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Synthesis of neamine–carboline conjugates for RNA binding and their antibacterial activities

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ABSTRACT

Three types of neamine-β-carboline conjugates were synthesized in good yields by the coupling of neamine and β-carboline-3-carboxylic acids using aliphatic diamine as a linker. The binding properties of these conjugates to 16S rRNA and 18S rRNA were evaluated by surface plasmon resonance (SPR), showing that some conjugates had stronger binding affinities than neamine. In vitro antimicrobial activities were also evaluated and the results showed that some synthetic compounds exhibited better antibacterial activities than neamine. The preliminary structure–activity relationship was discussed. The present experimental data demonstrated that synthetic neamine–carboline conjugates might hold the potential as new antibiotics.

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1. Introduction

Aminoglycosides have been long used as potent broad-spectrum antibiotics for the treatment of infections caused by aerobic Gram-negative and Gram-positive bacteria. Previous studies showed that aminoglycosides could bind to various RNA targets[1–6] such as rRNA, tRNA and mRNA. However, aminoglycosides are not ideal antibiotics due to their toxicities and adverse effects caused by the lack of selectivity towards different RNA targets. That caused sharply increasing interests in understanding the interactions between RNA and ligands, resulting in the escalating number of research works such as studying the three dimensional structures of RNA–ligand complexes.[7] Therefore, many efforts[8–12] have been made to design and synthesize specific RNA binders, which may have potential activities against bacteria or virus infections. However, there is not a solid way to design molecules targeting RNA because RNA can form intricate structures. Previous work disclosed that neamine is the minimal consensus unit[7,13] of aminoglycoside antibiotics bound to A-site, TAR RNA, or RRE IIB RNA. Since aminoglycosides possess amino and hydroxyl functionalities and are positively charged around neutral pH condition, which contribute to the binding with RNA by hydrogen bonding and electrostatic interactions, most of the previous efforts tended to strengthen the RNA binding affinities by increasing the number of hydrogen bonding or electrostatic interactions. It turned out to have limited improvements. On the other hand, some aromatic compounds[14] can act as stackers or intercalators to interact with either double-stranded RNA or DNA. But polyaromatic hydrocarbons may have potential carcinogenic activity. The β-carboline[15,16] ring system is present in many naturally occurring alkaloids, among which β-carboline-3-carboxylic acid occurs in *Symplocos serchuensis*, a food plant indigenous to the south of China. We assumed that the combination of aminoglycoside and β-carboline might enhance both the affinity and specificity to RNA. Furthermore, it can also decrease the polarity of aminoglycoside derivatives and improve absorption characteristics of the designed compounds. We hereby report the synthesis of some neamine-β-carboline conjugates, their RNA binding affinities, and their antibacterial activities.

2. Results and discussion

2.1. Chemistry

The neamine structure and carboline moiety were connected by a flexible tether. Neamine (**1**), β-carboline-3-carboxylic acid derivatives **4a**, **4b** and **5** were obtained according to the known procedure.[17–19] As shown in Scheme 1, neamine was treated with triflyl azide[20] in the presence of $CuSO_4$ and triethylamine to produce tetraazidoneamine, which was followed by benzoylation, providing compound **2** in 54% isolated yield. Compound **2** was reacted with trifluoromethanesulfonic anhydride, providing the triflate intermediate, which was subsequently converted to compounds

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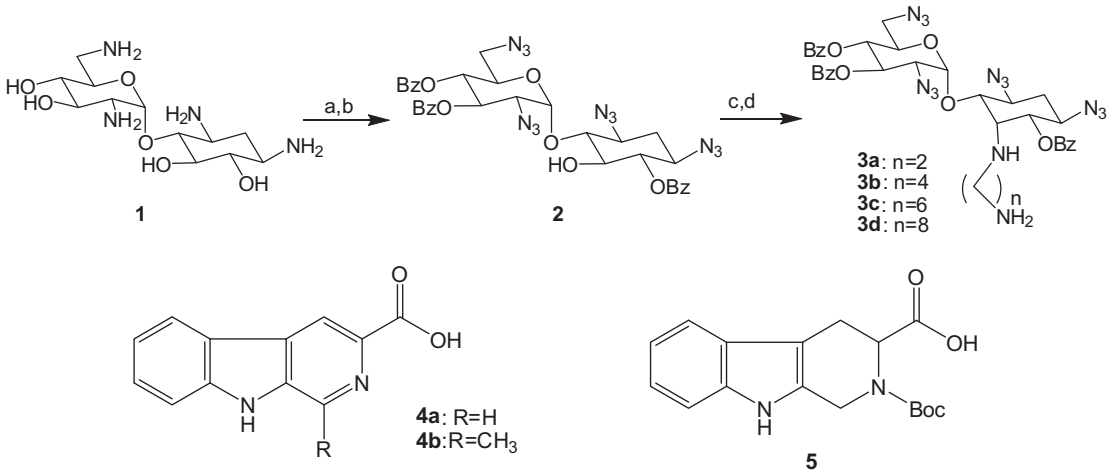


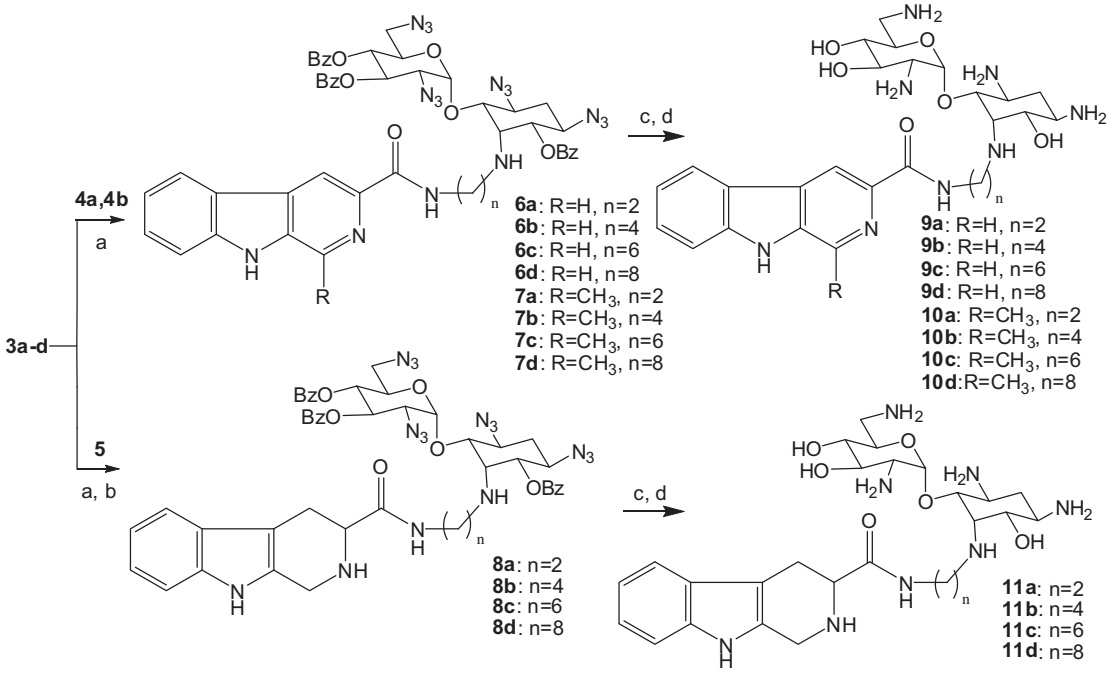
Scheme 1. Synthesis of compounds **3a–d** and the structures of compounds **4a**, **4b**, **5**. Reagents and conditions: (a) TfN_3, $CuSO_4$, Et_3N, CH_3CN; (b) benzoyl chloride, pyridine, 54%; (c) Tf_2O, pyridine, CH_2Cl_2; (d) $NH_2(CH_2)_nNH_2$, n=2,4,6,8, CH_3CN, 40% for **3a**, 48% for **3b**, 47% for **3c**, 47% for **3d**.

3a–d via amination using the corresponding aliphatic diamines. It is noteworthy that the high regioselectivity was achieved when the hydroxyl groups of neamine were protected with benzoate instead of acetate that was previously used in the literatures, leading to the 5-hydroxyl group of compound **2** exposed. Moreover, with more robust protective group (benzoyl vs acetyl), the side reaction between esters and diamines was alleviated, resulting in the increased overall yield of compounds **3a–d**.

With the amino-containing neamine derivatives **3a–d** and carboline carboxylic acid derivatives **4a**, **4b**, **5** in hand, the coupling reaction was carried out (Scheme 2). Compounds **6a–d** and **7a–d** were obtained by the coupling of amines **3a–d** and acids **4a**, **4b**. In the same way, compound **5** was condensed with **3a–d** to yield the corresponding amide products, which were followed by Boc-deprotection under acidic conditions at room temperature to produce **8a–d**. Due to the poor solubility of carboline carboxylic acids, the coupling reaction was performed in DMF solution. The amide-bond formation was efficient when 1-hydroxybenzotriazole (HOBT) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (TBTU) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) were used, and the reaction was completed very soon after the addition of DIPEA was finished, showing a single product spot on TLC, which greatly facilitated the product purification. Finally, compounds **6a–d**, **7a–d** and **8a–d** were saponificated with sodium methoxide in methanol, and followed by reduction with H_2S to provide the target compounds **9a–d**, **10a–d** and **11a–d**, respectively. The structures of all of the final products and intermediates were identified by their ^1H NMR, ^{13}C NMR and high resolution mass spectra.

2.2. Bioassay

2.2.1. RNA binding affinities of the neamine–carboline conjugates. The interactions between the synthetic compounds and RNA were evaluated by surface plasmon resonance (SPR) assay[21]



Scheme 2. Synthesis of neamine–carboline conjugates **9a–d**, **10a–d**, **11a–d**. Reagents and conditions: (a) TBTU, HOBT, DIPEA, DMF; 65% for **6a**, 70% for **6b**, 50% for **6c**, 74% for **6d**, 67% for **7a**, 60% for **7b**, 66% for **7c**, 79% for **7d**; (b) HCl/ethyl acetate, 37% for **8a**, 44% for **8b**, 75% for **8c**, 83% for **8d**; (c) CH_3OH/CH_3ONa; (d) H_2S, $Py/Et_3N/H_2O$, 70%.

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