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Joaquín M. Campos Rosa,
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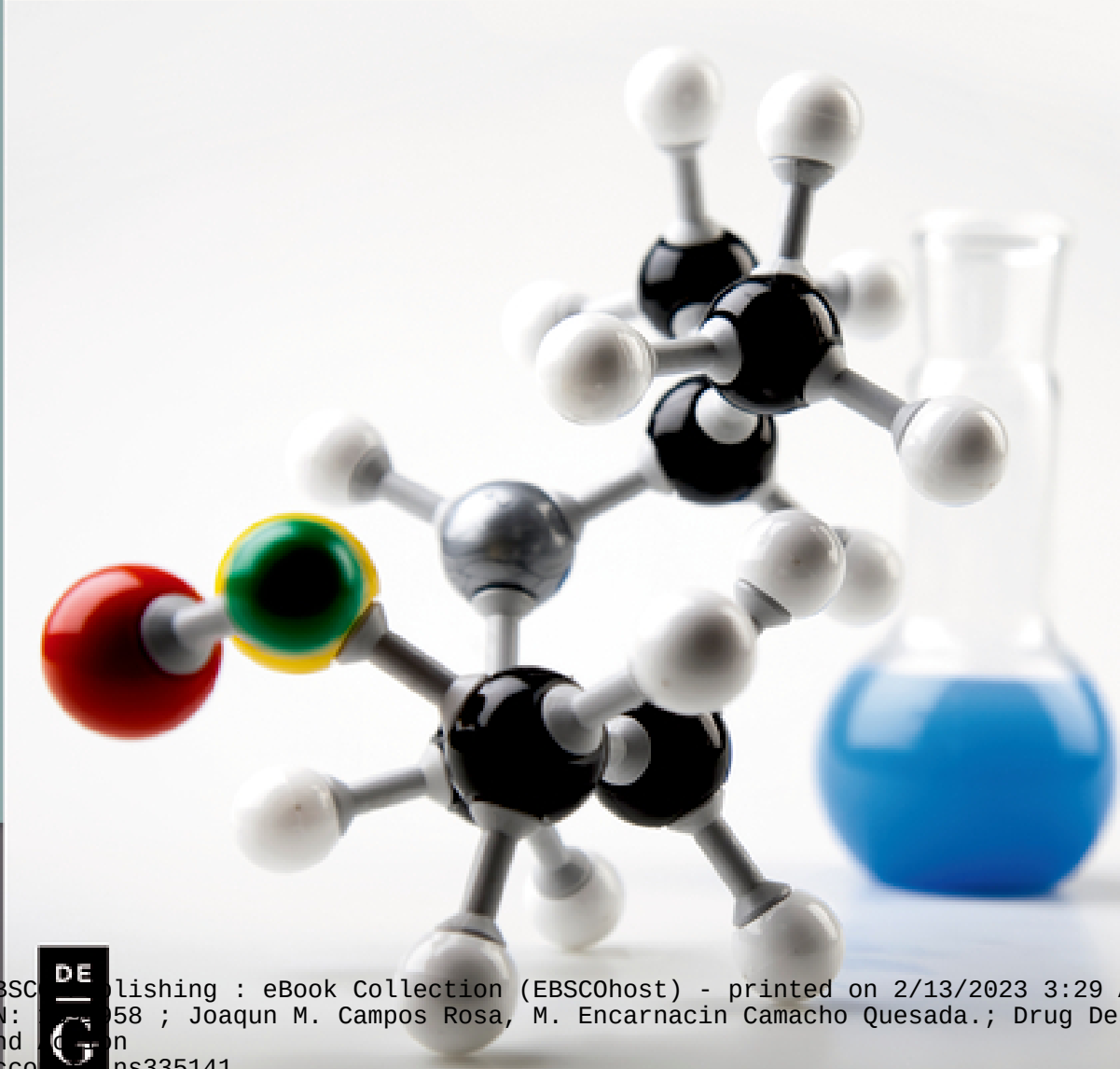
PHARMACEUTICAL CHEMISTRY

VOLUME 1: DRUG DESIGN AND ACTION



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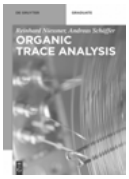

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Pharmaceutical Chemistry

Volume 1: Drug Design and Action

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"You can teach a student a lesson for a day; but if you can teach him to learn by creating curiosity, he will continue the learning process as long as he lives"

Clay P. Bedford (1903–1991)

Prologue

Global objectives of pharmaceutical chemistry

1. To understand the interrelation between structure, physico-chemical properties, pharmacological activity, and therapeutic utility.
2. To know the methods and strategies used in the generation of drugs.
3. To know the interactions between drugs and their biological targets.
4. To know and propose the structural modifications that affect the properties of the drugs.
5. To know the general methods and the synthetic strategies for the preparation of drugs.
6. To know the analytical and spectroscopic methods applicable to the structural identification and elucidation of drugs, and related compounds.
7. To be able to name and formulate a drug in accordance with the systematic IUPAC nomenclature.
8. To know and become able to predict the transformation of drugs in the body.
9. To know and be able to estimate the risks associated with the use of reagents, solvents and the development of processes in the chemical laboratory.
10. To know how to acquire and use information related to drugs.

The objective of pharmaceutical chemistry is the chemical study of drugs and the active ingredients of drugs in order to determine the relationship between chemical structure, physicochemical properties, reactivity, and biological response, with the ultimate aim of providing the knowledge necessary for the creation of new drugs. Since most of the drugs are organic in nature, pharmaceutical chemistry is mainly based on the knowledge of organic chemistry, although it requires a strong familiarity with and a solid base in biochemistry. It is also nourished by other sciences such as a) pharmacognosy, which studies natural products as a source of new active principles; b) pharmacology, which allows the establishment of experimental models for the evaluation of new active principles; and c) molecular pharmacology. The latter tries to explain the biological effects at the molecular level, interpreting the phenomena related to the association between a drug and the biomolecules that trigger its action, all from the point of view of structural and physicochemical properties.

Although drug design in its origins focused primarily on the simple chemical modifications of naturally occurring molecules, the current design trends are based on the study of drug interactions with their targets at the molecular level. The development of molecular biology and genetic engineering over the last decade has allowed the detailed study of many targets in the action of drugs, such as enzymes, membrane receptors, and nucleic acids. Therefore, presently a part of the design of new drugs is based on drug-receptor interactions.

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The complete work consists of the following two volumes:

Pharmaceutical Chemistry
Volume 1: Drug Design and Action

Pharmaceutical Chemistry
Volume 2: Drugs and their Biological Targets

After the first part, in which general principles are explained, in the second volume the knowledge acquired for the establishment of the therapeutic arsenal according to the different molecular objectives is applied. There are excellent treatises of pharmaceutical chemistry or medicinal chemistry, but in general they require that the reader has a solid base. Our work is aimed at students of pharmacy and chemistry who intend to enter the exciting world of drug development. Therefore, we have not tried to cover this study in an exhaustive way, but rather to establish the bases that in a first stage allow the fostering of interest in this scientific field. This is our humble goal, and if we succeed, we will feel satisfied that our objective has been fully attained. We have tried to achieve a balance between chemical and biological aspects, highlighting the strong multidisciplinary character of this science. As far as possible, the number of drugs of both volumes has been reduced to a minimum, sufficient to understand the philosophy of pharmaceutical chemistry and without overburdening the beginner with more and more examples, and therefore we hope to avoid a "*can't see the wood for the trees*".

The synthesis of drugs is dealt with from a double point of view in Chapter 8 of this first volume: the retrosynthetic analysis which allows the bond-breaking of the molecule to arrive at structurally simpler starting materials and which will allow us to carry out the direct and real process of synthesis in a rational way. The basis of biology is chemistry, which permits the creation of drugs (chemists acting as molecular architects), as well as the analysis of the interactions between the drug and its biological objective, which will permit the design of more active structures after their optimization. Exercises are given in this first volume along with their solutions, allowing the reader to assess to what degree he or she has understood.

The work shown here is the result of extensive teaching experience at the Faculty of Pharmacy of Granada University. We want to thank the role of the students in the noble task of teaching. They give meaning to our work and stimulate us to keep both knowledge and methodology up to date. We want to thank our parents, partners, and children for the support we have received. They have demonstrated that constancy is fundamental to achieving our objectives, while we have neglected our families during the time devoted to this work.

It is the explicit desire of the authors to receive any suggestions, additions, and corrections which will surely make possible an expanstion of the contents of the work.

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1 Basic concepts in pharmaceutical chemistry

1.1 Goals

- To know the tasks of pharmaceutical chemistry.
- To know and understand the concepts of drugs and medicines.
- To understand the multidisciplinary nature of this discipline.
- To introduce the concepts of patent and pharmaceutical industry.
- To know the global process through which new drugs are discovered and the methodologies used over time.
- To know the main stages of development of a new drug and its cost.

1.2 Basic concepts and purposes of pharmaceutical chemistry

According to the IUPAC specialized commission "Pharmaceutical Chemistry is related to the discovery, development, identification, and interpretation of the mechanism of action of biologically active compounds at the molecular level. Drugs will be emphasized, but the interest of the pharmaceutical chemist will not be restricted only to drugs, but will also include biologically active compounds in general. Pharmaceutical chemistry will also address the study, identification, and synthesis of the metabolic products of drugs and related compounds. In short, pharmaceutical chemistry is responsible for the design, synthesis, and analysis of drugs. Scheme 1.1 shows the general method of work in pharmaceutical chemistry.

After the application of Scheme 1.1, the ideal new drug has to fulfil the following conditions:

1. new patentable chemical entity capable of being registered;
2. its synthetic process should not exceed four steps and should not include any heavy metal catalysts or environmentally problematic wastes; Purity > 99 %;
3. stable up to 70 °C, even in a humid environment, and stable against light;
4. it has to possess solid-state properties (crystalline, nonexistence of polymorphic and nonhygroscopic forms);
5. solubility in water;
6. > 90 % oral bioavailability;
7. High activity with a pharmacokinetic profile that allows it to be given once daily with a dose of 5–10 mg.

Pharmaceutical chemistry has three fundamental objectives:

1. modification of structures that have a well-known physiological action, i.e. obtaining new drugs from others already known: molecular manipulation;

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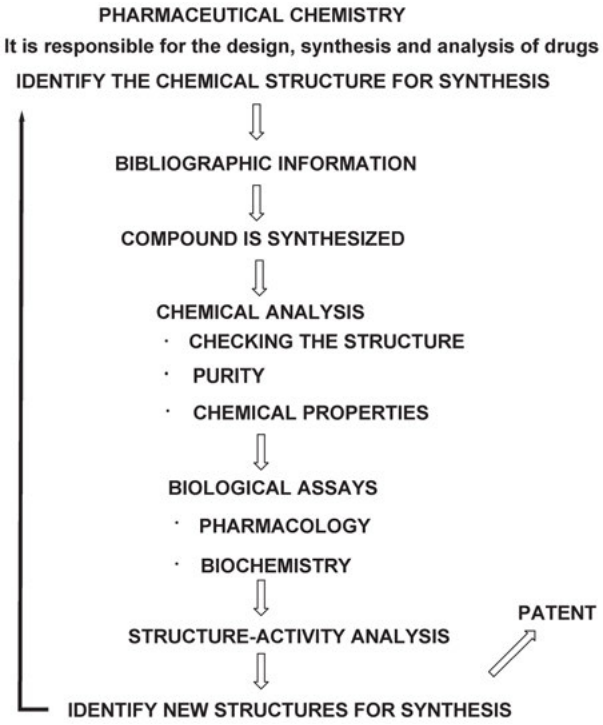


Scheme 1.1: The general method of work in pharmaceutical chemistry.

2. it provides the necessary knowledge for the development of new drugs: drug design;
3. In addition, drug analysis: the use of very sensitive analytical techniques is essential for the quality control that determines the efficacy and safety of the medicines. On the other hand, metabolite analysis is a key aspect in the pharmacokinetic studies that determine the bioavailability and duration of the therapeutic response. Purity tests set the limit for acceptable impurities. If the tests have to determine the amount of an active substance in a medicinal product, it must be separated from other accompanying substances by applying separation techniques.

There are a number of definitions that should be known:
Drug: any raw material of animal or vegetable origin that contains one or several active principles which, introduced into the body by any route of administration, produces an alteration of the natural functioning of the central nervous system of the individual and is also susceptible of creating dependence, whether psychological, physical, or both. In English, a drug is also a biologically active substance (capable of interacting with the biological environment), chemically pure and with therapeutic

action, i.e. capable of curing, mitigating, or preventing disease in humans or animals (for example, acetylsalicylic acid).

Medicine: the drug in the proper dosage form, used in medicine (for example, Aspirin®, Fig. 1.1). It is synonymous with drug. Hence, the terms "Medicinal Chemistry" or "Therapeutical Chemistry" are used interchangeably.

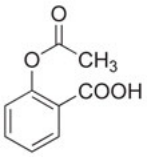


Fig. 1.1: Acetylsalicilic acid (Aspirin®).

The mere disposition of active drugs is not sufficient for their clinical application: it is necessary to formulate medicines that can be introduced into the organism by the appropriate route for each patient. For example, acetylsalicylic acid, a drug widely used as an analgesic, antipyretic, blood thinner, and antirheumatic, could not be used without a previous physicochemical transformation which would allow its absorption and, if necessary, neutralize its ulcerogenic properties, contraindicated for certain patients. It has been demonstrated that the gastrointestinal dissolution of acetylsalicylic acid is the slowest step, and therefore determinant of its rate of absorption; Therefore, several forms of oral administration are required:

1. micronization of its crystalline form to an ultrafine powder of high dissolution rate, as in tablets known under the trade name of Aspirin®;
2. its galenic formulation with antiacids or buffer substances, to form locally soluble acetylsalicylates (effervescent Aspirin®);
3. the use of enteric-coated tablets that avoid direct contact of the drug with the gastric mucosa, even if it is detrimental to absorption.

We will study drugs (pure substances) and not medicines, in this collection.

1.3 Historical development of pharmaceutical chemistry

We can distinguish three great periods:

1.3.1 The pre-scientific period (~ 3000 years BC until the 19th century)

In ancient times, scientists were philosophers and erudite people, so that the different sciences were purely empirical. Some of the natural products, either as such or in

the form of derivatives, were often used for various purposes, such as arrow poisons, complements for religious rituals, or even cosmetics.

Belladonna:	Today	→	antimuscarinic drug
	Previously	→	cosmetic or poison
Curare:	Today	→	muscle relaxant
	Previously	→	poison

1.3.2 Scientific period (19th century to 1960)

From the nineteenth century and after the French Revolution (at the end of the eighteenth century), the sciences went from being empirical to being sciences based on experimentation. Organic chemistry was developed, and as a consequence, synthetic products began to be used. The first occasion in which a synthetic organic product was used to interfere with vital processes was probably during the first half of the 19th century when ether and chloroform were introduced as anesthetics. Because of this, initial efforts to search for new synthetic drugs focused primarily on anesthetics and hypnotics, and subsequently on analgesics. Physiology was also developed, and most diseases were listed and classified. A key figure in this period is the German immunologist Paul Ehrlich (1854–1915), who thought that drugs were able to distinguish human cells from those of parasites. This assumption was reinforced by his previous experiences on the selective staining of different tissues of mammals with dyes, as well as his studies on the selectivity of antibodies to the corresponding antigens (substances that cause the formation of antibodies when introduced into the body). He is the father of chemotherapy, which he defined as the use of drugs that harm the invading organism without causing harm to the host. This greatest contribution to the advancement of pharmaceutical chemistry is probably the original ideas that he proposed about the mode of action of the drugs. Thus, he postulated the existence of receptors in mammalian cells (a receptor is a macromolecule to which various ligands or compounds selectively bind that cause a specific biological effect). He distinguished two parts in antigens and chemotherapeutic agents:

1. haptophore groups: responsible for the union;
2. zoxoplastic groups: responsible for toxicity.

1.3.3 Current period (from the 1960s to the present)

With the development of biochemistry and molecular pharmacology, the receptors and the mechanism of action of the drugs began to be known, and so it is logical to think of a structure-activity relationship (SAR). If it is accepted that the activity of a

drug is due to the chemical interaction of this drug with a hypothetical cellular receptor, it is logical to consider that its physicochemical properties and therefore its structur, must be in direct relation to its activity. In 1964, the two most solid and general procedures of the quantitative structure-activity relationship (QSAR) appear:

- the Hansch–Fujita method;
- the Free–Wilson method.

Nowadays, with these and other theoretical studies drugs can be rationally designed.

1.4 Patents

A patent is a title that grants the right to manufacture and market the object of the patent during the period of validity (which is usually 20 years). That which is patented must be novel, implying that it has not been disclosed, and must have an inventive step, that is, it should not be obvious to a person skilled in the art. One of the hot topics in the patent field is the "chiral switch". During the period from 1983 to 1987 period, 30 % of the approved drugs were pure enantiomers, 29 % were racemic, and 41 % were achiral. Nowadays, most of the drugs that reach the market are achiral or pure enantiomers. The racemic problem is that each of the enantiomers normally has a different level of activity. In addition, the enantiomers may differ in the way in which they are metabolized and in their side effects. Therefore, it is better to market a pure enantiomer rather than a racemic one. The issue of chiral change is mostly related to racemic drugs that have been on the market for several years and for which the 20-year patent is on the point of expiring. Through the chiral shift towards a pure enantiomer, the pharmaceutical companies can argue that it is a new invention and that therefore a new patent can be formalized. However, they have to prove that the pure enantiomer represents an improvement over the original racemic, and that such a fact was not predictable when the racemic was originally patented. Examples of drugs for which chiral change has been performed are salbutamol and omeprazole (Fig. 1.2).

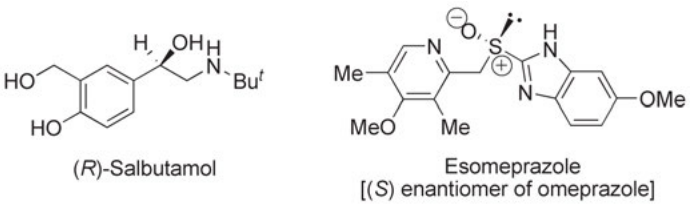


Fig. 1.2: The chiral switch has been carried out in some drugs.

1.5 Multidisciplinary nature of this discipline

For the development of pharmaceutical chemistry, a solid chemical knowledge, especially of organic chemistry, is not enough, but requires a strong biological base, concretized in a rational foundation of biochemistry.

Compounds that exceed a certain threshold value upon binding to the biological target or modulating some functional signals are called “hits”. On the other hand, a lead is a compound or a series of compounds with proven activity and selectivity that meet the criteria for drug development such as originality, patentability and accessibility (by extraction or synthesis). Pharmaceutical chemistry relies on (a) pharmacognosy, which studies drugs as a source of active principles – such active principles themselves constitute authentic drugs and serve as models for obtaining new drugs by molecular manipulation; (b) pharmacology and pharmacodynamics, which study the action of drugs and their mechanism. Having checked the pharmacological action of a drug, its pharmaceutical form allowing its administration to the patient should be given. The adequate drug formulation requires biopharmaceutical studies (i.e. those factors which influence the bioavailability of drugs) and pharmacokinetics, which refer to the kinetics of absorption, distribution, metabolismm and excretion of the drugs and their therapeutic response or toxicity in animals and man. Biopharmacy and pharmacokinetics will therefore complete the cycle of the drug when introduced into the galenic formulation (Fig. 1.3).

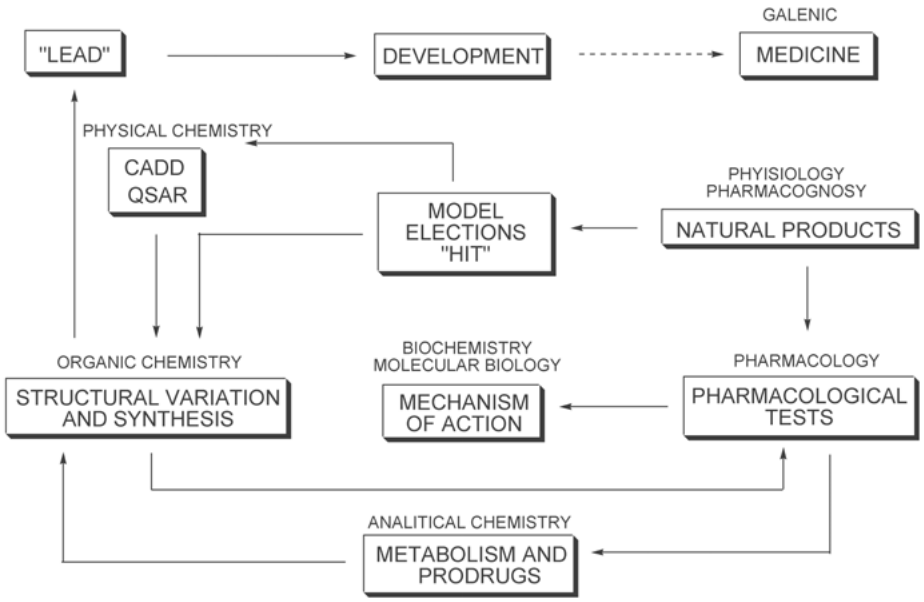


Fig. 1.3: Relationship of the different disciplines that affect pharmaceutical chemistry.

1.6 Origin of drugs

- Drugs of natural origin:
  1. vegetal (25 %); there are many extractable drugs from phanerogams and among them, we highlight the alkaloids, such as quinine, reserpine, and morphine;
  2. animal (18 %), e.g. insulin, hypoglycemic substance obtained from ox fresh pancreas, sex hormones, and corticosteroids.
  3. mineral (7 %); this is the case of aluminum salts to alleviate acidity of the stomach, or talc (silicates) to relieve pruritus and as a base for ointments.
- Drugs of semisynthetic origin: they are obtained by partial synthesis from a structure of natural origin, for example semisynthetic penicillins, etc.
- Drugs of synthetic origin: estradiol is a natural estrogen, ethinylestradiol is a semisynthetic derivative, while diethylstilbestrol is a synthetic product (Fig. 1.4).

Fig. 1.4: Examples of natural, semisynthetic, and synthetic drugs.

These last two groups constitute ≈ 50 % and are those that are usually studied by Pharmaceutical Chemistry.

1.7 Other definitions

The action of a drug refers to the modification that it produces in the functions of the organism, in the sense of increasing or diminishing them. Drugs never create new functions or alter the characteristics of the system on which they act: they only modify them. The effect or response of a drug is the manifestation of pharmacological action, which can be appreciated by the observer's senses or by simple devices (Fig. 1.5).

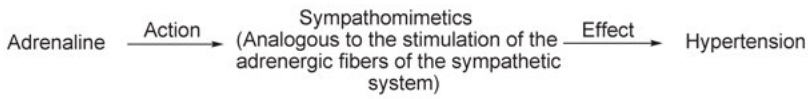


Fig. 1.5: Action and effect of adrenaline (also called epinephrine).

1.8 Classification of drugs

Pharmacological effect: Drugs are grouped depending on the biological effect they produce, e.g. analgesics. However, there are many biological goals and mechanisms by which analgesics can have an analgesic effect. Therefore, it is not possible to identify a common characteristic shared by all analgesics. For example, Aspirin® and morphine act on different goals and have no structural relationship.
Chemical structure: Many drugs have a common skeleton and are grouped according to this criterion, e.g. penicillins, barbiturates, opiates, catecholamine. For example, penicillins contain the β-lactam ring and kill the bacteria by the same mechanism. However, it is not infallible. Sulfonamides have a common structure and are fundamentally antibacterial agents. However, some sulfonamides are used for the treatment of diabetes.
Biochemical process: Generally a chemical messenger or neurotransmitter, e.g. antihistamines, cholinergics. It is more specific than that of the pharmacological effect, since it identifies the system on which the drugs act.
Molecular objective: There are compounds that are grouped according to the enzyme or receptor with which they interact; e.g. anticholinesterases are a group of drugs that act by inhibiting the enzyme acetylcholinesterase. This is the most useful classification with respect to pharmaceutical chemistry.

1.9 Process of discovery of a drug

Successful research and development of a drug carries with it gigantic costs that can fluctuate around 1,4 billion dollars (Fig. 1.6). These astronomical costs are due to the fact that of 5,000 candidate molecules only 1,000 become objective compounds and a dozen become "leaders", that is to say, they are promising, and of those thousands only one will arrive without problems up to the last phase of development. However, if only one of these drugs complies with all basic and clinical evaluations and is patented, the initial multimillion-dollar investment will be virtually paid off.

A drug may take 12 years from the initial discovery state to reach the market, and while estimates of costs vary, the Association of the British Pharmaceutical Industry puts it at $ 1.4 bn per drug. Just 1 in 5,000 drug candidates make it all the way from the drug discovery phase to licensing approval.

The number of biological targets is expected to increase tenfold for the treatment of diseases with the increasing advancement of proteomics, genomics, and molecular pharmacological techniques. Also being worked on is the development of other new drugs, including gene therapy and nanotechnology. The goal of pharmaceutical chemistry is to make the drug development process more cost-effective, shortening the time between the discovery, preclinical testing, and registration steps. This is why the rational design of drugs is at present of such a large dimension.

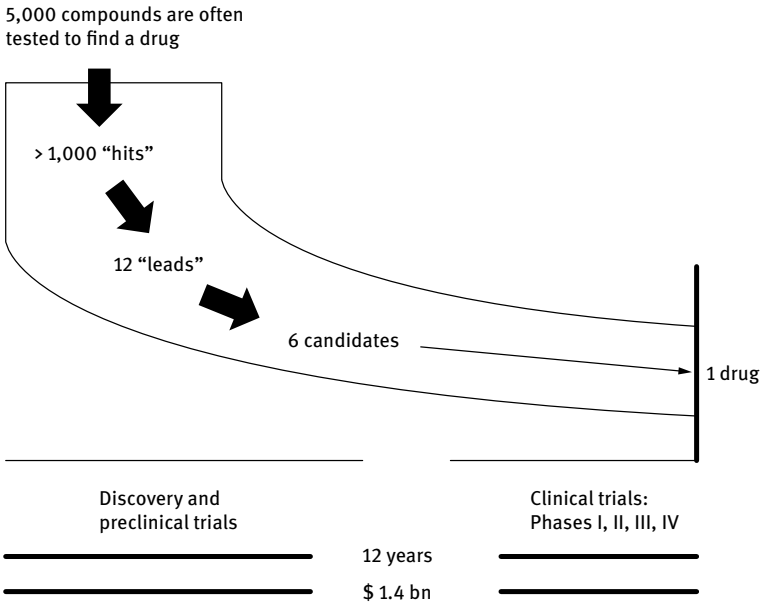


Fig. 1.6: "Bottleneck" process outlining the difficulty of the drug discovery process.

1.10 Phases of clinical studies

Phase I: It is not yet useful to test the efficacy of the drug. Phase I studies attempts to determine the potential toxic effect of the drug in humans by administering small doses to a small number of healthy volunteers. In addition, pharmacokinetic and pharmacodynamic parameters are measured.

Phase II: In Phase II studies, the drug is administered to a small number (greater than in Phase I) of people suffering from a particular disease in order to clearly demonstrate the potential therapeutic benefit of the drug. This is a first measure of efficacy, but above all it is to determine the best doses and modes of distribution (oral, intravenous, intramuscular, etc.) and to confirm the results of the Phase I tests.

Phase III: Phase III studies involve a larger number of patients with an established dose range and final administration form in order to redefine the knowledge obtained in Phase II studies. It aims to confirm the efficacy and safety of the drug on a large scale. Once Phase III studies are completed, the pharmaceutical company can apply for approval of the drug for marketing. This research process can last from 7 to 15 years and is the most expensive of the entire research process.

Phase IV: An even larger population or a specific subgroup, evaluation of the long-term effects of the drug, or even its test in other indications.

2 Drug nomenclature

2.1 Goals

- Knowledge of drug nomenclature: Types.
- Knowledge of the International Nonpropietary Name (INN).
- Knowledge of the systematic nomenclature: the IUPAC rules for naming organic molecules.
- Knowledge of other nomenclatures.

2.2 Nomenclature of drugs

Drugs can be named in several ways.

Coded name: Usually with the initials of the laboratory, chemist, or research team that prepared or tested the drug for the first time, followed by a number. This name does not tell us anything about the structure or the pharmacological action.

Chemical name: Describes in an unambiguous way the structure of the drug. It is produced in accordance with IUPAC standards. Since the chemical name can be very complicated, it is not suitable for routine use.

Registered name: The name given by each manufacturer. Normally, a drug is patented by different industries, and therefore it can appear on the market with several names. It is symbolized with the symbol ® to the right and top of the name. The first letter of each word that is part of the name must be capitalized. It says nothing about structure or action.

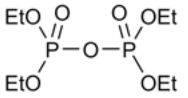
International nonproprietary name (INN): This is the name of the drug with which it is identified as a specific substance and independent of its manufacturer. The first letter must be lowercase or all uppercase. Since 1976, the WHO (World Health Organization) is responsible for developing international standards. The name should be brief, concise, and meaningful. The relationship between substances of the same group and with the same pharmacological activity is evidenced by the use of some characteristic particle. Table 2.1 shows some of these particles:

Table 2.1: Particles used in the construction of the international common denominations (selection).

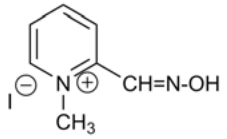
Particle	Category	Compound
-azepam	Benzodiazepines	Diazepam
-bamate	Diol anxiolytics	Meprobamate
-barb-	Barbiturates	Phenobarbital
-caine	Local anesthetics	Procaine
ceph-	Cephalosporins	Cefalotine
-ciline	Penicillins	Ampicillin
sulfa-	Sulfonamides	Sulfathiazol

DOI 10.1515/9783110528480-003

Acronyms: These are used in the drugs of Anglo-Saxon countries (Fig. 2.1).



TEPP (Organophosphorus insecticide)
TetraEthyl PyroPhosphate



2-PAM (Organophosphorus antidote)
2-Pyridine Aldoxime Methyl Iodide

Fig. 2.1: Acronyms used to name some drugs.

2.3 Systematic chemical names

Table 2.2 shows the order of the various chemical-organic functions, from the major importance (ammonium salts) to the minor one (ethers).

Table 2.2: Main functional groups in descending order of priority.

Generic name	Functional group	Prefix (Substituent)	Suffix (principal chain)
1. Ammonium salts	$R_4N^+X^-$		Ammonium halides
2. Carboxylic acids	R-COOH	Carboxy-	Carboxilic acid –oic/-ic acid
3. Anhidrydes	$(R\text{-}CO)_2O$		–oic anhydride
4. Esters	R-COOR′	R-oyloxy- R-carbonyloxy- R′-oxycarbonyl-	R′ carboxylate R′–ate
5. Acid halides	R-CO-X	haloformyl-	-oyl halide
6. Amides	R-CONH-R′	R′-carbamoyl- R-amido- R-carboxamido-	R-amide
7. Nitriles	R-CN	cyano-	-carbonitrile -nitrile
8. Aldehydes	R-CHO	formyl- oxo-	-carbaldehyde -al
9. Ketones	-CO-	oxo-	-one
10. Alcohols, phenols	R-OH, Ar-OH	hydroxy-	-ol
11. Thiols	R-SH	mercapto-	-thiol
12. Amines	$R\text{-}NH_2$	amino-	-amine
13. Ethers	R-O-R′	oxy-	-ether

2.4 Polyfunctional acyclic compounds

First, the main function has to be identified. Next, a structural fragment has to be chosen, and it will be considered as main, applying the norms of the IUPAC.

The hypnoanalgesic methadone contains two functions (ketone and amine), of which the ketone is the priority one and therefore is named as a suffix. This numbers the end closest to the main function,and chooses as the main chain, which is the longest containing the main function. An example is shown in Fig. 2.2.

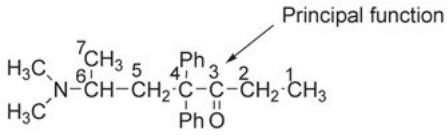


Fig. 2.2: Methadone (hypnoanalgesic).

The drug primocarcin has a secondary ketone function (prefix) and two amide (priority) functions. In the ester and amide functions, the chain to be considered is that which contains the carbonyl group. Since it is not possible to find a chain containing two amide functions, the main chain will include a chain of six carbons and a double bond (Fig. 2.3).

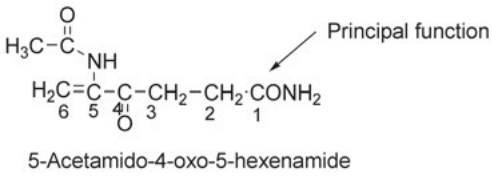


Fig. 2.3: Primocarcin (antineoplastic and antimicrobial agent).

In the hypnotic chlorhexadol, there is no carbon chain containing the two alcohol functions, with priority over the ether function (halogen is not considered a functional group). The chain containing five carbons is selected as the principal one. It is numbered by giving the lowest number to the main function (Fig. 2.4).

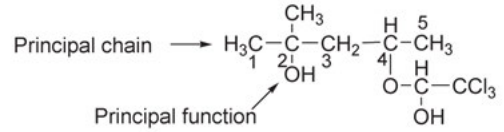


Fig. 2.4: Chlorhexadol (hypnotic agent).

Finally, let us look at the case of the acetylcholine cholinergic neurotransmitter (Fig. 2.5).

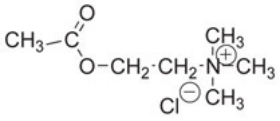


Fig. 2.5: Acetylcholine (AcC).

The main function is the ammonium group and hence the name is: (2-acetoxyethyl)trimethylammonium chloride.

2.5 Monocyclic compounds

The same criteria are used in choosing the main chain or main cycle.

Consider the following difunctionalized molecule (Fig. 2.6).

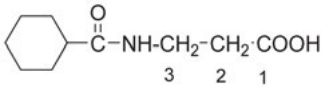


Fig. 2.6: A difunctionalized molecule.

The main function is the carboxylic acid, and the amide function is the secondary one. The correct name is 3-cyclohexanecarboxamidopropanoic acid.

The procaine local anestheticis is named as a benzoic acid derivative, since the carbonyl group of the ester function is attached directly to the benzene ring. There are three different ways of naming procaine (Fig. 2.7).

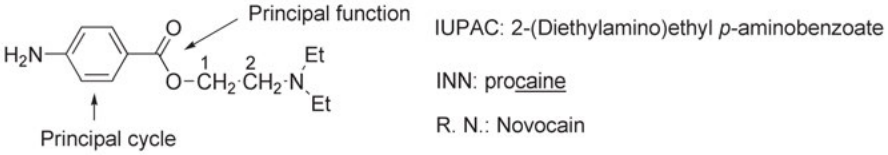


Fig. 2.7: Several ways of naming procaine.

In adrenaline (neurotransmitter), the main chain is the one containing the alcoholic hydroxyl group (preferred over phenolic hydroxyls). In addition, a correct nomenclature must include the configuration of the stereogenic centres when indicated in the structure (Fig. 2.8).

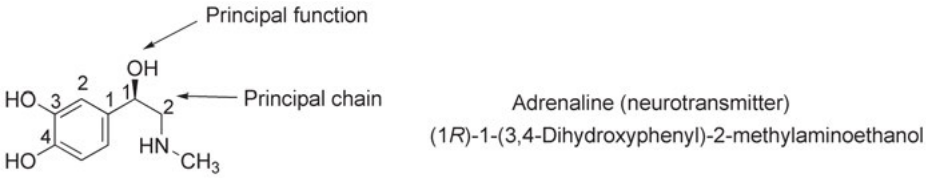
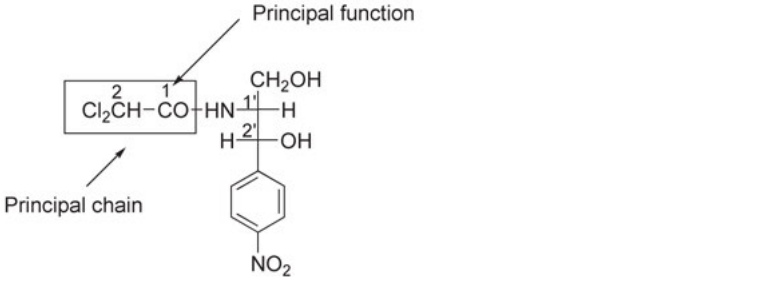


Fig. 2.8: Adrenaline (neurotransmitter).

Another example is the antimicrobial chloramphenicol, for which two systematic names are given (A and B). If the carbonyl group corresponding to the major function (carboxamide) is chosen as the main chain, a complex-systematic name (A) results. For the type of RCONHR′ amides, where R′ is much more complex than R, the IUPAC rules support alternative B, where R′ is considered prime (Fig. 2.9).



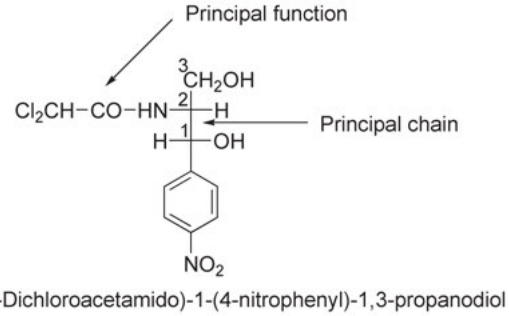


Fig. 2.9: Chloramphenicol (antibacterial agent).

For the nomenclature of antibacterial agents, sulfonamides, the common name sulfanilamide for the 4-aminobenzenesulfonamide unit (from sulfanilic acid) is taken as the basis. Prefixes N^1 and N^4 are used as locators of their two nitrogen atoms (Fig. 2.10).

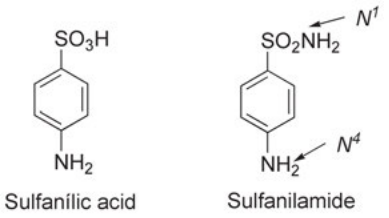


Fig. 2.10: Sulfanilic acid and sulfanilamide.

Example: Sulfanitran (Fig. 2.11).

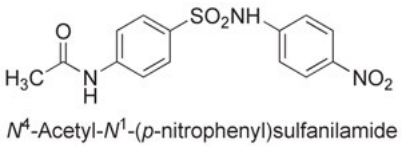


Fig. 2.11: Sulfanitran (antibacterial agent).

2.6 Polycyclic aromatic hydrocarbons (PAHs)

PAHs are organic compounds formed by two or more fused aromatic rings. The rings may be in a straight, angled, or clustered shape. The simplest condensed structure formed by only two aromatic rings is naphthalene, and the three-ring compounds are anthracene and phenanthrene.

The prefix for this hydrocarbon corresponds to the polycyclic system with the maximum number of nonaccumulated double bonds. If this number is not reached the letter *H* with a number will indicate the state of hydrogenation. Most of the condensed polycyclic hydrocarbons have a common name (Fig. 2.12).

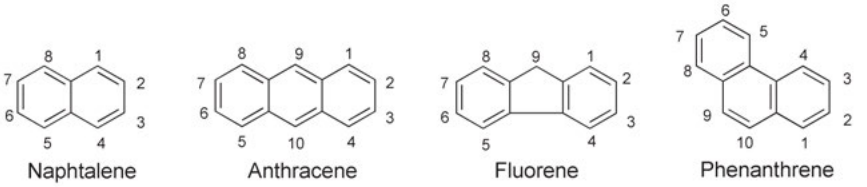


Fig. 2.12: Some condensed polycyclic hydrocarbons and numbering.

Compounds without a common name are denominated by combining the fundamental component (common name system with the highest number of rings) with the prefixes representing the remaining cyclic components fused with it. The names of the hydrocarbons themselves are used as prefixes, some of them abbreviated: benzo, naphtho, phenanthro, anthra.

The face by which the cyclic component is attached to the fundamental one is designated by a locator (a cursive letter *a*, *b*, *c* …) which is ascribed in alphabetical order on each side of the fundamental nucleus, beginning with the carbon atoms 1 and 2 (side *a*).

If the condensed system has two rings and does not have a common name, the fundamental component will be the major ring named as cycloheptene, cyclooctene, cyclononene, etc., which indicates the maximum number of unsaturations (Fig. 2.13).

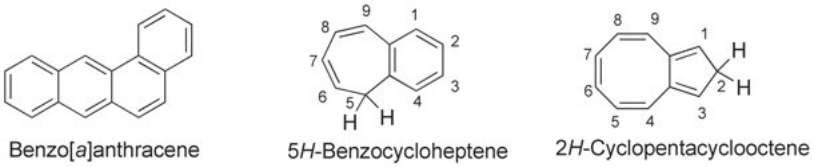


Fig. 2.13: Some condensed bycyclic hydrocarbons, in which one of the rings does not have a common name.

A condensed polycyclic system must be numbered for the location of the substituents or functional groups. First, the polycyclic system must be oriented, to finally proceed to the numbering of each vertex. To orient the polycyclic system it must be drawn so that

(a) a maximum number of rings are aligned in a horizontal row;
(b) a maximum number of rings is located in the first upper right quadrant; the vertical line is drawn on the inner side of the leftmost cycle;
(c) when two orientations meet the above requirements, the one with the lowest number of rings below the horizontal and to the left is chosen.

An example is the orientation of the chrysene (Fig. 2.14).

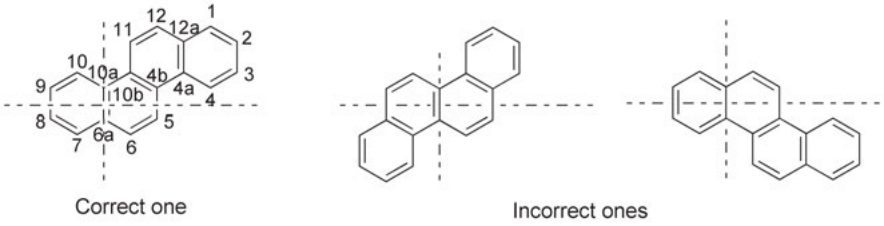


Fig. 2.14: Orientation of chrysene.

Once the system has been oriented, the number 1 is assigned to the position immediate to the condensation in the ring that is (a) higher and (b) more to the right-hand

side. The numbering is continued clockwise. The carbon atoms common to two or more rings are not numbered correlatively, but are designated by the addition of the letters *a*, *b*, *c*, and so on, to the immediately preceding numeral. The inner atoms of the polycyclic system follow the last exterior, also clockwise. An example is fluorine (Fig. 2.15).

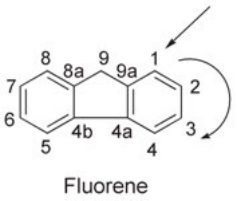


Fig. 2.15: Numbering of fluorene.

2.7 Partly or fully hydrogenated polycyclic hydrocarbons

If the condensed hydrocarbon leaves a hydrogen atom free in one position, it is named *H*. If several positions are left free, they are named dihydro-, tetrahydro-, hexahydro-, preceded by corresponding locators (even multipliers). If the molecule does not contain any double bonds, the prefix perhydro- is used. If there is an odd number of hydrogenated positions a hydrogen with the lowest possible locator and the other even numbered positions are indicated as explained (Fig. 2.16).

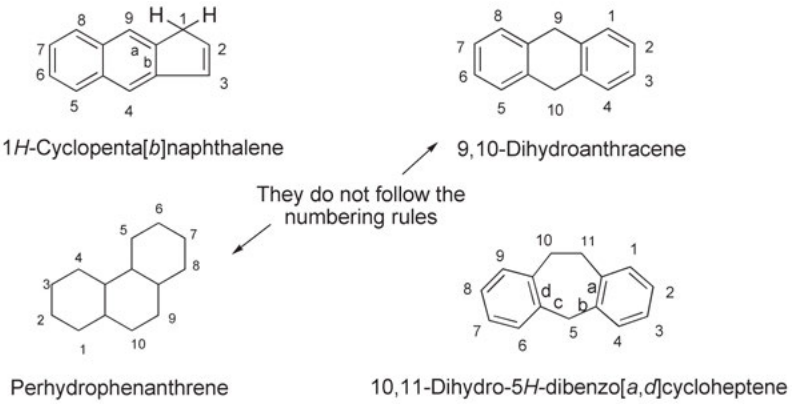


Fig. 2.16: Partly or fully hydrogenated polycyclic hydrocarbons.

Tetracyclines are an important group of antibiotics structurally derived from naphthacene, partially hydrogenated, and with a high degree of functionalization. In almost all cases (all natural and many of the semisynthetic ones) the main function is

a carboxamide, whose preference in numbering gives it position 2. Thus, the tetracyclines will be naphtacene-2-carboxamides, although they are usually drawn oriented with position 1 in the lower right side. An example would be chlortetracycline (Aureomycin®, Fig. 2.17).

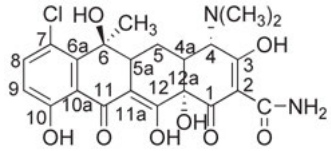


Fig. 2.17: Chlortetracycline (Aureomycin®).

The hydrogenated positions are eight: 1, 4, 4*a*, 5, 5*a*, 6, 11, and 12*a*. The complete systematic name would be as follows: 7-chloro-4-dimethylamino-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydronaphthacene-2-carboxamide. Note that positions 1 and 11 are referred to as hydrogenated, in spite of having carbonyl groups, since these ketone functions are prefixed "oxo" in the name and do not give rise to the suffix "one".

2.8 Bicyclic hydrocarbons

2.8.1 Bridge systems

They are compounds that share two atoms called bridgeheads. They are named by adding the prefix "bicyclo" followed by the number of atoms between the bridgeheads (in brackets), separated by points and ordered from major to minor, ending with the name of the alkane resulting from the sum of all the atoms of carbon of the bicyclic base system (Fig. 2.18).

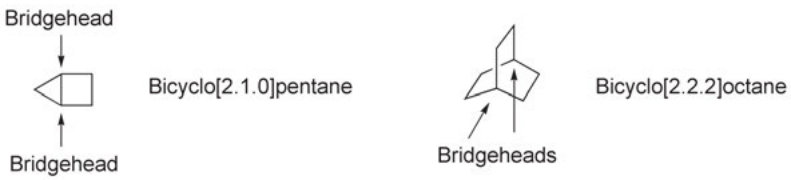
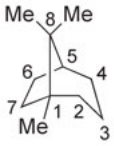


Fig. 2.18: Bridge systems.

The numbering of these systems is startedat the bridgehead, is continued by the longest chain to the other bridgehead, then the intermediate chain and finally, the shortest one (Fig. 2.19).



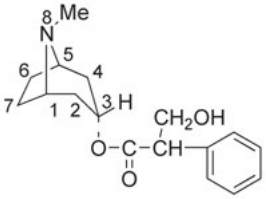
1,8,8-Trimethylbicyclo[3.2.1]octane

Fig. 2.19: Numbering of a bridge system.

2.8.2 Bicyclic systems with heteroatoms

The type and position of heteroatoms (atoms other than carbon and hydrogen) are indicated by a prefix and a numbering, respectively. The three most frequent heteroatoms, O, N, and S, are indicated by the prefixes "oxa", "aza", and "thia", respectively. The order of priority between them is O > S > N. Consider two examples of pharmaceutical significance, beginning with a tropane alkaloid.

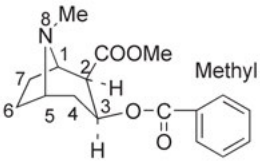
(a) **Atropine (antimuscarinic drug).** The compounds of this family contain the fundamental nucleus of 8-methyl-8-azabicyclo[3.2.1]octane, commonly known as "tropane" (Fig. 2.20).



8-Methyl-8-azabicyclo[3.2.1]oct-3α-yl 2-phenyl-3-hydroxypropionate
or 8-methyl-8-azabicyclo[3.2.1]oct-3α-yl tropate

Fig. 2.20: Atropine.

(b) We have another related example in the local anesthetic cocaine (Fig. 2.21).



Methyl 3β-benzoxy-8-methyl-8-azabicyclo[3.2.1]octane-2β-carboxylate

Fig. 2.21: Cocaine.

(c) **Penicillins and cephalosporins** are included within the general class of "β-lactams" because they have a four-membered lactam as a common structural feature. In all cases, this ring is condensed with another five- or six-membered heterocycle, giving rise to penicillins and cephalosporins, respectively. We then establish the systematic names of penilicillin G and cephalothin (Fig. 2.22).

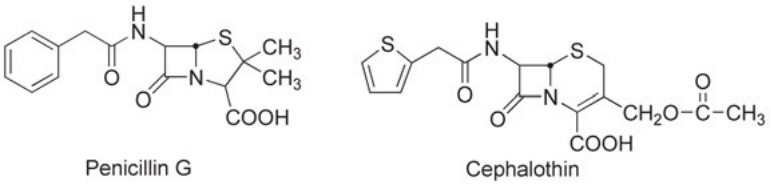


Fig. 2.22: A penicillin and a cephalosporin.

For the nomenclature of these drugs there are several possibilities, from a totally systematic name, through semisystematic names, to a common serial name.

Let us look at the different forms of nomenclature of the three nuclei (Fig. 2.23).

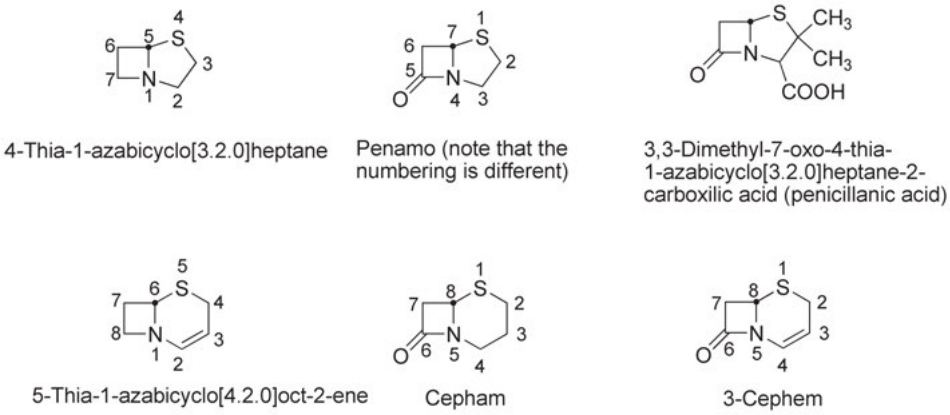


Fig. 2.23: Several possibilities of naming penicillins and cephalosporins.

Consequently, the systematic names of penicillin G and cephalothin are as follows:
Penicillin G: 6-(Phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]-heptane-2-carboxylic acid; alternative: 6-(Phenylacetamido)penicillanic acid;
Cephalothin: 3-(Acetoxymethyl)-7-[2-(2-thienyl)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid; alternatively: 7-(2-(2-thienyl)acetamido] cephalosporanic acid. It is convenient to show the names of two radicals derived from thiophene (Fig. 2.24).

2.8.3 Spiro or spirane systems

It is said that two rings are united to form a spiro structure when they share a single atom, and this is the unique union that exists between them. The common atom is

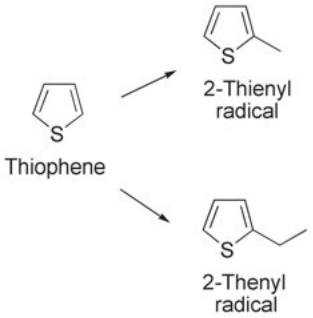


Fig. 2.24: Two radicals derived from thiophene.

called the "spiro atom". To name them, there are two valid options. In the first, spiro is written first, followed by square brackets of the number of carbon atoms attached to the spiro atom, ordered from smaller to the largerrings, separated by a point and then the linear hydrocarbon containing the same total number of carbon atoms is named. Let us look at two examples (Fig. 2.25).

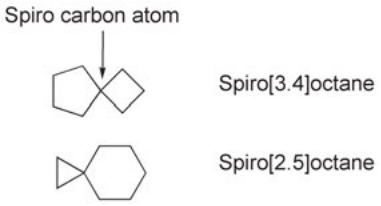
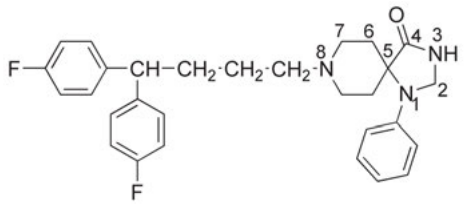


Fig. 2.25: Examples of spiro compounds.

They are numbered beginning with the carbon atom of the smallest chain next to the spiro carbon, continue through the spiranoic carbon, and finally continue to number the major cycle. If there are substituents, try to give them the lowest possible locator (Fig. 2.26).



1-Phenyl-8-[4,4-bis(*p*-fluorophenyl)butyl]-1,3,8-triazaspiro[4.5]decan-4-one

Fig. 2.26: Fluspirilene (antipsychotic agent).

The second or alternative option to name these spiro compounds is to put the name of the major cycle before the smaller one and insert the word "spiro". Each cycle maintains its own numbering, although the carbons of the mentioned cycle are marked with primes at the end (Fig. 2.27).

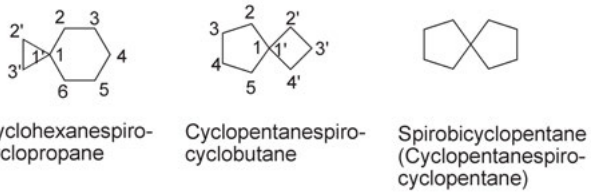


Fig. 2.27: Another form of naming and numbering spiro compounds.

2.9 Heterocycles

Heterocycle denominates any cyclic system in which one or more links are constituted by heteroatoms, i.e. atoms other than carbon. Most heterocyclic systems have a common name: pyrrole, furan, thiophene, pyridine, indole, and quinoline. Those that do not have a common name are named combining a series of prefixes and roots. The prefixes indicate the heteroatom: oxa- (O), thia- (S), aza (N), in this order of priority if there is more than one heteroatom in a cycle. The roots indicate the size of the ring and its degree of saturation. Hantzsch and Widman introduced a nomenclature system for 5- and 6-membered nitrogen heterocycles which has spread to other heterocyclic rings.

The Hantzsch–Widman method is the most often used to name heterocycles that do not have bridges. The roots corresponding to heterocycles of three to ten atoms are indicated in Tab. 2.3. It consists of five sections: the first column shows the size of the cycle; the following two contain the roots to be used when the heterocycle contain nitrogen and the latter two the roots for heterocycles without nitrogen. In addition, the particles are different if the cycle contains the maximum number of nonaccumulated double bonds (unsaturated, columns 2 and 4) or fully saturated (columns 3 and 5). Nitrogen heterocycles of six to ten members are an exception, since their total saturation is expressed in the usual way with the prefix "perhydro" preceding the name of the unsaturated compound.

In those heterocycles in which two or more identical heteroatoms exist, they will be indicated by a multiplier di, tri, etc., before the corresponding prefix. The numbering of the cycles with a single heteroatom always begins in this one. If the heteroatoms are of a different nature, they are numbered beginning with the higher priority O > S > N. Before developing the nomenclature of some examples of heterocyclic drugs, we will proceed to name the carbonic acid derivatives, which are important reagents

Table 2.3: Common name endings for heterocyclic compounds

	Nitrogen cycles		Nonnitrogen cycles	
Size	**Unsaturated**	**Saturated**	**Unsaturated**	**Saturated**
3	-irine	-iridine	-irene	-irane
4	-ete	-etidine	-ete	-etane
5	-ole	-olidine	-ole	-olane
6	-ine	*	-in	-ane
7	-epine	*	-epin	-epane
8	-ocine	*	-ocin	-ocane
9	-nonine	*	-nonin	-nonane

*Perhydro followed by the termination of the unsaturated heterocycles.

in the synthesis of drugs or form part of the structures of important groups of drugs (Fig. 2.28).

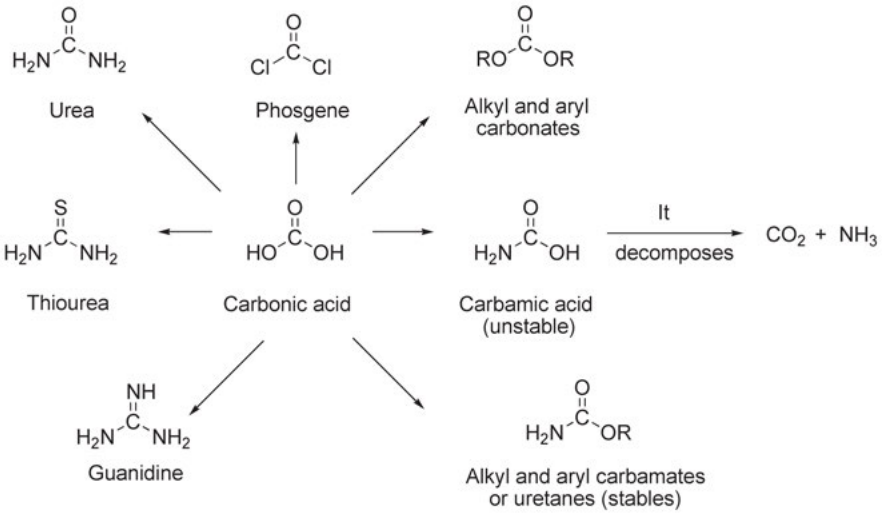
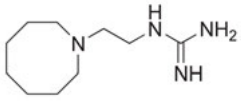


Fig. 2.28: Carbonic acid derivatives.

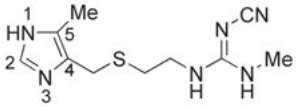
Consider the antihypertensive agent, guanethidine; the prefix perhydrowill be used to indicate the saturation (Fig. 2.29).



N-(2-Perhydro-1-azocane-1-yl)ethyl]guanidine

Fig. 2.29: Guanethidine (antihypertensive agent).

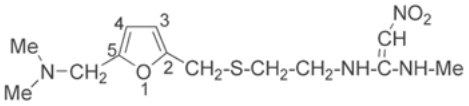
Consider the antiulcer agent cimetidine (Fig. 2.30).



2-Cyano-3-methyl-1-{[2-(5-methyl-1*H*-imidazole-4-yl)methylthio]ethyl}guanidine

Fig. 2.30: Cimetidine (antiulcer agent).

The drug ranitidine (also antiulcerous) contains three amino groups, two of which are united to the same carbon of a unit of ethylene. Accordingly, the fundamental structural unit is a vinylidenediamine, or 1,1-ethylenediamine (Fig. 2.31).



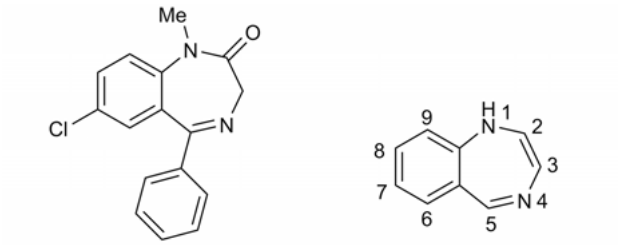
2-Furyl radical 2-Furfuryl radical

The divalent radicals CH_2=C=, -CH=CH- and -CH_2CH_2- are denominated as vinylidene, vinylene and ethylene, respectively

N-{2-[(5-Dimethylaminomethylfurfuryl]thioethyl}-*N'*-methyl-2-nitrovinylidenediamine (or -1,1-ethylenediamine)

Fig. 2.31: Ranitidine (antiulcer agent).

A group of great importance within the heterocyclic nucleus drugs are the so-called "benzodiazepines", with multiple actions but mainly anxiolytic, anticonvulsive, sedative, and hypnotic drugs. One of the simplest drug is diazepam (Fig. 2.32).



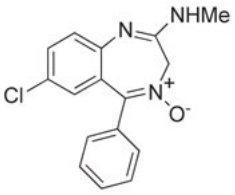
Diazepam 1*H*-1,4-Benzodiazepine

7-Chloro-5-phenyl-1-methyl-1,3-dihydro-1,4-benzodiazepine-2-one

Fig. 2.32: Diazepam.

In *Chemical Abstracts* diazepam receives a name almost equivalent, although with the incorporation of hydrogen indicated by "2*H*", which the nomenclature IUPAC considers unnecessary.

Another example is chlordiazepoxide or Librium® (Fig. 2.33).



7-Chloro-5-phenyl-2-methylamino-3*H*-1,4-benzodiazepine-4-oxide

Fig. 2.33: Librium®.

The frequency of heterocyclic systems in compounds of natural origin determines the proliferation of common names, among which we refer to the most frequent ones in Fig. 2.34 (five-membered heterocycles) and Fig. 2.35 (six-membered heterocycles).

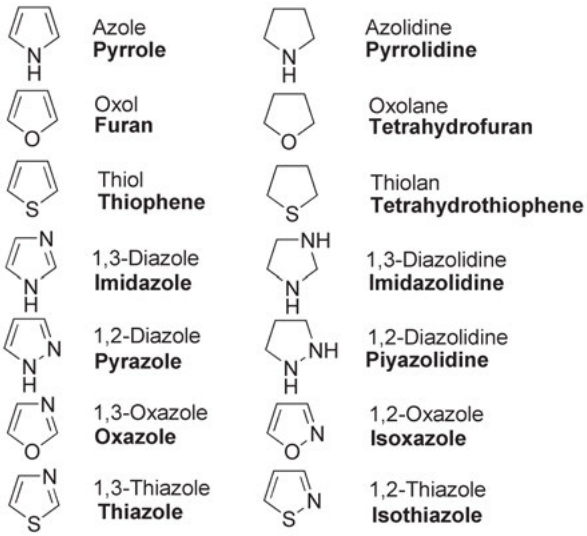


Fig. 2.34: Selected five-membered heterocyclic skeletons.

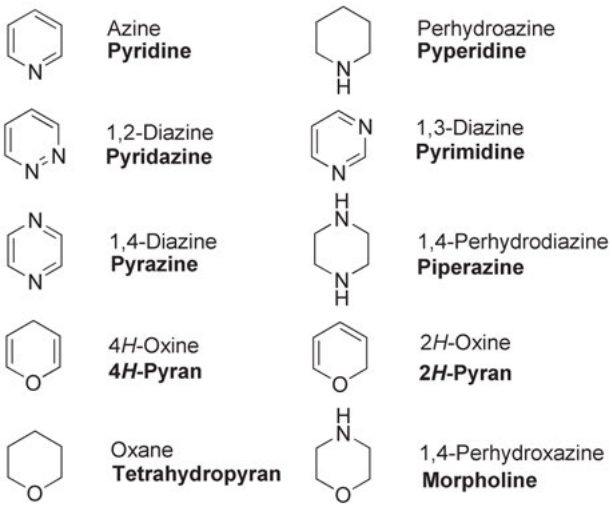


Fig. 2.35: Selected six-membered heterocyclic skeletons.

2.9.1 Condensed heterocycles

Most important is to choose a fundamental component and name the secondary components as prefixes, usually ending in "o". Where the name of a (isolated) component requires localizers for hetero atoms (e.g. 1,3,4-triazole), and these numbers do not correspond to those of the system after fusion, they should be indicated in square brackets, apart from the localizers for fusion, which also go in a pair of square brackets.

When the secondary component to be named is furan, thiophene, pyridine, quinoline, isoquinoline, pyrimidine, or imidazole, the terms "furo", "thieno", "pyrido", "quino", "isoquino", "pyrimidino" and "imidazo", respectively, are used.

Finally, if a heteroatom is at the confluence of two rings, separation of the system into components will be considered part of the two that result. For example (Fig. 2.36):

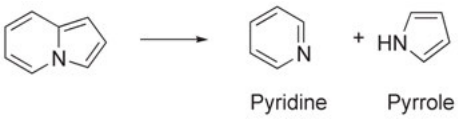


Fig. 2.36: Separation of a bicyclic system into its components, when the heteroatom is at the confluence of two rings.

2.10 Numbering of condensed heterocycles

The numbering of the condensed heterocycle follows the same orientation and start operations in the upper right ring as described for nonheterocyclic systems. The heteroatoms common to two or more rings now have their own locator, a number that is not followed by a letter, as in the carbocyclic systems. When more than one correct orientation is possible, the following criteria are applied until the ambiguity is eliminated:

(a) lowest numbering to the heteroatoms together;
(b) lowest numbering for the most preferred heteroatom;
(c) lowest numbering for carbons common to rings;
(d) lowest numbering to hydrogenated positions.

First the common link is located, and then the simple heterocycles that compose it are named (simple component is one that has a common name but with the most complex structure possible).

The heterocycle, which gives the compound the name, is the heterocycle base; this is preceded by a bracket with two numbers and a letter indicating the common link, and before the bracket the nonbase heterocycle is placed as a prefix. The lowercase letter locates the common link of the base heterocycle, and the numbers locate the nonbase heterocycle common bond. The sense traversed by the base heterocycle is then matched to the path of the nonbase heterocycle. Finally, the complete condensed heterocycle is numbered.

The most commonly used prefixes are furan, imidazo (imidazole), isoquino (isoquinoline), pyrido (pyridine), pyrazine (pyrazine), pyran (pyran), pyrimido (pyrimidine), quinoline (quinoline), thieno (thiophene), pyrrolo (pyrrole), and pyrazole (pyrazole).

We will number the following condensed heterocycle as an example (Fig. 2.37).

Fig. 2.37: Naming and numbering a condensed bisheterocycle, having one a nitrogen atom.

2.11 Criteria for choosing the base heterocycle

1. The one containing nitrogen (pyridine versus pyran).
2. If there is no nitrogen, the one containing the heteroatom other than N, in the order of preference set (O > S) (Fig. 2.38).

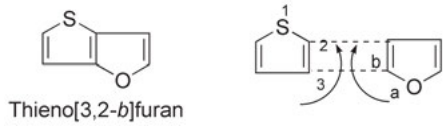


Fig. 2.38: Naming and numbering a condensed bisheterocycle, not having a nitrogen atom.

3. The one with the highest number of cycles in the system (Fig. 2.39).

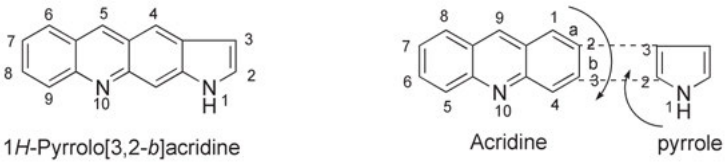


Fig. 2.39: The highest number of cycles is the main component for a condensed heterocycle.

4. The one with the largest ring (Fig. 2.40).

Fig. 2.40: The largest ring is the main component for a condensed bisheterocycle with the same heteroatom.

5. A component containing a heteroatomwith the higher priority (O > S > N) (Fig. 2.41).

Fig. 2.41: The component containing a heteroatom with the higher priority (O > S > N) is the main component for a condensed bisheterocycle with the same size.

6. Of the two components that have the same size, number and type of heteroatomic bases, the one that is considered to have the lower numbering for the heteroatoms is chosen as the prefix (Fig. 2.42).

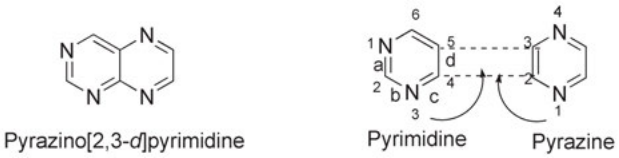


Fig. 2.42: The component with the lower numbers for the heteroatoms before fusion is the main component for a condensed bisheterocycle with the same heteroatom.

Consider the following examples. In the case of doxepin, the central heterocycle is an oxepine, partially hydrogenated and condensed with two benzenes (Fig. 2.43).

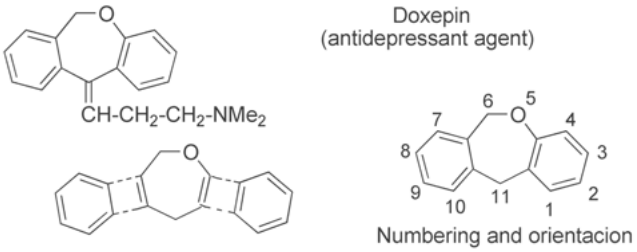


Fig. 2.43: Numbering and orientation of doxepin.

Thus, it is a dibenzo[*b,e*]oxepine. Their numbering must match the lowest possible number (5) to the oxygen. Its systematic name is: 11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenzo[*b,e*]oxepine (Fig. 2.44).

Clotiapine raises another problem (Fig. 2.44).

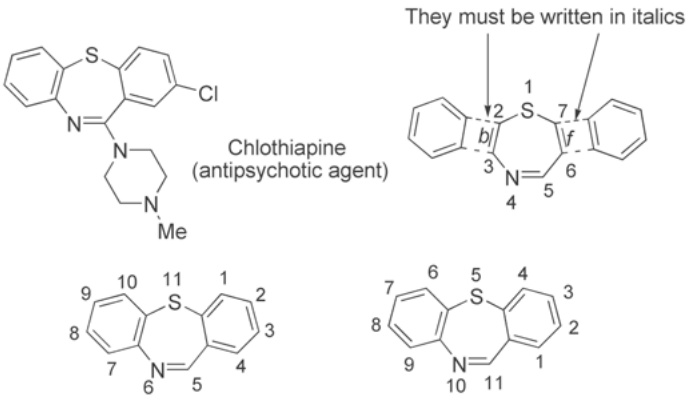


Fig. 2.44: Numbering and orientation of chlothiapine.

The second numbering is correct, since sulfur is preferential in relation to nitrogen. Since the positions of S and N after condensation (5 and 10) do not coincide with their locators in 1,4-thiazepine, these should be indicated in brackets: 2-chloro-11-(4-methyl-1-piperazinyl) dibenzo[*b,f*]-1,4-thiazepine.

2.12 Heterocycles condensed with benzene

They are named by placing the "benzo" prefix in the name of the heterocycle, losing the final "o" if the heterocycle begins with a vowel. The position of the heteroatoms in the condensed end system is indicated by locators, and with a letter the side by which it binds to benzene. Examples are shown in Fig. 2.45.

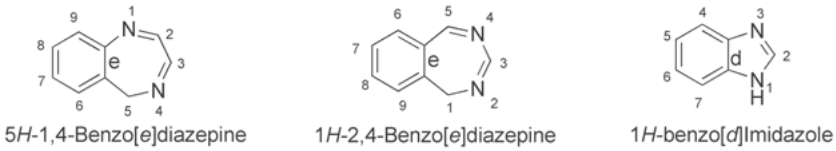


Fig. 2.45: Heterocycles condensed with benzene.

After Fig. 2.46, where some of the most important heterocyclic systems are selected, a couple of examples of drugs will be proposed, in which several aspects treated in this chapter are consolidated.

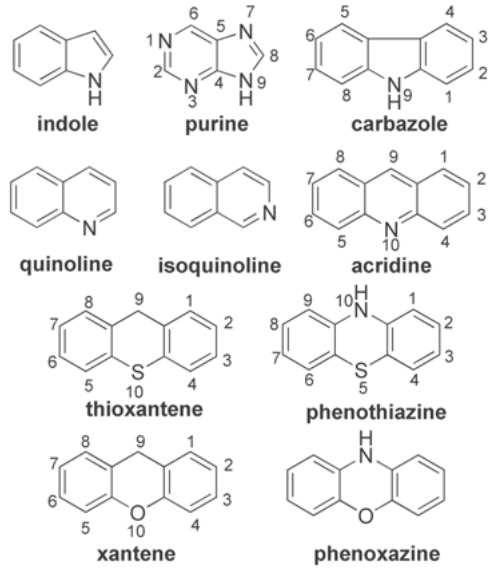


Fig. 2.46: Names of some condensed heterocyclic systems selected, in many cases, with a specific numbering system.

Consider the case of a phenothiazine with a substituent at its 10-position, which contains a spiro derivative (Fig. 2.47).

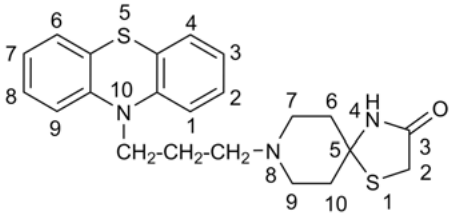


Fig. 2.47: A phenothiazine with a substituent thatcontains a spiro derivative.

Finally, let us look at another example in the area of benzodiazepines. The first is the hypnotic-sedative drug estazolam (Fig. 2.48).

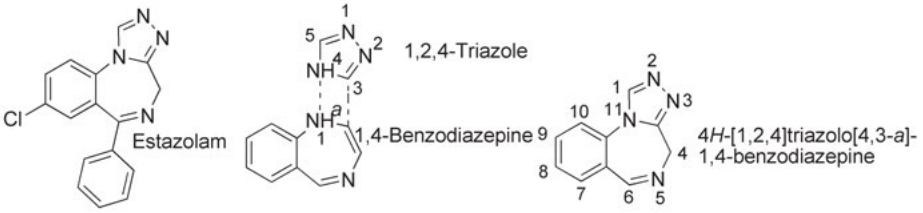


Fig. 2.48: Name and numbering of estazolam.

2.13 Exercises

A) Name the following drugs:

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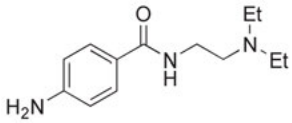

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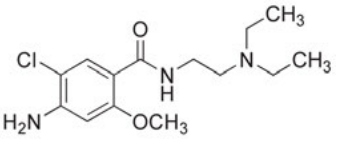

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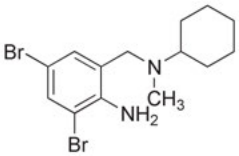

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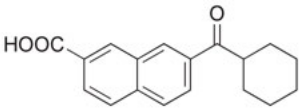

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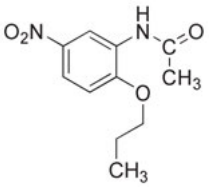

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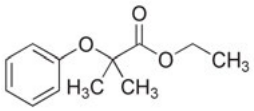

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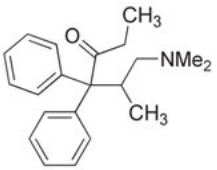

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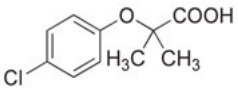

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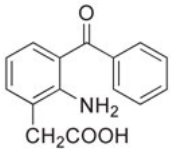

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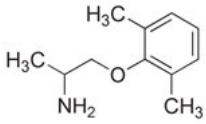

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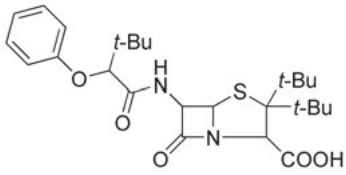

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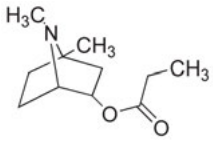

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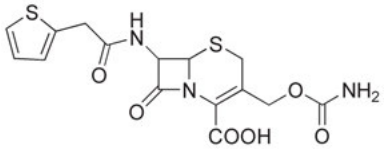

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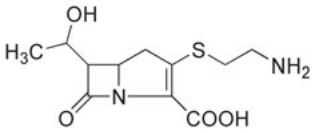

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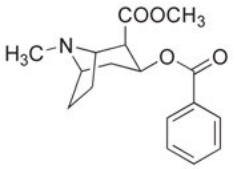

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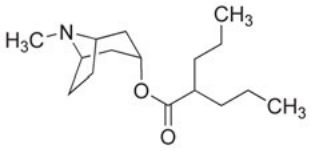

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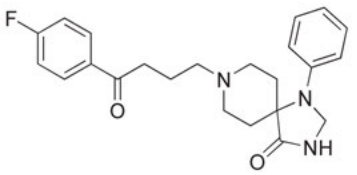

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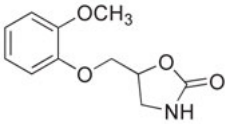

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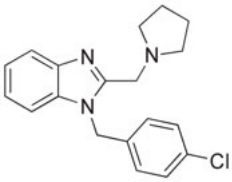

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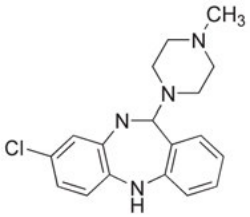

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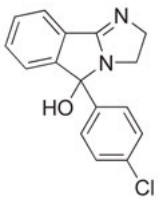

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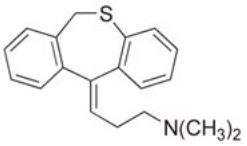

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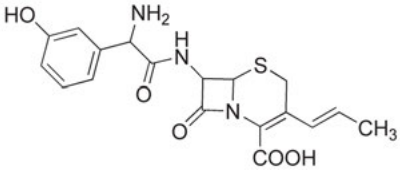

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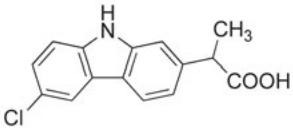

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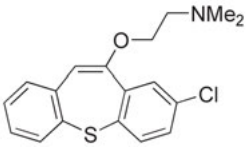

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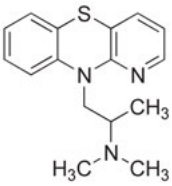

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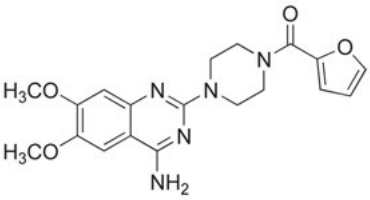

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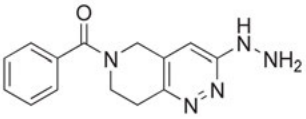

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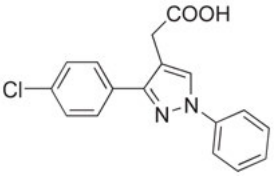

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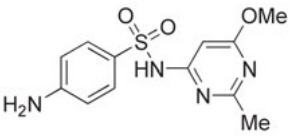

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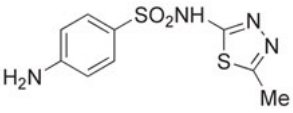

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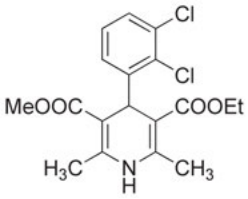

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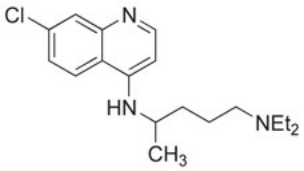

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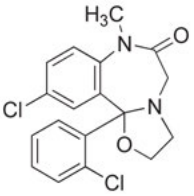

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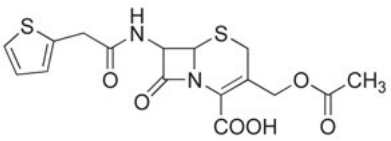

B) Formulate the following drugs:

1) 2-(4-Phenyl-3-fluorophenyl)propionic acid.
2) 2-[2-(2,6-Dichlorophenylamino)phenyl]acetic acid.
3) Ethyl 7-chloro-4-ethoxy-6-fluoroquinoline-3-carboxylate.
4) 7-Chloro-10-(2-dimethylaminoethyl)-5,10-dihydrodibenzo[*b,e*][1,4]diazepin-11-one.
5) 3-(4,5-Diphenyloxazol-2-yl)propionic acid.
6) 5-(3-Methylamino)propyl-5*H*-dibenzo[*b,f*]azepine.
7) 10-(3-Dimethylaminopropyl)-9,9-dimethyl-9,10-dihydroacridine.
8) Ethyl-7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-benzo[*e*][1,4]diazepine-3-carboxylate.
9) 5-Dimethylamino-9-methyl-2-propylpyrazolo[1,2-*a*][1,2,4]benzotriazine-1,3(2*H*)-dione.
10) 3-Acetoxy-5-(2-diethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5*H*)-one.
11) 5-(2-Fluorophenyl)-1-methyl-7-nitro-1,3-dihydrobenzo[*e*][1,4]diazepine-2-one.
12) 2-Methyl-3-(2-methylphenyl)-quinazoline-4(3*H*)-one.
13) 7-[(2-Amino-2-phenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-2-carboxilic acid.
14) 11-Chloro-12b-phenyl-2,8-dimethyl-8,12b-dihydro-5*H*-[1,3]oxacino[3,2-*d*][1,4]benzodiazepine-4,7-dione.

15) 6-(2-Phenoxybutanamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
16) 2-Butyryl-10-{3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl} phenothiazine.
17) 4-[4-(4-Chlorophenyl)-4-hydroxypiperidine-1-yl]-1-(4-fluorophenyl)butan-1-one.
18) *N*-(4-Chlorobenzyl)-*N*′,*N*′-dimethyl-*N*-pyridine-2-yl-ethylene-1,2-diamine.
19) 3,3-Dimethyl-6-(2,6-dimethoxybenzamido)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
20) 1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-*tert*-butylaminoethanol.

3 Search for prototypes

3.1 Goals

- To know the global process through which new prototypes or serial heads are discovered and the methodologies used over time.
- To know the importance of isolation, purification and structural determination of drugs.

3.2 Traditional and current discovery of new drugs

One of the greatest difficulties that the student finds when studying pharmaceutical chemistry is both the high number and the great structural diversity of the drugs to be memorized. Therefore, in order to facilitate the learning of this discipline, the authors have decided to minimize the number of structures and, in addition, the chemical structures detailed in these first general chapters will be later studied in the corresponding descriptive themes in Volume 2 of this series.

The first thing required to begin a pharmaceutical chemistry project is to have a leader, that is, a compound that can be considered as therapeutically useful. The level of biological activity may not be particularly noticeable, because this is not a fundamental issue. The lead compound is not intented to be used in clinical practice. It is only the starting derivative from which a clinically useful compound can be developed. It does not matter whether or not this compound is toxic or has side effects. One of the fundamental objectives of pharmaceutical chemistry is the search for drugs that are more potent, more selective, and less toxic in their therapeutic action.

Lead compounds can be obtained from a variety of natural sources, such as flora and fauna, or synthetic compounds prepared in the laboratory. If a drug or poison produces a biological effect it is because there must be a molecular target in the body. Many of the earliest known drugs, such as the analgesic morphine (Fig. 3.1), are natural compounds derived from plants that coincidentally interacted with a molecular target of the human body. Subsequently, chemical messengers or neurotransmitters began to be discovered. These have a short lifespan and are released by the nerves to interact with specific cellular targets. For example, since the 1970s a great variety of peptides and proteins have been discovered that act as natural analgesics (enkephalins and endorphins) of the body itself. Quinine is a natural alkaloid with antipyretic, antimalarial, and analgesic properties.

However, few chemical messengers have been identified, either because they are present in very small amounts or because they have such a short half-life that their isolation is not possible. In fact, today many chemical messengers are unknown. This implies that many of the potential biological targets of the human body remain hid-

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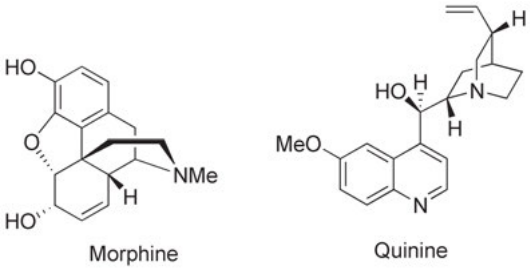


Fig. 3.1: Lead compounds such as morphine and quinine.

den. However, advances in genomics and proteomics have changed the whole picture of new drug development. Several genome projects have elucidated the DNA of humans and other life forms and have discovered a large number of new proteins that are biological targets for the future.

These biological targets have been hidden for so long that their natural chemical messengers are also unknown, and for the first time, pharmaceutical chemistry is facing new targets without leading compounds that interact with them. Such targets have been defined as orphan receptors, and the current challenge is to find chemical compounds that interact with each of these targets to discover what their functions are and to see if they are appropriate as drug targets.

3.2.1 Screening of natural products

With this search procedure, a large number of chemical compounds, natural or synthetic, are subjected to a battery of pharmacological tests, in search of an unknown or hypothetical action. This mass trial is one of the most costly and least active procedures; however, it has been successfully used in some fields, such as in the discovery of new antibiotics such as chloramphenicol (Fig. 3.2), isolated from *Streptomyces venezuelae* in the general microorganism screening programme at Parke-Davis Laboratories in the USA.

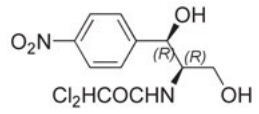


Fig. 3.2: Chloramphenicol

Natural products are an important source of biologically active compounds. Generally, the natural source has some form of biological activity, and the compound responsible for this activity is known as the active principle. This structure can act as a leader compound. Most biologically active natural products are secondary metabolites with

complex structures. Unfortunately, this complexity makes its synthesis difficult, and the compound generally has to be extracted from its natural source, a slow, expensive, and inefficient process. Therefore, the design of simpler compounds is usually an effective approach for the development of new drugs.

Plants have always been a rich source of leading compounds (e.g. morphine, cocaine, quinine, tubocurarine, nicotine, and muscarin). Many of them are useful drugs in themselves (e.g. morphine and quinine), and others have been the basis for synthetic drugs (e.g. local anesthetics developed from cocaine).

Microorganisms such as bacteria and fungi have also been the source of drugs and leading compounds. The screening of microorganisms became very popular after the discovery of penicillin. Land and water samples have been collected from all over the world to study new strains of fungi and bacteria and have resulted in a huge arsenal of antibacterial agents such as cephalosporins, tetracyclines, aminoglycosides, rifamycins (Fig. 3.3), and chloramphenicol.

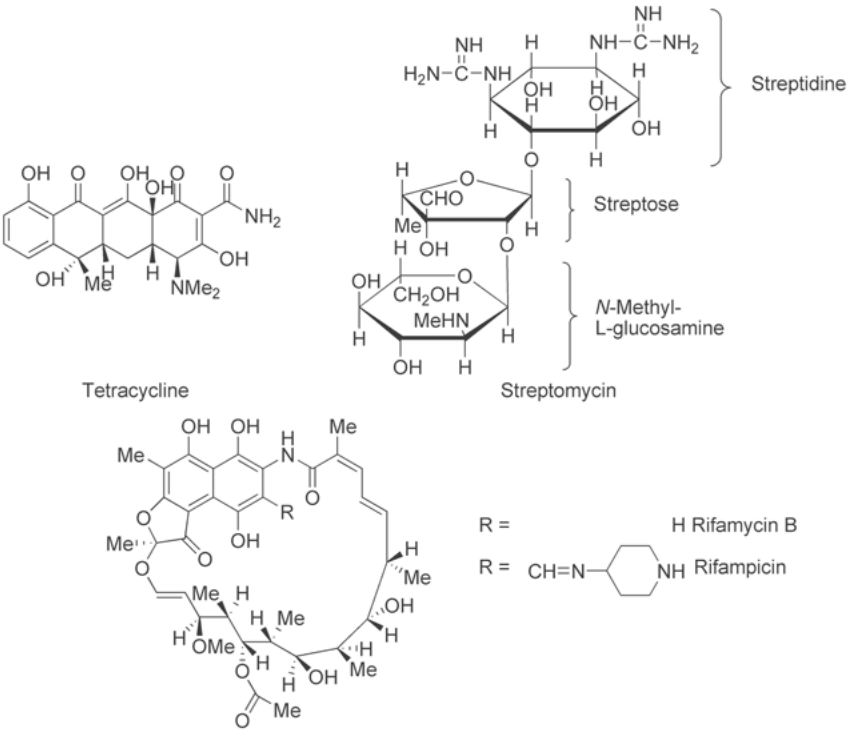


Fig. 3.3: Naturally existing or semisynthetic antibiotics.

Poisons and toxins have been used as lead compounds in the development of new drugs. For example, the teprotide (nonapeptide isolated from the Brazilian viper *Both-*

rops jararaca) was the leading compound for the development of the antihypertensive agent captopril. The teprotide contains the strange pyroglutamic acid in its *N*-terminal part and the proline in its C-terminal part (Fig. 3.4).

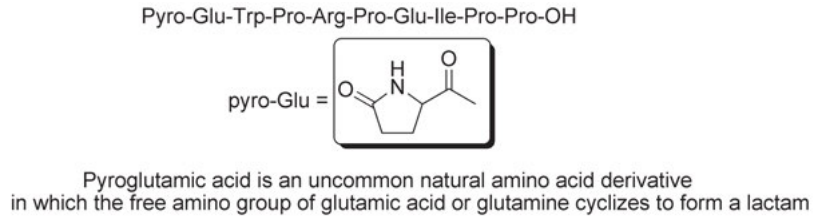


Fig. 3.4: Teprotide.

3.2.2 Existing drugs used as leaders

The molecular manipulation of known drugs consists of a progressive modification of the chemical structure of chemical substances that possess a certain biological activity. Many companies use drugs established by their competitors as leading compounds to design a drug that allows them to establish themselves in the same market area. The aim is to modify the structure sufficiently to avoid on the one hand, the restrictions of the patent, and on the other to improve the therapeutic properties. For example, the antihypertensive captopril was used by several companies as a lead compound to produce their own antihypertensive agents (Fig. 3.5).

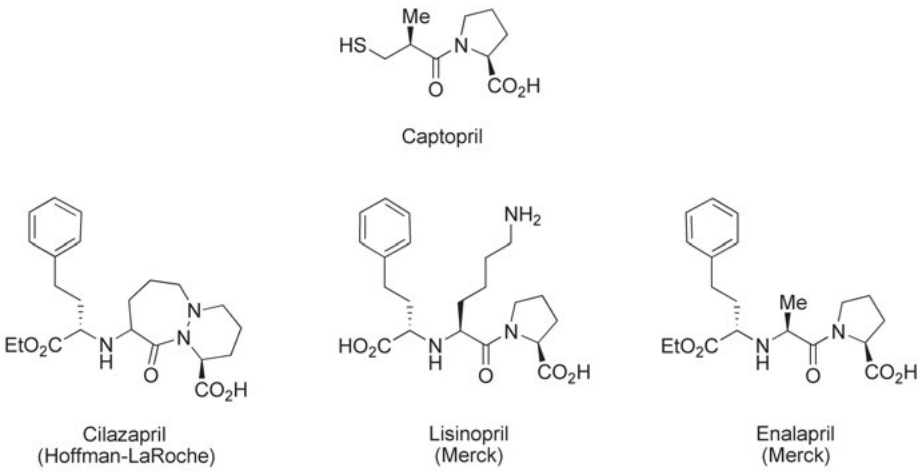


Fig. 3.5: Captopril and “me too” drugs.

Although often neglected as "twin" drugs, they sometimes show improvements over the original drug (better drugs: "me better"). For example, modern penicillins are more selective, more potent; and more stable than the original penicillins.

An existing drug may have another minor property or an undesirable effect that may be useful in another area of medicine. In this way, the drug could act as a leader on the basis of its side effects. Consequently, the aim would be to increase the side effect and eliminate the major biological activity. This has been described as the "selective optimization of side activities" (SOSA) approach.

For example, most sulfonamides have been used as antibacterial agents. However, some sulfonamides can not be used clinically because they produce hypoglycemia and as a consequence cause seizures. Accordingly, structural modifications were performed to eliminate the antibacterial activity and potentiate hypoglycemic activity. This led to the antidiabetic agent tolbutamide (Fig. 3.6). Similarly, the development of sulfonamide-type diuretics such as chlorothiazide arose from the observation that sulfanilamide has a diuretic effect at high doses (due to its action on the carbonic anhydrase enzyme).

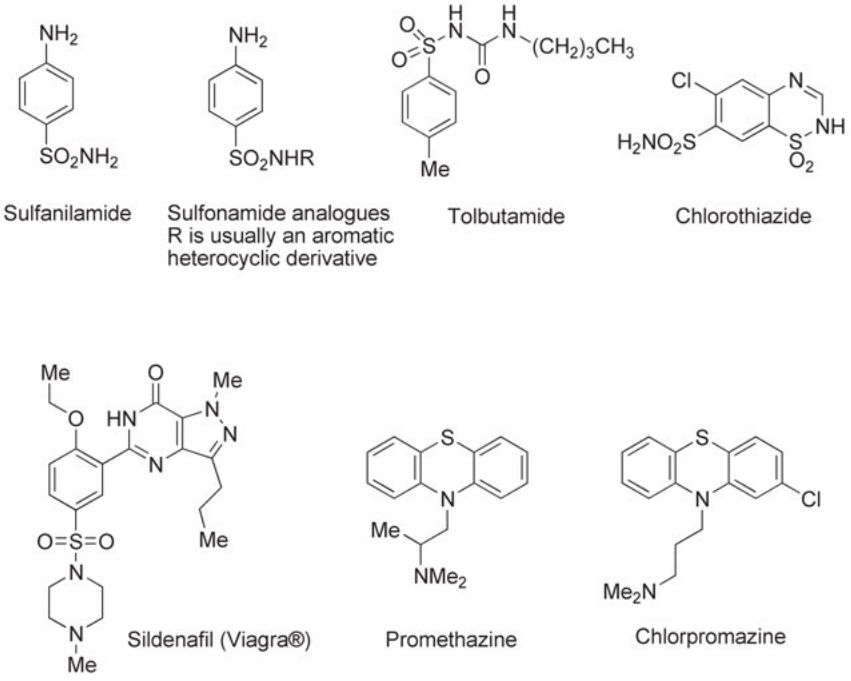


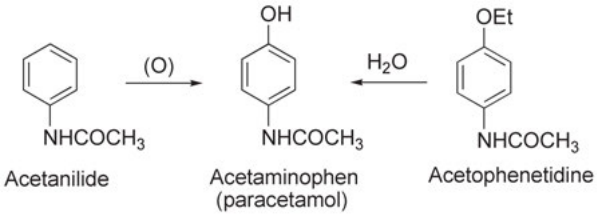
Fig. 3.6: Drugs developed through potentiation of a side effect.

In some cases, the side effect may be strong enough for the drug to be used without modification. For example, the drug sildenafil (Viagra®) that treats male impotence (Fig. 3.6) was initially designed as a vasodilator to treat angina and hypertension.

Chlorpromazine is used as a neuroleptic (a neuroleptic or antipsychotic is a drug that is commonly, but not exclusively, used for the treatment of psychosis) in psychiatry, but developed from the antihistamine agent promethazine. It may seem strange, but it was known that promethazine has sedative effects, so pharmaceutical chemists modified the structure to increase the sedative effects at the expense of antihistamine activity.

3.2.3 Isolation and identification of drug metabolites

Acetalinide and acetophenidine are converted in the body in paracetamol (INN), which is actually the active drug (analgesic-antipyretic) in cases of intolerance to Aspirin® (Scheme 3.1).



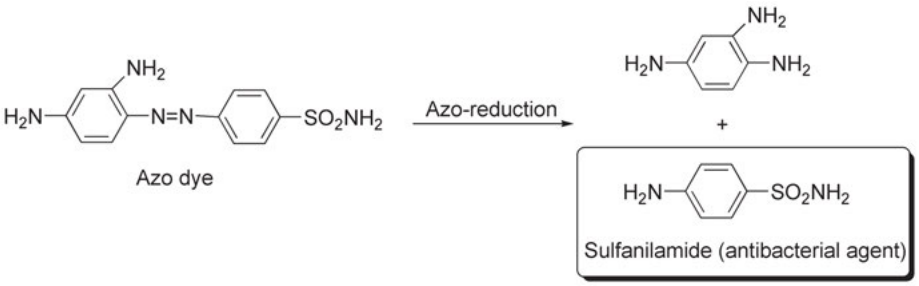
Scheme 3.1: Relationship between paracetamol and its two metabolic precursors.

3.2.4 Examples of serendipity

The term serendipity is used more and more in science to describe the way in which many of the great discoveries have been made. Chance plays a very important role in unforeseen valuable findings, when luck favors the prepared mind, in the words of Pasteur (one of the beneficiaries of serendipity). This term can be defined as "the ability to make discoveries by accident and sagacity, when one is looking for something else". It was 1754 when the English writer Horace Walpole encountered an ancient story from Asia, which occurred in Serendip, a former name of the present country of Sri Lanka, also previously known as the Kingdom of Ceylan. The monarch of that country sent his three children to travel the world to get the essential items he needed. Serendip's princes visited the villages, had remarkable experiences, and returned with far more valuable finds than their father had asked them. Serendipity was decisive in the discovery of America, since we know that what Columbus was looking for was a shorter way to reach the Indies.

Some notable examples are (Scheme 3.2, Fig. 3.7 and Fig. 3.8) the following.

(a) For example, *prontosil rubrum*, which as initially synthesized as an azo dye, useful for staining microorganisms, casually opening the field of chemotherapy when tested in vivo and demonstrated its antibacterial therapeutic activity (Scheme 3.2).



Scheme 3.2: Example of metabolic reduction.

(b) Rubber industry workers were repelled by alcohol. This fact was caused by an antioxidant agent used in the process of making rubber. Ethanol is metabolized by sequential metabolic oxidation, first to acetaldehyde by alcohol dehydrogenase (ADH) and then to acetic acid by means of aldehyde dehydrogenase (ALDH). Disulfiram irreversibly inhibits the oxidation of acetaldehyde, causing a considerable increase in acetaldehyde concentrations after the ingestion of alcohol, which was so unpleasant that workers preferred not to drink. The antioxidant agent became the leading compound for the development of disulfiram (Antabuse), used for the treatment of chronic alcoholism. It is believed that the ability of disulfiram to react with the sulfhydryl groups of essential proteins (generating diethyl dithiocarbamate) is important for its activity (Fig. 3.7).

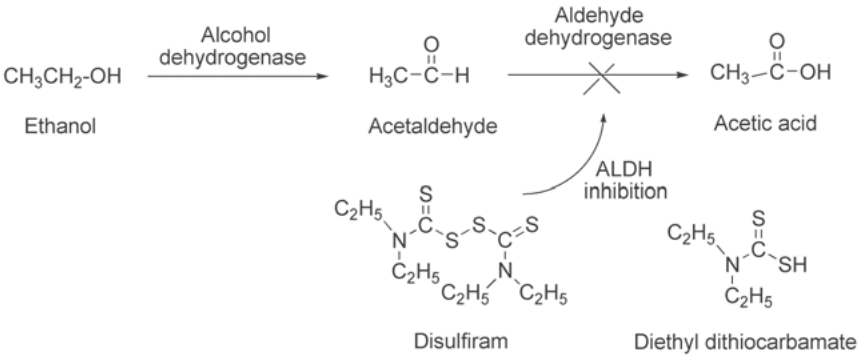


Fig. 3.7: Inhibition of aldehyde dehydrogenase by disulfiram.

(c) Clonidine was initially designed as a nasal vasoconstrictor. Clinical trials revealed that this effect was caused by a marked drop in blood pressure, making it an important antihypertensive agent.
(d) Imipramine was synthesized as an analogue of chlorpromazine and was initially used as an antipsychotic agent. It was found, however, to alleviate depression, which led to the development of a number of compounds classified as tricyclic antidepressants.

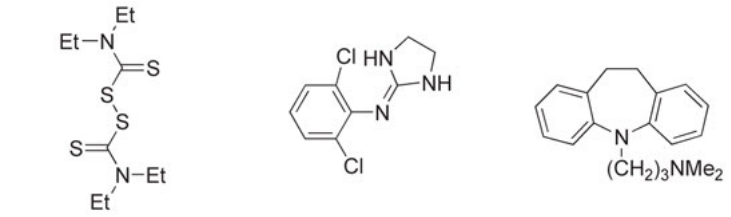


Fig. 3.8: Examples of drugs discovered by serendipity.

3.3 Planned syntheses of new chemical compounds on rational bases

It is the golden dream of pharmaceutical chemists and pharmacologists. The ultimate aim in the synthesis of a drug is to prepare one for the "measurement" of the biological function to be modified.

3.4 Isolation and purification

If the compound (or active principle) is present in a mixture of other compounds, then it must be isolated and purified. The ease with which the active ingredient can be purified and isolated depends to a large extent on its structure, stability, and the amount of the compound. For example, Fleming recognized the antibiotic properties of penicillin and its nontoxic characteristics for humans, but did not consider it for clinical use, because he was not able to purify it. He could isolate it in an aqueous solution, but whenever he tried to eliminate the water, the drug was decomposed. It was not until the development of new experimental procedures such as lyophilization and chromatography that the isolation and purification of both penicillin and other natural products became possible.

3.5 Structural determination

Nowadays a structural determination can take a week of work but in the past, it could be carried out for two to three decades. For example, the empirical formula of cholesterol was known in 1888, but its chemical structure was not completely established until 1932 by x-ray crystallography (Fig. 3.9).

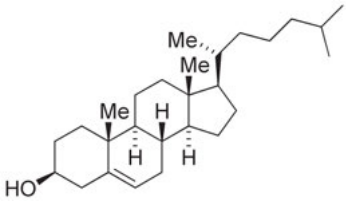


Fig. 3.9: Cholesterol.

In the past, structures were degraded to simpler compounds, which could be further degraded to readily recognizable fragments. From these smaller fragments a possible structure was proposed, but the only way to test the proposed structure was to carry out its total synthesis and compare its physical and chemical properties with those of the natural compound.

Today structural determination is a relatively simple process, and it is only necessary to carry out its total synthesis to corroborate its structure when it has been obtained in minimal quantities. The most useful analytical techniques for structural determination are x-ray crystallography and NMR spectroscopy. The application of the former technique allows the obtaining of an "instant photograph" of the molecule, but a suitable crystal of the molecule is required. The latter technique is used more routinely and can be carried out on any sample, whether solid, oily, or liquid. There are different NMR experiments that can be used to establish the structure of complex molecules, such as two-dimensional NMR techniques.

In cases where there is not enough sample for an NMR analysis, mass spectrometry can be very useful. The fragmentation model can provide important clues about the structure, but it does not definitively prove the chemical structure. In this case, complete synthesis would be required as the final test.

4 Optimation of prototypes

4.1 Goals

- To know the different tools of structural variation and their use in prototype optimization or in the discovery of new drugs.
- To start with the concept of the cost of research: the idea that starting from active compounds it is possible to produce other active compounds is an economic concept.

4.2 Molecular manipulation

Molecular manipulation consists of a progressive modification of the chemical structure of substances that possess a certain biological activity (prototypes or series heads); it is the most frequent and, so far, the most cost-effective procedure for the genesis of new drugs. 80—90 % of the current drugs have been obtained in this way.

Since there is a high probability that a molecule obtained by modification of an active prototype has useful properties, this drug-screening process is usually more productive than the assay, without a sufficiently solid base, of novel compounds isolated from nature or synthesized at the laboratory. In addition, it offers economic advantages, since both the synthetic methods and the pharmacological tests of the analogues will be similar to those used for the reference compound.

4.2.1 Purpose

- development of substitutes and therapeutic copies;
- development of drugs with a different action spectrum:
  - transformation of agonists into antagonists;
  - separation of one of the components of the action;
- modification of pharmacokinetics;
- Modification of the distribution;
- to increase chemical stability.

4.2.1.1 Development of substitutes and therapeutic copies

1) Development of existing drug substitutes, more powerful if possible. Examples:
   - the passage of pronetalol (β-adrenergic blocker) to propranolol, with greater potency than the previous one (Fig. 4.1);

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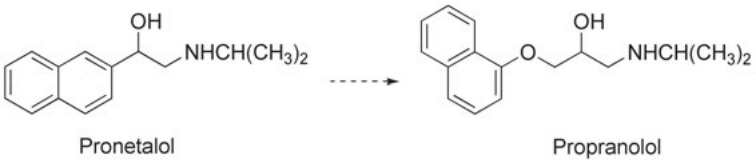


Fig. 4.1: Transition from pronetalol to propranolol.

– transformation of (*S*)-1-(3-mercaptopropionyl)-L-proline into captopril {(2*S*)-*N*-[3-mercapto-2-methylpropionyl]-L-proline}, an antihypertensive agent, ten times more potent than its demethylated analogue (Fig. 4.2).

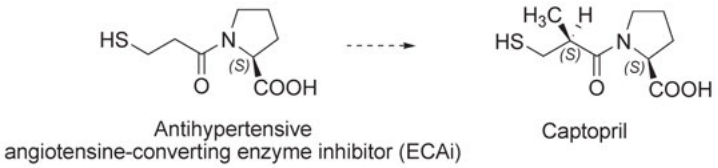


Fig. 4.2: Transition from (*S*)-1-(3-mercaptopropionyl)-L-proline into captopril.

2) The development of therapeutical copies is a quick option to find new patentable formulas that can successfully compete in the market. They require less economic investment but must compete with existing drugs of proven efficacy in the same therapeutic group. Their commercial success is conditioned by the galenic or therapeutic advantages that they provide with respect to existing drugs. From the antihypertensive drug enalapril, compounds such as lisinopril and cilazapril were developed (Fig. 4.3).

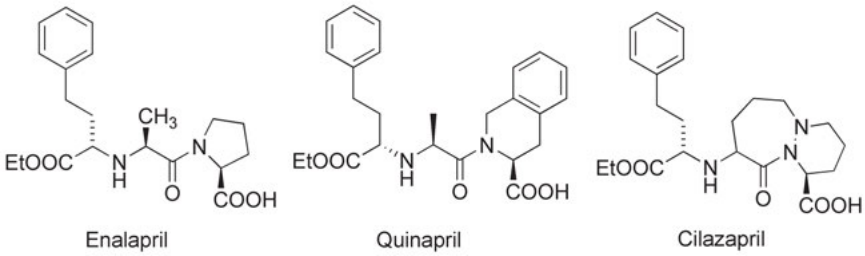


Fig. 4.3: Development of therapeutical copies.

4.2.1.2 Development of drugs with different spectrum of action

1) Transformation of agonists into antagonists. Thus, the β-adrenergic antagonist dichloroisoprenaline is obtained from the isoprenaline agonist by substituting the phenolic hydroxyl groups for chlorine atoms (Fig. 4.4).

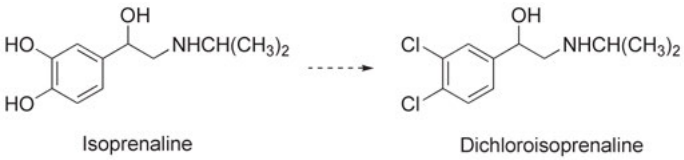


Fig. 4.4: Development of an antagonist (dichloroisoprenaline) from an agonist (isoprenaline).

2) Separation of any component to enhance or modify the action of the prototype. Examples:
   - the virilizing action of testosterone is lost when it is transformed into a 19-noresteroid, norethrandolone, which is used as an anabolic drug (Fig. 4.5);

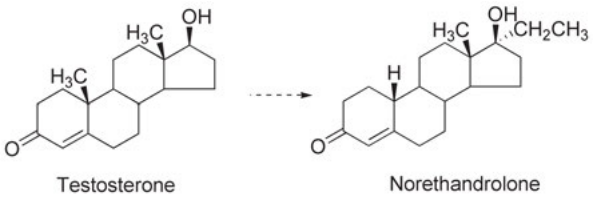


Fig. 4.5: Norethandrolone that has not the virilising action of testosterone.

   - the weak uricosuric character of phenylbutazone, attributed to the acidity of the hydrogen at 4 position, can be enhanced by substituting its butyl group for an electron-withdrawing phenylsulfinylethyl group, which reinforces the acidic character, resulting in sulfinpyrazone (more potent uricosuric) (Fig. 4.6).

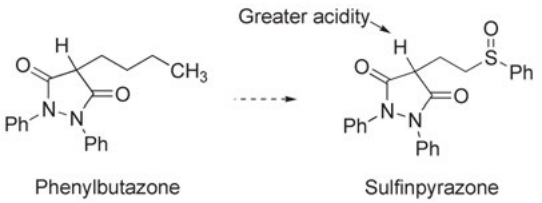


Fig. 4.6: Sulfinpyrazone has a higher uricosuric activity than phenylbutazone.

4.2.1.3 Modification of pharmacokinetics

The dose-effect relationship can be modified with structural changes that alter the rate of metabolism and/or excretion. Example: passage of tolbutamide, oral antidiabetic of short duration of action, to clorpropamide of a more lasting action (Fig. 4.7).

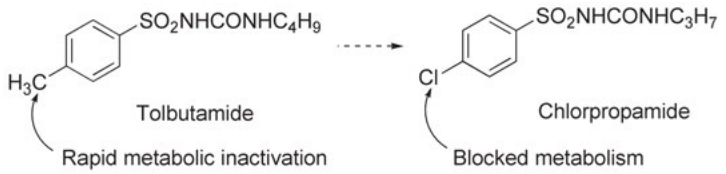


Fig. 4.7: From an oral short-acting antidiabetic to a one with a more-acting effect.

4.2.1.4 Modification of distribution

This allows the drug to reach the different organs and tissues in which it acts. This purpose can be achieved through various procedures:

1. Introducing a fixed ionic charge to prevent the passage through the blood-brain barrier (BBB) (Fig. 4.8).

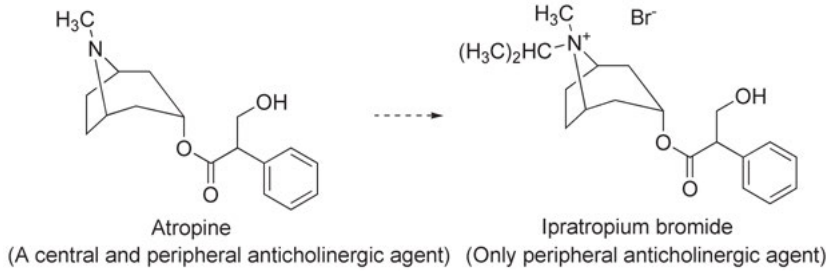


Fig. 4.8: Introducing a fixed ionic charge to prevent the passage through the blood-breain barrier.

2. Using carrier groups to increase cell or tissue selectivity of the drug.
   The active structure of nitrogen mustards, nonselective alkylating agents, can be transformed into useful anticancer agents by increasing their selectivity by rapidly dividing cells. To this end, fixed conveyor groups are introduced on the N, which facilitate the active transport of the thus latent drug to the sites of action. Transporting groups such as L-phenylalanine or uracil, present in melphalan and uramustine, can be used, because tumor tissues synthesize proteins and DNA at a faster rate than healthy tissues, so that their demand for amino acids and bases is greater. Estramustine (estradiol + mustine) shows a selective distribution to estrogen-dependent breast tumours (Fig. 4.9).

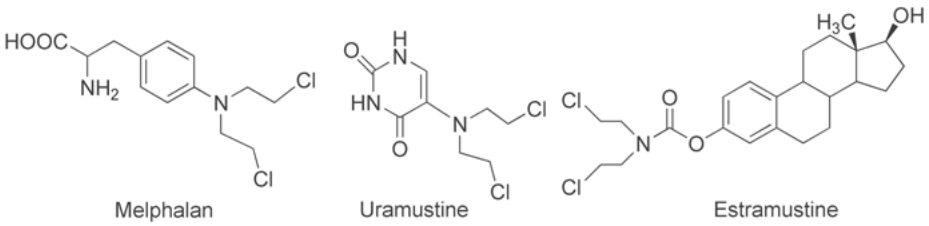


Fig. 4.9: Carrier groups increase cell or tissue selectivity of the drug.

3. Increased chemical stability, mainly against the acidic environment, to make it possible for the drug to be administered orally. Thus, by modifications in the side chain of penicillins, active compounds are obtained orally, with greater resistance to the acidic environment (Fig. 4.10).

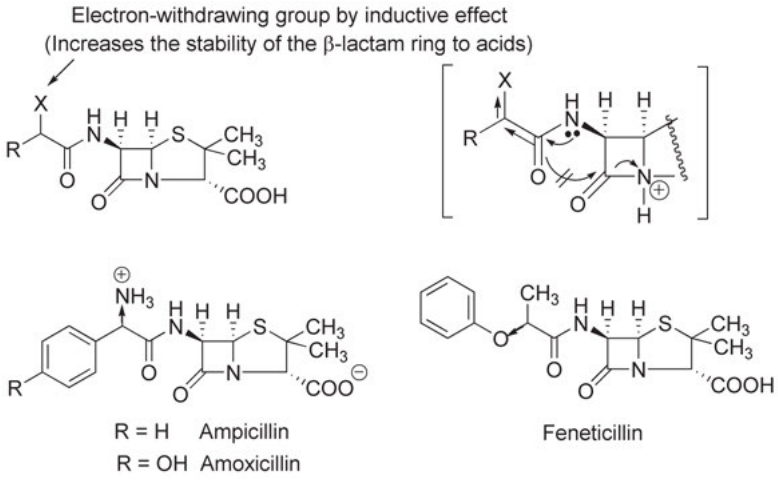


Fig. 4.10: Increased chemical stability.

4.2.2 Strategies

There are three possible strategies: Modulative, disjunctive, and conjunctive structural variations.

4.3 Modulative structural variation

This makes limited transformations in the structure of the model, which retains its fundamental structure:

- vinilogy;
- homology;
- introduction of cyclic systems;
- introduction or substitution of polar groups, by nonpolar bulky ones;
- isosterism and bioisosterism.

4.3.1 Vinylogy

It has been shown that certain molecules differing in one or more vinyl groups (CH=CH) located in the side chain or included in a cycle may have similarity in their pharmacological properties. Procaine vinylogues A and B are also local anesthetics. The hydrogenated compound C, homologous to A (a homologue of a given compound is the analogue to it resulting from the addition (or subtraction) of one or more CH_2 to a chain or ring), lacks activity (Fig. 4.11).

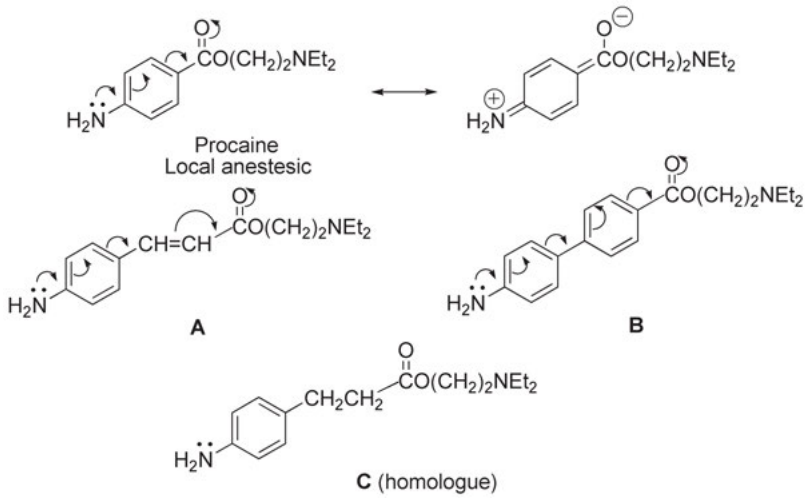


Fig. 4.11: Active vinylogues (**A** and **B**) of procaine; **C** is an inactive homologue of procaine.

- The resonant effect is not lessened by distance. The inductive effect does.
- If the electron density of a given area of a molecule is important for its binding to the receptor, the biological activity can be maintained in the reference vinylogues. Sometimes, some surprising properties can be found in vinylogous prod-

ucts. Thus, the acetylcholine (AcC) vinilogue has nicotinic and no muscarinic activity, while AcC presents both (Fig. 4.12).

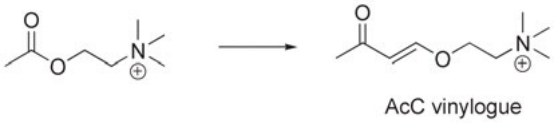


Fig. 4.12: Acetylcholine and a vinylogue.

– Vinylogy serves to demonstrate if resonance effects are important in terms of activity (Fig. 4.13).

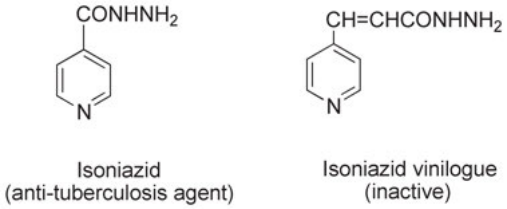


Fig. 4.13: Vinylogy can give rise to an inactive drug.

This example demonstrates that the activity lies in the distance that exists between the ring and the chain, which disappears when the activity increases, by introducing a vinyl group.

Vinylogy has also been applied in the opposite sense. Thus, the removal of the benzene ring from the sweetener dulcin gives rise to ethoxyurea, an equally sweet substance (Fig. 4.14).

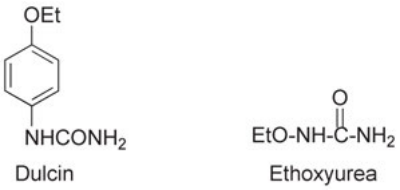


Fig. 4.14: Example in which elimination of a benzene ring maintain the sweetener characteristic.

4.3.2 Homology

Homologues are those molecules that differ from one another in a methylene group or more. Example: the antinicotinic drug hexamethonium (ganglioplejic effect, which blocks the sympathetic and parasympathetic glanglionic nerve transmission) and its decamethylene homologue decamethonium (curarizant effect, with a nondepolarizing skeletal muscle relaxant activity) (Fig. 4.15).

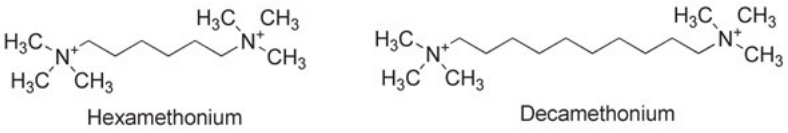


Fig. 4.15: Examples of homologues.

4.3.3 Introduction of cyclic systems

This approach is useful for the study of the active conformation in flexible molecules. The formation of a ring restricts the conformational freedom of the original molecule. This modification may also entail the creation of new stereogenic centres in the molecule. Examples: chlorpromazine and thioridazine (both phenothiazine neuroleptics), ondansetron (antiemetic) and cilansetron (an even more potent antiemetic) (Fig. 4.16).

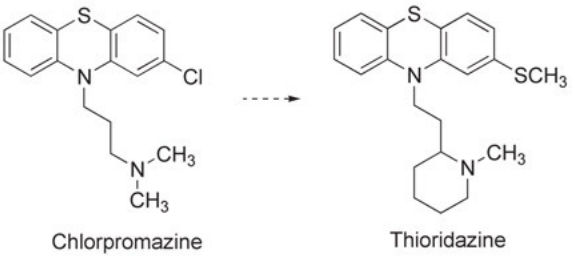


Fig. 4.16: Introduction of cycles.

4.3.4 Introduction or substitution of polar groups, by nonpolar bulky ones

This is a procedure of particular interest for converting agonists into antagonists. An antagonist is a substance having an action opposite to another to which it refers (Fig. 4.17).

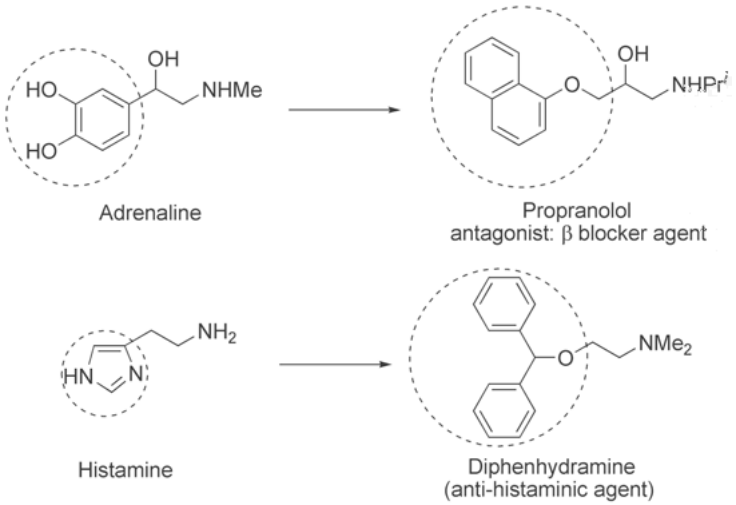


Fig. 4.17: Examples for the conversion of agonist into antagonist drugs.

4.3.5 Isosterism and bioisosterism

One of the most frequent criteria for molecular variation is that of isosterism, which essentially consists of substituting atoms or groups of atoms equivalent in size and electronic distribution. It is a chemical concept.

- Langmuir concept (1919).
- Grimm's hydride displacement law (1925).
- Peripheral Isoelectricity (Erlenmeyer, 1932).

1) Langmuir defined isosteres as molecules or groups of atoms with the same number of atoms and valence electrons (Fig. 4.18).

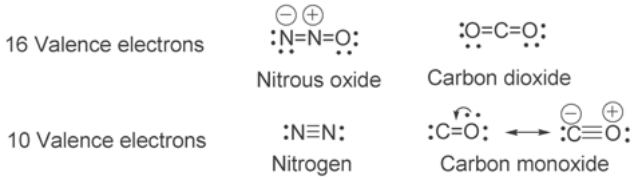


Fig. 4.18: Examples of isosteric molecules.

2) Grimm formulated the so-called hydride displacement law, according to which the addition of a hydrogen atom to an atom of atomic number "n" provides a species with the same properties of the atom of higher atomic number "n + 1" (Fig. 4.19).

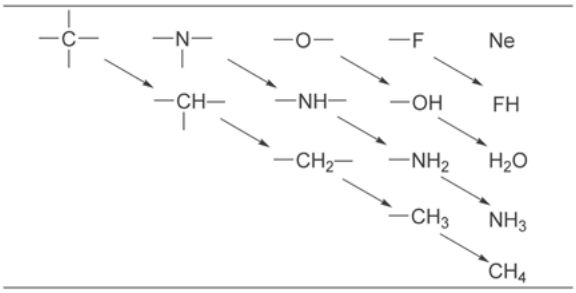


Fig. 4.19: Grimm's hydride displacement law. In each vertical column the atom is followed by its pseudoatom.

In this way, families of "pseudo-atoms" with common electronic characteristics are originated.

3) In 1932 Erlenmeyer extended the concept of isosterism by proposing a broader definition of isosteres as those elements, molecules or ions with a similar electronic distribution in their valence layer. The concept of isosterism was thus extended to the elements of a column of the periodic system (for example, carbon would be isostere of silicon, oxygen of sulphur, and so on). In this way, the so-called annular equivalents were defined (clusters that can be interchanged in a ring without giving rise to a substantial change in the physical and chemical properties of the latter: the following groups -CH=CH- and -S- are an example of equivalent ring groups that permit the explanation of the analogies between benzene and thiophene. The above criteria lead to a series of "ring equivalents", widely used for the design of analogues (Fig. 4.20).

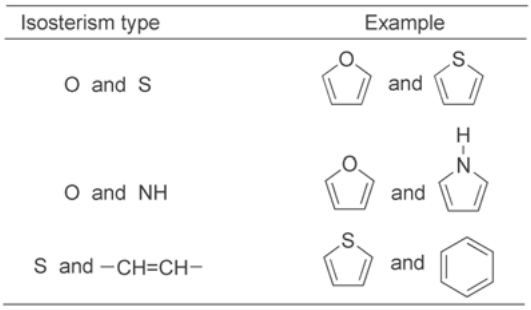


Fig. 4.20: Isosteric equivalences between some aromatic rings.

Cyclo-equivalents are the atoms or groups of atoms that can be replaced in cycles without having a marked variation in their properties. All of the above are classical isosteres.

Friedman in 1951 introduced the term of bioisosterism (a biological concept) to designate those molecules or atomic groups responsible for the same biological (or antagonistic) activity as a consequence of a similarity in their physical and chemical properties. Thus the "nonclassical isostere" arise corresponding to those groups of atoms that, when introduced into a given molecule, generate compounds whose shape, size, or other properties make them bioequivalent, despite not being isoelectronics. The term of bioisosterism acquires a broader character than the strictly chemically notion mentioned before. It is important to keep in mind that the term bioisostere will be meaningless if the property or properties that make it comparable to a pair of chemical species are not indicated. Thus, for example, two classical isosteres according to Grimm's law such as -OH and -Cl, can be considered as bioisosteres in volume but not in terms of their lipophilia or in their electronic distribution.

It is possible to indicate the following properties:

(a) **Size:** H, F
Br, Pr^i
I, Bu^t

The fluorine atom is considerably smaller than the other halogens. The fluorine derivatives differ from the rest of the halogen derivatives in which the fluorine atom forms particularly stable carbon bonds and, unlike what happens to the other halogens, is very rarely ionized or displaced. Therefore, due to both its chemical inertia and its small size, fluorine is often compared to hydrogen.

(b) **Electronic distribution and polarizability** (Fig. 4.21):

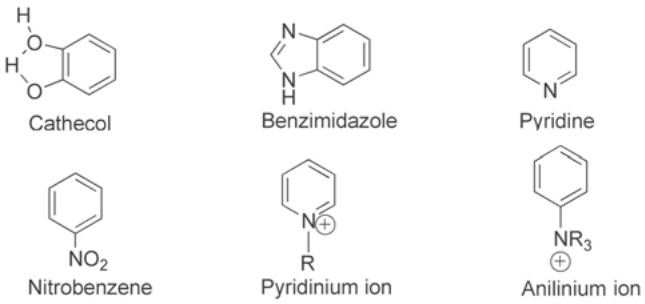


Fig. 4.21: Bioisosteres based on analogous electronic distribution and polarizability.

Catechol is a bioisostere of benzimidazole in the sense that while in the first case a second ring may be formed through an intramolecular bond, in the second the imidazole ring mimics the "five-membered ring" of catechol through a cycle formed with covalent bonds.

In the same way, the bioisosterism between thiourea, *N*-cyanoguanidine and β-nitroketeneaminal groups (Fig. 4.22) has been demonstrated in histamine H_2-

receptor antagonists, also known as H_2-blockers (burimamide, cimetidine, and ranitidine). We will go more deeply into this aspect in Chapter 7 of Volume 2 of this work.

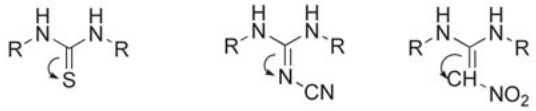


Fig. 4.22: Bioisosterism between the thiourea, *N*-cyanoguanidino, and β-nitroketeneaminal groups.

When the biological activity depends fundamentally on the distribution of charges and polar effects of the molecule, the maintenance of these factors can lead to bioisosteric equivalences between very different molecules. Pyridine and nitrobenzene may serve to illustrate this possibility. To understand this relationship we compare the structures of benzene with that of pyridine and those of pentagonal aromatic heterocycles, such as furan, thiophene, and pyrrole (Scheme 4.1).

The consequences are very evident: pyridine will react fundamentally according to a S_NAr (nucleophilic aromatic substitution), while the three aromatic pentagonal heterocycles will do so according to the S_EAr (aromatic electrophilic substitution).

Pyridine and nitrobenzene resist S_EAr, and when they do so under these conditions, they direct the entrance of the electrophilic groups (E^+) towards the *meta* position. This suggests a certain polar similarity and consequently, the possibility of bioequivalence: *N,N*-Diethyl-*m*-nitrobenzamide, for example, possesses analeptic properties (an analeptic agent is a stimulating drug of the central nervous system) very similar to those of its pyridine analogue, the nikethamide (Fig. 4.23).

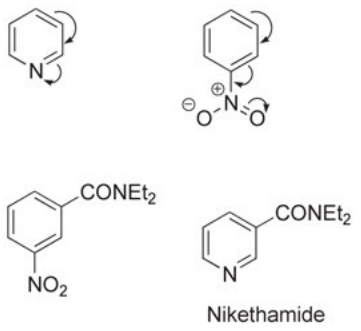
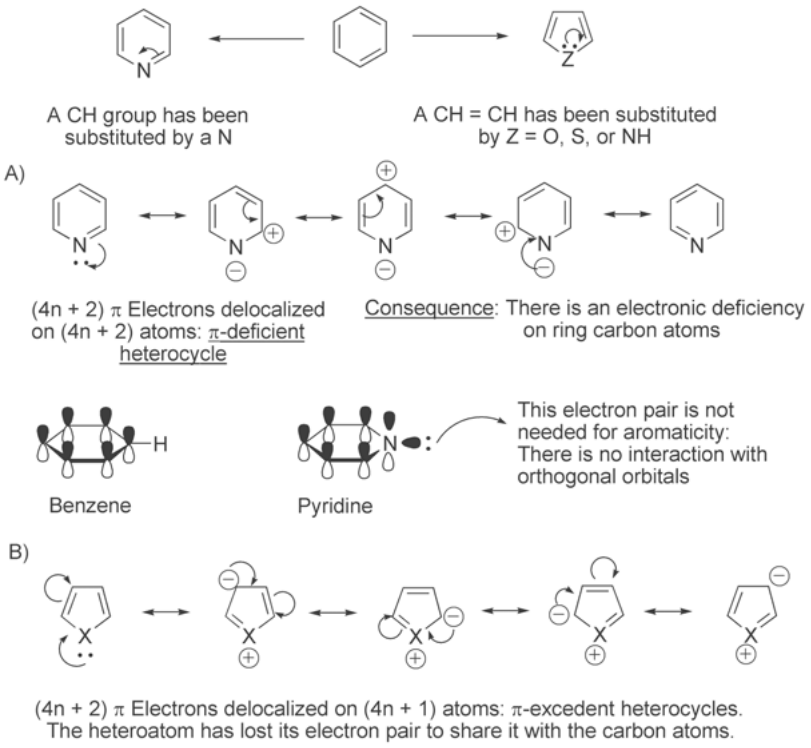


Fig. 4.23: *N,N*-Diethyl-*m*-nitrobenzamide and nikethamide possess similar analeptic properties.



Scheme 4.1: A π-deficient aromatic heterocycle (pyridine) and π-excedent aromatic heterocycles (furan, thiophene, and pyrrole).

(c) Solubility in lipids, as in the -CH_2- and -S- groups, or in the trimethylene and *p*-phenylene groups (Fig. 4.24).

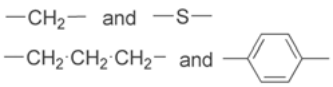


Fig. 4.24: Groups with the same solubility in lipids.

(d) pK_a, as in the acidic groups in Fig. 4.25.

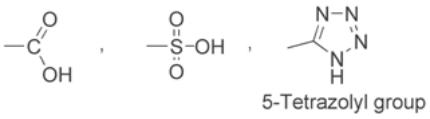
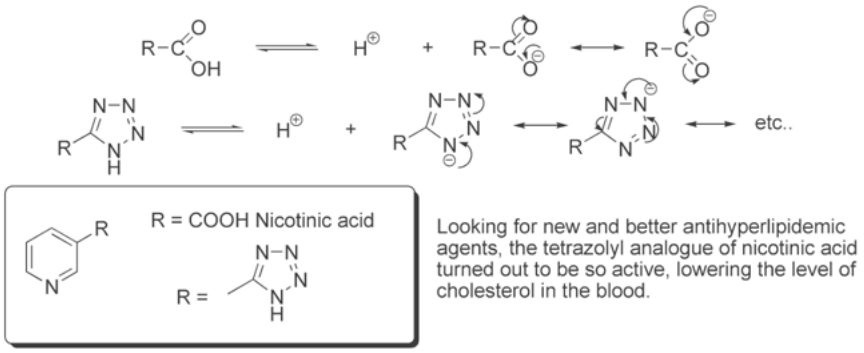


Fig. 4.25: Groups with a similar acidity.

In principle, the acidic character of the 5-tetrazolyl moiety and consequently its bioisosteric relationship with the carboxylic acid group (Scheme 4.2) may be surprising:



Scheme 4.2: Acid characters of the carboxyl and of the 5-tetrazolyl groups.

While the acidity of the carboxylic acid ($pK_a \approx 4.2–4.4$) is related to the resonance stabilization of the carboxylate anion, the acidity of tetrazole ($pK_a \approx 4.9$) is attributed to the delocalization of the negative charge on each of the nitrogen atoms of the five-membered ring. Although the greater number of resonant forms of tetrazole, which contribute to the final hybrid, might suggest that the resonance energy of tetrazole was more effective than that of the carboxylate anion, the higher electronegativity of the oxygen atom relative to that of nitrogen is a decisive factor to justify the higher acidity of the carboxylic acid group.

(e) Ability to establish hydrogen bonds, as in the –OH group of phenol, –NH of CH_3SO_2NH-, and R-NH-CO-NH-.

4.4 Disjunctive replication

This means reducing the structure of the model until you keep nothing more than the essential part. These analogues are partial replicates of the prototype drug. The technique of opening cycles is used. Disjunction: action and effect of separating.

(a) Procaine is the result of the simplification of cocaine (Fig. 4.26).
(b) Some hypnoanalgesics derived from the simplification of morphine (Fig. 4.27).

From the comparison of these structures it can be deduced that the analgesic activity of morphine is associated with the presence of a benzene ring attached to a quaternary carbon and this to a tertiary amine through a two-carbon chain; this fragment is the pharmacophore of the hypnoanalgesics.

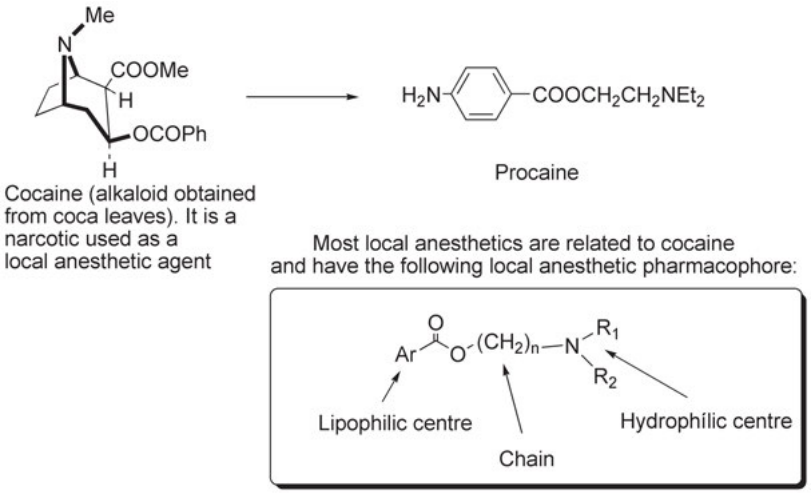


Fig. 4.26: Simplification of the prototype (disjunctive replication), cocaine.

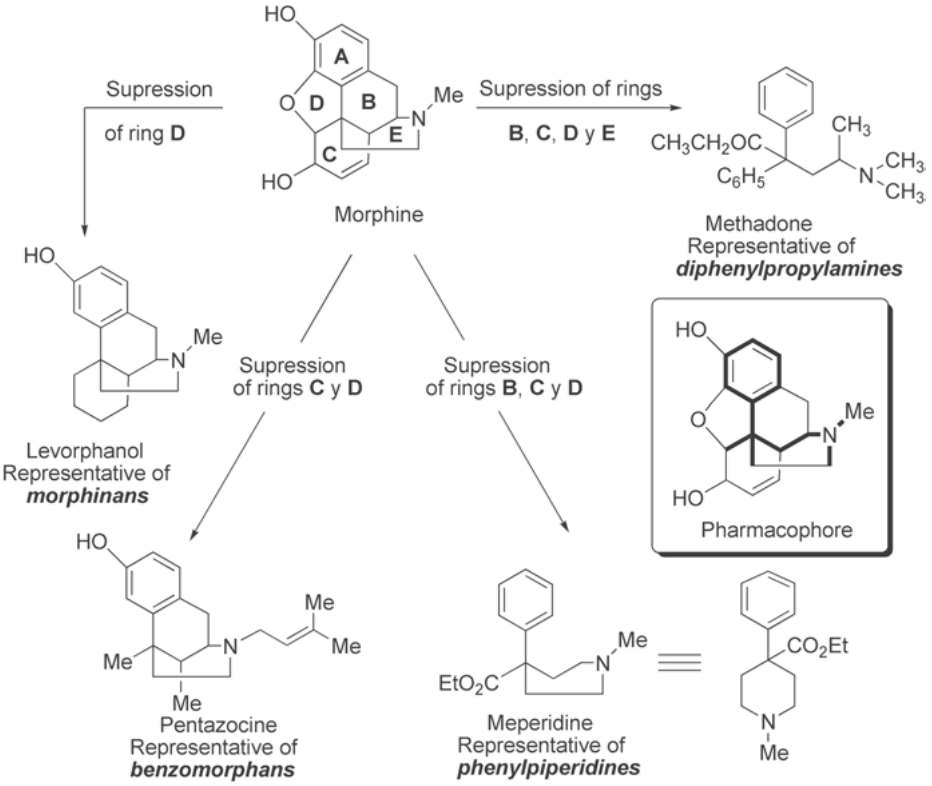


Fig. 4.27: Simplification of the prototype (disjunctive replication), morphine.

4.5 Conjunctive replication

Larger replicas than the modelare made. It has two aspects:

– molecular duplication (of interest in the development of antimetabolites, Fig. 4.28).

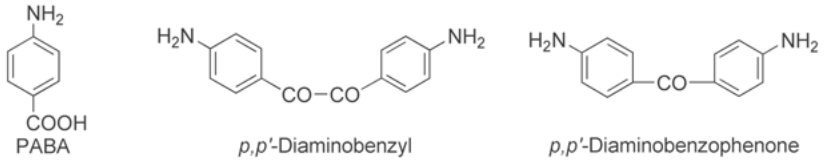


Fig. 4.28: PABA conjuctive replications.

Antimetabolites have a structure very similar to the natural substrate, giving rise to products that are biologically inhabibleas they incorporate molecules different from the natural ones.

– Hybrid or molecular combination. This involves the combination of two different molecules (Fig. 4.29).

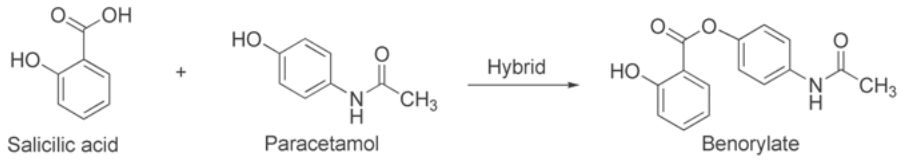


Fig. 4.29: Molecular combination of the prototype (disjunctive replication), salicylic acid and paracetamol.

4.6 Peptidomimetics

Biologically active molecules containing amide bonds normally suffer from pharmacokinetic hazards. Bioisosteric transformations have been carried out in the carboxamide group in order to increase its stability with great success in the area of peptidomimetics (these can be defined as structures capable of replacing peptides in their interactions with receptors and enzymes). The most established modifications are as follows: *N*-methylation, change of configuration (configuration D), formation of a retroamide or azapeptide, use of aminoisobutyric acid or dehydroamino acids, substitution of the amide bond by an ester (depsipeptides), introduction of the ketomethylene group, introduction of the thioamide group, reduction of the amide carbonyl group, and use of an olefinic double bond (Fig. 4.30).

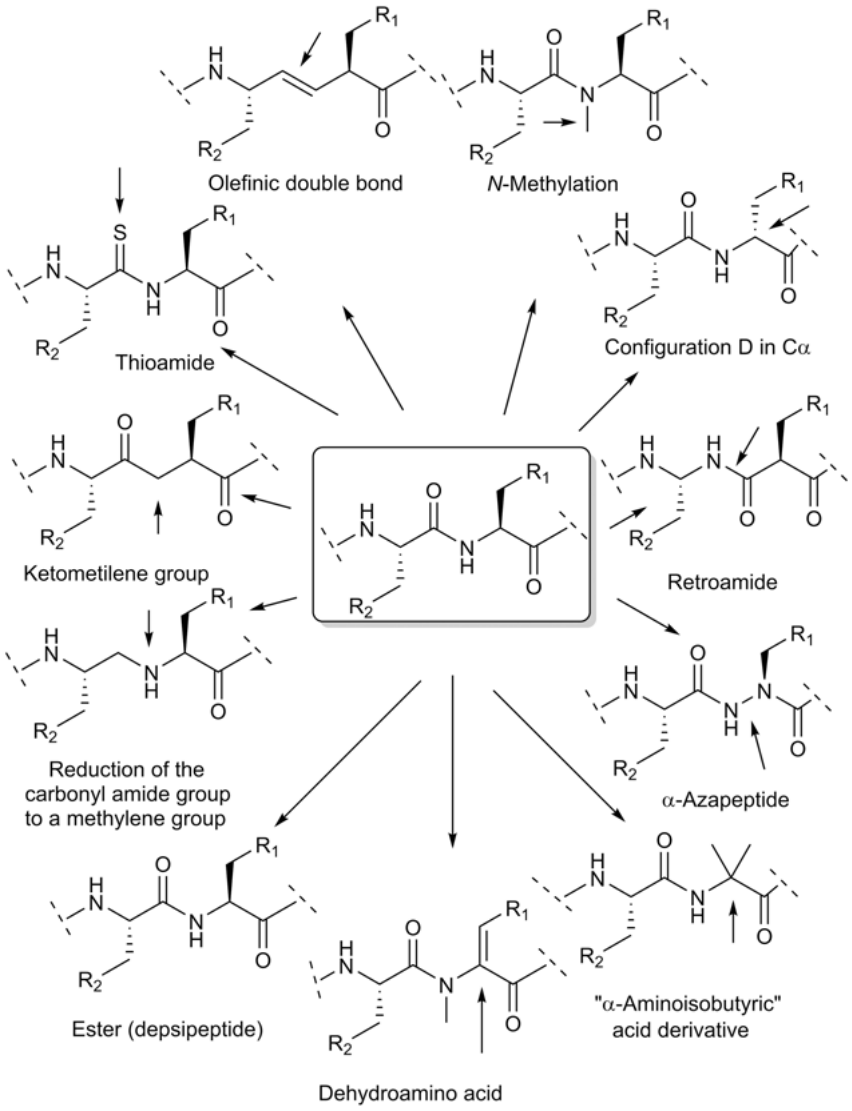


Fig. 4.30: Isosteric substitutions of the peptidic bond.

The most well-known peptidomimetic is morphine, which owes its analgesic action to its binding capacity to opioid receptors such as the endogenous peptides, enkephalins and endorphins (Fig. 4.31).

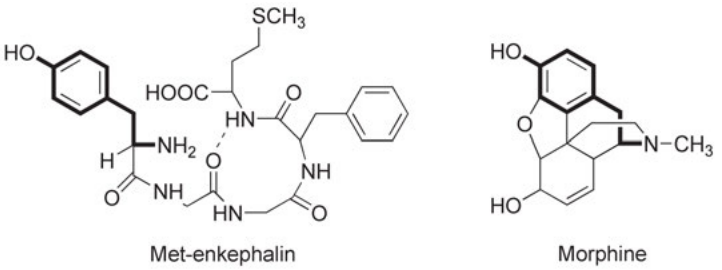
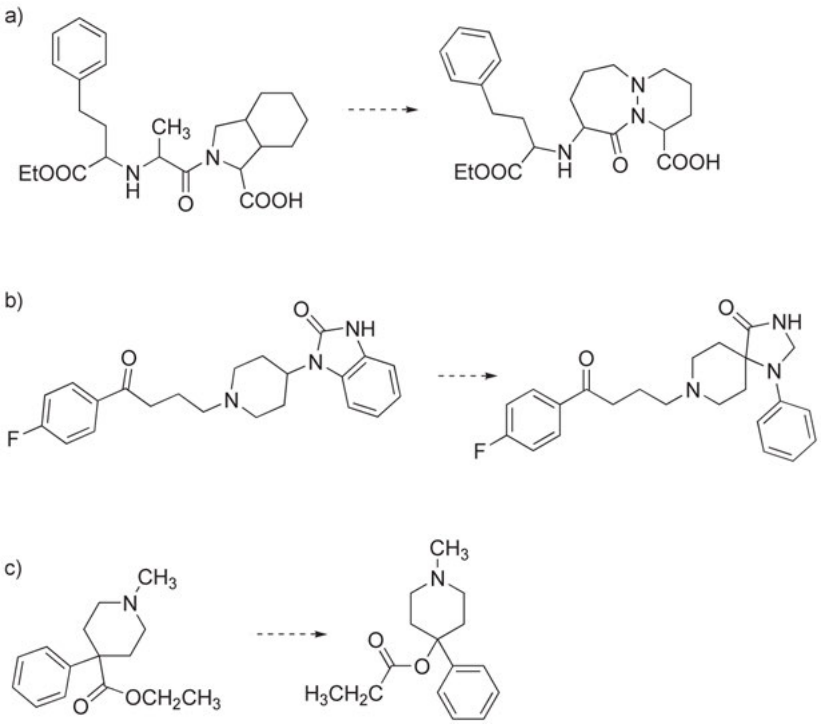


Fig. 4.31: Met-enkephalin and morphine.

4.7 Exercises

1) Indicate the molecular modification criteria used in the design of the following drugs, giving a reasoned explanation:



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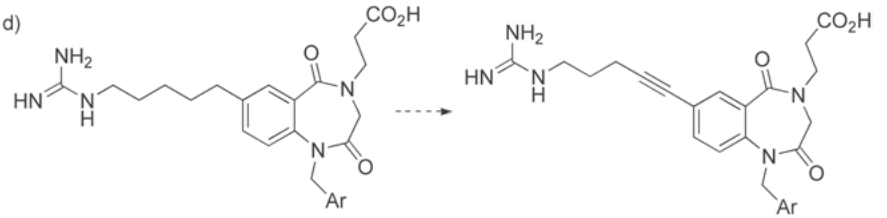

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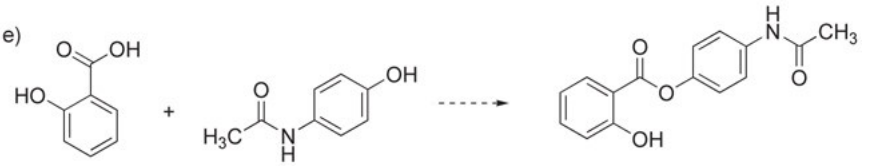

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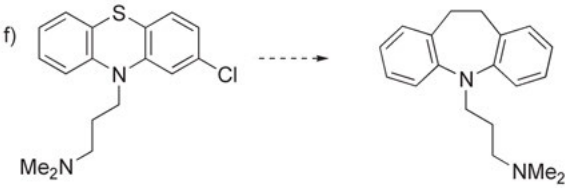

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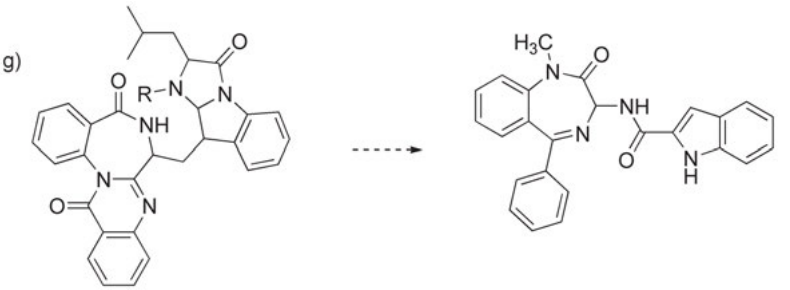

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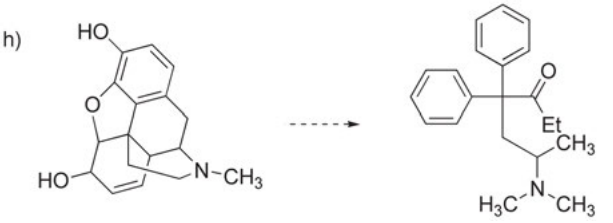

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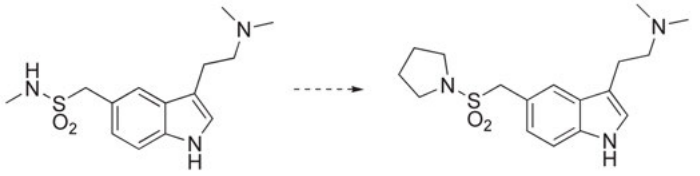

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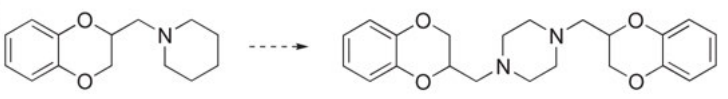

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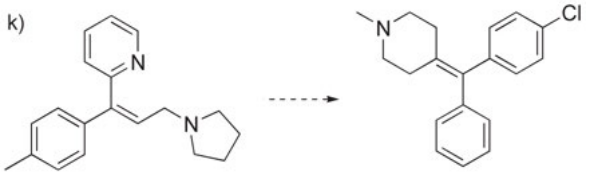

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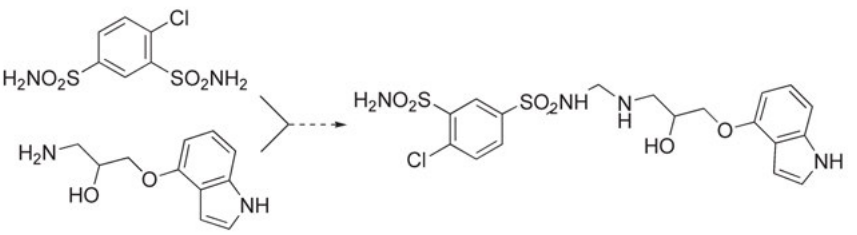

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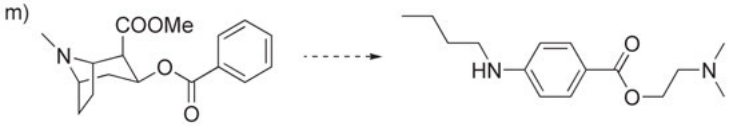

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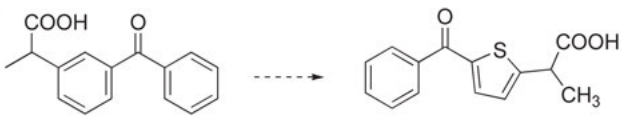
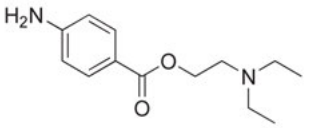
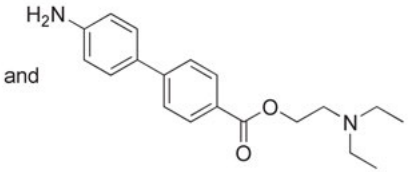
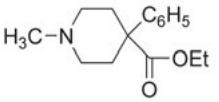
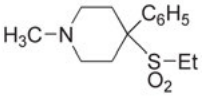
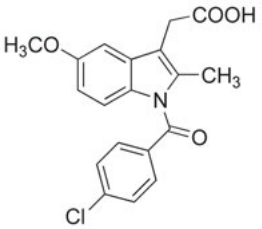
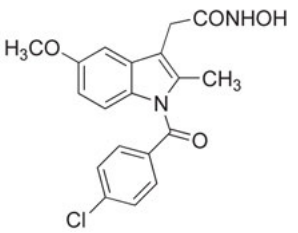
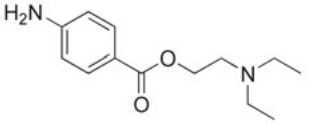
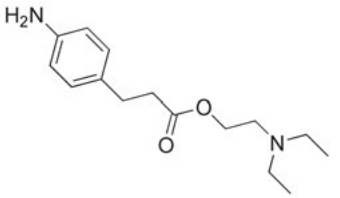


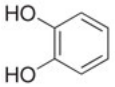
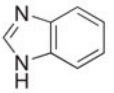
2) Given the following pairs of structures, indicating if they are isosteres, homologues, or vinylogues:

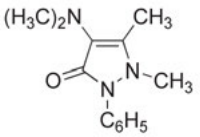
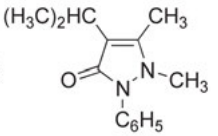
a)  and 

b)  and 

c)  and 

d)  and 

e)  and 

f)  and 

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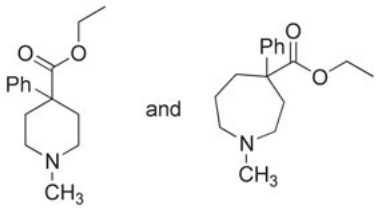

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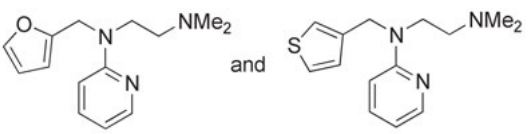

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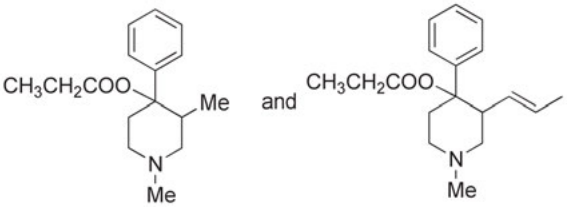

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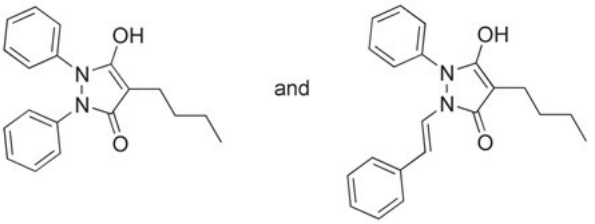
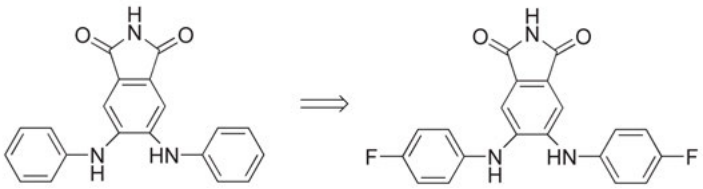


3) Explain the purpose of the molecular modification achieved when switching from one drug to the other:

a)



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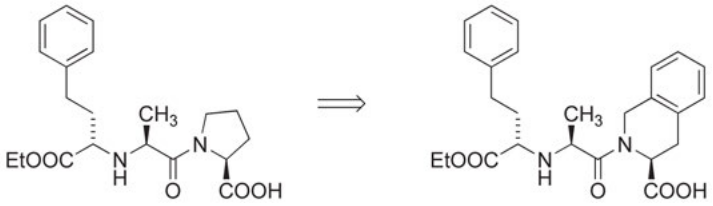

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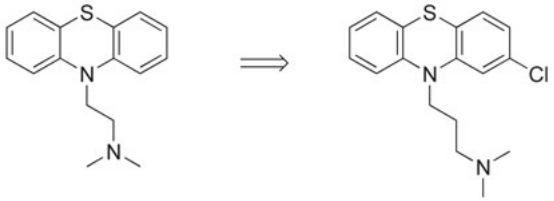

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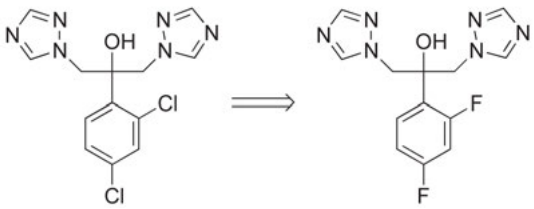

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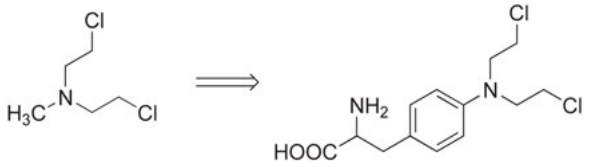

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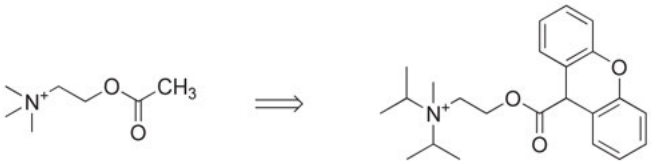

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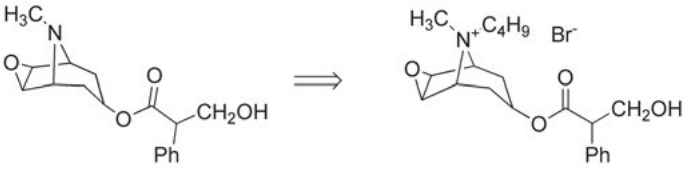

5 Biological targets and receptors for drugs

5.1 Goals

- To understand the concept of biological target and natural ligand.
- To know the interactions that allow drug-receptor molecular recognition as a cause of chemical affinity, and efficacy or intrinsic activity.
- To know the stereochemical requirements of the drugs.
- To know the existence of drugs that do not bind at the receptor-binding site.

5.2 Membrane receptor

A membrane receptor is a macromolecule embedded in the cell membrane, with one part of its structure oriented towards the outside and the other towards the interior of the cell.

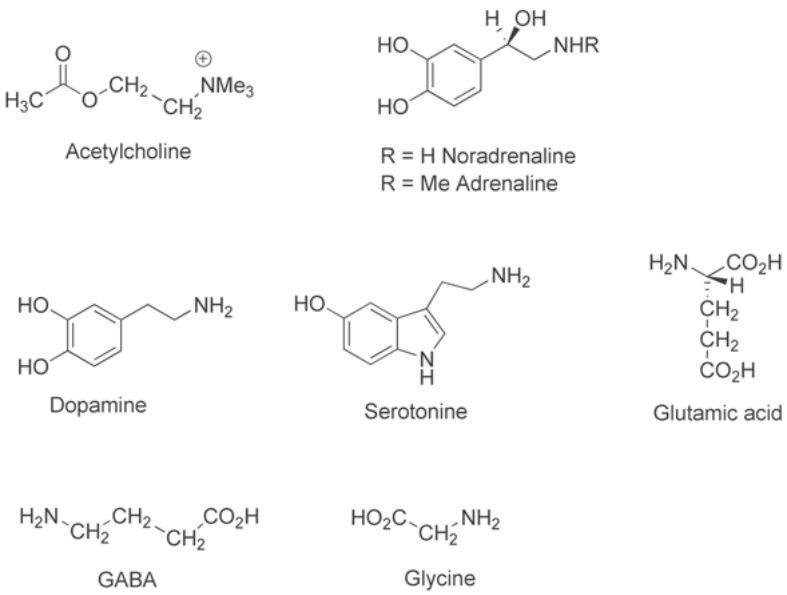

Fig. 5.1: Examples of neurotransmitters and the hormone adrenaline.

There are a variety of chemical messengers or neurotransmitters that interact with receptors: some are simple molecules, such as a quaternary ammonium salt (acetylcholine), monoamines (noradrenaline, dopamine and serotonin) or amino acids (e.g.

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γ-aminobutyric acid GABA), glutamic acid, and glycine) (Fig. 5.1). Other chemical messengers are more complex, and include lipids such as prostaglandins, neuropeptides such as endorphins and enkephalins, and peptidic hormones such as angiotensin.

5.3 Affinity and intrinsic activity; agonists and antagonists

There are two parameters defining the behaviour of the drug in its relationship with receptors:

1. its ability to bind to receptors or affinity;
2. the ability to activate them, intrinsic activity or effectiveness.

According to the presence and absence of the described properties, drugs are classified in:

- agonists: substances that possess receptor affinity and intrinsic activity;
- antagonists: drugs that possess affinity, but not intrinsic activity, so they occupy the receptor but are unable to activate it. In addition, they will oppose its occupation by agonists and will prevent it from producing an effect.

$$F + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} FR \longrightarrow E\ (Effect)$$

$$E = \alpha\,[FR]$$

Pure agonist: $\alpha = 1$ Pure antagonist: $\alpha = 0$

Partial agonist: $0 < \alpha < 1$

The receptor may be

- linked to an ion channel;
- have catalytic capacity;
- be associated to a G protein;
- be intracellular.

5.4 Types of receptors

5.4.1 Ionic channels

The membrane is formed by a bilayer of molecules, whereby the centre of the cell membrane is hydrophobic (represented by wavy lines in Fig. 5.2), whereas the termini, which are directed towards the outside and to the cytoplasm of the cell, are hydrophilic (represented by circles in Fig. 5.2). This characteristic makes it diffi-

cult for polar molecules and ions to enter or leave the cell, and the movement of sodium and potassium ions through the membrane is crucial for the functioning of the nerves.

Ionic channels are complexes formed by five protein subunits that cross the cell membrane. The center of the complex is hollow and is furrowed by polar amino acids, which translates into a hydrophilic tunnel. Ions can traverse the fat barrier of the cell membrane, moving through these hydrophilic channels or tunnels. However, there has to be some kind of control. In other words, there must be a lock that opens or closes as needed. In the idle state, the ion channel remains closed. However, when a chemical messenger binds to the outer binding site of the receptor protein (one part of which is the ion channel), an induced adjustment occurs which causes the protein to change its shape, the channel to open, allowing the passage of the ions through the channel.

Ionic channels are specific for certain ions. For example, there are different cationic channels for Na^+, K^+, and Ca^{2+} ions. There are also anionic channels for the Cl^- anion.

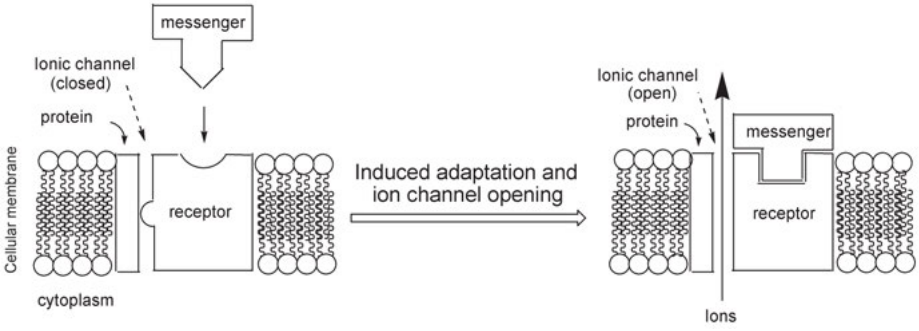


Fig. 5.2: Structure of an ionic channel.

Example: Nicotinic receptor of neurotransmitter acetylcholine.

5.4.2 Receptors with an intrinsic catalytic activity

The binding of a ligand on the extracellular domain of the receptor triggers the activation of an enzymatic system located in the intracellular domain of such a receptor (Fig. 5.3).

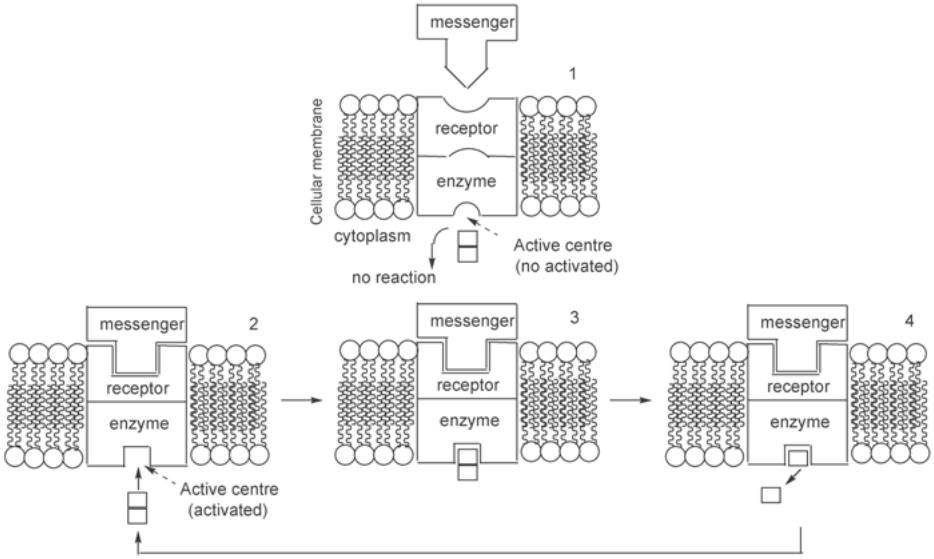


Fig. 5.3: Mechanism of activation of an enzymatic system associated with a membrane receptor: (1) rest state; (2) the enzyme acquires a productive conformation by interaction of the messenger with the receptor; (3) and (4): enzymatic process and return to (2).

Example: Certain protein kinases.

5.4.3 Receptors bound to G proteins

They lead to the formation of secondary messengers that are responsible for biochemical responses. They consist of the binding of the L-R complex with a G protein (so called because it is associated with the guanine nucleotide, GDP). G proteins are composed of three subunits, called α, β, and γ. Following the interaction of the G protein with the ligand-receptor complex, a series of conformational changes are derived leading to the exchange of GDP by GTP and to the dissociation of the γ-GTP complex.

Such a complex then interacts with an intracellular effector, such as adenylate cyclase, resulting in its activation with the consequent formation of the secondary messenger cAMP or inositol 1,4,5-triphosphate (IP_3), respectively. The cAMP is responsible for the activation of protein kinases, which in turn activate certain enzymes by phosphorylation. IP_3 results in the emptying of the Ca^{2+} storage vesicles, whose increase in the intracellular level is responsible for effects as diverse as smooth muscle contraction, glandular secretion or the release of certain neurotransmitters. Finally, the hydrolysis of a phosphate unit of the α-GTP complex leads to the regeneration of the α-GDP subunit and its combination with the β- and γ-subunits to give rise to the functional G protein again (Fig. 5.4).

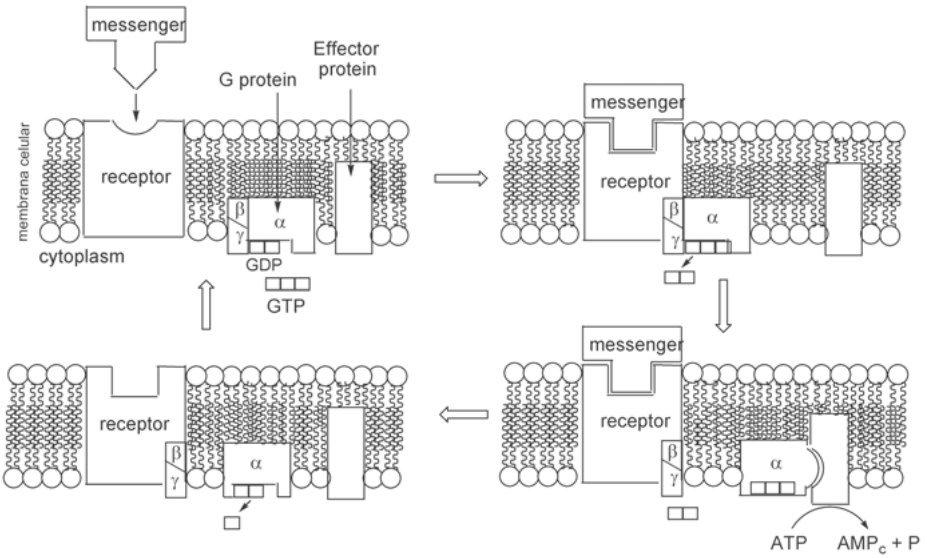


Fig. 5.4: Formation of a secondary messenger by activation of a G protein.

Examples: muscarinic acetylcholine receptor, dopaminergic receptors, and opiod receptors.

5.4.4 Intracellular receptors

These are characteristic of steroid hormones (Fig. 5.5).

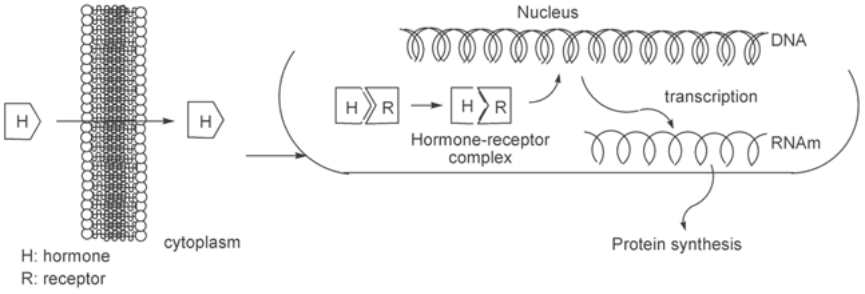


Fig. 5.5: From the messenger to the control of gene transcription.

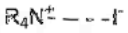
Intracellular receptors are specific to steroid hormones (sex hormones, glucocorticoids, vitamin D), and thyroid hormones. Steroid receptors are located at the level

of the cell nucleus in certain chromatin sequences leading to the initiation of transcription and protein synthesis.

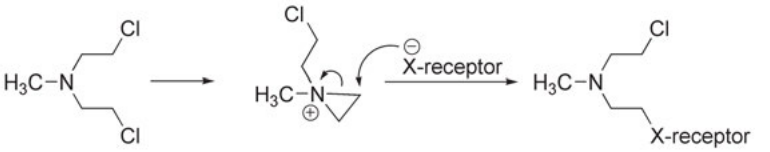
5.5 Types of bonds: energy range (kJ/mol) per interaction

5.5.1 Intramolecular bonding interactions

– Ionic bond (400-4,000, strong); example:

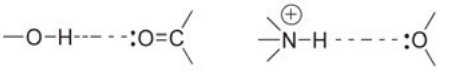


– Covalent bond (150-1,100, strong); example:

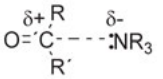


5.5.2 Intermolecular interactions

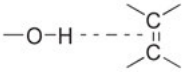
– Hydrogen bond (10-40, moderate); example:



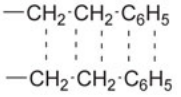
– Dipole-dipole (5-25, moderate); example:



– Charge transfer or dipole-induce dipole (2-10, weak); example:



– van der Waals and hydrophobic bonds (0.05-40, weak, although they may become quite strong due to many interactions); example:



The covalent bond constitutes the bond of greatest strength in the scale of energies of interaction between two molecules. Due to its stability, this link can be considered practically irreversible.

The action between the drug and the receptor has to be maintained for a relatively short period of time, which means that a reversible interaction is required. The reversibility of this union assumes that the links that hold it are relatively weak. Among the bonds with these characteristics, the ionic bond is the most stable and is established between charged groups of the drug and the receptor macromolecule. As for the drug, the ammonium groups are ionized permanently, and at physiological pH there are other very common groups such as carboxylate, sulfonamido, amino, and many nitrogenous heterocycles. In this way, the drug ions and the oppositely charged charges of the receptor zone may attract each other by establishing an ionic bond.

The molecules composed of atoms of different electronegativities have an asymmetric distribution of their electronic clouds, which translates into the existence of electronic dipoles. These dipoles within a cell or in aqueous medium can be attracted by a nearby ion, establishing the so-called ion-dipole interactions. A permanent dipole may also interact with another permanent dipole resulting in a dipole-dipole interaction. Because the charge of a dipole is lower than that of an ion, the ion-dipole and dipole-dipole interactions are weaker than those of the ionic bonds.

A particular type of dipolar bond is the hydrogen bond, which is established between a weakly acidic hydrogen atom, bonded to an electronegative atom by a covalent bond, and a base that acts as an electron donor. Usually the groups having hydrogen atoms suitable for this type of bond are OH (alcohols, phenols, oximes, etc.), NH (amines, π-excess nitrogen heterocycles, e.g. imidazole and SH (thiols). As for the electron-releasing bases, there are anions (carboxylate, phosphate, sulfate), as well as any group possessing an unshared pair of electrons, especially amines, alcohols, ethers and carbonyl groups. Water makes up hydrogen bonds very easily, and can act both as a donor and as an acceptor.

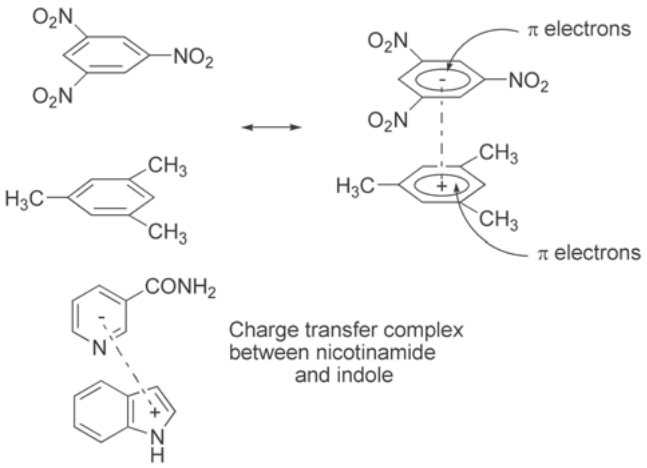


Fig. 5.6: Examples of charge-transfer complexes.

The charge transfer complexes are formed by the electrostatic attraction between an electron-realeasing molecule and an acceptor molecule; although the ionic form that can be represented as $Donor^{+}$-$Acceptor^{-}$ contributes only slightly to the resonance hybrid of these complexes, it increases their stability (Fig. 5.6).

These complexes can be considered as an ionic pair, with the property of undergoing an observable transition of charge between the donor that acquires positive charge and the acceptor that acquires a negative one.

The van der Waals bond belongs to the hydrocarbon chains and is at the weakest end of the intermolecular bond scale. It has its origin in the transient polarization of the electronic cloud surrounding the molecule. Thus, when two hydrocarbon chains approach, a mutual polarization that determines a small attraction is established. An important concept to note is that, although a single bond of this type is not of great importance in stabilizing the drug-receptor complex, in molecules with a large number of hydrocarbon groups, the total sum of the van der Waals bonds that can be settled contributes significantly to the interaction.

The hydrogen bond is a particular case of charge transfer occurring through a weakly acidic hydrogen atom, attached to the acceptor molecule in a covalent form, and a base that acts as a donor of the electrons that will establish the hydrogen bond.

5.5.3 Hydrophobic bond

In the aqueous media, the van der Waals bond is reinforced by the entropic variation of the system resulting from the desolvation that occurs when two organic molecules approach by their lipophilic part, with the consequent increase of the entropy of the system (Fig. 5.7). Although the hydrocarbon moieties are ordered, a considerably larger

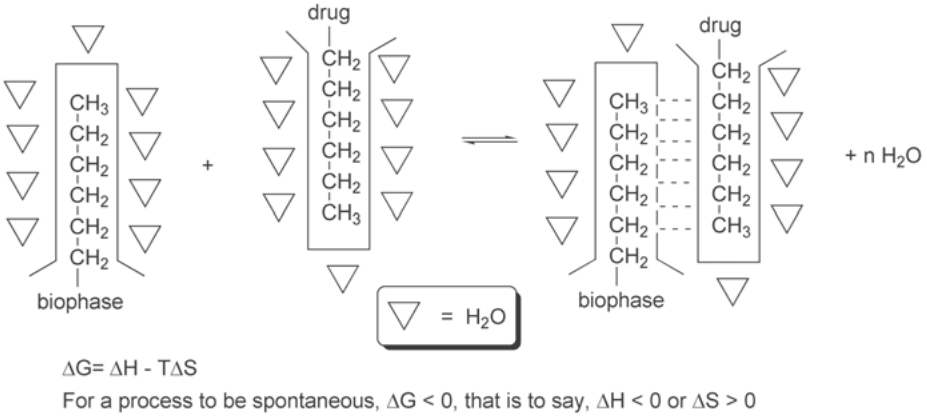


Fig. 5.7: Entropic increase derived from the desolvation required for binding of a drug to its biological target.

number of molecules becomes disordered, with the consequent increase of the positive value of ΔS and negative that of ΔG. This reinforcement of the van der Waals bond constitutes the so-called hydrophobic bond of great importance in biological media.

Figure 5.8 represents the type of the most frequent interactions of procaine with the biophase acceptor zones.

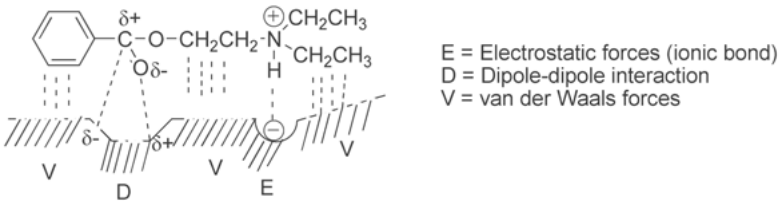


Fig. 5.8: Types of chemical interactions between procaine and the active site of its receptor.

5.6 Conformation and activity: use of rigid analogues

Conformation is defined as the nonidentical spatial ordering of the atoms of a molecule due to its rotation around one or more single bonds. Let us assume that situation (a) represents the active conformation of an agonist that binds to the receptor through its A and B groups, which causes the biological response through its C group, after interacting with the corresponding complementary groups A′, B′, and C′ of the receptor. Situation (b) represents an antagonist molecule, sinceit is capable of binding to the receptor, but because it does not have the C group, it would be incapable of giving any biological response. Finally, (c) would represent an isomer of the molecule of (a), with antagonistic activity, for not having the group C in the proper arrangement to interact with C′ of the receptor (Fig. 5.9).

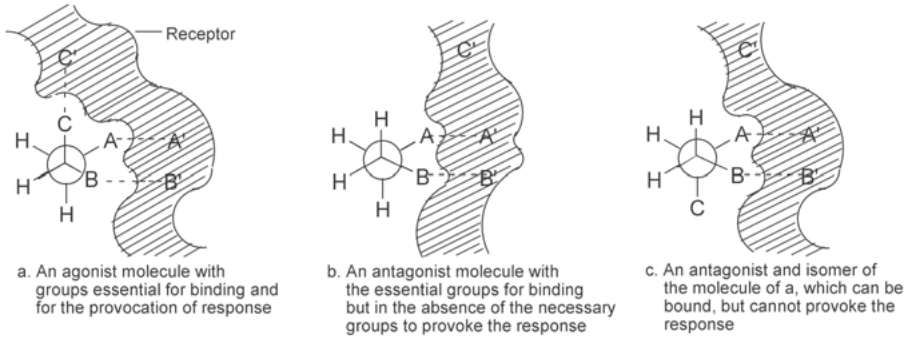


Fig. 5.9: Active conformation of an agonist [(a)], and conformations of two antagonists [(b) and (c)] interacting with a hypothetical receptor.

The pharmacophore conformation is not necessarily the preferred conformation in crystalline or dissolution state and may be a thermodynamically unstable conformation. In some cases, the energy of binding to a receptor can compensate for the barrier of forming an unstable conformation (Fig. 5.10).

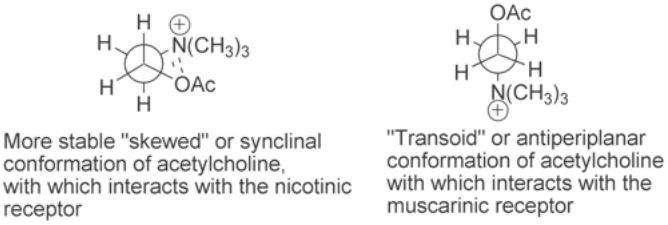


Fig. 5.10: Preferred "skewed" or synclinal conformation of acetylcholine, and the transoid or antiperiplanar one, that acetylcholine acquires upon acting on the muscarinic receptor.

One of the most commonly used methods for the determination of the active conformation of flexible drugs consists in the study of rigid analogues, in which the conformational possibilities are partially restricted.

The formation of cycles is one of the most frequently used methods for the study of the active conformation of flexible molecules. A classic example of cycle formation is the study carried out on various acetylcholine analogues, in which various conformations are mimicked (Fig. 5.11).

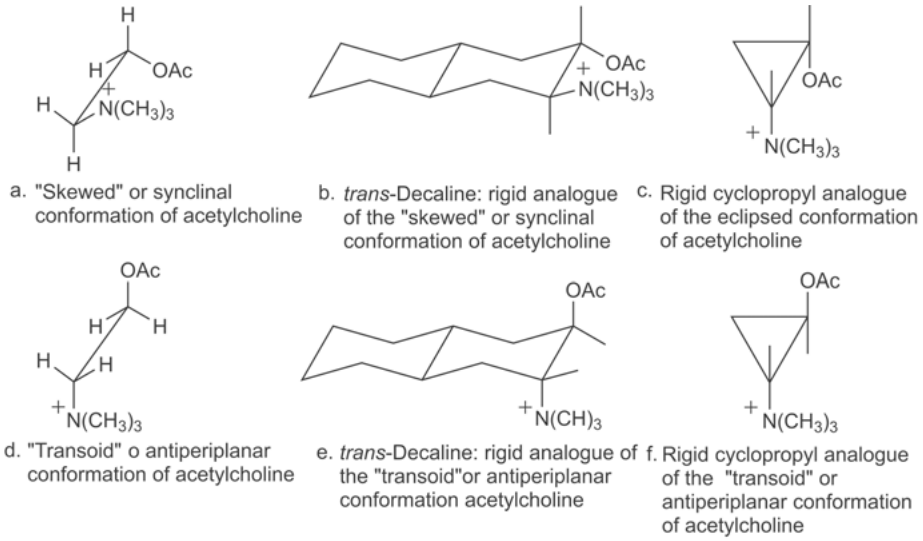


Fig. 5.11: Acetylcholine cyclic analogues.

While analogues derived from decalin were devoid of cholinergic activity, cyclopropane analogues support the theory that the antiperiplanar conformation is involved in the interaction with the muscarinic receptor and in addition, it is more easily hydrolyzed by acetylcholinesterase.

The lack of activity of the decaline derivatives reveals one of the limitations of the use of rigid analogues. Thus, additional atoms and bonds that are introduced to provide rigidity to the structure can give rise to important changes in the physical and chemical properties with respect to the original molecule.

A thorough study of the anti-anxiety drug 4-(4-hydroxypiperidino)-4′-fluorobutyrophenone has been carried out using conformers in order to determine the possible steric requirements of the hydroxyl group (Fig. 5.12).

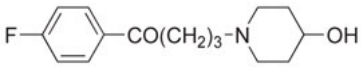


Fig. 5.12: 4-(4-Hydroxypiperidino)-4′-fluorobutyrophenone.

We will only represent the chair with the OH in equatorial or axial position (Fig. 5.13).

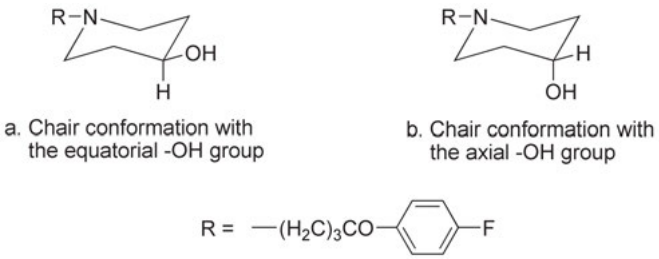


Fig. 5.13: Chair conformations of 4-(4-hydroxypiperidino)-4′-fluorobutyrophenone.

Boat and twist-boat conformations have been excluded because of their high energy.

When subjected to muscle relaxation tests, they presented the following order of activity or relative power **b** > **c** > **a**, which implies that the oxygenated function should preferably be in the axial position: the probable pharmacophore conformation would be **b**, *i.e.* the conformer with the axial hydroxyl group (Fig. 5.14).

The structure of a prototype can be manipulated by limiting its conformational freedom around certain single bonds, as can be seen in the hypotensor clonidine. It is a α_2-adrenergic agonist. Its structure is characterized by having an imidazolidine subunit attached to an aza-styrene moiety with two chlorine atoms at *ortho* positions. Clonidine has a restricted rotation by steric hindrance and is 30 times more active than its isomer with free rotation around the nitrogen-phenyl bond (with the two chlorine

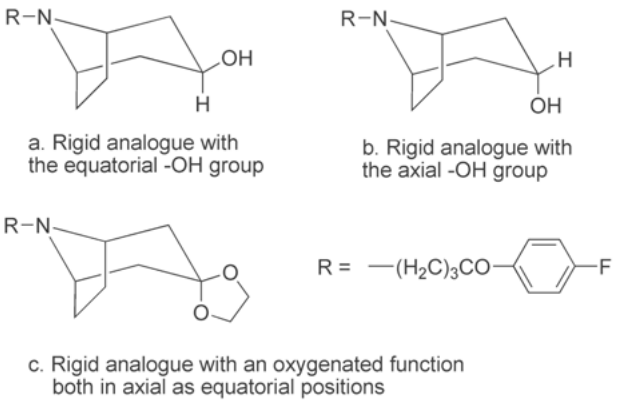


Fig. 5.14: Use of conformers in order to determine the possible steric requirements of the hydroxyl group.

atoms at positions 3,4). These facts can be interpreted taking into account that the conformational constraint fixes the optimal geometry and diminishes the possible interactions with other targets. Clonidine is a very basic substance ($pK_a = 13$) and therefore its protonated form is predominant in the biophase. X-Ray studies confirm the exo-imine of the cycilic guanidine moiety of clonidine, in which the *ortho*-dichloro aromatic ring lies on a plane different from that of the imidazoline system with an angle of 75° (Fig. 5.15).

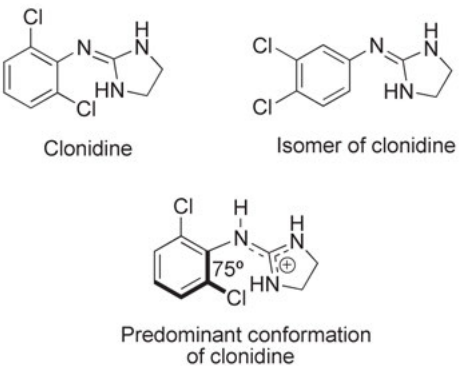


Fig. 5.15: Clonidine (predominant conformation according to x-ray studies) and its less active isomer.

Molecular modelling studies indicate that there is a distance of 0.51 nm between the two nitrogen atoms of the imidazolidine system and the centre of the aromatic ring, similar to the distance that occurs in adrenaline (a natural agonist of the α-adrenergic receptors), between the NH_3^+ group and the centre of the cathecol ring (Fig. 5.16).

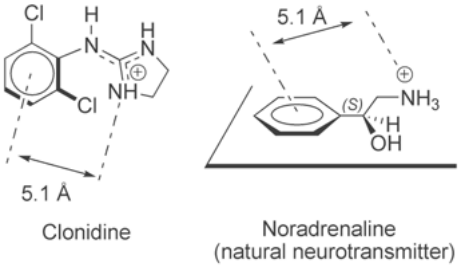
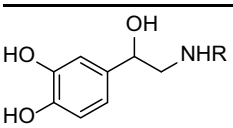


Fig. 5.16: Similar distances occur between the nitrogen atoms of the the five-membered guanidino moiety and the center of the benzene ring in clonidine, and the ammonium group and the centre of the catechol moiety of noradrenaline.

5.7 Absolute configuration and activity: difference between enantiomers

It has been implicitly established in the previous section that the three-dimensional orientation of the functional groups is fundamental for a correct adaptation to the receptor. For example, the bronchodilator activity of (*R*)-isoprenaline is about 800 times greater than that of its (*S*)-enantiomer. Similar stereoselectivity is also observed between the enantiomers of catecholamines noradrenaline and adrenaline (Tab. 5.1).

Table 5.1: Differences in the bronchodilator activity between catecholamines.



R = H Noradrenaline
R = Me Adrenaline
R = Pr^i Isoprenaline

	Relative bronchodilatation to the (*R*)-(-)-noradrenaline	
(*R*)-(-)-Noradrenaline	100	*RIS* = 71
(*S*)-(+)-Noradrenaline	1.4	
(*R*)-(-)-Adrenaline	5800	*RIS* = 45
(*S*)-(+)-Adrenaline	130	
(*R*)-(-)-Isoprenaline	27000	*RIS* = 818
(*S*)-(+)-Isoprenaline	33	

A simple explanation of the different activity of the enantiomers is provided by the Easson–Stedmann hypothesis according to which, if one considers that in the adaptation of the stereogenic centre to the receptor requires at least the interaction through

three points, only one of the enantiomers may simultaneously establish such interactions (Fig. 5.17).

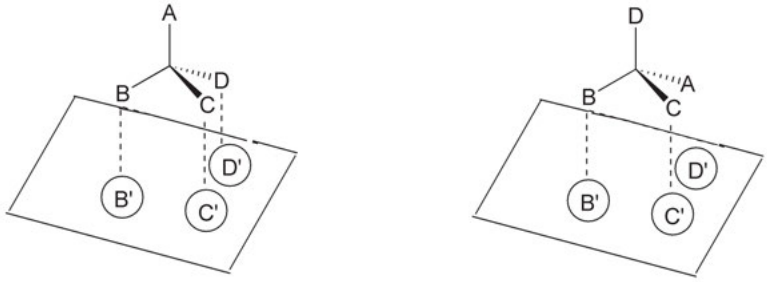


Fig. 5.17: Three point-interaction model.

The more active enantiomer is referred to as eutomer and the least as distomer; the relation of activities between both is called eudysmic ratio.

5.8 Relative configuration and activity

Similarly, alterations in the relative configurations of the substituents of an aliphatic cyclic derivative or an olefin may have repercussions for the recognition by the receptor, as it could lead to a loss of complementarity and accordingly reduction of affinity and intrinsic activity (Fig. 5.18).

As an example, we have the case of cisplatin, which is an important anticancer agent, while its *trans* isomer (transplatin) does not present any useful pharmacological activity (Fig. 5.19).

Sulindac is a nonsteroidal antiinflammatory drug (NSAID) of the arylacetic acid class that evidences the importance of the configuration of the double bond in the biological activity. The (*Z*) isomer is the active drug, while the (*E*)-isomer or isosulindac is less active.

This difference in activity between the two geometric isomers led to the identification of the bioactive conformation of indomethacin, another NSAID of the group of aryl acetic acids with an indole nucleus. Indomethacin was the prototype for the development of sulindac. However, in presenting an amide function involving a *p*-chlorobenzoyl residue attached to the indole nitrogen, it is possible that it undergoes enzymatic hydrolysis, which gives rise to certain CNS side effects. Therefore, sulindac was designed and a new bioisosteric relationship was discovered between the indomethacin indole system and the indene ring of sulindac. When considering the structure of the active diastereoisomer of sulindac [(*Z*)-isomer)], it was suggested that the **A** conformation is the bioactive conformation of indomethacin (Fig. 5.20).

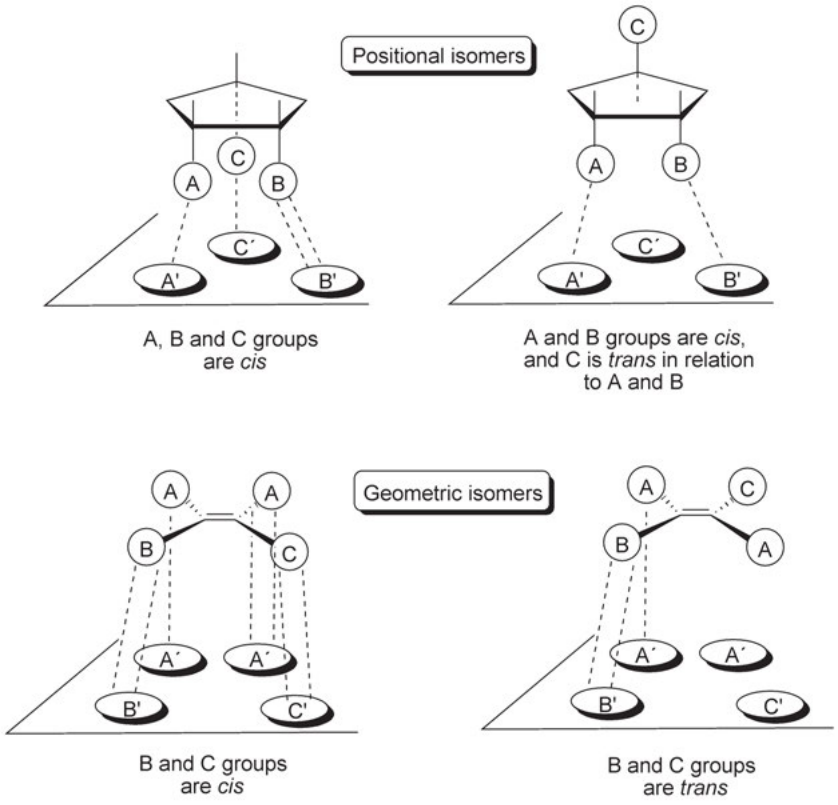


Fig. 5.18: Relative configurations and ligand-receptor molecular recognition.

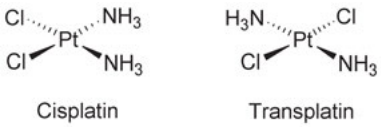


Fig. 5.19: Cisplatin and transplatin.

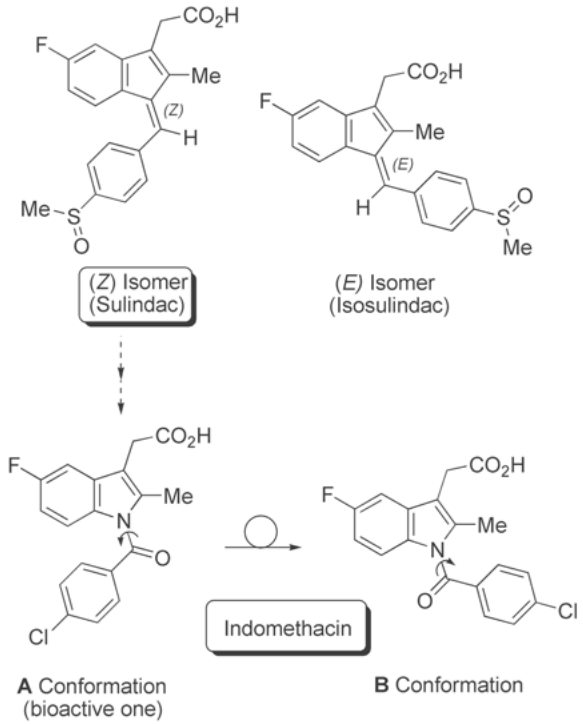
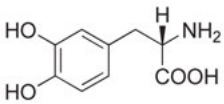


Fig. 5.20: Sulindac, isosulindac, and bioactive conformation of indomethacin.

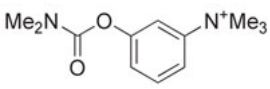
5.9 Exercises

1) Indicate the possible binding forces that will bind the following drugs to their receptor:

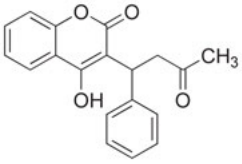
(a) Levodopa



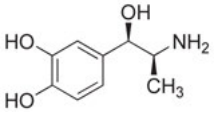
(b) Neostigmine



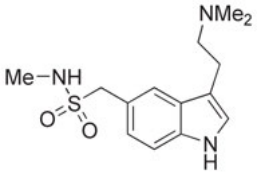
(c) Warfarin



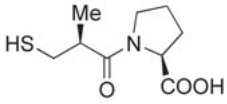
(d) α–Methylnoradrenaline



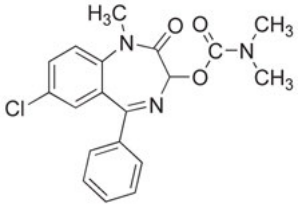
(e) Sumatriptan



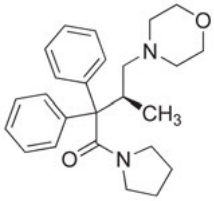
(g) Captopril



(f) Camazepam

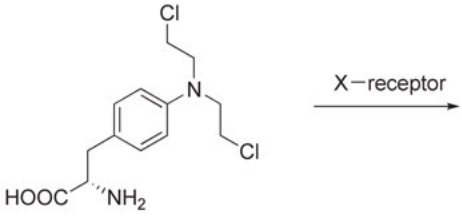


(h) Dextromoramide

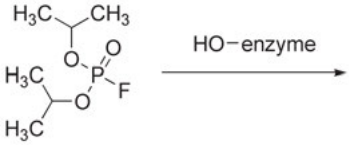


2) Indicate how a covalent bond will be formed between the following drugs and their specific receptors:

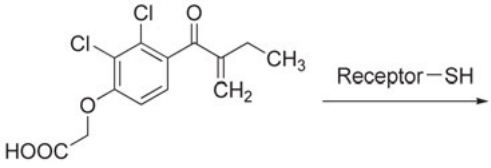
(a) Melphalan



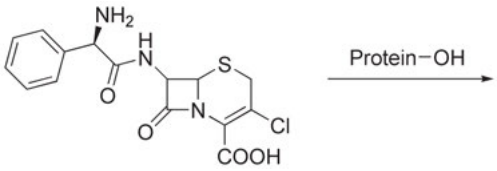
(b) Fluostigmine



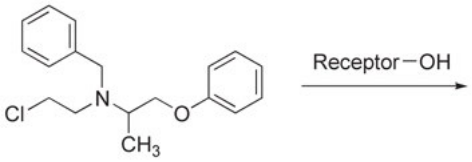
(c) Ethacrynic acid



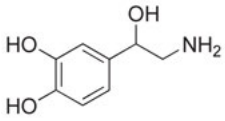
(d) Cefaclor



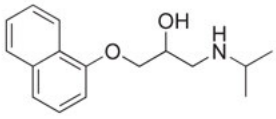
(e) Phenoxybenzamine



3) Propranolol is a β-adrenergic receptor antagonist that acts as a cardiovascular agent. The *S*-enantiomer is the active isomer, although it is used clinically as the racemate. Draw the structure of this enantiomer and compare it with that of the neurotransmitter (*R*)-noradrenaline, explaining the antagonism. Represent the binding forces that will bind each of these molecules to the β-adrenergic receptor.

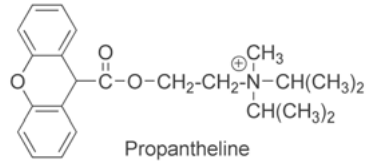


Noradrenaline

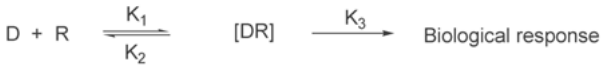


Propranolol

4) Propantheline is an acetylcholine antagonist drug. (a) Show the Drug-Receptor (D-R) interaction zones through the different binding forces and compare them with those of acetylcholine. (b) Given the following interpretation for the D-R interaction responsible for the pharmacological response, compare the values of the rate constants for an agonist such as acetylcholine, an antagonist such as propantheline, and for an inactive compound.



Propantheline

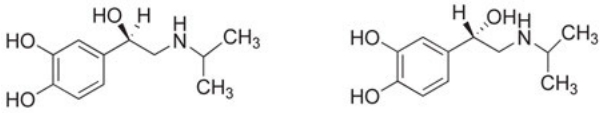


5) Justify the possible difference in activity of the following pairs of structures in their binding to the receptor, indicating whether they are conformational isomers, enantiomers or diastereoisomers:

(a)

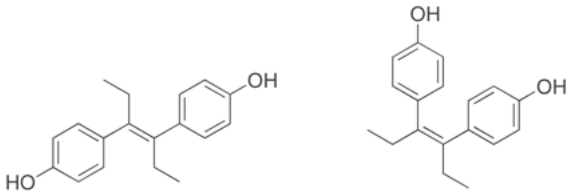
Cyclopropane analogues of acetylcholine

(b)



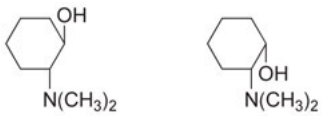
Isoprenaline

(c)



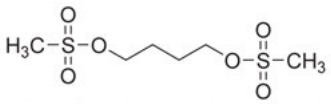
Diethylstilbestrol

(d)



2-Dimethylaminocyclohexanol

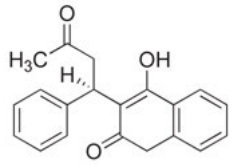
(e)



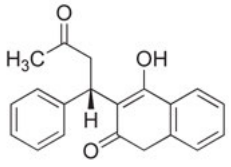
Busulfan (antineoplastic agent)

Rigid analagues of busulfan

(f)

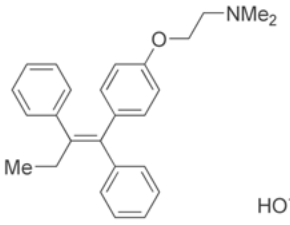


(*R*)-Warfarin

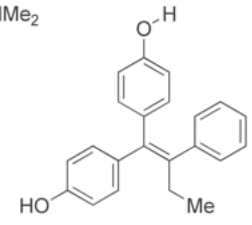


(*S*)-Warfarin

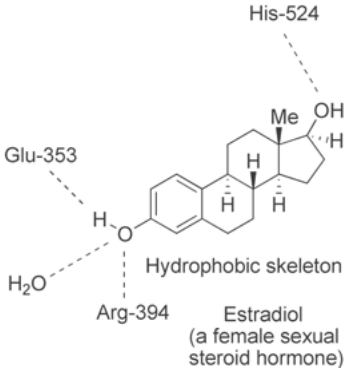
6) Tamoxifen acts as an estrogen receptor antagonist. Suggest how you can join the receptor to manifest that effect. The tamoxifen metabolite, however, acts as an agonist rather than as an antagonist. Why?



Tamoxifen



Tamoxifen metabolite



6 Quantitative drug design: parameters and quantitative structure activity relationships

6.1 Goals

- To know the QSAR tool as an instrument for optimizing a prototype and reducing its cost.
- To know the tool of molecular modelling as a research method for discovering more selective and more economical new drugs.
- To know superficially other current tools in the search for new drugs.

6.2 Introduction

By drug design we mean the obtaining of active molecules from a pharmacological point of view, based on previous considerations that predict its activity.

The historical birth of the QSAR (acronym for **q**uantitative **s**tructure-**a**ctivity **r**elationship) idea was in the year 1870, when the biological activity (BA) was postulated to be a function of the chemical structure:

$$\text{BA} = \text{f}(\text{chemical structure}). \tag{6.1}$$

BA, measured in the form of log (1/C), where C is the molar concentration of the drug capable of producing a certain activity, is a function of the physicochemical parameters of the molecules:

$$\log(1/\text{C}) = \text{f}'(\text{electronic} + \text{hydrophobic} + \text{steric parameters}). \tag{6.2}$$

A widely-used method is the Hansch—Fujita method, which establishes a correlation between the biological activity and a linear combination of parameters representing the physicochemical changes within a number of molecules. The dependence of biological activity with the electronic, hydrophobic and steric parameters (eq. (6.2)) is the simplest relation of a great variety of Hansch equations. Equations have been used in the last four decades relating the BA to almost all possible conceivable combinations of lipophilic, polarizability, electronic, steric parameters, with or without other additional indicators (among others, molecular orbital parameters). In this introductory course, we will study only the simplest forms of the Hansch equations. Herein we will study only the simplest forms of the Hansch equations.

Since Hammett studies obtained a quantitative expression of the reactivity of organic substances, they represent the background as a function of their structures (Fig. 6.1).

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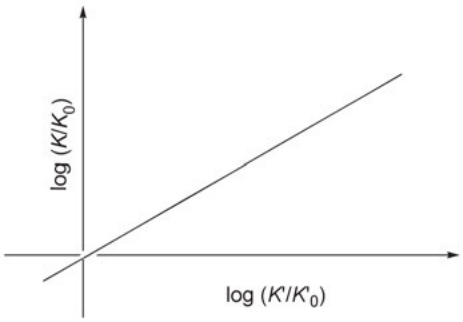


Fig. 6.1: Correlation between the dissociation constants of unsubstituted and substituted benzoic acids (abscissa axis) and those of phenylacetic acids (ordinate axis) with the same substitution patterns (*meta* and *para*).

6.2.1 Electronic parameters

$$\log \frac{K}{Ko} = \rho \log \frac{K'}{K'o}$$

K_0 and K_0' represent equilibrium constants of unsubstituted compounds and K or K′ of the substituted derivatives. The abscissa values are calculated from the dissociation constants of unsubstituted and substituted benzoic acids. On the other hand, the ordinate values are obtained from phenylacetic acids with the same substitution patterns (Fig. 6.1). The substitution refers to *meta* and *para* positions, and never to *ortho* positions, because of possible incidence of the steric effect:

$$XC_6H_4CH_2COOH + H_2O \rightarrow XC_6H_4CH_2COO^- + H_3O^+ \tag{6.3}$$

Y-axis values,

$$XC_6H_4COOH + H_2O \rightarrow XC_6H_4COO^- + H_3O^+ \tag{6.4}$$

X-axis values.

ρ is the slope of the line. The values of the abscissa axis are always those of benzoic acid and are called σ (Hammett's constant). Therefore, it is possible to write

$$\log \frac{K}{Ko} = \rho\sigma \tag{6.5}$$

Interpretation of Hammett constants

When a G group attracts electrons, it stabilizes the carboxylate group and strengthens the acid, while when G releases electrons it exerts the opposite effect (Fig. 6.2).

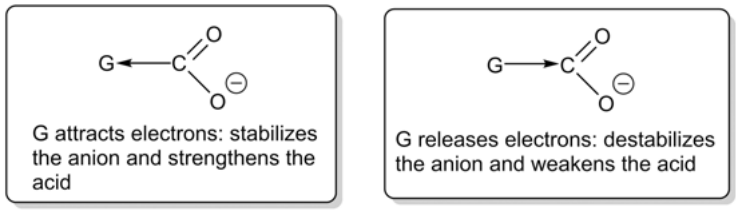


Fig. 6.2: Stabilization or destabilization of the carboxylate anion depending on the electronic nature of G.

Therefore, electron-withdrawing substituents have positive σ values, and electron donors have negative values. The hydrogen has a value of σ = 0.

The Hammett constant takes into account two electronic effects: the inductive and the resonance or mesomeric effect. Hence, the value of σ of a particular substituent will depend on whether the substituent is *meta* or *para*. This is indicated by the subscript *m* or *p* after σ. For example, the nitro group has a value of $\sigma_m = 0.71$ and $\sigma_p = 0.78$. In the *meta* position, the attracting electron effect is due to the inductive

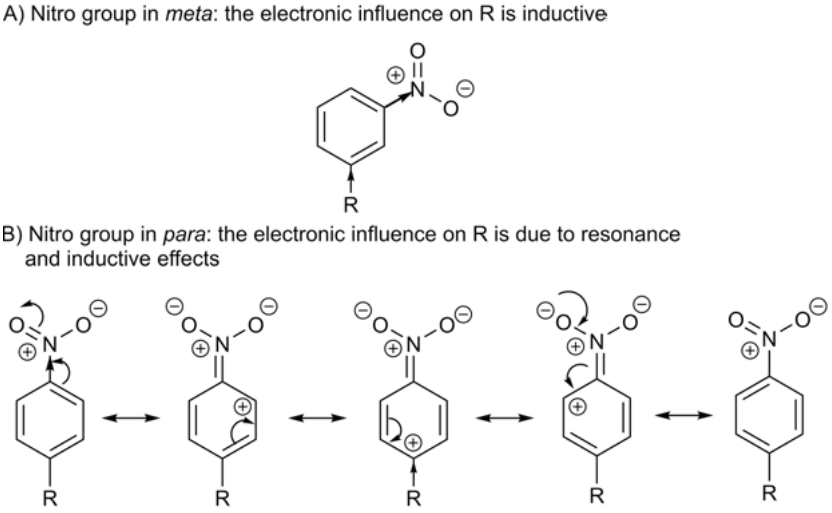


Fig. 6.3: Effects of the nitro group at the *meta* and *para* positions.

influence of the substituent, while in the *para* position, both inductive and resonant effects play a leading role, so the σ_p-value is greater (Fig. 6.3).
However, for the hydroxyl group, $\sigma_m = 0.12$ and $\sigma_p = -0.37$. In the *meta* position it has a withdrawing-electron influence, as a consequence of the inductive effect -I. In the *para* position, the electron-donating influence, due to the resonance of the electron pair of the hydroxyl group, is more important than the withdrawing-electron effect caused by the induction effect (-I) (Fig. 6.4).

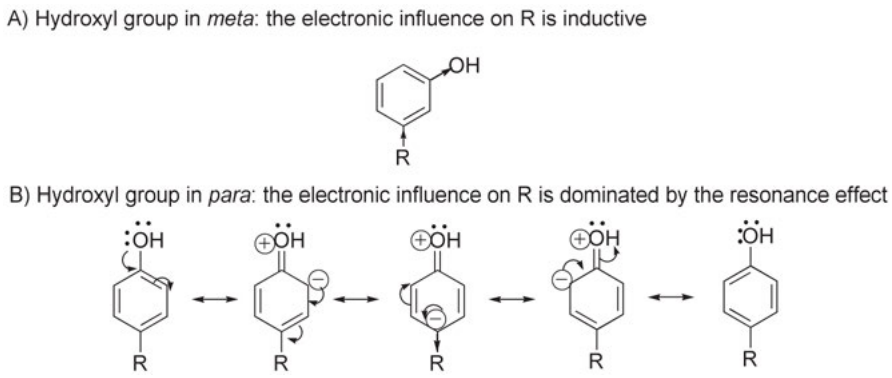


Fig. 6.4: Effects of the phenol group at *meta* and *para* positions.

It is said that a group possesses an -I effect if it acquires negative charge by induction; the effect is called +I if the charge acquired by induction is positive; similarly, it is said to have a -R (or +R) effect if it acquires negative (or positive) charge by resonance.

There are limitations as to the electronic constants described so far: for example, the constants of the Hammett substituents cannot be measured for *ortho* substituents, because the possible electronic effect is distorted by the steric effect.

6.2.2 Hydrophobic parameters: partition coefficient and hydrophobic substituent constant

$$P = [\text{drug}]_{\text{octanol}}/[\text{drug}]_{\text{water}}$$

The BA has usually two ways of behaviour versus the lipophilicity of the compounds (Fig. 6.5):

$$\log(1/C) = k_1 \log P + k_2 \quad \text{Lineal equation,} \tag{6.6}$$

$$\log(1/C) = -k_1(\log P)^2 + k_2 \log P + k_3 \quad \text{Parabolic equation.} \tag{6.7}$$

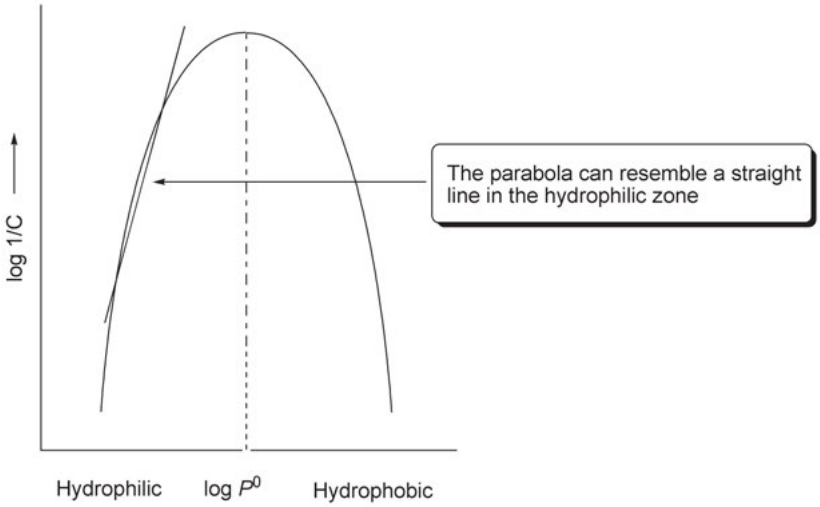


Fig. 6.5: Parabolic dependence of the biological response against the logarithm of the partition coefficient *n*-octanol/water.

Hansch and Fujita asserted that the contribution of a given substituent to the log *P* is a constant value. They defined the hydrophobic substituent constant by eq. (6.8):

$$\pi_x = \log P_{RX}/P_{RH}. \tag{6.8}$$

The more positive the π_x value, the more lipophilic the substituent, and viceversa.

As an example, consider the log *P* values of benzene (log *P* = 2.13), chlorobenzene (log *P* = 2.84) and benzamide (log *P* = 0.64). Benzene is the reference compound, and the substituent constants of the Cl and the $CONH_2$ group are 0.71 ($\pi_{Cl} = \log P_{Clbenzene} - \log P_{benzene}$) and −1.49 ($\pi_{CONH2} = \log P_{benzamide} - \log P_{benzene}$), respectively. Once these values are obtained, the theoretical log *P* value of *m*-chlorobenzamide can be calculated:

$$\log P_{m-clorobenzamide} = \log P_{benzene} + \pi_{Cl} + \pi_{CONH2} = 2.13 + 0.71 + (-1.49) = 1.35.$$

The value observed of this compound is 1.35. It should be noted that the values of the aromatic substituents are different from those of the aliphatic substituents.

Let us calculate the log $P_{paracetamol}$, considering the three possibilities of calculation: from phenol, acetanilide and benzene (Fig. 6.6).

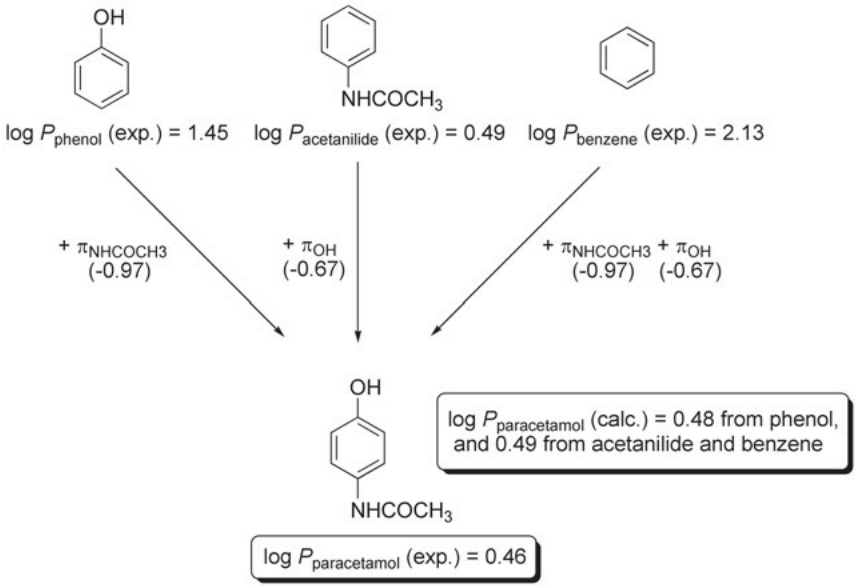


Fig. 6.6: Prediction of log *P* of paracetamol. See Tab. 6.1 for values of $\pi_{NHCOCH3}$ and π_{OH}.

Hansch equations can be written (eqs. (6.9) and (6.10)):

$$\log(1/C) = -k_1(\log P)^2 + k_2 \log P + k_3, \tag{6.9}$$

$$\log(1/C) = -k_4\pi^2 + k_5\pi + k_6, \tag{6.10}$$

where C is the concentration of the drug that produces a certain effect. The terms k_i are regression coefficients derived from the statistical treatment of the curves by the method of least squares (or least squares fitting).

6.2.3 Steric parameters

The steric characteristics of a molecule are intimately related to the ability of a molecule to bind to its receptor and thus, to elicit its biological response.

1. The steric parameter of Taft (E_s) has been derived studying the acid-catalyzed hydrolysis of aliphatic esters (eq. 6.11):

$$Es = \log k_X/k_o, \tag{6.11}$$

where k_x is the rate constant of the substituted compound, and k_o is the rate constant of the methyl ester.

2. Another measure of the steric factor is given by the molar refractivity (MR, eq. (6.12)):

$$\mathrm{MR} = (n^2 - 1)/(n^2 + 2) \times \mathrm{MW/d}, \tag{6.12}$$

where n is the refractive index, MW is the molecular weight, and d is the density. The term MW/d defines a volume, whereas $(n^2 - 1)/(n^2 + 2)$ is a corrective term.

Table 6.1 shows the electronic, hydrophobic, and steric descriptors of a number of substituents.

Table 6.1: Electronic, hydrophobic, and steric descriptors.

Substituent	Aromatic π	Aliphatic π	σ_m	σ_p	MR[a]	E_s
H	0.00	0.00	0.00	0.00	1.03	0.00
Br	0.86	0.60	0.39	0.23	8.88	−1.16
Cl	0.71	0.39	0.37	0.23	6.03	−0.97
F	0.14	−0.17	0.34	0.06	0.92	−0.46
I	1.12	1.00	0.35	0.18	13.94	−1.40
NO_2	−0.28	−0.85	0.71	0.78	7.36	−2.52
NMe_2	0.18	−0.30	−0.15	−0.83	15.55	
$^+NMe_3$	−5.96	−5.26	0.88	0.82		−2.84
NHMe	−0.47	−0.67	−0.30	−0.84	10.33	
NH_2	−1.23	−1.19	−0.16	−0.66	5.42	−0.61
$NHCOCH_3$	−0.97		0.21	0.00	14.93	
O^-	−3.87		−0.47	−0.81		
OH	−0.67	−1.12	0.12	−0.37	2.85	−1.12
OCH_3	−0.02		0.12	−0.27	7.87	−0.55
OEt	0.38	0.03	0.10	−0.24	12.47	
CN	−0.57	−0.84	0.56	0.66	6.33	−0.51
CHO	−0.65		0.35	0.42	6.88	
CO_2H	−0.32		0.37	0.45	6.93	
CF_3	0.88		0.43	0.54	5.02	−2.40
CH_3	0.56	0.50	−0.07	−0.17	5.65	−1.24
CH_2OH	−1.03		0.00	0.00	7.19	−1.21
$COCH_3$	−0.55		0.38	0.50	11.18	
C_6H_5	1.96	2.15	0.06	−0.01	25.36	−3.79
SO_2CH_3	−1.63		0.60	0.72	13,49	

[a] The value of MR is used multiplied by 0.1.

It is advisable for the reader to know in a qualitative way the most important electron-releasing and -withdrawing groups ordered according to their relative electronic strength.

(a) Electron-releasing groups:
- *strong*: NH_2, NHR, NR_2, O- (+R);
- *intermediate*: OH, OR (+R, -I);
- *weak*: Ph (+R), Me, Et (+I), NHCOR (+R, -I).

(b) Electron-withdrawing groups:
- *strong*: NO_2 (-R, -I), NR_3^+ (-I);
- *intermediate*: CN, CHO, COR, CO_2H (-R, -I);
- *weak*: F, Cl, Br, I (+R, -I).

6.3 Craig plot

Although there are tables with the values of σ and π for a large set of substituents, it is often easier to visualize them using the Craig plot (Fig. 6.7).

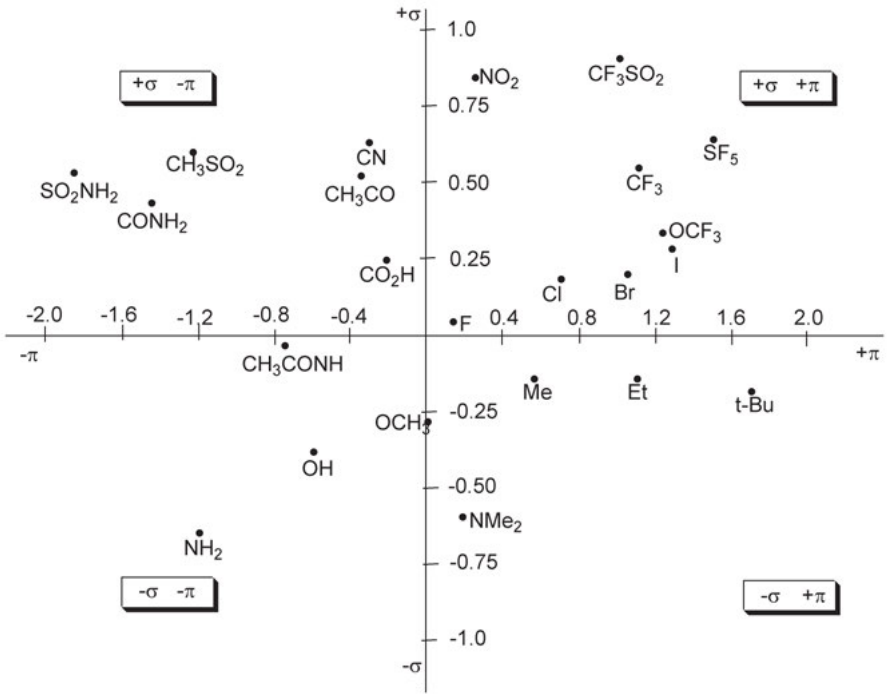


Fig. 6.7: Craig plot with the σ and π values of several substituents.

It is possible to see at a glance which substituents have positive values of π- and σ-parameters, which have negative values and which have one positive and the other negative values. It is easy to see which substituents have similar values of π; for ex-

ample, the ethyl, bromo, trifluoromethyl, and trifluoromethylsulfonyl groups are approximately in the same vertical of the representation. Therefore, these groups could be interchanged in drugs in which the main factor affecting biological activity is π. Similarly, groups in the same horizontal are isoelectronic or have similar values of σ (e.g. CO_2H, Cl, Br, I).

6.4 Hansch equation

The Hansch analysis correlates biological activity with physicochemical properties by linear regression analysis, multiple linear regression or nonlinear regression. Since practically all the parameters used in the Hansch analysis are linear values related to free energy (for example, derived from velocity or equilibrium constants), the terms "linear approach related to free energy" or "extratermodynamic approach" are used, as synonyms of Hansch's analysis. In its simplest version, the general form of the Hansch equation is the following eq. (6.13):

$$\log(1/C) = k_1\sigma - k_1(\log P)^2 + k_2 \log P + k_4 E_S + k_5. \tag{6.13}$$

The accuracy of the adjustment of the equation to the experimental data can be estimated through the correlation coefficient (r^2). The fit is perfect when $r^2 = 1$. It is assumed that the equation is correct when $r = 0.9$ (or the same, $r^2 = 0.81$). The parameters selected for the "best equation" must be independent (i.e. the coefficient r should not be greater than 0.6-0.7; exceptions to this rule are combinations of linear and quadratic terms, such as log P and $(\log P)^2$ that are normally highly correlated, with values of $r > 0.9$). Perhaps the most important consequence of Hansch's equations is the subsequent interpretation in physical-chemical terms of biological activity, which entails a better understanding of what happens at the molecular level.

With the equation obtained, in addition to a better understanding of the interactions, it will be possible *to predict* the structure of new compounds from the same family for which an optimum activity would be expected.

The number of compounds required to define a Hansch equation is a function of the number of variables that are to be introduced in the equation. As a general rule, it is accepted that for each independent variable, at least 5 compounds are necessary.

6.5 3D QSAR model

In recent years a method known as 3D QSAR has been developed, according to which the three-dimensional properties of the molecules as a whole are considered rather than considering individual substituents. The philosophy of the 3D QSAR model lies around the assumption that the most important characteristics of molecules are their overall size and shape, in addition to their electronic properties.

The best-known model is CoMFA (acronym of **co**mparative **m**olecular **f**ield **a**nalysis) which assumes that drug-receptor interactions are noncovalent, and that changes in biological activity correlate with changes in the steric and/or the electrostatic fields of drugs.

Networks or grids are increasingly used to measure the molecular properties. There are several molecular properties that can be measured as fields. A field can be defined as the influence that a given property exerts on the space surrounding the molecule. Consider a magnet as an example: it creates a magnetic field around it, which is stronger in the area of space closest to it. The most frequently measured molecular fields are steric and electrostatic. They can be measured by placing the molecule in a three-dimensional network. Next, a probe atom such as a proton or an sp^3 hybridized carbocation is placed at each point in the network and a computer programme calculates the steric and electrostatic interactions between the probe atom and the molecule. With respect to the steric field, it will increase as the probe approaches the molecule, while in relation to the electrostatic field, there will be an attraction between the positively-charged probe and the electronically-rich zones of the molecule, and a repulsion interaction between the probe and electronically-deficient zones of the molecule. The points of the network having the same steric energy value are connected by contour surfaces, which define a steric field. A similar process will be carried out to measure electrostatic interactions. It is also possible to measure the hydrophobic field using water molecules as a probe.

A frequent problem in drug design is to decide on what conformation the drug molecule is when it links to the binding site of the biological target (active conformation). This is particularly true for flexible molecules that can adopt a large number of conformations. One might think that the most stable conformation is the active one. However, it may be that the less stable conformation is the active one: binding interactions with the target can result in an energy gain that compensates for the energy required to adopt that conformation. The simplest way to identify an active conformation is by studying the x-ray crystal structure of the complex between the protein and the ligand (drug). The structure of the ligand itself can be obtained from the Cambridge Structural Database (CSD), while that of the protein-ligand complexes can be obtained from the Protein Data Bank (PDB). The protein-ligand complex can be downloaded and studied through molecular modelling programmes, whereby the ligand conformation can be identified. However, not all proteins can easily crystalize, and so other methods that are beyond the scope of this text must be used.

It is essential in the 3D QSAR study that the molecules are all in their active conformation, and that they are placed in the network in exactly the same way. In other words, they have to be correctly aligned, thereby identifying the pharmacophore.

6.6 CoMFA advantages over traditional QSAR

Some of the problems associated with traditional QSAR are as follows.

(a) Only molecules of similar structure can be studied.
(b) The validity of numerical descriptors may be in question. These descriptors are obtained by measuring reaction rates and equilibrium constants of model reactions, and their values are tabulated in the specific scientific literature. However, the separation of one property from another is not always possible during experimental measurements. For example, the steric parameter of Taft cannot be considered purely to be a steric factor, because the reaction rates measured and used to define it are also affected by electronic factors. On the other hand, the *n*-octanol/water partition coefficients used for the calculation of log *P* are affected by the donor and acceptor nature of the hydrogen bonds of the molecules.
(c) Descriptors of unusual substituents may not be known.
(d) It is necessary to synthesize a set of molecules in which the substituents are varied to study a particular property (e.g. hydrophobicity), and these syntheses may be difficult.

These problems can be avoided with CoMFA, which has the following advantages.

(a) Favorable and unfavorable interactions are represented graphically by 3D contour surfaces around the representative molecule. A graphical representation like this is easier to visualize than a mathematical equation.
(b) The properties of molecules are calculated by a computer program. There is no dependence on experimental or tabulated values. There is no need to restrict the study to molecules of similar structure. Molecules can be studied by CoMFA as long as they share the same pharmacophore and interact in the same way with the biological target.
(c) Graphical representations of favourable and unfavourable interactions allow pharmaceutical chemists to design new structures. For example, if the boundary surface exhibits a favorable steric effect at a particular site, this may imply that the binding site of the biological target has an additional space that allows the drug to be extended to improve the receptor-drug interaction.
(d) The 3D QSAR approach can be used without knowledge of the biological target.

6.7 Potential problems of CoMFA

Some of the problems associated with CoMFA are as follows.

(a) It is very important to know the active conformation of each of the studied molecules. Identification of the active conformation is easy on rigid structures such as steroids, but is more difficult on flexible molecules in which various rotations of the single bonds are possible. Therefore, it would be advisable to have a

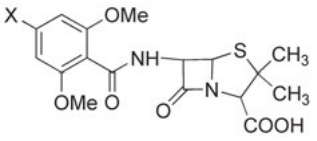
conformationally biologically active restricted analogue that can act as a guide for the active conformation. The most flexible molecules could then be constructed in the computer, with the conformation resembling that of the rigid analogue. This may be very useful in proposing the most likely active conformations of the ligands, if the structure of the binding site of the biological target are known.

(b) 3D QSAR provides a summary of how structural changes in drugs affect biological activity, but it is very dangerous to attempt to go further. For example, a 3D QSAR model may indicate that increasing the size of the molecule in a given location increases the activity. It might be suggested that an accessible hydrophobic pocket exists that allows extra bonding interactions. On the other hand, it is possible that the additional steric increase causes the molecule to bind with a different orientation with respect to the other molecules included in the study, and that this can be the cause of increased activity.

6.8 Exercises

1. Knowing that the $\log P_{\text{benzene}} = 2.13$, determine the $\log P$ values of the following compounds (the experimentally observed values are indicated in parentheses):
   (a) *m*-Xylene (3.20)
   (b) Mesitylene (1,3,5-trimethylbenzene) (3.43)
   (c) Hexamethylbenzene (2.33)
   (d) 1,3-Dinitrobenzene (1.49)
   (e) 2,4-Dihydroxybenzoic acid (1.44)
   Notice the increasing difference between the calculated and observed values in the cases (a)–(c), and try to give an explanation. Do you find any justification for the deviation between the experimental and the calculated values?

2. A correlation between the bacteriostatic activity of methicillin-related penicillins and the π and σ values can be established for the X substituents on the aromatic nucleus:



X = H: Methycilin

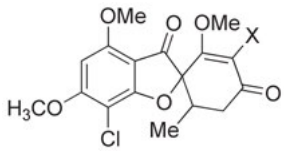
The equation obtained for the bacteriostatic activity is

$$\log(1/C) = -0.245\pi + 1.720\sigma + 1.776 \quad (n = 10, r = 0.929).$$

   (a) Comment on these two equations.
   (b) Propose different substituents to increase or decrease biological activity.

3. When studying the influence of substituent X on the activity of griseofulvin, the following QSAR relation was obtained:

$$\log(1/\text{MIC}) = 0.56 \log P + 2.19\sigma_X - 1.32 \quad n = 22 \quad r = 0.93.$$

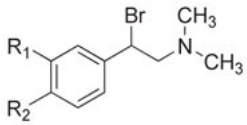


   (a) What kind of substituents will give rise to maximum activity?
   (b) Knowing that the antibiotic activity depends on an enone system that facilitates the nucleophilic attack to griseofulvin by the –SH groups, what relationship does it find between this mechanism and the previous equation?

   Propose the attack reaction of the nucleophile mentioned above.

4. The adrenergic blocking activity of β-halo-β-arylethylamines can be expressed by the following equation:

$$\log(1/\text{ED}_{50}) = 1.22\,\pi - 1.59\sigma + 7.0 \quad n = 35 \quad r = 0.92.$$



   The compounds exhibit hepatic toxicity through a DNA alkylation mechanism represented by the equation

$$\log(1/\text{ED}_{50}) = 1.15\,\pi - 1.5\sigma^{+} + 7.89 \quad n = 22 \quad r = 0.93.$$

   (a) Comment on these equations.
   (b) Propose a DNA alkylation mechanism for this type of compound.
   (c) Depending on the alkylation mechanism, explain why the parameter σ^{+} is used in the second equation.

5. The inhibitory activity of the monoamine oxidase produced by the benzylhydrazines R-C_6H_4-CH_2-NH-NH_2 in mice has been studied. For this, the necessary dose of drug before extracting their brain has been measured to produce a maximum response in the administration of L-DOPA to mice. The equation representing the inhibitory activity *in vivo* is

$$\log(1/\text{C}) = 0.304\,\pi - 0.183\pi^2 + 6.346 \quad n = 11 \quad r = 0.856.$$

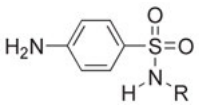
(a) How and why does the in vivo inhibitory activity depend on the π value of R?
(b) Of the following substituents, whose π value is given in parentheses, what seems to be more interesting to increase the in vivo response?

H (0.0); Cl (0.71); Br (0.86); Me (0.56); *iso*-Pr (1.53); phenyl (1.96)

6. The in vitro antibacterial activity of sulphonamides **6.3** can be described by the following two equations:

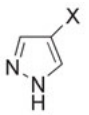
$$\log(1/C) = -0.693 pK_a + 6.405 \quad n = 25 \quad r = 0.962,$$
$$\log(1/C) = 1.128\sigma + 0.398 \quad n = 25 \quad r = 0.975.$$

(a) What is the relationship between the two equations?
(b) It has been suggested that the active species is ionized sulfonamide, according to these equations. Why?
(c) What substituents are most suitable for the antibacterial activity?
(d) If antibacterial activity is studied *in vivo*, a parabolic dependence of the activity in relation to pK_a is observed. How can this observation be explained?



6.3

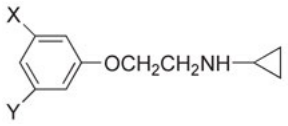
7. Pyrazoles **6.4** show inhibition of rat ADH (alcohol dehydrogenase hepatic), and may be utilized to prevent the conversion of methanol into formaldehyde and thus prevent methanol intoxication. The model relates the inhibition constant to the physico-chemical characteristics of the substituents X. Analyze the characteristics of the model and as an example, calculate the $\log 1/K_i$ for a derivative **6.4** in which R = Cl.



6.4 X = H, CN, NO_2, NH_2, OCH_3, OEt, CH_3...

$$\log 1/K_i = 1.22(\pm 0.16)\log P - 1.80(\pm 0.78)\sigma_m + 4.87(\pm 0.28)$$
$$n = 14, \quad r^2 = 0.970, \quad s = 0.316$$
$$c\log P_{pirazol} = 0.28$$

8. The following QSAR equation was obtained for the antidepressant activity in humans, from a family of MAO inhibitors (iMAO) that respond to the chemical structure:

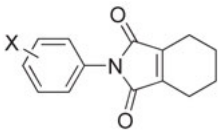


$$\log 1/C = 0.398\,\pi + 1.089\,\sigma + 1.03\,E_s + 4.541$$
$$n = 9,\ r = 0.955$$

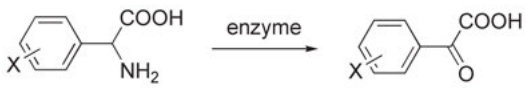
   (a) Indicate on which parameters the inhibitory activity depends.
   (b) Indicate the type of substituents that would be introduced in the aromatic ring to improve such an activity.
   (c) Show two examples of substituents that would improve the activity.

9. The following QSAR was obtained for activity of the pesticide indicated in the structure. Explain the meanings of each term, and identify the type of substitute that could improve the activity.

$$\log 1/C = +\,1.08\,\pi + 2.41\,\sigma + 5.25$$
$$n = 16,\ r = 0.84$$



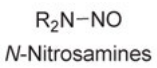
10. The following reaction quantitatively relates the activity of an enzyme extracted from a lamb kidney with the amino acid oxidase (MAO) activity, caused by phenylglycines with different substituents in *meta* and *para*.



$$\log 1/K_m = 0.3\,\pi + 0.6\,\sigma + 0.21\,E_s + 2.3$$
$$n = 5,\ r = 0.860$$

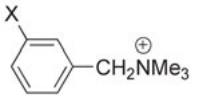
   (a) What parameters affect the enzyme affinity of the substrate?
   (b) How do these parameters have an influence, and what substituents should be introduced into the ring to increase the enzyme activity?

11. The following QSAR equation is related to the mutagenic activity of a series of nitrosamines. What kind of substituents will result in higher mutagenic activity?



$$\log 1/C = +0.92\,\pi + 2.08\,\sigma - 3.26$$
$$n = 12,\ r = 0.794$$

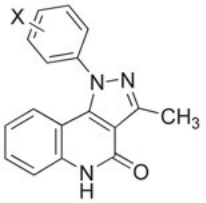
12. The muscarinic effects of a series of *m*-substituted benzyltrimethylammonium derivatives, expressed as BR (biological response), are indicated in the following equation:



$$BR = 1.30\,\pi - 0.41\,E_s + 5.86$$
$$n = 10,\ r = 0.90$$

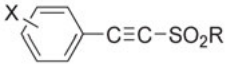
(a) What parameters depend on this response?
(b) What substituents chould be introduced to increase the activity?

13. Given the following QSAR equation, indicate the factors that would increase the biological activity in the represented structure, and propose substituents that would improve such an activity.



$$\log 1/IC_{50} = 0.481\,E_s + 0.606\,\pi + 4.81$$
$$n = 20,\ r = 0.93$$

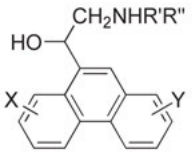
14. The antifungal activity against *Clanosporium Cucumerinum* from a series of aryletinylsulfones is expressed by the following equation:



$$pIC_{50} = 1.10\,\sigma + 0.84\,\pi + 2.10\,E_s$$
$$n = 25,\ r = 0.89$$

(a) What parameters does it depend on?
(b) List some substituents to improve the activity.

15. The antimalarial activity of a series of aminoalcohols derived from phenanthrene is reflected in the following QSAR equation. With examples indicate the substituents that will favor the biological activity.



$$\log 1/C = 0.27\,\pi_x + 0.40\,\pi_y + 0.65\,\sigma_x + 0.88\,\sigma_y + 2.34$$

$$n = 102,\ r = 0.913$$

7 Metabolic processes in drugs: other methodologies available for the discovery of new drugs

7.1 Goals

- To introduce the student into the concept of pharmacokinetics applied to the discovery of new drugs.
- To introduce the student to the concept of prodrug as one of the solutions available to reduce the toxicity of the drug.

7.2 Metabolism studies and their use in the discovery of new drugs

The action of drugs does not only depend on their capacity to develop a pharmacological response. It is also of great importance that they have pharmacokinetic properties which allow them to reach the required place for their action, and that their toxicity is minimal. Given the high degree of structural variability of drugs and the diversity of known metabolic reactions, it is necessary to establish relationships between their chemical structure and their pharmacokinetic properties: ADME (acronym for **a**bsorption, **d**istribution, **m**etabolization, and **e**xcretion).

The physico-chemical properties of a drug will determine its ability to cross biological membranes, to deposit in fatty tissues, to bind to serum proteins, or to bind to its specific receptors to exert its action, and finally to undergo metabolic transformation and elimination.

We will detail the two most important steps in the development of new drugs that are absorption and metabolism.

7.3 Absortion

In any of the routes of administration, except intravenous, the drug has to cross biological membranes to reach its place of action. Since this is a critical step in the action of a drug, it must be taken into account. For example: in the gastrointestinal system, pH values vary from 1–3 in the stomach (due to the secretion of hydrochloric acid) to a value of 8 in the small intestine (ileum) and in the ascending colon. Therefore, the absorption of a drug is not equally effective in the different parts of the gastrointestinal system.

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Neutral and lipid-soluble compounds are assured of their systemic action when administered orally, whereas the absorption of acids and bases depends on their dissociation constant (pK_a) and the pH of the medium, which are related according to the Henderson–Hasselbach equation:

$$pH = pK_a + \log [\text{basic form}]/[\text{acid form}]$$

E.g. Aspirin® (Fig. 7.1).

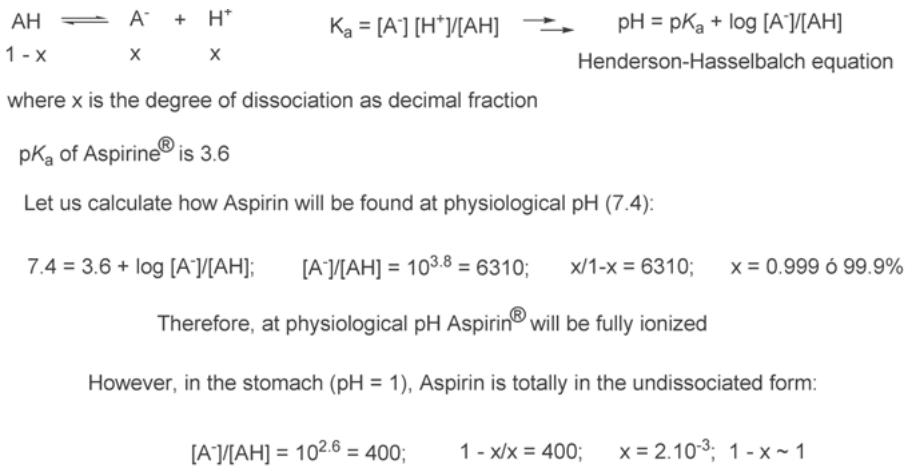


Fig. 7.1: Calculation of the percentage of ionization of Aspirin® as a function of the pH of the medium.

A weak acid such as Aspirin® with a pK_a of 3.6 is practically in a nonionized form under the acidic conditions of the stomach, and for this reason is rapidly absorbed. Once in the plasma (pH = 7.4), it ionizes almost completely and has no tendency to diffuse back into the stomach (Fig. 7.2).

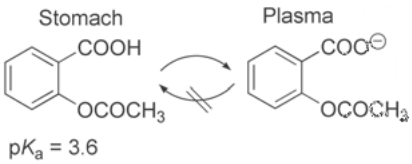


Fig. 7.2: Forms in which Aspirin® is present in the stomach and plasma.

One of the objectives of pharmaceutical chemistry is to try to predict if a substance can be active, and if it can become a good drug. Although, of course, this is only known by synthesizing and testing it, Lipinski's rules can help us in predicting oral absorption.

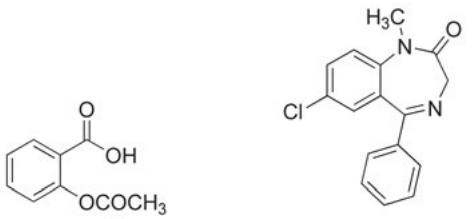
7.4 Lipinski's rules

Lipinski's rules emerged from a study of a wide-ranging oral drug group (WDI = Word Drug Index, more than 50,000 compounds) where its physicochemical properties were statistically correlated with its oral absorption profile, which in turn is related to its ability to cross membranes. It was observed that the drugs with the best oral absorption were those with a good balance between molecular weight (MW), lipid solubility and water solubility. These properties can be expressed quantitatively by means of 4 descriptors.

1. Solubility in lipids expressed by log *P*
   - Calculated log *P* (c log *P*) < 5 (Hansch)
   - Moriguchi log *P* (m log *P*) < 4.15
2. Molecular weight < 500
3. H-bond donor groups < 5
4. H-bond acceptor groups < 10

Lipinski's rules are currently considered to be a good method to predict which structures with a pharmacological action will have good oral absorption. They are also known as the "rule of 5", because the parameter cutoff values all contained 5s. In general, the more a compound is deviated from the Lipinski parameters, the lower the probability of its overcoming the more advanced stages of drug development (because it does not have a good oral absorption profile). Compounds that conform to these parameters are said to have drug properties. Despite the development of computational methods, none of these overcome these simple rules in the ease of handling, nor are they used so widely.

Exercise: Apply Lipinski's rules to the following drugs (Fig. 7.3):



Aspirin®

MW = 180 g/mol
mlog *P* = 1.70
H Acceptor groups = 4
H Donor groups = 1

Diazepam

MW = 284 g/mol
mlog *P* = 3.36
H Acceptor groups = 3
H Donor groups = 0

Fig. 7.3: Lipinski's rules applied to Aspirin® and diazepam.

7.5 Metabolism

We are now going to dedicate a broader section to the metabolism process, in which we will describe the metabolism of drugs from the chemical point of view, because we can design drugs whose metabolism is accelerated or reduced, but we have to know how they are metabolized. With the joint process of metabolism and elimination ends the action of drugs. Although metabolism is essentially a mechanism of detoxification, in some cases it produces the opposite, that is to say, toxicity of a drug, since toxic metabolites can be formed.

On the other hand, many compounds called prodrugs are inactive and are activated as drugs by metabolic processes, or it may happen that the metabolism causes changes in the pharmacological concentration of a compound. Therefore, the knowledge and prediction of metabolism is essential in the development of drugs.

Biotransformation of drugs can be classified into two broad groups.

(a) Phase I reactions directed to the formation of more water-soluble metabolites by unmasking or introduction of polar groups, such as COOH, OH, and NH_2.
Phase I reactions are catabolic (oxidation, reduction, hydrolysis) and are usually products with a higher chemical reactivity and paradoxically may be more toxic or carcinogenic than before. Catabolic reactions are those where compounds are degraded to smaller molecules. e.g. glycolysis is the catabolic pathway of the carbohydrate degradation in the body. On the other hand, anabolic reactions are those where new molecules are synthesized from precursors. For example, protein synthesis is an anabolic process, because proteins are generated from amino acids (precursors).

(b) Phase II reactions complete the above with the formation of conjugates with sulfuric acid, glucuronic acid or amino acids with existing polar groups or created in phase I, thus forming more water soluble species that are eliminated by the renal route. Phase II reactions are anabolic and often give inactive products (with some exceptions such as minoxidil sulfate).
Reaction of Phases I and II occur mostly in the liver.

7.5.1 Phase I reactions

7.5.1.1 Oxidation reactions

The main catalysts of the oxidation reactions are the cytochromes P-450, which are hemoproteins. The oxidation process of a RH drug can be schematized as follows (Fig. 7.4):

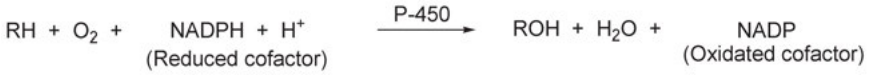


Fig. 7.4: Oxidation of a RH drug by P-450.

Nicotinamide adenine dinucleotide in its reduced form (NADPH) provides the system witone proton and two electrons, transforming it into the pyridinium derivative $NADP^+$ (Fig. 7.5).

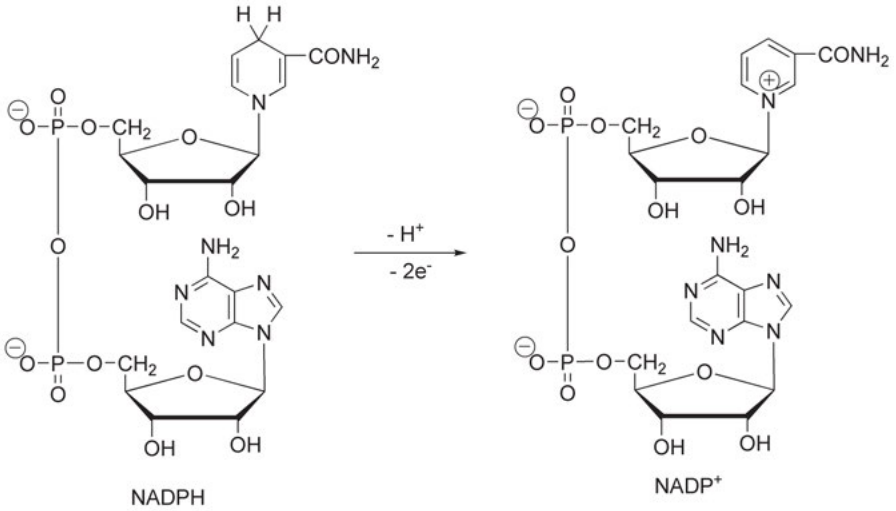
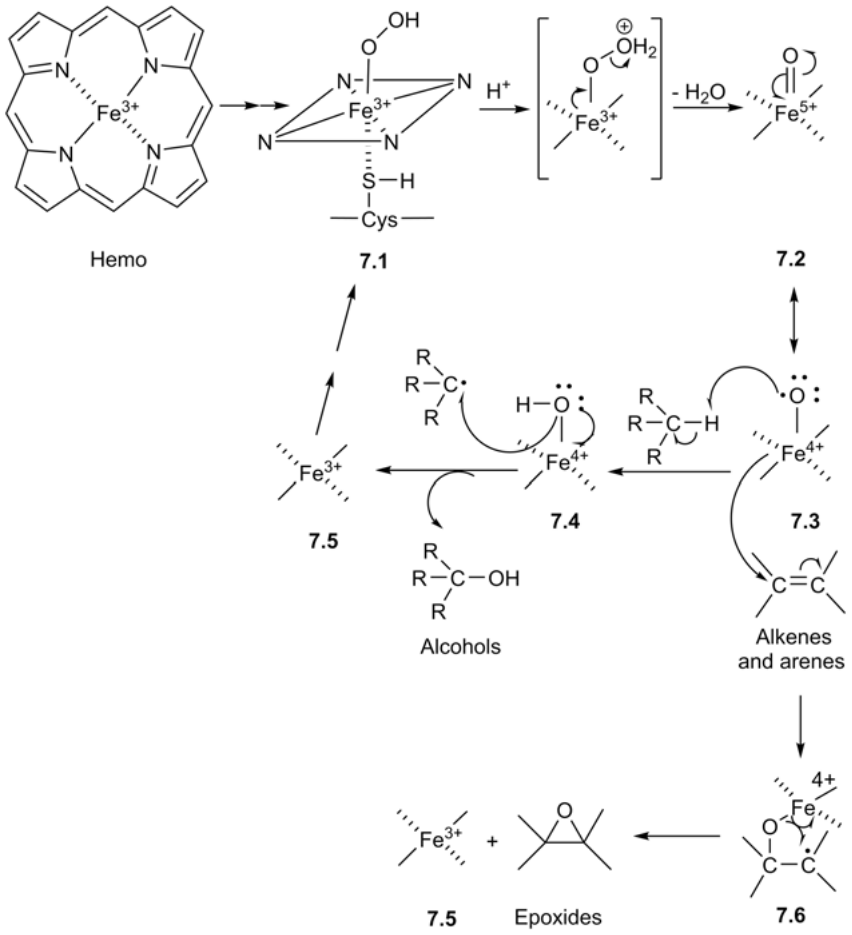


Fig. 7.5: Coupled transformation of the NADPH cofactor in the oxidation reactions catalyzed by cytochromes P-450.

These enzymes have the heme group as cofactor, a porphyrin containing Fe^{3+}, which in its reactive form of Fe^{5+} or Fe^{4+}, performs essentially hydroxylation and epoxidation reactions. The Fe^{3+} hydroperoxide is species **7.1**, where N represents the four pyrrolic nitrogen atoms, and the fifth ligand is a cysteine residue of the enzyme. This species is converted by protonation and dehydration into the Fe^{5+} (**7.2**) species, which is in resonance with Fe^{4+} (**7.3**). This active species breaks a C-H bond homolytically to give an alkyl radical and species **7.4** which, by radical coupling originate alcohols and regenerate the heme group. On the other hand, the alkenes and arenes undergo the addition of radical **7** and later on, they become epoxides (Scheme 7.1).



Scheme 7.1: Mechanisms of oxidation reactions of alkanes, alkenes, and arenes catalyzed by cytochromes P-450.

The ease of oxidation is parallel to that which would be expected by the action of the chemical reagents. Thus the aryl, benzyl, aromatic, alkyl, oxidation of amines and *O*-, *S*- and *N*-dealkylations positions are oxidized:

(1) The α positions of the carbonyl undergo oxidation.
(2) The aromatic oxidations take place in the activated position of the rings against the electrophilic attack. The presence of electron-donor groups favours it, while a ring with electron-withdrawing groups is deactivated and its oxidation is difficult. When there is more than one ring, oxidation takes place preferably over the more activated one and in *para* position (because it is the most activated locus and with less steric hindrance).

Example: Diazepam (Fig. 7.6).

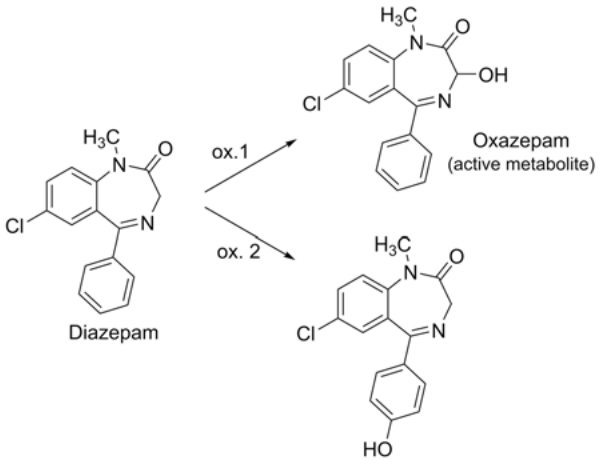


Fig. 7.6: Metabolism of diazepam.

Example: Phenacetin (Fig. 7.7).

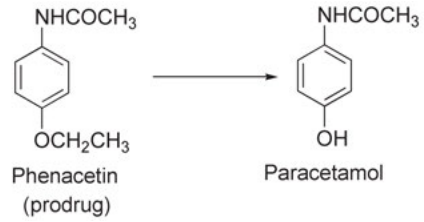
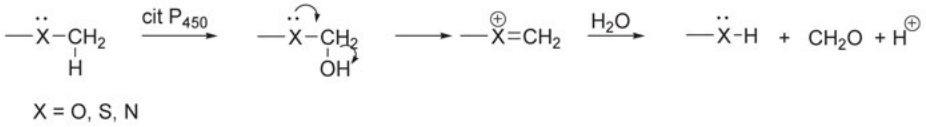


Fig. 7.7: Metabolism of phenacetin.

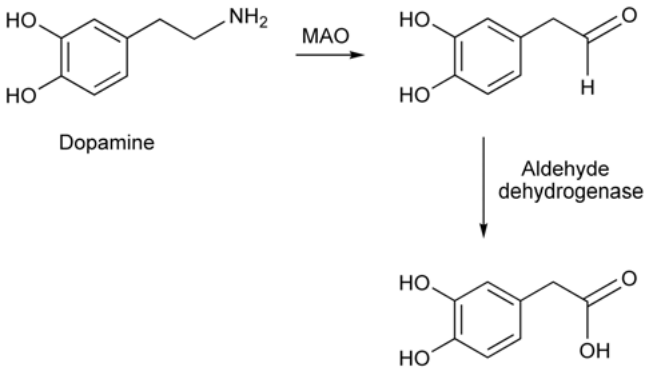
The O-, S-, and N-dealkylations are hydroxylation reactions occurring on the α-carbon of the heteroatom and are followed by hydrolysis.

The proposed mechanism (Scheme 7.2) is:



Scheme 7.2: Metabolism of O-, S- and N-dealkylations.

There are other metabolic oxidation processes, such as the oxidative deamination of dopamine, catalyzed by enzymatic systems other than cytochromes P450 (Scheme 7.3):



Scheme 7.3: Oxidative deamination of dopamine.

The most frequent reaction of the primary amines is the oxidative deamination by the action of the monoaminoxidase (MAO) in the unsubstituted amines in α.

7.5.1.2 Reduction reactions

Although the main metabolic pathway of drugs in mammals is oxidation, certain compounds whose functional groups are the azo, nitro, and carbonyl group tend to be biotransformed by reduction to other functional groups such as amino and hydroxyl, directly susceptible to conjugation.

Example: Methadone (Fig. 7.8).

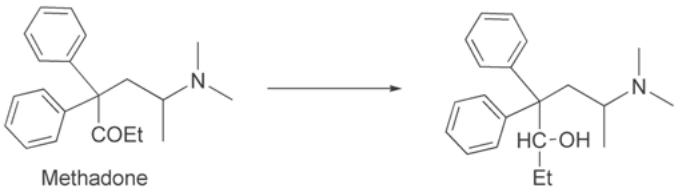
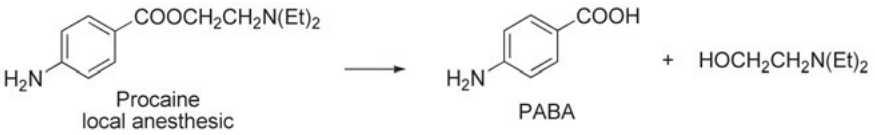


Fig. 7.8: Reductive metabolism of methadone.

7.5.1.3 Hydrolysis reactions

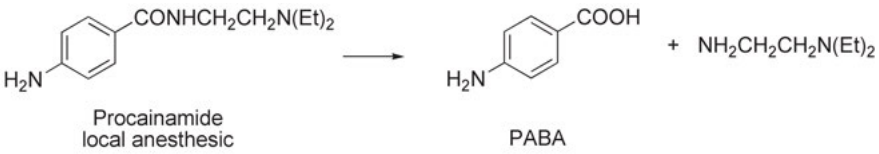
It is the immediate form of metabolism of esters and amides and takes place by the action of esterases and amidases that are very widespread in the organism.

Example: Procaine (Scheme 7.4).



Scheme 7.4: Metabolic hydrolysis of procaine.

The amides hydrolyze more slowly than the esters; e.g., procainamide is more stable than procaine against hydrolysis (longer half-life) (Scheme 7.5).

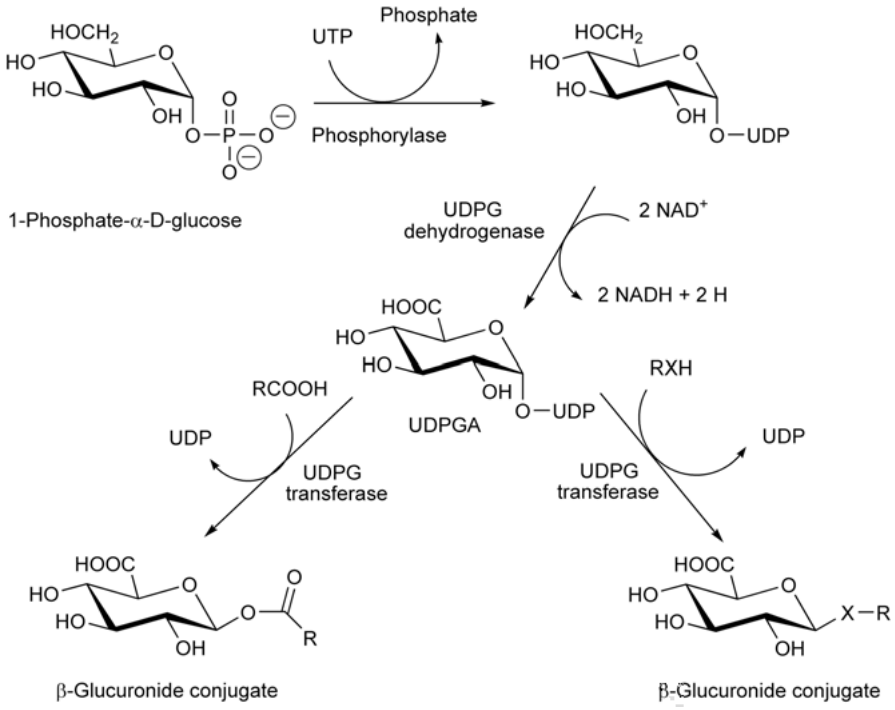


Scheme 7.5: Hydrolysis of procainamide.

7.5.2 Phase II reactions

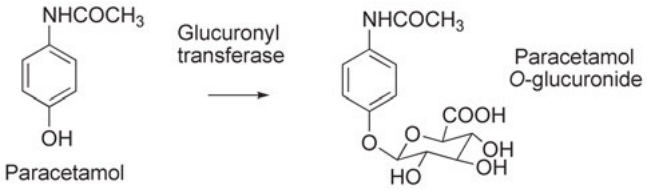
7.5.2.1 Conjugation reactions

These take place by the reaction of existing polar groups in a drug, and H_2SO_4, glucuronic acid, glutathione, sugars, or amino acids such as glycine, and also acetylation and methylation giving directly excretable compounds. Conjugation with glucuronic acid is probably the most important of all the Phase II reactions. This is probably because there is a good supply of glucuronic acid in the body. Numerous alcohols, phenols, amines, thiols, and some carboxylic acids are metabolized by this route. The xenobiotic reacts with the activated form of glucuronic acid, glucuronic acid uridine diphosphate (UDPGA), to form a glucuronide conjugate very soluble in water (Scheme 7.6). The reaction is catalyzed by uridine diphosphate glucuronyl transferases (UDPG transferases).



Scheme 7.6: Mechanism of formation of glucuronide conjugates. UTP is uridine triphosphate and X is O (alcohols and phenols), S (thiols) or NH (amines).

Example: Scheme 7.7.

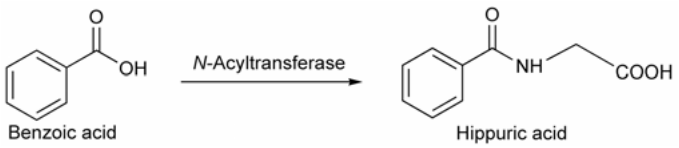


Scheme 7.7: Paracetamol conjugated with glucuronic acid.

The reaction takes place on the anomeric carbon of the glucuronic acid giving rise to acetals.

Certain amino acids participate in the reaction of phase II metabolites from aromatic carboxylic acids. Glycine is the amino acid that is commonly involved in these conjugations.

Example: Scheme 7.8.

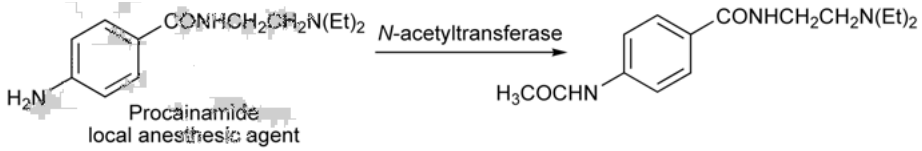


Scheme 7.8: Metabolization of benzoic acid.

Benzoic acid is introduced into the body through diet, as it is widely used as a preservative (both in its acid form and as a sodium, potassium, or calcium salt), although is not a drug.

Acetylation is the main route of metabolization for amino groups and is mediated by acetyl-CoA.

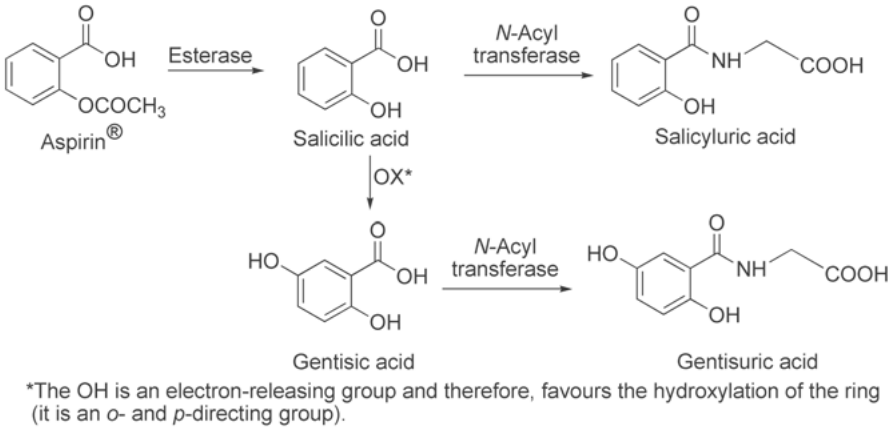
Example: Scheme 7.9.



Scheme 7.9: Acetylation of procainamide.

The half-life of *N*-acetylprocainamide is twice than that of procainamide and has no undesirable side effects.

Example: Metabolism of Aspirin® (Scheme 7.10).



Scheme 7.10: Metabolism of Aspirin®.

7.5.2.2 Conjugation reactions with glutathione

Glutathione is a tripeptide containing a thiol group of great importance in the detoxification of drugs and xenobiotics. In the body an equilibrium exists between the reduced form (GSH) and the oxidized form (GS-GS). Conjugation reactions of GSH are catalyzed by glutathione transferases. The conjugative reactivity of GSH is due to its thiol group (pK_a 9.0), which makes it a very effective nucleophile. The nucleophilic character is enhanced by deprotonation to a thiolate form. Once formed, the GSH conjugates can be excreted as such, but usually undergo further biotransformations. The cleavage of the glutamyl and cysteinyl moieties by means of peptidases leaves a cysteine conjugate, which may be *N*-acetylated to give rise to an *N*-acetylcysteine conjugate. The latter conjugates are known as mercapturic acids (Fig. 7.9).

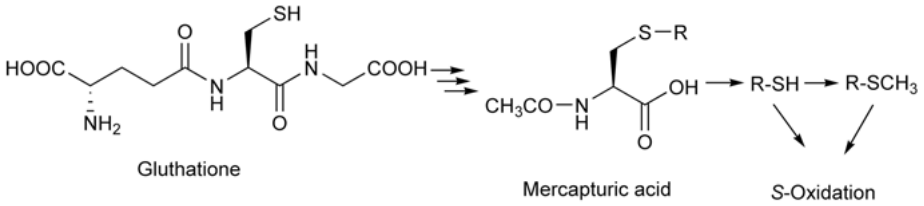


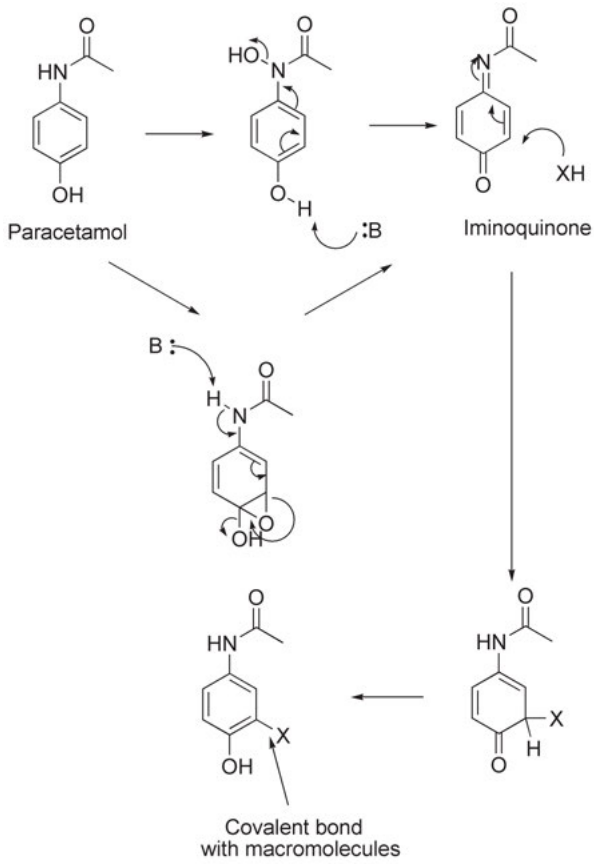
Fig. 7.9: Glutathione breakdown.

GSH is added to α,β-unsaturated carbonyl compounds, a typical case in which the xenobiotic substrate is the toxic compound acrolein. The attack occurs on the activated CH_2 group. Quinones (*ortho*- and *para*-) and iminoquinones are strongly structurally related to α,β-unsaturated carbonyl compounds (Scheme 7.11).

Many *N*-hydroxylated products can be chemically unstable and dehydrated, producing electrophilic species of the imine or iminoquinone type, which may be toxic. The iminoquinone may also be produced through epoxide type intermediates. Scheme 7.11 shows the transformation of paracetamol into an iminoquinone through a previous *N*-oxidation reaction. In Scheme 7.11 XH represents glutathione or a nucleophile present in endogenous macromolecules.

Large doses of acetaminophen cause liver and kidney damage in humans (the maximum recommended dose for an adult is 3–4 g per day at most). In therapeutic doses, acetaminophen is not very toxic, but in high doses it causes hepatic necrosis and renal lesions associated with a decrease in the glutathione reserves.

The treatment preferred for an overdose of paracetamol is the administration (usually in atomized form) of *N*-acetyl-L-cysteine, which is processed bythe cells to L-cysteine, and used in de novo synthesis of glutathione.



Scheme 7.11: Formation of iminoquinones (possible cytotoxic agents) in the oxidative metabolism of paracetamol.

7.6 Prodrug concept

Prodrugs are inactive compounds which give rise to a metabolite responsible for pharmacological activity. The design of prodrugs is usually carried out with the purpose of modifying some pharmacokinetic or galenic characteristics of the drug in order to improve its therapeutic application. Here are some of the most frequent applications.

7.6.1 Improvements in the galenic characteristics

Sometimes prodrugs are used due to issues of a galenic nature, such as increasing water solubility to prepare dosage forms with water. Thus, for example, prednisolone is a steroidal antiinflammatory agent poorly soluble in water and therefore not admin-

istrable parenterally; its conversion into the corresponding hemisuccinate results in a water-soluble derivative, which can revert to the active drug by hydrolysis by the action of a plasma esterase (Fig. 7.10).

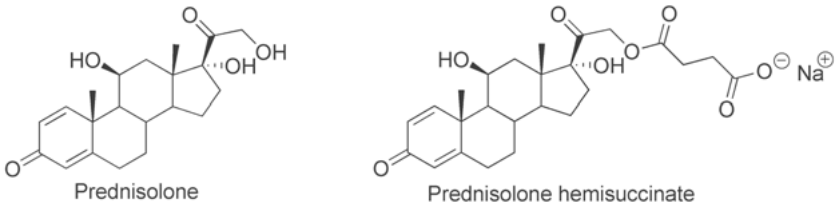


Fig. 7.10: Prednisolone hemisuccinate is a prodrug of prednisolone.

At other times, they are intended to improve the organoleptic characteristics in the pharmaceutical formulations. For example, chloramphenicol is an antibiotic of an intensely bitter taste that can be incorporated into syrups in the form of the corresponding tasteless palmitate (Fig. 7.11).

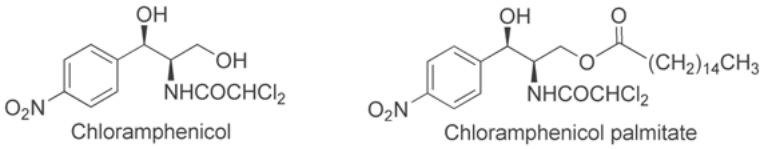


Fig. 7.11: Tasteless chloramphenicol palmitate.

7.6.2 Pharmacokinetic improvements

These can affect the release of the drug. For example in hormones such as testosterone (an androgenic and anabolic hormone), a slow and constant release can be achieved through palmitate. In this way the resulting prodrug is suitable for intramuscular administration at relatively high doses, accumulating in fatty tissues from which it will slowly be released by hydrolysis. This is the basis of the so-called "depot" action, which represents an important improvement both in the drug dosage regimens and in the resulting plasma levels (Fig. 7.12). Thus, very wide administrations will be possible that will allow the attainment of plasma levels of the hormone similar to their physiological levels.

Absorption may also be favourably modified by the use of prodrugs. This is the case of ampicillin, whose oral absorption is scarce due to its amphoteric character (it has -NH_2 and -COOH groups, which ionize to -NH_3^+ and -COO^- and is not well absorbed) (Fig. 7.13). Pivampicillin, a prodrug of ampicillin, is better absorbed than its parent drug.

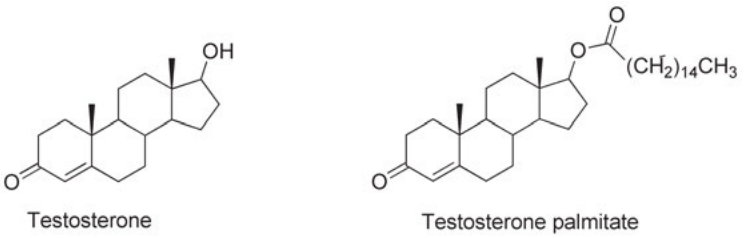


Fig. 7.12: Testosterone prodrug.

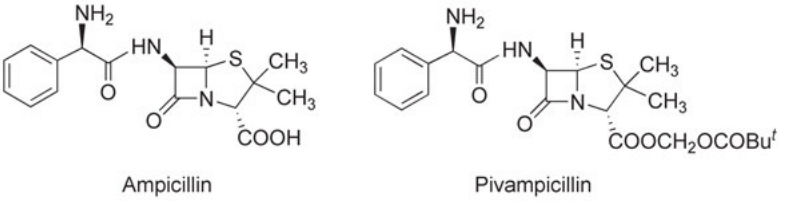
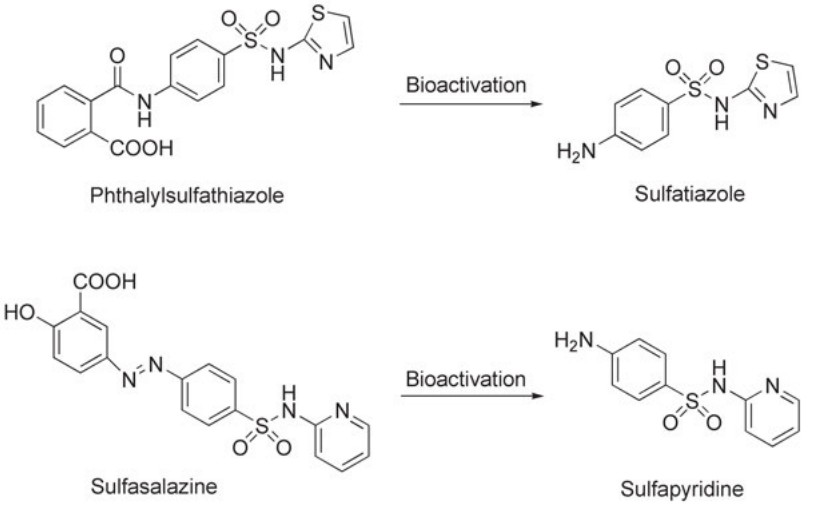


Fig. 7.13: Pivampicillin, prodrug of ampicillin.

The use of prodrugs may also allow modification of the distribution. An example of this is found in antibacterial sulfonamides. These compounds have a polar group which prevents their intestinal absorption. The metabolic elimination of this group by the intestinal bacterial flora leads to the active sulfonamide. As the release takes place in the final part of the gastrointestinal tract, its use is limited to the treatment



Scheme 7.12: Bioactivation of phthalylsulfathiazole and sulfasalazine.

of localized infections in this area. Phthalylsulfathiazole and sulfasalazine are representative examples of two of the most common strategies used in the design of these compounds. The former is considered to be a sulfathiazole protransporter in which the phthalyl group behaves as a labile modulating group, since it requires a hydrolytic process to provide the active species. On the other hand, sulfasalazine is an example of a bioprecursor prodrug, since it requires a nonhydrolytic activation process such as the reduction of the azo group (Scheme 7.12).

7.7 Modulation of drug metabolism

The metabolic processes causing toxicity are often related to the oxidative reactions of phase I, in which are generated high reactivity intermediates such as epoxides or free radicals, which interact easily with biomolecules inactivating them. To avoid this problem, different strategies can be adopted as the following:

(a) Completely suppress metabolic processes by administering drugs that are easily eliminated or that are resistant to these processes.
(b) Focus metabolic reactions on parts of the structure that do not give rise to toxic compounds or facilitate other non-oxidative metabolic processes.

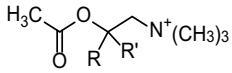
7.8 Suppression of the metabolic processes

This strategy consists of the design of drugs that are stable against metabolic reactions. These types of substances are called hard drugs. They are very lipophilic compounds and tend to accumulate in the fatty tissues, producing long-term lesions. In addition, complete suppression of a drug metabolism is impossible in practice, because even if only a small percentage of metabolic reactions occur, these could produce toxic compounds. However, the principles on which hard drugs are based have served to prevent the first-pass effect of drug degradation in the liver before reaching the general circulation, as well as to prolong the action of drugs whose degradation is much faster than desirable.

One way to hinder the metabolism is to protect the group vulnerable to reaction through electronic or steric effects. For example, the hydroxylation of carbon directly attached to the nitrogen in the first *N*-dealkylation step of amines can be blocked by the presence of a bulky nitrogen-bonded group, which hinders the access of the enzyme. Hydroxylation of aromatic rings can also be blocked by the introduction of steric hindrance as well as by the presence of electron-withdrawing groups on the aromatic ring. A more robust group to this reactionmay be substituted in order to avoid the hydrolysis of an ester group, such as an amide or by the introduction of a bulky group close to the position of the ester.

An example of such modifications is acetylcholine derivatives (Table 7.1) designed to extend the half-life of this neurotransmitter, the ester linkage which is rapidly hydrolyzed by plasma esterases.

Table 7.1: Design of acetylcholine analogues.



R	R′	Hydrolysis velocity
H	H	500 (acetylcholine)
CH_3	H	15
CH_3	CH_3	0

7.9 Promotion of nonoxidative metabolism

Drugs that are metabolized through a route that does not contain oxidative reactions are called soft drugs, designed to be inactivated in a controlled and predictable way. A soft drug can be defined as a biologically active compound, which is characterized by having a predictable and controllable *in vivo* destruction process (metabolism), preferably by means of a single hydrolytic process, to produce nontoxic metabolites, after having carried out its therapeutic role.

The easiest way to access this type of compounds is to incorporate groups vulnerable to hydrolysis or other nonoxidative reactions. One example is the muscle-relaxant decamethonium in which the substitution of two CH_2-CH_2 groups by two ester groups facilitates the hydrolysis reactions and avoids the toxicity accumulation problems of decamethonium (Fig. 7.14).

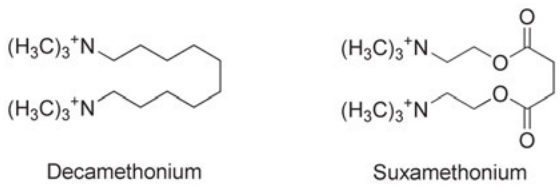


Fig. 7.14: Hard (decamethonium) and soft (suxamethonium) drugs.

The concept of soft drug should not be confused with that of prodrug: while a prodrug is an inactive derivative which is activated *in vivo* in a predictable active drug manner, a soft drug is an active species, but designed in such a way that it will undergo a predictable transformation or metabolism to an inactive metabolite. Accordingly,

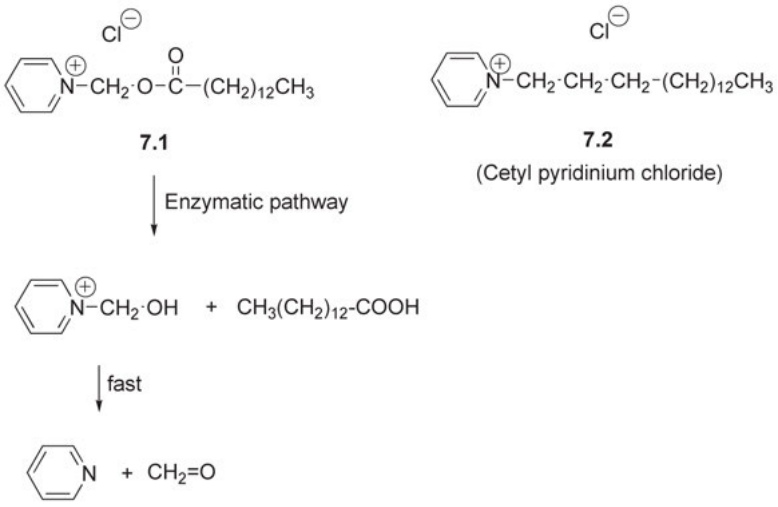
the common feature of prodrugs and soft drugs is that an in vivo transformation is involved in either activation (prodrug) or inactivation (soft drug). According to both definitions, the two concepts are opposed to each other.

The concept of soft drug can be very useful in the design of drugs with a better therapeutic index. The fundamental goal of drug design is not only the search for molecules with a maximum biological activity. It is important to bear in mind that within a series of compounds, the optimum is not necessarily the one with the greatest activity, but the one with the highest therapeutic index. This parameter is a quantitative measure of the activity/toxicity ratio. For example, if the activity is quantified by means of the effective dose 50 (ED_{50}) and the toxicity as the lethal dose 50 (LD_{50}), since the values of ED_{50} and LD_{50} are in an inverse relationship with activity and toxicity, respectively, the therapeutic index (TI) is expressed in accordance with eq. (7.1):

$$\text{TI} = \text{Activity/Toxicity} = LD_{50}/ED_{50}. \tag{7.1}$$

The optimization of a prototype hit involves attempting to achieve the maximum TI, which can be achieved by lowering the denominator of the LD_{50}/ED_{50} fraction by increasing the activity, or by increasing the numerator by decreasing the toxicity.

The soft drug **7.1** is an isosteric analogue of the antibacterial agent cetylpyridinium chloride **7.2**. Both compounds have the same length of the hydrophobic chain and have remarkable antimicrobial properties. This is due to the fact that **7.1** can undergo an easy hydrolytic deactivation, thereby destroying the positive charge of the pyridinium ring (Scheme 7.13).

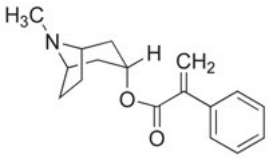


Scheme 7.13: Soft analogue of cetylpyridinium chloride and its metabolic transformation.

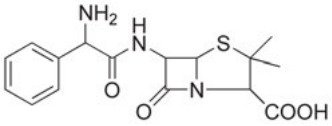
7.10 Exercises

1. Propose reasonable Phase I metabolic reactions that may occur in the following drugs:

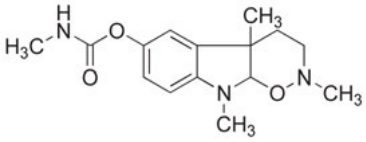
(a) Apoatropine



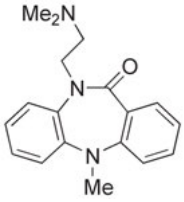
(b) Ampicillin



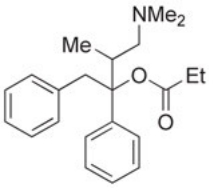
(c) Eseridine



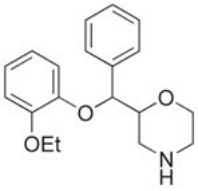
(d) Dibenzepine



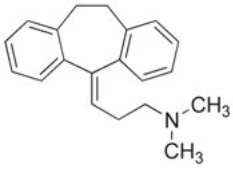
(e) Propoxyphene



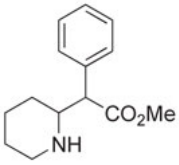
(f) Reboxetine



(g) Amitriptyline

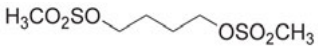


(h) Methylphenidate

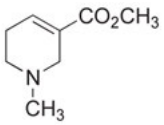


2. Explain how the following metabolic transformations occur, detailing the steps:
   (a) Methylphenobarbital [1-methyl-5-ethyl-5-phenylbarbituric acid] into 5-ethyl-5-(4-hydroxyphenyl)barbituric acid.
   (b) 1-(*p*-Tolyl)-*N*-methyl-2-propanamine into [4-(2-aminopropyl)phenyl]methanol
   (c) Adrenaline [1-(3,4-dihydroxyphenyl)-2-methylaminoethanol] into 1-(3,4-dihydroxyphenyl)-2-aminoethanol, and this into 2-(3-methoxy-4-hydroxyphenyl)-2-hydroxyacetic acid.
   (d) Indomethacin [2-(2-methyl-5-methoxy-1-(*p*-chlorobenzoyl)-3-indolyl)acetic acid] into the 2-(2-methyl-5-hydroxy-3-indolyl)acetic acid 5-glucuronide.

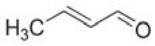
3. Tripeptide glutathione (γ-glutamyl-cysteinyl-glycine) is widely distributed in mammalian tissues. One of its physiological functions is to react with all kinds of electrophilic species, thus avoiding the toxicity that would derive from the reaction of these with biomolecules.
   (a) Formulate the structure of glutathione.
   (b) Propose the mechanism by which the following compounds are reacted with glutathione:
   (a′) *N*-(4-Chloromethylthyazole-2-yl)acetamide
   (b′) Busulfan



   c′) Arecoline

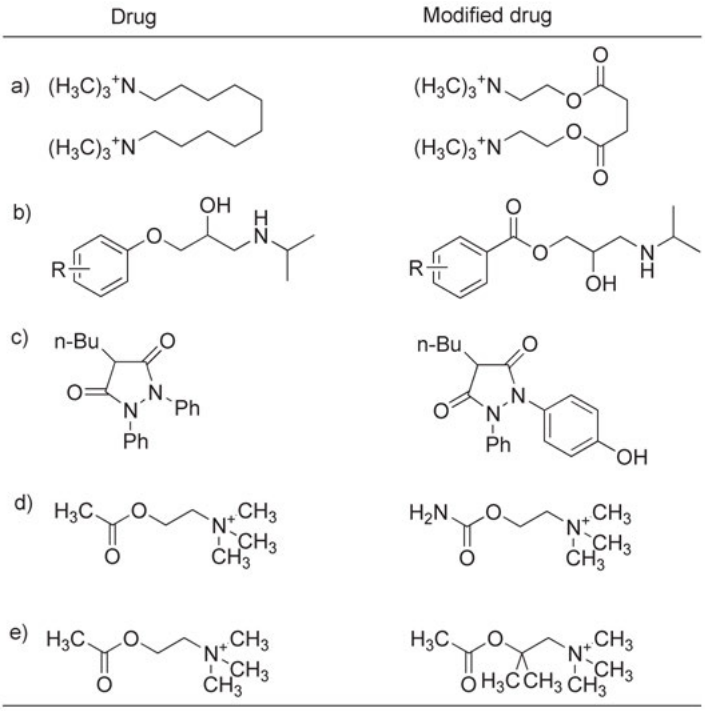


   d′) Crotonaldehyde

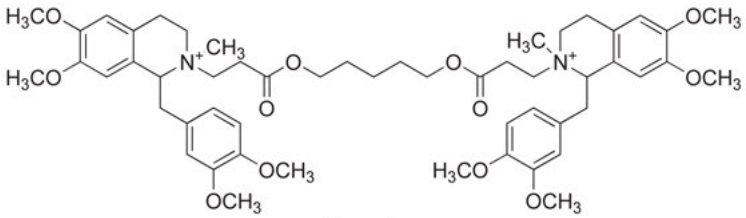


4. Classify the compounds on the right as “soft” or “hard” analogues of those on the left, according to the structural modification performed (D = Drug):
   (a) D-$N(CH_3)_2$ D-$N(CH_3)C(CH_3)_3$
   (b) D-CH_3 D-$COOCH_3$
   (c) D-$COOC_2H_5$ D-$COOC(CH_3)_3$
   (d) D-C_6H_5 D-C_6H_4-*p*CF_3
   (e) D-CH_2COOR D-CH_2CONHR
   (f) D-$COO(CH_2)_2N^+R_3$ D-$COOCH_2N^+R_3$

5. Explain the modification made in the following drugs when preparing them as modified drugs:



6. Atracurium was designed as a soft muscle relaxant in which two ester groups are introduced in the two β positions with respect to the quaternary nitrogens in the linker chain. Their presence makes it possible for a spontaneous elimination reaction to take place at physiological temperature and pH, aided by the acidity of neighboring carbonyl protons. Specify the removal mechanism that takes place.



Atracurium

8 Synthetic drug strategies

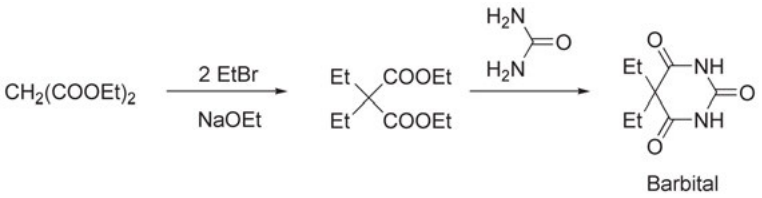
8.1 Goals

- Knowledge of retrosynthetic analysis as a way to simplify the structure of the target molecule until reaching simple starting materials.
- Ability to propose the synthesis phase, based on the information obtained in the retrosynthetic analysis, based on mechanisms of reaction and reactivity of organic compounds.

8.2 Introduction to disconnections

To carry out an analytical approach to the design of organic synthesis a basic knowledge of organic chemistry is required. The strategy followed is one of backward analysis, i.e. from products to reagents which is called retrosynthetic analysis. The methodology consists of gradually "disarming" the product by breaking strategic bonds to give simpler fragments that we call building blocks or synthons. Bond-breaking is called a disconnection.

Suppose we want to prepare barbital, the first barbiturate synthesized with a hypnotic-sedative activity. Its synthesis is carried out starting from diethyl malonate and ethyl bromide, in the presence of sodium ethoxide, by an S_N2 process, due to the acidity of the hydrogen atoms of the malonate C-2. It is then condensed with urea in abasic medium to give barbital (Scheme 8.1).



Scheme 8.1: Synthesis of barbital.

Suppose, however, that this barbiturate has not been synthesized before and that we must design its synthesis. In this case the starting products are unknown, and all that is known is the structure of the target molecule (TM). It is obviously necessary to start with this structure and work backwards. The key to the problem is the TM functional groups, which in our case will be: nitrogen atoms, carbonyl groups at positions 4 and 6, and C-5.

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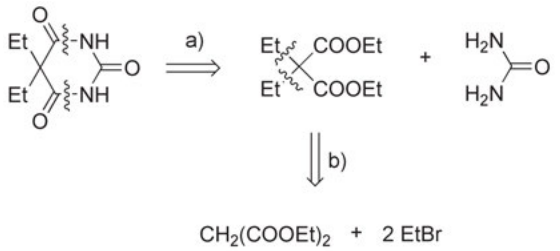
There are one or several valid disconnections for most functional groups, i.e. imaginative processes that reverse the actual chemical reactions by means of the rupture of a bond in the TM, to lead to a new compound, from which the TM can be synthesized. In this case, the first disconnection (a) will be that of a C–N bond, which leads to the precursors diethyl 2,2-diethylmalonate and urea (Scheme 8.2).



Scheme 8.2: Retrosynthesis of barbital.

The second (b), that of a C–C bond of a 1,3-dicarbonyl compound, leads to diethyl malonate and ethyl bromide. Alkylation of diethyl malonate proceeds well when primary halides are used, since it is an S_N2. When it is necessary to use secondary halides, it will be necessary to look for another alternative, as we will see later.

8.3 Definitions

Disconnection: the analytical operation that consists of the rupture of a bond which converts the molecule into a starting product. It is the reverse operation of a chemical reaction. It is represented by and a crossed wavy line perpendicular to the bond that is fragmented.

FGI (functional group interconversion): is the substitution of a functional group for another that allows the realization of the disconnection. This is again the inverse of a chemical reaction and is represented with the same symbol of the disconnection and the FGI acronym on the double arrow.

Reagent: the compound whose reaction leads to an intermediate in the proposed synthesis, or leads to the TM. It is the synthetic equivalent of a synthon.

Synthetic equivalent: a reagent that plays the role of a synthon when it cannot be used, usually due to its instability.

Synthon: a fragment (usually an ion), produced by a disconnection.

Target molecule: the molecule whose synthesis is intended. It is represented as TM, followed by its corresponding number.

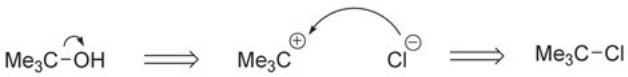
8.4 Rules to make a good disconnection

- A logical mechanism of reaction.
- The greatest simplicity possible.
- Leading to readily available starting materials.

As is well known, *tert*-butyl alcohol can be obtained by hydrolysis of *tert*-butyl chloride (Scheme 8.3).

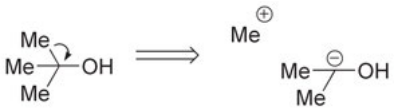
Scheme 8.3: Synthesis of *tert*-butyl alcohol.

The mechanism for the inverse imaginary reaction would be (Scheme 8.4).



Scheme 8.4: Retrosynthesis of *tert*-butyl alcohol.

This would be the logical mechanism, whereas if any other TM bonds such as C–Me are broken, the intermediate species Me^+ and Me_2C^-OH would probably not exist (Scheme 8.5).



Scheme 8.5: Illogical disconnection of *tert*-butyl alcohol.

Another example: diethyl 2-benzylmalonate is seen in Fig. 8.1.

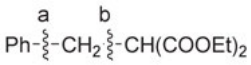
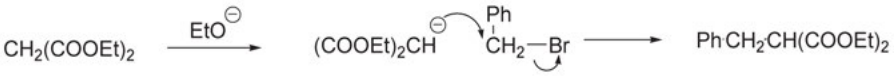


Fig. 8.1: Two possible disconnections of diethyl 2-benzylmalonate.

Of the two possible disconnections, breaking bonds by (a) or (b), the best disconnection is (b), since it leads to an anion and a cation, both stabilized. Therefore, the correct disconnection would be as in Scheme 8.6.

Scheme 8.6: Correct disconnection of diethyl 2-benzylmalonate.

The preparation of the molecule would therefore be through a malonic ester synthesis (Scheme 8.7).

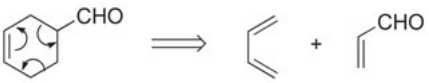


Scheme 8.7: Synthesis of diethyl 2-benzylmalonate.

Another type of reaction in which it is very easy to deduce the disconnection are the Diels–Alder reactions: for example, the reaction between 1,3-butadiene and acrolein would be as shown in Scheme 8.8.

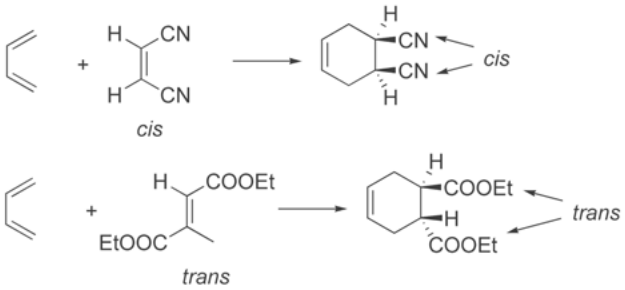
Scheme 8.8: Diels–Alder reaction.

We now formulate the disconnection of the product (Scheme 8.9).



Scheme 8.9: Disconnection of the Diels–Alder product.

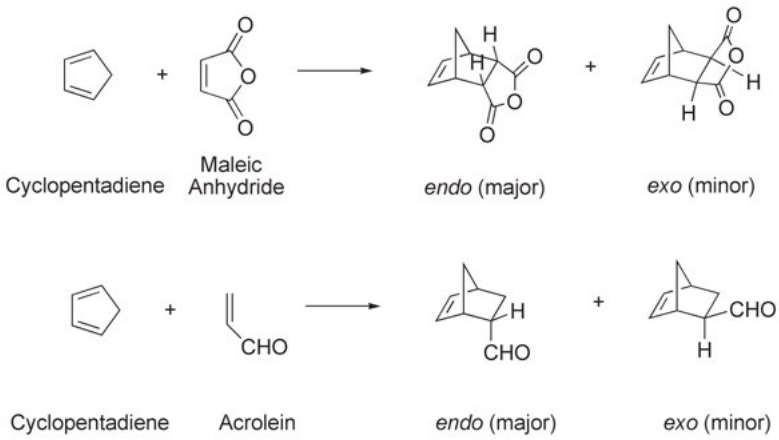
The double bond in the six-member ring tells us where to start the disconnection. The Diels–Alder reaction is a *syn* addition, both with respect to diene and dienophile (Scheme 8.10).



Scheme 8.10: *syn* Addition of the Diels-Alder product.

8.5 *endo* selectivity

When a diene reacts with a dienophile, two isomeric Diels–Alder products called *endo* and *exo* adducts, can be formed. When the electron-withdrawing group of the dienophile is next to the new double bond formed, the compound is called *endo*. When the electron-withdrawing group of the dienophile is far from the new double bond the compound is called *exo* (Scheme 8.11).



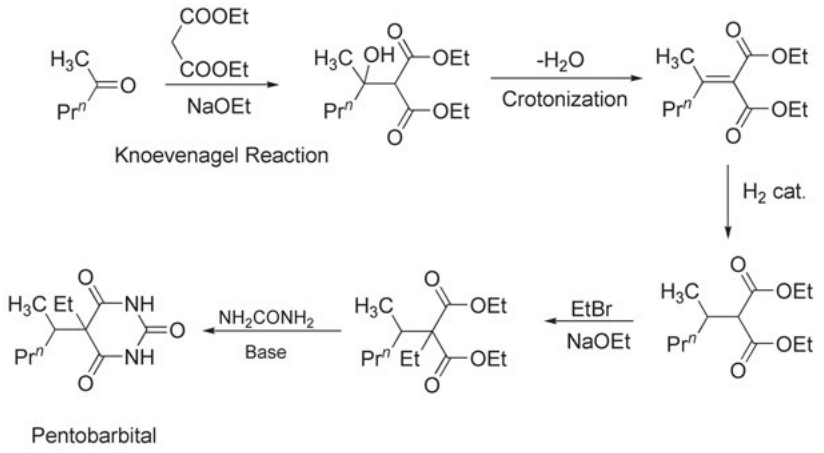
Scheme 8.11: *endo* and *exo* adducts of the Diels–Alder reaction.

We will use these concepts in the synthesis of buprenorphine.

8.6 Synthesis of various barbiturates

8.6.1 Pentobarbital

In the case where we have branched substituents, such as pentobarbital used as an antiepileptic, hypnotic and sedative drug, alkylation of the diethyl malonate in a basic medium with the 2-bromopentane cannot be carried out, because being a secondary halide the elimination reaction predominates. In these cases Knoevenagel reaction and subsequent reduction of the double bond yield the desired product. The introduction of the ethyl substituent is carried out by the classical method from ethyl 2-(2-pentyl)malonate (Scheme 8.12).

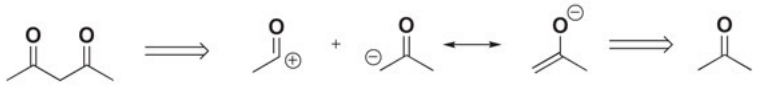


Scheme 8.12: Synthesis of pentobarbital.

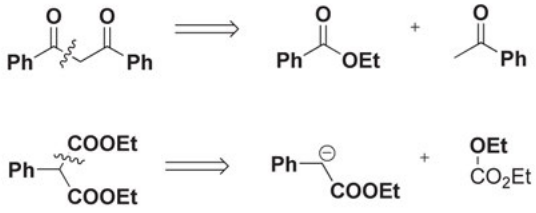
8.6.2 Phenobarbital

An interesting case is the preparation of phenobarbital, the first synthesized barbiturate. The preparation of the diethyl phenylmalonate is not made by direct alkylation with phenyl halide, since these derivatives are very unreactive against S_N2. 1,3-Dicarbonyl compounds can be disconnected through the α,β-bond (Scheme 8.13), and the retrosynthetic analysis leads to the carbanion of ethyl phenylacetate, and diethyl carbonate.

For 1,3-dicarbonyl compounds:



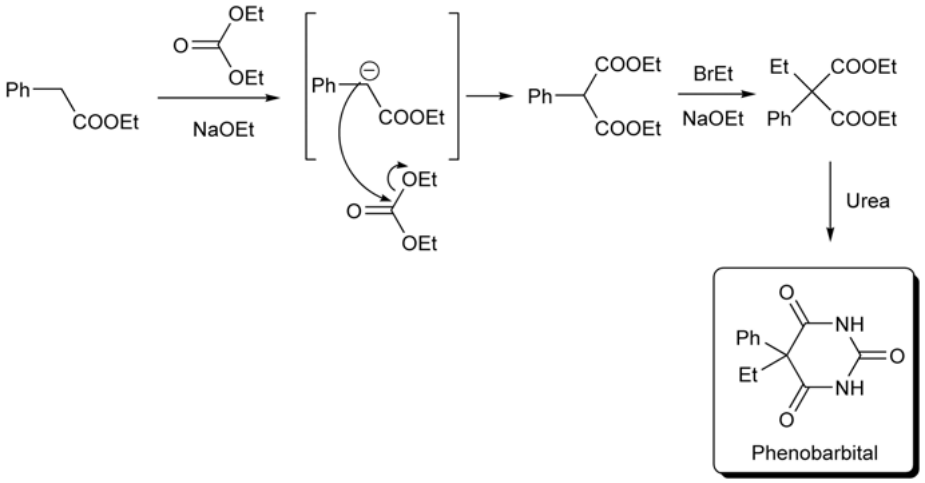
For the molecule:



Compound $CO(OEt)_2$ is diethyl carbonate, readily available. Instead:

Scheme 8.13: Retrosynthesis of 1,3-dicarbonyl compounds.

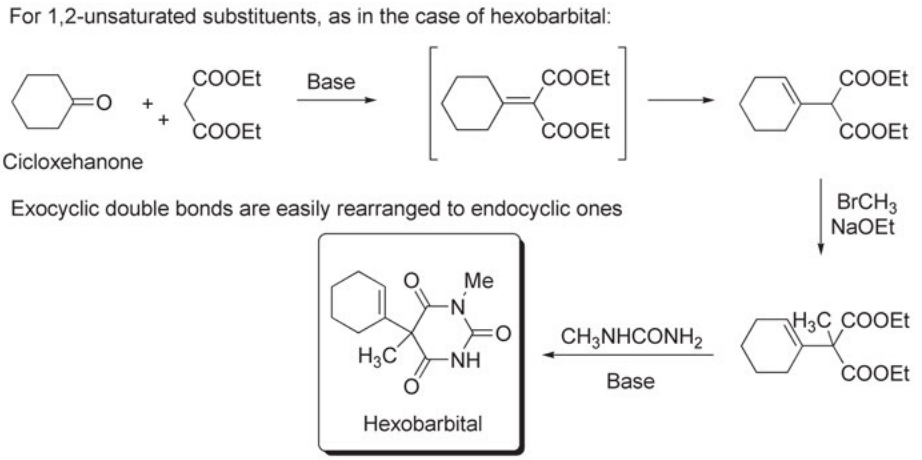
Scheme 8.14 shows the synthesis of phenobarbital.



Scheme 8.14: Synthesis of phenobarbital.

8.6.3 Hexobarbital

The introduction of the 1-cyclohexenyl substituent at the α-position of the malonic ester is effected through a Knoevenagel condensation from cyclohexanone. However, the conjugated diester is isomerized in the basic medium to the nonconjugated product, which in this case is more stable, because it is not as destabilized by steric interactions as the conjugated tautomer (Scheme 8.15).

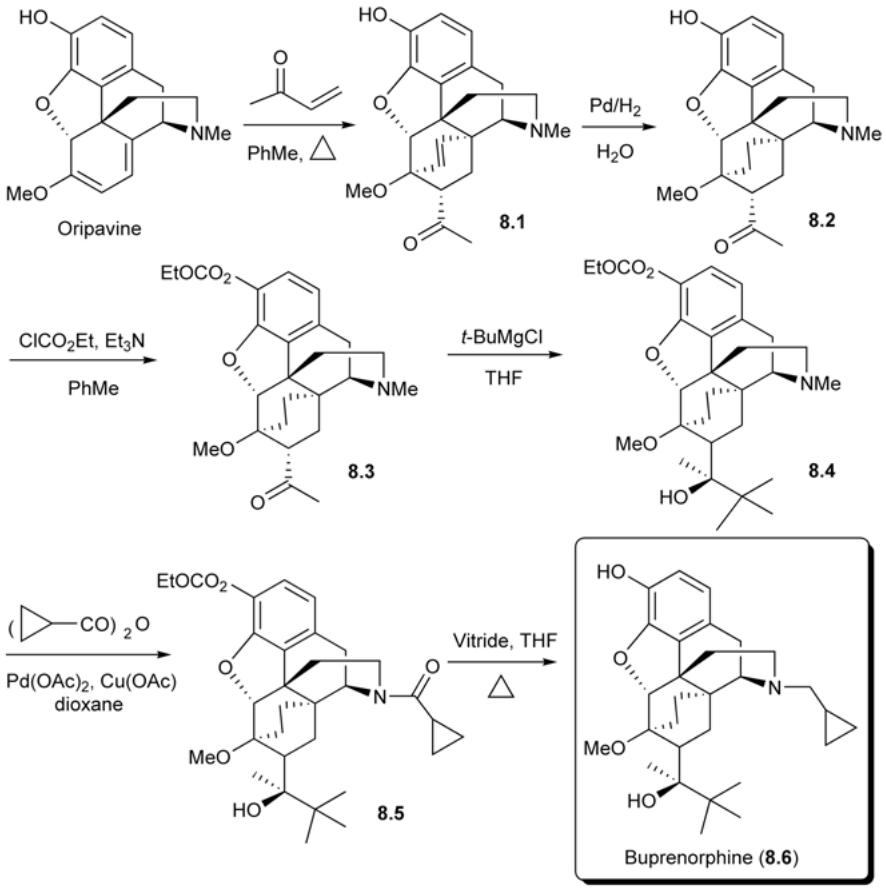


Scheme 8.15: Synthesis of hexobarbital.

8.7 Buprenorphine

Buprenorphine (Scheme 8.16) may be used as an alternative to methadone in the treatment of withdrawal symptoms, and is the result of the formation of an additional six-membered cycle between positions 6 and 14 of the opiate skeleton. From a retrosynthetic point of view, this additional cycle with a double bond and with the acetyl moiety can be prepared by means of the Diels–Alder reaction of the opioid scaffold with the methyl vinyl ketone. Finally, the reaction of resulting ketone with Grignard reagents can lead to the so-called Bentley derivatives.

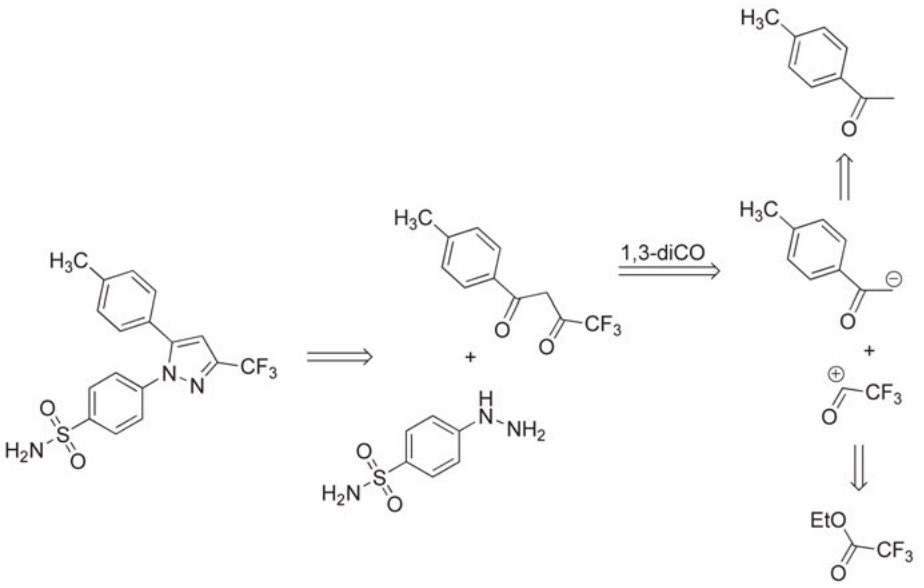
Scheme 8.16 shows the synthesis of buprenorphine from oripavine via its conversion to the *endo* Diels–Alder adduct **8.1**, the saturated derivative **8.2**, the *O*-carbonate **8.3**, and the *tert*-butyl carbinol **8.4**. The palladium-catalyzed *N*-demethylation of **8.4** in the presence of cyclopropylmethylcarboxylic acid anhydride gives rise to the acyl amide **8.5**, whose treatment with Vitride furnish buprenorphine (**8.6**).



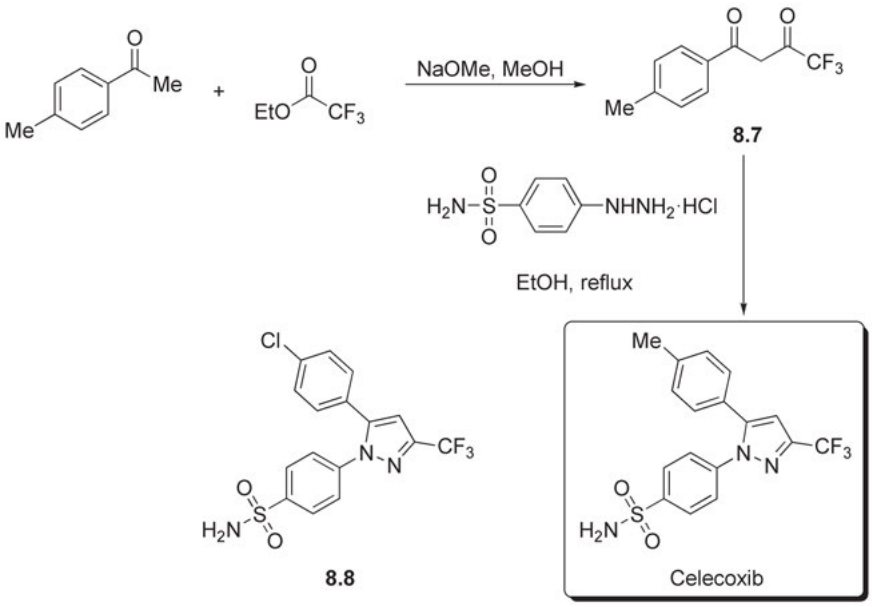
Scheme 8.16: Synthesis of buprenorphine.

The C-heteroatom bond, generally O, N, or S, in a hydrocarbon chain or cycle is usually the most suitable point for dissociation into the heterocyclic compounds. We will raise the problem of carrying out the retrosynthesis of a COX-2 inhibitor, such as celecoxib (Scheme 8.17).

Scheme 8.18 describes one of the syntheses of celecoxib. Dione **8.7** is prepared by Claisen condensation between 4-methylacetophenone and ethyl trifluoroacetate in the presence of NaOMe in methanol at reflux. The formation of the diarylpyrazole from the condensation between β-diketone **8.7** and 4-sulfonamidophenylhydrazine hydrochloride then leads to celecoxib. The corresponding chlorophenylpyrazolyl analogue **8.8** is potent (IC_{50} = 0.01 μM versus COX-2), selective (IC_{50} = 17.8 μM versus COX-1), and effective. However, its plasma half-life is too long. Substitution of the chlorine atom by the methyl group accelerates the metabolism to give benzoic acid *via* an *in vivo* oxidation process.



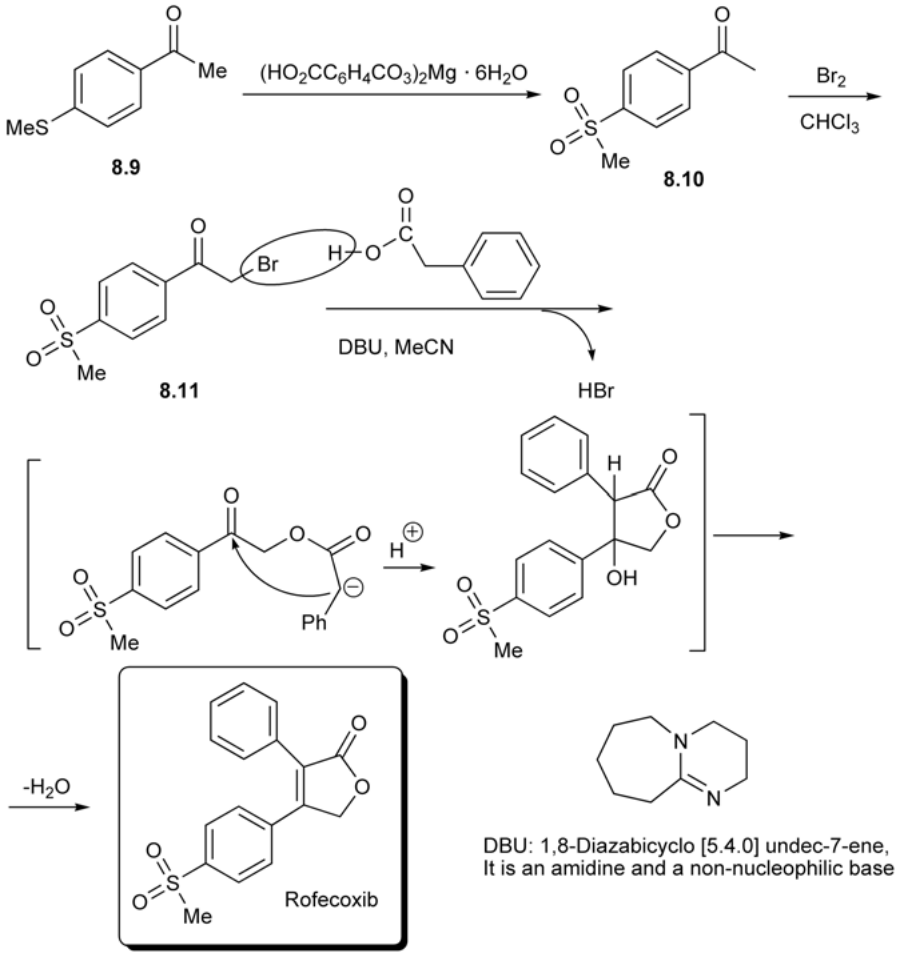
Scheme 8.17: Retrosynthesis of celecoxib.



Scheme 8.18: Synthesis of celecoxib.

8.8 Rofecoxib

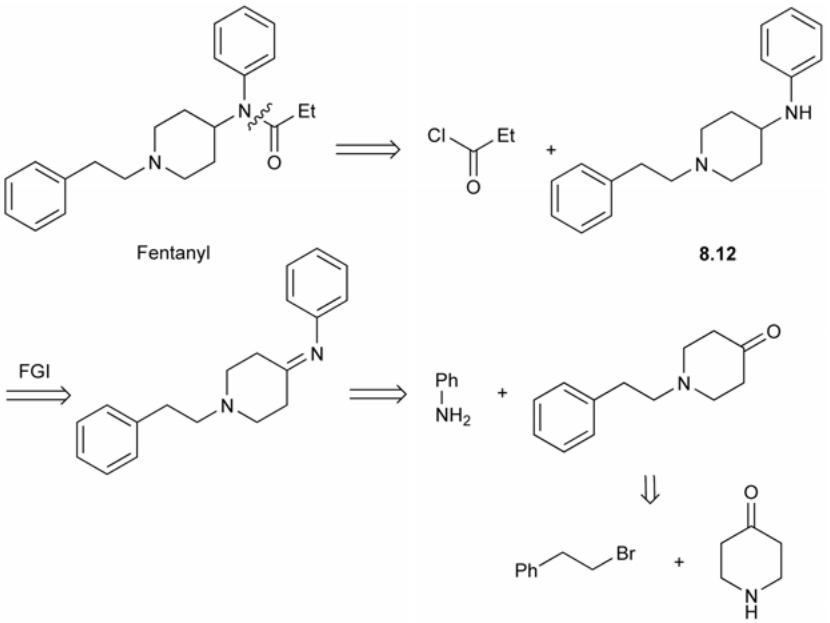
In the original Merck patent published in 1995, rofecoxib is synthesized in three steps from 4-methylthioacetophenone **8.9**, prepared in turn from the Friedel–Crafts acylation of thioanisole. As shown in Scheme 8.19, the use of an excess of magnesium monoperoxyphthalate hexahydrate (MMPP, a cheap, safe and commercially available substitute for *m*-chloroperbenzoic acid, MCPBA) results in sulfone **8.10**, which is brominated to give compound **8.11**. This phenacyl bromide is cyclized with phenylacetic acid under the influence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to yield rofecoxib. The ketoester, which is formed from esterification, undergoes an intramolecular Claisen condensation to yield the furanone ring of rofecoxib.



Scheme 8.19: Synthesis of rofecoxib.

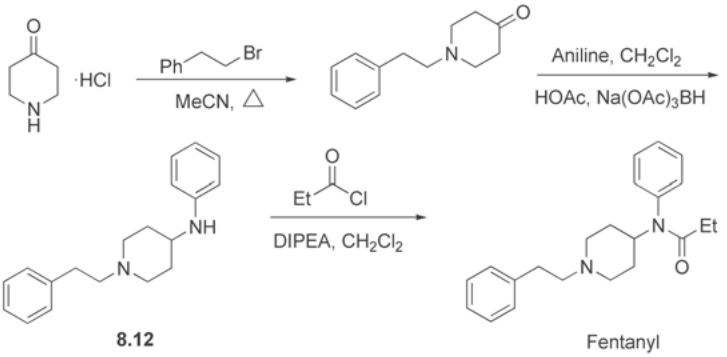
8.9 Fentanyl

Fentanyl is an opiate synthetic narcotic agonist used in medicine for its analgesic and anesthetic actions. Scheme 8.20 shows its retrosynthetic process.



Scheme 8.20: Retrosynthesis of fentanyl.

The fentanyl synthesis is performed in three steps, starting with 4-piperidone hydrochloride. It reacts with phenethyl bromide, giving rise to *N*-phenyl-4-piperidone, which is subsequently subjected to a reductive amination to give **8.12**. Finally, **8.12** reacts with propionic chloride to yield fentanyl (Scheme 8.21).

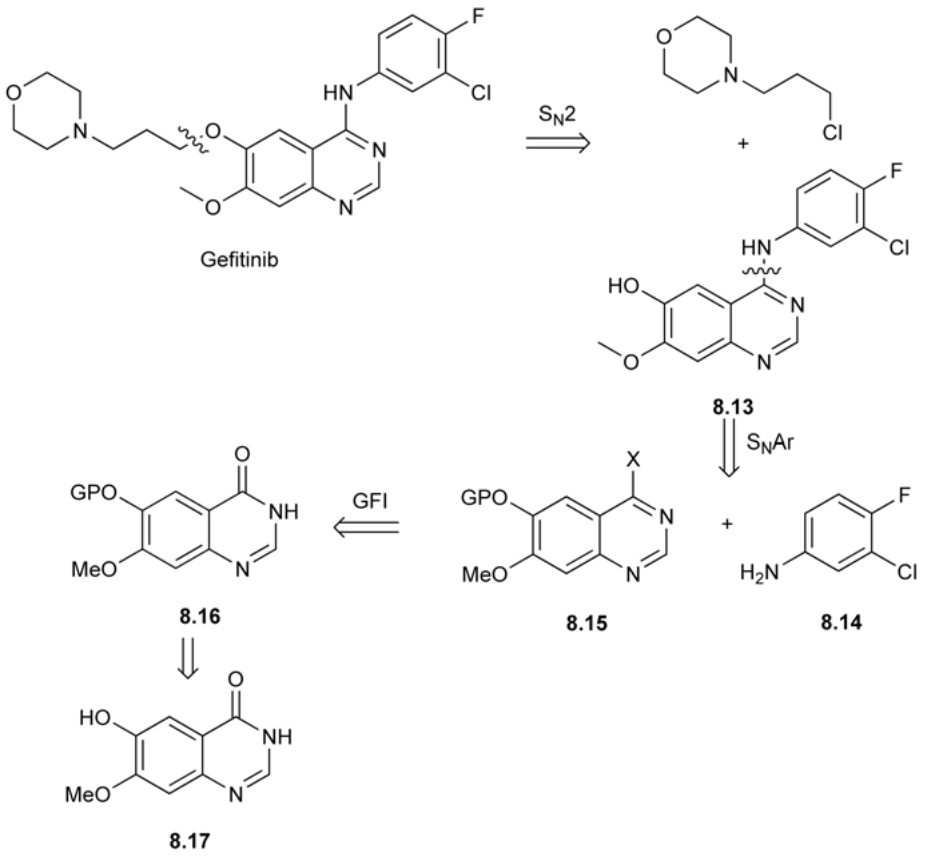


Scheme 8.21: Synthesis of fentanyl.

8.10 Gefitinib

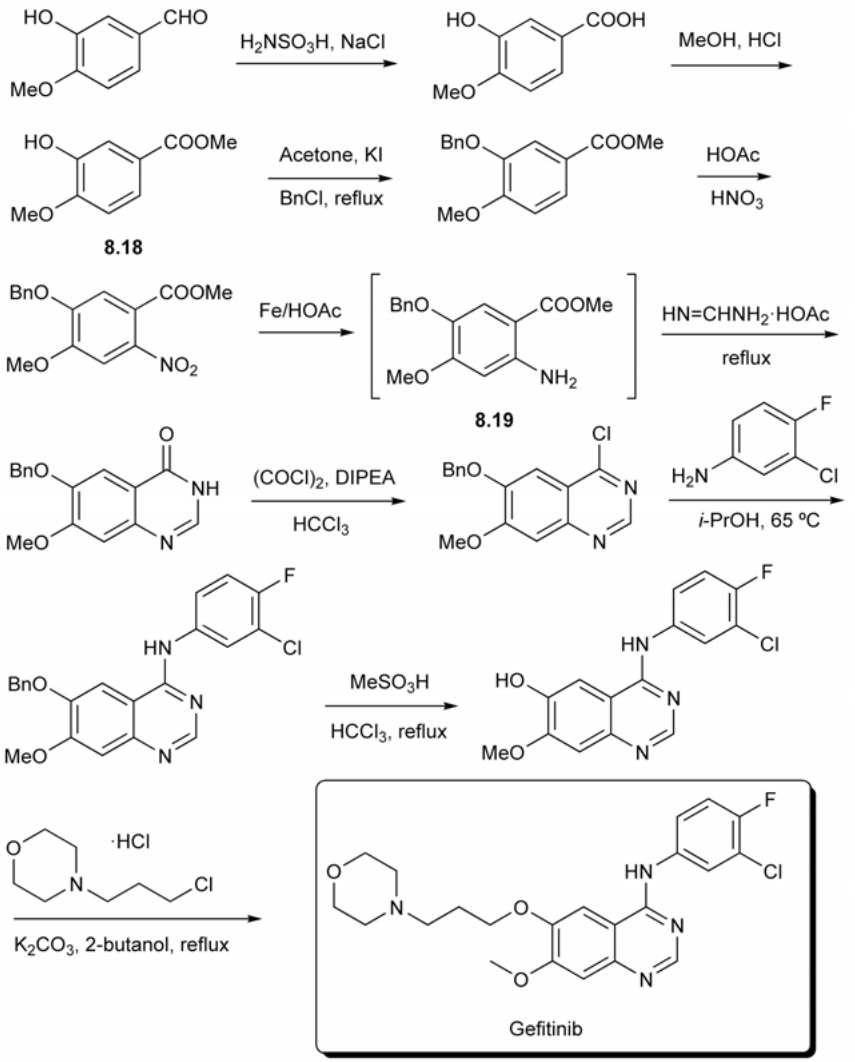
Epidermal growth factor receptor (EGFR) is a tyrosine kinase of the erb-B family involved in the activation of the cascade of signals that control cell proliferation. Gefitinib inhibits EGFR autophosphorylation and disrupts the cell-signaling pathway mediated by this receptor.

The retrosynthetic analysis begins with the disconnection of the 4-propylmorpholine side-chain that is incorporated by an S_N2 *O*-alkylation reaction of compound **8.13** on 4-(3-chloropropyl)morpholine. Disconnection of 3-chloro-4-fluoroaniline **8.14**, based on a S_NAr reaction, generates quinazoline **8.15**. This compound is obtained from quinazolinone **8.16**, which is prepared from 6,7-dimethoxyquinazolin-4(3*H*)-one **8.17** (Scheme 8.22).



Scheme 8.22: Retrosynthesis of gefitinib.

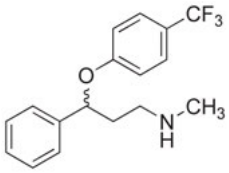
The synthesis of gefitinibis outlined in Scheme 8.23. The general synthesis of gefitinib begins with a quinazolinone as the starting material, which acts as the central skeleton of the molecule. The free phenolic group of **8.18** is protected as benzyl ether, to prevent it from reacting with other reagents in later phases. Reaction of nonisolated aniline **8.19** with amidine gives rise to the quinazolone moiety, which through its convertion to the chlorine derivative allows its substitution by 3-chloro-4-fluoroaniline. Deprotection of the phenolic group and reaction with an alkyl halide introduces the second major substituent to give rise to gefitinib.



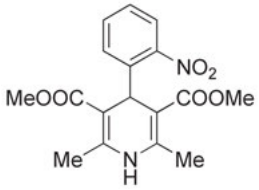
Scheme 8.23: Synthesis of gefitinib.

8.11 Exercises

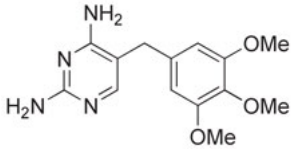
1. Propose the retrosynthesis and synthesis of the following drugs:
   (a) (*RS*)-fluoxetine (Prozac®).



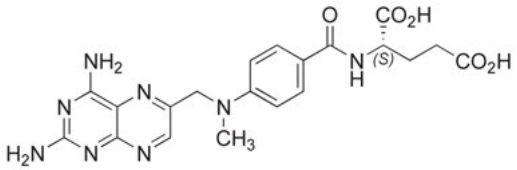
   (b) Nifedipine



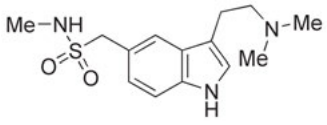
   (c) Trimethoprim.



   (d) Methotrexate (MTX).



   (e) Sumatriptan.



9 Solutions to the exercises

9.1 Exercises to chapter 2

(A) Name the following drugs:

1) 4-Amino-*N*-[2-(diethylamino)ethyl]benzamide.
2) 4-Amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide.
3) 2-Amino-3,5-dibromo-*N*-cyclohexyl-*N*-methylbenzylamine.
4) 7-(Cyclohexylcarbonyl)-2-naphthoic acid.
5) *N*-(5-Nitro-2-propoxyphenyl)acetamide.
6) Ethyl 2-phenoxy-2-methylpropanoate.
7) 6-(Dimethylamino)-5-methyl-4,4-diphenylhexane-3-one.
8) 2-(4-Chlorophenoxy)-2-methylpropanoic acid.
9) (2-Amino-3-benzoylphenyl)acetic acid.
10) 1-(2,6-Dimethylphenoxy)propane-2-amine.
11) 6-(Phenoxypropanamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
12) 4,7-Dimethyl-7-azabicyclo[2.2.1]heptane-2-yl propionate.
13) 7-[2-(Thiophene-2-yl)acetamido]-3-[(carbamoyl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
14) 3-[(2-Aminoethyl)thio]-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylic acid.
15) 2-Methoxycarbonyl-8-methyl-8-azabicyclo[3.2.1]octane-3-yl benzoate
16) Propyl 8-methyl-8-azabicyclo[3.2.1]octane-3-yl-pentanoate.
17) 8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.
18) 5-[(2-Methoxyphenoxy)methyl]oxazolidine-2-one.
19) 1-(*p*-Chlorobenzyl)-2-[(1-pyrrolidinyl)methyl]-1*H*-benzimidazole.
20) 8-Chloro-11-(4-methylpiperazin-1-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine.
21) 5-(4-Chlorophenyl)-3,5-dihydro-2*H*-imidazo[2,1-*a*]isoindole-5-ol.
22) 11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenzo[b,e]thiepine.
23) 2-Bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine.
24) 7-(α-Amino-α-(3-hydroxyphenyl)acetamido)-8-oxo-3-(1-propene-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid.
25) 2-(6-Chloro-9*H*-carbazol-2-yl)propionic acid.
26) 8-Chloro-10-(2-dimethylaminoethyloxy)dibenzo[*b*,*f*]thiepine.
27) 10-(2-Dimethylaminopropyl)-10*H*-pyrido[3,2-*b*][1,4]benzothiazine.
28) 4-Amino-2-[4-(furan-2-carbonyl)-1-piperazinyl]-6,7-dimethoxyquinazoline.
29) 6-Benzoyl-3-hydrazino-5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazine.

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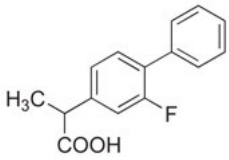
30) 2-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]aceticacid.
31) N^1-(6-Methoxy-2-methylpyrimidine-1-methyl)sulfanilamide.
32) N^1-(5-Methyl-1,3,4-thiadiazole-2-yl)sulfanilamide.
33) Ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.
34) 7-Chloro-*N*-(5-diethylamino)pentane-2-yl)quinazoline-4-amine.
35) 10-Chloro-11*b*-(2-chlorophenyl)-7-methyl-3,5,7,11*b*-tetrahydro-2*H*-oxazolo[3,2-*d*][1,4]benzodiazepine-6-one.
36) 3-(Acetoxymethyl)-7-[2-(2-thienyl)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid.

(B) Formulate the following drugs:

1)



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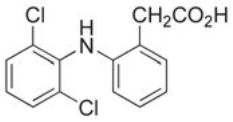

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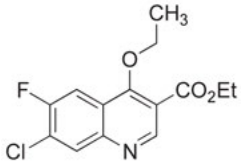

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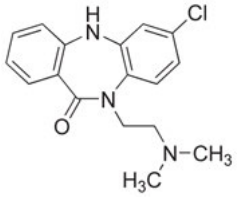

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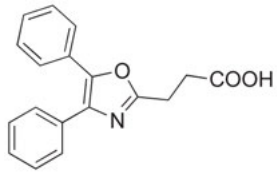

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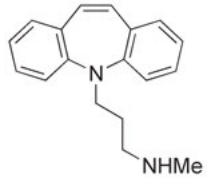

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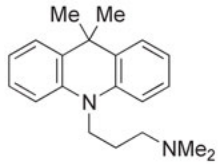

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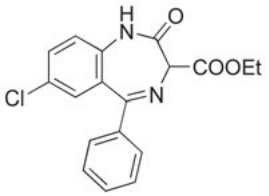

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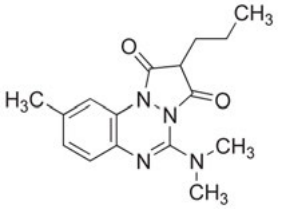

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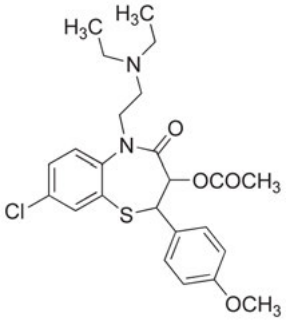

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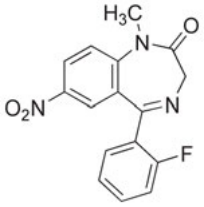

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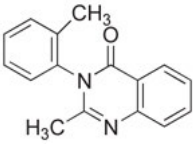

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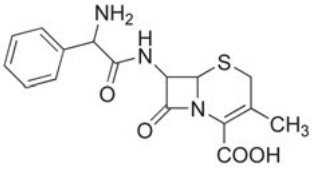

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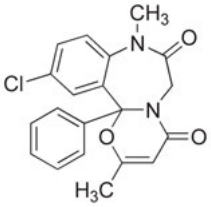

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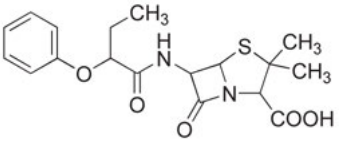

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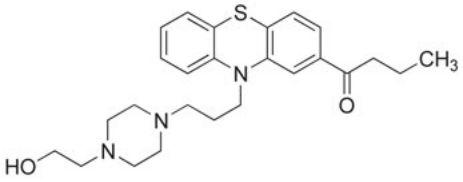

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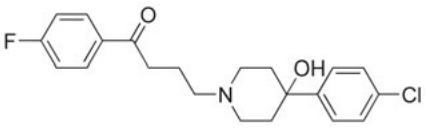

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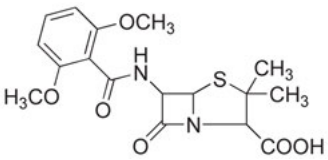

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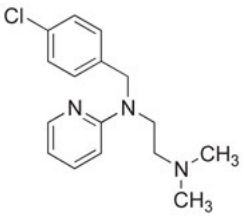

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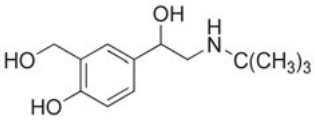


9.2 Exercises to chapter 4

1. (a) Modulative structural modification due to a ring size variation.
   (b) A modulative variation due to reorganization and dissociation of the rings.
   (c) Modulative structural variation by isomerization.
   (d) Modulative structural variation by formation of a rigid analogue.
   (e) Conjunctive replication by formation of a hybrid or a molecular combination.
   (f) Structural modulative variation by bioisosterism.
   (g) Disjunctive replication.
   (h) Disjunctive replication.
   (i) Modulative structural variation by formation of a cycle.
   (j) Conjunctive replication: Molecular duplication.
   (k) Modulative structural variation by bioisosterism.
   (l) Conjunctive replication by association of two molecules (antihypertensive + diuretic drugs).
   (m) Disjunctive replication (simplification of the structure).
   (n) Modulative structural variation due to the formation of a cycle.
   (o) Modulative variation by a bioisosteric change (suprophen: a drug with analgesic and anti-inflammatory properties).

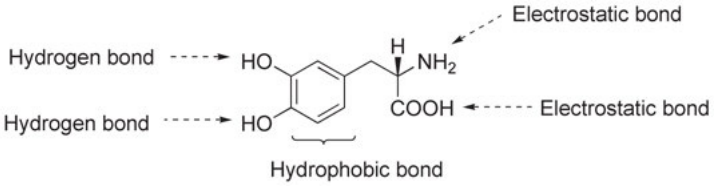
2. (a) Vinyologous: procaine and its active vinylogue.
   (b) Isosteres: change of the carbonyl and sulfone groups (meperidine and its isostere that is also a hypnoanalgesic drug).
   (c) Isosteres: Indomethacin and oxametacin (an isosteric anti-inflammatory agent).

(d) Homologues: Procaine and its inactive counterpart.
(e) Isosteres: Cathecol andbenzimidazole.
(f) Isosteres: 4-Dimethylaminoantipyrine and 4-isopropylantipyrine, both analgesic and antipyretic agents.
(g) Homologues.
(h) Isosteres: Hypoxanthine and 6-mercaptopurine.
(i) Isosteres: Methaphenilene and methapyrilene.
(j) Vinylogues: Pethidine (meperidine) and its vinilogue.
(k) Vinylogues: Phenylbutazone and styrrilbutazone.

3. (a) Modification of pharmacokinetics by blocking the metabolism by the introduction of fluorine atoms into the aromatic rings: longer duration of action. The compound on the left is CGP 52411, an enzymatic inhibitor that acts on the active site of the epidermal growth factor receptor (EGFR), useful as an antitumour agent. This compound undergoes oxidative metabolism at the *para* position of the aromatic ring. The introduction of F resulted in **CGP53353**. This same procedure was successfully applied in the synthesis of gefitinib, which is a drug used for certain breast, lung and other cancers.
(b) Transformation of an agonist into antagonist (hypoxanthine, a metabolite, and 6-mercaptopurine, an antitumour agent by antagonism).
(c) Development of therapeutic copies: enalapril and its therapeutic copy, quinapril.
(d) Activity change (homology allowed by chance the interaction with another biological target): Dietazine, a H_1 antihistaminic drug, and chlorpromazine, a neuroleptic change.
(e) Reduction of toxicity: The change of the chlorine atoms of the compound **UK47265** by F atoms led to the antifungal fluconazole, lacking toxicity.
(f) Improvement of distribution so that it reaches the organs where it has to exercise its action: Mechlorethamine and melphalan.
(g) Change of the spectrum of action: transformation of an agonist into an antagonist, by introduction of bulky groups (acetylcholine and propantheline).
(h) Improvement of distribution: The compound does not cross the BBB with the quaternization of nitrogen and acts only at the peripheral level (scopolamine and scopolamine butylbromide).

9.3 Exercises to chapter 5

1. (a)



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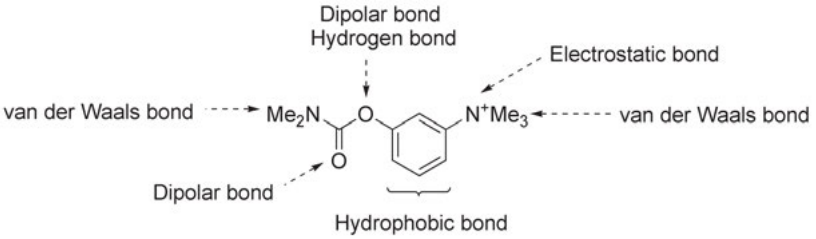

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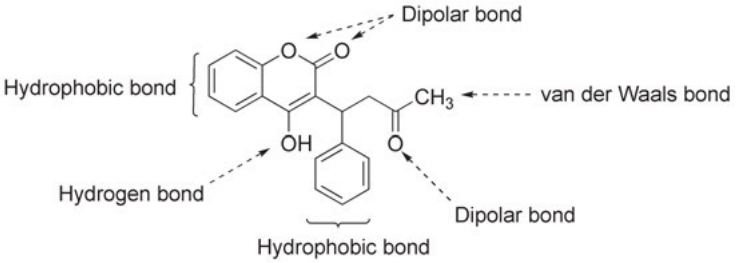

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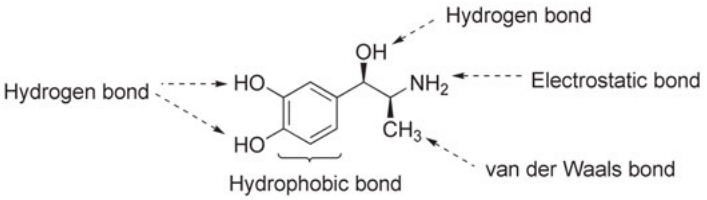

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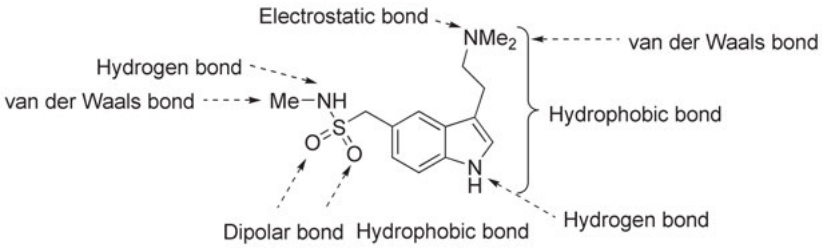

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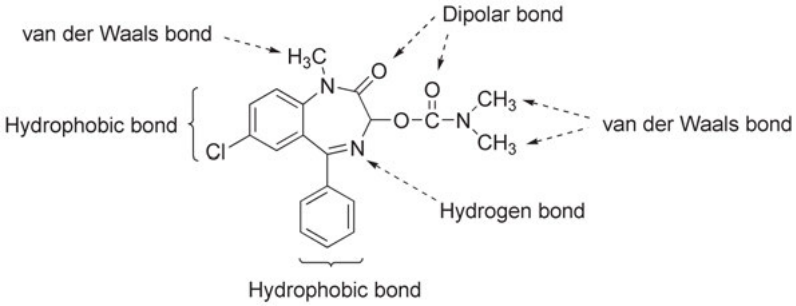

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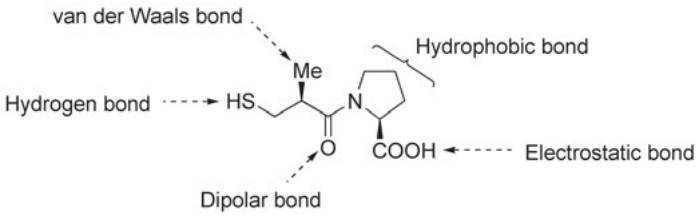
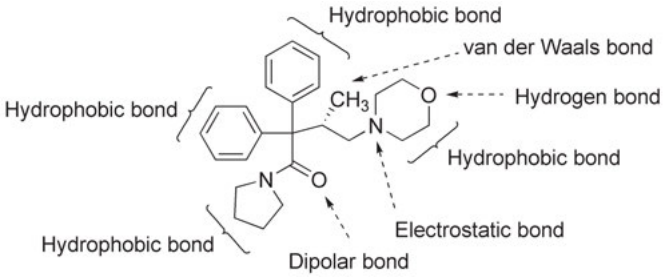


(h)



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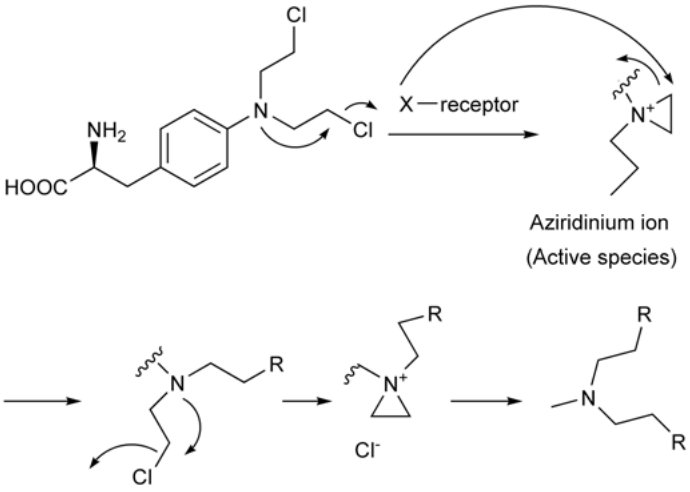
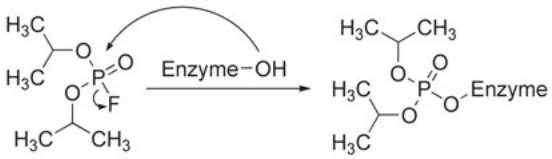


(b)



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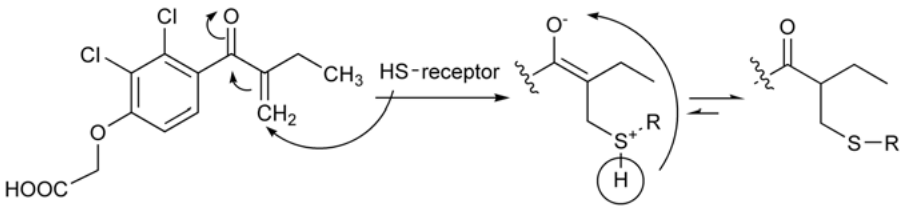

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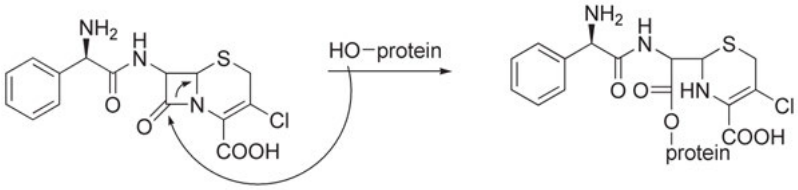

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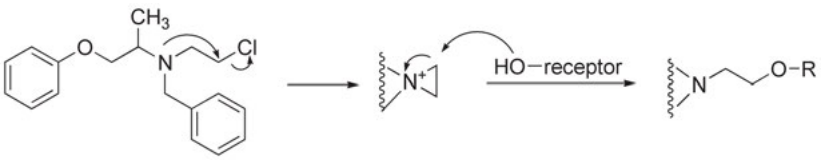

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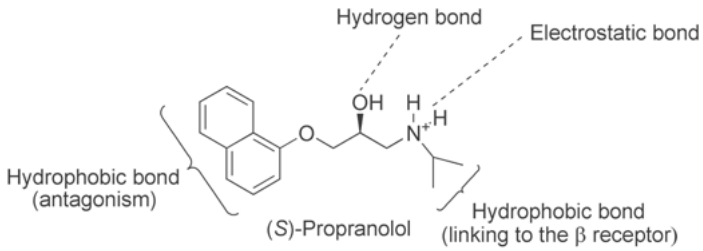
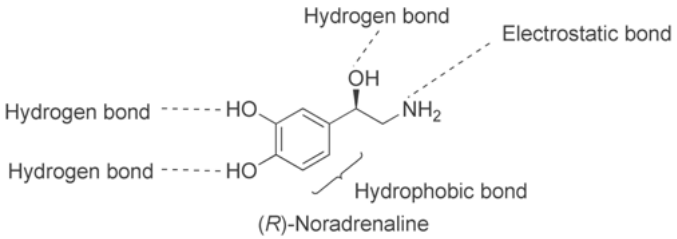
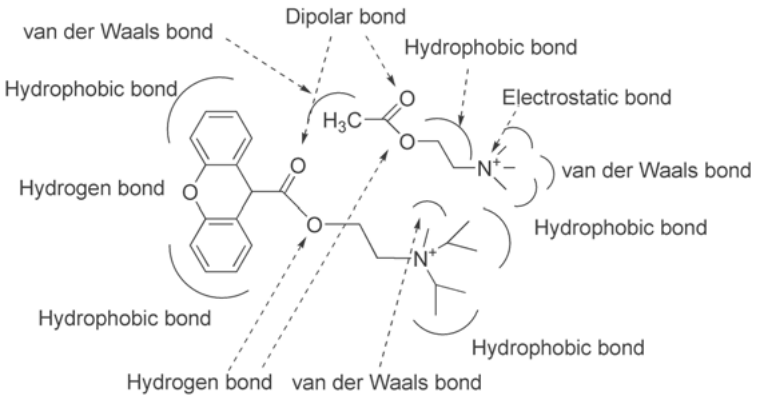


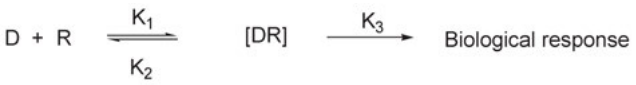


4. (a)



Hydrophobic interactions cause it to act as an antagonist.

(b)



Agonist: big $K_1 \geq K_2, K_3$
Antagonist: $K_1 \geq K_2, K_3 = 0$
Partial agonist: small $K_1 \geq K_2, K_3$
Inactive compound: $K_1 \leq K_2$

5. (a)

cis Diastereomers *trans*

Nicotinic agonist

Muscarinic agonist
It mimics the antiperiplanar conformation of acetylcholine

(b)

R(-) *S*(+)

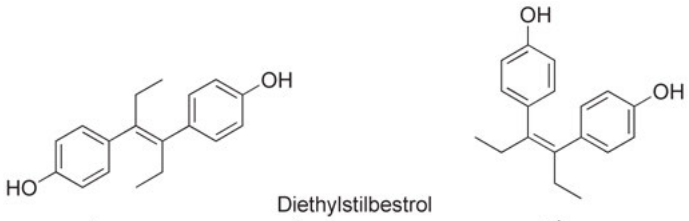
Potent β agonist
Weak α antagonist

Enantiomers of isoprenaline

Weak β agonist
α Antagonist

Eutomer (bronchodilator activity)

(c)



trans

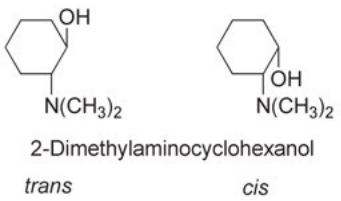
Diethylstilbestrol diastereomers

cis

Higher estrogenic activity; it has the OH groups oriented as in estradiol

Weakly active

(d)

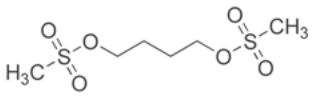


2-Dimethylaminocyclohexanol

trans *cis*

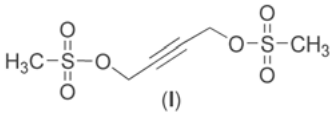
Diastereomers
Geometric and optical isomers
Enzymatic inhibidors
They have different coupling ability to the enzyme

(e)

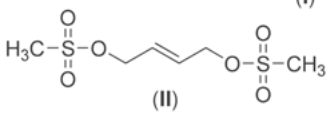


Busulfan (antineoplastic agent)

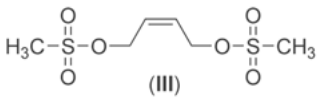
It acts by alkylation of nucleophilic groups of the biological target



(I)



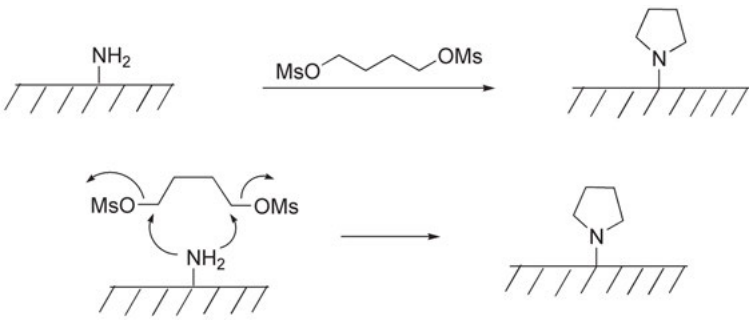
(II) *trans*

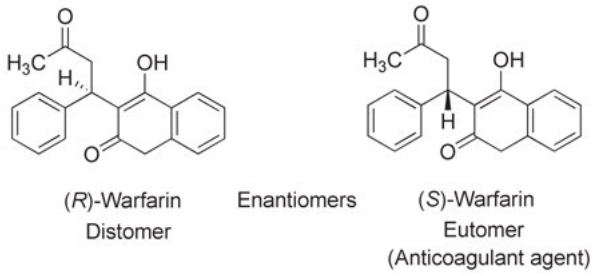


(III) *cis*

Diastereomers
Rigid busulfan analogues

Only the *cis* isomer has potency similar to that of the flexible drug. It follows that the antineoplastic activity is related to the ability to form a pyrrolidine derivative by bis-1,4-alkylation of some amino groups suitably disposed in the biological target.





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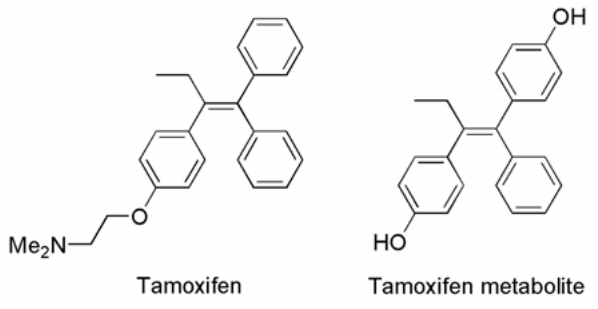
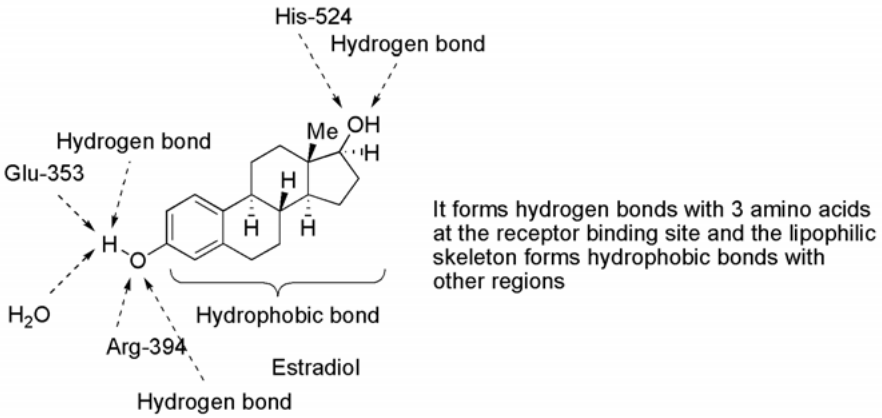




The hydrophobic pocket is quite spacious, except in the area where the phenol binds: this is a narrow zone which only accepts a flat ring, and due to this the phenolic ring determines the orientation of the rest of the molecule.

Tamoxifen metabolite would bind to the estrogen receptor in the same way as estradiol, while tamoxifen, with its dimethylaminoethyl group, would not fit into the receptor hole. In addition, it could not form all the hydrogen bonds needed for the bond.

9.4 Exercises to chapter 6

1. (a) *m*-Xylene (3.20)

$$\pi_{\text{Me (aromatic)}} = 0.56$$

$$\log P_{\text{mesitylene}} = \log P_{\text{benzene}} + 2\pi_{\text{Me}} = 2.13 + (2 \times 0.56) = 3.25$$

(b) Mesitylene (1,3,5-trimethylbenzene) (3.43)

$$\log P_{\text{mesitylene}} = \log P_{\text{benzene}} + 3\pi_{\text{Me}} = 2.13 + 1.68 = 3.81$$

(c) Hexamethylbenzene (2.33)

$$\log P_{\text{hexamethylbenzene}} = \log P_{\text{benzene}} + 6\pi_{\text{Me}} = 2.13 + 3.36 = 5.49$$

The fact that the experimental value is lower than that calculated one may be due to the large number of substituents in the benzene ring and to its electron-donating effect that causes this partition coefficient to fall.

(d) 1,3-Dinitrobenzene (1.49)

$$\pi_{\text{NO2 (aromatic)}} = -0.28$$

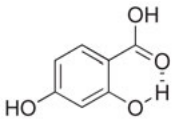
$$\log P_{\text{nitrobenzene}} = \log P_{\text{benzene}} + 2\pi_{\text{NO2}} = 2.13 - 0.56 = 1.57$$

(e) 2,4-Dihydroxybenzoic acid (1.44)

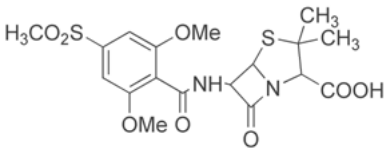
$$\pi_{\text{COOH (aromatic)}} = -0.32; \pi_{\text{OH (aromatic)}} = -0.67$$

$$\begin{aligned}\log P_{\text{2,4-dihydroxybenzoic acid}} &= \log P_{\text{benzene}} + \pi_{\text{COOH}} + 2\pi_{\text{OH}} \\ &= 2.13 - 0.32 - 1.34 = 0.47\end{aligned}$$

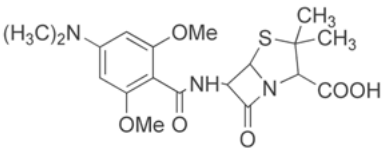
In this case, the difference in values is due to the presence of an intramolecular bond that increases the lipophilicity of the molecule with respect to the calculated value.



2. The negative value of the coefficient of π indicates that the activity is favored by hydrophilic substituents ($\pi < 0$); since σ has a positive coefficient, the electron-withdrawing substituents favor potency. Thus, both s polar and an electron-withdrawing group will yield a compound of optimal activity, whereas an electron-donating group will yield a weak methicillin derivative; for example:



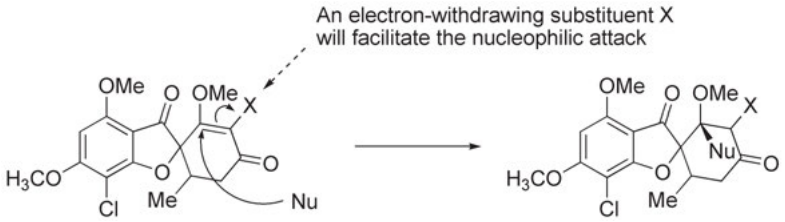
The p-SO_2CH_3 group is polar (π = -0.50) and an electron-withdrawing (σ = 0.72). If we replace it in the QSAR equation, we will obtain log (1/C) = 3.14



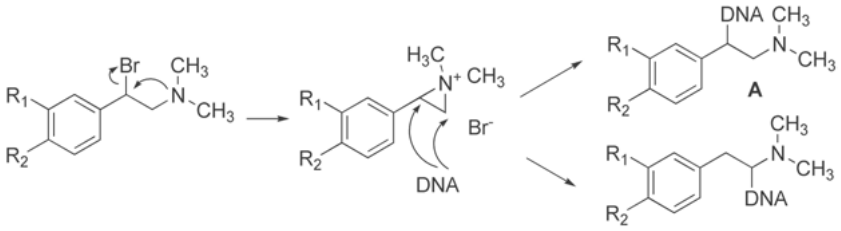
The p-$N(CH_3)_2$ group is slightly lipophilic (π = 0.18) and an electron-donating group (σ = -0.83). If we replace it in the QSAR equation, we will obtain log (1/C) = 0.30

The foregoing values allow the prediction that the activity of *p*-methylsulfonylmethacyllin would be some 700 times higher than expected for *p*-dimethylaminomethylcillin. However, these predictions must be verified by synthesis and assay of the compounds.

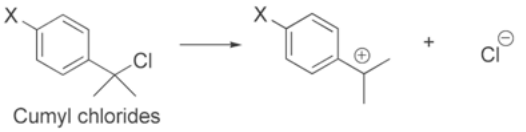
3. (a) Those substituents that have a high partition coefficient (log *P*) and that are electron-withdrawing groups.
   (b) An electron-withdrawing substituent X will be needed to facilitate the nucleophilic attack of a thiol group (-SH).
   Mechanism of nucleophilic attack reaction:



4. (a) The first equation indicates that adrenergic blocking activity depends on lipophilicity (π) and on electronic effects (σ).
   The second equation shows that hepatic toxicity (as well as activity) increases with the presence of substituents in the aromatic ring that increase lipophilicity (π positive) and that are electron-donating groups (σ negative), such as $-NMe_2$.
   (b) Mechanism of alkylation:



(c) Many reations create positive charges that can be stabilized by delocalization via resonance with the substituent. Therefore, a new substituent effect scale was produced for groups that stabilized positive charges via resonance (σ^+), such as in the intermediate that gives rise to the alkylated DNA compound **A**. The σ^+ scale is based upon the heterolysis (S_N1) reaction of *para*-substituted cumyl chlorides (phenyldimethylchloromethanes).



Cumyl chlorides

5. (a) The inhibitory activity depends on the distribution coefficient as this is important in the transportation of the drug at the physiological level.
   (b) To calculate the best value of π, the derivative of the equation with respect to π has to be calculated:

$$d(\log 1/C)/d\pi = 0.34 - 2(0.183\,\pi) = 0,$$
$$\pi = 0.304/0.366 = 0.831.$$

   Of the proposed substituents, the closest to this value is Br (0.86). The Br substituent would be therefore the best group to improve the in vivo inhibitory activity.

6. (a) The second equation indicates that the activity is favored by electron-withdrawing substituents (σ positive values).
   According to the first equation, the lower the absolute value of pK_a, the higher the activity, i.e. the activity will be favored by substituents that increase the acidity of the substituents.
   An electron-withdrawing R substituent in the structure of the substituents will stabilize the anion that would be formed by the abstraction of a proton in structure **6.3**. Thus, both equations are related to the same parameter: the acidity of thesubstituents.
   (b) The fact that the activity increments on increasing the acidity is indicative that the compound will act in its ionized form.
   (c) Electron-withdrawing substituents, such as halogens (-Br, -Cl), $-NO_2$, $-CF_3$, would improve the activity.
   (d) The parabolic dependence of the activity on pK_a is explained by the influence of the ionization on the penetration through the bacterial membranes. Thus, a fully ionized substituent would be very hydrophilic and would not go through the membrane. A balance between hydrophilicity and lipophilicity is required, so that part of the drug will have to be in the non-ionized form to cross the biological membrane.

7. It depends on hydrophobic and electronic parameters, and substituents lipophilic and electron-donanting will increase $\log(1/K_i)$:
   - for the –Cl substituted-pyrazol:

$$\log P = 0.28(\text{pyrazole}) + 0.71(\text{for aromatic } -\text{Cl}) = 0.99;$$

   - for the –Cl substituted-pyrazole:

$$\log 1/K_i = 1.22 \times 0.99 + 1.80 \times 0.37 + 4.87 = 6.75.$$

8. (a) It depends on hydrophobic, electronic and steric parameters.
   (b) The activity will be favoured by lipophilic substituents ($\pi > 0$), electron-withdrawing ($\sigma > 0$) and not bulky substituents ($E_s < 0$).
   (c) Examples: -F and $-CF_3$

9. Biological activity correlates with hydrophobic and electronic parameters. It is favored by the presence of substituents that are both lipophilic (apolar) ($\pi > 0$) and electron-withdrawing groups ($\sigma > 0$), such as –Br, and $-SEt_2$.

10. (a) It depends on hydrophobic, electronic and steric parameters.
    (b) The activity will be favoured by the presence of lipophilic substituents ($\pi > 0$), electron-withdrawing groups ($\sigma > 0$) and not bulky surrogates ($E_s < 0$). Example: $-CH_2F$, $-SCH_3$.

11. Lipophilic ($\pi > 0$) and electron-withdrawing substituents ($\sigma > 0$), such as halogens (-Br, -Cl, -I), must be introduced.

12. (a) It depends on lipophilic and steric parameters.
    (b) Hydrophobic ($\pi > 0$) and quite voluminous ($E_s > 0$) substituents would be introduced. Examples: $-Pr^n$, $-Bu^n$, $-Bu^t$, -Ph

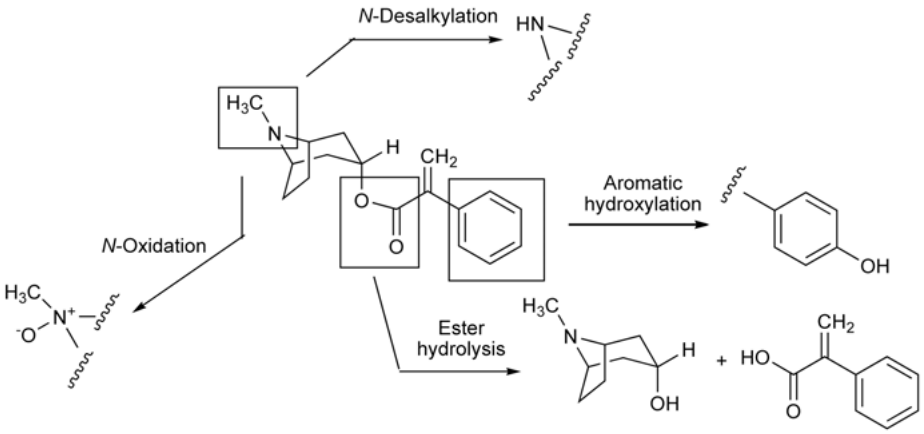
13. The activity would be improved with lipophilic substituents ($\pi > 0$) and small substituents ($E_s < 0$), such as $-CH_2Cl$, $-CH_2F$, $-CH_3$, -SH.

14. (a) It depends on electronic, hydrophobic, and steric parameters. The biological activity will be favoured with electron-withdrawing ($\sigma > 0$), lipophilic ($\pi > 0$) and small substituents ($E_s < 0$).
    (b) Examples: $-SCH_3$, -F, -Cl, $-CH_2F$.

15. The QSAR equation resulting from the multiple linear regression analysis for the antimalarial activity indicates that the two substituents X and Y of the substituted aromatic rings will be affected by the same type of parameters (hydrophobic and electron), and in the same order of magnitude ($\pi > 0$ and $\sigma > 0$). Therefore, the activity will be favoured by lipophilic and electron-withdrawing substituents, such as –Cl, -Br, -I, $-CH_2Br$, $-CCl_3$.

9.5 Exercises to chapter 7

1. (a)



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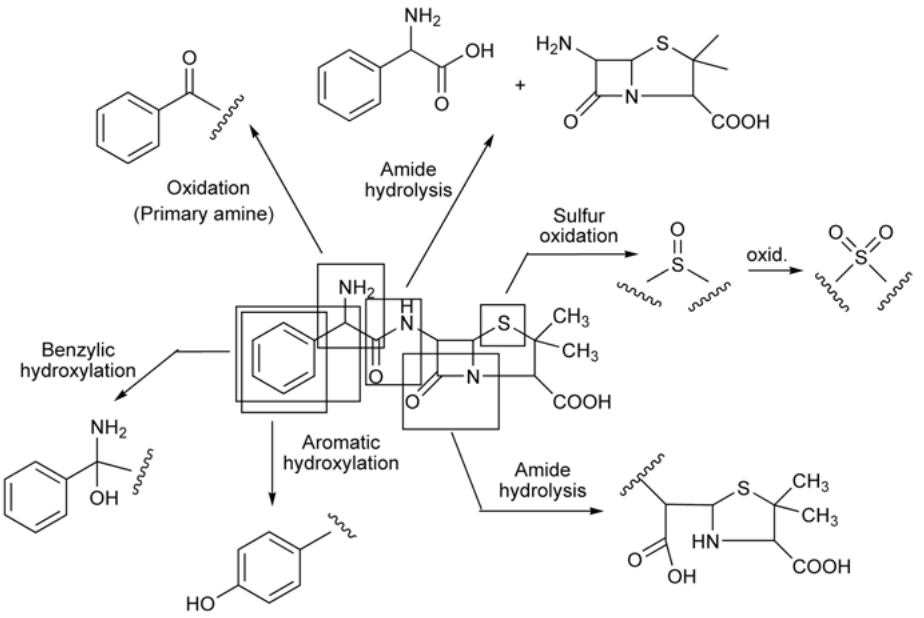

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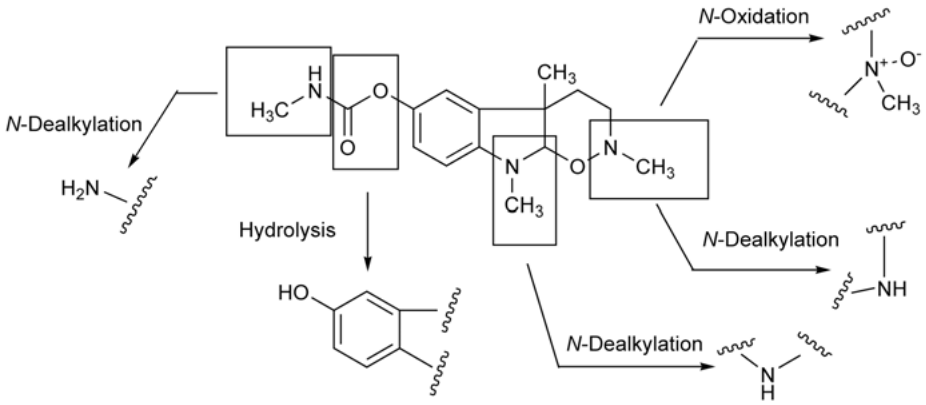

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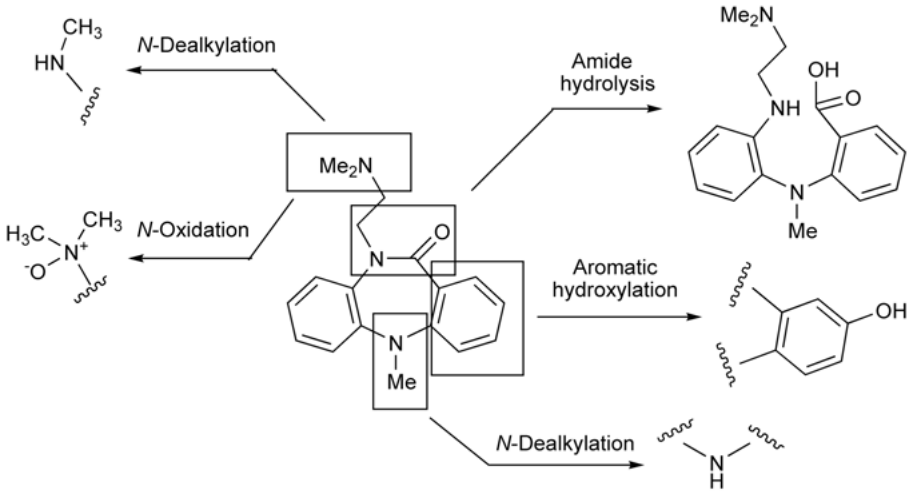
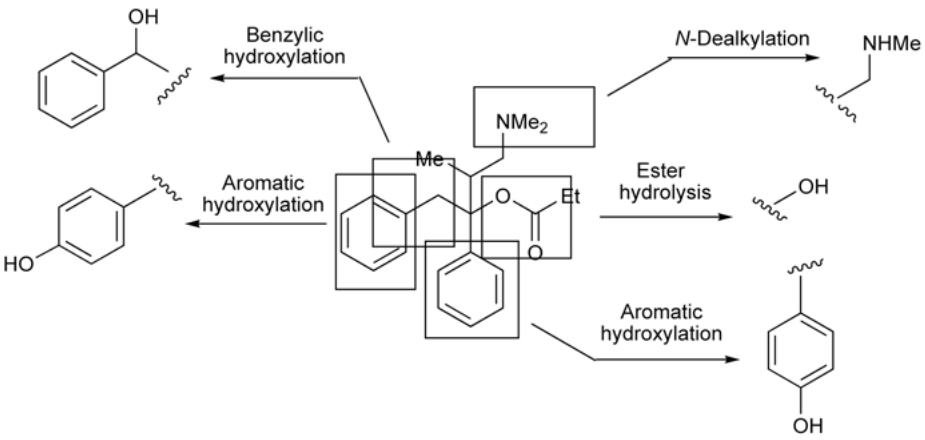
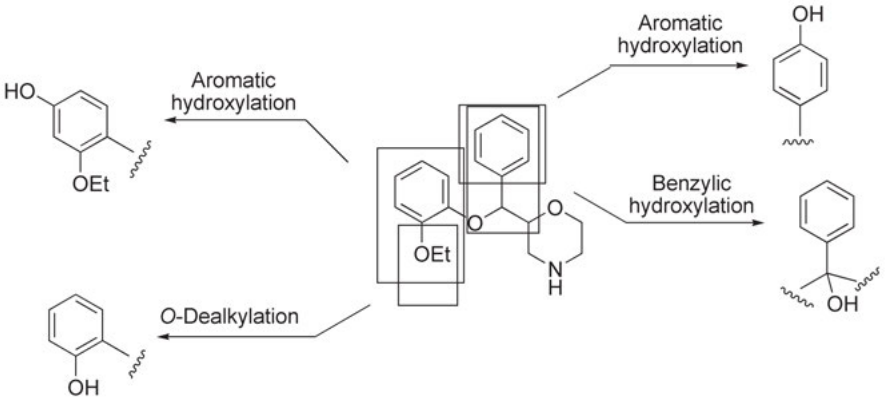


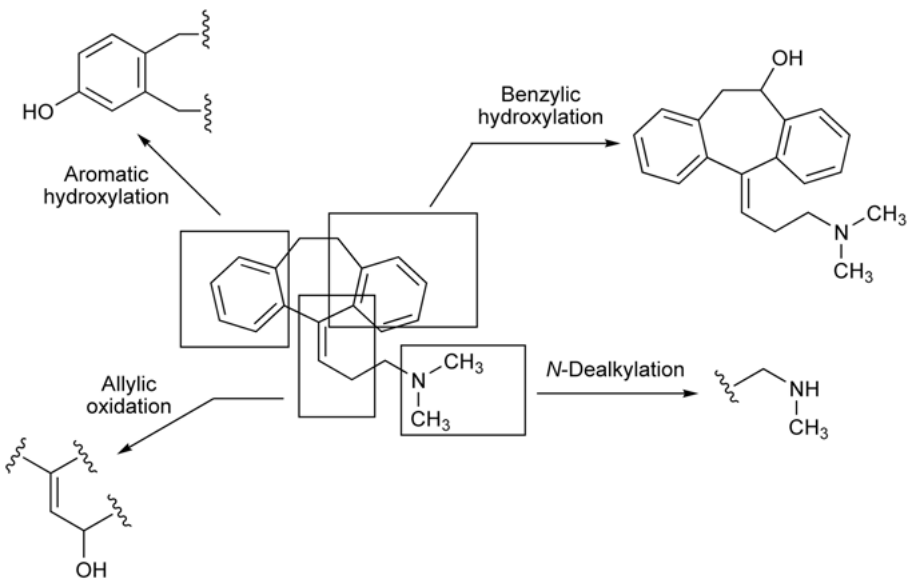
(e)



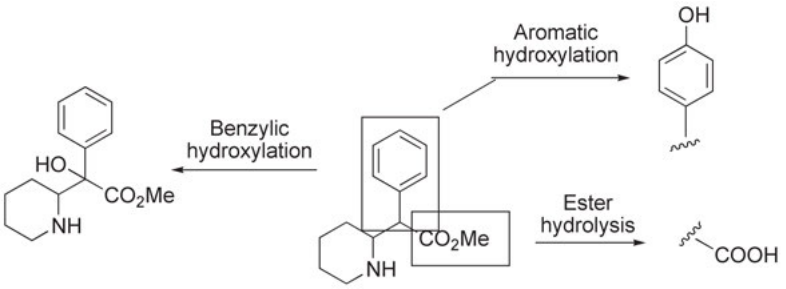
(f)



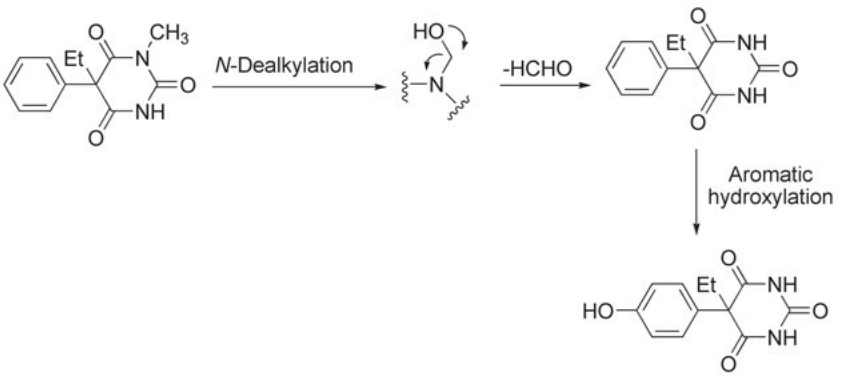
(g)



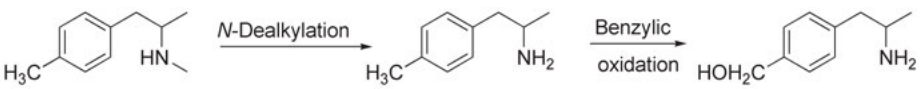
(h)



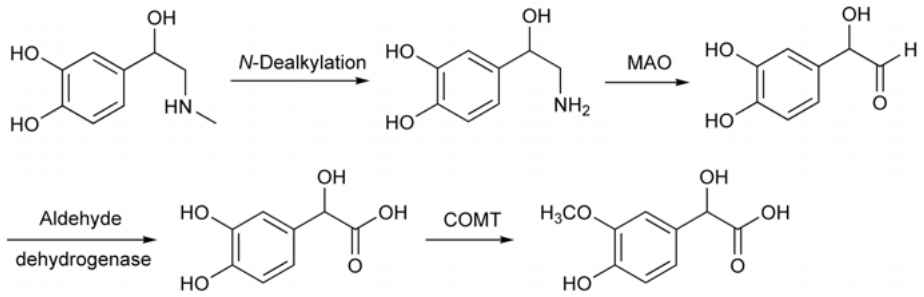
2. (a)



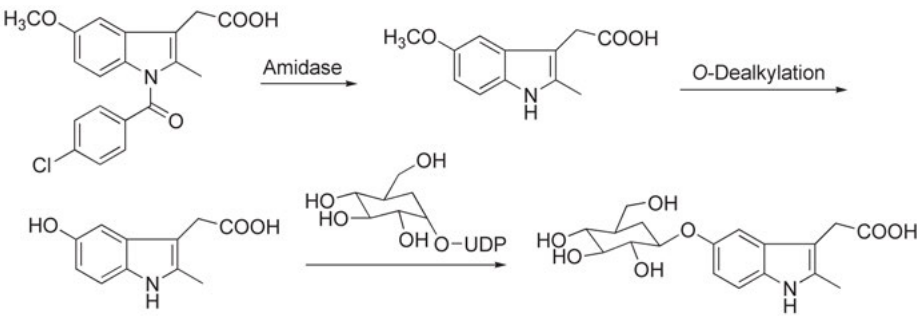
(b)



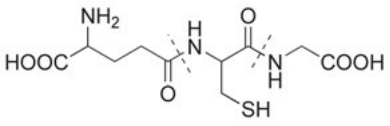
(c)



(d)

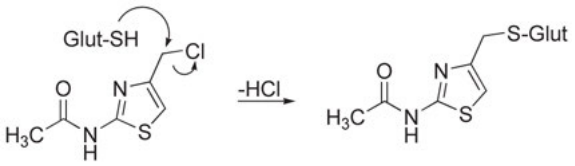


3. (a)



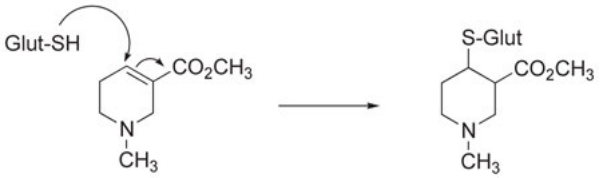
Glu-Cys-Gly

(a′)

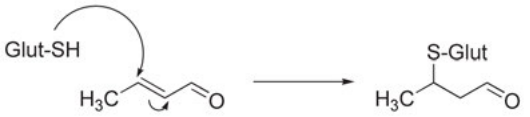


(b′)

(c′)



(d′)



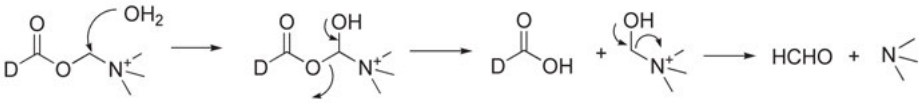
4. (a) D-N(CH_3)C(CH_3)$_3$ is a hard analogue of D-N(CH_3)$_2$.
   (b) D-COOCH_3 is a soft analogue of D-CH_3.
   (c) D-COOC(CH_3)$_3$ is a soft analogue of D-COOC_2H_5.

The *t*-Bu$^+$ catión is stable and degradation of the ester occurs at physiological pH.

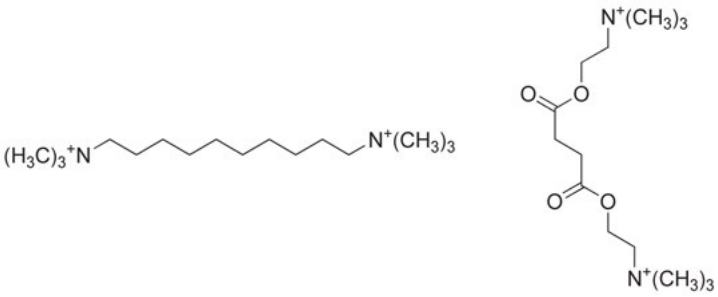
(d) D-C_6H_4-pCF_3 is a hard analogue of D-C_6H_5.

(e) D-CH_2CONHR is a hard analogue of D-CH_2COOR because the former is more difficult to hydrolyze.

(f) D-COO$CH_2N^+R_3$ is a hard analogue of D-COO$(CH_2)_2N^+R_3$ because the former is an unstable acyloxymethylammonium derivative.

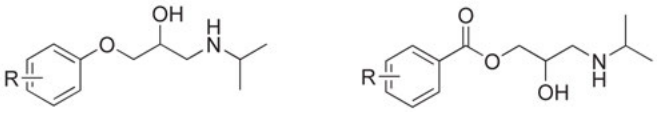


5. (a)



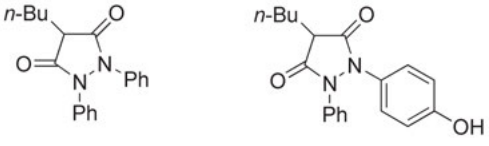
It has been transformed into a soft analogue because its hydrolytic metabolism is facilitated in the modified drug.

(b)



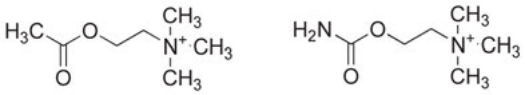
The second drug is a soft analogue of aryloxypropanolamine (with an ester group easy to hydrolyze).

(c)



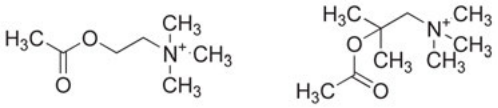
The second drug is a soft analogue: it is an active metabolite of phenylbutazone.

(d)



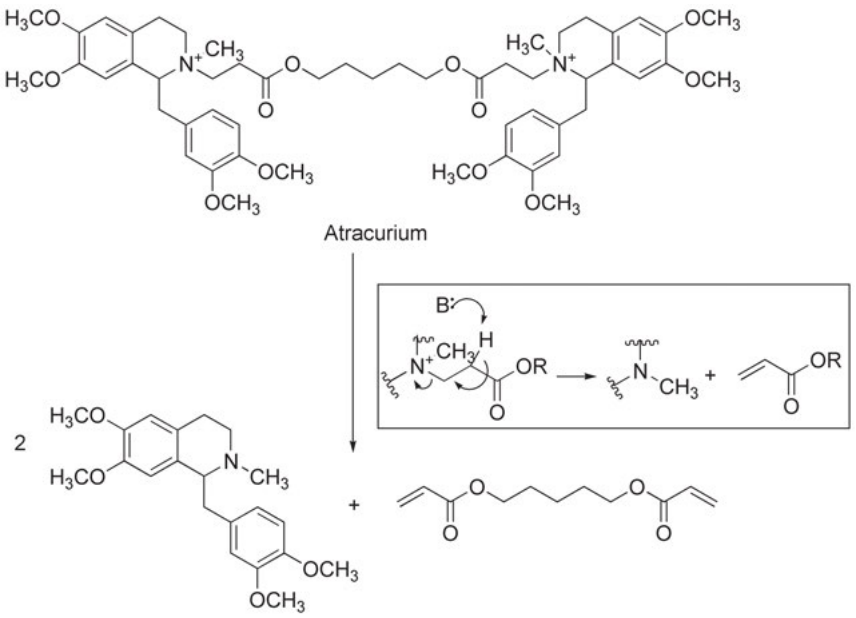
Hard analogue: The first drug is transformed into a carbamate more resistant to hydrolysis.

(e)



Hard analogue by introduction of a steric hindrance in the proximity of the ester group that hinders its hydrolysis.

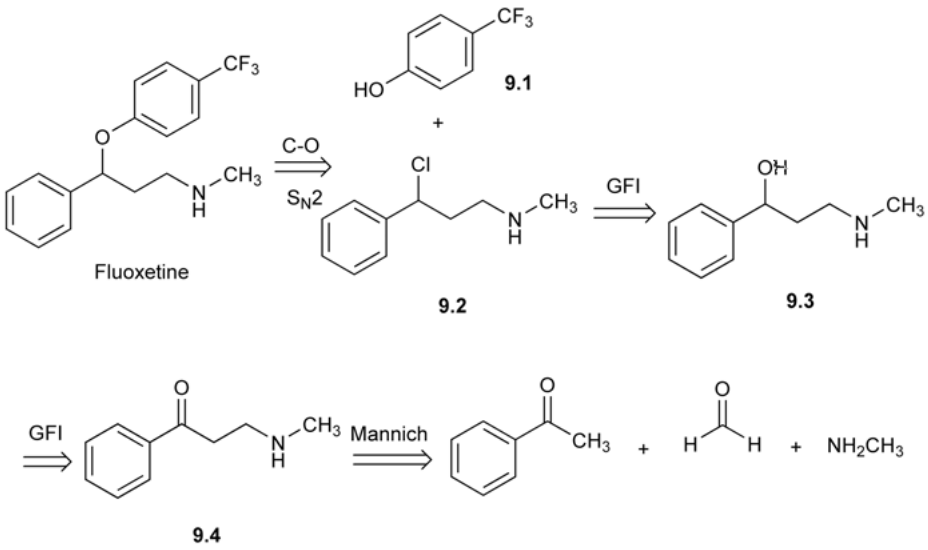
6.



9.6 Exercises to chapter 8

(a) (*RS*)-fluoxetine

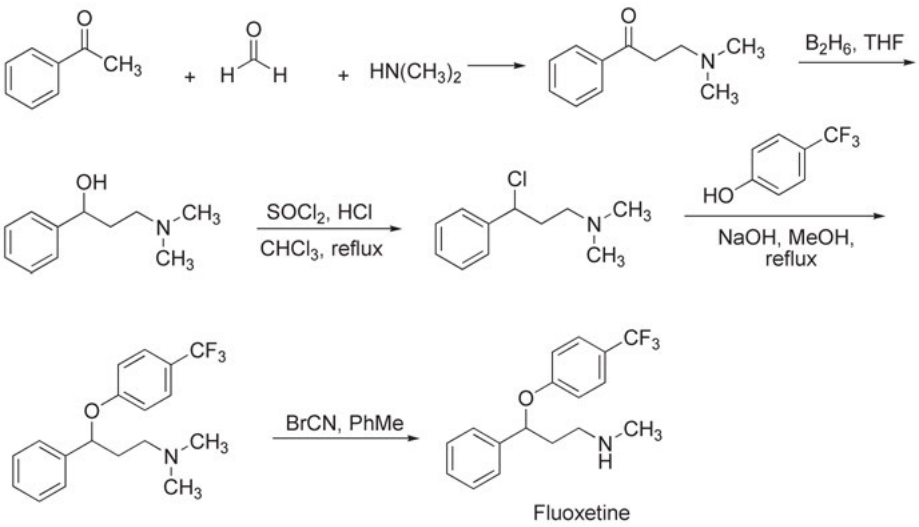
Fluoxetine (Prozac®) was marketed for the first time in 1986. Although it has been on the market for 25 years, it remains one of the most prescribed antidepressant drugs.



Scheme 9.1: Retrosynthetic analysis of fluoxetine.

The disconnection process begins with the cleavage of the C–O bond. The cleavage of the C–O bond leads to the *p*-trifluoromethylphenol **9.1** and the functionalized amine **9.2**, the precursor of which is the aminoalcohol **9.3**. The increase in the oxidation state of the hydroxyl function generates β-aminoketone **9.4**, whose disconnection process, based on a Mannich reaction, leads to acetophenone, formaldehyde and methylamine (Scheme 9.1).

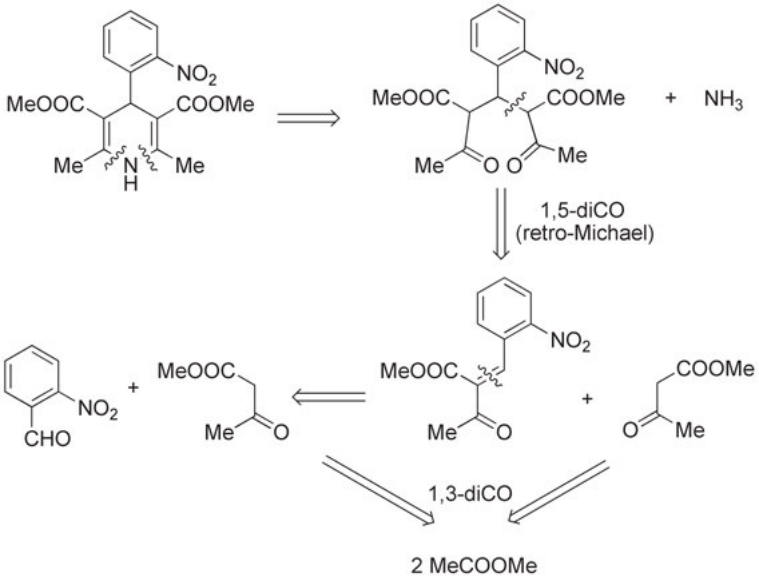
Fluoxetine prepared according to the synthesis described in Scheme 9.2 is obtained in racemic form.



Scheme 9.2: Synthesis of racemic fluoxetine.

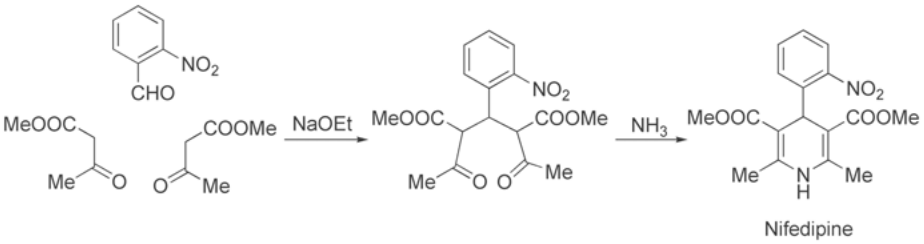
(b) Nifedipine

Nifedipine is a calcium channel blocker of the dihydropyridine type, used in medicine for the relief of angina pectoris, as well as for arterial hypertension.



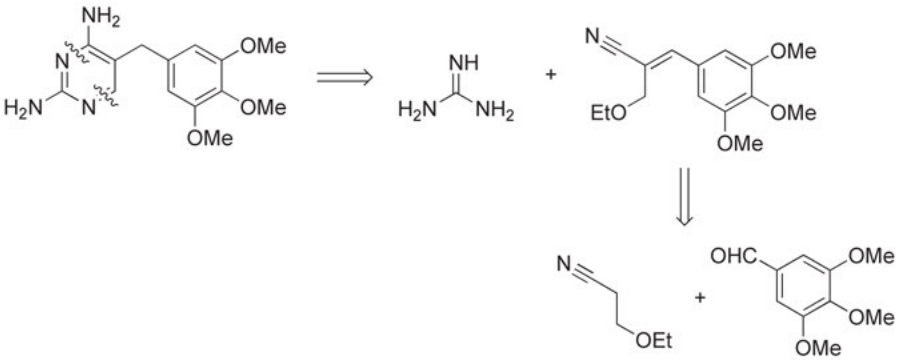
Scheme 9.3: Retrosynthesis of nifedipine.

1,4-Dihydropyridines are obtained from Hantzsch synthesis, i.e. they should be formed from one mole of aldehyde, two moles of 1,3-diCO compound, and one mole of ammonia.
The necessary β-ketoester to react with *o*-nitrobenzaldehyde (Scheme 9.4) is prepared previously by the Claisen condensation of ethyl acetate.



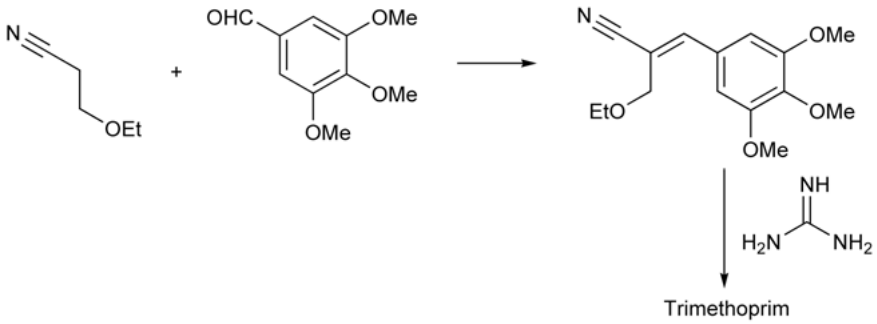
Scheme 9.4: Synthesis of nifedipine.

(i) Trimethoprim
Trimethoprim is a bacteriostatic antibiotic derived from a trimethoxybenzylpyrimidine and almost exclusively used in the treatment of urinary tract infections. Its retrosynthesis is shown in Scheme 9.5.



Scheme 9.5: Retrosynthesis of trimethoprim.

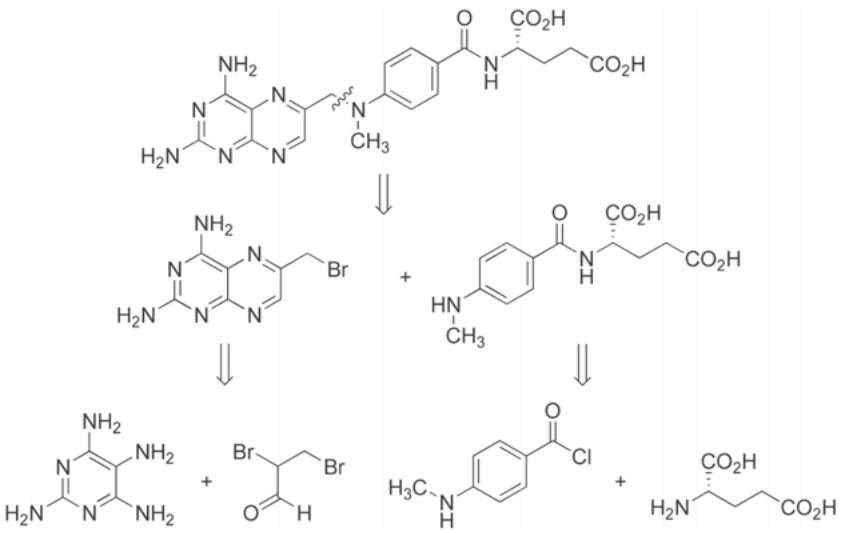
Synthesis begins with an aldol condensation of the benzaldehyde derivative with 3-ethoxypropionitrile. The ethoxy group in an allylic position can be displaced by a nucleophile. An amino group of guanidine is the nucleophile in this displacement process, while the second amino group is added to the cyano group. Proton 1,3-rearrangement gives rise to the drug (Scheme 9.6).



Scheme 9.6: Synthesis of trimethoprim.

(i) Methotrexate (MTX)

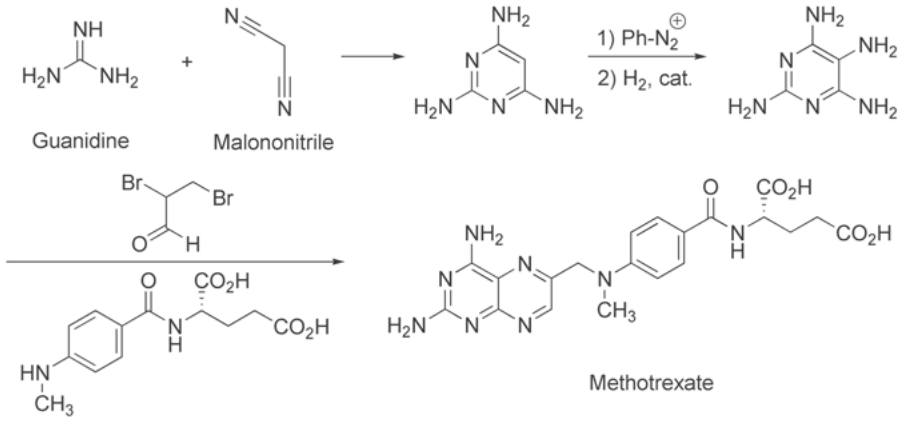
MTX is an antimetabolite that has antiproliferative and immunosuppressive activity by competitively inhibiting the enzyme dihydrofolate reductase (DHFR). This is a key enzyme in the metabolism of folic acid that regulates the amount of intracellular folate available for the synthesis of proteins and nucleic acids. It prevents the formation of tetrahydrofolate necessary for the synthesis of nucleic acids. Its retrosynthesis is shown in Scheme 9.7.



Scheme 9.7: Retrosynthesis of methotrexate.

The route begins with formation of the pyrimidine base by condensation between guanidine and malononitrile, followed by the introduction of the new amino

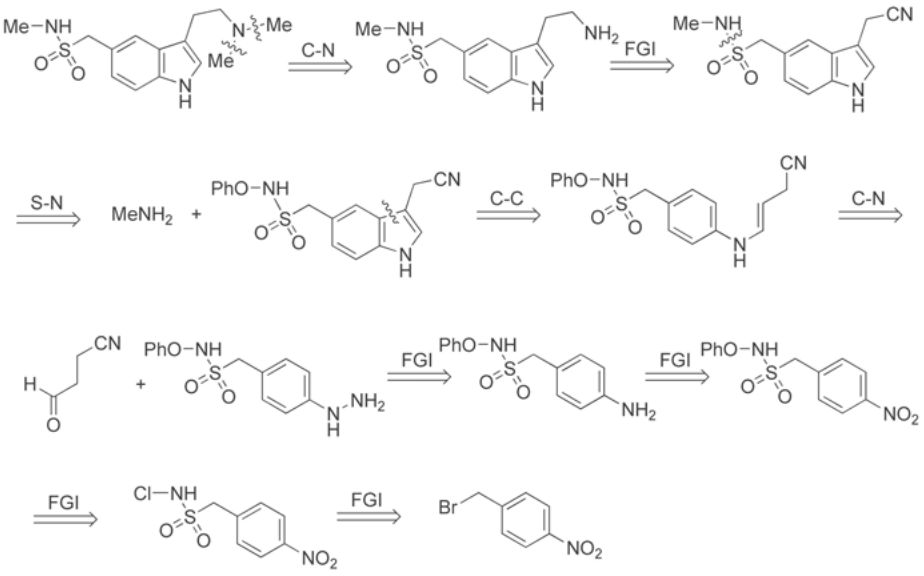
group by diazo coupling and subsequent reduction. The next step builds up the molecule in a single-step one-pot synthesis (Scheme 9.8).



Scheme 9.8: Synthesis of methotrexate.

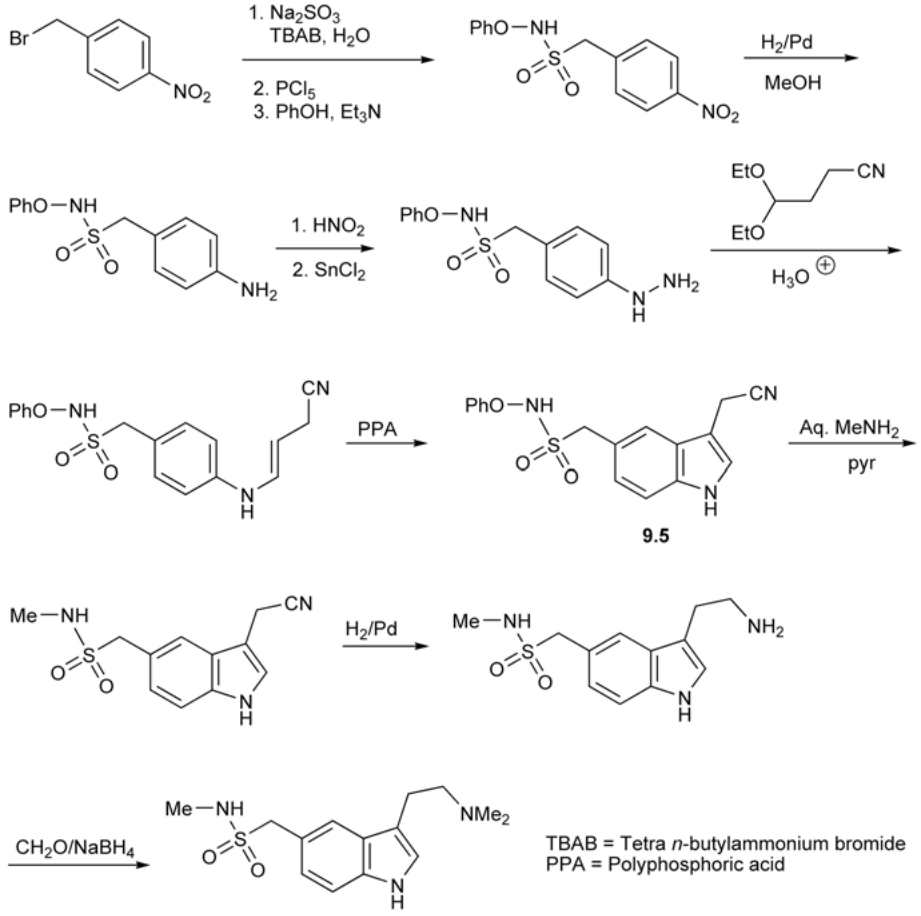
(k) Sumatriptan

Sumatriptan is a medicine that belongs to the group of triptans and is used for the treatment of migraine. Its retrosynthesis is shown in Scheme 9.9.



Scheme 9.9: Retrosynthesis of sumatriptan.

The synthesis of sumatriptan is shown in Scheme 9.10. Sumatriptan was the first serotonergic agonist introduced in therapeutics in 1991 by Glaxo. For its synthesis, the 4-substituted aniline by an *N*-methylsulfamoylmethyl group is the starting material. Aniline nitrogen is converted into diazonium salt with nitrous acid. Its reduction with tin (II) chloride yields the corresponding arylhydrazine, which is condensed with 3-cyanopropionaldehyde diethyl acetal to give the hydrazine, which undergoes a Fisher rearrangement to give indole **9.5**. Finally, the reduction of the nitrile to primary amine and its treatment with an excess of formaldehyde and sodium borohydride, leads to the *N*,*N*-dimethyl derivative (sumatriptan).



Scheme 9.10: Synthesis of sumatriptan.

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