Modern drug discovery technologies: opportunities and challenges in lead discovery

http://www.producao.usp.br/handle/BDPI/49919

Downloaded from: Biblioteca Digital da Produção Intelectual - BDPI, Universidade de São Paulo
Modern Drug Discovery Technologies: Opportunities and Challenges in Lead Discovery

Rafael V.C. Guido, Glaucius Oliva and Adriano D. Andricopulo*

Laboratório de Química Medicinal e Computacional, Instituto de Física de São Carlos, Universidade de São Paulo, Av. Trabalhador São-Carlense 400, 13560-970 São Carlos-SP, Brazil

Abstract: The identification of promising hits and the generation of high quality leads are crucial steps in the early stages of drug discovery projects. The definition and assessment of both chemical and biological space have revitalized the screening process model and emphasized the importance of exploring the intrinsic complementary nature of classical and modern methods in drug research. In this context, the widespread use of combinatorial chemistry and sophisticated screening methods for the discovery of lead compounds has created a large demand for small organic molecules that act on specific drug targets.

Modern drug discovery involves the employment of a wide variety of technologies and expertise in multidisciplinary research teams. The synergistic effects between experimental and computational approaches on the selection and optimization of bioactive compounds emphasize the importance of the integration of advanced technologies in drug discovery programs. These technologies (VS, HTS, SBDD, LBDD, QSAR, and so on) are complementary in the sense that they have mutual goals, thereby the combination of both empirical and in silico efforts is feasible at many different levels of lead optimization and new chemical entity (NCE) discovery. This paper provides a brief perspective on the evolution and use of key drug design technologies, highlighting opportunities and challenges.

Keywords: Drug discovery, ligand-based drug design, high throughput screening, virtual screening, lead discovery.

INTRODUCTION

In the early stages of the drug discovery process, chemical libraries varying widely in size and complexity are screened for the identification of new hits (i.e., ligands, bioactive compounds) [1,2]. The selection of a small fraction of compounds with sufficient promise for further optimization is a major challenge at this stage of this lengthy and risky process [1-3]. Traditional strategies in medicinal chemistry are often combined with modern structure-based (SBDD) and ligand-based drug design (LBDD) approaches to explore the vast chemical and biological space as a key component in the process of hit-to-lead generation, lead optimization and new chemical entity (NCE) discovery [3-7]. The challenge lies in the integration of these and other approaches at different stages in order to improve pharmacodynamic and pharmacokinetic properties of lead compounds at multiple levels of complexity [8-10]. The aim of this perspective is to provide the reader with a brief overview of the use and evolution of some key drug discovery technologies involved in the processes of hit identification and lead discovery, highlighting challenges and future directions.

1. NATURAL PRODUCTS

Natural products have been a major source of new chemical leads for centuries. In fact, natural products and their derivatives correspond to nearly 30% of the small-molecule drugs currently available [11, 12]. The research in the field of natural products chemistry has significantly evolved to incorporate state-of-the-art multidisciplinary approaches, including a variety of methods in medicinal chemistry, biochemistry, molecular biology and genomics. Moreover, in order to explore the vast chemical and biological diversity, several techniques (e.g., miniaturization bioassays, coupling chromatographic and spectroscopic techniques, higher resolution columns) have experienced significant advances in recent years, allowing the identification and characterization of several bioactive compounds. This complex process consists of a sequence of interactive steps, requiring the integration of different approaches (Fig. 2). Although the goal is to investigate a wide and diverse range of specimen types, the remarkable number of species in our planet (e.g., 300,000 – 400,000 species of plants) requires the use of robust and efficient strategies to select and acquire relevant sources of natural products [13]. Ethnobotanical studies and bioprospection strategies are often used to identify which specimen or parts of natural sources are more likely to produce attractive bioactive chemotypes. This is very useful for exploring the relationships between the genetic biodiversity and the environmental factors to chemodiversity [14].

One of the major challenges in natural products drug discovery is the identification and selection of valuable lead compounds from a number of equally active samples. In general, once a sample with promising biological activity has been identified, further bioassays-directed fractionation are carried out to isolate the active(s) constituent(s). Advances in extraction, isolation and purification, as well as in analytical and spectroscopic techniques have significantly assisted the rapid and reliable structural data elucidation, thereby allowing the discovery of novel chemical leads.
A striking example of natural products as a relevant source of new lead compounds regards the discovery of paclitaxel (Taxol®), one of the most powerful and commercially successful anticancer drugs, which presents a unique mechanism of action as a microtubule-stabilizing agent [15]. Paclitaxel was first isolated from the bark of the *Taxus brevifolia* Pacific yew tree as part of a random collection expedition for the National Cancer Institute (NCI) [16]. Due to its potent cytotoxic activity in several *in vivo* assays and the elucidation of the mechanism of action, paclitaxel and its analog docetaxel (Taxotere®) are now well-established anticancer agents useful for breast and ovarian carcinoma treatment. However, the structural complexity of paclitaxel impairs the development of time and cost-effective synthetic routes (e.g., the total synthesis of taxol requires 35 to 51 steps, with the highest yield of 0.4%) [17]. Subsequently, the development of a semi-synthetic route to paclitaxel allowed the development of a more efficient production process, particularly regarding the decreased need for harvesting the yew tree, nonetheless, production still depends on plant-based processes with accompanying limitations in terms of scale and sustainability [18]. Recently, an elegant approach integrating the knowledge of the natural products biosynthesis with molecular biology in *Escherichia coli* has significantly enhanced the production of taxadiene, the first committed paclitaxel intermediate,

**Table 1. Drug Design Approaches for the Identification of Biologically Active Molecules**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Century</th>
<th>Chemical Technology</th>
<th>Advantage</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Products</td>
<td>XIX</td>
<td>Compound isolation and structural characterization</td>
<td>Remarkable chemical diversity and spectrum of biological activities</td>
<td>Mixture of components, complex structures and limited amounts</td>
</tr>
<tr>
<td>Analog design</td>
<td>XX</td>
<td>Molecular modification, SAR and QSAR investigations</td>
<td>Compounds with <em>in vitro/in vivo</em> activity</td>
<td>Identification of compounds with significant biological/clinical benefits</td>
</tr>
<tr>
<td>Combinatorial Chemistry/High Throughput Screening</td>
<td>XX (1990s)</td>
<td>Parallel synthesis/automated (large-scale) assays</td>
<td>Synthesis and biological evaluation of large collections of compounds</td>
<td>High rates of false positive compounds</td>
</tr>
<tr>
<td>Virtual Screening (VS)</td>
<td>XX (1990s)</td>
<td>Structure- and ligand-based drug design (SBDD)</td>
<td>Identification of new molecular scaffolds</td>
<td>Accuracy of scoring and selection of true binders</td>
</tr>
<tr>
<td>Fragment-Based Drug Discovery (FBDD)</td>
<td>XXI</td>
<td>Structure- (SBDD) and Ligand-based drug design (LBDD)</td>
<td>High quality interaction with the target/efficient optimization</td>
<td>Low sensitive methods, availability of structural data</td>
</tr>
</tbody>
</table>
approximately 15,000-fold in comparison to the control [19], thereby providing greater efficacy and lower cost to new anticancer agents.

The use of natural products toward the identification of quality leads will continue to be a critical factor in drug discovery. Considering that inappropriate physicochemical properties are a major cause of attrition in drug development, the discovery of new molecular scaffolds (lead compounds) from small molecule natural products would be extremely helpful, especially those with low structural complexity and in agreement with the Lipinski’s rule of five (i.e., key physicochemical properties that indicate the druglikeness of molecules, such as molecular mass < 500 Da; cLogP < 5; number of hydrogen-bond donors < 5; number of hydrogen-bond acceptors < 10) [20].

2. ANALOG DESIGN

In drug design, the definition of analog consists of a molecule that shares structural and pharmacological similarities with the original compound [21]. Based on that, three categories can be derived: (i) direct analogs – molecules possessing chemical and pharmacological similarities; (ii) structural analogs – molecules possessing chemical similarities; and (iii) functional analogs – chemically different molecules exhibiting similar pharmacological properties.

The first category is characterized by improved versions of commercially available drugs in terms of pharmacodynamic and/or pharmacokinetic properties. This incorporates the so-called “me-too” drugs (i.e., drugs that are structurally similar to known drugs), including, for instance, the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, also known as statins, and the proton pump inhibitor esomeprazole (1), which is the (S)-enantiomer of the racemic (S), (R)-omeprazole (2). Esomeprazole showed clinical advantages over the racemic omeprazole, such as higher bioavailability and improved inhibition of gastric acid secretion (Fig. 3) [22].

The second category includes compounds designed as patentable analogs of the original drug, which, however, presented new (and unexpected) biological activities. An important example is sildenafil (3), a phosphodiesterase type-5 (PDE5) inhibitor, originally designed as an antihypertensive agent that revealed unexpected activity on male erectile dysfunction during clinical studies (e.g., penile erections were a common side effect in the Phase I studies) (Fig. 3) [23]. After the approval of sildenafil in 1998 as the first oral treatment for erectile dysfunction, scientists at Pfizer started to look at other potential uses for this drug. The investigations revealed a close relationship between the upregulation of PDE5 gene expression and pulmonary hypertensive lungs. Later, it was found that the inhibition of PDE5 had anti-pulmonary hypertensive activity, with selective effects on the pulmonary vascular resistance as indicated in the clinical trials. In 2005, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) obtained approval for sildenafil as a new treatment for pulmonary arterial hypertension [23].

The last category is known as “functional analogs”, where molecules in this class show similar binding properties for a common molecular target, regardless of their structural differences. Representative examples include, but are not limited to: gabazine (4) as a functional analog of (+)-bicuculline (5) (GABA-A receptor antagonists) [24], and zopiclone (6) and zolpidem (7) as functional analogs of benzodiazepines (selective benzodiazepine receptors agonists) (Fig. 3) [25].

According to the strategy employed, the degree of structural similarity to the original scaffold can vary considerably, for example, (i) substitution of elements or small groups (e.g., isostericism [26]), (ii) swapping fragments of molecule (e.g., bioisostericism [27]), or (iii) replacement of the original scaffold (e.g., scaffold hopping [28]). Currently, the design of analogs is remarkably boosted by in silico techniques. The application of cheminformatics tools significantly enhanced the search of analogs and the development of structure activity relationships (SAR).

3. COMBINATORIAL CHEMISTRY AND HIGH THROUGHPUT SCREENING

The definition and assessment of both chemical and biological space have revitalized the screening process
Combinatorial Chemistry & High Throughput Screening, 2011, Vol. 14, No. 10

Guido et al.

model and emphasized the importance of exploring the intrinsic complementary nature of classical and modern methods in drug research [1, 2]. Advances in organic synthesis along with a wide range of exceptional opportunities of pharmaceutical applications provided strong motivation for the development of combinatorial chemistry as a valuable tool for accelerating the processes of lead discovery and optimization [29]. The subsequent widespread use of combinatorial chemistry has allowed the generation of large collections of small organic molecules available for a variety of drug discovery projects [30]. Simultaneously, the improvements in robotic and miniaturization associated to the advances in genomics and proteomics enabled the development of high throughput screening (HTS) as a versatile tool for the rapid and large-scale screening of chemical libraries [31]. In the pharmaceutical industry, the integration of combinatorial chemistry and HTS has become one of the most important ways for the identification of novel hits and leads in the early stages of the drug discovery process [32].

Typically, HTS campaigns identify hundreds or thousands of hits (i.e., compounds with in vitro activity usually in the low- to mid-micromolar range) for further analysis. Depending on the complexity of the assay employed, many of the hits can interfere, disrupt or inhibit with assay components other than the protein of interest, thereby increasing the number of false positives (i.e., molecules that appear to be active against the target protein, but turn out to be uninteresting compounds) [31]. In line with this, intrinsic limitations related to the detection methods (in all steps of the analysis process) and promiscuous behavior of several compounds of the chemical libraries (e.g., aggregation, reactivity), have a considerable impact on the quality of the HTS hits. Therefore, several strategies have been employed to monitor and control the quality and accuracy of the in vitro assays in order to minimize the selection of false positives. For example, the use of chemoinformatic tools, either previously or in connection with HTS methods, has significantly contributed to reduce the assay-to-lead attrition rate observed from HTS, through the evaluation of the structural diversity and lead- and drug-like properties of the library compounds.

Since the introduction of HTS in the mid 1990s, much emphasis has been put on the increase of both screening capacity (i.e., technologies for automation and miniaturization) and the size and diversity of the chemical libraries. However, recent strategies have been progressively moving away from this traditional quantitative perspective to a more qualitative paradigm, focusing on the screening of representative collections of compounds libraries populated with pharmacophore scaffolds that reflect active ligands with...
lead- or drug-like properties, as well as in highly reliable counter screening and validation screening tools (Fig. 4).

**Fig. (4).** HTS Workflow.

In the early days, HTS technologies were exclusively found in the pharmaceutical industry. With the advances in the field and the decreased complexity of the approach in terms of infrastructure, equipments and human resources, the use of HTS has significantly spread worldwide [33]. Indeed, over the past years, there was a notable increase in the number of screening centers suitably equipped to conduct medium- and high-throughput screening activities [34]. Several other changes have boosted these developments, including price reduction of the automation instrumentation sector, popularization of the systems and software, and availability of commercial compound library sets.

A relevant example of the application of HTS in academia can be observed in the search for novel inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MtPtpB), an essential virulence factor possessed by all mycobacterial species [35]. The HTS was performed at the Indiana University Chemical Genomics Core Facility where a structurally diverse, pharmacophore-rich, drug-like small molecule library of 7500 compounds was screened against MtPtpB in 384-well plates [36]. Briefly, the initial screen identified 147 hits that showed enzyme inhibition higher than 50% at a concentration of 10 μM. Subsequently, counter screen assays against a panel of ten protein tyrosine phosphatases led to the identification of 40 hits presenting highly selective inhibition of MtPtpB. The structural similarity of the selective hits was assessed, and two distinct structural groups stood out as the most promising MtPtpB inhibitors: (i) the piperazinyl-thiophenyl-ethyloxalamide (8 and 9) derivatives, and (ii) the 2-oxo-1,2-dihydrobenzo-[cd]indole-6-sulfonamide (10) (Fig. 5). Further biochemical evaluation showed that the compounds were either competitive (8 and 9) or non-competitive (10) inhibitors of MtPtpB, with dissociation constants \((K_i)\) in the low micromolar range (Fig. 5). Since the ultimate goal of the work was the discovery promising anti-tuberculosis agents, the inhibitory activity of the growth of *M. tuberculosis* in macrophages was determined. The results indicated that the compounds impaired the ability of mycobacterium to survive within macrophages, causing a significant reduction of the mycobacterial load in infected cells.

It is important to note that the success of HTS strategies in the discovery of high quality leads requires a combination of factors, including: (i) the design of robust secondary assays to validate the hits as active compounds (i.e., true binders capable of interacting with the target in a specific manner), and (ii) the development of consistent ligand- and structure-based *in silico* methods to efficiently generate privileged collections of compounds, avoiding the selection of false positives or compounds with insufficient drug-like characteristics.

### 4. VIRTUAL SCREENING

Drug discovery is currently driven by innovation and knowledge employing a combination of experimental and computational methods. One of the most important challenges for the pharmaceutical industry is the identification of innovative NCEs from an incredibly large reservoir of real and virtual possible compounds [4, 5]. Over the past decade, the high-performance computers, algorithms, methods and expertise have evolved and transformed LBDD and SBDD methods in tools of large impact in modern drug discovery [2, 3]. Currently, there are two main approaches to VS studies: (i) structure-based virtual screening (SBVS), which relies on the knowledge of the 3D structures of target proteins to prioritize compounds by their complementarity to the binding site; and, (ii) ligand-based virtual screening (LBVS), where no information on the protein is needed, instead, compounds known to bind to the protein (or molecules with known biological activity) are used as queries to search databases for new molecules possessing the same biological activity [1, 2]. The general steps employed in VS experiments in order to identify promising hits or leads from large collections of compound are shown in Fig. (6). This is of great value for researchers in small biotechnology companies, academic institutions and other organizations involved in drug discovery, in which hit and lead discovery are not fuelled by HTS.

Although much progress has been made in the generation of representative bioactive conformations by automated sampling procedures, the scoring functions employed for the selection of the most relevant poses are under constant development [3, 37]. Scoring functions implemented in docking programs make different assumptions and simplifications in the evaluation of complexes and do not fully account for a number of physical phenomena that determine the process of molecular recognition, binding affinity and selectivity [38]. For example, ligand-receptor binding events are driven by a combination of enthalpic and entropic effects, where either entropy or enthalpy can dominate specific interactions. In this respect, evolution of sophisticated algorithms along with advanced and specialized computer hardware will enable enhanced description of the molecular phenomena related to ligand binding and affinity (e.g., ligand-induced fit, the role of water molecules in the binding process, determination of the
protonation states, the entropic and enthalpic contributions and compensations upon complex formation, so on), thereby improving the accuracy of future predictions of novel lead candidates.

The importance of integrating computational and experimental techniques toward the discovery of high quality lead compounds. An example can be seen in the integrated medicinal chemistry approach employed toward the discovery of new inhibitors of *Schistosoma mansoni* purine nucleoside phosphorylase (*Sm*PNP), a key enzyme involved in the purine salvage pathway of *S. mansoni*, one of the causative agents of human schistosomiasis. In this work, the development of a structure-based pharmacophore model for VS of ligands of *Sm*PNP allowed the identification of three thioxothiazolidinones derivatives with substantial *in vitro* inhibitory activity against the parasite enzyme. Synthesis, biochemical evaluation and structure-activity relationship (SAR) investigations led to the successful development of a small set of thioxothiazolidinone derivatives harboring a novel chemical scaffold as new reversible and competitive inhibitors of *Sm*PNP with affinity values in the low micromolar range. The high affinity inhibitors (11–13) represent new potential lead compounds for further development for the therapy of schistosomiasis.

The influence of the synergy effects between HTS and VS on the selection of hits and lead compounds is a good example of the integration of advanced technologies in drug discovery programs. Since VS methods were designed for the search of large databases of compounds and selection of a reduced number of candidates for biological evaluation, they can be efficiently merged as complementary tools for enriching HTS libraries with drug- and lead-like molecules, as well as eliminating compounds that have unwanted characteristics for further development. The VS approach also provides opportunities for prospective HTS database analysis, being capable of extracting useful information for database mining. Other applications include, compound-filtering, database-mining, and rapid analysis of large databases subjected to HTS procedures. Finally, these investigations are also valuable for the elucidation of the structural basis underlying molecular recognition, thereby being attractive in lead discovery, drug design and medicinal chemistry.

### 5. FRAGMENT-BASED DRUG DISCOVERY

Fragments are characterized as low molecular weight compounds harboring chemical scaffolds and functionalities
Fragment-based drug discovery (FBDD) approaches rely on the establishment of high-quality interactions between molecular fragments and the corresponding binding site through the incorporation of successive and specific substituents. In this respect, the ligand efficiency (LE) concept is an important metric used to judge whether the fragment optimization procedure has been conducted properly [45]. By definition, LE is the free energy of binding (ΔG) divided by the number of heavy atoms (N) (LE = ΔG/N) [45]. Alternatively, it can be indicated as the ratio between the logarithm of the IC_{50} (pIC_{50}, where IC_{50} refers the concentration of compound required for 50% inhibition of the target enzyme) and the number of heavy atoms (N) in the molecule (LE = pIC_{50}/N) [46], or the ratio between the logarithm of the inhibition constant (pK_{i}) and the molecular weight (MW) of the compound (LE = pK_{i}/MW) [47]. In any case, for the purposes of FBDD, the binding affinity of the modified molecular fragment should be the sum of the individual optimized interactions in the binding site [48]. However, even the most advanced scoring functions currently available are not able to accurately predict the binding affinity of bioactive fragments. Therefore, reliable experimental methods are necessary to assist the development of FBDD approaches [46].

The efficient application of FBDD methods for lead discovery faces two main challenges: (i) the continued development of robust methods to detect bioactive molecular fragments, and (ii) the constant progress of strategies and methods for the optimization of the biological and binding properties of the selected fragments (e.g., lead generation). In order to address these critical issues, structural biology methods, such as X-ray crystallographic and nuclear magnetic resonance (NMR), have been successfully applied [49]. NMR, the first important approach to FBDD, is used to detect the chemical shifts induced by the fragment binding, and subsequently to determine the experimental binding mode of the molecule (Fig. 8). The application of NMR in FBDD has prompted the development of a strategy known as “SAR by NMR” [50], which has been widely employed with a considerable number of successful examples described [51].

High-throughput X-ray crystallography methods are also efficiently applied in FBDD [52]. The approach starts with

![Diagram](image-url)
the screening of libraries composed by hundreds of small fragments partitioned into cocktails. The crystals of the biological target are separately crystallized (e.g., soaked or co-crystallized) with each cocktail, and then the structure is solved, allowing the direct detection of the hit (fragment) bound to the protein through the electron density map. This opens new possibilities for the use of SBDD methods in the process of hit-to-lead optimization. In the early stages, the approaches employed for fragment-based screening generally do not involve crystallographic methods, which become essential in the following steps of hit identification and lead generation, allowing the complementarity between a protein active site and drug-like molecules to be rapidly and effectively explored. Pre-screening methods usually include NMR, surface plasmon resonance (SPR), isothermal titration calorimetry (ITC) and VS (Fig. 8).

Once a promising fragment is identified (i.e., a ligand with macromolar affinity), the process of hit-to-lead optimization focus on the optimization of pharmacodynamic properties (e.g., affinity, selectivity). However, turning a low affinity hit ($K_d > 10 \mu M$) into a high affinity ligand is a challenging task, which requires significant efforts in medicinal chemistry. This process most often entails the enhancement of the molecular weight, lipophilicity, number of hydrogen bonding groups, rings and rotatable bond counts [50]. In addition to the improvements in potency or pharmacodynamic properties, the process must also focus on the optimization of metabolic stability and oral bioavailability of the compounds in order to avoid failures during clinical development due to inadequate pharmacokinetic properties or off-target side effects [53-55].

A relevant example of the power of FBDD towards the identification of high quality leads can be seen in the discovery of inhibitors of the molecular chaperone heat shock protein 90 (Hsp90), an attractive molecular target for the development of anticancer agents [56, 57]. The

![Fig. (8). Key elements in fragment-based drug discovery.](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_d$</th>
<th>LE</th>
<th>Cell IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(14)</td>
<td>$250 \mu M$</td>
<td>0.38</td>
<td>1.9 M</td>
</tr>
<tr>
<td>(15)</td>
<td>$790 \mu M$</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>(16)</td>
<td>$0.0048 \mu M$</td>
<td>0.45</td>
<td>1.9 M</td>
</tr>
<tr>
<td>(17)</td>
<td>$0.00054 \mu M$</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>(18)</td>
<td>$0.00071 \mu M$</td>
<td>0.57</td>
<td>0.048 M</td>
</tr>
</tbody>
</table>

$K_d$ = dissociation constant; LE = Ligand Efficiency = $-\Delta G/N$, where $N$ = number of heavy atoms. Cell IC$_{50}$ = concentration of compound required for 50% growth inhibition of the HCT116 cells.

![Fig. (9). HSP90 inhibitors discovered by FBDD.](image)
development of the approach started with the screening by NMR of a fragment library containing about 1,600 compounds. Subsequently, 125 hits were progressed into high-throughput X-ray crystallography. Out of these, 26 fragment crystal structures were obtained, with the most representative compounds (14 and 15) exhibiting affinity in the high micromolar range (Fig. 9). The use of SBDD methods greatly improved the binding affinity of initial hits, leading to extremely potent ligands (nanomolar and femtomolar $K_i$, 16 and 17, respectively), with good ligand efficiency and in vitro activity (Fig. 9). It is important to emphasize that the hit-to-lead optimization process resulted in an outstanding improvement of the affinity for HSP90 by over a million-fold with the addition of very few heavy atoms. Further lead-to-NCE strategies conducted on (17) dramatically enhanced its pharmaceutical properties, as well as provided the basis for the elucidation of the mechanism of action. The ultimate drug candidate (18) is now under evaluation in clinical trials for the treatment of cancer.

CONCLUSION

In the past decades, there has been a remarkable progress in the development of state-of-the-art drug discovery technologies, with particular emphasis on the processes of hit identification and lead generation and optimization. In line with the significant scientific advances in the area of medicinal chemistry, drug design approaches have become much more versatile and powerful. The integration of experimental and computational methods continues to play a vital role in drug design, creating wonderful opportunities and challenges in several stages of the drug discovery and development process. Although there are many fundamental aspects to be further explored in HTS, combinatorial chemistry, SBDD, LBDD, VS, SAR by NMR, FBDD, and so on, what is clear is that these and other advances will continue to enable and expand the application of these approaches in the discovery of NCEs for a vast variety of target proteins, and it is expected to remain so for the foreseeable future.

REFERENCES


