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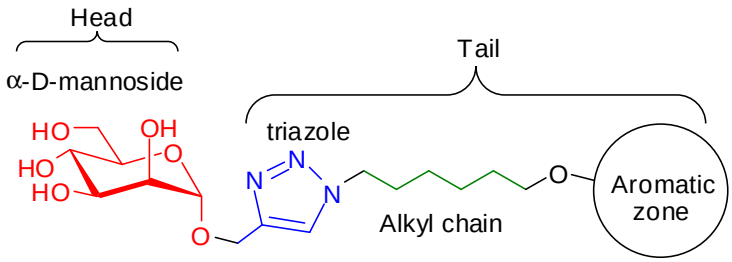

Assembly and Inhibitory Activity of Monovalent Mannosides Terminated with Aromatic Methyl Esters: The Effect of Naphthyl Groups

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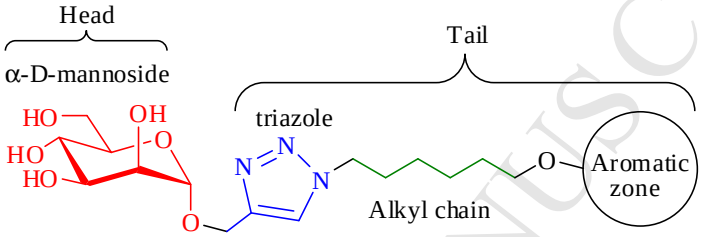

Abstract: A series of monovalent α-D-mannoside ligands terminated with aromatic methyl esters have been synthesized in excellent yields using the Cu(I) catalyzed azide-alkyne 1,3-dipolar cycloaddition ("click chemistry"). These mannosides were designed to have a unique aglycone moiety (tail) that combines a triazole ring attached to aromatic methyl esters via a six carbon alkyl chain. The mannose unit of these ligands was linked at the *ortho*, *meta*, and *para* positions of substituted methyl benzoates and 1-, 3-, and 6-substituted methyl 2-napthaoates. In hemagglutination assays, ligands (**32A-38A**) showed better inhibitory activities than the standard inhibitor, methyl α-D-mannopyranoside. Overall, the naphthyl-based mannoside ligand (**37A**) showed the best activity and therefore merits further development.

Key words: α-D-mannosides; click chemistry; FimH; hemagglutination.

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1. Introduction

Urinary tract infections (UTIs), are one of the most common bacterial infections, affecting millions of people around the world each year.[1-3] (UTIs) are mainly caused by strains of the gram negative uropathogenic bacteria, *Escherichia coli* (UPEC).[4] The vast majority of *E. coli* express Type 1 fimbriae or pili, which are hair-like protein structures present on the cell surfaces. UPEC bind to the urinary tract endothelial surface through the 200 to 500 fimbriae which extend from the surface of each bacterial cell. At the tip of each pili there is an adhesin protein known as FimH, a lectin that uniquely interacts with terminal α-D-mannopyranoside residues of the *N*-linked glycoprotein Uroplakin Ia (UPIa) on the endothelial surface, enabling adherence and invasion of the host cell and at the same time preventing the rapid clearance of *E. coli* from the UTI by the bulk flow of urine.[5] The carbohydrate recognition domain (CRD) of the FimH protein consists of amino acids with hydrophilic side chains that can establish a network of hydrogen bonds with the C2, C3, C4, and C6 hydroxyl groups of an α-D-mannopyranoside. It is now well established that the entrance (tyrosine gate) to the mannose-binding pocket of FimH is formed by two tyrosine residues (Tyr48 and Tyr137) and one isoleucine residue (Ile52) which support hydrophobic contacts.[6] Consequently, the introduction of an aromatic moiety in the mannosyl tail (aglycon) can establish favorable π-π interactions with the aromatic side chains of Tyr48, and Tyr137, thus enhancing the affinity of aromatic mannosides relative to the alkyl ones.[7-9] Crystal structures and docking studies of biphenyl O- and C-glycosides of α-D-mannopyranose complexed with FimH revealed that the hydrophobic rim formed by Tyr48, Tyr137, and Ile52 is not reached by the first

phenyl ring, but the outer phenyl ring induces π-π interactions with the phenyl groups of the tyrosines in the tyrosine gate, enhancing the affinity of α-D-mannoside ligands for FimH.[10-13]

Recently, a number of monovalent mannose-based FimH antagonists with diverse mannosyl tails such as *n*-heptyl α-D-mannoside,[14] and multimeric versions,[15-18] biphenyl α-D-mannosides,[10] and their derivatives,[19] indolinylphenyl and (aza)indolylphenyl α-D-mannosides,[20] thiazolylaminomannosides,[21] squaric acid mannosides,[22,23] mannosyl trizoles,[24] mannosyl ferrocenes,[25] mannosylated *N*-arylsubstituted 3-hydroxypyridine-4-ones,[26] branched α-D-mannosides,[27] C-glycosides[12] and others[28-31] have been reported. In addition, it has recently been suggested that orally administrated acid-resistant mannopyranosides are medicines against Crohn's disease.[11,32-36]

An overview of FimH antagonists designed so far revealed three classes: (i) α-D-mannosides with an alkyl chain in the tail, (ii) α-D-mannosides with an aryl glycoside at the start of the tail, (iii) α-D- mannosides with an extended planar glycoside starting the tail. It becomes obvious that the nature of the mannosyl tail (aglycone: elongated alkyl, substituted aromatic, and extended aromatic) plays a fundamental role in binding affinity, and therefore, altering its structure might influence the inhibitory potency toward type 1 fimbriated *E. coli*.

The Cu(I)-catalyzed 1,3-dipolar cycloaddition between terminal alkynes and azides (click chemistry) has proven to be a powerful tool in the synthesis of neoglycoconjugates.[37] Following our interest in using click chemistry for the synthesis of mannoside ligands[38], we present herein the assembly and the activity of a series of alkyl

α-D-mannosides each terminated with a different aryl methyl ester moiety prepared by clicking a common propargyl mannoside onto a series of alkyl azide-modified aromatic methyl esters. The positions of substitution of the aromatic methyl esters were systematically varied and both phenyl and naphthyl cores were used to determine the best geometry for mannose-FimH recognition. It is worth mentioning that the choice to incorporate aromatic methyl esters in the mannosyl tail was based on recent finding that phenolic mannosides having methyl esters in the 3-, 4-, and 3,5-positions and biphenyl mannosides bearing one or two methyl esters on the *meta* position(s) of the outer phenyl ring showed high affinity for FimH.[10] However, a potential drawback of α-D-mannoside ligands with aglycones having biphenyl system directly attached to the mannose moiety is their limited conformational flexibility, which could hamper an optimal fit with the tyrosine gate.[20] In order to increase the conformational flexibility, the inner phenyl ring of the biphenyl moiety was replaced by a triazolyl-methyl moiety that is attached to the outer phenyl ring through a six carbon alkyl chain (Figure 1a). Furthermore, we chose to evaluate both naphthyl and phenyl moieties as terminal aromatic groups to test the importance of volume at this position.

2. Results and Discussion

In this report, we describe the modification of the biphenyl mannoside **A** (Figure 1a) following the synthetic strategy outlined in Figure 1b which involves the preparation of propargyl-functionalized peracetylated mannose as terminal alkyne component (sugar template) and azido-methyl esters as coupling partners.

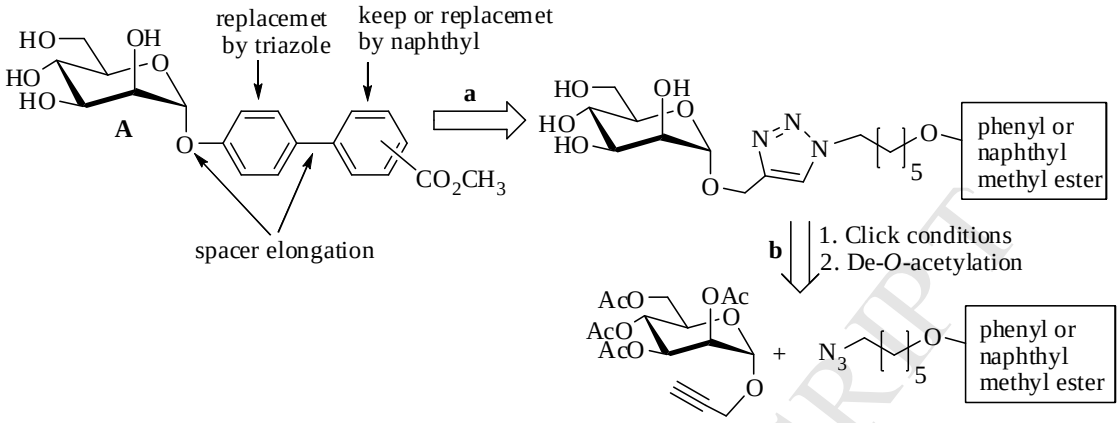
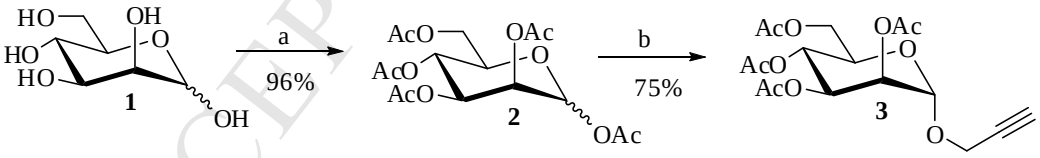


Figure 1. Design of FimH ligands (a) and synthetic strategy (b).

2.1. Synthesis of terminal alkyne component.

As depicted in (Scheme 1), prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**) was obtained in two steps from D-mannose according to the procedure we have used previously.[39] Thus, D-mannose (**1**) was converted into the corresponding peracetate (**2**) using pyridine and acetic anhydride. Treatment of (**2**) with propargyl alcohol under Lewis acid catalysis afforded the *α*-anomer (**3**) selectively in 75% yield.

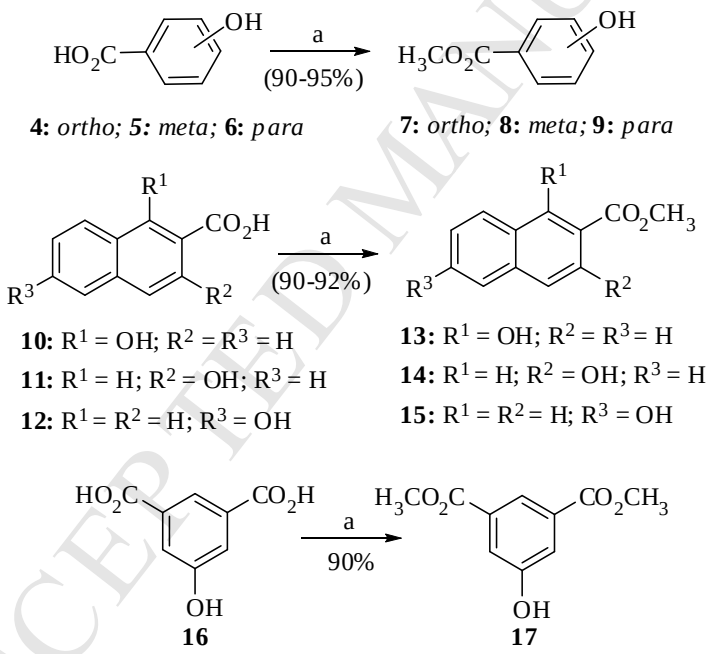


Scheme 1. Synthesis of propargyl mannoside **3**. Reagents and conditions: (a) Ac_2O, pyridine, 0 ^oC-r.t.; (b) propargyl alcohol, $BF_3.OEt_2$, CH_2Cl_2, -10 ^oC-r.t.

2.2. Synthesis of azido derivatives

The azides (**25-31**) having six carbon alkyl chains were synthesized via a three-step sequence that involved forming methyl esters of hydroxyarylcarboxylic acids followed by

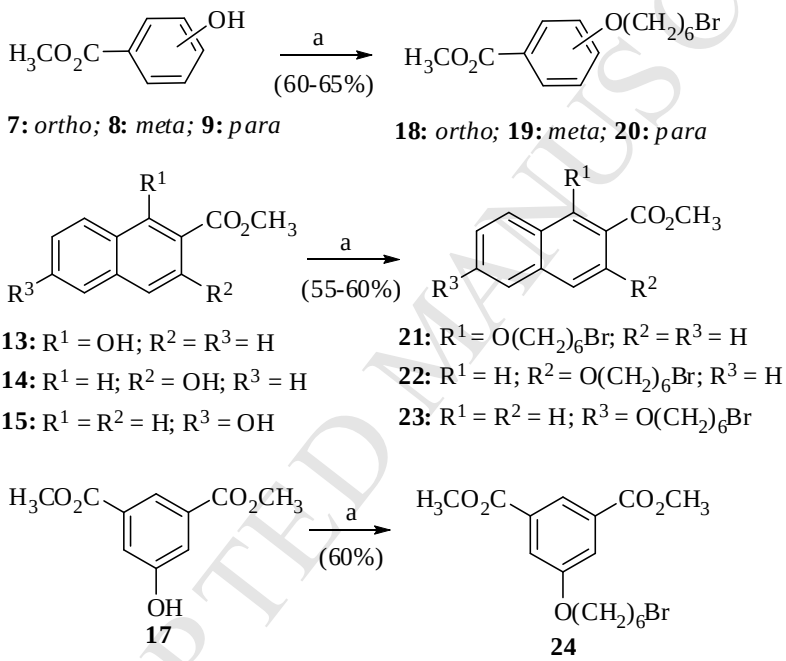
phenolic *O*-alkylation with 1,6-dibromohexane and subsequent azide substitution of the remaining bromide. As outlined in Scheme 2, the synthesis of azides began by forming methyl esters of compounds of the hydroxybenzoic acid family (**4-6**), hydroxy-2-naphthoic acid family (**10-12**), and 5-hydroxyisophthalic acid (**16**) under conventional conditions to give: methyl 2-hydroxybenzoate (**7**),[40] methyl 3-hydroxybenzoate (**8**),[41] methyl 4-hydroxybenzoate (**9**),[42] methyl 1-hydroxy-2-naphthoate (**13**),[43] methyl 3-hydroxy-2-naphthoate (**14**),[44] methyl 6-hydroxy-2-naphthoate (**15**),[45] and dimethyl 5-hydroxyisophthalate (**17**)[46] in excellent yields.



Scheme 2. Synthesis of methyl esters. Reagents and conditions: (a) H_2SO_4, (cat.), MeOH, reflux.

The phenolic *O*-alkylation of methyl benzoates (**7-9**), methyl naphthoates (**13-15**) and the diester (**17**) was carried out using 1,6-dibromohexane, K_2CO_3, and a catalytic

amount of KI in refluxing acetone. The alkylated methyl esters: methyl 2-(6-bromohexyloxy)benzoate (**18**), methyl 3-(6-bromohexyloxy)benzoate (**19**), methyl 4-(6-bromohexyloxy)benzoate (**20**),[42] methyl 1-(6-bromohexyloxy)-2-naphthoate (**21**), methyl 3-(6-bromohexyloxy)-2-naphthoate (**22**), methyl 6-(6-bromohexyloxy)-2-naphthoate (**23**), and dimethyl 5-(6-bromohexyloxy)isophthalate (**24**),[47] were obtained in good yields (Scheme 3).

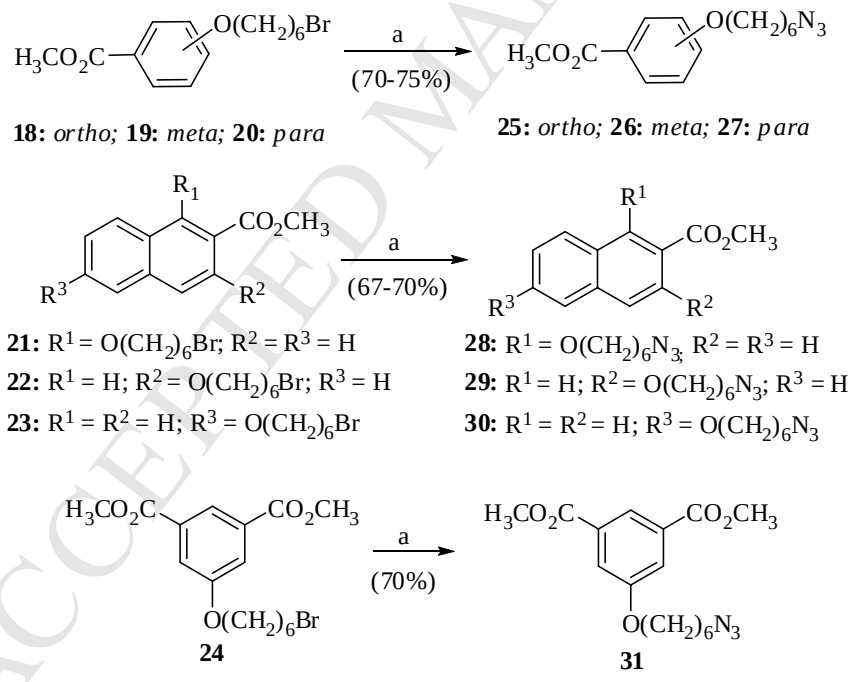


Scheme 3. *O*-alkylation of methyl esters. Reagents and conditions: (a) 1,6-dibromohexane, K_2CO_3, KI (cat.), acetone, reflux (24 h).

It is noteworthy that 1,6-dibromohexane was used in excess to avoid the formation of unwanted products. The ^{1}H-NMR spectra confirmed the structures of the alkylated methyl esters by the presence of two triplets around 4.02 and 3.44 ppm for the -CH_2OAr and –CH_2Br groups, respectively. In the ^{13}C-NMR spectra, the structures were also

confirmed by the presence of two peaks around 68.0 ppm for the -CH_2OAr group and 33.8 ppm for the –CH_2Br group.

Finally, azidation of the alkylated methyl benzoates (**18**-**20**), of the methyl 2-naphthoates (**21**-**23**), and of the diester (**24**) was carried out using NaN_3 in DMF at 100 ˚C to yield the azides: methyl 2-(6-azidohexyloxy)benzoate (**25**), methyl 3-(6-azidohexyloxy)benzoate (**26**), methyl 4-(6-azidohexyloxy)benzoate (**27**)[47] , methyl 1-(6-azidohexyloxy)-2-naphthoate (**28**), methyl 3-(6-azidohexyloxy)-2-naphthoate (**29**), methyl 6-(6-azidohexyloxy)-2-naphthoate (**30**), and dimethyl 5-(6-azidohexyloxy)isophthalate (**31**)[47] in good yields (Scheme 4).

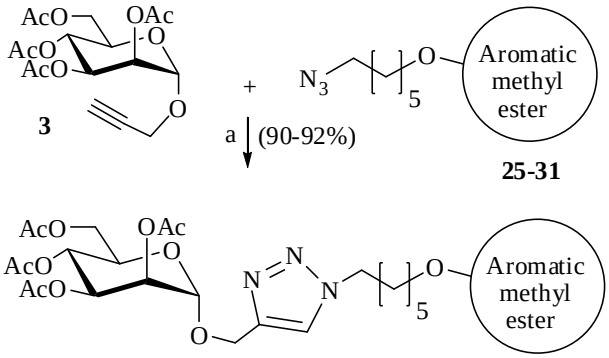


Scheme 4. Azidation of alkylated methyl esters. Reagents and conditions: (a) NaN_3, DMF (100 ^{o}C), 24 h.

The ^{13}C-NMR spectra were a good indicator for the formation of azides, as each contained a new peak around 51.0 ppm for the -CH_2N_3 carbon and did not contain a peak at 33.8 ppm that was due to the –CH_2Br group.

2.3. Synthesis of acetylated mannosides via click chemistry

With the key intermediates, propargyl mannoside (**3**) and azido derivatives (**25-31**) in hand, we used copper-catalyzed click chemistry to combine them.[38,48,49] Thus, the Huisgen [3+2] cycloadditions between the sugar alkyne and the various synthesized azides were easily realized under the promotion of sodium ascorbate and copper sulphate pentahydrate in a mixture of THF and H_2O at room temperature, affording the desired acetylated α-D-mannosides (**32-38**) in excellent yields (Scheme 5). The structures of products (**32-38**) were supported by the appearance of the signals of triazole protons at 7.57, 7.56, 7.53, 7.59, 7.61, 7.58, and 7.66 ppm, respectively, in their ^{1}H-NMR spectra. In the ^{13}C-NMR spectra, the triazole carbons appeared at 143.4 and 122.9 ppm for compound (**32**), 143.6 and 122.8 ppm for compound (**33**), 143.5 and 122.9 ppm for compound (**34**), 143.5 and 122.8 ppm for compound (**35**), 143.4 and 122.9 ppm for compound (**36**), 143.4 and 122.9 ppm for compound (**37**), and 143.2 and 122.8 ppm for compound (**38**), further confirming their structures.

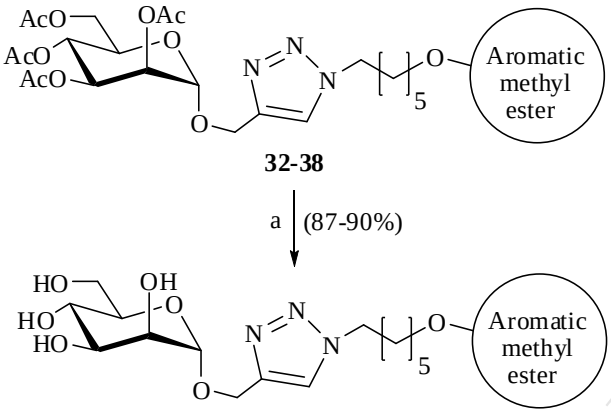


32: aromatic methyl ester = **7**
33: aromatic methyl ester = **8**
34: aromatic methyl ester = **9**
35: aromatic methyl ester = **13**
36: aromatic methyl ester = **14**
37: aromatic methyl ester = **15**
38: aromatic methyl ester = **17**

Scheme 5. Synthesis of acetylated α-D-mannosides. Reagents and conditions: (a) $CuSO_4.5H_2O$, sodium ascorbate, THF/H_2O (1:1) ratio, (25 ^oC), 24 h.

2.4. Removal of O-acetyl protecting groups

Due to the poor solubility of acetylated α-D-mannosides (**32-38**) in methanol, the mannosides were dissolved in a 1:1 mixture of THF and methanol and treated with 0.5 M $NaOCH_3$/methanol solution for 4 h at room temperature. Neutralization by the addition of ion-exchange resin Amberlite IR-120(H^+) until pH = 7 gave the corresponding de-*O*-acetylated α-D-mannosides (**32A**-**38A**) in excellent yields (Scheme 6). Removal of the acetates from compounds (**32**-**38**) was confirmed by the disappearance of the signals of the methyl protons in the ^{1}H-NMR spectra and those of the methyl carbons in the ^{13}C-NMR spectra.



32A: aromatic methyl ester = **7**
33A: aromatic methyl ester = **8**
34A: aromatic methyl ester = **9**
35A: aromatic methyl ester = **13**
36A: aromatic methyl ester = **14**
37A: aromatic methyl ester = **15**
38A: aromatic methyl ester = **17**

Scheme 6. De-*O*-acetylation of monovalent α-D-mannosides. Reagents and conditions: (a) 0.5 M MeONa in MeOH/THF (1:1 ratio), 25 ^{o}C, 4h.

2.5. Biological Activity

The mannoside ligands (**32A-38A**) were tested as inhibitors of the hemagglutination[22,26] of quinea-pig *erythrocytes* by type 1 piliated *E. coli* strain HB101 (pPKI4). The result of the hemagglutination test is expressed as inhibition titer (IT) that indicates the lowest concentration of the inhibitor at which no agglutination occurs. The inhibition titer (IT) is then compared to a reference inhibitor such as methyl α-D-mannoside (MeαMan) giving relative inhibition titer (RIT). The results of the tested ligands are summarized in Table 1 below.

Table 1: Inhibition of hemagglutination of quinea-pig *erythrocytes* by type1 piliated *E. coli strain* HB101 (pPKI4)

Tested ligand	HAI[a](mM)	[b]**RIT**
MeαMan	9.6	1
32A	0.296	32
33A	0.205	47
34A	0.169	57
35A	0.091	105
36A	0.073	131
37A	0.047	204
38A	0.135	71

. [a]Based on the average value from three independent tests. [b]Based on the reference inhibitor MeαMan

All tested ligands showed better inhibitory potency than the reference inhibitor MeαMan. The *meta* (**33A**) and the *para* (**34A**) orientational isomers showed a 47-fold and 57-fold improvement in activity relative to the standard inhibitor methyl α-D-mannoside (MeαMan) and were found to be more effective than the *ortho* isomer. This result implies that the *ortho* substitution was less preferred for activity while the *para* substitution was preferred to the *meta* substitution. However, incorporation of a second methyl ester in the other *meta* position of ligand (**33A**) such as ligand (**38A**) showed a significant a 71-fold improvement in potency relative to MeαMan. In fact, this constitutes a 1.5-fold improvement in activity relative to the *meta* monoester ligand (**33A**). As expected, the naphthyl-based ligands (**35A**-**37A**) showed better activity than the analogous phenyl-based mannoside ligands (**32A**-**34A**). We presume that the naphthyl residue contacts a larger proportion of the tyrosine gate. In the series of naphthyl-based

mannosides, ligand (**37A**) was found to be the most potent and showed 200-fold improvement in potency relative to methyl α-D-mannoside.

In order to compare these results to those from previous studies, we have complied a Table listing results from many studies (Table S1 in supporting information). Most studies compare new compounds to those for either methyl α-D-mannopyranoside as here or heptyl α-D-mannopyranoside, found to be 29 times more effective than the former in a direct comparison.[24] The phenyl glycoside is about half as effective as heptyl α-D-mannopyranoside and simple biphenyl glycosides are about 15 times more effective.[10] The best compound prepared here was found to be about 200 times better than methyl α-D-mannopyranoside or about 7 times better than heptyl α-D-mannopyranoside. Mannosyl triazoles with *N*-substituents on the triazole rings being substituted phenyl groups or substituted benzyl groups have been evaluated before but none were found to be as effective as the heptyl glycoside.[24] Although the implemented chemistry presented in this work is rather simple and standard, the obtained mannoside ligands are novel and interesting. Indeed, the outcome of this study is seven mannoside ligands that are structurally different from those previously reported.

3. Conclusions

In summary, application of simple chemical transformations of aromatic hydroxy acids (benzoic and naphthaoic) has generated a series of alkyl azide-modified aromatic methyl esters. Click coupling between known prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside and the prepared azides allowed efficient syntheses of unique α-D-

mannoside ligands having a flexible tail (aglycone) that combines alkyl and aryl moieties. The inhibitory capacity of the obtained ligands (**32A-38A**) listed in Table 1 toward FimH lectin were determined using a hemagglutination assay. All screened ligands show much better inhibitory activity than the standard inhibitor, methyl α-D-mannopyranoside. Unlike their phenyl counterparts, the naphthyl-based mannosides (**35A-37A**) showed better activity with ligand (**37A**) being the most active. It is significantly better than previously studied triazole mannosides and also heptyl α-D-mannopyranoside. Hence, it is a logical starting point for further development.

4. Experimental section

4.1 Hemagglutination tests

A recombinant type 1 fimbriated *E. coli* strain, E. coli HB 101 (pPKl4), used was cultured according to the protocol reported in the literature.[22,26] Guinea pig *erythrocytes* were isolated and used as described.[22,26] Hemagglutination tests were performed in V-shaped 96-well microtitre plates (Nunc). The compounds were suspended in distilled deionized water and serially diluted solutions (10 μl) were thoroughly mixed with bacteria suspension (10 μl) in wells. After 10 min, guinea pig *erythrocytes* (10 μl) were added and hemagglutination was read after approximately 10min at room temperature.

4.2. Synthesis

4.2.1 General

Melting points were determined with a SMP3 melting point apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded at 300 K in 5 mm NMR tubes on

solutions in $CDCl_3$ on a Bruker Avance 400 MHz spectrometer operating at 400 MHz and 100 MHz for ^{1}H-NMR spectra and ^{13}C-NMR spectra, respectively, with TMS as internal reference unless otherwise indicated. The carbon and hydrogen atoms were assigned following analysis of their one dimensional (^{1}H, ^{13}C) and two dimensional (COSY, HSQC, and HMBC) NMR spectral data. Chemical shifts are given in parts per million (ppm) (+/- 0.01 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ABq = AB quartet), coupling constant (*J*) in Hertz (Hz). High-resolution mass spectra were recorded on a Bruker Micro-TOF mass spectrometer using electrospray ionization. The reactions were monitored by thin layer chromatography (TLC) on Merk silica gel 60 F_{254} plates. Compounds were visualized by UV light (λ= 254 nm) and were located by spraying the plate with a solution of 2% ceric sulfate in 1M H_2SO_4 followed by heating on a hot plate until color developed. Compounds were purified on silica gel (70-230 mesh) by column chromatography using specified eluents. Dichloromethane (DCM) was first dried with calcium chloride, and refluxed over calcium hydride for one hour followed by distillation. Pyridine was dried by refluxing over calcium hydride followed by distillation over activated 4Å molecular sieves.

4.2.2. General Procedure for Alkylation of Methyl Esters

Compounds (**18**, **19**, and **21-23**) were synthesized according to the following procedure. To a stirred solution of methyl ester in acetone (200 mL), 1,6-dibromohexane (3 equiv.) and K_2CO_3 (3 equiv.) were added. The resulting reaction mixture was refluxed

for 48 h then cooled to room temperature, filtered and concentrated. Purification was then achieved by either recrystallization or column chromatography.

*4.2.2.1. Methyl 2-(6-bromohexyloxy)benzoate (**18**)*

The general procedure with compound **7** (3.10 g, 20.3 mmol) and 1,6-dibromohexane (9.3 mL, 60.9 mmol), followed by column chromatography (EtOAc:Hexanes, 1:7, R_f = 0.5) afforded compound **18** as a pale yellow oil (4.50 g, 60%): ^{1}H NMR δ 7.77- 6.93 (m, 4H, Ar-H), 4.04 (t, J = 6.4 Hz, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.42 (t , J = 6.4 Hz, 2H, CH_2Br), 1.85-1.25 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2Br$); ^{13}C NMR δ 166.6 (C=O), 158.8, 131.2, 129.2, 121.7, 119.7, 112.8 (Ar-C), 68.7 (OCH_2), 53.7 (OCH_3), 33.4 (CH_2Br), 29.7, 28.5, 27.9, 25.3 ($BrCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{14}H_{19}BrNaO_3$ $[M+Na]^+$ 337.0415. Found 337.0421.

4.2.2.2. Methyl 3-(6-bromohexyloxy)benzoate (***19***)

The general procedure with compound **8** (3.00 g, 19.70 mmol) and 1,6-dibromohexane (9.1 mL, 59.10 mmol), followed by column chromatography (EtOAc:Hexanes, 1:7, R_f = 0.5) afforded compound **19** as a colorless viscous oil (4.50 g, 72%): ^{1}H NMR δ 7.58-7.02 (m, 4H, Ar-H), 3.93 (t, J = 6.4 Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.36 (t , J = 6.8 Hz, 2H, CH_2Br), 1.85-1.44 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2Br$); ^{13}C NMR δ 166.7 (C=O), 158.9, 131.2, 129.2, 121,7, 119.7, 114.5 (Ar-C), 67.7 (OCH_2), 52.0 (OCH_3), 33.6 (CH_2Br), 32.5, 28.9, 27.8, 25.1 ($BrCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{14}H_{19}BrNaO_3$ $[M+Na]^+$ 337.0415. Found 337.0423.

4.2.2.3. Methyl 1-(6-bromohexyloxy)-2-naphthoate (***21***)

The general procedure with compound **13** (3.00 g, 14.8 mmol) and 1,6-dibromohexane (6.80 mL, 44.4 mmol), followed by column chromatography (EtOAc:Hexanes, 1:7, R_f = 0.5), afforded compound **21** as a pale orange viscose oil (4.0g, 74%): ^{1}H NMR δ 8.27-7.53 (m, 6H, naphthalene-**H**), 4.10 (t, J = 6.5, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 3.42 (t, J = 6.8, 2H, CH_2Br), 1.97-1.54 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2Br$); ^{13}C NMR δ 166.7 (C=O), 157.3, 136.6, 128.7, 128.2, 127.8, 126.7, 126.4, 123.6, 123.4, 119.2 (naphthalene-**C**), 76.1 (OCH_2), 52.1 (OCH_3), 33.8 (CH_2Br), 33.8, 32.7, 28.0, 25.3 ($BrCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{18}H_{21}BrNaO_3$ $[M+Na]^+$ 387.0572. Found 387.0564.

4.2.2.4. Methyl 3-(6-bromohexyloxy)-2-naphthoate (***22***)

The general procedure with compound **14** (3.00 g, 14.8 mmol) and 1,6-dibromohexane (6.8 mL, 44.4 mmol), followed by column chromatography (EtOAc:Hexanes, 1:7, R_f = 0.4), afforded compound **22** as a yellow oil (3.7g, 55%): ^{1}H NMR δ 8.45-7.50 (m, 6H, Ar-H), 4.28 (t, J = 6.4, 2H, OCH_2), 4.11 (s, 3H, OCH_3), 3.60 (t, J = 6.7, 2H, CH_2Br), 2.11-1.72 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2Br$); ^{13}C NMR δ 166.9 (C=O), 155.1, 136.1, 132.6, 128.7, 128.3, 127.5, 126.4, 124.3, 122.2, 107.7 (naphthalene-**C**), 68.5 (OCH_2), 52.2 (OCH_3), 33.9 (CH_2Br), 32.7, 29.00, 27.9, 25.3 ($BrCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{18}H_{21}BrNaO_3$ $[M+Na]^+$ 387.0572. Found 387.0569.

4.2.2.5. Methyl 6-(6-bromohexyloxy)-2-naphthoate (***23***)

The general procedure with compound **15** (1.96 g , 9.69 mmol) and 1,6-dibromohexane (3.0 mL, 19.4 mmol), followed by recrystallization from EtOAc afforded compound **23** as an off white solid (2.0 g, 56%): mp 55 ˚C; ^{1}H NMR δ 8.52-7.13 (m, 6H, Ar-H), 4.09 (t, J = 6.3, 2H, OCH_2), 3.96 (s, 3H, OCH_3), 3.44 (t, J = 6.7, 2H, CH_2Br), 1.91-1.54 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2Br$); ^{13}C NMR δ 167.5 (C=O), 159.1, 137.3, 130.9, 127.9, 126.8, 126.0, 125.2, 119.9, 106.5 (naphthalene-**C**), 68.0 (OCH_2), 52.1 (OCH_3), 33.8 (CH_2Br), 32.7, 29.1, 28.0, 25.4 ($OCH_2(\mathbf{C}H_2)_4CH_2Br$). HRMS (ESI): *m/z* calcd for $C_{18}H_{21}BrNaO_3$ $[M+Na]^+$ 87.0572. Found 387.0570.

4.2.3. General Procedure for the Synthesis of Azido-Compounds.

To a stirred solution of alkylated methyl ester in DMF (40 mL) was added NaN_3 (2 equiv.) and the resulting reaction mixture was stirred for 24 hrs at 100˚C, cooled down to room temperature, and filtered. The filtrate was washed with water (75 mL) and the product was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. Purification was then achieved by column chromatography (EtOAc:Hexanes, 1:1).

4.2.3.1. Methyl 2-(6-azidohexyloxy)benzoate (***25***)

The general procedure with compound **18** (3.50 g, 11.1 mmol) and NaN_3 (1.44 g, 22.2 mmol), yielded a yellow oil (2.40 g, 75%): R_f = 0.9 (EtOAc/Hexanes,1:1); ^{1}H NMR δ 7.84-6.82 (m, 4H, Ar-H), 3.90 (t, J = 6.9, 2H, OCH_2), 3.72 (s, 3H, OCH_3), 3.15 (t, J = 6.4, 2H, CH_2N_3), 1.70-1.24 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2N_3$); ^{13}C NMR δ 166.5 (C=O), 158.1, 133.0, 131.1, 119.6, 112.8 (Ar-C), 68.2 (OCH_2), 51.4 (CH_3), 50.9 (CH_2N_3), 28.6,

28.4, 26.0, 25.2 ($N_3CH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_3Na_1O_3$ $[M+Na]^+$ 300.1324. Found 300.1328.

4.2.3.2. Methyl 3-(6-azidohexyloxy)benzoate (***26***)

The general procedure with compound **19** (3.50 g, 11.1 mmol) and NaN_3 (1.44 g, 22.2 mmol), yielded a yellow oil (2.00 g, 66%): R_f = 0.9 (EtOAc/Hexanes,1:1). ^{1}H NMR: δ 7.59-7.03 (m, 4H, Ar-H), 3.94 (t, J = 6.4, 2H, CH_2O), 3.86 (s, 3H, OCH_3), 3.22 (t, J = 6.6, 2H, CH_2N_3), 1.79-1.32 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2N_3$); ^{13}C NMR: δ 166.7 (C=O), 158.9, 131.2, 129.2, 121.7, 119.6, 114.5 (Ar-C), 67.8 (OCH_2), 51.9 (CH_3), 51.2 (CH_2N_3), 28.9, 28.6, 26.3, 25.5 ($N_3CH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{14}H_{19}N_3NaO_3$ $[M+Na]^+$ 300.1324. Found 300.1291.

4.2.3.3. Methyl 1-(6-azidohexyloxy)-2-naphthoate (***28***)

The general procedure with compound **21** (3.50 g, 9.60 mmol) and NaN_3 (1.25 g, 19.2 mmol), yielded a brown to redish oil (1.80 g, 60%): R_f = 0.9 (EtOAc/Hexanes,1:1); ^{1}H NMR δ 8.27-7.53 (m, 6H, naphthalene-**H**), 4.12 (t, J = 6.5, 2H, CH_2O), 3.97 (s, 3H, OCH_3), 3.29 (t, J = 6.9, 2H, CH_2N_3), 1.98-1.44-1.98 (m, 8H, $OCH_2(C\mathbf{H}_2)_4CH_2N_3$); ^{13}C NMR: δ 166.8 (C=O), 157.4, 136.7, 128.8, 128.3, 127.9, 126.7, 126.5, 123.6, 123.5, 119.3 (naphthalene-**C**), 76.3 (OCH_2), 52.3 (OCH_3), 51.5 (CH_2N_3), 30.3, 28.9, 26.7, 25.8 ($N_3CH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{18}H_{21}N_3NaO_3$ $[M+Na]^+$ 350.1481. Found 350.1486.

4.2.3.4. Methyl 3-(6-azidohexyloxy)-2-naphthoate (***29***)

The general procedure with compound **22** (1.20 g , 3.30 mmol) and NaN_3 (0.43 g, 6.6 mmol), yielded a pale yellow oil (0.86 g , 67%): R_f = 0.9 (EtOAc/Hexanes,1:1); ^{1}H

NMR δ 8.52-7.14 (m, 6H, naphthalene-**H**), 4.10 (t, J = 6.9, 2H, OCH_2), 3.96 (s, 3H, OCH_3), 3.30 (t, J = 6.4, 2H, CH_2N_3), 1.90-1.48 (m, 8H, $OCH_2(CH_2)_4CH_2N_3$); ^{13}C NMR δ 166.9 (C=O), 155.1, 136.1, 132.6, 128.7, 128.3, 127.5, 126.4, 124.3, 122.1, 107.7 (naphthalene-**C**), 68.5 (OCH_2), 52.2 (OCH_3), 51.4 (CH_2N_3), 29.0, 28.8, 26.5, 25.7 ($N_3CH_2(CH_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{18}H_{21}N_3NaO_3$ $[M+Na]^+$ 350.1481. Found 350.1392.

4.2.3.5. Methyl 6-(6-azidohexyloxy)-2-naphthoate (***30***)

The general procedure with compound **23** (1.00 g, 2.74 mmol) and NaN_3 (0.36 g, 5.5 mmol), yielded an off white solid (0.93 g, 70%): mp 51-53 ˚C; ^1H NMR (acetone-d_6) δ 8.52-7.14 (m, 6H, naphthalene-**H**), 4.10 (t, J = 6.8, 2H, OCH_2), 3.96 (s, 3H, OCH_3), 3.30 (t, J = 6.4, 2H, CH_2N_3), 1.90-1.46 (m, 8H, $OCH_2(CH_2)_4CH_2N_3$); ^{13}C NMR δ 167.5 (C=O), 159.1, 137.3, 131.0, 130.9, 128.0, 126.9, 126.0, 125.3, 119.9, 106.5 (naphthalene-**C**), 68.0 (OCH_2), 52.2 (OCH_3), 51.5 (CH_2N_3), 29.1, 28.9, 26.6, 25.8 ($N_3CH_2(CH_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{18}H_{21}N_3NaO_3$ $[M+Na]^+$ 350.1481. Found 350.1498.

4.2.4. General procedure for the synthesis of acetylated mannosides (**32-38**)

To a stirred solution of azide and propargyl mannoside (1 equiv.) in THF (35 mL) was added sodium ascorbate (154 mg) followed by copper (II) sulphate pentahydrate (77 mg, in 35mL of H_2O) in one portion, the heterogeneous mixture was stirred vigorously for 24 hrs. THF was then removed under reduced pressure and CH_2Cl_2 (50 mL) was added. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated.

4.2.4.1. Mannoside **(32)**

The general procedure with compound **25** (0.60 g, 2.16 mmol) and propargyl mannoside **3** (0.84 g, 2.16 mmol), followed by purification by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded compound **32** as a pale yellow oil (90%): ^{1}H NMR δ 7.73-6.89 (m, 4H, Ar-H), 7.57 (s, 1H, triazole H), 5.27-5.19 (m, 3H, H-2, H-3, H-4), 4.91 (s, 1H, H-1), 4.92, 4.78 (ABq, J_{AB} = 12.2 Hz, 2H, H-1'), 4.34 (t, J = 7.2, 2H, CH_2N), 4.26 (dd, J = 12.1, 5 Hz, 1H, H-6b), 4.08-3.97 (m, 4H, H-5, H-6a, Ar-OC**H**$_2$), 3.83 (s, 3H, OCH_3), 2.10-1.36 (m, 20H, $NCH_2(CH_2)_4OCH_2$, CO**C**H_3); ^{13}C NMR δ 170.7, 170.0, 169.9, 169.7, 166.7 (5 x C=O), 158.5, 133.4, 131.5, 120.3, 120.1, 113.1 (Ar-**C**), 143.4 (CH=**C**), 122.9 (**C**H=C), 96.8(C-1), 69.4 (C-5), 69.0 (C-2), 68.7 (C-3), 68.4(Ar-OCH_2), 66.0 (C-4), 62.4 (C-1'), 61.0 (C-6), 51.9 (OCH_3), 50.2 (NCH_2), 30.1, 28.4, 26.0, 25.3 ($NCH_2(CH_2)_4CH_2O$), 20.9, 20.8, 20.7 (4 x CO**C**H_3). HRMS (ESI): *m/z* calcd for $C_{31}H_{41}N_3NaO_{13}$ $[M+Na]^+$ 686.2537. Found 686.2630.

4.2.4.2. Mannoside (**33**)

The general procedure with compound **26** (0.66 g, 2.38 mmol) and propargyl mannoside **3** (0.93 g, 2.38 mmol), followed by purification by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded mannoside **33** as a colorless viscous oil (90%): ^{1}H NMR δ 7.60-7.04 (m, 4H, Ar-H), 7.56 (s, 1H, triazole H), 5.30-5.22 (m, 3H, H-2, H-3, H-4), 4.93 (s, 1H, H-1), 4.82, 4.66 (ABq, J_{AB} = 12 Hz, 2H, H-1'), 4.36 (t, J = 8, 2H, CH_2N), 4.29 (dd, J = 12, 4 Hz, 1H, H-6b), 4.10-3.96 (m, 4H, H-5, H-6a, Ar-OCH_2), 3.88 (s, 3H, OCH_3), 2.13-1.41 (m, 20H, $NCH_2(CH_2)_4OCH_2$, CO**C**H_3); ^{13}C NMR δ 170.8, 170.1, 170.0, 169.8, 167.0 (5 x C=O), 159.0, 131.5, 129.5, 122.0, 120.0, 114.7 (Ar-**C**)

143.6 (CH=**C**), 122.8 (**C**H=C), 96.9 (C-1), 69.5 (C-5), 69.1(C-2), 68.8 (C-3), 67.9 (Ar-OCH_2), 66.2 (C-4), 62.5 (C-1'), 61.2 (C-6), 52.3 (OCH_3), 50.4 (NCH_2), 30.3, 29.0, 26.3, 25.6 (NCH_2(**C**H_2)$_4$$CH_2O$), 21.0, 20.9, 20.8 (4 x CO**C**H_3). HRMS (ESI): *m/z* calcd for $C_{31}H_{41}N_3NaO_{13}$ $[M+Na]^+$ 686.2537. Found 686.2485.

4.2.4.3. Mannoside (***34***)

The general procedure with compound **27** (0.60 g, 2.16 mmol) and propargyl mannoside **3** (0.84 g, 2.16 mmol), followed by purification by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded compound **34** as a pale yellow syrup (90%): ^{1}H NMR δ 7.91-6.81 (m, 4H, Ar-H), 7.53 (s, 1H, triazole H), 5.25-5.18 (m, 3H, H-2, H-3, H-4), 4.89 (s, 1H, H-1), 4.88, 4.61 (ABq, J_{AB} = 12.3 Hz, 2H, H-1'), 4.32 (t, J = 7.2, 2H, CH_2N), 4.24 (dd, J = 12.2, 5 Hz, 1H, H-6b), 4.06-3.92 (m, 4H, H-5, H-6a, Ar-OCH_2), 3.81 (s, 3H, OCH_3), 2.08-1.34 (m, 20H, NCH_2(C**H**$_2$)$_4$$OCH_2$, CO**C**$H_3$); ^{13}C NMR δ 170.6, 170.0, 169.9, 169.6, 166.8 (5 x C=O), 162.7, 131.5, 122.4, 114.0 (Ar-**C**), 143.5 (CH=**C**), 122.7 (**C**H=C), 96.8 (C-1), 69.4 (C-5), 69.0 (C-2), 68.7 (C-3), 67.7 (Ar-OCH_2), 66.0 (C-4), 62.3 (C-1'), 61.0 (C-6), 51.9 (OCH_3), 50.2 (NCH_2), 30.1, 28.8, 26.2, 25.4 (NCH_2(**C**H_2)$_4$$CH_2O$), 20.8, 20.7, 20.6 (4 x CO**C**H_3). HRMS (ESI): *m/z* calcd for $C_{31}H_{41}N_3NaO_{13}$ $[M+Na]^+$ 686.2537. Found 686.2531.

4.2.4.4. Mannoside (***35***)

The general procedure with compound **28** (0.41 g, 1.25 mmol) and propargyl mannoside **3** (0.50 g, 1.25 mmol), followed by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded mannoside **35** as a colorless viscous oil (90%): ^{1}H NMR δ 8.24-7.52 (m, 6H, naphthalene-**H**), 7.59 (s, 1H, triazole H), 5.32-5.24 (m, 3H, H-2, H-3, H-4),

4.95 (s, 1H, H-1), 4.84, 4.67 (ABq, J_{AB} = 12.3 Hz, 2H, H-1'), 4.39 (t, J = 7.1, 2H, CH_2N), 4.30 (dd, J = 12.2, 5 Hz, 1H, H-6b), 4.12-4.09 (m, 4H, H-5, H-6a, Ar-OCH_2), 4.08 (s, 3H, OCH_3), 1.69-1.23 (m, 20H, $NCH_2(CH_2)_4OCH_2$, $COCH_3$); ^{13}C NMR δ 170.8, 170.1, 170.0, 169.8 ,166.8 (5 x C=O), 157.4, 136.8, 128.8, 128.4, 127.9, 126.8, 126.6, 123.6, 123.5, 119.3 (naphthalene-**C**), 143.5 (CH=**C**), 122.8 (**C**H=C), 96.9 (C-1), 76.1 (Ar-OCH_2), 69.5 (C-5), 69.1(C-2), 68.8 (C-3), 66.1 (C-4), 62.4 (C-1'), 61.2 (C-6), 52.3 (OCH_3), 50.4 (NCH_2), 30.3, 30.2, 26.5, 25.6 ($NCH_2(CH_2)_4CH_2O$), 20.9, 20.8, 20.7 (4 x $COCH_3$). HRMS (ESI): *m/z* calcd for $C_{35}H_{43}N_3NaO_{13}$ $[M+Na]^+$ 736.2694. Found 736.2673.

4.2.4.5. Mannoside (***36***)

The general procedure with compound **29** (0.60 g , 1.83 mmol) and propargyl mannoside **3** (0.72 g, 1.83 mmol), followed by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded compound **36** as a yellow oil (90%): ^{1}H NMR δ 8.29-7.18 (m, 6H, naphthalene-**H**), 7.61 (s, 1H, trizole H), 5.32-5.24 (m, 3H, H-2, H-3, H-4), 4.95 (d, J = 1.3, 1H, H-1), 4.82, 4.63 (ABq, J_{AB} = 12.3 Hz, 2H, H-1'), 4.40 (t, J = 7.1, 2H, CH_2N), 4.31 (dd, J = 12.2, 5 Hz, 1H, H-6b), 4.19-4.08 (m, 4H, H-5, H-6a, Ar-OCH_2), 3.94 (s, 3H, OCH_3), 2.15-1.41 (m, 20H, $NCH_2(CH_2)_4OCH_2$, $COCH_3$); ^{13}C NMR δ 170.7, 170.0, 169.9, 169.7, 166.7 (5 x C=O), 155.0, 136.1, 132.6, 128.6, 128.4, 127.5, 126.4, 124.3, 122.0, 107.6 (naphthalene-**C**), 143.4 (CH=**C**), 122.9 (**C**H=C), 96.8 (C-1), 69.5 (C-5), 69.0 (C-2), 68.7 (C-3), 68.3 (Ar-OCH_2), 66.1 (C-4), 62.4 (C-1'), 61.0 (C-6), 52.2 (OCH_3), 50.2 (NCH_2), 30.1, 28.8, 26.0, 25.4 ($NCH_2(CH_2)_4CH_2O$), 20.9, 20.8, 20.7 (4 x $COCH_3$). HRMS (ESI): *m/z* calcd for $C_{35}H_{43}N_3NaO_{13}$ $[M+Na]^+$ 736.2694. Found 736.2710.

4.2.4.6. Mannoside (***37***)

The general procedure with compound **30** (0.50 g , 1.53 mmol) and propargyl mannoside (0.60 g, 1.53 mmol), followed by purification by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded compound **37** as a yellow oil (90%). ^{1}H NMR (acetone d_6) δ 8.52-7.72 (m, 6H, naphthalene-**H**), 7.58 (s, 1H, trizole H), 5.33-5.24 (m, 3H, H-2, H-3, H-4), 4.95 (d, J = 1.2, 1H, H-1), 4.84, 4.67 (ABq, J_{AB} = 12.3 Hz, 2H, H-1'), 4.39 (t, J = 7.2, 2H, CH_2N), 4.30 (dd, J = 12.2, 5 Hz, 1H, H-6b), 4.13-4.07 (m, 4H, H-5, H-6a, Ar-OCH_2), 3.96 (s, 3H, OCH_3), 2.15-1.44 (m, 20H, $NCH_2(CH_2)_4OCH_2$, $COCH_3$); ^{13}C NMR (acetone d_6) δ 170.7, 170.0, 169.9, 169.7, 166.7 (5 x C=O), 155.0, 136.1, 132.6, 128.7, 128.4, 127.5, 126.4, 124.3, 122.0, 107.6 (naphthalene-**C**), 143.4 (CH=**C**), 122.9 (**C**H=C), 96.8 (C-1), 69.5 (C-5), 69.0 (C-2), 68.7 (C-3), 68.3 (Ar-OCH_2), 66.1 (C-4), 62.4 (C-1'), 61.0 (C-6), 51.9 (OCH_3), 50.2 (NCH_2), 30.1, 28.8, 26.0, 25.4 ($NCH_2(CH_2)_4CH_2O$), 20.9, 20.8, 20.7 (4 x $COCH_3$). HRMS (ESI): *m/z* calcd for $C_{35}H_{43}N_3NaO_{13}$ $[M+Na]^+$ 736.2694. Found 736.2687.

4.2.4.7. Mannoside (***38***)

The general procedure with compound **31** (0.60 g , 1.79 mmol) and propargyl mannoside **3** (0.70 g, 1.79 mmol), followed by purification by column chromatography (EtOAc:Hexanes, 1:1, R_f = 0.2) afforded compound **38** as a pale yellow oil (90%):^{1}H NMR δ 8.24, 7.71 (2s, 3H, Ar-H), 7.66 (s, 1H, trizole H), 5.33-5.26 (m, 3H, H-2, H-3, H-4), 4.88 (s, 1H, H-1), 4.87, 4.70 (ABq, J_{AB} = 12.3 Hz, 2H, H-1'), 4.41 (t, J = 6.2, 2H, CH_2N), 4.31 (dd, J = 12.4, 5.2 Hz, 1H, H-6b), 4.14-4.03 (m, 4H, H-5, H-6a, Ar-OCH_2), 3.94 (s, 6H, 2 x OCH_3), 2.17-1.45 (m, 20H, $NCH_2(CH_2)_4OCH_2$, $COCH_3$); ^{13}C NMR δ

170.5, 169.8, 169.7, 169.5, 165.8 (6 x C=O), 158.9, 131.5, 122.6, 119.5 (Ar-C), 143.2 (CH=**C**), 122.8 (**C**H=C), 96.6 (C-1), 69.2 (C-5), 68.9 (C-2), 68.5 (C-3), 68.0 (Ar-OCH_2), 65.9 (C-4), 62.2 (C-1'), 60.8 (C-6), 52.2 (2 x OCH_3), 50.1 (NCH_2), 30.0, 28.6, 26.0, 25.3 ($NCH_2(\mathbf{C}H_2)_4CH_2O$), 20.7, 20.6, 20.5 (4 x CO**C**H_3). HRMS (ESI): *m/z* calcd for $C_{33}H_{43}N_3NaO_{15}$ $[M+Na]^+$ 744.2592. Found 744.2585.

*4.2.5. General procedure for de-O-acetylation of mannosides (**32-38**)*

To a stirred solution of a given acetylated mannose in CH_3OH (5mL) and THF (5mL) was added sodium methoxide (0.5 M in CH_3OH,1 mL), the reaction mixture was stirred for 4 h at room temperature and neutralized with Amberlite IR120 (H+), filtered and concentrated. The resulting residue was then purified by column chromatography (EtOAc/CH_3OH = 2:1).

4.2.5.1. Mannoside (***32A***)

Mannoside **32A** prepared from **32** according to the general procedure as a white solid (87%):^{1}H NMR δ 7.65-6.84 (m, 5H, Ar-H, triazole H), 5.23, 5.07 (2 x bs, 3H, OH), 4.84-4.23 (m, 6H, H-1, H-1', NCH_2, OH), 3.89-3.47 (m, 11 H, H-2, H-3, H-4, H-5, H-6, OCH_2, OCH_3), 1.80-1.27 (m, 8H, $NCH_2(C\mathbf{H}_2)_4CH_2O$); ^{13}C NMR δ 166.8 (C=O), 158.5, 133.5, 131.5, 120.2, 120.0, 113.2 (Ar-**C**), 143.7 (CH=**C**), 123.5 (**C**H=C), 99.5 (C-1), 72.8 (C-5), 71.3 (C-3), 70.6 (C-2), 68.5 (Ar-OCH_2), 66.5 (C-4), 61.0 (C-1'), 60.0 (C-6), 51.9 (OCH_3), 50.2 (NCH_2), 30.1, 28.8, 26.0, 25.3 ($NCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{23}H_{33}N_3NaO_9$ $[M+Na]^+$ 518.2114. Found 518.1762.

4.2.5.2. Mannoside (***33A***)

Mannoside **33A** was prepared from **33** according to the general procedure as a colorless oil (88%): ^{1}H NMR δ 7.69-7.01 (m, 5H, Ar-H, triazole H), 5.31, 5.14 (2 x bs, 3H, OH), 4.90 (s, 1H, H-1), 4.81 (bs, 1H, OH), 4.69, 4.54 (ABq, J_{AB} = 11.9 Hz, 2H, H-1'), 4.29-3.76 (m, 13H, H-2, H-3, H-4, H-5, H-6, OCH_2, NCH_2, OCH_3), 1.87-1.33 (m, 8H, $NCH_2(C\mathbf{H}_2)_4CH_2O$); ^{13}C NMR δ 167.0 (C=O), 159.0, 131.4, 129.5, 123.6, 119.9, 114.7 (Ar-**C**), 143.9 (CH=**C**), 121.9 (**C**H=C), 99.6 (C-1), 72.9 (C-5), 71.4 (C-3), 70.6 (C-2), 67.9 (Ar-OCH_2), 66.6 (C-4), 61.1 (C-1'), 60.1 (C-6), 52.2 (OCH_3), 50.4 (NCH_2), 30.2, 29.0, 26.3, 25.6 ($NCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{23}H_{33}N_3NaO_9$ $[M+Na]^+$ 518.2114. Found 518.2116.

4.2.5.3. Mannoside (***34A***)

Mannoside **34A** prepared from **34** according to the general procedure as a white solid (87%): ^{1}H NMR δ 7.94-6.84 (m, 5H, Ar-H, triazole H), 5.15, 5.03 (2 x bs, 3H, OH), 4.91 (s, 1H, H-1), 4.70-4.53 (m, 3H, H-1', OH), 4.30-3.53 (m, 13H, H-2, H-3, H-4, H-5, H-6, OCH_2, NCH_2, OCH_3), 1.88-1.25 (m, 8H, $NCH_2(C\mathbf{H}_2)_4CH_2O$); ^{13}C NMR δ 166.9 (C=O), 162.9, 131.7, 122.5, 114.2 (Ar-**C**), 143.9 (CH=**C**), 123.5 (**C**H=C), 99.6 (C-1), 72.8 (C-5), 71.0 (C-3), 70.2 (C-2), 67.9 (Ar-OCH_2), 66.8 (C-4), 61.2 (C-1'), 60.2 (C-6), 51.9 (OCH_3), 50.4 (NCH_2), 30.2, 29.0, 26.4, 25.6 ($NCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{23}H_{33}N_3NaO_9$ $[M+Na]^+$ 518.2114. Found 518.1981.

4.2.5.4. Mannoside (***35A***)

Mannoside **35A** prepared from **35** according to the general procedure as a colorless oil (85%): ^{1}H NMR δ 8.18-7.49 (m, 7H, naphthalene-**H**, triazole H), 5.31, 5.14

(2 x bs, 3H, OH), 4.93 (s, 1H, H-1), 4.91 (bs, 1H, OH), 4.66, 4.54 (ABq, J_{AB} = 12.2 Hz, 2H, H-1'), 4.28 (t, J = 6.7 Hz, 2H, NCH_2), 4.01 (t, J = 6.3 Hz, 2H, OCH_2), 3.89-3.64 (m, 9H, H-2, H-3, H-4, H-5, H-6, OCH_3), 1.87-1.35 (m, 8H, $NCH_2(CH_2)_4CH_2O$); ^{13}C NMR δ 166.8 (C=O), 157.4, 136.8, 128.8, 128.4, 127.9, 126.8, 126.7, 123.6, 123.5, 119.3 (naphthalene-**C**), 143.9 (CH=**C**), 123.5 (**C**H=C), 99.6 (C-1), 76.2 (Ar-OCH_2), 72.9 (C-5), 71.5 (C-3), 70.8 (C-2), 66.7 (C-4), 61.2 (C-1'), 60.1 (C-6), 52.3 (OCH_3), 50.4 (NCH_2), 30.3, 26.5, 25.6 ($NCH_2(CH_2)_4CH_2O$), HRMS (ESI): *m/z* calcd for $C_{27}H_{35}N_3NaO_9$ $[M+Na]^+$ 568.2271. Found 568.2306.

4.2.5.5. Mannoside (***36A***)

Mannoside **36A** prepared from **36** according to the general procedure as yellow oil (87%): ^{1}H NMR δ 8.23 (s, 1H, triazole-H), 7.76-7.11 (m, 6H, naphthalene-**H**), 4.93-4.53 (m, 7H, H-1, H-1', OH) 4.27-3.57 (m, 13H, H-2, H-3, H-4, H-5, H-6, OCH_3, OCH_2, NCH_2), 1.85-1.32 (m, 8H, $NCH_2(CH_2)_4CH_2O$); ^{13}C NMR δ 166.8 (C=O), 155.0, 136.0, 132.5, 128.6, 128.4, 127.4, 126.5, 124.3, 122.0, 107.7 (naphthalene-**C**), 143.8 (CH=**C**), 123.6 (**C**H=C), 99.5 (C-1), 72.8 (C-5), 71.3 (C-3), 70.7 (C-2), 68.4 (Ar-OCH_2), 66.6 (C-4), 61.0 (C-1'), 60.0 (C-6), 52.2 (OCH_3), 50.2 (NCH_2), 30.1, 28.8, 26.1, 25.4 ($NCH_2(CH_2)_4CH_2O$), ($NCH_2(CH_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{27}H_{35}N_3NaO_9$ $[M+Na]^+$ 568.2271. Found 568.2310.

4.2.5.6. Mannoside (***37A***)

Mannoside **37A** prepared from **37** according to the general procedure as a white solid (87%): ^{1}H NMR: (CD_3OD) δ 8.02 (s, 1H, triazole-H), 7.97-7.17 (m, 6H, naphthalene-**H**), 4.84 (d, J = 1.2, 1H, H-1), 4.79, 4.62 (ABq, J_{AB} = 12.3 Hz, 2H, H-1'),

4.43 (t, J = 7.9, 2H, NCH_2), 4.11 (t, J = 6.2, 2H, OCH_2), 3.94(s, 3H, OCH_3), 3.32-3.20 (m, 6H, H-2, H-3, H-4, H-5, H-6), 1.62-1.38 (m, 8H, $NCH_2(C\mathbf{H}_2)_4CH_2O$); ^{13}C NMR: ($CD_3OD$) δ 168.9 (C=O), 160.6, 138.9, 131.9, 131.8, 129.2, 128.0, 126.6, 126.2, 121.0, 107.5 (naphthalene-**C**), 145.3 (CH=**C**), 125.3 (**C**H=C), 100.8 (C-1), 75.0 (C-5), 72.5 (C-3), 72.0 (C-2), 69.0 (Ar-OCH_2), 68.6 (C-4), 63.0 (C-1'), 60.7 (C-6), 52.6 (OCH_3), 51.3 (NCH_2), 31.2, 30.0, 27.2, 26.6 ($NCH_2(\mathbf{C}H_2)_4CH_2O$), HRMS (ESI): *m/z* calcd for $C_{27}H_{35}N_3NaO_9$ $[M+Na]^+$ 568.2271. Found 568.2268.

4.2.5.7. Mannoside (***38A***)

Mannoside **38A** prepared from **38** according to the general procedure as a white solid (87%): ^{1}H NMR δ 8.21(s, 1H, Ar-H), 7.73 (s, 1H, triazole H), 7.67 (s, 2H, Ar-H), 5.28 (bs, 3H, OH), 4.94 (s, 1H, H-1), 4.72, 4.59 (ABq, J_{AB} = 11.3 Hz, 2H, H-1'), 4.35-3.56 (m, 14H, H-2, H-3, H-4, H-5, H-6, OCH_3, OCH_2, NCH_2, OH), 1.92-1.39 (m, 8H, $NCH_2(C\mathbf{H}_2)_4CH_2O$); ^{13}C NMR δ 166.1 (2 x C=O), 159.1, 131.7, 122.8, 119.7 (Ar-**C**), 143.8 (CH=**C**), 123.5 (**C**H=C), 99.3 (C-1), 72.8 (C-5), 71.3 (C-3), 70.7 (C-2), 68.3 (Ar-OCH_2), 66.6 (C-4), 61.1 (C-1'), 60.4 (C-6), 52.4 (2 x OCH_3), 50.4 (NCH_2), 30.2, 26.9, 26.3, 25.5 ($NCH_2(\mathbf{C}H_2)_4CH_2O$). HRMS (ESI): *m/z* calcd for $C_{25}H_{53}N_3NaO_{11}$ $[M+Na]^+$ 576.2169. Found 576.2148.

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Supplementary data

Supplementary data to this article can be found at …

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Highlights

- Two series of novel monovalent α-D-mannosides were designed and synthesized.
- Click chemistry was employed to construct the monovalent α-D-mannosides.
- Designed α-D-mannosides were tested as inhibitors of FimH lectin.
- In the series of naphthyl-based mannosides, ligand **37A** was found to be the most potent.