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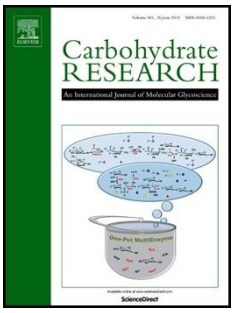

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Author: Chunyan Liu, Linyu Hou, Aiguo Meng, Gang Han, Weiguo Zhang, Shende Jiang

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Design, synthesis and bioactivity evaluation of Gal*f* mimics as antitubercular agents

Chunyan Liu[a,] *, Linyu Hou[b] , Aiguo Meng[c] , Gang Han[a] , Weiguo Zhang[a] and Shende Jiang[d]

[a] *School of Pharmacy, North China University of Science and Technology, Tangshan 063000, P. R. China*
[b] *School of Public Health, North China University of Science and Technology, Tangshan 063000, P. R. China*
[c] *Affiliated Hospital, North China University of Science and Technology, Tangshan 063000, P. R. China*
[b] *School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, P. R. China*

Highlights

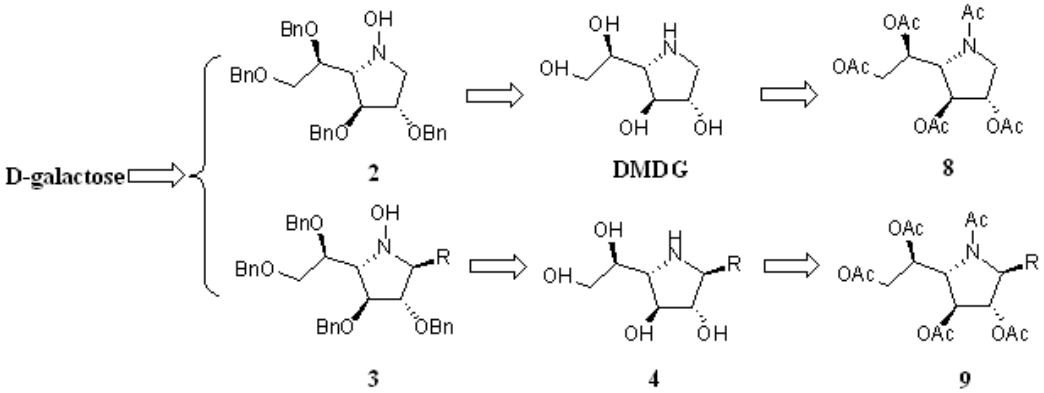

Figure. Chemical Structures of DMDG and Gla*f* mimics

* Corresponding author. School of Pharmacy, North China University of Science and Technology, Tangshan 063000, P.R. China. e-mail: chunyanliu@ncst.edu.cn

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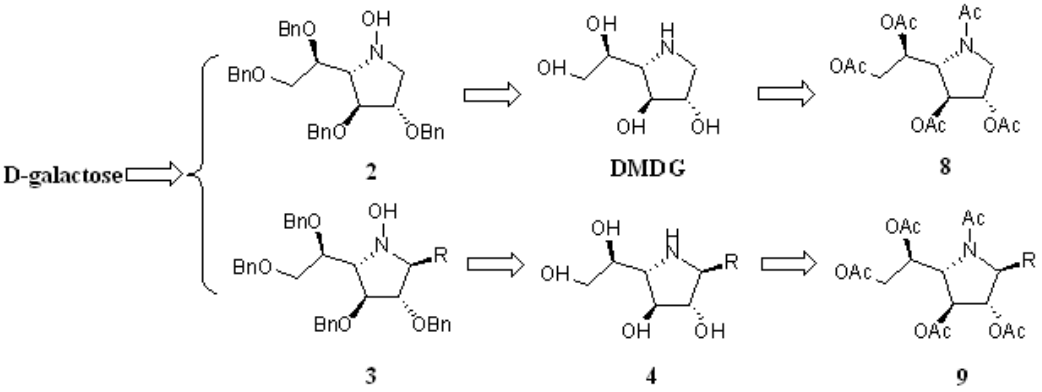
Graphical Abstract

Design, synthesis and docking studies of Gal*f* mimics as antitubercular agents

Chunyan Liu[a,*], Linyu Hou[b], Aiguo Meng[c], Gang Han[a], Weiguo Zhang[a] and Shende Jiang[e]

A series of novel Gal*f* mimics have been synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral and element analysis. All the newly prepared compounds were screened for their antitubercular activities. Bioactivity assays manifested that most of Gal*f* mimics exhibited good antitubercular activities. Especially compound **4d** and **4e** displayed remarkable antitubercular efficacies, which were comparable to ethambutol.

[a] *School of Pharmacy, North China University of Science and Technology , Tangshan 063000, P.R. China*
[b] *School of Public Health, North China University of Science and Technology, Tangshan 063000, P. R. China*
[c] *Affiliated Hospital, North China University of Science and Technology, Tangshan 063000, P.R. China*
[b] *School of Pharmacy, Xuzhou Medical College, Xuzhou, Jiansu 221004, China*
[e] *School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, P. R. China*



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ABSTRACT

A series of novel Gal*f* mimics have been synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral and element analysis. All the newly prepared compounds were screened for their antitubercular activities. Bioactivity assays manifested that most of Gal*f* mimics exhibited good antitubercular activities. Especially compound **4d** and **4e** displayed remarkable antitubercular efficacies, which were comparable to ethambutol.

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1. Introduction

Tuberculosis (TB), caused by infection with the bacterium *M. tuberculosis*, remains a major global health problem, responsible for ill health among millions of people each year.[1] The current treatment for susceptible strains requires long treatment periods with multiple antibiotics, as no new TB drugs have been introduced into clinical use in the past 4 decades.[2] The emergence of multi-drug and extensively-drug resistant strains of *M. tuberculosis* has further contributed to the urgent need for the development of anti-tubercular agents with novel modes of action.[3]

The structure of the mycobacterial cell wall serves as a significant permeability barrier to the passage of antibiotics into the organism.[4] Galactofuranose (Gal*f*) residues are present in the mycolyl-arabinogalactan-peptidoglycan (mAGP) complex, the major structural element of the cell wall, and play a pivotal role in the virulence and the viability of TB.[5] The biosynthetic precursor of Gal*f*-containing glycoconjugates is uridine 5'-diphosphate (UDP) Gal*f*, which is generated by the enzyme UDP-galactopyranose mutase (UGM). UGM is a flavoenzyme that catalyzes the isomerization of UDP-galactopyranose (UDP-Gal*p*) to UDP-galactofuranose (UDP-Gal*f*) and then the production of the biosynthetic glycosyl donor UDP-Gal*f* is used by galactofuranosyl transferases.[6] Absence of UGM and Gal*f* in mammals,[7] along with the fact that biosynthesis of Gal*f* residues are essential for cell wall biosynthesis and the viability of mycobacteria,[8] makes UGM a potential selective target for therapeutic intervention. There have been significant efforts directed towards the development of different substrate analogues and transition state mimics of Gal*f* residues, which have been synthesized and screened against UGM in the recent past. [9]

Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products and useful as potent glycosidase inhibitors.[10] Recently these iminosugars, both natural and unnatural, have been of intense interest due to their promising chemotherapeutic properties against diabetes, cancer, tuberculosis and viral infections.[11] Amongst iminosugars, five-membered pyrrolidine compounds such as 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) and 2,5-dideoxy-2,5-imino-D-glycero-D-manno-heptitol (homo DMDP) are selective inhibitors of α- and β-glucosidases.[12] The 1,4-dideoxy-1,4-imino-D-galactitol (DMDG) is the Gal*f* mimic and possesses inhibitory activity on the growth of TB,[13] thus the Gal*f* mimic may have therapeutic potential. A few of DMDG derivatives[14] designed to inhibit UGM have been reported, however, only some have shown weak inhibition of the activity towards UGM. In the previous study, we also described the synthesis of a Gal*f* disaccharide by nucleophilic addition of L-arabinofurano-alkyne to iminogalactitol-derived nitrone.[15]

Recent contributions by various leaders in the field seemed to suggest that C1-alkyl, vinyl, and aryl-substituted pyrrolidine and piperidine iminosugars be more selective inhibitors of glycosidases through stronger interactions with the aglycon binding site or with lipophilic pockets around the enzymes' active sites.[16] We thus reasoned that C1-alkyl and aryl substituted Gal*f* mimic may generate an original scaffold for biological evaluation. These guiding results, in line with our interest in designing Gal*f* mimics (Figure 1) as UGM inhibitors, we now describe the synthesis of C1-alkyl and aryl-substituted Gal*f* mimics and evaluated for their anti-tubercular activity.

2. Results and discussion

2.1. Chemistry

Recent work conducted in our laboratory has shown the utilization of cyclic nitrone toward the synthesis of iminosugars and their biological evaluation.[17] Thus, in continuation of our research interest for the synthesis of DMDG and novel iminosugars based on the cyclic nitrone **1** as an important intermediate, the synthetic pathways are illustrated in Figure 2. Our synthetic approach of DMDG depended on the iminogalactitol-derived nitrone **1** on *N-O* bond reductive cleavage followed by deprotection of benzyl functionality, which is different from the reported synthetic methods.[18] While the synthesis of C1-β-alkylated or C1-β-arylated pyrrolidine iminosugar **4** is based on the coupling of the sugar entities by a 1,3-dipolar cycloaddition process between nitrone **1** and an alkyl- or aryl- group as a dipolarophile followed by deprotection of benzyl functionality. A major advantage of this methodology is the very high β-stereoselectivity of the cycloadditions onto nitrone **1**, as shown in our previous studies[17] and other groups.[19]

For the synthesis of the iminogalactitol-derived nitrone **1**, we employed D-galactose as a chiral building block to afford 2,3,5,6-*tetra*-*O*-benzyl-D-galactofuranose **5**. The lactol **5** was

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sequentially reacted with hydroxylamine hydrochloride and then selectively silylated by *tert*-butyldimethylsilyl chloride to afford an inseparable mixture of E/Z-oxime derivatives **6**. The synthesis of nitrone **1** was obtained from oxime derivatives **6**, based on intramolecular S_N2 reactions carried out by oximate anion, which occurred with inversion of configuration at the attacked carbon atom. The methodology involved the intramolecular alkylation of an oxime have been successfully adopted by other groups.[20]

The utility of nitrone **1** was demonstrated in the synthesis of the known pyrrolidine iminosugar DMDG (Scheme 2). Thus, reduction of *C=N* in nitrone **1** with sodium borohydride afforded compound **2** in good yield, but **2** was not very stable to storage. In the next step, one pot *N—O* bond by catalytic hydrogenation gave the targeted compound. The spectral and analytical data of DMDG were found to be in consonance with those reported.[13] Acetylation of DMDG was taken place in acetic anhydride and pyridine with N,N-dimethylaminopyridine as a catalysis and dichloromethane as solvent to afford compound **8**.

Targeting toward pyrrolidine iminosugar C-glycosides, we explored the 1,3-addition of Grignard to nitrone **1** (Scheme 3). This reaction in diethyl ether at 0°C was highly diastereo-selective and then afforded C1-β-alkylated or C1-β-arylated N-hydroxy pyrrolidine iminosugar **3** and its C1-epimer in the ratio 4:1, respectively. The spectral and analytical data of **3** were in agreement with the proposed structure's. Hydrogenolysis of compound **3** using hydrogen with Pd/C as catalysis gave **4**. Acetylation of iminosugar **4** was the same as that of DMDG to afford compound **9**.

This procedure was used to synthesize some distinct pyrrolidines (Figure 3), including DMDG in high yields and high purities. Next, biological evaluation of this focused library against tubercular activity was conducted.

2.2. Biological evaluation

The synthetic compounds were evaluated for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv strains by the broth microdilution assay method.[20] The minimum inhibition concentrations are showed in Table 1.

It's demonstrated that protected sugars showed excellent inhibitory potential as compared to partially or completely unprotected ones.[21] Surprisingly, Gal*f* mimics bearing benzyl or acetyl groups displayed no significant improvement in activity against *M. tuberculosis*, and acetylation of iminosugar seemed to show higher activity than benzylation of ones. DMDG with a MIC value of 12.5μg/mL was much more effective than protected compound **2** and **8**. Compound **4a** and **4b** showed also a MIC value of 12.5μg/mL. The MIC value was higher than or similar to that of benzyled ones **3a** or **3b**, and superior to that of acetyled ones **9a** and **9b**. Compound **4c** with a MIC value of 6.25μg/mL showed a good activity, which was more effective than compound **3c** bearing benzyl groups and as effective as compound **9c** bearing acetyl groups. In contrast, compounds **4d** and **4e** exhibited promising activity with MIC values of 3.13μg/mL, which showed significantly higher activity than the protected compound. Despite these two Gal*f* mimics were less active than the main drug isoniazid, whose MIC values were close to that of the "second-line" drug in clinical use as ethambutol. The results revealed that pyrroles carrying a aryl-substituent at the 2-position were optimal for antimycobacterial activity.

3. Conclusions

In summary, Gal*f* mimics have been synthesized. The structures proposed for all synthesized compounds were confirmed by spectroscopic data and elemental analysis, and they were evaluated for their antibacterial properties. Both synthesized compounds (**4d** and **4e**) showed moderate to good anti-tubercular activity compare to antibacterial drug (ethambutol). Gal*f* mimics can be considered as an initial leads for the development of better anti-tubercular agents.

4. Experimental

4.1. General methods

Chemicals purchased from commercial vendors were used without purification. Infrared spectra were recorded using a Shimadu FTIR-8400s Fourier Transform spectrometer as a thin film on KBr plates. NMR spectra were recorded on a Bruker AV-300 at 300MHz (^{1}H) and 75 MHz (^{13}C), or a Bruker AV-600 at 600MHz (^{1}H) and 150 MHz (^{13}C) and were referenced to the internal standard tetramethylsilane, in the respective deuterated solvents. Coupling constants (*J*) are reported in Hertz. $CDCl_3$ was empolyed for protected compounds and D_2O or CD_3OH for free sugar. Mass spectra were recorded on a mass spectrometer. Elemental analyses were performed by the analytical services at Nankai University (Tianjin). Flash chromatography was performed on silica gel (300-400 mesh). TLC was run on pre-coated aluminium plates (Merck Kieselgel 60 F254) and the spots were visualized with UV light and basic aqueous potassium permanganate followed by heating.

4.1.1 1-deoxy-2,3,4,5-tetra-*O*-benzyl-1,4-hydroxyl-amino-D-galactofuranose (2)

To a solution of nitrone **1** (1g, 1.86mmol) in dry methanol (15mL) was added dropwise HCl (2N in methanol, 0.92ml) at 0ºC. The reaction mixture was vigorously stirred for 5 min, followed by slow addition of sodium borohydride (0.1g, 1.86mmol). After 4h stirring, the reaction was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to give an oil. The crude residue was purified by flash chromatography (petroleum ether/AcOEt=5/2) to afford **2** (0.93g, 93%) as a colourless oil. IR(KBr, cm^{-1}): 3387, 3086, 3063, 3031, 2869, 1604, 1496, 1454, 1363, 1251, 1073, 1027; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H, *N-OH*), 7.27－7.37 (m, 20H, H_{Ar}), 4.69－4.71 (d, 1H, *J*=11.8Hz, O*CH*$_2$Ph), 4.55－4.58 (d, 1H, *J*=11.8Hz, O*CH*$_2$Ph), 4.50－4.53 (d, 1H, *J*=11.9Hz, O*CH*$_2$Ph), 4.37－4.47 (m, 5H, O*CH*$_2$Ph), 3.95－3.96 (q, 1H, *J*=5.1Hz, H-3), 3.85 (br q, 2H, H-2 and H-5), 3.77－3.79 (dd, 1H, *J*=1.8Hz and *J*=8.5Hz, H-6a), 3.63－3.68 (dd, 1H, *J*=2.3Hz and *J*=7.8Hz, H-6b), 3.22－3.25 (d, 1H, *J*=10.6Hz, H-4), 3.01 (brq, 1H, H-1a), 2.88－2.92 (dd, 1H, *J*=5.7Hz and *J*=5.0Hz, H-1b); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 61.9 (*C*1), 67.8 (*C*4), 71.9, 72.6 and 73.3 (O*CH*$_2$Ph), 73.5 (*C*6), 73.7 (O*CH*$_2$Ph), 78.6 (*C*5), 85.1 (*C*2), 85.7 (*C*3), 127.5－128.4 (*CH*$_{Ar}$), 136.9, 137.1, 137.2 and 137.9 (Cq$_{Ar}$); MS-EI (m/z): 562 (M^++Na); Anal. Calc. For $C_{34}H_{37}NO_5$: C, 75.67; H, 6.91; N, 2.60; found: C, 75.58; H, 6.95; N, 2.58.

4.1.2 1-deoxy-1,4-imino-D-galactofuranose (DMDG)

To a stirred solution of **2** (1g, 1.85 mmol) in 5:1 MeOH: EtOAc (20 mL) was added Pearlman's catalyst (20% $Pd(OH)_2$/C, Degussa type, 1g) and acetic acid (10 drops). The flask was purged under vacuum and H_2 (3 bar) introduced. This process was repeated 5 times and the reaction allowed to stir vigorourly under H_2 (3 bar) overnight. The catalyst was removed by

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filtration and washed thoroughly with hot MeOH. The combined filtrates were then evaporated in vacuo to give a colourless oil. The oil was filtered through Amberlite OH resin to give **DMDG** (0.19g, 63%). $[\alpha]^{20}_{D}$ +2.7 (c 1.8, H_2O); lit. [12], $[\alpha]^{20}_{D}$ +3.0 (c 2.4, H_2O); ^{1}H NMR(300 MHz, D_2O) δ 4.01(dt, 1H, H-3), 3.93–3.96 (m, 1H, H-2), 3.62–3.66 (m, 1H, H-5), 3.58 (dd, 1H, *J*=3.5Hz and *J*=11.8Hz, H-6b), 3.45 (dd, 1H, *J*=6.6Hz and *J*=12.0Hz, H-6a), 3.19 (s, 1H, *NH*), 2.99 (dd, 1H, *J*=4.9Hz and *J*=12.4Hz, H-1b), 2.85–2.83 (m, 1H, H-4), 2.79 (dd, 1H, *J*=2.8Hz and *J*=12.5Hz, H-1a); ^{13}C-NMR (75 MHz, D_2O) δ 60.9 (*C*1), 61.8 (*C*4), 68.3 (*C*6), 69.4 (*C*5), 75.6 (*C*2), 76.8 (*C*3); MS-EI (m/z): 186 (M^++Na); Anal. Calc. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.08; H, 8.11; N, 8.53.

4.1.3 *N*-acetyl-1-deoxy-2,3,4,5-tetra-*O*-acetyl-1,4-imino-D-galactofuranose (8)

To a stirred solution of **DMDG** (0.19g, 1.17 mmol) in dry pyridine (20 mL) was added acetic anhydride (5 mL, 53mmol) and 4-dimethylaminopyridine (0.1g, 0.82 mmol) at r.t. overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified *via* flash column chromatography (petroleum ether/AcOEt=7/1) to give product **8** (0.32g, 73%) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.20-5.23 (m, 1H, H-3), 5.16-5.18 (d, 1H, *J*=4.2Hz, H-2), 4.96-4.99 (t, 1H, *J*=10.8Hz, H-5), 4.57-4.60 (dd, 1H, *J*=5.3Hz and *J*=10.6Hz, H-6b), 4.12-4.15 (m, 1H, H-6a), 3.07-3.09 (dd, 1H, *J*=4.7Hz and *J*=10.3Hz, H-4), 2.95-3.02 (m, 2H, H-1), 2.13-2.14 (s, 3H, *N(O)*C*Me*), 2.01-2.09 (m, 12H, OC*Me*); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 20.6, 20.7, 20.7, 20.8 (OC*Me*), 22.7 (NOC*Me*), 62.9 (*C*1), 65.5(*C*4), 69.8 (*C*6), 71.3 (*C*5), 78.4 (*C*2), 80.1 (*C*3), 169.0, 169.4, 169.7, 169.9, 170.1 (C=O); MS-EI (m/z): 396 (M^++Na); Anal. Calc. For $C_{16}H_{23}NO_9$: C, 51.47; H, 6.21; N, 3.75; found: C, 51.49; H, 6.15; N, 3.78.

4.1.4 1-methyl-1-deoxy-2,3,4,5-tetra-*O*-benzyl-1,4-hydroxyl-amino-D-galactofuranose (3a)

To a solution of nitrone **1** (1g, 1.86mmol) in dry diethyl ether (15mL) was added dropwise methylmagnesium bromide (1M in diethyl ether, 2mL) under nitrogen at 0ºC. The reaction mixture was stirred for 30min at room temperature, quenched with saturated ammonium chloride solution and then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to give an oil. The crude residue was purified by flash chromatography (petroleum ether/AcOEt=5/1) to afford a colourless oil **3a** (0.81g, 78%). IR (KBr, cm^{-1}): 3385, 3088, 3063, 3030, 2866, 1605, 1496, 1454, 1363, 1308, 1251, 1073, 1027; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.20－7.32 (m, 20H, H_{Ar}), 5.62 (s, 1H, *N-OH*), 4.76－4.78 (d, 1H, *J*=11.6, OCH_2Ph), 4.54－4.58 (d, 2H, *J*=11.9, OCH_2Ph), 4.47－4.52 (m, 3H, OCH_2Ph), 4.32－4.38 (dd, 2H, *J*=14.69 and *J*=11.60, OCH_2Ph), 3.84－3.85 (m, 2H, H-2 and H-3), 3.76－3.77 (m, 2H, H-5 and H-6b), 3.73－3.74 (m, 1H, H-6a), 3.50－3.52 (t, 1H, H-4), 3.42 (t, 1H, H-1), 1.21－1.22 (d, 3H, *J*=6.48, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 28.7 (CH_3), 62.7 (*C*1), 68.9 (*C*4), 72.1, 72.8 and 73.9 (OCH_2Ph), 74.2 (*C*6), 74.5 (OCH_2Ph), 79.1 (*C*5), 85.7 (*C*2), 86.0 (*C*3), 127.7－128.9 (CH_{Ar}), 137.4, 137.5, 137.6, and 138.0 (Cq_{Ar}); MS-EI (m/z): 576 (M^++Na); Anal. Calc. For $C_{35}H_{39}NO_5$: C, 75.92; H, 7.10; N, 2.53; found: C, 75.89; H, 7.12; N, 2.48.

4.1.5 1-methyl-1-deoxy-1,4-imino-D-galactofuranose (4a)

Following the same procedure as **DMDG**, compound 4**a** was obtained as a colourless oil, yield 76%. ^{1}H-NMR (600 MHz, CD_3OD) δ 4.93 (s, 4H, OH), 3.99－4.01 (t, 1H, *J*=6.4, H-3), 3.86－3.88 (d, 1H, *J*=3.2, H-2), 3.63－3.68 (m, 3H, H-6 and H-5), 3.37 (m, 1H, H-4), 3.26－3.28 (m, 1H, H-1), 1.91 (s, 1H, *N-OH*), 1.38－1.40 (d, 3H, *J*=6.24, CH_3); ^{13}C-NMR (150 MHz, CD_3OD) δ 28.8 (CH_3), 61.1 (*C*1), 62.3 (*C*4), 68.9 (*C*6), 70.2 (*C*5), 75.9 (*C*2), 77.1 (*C*3); MS-EI (m/z): 200 (M^++Na); Anal. Calc. For $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.90; found: C, 47.48; H, 8.56; N, 7.89.

4.1.6 *N*-acetyl-1-methyl-1-deoxy-2,3,4,5-tetra-*O*-acetyl-1,4-imino-D-galactofuranose (9a)

Following the same procedure as **8**, compound **9a** was obtained as a colourless oil, yield 81%, ^{1}H-NMR (600 MHz, CD_3Cl) δ 5.17－5.20 (m, 1H, , H-3), 5.14－5.17 (m, 1H, H-2), 4.93－4.94 (m, 1H, H-5), 4.52－4.56 (m, 1H, H-6b), 4.11－4.12(m, 1H, H-6a), 3.95－4.08 (m, 1H, H-4), 3.24－3.25(m, 1H, H-1), 2.14 (s, 3H, *N(O)*C*Me*), 1.96－2.05 (m, 12H, *OCMe*), 1.48－1.53 (d, 3H, *J*=6.39, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 20.6, 20.7, 20.7, 20.9 (OC*Me*), 22.7 (NOC*Me*), 29.8 (CH_3), 63.9 (*C*1), 64.1 (*C*4), 69.9 (*C*6), 71.3 (*C*5), 77.2 (*C*2), 78.4 (*C*3), 169.1, 169.3, 169.4, 170.0, 170.1 (C=O); MS-EI (m/z): 410 (M^++Na); Anal. Calc. For $C_{17}H_{25}NO_9$: C, 52.71; H, 6.50; N, 3.62; found: C, 52.80; H, 6.46; N, 3.58.

4.1.7 1-ethyl-1-deoxy-2,3,4,5-tetra-*O*-benzyl-1,4-hydroxyl-amino-D-galactofuranose (3b)

Following the same procedure as **3a**, compound **3b** was obtained as a colourless oil, yield 92%, IR(KBr, cm^{-1}): 3383, 3089, 3063, 3031, 2867, 1605, 1496, 1453, 1363, 1308, 1251, 1073, 1027; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.21－7.35 (m, 20H, H_{Ar}), 5.59 (s, 1H, *N-OH*), 4.77－4.79 (d, 1H, *J*=11.63, OCH_2Ph), 4.53－4.56 (d, 2H, *J*=11.59, OCH_2Ph), 4.48－4.53 (m, 3H, OCH_2Ph), 4.33－4.35 (dd, 2H, *J*=12.51, *J*=11.89, OCH_2Ph), 3.85－3.87 (m, 2HH-2 and H-3), 3.77－3.79 (m, 2H, H-5 and H-6b), 3.73-3.75 (m, 1H, H-6a), 3.51-3.53 (t, 1H, H-4), 3.41 (t, 1H, H-1), 1.36-1.38 (d, 2H, *J*=5.83, CH_2), 0.96-0.98 (m, 3H, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 29.9 (CH_2), 21.6 (CH_3), 62.1 (*C*1), 68.0 (*C*4), 72.3, 72.9 and 73.8 (OCH_2Ph), 74.1 (*C*6), 74.4 (OCH_2Ph), 78.9 (*C*5), 85.3 (*C*2), 85.9 (*C*3), 127.3－129.0 (CH_{Ar}), 137.3, 137.5, 137.5, and 138.1 (Cq_{Ar}); MS-EI (m/z): 590 (M^++Na); Anal. Calc. For $C_{36}H_{41}NO_5$: C, 76.16; H, 7.28; N, 2.47; found: C, 76.18; H, 7.33; N, 2.48.

4.1.8 1-ethyl-1-deoxy-1,4-imino-D-galactofuranose (4b)

Following the same procedure as **DMDG**, compound **4b** was obtained as a colourless oil, yield 83%, ^{1}H-NMR (600 MHz, CD_3OD, δ ppm): 4.95 (s, 4H), 3.99－4.03 (t, 1H, *J*=6.42, H-3), 3.87－3.89 (m, 1H, H-2), 3.62－3.67 (m, 3H, H-6 and H-5), 3.38 (m, 1H, H-4), 3.29－3.31 (m, 1H, H-1), 1.92 (s, 1H, *N-OH*), 1.35－1.38 (m, 2H, CH_2), 0.92－0.95 (d, 3H, *J*=5.86, CH_3); ^{13}C-NMR (150 MHz, CD_3OD) δ 29.6 (CH_2), 20.8(CH_3), 61.5 (*C*1), 62.6 (*C*4), 68.8 (*C*6), 71.3 (*C*5), 76.0 (*C*2), 77.4 (*C*3); MS-EI (m/z): 214 (M^++Na); Anal. Calc. For $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32; found: C, 50.31; H, 8.97; N, 7.29.

4.1.9 *N*-acetyl-1-ethyl-1-deoxy-2,3,4,5-tetra-*O*-acetyl-1,4-imino-D-galactofuranose (9b)

Following the same procedure as **8**, compound **9b** was obtained as a colourless oil, yield 88%, ^{1}H-NMR (600 MHz, CD_3Cl) δ 5.12－5.15 (1H, m, H-3), 5.04－5.06 (m, 1H, H-2), 4.92－4.93 (m, 1H, H-5), 4.52－5.55 (m, 2H, H-6), 3.96－4.09 (m, 2H, H-1 and H-4), 2.13 (s, 3H, *N(O)*C*Me*), 1.95－2.03 (m, 12H, OC*Me*), 1.41－1.50 (m, 2H, CH_2), 0.96－0.99 (m, 3H, CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 20.6, 20.7, 20.7, 20.9 (OC*Me*), 22.6 (NOC*Me*), 29.1 (CH_2), 21.3 (CH_3), 62.7 (*C*1), 63.3 (*C*4), 67.9 (*C*6), 70.2 (*C*5), 76.1 (*C*2), 77.7 (*C*3), 169.0, 169.3, 169.3, 169.6, 170.0 (C=O); MS-EI (m/z): 424 (M^++Na); Anal. Calc. For $C_{18}H_{27}NO_9$: C, 53.86; H, 6.78; N, 3.49; found: C, 53.83; H, 6.81; N, 3.44.

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4.1.10 1-phenyl-1-deoxy-2,3,4,5-tetra-*O*-benzyl-1,4-hydroxyl-amino-D-galactofuranose (3c)

Following the same procedure as **3a**, compound **3c** was obtained as a colourless oil, yield 89%, IR(KBr, cm^{-1}): 3343, 3106, 3087, 3063, 3031, 2869, 1604, 1496, 1454, 1365, 1076, 1028; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.07－7.46(m, 25H, H_{Ar}), 4.96 (s, 1H, *N-OH*), 4.56－4.58 (d, 2H, *J*=12.1, O*CH*$_2$Ph), 4.53－4.55 (d, 2H, *J*=12.0, O*CH*$_2$Ph), 4.36－4.39 (d, 2H, *J*=11.8, O*CH*$_2$Ph), 4.32－4.35(d, 2H, *J*=11.60, O*CH*$_2$Ph), 4.23 (d, 1H, *J*=7.2 Hz, H-3), 4.11 (dd , 1H, *J*=2.7 and 3.2 Hz, H-2), 4.06 (dd, 1H, *J*=3.4 and 7.1 Hz, H-5), 3.89 (dd, 1H , *J*= 3.7 and 8.7 Hz, H-6a), 3.78 (t, 1H, *J*=6.9 Hz, H-6b), 3.69－3.75 (m, 1H, H-4), 3.49－3.51 (t, 1H, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 66.7 (*C*1), 68.9 (*C*4), 71.6, 72.0, 73.5 (O*CH*$_2$Ph), 74.0 (*C*6), 74.3 (O*CH*$_2$Ph), 78.6 (*C*5), 83.7 (*C*2), 87.1 (*C*3), 127.2－128.7 (*C*H$_{Ar}$), 137.8, 138.1, 138.2, 138.4 and 139.4 (Cq$_{Ar}$); MS-EI (m/z): 638 (M^++Na); Anal. Calc. For $C_{40}H_{41}NO_5$: C, 78.02; H, 6.71; N, 2.27; found: C, 78.05; H, 6.73; N, 2.23.

4.1.11 1-phenyl-1-deoxy-1,4-imino-D-galactofuranose (4c)

Following the same procedure as **DMDG**, compound **4c** was obtained as a colourless oil, yield 81%, ^{1}H-NMR (300 MHz, D_2O) δ 7.32－7.41 (m, 5H, H_{Ar}), 4.09 (dd, 1H, *J*=7.5 and 8.8Hz, H-3), 3.93 (t, 2H, H-2 and H-1a), 3.72 (dd, 1H, *J*=4.7 and 11.2Hz, H-5 and H-1b), 3.68 (dd, 1H, *J*=4.9 and 10.7Hz, H-6a), 3.63 (dd, 1H, *J*=6.3 and 11.6Hz, H-1), 3.19 (dd, 1H, *J*=2.5 and 6.8Hz, H-4); ^{13}C-NMR (75 MHz, DO_2) δ 61.8 (*C*1), 62.4 (*C*4), 64.0 (*C*6), 71.3 (*C*5), 77.5 (*C*2), 82.2 (*C*3), 127.3, 128.2, 128.9, 129.0 (*C*H$_{Ar}$), 139.7 (Cq$_{Ar}$); MS-EI (m/z): 262 (M^++Na); Anal. Calc. For $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85; found: C, 60.27; H, 7.19; N, 5.81.

4.1.12 *N*-acetyl-1-phenyl-1-deoxy-2,3,4,5-tetra-*O*-acetyl-1,4-imino-D-galactofuranose (9c)

Following the same procedure as **8**, compound **9c** was obtained as a colourless oil, yield 91%, IR(KBr, cm^{-1}): 2938, 1743, 1653, 1604, 1496, 1454, 1372, 1365, 1225, 1076, 1107, 1028; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35－7.43 (m, 5H, H_{Ar}), 5.08 (m, 1H, H-3), 4.99 (m, 1H, H-2), 4.26 (d, 1H, *J*=7.3Hz, H-5), 4.12 (dd, 1H, *J*=3.1 and 4.5Hz, H-6a), 4.08 (dd, 1H, *J*=3.4 and 7.2 Hz, H-6b), 3.91 (dd, 1H, *J*=4.2 and 8.6 Hz, H-4), 3.65 (dd, 1H, *J*=6.3 and 11.6 Hz, H-1), 2.14(s, 3H, *N(O)*C*Me*), 1.98－2.06 (m, 12H, OC*Me*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.7, 20.7, 20.8, 20.9 (OC*Me*), 22.6 (NOC*Me*), 62.7 (*C*1), 63.1 (*C*4), 64.6 (*C*6), 71.9 (*C*5), 79.1 (*C*2), 82.6 (*C*3), 127.1, 128.2, 128.8, 128.8 (*C*H$_{Ar}$), 139.8 (Cq$_{Ar}$), 169.0, 169.3, 169.4, 169.9, 170.1 (C=O); MS-EI (m/z): 472 (M^++Na); Anal. Calc. For $C_{22}H_{27}NO_9$: C, 58.79; H, 6.06; N, 3.12; found: C, 58.72; H, 6.09; N, 3.11.

4.1.13 1-ρ-benzyloxyphenyl-1-deoxy-2,3,4,5-tetra-*O*-benzyl-1,4-hydroxyl-amino-D-galactofuranose (3d)

Following the same procedure as **3a**, compound **3d** was obtained as a colourless oil, yield 91%, IR (KBr, cm^{-1}): 3136, 1615, 1516, 1454, 1401, 1247, 1124, 1027; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28－7.45(m, 25H, H_{Ar}), 7.08 (dd, 2H, *J*=3.6 and 7.3Hz, H_{Ar}), 6.93 (d, 2H, *J*=8.7Hz, H_{Ar}), 5.03 (s, 1H, *N-OH*), 4.72－4.73 (d, 2H, *J*=10.5, O*CH*$_2$Ph), 4.54－4.56 (d, 2H, *J*=12.0, O*CH*$_2$Ph), 4.52－4.53 (d, 2H, *J*=11.8, O*CH*$_2$Ph), 4.34－4.36 (d, 2H, *J*=11.6, O*CH*$_2$Ph), 4.30－4.32(d, 2H, *J*=11.6, O*CH*$_2$Ph), 4.19－4.20 (d, 1H, *J*=7.2Hz, H-3) , 4.08－4.11 (m, 2H, H-2 and H-5), 4.05－4.05 (dd, 1H, *J*=3.2 and 6.7Hz, H-6a), 3.83－3.85 (dd, 1H , *J*=3.9 and 8.7Hz, H-6b), 3.76－3.78 (t, 1H, *J*=7.1Hz, H-4), 3.69－3.75 (m, 1H, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 66.8 (*C*1), 68.9 (*C*4), 71.7, 72.0, 73.4 (O*CH*$_2$Ph), 73.7 (*C*6), 78.1 (*C*5), 83.4 (*C*2), 87.1 (*C*3), 114.8, 127.5－129.8 (*C*H$_{Ar}$), 137.0, 137.6, 137.9, 138.0, 138.1 and 156.5 (Cq$_{Ar}$); MS-EI (m/z): 744 (M^++Na); Anal. Calc. For $C_{47}H_{47}NO_6$: C, 78.20; H, 6.56; N, 1.94; found: C, 78.18; H, 6.59; N, 1.95.

4.1.14 1-ρ-hydroxyphenyl-1-deoxy-1,4-imino-D-galactofuranose (4d)

Following the same procedure as **DMDG**, compound **4b** was obtained as a colourless oil, yield 83%, IR (KBr, cm^{-1}): 3198, 1617, 1512, 1401, 1262, 1179, 1124, 1074; ^{1}H-NMR (300 MHz, D_2O) δ 7.26－7.28 (d, 2H, *J*=8.7Hz, H_{Ar}), 6.86－6.87 (d, 2H, *J*=8.8Hz, H_{Ar}), 4.12－4.13 (dd, 1H, *J*=7.3 and *J*=9.1Hz, H-3), 3.93－3.94 (t, 1H, *J*=7.2Hz, H-2), 3.90－3.91 (d, 1H, *J*=9.5Hz, H-5), 3.88－3.89 (t, 1H, *J*=7.5Hz, H-6a), 3.67－3.74 (m, 2H, H-6a and H-1), 3.28－3.22 (m, 1H, H-4); ^{13}C-NMR (75 MHz, DO_2) δ 61.6 (*C*1), 62.0 (*C*4), 63.3 (*C*6), 69.7 (*C*5), 76.9 (*C*2), 81.3 (*C*3), 115.8, 125.8－130.4 (*C*H$_{Ar}$), 153.7 (Cq$_{Ar}$); MS-EI (m/z): 278 (M^++Na); Anal. Calc. For $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49; found: C, 56.43; H, 6.69; N 5.48.

4.1.15 N-acetyl-1-ρ-acetyloxyphenyl-1-deoxy-2,3,4,5-tetra-O-acetyl-1,4-imino-D-galactofuranose (9d)

Following the same procedure as **8**, compound **9d** was obtained as a colourless oil, yield 92%, IR (KBr, cm^{-1}): 3133, 1741, 1650, 1601, 1497, 1454, 1401, 1365, 1225, 1076, 1107, 1027; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.24－7.25 (d, 2H, *J*=9.4Hz, H_{Ar}), 6.80－6.81 (d, 2H, *J*=9.1Hz, H_{Ar}), 5.06 (m, 1H, H-3), 4.96-4.97 (m, 1H, H-2), 4.23－7.25 (d, 1H, *J*=6.6Hz, H-5), 4.10－4.11 (dd, 1H, *J*=2.9 and 4.9Hz, H-6a), 4.07－4.08 (dd, 1H, *J*=3.7 and 7.8Hz, H-6b), 3.90－3.92 (dd, 1H, *J*=4.1 and 8.4 Hz, H-1), 3.65－3.66 (dd, 1H, *J*=6.2 and 10.7 Hz, H-4), 2.14(s, 3H, *N(O)*C*Me*), 1.97－2.06 (m, 15H, OC*Me*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.1, 20.7, 20.8, 20.8, 20.9 (OC*Me*), 22.9 (NOC*Me*), 62.6 (*C*1), 63.4 (*C*4), 65.0 (*C*6), 70.8 (*C*5), 79.0 (*C*2), 83.1 (*C*3), 116.0, 125.7－130.1 (*C*H$_{Ar}$), 155.7 (Cq$_{Ar}$), 168.1, 169.0, 169.2, 169.4, 169.8, 170.0 (C=O) ; MS-EI (m/z): 530 (M^++Na); Anal. Calc. For $C_{24}H_{29}NO_{11}$: C, 56.80; H, 5.76; N, 2.76; found: C, 56.77; H, 5.79; N, 2.75.

4.1.16 1-(3'-methoxy-4'-benzyloxy)-phenyl-1-deoxy-2,3,4,5-tetra-O-benzyl-1,4-hydroxyl-amino-D-galactofuranose (3e)

Following the same procedure as **3a**, compound **3e** was obtained as a colourless oil, yield 84%, IR (KBr，cm^{-1}): 3136, 1615, 1518, 1454, 1403, 1247, 1121, 1024; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.45 (m, 25 H, H_{Ar}), 7.08－7.09 (d, 1H, *J*=3.2Hz, H_{Ar}), 6.99-7.00 (dd, 1H, *J*=3.2 and 7.8Hz, H_{Ar}), 6.93－6.94 (d, 1H, *J*=8.4Hz, H_{Ar}), 5.06 (s, 1H, *N-OH*), 4.75 (m, 2H, O*CH*$_2$Ph), 4.69 － 4.71 (d, 2H, *J*=11.3Hz, O*CH*$_2$Ph), 4.56 － 4.57 (d, 2H, *J*=12.0Hz, O*CH*$_2$Ph), 4.52－4.53 (d, 2H, *J*=12.0Hz, O*CH*$_2$Ph), 4.34－4.35 (d, 2H, *J*=11.8, O*CH*$_2$Ph), 4.19－4.20 (d, 1H, *J*=7.0 Hz, H-3), 4.06－4.11 (m, 2H, H-2 and H-5), 3.91(s, 3H, OCH_3), 3.89－3.90 (m, 1H, H-6a), 3.84－3.85 (dd, 1H, *J*=3.9 and 9.0 Hz, H-6b), 3.75－3.76 (dd, 1H, *J*=7.0 and 9.0Hz, H-4), 3.66－3.71 (m, 1H, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 56.1 (OCH_3), 67.0 (*C*1), 68.7 (*C*4), 71.7, 72.0, 73.5 (O*CH*$_2$Ph), 73.7, (*C*6), 78.0 (*C*5), 83.5 (*C*2), 87.2 (*C*3), 111.6, 113.7, 121.5 (*C*H$_{Ar}$), 127.5－128.5 (*C*H$_{Ar}$), 131.8, 137.1, 137.9, 138.1, 138.2, 148.1 and 148.4 (Cq$_{Ar}$); MS-EI (m/z): 774 (M^++Na); Anal. Calc. For $C_{48}H_{49}NO_7$: C, 76.67; H, 6.57; N, 1.86; found: C, 76.66; H, 6.54; N, 1.83.

4.1.17 1-(3'-methoxy-4'-hydroxy)-phenyl-1-deoxy-1,4-imino-D-galactofuranose (4e)

Following the same procedure as **DMDG**, compound **4e** was obtained as a colourless oil, yield 77%, IR(KBr，cm^{-1}): 3209, 1637, 1401, 1276, 1252, 1132, 1038; ^{1}H-NMR (D_2O, 300 MHz)

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δ 6.99－7.01 (d, 1H, *J*=8.3Hz, H_{Ar}), 6.91 (s, 1H, H_{Ar}), 6.87－6.88 (d, 1H, *J*=5.2Hz, H_{Ar}), 4.05－4.06 (dd, 1H, *J*=7.5 and 8.7Hz, H-3), 3.90－3.91 (t, 1H, *J*=7.3Hz, H-2), 3.81 (s, 3H, OCH_3), 3.79－3.80 (d, 1H, *J*=9.4Hz, H-5), 3.71－3.72 (m, 2H, H-6), 3.65－3.66 (dd, 1H, *J*=6.4 and 11.6Hz, H-4), 3.20－3.21 (dd, 1H, *J*=6.4 and 11.1Hz, H-1); ^{13}C-NMR (75 MHz, DO_2) δ 56.1 (OCH_3), 61.7 (*C*1), 62.4 (*C*4), 63.5 (*C*6), 69.3 (*C*5), 77.4 (*C*2), 81.9 (*C*3), 112.7, 114.4 and 119.6 (CH_{Ar}), 132.6, 145.4 and 147.4 (Cq_{Ar}); MS-EI (m/z): 308 (M^++Na); Anal. Calc. For $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91; found: C, 54.71; H, 6.74; N 4.90.

4.1.18 *N*-acetyl-1-(3'-methoxy-4'-acetyloxy)-acetyloxyphenyl-1-deoxy-2,3,4,5-tetra-*O*-acetyl-1,4-imino-D-galactofuranose (9e)

Following the same procedure as **8**, compound **9e** was obtained as a colourless oil, yield 93%, IR (KBr, cm^{-1}): 3142, 1745, 1651, 1601, 1496, 1454, 1403, 1365, 1225, 1076, 1107, 1027; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.03－7.04 (d, 1H, *J*=8.7Hz, H_{Ar}), 6.95-6.97 (dd, 1H, *J*=2.3 and 8.6Hz, H_{Ar}), 6.88－6.90 (d, 1H, *J*=2.4Hz, H_{Ar}), 5.05 (m, 1H, H-3), 4.88－4.89 (m, 1H, H-2), 4.26－4.27 (d, 1H, *J*=7.2Hz, H-5), 4.12－4.13 (dd, 1H, *J*=3.3 and 5.2Hz, H-6a), 4.07－4.08 (dd, 1H, *J*=3.5 and 7.1 Hz, H-6b), 3.90－3.91 (dd, 1H, *J*=3.7 and 7.9Hz, H-4), 3.83 (s, 3H, OCH_3), 3.63－3.64 (dd, 1H, *J*=6.1 and 11.2Hz, H-1), 2.14 (s, 3H, *N(O)*C*Me*), 1.95-2.04 (m, 15H, OC*Me*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.1, 20.6, 20.8, 20.8, 20.9 (OC*Me*), 22.9 (NOC*Me*), 56.1 (OCH_3), 62.6 (*C*1), 63.7 (*C*4), 64.9 (*C*6), 69.9 (*C*5), 79.1 (*C*2), 82.2 (*C*3), 112.8, 114.6 and 119.7 (CH_{Ar}), 131.8, 144.4 and 147.1 (Cq_{Ar}), 168.0, 169.1, 169.3, 169.3, 169.8, 170.1 (C=O); MS-EI (m/z): 560 (M^++Na); Anal. Calc. For $C_{25}H_{31}NO_{12}$: C, 58.86; H, 5.81; N, 2.61; found: C, 58.82; H, 5.81; N, 2.60.

4.2. Biological evaluation

The mycobacterial strains, which were cultivated on Middlebrook 7H9 Broth supplemented with oleic acid-albumin-dextrose-catalase (OADC) enrichment and prepared in 0.9% NaCl solution to get inoculum density of 5×10^5 cells/mL, were dispensed into each well, except the blank. 125 mL of each test material solution and the standard drug isoniazid and ethambutol, prepared by dissolving in DMSO and further dilution in Middlebrook 7H9 Broth, was added to well 1 of the lane in duplicate followed by serial double dilutions to well 14 of the lane, 100 μg/mL at well 1 to 0.012 μg/mL at well 14. The last two wells in the lane were used as a sterile and growth control respectively. Growth inhibition was determined after 3 days of incubation at 37 °C and the MIC values were determined as minimum concentration inhibiting the growth of tested tuberculosis strains in relation to the probe with no tested compound. Tests were carried out three times in duplicate and isoniazid and ethambutol were used as positive controls.

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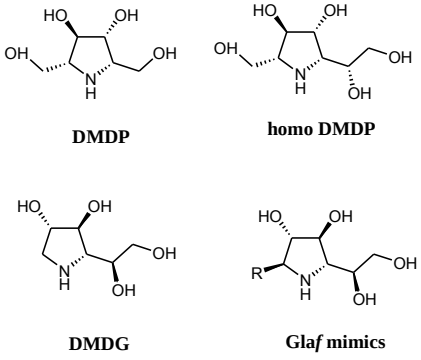

Figure 1. Chemical Structures of iminosugars and Gal*f* mimics

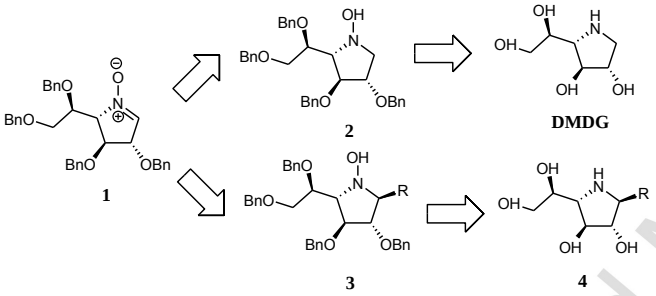

Figure 2. Synthetic pathways of DMDG and Gal*f* mimics

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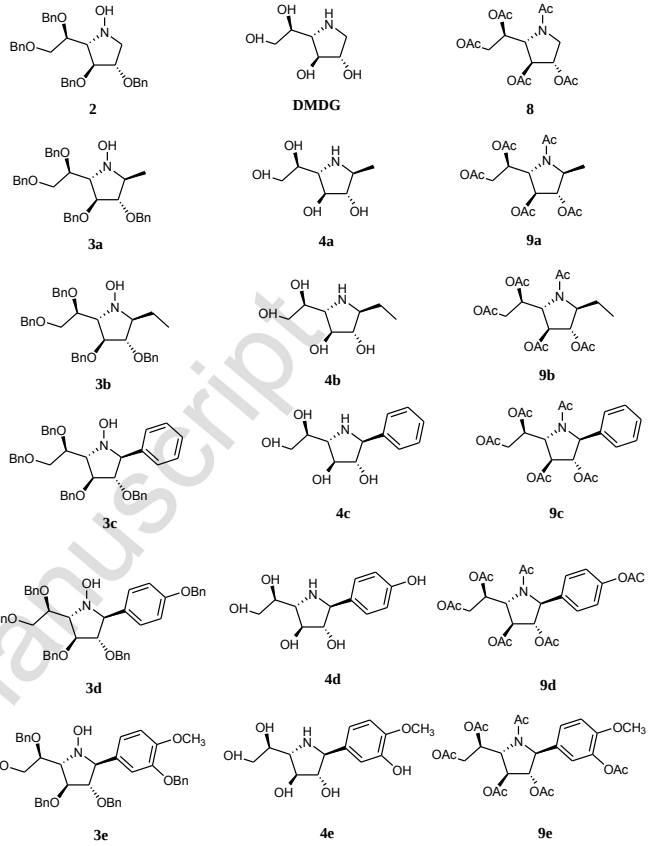
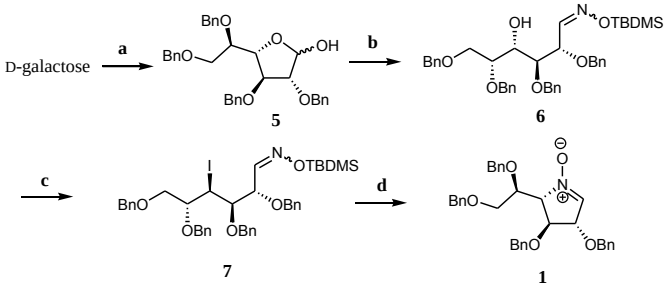


Figure 3. Chemical Structures of Gal*f* mimics



Scheme 1 Reagents and conditions: (a) i. $TsOH.H_2O$, methanol, reflux; ii. NaH, DMF, 0°C, Bu_4NI, BnBr, rt; iii. $MeCN:H_2O:TFA$ = 5:3:1, reflux; (b) i. $NH_2OH.HCl$, MeOH, NaOMe, reflux; ii. TBDMSCl, pyridine; (c) I_2, PPh_3, imidazole, toluene, reflux; (d) TBAF, toluene, reflux.

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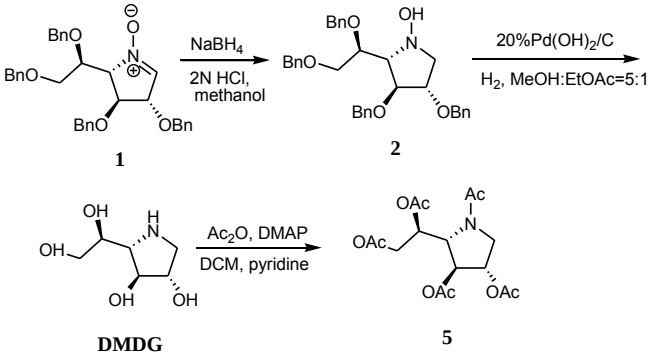
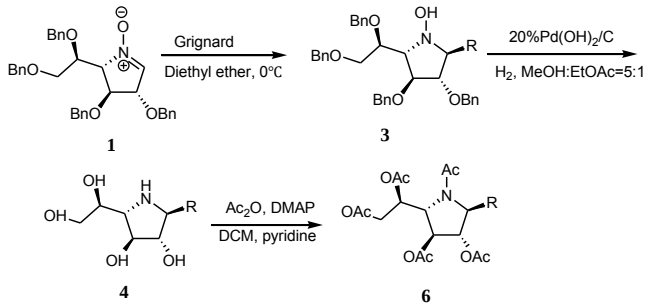


Scheme 2. Synthesis of DMDG



Scheme 3. Synthesis of novel iminosugars

Table 1 MIC value (μg/mL) of antimycobacterial activity of synthesized compounds and reference drug

compound	MIC (μg/mL)	compound	MIC (μg/mL)
2	>25	**3c**	12.5
DMDG	12.5	**4c**	6.25
8	>25	**9c**	6.25
3a	>25	**3d**	12.5
4a	12.5	**4d**	3.13
9a	6.25	**9d**	6.25
3b	12.5	**3e**	>25
4b	12.5	**4e**	3.13
9b	6.25	**9e**	6.25
isoniazid	0.024	ethambutol	1.56

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