

## Chemistry for Chemical Genomics

Lutz Weber

### Summary

New methods and strategies have been developed to design and use small molecules that allow the functional dissection of molecular pathways, cells, and organisms by selective small-molecule ligands or modulators. In this overview, we are focusing on diversity aspects, design methods, and chemical synthesis strategies for the application of small molecules as tools for chemical genomics. Examples for different successful chemical-genomics strategies include the selection of diverse drug-like molecules, target family-focused compound libraries, natural-product chemistry, and diversity-oriented synthesis.

**Key Words:** Chemical diversity; compound design; diversity-oriented synthesis; drug-like compounds; molecular properties; natural products; rule of five; structure–activity relationship; target-focused compound libraries.

### 1. Introduction

Organic chemistry is the science of the synthesis and properties of molecules that are constructed from only a few atom types, such as carbon, hydrogen, nitrogen, oxygen, and sulfur, with carbon atoms constituting the majority of the core of these chemicals. As these atoms are also the building blocks of naturally occurring peptides or oligonucleotides, this chemistry was termed *organic*, as opposed to other disciplines of chemistry. Such chemicals, commonly referred to as *small molecules*, are valuable as medicines to treat diseases ranging from headache to cancer.

Small molecules have recently proven to be extremely useful tools to explore the functions of the cell at the genome level, giving rise to the new paradigm of chemical genomics. The functional dissection of molecular pathways, cells, and organisms by having a small-molecule ligand or modulator for every gene product, was the vision of Stuart L. Schreiber, one of the pioneers of the chemical genomics field (*1*).

From: *Methods in Molecular Biology*, vol. 310: *Chemical Genomics: Reviews and Protocols*  
Edited by: E. D. Zanders © Humana Press Inc., Totowa, NJ

Several recent reviews and books deal with the implication of chemical genomics towards drug discovery (2–5). The chemical genomics paradigm is seen as a logical follow-up of the Human Genome Project, and several public initiatives on chemical genomics have been started on national levels. Thus, in the United States, the National Human Genome Research Institute has set up a chemical libraries plan that moves the National Institutes of Health into high-throughput screening and small-molecule development to “determine function and therapeutic potential of genes and to define molecular networks.” In Germany, the Nationale Genomforschungsnetz initiated a chemical genomics platform by assembling synthetic compound libraries as probes for protein function. These compounds will help to validate new targets for novel therapies more rapidly, and will enable researchers in the public and private sectors to take these targets and move them through the drug-development pipeline.

In this overview we would like to focus on some chemical aspects, problems, and solutions to the application of small molecules as tools for chemical genomics.

## 2. Diversity of Small Molecules

What are small molecules? For the sake of simplicity, let us consider only those organic chemicals as small molecules that have a molecular weight of less than 1000 Dalton. Such a definition is by its nature arbitrary, but allows separating out other classes of organic molecules such as molecules that are oligomers of smaller building blocks such as, for example, proteins, oligonucleotides, or oligosaccharides. The number of all possible and different small molecules with a molecular weight below 1000 is assumed to exceed  $10^{60}$ . To be a specific modulator of a target protein, a small molecule has to act as a ligand, binding to its target. As opposed to large molecules, small molecules have an average interaction area of up to  $400 \text{ \AA}^2$  with their target—which is, for example, the size of a typical enzyme substrate site. This relatively small interaction area poses a serious problem to the whole concept of chemical genomics—is it at all possible to find a specific small molecule for each gene product? Indeed, it appears more likely that small molecules are promiscuous and may interact rather with a range of targets that have similar binding sites. Many of these “unwanted” interactions might not result in undesired effects, giving way to selective drugs *in vivo*. In odd cases, such secondary interactions may cause toxicities or other side effects; in lucky cases, these secondary interactions might be the real reason why a particular small molecule is an effective drug. Therefore, the rational design of such dual- or triple-action compounds has emerged as a new paradigm (6).

The functional, biological diversity of small molecules appears to be inherently more limited than that of large molecules. Whereas the diversity of oligomers

can be described by metrics like sequence and secondary, tertiary, and quaternary structure, the diversity of small molecules is harder to capture. The development of qualitative and quantitative measures for the chemical diversity of small molecules has only started to evolve with the advent of combinatorial chemistry, which enabled the synthesis of a large number of small molecules in one experiment.

As opposed to large molecules, the required high functional diversity of small molecules has to be packed into a rather small volume made up of only 20–30 non-hydrogen atoms. To bind efficiently at a protein–ligand site, most of the small-molecule ligand's binding energy must come from sites not exploited by the natural protein ligand. The limited molecular volume has to interact with the target protein with a maximum binding energy per atom to achieve both the required affinity and specificity. This binding energy has been calculated for maximal free-energy contributions per non-hydrogen atom with approx 1.5 kcal/mol across a wide variety of macromolecule–small-molecule interactions. The empirical data also revealed a significant trend to smaller contributions per atom as the relative molecular mass of the ligand increases (6). Thus, small-molecule ligands are binding to their targets with approximately three times more binding energy per unit area than protein ligands (8). As subnanomolar binding can be achieved with ligands containing as few as 10–20 atoms, the remaining 10–20 atoms could potentially be used to obtain selectivity. The likelihood of obtaining the desired functional diversity for small molecules is also correlated to the nature of the biological targets of interest. Thus, it is more likely to find enzyme inhibitors than small molecules that block protein–protein interactions (8).

Functional diversity of small molecules for chemical genomics experiments can therefore be defined in terms of obtaining maximum affinity to a given target protein by a minimum of molecular volume in order to minimize unwanted binding to other proteins. The realization of this Max–Min concept in a library of small-molecule compounds poses a serious challenge to organic chemists. As the molecular volume of small molecules is rather similar and does not leave enough room for major variations, the only way to obtain both affinity and selectivity is a maximum diverse distribution of atoms in this small volume. This can not be achieved by varying a small number of building blocks like the 20 amino acids for proteins, but requires the whole repertoire of organic chemistry to assemble novel chemical scaffolds. This recent understanding has led not only to a reappraisal of natural-product chemistry but also to a series of initiatives that aim at the development of novel chemistries to obtain chemical diversity.

## **2.1. Drug-Like Compound Libraries**

A large range of small-molecule physico-chemical properties can be computed and used for diversity selection and drug likeliness. Thus, drug-like mole-

cules should follow the “rules of five” that requires a  $\log P \leq 5$ , molecular weight  $\leq 500$ , number of hydrogen bond acceptors  $\leq 10$ , and number of hydrogen bond donors  $\leq 5$ . Molecules violating more than one of these rules may have problems with bioavailability (9) or the likelihood of having good drug properties (10). A polar surface area of  $<120 \text{ \AA}^2$  has been shown to correlate with bioavailability and can be computed in a straightforward way (11). A new method based on quantum chemistry performs the rapid, automated fragment-wise construction of an approximate charge density ( $\sigma$ -profiles) on the molecular surface—describing better the surface of the ligand a target protein will interact with (12).

An optimally diverse compound library of drug-like molecules for chemical genomics experiments would be a collection of representatives from a variety of compound clusters of similar molecules. A comparison between various simple and more complex structural descriptors and clustering methods has been given by Brown and Martin (13), using large sets of different molecules. Interestingly, the simplest method, counting 153 different substructure keys using a priori knowledge about substructure elements from a fragment dictionary, provided a better similarity measure than using more complex two- or three-dimensional criteria. This points to the difficulty of generating general representations of molecules, and it is probably impossible to hope to characterize a large, diverse data set by a small set of representatives. Calculated octanol-water partition coefficients, molar refractivities, or dipole moments can be used as additional criteria to assemble a useful library for biological testing (14). Exclusion criteria should also include knowledge on promiscuous or reactive substructures such as, for example, excluding compounds that exhibit thiourea, nitro, or  $\alpha$ -halo-keto groups such as defined by Rishton (15).

The above principles have been applied with success to select compound libraries for chemical genomic experiments. We would like to give two representative examples for such a successful selection.

Monastrol was identified as a novel antimitotic compound from a selected library of 16,320 commercially available compounds (16). The library was screened by applying a series of phenotype-based screens, selecting 139 compounds that induced phosphonucleolin levels, then subsequently eliminating 52 compounds from these 139 that targeted tubulin and a further 42 antimitotic compounds that target the interphase cytoskeleton, leaving overall only 5 compounds with the desired cellular effect. From these, monastrol arrests mammalian cells in mitosis with mono-astral spindles surrounded by a ring of chromosomes. The target of monastrol was found to be the mitotic motor protein Eg5, a bipolar kinesin known to be required for spindle bipolarity. This cellular activity of monastrol is very sensitive to structural changes: the chemically similar DHP2 compound is already completely inactive (**Fig. 1**).

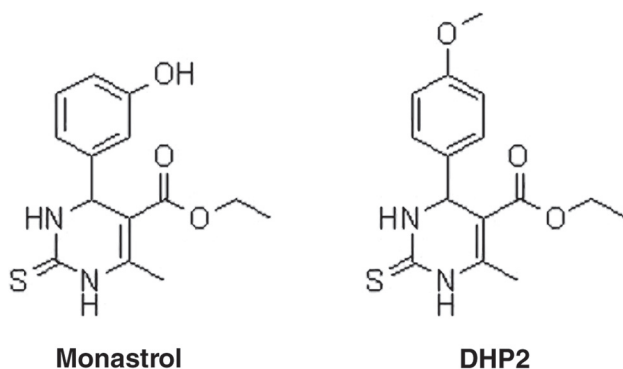


Fig. 1.

In a conceptually similar experiment, compounds were selected from commercial vendors to give a screening library of 73,400 diverse, drug-like molecules that comply with the rules of five. Screening of this library in a permeable yeast two-hybrid system was accomplished to select molecules that block the protein-protein interaction of cI-DBD-H-Ras(G186) with AD-Raf-1, but not of LexA-DBD-hsRBP7 and AD-hsRBP4. From this library, 38 active compounds were selected for further screening in mammalian cells to inhibit serum-induced transcriptional activation through SRE and AP-1 sites from the c-fos promoter. MCP1 was then selected by performing additional cell-based screening to remove unselective or toxic compounds (17). Interestingly, the chemical structure of MCP1 resembles other structures that are able to inhibit protein-protein interactions, such as, for example, FKB-001 (18), featuring flexible side chains that enable the molecule to fold into cavities at the protein surface. On the other hand, both molecules (Fig. 2) are accessible via fast and parallel synthesis methods (19).

As opposed to selecting libraries of general molecules from historic compound collections, for combinatorial libraries the problem of a diversity metric is simplified due to the limited number of building blocks that are used for their synthesis. Using volume, lipophilicity, charge, and H-bond donor or acceptor descriptors, it was shown that combinatorial libraries may be designed to exhibit the same diversity as commercial drugs with respect to the density of these structural fragments (20). Subsets from a large virtual library can then be chosen by D-optimal design to assemble an information-rich diverse library. More advanced methods (CATS and TOPAS) have been developed recently to select and synthesize compounds for screening based on two-dimensional criteria (21,22).

## 2.2. Target-Family Compound Libraries

Proteins of a certain family usually exhibit structurally similar binding sites; a prominent example is the adenosine triphosphate (ATP)-binding site of the

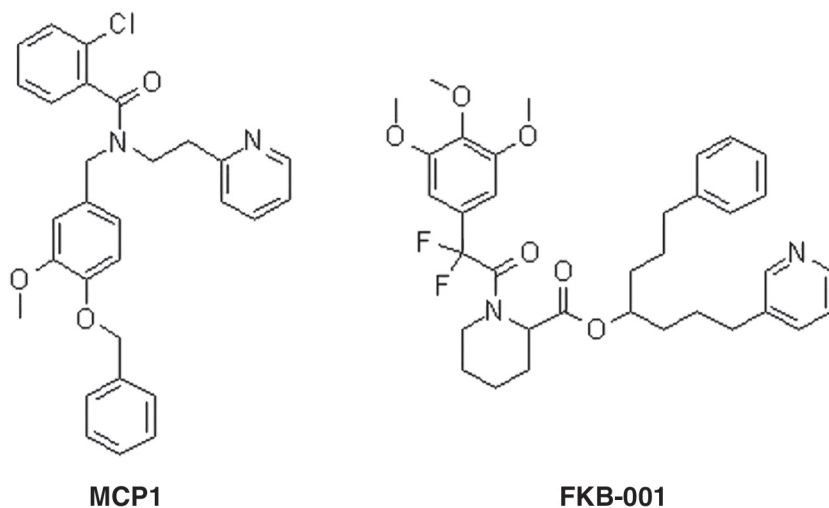


Fig. 2.

approx 518 kinases identified so far, also called the human kinome (**23**). Not surprisingly, compounds that mimic the structural features of ATP are used with success to synthesize more or less selective kinase inhibitors. These inhibitors can be used both as tool compounds to study the effect of a particular kinase in cell signaling events or as potential drug candidates. A great deal of chemical, biological, and biostructural information on kinase inhibitors is available and provides a straightforward starting point for designing compound libraries that target kinases. In a recent example, biostructural information was used to classify kinases according to the similarity of their small-molecule ligands, and develop a fast virtual screening method—structural interaction fingerprint (SIFt)—that allowed rapid identification of novel and selective transforming growth factor- $\beta$  kinase inhibitors. This method, based on experimental data, combines for the first time protein sequence homology and the chemical structure information of the ligand into one truly chemo-genomic method (**24**).

In another example of combinatorial parallel chemistry, we have recently used the Ugi three-component reactions (Ugi 3-CR) to construct a library of 16,840 protease inhibitors (**25**). It has been demonstrated previously that the Ugi-3CR reaction provides a useful chemical scaffold for the design of serine protease inhibitors: *N*-substituted 2-substituted-glycine *N*-aryl/alkyl-amides have been identified that are potent factor Xa, factor VIIa, or thrombin inhibitors. The three variable substituents of this scaffold, provided by the amine, aldehyde, and isonitrile starting materials, span a favorable pyramidal pharmacophoric scaffold that can fill the S1, S2, and S3 pockets of the respective protease. This library was screened against five proteases (factor Xa, trypsin, uro-

kinase, trypsin, and chymotrypsin) at different concentrations to create an exhaustive structure–activity relationship (SAR) data set. Using this SAR, both selective and potent inhibitors could be identified against all five proteases, such as the four prototypic factor Xa inhibitors shown in **Fig. 3**.

### 2.3. Natural Products

By intuition, natural products are thought to exhibit a higher degree of complexity than traditional synthetic drugs (**26**). This hypothesis was verified by analyzing the chemical core structures of natural products (**27**). In addition, natural products tend to have a higher molecular weight, more oxygen atoms, and fewer nitrogen atoms than synthetic drug molecules. A quantitative index of complexity was developed that uses the number and size of rings and the connectivity of each atom (**28**). Alternatively, complexity can be defined as the number of domains or substructures contained in a molecule that are available for interacting with the target. A molecule with low complexity has fewer interaction sites than a molecule with greater complexity, that can therefore be more selective than simple compounds, also yielding fewer hits in primary screens (**29**). Libraries of natural products can be obtained either as purified compounds or as extracts from microbes or plants. Although most natural products do not follow the rules of five, finding natural-product drug candidates has been a successful enterprise in the past—almost half of the small-molecule drugs on the market are either directly natural products or chemically derived from those.

However, the total synthesis of these complex structures poses a serious challenge to organic chemistry, resulting often in the inability to follow up first hits quickly by resynthesis and derivatization. Thus, the synthesis of complex natural products using efficient strategies, often accompanied by the development of novel reagents and reactions, was considered the “royal” discipline of organic chemists in the past. Today, we observe that those natural-product-oriented organic chemists are broadly using the developed know-how to bring together the pharmacophores of structurally diverse natural products with methods of combinatorial chemistry.

As a representative example, the rather complex natural-product dysidiolide was synthesized by methods amenable to combinatorial synthesis (**30**). Using a cycloaddition-based approach to the dysidiolide core, a solid-phase synthesis of epi-dysidiolide (**Fig. 4**) and analogs thereof was developed.

The total synthesis proceeds in >10 steps on solid phase and includes various transformations, including an asymmetric Diels–Alder reaction, oxidation with singlet oxygen, and olefin metathesis. This synthesis sequence is among the most advanced and demanding solid-phase syntheses developed so far for chemical genomics experiments. It demonstrates that the total synthesis of complex natural products in multi-step sequences on solid phase is feasible.

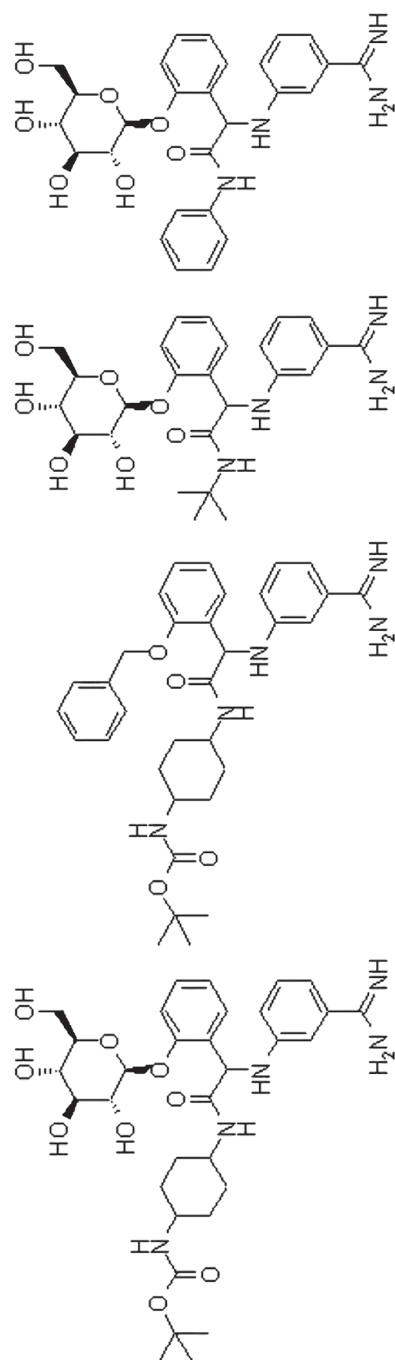


Fig. 3.



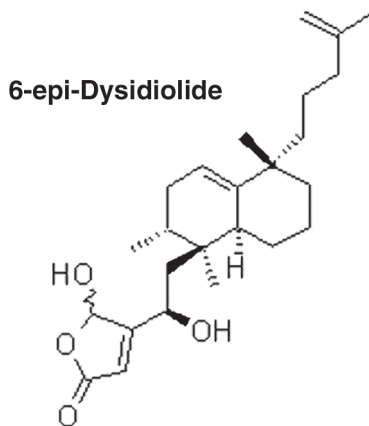


Fig. 4.

Moreover, the biological investigation of dysidiolide analogs has yielded selective Cdc25 inhibitors with high potency in enzymatic and cellular assays.

### 3. Diversity-Oriented Synthesis

Many natural products have been directly developed in the past as drugs—without the possibility for a significant synthesis of potentially better analogs. This observation has inspired a new strategy of synthesizing natural-product-like compounds using combinatorial, diversity-oriented synthesis (DOS) (**31**). Thereby, the generation of molecular complexity by reaction sequences that are amenable to combinatorial chemistry has become an important theme of recent research (**32**). Optimized reactions have been utilized to create compound libraries that are comparable in terms of structural diversity with natural products. In one example, the alkaloid martinelllic acid has been the target for transition metal-catalyzed hetero-Diels-Alder reactions. Surprisingly, a reaction was found that yielded the desired scaffold in one step by a novel three-component coupling. In another example, a hetero-Diels-Alder scaffold was used to synthesize peptidomimetics, aiming to arrive at conformationally and proteolytically stable products derived from biologically active peptides (**33**).

In a different approach, one may synthesize molecular scaffolds that have not been found in nature. These templates are often also called *new chemotypes*, expressing the hope of finding interesting and unexpected biological activities. For example, cycloadditions, imine formation, and Michael reactions are used to generate such novel backbones (**34,35**).

Poly-substituted aromatic rings are difficult to synthesize—in a recent work, inhibitors of the cholesterol ester transfer protein (CETP) were synthesized, using a highly sophisticated assembly of basic organic reactions and comprising

a three-component reaction (36). This work certainly represents one of the best examples of how combinatorial chemistry has merged with the synthesis of high-diversity, complex compounds.

Multi-component reactions, first misinterpreted as rather rare exceptions in organic chemistry, are now commonly regarded as useful tools to generate highly diverse compound libraries. Only four synthetic steps are needed to generate complex, almost baroque structures (37) using an Ugi-type MCR, a Diels-Alder reaction, and a final olefin metathesis. Other examples of similar diversity-generating reaction sequences have been published, using oxidative bond formations or macrocyclization strategies by building up peptide scaffolds that are then cyclized via olefin metathesis (38).

In most recent developments, it has been possible to devise synthetic strategies whereby a variety of chemical scaffolds can be obtained in one scheme (39). Whereas in former examples of combinatorial synthesis a large number of compounds were synthesized that all shared the same chemical backbone, this new technology is opening new ways toward a diversity that can be used for chemical genomics in a designed strategy (40).

#### 4. Summary

The success of merging genomics and chemistry will depend on finding small molecules that can interact specifically with a given protein target molecule. This goal might be especially difficult to achieve when dealing with proteins that are similar in their sequence, three-dimensional structure, or function, as are kinases. One way, as outlined in this chapter, is to improve chemical methods to arrive at suitable small molecules. However, the concept of chemical genomics might also inspire and call for completely new technologies that integrate chemistry and genomics even better.

As an illustration, we would like to cite the work of Shokat (41). To allow for the fast selection of suitable molecules, the three-dimensional structure of the v-Src kinase was changed through site-directed mutagenesis, creating a new binding pocket in the vicinity of the active site while retaining its catalytic properties. It was then shown that an ATP analog, created through introducing a side chain by chemical means into ATP, resulted in a highly specific substrate that is converted only by the mutated v-Src kinase and not by other members of this large enzyme family. It was thereby possible to study the pharmacological role of v-Src kinase without affecting other kinases. This method is the first experimental merger of genomics and small-molecule chemistry, allowing the creation of tools for chemical genomics studies. Other ideas along these lines may include variants of dynamic combinatorial libraries (42) or click chemistry (43), where the target protein assists the synthesis of the small molecule by selecting a binding molecule out of a large pool of possible molecules.

The examples described here in any case illustrate a new quality of investigating the interaction of small molecules within complex biological systems. How can one use the chemical-genomics answers obtained to design better drugs, more rapidly and more efficiently? Typically, the biological responses towards a chemical entity are complex and multi-dimensional, such as gene-expression patterns, protein binding, phenotype reversals, and phenotype inductions. Multi-dimensional optimization algorithms will be required to translate such biological feedback into the creation of better drugs. In low-dimensional optimization spaces, traditional structure-activity relationships work well. Higher-dimensional search spaces, as provided by chemical genomics, need heuristic optimization procedures, as exemplified by neuronal networks or genetic algorithms (42). Genetic algorithms utilize biological genomics information in combination with a recently introduced, DNA-like description of small synthetic molecules, to provide an opportunity for optimizing small molecules more efficiently using nature's evolutionary principles. Ultimately, one could envisage a co-evolutionary drug-discovery process that would enable the discovery of novel drug targets by using small molecules, which are then improved by respective biological feedback loops into highly potent and selective new drug candidates.

## References

1. Schreiber, S. L. (1998) Chemical genetics resulting from a passion for synthetic organic chemistry. *Bio. Med. Chem.* **6**, 1127–1152.
2. Kubinyi, H. and Müller, G. (eds.). (2004) Chemogenomics in drug discovery, a medicinal chemistry perspective. In *Methods and Principles in Medicinal Chemistry*, Wiley-VCH, Weinheim, Germany.
3. Ferenc Darvas, F., Guttman, A., and Dormann, G. (2004) *Chemical Genomics*. Marcel Dekker, New York.
4. Salemme, F. R. (2003) Chemical genomics as an emerging paradigm for post-genomic drug discovery. *Pharmacogenomics* **4**, 1–11.
5. Crews, C. M. and Splittgerber, U. (1999) Chemical genetics: exploring and controlling cellular processes with chemical probes. *TIBS* **5**, 317–320.
6. Morphy, R., Kay, C., and Rankovic, Z. (2004) From magic bullets to designed multiple ligands. *Drug Discovery Today* **9**, 641–651.
7. Kuntz, I. D., Chen, K., Sharp, K. A., and Kollmann, P. A. (1999) The maximal affinity of ligands. *Proc. Natl. Acad. Sci. USA* **96**, 9997–10,002.
8. Spencer, R. (1998) High-throughput screening of historic collections: observations on file size, biological targets, and file diversity. *Biotechnol. Bioeng.* **61**, 61–67.
9. Lipinski, C. A., Lombardo, F., Dominy, B. W., and Feeney, P. J. (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug. Delivery Rev.* **23**, 4–25.
10. Proudfoot, J. R. (2002) Drugs, leads, and drug-likeness: an analysis of some recently launched drugs. *Bioorg. Med. Chem. Lett.* **12**, 1647–1650.

11. Ertl, P., Rohde, B., and Selzer, P. (2000) Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *J. Med. Chem.* **43**, 3714–3717.
12. www.cosmologic.de. Accessed on March 30, 2005.
13. Brown, R. D. and Martin, Y. C. (1996) Use of structure-activity data to compare structure-based clustering methods and descriptors for use in compound selection. *J. Chem. Inf. Comput. Sci.* **36**, 572–584.
14. Shemetulskis, N. A., Dunbar, J. B., Dunbar, B. W., Moreland, D. W., and Humblet, C. (1995) Enhancing the diversity of a corporate database using chemical clustering and analysis. *J. Comp. Aided Mol. Design* **9**, 407–416.
15. Rishton, G. M. (1997) Reactive compounds and in vitro false positives in HTS. *Drug Discovery Today* **2**, 382–384.
16. Mayer, T. U., Kapoor, T. M., Haggarty, S. J., King, R. W., Schreiber, S. L., and Mitchison, T. J. (1999) Small molecule inhibitor of spindle bipolarity identified in a phenotype-based screen. *Science* **286**, 971–974.
17. Kato-Stankiewicz, J., Hakimi, I., Zhi, G., et al. (2002) Inhibitors of Ras-Raf-1 interaction identified by two-hybrid screening revert Ras-dependent transformation phenotypes in human cancer cells. *Proc. Nat. Acad. Sci. USA* **99**, 14,398–14,403.
18. Dubowchik, G. M., Vrudhula, V. M., Dasgupta, B., et al. (2001) 2-Aryl-2,2-difluoroacetamide FKBP12 ligands: synthesis and X-ray structural studies. *Org. Lett.* **3**, 3987–3990.
19. Lu, Y., Sakamuri, S., Chen, Q.-Z., et al. (2004) Solution phase parallel synthesis and evaluation of MAPK inhibitory activities of close structural analogues of a Ras pathway modulator. *Bioorg. Med. Chem. Lett.* **14**, 3957–3962.
20. Martin, E. J., Blaney, J. M., Siani, M. A., Spellmeyer, D. C., Wong, A. K., and Moos, W. H. (1995) Measuring diversity: experimental design of combinatorial libraries for drug discovery. *J. Med. Chem.* **38**, 1431–1436.
21. Schneider, G., Chomienne-Clement, O., Hilfiger, L., et al. (2000) Virtual screening for bioactive molecules by evolutionary de novo design. *Angew. Chemie Int. Ed.* **39**, 4130–4133.
22. Schneider, G., Lee, M.-L., Stahl, M., and Schneider, P. (2000) De novo design of molecular architectures by evolutionary assembly of drug-derived building blocks. *J. Comput. Aided Mol. Des.* **14**, 487–494.
23. Manning, G., Whyte, D. B., Martinez, R., Hunter, T., and Sudarsanam, S. (2002) The protein kinase complement of the human genome. *Science* **298**, 1912–1934.
24. Deng, Z., Chuaqui, C., and Singh, J. (2004) Structural Interaction Fingerprint (SIFT): a novel method for analyzing three-dimensional protein-ligand binding interactions. *J. Med. Chem.* **47**, 337–344.
25. Weber, L. Fractal theory applied to structure-activity relationships. Euro-QSAR 2004, Istanbul, Turkey, September 5–10, 2005.
26. Verdine, L. G. (1996) The combinatorial chemistry of nature. *Nature* **384**, 11–13.

27. Lee, M.-L. and Schneider, G. (2001) Scaffold architecture and pharmacophoric properties of trade drugs and natural products. *J. Comb. Chem.* **3**, 284–289.
28. Barone, R. and Chanon, M. (2001) A new and simple approach to chemical complexity. Application to the synthesis of natural products. *J. Chem. Inf. Comput. Sci.* **41**, 269–272.
29. Hann, M. M., Leach, A. R., and Harper, G. (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* **41**, 856–864.
30. Brohm, D., Metzger, S., Bhargava, A., Müller, O., Lieb, F., and Waldmann, H. (2002) Natural products are biologically validated starting points in structural space for compound library development: solid phase synthesis of dysidiolide-derived phosphatase inhibitors. *Angew. Chem. Int. Ed.* **41**, 307–311.
31. Schreiber, S. L. (2000) Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* **287**, 1964–1969.
32. Weber, L. (2000) High-diversity combinatorial libraries. *Curr. Opin. Chem. Biol.* **4**, 295–302.
33. Creighton, C. J., Zapf, C. W., Bu, J. H., and Goodman, M. (1999) Solid-phase synthesis of pyridones and pyridopyrazines as peptidomimetic scaffolds. *Org. Lett.* **1**, 1647–1649.
34. Peng, G., Sohn, A., and Gallop, M. A. (1999) Stereoselective solid-phase synthesis of a triaza tricyclic ring system: a new chemotype for lead discovery. *J. Org. Chem.* **64**, 8342–8349.
35. Brooking, P., Crawshaw, M., Hird, N. W., et al. (1999) The development of a solid-phase tsuge reaction and its application in high throughput robotic synthesis. *Synthesis* **11**, 1986–1992.
36. Paulsen, H., Antons, S., Brandes, A., et al. (1999) Stereoselective Mukaiyama-Michael/Michael/Aldol domino cyclization as the key step in the synthesis of penta-substituted arenes: an efficient access to highly active inhibitors of cholesteryl ester transfer protein (CETP). *Angew. Chem. Int. Ed.* **38**, 3373–3375.
37. Lee, D., Sello, J. K., and Schreiber, S. L. (2000) Pairwise use of complexity-generating reactions in diversity-oriented organic synthesis. *Org. Lett.* **2**, 709–712.
38. Reichwein, J. F., Wels, B., Kruijtz, J. A. W., Versluis, C., Liskamp, R. M. J. (1999) Rolling loop scan: an approach featuring ring-closing metathesis for generating libraries of peptides with molecular shapes mimicking bioactive conformations or local folding of peptides and proteins. *Angew. Chem. Int. Ed.* **38**, 3684–3687.
39. Taylor, S. J., Taylor, A. M., and Schreiber, S. L. (2004) Synthetic strategy toward skeletal diversity via solid-supported, otherwise unstable reactive intermediates. *Angewandte Chemie* **43**, 1681–1685.
40. Burke, M. D. and Schreiber, S. L. (2004) A planning strategy for diversity-oriented synthesis. *Angewandte Chemie* **43**, 46–58.
41. Shah, K., Liu, Y., Deirmengian, C., and Shokat, K. M. (1997) Engineering unnatural nucleotide specificity for Rous sarcoma virus tyrosine kinase to uniquely label its direct substrates. *Proc. Nat. Acad. Sci. USA* **94**, 3565–3570.

42. Huc, I. and Lehn, J.-M. (1997) Virtual combinatorial libraries: dynamic generation of molecular and supramolecular diversity by self-assembly. *Proc. Natl. Acad. Sci. USA* **94**, 2106–2110.
43. Lewis, W. G., Green, L. G., Grynszpan, F., et al. (2002) Click chemistry in situ: acetylcholinesterase as a reaction vessel for the selective assembly of a femtomolar inhibitor from an array of building blocks. *Angew. Chem. Int. Ed.* **41**, 1053–1057
42. Illgen, K., Enderle, T., Broger, C., and Weber, L. (2000) Simulated molecular evolution in a full combinatorial library. *Chem. Biol.* **7**, 433–441.

Chemical Genomics

Reviews and Protocols

Zanders, E.D. (Ed.)

2005, XII, 280 p., Hardcover

ISBN: 978-1-58829-399-2

A product of Humana Press