Molecular diversity through sugar scaffolds

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Monosaccharides provide an excellent platform to tailor molecular diversity by appending desired substituents at selected positions around the sugar scaffold. The presence of five functionalized and stereo-controlled centres on the sugar scaffolds gives the chemist plenty of scope to custom design molecules to a pharmacophore model. This review focuses on the peptidomimetic developments in this area, as well as the concept of tailoring structural and functional diversity in a library using carbohydrate scaffolds and how this can lead to increased hit rates and rapid identification of leads, which has promising prospects for drug development.

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▼ In the current era of genomics, proteomics, glycomics and other –omics, the exponential increase in potential therapeutic targets is placing an ever-increasing demand on access to novel and diverse chemical libraries. The underlying consensus is that in any new hit discovery process, the chance of finding a first small molecule hit is proportional to the level of molecular diversity in the examined library. By contrast, QSAR is much harder to obtain from a structurally unrelated set of hits. Rapid access to high molecular diversity within one class of molecules should provide not only improved hit discovery but also more efficient hit-to-lead development.

Molecular diversity?

Molecular diversity [1,2] is based on the 'similar property principle' [3], which states that structurally similar molecules should reveal similar physicochemical and biological properties. Even though physicochemical and, particularly, biological properties are hard to correlate with molecular properties, many models exist using a set of 1D (physicochemical), 2D (topological) or 3D (geometrical) descriptors [4–9] to describe molecular diversity or similarity. In particular, 2D descriptors, such as fingerprints, have been used widely in quantifying molecular diversity because they are fast to compute and readily compared [10]. Although 2D descriptors are valuable in comparing structurally unrelated compounds, they lack information about the shape and localization of functional groups, making them poor when comparing structurally related compounds, such as isomers. By contrast, 3D descriptors [4] are more computationally intensive because they have to consider the conformational flexibility of a compound, which, itself, adds a degree of uncertainty to the descriptors.

One way to 'interpret' molecular diversity is to split it into a functional part and a structural part, and then reduce the structural part to just the rigid portion of the scaffold. Peptide libraries, for example, can be described in terms of functional diversity, type of side chains (or substituents), structural diversity and relative orientation of the side chains [11,12]. These orientations are defined by the Cα–Cβ bonds that link the side chain to the backbone. Proteins and peptides are one of nature's ways of creating a high level of molecular diversity through different types of amino acids and by secondary and tertiary conformations (e.g. turns, loops, α-helix and β-sheets). This split of molecular diversity can be applied to scaffolds, which are merely there to control the relative orientation of the functional groups and provide only a small contribution to the biological property of the compound. In addition, the structural part of the diversity can be directly compared between different scaffolds.

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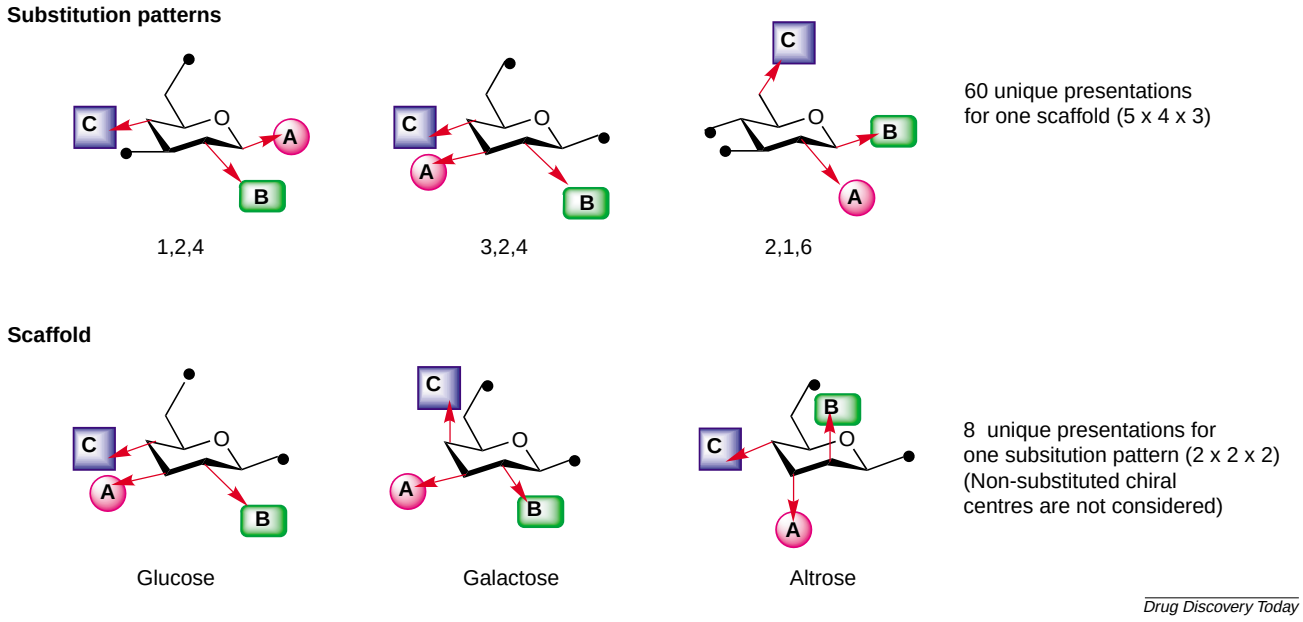

Figure 1. Illustration of the structural diversity (for three substituents, A, B and C) that is accessible through pyranose scaffolds. A unique presentation of ABC is formed through selecting a substitution pattern and a scaffold. This figure illustrates that the maximum number of unique presentations for the three substituents using pyranose scaffolds is 480 (60 × 8).

Sugars and molecular diversity

The monosaccharide-based scaffold contains five chiral, functionalized positions. In principle, various substituents can be appended at each position and chirality at that centre can be altered. Sugar scaffolds provide an unparalleled opportunity to generate libraries of high functional and structural diversity. If, for example, three different pharmacophore groups (read substituents) are positioned on glucose, 60 unique products are formed, all with similar molecular properties (e.g. same molecular weight and same type of functional groups) but with different orientations of the pharmacophore groups, which is achieved by just altering the position of each substituent (A, B and C) around the scaffold. It is possible to get an additional 36 unique products by just altering one of the substituted chiral centres. Figure 1 and Table 1 show the relationship between the number of unique presentations and the number of substituents and scaffolds.

How structurally diverse are all these virtual products and how does the sugar scaffold compare with other scaffolds, such as proteins or peptides? To quantify structural diversity, the last rigid bond from the sugar scaffold to the substituent could be considered as a vector, resulting for each unique ABC product in a set of three vectors (independent of the nature of the substituent). Geometrical properties, such as dihedral angles and distances, are then calculated for each three-vector set. To visualize the structural diversity, the angles, dihedral angles and distances of each unique product are subjected to principal component analysis (PCA) and the scorings of the first two dominant principal components, PCA1 and PCA2, are plotted (Fig. 2). A similar analysis was carried out on 200,000 tripeptide sequences found in the crystal structures of a structurally diverse subset of proteins by using the vectors representing the Cα–Cβ bonds. Figure 2 shows the comparison of a sugar-based library (using only the α and β anomers of D-glucose, D-mannose, D-allose and D-galactose) with the diverse tripeptide set above.

The comparison shows that most peptide structures can be mimicked effectively with a subset of these sugar scaffolds, especially tighter turns, such as Turn I′ or gamma Turn inverse (gTurn Inv). Other turns, such as Turn II and Turn II′ or even α-helices (aHelix), are at least partially covered. In addition, one single scaffold (α-D-Glc or β-D-GlcNAc) provides access to many areas in the diversity space and other sugar scaffolds fill up the voids in between. The result is an evenly distributed, structural diversity, which, in this example, is accessed through eight scaffolds.

Peptidomimetics and sugar scaffolds

Most biological processes are controlled by molecular interactions that involve peptides and proteins. Drug discovery processes often start by identifying peptides that interact with a specific receptor or enzyme by using

well-established combinatorial peptide chemistry approaches. In some fortunate cases, bioactive peptides have been used directly as therapeutic agents; however, in general, they are not suitable as drugs because of their well-documented pharmacokinetic problems (susceptible to proteolysis, poor oral availability and rapid excretion by the liver and kidney). The conversion of bioactive peptides into more drug-like molecules has often been approached systematically by identifying the key elements responsible for activity in terms of essential amino acid residues and their presentation in space. Bioactive molecules derived from such strategies are commonly labelled as peptidomimetics and, as the name suggests, aim to closely resemble the peptides from which they originated.

Peptidomimetic concepts [13] and synthetic strategies [14–18] were increasingly investigated from 1980 onwards. Approaches have varied greatly, from peptide-like templates, such as pseudopeptides, peptoids, retroinverso peptides and cyclic peptides, to using organic scaffolds that bear little resemblance to the peptide backbone, such as bicyclo(2.2.2)octane scaffold [19], cyclohexane-based scaffolds [20] or bicyclic heterocycles [21] to name but a few. Work on peptidomimetics has been reviewed extensively [14–18,22,23].

Table 1. Relationship between the number of unique presentations and the number of substituents and scaffolds.

	AB[a]	ABC[a]	AAB[a]	ABCD[a]
One scaffold (i.e. α–D-Glc)	20	60	30	120
Two scaffolds differing only at one stereo centre	28	96	48	216
32 different scaffolds – maximum unique patterns	80	480	240	1920

[a]AB: 2 different substituents; ABC: 3 different substituents; AAB: three substituents, two of them the same; ABCD: four different substituents.

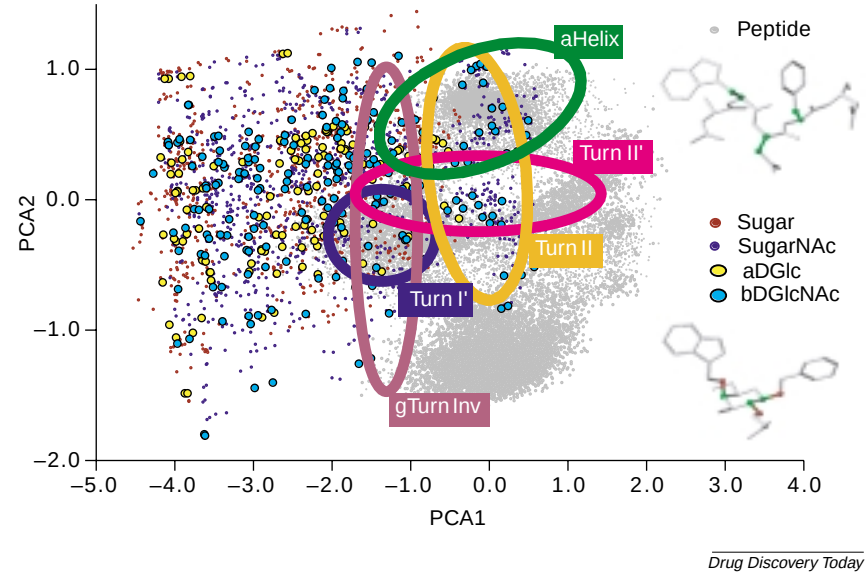

Figure 2. Comparison of geometrical diversity accessible through sugar scaffolds or peptide backbones. Each point in the diagram represents a set of three vectors derived from appending three substituents to a scaffold (peptide in grey, sugar in colour) where the vector represents the covalent bond between the scaffold and the substituent. Vector sets are subjected to principle component analysis (only two dominant principle components, PCA1 and PCA2, are depicted here). The coloured elipses represent the areas covered by selected peptide structures found in bioactive peptides.

In the past decade, several groups have developed synthetic methods to transfer the described concept to sugar scaffolds (Fig. 3). The carbohydrate scaffolds have been wide ranging: scaffolds, such as tetrahydrofuran rings derived from D-mannitol [24], artificial amino pyranose rings [25] and the chemically challenging natural glycosides, such as β-mannoside [26], have been investigated (for comprehensive reviews see [27–29]). However, it was Hirschmann *et al.* [30–32] who conducted the pioneering work in this area and successfully demonstrated the use of β-D-glucose in the synthesis of somatotropin release-inhibiting factor peptidomimetics targeting the somatostatin (SST) receptors. Three residues, FWK, contain the necessary functional information, but it is the relative positioning of these side chains in space that determine the affinity for one or more of the SST1–5 receptors. Substituents mimicking these amino acid side chains were positioned on a β-D-glucose scaffold in a way that ensured that the distances between the pharmacophore groups were similar to those of somatostatin. Several products were designed and synthesized that showed good activity against the SST receptors. In addition, sugar-based tachykinin NK_1 antagonists were identified from the same set of compounds [32].

The Hirschman group later demonstrated that compounds with modulated receptor subtype affinity are obtained by altering stereochemical centres in the scaffold. D-Glucose, L-glucose and L-mannose structural isomers were synthesized and displayed different subtype selectivity for somatostatin receptors [33]. More recently, Capozzi *et al.* [34] developed fused heterocyclic-carbohydrate products, which successfully

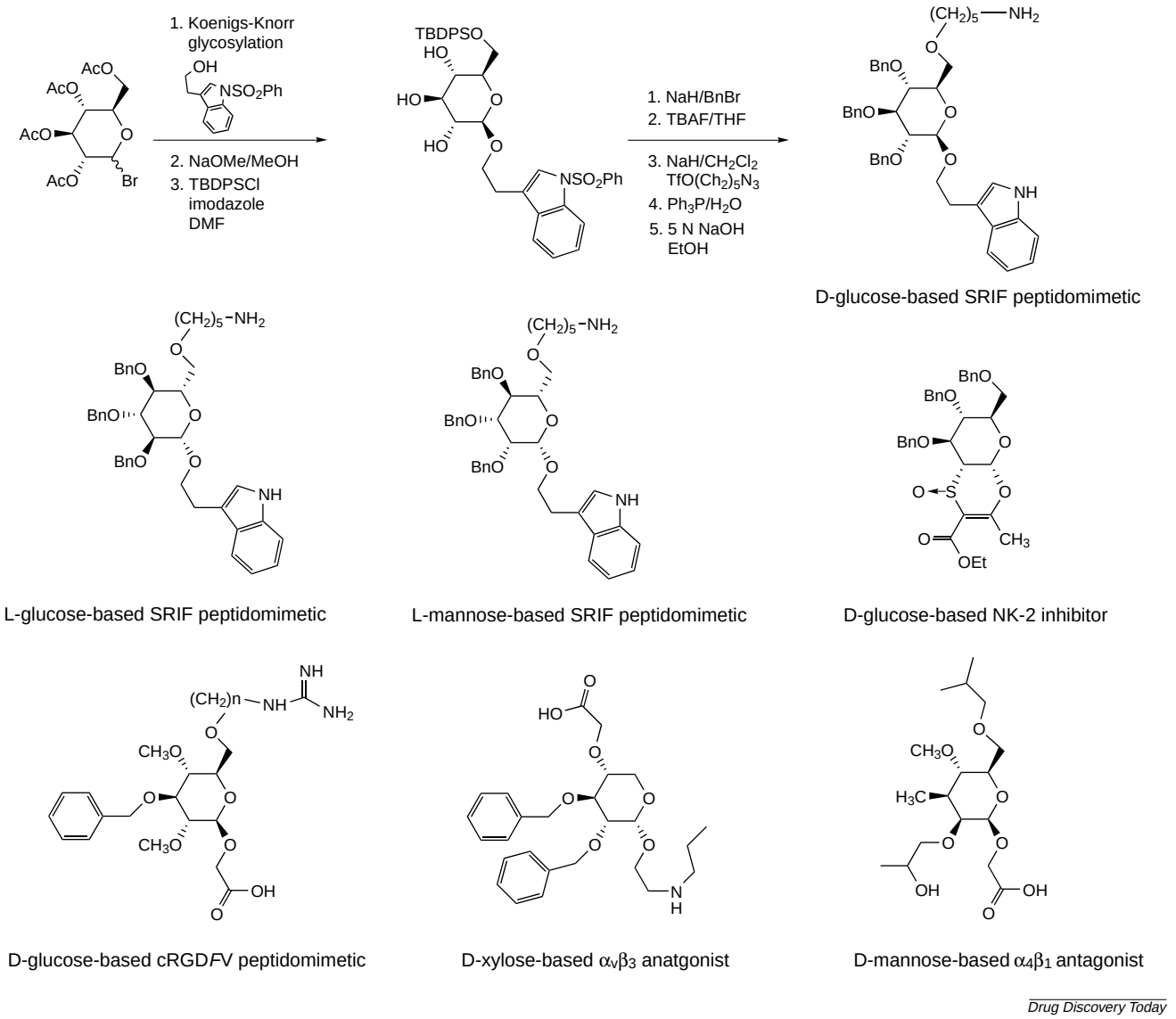

Figure 3. Examples of sugar derived peptidomimetics. Abbreviations: DMF, dimethyl formamide; TBAF, tetrabutylammonium fluoride; TBDPSCl, tert-butyldiphenylsilyl chloride.

mimicked the biological function of the bicyclic hexapeptide, nepadutant, at the NK_2 receptor.

Sugar-based peptidomimetics were also developed for the integrin family. RGD (Asp-Arg-Gly)-containing ligands, such as fibronectin, vitronectin and fibrinogen, bind with different affinities to individual integrin receptors and this selectivity has been associated with different conformational presentation of the RGD segment in the ligand [35]. Nicolaou *et al.* [36] employed the carbohydrate scaffold principle to design and synthesize a series of mimetics of the highly bioactive cyclic peptide cRGD*F*V. Here, side chains containing carboxylic acid and guanidine were introduced regioselectively through extensive chemistries. Scaffold types and substitution patterns were altered in the series, but no activity was reported. Similarly, Moitessier *et al.* [37] reported the design and synthesis of a stereodiverse library of RGD mimetics. D-Glucose-based starting materials were produced individually, containing 1, 2 or 3 carboxylic acid side chains at varying positions around the pyranose scaffold. Alkyl amine substituents were introduced on the scaffold and, using a mixing and deconvolution combinatorial chemistry approach, several compounds were identified that displayed modest antagonist activity at the $\alpha_v\beta_3$ integrin receptor.

Kessler's group have provided an impressive demonstration of structural mimetic design for the α_4 integrins [26].

Starting from identifying a bioactive cyclic peptide and NMR determination of bioactive peptide conformations, molecular modelling was used to design a small set of mimetics based on β-D-mannopyranose. This led to the identification of $\alpha_4\beta_1$-selective integrin antagonists.

A further example of successful peptidomimetic design using carbohydrate scaffolds is provided by Hanessian *et al.* [38], who applied the concept for the development of non-peptidic SH2-domain ligands. A small library of *O*-substituted aryl D-glucose was produced and led to the identification of several compounds that inhibited the growth of two carcinoma cell lines in the low micromolar range, indicating cell penetration for these carbohydrate-based compounds.

Carbohydrate scaffolds in combinatorial chemistry

Many combinatorial approaches involving carbohydrates have been investigated. As an example, the structural diversity of carbohydrates has been coupled with the extremely powerful Ugi four component condensation reaction in both solution and on solid phase [39–45]. The advantages and disadvantages of preparing compound libraries on solid phase are well documented [46], but despite the requirement for extensive synthetic method development, solid phase organic synthesis is still an attractive and powerful method for compound library preparation. Sofia *et al.* [47] demonstrated this by generating a large library of disaccharide-based moenomycin mimetics and identified several compounds that displayed high activity against Gram-positive bacteria. In this example, an uronic acid scaffold was loaded onto TentaGel and structures were diversified in two positions with carbamate- and amide-forming reactions.

Orthogonally protected scaffolds of D-glucose [48] and D-galactose [49] have been used by Kunz's group to exploit the concept of regioselective introduction of a variety of substituents using solid supported chemistry (Fig. 4). The chemistries include ether bond formation, carbamate formations and a glycosylation-release strategy enabling the use of up to four diversification points per scaffold. The concept was explored further in the synthesis of several diverse libraries on solid support [50]. It is unclear whether this patented strategy has been applied further in drug discovery projects. Hirschmann *et al.* also described orthogonally protected β-D-glucose scaffolds for library development [51].

An efficient solid phase synthetic method for generating regiodiverse carbohydrate scaffolded libraries is described by Sofia *et al.* [52] (Fig. 4). The authors used two amino glucoronic acid building blocks (i.e. two substitution patterns) to introduce three pharmacophore groups on the scaffolds. The regioselective introduction of each group was realized by employing a carboxylic acid, a free hydroxy group and a protected amino group in the building blocks.

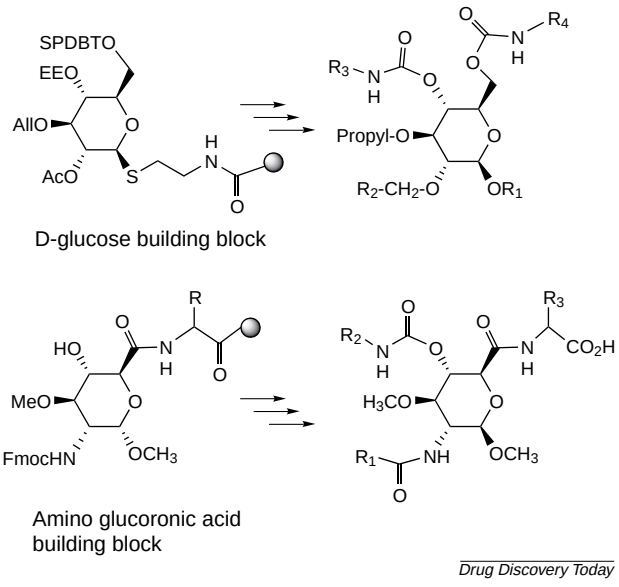

Figure 4. Orthogonally protected D-glucose and amino glucoronic building blocks that are used in combinatorial library production.

Sugar scaffolds to tailor diversity in libraries

One benefit of carbohydrate-based scaffolds lies in the ability to produce rigid, unique products with well-defined, 3D orientation of selected substituents. The concept of designing shape and surface properties of such products to mimic known peptide ligands has been well demonstrated in the above examples. Historically, it has proved difficult to design and produce single mimetics that maintain the level of bioactivity and selectivity of the original/natural ligand. This is due, in part, to a loss of positional and conformational overlay with the natural ligand, probably because of the inaccuracies involved in estimating exact positions and conformations. Small, seemingly innocuous, molecular modifications often cause major changes in bioactivity profiles. More often than not, little is known about the exact bioactive shape of a ligand, leading to a limited level of geometrical guidance in the single molecule design.

To compensate for these inaccuracies or lack of conformational knowledge, it is necessary to incorporate more compounds into the initial design that cover a broader level of structural and functional diversity. Ideally, this broader diversity space should be explored systematically in a scanning-like fashion. The term 'tailoring diversity of the library' is used to describe the concept of systematically exploring a predefined area in the diversity space.

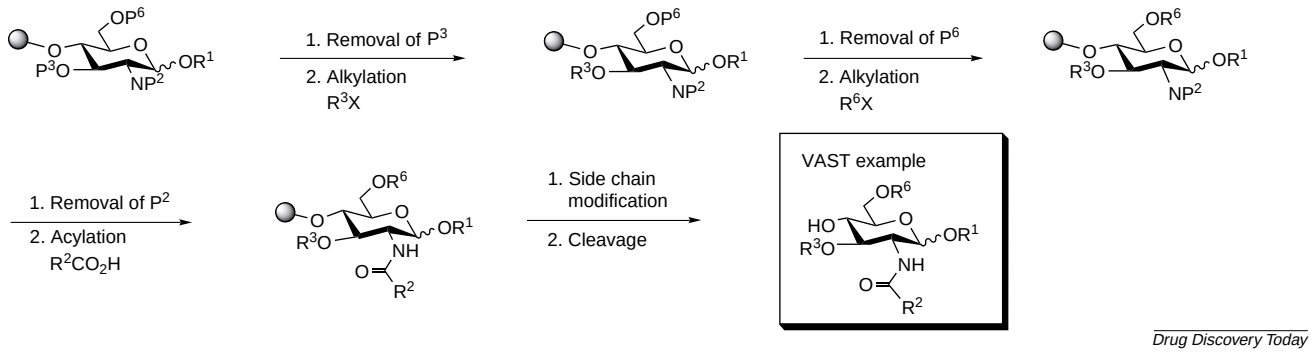

Figure 5. An example of on-resin diversification using orthogonally protected building blocks.

In this respect, the diversity analysis in Figure 2 demonstrates that carbohydrate scaffolds provide a good opportunity to address these needs. The geometrical diversity analysis of carbohydrate scaffolds illustrates that: (1) a single carbohydrate scaffold provides a template to append substituents in many ways (60 isomers if using three substituents), resulting in unique and rigid products with well-defined geometry; and (2) low numbers of scaffolds are sufficient to cover a broad range of structural diversity in an even, uniform and systematic way.

Several years ago we started developing a solid phase synthetic technology [Versatile Assembly on Sugar-like Templates (VAST™)] based on carbohydrate-derived building blocks and combinatorial synthetic chemistries that enabled parallel production of libraries of controlled structural and functional diversity.

The VAST™ technology is based on the following criteria:

- Stability – the linker and orthogonal protecting groups must be stable to all derivatization steps and the final product must be stable to cleavage conditions.
- Chemistry – applicable to a wide variety of reaction types, reagents and monomers, as well as to building blocks, producing single products in high purity and acceptable yield.
- Selectivity – chemo-, stereo- and regioselective control of amino and hydroxyl functions.
- Building blocks – a need for orthogonally protected building blocks.
- Molecular diversity – covers a broad range of molecular (bioactive) diversity space through a minimum number of building blocks.
- Drug-like products – metabolic stability and good bioavailability of the final products.
- User friendly – flexible, reproducible and robust reaction protocols, easily performed by automated synthesizers or manual processes.

Scientists at Alchemia (http://www.alchemia.con.au/) have experience in the area of orthogonal protection of carbohydrate building blocks [53] and have used this technology platform to establish a series of proprietary, carbohydrate-like building blocks, which have been further examined in our VAST™ solid phase strategy. Figure 5 illustrates the concept on an example building block.

In this example, four groups are introduced regioselectively on solid phase and in a stepwise fashion. An initial off-resin glycosylation followed by resin attachment sets up the first substituent (R1, steps not shown). Two *O*-alkylations and amide bond formation are followed by side chain modifications (e.g. converting an amine into a guanidine) to generate the desired products after cleavage. The main diversification steps are carried out on resin, which simplifies the manipulations of the library. Such libraries can be produced manually (e.g. IRORI or Bohdan) or in an automated fashion [e.g. Chemspeed (http://wwww.chemspeed.com)] and the average purity of the crude products is 69%. All products are purified by automated mass-directed fractionation to a final purity of more than 95% by evaporative light-scattering detection, thus minimizing false positives in our screening programmes. The range of purified products yields is 10–60%.

Design of VAST™ library targeted to SST5 and MC4

To demonstrate the concept, two closely related GPCR receptors, MC4 and SST5, were selected as targets and structural information of known ligands used to design an initial library (400 compounds) of tailored geometrical and functional diversity.

Melanocortin and somatostatin receptors (Box 1) have common features in the nature of their ligands (i.e. core to the activity is the presence of two or more aromatics and a positive charge). We decided to design a VAST™ library tailored to MC4 and SST5 by incorporating geometrical

and functional features based on known, highly active ligands. A more empirical scanning approach was taken by incorporating several 'unique presentations' and a range of substituents to mimic the aromatic and positively charged residues expected to elicit a biological response.

The library was designed as follows:

- Eight unique presentations were selected (four scaffolds, two substitution patterns each).
- A set of aromatics and positive charges were used to mimic the essential residues.
- For each presentation the same combinations of substituents were used, resulting in eight sets of compounds, in which each set is represented by the same number of compounds and each compound in one set has one isomer in all other sets.

The designed libraries fit well within the rules of drug-likeness as established by Lipinski [54] and 65% of the library fulfils at least three out of four rules (molecular weights are in the 500–600 range).

A library of 400 compounds was synthesized based on the above description and screened (after purification to >95%) in radioligand binding assays against MC4 and SST5 at concentrations of 10μM–1nM. At first glance the focused library generated an unusually high number of highly active compounds. What is most fascinating is the ease with which SAR analysis of these results, based on structural and functional characteristics, can be carried out. Table 2 shows a comparison of four unique presentations (each represented by the same number of compounds) and their respective hit rates.

Different hit rates for unique presentation sublibraries (represented by the same number of compounds and the same set of substituents) illustrates that the relative 3D orientation of the substituents in these compounds plays

Box 1. Biological functions of somatostatin and melanocortin receptors

The tetradecapeptide somatostatin is widely distributed in the endocrine and exocrine system, where it has an essential role in regulating hormone secretion [55–57]. Somatostatin receptors are also expressed in tumours and peptide analogues of somatostatin affecting mainly SST5, such as octreotide, lanreotide, vapreotide and seglitide [58–61], which have antiproliferative effects. They are used clinically for the treatment of hormone-producing pituitary, pancreatic and intestinal tumours. The 'core sequence' in somatostatin responsible for its biological activity is Phe-Trp-Lys (FWK).

The melanocortin peptides have several physiological effects. MC4 is present in high concentrations in the hypothalamus and has been established as an important factor in energy homeostasis and as part of a signalling pathway involved in body weight regulation [62,63]. The central 'core sequence' in the melanocortins responsible for biological activity is His-Phe-Arg-Trp (HFRW). Several different peptide analogues displaying either agonist or antagonist activity are currently in different stages of development [64,65].

Table 2. Percentage hit rates, in which a hit is defined as compounds that cause more than 50% ligand displacement at a 10 μM concentration.

Unique presentation	Scaffold	Substitution pattern	% Hits at MC4	% Hits at SST5
1	A	A	11	38
2	A	B	34	14
3	B	A	83	99
4	B	C	71	98

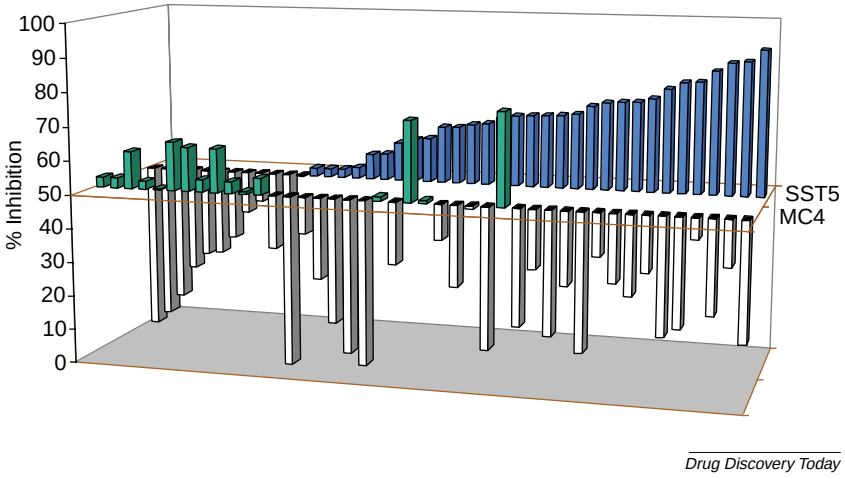

Figure 6. Percent inhibition of a subset of VAST™ compounds (from a 400-member first generation library) at 1 μM in SST5 (blue) and MC4 (green) radio-ligand binding assays. Colour indicates over 50% inhibition.

an important role in the final activity profile of the compound. Both entries 1 and 2 use the same scaffold but different substitution patterns. The substitution pattern in 1 favours interaction with the SST5 receptor, whereas the substitution pattern in 2 clearly leads to improved interaction with the MC4 receptor. Using the same substitution pattern, but changing only one stereo centre on the scaffold, leads to dramatically improved binding to the SST5 and MC4 receptors (entry 1 and 3 differ only in one stereo centre).

Furthermore, by taking a somewhat empirical approach in the design (to allow a level of structural and functional diversity in the library), we have identified selective potent SST5 and MC4 agonists from a first generation library (Fig. 6). One of these potent hits was examined in preliminary *in vivo* pharmacokinetic studies and demonstrated excellent metabolic stability, with a half life of 4.6 h.

Future prospects

Carbohydrates form a natural source for stereodiverse scaffolds, which, through orthogonal protection and modular chemistries, enable medicinal chemists to systematically alter shapes and surface properties of molecules to suit selected targets. The opportunity to create molecular diversity in a modular, systematic and tailored way (structurally and functionally) is unique to carbohydrates. It is self evident that such approaches are not limited to mimicking peptides. Molecular diversity can be tailored, at least in principle, to any target. We have applied this concept in other therapeutic areas in which no bioactive peptides have been discovered, such as the ATP binding site in kinases and a series of bacterial cell wall targets. In all cases we have been able to identify hits in first generation libraries, some of which have been developed to leads and are currently being investigated in pharmacokinetic studies.

Carbohydrate-like scaffolds are being used increasingly in drug design and development projects. The prospect for successful development of a commercial drug based on the sugar scaffold principle is high given the promising stability, pharmacokinetic data and level of activity that has been observed to date.

References

1 Martin, E.J. *et al.* (1995) Measuring diversity: experimental design of combinatorial libraries for drug discovery. *J. Med. Chem.* 38, 1431–1436
2 Dean, P.M. (1995) *Molecular Similarity in Drug Design*, Chapman & Hall
3 Johnson, M.A. and Maggiora, G.M. (1990) *Concepts and Application of Molecular Similarity*, Wiley-Interscience.
4 Makara, G.M. (2001) Measuring molecular similarity and diversity: total pharmacophore diversity. *J. Med. Chem.* 44, 3563–3571
5 Beno, B.R. and Mason, J.S. (2001) The design of combinatorial libraries using properties and 3D pharmacophore fingerprints. *Drug Discov. Today* 6, 251–258
6 McGregor, M.J. and Muskal, S.M. (2000) Pharmacophore fingerprinting. 2. Application to primary library design. *J. Chem. Inf. Comput. Sci.* 40, 117–125
7 Mason, J.S. *et al.* (1999) New 4-point pharmacophore method for molecular similarity and diversity applications: overview of the method and applications, including a novel approach to the design of combinatorial libraries containing privileged substructures. *J. Med. Chem.* 42, 3251–3264
8 Pearlman, R.S. and Smith, K.M. (1999) Metric validation and the receptor-relevant subspace concept. *J. Chem. Inf. Comput. Sci.* 39, 28–35
9 Brown, R.D. and Martin, Y.C. (1997) The information content of 2d and 3d structural descriptors relevant to ligand-receptor binding. *J. Chem. Inf. Comput. Sci.* 37, 1–9
10 Gorse, D. and Lahana, R. (2000) Functional diversity of compound libraries. *Curr. Opin. Chem. Biol.* 4, 287–294
11 Bourne, G.T. *et al.* (1996)) b-turn nomenclature: a topographical classification system. In *Peptides: Chemistry, Structure and Biology* (Kaumaya, P.T.P. and Hodges, R.S., eds), pp. 354–355, Mayflower Scientific
12 Tran, T.T. *et al.* (2000). The side-chain classification of loops from high-resolution protein crystal structures. In *Peptides for the New Millenium* (Fields, G.B. *et al.*, eds), pp. 320–321, Kluwer Academic Publishers
13 Farmer, P.S. (1980) In *Drug Design* (Vol. 10) (Ariens, E.J., ed.), p. 119, Academic New York
14 Zuckermann, R.N. *et al.* (1992) Peptoids: a modular approach to drug discovery. *Proc. Natl. Acad. Sci. U. S. A.* 89, 9367–9371
15 Kahn, M. *et al.* (2002) Design, synthesis, and application of peptide secondary structure mimetics. *Mini. Rev. Med. Chem.* 2, 447–462
16 Janda, K.D. *et al.* (2002) Peptidomimetics and peptide backbone modifications. *Mini. Rev. Med. Chem.* 2, 447–462
17 Rich, D.H. *et al.* (2002) Designing non-peptide peptidomimetics in the 21st century: inhibitors targeting conformational ensembles. *J. Med. Chem.* 45, 541–558
18 Houghten, R.A. *et al.* (1999) New opioid peptides, peptidomimetics, and heterocyclic compounds from combinatorial libraries. *Biopolymers* 51, 379–390
19 Bélanger, P.C. and Dufresne, C. (1986) Preparation of *exo*-6-Benzyl-*exo*-2-(*m*-hydroxyphenyl)-1-dimethylaminomethylbicyclo[2.2.2]octane. A non-peptide mimetic of enkephalins. *Can. J. Chem.* 64, 1514–1520
20 Olsen, G.L. *et al.* (1989) Concepts and progress in the design of peptide mimetics, beta turns and thyrotropin releasing hormone. In *Proc. Biotechnol. (U. S. A.)*, pp. 348–360, Conference Management Association
21 Kahn, M. *et al.* (1998) Highly efficient and versatile synthesis of libraries of constrained beta-strand mimetics. *Bioorg. Med. Chem. Lett.* 8, 2321–2326
22 Olsen, G. *et al.* (1993) Concepts and progress in the development of peptide mimetics. *J. Med. Chem.* 36, 3039–3049
23 Gante, J. (1994) Peptidomimetics – tailored enzyme inhibitors. *Angew. Chem. Int. Ed. Engl.* 33, 1699–1720
24 Hanessian, S. *et al.* (2000) Tetrahydrofuran as a scaffold for peptidomimetics. Application to the design and synthesis of conformationally constrained metalloproteinase inhibitors. *Tetrahedron* 56, 7643–7660
25 Ghosh, M. *et al.* (2000) Efficient synthesis of a stereochemically defined carbohydrate scaffold: carboxymethyl 2-acetamido-6-azido-4-*o*-benzyl-2-deoxy-β-D-glucopyranoside. *J. Org. Chem.* 65, 8387–8390
26 Boer, J. *et al.* (2001) Design, synthesis, and biological evaluation of $\alpha_4\beta_1$ integrin antagonists based on β-D-mannose as a rigid scaffold. *Angew. Chem. Int. Ed. Engl.* 40, 3870–3873
27 Gruner, S. *et al.* (2002) Carbohydrate-based mimetics in drug design: sugar amino acids and carbohydrate scaffolds. *Chem. Rev.* 102, 491–514
28 Schweizer, F. (2002) Glycosamino acids: building blocks for combinatorial synthesis-implications for drug discovery. *Angew. Chem. Int. Ed. Engl.* 41, 231–253

29 Peri, F. *et al.* Carbohydrate-based scaffolds for the generation of sortiments of bioactive compounds. *Monatshefte Chem.*133, 369–382
30 Hirschmann, R. *et al.* (1992) Nonpeptidal peptidomimetics with a β-D-glucose scaffolding. A partial somatostatin agonist bearing a close structural relationship to a potent, selective substance P antagonist. *J. Am. Chem. Soc.* 114, 9217–9218
31 Hirschmann, R. *et al.* (1993) *De novo* design and synthesis of somatostatin non-peptide peptidomimetics utilizing β-D-glucose as a novel scaffolding. *J. Am. Chem. Soc.* 115, 12550–12568
32 Hirschmann, R. *et al.* (1996) Synthesis of potent cyclic hexapeptide NK-1 antagonists: use of a minilibrary in transforming a peptidal somatostatin receptor ligand into an NK-1 receptor ligand via a polyvalent peptidomimetic. *J. Med. Chem.* 39, 2441–2448
33 Hirschmann, R. *et al.* (1998) Modulation of receptor and receptor subtype affinities using diastereomeric and enantiomeric monosaccharide scaffolds as a means to structural and biological diversity. A new route to ether synthesis. *J. Med. Chem.* 41, 1382–1391
34 Capozzi, G. *et al.* (2002) Design, synthesis and biological activity of carbohydrate containing peptidomimeticis as new ligands for the human Tachykinin NK-2 receptor. *Bioorg. Med. Chem. Lett.* 12, 2263–2266
35 Dechantsreiter, M.A. *et al.* (1999) *N*-Methylated cyclic RGD peptides as highly active and selective $\alpha_v\beta_3$ integrin antagonists. *J. Med. Chem.* 42, 3033–3040
36 Nicolaou, K.C. *et al.* (1997) Design, synthesis and biological evaluation of carbohydrate-based mimetics of cRGD*f*V. *Tetrahedron* 53, 8751–8778
37 Moitessier, N. *et al.* (2001) Design, synthesis and preliminary biological evaluation of a focused combinatorial library of stereodiverse carbohydrate-scaffold-based. *Bioorg. Med. Chem. Lett.* 9, 511–523
38 Hanessian, S. *et al.* (1999) Design and synthesis of functionalized glycomers as non-peptidic ligands for SH2 binding and as inhibitors of A-431 Human epidermoid and HT-29 colon carcinoma cell lines. *Bioorg. Med. Chem. Lett.* 10, 439–442;
39 Dömling, A. and Ugi, I. (2000) Multi-component reactions with isocyanides. Angew. Chem. Int. Ed. Engl. 39, 3168–3210
40 Goebel, M. and Ugi, I. (1995) Beyond peptide and nucleic acid combinatorial libraries-applying unions of multicomponent reactions towards the generation of carbohydrate combinatorial libraries. *Tetrahedron Lett.* 36, 6043–6046
41 Lockhoff, O. (1998) An access to glycoconjugate lLibraries through multicomponent reactions. *Angew. Chem. Int. Ed. Engl.* 37, 3436–3439
42 Park, W.K.C. *et al.* (1996) Rapid combinatorial synthesis of aminoglycoside aAntibiotic mimetics: use of a polyethylene glycol-linked amine and a neamine-derived aldehyde in multiple component condensation as a strategy for the discovery of new inhibitors of the HIV RNA rev responsive element. *J. Am. Chem. Soc.* 118, 10150–10155
43 Sutherlin, D. *et al.* (1996) Generation of C-glycoside peptide ligands for cell surface carbohydrate receptors using a four-component condensation on solid support. *J. Org. Chem.* 61, 8350–8354
44 Oertel, K. *et al.* (2000) Stereoselective combinatorial Ugi-multicomponent synthesis on solid phase. *Angew. Chem. Int. Ed. Engl.* 39, 1431–1433
45 Ziegler, T. *et al.* (2000) Preparation of bioconjugates through a Ugi reaction. *Angew. Chem. Int. Ed. Engl.* 39, 2109–2112
46 Balkenhohl, F. *et al.* (1996) Combinatorial synthesis of small organic molecules. *Angew. Chem. Int. Ed. Engl.* 35, 2288–2337
47 Sofia, M. *et al.* (1999) Discovery of novel disaccharide antibacterial agents using a combinatorial library approach. *J. Med. Chem.* 42, 3193–3198
48 Opatz, T. *et al.* (2003) D-Glucose as a pentavalent chiral scaffold. *Eur. J. Org. Chem.* 8, 1527–1536
49 Kallus, C. *et al.* (1999) Combinatorial solid-phase synthesis using D-Galactose as a chiral five-dimension-diversity scaffold. *Tetrahedron Lett.* 40, 7783–7786
50 Opatz, T. *et al.* (2002) D-Glucose as a multivalent chiral scaffold for combinatorial chemistry. *Carbohydr. Res.* 337, 2089–2110
51 Hirschmann, R. *et al.* (2000) Development of an efficient regio- and stereoselective route to libraries based on the β-D-Glucose scaffold. *J. Org. Chem.* 65, 8307–8316
52 Sofia, M.J. *et al.* (1998) Carbohydrate-based small-molecule scaffolds for the construction of universal pharmacophore mapping libraries. *J. Org. Chem.* 63, 2802–2803
53 Dekany, G. *et al.* (2000) Protecting groups for carbohydrate synthesis, PCT WO-00/42057
54 Lipinski, C.A. *et al.* (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* 46, 3–26
55 Patel, Y.C. (1999) Somatostatin and its receptor family. *Front. Neuroendocrinol.* 20, 157–198
56 Csaba, Z. and Dournaud, P. (2001) Cellular biology of somatostatin receptors. *Neuropeptides* 35, 1–23
57 Reisine, T. (1995) Somatostatin receptors. *Am. J. Physiol.* 269, G813–G820
58 Bauer, W. *et al.* (1982) SMS201-995: A very potent and selective octapeptide analogue of somatostatin with prolonged action. *Life Sci.* 31, 1133–1140
59 Lamberts, S.W.J. *et al.* (1996) Drug therapy: Octreotide. *N. Engl. J. Med.* 334, 246–254
60 Robinson, C. and Castaner, J. (1994) Lanreotide acetate. *Drugs Future* 19, 992–999
61 Reisine, T. and Bell, G.I. (1995) Molecular biology of somatostatin receptors. *Endocr. Rev.* 16, 427–442
62 Fisher, S.L. *et al.* (1999) Melanocortin-4 receptor: a novel signalling pathway involved in body weight regulation. *Int. J. Obes.* (Suppl. A) 23, 54–58
63 Campfield, L.A. *et al.* (1998) Strategies and potential molecular targets for obesity treatment. *Science* 280, 1383–1387
64 Al-Obeidi, F. *et al.* (1989) Design of a new class of super potent cyclic α-melanotropins based on quenched dynamics solutions. *J. Am. Chem. Soc.* 111, 3413–3416
65 Hruby, V.J. *et al.* (1995) Cyclic lactam α -melanocortin analogues of Ac-Nle^4-cyclo(Asp^5,D-Phe^7,Lys^{10}) α -melanocyte-stimulating hormone-(4-10)-NH_2 with bulky aromatic amino acids at position 7 show high antagonist potency and selectivity at specific melanocortin receptors. *J. Med. Chem.* 38, 3454–3461

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