

THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

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Abstract | The role of the medicinal chemist in drug discovery has undergone major changes in the past 25 years, mainly because of the introduction of technologies such as combinatorial chemistry and structure-based drug design. As medicinal chemists with more than 50 years of combined experience spanning the past four decades, we discuss this changing role using examples from our own and others' experience. This historical perspective could provide insights in to how to improve the current model for drug discovery by helping the medicinal chemist regain the creative role that contributed to past successes.

A GUIDE TO DRUG DISCOVERY

LEAD COMPOUND

A chemical structure or series of structures that show activity and selectivity in a pharmacological or biochemically relevant screen.

STRUCTURE–ACTIVITY RELATIONSHIP

The correlation of structural features with the activity of compounds in a given assay.

COMBINATORIAL TECHNOLOGY

Synthetic technologies to generate compound libraries rather than single compounds.

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Medicinal chemists prepare and/or select appropriate compounds for biological evaluation that, if found to be active, could serve as LEAD COMPOUNDS. They then evaluate the STRUCTURE–ACTIVITY RELATIONSHIPS (SARs) of analogous compounds with regard to their *in vitro* and *in vivo* efficacy and safety. Today, medicinal chemists who are engaged in drug discovery are part of interdisciplinary teams, and must therefore understand not only the field of organic chemistry, but also a range of other disciplines to anticipate problems and interpret developments to help move the project forward.

As highlighted in this article, the role of the medicinal chemist has changed significantly in the past 25 years. In the early era ('then') of drug discovery (1950 to about 1980), medicinal chemists relied primarily on data from *in vivo* testing. In the more recent ('now') period (about 1980 to the present), the development of new technologies, such as high-throughput *in vitro* screening, large compound libraries, COMBINATORIAL TECHNOLOGY, defined molecular targets and structure-based drug design, has changed that earlier and relatively simple landscape. Although these new technologies present many opportunities to the medicinal chemist, the multitude of new safety requirements that have arisen has also brought unanticipated hurdles for the task of translating *in vitro* activity to *in vivo* activity.

Simultaneously, the knowledge base that supports drug research has expanded considerably, increasing the challenge for chemists to understand their fields of expertise. The demonstration of adequate clinical safety and efficacy in humans has also become more complex, and ever-increasing amounts of data are now required by regulatory agencies. In fact, despite the use of many new technologies, and the growing resources and funding for drug research, the number of launches of new medicines in the form of NEW MOLECULAR ENTITIES (NMEs) has been generally decreasing for more than a decade. Clearly, the difficulty and complexity of drug research has increased in the past two decades. It is our aim with this article to discuss how these changes have influenced the role of medicinal chemists and to suggest ways to help them to contribute more effectively to the drug discovery process.

The process of drug discovery

Inventing and developing a new medicine is a long, complex, costly and highly risky process that has few peers in the commercial world. Research and development (R&D) for most of the medicines available today has required 12–24 years for a single new medicine, from starting a project to the launch of a drug product (FIG. 1). In addition, many expensive, long-term research

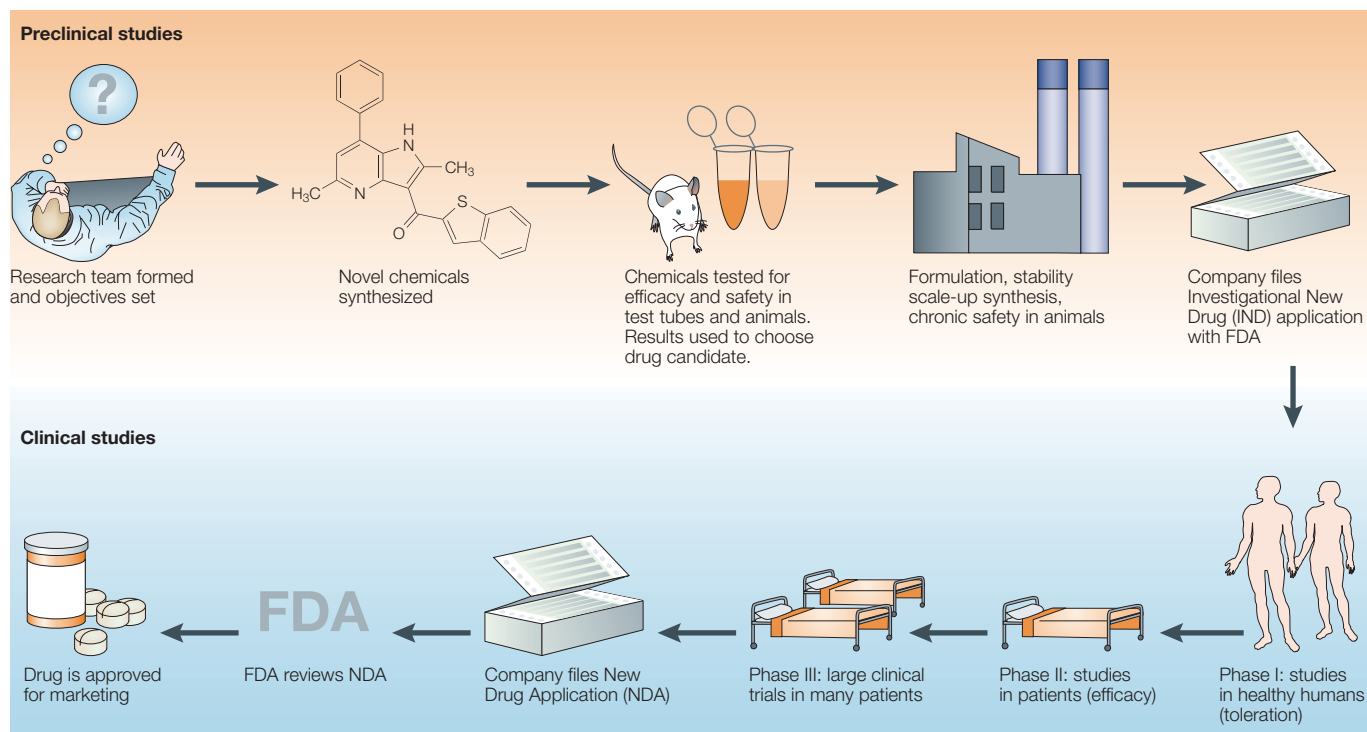


Figure 1 | Stages in the drug discovery process. The drug discovery process begins with the identification of a medical need, including a judgement on the adequacy of existing therapies (if there are any). From this analysis, together with an appraisal of the current knowledge about the target disease, will come hypotheses on how to possibly improve therapy — that is, what efficacy, safety or mechanistically novel improvements will advance the method of drug treatment for patients with the target disease? On the basis of these hypotheses, specific objectives will be set for the project. Then, testing selected chemicals in appropriate biological tests can begin. Key subsequent steps in the process include detecting relevant biological activity (a ‘hit’) for a structurally novel compound *in vitro*, then finding a related compound with *in vivo* activity in an appropriate animal model, followed by maximizing this activity through the preparation of analogous structures, and finally selecting one compound as the drug development candidate. This drug candidate then undergoes toxicological testing in animals, as required by law. If the compound passes all these tests, all the accumulated research data are assembled and submitted as an Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) in the United States (or comparable agency in other countries) before clinical trials are initiated. In the clinic, there is sequential evaluation in normal human volunteers of toleration (Phase I), efficacy and dose range in patients (Phase II), followed by widespread trials in thousands of appropriate patients to develop a broad database of efficacy and safety. For the few (4–7%) drug candidates that survive this series of development trials, a New Drug Application (NDA) that contains all the accumulated research data is filed for thorough review by the experts at the FDA. Only with their approval can the new drug be offered to doctors and their patients to treat the disease for which it was designed.

projects completely fail to produce a marketable medicine. The cost for this overall process has escalated sharply to up to an estimated US \$1.4 billion for a single new drug¹. All of the funds to support this research usually come from the income of the private pharmaceutical company that sponsors the work. In the research (‘R’; discovery) phase, only a fraction of the scientific hypotheses that form the basis for a project actually yield a drug candidate for development. In the drug development (‘D’) phase, experience has shown that only approximately 1 out of 15–25 drug candidates survives the detailed safety and efficacy testing (in animals and humans) required for it to become a marketed product. And for the few drug candidates that successfully become marketed products, some will not recover their costs of development in the competitive marketplace, and only approximately one in three will become a major commercial product. Clearly, this is a high-stakes, long-term and risky activity, but the potential benefits to the millions of patients with serious diseases provide a

constant motivating force. At virtually every phase — from project initiation to discovery, development and planning for marketing for a new drug — the modern medicinal chemist can have a role.

The role of the medicinal chemist

The modern medicinal chemist, although part of a team, has a particularly crucial role in the early phases of drug discovery. The chemist, trained to prepare new chemicals and with an acquired knowledge of the target disease and of competitive drug therapies, has an important part in framing the hypothesis for the new drug project, which then sets the objectives for the project. The chemist also helps to decide which existing chemicals to screen for a lead compound and which screening hits need to be re-synthesized for biological evaluation. Purification and proper characterization of the new chemicals is also the responsibility of the chemist. When an *in vitro* ‘hit’ is identified, the chemist decides on what analogous compounds should be obtained or synthesized to explore the

NEW MOLECULAR ENTITY (NME). A medication containing an active ingredient that has not been previously approved for marketing in the United States in any form.

HIT
A biologically active compound that exceeds a certain activity threshold in a given assay.

SARs for the structural family of compounds in an effort to maximize the desired activity. Developing *in vivo* activity for the hit compound in an appropriate animal model is also mainly the responsibility of the chemist. This can often be one of the most difficult steps to accomplish because several factors, such as absorbability, distribution *in vivo*, rate of metabolism and rate of excretion (ADME), all present hurdles for the chemist to solve in the design and preparation of new, analogous chemicals for testing. The goal at this stage is to maximize efficacy while minimizing side effects in an animal model.

For the medicinal chemist to address all the challenges outlined above, several skills are required. These include a thorough knowledge of modern organic chemistry and medicinal chemistry, an understanding of the biology that relates to the target disease, an understanding of the pharmacological tests used in the project and sufficient knowledge of the factors that influence ADME characteristics of chemicals *in vivo*. Furthermore, they should also have an understanding of clinical medicine that pertains to the target disease; knowledge of the regulatory requirements for related drugs; a current knowledge of competitive therapies, both in the market and under development by competitors; a thorough knowledge of the literature that is relevant to the target disease; familiarity with the many newer technologies available to facilitate drug discovery; and an entrepreneurial attitude in behaving as an innovator and inventor. Finally — and of crucial importance to the timely success of the project — the chemist must show superior interpersonal skills throughout the life of the project to interact effectively with colleagues from other disciplines to achieve project goals.

The medicinal chemist — then and now

Then (1950s–1980s). About 25–45 years ago, a medicinal chemist's tasks differed in some ways from those of a chemist today; an example of a successful project from this era (the development of the anti-inflammatory agent piroxicam (Feldene; Pfizer)) is highlighted in BOX 1. At that time, the medicinal chemist and a pharmacologist counterpart were the main drivers of the research programme: compounds were designed and individually synthesized by the chemist in gram quantities to accommodate the need for testing in whole animals by the pharmacologist. Given the limited synthetic methodology available, these syntheses were often time-consuming and, even with one or two technical assistants working in the laboratory, the output from one chemistry laboratory was limited to an average of one to three compounds per week. Commercially available starting materials were often limited. The chemist had only a few tools (for example, infrared and ultraviolet spectroscopy, and column chromatography) to assist with compound characterization and purification. Outsourcing was rare; all tasks, including bulk syntheses, toxicological testing and analogue synthesis, were done in-house. The creativity and intuition of the medicinal chemist was pivotal to the success of the programme, although given the limited number of compounds produced, serendipity had a large role as well.

Projects generally used *in vivo* models for primary screening, as little was known about the detailed biological mechanisms involved in most diseases. *In vitro* testing against a key enzyme or specific receptor involved in the disease process was usually not possible; as discussed in BOX 2 (which describes the discovery of the antipsychotic ziprasidone (Geodon; Pfizer)), *in vitro* receptor-based pharmacology only became common in the 1980s and 1990s. In addition, compound collections for exploratory biological screening were limited. The data generated from the test models were compiled, analysed and displayed by hand in the form of charts and graphs. Similarly, searching the literature for relevant information involved the handling of bound volumes taken individually from the library shelves.

Small companies tend to rely on informal communication and timelines, and this was often the case in the smaller pharmaceutical industry 'then'. For the medicinal chemist, the benefit of this informality was ready access to colleagues in other disciplines to evaluate a compound that the chemist was interested in. The disadvantage came once a chemist's compound was selected for further development. The chemist, who would probably have moved on to another project, usually heard little or nothing about the drug candidate until the (often) bad news came back that the candidate had failed some key test. Keeping abreast of the progress of the drug candidate required the same proactive, informal action that the chemist had used previously to periodically contact the appropriate scientists in other disciplines to get some news about the drug candidate. To address these issues, most organizations in the 1980s established interdisciplinary matrix teams for each drug candidate to facilitate information exchange and joint planning between departments, such as chemistry, biology, pharmaceuticals, toxicology, PHARMACOKINETICS, clinical medicine and regulatory affairs, all of which have important roles in drug development.

Overall, the process of drug discovery 'then' was slower and operated from a relatively smaller knowledge base. Several factors combined to slow the process: there was less known about diseases, there were fewer available compounds to screen, there were no computerized technologies for handling information and data, there was a need to manually search the literature, there was a need to individually prepare gram quantities of each new compound for testing, and chemists rarely received information from other disciplines about their development candidates. On the other hand, once a lead was identified in the primary *in vivo* test model, many of the pharmacokinetic (ADME) problems were mainly in hand or could be rapidly addressed, thereby expediting the selection of a drug candidate to study in the clinic.

Now (1980s–present). Despite some differences from the earlier era of drug discovery described above, medicinal chemists today face many of the same tasks and challenges that they did 40 years ago. So, the chemist still selects the appropriate structural series of compounds to follow and pursues the SARs to identify suitable drug candidates for advancement to safety and clinical testing.

PHARMACOKINETICS

The study of the absorption, distribution, metabolism, excretion and interactions of a drug.

But today's chemist has a much wider range of tools to help overcome the numerous hurdles in the drug discovery process. These new tools include advances in synthetic, analytical and purification technology, such as transition-metal-catalysed carbon-carbon bond-forming reactions, high-field NMR and preparative high-performance liquid chromatography (HPLC), as well as computer-assisted literature and data retrieval and analysis. The recent trend towards outsourcing many routine, tedious aspects of the drug discovery process has freed today's chemist to spend more time on new

compound design. In addition, two powerful technologies have put numbers on the chemist's side: combinatorial chemistry (combiChem) and high-throughput screening (HTS). CombiChem allows chemists to generate rational, focused libraries of compounds that define SARs in a fraction of the time that was required 'then'. Depending on where they work, chemists can design, synthesize and purify libraries themselves, or hand over the final synthesis steps to a group of chemists designated for this purpose. This group might also make lead-compound libraries that target specific receptor or

Box 1 | Discovery of piroxicam (1962–1980)

The project that produced the novel anti-arthritic and anti-inflammatory agent piroxicam (Feldene; Pfizer) began in 1962 and led to the product launching into key European markets in 1980. A detailed history of this 18-year process, including the failures and setbacks along the way, has been described elsewhere^{12,18}, so only a brief outline will be given here.

The original research team assigned to produce a new anti-inflammatory agent at Pfizer consisted of just two people — a medicinal chemist and a pharmacologist. Both were new to the area of inflammation research and had to educate themselves on all aspects of this therapeutic area. Several therapies for treating the symptoms of arthritis were already available or in development at other companies. These therapies included aspirin, indomethacin, diclofenac, ibuprofen and others. The medicinal chemist noted that all of these agents were from one chemical class — the carboxylic acids. Members of this chemical class were known to be rapidly metabolized and excreted, therefore necessitating multiple daily dosing (three to six times a day) of these drugs to maintain control of the pain and swelling of arthritis. These multiple daily doses were a feature that patients found to be undesirable and led to poor compliance. Furthermore, high daily doses (up to 16 g of aspirin) were required for some of these relatively non-potent agents, therefore placing a heavy load on the gastrointestinal tract, liver and kidneys, and consequently increasing the potential for toxicity.

In the early period of the project that eventually produced piroxicam, a set of project objectives were gradually developed that guided the project in the succeeding years. These objectives were to:

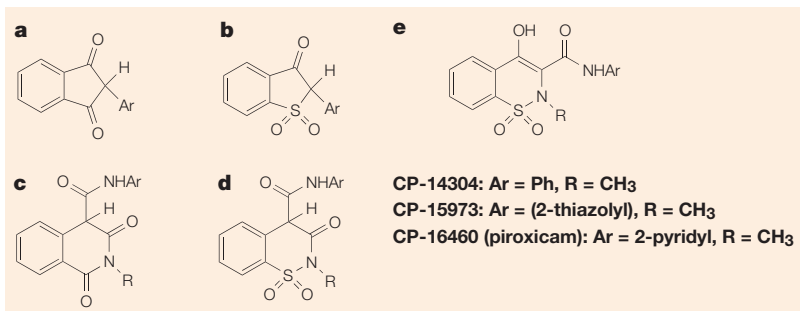
- seek a structurally novel compound with acidic properties, but not a carboxylic acid.
- seek a highly potent anti-inflammatory agent in animal models that was predictive of clinical activity and to use as controls the drugs known to be efficacious in humans.
- identify an active agent that resists metabolism that would produce a long plasma half-life in animals and in humans, and consequently lead to reduced frequency of dosing in humans.
- seek a very safe agent that arthritic patients could use over long periods of time to treat their chronic disease.

These stringent objectives placed formidable hurdles in the pathway to success and prolonged the time required to successfully achieve the goal.

The synthesis of gram quantities of compounds designed by the chemist then began, all of which were thought to have the potential to fulfill the project objectives. The acidity (pK_a) of each structure was measured and the serum half-life in dogs was determined for selected analogues to guide the synthesis programme. Using *in vivo* animal models of inflammation (this was before prostaglandins were known to be involved in inflammation), several families of compounds were found and partially developed (a–d), but each failed during a 5-year period (reviewed in REF. 12) before the first 'oxicam' shown in panel e (CP-14304) was synthesized (see figure). The synthesis of this particular compound was a 'back burner' probe based on the intuition of the chemist. The introduction of a carboxamide function into the molecule proved to be a key factor in increasing anti-inflammatory activity and for increasing acidity. Structure-activity relationships (SARs) for several hundred analogous oxicam structures produced improved activity and safety, and, eventually, through a series of three development candidates (see figure parts c and e), led to piroxicam as the agent that best met the project objectives.

Extensive clinical trials confirmed the efficacy and safety of the new drug, leading to approvals and launches into major European markets in 1980, 18 years after the project was started. The drug provided around-the-clock symptom control

for arthritis patients with just one 20-mg dose per day, leading to widespread acceptance by patients and making Feldene one of the most successful drugs in the 1980s. After 1992, major protective patents expired and generic brands of piroxicam dominated the market.



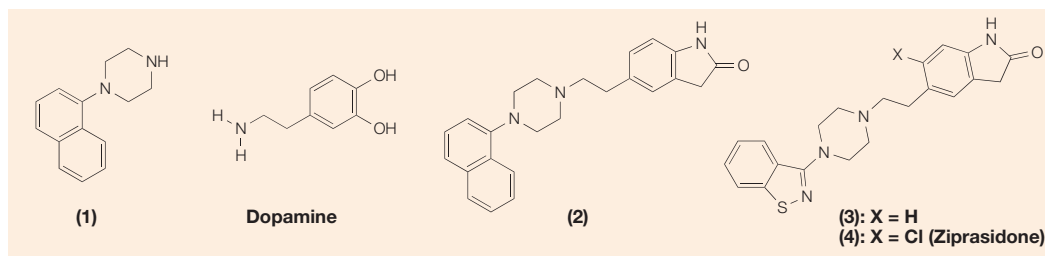
Box 2 | **Discovery of ziprasidone (1984–2001)**

Ziprasidone (Geodon; Pfizer) was launched in 2001 for the treatment of schizophrenia, a debilitating mental disease characterized by delusions, social withdrawal, suicidal behaviour and cognitive decline. The project that led to the discovery of ziprasidone relied primarily on disease-relevant animal models as had piroxicam (BOX 1), but, in addition, *in vitro* receptor-binding assays helped to find an agent that would lead to a significant advance over the already-available treatment.

The disease-relevant animal models for the ziprasidone discovery programme go back to the 1950s and the discovery of the first drug for schizophrenia (chlorpromazine), an anti-allergy drug that was serendipitously found to produce a calming effect in psychotic patients¹⁹. Paul Janssen, who had set up a medical research laboratory in 1953, studied the potential for discovering new antipsychotic drugs based on chlorpromazine by using it as a control drug in animal models designed to predict clinical activity. The models that Janssen developed relied on the ability of chlorpromazine to block the locomotor effects of stimulants such as amphetamine and apomorphine. Testing new agents that mimicked this activity of chlorpromazine led to his discovery of the first-generation antipsychotic drug haloperidol²⁰. These models were still being used in the 1980s and therefore contributed to the discovery of ziprasidone.

As a supplementary approach to *in vivo* animal models as the primary screen, *in vitro* receptor-based pharmacology emerged in the 1980s and 1990s and came to dominate the field of antipsychotic drug research. This was based on the finding that agents such as haloperidol are effective antipsychotic drugs at the mechanistic level by virtue of their blockade of dopamine type 2 (D_2) receptors. In addition, clozapine — the first ‘atypical’ antipsychotic drug (so-called because it lacks the undesirable motor side effects of haloperidol and chlorpromazine, known as extrapyramidal symptoms (EPS)) — binds to both D_2 and 5-hydroxytryptamine type 2 (5-HT₂) receptors. The 5-HT₂ receptor for the neurotransmitter serotonin is thought to afford protection from EPSs that are caused by excessive D_2 -receptor blockade²¹, and this hypothesis initiated a search for an agent with a favourable (>10-fold) ratio of D_2 - to 5-HT₂-receptor blockade²².

The search for ziprasidone began by considering the structure of naphthylpiperazine (compound 1 in the figure). Compound 1 was reported to be a potent ligand for serotonin receptors, including the 5-HT₂ receptor²³. Combining compound 1 with the structure of dopamine, the natural ligand for the D_2 receptor, and then substituting the catechol with an oxindole as a surrogate produced the combined D_2 and 5-HT₂ antagonist compound 2 (see figure). Compound 2 seemed to be the perfect antipsychotic agent, at least in rats²⁴. Further testing in monkeys, however, was disappointing, and attention switched to a new series derived from the 1,2-benzisothiazole group, which proved to have even more potent D_2 -receptor blockade while adding potent 5-HT₂-receptor blockade that afforded the desired $D_2/5-HT_2$ ratio²⁵. Fine-tuning of the structure–activity relationship in this new series led from the prototype compound 3 to compound 4 (ziprasidone; see figure)²⁶. Finally, the discovery programme confirmed the validity of the $D_2/5-HT_2$ hypothesis using disease-relevant animal-model testing, which demonstrated efficacy without EPS liability. Following the 5-year-long discovery phase, another 9 years of clinical testing and 3 years to address regulatory requirements were needed before approval of ziprasidone was given by the FDA. Extensive clinical testing validated the discovery approach, and today hundreds of thousands of patient-days of use have demonstrated the efficacy and safety of ziprasidone as it continues to help patients afflicted with this lifelong, devastating disease.

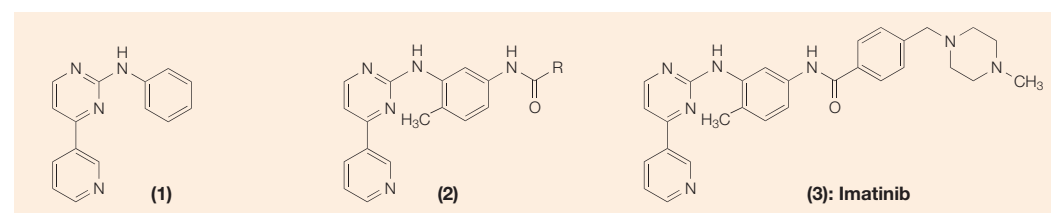


enzyme families to provide better quality leads that are suitable for library follow up. The development of HTS of large sample collections, including the designed libraries, has produced marked decreases in the personnel, time and money required to identify compounds that hit a specific biological target, although many companies are struggling to triage the large number of screening hits to viable lead compounds that can support a successful drug discovery project. In this struggle, costs can escalate significantly as the generation of large amounts of data is not the same as generating viable, quality leads. Finally, new graphics software, such as Excel and Spotfire², can facilitate the retrieval and analysis of the mountain of data generated from screening compound libraries in a large panel of *in vitro* assays.

The molecular genetics revolution³ has driven the development of another key ingredient in today’s drug discovery model: the use of molecularly defined biological targets, such as enzymes, receptors and transporters. The desire for defined molecular targets for drug discovery, in contrast to the clinically based animal-model approach used in the early era of drug discovery discussed above, derives from several factors. One is the advantage of a known mechanism of action over a ‘black-box’ (that is, unknown) mechanism obtained from animal-model testing that could produce unanticipated toxicity during drug development. Another is the use of structure-based drug design, which allows the chemist to design new compounds by directly visualizing the interaction of a lead compound with the target protein through X-ray crystallographic

Box 3 | **Discovery of imatinib mesylate**

An illustration of the role of a defined molecular target coupled with structure-based drug design in drug discovery comes from the story of imatinib mesylate (Gleevec; Novartis), a selective tyrosine kinase inhibitor approved for the treatment of CHRONIC MYELOGENOUS LEUKAEMIA. The discovery of the oncogenes in the 1970s promised to aid the discovery of oncological drugs with reduced toxicity. In contrast to the cancer drugs in use then, which nonspecifically inhibited DNA synthesis and cell division, an oncogene inhibitor should be selectively toxic to cancer cells. Zimmerman and the Novartis group chose the tyrosine kinase BCR–ABL — which is created by a reciprocal chromosomal translocation that produces the *BCR–ABL* gene — as their target, as it is found only in leukaemic cells²⁷. Inhibiting this molecularly defined target therefore reduces toxicity and maximizes the desired therapeutic effect. They chose compound 1 (see figure), an inhibitor of protein kinase C, as the starting point for the medicinal chemistry programme. Addition of the amide and methyl groups to the phenyl ring (see figure, compound 2) added the potency and selectivity needed for BCR–ABL inhibition, and addition of the piperazinylmethyl group (to generate imatinib, compound 3) was required for water solubility and oral bioavailability. Here is where the second advantage of a defined molecular target provides a crucial insight: when the X-ray crystal structure of imatinib bound to BCR–ABL was solved, it was found that the piperazine ring made significant contacts with the enzyme and was not just providing improved water solubility²⁸. More importantly, these X-ray structure data provide insight into how mutations in the *BCR–ABL* gene produce an imatinib-resistant form of the enzyme, which offers the potential for designing new drugs to overcome this resistance.



analysis, but which is only possible with a molecularly defined target protein⁴. A recent example from the new era of drug discovery described in BOX 3 (the kinase inhibitor imatinib mesylate (Gleevec; Novartis)) illustrates these advantages, which are now so well established that retreat to the black-box models of yesteryear is no longer feasible.

Recent changes – medicinal chemistry today
New techniques for addressing pharmacokinetic issues.
 The emphasis on *in vitro* screening of compounds against molecularly defined targets, although rapid and specific, has additional consequences for today's medicinal chemist. As the primary screen used to guide SAR studies, *in vitro* data do not help chemists to overcome the pharmacokinetic liabilities of their compounds. On the other hand, relying on *in vivo* animal models for the evaluation of pharmacokinetic performance suffers from a potentially serious drawback: differences between absorption and metabolism of drugs in humans and rats (a common test species) can lead to the development of drugs that work only in rats and not in humans. To help overcome this limitation, *in vitro* screens have been developed that are predictive of human pharmacokinetic performance, for example, by measuring a compound's degradation by preparations of human microsomes or hepatocytes or by recombinant human CYTOCHROME P450 ENZYMES. In addition to assessing metabolic stability, P450 assays can determine whether a compound is likely to interfere with the metabolism of other drugs that a patient is taking by virtue of inhibiting the P450 enzyme required for their elimination. Permeability and transporter assays have also been developed to characterize drug uptake into or

efflux from the target organ(s) (for a review of the P-glycoprotein (Pgp) transporter in drug development, see REF. 5). So, today's chemist has a complex array of *in vitro* SAR patterns to discern and interpret to plan the preparation of compounds for follow up (for a review of the screening data typically used in the drug discovery process, see REF. 6). Selected compounds must also be profiled *in vivo* to assess how well the *in vitro* data predict *in vivo* performance. Further *in vivo* testing is then required to show that the compound attains levels at the target organ commensurate with achieving the desired biological effect that is proposed to result from the *in vitro* activity.

Final testing might involve a disease-relevant animal model, although these data must be interpreted cautiously owing to several limitations. For example, many diseases, such as stroke, atherosclerosis and Alzheimer's disease, do not have clinically effective drugs that can validate a disease-progression-relevant animal model. Also, older models are based on drugs that work by certain mechanisms, and might not fairly assess drugs that are developed against a new mechanism. As such, the disease-relevant animal model is only one of many assays used to evaluate new compounds and, coming later in the testing sequence, has less impact on decisions made by today's chemists.

Synthesis of 'drug-like' compounds. Another strategy to overcome pharmacokinetic liabilities is the prediction and synthesis of compounds with 'DRUG-LIKE' properties. Highly lipophilic, high-molecular-mass compounds tend to have more potent *in vitro* binding activity, by virtue of excluding water from the enzyme or receptor surface and thereby picking up additional hydrophobic

CYTOCHROME P450

Members of the cytochrome P450 superfamily of haem proteins have a key role in the metabolism of drugs, and so understanding the roles of these enzymes is important for issues such as drug bioavailability and drug–drug interactions.

CHRONIC MYELOGENOUS LEUKAEMIA

A haematological cancer characterized by excessive proliferation of cells of the myeloid lineage.

DRUG-LIKE

Sharing certain characteristics with other molecules that act as drugs. The set of characteristics — such as size, shape and solubility in water and organic solvents — varies depending on who is evaluating the molecules.

interactions. But these compounds are usually not drug-like because of their low water solubility, and they generally fail in further development because of poor pharmacokinetics and oral BIOAVAILABILITY. Lipinski *et al.*⁷ formulated the ‘rule-of-five’ to predict drug-likeness, which consists of four important properties, each related to the number 5 (molecular mass <500 Da; calculated LOGP <5; hydrogen-bond donors <5; and hydrogen-bond acceptors <10). The rule is based on data in the literature for a large number of compounds, including all known drugs, that correlate physical properties with oral bioavailability. Support for the rule as a predictor of drug-likeness comes from observing weaknesses in the development pipelines of major pharmaceutical companies owing to failure to adhere to the rule-of-five⁸. Computational calculations routinely predict rule-of-five properties for prospective compounds in a chemist’s SAR plans to guide compound selection, although this guidance comes at the cost of adding complexity to an already complex set of *in vitro* data.

Use of *in vitro* toxicity screens to reduce attrition.

Completing the *in vitro* screens that the chemist uses to select the next compound to synthesize are the toxicity screens that weed out compounds predicted to fail for safety reasons. The Ames test, and related *in vitro* tests for mutagenicity and carcinogenicity, has a long history, but recent additions to this list include the hERG channel, a cardiac potassium ion channel involved in cardiac repolarization following ventricle contraction during the heartbeat⁹. Drugs that bind to and inhibit the hERG channel can cause prolongation of the QT interval of the electrocardiogram, leading to loss of a synchronous heartbeat and eventually ventricular fibrillation, and even death. The danger posed by a drug that inhibits the hERG channel was illustrated by the deaths of patients taking the allergic rhinitis drug astemizole (Hismanal; Janssen), which led to its abrupt withdrawal from the market¹⁰. In the aftermath of this and other incidents of fatal complications from hERG-blocking drugs, the FDA is formulating guidelines to address the issue. Most pharmaceutical companies now have hERG screening in place to afford chemists an indication of the therapeutic index of their compounds for this end point¹¹.

BOX 4 summarizes the various criteria that today’s chemist must follow to develop a successful drug candidate. A recent literature example that illustrates many of the new techniques and testing hurdles for today’s medicinal chemist — a series of farnesyl transferase inhibitors — is given in BOX 5.

Final thoughts on the drug discovery process

The role of a champion in drug discovery. As a scientist involved at the very earliest stages of drug discovery, including the setting of project objectives, the medicinal chemist with leadership qualities has the opportunity to act as a champion for the drug candidate throughout the long R&D process. Championing a drug candidate was often a key factor in a successful drug project ‘then’

Box 4 | *In vitro* tests: ‘now’ and ‘then’

The following is a typical battery of tests for a modern drug discovery programme ‘today’; those marked with an asterisk were also in use ‘then’.

In vitro target

- Primary
- Whole cell
- Functional
- Selectivity assays

In vitro absorption, distribution, metabolism and elimination (ADME)

- Microsomal stability
- Hepatocyte stability
- P450 substrate
- P450 inhibitor
- Permeability
- Transporter efflux (for example, P-glycoprotein)
- Protein binding

Physical properties

- Rule-of-five
- *In silico* ADME

In vivo

- Functional
- *Secondary (behavioural, chronic)

Toxicity

- *Ames test
- Micronucleus test
- hERG half-maximal inhibitory concentration (IC₅₀)
- P450 induction
- Broad screening
- *Others (depending on project)

and was facilitated by the smaller project teams typical of this earlier era. For example, key publications concerning a new drug often had just two authors, the chemist and the biologist, who were essentially the drug champions. There is a multitude of commercially successful drugs today that survived a dark period during development only because a champion worked to keep the drug alive by finding answers to problems (see examples provided in REF 12).

To act as a champion for a drug candidate, a chemist with current knowledge of all aspects of the drug programme must take an enduring, pervasive interest in all aspects of the development process, especially in helping to solve those seemingly intractable challenges that inevitably arise during the long path to regulatory approval. Without a champion, a drug candidate can lose momentum and stall irreversibly during the years leading to regulatory approval. This is truer today than ever, because the process has become so much more complicated. And yet the contribution of a medicinal chemist can seem diluted by the presence of scientists from the many other disciplines that make up a typical drug discovery programme today, disciplines which have risen significantly in importance in recent years. In addition to the increased number of contributing scientific

BIOAVAILABILITY

The fraction or percentage of an administered drug or other substance that becomes available in plasma or to the target tissue after administration.

LOGP

The octanol/water partition coefficient is the ratio of the solubility of a compound in octanol to its solubility in water (also known as K_{ow}). The logarithm of this partition coefficient is called log P. It provides an estimate of the ability of the compound to pass through a cell membrane.

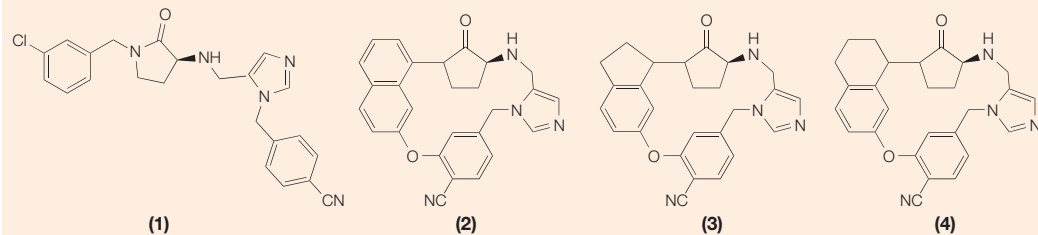
hERG

Human ether-a-go-go-related gene, the gene that encodes the α -subunit of the I_{Kr} channel, a major determinant of human cardiac repolarization.

Box 5 | Farnesyl transferase inhibitors

As one of the oncogenes characterized in the 1970s, *RAS* has been the target of numerous drug discovery efforts. Compounds that inhibit the enzyme farnesyl transferase (FTase) prevent the mutant form of *RAS* from causing tumour formation. A group at Merck has published extensively²⁹ on their FTase inhibitor programme, and examples from this programme are shown in the figure.

The table in the figure shows data for a set of compounds illustrating the criteria that the Merck group used to evaluate their compounds³⁰. Compound 1 shows potent *in vitro* activity for the primary endpoint, farnesyl transferase (FTase) inhibition (IC_{50} values are shown), as well as selectivity against geranyl geranyl transferase type I (GGTase), required for cell viability (IC_{50} values are shown). Even though it shows good oral bioavailability (F) — 81% — it inhibits the hERG channel (the inflection point for binding to the hERG channel by radioligand displacement assay (hERG IP) = 440 nM) and causes QT PROLONGATION in the dog at a dose that is unacceptable. Macrocyclization to give compound 2 overcomes the problem with inhibition of hERG while maintaining *in vitro* potency, selectivity and oral bioavailability. In addition, X-ray crystal structure data of compound 2 bound to FTase explain how the enzyme accommodates this structural change and aids in further drug design. Increasing flexibility by saturating one of the rings of the naphthyl core in compound 2 to produce compound 3 and compound 4 considerably increases *in vitro* potency. Compound 3, however, is unfortunately very potent at hERG (80 nM), whereas compound 4 is cleared rapidly (rate of plasma clearance in the dog (CLp) = 7.3 ml per min per kg). So, even though it is the least potent compound in the set, compound 2 is the best choice for further structure–activity relationship development, primarily because of its pharmacokinetics and safety margin. This example illustrates why today's chemist more often prefers to begin with compounds that possess better pharmacokinetic and selectivity properties, and then to proceed to optimize potency for the primary *in vitro* end point. (Func 1, cell-based radiotracer assay for FTase inhibition; Func 2, cell-based assay for inhibition of FTase substrate derivatization, given in the absence and presence of human serum; N/A, not available; P450, IC_{50} value for inhibition of human P450 3A4.)



FTase	1.9 nM	3.5 nM	0.15 nM	0.020 nM
GGTase	3.4 μ M	650 nM	18 μ M	390 nM
Func 1	0.52 nM	3.8 nM	0.22 nM	0.054 nM
Func 2	N/A	48/130 nM	3.0/3.0 nM	0.18/0.25 nM
hERG IP	440 nM	10.5 μ M	80 nM	7 μ M
CLp	5.8	1.1	2.1	7.3
F (%)	81	68	N/A	N/A
P450	1.0 μ M	8.0 μ M	6.6 μ M	N/A

sub-specialties today, the high cost and increased complexity of drug R&D today¹ can dwarf any one scientist's contribution.

Suggestions for improving the drug discovery process.

Recent data indicate that productivity has not kept pace with increasing resource allocation to the drug discovery process. We would like to suggest three ways to improve the current model for new drug discovery that would help the medicinal chemist to be more productive. The first stems from the current heavy reliance on *in vitro* screening for driving SARs early in a programme, at the risk of finding poor pharmacokinetics and oral bioavailability later on. Coordinating animal testing with *in vitro* testing early in the drug discovery process to pre-screen lead series *in vivo*, and then correlating *in vitro* pharmacokinetics screens

with *in vivo* data as soon as possible, might provide a firmer footing for the chemist to overcome any deficiencies in pharmacokinetics. Such testing might also help to identify lead compounds on the basis of their promising *in vivo* activity or pharmacokinetic properties that would have been rejected on the basis of *in vitro* testing alone.

The second suggestion is based on the need to have a committed drug champion to bring background information and a historical perspective (sometimes termed 'institutional memory'), and to suggest solutions to the myriad issues that arise throughout a drug's development. By appointing a small, permanent committee, which includes the medicinal chemist from the discovery team, to be involved with the entire drug development programme through to drug registration (and to work alongside the interdisciplinary matrix development

QT PROLONGATION

The QT interval is a measure of the total time of ventricular depolarization and repolarization. In recent years, several drugs have been withdrawn from the market because of unexpected reports of sudden cardiac death associated with prolongation of the QT interval. Blockade of the hERG channel has been linked to this effect.

teams), there would always be someone available to provide informed judgments on the basis of their medicinal chemistry background and experience on the project to help keep the drug on track during the many years required for its successful development.

Finally, as many of the most experienced chemists in the pharmaceutical industry reach retirement age, there remains the challenge of how to pass on their learning to the next generation. They possess tacit knowledge (that is, residing in the mind of the experienced scientist but not yet communicated to others) of the drug discovery experience that needs to be recognized, captured and then passed on to the young scientists (as outlined in REF. 13). Companies that accomplish this, by, for example, holding in-house workshops on drug design and lecture series on medicinal chemistry, will help to teach the next generation of scientists the art of successful drug discovery.

The changing landscape of the pharmaceutical industry.

Some basic questions about the new technologies and procedures now used for drug research, compared with the dwindling supply of new drugs approved in recent years, have been raised in recent news articles^{14–17}. For example, has the introduction of major changes in the drug discovery process caused the obvious drop in new drug output? Is this drop temporary, to last only until the new technologies begin to yield some products? Have the changes produced a decrease in output by stifling the creativity of the scientists (including the medicinal chemists) involved in drug discovery? Has the role of serendipity, so important to drug discovery in the past, been supplanted by robots? What has happened to the role of the medicinal chemist's intuition and creativity in producing quality drugs? How many of today's most successful drugs could have been made through the limited chemical pathways offered by combichem techniques? Making millions of new chemicals robotically does not, apparently, lead to more new drugs.

An important perspective on this discussion comes from a recent account¹⁷ of the key differences in the pharmaceutical industry experienced by a father–son pair of medicinal chemists, Leo Sternbach ('then', about

40–50 years ago, when he invented chlordiazepoxide (Librium; Hoffman-La Roche) and diazepam (Valium; Hoffman-La Roche)) and his son, Daniel ('now', currently a medicinal chemist at GlaxoSmithKline). By their account, the role of the medicinal chemist has changed considerably from that of a highly autonomous, independent inventor 'then' to a significant player in a large team that is increasingly influenced by the business units 'now'.

In our opinion, whatever the merits of the business decisions that led to this change, the role of serendipity, chemical intuition and creativity in thoughtfully selecting a chemical target to synthesize in order to discover the best-quality drugs has not diminished. There must always be an opportunity in research for the useful chance observation by a prepared mind. There are many examples of 'back burner' (that is, unauthorized) projects that have yielded important new drugs. Although the new technologies that have accelerated the process of drug discovery provide some undoubted benefits, the human factor remains an integral part of success in this endeavour. It is our hope that the accounts of successful drug discoveries presented here will serve as a reminder of the chemists whose decisions actually led to these success stories.

Today, the rapidly expanding knowledge base concerning diseases, their causes, symptoms and their effects on the human body holds great promise for the discovery of important new medicines. Sequencing the human genome also offers the opportunity for finding many more novel and selective therapies. Such discoveries will probably come from teams of scientists, including medicinal chemists, whose careers are devoted to this one task. The enormous cost of this task will be borne mainly by those pharmaceutical companies that can successfully generate the required research funds from the sale of their existing drugs.

Medicinal chemists today live in exciting times. They are key participants in the effort to produce more selective, more effective and safer medicines to treat the diseases of mankind. Their work can have a beneficial effect on millions of suffering patients — surely an important motivating factor for any scientist.

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Competing interests statement
The authors declare no competing financial interests.

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