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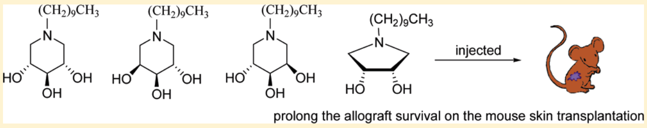
Synthetic N-Alkylated Iminosugars as New Potential Immunosuppressive Agents

Guan-Nan Wang, Yulan Xiong, Jia Ye, Li-He Zhang, and Xin-Shan Ye*

State Key Laboratory of Natural and Biomimetic Drugs and School of Pharmaceutical Sciences, Peking University, Xue Yuan Road No. 38, Beijing 100191, China

S Supporting Information

ABSTRACT: The new emerging immunosuppressive effects displayed by iminosugars have not been much investigated so far. Several new *N*-alkyl dideoxy iminoalditols were designed and synthesized to explore their immunosuppressive effects. These iminosugars inhibited the proliferation of mouse splenocytes and the secretion of both IFN-γ and IL-4, which are the hallmark cytokines of Th1 and Th2 cells, respectively. Some compounds exerted good inhibitory effects. More importantly, the synthetic iminosugars prolonged the allograft survival in the mouse skin transplantation experiment. Our results provide a lead for further elucidation of the structure—activity relationships and modifications of iminosugars for better immunosuppressive agents.



KEYWORDS: Iminosugar, immunosuppressive agent, mouse skin allograft, synthesis

The search to find better immunosuppressants has been stimulated by the need to improve transplant survival and to decrease the toxicity of current agents. The main clinically used immunosuppressive drugs, such as cyclosporin A (CsA), sirolimus, tacrolimus, and mycophenolate mofetil, have significant side effects including hypertension, dyslipidemia, hyperglycemia, and neurotoxicity and may lead to liver and kidney injury.[1−3] So, more effective and safer immunosuppressants are in great demand.

Iminosugars, widespread in plants and microorganisms, are carbohydrate mimetics in which the endocyclic oxygen is replaced by nitrogen.[4] These kinds of compounds raise many synthetic challenges, and as inhibitors or chaperones of carbohydrate-processing enzymes,[5] they open the way to treat a wide range of diseases including diabetes,[6] viral infections,[7] tumor metastasis,[8] and lysosomal storage disorders.[9] However, the use of iminosugar derivatives as immunosuppressive agents is an area that is less explored. To date, only castanospermine, a naturally occurring indolizidine alkaloid (bicyclic polyhydroxylated iminosugar), has been found to exhibit some immunosuppressive activity.[10,11] Our recent investigation disclosed that some synthetic iminosugars, especially N-alkylated derivatives, displayed immunosuppressive activity in vitro.[12−14] On the basis of the previous studies in our group, in this report, new N-alkylated 1,5-dideoxy-l,5-iminopentitols and N-alkylated 1,4-dideoxy-l,4-iminotetritol have been synthesized. These iminosugars show inhibitory effects on proliferation of mouse splenocytes induced by concanavalin A (Con A) as well as the secretion of cytokines from the mouse splenocytes. More importantly, the inhibitory effects of these iminosugars have been confirmed in the mouse skin transplantation model.

Iminosugars continue to be of great synthetic interest because of the intrinsically pharmacological potential and the need for more potent and selective compounds.[15] 1,5-Dideoxy-l,5-iminopentitols **1−3** (Figure 1) were isolated from *Eupatorium fortunei* TURZ by Kusano and co-workers in 1995 and have been shown to be the active components of the extracts of this plant, which are traditionally used in Chinese and Japanese folk medicine as diuretic, antipyretic, emmenagogue, and antidiabetic agents.[16] Since then, a number of new derivatives of compounds **1−3** have been synthesized and have been displayed to be good inhibitors of glycosidases.[17−21]

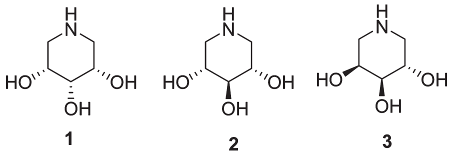


Figure 1. 1,5-Dideoxy-l,5-iminopentitols isolated from *E. fortunei* TURZ.

Previously, a one-pot tandem reaction to construct *N*-substituted δ-lactams was reported by us.[22] On the basis of this reaction, a new and expeditious approach to the synthesis of N-alkylated dideoxy-iminoalditols was developed. As shown in Scheme 1, the exoglucal **4** was easily prepared from methyl α-D-glucopyranoside through short three steps[23] or five steps in high overall yield (77%).[12] The ozonolysis of compound **4** at −78 °C gave the methoxyl acetal lactone **5**, which was then subjected to the one-pot amination and cyclization tandem reaction providing N-substituted δ-lactams in high yield. The N-substituted δ-lactams were subsequently reduced by BH_3-THF, which was followed by catalytic hydrogenolysis to afford N-alkylated 1,5-dideoxy-l,5-iminoxylitols **8a** and **8b** in excellent yield.

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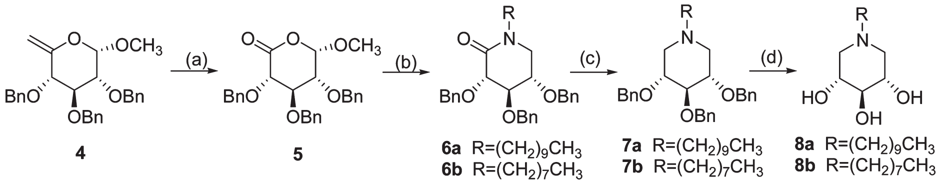
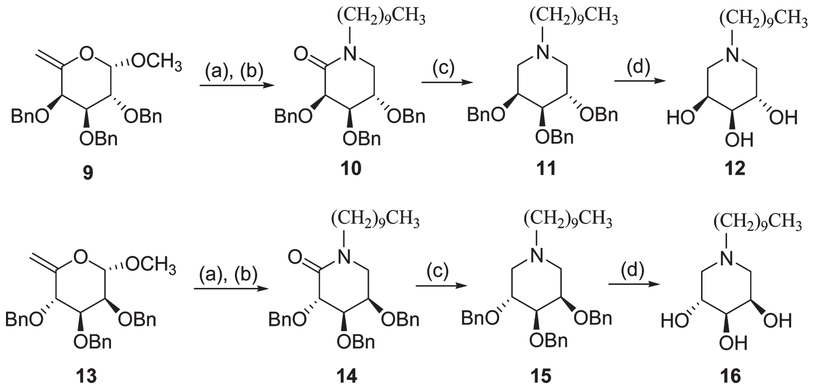
Scheme 1. Synthesis of N-Alkylated 1,5-Dideoxy-l,5-iminoxylitols[a]



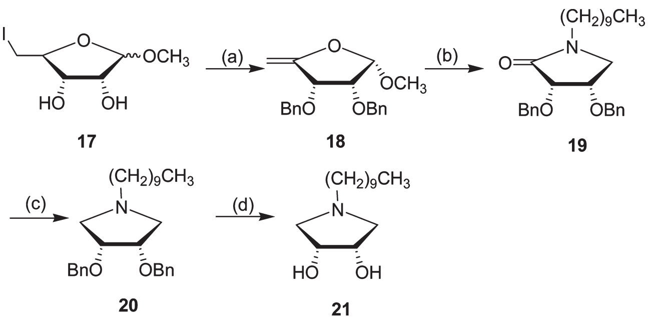
[a] Reagents and conditions: (a) O_3, MeOH, −78 °C, 100%. (b) $NaCNBH_3$, $ZnCl_2$, RNH_2, MeOH, reflux, 88% for **6a**, 82% for **6b**. (c) BH_3-THF, THF, reflux, 95% for **7a**, 93% for **7b**. (d) Pd/C, H_2, THF/H_2O/HOAc, 97% for **8a**, 100% for **8b**.

Scheme 2. Synthesis of Compounds 12 and 16[a]



[a] Reagents and conditions: (a) O_3, MeOH, −78 °C. (b) $NaCNBH_3$, $ZnCl_2$, RNH_2, MeOH, reflux, 88% for **10**, 91% for **14**. (c) BH_3-THF, THF, reflux, 96% for **11**, 93% for **15**. (d) Pd/C, H_2, THF/H_2O/HOAc, 98% for **12**, 98% for **16**.

Scheme 3. Synthesis of *N*-Decyl 1,4-Dideoxy-l,4-iminotetritol[a]



[a] Reagents and conditions: (a) BnBr, NaH, DMF, 72%. (b) (i) O_3, MeOH, −78 °C; (ii) $NaCNBH_3$, $ZnCl_2$, $CH_3(CH_2)_9NH_2$, MeOH, reflux, 90% for two steps. (c) BH_3-THF, THF, reflux, 95%. (d) Pd/C, H_2, THF/H_2O/HOAc, 98%.

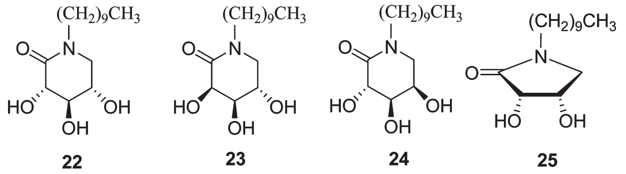


Figure 2. *N*-Decyl lactams used in the immunosuppressive assay.

Compounds **8a** and **8b** can be regarded as N-alkylated 5-de(hydroxymethyl)-1-deoxynojirimycin. Our synthetic strategy was then extended to prepare *N*-decyl 5-de(hydroxymethyl)-1-deoxygalactonojirimycin (**12**) and *N*-decyl 5-de(hydroxymethyl)-1-deoxymannonojirimycin (**16**) by a similar procedure starting from exogalactose and exomannose alkenes, respectively (Scheme 2). The reduction of lactams needs more explanation. It is known that lactams are generally reduced by reducing agents such as lithium aluminum hydride ($LiAlH_4$) and sodium borohydride. When $LiAlH_4$ was chosen as the reductant, it worked very well for the reduction of glucose type δ-lactams **6a** and **6b**; however, $LiAlH_4$ was not a good reductant for galactose type δ-lactam **10** and mannose type δ-lactam **14**. The yield for the reduction of compound **10** was poor (20%), and $LiAlH_4$ did not reduce the compound **14** at all. Although the $LiAlH_4$ reductive reaction could be influenced by many factors, it is proposed that the steric hindrance around the carbonyl group and the chelation of *cis*-benzylether with aluminum preventing the delivery of hydride are possible reasons for this phenomenon, since there are axial bonds with benzyloxy groups on them in both compound **10** and compound **14**. BH_3-THF was finally used to reduce different type lactams **10** and **14**, and both worked very smoothly. Although it was reported that in some circumstances the adduct of BH_3 product was too tight to release the free iminosugar,[24] BH_3-iminosugar was successfully dissociated by 6 N HCl during the workup operation.

Besides N-alkylated 1,5-dideoxy-l,5-iminopentitols, the N-alkylated 1,4-dideoxy-l,4-iminotetritol **21** was also designed since these kinds of structures have been rarely reported on both chemistry and biological activity. Our one-pot tandem procedure provides an expeditious access to this type of compounds. As shown in Scheme 3, the exoglycal **18** was prepared from the

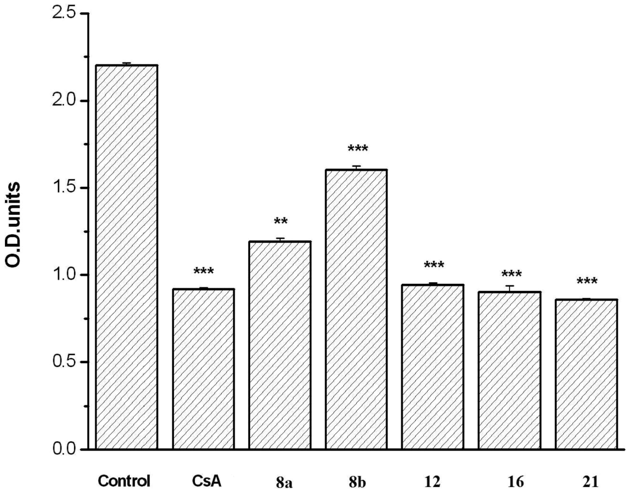


Figure 3. Effects of iminoalditols on Con A-induced mouse splenocytes proliferation were assessed by the MTT assay. Values are means ± SEMs; $^{**}p < 0.01$, and $^{***}p < 0.001$ vs control.

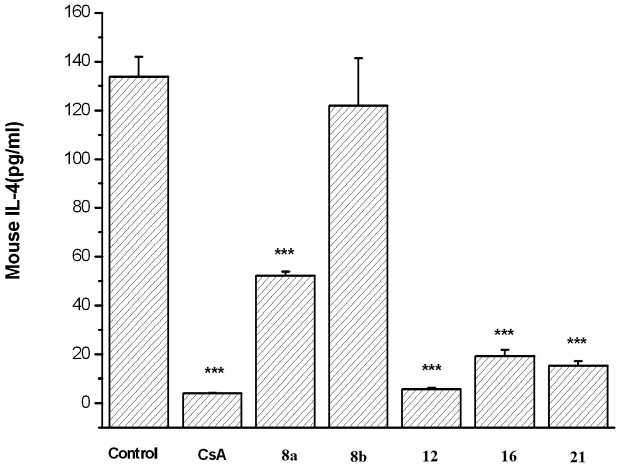


Figure 4. Effects of iminoalditols on the secretion of IL-4 from mouse splenocytes induced by Con A. Values are means ± SEMs; $^{***}p < 0.001$ vs control.

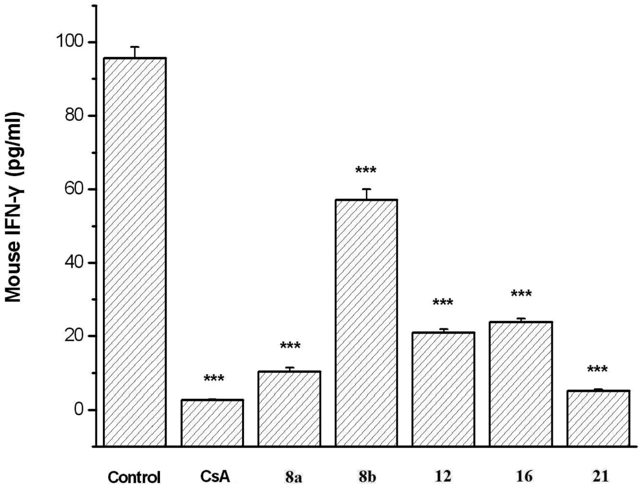


Figure 5. Effects of iminoalditols on the secretion of IFN-γ from mouse splenocytes induced by Con A. Values are means ± SEMs; $^{***}p < 0.001$ vs control.

corresponding 5-iodo-ribofuranoside **17**[25] through a one-step elimination and benzylation process. Ozonolysis of compound **18** followed by the tandem reaction gave *N*-decyl γ-lactam **19**. The lactam was subsequently reduced by using BH_3-THF to yield compound **20**, which was deprotected to afford the target compound **21**. On the other hand, to make comparison, *N*-decyl δ-lactams **6a**, **10**, and **14** and *N*-decyl γ-lactam **19** were also deprotected to provide compounds **22**, **23**, **24**, and **25**, respectively (Figure 2).[22]

With five iminoalditols **8a**, **8b**, **12**, **16**, and **21** and four lactams **22**–**25** in hand, their effects on mouse splenocyte proliferation induced by Con A were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, which measured the mitochondrial dehydrogenase activity of surviving cells (Figure 3). The mouse splenocytes were induced by 2.5 μg/mL of Con A with 30 μM concentration of each compound at 37 °C and 5% CO_2 for 48 h. The assays were conducted using the Con A-treated splenocytes as the experimental control and CsA (1 μM, 58.3% inhibitory rate) as the positive control.

None of the lactams **22**–**25** exhibited inhibitory effects of more than 40% on mouse splenocyte proliferation induced by Con A. However, most of the iminoalditols, as shown in Figure 3, displayed good inhibitory effects on splenocyte proliferation. Especially, the inhibitory rates of compounds **12** (57.2%), **16** (59.0%), and **21** (61.0%) were more than 50%. The inhibitory rate of compound **8a** (45.9%) was a little lower than that of compounds **12**, **16**, and **21** but much better than compound **8b** (27.1%). The only difference between compound **8a** and compound **8b** is the substituent group on the nitrogen atom, so it seems that *N*-decyl chain is much better than *N*-octyl chain on the behavior of inhibition. Moreover, the activity difference between lactams and iminoalditols indicates that some structural features are essential for inhibition, although there is a certain redundancy around the six- or five-membered iminosugars.

Next, we tested the effects of the N-alkylated dideoxy iminoalditols on the secretion of cytokines from mouse splenocytes. The spleen cells induced by 2.5 μg/mL of Con A were incubated with each compound at 37 °C and 5% CO_2 for 48 h. The amount of cytokines was measured with enzyme-linked immunosorbent assay. All of these five compounds showed inhibitory ability to the interleukin (IL)-4 secretion. As compared to the control, the levels of IL-4 secretion were reduced by 60.9, 8.7, 95.7, 85.6, and 88.6% when including 30 μM compounds **8a**, **8b**, **12**, **16**, and **21**, respectively (Figure 4, 96.8% for CsA at 1 μM). It was found that among the five dideoxy iminoalditols, compound **12** displayed the strongest inhibitory effects on the release of the cytokine IL-4.

The assay on secretion of interferon (IFN)-γ from splenocytes was similar to the assay of IL-4. The supernatant of the spleen cells was detected by mice IFN-γ ELISA kit. All of these five compounds showed inhibition to the IFN-γ secretion. The levels of IFN-γ secretion were reduced by 89.1, 40.3, 78.1, 75.0, and 94.7% when including 30 μM compounds **8a**, **8b**, **12**, **16**, and **21**, respectively (Figure 5, 97.1% for CsA at 1 μM). The inhibition efficiency of iminosugar **21** was the strongest out of the five compounds.

The T cells contain two classes of T lymphocytes, T helper cells (Th), and T cytotoxicity (Tc) cells. The Th cells are generally

Table 1. Effects of Compounds 8a, 12, 16, and 21 on Mouse Skin Allograft[a] (MST ± SE, Days)

compound	MST ± SE[b]
Vel	11.25 ± 1.83
8a	14.71 ± 1.70**[c]
12	14.14 ± 2.54*
16	15.20 ± 2.39**
21[d]	15.60 ± 0.55**

[a] Grafts were inspected daily and were considered to be rejected when no viable donor epidermis remained. [b] MST in days. Each group consisted of eight mice with half males and half females (body weight, 18−22 g). [c] $^*P < 0.05$, and $^{**}P < 0.01$ vs Vel group. [d] The subcutaneous LD$_{50}$ of compound **21** is 392.1 mg/kg in mouse.

subdivided into Th1 and Th2 cells, which are distinguished by the cytokines that they produce and the immune responses that they promote. Th1 cells produce pro-inflammatory cytokines like IFN-γ, TNF-β, and IL-2, while Th2 cells produce the cytokines such as IL-4, IL-5, IL-6, and IL-13. Th1 responses predominate in organ-specific autoimmune disorders, acute allograft rejection, and in some chronic inflammatory disorders. In contrast, Th2 responses predominate in chronic graft versus host disease, progressive systemic sclerosis, systemic lupus erythematosus, and allergic diseases. The cytokines (e.g., IFN-γ) secreted by the Th1 subset act primarily in cell-mediated response, whereas those (e.g., IL-4) secreted by the Th2 subset function mostly in B-cell activation and humoral response.[26] In the cytokine assay, we chose IFN-γ and IL-4, which are the hallmark cytokines for Th1 and Th2 cells, respectively.[27] From the assay of the cytokine secretion, it seems that compounds **8a**, **12**, **16**, and **21** suppress both Th1 and Th2 cells, whereas compound **8b** has a moderate inhibition toward Th1 cells selectively. Therefore, compounds **8a**, **12**, **16**, and **21** might show inhibition activity toward both humoral responses and cell-mediated immune responses, holding the potential to treat different kinds of immune diseases.

CsA is one of the strongest immunosuppressants, and it selectively inhibits the lymphocytes especially the Th cells.[28,29] The suppressive effects of compounds **8a**, **12**, **16**, and **21** on splenocyte proliferation and secretion of cytokines (IFN-γ and IL-4) are similar to CsA and better than any other synthetic iminosugars previously reported by our group.[30] Encouraged by the immunosuppressive results in vitro, compounds **8a**, **12**, **16**, and **21** were further tested on the mouse skin transplantation model. The BALB/c mouse was used as the donor, and the C57BL/6 mouse was used as the recipient. In this experiment, the compounds (50 μmoL/kg) or vehicle were subcutaneously injected in mice daily, starting from the day of transplant surgery until the time of rejection. The mean survival time (MST) of vehicle-treated grafts was 11 days. Compounds **8a**, **12**, **16**, and **21** prolonged the mouse skin allograft survival to 14−16 days, which means that the skin survived 3−5 days longer than vehicle-treated grafts (Table 1). None of the allograft mice died during administration. As the control, the mice with injection of CsA (20 μmoL/kg) did not show skin rejection within 19 days. Therefore, as compared with the vehicle, iminosugars **8a**, **12**, **16**, and **21** did prolong the mouse skin allograft survival, although the survival time resulted from these iminosugars was shorter than that of CsA.

On the basis of the results of the mouse skin allograft together with the splenocyte proliferation and cytokine assays, iminotetritol **21** was better than the others, although it is hard to further tell the suppression difference between compounds **8a**, **12**, and **16**. It seems that the long hydrophobic *N*-decyl group is more favored for the immunosuppressive activity, indicating that there might be a lipophilic pocket in the binding site of the target biomacromolecule. Moreover, the activity difference between lactams **22**−**25** and iminoalditols **8a**, **12**, **16**, and **21** in proliferation assays indicates that dideoxy iminoalditol scaffolds are good for inhibition. These *N*-decyl dideoxy iminoalditols not only showed good inhibition in the splenocyte proliferation and cytokine assays but also improved the mouse skin allograft survival by 3−5 days.

Generally, iminosugars are potent inhibitors of many carbohydrate-processing enzymes. All cytokines are *N*-glycoproteins. The immunosuppressive activities by these dideoxy iminoalditols may come from the *N*-glycoprotein-processing inhibition effects on these glycoproteins. However, there are other possibilities for the immunosuppressive effects of these iminoalditols with a long hydrophobic chain. These N-alkylated iminoalditols might bind to some lipophilic sites of proteins by the alkyl group. The mechanism of this kind of iminosugars working on immune system needs to be further explored.

In summary, we report herein the synthesis of hitherto unknown N-alkylated 1,5-dideoxy-l,5-iminopentitols and N-alkylated 1,4-dideoxy-l,4-iminotetritol by an expeditious strategy. These iminosugars inhibit the mouse splenocyte proliferation induced by Con A. Further studies revealed that the inhibitory effects on splenocyte proliferation may come from the suppression of both IFN-γ and IL-4 cytokines, which are the hallmark cytokines for Th1 and Th2 cells, respectively. Importantly, these iminosugars can prolong the allograft survival on the mouse skin transplantation model. Although the effects are not as good as CsA in mouse skin allograft at the current stage, to our knowledge, they are the first synthetic iminosugars that show immunosuppressive activities in animal model. It is a forward step for investigating immunosuppressive effects of iminosugars. Our results provide a lead for further elucidation of the structure−activity relationships on iminosugars and modifications for better immunosuppressive agents.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +(86)10-82805736. E-mail: xinshan@bjmu.edu.cn.

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■ ABBREVIATIONS

CsA, cyclosporin A; Con A, concanavalin A; Th, T helper cells; Tc, T cytotoxicity cell; MST, mean survival time; LD$_{50}$, median lethal dose

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(30) The structure and potency of compounds described in our previous research have been briefly summarized in the Supporting Information.