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Lead optimization

Scaffold hopping

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The aim of scaffold hopping is to discover structurally novel compounds starting from known active compounds by modifying the central core structure of the molecule. Scaffold hopping is a central task of modern medicinal chemistry requiring a multitude of techniques, which are discussed in this article. Their application has led to several molecules with chemically completely different core structures, and yet binding to the same receptor. Computational approaches for scaffold hopping highlight the challenges of the field that are still unsolved.

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In lead optimization, systematic decoration of a common scaffold and bioisosteric replacement are the predominant techniques of structural variation. Scaffold hopping is an approach to generate new chemistry, starting from any lead structure. This article describes success stories as well as computational procedures to "hop" from one scaffold to another one, to modify affinities and selectivities, to improve physicochemical and ADMET properties, and/or to arrive at patentable analogs.

Introduction

A look at the new drugs approved in 2002 [1] and 2003 [2] clearly reveals that many of the new chemical entities are actually small variations of existing medicines. There is a strong need to develop new approaches to the discovery of truly novel biologically active compounds. Here, we focus on a concept that is vividly, if somewhat casually, described by the term "scaffold hopping" (Box 1). This approach requires the availability of a template – a chemical structure displaying the desired biological activity, and it is based on the assumption that the same biological activity can be exerted by other compounds that maintain some essential features of the template but are structurally different otherwise.

The idea of scaffold hopping is clearly not new. Many important drug discoveries of the past were made by modifying structures of known drugs [3,4]. However, these early efforts were largely driven by observations either in clinical trials or animal studies pointing to other potential applications of known classes of drug-like compounds. The consideration of important protein–ligand interactions, the identification of key functional groups and their analogues did not play a major role.

When is a scaffold really new and when can it be considered as structurally different from another one? From a chemist's perspective, two scaffolds can be different if they are built up through different synthetic routes. There are numerous cases demonstrating that very small changes can have dramatic effects on the molecular properties, and thus a pharmacologist might judge from the function of a compound and will regard an agonist as being different from an antagonist, even if it the compounds differ by one minor substituent only. A patent attorney will have yet another different point of view. There is a full spectrum ranging from dramatic changes in the structure, for example, replacing a peptide chain by heterocyclic groups, to minor changes, such as the exchange of a carbon atom by a nitrogen atom in a ring system. Here, we focus on cases in which not merely a substructure, but the topology of a scaffold has been modified. Such cases are typically seen as significant scaffold modifications.

Examples of successful scaffold hopping

Numerous literature examples demonstrate that structurally different chemical structures can bind to the same target.

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Box 1. Why are we interested in scaffold hopping? A change of the central chemical template is often desirable for several reasons:

- A replacement of a lipophilic scaffold by a more polar one will increase the solubility of the compound.
- A substitution of a metabolically labile scaffold with a more stable or less toxic one will improve the pharmacokinetic properties. Experience indicates that in some cases, toxicity or other undesirable properties are essentially the property of the central scaffold. For example, some pyridines and imidazoles can have the undesirable property of binding to cytochrome P450 enzymes. Certain aminothiazoles are metabolically unstable.
- A replacement of a very flexible scaffold (such as a peptide backbone) by a rigid central scaffold can significantly improve the binding affinity and also the overall DMPK properties.
- Sometimes central scaffold is directly involved in interactions with the target protein. A change in the scaffold can lead to an improved binding affinity.
- A change in the central scaffold can lead to a novel structure that is patentable.

A few examples highlighting the concept of scaffold hopping are depicted in Figs. 1 and 2.

One of the early examples of successful scaffold hopping is the discovery of GABA-receptor ligands starting from the benzodiazepine core. After its discovery in the 1950s, many attempts were undertaken to enhance their pharmacokinetic and pharmacodynamic properties by changing substituents, but also by moving to a completely novel structures. Examples of compounds with a novel scaffold are Zopiclone, Zolpidem and Zaleplon (Fig. 1a) [5].

Another interesting set of examples are dopamine agonists. These molecules nicely demonstrate that starting from the natural ligand, both ligands with high structural similarity to dopamine (such as Fenoldopam) but also completely novel structures (such as Quinpirole) can be discovered (Fig. 1b) [6,7].

A diverse set of scaffolds was obtained in the anti-inflammatory field of the cyclooxygenase (COX) ligands. Interestingly, the recently approved COX-2 inhibitors all have rather similar structures (Fig. 1c) [8,9].

One of the most sought scaffold-variations is of course the move from peptidic ligands to ''small molecules''. Typically, peptides are natural ligands or substrates of the target in question. It can be challenging to convert peptides to compounds lacking amide bonds, especially when the peptide backbone is involved in key interactions with the enzyme such as in aspartic proteases. The evolution of thrombin inhibitors is a positive example; backbone interactions of the peptide substrate are not essential for binding [10]. Another example is the discovery of inhibitors for interleukin converting enzyme. In the orally bioavailable compound Pralnacasan [11], many structural features of the initial peptide L-761191 can still be identified. In addition, Pralnacasan is a pro-drug hiding both a carboxylate and an aldehyde function. A further example of successful peptide mimicry is the development of thyrotropin-releasing hormone (TRH) analogs. Three key pharmacophoric groups – the imidazole ring, the terminal amide and the pyroglutamate ring – could be attached to a cyclohexyl ring system instead to a peptide backbone, retaining high activity in an animal model (Fig. 2a) [12].

The sequence of marketed selective serotonin reuptake inhibitors (SSRIs) is another good example how a common binding motif can be interpreted with very different scaffolds: a mostly electron-deficient aromatic ring is coupled with a basic amine at a variable distance. A second aromatic residue completes the structure (Fig. 2b).

Another good example for scaffold hopping is given by the adenosine A_{2a}-antagonists: starting form the natural ligand adenosine (an agonist) or the natural product caffeine (a subtype-unselective antagonist), several companies made their way to more drug-like and especially more selective structures (Fig. 2c) [13].

Computational approaches to scaffold hopping

One of the pillars of modern medicinal chemistry is the similarity principle, which states that structurally related compounds display similar biological activities [14], because they can exert related effects as ligands of the same macromolecular receptor. Conversely, this means that the more distantly related two chemical structures are, the less probable it will be that they have the same biological effect. Does this imply that there is no rational basis for scaffold hopping? Molecular modeling and cheminformatics experts have tried to negate this question by inventing a host of computational procedures for the calculation of molecular similarity as independently as possible from the details of chemical structure. Regardless of the type of molecular similarity measure used, however, there is always a tradeoff between the degree of ''novelty'' of a proposed alternative structure and the probability to find a compound with the desired activity.

On an atomic level, interactions between receptors and ligands can roughly be understood in terms of hydrophobic contact and additional specific, most often polar, interactions [15]. Two compounds can thus be regarded as similar if their shapes match and if they can form the same directed interactions such as hydrogen bonds. Unfortunately, these descriptors are of little use if the chemical structure is known of a single active compound only, because drug-size molecules can typically adopt many alternative low-energy conformations of varying shape. However, if the compound is very rigid or if the biologically relevant conformation of one ligand is known from an X-ray structure, this conformation can be used as a template to search for novel structures. Shape and hydrogen-bonding capability as descriptors have the advantage of being completely independent from chemical structure – the molecules are regarded ''from outside'' as they act on a receptor. This increases the likelihood of identifying

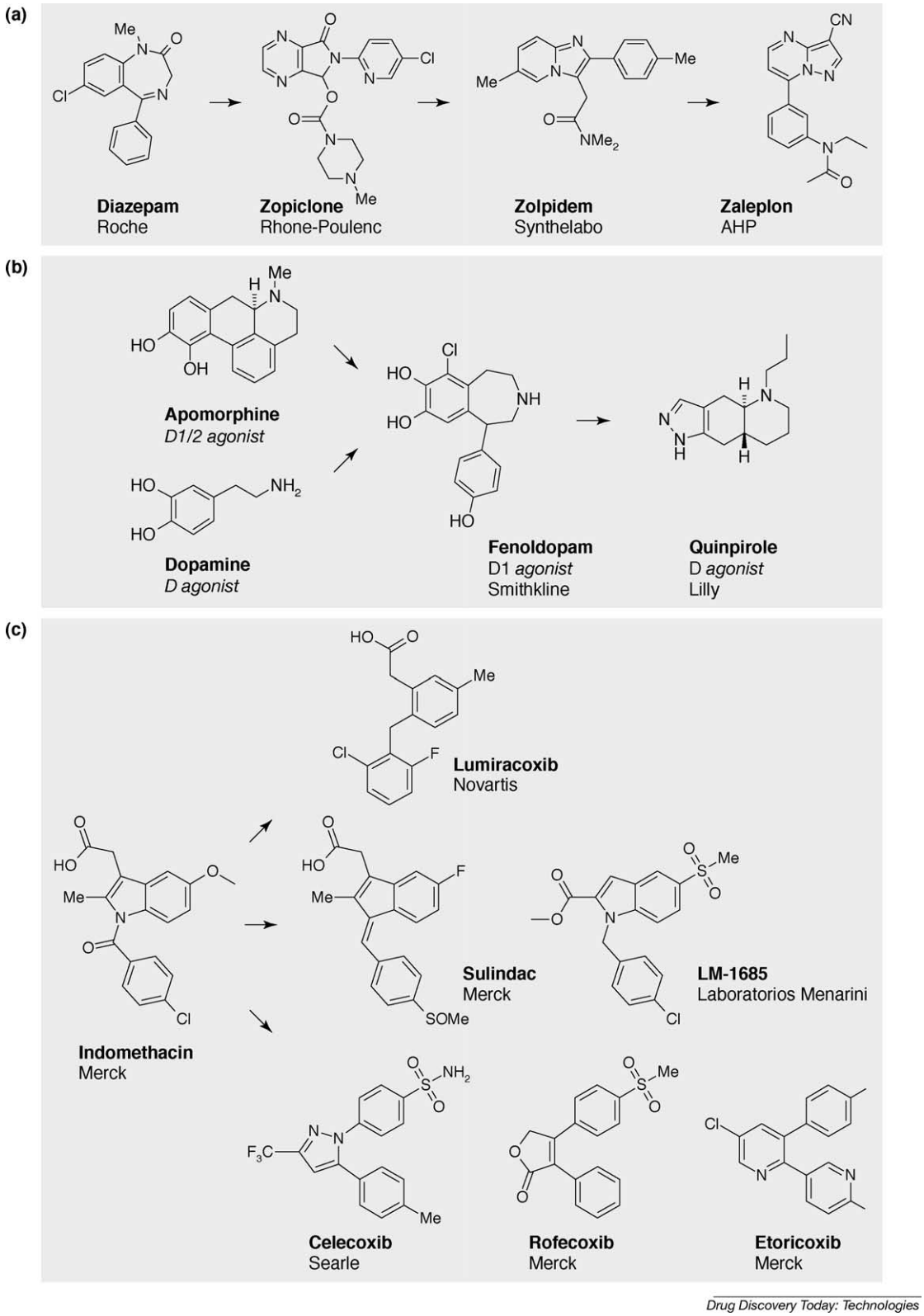

Figure 1. Literature examples for scaffold hopping. Shown are $GABA_A$ ligands binding to the benzodiazepine site (a), dopamine antagonists (b) and cyclooxygenase inhibitors (c).

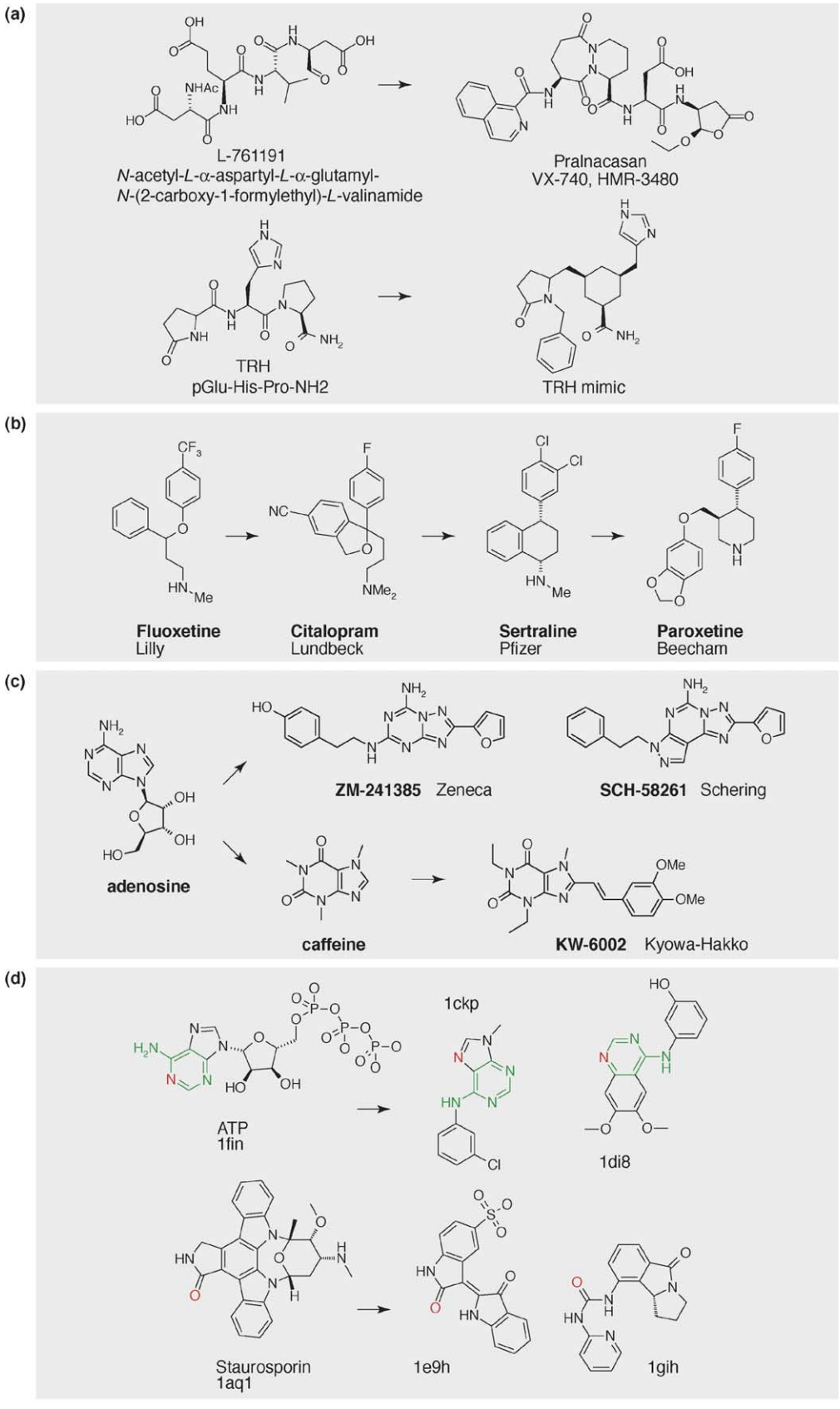

Figure 2. Literature examples for scaffold hopping. Shown are $GABA_A$ ligands binding to two examples of peptidomimetics (a), selective serotonin reuptake inhibitors (b), A_{2a}-antagonists (c) and inhibitors of cyclin-dependent kinase 2 (d).

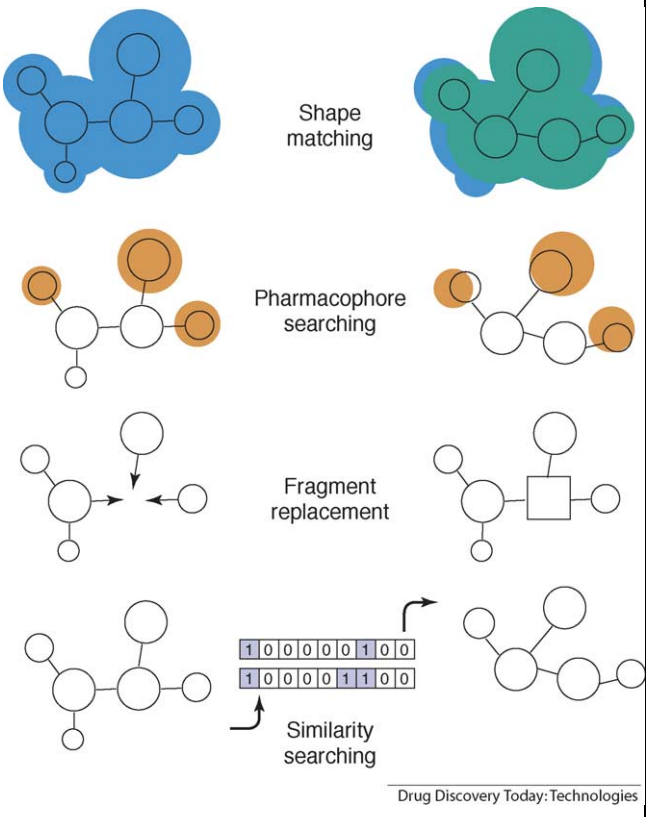

Figure 3. Schematic representation of four principal computational approaches to scaffold hopping. Many software programs offer combinations of several approaches, for example, pharmacophore searching combined with a shape filter can be a very powerful approach. Although shape matching and pharmacophore searching require 3D coordinates, fragment replacement can also be performed on planar chemical structures. Similarity searching is the most abstract of the three methods, because the molecular structure is intermediately encoded in a set of descriptors.

truly novel scaffolds. Many tools have been developed to flexibly superimpose molecules onto a rigid query structure, the earliest program probably being the program SEAL [16,17] (Fig. 3, Table 1).

Given a single (biologically relevant) 3D structure of an active ligand, it is possible to search for compounds mimicking exactly this structure, but it is impossible to distinguish those of its features that are essential for binding from others that are variable. Such a differentiation becomes possible if a series of ligands is known. If these ligands are structurally diverse but share common features and can adopt similar shapes, a 3D pharmacophore can be derived, that is, a minimal set of spatially oriented features a compound must possess to be active [18,19] (for good introductory texts also see http://www.netsci.org/Science/Cheminform). 3D pharmacophores have successfully been employed for scaffold hopping (see [20–23] and a recent review [24] for examples). Typically, 3D pharmacophores are built manually or in a semi-automated fashion and then large multiconformer databases of chemical structures are searched for compounds matching the pharmacophore.

Both flexible superposition and 3D pharmacophore searching methods can only retrieve known compounds from databases. Often, this might not be sufficient to discover novel scaffolds: even the largest corporate collection represents only a minute fraction of drug-like chemical space. In addition, any existing compounds could be covered by competitor patents, considering that most major pharmaceutical companies today restock their screening libraries from the same commercial sources. The *de novo* design program Skelgen [26,27] (De Novo Pharmaceuticals, http://www.denovopharma.com/) can take a set of 3D pharmacophore features and an inclusion shape (derived from a set of superimposed ligands) as input. Within this pseudo-receptor, the program then builds new ligand structures fulfilling the pharmacophore constraints. A recent validation paper proved that known estrogen receptor ligands can be redesigned in this manner [28]. Related applications have been reported for the tool LeapFrog (Tripos, http://www.tripos.com/) [29].

Another, much more common, approach to scaffold hopping is to search for replacements of a fragment of an active

Table 1. Properties of key methods in scaffold hopping

Method	Shape matching	Pharmacophore searching	Fragment replacement	Similarity searching
Specific examples	FlexS (BioSolveIT, http://www.biosolveit.de/) ROCS (Openeye Scientific Software, http://www.eyesopen.com)	Catalyst [25] (Accelrys, Inc, http://www.accelrys.com/), Unity (Tripos, http://www.tripos.com/), many others	CAVEAT (cchem.Berkeley.edu/~pabgrp/index.html), many company-specific, non-commercial tools	Daylight Fingerprints (http://www.daylight.com/), many company-specific, non-commercial tools
Pros	Fast, high success rate for relatively small or rigid compounds	A rational approach yielding clear answers, based on a maximum of information	Can be performed on 2D or 3D structure, high success rate	Fast and always applicable
Cons	Requires knowledge about bioactive conformation, relative importance of functional groups not specified	Requires knowledge about bioactive conformation and alignment	Calculations might yield many or no results depending on tolerance, results difficult to rank, degree of novelty depends on query	High degree of uncertainty because of high abstraction from chemical structure
References	[50]	http://www.netsci.org/Science/Cheminform [18–24]	[30,41]	[43,44]

compound rather than for entire compounds. One of the early 3D database searching programs, CAVEAT (http://www.cchem.berkeley.edu/~pabgrp/index.html), was implemented to solve exactly this problem [30]. As input it takes a single 3D structure, and the spatial (distance and angular) relationships between two or three single bonds (vectors) is used to search a database of chemical structures for suitable alternative fragments fitting onto these vectors. CAVEAT applications have been reported in the literature since the early 1990s (see [31] and the CAVEAT home page).

A third approach to generate ideas for novel ligands beyond what is contained in screening libraries is the recombination of ligand fragments: in the early nineties, the program SPLICE was written to post-process results of 3D database searching [32] (related and enhanced tools available from Drug Design Methodologies, http://www.new-drugdesign.com/). Two operations are preformed: portions of structures matching a 3D query that did not contribute to fulfilling a pharmacophore feature are cut off, and (partial) solution structures are assembled to into composite structures by linking fragments at overlapping bonds. Researchers at Vertex (http://www.vpharm.com/) recently published a related method called BREED, which instead on 3D database searching results operates on sets of superimposed X-ray structures of related enzyme complexes, and generates new structures by recombining inhibitor fragments connected by single bonds [33]. This is an attractive way of capitalizing on the vast amount of structural information contained in the Protein database (PDB, http://www.rcsb.org/pdb/) for many target classes, which could quickly lead to promising scaffold ideas, in particular in combination with results from crystal-based fragment screening [34,35]. Clearly, crystal structures of protein–ligand complexes are the richest source of information for the design of modified or novel scaffolds. Many examples of successful structure-based design have been reported, in particular for kinases [36–38]. A common element of such studies is the use of key interaction centers and the active site shape as constraints – the key elements of molecular recognition that were mentioned above. Fig. 2a shows structures of several ligands whose complex structures with CDK2 (cyclin-dependent kinase 2) have been solved over the years (the codes are reference IDs in the Protein Structure Database (PDB, http://www.rcsb.org/). Both the cofactor ATP and the unspecific inhibitor Staurosporin were starting points for the development of inhibitors. The conserved acceptor atom forming a hydrogen bond to the ''hinge'' sequence in the ATP binding site is marked in red. It becomes obvious that conserved substructures, such as the aminopyrimidine in the upper series, does not imply a conserved binding mode (Fig. 2d). This underlines the importance of structural information on protein–ligand complexes as a prerequisite for scaffold hopping.

Methods like CAVEAT and SPLICE, incorporating conformational properties of molecules, can provide new solutions that are not directly obvious on paper. Exchanging and recombining molecular fragments, however, is common practice in medicinal chemistry and does not always require 3D structural information. Closing or opening ring structures, replacing one ring system for another or modifying linker types and lengths between two ring systems can be effective procedures leading to new compound classes. Unless such modifications take place at the periphery of a structure, one can indeed speak of scaffold hopping through bioisosteric replacement. Substantial efforts have been made to generate substituent replacement rules [39,40] and databases (e.g. the Bioster database, http://www.accelrys.com/cases/bioster.html). Recognizing that the replacement of one ring system by another can be a powerful way of scaffold modification, researchers at GlaxoSmithKline have compiled a database of common ring systems that can be searched like a 2D version of CAVEAT [41].

A large number of molecular similarity methods has been developed that are explicitly based on the 2D structure of molecules (connectivity and atom types), but which nevertheless aim at describing similarity as independently as possible from substructure details. Unlike for 3D formats, where shape and interaction vectors are obvious descriptors, there is no unique recipe to achieve this goal in two dimensions. One typical approach is to generate vectors or bit string descriptions for molecules, from which similarity values can be calculated very quickly. Each element of such a vector denotes the presence or absence (or frequency of occurrence) of a small structural element or pharmacophore feature. Rarey and Dixon [42] have developed a similarity metric based on feature trees, which achieves abstraction from the molecular structure in a different manner. A feature tree is a ''shrunk'' version of a molecular graph, in which each node consists of an acyclic atom or an entire ring system with a set of assigned properties. For the calculation of a similarity value, two feature trees are explicitly matched onto each other. Because of the generalized representation of rings, the feature tree method is particularly good at substituting heterocycles for each other or identifying alternative ways of fusing rings. Details on similarity searching have recently been reviewed [43,44]. Clearly, the goal of similarity searching cannot be to identify an optimal single metric, but rather an optimal way to combine the results of different metrics, because each method focuses on slightly different features of compounds, and the relative importance of these features is not known. The combination of bioisosteric replacement with similarity searching could also be a powerful approach for scaffold hopping.

Both vector-based descriptions of molecules (so-called CATS correlation vectors [45]) and the feature tree method have been employed to design novel scaffolds in 2D *de novo*

design algorithms. In these algorithms, chemical structures are assembled through fragment joining, and the resulting new scaffolds evaluated by their similarity to the query. Ironically, the better these methods work, the less interesting the results will be: if the chemical space spanned by the fragments is complete, and if the search algorithm locates the global minimum, it will retrieve the query as the best answer. Thus, the success reported so far [46–48] relies on the fact that local minima in incomplete chemical spaces can yield interesting alternative scaffolds. In the feature tree fragment space method [49], this shortcoming has been addressed through the concept of a target similarity value: the level of dissimilarity to the query that the output structures should display is adjustable to high (conservative) or lower values (more drastic structural changes).

Summary and conclusion

The analysis of the available drugs for a given target clearly demonstrates that it is possible to find a set of structurally diverse compounds that bind to the same receptor. Therefore, the underlying assumption of scaffold hopping is clearly correct. However, it should be noted that serendipity has played a large role in many of these discoveries. In addition, a large number of new drugs are structurally rather close to known compounds. Therefore, there is a continued strong need to develop new approaches to identify novel compounds in a more straightforward, systematic fashion.

There are now a large number of tools available. The concept of scaffold hopping or bioisosteric replacement is now widely recognized as evident for example by the large number of publications using the word ''bioisostere'' in the title. Interestingly, some of these tools have been available for more than a decade.

So, why is the usage and the number of successful applications not larger? One possible explanation is that for a new target, it takes time to understand the relative importance of the different pharmacophore features. Multiple binding modes can sometimes obscure the picture and the interpretation of the structure-activity relationships can be misleading without knowledge of the 3D structure of the target. Another possible contributor is the limited success of the peptidomimetic approach. Many pharmaceutical companies have invested heavily in the past in peptide chemistry and subsequent effort to convert biologically active peptide into metabolically stable non-peptidic molecules. A further limitation is that synthetic tractability has not been taken into account in many computational approaches.

We believe that we now witness what could be called a ''second wave'' of scaffold hopping, driven by a new generation of 3D-structure-literate medicinal chemists, driven by an ever increasing number of available 3D protein structures, access to large databases on successful bioisosteric replacements and also driven by a change in focus away from the ''holy grail'' of peptidomimetic replacement towards more tractable tasks such as the replacement of ring systems with each other. The goal of computational methods for scaffold hopping should be the generation of new ideas for alternative structures are synthetically tractable and at the same time conserve specific essential features, or at least allow rational testing of the hypothesis whether a specific feature is essential.

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