glycopyranosides from the corresponding p-NP sugars, by reduction of the nitro moiety without any protection or deprotection steps[23]. The protocol was developed in presence of dithiothreitol (DTT) in methanol under microwave activation for 2 h. This quick methodology provided access to compounds O-1, O-2 and O-3 (Figure 3B) with very good respective yields of 97, 91 and 92%[23].
The IC50 values mentioned in the literature are somehow variable depending on the natural source of the tyrosinase but remain in the order range of mM[9a, 9b]. Our experimental value for arbutin was therefore in agreement with the literature, which thus validates the experimental protocol. The glycosidic linkage nature, the sugar moiety as well as the substitution on the aromatic ring may have an influence on the inhibition activity of tyrosinase. When we focused on the influence of nature of the aromatic cycle, it appeared that the phenolic group led overall to better tyrosinase inhibition (Table 3, Arbutin vs O-1). The nature of the sugar also demonstrated an important influence. Indeed, the presence of a fucose was unfavorable (Table 3, Compound S-3) whereas the presence of a galactose unit made it possible to gain in efficiency (Table 3, Compound S-2). In the case of galactose, the presence of the sulfur atom even made it possible to obtain a more effective molecule (Compounds S-2 and O-2). At this stage, the compound S-2 appeared as the best candidate, both regarding its IC50 value but also its stability against hydrolysis. Considering the first results, and the low activity differences regarding tyrosinase inhibition between S-arbutin and compound S-2, we have chosen to focus on the latter, obtained by a biocatalysed procedure.

3) Lectin recognition.

We then investigated the potency of inhibition of melanin transfer from melanocytes to the keratinocytes by the compounds. This process takes place through the activation of lectin-type receptors on the cell surface[89]. These lectins are capable of specifically recognizing glycan motifs, then triggering the migration process of melanin. The aim of this study was to consider the influence, or not, of the sulfur atom at the level of the sugar linkage. Given the promising in vitro results obtained for the compound S-2, we carried out this recognition test with this compound as well as its analogue in O-series O-2. To assess whether these new molecules can potentially be recognized by lectin-like receptors involved in melanin transfer (expressed at the surface of melanosomes and/or keratinocytes), we first set up in vitro screening on different lectins based on the GLYcoPROFILE® technology described by Landemarre et al[90]. The specificity and the nature of each lectin are reported in the supporting information. Lectin recognition tests were carried out in a 96-well plate (LEctPROFILE® plates). Compounds S-2 & O-2 were assessed for their ability to competitively displace the reference labelled ligand for each lectin. In that case, absorbance or fluorescence reads made it possible to determine the percentage of resulting bound reference ligands, bearing either a chromophore or a fluorophore. The results obtained for compound S-2 and O-2 are respectively presented in Figure 4.

First, it appeared clearly that both compounds S-2 and O-2 were perfectly recognized by the lectins specific for Gal and/or GalNAc motifs. The sulfur atom did not disturb osidic recognition from a global point of view, as both compounds O-2 and S-2 are roughly recognized by the same set of lectins and not recognized similarly by the others. Moreover, the interaction of the lectins seems better with O-2 compound than with S-2 and more specifically regarding the lectins ECA, PA-IL, PNA and RCA-I. The other important element was the preservation of a dose effect. In fact, when the inhibitor molecule was introduced in higher quantity, the binding percentage to receptors was greater, regardless the glycosidic linkage nature. Thioglycosides therefore seemed to be an excellent alternative for inhibiting the melanin transfer.

We further moved to in vitro tests on cell culture. In order to study and compare the potential interaction of S-2 and O-2 compounds with lectin-like receptors expressed at the surface of keratinocytes, we use the method of "neoprofile". A set of fluorescent neoglycoproteins (galactosylated, glucosylated and rhamnosylated) well known to interact in a "glycan-specifically" manner with the surface of normal human epidermal keratinocytes (NHEK) were incubated with the cells in the presence or not of the compounds. After washing, the resulting inhibition of neoglycoprotein shows the specificity of interaction of the corresponding compound. The binding percentage was indirectly measured through the ratio between the studied mixture fluorescence and the reference binding fluorescence. According to cell toxicity up to 1 mg/mL (determined by MTT test on same keratinocytes, data not shown), we chose to fix this concentration as the cell maximum concentration for the following studies. Several lower concentrations were then tested depending on the compounds. Thus, the higher inhibition percentage results in better compound recognition (Figure 5).
Experimental Section

2.1. Chemical synthesis

\(p\)-Nitrophenyl-\(\beta\text{-}-\)glucopyranoside, \(p\)-nitrophenyl-\(\beta\text{-}-\)galactopyranoside, \(p\)-nitrophenyl-\(\beta\text{-}-\)arabinopyranoside, \(p\)-nitrophenyl-\(\beta\text{-}-\)xylopyranoside, \(p\)-nitrophenyl-\(\beta\text{-}-\)glucuronoside were purchased from Carbosynth. \(p\)-Aminothiophenol, \(p\)-hydroxythiophenol and arbutin were purchased from Sigma Aldrich. All chemicals were used directly without purification. Chromatographic purifications of products were accomplished using a silica column in dichloromethane/methanol eluent. \(^1H\) NMR spectra were recorded on Avance III HD NanoBay Bruker at 400 MHz (\(^1\)H: 100 MHz) and were calibrated with residual D$_2$O or CD$_3$OD protons signals at 4.79 or 3.31 ppm respectively. Data are reported as follows: chemical shift (\(\delta\) ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiple), coupling constant (Hz), integration and assignment. \(^13\)C NMR spectra were calibrated with CD$_3$OD signal at 54.2 ppm. Data are reported as follows: chemical shift (\(\delta\) ppm) and attribution. All NMR assignments were made using COSY, HMBC and HSQC spectra. HRMS were performed on a Maxis Bruker 4G system.

Chemical thio-glycosylation

\(p\)-Hydroxyphenyl-\(\beta\text{-}-\)glucopyranoside (\(S\)-arbutin) was synthesized as colorless oil (80% yield) from \(\beta\text{-}-\)glucose and \(p\)-hydroxanisole according to an already published protocol\(^{13\text{a}}\). Characterization data were identical with those already described.

Enzymatic thio-glycosylation: General procedure 1: \(p\)-nitrophenyl-\(\beta\text{-}-\)glucopyranoside (1.0 equiv., 40 mg) and 20 equiv. of aminothiophenol were dissolved in Tris-Base/Tris HCl buffer (20 mM, pH 9, 2 mL). Thioglycollase mutant DGIg E159Q (80 nmol, 1.104 equiv.) was successively added and the mixture was stirred at room temperature overnight. Reaction was concentrated under reduced pressure and then purified by flash chromatography.

\(p\)-aminophenyl-\(\beta\text{-}-\)thiogalactopyranoside (\(S\)-1) was obtained using \(p\)-nitrophenyl-\(\beta\text{-}-\)glucopyranoside (0.13 mmol, 1.0 equiv.) according to the general procedure 1. The desired compound was obtained after flash chromatography (DCM/MeOH 9:1) as a white solid (38 mg, 99%). \(^1H\) NMR (D$_2$O, 400 MHz) \(\delta\): 7.64 (2H, d, J = 8.4 Hz, H-8), 8.62 (2H, d, J = 8.4 Hz, H-9), 4.57 (1H, d, J = 10.0 Hz, H-1), 3.89 (1H, dd, J = 1, 12.4 Hz, H-6), 3.72 (1H, dd, J = 5.6, 12.4 Hz, H-6'), 3.51 (1H, t, J = 8.8 Hz, H-3), 3.46 (2H, m, H-2, H-5), 3.27 (1H, t, J = 9.6 Hz, H-2').

\(p\)-aminophenyl-\(\beta\text{-}-\)thioglucopyranoside (\(S\)-2) was obtained using \(p\)-nitrophenyl-\(\beta\text{-}-\)galactopyranoside (0.13 mmol, 1.0 equiv.) according to the general procedure 1. The desired compound was obtained after flash chromatography (DCM/MeOH 9:1) as white solid (30 mg, 79%).

\(p\)-aminophenyl-\(\beta\text{-}-\)thiofucopyranoside (\(S\)-3) was obtained using \(p\)-nitrophenyl-\(\beta\text{-}-\)arabinopyranoside (0.14 mmol, 1.0 equiv.) according to the general procedure 1. The desired compound was obtained after flash chromatography (DCM/MeOH 9:1) as white solid (20 mg, 52%).

Conclusion

We have developed an original approach through enzymatic catalysis allowing access to arbutin analogs with very good yields. One of the best tyrosinase inhibitor was found to be compound S-2, a thiogalactoside. The molecular and cellular in vitro studies demonstrated a conservation of the osidic specificity of thioglycosides recognized by lectin-like as cell membrane receptors. In addition, the presence of the sulfur atom increased this recognition, while retaining the dose effect. The stability of the compound also gave it a longer lifespan and therefore a longer interaction with the receptors. This made it a double action compound, obtained by an eco-responsible process with high application potential in cosmetics.
p-aminophenyl-β-D-glucopyranoside (O-1) was synthesized as a white solid (97% yield) from p-aminophenyl-β-D-glucopyranoside according to an already published protocol[23]. Characterization data were identical with those already described.

p-aminophenyl-β-D-galactopyranoside (O-2) was synthesized as a white solid (91% yield) from p-aminophenyl-β-D-galactopyranoside according to an already published protocol[23]. Characterization data were identical with those already described.

p-aminophenyl-β-D-fucopyranoside (O-3) was synthesized as a white solid (97% yield) from p-aminophenyl-β-D-fucopyranoside according to an already published protocol[23]. Characterization data were identical with those already described.

2.2 Biological procedures

Tyrosinase inhibition tests

Tyrosinase inhibitor activity was measured by spectrophotometry based on the method presented by Masamoto et al[23], 10 μL of inhibitor solution at different concentrations in DMSO were placed into 96-wells microplate mixed with ammonium formate buffer (80 μL, 50 mM, pH 6.4) and 20 μL (0.8 mg/mL) of tyrosine was added. Just before the absorbance read at 450nm, 10 μL of mushroom tyrosinase (5000 U/mL) was added. The mixture was incubated at 27 °C for 10min. The absorbance value was recovered every 20 sec during 10 min. Arbutine was used as a positive control. Each measurement was performed at least in triplicate. The IC50, corresponding to the needed concentration to observe 50% loss of the enzyme activity, was calculated with GraphPad.

Acknowledgements

The authors thank the regions Centre Val de Loire and Bretagne for their financial support.

Keywords: Arbutin analogs • Carbohydrates • Enzyme Catalysts • Thioglucosidase • Whitening Agent


A biocatalyzed synthesis led to the preparation of a series of thioglycoside analogs of arbutin. These original molecules demonstrated potent tyrosinase inhibition properties, as well as the capacity to interact with lectins at the surfaces of cells. The presence of the sulfur atom prove therefore to increase the biological potency of these glycosides.

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