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Chemistry in the Pharmaceutical Industry

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INTRODUCTION

This chapter will discuss the role of chemistry within the pharmaceutical industry. Although the focus will be upon the industry within the United States, much of the discussion is equally relevant to pharmaceutical companies based in other first world nations such as Japan and those in Europe. The major objective of the pharmaceutical industry is the discovery, development, and marketing of efficacious and safe drugs for the treatment of human disease. Of course drug companies do not exist as altruistic, charitable organizations but like other share-holder owned corporations within our capitalistic society must achieve profits in order to remain viable and competitive. Thus, there exists a conundrum between the dual goals of enhancing the quality and duration of human life and that of increasing stock-holder equity. Much has been written and spoken in the lay media about the high prices of prescription drugs and the hardships this places upon the elderly and others of limited income. Consequently, some consumer advocate groups support governmental imposition of price controls, such as those that exist in a number of other countries, on ethical pharmaceuticals in the United States.

However the out-of-pocket dollars spent by patients on prescription drugs must be weighed against the more costly and unpleasant alternatives of surgery and hospitalization, which are often obviated by drug therapy. Consideration must also be given to the enormous expense associated with the development of new drugs. It can take 10 years or more from the laboratory inception of a drug to its registrational approval and marketing at an overall cost which is now \$600–800 million dollars and increasing. Only 1 out of 10 to 20,000 compounds prepared as drug candidates ever reach clinical testing in man and the attrition rate of those that do is >80 percent. The expense of

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developing a promising drug grows steadily the further through the pipeline it progresses; clinical trials can be several orders of magnitude more costly than the preclinical evaluation of a compound. While the sales of successful drugs that run the gauntlet and reach the shelves of pharmacies can eventually recoup their developmental expenses many times over, the cost of the drugs that fail is never recovered.

To a large extent, the difficulties associated with bringing a drug to market have arisen from the increasingly stringent but appropriate criteria that have been imposed by the Food and Drug Administration (FDA) in the United States and analogous regulatory agencies in other countries. It is unlikely that an occurrence like that of the thalidomide disaster, which resulted in horrible birth defects several decades ago, would happen again today. Furthermore the era of easy approval of "me-too" drugs is long past. During this era, which prevailed until the final two decades of the past century, it was possible to gain approval for drugs which, although they fell outside the scope of the patents covering a particular marketed drug, offered little advantage over the marketed agent. It is now necessary for a company to demonstrate that a drug, for which a New Drug Application (NDA) is submitted to the FDA, affords significant benefits in terms of efficacy and/or safety relative to the existing drug therapy. The approvability bar may be lowered for agents aimed at the treatment of life-threatening maladies such as cancer and AIDS or for those such as Alzheimer's disease where no effective therapy currently exists; but even in these cases it is incumbent upon the sponsoring company to provide compelling empirical evidence that their drug is safe and effective. The restrictions imposed by Health Maintenance Organizations (HMOs) can also have significant impact on the sales of any given drug. Most HMOs list only a select few drugs, for which they will cover costs, within any given category, such as antidepressants, antihypertensives, or cholesterol-lowering agents.

A major consequence of the financial and logistical impediments to the successful introduction of new drugs has been the high incidence of mergers and acquisitions among U.S.-based pharmaceutical companies in the recent past. These events have not occurred because bigger is necessarily better but because the critical mass of internal resources required to bring a drug from the test tube to the pharmacy continues to grow. In contrast to this trend among the major drug companies (often dubbed "big pharma") there has been a proliferation of start-up companies often founded by entrepreneurial scientists with "big pharma" or academic experience and financed by venture capital investment. While many such start ups are strictly bio-techs, others function as mini drug companies and are staffed by both chemists and biologists. Unlike their much larger brethren, the small companies cannot attempt to cover the breath of drug research but instead focus upon a particular therapeutic area and perhaps even a particular disease. Their mission is to discover drug candidates, which a large company may be interested in licensing and developing. The "big pharma" companies do not rely exclusively upon filling their developmental pipelines with drug candidates that have been discovered in-house but often enter into collaborations and licensing agreements to acquire the rights to promising agents from the labs of smaller companies or academic researchers.

MEDICINAL CHEMISTRY

Chemistry has long been an integral part of the pharmaceutical industry and its importance should not diminish. Many currently marketed drugs such as the antineoplastic agent, paclitaxel, and the antibiotic, vancomycin, are natural products. The extracts of plants and marine organisms and the products of soil bacteria fermentation will continue to be investigated as potential sources of powerful new drug substances. Chemists are certainly involved in this arena of drug discovery as they conduct the painstaking isolation, purification, and

structural characterization of pharmacologically active components which most often are present in minute amounts in the natural source and which have extremely complex chemical structures. The enormous advances in molecular biology have resulted in the successful development of bio-engineered therapeutic agents, for example, human insulin, Herceptin (Genentech drug for breast cancer), and Enbrel (Immunex drug for rheumatoid arthritis). It is anticipated that many other biomolecules may be forthcoming for the treatment of human disease.

However the great majority of existing drugs are small organic molecules (MW ~200–600) that have been synthesized by medicinal chemists. There is no reason to doubt that most drugs of the future will also fall in this category. It is thus important to define what is meant by "medicinal chemist" and what role is played by the practitioners of this sub-discipline in the pharmaceutical industry. A traditional and perhaps somewhat narrow definition of medicinal chemist is that of a researcher engaged in the design and synthesis of bioactive molecules. As part of their academic training many medicinal chemists carried out doctoral and postdoctoral work that involved the total synthesis of natural products and/or the development of synthetic methodology. They are hired by pharmaceutical companies because of the skills they have gained in planning and conducting the synthesis of organic compounds. While such skills can remain important throughout chemists' careers, they alone are insufficient for the challenging task of drug discovery in which, unlike the academic environment, synthetic chemistry is just a means to an end rather than an end in itself. Thus, the enterprising young chemical researcher who enters the industry must be able and willing to undergo an evolution from that of pure synthetic chemist who knows how to make compounds to that of medicinal chemist who also has an insight into what to make and why.

Such insight is gained by acquiring an expanded knowledge base. It is important for the medicinal chemist to know what structural components act as pharmacophores in existing drugs. Pharmacophores, which can be of varying complexity, comprise the essential structural elements of a drug molecule that enable it to interact on the molecular level with a biological macromolecule such as a receptor or enzyme and thus impart a pharmacological effect. The medicinal chemist must become skilled at analyzing the structure activity relationships (SAR) that pertain to the series of compounds on which he/she is working. That is, how does the activity in a biological test of analogs within the series change depending on the introduction of substituents of various size, polarity, and lipophilicity at various domains of the parent drug molecule? Elucidation of the SAR within a series of active compounds is the key to optimizing the potency and other desirable biological properties in order to identify a new chemical entity (NCE) as a bona fide drug candidate. Quantitative structure activity relationships (QSAR) are often employed in this effort; analyses employing linear free energy relationships, linear regression, and other techniques can be utilized to correlate biological activity with the electronic, steric, polarizability, and other physical/chemical parameters of the substituent groups on members of a series of structurally related compounds.

The synthesis and isolation of pure enantiomers has become increasingly important. In the past chiral drugs were most often marketed as racemic mixtures since it was not deemed cost-effective to provide them in enantiomercially pure form. However, in many cases one or the other enantiomers of an optically active drug may have a significantly greater level of the desired biological activity and/or less side effect liability than its antipode. Regulatory agencies such as the FDA now routinely require that each enantiomer of a chiral drug be isolated and evaluated in tests of efficacy, side effects, and toxicity. If one of the enantiomers is shown to be clearly superior then it is likely that it is the form that will be developed as the

drug candidate. Thus enantioselective chemical reactions which can afford a high enantiomeric excess(ee) of one or the other of a pair of enantiomers are valuable components of the medicinal chemist's synthetic tools. Enzyme chemistry plays a prominent role in drug R&D since isolated enzymes or microorganisms can often achieve an enantiospecific chemical transformation much more efficiently and economically than conventional synthetic methods. Many "big pharma" companies now have dedicated groups that exclusively study enzymatic reactions.

Research Strategies

The discovery of new drugs may occur by luck or serendipity or as the result of some brilliant insight. However pharmaceutical companies cannot depend on chance occurrences as a research strategy. The aforementioned "me-too" approach has hardly been abandoned and it is likely that the marketing of a novel drug will soon be followed by a number of competitors' agents but with the caveat that the latter offer some therapeutic advantage over the prototype.

The most scientifically sound approach is that of rational drug design, which is based on an understanding of the biochemical mechanisms underlying a particular disease. If, for example, overactivity or underactivity of a certain neurotransmitter system is believed to be responsible for a central nervous system (CNS) disorder such as depression, then medicinal chemists can endeavor to design agents capable of normalizing neurotransmission by their action upon the receptor proteins through which interneuronal communication is mediated. Cloning and expression of human genes to afford functional receptors and enzymes that can be studied in cell culture has been a tremendous advance in the ability to evaluate drug action at the molecular level. Likewise, molecular biology has afforded macromolecules that are essential to the life cycle of pathogens such as bacteria and viruses, thus enabling novel mechanistic strategies for the treatment of infectious disease. In many cases, X-ray crystallography has provided a detailed three-dimensional structure of a macromolecule such as an enzyme with and/or without a bound substrate. Researchers having expertise in computer assisted drug design (CADD) can depict the determined structure on silicon graphics terminals and in collaboration with medicinal chemists can propose drug molecules to fit the active site. Such detailed analysis of protein structure was instrumental in the design of a number of drugs that inhibit HIV protease, an enzyme essential to the integrity of the AIDS virus.

Up until now there have been approximately 1000 human proteins identified as potential targets for drug intervention in various diseases. It is estimated that the determination of the human genome will increase this number by at least tenfold. Therefore, it seems safe to predict that the rational approach to drug discovery will grow accordingly and with it the role of synthetic/medicinal chemistry. There will be intense competition within the pharmaceutical industry to determine the functional relevance of this multitude of new targets in the absence and presence of disease and a close nexus to this quest will be the search for compounds that can impart selective pharmacological effects upon the target proteins. But it is not likely that these goals can be met by employing only the classical iterative approach which entails one-compound-at-a-time synthesis and low volume testing. Instead the challenges of this exciting new era of research must be met by methodologies that can synthesize and test large numbers of compounds in a short period of time—that is, combinatorial chemistry and high-throughput screening (HTS). In the context of its application within pharmaceutical research, combinatorial chemistry should not be regarded as a separate discipline but instead as a technologically specialized part of medicinal chemistry. This topic will be discussed in detail in a later section of the chapter.

Another important interface occurs with chemists in process research and development.

In most cases medicinal chemists are not overly concerned with the cost, toxicity, or environmental impact of the starting materials, reagents and solvents they employ to synthesize target compounds since they are dealing with relatively small quantities of materials. Neither are reaction conditions employing very low or elevated temperatures and pressures problematic on the discovery scale. However these and other pragmatic considerations must be taken into account for the bulk scale preparation of experimental drugs. Process chemists must very often modify the synthetic procedures of their medicinal chemistry colleagues and in many cases devise an entirely new synthetic pathway. Process chemistry will also be discussed in an ensuing section.

Pharmacodynamics

Medicinal chemists must be generally knowledgeable about pharmacodynamics, that is, the effect of drugs upon biological systems. In addition to being aware of the state-of-the-art understanding of the biological mechanisms that underlie the particular diseases for which they are endeavoring to discover drug therapy they should know the basis of the various in vitro and in vivo tests that the biologists employ to evaluate both the potential efficacy and side-effect liability of the synthesized compounds. Because drug research covers a plethora of human diseases, each with its own unique combination of etiology and biochemical mechanisms, the number and diversity of biological tests are far too great to discuss in this chapter. Suffice it to say that in a general sense the primary and often even the secondary biological tests of drugs for a particular disease target are in vitro tests that can be run rather quickly, inexpensively, and on small amounts of compound. For example, these can be receptor binding assays for CNS drugs, enzyme assays for antihypertensive agents, inhibition of bacterial colony growth by antibiotics, and the killing of cultured cancer cells by oncolytic drugs. Encouraging in vitro results lead to in vivo testing in some appropriate animal model. In vivo tests are more laborious and costly but are necessary to establish that a drug is effective in an intact living organism; they can range from complex behavioral paradigms for CNS drugs to enhancement of survival time of tumor-implanted mice by experimental cancer drugs. Evaluation of a NCE's propensity to cause side effects is as important as efficacy testing. Even if a compound shows an encouraging level of the desired activity, a lack of selectivity can cause it to induce a number of undesirable pharmacological effects thus precluding its further development. The medicinal chemist must be able to interpret the results of the tests run on his/her compounds and use this information as a guide to further synthetic work.

Pharmacokinetics and Toxicity

It is also necessary that chemists are attuned to various aspects of pharmacokinetics (PK), that is, the effects of biological systems upon drugs. These aspects—absorption, distribution, metabolism and excretion (ADME)—are as critical as biological activity in determining whether a NCE is a viable drug candidate. A compound may exhibit high affinity for a biological receptor or potent inhibition of an enzyme in an in vitro assay but if it is poorly absorbed or rapidly metabolized to inactive species then it will be ineffective as a drug. For example, the empirically based Lipinsky's rules of five (Table 11.1) define the limits of such physical/chemical parameters as molecular weight, lipophilicity,

TABLE 11.1 Lipinski's Rules for Drug Absorption

Absorption of a drug following oral administration is favored by:

- Molecular weight is <500
- The drug molecule has <5 hydrogen bond donors
- The drug molecule has <10 hydrogen bond acceptors
- The distribution coefficient, log P, is <5

Source: Lipinski, C. A., Lombardo, F., Dominy, D. W., and Feeny, P. J., *Adv. Drug Delivery Rev.*, **23**, 3–25 (1997).

and hydrogen bond forming moieties that must be considered for the absorption of orally administered drugs. A compound with potent intrinsic activity can be rendered ineffective in vivo by its rapid conversion to inactive metabolites. The susceptibility of compounds to metabolic conversion can be assessed by incubating them with liver homogenates from various species including rodent, dog, monkey, and man or with cloned, expressed human hepatic enzymes. Analysis of the incubates by liquid chromatography/mass spectometry (LC/MS) can quantify the extent of metabolism and even identify some specific metabolites. In vivo adminstration of a NCE to one or several animal species is required to determine its oral bioavailability, half-life, and other PK properties such as distribution and elimination. If an unsatisfactory PK profile threatens to be the demise of an otherwise promising drug candidate, it falls upon the medicinal chemist to make structural permutations aimed at correcting the problem. If poor absorption is the problem this may entail modifying the lipophilicity of the drug molecule to render it more membrane permeable. A metabolic liability might be rectified by blocking the site of biotransformation with a metabolically inert atom or group.

Toxic effects upon blood or organs or the potential to cause gene aberrations will red flag a compound regardless of its having both excellent biological activity and PK properties. Promising lead compounds are screened in in vitro tests in bacteria and mammalian cells to determine whether they cause gene mutations and DNA damage. If they pass this hurdle the compounds are dosed on a daily basis for several weeks to several months in both a rodent and nonrodent (usually dog or monkey) species and the animals are observed for any adverse effects; the test animals are necropsied following conclusion of the study to ascertain whether any organ or tissue damage occurred. Unacceptable toxicological findings will invariably kill a drug candidate and again it is the medicinal chemist who will be called upon to save the day by devising and implementing structural modifications to eliminate the toxicity. This may be a more daunting task than overcoming a side effect or metabolic issue, especially if the toxicity is mechanism-based.

Drug Delivery

Drugs can be administered to patients in many ways. The most common and preferred route is oral administration and oral drugs are generally formulated as tablets or capsules in which a specific dose of the drug substance is homogeneously mixed with some inert filler or excipient. Some oral medications, such as pediatric formulations of antibiotics, are in solution form, as are injectable drugs. Obviously this requires satisfactory solubilization of the drug, preferably in aqueous medium. Compounds bearing some ionizable group such as a basic amine or an acidic function can usually be converted into water-soluble salts but neutral molecules present greater difficulties. In some cases the results of clinical trials will indicate that an experimental injectable drug shows promise of efficacy but does not elicit a robust response because its poor solubility limits the amount that can be administered and thus does not allow adequate plasma levels to be attained. Inadequate membrane permeability can restrict the absorption and bioavailability of an orally administered drug.

Medicinal chemists can respond to such findings by investigating the feasibility of preparing a suitable prodrug. A prodrug is a derivative in which a cleavable solubilizing group is covalently appended to the parent drug molecule, most often via a hetero atom such as oxygen or nitrogen. An effective prodrug is one which has much higher solubility than the parent drug and which following its administration is rapidly cleaved in vivo to achieve a therapeutically beneficial plasma concentration of the parent drug.

Patents

Patent protection on both its approved and experimental drugs is of critical importance to

a pharmaceutical company. Issued patents provide the company with exclusivity for the manufacture, use, and sale of its drug products and it is highly unlikely that a company would undertake the risks and costs of developing an agent for which it had no patent protection. There are several types of patents of which the "composition of matter" (COM) or "product" patent may be deemed to have the greatest value. An approved COM patent covers specifically claimed compounds of a certain structural chemotype and provides empirical evidence that the claimed compounds have been prepared, characterized, and found to have some utility. In order to be patentable the compounds must have structural novelty and cannot have been publicly disclosed either in the scientific or patent literature or by a presentation. But structural novelty alone is not sufficient grounds for a patent; it must be demonstrated that the compounds are useful and in the context of a drug patent the proposed utility is for the treatment of some disease. The basis of such utility is activity in appropriate and relevant biological tests. Clinical data may also be used in support of a patent application although in the great majority of cases the applications are filed well before any compound within the application reaches clinical trials.

Medicinal chemists are closely affiliated with the patent process and are most commonly the inventors listed on COM patents covering drug substances. The chemists and other researchers with whom they collaborate must provide the chemical and biological data for the patent and the chemists will also provide input as to the scope and claims of the patent. Since patents are legal documents that provide the assignee exclusive proprietary rights to the covered subject matter for 20 years from the date of the patent's issue, it is essential that all supportive data be accurate and instructive. If a patent is ever challenged by another party and is found to contain erroneous information then it could be invalidated. Moreover, in the United States, patents are granted on a "first-to-invent" basis. Thus if two or more parties submit applications on identical subject matter to the U.S. Patent Office then the patent will be awarded to the party that can prove that it had the earliest conception and reduction to practice of the subject matter. Therefore it is imperative that chemists maintain accurate records of all experimental work in a bound notebook and that such records are dated, signed, and witnessed.

Other types of drug-related patents include process, use, and formulation patents. Chemists are responsible for process patents, which describe an improved method of preparation of some drug substance but are minimally involved with the others. Use patents are based on the discovery of some unobvious utility of a compound that is either part of the public domain or covered by an existing patent; such discoveries are most likely to be made by biologists. Formulation patents disclose a preferred means of drug delivery of a known drug substance.

Clinical Trials

Even though there is no involvement of chemistry in the clinical evaluation of drugs, any discussion of the pharmaceutical industry must include clinical trials for the results of such trials determine whether or not an experimental drug has the combination of efficacy, safety, and tolerability which will allow it to achieve registrational approval and reach the market. If a drug candidate survives the hurdles of pharmacological, pharmacokinetic, and toxicological testing, the next customary step in the United States is the sponsoring firm's filing of an Investigational New Drug (IND) application with the FDA. This is a formal request to initiate clinical investigation in man and is accompanied by a detailed description of the planned studies and clinical protocols. Upon approval of the IND, Phase I clinical studies are initiated.

Phase I studies are conducted in healthy volunteers in order to establish the drug's safety and to determine appropriate dosage levels. If the drug is found to have an acceptable human pharmacokinetic profile and to be free of untoward side effect liabilities, it is advanced into Phase II trials, which are typically carried out in several hundred

patients and may last from six months to two years. Phase II trials are designed to ascertain the appropriate dosing regimen for the drug and whether it is effective in treating the target disease. Only about one third of drugs pass Phase II trials, most failing because of the lack of efficacy. Those that pass are advanced into Phase III trials which may involve from several hundred to several thousand patients and which can last from one to three years or even longer depending on the type of drug under study and the complexities of the study design. Phase III trials provide the ultimate test of an experimental drug since they are designed to verify the drug's effectiveness against the target disease as well as its safety. For agents that are intended for chronic use, studies also monitor adverse reactions that may develop only after long-term use and the development of tolerance. Clinical studies of many drug classes will commonly employ several patient groups of approximately equal size with one group receiving the experimental drug, another placebo (nondrug), and another a positive control, that is, a marketed drug used to treat the same disease for which the experimental agent is being evaluated. In order to minimize the possibility of bias in favor of the test drug, such studies are most often run in a double-blinded manner with neither patients nor clinical investigators knowing which group is receiving which treatment until the conclusion of the trial.

If a drug candidate is among the one in four to five that gets through Phases I–III and if statistical analysis of the clinical data supports its efficacy then the sponsoring firm will assemble the voluminous data into the NDA which is submitted to the FDA. Review of the NDA can take one to two years and often the FDA may request that additional information be provided or even that some additional studies be done. When approval is granted the company is then free to market the drug.

The results of clinical evaluation of an experimental drug can feed back into medicinal chemistry. For example, if a drug is found to fail because of poor bioavailability in humans then medicinal chemists will endeavor to design and prepare an analog with improved pharmacokinetic properties.

Summary

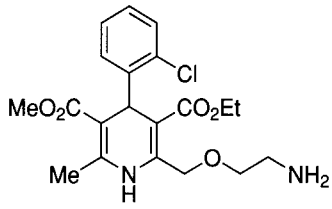
The preceding sections present what is an admittedly superficial overview of the very extensive and complex topic of medicinal chemistry, its role in the pharmaceutical industry, and its interface with other disciplines. An acquired understanding of relevant biology, pharmacology, toxicity, and so on is not just of heuristic value but is necessary for the chemist to engage in meaningful dialogue with their colleagues who work in these specialties. Successful drug discovery and development cannot be done by individuals working in isolation but requires the interactive collaboration of many researchers representing a multiplicity of scientific disciplines as depicted in Fig. 11.1. It may be argued that medicinal chemists are the most versatile generalists among these researchers in that they must have primary expertise in chemistry along with extensive knowledge of numerous other areas.

The following section presents examples of marketed drugs in a number of different therapeutic categories.

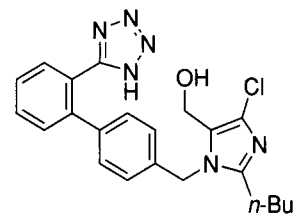
CARDIOVASCULAR AGENTS

Hypertension

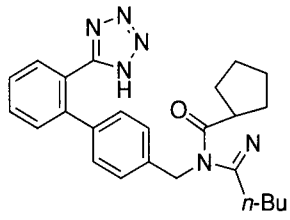
A variety of agents of several mechanistic types are currently available for the treatment of hypertension (elevated blood pressure). The dihydropyridine derivative amlodipine (Norvasc®/Pfizer) is a receptor-operated, calcium entry blocker that prevents Ca^{++} entry into vascular smooth muscle cells. Amlodipine is also useful for the treatment of angina. Losartan (Cozaar®/Merck) and irbesartan (Avapro®/Bristol-Myers Squibb) are angiotensin receptor antagonists that inhibit the action of angiotensin II on the AT_1 receptor. Metoprolol (Toprol®/AstraZeneca) is a cardioselective, β_1-adrenergic receptor blocking agent and is also useful in the treatment of angina.



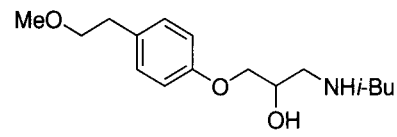
amlodipine



losartan



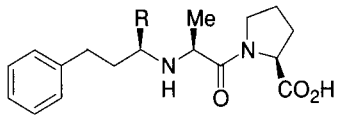
irbesartan



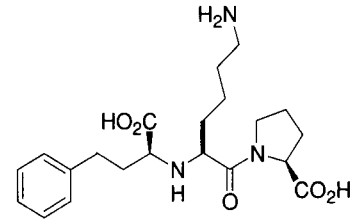
metoprolol

Congestive Heart Failure, Migraine, and Thrombolytic Agents

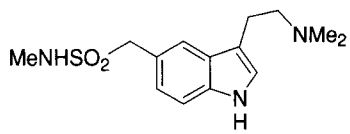
Enalapril (Vasotek®/Merck) and lisinopril (Zestril®/AstraZeneca and Prinvil®/Merck) are angiotensin-converting enzyme (ACE) inhibitors, useful in the treatment of congestive heart failure and hypertension by suppression of the renin–angiotensin–aldosterone system. Enalapril is an ethyl ester prodrug that is hydrolyzed in the liver to the active carboxylic acid enalaprilat. Sumatriptan is a selective agonist of serotonin (5-hydroxytryptamine) type-1 receptors (most likely the 5-HT_{1B} and 5-HT_{1D} subtypes) in the vasculature. It is thought to exert its beneficial effects on migraine headaches by selective constriction of certain large cranial blood vessels and/or possibly through suppression of neurogenic inflammatory processes in the central nervous system. Clopidogrel (Plavix®/Bristol-Myers Squibb, Sanofi-Synthelabo) is an inhibitor of ADP-induced platelet aggregation and is useful in the treatment of various thrombolytic events such as stroke and myocardial infarction.



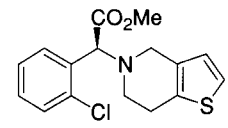
enalapril, R = CO_2Et
enalaprilat, R = CO_2H



lisinopril



sumatriptan



clopidogrel

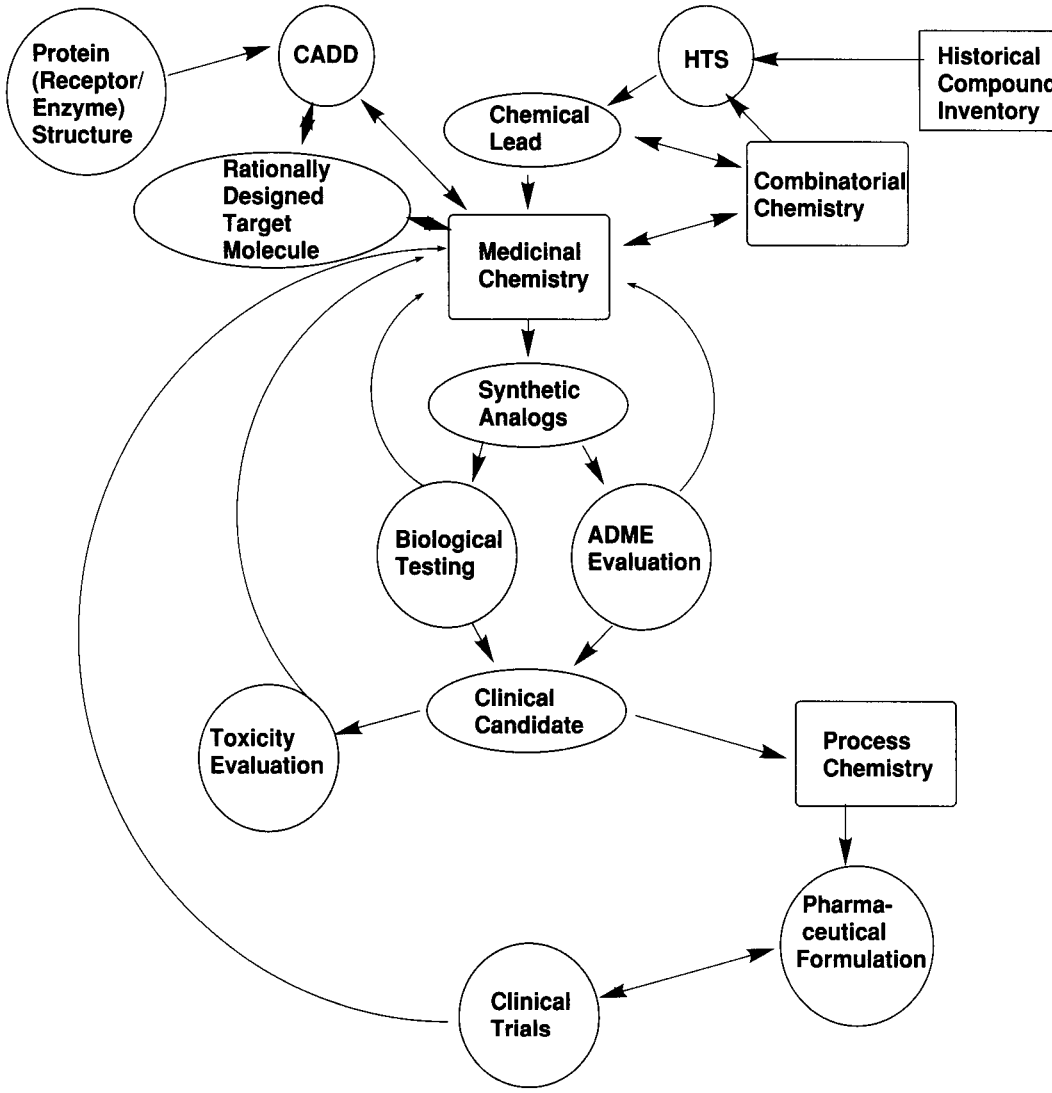


Fig. 11.1. Drug discovery and development is a complicated process that involves the interaction of researchers in various disciplines. Medicinal chemists may synthesize analogues based on chemical leads arising from the high throughput screening of combinatorial libraries or historical compound inventories. Alternatively, analogue synthesis can be based on the collaboration between medicinal chemistry and computer-assisted drug design to rationally design small molecules capable of interacting with a macromolecular biological target (receptor or enzyme). Subsequent biological, pharmacokinetic, and toxicological avaluations lead to identification of a drug candidate that, following development of a suitable bulk scale synthesis by process chemistry and pharmaceutical formulation, is advanced into clinical trials. Feedback to medicinal chemistry from any of these developmental steps can give rise to further synthetic modifications and refinements.

METABOLIC AGENTS

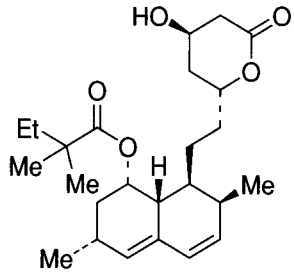
Hyperlipidemia

Simvastatin (Zocor®/Merck), pravastatin (Pravachol®/Bristol-Myers Squibb), atorvastatin (Lipitor®/Pfizer), and rosuvastatin (Crestor®/ AstraZeneca) are hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) that lower serum lipid levels by inhibiting cholesterol biosynthesis. Simvastatin and pravastatin are semi-synthetic, mevinic acid-derived antilipidemic agents whereas atorvastatin is a wholly synthetic, pentasubstituted pyrrolo heptanoic acid. Unlike pravas-

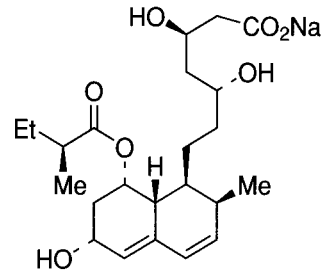
tatin, atorvastatin, and atorvastatin, simvastatin is a lactone prodrug which must be converted to the corresponding, ring-opened δ-hydroxy acid in vivo. A newer agent with a novel mechanism of action is ezetimibe (Zetia®/Merck, Schering Plough). Ezetimibe does not inhibit cholesterol biosynthesis in liver as do the statins but rather inhibits cholesterol absorption in the intestine. This novel action is complementary to the HMG-CoA reductase mechanism displayed by the statins. An innovative new product for the treatment of hyperlipidemia is Vytorin®. It was developed by Merck and Schering Plough and consists of a mixture of simvastatin and ezetimibe in one pill.

Diabetes

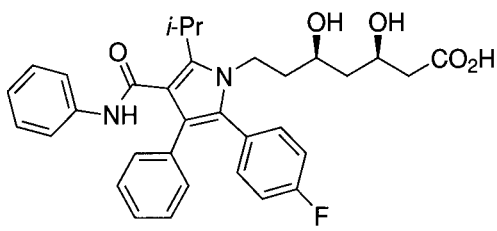
A variety of mechanistic agents are currently available for the treatment of type 2 (noninsulin-dependent) diabetes mellitus (NIDDM)]. Rosiglitazone (Avandia®/GlaxoSmithKline) is a thiazolidinedione (glitazone) antidiabetic agent and an agonist at the peroxisome proliferator-activated receptor$_{gamma}$ (PPAR$_{gamma}$). Activation of this receptor enhances insulin sensitivity in target tissues by increasing



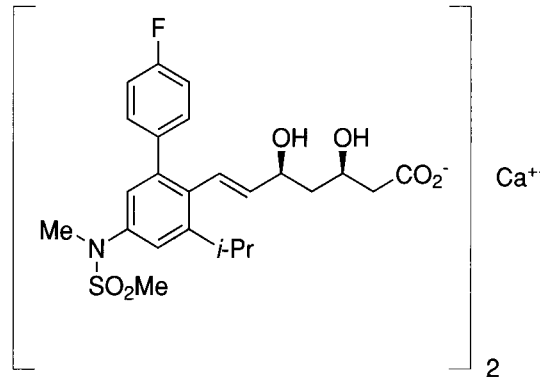
simvastatin



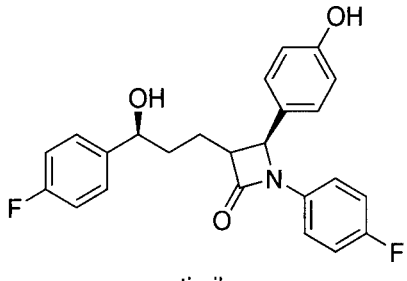
pravastatin



atorvastatin

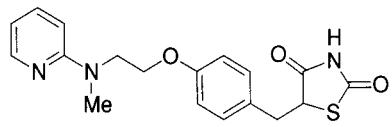


rosuvastatin

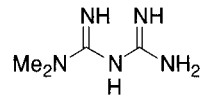


ezetimibe

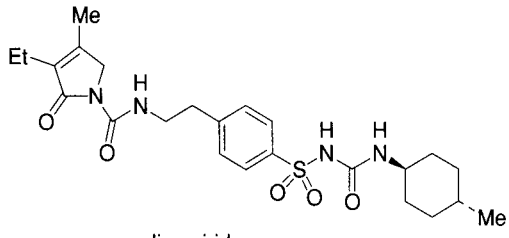
insulin-responsive gene transcription. Metformin (Glucophage®/Bristol-Myers Squibb) is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes. The compound acts by decreasing both hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Glimepiride (Amaryl®/Aventis) is in the sulfonylurea class of antidiabetic agents. Glimepiride is thought to lower blood glucose concentration by stimulating insulin secretion in pancreatic beta cells.



rosiglitazone



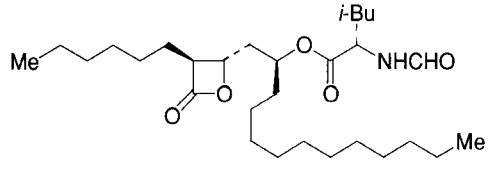
metformin



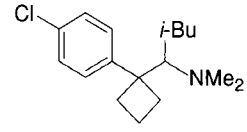
glimepiride

Obesity

Orlistat (Xenical®/Roche) is a reversible gastric and pancreatic lipase inhibitor. The compound has no effect on appetite suppression but rather acts by inhibiting dietary fat absorption from the GI tract. Sibutramine (Meridia®/Abbott) and its major active metabolites are re-uptake inhibitors of norepinephrine, serotonin, and dopamine and exert their beneficial effect through appetite suppression.



orlistat

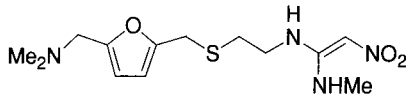


sibutramine

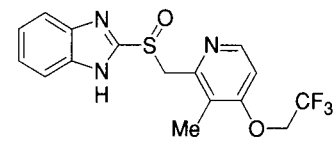
GASTROINTESTINAL AND GENITOURINARY AGENTS

Antisecretory

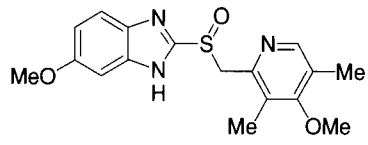
Ranitidine (Zantac®/GlaxoSmithKline) is a histamine H_2-receptor antagonist that inhibits the release of gastric acid and is useful in the treatment of a variety of hypersecretory conditions [dyspepsia, heartburn, duodenal and gastric ulcers, and gastroesophageal reflux (GERD)]. Lansoprazole (Prevacid®/TAP), omeprazole (Prilosec®/AstraZeneca), and esomeprazole (Nexium®/AstraZeneca) are benzimidazole gastric antisecretory agents and unrelated both chemically and pharmacologically to the H_2-receptor antagonists. These agents are known as proton pump inhibitors due to their ability to inhibit the H^+K^+-ATPase (the proton pump) in gastric parietal cells thereby blocking the secretion of hydrochloric acid. Esomeprazole is the S-enantiomer of omeprazole which is racemic and thus a mixture of both its R-and S-enantiomers. Lansoprazole and omeprazole are also useful in the management of duodenal and gastric ulcers, and GERD.



ranitidine



lansoprazole



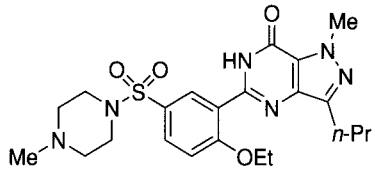
omeprazole

Benign Prostatic Hyperplasia and Urinary Urge Incontinence

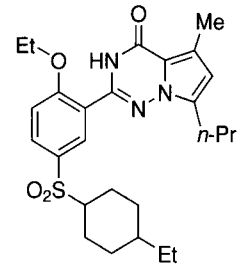
Doxazosin (Cardura®/Pfizer), tamsulosin (Flomax®/Boehringer Ingelheim), and alfuzosin (Uroxatral®/Sanofi-Synthelabo) are used in the management of benign prostatic hyperplasia (BPH). The compounds are postsynaptic, α_1-adrenergic blocking agents that relax prostatic tissue and increase urinary outflow in men. Because tamsulosin demonstrates selectivity for the α_{1A}-adrenergic receptor subtype located in prostate over that of α_{1B}-subtype located in vascular tissue, there is a reduced incidence of cardiovascular side effects (hypotension, dizziness, and syncope). Because doxazosin is not selective for the α_{1A}-subtype, it is also useful in the treatment of hypertension. Finasteride (Proscar®/ Merck) and dutasteride (Avodart®/ GlaxoSmithKline) are 5α-reductase inhibitors that block the conversion of testosterone to 5α-dihydrotestosterone (DHT). Because DHT is an androgen responsible for prostatic growth, inhibition of the 5α-reductase enzyme is beneficial in reducing prostatic enlargement.

Erectile Dysfunction

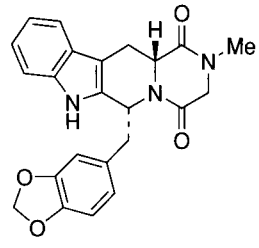
The pyrazolopyrimidinone derivative sildenafil (Viagra® /Pfizer), the indolopyrazinone



sildenafil



vardenafil



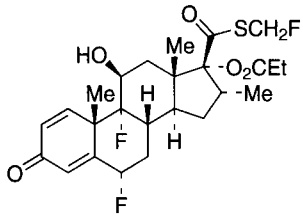
tadalafil

derivative tadalafil (Cialis® /Lilly ICOS), and the imidazotrizinone derivative vardenafil (Levitra® /Bayer) are selective inhibitors of the phosphodiesterase (PDE) type 5 enzyme. They act by selectively blocking the PDE type 5 isoenzyme ultimately causing vascular vasodilation in corpus cavemosal tissue which, in turn, leads to penile tumescence and rigidity.

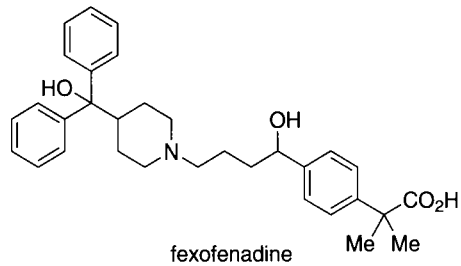
PULMONARY AGENTS

Asthma and Allergic Rhinitis

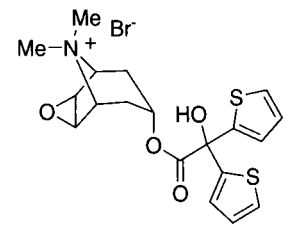
Fluticasone (Flovent®/GlaxoSmithKline) is a synthetic corticosteroid derivative that is a selective agonist at the human glucocorticoid receptor and useful in the treatment of asthma. Although the precise mechanism of fluticasone in asthma is unknown, it is believed it's anti-inflammatory property contributes to its beneficial effect. The butyrophenone derivative fexofenadine (Allegra®/ Aventis) is an antihistamine and used in the treatment of seasonal allergic rhinitis. Because fexofenadine does not readily cross the blood–brain barrier, it is considered a "nonsedating" antihistamine. More recently, the quaternary ammonium tricyle tiotropium bromide (Spiriva®/Boehringer-Ingelheim/Pfizer) has been introduced. It is a long-acting bronchodilator useful in the treatment of asthma and exerts its pharmacological effect through inhibition of the muscarinic M_3 receptor.



fluticasone



fexofenadine

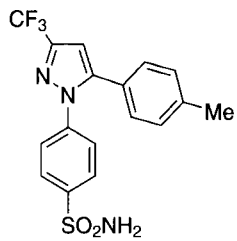


tiotropium bromide

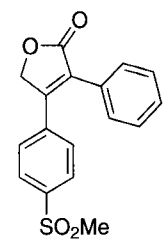
INFLAMMATION AND OSTEOPOROSIS

Arthritis

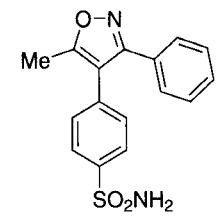
The diaryl pyrazole derivative celecoxib (Celebrex®/Pharmacia, Pfizer), the furanone derivative rofecoxib (Vioxx®/Merck), and the isoxazole derivative valdecoxib (Bextra®/ Pfizer) are selective cyclooxygenase type 2 (COX-2) inhibitors and are useful in the treatment of arthritis. The compounds exert their pharmacological effect by selectively blocking the COX-2 enzyme to produce an anti-inflammatory effect without adverse gastrointestinal side effects. In addition, they also display analgesic and antipyretic activities in animal models.



celecoxib



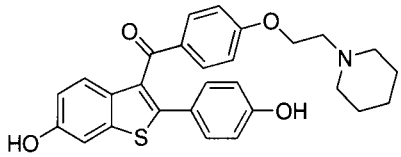
rofecoxib



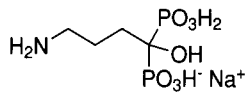
valdecoxib

Osteoporosis

The benzothiophene derivative raloxifene (Evista®/Lilly) is a selective estrogen receptor modulator (SERM). Raloxifene produces its biological actions via modulation (both activation and blockade) of estrogen receptors that ultimately results in decreased resorption of bone. The bisphosphonate derivative alendronate (Fosamax®/Merck), an inhibitor of osteoclast-mediated bone resorption, is also useful in the treatment of osteoporosis. Both raloxifene and alendronate are useful in the treatment of osteoporosis in postmenopausal women.



raloxifene

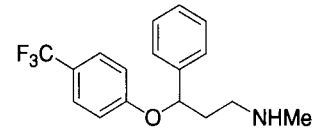


alendronate

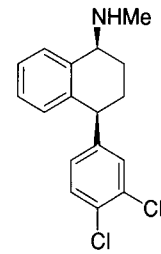
CENTRAL NERVOUS SYSTEM AGENTS

Antidepressants

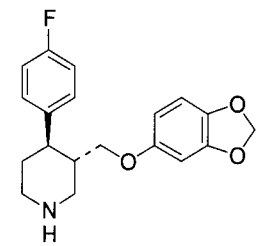
Fluoxetine (Prozac®/Lilly), paroxetine (Paxil®/GlaxoSmithKilne), and sertraline (Zoloft®/Pfizer) are selective serotonin reuptake inhibitors (SSRIs) and are useful in the treatment of depression. These agents potentiate the pharmacological actions of the neurotransmitter serotonin by preventing its reuptake at presynaptic neuronal membranes. In addition to its SSRI properties, venlafaxine (Effexor®/Wyeth-Ayerst) also appears to be a potent inhibitor of neuronal norepinephrine reuptake and a weak inhibitor of dopamine reuptake thereby enhancing the actions of these neurotransmitters as well. Venlafaxine is indicated for use in anxiety and depression.



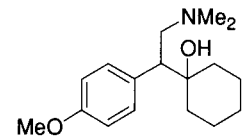
fluoxetine



sertraline



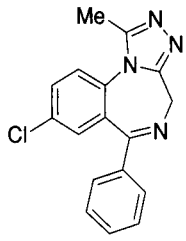
paroxetine



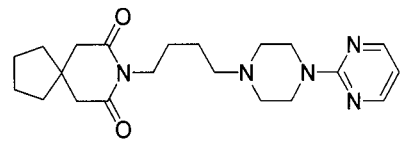
venlafaxine

Anxiolytics

Alprazolam (Xanax®/Pharmacia), a benzodiazepine derivative is used for the treatment of both anxiety and panic disorder and buspirone (Buspar®/Bristol-Myers Squibb) is indicated for the treatment of anxiety disorders. The mechanism of action of buspirone is distinct from that of the benzodiazepines and is believed to be mediated mainly through modulation of serotonergic neurotransmission via its interaction with the 5-HT_{1A} serotonin receptor subtype.



alprazolam



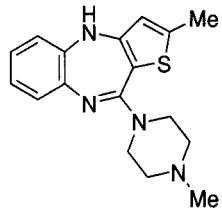
buspirone

Bipolar Disorders, Schizophrenia, and Epilepsy

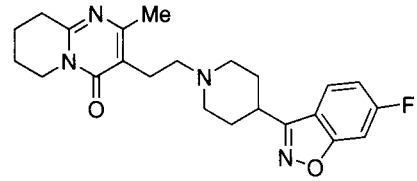
The thienobenzodiazepine derivative olanzapine (Zyprexa®/Lilly), and benzisoxazole risperidone (Risperidal®/Janssen) are atypical antipsychotic agents. Olanzapine is used in the treatment of bipolar disorder and risperidone is useful in the management of schizophrenia. It is believed that both compounds exert their beneficial effects through antagonism of serotonergic and dopaminergic receptors. A newer agent for the treatment of schizophrenia is aripiprazole (Abilify®/ Bristol-Myers Squibb, Otsuka). It is believed the pharmacological effects are mediated through a combination of partial agonist activity at the dopamine D_2 and serotonin 5-HT_{1a} receptors and antagonism at the serotinergic 5-HT_2 receptor. The γ-aminobutyric acid derivative (GABA) gabapentin (Neurontin®/ Pfizer) is useful in the treatment of epilepsy. Although structurally related to GABA, it has no GABA-ergic activity. The mechanism for its anticonvulsive actions is currently unknown.

Alzheimer's Disease

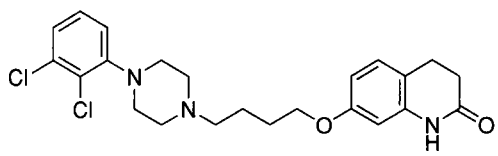
The indanone derivative donepezil (Aricept®/ Pfizer, Eisai) is an acetycholinesterase inhibitor and is structurally unrelated to other cholinesterase inhibitors. Because it increases the concentration of the neurotransmitter acetycholine at cholinergic sites, it is useful in the treatment of Alzheimer's disease (dementia). Another agent useful in the treatment of Alzheimer's disease is the adamantlyl amine derivative memantine (Namenda®/ Forest). Memantine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist and is thought to exert its pharmacological effect by blocking the



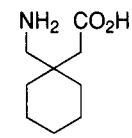
olanzapine



risperidone

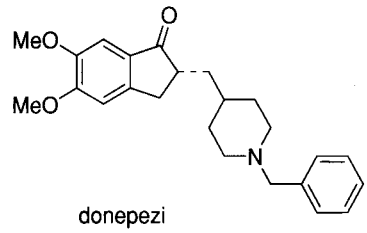


aripiprazole

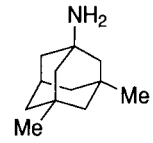


gabapentin

excitatory action of the amino acid glutamate on the receptor. Memantine has shown no evidence of preventing or slowing neurodegenaration in Alzheimer's patients.



donepezi

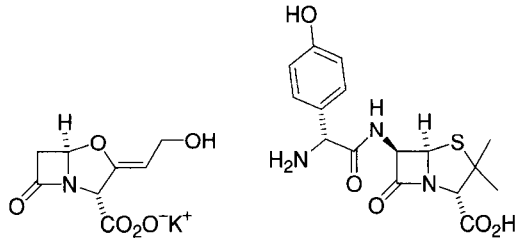


memantine

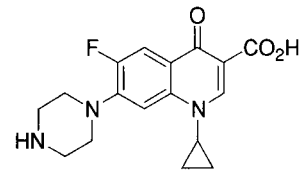
INFECTIOUS DISEASES

Antibacterials

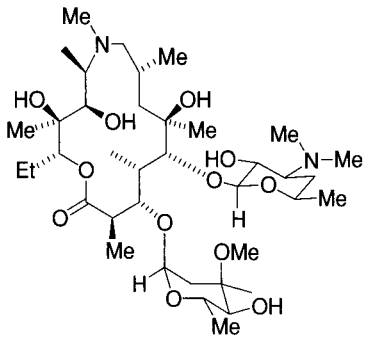
The primary driver for research in the antibacterial area over the past decade has been the emergence of resistant organisms. Important members of the ever-growing armamentarium of antibacterials include azithromycin (Zithromax®/Pfizer), linezolid (Zyvox®/Pharmacia), amoxicillin / clavulanate potassium (Augmentin®/GlaxoSmithKline), ciprofloxacin (Cipro®/Bayer) and daptomycin (Cubicin/Cubist). Azithromycin is a semisynthetic 9α-azalide analog of erythromycin possessing improved resistance to acid-mediated degradation, increased activity against gram-negative organisms, and improved pharmacokinetics. It's indications include the treatment of mild to moderate upper and lower respiratory tract infections and otitis media in pediatrics. Interestingly, azithromycin tends to concentrate in lung tissue which is the site of many bacterial infections. Amoxicillin/Clavulanate is one of the few approved drug mixtures and is a drug of choice for the treatment of otitis media. It is also an alternative treatment for anthrax exposure in pediatrics. Ciprofloxacin is a totally synthetic antibacterial that acts as a DNA gyrase inhibitor. It is active against a broad range of pathogens including both gram-positive and gram-negative aerobic bacteria and is effective against urinary tract and lower respiratory tract infections. Linezolid is a totally synthetic oxazolidinone derivative which has a unique mechanism of action resulting in a low potential for cross resistance to other antibacterials. Linezolid is indicated for the treatment of community acquired pneumonia, MRSA, and VRE infections and has the distinctive characteristic of being 100% orally bioavailable. Daptomycin (Cubicin®/Cubist), a cyclic lipopeptide of molecular formula $C_{72}H_{101}N_{17}O_{26}$, is a bactericidal antibacterial agent used for the treatment of infections caused by gram-positive bacteria including those that are resistant to standard antibacterial regimens.



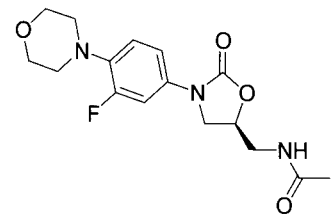
amoxicillin / clavulanic Acid



ciprofloxacin



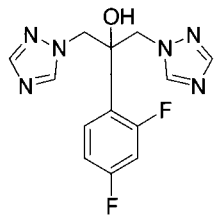
azithromycin



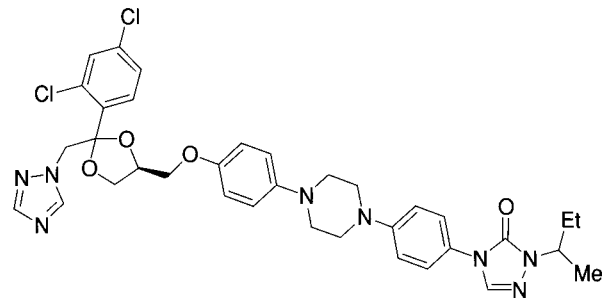
linezolid

Antifungals

The increasing immunocompromised patient population has exacerbated the need for effective antifungal agents to combat opportunistic fungal infections that arise in these patients. Fluconazole, an achiral triazole derivative, is indicated for the treatment of systemic candidiasis as well as meningitis caused by *Cryptococcus neoformans*. Itraconazole (Sporanox®/Janssen, Ortho Biotech), a mixture of four diastereomers, is used to treat aspergillosis, oral candidiasis, and histoplasmosis. These agents are structurally related to other imidazole-based antifungals such as ketoconazole and miconazole but have better antifungal activity and broader coverage.



fluconazole

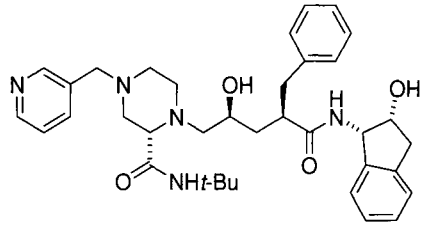


itraconazole

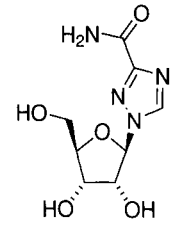
Antivirals

Antiviral research has become a major focus in the pharmaceutical industry over the past decade as evidenced by the marketing of a plethora of antiviral agents active against HIV/AIDS, Hepatitis B and C, and RSV. Indinavir (Crixivan®/Merck) is one of a group of HIV protease inhibitors and is used in conjunction with other antiretroviral chemotherapeutic agents for the treatment of AIDS in adults and adolescents. It is a Phe-Pro scissile bond peptidomimetic with a hydroxyindane moiety that was optimized for selectivity and potency. More recently, atazanavir sulfate (Reyataz®/Bristol-Myers Squibb) was introduced as the latest protease inhibitor. Clinical data suggests that atazanavir may have a more favorable hypertriglyceridemia profile as compared to other protease inhibitors. Ribavirin (Rebetron®/Schering Plough and Virazole®/ICN) is a synthetic nucleoside used to treat respiratory syncytial virus (RSV) in hospitalized infants and is also used in combination therapy with interferon for the treatment of chronic hepatitis C. Efavirenz (Sustiva®/Bristol-Myers Squibb) is

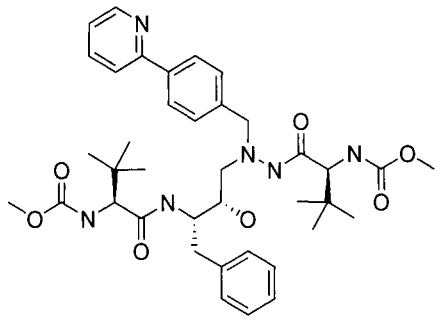
a synthetic nonnucleoside reverse transcriptase inhibitor (NNRTI) used in conjunction with other antiretroviral agents for the treatment of HIV.



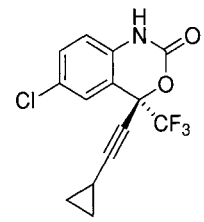
indinavir



ribavirin



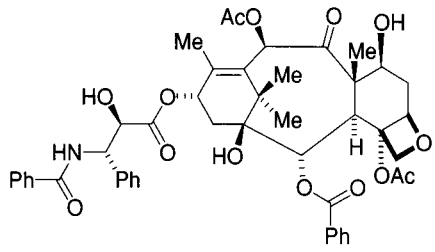
atazanavir



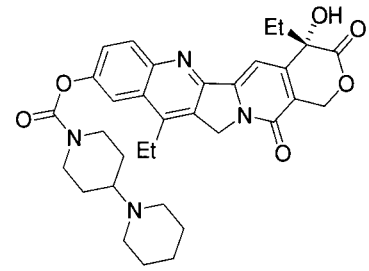
efavirenz

ANTINEOPLASTICS

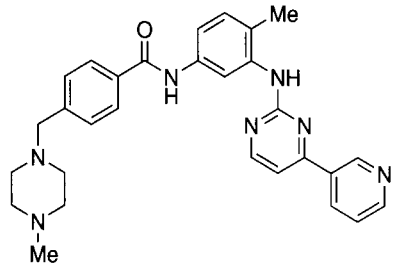
Paclitaxel (Taxol®/Bristol-Myers Squibb) and irinotecan (Camptosar®/Pharmacia) were discovered as a result of natural product extract screening done at the NIH in the late 1960s by Monroe Wall and Mankush Wani. Paclitaxel is a naturally occurring diterpene that exerts its antineoplastic effect via stabilization of the mitotic spindle during cell replication. It is used for the treatment of nonsmall cell lung, breast, ovarian, and esophageal carcinomas as well as Kaposi's sarcoma. Irinotecan is a prodrug that upon release of the piperidinylpiperidine carbamate moiety reveals the pharmacologically active parent SN-38 which is itself a derivative of the naturally occurring camptothecin. Irinotecan exerts its antineoplastic activity via the inhibition of Type I DNA topoisomerase and stabilization of the transiently formed Topoisomerase I/DNA cleavable complex. Tamoxifen (Nolvadex®/AstraZeneca), a nonsteroidal antiestrogen chemotherapeutic possessing both agonistic and antagonistic properties, is used for the treatment and prevention of breast cancer. Imitanib (Gleevac®/Novartis), an inhibitor of Bcr-Abl tyrosine kinase recently received FDA approval for the treatment of chronic myelogenous leukemia. Bortezomib (Velcade®/Millenium and Ortho Biotech), an iv ubiquitin proteosome inhibitor, is used for the treatment of multiple myeloma in pateints who have been refractory to other chemotherapeutic regimens. Cetuximab (Erbitux®/ImClone, Merck KGaA, and Bristol-Myers Squibb) a human–murine chimeric monoclonal antibody that blocks the epidermal growth factor receptor (EGFR), was developed for the treatment of irinotecan-refractory colorectal cancer. This agent is also used in patients who are irtolerant of irinotecan-based therapy. The small molecule EGFR tyrosine kinase inhibitor gefitinib (Iressa®/AstraZeneca) is used to treat nonsmall cell lung cancer.



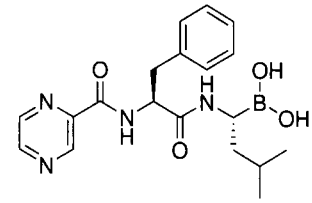
paclitaxel



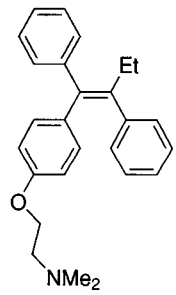
irinotecan



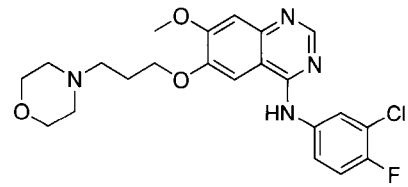
imatinib



bortezomib



tamoxifen

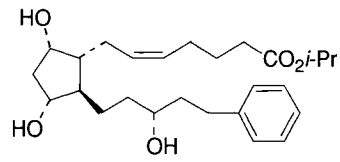


gefitinib

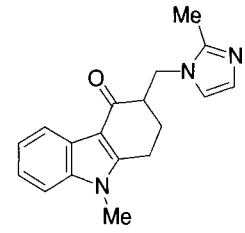
MISCELLANEOUS AGENTS

Glaucoma and Nausea

Latanoprost (Xalatan$/Pharmacia & Upjohn) is a topical, ocular hypotensive agent used to treat glaucoma. The compound is a synthetic analogue of the naturally occurring prostaglandin PGF2α and is thought to reduce intraocular pressure by increased outflow of the aqueous humor. Odansetron (Zofran®/GlaxoSmithKline) is a selective, serotonergic, 5-HT_3 receptor antagonist and is used to ameliorate nausea and vomiting associated with chemotherapy-induced emesis.



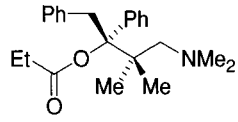
latanoprost



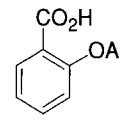
odansetron

Analgesics

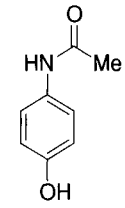
Propoxyphene, along with aspirin, acetominophen, and ibuprofen are among the most widely used agents for the treatment of mild to moderate pain.



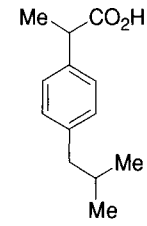
Propoxyphene



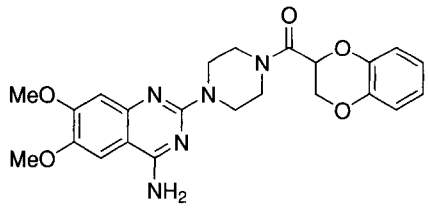
Aspirin



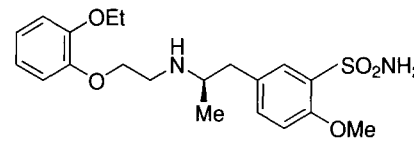
Acetominophen



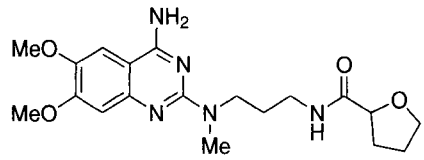
Ibuprofen



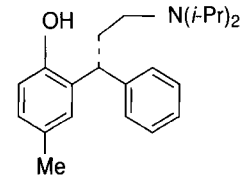
doxazosin



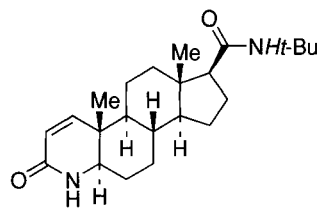
tamsulosin



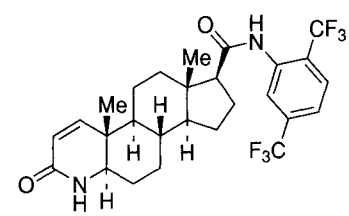
alfuzosin



tolterodine



finasteride



dutasteride

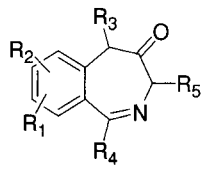
SMALL MOLECULE HIGH THROUGHPUT SYNTHESIS

The field of nonoligomeric, small molecule high throughput synthesis came into existence

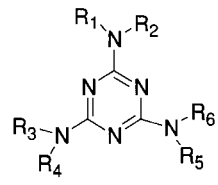
in 1992. Since then, small molecule library synthesis has affected drug discovery efforts in lead identification, as well as lead optimization. In a recent review, R. Dolle has categorized synthetic libraries as follows: (1) discovery libraries: libraries synthesized with no preconceived notion about which molecular target it may be active against. These libraries tend to be large in size, typically >5000 compounds.(2) targeted libraries: these libraries are biased in their design and contain a pharmacophore known to interact with a specific target, or a family of targets.(3) optimization libraries: libraries are constructed around an existing lead with the intent to improve potency, selectivity, pharmacokinetic profile, etc. These libraries tend to be smaller in size, usually ranging from tens up to a few hundred compounds.

Discovery Libraries

Researchers have employed several different strategies to create populations of molecules that are used for broad-based screening. One strategy is to synthesize libraries of "privileged pharmacophores" such as benzodiazepines (1), triazines (2), and so on. A second strategy is to design scaffolds or templates for library synthesis that are based on important molecular recognition. Libraries of β-turn mimetics (3) synthesized by Ellman et al. are examples of templates for molecular recognition.



1



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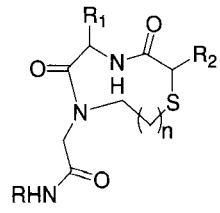
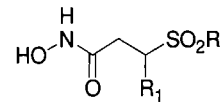


3

Targeted Libraries

Libraries targeted towards proteolytic enzymes, nonproteolytic enzymes, G-protein coupled receptors (GPCRs) and ion-channels have been very successful in lead identification. Libraries of hydroxamates (4), hydroxy ethylenes (5), boronic acids (6) and αketo sulfonamides (7) have been prepared as inhibitors of metallo-, aspartyl, serine and cysteine proteases respectively, using either solid phase or solution phase synthesis.

The discovery of chemical encoding technologies and radio-frequency (Rf) encoded synthesis have had a major impact on synthesis of lead discovery libraries. Both technologies utilize resin-based split-pool synthesis to prepare large arrays of compounds. Libraries of >50K members were prepared by using chemically encoded beads. Chemical encryption, in the form of unique chemical markers (tags), is associated with synthetic identity of the library member tethered to the resin bead. The technology for chemical encoding was pioneered by W. Clark Still and subsequently commercialized by Pharmacopeia, Inc. Restricted amount (200–300 μg), lack of analytical characterization of library members, and the requirement of a specialized screening format for chemically encoded libraries have limited the utility of this technology. Radio-frequency encoded synthesis, developed and commercialized by IRORI, Inc. overcomes the afore mentioned limitations while retaining the efficiency of split-pool synthesis. Libraries of 10–15K members can be prepared, with individual members quantitated and characterized by LC/MS. Most pharmaceutical companies have utilized Rf-encoded synthesis in their lead identification efforts.



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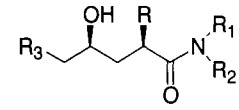

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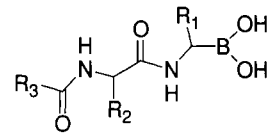

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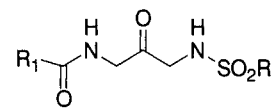

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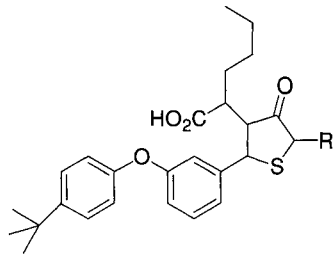
Structure-based design has been effectively utilized in synthesis of inhibitors of non-proteolytic enzymes. Inhibitors of MurB, an essential bacterial enzyme required for biosynthesis of peptidoglycan, were identified using the X-ray structure of the enzyme for library design. Thiazolidinone inhibitors (8) thus identified are the first examples of small molecule inhibitors of MurB.

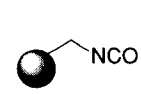


8

Substituted indoles ($5HT_{2a}$; D4 and α_{2a} receptor antagonists) and piperazines (δ opiod antagonists) are representative chemotypes targeted towards GPCRs.

Advances made in solid phase extraction (SPE) and in development of resin-based scavengers have increased the versatility of chemistries implemented for synthesis of targeted libraries. A combination of cation exchange (SCX) and anion exchange (SAX) resin was effectively utilized to prepare libraries of highly substituted amides.

Scavenger resins and polymer-bound reagents are routinely used to prepare medium-sized (500–1000 member) libraries. Polymer-bound isocyanates (9) and aldehydes (10) are used to remove amines from reaction mixtures, while polymer-bound thiols (11) are used to scavenge halides.



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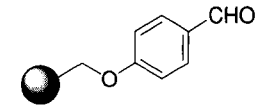

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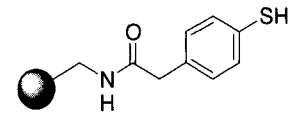
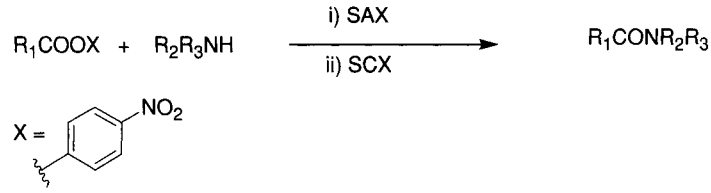


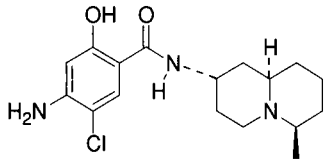
11

Optimization Libraries

Starting with a lead structure, researchers have demonstrated that parallel synthesis can



be effectively utilized to optimize activity, as well as reduce timelines for optimization. Parallel synthesis strategy was implemented to identify more potent analogs of influenza hemagglutinin inhibitor (12) (IC_{50} = 4 μg/ml). Solid phase extraction was used to automate preparation of >400 analogs resulting in identification of compounds (13) (IC_{50} = 20 ng/ml) and (14) (IC_{50} = 20 ng/ml).



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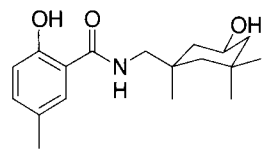

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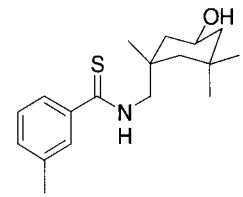
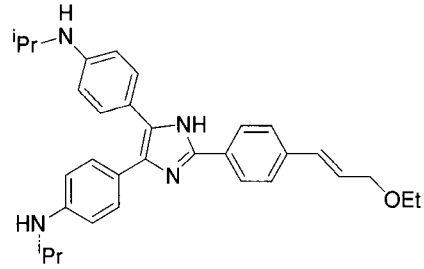


14

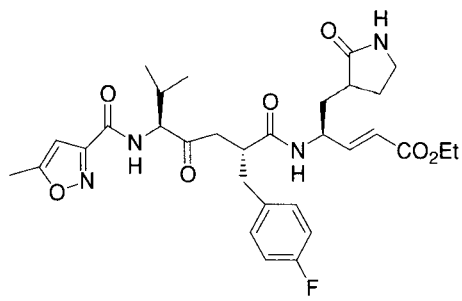
During the past 10 years, the pharmaceutical industry has expended significant resource in developing and assimilating technologies to increase synthesis throughput and decrease preclinical time lines. There are numerous examples in the literature demonstrating effective use of high throughput synthesis for lead discovery and optimization. There are two publicly known examples of clinical candidates that have emerged directly from optimization libraries. Ontogen Corporation identified OC144-093, (15) (IC_{50} = 50 nM) as a P-glycoprotein modulator and Agouron Pharmaceuticals reported identification of AG-7088, (16) (k_{obs}/I = 1,470,000 M^{-1} S^{-1}), a clinical candidate for treatment of rhinovirus infection.



15

CHEMICAL PROCESS R&D IN THE PHARMACEUTICAL INDUSTRY

Most of the active pharmaceutical ingredients (APIs) of commercially available pharmaceuticals are manufactured either by chemical syntheses or microbial fermentations. However, some of the active ingredients are directly obtained from natural sources. This section addresses the development and manufacture of APIs. Recent trend shows that >75 percent of the drug candidates in development are chiral and of complex structure. Incessant demand to shorten the timelines for the discovery, development and launch of NCEs coupled with environmental concerns has necessitated the development of higher yielding, more robust and environmentally friendly processes in shorter times. The success of a pharmaceutical company greatly depends not only on discovering blockbuster NCEs but also on its ability to design, optimize and scaleup a chemical process to commercial manufacturing with increasing rapidity. The chemical manufacturing process must be a robust procedure capable of operating routinely in a manufacturing environment.



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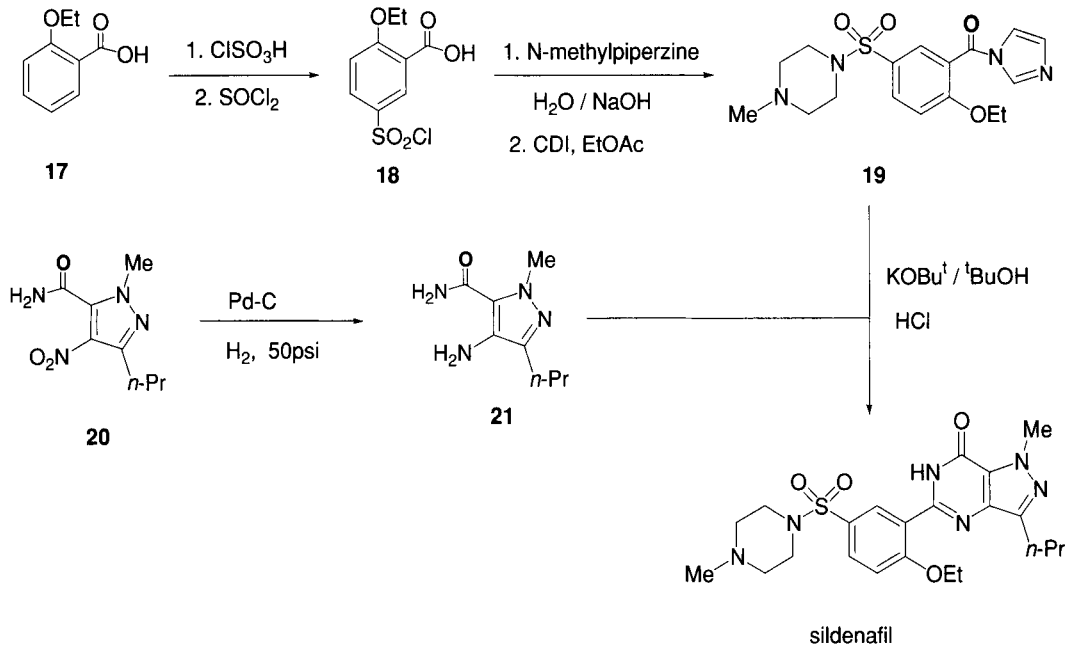
Considerable attention has to be given to various parameters in developing a manufacturing process for an API, including for example: efficiency of the synthesis, availability and cost of starting materials, toxicity of the reagents, stability and toxicity profiles of intermediates, formation of byproducts, and safe disposal of waste materials. Data from various aspects of chemical process development, including process structure and flowsheet, operational guidelines, optimization, process management, process control, fault diagnostics and equipment management need to be in place in order to support a smooth transition from laboratory to manufacturing plant. Safety is another critical factor requiring consideration for large-scale manufacture. All reactions should undergo a process hazard analysis for incident-free and successful plant implementation before scale-up. The use of automation in accelerating the design of cost-effective and well-understood synthetic processes has been demonstrated over the past few years by pharmaceutical companies and a few research groups in academia and is now beginning to grow very rapidly. Automation concepts and tools such as statistical design of experiments and parallel experimentation using in-house built reactor blocks or commercially available systems such as Zymark robots, ReactArray, Bohdan, Argonaut's Surveyor, or Mettler Toledo MultiMax will play a major role in increasing the productivity of process R&D with respect to speed and economics, as well as obtaining process knowledge. The application of microreaction technology (micropiloting) is another area that is growing rapidly to understand the chemical engineering aspects of process development. Some beneficial features of microreaction technology include mixing efficiency, enhanced heat transfer, and more uniform residence time distributions.

Production and logistical processes are becoming more complex due to an increasing number of products and smaller batch sizes. To manage this, supply chain optimization and production planning activities need to be addressed. Production simulation can be used for performance measurements and capacity assessments of manufacturing as well as material and information flow processes. Some applications of production simulation include bottleneck analysis, examination of process alternatives, assessment of investment decisions and solution of sequencing problems. Batch process development is a fairly complex series of engineering tasks. In the pharmaceutical industry, the production of a majority of APIs is based on a batch concept. This concept offers many advantages with respect to quality assurance as an individual batch can be accepted or rejected. However, the scale-up of the batch size without proper controls may lead to problems. The variety of the equipment involved often does not facilitate the scale-up process. In order to avoid scale-up problems, continuous or semi-continuous processes need to be adopted as alternatives to a batch production.

Crystallization, filtration, drying and milling (if required) are other important factors that need to be defined well before a process to manufacture solid APIs is finalized. Physicochemical properties of APIs play a vital role in providing the pharmaceutical drug products with desired bioavailability, manufacturing properties, and good final product quality. Particle size, density, flowability, polymorphism, hygroscopicity, and stability are critical properties for solid APIs in the formulation development. Polymorphism is very important in determining the physical properties of various crystal forms of a drug for optimal chemical and formulation processing, as well as for satisfying regulatory and patent issues for producing consistent solid forms of a drug.

The following flow diagrams show the preparation of APIs of some widely used pharmaceutical drugs in today's market. Scheme-1 shows the preparation of sildenafil. This route has a greater synthetic convergency than other published routes.

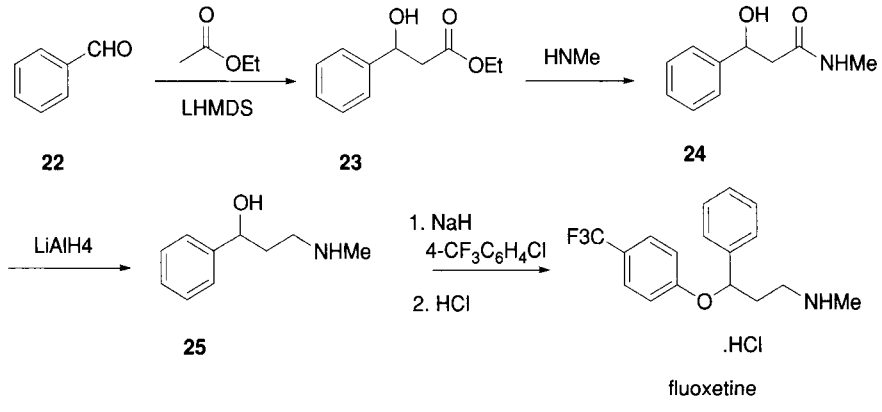
Scheme-1



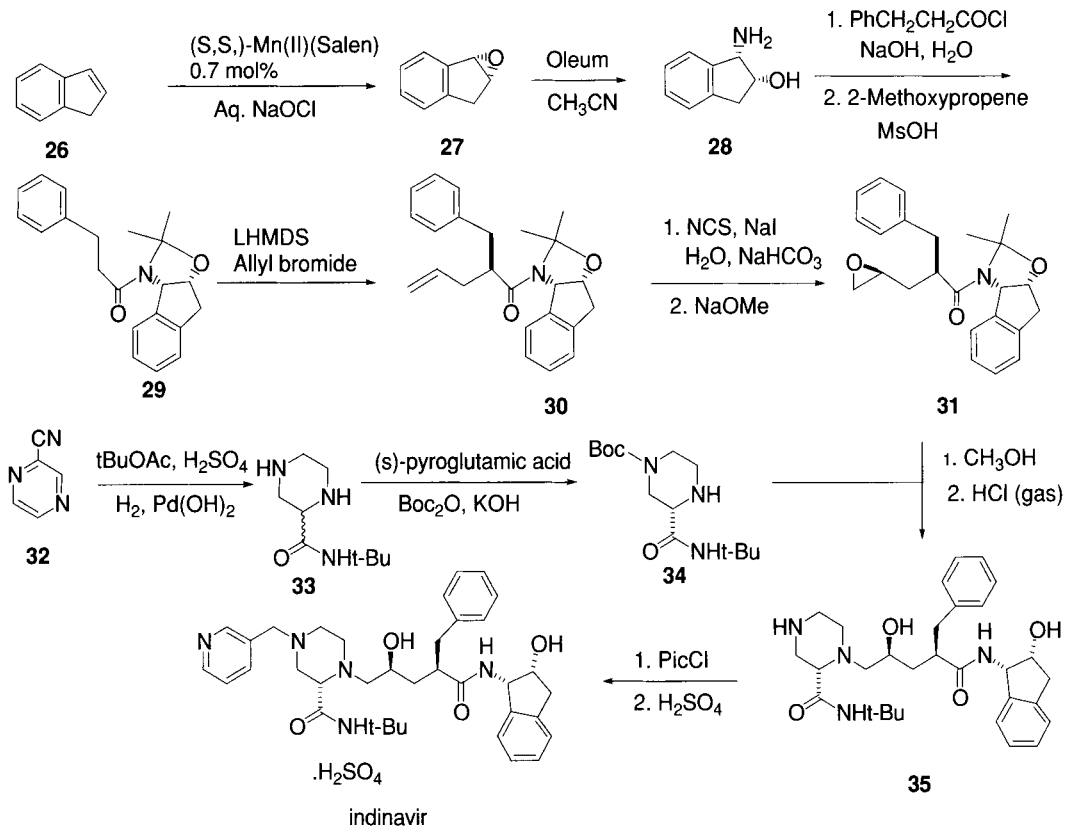
Synthesis of fluoxetine as a racemic mixture is shown in scheme-2. Recently several patents and publications have appeared in the literature describing the synthesis of (S)- and (R) enantiomers.

The single enantiomer of indinavir has five stereogenic centers, four of which are derived either directly or indirectly from epoxide (27). Synthesis of indinavir sulfate developed by Merck is shown in Scheme-3.

Scheme-2



Scheme-3



CONCLUSION

The discovery and development of novel therapeutic agents by the pharmaceutical industry has afforded physicians an extensive armamentarium to fight a wide range of human disease. Of course there remains the opportunity for even more effective drugs with greater benefit-to-risk ratios than those currently available. The elucidation of the human genome will eventually lead to the identification of many new macromolecular targets for drug intervention. Chemistry has been and will likely continue to remain at the forefront of pharmaceutical research which will afford the drugs of the future.

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