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Synthesis and glycosidase inhibitory profiles of functionalised morpholines and oxazepanes

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ABSTRACT

In this work libraries of morpholines and oxazepanes have been prepared via the reductive amination reaction between dialdehydes, derived from carbohydrates, and a range of amines. In this way, functionalised morpholines and oxazepanes have been prepared that include N-alkylated derivatives, disaccharide analogues, and ester containing derivatives. The abilities of these functionalised morpholines and oxazepanes to inhibit a broad panel of glycosidase enzymes, that are associated with a range of diseases, have been probed and in this way new inhibitors of a range of glycosidases, but particularly β-D-galactosidase derived from Bovine kidney, have been discovered. *N*-Alkyl morpholines demonstrated the best inhibition profiles for this enzyme and derivatives (**15a**)–(**15d**) acted as non-competitive inhibitors with IC_{50} values of 55.1–88.6 μM. Within this study, some preliminary structure–activity relationships are proposed, and it is demonstrated that N-substituted morpholines display better inhibitory profiles for the enzymes analysed than any of the N-substituted oxazepanes.

1. Introduction

As our knowledge and understanding of biological systems develops, the fundamental importance of cellular oligosaccharides becomes increasingly apparent. Thus, advances in the fields of cellular biochemistry and molecular biology have revealed that oligosaccharides present on the cell surface are used by cells to communicate with the extracellular environment,[1] for example through cell–cell recognition and cell-external agent interactions. In addition, cell surface oligosaccharides play fundamental roles in disease processes such as inflammation, viral and bacterial infections, and cancer metastasis.[1,2] The application of this knowledge to the development of novel pharmaceuticals has immense potential and provides the basis for new carbohydrate therapeutics.[3] Oligosaccharides present on the cell surface are formed via a series of tightly controlled enzyme mediated reactions within the endoplasmic reticulum and Golgi apparatus. Blocking any of the protein glycosylation or oligosaccharide processing reactions which occur in this way is thus a useful tool for altering or impeding the formation of the elaborate cell surface oligosaccharides.[4] When this allows disruption of the synthesis of oligosaccharides involved in disease processes, opportunities become available to tune or halt the on-set and progression of the disease. This has important implications for the potential therapeutic intervention in the biosynthesis of oligosaccharides associated with many diseases including cancer, diabetes, viral infections and lysosomal storage disorders.[5]

Considerable progress has been made in recent years concerning the isolation and synthesis of inhibitors of glycosidase enzymes involved in oligosaccharide synthesis and processing.[6] The great potency and specificity of these inhibitors are related to their ability to mimic transition states involved in enzyme mediated oligosaccharide processing; both conformational and electrostatic influences are postulated to be important in the active site binding.[7] For example, it is postulated that iminosugars may be able to inhibit glycosidase enzymes by mimicking the conformation and charge of the oxycarbenium ion intermediate (A), rather than the carbocation (B) (Scheme 1).[8]

Since partial cleavage of the glycosidic bond intensifies the positive charge generated in the oxygen or anomeric carbon of the natural glycoside, substitution of one of these two atoms by a protonated nitrogen will mimic, in the transition state, the charge in these centres, and hence offers opportunities for inhibition of the enzyme.[9] For example, nojirimycin (**1**), and 1-deoxynojirimycin (DNJ) (**2**), (Scheme 2) are well documented inhibitors of α-glucosidases that are believed to interact with the enzyme receptors through their protonated forms.[10]

D-Isofagomine (**3**, Fig. 1) is a further iminosugar demonstrating potent inhibition of a β-glucosidase, but weaker inhibition of an α-glucosidase (0.11 and 86 μM, respectively).[11,12] The weaker inhibition of α-glycosidases is postulated to be due to the lack of an essential hydroxyl group for interaction with the enzyme's active site.[13]

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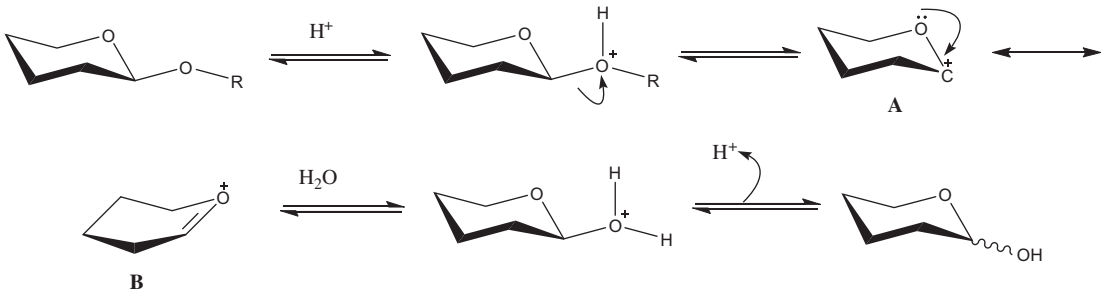
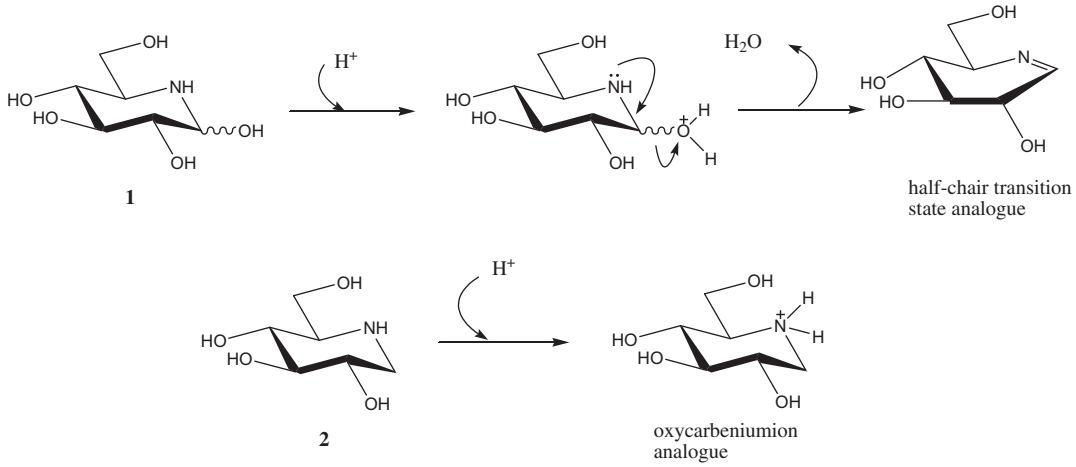


Scheme 1.



Scheme 2.

Castanospermine (**4**) and Swainsonine (**5**) (Fig. 2) are bicyclic iminosugars of great value as glycosidase inhibitors.[14] Thus castanospermine (**4**) is a potent and specific inhibitor of mammalian and plant α- and β-D-glucosidases in vitro and in vivo with percentage inhibition values of 100% (K_i 0.1 μM) against lysosomal α-glucosidase, and 96% (K_i 7 μM) against lysosomal β-glucosidase. Swainsonine is a potent inhibitor of glycosidases that shows anti-cancer activity both in vitro and in vivo (inhibitor of α-mannosidase (jack bean), K_i = 155 nM and dGMII K_i = 20 nM).[15]

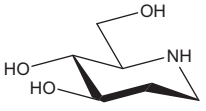


Figure 1.

Recently Fernández et al. reported a new family of highly selective glycosidase inhibitors in which the sp^3 amine-type nitrogen typical of azasugars is replaced by a pseudoamide-type (urea, thiourea, carbamate, thiocarbamate, isourea) nitrogen atom, with a substantial sp^2 character.[16] Interestingly, the neutral sp^2-azasugars (**7**) and (**8**) with 1-deoxy-6-oxa-*N*-(thio)-carbamoyl-(+)-calystegine B_2 structures, exhibited very selective and strong inhibitory activity against the mammalian cytosolic β-glucosidase/β-galactosidase (bovine liver) (Fig. 3). The corresponding inhibition constant (K_i) values (2.5 and 30 μM, respectively) were indicative of a more potent inhibition for this particular enzyme than the natural compound (**6**) (K_i = 45 μM), suggesting a 1-azasugar inhibition mode.

Fernández et al. proposed that the corresponding epimers at C-3 should act as galactomimetics and, consequently, inhibit the β-glucosidase/β-galactosidase. This was confirmed by the synthesis of (**9**) and (**10**) (Fig. 4). From the observed K_i value for this mixture (750 ± 60 μM) a K_i value of 68 ± 6 μM was estimated for (**10**), and this if of the same order of magnitude as the value previously

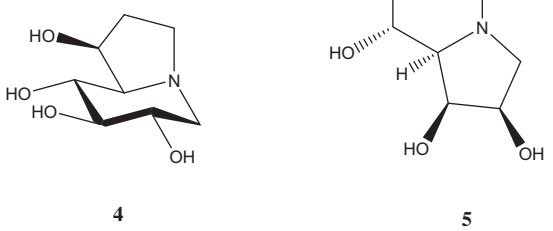


Figure 2.

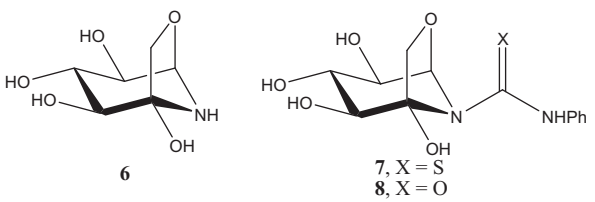
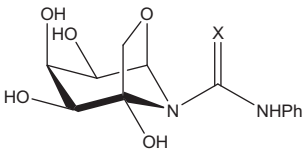


Figure 3.

found for the glucomimetic epimer (**8**). This result confirms that compound (**10**) behaves as a galactomimetic and strongly supports a 1-azasugar mode of action for calystegine glycosidase inhibitors. The nitrogen substituent probably projects into the algyconic binding site of the enzyme, providing addition interactions, which offers a possibility for further improvement of the molecular design.

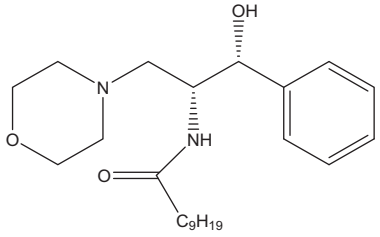
2. Results and discussion

As highlighted above, there has been a long standing interest in the design and synthesis of new carbohydrate derivatives, as potential inhibitors of carbohydrate processing enzymes. We have previously reported a new synthetic method that allows selective entry to morpholines and oxazepanes, via a reductive amination protocol, but have not previously probed the ability of these derivatives to inhibit glycosidase enzymes.[17] This programme therefore focussed on the synthesis of a wider range of morpholine and oxazepane targets, and a determination of their ability to inhibit a range of glycosidase enzymes. At the outset of the programme it was postulated that oxazepanes prepared in this way may mimic higher sugar frameworks that have previously been shown to have glycosidase inhibitory, and antibacterial, activities.[18,19] In addition, it was anticipated that the morpholine derivatives may afford useful inhibitory profiles, since one of the earliest glycosphingolipid (GSL) biosynthesis inhibitors was the morpholine analogue 1-phenyl-2-decanoyl-amino-3-morpholine-1-propanol (PDMP) (**11**) (Fig. 5).[20,21] Michaelis–Menten kinetics demonstrate that PDMP is a reversible, mixed type inhibitor for ceramide with an inhibitory constant of 0.7 μM.



9, X = S
10, X = O

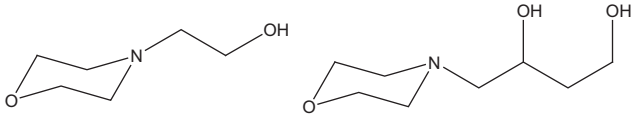
Figure 4.



PDMP, **11**

Figure 5.

Moreover, even structurally simple morpholine derivatives such as (**12**) and (**13**) (Fig. 6) have been shown to be good uncompetitive inhibitors of β-glucosidase (K_i 6.2×10^{-4} and 6.4×10^{-4} M, respectively).[22]

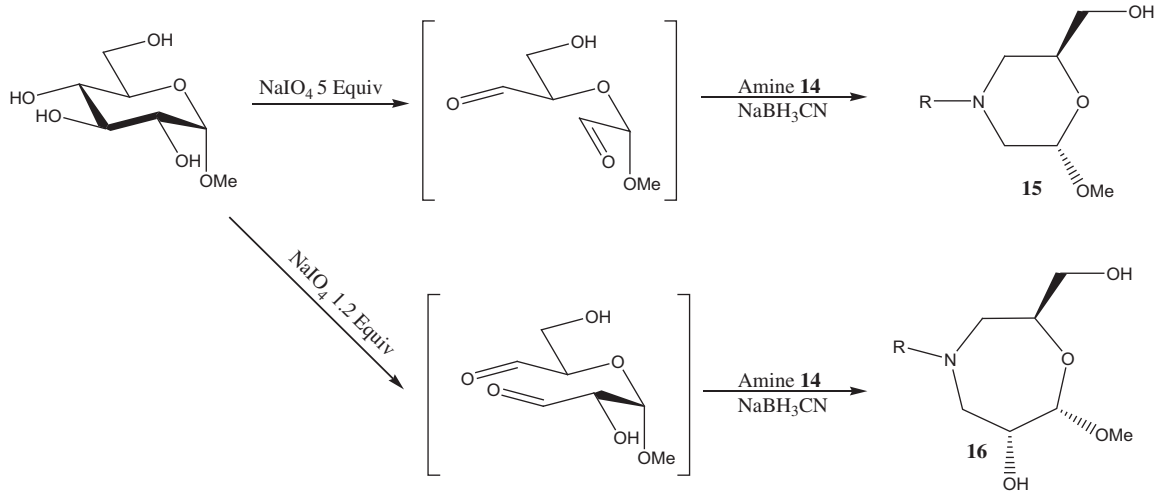


12 **13**

Figure 6.

2.1. Synthesis of morpholines and oxazepanes

Entry to morpholines and oxazepanes was accomplished as described previously, and as depicted in Scheme 3. In order to establish structure–activity relationships, a range of functionalised amines were used within the methodology, as summarised in Table 1. For example the effect of N-alkylation could be probed by using amines (**14a**)–(**14e**), and it was postulated that this could prove beneficial since N-alkylation has been demonstrated to increase the inhibitory properties of iminosugars such as deoxynojirimycin.[23] Hydroxylamine (**14f**) was also selected for utilisation, to probe the effect of the additional hydroxyl functionality on the glycosidase inhibition profiles. Incorporation of additional hydroxyl functionalities, for example within *N*-hydroxyethyl-DNJ (Miglitol), has again led to inhibitors with more favourable profiles compared with the parent compound.[24] Amines (**14g**) –(**14j**) were selected to probe the effect of the ester functional group on inhibition, for example, by providing additional functionalities for hydrogen bonding interactions. Finally, the carbohydrate derived amines (**14k**) and (**14l**) were incorporated to allow the selectivity of inhibition of the disaccharide mimics (**15k–15l**) and (**16k–16l**) to be analysed. Such derivatives have previously been reported to afford



Scheme 3.

Table 1
Percentage yields for the formation of morpholines and oxazepanes prepared according to Scheme 1

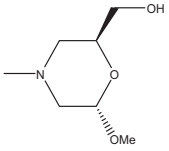
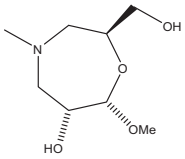
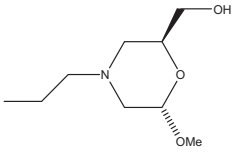
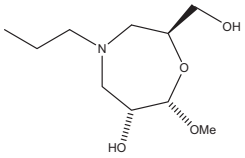
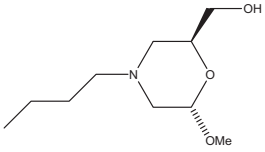
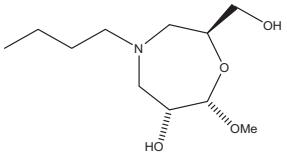
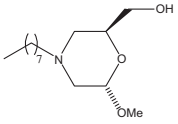
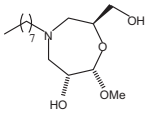
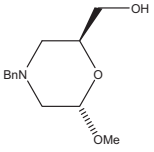
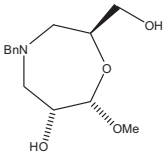
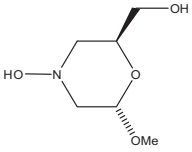
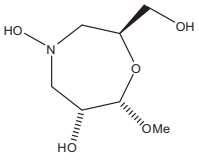
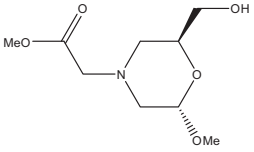
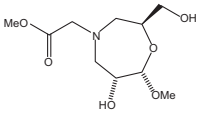
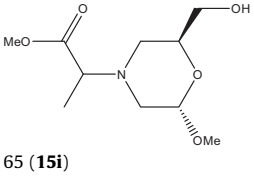
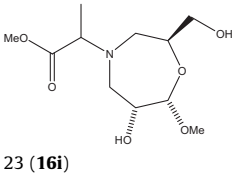
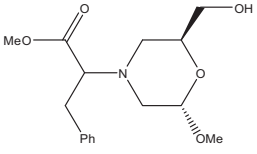
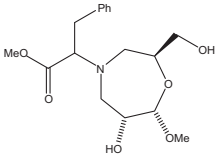
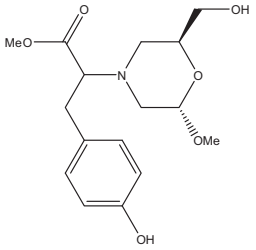
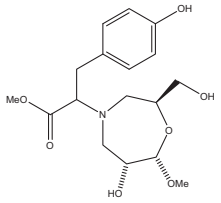
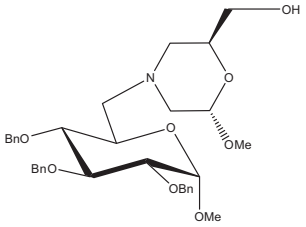
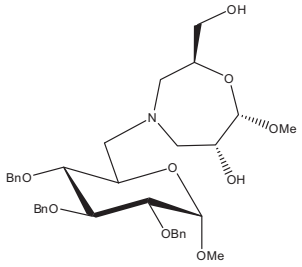
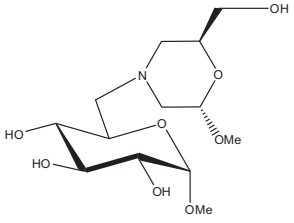
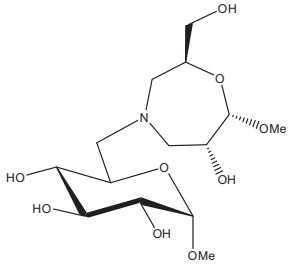
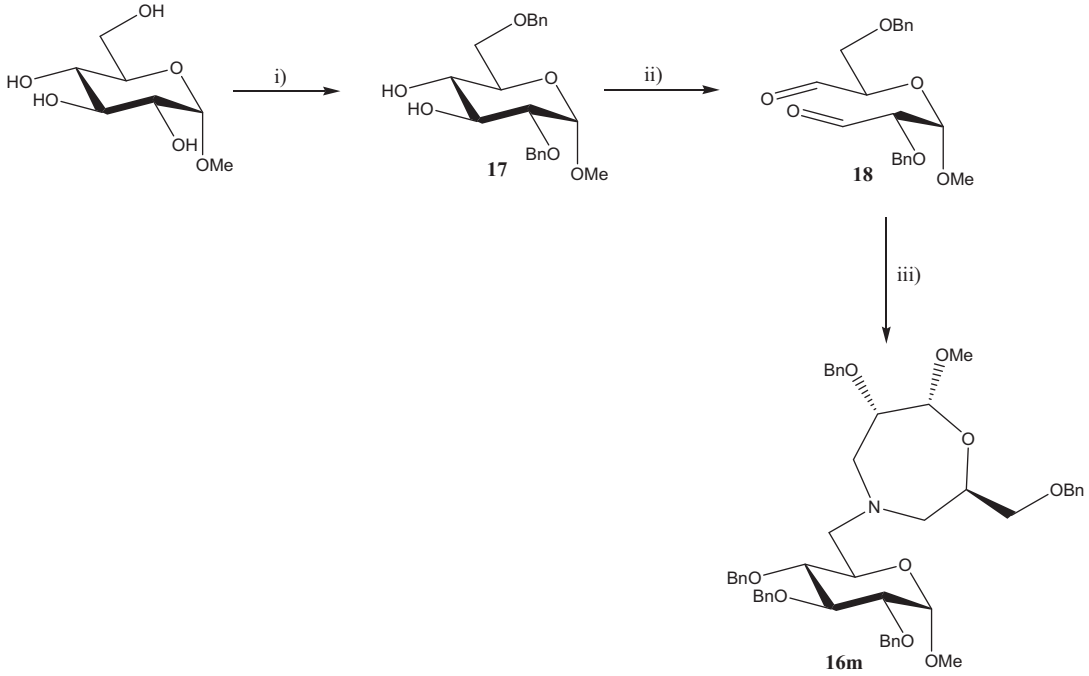
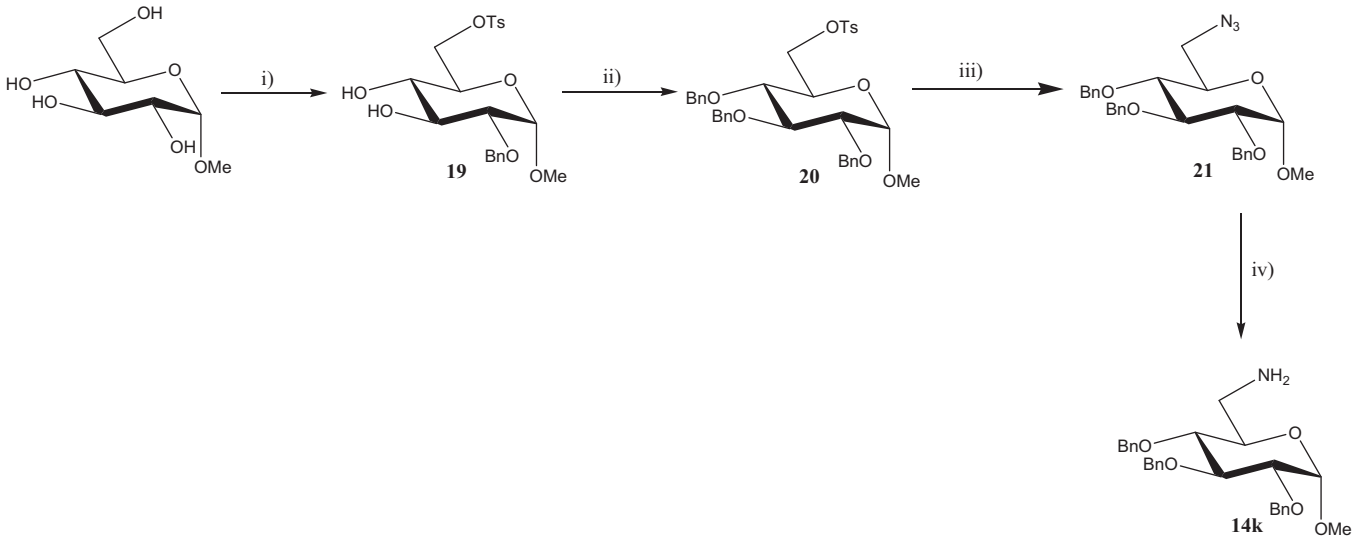
Amine	Morpholine, yield	Oxazepane, yield
$MeNH_2$ (**14a**)	25 (**15a**) 	0 (**16a**) 
$PrNH_2$ (**14b**)	35 (**15b**) 	42 (**16b**) 
$BuNH_2$ (**14c**)	70 (**15c**) 	35 (**16c**) 
$OctNH_2$ (**14d**)	25 (**15d**) 	23 (**16d**) 
$BnNH_2$ (**14e**)	84 (**15e**) 	41 (**16e**) 
NH_2OH (**14f**)	25 (**15f**) 	0 (**16f**) 
Glycine-OMe (**14g**)	31 (**15g**) 	9 (**16g**) 
Alanine-OMe (**14h**)	47 (**15h**) 	11 (**16h**) 
Phenyalanine-OMe (**14i**)	65 (**15i**) 	23 (**16i**) 

Table 1 (*continued*)

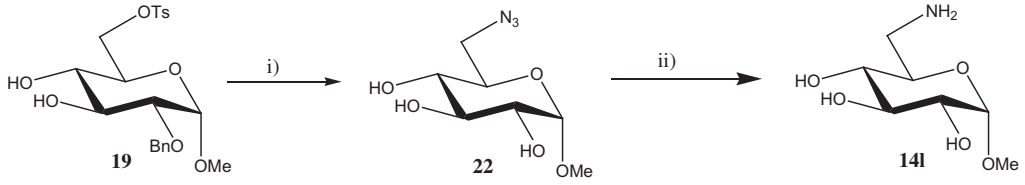
Amine	Morpholine, yield	Oxazepane, yield
Tyrosine-OMe (**14j**)	70 (**15j**) 	13 (**16j**) 
Methyl glucopyranoside amine (**14k**)	34 (**15k**) 	31 (**16k**) 
Methyl glucopyranoside amine (**14l**)	24 (**15l**) 	0 (**16l**) 



Scheme 4. Reagents and conditions: (i) (a) Bu_2SnO, toluene, reflux, o/n; (b) BnBr, toluene, reflux o/n, 66%; (ii) $NaIO_4$ (5 equiv), MeOH, H_2O, 22.5 h; (iii) (**14k**), $NaCNBH_3$, MeOH, 2 M HCl, rt, 18 h, 72% over steps (ii) and (iii).



Scheme 5. Reagents and conditions: (i) TsCl, pyr., 0 °C, 8 h, 51%; (ii) NaH (60% in mineral oil), BnBr, DMF, 0 °C–rt, o/n, 100%; (iii) NaN_3, DMF, ~85 °C, 6 h, 81%; (iv) b) Raney Ni (50%), H_2, THF, rt, o/n, 92%.



Scheme 6. Reagents and conditions: (i) NaN_3, DMF, reflux, 3 h, 63%; (ii) Raney Nickel (50%), H_2, MeOH, o/n, 100%.

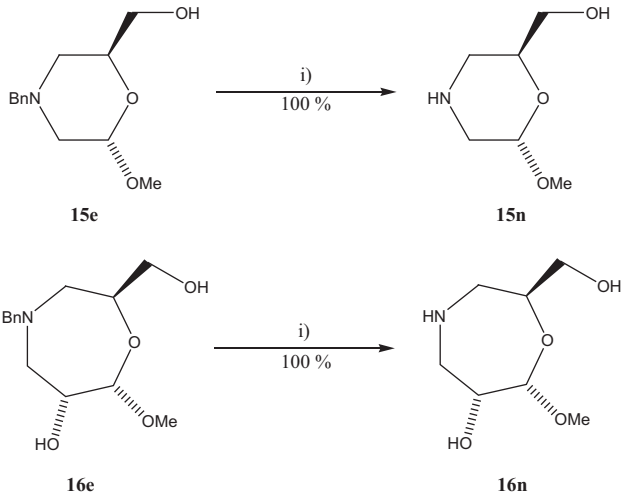
more selective inhibition of specific glycosidases compared with their monosaccharide counterparts.[25]

From Table 1 it is evident that the methodology generally proved more effective for entry to the morpholines than to the oxazepanes. In some cases no oxazepane could be isolated from the reaction mixtures, due to the formation of complex mixtures of products. Whilst it is acknowledged that the yields were generally only moderate, preparation of the derivatives in one pot, from commercially available starting materials (except for amines **14k** and **14l**, vide infra), allowed rapid entry to the targets for enzyme inhibitory studies. Effort was made to optimise the synthetic component of this programme, thus an alternative approach was developed for entry to oxazepanes, that used the C-2, C-6-di-*O*-Bn protected dialdehyde (**18**) derived from diol (**17**) in the reductive amination approach (Scheme 4). Yields were significantly increased for the key reductive amination protocol using dialdehyde (**18**), for example when amine (**14k**) was utilised the yield of oxazepane (**16m**) was increased to 72%. However, whilst this approach does offer scope for future development, the original methodology outlined in Scheme 3 was used in preference in this programme, due to its flexibility to afford rapid one pot entry to the required derivatives.

The only amines used within the methodology that required synthesis were amines (**14k**) and (**14l**); these were prepared according to Schemes 5 and 6. Thus the tri-*O*-benzyl protected amine (**14k**) was prepared by reduction of azide (**21**) using Raney nickel catalysis. The azide was itself prepared via displacement of the tosylate within (**20**) with sodium azide and all of these transformations proceeded smoothly with good synthetic yields.

For access to amine (**14l**), the requirement for protecting group strategies was eliminated by using tosylate (**19**). This offered an obvious advantage in terms of the number of steps required to prepare amine (**14l**), and also afforded a better overall conversion yield. Thus the azide (**22**) was again prepared by displacement of the tosylate within (**19**). Reduction of the azide functional group of (**22**) using Raney nickel in methanol for 18 h afforded amine (**14l**) in quantitative yield.

When amines (**14k**) and (**14l**) were utilized in the reductive amination protocol, better yields of morpholines and oxazepanes were afforded using amine (**14k**). However, deprotection of the morpholine and oxazepane targets (**15k**) and (**16k**) was necessary prior to enzyme inhibition studies. Whilst this could be achieved in quantitative yield using hydrogenation in the presence of a palladium hydroxide catalyst, this again introduced an additional synthetic step, which was considered to be undesirable. For future



Scheme 7. Reagents: (i) $Pd(OH)_2/C$, H_2, MeOH.

studies, the utilization of amine (**14l**) would therefore be considered beneficial compared to the utilization of amine (**14k**).

In order to fully probe the importance of an *N*-alkyl group for enzyme inhibition, the *N*-benzyl derivatives (**15e**) and (**16e**) were also deprotected to afford morpholine (**15n**) and oxazepane (**16n**) using hydrogenolysis in the presence of $Pd(OH)_2/C$ (Scheme 7). This completed the synthetic part of the programme.

2.2. Assessing the glycosidase inhibitory properties of the morpholines and oxazepanes

Having prepared a broad range of morpholines and oxazepanes, the inhibitory properties of these derivatives were next assessed using a panel of glycosidase enzymes that are associated with a range of disease processes. Thus the panel of enzymes consisted of α- and β-glucosidases, which are involved in Gaucher's disease,[26] Pompe's disease[27] as well as diabetes[6b] and HIV;[28] α- and β-mannosidase enzymes which are anticancer targets, with specific involvement in metastasis and tumour progression;[29] α- and β-galactosidase enzymes which are implicated in Krabbe's disease[30] and GM1 gangliosidosis,[31] respectively; α-fucosidase and naringinase enzymes which are targets for developing treatments for liver and colorectal cancers;[32] *N*-acetyl-β-glucosaminidase and *N*-acetyl-β-hexoaminidase which can be targeted towards treatment of breast cancer.[33] The inhibitory profiles were determined based upon the enzymatic cleavage of *para*-nitrophenol from the respective *para*-nitrophenyl-D-pyranoside. Summarised in Tables 2 and 3 are the results of the inhibition studies using the morpholines (**15a**)–(**15n**), and the oxazepanes (**16b**)–(**16n**), respectively.

In general, from Tables 2 and 3, it can be seen that the morpholine derivatives afforded better inhibition of a wider range of enzymes than the oxazepanes. Thus a range of morpholine inhibitors were identified for the α-D-glucosidase enzymes (for example (**15a**,**15b**,**15f**,**15l**)), the *N*-acetyl-β-D-glucosaminidase enzyme (Bovine kidney) (for example (**15c**,**15f**,**15l**,**15n**)) and the β-D-galactosidase enzyme (Bovine kidney) (all morpholines analysed). In contrast, *N*-alkyl oxazepanes (**15b**) and (**15c**) showed modest inhibition against β-D-galactosidase (Bovine kidney) and *N*-acetyl-β-glucosaminidase (Bovine kidney). Whilst many of the compounds demonstrated weak inhibition of a range of the enzymes analysed, for the purposes of further analysis, inhibition of less than 40% at 1 mg/ml was considered insufficient to warrant further analysis. Where inhibition was greater than this, as highlighted in Tables 2 and 3, further studies were performed to establish IC_{50} and K_i values, as well as to establish the mechanism of inhibition, via Lineweaver–Burk analysis. These established that morpholine (**15a**) shows moderate inhibition against β-D-galactosidase (IC_{50} 88.6 μM, K_i = 126 μM) and acts as a non-competitive inhibitor (Fig. 7).

Morpholines (**15b–15d**) also showed good inhibition against β-D-galactosidase with IC_{50} values of 75.5 μM, 70.3 μM and 55.1 μM, respectively. These compounds were also determined to act as non-competitive inhibitors. Compound (**15f**) shows good inhibition against β-D-galactosidase (IC_{50} = 30.6 μM, K_i = 20.2 μM) where it shows non-competitive inhibition (Fig. 8) and also against α-D-glucosidase where stronger inhibition is seen against α-D-glucosidase from *S. cerevisiae* than for the other two glucosidases (*B. stearothermophilus* and Rice (*O. sativa*)).

Compound (**15f**) also inhibits *N*-acetyl-β-D-glucoaminidase (Bovine kidney). Finally, disaccharide analogue (**15l**) shows excellent inhibition of α-D-glucosidase from *S. cerevisiae* and *B. stearothermophilus*. Comparing the inhibitory properties of the disaccharide analogue (**15l**) with that of the N-unsubstituted morpholine

Table 2
Inhibitory activity of compounds (**15a**)–(**15n**) towards glycosidases[a]

Enzyme	% Inhibition										
	(**15a**)	(**15b**)	(**15c**)	(**15d**)	(**15f**)	(**15g**)	(**15h**)	(**15i**)	(**15j**)	(**15l**)	(**15n**)
α-D-Glucocosidase (*S. cerevisiae*)	24	8	NI	NI	**58**	NI	NI	NI	NI	**77**	NI
α-D-Glucosidase (*B. stearothermophilus*)	NI	9	NI	NI	NI	NI	NI	NI	NI	**66**	NI
α-D-Glucosidase Rice (*O. sativa*)	NI	NI	NI	NI	29	NI	NI	NI	NI	NI	NI
β-D-Glucosidase Almond (*Prunus* sp.)	NI	NI	NI	NI	NI	NI	NI	NI	NI	28	4
α-D-Mannosidase Jack bean (*C. ensiformis*)	NI	NI	NI	NI	NI	NI	ND	ND	ND	NI	NI
β-D-Mannosidase (*Cellullomonas fimi*)	NI	NI	NI	6	NI	NI	NI	NI	NI	33	5
N-Acetyl-β-D-glucosaminidase Bovine kidney	NI	NI	8	NI	**72**	NI	NI	NI	NI	11	10
α-D-Galactosidase Green coffee beans (*Coffea*)	NI	NI	NI	NI	NI	NI	NI	NI	NI	31	NI
β-D-Galactosidase Bovine kidney	**48**	**54**	**45**	**51**	**82**	36	14	5	12	**50**	27
Naringinase *P. decumbens*	NI	9	7	NI	NI	NI	NI	NI	NI	11	9.0

Results in bold are deemed significant.
[a] % of inhibition at 1 mg/ml concentration, optimal pH and 28 °C, NI = no significant inhibition. ND = not determined.

Table 3
Inhibitory activity of oxazepanes towards glycosidases[a]

Enzyme	% Inhibition										
	(**16b**)	(**16c**)	(**16d**)	(**16e**)	(**16f**)	(**16g**)	(**16h**)	(**16i**)	(**16j**)	(**16k**)	(**16n**)
α-D-Glucosidase (*S. cerevisiae*)	10	8	NI	NI	NI	NI	NI	NI	NI	NI	NI
α-D-Glucosidase (*B. stearothermophilus*)	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	8
α-D-Glucosidase Rice (*O. sativa*)	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
β-D-Glucosidase Almond (*Prunus* sp.)	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
α-D-Mannosidase Jack bean (*C. ensiformis*)	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
β-D-Mannosidase (*Cellullomonas fimi*)	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
N-Acetyl-β-D-glucosaminidase Bovine kidney	25	32	ND	ND	ND	ND	NI	NI	NI	NI	9
α-D-Galactosidase Green coffee beans (*Coffea*)	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	6
β-D-Galactosidase Bovine kidney	32	23	NI	NI	NI	NI	NI	NI	NI	NI	16
Naringinase *P. decumbens*	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

Results in bold are deemed significant.
[a] % of inhibition at 1 mg/ml concentration, optimal pH and 28 °C, NI = no inhibition, ND = not determined.

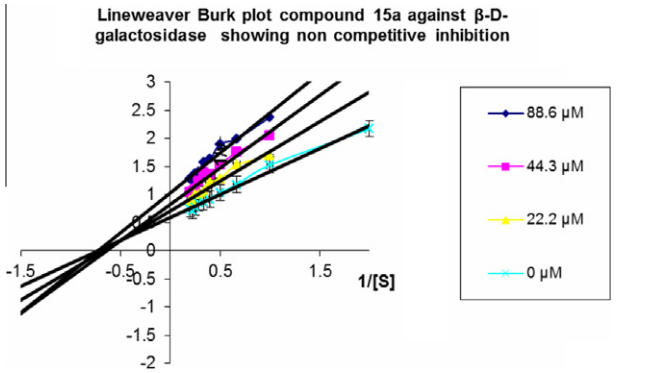


Figure 7. Lineweaver Burk plot of compound (**15a**) showing non competitive inhibition.

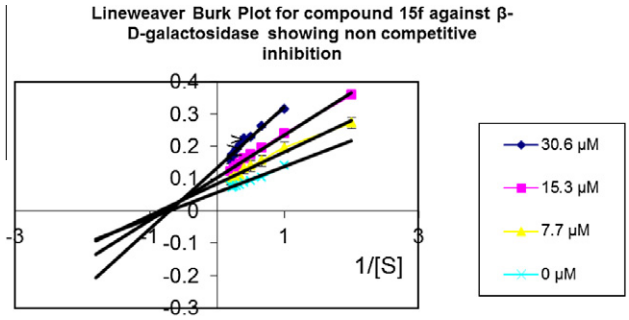


Figure 8. Lineweaver Burk plot of compound (**15f**) showing non competitive inhibition.

(**15n**) illustrates that (**15l**) offers selective inhibition of α-D-glucosidase.

3. Conclusion

In conclusion, within this study libraries of morpholines and oxazepanes have been prepared and the abilities of these derivatives to inhibit a wide range of glycosidase enzymes have been probed. As a result of the observations above it is possible to propose some preliminary structure activity relationships, to summarise the inhibitory properties of the compounds analysed. In general, better inhibitory profiles are displayed against a panel of glycosidase enzymes by morpholines compared with oxazepanes. Moreover, substitution at the nitrogen atom within the morpholine generally leads to improved inhibition of the β-D-galactosidase enzyme derived from Bovine kidney. For example, when *N*-alkyl substituents are introduced, greater inhibition of this β-D-galactosidase enzyme is obtained for higher homologues, thus *N*-octyl morpholine (**15d**) afforded a lower IC_{50} value than *N*-methyl morpholine (**15a**). The introduction of an additional hydroxyl group, within morpholine derivative (**15f**), is also well tolerated with this affording the lead inhibitor of the β-D-galactosidase enzyme, from within this programme. Since β-galactosidase is an enzyme involved in the lysosomal storage disorder GM1 gangliosidosis,[34] it would be pertinent to extend this study to encompass a wider range of β-galactosidase enzymes. Introduction of additional ester functional groups, or aromatic side chains, through the incorporation of amino acid derivatives within the synthetic programme did not afford strong inhibitors of any of the enzymes analysed. However, incorporation of additional hydroxyl groups within the inhibitors, through the use of carbohydrate derived amines did prove beneficial, particularly for the selective inhibition of α-D-glucosidase (*B. stearothermophilus)* and β-D-galactosidase enzyme (Bovine kidney) as shown by (**15l**). Given the general ability of a range of derivatives to inhibit the β-D-galactosidase enzyme (Bovine kidney), some structure–activity relationship guidelines are summarised in Figure 9.

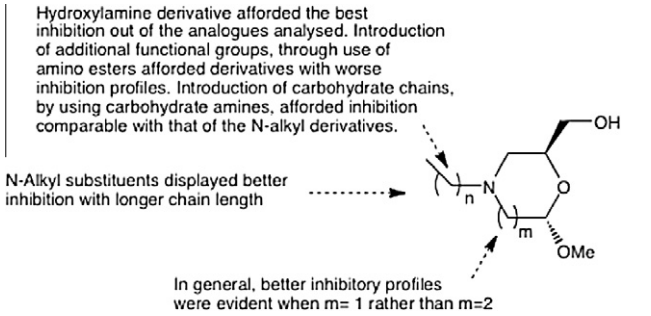


Figure 9. Structure–activity relationships for inhibition of the β-D-galactosidase enzyme (Bovine kidney) using morpholine derivatives.

4. Experimental

Melting points were obtained using an Electrothermal digital melting point apparatus.

Specific rotation measurements were measured using a Perkin Elmer 341 polarimeter. Solutions were made using $CHCl_3$ or MeOH and measurements were taken at a wavelength of 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1720-X FT-IR spectrometer. Liquid samples were placed as thin films between sodium chloride plates. Absorption maxima frequencies are measured in wavenumbers (cm^{-1}). The following abbreviations are used to report the degree of absorption: s (strong), m (medium), w (weak), br (broad).

All ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-250 spectrometer or a Bruker AMX-400 spectrometer using $CDCl_3$ or CD_3OD as an internal standard. ^1H NMR spectra were recorded at 250 MHz or 400 MHz and chemical shifts (δ_H values) are quoted in units of parts per million (ppm). The following abbreviations are used: s (singlet), d (doublet), t (triplet), app. t (apparent triplet), dd (double doublet), dt (double triplet), ddd (double double doublet) and quin (quintet). Coupling constants (*J* values) are measured in hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 63 MHz or 101 MHz using $CDCl_3$ as an internal standard and chemical shifts (δ_C values) are quoted in units of ppm.

High resolution mass spectrometric data were recorded on a Hewlett Packard Series 1050 spectrometer for chemical ionisation (CI) or electron impact ionisation (EI) or a Bruker MicroTof LC TOF MS for electrospray ionisation (ESI). Molecular ions and molecular ion fragments are reported as mass/charge (*m/z*) ratios.

Flash chromatography was performed on Silica Gel 60 (Merck or Fisher) using head pressure by means of compressed air or bellows. TLC analysis was performed using Merck silica 60 F_{254} aluminium backed plates of 0.2 mm depth. Compounds were visualised on TLC plates using UV light (λ = 254 nm) or using an ethanol/sulfuric acid dip (25:1), phosphomolybdic acid (20% ethanol), vanillin or ninhydrin spray.

All chemicals and solvents were obtained from Aldrich, Fisher Scientific or Lancaster and used as required. Anhydrous solvents were used as bought and glassware oven-dried prior to use. Experimental procedures were carried out under an argon atmosphere when an inert atmosphere was required.

4.1. General method for access to morpholines

4.1.1. Step 1: Synthesis of dialdehyde

A solution of sodium periodate (5 equiv) in distilled water was added dropwise to a stirred solution of methyl α-D-glucopyranose (1 equiv) in methanol at 0 °C, and the reaction mixture stirred at room temperature for 15 h. The reaction mixture was concentrated in vacuo and the resulting colourless solid suspended in ethyl acetate, filtered through Celite® and concentrated in vacuo to yield the crude dialdehyde.

4.1.2. Step 2. Reductive amination reaction to afford morpholines

Sodium cyanoborohydride (5 equiv) was added to a stirred solution of the amine (1 equiv), dialdehyde (3 equiv), and 10 Å molecular sieves in methanol. The pH of the reaction mixture was adjusted to 7 with 2 M HCl (soln in Et_2O). After stirring for 24 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was partitioned between H_2O and ethyl acetate, the organic layer was extracted and the aqueous phase washed with ethyl acetate (4 × 80 ml) and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography to yield the morpholines.

4.1.3. 6-Methoxy-4-methyl-morpholin-2-yl-methanol, 15a

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded morpholine **15a** in 25% yield as a yellow oil; $[\alpha]_D^{20}$ +88.4 (*c* 0.90, MeOH); ν_{max} (thin film) 3459 (O–H), 2941 (C–H), 2346, 1647, 1451 (C–N), 1133 (C–O–C), 1052 (C–O) cm^{-1}; ^1H NMR (250 MHz; CD_3OD) 2.14 (3H, s, NCH_3), 2.28 (1H, dd, *J* = 2.5, 12.0 Hz, H-5), 2.53 (1H, dd, *J* = 1.0, 12.0 Hz, H-5), 3.18 (3H, s, OCH_3), 3.43–3.50 (4H, m, 2 × H-3, 2 × H-7), 3.91–3.94 (1H, m, H-2), 4.52 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (63 MHz; CD_3OD) 44.10 ($RNCH_3$), 54.20 (C-5), 55.75 (OCH_3), 62.95 (C-3)(C-7), 70.26 (C-2), 98.22 (C-6); *m*/*z* (CI) M^+ requires 161.1053. Found 161.1052.

4.1.4. 6-Methoxy-4-propyl-morpholin-2-yl-methanol, 15b

The general procedure for the synthesis of morpholines with purification by column chromatography (10:1 EtOAc–MeOH) afforded **15b** as a yellow oil in 35% yield; $[\alpha]_D^{20}$ +127.0 (*c* 1.35, MeOH); ν_{max} (thin film) 3428 (O–H), 2924 (C–H), 2526, 1650, 1454 (C–N), 1126, (C–O–C), 1043 (C–O) cm^{-1}; ^1H NMR (250 MHz; CD_3OD) 0.92 (3H, t, *J* = 7.5 Hz, H-10), 1.54 (3H, sextet, *J* = 7.5 Hz, H-9), 1.96 (1H, t, *J* = 11.0 Hz, H-3), 2.14 (1H, dd, *J* = 2.5, 9.0 Hz, H-5), 2.24–2.32 (2H, m, H-8), 2.88 (2H, app t, *J* = 12.0 Hz, H-3, H-5), 3.40 (3H, s, OCH_3), 3.52 (1H, dd, *J* = 5.0, 11.5 Hz, H-7), 3.57 (1H, dd, *J* = 5.0, 11.5 Hz, H-7), 3.98 (1H, dtd, *J* = 2.0, 5.0, 11.0 Hz, H-2), 4.71 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (63 MHz; CD_3OD) 12.60 (C-10), 20.47 (C-9), 55.36 (OCH_3), 56.40 (C-3), 57.21 (C-5), 62.56 (C-8), 64.76 (C-7), 70.43 (C-2), 98.60 (C-6); *m*/*z* (CI) M^+ requires 189.1365. Found 189.1372.

4.1.5. 6-Methoxy-4-Butylmorpholin-2-yl-methanol, 15c

The general procedure for the synthesis of morpholines purification by column chromatography (10:1 EtOAc–MeOH) afforded **15c** as a yellow oil in 70% yield; $[\alpha]_D^{20}$ +59.2 (*c* 0.90, MeOH); ν_{max} (thin film) 3411 (O–H), 2931 (C–H), 2335, 1650, 1455 (C–N), 1367, 1135 (C–O–C), 1053 (C–O) cm^{-1}; ^1H NMR (250 MHz; CD_3OD) 0.72 (3H, t, *J* = 7.0 Hz, H-11), 1.07–1.16 (2H, m, H-10), 1.26–1.32 (2H, m, H-9), 1.80 (1H, t, $J_{3-2} = J_{3-3}$ = 11.0 Hz, H-3), 1.98 (1H, dd, J_{5-6} = 2.5 Hz, J_{5-5} = 12.0 Hz, H-5), 2.10–2.19 (2H, m, H-8), 2.69 (2H, t, *J* = 12.0 Hz, H-3, H-5), 3.17 (3H, s, OCH_3), 3.33 (2H, app d, = *J* 5.0 Hz, H-7), 3.75 (1H, dtd, *J* = 2.3, 5.0, 7.3 Hz, H-2), 4.51 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (63 MHz; CD_3OD) 14.76 (C-11), 22.12 (C-10), 29.31 (C-9), 55.41 (OCH_3), 56.23 (C-3), 57.06 (C-5), 60.32 (C-8), 64.65 (C-7), 70.25 (C-2), 98.46 (C-6); *m*/*z* (CI) M^+ requires 203.1512. Found 203.1513.

4.1.6. 6-Methoxy-4-octylmorpholin-2-yl-methanol, 15d

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded **15d** as a yellow oil in 25% yield; $[\alpha]_D^{20}$ +146.7 (*c* 0.55, MeOH); ν_{max} (thin film) 3401 (O–H), 2925 (C–H), 1629, 1448 (C–N), 1362, 1137 (C–O–C), 1049 (C–O); ^1H NMR (250 MHz, CD_3OD) 0.92 (3H, t, *J* = 6.6 Hz, H-15), 1.29 (10H, s, H-14, H-13, H-12, H-11, H-10), 1.52 (2H, quin, *J* = 7.5 Hz, H-9), 1.95 (1H, t, *J* = 11.5 Hz, H-3), 2.15 (1H, dd, *J* = 2.5, 11.5 Hz, H-5), 2.24–2.39 (2H, m, H-8), 2.88 (2H, t, *J* = 11.5 Hz, H-3, H-5), 3.39 (3H, s, OCH_3), 3.51 (1H, dd, *J* = 5.0, 11.5 Hz, H-7), 3.58 (1H, dd, *J* = 5.0, 11.5 Hz, H-7), 3.97 (1H, dtd, J_{2-3} = 2.5, 5.0, 11.0 Hz, H-2), 4.70 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (63 MHz, CD_3OD) 14.91 (C-15), 24.15, 29.09, 30.83, 31.06, 33.43 (5 × CH_2), 27.34 (C-9), 55.36 (OCH_3), 56.43 (C-3), 57.26 (C-5), 60.70 (CH_2), 64.77 (C-7), 70.44 (C-2), 98.62 (C-6); *m*/*z* (CI) M^+ requires 259.2147. Found 259.2134.

4.1.7. (4-*N*-Benzyl-(6*S*)-methoxy-morpholin-(2*S*)-yl)-methanol (15e)

The general procedure for the synthesis of morpholines with purification by column chromatography (2% MeOH in CH_2Cl_2) afforded **15e** as a golden syrup in 84% yield. $[\alpha]_D^{20}$ +96.1 (*c* 1.0, $CHCl_3$) (lit.[17a] +91.5 (*c* 1.0, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 3418 (br, s, OH), 2908 (s, CH), 2825 (s, CH), 1057 (s, C–O), 737 (s, CH (arom)); δ_H (250 MHz; $CDCl_3$) 2.08 (1H, app. t, *J* 11.0, C(3)H), 2.24 (1H, dd, *J* 11.5, 3.0, C(5)H), 2.73 (1H, dd, *J* 11.0, 2.0, C(3′)H), 2.85 (1H, dd, *J* 12.0, 2.0, C(5′)H), 3.41 (1H, s, OCH_3), 3.48 (1H, d, *J* 13.0, NCH_2Ph), 3.52–3.64 (3H, m, C(7)H, NCH_2Ph), 4.04–4.09 (1H, m, C(2)H), 4.72 (1H, d, *J* 1.5, C(6)H), 7.23–7.33 (5H, m, Ph); δ_C (63 MHz; $CDCl_3$) 54.0 (C5), 55.6 (OCH_3), 56.0 (C3), 63.7 (NCH_2Ph), 64.5 (C7), 69.3 (C6), 97.7 (C2), 127.7–129.9 (ArC), 137.0 (ArC); *m*/*z* (CI) 238 ($[M+H]^+$, 96%), 237 ($[M]^+$, 100%), 206 (81), 205 (51), 176 (43). Found $[M]^+$ 237.1367, $C_{13}H_{19}NO_3$ requires 237.1365.

4.1.8. 2-Hydroxymethyl-6-methoxy-morpholin-4-ol, 15f

The general procedure for the synthesis of morpholines with purification by column chromatography (10:1 EtOAc–MeOH) afforded **15f** as a yellow oil in 25% yield; $[\alpha]_D^{20}$ +61.4 (*c* 0.44, MeOH); ^1H NMR (400 MHz, CD_3OD) 1.57 (1H, t, *J* = 11.0 Hz, H-3), 1.72 (1H, dd, *J* = 2.5, 11.0 Hz, H-5), 2.38 (2H, app t, *J* = 11.0 Hz, H-3, H-5), 2.63 (3H, s, OCH_3), 2.71–2.74 (2H, m, H-7), 3.10–3.19 (1H, m, H-5), 3.82 (1H, t, *J* = 2.5 Hz, H-1); ^{13}C NMR (100 MHz, CD_3OD) 46.0 (C-3), 47.6 (C-5), 54.9 (OCH_3), 63.8 (C-7), 69.2 (C-2), 97.4 (C-6); *m*/*z* (CI) $[M+H]^+$ requires 164.0845. Found 164.0921.

4.1.9. 2-Hydroxymethyl-6-methoxymorpholin-4-yl acetic acid methyl ester, 15g

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded **15g** as a clear oil in 31% yield; $[\alpha]_D^{20}$ +96.1 (*c* 1.00, MeOH); ν_{max} (film) 3421 (O–H), 2079, 1736, 1644, 1552, 1394 (C–N), 1289, 1223 (C–O–C), 1052 (C–O); ^1H NMR (400 MHz, CD_3OD) 2.35 (1H, t, *J* = 11.0 Hz, H-3), 2.56 (1H, dd, *J* = 2.5, 11.5Hz, H-5), 2.88 (1H, dd, *J* = 2.0, 11.0 Hz, H-3), 2.94 (1H, dd, *J* = 1.0, 11.5 Hz, H-5), 3.30 (2H, d, *J* = 7.0 Hz, H-8), 3.42 (3H, s, OCH_3), 3.55 (1H, dd, *J* = 5.5, 11.5 Hz, H-7), 3.59 (1H, dd, *J* = 5.5, 11.5 Hz, H-7), 3.73 (3H, s, $COCH_3$), 4.03 (1H, dtd, *J* = 2.5, 5.5, 11.0 Hz, H-2), 4.73 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (100 MHz, CD_3OD) 52.00 ($COOCH_3$) 54.80 (C-3), 55.00 (OCH_3), 55.90 (C-5), 59.20 (C-8), 64.20 (C-7), 69.90 (C-2), 98.10 (C-6), 171.7 ($COOCH_3$); *m*/*z* (CI) M^+ requires 219.1107. Found 219.1094.

4.1.10. 2-(2-Hydroxymethyl-6-methoxymorpholin-4-yl)-propionic acid methyl ester, 15h

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded **15h** as a clear oil in 47% yield; $[\alpha]_D^{20}$ +65.5 (*c* 1.00, MeOH); ν_{max} (thin film) 3447 (O–H), 1710, 1644, 1552, 1408 (C–N), 1276, 1144 (C–O–C), 1052 (C–O); ^{1}H NMR (250 MHz, CD_3OD) 1.07 (3H, d, *J* = 7.5 Hz, H-9), 2.14 (1H, t, *J* = 11.5 Hz, H-3), 2.32 (1H, dd, *J* = 2.5, 11.5 Hz, H-5), 2.63 (2H, t, *J* = 11.5 Hz, H-3, H-5), 3.11 (1H, m, H-8), 3.18 (3H, s, OCH_3), 3.29–3.37 (2H, m, H-7), 3.49 (3H, s, $COOCH_3$), 3.77 (1H, dtd, *J* = 2.0, 5.0, 11.5 Hz, H-2), 4.49 (1H, d, *J* = 2.5 Hz, H-6); ^{13}C NMR (63 MHz, CD_3OD) 15.36 (C-9), 51.80 (C-5), 52.29 (C-3), 55.41 ($COOCH_3$), 63.81 (C-8), 64.63 (C-7), 70.84 (C-2), 98.68 (C-6), 174.77 ($COOCH_3$); *m*/*z* (CI) M ($C_{10}H_{17}NO_5$) requires 233.1263. Found 233.1262.

4.1.11. 2-(2-Hydroxymethyl-6-methoxymorpholin-4-yl)-9-phenyl propionic acid methyl ester, 15i

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded **15i** as a clear oil in 65% yield; $[\alpha]_D^{20}$ +67.0 (*c* 1.00, MeOH); ν_{max} (thin film) 3395 (O–H), 2973 (C–H), 2000, 1736, 1631, 1394 (C–N), 1210 (C–O–C), 1026 (C–O); ^{1}H NMR (250 MHz, CD_3OD) 2.35 (1H, t, *J* = 11.0 Hz, H-3), 2.57 (1H, dd, *J* = 2.5, 11.5 Hz, H-5), 2.88–3.07 (4H, m, H-3, H-5, H-9), 3.41 (4H, m, H-8, OCH_3), 3.52–3.55 (5H, m, H-7, $COOCH_3$), 3.99 (1H, dtd, *J* = 2.5, 5.0, 11.0 Hz, H-2), 4.72 (1H, d, *J* = 2.5Hz, H-6), 7.15–7.29 (5H, m, Ar-H); ^{13}C NMR (63 MHz, CD_3OD) 36.86 (C-3), 51.98 (OCH_3), 52.04 (C-5), 55.02 (C-9), 55.52 (C-8), 64.59 (C-7), 71.05 (C-2), 71.39 ($COOCH_3$) 98.75 (C-6), 128.06–130.76 (Ar-C), 173.10 ($COOCH_3$); *m*/*z* (CI) $[M+H]^+$ requires 310.1654. Found 310.1653.

4.1.12. 2-(2-Hydroxymethyl-6-methoxymorpholin-4-yl)-9-(4-hydroxyphenyl)-propionic acid methyl ester, 15j

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded **15j** as a clear oil in 70% yield; $[\alpha]_D^{20}$ +65.6 (*c* 1.00, MeOH); ν_{max} (thin film) 3395 (O–H), 2315, 1736, 1210 (C–O–C), 1000 (C–O); ^{1}H NMR (250 MHz, CD_3OD) 2.09 (1H, t, *J* = 11.0 Hz, H-3), 2.33 (1H, dd, *J* = 2.5, 12.0 Hz, H-5), 2.60–2.77 (4H, m, H-3, H-5, H-9), 3.10–3.12 (1H, m, H-8), 3.18 (3H, s, OCH_3), 3.28–3.32 (5H, m, $COOCH_3$, H-7) 3.77 (1H, m, H-2), 4.49 (1H, app s, H-6), 6.42–6.48 (2H, m, H-11), 6.76–6.80 (2H, m, H-12); ^{13}C NMR (63 MHz, CD_3OD) 36.00 (C-9), 51.91 ($COOCH_3$), 52.09 (C-5), 54.96 (C-3), 55.46 (OCH_3), 64.56 (C-7), 70.98 (C-2), 71.74 (C-9), 98.75 (C-6), 116.55–131.66 (Ar-C), 157.55 (C-13), 173.33 ($COOCH_3$); *m*/*z* (CI) $[M+H]^+$ requires 326.1603. Found 326.1602.

4.1.13. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-((6*S*)-methoxy-(2*S*)-hydroxymethyl-morpholin-4-yl)-α-D-glucopyranoside (15k)

The general procedure for the synthesis of morpholines with purification by column chromatography (EtOAc) afforded (**15k**) as a yellow oil in 34% yield; $[\alpha]_D^{20}$ +63.7 (*c* 1.0, $CHCl_3$) (lit.[17a] +61.5 (*c* 1.0, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 3466 (m, OH), 2916 (m, CH), 1497 (m, C=C (arom)), 1453 (m, C=C (arom)), 1054 (s, C–O), 738 (s, CH (arom)), 697 (s, CH (arom)); δ_H (400 MHz, $CDCl_3$) 2.22 (1H, t, *J* = 11.0 Hz, H-3a), 2.39 (1H, dd, *J* = 11.52.5 Hz, H-5), 2.50 (1H, dd, *J* = 14.0, 7.5 Hz, H-6), 2.70 (1H, d, *J* = 13.5Hz, H-6′), 2.81 (1H, d, *J* = 11.0Hz, H-3a′), 2.86 (1H, d, *J* = 11.5 Hz, H-5a′), 3.33 (1H, dd, *J* = 10.0, 9.0 Hz, H-4), 3.37 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.47 (1H, dd, *J* = 9.5, 3.5 Hz, H-2), 3.55 (1H, dd, *J* = 11.5, 6.0 Hz, H-7a), 3.65 (1H, dd, *J* = 11.5, 3.5 Hz, H-7a′), 3.85–3.89 (1H, m, H-5), 3.97 (1H, t, *J* = 9.5 Hz, H-3), 4.01–4.03 (1H, m, H-2a), 4.54 (1H, d, *J* = 3.5 Hz, H-1), 4.64–4.67 (3H, m, H-6a, OCH_2Ph), 4.79 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.80 (1H, d, *J* = 10.5 Hz, OCH_2Ph), 4.91 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.97 (1H, d, *J* = 10.5Hz, OCH_2Ph), 7.24–7.49 (15H, m, Ph); δ_C (101 MHz; $CDCl_3$) 54.6 (C-3a), 55.0 (OCH_3), 55.8 (OCH_3), 56.4 (C-5a), 58.6 (C-6), 64.3 (C-7a), 69.0 (C-2a), 69.5 (C-5), 73.4 (OCH_2Ph), 75.0 (OCH_2Ph), 75.9 (OCH_2Ph), 79.6 (C-4), 80.0 (C-2), 82.1 (C-3), 97.3 (C-6a), 98.0 (C-1), 127.7–128.5 (ArC), 138.2–138.7 (ArC); *m*/*z* (CI) 594 ($[M+H]^+$, 74%), 502 (40), 160 (100), 148 (48), 130 (59). Found $[M+H]^+$ 594.3077, $C_{34}H_{44}NO_8$ requires 594.3067.

4.1.14. Methyl 6-deoxy-6-((6*S*)-methoxy-(2*S*)-hydroxymethyl-morpholin-4-yl)-α-D-glucopyranoside, 15l[8]

The general procedure for the synthesis of morpholines with purification by column chromatography (1:1 MeCN–H_2O) afforded (**15l**) as a colourless syrup in 24% yield; $[\alpha]_D^{20}$ +108 (*c* 0.87, MeOH) (lit.[8] +104 (*c* 0.5, MeOH)); ν_{max} (NaCl disc/cm^{-1}) 3368 (br, s, OH), 2924 (m, CH), 1194 (m, C–N), 1048 (C–O); δ_H (400 MHz, CD_3OD) 2.28 (1H, app. t, *J* = 11.0 Hz, H-3a), 2.38 (1H, dd, *J* = 12.0, 2.5 Hz, H-5a), 2.60 (1H, dd, *J* = 13.5, 7.0 Hz, H-6), 2.87 (1H, dd, *J* = 13.5, 4.5 Hz, H-6′), 2.96 (1H, d, *J* = 11.5 Hz, H-3a′), 3.17 (1H, d, *J* = 12.0 Hz, H-5a′), 3.23 (1H, dd, *J* = 9.5, 9.0 Hz, H-4), 3.40–3.44 (1H, m, H-2), 3.42 (1H, dd, *J* = 15.0, 4.0 Hz, H-2), 3.42 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.58 (2H, dd, *J* = 5.0, 3.5 Hz, H-7a), 3.65 (1H, app. t, *J* = 9.5 Hz, H-3), 3.77–3.83 (1H, m, H-5), 3.99–4.05 (1H, m, H-2a), 4.66 (1H, d, *J* = 4.0 Hz, H-1), 4.74 (1H, d, *J* = 1.5 Hz, H-6a); δ_C (101 MHz, CD_3OD) 55.0 (OCH_3), 56.2 (OCH_3), 56.9 (C-5a), 57.4 (C-3a), 61.5 (C-6), 64.2 (C-7a), 69.9 (C-5), 70.2 (C-6a), 73.3 (C-2), 74.6 (C-3), 74.9 (C-4), 98.1 (C-2a), 101.4 (C-1); *m*/*z* (ESI) 324 ($[M+H]^+$, 26%). Found $[M+H]^+$ 324.1653, $C_{13}H_{26}NO_8$ requires 324.1653.

4.1.15. ((6*S*)-Methoxy-morpholin-(2*S*)-yl)-methanol (15n)

Pd/C (65.6 mg, 10% loading) was added to a dry argon-filled flask. Compound **15e** (103 mg, 0.432 mmol) was dissolved in MeOH (4 mL) and added to the flask. TFA (0.06 mL, 0.864 mmol) was added and the reaction stirred. The flask was evacuated and a H_2 atmosphere introduced (process repeated four times). The solution was stirred overnight then filtered through Celite® and washed with MeOH. The solvent was removed in vacuo to afford (**15n**) as a syrup (156 mg, 100%). $[\alpha]_D^{20}$ +12.0 (*c* 1.1, MeOH) (lit.[17a] +9.6 (*c* 0.7, MeOH)); ν_{max} (NaCl disc/cm^{-1}) 3422 (br, s, NH, OH), 1205 (m, C–N), 1134 (m, C–O), 1052 (m, C–O); δ_H (400 MHz, CD_3CD) 3.10 (1H, dd, *J* 11.5, 1.0, C(3)H), 3.21 (1H, dd, *J* 13.0, 2.5, C(5)H), 3.29–3.31 (1H, m, C(5′)H), 3.32–3.36 (1H, m, C(3′)H), 3.49 (3H, s, OCH_3), 3.67 (2H, dd, *J* 4.5, 0.5, C(7)H), 4.13–4.18 (1H, m, C(2)H), 4.98 (1H, app. d, *J* 1.5, C(6)H); δ_C (101 MHz, CD_3CD) 45.0 (C5), 46.2 (C3), 55.2 (OCH_3), 63.0 (C7), 66.6 (C6), 95.3 (C2); *m*/*z* (CI) 148 ($[M+H]^+$, 100%), 147 ($[M]^+$, 31%), 116 (39), 115 (25). Found $[M]^+$ 148.0980, $C_6H_{13}NO_3$ requires 147.0892.

4.2. General method for access to 7-hydroxymethyl-[1,4]-oxazepanes

4.2.1. Step 1: Synthesis of dialdehyde

A solution of sodium periodate (1.2 equiv) in distilled water was added dropwise to a stirred solution of methyl α-D-glucopyranoside (1 equiv) in methanol at 0 °C. The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo. The resulting colourless solid was dissolved in ethyl acetate, filtered through Celite® and concentrated in vacuo to yield the crude dialdehyde as a clear oil.

4.2.2. Step 2: Reductive amination reactions to afford 2-hydroxymethyl-7-methoxy-[1,4]-oxazepan-6-ols

Sodium cyanoborohydride (5 equiv) was added to a stirring solution of amine (1 equiv), dialdehyde (3 equiv) and 10 Å molecular sieves in methanol (40 ml). The pH of the reaction mixture was adjusted to 7 by the addition of 2 M HCl (soln Et_2O). After stirring

for 18 h at room temperature, the reaction mixture was concentrated in vacuo, partitioned between H_2O and ethyl acetate (4×80 ml) and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo to yield the [1,4]-oxazepanes.

4.2.3. 2-Hydromethyl-7-methoxy-4-propyl-[1,4]-oxazepan-6-ol (16b)

The general procedure for the synthesis of oxazepanes with purification by column chromatography (10:1 EtOAc–MeOH) afforded [1,4]-oxazepane (**16b**) as a yellow oil in 42% yield; $[\alpha]_D^{20}$ +96.8 (*c* 0.82, MeOH); ν_{max} (thin film) 3383 (O–H), 2935 (C–H), 1648, 1462 (C–N), 1185 (C–O–C), 1068 (C–O) cm^{-1}; ^1H NMR (250 MHz; CD_3OD) 0.96 (3H, t, *J* = 7.5 Hz, H-11), 1.52–1.67 (2H, m, H-10), 2.53–2.63 (3H, m, H-9, H-3), 2.73 (1H, dd, *J* = 2.5, 12.5, H-5), 2.97–3.10 (2H, m, H-3, H-5), 3.50 (3H, s, OCH_3), 3.47 (1H, dd, *J* = 6.0, 11.0 Hz, H-8), 3.56 (1H, dd, *J* = 6.0, 11.0 Hz, H-8), 3.93 (1H, ddd, *J* = 2.0, 2.5, 8.0 Hz, H-6), 4.08–4.12 (1H, m, H-2), 4.64 (1H, d, *J* = 2.0 Hz, H-7); ^{13}NMR (63 MHz, CD_3OD) 10.84 (C-11), 19.91 (C-10), 54.71 (C-5), 55.00 (OCH_3), 58.17 (C-3), 60.63 (C-9), 63.70 (C-8), 69.45 (C-6), 71.26 (C-2), 101.83 (C-7); *m*/*z* (CI) M^+ requires 219.1471. Found 219.1434.

4.2.4. 4-Butyl-2-hydromethyl-7-methoxy-[1,4]-oxazepan-6-ol (16c)

The general procedure for the synthesis of oxazepanes with purification by column chromatography (EtOAc) afforded [1,4]-oxazepane (**16c**) as a yellow oil in 35% yield; $[\alpha]_D^{20}$ +81.2 (*c* 1.00, MeOH); ν_{max} (thin film) 3443 (O–H), 2100, 1641, 1105 cm^{-1} ^1H NMR (250 MHz, CD_3OD) 0.97 (3H, t, *J* = 7.0 Hz, H-12), 1.32–1.40 (2H, m, H-11), 1.52–1.57 (2H, m, H-10), 2.58 (1H, dd, *J* = 9.0, 13.0 Hz, H-5), 2.68 (2H, t, *J* = 7.5 Hz, H-9), 2.76 (1H, dd, *J* = 1.5, 12.5 Hz, H-3), 3.01–3.13 (2H, m, H-3, H-5), 3.46 (3H, s, OCH_3), 3.45 (1H, dd, *J* = 5.5, 11.0 Hz, H-8), 3.55 (1H, dd, *J* = 5.5, 11.0 Hz, H-8), 3.96 (1H, ddd, *J* = 1.5, 3.5, 9.0 Hz, H-6), 4.12 (1H, dtd, *J* = 1.5, 5.5, 11.0 Hz, H-2), 4.62 (1H, d, *J* = 3.5 Hz, H-7); ^{13}C NMR (63 MHz, CD_3OD) 14.74 (C-12), 21.89 (C-11), 24.60 (C-10), 56.14 (C-3), 56.58 (OCH_3), 59.84 (C-5), 59.97 (C-9), 65.15 (C-8), 70.68 (C-6), 72.53 (C-2), 103.22 (C-7); *m*/*z* (CI) M^+ requires 233.1627. Found 233.1701.

4.2.5. 2-Hydroxymethyl-7-methoxy-4-octyl-[1,4] oxazepan-6-ol (16d)

The general procedure for the synthesis of oxazepanes with purification by column chromatography (EtOAc) afforded [1,4]-oxazepane (**16d**) as a yellow oil in 23% yield; $[\alpha]_D^{20}$ +90.6 (*c* 0.81, MeOH); ν_{max} (thin film) 3412 (O–H), 2925 (C–H), 1639, 1465 (C–N), 1061 (C–O); ^1H NMR (250 MHz, CD_3OD) 0.94 (3H, t, *J* = 6.5 Hz, H-16), 1.35 (10H, s, H-11, H-12, H-13, H-14, H-15), 1.59 (2H, m, H-10), 2.56–2.82 (4H, m, 1 × H-3, 1 × H-5, 2 × H-9), 3.02–3.11 (2H, m, 1 × H-3, 1 × H-5), 3.51 (3H, s, OCH_3), 3.51–3.59 (2H, m, H-8), 3.99 (1H, ddd, *J* = 1.5, 3.5, 7.5 Hz, H-6), 4.11–4.19 (1H, m, H-2), 4.65 (1H, d, *J* = 3.5 Hz, H-7); ^{13}C NMR (63 MHz, CD_3OD) 13.36 (C-16), 22.61, 27.22, 29.29, 29.44, 31.88 (C-11, C-12, C-13, C-14, C-15), 26.52 (C-10), 54.60 (C-5), 55.05 (OCH_3), 58.33 (C-3), 58.71 (C-9), 63.62 (C-8), 69.12 (C-6), 71.01 (C-2), 101.66 (C-7); *m*/*z* (CI) M^+ requires 289.2253. Found 289.2282.

4.2.6. 4-*N*-Benzyl-(2*R*)-hydroxymethyl-(7*R*)-methoxy-[1,4]-oxazepan-(6*S*)-ol (16e)

The general procedure for the synthesis of morpholines with purification by column chromatography (100% EtOAc–10% MeOH in CH_2Cl_2) afforded (**16e**) as a golden syrup in 41% yield. $[\alpha]_D^{20}$ +75.1 (*c* 0.7, MeOH) (lit.[17a] +66 (*c* 0.7, $CHCl_3$)); ν_{max} (NaCl disc/cm $^{-1}$) 3385 (br, s, OH), 2931 (s, CH), 1494 (m, C=C (arom)), 1058 (s, C–O), 856 (m, CH (arom)), 750 (m, CH (arom)); δ_H (250 MHz; $CDCl_3$) 2.41 (1H, dd, *J* 12.5, 9.5, C(3)H), 2.69 (1H, d, *J* 12.5, C(5)H), 2.89 (1H, d, *J* 12.5, C(3′)H), 3.03 (1H, dd, *J* 12.5, 7.0, C(5′)H), 3.49 (3H, s, OCH_3), 3.44–3.54 (2H, m, C(8)H), 3.74 (2H, s, NCH_2Ph), 3.98 (1H, app. dd, *J* 6.5, 4.0, C(6)H), 4.18–4.25 (1H, m, C(2)H), 4.53 (1H, d, *J* 4.0, C(7)H), 7.24–7.38 (5H, m, Ph); δ_C (63 MHz; $CDCl_3$) 54.8 (C5), 56.5 (OCH_3), 58.6 (C3), 63.5 (NCH_2Ph), 65.0 (C8), 69.4 (C6), 72.5 (C2), 102.5 (C7), 128.1–129.5 (ArC), 137.7 (ArC); *m*/*z* (CI) 268 ($[M+H]^+$, 100%), 133 (22), 120 (64). Found $[M+H]^+$ 268.1548, $C_{14}H_{22}NO_4$ requires 268.1549.

4.2.7. 6-Hydroxy-2-hydroxymethyl-7-methoxy-[1,4]-oxazepan-4-yl-acetic acid methyl ester (16g)

The general procedure for the synthesis of oxazepanes with purification by column chromatography (EtOAc) afforded [1,4]-oxazepane (**16g**) as a clear oil in 9% yield; $[\alpha]_D^{20}$ +67.0 (*c* 1.00, MeOH); ν_{max} (thin film) 3500 (O–H), 2100, 1723, 1618, 1368 (C–N), 1223 (C–O–C), 1079 (C–O); ^1H NMR (250 MHz, CD_3OD) 2.52 (1H, dd, *J* = 9.0, 12.5 Hz, H-3), 2.67–2.80 (3H, m, H-3, 2 × H-5), 3.21–3.34 (7H, m, 2 × H-8, 2 × H-9, OCH_3). 3.50 (3H, s, $COOCH_3$), 3.71 (1H, ddd, *J* = 2.0, 3.5, 7.5 Hz, H-6), 3.88 (1H, dtd, *J* = 2.0, 6.0, 9.0 Hz, H-2), 4.40 (1H, d, *J* = 3.5 Hz, H-7); ^{13}C NMR (63 MHz, CD_3OD) 52.48 ($COOCH_3$), 56.54 (C-5), 56.56 (OCH_3), 58.99 (C-3), 60.52 (C-8), 65.04 (C-9), 71.84 (C-6), 74.49 (C-2), 103.51 (C-7), 173.67 ($COOCH_3$); *m*/*z* (CI) $[M+H]^+$ requires 250.1290. Found 250.1284.

4.2.8. 6-Hydroxy-2-hydroxymethyl-7-methoxy-[1,4]-oxazepan-4-yl-acetic acid methyl ester (16h)

The general procedure for the synthesis of oxazepanes with purification by column chromatography (EtOAc) afforded [1,4]-oxazepane (**16h**) as a clear oil in 11% yield; $[\alpha]_D^{20}$ +67.0 (*c* 1.00, MeOH); ν_{max} (thin film) 3394 (O–H), 2921 (C–H), 1723, 1605, 1447 (C–N), 1144 (C–O–C), 1053 (C–O); ^1H NMR (250 MHz, CD_3OD) 1.33 (3H, d, *J* = 11.5 Hz, H-10), 2.73–3.13 (4H, m, 2 × H-3, 2 × H-5), 3.44–3.61 (5H, m, 2 × H-8, H-9, OCH_3), 3.71 (3H, s, $COOCH_3$), 3.86 (1H, ddd, *J* = 2.0, 3.5, 8.0 Hz, H-6), 4.00–4.03 (1H, m, H-2), 4.61 (1H, d, *J* = 3.5 Hz, H-7); ^{13}C NMR (63 MHz, CD_3OD) 16.31 (C-10), 52.37 ($COOCH_3$), 53.00 (C-5), 56.67 (OCH_3), 57.08 (C-3), 64.41 (C-9), 65.00 (C-8), 71.79 (C-6), 73.98 (C-2), 103.63 (C-7), 175.59 ($COOCH_3$); *m*/*z* (CI) $[M+H]^+$ requires 264.1447. Found 264.1149.

4.2.9. 2-(6-Hydroxy-2-hydroxymethyl-7-methoxy-[1,4]oxazepan-4-yl)-10-phenyl propionic acid methyl ester (16i)

The general procedure for the formation of oxazepanes with purification by column chromatography (EtOAc) afforded [1,4]-oxazepane (**16i**) as a clear oil in 23% yield; $[\alpha]_D^{20}$ +18.5 (*c* 1.00, MeOH); ν_{max} (thin film) 3473 (O–H), 2079, 1631, 1486 (C–N), 1053 (C–O); ^1H NMR (250 MHz, CD_3OD) 2.84–2.97 (2H, m, 1 × H-3, 1 × H-5), 3.05–3.11 (2H, m, 1 × H-3, 1 × H-10), 3.18–3.27 (2H, m, 1 × H-5, 1 × H-10), 3.57–3.66 (5H, m, 2 × H-8, OCH_3), 3.77 (3H, s, $COOCH_3$), 3.86 (1H, t, *J* = 7.5 Hz, H-9), 3.94 (1H, ddd, *J* = 1.5, 3.5, 8.0 Hz, H-6), 4.10–4.18 (1H, m, H-2), 4.69 (1H, d, *J* = 3.5 Hz, H-7), 7.28–7.44 (5H, m, Ar-H); ^{13}C NMR (63 MHz, CD_3OD) 37.47 (C-10), 52.23 ($COOCH_3$), 52.90 (C-5), 56.58 (OCH_3), 57.87 (C-3), 64.94 (C-8), 71.09 (C-9), 71.73 (C-6), 73.81 (C-2), 103.53 (C-7), 127.96–130.62 (Ar-C), 174.34 ($COOCH_3$); *m*/*z* (CI) $[M+H]^+$ requires 340.1760. Found 340.1758.

4.2.10. 2-(6-Hydroxy-2-hydroxymethyl-7-methoxy-[1,4]-oxazepan-4-yl)-10-(4-hydroxyphenyl)-propionic acid methyl ester (16j)

The general procedure for the synthesis of oxazepanes with purification by column chromatography (EtOAc) afforded [1,4]-oxazepane (**16j**) as a clear oil in 13% yield; $[\alpha]_D^{20}$ +42.1 (*c* 1.00, MeOH); ν_{max} (thin film) 3447 (O–H), 2052, 1723, 1631, 1460 (C–N), 1368, 1250 (C–O–C), 1065 (C–O); ^1H NMR (250 MHz, CD_3OD)

2.82–2.99 (3H, m, 1 × H-3, 1 × H-5, 1 × H-10), 3.04–3.10 (2H, m, 1 × H-3, 1 × H-10), 3.30–3.35 (1H, m, H-5), 3.55–3.57 (5H, m, 2 × H-8, 2 × OCH_3), 3.75–3.81 (4H, m, 1 × H-9, $COOCH_3$), 3.92–3.94 (1H, m, H-6), 4.06–4.09 (1H, m, H-2), 4.67 (1H, d, *J* = 4.5 Hz, H-7), 6.82 (2H, d, *J* = 8.5 Hz, Ar-H), 7.17 (2H, d, *J* = 8.5 Hz, Ar-H); ^{13}C NMR (63 MHz, CD_3OD) 36.66 (C-10), 52.26 ($COOCH_3$), 52.70 (C-5), 56.61 (OCH_3), 58.08 (C-3), 64.97 (C-8), 71.30 (C-9), 71.59 (C-6), 73.87 (C-2), 103.52 (C-7), 116.67 (C-12), 131.60 (C-13), 157.48 (C-14), 174.55 ($COOCH_3$); *m/z* (CI) $[M+H]^+$ requires 356.1709. Found 356.1707.

4.2.11. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-((2*R*)-benzyloxymethyl-(6*S*)-benzyloxy-(7*R*)-methoxy-[1,4]-oxazepan-4-yl)-α-D-glucopyranoside (16m)

The general procedure for the synthesis of morpholines with purification by column chromatography (4:1 toluene/EtOAc) afforded (**16m**) as a golden syrup in 72% yield; $[\alpha]_D^{20}$ +13.1 (*c* 1.06, $CHCl_3$); ν_{max} (NaCl disc/cm^{-1}) 2911 (s, CH), 1494 (s, C=C (arom)), 1453 (s, CH_2), 1070 (s, C–O), 737 (s, CH (arom)), 697 (s, CH (arom)); δ_H (400 MHz, $CDCl_3$) 2.68 (1H, dd, *J* = 13.0, 8.0 Hz, H-6), 2.71 (1H, dd, *J* = 13.5, 4.5Hz, H-3a), 2.86 (1H, dd, *J* = 13.5, 2.5 Hz, H-5a), 2.94 (1H, d, *J* = 13.0 Hz, H-6′), 3.00 (1H, dd, *J* = 13.5, 4.0 Hz, H-3a′), 3.17 (1H, dd, *J* = 13.5, 4.0 Hz, H-5a′), 3.25 (1H, app. t, *J* = 9.5 Hz, H-4), 3.33 (3H, s, OCH_3), 3.38 (3H, m, H-2, 8a), 3.44 (3H, s, OCH_3), 3.56–3.60 (1H, m, H-6a), 3.80 (1H, app. t, *J* = 8.0 Hz, H-5), 3.99 (1H, t, *J* = 9.5 Hz, H-3), 4.23–4.27 (1H, m, H-2a), 4.49–4.53 (4H, m, H-1, OCH_2Ph), 4.57 (1H, d, *J* = 12.5 Hz, OCH_2Ph), 4.60 (1H, d, *J* = 12.5 Hz, OCH_2Ph), 4.64 (1H, d, *J* = 12.0Hz, OCH_2Ph), 4.75–4.81 (3H, m, H-7a, OCH_2Ph), 4.89 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.98 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 7.15–7.33 (20H, m, Ph); δ_C (101 MHz, $CDCl_3$) 55.2 (C-5a), 55.5 (OCH_3), 55.7 (OCH_3), 57.5 (C-3a), 58.8 (C-6), 68.5 (C-2a), 69.4 (C-5), 71.6 (OCH_2Ph), 71.9 (C-8), 73.1 (OCH_2Ph), 73.2 (OCH_2Ph), 74.9 (OCH_2Ph), 75.6 (OCH_2Ph), 77.2 (C-6a), 79.7 (C-4), 79.9 (C-2), 81.9 (C-3), 97.8 (C-1), 100.6 (C-7a), 127.4–128.9 (ArC), 137.7–138.6 (ArC); *m/z* (ESI) 804 ($[M+H]^+$, 100%). Found $[M+H]^+$ 804.4116, $C_{49}H_{58}NO_9$, requires 804.4106.

4.2.12. (2*R*)-(Hydroxymethyl)-(7*R*)-methoxy-[1,4]-oxazepan-(6*S*)-ol (16n)

Compound **15e** (100 mg, 0.374 mmol) was dissolved in MeOH (2 mL) and added to $Pd(OH)_2/C$ (26.2 mg, 20% loading) in a dry flask. TFA (0.2 mL) was added and the flask was evacuated. A hydrogen atmosphere was then introduced. The evacuation process was repeated three times. The contents were left to stir overnight before filtration through Celite® and washing with 1:1 CH_2Cl_2–MeOH. The filtrate was concentrated in vacuo to afford (**16n**) as a syrup (156 mg, 100%). $[\alpha]_D^{20}$ +19.7 (*c* 1.35, MeOH) (lit.[17a] +72.7 (*c* 1.0, MeOH)); ν_{max} (NaCl disc/cm^{-1}) 3382 (br, s, OH, NH), 1677 (s, NH (bend)), 1202 (s, C–N), 1133 (s, C–O), 1076 (s, C–O); δ_H (400 MHz, CD_3CD) 3.06 (1H, dd, *J* 13.5, 10.5, C(3)H), 3.32–3.36 (1H, m, C(5)H), 3.43–3.45 (1H, m, C(3′)H), 3.47–3.49 (1H, m, C(5′)H), 3.53–3.57 (4H, m, C(8)H), OCH_3), 3.62 (1H, dd, *J* 11.5, 5.0, C(8′)H), 4.29 (1H, dd, *J* 6.5, 4.0, C(6)H), 4.41–4.46 (1H, m, C(2)H), 4.71 (1H, d, *J* 4.0, C(7)H); δ_C (101 MHz, CD_3CD) 47.0 (C5), 50.8 (C3), 56.3 (OCH_3), 63.9 (C8), 68.4 (C6), 70.1 (C2), 101.7 (C7); *m/z* (ESI) 178 ($[M+H]^+$, 100%). Found $[M+H]^+$ 178.1079, $C_7H_{15}NO_4$ requires 178.1074.

4.2.13. Methyl 2,6-di-*O*-benzyl-α-D-glucopyranoside (17)[23]

Methyl α-D-glucopyranoside (5.04 g, 25.9 mmol) and dibutyltin oxide (9.69 g, 38.9 mmol) in anhydrous toluene (100 mL) were heated at reflux at 137 °C overnight, under argon. The contents were evaporated to dryness in vacuo. Benzyl bromide (15 mL) and anhydrous toluene (15 mL) were added to the resultant yellow solid, and the reaction was set to reflux overnight at 147 °C, under argon. Upon completion, the reaction was cooled and the solvent removed in vacuo. The contents were partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (1:1 toluene/EtOAc) yielded (**17**) as a white solid (6.40 g, 66%). Mp 81–83 °C (lit.[23] 85–87 °C); $[\alpha]_D^{20}$ +65.8 (*c* 1.0, $CHCl_3$) (lit.[35] +59.8 (*c* 1.1, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 3428 (br, s, OH), 2914 (s, CH), 1497 (m, C=C (arom)), 1454 (m, C=C (arom)),1054 (s, C–O), 738 (s, CH (arom)), 698 (s, CH (arom)); δ_H (400 MHz, $CDCl_3$) 2.92 (1H, d, *J* = 2.5 Hz, H-3), 2.94 (1H, d, *J* 3.0, C(4)O*H*), 3.33 (3H, s, OCH_3), 3.37 (1H, dd, *J* = 9.5, 3.5 Hz, H-2), 3.57 (1H, dt, *J* = 9.0, 3.0 Hz, H-4), 3.66–3.71 (3H, m, H-5,6), 3.90 (1H, dt, *J* = 9.0, 2.5 Hz, H-3), 4.54 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.58–4.66 (3H, m, H-1, OCH_2Ph), 4.70 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 7.32–7.35 (10H, m, Ar-H); δ_C (101 MHz, $CDCl_3$) 55.0 (OCH_3), 69.2 (C-6), 69.5 (C-5), 70.8 (C-4), 72.8 (C-3), 72.8 (OCH_2Ph), 73.4 (OCH_2Ph), 78.9 (C-2), 97.5 (C-1), 127.4–128.3 (ArC), 137.7 (ArC); *m/z* (ESI) 397 ($[M+Na]^+$, 100%). Found $[M+Na]^+$ 397.1638, $C_{21}H_{26}NaO_6$ requires 397.1622.

4.2.14. Methyl-[*O*^{6}-(toluene-4-sulfonyl)]-α-D-glucopyranoside (19)

Methyl α-D-glucopyranoside (3.02 g, 15.61 mmol) was dissolved in pyridine (30 mL) and cooled to 0 °C under argon. Toluene sulfonyl chloride (2.98 g, 15.6 mmol) was added and the solution was stirred for 8 h at 0 °C. The mixture was then concentrated in vacuo and the crude mixture was purified by flash column chromatography (EtOAc) to isolate (**19**) as a white solid in 51% yield; mp 105–106 °C (lit.[36] 104–106 °C); $[\alpha]_D^{20}$ +91 (*c* 1.01, $CHCl_3$)) (lit.[24] +104 (*c* 1.0, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 3371 (br, s, OH), 1449 (m, C=C (arom)), 1361 (s, SO_2 (antisymmetric)), 1176 (s, C–O), 1146 (m, SO_2 (symmetric)), 1060 (m, C–O), 666 (m, CH (arom)); δ_H (250 MHz, $CDCl_3$) 2.43 (3H, s, PhC*H*$_3$), 3.33 (3H, s, OCH_3), 3.39–3.51 (2H, m, H-2,4), 3.68–3.75 (2H, m, H-3,5), 4.22–4.33 (2H, m, H-6), 4.66 (1H, d, *J* = 3.5 Hz, H-1), 7.27–7.35 (2H, m, Ph), 7.77–7.85 (2H, m, Ph); δ_C (63 MHz; $CDCl_3$) 22.1 (PhCH_3), 55.7 (OCH_3), 69.7 (C-6) 69.8 (C-5), 70.0 (C-4), 72.1 (C-2), 74.4 (C-3), 99.8 (C-1), 128.4–145.3 (ArC).

4.2.15. Methyl-[*O*^{6}-(toluene-4-sulfonyl)]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (20)

Methyl-[*O*^{6}-(toluene-4-sulfonyl)-α-D-glucopyranoside (**19**) (364 mg, 1.04 mmol) was dissolved in anhydrous DMF (20 mL) and cooled to 0 °C. Sodium hydride (12.5 mg, 3.13 mmol) was added portionwise, followed by benzyl bromide (0.37 mL, 3.13 mmol). The reaction mixture was stirred under argon, warming to room temperature overnight. DMF was removed under pressure and the resultant liquid was partitioned between water (75 mL) and EtOAc (75 mL). The aqueous phase was further extracted with EtOAc (2 × 75 mL). The combined organic phases were washed with water (75 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude mixture was purified by flash column chromatography (4:1 hexane/EtOAc) to afford (**19**) as a clear oil in 100% yield; $[\alpha]_D^{20}$ +36 (*c* 1.0, $CHCl_3$) (lit.[37] +25 (*c* 2.26, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 1363 (s, SO_2 (antisymmetric)), 1177 (s, C–O), 1137 (s, SO_2 (antisymmetric)), 1093 (s, C–O), 812 (s, CH (arom)), 738 (s, CH (arom)) 698 (s, CH (arom)); δ_H (250 MHz, $CDCl_3$) 2.05 (3H, s, PhC*H*$_3$), 3.31 (3H, s, OCH_3), 3.43–3.49 (2H, m, H-2,4), 3.72–3.79 (1H, m, H-5), 3.94 (1H, t, *J* = 9.0 Hz, H-3), 4.17–4.20 (2H, m, H-6), 4.42 (1H, d, *J* = 10.5 Hz, OCH_2Ph), 4.51 (1H, d, *J* = 3.5 Hz, H-1), 4.62 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.75–4.84 (3H, m, OCH_2Ph, OCH_2Ph), 4.97 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 7.12–7.16 (2H, m, Ph), 7.26–7.38 (15H, m, Ph), 7.75–7.78 (2H, m, Ph); δ_C (63 MHz; $CDCl_3$) 22.0 (PhCH_3), 55.8 (OCH_3), 68.9 (C-5), 69.0 (C-6), 73.9 (OCH_2Ph), 75.4 (OCH_2Ph), 76.1

(OCH_2Ph), 77.3 (C-2), 80.1 (C-4), 82.3 (C-3), 98.5 (C-1), 128.1–130.2 (ArC), 138.2–139.0 (ArC); *m/z* (CI) 618 ($[M]^+$, 6%), 527 (90), 389 (45), 281 (43), 253 (100), 131 (99). Found $[M]^+$ 618.2274, $C_{35}H_{38}O_8S$ requires 618.2287.

4.2.16. Methyl 6-deoxy-6-azido-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (21)

Tosylate (**20**) (503 mg, 0.814 mmol) was dissolved in anhydrous DMF (15 mL). Sodium azide (264 mg, 4.06 mmol) was added and the solution heated to ~85 °C under reflux, under an argon atmosphere for 6 h. The solvent was removed before the residue was partitioned between water (75 mL) and EtOAc. The aqueous layer was further extracted with EtOAc (2 × 75 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography (2:1 hexane/EtOAc) afforded (**21**) as a clear golden oil in 81% yield; $[\alpha]_D^{20}$ +32.6 (*c* 1.0, $CHCl_3$) (lit.[38] +48.2 (*c* 1.0, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 2921 (m, CH), 2100 (s, N_3), 1454 (C=C (arom)), 1073 (m, C–O), 737 (m, CH (arom)), 698 (m, CH (arom)); δ_H (250 MHz, $CDCl_3$) 3.32 (1H, dd, *J* = 13.0, 5.5 Hz, H-6), 3.35 (1H, dd, *J* = 13.0, 5.5 Hz, H-6'), 3.40 (3H, s, OCH_3), 3.41–3.48 (1H, m, H-4), 3.54 (1H, dd, *J* = 9.5, 3.5 Hz, H-2), 3.78 (1H, ddd, *J* = 10.0, 5.5, 2.5 Hz, H-5), 3.98 (1H, t, *J* = 9.0 Hz, H-3), 4.57 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.61 (1H, d, *J* = 3.5 Hz, H-1), 4.66 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.80 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.81 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.90 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 5.00 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 7.21–7.36 (15H, m, Ph); δ_C (63 MHz; $CDCl_3$) 51.8 (C-6), 55.8 (OCH_3), 70.3 (C-5), 73.8 (OCH_2Ph), 75.6 (OCH_2Ph), 76.2 (OCH_2Ph), 78.7 (C4), 80.3 (C-2), 82.2 (C-3), 98.4 (C-1), 128.1–128.9 (ArC), 138.3–139.0 (ArC); *m/z* (CI) 488 ($[M-H]^+$, 2%), 398 (100), 338 (35), 253 (46). Found $[M-H]^+$ 488.2173, $C_{28}H_{30}N_3O_5$ requires 488.2185.

4.2.17. Methyl 6-deoxy-6-amino-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (14k)

Raney Nickel (0.627 g, 50% in water) was added to an argon-filled flask and MeOH (10 mL) was added, followed by (**21**) (1.88 g, 0.72 mmol). The flask was evacuated and a hydrogen atmosphere introduced. The evacuation process was repeated three times, the contents were left to stir at room temperature for 24 h. Upon completion of the reaction, the mixture was filtered through Celite® and washed with methanol. The filtrate was concentrated in vacuo to yield (**14k**) as a colourless solid in 92% yield; $[\alpha]_D^{20}$ +54.8 (*c* 1.0, $CHCl_3$) (lit.[39] +67 (*c* 1.0, $CHCl_3$)); ν_{max} (NaCl disc/cm^{-1}) 3367 (br, m, NH), 2917 (m, CH), 1453 (m, C=C (arom)), 1069 (s, C–O), 737 (s, CH (arom)), 697 (s, CH (arom)); δ_H (400 MHz, $CDCl_3$) 1.54 (2H, br. s, NH_2), 2.72 (1H, dd, *J* = 13.5, 6.5 Hz, H-6), 2.98 (1H, dd, *J* = 13.5, 3.0 Hz, H-6'), 3.33 (1H, d, *J* = 9.5 Hz, H-4), 3.37 (3H, s, OCH_3), 3.50 (1H, dd, *J* = 9.5, 3.5 Hz, H-2), 3.56 (1H, ddd, *J* = 9.5, 6.5, 2.5 Hz, H-5), 4.00 (1H, t, *J* = 9.5 Hz, H-3), 4.56 (1H, d, *J* = 3.5 Hz, H-1), 4.61 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.67 (1H, d, *J* = 12.0 Hz, OCH_2Ph), 4.80 (1H, d, *J* = 12.5 Hz, OCH_2Ph), 4.83 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 4.88 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 5.00 (1H, d, *J* = 11.0 Hz, OCH_2Ph), 7.26–7.37 (15H, m, Ph); δ_C (101 MHz; $CDCl_3$) 42.8 (C-6), 55.0 (OCH_3), 71.7(C5),73.3 (OCH_2Ph), 74.9 (OCH_2Ph), 75.7 (OCH_2Ph), 78.5 (C-4), 80.1 (C-2), 82.1 (C-3), 97.9 (C-1), 127.6–128.5 (ArC), 138.1–138.7 (ArC); *m/z* (CI) 464 ($[M+H]^+$, 100%), 372 (82), 325 (61), 234 (54), 106 (56). Found $[M+H]^+$ 464.2430, $C_{28}H_{34}NO_5$ requires 464.2437.

4.2.18. Methyl 6-deoxy-6-azido-α-D-glucopyranoside (22)

Methyl-[O^6-(toluene-4-sulfonyl)]-α-D-glucopyranoside (**19**) (4.00 g, 11.5 mmol) was solubilised in DMF (50 mL) and sodium azide (2.99 g, 45.9 mmol) was added. The solution was heated to 90 °C under reflux for 3 h. The contents were cooled and partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was further extracted with EtOAc (2 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography (1:1 hexane/EtOAc) afforded (**20**) as a colourless syrup in 63% yield; $[\alpha]_D^{20}$ +113.5 (*c* 1.03, MeOH), (lit.[40] +126 (*c* 1.0, MeOH)); ν_{max} (NaCl disc/cm^{-1}) 3350 (br, s, OH), 2095 (s, N_3), 1122 (s, C–O), 1048 (s, C–O); δ_H (400 MHz, CD_3OD) 3.29 (1H, dd, *J* = 10.0, 9.0 Hz, H-4), 3.43 (1H, dd, *J* = 13.0, 6.5 Hz, H-6), 3.45 (1H, dd, *J* = 10.0, 4.0 Hz, H-2), 3.47 (3H, s, OCH_3), 3.54 (1H, dd, *J* = 13.0, 2.5 Hz, H-6), 3.63 (1H, dd, *J* = 10.0, 9.0 Hz, H-3), 3.71 (1H, ddd, *J* = 9.0, 6.5, 2.5 Hz, H-5), 4.73 (1H, d, *J* = 4.0 Hz, H-1); δ_C (101 MHz, CD_3OD) 52.7 (C-6), 55.7 (OCH_3), 72.5 (C-4), 72.6 (C-5), 73.4 (C-2), 74.8 (C-3), 101.3 (C-1); *m/z* (EI) 242 ($[M+Na]^+$, 94%). Found $[M+Na]^+$ 242.0748, $C_7H_{13}N_3NaO_5$ requires 242.0747.

4.2.19. Methyl 6-deoxy-6-amino-α-D-glucopyranoside (14l)

Raney Ni (366 mg) was added to (**22**) (213 mg, 0.973 mmol) in a dry flask. MeOH (10 mL) was added and the flask evacuated. A H_2 atmosphere was introduced, the evacuation process was repeated three times and then the reaction was left to stir overnight. The contents were filtered through Celite® and rinsed with MeOH. The solvent was removed in vacuo to afford (**14l**) as a colourless syrup (189 mg, 100%). $[\alpha]_D^{20}$ +90.6 (*c* 1.15, MeOH) (lit[41] +139 (*c* 1.0, H_2O)); ν_{max} (NaCl disc/cm^{-1}) 3422 (s, OH, NH), 1676 (s, NH (bend)), 1144 (m, C–O), 1055 (m, C–O); δ_H (400 MHz, CD_3CD) 2.77 (1H, dd, *J* = 14.0, 7.5 Hz, H-6), 3.04 (1H, d, *J* = 12.5 Hz, H-6'), 3.21 (1H, t, *J* = 9.5 Hz, H-4), 3.39 (3H, s, OCH_3), 3.42–3.44 (1H, m, H-2), 3.45–3.55 (1H, m, H-5), 3.65 (1H, t, *J* = 9.5 Hz, H-3) 4.72 (1H, d, *J* = 3.5Hz, H-1); δ_C (101 MHz, CD_3CD) 43.7 (C-6), 55.6 (OCH_3), 73.2 (C-5), 73.3 (C-4), 73.5 (C-2), 74.9 (C-3), 101.2 (C-1); *m/z* (ESI) 194 ($[M+H]^+$, 100%). Found $[M+H]^+$ 194.1023, $C_7H_{15}NO_5$ requires 194.1020.

4.3. Enzyme inhibition assays

Enzyme solution (10 μl) was pipetted into the wells of a flat-bottomed 96-well plate. Three wells per sample were used and three wells were used for a control. The test solution (or dH_2O for controls) (10 μl) was then pipetted into each well. The enzyme and test solutions where then pre-incubated at 27 °C for 10–20 min (the same length of time as required for the incubation with the substrate). Substrate solution (50 μl) was then pipetted into the wells and this was incubated at 27 °C for 10–20 min. After this incubation time, 70 μl of glycine solution was added to each well, and the absorbance read immediately at 405 nm on the Tunable $VERSA_{max}$ microplate reader. The K_i value and enzyme inhibition mode were determined from the slope of the Lineweaver–Burk plots and double reciprocal analysis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.07.019.

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