CHEMBIOCHEM

Target-Family-Oriented Focused Libraries for Kinases—Conceptual Design Aspects and Commercial Availability

Olaf Prien*[a]

Dedicated to Professor Dr. Helmut Vorbrüggen on the occasion of his 75th birthday

Introduction

Parallelization and automation techniques have significantly altered the drug-discovery process over the past few years. Highly sophisticated robotic systems allow screening, processing, and analysis of the generated data sets of a million compounds within several days. Automation in the medicinal chemistry section allows the synthesis of large multipurpose screening libraries or, in turn, may provide mid-sized libraries suitable for elucidating preliminary SAR trends of hits, thus speeding up the lead identification and optimization.

Nevertheless, the screening of compounds is a costly enterprise, and both the availability of sufficient protein quantities and a robust assay amenable for high throughput are prerequisites in conducting the screening of large compound numbers.

Should only a limited amount of protein be available or the assay design allow only a medium throughput, a broad screening approach appears questionable, and the screening of selected compound sets instead seems favorable. Additionally, such compound arrays can be used for rapid chemical-target validation or general drugability assessments.

The human kinome comprises a minimum of 518 different kinases.[1] Undoubtedly, the kinase protein family comprises a rich source of validated targets, such as bcr-abl, EGFR, or VEGF. These enzymes play fundamental roles in many biochemical pathways, such as cell differentiation, cell-cycle control, and apoptosis. All such mechanisms are tightly regulated and entail a well-functioning and balanced counterplay of all biochemical switches involved. Up- or down-regulation of individual kinases due to malfunction may result in the onset of cancer or other diseases, for example, diabetes or inflammation.

However, the presence of closely related but distinct targets requires some alterations of common library-design approaches, especially in view of employing virtual descriptors and generalizing target criteria. This effort implies more than just collecting compounds derived from various structural classes.

In the meantime, several companies have commercialized their focused libraries of tentative kinase inhibitors. Whereas several of these focus primarily on the established set of kinase-related scaffolds, others claim to address this matter through the design of novel scaffolds.

This article will summarize conceptual approaches toward the design and the synthesis of focused libraries specifically generated to inhibit kinases, and will reflect some more recent commercial activities in this field. In general, approaches for library design are driven either by structural or by descriptor properties. In the recent past, promising approaches to designing target-family-oriented libraries have surfaced for both areas.

Conceptual Design of Target-Oriented Libraries

All kinases function through the binding of ATP, transferring a phosphate group onto a hydroxyl group. In view of the fact that the conserved ATP sites bear a high degree of similarity, the identification and synthesis of a selective, potent, and safe ATP-competitive small-molecule kinase inhibitors was regarded a challenge and has been discussed controversially in the scientific community over the past years.[2] Nevertheless, this area has been pioneered by the success story of Gleevec.[3] Several other small molecules are due to follow, for example, Iressa,[4] Fasudile,[5] CYC202,[6] BAY 43–9006,[7] and PTK787/ZK222584 (Scheme 1).[8]

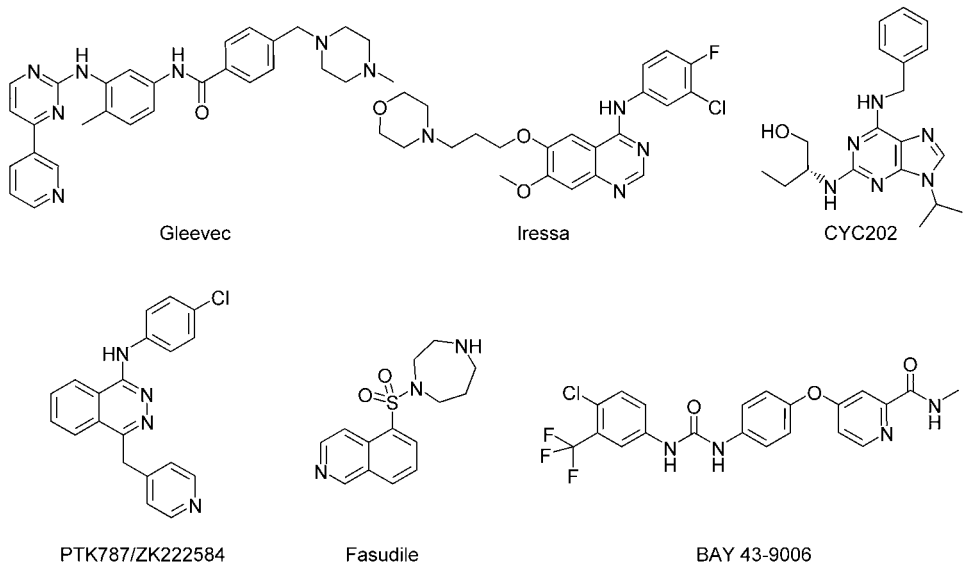
By definition[9] focused (also directed or biased) libraries comprise a limited number of building blocks, chosen on the basis of pre-existing information, to validate any hypothesis or to prove a particular activity.

Recent reviews[10,11] have analyzed the application of computational methods for the design of small-molecule kinase inhibitors. Whereas a lot of information is available on the design of focused libraries for individual targets and structures, very little is published[12] about the more generic product-oriented design of libraries for whole target families or subfamilies thereof, for example, cdk's.[13]

Kimmich and Park[14] have nicely summarized the most recent efforts in the field of compound-library synthesis of tentative kinase inhibitors. Besides peptide and natural-product li-

[a] *Dr. O. Prien*
Medicinal Chemistry, Research Center Europe, Schering AG
13342 Berlin (Germany)
Fax: (+49) 30-468-97039
E-mail: olaf.prien@schering.de

  DOI: 10.1002/cbic.200400117



Scheme 1. *Chemical structures of some small-molecule kinase inhibitors that have been marketed or are undergoing clinical trials.*

braries, most of their referenced examples deal with the generation of small libraries around individual validated hits rather than the conceptual design of addressing the entire target family.

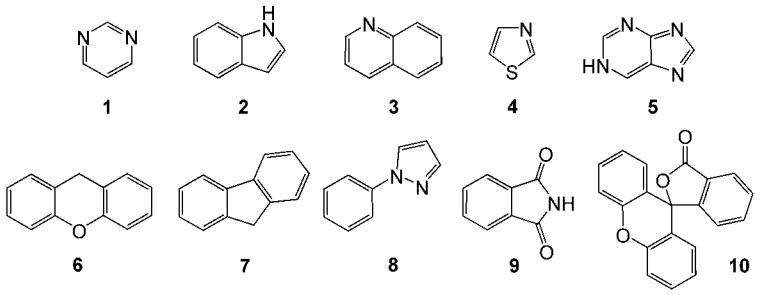
Monoselectivity for ATP-competitive kinase inhibitors[15] appears equivocal in view of the 518 distinct kinases already identified.[16] Dual selectivity or multiplex specificity[17] in the kinase sector is more probable, and library design for whole target classes or subfamilies becomes more noticeable. Such libraries are deliberately tailored to address multiple targets within a given subfamily and therefore may serve as a precious source for rapid chemical-target validation, to gain selectivity data for specific scaffolds or to provide valuable SAR directions on which other processes, for example, a hit-to-lead-process, may follow up.

In 1999, Bajorath et al. outlined a molecular scaffold-based design concept for combinatorial libraries focused on inhibitor binding at the ATP site of protein kinases.[18] Here for the very first time, to the best of our knowledge, a detailed docking-based approach was published that combined an initial docking experiment into the ATP pocket, which serves to identify suitable molecular scaffolds, with the design of target-family-oriented libraries around these scaffolds for the kinase superfamily.

A total of 75 scaffolds bearing tentative binding properties toward the ATP-binding pocket in kinases were identified either by docking calculation or by comparison of known inhibitors.

Subsequently, three different libraries were computed by applying different strategies, and the scaffold distribution within these collections was analyzed. Here it turned out that very few scaffolds form the basis of a lot of the compounds (Scheme 2). Though the result varies from library to library, a few scaffolds occur with high frequency. Furthermore, a small number of scaffolds dominate the majority of compounds in each library.

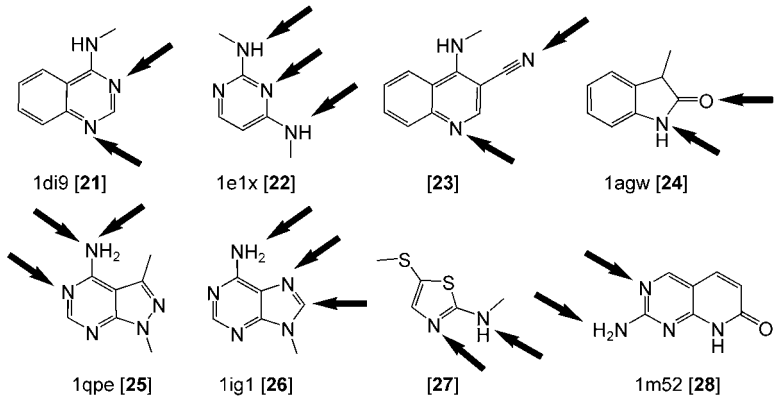
Recently, Müller presented the structure-driven concept of target-family-directed master keys; this reflects another view of library design around matured structural features.[19] The author exemplified this pharmacophore-based concept for the 2-aryl-indole scaffold, which shows a preferred affinity for the GPCR family, and also mentioned the 5,5-*trans*-fused lactam moiety as a serine protease-directed scaffold. Furthermore, several structural motifs, for example, 2-aminothiazole, do not reveal any correlation to a specific target family, but show general pharmaceutical potential and may therefore also be regarded as privileged structures.



Scheme 2. *Structures of the 10 most frequently occurring scaffolds. Scaffolds* ***1***, ***3***, *and* ***6*** *account for a total of 29% of all entities in all three computed libraries.*[18]

Though no kinase specific master keys are explicitly mentioned in this account, the underlying idea of this concept can also be transferred to the kinase family. The hinge region in the ATP site of kinases allows the formation of at least three hydrogen bonds. Nearly all inhibitors bind at the hinge region, and the formation of at least one hydrogen bond appears to be crucial. X-ray analyses reveal that the majority of inhibitors form two or even all three hydrogen bonds. Scheme 3 shows some prominent kinase-family-related core structures. The arrows indicate attachment points for the formation of hydrogen bonds with the hinge region, as suggested by X-ray analysis or modeling experiments for individual class representatives. The available pdb codes are also listed.[20]

In the past, only a few novel ATP-mimetic cores have emerged in kinase-inhibitor programs in industry, and their use is effectively and competitively shared by many companies. In the kinase-inhibitor sector, among others, the aminopyrimidine core has emerged as a privileged structure that many compa-



Scheme 3. *Potential kinase family-related core structures; the arrows indicate hydrogen bond interactions with the protein's hinge region.*

nies have focused on for at least two reasons. First, this scaffold is highly amenable to parallel synthesis, allowing facile and broad decoration on various scaffold positions, and, second, depending on the substitution pattern, the core structure allows the formation of several hydrogen bonds to the protein hinge region.[22] Consequently, this significant interest is reflected in the dramatic increase in kinase-related pyrimidine patent applications over the past few years tightening the freedom to operate in this particular class.

Numerous other prominent scaffolds with tentative kinase-inhibitory potential have been compiled in several recent reviews.[29]

Focusing on privileged structures also has potential shortcomings you could refer to as the *Casablanca effect*: going every night into the same bar, meeting the same people, or in other words: screening the same set of compounds over and over again against related targets results in identifying the same scaffold classes again and again without coming up with something really new. Hence, the ratio of privileged structures in the library must not be overweighed.

Currently, the Institute of Cancer Research, University of London (UK) offers more practical insights for designing and synthesizing focused libraries for kinases around specific leads to their students.[30]

Target-Specific Aspects of Ligand and Protein Space

Based on the Burden Chemical Abstract Service University of Texas (BCUT) concept for the description of molecular structures, the identification of a so-called "receptor-relevant subspace"[31] offers another opportunity to reduce the number of compounds relevant for exploring inhibition within a target family of interest.

This concept was described by Pearlman and Smith,[31] who reported a novel approach for an activity-seeded, structure-based clustering of compounds, for which experimental IC_{50} values against the target of interest are available, in a multidimensional descriptor space, named "chemspace". The positional relationship of structures, each encoded through their BCUT values, is analyzed to identify a reduced set of BCUT metrics that best cluster compounds with similar affinity for the given target. The authors exemplified the successful application of this method to the identification of ACE inhibitors in a very limited subset of compounds from the Modern Drug Data Report database,[32] which nicely clustered along a relevant metric axis.

The practical application of the BCUT concept described above was successfully conducted for ATP-site-directed kinase inhibitors by Pirard and Pickett[33] in 2000. BCUTs were computed for 770 entities active against five different kinases and combined with a partial least-squares discrimination analysis. This procedure allowed the correct classification of ligands with respect to their target. Moreover, the applied method was compared with the performance of other computational descriptors, for example, Daylight 2D fingerprints or multipharmacophore models, regarding their ability to distinguish between the various structural classes of ligands and ligand binding to different kinase subfamilies. Though somewhat successful, their evaluation also revealed certain shortcomings. In combination with a partial least-squares discrimination analysis BCUTs provide the opportunity to distinguish between ligands of related proteins, but interpretation of results has to be done carefully and strongly depends on the chosen descriptor set. The authors consider compound analysis by easily calculated BCUT parameter as a valid alternative. However, the more computationally intense three- to four-point pharmacophore-type descriptors have shown better predictivity for the classification of unknown compounds.

Nevertheless, BCUT analysis may also be regarded a versatile tool to access the degree of redundancy and overlap between libraries. Though, it should be remembered that neighboring BCUT values in the chemspace do not necessarily indicate redundant molecules but could also indicate compounds derived from different scaffolds with diametrically opposed pharmacodynamic properties.

Besides mapping the ligand space, analyzing the protein space also provides valuable clues for the development of tentative binders. Moreover, valuable trends for selectivity can be extracted therefrom.

The utility of a structural classification of protein kinases by so called "target-family landscapes"[34] has been exemplified by a study of Naumann and Matter.[35] They analyzed the ATP-binding-site structure of 26 different kinases, describing their protein–ligand interaction features by GRID[36] molecular interaction fields. The interaction energies derived for different probes were subjected to a chemometric analysis that yielded the target-family landscapes as principal component analysis (PCA) score plots as well as 3D contour plots for every probe and every principal component. These contour plots were shown to facilitate the design of selective ligands, since they point to structural differences between kinase subfamilies separated by a given principal component.

Narrowing the library-design process to some "hot" spots within the virtual descriptor space surely would speed up the

selection and synthesis process, but diversity and novelty issues have to be carefully considered. Whilst the inhibitor search is focused onto such islands of interest, new potential scaffold classes lying offside are liable to be overlooked. Hence, the odds of identifying some inhibitor in a completely new scaffold class will be decreased dramatically.

Nevertheless, the multitude of approaches and concepts has been validated and will therefore yield valuable directions, if proper data points are provided. However, information derived from biological and chemistry space have to be matched precisely in order to maximize the desired outcome.

Targeted Libraries from Commercial Sources

The majority of screening-compound vendors currently offer kinase-targeted libraries off the shelf. Several vendors display structural features within their flyers and homepages. All companies approached by us so far were readily open to discuss structural details and design concepts under confidentiality agreement in case of further interest. Many companies claim their scaffolds to be novel, and compounds derived thereof may be patentable. Nevertheless, this needs to be checked for each case individually.

On the internet Bioscreening.com[37] displays a table of such companies offering compound collections for specific target families referred to as: "that may have a higher probability of interacting with potential drug targets". Among libraries for other target families, several vendors are also offering libraries specifically made for kinase inhibition.

Besides this orienting overview, a detailed media-search gave access to additional sources for commercial libraries of this type. Detailed information about quality and content of the offered libraries were gathered from vendor homepages, flyers, and personal contacts.

Table 1 summarizes the current status of commercially available focused libraries of tentative kinase inhibitors. In many cases, such libraries do not remain static but are being updated, expanded an/or refined constantly. Therefore, this overview can only provide a snapshot of the current environment.

Looking at individual vendors of such inhibitor libraries in greater detail reveals significant differences in rationale, design approach, and library size. Moreover, several suppliers offer special services to synthesize libraries tailored to the customer's demands, lead follow-up services on initial hits from their libraries, and say they are flexible with respect to compound formatting and handling. Other companies, such as Synergix Ltd.[38] or Scynexis[39] offer the exclusive synthesis of focused libraries on demand. Due to this exclusivity, their service and quality of the approach will not be considered in this context.

The SoftFocus kinase-targeted library is marketed by BioFocus.[40] The company started offering target-specific libraries in 1999. This library currently comprises some 14 sublibraries (SFK01 to SFK33), some of which are claimed to be designed against specific subfamilies, for example, p38 MAP kinases or the cdk2/4 family, or target a broader range of kinases, for example, SFK02, which was designed to inhibit predominantly tyrosine kinases (ZAP, PGDF, EGF, Ick, abl). The entire collection encompasses 20 scaffolds with some 1000 to 1500 individual entities, each. The cornerstones of their design concept are protected through patents[41] outlining some aspects of how to generate focused libraries for entire target families. BioFocus collaborate with Prof. Sir Philip Cohen from the University of Dundee.

Initially, ChemDiv[42] started their focused-library program for kinases in 2001. The current library contains approximately 20000 entities split into about 600 sublibraries. The size is somewhat static but the content is said to be updated constantly.

Currently, some 1500 kinase ligands taken from publications and drug indexes have been analyzed by Kohonen maps.[43] Information derived therefrom has been used to develop bioisosteric and pharmacophore clustering rules that, together with 2D and 3D similarity, have been applied to generating novel scaffolds. While moving on in the design process, other aspects, for example, synthetic accessibility and estimated pharmacokinetic properties, are also taken into consideration.

TimTec[44] advertise their ActiMol compound collection, which has been available since autumn 2002. It is claimed that the entire set of ActiMol compound collections have undergone rigorous structural fragment filtration and diversity selection. The ActiTarg-K collection, in particular, comprises 960 preplated compounds and represents a diverse selection from some 4000 individual entities. The collection is based on established scaffolds referenced in the scientific and patent literature for their kinase-inhibitory properties, modified, for example, by embedding into polycyclic structures or annulated ring systems. Prices and available compound amounts of this library are mentioned on their internet page.[44]

More recently, in 2003, ChemOvation introduced their Kinase Enterprise Library,[45] which is available on a nonexclusive basis. This collection is currently marketed in collaboration with

Table 1. *Current status and availability of commercial libraries with tentative kinase inhibitor properties.*

Company	Current approximate library size	Structural information available	Internet Link
AdvancedSynTech	n.a.	[e]	[55]
Asinex	5000	[a], [d]	[46]
BioFocus	16000	[f]	[40]
ChemDiv	20000	[f]	[42]
ChemOvation	1000	[b]	[45]
Enamine	31000	[a]	[48]
IF Lab	13000	[a]	[53]
InterBioScreen	flexible, on customer's demand	[c]	[47]
Pharmacopeia	[f]	[f]	[54]
ChemBridge	[f]	[f]	[51]
Specs	flexible, on customer's demand	[e]	[50]
TimTec	4000	[c]	[44]

[a] Download of full data set as .db file after internet log-in. [b] Full data set provided upon request. [c] Partial data set provided upon request. [d] Additional data (log *P*, docking scores, etc.) provided. [e] No information available upon request. [f] Data available under the conditions of a secrecy agreement.

LeadDiscovery. Library design includes analysis of ADME properties and Lipinski's rules, as well as virtual docking studies and diversity analysis by using Tanimoto fingerprints.

The physically available library has been built up from some 20 different scaffolds featuring selected key pharmacophores, mainly pyridopyrimidines, quinazolines, and other heterocyclic core structures. Each scaffold is represented by approximately 125–150 derivatives. The current size of some 800 derivatives is expected to grow to a total of nearly 3000 chemical entities shortly. A maximum of 15 mg per compound will be available.

The Asinex[46] library comprises about 5000 compounds thought to be active against 11 different kinase targets. These entities were designed through the proprietary P3S technology by applying rigorous in silico filtering criteria. This library-design approach is outlined in greater detail on the Asinex homepage[46] and can be analyzed there. All compounds are provided with additional docking scores as well as physicochemical parameters. A detailed pricing list is available upon request, and up to 100 mg per individual compound may be available.

InterBioscreen[47] pursue a somewhat different approach. They offer to screen their compound collection of approximately 350 000 entities according to each individual customer request. The computational methods applied are claimed to have been validated against a reference data base of known inhibitors; details of this concept are outlined on the internet.[33] Upon a customer's request on library size and potential target or subfamily of interest, InterBioscreen will propose a collection of tentative inhibitors. Due to the dynamic nature of every compound collection, it is likely that each request by this approach will yield different results.

Enamine[48] have entered the field of targeted libraries in collaboration with the ChemBio Center of the Kiev National University. Their kinase library currently addresses 15 different targets and comprises of about 31 000 compounds. Enamine apply various filters to the design of compounds, mainly on the basis of 2D and 3D molecular information. Some aspects of their approach are outlined on the internet.[49]

The Specs[50] approach for the generation of target-oriented libraries is different again. Since late 1999 they have employed a predictive algorithm for biological activity to "fish" promising compounds from their stock collection of 230 000 entities. This algorithm calculates compound-specific descriptors, which are then compared with descriptors computed for reference compounds with proven activity against the given target. This information for a large and diverse training set was collected from the literature. The threshold for the predicted activity will be set by the customer. Currently, the Specs collection comprises approximately 400 entities with a high predicted activity (>0.7) against a set of five different kinases.

In 2001 ChemBridge[51] introduced a targeted library to be screened against kinases. Prior to compound synthesis, the interaction characteristics of some target-related proteins and their referenced ligands were analyzed, and the computed ligand descriptors were entered into a database. Different descriptor combinations were then used to identify novel, target-biased entities.

At the beginning of 2004, IF Lab[52] launched their kinase-inhibitor library, which comprises 13 000 entities. These compounds resulted from virtual screening against a set of kinases; constraint filter criteria, for example, molecular weight below 500, less than seven rotatable bonds and less than five hydrogen donors or acceptors were applied thereafter. The top-scoring entities were evaluated against the general kinase-inhibitor pharmacophore model published by Novartis colleagues recently.[11] The content of this library can be downloaded[53] directly in a .db or .sdf file format, and the compounds are physically available in larger quantities upon request.

Pharmacopeia[54] are advertising a compound collection biased against disease-related targets in the kinase family. Advanced SynTech[55] are also offering a protein-kinase-targeted library; in both cases no additional information was available upon request.

Evidently, the majority of vendors rely on the use of computational methods to identify tentative binders. Such tools are employed to filter existing compound collections or to design novel compounds, either by employing multidimensional pharmacophore models or derived from privileged fragments. In summary, the conceptual diversity of the different vendors adequately mirrors the plethora of design concepts discussed and established in the literature.

Current Practical Approaches and Examples

In 2002 Aventis disclosed some design aspects of their in-house collection of tentative kinase inhibitors.[56] The theoretical framework of their concept relies on capturing public and proprietary information for both biological and chemical space. Subsequently, computational tools are employed to calculate the corresponding descriptors. Finally, information from the biological targets and the chemical structures and their properties are matched; this results in a knowledge-driven biased library design.

By applying this model to cherry-pick compounds from their in-house compound collection, Aventis reported an approximately tenfold increased hit rate in a particular kinase assay.

Conclusion

Nowadays numerous commercial vendors are offering collections of tentative small-molecule kinase inhibitors. Their approaches to designing and synthesizing such libraries are rather diverse.

Nevertheless, each subset selection claims the opportunity to increase the initial hit rate in kinase assays.

The design and establishment of a focused library of tentative small-molecule kinase inhibitors, itself serving as a precious hit source, remains a moving target in modern library design. Besides kinase-inhibitory activity, selectivity criteria within and between subfamilies, as well as accurate physicochemical parameters and reduced toxicity, make this a multidisciplinary challenge.

The rationale of designing focused libraries for target families has matured during the past few years. Despite individual

strength, none of the described methods (BCUT, 2D and 3D fingerprints, three-point pharmacophore models, etc.) will succeed solely in identifying promising compounds from large libraries. Thus, a reasonable combination of several methods together with solid medicinal-chemistry expertise will enhance the probability of identifying relevant compounds.

Moreover, from an intellectual property perspective, the de novo design of scaffolds and proprietary compounds derived therefrom deserves more attention. Drug-design tools and well-elaborated algorithms have matured in the past, providing a valuable tool box for chemists supporting a design and selection process fostered by medicinal chemist's experience and intuition.

Acknowledgements

The author would like to thank Heidrun Dorsch from the Office of Technology at Schering for providing useful information on commercial libraries. Stimulating discussions with Judith Günther, Michael Grimm, and Hans Briem from computational chemistry and numerous colleagues from MedChem are also gratefully acknowledged.

Keywords: drug design · focused library · inhibitors · kinases · molecular modeling

[1] G. Manning, D. B. Whyte, R. Martinez, T. Hunter, S. Sundarsanam, *Science* **2002**, *298*, 1912 – 1934.
[2] C. L. Sawyers, *Genes Dev.* **2003**, *17*, 2998 – 3010.
[3] S. G. O'Brien, F. Guilhot, R. A. Larson, I. Gathmann, M. Baccarani, F. Cervantes, J. J. Cornelissen, T. Fischer, A. Hochhaus. T. Hughes, K. Lechner, J. L. Nielsen, P. Rousselot, J. Reiffers, G. Saglio, J. Shepherd, B. Simonsson, A. Gratwohl, J. M. Goldman, H. Kantarjian, K. Taylor, G. Verhoef, A. E. Bolton, R. Capdeville, B. J. Druker, *N. Engl. J. Med.* **2003**, *348*, 1048 – 1050.
[4] J. S. Ochs, *Int. J. Radiat. Oncol. Biol. Phys.* **2004**, *58*, 941 – 949.
[5] T. Asano, I. Ikegaki, S. Satoh, M. Seto, Y. Sasaki, *Cardiovasc. Drug Rev.* **1998**, *16*, 76 – 78.
[6] S. R. Whittaker, M. I. Walton, M. D. Garrett, P. Workman, *Cancer Res.* **2004**, *64*, 262 – 272.
[7] L. A. Sorbera, J. Castañer, J. Bozzo, P. A. Leeson, *Drugs Future* **2002**, *27*, 1141 – 1147.
[8] J. Drevs, M. Medinger, C. Schmidt-Gersbach, R. Weber, C. Unger, *Curr. Drug Targets* **2003**, *4*, 113 – 121.
[9] D. Maclean, J. J. Baldwin, V. T. Ivanov, Y. Kato, A. Shaw, P. Schneider, E. M. Gordon, *Pure Appl. Chem.* **1999**, *71*, 2349 – 2365.
[10] J. R. Woolfrey, G. S. Weston, *Curr. Pharm. Des.* **2002**, *8*, 1527 – 1545.
[11] P. Traxler, P. Furet, *Pharmacol. Ther.* **1999**, *82*, 195 – 206.
[12] T. Honma, K. Hayashi, T. Aoyama, N. Hashimoto, T. Machida, K. Fukasawa, T. Iwama, C. Ikeura, M. Ikuta, I. Suzuki-Takahashi, Y. Iwasawa, T. Hayama, S. Nishimura, H. Morishima, *J. Med. Chem.* **2001**, *44*, 4615 – 4627.
[13] I. R. Hardcastle, B. T. Golding, R. J. Griffin, *Annu. Rev. Pharmacol. Toxicol.* **2002**, *42*, 325 – 348.
[14] R. D. A. Kimmich, W. K.-C. Park, *Comb. Chem. High Throughput Screening* **2003**, *6*, 661 – 672.
[15] S. P. Davies, H. Reddy, M. Caivano, P. Cohen, *Biochem. J.* **2000**, *351*, 95 – 105.
[16] G. Manning, D. B. Whyte, R. Martinez, T. Hunter, S. Sundarsanam, *Science* **2002**, *298*, 1912 – 1934.
[17] J. Adams, P. Huang, D. Patrick, *Curr. Opin. Chem. Biol.* **2002**, *6*, 486 – 492.
[18] F. L. Stahura, L. Xue, J. W. Godden, J. Bajorath, *J. Mol. Graphics Modell.* **1999**, *17*, 1 – 9.
[19] G. Mueller, *Drug Discovery Today* **2003**, *8*, 681 – 691.
[20] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, P. E. Bourne, *Nucleic Acids Res.* **2000**, *28*, 235 – 242.
[21] L. Shewchuk, A. Hassell, B. Wisely, W. Rocque, W. Holmes, J. Veal, L. F. Kuyper, *J. Med. Chem.* **2000**, *43*, 133 – 139.
[22] C. E. Arris, F. T. Boyle, A. H. Calvert, N. J. Curtin, J. A. Endicott, E. F. Garman, A. E. Gibson, B. T. Golding, S. Grant, R. J. Griffin, P. Jewsbury, L. N. Johnson, A. M. Lawrie, D. R. Newell, M. E. M. Noble, E. A. Sausville, R. Schultz, W. Yu, *J. Med. Chem.* **2000**, *43*, 2797 – 2804.
[23] A. Wissner, D. M. Berger, D. H. Boschelli, M. B. Floyd, L. M. Greenberger, B. C. Gruber, B. D. Johnson, N. Mamuya, R. Nilakantan, M. F. Reich, R. Shen, H.-R. Tsou, E. Upesacis, Y. F. Wang, B. Wu, F. Ye, N. Zhang, *J. Med. Chem.* **2000**, *43*, 3244 – 3256.
[24] M. Mohammadi, G. McMahon, L. Sun, P. C. Tang, P. Hirth, B. K. Yeh, S. R. Hubbard, J. Schlessinger, *Science* **1997**, *276*, 955 – 960.
[25] X. Zhu, J. L. Kim, J. R. Newcomb, P. E. Rose, *Structure* **1999**, *7*, 651 – 661.
[26] N. S. Gray, L. Wodicka, A.-M. W. H. Thunnissen, T. C. Norman, S. Kwon, F. H. Espinoza, D. O. Morgan, G. Barnes, S. LeClerc, L. Meijer, S.-H. Kim, D. J. Lockart, P. G. Schultz, *Science* **1998**, *281*, 533 – 538.
[27] K. S. Kim, S. D. Kimball, R. N. Misra, D. B. Rawlins, J. T. Hunt, H.-Y. Xiao, S. Lu, L. Qian, W. C. Han, W. Shan, T. Mitt, Z.-W. Cai, M. A. Poss, H. Zhu, J. S. Sack, J. S. Tokarski, C. Y. Chang, N. Pavletich, A. Kamath, W. G. Humphreys, P. Marathe, I. Bursuker, K. A. Kellar, U. Roongta, R. Batorsky, J. G. Mulheron, D. Bol, C. R. Fairchild, F. Y. Lee, K. R. Webster, *J. Med. Chem.* **2002**, *45*, 3905 – 3927.
[28] M. Barvian, D. H. Boschelli, J. Cossrow, E. Dobrusin, A. Fattaey, A. Fritsch, D. Fry, P. Harvey, P. Keller, M. Garrett, F. La, W. Leopold, D. McNamara, M. Quin, S. Trumpp-Kallmeyer, P. Toogood, Z. Wu, E. Zhang, *J. Med. Chem.* **2000**, *43*, 4606 – 4616.
[29] A. Levitzki, A. Gazit, *Science* **1995**, *267*, 1782 – 1788; T. L. Underiner, B. Ruggeri, D. E. Gingrich, *Curr. Med. Chem.* **2004**, *11*, 731 – 745; A. Huwe, R. Mazitschek, A. Giannis, *Angew. Chem.* **2003**, *115*, 2170 – 2187; *Angew. Chem. Int. Ed.* **2003**, *42*, 2122 – 2138; .
[30] http://www.icr.ac.uk/education/studentships/collins.html
[31] R. S. Pearlman, K. M. Smith, *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 28 – 35.
[32] Modern Drug Data Report database is distributed by MDL Information Systems, San Leandro, CA (USA).
[33] B. Pirard, S. D. Pickett, *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1431 – 1440.
[34] M. A. Kastenholz, M. Pastor, G. Cruciani, E. E. J. Haaksma, T. Fox, *J. Med. Chem.* **2000**, *43*, 3033 – 3044.
[35] T. Naumann, H. Matter, *J. Med. Chem.* **2002**, *45*, 2366 – 2378.
[36] P. J. Goodford, *J. Med. Chem.* **1985**, *28*, 849 – 857.
[37] http://www.bioscreening.com/targeted_libraries.htm
[38] http://www.drugdesign.com/services.html
[39] http://www.scynexis.com/
[40] http://www.biofocus.com/pages/prod__kinase__target__alli.mhtml
[41] WO2003004147(A2), WO9926901.
[42] http://www.chemdiv.com/discovery/libraries1.phtml
[43] T. Kohonen, *Self-Organizing Maps*, 2nd ed, Springer, Berlin, **1997**.
[44] http://www.timtec.net/products/actimol.htm
[45] http://www.leaddiscovery.co.uk/reports/Kinase-inhibitors.html
[46] http://www.asinex.com/prod/targ.html
[47] http://www.ibscreen.com/highhit.shtml
[48] http://www.enamine.relc.com/en/targeted.html
[49] http://www.enamine.relc.com/en/tlgen2.html
[50] http://www.specs.net
[51] http://www.chembridge.com/chembridge/combinatorial_libraries.html
[52] http://www.iflab.kiev.ua/eng/about/news/215/
[53] http://www.iflab.kiev.ua/eng/downloads/149/
[54] http://www.pharmacopeia.com/dcs/libs.html
[55] http://www.advsyntech.com/focused.htm
[56] http://www.beilstein-institut.de/; abstract and proceedings from a referenced presentation, held in May 2002 in Bozen (Italy), can be accessed through the event archive; http://www.beilstein-institut.de/bozen2002/proceedings/baringhaus/baringhaus.html

Received: April 22, 2004

