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Preliminary communication

Synthesis and screening of galactose-linked nitroimidazoles and triazoles against *Mycobacterium tuberculosis*

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ABSTRACT

A series of galactose-linked nitroimidazoles/triazoles were synthesised and screened against *Mycobacterium tuberculosis* $H_{37}Rv$. Preliminary results were promising with MIC values in the range 1.56–12.5 μg/mL. Most importantly they are active under aerobic condition under which metronidazole is inactive.

1. Introduction

Starting from streptomycin many antimycobacterials are known and are commercially available, but the biggest problem in the antimicrobial drug therapy/discovery has come to be the drug resistance. *Mycobaterium tuberculosis* (*M.tb*) has developed to the stage of being extensively drug resistant (XDR-TB) and is often so to at least rifampicin and isoniazid from among the first line anti-TB drugs in addition to being resistant to any of the fluoroquinolones, and to one or the other of the three injectable second-line anti-TB drugs such as capreomycin, kanamicin, and amikacin used in the treatment of TB [1]. This along with the alarming fact that an estimated 1.7 million people a year die from TB (estimated for the year 2009) – equivalent to nearly 4700 deaths a day [2] underlines the worsened global TB burden currently. Last decade saw resurgence in the TB drug pipeline, with many promising candidates at various stages of clinical trials [3], but the exceedingly high attrition rate associated with any drug development effort makes research into new anti-TB drugs a continuing urgent global health priority.

Sugars are the privileged class of scaffolds in antibacterial drug discovery [4], in particular D-galactose, that plays an important role in the cell wall architecture of mycobacterium, existing in the rare furanose form in the cell wall arabinogalatan [5,6]. The enzymes involved in its biosynthesis are unique to pathogenic microbes and hence potential targets for chemotherapy. In the past many galactose derivatives were synthesized and screened against *M.tb* some of which proving to be promising. Tripathi and coworkers have reported a series sugar-derived aminoalcohols [7–9] active against the mycobacterium.

Likewise, de Almedia and coworkers reported a series of galactopyranosyl diamines and amino alcohols active against *M.tb* [10,11]. The striking commonality among all of the potent molecules in these reports is the presence of a diacetone galactose moiety. Representative galactopyranosyl amino alcohols active against mycobacteria are shown in Fig. 1.

Metronidazole (Fig. 2) a synthetic analog of the naturally occurring azomycin was originally developed against parasitic infection. In 1962, the antibacterial activity of metronidazole was discovered by chance when it cured a patient with both trichomonad vaginitis and bacterial gingivitis [12]. Eventually metronidazole was found to be effective against gram-positive and gram-negative anaerobes. However while it was found to be bactericidal against *M.tb* under anaerobic condition [13] it was proven inactive under aerobic condition [13,14] during *in vitro*

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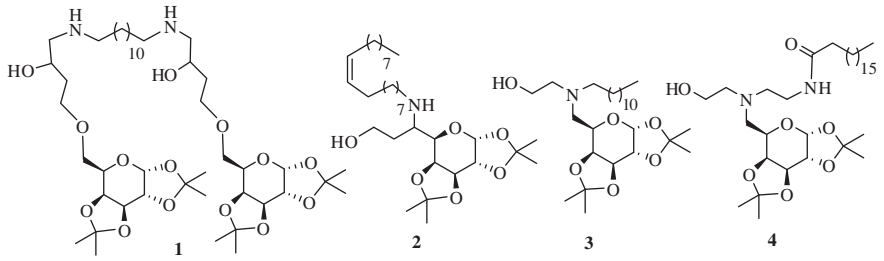


Fig. 1. Representative di-*O*-isopropylidene-D-galactopyranose-linked aminoalcohols active against mycobacterium.

studies. *In vivo* studies of metronidazole against mycobacterium in mouse model was not promising [15]. However owing to the difference in the pathophysiology of rodents and humans there are hopes that metronidazole may have unique activity against an anaerobic sub-population of the bacilli in humans. Dormant population under the anaerobic condition is the possible reason for prolonged duration of TB treatment. With the aim of evaluating the possible use of metronidazole as a second-line drug in combination with other drugs, phase II clinical trial was initiated against pulmonary tuberculosis in South Korea [16]. Apart from this other bicyclic nitroimidazole derivatives PA-824 and OPC-67683 (Fig. 2) are in different stages of clinical trials which are active against both active and dormant mycobacteria [3].

Incorporation of cell wall constituent sugars to the bioactive molecules was shown to increase the efficacy against the *M.tb*. For example *N*-D-arbinofuranosyl-*N*′-[*p*-(isoamyloxy)phenyl]-thiourea was found to be more active than the parent molecule *N*, *N*′-bis[*p*-(isoamyloxy)phenyl]-thiourea (THC), which is already known for the antimycobacterial activity. Interestingly out of the different sugars used, D-arabinofuranose, a cell wall constituent of the mycobacterium, gave most promising results [17,18]. As a part of our ongoing work on bioactive carbohydrate derivatives we planned to study the synergistic effect of incorporating the nitroimidazole moiety into derivatives of galactose, another important sugar constituent of the cell wall of *M.tb*. Two different classes of galactose-linked nitroimidazoles were synthesized and were screened for activity against *M.tb*; and the results are presented below.

2. Chemistry

The synthesis of the two different sets of molecules was carried out starting from the known common starting material, namely, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**) [19]. When compound **5** was treated with racemic epichlorohydrin (ECH) in the presence of NaH in anhydrous DMF crystalline 6-*O*-(2,3-epoxypropyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**) was obtained as a diastereomeric mixture (Scheme 1) in 85% of isolated yield. The ^{1}H NMR spectrum of the epoxypropyl ether **6** had two doublets of equal integrals at δ 5.54 and 5.53 with $J = 5.0$ Hz corresponding to the *R*-/*S*-isomers. Other proton signals were also likewise observed in pairs at the expected chemical shifts. The two possible ways of looking at this nucleophilic reaction have been depicted in Scheme 1 (Path A and Path B). In Path A the conjugate base (**5a**) of the alcohol **5** formed by the abstraction of the alcoholic proton in **5** reacts at C-3 of the ECH moiety. The epoxide ring-opening followed by the expulsion of the Cl^- anion from C-1 leads to the formation of the epoxypropyl ether **6**. Alternatively, as shown in Path B (Scheme 1), product **6** can also result from a direct nucleophilic attack of the anion **5a** at C-1 of the ECH moiety and the subsequent displacement of the Cl^- anion present on the carbon atom. In an attempt to obtain a possible clarification on this, the alcohol **5** was treated with enantiomerically pure ECH [(*R*-) and (*S*-)] in separate experiments and the resulting products were analyzed. It was found that in both experiments the product **6** obtained was again in the form of mixture of diasteriomers.

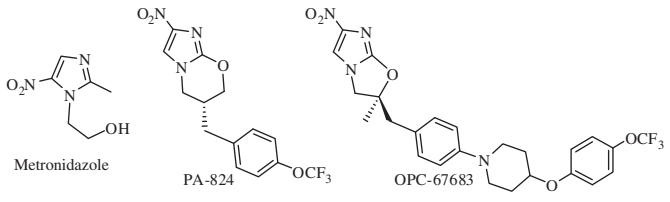
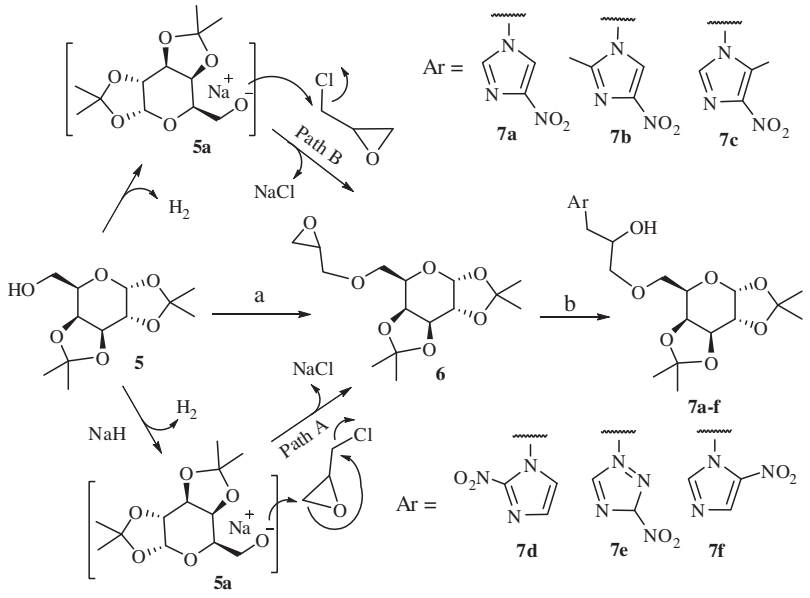


Fig. 2. Nitroimidazole derivatives active against mycobacterium.

This observation can be explained only if the reaction is considered to occur in the following manner. Reaction of **5a** at C1 of the ECH moiety by an S_N2 mechanism results in the direct displacement of the chloride anion as depicted in Fig. 3, Path A leaving the configuration of the epoxide **6a** unaffected. On the other hand, an attack of **5a** at the C3 of the ECH moiety from the side opposite to the oxirane bridge, again in an S_N2 fashion, leads to the opening of the epoxide ring. The ring-opening can concomitantly give rise to the epoxypropyl ether **6b** directly with the epoxide bridge having migrated from C3-C2 to C2-C1 of the ECH residue, as depicted in Path B, Fig. 3; and **6b** formed now has a configuration different from the ether formed by Path A (Fig. 3). Alternatively, the oxirane ring-opening and the chloride displacement can also be considered to take place in discrete steps in which case the oxy anion **6c** is formed as an intermediate resulting from the backside attack of **5a** on C3 of the ECH molecule (Path C, Fig. 3). The subsequent epoxide ring-closure and the consequent chloride displacement result in the formation of the product **6b** (Path C, Fig. 3) of the same configuration as obtained following Path B (Fig. 3). Thus the product obtained in the form of a diastereomeric mixture on reaction of **5a** with both (*R*)- and (*S*)-ECH shows clearly that it operates equally by Path A and Path B/C. Complete inversion of stereochemistry has been demonstrated in the epoxide ring-opening reaction of enatiomerically pure ECH with 1-naphthol under milder condition [20].

The diastereomeric mixture of **6** was subjected to epoxide ring opening at the less substituted end with different nitroimidazoles and triazoles in the presence of sodium hydride in anhydrous dimethylformamide to get the alcohols **7a**–**f** in good yields (Scheme 1). With a view to finding the effect of lipophilicity of the molecules on their activity compounds **7a**–**f** were further derivatised by protecting the secondary hydroxyl group on the exocyclic propyl residue of the respective compound as the corresponding palmitoyl esters **8a**–**f** on the one hand and as the corresponding trifluoromethoxy benzyl ethers **9a**–**d** on the other (Scheme 2). Another set of molecules **11a**–**f** in which the nitroimidazolyl residue was attached directly to the C-6 of the galactopyranose moiety was also prepared for evaluation of the antimycobacterial



Reagents and conditions: (a) NaH, ECH, DMF, 0 °C to 60 °C, 12 h, 85%; (b) nitroimidazole/triazole, NaH, DMF, 0 °C to 80 °C, 12 h.

Scheme 1. Synthesis of galactose-linked nitroimidazoles and triazoles.

activity. The synthesis was accomplished in the following manner. The diacetonide **5** was first converted to its known 6-deoxy-6-iodo-derivative **10** [21] by refluxing it (**5**) with iodine and triphenyl-phosphine in the presence of imidazole in anhydrous toluene. The iodo- derivative **10** was then subjected to a displacement reaction with different nitroimidazoles/triazoles as desired to get **11a-f** in very good yields (Scheme 3).

3. Biological screening

All the newly synthesized compounds were subjected to *in vitro* antimycobacterial studies against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) using agar dilution method along with three standard first-line drugs, namely, isoniazid, rifampicin and ethambutol as positive control and the results have been summarised in Table 1.

4. Results and discussion

Preliminary screening of the molecules against the drug resistant strain $H_{37}R_V$ gave promising results with MIC in the range 1.56–12.5 μg/mL; all the compounds tested were more active than metronidazole as such under aerobic condition. Compounds **7a**, **7c** and **7d** were proved to be the best with an MIC value of 1.56 μg/mL (entries 1,3 & 4 respectively, Table 1) equal to that obtained for ethambutol (entry 22, Table 1) which was used as one of the positive controls (along with rifampicin and isoniazid, entries 23 & 24 respectively, Table 1). Compounds **8b**, **8c**, **8f**, **9a**, **9b**, **9d** and **11c** also showed very good efficacy with an MIC value of 3.13 μg/mL (Table 1). The hydroxyl group in compounds **7a**, **7c** and **7d** was found to be of importance for the activity as evident from the fact that its protection either as the palmitoyl ester (**8a**, **8c** and **8d** respectively) or the trifluoromethoxybenzyl ether (**9a**, **9d** and **9e** respectively) led to a decrease in the activity despite the increased lipophilicity of the molecule (Table 1). However, in the case of compound **7b**, its derivatization to the corresponding palmitoyl ester **8b** as well as as 4-(trifluoromethoxy)benzyl ether **9b** led to an enhancement in the activity with the MIC value having improved to 3.13 μg/mL for **8b** and **9b** (entries 7 & 13, Table 1) from an initial value in excess of 12.5 μg/mL (entry 2, Table 1). In general, the nitroimidazole derivatives seemed to perform better than the triazolyl derivatives (entries 5, 10, 15 & 20, Table 1). Likewise, compounds in which the sugar moiety is attached to the heterocycle *via* the three-carbon spacer group (compounds **7a**, **c** and **d**) performed more effectively than those formed (compounds **11a**, **c** and **d**) through direct linkage. This also possibly points towards the role of a hydroxyl group-containing linker in imparting activity to a molecule.

As the compounds evaluated in this study have been as mixtures of their enantiomers, efforts are currently underway towards the synthesis of optically pure *R*- and *S*- isomers along with their detailed biological studies including cytotoxicity.

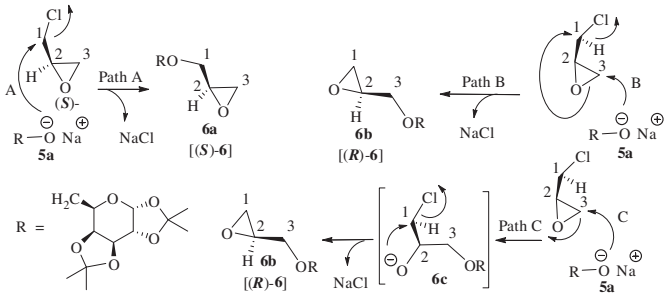
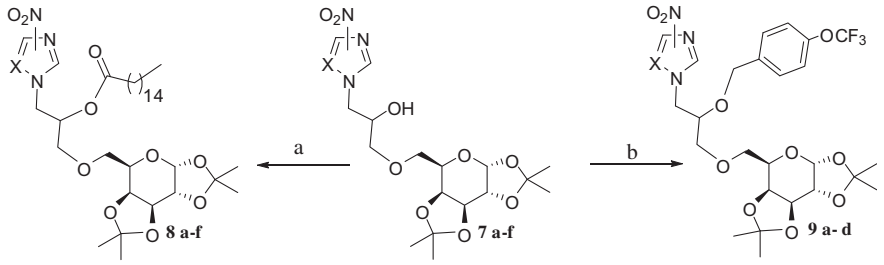


Fig. 3. Possible modes of reaction of 5a with ECH.

5. Conclusion

Synergy in the effectiveness of nitroimidazoles as antimycobacterial agents was observed, as expected, when the heterocycles were linked to the carbohydrate moiety, namely, D-galactose *via* a *n*-propyl linker. Promising results show that simple sugar-derived nitroimidazoles can serve as active antituberculosis agents under aerobic condition unlike metronidazole that is active only under anaerobic condition. The work is being extended to find structural analogs of some of the molecules reported here with a view to achieve improvements in their antitubercular activity.



Reagents and conditions: (a) Dry DCM, pyridine, palmitoyl chloride, 0 °C to RT, 8 h; (b) NaH, 4-(trifluoromethoxy)benzyl bromide, DMF, 0 °C to RT, 5 h.

Scheme 2. Derivatisation of galactose-linked nitroimidazoles and triazoles.

6. Experimental section

6.1. General

All reagents and chemicals were purchased from Sigma–Aldrich and were used without further purification. TLC experiments were performed on 0.2 mm Merck pre-coated silica gel 60 F_{254} aluminium sheets and the spots were visualized under a UV lamp and (or) by dipping in an ethanolic solution of sulphuric acid (5%, v/v) followed by heating. Final purifications were performed on column of silica gel 200–400 mesh. Melting points were determined on a Büchi melting point (B-540) apparatus and are uncorrected. Specific rotations were recorded on a Rudolph Autopol IV Polarimeter at 20–22 °C. NMR spectra were recorded on Bruker Avance DPX (400 MHz) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced to the internal standard, tetramethylsilane, in the respective deuterated solvents. Coupling constants (*J*) are reported in Hertz. Abbreviations used in reporting the ^{1}H NMR data are: s-singlet, d-doublet, dd-double doublet, *p*t-pseudo triplet and m-multiplet. Mass spectra were recorded on MALDI (Bruker Daltonics, Ultraflex TOF/TOF) spectrometer.

6.2. Synthesis of 6-O-(2,3-epoxypropyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**6**)

To a solution of **5** (5 g, 20 mmol) in anhydrous DMF (50 mL) maintained over an ice-bath was added NaH (1.5 g, 60% suspension in mineral oil) with stirring. After 15 min, epichlorohydrin (15 mL, 50 mol equiv) was added and the mixture was stirred at 80 °C overnight (16 h). After the completion of the reaction a few drops of methanol were added and the solvent was evaporated off under reduced pressure. The crude product was taken up in CH_2Cl_2 (200 mL) and was washed successively with water and brine. The organic layer was then dried over anhydrous sodium sulfate and was concentrated under reduced pressure. The crude product was purified by column chromatography to get pure **6** (5.15 g) as a colorless solid.

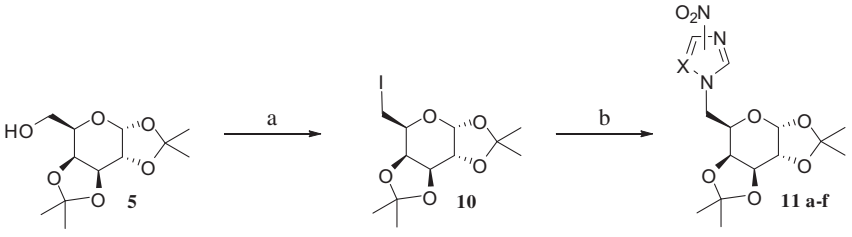
Yield 85%; mp 67.0–68.5 °C; $[\alpha]_D$ −77 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54, 5.53 (2xd, J = 5Hz, 1H, H-1, *R*-, *S*-), 4.61, 4.59 (2xdd, J_1 = 7.8 Hz, J_2 = 2.4 Hz 1H, H-3, *R*-, *S*-), 4.31 (dd, J_1 = 5 Hz, J_2 = 2.4 Hz, 1H, H-2, *R*-, *S*-), 4.26, 4.24 (2xdd, J_1 = 7.8 Hz, J_2 = 1.9 Hz, 1H, H-4, *R*-, *S*-), 4.01–3.97 (m, 1H, H-5, *R*-, *S*-), 3.84–3.62 (m, 3H, H-6a, b and H-1′a, *R*-, *S*-), 3.50, 3.43 (2xdd, J_1 = 11.6, J_2 = 5.6, H-1′b, *R*-, *S*-), 3.20–3.15 (m, 1H, H-2′ *R*-, *S*-), 2.79 (*p*t, J = 4.7, J = 4.4, 1H, H-3′a, *R*-, *S*-), 2.63, 2.60 (2xdd, J_1 = 5 Hz, J_2 = 2.6 Hz, 1H, H-3′b *R*-, *S*-), 1.54, 1.44 (2s, 2x3H, $-C(CH_3)_2$, *R*-, *S*-), 1.33 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.22, 108.53, 96.34, 72.25, 71.84, 2x71.15, 2x70.64, 2x70.58, 70.23, 70.06, 67.02, 66.69, 50.8, 50.7, 44.42, 44.3, 2x26.03, 2x25.94, 2x24.91, 2x24.42 (*R*-, *S*-); IR (Neat) ν_{max} 2988, 2930, 1382, 1255, 1211, 1169, 1105, 1069, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{15}H_{24}O_7$: 316.347. Found: 339.407 $[M + Na]^+$, 357.419 $[M + K]^+$.

6.3. General procedure for the synthesis of compounds **7a–f**

To a suspension of the nitromidazoles/nitrotriazole (2.5 mmol) in anhydrous DMF (5 mL) maintained over an ice-bath, NaH (60% suspension in mineral oil, 1 mol equiv) was added and the mixture was stirred. After 15 min 6-*O*-(2,3-epoxypropyl)-1:2,3:4-di-*O*-isopropylidene-α-D-galactopyranose (**6**, 1 mmol) was added and the stirring was continued. After the completion of the reaction, a few drops of methanol were added. The solvent was evaporated off under reduced pressure and the crude product was purified by column chromatography (except in the case of compound **7f** which was directly converted to **8f**, the corresponding palmitoyl ester.

6.3.1. 6-O-[2-Hydroxy-3-(4-nitroimidazolyl)propyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**7a**)

To a suspension of 4-nitromidazole (0.28 g, 2.5 mmol) in anhydrous DMF (5 mL) maintained over an ice-bath, NaH (60% suspension in mineral oil, 1 mol equiv) was added and was stirred. After 15 min 6-*O*-(2,3-epoxypropyl)-1:2,3:4-di-*O*-isopropylidene-α-D-galactopyranose (**6**, 0.32 g, 1 mmol) was added and the stirring was continued. After the completion of the reaction, a few drops of



Reagents and conditions: (a) Iodine, PPh_3, imidazole, dry toluene, reflux, 4h; (b) NaH, nitroimidazole/ triazoles, DMF, 0 °C to 80 °C, 12 h.

Scheme 3. Synthesis of C-6-linked nitroimidazoles and triazoles by direct displacement reaction.

Table 1
Results of *in vitro* assay of compounds synthesized against *M.tb* H37Rv.

Entry	Molecule	MIC (μg/mL)
1	**7a**	1.56
2	**7b**	>12.5
3	**7c**	1.56
4	**7d**	1.56
5	**7e**	12.5
6	**8a**	>12.5
7	**8b**	3.13
8	**8c**	3.13
9	**8d**	6.25
10	**8e**	6.25
11	**8f**	3.13
12	**9a**	3.13
13	**9b**	3.13
14	**9d**	3.13
15	**9e**	6.25
16	**11a**	>12.5
17	**11b**	>12.5
18	**11c**	3.13
19	**11d**	6.25
20	**11e**	12.5
21	**11f**	12.5
22	Ethambutol	1.56
23	Isoniazid	0.05
24	Rifampicin	0.10

MIC – Minimum concentration required for complete inhibition.

methanol were added. The solvent was evaporated off under reduced pressure and the crude product was purified by column chromatography.

Yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, $J = 1.5$ Hz ^{1}H, ArH, *R*-, *S*-), 7.52 (*p*t, $J_1 = 1.6$, $J_2 = 1.8$, 1H, ArH, *R*-, *S*-), 5.57, 5.55 (2xd, $J = 5$ Hz, 1H, H-1, *R*-, *S*-), 4.63, 4.62 (2x*p*t, $J_1 = 2.3$ Hz, $J_2 = 2.4$ Hz, 1H, H-3, *R*-, *S*-), 4.36–4.33 (m, 1H, H-2), 4.24–4.20 (m, $J = 1.9$ Hz, 1H, H-4, *R*-, *S*-), 4.18–4.05 (m, 3H, H-3′a, b, *R*-, *S*- and H-2′, *R*-, *S*-), 4.00–4.96 (m, $J = 1.9$ Hz, 1H, H-5, *R*-, *S*-), 3.78–3.62 (m, 3H, H-6a, b, *R*-, *S*- and –OH, *R*-, *S*-), 3.57–3.47 (m, 2H, H-1′, *R*-, *S*-) 1.54, 1.46 (2xs, 2x3H, $-C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 136.8 (Ar-C, *R*-, *S*-), 120.4 (ArC-2, *R*-, *S*-), 2x109.6, 2x108.9 (2x-*C*$(CH_3)_2$, *R*-, *S*-), 96.28 (C-1, *R*-, *S*-), 72.17, 71. 68 (C-1′, *R*-, *S*-), 7.13 (C-4, *R*-, *S*- and C-6, -*R*/-*S*), 70.65 (C-3, *R*-, *S*-), 70.44 (C-2, -*R*/-*S* and C-6, -*R*/-*S*), 70.37 (C-2, -*R*/-*S*), 69.41, 68.83 (C-2′, *R*-, *S*-), 67.46, 66.87 (C-5, *R*-, *S*-) 50.68, 50.57 (C-3′, *R*-, *S*-) 26.00, 25.93, 24.85, 24.46, 24.42 (4x-CH_3, *R*-, *S*-); IR (Neat) ν_{max} 3383, 2972, 2930, 1544, 1492, 1379, 1337, 1214, 1108, 1069, 1003 cm-1; MALDI-TOF MS: *m*/*z* calculated for $C_{18}H_{27}N_3O_9$: 429.422. Found: 452.603 $[M + Na]^+$, 468.600 $[M + K]^+$.

6.3.2. 6-O-[2-Hydroxy-3-(2-methyl-4-nitroimidazolyl)propyl]-1,2:3, 4-di-O-isopropylidene-α-D-galactopyranose (**7b**)

Yield 68%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86, 7.85 (2xs, 1H, ArH, *R*-, *S*-), 7.52 (*p*t, $J_1 = 1.6$ Hz, $J_2 = 1.8$ Hz, 1H, ArH, *R*-, *S*-), 5.57, 5.55 (2xd, $J = 4.8$ Hz, 1H, H-1, *R*-, *S*-), 4.64, 4.62 (2x*p*t, $J_1 = 2.2$, $J_2 = 2.3$, 1H, H-3, *R*-, *S*-), 4.36–4.33 (2xdd, $J_1 = 2.4$ Hz, $J_2 = 5$ Hz, 1H, H-2, *R*-, *S*-), 4.23–4.20 (2xdd, $J_1 = 2$ Hz, $J_2 = 2.8$ Hz, 1H, H-4, *R*-, *S*-), 4.09–3.94 (m, 4H, H-3′a, b, *R*-, *S*-, H-2′, *R*-, *S*- and H-5, *R*-, *S*-), 3.80–3.65 (m, 3H, H-6a, b, *R*-, *S*- and –OH, *R*-, *S*-), 3.59–3.50 (m, 2H, H-1′, *R*-, *S*-) 2.44 (s, 3H, Ar-CH_3, *R*-, *S*-), 1.53, 1.45 (2xs, 2x3H, $-C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 120.8 (Ar-C, *R*-, *S*-), 2x109.6, 2x108.8 (2x-*C*$(CH_3)_2$, *R*-, *S*-), 96.29 (C-1, *R*-, *S*-), 72.32, 71.93, 71.18, 71.12, 70.68, 70.54, 70.44, 70.36, 69.63, 69.16, 67.46, 66.87 (C-2,3,4,5,6,1′ and 2′, *R*-, *S*-), 49.38, 49.28 (C-3′, *R*-, *S*-) 26.00, 25.93, 24.85, 24.46, 24.42 (4x-CH_3, *R*-, *S*-), 13.1 (Ar-CH_3, *R*-, *S*-); IR (Neat) ν_{max} 3316, 2986, 2932, 1542, 1505, 1458, 1380, 1294, 1255, 1169, 1109, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{19}H_{29}N_3O_9$: 443.448. Found: 466.659 $[M + Na]^+$, 482.642 $[M + K]^+$.

6.3.3. 6-O-[2-Hydroxy-3-(5-methyl-4-nitroimidazolyl)propyl]-1,2:3, 4-di-O-isopropylidene-α-D-galactopyranose (**7c**)

Yield 75%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48, (s, 1H, ArH, *R*-, *S*-), 5.55 (*p*t, $J = 5$ Hz, 1H, H-1, *R*-, *S*-), 4.64, 4.61 (2x*p*t, $J = 2.36$, 1H, H-3, *R*-, *S*-), 4.35–4.33 (m, 1H, H-2, *R*-, *S*-), 4.23–4.20 (2xdd, $J = 2$ Hz, $J = 2.8$ Hz, 1H, H-4, *R*-, *S*-), 4.08–4.00 (m, 3H, H-3′a, b, *R*-, *S*- and H-2′, *R*-, *S*-), 3.99–3.97 (m, 1H, H-5, *R*-, *S*-), 3.80–3.66 (m, 3H, H-6a, b, *R*-, *S*- and –OH, *R*-, *S*-), 3.59–3.52 (m, 2H, H-1′, *R*-, *S*-) 2.61 (s, 3H, Ar-CH_3, *R*-, *S*-), 1.53, 1.45 (2xs, 2x3H, $-C(CH_3)_2$, *R*-, *S*-), 1.33 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 135.7, 131.0, 130.94 (Ar-C, *R*-, *S*-), 2x109.5, 2x108.8 (2x-C_2-*C*-C_2-, *R*-, *S*-), 96.28 (C-1, *R*-, *S*-), 72.42, 72.03, 71.17, 71.11, 71.07, 70.64, 70.61, 70.51, 70.42, 70.35, 69.07, 68.59, 67.39, 66.86 (C-2,3,4,5,6,1′ and 2′, *R*-, *S*-), 48.61, 48.55 (C-3′, *R*-, *S*-) 26.02, 25.96, 24.86, 24.44, 24.41 (4x-CH_3, *R*-, *S*-), 10.37 (Ar-CH_3, *R*-, *S*-); IR (Neat) ν_{max} 3363, 2986, 2931, 1573, 1499, 1378, 1350, 1268, 1255, 1169, 1108, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{19}H_{29}N_3O_9$: 443.448. Found: 466.601 $[M + Na]^+$, 482.610 $[M + K]^+$.

6.3.4. 6-O-[2-Hydroxy-3-(2-nitroimidazolyl)propyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (7d)

Yield 60%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29, 7.26 (2xd, $J = 1$ Hz, 1H, ArH, *R*-, *S*-), 7.12 (*p*t, $J_1 = 1.3$ Hz, $J_2 = 1.1$ Hz, 1H, ArH, *R*-, *S*-), 5.55, 5.54 (2xd, $J = 5$ Hz, 1H, H-1, *R*-, *S*-), 4.68–4.60 (m, 2H, H-3R, S-and H-3′a, *R*-, *S*-), 4.48–4.38 (m, 1H, H-3′b, *R*-, *S*-), 4.35–4.33 (m, 1H, H-2, *R*-, *S*-), 4.24–4.20 (m, 1H, H-4, *R*-, *S*-), 4.16–4.08 (m, 1H, H-2′, *R*-, *S*-), 4.00–4.39 (m, 1H, H-5, *R*-, *S*-), 3.78–3.53 (m, 5H, H-6a, b, *R*-, *S*-, H-1′a, bR, S-and –OH, *R*-, *S*-), 1.54, 1.44 (2xs, 2x3H, $-C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.9, 127.5, 127.3 (Ar-C, *R*-, *S*-), 2x109.5, 2x108.9 (2x-*C*$(CH_3)_2$, *R*-, *S*-), 96.26 (C-1, *R*-, *S*-), 72.70, 72.23, 71.14, 70.63, 70.48, 70.43, 70.38, 69.51, 69.15, 67.48, 66.70 (C-2,3,4,5,6,1′ and 2′, *R*-, *S*-), 52.23, 52.11 (C-3′, *R*-, *S*-) 26.02, 26.00, 25.94, 24.88, 24.46, 24.40 (4x-CH_3, *R*-, *S*-); IR (Neat) ν_{max} 3388, 2986, 2933, 1666, 1540, 1489, 1366, 1256, 1212, 1167, 1107, 1069, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{18}H_{27}N_3O_9$: 429.422. Found: 452.392 $[M + Na]^+$, 469.314 $[M + K]^+$.

6.3.5. 6-O-[2-Hydroxy-3-(3-nitro-1,2,4-triazolyl)propyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**7e**)

Yield 60%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) 8.37, 8.36 (2xs, 1H, Ar-HR, S), 5.56, 5.53 (2xd, $J = 5$ Hz, 1H, H-1, *R*-, *S*-), 4.63–4.61 (dd, $J_1 = 2.4$, $J_2 = 7.8$, 1H, H-3, *R*-, *S*-), 4.46–4.31 (m, 3H, H-3′a, b, *R*-, *S*- and H-2, *R*-, *S*-), 4.26–4.15 (m, 2H, H-4, *R*-, *S*-and H-2′, *R*-, *S*-), 4.01–3.96 (m, 1H, H-5, *R*-, *S*-), 3.79–3.60 (m, 4H, H-6a, b, *R*-, *S*-, –OH, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.57–3.49 (m, 1H, H-1′b, *R*-, *S*-), 1.54, 1.44 (2xs, 2x3H, $-C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.56, 146.3, 146.2 (Ar-C, *R*-, *S*-), 2x109.5, 2x108.9 (2x-*C*$(CH_3)_2$, *R*-, *S*-), 96.26 (C-1, *R*-, *S*-), 72.55, 71.95, 71.31, 71.16, 71.09, 70.65, 70.60, 70.45, 70.34, 68.80, 68.27, 67.61, 66.98 (C-2,3,4,5,6,1′ and 2′, *R*-, *S*-), 53.78, 53.77 (C-3′, *R*-, *S*-) 25.98, 25.92, 24.85, 24.82, 24.43, 24.38 (4x-CH_3, *R*-, *S*-); IR (Neat) ν_{max} 3422, 2987, 2932, 1635, 1555, 1414, 1380, 1256, 1212, 1170, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{17}H_{26}N_4O_9$: 430.410. Found: 453.580 $[M + Na]^+$, 469.604 $[M + K]^+$.

6.4. General procedure for the synthesis of compounds **8a–e**

To a solution of alcohol **7a–e**, (1 mmol) in pyridine-CH_2Cl_2 (1:1, 10 mL) maintained over an ice-bath was added slowly palmitoyl chloride, (2 mmol) and the mixture was stirred at room temperature for 8 h. After the completion of the reaction, the solvent was evaporated off under reduced pressure. The crude product was subjected to chromatographic purification to get pure compound.

*6.4.1. Synthesis of 1,2:3,4-di-O-isopropylidene-6-O-[3-(4-nitroimidazolyl)-2-palmitoyloxypropyl]-α-D-galactopyranose (**8a**)*

Yield 82%; Syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95, 7.93 (2xd, J = 1.5 Hz, 1H, ArH, *R*-, *S*-), 7.53, 7.51 (2xd, J = 1.5 Hz, 1H, ArH, *R*-, *S*-), 5.61, 5.58 (2xd, J = 5 Hz, 1H, H-1, *R*-, *S*-), 5.23–5.16 (m, 1H, H-2′, *R*-, *S*-), 4.64, 4.62 (*p*t, J_1 = 2.5 Hz, J_2 = 2.6 Hz, 1H, H-3, *R*-, *S*-), 4.37–4.31 (m, 3H, H-3′a, b, *R*-, *S*- and H-2, *R*-, *S*-), 4.25–4.21 (2xdd, J_1 = 1.9 Hz, J_2 = 4.8 Hz, 1H, H-4, *R*-, *S*-), 4.00–3.96 (m, 1H, H-5, *R*-, *S*-), 3.74–3.69 (m, 1H, H-6a, *R*-, *S*-), 3.62–3.56 (m, 2H, H-6b, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.32–3.26 (m, 1H, H-1′b, *R*-, *S*-), 2.32 (t, J = 7.5 Hz, 2H, −$COCH_2$-, *R*-, *S*-), 1.61, 1.25 (2xbr s, 26H, −CH_2-, *R*-, *S*-), 1.54, 1.48 (2xs, 2x3H, −$C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, −$C(CH_3)_2$, *R*-, *S*-), 0.87 (t, J = 6.8 Hz, 3H, −CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.57 (−CO−, *R*-, *S*-), 137.13, 120.56, 120.51 (Ar-C, *R*-, *S*-), 2x109.5, 2x108.9, 96.35 (C-1, *R*-, *S*-), 71.17, 71.06, 70.72, 70.70, 70.68, 70.42, 70.39, 70.39 (C-2,3 and 6, *R*-, *S*-), 69.71, 69.37 (C-2′, *R*-, *S*-), 67.61, 67. 44 (C-1′, *R*-, *S*-), 67.04, 66.87 (C-5, *R*-, *S*-), 47.68 (C-3′, *R*-, *S*-), 34.12, 31.91, 29.68, 29.65, 26.62, 29.58, 29.42, 29.35, 29.19, 29.05, 24.79, 22.68 (−CH_2- palmitoyl), 26.02, 25.96, 25.94, 24.86, 24.49 (4x-CH_3, *R*-, *S*-), 14.11 (−CH_3, palmitoyl); IR (Neat) ν_{max}, 2925, 2849, 1742, 1545, 1378, 1289, 1212, 1170, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{34}H_{57}N_3O_{10}$: 667.830. Found: 690.910 [M + Na] $^+$.

*6.4.2. 1,2:3,4-di-O-isopropylidene-6-O-[3-(2-methyl-4-nitroimidazolyl)-2-palmitoyloxypropyl]-α-D-galactopyranose (**8b**)*

Yield 78%; Thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91, 7.90 (2xs, 1H, ArH, *R*-, *S*-), 5.59, 5.58 (2xd, J = 5 Hz, 1H, H-1, *R*-, *S*-), 5.21–5.11 (m, 1H, H-2′, *R*-, *S*-), 4.65, 4.63 (2x*p*t, J = 2.4 Hz, 1H, H-3, *R*-, *S*-), 4.36–4.35 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-) 4.30–4.12 (m, 3H, H-3′a, b, *R*-, *S*- and H-4, *R*-, *S*-), 4.02–3.97 (m, 1H, H-5, *R*-, *S*-), 3.81–3.57 (m, 3H, H-6a, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.50–3.46 (m, 1H, H-1′b, *R*-, *S*-), 2.48, 2.47 (2xs, 3H, Ar-CH_3) 2.32 (t, J = 7.5 Hz, 2H, −$COCH_2$-, *R*-, *S*-), 1.58, 1.26 (2xbr s, 26H, −CH_2-, *R*-, *S*-), 1.54, 1.48 (2xs, 2x3H, −$C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, −$C(CH_3)_2$, *R*-, *S*-), 0.88 (t, J = 6.6 Hz, 3H, −CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.69, 172.65 (−CO−, *R*-, *S*-), 146.75, 145.46, 145.40, 120.86, 120.81 (Ar-C, *R*-, *S*-), 109.60, 108.61, 96.35 (C-1, *R*-, *S*-), 71.17, 71.06, 70.72, 70.70, 70.68, 70.42, 70.39, 70.39 (C-2,3 and 6, *R*-, *S*-), 69.71, 69.37 (C-2′, *R*-, *S*-), 67.61, 67. 44 (C-1′, *R*-, *S*-), 67.04, 66.87 (C-5, *R*-, *S*-), 47.68 (C-3′, *R*-, *S*-), 34.12, 31.91, 29.68, 29.65, 26.62, 29.58, 29.42, 29.35, 29.19, 29.05, 24.79, 22.68 (−CH_2- palmitoyl), 26.02, 25.96, 25.94, 24.86, 24.44, 24.49, 22.68 (4x-CH_3 R, S), 14.11, 13.07 (−CH_3, palmitoyl and Ar-CH_3, *R*-, *S*-); IR (Neat) ν_{max}, 2925, 2854, 1742, 1541, 1378, 1293, 1212, 1171, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{35}H_{59}N_3O_{10}$: 681.857. Found: 704.885 [M + Na] $^+$, 720.900 [M + K]$^+$.

*6.4.3. 1,2:3,4-di-O-isopropylidene-6-O-[3-(5-methyl-4-nitroimidazolyl)-2-palmitoyloxypropyl]-α-D-galactopyranose (**8c**)*

Yield 75%; Thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H, ArH, *R*-, *S*-), 5.56, 5.55 (2xd, J = 5 Hz, 1H, H-1, *R*-, *S*-), 5.17–5.09 (m, 1H, H-2′, *R*-, *S*-), 4.64, 4.62 (2x*p*t, J_1 = 2.2 Hz, J_2 = 1.8 Hz, 1H, H-3, *R*-, *S*-), 4.35–4.34 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-) 4.33–4.28 (m, 1H, H-4, *R*-, *S*-), 4.25–4.16 (m, 2H, H-3′a, b, *R*-, *S*-), 4.00–3.97 (m, 1H, H-5, *R*-, *S*-), 3.81–3.56 (m, 3H, H-6a, *R*-, *S*- and H-1′a *R*-, *S*-), 3.50–3.46 (m, 1H, H-1′b, *R*-, *S*-), 2.67, (s, 3H, Ar-CH_3) 2.30 (t, J = 7.5 Hz, 2H, −$COCH_2$-, *R*-, *S*-), 1.56, 1.26 (2xbr s, 26H, −CH_2-, *R*-, *S*-), 1.54, 1.48 (2xs, 2x3H, −$C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, −$C(CH_3)_2$, *R*-, *S*-), 0.88 (t, J = 6.6 Hz, 3H, −CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.67 (−CO−, *R*-, *S*-), 135.59 (Ar-C, *R*-, *S*-), 109.57, 108.74, 96.33 (C-1, *R*-, *S*-), 70.70, 70.62, 70.38, 70.00, 69.70, 68.21, 67.16, 66.97, 45.02, 34.05, 31.91, 29.68, 29.64, 29.62, 29.58, 29.41, 29.35, 29.19, 29.13, 26.03, 25.99, 24.86, 24.71, 24.46, 22.68, 14.11, 10.35, (*R*-, *S*-); IR (Neat) ν_{max}, 2925, 2854, 1742, 1566, 1501, 1460, 1351, 1284, 1211, 1171, 1070, 1005 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{35}H_{59}N_3O_{10}$: 681.857. Found: 704.784 [M + Na] $^+$, 720.780 [M + K]$^+$.

*6.4.4. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(2-nitroimidazolyl)-2-palmitoyloxypropyl]-α-D-galactopyranose (**8d**)*

Yield 86%; Thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26, 7.11 (2xs, 2H, ArH, *R*-, *S*-), 5.56, 5.55 (2xd, J = 5 Hz, 1H, H-1, *R*-, *S*-), 5.35–5.30 (m, 1H, H-2′, *R*-, *S*-), 5.00–4.92 (m, 1H, H-3′a, *R*-, *S*-), 4.65–4.51 (m, 2H, H-3, *R*-, *S*- and H-3′b, *R*-, *S*-), 4.35 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-) 4.25–4.22 (m, 1H, H-4, *R*-, *S*-), 4.01–3.97 (m, 1H, H-5, *R*-, *S*-), 3.73–3.59 (m, 3H, H-6a, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.50–3.44 (m, 1H, H-1′b, *R*-, *S*-), 2.23 (t, J = 7.5 Hz, 2H, −$COCH_2$-, *R*-, *S*-), 1.56, 1.26 (2x br s, 26H, −CH_2-, *R*-, *S*-), 1.54, 1.48 (2xs, 2x3H, −$C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, −$C(CH_3)_2$, *R*-, *S*-), 0.88 (t, J = 6.6 Hz, 3H, −CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.55 (−CO−, *R*-, *S*-), 128.04, 127.05, 126.93 (Ar-C, *R*-, *S*-), 109.46, 108.69, 96.34 (C-1, *R*-, *S*-), 71.15, 70.69, 70.54, 70.47, 70.43, 69.86, 69.77, 68.70, 66.87, 66.83, 49.35,49.18, 33.91, 31.91, 29.68, 29.64, 29.59, 29.43, 29.35, 29.20, 29.02, 26.05, 25.97, 24.90, 24.64, 24.44, 22.68, 14.11, (*R*-, *S*-); IR (Neat) ν_{max}, 2925, 2849, 1743, 1556, 1504, 1378, 1307, 1285, 1210, 1171, 1071, 1005 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{33}H_{57}N_4O_{10}$: 667.830. Found: 700.871 [M + Na]$^+$, 707.801 [M + K]$^+$.

*6.4.5. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(3-nitro-1,2,4-triazolyl)-2-palmitoyloxypropyl]-α-D-galactopyranose (**8e**)*

Yield 86%; Thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42, 8.41 (2xs, 1H, ArH, *R*-, *S*-), 5.57 (d, J = 5Hz, 1H, H-1, *R*-, *S*-), 5.35–5.30 (m, 1H, H-2′, *R*-, *S*-), 4.68–4.53 (m, 3H, H-3, *R*-, *S*- and H-3′a, b R-, *S*-), 4.35 (dd, 1H, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-) 4.23, 4.21 (2x*p*t, J = 1.9 Hz, J = 2 Hz, 1H, H-4, *R*-, *S*-), 4.00–3.98 (m, 1H, H-5, *R*-, *S*-), 3.76–3.48 (m, 4H, H-6a, b, *R*-, *S*- and H-1′a, b, *R*-, *S*-), 2.32 (t, J = 7.5 Hz, 2H, −$COCH_2$-, *R*-, *S*-), 1.59, 1.26 (2xbr s, 26H, −CH_2-, *R*-, *S*-), 1.54, 1.48 (2xs, 2x3H, −$C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, −$C(CH_3)_2$, *R*-, *S*-), 0.88 (t, J = 6.6 Hz, 3H, −CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.62 (−CO−, *R*-, *S*-), 146.49, 146.44 (Ar-C, *R*-, *S*-), 109.57, 108.74, 96.34 (C-1, *R*-, *S*-), 71.12, 70.70, 70.61, 70.38, 69.42, 69.23, 68.57, 68.37, 67.11, 66.96, 50.54, 34.08, 31.91, 29.68, 29.64, 29.59, 29.42, 29.35, 29.19, 29.05, 26.04, 25.98, 24.84, 24.72, 24.46, 22.68, 14.11 (*R*-, *S*-); IR (Neat) ν_{max}, 2923, 2848, 1743, 1540, 1360, 1289, 1214, 1171, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{34}H_{57}N_4O_{10}$: 667.84. Found: 690.77 [M + Na] $^+$.

*6.4.6. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(5-nitroimidazolyl)-2-palmitoyloxypropyl]- α-D-galactopyranose (**8f**)*

Yield 86%; Thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96, 7.94, 7.54, 7.52 (4xd, J = 1.5 Hz, 2H, ArH, *R*-, *S*-), 5.61, 5.58 (2xd, J = 5Hz, 1H, H-1, *R*-, *S*-), 5.23–5.16 (m, 1H, H-2′, *R*-, *S*-), 4.65, 4.63 (2x*p*t, J = 2.5 Hz, 1H, H-3, *R*-, *S*-), 4.41–4.29 (m, 3H, H-2, *R*-, *S*- and H-3′a, b, *R*-, *S*-) 4.25–4.21 (m, 1H, H-4, *R*-, *S*-), 4.00–3.97(m, 1H, H-5, *R*-, *S*-), 3.75–3.70 (m, 1H, H-6a, *R*-, *S*-), 3.50–3.46 (m, 2H, H-6b, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.37–3.27 (m, 1H, H-1′b, *R*-, *S*-), 2.33 (t, J = 7.5 Hz, 2H, −$COCH_2$-, *R*-, *S*-), 1.59, 1.26 (2xbr s, 26H, −CH_2-, *R*-, *S*-), 1.54, 1.48 (2xs, 2x3H, −$C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, −$C(CH_3)_2$, *R*-, *S*-), 0.88 (t, J = 6.6 Hz, 3H, −CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.58 (−CO−, *R*-, *S*-), 148.22, 137.12, 120.54, 120.49 (Ar-C, *R*-, *S*-), 109.7, 108.7 (2x -*C*$(CH_3)_2$, *R*-, *S*-), 96.36 (C-1, *R*-, *S*-), 71.17, 71.07, 70.73, 70.69, 70.41, 69.71, 69.38, 67.61, 67.44, 67.05, 66.87, 47.67, 34.12, 31.91, 29.68, 29.64, 29.62, 29.57, 29.42, 29.35, 29.19, 29.05, 26.02, 25.96, 24.86, 24.79, 24.48, 22.68, 14.11, (*R*-, *S*-); IR (Neat) ν_{max} 2923, 2848, 1743, 1540, 1360, 1289, 1214, 1171, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{34}H_{57}N_3O_{10}$: 667.830. Found: 690.775 [M + Na] $^+$.

*6.5. General procedure for the synthesis of compounds **9a**, **b**, **d** and **e***

To a solution of alcohol (**7a**, **b**, **d** or **e**, 1 mmol) in anhydrous DMF (5 mL) maintained over an ice-bath was added NaH (60% suspension in mineral oil, 1.1 mol equiv) and was stirred. After 15 min,

4-(trifluoromethoxy)benzyl bromide (1 mol equiv) was added and stirred at room temperature for 5 h. After the completion of the reaction, the excess sodium hydride was quenched by adding a few drops of methanol. The solvent was evaporated off under reduced pressure and the crude product was subjected to chromatographic purification to get pure **9a**–**e**.

*6.5.1. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(4-nitroimidazolyl)-2-(4-trifluoromethoxy)benzyloxypropyl]-α-D-galactopyranose (**9a**)*

Yield 75%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69, 7.88, 7.51, 7.50 (4xd, J = 1.5 Hz, 2H, imidazole-H, *R*-, *S*-), 7.27–7.19 (m, 4H, ArH, *R*-, *S*-), 5.59, 5.55 (2xd, J = 5 Hz, 1H, H-1, *R*-, *S*-), 4.65–4.60 (m, 2H, $-CH_2$a- (benzylic), *R*-, *S*- and H-3, *R*-, *S*-), 4.51–4.46 (2xd, J = 11.8 Hz, 1H, $-CH_2$b- (benzylic), *R*-, *S*-), 4.34 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-), 4.27–4.13 (m, 3H, H-4, *R*-, *S*- and H-3′a, b, *R*-, *S*-), 3.98–3.94 (m, 1H, H-5, *R*-, *S*-), 3.86–3.79 (m, 1H, H-2′, *R*-, *S*-), 3.72–3.68 (m, 1H, H-6a, *R*-, *S*-), 3.65–3.55 (m, 2H, H-6b, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.35–3.29 (m, 1H, H-1′b, *R*-, *S*-), 1.53, 1.51, 1.47, 1.45 (4xs, 6H, $-C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.18, 135.71, 129.14, 129.10, 121.12, 120.58, 109.59, 108.70, 108.65, 96.36, 71.31, 71.11, 70.70, 70.37, 68.78, 68.50, 67.21, 67.01, 49.12, 26.03, 25.94, 24.86, 24.44 (*R*-, *S*-); IR (Neat) ν_{max} 3124, 2992, 2925, 1544, 1514, 1492, 1379, 1338, 1260, 1216, 1167, 1071, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{26}H_{32}F_3N_3O_{10}$: 603.542. Found: 626.791 $[M + Na]^+$, 642.807 $[M + K]^+$.

*6.5.2. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(2-methyl-4-nitroimidazolyl)-2-(4-trifluoromethoxy)benzyloxypropyl]-α-D-galactopyranose (**9b**)*

Yield 68%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H, Imidazole-H, *R*-, *S*-), 7.21–7.15 (m, 4H, ArH, *R*-, *S*-), 5.56 (*p*t, J = 5 Hz, 1H, H-1, *R*-, *S*-), 4.64–4.59 (m, 2H, $-CH_2$a- (benzylic), *R*-, *S*- and H-3, *R*-, *S*-), 4.44–4.41 (m, 1H, $-CH_2$b- (benzylic), *R*-, *S*-), 4.36–4.34 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-), 4.23–4.15 (m, 2H, H-4, *R*-, *S*- and H-3′a, *R*-, *S*-), 4.07–3.97 (m, 2H, H-5, *R*-, *S*- and H-3′b, *R*-, *S*-), 3.78–3.62 (m, 3H, H-2′, *R*-, *S*-, H-6a, b, *R*-, *S*- and H-1′a, *R*-, *S*-), 3.54–3.46 (m, 1H, H-1′b, *R*-, *S*-), 2.39 (s, 3H, Ar-CH_3), 1.53, 1.46 (2xs, 6H, $-C(CH_3)_2$, *R*-, *S*-), 1.34 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.02, 146.51, 145.44, 135.69, 129.21, 121.08, 120.78, 109.57, 108.64, 96.36, 71.50, 71.43, 71.21, 70.86, 70.69, 70.64, 70.38, 69.27, 69.05, 67.25, 67.12, 48.37, 26.01, 25.94, 24.85, 24.45, 24.40, 13.14, 13.10, (*R*-, *S*-); IR (Neat) ν_{max} 3124, 2985, 2925, 1540, 1506, 1380, 1293, 1260, 1216, 1167, 1071, 1003 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{27}H_{34}F_3N_3O_{10}$: 617.568. Found: 640.768 $[M + Na]^+$, 656.778 $[M + K]^+$.

*6.5.3. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(2-nitroimidazolyl)-2-(4-trifluoromethoxy)benzyloxypropyl]-α-D-galactopyranose (**9d**)*

Yield 65%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.10 (m, 6H, ArH, *R*-, *S*-), 5.55 (d, J = 5 Hz, 1H, H-1, *R*-, *S*-), 4.80–4.76 (dd, J_1 = 4 Hz, J_2 = 13.9 Hz, 1H, H-3′a, *R*-, *S*-), 4.63–4.57 (m, 2H, H-3, *R*-, *S*- and $-CH_2$a- (benzylic), *R*-, *S*-), 4.50–4.41 (m, 2H, H-3′b, *R*-, *S*- and $-CH_2$b-(benzylic), *R*-, *S*-), 4.34–4.32 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-), 4.25–4.21 (m, 1H, H-4, *R*-, *S*-), 4.05–3.98 (m, 1H, H-5, *R*-, *S*-), 3.86–3.89 (m, 1H, H-2′, *R*-, *S*-), 3.74–3.55 (m, 4H, H-6a, b, *R*-, *S*- and H-1′a, b, *R*-, *S*-), 1.53, 1.45 (2xs, 6H, $-C(CH_3)_2$, *R*-, *S*-), 1.33 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.86, 136.06, 129.19, 129.13, 127.94, 127.63, 127.55, 121.69, 120.98, 109.40, 108.66, 96.34, 71.20, 71.16, 70.73, 70.67, 70.43, 69.74, 69.69, 67.19, 66.87, 50.40, 50.22, 50.40, 50.22, 26.04, 25.98, 24.88, 24.46, 24.40 (*R*-, *S*-); IR (Neat) ν_{max} 3118, 2985, 2932, 2362, 1540, 1488, 1370, 1259, 1213, 1165, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{26}H_{32}F_3N_3O_{10}$: 603.542. Found: 626.791 $[M + Na]^+$, 642.807 $[M + K]^+$.

6.5.4. 1,2:3,4-Di-O-isopropylidene-6-O-[3-(3-nitro-1,2,4-triazolyl)-2-(4-trifluoromethoxy)benzyloxypropyl]-α-D-galactopyranose (9e)

Yield 70%; Thick syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32, 8.31 (2xs, 1H, triazole-H, *R*-, *S*-), 7.42–7.15 (m, 4H, ArH, *R*-, *S*-), 5.55 (d, J = 5 Hz, 1H, H-1, *R*-, *S*-), 4.64–4.60 (m, 2H, $-CH_2$a- (benzylic), *R*-, *S*- and H-3, *R*-, *S*-), 4.58–4.53 (m, 1H, H-3′a, *R*-, *S*-), 4.49–4.45 (2xd, J = 12 Hz, 1H, $-CH_2$b-(benzylic), *R*-, *S*-), 4.44–4.37 (m, 1H, H-3′b, *R*-, *S*-), 4.35–4.33 (2xdd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2, *R*-, *S*-), 4.23–4.19 (m, 1H, H-4, *R*-, *S*-), 4.02–3.96 (m, 2H, H-5, *R*-, *S*-and H-2′, *R*-, *S*-), 3.76–3.56 (m, 4H, H-6a, b, *R*-, *S*- and H-1′a, b, *R*-, *S*-), 1.53, 1.52, 2x1.45 (4xs, 6H, $-C(CH_3)_2$, *R*-, *S*-), 1.33 (s, 6H, $-C(CH_3)_2$, *R*-, *S*-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.97, 146.47, 135.71, 130.14, 129.32, 129.27, 121.67, 121.01, 119.11, 109.49, 108.68, 96.34, 75.36, 71.19, 71.14, 70.77, 70.67, 70.51, 70.37, 69.37, 67.32, 67.02, 52.14, 52.05, 26.03, 25.96, 24.84, 24.44, 24.41 (*R*-, *S*-); IR (Neat) ν_{max} 3131, 2989, 1553, 1504, 1382, 1307, 1259, 1070, 1004 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{25}H_{31}F_3N_4O_{10}$: 604.530. Found: 627.529 $[M + Na]^+$, 643.795 $[M + K]^+$.

*6.6. General procedure for the synthesis of compounds **11a**–**f***

To a suspension of nitroimidazole/nitrotriazole (2 mmol) in anhydrous DMF (5 mL) maintained over an ice-bath, NaH (60% suspension in mineral oil, 1 mol equiv) was added and stirred. After 15 min, compound **10** (1 mmol) was added and stirred at 100 °C overnight. After the completion of the reaction, the solvent was evaporated off under reduced pressure. The crude product was taken up in CH_2Cl_2 and was extracted with water. The organic layer was dried over anhydrous sodium sulfate and was concentrated under reduced pressure. The crude product was subjected to column chromatography to get pure **11a**–**f**.

*6.6.1. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(4-nitroimidazolo)-α-D-galactopyranose (**11a**)*

Yield 74%; Thick syrup; $[\alpha]_D$ −70.1 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87, 7.52 (2xd, J = 1.5 Hz, 2H, ArH), 5.54 (d, J = 5Hz, 1H, H-1), 4.66 (dd, J_1 = 2.5 Hz, J_2 = 7.8 Hz, 1H, H-3), 4.37 (dd, J_1 = 2.5 Hz, J_2 = 5Hz, 1H, H-2), 4.28–4.15 (m, 3H, H-4 and H-6a, b), 4.03–4.00 (m, 1H, H-5), 1.47, 1.43, 1.36, 1.31 (4xs, 12H, 2x-$C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.05, 136.59, 120.01, 110.09, 109.04, 96.26, 70.93, 70.73, 70.14, 66.96, 48.36, 25.96, 25.88, 24.70, 24.38; IR (Neat) ν_{max} 3136, 2989, 2934, 1674, 1546, 1493, 1337, 1290, 1169, 1004, 901, 859 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{15}H_{21}N_3O_7$: 355.343. Found: 378.403 $[M + Na]^+$.

*6.6.2. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(2-methyl-4-nitroimidazolo)-α-D-galactopyranose (**11b**)*

Yield 70%; Colorless solid; mp 117–118 °C; $[\alpha]_D$ −69.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H, ArH), 5.53 (d, J = 5 Hz, 1H, H-1), 4.65 (dd, J_1 = 2.4 Hz, J_2 = 7.8 Hz, 1H, H-3), 4.35 (dd, J_1 = 2.4 Hz, J_2 = 5Hz, 1H, H-2), 4.15 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, H-4), 4.12–4.04 (m, 2H, H-6a, b), 4.02–3.99 (m, 1H, H-5), 2.44 (s, 3H, Ar-CH_3), 1.48, 1.45, 1.36, 1.32 (4xs, 12H, 2x-$C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.56, 145.17, 120.27, 110.10, 109.05, 96.32, 70.86, 70.76, 70.20, 66.58, 46.96, 26.01, 25. 94, 24.72, 24.44, 13.17; IR (Neat) ν_{max} 3136, 2989, 2934, 1674, 1546, 1493, 1337, 1290, 1169, 1004, 901, 859 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{16}H_{23}N_3O_7$: 369.370. Found: 370.507 $[M + H]^+$, 392.475 $[M + Na]^+$.

*6.6.3. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(5-methyl-4-nitroimidazolo)-α-D-galactopyranose (**11c**)*

Yield 78%; glassy solid; $[\alpha]_D$ −73.3 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H, ArH), 5.52 (d, J = 5 Hz, 1H, H-1), 4.65 (J_1 = 2.5 Hz, J_2 = 7.8 Hz, 1H, H-3), 4.35 (dd, J_1 = 2.5 Hz, J_2 = 5Hz, 1H, H-2), 4.14–4.10 (m, J = 1.8 Hz, J = 7.8 Hz, 3H, H-4, H-6a, b), 4.02–3.98 (m, 1H, H-5), 2.64 (s, 3H, Ar-CH_3), 1.49, 1.43, 1.36, 1.31

(4xs, 12H, 2x-C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.22, 135.74, 131.73, 109.54, 108.65, 96.34, 71.06, 70.85, 70.30, 67.08, 45.55, 24.92, 24.75, 23.53, 23.16, 9.17; IR (Neat) ν_{max} 3131, 2987, 2925, 1673, 1570, 1498, 1349, 1255, 1212, 1169, 1005 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{16}H_{23}N_3O_7$: 369.370. Found: 392.470 $[M + Na]^+$.

6.6.4. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(2-nitroimidazolo)-α-D-galactopyranose (**11d**)

Yield 69%; Colorless solid; mp 94.5–96 °C; $[\alpha]_D$ −37.1 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24, 7.13 (2xd, J = 0.9 Hz, 2H, ArH), 5.49 (d, J = 5 Hz, 1H, H-1), 4.99 (dd, J_1 = 3.8 Hz, J_2 = 14 Hz, 1H, H-6a), 4.64 (dd, J_1 = 2.5 Hz, J_2 = 7.8 Hz, 1H, H-3), 4.46 (dd, J_1 = 8.2 Hz, J_2 = 14 Hz, 1H, H-6b), 4.32 (dd, J_1 = 2.5 Hz, J_2 = 5 Hz, 1H, H-2), 4.24 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, H-4), 4.17–4.14 (m, J = 1.8 Hz, J = 3.8 Hz, 1H, H-5), 1.46, 1.37, 1.35, 1.28 (4xs, 12H, 2x-C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.81, 126.67, 109.56, 108.64, 96.37, 71.16, 70.88, 70.38, 66.66, 49.67, 24.86, 24.62, 23.61, 23.16; IR (Neat) ν_{max} 3151, 2985, 2925, 1539, 1488, 1365, 1255, 1212, 1166, 1069, 1005 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{15}H_{21}N_3O_7$: 355.343. Found: 377.545 $[M + Na]^+$, 394.588 $[M + K]^+$.

6.6.5. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(3-nitro-1,2,4-triazolo)-α-D-galactopyranose (**11e**)

Yield 78%; syrup; $[\alpha]_D$ −14.9 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H, ArH), 5.49 (d, J = 4.8 Hz, 1H, H-1), 4.67 (dd, J_1 = 2.4, J_2 = 7.8 Hz, 1H, H-3), 4.45–4.43 (m, 2H, H-6a, b), 4.35 (dd, J_1 = 2.4 Hz, J_2 = 4.8 Hz, 1H, H-2), 4.26–4.23 (m, 1H, H-5), 4.20 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, H-4), 1.48, 1.42, 1.36, 1.29 (4xs, 12H, −C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.93, 110.12, 109.26, 96.14, 70.93, 70.77, 70.26, 66.22, 51.93, 25.92, 25.86, 24.81, 24.31; IR (Neat) ν_{max} 3131, 2988, 2932, 1555, 1504, 1380, 1308, 1255, 1212, 1168, 1068, 1006, 835 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{14}H_{20}N_4O_7$: 356.331. Found: 379.661 $[M + Na]^+$, 395.686 $[M + K]^+$.

6.6.6. 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(5-nitroimidazolo)-α-D-galactopyranose (**11f**)

Yield 72%; syrup; $[\alpha]_D$ −70.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87, 7.52 (2xd, J = 1.4 Hz, 2H, ArH), 5.54 (d, J = 5 Hz, 1H, H-1), 4.65 (dd, J_1 = 2.4, J_2 = 7.8 Hz, 1H, H-3), 4.36 (dd, J_1 = 2.4 Hz, J_2 = 5 Hz, 1H, H-2), 4.24–4.15 (m, J = 1.8 Hz, 3H, H-4 and H-6a, b), 4.03–4.01 (m, J = 1.8 Hz, 1H, H-5), 1.47, 1.43, 1.36, 1.31 (4xs, 12H, 2x-C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.57, 119.96, 110.10, 109.03, 96.27, 70. 92, 70. 73, 70.14, 66.96, 48.35, 25.97, 25.89, 24.71, 24.38; IR (Neat) ν_{max} 3140, 2986, 2935, 1544, 1492, 1383, 1289, 1212, 1068, 1005, 823 cm^{-1}; MALDI-TOF MS: *m*/*z* calculated for $C_{15}H_{21}N_3O_7$: 355.343. Found: 378.461 $[M + Na]^+$, 394.435 $[M + K]^+$.

6.7. Agar dilution method

Ten-fold serial dilutions of each test compound/drug were incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement (Drug concentration from 12.5 μg/mL to 0.78 μg/mL). Inoculum of *M.tb* H_{37}Rv was prepared from fresh Middlebrook 7H11 agar slants with OADC Growth Supplement was adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of approximately 10^7 cfu/mL. A 5 μL amount of the bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to give the complete inhibition of bacterial growth.

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