Carbohydrate-Based Scaffolds in Drug Discovery

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Abstract: Carbohydrates have been proven as valuable scaffolds to display pharmocophores and the resulting molecules have demonstrated useful biological activity towards various targets including the somatostatin receptors (SSTR), integrins, HIV-1 protease, matrix metalloproteinases (MMP), multidrug resistance-associated protein (MRP), and as RNA binders. Carbohydrate-based compounds have also shown antibacterial and herbicidal activity.

Key Words: Carbohydrates, combinatorial chemistry, carbohydrate scaffolds, mimetics.

INTRODUCTION

Following the first publication describing the successful use of carbohydrates as new scaffolds in the area of peptidomimetics [1], there has been a growing interest in this field and certain aspects have recently been reviewed; ranging from combinatorial oligosaccharide and glycopeptide synthesis [2-7] or the use of sugar amino acids [5,8] in peptide chemistry to the development [9] and use of carbohydrate scaffolds to mimic bioactive molecules [10-14]. The present review aims to provide an overview of drug discovery approaches that have utilized carbohydrates as scaffolds to display chemical functionalities, which have the potential to interact with a receptor or enzyme.

The concept that a bioactive molecule consists of pharmacophoric components that are responsible for binding along with an inert and non-binding component that acts as a scaffold and holds the pharmacophores in place, was developed in the field of peptidomimetics where in the case of peptide ligands or substrates for instance, usually a small number of amino acid side chains form direct interactions with a receptor or enzyme, whereas the peptide backbone (and other amino acid residues present) provide the structure or scaffold that controls the relative positioning of the binding side chains. Essentially, the bioactivity of a peptide ligand is considered as originating from functional and structural properties and thus molecules that share the same functional and structural requirements are expected to share the same biological activity. This theoretical approach allows the design of drug-like molecules from known bioactive but non-drug like peptides, by replacing the metabolically labile peptide backbone with drug-like scaffolds, and introducing suitable substituents that mimic the essential side-chains.

CARBOHYDRATES AS SCAFFOLDS

Where knowledge regarding structural requirements for binding is available, for example *via* analysis of crystallographic and/or NMR data obtained after co-crystallisation of the target protein with a natural or synthetic ligand/substrate, rigid scaffolds are designed to accurately mimic the 'perfect' positioning of the substituents. A binding mode is proposed and single mimetics produced to test the model. However, it is more often the case that the bioactive conformation of the peptide is less defined, which leads to difficulties in scaffold selection. Consequently many structural presentations will need to be incorporated in the design to increase the likelihood of a successful outcome. Where, as often is the case, a large number of compounds are required to test the concept, an approach that employs parallel synthesis is favoured.

The ideal scaffold should be both chemically and biologically stable and contain rigidity to enable the molecule to maintain a controlled three-dimensional presentation of pharmacophores. However, the spatial orientation of the pharmacophores has to be adjustable to generate the presentation required for tightest binding. Additional attachment points distant from the binding components are desirable for the introduction of additional functional groups that can be used to manipulate the pharmacokinetic (PK) parameters of the resulting molecules, e.g. to improve solubility, permeability, etc.

Whilst aromatic systems may appear to be a good starting point as derivatives are readily available and substituents relatively easy to introduce, aromatic systems as exemplified by structure **1** are generally flat molecules, making a true three-dimensional presentation of substituents difficult. On the other hand, whilst natural products like alkaloids (**2**) may have a well-defined rigid three-dimensional structure, the introduction of substituents in the desired positions may be chemically challenging, thus rendering them unsuitable for the synthesis of compound libraries. Peptides such as compound **3** provide an easy way to assemble a large variety of pharmacophores, but often lack rigidity and may suffer from stability problems in a biological environment. Conversely, carbohydrates (**4**) provide a relatively rigid core with a number of functional groups (mostly hydroxyls) in defined spatial orientations. The advantage of carbohydrates is that they provide a series of scaffolds, in which all possible isomers either occur naturally or are available *via* inversion of individual positions.

Substituted carbohydrate derivatives are generally quite stable and usually display reasonable to good stability to

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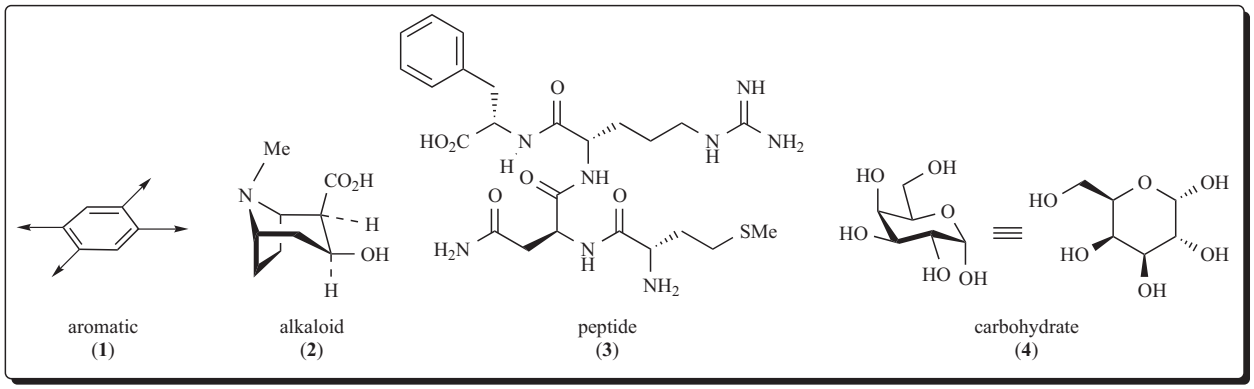


gastric acids and liver metabolism once the hemi-acetal is converted to a glycoside. Labile carbohydrates such as unsubstituted oligo- and polysaccharides, however, usually undergo rapid metabolism in a biological environment. The PK parameters and the level of drug-likeness of the substituted carbohydrates are really dictated by the properties of the substituents it carries, rather than the scaffold itself. There are in fact a number of carbohydrate-based drugs on the market and in different stages of development that illustrate the drug-like characteristics of substituted carbohydrates, from stability to oral availability [15]. For example, the highly functionalized Sanofi-Synthelabo pentasaccharide product, Idraparinux sodium [16], which carries a number of sulfates, carboxylates and methoxy substituents, has an elimination half-life of 120 hours.

Stereochemical variation at each attachment point is possible simply through the use of an alternative carbohydrate scaffold. In fact, of the simple hexopyranoses (the most common carbohydrates are hexopyranoses) there are five possible substitution sites related to five stereocenters with two possible orientations (axial and equatorial), equating to 2^5=32 possible scaffolds. Some examples are structures **5-7**.

A single carbohydrate scaffold can be used to generate many presentations simply by varying the order of the substituents around the carbohydrate ring. Structures **8** and **9** are both derived from a β-D-galactose scaffold and contain the same three substituents, but with two different substitution patterns: 1,2,3- and 3,2,1-, respectively. In both patterns the points of attachment are the same, only the order of the substituents has changed, giving a pair of quasi enantiomers. Other substitution patterns will display the same substituents in different spatial orientations and changing the scaffold will further increase the variety of three-dimensional unique presentations. When multiple carbohydrate scaffolds are employed, a large number of regio-isomers of the same molecular weight can be produced.

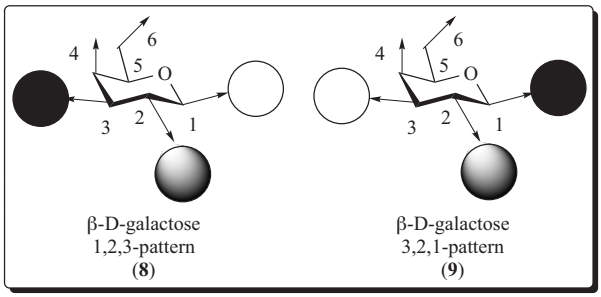


Table **1** shows the relationship between the number of unique presentations and the number of substituents and scaffolds. For example, using only one scaffold with 4 different substituents, there are already 120 different ways of presenting these substituents to a potential binding site. This increases to almost 2000 different presentations with the maximum number of hexopyranoses. If furanoses or disaccharides were included, this number would rise even further. When traditional medicinal chemistry modifications of the

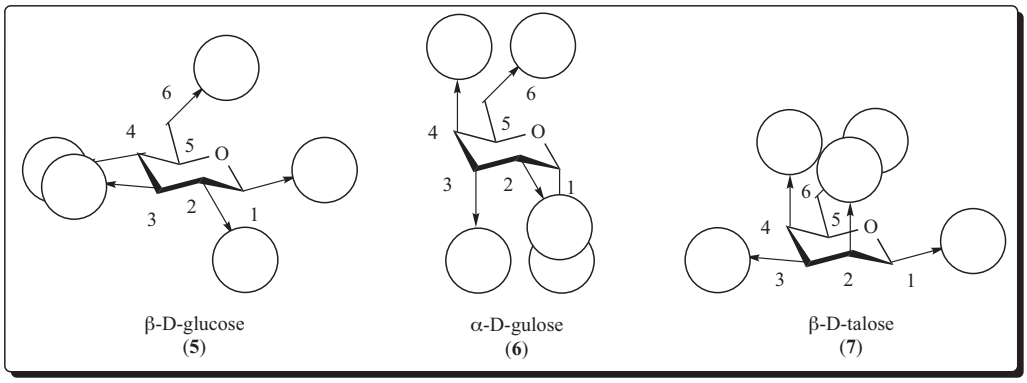


Table 1. Variation in the Number of Unique Presentations Available from Single or Multiple Scaffolds with Two (AB), Three (ABC), or Four (ABCD) Different Substituents

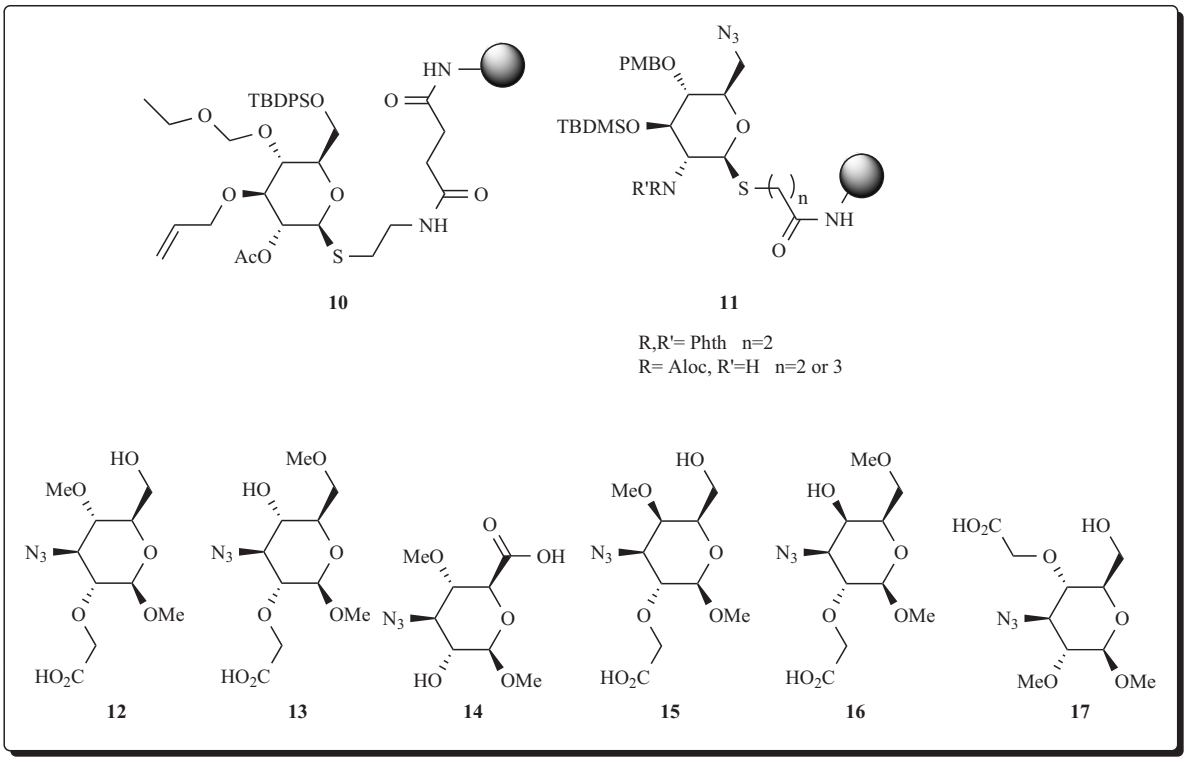
	AB	ABC	ABCD
One scaffold (e.g. α-D-Glc)	20	60	120
Two scaffolds differing at only one stereocentre	28	96	216
32 different scaffolds – maximum unique patterns	80	480	1920

individual substituents are included, such as variation of chain length, pKa, electron density, or steric bulk, it becomes clear that with this combination of conformational and chemical diversity carbohydrate scaffolds have the potential to be a powerful tool in drug discovery and development.

A systematic analysis of the 'conformational space' occupied by substituents on a carbohydrate scaffold reveals their potential [10]. Taking the case of three substituents on a number of different scaffolds with different substitution patterns as an example for a more detailed analysis, the centres of the pharmacophoric groups in the substituents and the centre of the carbohydrate ring can be taken as reference points and the three-dimensional shape of the molecule defined by using these reference points. Different scaffolds and different substitution patterns will lead to different presentations of the motif. The same principle can be applied to a tripeptide and comparison of the conformational space of both the trisubstituted carbohydrate scaffold and the tripeptide shows a very good overlap where almost all 'peptide space' is covered by carbohydrate scaffolds. In addition carbohydrates can access conformations that are not accessible to natural tripeptides.

The challenge with carbohydrates is the need to individually address single positions around the ring for the introduction of substituents. This issue has been addressed by several authors, including Kunz and co-workers [17-22] who have developed a set of orthogonally protected carbohydrate scaffolds (Structures **10** and **11**) for solid phase approaches that allow specific access to each position around the carbohydrate ring.

The most notable approach to date to exploit the structural diversity of carbohydrates is the development of a series of building blocks as scaffolds for a universal pharmacophore mapping library by Sofia and co-workers [23-25]. The six building blocks (**12**-**17**) shown below utilize a β-D-glucose or a β-D-galactose core from which a hydroxy group, a carboxylic acid and an amine, the latter masked as an azide, function as attachment points for the chosen pharmacophores.



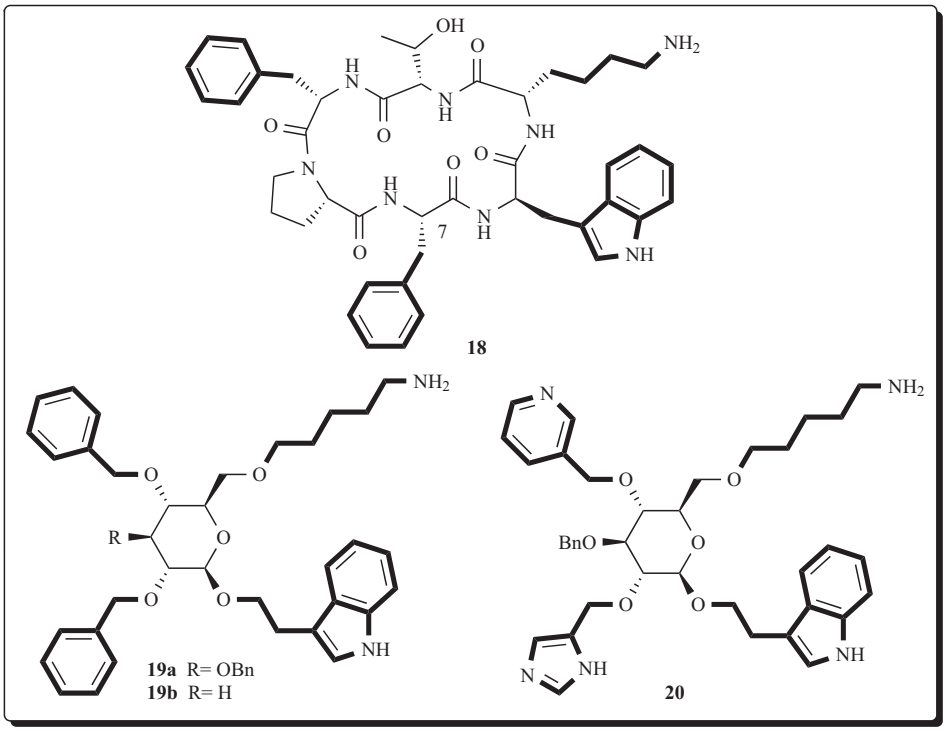
SST AND NK RECEPTORS

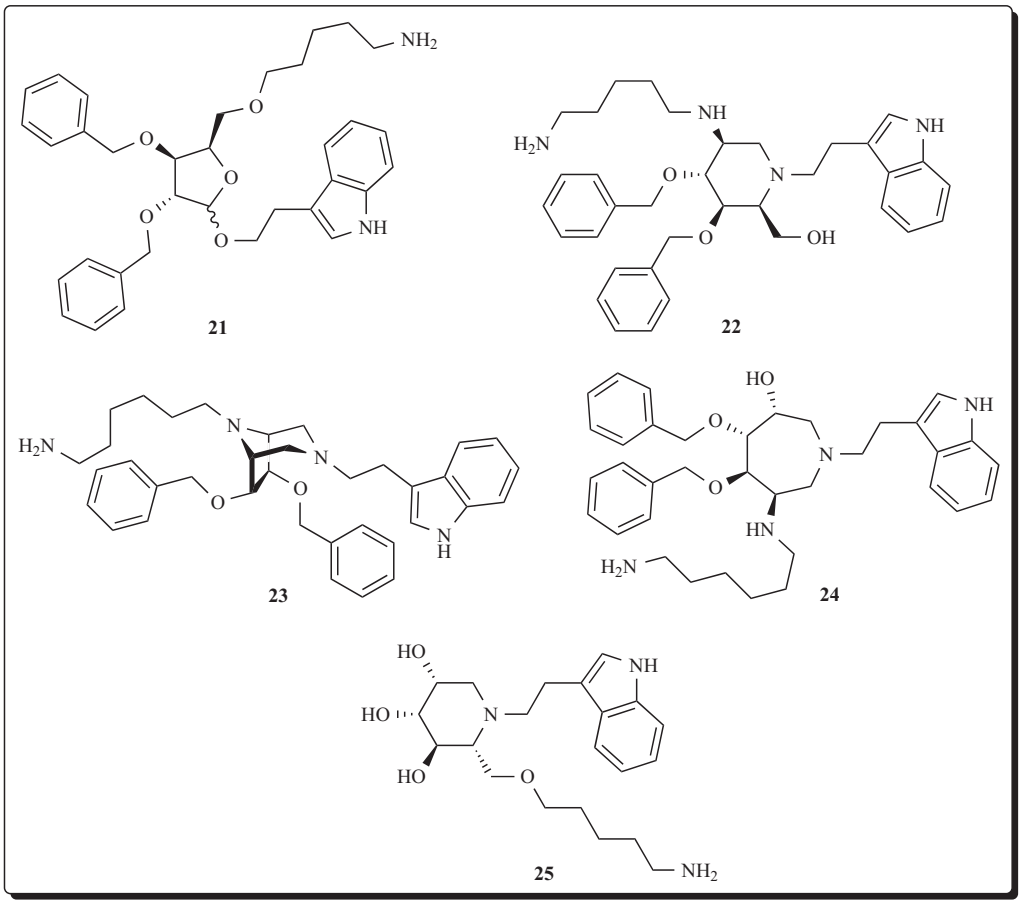
Hirschmann and co-workers were the first to employ sugar scaffolds as peptide mimetics during their investigation on somatostatin (somatotropin release inhibiting factor, SRIF) mimetics [1,26-28]. This work formed a landmark achievement in the field of templated drug design and development. Glucose derived compounds **19a** and **19b** were designed to mimic the active conformation of the cyclic hexapeptide L-363,301 (**18**), itself a potent somatostatin receptor agonist. NMR analysis of **18** indicated the existence of a type II′ β-turn, which was used to optimise the positions of the side chain mimetics in the glucose derivatives **19**. The distances between the side chains, *i.e.* phenyl ring (Phe), indole ring (Trp) and alkylamine (Lys), were compared for compounds **18** (NMR) and **19** (molecular modelling) and the data indicated reasonable spatial overlapping of the structures [1,28]. Phrase

Indeed, compounds **19a** and **19b** were found to bind to the somatostatin receptor with an IC_{50} of 9.5μM and 1.3 μM respectively [1]. Most importantly, compound **19b** inhibited GRF-induced growth hormone release in a functional assay, with an IC_{50} of 3μM, strongly suggesting that the binding of this peptide mimetic agonist is specific and that the SST receptor recognizes the ligand **19b** as a true SRIF mimetic [27]. Further Structure-Activity Relationship (SAR) studies involved functional changes, such as removal of individual substituents and replacement of the 4-benzyl substituent with imidazole carrying substituents [28].

The utility of sugar scaffolds as peptide backbone surrogates has been extended to readily available L-glucose and L- mannose [29]. By changing only the sugar template from D-glucose to L-glucose and L-mannose, the side chains are now situated in different representations, thus mimicking different conformations of the cyclic peptide **18**. Comparing the affinities of the different mimetics it was concluded that the position of the Phe^7 moiety of peptide **18** is likely to be axial in the active conformation. Furthermore, the replacement of the 2-benzyl substituent with an imidazole substituent led to sub-micromolar IC_{50} activity against the hSSTR1-4 subtypes [29] while being inactive against hSSTR5. This mirrors the improvement of hSSTR-activity observed when a phenylalanine of an active cyclic hexapeptide is replaced with a histidine, providing further parallelism between the peptides and their sugar-based mimetics. More recently, a comprehensive SAR study of the congeners of compound **19** was accomplished in the same laboratory [26]. A series of compounds containing various heterocyclic rings at the 4 position, including imidazole, pyrazine and various pyridine derivatives, were prepared systematically and their affinities towards somatostatin receptors examined. Significant affinity enhancement was achieved, especially for the SST4 receptor, with the best compound (**20**) having an IC_{50} of 53nM against the SST4 receptor.

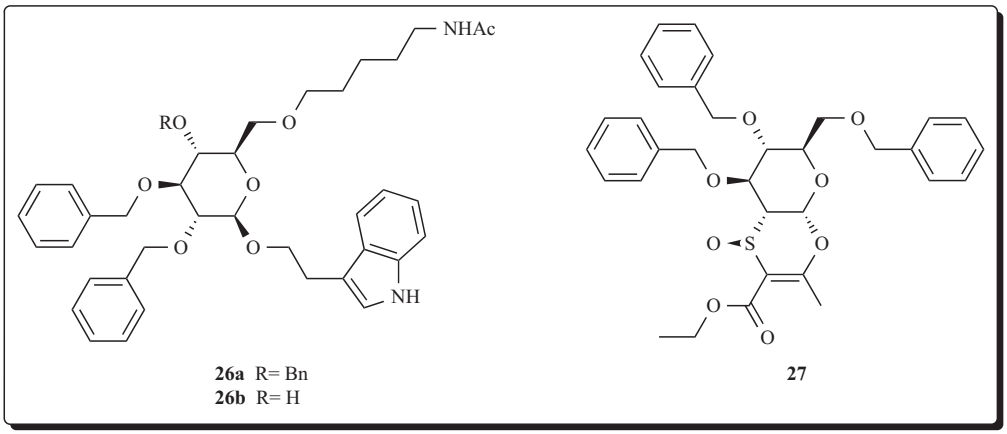
Furanose scaffolds have also been used to build mimetics targeting SST receptors. In a radio-ligand binding assay compound **21** exhibited an IC_{50} of 23μM, which is of a similar level of activity as its original lead **19b**. The same lead structure and data from peptidic somatostatin mimetics led to the design of a series of compounds based on iminosugars with 5-, 6-, and 7-membered rings as scaffolds, as well as some bicyclic carbohydrate derived scaffolds [30]. Some examples are compounds **22**, **23** and **24**. All 6 compounds synthesized exhibited similar IC_{50} values, ranging from 10 to 15 μM, and indicating good structural overlay.





1-Deoxymannojirimycin has been utilized as a scaffold to synthesize the somatostatin mimetic **25**. Despite the lack of Phe mimicking phenyl groups, the compound exhibited a K_i of 26 μM for the SST receptor in an unspecific assay, with preferential binding to SSTR4 compared to SSTR5 [31].

Interestingly, some of these somatostatin mimetics also show activity at other receptors. For instance compound **19a** is a β2-adrenergic antagonist with an IC_{50} of 3μM, and both **19a** and **19b** display an affinity for the substance P receptor (SPR, NK-1) with IC_{50}'s of 0.12μM and 0.18μM, respectively. In contrast, compound **26a**, the N-acetylated derivative of **19a**, loses all activity at the SST receptor, and instead is a potent NK-1 antagonist with an IC_{50} of 60nM [27]. Removal of the 4-benzyloxy group in **26a**, a group important for binding to the SST receptor, and leaving a free hydroxyl (**26b**), increases affinity further to an IC_{50} of 27nM at the NK-1 receptor [29].



Carbohydrate scaffolds have also been used to target the NK-2 receptor [32]; bicyclic systems derived from the cycloaddition between glycals and α,α'-dioxothiones were synthesized with different substituent patterns and compound **27** was found to have a K_i of 0.25μM at the NK-2 receptor.

INTEGRINS

Integrins are proteins that are involved in cell-cell recognition and cell adhesion. The key peptide sequence Arg-Gly-Asp (RGD) is often part of the recognition motif used by natural ligands and it is believed that the distance between the guanidine and the carboxylic moieties of the peptide is the decisive factor in the binding. Several cyclic peptide inhibitors have been identified and their NMR structure used for the design of small molecule peptidomimetics.

Monosaccharides have been incorporated as scaffolds in peptide mimetics targeting the integrin receptor family. Nicolaou and co-workers reported the solution phase synthesis of a small library of nine compounds based on mannose, glucose and arabinose scaffolds and designed to mimic the known inhibitor cyclic peptide **28** (cRGD*F*V) [33]. The library design saw the carboxylic group located either in position 1 or 2 of the sugar, while the guanidine moiety was tethered at position 6 *via* an alkyl chain of varying length, thus effectively scanning the distance between these two pharmacophores. A 3-benzyloxy group present mimicked the phenylalanine in all cases and all remaining hydroxyl groups were capped as methyl ethers. Although none of the compounds showed activity at the desired $\alpha_v\beta_3$ receptor, compound **29** showed modest activity at the related $\alpha_{II}\beta_3$ receptor with an IC_{50} of 85μM.

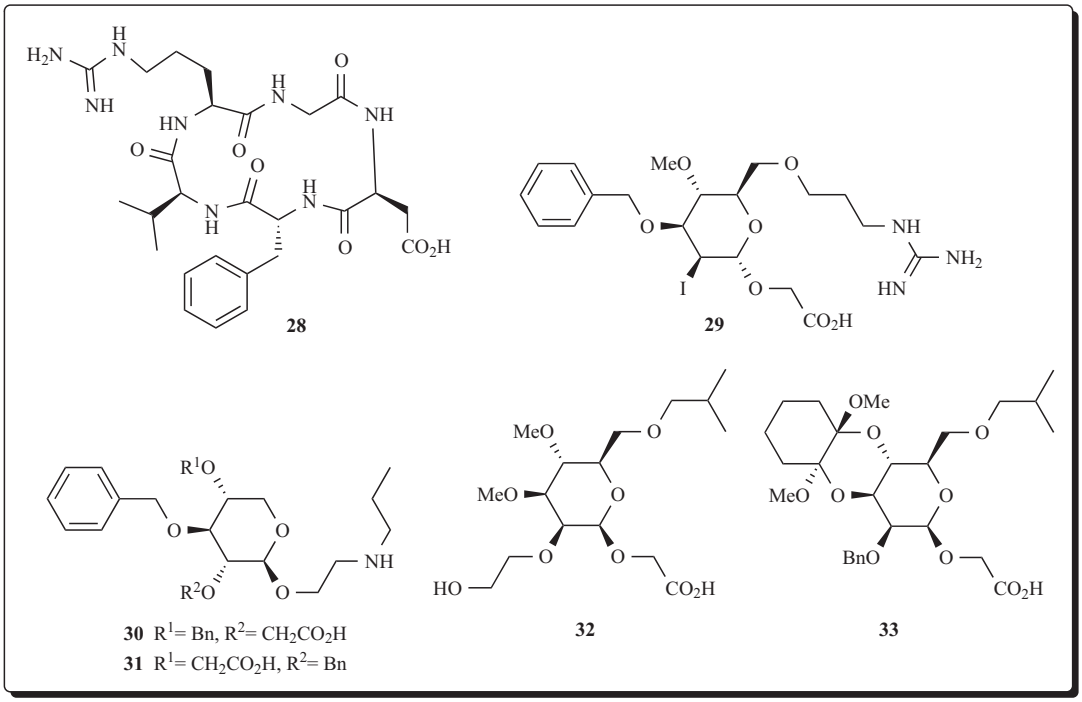
A similar approach targeting the $\alpha_{II}\beta_3$ receptor led to the preparation of four RGD mimetics from xylose [34]. A secondary amino group in the anomeric position was employed as an arginine mimetic, whilst the molecules also contained 0-2 benzyl and 1-3 glycolic substituents to mimic phenylalanine or aspartic side chains, respectively. Highest binding was observed for compound **30** with an IC_{50} of 20μM. The same scaffold was used to prepare a 126-membered library in the form of compound mixtures, which were tested and subsequently deconvoluted. This approach led to the discovery of compound **31**, which was found to be moderately active at the $\alpha_v\beta_3$ receptor [35].

Guided by the NMR solution conformations of an active cyclic peptide, molecular modelling was employed to design a small set of carbohydrate-based mimetics based on β-D-mannopyranose [36]. The program led to the identification of $\alpha_4\beta_1$ selective integrin antagonist **32**. The same scaffold was used in the search for a $\alpha_4\beta_7$ selective inhibitor and led to the discovery of compound **33** with an IC_{50} of 420μM [37].

ANTIBACTERIALS

A 99-membered library based on two furanose sugar amino acid building blocks was prepared using a solution phase approach [38]. The *arabino* and *lyxo* isomers of **34** were converted to the desired compounds, represented by compound **35**, and the library was submitted for antibacterial screening but no data was given.

The antibacterial activity of compound **36**, a degradation product of the highly active antibiotic moenomycin A, was used to design a library of 1300 compounds based on a disaccharide scaffold, which were synthesized using solid phase techniques [39]. Moenomycin A inhibits the transglycosylase activity of the penicillin-binding proteins, disrupting the synthesis of the bacterial cell wall. Screening for an-



tibacterial activity revealed several compounds, including compound **37**, with an MIC of 3-12 μg/mL at a number of resistant strains.

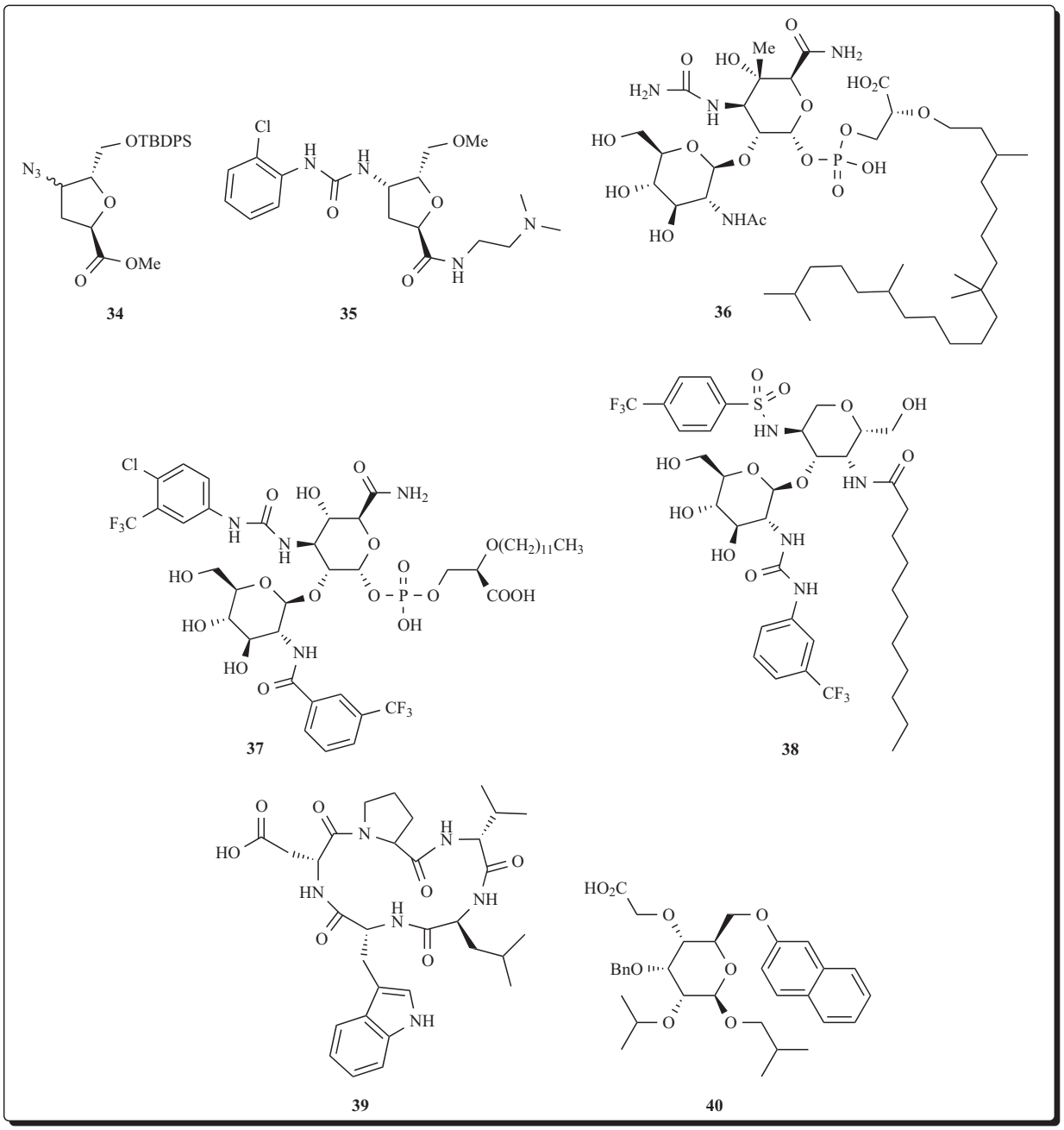
The same Moenomycin lead was used for the design of a library of disaccharides [40]. A number of compounds with MIC values ranging from 1-4 μg/mL were obtained and found to be active against a broad panel of Gram-positive bacteria, including many clinical isolates of vancomycin-resistant enterococci and methicillin-resistant *staphylococcus aureus*. The structure of one active (**38**) is shown below.

ENDOTHELIN RECEPTOR

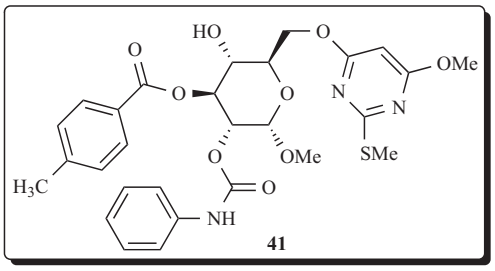
During a search for a CNS penetrating mimetic of the cyclic peptide endothelin antagonist BQ123 (**39**) [41], involving molecular modelling studies, a number of compounds based on glucose and allose scaffolds were synthesized, including derivative **40**. However no significant binding was observed for the endothelin receptor.

HERBICIDALS

By introducing pyriminidinyl groups as substituents on a D-glucose scaffold a library was produced targeting the ace-



tolacetate-synthase (ALS). [42] A mixed solution and solid phase approach was used to generate a set of compound mixtures containing a total of 237 individual compounds, whose activity was tested in a root growth inhibition assay for ALS activity and a number of compounds showed activity in the 10-100μM range. One representative structure from the library is shown below (**41**).



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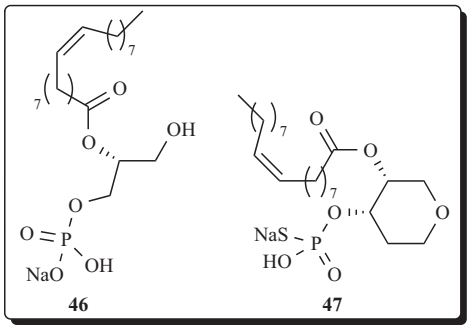
HIV-1 PROTEASE

Carbohydrate scaffolds were employed in the search for compounds that bind to aspartic proteases, of which HIV-1 protease is a member, since carbohydrate scaffolds were thought to provide the necessary stereochemical information to display the necessary binding elements in the right spatial orientation [43]. From a selection of several mannose and glucose derivatives, compound **42** proved to be the most active with an IC_{50} of 3.81μM. Introduction of sidechains as in compound **43**, which were intended to participate favourably in additional hydrogen bonding at the binding site, did not improve binding [44]. The use of 1-deoxymannojirimycin as a scaffold to introduce a positive charge similar to the proposed binding conformation of **44** led to the synthesis of compound **45** [44,45]. However, **45** still showed only moderate binding to HIV-1 protease.

LPA RECEPTOR

A series of mimetics of 2-oleoyl lysophosphatidic acid (2-oleoyl LPA, **46**) were designed, synthesized and tested against all three LPA receptors [46]. Subtype-selective agonists for LPA_1 and LPA_3, as well as an LPA_3-selective antagonist were identified. Compound **47** was found to be LPA_3-selective with an EC_{50} of ~0.5nM.

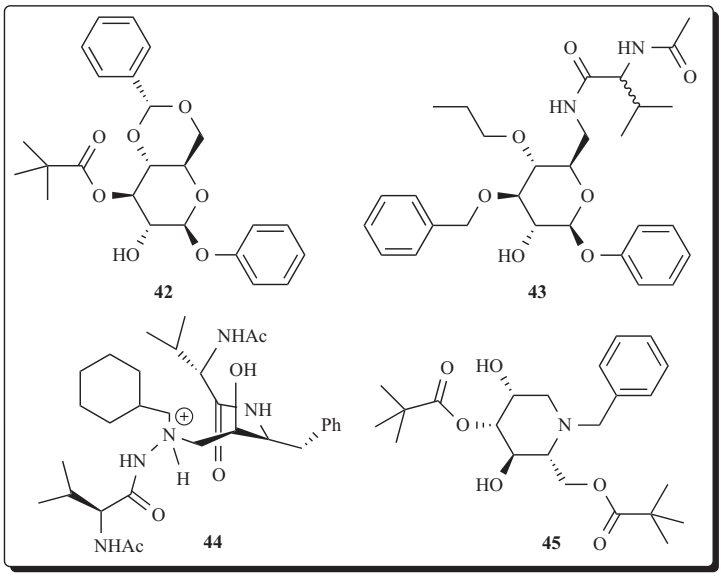


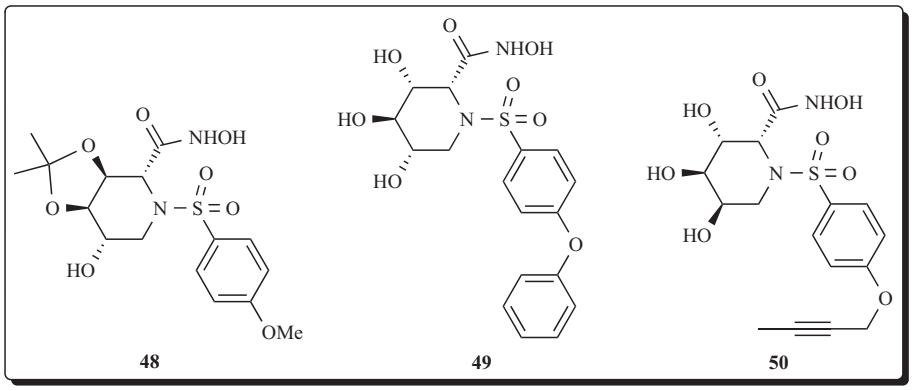
46 **47**

MMP AND TACE

The metalloproteinases family consists of two classes of zinc-containing enzymes; the matrix metalloproteinases (MMPs), and disintegrin and metalloproteinases (ADAMs), of which the TNF-α converting enzyme (TACE) is a prominent member. Based on the structures of known MMP inhibitors, a hydroxamic acid and an aromatic sulphonamide were incorporated as structural motifs on a 1-deoxynojirimycin scaffold [47]. This led to the discovery of a number of actives inhibiting MMP-1, MMP-3, MMP-9, and TACE. One of the actives was compound **48**, which had a K_i of 3.7nM at MMP-3 and about 5-10 fold higher at the other MMPs. Modification of the stereochemistry around the piperidine ring and variation of the substituent on the sulphonamide gave a number of derivatives with varying activity and selectivity [48-50]. The most active compounds were **49** with a K_i of 0.06nM at MMP-9 and **50** with a K_i of 0.53nM at TACE.

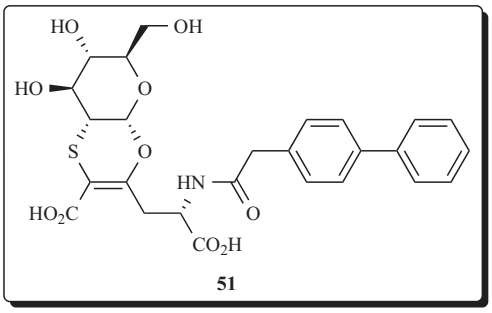
A bicyclic scaffold derived from the cycloaddition between a glucal and a α,α'-dioxothione [51] has been em-





48 **49** **50**

ployed, together with crystallographic data for MMP-12 and NMR studies to optimize the interaction with the protein. As a result, compound **51**, the first carbohydrate-based inhibitor for MMP-12 was discovered and this compound exhibited an IC_{50} of 490μM. A similar scaffold was used to target the NK-2 receptor, discussed above.



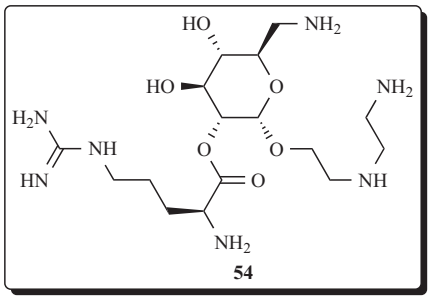
51

P-gp AND MRP

With the goal of reversing multiple drug resistance mediated by transporter proteins, an approach that utilised molecular modelling and with a focus on the structural lead of hapalosin (**52**), led to the design of a number of glucose-based compounds [52]. However, none of the compounds synthesized were effective in inhibiting P-glycoprotein (P-gp) mediated drug efflux, but some compounds did show antagonist activity towards multidrug resistance-associated protein (MRP) similar to hapalosin. One such example is compound **53**.

RNA BINDERS

A small library of 1,3-hydroxyamines based on an aminoglucopyranose building block was designed and synthesized, producing compounds that exhibited a range of specificities during tests using a surface plasmon resonance assay against different bacterial RNAs, whilst the best K_d obtained was 30μM for compound **54** [53].



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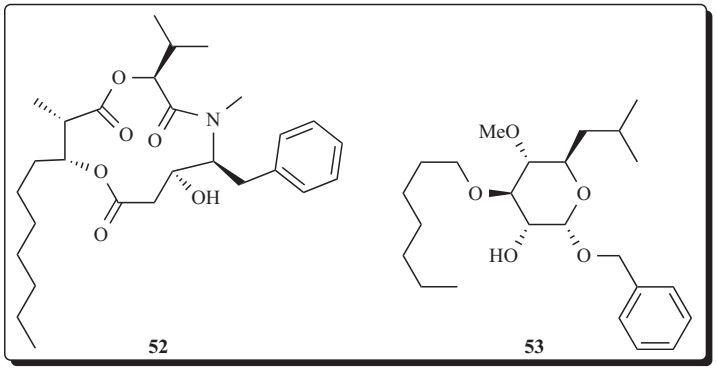
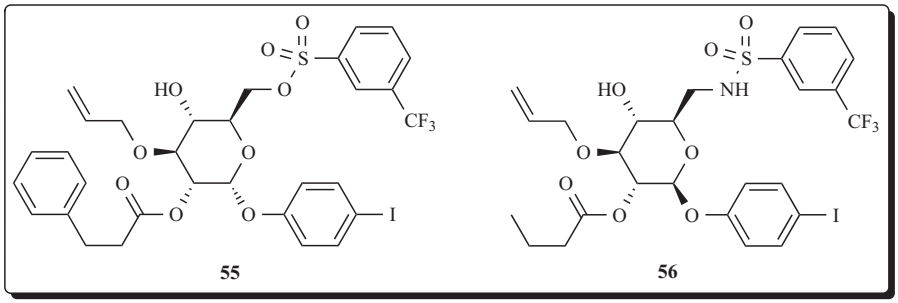
SH-2 DOMAIN

In an effort to find a non-peptide antagonist to the Src homology 2 (SH-2) binding domain [54], crystallographic data for high affinity phosphotyrosyl peptide ligands such as Y^PVNV provided the basis for the design of a small glucose-based library of 22 compounds. The best binding result was obtained for compound **55** with an IC_{50} of 2.00μM against EGF and HGF expressing A-431 cell lines. Based on these results the same group produced another small library tar-



52 **53**



55 **56**

geted at inducing apoptosis in human glioblastoma cells [55]. It could be shown that the active compounds (**56** as one example) displayed a selective inhibition of DNA synthesis.

SUMMARY

The first publication of the use of a carbohydrate scaffolds for the design and synthesis of peptidomimetic compounds in 1990 has generated a growing interest in the use of these scaffolds for the drug discovery process. Since then biologically active molecules from carbohydrate-based approaches were found for a number of very different targets, most notably in the area of G-protein coupled receptors (for example the somatostatin receptor), integrins, matrix metalloproteinases (MMPs), and the multidrug resistance-associated protein (MRP), as well as compounds that show antibacterial or antiviral activity.

Orthogonal combinations of protecting groups for solution and solid phase approaches together with a variety of chemical linking strategies offer the possibility to introduce a huge variety of pharmacophoric groups around basic carbohydrate scaffolds in a stereodefined manner. This allows a multitude of presentations of individual binding motifs as well as broad mapping approaches to probe binding sites on targets of biological relevance.

Although there is only limited pharmacokinetic data available at this point in time, substituted carbohydrates do not seem to be intrinsically unstable under physiological conditions and their physical and pharmacokinetic properties are largely determined by the substituents introduced. With the tools at hand to explore this new class of small molecule scaffold it may only be a question of time until we see the first results of a carbohydrate-based drug discovery approach in the clinic.

ABBREVIATIONS

PK = Pharmacokinetic

SRIF = Somatotropin Release Inhibiting Factor

SAR = Structure-Activity Relationship

MMPs = Matrix Metalloproteinases

ADAMs = Disintegrin and Metalloproteinases

TACE = TNF-α Converting Enzyme

P-gp = P-glycoprotein

MRP = Multidrug Resistance-associated Protein

SH-2 = Src homology 2

2-oleoyl LPA = 2-Oleoyl lysophosphatidic acid

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