

CHAPTER 1

Introduction

1.1 AIMS

The aims of this chapter are to introduce the structure of medicinal chemistry and to show how the subject has developed. By the end of this chapter you should know the salient points concerning:

- the basis for the classification of drugs;
- the targets for the medicinal chemist;
- the stages in the development of a drug; and
- the history of medicinal chemistry.

Medicinal chemistry is concerned with the chemistry of compounds that have a beneficial effect on a disease. Its objective is to enhance this beneficial therapeutic effect of a compound by modifying its structure and to remove unwanted side effects through an understanding of the chemistry by which the compound exerts its biological effects. Once a lead substance with a useful biological effect has been discovered, the medicinal chemist must undertake a series of structural variations in order to establish a pattern of structure: activity relationships leading to an enhancement of the useful biological effect. While the medicinal chemist is primarily concerned with the synthesis of new therapeutic agents, there must be a considerable interaction with other disciplines; medicine and biology for the description of the disease state and the development of the bio-assay, pharmacology for the definition of the site of action and pharmacy for the delivery of the compound to the living system.

1.2 THE CLASSIFICATION OF DRUGS

Drugs may be classified in a number of ways. One way is in terms of the nature of the disease that they are being used to treat. Thus there are compounds that are used to treat infectious diseases. Second, there are compounds that are used to treat cancers and third, non-infectious

diseases. The chemistry of infectious diseases is concerned with the development of drugs to injure an invading organism with minimal injury to the host. The targets are often the differences between the viral, bacterial, fungal or parasitic cells and those of man. This is the area of the antibiotics. The medicinal chemistry that is used in the treatment of cancers involves the use of drugs to destroy an aberrant cell within the host. The targets of cancer chemotherapy are the differences between the rapidly proliferating cancer cells and normal cells. Cancer chemotherapy is often used in conjunction with other forms of treatment such as radiotherapy. The chemistry of non-infectious diseases involves a study of the selective action of a drug on one cell or receptor in the host. In some cases the drugs are developed as mimics of natural hormones.

The drugs that are used in the treatment of non-infectious diseases can be further sub-divided in terms of their targets. There are a group of hormones known as neurotransmitters that are formed at nerve endings and convey the consequences of a nerve impulse to a receptor or an effector cell. There are drugs, which affect primarily the neurotransmitters in the central nervous system including the brain and the spinal cord. These include the psychotropic agents, the anti-depressants, hypnotics and analgesics. There are those agents, which affect the peripheral nervous system including the local anaesthetics. Another group of substances are those, which affect the circulatory system acting as anti-hypertensive and anti-thrombotic agents. These may interact with local hormones. These are a family of compounds that have a metabolic or endocrine target. These are compounds that are modifications of circulatory hormones that may be used as oral contraceptives or to correct a hormone deficiency. Finally there are those compounds, which target the immune system such as the immunosuppressive agents. However there is an overlap between these classes and a compound may show several types of biological activity.

The pattern of usage and the length of time over which a drug may be administered varies between the classes. Hence the extent to which side-effects can be tolerated varies quite widely. For example, an antibiotic may be given for a few days while a compound, which is given to correct a hormone deficiency or as an immunosuppressive agent may be administered for years.

1.3 TARGETS FOR THE MEDICINAL CHEMIST

1.3.1 Hormones as Targets

The body produces substances known as hormones, which regulate body functions. These can be circulatory hormones such as the steroid

and peptide hormones. They are produced by one organ and are then transported to their target organ. Others, such as histamine are local hormones, which are produced by one cell and have their action on adjacent cells. These are sometimes known as autocooids. The third group are the neurotransmitters, which are formed and have their action at nerve endings. A fourth group are the 'second messengers'. These are compounds that are formed within a cell often as a result of an external stimulus via a *trans*-membrane protein. They control the function of various enzyme systems within the cell.

Many hormones and neurotransmitters exhibit their cell-signalling biological activity by binding to a receptor on a cell surface. The receptor may be part of a *trans*-membrane protein, which crosses the cell wall. This binding to a *trans*-membrane protein then initiates a sequence of events within the cell. Other hormones have to cross the cell wall and exert their biological activity by binding to nuclear receptors within the cell. This activates the nucleic acids and initiates the DNA–RNA–protein sequence of events.

The hormones are biosynthesized by a series of steps and once they have produced their biological effects, they are metabolized and excreted. The medicinal chemist may interact with this sequence in a number of ways. The chemist may synthesize the biological compound itself and use it to correct a deficiency or an agonist may be prepared. An agonist is a relative of the naturally occurring substance that also binds to the receptor and elicits the same biological effect. A partial agonist is a compound, which binds but does not elicit the full response. In contrast to this an antagonist binds to the receptor site but does not produce the biological effect. It may block the effect of an agonist. Often agonists and antagonists have quite similar structures for both have to bind to the receptor.

The enzymes which mediate the biosynthesis of the naturally-occurring compound may be inhibited by a drug. Hence the hormone will not be formed and its biological effect will not be observed. Many enzymes are regulated by a metabolite from a later stage in the biosynthetic pathway. This type of feedback regulation may be used to moderate the amount of biosynthesis that occurs. The release of a compound from storage may also be a regulatory step. When enzyme systems are targets for drugs, the binding may be of a competitive and reversible nature or it may be irreversible. Sometimes the product of the reaction of the enzyme with an artificial substrate may then react with the enzyme itself preventing the enzyme from catalyzing further transformations. This type of inhibition is known as suicide inhibition.

Once a hormone or neurotransmitter has completed its biological function, it may be metabolized and excreted or it may participate in the

1.4 THE STAGES IN THE DEVELOPMENT OF A DRUG

The first stage in the development of a drug involves the establishment of a reliable bio-assay. This may be an antibiotic screen or a screen against a particular tumour cell line. It may involve enzyme or receptor assays. These days whole animal tests are rare in the primary screens although in previous years, they have played an important part. Nevertheless because of the complexity of biological systems, there are still situations in which whole animal tests have to be used to obtain information on a potential drug. Modern enzyme or receptor screens can be very rapid and have a high throughput allowing small amounts of many thousands of compounds to be screened within weeks. This in turn has led to new synthetic methodologies in organic chemistry such as combinatorial synthesis in order to generate a suitable range of compounds for testing.

There are a number of sources of lead compounds. These may be obtained by screening natural products particularly from plants that have been used in folk medicine. The lead compound may arise from random screening or from the clinical observation of a side effect of an existing drug. The rational design of a lead compound based on the structural modification of a hormone or an active site model, is an intellectually satisfying approach.

Once a lead compound has been identified, there is a progressive structural modification to enhance the activity and to identify the contribution of electronic and steric factors to the biological activity. This can be with the aid of computer based molecular-modelling techniques. The establishment of quantitative structure: activity relationships (QSAR) can lead to the identification of a part of the molecule that is responsible for the activity, the pharmacophore.

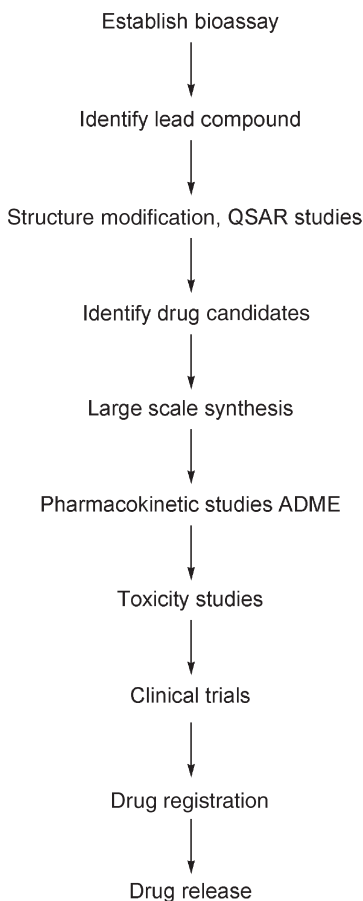
Drug metabolism studies and pharmacokinetic studies then follow. The identification of the metabolites of a drug can involve the medicinal chemist in the preparation of labelled material. Once a compound is under serious consideration as a drug candidate, animal toxicity studies are undertaken. On the chemical side the formulation and development of a manufacturing route and appropriate analytical methods have to be undertaken. Clinical studies then follow. The phase I trials involve healthy volunteers and aim to establish the acceptability of a compound in man and obtain some pharmacokinetic data, phase II trials are with a limited number of patients and aim to establish the efficacy of the drug. This includes proof of the principle underlying the activity. Finally phase III large-scale trials are used to establish the efficacy of a drug compared to its rivals. Evidence has to be obtained concerning the safety

of the drug and any contra-indications for its use. During any one of these phases development may be stopped if toxicity is detected. The submissions to the drug safety and drug registration committees then follow such as the Medicines and Health Care Products Regulatory Authority and the U.S. Food and Drug Administration. Finally if a compound is to be prescribed in the National Health Service, its effectiveness has to be assessed and a recommendation made by the National Institute of Clinical Excellence (NICE). The current time scale between the initial programme and the release of a compound for use may be between 10 and 15 years and the cost may be of the order of £500 million pounds. The need for patent protection in these circumstances is obvious. This sequence of events is summarized in Scheme 2.

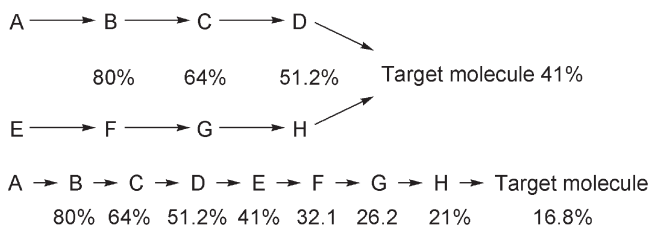
1.5 THE SYNTHESIS OF A DRUG

Synthetic organic chemistry is one of the corner stones of medicinal chemistry. There are a number of criteria by which a synthesis may be evaluated in a medicinal chemistry context. A convergent synthesis rather than a linear synthesis (Scheme 3) has significant advantages. Not only are there benefits in terms of yield but there is increased flexibility. Structural variation is possible in one arm of the synthesis while keeping the other constant and vice versa. This enables structure: activity studies to be made more easily. Metabolic studies require the preparation of labelled material. It is necessary to explore not only what happens to the intact drug in the body but also to trace metabolic fragments. A convergent synthesis makes labelling different parts of the molecule easier. If a chiral centre is created in the drug then the synthesis should not only be stereospecific but also enantiospecific. The targets for most drugs are chiral. Although the required biological activity may reside in one enantiomer, the other enantiomer may have different, potentially toxic properties. A racemic mixture has to be avoided. Biotransformations involving a chiral enzymatic step have an increasingly important role to play in the preparation of a single enantiomer.

While retrosynthetic analysis must play an important role in the design of a synthetic scheme, economic considerations in terms of the availability of starting materials play an equal part. The art of synthesis in a medicinal chemistry context lies in the combination of retrosynthetic analysis with the identification of readily available basic building blocks in the target structure. The dissection of a structure into its basic building blocks can also be a useful way of remembering the structure of drugs.



Scheme 2 *Stages in the development of a drug*



Scheme 3 *The effect of an 80% yield at each step on a convergent and a linear synthesis*

In recent years high throughput enzyme and receptor screens have been developed which require large numbers of small samples for testing. This has placed considerable demands on synthetic chemists who have responded by introducing automated combinatorial methods

of synthesis. The object of a combinatorial synthesis is to maximize the number of compounds that might be produced by simple combinations of starting materials and reagents to generate a library of related structures. The reactions are usually carried out by attaching the starting materials to a solid phase such as a resin by a linker. In a simple example there might be two starting materials, A and B, which are attached to separate sets of resins. These are mixed and split into two and each is then reacted with either C or D to give four compounds. If these are mixed and split again to be combined with E and F, there are eight possible combinations ($2 \times 2 \times 2$). Although this is a small library, larger libraries (e.g. $5 \times 5 \times 5 = 125$) can be developed quite rapidly.

Once a drug reaches the stages of toxicity and clinical trials, relatively large quantities will be required. A number of additional chemical features have to be considered. Steps involving low yields and difficult separations must be eliminated. The large-scale use of hazardous reagents or those, which produce toxic residues have to be avoided. A laboratory synthesis may need to be redesigned to overcome these problems. In the subsequent chapters we will see how various syntheses fulfil these criteria.

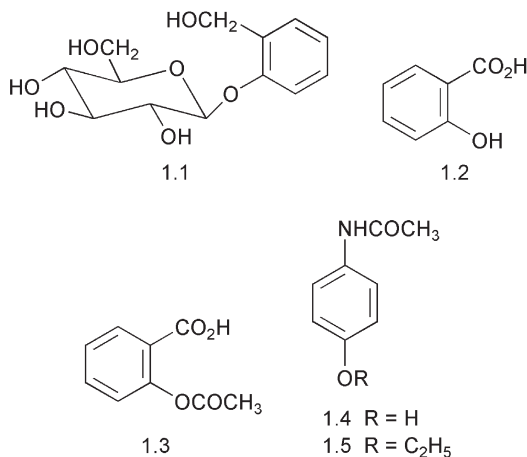
1.6 THE HISTORY OF MEDICINAL CHEMISTRY

There is a long history of plants being used to treat various diseases. They figure in the records of early civilisations in Babylon, Egypt, India and China. The therapeutic properties of plants were described by the Ancient Greeks and by the Romans and are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus. Some metals and metal salts were also used at this time. In the Middle Ages various 'Materia Medica' and pharmacopeas brought together traditional uses of plants. The herbals of John Gerard (1596), John Parkinson (1640) and Nicolas Culpeper (1649) provide an insight into this widespread use of herbs. Exploration in the seventeenth and eighteenth centuries led to the addition of a number of useful tropical plants to those of European origin.

The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry. Their development is intertwined. The isolation of a number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud.

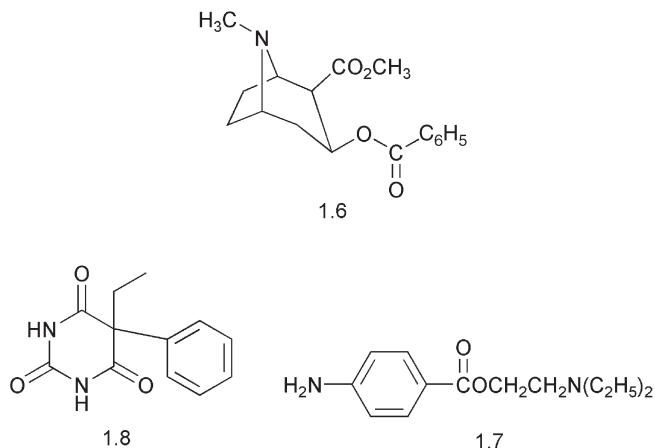
General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)). Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery. The hypnotic activity of chloral (trichloroethanal) (1869) was also reported.

Many of the developments after the 1860s arose from the synthesis of compounds specifically for their medicinal action. Although the use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin **1.1** and of salicylic acid **1.2** were developed in the 1860s and 1870s. *p*-Hydroxyacetanilide **1.4** (paracetamol) and phenacetin **1.5** (1886) were also recognized as pain-killers. Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin **1.3** in 1899. However its mode of action was not established until 1971.

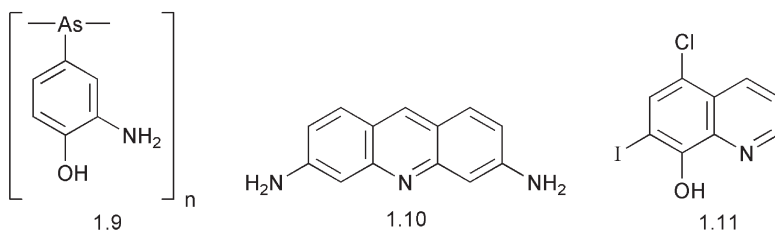


The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time.

Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine **1.6** led to benzocaine (1892) and procaine **1.7** (1905). The barbiturates, veronal (1903) and phenobarbital **1.8** (1911) were introduced as sleeping tablets.

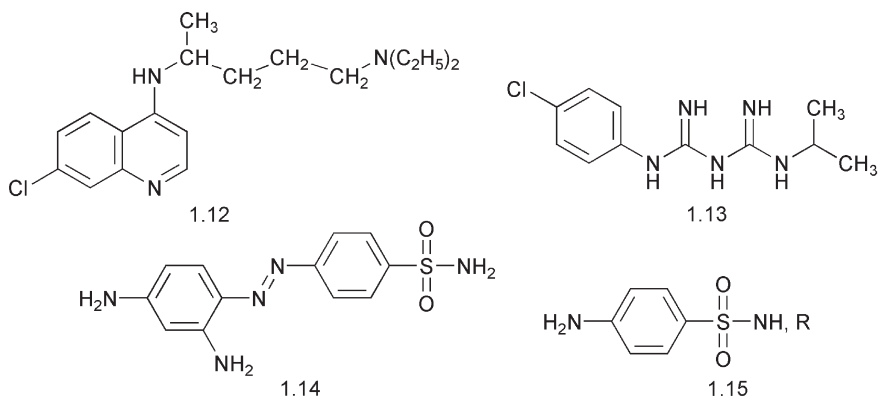


Once ideas of chemical structure were formulated in the mid-nineteenth century, the first theories of the relationships between chemical structure and biological activity began to emerge. Thus Crum-Brown and Fraser (1869) noted that a 'relationship exists between the physiological action of a substance and its chemical composition' leading to the idea that cells can respond to the signals from specific molecules. On the basis of observations that certain dyes selectively stained micro-organisms, Ehrlich in the 1890s put forward the idea that there were specific receptors for biologically active compounds – 'lock and key' relationships. This led to the examination in 1904 of dyestuffs such as trypan red for the treatment of trypanosomiasis and the development (1907) of salvarsan **1.9** for the treatment of syphilis by what turned out to be a false structural analogy (see Chapter 6). In the First World War acriflavine and proflavine **1.10** dyestuffs were used for the treatment of sepsis in wounds. The work of Meyer and Overton (1899–1901) to relate a physical property (the oil: water distribution co-efficient) to biological activity (anaesthesia) were the first rudimentary QSAR. Another quantitative measurement that was made was the chemotherapeutic index, which was the ratio of the minimum curative dose to the maximum tolerated dose (CD50/LD50).

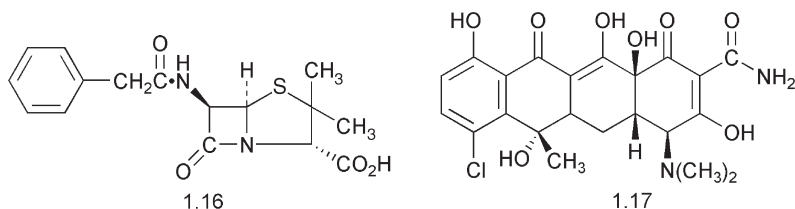


The action of acetylcholine on nerve tissue had been recognized in the late nineteenth century. Barger and Dale (1910) examined the response of various tissues to acetylcholine agonists and showed that there were different receptor sub-types; some responding to muscarine and others to nicotine.

The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins. It was also a period in which there was exposure of many Europeans to tropical diseases. The iodinated quinolines such as entero-vioform **1.11** were introduced to combat amoebic dysentery and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness. Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) and later chloroquine **1.12** (1943) and paludrine **1.13** (1946) were introduced as quinine replacements.



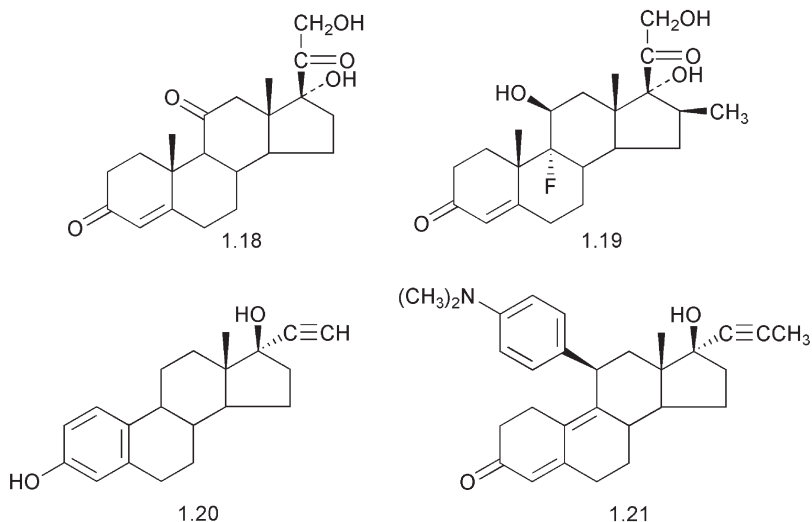
In 1935 Domagk observed the anti-bacterial action of the sulfonamide dyestuff, prontosil red **1.14**, from which the important family of sulfonamide **1.15** anti-bacterial agents were developed. The activity of these compounds as inhibitors of folic acid biosynthesis was rationalized by Woods (1940) as anti-metabolites of p-aminobenzoic acid. With the onset of the Second World War, there was a need for new antibiotics. In 1929 Fleming had observed that a strain of *Penicillium notatum* inhibited the growth of a *Staphylococcus*. In 1940–1941 Chain, Florey and Heaton isolated benzylpenicillin **1.16**. After considerable chemical work, the β -lactam structure for the penicillins was established. The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including streptomycin (1944), chloramphenicol (1949) and the tetracyclines such as aureomycin **1.17** (1949).



Several different aspects of medicinal chemistry developed in parallel through the second half of the twentieth century. Although they did not develop independently, it is easier to follow their progression by considering them separately.

The structures of the steroid hormones were established in the 1930s and 1940s. The discovery in 1949 of the beneficial effect of cortisone **1.18** in alleviating the inflammation associated with rheumatism provided the stimulus for synthetic activity in this area. A number of anti-inflammatory semi-synthetic corticosteroids such as prednisolone, betamethasone **1.19** and triamcinolone became available in the late 1950s and 1960s.

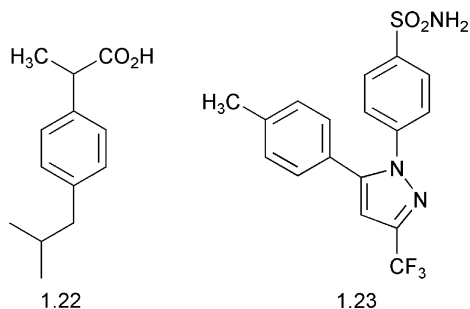
Animal experiments to develop steroidal oral contraceptives were carried out before the Second World War but the first preparations (*e.g.* Enovid[®]) containing a synthetic estrogen, for example ethynylestradiol **1.20** and progestogen were not available until 1959. Subsequent preparations have been developed to reduce the estrogen level. Mifepristone **1.21**, which is an anti-progestogen and forms the basis of the ‘morning-after pill’, was introduced in 1985. Whereas many of the medicines that had been developed prior to this time were administered for only short periods of time, this was not true of the steroids and concerns developed over the effects of long-term therapy.



Problems associated with separating the anti-inflammatory activity from the mineralcorticoid activity of the cortical steroids led to interest in the development of non-steroidal anti-inflammatory agents (NSAIDs). The long-term use of aspirin as a pain-killer for arthritic conditions brought side-effects such as stomach ulcers. Indomethacin and ibuprofen (nurofen[®]) **1.22** were introduced in 1965 and 1971 respectively as alternatives.

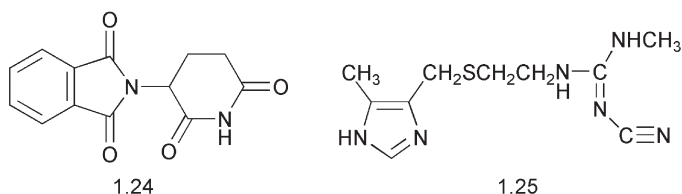
During the 1960s the prostaglandin hormones were implicated in inflammation and in the protection of the stomach against ulcers. In 1971 aspirin was shown to inhibit the biosynthesis of the prostaglandins from arachidonic acid by the enzyme system, cyclo-oxygenase. The subsequent realization that there were several forms of cyclo-oxygenase provided the framework for developing selective non-steroidal anti-inflammatory agents that only targeted some of the multiple activities of the prostaglandins. One result was the introduction in 1999 of celecoxib (Celebrex[®]) **1.23** and rofecoxib (Vioxx[®]) as selective cyclo-

oxygenase (COX-2) inhibitors. Recently cardiovascular side effects of these compounds have begun to emerge and Vioxx[®] has been withdrawn.



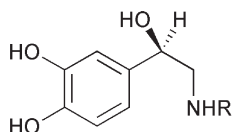
A number of developments took place in the 1960s, which changed medicinal chemistry. It was found that a drug, thalidomide **1.24**, which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children. The consequences of this teratogenic effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines. Unfortunately there was some tardiness in the recognition of this side-effect. Second in 1964 Hansch published correlations between substituent effects (Hammett parameters) and the biological activity of some aromatic compounds. These QSAR began to provide a framework for the systematic development of drugs and for decisions to be made in the planning of a research programme.

The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine **1.25** (1976) and then ranitidine (1981). The reasoning behind this work had a major impact on the development of medicinal chemistry.



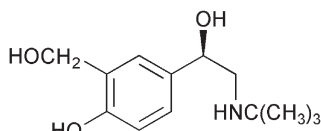
Adrenalin (epinephrine) **1.26** was the first substance to be recognized as a hormone (1901). The adrenergic receptors were divided in the α - and β -receptors by Ahlquist in 1948 based on their responses to selective agonists, *e.g.* isoprenaline **1.27**. The β -receptors were subsequently subdivided by Lands. This, together with an understanding of the metabolism of adrenalin (epinephrine) led to the discovery of

salbutamol **1.28** (1967) as a selective β_2 agonist in the treatment of asthma.

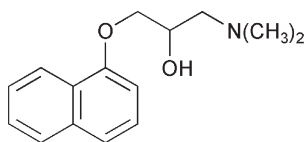


1.26 R = CH₃

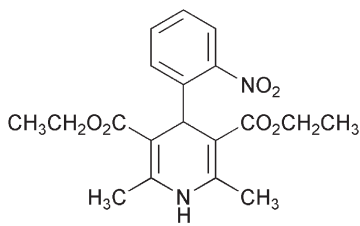
1.27 R = CH(CH₃)₂



1.28

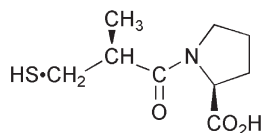


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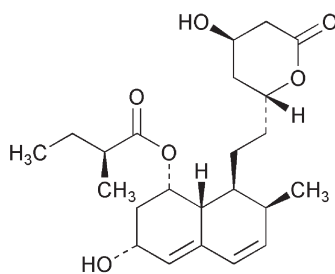


1.30

The development of drugs such as propranolol **1.29** (1964) and atenolol (1970), which blocked the β_1 receptors in cardiac muscle, was a major advance in the treatment of heart disease. Another important group of drugs with cardiovascular properties that were developed in the 1960s were those that block the movement of calcium ions through ion-channels. These were dihydropyridines such as nifedipine **1.30** (1967). Angiotension converting enzyme (ACE) inhibitors such as captopril **1.31** (1977) and enalapril (1984) are further valuable anti-hypertensive agents. The association of high cholesterol levels with circulatory diseases led to the development of cholesterol biosynthesis inhibitors. A major family of drugs with this activity are the statins exemplified by lovastatin **1.32** (1987) and simvastatin (1988). The statins are now widely prescribed for reducing cholesterol levels.

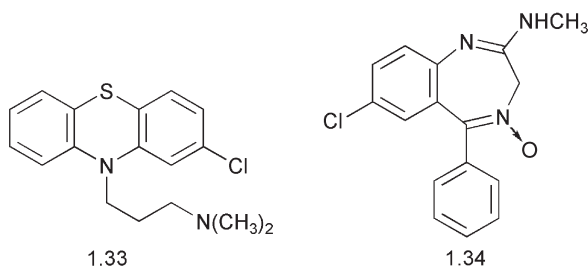


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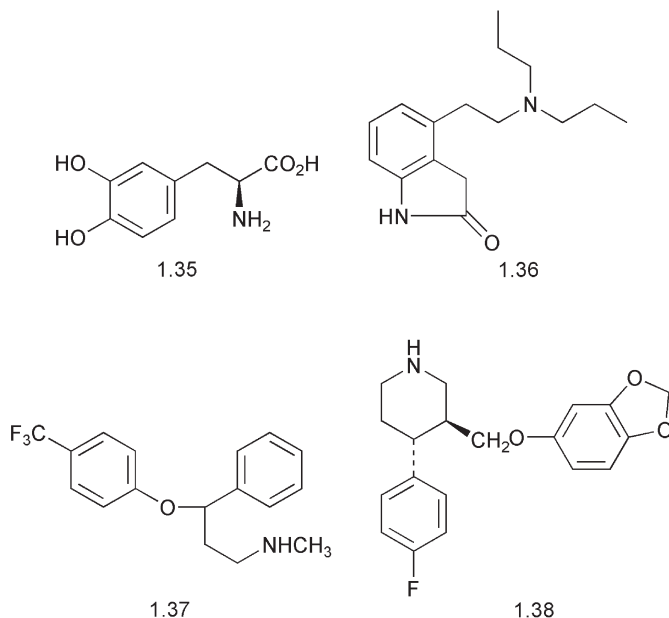


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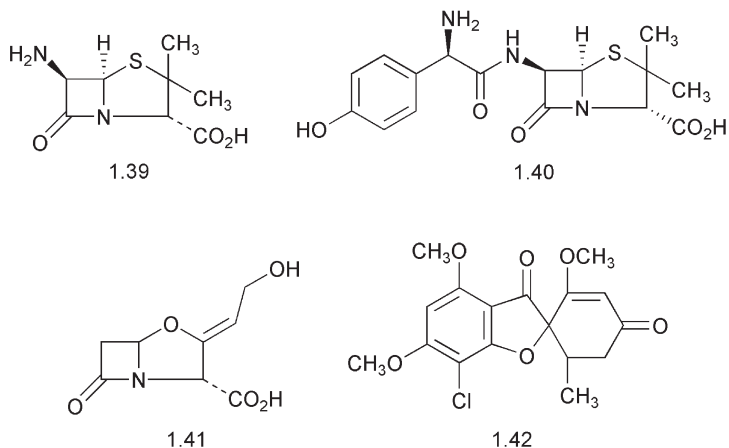
Medicinal chemistry has revolutionized the treatment of mental disease during the second half of the twentieth century. An increasing understanding of the role of various neurotransmitters in the brain has played an important part in this. A number of anti-depressants and anti-psychotic agents were developed in the 1950s including the phenothiazine, chlorpromazine **1.33** (1952), the tricyclic compounds such as imipramine (1957) and the butyrophenones such as haloperidol (1958). The benzodiazepine tranquilizers such as librium **1.34** (1960) and valium (1963) were the forerunners of a large family of drugs.



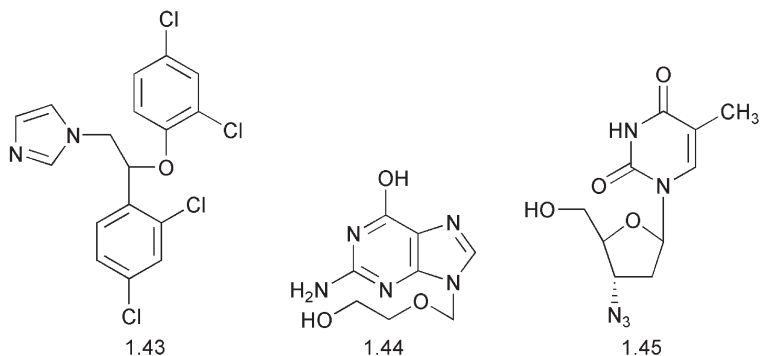
The discovery in 1950 that a dopamine deficiency was associated with the neurodegenerative disease known as Parkinson's disease, led to various strategies to overcome this dopamine deficiency. Unfortunately just administering dopamine was unsuccessful because it did not reach the brain. However a successful treatment made use of its biosynthetic precursor, L-DOPA **1.35** (1961). DOPA decarboxylase inhibitors such as carbidopa were developed to increase the amount of L-DOPA reaching the brain by preventing its decarboxylation before it reached the blood:brain barrier. Dopamine agonists such as pergolide (1988) and ropinirole **1.36** (1996) and inhibitors of dopamine metabolism such as tolcapone (1997) have provided other methods of treatment. Whereas diminished dopamine levels have been associated with neurodegenerative diseases, excessive responses to dopamine and other neurotransmitters are associated with different conditions. Some aspects of depression have been associated with reduced levels of the neurotransmitter, serotonin. This has culminated in the development of selective serotonin reuptake inhibitors such as fluoxetine (Prozac[®]) **1.37**, paroxetine (Seroxat[®]) **1.38**, sertindole (1996) and olanzapine (1996).



A major problem associated with the treatment of many infectious diseases has been the development of resistant organisms. This has been found with viruses, bacteria and with parasitic organisms such as malaria. Strains of *Staphylococcus aureus* that were resistant to the natural penicillins were already starting to appear by the late 1940s. The penicillins that were used in the late 1940s and 1950s also had problems of stability associated with them. A significant step forward came in 1959 when methods for the commercial isolation of the 6-amino-penicillanic acid **1.39** core of the penicillins were developed. This permitted the synthesis of a range of semi-synthetic penicillins with enhanced stability and activity. Methicillin, ampicillin and amoxicillin **1.40** were introduced in 1960, 1961 and 1964 respectively. The related cephalosporin β -lactam antibiotics, cephaloridine, cephaloxin and cefaclor were introduced in 1964, 1967 and 1974 respectively. The development of resistant strains of bacteria possessing β -lactamases that degrade the penicillins, has become a serious problem. The combination of a β -lactamase inhibitor, clavulanic acid **1.41** (1976) with a penicillin, amoxicillin, in an antibiotic preparation known as Augmentin[®], was one useful approach to the problem. However methicillin resistant strains of *Staphylococcus aureus* (MRSA) are an increasing problem. Although these may be combated with a different type of antibiotic, vancomycin, strains that are resistant even to this antibiotic are beginning to appear.



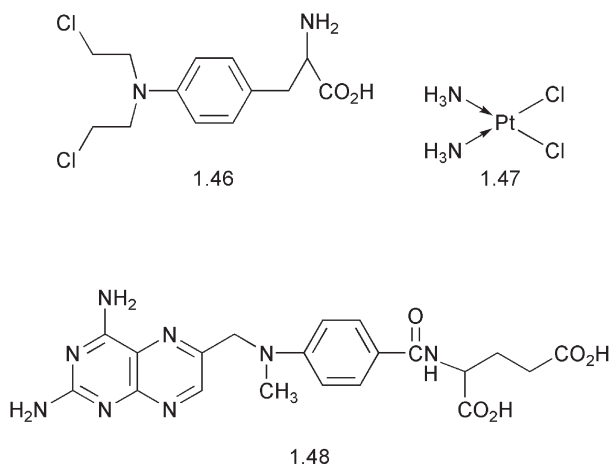
Fungal infections of man are mainly confined to the skin. A number of useful antifungal agents have been developed. The structure of the anti-fungal microbial metabolite, griseofulvin **1.42**, was established in 1952 and it was launched in 1959. Inhibition of the sterol component of the fungal cell wall has provided the basis of the action of a family of anti-fungal agents known as the azoles. These include miconazole **1.43** (1972), ketoconazole (1980) and fluconazole (1988).



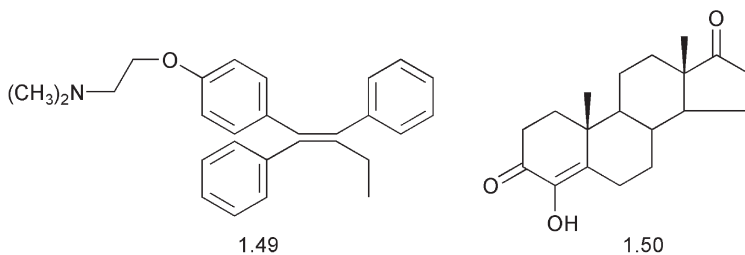
Whereas the bio-assay of anti-bacterial and anti-fungal agents is relatively straightforward, a virus requires its host-cell in which to replicate. Hence the bio-assay of anti-viral agents was more difficult until cell culture techniques were developed. Anti-viral agents active against the herpes virus include acyclovir **1.44** (1981). The identification of the viral origin of HIV-AIDS in 1983 led to the introduction of azidothymidine **1.45** (AZT) in 1987 to combat this disease. More recently (1999) zanamavir (Relenza[®]) and oseltamivir (Tamiflu[®]) have been developed for the treatment of 'flu'.

A key change in the bio-assay of drugs in the latter part of the twentieth century involved the development of receptor and enzyme bio-assays and the use of cell culture techniques. Many of the screens are very rapid and can cope with large numbers of samples. High throughput screening has changed the scale and rate at which compounds are produced for bio-assay.

The development of cancer chemotherapy has reflected this shift in screening from the use of animal models towards cell-lines associated with particular tumours. Many of the earlier drugs were alkylating agents developed from the chemical warfare agent, mustard gas. These included cyclophosphamide and melphalen **1.46**. The important observation, made in 1969, that the products from electrolysis using platinum electrodes, slowed down the growth of bacteria, led to the development of the anti-tumour drug, cis-platin **1.47**. Another approach involved blocking the biosynthesis of DNA using drugs known as anti-metabolites, which was exemplified by methotrexate **1.48**. Natural products, such as the Vinca alkaloids, vincristine and vincalkebostine and more recently, taxol[®] (paclitaxel) from the yew tree are useful tumour inhibitory agents.



The recognition that a significant proportion of breast cancers are estrogen dependent, led to the development of compounds that target the estrogen receptor (tamoxifen, **1.49**) or inhibit estrogen biosynthesis (formestane, **1.50**, 1993; anastrozole, 1995). The use of monoclonal antibodies (*e.g.* herceptin) which recognize and specifically target particular cancer cells and prevent them developing is a very important advance.



The impact of genomics on medicine and the recognition of genetic differences associated not only with specific diseases but also with the susceptibility to disease, is likely to lead to significant new treatments and refinements of older treatments. While many of these may involve the surgical introduction of particular cells, their ultimate success will retain a medicinal chemistry input. The diagnostic tests for many of these conditions also requires the skills of the medicinal chemist.