Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

Charting, Navigating, and Populating Natural Product Chemical Space for Drug Discovery

Hugo Lachance,[†,§] Stefan Wetzel,[†,‡] Kamal Kumar,[†,‡] and Herbert Waldmann*[,†,‡]

[†]Departmen of Chemical Biology, Max Planck Institute of Molecular Physiology, Otto-Hahn-Strasse 11, 44227 Dortmund, Germany

[‡]Chemische Biologie, Technische Universität Dortmund, Dortmund, Germany

INTRODUCTION. NATURAL PRODUCTS: STRONGHOLDS FOR DRUG DISCOVERY

Historically, natural products (NPs) have played a key role in the development of chemotherapy,[1,2] and to this very day numerous marketed drugs are of natural origin, either as original compounds or after modification.[3] Between 2000 and 2006, 26 plant-derived natural products were at some stage of development into drugs, and in 2005 alone, plant-derived drugs sold for an estimated $18 billion.[4−12] Natural products have had a particularly high impact in antibiotic and cancer drug discovery.[13−21] The diversity of natural products is continuously being expanded and most notably has recently been extended to molecules originating from deep seas and cold seas.[22−24] In the quest for new biologically active molecules, natural products have often served as structural "muse" for the design of small molecule libraries, in particular to define library scaffolds based on the activity of the parent molecule.[25−27] In this respect, the case of the morphine alkaloids (Figure 1) is particularly telling. Morphine itself inspired the development of potent analgesics such as codeine, heroine, and etorphine through derivatization and the preparation of structurally simplified analogues such as morphinanes, benzomorphanes, phenylpiperidines, and the simplest one, methadone. Remarkably, in the direction of both increasing and decreasing complexity analgesic activity is retained to different degrees and with different affinities for opioid receptor subtypes. It is important to consider the biosynthetic origin of natural products originating from different organisms and cellular environments, since biosynthesis typically proceeds with sequential binding of the biosynthetic intermediates to different proteins. In addition, the multifaceted biological purposes and roles for which natural products are synthesized by organisms require bioavailability and access to their protein targets in organisms. Importantly, both individual NPs and structurally closely related members of particular NP classes display multiple, well-defined biological activities and thus most likely bind to and influence the function of multiple protein targets. Therefore, natural products can be viewed to embody "privileged structures" evolved in nature to possess these properties, positioning them as prevalidated starting points for library design.[25−27] To leverage the full advantage of the biological relevance and activity of NPs, as well as the particular structural features and diversity encoded into them in the process of evolution, a systematic approach to chart, analyze, and navigate the chemical space defined by natural products and the correlation of their structures with bioactivity are needed. Recently developed cheminformatics tools and methods (e.g., for analysis of natural product chemical space or the identification of ubiquitous molecular features of natural products to define "natural-product-likeness") can identify biologically relevant parts of chemical space. These spaces can then be accessed by means of natural-product-like and natural-product-inspired compound libraries. Their synthesis needs to take full advantage of current synthesis strategies and methodology and calls for the development of new synthesis methods amenable to compound library generation.

In this review, the particular nature of natural products compared to screening compounds and drugs is analyzed. Tools for interactive visualization of chemical space are introduced, and the chemical space of natural products is delineated. The synthesis of representative NP-inspired compound collections is described and the potential of chemoinformatics analyses is illustrated to direct synthesis efforts and to identify unexplored areas of chemical space for the development of biologically relevant molecule classes.

NATURAL PRODUCT PROPERTIES

Natural products have long since been regarded as a class of compounds with particular molecular properties and distinct structural features. They form a rather heterogeneous class of compounds differentiated by their source organism, biosphere of origin, and biological role. Molecular properties of subclasses may differ significantly as shown by Grabowski and Schneider for NPs from the deep sea, which contain significantly more halogen atoms than NPs from other habitats.[28] Knowledge about NP subclasses is very heterogeneous. Natural products from plants, for instance, have been studied widely for centuries, whereas marine natural products from the deep seas have been in focus only recently. To navigate this heterogeneous chemical space, mainly molecular-property-based and structure-based methods have been developed. Both provide complementary, yet distinct perspectives on chemical space. Regardless of the method, each analysis can only reflect the knowledge (i.e., compounds) known at the given time, and the insights gained may be subject to change in the future.

Several chemoinformatics analyses of the properties of different sets of natural products performed during the past 2 decades[28−31] consistently found that natural products differ significantly from synthetic compounds (mostly commercially available screening libraries) in several molecular properties. Natural products in general incorporate more oxygen atoms and fewer nitrogen atoms per molecule than synthetic compounds or drugs. They also contain more stereogenic

Received: February 29, 2012
Published: April 26, 2012

dx.doi.org/10.1021/jm300288g | J. Med. Chem. 2012, 55, 5989−6001

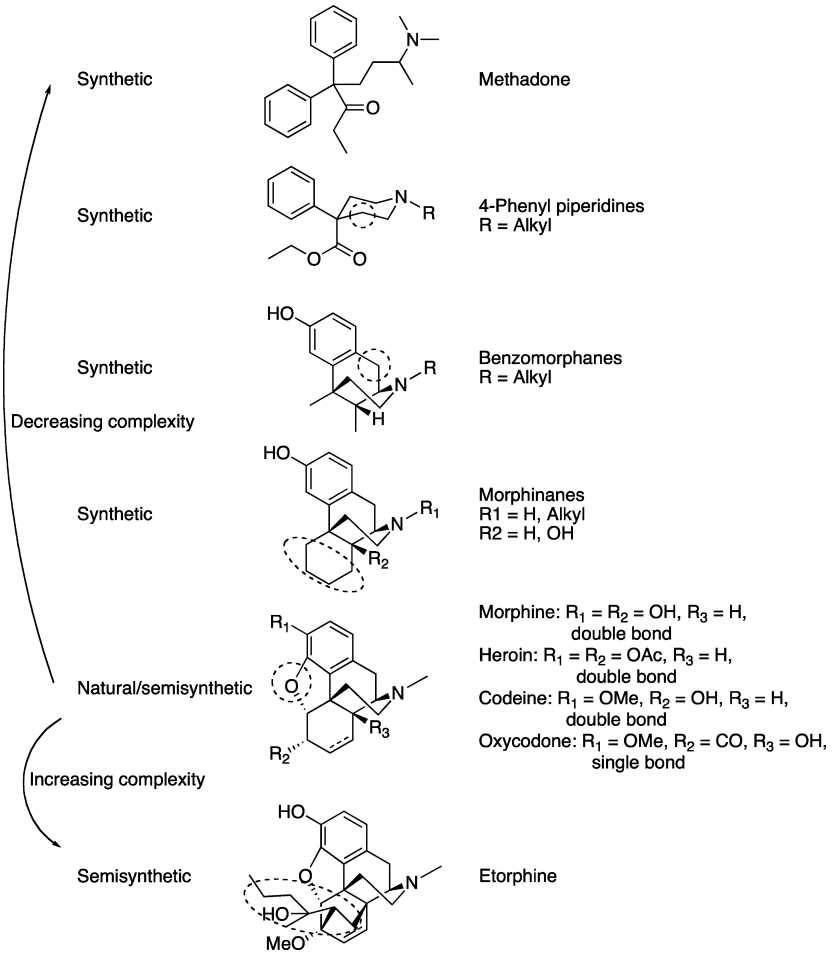


Figure 1. Analgesic compounds derived from the natural product morphine.

centers, more fused rings, but fewer aromatic rings and rotatable bonds than synthetic compounds or drugs, implying that natural products embody more rigid, nonflat three-dimensional structures. This particular feature may positively influence the probability of clinical success of drug candidates as recently delineated by Lovering and co-workers who found that the degree of unsaturation and chirality of compounds increases during drug development.[32] Moreover, the rates of compounds not adhering to the rule-of-five are largely similar for drugs and natural products (in both cases ~10%). Interestingly, some analyses concluded that (commercially available) natural-product-like libraries are more similar to synthetic compounds than to natural products.[30]

NATURAL PRODUCT CHEMICAL SPACE

Chemical space can be mapped based on molecular properties by means of principal component analysis (PCA). In brief, PCA computes the position of every compound in a two- or three-dimensional coordinate system based on a set of computed properties. A powerful method for charting chemical space by PCA is ChemGPS, developed by Oprea and Gottfries. ChemGPS uses 72 properties and defines a three-dimensional coordinate system by PCA transformation of the property vectors of 400 reference compounds. The positions of all analyzed compounds are then interpolated from the reference set. Application of ChemGPS to natural products identifies many compounds outside the chemical space defined by the reference set due to the particular and very diverse molecular properties of NPs. Hence, a new reference base was created leading to ChemGPS-NP. The new reference set comprises more than 1700 molecules, 4 times as many as the initial reference set compiled for druglike molecules.[33] ChemGPS and ChemGPS-NP have been used to analyze the mode of action of anticancer compounds and cyclooxygenase (COX) inhibitors. A map of NP chemical space produced by ChemGPS-NP is shown in Figure 2.

The shape of NP chemical space charted by ChemGPS-NP is a rather well-defined cylindrical cloud of compounds with only a few outliers. Of the first three principal components t1 describes size, shape, and polarizability, t2 expresses conjugation-dependent properties and aromaticity, and t3 relates to polarity, lipophilicity, and hydrogen bond potential. This loading differs from the ChemGPS for medicinal chemistry compounds where t1 describes size and shape, t2 relates to lipophilicity, and t3 confers flexibility vs rigidity and polarity. These changes reflect the known differences in natural products. On one hand, aromaticity is much less common in NPs than in drugs, rendering it more discriminative among NPs and hence higher up in the principal components. On the other hand, NPs are much more rigid, and thus, rigidity is less discriminative and shifted to lower rank principal components.[30] The ChemGPS-NP utilizes eight principal components to describe chemical space, whereas ChemGPS used only six. This indicates the larger diversity found in the properties of natural products compared to those of medicinal chemistry compounds.

dx.doi.org/10.1021/jm300288g | J. Med. Chem. 2012, 55, 5989−6001

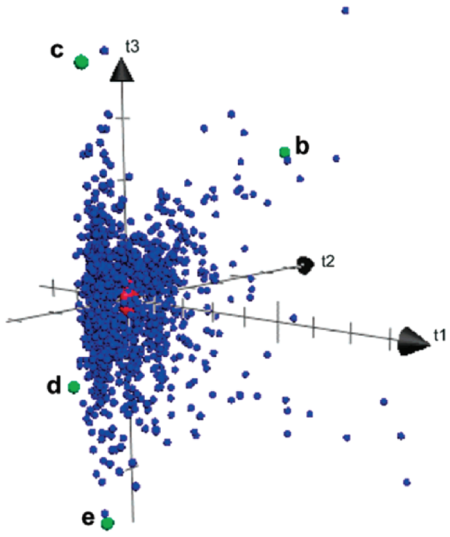


Figure 2. Natural product chemical space as charted by ChemGPS-NP. Reproduced with permission from *Journal of Natural Products*.[33] Copyright 2007 American Chemical Society and American Society of Pharmacognosy.

In general, PCA-based approaches can process and map hundreds of thousands of molecules in reasonable computer time. They are well suited to map compound sets into chemical space and determine their overlap, for instance, with a known reference set. Thus, mode-of-action hypotheses or putative targets can be identified. However, the use of such approaches to guide synthetic chemistry remains to be established because of the complex and almost incomprehensible relationship between the position of compounds in chemical space and their structural features.

To guide chemical synthesis efforts, Waldmann and co-workers developed a scaffold-based hierarchical classification of natural products (Figure 3), exploring the structural perspective to chemical space.[34,35] Briefly, the authors isolate the molecular scaffold and deconstruct it one ring at a time, thereby generating a scaffold hierarchy branch. Combination of the branches from many molecules yields a tree diagram representing the scaffold space covered by the compound set. Scaffold Hunter, a Java-based computer program, facilitates interactive visualization of and navigation through scaffold trees as well as annotation of scaffolds with any property, for instance, biological activity. Scaffold Hunter enables educated nonexperts, such as chemists and biologists, to view and interact with their compound-related data in a scaffold tree generated by ScaffoldTreeGenerator. Scaffold Hunter and ScaffoldTreeGenerator are available free of charge from www.scaffoldhunter.com.[36,37]

Charting of NP chemical space by the scaffold tree approach is shown in Figure 3. It readily displays the most common scaffolds, each of which represents at least 300 molecules in the dictionary of natural products (i.e., one of the most

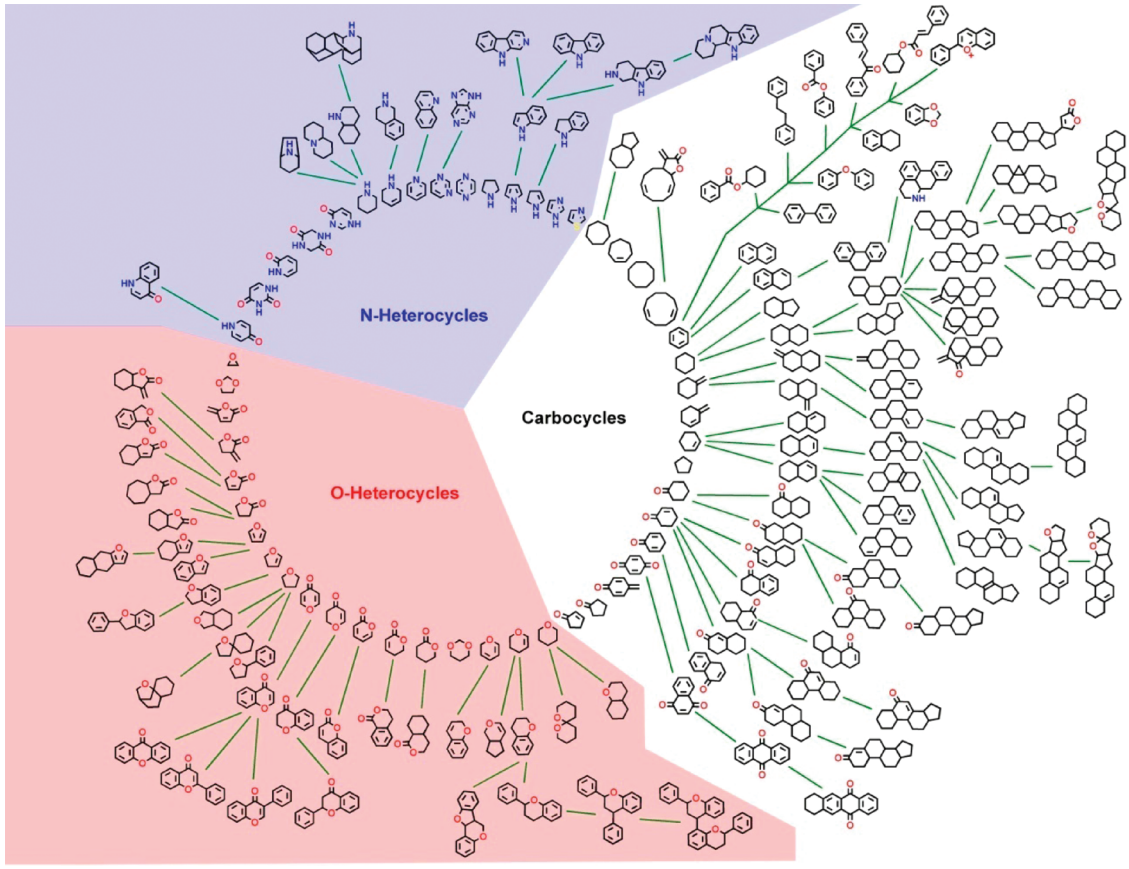


Figure 3. Natural product scaffold tree according to the SCONP approach. Reproduced with permission from Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. Charting Biologically Relevant Chemical Space: A Structural Classification of Natural Products (SCONP). *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17272−17277.[34] Copyright 2005 National Academy of Sciences, U.S.A.

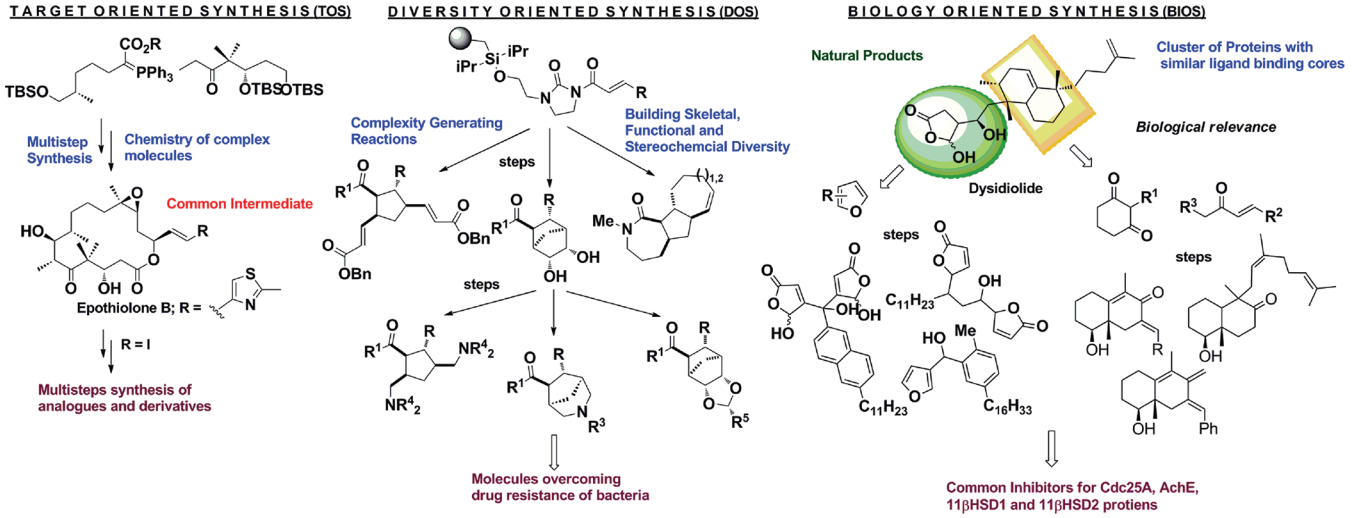


Figure 4. Synthesis concepts targeting complex natural products: NP-inspired and small molecule libraries.

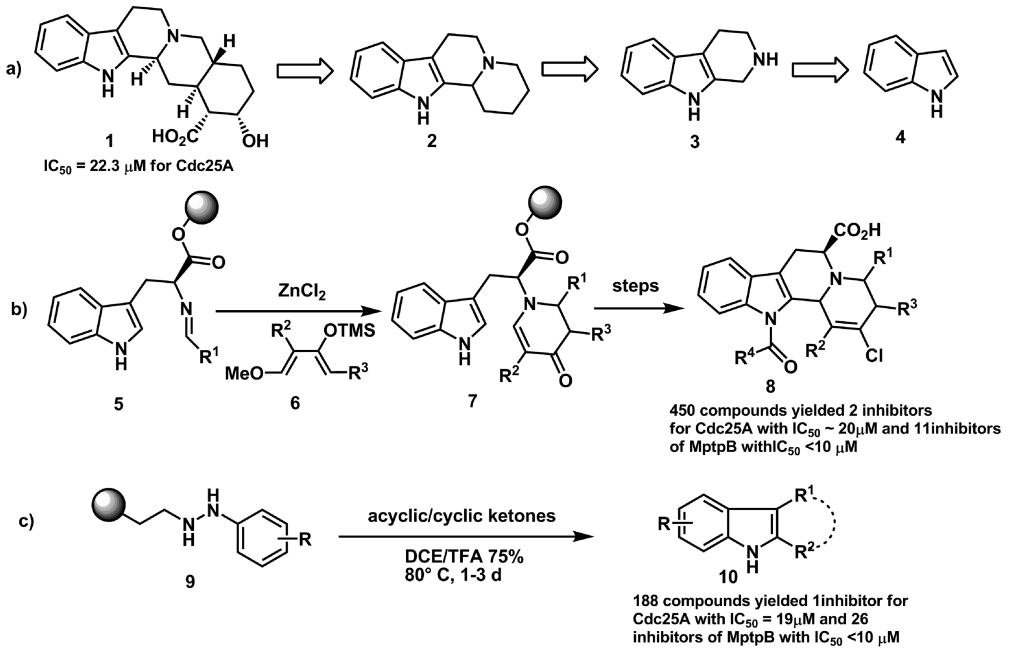


Figure 5. (a) Structural simplification of complex alkaloid structure leads from the pentacyclic scaffold to tetracyclic indoloquinolizidines followed by *β*-carbolines and indoles. (b) Solid phase synthesis of a compound library with indoloquinolizidine scaffold. (c) Traceless solid phase synthesis of a *β*-carboline and indole compound collection.

comprehensive resources of NP structures). The classification shows large carbocyclic and O-heterocyclic sections and a smaller N-heterocyclic part, confirming results of earlier studies of natural product properties. The scaffold tree also visualizes the relationships between structures, providing a map with systematically delineated paths to navigate in chemical space.

In comparison to the ChemGPS-NP approach, the scaffold tree displays a smaller number of molecules but these in a more intuitive, structure-based way. This illustrates the complementary nature of ChemGPS-NP and the scaffold trees as well as one of the main criteria for choosing one approach or the other.

A related but different approach to charting structural space is Molwind. Molwind maps any hierarchical classification of compounds onto a sphere. Similar compounds are grouped next to each other, and different levels of detail (e.g., scaffolds or compounds) are visible depending on the zoom level. Currently, Molwind is still under development and no version was available at the time of this review.[38]

EXPLORING NATURAL PRODUCT CHEMICAL SPACE: SYNTHESIS OF NATURAL PRODUCT INSPIRED COMPOUND COLLECTIONS

NPs often appear to be structurally too complex to pursue and synthesize. Their structures seem to be too large for medicinal chemistry research, and they often are not available in sufficient amounts from natural sources for further development. Yet natural products provide inspiration for synthesis to the organic chemistry community, and various highly inspiring up-scaled total syntheses of complex NPs and their analogues have been reported recently.[39−42] However, in general the complexity of NPs limits the synthesis of analogue libraries with a size attractive to medicinal chemistry research and, thereby, also the

exploration of their potential in biomedical research and drug discovery. To overcome these limitations and provide natural-product-like and natural-product-inspired biologically relevant compound collections, diversity oriented synthesis (DOS)[43] and biology oriented synthesis (BIOS)[44−46] have been introduced as approaches to access unexplored natural product chemical space (Figure 4). DOS aims to populate the chemical space by generating diverse and complex molecular skeletons, which in many cases are related to NP architectures, in a combinatorial fashion. Using pairs of complexity-generating reactions, in which the product of one reaction is the substrate for another, DOS provides access to diverse and complex scaffolds.

BIOS builds on the biological relevance and prevalidation of natural products and aims at the synthesis of focused compound libraries based on a given NP scaffold.[47] It was developed with the goal to establish a logic and method to reduce the structural complexity of NPs while retaining their bioactivity. This logic enables the systematic analysis of NP structural complexity, their mutual relationship, and a link to the structural diversity in the binding sites of target proteins. It inspires the synthesis of compound collections with structures approaching the complexity of NPs in the required formats like solid-phase synthesis. These libraries are exected to approach NP performance in biochemical and biological screens (Figure 4), to yield relatively high hit rates at comparably small library size, thereby reducing the need for engagement in high throughput technologies. For a detailed discussion of the development of BIOS see ref 44, in particular section 4 (Where Do We Come from and Where Are We Going?).

The focused libraries thus obtained may target proteins with similar ligand binding cores[48] and deliver inhibitors for a cluster of proteins. In principle, both strategies search and employ structural simplification for library design while trying to access chemical space populated with biologically relevant molecules. For instance, the structurally complex alkaloids yohimbine and ajmalicine were identified as inhibitors of the protein phosphatase Cdc25A. In a BIOS approach, structural simplification of the yohimbine (**1**) scaffold led from the pentacyclic via tetracyclic to tricyclic and bicyclic indole-based scaffolds (Figure 5a). The tetracyclic indoloquinolizidine (**2**) collection was synthesized on solid phase by means of a Lewis acid mediated tandem Mannich−Michael reaction of electron-rich dienes (**6**) with resin bound aldimines (**5**) to yield immobilized enaminones (**7**) as the key reaction. Subsequently the tetracyclic vinyl chlorides (**8**) and related ketones were obtained in viable yields (Figure 5b).[49] Compound collections based on β-carboline and indole scaffolds were generated by means of a traceless Fischer indole synthesis on the solid phase (Figure 5c).[50] Solid supported hydrazine (**9**) was treated with diverse cyclic and acyclic ketones in the presence of acid, and the indole derivatives were released. Two molecules from the indoloquinolizidine compound collection were identified as inhibitors of Cdc25a with IC_{50} values comparable to that of the pentacyclic natural product.[45,48] Interestingly, the structurally simpler compound collections with three- and two-membered rings also yielded one inhibitor of Cdc25A with an IC_{50} in the same range. Extending this screen to other phosphatases allowed the identification of structurally new inhibitors of the *Mycobacterium tuberculosis* protein tyrosine phosophatase B from the same libraries. Thus, structural simplification of the NP retained the kind of activity of the structurally more complex parent NP and the activity could be translated to other proteins. NP-derived and NP-inspired libraries with built-in functional and stereochemical diversity may serve as efficient tools to study the biological functions of therapeutically relevant protein targets and also to discover unknown targets for new research programs.

In the following sections relevant examples are described in which the results of chemical space analysis were successfully combined with state-of-the-art synthesis strategies and methodology in order to develop novel small molecule modulators of protein function. One approach identifies promising "holes" in chemical structure space linked to modulation of a particular target protein that can be explored by synthetic chemistry. Another example maps paths of proven biological relevance in chemical structure space to connect known structure types to novel biological targets. The third case utilizes DOS synthetic methodology and chemical design to rapidly fill large parts of underexplored chemical space. The last example illustrates how available bioactivity databases can be mapped onto natural product chemical space to identify potential protein targets for natural product chemotypes. Whereas the approaches differ in their aim and in their methodology, they all share a common goal: the exploration of novel and biologically relevant parts of chemical space.

STRUCTURE-GUIDED NAVIGATION OF CHEMICAL SPACE

Mapping of chemical space allows for a quick and efficient visualization of the coverage of a given subspace by a defined set of chemical structures (i.e., compound collections). But most importantly it allows for the identification of areas of chemical space not covered by the same set of chemical structures. To this end, Waldmann and co-workers introduced the concept of "virtual scaffolds" that denote scaffolds that do not represent molecules in an investigated compound set.[37] These scaffolds result from the scaffold deconstruction during hierarchy creation and fill the gaps that would otherwise occur in the hierarchy. "Brachiation", a second concept employed to create hypotheses guiding synthesis efforts, describes the movement along branches in a tree that correlates chemical structures hierarchically toward less complex scaffolds with retained, yet varied bioactivity. This concept builds on the notion that often one decisive part of a molecule contributes much of the biological relevance which is widely explored in fragment-based drug discovery. To identify promising virtual scaffolds, Scaffold Hunter is used to chart the chemical space covered by a compound collection used in a screening campaign (e.g., as published in PubChem). The scaffolds are then annotated with their biological activity. Virtual scaffolds found between a more complex and a simpler scaffold displaying related biological activities are very likely to be biologically active on the same target. It is important to note that these virtual scaffold structures are not part of the analyzed data set, thus providing potential new guiding chemical structures for the initiation of medicinal chemistry efforts.

An in silico validation of this approach was first achieved using the PubChem database as primary data source and the WOMBAT database, a database with small molecules and associated bioactivity data extracted from the literature, as the data set to identify virtual scaffold classes likely to have the same kind of bioactivity. In total, 14 virtual scaffolds with activity against five different targets were identified from PubChem. For each of these scaffolds, compounds active against the same target could be retrieved from Wombat. One

example of virtual scaffold **10** from a serotonin (5-HT) receptor screen in PubChem and the corresponding active molecules from Wombat is shown in Figure 6.

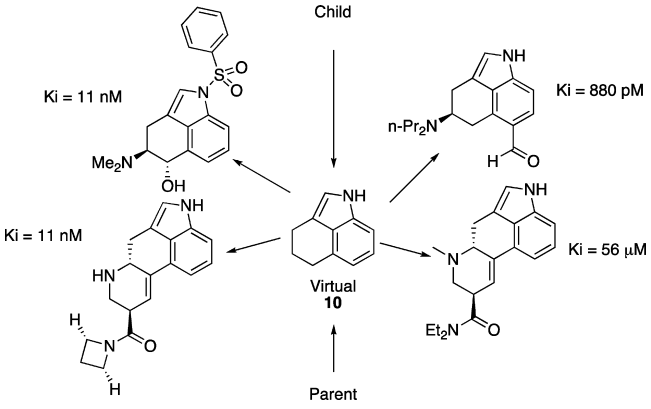


Figure 6. Virtual scaffold identification and exploration: in silico virtual scaffold validation.

These results demonstrate that gaps in a biologically annotated scaffold branch are very likely to be filled with relevant biologically active molecules.

This approach was further applied prospectively to guide the identification of novel inhibitors or activators of pyruvate kinase. Of the 51 415 molecules tested on pyruvate kinase as reported in PubChem (assay identification 361), 472 were found to inhibit pyruvate kinase while another 130 were found to be activators of the enzyme. The application of Scaffold Hunter to this data set generated close to 36 000 scaffolds distributed over 767 branches. The identified virtual scaffolds represented 24% (8684) of the scaffolds in the initial data set. Filtering these scaffolds using diverse parameters related to their biological activities produced 65 virtual scaffolds surrounded by scaffolds annotated with biological activity. Waldmann and co-workers tested 107 compounds representing 4 of these 65 scaffolds (Figure 7). Nine of these compounds showed inhibition or activation in the range of 1−10 μM. These new molecules modulating pyruvate kinase activity correlate well with the biological activity recorded for the neighbors of the branch's virtual scaffolds. Branches containing inhibitors or activators yielded inhibitors or activators of pyruvate kinase, respectively. Furthermore these hits meet the rule-of-five criteria. The hit rate in this screen was 10 times higher than the hit rate recorded for the underlying pyruvate kinase high-throughput screening (HTS) campaign. These findings illustrate the value of chemical space analysis using graphical tools such as Scaffold Hunter to identify biologically relevant gaps and thus guide chemistry and biology. The white spots in chemical space may directly lead to the identification of

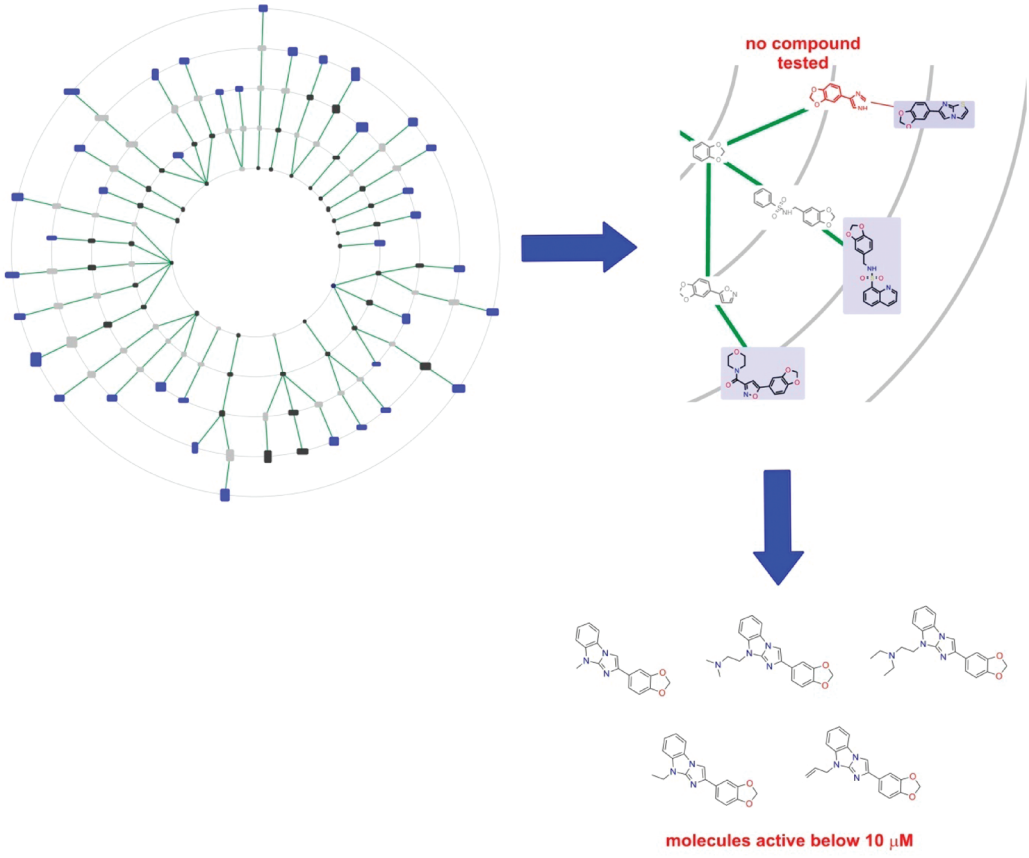


Figure 7. Visualization of the pyruvate kinase modulator space as covered in the Pubchem pyruvate kinase test set. Four scaffold families were selected (two shown) based on their close relationship to active scaffold families. Screening of 107 compounds comprising one of these four scaffolds yielded nine compounds in the 1−10 μM range. Reproduced with permission from Wetzel, S.; Klein, K.; Renner, S.; Rauh, D.; Oprea, T. I.; Mutzel, P.; Waldmann, H. Interactive Exploration of Chemical Space with Scaffold Hunter. *Nat. Chem. Biol.* **2009**, *5*, 581−583.[37] Copyright 2009 Nature Publishing Group.

dx.doi.org/10.1021/jm300288g | *J. Med. Chem.* 2012, 55, 5989−6001

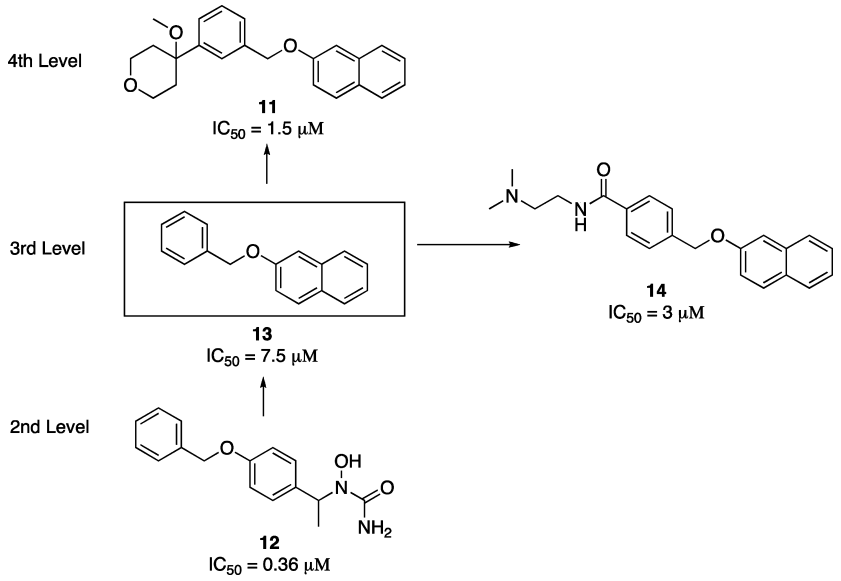


Figure 8. Scaffolds of compounds with 5-LOX inhibitory activity and hits obtained.

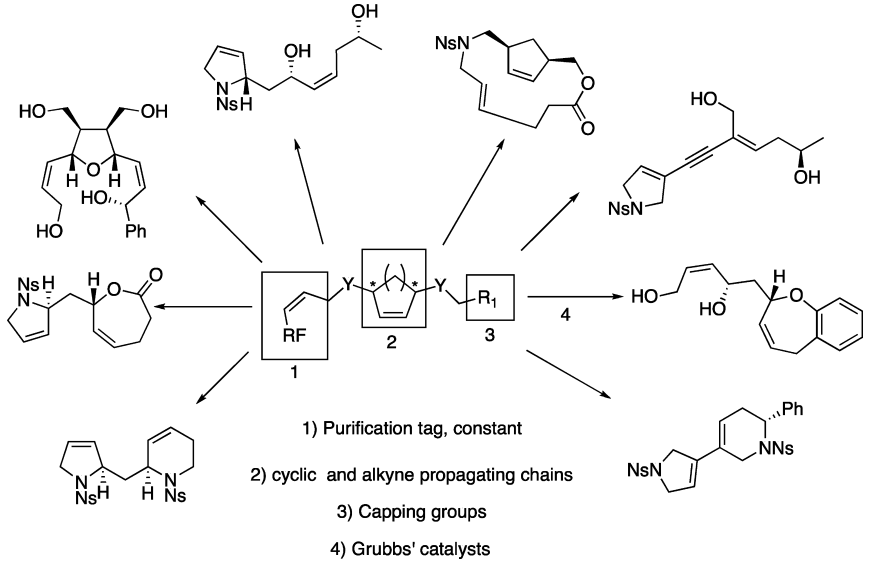


Figure 9. Efficient generation of complexity using Grubbs metathesis as key step.

biologically relevant structure classes for medicinal chemistry programs and drug discovery.

BIOACTIVITY-GUIDED NAVIGATION OF CHEMICAL SPACE

The generation and organization of structural scaffolds can be guided by chemical rules as described in the Scaffold Hunter example. An alternative approach to the generation of scaffold trees from a complex data set is the use of biological activities as the prevalent organizing criterion. In this process of scaffold tree generation, when a complex structure is deconstructed, the selected smaller "parent" scaffold has to retain the same kind of bioactivity as described for the child structure. The resulting biology-guided scaffold tree generation procedure was developed and applied by Waldmann and co-workers[36] to data sets available from the WOMBAT database to identify tree branches with conserved biological activity. The length of these branches varied significantly depending on the data set explored. The disconnection of the morphine-based analgesics described in Figure 1 is a typical branch generated through this process. In this case, six levels of scaffold simplification can be generated while retaining similar, yet varied bioactivity.

In the course of this analysis, missing links are also identified, which are represented by scaffolds of molecules in the data set that are not annotated with known biological activity for the target of interest. This gap in the charted structure-related biological space may provide an opportunity for the discovery of bioactive molecules. To investigate this notion, inhibitors for a wide range of targets described in WOMBAT were investigated including 5-lipoxygenase (5-LOX) inhibitors. In this branch of the tree, the tricyclic scaffold level was not annotated with respect to 5-LOX in the WOMBAT database (Figure 8).

The child structure **11** of the gap scaffold has a reported IC_{50} of 1.5 μM,[51] and the parent structure **12** has a reported IC_{50} of 0.36 μM[52] in a different 5-LOX assay. Investigation of the three-ring-containing scaffold **13** in a 5-LOX assay yielded an inhibitor with an IC_{50} of 7.5 μM, and the related, slightly larger

dx.doi.org/10.1021/jm300288g | J. Med. Chem. 2012, 55, 5989−6001

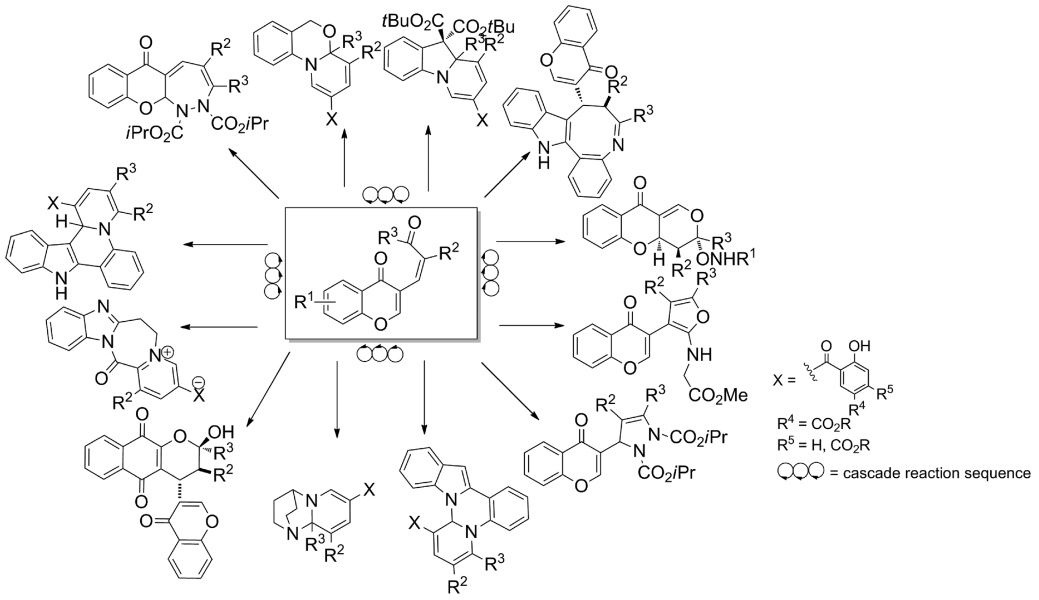


Figure 10. Branching cascades to provide efficient and quick access to complex skeletal diversity.

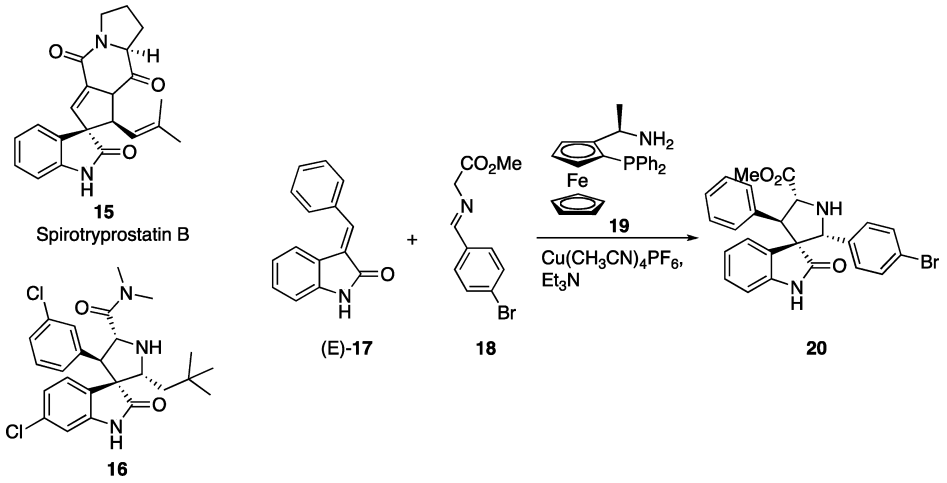


Figure 11. Identification of the spirooxindole scaffold and library preparation.

derivative **14** was found to have an IC_{50} of 3 μM. This example illustrates the potential of biology-guided scaffold tree construction to identify novel biologically relevant starting points for compound library development.

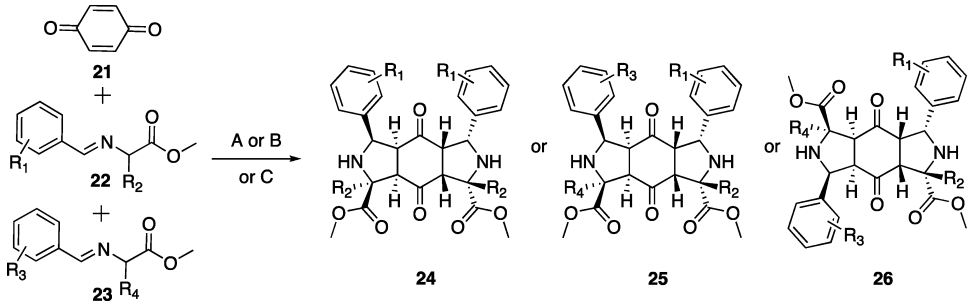
NEW STRATEGIES FOR COMPOUND COLLECTION SYNTHESIS: THE FAST AND THE VARIOUS

For the successful discovery of small molecule modulators of protein function, library design based on diversity, novelty, and biological relevance must go hand-in-hand with the development of new synthesis methods enabling the efficient synthesis of the desired compound collections. One noteworthy example highlighting the power and the potential of state-of-the-art synthesis methodology to meet these demands is the preparation of a highly complex and diverse compound collection by Nelson et al.[53,54] Their approach relies on the fast and efficient generation of simple basic buiding blocks suitable for a series of cascading ring-closing and ring-opening or ene−yne metathesis reactions (Figure 9). These core building blocks consist of three parts, a constant fluorinated tag, a propagating core with cyclic structure or containing alkynes, and a capping group. The role of the fluorinated tag is the simplification of the purification step using fluorous solid-phase extraction. The cyclic propagating core allows cascade propagation through ring-closing and ring-opening metathesis, while the alkyne containing propagating unit allows for the propagation through ring-closing ene−yne metathesis cascades. These sequences of reactions are initiated through the terminal alkene capping groups. This approach allows the generation of more than 84 different molecules possessing unusual scaffolds. Analysis of the generated scaffolds in the form of a scaffold tree revealed a high level of diversity as well as several previously unknown scaffolds.

In another synthetic strategy based on cascade or domino reaction sequences, skeletal diversity and molecular complexity were simultaneously incorporated in the resulting focused compound collections. On the basis of the branching pathway approach in DOS, a multifunctional substrate was designed to facilitate diverse domino reaction sequences on treating it with different nulceophiles, each leading to formation of a different scaffold.[55] The branching cascades could very efficiently and easily provide diverse molecular scaffolds that include natural

dx.doi.org/10.1021/jm300288g | J. Med. Chem. 2012, 55, 5989−6001

Scheme 1. Creating Eight Stereogenic Centers at Once with Good Control[a]



[a](A) 3 mol % (*R*)-FeSulPhos, 3 mol % $Cu(CH_3CN)_4BF_4$, imine **22**, 20 mol % DIPEA, toluene, rt, 16 h; (B) (i) 3 mol % (*R*)-FeSulPhos, 3 mol % $Cu(CH_3CN)_4BF_4$, 1 equiv of imine **22**, 20 mol % DIPEA, rt, 1 h, (ii) imine **23**, toluene, rt, 15 h; (C) (i) 3 mol % (*R*)-FeSulPhos, 3 mol % $Cu(CH_3CN)_4BF_4$, 1 equiv of imine **22**, 20 mol % DIPEA, toluene, rt, 1 h, (ii) imine **23**, 30 mol % $Cu(CH_3CN)_4BF_4$, 30 mol % Et_3N, THF, rt, 15 h.

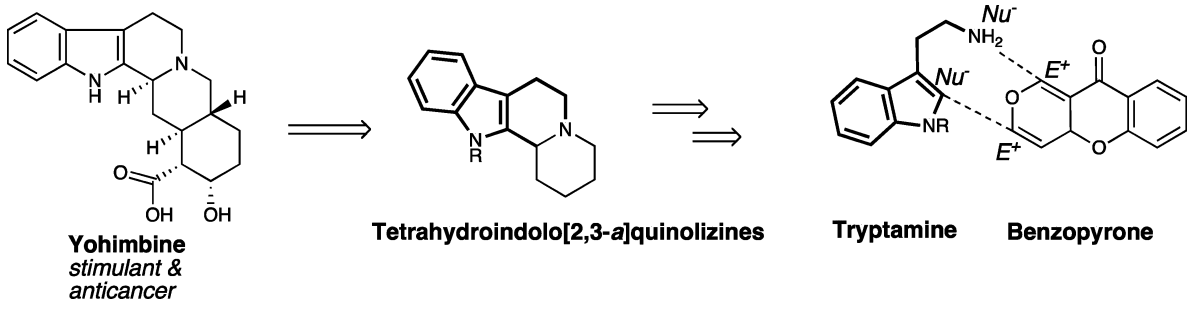


Figure 12. Tetrahydroindolo[2,3-*a*]quinolizine scaffold identified from natural products: Nu^-, nucleophilic site; E^+, electrophilic site.

product based scaffolds, medicinally relevant architectures, and novel molecular entities (Figure 10).

The biological evaluation of the above-mentioned libraries is yet to be performed, and it will be interesting to see how relevant these new scaffolds will be and which bioactivities they will exhibit. Such library approaches are crucial for the exploration of new underexploited and hopefully relevant parts of chemical space.

The known activity of the spirooxindole core such as represented in the natural product spirotryprostatin B (**15**) and synthetic compound **16** (Figure 11) inspired the development of enantioselective methods to access this core. This could be achieved using a 1,3-dipolar addition between α,β-unsaturated oxindole **17** and the ylide of the Schiff base **18** in the presence of a catalytic amount of copper and a ferocene derived chiral ligand **19** (Figure 11).[56] This method allowed for the preparation of a small library with good control of the stereochemical outcome of the reaction, with ee ranging between 84% and 98% and acceptable to good yields of 41−97%. The screening of this 18 member library for activity in a BSC-1 mitotic cell arrest phenotypic assay showed that one compound (**20**) arrested the cell cycle in the G2/M phase in concentration as low as 2 μM by interfering with microtubule polymerization via an as yet unidentified mechanism. The finding that one active molecule can be found in such a small focused library highlights the importance of the selection of the core in library design and the relevance of natural products for inspiration in the identification of biologically active molecules.

Introducing variety while controlling stereochemistry remains a challenge, and any method allowing for good stereocontrol is desirable. This challenge was successfully met in the one-pot synthesis of a library of complex molecules containing eight stereogenic centers using a tandem 1,3-dipolar cycloaddition employing 1,4-benzoquinone (**21**) and two imines (**22** and **23**) (Scheme 1).[57]

To achieve this goal, a one-pot tandem double cycloaddition sequence using *p*-benzoquinone and azomethine ylides was developed.[57] This reaction sequence allowed for the formation of four new carbon−carbon bonds and eight new stereogenic centers with excellent control, generating one stereoisomer from the potential 512. The versatility of this method can further be increased by controlling the order of addition of the ylide reagents to afford both enantiomers of a given cycloadduct with excellent control. It is then possible to access compound **24**, **25**, or **26** depending on the chosen conditions. The compounds thus generated allow for the rapid exploration of uncharted chemical space.

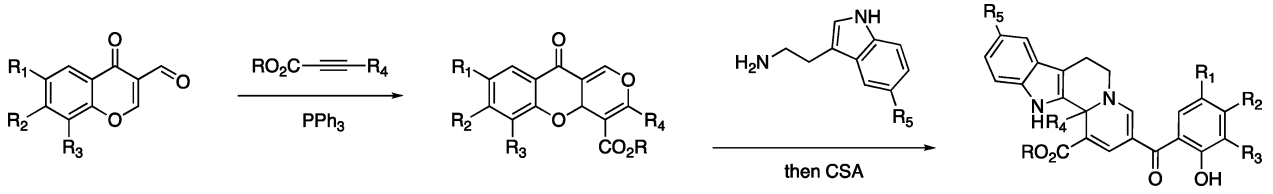
The fact that this method is one-pot and consists of a multistep sequence providing access to several stereogenic centers while retaining good control over their formation is the basis for the potential preparation of a larger library composed of more than 240 600 members with the use of simple reagents such as 20 amino acids, 20 aldehydes, 1,4-benzoquinone, and a catalytic chiral ligand. Such synthesis relates closely to the processes found in nature where few and simple reagents are used with highly efficient biocatalysts to potentially generate a large number of variations.

In the following example (Figure 12), the tetrahydroindolo-[2,3-*a*]quinolizine core was identified in many natural products including yohimbine, a known stimulant with anticancer activity. The complexity of such natural products limits their use as starting point for library design.

To this end, the design of an efficient and flexible synthesis of the desired core was undertaken. This led to the development of a cascade reaction involving chromones, acetylenic esters, and tryptamines to generate a focused library containing the identified key moiety (Scheme 2). This rapid reaction, typically

dx.doi.org/10.1021/jm300288g | *J. Med. Chem.* 2012, 55, 5989−6001

Scheme 2. Twelve-Step Cascade Reaction for the Preparation of a Natural-Product-Inspired Library



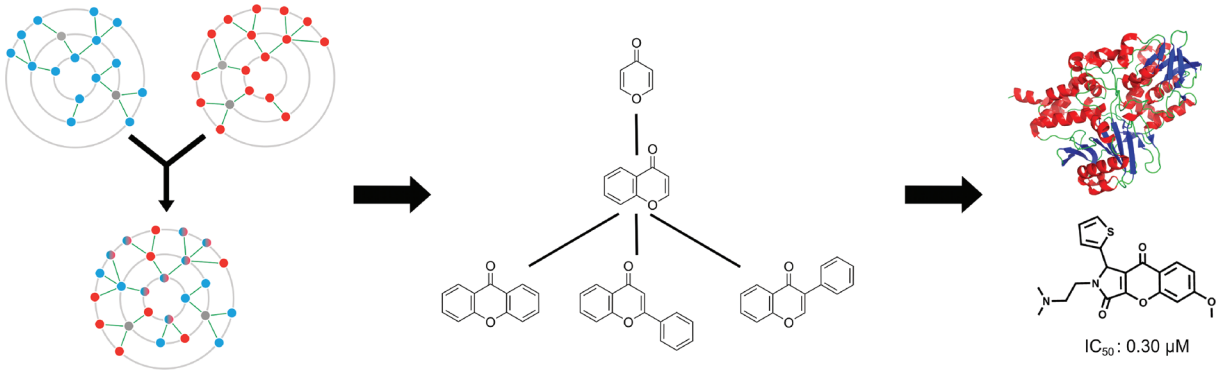


Figure 13. Target annotation for natural product chemotypes. From the merged scaffold trees of synthetic compounds annotated with biological activity (blue circles) with natural products (red circles) results a merged tree with cross-annotated nodes (purple circles). A library around five scaffolds from the γ-pyrone branch was assembled and tested for three potential target families identifying several inhibitors for each family. Reproduced with permission from Wetzel, S.; Wilk, W.; Chammaa, S.; Sperl, B.; Roth, A. G.; Yektaoglu, A.; Renner, S.; Berg, T.; Arenz, C.; Giannis, A.; Oprea, T. I.; Rauh, D.; Kaiser, M.; Waldmann, H. A Scaffold Tree Merging Strategy for Prospective Bioactivity Annotation of gamma-Pyrones. *Angew. Chem., Int. Ed.* **2010**, *49*, 3666−3670.[59] Copyright 2010 Wiley-VCH Verlag GmbH & Co. KGaA.

requiring less than 1 h for completion, includes a 12-step sequence and generated a library of 26 compounds with yields ranging from 20% to 91%.[58]

Because of the antimitotic activity of many natural products containing the targeted core, this library was tested for its possible effect on cell division processes in a BSC-1 phenotypic assay. Despite its limited size, the screening of this library generated a strong modulator of centrosome integrity. It was found that the most active compound, centrocountin 1 (R = Me; R_2, R_3, R_4, R_5, R_6 = H), induced multipolar cell division leading to the formation of three daughter cells during mitosis in concentrations as low as 1.5 μM. Further evidence indicated that the centrosome is either fragmented or amplified during mitosis. Target identification by means of a chemical proteomics approach revealed that centrocountin 1 interacts with the centrosomal proteins NPM and Crm1. This unprecedented biological activity combined with the observed antiproliferative and mitotic arrest inducing apoptosis of cancer cells can serve as inspiration for a new drug discovery program.

FROM CHEMICAL TO BIOLOGICAL SPACE: PROSPECTIVE TARGET ANNOTATION

For identification of the targets of bioactive molecules powerful methods are available (i.e., chemical proteomics). However, the initial knowledge about potential targets of small molecules is highly desirable to focus the search and test hypotheses in focused biochemical and biological assays. In particular natural products often are not annotated for bioactivity on the molecular level. Waldmann and co-workers recently described the merging of scaffold trees derived from databases particularly annotated with bioactivity as an approach for prospective target annotation.[59] In a merged scaffold tree generated with data from the Wombat database and the dictionary of natural products they identified three potential target classes for five different γ-pyrone scaffolds, namely, monoamine oxidases A and B, the signal transducer and activator of transcription (STAT) proteins, and acid sphingomyelinase (aSMase). Subsequently, the authors assembled a 500-membered compound collection incorporating five different scaffolds from the γ-pyrone branch. Screening of these compounds in biochemical assays for the identified potential targets yielded a diverse set of inhibitors. A variety of monoamine oxidase inhibitors was identified including submicromolar and isoenzyme specific compounds (Figure 13). In the case of the STAT proteins, the screen identified a chemotype that had been described before by Berg and co-workers,[60] albeit with a different selectivity profile. Activity of one compound in a more demanding cell-based assay was also reported. Three inhibitors of aSMase were described, all of which do not inhibit the neutral isoenzyme at the maximal concentration tested. These inhibitors possess more advantageous physicochemical properties than the known natural product molecule whose two lipophilic side chains seem to be critical for its activity. The authors conclude that their method could be applied early in the discovery process as a hypothesis-generating approach leading to candidate compounds for further development. Moreover, they also identified scaffolds of similar or even larger size than the annotated scaffold. This feature is complementary to the brachiation approach, which generally leads to smaller scaffolds in the same branch.

SUMMARY

Natural products are a heterogeneous group of compounds with diverse, yet particular molecular properties compared to synthetic compounds and drugs. All relevant analyses show that natural products indeed occupy parts of chemical space not explored by available screening collections while at the same time largely adhering to the rule-of-five. This renders them a

valuable, unique, and necessary component of screening libraries used in drug discovery. With ChemGPS-NP on the Web and Scaffold Hunter two tools are available to the scientific community to guide exploration of biologically relevant NP chemical space in a focused and targeted fashion with a view to guide novel synthesis approaches. Several of the examples given illustrate the possibility of bridging the gap between computational methods and compound library synthesis and the possibility of integrating cheminformatics and chemical space analyses with synthetic chemistry and biochemistry to successfully explore chemical space for the identification of novel small molecule modulators of protein function.

The examples also illustrate the synergistic potential of the chemical space concept and modern chemical synthesis for biomedical research and drug discovery. Chemical space analysis can map underexplored biologically relevant parts of chemical space and identify the structure types occupying these parts. Modern synthetic methodology can then be applied to efficiently fill this "virtual space" with real compounds.

From a cheminformatics perspective, there is a clear demand for open-source and easy to use tools that can be readily applied by educated nonspecialist chemists and biologists in their daily research. This will include further development of Scaffold Hunter, ChemGPS-NP, and related approaches on the Web. Such a "cheminformatics toolbox" would enable chemists and biologists to mine their own data in an intuitive and highly interactive process and without the need for specialized computer science and cheminformatics expertise. We anticipate that it may be a viable, if not necessary, step for research initiatives based on large high-throughput screening campaigns, in particular in the pharmaceutical industry, to make the most out of the recent advances in computational tools in order to leverage and take full advantage of the large data sets generated and available in house. There are "holes" in these data sets that can and should be identified and explored by chemistry and biology.

AUTHOR INFORMATION

Corresponding Author

*Phone: +49 (0) 231 133 2400. E-mail: herbert.waldmann@mpi-dortmund.mpg.de.

Present Address

[§]Département de Chimie, Pharmaqam, Université du Québec à Montréal, Montréal, Canada.

Notes

The authors declare no competing financial interest.

Biographies

Hugo Lachance obtained his B.Sc. (Pharmaceutical Chemistry, COOP) in 2000 from Université de Sherbrooke, Canada, and received his Ph.D. in Organic Chemistry at the University of Alberta, Canada, in 2006 under the supervision of Prof. Dennis Hall. He then moved to the Max-Planck Institute of Molecular Physiology in Dortmund, Germany, to pursue postdoctoral work in chemical biology as an NSERC of Canada Postdoctoral Fellow, under the guidance of Prof. Herbert Waldmann. He went on with a postdoctoral stay at Université de Montréal, Canada, in bio-organic chemistry in the group of Prof. Jeffrey Keillor and is now Scientific Coordinator at Pharmaqam and Adjunct Professor at Université du Québec à Montréal, Canada. His research interests include asymmetric methodology, bioactive natural products, biological target identification, and protein labeling.

Stefan Wetzel joined the department of Prof. Waldmann at the Max Planck Institute of Molecular Physiology after his chemistry studies at the University of Regensburg, Germany, and University Heidelberg, Germany. In his doctoral work he developed novel computational approaches for the design of focused biologically relevant libraries, applying methods from the fields of cheminformatics, bioinformatics, computational chemistry, and biochemical assays. His doctoral work was followed by a postdoctoral stay at Novartis where he worked in the field of quantitative biology and computational systems biology. Stefan Wetzel currently works at an international management consultancy.

Kamal Kumar obtained his Ph.D. from Guru Nanak Dev University, Amritsar, India, under the supervision of Prof. M. P. S. Ishar. After a postdoctoral stay as an Alexander von Humboldt Fellow with Prof. M. Beller at Rostock, Germany, in 2002, he joined the group of Prof. H. Waldmann in the Department of Chemical Biology at the Max Planck Institute of Molecular Physiology. Since May 2006, he has been leading a group in the same department. His research interests include the development of new synthetic methods toward natural-product-based libraries, cascade reactions, complexity generating annulations, and probing of biological functions with small molecules.

Herbert Waldmann received his Ph.D. in 1985 from the University of Mainz, Germany, under the guidance of Prof. H. Kunz in Organic Chemistry, after which he completed a postdoctoral appointment with Prof. Dr. G. Whitesides at Harvard University, MA. He was appointed as Professor of Organic Chemistry at the University of Bonn, Germany (1991), full Professor of Organic Chemistry at the University of Karlsruhe, Germany (1993), and Director at the Max Planck Institute of Molecular Physiology, Dortmund, Germany, and Professor of Organic Chemistry at the University of Dortmund, Germany (1999). His research interests lie in chemical biology research employing small molecule and protein probes and microarray technology.

ACKNOWLEDGMENTS

The work presented in this Perspective is the culmination of many years of work and the implications from numerous present and past co-workers whose names can be found in the publications resulting from their work. We are grateful for their commitment to high quality research and for their desire to tackle and solve fundamental problems of chemical biology and medicinal chemistry. The work described here is achieved by a combination of methods in chemistry, biology, and computer science by skilled and motivated co-workers in a multidisciplinary approach. We also thank our numerous and valuable collaboration partners whose names can be found as coauthors of the resulting publications. These partners allowed our research to access new heights otherwise unaccessible. This research was supported by the Max-Planck-Gesellschaft, the Deutsche Forschungsgemeinschaft, the Bundesministerium für Bildung and Forschung, the Alexander von Humboldt-Stiftung, the Volkswagen-Stiftung, the European Union (funding from the European Research Council under the European Union's Seventh Framework Programme (Grant FP7/2007-2013)/ERC Grant 268309), the Land Nordrhein-Westfalen, the Fonds der Chemischen Industrie, Novartis AG, Bayer CropScience AG, BASF AG, and AnalytiCon GmbH.

ABBREVIATIONS USED

NP, natural product; PCA, principal component analysis; SCONP, structural classification of natural products; DOS, diversity oriented synthesis; BIOS, biology oriented synthesis; MptpB, *Mycobacterium* protein tyrosine phosphatase B;

Cdc25A, cell division cycle 25 homologue A; 5-HT, 5-hydroxytryptamine receptor; 5-LOX, 5-lipoxygenase; Ns, 2-nitrophenylsulfonyl; DIPEA, diisopropylamine; FeSulPhos, 2-(*tert*-butylthio)-1-(diphenylphosphino)ferrocene; CSA, camphor sulfonic acid; NPM, nucleophosmin; Crm1, chromosome region maintenance; STAT, signal transducer and activator of transcription; aSMase, acid sphingomyelinase

REFERENCES

(1) Borchart, J. K. The Beginnings of Drug Therapy: Ancient Mesopotamian Medecin. *Drug News Perspect.* **2002**, *15*, 187−192.
(2) Solecki, R. S. Shanidar IV, a Neanderthal Flower Burial in Northern Iraq. *Science* **1975**, *190*, 880−881.
(3) Clardy, J.; Walsh, C. Lessons from Natural Molecules. *Nature* **2004**, *432*, 829−837.
(4) Maggon, K. Best-Selling Human Medicines 2002−2004. *Drug Discovery Today* **2005**, *10*, 739−742.
(5) Newman, D. J.; Cragg, G. M. Marine Natural Products and Related Compounds in Clinical and Advance Preclinical Trials. *J. Nat. Prod.* **2004**, *67*, 1216−1238.
(6) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Last 25 Years. *J. Nat. Prod.* **2007**, *70*, 461−477.
(7) Newman, D. J.; Cragg, G. M.; Snader, K. M. Natural Products as Sources of New Drugs over the Period 1981−2002. *J. Nat. Prod.* **2003**, *66*, 1022−1037.
(8) Saklani, A.; Kutty, S. K. Plant-Derived Compounds in Clinical Trials. *Drug Discovery Today* **2003**, *13*, 161−171.
(9) Kingston, D. G. I.; Newman, D. J. The Search for Novel Drug Leads to Predominately Antitumor Therapies by Utilizing Mother Nature's Pharmacophoric Libraries. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 207−227.
(10) Ojima, I. Modern Natural Products Chemistry and Drug Discovery. *J. Med. Chem.* **2008**, *51*, 2587−2588.
(11) Banerjee, S.; Wang, Z.; Mohammad, M.; Sarkar, F. H.; Mohammad, R. M. Efficacy of Selected Natural Products as Therapeutic Agents against Cancer. *J. Nat. Prod.* **2008**, *71*, 492−496.
(12) Butler, M. S. Natural Products to Drugs: Natural Product-Derived Compounds in Clinical Trials. *Nat. Prod. Rep.* **2005**, *25*, 475−516.
(13) Mann, J. Natural products in cancer chemotherapy: past, present and future. *Nat. Rev.Cancer* **2002**, *2*, 143−148.
(14) Miller, K.; Neilan, B.; Sze, D. M. Y. Development of Taxol and Other Endophyte Produced Anti-Cancer Agents. *Recent Pat. Anti-Cancer Drug Discovery* **2008**, *3*, 14−19.
(15) Heilmann, J. Wirkstoffe auf Basis Biologisch Aktiver Naturstoffe. *Chem. Unserer Zeit* **2007**, *41*, 376−389.
(16) Horwitz, S. B. Personal Recollections on the Early Development of Taxol. *J. Nat. Prod.* **2004**, *67*, 136−138.
(17) Cragg, G. M. Paclitaxel (Taxol): A Success Story with Valuable Lessons for Natural Product Drug Discovery and Development. *Med. Res. Rev.* **1998**, *18*, 315−331.
(18) Wall, M. E. Camptothecin and Taxol: Discovery to Clinic. *Med. Res. Rev.* **2008**, *18*, 299−314.
(19) Cragg, G. M.; Newman, D. J. A Tale of Two Tumor Targets: Topoisomerase I and Tubulin. The Wall and Wani Contribution to Cancer Chemotherapy. *J. Nat. Prod.* **2004**, *67*, 232−244.
(20) Oberlies, N. H.; Kroll, D. J. Camptothecin and Taxol: Historic Achievements in Natural Products Research. *J. Nat. Prod.* **2004**, *67*, 129−135.
(21) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. Impact of Natural Products on Developing New Anti-Cancer Agents. *Chem. Rev.* **2009**, *109*, 3012−3043.
(22) Haefner, B. Drugs from the Deep: Marine Natural Products as Drug Candidates. *Drug Discovery Today* **2003**, *8*, 536−544.
(23) Skropeta, D. Deep-Sea Natural Products. *Nat. Prod. Rep.* **2008**, *25*, 1131−1166.
(24) Lebar, M. D.; Heimbegner, J. L.; Baker, B. J. Cold-Water Marine Natural Products. *Nat. Prod. Rep.* **2007**, *24*, 774−797.
(25) Breinbauer, R.; Vetter, I. R.; Waldmann, H. From Protein Domains to Drug Candidates: Natural Products as Guiding Principles in the Design and Synthesis of Compound Libraries. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878−2890.
(26) Breinbauer, R.; Manger, M.; Scheck, M.; Waldmann, H. Natural Product Guided Compound Library Development. *Curr. Med. Chem.* **2002**, *9*, 2129−2145.
(27) Quinn, R. J.; Carroll, A. R.; Pham, N. B.; Baron, P.; Palframan, M. E.; Suraweera, L.; Pierens, G. K.; Muresan, S. Developing a Drug-like Natural Product Library. *J. Nat. Prod.* **2008**, *71*, 464−468.
(28) Grabowski, K.; Schneider, G. Properties and Architecture of Drugs and Natural Products Revisited. *Curr. Chem. Biol.* **2007**, *1*, 115−127.
(29) Henkel, T.; Brunne, R. M.; Muller, H.; Reichel, F. Statistical Investigation into the Structural Complementarity of Natural Products and Synthetic Compounds. *Angew. Chem., Int. Ed.* **1999**, *38*, 643−647.
(30) Feher, M.; Schmidt, J. M. Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218−227.
(31) Ertl, P.; Schuffenhauer, A. In *Natural Products as Drugs*; Petersen, F., Amstutz, R., Eds.; Birkhaeuser Verlag: Basel, Switzerland, 2007.
(32) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.
(33) Larsson, J.; Gottfries, J.; Muresan, S.; Backlund, A. ChemGPS-NP: Tuned for Navigation in Biologically Relevant Chemical Space. *J. Nat. Prod.* **2007**, *70*, 789−794.
(34) Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. Charting Biologically Relevant Chemical Space: A Structural Classification of Natural Products (SCONP). *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17272−17277.
(35) Schuffenhauer, A.; Ertl, P.; Roggo, S.; Wetzel, S.; Koch, M. A.; Waldmann, H. The Scaffold Tree: Visualization of the Scaffold Universe by Hierarchical Scaffold Classification. *J. Chem. Inf. Model.* **2007**, *47*, 47−58.
(36) Renner, S.; van Otterlo, W. A. L.; Dominguez Seoane, M.; Möcklinghoff, S.; Hofmann, B.; Wetzel1, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. I.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. Bioactivity-Guided Mapping and Navigation of Chemical Space. *Nat. Chem. Biol.* **2009**, *5*, 585−592.
(37) Wetzel, S.; Klein, K.; Renner, S.; Rauh, D.; Oprea, T. I.; Mutzel, P.; Waldmann, H. Interactive Exploration of Chemical Space with Scaffold Hunter. *Nat. Chem. Biol.* **2009**, *5*, 581−583.
(38) Herhaus, C.; Karch, O.; Bremm, S.; Rippmann, F. MolWind: Mapping Molecule Spaces to Geospatial Worlds. *Chem. Cent. J.* **2009**, *3*, P32.
(39) Mendoza, A.; Ishihara, Y.; Baran, P. S. Scalable Enantioselective Total Synthesis of Taxanes. *Nat. Chem.* **2012**, *4*, 21−25.
(40) Su, S.; Rodriguez, R. A.; Baran, P. S. Scalable, Stereocontrolled Total Synthesis of (±)-Axinellamines A and B. *J. Am. Chem. Soc.* **2011**, *133*, 13922−13925.
(41) Shi, J.; Manolikakes, G.; Yeh, C.-H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. S. Scalable Synthesis of Cortistatin A and Related Structures. *J. Am. Chem. Soc.* **2011**, *133*, 8014−8027.
(42) Burns, N. Z.; Krylova, I. N.; Hannoush, R. N.; Baran, P. S. Scalable Total Synthesis and Biological Evaluation of Haouamine A and Its Atropoisomer. *J. Am. Chem. Soc.* **2009**, *131*, 9172−9173.
(43) Burke, M. D.; Berger, E. M.; Schreiber, S. L. A Synthesis Strategy Yielding Skeletally Diverse Small Molecules Combinatorially. *J. Am. Chem. Soc.* **2004**, *126*, 14095−14104.
(44) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. Biology-Oriented Synthesis. *Angew. Chem., Int. Ed.* **2011**, *50*, 10800−10826.
(45) Bon, R. S.; Waldmann, H. Bioactivity-Guided Navigation of Chemical Space. *Acc. Chem. Res.* **2010**, *43*, 1103−1114.
(46) Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. Biology-Inspired Synthesis of Compound Libraries. *Cell. Mol. Life Sci.* **2008**, *65*, 1186−1201.

(47) Nören-Müller, A.; Corrêa, I. R.; Prinz, H.; Rosenbaum, C.; Saxena, K.; Schwalbe, H. J.; Vestweber, D.; Cagna, G.; Schunk, S.; Schwarz, O.; Schiewe, H.; Waldmann, H. Discovery of Protein Phosphatase Inhibitor Classes by Biology-Oriented Synthesis. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 10606−10611.
(48) Koch, M. A.; Wittenberg, L.-O.; Basu, S.; Jeyaraj, D. A.; Gourzoulidou, E.; Reinecke, K.; Odermatt, A.; Waldmann, H. Compound Library Development Guided by Protein Structure Similarity Clustering and Natural Product Structure. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16721−16726.
(49) Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. Traceless Fischer Indole Synthesis on the Solid Phase. *Chem. Commun.* **2003**, 1822−1823.
(50) Correa, I. R.; Nören-Müller, A.; Ambrosi, H.-D.; Jakupovic, S.; Saxena, K.; Schwalbe, H.; Kaiser, M.; Waldmann, H. Identification of Inhibitors for Mycobacterial Protein Tyrosine Phosphatase B (MptpB) by Biology-Oriented Synthesis (BIOS). *Chem.—Asian J.* **2007**, *2*, 1109−1126.
(51) Ducharme, Y.; Brideau, C.; Dube, D.; Chan, C. C.; Falgueyret, J. P.; Gillard, J. W.; Guay, J.; Hutchinson, J. H.; McFarlane, C. S. Naphthalenic Lignan Lactones as Selective, Nonredox 5-Lipoxygenase Inhibitors. Synthesis and Biological Activity of (Methoxyalky1)thiazole and Methoxytetrahydropyran Hybrids. *J. Med. Chem.* **1994**, *37*, 512−518.
(52) Stewart, A. O.; Bhatia, P. A.; Martin, J. G.; Summers, J. B.; Rodriques, K. E.; Martin, M. B.; Holms, J. H.; Moore, J. L.; Craig, R. A.; Kolasa, T.; Ratajczyk, J. D.; Mazdiyasni, H.; Kerdesky, F. A.; DeNinno, S. L.; Maki, R. G.; Bouska, J. B.; Young, P. R.; Lanni, C.; Bell, R. L.; Carter, G. W.; Brooks, C. D. Structure−Activity Relationships of *N*-Hydroxyurea 5-Lipoxygenase Inhibitors. *J. Med. Chem.* **1997**, *40*, 1955−1968.
(53) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. Synthesis of Natural-Product-like Molecules with Over Eighty Distinct Scaffolds. *Angew. Chem., Int. Ed.* **2009**, *48*, 104−109.
(54) Waldmann, H. Killing 84 Birds with One Stone. *Nat. Chem. Biol.* **2009**, *5*, 76−77.
(55) Liu, W.; Khedkar, V.; Baskar, B.; Schürmann, M.; Kumar, K. Branching Cascades: A Concise Synthetic Strategy Targeting Diverse and Complex Molecular Frameworks. *Angew. Chem., Int. Ed.* **2011**, *50*, 6900−6905.
(56) Antonchick, A. P.; Gerding-Reimers, C.; Catarinelle, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. Highly Enantioselective Synthesis and Cellular Evaluation of Spirooxindoles Inspired by Natural Products. *Nat. Chem.* **2010**, *2*, 735−740.
(57) Potowski, M.; Schürmann, M.; Preut, H.; Antonchick, A. P.; Waldmann, H. Programmable Enantioselective One-Pot Synthesis of Molecules with Eight Stereocenters. *Nat. Chem. Biol.* **2012**, *8*, 428−430.
(58) Dückert, H.; Pries, V.; Khedar, V.; Menninger, S.; Bruss, H.; Bird, A. W.; Maliga, Z.; Brockmeyer, A.; Janning, P.; Hyman, A.; Grimme, S.; Schürmann, M.; Preut, H.; Hübel, K.; Ziegler, S.; Kumar, K.; Waldmann, H. Natural Product-Inspired Cascade Synthesis Yields Modulators of Centrosome Integrity. *Nat. Chem. Biol.* **2012**, *8*, 179−184.
(59) Wetzel, S.; Wilk, W.; Chammaa, S.; Sperl, B.; Roth, A. G.; Yektaoglu, A.; Renner, S.; Berg, T.; Arenz, C.; Giannis, A.; Oprea, T. I.; Rauh, D.; Kaiser, M.; Waldmann, H. A Scaffold Tree Merging Strategy for Prospective Bioactivity Annotation of gamma-Pyrones. *Angew. Chem., Int. Ed.* **2010**, *49*, 3666−3670.
(60) Mueller, J.; Sperl, B.; Reindl, W.; Kiessling, A.; Berg, T. Discovery of Chromone-Based Inhibitors of the Transcription Factor STAT5. *ChemBioChem* **2008**, *9*, 723−727.