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# Synthesis of branched seven-membered 1-*N*-iminosugars and their evaluation as glycosidase inhibitors

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# ABSTRACT

Four branched tetra- and pentahydroxylated azepanes have been synthesized from a common azepane precursor through dihydroxylation followed by deoxygenation. They have been assayed as glycosidase inhibitors on a panel of 22 glycosidases and one methylated azepane displayed selective, competitive, and moderate inhibition toward bovine kidney  $\alpha$ -L-fucosidase.

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#### 1. Introduction

Interest continues to mount in new applications of natural and synthetic glycosidase inhibitors to basic research and medicine as iminosugar-based inhibitors<sup>1</sup> have been shown to exhibit potent activity on diabetes,<sup>2</sup> HIV infection,<sup>3</sup> viral infections<sup>4</sup> or cancer<sup>5</sup> leading sometimes to therapeutics.<sup>6</sup> In the last two decades, 1-Niminosugars have emerged as a major new class of very potent glycosidase inhibitors by virtue of their resemblance with the carbocationic form of glycosidase transition state. The most famous molecule of this family, coined isofagomine 1, was reported by Bols<sup>7</sup> and proved to be a strong  $\beta$ -glucosidase inhibitor. As expected, the potency of isofagomine was further improved by introducing a hydroxyl group at the C-2 position to afford noeuromycin **2**, a nanomolar  $\beta$ -glucosidase inhibitor.<sup>8</sup> Meanwhile, many other sugar analogs with nitrogen at the pseudoanomeric position have been prepared<sup>9</sup> including branched derivatives such as compounds **3–6** (Fig. 1).<sup>10</sup> The introduction of an extra tertiary hydroxyl group was justified in order to hold the sugar hydroxyl groups in the correct topological orientation and hopefully generate more selective and potent glycosidase inhibitors. This modification was also applied to polyhydroxylated pyrrolidine generating compounds such as **7**<sup>11</sup> and **8** (Fig. 1), this latter displaying promising activity as corrector of del508-CFTR involved in cystic fibrosis.12

# 2. Synthesis

In an ongoing program on the design of new glycosidase inhibitors, our group has recently reported the synthesis<sup>13</sup> and biological evaluation<sup>14</sup> of ring homologs of noeuromycin. We would like to report herein our results on branched derivatives of these compounds. We used a similar strategy as the one developed by Pandey<sup>15</sup> based on the dihydroxylation of the exoalkene present on the available azacycle **9**. Dihydroxylation of **9** using OsO<sub>4</sub> and NMO afforded the separable diols **10** and **11** (93% yield) which were hydrogenolyzed under mild acidic conditions to afford the corresponding pentahydroxylated azepanes **12** and **13** as their hydrochloride salts (Scheme 1).

As tetrahydroxylated azepanes have been proved to be potent glycosidase inhibitors,<sup>16</sup> we were also interested in synthesizing branched analogs of these compounds and introducing some conformational bias with an extra methyl group. Tosylation of the neopentylic alcohol in diol **10** furnished the crude tosylate in good yield which was directly reduced with Superhydride<sup>®</sup> to yield the corresponding deoxy derivative **14** (68% yield over two steps). Final hydrogenolysis furnished the branched tetrahydroxyazepane **15** as its hydrochloride salt (Scheme 2). The same sequence was applied to diol **11** to furnish the intermediate **16** (65% yield) and the branched tetrahydroxyazepane **17**.

# 3. Structure determination

The configuration of compounds **15** and **17** was confirmed by NOESY experiments. While the  $CH_3$  group in compound **15** showed





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Figure 1. Structure of isofagomine 1, noeuromycin 2 and branched derivatives 3-8.



Scheme 1. Synthesis of pentahydroxylated azepanes 12 and 13.



Scheme 2. Synthesis of tetrahydroxylated azepanes 15 and 17.

a strong NOE effect with H-4 and H-6a and a medium NOE effect with H-6b, the  $CH_3$  group in compound **17** showed a strong NOE effect with H-6b and a medium NOE effect with H-4 and H-6a demonstrating a *cis* relationship for H-4 and the methyl group in compound **15** and a *trans* relationship for H-4 and the methyl group in compound **17** (Fig. 2) and enabling the unambiguous deduction of the configuration of related compounds **12** and **13**.

#### 4. Glycosidase inhibition assay

Azepanes **12**, **13**, **15**, and **17** were assayed for their inhibitory activity toward 22 commercially available glycosidases.<sup>17</sup> They did not inhibit the following enzymes at 1 mM concentration and optimal pH: coffee bean  $\alpha$ -galactosidase,  $\beta$ -galactosidases from *Aspergillus oryzae* and *Escherichia coli*, rice  $\alpha$ -glucosidase, amyloglucosidase from *Aspergillus niger*, snail  $\beta$ -mannosidase,  $\beta$ -N-acetyl-glucosaminidases from jack bean and bovine kidney. For other enzymes the results are shown in Table 1.



Figure 2. Main NOE data for tetrahydroxylated azepanes 15 and 17.

All the branched azepanes were found to be weak glycosidase inhibitors except for azepane 17 which displayed selective and moderate competitive L-fucosidase inhibition. This last result can tentatively be explained by the presence of the methyl group and the adjacent hydroxyl group which partially display the configuration of L-fucose. Compared to the noeuromycin ring homologs, introduction of an extra hydroxyl group on the carbon that bears the hydroxymethyl group appears detrimental to the inhibition potency of this family of compounds. Compared to tetrahydroxylated azepanes, introduction of an additional hydroxymethyl group on the tetrahydroxyazepane scaffold also strongly affects the glycosidase inhibition of these compounds. Such observation has already been made in the case of polyhydroxylated azepanes mimicking glyconojirimycins.<sup>18</sup> In conclusion, increasing the size and lowering the conformational flexibility of seven-membered iminosugars by introducing an extra CH<sub>3</sub> or CH<sub>2</sub>OH group mainly abolishes inhibitory potency and therefore draws the size limits for a glycosidase iminosugar-based inhibitor.

#### 5. Experimental section

### 5.1. General methods

Melting points (mp) were determined with a Büchi B-535 apparatus and are uncorrected. Optical rotations were measured at Download English Version:

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