1

THE ROLE OF MEDICINAL CHEMISTRY IN DRUG DISCOVERY

John A. Lowe, III

1.1 INTRODUCTION

This volume represents the efforts of the many chemists whose ability to master both synthetic and medicinal chemistry enabled them to discover a new drug. Medicinal chemistry, like synthetic chemistry, comprises both art and science. It requires a comprehensive mind to collect and synthesize mountains of data, chemical and biological. It requires the instinct to select the right direction to pursue, and the intellect to plan and execute the strategy that leads to the desired compound. Most of all, it requires a balance of creativity and perseverance in the face of overwhelming odds to reach the goal that very few achieve—a successfully marketed drug.

The tools of medicinal chemistry have changed dramatically over the past few decades, and continue to change today. Most medicinal chemists learn how to use these tools by trial and error once they enter the pharmaceutical industry, a process that can take many years. Medicinal chemists continue to redefine their role in the drug discovery process, as the industry struggles to find a successful paradigm to fulfill the high expectations for delivering new drugs. But it is clear that however this new paradigm works out, synthetic and medicinal chemistry will continue to play a crucial role. As the chapters in this volume make clear, drugs must be successfully synthesized as the first step in their discovery. Medicinal chemistry consists of designing and synthesizing new compounds, followed by evaluation of biological testing results and generation of a new hypothesis as the basis for further compound design and synthesis. This chapter will discuss the role of both synthetic and medicinal chemistry in the drug discovery process in preparation for the chapters that follow on the syntheses of marketed drugs.

The Art of Drug Synthesis. Edited by Douglas S. Johnson and Jie Jack Li

1.2 HURDLES IN THE DRUG DISCOVERY PROCESS

Although the tools of medicinal chemistry may have improved considerably (as discussed below), the hurdles to discovering a new drug have outpaced this improvement, accounting to a certain extent for the dearth of newly marketed drugs. Discussion of some of these hurdles, such as external pressures brought on by the public media and the stock market, lies outside the scope of this review. Instead, we will discuss those aspects of drug discovery under the control of the scientists involved.

One of the first challenges for the medicinal chemist assigned to a new project is to read the biology literature pertaining to its rationale. Interacting with biology colleagues and understanding the results from biological assays are critical to developing new hypotheses and program directions. Given the increasing complexity of current biological assays, more information is available, but incorporating it into chemistry planning requires more extensive biological understanding. This complexity applies to both the primary in vitro assay for the biological target thought to be linked to clinical efficacy, as well as selectivity assays for undesired off-target in vitro activities. Some of the same considerations apply to the increasingly sophisticated assays for other aspects of drug discovery, such as ADME (absorption, distribution, metabolism, and elimination) and safety, as summarized in Table 1.1.

The reader is referred to an excellent overview of the biology behind these assays, and their deployment in a typical drug discovery program (Lin et al., 2003). The tools for addressing each of these hurdles fall into two categories, in silico modeling and structure-based drug design, which are covered in Sections 1.3.1 and 1.3.2. Obviously, the final hurdle is in vivo efficacy and safety data, which generally determine a compound's suitability for advancement to clinical evaluation.

TABLE 1.1. Important Considerations for the Medicinal Chemists

In Vitro Target	In Vitro ADME[a]	Physical Properties	In Vivo	Safety
Primary assay	Microsomal stability (rat, human)	Rule-of-Five	Functional	Ames test
Whole cell assay	Hepatocyte stability (rat, human)	In silico ADME[a] (see Section 1.3.1)	Behavioral animal models (efficacy)	Micronucleus test
Functional assay	P450 substrate	Solubility	PK/PD[c]	HERG[d] IC_{50}
Selectivity assays	P450 inhibitor	Crystallinity (mp, stable polymorph)		P450 induction
	Permeability			Broad ligand screening
	Transporter efflux (e.g., P-gp[b])			Others (depending on project)
	Protein binding			

[a]Absorption, distribution, metabolism, and elimination; [b]P-glycoprotein; [c]Pharmacokinetics/pharmacodynamics; [d]Concentration for 50% inhibition of the function of the delayed rectifier K^+ channel encoded by the *human ether a-go-go related-gene* (HERG).

1.3 THE TOOLS OF MEDICINAL CHEMISTRY

1.3.1 In Silico Modeling

To overcome the many hurdles to discovering a new drug, medicinal chemists must focus on synthesizing compounds with drug-like properties. One of the first tools developed to help chemists design more drug-like molecules takes advantage of an area totally under the chemist's control—the physical properties of the compounds being designed. These are the rules developed by Chris Lipinski, sometimes referred to as the "Rule-of-Five" (Ro5), which describe the attributes drug-like molecules generally possess that chemists should try to emulate (Lipinski et al., 2001). The Ro5 states that drug-like molecules tend to exhibit four important properties, each related to the number 5 (molecular weight <500; cLogP, a measure of lipophilicity,<5; H-bond donors <5; and H-bond acceptors <10). The Ro5 can be applied all the way from library design in the earliest stages of drug discovery to the final fine-tuning process that leads to the compound selected for development. Correlating microsomal instability and/or absorption/efflux with Ro5 properties can also provide insight about the property most important for gaining improvement in these areas.

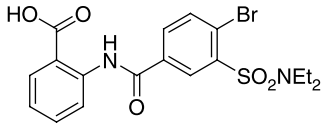
As is the case with any good model, the Ro5 is based on data, in this case from hundreds of marketed drugs. Using more specific data, models to address each of the hurdles in the drug discovery process have been developed (for comprehensive reviews, see Beresford et al., 2004; van de Waterbeemd and Gifford, 2003; Winkler, 2004). These include models of solubility (Cheng and Merz, 2003; Hou et al., 2004; Liu and So, 2001), absorption/permeability (Bergstroem, 2005; Stenberg et al., 2002), oral bioavailability (Stoner et al., 2004), brain penetration (Abbott, 2004; Clark, 2003) and P450 interaction (de Graaf et al., 2005). More recently, the solution of X-ray crystal structures of the P450 enzymes 3A4 (Tickle et al., 2005) and 2D6 (Rowland et al., 2006) should enable application of structure-based drug design (see below) to help minimize interactions with these metabolic enzymes. Models for safety issues, such as genotoxicity (Snyder et al., 2004) and HERG (*human ether a-go-go related-gene*) interaction (which can lead to cardiovascular side effects due to QT prolongation) (Aronov, 2005; Vaz and Rampe, 2005) are also being developed. Although this profusion of in silico models offers considerable potential for overcoming hurdles in the drug discovery process, the models are only as good as the data used to build them, and often the best models are those built for a single project using data from only the compounds prepared for that specific project.

The models described above can be used, alone or in combination with structure-based drug design (see Section 1.3.2), to screen real or virtual libraries of compounds as an integral part of the design process. These improvements in library design, coupled with more efficient library synthesis and screening, provide value in both time and cost savings. The move towards using this library technology has been accelerated by the availability of a new resource for library generation: outsourcing (Goodnow, 2001). Contract research organizations (CROs) in the United States or offshore provide numerous synthetic services such as synthesis of literature standards, templates and monomers for library preparation, and synthesis of libraries (D'Ambra, 2003). These capabilities can relieve in-house medicinal chemists of much of the routine synthetic chemistry so they can focus on design and synthesis to enable new structure-activity relationships (SAR) directions. For an overview of the process as it fits together for the successful discovery of new drugs, see Lombardino and Lowe, 2004.

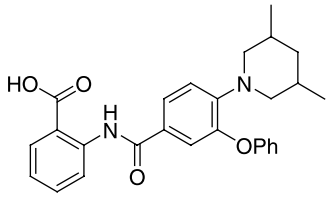
1.3.2 Structure-Based Drug Design (SBDD)

Progress in SBDD has been steady over the past two decades such that it has become a generally accepted strategy in medicinal chemistry, transforming the way medicinal chemists decide how to pursue their series' SAR. Although obtaining X-ray crystallographic data for SBDD was achieved early on, it has taken many years to learn how to interpret, and not over-interpret, this data. Structural information on the protein target provided by X-ray crystallography offers the greatest structural resolution for docking proposed ligands, but other spectroscopic techniques, such as nuclear magnetic resonance (NMR), have demonstrated their utility as well. X-ray crystallography, however, is generally restricted to analysing soluble proteins such as enzymes. Also required is a ready source of large quantities of the target protein for crystallization, as is often the case for proteins obtained from microorganisms grown in culture.

Bacterial proteins are an ideal starting point for SBDD, as in the case of the β-ketoacyl carrier protein synthase III (FabH), the target for a recent SBDD-based approach (Nie et al., 2005). FabH catalyzes the initiation of fatty acid biosynthesis, and a combination of X-ray data along with structures of substrates and known inhibitors led to selection of a screening library to provide a starting point for one recent study. Following screening, co-crystallization of selected inhibitors then guided the addition of functionality to take advantage of interactions with the enzyme visualized by X-ray and docking studies. A 50-fold improvement in enzyme inhibitory potency was realized in going from structure **1** to **2**, accounted for by amino acid side-chain movements revealed by X-ray co-crystal structures of both compounds with the enzyme. Although much remains to be learned so that these side-chain movements can be predicted and exploited for new compound design, the study nonetheless provides a successful example of the implementation of SBDD in drug design.



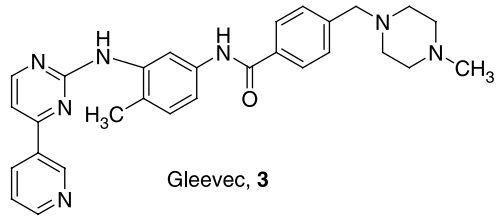
1

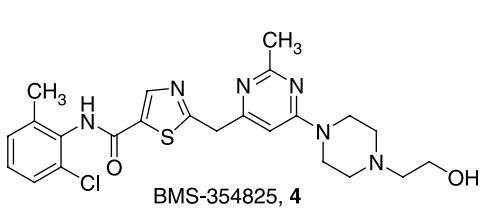


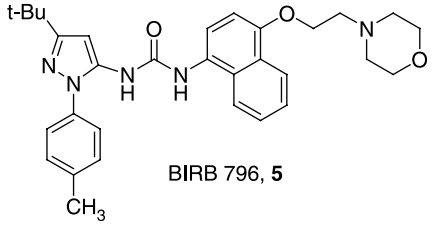
2

Although human proteins are more challenging to obtain in sufficient quantity for crystallization, modeling based on X-ray crystal structures has been successfully applied to many human targets. Probably the best-known efforts have been in the kinase area in search of anticancer drugs, which has been reviewed recently (Ghosh et al., 2001). For example, X-ray crystallographic data revealed important aspects of the binding of the anticancer drug Gleevec (**3**) to its target, the Bcr-Abl kinase, including the role of the pendant piperazine group, added originally to improve solubility, and the requirement for binding to an inactive conformation of the enzyme (Schindler et al., 2000). Combined with studies of the mutations responsible for Gleevec-resistant variants of Bcr-Abl, these studies enabled design of a new compound, BMS-354825 (**4**), active against most of these resistant mutants (Shah et al., 2004). More recently, non-ATP binding site inhibitors have been discovered and modeled by SBDD. For example, SBDD helped to characterize a new class of p38 kinase inhibitors that bind to a previously unobserved conformation of the enzyme that is incompatible with ATP binding (Pargellis et al., 2002). Insights from

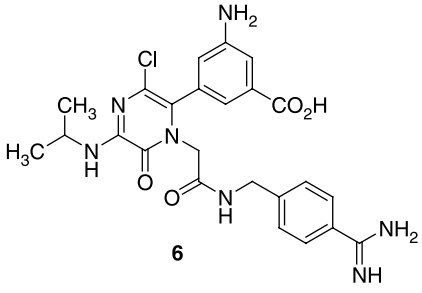
SBDD then guided design of a picomolar p38 kinase inhibitor based on binding to this site, BIRB 796 (**5**).

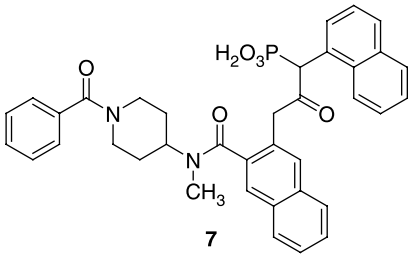






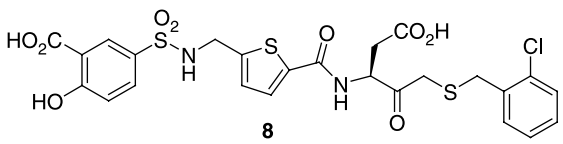
SBDD approaches to other soluble proteins have produced inhibitors of the tissue factor VIIa complex (Parlow et al., 2003) and cathepsin G (Greco et al., 2002). In the case of factor VIIa inhibitors, X-ray data provided information for both designing a new scaffold for inhibitors and for simultaneously improving binding affinity and selectivity over thrombin. Compound **6** from this work was advanced to clinical trials based on its potency and selectivity for factor VIIa inhibition. The cathepsin G inhibitor program revealed a novel binding mode for an alpha-keto phosphonate to the enzyme's oxyanion hole and active site lysine, as well as an opportunity to extend groups into a vacant binding site to improve potency. The result was a nearly 100-fold increase in inhibition following an SAR study of this direction using the amide group in compound **7**.



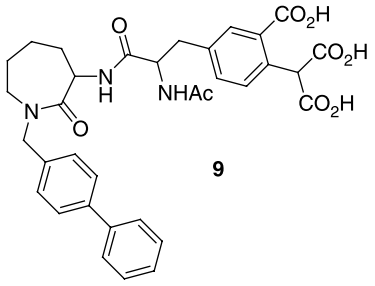


Another spectroscopic technique that has been widely applied to drug design is nuclear magnetic resonance (NMR) spectroscopy (Homans, 2004). Both X-ray crystallography and NMR can be used to take advantage of the opportunity to screen fragments, small molecules with minimal enzyme affinity, but which can be linked together with structural information to form potent inhibitors (Erlanson et al., 2004). For example, a recent approach to caspase inhibitors generated its lead structure by tethering an aspartyl moeity to a salicylic acid group; an X-ray co-crystal structure of the most potent compound **8** was found to mimic most of the interactions of the known peptidic caspase inhibitors

(Choong et al., 2002). Another example explored replacement of the phosphate group found in most Src SH2 domain inhibitors with various heteroatom-containing groups by soaking fragments into a large crystal and obtaining X-ray data, leading to the 5 nM malonate-based inhibitor **9** (Lesuisse et al., 2002).

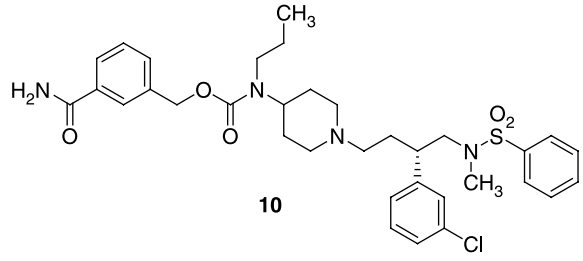


8

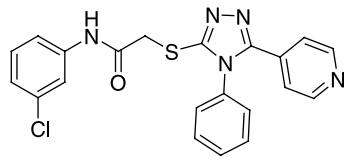


9

For proteins that are not water soluble, such as membrane proteins, techniques that depend on crystallization are very challenging. Homology modeling is an alternative that can be applied to transmembrane proteins such as the G-protein-coupled receptors (GPCRs), which are the target of many marketed drugs. Based on X-ray data for a prototype member of this family of proteins, bovine rhodopsin, a number of homology models for therapeutically relevant GPCRs have been built. In the case of the chemokine GPCR CCR5, a target for AIDS drugs, a homology model afforded an appreciation of the role of aromatic interactions and H-bonds involved in binding antagonists (Xu et al., 2004). A three-dimensional QSAR model was next developed based on a library of potent antagonists, and then combined with the homology model to confirm important interactions and indicate directions for new compound design, resulting in compound **10**, a subnanomolar CCR5 antagonist. A more sophisticated approach based on docking of virtual compounds to a homology model for the neurokinin NK-1 receptor for the neurotransmitter peptide substance P has revealed structurally novel antagonists (Evers and Klebe, 2004). The most potent of these, ASN-1377642 (**11**), overlaps nicely with CP-96,345, the literature NK-1 receptor antagonist on which the pharmacophore used for virtual screening was based. Similar combinations of SBDD-based technology are providing insights for new compound design in numerous areas of medicinal chemistry.



10



ASN-1377642, **11**

1.4 THE ROLE OF SYNTHETIC CHEMISTRY IN DRUG DISCOVERY

Some may ask why anything needs to be said about synthetic chemistry as a tool for drug discovery; after all, it is common to hear that "we can make anything." On the other hand, we can only carry out biological evaluation of compounds that have been synthesized.

Once the evaluation of biological activity and physical properties has been used to design new targets, a suitable synthetic route must be developed. However, considerations of what can be readily prepared factor into design much earlier. Chemists typically recognize familiar structural features for which they know a feasible synthetic route as they analyze data and properties. Design is guided by what can be readily made, especially what can be prepared as a library of compounds, so that work can begin immediately toward initiating the next round of biological testing.

Although there will always be limitations to what can be synthesized based on our imperfect knowledge, recent developments in two areas have facilitated the chemist's job: analysis/purification and synthetic methodology. In the first area, routine high-field NMR instruments allow 1H-NMR and 13C-NMR characterization of small amounts ($<$10 mg) of organic compounds. Liquid-chromatography/mass spectroscopy (LCMS) and other rapid analytical techniques, combined with medium- and high-pressure chromatography, allow for ready separation of reaction mixtures. New technologies such as reactor chips and miniaturization, supercritical fluids and ionic fluid reaction solvents, and chiral separation techniques will continue to improve synthetic capabilities.

In the second area, two recent advances have transformed synthetic methodology: transition-metal catalyzed cross-coupling reactions (Nicolaou et al., 2005) and olefin-metathesis technology (Grubbs, 2004). The formation of carbon–carbon bonds is probably the most fundamental reaction in synthetic chemistry. For the first several decades of the twentieth century, this reaction depended primarily on displacement of electrophilic leaving groups by enolate anions (or enamines) or addition of organometallic (e.g., Grignard) reagents. The advent of palladium-catalyzed coupling of more stable derivatives, such as olefins and acetylenes, boronic acids/esters, and tin or zinc compounds changed this simple picture. At the same time, the development of air-stable catalysts for producing complex carbon frameworks by metathesis of olefins expanded the chemist's repertoire. These methods allow much greater flexibility and tolerance for sensitive functional groups, enabling construction of more complicated, highly functionalized carbon frameworks.

Assembling this methodology, along with that developed over the previous century, into library-enabled synthesis allows the preparation of the large numbers of compounds favored for today's search for lead compounds using high-throughput screening (HTS) and in lead compound follow-up. Combinatorial chemistry was initially facilitated by developments in robotic handling technology and, for solid-phase synthesis, by Merrifield peptide synthesis. Both solution-phase (Selway and Terret, 1996) and solid-phase (Ley and Baxendale, 2002) parallel syntheses allow generation of large chemical libraries. The emphasis on these new technologies, combined with the cross-coupling and olefin metathesis synthetic methodologies, facilitates the synthesis of new classes of compounds with complex carbon frameworks. Their emergence as lead series and the ensuing follow-up are largely the result of their preponderance in the collection of compounds screened. In other words, it can be argued that synthetic methodology creates the chemical space that is available for screening and hence influences in a very profound way the medicines available to mankind. As the syntheses in the succeeding chapters make clear, synthetic chemistry plays a significant role alongside medicinal chemistry in the drug discovery process.

REFERENCES

Abbott, N. J. (2004). *Drug Discovery Today: Technologies*, 1(4): 407–416.

Aronov, A. M. (2005). *Drug Discovery Today*, 10(2): 149–155.

Beresford, A. P., Segall, M., and Tarbit, M. L. H. (2004). *Curr. Opin. Drug Discov. Dev.*, 7(1): 36–42.

Bergstroem, C. A. S. (2005). *Basic Clin. Pharmacol. Toxicol.*, 96(3): 156–161.

Cheng, A. and Merz, K. M., Jr. (2003). *J. Med. Chem.*, 46(17): 3572–3580.

Choong, I. C., Lew, W., Lee, D., Pham, P., Burdett, M. T., Lam, J. W., Wiesmann, C., Luong, T. N., Fahr, B., DeLano, W. L., McDowell, R. S., Allen, D. A., Erlanson, D. A., Gordon, E. M., and O'Brien, T. (2002). *J. Med. Chem.*, 45(23): 5005–5022.

Clark, D. E. (2003). *Drug Discovery Today*, 8(20): 927–933.

D'Ambra, T. E. (2003). *Abstracts, 36th Middle Atlantic Regional Meeting of the American Chemical Society*, Princeton, NJ, United States, June 8–11, 16.

de Graaf, C., Vermeulen, N. P. E., and Feenstra, K. A. (2005). *J. Med. Chem.*, 48(8): 2725–2755.

Erlanson, D. A., McDowell, R. S., and O'Brien, T. (2004). *J. Med. Chem.*, 47(14): 3463–3482.

Evers, A. and Klebe, G. (2004). *J. Med. Chem.*, 47(22): 5381–5392.

Ghosh, S., Liu, X.-P., Zheng, Y., and Uckun, F. M. (2001). *Curr. Cancer Drug Targets*, 1(2): 129–140.

Goodnow, R. A., Jr. (2001). *J. Cellular Biochem.*, (Suppl. 37): 13–21.

Greco, M. N., Hawkins, M. J., Powell, E. T., Almond, H. R., Jr., Corcoran, T. W., de Garavilla, L., Kauffman, J. A., Recacha, R., Chattopadhyay, D., Andrade-Gordon, P., and Maryanoff, B. E. (2002). *J. Am. Chem. Soc.*, 124(15): 3810–3811.

Grubbs, R. H. (2004). *Tetrahedron*, 60(34): 7117–7140.

Homans, S. W. (2004). *Angew. Chem., Int. Ed.*, 43(3): 290–300.

Hou, T. J., Xia, K., Zhang, W., and Xu, X. J. (2004). *J. Chem. Inf. Comput. Sci.*, 44(1): 266–275.

Lesuisse, D., Lange, G., Deprez, P., Benard, D., Schoot, B., Delettre, G., Marquette, J.-P., Broto, P., Jean-Baptiste, V., Bichet, P., Sarubbi, E., and Mandine, E. (2002). *J. Med. Chem.*, 45(12): 2379–2387.

Ley, S. V. and Baxendale, I. R. (2002). *Nat. Rev. Drug Discov.*, 1(8): 573–586.

Lin, J., Sahakian, D. C., de Morais, S. M. F., Xu, J. J., Polzer, R. J., and Winter, S. M. (2003). *Curr. Top. Med. Chem.*, 3(10): 1125–54.

Lipinski, C. A., Lombardo, F., Dominy, B. W., and Feeney, P. J. (2001). *Adv. Drug Deliv. Rev.*, 46(1–3): 3–26.

Liu, R. and So, S.-S. (2001). *J. Chem. Inf. Comput. Sci.*, 41(6): 1633–1639.

Lombardino, J. G. and Lowe, J. A. (2004). *Nat. Rev. Drug Discov.*, 3(10): 853–862.

Nicolaou, K. C., Bulger, P. G., and Sarlah, D. (2005). *Angew. Chem., Int. Ed.*, 44(29): 4442–4489.

Nie, Z., Perretta, C., Lu, J., Su, Y., Margosiak, S., Gajiwala, K. S., Cortez, J., Nikulin, V., Yager, K. M., Appelt, K., and Chu, S. (2005). *J. Med. Chem.*, 48(5): 1596–1609.

Pargellis, C., Tong, L., Churchill, L., Cirillo, P. F., Gilmore, T., Graham, A. G., Grob, P. M., Hickey, E. R., Moss, N., Pav, S., and Regan, J. (2002). *Nat. Struct. Bio.*, 9(4): 268–272.

Parlow, J. J., Case, B. L., Dice, T. A., Fenton, R. L., Hayes, M. J., Jones, D. E., Neumann, W. L., Wood, R. S., Lachance, R. M., Girard, T. J., Nicholson, N. S., Clare, M., Stegeman, R. A., Stevens, A. M., Stallings, W. C., Kurumbail, R. G., and South, M. S. (2003). *J. Med. Chem.*, 46(19): 4050–4062.

Rowland, P., Blaney, F. E., Smyth, M. G., Jones, J. J., Leydon, V. R., Oxbrow, A. K., Lewis, C. J., Tennant, M. G., Modi, S., Eggleston, D. S., Chenery, R. J., and Bridges, A. M. (2006). *J. Biol. Chem.*, 281: 7614–7622.

Schindler, T., Bornmann, W., Pellicena, P., Miller, W. T., Clarkson, B., and Kuriyan, J. (2000). *Science*, 289: 1938–1942.

Selway, C. N. and Terrett, N. K. (1996). *Bioorg. Med. Chem.*, 4(5): 645–654.

Shah, N. P., Tran, C., Lee, F. Y., Chen, P., Norris, D., and Sawyers, C. L. (2004). *Science*, 305: 399–402.

Snyder, R. D., Pearl, G. S., Mandakas, G., Choy, W. N., Goodsaid, F., and Rosenblum, I. Y. (2004). *Environmental and Molecular Mutagenesis*, 43(3): 143–158.

Stenberg, P., Bergstroem, C. A. S., Luthman, K., and Artursson, P. (2002). *Clin. Pharmacokinet.*, 41(11): 877–899.

Stoner, C. L., Cleton, A., Johnson, K., Oh, D.-M., Hallak, H., Brodfuehrer, J., Surendran, N., and Han, H.-K. (2004). *Int. J. Pharmaceutics*, 269(1): 241–249.

Tickle, I. J., Vonrhein, C., Williams, P. A., Kirton, S. B., and Jhoti, H. (2005). (Astex Technology Ltd., UK), US patent 2005159901.

van de Waterbeemd, H. and Gifford, E. (2003). *Nat. Rev. Drug Discovery*, 2(3): 192–204.

Vaz, R. J., Li, Y., and Rampe, D. (2005). *Prog. Med. Chem.*, 43: 1–18.

Winkler, D. A. (2004). *Drugs Fut.*, 29(10): 1043–1057.

Xu, Y., Liu, H., Niu, C., Luo, C., Luo, X., Shen, J., Chen, K., and Jiang, H. (2004). *Bioorg. Med. Chem.*, 12(23): 6193–6208.