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Peptidomimetics, Glycomimetics and Scaffolds from Carbohydrate Building Blocks

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Saccharides, due to their high density of functional groups and availability as chiral building blocks are scaffolds for bioactive compound discovery. Pyranosides and iminosugar-based peptidomimetics have been synthesised as ligands for somatostatin receptors and HIV protease. The synthesis of polyhydroxylated macrolides related to natural products and cyclophanes has been achieved from carbohydrate fragments with a view to investigation of their potential as scaffolds. In addition, the trajectory of aromatic systems grafted to saccharides have been studied and this has led to the synthesis of probes for the study of carbohydrate protein interactions. These compounds include geometrically diverse bivalent glycomimetics derived from scaffolds that are hybrids of sugars and aromatic groups.

Introduction

Sugars have scaffolding roles in nature, presenting recognition groups in a defined orientation for binding to a receptor. As an example, the tetrasaccharide sialyl Lewis X, which plays an important role in cell–cell adhesion that occurs during the immune response and inflammatory disease, contains an *N*-acetylglucosamine (GlcNAc) scaffolding residue.[1] The hydroxy groups at O-3 and O-4 of GlcNAc facilitate the presentation of the fucose and the sialylgalactose disaccharide in a conformation that enables particular functional groups on these residues to make critical binding interactions with the selectin receptors. The introduction of a sulfate to the GlcNAc scaffold at the 6-OH group leads to the generation of an endogenous high-affinity ligand for L-selectin (Figure 1).[2]

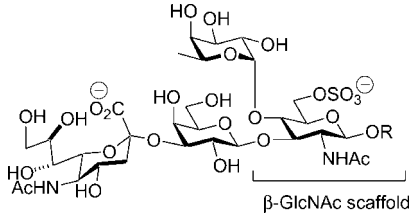

Figure 1. A naturally occurring saccharide scaffold: The 3-, 4- and 6-OH groups of GlcNAc present fucose, sialylgalactose and SO_3^- groups as important components of a high-affinity ligand for L-selectin.

Nicolaou, Hirschmann and co-workers have first shown that β-D-glucopyranose is a suitable scaffold for the presentation of the pharmacophoric amino acid side chains of peptide hormones in a similar orientation to that of the native peptide hormone itself.[3] In this example, pharmacophoric groups, which correspond to the amino acid side chains of the tripeptide Phe-Trp-Lys were attached to the pyranose providing **1**. The glucopyranose replaces the peptide backbone and projected the binding groups in the direction of their respective receptor subsites (Figure 2).

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Paul Murphy received his BSc in Chemistry (1990) and his PhD in Organic Chemistry (1994) from the National University of Ireland, Galway. His PhD work was carried out under the supervision of Dr. Niall Geraghty. He then took up a Chiroscience Postdoctoral Fellowship at the University of York working with Professor Richard J.K. Taylor. He was appointed in 1996 as a lecturer at University College Dublin and subsequently in 2006 to the post of Associate Professor in Bioorganic Chemistry. Professor Murphy is a Science Foundation Ireland Principal Investigator and played a key role in establishment of the Centre for Synthesis and Chemical Biology at UCD. He has been a research visitor at the University of Pennsylvania and the University of Mainz. He is a member of the Scientific Advisory Board of ERA Chemistry and of the Editorial Board of Carbohydrate Research. His group are currently active in synthesis and application of novel scaffolds, macrocyclic structures, peptidomimetics, glycolipids and glycomimetics.

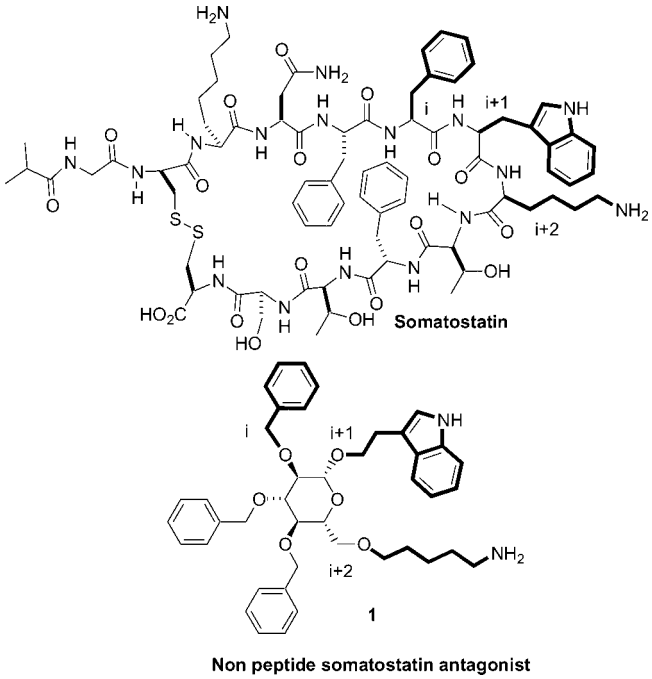


Figure 2. Structure of somatostatin and tripeptide mimetic **1**: the 1-,2- and 6-OH groups of β-D-glucopyransoe present the side chains of tryptophan, phenylalanine and lysine as components of a ligand for somatostatin receptors.

Chemists have consequently been interested in the development of monosaccharides as scaffolds as they are chiral, they have multiple functional groups which facilitate the introduction of pharmacophoric groups and generally they have rigid conformation. The investigation of carbohydrate templates for drug discovery has thus become an active research area. Amino sugars,[4] iminosugars,[5] sugar amino acids[6] and disaccharides[7] have been introduced and the solid phase syntheses of libraries based on carbohydrates have been achieved.[8,9] The application of saccharides in combinatorial, bioorganic and medicinal chemistry have been reviewed.[10] Carbohydrate scaffolds have been applied in both peptidomimetic[11] and glycomimetic research[12] with a view to the modulation of peptide-protein, carbohydrate-protein and carbohydrate-nucleic acid interactions.

In this Microreview a perspective of work that has been carried out at University College Dublin is provided. This research has included the design and synthesis of saccharide-based peptidomimetics, the incorporation of saccharide fragments into hybrid macrocyclic scaffolds and the synthesis of model bivalent ligands for the study of carbohydrate–protein interactions. Structural studies relating to aromatic groups presented on saccharide scaffolds have formed part of the research work.

Synthesis of Non-Peptide Peptidomimetics

A goal of peptidomimetic research, is the development of inhibitors of peptide–protein or protein–protein interactions with improved pharmacokinetic properties.[13] The glucoside derivative **1** (Figure 1) is considered to be a Type-III peptidomimetic, according to the classification provided by Ripka and Rich.[14] The Type-III peptidomimetics contain the necessary binding groups appropriately positioned on a non-peptide scaffold so that they can bind to the same subsites as the native peptide. These are distinct from Type-1 peptidomimetics which are defined as structures which mimic the topography of the amide bond (e.g. peptides where an amide bond isostere is incorporated) and Type-2 peptidomimetics, which are non-peptide compounds that inhibit a peptide–protein interaction, but whose binding groups do not necessarily interact at the same subsites as that of the native peptide. That sugars have promise in this area has been further supported by cheminformatic analysis which has indicated that most short peptides can be mimicked effectively by grafting amino acid side chains to a subset of pyranose scaffolds and the saccharide scaffolds have the potential to access conformational space not available to peptides.[15] Consequently, saccharides have the potential to be developed as both type-II and type-III peptidomimetics. Sugar amino acids have been classified as dipeptide isosteres by Kessler, showing that they can be considered as scaffolds for synthesis of type-I peptidomimetics also. In addition to the cases where saccharides have been investigated as somatostatin mimetics and HIV-protease inhibitors, they have been applied to the synthesis of cyclic endothelin antagonists,[16] thrombin inhibitors,[17] multidrug-resistant-associated protein inhibitor,[18] cytomegalovirus inhibitors,[19] integrin ligands,[20] fibrinogen receptor ligands,[21] LPA agonists and antagonists,[22] rhodopeptin mimetics,[23] cysteine protease calpain inhibitors[24] and inhibitors of the growth of human cell lines.[25]

Synthesis of a β-Turn Mimetic Based on 1-Deoxymannojirimycin

Somatostatin (SST) is a tetradecapeptide that regulates, through binding to its receptors (SSTR) a number of processes including the release of growth hormone and other pituitary hormones. It also plays a role in neuronal transmission. The side chains of the amino acid side chains of Phe (*i*), Trp (*i* + 1) and Lys (*i* + 2) of somatostatin with a β-turn conformation are important in the binding of SST to its receptors.[13] The initial work by Hirschmann, Nicolaou and co-workers which involved the grafting of side chains of Phe, Trp and Lys to the 2-, 1- and 6-OH groups of β-D-glucopyranose, respectively, providing **1** (Figure 1) as a ligand for somatostatin receptors with an IC_{50} value of 1.3 μM.[4] The grafting of different heteroaromatic moieties onto the scaffold at O-2 and O-4 has since led to the identification of β-D-glucopyranoside-based ligands with significantly enhanced affinities at human SSTR subtypes.[26]

Iminosugar-based mimetics of somatostatin have also been of interest, the first example being reported from the group of Le Merrer.[5] Iminosugars are structural analogues of pyranosides, in which the ring oxygen atom is replaced by a nitrogen atom. Iminosugars themselves have been of significant interest as glycosidase inhibitors[27] and some

have found clinical use[28] prompting the development of a range of syntheses to these and related compounds.[29] The use of iminosugars as scaffolds for bioorganic and medicinal chemistry offers the possibility, not available to pyranosides, of incorporating a charged hydrogen-bond donor through protonation of the ring nitrogen atom which would occur at physiological pH. In addition pharmacophoric groups can be grafted to the nitrogen atom. Synthetic routes to peptidomimetics based on iminosugars have not been explored to the same extent as that of pyranosides. The synthesis of **2** (Figure 3), a Trp-Lys mimetic, lacking the benzyl groups found in other sugar-based ligands was carried out from 1-deoxymannojirimycin (DMJ).[30] This compound had a K_i in a non-specific somatostatin receptor assay of 26 μM and showed preferential binding to sst4 receptors over sst5 receptors; **2** inhibited binding of the control ligand to sst4 receptors by 46% and 48% (both at 1.0 μM), respectively, whereas the compound did not show any binding to sst5 receptors at 1.0 μM. The points of attachment of the pharmacophore groups on the iminosugar scaffold provide a different spatial distance between the indole and lysine than in other sugar based somatostatin mimetics. The synthesis of further analogues of **2** for biological evaluation will be of interest.

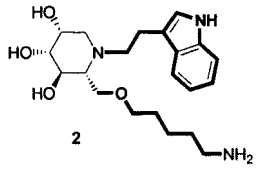
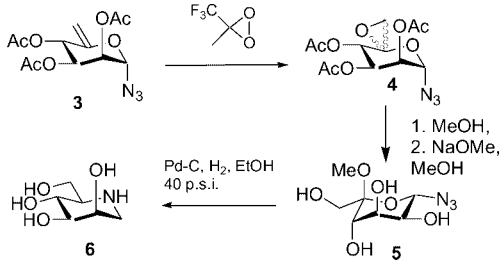


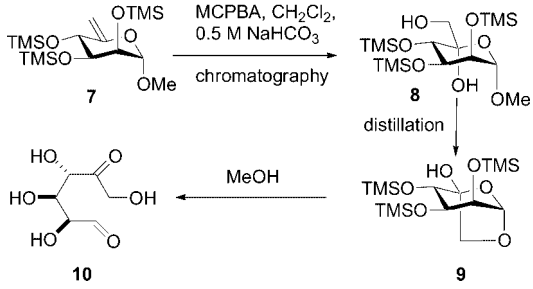
Figure 3. Structure of the dipeptide mimetic **2**.

The synthesis of the dipeptide mimetic **2** required that DMJ (**6**) was first prepared. The epoxide **4** was obtained from tri-*O*-acetyl-6-deoxyhex-5-enopyranosyl azide (**3**). The methanolysis of **4** and subsequent deacetylation gave the 5-*C*-methoxyglycopyranosyl azide derivative **5**. A catalytic reductive cascade reaction from **5** led to the formation of **6** (Scheme 1).[31] This approach was used in a general synthesis of iminosugars,[32] and this has included the development of a synthesis of castanospermine and 1-epicastanospermine.[33]



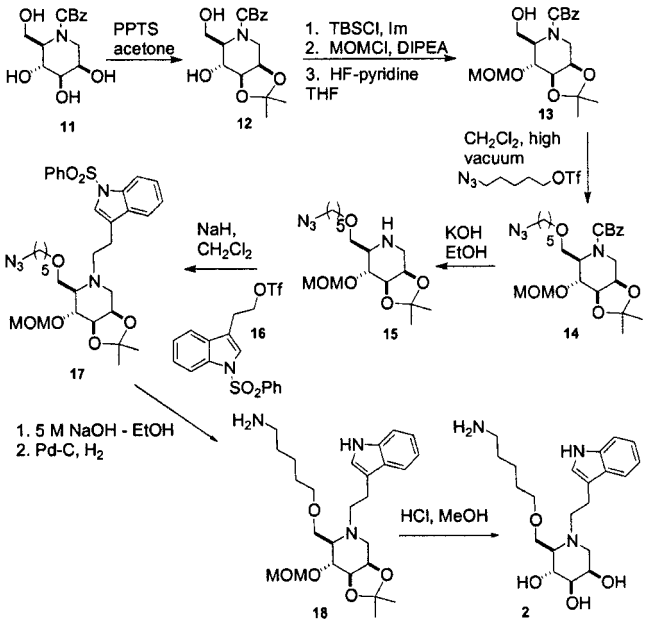
Scheme 1. Synthesis of 1-deoxymannojirimycin.

D-*lyxo*-Hexos-5-ulose (**10**),[34] which is the key intermediate used in the synthesis of DMJ by Baxter and Reitz,[35] was also prepared. An epoxidation hydrolysis of **7** gave the hemiketal **8**. Attempts to purify **8** by distillation led to its efficient conversion to **9**. The labile TMS groups were easily removed from **9** to give **10** (Scheme 2).



Scheme 2. Synthesis of 1,5-dicarbonyl precursors to DMJ.

1-Deoxymannojirimycin was next converted into **11**[30] and the subsequent reaction of **11** in acetone using PPTS gave **12**. The TBS and MOM groups were introduced and the TBS group was subsequently removed using HF-pyridine to give **13**. Alkylation of the primary hydroxy group under nonbasic conditions gave the pentyl azide derivative **14**. Removal of the Cbz protecting group under basic conditions gave **15**. The alkylation of the nitrogen atom of **15** with the triflate **16** gave **17**. Removal of the sulfonamide and reduction of the azide group gave **18**, which, when treated with HCl/MeOH, gave the peptidomimetic **2** (Scheme 3).



Scheme 3. Synthesis of the dipeptide mimetic **2**.

Design and Synthesis of Inhibitors of HIV-1 Protease

The active site of aspartic acid proteases consists of binding subsites, which recognise peptide side chains, permitting selective peptide hydrolysis to be achieved. These enzymes

employ an enzyme-bound water molecule as a nucleophile and the active site also contains two important aspartic acid residues.[36] Several aspartic acid proteases are of interest as therapeutic targets, including renin, memapsin 2 (β-secretase) and the clinically relevant HIV protease which are involved in hypertension, Alzheimer's disease and HIV infection, respectively. The lack of bioavailability of aspartic acid protease inhibitors, due to their high peptide character, has prevented many compounds gaining clinical approval. Peptide substrates for aspartic acid proteases bind in β-strand conformations and putative inhibitors of aspartic acid proteases were designed based on saccharide scaffolds. The design approach used the coordinates of the inhibitor **19** bound to HIV-1 protease.[37] The de novo software Growmol,[38] which explores the generation of molecules with the potential to bind in active sites, generated a cyclohexane derivative as a potential binding ligand in the environment occupied by **19**. This cyclohexane was superimposed on **19** generating **20** and further structural modifications led to the suggestion that β-D-mannopyranosides **21** or related β-D-glucopyranosides could replace part of the peptide structures known to bind to these enzymes. A substituent attached at C-1, aided by the *exo*-anomeric effect, would be projected with the correct orientation into the S_1 subsite. Functionalisation of the 3-OH and 4-OH would possibly place groups into the S_1' and S_2 subsites. A 6-deoxy-6-amino glycoside could be used for the synthesis of amide derivatives, which would be useful for introducing further diversity and the amide group would be capable of hydrogen bonding with residues of the enzyme. Many inhibitors of aspartic proteases, including **19**, as well as those that are clinically used for HIV infection and the naturally occurring aspartic protease inhibitor pepstatin, contain the hydroxyethylene isoster. It is accepted that the interaction of the isosteric hydroxy group with the enzyme is important for complex stability; the correct stereochemistry of this hydroxy is usually essential for tight binding. In this case the 2-OH group of the mannose scaffold had the desired overlap with the hydroxy group of inhibitor **19**.[39] The three dimensional structures of other HIV-1 protease-ligand complexes and the consideration to synthesise both hydroxy isomers led to the suggestion of mannosides **21** and related glucosides as targets for synthesis (Figure 4).

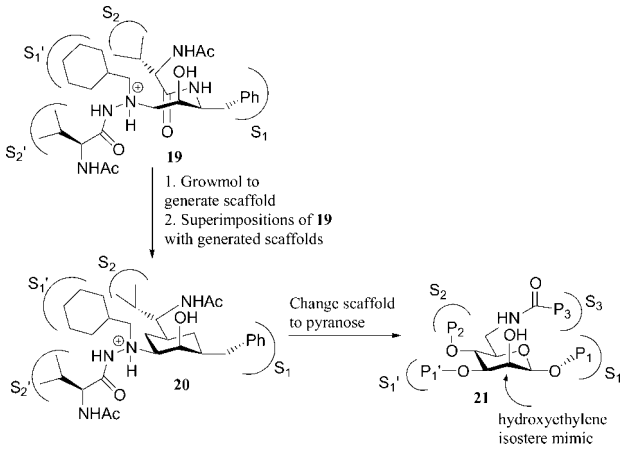


Figure 4. Design of putative mannopyranoside and glucopyranoside based HIV-protease inhibitors.

A series of putative peptidomimetic inhibitors of HIV-1 protease (e.g. **22**–**24**, Figure 5) that incorporated β-D-mannopyranose and β-D-glucopyranose as scaffolds[40] were synthesised and these compounds were moderate inhibitors (IC_{50} = 3.81–8.95 μM) of HIV-1 protease activity. The mannoside **25**, incorporating the compatible azide, methoxyphenylmethyl ether and TIPS groups, was used in the synthesis of **24**.

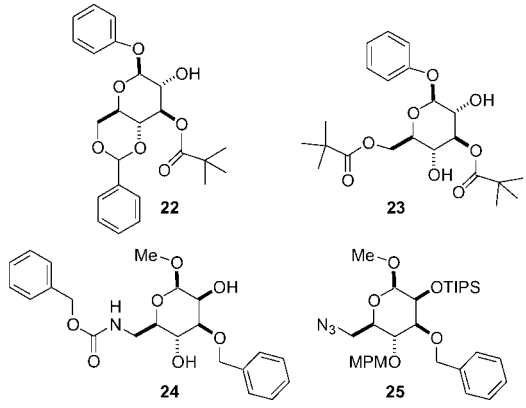
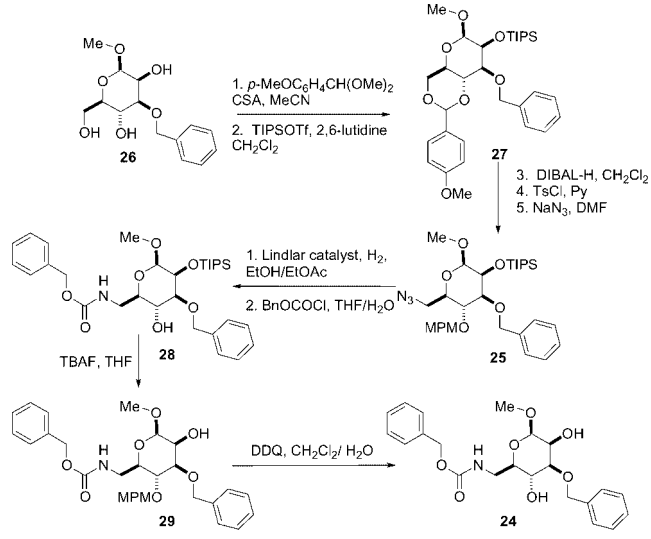


Figure 5. Mannopyranoside and glucopyranoside derivatives **22**–**24** were synthesised for evaluation as inhibitors of HIV-1 protease. Mannopyranoside derivatives were synthesised from **25**.

The synthesis of β-mannopyranoside **24** succeeded from the triol **26**. The triol **26** was converted first of all to **27** and the subsequent regiospecific reduction of the acetal **27**, followed by preparation of the 6-*O*-tosylate and subsequent substitution of the tosylate with an azide gave **25**. The azide **25** was reduced to an amine that was then converted into the carbamate **28**. The removal of the TIPS group from **28** provided **29**. Oxidative removal of the 4-methoxybenzyl group from **29** provided **24** (Scheme 4).



Scheme 4. Synthesis of **24**.

The iminosugar-based peptidomimetic **30** was next selected for synthesis in an effort to develop more potent saccharide-based inhibitors. The rationale used was based on the hypothesis that inhibitor **23** was binding to HIV proteases as indicated in Figure 6. The iminosugar nitrogen atom of **30** offered the possibility of contributing a charged hydrogen-bond donor, contrasting with **23** which has an oxygen atom.[41]

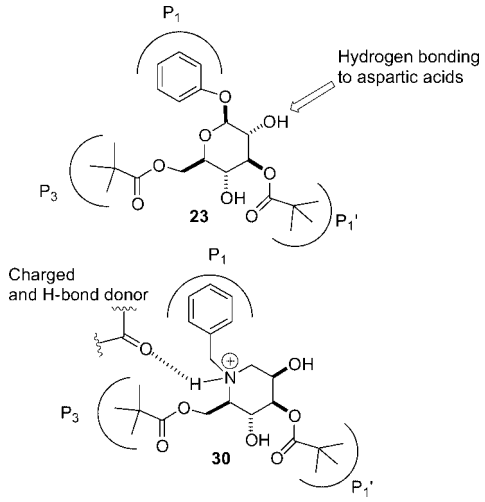
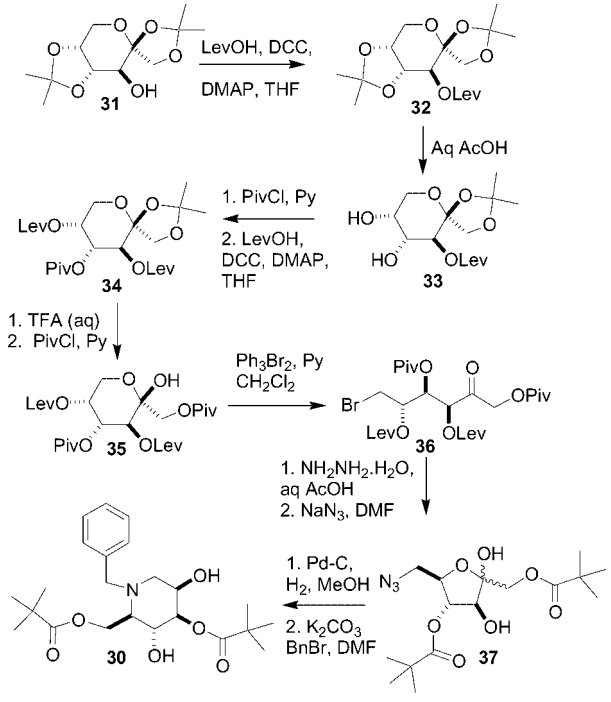


Figure 6. Design of an iminosugar peptidomimetic.

The synthesis of **30** was carried out as shown in Scheme 5. Thus, compound **32** was prepared from **31**, which was readily obtained from D-fructose.[42] The 4,5-di-*O*-isopropylidene group of **32** was selectively hydrolysed to give **33**. Regioselective pivaloylation of the 4-OH group of **33** followed by introduction of a levulinoyl group at C-4 gave **34**. Hydrolysis of the remaining isopropylidene group followed by another regioselective pivaloylation gave **35**. Bromination gave the acyclic bromofructose derivative **36**. The levulinate groups were then removed selectively and substitution of the bromide for an azide group gave **37**. Catalytic hydrogenation of **37**, an intermediate related to that used by Stuetz and co-workers in their synthesis of 1-deoxymannojirimycin,[43] and subsequent *N*-benzylation gave the target DNJ derivative **30**.



Scheme 5. Synthesis of peptidomimetic **30** from D-fructose.

The DMJ derivative **30** was not active as an inhibitor of HIV-1 protease. A second series of glucopyranoside derivatives synthesised were also not active. These results indicate that the activity displayed by compounds in Figure 4 may be due to a different mode of action than that hypothesized. Nevertheless, novel strategies and intermediates for the synthesis of peptidomimetics based on polyhydroxylated pyranosides and iminosugars emerged during the course of the investigation.

Presentation of Groups on Carbohydrate Scaffolding – Structural Considerations

The understanding of how groups orient themselves when attached to saccharide scaffolds is of relevance to their application in bioactive molecule design and synthesis. The geometry of aromatic groups grafted to saccharides through amide linkages, have been examined.

Aromatic glycosyl amides[44] which are related to β-glycosyl amido derivatives that have been reported previously[45,46] were prepared. This and the previous work provided evidence that antiperiplanar (*anti*) rather than synperiplanar (*syn*) conformations are preferred for these amides (Figure 7). The secondary amides (Figure 7, R = H) show a single set of signals in the NMR spectra, consistent with the (*Z*)-amide isomer **39** being strongly favoured over **38**. For tertiary amides (R ≠ H) two rotamers (*E*)-*anti* and (*Z*)-*anti* isomers could be detected by NMR and there was a strong preference for the (*E*)-*anti* isomer **38** (85:15).

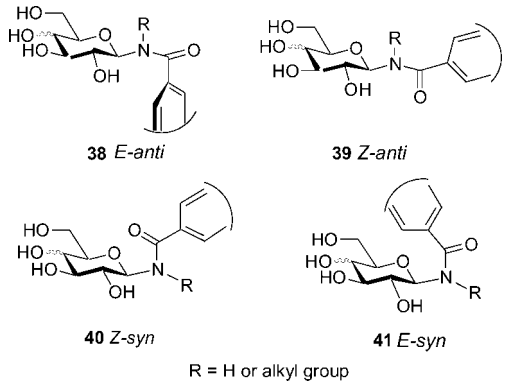


Figure 7. Structure–nomenclature relationship for *N*-glycosylamides. (*Z*)-*anti* is preferred when R = H and (*E*)-*anti* is preferred when R ≠ H.

N-Glycosylthiophene-2-carboxamides[47] (Figure 8) also preferentially adopt the (*Z*)-*anti* structure. Both experimental and theoretical studies have suggested that the *s-cis* iso-

mer **42** is preferred relative to the *s-trans* isomer **43**, a preference that has been noted for thiophene-2-carbonyl derivatives.[48]

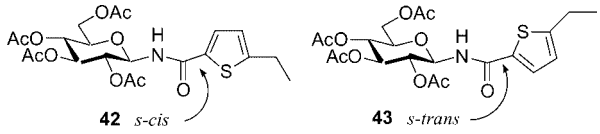


Figure 8. Structures of *N*-glycosylthiophene-2-carboxamides. The *s-cis* conformation is preferred to *s-trans*.

Secondary anilides and tertiary anilides from glucuronic acid were also prepared (Figure 9).[49] The secondary anilide amide group prefers a (*Z*)-*anti* arrangement as shown for **44**, whereas tertiary anilides showed a strong preference for the (*E*)-*anti* structures as depicted for **45**.

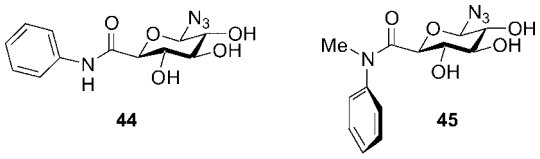


Figure 9. Preferred structural isomers for secondary and tertiary glucuronic acid anilides.

Consequently for aromatic *N*-glycosylamides and for anilides of glucuronic acid, the trajectory of the aromatic group depends on whether a secondary or tertiary amide is present and this could be taken into consideration in the design of bioactive molecules based on these and related carbohydrate templates. For the thiophene derivatives the trajectory of substituents bonded to a thiophene ring are controlled by the preference for a (*Z*)-*anti* structure by a preference for the *s-cis* isomer. A hypothetical application based on these structural observations is shown in Figure 10 based on the anilides of glucuronic acid.

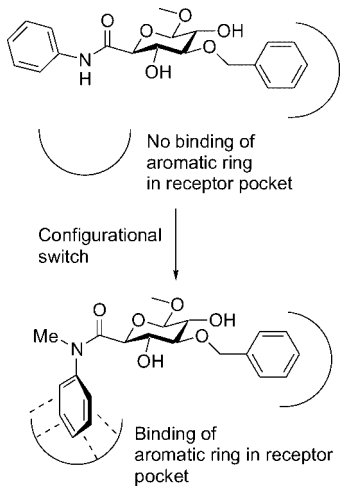


Figure 10. Hypothetical application of configurational switching of amides on saccharide scaffolds. For the secondary anilide (top) the aromatic group is not oriented in the direction of the binding pocket. After the configurational switch (bottom) the aromatic group can bind.

Synthesis of Novel Hybrid Macrocyclic Scaffolding

The generation of novel polyfunctional scaffolds from a monosaccharide is a means of further increasing the number of privileged scaffolds available in medicinal chemistry. Chimeric scaffolds such as **46** (Figure 11) that are hybrids of β-D-glucopyranose and benzodiazepines have, for example, been synthesised.[50] These efforts have been rationalised in that they generate novel molecular scaffolds with the potential to explore receptor space not accessible to pyranoside or benzodiazepine scaffolds when applied individually.

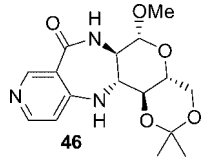


Figure 11. A chimeric or hybrid benzodiazepine-glucopyranoside scaffold.

Examples of novel bioactive compounds that have been synthesised based on hybrid polycyclic systems include tachykinin NK-1 receptor antagonists,[51] SSTR receptor ligands,[5] hapalosin mimetics,[52] matrix metalloproteinase inhibitors[53] and Ras protein activator inhibitors.[54] Also new scaffolds have been synthesised and these include natural-product-like scaffolds,[55] spirocyclic compounds,[56–58] fused polycyclic compounds for development of libraries,[59] and hybrids of sugars and N-heterocycles.[60]

Synthesis of Polyhydroxylated Oxamacrolide Scaffolding

The synthesis of novel polyhydroxylated oxamacrolide scaffolds such as **53** and **54**[61] has been achieved. The structure and biological properties of resorcylic acid and salicylic acid natural products combined with the potential of carbohydrate-derived scaffolds in compound library development has inspired the synthesis of **53** and **54** as structural analogues of natural polyketide-derived macrolides (Figure 12). The diverse biological effects observed for these natural products imply that these structures are based on a privileged or evolutionarily selected scaffold[62] that codes properties required for binding to proteins. Pochonin C[63] (**47**) and radicicol[64] (**48**) are both ATPase inhibitors, whereas zearalenone (**50**) is an agonist for mammalian estrogen receptors.[65] Aigialomycin D (**49**) inhibits the kinases CDK and GSK-3,[66] whereas (5*Z*)-7-Oxozeaenol[67] (**51**) and LL-783,277[68] (**52**) inhibit the kinases TAK-1 and MEK, respectively.

The synthesis of **53** was achieved from the D-mannitol derivative **56**. The Mitsunobu coupling reaction of the benzoic acid **55** and the D-mannitol derivative **56** gave **57**. Ring closing metathesis[69] (RCM) of **57** gave **58** with high (*E*) selectivity and subsequent hydrogenation gave **53** (Scheme 6). Macrolactone **54** containing an alkene group was prepared from related MOM-protected D-mannitol pre-

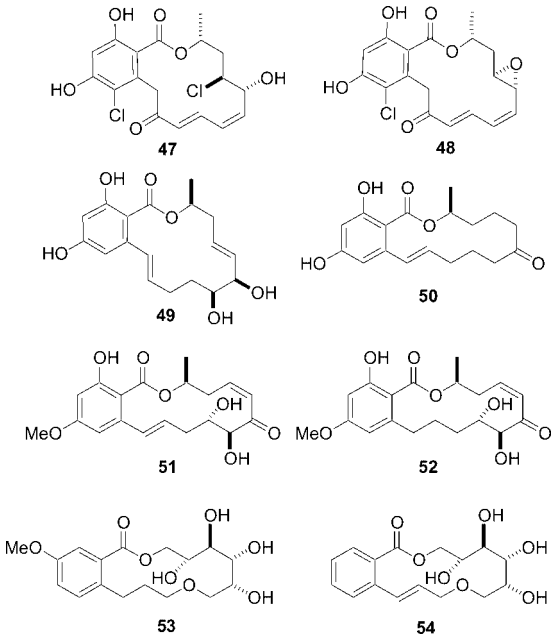
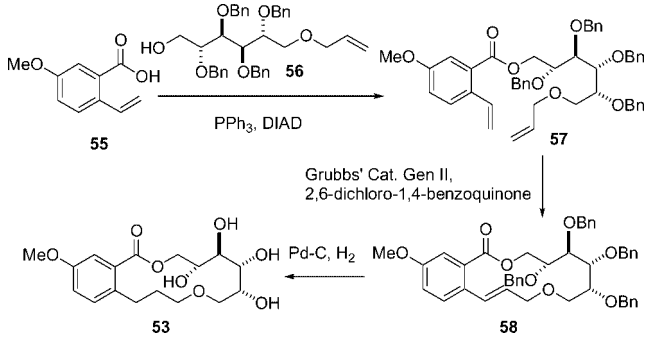


Figure 12. Structures of benzomacrolactones.

cursors. A preliminary screening of the hydroxylated products against a panel of 45 kinases has shown that they are not potent inhibitors of kinases, suggesting that structures based on a resorcylic acid or salicylic acid may be required to obtain inhibitors of kinases. The further development of polyhydroxylated macrolides with a view to the synthesis of bioactive compounds is underway.

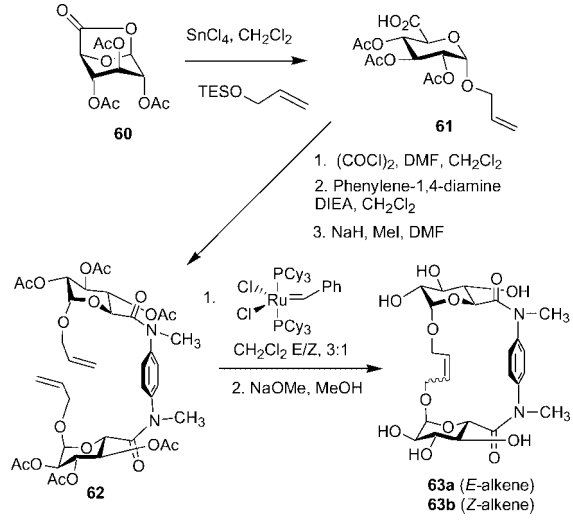


Scheme 6. Synthesis of a polyhydroxylated oxamacrolide.

Synthesis of Scaffolds Based on Cyclophane-Sugar Hybrids

Polyhydroxylated analogues of cyclophanes, which incorporate two saccharides have been synthesised.[70] Ring-closing metathesis was again employed for the construction of the macrocyclic ring from bivalent glucuronic acid anilides (Scheme 7). The dimeric compound **62** has a folded structure as both amide groups adopt (*E*)-*anti* structures and as a consequence RCM proceeds and the macrocycle **63** is obtained. Metathesis of **64** led to the formation of oligomeric derivatives **65** as a result of cross metatheses (Figure 13). The amides of **64** preferentially adopt (*Z*) configurations that preclude the folding required to facilitate RCM.

The synthesis of the metathesis substrates were achieved by glycosidation of the 6,1-lactone donor **60**[71] promoted by tin(IV) chloride to give **61**. The origin of the α-selectivity from this donor is due to a tin(IV) chloride catalysed anomerisation of the initially formed β-glycoside, the rate of anomerisation being enhanced by the carboxylate.[72] The acid **61** was then converted into the secondary amide **64** via the corresponding acid chloride (Figure 13). Methylation of the amide groups of **64** gave **62** (Scheme 7).



Scheme 7. Synthesis of polyhydroxylated cyclophane analogues.

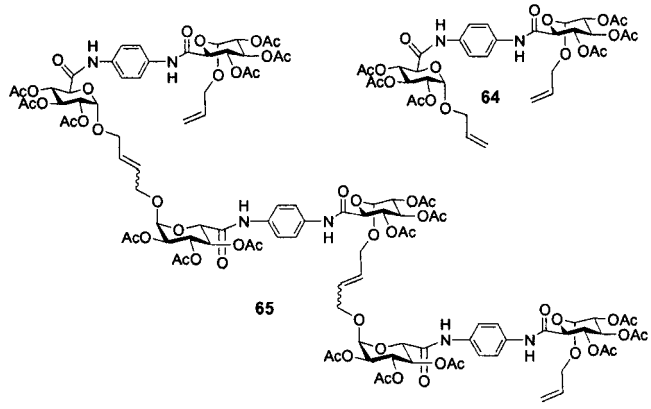


Figure 13. Structure of **65** obtained from **64**.

Monte Carlo conformational searching protocols (SUMM method) available in Macromodel 8.5[73] were employed to search for the low-energy structural isomers of **63a** and macrocycle **66**, the latter being obtained via a pentenyl glycoside analogue of **61**. These computational studies were correlated with 2D NOESY/ROESY spectra of the macrocyles. On the basis of experimental and theoretical observations it was suggested that the carbohydrates are in a U-shape for **63a**. The larger macrocycle **66** can access both U-shaped and S-shaped arrangements (Figure 14). As an extension to this work it was shown that the cyclophane analogue **66** displayed phenomena similar to β-cyclodextrin (β-CD).

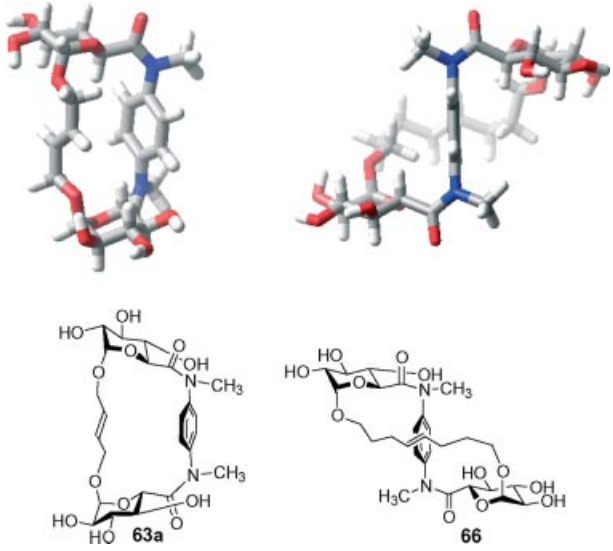


Figure 14. Low-energy structures obtained using Macromodel for paracyclophane-saccharide hybrids **63a** and **66**.

In addition, molecular modelling has also been used to examine the structural relationship of **63a** to the α-helix peptide backbone and has established that such scaffolds may have potential in the application of polyfunctional cyclophanes in the synthesis of peptidomimetics.[71]

Bivalent Model Systems for Study of Carbohydrate-Protein Interactions – Structural Considerations and Synthesis

The traditional view of signal transduction is that a bimolecular interaction of a ligand with a protein receptor results in sending a signal from the outside of a cell to the inside. However, it is becoming clear that the clustering of protein receptors and ligands is required for optimal signalling. Thus, cellular signalling is being attributed to self-assemblies that result from non-covalent recognition of receptors and cross-linking ligands.[74] The nature of glycoproteins and glycolipids, presenting multiple copies of a carbohydrate ligand, and the multivalent nature of lectins facilitates the formation of a lectin-carbohydrate lattice at cell surfaces. Such interactions lead to concentration of the glycoprotein or glycolipid within a lattice that acts as a signalling complex. Alternatively, the inhibition of signalling could be an outcome of lattice formation, particularly if signalling molecules are constrained at sufficiently large distances within the lattices. In order to probe in more detail the relationship between bivalent ligand structure[75] and the modulation of carbohydrate-lectin interactions, a series of geometrically constrained bivalent ligands have been synthesised.[45,76]

Bivalent galactosides **67** and **68** were prepared. The major conformational isomer (83%) adopted by **67** in D_2O is either U-shaped **67a** and/or S-shaped **67b** (Figure 15). This conclusion can be made based on NMR studies which support the tendency of tertiary glycosyl amides to adopt preferentially the (*E*)-*anti* structure (Figure 7). There is evidence for the presence of structural isomers **67c** and/or **67d** to a lesser degree by ^{1}H NMR (17%). In contrast, the secondary glycosyl amides **68** adopt exclusively (*Z*)-*anti* structures, which can be represented by the structures in Figure 16. The galactose residues are in a geometrically distinct fashion for each ligand and consequently, clusters which hypothetically would result from binding these ligands should have different structures.

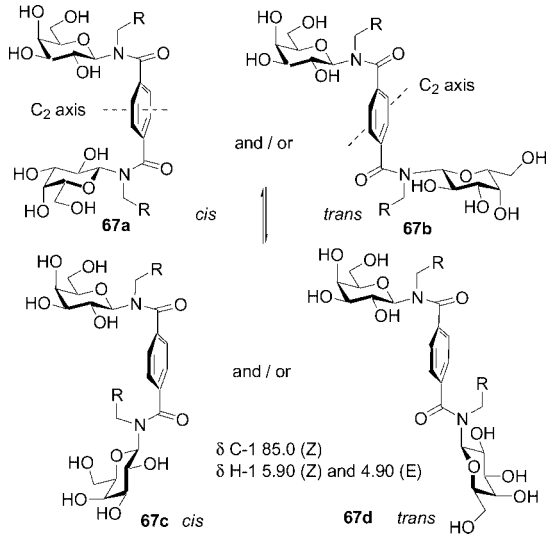


Figure 15. Structure of **67**. Isomer **67a/67b** is preferred to **67c/67d** (83:17).

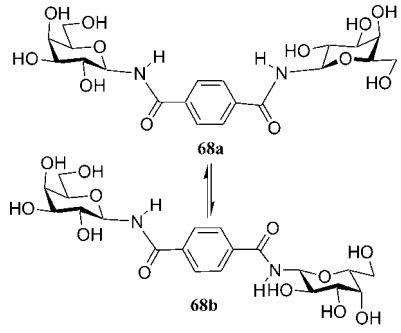


Figure 16. Structure of **68**.

Additionally, **67** and **68** can themselves be considered as scaffolds. Mannose residues were grafted to structural analogues of **68** to give **69**–**71** (Figure 17) in order to illustrate the potential of these saccharide-terephthalamide hybrids as scaffolds. Bivalent mannosides **69**–**71** have the potential cross-link mannose receptors and consequently generate lattices or clusters. Because of a limited number of degrees of conformational freedom and studies of the structural preferences for glycosyl amides (Figure 7, Figure 15), it is possible to predict the geometry of the mannose residues. Therefore, calculation of the low-energy structural isomers of **69**–**71** have shown that the mannoside component is in a geometrically distinct fashion for each ligand.[76] The bivalent carbohydrate geometry as well as the mannose–mannose distance of **69**–**71** are determined by location on

the scaffold and are unique for each compound. Biological evaluation of such ligands will be used to address structural questions at the model level concerning interactions of carbohydrate ligands and lectins. In addition, the bivalent mannoside **72** was prepared and is based on a scaffold that is derived from glucuronic acid and phenylenediamine.[77]

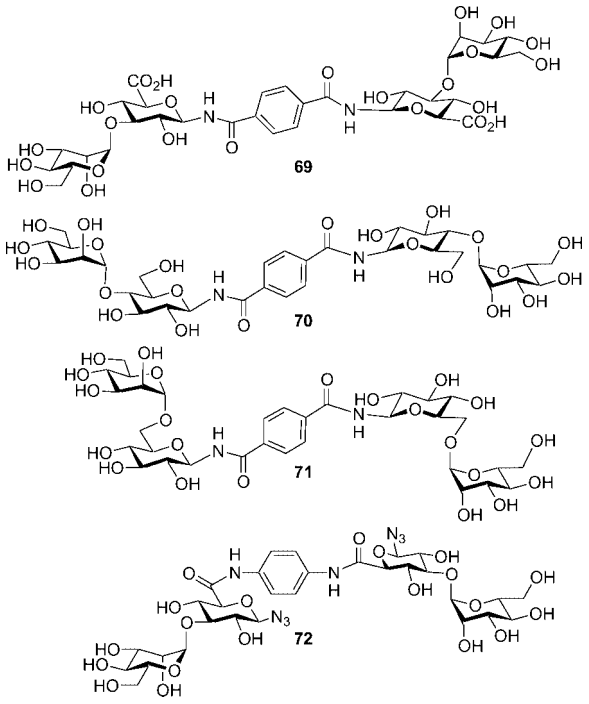
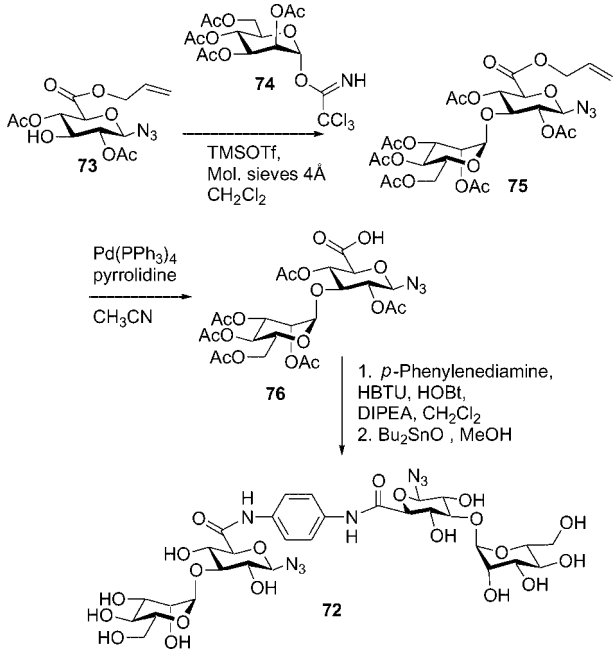


Figure 17. Structures of **69**–**72**.

The synthesis of **72** is summarised in Scheme 8. The Schmidt–Michel glycoside coupling reaction of sugar amino acid **73** with trichloroacetimidate donor **74** gave **75**.



Scheme 8. Synthesis of **72**.

The allyl ester protecting group was then removed by palladium catalysis to give acid **76**. Coupling of **76** with *p*-phenylenediamine promoted by HBTU/HOBt gave the desired protected divalent compound. Removal of the acetate protecting groups was achieved using dibutyltin oxide in methanol to give the target compound **72**.

Conclusions

There has been progress in application of monosaccharides and iminosugars as scaffolds for the synthesis of peptidomimetics. Such developments are dependant on development of strategies for carrying out regioselective and chemoselective reactions to introduce recognition groups on sugar scaffolds, as well as developments of efficient syntheses of iminosugars. The synthesis of new polyhydroxylated cyclic compounds derived at least in part from saccharide building blocks will provide new scaffolds for explorations in chemical biology, drug discovery and supramolecular chemistry. Structural considerations as to how groups are oriented on sugar scaffolds are of relevance to these areas. Structural considerations have led to the synthesis of geometrically diverse bivalent ligands as tools for probing carbohydrate-protein interactions.

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