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Fluorinated piperidine iminosugars and their *N*-alkylated derivatives: Synthesis, conformational analysis, immunosuppressive and glycosidase inhibitory activity studies

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ABSTRACT

The fluorinated piperidine iminosugars **2a-4a** and their *N*-octyl and *N*-decyl derivatives **2b,c-4b,c** were synthesized from D-mannose/D-xylose using nucleophilic fluorination as the key step. The conformation of iminosugars **2**/**3**, either $^{2}C_{5}$ or $^{5}C_{2}$, was assigned based on the ^{1}H NMR studies at different pH. Immunomodulatory activity of **2a,c-4a,c** was examined using Mixed Lymphocyte Reaction (MLR) and B-cell assay. The *N*-alkylated fluorinated D-*manno*-iminosugars **3b/4b** were found to be better immunosuppressive agents ($IC_{50} = 5–6\ \mu M$) on T-cells. The fluorinated iminosugar **3a/4a** act as potent and selective inhibitors of β-glucosidase ($IC_{50} = 4–8\ \mu M$). The *N*-alkyl-iminosugars **4b-c** were found to be moderate inhibitors of α-glucosidase (yeast) and α-galactosidase (coffee beans), respectively.

1. Introduction

Iminosugars are cyclic sugars in which the ring oxygen atom is replaced with the nitrogen atom.[1] The potent glycosidase inhibitory activity of iminosugars resulted into the discovery of *N*-hydroxyethyl-DNJ (Miglitol) **1a** and *N*-butyl-DNJ (Zavesca) **1b** as drugs for the treatment of type-II diabetes and lysosomal storage disorder, respectively.[2] Apart from glycosidase inhibitory activity, iminosugars are being investigated as immunomodulators. Natural compounds which possess immunomodulatory activity are glycoproteins,[3] lipids,[4] polynucleotides,[5] polysaccharides,[6] heterocycles,[7] nucleosides[8] and glycosylceramides.[9] In addition, there are number of synthetic compounds such as cyclosporine, tacrolimus and their analogues which balance the immune system and act as adjuvant therapeutic agents for the treatment of tumour, viral infection and solid organ transplantation.[10] In the development of new immunomodulator agents, the class of iminosugars has attracted a great deal of interest. For example, bi-cyclic indolizidine iminosugars such as castanospermine, kifunensine act as immunosuppressive agents while; swainsonine acts as immunostimulator.[11] The *N*-pentafluorobenzyl-1-deoxynojirimycin **1c** acts as immunosuppressant for the treatment of Th2-mediated immune diseases suggesting the role of the fluorine atom in augmenting the immunomodulatory activity.[12] Recently, we demonstrated that the immunosuppressive activity of castanospermine is altered by replacement of C-1 hydroxyl functionality with 1*S*/1*R*-hydroxymethyl group wherein; the C-1(*S*) hydroxymethyl substituted castanospermine showed significant immunostimulating property by up-regulation of TH1/TH2 cytokine ratio (IL-6 and IL-4) with their excellent cell proliferating activity.[13] In the continuation of our work in this area,[14] we were particularly interested in the fluorinated piperidine diols the chemical isoster of hydrogen and hydroxyl groups in 3,4,5-piperidine triols **1d-e**[15] that are isolated from the *Eupatoriumfortunei TURZ* plant extract and are traditionally used in Chinese and Japanese folk medicine as antidiabetic, antipyretic, and diuretic agents.[16] We anticipated that, inclusion of the fluorine atom in 3,4,5-piperidine triol as well as *N*-alkylation-in particular the *N*-octyl/decyl derivatives may change the physicochemical properties such as liphophilicity, metabolic stability and

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bio-availability so as to demonstrate better immunomodulatory activity.[10,17] Although, a number of *N*-alkyl mono-and bi-cyclic iminosugars were evaluated for glycosidase inhibitory activity, no report is available on the immunomodulatory activity study of *N*-alkyl fluorinated piperidine iminosugars. In view of these aspects, we now report the synthesis, immunosuppressive and glycosidase inhibitory activity of hitherto unknown mono- and *gem*-di-fluorinated piperidine iminosugars **2a-4a** and their *N*-alkyl derivatives **2b,c, 3b,c, 4b,c** (Fig. 1).

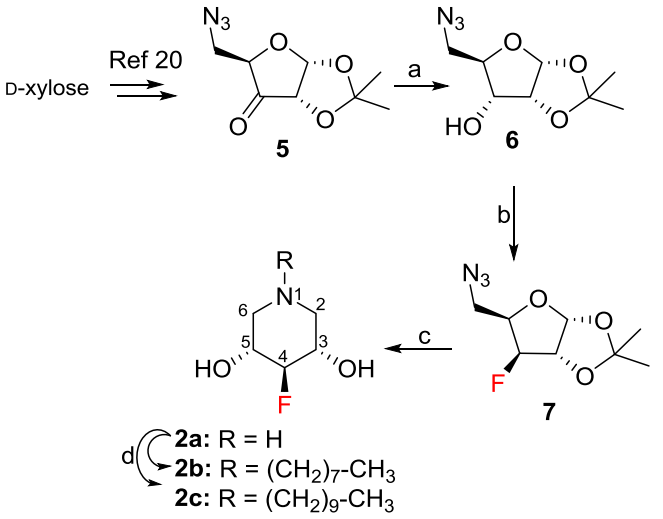
In general, the synthesis of mono- and di-fluorinated iminosugars involves S_N2 substitution of -OTs/-OTf group in iminosugar framework using fluorinated nucleophiles such as CsF and/or DAST[18] while; di-fluorinated iminosugars are prepared *via* the [2,3] Wittig rearrangement of difluoroallylic alcohols (the Percy's method).[19] Other methods involve use of HF/SbF_5 catalysed hydrofluorination.[20] We have exploited DAST and CsF as nucleophilic fluorinating agents in the synthesis of mono- and di-fluorinated piperidine iminosugars **2a-c, 3a-c** and **4a-c**. Amongst, newly synthesized nine iminosugars, *N*-alkylated fluorinated D-*manno*-iminosugars **3b/4b** were found to be better immunosuppressive agents. The fluorinated iminosugar **3a/4a** act as potent and selective inhibitors of β-glucosidase ($IC_{50} = 4–8\ \mu M$). Our results in this direction are depicted below.

2. Results and discussion

2.1. Synthesis

As shown in Scheme 1, target molecules **2a-c** were prepared from 1,2-*O*-isopropylidene-5-azido-3-oxo-D-xylofuranose **5** that was obtained from D-xylose as reported earlier.[21] In the next step, reduction of the ketone group in **5** gave 5-azido-D-ribofuranose **6**. The C-3 hydroxyl group in **6** was converted to C3-OTf (using Tf_2O in pyridine) that on S_N2 displacement with CsF in *t*-butanol gave (3*R*)-fluorinated-xylose derivative **7**.[22] Treatment of **7** with TFA:water gave hemiacetal that on reductive aminocyclization using H_2, 10% Pd/C afforded C4-fluoro-piperidine-iminosugar **2a**.

The *N*-alkylation of **2a** using *n*-octyl bromide and *n*-decyl bromide, using K_2CO_3 in DMF at 80 °C, afforded corresponding *N*-alkylated piperidine iminosugars **2b** and **2c** in good yields.



Scheme 1. a) $NaBH_4$, MeOH:H_2O; b) (i) Tf_2O, Py, DCM; (ii) CsF, t-BuOH, 80 °C, 84%; c) (i) TFA:H_2O (3:2); (ii) H_2, Pd-C, MeOH 75%; d) K_2CO_3, DMF, R-Br, 80 °C.

The synthesis of C5-mono-fluorinated piperidine iminosugar **3a** commenced with iminosugar **8** that was prepared from D-mannose using known reaction procedure.[23] In the next step (Scheme 2), protection of the ring nitrogen in **8** using Boc-anhydride and Et_3N gave **9**. Treatment of **9** with DAST (as nucleophilic fluorinating agent) afforded **10** with retention of configuration[24] at C5 (*vide infra*) due to the neighbouring group participation of *N*-Boc functionality.[25] In the next stage, removal of 3,4-*O*-isopropylidene and *N*-Boc groups in **10** using 4 M HCl in dioxane gave C5-fluorinated-piperidine iminosugar **3a** in good yield. The *N*-alkylation reaction of **3a**, separately, with *n*-octyl bromide and *n*-decyl bromide in the presence of K_2CO_3 in DMF at 80 °C afforded **3b** and **3c**, respectively. For the synthesis of *gem*-di-fluorinated piperidine iminosugar **4a**, compound **9** was treated with Dess-Martin periodinane oxidation that afforded 5-oxo-piperidine derivative **11**. Reaction of **11** with DAST (3.0 eq) gave *gem*-di-fluorinated compound **12**. De-protection of 3,4-*O*-isopropylidene and *N*-Boc groups in **12** using 4 M HCl in dioxane gave *gem*-di-fluorinated piperidine iminosugar **4a** in 86%

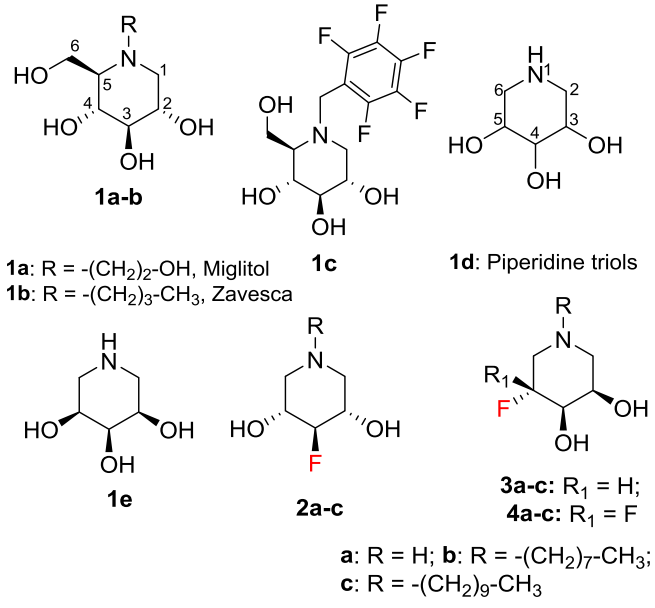
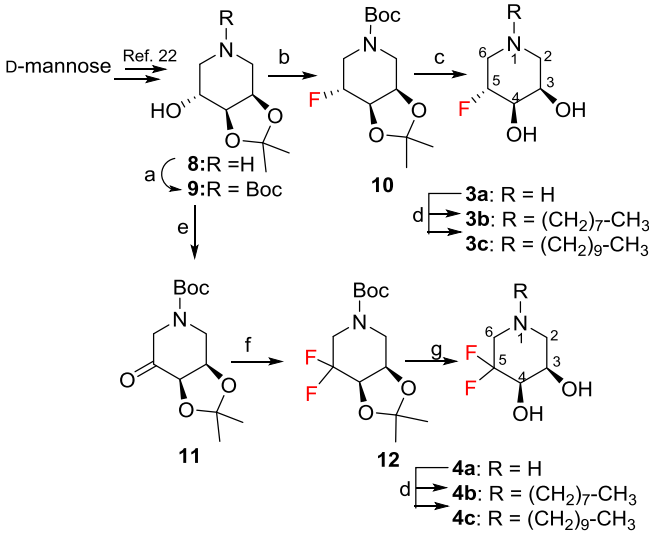


Fig. 1. Piperidine-iminosugars.



Scheme 2. a) $(Boc)_2O$, TEA, DCM, 24 h, 85%; b) DAST, DCM, 1 h, 0 °C, 90%; c) 4 M HCl, MeOH, 0 °C, 3 h, 84%; d) K_2CO_3, DMF, R-Br, 80 °C; e) DMP, DCM, 12 h, 85%; f) DAST, DCM, 1 h, 0 °C, 87%; g) 4 M HCl, MeOH, 0 °C, 3 h, 86%.