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Short communication

Synthesis of berbamine acetyl glycosides and evaluation of antitumor activity

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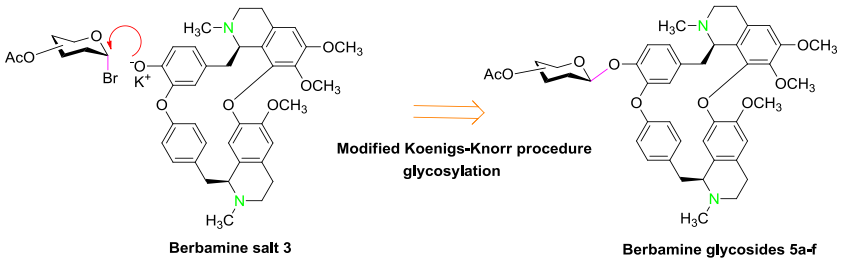
HIGHLIGHTS

- A series of berbamine (natural alkaloid) glycosides was synthesized.
- The new glycosides were evaluated for their antitumor activity in vitro.
- Most of the berbamine glycosides manifested potent cytotoxic activity.
- The most potent compound showed an IC_{50} of 0.30 μM against L1210 leukemia cell line.

GRAPHICAL ABSTRACT



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ABSTRACT

A series of berbamine glycosides was designed, synthesized and evaluated as a new class of antitumor agents. An efficient glycosylation route was developed for berbamide derivatives. The newly synthesized glycosides were evaluated for their cytotoxic activity in vitro against a human leukemia cell line K562, a human lung adenocarcinoma cell line A549 and mouse lymphocytic leukemia cells L1210. In contrast to berbamine most of its glycosides manifested potent cytotoxic activities. The acetyl glycosyl berbamine **5a**, **5d** caused distinct improvement against K562, A549 and L1210. It is suggested that the acetyl D-glucose residue has affinity to these cancer cells.

1. Introduction

From ancient to modern times medicine has been closely linked to the use of traditional medicines and natural products (NPs). Currently roughly half (49%) of the New Chemical Entities (NCEs) introduced are natural products, semi-synthetic natural product analogs or synthetic compounds based on natural products. Utilizing scaffolds of natural products combined with synthetic modifications is clearly an advantageous strategy in drug design [1]. Berbamine is a natural product derived from the plant Berberis amurensis (xiaoboan), which has been used extensively in Asia and Europe for the treatment of various ailments. Due to its bis-benzylisoquinoline alkaloid structure, berbamine has been demonstrated to possess a number of interesting and potent biological activities [2–6], such as an agent against human breast cancer cells, inducing apoptosis in human myeloma cells and suppression of human lung cancer cell growth. It was found by our group that berbamine can selectively induce cell death of both Gleevec sensitive and resistant-Phþ chronic myeloid leukemia (CML) cells [7] and selectively induce caspase-3-dependent apoptosis of leukemia

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NB4 cells via the survivin-mediated pathway [8]. In order to explore the effects and mechanism of berbamine on antitumor activity, we endeavored to make synthetic analogs of berbamine. A handful of the synthetic berbamine derivatives have been reported [9–12]. However, the glycosylation derivatives of berbamine for antitumor activity to the best of our knowledge have not been reported.

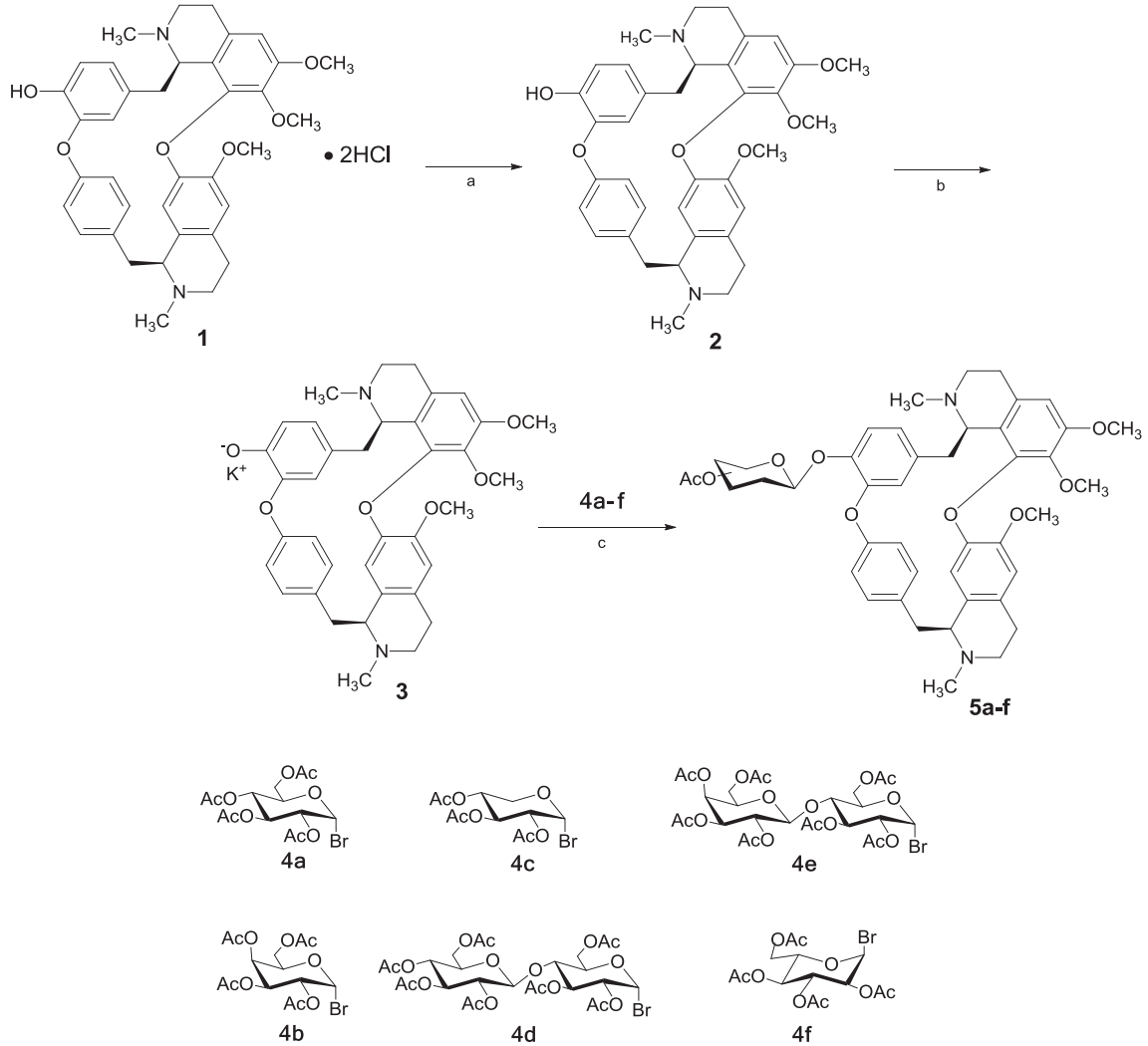
With their high density of defined spatial orientations and their relative rigidity, carbohydrates provide excellent platforms upon which to explore unique features for the drug-discovery process [13]. Substituted carbohydrate derivatives are generally quite stable and usually display reasonable stability to gastric acids and liver metabolism, which is in contrast to unsubstituted saccharides that usually undergo rapid metabolism in a biological environment [14]. There is a number of acetyl glycosides lead compounds that demonstrate more active than their unsubstituted carbohydrate analogs [15,16]. We aimed to synthesize the acetyl glycosides of berbamine for potential therapeutic treatment.

2. Results and discussions

2.1. Chemistry

The synthesis of the berbamine glycosides is illustrated and outlined in Schemes 1 and 2. Pharmaceutical grade berbamine dihydrochloride **1** was neutralized and alkalified to afford the solid berbamine salt **3** using sodium bicarbonate and solid KOH.

The critical step in our analog production was optimizing the formation of the berbamine phenolate. Carbohydrates carrying an aromatic aglycon are important natural products and thus key synthetic targets. The glycosylation of the phenols in an alkaloid is a challenge. First the phenolichydroxyl phenols are ambident nucleophiles in the glycosylation. A second problem is steric hindrance from substituents on the alkaloid compound (Fig. 1) [17,18]. Compared to acetate and trichloroacetimidate glycosyl donors, a glycosyl halide is better in an alkaline acceptor system. Initially we used the Michael procedure [19] which is predominantly used for the glycosylation of the phenols (i.e., the use of a glycosyl halide in combination with a phenolate dissolved in aprotic solvents under phase-transfer catalyst conditions). After many trials it was proved that the procedure was not suitable for berbamine. For our glycosylation route a modified Koenigs–Knorr procedure was finally chosen. The glycopyranosyl bromides **4a**–**f** were prepared according to the methods described elsewhere [20] and then the abovementioned glycosyl bromide reacted with berbamide salt **3** via the modified Koenigs–Knorr procedure to afford the corresponding berbamide glycosides **5a**–**f**. After the screening of catalysts and solvents, silver oxide and acetonitrile were chosen and proved to be effective for the berbamine glycosylation.



Scheme 1. Synthesis of berbamine glycosides **5a**–**f**. Reagents and conditions: (a) sat $NaHCO_3$ aq, CH_2Cl_2, neutralization. (b) KOH, water, pH = 13, 5 h, 40 °C. (c) **4a**–**f**, Ag_2O, dry CH_3CN, 4 Å ms, 40 °C, overnight.