Part I
General Aspects

Analogue-based Drug Discovery II. Edited by János Fischer and C. Robin Ganellin
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Optimizing Drug Therapy by Analogues

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The medicinal chemist has a complex task to discover a useful new drug molecule. Among the different ways to accomplish this, the use of analogue research has been the most successful over the years, and most of the improvements in drugs have been obtained this way. This chapter will summarize the main aspects and demonstrate how analogues in a class of drugs are used to optimize drug therapy.

1.1
Introduction

The term analogue (from the Greek *analogos*) means proportionate, but in everyday terms we use it to indicate similarities between things. In medicinal chemistry, an *analogue drug* [1] has a chemical and/or pharmacological relationship with another drug. *Structural analogues* are drugs that have a similar chemical structure but quite different pharmacological properties, whereas *pharmacological analogues* are drugs that have a similar pharmacological activity without any discernible chemical or structural relationship.

About half the drugs are analogues in both respects, and we therefore call them *full analogues* that are structural and pharmacological analogues. One special class of full analogues is considered to be *direct analogues* if they have identical pharmacophores – that is, they can be described by a general structure that includes most of the chemical skeleton. There are only a few drugs for which no successful analogues have been discovered, these we have termed standalone drugs [2]. Because of the experimental nature of structure–activity relationships (SARs), the term analogue is descriptive and not exact, nevertheless it is a useful tool in classifying the 6000 different drugs used nowadays. An analogue class is a group of drugs that displays similar *in vitro* and *in vivo* pharmacological properties; therefore, they are either pharmacological or full analogues. The first drug in the class (often termed "first in class") used as a lead for the development of analogues can be considered a "pioneer drug." A pioneer drug is therefore the first marketed drug in an analogue class. After the discovery of a pioneer

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drug, there are almost always efforts to improve upon it with analogues in order to obtain new drugs with better therapeutic properties.

A drug can be characterized by several chemical and pharmacological properties. Even a minor structural change can sometimes modify all these properties. In order to illustrate key concepts in the optimization of drug therapy by analogues, it is necessary to simplify this question and we will always focus on a dominant property in a given analogue class.

1.2 Pharmacodynamic Characteristics

Pharmacodynamics refers to the study of drug actions in living organisms and includes the dominant activity along with possible adverse effects.

1.2.1 Potency

The potency of a drug refers to the amount of drug required to achieve a defined biological activity. The smaller the dose required, the more potent the drug.

The discovery of the histamine H_2-receptor antagonist cimetidine in 1971 was a pioneer invention in the treatment and prevention of peptic ulcer and gastroesophagitis. Cimetidine is used in a daily dose of 800 mg.

The application of analogue-based drug research provided ranitidine (1976), roxatidine (1979), famotidine (1979), and nizatidine (1980), which are more potent drugs and are effective at a lower dosage. Table 1.1 shows daily doses in comparison to cimetidine. Famotidine is the most potent member of the analogue class (Figure 1.1) [3].

Statins are HMG-CoA reductase inhibitors (Figure 1.2). Based on their *in vitro* effects, rosuvastatin is the most potent analogue and is followed in rank order by atorvastatin, simvastatin, and pravastatin [4] (Table 1.2). The same rank order of potency has been observed in clinical trials.

Table 1.1 Comparison of approximately equivalent daily doses of H_2-receptor antagonists.

Drug	Daily dose (mg)	Molecular weight (Da)
cimetidine	800	252
nizatidine	300	331
ranitidine	300	314
roxatidine	150	385[a)]
famotidine	40	337

a) Administered as acetate hydrochloride.

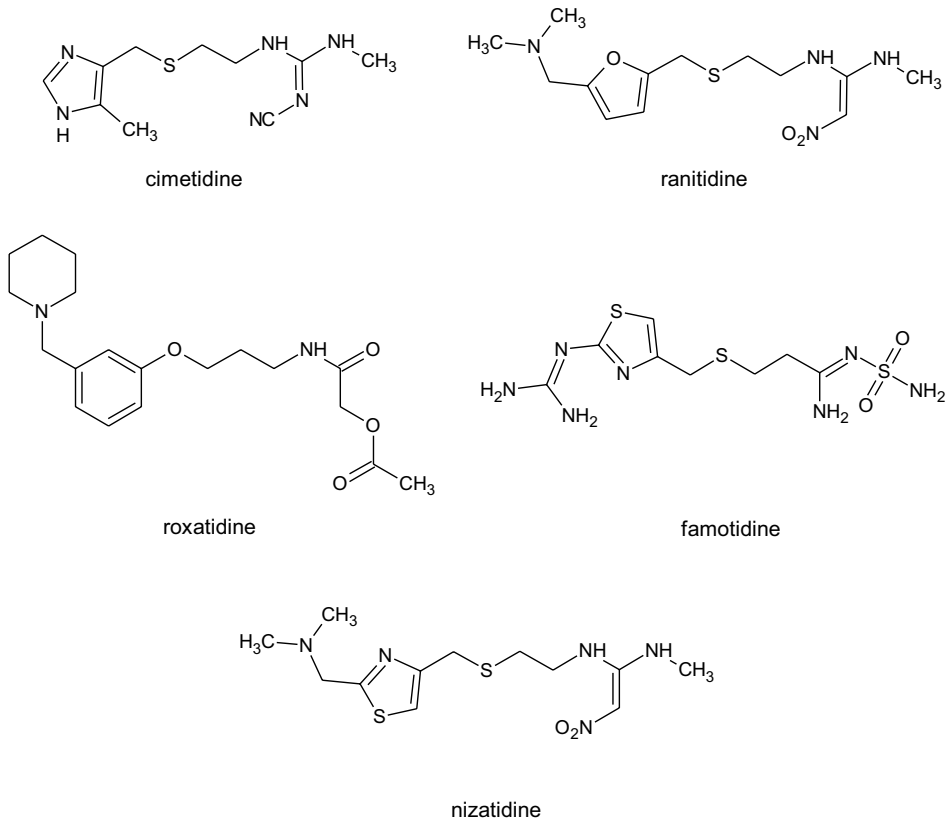


Figure 1.1 Structures of H_2-receptor antagonists.

1.2.2
Improving the Ratio of Main Activity and Adverse Effects

There are no drugs without some adverse effects. One important goal of analogue-based discovery approaches is to design improved drugs with a better ratio of efficacy to adverse effects.

Table 1.2 Inhibitory effects of various statins *in vitro*.

Drug	IC_{50} (nM)	Molecular weight (Da)
pravastatin	44.1	424
simvastatin	11.2	419
atorvastatin	8.2	559
rosuvastatin	5.4	482

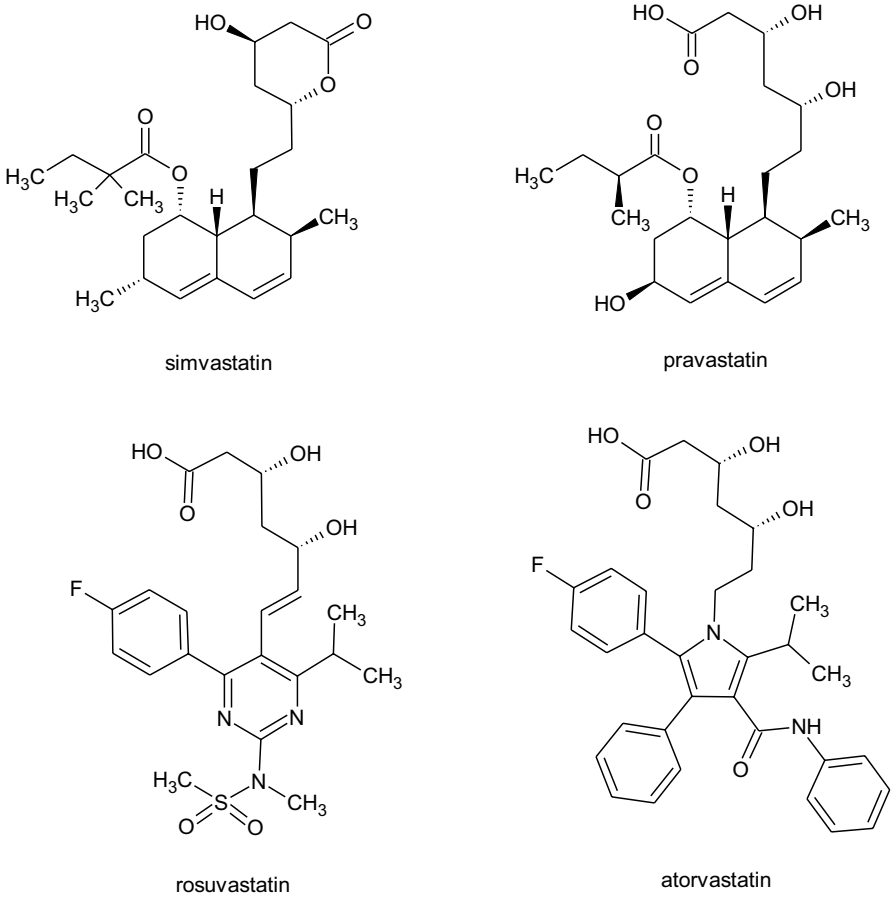


Figure 1.2 Structures of HMG-CoA reductase inhibitors.

1.2.2.1 **Improving Selectivity Through Receptor Subtypes**

The opportunity for improvement is clear if the mechanism of the adverse effect is known and one such example is found in the case of the adrenergic β-receptor blockers (Figure 1.3). The pioneer drug of β-receptor blockers is propranolol, invented in 1962. Subsequently, it was discovered that β-receptors occur as subtypes, for example, β_1 (in the heart) and β_2 (mediating smooth muscle relaxation). Propranolol blocks both β_1- and β_2-receptors. However, blocking β_2-receptors in bronchitis and asthma can be harmful, and analogue research successfully focused on producing selective β_1-blockers. The first β_1-selective blocker practolol was invented in 1964, but it was withdrawn from the market due to an unusual side effect, an oculomucocutaneous reaction that can lead to blindness. This is fortunately not a class effect, and many other selective blockers were developed and used in cardiology, such as atenolol, betaxolol, metoprolol, celiprolol, nebivolol, and bisoprolol [5] as β_1-selective blockers.

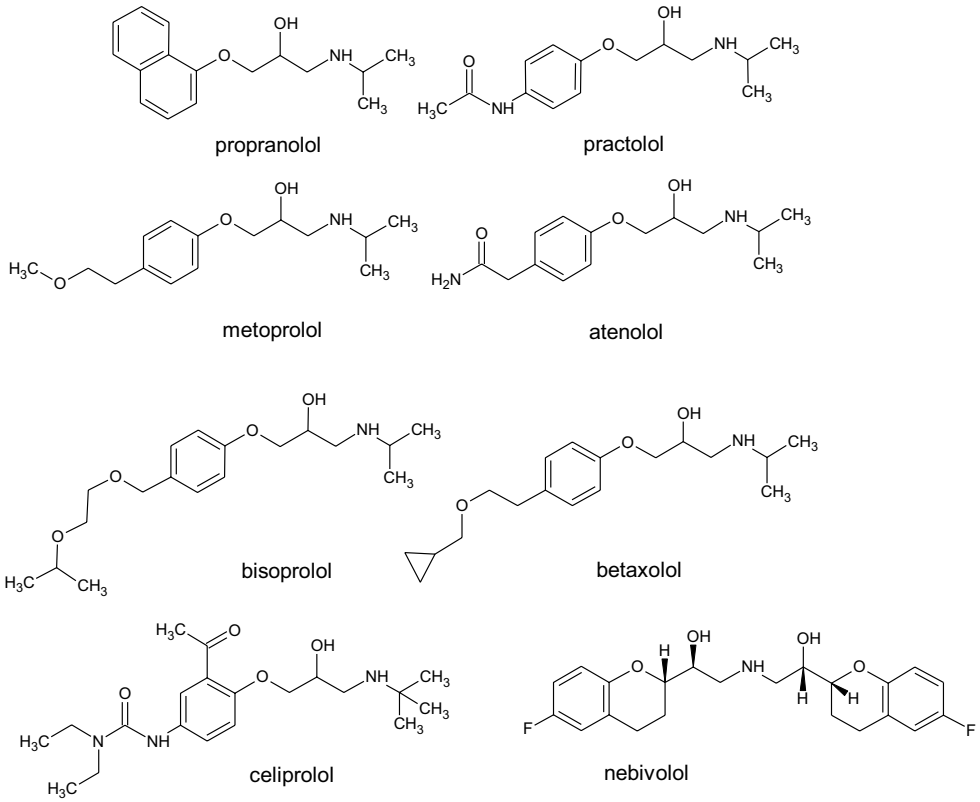


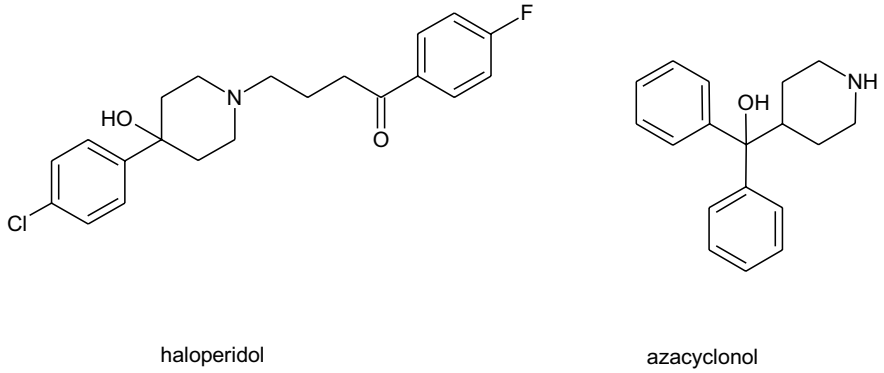
Figure 1.3 Structures of adrenergic β-receptor blockers.

1.2.2.2 Improving Selectivity Through Unrelated Receptors

Treatment with cimetidine for antiulcer therapy, the pioneer H_2-receptor histamine antagonist drug, resulted in a low incidence of gynecomastia as an unwanted side effect. This was traced to a low level of antiandrogenic activity. Thus, cimetidine was shown to competitively inhibit the binding of ^{3}[H]dihydrotestosterone to its cytoplasmic receptor and to decrease its specific nuclear uptake in rat ventral prostate slices [6]. Subsequent H_2-receptor antagonist analogues were an improvement since they generally did not show this effect.

1.2.2.3 Improving Selectivity by Tissue Distribution

Antihistamines, useful in allaying the symptoms of allergic responses such as rhinitis and itching eyes when the pollen count is high, have been in general use for over 60 years. Their use has, however, been somewhat limited by a high incidence of drowsiness or sedation. Early attempts to separate the sedative effects from the antihistaminic action were not very successful, and it took many years until it was realized that these activities were connected. In particular, the work of Schwartz and



haloperidol azacyclonol

Figure 1.4 Structures of haloperidol and azacyclonol.

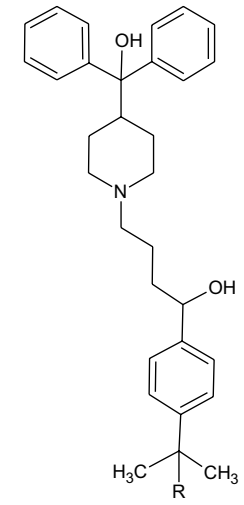
his colleagues in Paris demonstrated that histamine is a neurotransmitter in histaminergic nerves in the central nervous system (CNS) [7]. Histamine, acting on the histamine H_1-receptor in the brain, was shown to be a stimulant of wakefulness; blocking these receptors leads to a loss of alertness resulting in drowsiness. Some attempts were made to synthesize compounds that were selective for the peripheral versus the central H_1-receptors. Although such claims were made, they were not substantiated and, indeed, the use of molecular biology has demonstrated that there is no difference between the central and peripheral histamine H_1-receptors. There are some differences in the H_1-receptors between species but not within a species.

It follows that if it is not possible to separate the activity between peripheral and central histamine H_1-receptors, then it is necessary to limit the access of antihistamine drugs to the CNS. The first compound to establish itself on this basis was terfenadine, but it was not originally developed as an antihistamine. Terfenadine was developed for CNS actions (dopamine antagonism) and calcium ion-channel blocking [8]. It was chemically related (as a combination of analogues) to haloperidol and azacyclonol (Figure 1.4) but found to be restricted to peripheral systems and to act as an antihistamine; indeed, it became the first member of a new class of drugs identified as nonsedative antihistamines and was very successful. This was followed by astemizole and then by other drugs that were synthesized as analogues of previously established active but sedating antihistamines (see Table 1.3 and Figure 1.5 for some examples).

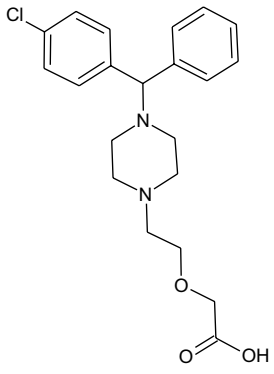
Astemizole arose from a research program at Janssen Pharmaceutica reportedly aimed at antihistamines having a long duration of action and a low risk of provoking central and anticholinergic effects [9].

Some of the above-mentioned products were later withdrawn because of an unwelcome side effect on heart caused by the blockade of the hERG (human ether-a-go-go-related gene) potassium ion channel that gives rise to cardiac arrhythmias. This led to a search for new analogues.

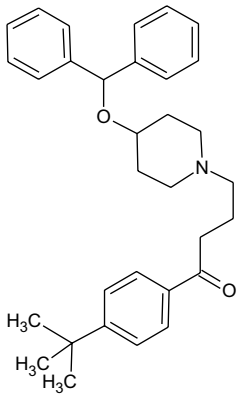
The reasons why the compounds have low concentrations in the brain are complex and not fully understood. Some important factors that determine low brain con-



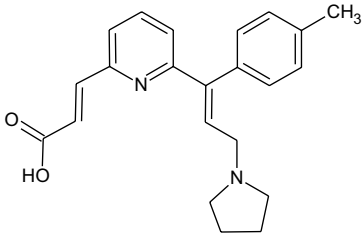
R = Me, terfenadine
R = COOH, fexofenadine



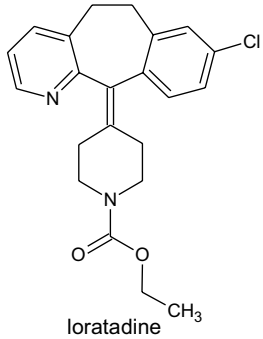
cetirizine



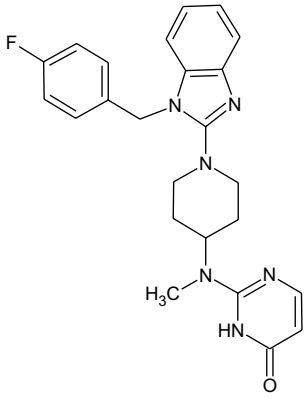
ebastine



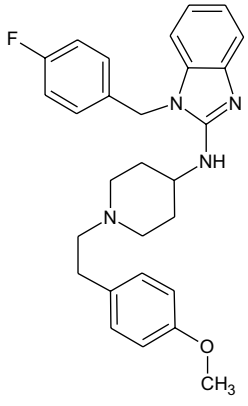
acrivastine



loratadine



mizolastine



astemizole

Figure 1.5 Structures of H_1-antihistamines.

Table 1.3 H_1-antihistamines that have low incidence of sedative effects.

Drug	Type	Launch
terfenadine	pioneer, chance discovery	1981 (withdrawn, 1997)
astemizole	pharmacological analogue	1983 (withdrawn, 1999)
cetirizine [10]	metabolite of hydroxizine	1987
acrivastine [11]	analogue of triprolidine	1988
loratadine [12]	analogue of azatidine	1988
ebastine [13]	analogue of diphenylpyraline and terfenadine	1990
fexofenadine	metabolite of terfenadine	1996
mizolastine	analogue of astemizole and temelastine	1998

centrations are (i) high binding to brain tissue proteins, (ii) poor penetration of the blood–brain barrier, and (iii) high binding to the P-glycoprotein (Pgp) efflux pump.

1.2.2.4 Improving Selectivity of Nonreceptor-Mediated Effects

In many cases, the mechanisms causing side effects are not known. Platinum compounds (Figure 1.6) play a major role in oncology. Cisplatin may cause regression and control of various tumors, such as testicular, ovarian, head, neck, and colon carcinoma. However, among its side effects, renal damage can be observed. Analogues have overcome this problem; thus, for carboplatin, the nephrotoxicity is much lower [14], and oxaliplatin is devoid of nephrotoxicity [15].

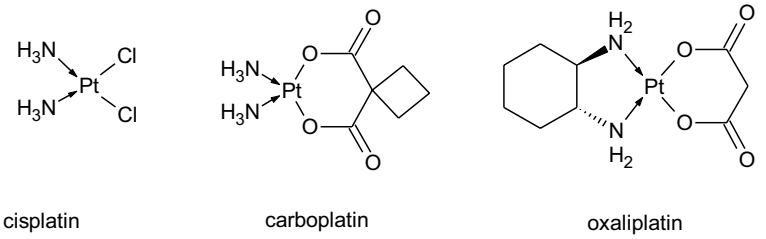
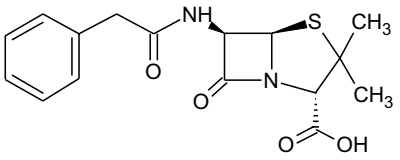


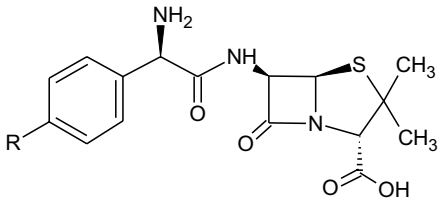
Figure 1.6 Structures of platinum compounds.

1.2.3 Improving the Physicochemical Properties with Analogues

Benzylpenicillin (penicillin G) (Figure 1.7), which is acid-sensitive, is rapidly destroyed by gastric fluid at pH 2. The pioneer penicillin drug was administered by intramuscular injection to avoid this problem, but this was not convenient for the patients. Through analogues, where an electron-withdrawing substituent was introduced in the side chain, the acid sensitivity of the β-lactam ring was reduced. A range

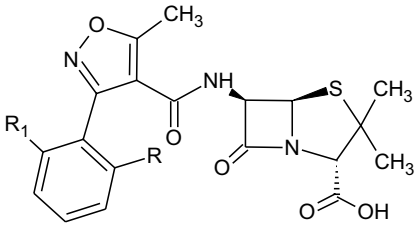


benzylpenicillin



ampicillin, R = H

amoxicillin, R = OH

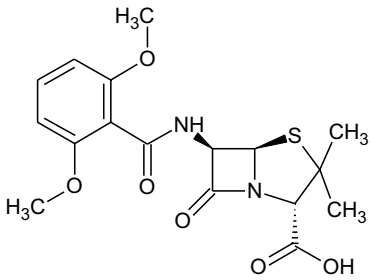


R = H, R_1 = H, oxacillin

R = H, R_1 = Cl, cloxacillin

R = F, R_1 = Cl, flucloxacillin

R = Cl, R_1 = Cl, dicloxacillin



methicillin

Figure 1.7 Benzylpenicillin and analogues.

of such analogues proved to be resistant to acid hydrolysis and they could be given orally (e.g., ampicillin [16]).

1.2.4 Analogues to Reduce the Resistance to Anti-Infective Drugs

1.2.4.1 Antibiotics

Resistance to antibiotics has become an increasing problem all over the world, and the need to find new agents continues [17].

The widespread use of penicillin G led to an alarming increase of penicillin-resistant *Staphylococcus aureus* infections in 1960. A solution to the problem was the design of penicillinase-resistant penicillins. The first such analogue was methicillin [18]; however, it was acid-sensitive and it was inactive against Gram-negative bacteria. Methicillin is no longer used clinically because better analogues (Figure 1.7) have been discovered, such as oxacillin [19], cloxacillin [20], flucloxacillin [21], and dicloxacillin [21] that were stable to β-lactamase enzyme of *S. aureus* and had acid stability.

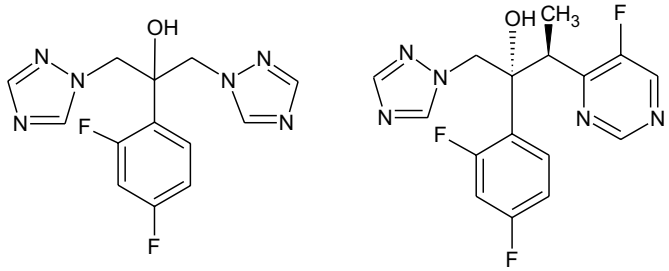


Figure 1.8 Structures of fluconazole and voriconazole.

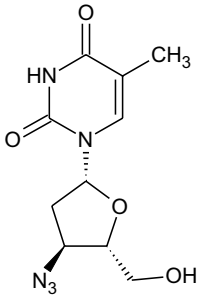
1.2.4.2 **Antifungal Drugs**

A very important subclass of antifungal drugs is the azoles. Until the 1980s, while these drugs were used only topically, no resistance was detected. Since the introduction of the systemically active azoles, resistance has emerged. Even in the case of fluconazole, which is the most potent member of this analogue class, a resistance was observed in *Candida* infections. In this case, voriconazole, an analogue of fluconazole (Figure 1.8), has been used with a good result [22].

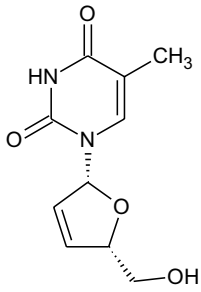
1.2.4.3 **Antiviral Drugs**

Although the first generation of anti-AIDS drugs provided key medicines for the treatment of the disease, the emergence of HIV-1 strains resistant to various drug classes prompted efforts to discover analogues with broader activity profiles. Successful analogue design approaches have led to improved pharmacological profiles that include suppression of viral resistance for two of the three classes where multiple drugs have reached the market, the nonnucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors. For the nucleoside reverse transcriptase inhibitor class, the marketed drugs were generally discovered while generating analogues of zidovudine (stavudine, didanosine, tenofovir disoproxil, abacavir, and lamivudine) (Figure 1.9) with improved therapeutic index, and benefits with regard to resistance profiles were empirically uncovered [23].

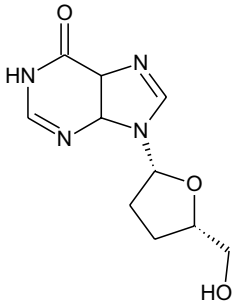
Etravirine [24] (Figure 1.10), the most recent NNRTI to reach the market, is a pharmacological analogue of the first-generation NNRTIs and displays activity against a broad panel of drug-resistant reverse transcriptase (RT) mutants. Structurally, it bears no resemblance to any of the first-generation inhibitors and it emerged by iterative design starting with the earlier alpha-APA class over a period of many years. Optimization was guided throughout by structural information. Molecular conformational flexibility is apparently a key attribute that allows the molecule to effectively bind in multiple modes to the conformationally mobile NNRTI binding site of numerous clinically relevant RT mutants. The close structural analogue, rilpivirine [25], is in phase III trials.



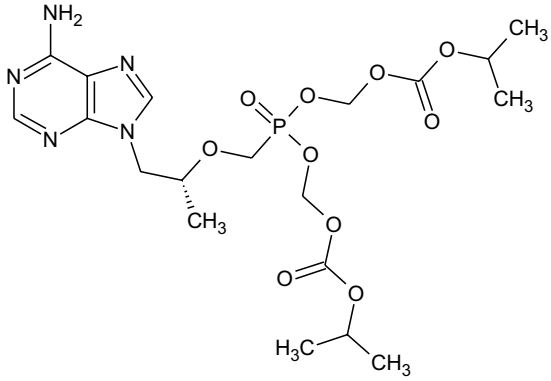
zidovudine



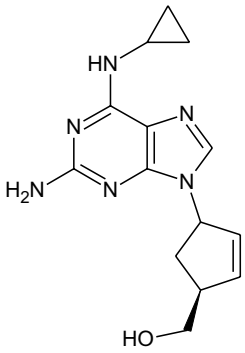
stavudine



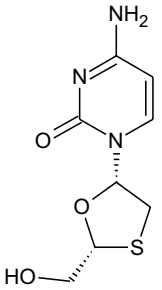
didanosine



tenofovir disoproxil

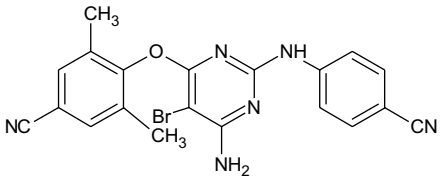


abacavir

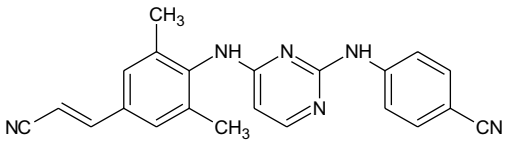


lamivudine

Figure 1.9 Structures of zidovudine and analogues.



etravirine

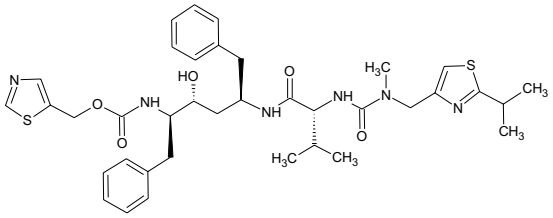


rilpivirine

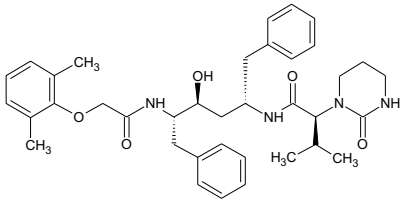
Figure 1.10 Structures of etravirine and rilpivirine.

Among the HIV-1 protease inhibitors, analogue approaches specifically attempting to improve resistance profiles have also given drugs that have reached the market. Cocrystal structure information of ritonavir (Figure 1.11), a first-generation protease inhibitor, bound to HIV-1 protease, was used to design lopinavir [26]. Removal of the isopropylthiazole group of ritonavir that interacts with valine-82 led to decreased sensitivity to the protease mutants selected by ritonavir. This modification, along with the modification of the other thiazole ring in ritonavir, also substantially improved the CYP inhibition profile of lopinavir.

The design of amprenavir [27] and darunavir [28] (Figure 1.12) emphasized the importance of interactions between the inhibitors and the conserved elements of the

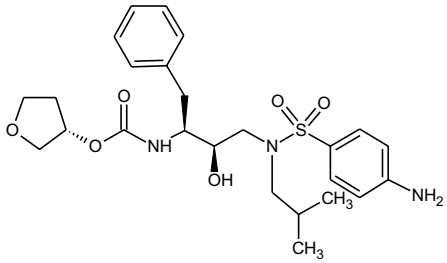


ritonavir

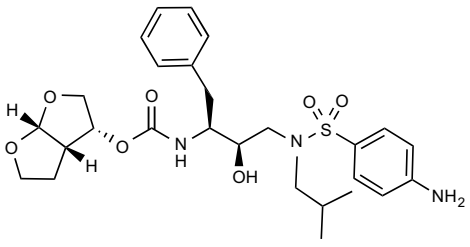


lopinavir

Figure 1.11 Structures of ritonavir and lopinavir.



amprenavir



darunavir

Figure 1.12 Structures of amprenavir and darunavir.

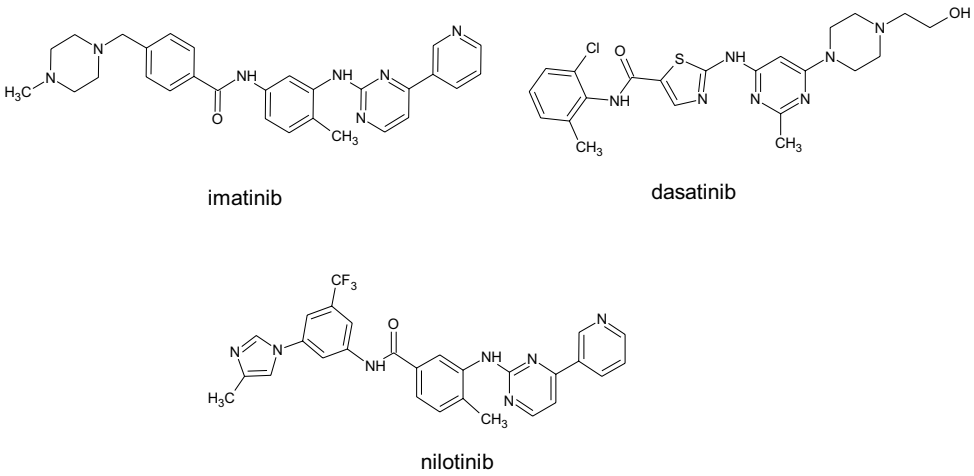


Figure 1.13 Structures of imatinib, dasatinib, and nilotinib.

protein backbone of the wild-type enzyme as a means to attaining excellent potency against mutant strains resistant to the first-generation inhibitors.

1.2.5
Analogue Research in Resistance to Drug Therapies in Cancer Treatment

Imatinib (Figure 1.13) is the pioneer drug for the treatment of chronic myologenous leukemia (CML). However, a significant number of patients develop resistance to imatinib. New analogues, such as dasatinib [29] and nilotinib [30], have been introduced recently, and it is hoped that these analogues will be effective also in imatinib-resistant cases.

1.3
Pharmacokinetic Characteristics

Pharmacokinetics is the study of the metabolism of drugs with particular emphasis on the time required for absorption, duration of action, distribution in the body, and method of excretion. Through analogue design, the pharmacokinetic parameters (ADME) of a pioneer drug or a drug class can be optimized.

1.3.1
Improving Oral Bioavailability

A good oral bioavailability is necessary in most cases because the oral application of a drug is preferred to an injection therapy.

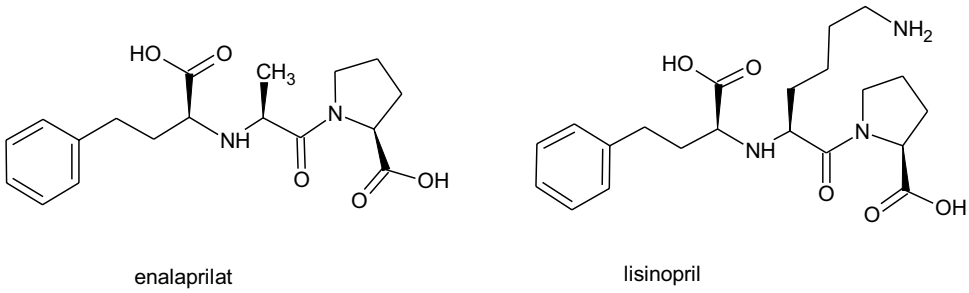


Figure 1.14 Structures of enalaprilat and lisinopril.

1.3.1.1 **Improving Absorption**

The angiotensin-converting enzyme (ACE) inhibitor enalaprilat (Figure 1.14) is not orally absorbed but is available for intravenous administration when oral therapy is not appropriate, for example, in hypertensive emergencies. The ethyl ester prodrug, enalapril has an excellent oral bioavailability but requires hydrolysis by esterases. The analogue-based drug research afforded the lysylproline analogue, lisinopril [31], which has an acceptable bioavailability and it does not require metabolic activation.

1.3.1.2 **Improving Metabolic Stability**

The pioneer antifungal miconazole (Figure 1.15) and its analogue tioconazole [32] are clinically effective drugs, when administered by the topical route, against fungal infections of vagina and skin. Unfortunately, tioconazole and other imidazole derivatives of that time showed only poor efficacy in animal models of fungal infection when given by either the intravenous or the oral routes. Pharmacokinetic studies indicated that these agents were very susceptible to metabolic inactivation, resulting in low oral bioavailability and low plasma levels. They were also very lipophilic and highly bound to plasma proteins, which resulted in very low circulating levels of the unbound, active form. The first orally active antifungal drug was ketoconazole [33], which was discovered at Janssen Pharmaceutica. Ketoconazole was metabolically less susceptible than earlier imidazole derivatives, resulting in good oral bioavailability; however, it was metabolized such that less than 1% of unchanged drug was excreted through urine. In addition, although ketoconazole was less lipophilic than the earlier derivatives, leading to high blood levels, it remained highly protein-bound with less than 1% in unbound form.

Introducing a polar hydroxyl group and a more polar 1,2,4-triazole ring led to UK-47265. It was 100 times more potent than ketoconazole when dosed via either the oral or the intravenous routes; however, its *in vitro* activity against fungi was modest. Unfortunately, UK-47265 proved to be hepatotoxic in mice and dogs and teratogenic in rats; therefore, it was not developed further. Researchers at Pfizer continued to

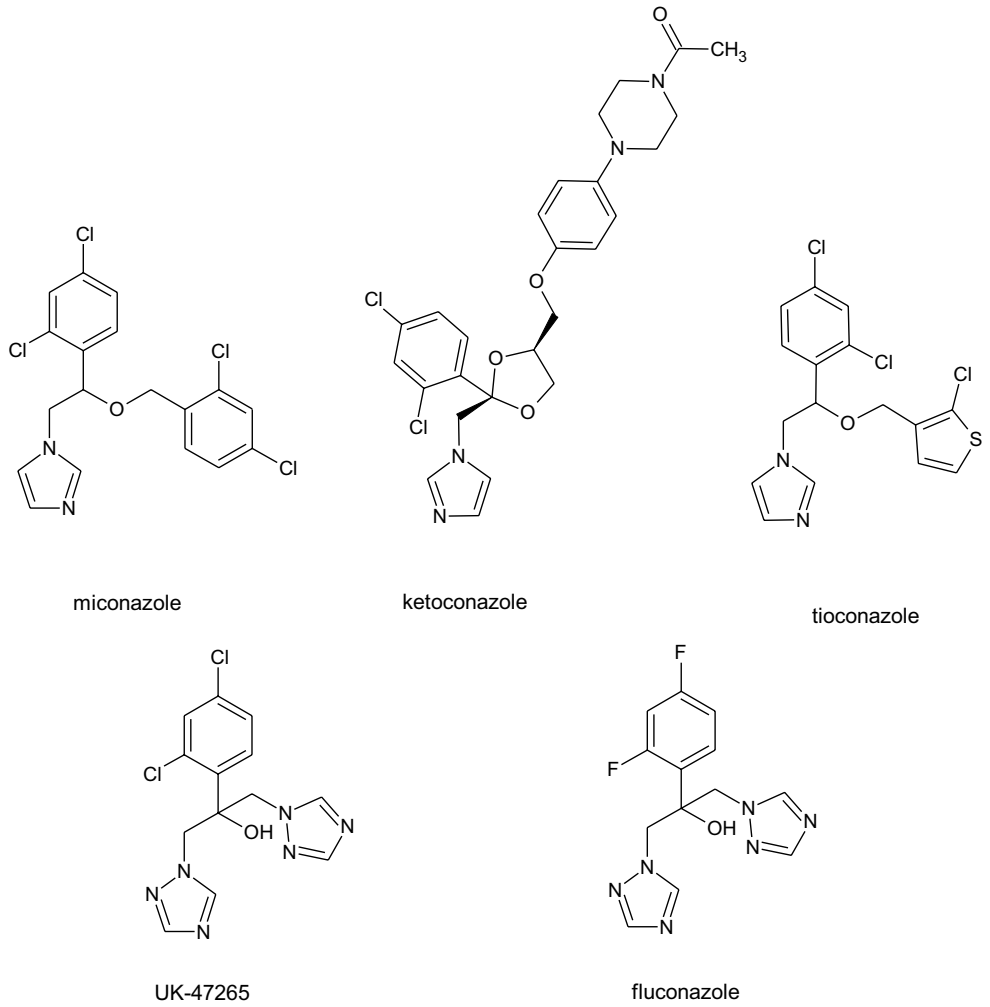


Figure 1.15 Structures of miconazole and analogues.

study further analogues, and the 2,4-difluoro derivative (fluconazole, UK-49858) showed high efficacy without any safety problem. Fluconazole [34] has a plasma half time of 5.1 h and 75% of the drug is excreted unchanged through urine.

1.3.2
Drugs with a Long Duration of Action

Captopril [35] was the first orally active ACE inhibitor (angiotensin-converting enzyme) to reach the marketplace. It is rapidly absorbed with a bioavailability of about 75%. Peak drug concentrations in plasma occur within 1 h of dosing, and the drug is then cleared rapidly ($t_{1/2}$ about 2 h); therefore, a dosage regimen of two- to

Table 1.4 Elimination half-life values of ACE inhibitors [31].

Drug	Elimination half-life (h)
captopril	2
benazepril	11
cilazapril	10
enalapril	11
fosinopril	12
lisinopril	12
perindopril	>24
ramipril	8–14
trandolapril	16–24

three times daily is necessary. Since food reduces the oral bioavailability of captopril, the drug should be given 1 h before meals.

Hypertension usually requires a lifelong treatment; therefore, the long-acting analogues of captopril are advantageous (Table 1.4, Figure 1.16). The long-acting once-daily dosing has practical benefits by improving patient compliance. The clinical advantage of full 24-h control of blood pressure is important to prevent cardiovascular events (e.g., myocardial infarction and stroke). The oral bioavailability of the long-acting ACE inhibitors is only slightly reduced by food.

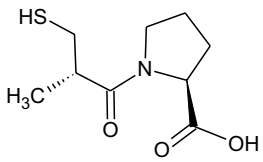
The case of the calcium channel antagonists, dihydropyridines, shows a similar picture. The pioneer drug nifedipine has a short duration of action. The long-acting analogues, such as felodipine, lacidipine, and amlodipine are more convenient for the lifelong treatment of hypertension (Table 1.5, Figure 1.17).

Table 1.5 Elimination half-life values of calcium antagonist dihydropyridines [36].

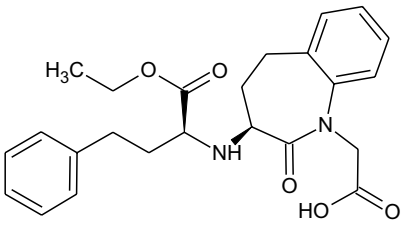
Drug	Elimination half-life (h)
nifedipine	2–4
felodipine	10–15
lacidipine	7–18
amlodipine	30–50

1.3.3
Ultrashort-Acting Drugs

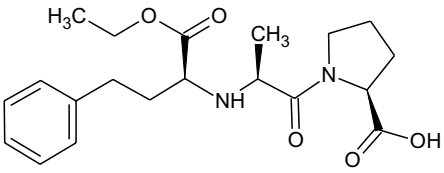
Esmolol [37] (Figure 1.18) is a β_1-selective blocker with a very short duration of action. It is administered intravenously and used when β-blockade of short duration is desired in patients in whom adverse effects of bradycardia, heart failure, or hypotension may necessitate its rapid withdrawal. It is used in emergency situations during critical care medication.



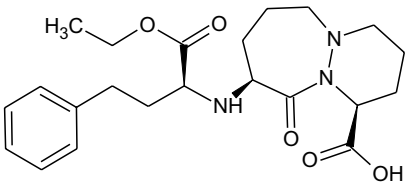
captopril



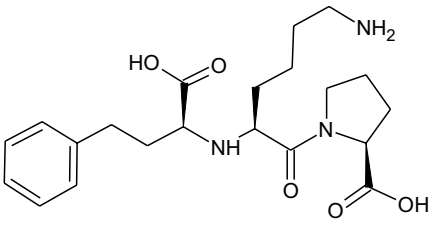
benazepril



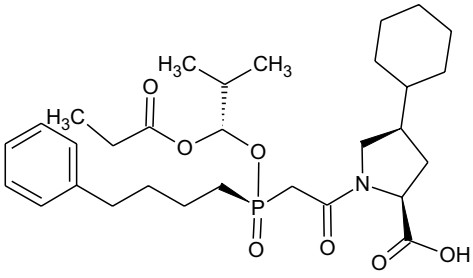
enalapril



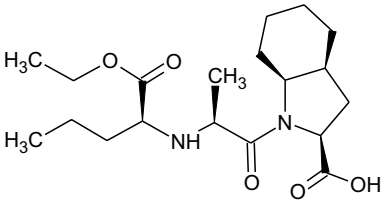
cilazapril



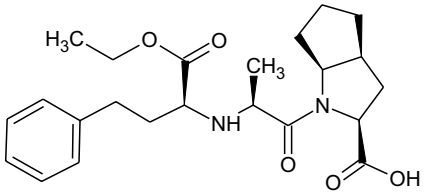
lisinopril



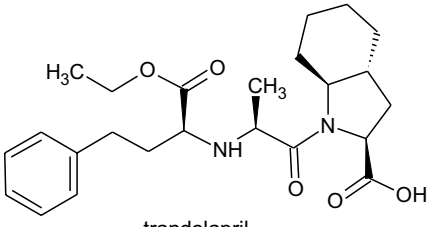
fosinopril



perindopril

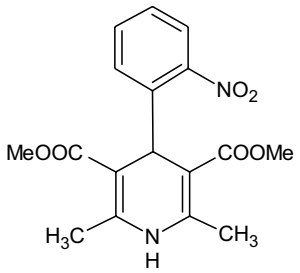


ramipril

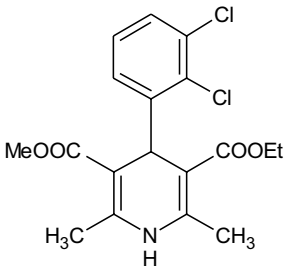


trandolapril

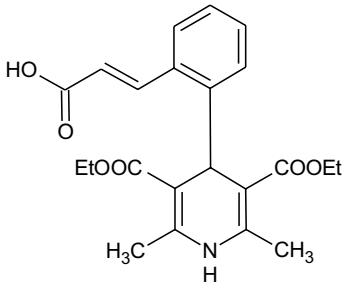
Figure 1.16 Structures of ACE inhibitors.



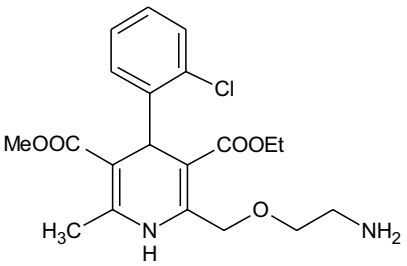
nifedipine



felodipine



lacidipine



amlodipine

Figure 1.17 Structures of nifedipine and analogues.

This special analogue type is called a soft drug. It is active only as an ester that loses its activity after metabolic hydrolysis. Esmolol's distribution half-life is 2 min and its elimination half-life is 9 min.

The same principle is used in the case of loteprednol etabonate (Figure 1.19), which is a glucocorticoid soft drug that has a good local activity after it is topically administered to the eye. Since it is rapidly deactivated after reaching the general circulation, it does not display systemic side effects.

1.3.4
Decreasing Interindividual Pharmacokinetic Differences

Interindividual pharmacokinetic differences result when a significant number of patients require a higher or multiple doses of a drug to achieve symptom relief and healing.

Omeprazole [38] is the pioneer proton pump inhibitor that shows an interindividual variability in pharmacokinetics. Analogue-based drug discovery afforded pantoprazole (Figure 1.20), which possesses linear, highly predictable pharmacokinetics. It has a lower variability in pharmacokinetics compared to omeprazole,

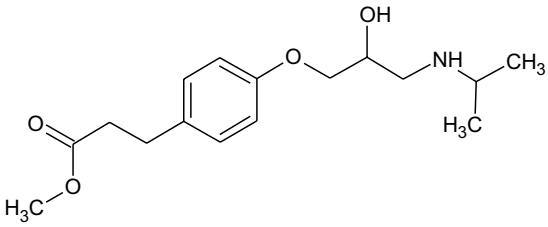


Figure 1.18 Structure of esmolol.

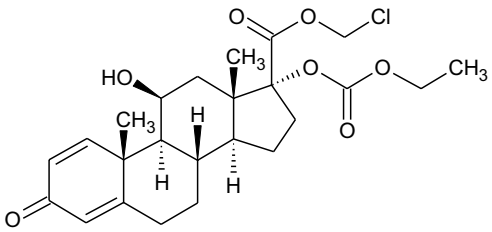
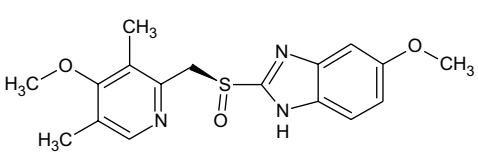


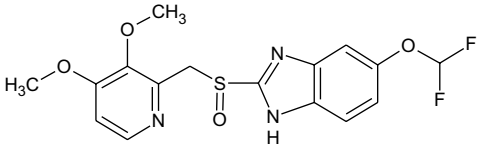
Figure 1.19 Structure of loteprednol etabonate.

particularly with respect to bioavailability. The pharmacokinetics of pantoprazole-sodium [39] is almost the same in patients with gastrointestinal diseases and those with renal failure, and in the elderly, so that no dose adjustment is required.

The drawback of omeprazole could also be overcome by using its (*S*)-enantiomer (esomeprazole) whose bioavailability is about double that of the racemate.



esomeprazole



pantoprazole

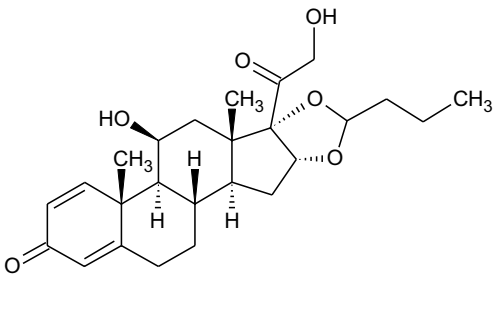
Figure 1.20 Structures of proton pump inhibitors.

1.3.5
Decreasing Systemic Activity

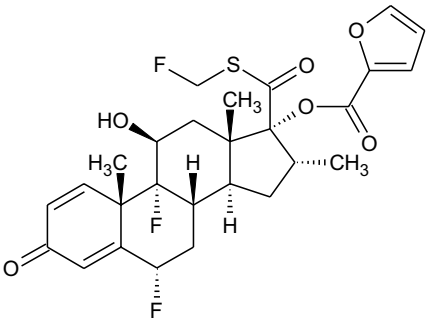
In the intranasal and inhalation application of corticosteroids in the treatment of asthma and rhinitis, it is important to decrease the systemic availability of these drugs to avoid their adverse effects, such as adrenocortical insufficiency and osteoporosis. Analogue research afforded budenoside and fluticasone with low oral (systemic) bioavailability (Table 1.6, Figure 1.21).

Table 1.6 Oral bioavailability of inhaled corticosteroids [40].

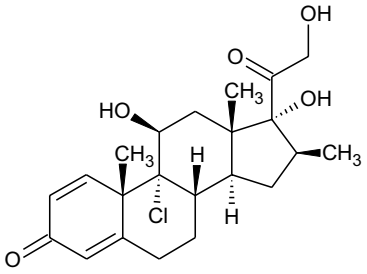
Drug	Oral (systemic) bioavailability (%)
beclomethasone	15–20
budenoside	10
fluticasone	<2



budesonide



fluticasone furoate



beclomethasone

Figure 1.21 Structures of corticosteroids.

1.4 Drug Interactions

1.4.1 Decreasing Drug Interactions

Cimetidine inhibits CYPs (e.g., CYP1A2, CYP2C9, and CYP2D6), an important class of drug-metabolizing enzymes. This interaction inhibits the metabolism of certain

drugs such as propranolol, warfarin, diazepam, and theophylline, thus producing effects equivalent to an overdose of these medicines. It is therefore advisable to avoid coadministration. These effects are avoided by analogues such as ranitidine and famotidine [41].

1.4.2
Increasing Drug Interactions

Because of the potency of inhibition of cytochrome P-450 by ritonavir, it was found that combination of other HIV-1 protease inhibitors with ritonavir led to increased plasma levels of these drugs. Analogue research starting from ritonavir afforded the more potent lopinavir (Figure 1.11). However, lopinavir's plasma half-life is low. In a combination of ritonavir and lopinavir, known as Kaletra, ritonavir inhibits the P-450-mediated metabolism of lopinavir and therefore the combination is remarkably effective [42]. This CYP3A4 inhibition by ritonavir has been exploited to increase the exposure of other anti-AIDS drugs that are metabolized by this particular CYP.

1.5
Summary

The chapter gives an overview of the possibilities of analogue research, illustrated with examples. Drug therapy can be optimized with the help of analogue research in the following 12 ways:

- Increasing potency
- Improving the ratio of the main activity and the adverse effects:
  - –Improving selectivity through receptor subtypes
  - –Improving selectivity through unrelated receptors
  - –Improving selectivity by tissue distribution
  - –Improving selectivity of nonreceptor-mediated effects
- Improving the physicochemical properties with the help of analogues
- Decreasing resistance to anti-infective drugs
- Decreasing resistance to anticancer agents
- Improving oral bioavailability
  - –Improving absorption
  - –Improving metabolic stability
- Long-acting drugs for chronic diseases
- Ultrashort-acting drugs in emergency cases
- Decreasing interindividual pharmacokinetic differences
- Decreasing systemic activities
- Decreasing drug interactions with the help of analogues
- Synergistic interactions between analogues

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Erika M. Alapi was born in Pasztó, Hungary, in 1974. She received her MSc degree in chemistry at the Faculty of Science of Eötvös Loránd University in Budapest. She is working as a medicinal chemist in the field of CNS and preparing her PhD thesis "Optimizing Therapy by Analogues" under the supervision of Professor János Fischer at Gedeon Richter Pharmaceutical Plc. She contributed to *Analogue-Based Drug Discovery* I as a coauthor.

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János Fischer is a Senior Research Scientist at Richter Plc., Budapest, Hungary. He received his MSc and PhD degrees in organic chemistry from the Eotvos University of Budapest under Professor A. Kucsman. Between 1976 and 1978, he was a Humboldt Fellow at the University of Bonn under Professor W. Steglich. He has worked at Richter Plc. since 1981 where he participated in the research and development of leading cardiovascular drugs in Hungary. His main interest is analogue-based drug discovery. He is the author of some 100 patents and scientific publications. In 2004, he was elected as a Titular member of the Chemistry and Human Health Division of IUPAC. He received an honorary professorship at the Technical University of Budapest.

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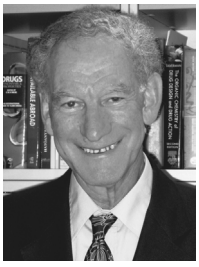

C. Robin Ganellin studied chemistry at London University, receiving a PhD in 1958 under Professor Michael Dewar, and was a Research Associate at MIT with Arthur Cope in 1960. He then joined Smith Kline & French Laboratories in the UK and was one of the coinventors of the revolutionary drug, cimetidine (also known as Tagamet). In 1986, he was made a Fellow of the Royal Society and appointed to the SK&F Chair of Medicinal Chemistry at University College London, where he is now Professor Emeritus of Medicinal Chemistry. Professor Ganellin is coinventor of over 160 patents and has authored over 260 scientific publications. He was President of the Medicinal Chemistry Section of the IUPAC and is Chairman of the IUPAC Subcommittee on Medicinal Chemistry and Drug Development.

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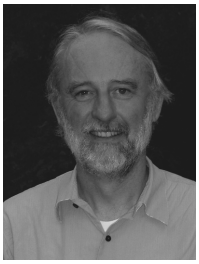

John Proudfoot is a Medicinal Chemist with over 20 years of experience in drug design, ranging from fragment-based lead identification to late-stage lead optimization. He received his doctorate from the University College Dublin in Ireland, working with Professor Dervilla Donnelly. After postdoctoral studies under Professor Carl Djerassi at Stanford University and under Professor John Cashman at the University of California, San Francisco, he joined Boehringer Ingelheim Pharma in 1987. He is a coinventor of 28 issued US patents, including the one for the marketed drug, nevirapine, the first nonnucleoside HIV-1 reverse transcriptase inhibitor to receive regulatory approval.