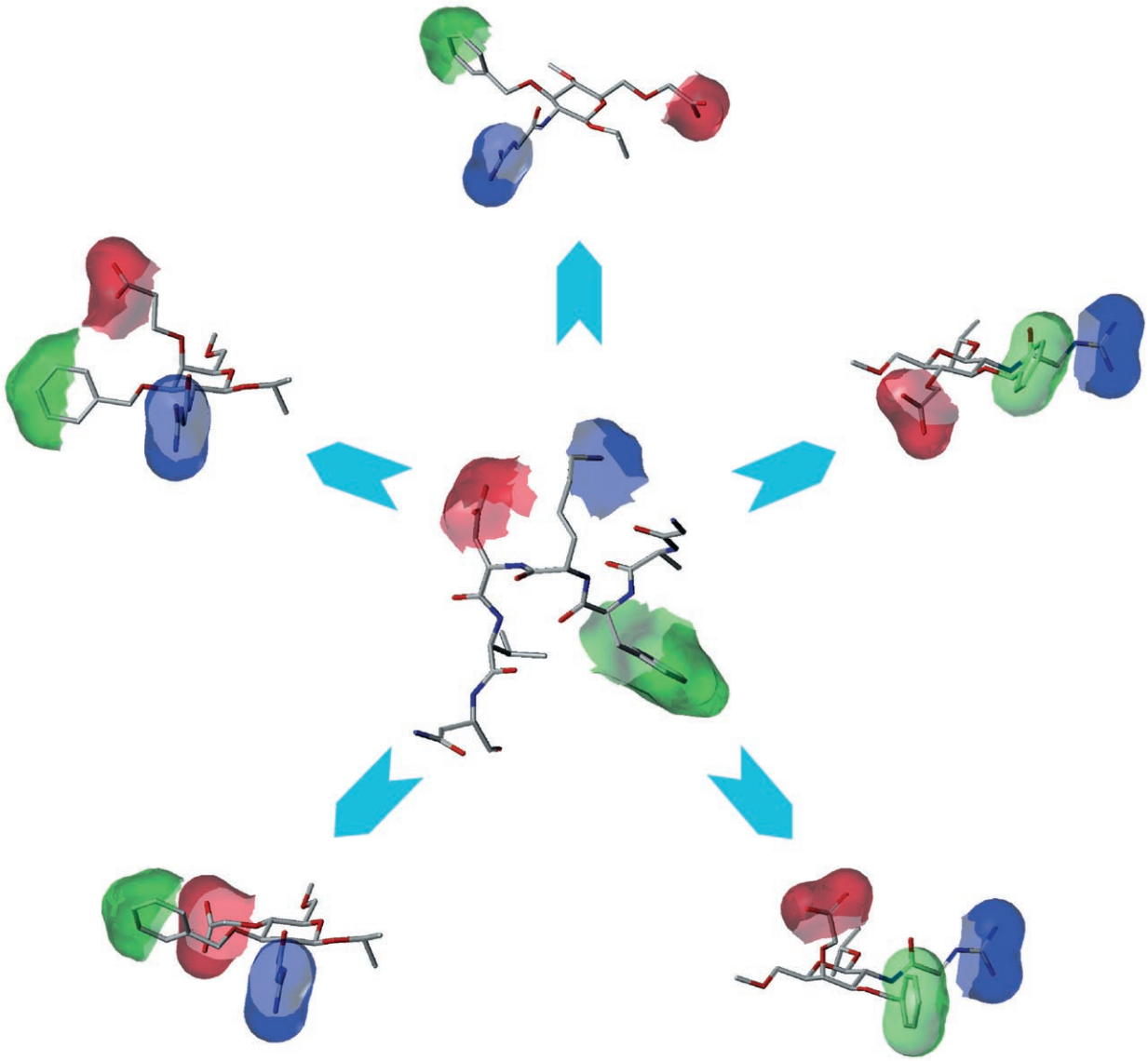
Carbohydrates as Scaffolds in Drug Discovery



Peptide ⇒ Carbohydrate ⇒ Drug Candidate

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Carbohydrates as Scaffolds in Drug Discovery

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Drug discovery has long suffered from the difficulty of having to place pharmacophoric groups in just the right spatial arrangement to elicit the desired biological response. Although some molecule classes have been discovered that seem to be privileged structures for at least some drug–receptor interactions, there remains the challenge to design and synthesize molecules with high specific affinity to pharmacologically important targets. With their high density of stereochemical information and their relative rigidity, carbohydrates provide excellent platforms upon which to display a number of substituents in a sterically defined way, hence offering the opportunity to harness their unique features for the drug-discovery process. This review highlights the progress that has been made in the development of carbohydrate scaffolds for drug discovery.

1. Introduction

After the first publication[1] of the successful use of carbohydrates as new scaffolds in the area of peptidomimetics, there has been a growing interest in the use of carbohydrates as scaffolds for drug discovery. A number of reviews in recent years have discussed some aspects of the field, 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 aim of this review is to provide an overview of drug-discovery approaches using carbohydrates as scaffolds to display chemical functionalities that have the potential to interact with a receptor or enzyme. This article covers targeted approaches that describe the syntheses of compounds that aim for a specific receptor or enzyme, as well as general chemical approaches in which synthetic methods are explored that enable the synthesis of compound libraries for screening. Compounds or compound libraries that target carbohydrate-processing enzymes (such as glycosidases and glycosyl transferases) or carbohydrate-recognizing receptors (such as selectins) are generally not considered herein. Also outside the scope of this review is the synthesis of glycopeptides or peptides that incorporate carbohydrates as turn mimetics and the synthesis of oligosaccharides or nucleotide derivatives and oligonucleotides.

'Templated' drug design and development originated in the field of peptidomimetics and is based on the concept that bioactive molecules consist of binding components (or pharmacophore groups), which directly interact with the target, and nonbinding components, which form the framework of the bioactive molecule. In the case of peptide ligands or substrates, for instance, usually a small number of amino acid side chains form direct interactions with their receptor or enzyme, whereas the peptide backbone (and other amino acid residues) provide the structure or scaffold that controls the relative positioning of the binding side chains. Essentially, the bioactivity of a peptide ligand is considered to originate 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.

Scaffold selection in a drug-discovery approach is determined by the level of knowledge and certainty about structural requirements for target binding. For cases in which these are known, for example, through co-crystallisation of the target protein with a natural or synthetic ligand/substrate and analysis of the resulting crystallographic data or through NMR binding analysis, rigid scaffolds are designed to accurately mimic the "perfect" positioning of the substituents. A binding mode is proposed, and single mimetics are produced to test the model.

Often the bioactive conformation of the peptide is less defined, leading to difficulties in scaffold selection. In this case, many structural presentations need to be incorporated into the design. A larger number of compounds are required to test the concept, and where possible, parallel synthesis is the method of choice.

The ideal scaffold for this "biomimetic" approach has a low molecular weight and a chemically stable nonbinding core with a number of functional groups of orthogonal reactivity. The core must be rigid to allow a controlled three-dimensional presentation of pharmacophores. The spatial orientation of the functional groups has to be adjustable to generate the presentation required for tightest binding, and the resulting molecule will require reasonable biological stability. Additional attach-

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ment points away from the binding structures are desirable to be able to manipulate the pharmacokinetic (PK) parameters of the resulting molecules by the introduction of additional functional groups, for example, to improve such factors as solubility and permeability.

No scaffold is able to satisfy all these demands equally well. Aromatic systems, for instance, may be a good starting point, as derivatives are readily available and substituents are relatively easy to introduce. On the other hand, they are generally flat molecules, making a true three-dimensional presentation of any substituents difficult. Natural products such as alkaloids may have a well-defined rigid three-dimensional structure, but the introduction of substituents in the desired positions may be chemically challenging and unsuitable for the synthesis of compound libraries. Peptides provide an easy way to assemble a large variety of pharmacophores, but they are often not rigid enough and are labile in biological environments.

Carbohydrates provide a relatively rigid core with a number of functional (mostly hydroxy) groups 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 by the inversion of individual positions (Figure 1). The challenge with carbohydrates is the ability to individually address single positions along the ring for the introduction of substituents. However, this problem has been addressed by several authors (as discussed below), most comprehensively by Kunz and co-workers,[15–20] and orthogonally protected carbohydrate scaffolds have been developed for solution- and solid-phase approaches that allow specific access to each position along the carbohydrate ring (Figure 2a).

Contrary to common perception, substituted carbohydrate derivatives are generally quite stable. Substituted carbohydrates usually display reasonable to good stability toward gastric acids and liver metabolism once the hemiacetal is converted into a glycoside. Labile carbohydrates are the unsubstituted oligo- and polysaccharides, which are usually rapidly processed in a biological environment.

The PK parameters and the level of drug-likeness of substituted carbohydrates are mostly dictated by the nature of the substituents present. There are, in fact, a number of carbohydrate-based drugs on the market and in different stages of development which illustrate the drug-like characteristics of substituted carbohydrates, from stability to oral availability.[21] One example of the excellent biological stability of a highly functionalized carbohydrate is the Sanofi–Synthelabo pentasaccharide product Idraparinux sodium,[22] which carries a number of sulfates, carboxylates, and methoxy substituents and has an elimination half-life of 120 h.

The most notable approach to date that exploits 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 shown in Figure 2b use a β-D-glucose and a β-D-galactose core from which a hydroxy group, a carboxylic acid, and an amine masked as an azide are displayed in different orientations to serve as attachment points for the chosen pharmacophores.

The possibility of using carbohydrates as three-dimensional scaffolds is indeed appealing. By presenting a set of substituents on different scaffolds and in different patterns, a large number of isomers of the same molecular weight can be generated that present the same substituents in a variety of spatial orientations (see Figure 3 for examples).

A systematic analysis of the 'conformational space' occupied by substituents on a carbohydrate scaffold reveals the potential.[10] Looking at simple hexopyranoses (the most common

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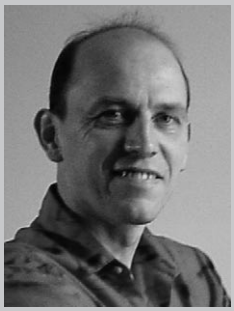

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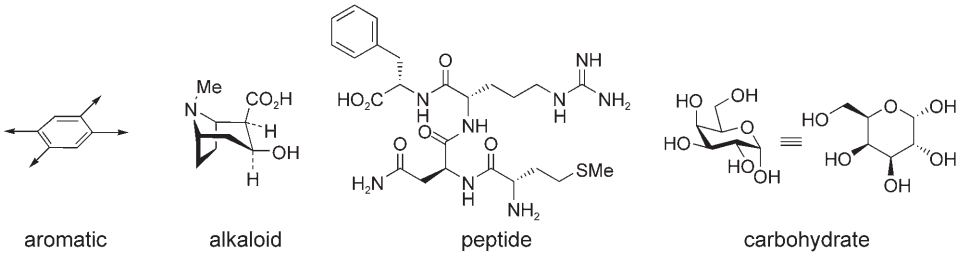


Figure 1. Scaffolds for drug discovery.

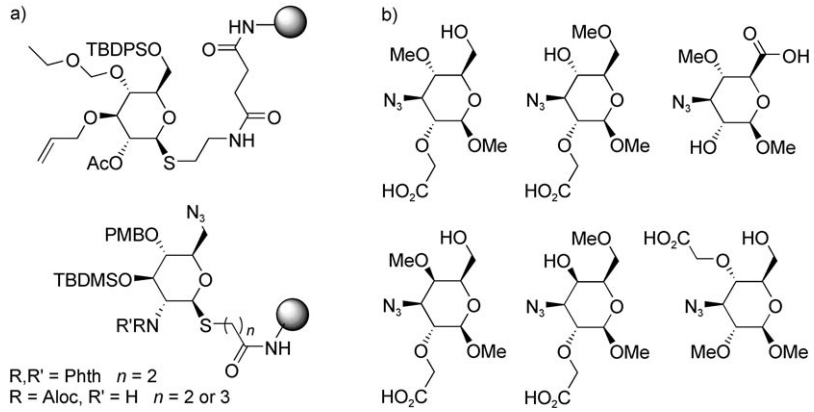


Figure 2. Carbohydrate building blocks: a) orthogonal protection group strategies (Kunz and co-workers); b) building blocks for universal pharmacophore mapping library (Sofia and co-workers).

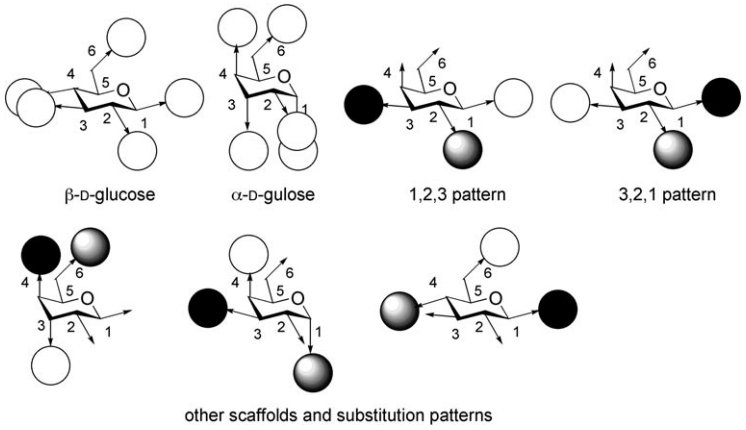


Figure 3. The various orientations of substituents on carbohydrate scaffolds.

carbohydrates), there are five possible substitution sites related to five stereocentres, each with two possible orientations (axial and equatorial); this means there are $2^5 = 32$ possible scaffolds. The examples in Figure 3 show the β-D-glucose and the α-D-gulose scaffolds. It is also apparent that if different substituents are used, they can be displayed on the same scaffold as positional isomers by using different substitution patterns. In the example in Figure 3, three different substituents are attached to a β-D-galactose scaffold in two different substitution patterns. In the 1,2,3 and the 3,2,1 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 display the same substituents in different spatial orientations, and changing the scaffold further increases the variety of three-dimensional presentations.

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 can be 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, in which almost all 'peptide space' is also covered by carbohydrate scaffolds. Moreover, carbohydrates can access conformations that are not accessible to natural tripeptides.

The fact that different substitution patterns can be chosen on the same scaffold to generate more presentations of the same binding motif leads to a large increase of the possible number of unique presentations for any particular combination of pharmacophores. Table 1 shows the relationship between the number of unique presentations and the number of substituents and scaffolds. For example, with only one scaffold and four different substituents, there are already 120 different ways to present 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 individual substituents are included, such as variation of chain

Table 1. Unique presentations as a function of the number of substituents and scaffolds.

Number of Scaffolds	Substituents AB	ABC	ABCD
1 (example: α-D-Glc)	20	60	120
2 (differing at only one stereocentre)	28	96	216
32 (max. number of unique patterns)	80	480	1920

length, pK_a, electron density, and 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.

2. Targeted Approaches

2.1. SST and NK receptors

The concept that sugars could provide suitable scaffolds to mimic particular peptide folds was pioneered by Hirschmann and co-workers in 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.

D-Glucose-derived compounds **2a** and **2b** were designed to mimic the active conformation of the cyclic hexapeptide L-363,301 (**1**), a potent somatostatin receptor agonist (Figure 4) with an IC_{50} value in the low nanomolar range. NMR spectroscopic analysis of **1** indicated the presence of the type II′ β turn, and this was used to determine the best positioning of the side-chain mimetics in the glucose derivatives **2**. The distances between the side chains, that is, the phenyl rings (Phe), indole ring (Trp), and alkylamine (Lys), were compared for compounds **1** (NMR) and **2** (molecular modelling), and the data indicated a reasonable spatial overlap of the structures.[1,28]

In a radioligand displacement assay, compounds **2a** and **2b** bound to the somatostatin receptor in a dose-dependent manner with IC_{50} values of 9.5 and 1.3 μM, respectively.[1] Importantly, compound **2b** inhibits the growth hormone releasing factor (GRF)-induced growth hormone release in a functional assay with an IC_{50} value of 3 μM, which strongly suggests that the binding of this peptide mimetic agonist is specific and that the somatostatin (SST) receptor recognizes ligand **2b** as a true SRIF mimetic.[27] Further structure–activity relationship (SAR) studies involved functional changes such as the removal of individual substituents and replacement of the 4-benzyl substituent with imidazole-carrying substituents.[28]

Hirschman and co-workers further demonstrated the utility of sugar scaffolds as peptide backbone surrogates by exploiting 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 situated in different representations, thus mimicking a different conformation of the cyclic peptide **1**. Comparing the affinities of the different mimetics led to the conclusion that the position of the Phe 7 moiety of peptide **1** is likely to be axial in the active conformation.

Replacement of the 2-benzyl substituent with an imidazole substituent[29] led to sub-micromolar IC_{50} activity against the human SST receptor subtypes 1–4 (hSSTR1–4), while being inactive against hSSTR5. This mirrors the improvement of hSSTR inhibition observed when a phenylalanine residue of an active cyclic hexapeptide is replaced by histidine, providing further parallelism between the peptides and their sugar-based mimetics.

More recently, comprehensive SAR studies of the congeners of compound **2** were conducted in the same laboratory.[26] A series of compounds was synthesized in which the 4-benzyl group was systematically substituted with heterocyclic rings, and the affinities toward somatostatin receptors were examined. The substituents included imidazole, pyrazine, and various pyridine derivatives. Significant affinity enhancement was observed especially for SSTR4. The best compound, **3**, had an IC_{50} value of 53 nM against SSTR4.

Another mimetic that targets SST receptors, but which is based on a furanose scaffold was reported early on by Papageorgiou and co-workers.[30] In a radioligand binding assay, compound **4** showed an IC_{50} value of 23 μM, which is of a similar level of activity as that of its original lead, **2b** (Figure 5).

Based on the same lead structure and data from peptidic somatostatin mimetics, Depezay and co-workers designed a series of compounds based on iminosugars with 5-, 6-, and 7-membered rings as scaffolds as well as some bicyclic carbohydrate-derived scaffolds.[31] Some examples are the compounds **5**, **6**, and **7** shown in Figure 5. The activities of all six compounds synthesized were quite similar, with IC_{50} values ranging from 10 to 15 μM, indicating good structural overlay.

A similar approach was taken by Murphy and co-workers using 1-deoxymannojirimycin as a scaffold to synthesize the somatostatin mimetic **8** (Figure 5). Despite the lack of phenyl groups in the side chain to mimic Phe, the compound still has a K_i value of 26 μM for the SST receptor in an unspecific assay, with preferential binding to SSTR4 over SSTR5.[32]

Interestingly, some of these somatostatin mimetics also show activity at some other receptors. For instance, compound **2a** is a β2-adrenergic antagonist with an IC_{50} value of 3 μM, and both **2a** and **2b** display an affinity for the substance P receptor (SPR, also neurokinin receptor NK-1) with IC_{50} values of

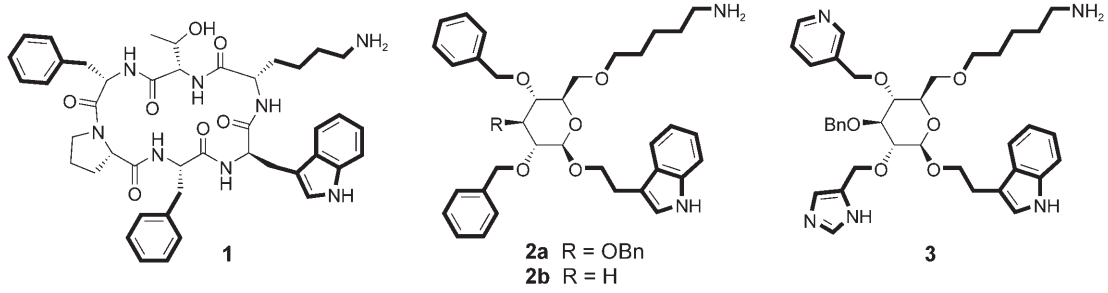


Figure 4. Carbohydrates as SRIF mimetics.

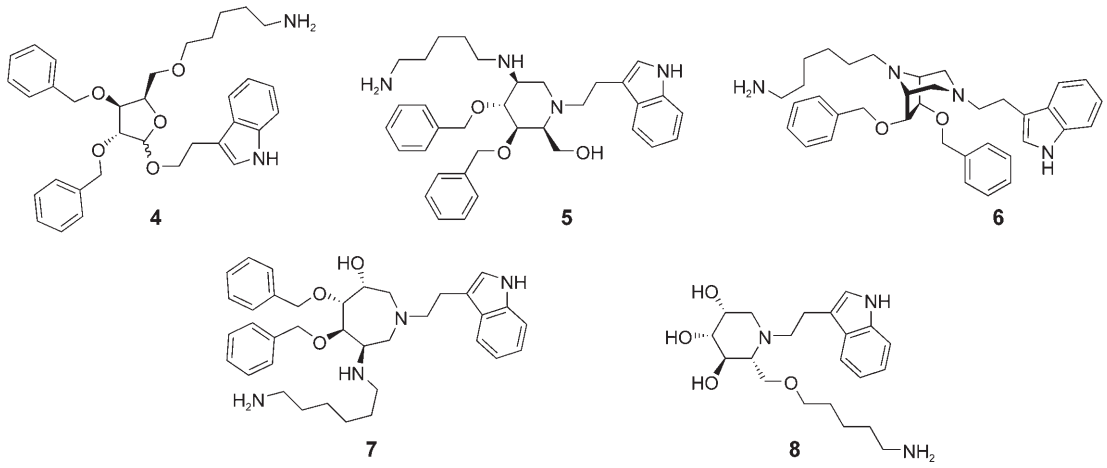


Figure 5. Carbohydrate derivatives that target somatostatin receptors.

0.12 and 0.18 μM, respectively. The parent peptide **1** shows no activity at either of the receptors. In contrast, compound **9a**, the N-acetylated derivative of **2a**, loses all activity at the SST receptor and turns into a potent NK-1 antagonist with an IC_{50} value of 60 nM[27] (Figure 6). By removing the 4-benzyloxy

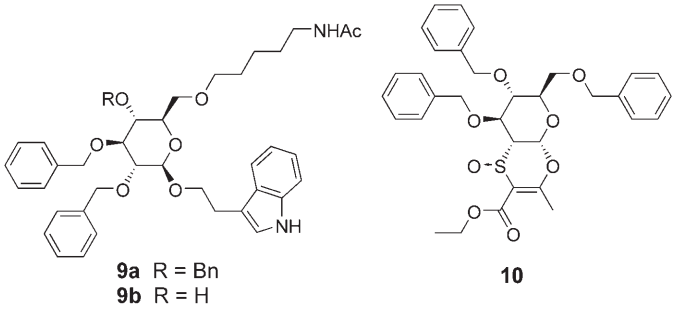


Figure 6. NK-1 and NK-2 receptor actives.

group in **9a**, which is important for binding to the SST receptor, and leaving a free hydroxy group (in **9b**), this affinity is further improved to an IC_{50} value of 27 nM at the NK-1 receptor.[29]

The NK-2 receptor can also be targeted by using a carbohydrate scaffold, as shown by Nativi, Altamura, and co-workers. Bicyclic systems derived from the cycloaddition between glycals and α,α′-dioxothiones were synthesized with different substituent patterns, and compound **10** was found to have a K_i value of 0.25 μM at the NK-2 receptor[33] (Figure 6).

2.2. Integrins

Integrins are a class of proteins that facilitate cell–cell recognition and cell adhesion, and many natural ligands contain the key peptide sequence Arg-Gly-Asp (RGD) as part of the recognition motif. It is believed that the distance between the guanidine and the carboxylic acid moieties of the peptide is the decisive factor in binding. Several cyclic peptide inhibitors have been identified, and their NMR structures have been used for the design of small-molecule peptidomimetics.

Monosaccharide scaffolds have proven to be particularly well-employed as surrogates for the peptide backbone of ligands for the integrin receptor family. Nicolaou and co-workers reported the solution-phase synthesis of a small library of nine compounds designed to mimic the known inhibitor, cyclic peptide **11** (*c*RGDFV)[34] shown in Figure 7. The carbohydrate scaffolds used included mannose, glucose, and arabinose. In the design of the glucosides, the carboxylic group was located either in position 1 or 2 of the sugar, while the guanidine moiety resided in position 6 with various chain lengths. This strategy effectively scanned the distance between the guanidine and carboxylic groups in the small library. A 3-benzyloxy group mimicked the phenylalanine in all cases, and all remaining hydroxy groups were capped as methyl ethers.

None of the compounds showed activity at the desired $\alpha_v\beta_3$ receptor, for which **11** has an IC_{50} value of 8 μM. However, one of the compounds, **12**, showed modest activity at the related $\alpha_{II}\beta_3$ receptor with an IC_{50} value of 85 μM.

A similar approach was followed by Chapleur and co-workers[35] targeting the $\alpha_{II}\beta_3$ receptor. Four RGD mimetics were prepared from xylose. A secondary amino group in the anomeric position was employed as an arginine mimetic; the molecules also contained 0–2 benzyl and 1–3 glycolic acid substituents as phenylalanine and aspartic acid side chains, respectively. The highest-affinity binding was observed for compound **13**, with an IC_{50} value of 20 μM (Figure 7).

Using the same scaffold, the same research group prepared a 126-member library in the form of compound mixtures, which were tested and subsequently deconvoluted. This approach led to the discovery of compound **14**, which was found to be moderately active at the $\alpha_v\beta_3$ receptor.[36]

More recently, Kessler's research group demonstrated the success of this peptidomimetic design.[37] 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. The program led to the identification of the $\alpha_4\beta_1$-selective integrin an-

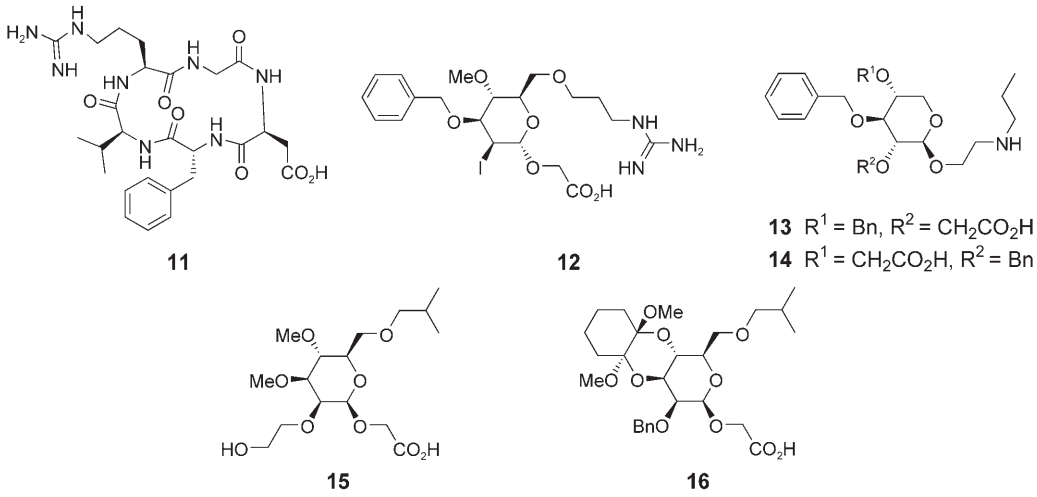


Figure 7. Ligands for the integrin receptor family.

tagonist **15** (Figure 7). The same scaffold was used in the search for a $\alpha_4\beta_7$-selective inhibitor and led to the discovery of compound **16**, which has an IC_{50} value of 420 μM.[38]

2.3. MMP and TACE

The family of metalloproteinases is a group of zinc-containing enzymes and consists of two classes. One is the matrix metalloproteinases (MMPs), the other class are the disintegrin and metalloproteinases (ADAMs), of which the TNF-α converting enzyme (TACE) is a prominent member.

Based on the structures of known MMP inhibitors, Tsukida, Nishimura, and co-workers decided to display hydroxamic acid and an aromatic sulfonamide as structural motifs on a 1-deoxynojirimycin scaffold.[39] This led to the discovery of a number of actives that inhibit MMP-1, MMP-3, MMP-9, and TACE. One of the actives was compound **17**, which had a K_i value of 3.7 nM at MMP-3 and values ~5–10-fold higher toward the other MMPs (Figure 8). Modification of the stereochemistry around the pyrimidine ring and variation of the substituent on the sulfonamide gave a number of derivatives with varying activity and selectivity.[40–42] The most active compounds were **18**, with a K_i value of 0.06 nM at MMP-9 and **19**, with a K_i value of 0.53 nM at TACE.

Nativi and co-workers used a bicyclic scaffold derived from the cycloaddition between a glucal and an α,α′-dioxothione.[43] With crystallographic data for MMP-12 together with NMR studies, they optimized the interaction with the protein. As a result compound **20** was discovered as the first carbohydrate-based inhibitor for MMP-12 and showed an IC_{50} value of 490 μM (Figure 8).

2.4. Antivirals

HIV-1 protease belongs to the family of aspartic proteases. Analysis of the active conformation of known aspartic protease inhibitors such as **21** led Murphy, Smith III, and co-workers to conclude that a carbohydrate scaffold provides the necessary stereochemical information to display the required binding elements in the correct spatial orientation.[44] Out of several mannose and glucose derivatives, **22** proved to be the most active, with an IC_{50} value of 3.81 μM. Introduction of side chains (as in compound **23**) to pick up additional hydrogen bonds in the binding site did not lead to an improvement in binding affinity[45] (Figure 9).

The use of 1-deoxymannojirimycin as a scaffold to introduce a positive charge similar to the proposed binding conformation of **21** (Figure 9) led to the synthesis of compound **24**.[45,46] However, **24** still showed only moderate binding to HIV-1 protease.

The human cytomegalovirus (CMV) is a widespread member of the herpes virus family. Van der Eycken and co-workers[47]

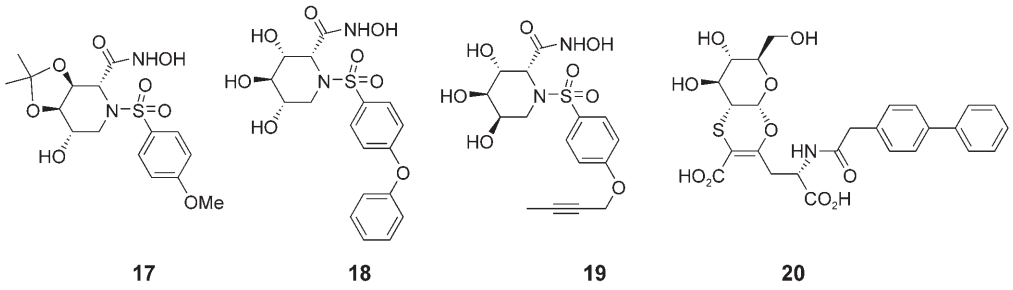


Figure 8. Inhibitors for matrix metalloproteinases.

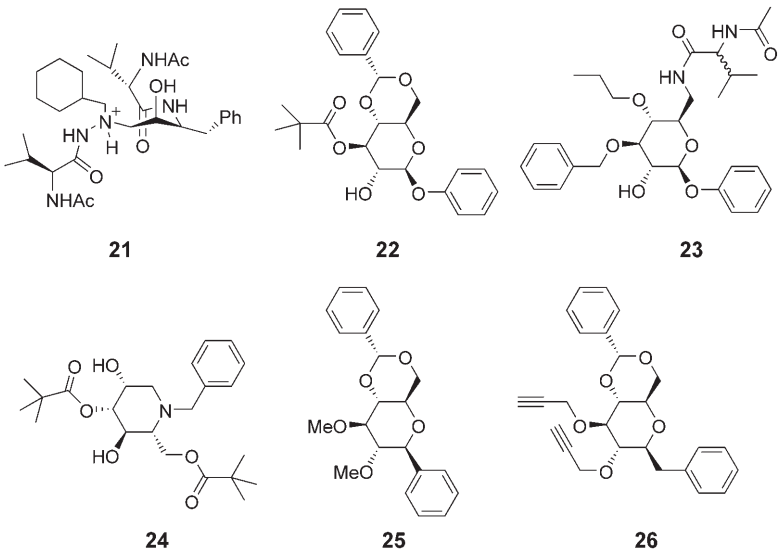


Figure 9. Inhibitors of HIV-1 protease and compounds active against CMV.

discovered that compound **25** (Figure 9) showed good activity as a CMV inhibitor and developed a series of analogues, of which **26** showed the highest activity against two different CMV strains in an assay in human embryonic lung cells, with an IC_{50} value of 0.5 $\mu g\,mL^{-1}$.

based compounds. None of the compounds synthesized was effective in inhibiting P-glycoprotein (P-gp)-mediated drug efflux, but some compounds showed antagonist activity toward multidrug-resistance-associated protein (MRP) similar to that of hapalosin. Figure 10 shows one of the structures synthesized (compound **30**).

2.7. SH2 domain

Hanessian et al. synthesized compounds in an effort to find a nonpeptide antagonist to the Src homology 2 (SH2) binding domain.[50] 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 **31** (Figure 11) with an IC_{50} value of 2.00 μM against EGF- and HGF-expressing A-431 cell lines.

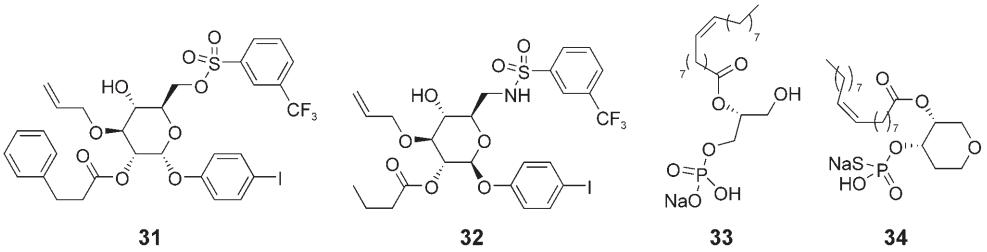


Figure 11. SH2 binding domain antagonists and LPA mimetics.

2.5. Endothelin receptor

In search of a CNS-penetrating mimetic of the cyclic peptide endothelin antagonist BQ123 (**27**), Billington and co-workers[48] undertook molecular modelling studies and synthesized a number of compounds based on glucose and allose scaffolds, including derivative **28** (Figure 10). However, no significant binding was observed for the endothelin receptor.

2.6. P-gp and MRP

With the goal of reversing multiple drug resistance mediated by transporter proteins, Armstrong and co-workers[49] followed the structural lead of hapalosin (**29**). The approach guided by molecular modelling led to the design of a number of glucose-

Based on these results, the same group produced another small library targeted at inducing apoptosis in human glioblastoma cells.[51] It was shown that the active compounds (**32** as one example) displayed selective inhibition of DNA synthesis.

2.8. LPA receptors

Kanai, Shibasaki, and co-workers designed and synthesized a series of mimetics of 2-oleoyl lysophosphatidic acid (2-oleoyl LPA, **33**, Figure 11) and tested them against all three LPA receptors.[52] Subtype-selective agonists for LPA_1 and LPA_3, as well as an LPA_3-selective antagonist were identified. Structure **34** is an example of an LPA_3-selective compound with an EC_{50} value

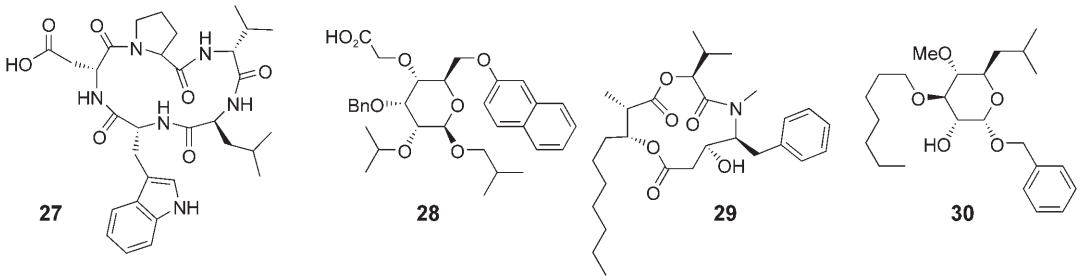


Figure 10. Compounds that targeting the endothelin receptor and multidrug-resistance-associated protein (MRP).

of ~0.5 nM, which compares well with 2-oleoyl LPA (**33**), which has an EC_{50} value of 50–100 nM.

2.9. Antibacterials

A 99-member library based on two furanose sugar amino acid building blocks was synthesized by Fleet and co-workers.[53] Compounds **35** and **36** are two representative examples from the library (Figure 12). The library was submitted for antibacterial screening, but no data was given.

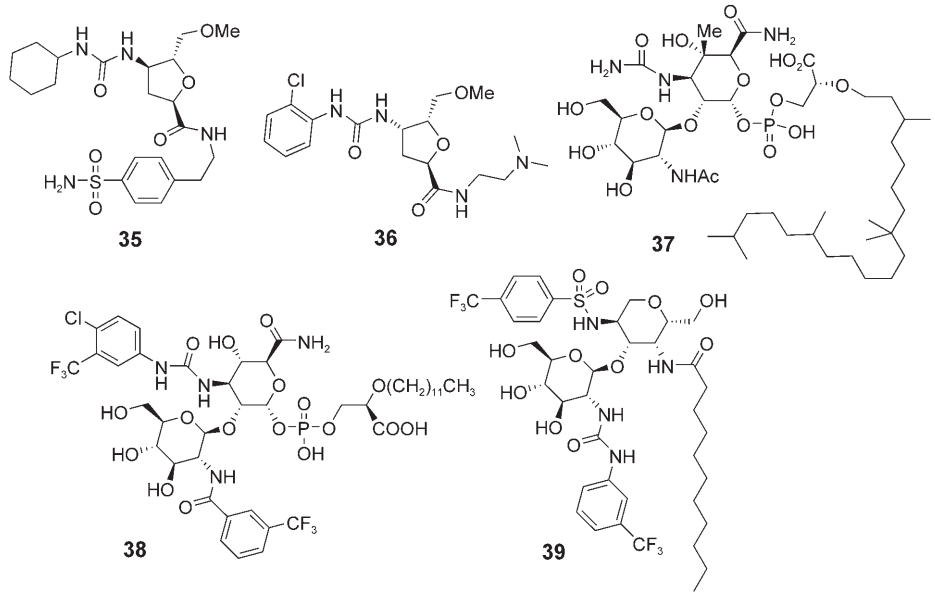


Figure 12. Carbohydrate-derived compounds with antibacterial activity.

Sofia and co-workers designed a library for antibacterial activity based on the activity of compound **37**, which is a degradation product of the highly active antibiotic moenomycin A. Moenomycin A inhibits the transglycosylase activity of the penicillin-binding proteins, disrupting the synthesis of the bacterial cell wall. Using solid-phase techniques, they synthesized 1300 compounds based on a disaccharide scaffold to be screened for antibacterial activity.[54] Several of these, including compound **38** (Figure 12), showed good activity with a MIC value of 3–12 $\mu g\,mL^{-1}$ toward a number of resistant strains. Moenomycin A itself has a MIC value of ~0.25 $\mu g\,L^{-1}$, depending on the strain.

Following the same moenomycin lead, Meutermans and coworkers[55] reported the synthesis of a library of disaccharides, producing a number of compounds with MIC values in the range of 1–4 $\mu g\,mL^{-1}$, which were 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 (compound **39**) is shown in Figure 12.

2.10. RNA binders

Wong and co-workers designed a small library of 1,3-hydroxyamines based on an aminoglucopyranose building block.[56] The resulting compounds were tested with a surface plasmon resonance assay against different bacterial RNAs. The various library members showed different specificities for the RNAs tested, and the best K_d value obtained was 30 μM for compound **40** (Figure 13).

2.11. Herbicidals

Li and co-workers[57] used a mixed solution and solid-phase approach to generate a set of compound mixtures containing a total of 237 individual compounds. By introducing pyriminidinyl groups as substituents on a D-glucose scaffold, a library was produced to target acetolactate synthase (ALS). The library was tested in a root-growth inhibition assay for ALS activity, and a number of compounds showed activity in the 10–100 μM range. One representative structure (compound **41**) is given in Figure 13.

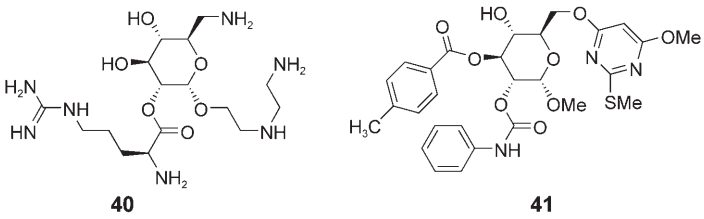


Figure 13. Structures of an RNA binder and a compound with herbicidal activity.

3. Chemistry-Driven Approaches

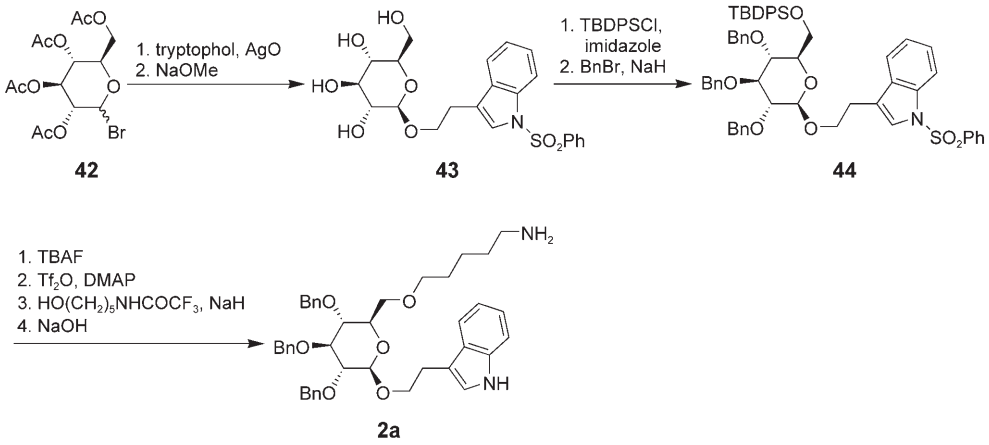
The following sections focus on solution- and solid-phase libraries that have been synthesized to develop the chemistry for the production of larger libraries based on carbohydrate building blocks or to prove the suitability of certain building blocks for library syntheses that are carried out not necessarily with specific targets in mind. For this purpose, some of the libraries discussed in the previous section are also revisited, and the chemistry is discussed in greater detail.

The approaches using solution-phase synthesis vary greatly, from laborious single-compound syntheses to the synthesis of libraries containing several thousand compounds, including the use of solid-phase reagents and scavengers. The solid-phase syntheses generally aim for greater numbers, with one or more common building blocks linked to the supporting resin.

3.1. Solution phase

3.1.1. Pyranose scaffolds

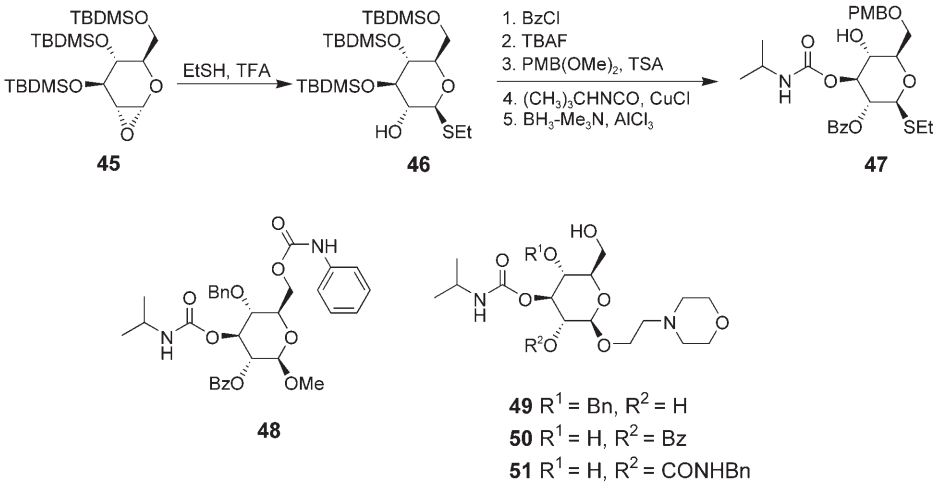
As discussed in the previous section, glucopyranose was the first carbohydrate scaffold to be used in a peptidomimetic approach to drug development. Compound **2a**[1] was designed by Hirschmann and co-workers as a SRIF mimetic displaying all the side chain elements necessary for binding. It was synthesized following a straightforward seven-step synthesis starting from acetobromoglucose **42** as depicted in Scheme 1. Using small library of nine compounds. Compound **45** was treated with ethanethiol under acid catalysis to give the ethyl β-D-thioglucoside **46**. Benzoylation, removal of the silyl protecting groups, and installation of the 4,6-acetal was followed by carbamate formation at the 3-OH group and reductive ring-opening of the anisylidene acetal to give the common intermediate **47**. By protecting-group manipulation, glycosylation with 2-bromoethanol, displacement of the bromine with a number of amines, and introduction of carbamates in other positions, a total of nine compounds with different substitution patterns were synthesized, some of which (**48**–**51**) are depicted in Scheme 2.



Scheme 1. Synthesis of the first carbohydrate-based peptidomimetic **2a**.

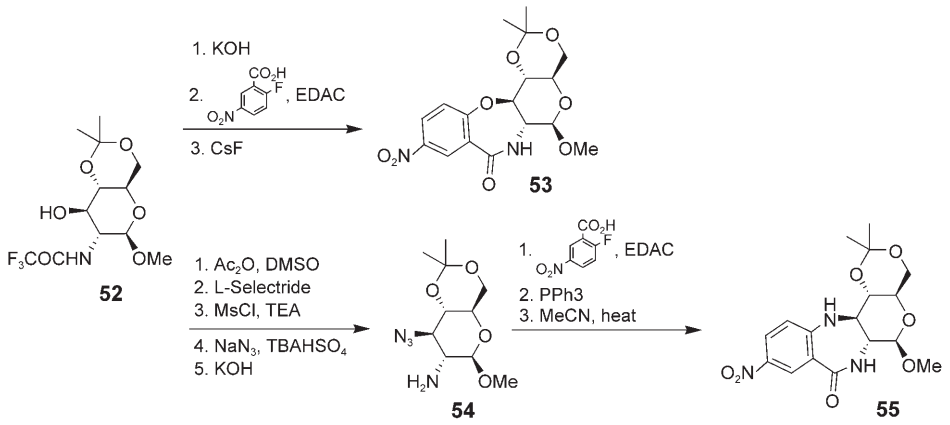
The same research group also synthesized a more constrained sugar-based benzodiazepine scaffold and used this approach to generate a selection of six compounds, exploring different ways of diazepine formation leading to substituted benzodiazepines, benzoxazepines, and pyridyldiazepines.[59] Scheme 3 shows two approaches starting from the common precursor **52** and leading to either the oxazepine or the diazepine scaffold.

Königs–Knorr conditions for the introduction of the anomeric substituent and Zemplen conditions for the removal of the acetates, the β-D-glucose intermediate **43** was selectively protected at position 6 using TBDPS chloride followed by benzylation of the remaining free hydroxy groups to give **44**. After removal of the TBDPS group and triflation, the amine-bearing side chain was introduced in a TFA-protected form by displacement of the triflate. General deprotection using sodium hydroxide in ethanol at reflux gave the final product **2a**. The related 3-deoxy derivative **2b** was synthesized by following a similar route after radical deoxygenation of a suitably protected precursor. More than 50 derivatives of the original actives covering different stereoisomers and a number medicinal chemistry changes were synthesized and described in subsequent publications.[26–29]



Scheme 2. A range of diverse structures were derived from building block **47**.

Hirschmann, Smith III, and co-workers developed a methodology to generate more diverse structures for broader screening as well.[58] For this purpose they used epoxide **45** to generate the building block **46**, which was then diversified into a The oxazepine was generated by deprotection of the amine in **52**, amide coupling with 2-fluoro-5-nitrobenzoic acid, and ring closure by aromatic substitution to give compound **53**. The diazepine formation required oxidation of the 3-hydroxy group of the carbohydrate ring followed by reduction to reverse the original stereochemistry at that position; subsequent mesylation, displacement with azide, and cleavage of the amide led to the formation of amide **54**. This was then treated with 2-fluoro-5-nitrobenzoic acid, the azide was reduced to the



Scheme 3. Oxazepines and diazepines from carbohydrate precursors.

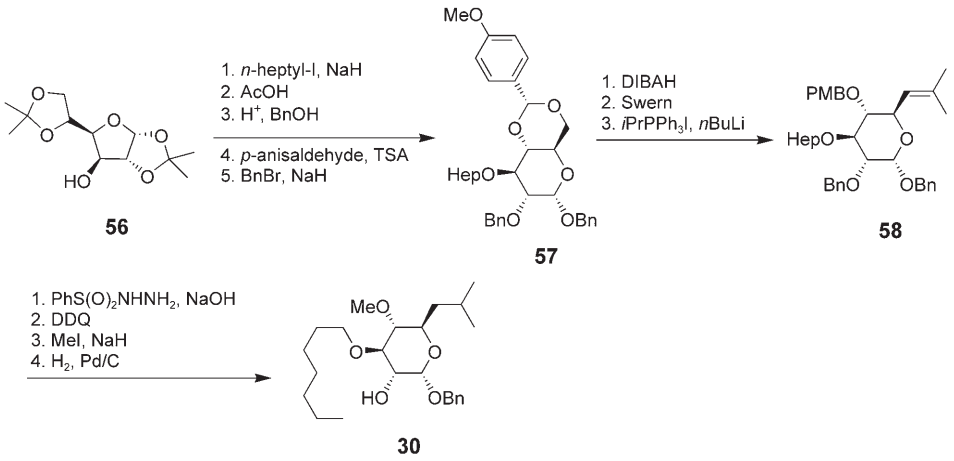
amine, and the diazepine was formed in an intramolecular aromatic substitution reaction to give **55**. The pyridyldiazepines were synthesized in a similar manner using different chloronicotinic acids.

In an effort to achieve the right distances between pharmacophore groups, Armstrong and co-workers,[49] in their work on the hapalosin mimetic **30**, extended the glucose skeleton to include an isopropyl group directly linked to C6 of the carbohydrate ring. Starting from diacetone-D-glucose **56** they synthesized *p*-anisylidene derivative **57**, which was then selectively ring-opened to expose the 6-OH group of the glucose ring. Oxidation to the aldehyde and Wittig-type chemistry allowed the extension of the pyranose scaffold to give product **58**. Selective reduction of the double bond followed by removal of PMB, methylation, and selective debenzylation gave the target compound **30** (Scheme 4).

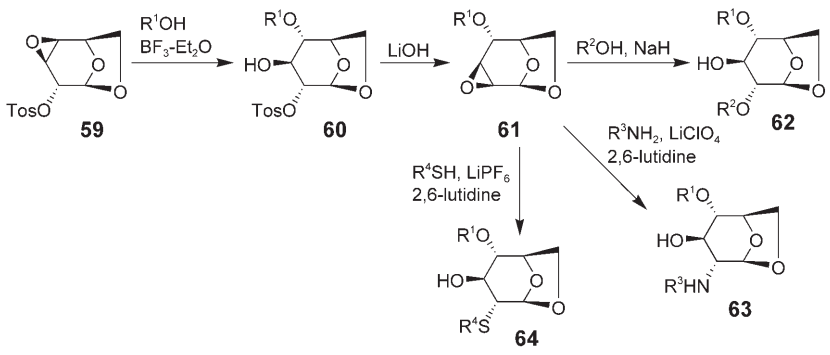
Using the glucose derivative levoglucosane as a rigid scaffold, Brill and Tirefort[60] synthesized a library of 28 compounds starting from the epoxide **59**, which was opened by attack of an alcohol under BF_3-etherate catalysis to give the tosylate **60**. Treatment with base generated another epoxide **61**, which in turn was opened with alkoxides, nitrogen, or sulfur nucleophiles to give the corresponding products of the general structures **62**, **63**, and **64** (Scheme 5).

Chapleur and co-workers[36] set out to synthesize a library of RGD mimetics based on the xylose scaffold. To minimize the synthetic and purification effort, they chose a 'mix and divide' strategy. Compound mixtures were synthesized, and a combination of arrangement in orthogonal libraries and a recursive deconvolution strategy was used to identify actives. Starting from D-xylose, Fischer glycosylation with allyl alcohol gave xyloside **65**, which was separated into the anomers. Random benzylation gave a mixture of mono- and dibenzylated compounds, which were further alkylated with bromoacetic acid *tert*-butyl ester leading to all possible isomers of structure **66**. Ozonolysis followed by reduction of the aldehyde, bromination, and displacement with a number of different amines gave the final libraries with a total of 126 compounds of the general structure **67** (Scheme 6a).

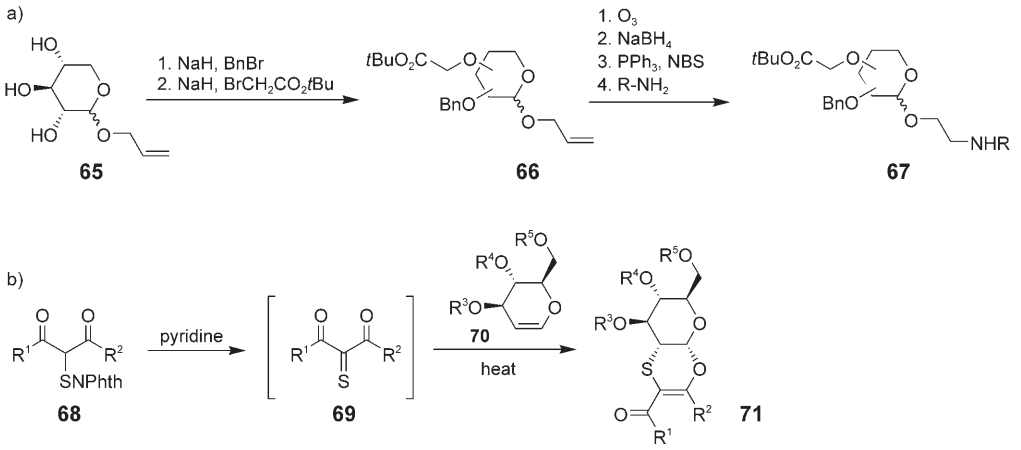
Another carbohydrate scaffold was used by Nativi, Altamura, and co-workers in their synthesis of carbohydrate-based peptidomimetics for the NK-2 receptor.[33] A number of different glu-



Scheme 4. Synthesis of a hapalosin mimetic.



Scheme 5. The levoglucosan scaffold as a starting point for library synthesis.



Scheme 6. a) Synthesis of RGD mimetics and b) a constrained scaffold for the synthesis of carbohydrate-based peptidomimetics for the NK-2 receptor.

cals were treated with α,α′-dioxothiones in a regio- and stereoselective inverse-electron-demand [4+2] cycloaddition reaction. Scheme 6b shows the synthetic path followed. The α,α′-dioxothiones **69** are formed under mild basic conditions from the precursor **68** and reacted with the glycal **70** to give the bicyclic addition product **71**. A total of 14 different structures were prepared following this route.

Van der Eycken and co-workers used the glucose derivative **72** as starting point in their synthesis of a small library of antiviral compounds.[47] Formation of the glucosyl bromide by reaction with oxalylbromide and subsequent Grignard substitution gave the intermediate **73** (Scheme 7). The benzyl protecting groups could be selectively removed under hydrogenation conditions using palladium on charcoal as a catalyst. Introduction of the acetal was followed by alkylation of the free hydroxy groups to give compound **26**. Through the use of a 1-C-phenyl scaffold instead of a 1-C-benzyl scaffold, and by introducing different aromatic acetals and using different alkylating reagents, a number of different derivatives were synthesized.

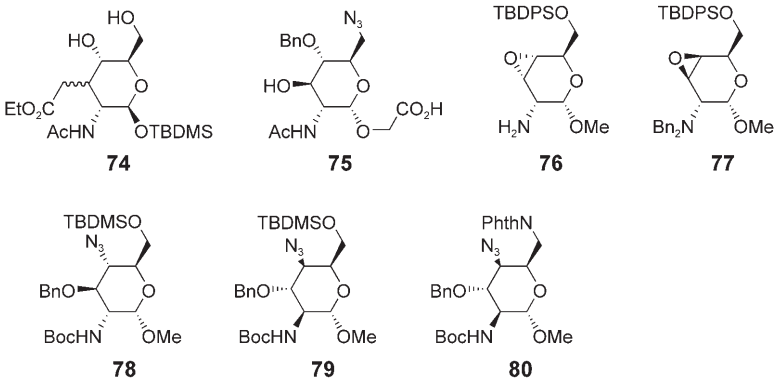
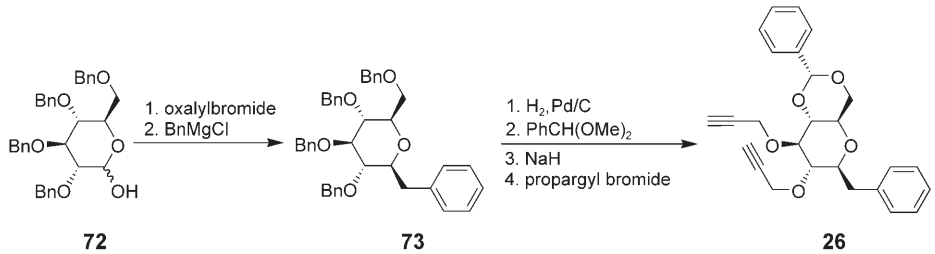


Figure 14. Some additional pyranose building blocks for library synthesis suggested in the literature.



Scheme 7. Synthesis of a compound with antiviral activity.

Some carbohydrate structures were synthesized and suggested as suitable building blocks without the synthesis of a small-scale library to support that claim. But as the functionalities contained in these molecules are generally easily manipulated, it seems likely that they could be useful additions to the pool of carbohydrate scaffolds for the 3D presentation of pharmacophore side chains. Some examples are shown in Figure 14 and in the other appropriate sections of this review.

Capozzi, Nativi, and co-workers suggested compound **74** as a suitable building block, which was synthesized in six steps from an easily accessible *N*-acetylglucosamine derivative.[61]

Ghosh et al. generated scaffold **75** in an eight-step synthesis starting from *N*-acetylglucosamine.[62] In this case, a library of 12000 compounds was produced, however, neither examples of library compounds nor the methods used for library generation were reported. Jensen's research group[63] developed glucosamine 3,4-epoxide scaffolds **76** and **77** in which the epoxide was opened by thiols. Moitessier and co-workers synthesized two *gluco* diamines (such as **78**), an *ido* diamine **79**, and the *ido* triamine **80** as potential scaffolds and showed that the masked amines could be successfully deprotected and coupled to protected amino acids.[64]

3.1.2. Furanose scaffolds

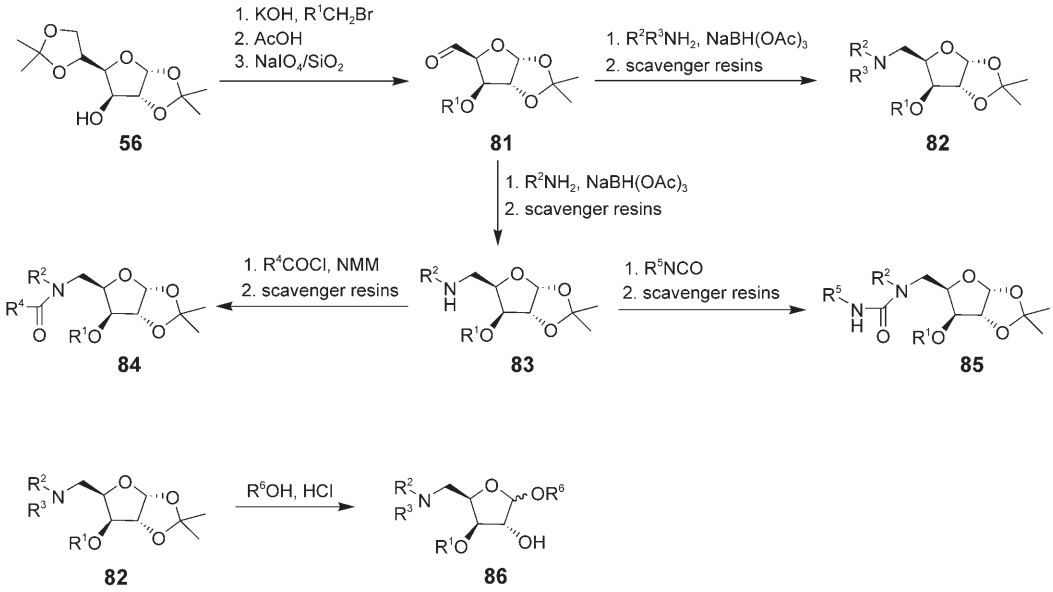
The largest carbohydrate-based libraries reported so far have used a furanose scaffold. Boldi and co-workers[65] started from diacetone-D-glucose **56** by alkylation of the free 3-hydroxy group, selective cleavage of the 1,2-acetonides, and cleavage of the diols with sodium periodate adsorbed on silica gel to give the corresponding aldehydes **81** as central building blocks for subsequent library synthesis (Scheme 8). Aldehyde **81** was reductively aminated with primary or secondary amines leading to compounds of the general structures **82** and **83**. Excess reagents were scavenged by sequential treatment with Amberlite IRA-743 resin and either PS-4-benzyloxybenzaldehyde resin in the case of the primary amines or with PS-isocyanate resin for the secondary amines. Secondary amines **83** were further treated with various acid chlorides or isocyanates to give the corresponding derivatives **84** and **85**, respectively. In some cases, the products obtained were further diversified by formation of glycosides **86** from the corresponding 1,2-acetonides under acidic conditions. Several libraries containing 5000 compounds each were produced by following this approach. An attempt to perform the library synthesis on solid phase led to only poor yields and purities in this case.

The Fleet research group developed a different furanose scaffold for the production of solution-phase libraries[53] (Scheme 9). Starting from L-gulonolactone **87**, the L-*arabino* and L-*lyxo* derivatives of **88** were prepared in a seven- and eight-step synthesis. The L-*lyxo* derivative of this protected sugar amino acid was then selectively deprotected and methylated at the oxygen atom, the azide was reduced, and the resulting free amine was allowed to react with a range of isocyanates and isothiocyanates to give the intermediates **89**. Treatment of the ester with free amine at elevated temperatures and addition of anhydride resin to remove excess amine gave the final library compounds **90**. A 99-member library was prepared in this way.

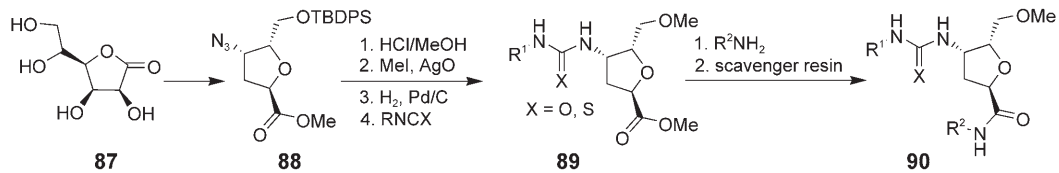
Other furanose scaffolds that have been suggested as potential building blocks for carbohydrate-based libraries are shown in Figure 15. Capozzi, Nativi, and co-workers[61] synthesized compound **91** in nine steps from D-ribonolactone, and Jiménez-Barbero, Nicotra, and co-workers proposed the bicyclic compounds **92**–**94** as scaffolds, which were derived from fructofuranose.[66] Fleet and co-workers synthesized a series of furanose sugar amino acids (some examples are **95**–**98** in Figure 15) as potential scaffolds.[67,68]

3.1.3. Iminosugar scaffolds

With the nitrogen atom included in the ring, iminosugars provide a carbohydrate-based scaffold with a different geometry. The chemistry for the manipulation of the individual positions around the ring can also be quite different, as glycosylation, for example, is not possible. Le Merrer et al. were the first to make use of an iminosugar as a scaffold for the development



Scheme 8. A large and diverse library was synthesized using furanose scaffolds.



Scheme 9. Reaction sequence for a library based on a furanose scaffold.

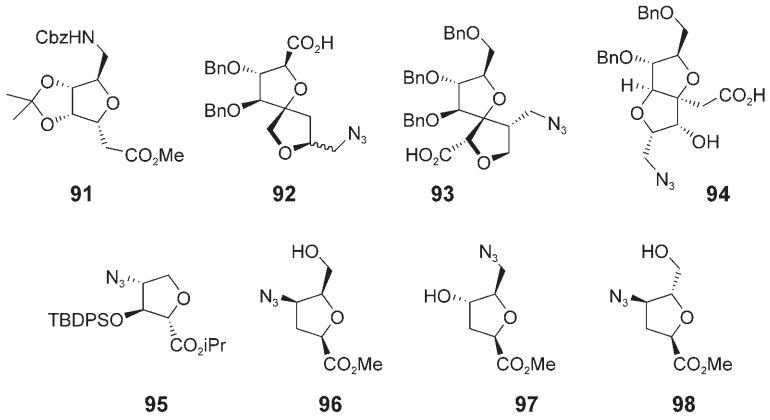


Figure 15. Furanose scaffolds that have been suggested as potential building blocks for carbohydrate-based libraries.

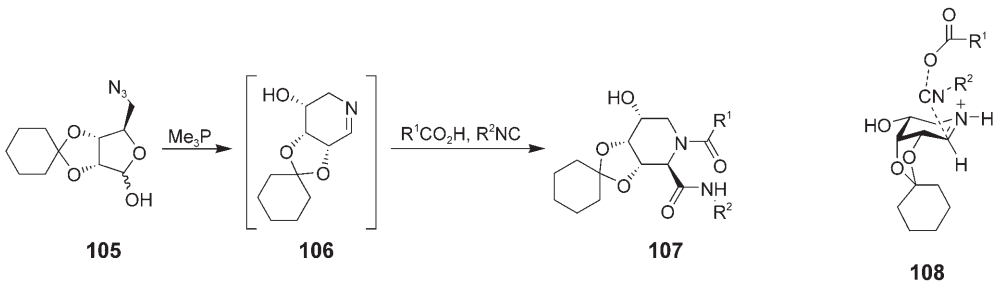
of peptidomimetic compounds in their synthesis of somatostatin mimetics[31] (Scheme 10).

Commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol was converted into 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol (**99**) in two steps. Reaction with tryptamine gave a mixture of the L-*gulo*-configured compound **100** and the 1,6-imino-D-mannitol **101**. Introduction of suitable protecting groups followed by introduction of the amino functionality and deprotection gave either the 2,5-imino-L-iditol **102** or the 1,5-imino-L-iditol **103** starting from compound **100**, or the 1,6-imino-D-mannitol **104** starting from **101**. A total of six different scaffolds were prepared, including the structures shown in Scheme 10 as well as scaffolds of 1,5-imino-L-gulitol, 2,5-diazabicyclo[2.2.2]octane, and 3,8-diazabycyclo[3.2.1]octane.[31]

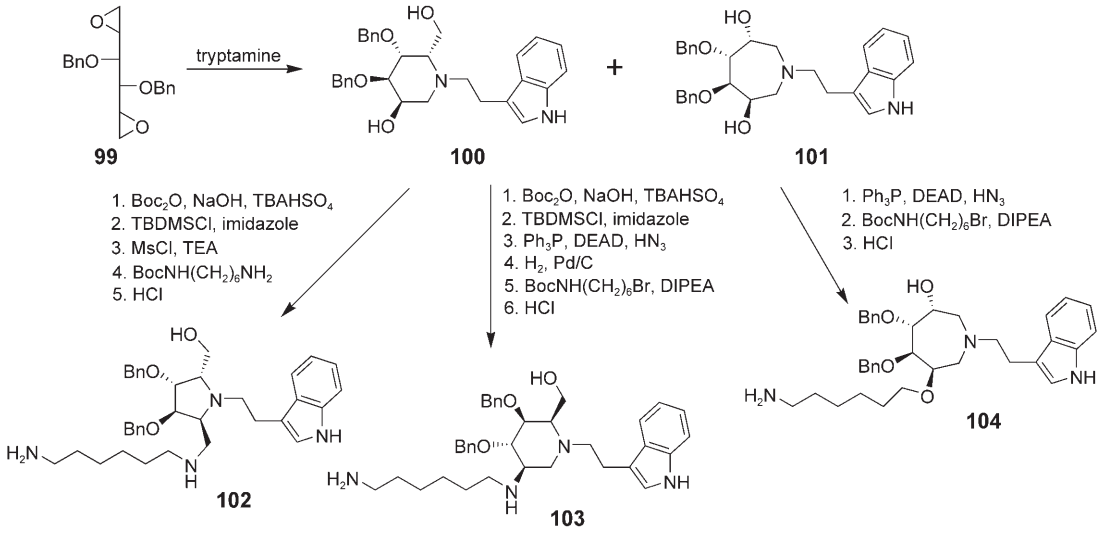
Overkleeft and co-workers[69,70] used a Staudinger–aza-Wittig–Ugi three-component reaction to arrive at the iminosugar scaffold **107**. Starting from 5-azido ribose derivative **105**, the intermediate enamine **106** was allowed to react with different acids and isonitriles in a one-pot reaction to give product **107**, presumably via the transition state **108**. 12 compounds of the general structure **107** were synthesized (Scheme 11) together with six compounds of a bicyclic structure (see Section 3.1.5).

3.1.4. Disaccharide scaffolds

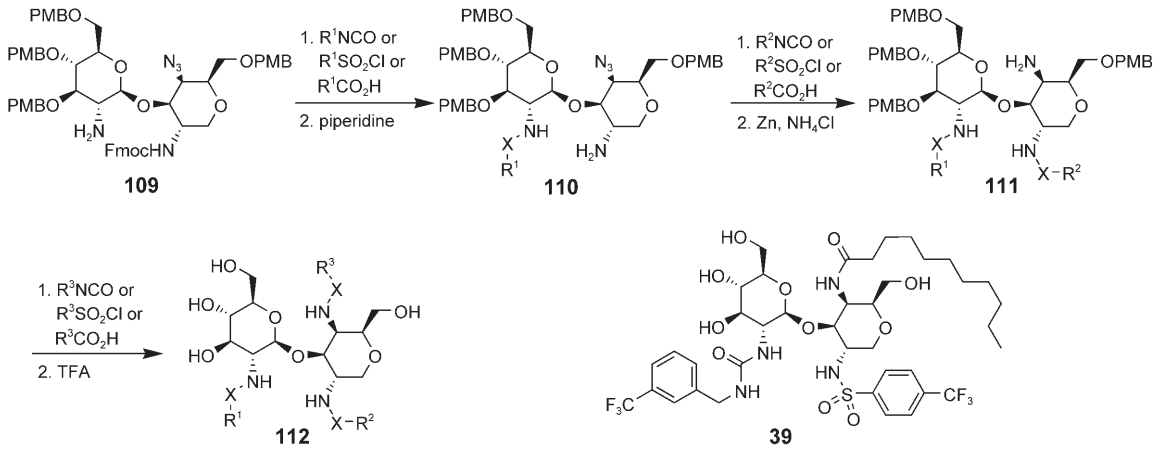
A disaccharide scaffold was used by Meutermans and co-workers to generate a library of several hundred compounds in a solution-phase approach.[71] Starting from disaccharide **109**, the masked amino groups were sequentially deprotected and reacted with isocyanates, sulfonyl chlorides, or carboxylic acids to introduce a diverse range of substituents in the final products of the general structure **112**. Compound **39** is an example from the library that showed good antibacterial activity against a range of Gram-positive bacteria (Scheme 12).



Scheme 11. Synthesis and diversification of an iminosugar scaffold.



Scheme 10. Use of iminosugars as scaffolds.



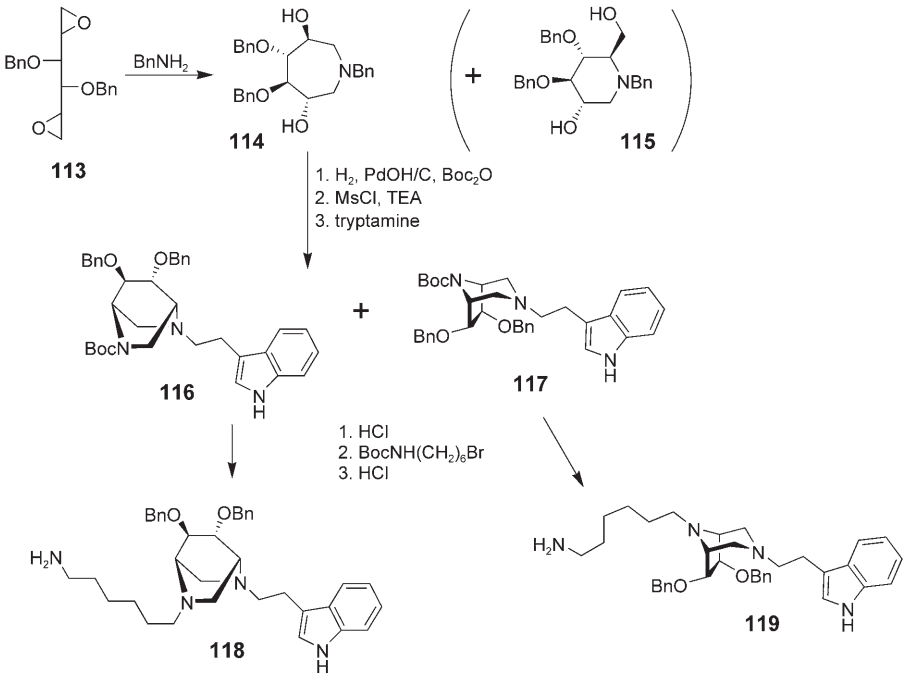
Scheme 12. Disaccharide scaffolds used in the synthesis of combinatorial libraries.

3.1.5. Carbohydrate-derived scaffolds

Different iminosugars have also been used to generate bicyclic structures that were then explored as structural scaffolds for the display of functional groups. Le Merrer et al.[31] started from 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-L-iditol **113** to get to the bicyclic structures **116** and **117** via compound **114** after reaction with benzylamine, selective N-debenzylation with simultaneous Boc protection of the free amine, mesylation of the hydroxy groups, and treatment with tryptamine (Scheme 13). Separation of **116** and **117** was followed by deprotection of the amine, reaction with 6-bromo-*N*-Boc-hexylamine, and liberation of the amine in the side chain to give the final compounds **118** and **119**, which both showed activity at the somatostatin receptor.

Overkleeft and co-workers generated another bicyclic scaffold by deprotection and oxidation of **120** to the aldehyde **121**.[69,70] Reduction of the azide gave the bicyclic enamine **122**, which was then reacted in a Staudinger–aza-Wittig–Ugi three-component reaction with a carboxylic acid and an isonitrile to give the final compound **123**. A total of six different compounds were synthesized using this approach (Scheme 14a).

A thiazolidine lactam was used by Geyer and co-workers[72] to generate the bicyclic system **128**, which displays functionalities similar to hapalosin (**29**) on a rigid scaffold. Compound **124** was prepared from D-glucuronic acid and L-cysteine methyl ester in two steps followed by the treatment with triflic anhydride to give the key intermediate **125**, which possesses a number of reactive centres that can be selectively manipulated. Conjugate addition with ammonium formate and acylation of the amine gave amide **126**. Further elaboration of the scaffold finally gave the fully functionalized product **128** (Scheme 14b). Another two similar compounds including one deoxy derivative were also described.

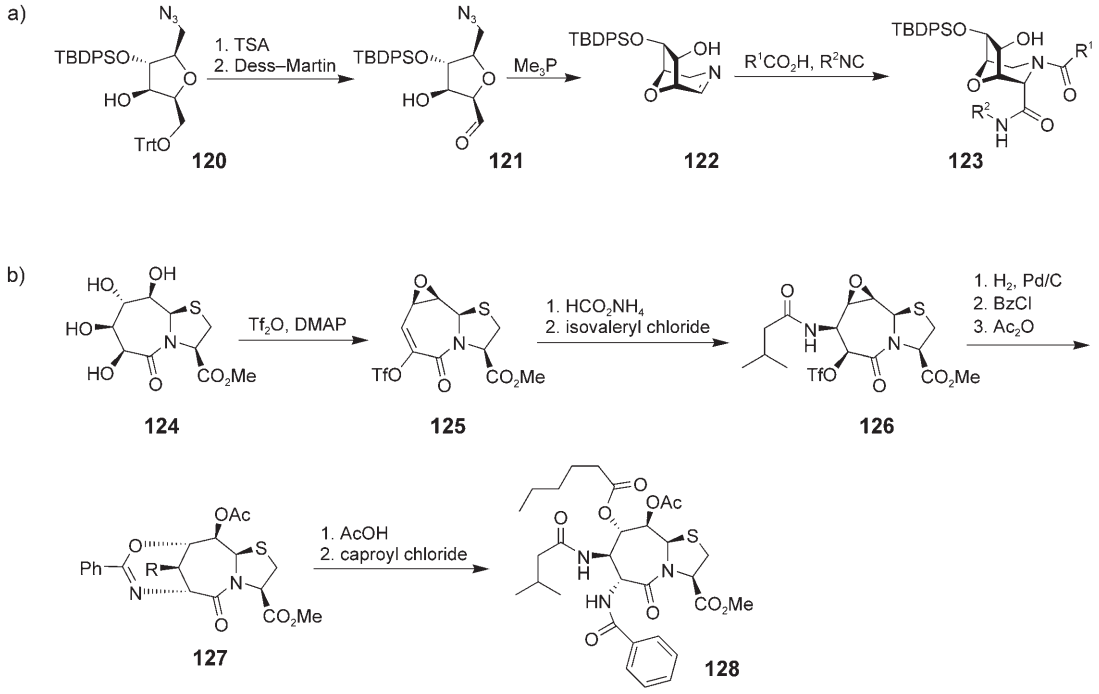


Scheme 13. Rigid scaffolds derived from carbohydrates.

3.2. Solid-phase libraries

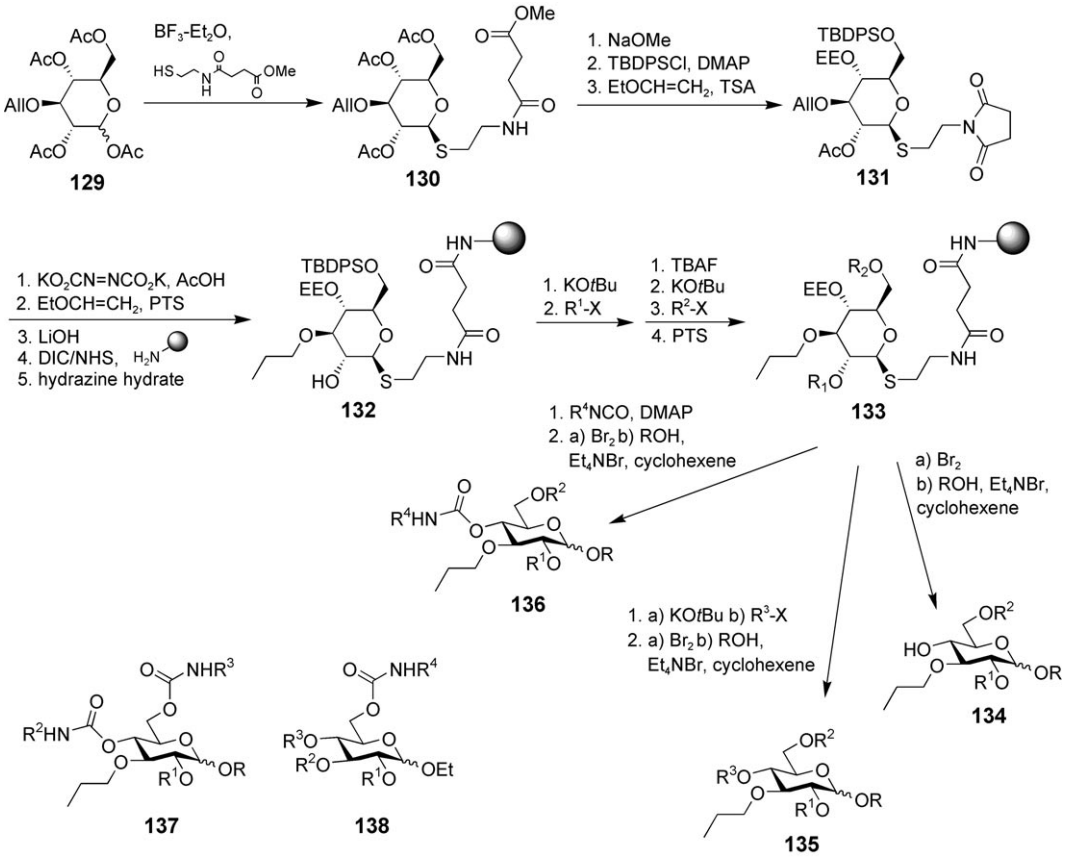
3.2.1. Pyranose scaffolds

Pyranose scaffolds were the first carbohydrate-based scaffolds to be used in solid-phase library syntheses. Kunz and co-workers developed the orthogonally protected glucose derivative **131** as a scaffold, linked it to aminomethyl polystyrene resin, and showed that the positions on the carbohydrate ring could be individually manipulated[15]



Scheme 14. a) Generation of a bicyclic scaffold via a Staudinger–aza-Wittig–Ugi reaction; b) synthesis and decoration of a bicyclic scaffold derived from D-glucuronic acid and L-cysteine.

(Scheme 15). Starting from readily available glucose derivative **129**, glycosylation under standard conditions gave the thioglycoside **130**. Treatment with sodium methanolate, followed by selective protection of the 6-position and introduction of the ethylethoxy group at the 4-position gave the key intermediate **131**. Preliminary experiments showed that attempts to remove



Scheme 15. The use of a D-glucose scaffold in solid-phase combinatorial synthesis.

the allyl group on solid phase led to side reactions; hence the double bond was reduced using diimide. Opening of the succinimide, coupling to aminomethyl polystyrene resin using DIC/NHS, and removal of the acetate group gave resin **132**, the starting point for the synthesis of a small library of 28 compounds. Ether side chains were introduced by deprotonating with KO*t*Bu and reaction with alkyl or benzyl halides in DMF for the 2-position and the 6-position after deprotection to give **133**. The ethylethoxy group in the 4-position was removed either without further alkylation of the free hydroxy group (to give **134**) or followed by another alkylation step (for **135**). Alternatively this position was reacted with an isocyanate to give the corresponding carbamate **136**. Treatment with bromine cleaved the carbohydrate from the resin to give an anomeric bromide, which was further treated with primary alcohols to give the final compounds of the general structures **134**–**138**. The purity of the final mixed anomers was 75–95% (HPLC). In this strategy, four of the five hydroxy groups in the glucose ring are accessible for manipulation with only the 3-position being fixed as an *n*-propyl side chain.

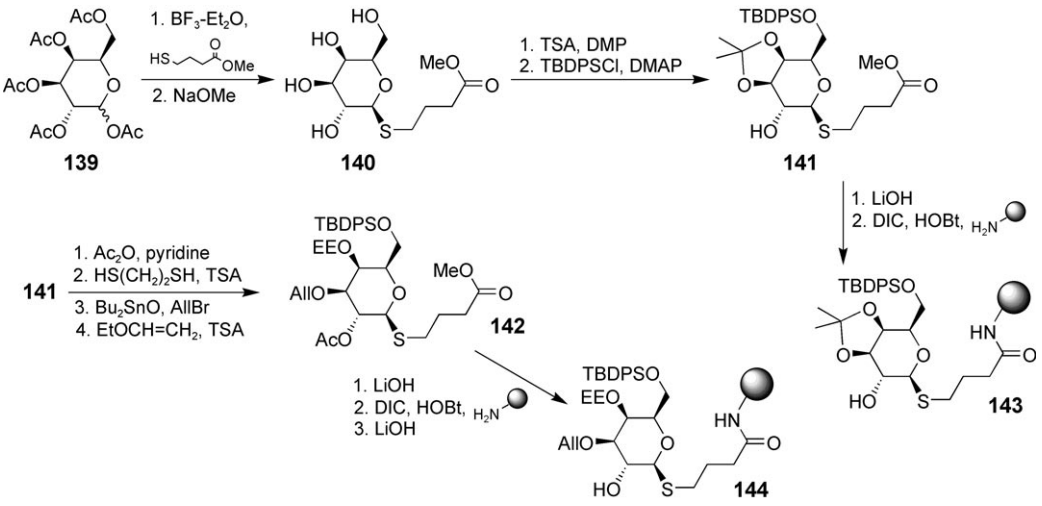
A further 2,6-alkyl glucoside library of 18 compounds (general structure **134**) and a 2-alkyl-4,6-carbamoyl glucoside library (general structure **137**, 60 compounds), generated using the same methodology, were also described,[16] as well as the attachment of amino acids at the same positions through either the amino or carboxyl groups (27 compounds).[18] The ability to selectively remove the allyl group with *p*-toluenesulfinic acid and tetrakis(triphenylphosphine)palladium in DME enabled the synthesis of a library with all five positions on the glucose scaffold accessible for substitution.[17] 36 compounds of the general structure **138** were made, for which R^1 is methyl or substituted benzyl, R^2 and R^3 is an ester or a carbamate, and R^4 is a substituted phenyl group.

Kunz and co-workers also took a similar approach in the synthesis of libraries based on galactose scaffolds.[20] Starting from peracetylated galactose, building blocks **141** and **142** were synthesized in four and eight steps, respectively (Scheme 16). Hydrolysis of the methyl ester and coupling to aminomethyl polystyrene resin (followed by deacetylation in the case of building block **142**) gave the resins **143** and **144**, which were then used for library synthesis. Compound **143** was alkylated at the 2-position and the TBDPS group on the 6-position removed. The 6-hydroxy group was then treated before cleavage with either an alkylating reagent, an isocyanate, or carbonyl diimidazole followed by a secondary amine to give library members of the structures **146**, **147**, and **148** (Scheme 17). Resin **144** was subjected to the same reaction conditions to generate the 2,6-alkyl-3,4-carbamoyl galactosides **150** and the 2-alkyl-3,4,6-carbamoyl galactosides **151** (Scheme 18). Several hundred compounds of the general structures **146**, **147**, **148**, **150**, and **151** were prepared.

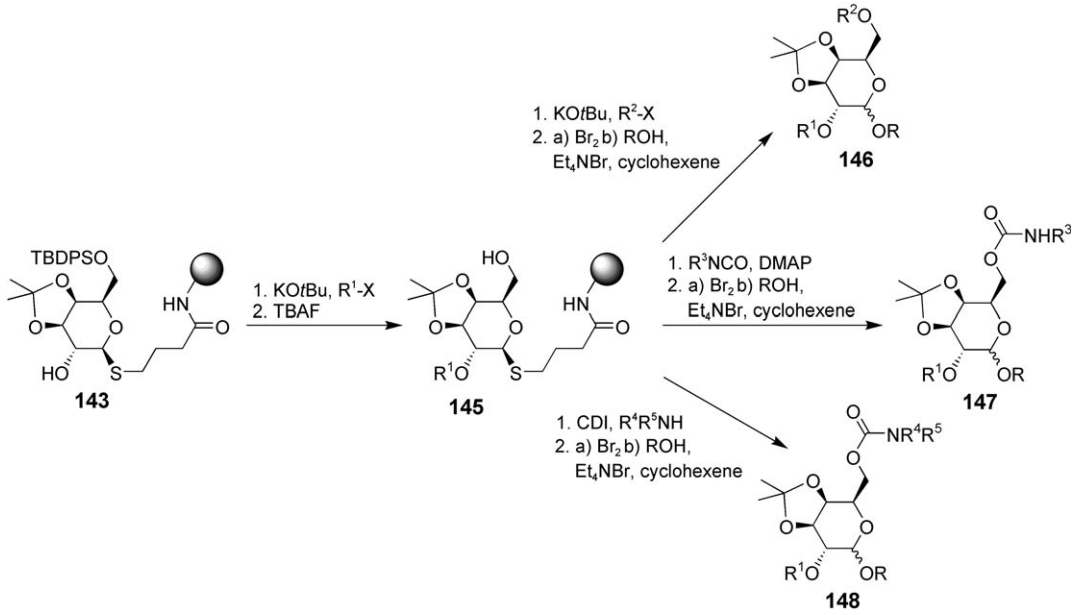
Sofia and co-workers used D-glucuronic acid derivatives to link these to a trityl-linked tentagel resin through a number of different amino acids.[24,25] The two scaffolds **154** and **157** were prepared in seven and eight steps, respectively, and were subsequently decorated with different substituents using amide and carbamate linkages. The carbohydrate–amino acid conjugate was then cleaved from the resin. A set of 16 libraries with 48 compounds each was prepared.

Scheme 19 shows the synthesis of the monosaccharide building blocks **154** and **157** that were used for these libraries. The synthesis of **154** started from methyl β-D-glucoside **152** with a periodate cleavage and condensation with nitromethane, followed by suitable protection to give the intermediate **153**. The nitro group was reduced and protected and C6 of the carbohydrate was oxidized to the acid to give the desired building block **154**. The synthesis of building block **157** started from D-glucosamine hydrochloride (**155**), which was N-protected and glycosylated using Fischer conditions. Introduction of the 4,6-isopropylidene group and methylation of the remaining free hydroxy group led to the intermediate **156**. Removal of the acetonide was followed by oxidation of C6 and a change of the amine protecting group to arrive at building block **157**.

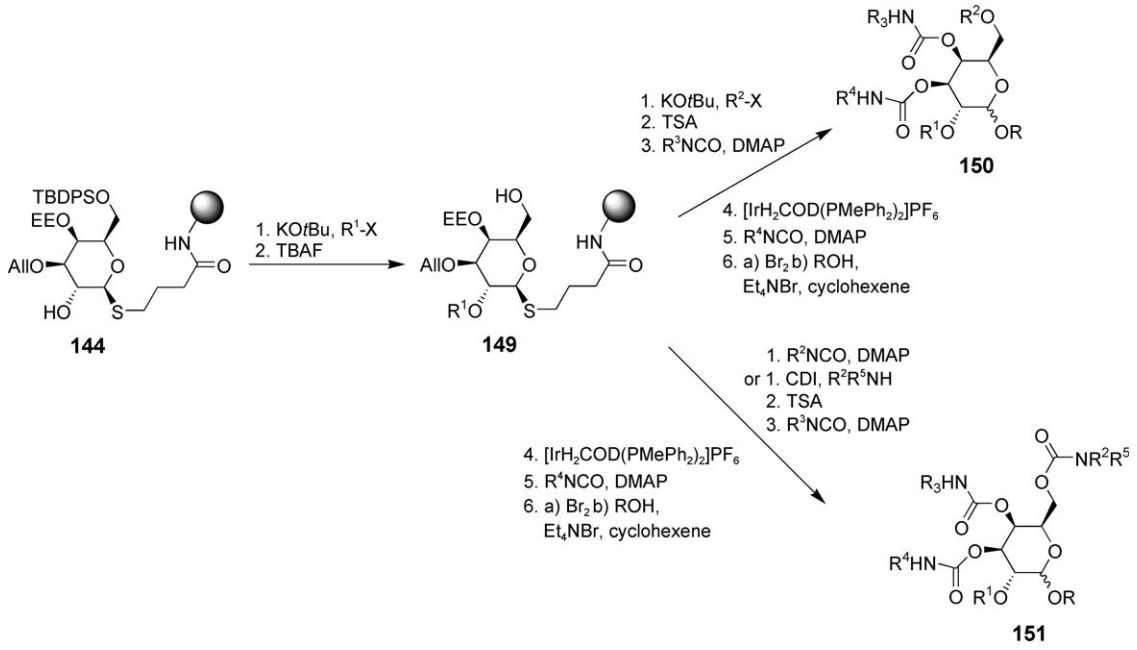
Both **154** and **157** were coupled to trityl-linked tentagel modified as a leucine ester (Scheme 20). The 4-hydroxy group was treated with an isocyanate to give the carbamate, the amines were deprotected and coupled to an acid, and in the



Scheme 16. A D-galactose scaffold for combinatorial solid-phase synthesis.



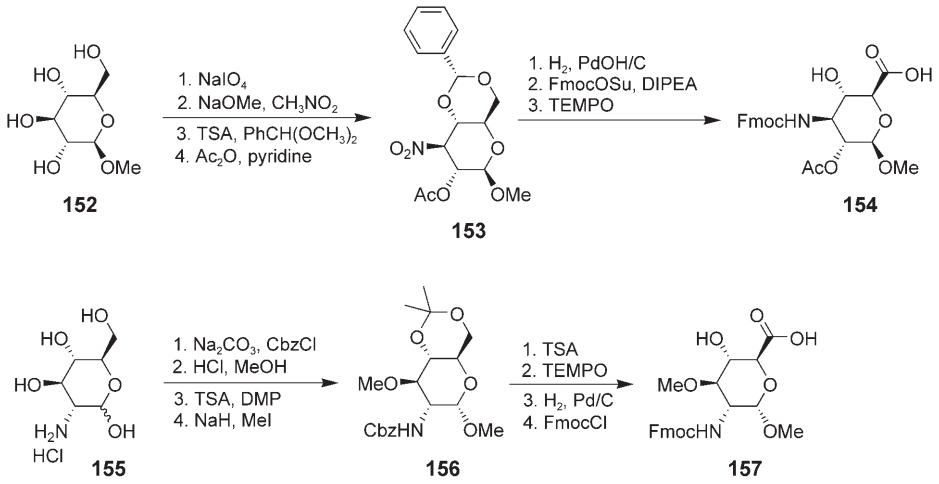
Scheme 17. Diversification of a D-galactose scaffold in solid-phase synthesis.



Scheme 18. Use of all five available positions on a D-galactose scaffold.

case of building block **154**, the acetate was removed, and the compounds were cleaved from the resin to give structures such as **159** and **161**. The purity of the cleaved compounds was reported to be $>90\,\%$.[24]

Sofia and co-workers also developed a series of 3-azido pyranose scaffolds for use in library synthesis by using the same principles outlined above.[23] Starting from readily available 3-azido glucose derivative **162** the key intermediate **163** was prepared by forming the bromide, Königs–Knorr glycosylation, and protection of the 4,6-diol (Scheme 21). The six building blocks **164** to **169** were prepared in a further five or seven steps. Scaffold **165** was chosen for the production of a small 48-member library (Scheme 22). For this purpose, Fmoc-protected histidine was linked to Rink amide resin, and **165** was coupled to the amine after deprotection with piperidine to give the resin **170**. The free hydroxy group was treated with eight different isocyanates, the azide was reduced under Staudinger conditions, and the free amine was coupled to six different carboxylic acids. Treatment with TFA liberated the compounds with the general structure **172** from the resin. A total



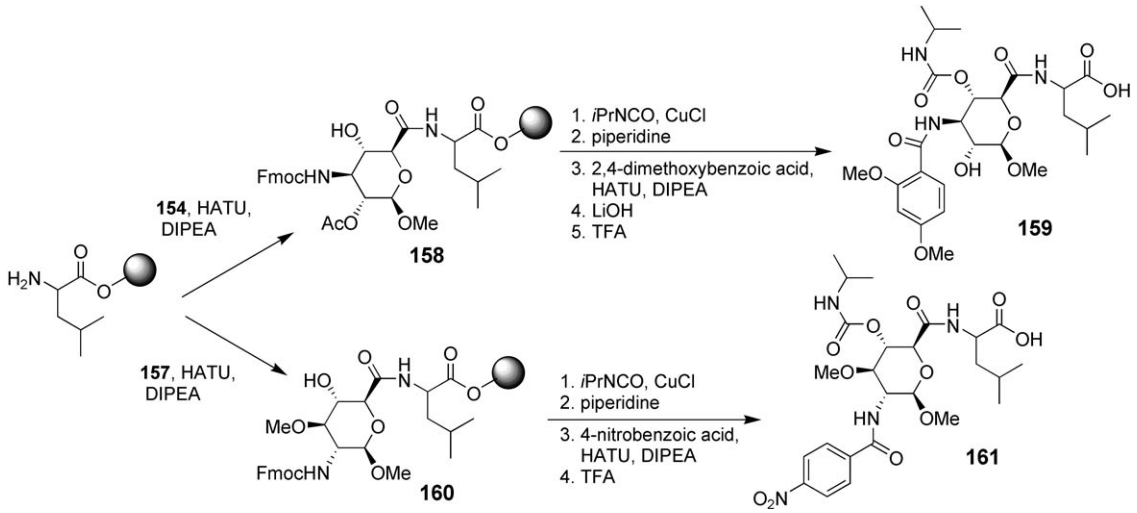
Scheme 19. Synthesis of a scaffold for solid-phase combinatorial synthesis based on D-glucuronic acid.

of 48 compounds were synthesized this way, and the chemistry is expected to be directly transferable to the other building blocks.

Brill and co-workers[73,74] used the levoglucosan derivative **59** in their approach to develop a diverse library based on a glucopyranose scaffold. After allowing compound **59** to react with various hydroxycarboxylic acid methyl esters under BF_3-etherate catalysis, the ester was hydrolysed and the epoxide was formed simultaneously. The resulting free acid was coupled to the Rink amine on either PS or RAM resin (Scheme 23). Reactions were carried out to open the epoxide with alkoxides, amines, and thiols. When the resulting compounds **175**–**177** contained aryl iodides these were treated under Pd-mediated coupling conditions and diversified further using aromatic and heteroaromatic boronic acids or acetylene derivatives. All final compounds were cleaved from the resin by treatment with TFA; 66 compounds were prepared.

Nicotra and co-workers developed the *cis*-fused perhydrofuropyran **186** as scaffold for the synthesis of a solid-phase library.[75] The PNB (*p*-nitrobenzoyl)-protected perhydrofuropyran **185** was synthesized in eight steps from methyl α-D-glucopyranoside **181** (Scheme 24) by suitable protection and reaction with allyltrimethylsilane to form the C-glycoside **183**, which was then treated with iodine. The iodide was then displaced with azide to give **185**. The unprotected **186** was synthesized following a similar route in a total of six synthetic steps. Compound **185** was then coupled to Wang resin and the *p*-nitrobenzoyl ester of the 4-hydroxy group was cleaved; alternatively compound **186** was coupled to PS-DES-SiCl resin. The resin-bound scaffold **187** was then either esterified or treated with a chloroformate followed by an amine to give the esters and carbamates **188**. Reduction of the azide was then followed by reaction of the free amine **189** with acids, sulfonyl chlorides, isocyanates, isothiocyanates, or aldehydes to give the corresponding products **190** and **191**. A total of 37 compounds were prepared following this approach, and the resulting library was screened in a cell-proliferation assay.

Another pyranose scaffold was developed by Kunz and coworkers[19] using the 2,6-diaminoglucoses **192**, and the complete orthogonality of the chosen protecting group pattern was proven by selectively deprotecting each position and coupling the free hydroxy groups or amines to amino acid derivatives on Rink amide tentagel (Figure 16). However, no library synthesis was reported using this building block



Scheme 20. Diversification of a D-glucuronic acid scaffold.

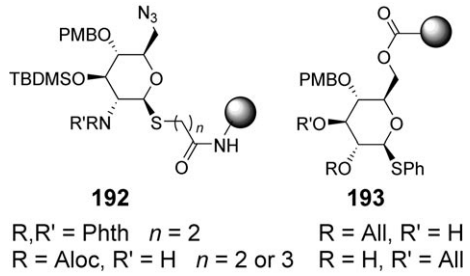
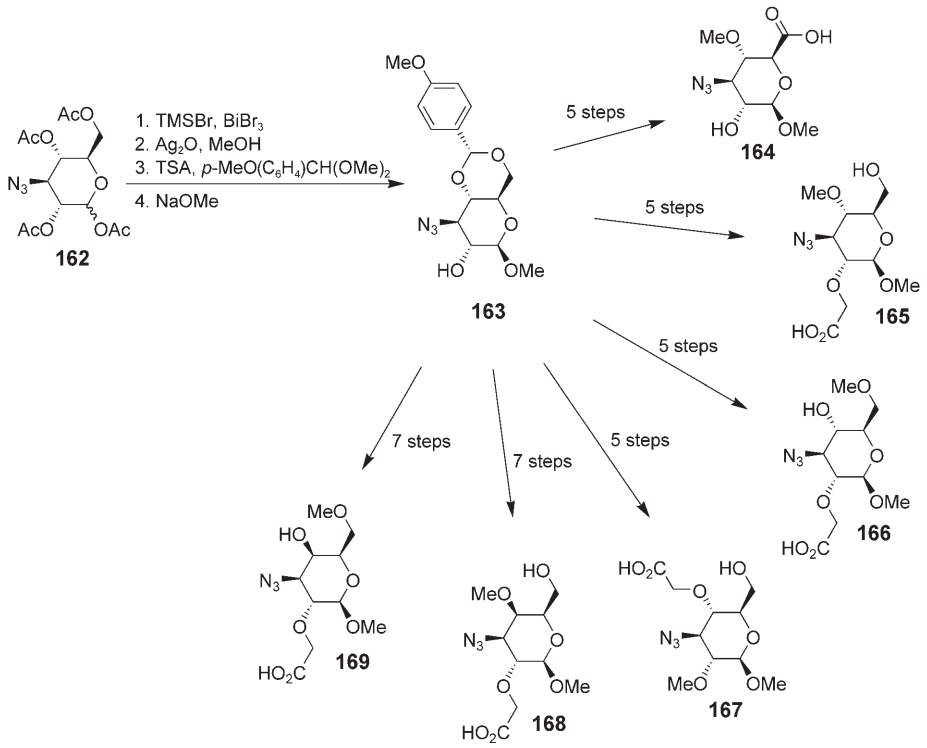


Figure 16. Other pyranose building blocks for combinatorial solid-phase synthesis.



Scheme 21. Synthesis of a series of building blocks for a universal pharmacophore-scanning library.

Peri, Nicotra, and co-workers showed that the glucose derivative **193** could be successfully loaded directly onto HO_2C-tentagel or onto amino-PS/DV resin after reaction with succinic anhydride.[76] The orthogonality of the protecting groups was demonstrated in solution phase, and the solid-phase synthesis of carbohydrate-derived libraries is still under investigation (Figure 16).

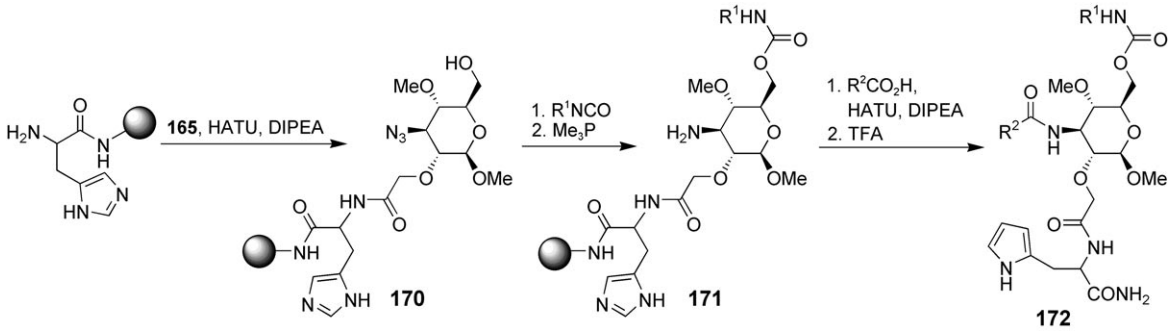
3.2.2. Furanose scaffolds

Boldi and co-workers attempted to use furanoses as scaffolds for solid-phase library synthesis.[65] However, the reductive amination reaction to link the aldehyde **194** to an amino acid coupled to a Wang-derived resin or PAL resin gave the desired products in only poor yield and low purity. Therefore, the final products **197** were found to be consistently impure, and the solid-phase approach was not continued further (Scheme 25).

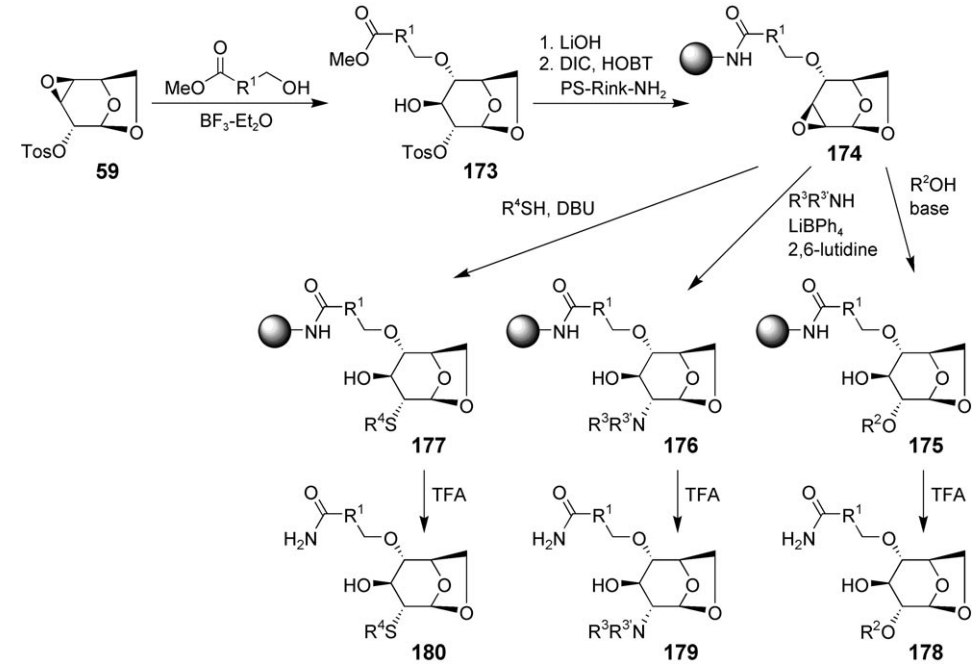
3.2.3. Disaccharide scaffolds

Disaccharides as scaffolds were explored by Sofia and co-workers.[25,54] In a proof-of-principle library, the esters and amides of resin-loaded disaccharide **198** were cleaved with lithium hydroxide, and the free amine was coupled to a number of different carboxylic acids (Scheme 26). Masking of the free hydroxy groups was followed by reduction of the azide under Staudinger conditions, urea formation, and cleavage from the resin. A set of 48 compounds of the general structure **200** was synthesized, however, no details about the synthesis of the disaccharide or the type of resin used was given.[25]

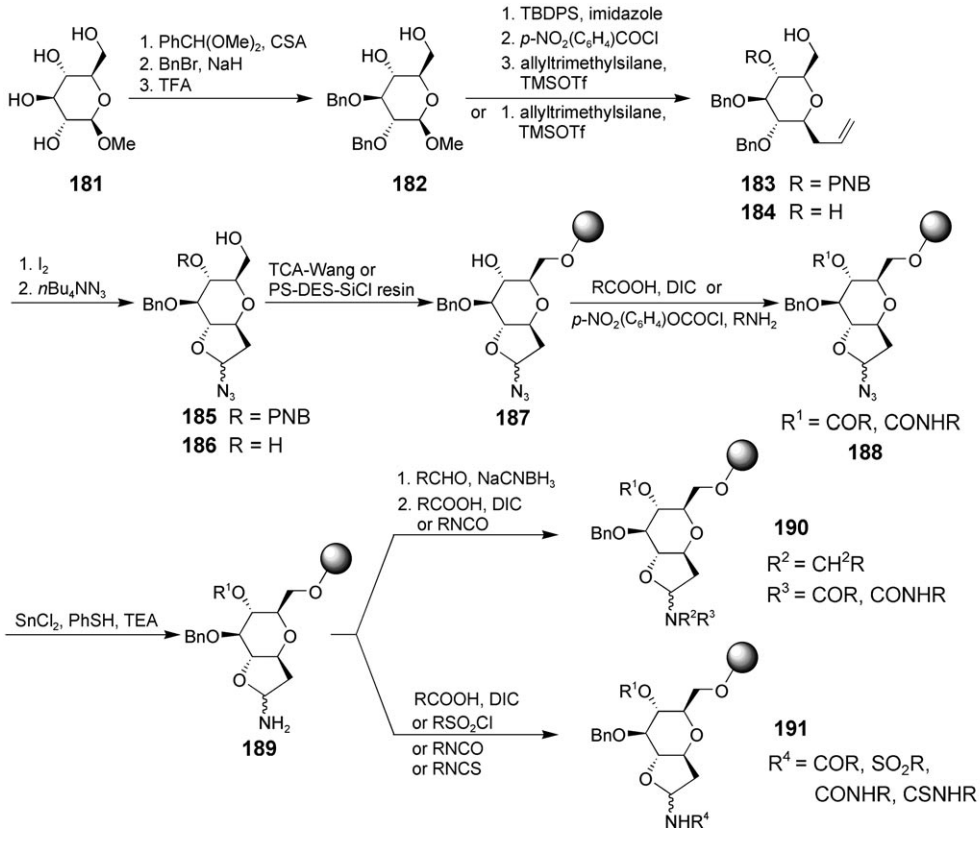
A similar scaffold was used by the same group in the synthesis of a 1300-member library targeted against bacterial transglycosylases.[54] Here, the disaccharides were synthesized in a



Scheme 22. Diversification of a building block for a universal pharmacophore-scanning library.



Scheme 23. Use of a levoglucosan scaffold in combinatorial solid-phase synthesis.



Scheme 24. Perhydrofuropyrans as library scaffolds.

solution-phase approach and then linked to aminoethyl–photolinker AM resin by their carboxyl groups. The synthesis of the library is outlined in Scheme 27. The selective removal of the levulinate in **201** was followed by the formation of a carbamate and hydrolysis of the thioglycoside to give the hemiacetal **202**. This was then allowed to react with different lipid phosphoramidites and oxidized to form the corresponding phosphates. Deprotection and cleavage from the resin gave compounds with the general structure **203**.

A similar process was followed in the case of the various disaccharides generated from 3-azido glucuronic acid, containing either a suitably protected glucosamine or galactosamine unit at the 2-position (compound **204**). Here, the R′ protecting group was removed first to couple the amine with a number of carboxylic acids. The next point of diversification was the azido group, which was reduced and converted into either an amide or urea. The remaining sequence is very similar to the one leading to product **203**, giving compounds of the general structure **206**.

3.2.4. Carbohydrate-derived scaffolds

Van Boom, Overkleeft, and coworkers developed a synthesis of 2,5-anhydro-D-glucitol derivative **209**, which was coupled to solid phase, decorated with the desired substituents, and cleaved using ring-closing metathesis to generate a small library of nine functionalized derivatives based on the 1,5-dioxabicyclo-[4.3.0]non-3-ene scaffold[77] (Scheme 28). Tosylate **207** was prepared from D-mannitol in three steps and the required protecting groups were installed to give intermediate **208**. The allyl group required for ring closure/cleavage was introduced, and the primary hydroxy group was liberated and oxidized using the Dess–Martin periodinane. The resulting aldehyde was reacted under Wittig conditions to give acid **209** after removal of the TBDPS group. Compound **209** was then coupled to Rink amide resin, and the side chains were introduced by either a

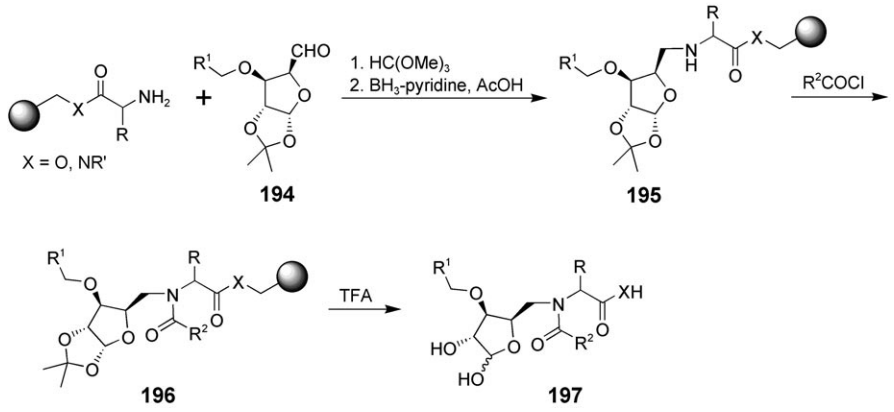
carbamate or an amide linkage. Treatment of the intermediate **211** with Grubbs' catalyst led to simultaneous ring-closing metathesis and cleavage from the resin to give the desired oxacycles **212**.

4. Summary and Outlook

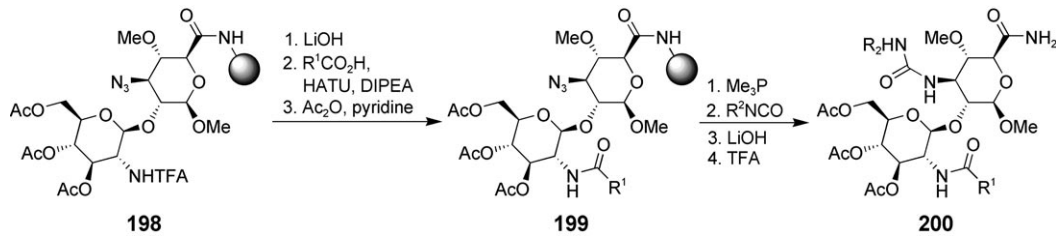
The first publication on the use of a carbohydrate scaffold for the design and synthesis of a peptidomimetic compound in 1990 generated a growing interest in the use of such scaffolds for the drug-discovery process. A number of building blocks have been designed that allow orthogonal access to the individual positions on the carbohydrate scaffold, and solution- and solid-phase libraries have been generated using these building blocks, with individual libraries containing up to several thousand compounds.

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 (such as the somatostatin receptor), integrins, matrix metalloproteinases (MMPs), the multidrug-resistance-associated protein (MRP), and compounds that show antibacterial or antiviral activity.

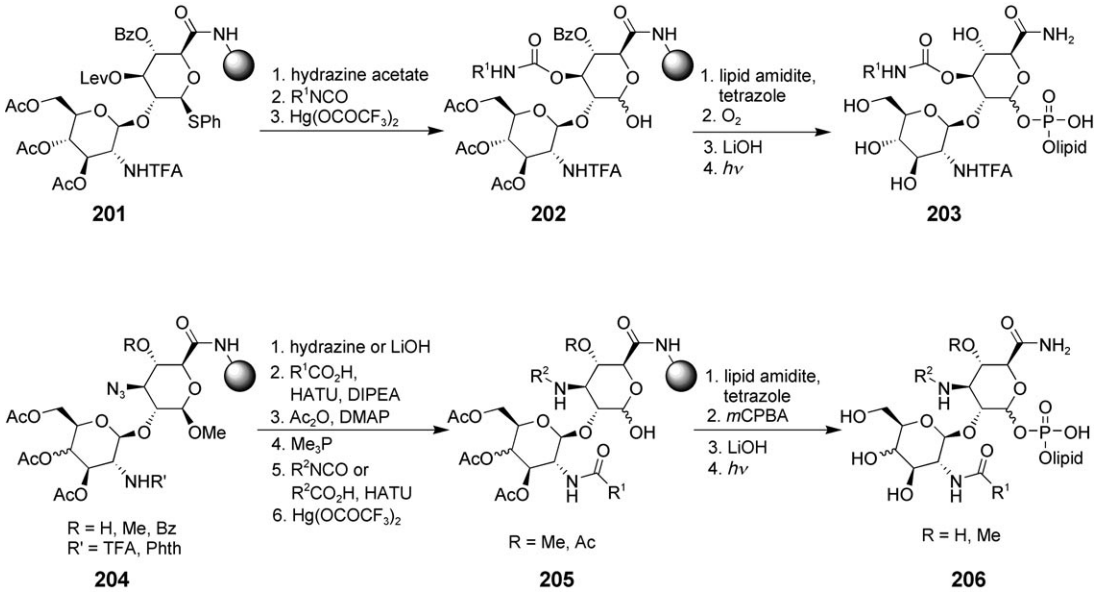
Orthogonal combinations of protecting groups for solution- and solid-phase approaches together with a variety of chemical linking strategies offer the possibility to introduce a huge variety of pharmacophoric groups around basic carbohydrate scaf-



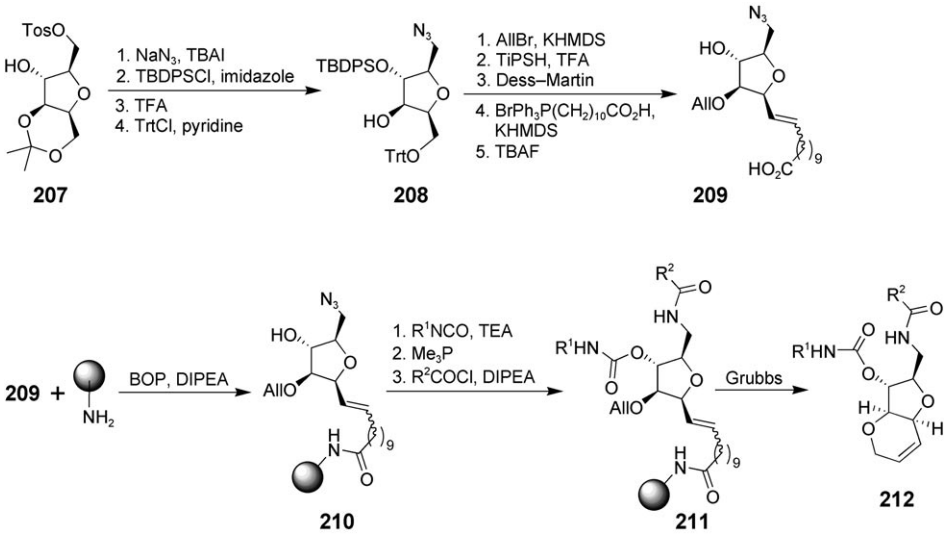
Scheme 25. Use of a furanose scaffold in combinatorial solid-phase synthesis.



Scheme 26. Development of a solid-phase combinatorial library based on a disaccharide scaffold.



Scheme 27. Synthesis of a library based on disaccharide scaffolds.



Scheme 28. Library synthesis using a carbohydrate-derived scaffold.

folds in a stereochemically defined 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, 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 scaffolds, it may only be a question of time until we see the first results of a carbohydrate-based drug-discovery approach in the clinic.

5. Summary Tables

Table 2. Solution-phase syntheses.

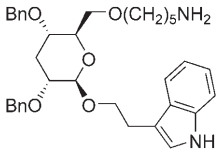
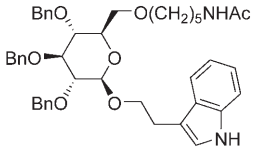
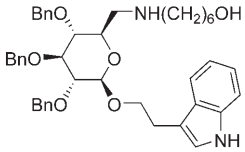
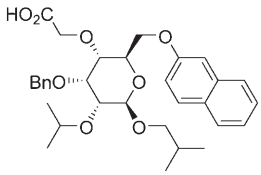
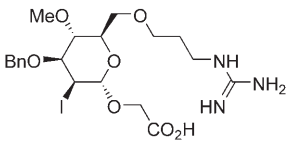
Entry	Representative Structure	No. Compds	Target	Activity	Ref.
1		2	SSTR	$IC_{50} = 1.3\ \mu M$	[1]
2		3	SSTR substance P receptor	– $IC_{50} = 60\ nM$	[27]
3		17	SSTR	$IC_{50} = 5.1\ \mu M$	[28]
4		8	endothelin receptor	inactive	[48]
5		9	integrins	$IC_{50} = 85\ \mu M$ ($\alpha_{IIb}\beta_3$)	[34]

Table 2. (Continued)

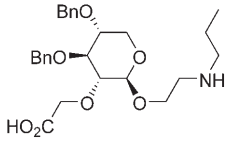
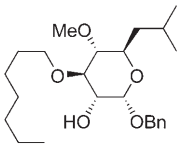
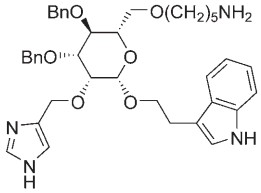
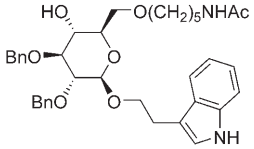
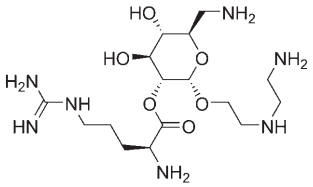
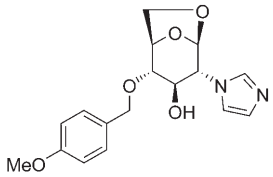
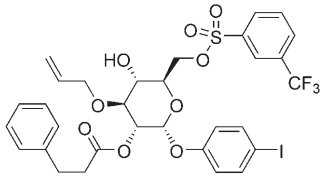
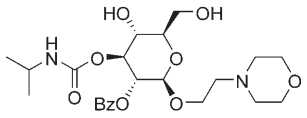
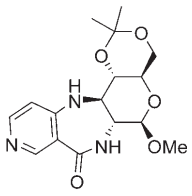
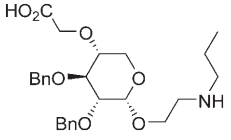
Entry	Representative Structure	No. Compds	Target	Activity	Ref.
6		4	integrins	$IC_{50} = 20\ \mu M$ ($\alpha_{IIb}\beta_3$)	[35]
7		1	P-gp MRP	low activity active	[49]
8		21	SSTR	$IC_{50} = 0.1\ \mu M$ (SSTR4)	[29]
9		21	NK-1 receptor	$IC_{50} = 27\ nM$	[29]
10		24	RNA	$K_d = 30\ \mu M$	[56]
11		28	no target	–	[60]
12		22	EGF HGF	$IC_{50} = 2\ \mu M$ $IC_{50} = 3\ \mu M$	[50]
13		9	no target	–	[58]
14		6	no target	–	[59]
15		126[a]	integrins	active ($\alpha_v\beta_3$)	[36]

Table 2. (Continued)

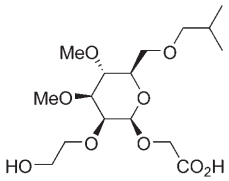
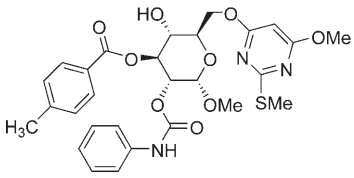
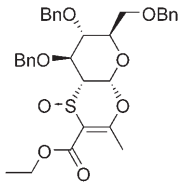
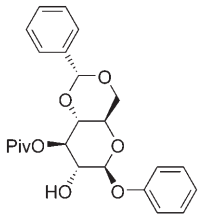
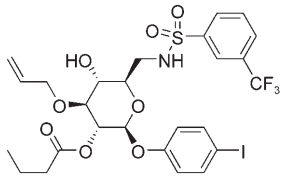
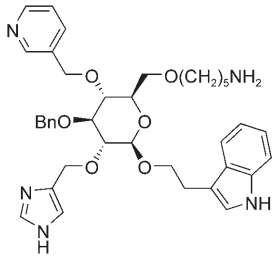
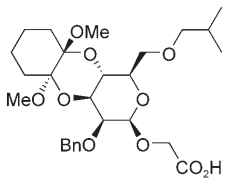
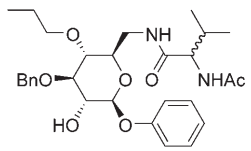
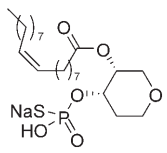
Entry	Representative Structure	No. Compds	Target	Activity	Ref.
16		8	integrins	low activity ($\alpha_4\beta_1$)	[37]
17		237[a,b]	herbicidal	low activity	[57]
18		14	NK-2	K_i = 0.25 μM	[33]
19		9	HIV-1 protease	K_i = 3.81 μM	[44]
20		17	DNA synthesis, apoptosis	IC_{50} = 6.5 μM	[51]
21		15	SST4R	K_i = 53 nM	[26]
22		18	integrins	IC_{50} = 420 μM ($\alpha_4\beta_7$)	[38]
23		8	HIV-1 protease	low activity	[45]
24		40	LPAR	EC_{50} = 0.5 nM (LPA_3R)	[52]

Table 2. (Continued)

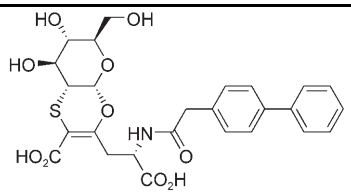
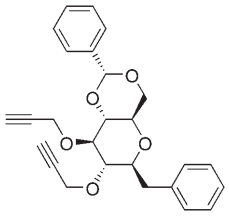
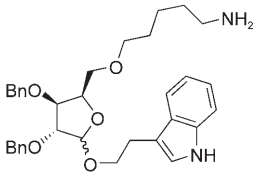
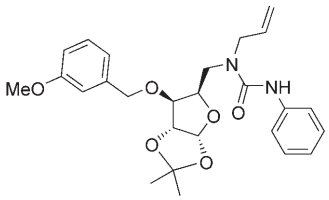
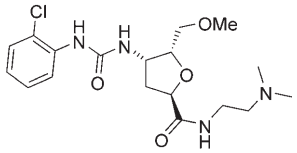
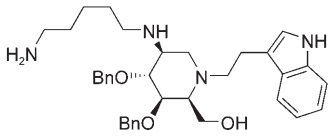
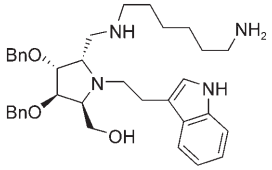
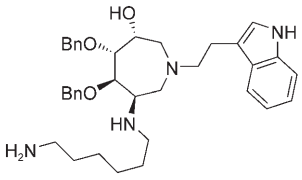
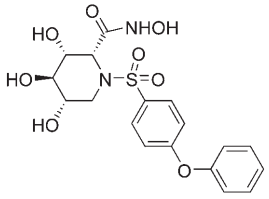
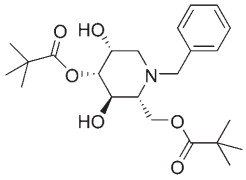
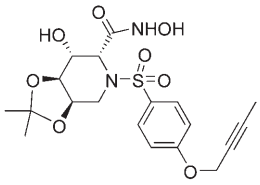
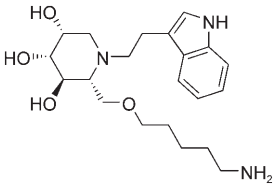
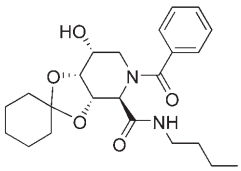
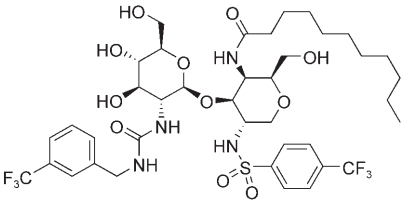
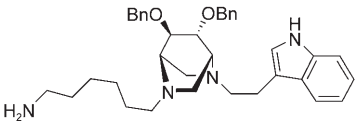
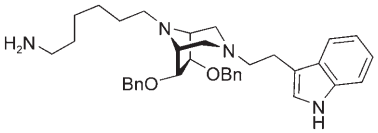
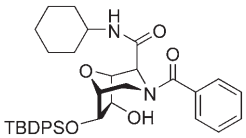
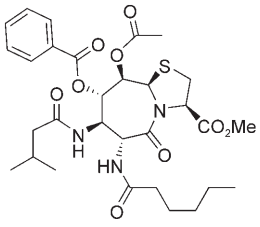
Entry	Representative Structure	No. Compds	Target	Activity	Ref.
25		2	MMP-12	$IC_{50}=490\ \mu M$	[43]
26		21	CMV	$IC_{50}=1.2\ \mu M$	[47]
27		1	SSTR	$IC_{50}=23\ \mu M$	[30]
28		>5000	no target	–	[65]
29		99	antibacterial	–	[53]
30		6	SSTR	$IC_{50}=12\ \mu M$	[31]
31		6	SSTR	$IC_{50}=14\ \mu M$	[31]
32		6	SSTR	$IC_{50}=10\ \mu M$	[31]
33		7	MMP TACE	$K_i=0.06$ nM (MMP-9) $K_i=2.3$ nM	[39,41,42]

Table 2. (Continued)

Entry	Representative Structure	No. Compds	Target	Activity	Ref.
34		8	HIV-1 protease	low activity	[45,46]
35		5	TACE	K_i = 0.57 nM	[40]
36		1	SSTR	K_i = 26 μM	[32]
37		18	no target	–	[69,70]
38		100s	transglycosylase	active	[71]
39		6	SSTR	IC_{50} = 15 μM	[31]
40		6	SSTR	IC_{50} = 12 μM	[31]
41		18	no target	–	[69,70]
42		3	no target	–	[72]

[a] Compound mixtures produced. [b] Partially solid phase.

Table 3. Solid-phase syntheses.

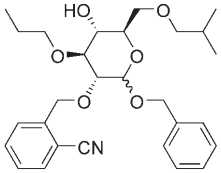
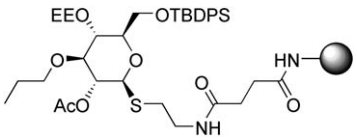
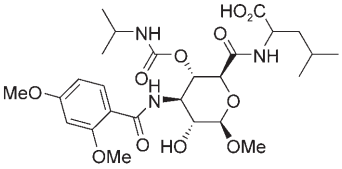
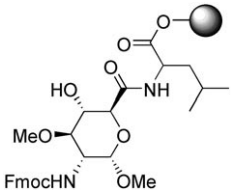
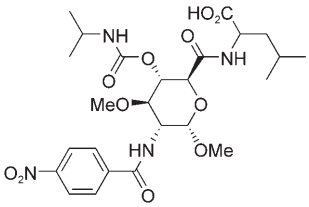
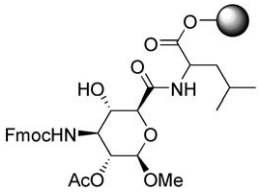
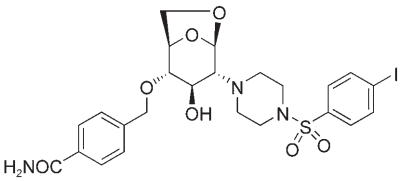
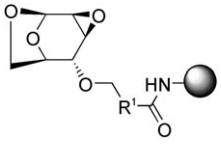
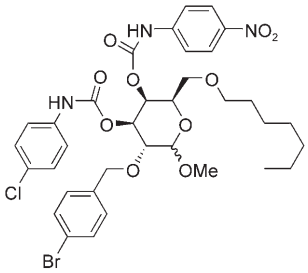
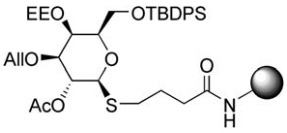
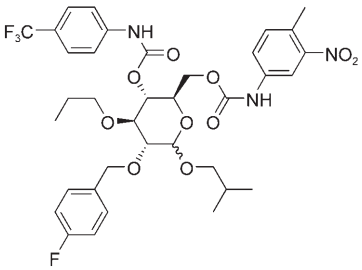
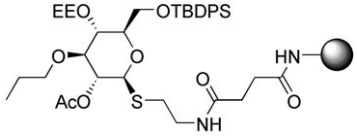
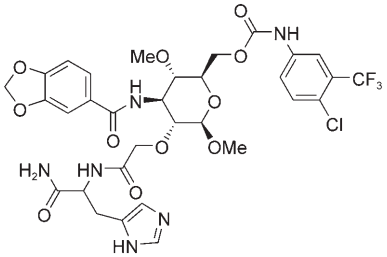
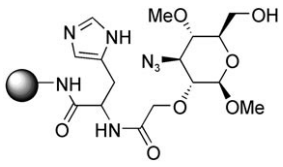
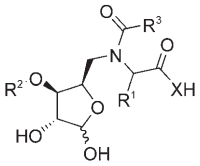
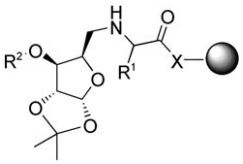
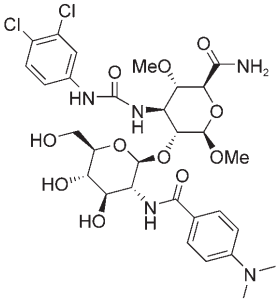
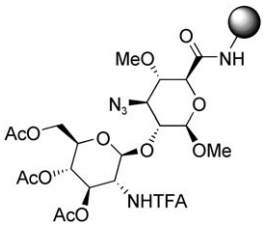
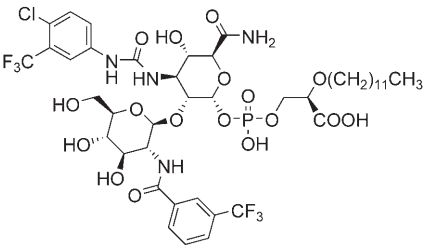
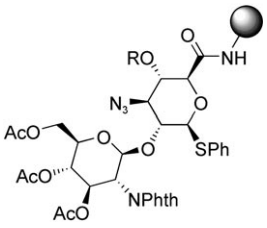
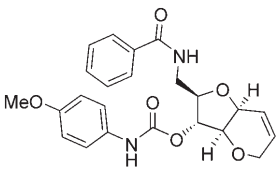
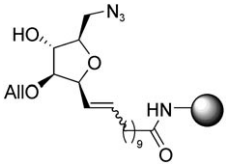
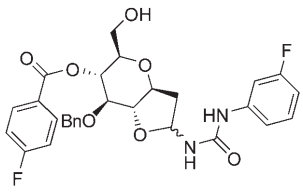
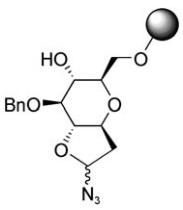
Entry	Representative Structure	Building Block	No. Compds	Target	Activity	Ref.
1			28	no target	–	[15]
2			768	no target	–	[24, 25]
3			768	no target	–	[24, 25]
4			66	no target	–	[73, 74]
5			100s	no target	–	[20]
6			78, 36	no target	–	[16–18]
7			48	no target	–	[23]

Table 3. (Continued)

Entry	Representative Structure	Building Block	No. Compds	Target	Activity	Ref.
8			–	no target	–	[65]
9			48	no target	–	[25]
10			1300	transglycosylase	active	[54]
11			9	no target	–	[77]
12			37	cell proliferation	$IC_{50} = 26\ \mu M$	[75]

Glossary

All	allyl
Aloc	allyloxycarbonyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Bz	benzoyl
Cbz	benzyloxycarbonyl
CDI	1,1′-carbonyldiimidazole
CSA	10-camphorsulfonic acid
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAH	diisobutylaluminium hydride
DIC	*N*,*N*′-diisopropylcarbodiimide
DIPEA	*N*-*N*′-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMP	dimethyl phthalate
EDAC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
EE	ethoxyethyl
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxybenzotriazole
KHMDS	potassium hexamethyldisilazane
*m*CPBA	*m*-chloroperoxybenzoic acid
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NHS	*N*-hydroxysuccinimide
NMM	*N*-methylmorpholine
PAL	aminomethyl-3,5-dimethoxyphenoxyvaleric acid
Phth	Phthalyl
PNB	*p*-nitrobenzoyl
PMB	*p*-methoxybenzyl
PS	polystyrene
PS-DES	butyldiethylsilane polystyrene
PTS	*p*-toluenesulfonamide
RAM	aminomethylated polystyrene
Su	succinimide
TBA	tetra-*n*-butylammonium
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-pyridinyloxy, free radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TMS	trimethylsilyl
Tos	toluene-4-sulfonyl
Trt	trityl
TSA	*p*-toluenesulfonic acid

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Keywords: carbohydrate scaffolds · carbohydrates · combinatorial chemistry · drug discovery · mimetics

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